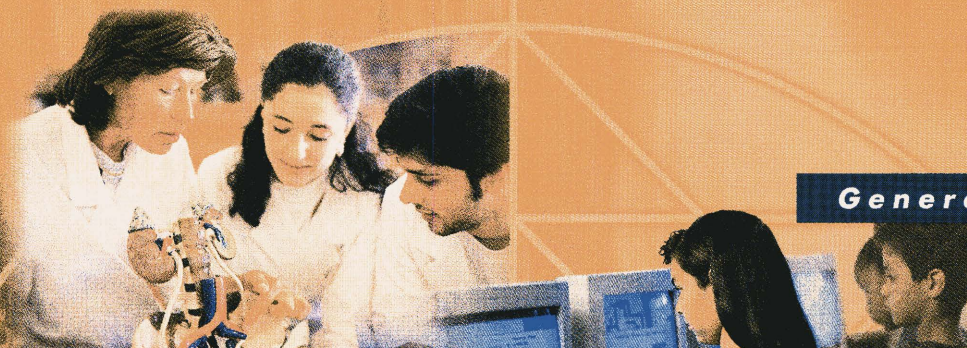


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**Euro-Mediterranean
S&T Cooperation**



*Project Reports
Edition 1998
VOLUME II*



CONFIRMING THE INTERNATIONAL
ROLE OF COMMUNITY RESEARCH

EUROPEAN COMMISSION

Edith Cresson, Member of the Commission responsible for Research, Innovation, Education, Training and Youth.

DG XII/E2 – Programme INCO-MED

Contact: Brian W. Brown

European Commission, Rue de la Loi 200,

B-1049 Brussels

Tel (+32) 2 29 63628

Fax (+32) 2 29 66252

E-mail: brian.brown@dg12.cec.be

European Commission

**Directorate-General XII:
Science, Research and Development**

**Euro-Mediterranean
S&T
Cooperation**

**1998 edition
Vol II**



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Published by the EUROPEAN COMMISSION

Directorate-General XII - Science, Research and Development - B-1049 Brussels

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A great deal of additional information on the European Union is available on the Internet. It can be accessed through the Europa server (<http://europa.eu.int>).

Cataloguing data can be found at the end of this publication.

Luxembourg: Office for Official Publications of the European Communities, 1998

ISBN 92-828-7276-9

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Printed in Belgium

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FOREWORD

The Mediterranean has always evoked the great image of civilisations and of socio-historical continuities for many centuries. Fragile lands, vulnerable ecosystems and traditional socio-economic systems are increasingly affected by demands of modernisation and developmental efforts. Expanding population, urban concentrations, industrialisation, heavy tourism and competing and conflicting demands on natural resources, require thoughtful planning and management.

Increasingly, therefore, the challenge is one of how to cope with and accommodate a variety of developmental demands in a rather “stressed” environment. Such terms as “vulnerability”, “fragility”, “sustainability” or “carrying capacity” exemplify the underlying principles of systematic research and the need for cooperation within a larger socio-political framework. The ongoing efforts point also out to the need to mobilise resources beyond administrative frontiers and to implement joint concerted action. Scientific and Technological (S&T) cooperation has then become a manifest need of Euro-Mediterranean actions.

The European Union has early emphasised and invested in various facets of S&T development and cooperation with Mediterranean Partner Countries. Numerous bilateral and multilateral agreements, ad-hoc workshops, a Ministerial meeting, conferences and TRTD activities of mutual interest summarise the evolution of the EU policy initiative. They reflect the search for common solutions and the urgency for both corrective and preventive actions regarding a variety of environmental and energy related concerns as well as agricultural policy questions and problems of public health.

Systematic efforts were launched in 1992 with the *Avicenne Initiative* (1992-1994). The underlying dimension of this action has been a problem-solving approach on agreed upon priorities, involving regional schemes and shared concerns which reflect mutual areas of interest. This effort continued under the same premises in the context on the INCO programme (1995-1998) and in particular in the frame of the INCO-DC activity (S&T cooperation with developing countries).

The mechanisms for the above have been a sustained political dialogue institutionalised in the forum of *Monitoring Committee for Euro-Mediterranean S&T Cooperation* where all EU Member States as well as the 12 Mediterranean Partner Countries are represented together with the European Commission. The main input of this Committee, through successive meetings starting as early as 1995, has been recommendations on policy implementation, future actions of regional relevance and priority settings for common RTD activities.

Building on such experience and cumulative research results, the EU has decided to further strengthen the S&T cooperation with Mediterranean partner countries. This commitment was explicitly expressed in the 5th Framework Programme (1998-2002), where a distinct activity, INCO-MED, reinforces excellence in research and cooperative approaches to mutual problems. Moreover, the 5th Framework Programme is now open for participation to Mediterranean Partner Countries for all specific programmes and activities under relevant terms and conditions.

We are convinced that Research, Technological Development and Innovation are important and necessary keys to urgent socio-economic demands and to contribute to the development of a real Euro-Mediterranean Partnership.

J. GABOLDE
*Director, International S&T
Cooperation*

INTRODUCTION

This catalogue of contracts is the fourth edition of cooperation projects on Science and Technology contracted between the EU and Mediterranean Partner Countries from 1989 to 1998.

Looking back at this period of activity there were a series of successive preparatory actions which led to some 250 joint RTD contracts and more than 50 accompanying measures which reinforced the implementation of the programme. These early efforts include "Science and Technology for Development" (STD3) and "International Scientific Cooperation" (ISC) programmes which had some involvement with Mediterranean case studies.

The creation of the Avicenne Initiative by the European Union in 1992 formally inaugurates the Euro-Mediterranean RTD cooperation activities. Between 1992 to 1994, three particular areas were promoted, namely environmental protection with a particular focus on water related issues, use of renewable energies and health. 71 contracts with a financial European Community contribution of 26 MECU have been concluded during this period.

By 1995 the Euro-Mediterranean cooperation became part of the 4th Framework Programme of the EU in the context of the INCO-DC activity. During this time, emphasis was placed on integrated water resources management and related technologies for purification and reuse, coastal zone protection and preservation, forests and drylands, ecosystems related research, marine science, infectious diseases and public health, restoration of the cultural heritage, information and communication technologies and finally production systems in agriculture, research on crop plants, animals and trees. Some 114 joint RTD contacts received a financial contribution of 50 MECU from the INCO-DC programme involving 470 research institutions in both Member States and all 12 Mediterranean Partner Countries. This effort applies on shared cost and concerted RTD actions.

It became obvious that in later years the Euro-Mediterranean S&T cooperation gained importance in commonly selected S&T sectors of regional relevance for the Mediterranean area. The RTD results obtained so far tend to emphasise the need of a coordinated activity on capacity-building in S&T sectors, excellency research and innovation as well as appropriate use of research results by end-users.

The research presented in the volume reflects not only the increased emphasis on holistic approaches, on valid and reliable data and on innovative technological solution. It underscores also the need for integrated approaches and the emphasis on sustainability because of the complexity, interdisciplinarity and vast web of interactions in problems important for the socio-economic development of the Mediterranean.

The project data sheet provided for each contract contains a short description of the objectives of the work, the activities and methodologies, the expected outcome and whenever appropriate the final research results. Finally, four indexes are provided which should help the reader to find projects or partners according to his/her interests.

M. KAYAMANIDOU
Euro-mediterranean S&T cooperation

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**FEASIBILITY AND EFFECTS OF SHIFTING THE MIX OF TERTIARY CARE,
PRIMARY CARE AND PREVENTIVE AND PROMOTION IN DEALING WITH
CARDIOVASCULAR DISEASE IN LEBANON AND TURKEY**

Co-ordinator: American University of Beirut, Beirut, Lebanon (Mustafa Khogali)

OBJECTIVES

Since Cardiovascular Disease (CVD) in the Eastern Mediterranean Region is characterized by a strong and growing bias towards inefficient tertiary care (TC), non-rationalized case management at the ambulatory primary care level (PC), and absence of prevention and promotion (pp), this study seeks to:

- Prove that shifting the present TC/PC/PP mix towards prevention-promotion and rationalized case management at primary care level is:
 - Feasible and affordable
 - Brings about health benefits
 - Has the potential to reduce the financial burden of CVD on the community
- Test the feasibility of an intervention package, consisting of three components: (1) PP: Introducing PP at the community level; (2) PC: Rationalizing and improving quality of ambulatory case management; and (3) TC: Shift from TC towards PC and PP.
- Document the effects of the intervention package on:
 - The mix of choices of TC/PC/PP by users
 - Risk factors, risk perception and quality of case management
- Document the potential for reduction of costs through shifting away from TC and rationalizing case management at the PC level.

ACTIVITIES

This study will be conducted in two different countries (Gulverin-Turkey, and Beirut-Lebanon) by a network of partners from five Universities (Department of Family Medicine, American University of Beirut Medical Center, Lebanon; Department of Public Health, Hacettepe University, Ankara - Turkey; Department of Public Health, Institute of Tropical Medicine, Antwerpe-Belgium; Department of Tropical Hygiene and Public Health, Heidelberg University, Germany; and Turkish German Health Foundation, Giessen-Germany).

The study will be conducted via three phases:

Phase I:

Baseline data about risk factors, risk perception, quality of care and costs of PC, TC/PC/PP mix of choice of provider and appropriateness and costs of TC of CVD in Lebanon and Turkey will be documented using the CINDI/MONICA research instrument and Focus group interviews.

Phase II:

Application of the Intervention package that consists of 3 components:

- PP: Community Intervention, Prevention and Promotion: Consists of a multitude of small group activities organized around self-help and healthy lifestyles in Turkey and Lebanon.
- PC: Improvement of Quality of Ambulatory Case Management: Includes improvement of quality of care delivered by PC providers to study population in Lebanon and Turkey through clinical audits, standard diagnosis, treatment and follow up protocols in addition to improving laboratory facilities.
- TC: Shift from TC to PC and PP: Shifting population demand, provider-induced demand, and policy context from TC towards rationalized ambulatory case management and prevention promotion through referral audit; monitoring and feedback of provider behavior; dialogue with consumers, providers and policy makers on basis of components 1 and 2; and study of costs and appropriateness of tertiary care for CVD in Lebanese private hospitals.

Phase III

Post - intervention evaluation of the effects of the intervention packages on risk factors, risk perception, quality of care, TC/PC/PP mix of choice of provider and potential cost reduction.

EXPECTED OUTCOMES

- ⇒ Establishment of baseline data on risk factors, risk perception, quality of care and costs of primary care, TC/PC/PP mix of choice of provider, appropriateness and costs of TC in both countries Lebanon and Turkey
- ⇒ Following the intervention, the project will generate a systematic documentation of the process of implementing the interventions, including: strategies followed, resistance met, costs, acceptability for target groups and decision makers.
- ⇒ Reduction of risk factors among the study groups that include: reduction in smoking, lowering mean blood pressure, reduction of prevalence of hypertension, obesity and severe hyperlipidemia
- ⇒ Change in primary care system to induce adequate control of hypertensive and diabetic patients, adherence to standard protocols, satisfaction of community/patients with health centers services and reduction in unit cost per patient
- ⇒ Achieve the shift of the present TC/PC/PP mix towards prevention and promotion and rationalized case management at the primary care level in Lebanon and Turkey that will be reflected in the health benefits, and reduction of the financial burden of CVD to the community.

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PARTNERS

THE AMERICAN UNIVERSITY OF BEIRUT
Department of Family Medicine and Internal Medicine
Faculty of Medicine
P.O. Box 113-6044
Beirut
Lebanon

M. Khogali
Tel.: +961/1/35.34.65
Fax: +961/1/74.44.64
E-mail: khogali@aub.edu.lb

**PRINCE LEOPOLD INSTITUTE OF TROPICAL
MEDICINE**
Dept. of Public Health
Nationalestraat 155
2000 Antwerpen
Belgium

W. Van Lerberghe
Tel.: +32/3/247.62.86
Fax: +32/3/247.62.58
E-mail: wlerberghe@itg.be

RUPRECHT-KARLS-UNIVERSITÄT HEIDELBERG
Dept. of Tropical Hygiene and Public Health
Im Neuenheimer Feld 324
69120 Heidelberg
Germany

O. Razum
Tel.: +49/6221/56.25.78
Fax: +49/6221/56.50.37
E-mail: oliver.razum@urz.uni-heidelberg.de

HACETTEPE PUBLIC HEALTH FOUNDATION
Dept. of Public Health
Gevher Nesibe Sokak No.6
06100 Sıhhiye/Ankara
Turkey

S. Tezcan
Tel.: +90/312/324.39.75
Fax: +90/312/311.00.72
E-mail: nalksav@tr-net.net.tr

TURKISH GERMAN HEALTH FOUNDATION
Sağlık Vakfı
Friedrichstr. 13
35390 Giessen
Germany

Y. Bilgin
Tel.: +49/641/77.511
Fax: +49/641/75.653

HOSPITAL NEAR-MISS ENQUIRIES AS A STRATEGY TO IMPROVE THE QUALITY OF OBSTETRIC CARE IN BENIN, IVORY COAST AND MOROCCO

Co-ordinator: London School Of Hygiene And Tropical Medicine, London, United Kingdom
(Carine Ronsmans)

OBJECTIVES

- to promote appropriate action through consensus building among the different partners in Safe Motherhood
- to develop and implement a new strategy to improve obstetric care in referral hospitals by using near-miss event enquiries as a mechanism for the evaluation and improvement of the quality of obstetric care. The new strategy will involve:
 - establishing a near-miss enquiry committee in each country;
 - developing a pragmatic framework for assessing quality of care (QoC) specific to the local resource environment in each of the three countries, including the identification of valid and reliable criteria for the definition of near-miss events and of substandard care and avoidable factors which contribute to women experiencing near miss events;
 - conducting in-depth confidential enquiries in a subset of cases of near-miss events to document the nature of substandard care and avoidable factors;
 - conducting a quantitative assessment in the entire sample of near miss cases to document the frequency of substandard care and avoidable factors;
 - making recommendations concerning the improvement of clinical care and organisational procedures and setting realistic and acceptable targets for selected elements of substandard care;
 - monitoring these targets.
- to evaluate the success of the intervention by examining the mechanisms implemented to support the near-miss enquiry process, by recording the attitudes and perceptions of key actors in relation to the enquiry process, and by examining the changes brought about by the enquiry process.
- to examine the feasibility of initiating and sustaining a near-miss enquiry approach and to disseminate the findings of the research to organizations committed to Safe Motherhood

ACTIVITIES

This is an operational research project concerned with the feasibility of initiating and sustaining a dynamic process of enquiries into avoidable and substandard care factors in obstetric care in six health facilities in three African countries (Benin, Côte d'Ivoire and Morocco). The study design involves a staged implementation of near-miss enquiry activities, combined with efforts to evaluate the organisation and management of, and the changes brought about by, the enquiry process. The study will use a combination of questionnaires, interviews, site visits and detailed case studies to document the working of the enquiry process.

The implementation of the near-miss enquiry approach will consist of seven steps:

- Form a Near-miss Enquiry Committee (1 month);
- Develop a QoC framework (3 months);
- Develop a data collection and analysis plan for near-miss enquiries (3 months);
- Train hospital staff, initiate data collection and analyse data (6 months);
- Re-assess the QoC framework, select a limited number of QoC elements for which targets can be set, set targets (3 months);
- Resume data collection using selected targets (6 months);
- Analyse progress, report and disseminate (3 months).

The success of the intervention will be measured through analysis of written documents (policy statements and health strategy reports, health service records), quantitative analysis of targeted criteria and interviews with the participants in the enquiry process. The intervention will be considered successful if:

- all the steps listed above have been established,

- progress towards targets has been made,
- the participants in the enquiry process understand its purpose and are favourable to its application.

EXPECTED OUTCOME

The expected outcomes of this research include:

- initiating and/or sustaining a constructive debate on issues related to QoC in Benin, Ivory Coast and Morocco;
- developing near-miss enquiry tools appropriate for further use by managers and providers of obstetric services in Benin, Ivory Coast and Morocco;
- providing guidelines on how this method can be generalised to other developing countries;
- strengthening the research capacity in each of the study sites;
- setting up a collaborative network to study and promote the use of the near-miss enquiry approach;
- enhancing political commitment towards Safe Motherhood.

FOLLOW-UP

Six workshops (WS) will be held to support the development and implementation of the near-miss enquiry strategy and the promotion of the dissemination of the findings. Two in-country WSs will aim at reaching consensus on what constitutes a near-miss event and avoidable and substandard care factors. These WSs will be followed by an international WS aimed at harmonizing the definition of criteria across sites. After completion of six months of data collection an in-country WS will be held to re-assess the QoC framework. The EU partners will then meet in Trieste to discuss the progress of the research. The final dissemination of the findings will take place in-country and internationally.

Each country will produce annual reports documenting the progress of the research and summarizing preliminary findings. At the end of the project, a final report summarizing the main findings of the study will be produced. The findings presented at the international dissemination workshop will be summarized in a portfolio.

PARTNERS

LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE

Dept. of Epidemiology and Population Health
Maternal and Child Epidemiology Unit
Keppel Street
London WC1E 7HT
United Kingdom

C. Ronsmans
Tel.: +44/171/299.46.84
Fax: +44/171/299.46.63
E-mail: c.ronsmans@lshtm.ac.uk

PRINCE LEOPOLD INSTITUTE OF TROPICAL MEDICINE

Department of Public Health
Nationalestraat 155
2000 Antwerpen
Belgium

W. Van Lerberghe
Tel.: +32/3/247.62.86
Fax: +32/3/247.62.58
E-mail: wlerberghe@enov.itg.be

CENTRE DE RECHERCHE EN REPRODUCTION HUMAINE ET EN DEMOGRAPHIE

01 BP 1822 Recette Principale
Cotonou
Benin

E. Alihonou
Tel.: +229/30.00.01
Fax: +229/30.12.88
E-mail: cerrhud@syfed.bj.refer.org

BUREAU FOR INTERNATIONAL HEALTH

Istituto per l'Infanzia Burlo Garofolo Ufficio
Cooperazione Internazionale
Via dell'Istria 65/1
34137 Trieste
Italia

A. Bacci
Tel.: +39/040/378.52.36
Fax: +39/040/378.54.02
E-mail: bih-burlo@up.spin.it

CENTRE HOSPITALIER UNIVERSITAIRE DE YOPOUGON

Cellule de la Recherche en Santé de Reproduction
Service de Gynecologie-Obstetrique
21 BP 632
Abidjan 21
Ivory Coast

C. Wellfens-Ekra
Tel.: +225/46.61.70
Fax: +225/46.67.27

INSTITUT NATIONAL D'ADMINISTRATION SANITAIRE

Collège de la Santé
Route de Casablanca Km 4.5
Rabat
Morocco

A. Laabid
Tel.: +212/7/69.16.26
Fax: +212/7/69.16.26
E-mail: inas@mtds.com

THE PRACTICE OF HEALTH CARE REFORM: LESSONS FOR THE FUTURE

Co-ordinator: Prince Leopold Institute Of Tropical Medicine, Antwerpen, Belgium
(Wim Van Lerberghe)

OBJECTIVES

- It will develop a framework for characterising and documenting:
 - the factors fundamental for an adequate understanding of past, current and proposed policy changes, namely: the problems, the principles, the purposes, the proposals and the protagonists in the processes of reform in the countries of the participating groups, both in Europe and in Developing Countries;
 - the strategies for implementing these reform exercises
 - the (desirable and undesirable) achievements of these reform exercises
- It will develop a manual for systematic and comparable documentation of the reform process, with focus on (i) the identification of the paradigms underlying the reform agendas, and on (ii) (institutional) strategies used to gain support for and overcome resistance against implementing these reform agendas.
- It will provide systematic documentation of reform exercises in partner countries as a basis for a comparative analysis of the approaches and strategies to planning and implementing health care reform.
- It will promote discussion and exchange of ideas on the manual and the framework through the establishment of a discussion group on the Internet.

ACTIVITIES

This concerted action builds on a number of case studies. After completing a literature review and a review of experience with the ongoing reform exercises in the partner countries (Sweden, Belgium, Central-America, Nicaragua-Guatemala, Lebanon, Morocco, Mozambique, Portugal, Thailand), a provisional analytical framework for describing rationale, agendas and implementation arrangements of the reform exercises as well as a provisional framework for systematic documentation of the process of reform are agreed upon by the different partners at a first partner meeting. The various partners will utilise these draft frameworks to describe and document the reform process in their respective countries. Validation of the documentation is done through peer review during exchange visits. The various documented country experiences are then collated and compared at a second partner meeting that leads to a revised documentation framework. The process is then repeated, leading to systematic documentation, in comparable formats, and validated through peer review, of the reform process in the participating countries. The various country reports are compared at a closing meeting that produces the following deliverables: (i) a reform process documentation manual; (ii) case study descriptions; (iii) a comparative analysis of the case studies with identification of common patterns and the do's and don'ts in the practice of reform.

There are thus five major steps in the concerted action:

Step 1. a) literature review; partner meeting to b) draft an initial analytical framework for describing the problems, the principles and purposes, the proposals, the protagonists and the implementation arrangements of reforms; c) draft a framework for systematic documentation of the reform process; d) organise a discussion group on the frameworks on the internet.

Step 2. a) first round of documentation of the reform process in the participating countries, with b) structured peer validation of the observations, according to a methodology agreed upon during the first partner meeting.

Step 3. partner meeting to a) compare provisional results (validation, comparability, feasibility, congruence), b) review the framework through a consensus generating method; c) attempt a first draft

of the manual, in preparation of the second round of documentation; and d) disseminate the new version of the framework and the draft manual through the Internet discussion group.

Step 4. a) second round of documentation of the reform process in the participating countries, with b) structured peer validation of the observations.

Step 5. partner meeting for a) collation and comparative analysis of the documented reform processes, for b) evaluation of the usefulness of the framework and manual; in order to c) produce their final version, taking into account comments obtained through the Internet.

EXPECTED RESULTS & FOLLOW-UP

Activities and deliverables	Month	Milestones
Step 1 Preparation		
1.1. Literature review	1-2	
1.2. Circulation of literature review	3-4	
1.3. Partner Meeting I. (Portugal) Draft analytical and documentation frameworks.	4	Partner meeting 1
<i>1.4. Organisation of a discussion group on the Internet</i>	4	
Step 2 First round of documentation of country reform exercises		
2.1. Documentation using the frameworks	5-15	
2.2. First country report (draft)	10	
2.3. Peer validation of country documentation through exchange visits	12-13	
2.4. Revised country report	14	Country reports round 1 available
Step 3. Mid term evaluation		
3.1. Partner Meeting II. (country to be decided) Revised frameworks	15	Partner meeting 2
<i>3.2. Revised frameworks on the Internet</i>	16	
Step 4. Second round of documentation of country reform exercises		
4.1. Further documentation using the revised frameworks	16-28	
4.2. Peer validation of country documentation through exchange visits	18-24	
4.3. Production of country reports	25-26	
4.4. Circulation of country reports	26-28	Country reports round 2 available
Step 5. Analysis		
5.1. Partner meeting III. (country to be decided) Evaluation of frameworks; comparison of country experiences	29	Partner meeting 3
5.2. Final reports: Documentation manual; Country case studies; Comparative analysis of documented country experiences	30-34	
5.3. Publication final reports	35-36	Final reports available

PARTNERS

PRINCE LEOPOLD INSTITUTE OF TROPICAL MEDICINE

Dept Of Public Health
Nationalestraat 155
2000 Antwerpen
Belgium

Pr Wim Van Lerberghe
Tel.: 32-3-247.62.86
Fax: 32-3-247.62.58
E-mail: Wlerberghe@Enov.Itg.Be

MINISTERIO DE SALUD PUBLICA Y ASISTENCIA SOCIAL

Unidad Ejecutora Del Programa De Mejoramiento De Los Servicios De Salud
6a, Avenida 3-45, Zona 11
Guatemala City
Guatemala

Dr Angel Fernando Sanchez Viesca
Tel.: 502-475.21.57
Fax: 502-475.21.57
E-mail: Asanchez@Ops.Org.Gt

MINISTRY OF PUBLIC HEALTH

Health Sector Rehabilitation Project
Museum Street
Beirut
Liban

Ms May Awar
Tel.: 961-1-61.57.24
Fax: 961-1-61.57.30
E-mail: Mphealth@Cnrs.Edu.Lb

MINISTRY OF HEALTH

Ressma - Reseau D'economie Et Systemes De Sante Du Maghreb
Blvd Mohammed V
Rabat
Maroc

DR XXX
Tel.:
Fax:
E-mail:

CENTRO DE INVESTIGACAO PARA A SAUDE & DESENVOLVIMENTO

Health Sector Reform - So3
Caixa Postal 402
Maputo
Mozambique

Dr Aurelio Gomes
Tel.: 258-1-45.01.26
Fax: 258-1-42.52.55
E-mail: Gomes@Lelo.Uem.Mz

UNIVERSIDADE NOVA DE LISBOA

Centro De Malaria E Outras Doencas Tropicais
Rua Da Junqueira 96
1300 Lisbon
Portugal

Pr Paulo Ferrinho
Tel.: 351-1-363.96.28
Fax: 351-1-363.21.05
E-mail: Pmfemdt@Feunl.Fe.Unl.Pt

KAROLINSKA INSTITUTE

Div. Of Int'l Health Care Research Dept Of Public Health
Sciences
171 76 Stockholm
Sweden

Pr Goran Tomson
Tel.: 46-8-5177.6629
Fax: 46-8-31.15.90
E-mail: Staff-Ihcar@Phs.Ki.Se

MINISTRY OF PUBLIC HEALTH

Office Of Health Care Reform
Tivanont Road Maung District
11000 Nontaburi
Thailande

Dr Sanguan Nitayarumphong
Tel.: 66-2-590.11.21
Fax: 66-2-591.85.10
E-mail: Sanguan@Health.Morph.Th

ADVANCED DISINFECTION AND HEALTH CARE ASPECTS OF WASTEWATER RECLAMATION AND RE-USE AGRICULTURE IN MEDITERRANEAN REGIONS

Co-ordinator: Community of Mediterranean Universities, Bari, Italy (Lorenzo Liberti)

OBJECTIVES

- Comparison of different disinfecting technologies in terms of germicidal effect as well as formation of harmful by-products;
- Investigation of health implications and waterborne disease spread out by partially disinfected wastewater with special attention to epidemiological and toxic effects on aquatic life and humans;
- Evaluation of low-cost technology systems of wastewater treatment for agricultural reuse appropriate to Mediterranean Countries;
- Optimisation of schemes for wastewater utilisation in agriculture by reference to crops, pedology, groundwater vulnerability, irrigation methods and management aspects.

ACTIVITIES

The research methodology is based on parallel investigations of various aspects related to wastewater treatment, to agricultural reuse and to human health care. In particular:

- ◇ Engineering and sanitary of advanced disinfection. Comparison of different disinfection technologies (i.e. ozone, chlorination, hydroge peroxide, ultraviolet, rays, silver and other heavy metal ions) in terms of germicidal effect as well as formation of harmful by-products formation will be made at pilot and/or full scale level;
- ◇ Low-cost technology wastewater treatment systems. Low-cost technology systems of wastewater treatment for agricultural reuse appropriate to Mediterranean countries such as high rate algal ponds that accounts also for heavy metals content of wastewater will be evaluated at pilot and field level. An optimisation of schemes for wastewater utilisation in agriculture by reference to crops, penology, groundwater vulnerability, irrigation methods and organisational aspects will be assessed;
- ◇ Environmental impacts on sea and ground water. Reduction of rates of nitrification in secondary treatment as result of exposure to heavy metals will be measured as a means to evaluate the epidemiological and toxic effects on aquatic life and deep groundwater of partially disinfected wastewater;
- ◇ Investigation of health implications and waterborne diseases. Appropriate methodologies for measuring the diffusion of waterborne diseases and related pathogens in wastewater and detecting endemic Mediterranean species and selected DBP and listed chemicals in food will be assessed.

RESULTS SO FAR

Italy

- ⇒ Till the end of 1996, the investigation of UV disinfection effectiveness for treating clariflocculated and filtered activated sludge secondary effluents from West Bari Municipal Wastewater Treatment plant has been carried out by a purposely built 100m³/h pilot plant. The main results achieved at the end of such investigation have been the following :
 - an UV dose of approximately 100 MWs/cm² is necessary to achieve the target total coliforms limit (2 CFU/100ml);
 - the quality of the UV treated effluents result in compliance with Italian and International Standards for agricultural reuse;
 - at least under the investigated condition and analytical procedures, it seems that UV-promoted formation of disinfection by-products does not occur as indicated by both chemical and toxicological evidences.
- ⇒ As for the fundamental studies aimed to quantify the real UV dose provided to UV treated wastewater, by an advanced laser-device, under fixed operative conditions (water flow-rate and quality), the validity of two theoretical models (P55 and RTD) has been assessed. The most

significant result obtained during the reference period has demonstrated that the real UV dose inside the investigated UV reactor is by far to be constant but strongly depends upon the wastewater hydrodynamics and quality, the distance from the UV source, and the type of UV lamps configuration (submerged or not).

Israel

⇒ There are two main parts of the results:

First : the die-off kinetics of E. coli-B and MS2 bacteriophage upon exposure to hydrogen peroxide alone and/or with silver or copper ions.

Second : the kinetics of toxicity of peroxide and silver, combined or separated on E. coli K12 (a wild type strain) and on the luminescence of recombinant E. Coli K12. The induction of stress genes by the above agents is also tested.

The results of the first part are as follows:

- The combination of peroxide and silver ions, rather than each one separately was the most effective in inactivating E. coli-B; however, silver ions were more effective than peroxide;
- A reduction of more than 5 logs in the viability of E. coli-B was achieved after 5 hour exposure to silver ions, as opposed to 24 hours exposure to peroxide in order to obtain a similar die-off;
- Silver ions were more efficient at pH-9 while peroxide was not pH dependent at the pHs tested (6.0, 7.0 and 9.0);
- Preliminary results showed that copper, when used in combination of peroxide, was most effective at 250 and 500 ppb, causing about 3 log reduction in E. coli after 2hr. exposure;
- MS2, in contrast to E. coli-B was susceptible to peroxide, where as silver ions were ineffective in killing the virus at both high and low pH;
- In general, a 3 log reduction, using 30 ppm peroxide and 30 ppb silver ions, required an exposure of 77 min for E. coli-B and 802 min for MS2.

The results of the second part are as follows:

- A concentration combination 30 ppm peroxide and 30 ppb silver exhibited a mild toxicity against E. coli K-12 (approx. 2-3 log reduction after an exposure of 60 min);
- A synergistic effect on the viability of E. coli K-12, and on the luminescence of recombinant E. coli, in which luminescence serves as a reporter for the general metabolic state of the bacteria was found;
- Using bacterial luminescence as a reporter system for stress gene expression revealed that peroxide induces a wide array of stress responses (DNA, protein damages and oxidative ones) while silver induced stresses responding to protein damages. It is possible that the combined toxic effect of these agents is related to elevated damages to cellular protein moieties.

⇒ Concluding this stage of the study it seems that the combination of peroxide and silver can serve as a secondary long acting residual disinfectant.

Morocco

⇒ Apparent removal rates are not convenient for comparison between different systems covering different areas of land and receiving different wastewater flows. A mode of expression of the results has been adopted which relates the concentration of FC removed to the area of land occupied by the treatment train and to the flow of wastewater applied per daily, a factor of specificity that takes into account the area and the daily flow.

⇒ In this way, large differences in the FC specific removal rates between the HARP and the WASP trains are observed on the basis of the chlorophyll content. An improvement of 1.5 times is recorded for the maturation and the facultative stages. We recorded respectively 4 and 1.7 times in favour of the HRAP. This FC removal improvement is correlated with the chlorophyll a content.

⇒ The same effect of the chlorophyll as those shown on FC removal are shown on nitrogen and orthophosphate removals. They show the superiority of the HRAP components over those of the WSP due to their content in chlorophyll.

⇒ On another hand, the agronomical experiments show that the most interesting result obtained on nitrogen leaching beyond the root zone is given by alfalfa. This crop is revealed as an excellent nitrogen exporter.

⇒ Under normal conditions, alfalfa is a nitrogen fixing crop. This is achieved through the nodules heard by the roots. The amount of atmospheric nitrogen fixed should be added to the amount of nitrogen applied with the successive irrigations and therefore this will push the balance toward a

positive figure indicating a nitrogen leaching beyond the root zone. Under our conditions, however, no nodules were formed on the roots. This is why our balance is negative demonstrating the powerful nitrogen uptake by alfalfa that helps in controlling nitrogen leaching beyond the root zone.

- ⇒ We do not have any explanations for the absence of the nodules on the roots at Ouarzazate. Probably this is due to an inhibition effect exerted by the nitrogen content of the large amount of mineral nitrogen occurring in the experimental soil or/and by an inhibitory effect of the saline conditions that prevail in the area of Ouarzazate.

Malta

- ⇒ The ultimate purpose of Malta's contribution to this project is to provide data on which a more ecologically sound strategy will be available for wastewater treatment and reuse. At present, the major source of chlorination DBP that may reach the marine environment in Malta is the cooling of thermal power stations using seawater. However, a five-fold increase in the production of treated wastewaters is being planned for the next five years. Such treated wastewaters that may be produced in excess of that required for reuse in agriculture and industry, will be chlorinated and probably discharged into the sea. This will then be the most significant source of chlorination DBP in the marine environment.
- ⇒ In the first stage of our investigations, the biological impact of discharge of untreated sewage through the major sewage outfall in Malta, was assessed through a number of field studies, through the use of satellite remote sensing of the area, and through field monitoring of biomarker of stress in fish collected in the same locality. Such data indicates that this biological impact is highly significant and that sewage treatment is highly desirable.
- ⇒ The efficiency of such treatment plants may however be jeopardised by pollutants (i.e. in industrial effluents) in the receiving wastewaters. This was in fact proved through a simple experimental protocol that was purposely developed. This test measures the reduction in nitrification efficiency of such plants on exposure to industrial effluents. Effluents from local tannery and metal industries may be expected to negatively affect the efficiency of such sewage treatment plants.
- ⇒ A number of laboratory based ecotoxicological tests were carried out to assess biological impact of bromoform and chloroform (major DBP in marine environment) on selected marine organisms. These included acute toxicity tests on adult marine snails; on embryo and young larval stages of a sea urchin; as well as on the behavioural and physiological responses of snails and bivalves to these DBP. All these experiments indicate that populations of certain species are at risk when exposure to the levels of chlorination DBP to be encountered in the field as a result of chlorination sources as identified above.

Spain

- ⇒ Production of olive oil inevitably leads to the creation of highly polluting effluents. The problem of this waste has become critical over the last few years in many Mediterranean countries. In this context, experiments have been carried out to reduce the chemical oxygen demand (COD) using several purification systems that may easily be applied, especially on a small scale.
- ⇒ It was decided to use a methodological approach divided into two principal phases :
- treatment with the *Aspergillus niger* (ATCC 10864) fungus;
 - subsequent biological treatment with aerobic micro-organisms from the washings of the discharge.
- ⇒ We have noted an active purifying effect on effluents, both with *Aspergillus niger* and Aerobic bacteria from washings of the discharge. COD has been reduced by 50%. However, it appears that the effect of the Aerobic bacteria on effluents already treated with *Aspergillus niger* is additive and cumulative reduction of 75% can be achieved.

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PARTNERS

COMMUNITY OF MEDITERRANEAN

UNIVERSITIES

Piazza Umberto I

70121 Bari

Italy

Lorenzo Liberti

Tel.: +39-80-556 07 86

Fax: +39-80-546 02 82

UNIVERSITY OF PORTSMOUTH

Department of Civil Engineering

Town Mount

Hampshire Terrace

Portsmouth PO1 3QL

United Kingdom

John Butler

Tel.: +44-1705-84 24 23

Fax: +44-1705-84 25 21

INSTITUT AGRONOMIQUE ET VETERINAIRE

HASSAN II

B.P. 6202

Rabat

Morocco

Bouohaib El Hamouri

Tel.: +212-7-77 81 10

Fax: +212-7-775 83 87

UNIVERSIDAD AUTONOMA DE BARCELONA

Facultad Ciencias

Unitat d'Hidrogeologia

08193 Bellaterra

Spain

Josep Trilla-Arrufat

Tel.: +34-3-581 12 59

Fax: +34-3-581 12 63

UNIVERSITY OF MALTA

Department of Biology

Marine Ecotoxicology Laboratory

MSIDA

Malta

Victor Axiak

Tel.: +356-34 24 88

HEBREW UNIVERSITY OF JERUSALEM

Department of Environmental Sciences

91904 Jerusalem

Israel

Hillel Shuval

Tel.: +972-2-58 61 61

Fax: +972-2-63 53 88

MAXIMISING MATERNAL HEALTH STRATEGIES TO REDUCE MATERNAL MORBIDITY AND MORTALITY IN THE PRIMARY HEALTH CARE SECTOR

Co-ordinator: London School of Hygiene and Tropical Medicine, London, United Kingdom
(Oona Campbell & Gillian Lewando-Hundt)

OBJECTIVES

- To consider what should be done about positive health and well-being for women;
- To determine what constitutes effective antenatal and postnatal care;
- To set policies on the appropriate place and care provider for normal delivery;
- To make the link to the first referral level to ensure adequate referral to emergency obstetric services when complications occur.

ACTIVITIES

- ◇ To develop a network of researchers with links to health providers and policy makers from Jordan, Lebanon, Egypt and the Autonomous and Occupied Palestinian Territories by organising three international meetings to explore research issues of mutual concern. These would be aimed at improving maternal health, and would explore the above four issues in relation to the primary health care sector;
- ◇ To arrange a number of one to two week exchanges within the Third Mediterranean Countries and between the European Union Countries and the Third Mediterranean Countries to develop collaborative research link;
- ◇ To prepare an Arabic, French and English newsletter on maximising maternal health for widespread dissemination.

EXPECTED OUTCOME

- ⇒ Understanding the issues related to improving maternal health is a new field of research which requires new approaches and is currently a focus of international concern;
- ⇒ The proposed network would redress the paucity of regional work in the Mediterranean area;
- ⇒ The development of a network of researchers with links to practitioners and administrators from four adjacent countries focusing on one particular area of primary health care - maternal health - will enable research links to be developed and strengthened by both the meetings and the exchange visits. The size of the network is a considerable one for a new research area, and the TMC-TMC collaboration and complementarity is a strength;
- ⇒ Innovation strategies, practice and research emerging from the network could be disseminated internationally through the newsletter and through other activities of Safe Motherhood Initiative.

FOLLOW-UP

- ▶ The MAMAH network has organised two meetings, the first in Cairo in December 1995 and the second in Amman in October 1996. Proceedings of these meetings are available on request. A third meeting is planned for the end of 1997;
- ▶ The MAMAH newsletter has published two issues that have been distributed widely in the Maghreb and Mashrak. Further issues are planned. It is published in Arabic, English and French;
- ▶ Small grants have been given to participants to undertake small research studies in the area of maternal health. Two of these were on maternal mortality and one was on anaemia. Further small grants are planned;
- ▶ Visits have taken place between the participants. At this stage they have been between Italy and London and the Autonomous Palestinian Territories and London. Visits between the participants in the region are planned;

- ▶ The network has made steps towards profiling the state of maternal health in the region and a paper is being drafted summarising this. The participants are focusing on collaborative issues for research and intervention in the region that will improve Arab maternal health.

PARTNERS

LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE

Maternal and Child Epidemiology Unit
Keppel Street
London WC1E 7HT
United Kingdom

Oona Campbell & Gillian Lewando-Hundt
Tel.: +44-171-927 20 02
Fax: +44-171-637 11 73

UNITED NATIONS RELIEF WORKS ADMINISTRATION

El Thalathini Ashkolon 781
Gaza City
West Bank and Gaza Strip

Ayoub El Alem
Tel.: +972-7-82 22 54
Fax: +972-7-82 17 65

MINISTRY OF HEALTH

Child Survival Project
Abdul Megeed Rimily Street 1
Cairo
Egypt

Mustafa Kassas - Ala Abdel Halim -
Salwa F. Makar
Tel.: +20-2-354 76 91
Fax: +20-2-356 46 49

EGYPTIAN FERTILITY CARE SOCIETY

P.O. Box 126
Giza
Egypt

Nagla Al Nahal
Tel.: +20-2-347 06 74
Fax: +20-2-346 87 42

FAMILY HEALTH GROUP

P.O. Box 1073
Marj El Hamam
Amman
Jordan

Raeda Al Qutob
Tel/Fax: +962-6-84 25 76

LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE

Department of Public Health and Policy
Keppel Street
London WC1E 7HT
United Kingdom

Gillian Lewando Hundt
Tel.: +44-171-636 86 36

AMERICAN UNIVERSITY OF BEIRUT

Faculty of Health Sciences
Beirut
Lebanon

Mary Deeb
Tel.: +961-1-34 04 60
Fax: +961-1-212 47 81 995

AMERICAN UNIVERSITY OF BEIRUT

Faculty of Medicine
Department of Obstetric/Gynecology
Beirut
Lebanon

Naji Aswad
Tel.: +961-1-43 13 10

JORDAN UNIVERSITY OF SCIENCE & TECHNOLOGY

Public Health Department
P.O. Box 3030
Irbid
Jordan

Salah Mawajdeh
Tel.: +962-2-29 51 11
Fax: +962-2-29 51 23

UNIVERSITY OF JORDAN

School of Nursing
11942 Amman
Jordan

Sawsan Majali-Mahasneh
Tel.: +962-6-84 35 55 (ext. 2)
Fax: +962-6-83 23 18

ISTITUTO PER L'INFANZI

Bureau For International Health
Via dell Istria 65
34137 Trieste
Italy

Alberta Bacci
Tel.: +39-40-37 82 36
Fax: +39-40-37 82 16

GOVERNMENT PUBLIC HEALTH SERVICES

Public Health Division

Ain Musbah

Ramallah

Westbank and Gaza Strip

Nadim Aladili

Tel.: +972-2-958 33 94

AL NADA CENTRE FOR WOMEN'S HEALTH AND NUTRITION

Ramallah

Westbank and Gaza Strip

Salwa A-Najjar-Khateeb

Tel.: +972-2-995 75 20 / 998 74 82

RIMAL CLINIC

Gaza City

West Bank and Gaza Strip

Yehia Abed

Tel.: +972-7-86 98 20

Fax: +972-7-85 63 39

DAMASCUS UNIVERSITY

Faculty of Medicine

Department Community Medicine

P.O. Box 9241

Damascus

Syria

Hyam Bashour

Tel.: +963-11-661 83 28

Fax: +963-11-442 23 74

MINISTRY OF HEALTH

Palestinian National Authority

Gaza Health Services Research Centre

Rimal Clinic

Gaza City

West Bank and Gaza Strip

Dina Abu Shaaban

Tel/Fax: +972-7-86 98 20

EVALUATION & IMPROVEMENT OF MATERNAL AND CHILD PREVENTIVE RESOURCES & SERVICES OF THE PALESTINIANS IN GAZA (PALESTINIAN AUTONOMOUS TERRITORIES) AND OF THE BEDOUIN ARABS IN THE NEGEV (ISRAEL)

Co-ordinator: London School of Hygiene and Tropical Medicine, London, United Kingdom
(Gillian Lewando-Hundt)

OBJECTIVES

- To identify models of care of existing maternal and child health (MCH) services and their impact on health outcomes & behaviour in two populations in the Mediterranean area and evaluate their relative effectiveness;
- To explore the influence of household and community resources on maternal and child health in these areas;
- To develop and promote strategies to increase the utilisation, accessibility and quality of MCH services;
- To combine the methods and knowledge of anthropology and epidemiology in order to develop an interdisciplinary framework for the valuation of MCH services & delivery in order to promote innovative multisectorial health reform.

ACTIVITIES

- ◇ An evaluation of the MCH services and resources, lay and professional, amongst the Bedouin Arabs in the Negev (Israel), and amongst Palestinian in Gaza will be carried out. Use of services providing antenatal, natal and postnatal care were taken into account up to six months after delivery with the application of cohort sampling and interviewing methods. The existing structures of the related health services were also monitored and some types of records were reviewed;
- ◇ Interventions in the MCH services & care within the clinics and the communities *have been* designed and *are being carried out during 1998-9. These ranges from changing internal drug distribution within clinics, to developing school based health promotion and advocacy. Process and Outcome evaluation criteria will be used in both settings;*
- ◇ The fostering of dissemination and cooperation between European, Israeli & Palestinian researchers, clinicians, policy makers & health personnel within the context of a changing political environment through workshops, seminars and visits during the course of the study will be another essential activity of this project. *Members of the teams have met with each other and attended meetings in the UK and Jordan.*

EXPECTED RESULTS

Scientific Results leading to improved service provision:

- ⇒ The main findings have been summarised in reports, which have been disseminated in both local settings at workshops. There has been lively discussion of these findings and model interventions have been developed through these meetings. The interventions are ongoing and will be evaluated during 1999.

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PARTNERS

LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE

Health Promotion Sciences Unit
Department of Public Health and Policy
Keppel Street
London WC1 7HT
United Kingdom

Gillian Lewando-Hundt
Tel.: +44-171-636 86 36
Fax: +44-171-637 32 38

BEN GURION UNIVERSITY OF THE NEGEV

Faculty of Health Sciences
P.O. Box 653
84105 Beer-Sheva
Israel

Ilana Belmaker
Tel.: +972-7-646 11 11/628 09 49
Fax: +972-7-623 14 63

MINISTRY OF HEALTH

Rimal Clinic
Gaza City
P.O. Box 5
Gaza City
West Bank and Gaza Strip

Yehiah Abed
Tel/Fax: +972-7-86 98 20
E-mail: 100274.3716@compuserve.com

**PRISE EN CHARGE DE PROBLEMES DE SANTE CHRONIQUES ET LEUR
IMPLICATION DANS L'ORGANISATION DES SOINS DE SANTE**

Coordinateur: Prins Leopold Instituut voor Tropische Geneeskunde, Antwerpen, Belgium
(Wim Van Lerberghe)

OBJECTIFS

La recherche vise à étudier par quelles interventions et sous quelles conditions la prise en charge de malades chroniques peut être améliorée par les services de santé de base en Turquie et au Liban. Il s'agira :

- D'identifier et d'analyser les obstacles actuels à une prise en charge globale des malades chroniques par les services de santé de base;
- De tester des hypothèses de recherche formulées sous forme de stratégies de changement (stratégies techniques, méthodologiques, organisationnelles et relationnelles) destinées à améliorer cette prise en charge;
- D'analyser les effets induits par ces interventions sur le comportement des acteurs, sur le système de soins et finalement sur la prise en charge des malades chroniques;
- De formuler des recommandations de généralisation de ces changements pour la Turquie et le Liban;
- D'étudier en parallèle l'applicabilité de ces changements;
- De renforcer les capacités de recherche des instituts impliqués.

Méthodologie

Les hypothèses de changement identifiées à ce stade concernent :

- La rationalisation des décisions de diagnostic, de traitement et de suivi des malades chroniques;
- L'introduction de soins à domicile en complément aux soins de services de santé de base;
- L'amélioration du dossier médical individuel;
- L'intensification du dialogue avec la population;
- L'amélioration du travail d'équipe au niveau du service de santé de base.

Ces hypothèses seront testées au niveau des trois centres de santé urbains. Ceci implique :

- L'élaboration d'outils de prise en charge techniquement pertinents;
- La prise en compte des "résistances au changement" auxquelles on peut s'attendre de la part du personnel des centres de santé et éventuellement de la population.
- La méthodologie de recherche-action associera étroitement au processus de recherche des agents de santé (on les qualifiera de "chercheurs opérationnels", pour les distinguer des chercheurs extérieurs sans responsabilités opérationnelles au niveau des services de santé). Leur implication est essentielle pour parvenir à mieux comprendre les enjeux du changement tels qu'ils sont perçus par le personnel des centres de santé, pour formuler des modalités de mise en oeuvre du changement qui soient à priori acceptables, et pour observer de l'intérieur les effets induits par les interventions.
- Le monitoring permanent des résultats devrait permettre d'affiner les hypothèses et de réorienter les interventions si nécessaire. Il sera basé sur des informations provenant :
 - du système d'information sanitaire;
 - de l'observation participante des activités des services de santé de base;
 - d'enquêtes et études particulières lorsque, ni le système d'information, ni l'observation participante ne seront en mesure de fournir les informations nécessaires.

ACTIVITES

Phase préparatoire

- ◇ Séminaire entre chercheurs : discussion globale des stratégies à introduire;
- ◇ Description analytique de la situation de départ;

- ◇ Elaboration d'outils techniques pour la prise en charge (instructions, échéanciers, fiches opérationnelles, etc.);
- ◇ Constitution de l'équipe de recherche (chercheurs opérationnels et extérieurs);
- ◇ Stages du personnel des centres de santé

Phase active

- Formulation des hypothèses concrètes de changement;
- Création de conditions favorables au changement;
- Mise en place des outils nécessaires au recueil des données;
- Mise en oeuvre progressive des stratégies de changement (en d'autres termes : test des hypothèses);
- Identification des conditions spécifiques d'introduction du changement (notamment à partir de la comparaison entre terrains turques et libanais) comme facteurs importants pour l'analyse de reproductibilité;
- Monitoring des effets des interventions, réorientation si pertinent;
- Réunions bisannuelles du comité du suivi;
- Formations complémentaires (stages du personnel des centres de santé, formation de médecins en santé publique).

Phase finale

- Evaluation finale des effets produits par la recherche-action;
- Création des conditions de maintien des acquis;
- Définition des conditions de reproductibilité;
- Séminaire de synthèse;
- Diffusion des résultats.

PARTENAIRES

PRINS LEOPOLD INSTITUUT VOOR TROPISCHE GENEESKUNDE

Department of Public Health
Nationalestraat 155
2000 Antwerpen
Belgium

Wim Van Lerberghe
Tel.: +32-3-247 62 86
Fax: +32-3-247 62 58

AMERICAN UNIVERSITY OF BEIRUT

Faculty of Medicine
Department of Family Medicine
P.O. Box 113-6044
Beirut
Lebanon

Mustafa Khogali
Fax: +961-1-21 24 44 58 17

RUPRECHT-KARLS-UNIVERSITÄT HEIDELBERG

Department of Tropical Hygiene and Public Health
Im Neuenheimer Feld 324
69120 Heidelberg
Germany

Oliver Razum
Tel.: +49-6221-56 25 78
Fax: +49-6221-56 49 18

HACETEPPE UNIVERSITY

Department of Public Health
Ankara
Turkey

M. Bertan
Tel.: +90-312-324 39 75
Fax: +90-312-311 00 72

TÜRKISCH-DEUTSCHE GESUNDHEITSSTIFTUNG E.V.

türk-alman saglik vakfi
Bundeszentrale
Friedrichstraße 13
6300 Gießen
Germany

Y. Bilgin
Tel.: +49-641-775 11 / 755 66
Fax: +49-641-756 53

SPATIAL, MEDICAL, EPIDEMIOLOGICAL, ECONOMICAL AND SOCIO-CULTURAL KEY FACTORS AND TREATMENT OF CHRONICAL HEALTH PROBLEMS IN MAGHREB CITIES

Co-ordinator: ORSTOM, Paris, France (Bernard Hours)

OBJECTIVES

- To identify specific key urban factors affecting health, within their environmental, epidemiological and social context with the aim of improving the design of operational strategies for the management of sexually transmitted diseases (STDs) and other chronic diseases within the existing health system.

ACTIVITIES

Multidisciplinary research will be done in two cities: Tlemcem (Algeria) and Safi (Morocco)

- ◇ Geographical epidemiology will map zones and risk populations with the aim of identifying risks' factors in relation to the available health care systems and other spatial and social structures. The relation between environmental factors and health are to be identified against the background of the existing health care system;
- ◇ Action research (epidemiological and public health approach) will be aimed at optimising the capacity of the health care structures to cope with chronic diseases through the testing of certain science based approaches in a real-life setting;
- ◇ Qualitative anthropological surveys of the socio-cultural status of disease and the specifically mobilised family resources and therapeutic strategies will be completed.

EXPECTED OUTCOME

- ⇒ From the mapping exercise, multilayer maps will be prepared describing in detail the health care systems of the Tlemcem and Safi;
- ⇒ The action research will provide an insight into the applicability of certain novel health care models under the conditions found in the two cities;
- ⇒ The anthropological surveys will provide insights into population's decision making processes and hence will improve the understanding of the reasons for success or failure of certain health care strategies.

PARTNERS

**INSTITUT FRANÇAIS DE RECHERCHE
SCIENTIFIQUE POUR LE DÉVELOPPEMENT EN
COOPÉRATION - ORSTOM**

Département Santé
Rue Lafayette 213
75480 Paris

France

Bernard Hours
Tel.: +33-1-48 03 77 09
Fax: +33-1-42 09 32 75

**PRINS LEOPOLD INSTITUUT VOOR TROPISCHE
GENEESKUNDE**

Unité de Recherche & Enseignement en Santé Publique
Nationalestraat 155
2000 Antwerpen

Belgium

Guy Kegels
Tel.: +32-3-247 62 91
Fax: +32-3-247 62 57

**INSTITUT NATIONAL D'ADMINISTRATION
SANITAIRE**

College Santé
Route de Casablanca Km 15
Rabat

Morocco

Mohammed Zayyoun
Tel.: +212-7-29 98 34
Fax: +212-7-69 16 26

UNIVERSITÉ DE TLEMCEEN

Institut de Biologie
Domaine Universitaire
Tlemcen

Algeria

Dalila Zerhouni
Tel.: +213-7-20 77 01

EFFET DE L'INGESTION DES PRODUITS LAITIERS FERMENTÉS SUR LA CAPACITÉ IMMUNITAIRE DES SUJETS BIEN NOURRIS ET MALNOURRIS

Co-ordinator: Instituto de Nutrición y Bromatología, Madrid, Spain (Ascención Marcos)

OBJECTIVES

- Comparative effects of yoghurt (enriched with non-pathogenic lactic bacterial) and milk consumption on immunocompetence in a healthy population;
- Comparative effects of yoghurt (enriched with non-pathogenic lactic bacteria) and milk consumption on immunocompetence and on nutritional recovery on two malnourished groups:
 - young patients (12-18 years old) suffering from anorexia nervosa (eating disorder increasingly seen in developed countries);
 - malnourished African children (4-24 months).
- According to STD programme, within general objectives, we tried to establish the role played by fermented dairy products on immune capacity and thereby on nutritional status and recovery.

ACTIVITIES

- ◇ One of the causes of the increased susceptibility to infectious disease of malnourished individuals is an impaired immune function. In addition, immunocompetence has been shown to be depleted by infection and to be a sensitive and functional measure of the nutritional status. This work was aimed at assessing the effect of yoghurt (enriched with non-pathogenic lactic bacteria) consumption on immune capacity and thereby on nutritional status and recovery in three groups:
 - control, consisting of 50 healthy subjects (12-18 years old);
 - twenty patients (12-18 years old) suffering from anorexia nervosa (eating disorder increasingly in developed countries);
 - twenty malnourished African children (4-24 months).
- ◇ Each group was divided into two subgroups:
 - 300 ml/day yoghurt consumption during 2 months;
 - 300 ml/day milk consumption during 2 months.
- ◇ Dietary intake and anthropometric parameters (weight, height, body mass index, ideal body weight percentage, skin folds) were measured. The following immunological parameters: lymphocyte proliferation, B lymphocytes (CD19), T lymphocyte subsets (CD2, CD3, CD4, CD8), NK lymphocytes (CD57), serum C3 and C4 complement factors and interferon production were evaluated.

RESULTS

Spain

- ⇒ Thirty patients with anorexia nervosa (aged 10-19- were tested) in a 10 weeks follow-up study. The patients were divided in two groups depending on their dairy intake of (1) milk or (2) yoghurt (3/day). Calories supplied by milk or yoghurt were similar. The rest of the dietary calories supplied was similar in both groups. Measurements were carried out in three stages:
 - at the admission to the hospital;
 - after six weeks;
 - after ten weeks of the admission.
- ⇒ The results were compared with 35 young women's volunteers matched by age, sex and socio-cultural level, who were also divided in two groups like the anorexic patients.
- ⇒ Regarding food habits of the patients tested, 13% and 19% of patients in groups 1 and 2, respectively suffered from vomiting.
- ⇒ None of the patients had menstruation at the beginning of the study. 25% and 17% of patients receiving yoghurt or milk therapy, respectively recovered menstruation at the end of the study. Diarrhea symptoms after refeeding decreased in the group with yoghurt therapy.

- ⇒ The dietary profile for both groups of patients was similar and showed a significant higher percentage of carbohydrates and lower percentage of lipids in comparison with both groups of controls.
- ⇒ In relation to anthropometry, as expected, no modifications were found between both groups of anorexic patients in each stage. However, in both groups of patients, there was a significant increase of weight, BMI and IBW percentage in stage 2, which remained at the same level in stage 3, in comparison with stage 1. Despite the fact that there was an increase of ponderal values in anorexia nervosa patients, all the parameters were lower than in controls. BMI values did not reach 19, the lowest level necessary to be within the normal range.
- ⇒ Haematological parameters of anorexia nervosa patients were within the normal range in both groups, however, all of them showed values below controls. In relation to leukocyte profile, those patients submitted to the yoghurt therapy showed higher eosinophil levels at stage 2, while eosinophil counting was higher in patients undergoing milk intake at stage 3. Regarding lymphocyte subset percentages, significant differences were found in stages 2 and 3, in comparison with stage 1. In general, there was a better situation for those patients under yoghurt therapy. Serum immunoglobulins (Ig G, A and M) and C3 and C4 complement factors were significantly higher in those patients with yoghurt therapy.

France

- ⇒ Yoghurt intake on stimulation of immune response was investigated on Peyer patches, spleen and blood. Interferon- γ , lymphocyte proliferation and the rate of different immunocompetent cells were evaluated.
- ⇒ The study was carried out in Wistar-Furth female rats aged 8 weeks that were submitted to a semi-synthetic diet enriched with yoghurt or milk (35%) for 4 weeks. Immunocompetent cells, previously removed, were cultured in presence of Con A or yoghurt bacteria (*Lactobacillus bulgaricus* and *Streptococcus thermophilus*). Interferon- γ was measured in the supernatants by ELISA and the immunocompetent cells were determined by flow cytometry.
- ⇒ Yoghurt bacteria were capable to stimulate Interferon- γ both in Peyer patches and spleen, and in addition induced cell proliferation in Peyer patches, spleen and blood. However, no modifications were found in immunocompetent cell rates, except B lymphocytes of Peyer patches, which increased after yoghurt intake.
- ⇒ Regular consumption of lactic bacteria induced an increase in non-specific responses against mitoges (ConA), which could suggest an important role of non-pathogen bacteria by improving immunological balance as well as by maintaining host-resistance against pathogen agents. This finding may be significant especially in malnutrition or anorexia nervosa patients where the immune system is depressed.

Morocco

- ⇒ In order to evaluate the effect of nutritional refeeding on Interferon- γ production in malnourished children, 15 infants aged among 6 and 30 months with a weight/height between 60 and 80% (NCHS tables) were admitted to the Paediatric Hospital in Rabat (PO) until they reached 90% of their weight/height ratio (P1). Hospitalisation period average was 30 days. During this period, children received fermented milk diet with a caloric density of 100 cal/100 ml in addition to a vitamin and mineral supplementation. The consumption was 100 cal/kg/d for 10 days and 150-200 cal/kg/d there after.
- ⇒ In addition, an iron supplementation (100 mg/d) was included in the diet after the 10th day of hospitalisation.
- ⇒ Blood mononuclear cells were isolated and cultured with lactic bacteria *Lactobacillus bulgaricus* and *Streptococcus thermophilus* for 72 hours. The cell-free supernatants from cultures were assayed for Interferon- γ by ELISA. The samples were collected in PO and P1.
- ⇒ Although iron supplementation was administrated to the children, their haemoglobin values, which were lower than 11 g/dL in PO, only reached normal levels 3 months after the admission in hospital. Interferon- γ production in malnourished children was lower than 10 pg/mL in PO. After refeeding (P1) Interferon- γ production was higher than 150 pg/mL.
- ⇒ Conclusion: the low haemoglobin values found in the malnourished children did not affect Interferon- γ production after refeeding. Children showed a good tolerance when yoghurt was included in the diet. Yoghurt intake enhanced Interferon- γ production. Thus, it would be

important to stress the fact that this cytokine production may act as an immunological protection against pathogen micro-organisms in infants who are particularly sensitive to infections since they are malnourished.

PARTNERS

UNIVERSIDAD AUTONOMA DE MADRID

Fac. Farmacia
Instituto de Nutricion y Bromatologia
Ciudad Universitaria
28040 Madrid
Spain

A. Marcos
Tel.: +34/1/394.18.10
Fax: +34/1/394.18.29

INSTITUT AGRONOMIQUE ET VÉTÉRINAIRE HASSAN II

Dépt. de Nutrition Humaine
B.P. 6202 Rabat-Instituts
Rabat
Morocco

A. Lemtouni
Tel.: +212/777.09.35/7078
Fax: +212/777.81.10/5838

INSERM-GERM

Faculté de Médecine Xavier Bichat
Rue Henry Huchard 16
75018 Paris
France

D. Lemonnier
Tel.: +33/1/44.85.61.67
Fax: +33/1/44.85.61.67

**AN APPLIED INTERDISCIPLINARY RESEARCH PROJECT TO INVESTIGATE
THE UTILISATION AND PERCEPTION OF HEALTH CARE SYSTEMS BY
INFANTS AND THEIR FAMILIES**

Co-ordinator: Centre International de l'Enfance, Paris, France (Anne Tursz)

OBJECTIVES

This research carried out in four developing countries (Algeria, Morocco, Congo, Togo) by multidisciplinary teams combining the fields of epidemiology, anthropology or sociology, and economics, had the following objectives :

- To analyse the utilisation of diverse components of the health system by children under five.
- To analyse the users' and health professionals' views of illness and health care.
- To strengthen the capacity of researchers to conduct multi-disciplinary research projects in the field of child-health;
- Using the results from the above analysis, to promote sustainable and appropriate action and improve child care.

ACTIVITIES

Data from a descriptive first phase had been gathered in the four countries during the STD2 programme. This phase included an epidemiological study of the use of the different types of health facilities caring for children, and an anthropological study in families both using and not using these facilities, as well as among health personnel (physicians and allied health personnel in the public sector, private physicians and nurses, and tradipractitioners). The research began later in the Congo than in the other countries. It was carried out with considerable difficulty because of serious social and political problems in three of the countries beginning in late 1992 (Algeria, Congo, Togo). The work in this project was as follows :

- ◇ The completion of data collection of the first phase for the Congo;
- ◇ The continuation of analysis of epidemiological data and anthropological information collected during the first phase;
- ◇ The development of specific research projects on topics identified during the first phase of the research (the utilisation of medicinal drugs by children in Togo, emergencies, therapeutic interventions, and behaviour of health personnel in Morocco);
- ◇ The development of training activities and applied research;
- ◇ The organisation of meetings on research progress.

Teaching activities have been carried out primarily in Algeria, and have consisted of the development of innovative teaching methods using results from the anthropological study (the contents of interviews with families on health seeking behaviour for sick children). These activities have targeted health professionals in initial training programmes (nurses) or in the context of continuing education (interns and residents in hospital departments). In Morocco, activities were carried out at the level of health centres and "diagnostic centres" with the objective of improving the rate of utilisation of curative facilities and of reducing the percentage of "unjustified" emergencies and self-referrals.

RESULTS

- ⇒ In all the countries, results converged and demonstrated the association between problems of health seeking behaviour encountered by families on the one hand, and problems of the functioning of health services on the other. At the family level, one is particularly struck by the length of the delay between first symptoms and consultation, and by the high frequency of self-medication at home. Recourse to traditional practitioners appears to be of modest importance. It appears that, more than there being a problem of incorrect use of health services by patients, there is a problem of delayed recourse to these services. Patients often arrive at hospitals late, after complex therapeutic itineraries, with the consultation taking place under emergency conditions and with sometimes high mortality among hospitalised children. However, families have a good

understanding of how the health system functions. Rather, it appears families are discouraged by the considerable problems posed by social relations and communication with health care personnel. A teaching programme such as the one developed in Algeria thus appears justified since it would allow professionals to understand the complexity of health seeking behaviour and their own role in problems of health system functioning. In Morocco, a relative failure of activities undertaken by the Moroccan team was attributed primarily to the lack of sociological input on the role of families and on interaction between them and health care personnel.

- ⇒ A final seminar brought together all of the participants in March of 1996. Future collaboration is planned: an extension of training activities in the Congo and in Togo; development of a project on the use of drugs in Congo and Togo; activities at the level of health care centres in all the countries, with integration of results of this research into existing programmes, as is already the case with the National Plan for Health Development in Congo.
- ⇒ The complete results of the research programme will be published as a special issue of the "Revue d'Epidémiologie et de Santé Publique", which will appear in early 1997.

PARTNERS

CENTRE INTERNATIONAL DE L'ENFANCE

Château de Longchamp
Bois de Boulogne
75016 Paris

France

Anne Tursz
Tel.: +33-1-45 20 79 92
Fax: +33-1-45 25 73 67

PRINS LEOPOLD INSTITUUT VOOR TROPISCHE GENEESKUNDE

Public Health Research and Training Unit
Nationalestraat 155
2000 Antwerpen

Belgium

Bruno Dujardin
Tel.: +32-3-247 62 86
Fax: +32-3-216 14 34

MINISTERE DE LA SANTE

Service de Pédiatrie
CHU Alger-Est
35165 Ain-Taya, Wilaya de Bourmedes

Algeria

Jean-Paul Grangaud
Tel.: +213-2-76 81 61
Fax: +213-2-86 81 24

INSTITUT NATIONAL D'ADMINISTRATION SANITAIRE

Km 5, Route de Casablanca
Rabat

Morocco

Radouane Belouali
Tel.: +212-7-79 16 26
Fax: +212-7-79 10 82

UNIVERSITE NATIONALE DU BENIN

Faculté de Médecine
Service de Pédiatrie
B.P. 12971

Lomé

Togo

Kossi Assimadi
Tel.: +228-21 17 21
Fax: +228-21 03 43

MINISTERE DE LA SANTE

Direction de la Santé Maternelle et Infantile
B.P. 13217
Brazzaville

Congo

Samuel Nzingoula
Tel.: +242-83 55 53
Fax: +242-83 62 44

**IDENTIFICATION DES CONDITIONS D'AMELIORATION DE LA
REFERENCE/CONTRE-REFERENCE DANS LES DISTRICTS DE SANTE**

Coordinateur: Institut National d'Administration Sanitaire, Rabat, Morocco
(Ahmed Laabid)

OBJECTIFS

- Tester l'impact de l'introduction d'outils techniques reconnus (partogramme, fiche de référence/contre référence, etc.):
- l'émergence d'un réel dialogue entre les professionnels de santé des deux échelons de district;
 - la qualité de la prise en charge des patients.

ACTIVITES

Maroc

- ◇ Etude du système de référence et contre-référence (RCR) entre les centres de santé et les hôpitaux de référence (provinces de Sefrou et de Khémisset);
- ◇ Mesures d'accompagnement : formation du personnel, révision du système d'information, renforcement des activités de supervision, dialogue direct entre les médecins des deux niveaux du district;
- ◇ Etude du comportement des professionnels et de la population vis-à-vis de la référence/contre-référence.

Congo

- ◇ Etude du système de référence entre les centres de santé intégrés et les services de référence (districts de Makelekele et Dolisie);
- ◇ Mesures d'accompagnement : motivation du personnel et de la population utilisatrice, exonération des droits de consultations et d'examen paracliniques aux patients référés, formation du personnel, ébauche d'algorithme, etc.

Tchad

- ◇ Etude du système de référence et contre-référence dans le district de Bousso entre les infirmiers et les médecins;
- ◇ Mesures d'accompagnement : introduction de stratégies curatives au premier échelon, introduction de grilles de suivi des indicateurs, formation du personnel, réunions d'équipes, suivi des cas référés, etc.

Suisse

- ◇ Etude auprès des praticiens sur les problèmes de communication avec l'hôpital (Canton de Jura);
- ◇ Etude auprès des cliniques de 2 hôpitaux (Delémont et Porrentruy) sur les perceptions des problèmes de communication avec les praticiens;
- ◇ Etude du cheminement des malades hospitalisés en médecine interne (Delémont) du processus de décision ayant conduit à l'hospitalisation et de la communication médecin/malade;
- ◇ Analyse des lettres de référence et contre-référence.

RESULTATS

Congo

Malgré les difficultés rencontrées dans la mise en oeuvre de la recherche (troubles socio-politiques), les résultats enregistrés sont encourageants :

- ⇒ Le système de santé est mieux connu par le personnel et les utilisateurs.
- ⇒ Les références sont de plus en plus acceptées grâce à l'effort d'explications, les contres-références s'installent progressivement, la qualité de l'accueil et la tenue des supports d'informations s'améliorent de manière significative.
- ⇒ Les faux positifs et les faux négatifs qui caractérisent la consultation curative dans les centres de santé tendent à regresser avec notamment l'introduction d'outils de gestion appropriés.

- ⇒ L'enthousiasme pour la recherche s'est entretenu et étendu à d'autres structures sanitaires.
- ⇒ L'école de santé publique dispense un module sur le système de référence et contre-référence.

Maroc

- ⇒ Dans les deux districts sites du projet, le système de référence et contre-référence a démontré sa pertinence et son efficacité comme stratégie de dynamisation du travail de gestion de l'équipe de district. C'est ainsi que l'objectif d'émergence d'un dialogue entre médecins des centres de santé et ceux de l'hôpital de référence a été relativement atteint. On assiste dès lors à une série de réactions en chaîne articulées autour de la problématique de RCR et touchant l'ensemble des aspects qui préoccupent les gestionnaires : organisation des soins, système d'information, gestion des ressources humaines, gestion de la technologie, formation continue, recherche, etc.
- ⇒ Parmi les dysfonctionnements identifiés à l'aide de cette nouvelle approche, bon nombre ont pu être résolus tels que :
 - la charge de travail du médecin généraliste a été allégée grâce à une délégation des tâches au personnel infirmier;
 - la faible compliance des malades référés a été améliorée grâce à l'établissement de critères de référence pertinents;
 - l'inadaptation du système d'information existant en matière de gestion des soins curatifs a été corrigée grâce à l'introduction d'un nouveau système adapté aux besoins locaux;
 - l'absence d'implication des médecins hospitaliers dans la supervision des centres de santé a été en partie dépassée.
- ⇒ En définitive, l'apport du projet constitue un acquis majeur pour les deux équipes ayant participé à la recherche dans la mesure où elles sont imprégnées d'une logique de santé publique et dotées d'outils de gestion pertinents et efficaces. A l'échelle nationale, le système d'information pour la gestion des soins curatifs testé dans le cadre de ce projet est maintenant généralisé à l'ensemble du pays.

Tchad

- ⇒ L'opérationnalisation de la recherche a connu d'énormes difficultés : absentéisme fréquent du personnel, par ailleurs non payé, impossibilité de déplacements des superviseurs et de la population pour diverses raisons (absence de sécurité, pluies), instabilité de l'équipe de recherche, etc.
- ⇒ La recherche menée au Tchad a montré les limites du processus de références et contre-références à cause de plusieurs facteurs :
 - insuffisance des ressources techniques, de médicaments et de personnel qualifié;
 - existences de barrières naturelles difficiles à contourner telles que les grandes distances entre le niveau de soin qui réfère et celui qui reçoit la référence;
 - représentation négative que se fait la population des centres de santé.
- ⇒ Ces faits ont été illustrés à travers les résultats obtenus qui montrent un plus grand succès des références émises pour des services à proximité, un rayonnement limité à cinquante kilomètres pour les césariennes d'une maternité. Cette recherche a également mis en évidence la tendance croissante des références non justifiées établies par les infirmiers travaillant à proximité des médecins.

Suisse

- ⇒ Bien que le système de référence et contre-référence est bien établi et semble être assez fonctionnel dans le Canton Jura, il y a d'importants problèmes de communication entre les différents partenaires impliqués.
- ⇒ L'étude a montré une perte d'informations au cours du chemin thérapeutique. Pour le patient, cela doit être une expérience plutôt troublante car, comme il a été démontré lors des interviews, le malade n'a pas toujours compris pour quelle raison on lui répétait les mêmes questions et pourquoi des examens ont été refaits alors qu'ils venaient assez souvent d'être effectués quelques heures auparavant. A la longue, cela pourrait entraîner une perte de confiance des médecins qui sont déjà de plus en plus mis en question.
- ⇒ La perte économique est difficile à chiffrer mais, avec des estimations plutôt conservatrices, on peut calculer que seul dans l'hôpital de Delémont et dans le service de médecine interne, un montant d'environ 150.000 Francs Suisses pourrait être économisé chaque année grâce aux 1400 admissions annuelles. Ce calcul se base uniquement sur des examens de laboratoire ou d'autres

examens techniques qu'il faut répéter en raison de la non disponibilité des données du praticien. L'expertise fondamentale du médecin n'est ainsi guère valorisée et indique un non respect de la valeur du savoir du patient. L'expérience de la relation du praticien avec son patient n'est pas pleinement exploitée. Cela concerne particulièrement les informations psycho-sociales qui, dans tous les cas, ne sont pas très sollicitées par les cliniciens. Les praticiens n'y voient pas non plus une information importante à fournir, en considérant l'hôpital plutôt comme une institution technique qui n'intervient pas à ce niveau.

- ⇒ Bien que l'étude ait seulement touché le problème de communication entre médecin et patient, des lacunes importantes ont été démontrées. Le malade n'est assez souvent informé ni sur le diagnostic ni sur le traitement à suivre. Cela semble être plutôt un problème de l'hôpital car, au moins dans la perception des cliniciens, cela n'est pas le cas pour le patient qui vient d'être référé. Par contre, les praticiens se rendent bien compte de ces problèmes de communication à l'intérieur de l'hôpital.
- ⇒ Jusque là, la lettre de contre-référence n'est pas encore un outil d'échange. Evidemment, informer le praticien du séjour à l'hôpital n'est pas une priorité pour les cliniciens. Elle est révélatrice que la vitesse de la réponse ne présente pas une préoccupation pour eux.
- ⇒ Entre les médecins praticiens et les médecins cliniciens, le grand potentiel d'amélioration se trouve dans un premier temps au niveau de l'hôpital.

PARTENAIRES

INSTITUT NATIONAL D'ADMINISTRATION

SANITAIRE

Collège de Santé
Route de Casablanca km 4,5

Rabat

Morocco

Ahmed Laabid

Tel/Fax: +212-7-69 16 26

PRINS LEOPOLD INSTITUUT VOOR TROPISCHE

GENEESKUNDE

Departement Volksgezondheid

Nationalestraat 155

2000 Antwerpen

Belgium

B. Dujardin

Tel.: +32-3-247 62 88

Fax: +32-3-247 62 58

INSTITUT SUPERIEUR DES SCIENCES DE LA

SANTE

Soins de Santé Primaires

BP 2672

Brazzaville

Congo

Dr. Ambendet

Tel.: +242-81 31 32

Fax: +242-83 01 07

GTZ

Division Health-Population-Nutrition

Postfach 5180

65726 Eschborn

Germany

H. Görgen

Tel.: +49-6196-79 12 15

Fax: +49-6196-79 71 04

PROJET SOINS DE SANTE PRIMAIRE-REGION

NIARI

B.P. 1154

Brazzaville

Congo

Dr. Bakala

Tel.: +242-83 74 77

Fax: +242-83 01 07

MINISTERE DE LA SANTE

Programme de Santé de l'Institut Tropical Suisse

B.P. 972

N°Djaména

Tchad

G. Reoulengar

Tel/Fax: +235-51 30 60

INSTITUT TROPICAL SUISSE

Département de Santé Publique et Epidémiologie

Socinstrasse 57

4002 Bâle

Switzerland

N. Lorenz

Tel.: +41-2-84 81 11

Fax: +41-2-71 79 51

**HEALTH AND THE CURRENT ECONOMIC CRISIS IN BRAZIL: THE IMPACT ON
THE HEALTH AND CARE OF MOTHERS AND CHILDREN**

Co-ordinator: Escuela Andaluza de Salud Publica, Granada, Spain
(Maria del Mar Garcia Calvente)

OBJECTIVES

- To describe and document the political, economic and health policy changes in Pelotas, Brazil in the past decade;
- To document levels and trends in maternal and child health status and health care provision and utilisation between 1982 - 1992;
- To make policy recommendations based on the research conclusions.

ACTIVITIES

Phase 1 included three studies :

- ◇ A study of changes in health policies and health care provision with emphasis on maternal and child care. This study provided data on recent trends in these areas to document historical changes in the city;
- ◇ Anthropological studies based on interviews with members of different groups involved in health care. The aim here was to investigate the perception of the population and of the health providers regarding changes in health services;
- ◇ A study on socio-economic trends intended to document political and economical changes that took place during the decade and how these have affected the quality of life.

This Phase 1 studies will result in a detailed description of changes in health sector and the perception of the population and providers relative to these changes.

Phase 2 of the study involved six separate studies focusing on maternal and child health indicators. The studies in this phase included :

- ◇ A perinatal study in three maternity hospitals during twelve months;
- ◇ A descriptive infant mortality and nested infant mortality case-control study to identify all deaths among cohort children and ascertain cause and compare their characteristics with those of control children from the same birth cohort;
- ◇ A hospital morbidity study to provide data on the causes of all hospital admissions;
- ◇ A follow-up study to trace a 20 per-cent sub-sample of approximately 2000 children at 6-12 months of age and 400 pre-term and/or low birth-weight children;
- ◇ Finally, a maternal study on health, fertility and family planning utilisation to provide data on past reproductive history.

The data from these studies are compared to data collected to assess changes during the decade that will be analysed in the light of the overall scenario of economic and health sector changes.

RESULTS

- ⇒ There was a reduction in the number of births in this period, 6,011 in 1982 and 5,04 in 1993, suggesting an increased utilisation of contraceptives or abortions since there was an increase in the number of women in fertile age. A breakdown by socio-economic status shows that the reduction of 707 births in 1993 was not evenly distributed as there were around 1,000 births less in the poorest groups and 300 more in the high-income strata.
- ⇒ There were also important variations in the nutritional status of the mother, in the decade the mean height increased from 156.4 cm in 1982 to 159.9 cm in 1993, and weight in the beginning of pregnancy was also substantially higher in 1993, 62,1 Kg compared to 58 Kg in 1982. Antenatal care attendances also increased in 1993, with a mean of 7.6 attendances compared to 6.6 in 1982 and medical assistance during delivery increased from 61 per cent in 1982 to 88.3 per cent in 1993. Despite these improvements the proportion of low birthweight (<2,500 g) showed a slight increase in the proportion of pre-term births (5,6 and 7,5 per cent, respectively) and intra-uterine

growth retardation (15,0 per cent in 1982 and 17,5 per cent in 1993) The reason for these unexpected findings are still being analysed.

- ⇒ There was an important reduction in the perinatal mortality, from 32.2/1000 births in 1982 to 22.1/1000 births in 1993, and the reduction of perinatal deaths was equally observed both in the fetal and in the early neonatal period. Regarding breastfeeding, there was an increase in the proportion of babies being breastfed in the first months of life. At three months of age, for example, the prevalence of full breastfeeding was 53 per cent in 1993 in relation to around 33 per cent in the previous decade. As far as the nutritional status at 12 months of age is concerned, there were changes according to the indicator. Thus, there was a slight increase in the proportion of children with low height for age, 6.1 per cent compared to 5.3 per cent in 1982. On the other hand, a reduction was observed in the prevalence of low weight for age, 5.4 per cent in 1982 and 3.8 per cent in 1993, and weight for height. Finally, an important progress was detected in the infant mortality rates, with a drop from 36,4/1,000 liver births in 1982 to 21,1/1,000 in 1993. The results of this study will certainly contribute to the understanding of the evolution of the health status of mothers and children during the last decade and in planning new preventive actions.

PARTNERS

ESCUELA ANDALUZA DE SALUD PUBLICA

Apartado De Correos 2070

18080 Granada

Spain

Maria del Mar Garcia Calvente

Tel.: +34-5-827 50 44

Fax: +34-5-827 05 51

UNIVERSIDADE FEDERAL DO PELOTAS

Faculdade de Medicina

Departamento de Medicina Social

Caixa Postal 464

96001 Pelotas

Brazil

Fernando Barros

Tel.: +555-3-271 24 42

Fax: +555-3-271 26 45

LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE

Department of Public Health and Policy

Keppel Street

London WC1E 7HT

United Kingdom

Patrick Vaughan

Tel.: +44-171-927 24 31

Fax: +44-171-637 53 91

3. Health

3.2. Disease specific research

**CD'S FOR DC'S: DEVELOPMENT OF THE COMPACT DISC (CD) AS A NOVEL,
COST-EFFECTIVE & VERSATILE PLATFORM FOR IMMUNOASSAYS FOR
INFECTIOUS DISEASES**

Co-ordinator: Glasgow University, Institute of Biomedical and Life Sciences,
Glasgow, United Kingdom (John Kusel)

OBJECTIVES

The aim of this project is to develop, test and validate an immunoassay system an immunoassay system derived from compact disc (CD) technology. This should meet the scientific, medical and economic needs of developing countries (DC's). This will be done in collaboration with a European SME (Molecular Drives Ltd) which has developed a prototype CD-based diagnostic system. This now requires to be adapted for use in the diagnosis of infectious diseases in DC's.

Immunoassays are widely used in scientific research and clinical diagnosis. The CD-based system uses a modified compact disc as a solid-phase platform upon which antigens or antibodies can be immobilised and standard immunoassays performed. A modified CD-player is used to read the results which is currently in an early development stage.

Scientific and Technical Objectives

The scientific objectives of the project are to produce a modified CD as a platform for immunoassays used in a diagnosis and research. This will also involve training scientists from DCs in the new technology during the development process. The application of diagnostic and information technology is also an important part of the process. The technical objectives are a mainly a series of increasingly rigorous tests of all parts of the CD-based system as described below.

- Develop and optimise the design and geometry of the CD assembly (including disc architecture, template format, sector size, number of wells per sector, depth and capacity of antigen wells);
- Standardise the assay protocol, with respect to antigen quality (crude, purified, recombinant), serum dilution, immunoconjugates substrates, detection systems and enhancement chemistries, incubation times and washing stringencies using commercial human serum proteins and appropriate rabbit antisera;
- Examine the efficiency of the discs by direct comparison with microtitre plates using well-characterised rubella sera obtained from a Rubella Reference Laboratory (I-III in Glasgow laboratory);
- Subject discs to more rigorous quality assessment by testing with sera from patients attending a clinic in a tropical medicine institute (Heidelberg). In these assays the results of assays with discs will be directly compared with those obtained by parallel routine testing using current clinical methods;
- Develop discs loaded with different combinations of antigens, for use as diagnostic and/or other research tools;
- Compare discs with microtitre plate for diagnostic antigen-capture assays using anti-Sm31 monoclonal antibodies (iv-vi in Heidelberg laboratory);
- Subject all discs to ultimate "field" testing through the DC laboratories (Egypt and India) using well-defined infection sera from people living in endemic and epidemic areas and harbouring helminth- (schistosomiasis, bancroftian filariasis, echinococcosis) or viral infections. In these studies, the results from the discs will be compared with those from other serological tests, routinely performed in the laboratories of the DC Partners. This work will be carried out by DC Partners trained in the first year in the use of the CD-system in the Glasgow and Heidelberg laboratories. It should be noted that as the work progresses, the origin of the sera is from regions

of greater exposure to multiple diseases, thus increasing the rigor and diversity of the test carried out and ensuring comprehensive testing of the CD platform.

Criteria for verification

At each stage of the work, sera of known, but very different origin, will be assayed for antibody (or antigen) using both discs and microtitre plates as solid-phase platforms generating chromogenic or fluorescent signals. In all these assessments the key criteria for comparison will be assay sensitivity, specificity and reproducibility.

Long term objectives

This project will be considered a success if, at its conclusion, the various assays carried out on the CD disc are reliable, sensitive and specific for a particular disease with the results readily quantified and stored. The availability of the apparatus for widespread use in developing countries is a long-term objective.

ACTIVITIES

0-6 months

- ◇ Glasgow lab begins immunoassay optimisation with defined proteins and rabbit antisera.
- ◇ DC scientists are trained in Glasgow and Heidelberg in assay design and development, use of equipment and software. Their training also involves a research project solving an immunodiagnostic problem.

7-12 months

- ◇ Glasgow laboratory will test discs with Rubella infection sera, and results compared with ELISA readings.
- ◇ Heidelberg will test discs with non-endemic parasite sera.
- ◇ DC scientists develop and test diagnostic discs - Single Antigen Discs (SADs) and Double Antigen Discs (DADs).

13-18 months

- ◇ Completion of testing of discs with Rubella sera by Glasgow University.
- ◇ Glasgow University makes Single Organism Double Antigen Discs (SODADs).
- ◇ DC scientists begin to use CD discs in CD instruments/readers for serodiagnosis in their own countries.

19-24 months

- ◇ Glasgow laboratory produces Multi-Organism Double Antigen Discs (MODADs) and Multi-Organism Multi Antigen Discs (MOMADs). Heidelberg test for quality the MODADs and MOMADs. Both laboratories will now extend the use of the discs by introducing antigen capture techniques.
- ◇ DC laboratories continue to use SADs and DADs.

25-30 months

- ◇ DCs use a variety of discs for diagnosis. The use of MODADs and MOMADs for multi-disease diagnosis.
- ◇ Other techniques (antigen capture) used by Glasgow and Heidelberg.

31-36 months

- ◇ Glasgow and Heidelberg will explore potential of discs as a centrifuge or in fluorescent assays.
- ◇ India and Egypt continue studies on the variety of diagnosis, but not yet using more advanced developments in (a). At yearly intervals, reports are sent to all Partners and meeting arranged to discuss results.

EXPECTED RESULTS

This will cover project methodology, milestones, deliverables and expected outcomes.

Project methodology

Compact Disc (CD) Assembly

Many immunoassays depend on the adsorption of antigen or antibody onto a plastic microtitre plate. The modified CD-based system described here can replace both the microtitre plate and other associated equipment. The modified CD consists of three discs.

The discs on the bottom (Disc A) is a conventional silver-plated CD, which is digitized to store and read information necessary for spinning the discs in a customised CD player. Disc B is a plastic "spider" template into which sectors are inserted and flooded with serum to perform the immunoassays. The sectors contain microwells (2-3ul capacity), which are coated with antigen or antibody. The number of sera assayed per disc depends on the number of sectors in each disc – one serum per sector. The number of sector per disc can vary from 8-32 depending on the combination of antigens on the disc. The number of wells per sector can range from 10-48 again depending on the required panel of diseases. Disc C is a plastic cover with holes around the middle through which the assay is performed using a "flood and fill" technique. Once the assay is completed the three disc structure is placed in a modified CD reader which measures the optical densities of the assay reactions at 50 points in each well with software designed to store the data onto a PC. The work will be carried out as follows:

- ⇒ Design of the CD assembly (Glasgow laboratory)
The prototype CD assembly requires development in terms of the physical nature and design of the discs. This will be addressed immediately on project commencement and will require input from the DC scientists so that discs tailored for use in their own DC can be constructed.
- ⇒ Optimisation of the assay platform (Glasgow laboratory with assistance from DC scientists)
The assay procedure will be optimised and protocols standardised so that discs are an efficient platform for immunochemical assays. The studies will address a variety of parameters with a view to finding the most optimally sensitive assay system and method. This will then be used to directly compare the results of immunoassays performed on discs with those in 96-well plates using rubella virus antigen and defined patient sera from the International Rubella Reference Laboratory.
- ⇒ Quality assurance testing of developed assay (Heidelberg)
The institute in Heidelberg has sera from 20-30 patients suspected of having parasitic infections. A series of immunodiagnostic tests can be performed comparing diagnosis using disc and a standard microtitre plate. This will give a direct comparison of the efficiency of CDs using a variety of parasite antigen types and clinical specimens of undefined parasite status. Heidelberg and Glasgow will develop an antigen capture immunoassay using the CD. These are often necessary in the diagnosis of current or recent parasitic infections.
- ⇒ "Field testing" the discs (Egypt and India)
The DC scientists will return to the respective countries after the first year and begin to "field test" the CD platforms using well-characterised sera from banks already present in their laboratories. The CDs will be most rigorously tested here using complex sera i.e. from infected people living in endemic areas. Egypt will examine the discs for efficiency of diagnosis of parasitic infections (schistosomiasis, bancroftian filariasis and echinococcosis) and India will examine them for efficiency of diagnosis of parasitic (bancroftian filariasis) and viral (hepatitis B) infections.
- ⇒ Development of combinatorial discs (Heidelberg, Egypt, India)
Once the discs have been tested and assessed for quality and usefulness in diagnosis, alternative discs will be formatted on the CD to produce discs suitable for research purposes. There will be templates for the assay of many sera against two diseases or those allowing the assay of a few sera (up to a maximum of eight) for ten diseases.

By the end of the study the CDs will have been comprehensively tested with respect to the quality of the parasite (different helminths and viruses), antigen (pure, crude, recombinant), sera (from "simple" to diagnosis and research of infectious diseases in the DCs).

Milestones

0-6 months

- Conference before commencement of work;
- CD design and immunoassays optimisation with known proteins and rabbit antisera;
- DC scientists train and assist in assay design and development etc.

7-12 months

- Partner 1 - testing discs with clinical specimens (defined rubella infection sera);
- Partner 2 - testing discs with clinical specimens ("simple" parasite infection sera, non-endemics);
- DC scientists (Partner 3 & 4) develop diagnostic discs (SADs and DADs) for own labs.

13-18 months

- Reports sent to all Partners - Meeting at Partner 2's Institute for discussions;
- Testing disc with Rubella infection complete;
- Partner 1 creates SO-DADs and SO-MADs for schistosomiasis;
- Partner 2 creates SO-DADs and SO-MADs with schistosomiasis infection sera;
- DCs begin using CDs (for serodiagnosis - "complex" sera in their own countries).

19-24 months

- Partner 1 creates MO-DADs and MO-MADs as a research tool for multi-disease diagnosis;
- Partner 2 examines MO-DADs and MO-MADs for quality;
- Partner 1 develops antigen-capture assay using anti-Sm31 monoclonals on CDs;
- DCs continue studies using diagnostic discs.

25-30 months

- Reports sent to all Partners - Meeting at Partner 3's institute for discussions;
- DCs use MO-DADs and MO-MADs as research tools for multi-disease diagnosis;
- Partner 2 tests Sm31 antigen-capture assay on CDs.

31-36 months

- DCs continue/complete studies using diagnostic and research discs;
- Partner 1 explores fluorescence detection systems and other uses of spinning disc (e.g. centrifuge for blood-group typing, microscope for IFAT assays);
- Partner 2 explores possibility of centrifugation/microscope applications if successfully developed;
- Final reports sent to all Partners - Meeting at Partner 4's institute for over-all discussions.

Deliverables

In each of the activities described under milestones, quantitative will be derived from antigens on disc reacting with defined and unknown anti-sera. This quantitative data will be in the form of optical density readings, and will be directly compared with similar data derived from other kinds of tests (e.g. ELISA) with the same antigen and sera. Thus, strictly defined verification of the efficiency of the discs at each stage will be obtained.

EXPECTED OUTCOMES

We anticipate that at the end of the project a database showing very good agreement in specificity and sensitivity between CD discs and other tests in a variety of diagnostic tests. It is anticipated that the precision and accuracy of the CD discs in diagnosis will have been demonstrated and its versatility as a platform for other clinical tests.

PARTNERS

UNIVERSITY OF GLASGOW

Institute of Biomedical & Life Sciences
Division of Biochemistry/Molecular Biology
G12 8QQ Glasgow
United Kingdom

J. Kusel
Tel.: +44/141/330.46.21
Fax: +44/141/330.46.20
E-mail: gbca66@udcf.gla.ac.uk

RUPRECHT-KARLS-UNIVERSITÄT HEIDELBERG

Abt. Tropenhygiene/Öffentliches Gesundheitswesen
Im Neuenheimer Feld 324
69120 Heidelberg,
Germany

A. Ruppel
Tel.: +49/6221/56.50.44
Fax: +49/6221/56.59.48
E-mail: Andreas_Ruppel@krzmail.krz.uni-heidelberg.de

AIN SHAMS UNIVERSITY CAIRO

Research & Training Centre on Vectors of Diseases
Abassia Square
11566 Cairo
Egypt

R. Ramzy
Tel.: +20/2/283.96.22
Fax: +20/2/283.96.22
E-mail: Reda_M@frcu.eun.eg

ANNA UNIVERSITY, CENTRE FOR BIOTECHNOLOGY

Sardar Patel Road
600 025 Chennai (Madras), Tamil Nadu
India

P. Kaliraj
Tel.: +91/44/235.07.72
Fax: +91/44/235.02.99
E-mail: cbiotech@glasmd01.vsnl.net.in

**CYSTIC ECHINOCOCCOSIS (HYDATIDOSIS) IN THE EASTERN
MEDITERRANEAN AND MIDDLE EAST - DIAGNOSTIC TOOLS FOR PUBLIC
HEALTH AND EPIDEMIOLOGY**

Co-ordinator: University of Salford, Salford, United Kingdom (Philip S Craig)

OBJECTIVES:

- Evaluate new approaches for molecular diagnosis
- Active and retrospective screening for prevalence of CE
- Transmission patterns of *E.granulosus* in Eastern Mediterranean

ACTIVITIES:

- ◇ Identification of *Echinococcus* DNA sequences for diagnosis/detection
- ◇ Human CE screening with serological confirmation of communities in endemic areas
- ◇ Application of diagnostic tools for epidemiological and transmission studies

EXPECTED OUTCOME:

- ⇒ Regional perspective on actual prevalence and endemicity of cystic echinococcosis
- ⇒ Standardisation and development of molecular and immunodiagnostic tests for CE and echinococcosis
- ⇒ Understanding of the transmission patterns, strain types and epidemiology of *E.granulosus* in the region.

PARTNERS

UNIVERSITY OF SALFORD

Department of Biological Sciences
Salford
M5 4WT
United Kingdom

Professor Philip S Craig

Tel.: 0161-295-5488

Fax: 0161-295-5210

Email: p.s.craig@biosci.salford.ac.uk

ARISTOTELLIAN UNIVERSITY OF THESSALONIKI

Laboratory of Parasitology and Parasitic Diseases
Faculty of Veterinary Medicine
Thessaloniki
Greece

Professor C A Himonas

Tel.: 30 31 999941

Fax: 30 31 999947

BEN GURION UNIVERSITY OF THE NEGEV

Department of Microbiology and Immunology
PO Box 653
Beer Sheva
Israel

Professor Joseph El-On

Tel.: 972 7 400899

Fax: 972 7 6277453

E-mail: jelon@bgumail.bgu.ac.il

THE HEBREW UNIVERSITY

Kuvin Centre for Infectious and Tropical Diseases
Hadassah Medical School
PO Box 12272
Jerusalem
Israel

Professor Joseph Hamburger

Tel.: 972 26758081

Fax: 972 2 675 8082

E-mail: hambu@cc.huji.ac.il

DEPARTMENT OF BIOLOGICAL SCIENCES

Yarmouk University
Irbid
Jordan

Professor Sami Abdel-Hafez

Tel.: 962 2271100

Fax: 962 2246575

E-mail: skhafez@yu.edu.jo

AINS SHAMS UNIVERSITY

Research and Training Centre of Vectors of Disease
Abbassia Square
Cairo
Egypt

Dr Reda M R Ramzy

Tel.: 202 283 9622

Fax: 202 283 9622

**A PROPOSAL TO ASSESS THE IMPACT ON FAMILIES AND STATE OF
TRAUMATIC INJURY RELATED DISABILITY AMONG ADULTS IN LEBANON
AND PALESTINE.**

Coordinator: University of Cambridge, Cambridge, United Kingdom (K. Sen)

OBJECTIVE

Both Lebanon and the Occupied Territories are faced with health structures that are being reorganised and effected by a period of prolonged conflict. The main focus of this study is to evaluate specific services currently being provided to vulnerable populations among disabled adults in Lebanon and elderly people in the Occupied Territories, in terms of their equity and effectiveness. The overall objective of the study is to explore the cost of disability in terms of foregone incomes, quality of life and suffering for disabled adults and their carers' in the aftermath of conflict.

ACTIVITIES

Four main phases have been in process.

- ◇ The first has involved consolidating institutional links with government departments and other organisations involved in the provision of services in both regions. There have been reviews of local literature and data sources on disability and chronic morbidity and its social consequences complemented by a service audit in each region.
- ◇ The second phase has involved extensive research and discussion to develop instruments and their local validation to test functional well being and appropriate terms to understand issues related to the quality of life in situations of conflict. During this phase specific training has been provided to local researchers in the use of the instruments which involve both quantitative and qualitative techniques.
- ◇ The third phase consisted of the main field work in both regions and has involved undertaking a prevalence studies to ascertain the nature and extent of disabilities in the community among adults and older people. In Lebanon there has been a focus on the extent to which war injury may have inflated the disability rate. The presence of continued chronic morbidity from the onset of injury in terms of anxiety and or depression is currently being analysed in Lebanon as a marker for mental health state. In Lebanon also there is preparation to use the PTSD schedule (post trauma stress disorder) to determine whether mental trauma is associated with functional mobility among adults. The attempt to assess disability from a holistic perspective (physical and mental well being) is expected to be a major innovation in the region. Similarly the explorations on the use of PTSD, to examine chronic mental health states is also an innovation. This phase has involved active collaboration through discussion and debate between the collaborating partners from the different regions during the summer of 1998.

In Palestine, socio demographic information has documented living arrangements among vulnerable older people, identified the main care giver and extent of service usage as well as access to services. The cost of disability will be ascertained in relation to direct costs such as out of pocket expenditure for health and social care and income foregone from loss of employment (if applicable) during the previous year. Second, a sub sample of disabled people will be the subject of in-depth interviewing to assess the efficacy of existing service provision and to ascertain the quality of life for those with disabilities, in terms of both perceived and actual need for services. This will include the needs of main carers' in both regions.

- ◇ The fourth and final phase will involve data analysis and the writing and presentation of reports primarily in country, but also in the European region. There will be a concerted effort at international dissemination of this important and much neglected topic (mental and physical disabilities) in a largely neglected region of the world and in the context of health systems research.

EXPECTED OUTCOME

- ⇒ Provide and estimate of the prevalence and type of disabilities in the two regions
- ⇒ Evaluate current service provision in terms of its equity, effectiveness and cost
- ⇒ Provide an indication of population need and demand for services
- ⇒ Recommend which services may be expanded and which could be reduced.
- ⇒ First ever regional network on issues of disability, war and reconstruction that will be locally organised and managed.

FOLLOW UP

In Lebanon a workshop is proposed to discuss jointly with relevant Ministries and other international organisations, the integration of the findings from the study with current plans for support of adults with disabilities in the context of post-conflict reconstruction. In Palestine, the research agency has been working closely with the Palestine National Authority to provide information for their service plans for vulnerable groups. The preliminary findings have generated sufficient interest for most service providers to seek information, advice and guidance from the research agency and to call for a national conference on the subject of vulnerable groups and service need.

PARTNERS

UNIVERSITY OF CAMBRIDGE

Institute of Public Health
The Medical Research Council
Biostatistics Unit
University Forvie Site
Robinson Way
Cambridge CB2 2RS
United Kingdom

K. Sen
Tel.: +44-1223-33 03 66
Fax: +44-1223-33 03 65

THE AMERICAN UNIVERSITY OF BEIRUT

Department of Health Sciences
Bliss Street
P.O. Box 11-0236
Beirut
Lebanon

A. Sibai
Tel.: +961-1- 35 00 00 (ext. 4647)
Fax: +961-1-21 24 44.5801

AID TO THE AGED (ATTA)

Harhash Building
P.O. Box 21358
Beit-Hanina
Jerusalem
West Bank and Gaza Strip

M. Sansur
Tel/Fax: +972-2-81 20 32

INSTITUT NATIONAL D'ÉTUDES DÉMOGRAPHIQUES

Rue du Commandeur 27
75675 Paris Cedex 14
France

M. Khlat
Tel.: +33-1-42 18 21 49
Fax: +33-1-42 18 21 99

**DEVELOPMENT AND IMMUNOLOGICAL EVALUATION OF VACCINE FOR
CANINE VISCERAL LEISHMANIASIS**

Co-ordinator: Royal Tropical Institute, Amsterdam, The Netherlands (Linda Oskam)

OBJECTIVES

- Purification of a defined parasite antigen, dp72, for use in laboratory vaccine trials against canine leishmaniasis;
- Development of molecular biological methods, specifically reverse transcriptase-polymerase chain reaction (RT-PCR), to measure cytokine responses, interleukin (IL)-4, -10, tumour necrosis factor (TNF)- α , and interferon (IFN)-gamma, in vaccinated dogs following infection;
- Examination of Th1 and Th2 responses to vaccine antigens in the experimental model for canine leishmaniasis;
- Identification of a suitable site in western Turkey where a vaccine field trial can be carried out.

ACTIVITIES

- ◇ Development of RT-PCR for the detection of lymphokine levels in dogs;
- ◇ Collection of samples from diseased, asymptomatic and healthy dogs in Turkey, Israel and Portugal and testing of these samples in the RT-PCR;
- ◇ Preparation of the dp72 antigen to be used in vaccine studies to be carried out on inbred Beagles in Portugal;
- ◇ Execution of surveys on canine VL in Western Turkey in the region near Izmir. Longitudinal studies will be used in order to determine the best site for field trials of the canine VL.

EXPECTED OUTCOME

- ⇒ Identification of the cytokines important for the prediction of outcome of infection with Leishmania in dogs;
- ⇒ Assessment of the use of dp72 as a vaccine for leishmaniasis in dogs in a clinical trial;
- ⇒ Identification of a site for a future field trial.

PARTNERS

ROYAL TROPICAL INSTITUTE

Department of Biomedical Research
Meibergdreef 39
1105 AZ Amsterdam
The Netherlands

Linda Oskam
Tel.: +31-20-566 54 41
Fax: +31-20-697 18 41
E-mail: bo@mail.support.nl

HEBREW UNIVERSITY

Hadassah Medical School
Department of Parasitology
Kuvim Centre
P.O. Box 1172
91010 Jerusalem
Israel

C.L. Jaffe
Tel.: +972-2-675 80 76
Fax : +972-2-675 74 25
E-mail: cjaffe@cc.huji.ac.il

UNIVERSIDADE NOVA DE LISBOA

Instituto de Higiene e Medicina Tropical
Rua de Junqueira 96
1300 Lisbon
Portugal

Pedro Abranches
Tel.: +351-1-363 21 41
Fax: +351-1-362 24 58
E-mail: cmdt@esoterica.pt

EGE UNIVERSITY

Medical Faculty
Department of Parasitology
35100 Bornova - Izmir
Turkey

Ali Ozcel
Tel.: +90-232-339 82 90
Fax: +90-232-388 13 47
E-mail: ozbel@bornova.ege.edu.tr

**THEILERIA ANNULATA MACROSCHIZONT-INFECTED CELLS IN
VACCINATION AND DISEASE**

Co-ordinator: University of Edinburgh, Edinburgh, United Kingdom (Roger Spooner)

OBJECTIVES

- To study the effect of cell line vaccination on the epidemiology of theileriosis;
- To investigate the mechanisms underlying clinical reactions to macroschizont-infected cell lines;
- To improve vaccine production and diagnostic tests based on macroschizont antigens; to develop a test for protective immunity;
- To characterise and isolate the antigens on macroschizont infected cells involved in the generation of immunity and pathogenesis;
- To evaluate diagnostic reagents in epidemiological studies in Tunisia and Turkey¹.

ACTIVITIES

- ◇ To monitor the efficacy of cell line vaccination in Turkey and Tunisia;
- ◇ To select and validate diagnostic tests and assess their specificity. In particular to study cross reactions between *T. annulata* and *T. Hirci/lestouardi*;
- ◇ To study the cytokine production of potential vaccine cell lines and their correlation with pathology;
- ◇ To study the role of cytokines and antigen EU 106 in the production of attenuated cell line vaccines without prolonged culture;
- ◇ To isolate and sequence parasite derived peptides expressed by infected cells and identify which are recognised by cytotoxic T cells from immune animals;
- ◇ To identify the role of MHC polymorphism and T cell receptor repertoire in protective and pathogenic CD4 T cell responses to *T. annulata*;
- ◇ To characterise and isolate novel antigens found on macroschizonts and the surface of infected cells. To study their roles in protective immunity;
- ◇ To assess immunoreactivity of macroschizont antigens with cells from naturally infected or vaccinated cattle;
- ◇ To evaluate diagnostic reagents produced by this project and IC18-CT95-009¹.

EXPECTED OUTCOME

- ⇒ Defining whether cell line vaccination has any effect on the epidemiology of theileriosis;
- ⇒ Development of methods for producing cell line vaccines without attenuation which are safe and effective;
- ⇒ Understanding of the mechanisms by which macroschizont-infected cells and macroschizont antigens induce immunity and pathology and cell line vaccines induce protection;
- ⇒ Identification of potential macroschizont antigens for inclusion in subunit vaccines and antigens involved in pathological immune responses which should be excluded;
- ⇒ Validate new diagnostic techniques for theileriosis for both sensitivity and specificity.

¹ Integrated control of ticks and tick-borne diseases (ICTTD) : vaccine development, improve diagnostics, genetic resistance and delivery systems (IC18-CT95-009)

PARTNERS

UNIVERSITY OF EDINBURGH

Centre for Tropical Veterinary Medicine
Laboratory of Medicine
Easter Bush Street
Roslin EH25 9RG
United Kingdom

Roger Spooner
Tel.: +44-131-650 62 28
Fax: +44-131-445 50 99
E-mail: roger.spooner@ed.ac.uk

ÉCOLE NATIONALE DE MÉDECINE VÉTÉRINAIRE

Department of Clinical Sciences
Laboratory of Parasitology
2020 Sidi Thabet, Ariana
Tunisia

Mohamed Aziz Darghouth
Tel.: +216-1-55 24 60 / 200
Fax: +216-1-55 24 41

UNIVERSITY OF ANKARA

Faculty of Veterinary Medicine
Department of Protozoology & Medical Entomology
Irfan Baslug Caddesi
06110 Diskapi - Ankara
Turkey

Fahri Sayin
Tel.: +90-312-316 03 13
Fax: +90-312-316 44 72

FORSCHUNGSINSTITUT BORSTEL

Veterinary Infectiology & Immunology
Parkallee 22
23845 Borstel
Germany

Jabbar S. Ahmed
Tel.: +49-4537-104 28
Fax: +49-4537-104 04

ROSLIN INSTITUTE

Division of Molecular Biology
Roslin - Midlothian EH25 9PS
United Kingdom

Elizabeth J. Glass
Tel.: +44-131-440 27 26
Fax: +44-131-440 04 34
E-mail: liz.glass@bbsrc.ac.uk

**MONITORING WATER FOR CONTAMINATION BY SCHISTOSOMES :
DEVELOPMENT AND FIELD TESTING OF NEW TECHNOLOGIES AND
APPROACHES**

Co-ordinator: Universität Heidelberg, Heidelberg, Germany (Andreas Ruppel)

OBJECTIVES

- Monitoring schistosome-polluted water by PCR;
- Monitoring of schistosome-infected snails by detecting schistosomal antigens and by PCR;
- Monitoring the ratio of prepatent/patent infections in snails for rapid preliminary assessment of schistosomiasis prevalence in humans;
- Monitoring of snails prepatent/patent infections after mass-treatment for possible timing of retreatment;
- Develop DNA and antigen-based technologies for monitoring Sm and Sh in water and in snails.

ACTIVITIES

- ◇ Preparation of monoclonal antibodies (Mab) for detection of *S. haematobium* infected snails;
- ◇ Monitoring snails for infection by detecting schistosomal antigens;
- ◇ Developing PCR-based tools for monitoring schistosomes in water and snails;
- ◇ Monitoring of schistosome infestation of water by PCR;
- ◇ Collection of biological materials in the field for development of the monitoring tools;
- ◇ Evaluation the relation between human infection and prepatent/patent infection in snails;
- ◇ Examining the fall and rise of prepatent/patent ratio of snail infection after mass treatment;
- ◇ Preparation for an organisation of field studies involved in tasks no 2, 4, 5, 6 and 7.

EXPECTED OUTCOME

Development of a rapid testing system for identification of schistosome infected snails.

PARTNERS

RUPRECHT-KARLS-UNIVERSITÄT HEIDELBERG

Institut für Tropenhygiene und Öffentliches
Gesundheitswesen
Im Neuenheimer Feld 324
69120 Heidelberg
Germany

Andreas Ruppel
Tel.: +49-6221-56 33 97 / 56 50 44
Fax: +49-6221-56 59 48

THE HEBREW UNIVERSITY OF JERUSALEM

Hadassah Medical School
Department of Parasitology
P.O. Box 12272
91120 Jerusalem
Israel

Joseph Hamburger
Tel.: +972-2-75 80 82
Fax: +972-2-43 25 27

AIN-SHAMS UNIVERSITY

Faculty of Science Building
Research & Training Centre on Vectors of Diseases
Abbassia - Cairo
Egypt

Reda Ramzy
Tel/Fax: +20-2-283 96 22

UNIVERSITÉ DE PERPIGNAN

Centre de Biologie et d'Ecologie Tropicale &
Méditerranéenne
Avenue de Villeneuve
66860 Perpignan Cedex
France

Joseph Jourdane
Tel.: +33-4-68 66 20 50
Fax: +33-4-68 66 22 81
E-mail: jourdane@univ-perp.fr

**CRYPTOSPORIDIUM OOCYST WALL PROTEIN (COWP) : A TOOL FOR
STUDYING PARASITE HOST-CELL INTERACTIONS & DESIGNING
PREVENTION MEASURES AGAINST CRYPTOSPORIDIUM INFECTION**

Co-ordinator: Università degli Studi di Roma la Sapienza, Roma, Italy (Andrea Crisanti)

OBJECTIVES

- To elucidate the role played by COWP in parasite-host cells interactions;
- To assess the prevalence of Cryptosporidium infection among diarrhoea cases as well as to identify risk factors involved in parasite transmission in rural areas of Morocco and Tunisia.

ACTIVITIES

- ◇ Generation of a collection of recombinant COWP-deleted constructs;
- ◇ Deletion mapping of COWP binding sequences to Enterocytes;
- ◇ Identification of the host cell recognised by COWP;
- ◇ Development of COWP antibodies;
- ◇ Assessment of antiparasitic activity of COWP antibodies;
- ◇ Validation of a diagnostic assay based on COWP detection methods (PCR, ELISA or immunofluorescence);
- ◇ Utilisation of the validated diagnostic assay to determine the prevalence of Cryptosporidium infection in different groups of individuals;
- ◇ Identification of risk factors for Cryptosporidium infection in a case control study.

EXPECTED OUTCOME

- ⇒ A new tool for Cryptosporidium diagnosis;
- ⇒ The epidemiology of Cryptosporidium diarrhoea clusters will be clarified in two Maghreb countries;
- ⇒ Research capacity in diarrhoeal diseases epidemiology + Cryptosporidium biology will be reinforced in Tunis and Morocco.

PARTNERS

UNIVERSITÀ DEGLI STUDI DI ROMA "LA SAPIENZA"
Piazzale Aldo Moro 5
00185 Roma
Italy

Andrea Crisanti
Tel.: +39-6-499 11
Fax: +39-6-594 54 39

INSTITUT PASTEUR DU MAROC
Laboratoire de Parasitologie
Place Charles Nicolle 1
Casablanca
Morocco

Saida Ibrahimi

INSTITUT PASTEUR
Laboratoire d'Epidemiologie
Place Pasteur 137
B.P. 74
1002 Tunis-Belvédère
Tunisia

Riadh Ben Ismael

**HEALTH SYSTEMS AND THE PREVENTION OF GENETIC DISEASES:
APPLICATION TO HEMOGLOBIN DISORDERS**

Co-ordinator: Hospital Henri Mondor, Creteil, France (Michel Goossens)

OBJECTIVES

- To evaluate the economic cost of two major genetically inherited diseases;
- To evaluate the social perception of the concept of genetic diseases and the eventual request for prevention through prenatal diagnosis;
- To define the spectrum of the mutations causing hemoglobinopathies in Tunisia and Morocco and to compare the current techniques available for detecting the mutations and performing the prenatal diagnosis (costs, reproducibility, rapidity, etc.).

ACTIVITIES

- ◇ Economic costs of Thalassemia and Sickle cell anemia has been estimated by a retrospective analysis of about 300 patients medical files. This analysis will include the study of various parameters such as expenses during hospitalisation and expenses during ambulatory treatment as well as indirect costs;
- ◇ The social perception was studied by a group of social workers and psychologists on a sample of patients affected with hemoglobinopathies as well as on a control groups in both countries;
- ◇ The haemoglobin gene mutations were characterised by various PCR-based techniques. An evaluation of these techniques was carried out to find out which one would be the most adapted to performing the prenatal diagnosis under field conditions. The use of non radioactive probes was also evaluated.

OUTCOME

- ⇒ The economic costs of beta-thalassemia and sickle cell anemia has been assessed along with the social perception of these diseases in each of the two countries, Tunisia and Morocco, where consanguinity is frequent in some ethnic groups ;
- ⇒ The spectrum of thalassemia mutations has been determined in each regions of the two countries. The results of these molecular epidemiology are now used in genetic counselling and prenatal diagnosis. The technology transfer carried out during the research programme has allowed implementation of a prenatal diagnosis laboratory in each country, in Tunis and in Casablanca.
- ⇒ Overall, the results obtained during the three years of the programme constitute a solid basis to improve management of two hereditary diseases that are a public health burden in Tunisia and Morocco.

FOLLOW-UP

The three centres involved in this partnership will remain in close contact and will continue to exchange information, technology and ideas. In particular, the laboratories in Tunis and Casablanca will continue to develop and adapt the relevant molecular techniques, with the help of the French partner, if needed.

PUBLICATION

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PARTNERS

HOSPITAL HENRI MONDOR

Laboratoire de Biochimie
Avenue du Maréchal de Lattre de Tassigny 51
94010 Creteil
France

Michel Goossens
Tel.: +33-1-49 81 28 61
Fax: +33-1-49 81 22 19

INSTITUT PASTEUR DE TUNIS

Laboratoire d'Immologie, d'Immunopathologie et
d'Hématologie (LIIPH)
Place Pasteur 13
B.P. 74
1002 Tunis-Belvédère
Tunisia

Koussay Dellagi
Tel.: +216-1-78 96 08
Fax: +216-1-79 18 33

INSTITUT PASTEUR DU MAROC

Laboratoire de Génétique et de Biologie Moléculaire
Route Casablanca
B.P. 180
Rabat
Morocco

Sellama Nadifi
Tel.: +212-7-69 02 17
Fax: +212-7-69 15 61

**ENTAMOEBIA HISTOLYTICA: PARASITE AND HOST DETERMINANTS
OF TISSUE INVASION**

Co-ordinator: Universität Tübingen, Tübingen, Germany (Gert Dieter Burchard)

OBJECTIVES

To better understand the pathophysiology of invasive amebiasis through analysing the host-parasite interrelation in human infections of the intestinal parasite *Entamoeba histolytica* at the molecular, clinical and epidemiological level.

ACTIVITIES

- ◇ Monoclonal antibodies selectively recognizing only cysts of pathogenic *Entamoeba histolytica* or non-pathogenic *Entamoeba dispar* are developed;
- ◇ Antigens recognized by monoclonal antibodies are examined in order to assess their location and functional significance;
- ◇ *Entamoeba histolytica* and *Entamoeba dispar* are detected and differentiated using an improved colorimetric polymerase chain reaction method directly from faecal samples;
- ◇ Cell surface molecules of pathogenic *E. histolytica* and nonpathogenic *E. dispar* and their relation to virulence are examined;
- ◇ Epidemiologic studies are under way in Diyarbakir/Turkey and in Cairo/Egypt in order to assess the prevalence of *E. histolytica* infections.

RESULTS

- ⇒ Monoclonal antibodies were produced that specifically recognise native and fixed cysts of *E. histolytica* as well as against native and fixed cysts of *E. dispar*. Serological studies have shown that *E. dispar* itself can elicit a specific serum antibody response. An improved method based on the PCR-SHELA technique has been developed to identify *E. histolytica* and *E. dispar* in human faeces. This method is suitable for use with large numbers of specimens.
- ⇒ The prevalences of *E. histolytica* and *E. dispar* were determined separately in Eastern Turkey using stool microscopy, PCR and serological methods. According to PCR classification the prevalence of *E. dispar* was 13% whereas not a single case of *E. histolytica* was detected. Anti-*E. histolytica* serum antibodies were found in 0.6% of the population using an ELISA with a recombinant antigen. It is concluded that the prevalence of *E. dispar* in the Diyarbakir area is high but that the prevalence of *E. histolytica* is very low.
- ⇒ The presence of gene of cysteine proteinase 1 (ACP1) in non pathogenic *E. dispar* strains was demonstrated.
- ⇒ Episomal transfection and continuous expression of heterologous genes in *E. dispar* were achieved. This is the first report of stable expression of a foreign gene in *E. dispar* using upstream and downstream regulatory sequences of *E. histolytica* ribosomal protein L21 gene. Using solvent extraction as well as hydrophobic and anion exchange chromatography, two distinct lipid-anchored glycolipids whose composition was indicative of an LPG and a lipophosphopeptidoglycan (LPPG) were characterised. A direct correlation was observed between the relative abundance of these molecules in different amebic isolates and their virulence. A novel monoclonal antibody that reacts with the LPG of virulent strains has been cloned.

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PARTNERS

EBERHARD-KARLS-UNIVERSITÄT TÜBINGEN
Institut für Tropenmedizin
Keplerstraße 15
72074 Tübingen
Germany

Gerd-Dieter Burchard
Tel.: +49-7071-29 23 65
Fax: +49-7071-29 60 21

THE WEIZMANN INSTITUTE OF SCIENCE
Department of Membrane Research & Biophysics
76100 Rehovot
Israel

David Mirelman
Tel.: +972-8-34 31 60
Fax: +972-8-46 82 56

DICLE UNIVERSITY
School of Medicine
Division of Gastroenterology
21280 Diyarbakir
Turkey

Vedat Göral
Tel.: +90-412-248 84 43
Fax: +90-412-248 84 40

EL-HUSSEIN UNIVERSITY HOSPITAL
Department of Tropical Medicine
1891 Al-Darasa
Cairo
Egypt

Mohamed Abd-Alla
Tel.: +20-2-510 91 04 / 510 91 40
Fax: +20-2-510 41 46

**LONDON SCHOOL OF HYGIENE & TROPICAL
MEDICINE**
Department of Medical Parasitology
Keppel Street
London WC1E 7HT
United Kingdom

John Ackers
Tel.: +44-171-927 23 07
Fax: +44-171-636 87 39

**ENVIRONMENTAL CONTROL OF SCHISTOSOMIASIS IN IRRIGATION
SCHEMES OF THE MEDITERRANEAN REGION**

Co-ordinator: Prins Leopold Instituut voor Tropische Geneeskunde, Antwerp, Belgium
(Bruno Gryseels)

OBJECTIVES

- To develop sustainable, environmental methods for the control of schistosomiasis in irrigation schemes in the Mediterranean region;
- To promote exchanges and collaboration between schistosomiasis control programmes;
- To reinforce European and Mediterranean engineering capacity in environmental disease control.

ACTIVITIES AND RESULTS

The research is carried out in two typical situations : a dry Maghreb area with a modern irrigation system in Morocco, a highly endemic area with traditional irrigation in Egypt.

⇒ Morocco

It was attempted to control vector snail populations and reduce water contact in irrigation siphons, the main transmission sites for urinary schistosomiasis. After a cross-sectional snail survey, three interventions and three control villages have been followed up during one year. This survey, completed by a study of the length profile of a secondary canal and some of its tertiaries, confirmed the concentration of the local intermediate host *Bulinus truncatus* in tertiary syphon boxes. Now, around one village all syphon boxes have been covered with steel plates to obstruct light and thus hamper snail development. At the same time, water and water contamination is restricted. In another village, snails are regularly brushed away from the sides of the syphon boxes in an intensified cleaning and maintenance programme. At a third site, the dimensions of the siphon have been reduced to increase mean flow velocity and control snails. The other villages serve as a control. During one year since this intervention, longitudinal malacological and technical studies are carried out, supported by snail experiments (i.e. snail and eggs' resistance to desiccation) in the laboratory as well as in the field, calculations on hydraulic aspects of the siphons and a comparison with similar irrigation schemes. Sociological studies have shown the importance of the siphon boxes in domestic water supply, especially in parts of the scheme where the water table is more than 100m below the surface. Between irrigation turns, the tertiary siphons constitute the only source of water available. Any intervention on siphons that limits access to water, can only be sustainable if alternate water supply is provided. Water in traditionally used underground cisterns proved to be relatively easy to treat and is thus a valid alternate safe water supply. Community surveys have been carried out before the intervention, combined with selective treatment. Epidemiological studies have shown that prevalence is now below 2 % in most villages, precluding the planned epidemiological evaluation of the intervention. On the other hand, perspectives for a more ambitious objective of parasite elimination and/or eradication are opened. The active population screening programme of the Ministry of Health was re-evaluated, alternate diagnostic methods tested and operational research oriented towards health system research for improved and more targeted coverage. Diagnostic research has indeed shown that more sensitive or repeated samplings increase the patient yield only marginally and that improving coverage and compliance is much more important. Protocols for further integration in the health services are being developed. Active links have been established with national, regional and local departments of the ministries of Agriculture, Public Health and Interior.

⇒ Egypt

The feasibility of interventions to reduce human exposures, in particular community laundry basins, has been examined. Besides a terminal and social evaluation, an epidemiological survey will evaluate the impact of such laundry basins, by comparison of reinfection rates after treatment in three intervention villages as compared to three control villages. Parasitological surveys have been carried out to select suitable ezba's or hamlets for the intervention studies. Focus group

discussion and an extensive literature review have provided the social background for the construction of laundry basis. Technical and engineering conditions have been studied and an appropriate design for communal laundry basins is being developed.

PARTNERS

**PRINS LEOPOLD INSTITUUT VOOR TROPISCHE
GENEESKUNDE**
Nationalestraat 155
2000 Antwerp
Belgium

Bruno Gryseels
Tel.: 32-3-247 62 00
Fax: 32-3-237 67 31
E-mail: bgryseels@itg.be

UNIVERSITY OF LEIDEN
Medical Faculty
Department of Parasitology
P.O. Box 9605
2300 RC Leiden
The Netherlands

Eline Boelee
Tel.: +31-71-527 68 59
Fax: +31-71-527 68 50

**INSTITUT AGRONOMIQUE ET VÉTÉRINAIRE
HASSAN II**
Département de Parasitologie
B.P. 6202 - Institutes
10101 Rabat
Morocco

Khalid Khallaayoune
Tel.: +212-7-77 64 32
Fax: +212-7-77 22 20

MINISTRY OF HEALTH
Division of Endemic Diseases Control
Magless El Shaab Street 6
Cairo
Egypt

Abdel Aziz Hamad Wafa
Tel.: +20-2-354 71 99
Fax: +20-2-360 17 56

WAGENINGEN AGRICULTURAL UNIVERSITY
Department of Irrigation and Soil & Water Conservation
Nieuwe Kanaal 11
6709 PA Wageningen
The Netherlands

Frans Huibers
Tel.: +31-317-48 42 67
Fax: +31-317-48 47 59

DANISH BILHARZIOSIS LABORATORY
Jaegersborg Allé 1 D
2920 Charlottenlund
Denmark

Henry Madsen
Tel.: +45-39 62 61 68
Fax: +45-39 62 61 21

**RODENT ECOLOGY FOR THE EPIDEMIOLOGY AND CONTROL OF
CUTANEOUS LEISHMANIASIS IN NORTH AFRICA AND WEST ASIA**

Co-ordinator: Liverpool School of Tropical Medicine, Liverpool, United Kingdom
(R.W. Ashford)

OBJECTIVES

The main thrust of this project is a medium term study of the population dynamics of *Psammomys obesus*.

ACTIVITIES

- ◇ A minimum of 20 individuals will be sampled monthly through 2 1/2 years and examined for *Leishmania* infection by culture of lesions;
- ◇ The inhabitants of a selected colony will be captured, marked and released for the direct observational study of their longevity, behaviour and movements, over the entire study period;
- ◇ Pregnant females will be kept in captivity and their offspring will be reared in order to produce a base-line curve of age against eye-lens weight;
- ◇ The geographical distribution and population density of *P. obesus* will be determined and mapped in detail in an area of 1 - 10 km²;
- ◇ Standardised observations will be made on potential predators;
- ◇ Captured animals will be examined for parasites other than *Leishmania*;
- ◇ Specimens will be prepared and tissue samples preserved for taxonomic comparison by morphometry.

Sandfly studies at M'sila

- ◇ Sandfly (*P. papatasi* and others) numbers will be compared throughout three seasons in a variety of *P. obesus* colonies in different habitats;
- ◇ Sandflies will be dissected. Parasites will be isolated and identified;
- ◇ Results obtained at Sidi Bouzid will be used as a baseline for comparison with *P. obesus* populations in other North African and West Asian countries. In particular, apparently different populations and, possibly, a second species exists in Libya and Israel.

EXPECTED OUTCOME

Improved understanding of population dynamics of *P. obesus* and sandflies in the north African region.

PARTNERS

LIVERPOOL SCHOOL OF TROPICAL MEDICINE

Pembroke Place
Liverpool L3 5QA
United Kingdom

R.W. Ashford
Tel.: +44-151-708 93 931

INSTITUT PASTEUR

B.P. 76
1002 Tunis Belvédère
Tunisia

Riadh Ben Ismael
Tel.: +216-1-79 24 29
Fax: +216-1-79 18 93

**VARIABILITE GENETIQUE DE L. INFANTUM, AGENT DE LA LEISHMANIOSE
VISCERALE: COROLLAIRES EPIDEMIOLOGIQUES**

Coordinateur: ORSTOM, Montpellier, France (Michel Tibayrenc)

OBJECTIFS

- Etablir un marquage multigénique fin des souches de L. Infantum dans 3 pays d'endémie méditerranéens (Algérie, Tunisie, Espagne);
- Interpréter les données en termes de génétique des populations pour élucider la nature biologique réelle des variants identifiés, et d'estimer les mouvements de ces variants d'un lieu à l'autre;
- Confronter les résultats de l'analyse génétique aux données de terrain, et en tirer les conclusions épidémiologiques utiles;
- Assurer, à la faveur de ces études, les transferts technologiques souhaitables (homogénéisation des techniques entre les 4 laboratoires participants, accueil réciproque de chercheurs et de techniciens pour formations de courte et moyenne durée).

ACTIVITES

- ◇ Collecte et culture des souches
 - Isolats déjà disponibles, sur lesquels on pourra entreprendre d'emblée la caractérisation multigénique;
 - Nouveaux isolats, obtenus sur le terrain dans le cadre de la présente étude.
- ◇ Marquage multigénique
 - Electrophorèses d'isoenzymes;
 - Electrophorèse en champ pulsé;
 - Analyse du polymorphisme de restriction (RFLP);
 - Random primers ('RAPDs').
- ◇ Analyse des données
 - Génétique des populations : méthodes classiques de génétique des populations, ainsi que les tests statistiques spécifiques qui ont été développés par le laboratoire de Montpellier;
 - Analyse phylogénétique. Méthodes simples : estimation du pourcentage de bandes différentes existant entre deux isolats donnés.
- ◇ Confrontation avec les données de terrain
- ◇ Transfert de technologie.

RESULTATS

- ⇒ Identification des implications épidémiologiques de la variabilité génétique de L. infantum dans le Bassin Méditerranéen.
- ⇒ Nouvelles techniques perfectionnées.
- ⇒ Random Amplification de Polymorphique DNA (RAPD);
- ⇒ Isolation de nouveaux stocks;
- ⇒ Nouveaux stocks de Leishmania infantum analysés.

PUBLICATIONS SELECTIONNEES

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PARTENAIRES

INSTITUT FRANÇAIS DE RECHERCHE SCIENTIFIQUE POUR LE DEVELOPPEMENT EN COOPERATION (ORSTOM)

Laboratoire de Génétique des Parasites et des Vecteurs
Avenue Agropolis 911
B.P. 5045
34032 Montpellier Cedex 01
France

Michel Tibayrenc
Tel.: +33-4-67 61 75 07
Fax: +33-4-67 54 78 00 / 67 61 74 97

INSTITUT PASTEUR DE TUNIS

Laboratoire d'Epidémiologie et d'Ecologie Parasitaire
Place Pasteur 13
B.P. 74
1002 Tunis - Belvédère
Tunisia

Ikram Guizani
Tel.: +216-1-79 24 29
Fax: +216-1-79 18 33

INSTITUTO DE SALUD CARLOS III

Centro Nacional de Microbiología
Servicio de Parasitología
28220 Majadahonda (Madrid)
Spain

Jorge Alvar
Tel.: +34-1-638 00 11
Fax: +34-1-639 18 59

HOPITAL PARNET

Institut des Sciences Médicales d'Algérie
Laboratoire Central
Avenue Pasteur
16040 Alger
Algeria

Dalila Aïtchafa
Tel.: +213-2-64 78 15
Fax: +213-2-59 76 73

**A NEW VECTOR SERVING ANTIGEN PREPARATION FOR DIAGNOSIS,
VACCINATION AND EPIDEMIOLOGICAL SURVEILLANCE OF L. INFANTUM
AND L. MAJOR**

Co-ordinator: Vrije Universiteit Brussel, Brussels, Belgium (R. Hamers)

OBJECTIVES

- To develop a novel vaccine candidate through isolation of appropriate antigens and cloning these into the pseudomonas lipoprotein vector;
- To verify the efficiency of these vaccines in mice and dog models, the latter to be developed in Algeria and Morocco.

ACTIVITIES

- ◇ Characterisation of GP63 from field isolates and cloning and subcloning of regions of interest of GP63 (protein analysis, gene expression, gene structures);
- ◇ Cloning of the GP63 genes into the Pseudomonas vector;
- ◇ Acquisition of basic data on specific immunological responses of the human and canine populations at risk;
- ◇ Testing of cloned GP63 with regard to their immunogenic activity in dog and mouse models followed by immunising dog-models with the most efficient clones;
- ◇ Development of a candidate vaccine based on the identified immunising clones;
- ◇ Testing of resistance of immunised animals against natural parasites less or more virulent (L. major / mouse model) or recent field isolates (L. infantum / dog model);
- ◇ Development of a diagnosis technology based on antigens and to be carried out on blood samples.

EXPECTED OUTCOME

- ⇒ Improved knowledge of the genetic basis of antigens of L. infantum and L. major;
- ⇒ Several antigens isolated, cloned on pseudomonas and tested in different animal models with regard to their vaccination efficiency;
- ⇒ Novel approach to develop and test a vaccine that might be useful also for other vaccine preparations.

RESULTS

- ⇒ Production of L. major lipoprotein/GP63 fusion protein.
- ⇒ Cloning of L. infantum GP63 gene.
- ⇒ Use of GP63 fusion protein to detect antibodies in human infection by L. major and L. infantum.
- ⇒ Use of GP63 fusion protein to elicit antibodies in mice and detection of GP63 variants in old and new world Leishmania.
- ⇒ Establishment of canine models for L. infantum and L. major infection.

PUBLICATIONS

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PARTNERS

VRIJE UNIVERSITEIT BRUSSEL

Department of Molecular Biology
Paardenstraat 65
1640 St Genesius Rode
Belgium

R. Hamers
Tel.: +32-2-358 34 17
Fax: +32-2-359 03 90

UNIVERSIDAD DE MURCIA

Department of Microbiologia
Murcia
Spain

Manuel Segovia
Tel.: +34-68-83 30 00
Fax: +34-68-83 54 18

HÔPITAL PARNET

Centre Hospitalier Universitaire
Laboratoire Central
Code Postal 16040
Alger
Algeria

S. Belazzoug
Tel.: +213-2-59 68 05
Fax: +213-2-59 96 73

INSTITUT AGRONOMIQUE ET VÉTÉRINAIRE

HASSAN II
Rabat
Morocco

A. Dakkak
Tel.: +212-7-77 81 10
Fax: +212-7-77 58 38

MOLECULAR GENETICS OF FAMILIAL MEDITERRANEAN FEVER

Co-ordinator: Son Dureta Hospital, Palma de Mallorca, Spain (Bartolomeu Jaume Roig)

OBJECTIVES

→ To describe better the molecular defects leading to familial Mediterranean fever (FMF).

ACTIVITIES

- ◇ Identification of a sufficient number of FMF families and preparation of a detailed clinical description of a series of Turkish, Spanish and non-Askhenazi Jewish patients with FMF serving as a basis for an optimal genetic mapping of the molecular defects in FMF;
- ◇ Genetic and physical mapping of the candidate regions of the FMF gene, first through the exclusion of gene-regions that have a recombinant event in an affected individual, and second, by a continuous mapping of identified candidate regions. The location of the disease gene will then be identified by molecular genetic techniques and through studying linkage disequilibria in each of the ethnic groups.

EXPECTED OUTCOME

⇒ The molecular basis of FMF and other forms of arthritis should be understood better, thus providing an opportunity for improved early diagnosis, therapy and prevention.

PARTNERS

SON DURETA HOSPITAL

Son Armadans 10
07014 Palma de Mallorca
Spain

Bartolomeu Jaume Roig

Tel.: +34-71-
Fax: +34-71-28 43 60

UNIVERSITY OF ANKARA

Department of Internal Medicine & Immunology
Ankara
Turkey

Giner Tokgoz

Fax: +90-4-310 63 70

TEL AVIV UNIVERSITY

Children's Medical Center of Israel
Kaplan Street 14
49202 Petah-Tikva
Israel

Y. Danon

Tel.: +972-3-924 75 15
Fax: +972-3-924 75 15

EPIDEMIOLOGY, DIAGNOSIS AND CONTROL OF LEISHMANIASIS IN THE MEDITERRANEAN REGION

Co-ordinator: Royal Tropical Institute, Amsterdam, The Netherlands (Linda Oskam)

OBJECTIVES

- To develop and employ new tools for the diagnosis and epidemiological surveys of endemic areas;
- To develop a vaccine for canine leishmaniasis and study the immunology of visceral leishmaniasis (VL) in mouse models.

ACTIVITIES

Turkey

- ◇ Establishment of a referral network with all the major hospitals in the Izmir region;
- ◇ Comparison of different diagnostic techniques;
- ◇ Performance of epidemiological studies in Manisa district in order to establish a suitable site for field studies.

Portugal

- ◇ The performance of vaccination studies using the experimental dog model.

Israel

- ◇ Strain identification of Turkish and Israeli isolates;
- ◇ Protection studies with the pure antigen dp72 in mice;
- ◇ Comparison of serological methods for diagnosis of VL;
- ◇ Identification of diagnostic antigens.

The Netherlands

- ◇ Strain identification of Turkish and Israeli isolates;
- ◇ Optimisation of the polymerase chain reaction (PCR) and use of this technique in epidemiological and vaccination studies;
- ◇ Comparison of the direct agglutination test (DAT) with other immunological techniques;
- ◇ Three meetings of the principal investigators to co-ordinate collaborative research efforts;
- ◇ Training of researchers from participating laboratories in various immunological and molecular biological techniques needed to meet the project goals.

RESULTS

- ⇒ A referral network with all the major hospitals in the Izmir region was established. A total of 51 suspected VL patients and 8 cutaneous leishmaniasis suspects were referred. Diagnosis of VL by several techniques, including parasite culture, microscopic examination of biopsy samples, ELISA, IFAT, DAT and PCR, was compared. Parasites were detected in stained smears from 16/51 VL and all CL suspected cases. All of the VL cases were also positive by DAT. IFAT and DAT appeared to be the most sensitive serological techniques. IFAT titers appeared to decrease more rapidly following treatment than ELISA or DAT titers. An area in the Manisa district, approximately 45 kilometres north-east from Izmir, was chosen as a site for field studies. In Manisa City 527 children, ages 5 to 12, were examined for VL. Eight children showed signs of hepatosplenomegaly and 91 signs of lymphadenopathy; 11 blood samples were positive by either DAT, IFAT or ELISA; 158 samples tested by PCR were all negative. Eighteen dogs from Manisa examined for anti-Leishmania antibodies were negative.
- ⇒ The effect of route and parasite stage on the course of the infection was compared. Dogs inoculated with promastigotes intradermally (ID) developed anti-Leishmania antibodies more rapidly than dogs infected with amastigotes intravenously (IV), but the antibody titers were much higher and remained elevated longer in animals injected IV. Moderate clinical signs of disease

were only found in dogs infected with amastigotes IV. Three to five months' post-infection antigens specific proliferation of peripheral blood mononuclear cells (PBMC) were found in 3/5 dogs inoculated ID with promastigotes. Six dogs previously inoculated IV, four with promastigotes and two with amastigotes, were rechallenged by inoculation IV with amastigotes. From the results of this study it appears that one infection with promastigotes IV does not impact protective immunity to dogs against a second challenge.

- ⇒ The antigens' gp63, dp72, gp70 and crude lysates were used in skin testing in infected dogs. All of the dogs used had been infected, 8-36 months previously, with either amastigotes IV (2 dogs) or promastigotes ID (5 dogs). A healthy, parasite-free dog was used as a negative control. None of the dogs showed a response when injected the first time with pure leishmanial antigens, and only dogs infected with promastigotes ID reacted to the first injection of total parasite lysate. Reaction size appeared to be inversely correlated to the length of time passed between the parasite inoculation and skin testing. Recently infected animals (8-10 months previously) gave strong reactions within 24-48 hours. Dogs infected 25-42 months previously showed either reactions after 72 hours or no reaction at all. Reactions in the second skin test, carried out two weeks later, were stronger and even the negative control dog became positive. All of the amastigote infected dogs were negative on first testing, but gave very strong and rapid skin reactions on retesting. These reactions were much stronger than in those of a dog infected with promastigotes at the same time. All dogs tested a second time with gp63 showed a skin reaction, but only promastigote infected dogs had a reaction to gp70. None of the dogs showed a skin test reaction to dp72.
- ⇒ Investigations into the protection of BALB/c mice by the pure protein dp72 showed that Transfer of the hyperimmune sera and antigen specific T-cells to naive mice demonstrated that the protection of BALB/c mice by the pure protein dp72 is T-cell mediated and not dependent on antibody mediated mechanisms. In vitro depletion experiments demonstrated that CD4+ T-cells alone can mediate protection.
- ⇒ Three different diagnostic methods, DAT, ELISA and Western blotting, for human VL were compared. The ability of the different assays to monitor drug therapy and predict a successful outcome was determined. The DAT and ELISA gave essentially the same results : while changes in the titers became evident only 2-4 months after the initiation of treatment, it took at least 10 months for the antibody titers to return to normal levels. Antibody reactions against two pure proteins, gp70 and dp72, were also monitored in two of the patients by Western blotting. Antibody reactions with these proteins drop to normal levels by four to six months post-treatment. This suggests that pure proteins may be useful in monitoring patient status following therapy.
- ⇒ A genomic expression library for *L. donovani* chagasi was screened using serum from a naturally infected dog. Four clones recognised by the sera were isolated and the inserts were sequenced. Two clones showed good homology with hsp70 and hsp83 of *Leishmania*, one clone with the GeneB/C of *L. major* and one clone showed no homology to any sequence in the data bank. Northern blot hybridisation showed that all four clones are expressed by promastigotes of *L. d. infantum*. All clones were subcloned for high level expression of the polypeptide. The fusion polypeptide of one of the clones was expressed and purified for use in further studies.
- ⇒ Five *Leishmania* isolates from Israel were cultured and typed : 2 isolates were *L.d. donovani*, 1 *L.d. infantum* and 2 *L. tropica*. Fourteen Turkish *Leishmania* isolates obtained from UEGE.DP were cultured and typed : all isolates from VL patients and dogs were typed as *L.d. infantum*, 2 isolates from CL patients were characterised as *L. tropica* and 1 as *L. major*. This last finding is remarkable, since it would be the first finding of *L. major* in this part of Turkey.
- ⇒ The PCR for the detection of *Leishmania* in blood lymph node and bone marrow samples was optimised. By using a different DNA polymerase and employing more PCR cycles, it is now possible to routinely detect 10-100 fg of parasite DNA in a sample; this is equivalent to less than 1 parasite. False-positive results were further reduced by the incorporation of the UNG/dUTP system in the PCR and by the inclusion of more negative control samples.

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PARTNERS

KONINKLIJK INSTITUUT VOOR DE TROPEN
N.H. Swellengrebel Laboratory of Tropical Hygiene
Meibergdreef 39
1105 AZ Amsterdam
The Netherlands

Linda Oskam
Tel.: +31-20-566 54 46
Fax: +31-20-697 18 41

HEBREW UNIVERSITY - HADASSAH MEDICAL SCHOOL
Department of Parasitology
P.O. Box 1172
91010 Jerusalem
Israel

Charles L. Jaffe & Lee Schnur
Tel.: +972-2-42 80 82
Fax: +972-2-78 40 10

EGE UNIVERSITY
Medical Faculty
Department of Parasitology
35100 Bornova
Turkey

Ali Özcel
Tel.: +90-51-39 82 90
Fax: +90-51-88 28 52

INSTITUTO DE HIGIENE E MEDICINA TROPICAL
Rua da Junqueira 96
1300 Lisboa
Portugal

Pedro Abranches
Tel.: +351-1-363 21 41
Fax: +351-1-363 21 05

MOLECULAR EPIDEMIOLOGY OF HEMOGLOBIN, MOLECULAR BIOLOGY OF GLOBIN GENE EXPRESSION AND PREVENTION OF THALASSEMIA

Co-ordinator: University of Cagliari, Cagliari, Italy (Antonio Cao)

OBJECTIVES

- To improve the level of understanding of fundamental biochemical mechanisms that regulate the in vitro expression of globin genes during different phases of postnatal development;
- To contribute to the control and prevention of thalassemia.

ACTIVITIES

- ◇ Collection of data on the occurrence of different DNA-mutations in DNA causing thalassemia and related hemoglobinopathies in the three countries from where participants are included (Italy, Malta & Cyprus);
- ◇ Testing of new-born babies and premarital couples in addition to antenatal maternal and fetal testing;
- ◇ Follow up of probands with a variety of haemoglobin structure abnormalities (including sickle cell disease and fetal Hb variants) or biosynthesis (i.e. the different types of thalassemia) employing state of the art haematology, protein chemistry and molecular biology techniques;
- ◇ Precise documentation of the incidence of different hemoglobinopathies and thalassemias in the populations of Malta, Sardinia and Cyprus including identification of mutations;
- ◇ Genotype-phenotype correlation in the most frequent β -thalassemia mutations (i.e. β^{39} and $\beta^{IVSI-110}$) in the Maltese, Sardinian and Cypriot populations to evaluate possible expression differences due to the ethnic origin;
- ◇ Identification of couples at risk of having progeny with clinically significant hemoglobinopathy or thalassemia;
- ◇ Evaluation of findings in experimental systems (in vitro transfections and in vivo footprinting).

RESULTS

- ⇒ In our studies we have been able to define the spectrum of β - and α -thalassemia mutations in the three countries participating in this project. This information has been used to set up a strategy for carrier identification and fetal testing of all Mediterranean origin populations. We have also set up the technique to establish the genotype of the oocytes in the mouse, as necessary step to carry out preimplantation diagnosis.
- ⇒ In this part of the study we have identified and described a new β -chain variant and a number of mild β -thalassemia mutations (frameshift at codon 59, IVSII nt 844 (C → G), -92 (C → T). One of these mutations, IVSII nt844 (C → G), is completely silent in the heterozygous state and results in the carrier state phenotype when in homozygosity. The -92 mutation is also a silent mutation, while frameshift at codon 59 is obviously a β^0 -thalassemia mutation.
- ⇒ We have expanded also our knowledge on the correlation between genotype and phenotype in the field of β^0 -thalassemia mutations. On this topic, we have been able to quantify the residual output of β -thalassemia gene affected by a β -thalassemia mutation by quantifying the HbA level in compound heterozygosity for the β^0 -thalassemia mutation and a Hb variant.
- ⇒ We have studied the in vitro expression of the different β -thalassemia mutations to date described affecting the proximal and distal CAAC box and found a defined correlation with their phenotype effect in vivo.
- ⇒ Finally, we have, independently from others, cloned the Erythroid Kruppel like Factor (EKLF) gene, which codes for an essential transcription factor for the expression of the β -globin gene and mapped to chromosome 19p13.2-p13.3. We have also identified two polymorphisms of the EKLF gene, which may be useful for further linkage analysis between this gene and different β -thalassemia carriers unlinked to the β -globin cluster.

FOLLOW-UP

Our planning for the next year is as follows:

- Start in our countries preimplantation diagnosis in those couples who already had a number of abortion and who, after counselling, are willing to carry out this approach in order to have healthy children without the risk of pregnancy interruption;
- Try to set up on large scale the technique recently developed for making fetal diagnosis by analysis of fetal cells in maternal circulation. This technique is based on PCR amplification of the DNA from single fetal cell recovered after identification by ϵ or γ globin chain staining in slides prepared from maternal blood;
- Definition of the reasons for the occurrence in some cases of a mild phenotype in patients homozygous for different β^0 -thalassemia. In this project we are planning to carry out whole genome analysis with polymorphic microsatellites spanning the human chromosomes in patients with mild different β -thalassemia versus patients with thalassemia major carrying the same mutation and originating from the same region;
- Definition of the molecular defect in cases of different β -thalassemia not linked to the β -globin gene. In case of negative results we plan whole genome linkage analysis as before.

These studies need a large number of patients from different countries, that will be available by a collaborative Mediterranean project.

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PARTNERS

UNIVERSITY OF CAGLIARI

Istituto di Clinica e Biologia Dell "Eta Evolutiva"
Via Jenner S/N
09121 Cagliari
Italy

Antonio Cao
Tel.: +39-70-50 33 41
Fax: +39-70-50 36 96

HOSPITAL ARCHBISHOP MAKARIOS III

Cyprus Thalassaemia Centre
Acropolis Avenue
138 Nicosia
Cyprus

Mike Angastiniotis
Tel.: +357-2-49 36 00
Fax: +357-2-31 57 39

UNIVERSITY OF MALTA

Department of Physiology and Biochemistry
Msida
Malta

Alex Felice
Tel.: +356-31 43 92
Fax: +356-31 05 77

COMPARATIVE EVALUATION OF CLASSICAL AND MOLECULAR TOOLS FOR THE DIAGNOSIS AND FOR ECO-EPIDEMIOLOGICAL INVESTIGATIONS OF LEISHMANIASIS

Co-ordinator: Institut Pasteur de Tunis, Tunis-Belvédère, Tunisie (Riadh Ben-Ismael)

OBJECTIVES

- To develop a DNA probe specific for *Leishmania infantum*; to measure its general efficiency for diagnosis of human and canine leishmaniasis (in particular during disease development in the dog), using the dot blot technique; to evaluate the results with those obtained by non-molecular, classical methods;
- To evaluate the comparative sensitivities and specificities of kDNA probes for the identification of *L. infantum*;
- To measure cytokine production by PBMC in response to parasite antigen to understand the TH1 versus TH2 balance in clinical groups as a function of age;
- To measure the intrinsic validity and extrinsic validity parameters for DNA probes specific for *Leishmania major*, as used in the dot blot technique for the diagnosis of zoonotic cutaneous leishmaniasis in man; and, to compare the results with the estimates of these parameters for classical techniques (direct examination, culture, inoculation of animals, serology);
- To evaluate squash blotting, ELISA and classical dissection techniques for the detection of *Leishmania* in the phlebotomine vector, for the pairs *Phlebotomus papatasi/Leishmania major*, *P. perniciosus/Leishmania infantum* and *P. perfiliewi/L. infantum*.

ACTIVITIES

- ◇ Phlebotomine sandflies necessary for the various molecular tasks were successfully collected from different regions of Tunisia;
- ◇ For the evaluation of the sensitivity and specificity of probes for dot-blotting promastigotes of *L. infantum* 3E9/HaeIII-12 and 3B8/HaeIII-2, the two mini-circle kinetoplast (k) DNA probes were tested using 49 promastigote preparations, including 7 different species of *Leishmania* and *Sauroleishmania tarentolae* originating from several Old World countries. Promastigotes were cultured in RPMI medium with foetal calf serum. Serial dilutions of 10^6 , 10^5 , 10^4 and 10^3 promastigotes were applied to replicate nylon DNA transfer membranes using a vacuum blot apparatus;
- ◇ For the evaluation of the diagnostic potential of probes specific for *L. infantum* infecting man and dog and comparison with classical techniques' samples were collected from 32 human cases and 152 dogs;
- ◇ In a basic health care centre in the Sidi Bouzid focus, 54 patients were selected as having ZCL on a clinical basis (epidemiological context, clinical presentation and site of lesion, duration of lesion for more than 3 weeks, inefficacy of antibiotics). The patient sample constituted 25 males (43%) and 29 females (57%) varying in age from 2 to 81 years old. The number of lesions per patient varied from 1 to 11 (average = 3). 30 patients had already started a course of Glucantime treatment;
- ◇ Samples were taken from each lesion for :
 - a direct dermal smear on a microscope slide was coloured by the May-Gunwald-Giemsa technique and read with an optic microscope at x1000 magnification (54 patients);
 - a culture was made in NNN medium with Penicillin G (800 U/ml rabbit blood and Streptomycin (500mg/ml rabbit blood) (49 patients);
 - 3 to 6 drops of dermal fluid (ca. 5ml each) were spotted on to a Genescreen Plus nylon DNA transfer membrane; after the normal denaturation and neutralisation processes, each membrane

was treated with proteinase K (100 mg/ml in 0.1M Tris-HCl pH 7.5) for 1 hour at 37°C (54 patients);

•dermal fluid was inoculated in to the hind footpads of a Balb/c mouse.

A blood sample was taken for ELISA and IFAT tests.

RESULTS

- ⇒ In general, serological tests were the most sensitive (73% for IFAT, 94.6%% for ELISA), followed by the Balb/c inoculation (48.2%):
- Balb/c mice (MI): the lesions appeared from 4 to 9 weeks (max. 67 days);
 - NNN cultures (C): 12 were positive within the first week and 3 in the second week of subcloning. Only one of the samples giving a positive culture was negative in Balb/c mice;
 - Direct smear (DS): of the 26 samples positive in Balb/c mice only 12 (46.15%) were also positive by direct smear, but 4 smears were positive when the Balb/c results were negative;
 - ELISA: soluble antigens were prepared by the classical technique from a Tunisian strain of *L. major* (MPSA/TN/86/RON44; zymodeme MON-25/LON-1) and uses at 1/500 dilution; sera were diluted at 1/100; positive and negative controls were used on each ELISA plate; spectrophotometry reading was at 420 nm;
 - IFAT : the same strain of *L. major* was used; sera were diluted 1/50 in PBS, and the fixed antibodies were revealed with anti-human antiglobulins labelled with fluorescein;
 - Dot blots: samples from 54 patients were hybridised with the 85 bp universal probe (SU), the 450 bp TaqI probe (TaqI) and the 250 bp AvaII probe (AvaII) (see section B.2.2 of first technical report). Autoradiographic exposure was set at one week for the first two probes and two weeks for the third probe. The presence of *Leishmania* parasites in the samples was confirmed by at least one direct test. The variable number of dot-blot samples (3-6) made for each lesion was shown to be adequate, even though the intensity of the autoradiographic signal varied both within and among lesion samples.
- ⇒ However, only some of the patients' lesions had demonstrable parasites, and so the evaluation of the various indirect techniques can be better estimated after selection of the positive patient sample. This "gold standard" was the positivity demonstrated by at least one of the three classical techniques that allow visualisation of the parasite, namely direct smear, culture and Balb/c inoculation. The gold-standard sample is constituted by 30 patients among the total of 54. For this sample the dot blot sensitivity was 46.7% (14/30) or 40.0% (12/30) depending on the probe. The 24 patients not showing any parasites in their lesions, when assessed by the three gold-standard tests, constituted the negative control sample that permitted calculation of the specificity of each of the indirect tests. The specificity was 100% for all techniques except for ELISA and IFAT.
- ⇒ Probe 3E9/HaeIII-12 (= 3E9) can be considered as an excellent tool for the specific identification of *L. infantum* in Tunisia (and in the Mediterranean Basin in the absence of *L. donovani*) when 10^5 or fewer promastigotes are used: then, both the specificity and predictive value of the positive result were 100%. As with most diagnostic tools, there is a trade-off between specificity and sensitivity, with a loading of 10^5 promastigotes being optimal.
- ⇒ Probe 3B8/HaeIII-2 (=3B8) was assessed to be less efficient than 3E9, its sensitivity being one order less and the predictive value of a negative result never reaching 100%.

Achievements

- ⇒ Measurement of the intrinsic validity parameters for DNA probes specific for *L. major*, as used in the dot blot technique for the diagnosis of ZCL in man, and comparison of the results with the estimates of these parameters for classical techniques (direct examination, culture, inoculation of animals, serology).
- ⇒ Using the KDNA probes previously isolated, the dot-blot DNA test was shown to be 100% specific, as were the three direct visualisation tests (direct smear, Balb/c mouse inoculation, NNN culture). The serological tests (IFAT, ELISA) showed significantly lower specificity but higher sensitivity. Inoculation of Balb/c mice proved to be the test with highest "global efficiency". The

dot blot test is, therefore, a useful addition to the battery of tests now available for diagnosis of ZCL due to *L. major*, performing as well as all tests except inoculation of Balb/c mice and, unlike the serological tests used, having 100% predictive value of a positive result.

- ⇒ Confirmation was obtained of the diagnostic value of a ribosomal IGS DNA probe for the identification in different regions of Tunisia of *P. papatasi*, the only known vector of *L. major* in north Africa. Development was started of DNA probes specific for the most abundant and widespread Tunisian vectors of *L. infantum*: restriction mapping, subcloning and sequencing permitted the identification of DNA fragments and internal repeat sequences that showed marked specificity for *P. perniciosus* and *P. perfiliewi*.

PARTNERS

INSTITUT PASTEUR DE TUNIS

Laboratoire d'Epidémiologie et d'Ecologie Parasitaire
B.P. 74
1002 Tunis-Belvédère
Tunisia

Riadh Ben-Ismael
Tel.: +216-1-79 24 29
Fax: +216-1-79 18 33

BRITISH MUSEUM OF NATURAL HISTORY

Division of Medical & Veterinary Entomology
Biochemistry Department
Cromwell Road
London SW7 5BD
United Kingdom

Paul D. Ready
Tel.: +44-171-938 93 56 / 87 47
Fax: +44-171-938 89 37

INSTITUTO DE HIGIENE E MEDICINA TROPICAL

Departamento de Disciplina de Protozoologia
Rua da Junqueira 96
1300 Lisboa
Portugal

Pedro Abranches
Tel.: +351-1-363 21 41
Fax: +351-1-363 21 05

IMPERIAL COLLEGE OF SCIENCE, TECHNOLOGY & MEDICINE

Department of Biology
London SW7 2AZ
United Kingdom

Deborah Smith
Tel.: +44-171-594 52 82

**MOLECULAR MECHANISMS OF GENETIC VARIABILITY IN THE EXPRESSION
OF MAJOR HEMOGLOBINOPATHIES : PROGNOSTIC VALUE OF GENETIC
FACTORS AND THERAPEUTIC PERSPECTIVES**

Co-ordinator: Hôpital Robert Debré, Paris, France (Rajagoal Krishnamoorthy)

OBJECTIVES

- To understand the genetic and molecular bases of the variable phenotypic expression of major hemoglobinopathies and in particular sickle cell disease (SCD);
- To rationalise the therapeutic induction of foetal haemoglobin (HbF) in hemoglobinopathies by pharmacological means.

ACTIVITIES

- ◇ To appreciate :
 - the feasibility of a comprehensive program on SCD based upon neonatal screening, parental education and early medical follow-up in an African setting;
 - the impact of this program on the related morbidity and mortality (natural history).
- ◇ Epidemiology of G6PD deficiency and its interaction with SCD;
- ◇ Comparison of severe form of African sticklers with mild ones from India to assess the prognostic value of associated genetic modifiers (genetic polymorphism of the critical regulatory DNA elements of the beta-globin gene cluster, alpha-globin gene status, genetic propensity to express HbF);
- ◇ Hydroxyurea treatment in paediatric SCD patients and follow up;
- ◇ Recruitment of families for studying genetic modifier involved in the genetic control of HbF expression (F-cell genetics).

RESULTS

- ⇒ In the social context of Benin, an affected new-born with SCD is rarely retrieved for regular clinical follow-up. We circumvented this difficulty by focusing our attention on identifying pregnancies' at-risk for giving birth to a child with SCD and by providing information and counselling. A total of 2300 pregnancies was followed : 5% of the pregnancies with SCD were managed clinically. 1028 new-borns were available for neonatal screening and 12% had SCD with 64% traits. 91 new-borns entered the clinical surveillance programme (75% compliance of the parents) which included prophylaxis against infections. Among them 25% had an associated G6PDH deficiency (G6PDA-).
- ⇒ Effect of active prenatal management on pregnancy outcome in sickle cell disease (42SS and 66 SC) in an African (Benin) setting was evaluated and revealed that the SCD-related events are few and mild and that the reported poor outcome of pregnancy in SCD in Africa reflects the inadequate management rather than the intrinsic severity of the disease. The two maternal deaths observed were cases of SC rather than SS and their relatively benign course before pregnancy make them less-concerned and less-compliant during pregnancy and are prone to harmful complications in late pregnancy.

- ⇒ Contribution to the culture of continuous learning : participation to the first regional specialised course of haematology on SCD held at Cotonou BENIN (12-16 Dec. 1995) with the aim of disseminating the state of the art of biological and clinical aspects of SCD to trainees from 11 different African countries. A "SCD network" among these countries was formulated.
- ⇒ The prevalence of G6PD deficiency by "spot test" in Mauritius is 5.5% (school and blood donor screening n = 1435). Molecular analysis (PCR RFLP, SSCP, Nucleotide sequencing) confirmed the phenotype data but also revealed the nature of mutant alleles (G6PD Orissa, Kerala Kalyan, Med-Union, Hammersmith, A-) consistent with the ancestral population input. The allele G6PD Orissa emerged as the major deficient variant among the Indo-Mauritanans. We could not observe SCD in association with G6PD deficiency in this population. More SCD cases need to be screened. Transfer of knowledge and know-how was extremely efficient and a specialised centre for hemoglobinopathies was set up and now functions autonomously.
- ⇒ Extensive comparison of regulatory region polymorphisms of the beta-locus in Indian and different African sickle cell traits (taking into account the α globin gene status) revealed that the sickle cell gene from India has intrinsic thalassemic characteristics with resulting reduced expression of HbS which would contribute along with elevated HbF expression to the attenuated form of the disease in India as compared to severe form in Africa.
- ⇒ A large three generation family consisting of 60 members with 16 presenting a α -globin gene cluster dependent HPFH (moderate increase in HbF in the basal state with further increase in response to anaemic stress) from Algeria was characterized at the molecular level and found to have a mutation in the distal CCAAT box of the G-gamma globin gene and the HPFH was named « G-gamma-beta+ Algerian HPFH ». This variant stresses the contribution of the distal CCAAT box in the developmental regulation of HbF.
- ⇒ Clinical trial of hydroxyurea (HU) treatment for the past 4-years of the first generation African SCD children followed at Paris (21 males and 8 females, aged range : 4-19 years) studied for cellular and molecular response revealed :
 - an excellent compliance;
 - all were "responders" in terms of increase (1-5 to 16-fold) in HbF except one with variable delay (6 to 24 months) ;
 - SCD with "Senegal" haplotype had higher increment in HbF than others;
 - absence of HU dose – dependence, age and gender in HbF increase (both F cell and F/F cell) ;
 - beneficial affect of HU (in terms of hospitalisation for vaso-occlusive crisis or acute thoracic syndrome/patient-year is not limited to increment to HbF alone;
 Correction of iron deficiency, commonly observed during HU treatment, caused increment in HbF. In conclusion, HU treatment appears as an efficient cost-effective alternative for situations where exchange transfusion was the rule (excepting strokes) and thus avoiding transfusion-associated risks.
- ⇒ Studies of linked (beta - globin gene cluster polymorphism) and unlinked loci (prothrombin, factor V, Angiotensin converting enzyme, Angiotensinogen, Renin, Mannose binding protein, Cystathione beta synthase, Methylene tetrahydrofolate reductase) failed to reveal any epistatic effect of these loci on the acute complications of SCD excepting angiotensinogen gene polymorphism. Ongoing studies must confirm this finding.
- ⇒ During this study we encountered an exceptional case with a novel sickle cell syndrome in heterozygous state (HbS Oman) which summarises the effect of the two (cis) linked mutations affecting the volume and shape of the red cell in an atypical manner.HU caused reduction in serum iron, supplementation of which, further increased the HbF level all leading to the conclusion that UH treatment appears as an efficient cost-effective alternative for situations where exchange transfusion was the role (excepting strokes) and thus avoiding transfusion-associated risks.

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PARTNERS

HOPITAL ROBERT DEBRÉ
INSERM U120
Pharmacologie du Développement
Boulevard Sérurier 48
75935 Paris Cedex 19
France

Rajagoal Krishnamoorthy
Tel.: +33-1-40 03 19 01
Fax: +33-1-40 03 19 25

HOPITAL ROBERT DEBRÉ
Biochimie Génétique
Boulevard Sérurier 48
75935 Paris Cedex 19
France

Jacques Elion
Tel.: +33-1-40 03 23 39
Fax: +33-1-40 03 20 20

HOPITAL TENON
Laboratoire d'Hématologie
Assistance Publique
Rue de la Chine 4
75970 Paris Cedex 20
France

Robert Girot
Tel.: +33-1-40 30 61 97
Fax: +33-1-45 67 91 56

HAMMERSMITH HOSPITAL
Department of Haematology
Ducanne Road
London W12 ONN
United Kingdom

Lucio Luzzatto
Tel.: +44-181-740 32 34
Fax: +44-181-472 93 35

CENTRE MUSTAPHA
Centre de Transfusion
16000 Alger
Algeria

HOSPITALO-UNIVERSITAIRE

Khadoudja Nafa
Tel.: +213-1-21 65 36 42

SSR CENTRE
Centre de Recherches Médicales
Moka
Mauritius

Navarathnam Kotea
Tel.: +230-454 64 01

CENTRALE UNIVERSITAIRE DES SCIENCES & SANTÉ
Département d'Entomologie Médicale
B.P. 288
Yaounde
Cameroon

Jean-Marie Bodo
Tel.: +237-23 22 32
Fax: +237-23 00 61

CENTRE NATIONAL HOSPITALIER ET UNIVERSITAIRE
Faculté des Sciences de la Santé
Clinique des Maladies du Sang
B.P. 188
Cotonou
Benin

Cherif Rahimy
Tel.: +229-30 09 38
Fax: +229-31 38 09

**PHOTOTHERAPEUTIC POTENTIAL OF CELL-DIRECTED (BACTERIO)
CHLOROPHYLL CONJUGATES**

Co-ordinator: Universität München, München, Germany (Hugo Scheer)

OBJECTIVES

- Modification of natural Chlorophylls and Bacteriochlorophylls with improved phototoxicity;
- Characterisation and engineering of their excited states photophysics and photochemistry;
- Uptake of photosensitising porphyrins into melanoma cells in cell culture. Choosing an adequate photosensitise and adequate irradiation conditions to kill melanoma cells;
- Site selective substitution of porphyrins to form stable inclusion complexes with dimeric cyclodextrins in order to enhance tumour selectivity;
- Conjugation of (bacterio) chlorophyll derivatives to amino acid and targeting peptides or proteins;
- Proof of selectivity in tumour models (microspheres in cell culture, microtumours on growing chicken embryos, heterotransplants of human tumours in nude mice).

ACTIVITIES

- ◇ The work is done in close co-operation between three groups in Germany, one group in the UK and two groups in Israel;
- ◇ Melanoma cells used in these studies are M2R mouse melanoma. A 375 amelanotic human melanoma and SKMEC 25 melanotic human melanoma;
- ◇ Uptake studies concentrate on two chlorophyll derived photosensitisers: Pd-bacteriopheophorbide ethyl ester and bacteriochlorophyll serine;
- ◇ Introduction of tert.butylphenoxy - and tert. butyl benzoic acid groups at position 3¹ of the photosensitising pigments and conjugation to aminoacid derivatives;
- ◇ Construction of dimeric β -cyclodextrins including biotinyl side groups and hydroxypropylation in order to enhance solubility in human blood plasma;
- ◇ Determination of stability constants of the drug-dicyclodextrin complexes;
- ◇ Proof of selectivity on tumour models using the biotin-avidin accumulation systems;
- ◇ Topical treatment of human tumours in nude mice.

RESULTS

- ⇒ Uptake studies showed concentration of the applied drugs up to 10^8 to 10^{10} molecules of the photosensitisers per tumour cell during 2-5 minutes of incubation in cell suspension. These numbers are extremely high in melanotic melanomas in comparison to non-melanotic tumours and point to a special uptake mechanism now under investigation.
- ⇒ Just very low fluence rates lead to cell death (LD 90 values below 1 J/cm² at the absorption maxima of the applied drugs). Laser diode arrays are constructed suitable for clinical application of the drugs.
- ⇒ Chemical modification of the drugs to stabilise inclusion into dimeric cyclodextrins yielded a 9000 fold better stability as compared with the complexes obtained with monomeric methyl β -cyclodextrin.
- ⇒ Spacer structure holding together the β -cyclodextrin moieties of β -cyclodextrin dimers in 6,6' or 2,2' positions was varied in length to adapt the dimers to the drugs to be complexed. The stability constants amount up to 10^7 (l/mol).
- ⇒ These complexes are stable enough to separate the drugs from the lipoprotein system in human plasma. The attachment of biotin and hydroxypropyl groups is now under investigation.
- ⇒ First animal experiments showed high yield of recovery from solid tumours after topical treatment. Pharmacokinetics were determined and treatment followed by magnetic resonance imaging.

PARTNERS

UNIVERSITÄT MÜNCHEN

Botanisches Institut
Menzinger Straße 67
80638 München
Germany

Hugo Scheer
Tel.: +49-89-17861-295
Fax: +49-89-17861-185
E-mail: scheer-h@botanik.biologie.uni.muenchen.de

UNIVERSITÄT DÜSSELDORF

Institut für Lasermedizin
Universitätstraße 1
40226 Düsseldorf
Germany

Joerg G. Moser
Tel.: +49-211-811-2608, -2623
Fax: +49-211-811-2631
E-mail: moserjg@uni-duesseldorf.de

UNIVERSITY OF MANCHESTER

Chemistry Department
Oxford Road
Manchester M13 9PL
United Kingdom

Anthony Gorman
Tel.: +44-161-275 46 14
Fax: +44-161-275 45 98
E-mail: E.j.thomas@man.ac.uk

MAX-BORN-INSTITUT FÜR NICHTLINEARE OPTIK UND KURZZEITSPEKTROSKOPIE

Rudower Chaussee 6
12489 Berlin
Germany

Dieter Leupold
Tel.: +49-30-6392-1340
Fax: +49-30-6392-1359
E-mail: leupold@mbi.fta-berlin.de

THE WEIZMANN INSTITUTE OF SCIENCE

Department of Biological Regulation
76100 Rehovot
Israel

Yoram Salomon
Tel.: +972-8-934 39 30
Fax: +972-8-934 41 16
E-mail: lhsalmon@wiccmail.weizmann.ac.il

THE WEIZMANN INSTITUTE OF SCIENCE

Department of Biochemistry
76100 Rehovot
Israel

Avigdor Scherz
Tel.: +972-8-948 23 36
Fax: +972-8-934 41 18
E-mail: Bcscherz@wiccmail.weizmann.ac.il

**MOLECULAR GENETICS OF APOE, ACE & AGT & THEIR EFFECTS ON
CARDIOVASCULAR DISEASE & CAROTID STENOSIS**

**Co-ordinator: Imperial College of Science, Technology and Medicine, London, United Kingdom
(Andrew Nicolaides)**

OBJECTIVES

This three year program conducted molecular genetic studies on patients with coronary artery disease, carotid/peripheral artery disease, and essential hypertension. The patients were recruited from four countries: England, Israel, Greece and Cyprus.

The specific objectives of the study were:

- Identify and collect blood specimens from individuals with cardiovascular diseases (coronary artery disease, carotid/peripheral artery disease) and essential hypertension and record the family histories of these individuals,
- study the association of gene polymorphisms of: (a) Apolipoprotein E (APOE) and Angiotensin Converting Enzyme (ACE) in subjects with cardiovascular diseases and hypertension, (b) angiotensinogen (AGT) T174M polymorphism in patients with essential hypertension,
- investigate the relationship between the gene polymorphisms of APOE and ACE with different classes of arterial wall appearance (Ultrasonic arterial score), (4) evaluate the relevance of ethnic differences in the effects of these genes on cardiovascular diseases.

The long-term objectives of the study are to enhance cardiovascular disease prevention programs and develop rapid, non-invasive, inexpensive, and safe strategies for the early identification of those individuals that may be at risk for developing premature cardiovascular diseases. In addition we would like to direct our combined efforts in designing appropriate tests for the identification of those individuals that may receive the most benefit from preventive drug therapies and programs.

ACTIVITIES:

The study was initiated in June 1996 and is due to be concluded at the end of October 1998. During this period the teams screened 834 individuals with coronary artery disease. Coronary artery disease was determined by (1) positive for myocardial ischemia exercise tolerance test and (2) coronary angiography. The angiography studies included records on the exact place and percentage of stenosis and ejection fraction values. Approximately 450 individuals undergone carotid artery examination by ultrasound Doppler scanning. The ultra sound screening included the measurements of plaques, intima-media thickness, and ultrasonic score (UBS). Predisposing factors were also noted for all the individuals of the study including the values of certain biochemical tests. Genetic studies concerning patients with essential hypertension were carried out on 156 individuals that have been included in the study after satisfying the following criteria: (a) onset of hypertension before the age of 60, (b) evidence of established hypertension defined by chronically treated hypertension or by diastolic blood pressure (BP) greater than 96 mm Hg at two consecutive visits for those with no antihypertensive treatment, (c) absence of secondary hypertension, (d) no exogenous factors that could influence BP. Israel, Greece, and Cyprus each contributed blood specimens from individuals with coronary artery disease. Also, Greece and Cyprus contributed blood specimens from individuals with blood pressure. Finally, England and Cyprus contributed blood specimens from those individuals that have undergone carotid artery examinations by ultrasonography. All blood specimens were collected after informed consent. Genetic analysis of the APOE, ACE, and AGT (T174M) gene polymorphisms were carried out using the polymerase chain reaction and oligonucleotides specific for each genetic locus tested.

RESULTS SO FAR

- ⇒ When the APOE genotype relative frequencies of coronary artery disease patients from Israel, Greece, and Cyprus were compared significant differences were observed among these three

study populations. Higher relative frequencies of APOE-2/3 and APOE-3/4 genotypes were noted in the group of patients from Israel when compared with the other two populations.

- ⇒ Significant differences among the three groups of cardiovascular disease patients (Israel, Greece, and Cyprus) were also observed when the ACE genotype relative frequencies were compared among these three group categories. The differences noted are primarily due to the Israel group that exhibited higher number of ACE-II and low numbers of ACE-DI individuals among those tested. The Cyprus group of patients demonstrated a higher ACE-DD frequency than the other groups from Israel and Greece.
- ⇒ APOE and ACE allele relative frequencies were also compared among the coronary artery disease patients from Israel, Greece, and Cyprus. Significant differences were observed primarily for the APOE-4 allele and the relative frequencies of ACE-D and ACE-I alleles among the three populations.
- ⇒ Comparisons carried out between "normal" (those individuals that had undergone coronary angiography but demonstrated no apparent stenosis in their arteries) individuals demonstrated no significant differences of APOE and ACE genotypes and alleles among the groups from Israel, Greece and Cyprus.
- ⇒ Blood specimens from individuals (from Cyprus and Greece) with hypertension have been genotyped for the AGT T174M polymorphism. When hypertensive individuals from Cyprus were compared with a random and a control group of individuals from Cyprus, no differences were observed among the relative frequency distributions of the genotypes TT, TM, and MM. When the T174M AGT polymorphism was studied in Greek hypertensive individuals and a control group of individuals from Greece, significant differences were observed. Significant differences, in the genotype relative frequency distributions of T174M AGT polymorphism, were also observed when the hypertensive individuals from Greece and Cyprus were compared. The observed differences were primarily due to the higher number of individuals exhibiting the MM genotype in the hypertensive group of patients from Greece.
- ⇒ The United Kingdom team has recently completed the screening of a large number of individuals (> 400 individuals) that have undergone carotid assessment by ultrasound. The blood specimens have been forwarded recently to Cyprus for molecular genotyping. At the time of preparation of this report this analysis was not completed. Therefore no conclusions may be drawn yet from these part of the study.

FOLLOW UP:

- ▶ Complete the genotyping of all the blood specimens that have been collected from individuals that have undergone arterial atherosclerosis assessment by ultrasound.
- ▶ Preparation and publication of results.

PUBLICATIONS

Effect of the APOE and ACE Genes on the Site of Atherosclerotic Lesions. CARILOU MA, MANOLI P, KOKKOFITOU A, KARAGRIGORIOU A, CONSTANTINOUC, MINA K AND ANGELIDES N.

Lp(a) levels are strongly associated with Coronary Artery Disease in Cyprus. CARILOU MA, HADJIVASILIOU M, KARAGRIGORIOU A, AVRAAMIDES P, AND ZAMBARTAS C.

Anticipated Publications:

At least three additional papers are expected to be published once the analysis of all the data is completed in November 1998.

PARTNERS

IMPERIAL COLLEGE OF SCIENCE, TECHNOLOGY AND MEDICINE Andrew Nicolaides
Tel.: +44-171-725 62 43
St Mary's Hospital Medical School Fax: +44-171-725 64 16
Irvine Laboratory for Cardiovascular Investigation and Research
10th Floor QEOM Wing
London W2 1NY
United Kingdom

ONASSIS CARDIAC SURGERY CENTRE Denis Cokkinos
Department of Cardiology Tel.: +30-1-930 60 58
Sygrou Avenue 356 Fax: +30-1-930 66 04
176 74 Athens
Greece

TEL AVIV UNIVERSITY Samuel Sclarovsky
Beilinson Medical Centre Tel.: +972-3-937 71 07
Department of Cardiology Fax: +972-3-924 98 50
49100 Petah Tikva
Israel

CYPRUS INSTITUTE OF NEUROLOGY AND GENETICS Marios Cariolou
Department of Molecular Genetics Tel.: +357-2-35 86 00
P.O. Box 3462 Fax: +357-2-35 82 37 / 8
1683 Nicosia
Cyprus

DOPAMINERGIC INVOLVEMENT IN LATENT INHIBITION AS AN ANIMAL MODEL OF ATTENTIONAL DYSFUNCTION IN SCHIZOPHRENIA

Co-ordinator: University of London, London, United Kingdom (Jeffrey A. Gray)

OBJECTIVES

- The central aim of the research was to identify brain areas in which alterations in dopaminergic function accompany and influence the phenomenon of latent inhibition (LI), i.e. weakened or retarded classical conditioning consequent upon unreinforced preexposure of a to-be-conditioned stimulus (CS).
- The guiding hypothesis was that LI is disrupted by increased, and enhanced by decreased, dopaminergic transmission in the nucleus accumbens.
- LI involves three conceptually distinct experimental phases: preexposure (CS preexposed or not depending upon the experimental condition), conditioning, and test of the conditioned response.
- A further hypothesis was that the influence upon LI of manipulations of dopaminergic function in the nucleus accumbens would be specific to the phase of conditioning.
- These hypotheses are set out in Gray et al. (1995).

ACTIVITIES

- ◇ Two main approaches were adopted.
 - In psychopharmacological experiments drugs were administered systemically and/or intracerebrally (directly into the nucleus accumbens) and their effects on LI established.
 - In experiments using intracerebral microdialysis, with the probes implanted in the nucleus accumbens, changes in extracellular levels of dopamine and dopamine metabolites were measured during behaviour in the LI paradigm.
- ◇ The main purpose of the grant to the London laboratory was to facilitate collaboration with Dr Ina Weiner's group in Tel Aviv. Professor Gray visited Tel Aviv twice during the tenure of the grant, and Dr Weiner visited London once. The principal results arising from the collaboration have been published in brief in two major reviews: Gray et al. (1995), which was jointly authored by the two groups (and also by Dr J. N. P. Rawlins' group in Oxford); and Gray et al. (1997), which is the published version of a paper presented at a symposium ('Basal ganglia-thalamocortical circuits and psychoneuropathology') jointly organised by Dr Weiner and Professor Gray at the 6th World Congress of Biological Psychiatry held in Nice, France, in June 1997. In addition, a theoretical paper based in part upon the results obtained in the experimental programme was presented at a conference in Montreal (Gray, in press). During the tenure of the grant, the London group was joined by Dr Paula Moran, on a Fellowship from the European Union. Detailed reports of the experimental results are currently in preparation.
- ◇ Experimental Details

Behaviour

The experiments were carried out on male Sprague-Dawley rats, weighing 250-275 g. Animals were housed from 2-6 per cage (in different experiments), under controlled temperature, lighting and humidity. They were given ad lib food and water for at least a week before starting experiments. We used our standard LI procedure based on conditioned suppression of licking for water by a CS associated with footshock, as fully described in Joseph MH et al. (1993) [Psychopharmacology, 110, 187-192], Peters SL & Joseph MH (1993) [Behav. Pharmacol. 4, 183-186] and Warburton EC et al. (1994) [Psychopharmacology, 114, 657-664]. In experiments in which conditioned suppression was rather high, the test was repeated on six successive days (without any further conditioning or presentation of shock) in order to determine the rates of extinction of the conditioned response.

Surgery

Stereotaxic surgery took place under equithesin or pentobarbitone anaesthesia at least 1 week after the animals arrived in the laboratory. For some experiments, guide cannulae were bilaterally implanted in the nucleus accumbens, for subsequent intracerebral drug administration in the waking state. For others, guides were implanted into the same structure for subsequent insertion of dialysis probes and measurement, by high-pressure liquid chromatography, of extracellular levels of dopamine and dopamine metabolites. Following surgery, animals were singly housed. After recovery (minimum, one week) LI was determined as above, including appropriate drug or vehicle treatment as indicated below.

Drug administration

Intracerebral infusions. The non-specific dopamine receptor antagonist, haloperidol, 5 mg, was taken up in 50 μ l of glacial acetic acid, diluted with isotonic saline, and neutralised to pH 6.5 at the meter with 2N NaOH to give a final concentration of 0.5 μ g/ μ l. Appropriate groups of animals were infused bilaterally with 1 μ l of vehicle containing 0.5 μ g haloperidol (1 min + 5 min diffusion) or vehicle alone, 15 minutes before the conditioning phase. The indirect dopamine agonist, amphetamine was administered (1 min + 5 min diffusion) as 5 μ g of d-amphetamine sulphate in 1 μ l vehicle.

Systemic injections. Amphetamine was injected intraperitoneally (i.p.) in a dose of 1 mg/kg; the cholinergic agonist, nicotine, subcutaneously in a dose of 0.6 mg/kg; and the dopamine receptor antagonists i.p. as follows: haloperidol in a dose of 0.5 mg/kg for blocking the effects of amphetamine and 0.1 mg/kg for potentiation of LI, SCH23390 (a dopamine D1 receptor antagonist) in a dose of 10-20 μ g/kg, and raclopride (a D2 receptor antagonist) in a dose of 1-2 mg/kg.

MAJOR RESULTS

- ⇒ Systemic administration of nicotine just prior to the conditioning phase abolished LI, as previously reported by our group [Joseph et al., 1993, *Psychopharmacology*, 110, 187-192]. This effect was reversed by concomitant systemic administration of either the D1 or the D2 dopamine receptor antagonist employed (Joseph et al., in preparation a). This result confirms the hypothesis that nicotine disrupts LI in virtue of its capacity to cause dopamine release, and indicates that both principal families of dopamine receptors are involved in the effect of such dopamine release upon LI.
- ⇒ Intra-accumbens administration of haloperidol just prior to conditioning, using a number of preexposures (10) that are insufficient to produce LI in untreated animals, caused the appearance of the LI effect as compared to both unoperated and vehicle-injected controls (Joseph et al., in preparation b). This result confirms an earlier finding in our group that permanent destruction of dopaminergic terminals in the nucleus accumbens (by local administration of the catecholamine-specific neurotoxin, 6-hydroxydopamine) similarly potentiates LI, and narrows down this effect to the conditioning phase of the LI paradigm. Together, these results provide strong support for the hypothesis that LI is enhanced by reduced dopaminergic transmission in the nucleus accumbens at the time of conditioning.
- ⇒ Intra-accumbens administration of haloperidol just prior to the time of conditioning blocked the disruptive effect upon LI of systemic nicotine administered at the same time (Joseph et al., in preparation a). This result confirms the hypothesis that the disruption of LI caused by systemic nicotine is due to dopamine release specifically in the nucleus accumbens.
- ⇒ For blockade of LI by systemic amphetamine, it has usually (but see below, point 6) been necessary to administer this drug on two occasions, typically one prior to the preexposure phase and the other prior to the conditioning phase (in our design, 24 hours apart). Using this design we additionally administered haloperidol or vehicle directly into the nucleus accumbens just prior to the time of conditioning, i.e., concomitantly with the second systemic administration of amphetamine. Under these conditions, haloperidol blocked the disruption of LI otherwise caused by systemic amphetamine (Joseph et al., in preparation b). These results are as predicted by our hypotheses in showing that (1) blockade of LI by amphetamine is due to dopamine release specifically in the nucleus accumbens and (2) the critical time for this effect is at conditioning.

- ⇒ In an experiment closely parallel to that described in 4, we substituted for the second systemic administration of amphetamine intra-accumbens amphetamine or vehicle just prior to the conditioning phase. LI was abolished in animals given two systemic administrations of amphetamine (confirming many previous reports) or given amphetamine systemically prior to preexposure and intra-accumbens prior to conditioning, but was preserved in animals given systemic amphetamine prior to preexposure and intra-accumbens vehicle prior to conditioning. These results (Joseph et al., in preparation b) offer further support for the hypothesis that amphetamine blocks LI by virtue of dopamine release specifically in the nucleus accumbens.
- ⇒ The need for two administrations of amphetamine in order to block LI contrasts with the effectiveness of nicotine when given only prior to conditioning. We proposed that this discrepancy may relate to the fact that dopamine release due to systemic nicotine is impulse-dependent (since nicotine acts on cell bodies of the mesolimbic dopaminergic projection located in the ventral segmental area), whereas that due to systemic amphetamine is initially independent of impulse traffic, as shown by the failure of calcium chelation in the nucleus accumbens to influence the measured change in extracellular dopamine levels [Warburton et al., 1996, *Behav. Pharmacol.*, 7, 119-129]. In response to a second administration of amphetamine, 24 hours later, however, there is an increase in the amount of dopamine release provoked in the nucleus accumbens, and this increase is blocked by removal of calcium from the dialysis stream. A second systemic administration of amphetamine may therefore acquire the capacity to block LI because of the impulse-dependent component of accumbens dopamine release that it provokes. In the Warburton et al. (1996) report, it was also observed that by about 45 minutes after a single systemic administration of amphetamine, removal of calcium began to reduce extracellular dopamine levels in the nucleus accumbens. Most previous studies of the effects of amphetamine upon LI have commenced behavioural testing about 15 minutes after drug administration, a time at which Warburton et al. saw no effect of calcium removal upon accumbens dopamine levels. We therefore re-examined this issue by varying the interval between a single systemic administration of amphetamine and the start of the conditioning session. We confirmed previous reports that with a 15-minute interval, LI was unchanged. With a 45-minute interval, however, LI was abolished (Moran et al., in preparation). This result supports the hypotheses that (1) the critical time at which changes in dopaminergic function affect LI is at conditioning and (2) increased dopamine release in the nucleus accumbens disrupts LI only if it reflects impulse traffic in the mesolimbic projection neurones.
- ⇒ We had previously developed methods for using *in vivo* intracerebral microdialysis to measure extracellular transmitter levels in the nucleus accumbens and corpus striatum during our standard LI procedure; and we had reported [Young, AMJ, Joseph, MH & Gray JA, 1993, *Neuroscience*, 54, 5-9] (i) that dopamine levels (and inferentially dopamine release) in the nucleus accumbens (but not in the corpus striatum) show a conditioned response to conditioned stimuli (tone or light) that have been subjected to Pavlovian pairing with an unconditioned stimulus (a foot-shock); and (ii) that this conditioned DA response is subject to LI by preexposure of the conditioned stimulus. During the tenure of the present grant, we have gone on to apply these methods to the case in which the Pavlovian pairing is between two 'neutral' stimuli (tone and light), neither of which is a biological reinforcer or initially causes dopamine release in the nucleus accumbens. Our findings (Young et al., 1998) demonstrate that (i) dopamine levels are increased in the nucleus accumbens during five Pavlovian pairings of two such neutral stimuli; (ii) if the second of these stimuli is then itself paired with a foot-shock unconditioned stimulus, both come to elicit a conditioned dopamine response (the phenomenon of sensory preconditioning, measured at neurotransmitter level); (iii) neither of these responses is seen in the corpus striatum; and (iv) they are also not seen if the relationship between the five presentations of light and five of tone is quasi-random. Thus, dopamine release in the nucleus accumbens appears to depend upon the associative significance of stimuli rather than their capacity to act as biological reinforcers. This result would not be predicted by any existing theory of mesolimbic dopamine function, since these tend to emphasise roles in reward, reinforcement or stress. A novel alternative hypothesis is presented by Gray (in press).

OUTCOME

- ⇒ Overall, the results of these experiments provide very strong support for the hypotheses under test. They establish clearly that increased impulse-dependent dopamine release in the nucleus accumbens at the time of conditioning, even if preexposure has taken place without pharmacological or other intervention, is sufficient to abolish LI; and that decreased dopaminergic transmission in the nucleus accumbens, also limited to the time of conditioning, is able to potentiate LI. They further suggest that the conditioned dopamine release observed in the nucleus accumbens as a result of Pavlovian conditioning does not depend upon the use of a biological reinforcer, but reflects rather the enhanced stimulus salience that arises from the formation of an associative link between any two stimuli.
- ⇒ The implications of these results for the role of dysfunction in the mesolimbic dopaminergic system in schizophrenia and for the neurobiology of consciousness are developed by Gray (in press).

FOLLOW-UP

- ▶ The research programme is continuing with support from The Wellcome Trust. Professor Gray is organising a workshop on schizophrenia for the European Brain and Behaviour Society at which both he and Dr Weiner will present the results of their collaboration.

PUBLICATIONS

- GRAY JA, JOSEPH MH, HEMSLEY DR, YOUNG AMJ, WARBURTON EC, BOULENGUEZ P, GRIGORYAN G A, PETERS SL, RAWLINS JNP, TAIB C-T, YEE BK, CASSADAY H, WEINER I, GAL G, GUSAK O, JOEL D, SHADACH E, SHALEV U, TARRASCH R AND FELDON J. (1995). The role of mesolimbic dopaminergic and retrohippocampal afferents to the nucleus accumbens in latent inhibition: implications for schizophrenia. *Behavioural Brain Research*, 71, 19-31.
- GRAY JA, MORAN PM, GRIGORYAN GA, PETERS SL, YOUNG AMJ & JOSEPH MH (1997). Latent inhibition: the nucleus accumbens connection revisited. *Behavioural Brain Research*, 88, 27-34.
- YOUNG AMJ, AHIER RG, UPTON RL, JOSEPH MH & GRAY JA (1998). Increased extracellular dopamine in the nucleus accumbens of the rat during associative learning of neutral stimuli. *Neuroscience*, 83, 1175-1183.
- GRAY JA (in press). Abnormal contents of consciousness: the transition from automatic to controlled processing. In: *Consciousness* (Eds HH Jasper, L Descarries, VF Castelluci & S Rossignol), Lippincott-Raven, Philadelphia.
- JOSEPH MH, PETERS SL AND GRAY JA (in preparation a) Reversal of nicotine disruption of latent inhibition at conditioning: the role of D1 and D2 receptors.
- JOSEPH MH, PETERS SL, MORAN PM, YOUNG AMJ AND GRAY JA (in preparation b) Modulation of latent inhibition in the rat by altered dopamine transmission in the nucleus accumbens at the time of conditioning.
- MORAN PM, JOSEPH MH AND GRAY JA (in preparation) Disruption of latent inhibition in the rat by amphetamine administered at conditioning only: implications for mechanisms of amphetamine disruption of latent inhibition.

PARTNERS

UNIVERSITY OF LONDON

Institute of Psychiatry
Department of Psychology
De Crespigny Park
Denmark Hill
London SE5 8AF
United Kingdom

Jeffrey Gray
Tel.: +44-171-703 54 11 / 919 32 45
Fax: +44-171-708 34 97

TEL AVIV UNIVERSITY

Department of Psychology
Ramat Aviv
69978 Tel Aviv
Israel

Ina Weiner & Joram Feldon
Tel.: +972-3-640 95 43
Fax: +972-3-640 95 47

3. HEALTH

3.1. Public health

Contract number: IC18-CT98-0352
Contract number: IC18-CT98-0349
Contract number: IC18-CT98-0346
Contract number: TS3-CT92-0144
Numéro de contrat: TS3-CT92-0112
Contract number: TS3-CT92-0088
Contract number: TS3-CT94-0282
Contract number: AVI-CT94-0003
Contract number: AVI-CT93-0011
Numéro de contrat: AVI-CT93-0012
Contract number: AVI2-CT93-031
Contract number: AVI-CT94-0010

3.2. Disease specific

Contract number : IC18-CT98-0367
Contract number : IC18-CT98-0354
Contract number : IC18-CT96-0036
Contract number : IC18-CT95-0004
Contract number : IC18-CT95-0023
Contract number : AVI-CT92-0018
Contract number : AVI-CT93-0008
Contract number : AVI-CT92-0002
Contract number : AVI2-CT93-107
Contract number : AVI-CT93-0014
Contract number : AVI-CT93-0004
Contract number : AVI-CT92-0010
Contract number : AVI-CT92-0003
Numéro de contrat : AVI-CT92-0013
Contract number : AVI-CT92-0009
Contract number : AVI-CT94-0001
Contract number : TS3-CT93-0244
Contract number : TS3-CT93-0253
Contract number : CI1-CT93-0005
Contract number : CI1-CT94-0122
Contract number : CI1-CT94-0126

4. Additional fields of mutual interest

4.1. Information and communication technologies

4.1.1. Contracts on Information and Communication Technologies with partners from Third Mediterranean countries

A EURO MEDITERRANEAN PROJECT FOR THE DEVELOPMENT OF UPGRADED SCIENCE AND ENGINEERING EDUCATION IN SOUTHERN MEDITERRANEAN UNIVERSITIES THROUGH THE USE OF TELEMATICS TECHNOLOGIES

Co-ordinator: United Nations Educational - U.N.E.S.C.O. Cairo, Egypt (Adnan Shihab-Eldin)

OBJECTIVES

The project aims at enabling a number of science and engineering faculty teams from different South Mediterranean (SM) universities to investigate the effectiveness of incorporating telematics (computing and networking technologies) for modernizing the teaching of basic and engineering sciences. The general objectives of the project are three fold:

- To develop, through experimentation, testing and evaluation, and through close support from EU counterpart academics and institutions, a representative set of viable pilot methods for telematics-based teaching and learning which can be analyzed, emulated and built upon by all interested SM universities, especially those with large student population.
- To evaluate, through sustained project-based effort, the effectiveness of incorporating telematics in upgrading the quality and cost-effectiveness of academic offerings in the generally-impooverished SM universities.
- To establish sustainable new channels and modalities of close collaboration between SM and EU science and engineering education and research institutions for the mutual benefit of both and for assisting in the creation of a common Mediterranean information society.

ACTIVITIES

Research investigations involve the development of eight courses, in the form of *pilot sub-projects*, in basic sciences and engineering. These sub-projects will be reinforced by two parallel *accompanying measures*, both aimed at providing intensive training to sub-project faculty teams by EU counterparts: faculty *training workshops* to be held in SM universities and conducted by EU counterparts, and short-term *training visits* for sub-project leaders in EU universities and centers.

Sub-projects, dedicated to the investigative development of foundation courses in basic sciences and engineering, will aim to establish improved formats and systems for lecture presentations, laboratory sessions and simulations, and students' assessment. Each sub-project, with a duration of 27 months, will be hosted by an academic department in an SM university and assigned an EU academic advisor.

Faculty training workshops in SM Universities are designed to provide faculty with the necessary training in basic information and communication technology skills and their effective utilisation in education. The workshops will also serve as a vehicle for comparison of sub-projects results and dissemination among invited faculty members from different SM universities. Each workshop, with a duration of 5 days, will be offered by two EU lecturers and attended by 25 participants from SM universities. A total of 6 workshops will be featured throughout the project duration.

Training visits to EU institutions are intended to enable senior investigators of sub-projects to acquire first hand experience in telematics applications in EU universities, obtain specialised training in needed areas, and establish direct channels of collaboration with EU centers and academics. One two-week training visit will be organised for each sub-project senior investigator during the first year of that sub-project. The visit will be hosted by one or (a maximum of) two EU university departments or centers with established experience and activities of relevance to the investigation carried out by the visitor. Furthermore, a regular *newsletter* and a *web site* are planned for the purpose of wider dissemination and participation and for networking the activities of the sub-projects with similar activities in SM and EU universities.

The project is set up as a partnership between the UNESCO Cairo Office (UCO), four EU institutions (Oxford University, The United Kingdom, University of Bordeaux I- Espace ALPHA, France, Université de Technologie de Compiègne, France, Politecnico di Torino, Italy) and three SM Universities (Cairo University, Egypt, The Hashemite University, Jordan, Information Technologies and Electronics Research Institute, Turkey). The project will be provided full management and co-

ordination by the UCO with the assistance of a steering committee in which each EU and SM partner is presented. The project duration is 33 months, with a commencement date of June 1, 1998.

EXPECTED RESULTS

The USEE-SM Project focuses on telematics applications in higher education. While it expedites the initial process for creating a sustainable “global information and communication area” within SM universities, the project will contribute, through enhanced faculty expertise and improved training of sciences and engineering graduates, to the growth of these technologies in SM private and public sectors. This in turn will contribute to economic and social development and enable SM countries to “participate in solving their regional development problems”. Furthermore, the project will contribute to enhancing EU awareness of conditions in SM universities and countries and strengthening EU capabilities in areas of SM information technology needs. Specifically, the project aims to achieve the following results:

- ⇒ Develop, through the *pilot sub-projects*, alternative methods and formats for lectures, tutorials, laboratory sessions and student assessment which could result in improved methods of dealing with the problems of heavily populated classes, costly library and laboratory facilities and professional isolation from international centers, commonly encountered in the majority of SM universities.
- ⇒ Provide a large cross section of SM faculty and students, through the *training workshops and the visits to EU Centers*, with advanced levels of knowledge and hands-on training on recent telematics technologies and their effective utilisation in education. This is expected to facilitate the establishment of a core of local experts who could be entrusted with the responsibility of offering training courses and preparing self-training kits on information and communication technology for the benefit of the SM academic community.
- ⇒ Utilise the *training workshops* as regular regional platforms for comparing, discussing and sharing the results of the project results and for generating awareness regarding the technological feasibility, requirements and cost of improving university teaching through telematics technologies.
- ⇒ Demonstrate the significance of providing SM universities and countries with adequate information and communication infrastructure facilities and resources.
- ⇒ Establish new channels of communication and interaction between SM and EU institutions and academic communities, which would serve as an effective vehicle in the sharing of information, experiences and human expert resources.

PARTNERS

UNITED NATIONS EDUCATIONAL - U.N.E.S.C.O.

Cairo Office
8 Abel Rahman Fahmy Street Garden City
11611 Cairo
Egypte

Adnan Shihab-Eldin
Tel.: 202-354.55.99
Fax: 202-354.52.96
E-mail: uhcai@Unesco.Org

UNIVERSITY OF OXFORD

Computing Services
Banbury Road 13
Ox2 6nn Oxford
United Kingdom

Alex Reid
Tel.: 44-1865-273.229
Fax: 44-1865-273.275
E-mail: alex.reid@oucs.ox.ac.uk

UNIVERSITE DE BORDEAUX I

Espace Alpha
Cours De Libération 351
33405 Talence
France

Prdr Alain Rahm
Tel.: 33-56.84.66.06
Fax: 33-56.84.66.99
E-mail: alain.rahm@u-bordeaux.fr

UNIVERSITÉ DE COMPIÈGNE

Centre Benjamin Franklin
B.P. 649-60206
Compiègne
France

Dr Menad Sidahmed
Tel.: 33-44.23.45.06
Fax: 33-44.23.44.77
E-mail: menad.sidahmed@hds.utc.fr

POLITECNICO DI TORINO

Corsa Duca Degle Abruzz 24
Torino
Italia

Pr Marco Mezzlana
Tel.: 39-11-564.66.29
Fax: 39-11-564.70.09
E-mail: marco@polito.it

UNIVERSITY OF CAIRO

12613 Giza
Egypte

Pr Atef Sherif
Tel.: 202-570.18.17
Fax: 202-572.34.86
E-mail: aosherif@cairo.eun.eg

HASHEMITE UNIVERSITY

P.O. Box 150459
13115 Zarka
Jordanie

Pr Mohamed Hamdam
Tel.: 962-9-886.142
Fax: 962-9-916.613

MIDDLE EAST TECHNICAL UNIVERSITY

Information Tech.& Electronic Inst. Electrical &
Electronic Eng.
Bloc D
Balgat Ankara
Turquie

Pr Askar Murat
Tel.: 90-312-210.46.00
Fax: 90-312-210.13.15
E-mail: askar@tbtkt.metu.edu.tr

SHORT TERM ACHIEVMENT OF A CORPUS-BASED MULTILINGUAL BASIC ARABIC LEXICAL DB AND RELATED RESOURCE-PRODUCTIVE TOOL-BOX (DIINAR-MBC)

Co-ordinator: Université Lumière-Lyon 2, France (Joseph Dichy)

OBJECTIVES

- To provide the field of multilingual natural language processing research and applications including Arabic with a tool-box comprising:
- **Textual corpora** gathering, encoding and indexing;
 - The building of a **corpus-based multilingual lexical dB** of limited extension, but aiming at being a reference dB for further lexical dB-s. The choice of general vocabulary is also related to the needs of specialised machine-aided translation and text-generation: specialised terminology and translation devices usually require a general vocabulary basis;
 - A **lexical purpose sentence tagger** will aim at providing the domain with a tool for analysing corpora and extracting morpho-syntactic information relevant to the constructing of lexical dBs;
 - It is, for the same reason, coupled with a **text-indexed, tagged and tree-decorated reference corpus**, which is likely to become in turn the starting point of other Arabic NLP development programmes.

The tool-box should benefit further research and development in Arabic NLP as widely as possible.

ACTIVITIES AND EXPECTED RESULTS

- ⇒ **ARCOLEX** [Arabic Raw Corpora for Lexical purposes]. This includes:
- **Raw Corpora** of 10 million Modern Standard Arabic words. Encoding follow the guidelines and standards of the TEI (*Text Encoding Initiative*) including the use of the SGML (*Standard Generalized Markup Language*),
 - a sample of a 100,000 words **textual dB** indexed according to TEI standards, and devised for lexical consultation objectives.
- ⇒ **LARUSA: a Lexical-purpose Arabic Unvowelled Sentence Analyser**
- combining stochastic and syntactic approaches (with the use of the above mentioned Tagged Reference Corpus),
 - using information from the lexical dB completed by Lyon 2, ENSSIB and IRSIT prior to the Proposal,
 - referring to the framework of the EAGLES, MULTEXT and MULTEXT-EAST Projects.
- ⇒ The ARCOLEX textual dB and the LARUSA sentence analyser is to give forth a parsed and tree-decorated **Tagged Reference Corpus** of around 200,000 words.
- ⇒ A **Starting-point Tagged Reference Corpus** 60,000 to 80,000 will be completed with a user-friendly interface.
- ⇒ **PROLEMAA** [= 'Prototype de Lexique Multilingue À partir de l'Arabe'] : a corpus-based general multilingual Lexical dB of about 10,000 Arabic lemmas, with French and English translations.
- The structure of the dB reflects both Semitic 'root-pattern' and 'pre- and suffixation' derivation systems. Lemmas are to be provided with **morpho-syntactic and some basic semantic specifiers**.
 - The dB will be based on LARUSA, the ARCOLEX Tagged Reference Corpus, as well as the lexical dB mentioned above, the English-Arabic lexical dB of 50,000 entries elaborated for machine-aided translation by IRSIT, and the experience of IERA in Arabic multilingual applications, lexical dB-s, and linguistic analysis.

- One of the essential resource-productive offshoots of the dB is the establishment of a set of **patterns and formats for the lexical lemmas of Arabic dictionaries and lexical dB-s**, in both corpus-based monolingual, and multilingual, contexts. .

FOLLOW-UP

- ▶ To be completed during the first year:
 - ARCOLEX Tagged Reference Corpus:
 - Definition (on a morphosyntactic basis) of the tagging as well as the tree decorating of Arabic sentences.
 - Elaborating of an interface for the hand tagging and tree-decorating of Arabic sentences.
 - Completing of the user-friendly interface for the semi-manual analysis of Arabic sentences.
 - ARCOLEX raw Corpora
 - Defining coding procedures complying to SGML and TEI standards.
 - ARCOLEX textual dB
 - Study on the representativeness of corpora in Modern Standard Arabic
 - Defining of feasible text-indexation procedures (TEI)
 - Elaborating and programming of a user-friendly interface for the manual indexing of a textual dB
 - Input of a representative sample of texts through the above interface.
 - PROLEMAA
 - Defining (a) general objectives, and (b) input and updating formats
 - Completing of the user-friendly interface for the input and updating of data.
 - Selecting 10.000 Arabic lemmas
 - Study of lexicon-syntax-semantics relations in Arabic, including the definition of specifiers and the completing of an input and updating interface (version 1).
 - LARUSA parser
 - Elaborating and programming of version 1.
- ▶ To be completed in the following year and a half:
 - ARCOLEX Tagged Reference Corpus
 - Input of corpus: 3 sections of 20.000 words each
 - PROLEMAA
 - Choice and input of a representative sample of lemmas.
 - Input of 10.000 lemmas (Arabic-French and Arabic-English)
 - LARUSA
 - Testing on corpora.
 - ARCOLEX Raw Corpora
 - 10 million words, encoded according to TEI standards
 - Guidelines & specifications documents
 - ARCOLEX Reference Corpus”
 - LARUSA
 - PROLEMAA

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PARTNERS

UNIVERSITÉ LUMIÈRE LYON 2

86, rue Pasteur
69365 Lyon Cedex 07
France

Joseph Dichy
Tel.: +33-4 78 69 70 53
Fax: +33-4 72 80 94 52
E-mail: dichy@univ-lyon2.fr

ENSSIB (École Nationale Supérieure des
Sciences de l'Information et des Bibliothèques)
17-21, bd du 11 nov. 1918
69623 Villeurbanne Cedex
France

Mohamed Hassoun
Tel.: +33-4 72 44 43 24
Fax: +33-4 72 44 27 8
E-mail: hassoun@enssib.fr

KATHOLIEKE UNIVERSITEIT NIJMEGEN

TCMO
P.O. Box 9103
6500 HD Nijmegen
The Netherlands

Everhard Ditters
Tel.: +31-243 612 641
Fax: +31-243 615 939
E-mail: E.Ditters@let.kun.nl

IRSIT (Institut Régional des Sciences
Informatiques et des Télécommunications)
P.O. Box 212 - Cité Mahrajène
1082 Tunis
Tunisia

Salem Ghazali
Tel.: +216-1 800 122
Fax: +216-1 787 827
E-mail: salem.ghazali@irsit.rntn.tn

ELECTRONICS RESEARCH INSTITUTE

El Tahrir Street – Dokki
Cairo
Egypt

Nadia Hegazi
Tel.: +20-2 259 16 44
Fax: +20-2 259 16 44
E-mail: eri2@frcu.eun.eg

IERA (Institut d'Études de Recherche
sur l'Arabisation)
P.O. Box 6261 (Insituts)
Agdal – Rabat
Morocco

Abdelkader Fassi Fehri
Tel.: +212-7 77 30 05
Fax: +212-7 77 20 65
E-mail: Fassi@atlasnet.net.ma

IRS-BASED DOCUMENT LOCALISATION (IDOL)

Co-ordinator: EPOS Etudes et Programmation en Optimisation et Software, France
(Rafik BelhadijKacem)

OBJECTIVES

The central aim of the project is to develop software for a *technical documents* localisation workstation supporting two European languages (English and French) as well as Arabic. This software will include not only sophisticated **document management**, designed for the translation environment, but also a **Translation Memory** engine that operates in the three languages of the project, with a view to expansion to other languages later. More global objectives include:

- Providing linguistic tools for users of less favoured languages, such as Arabic, to allow people in Developing countries (DC) to use their own language in their scientific, technological, economical and cultural exchanges with Europe and the rest of the world.
- Integrating DC, in particular those which have attained a higher level of development (such as Tunisia and Lebanon) into the global information society by means of information and communication technologies.
- Combining research skills established in DC institutions and industry with their EU counterparts to facilitate the growth of a global information and communication area allowing them to participate in solving their regional problems with regard to development.
- Innovative aspects of the project
 - Document localisation products already exist to help speakers of the more common European languages, but none of these products provide direct support for those translating into or out of Arabic. The IDOL project aims to redress this imbalance.
 - We are implementing innovative monolingual and bilingual parallel alignment techniques, applied to *Arabic and European* languages.
 - The proposed project is on the cutting-edge of (1) document localisation tools, (2) multilingual, full-text, Information Retrieval Systems (IRS), and (3) Translation Memory.

ACTIVITIES

◇ Arabic linguistic modules

To insure correct Arabic language processing, at the same level as English, the following linguistic modules are needed:

- General Arabic dictionary
- Bilingual dictionaries (English to Arabic and French to Arabic)
- Morphological analyser, to provide automatic normalisation/lemmatisation (i.e. to find the canonical form of each word).

These linguistic basic tools are needed for (1) parallel alignment (all languages), and (2) indexing and search (Arabic).

Parallel Alignment of texts is the establishment of correspondence between units in a mono/bi/multi-lingual text at paragraph, sentence, phrase or word level. The purpose of this WP is to adapt an existing alignment technique to (1) monolingual alignment, (2) to bilingual alignment with Arabic text, and (3) to take the text structure into account (chapters, sections, paragraphs, etc).

◇ Translation Checker (TRACER)

The general goal of TRACER is to partially *automate the process of proofreading translated documents* by using state of the art parallel alignment techniques (see WP6). Though TRACER will not be able to indicate all the errors, it focuses on the automatic detection of two types of errors:

- Across texts (terminology, missing parts, structure of the document, etc.)

- Within translated text (according to the style guides)

The existing laboratory module is to be extended in order to gradually take into account specific translation problems encountered by localisers and revisers. This will be done by successively incorporating more complex structural properties of the documents in question, manipulating more sophisticated linguistic objects and employing more powerful and varied computational methods.

◇ Translation Memory Engine

The purpose of this WP is to adapt and integrate the Alignment Techniques developed in the preceding WP to the IRS to build an Intelligent Translation Memory system dedicated to structured documents. The key issues pertaining to this method are:

- When indexing a document, the IRS affects an address to the document and to the subsets of the document: Chapters, sections, paragraphs, phrases and words. When this document is translated, the same indexing will be performed, so that the chapters, sections, and paragraphs of the source and target documents are perfectly aligned.
- When translating a document:
If the system finds a previous version of the document, it replaces automatically all the paragraphs which are identical in the two versions.
If there is no previous version of the document, the localiser searches in the whole database and delivers a ranked list of candidate paragraphs. The localiser chooses the most relevant paragraph (s) and uses its existing translation.

◇ Data conferencing

The efficiency and the quality of the localisation depends largely on the ease of communication between the people involved in the process: customers, project leaders, translators, reviewers, and desktop publishers.

The data conferencing tool enables two remote actors to work together on the same document, to exchange files and documents, with the possibility to talk on the phone at the same time.

As the projected Data Conferencing application intercepts keyboard, screen and mouse drivers commands, it will have a high performance level *whatever the network* is. This is particularly important in DCs.

EXPECTED OUTCOME

- ▷ EPOS is in charge of overall project management and is also primarily responsible for general integration and demonstration as well as the exploitation of the project's work. It will further be developing an Information Retrieval System (IRS) with support for Arabic and this will form part of a document management system for translators.
- ▷ UMIST's central role is to develop the translation memory (TM) engine of the program which will function in English, French and Arabic. It will develop the basic non-Arabic linguistic resources and bilingual lexicons used by the TM and document alignment modules. UMIST is also in charge of publicising the IDOL project.
- ▷ IME is responsible for the data conferencing capabilities. These capabilities will be merged into the final program to allow translations to be discussed by translators in different cities or even different countries simultaneously.
- ▷ ISSCO is responsible for creating TRACER, a translation checker that will enable translators to improve translation accuracy and consistency. It will also develop the document alignment modules that will prepare previously translated documents so that they may be entered directly into the memory of the TM module.
- ▷ UNIVERSAL is developing the Arabic linguistic resources needed both for the Translation Memory and Document Alignment modules. It will also be working closely with ISSCO and UMIST to assist with the implementation of their modules for the Arabic language.

FOLLOW-UP

- ▷ A basic prototype of the system components (Multilingual IRS, Translation Memory engine, Data Conferencing) is expected towards the end of 1998 with the final system ready by May 1999.
- ▷ The final products will be put on the Arabic World market in few months. Only final product refinement as well as commercial and technical documentation has to be finalised.
- ▷ Client / Server (NT / Windows) and stand-alone workstations (Windows or NT) are the operating platforms of IDOL.
- ▷ These products will be made available: (1) to third party suppliers, (2) directly to end users and (3) to system developers/integrators (e.g. OEM).

PARTNERS

EPOS Etudes et Programmation en Optimisation et Software
107, rue du Point du Jour
92100 Boulogne Billancourt
France

Rafik Belhadj Kacem
Tel.: 33 1 46 10 46 46
Fax: 33 1 47 61 19 00
E-mail: R.Belhadj@wanadoo.fr

UMIST
Centre for Computational Linguistics
PO Box 88
M60 1QD Manchester
United Kingdom

Dr Harold Somers, David Mowatt
Tel.: 44 1 61 200 31 07
Fax: 44 1 61 200 3099
E-mail: Harold@ccl.umist.ac.uk

INTEGRO MIDDLE EAST
1, Avenue Chehab
Beyrouth
Lebanon

Mohamed Issa
Tel.: 961 12 85 562
Fax: 961 12 85 303
E-mail: integro@inco.com.lb

ISSCO
Istituto Dalle Molle per gli Studi Semantici e Cognitivi
54, route des Acacias
CH-1227 Genève
Switzerland

Pr. Susan Armstrong
Tel.: 41 22 705 71 13
Fax: 41 22 300 10 86
E-mail: Susan.Armstrong@issco.unige.ch

UNIVERSAL
57, rue 9007
2023 Ben Arous
Tunisia

Mondher Zribi
Tel.: 216 1 392 144
Fax: 216 1 392 096
E-mail: Adn@gnet.tn

ARAMED (EXTENSION AND INTEGRATION OF ARABIC LINGWARE COMPONENTS IN A UNIFICATION-BASED MT SYSTEM FOR THE FIELD OF MEDICAL TERMINOLOGY AND CLASSIFICATION)

Co-ordinator: Universität des Saarlandes, Saarbrücken, Germany (Catherine Pease)

OBJECTIVES

- Translate into Arabic a part of the comprehensive medical terminology SNOMED (Systematized Nomenclature of Human and Veterinary Medicine)
- Create for the first time the basis for a German-Arabic Machine Translation System
- Widen the scope of a MT System originally written for West European languages by incorporating a language which, as the official language of 21 countries, is of great international importance.
- Develop a system which translates German and English medical texts and terminology into Arabic

ACTIVITIES

- ◇ Further development of an existing Morphological Generator for Arabic at the Egyptian Institute, and adaptation to the CAT2 MT system in order that it can process CAT2 translations.
- ◇ Creation of 2,000 entry Arabic dictionary for general language for use in the CAT2 MT system
- ◇ Translation from English into Arabic of 3,000 medical classifications taken from the SNOMED terminology
- ◇ Incorporation of the same 3,000 terms for English and German in the English and German lexicons.
- ◇ Establishment of a corpus of medical texts made up of the information slips accompanying prescriptions and other medicaments
- ◇ Development and testing of the CAT2 language components (grammars) for general language texts, medical terminology and medical texts (using the above corpus) for the language pairs English-Arabic and German-Arabic
- ◇ Development of a conversion program which can convert the Latin alphabet to and from the Arabic alphabet for use in both PC and Unix editors

OUTCOME

Scientific-Technical

- ⇒ The creation of a basis for writing an Arabic version of the SNOMED codes, thus bringing Arab physicians a step further into the world of medicine:
 - Arabic translations for 3,000 items of the English SNOMED terminology have been made
- ⇒ The provision of a basis for the use of automatic translation in the Arab world in the field of medicine:
 - A Morphological Generator has been interfaced to the CAT2 MT System, and can process CAT2 output;
 - Lexical entries for CAT2 have been made for 3,000 items of the SNOMED terminology in English and German;
 - A general language lexicon of 2,000 entries has been made for Arabic;
 - Medical terminology can be translated from German and English into Arabic in CAT2;
 - Simple general language sentences can be translated into Arabic;
 - Limited input from medical texts can be translated into Arabic
- ⇒ Gives the Arab world the opportunity to a) benefit from and b) contribute to the progress made in NLP and Machine translation, which is dominated by the industrialised West;

⇒ Contributes to the attempt of many scientists (in this case physicians) in the Arab world who are trying to encourage the use of the Arabic language in science and technology (as opposed to English, French or Latin terminology).

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PARTNERS

UNIVERSITÄT DES SAARLANDES

Martin Luther Straße 14

66111 Saarbrücken

Germany

Catherine Pease

Tel.: +49-681-389 51 26

Fax: +49-681-389 51 40

E-mail: cath@jai.uni-sb.de

ELECTRONIC RESEARCH INSTITUTE

El Tahrir Street Dokki

Cairo

Egypt

Nadia Hegazi

Tel.: +20-2-258 19 34

Fax: +20-2-259 16 44

E-mail: eri@frcu.evn.eg

UNIVERSITÉ DE PARIS VII

Traitement automatique du Language Nat.

Case 7003

Place Jussieu 2

75521 Paris

France

Laurence Danlos

Tel.: +33-1-44 27 56 96

Fax: +33-1-44 27 79 19

E-mail: danlos@jussieu.fr

**HIGH-PERFORMANCE COMPUTING FOR FINANCIAL PLANNING UNDER
UNCERTAINTY (HPC-FINANCE)**

Co-ordinator: University of Cyprus, Nicosia, Cyprus (Stavros A. Zenios)

OBJECTIVES

- This project aims at the development, implementation and testing of high-performance computing (HPC) models for:
 - valuation (pricing) of complex, interest-rate-sensitive financial instruments;
 - risk management of portfolios of such instruments.
- Using high performance computing in both phases of the project will not only enable us to address effectively these issues, but will also demonstrate the value of HPC for an important class of business applications;
- This project will develop stochastic optimisation models for financial planning under uncertainty and implement solution algorithms on HPC platforms;
- Simulation methods for valuation of financial instruments and the application of stochastic programming algorithms for portfolio management constitute the two phases of the project.

ACTIVITIES

- ◇ Models for pricing some of the most complex fixed-income securities (mortgages, insurance products, callable bonds) have already been developed and this project will continue on this earlier work.;
- ◇ Exact specification of model characteristics and data requirements;
- ◇ Evaluation and selection of the HPC hardware and software;
- ◇ Development of mathematical models for pricing key financial instruments and for portfolio management;
- ◇ Use of the HPC system for the development of distributed computing applications;
- ◇ Training and familiarization of the research teams with the use of the HPC for the development of distributed computing applications.

RESULTS SO FAR

- ⇒ The University of Cyprus is currently in the process of installing a Parsytec CC 16.
- ⇒ A meeting among the partners taking part to the project has already been held in Bergamo last August 1996 and a new meeting is going to be held in Crete in November 1996.
- ⇒ A model for designing and pricing callable bonds has been implemented and tested.
- ⇒ A survey of parallel algorithms for stochastic programming has also been compiled.

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PARTNERS

UNIVERSITY OF CYPRUS

Department of Public and Business Administration
P.O. Box 537
1678 Nicosia
Cyprus

Stavros A. Zenios
Tel.: +357-2-33 87 64
Fax: +357-2-33 90 63
E-mail: zenioss@atlas.pba.ucy.ac.cy

TECHNION - ISRAEL INSTITUTE OF TECHNOLOGY

Faculty of Industrial Engineering & Management
32000 Haifa
Israel

Mordecai Avriel
Tel.: +972-4-829 45 09
Fax: +972-4-823 51 94
E-mail: avriel@ie.technion.ac.il

UNIVERSITY OF BERGAMO

Informatics and Applications
Department of Mathematics, Statistics
Piazza Rosate 2
24129 Bergamo
Italy

Marida Bertocchi
Tel.: +39-35-27 75 17 / 711
Fax: +39-35-24 95 98
E-mail: marida@unibg.it

UNIVERSITY OF CAMBRIDGE

Judge Institute of Management Studies
Trumpington Street
Cambridge CB2 1A6
United Kingdom

Michael Dempster
Tel.: +44-1223-33 97 00
Fax: +44-1223-33 97 01
E-mail: mahd@cam.ac.uk

DIVISION OF ECONOMETRICS

Department of Probability and Mathematical Statistics
Sokolovska 83
Prague 8
Tchecoslovaquia

Jitka Dupacova
Tel.: +42-2-21 91 32 80
Fax: +42-2-232 33 16
E-mail: Dupacova@karlin.mff.cuni.cz

UNIVERSITÀ DELLA CALABRIA

Dipartimento Di Elettronica, Informatica e Sistemistica
87036 Rende (CS)
Italy

Lucio Grandinetti
Tel.: +39-984-49 47 18
Fax: +39-984-49 47 13
E-mail: musmanno@unical.it

**CENTRO RICERCHE SUL CALCOLO PARALLELO
E SUPERCALCOLATORI**

Complesso Monte S. Angelo
Edificio T. Via Cintia
80126 Napoli

Italy

Almerico Murli

Tel.: +39-81-67 56 26

Fax: +39-81-766 21 06

E-mail: murli@matna2.dma.unina.it

ERASMUS UNIVERSITEIT ROTTERDAM

Vakgroep FinBel/Kamer H14-14

Postbus 1738

3000 DR Rotterdam

The Netherlands

Jaap Spronk

Tel.: +31-10-408 12 82

Fax: +31-10-452 63 99

E-mail: spronk@finbel.few.eur.nl

UNIVERSITY OF CYPRUS

Department of Public and Business Administration

P.O. Box 537

1678 Nicosia

Cyprus

Hercules Vladimirov

Tel.: +357-2-33 87 62 / 3

Fax: +357-2-33 90 63

E-mail: hercules@atlas.pba.ucy.ac.cy

ERASMUS CENTER FOR FINANCIAL RESEARCH

P.O. Box 1738

Burg. Oudlaan 50

3000 DR Rotterdam

The Netherlands

Ton Vorst

Tel.: +31-10-408 12 70

Fax: +31-10-452 77 46

UNIVERSITÀ DI NAPOLI

Dipartimento de Matematica e Applicazioni

Centro Ricerche Sul Calcolo Parallelo e Supercalcolatori

80126 Napoli

Italy

Gerardo Toraldo

Tel.: +39-81-67 56 26

Fax: +39-81-766 21 06

E-mail: toraldo@matna2.dma.unina.it

PEACE BY HIGH PERFORMANCE COMPUTING (HPC)

Co-ordinator: Parsytec Computer Gmbh, Aachen, Germany (Anno Jordan)

OBJECTIVES

In the Middle East, the use of computer equipment in the civil industry and the scientific area has penetrated into a large number of activities, employing mainly Workstations and PCs. On the other side, the region faces a number of serious problems, which can be confronted only with the help of recent developments in low cost High Performance Computing (HPC). Of particular interest are embedded HPC systems, which can offer efficient solutions in applications, where human processing can be fully automated or greatly assisted:

- groundwater stream simulation, relevant for the analysis and prediction of migration and flow processes of ground water, ground water contamination by industrial pollution and salt water;
- sand movement simulation;
- oil exploration;
- analysis of composite material dynamics for mechanical engineering applications;
- air pollution simulation and prediction, also related to the change of the regional climate;
- explosive detection;
- medical diagnosis;
- fruit quality control and others.

The region has a large pool of highly qualified computer personnel. However, the skills for using HPC equipment in an efficient way are restricted to a group of scientists or engineers at specific institutions whose possibilities to cooperate in a complementary way with international groups or to participate in the recent developments in HPC is very limited. In addition the inter-regional co-operation in the Middle East and Israel is partly blocked by political and human barriers.

- The main objective of this project is to perform training, application development, and technology transfer measures in High Performance Computing in the Middle East. The project will start with centres in Egypt and Jordan. These centres will be linked by electronic means and will constitute for the first time a living network and basic infrastructure in the Middle East consisting of HPC sites, communication resources and hosts of expertise, which can cover the scientific and industrial needs of the region;
- Of highest importance is, that the co-operation will help to reduce political and human barriers between the formerly hostile countries in the Middle East, starting with Egypt, Jordan and Israel and with the vision to include further countries in the future.

ACTIVITIES

Phase 1: requirement Analysis (6 months)

- ◇ To identify topics in the scientific, educational, engineering and administrative areas where HPC concepts, equipment and S/W can contribute to the economic and social development;
- ◇ To identify possible parties willing to undertake measures for the further promotion of HPC in the region and bring together the parties needed for the creation of a self-sustainable network of excellence after the project;
- ◇ To examine ways of tapping the considerable existing capital of skills and expertise in HPC of expatriate scientists of the region now active in EU and US;
- ◇ To promote and disseminate the results of European projects, programmes and products in the area of HPC;
- ◇ To disseminate the information about the initiative in further countries in the region and North Africa, in order to convince more people to take part in the training;
- ◇ To fix a plan for the second phase of the project. This will provide a sound basis for decision processes concerned with the Mediterranean policy of the EU and linking regional (national) and European support programmes.

Phase 2: Implementation of parallel Computing Hardware, Training, Development of Applications

- ◇ HW-Implementation and basic training of local staff in selected centres;
- ◇ Training courses : this includes a general presentation of concepts and applications of parallel processing and practical exercises;
- ◇ Application development by local scientists and engineers. The application development will be conducted by tutors of the host organisations in Egypt and Jordan. Links to existing relevant applications (codes) in Europe (e.g. EUROPORT projects) will be formed and supported by Parsytec and NTUA;
- ◇ Final evaluation and information dissemination. The dissemination will proceed with the presentation of achieved results. The establishment and the capabilities of the HPC centres are to be made known to the largest possible set of potential users. The purpose of this activity is to promote the hosting of an increasing number of potential applications, diffusing at the same time as much as possible the accumulating experience;
- ◇ The participation of scientists from Israel in selected events or/and training courses will support the preparation of inter-regional projects for the future.

RESULTS SO FAR

- ⇒ The first six months of the project were used for performing initial awareness measures in Egypt and Jordan and for first training measures related to parallel computing HW and SW. These events were attended by the experts of the participating organisations and guests from other research centres in the region. Besides that, a deeper analysis of the status of HPC in Egypt and Jordan has been performed which shows, that HPC and its implications are more or less unknown in the business and industrial community and in a very early stage in the Research and University environment.
- ⇒ The project has been presented at the Medinterprise Conference in Cairo, May 1996 for a community of about 200 researchers and engineers. Due to this broad awareness, scientists not only from the participating centres were motivated to take part in the first training measures at the National Technical University in Athens, as the participation of people from Palestine has demonstrated. Furthermore ECTRA (the managing organisation in Egypt) has organised direct presentations of the HPC technology at industrial enterprises and has started to contact further sectors and groups in Egypt, including the political level.
- ⇒ About three months earlier than originally planned the first training courses at the NTUA took place, which resulted also in an earlier installation of the parallel computing HW directly at Al al-Bayt University near Amman and the Electronics Research Institute in Cairo. Therefore the HW is already in use for initial tests of HPC in different application fields and will be used for first real R&D tasks in the very next time. All over all, the project is ahead of schedule and the co-operation of all partners including the Israelis shows promising aspects for the future.

PARTNERS

PARSYTEC COMPUTER GMBH

European Cooperation Division
Auf der Huels 183
52068 Aachen
Germany

Anno Jordan
Tel.: +49-241-9696-0 (452)
Fax: +49-241-9696-500
Email: jordan@parsytec.de

NATIONAL TECHNICAL UNIVERSITY OF ATHENS

Division of Computer Science
Heron Polytechniou
Zographou 9
15773 Athens
Greece

George Stassinopoulos
Tel.: +30-1-772 25 31
Fax: +30-1-772 25 34
E-mail: stassin@cs.ntua.gr

EGYPTIAN CONSULTING AND TRADING CO (ECTRA)

Research and Development
Hassan Sabri 12A
Cairo
Egypt

Nabil Motosh
Tel.: +20-2-340 43 47 / 341 86 02
Fax: +20-2-341 15 82

AL AL-BAYT UNIVERSITY

P.O. Box 772
JO Jubyha
Amman
Jordan

Ihsan Mahasneh
Tel.: +962-6-84 01 90
Fax: +962-6-84 67 21

ELECTRONICS RESEARCH INSTITUTE

Computers and Systems
El Tahrir
Giza
Egypt

Ashraf Abdel Wahab
Tel/Fax: +20-2-335 16 31
E-mail: eri@frcu.eun.eg / ashraf@eri.sci.edu

TEL AVIV UNIVERSITY

Biomedical Engineering
P.O. Box 39040
69978 Tel Aviv
Israel

Shmuel Einav
Tel.: +972-3-640 94 18
Fax: +972-3-642 95 40
E-mail: einav@eng.tau.ac.il

A MULTIMEDIA TOOL FOR NATURAL RESOURCES MANAGEMENT AND ENVIRONMENTAL EDUCATION (GAIA)

Co-ordinator: Environmental Software and Services, Gumpoldskirchen, Austria (Kurt Fedra)

OBJECTIVES

- To develop, in collaboration with partners from seven developing countries, a multi-media framework and set of demonstration cases at a regional or local scale, addressing regional priority problems of natural resources management;
- To implement this system at the participating institutions for both educational use and project activities, and obtain practical classroom and project experience in its application, as the basis of further, local developments;
- To provide wider access, and possibilities for active contribution, to the system through a wide-area network (Internet) World Wide Web.

ACTIVITIES

- ◇ Preparation, dissemination, and analysis of a requirements and constraints questionnaire and report;
- ◇ Implementation of the GAIA information system:
Development includes the preparation of a workstation based version for classroom teaching of the GAIA environmental information system, linked to a World Wide Web implementation for distance learning and dissemination, that includes a number of case studies prepared by the project partners in Argentina, China, Egypt, Mexico, Thailand, Venezuela and Zimbabwe.
- ◇ The case studies are embedded within the conceptual framework of Agenda 21, and address:
Argentina Communicable Diseases in Urban Centres, Urban Air Pollution
China Sustainable Urban Development
Egypt Coastal Zone development and Climate Change
Mexico Urban Air Pollution
Thailand Deforestation and Land Degradation
Venezuela Deforestation and the Politics of Land Ownership
Zimbabwe Landuse in Dry Tropical Savannahs
- ◇ The case studies are implemented in multi-media format for web publishing, and are also linked to the hypertext system of the workstation version.

EXPECTED OUTCOME

- ▷ To improve the management of natural resources and the environment through better management and training tools, based on modern multi-media methods and wide-area networking information technology;
- ▷ To develop an information network of collaborating institutions, linking European institutions with partners in a number of developing countries that have traditional or emerging ties with European countries;
- ▷ To develop and disseminate, together with the partners in the DCs, a multi-media training tool with illustrative case study applications for natural resources and environmental management;
- ▷ To help developing the institutional capabilities in the developing countries, both concerning methods, tools, and approaches used in natural resources management and teaching of these methods, as well as the information and networking technology required to access and to disseminate resource management information.

PARTNERS

ENVIRONMENTAL SOFTWARE AND SERVICES

ESS GmbH
Advanced Computer Applications
Kalkgewerk 1
P.O. Box 100
2352 Gumpoldskirchen
Austria

Kurt Fedra
Tel.: +43-2252-633 05
Fax: +43-2252-633 059
E-mail: kurt@ess.co.at
Other contacts:
Lothar Winkelbauer: lothar@ess.co.at
Thomas Vogele: thomas@ess.co.at

INTERNATIONAL CENTRE FOR CONSERVATION EDUCATION ICCE

Greenfield House
GL54 5TZ Guiting Power
Gloucestershire
United Kingdom

Jonathan Somper
Tel.: +44-1451-85 07 77
Fax: +44-1451-85 07 05
E-mail: 100417.325@compuserve.com

POLITECNICO DI MILANO

Centro Interdipartimentale di Ricerche in
Informatica Territoriale e Ambientale (CIRITA)
Via Ponzio 34/5
20133 Milano
Italy

Giorgio Guariso
Tel.: +39-2-23 99 35 59
Fax: +39-2-23 99 35 87
E-mail: guariso@elet.polimi.it

UNIVERSIDAD DE BELGRANO

Departamento de Investigación
Programa de Investigación y Desarrollo Ambiental
Zabala 1851 (1426)
Buenos Aires
Argentina

Angel Capurro
Tel.: +54-1-788 54 00
Fax: +54-1-788 88 40
E-mail: capurro@ub.edu.ar
Other contact:
Fernando Garcia: rtfido@criba.edu.ar

TSINGHUA UNIVERSITY

Department of MIS
School of Economics and Management
Beijing
China

Chunjun Zhao
Tel.: +86-10-62 78 55 36
Fax: +86-10-62 78 58 76
E-mail: semzcyj@tsinghua.edu.cn
Other:
Jingwei Huang: hjw-sem@mail.tsinghua.edu.cn

UNIVERSITY OF ALEXANDRIA

Institute of Graduate Studies and Research
163 Horreya Avenue Chatby 21526
P.O. Box 832
Alexandria
Egypt

M. El-Raey
Tel.: +20-3-422 76 88
Fax: +20-3-421 57 92
E-mail: igrs-alx@frcu.eun.eg

UNIVERSITY OF MEXICO

Ingeniería Ambiental
Facultad de Ingeniería
División Estudios de Posgrado
Ciudad Universitaria
Apartado Postal 70-256
Mexico D.F. 04510
Mexico

Rina Aguirre
Tel.: +52-5-622 30 01
Fax: +525-622-30 00 or 616 10 73
E-mail: rina@gauss.fi-p.unam.mx
Other contacts:
Ubaldo Inclan: gaia@gauss.fi-p.unam.mx
Enrique Diaz Mora: gaia@gauss.fi-p.unam.mx

ASIAN INSTITUTE FOR TECHNOLOGY

School of Advanced Technologies
P.O. Box 2754
Bangkok 10501
Thailand

R. Sadananda
Tel.: +662-524 57 02
Fax: +662-524 57 21
E-mail: sada@cs.ait.ac.th
Other contact:
Surendra Shrestha: surendra@ait.ac.th

UNIVERSIDAD DE LOS ANDES
Facultad de Ingeniería
Centro de Investigación
Proyectos en Simulación
5101 Meacuturida
Venezuela

UNIVERSITY OF ZIMBABWE
Institute for Environmental Studies
P.O. Box MP 167 Mount Pleasant
Harare
Zimbabwe

Giorgio Tonella
Tel.: +58-74-40 28 79
Fax: +58-74-40 28 72
E-mail: gaia-cesimo-1@ing.ula.ve

Bruce Campbell
Tel.: +263-4-30 32 11
Fax: +263-4-33 34 07
E-mail: bcampbell@esonet.zw
Other contact:
George Djolov: djolov@caddy.univen.ac.za

<p align="center">TELESUN - A WORLD WIDE MEDIA TELETEACHING SYSTEM FOR UNIVERSITIES</p>
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Co-ordinator: Université Joseph Fourier, Grenoble France (Pascal Sicard)

OBJECTIVES

- Implementation of a teleteaching multimedia system for universities based on Internet and high performance communication tools;
- Master level courses modelisation, production and diffusion;
- System behaviour studies and performance analysis through different platforms.

ACTIVITES

The project presentation and the main results (deliverable, lectures access ...) can be obtained at the following url: <http://www-telesun.imag.fr>. The co-operation is conducted on six sites, three located in Africa (Cameroon, Morocco, Tunisia) and the three others in Europe (Belgium, France). Every partner is dedicated to work on one of the following parts of the project:

- ◇ A virtual Video Cassette Recorder for real-time playback of audio and video clips.
- ◇ MMS base extended to different multimedia streams.
- ◇ Design and implementation of a distributed test and knowledge evaluation application.
- ◇ Design and implementation of mechanisms to assist the selection and the administration control of the appropriate communications elements.
- ◇ Implementation of remote or local image processing.
- ◇ Design and implementation of secure procedures to handle confidential data like examination procedures and grading.
- ◇ With the designed environment each university will offer a teleteaching course at the master level in accordance with the following pedagogical process:
 - A self-teaching phase. (www and other developed tools): Students can access text and still illustrations through a World Wide Web (WWW) client interface.
 - A tele-consultancy phase. (mailing system, white board ...): Students can set individual appointment with the lecturer in charge of the course by means of a mailing system. They will then use a white board for interactive questioning, answering and sketching.
 - A class phase.(teleconferencing ...): The lecturer is conducting a teleconferencing with all of the students taking the course.
 - A phase of remote test and knowledge evaluation (with developed tools)
 - Platform exploitation in the local and the international context.

EXPECTED RESULTS

Scientific – technical results

- ⇒ A complete and adaptable teleteaching environment over the project partners.
- ⇒ An efficient use and exploitation of the new communication technologies and multimedia concepts.
increase the co-operation between the different partners.
- ⇒ The teleteaching platforms are installed in the 6 sites. Every partner has today a Internet connection.
- ⇒ The multimedia teleteaching course (in HTML with video clips) corresponding to a self-teaching phase have been implemented (Security, Processor Architecture, Distributed Applications, Imaging processing, Networks Architecture, Aerial Manufacturing).
- ⇒ The specification and implementation phases of differents teleteaching applications are finished.

FOLLOW-UP

The next phase will take place within the last three months of the project. Each of the pilot universities will offer a lecture at the master (bac+5) level to other universities as multimedia material using the pedagogical process (self-teaching, tele-consultancy, tele-conferencing, test and knowledge evaluation) and developed tools during the project.

Within this experimentation, we will study the communication infrastructure impacts on the developed applications.

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PARTNERS

UNIVERSITE JOSEPH FOURIER GRENOBLE 1

(UFR d'Informatique)

Laboratoire Logiciels, Systèmes et Réseaux (LSR-IMAG)

BP 72 38402 ST Martin d'Hères Cedex

France

Pascal Sicard

Tel.: +33-4-76-82-72-92

Fax: +33-4-76-82-72-87

E-mail: Pascal.Sicard@imag.fr

UNIVERSITE DE MONASTIR

Ecole Nationale d'Ingénieur de Monastir (ENIM)

Laboratoire d'Automatique et d'Informatique Industrielle

(LA2I) - Route de Skanes 5019

5000 Monastir

Morocco

Salem Nasri

Tel.: 216-346-4703

Fax: 216-346-1900

E-mail: Salem.Nasri@enim.rnu.tn

UNIVERSITE DE RABAT

Ecole Nationale Supérieure d'Informatique et d'Analyse des Systèmes (ENSIAS)

Laboratoire de Génie Informatique - Abdelfdil Bennani - BP

713,

Rabat

Tunisia

Agdal Maroc

Tel.: 212 (7) 77 73 17

Fax: 212 (7) 77 72 30

E-mail: bennani@ensias.ac.ma

UNIVERSITE DE YAOUNDE

Ecole Nationale Supérieure Polytechnique (ENSP)

Laboratoire d'Electronique et de Traitement du signal

BP 8390

Cameroon

Emmanuel Tonye

Tel.: +237- 22 45 47

Fax: +237- 23 18 41

E-mail: etonye@polytech.uninet.cm

UNIVERSITE DE LYON

Institut National des Sciences Appliquées (INSA)

Laboratoire de Reconnaissance de Formes et Vision - Bt 403,

20, avenue Albert Einstein 69621 Villeurbanne Cedex

France

Jean-Michel Jolion

Tel.: +33- 72 43 88 05

Fax: +33- 72 43 85 38

E-mail: jolion@rfv.insa-lyon.fr

UNIVERSITE CATHILIQUE DE LOUVAIN

Unité d'Informatique

Faculté des sciences appliquées - Unité d'informatique, Place

ste Barbe n°2, B-1348 Louvain-la-Neuve,

Belgium

Marc Lobelle

Tel.: 010/47 32 74

Fax: 010/45.03.45

E-mail: ml@info.ucl.ac.be

ARABIC ENGLISH FRENCH SOFTWARE LOCALISATION TOOL (AREF)
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Co-ordinator: Bull S.A., Les Clayes-sous-Bois, France (Rafik Belhadj Kacem)

OBJECTIVES

- To increase the availability and use of software products in any language, including Arabic;
- To provide easy multilingual access to information and knowledge bases;
- To develop and implement a new Software Localisation Tool prototype (SLT), based on a multilingual environment and on work-group organisation. To be well accepted by potential users, the SLT must:
 - improve the quality and consistency of the localised software;
 - increase localisation productivity (i.e. reduce costs and shorten delay);
 - support any language;
 - be very simple to use, as the personnel involved in the localisation process have different skills (translators, terminologists, project managers, etc.). Repetitive tasks that are not really part of the translation work will be automated as much as possible. Moreover, the different steps of the localisation process must be linked together automatically.
- The Core of the SLT is the Multilingual Messages Base (MMB), which is designed to provide SLT users with rapid access to already translated and validated software messages, for incorporation in software products.

ACTIVITIES

- ◇ The Software Localisation Tool
 - The SLT provides the following functions, corresponding to the main steps of the software localisation process:
 - control and reception of the software (with configuration management);
 - storage in a multi-lingual multi-versioning structure;
 - extraction of software messages from sources files (in most cases, the messages to be localised are sent imbedded in the source or resource files);
 - evaluation of delta volumes between two successive versions (of the same Software) for each requested target language;
 - retrieval of already existing translations in the MMB;
 - manual translation of messages not found in the MMB;
 - validation of the manually translated messages in each target language;
 - reinsertion of the translated messages in the target sources files;
 - update of the MMB.
 - These functionalities are implemented on the Server(s) or on the Client(s) :
 - the server provides storage, as well as file export and import functions, and services such as MMB management, message extraction, delta evaluation, message reinsertion;
 - the stations support the graphical end-user interfaces with the system, through software tools and applications, in the Windows environment. Stations offer quick and easy access to server functions. The Localisation Work Station (LWS) is built to improve ergonomics, eliminate parameters, automate tasks, control data access and supervise operation. All LWSs function identically; they differ only in the language that they treat.
- ◇ Arabic Platform Development Tools
 - The main objective is to provide a set of Arabic Development Tools that will assure full transparency in the support of Arabic language, including the display, printing, data entry and communications. In addition, the task will generate a multilingual run-time layer that will perform all necessary operations involved with multilingual data processing. This layer will enable the same application code to use different languages in full transparency.
- ◇ The Multilingual Messages Base (MMB)

- The MMB is a Translation Memory for software messages. MMB is designed to provide Users, such as localisation teams, with rapid access to standard messages, for incorporation in software products, to be localised in several languages;
- The MMB offers a set of assistance tools for the retrieval and selection of appropriate messages. It is possible to formulate requests in Arabic, English or French quasi-natural languages. In future versions, it will be possible to use other languages;
- The core of the MMB is a new Full Text Retrieval System Prototype, called TAMIS;
- In AREF project, we have:
 - provided a trilingual corpus for software domain : 30.000 messages;
 - analysed 3.000 messages and loaded their linguistic parameters into a linguistic thesaurus.

RESULTS

- ⇒ SLT: the Software Localisation Tool, operating on Windows, three successive versions have been provided;
- ⇒ TAMIS: an arabic/english/french information Retrieval System prototype, operating on NT.

PARTNERS

BULL S.A.

Rue Jean Jaurès
78340 Les Clayes-sous-Bois
France

Rafik Belhadj Kacem
Tel.: +33-1-30 80 34 01
Fax: +33-1-30 80 70 78
E-mail: r.belhadj@frcl.bull.fr

TUNISIAN INSTITUTE FOR COMPUTATIONAL AND TELECOMMUNICATIONS RESEARCH

Arabization and Linguistics Department
B.P. 212
Cité Mahragane
1082 Tunis
Tunisia

Lamia Labeled
Tel.: +216-1-78 77 27
Fax: +216-1-78 78 27
E-mail: lamia.labeled@irsit.rnrt.tn

UMIST / CENTRE FOR COMPUTATIONAL LINGUISTICS

Department of Language Engineering
88 Manchester M60 1QD
United Kingdom

Harold Somers
Tel.: +44-161-200 31 07
Fax: +44-161-200 30 99
E-mail: harold@ccl.umist.ac.uk

INTEGRO MIDDLE EAST

Avenue Chehab 1
Beyrouth
Lebanon

Mohamed Issa
Tel.: +961-1-28 55 62
Fax: +961-1-28 53 03
E-mail: integro@inco.com.lb

EPOS

Rue du Point du Jour 107
92100 Boulogne
Billancourt
France

Michel Inglebert
Tel.: +33-1-46 10 46 46
Fax: +33-1-47 61 19 00

DISTRIBUTED OBJECT ORIENTED NUMERICAL SOFTWARE (DOONS)

Co-ordinator: Université Mohamed I, Oujda, Morocco (El Mostafa Daoudi)

OBJECTIVES

The aim of the project is to exploit all the power of C and C++ to build an intrinsic distributed object oriented (DOO) matrix computation package, keeping in mind generality, reusability, extensibility and efficiency. The leading feature of this project was the delivery of the Telmat TN310 parallel computer in Oujda in Summer 1996 (the first parallel machine in Moroccan universities).

This project is strongly linked with the project KIT-108 (NUMLINALG) in collaboration with PIP Laboratory of Mons Belgium and LIP Laboratory of ENS-Lyon France. The availability of a new parallel computer in Oujda has reinforced already existing co-operation between all partners. There was a strong interaction between the KIT and this ITDC project which provided the university of Oujda with the necessary platform for implementation and development.

ACTIVITIES

The implementation phases of ITDC-201 took about two years between the first project approval and the effective launch of the research work (from February 1995 to November 1996). Since then, an intensive effort has been carried on, both by Moroccan and European partners to catch the elapsed time.

RESULTS

Scientific-technical results

- ⇒ Exploitation of the symmetry in the parallelization of the two sided Jacobi method;
- ⇒ Parallel implementation of the one sided Jacobi method;
- ⇒ Parallel implementation of Maxwell's equations;
- ⇒ Study of parallel sparse Cholesky factorisation (in progress);
- ⇒ Parallel algorithms for automatic spoken recognition "Reconnaissance automatique de la parole" (in progress);
- ⇒ Parallel algorithms for image compression using neural network (in progress).

These results could never have been realised without the help of ITDC and KIT co-operation programmes (equipment, travels and subsistence...).

FOLLOW-UP

Several researchers from different fields are interested by using the HPCN. The establishment of a new co-operation with faculties who have participated to ITDC projects is planned. Since the ITDC #201 and KIT #108 are very benefits for all partners and in order to continue this successfully co-operation by working in the HPCN field in co-ordination and in co-operation with our European partners we have:

- ▶ Presented a new INCO-DC Project (KIT) (Collaboration with Mons-Belgium and Lille-France). This project is accepted for three years.
- ▶ Established an official co-operation, for 2 years, with Maghrebien researchers of Tunis Faculty since they have the TN310 parallel machine (the same as our parallel machine) obtained in the framework of the ITDC project.
- ▶ Presented a co-operation project "Action Intégrée" with IMAG Grenoble – France (Co-operation Morocco-France). We still not have the result of the evaluation.

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PARTNERS

UNIVERSITE MOHAMMED I

Faculté des Sciences,
Département de Mathématiques et d'Informatique
60 000 Oujda,
Morocco

El Mostafa Daoudi
Tel.: +212-6-74 47 47 / 48
Fax: +212-6-74 47 49
E-mail: pm@pip.fpms.ac.be

FACULTE POLYTECHNIQUE DE MONS

Laboratoire PIP
Rue de Houdain, 9
7 000 Mons
Belgium

Pierre Manneback
Tel.: +32-65-37 40 50
Fax: +32-65-37 42 00

ECOLE NORMALE SUPERIEURE DE LYON

Laboratoire LIP
46, Allée d'Italie
69 364 Lyon Cedex 07
France

Bernard Tourancheau
Tel: +33-4-72 72 84 34
Fax: +33-4-72 72 80 80

UNSTRUCTURED DOMAIN MAPPING FOR DISTRIBUTED MEMORY ARCHITECTURES

Co-ordinator: Bilkent University, Ankara, Turkey (Cevdet Aykanat)

OBJECTIVES

- Parallelization schemes for many applications on distributed memory architectures employ data parallelism by breaking the data structures supporting a computation into pieces and then assigning those pieces to different processors. These decomposition and assignment tasks constitute the domain mapping problem. The objective in the domain mapping is to find a mapping that minimises the communication overhead while maintaining almost the same workload for each processor. Mapping is very difficult for unstructured domains that typically arise in scientific and engineering computations. The domain-mapping problem is known to be NP-hard for unstructured domains. Hence, heuristics giving suboptimal solutions are used to solve the problem. Domain mapping is a pre-processing introduced for the sake of efficient parallelization. Hence, there is always a trade-off between the mapping quality and the execution time;
- The objective of DOMAP is to investigate, propose and develop new fast heuristics for domain mapping. The relative performances of the proposed and existing heuristics and the models used in these heuristics will be experimentally evaluated on a Parsytec's parallel CC system using various domains mapping benchmarks.

ACTIVITIES AND RESULTS

- ◇ Almost all domain decomposition methods proposed in the literature employ graph model that reduces the decomposition problem into the well-known graph partitioning problem. We showed the deficiencies of the graph model for decomposing sparse matrices for parallel matrix vector multiplication that constitutes the most crucial task in the parallelization of iterative solvers. We proposed two hypergraph models that avoid all deficiencies of the graph model. The proposed models enable the representation and hence the decomposition of unsymmetric square and rectangular matrices as well as symmetric matrices. Furthermore, they introduce a much more accurate representation for the communication requirement. The proposed models are also valid for a more accurate representation of the communication requirement for the decomposition of unstructured domains in general. The proposed models are also successfully exploited and reformulated to transform large linear programming programs into block angular forms for coarse-grain parallelization.
- ◇ The proposed models reduce the decomposition problem to the well-known hypergraph partitioning problem. We have been developing a multilevel hypergraph partitioning tool (PaToH) for experimenting both the validity of the proposed hypergraph models and the performance of the multilevel approach on hypergraph partitioning. Initial experimental results on large sparse matrices, selected from Harwell-Boeing collection and NETLIB suite, confirm both the validity of the proposed hypergraph models and the appropriateness of the multilevel approach to hypergraph partitioning. The initial version of PaToH yields considerably better results than the state-of-the-art graph partitioning tool Metis while it is as fast as Metis. We are currently working on improving both the solution quality and the speed performance of PaToH. We are planning to make the initial version of PaToH publicly available with the relevant documentation by the beginning of 1997.

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PARTNERS

BILKENT UNIVERSITY

Computer Engineering Department
06533 Bilkent
Ankara
Turkey

Cevdet Aykanat

Tel.: +90-312-266 41 33

Fax: +90-312-266 41 26

E-mail: aykanat@cs.bilkent.edu.tr

PARSYTEC COMPUTER GMBH

European Co-operations
Auf Der Hüls 183
52068 Aachen
Germany

C. Rietbrock

Tel.: +49-241-9696 400

Fax: +49-241-9696 50

E-mail: carsten@parsytec.de

PARALLEL COMPUTING APPLIED TO GEOGRAPHIC INFORMATION SYSTEMS

Co-ordinator: Faculté des Sciences de Tunis, Tunis, Tunisia (Zaher Mahjoub)

OBJECTIVES

- The theoretical aspect of the project is to deepen and generalise the design of an efficient and preferment algorithms parallelizing methodology. This methodology is based on algorithms task decomposition and inter-task dependence analysis;
- The practical aspect of the project consists in applying this methodology on a case study, i.e. the design of a vectorization and shape recognition tool in Geographic Information Systems by using neural networks' concepts.

ACTIVITIES

- ◇ Parallelization Methodology Design: Theoretical analysis, implementation on a particular target machine (i.e. an MIMD T9000-DSP based TN310 machine):
 - design of efficient parallel linear algebra algorithms;
 - design of an automatic parallelization tool for programs involving nested loops;
 - design and analysis of efficient parallel algorithms for particular problems in Graph theory (problems encountered in algorithms parallelization);
 - design of efficient parallel recursive matrix multiplication and inversion algorithms.
- ◇ Neural Networks (N.N.) and GIS:
 - State of the art;
 - choice of adequate N.N. architecture and learning algorithm for pattern recognition of cartographic data;
 - implementing the N.N. on a TN 310 transputer based machine;
 - parallelization of thinning algorithms on a TN 310;
 - design of an automatic N.N. code generation tool for parallel machines.

RESULTS

Concerning the parallelization methodology, a theoretical performance study has almost been achieved. A first set of experimental results, that have to be deepened, permitted to reach high speed-ups, particularly with the automatic parallelization tool. As to the the second aspect (N.N. and GIS), a practical implementation is currently in progress.

PARTNERS

FACULTE DES SCIENCE DE TUNIS
Département des Sciences de l'Informatique
Laboratoire Algorithmique et Programmation Parallèles
Le Belvédère
1060 Tunis
Tunisia

Zaher Mahjoub
Tel.: +216-1-87 26 00
Fax : +216-1-88 51 90

**INSTITUT REGIONAL DES SCIENCES
INFORMATIQUES ET DE
TELECOMMUNOCATIONS (IRSIT)**
B.P. 212
Cité Mahrajene
1082 Tunis
Tunisia

Mohamed Naceur Cheman
Tel.: +216-1-80 01 22
Fax : +216-1-78 78 27

SHAPE AND MOTION

Co-ordinator: Aalborg University, Aalborg, Denmark (Erik Granum)

OBJECTIVES

- The objective of this co-operation in the field of computer vision is to investigate robust techniques for continuous computation of shape primitives that facilitate interpretation of visual scenes, dynamic as well as static. The investigations will include both theoretical analyses and test implementations of these techniques in integrated and continuously operating vision systems;
- The European teams have approached active computer vision from a system perspective and developed continuously operating systems in the ESPRIT LTR project EP-7108 VAP II. The Israeli teams have a high level of expertise in methods, i.e. for motion analysis and for description and recognition of shapes. This collaboration provides opportunities to refine methods and systems on the basis of the joint experience. This includes testing and refining methods in system contexts, and achieving more robust system performance through integration of improved techniques.

ACTIVITIES

- ◇ Internal representations of objects and their characteristics are major issues for the consortia, which cover contrasting approaches using model-based as well as appearance based methods. Intensive investigations and analyses are carried out and progress is made towards the development of a unifying framework exploiting the best of the two approaches;
- ◇ View-planning aims to control active vision systems to optimal viewpoints for recognition of objects and/or their individual features. Optimal viewpoints have been defined from a priory geometrical model, and strategies have been developed for controlling active cameras to noise-insensitive views without knowing models of the observed object. Further progress is made on combining the criteria of optimality and the noise minimising strategy to a robust and model independent approach for view-planning;
- ◇ A control framework, the "Active Vision Shell", which supports intelligent Perception Action processes, is a direct result of the collaboration. It was inspired by exchanges between the teams of both software systems and designs of (active) stereo camera heads;
- ◇ The many combinations of the diversities of scientific approaches of the teams involved, have also inspired the development of a range of new "hybrid" methods for: indexing and accumulation of evidence, perceptual grouping, matching, geometric invariance, foveated vision, exploitation of log polar sampling of the sensor, and selection of spatial scales for various purposes of analysis.

RESULTS

The integration of alternative and improved methods into the active vision systems and the successive experimentation will result in development of a range of new and robust techniques. The added robustness will in particular be relevant for a faster move towards more industrial applications, where this robustness is crucial.

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PARTNERS

AALBORG UNIVERISTY

Laboratory of Image Analysis
Frederik Bajers Vej 7
Building D-1
9220 Aalborg
Denmark

Erik Granum
Tel.: +45-98 15 11 33
Fax: +45-98 15 40 08
E-mail: eg@vision.auc.dk

UNIVERSITY OF SURREY

Department of Electronic and Electrical Engineering,
Guildford GU2 5XH
United Kingdom

Josef Kittler
Tel.: +44-1483-50 92 94
Fax: +44-1483-34 139
E-mail: j.kittler@ee.surrey.ac.uk

LINKOPING UNIVERSITY

Department of Electrical Engineering
58 183 Linköping
Sweden

Gösta Granlund
Tel.: +46-13 28 13 03
Fax: +46-13 13 85 26
E-mail: gosta@isy.liu.se

INSITUT NATIONAL POLYTECHNIQUE DE GRENOBLE IMAG

Avenue Felix Viallet 46
38031 Grenoble
France

James Crowley
Tel.: +33-4-76 57 46 55
Fax: +33-4-76 57 46 02
E-mail: jlc@lifia.imag.fr

ROYAL INSTITUTE OF TECHNOLOGY

Department of Numerical Analysis and Computer Science
100 44 Stockholm
Sweden

Jan-Olof Eklundh
Tel.: +46-87 90 81 61
Fax: +46-87 23 03 02
E-mail: joe@bion.kth.se

UNIVERSITA DI GENNOVA

Via Opera Pia 11A
16145 Genova
Italy

Giulio Sandini
Tel.: +39-10-353 27 79
Fax: +39-10-353 29 48
E-mail: giulio@dist.unique.it

THE HEBREW UNIVERSITY OF JERUSALEM

Institute of Computer Science
Givat Ram
91904 Jerusalem
Israel

Shmuel Peleg
Tel.: +972-2-58 52 36
Fax: +972-2-58 54 39
E-mail: peleg@cs.huji.ac.il

WEIZMANN INSTITUTE OF APPLIED SCIENCE

Department of Applied Mathematics and
Computer Science
76100 Rehovot
Israel

Shimon Ullman
Tel.: +972-8-34 28 94
Fax: +972-8-34 41 22
E-mail: shimon@wisdom.weizmann.ac.il

TECHNION - ISRAEL INSTITUTE OF TECHNOLOGIES

Faculty of Computer Science
32000 Haifa
Israel

Alfred Bruckstein
Tel.: +972- 4-29 43 61
Fax: +972-4-29 43 53
E-mail: freddy@cs.technion.ac.il

TEL AVIV UNIVERSITY

Department of Computer Science
Ramat-Aviv
69978 Tel Aviv
Israel

Yehezkel Yeshurun
Tel.: +972-3-640 93 68
Fax: +972-3-640 93 57
E-mail: hezy@math.tau.ac.il

<p align="center">EXPLOITING GENETIC ALGORITHMS BY OPTIMISING INDUSTRIAL SITE CLUSTERING AND TELECOMMUNICATION NETWORK</p>

Co-ordinator: Cap Volmac B.V., Utrecht, The Netherlands (Arnold Koudijs)

OBJECTIVES

- Network design for gas, water, telecommunications, electricity or television cable is traditionally a manual process. The selection of possible itineraries and specifying the future network in full detail involves complex decision-making. Each decision made has high impact on decisions to be made in later stages of the process. Furthermore, numerous calculations must be made to ensure the network answers all optimisation demands such as the maximum loss of voltage, pressure or signal. Taking all this into account human designers often come up with a single network design; alternative solutions can not be compared because of lack of time;
- This abstract describes an application that supports the network design process. The application automatically designs fully specified networks for above mentioned disciplines by employing the descriptive power of expert-systems and the problem-solving capabilities of genetic algorithms. The application co-operates with a GIS toolbox to integrate the network design plans with management information kept in the GIS. The choice for a genetic algorithm was made because standard greedy techniques fail as choices made in one part of the network greatly influence the type of choices made in later stages. This could lead to the design of unacceptably expensive networks.

ACTIVITIES

- Automatic network design
- ◇ First an initial plan of the neighbourhood is represented in a GIS to the designer. The designer defines all itineraries that can be used by the network design application. The designer plans where the itineraries can be located under sidewalks, where they can cross roads and rivers, etc. The GIS keeps track of the different sorts of geographic information such as the sorts of soil, etc. The designer defines the location of the users of the network and the demands of these users (i.e. a company needs more power than a household). The designer also determines the possible locations of supply points. All this information has to be defined manually because it involves lots of considerations that are hard to formalise but do not require a lot of effort or time by a human expert. Examples of these considerations are: an amplifier for a cable network can not be placed in front of a driveway; the location for an electricity supply station is often heavily constrained by governmental laws; the location of a supply gas station will not be placed in the centre of the neighbourhood as it must be connected to other neighbourhoods in case of a pipe breakage;
- ◇ The initial map of all possible itineraries with user locations and possible supplier points, together with all other geographical information (i.e. about types of surfaces) that can have an impact on the cost and safety of the network is feeded to the network design algorithm. The algorithm also needs a database of possible network components together with the components' prices. As building a network means more than distributing randomly a selection of components over various locations, a small expert system is used which defines the logical dependencies of the components. This expert system also contains a number of heuristics that speeds up calculations of the feasibility of the network;
- ◇ There are several other parameters that are important when comparing alternative network solutions. These can be supplied as inputs. Examples are: the estimated increase in demand during the life-span of the network, the minimum and maximum capacity that can be delivered to a user, the maximum number of households that will be disconnected in case of a network failure or the minimum capacity of the network in case of such an error;
- ◇ In the third step the application will search for valid networks that answer the optimisation criteria. Criteria can for instance be costs or robustness. A genetic algorithm is used to generate a number of alternatives, the iterative process will be guarded by a survival of the fittest principle analogous with evolution in nature. This process will continue until an acceptable network design

is developed. An acceptable network is judged on both costs and quality. Although the heuristics used are most often sufficiently powerful to build valid networks, a selection of the presumed best alternatives will be simulated in dedicated network calculation tools for feasibility study. The best of the alternative network design plans, including an estimation of the cost and an overview of their implications, are then transported back to the GIS, ready to be examined by the designer;

- ◇ Confronted with several alternatives the designer can select the network that meets his/her needs best. In case of doubt, the designer can adjust the network and re-enter it in the application to be examined or to be filled in more completely in accordance with some information that was not available at the time of the design. When the geographic information plans change - something that happens all too often - the designer can adjust the network manually or transport it back to the application to adjust it automatically. The GIS, containing all necessary information about the neighbourhood and the network, can now be used to generate the final plans.

The genetic algorithm

- ◇ A genetic algorithm works with a population of solutions to a problem and tries to iteratively improve the population by repeated application of mutation (acting on one solution at the time) and crossover (using more than one solution). The search is focused on the observed best solutions by selection on *fitness* (cost in this case). The algorithm works by creating valid individuals - by using a *decoding* function - and selects the cheapest networks with higher probability for reproduction. The robustness of the networks (in case of malfunction) can be used as a secondary fitness measure, but it is preferred for simplicity's sake that this consideration is also incorporated in the cost by using prices both for investment and exploitation of the networks;
- ◇ The network design algorithm uses a *path-based* representation that connects a household to a supply point. These paths are combined to a network using a decoding function to form a tree-structure with or without extra recurrent connections. A local search technique (stochastic hill climbing) is then employed to fill in the details of the network. These details include, but are not limited to the thickness of the pipe or cable, the type of splitters used and the kind of containers that are used. In the case of gas and electricity the network is now tested on its performance in case of malfunction, by randomly selecting a number of connections to fail, and calculating the effect of this error in the network;
- ◇ Because of this stochastic filling in of the details of the networks, equivalent *genotypes* (clones) will not necessarily lead to equivalent networks. This has the positive side-effect that the genetic algorithm is not only searching for the cheapest network, but also to itineraries that lead often to cheap networks. This is desirable because such a combination of itineraries can be easily adapted when some details change without having to design a completely new network;
- ◇ Interesting networks (on cost and robustness) will be transported to the *hall of fame*, where they are more fully analysed and accepted or rejected based on this analysis. At the end of the search process, the most promising networks from the hall of fame are selected and transported to the GIS where they can be analysed by the designer. This process is fully parametrized, but can also run unsupervised.

RESULTS

The application has been tested on the design of telecommunication networks for Tunisian Telecom. Experiments suggest that the design process by using this tool can be reduced from several weeks to two days, while the cost of the automatically developed networks is reduced by 15% compared with hand developed networks. A Dutch energy supplier, providing television cabling, electricity and gas, has also applied the network design tool for their specific networks and preliminary results show that several types of networks can be designed simultaneously, so that mutual laying costs can be reduced. Research and application for these types of networks are still in progress.

PARTNERS

CAP VOLMAC B.V.
Daltonlaan 300
P.O. Box 2575
3500 GN Utrecht
The Netherlands

Arnold Koudijs
Tel.: +31-30-252 63 16
Fax: +31-30-252 70 45
E-mail: akoudijs@inetgate.capgemini.nl

**INSTITUT FÜR KYBERNETIK UND
SYSTEMTHEORIE**
Am Hülsenbusch 54
4630 Bochum
Germany

E. Von Goldammer
Tel/Fax: +49-2302-80 20 16
E-mail: ics@ics.prima.ruhr.de

**INSTITUT REGIONAL DES SCIENCES
INFORMATIQUES ET DES
TELECOMMUNICATIONS**
Rue Ibn Nadime 2
Cite Montplaisir
1082 Tunis
Tunisia

Salah Benabdallah
Tel.: +216-1-80 01 22
Fax: +216-1-78 78 27
E-mail: Salah.benabdallah@irsit.tn

**BOTTOM-UP ANALYSIS OF LOGIC PROGRAMMING LANGUAGES: THEORY,
PRACTICE AND APPLICATIONS**

Co-ordinator: Università di Pisa, Pisa, Italy (Giorgio Levi)

OBJECTIVES

The main objective is to provide a practical and general purpose environment for the development and application of global analysis tools for logic programming languages. Such tools are essential to obtain high performance implementations. The environment should provide capabilities for modular program analysis, different control strategies (pure sequential languages, PROLOG, concurrent languages) and constraint based languages. One relevant goal is also to promote interaction between the areas of deductive data bases and compilation techniques for logic languages. The unique approach taken in the project is to base the tools on a bottom-up semantics. To this end, the goal is to demonstrate the practical potential of starting from a clean and concise semantics core, combined with abstract interpretation, transformational methods and abstract compilation. Current implemented frameworks are based on top-down semantics and do not provide the above noted capabilities.

ACTIVITIES

- ◇ Design and application of abstract compilation techniques as an alternative to the more classic abstract interpretation;
- ◇ Application of abstract interpretation techniques to reason about different (abstract and concrete) semantics;
- ◇ Modular and abductive analysis;
- ◇ Modelling the control strategy of Prolog;
- ◇ Systematic design of analysis domains;
- ◇ Analysis of local suspension and of input-output demand for concurrent logic programs;
- ◇ Integration of bottom-up and top-down frameworks of analysis, and evaluation of these frameworks.

RESULTS

- ⇒ Design and application of abstract compilation techniques as an alternative to the more classic abstract interpretation. Previous work has indicated the potential benefit of this approach. However these applications appear limited to domains based on Prop and prior to our current collaboration it has not been clear if the approach can be applied to more general types of domains. We now succeeded to apply abstract compilation to the analysis of properties such as those obtained in the PLAI system using the Sharing domain and various enhancements. The results in this area are very promising and indicate an approach which is both theoretically clean and advantageous from the implementation point of view.
- ⇒ Application of abstract interpretation techniques to reason about different (abstract and concrete) semantics. The collecting semantics (SLD trees) has two equivalent top-down (transition system) and bottom-up (denotational) definitions. Both definitions are given in terms of a small set of basic semantic operators, directly related to the syntactic operators. More abstract (precise or approximated) semantics are obtained by defining the property one wants to model (observable) as a Galois insertion. A taxonomy of observable has been studied, where each class satisfies a set of axioms relating the Galois insertion and the basic semantic operators of the collecting semantics. The framework has also been successfully used as a foundation of a generalisation of declarative debugging, called abstract diagnosis.
- ⇒ Modular and abductive analysis. Compositional (deductive) analysis is the basis for the definition of the dual-notion of abductive analysis. We have introduced a practical method for abductive analysis of modular logic programs. This is obtained by reversing the deduction process, which is usually applied in static-data-flow analysis of logic programs. The approach is validated in the framework of abstract interpretation.

- ⇒ Modelling the control strategy of Prolog. A new (fixpoint, goal-independent) PROLOG semantics has been defined which accurately models the operational behaviour of some of the control features of PROLOG, namely the search rule, the cut, the not and var primitives. Some new problems arise in the abstraction process. The most interesting one is the need of downward approximations of constraints. These approximations are needed to handle termination properties and are independent from the specific abstract domain. For the usual upward approximation, we can use the traditional domains developed for pure logic programs. A framework based on such a semantics has been implemented and tested on a groundness dependencies analysis.
- ⇒ Systematic design of analysis domains. We have studied the basic algebraic properties of several operations for abstract domain composition, like reduced cardinal product, disjunctive completion, functional combination and tensor product. The reduced cardinal product, as well as several domain completions, has been proved to be fundamental in the systematic construction of “optimal” semantics for logic program analysis. The inverse operation for reduced cardinal product, which is complementation, has been introduced.
- ⇒ Analysis of local suspension and of input-output demand for concurrent logic programs. Analysing suspension allows to apply the technique of abstract compilation to suspension free concurrent programs, and hence allows to exploit the standard CLP analysis techniques for these languages. Similar techniques have been used to model the delay mechanisms of CLP languages.
- ⇒ A system was implemented which automatically detects termination and which can handle most of the examples in the literature.
- ⇒ Design and implementation of several prototypes for bottom-up execution of logic programs and of a framework for the computation of an abstract semantics for logic programs. A prototype of generic bottom-up abstract interpreter for CLP languages (CHINA) has been implemented.
- ⇒ Integration of bottom-up and top-down frameworks of analysis, and evaluation of these frameworks. Previous work on goal dependent and independent analyses (usually identified with top-down and bottom-up frameworks, respectively) has been extended, including a comparative evaluation of the frameworks in performing goal independent analyses.

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PARTNERS

UNIVERSITA DI PISA
Dipartimento di Informatica
Corso Italia 40
56125 Pisa
Italy

Giorgio Levi

UNIVERSITA DI UDINE
Dipartimento di Matematica e Informatica
Italy

Moreno Falaschi

UNIVERSIDAD POLYTECNICA DE MADRID
Facultad de Informática
Spain

Manuel Hermenegildo

KATHOLIEKE UNIVERSITEIT LEUVEN
Department of Computer Science
Belgium

Bart Demoen

BEN-GURION UNIVERSITY OF NEGEV
Department of Mathematics and Computer Science
Israel

Michael Codish

HEBREW UNIVERSITY OF JERUSALEM
Department of Computer Science
Israel

Yehoshua Sagiv

SURFMOD**Co-ordinator: Universität Stuttgart, Stuttgart, Germany (G. Pritschow)****OBJECTIVES**

SURFMOD considers the application of surface modelling and rapid prototyping technologies to the prototyping and/or reproduction of exact models in architecture, archaeology and geodetics. Furthermore it deals with applications of 3D modelling, visualisation and rapid prototyping in medical diagnosis, surgical planning, radiation therapy planning and the precision milling of prothesis. In summary the task of the project was the interdisciplinary exchange and co-operation between the institutes HTI (archeology), INRIA (medical applications) and ISW (production engineering) in the field of surface measuring and reconstruction. Besides it is aimed at to support HTI, developing itself a own surface modelling system.

ACTIVITIES AND RESULTS

The research institute INRIA in Sofia-Antipolis, France developed a software model for the reconstruction of medical objects. This model was integrated into the surface modelling system of the HTI and was further developed to a more advanced stage. ISW, sent a 3-D laser scanner to HTI in order to digitize the temple stones of Venus to facilitate the temple's reconstruction. HTI reconstructed the Temple of Venus. With help of the digitized data a model (1:140) was made using stereolithography. Research scientists from ISW and HTI did research work in Paris, France. This was necessary in order to digitize archaeological objects, e.g. the world's largest vase, which is originally from Cyprus. This vase is used as an object for the demonstration and for the verification of the developed software packages due to the nonuniform surface and the dimension of this object.

Apart from those practical team work during the execution of the project several workshops were hold in Nicosia, Stuttgart and Sophia-Antipolis even together with the industrie to have a good interchange of ideas and experiences in the field of surface reconstruction and rapid prototyping. Thus a good foundation could be set for a further co-operation considering on the one hand the understanding between the partners and on the other hand the preparation of new concepts for future common research work.

It is planned to use the surface modelling system of the HTI which could be developed even with the help of the KIT project to support the archeology in Cyprus.

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PARTNERS

UNIVERSITÄT STUTTGART
Institute for Control Technology (ISW)
Stuttgart
Germany

G. Pritschow

INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE (INRA)
Sophia-Antipolis
France

J.-D. Boissonnat

HIGHER TECHNICAL INSTITUTE (HTI)
Nicosia
Cyprus

M. Ioannides

COMPUCYPRUS

Co-ordinator: University of Leeds, Leeds, United Kingdom (Anthony G. Cohn)

OBJECTIVES

- To carry out research in the topics of Knowledge Representation and Reasoning (KRR) within the general context of computational logic. In particular, it aims to study how Logic Programming with its recent extensions of Constraint and Abductive Logic Programming can be used to study problems in KRR;
- To assist the Compulog-Net network of Excellence in its activities by taking on the task of the publication of the network's newsletter.

ACTIVITIES

- ◇ The project has facilitated the interaction and scientific collaboration of Cyprus with several nodes of the Compulog-Net. Each year Cyprus has taken two or three scientific trips to different nodes of the network developing further its research collaboration with them. This research was carried out mainly in the following areas :
 - Abductive Logic Programming Argumentation for Non-Monotonic Reasoning;
 - Abduction in Deductive Databases Temporal Reasoning and Abduction;
 - Abduction and Inductive Learning.
- ◇ The main problems covered were:
 - The formulation of appropriate semantics and computational models for abductive logic programming together with a general survey of the role of abduction in logic programming. Argumentation in Knowledge Representation and Reasoning with particular emphasis on Negation as Failure in Logic Programming and the generalisation of this to other frameworks for Non-monotonic Reasoning outside Logic Programming;
 - The problem of updating deductive databases and their evolution under non-deterministic and non-chronological updates;
 - The development of a simple framework for reasoning about actions with narratives and the role of abduction in such a framework;
 - The relation of abductive and inductive logic programming;
 - The role of abduction in learning from incomplete information and/or 'high-level' information.
- ◇ In parallel, the project was responsible for the publication of the Compulog-Net newsletter producing its first four issues. In these one can find a full account of the activities of the Network over the past three years together with other information about world-wide activities in the area of Computational Logic.

RESULTS

- ⇒ The newsletter of Compulog-Net called "Computational Logic".
- ⇒ The publications listed below.

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PARTNERS

UNIVERSITY OF LEEDS

Division of AI
School of Computer Studies
Leeds LS2 9JT
United Kingdom

Anthony G. Cohn
Tel.: +44-113-233 54 82
Fax: +44-113-233 54 68
E-mail: agc@scs.leeds.ac.uk

DFKI - COMPULOG-NET

Stuhlsatzenhausweg 3
66123 Saarbrücken
Germany

David Pearce
E-mail: pearce@dfki.uni.sb.de

UNIVERSITY OF CYPRUS

Department of Computer Sciences
Kallipoleos Street 75
P.O. Box 537
Nicosia
Cyprus

Antonis C. Kakas
Tel.: +357-2-36 05 89
Fax: +357-2-33 90 62
E-mail: antonis@tuning.cs.ucy.ac.cy

ELECTRONIC DATA INTERCHANGE

Co-ordinator: EDIFRANCE, Paris, France (C. Chiaramonti)

OBJECTIVES

- To introduce widely EDI techniques in Tunisia, including the adaptation of an Arabic interface. The pedagogical instrument that has allowed European companies to become acquainted with EDI techniques will be adapted to Arabic culture. The result will be the elaboration of the EDITIEL software in Arabic and a study on the introduction of EDI and electronic commerce in Tunisia.

ACTIVITIES

- ◇ EDITIEL adaptation into Arabic;
- ◇ Elaboration of the 0 version of EDITIEL in Arabic;
- ◇ Study on EDI application in Tunisia;
- ◇ Elaboration of the 1 version of EDITIEL in Arabic;
- ◇ Meeting in Tunis in order to present the first findings of the EDI/EC Study to various potential users, from Tunisia, Europe and Mediterranean Countries, including SMEs and organisations such as Chambers of Commerce and Industry;
- ◇ Workshop;
- ◇ Final version of EDITIEL in Arabic;
- ◇ Final report, including proposals to use EDITIEL in Arabic in other Arabic countries and recommendations to take into account specificities of the Arabic language in the EDIFACT-UN standard.

FOLLOW-UP

The final presentation of Arabic EDITIEL and the EDI study to representatives of various Arabic and Mediterranean countries will facilitate the dissemination of EDI knowledge into the rest of the Arabic World and will serve as a catalyst for EDI-related projects involving the EU and countries of the Mediterranean.

PARTNERS

EDIFRANCE
Tour Europe
92049 Paris la Défense Cedex 07
France

C. Chiaramonti
Tel.: +33-1-42 91 57 93
Fax: +33-1-42 91 60 26
E-mail: edifr@world.net.sct.fr

CENTRE NATIONAL DE L'INFORMATIQUE
Rue Belhassen Ben Châabane 17
1005 El Omrane
Tunis
Tunisia

Dr. Ben Sassi
Tel.: +216-1-89 40 15
Fax: +216-1-78 18 62

RAINFALL FORECASTS AND STRATEGIC IRRIGATION MANAGEMENT

Co-ordinator: Società di Ricerca e Servizi di Ingegneria (ISMES) S.P.A., Bergamo, Italy
(Stefano Clementel)

OBJECTIVES

The overall objective of the project was to develop and test a methodology for the optimal utilisation of meteorological rain forecast in the North of the Nile delta for a better understanding and protection against extreme hydrometeorological events and for the optimal use of available resources for irrigation purposes. Specific tasks of the project are:

- Set-up an integrated methodology for rainfall forecast and strategic irrigation management;
- Develop operating policies for the irrigation network of the Northwest Mediterranean Coast Region that optimise the contribution of the rainfall in agricultural land expansion;
- Layout of a hydrometeorological centre for the coastal strip between Alexandria and El Allum on the Egyptian border with Libya.

ACTIVITIES

- ◇ Territorial characterisation of a 'Pilot area' on the Nile delta;
- ◇ Hydrometeorological modelling with application of meteorological limited area model (LAM) to the area of the Nile delta;
- ◇ Development of multi-objective analysis models for irrigation management optimisation;
- ◇ Preliminary design of HW and SW of a hydrometeorological centre on the Nile delta.

Finally the methodology has been applied to hydro-meteorological data of the last ten years on the northern part of the delta and the possibility of optimisation of water management during rainy period was quantified.

OUTCOME

Scientific-technical results

- ▷ Application of meteorological Limited Area Models (LAM) to the Nile Delta
Two different time periods has been selected for the study. Both periods are located in the winter season when the Mediterranean perturbations affect the Nile Delta with heavy showers. The first period, ranging from 18 to 23 November 1994, is characterised by significant and intense precipitation. The second period, ranging from 3 to 14 December 1996 has been selected for the presence of days of intense rainfall alternated with drought periods. In order to produce the meteorological forecasting two different models have been used for the selected periods: the ECMWF (European Centre of Medium Range Weather Forecast) global model, that allows to reproduce the phenomena on the synoptic scale (800-1000 km), and the MEPHYSTO Limited Area Model (LAM), which runs in operative way at the Italian National Electric Board. Since forecasting reliability decrease with time, only to forecast at time +24 and +48 (tomorrow and the day after) where considered. The LAM model works also at +24 and +48 with a grid of 30 x 30 Km.
A statistical analysis of precipitation records, obtained from the Egyptian Meteorological Authorities in the period 1973-1996, has pointed out the principal rainfall events occurred in the Nile Delta.
The precipitation predicted by the models has been compared with the data recorded at the Egyptian stations. Furthermore, the fields of the upper atmosphere has been examined to understand the onset of rainfall events and to provide a definition of large scale weather regimes associated with rainfall over the Egyptian territory.
The results are encouraging: both models simulate the synoptic flow quite well and the precipitation events are time-centred. The use of the LAM in the Mediterranean part of Egypt,

where the flow regimes mostly pertain to the large-scale range, seems not to add a relevant contribute to the forecast, particularly when light precipitation occurred.

Moreover the lack of tuning of the LAM model parameters to run at lower latitudes, (the LAM is calibrated for Italian area, and Italian climate) could have affect the forecasting quality, in particular for light rain. The ECMWF model seems to produce good precipitation forecasting mainly when the moist processes are governed by dynamical forcing.

▷ Hydrological Balance of the Nile Delta

During the period from October to March some rainfall events usually occurs in the already irrigated area of the Nile Delta; part of this water is lost through the drainage system to the sea. Whenever a forecasting system of two-three days rainfall is implemented, a fraction of the irrigation water could be stored for successive use or distributed within the irrigation network considering the location and intensity of the forecasted rain.

First of all the response of the Delta area to rainfall events was studied, based on historical data set of thirteen rain gauges and on the corresponding discharges to the sea through out the main Nile branches of Damietta and of Rosetta.

The analysis of the hydrological balance in the Nile Delta area leads to a correlation expression between the water income to the Delta irrigated areas - from the Nile plus the rainfall - and the water consumption in the system plus the outcome to the sea. The correlation expression, even if derived from very general assumptions concerning rainfall distribution, irrigation needs, infiltration and evaporation values in the Delta area, can be use as a first estimation of the water volume from rainfall that can be used for storage or direct irrigation purposes in new areas at the Western coast. This correlation expression is proposed as a *preliminary estimator* to derive the upper limit of water volume available for new purposes at Delta Barrage, at rainfall event scale, by minimising the discharges to the Mediterranean Sea.

The application of the HYBAD model permits to calculate the daily volumes of the available fresh water from the Nile River at Delta Barrage that can be used for new purposes.

▷ Water Allocation Management

This activity s leads to the formulation of the water allocation optimisation model for water-supply-distribution in a pilot area of Western Delta, and to the implementation of such model using the numerical tool Solver from Microsoft Excel.

Four alternatives are available as harvesting places for the management of the excess water. These zones are: Delta Barrage pool, Maryout or Edko lakes, ground water and channel cross section at the Extension El Hamman Canal.

A “water supply and distribution system planning scheme” has been developed in order to provide the decision-makers with a set of optimal policies with regard to the selection of supply sources and the associated transmission lines in meeting the demands at various locations in the systems.

The available water comes from the Nile River and rainfall, and the water demand considers irrigation, minimum flow in the Nile for navigation and water quality purposes.

Pilot Area

The methodology has been applied to a Pilot Area using historical data of the last ten years. The Pilot Area is located on the West Delta near the North coast, and includes the irrigated area of El Nasr Canal after Pump Station N5 and the Extention of Bahig Canal. The first irrigated area is 27300 hectares wide and the second one 7560 hectares.

▷ Design of a hydrometeorological centre

A technical documentation have been produced containing the technical specification of hydrological and meteorological equipments, of the telecommunication system including both Meteor Burst system and a solution based on a Ku band satellite communication system.

Specification are given also for a reference configuration of the main computer system HW and SW; is based on a HP 9000 series 800 system; it is, of course, a basic reference, considering the extremely rapid evolution of commercial HW. The need for factory training and on site training, maintenance and spare parts and special tools are also been considered.

Promotion of achieved results

A Hydrometeorological Centre for the Coastal Zone will be established. The expected benefit from a Hydrometeorological Centre with a multi-discipline staff team have been analysed. Its priorities have to be set towards establishing global and integrated organisation and approach to Rainfall Forecast and Water Resources Management. Through this approach, emphasis has to be put on capacity building, monitoring network and a management system with hardware and software components.

The Centre can best be viewed as special interdisciplinary and integrated institution studying and collecting hydrometeorological data, generating a great variety of potential scenarios relating to the development of North Coast Region and increasing environmental and socio-economic awareness at the policy-making level. Several outputs can be brought from the Centre:

- Daily material on weather forecast in the area under consideration especially in the days of high/medium potential for rainfall;
- Daily water management scheme during the above named period in which use is made of different types of water and utilised for different purposes;
- Models and knowledge of various factors affecting future agricultural development;
- Short-term plans for the improvement of infrastructure in order to optimise the use of water obtained from different sources and used for different purposes;
- Long-term strategies of water use in the study area, which takes into consideration all the possible scenarios, which increases the system efficiency;
- Environmental Impact Assessment of each of future scenarios which allows for all the possible responses to changes that are going to take place due to the introduction of the new processes;
- New technologies which achieve a better resource utilisation towards water conservation;
- Dissemination of information and knowledge gained to decision-makers and practitioners.
- The Centre should be organised for forecast dissemination to potential interested users.

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PARTNERS

SOCIETA DI RICERCA E SERVIZI DI INGEGNERIA (ISMES) S.P.A.

Viale Giulio Cesare 29
24124 Bergamo

Italy

Stefano Clementel
Tel.: +39-35-30 75 30
Fax: +39-35-30 29 99

WATER MANAGEMENT RESEARCH INSTITUTE

Delta Barrage WRC Building

Cairo

Egypt

Dia-El-Din Ahmed El-Quosy
Tel.: +20-2-218 95 63
Fax: +20-2-218 95 61

CAIRO UNIVERSITY

Faculty of Engineering

Department of Irrigation & Hydraulics

Cairo

Egypt

Ibrahim El-Assouty
Tel.: +20-2-375 75 70
Fax: +20-2-36 33 65

ANALYSED CLIMATOLOGY OF RAINFALL OBTAINED FROM SATELLITE AND SURFACE DATA FOR THE MEDITERRANEAN REGION (ACROSS) - A VERSION FOR THE EASTERN MEDITERRANEAN REGION

Co-ordinator: University of Genova, Genova, Italy (Franco Siccardi)

OBJECTIVES

The major objective of this research is the improvement of the rainfall forecasting in the eastern Mediterranean region. To this end the following detailed objectives are set:

- To develop and demonstrate a methodology for total area or contouring, evaluation and interpretation of rainfall over-land and over-water anomalies in the target region as basis for ongoing climate-hydrological analysis and forecasting;
- To prepare a unified climatology of rainfall over that region;
- To describe the observed rainfall distribution through climatological analysis of satellite data (passive microwave);
- To identify and map the most significant departures from the long term average rainfall, as well as the characteristic space and time scales of extremes;
- To investigate the major effects of significant rainfall anomalies through related analyses of passive microwave data (land surface types) for the microwave period among 1978 and 1994.

ACTIVITIES

- ◇ Collecting ground-based rainfall data from WMO and local networks, development and calibration of techniques for the processing of SMMR and SSM/I images for rainfall and surface characteristics, acquisition and preparation of satellite images, development of graphical tools for data analysis and presentation;
- ◇ Application of techniques for SMMR data analysis and development of methods for the integration with land and sea surface data via GIS;
- ◇ Description and presentation of results through climatological atlases and time series of climatological data associated with surface characteristics;
- ◇ Open end of project seminar on remote sensing applied to weather/rainfall forecast in the Mediterranean region, bringing together all groups working on this subject and in particular all relevant projects currently funded under the AVICENNE programme.

RESULTS

- ⇒ The work undertaken during the first year of the project activity was mainly devoted to the acquisition of the basic data resources needed for the eventual development of dedicated research studies, and to the generation of initial overwater products based on SMMR satellite data (1978-87). In particular the collection, collation and analysis of raingauge data for suitable and available stations in the study area were addressed, in order to produce maps of average rainfall for months, seasons, years, plus maps, graphs and statistics for rainfall variability and departures from the norm. At the same time the collection and geo-registering of SMMR (1978-1987) and SSM/I (1987-1994) images prior to their preliminary analysis for over water rainfall within the study area to complement the above mentioned products, and so complete a regional picture for the Eastern Mediterranean. The definition of suitable graphical tools for presentation of project results was also addressed and the acquisition of ancillary data completed. The two data-sets were implemented within a relational database and a hydrologically oriented Geographical Information Systems (GIS).
- ⇒ The 30-seconds Digital Elevation Model of the Mediterranean region, obtained from USGS, was selected as the basic information over which both satellite and raingauge data are represented. A large number of raingauge and meteo-climatic stations were identified in the study area and the acquisition of data for the period 1978-1994 started. In particular daily rainfall series from the

NOAA / NCDC dataset were acquired and complemented with sparse data from the national networks (provided by partner institutions) in order to achieve the information density of about one raingauge per 625 km² (25 x 25 km grid).

- ⇒ Microwave satellite images were also collected for the period 1978-1994, both from SSMR and SSM/I sensors. In particular data from the SMMR were obtained in the form of Temperature Calibrated Tapes (TCTs) for the entire instrument operation period from 25 October 1978 to 20 August 1987 from the US National Space Science Data Centre. SSM/I images for the period 1987-1994 were obtained from the US Defence Meteorological Satellite Programme (DMSP) via the Marshall Space Flight Centre of NASA.

PARTNERS

UNIVERSITY OF GENOVA

Institute of Hydraulics
Montallegro 1
16145 Genova
Italy

Franco Siccardi
Tel.: +39-103-53 24 97
Fax: +39-103-53 24 81
E-mail: franck@idra.unige.it

UNIVERSITY OF BRISTOL

Department of Geography
Remote Sensing Unit
Bristol BS8 1SS
United Kingdom

Eric Barrett
Tel.: +44-1272-30 37 45
Fax: +44-1272-30 37 46
E-mail: e.c.barret@bris.ac.uk

MIDDLE EAST TECHNICAL UNIVERSITY

Civil Engineering Department
06531 Ankara
Turkey

Dogan Altinbilek
Tel.: +90-312-210 10 00 / 24 01
Fax: +90-312-210 12 62

UNIVERSITY OF JORDAN

Department of Geology
Amman
Jordan

Elias Salameh
Tel.: +962-6-84 35 55 (ext. 2331, 2345)
Fax: +962-6-84 68 41

INTERNATIONAL CENTER FOR AGRICULTURAL RESEARCH IN THE DRY AREA (ICAZDA)

P.O. Box 5466
Aleppo
Syria

Theib Y. Oweis
Tel.: +963-21-21 34 77 / 22 51 12 / 22 50 12
Fax: +963-21-21 34 90 / 22 51 05

SEMI-SHIFT-INVARIANT OPERATIONS FOR OPTICAL COMPUTING

Co-ordinator: The Weizmann Institute of Science, Rehovot, Israel (Isaia Glaser)

OBJECTIVES

- In this work, the potential performance of *free space* optoelectronic systems, implementing massively parallel *semi-shift-invariant* operations on two-dimensional data, will be evaluated. The evaluation process will include a theoretical study and the construction and experimental evaluation of key elements and a demonstration system or systems. The systems investigated combine “replication” of an input pattern, reconfigurable linear filtering and application of point-non-linearities. The replication is done optically, preferably with incoherent light, using a device such as a special diffractive element or a lenslet array. The filtering is done by masks whose transparency functions control their operation;
- The research will mostly target the following two computing paradigms:
 - multichannel correlator;
 - cellular machines.

ACTIVITIES

- ◇ **Design of optical architectures**
Preceding intensive investigation of any specific architecture, a theoretical comparison of alternative implementation schemes for both architectures (multichannel correlator and cellular machine) will allow selection of the best configurations. The simplicity of the optical configuration and its suitability for practical application will be especially taken into account. This study appears easier for the correlator case; the design of the cellular machine requires an accurate literature review. This study may lead to the design of original approaches.
- ◇ **Theoretical study of the performance of selected configuration candidates**
After the preliminary overview, detailed analysis of the performance capabilities of each approach will be used to select the best configuration for each of the two systems. As described in the previous paragraph, diffraction, aberrations, mechanical precision, and other related parameters will be investigated in depth. This analysis will include both theoretical (paper and pencil) and computer simulation.
- ◇ **Evaluation of suitable filters for the correlator**
An intuitive approach will allow design of adequate filters for recognition of multiple objects (possibly some road signs as a test case) giving relevant features for the post-processing stage.
- ◇ **Experimental demonstration of the two selected implementations**
The demonstration will show the practical feasibility and verify results from the analysis part of this work. This will include:

Multichannel correlator:

- use of an SLM for the input object;
- design of the non-reprogrammable, gray-scale masks;
- image replication;
- detection and display of the correlation output with a suitable optoelectronic and electronic system.

As a rough estimate, it is expected that about 100 channels, each with 100 x 100 resolvable pixels will be feasible for this demonstration.

Cellular machines:

- LED array, or a binary SLM device, will simulate the dilute emitters associated with the Pes;
- image replicator (diffractive or lenslet-array-based) device will implement the neighbour interconnects;
- non-reprogrammable (fixed) mask for neighbour selection;

- integrated optoelectronic detector array (possibly a photodiode array) and electronic to simulate detection and thresholding. Here, the feedback shall be electronic. The use of an LCLV for this function will be considered;
- a rough value of 100 Pes, each interconnected with a neighbourhood of 25, is expected to be feasible for this demonstration.

◇ Identification of direction(s) for future research

RESULTS

During the first and second years, the main thrust of the research was on miniaturising optical shift-invariant and semi-shift-invariant (convolvers/correlators) optical systems, and on developing suitable optical computing architectures to exploit them. On the optical side, both substrate mode optics and the LAHC (Lenslet Array Holographic Convolver) were investigated. In particular, a feasibility demonstrator for the LAHC was constructed, and several variations of the LAHC were introduced and analysed. On the systems/architecture side, a processing paradigm based on optical simulated annealing, combining optical semi-shift-invariant interconnections, an optical "Boltsman machine", and smart-pixels devices is being investigated, both in theory and through experiments with conventional correlators.

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PARTNERS

CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE

Centre Scientifique d'Orsay
 Institut d'Optique Théorique et Appliquée
 Bâtiment 503
 B.P. 147
 91403 Orsay Cedex
 France

Pierre Chavel
 Tel.: +33-1-69 35 87 41
 Fax: +33-1-69 35 87 00
 E-mail: pierre.chavel@iota.u-psud.fr

THE WEIZMANN INSTITUTE OF SCIENCE

Department Physics of Complex Systems
 P.O. Box 26
 76100 Rehovot
 Israel

Isaia Glaser
 Fax: +972-3-672 08 95
 E-mail: feglaser@weizmann.weizmann.ac.il

COOPERATION IN VLSI - CIRCUIT DESIGN TRAINING

**Co-ordinator: Interactional Microelectronic Center (IMEC), Leuven, Belgium
(E. Bourdeaud'hui)**

OBJECTIVES

- The aim of this project is to integrate academic institutions from Mediterranean non-member states in the European Unions activities to train engineering and computer science students in VLSI design. A first phase of the project focused on a feasibility study to identify appropriate academic institutions in a number of countries of the region. The partners from Turkey and Malta were then selected to participate in European design training according to the rules and provisions of the EUROCHIP project. Both in Turkey and in Malta a few subsidiaries of Western electronic companies are established to assemble components and systems for the local market and for export on the basis of low labour costs. Participating in EUROCHIP provided the universities with opportunities to train young engineers for the national industry and to prepare this for European co-operation;
- Design facilities in the universities were complemented in the beginning of the second phase of the project to reach European standards, courses were upgraded, trainers attended in lecturer courses. VLSI circuits are manufactured by EU companies following designs of student classes at the partners' locations.

ACTIVITIES

Malta

◇ **Microelectronics activities**

- A first ASIC design was submitted for fabrication in January 1994. A BCH decoder was designed by an undergraduate student as a final year project in the B. Eng. course. For this design, the SOLO 1400 design kit was used and it has been processed in the ES2 1.5 μm CMOS technology. Twenty samples were returned to the department and successfully tested on the ASIC Verification Tester;
- Four other SOLO 1400 designs, using 1.0 μm CMOS technology, were submitted for fabrication in May and June 1995. These designs were carried out by undergraduate students as part of the first year VLSI course work;
- At the postgraduate level, an integrated circuit implementing an analogue neural network architecture capable of on-chip learning has been designed using the Alcatel-Mietec 2.0 μm CMOS technology.

◇ **Training activities in microelectronics**

- In 1993, two senior Engineers from RAL visited the University of Malta to define a detailed programme for the first use of CAD tools and the associated training for staff members in order to enable them to develop their student courses;
- As Malta had some experience of an old version of Solo 1400, it was decided that the first chip to be undertaken should be designed using Solo 1400. As staff members had no experience whatsoever of more complex tools, the majority of the training in the first year concentrated on the Cadence suite;
- As the two key members of the University of Malta staff were engaged in PHD programme at the University of Surrey in the United Kingdom, the training courses were scheduled for late 1993. Two members of the University of Malta attended three separate courses at Rutherford Appleton Laboratory (RAL) covering Schematics and Simulation, Place and Route and Verilog. All three courses consisted of lectures and practical sessions, specifically targeted to enable new users with no previous experience of sophisticated CAD tools to produce a complete design as quickly as possible.

Turkey

◇ **Microelectronics activities**

- The microelectronics Activity is concentrated on the processing refinement and availability;

- In the frame of the IC A 17 Co-operative Action, is concentrated on the CMOS standard cell library conceptualisation and the design of ASIC's in their own processing facilities.
- In addition to the role they play within educational support to the universities and to the industry, they have trained students at the institute itself.

◇ **Training activities in microelectronics**

- In 1993, a two weeks' course has been organised at the INVOMEK division of IMEC to train the Marmara staff in the use of the CAD environment, acquired through the program. In total, two participants have assisted to this training;
- In 1994, one member of staff attended the EUROCHIP ASIC Testing Course at Hannover University. During the same year, two members of staff attended the VHDL Synopsys Training Course held at IMEC;
- In 1995, two members of the Marmara University attended to the EUROCHIP Course on Methods and Tools for Digital System Design held at IMEC.

The Istanbul Technical University, Istanbul

◇ **Microelectronics activities**

- In the frame of a co-operative research work running in the laboratory on Capacitive Threshold Logic, ten threshold logic blocks have been implemented and submitted to AMS to be fabricated in the 1.2 μm CMOS technology;
- In parallel, staff of the ITU Microelectronics Group have been co-operating with the ITU-ETA Asic Design Centre for the spec development, design and testing of integrated circuits for the Turkish electronics industry;
- Next to the design activities, the Istanbul Technical University Microelectronics Group is also active in the processing activity itself. They are in the possession of a small educational clean room, equipped with basic processing facilities for oxide growth, LTO, spin-on doping, diffusion, lithography and metallisation. For device testing, they have two semiconductor parameter analysers and a Keithly CV characterisation equipment.

◇ **Training activities in microelectronics**

- In 1993, a 2 weeks' course has been organised at the INVOMEK division of IMEC to train ITU staff in the use of the CAD environment, acquired through the Action. In total, 5 participants have attended this training;
- In 1994, one staff member and one assistant attended the VHDL Training Course at IMEC;
- At the University itself, they have organised their undergraduate and graduate courses according to the recent global developments and to the needs of the local industry;
- In parallel to these research projects, staff members gave different courses organised by the ITU-ETA Foundation for the design engineers of the local industry. The course topics were the following : introduction to ASIC technology, neural Networks and Fuzzy Systems, Advanced VLSI, design and Advanced Analogue IC Design.

The Middle East Technical University, Ankara

◇ **Microelectronics activities**

- Several ASIC designs have been submitted in 1994 and 1995. A total of 12 designs has been submitted for processing.

◇ **Training activities in microelectronics**

- In 1993, a 2 weeks course has been organised at the INVOMEK division of IMEC to train METU staff in the use of the CAD environment, acquired through the program;
- In 1994, a total of four R&D engineers and research assistants have attended the VHDL training course at IMEC;
- In 1995, one person of the Middle East Technical University attended the High Speed Silicon Design Course.

The Bilkent University, Ankara

◇ **Microelectronics activities**

- A total of 17 designs has been submitted for processing in the years 1994-1995.

◇ **Training activities in microelectronics**

- In 1993, a 2 weeks course has been organised at the INVOMEK division of IMEC to train Bilkent staff in the use of the CAD environment, acquired through the program;
- In 1994, two persons attended the High-Speed GaAs-Circuit design course at Berlin, Germany, and four persons attended the VHDL and Synopsys training course held at IMEC, Belgium.

RESULTS

- ⇒ The overall project has been very successful.
- ⇒ The participants attended the various training courses on ASIC design. Where necessary, local support has been offered to ensure proper training, education and research at the universities.
- ⇒ At the universities itself, a growth of interest in the microelectronics training has been assessed. This increasing interest in its turn motivated the Universities to set up more lecturer courses and expand the microelectronics infrastructure.
- ⇒ The emerging demand in ASIC's combined with possibility of developing and fabricating devices have lead to successful implementation of circuits in both CMOS and GaAs technologies. Circuits increasing in complexity and difficulty are maturing the local knowledge in integrated circuit design. Their impact towards industry-use have already been proven by commercial designs.

PARTNERS

IMEC

Invomec Division
Kapeldreef 75
3001 Leuven
Belgium

E. Bourdeaud'hui
Tel.: +32-16-281 250
Fax: +32-16-281 584
Other contact:
R. Van Overstraeten
Tel.: +32-16-281 373
Fax: +32-16-281 510

THE UNIVERSITY OF MALTA

Department of Microelectronics
Msida MSDO6
Malta

Joseph Micallef
Tel.: +356-33 39 95
Fax: +356-34 35 77

THE ISTANBUL TECHNICAL UNIVERSITY

Ayazaga Campus
80626 Istanbul
Turkey

Duran Leblebici
Tel.: +90-12-76 34 23
Fax: +90-12-76 36 79

THE MARMARA SCIENTIFIC AND RESEARCH CENTER

P.O. Box 21
41470 Gebze-Kocaeli
Turkey

Onder Yetis
Tel.: +90-26-26 41 23 00
Fax: +90-26-26 41 23 09

THE MIDDLE EAST TECHNICAL UNIVERSITY

Tubitak-Bilten
Odtu 06531
Ankara
Turkey

Gökhan Köseoglu
Tel.: +90-31-22 10 13 10
Fax: +90-31-22 10 13 15

THE BILKENT UNIVERSITY

06533 Bilkent
Ankara
Turkey

Mehmet Ali Tan
Tel.: +90-31-22 66 41 26
Fax: +90-31-22 66 41 27

RUTHERFORD APPLETON LABORATORY

Chilton
Didcot
Oxfordshire OX11 0QX
United Kingdom

John Mc Lean
Tel.: +44-1235-44 52 76
Fax: +44-1235-44 55 46

4.1.2. Further contracts within the INCO-DC Programme containing a co-operation with a Third Mediterranean Country

The summary reports for these projects have been published by the European Commission within the Esprit Programme – International Co-operation (ISBN 92-828-0805-X, available from the Office for Publications of the European Communities or the local retailer office of the European Commission)

PROJECT EP-20237 Inductive Logic Programming II (ILP-2)		
CO-ORDINATOR Katholieke Universiteit Leuven Dept. of Computer Science Celestijnenlaan 200A B - 3001 Heverlee Belgium		CONTACT POINT <i>Mr. Luc De Raedt / Maurice Bruynooghe</i> Tel.: +32 16 327 550 Fax: +32 16 327 996 E-mail: maurice@cs.kuleuven.ac.be
Keywords: <i>machine learning, logic programming, data mining, knowledge discovery</i>		
Start Date January 1, 1996		Duration 36 months

Computational Logic (CLN)		
CO-ORDINATOR Compulog Net, Deutsches Forschungszentrum für Künstliche Intelligenz (DFKI) Stuhlsatzenhausweg 3 D - 66123 Saarbruecken Germany		CONTACT POINT Mr. Jörg Siekmann Tel.: +49 681 302 5322 Fax: +49 681 302 5341 E-mail: compulog-net@dfki.uni-sb.de URL: http://www.compulog.org:8080
Keywords: <i>logic programming, computational logic, knowledge representation, language design, deduction systems, machine learning</i>		
Start Date June 24, 1996		Duration 36 months

PROJECT EP-25395 Electronic Commerce and the Alignment of Radio Production and Distribution – Online Services, Audio/Music on Demand and Electronic Programme Exchange (CARO)		
CO-ORDINATOR Sender Freies Berlin Masurenallee 8-14 D-14057 Berlin		CONTACT POINT <i>Mr. Thomas Kruithof</i> Tel.: +49 30 3031 5045 Fax: +49 30 3031 5049 E-mail: Thomas.Kruithof@sfb.de URL: http://www.sfb.de
Keywords: <i>electronic commerce, IPR, hypermedia, music industry, ISDN</i>		
Start Date January 1, 1998		Duration 24 months

PROJECT EP-961416 EDI, Internet and the Arab World (MEDEDI)		
CO-ORDINATOR VANEDI 10, rue de Fontenay, 92 340 Bourg-La-Reine France		CONTACT POINT <i>Mr. Amin ELSALEH</i> Tel.: +33 1 41 13 83 33 Fax: +33 1 46 65 20 94 E-mail: aminELSALEH@Compuserve.com
Keywords: <i>EDI, arabisation, Internet, electronic commerce, textile industry, networking</i>		
Start Date January 1, 1998		Duration 24 months

PROJECT EP-961578 Multimedia and Geographical Information System for the Development and Dissemination of Tourism Oriented Applications by Internet (MAGICTOURNET)		
CO-ORDINATOR Intecs Sistemi Via L. Gereschi 32 56127 Pisa Italy	CONTACT POINT Mrs. M. Nazzarelli Tel.: +39 50 545 111 Fax: +39 50 545 200	
Keywords: <i>multimedia, GIS, Internet, tourism</i>	Duration 18 months	Start Date January 1, 1998

PROJECT EP-961785 Apport des Technologies d'Information à la Gestion et à la Modélisation des Ressources en Eau en Zones Semi-Arides (ESIMEAU)		
CO-ORDINATOR ERCIM Domaine de Volluceau Rocquencourt B.P. 105 78153 Le Chesnay Cedex France	CONTACT POINT Mr. B. Larrouturou Tel.: +33 1 39 63 53 03 Fax: +33 1 39 63 58 88	
Keywords: <i>decision support, GIS, simulation, database management, water resources management</i>		
Start Date December 1, 1997		Duration 36 months

PROJECT EP-961798 Made to Ensure Garments, 2D-3D Approach (MTOM3D)		
CO-ORDINATOR ERCIM – INRIA Domaine de Voluceau – BP 105 F-78153 Le Chesnay Cedex France	CONTACT POINT Mr. Bruno Le Dantec Tel.: +33 1 39 63 50 35 Fax: +33 1 39 63 50 52 E-mail: bruno.le-dantec@inria.fr URL: http://www-ercim.inria.fr	
Keywords: <i>CAD, 3D modelling, textile industry</i>		
Start Date November 1, 1997		Duration 26 months

PROJECT EP-961977 Editeur Multimedia Interactif et Cooperatif (EMICO)		
CO-ORDINATOR Société A6-Mediaguide Research Department 6 Rue Paul Claudel F-91000 EVRY France	CONTACT POINT Mr. Gérard Claës Tel.: +33 1 60 77 72 06 Fax: +33 1 60 79 49 87 E-mail: 101467.633@Compuserve.com	
Keywords: <i>multimedia, standardisation, ISO 9004, arabisation, information society</i>		
Start Date December 1, 1997		Duration 36 months

PROJECT EP-962037		
Cooperation for the Development of Technical Tools for the Improvement of Industrial Communication in Textile/Clothing Industry (TEX.COM TOOLS)		
CO-ORDINATOR CLOTEFI Research and Development Dept. El. Venizelou Street – Attica 17676 Athens Greece	CONTACT POINT Mr. Nena Malliou Tel.: + 301 92 34 932 Fax: +301 92 35 603 E-mail: etakei@athena.compulink.gr	
Keywords: <i>EDI, standardisation, textile industry</i>		
Start Date October 1, 1997		Duration 36 months

PROJECT EP-962180		
Transfer and Advanced Use of Technologies of Manufacturing (TAUTEM)		
CO-ORDINATOR Matra Datavision Scientific Team 53 Avenue de l'Europe F-13082 Aix-en-Provence France	CONTACT POINT Mr. Antonio Scarcelli Tel.: +33 4 42 52 21 45 / 21 18 Fax: +33 4 42 52 20 46 E-mail: : a-scarcelli@aix.matra-dtv.fr URL: : http://www.matra-datavision.com	
Keywords: <i>CAM, CIM, forge industry</i>		
Start Date October 1, 1997		Duration 36 months

PROJECT EP-962329		
Mediterranean Information Network for the Arab World (MEDINA)		
CO-ORDINATOR IT Consult GmbH Universitätsallee 22 D-28359 Bremen Germany	CONTACT POINT Mr. T. Wittig Tel.: +49 421 218 2234 Fax: +49 421 218 7822 E-mail: ITConsult@acm.org	
Keywords: <i>electronic commerce, market analysis Fout! Bladwijzer niet gedefinieerd., trade regulations, standardisation</i>		
Start Date January 1, 1998		Duration 36 months

PROJECT INCO-DC95-410 Customisation, Implementation, Validation, Demonstration and Dissemination of European RTD Results in Quality Control Management for Process Industries (QCIME)		
CO-ORDINATOR IT Consult GmbH Klosterstrasse 33 D-28865 Lilienthal Germany	CONTACT POINT Mr. Thies Wittig Tel.: +49 421 218 23 34 Fax: +49 421 218 71 96 E-mail: ITConsult@acm.org	
Keywords: <i>quality control, CAD, ISO 9000</i>		
Start Date March 1, 1996		Duration 30 months

PROJECT INCO-DC95-507 Integrated Gas Flow and Gas Sensors by Using Porous Silicon Micromachining (POROUS TECH SENSORS)		
CO-ORDINATOR Institute of Microelectronics NCSR Demokritos Aghia Paraskevi Attikis GR-153 10 Athens Greece	CONTACT POINT Mrs. Androula G. Nassiopoulou Tel.: +301 65 33 781 Fax: +301 65 11 723 E-mail: nassio@cyclades.nrcps.ariadne-t.gr	
Keywords: <i>microelectronic, microsystems, porous silicon, gas sensors, technology transfer</i>		
Start Date March 1, 1996		Duration 36 months

PROJECT INCO-DC95-895 HPC Training, Applications Development and Technology Transfer in the Middle East and Israel (PEACE BY HPC)		
CO-ORDINATOR Parsytec Computer GmbH Roermonder Strasse 197 D-52072 Aachen Germany	CONTACT POINT Mr. Anno Jordan Tel.: +49 241 88890 Fax: +49 241 888950 E-mail: jordan@parsytec.de	
Keywords: <i>HPC, parallel processing, technology transfer, training</i>		
Start Date January 1, 1996		Duration 30 months

PROJECT INCO-DC95-1139		
High-Performance Computing for Financial Planning under Uncertainty (HPC-FINANCE)		
CO-ORDINATOR University of Cyprus Dep. of Public and Business Administration 75 Kallipoleos Street, PO Box 537 Nicosia Cyprus	CONTACT POINT Mr. Stavros Zenios Tel.: +357 2 338 762 - 357 2 338 763 Fax: +357 2 339 063 E-mail: zeniooss@atlas.pba.ucy.ac.cy	
Keywords: <i>HPC, parallel processing, distributed systems, financial applications, uncertainty management</i>		
Start Date April 1, 1996		Duration 30 months

KIT ACTION INCO-DC96-1352		
Iv-Iv Semiconductor Heterostructures for Opto- and Micro Electronic Applications (IV-IV SHOME)		
CO-ORDINATOR IEF/UPS Electronique Fondamentale 15, rue Georges Clemenceau, Orsay – 91405 CEDEX France	CONTACT POINT Mr. Lourtioz Tel.: +33 1 69 41 62 99 Fax: +33 1 69 41 88 89 E-mail: jean-michel.lourtioz@ief-paris-sud.fr	
Keywords: <i>semiconductors, wireless communications, heterobipolar transistors</i>		
Start Date December 31, 1997		Duration 36 months

PROJECT INCO-DC96-1620		
Système d'Information Multimedia pour l'Environnement Sub-Saharien (SIMES)		
CO-ORDINATOR INRIA, Domain de Voluceau BP 105, F-78153 Le Chesnay Cedex France	CONTACT POINT <i>Mr. Olivier Monga</i> Tel.: +33 1 39 63 55 11 Fax: +33 1 39 63 59 95 E-mail: olivier.monga@inria.fr	
Keywords: <i>multimedia, knowledge representation, databases</i>		
Start Date November 15, 1997		Duration 36 months

PROJECT INCO-DC96-1852		
A Generic Interactive Package for Systems Engineering Courses and Applications (GIPSECA)		
CO-ORDINATOR University of Sheffield Robotics Research Group Department of Automatic Control and Systems Engineering University of Sheffield Mappin Street, Sheffield S1 3JD UK	CONTACT POINT <i>Mr. Ali Zalzala</i> Tel.: +44 114 222 5647 / 44 114 222 5136 Fax: +44 114 273 1729 E-mail: a.zalzala@shef.ac.uk URL: http://www.shef.ac.uk	
Keywords: <i>multimedia, training, distant learning, systems engineering</i>		
Start Date April 1, 1998		Duration 48 months

PROJECT INCO-DC96-1868		
Mediterranean Science and Technology Information Network (MEDISAT)		
COORDINATOR Institut für Informatik in Entwurf und Fertigung zu Berlin GmbH Rudower Chaussee 5, Geb. 13.7 D-1284 Berlin Germany	CONTACT POINT <i>Mr. Michael Gey</i> Tel.: +49 30 6392 4471 Fax: +49 30 6392 4517 E-mail: gey@iief.fta-berlin.de	
Keywords: <i>information society, networking, information infrastructure</i>		
Start Date January 1, 1998		Duration 24 months

KIT ACTION INCO-DC96-2109		
Computational Logic for Flexible Solutions to Applications (CLFSA)		
CO-ORDINATOR K.A. Leuven Dep. of Computer Science Celestijnenlaan 200A, Heverlee 3001 Belgium	CONTACT POINT Mr. D. De Schreye Tel.: +32 16 327 544 Fax: +32 16 327 996 E-mail: Danny.DeSchreye@cs.kuleuven.ac.be	
Keywords: <i>logic programming, constraint solving, abductive logic programming, explicit negation</i>		
Start Date December 31, 1997		Duration 36 months

KIT ACTION INCO-DC96-2144
Developing Software Engineering Environments for Distributed Information Systems (S/E DISTRIBUTED)

CO-ORDINATOR CWI, Stichting Mathematisch Centrum Kruislaan 413, P.O Box 94079, 1090 GB Amsterdam Netherlands	CONTACT POINT Mr. Farhad Arbab Tel.: +31 20 592 40 56 Fax: +31 20 592 41 99 E-mail: FARHAD@CWI.NL
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Keywords: *distributed information systems, Internet, multimedia*

Start Date December 31, 1997		Duration 36 months
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PROJECT INCO-DC97-2496
A Workflow Management System for Maritime Industry (MARIFLOW)

CO-ORDINATOR METU SW Research and Development Inonu Bulv., 06531 Ankara Turkey	CONTACT POINT Mr. A. Dogac Tel.: +90 312 210 12 98 Fax: +90 312 210 12 59
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Keywords: *information infrastructure, maritime industry, workflow management*

Start Date open		Duration 24 months
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PROJECT INCO-DC97-2561
Airborne Remote Sensing and Simulation for Assessment, Monitoring and Surveillance of Southern Mediterranean Maritime Ecosystems (AMED)

CO-ORDINATOR Thomson-CSF-Radar 10, Av. de la Lere 29283 Brest France	CONTACT POINT Mr. G. Coppin Tel.: +33 2 98 31 25 72 Fax: +33 2 98 31 25 23
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Keywords: *HPCN, parallel processing, maritime information society, simulation, environmental monitoring*

Start Date open		Duration 24 months
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PROJECT INCO-DC97-2572		
Textile Application of High Performance Computing in the Middle East (THEME)		
CO-ORDINATOR Technical University of Athens Herioon Politechniou 9 157 73 Athens Greece	CONTACT POINT <i>Mr. G. Stassinopoulos</i> Tel.: +30 1 772 25 31 Fax: +30 1 772 25 34	
Keywords: <i>HPC, parallel processing, textile industry, machine vision</i>		
Start Date open		Duration 30 months

KIT ACTION INCO-DC97-2644		
Development of Parallel Algorithms for Irregular Problems (DAPPI)		
CO-ORDINATOR Technical University of Mons Rue de Houdain 9, 9000 Mons Belgium	CONTACT POINT <i>Mr. P. Mannebach</i> Tel.: +32 65 37 40 50 Fax: +32 65 37 45 00	
Keywords: <i>HPC, parallel processing, distributed algorithms, distributed environments, load malancing</i>		
Start Date open		Duration 36 months

PROJECT INCO-DC97-3070		
Modélisation Numérique de Crues via le Calcul Intensif Distribué (CRUCID)		
CO-ORDINATOR ERCIM-EEIG Domain de Voluceau, BP. 105 78153 Le Chesnay France	CONTACT POINT <i>Mr. F. El Dabaghi</i> Tel.: +33 1 39 63 53 43 Fax: +33 1 39 63 58 82	
Keywords: <i>HPC, parallel processing, simulation, flood modelling, CFD, GIS, environmental monitoring</i>		
Start Date open		Duration 24 months

PROJECT INCO-DC97-3101		
Healthcare Advanced Systems Network Architecture for Mediterranean Developing Countries (HANSA-Med)		
CO-ORDINATOR SOCRATES W2 BV Valeriaan 36, 5331 DA Kerkdriel Netherlands	CONTACT POINT <i>Mr. J. Weber</i> Tel.: +31 41 86 37 126 Fax: +31 41 86 37 127	
Keywords: <i>distributed software technologies, health care, hospital information systems, medical applications</i>		
Start Date open		Duration 24 months

PROJECT INCO-DC97-3125 IT Applied to Safety Systems to Support Development of Mediterranean Scuba Diving Tourism (EURIDICE)		
CO-ORDINATOR AQUATECH 25, Rue Baptistin Aprea 13620 Carry France	CONTACT POINT <i>Mr. T. Brizard</i> Tel.: +33 442 45 69 87 Fax: +33 442 45 69 87	
Keywords: <i>navigation systems, maritime information society, acoustic receivers</i>		
Start Date open		Duration 36 months

PROJECT INCO-DC97-3133 Natural Arabic Process Language Understanding System NAPLUS		
CO-ORDINATOR Impetus Engineering SA Dimitsanis 3-5 18 346 Athens Greece	CONTACT POINT <i>Mrs. T. King</i> Tel.: +30 1 924 18 00 Fax: +30 1 924 88 24	
Keywords: <i>natural language processing, linguistic rules, arabics, automatic translation</i>		
Start Date open		Duration 36 months

PROJECT INCO-DC97-3187 Serveur d'Images Numérisées d'Archives de la Méditerranée et du Monde Arabe (SINAMMA)		
CO-ORDINATOR BELGAVOX Rue de Verrewinkel 93 1180 Brussels Belgium	CONTACT POINT <i>Mr. M. Lints</i> Tel.: +32 2 375 44 89 Fax: +32 2 375 32 34	
Keywords: <i>multimedia, electronic commerce, film archives, information society, Internet, IPR</i>		
Start Date open		Duration 24 months

PROJECT INCO-DC97-3274 Mediterranean Textile Trade Network (MTTN)		
CO-ORDINATOR ASCONTEX Italy	CONTACT POINT <i>Mr. M. Gigot</i> Tel.: +32 2 375 44 89 Fax: +32 2 375 32 34	
Keywords: <i>electronic commerce, textile industry, information society, Internet</i>		
Start Date open		Duration 19 months

PROJECT INCO-DC97-3324 Cultural Journeys in the Information Society (CJIS)		
CO-ORDINATOR University of Cyprus Kallipoleos 75, P.O. Box 537 1678 Nicosia Cyprus	CONTACT POINT <i>Mr. C. Schizas</i> Tel.: +357 233 87 05 Fax: +357 233 90 62	
Keywords: <i>multimedia, electronic roads, information society, cultural networking</i>		
Start Date open		Duration 36 months

KIT ACTION INCO-DC97-3367 Training Teacher Educators for Using Computer-Based Cognitive Technologies in Teaching and Learning (TTE)		
CO-ORDINATOR University of EGE Bornova, 35100 Izmir Turkey	CONTACT POINT <i>Mr. A. Orhun</i> Tel.: +232 339 94 05 Fax: +232 339 94 05	
Keywords: <i>cognitive tools, teaching tools, learning tools, information society</i>		
Start Date open		Duration 24 months

4. Additional fields of mutual interest

4.2. Biotechnology

NEW APPROACHES TO LOCALISE AND SUSTAIN DRUG RELEASE IN THE COLON

Co-ordinator: University of Nottingham, Nottingham, United Kingdom (Stanley S. Davis)

OBJECTIVES

- Development of new dosage forms with the ability to reside for long periods of time in the colon. The newly developed drug carriers will be of two types:
 - mucoadhesive polymeric carriers;
 - buoyant platforms.

These are designed to deliver two classes of drugs: molecules aimed at local treatment of colon diseases and molecules susceptible to enzymatic degradation such as peptide drugs;

- *In vitro* and *in vivo* studies in which the mucoadhesive polymers will be tested as to their ability to function successfully, i.e. adhere to mucosal tissues or float in physiologic fluids;
- *In vivo* studies to test the viability of the hypothesis that prolongation of residence time in the colon can increase the bioavailability of enzyme susceptible drugs such as peptide drugs;
- Development of an animal model (pig) in which *in vivo* studies will be performed validates the prolonged residence time of the drug carriers.

ACTIVITIES

- ◇ Polymers blends of Eudragit® RL with Polycarbophil (acid form) in different ratios will be prepared and tested for physicochemical and mucoadhesion properties;
- ◇ Fabrication of mucoadhesive drug delivery systems. The optimal polymer blends will be formulated into solid dosage forms and tested with two drug markers (at least one of which will be a protein drug) in rats for regional GI mucoadhesion;
- ◇ New buoyant dosage forms will be prepared and tested *in vitro* and *in vivo* (dogs);
- ◇ Novel delivery systems will be prepared and tested for selfbuoyancy properties in bench chemostat;
- ◇ The novel formulations will be tested in pigs for increase in dosage form residence time using gamma scintigraphy;
- ◇ Pilot human studies will conclude the research.

OUTCOME

- ⇒ Localisation of anti-IBD drugs such as salicylate derivatives (5-amino salicylic acid) steroids with local action and hepatic clearance such as budesonide, immunosuppressive agents such as cyclosporine;
- ⇒ Early stages of colon cancer (when systemic prevention of possible metastasis in the blood comment is still not necessary);
- ⇒ GI absorption of highly lipophilic molecules;
- ⇒ GI absorption of peptide drugs or vaccines.

PARTNERS

THE UNIVERSITY OF NOTTINGHAM

Department of Pharmaceutical Sciences
School of Pharmacy
University Park
Nottingham NG7 2RD
United Kingdom

Stanly S. Davis
Tel.: +44-115-951 51 21
Fax: +44-115-951 51 22

HEBREW UNIVERSITY OF JERUSALEM

School of Pharmacy
P.O. Box 12065
91120 Jerusalem
Israel

Abraham Rubinstein
Fax: +972-2-643 62 46

**MICROTUBULE-ASSOCIATED PROTEINS AS DIAGNOSTIC DETERMINANTS
AND THERAPEUTICAL TARGETS FOR NEUROBLASTOMA TUMORS**

Co-ordinator: Max-Planck-Institut für Hirnforschung, Frankfurt/Main, Germany (Joachim Kirsch)

OBJECTIVES

- To develop immunohistological and molecular biology based tests for the diagnosis of neuroblastoma in human patients
- To quantitate the state of differentiation of neuroblastoma tumors by observer independent methods
- To investigate the use of non hydrolyzable antisense oligonucleotides as potential inducers of neuronal differentiation of this neoplasia in animal models.

ACTIVITIES

The diagnostic tests are both based on the discovery that human neuroblastoma tumors express a unique Microtubule-associated protein 2 (MAP2) component of 250 kDa that is not found in normal tissues or other types of tumors of neuroektodermal origin. The activities are therefore focused on:

- ◇ Elucidation of the primary structure of the neuroblastoma-specific MAP2 isoform,
- ◇ Generation of specific monoclonal antibodies against this isoform which fulfill all the criteria required for a diagnostic tool for pathological diagnosis,
- ◇ Construction of oligonucleotide primers for the polymerase chain reaction to allow the most sensitive detection of transcripts encoding the neuroblastoma-specific MAP2 isoform,
- ◇ Investigate in animal models whether inhibition of the expression of the neuroblastoma-specific MAP2 isoform by antisense oligonucleotides can induce differentiation of the tumor and thereby improve the patient's prognosis.

OUTCOME

Scientific-technical results

We have reached the most important milestone of our mutual project by characterizing the primary structure of neuroblastoma specific microtubule-associated protein 2 (NB-MAP2).

Furthermore, we set out to produce specific antibodies against the neuroblastoma-specific polypeptide. NB-MAP2 is characterized by a specific amino acid motif (W V D T Q A A G G E) which is present only in NB-MAP2 and not in normal human MAP2.

It turned out to be very difficult to produce monospecific antibodies directed against the NB-MAP2 specific epitope. Alternative approaches including in vitro immunizations will have to be employed.

The use of MAP2 specific antisense oligonucleotides induced a moderate degree of differentiation in cultured human neuroblastoma cells which has to be followed up by further experiments.

Patents

The results of this part have been disseminated by Patent Cooperation Treaty EP97/00320 based on EP96 10 0930.5 "Tool for the detection of NB-MAP2 specific expression and diagnostic as well as pharmaceutical applications thereof". The use of the methods described in this publication represents an improved diagnostic tool for the molecular biological (i.e. observer independent) diagnosis of neuroblastoma tumors.

The use of our method should allow the most sensitive detection of neuroblastoma specific mRNAs prior to bone marrow transplantations.

FOLLOW-UP

The first step towards a commercial application of the newly developed method should be a large scale clinical evaluation of our method for the detection of neuroblastoma.

PARTNERS

MAX-PLANCK-INSTITUT FÜR HIRNFORSCHUNG
Deutschordenstraße 46
60528 Frankfurt/Main
Germany

Joachim Kirsch
Tel.: +49-69-96769 262
Fax: +49-69-96769 441
E-mail : kirsch@mpih-frankfurt.mpg.de

THE WEIZMANN INSTITUTE OF SCIENCE
Department of Neurobiology
76100 Rehovot
Israel

Irith Ginzburg
Tel.: +972-8-342 799
Fax: +972-8-344 131

BIOSYNTHESIS OF NEW PYRIMIDINE DERIVATIVES IN ACTINOMYCIN-PRODUCING STREPTOMYCES FORMED AS A RESPONSE TO STRESS; THEIR ROLE AND FUNCTION

Co-ordinator: Technical University of Berlin, Berlin, Germany (Ullrich Keller)

OBJECTIVES

The objective of this project was to characterize the biological effects of a class of tetrahydropyrimidine compounds formed under salt and heat stress and their correlation with peptide antibiotic production in streptomycetes in particular actinomycin biosynthesis in *Streptomyces chrysomallus*.

- Investigation of the influence of tetrahydropyrimidine and of their formation on growth and differentiation of the producing organism by studying mutants unable to produce the compounds obtained by gene disruptions and gene replacements. Analysis of the role of the tetrahydropyrimidines as a self-resistance determinant in actinomycin production in *Streptomyces chrysomallus*.
- Mechanisms of salt stress responses in streptomycetes in terms of regulation of expression of the tetrahydropyrimidine gene cluster.
- Physico-chemical investigations of tetrahydropyrimidines action on cellular compounds such as DNA, RNA or protein by NMR spectroscopy; X-ray and biochemical techniques.
- Biotechnological optimization of in vitro systems of tetrahydropyrimidine synthesis involving recombinant enzymes.

ACTIVITIES

- ◇ Isolation and characterisation of diaminobutyrate acetylase and acetyl-diaminobutyrate cyclase from *Streptomyces chrysomallus*;
- ◇ Cloning of the genes of the diaminobutyrate acetylase and acetyl diaminobutyrate cyclase;
- ◇ Preparation of the disruption mutants with defects in either of the two genes;
- ◇ Expression of the tetrahydropyrimidine biosynthesis genes in heterologous and homologous hosts;
- ◇ Studies of the biogenesis and fate of compounds by NMR spectroscopy of whole cells and cell-free extract of producer strains and non-producing mutants of various streptomycetes;
- ◇ Investigation of metabolic and physiological responses to salt stress in *Streptomyces* by physiological and NMR studies using tetrahydropyrimidine producers and non-producing mutants;
- ◇ Investigation of tetrahydropyrimidines in their protection of DNA in protein-DNA interaction;
- ◇ Investigation of structure, function and dynamics of tetrahydropyrimidine-DNA and of the protection mechanisms of DNA from drugs;
- ◇ Investigation of the ability of the hydroxy derivative of tetrahydropyrimidine to inhibit transactivation of HIV-RNA by Tat;
- ◇ Exploring the mode of binding of tetrahydropyrimidines to DNA by NMR and biochemical techniques.
- ◇ Analysis of the tetrahydropyrimidine gene cluster.
- ◇ Disruptions of the various genes of the tetrahydropyrimidine biosynthesis gene cluster. Biochemical/phenotypical analysis of mutants unable to produce tetrahydropyrimidines
- ◇ Studies of regulation of expression of the salt stress gene cluster of tetrahydropyrimidine biosynthesis in *Streptomyces chrysomallus*.
- ◇ Characterization of recombinant tetrahydropyrimidine biosynthesis enzymes.
- ◇ Studies of the biogenesis and fate of compounds by NMR spectroscopy of whole cells and cell-free extract of producer strains and non-producing mutants of various streptomycetes.
- ◇ NMR studies of intracellular tetrahydropyrimidines in their interactions with cellular targets during responses to salt stress in *Streptomyces*

OUTCOME

This study will clarify the role of tetrahydropyrimidines as osmolytes and intracellular effectors in the salt and heat stress response in the *Streptomyces*. These compounds possess protection mechanisms of to various cellular targets of the bacterial cell and may exert similar effects in mammalian cell systems for the modulation of action of drugs and other therapeutic ligands. This may help to reduce side effects of drugs or improve the spectrum of therapeutic action of compounds. Study of regulation of tetrahydropyrimidine synthesis in *Streptomyces* will give insight in the general regulatory systems of stress response in respect of antibiotic production and other secondary metabolite formation.

FOLLOW-UP

It is planned to investigate the protecting effect of tetrahydropyrimidines on various macromolecular targets in cells by overexpression of the biosynthesis gene cluster in various hosts. In particular the effect of these compounds on the in vivo production of useful metabolites in various streptomycetes and fungi will be of great future interest. Furthermore, the development of a biotechnological production process of tetrahydropyrimidin biosynthesis in vivo is an important aim in the follow up of this project.

SELECTED PUBLICATIONS

- MALIN, G., IAKOBASHIVILI, R., and LAPIDOT, A. (1996) Effect of tetrahydropyrimidine derivatives from streptomycetes on DNA digest by restriction endonucleases. 24th FEBS-Meeting, Barcelona, p. 66
- KELLER, U., SCHAUERWECKER, F., BUHRKE, T., RIEDERER, B. (1996) Investigation of biosynthesis of compatible solutes in *Streptomyces* formed under salt stress. VAAM Workshop "Biology of Actinomycetes" (Wohlleben, W., org.) Tübingen, Germany (Sep. 29 - Oct. 01, 1996) p. P21
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PARTNERS

TECHNICAL UNIVERSITY OF BERLIN
Max-Volmer-Institut für Biophysikalische Chemie und
Biochemie
Fachgebiet Biochemie und Molekulare Biologie
Franklinstraße 29
10587 Berlin-Charlottenburg
Germany

Ullrich Keller
Tel.: +49-30-31 42 36 29
Fax: +49-30-31 42 47 83
E-mail: Ullrich@chem.TU-Berlin.de

WEIZMANN INSTITUTE OF SCIENCE
Organic Chemistry Department
76100 Rehovot
Israel

Aviva Lapidot
Tel.: +972-8-34 20 77
Fax: +972-8-34 41 23
E-mail: colapidot@wiccmail. Weizmann.ac.il

INTERSPECIFIC & INTERGENERIC PROTOPLAST FUSION IN RED ALGAE

Co-ordinator: Universität Tübingen, Tübingen, Germany (Rüdiger Hampp)

OBJECTIVES

- Red algae produce a variety of compounds of commercial interest. Most important among these products are polysaccharides used as gelling agents, such as agar-agar, carrageenan, etc. Yet, cultivation of red algae under controlled conditions is still a problem and restricted to very few species. Likewise, the breeding of superior culture varieties is not yet possible;
- The overall aim of the project is thus to make interesting species of red algae amenable to tissue culture techniques, and to combine traits of different genera by somatic hybridisation via protoplast fusion. *Porphyridium spec.* and *Rhodella reticulata* are unicellular red algae that can be easily cultivated, and *Gracilaria tikvahiae* is a major species for commercial polysaccharide production. The more specific long term goal of the project is to obtain unicellular agar-agar producing algae through intergeneric protoplast fusion of *Porphyridium* and *Gracilaria*. This will be achieved in a stepwise approach, starting from the isolation and regeneration of protoplasts in each species, and then proceeding from intraspecific to interspecific, and finally intergeneric fusions. This also involves analytical aspects, such as physiological, biochemical and genetic characterisation of parental strains and fusion progeny.

ACTIVITIES

- ◇ Culture of red algae, so far : *Porphyridium* and *Rhodella*;
- ◇ Production and characterisation of mutants, as well defined mutations provide genetic markers to distinguish parental strains from somatic hybrids after fusion;
- ◇ Isolation of protoplasts by selection of soil bacteria that produce enzymes capable of digesting the complex cell wall material of the unicellular algae;
- ◇ Biochemical analysis of cell wall composition by affinity labelling, denaturing polyacrylamide gel electrophoresis (SDS-PAGE), and enzymatic deglycosylation, in order to optimise the digestion strategy;
- ◇ Fusion of protoplasts by chemical (polyethylene glyco, PEG) and physical (electrofusion) methods;
- ◇ Selection, regeneration and characterisation of fusion products with respect to physiological, biochemical and genetic properties.

OUTCOME

- ⇒ Production of mutant strains
Apart from a previously isolated herbicide (sulfometuron methyl, SMM) resistant strain (van Moppes et al. 1989), and the pigment mutants described in Sivan & Arad (1993), new mutants of *Porphyridium* were obtained which are resistant against the herbicides diuron and atrazin. These strains were characterised for photosynthetic properties, pigment and cell wall composition (Sivan & Arad, 1995).
- ⇒ Protoplast isolation
As described in Sivan et al. (1992), protoplast isolation from *Porphyridium* was achieved with an enzyme preparation from a mixture of soil bacteria selected for this purpose. The same strategy was applied to isolate new bacterial strains for the digestion of *Rhodella reticulata* cell walls. The efficiency of these new enzymes in digesting the extracellular polysaccharide of *Rhodella* was optimised with respect to salinity, temperature and pH. So far, the activity is not as stable as desired, and the bacteria have not yet been identified.
- ⇒ Protoplast fusion
The first intraspecific fusions of *Porphyridium* protoplasts are described in Sivan et al. (1995), and Sivan & Arad (1996). The fusion was achieved by a PEG/heat shock treatment. Hybrids were

identified by the combination of parental traits, i.e. complementation of different phycoerythrin deficiency mutations, or double resistance against diuron and SMM. Cytological, biochemical, and molecular evidence (by randomly amplified polymorphic DNA - polymerase chain reaction, RAPD-PCR) clearly demonstrated genetic transfer, genetic complementation, and the completion of the parasexual cycle in the fusion progeny. For electrofusion, some basic parameters, such as fusion medium, cell alignment and (irreversible) breakdown voltage were established. So far, cell fusion has been hampered by incomplete cell wall removal, which is more critical for this method than for chemical fusion. A further improvement of protoplast isolation will be needed to successfully employ electrofusion techniques.

⇒ Biochemical characterisation of cell walls

Detailed chemical analysis has been performed mainly on the soluble, extracellular polysaccharide of *Porphyridium* (Arad 1988). The complete removal of the cell bound glycoproteins by SDS-PAGE and subsequent staining for sugar moieties. Digoxigenin labelling was used for a general overview, and lectin affinity for subsets of specific residues. The comparison of patterns obtained with undigested and digested cells, as well as total cells, secreted compounds, and purified cell walls, aims at the identification of components that may be unique to the cell bound wall layer and thus resistant to digestion with the bacterial enzymes. A well-defined screening of additional enzymes capable to remove these residues is now possible.

FOLLOW-UP

- The isolation of protoplasts from *Porphyridium* (and other species) will be further optimised to allow somatic hybridisation by electrofusion as well as chemical fusion with PEG;
- The labelling techniques developed for the detection of glycoproteins after electrophoresis can be modified for cytochemical staining of sections for electron microscopy. This kind of ultrastructural analysis will improve our understanding of cell wall structure and biosynthesis in unicellular algae. This is an important aspect also with regard to the introduction of cell wall properties of higher red algae (*Gracilaria*) into these organisms;
- When protoplasts of *Rhodella* are readily available, interspecific fusions will be performed with *Porphyridium* protoplasts. This should verify the viability of interspecific hybrids, as well as the ability of the unicellular algae to recombine with and express "foreign" genes. After that the stage will be set for intergeneric fusion attempts.

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PARTNERS

UNIVERSITÄT TÜBINGEN
Botanisches Institut
Auf Der Morgenstelle 1
72076 Tübingen
Germany

Rüdiger Hampp
Tel/Fax: +49-70-71290

BEN-GURION UNIVERSITY OF THE NEGEV
The Institute for Applied Research
P.O. Box 1025
Hashalom Street
84105 Beer Sheva
Israel

Alex Sivan
Tel.: +972-7-46 19 61
Fax: +972-7-27 16 12

STRUCTURE-FUNCTION STUDIES OF ENZYMES INVOLVED IN CHITIN DEGRADATION

Co-ordinator: European Molecular Biology Laboratory, Hamburg, Germany (Constantinos E. Vorgias)

OBJECTIVES

→ Chitin is the second most abundantly distributed polysaccharide throughout nature. This homopolymer of N-acetyl-glucosamine is not only the major constituent of the fungal cell wall and the arthropod exoskeleton but also an important nutrient source of carbon and nitrogen in the marine environment. These enzymes are produced and secreted from chitinolytic bacteria and are Chitinases (EC.3.2.1.14) and Chitobiases (EC.3.2.1.30). Chitinases have been classified into families 18 and 19 of glycosyl hydrolases. They hydrolyse chitin to oligosaccharides of which N,N'-diacetyl-glucosamine is the predominant product. N,N'-diacetyl-glucosamine is the substrate for Chitobiase (trivial name for N-acetyl-glucosaminidase) which is classified into family 20 of glycosyl hydrolases.

Specific objectives of the project are:

- To solve the structure of the *Serratia marcescens* chitinase A;
- To solve the structure of the *Serratia marcescens* chitobiase;
- To determine the sequence of the gene coding for chitinase from *Aeromonas caviae* and perform biochemical characterisation of the protein;
- To clone, overexpress, purify and crystallise the thermostable chitinase from *Streptomyces thermoviolaceus*.

ACTIVITIES AND RESULTS

◇ 3D structure determination of Chitinase A from *Serratia marcescens*
 The structure of Chitinase A (ChiA) was solved by multiple isomorphous replacement and comprises three domains. The N-terminal domain (residues 24 to 137), which is made up of β -sheet, connects through a hinge region (residues 138 to 158) to the main $\alpha\beta$ barrel domain (residues 159 to 442 and 517 to 563). The third domain, which has an $\alpha+\beta$ fold, is formed by an insertion in the barrel motif (residues 443 to 516). The average B value for protein atoms is 24.1Å². The N-terminal domain has a fold similar to that of the animal protein fibronectin type III (FnIII) module domains. Its function is yet unknown but might well facilitate the binding of the enzyme to the filamentous chitin substrate. The active site was identified by solving the structure of the enzyme with an oligomer of its natural substrate. The substrate binding site is formed by a long groove, located at the C terminal and of the β strands of the $\alpha\beta$ barrel. In all known enzymes with α/β barrel structure, the active site is located at the end of the barrel. The active site residues are proposed to be Glu315 and possibly Asp391. Evidence for this is as follows:

- site directed mutagenesis in the *Bacillus circulans* chitinase showed that the Glu204 to Gln mutation (Glu204 of *Bacillus* chitinase aligns with Glu315 of ChiA) decreased activity almost to zero;
- Glu315 and Asp391 are completely conserved in bacterial chitinases;
- the carboxylate oxygens of both residues are close to the C1 atom of the sugar ring.

The quality of the complex does not allow us to make clear suggestions of the mode of substrate binding and for the structural features of the specificity of the chitin polysaccharide. Most probably the catalytic event occurs in a manner similar to that of lysozyme, i.e. general acid-base catalysis, with retention of configuration of the anomeric conformation of the C1 atom of the sugar ring. Currently, we are working on the structural elucidation of the complex of ChiA with its natural inhibitor allosamidin.

- ◇ 3D structure determination of Chitobiase from *Serratia marcescens*
The 3-D structure of Chitobiase was also solved by multiple isomorphous replacement. Chitobiase has an eight stranded $\alpha\beta$ -barrel structure (domain III) surrounded by three additional domains:
 - domain I comprises residues 28 to 175. Two β -pleated sheets wrap around a hydrophobic core. The motif starts with a three turn α -helix that points into solvent. Domain I is connected to domain II by a fifty amino acid long linker (residues 175 to 225) which folds around the $\alpha\beta$ -barrel (domain III);
 - domain II (residues 225 to 334) shows two parallel helices and a seven stranded β -sheet (partly parallel and partly antiparallel) faces the solvent. The β -strands tilt about 30° to the helices.
 - domain III folds into an $\alpha\beta$ -barrel motif. It comprises 465 amino acids (residues 340 to 815). Eight β -strands inside and seven helices on the outside were found. The eighth helix is replaced by three helical segments and a β -strand. The C-terminal end of the barrel faces towards domain I. The active site was identified by substrate and inhibitor binding studies to be at the C-terminus of the $\alpha\beta$ barrel. Most prominent insertions of the barrel motif are a loop towards domain I and two helices pointing into solvent. A long helix expands around the barrel and completes domain III. This helix has a kink after 4 turns where a glycine is found. Domain IV folds into two small β -sheets.

Based on the structure of the complex with the substrate disaccharide chitobiose and on previous biochemical data, an acid-base reaction mechanism is proposed in which only one protein carboxylate acts as catalyst, while the nucleophile is provided by the polar aceamido group of the sugar in a substrate assisted reaction, known as neighbouring group participation or anchimeric assistance. This is the first example of a natural substrate complex for a glycosyl hydrolase with a sugar in the +1 and -1 site on each side of the scissile bond. The reaction proceeds with retention of anomeric configuration. The catalytic domain of the homologous hexosaminidases is modelled on the structure of the catalytic $\alpha\beta$ -barrel of chitobiase. Pathogenic mutations, previously classified by phenotype in the human Tay-Sachs and Sandhoff genetic diseases, are given a structural rationale.
- ◇ Cloning, overexpression purification and characterisation of a thermophilic chitinase from *Streptomyces thioviolaceus*
*The chitinase gene chi40 was isolated from the thermophilic bacterium *Streptomyces thioviolaceus* cloned in pET-15b (fused with 6 His for affinity purification) and efficiently overexpressed in *E. coli*. The recombinant chitinase has a molecular weight of 40 kDa, it is highly active and shows significant thermostability. The melting temperature measured by CD spectroscopy was 74-75°C. Two forms of the enzyme were isolated showing alternative folds that were isolated and characterised. Both forms show very close biochemical properties but differ in their molecular fold. We are currently trying to crystallise both forms and to study the structural features of the protein in terms of thermostability and folding.*
- ◇ Cloning and primary structure of a chitinase from *Aeromonas caviae*
*A DNA fragment from the soil bacteria *Aeromonas caviae* containing the gene encoding an extracellular chitinase (Chi) has been cloned and sequenced. Computer analysis deduced an open reading frame encoding a protein of 865 amino acid (aa) sequence that shows high homology to the ChiA of *Serratia marcescens*. Expression in *E. coli* yielded enzymatically active protein with an estimated molecular weight of 94 kd. The deduced aa sequence is 23 aa longer at the amino terminus than that determined experimentally by sequencing of the purified protein, suggesting that a leader sequence is removed during transport of the enzyme across the cell membrane. The C-terminus extension found in the chitinase from *Aeromonas caviae* is larger than the chitinase from *Alteromonas sp.* The C-terminus contains two small related sequences that probably arose by gene duplication. This domain also aligns with the last 40 residues of two more *Bacillus* cellulase gene products (CELA and CELB). These observations suggest to us that the C-terminal region of the *Aeromonas caviae* chitinase and the *Bacillus sp.* strain N-4 cellulases are functionally related and may be involved in the ability of these enzymes to degrade their highly hydrophobic substrates.*

Major scientific breakthroughs are:

 - the first crystal structure of the Chitinase A from *Serratia marcescens*;

- the first crystal structure of the Chitobiase from *Serratia marcescens*;
- the use of structural information from prokaryotic organisms to model the structure of a eucaryotic enzyme using a new algorithm. This novel approach helped us to give a working model on the structural basis of Tay-Sachs and Sandhoff.

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PARTNERS

EUROPEAN MOLECULAR BIOLOGY

LABORATORY

Molecular Biology & Crystallography Department

Notkestraße 85, geb. 25A

22603 Hamburg

Germany

Constantinos E. Vorgias

Tel.: +49-40-899 02-0

Fax: +49-40-899 02-149

THE HEBREW UNIVERSITY

Hadassah Medical School

91010 Jerusalem

Israel

Amos Oppenheim

Tel.: +972-2-75 73 09

Fax: +972-2-78 40 10

**ASSEMBLY AND DEGRADATION OF THE CYTOCHROME B-F COMPLEX IN
CHLOROPLASTS OF HIGHER PLANTS**

Co-ordinator: University of Cambridge, Cambridge, United Kingdom (John C. Gray)

OBJECTIVES

The overall goal is to study the assembly and degradation of a key component of the photosynthetic electron transport chain, the cytochrome b-f complex. The processes involved in the assembly of a multi-subunit complex will be studied. The inter-relationship between assembly and degradation will be examined.

ACTIVITIES

- ◇ To test the hypothesis that steady-state levels of the cytochrome b-f complex are determined by the amount of the Rieske Fe-S protein available for assembly. Identifying structural features of the Rieske protein essential for Fe-S cluster binding and for assembly with the other subunits of the complex;
- ◇ Determine turn-over rates of the different components of the cytochrome b-f complex under optimal and changing environmental conditions;
- ◇ To test the hypothesis that protein stability is afforded by proper assembly and that unassembled proteins are bound for rapid degradation;
- ◇ To characterise the degradation of unassembled subunits of the complex;
- ◇ Purification of proteases involved in degradation of unassembled Rieske protein.

OUTCOME

- ⇒ Determination of synthesis and degradation rates of the cyt complex subunits in wild-type and transgenic plants;
- ⇒ Analysis of assembly and degradation of Rieske mutants;
- ⇒ Characterisation of degradation of unassembled Rieske mutant;
- ⇒ Purification of proteases involved in the degradation of unassembled Rieske mutants;
- ⇒ The study will provide more information about the fate of unassembled proteins in the chloroplast, and the mechanisms utilised by the organelle to ensure stoichiometric levels of different components of a given complex. Insight into these processes might be useful in the future in attempts to engineer plants capable of dealing successfully with harsher growth conditions.

PARTNERS

UNIVERSITY OF CAMBRIDGE
Department of Plant Sciences
Downing Street
Cambridge CB2 3EA
United Kingdom

John C.Gray
Tel.: +44-1223-33 39 25
Fax: +44-1223-33 39 53

HEBREW UNIVERSITY OF JERUSALEM
Faculty of Agriculture
Department of Agricultural Botany
76100 Rehovot
Israel

Zach Adam
Tel.: +972-8-946 13 29
Fax: +972-8-946 77 63

CHARACTERISATION AND DEVELOPMENT OF BIOADHESIVE CONTROLLED DRUG DELIVERY SYSTEMS BASED ON MODIFIED POLYSACCHARIDES

Co-ordinator: Universiteit Gent, Gent, Belgium (Jean Paul Remon)

OBJECTIVES

The objective of this investigation is the modification of starches in order to produce acrylic grafted starches for bioadhesive applications.

- Chemical modification of starch in order to improve the bioadhesive characteristics of starch for the formulation of solid bioadhesive dosage forms;
- Evaluation of the modified starches in function of their compressibility, erosion behaviour *in vivo* in a dog model and their irritation potential.

ACTIVITIES

- ◇ Synthesis of grafted starches
This part of the research is performed at the Dept. of Chemical Engin. of the Ben Gurion University (Israel). The synthesis of the starch derivatives is via free radical initiation on the starch backbone (using chemical initiation and irradiation) and next reaction of the radical with polymerizable acrylic monomers.
- ◇ Evaluation of the modified starches
This part of the research is performed at the Lab. of Pharmaceutical Technology of the University of Gent (Belgium).
- ◇ Study on the interaction of the bioadhesive molecules and mucin using tensile strenght measurements. This method is a mechanical technique that give insight in the interaction between mucus located at the mucosal surface and bioadhesive polymers
- ◇ *In vivo* local irritation potential and erosion profile using the dog as a model

OUTCOME

Scientific-technical results

Methods: Preparation of graft polymers by ^{60}Co irradiation and/or by redox initiation with cerium ammonium nitrate was described in Report CII-CT94-0119. Two methods were used to load salicylic acid or theophylline into the graft copolymers obtained from starch and acrylic acid by ^{60}Co irradiation: incorporation of the drug during swelling of the graft copolymer in buffer solution and incorporation of the drug during preparation of tablets. The kinetics of drug release were followed in a dissolution system.

Bioadhesion of the tablets was measured using a tensile tester based on a published method. Bioadhesive tablets were tested in the dog. Irritation and erosion times were evaluated visually.

Graft Copolymers from Starches and Acrylic Monomers

Effect of Irradiation Time on Dissolution Kinetics

Grafting by ^{60}Co irradiation was performed for various periods of time. After stopping the irradiation, drugs were incorporated in the starch-grafted copolymers, and the kinetics of drug release were followed. Longer irradiation times increased the time required to release the loaded drug, the behavior of each model drug is better understood from the correlation of the rate of drug release with irradiation time. The release rate of salicylic acid, the smaller of the two molecules, is retarded only after long periods of irradiation (more than 8 h), whereas the release of theophylline seems to be indirectly proportional to irradiation time. To test the reproducibility further experiments were run for 24 h.

Effect of Weight Ratio of Starch to Acrylic Acid

A. Grafting of starches (2 wt.%) solution with various amounts of acrylic acid Two types of starch were grafted with acrylic acid by the irradiation method: potato starch and rice starch. Grafting of potato starch was performed with various amounts of acrylic acid (0.2, 0.5, and 1.0 g). When acrylic acid was grafted onto rice starch, similar or even higher amounts of acrylic acid were used. For the potato

starch-g-acrylic acid copolymers obtained with < 1 g of acrylic acid (weight ratio 1:1), the release was relatively fast (about 1 h). When the amount of acrylic acid was increased, the release of salicylic acid was retarded, less than 80% being released after about 5 h. When rice starch was grafted, even with low amounts of acrylic acid, the release of salicylic acid was slow (about 80% in 6 h).

B. Grafting starch solution (5 wt %) with small amounts of acrylic acid

Potato starch in a higher concentration (5 wt.%) was also grafted with small amounts of acrylic acid by the irradiation method. Again, when a small amount of acrylic acid was added, the release of salicylic acid was relatively quick (about 2 h). When the amount of acrylic acid was doubled, the release curve was similar to that of 2% starch, where less starch was used but the ratio was kept the same.

C. Comparison of the effect of two concentrations of starch on drug release

A comparison of the release curves of salicylic acid from potato starch-g-acrylic acid copolymer obtained with 2 or 5 wt % starch and the same amount of acrylic acid was made. The difference in the release curves is insignificant, and it is therefore somewhat puzzling that the release is quicker with higher amounts of starch. The slow release of theophylline from starch-g-acrylic acid copolymers obtained from 2 wt.% starch and higher amounts of acrylic acid was also investigated. The release of theophylline was significantly delayed as the amount of acrylic acid in the graft copolymer was increased. When the ratio of starch to acrylic acid was 1:12.5, total release of the model drug was obtained in about 10 h. However, when the ratio was tripled by increasing the amount of acrylic acid, only about 60% of the drug was released in the same period of time.

Swelling of Copolymers Obtained by ⁶⁰Co Irradiation

Since the extent of swelling is related to adhesion, the swelling of various samples of grafted starches was determined. For high degrees of swelling (~ x200), slippery materials are obtained. Results of swelling of grafted acrylic acid onto potato starch (2 wt.%) at a weight ratio of starch:acrylic acid of 1:5 are shown in Table 1. The extent of swelling was lower than the value mentioned above, and bioadhesion will be in keeping with the swelling values. The swelling of a sample of polyacrylic acid obtained under the same irradiation conditions was also measured for purposes of comparison (Table 1). The results in Table 1 also provide confirmation of the reproducibility of the method used for grafting the starch.

Table 1. Swelling of copolymers of potato starch grafted with acrylic acid*

Sample	Dry weight (g)	Weight after swelling for 24 h (g)	Swelling
18-15-2	0.322	12.7	x 39.4
18-18-1	0.213	10.7	x 50.5
18-33-1	0.243	9.4	x 37.5
18-33-2	0.273	9.1	x 33
18-33-3	0.223	11.0	x 49.3
18-15-1 (PAA)	0.122	22.5	x 184

*Weight ratio of potato starch to acrylic acid was 1:5; PAA = polyacrylic acid

Graft Copolymers from Maltodextroses and Acrylic Monomers

Water-soluble maltodextroses C*PUR 1910, C*PUR 1924 and C*PUR 1934 were used. Grafting experiments with ⁶⁰Co were performed with C*PUR 1910. Solutions of 2% or 5% maltodextrose were mixed with different amounts of acrylic acid (0.4 g and 2.0 g, respectively). The solutions were irradiated with ⁶⁰Co for 24 h. After irradiation, the samples that contained lower amounts of acrylic acid (irrespective of the concentration of the maltodextrose) were still liquids. The other samples were clear transparent gels. Two maltodextroses - C*PUR-1910 and C*PUR-1924 - were tested in grafting experiments by the Ce⁴⁺ initiation method: In both cases, the samples were hydrolyzed after the grafting procedure. The resulting products were found to be soluble in DMF, indicating that only acrylonitrile polymerized during the grafting procedure. Additional proof that the resulting product was indeed polyacrylonitrile was obtained from swelling experiments: the material did not swell at all. The gels obtained by the irradiation method were tested for the release of salicylic acid and the results are encouraging. However, a sample of acrylic acid alone has to be irradiated and the polyacrylic acid so obtained has to be used as a control: a model drug will be incorporated into it, and its release will be compared with the results to ascertain that the maltodextrose was indeed grafted.

Chemical Characterization of Graft Copolymers obtained by Chemical Initiation

The grafting onto starch was performed by chemical initiation with cerium ammonium nitrate, according to literature methods. Although acrylonitrile or mixtures of acrylic acid and acrylonitrile were used for polymerization, the best results were obtained when freshly distilled acrylonitrile alone was used as reactant. The graft copolymer of starch and acrylonitrile was tested using several techniques. In addition, we are at present investigating several methods by which to determine the molecular weight of polyacrylonitrile and/or that of polyacrylic acid grafted into starch.

Kinetics Of Slow Release Of Model Drugs From Tablets Obtained From Graft Copolymers Of Starch With Acrylic Acid

In bioadhesion measurements of the first generation of graft copolymers from starch, we encountered problems with preparation of tablets. To solve this problem, air-dried graft copolymers were shredded into small pieces by means of a blender. Powders so obtained were used to prepare tablets with the model drugs as described in Materials and Methods. Tablets with binder (polyvinylpyrrolidone) were also prepared. The release of salicylic acid from tablets obtained with graft copolymers from both potato and rice starch with the same amount of acrylic acid was significantly slower from the rice starch-*g*-acrylic acid copolymer (only about 70% release after 8 h). When binder was added to tablets prepared from the same batches of graft copolymers, the release of theophylline was similar for both rice and potato starch grafted copolymers. It seems that the results obtained reflect the effect of the binder, which eclipsed the differences observed above.

A comparative experiment was performed with a sample of dry grafted starch and a tablet obtained from the powdered form of the same grafted copolymer. The results gave a better release of the drugs from the tablets. In future, only powders made into tablets will thus be tested.

Bioadhesion Measurements

Effect of initiation method

Representative samples of grafted starches obtained by the two initiation methods were tested for their bioadhesive properties (Table 2). The best bioadhesion was found for rice starch grafted with acrylic acid by the ⁶⁰Co irradiation method. Potato starch grafted by the same method had bioadhesive properties similar to those of a physical mixture of pregelatinized starch with polyacrylic acid. Bioadhesion lower than the reference sample was measured on starches grafted by the redox method. One possible reason for this finding may be the fact that the final grafted starch obtained by the redox method has not only carboxylic groups but also amide groups (IR analysis and nitrogen content). Another factor that may prove even more crucial is the pH of the final graft copolymer. The effect of pH has to be tested in greater depth, not only on the preparations obtained by chemical initiation but also on materials prepared by irradiation.

Table 2. Bioadhesion of grafted starches by the two initiation methods

Sample #	Type of starch	Detachment force (N)	Work of adhesion (mJ)	Grafting method
JP-42-1	Potato	2.821 ± 0.758	0.864 ± 0.299	Irradiation
JP-42-2	Potato	1.271 ± 0.422	0.092 ± 0.057	Redox
JP-42-3	Rice	3.159 ± 0.785	0.872 ± 0.182	Irradiation
JP-42-4	Rice	1.372 ± 1.275	0.270 ± 0.323	Redox
Reference*		2.322 ± 1.298	0.443 ± 0.207	-

*Physical mixture

Effect of pH

At high pH (pH 10) at a ratio of starch to acrylic acid of 1:1.5, as expected, no bioadhesion was detected. After lowering the pH (pH 3), the same material showed some degree of bioadhesion. When the amount of acrylic acid was increased to a ratio of starch: acrylic acid of 1:5, some bioadhesion was measured, even at pH 10.

Effect of mono- and divalent cations

In the presence of Na⁺, the extent of bioadhesion was similar for the three starches tested. When divalent cations (Ca²⁺, Mg²⁺) were introduced, the bioadhesion measured was always higher for materials containing Ca²⁺ than for those with Mg²⁺. However, when Ca²⁺ and Mg²⁺ were added in higher amounts (× 2) and (× 4), the degree of bioadhesion dropped completely.

Grafted copolymers of maltodextroses and acrylic acids

Two maltodextroses (#1910 and #1924) grafted with acrylic acid in presence of Na⁺, Ca²⁺ and Mg²⁺ behaved similarly to the various starches. Grafted starches containing Ca²⁺ were more adhesive than those containing Na⁺ or Mg²⁺. In the case of the grafted maltodextroses, the materials containing Mg²⁺ showed higher bioadhesion. The difference between these two maltodextroses lies in their degree of oligomerization, the larger oligomer being #1924. Since the size of the oligomer seems to influence bioadhesion and possibly also drug release, it was decided to perform a controlled study on various maltodextroses with different degrees of oligomerization. The research, which includes grafting under various conditions, swelling measurements, preparation of tablets, drug release kinetics and finally bioadhesion tests is still under investigation.

In-Vivo Experiments In Dogs

Tablets prepared from some grafted copolymers were attached to the inside of the mouths of dogs (gingiva). The purpose of the experiments was to test whether toxicity and/or irritation developed with time. The bioadhesion time of the tablets in the dogs' mouths were for some formulations more than 40h. No irritation or toxicity was detected, even after the long periods of time.

Patents

A patent application is under preparation.

FOLLOW-UP.

Several potential commercial partners are contacted.

PARTNERS

UNIVERSITEIT GENT

Faculty of Pharmaceutical Sciences
Laboratory of Pharmaceutical Technology
Harelbekestraat 72
9000 Gent
Belgium

Jean Paul Remon
Tel.: +32-9-222 80 54
Fax: +32-9-222 82 36

BEN-GURION UNIVERSITY OF THE NEGEV

Faculty of Engineering Sciences
Department of Chemical Engineering
P.O. Box 653
84105 Beer Sheva
Israel

Joseph Kost
Tel.: +972-7-646 11 11 (switchboard)
Fax: +972-7-77 16 12

STRUCTURAL STUDIES AND COMPUTER SIMULATIONS OF SUBSTRATE AND INHIBITOR BINDING TO ACETYLCHOLINESTERASE

Co-ordinator: Université Libre de Bruxelles, Bruxelles, Belgium (Shoshana Wodak)

OBJECTIVES

- Gain insight into the structure - function relationships in AChE with regard to cholinergic ligands, by combining structural studies on complexes of AChE with representative examples of some important ligand families, with theoretical approaches that would allow relating the structural data to experimentally measured dynamic and thermodynamic properties;
- Other important objectives are the development of improved computer aided design tools for protein - drug interactions.

ACTIVITIES

- ◇ This project will combine structural studies by X-ray diffraction with theoretical computer simulations and molecular modelling approaches;
- ◇ To structure determination of complexes with AChE with ligands of fundamental and toxicological or therapeutic interest by X-ray crystallography;
- ◇ Analysis of the electrostatic properties of the enzyme active site and its surrounding using atomic and continuum models;
- ◇ Investigation of the effects of thermal motion and electrostatic field on the diffusion of water and ligands in the active site gorge;
- ◇ Mapping of binding sites and diffusion pathways of simple ligands in the active site cleft of AChE.

RESULTS

- ⇒ Crystal structures of 2 complexes of *Torpedo californica* AChE with Fasciculin, a snake venom toxin, and with a transition state analogue, Huperazine, were solved.
- ⇒ A Laue diffraction pattern was obtained for an orthorhombic crystal of *Torpedo* AChE, diffracting out to 2.8Å, in 4 msec.
- ⇒ Recombinant AChE was expressed in HEK293 cells, and purified. This material will be used in crystallisation trials.
- ⇒ Automatic procedures were applied to analyse the conformational differences between native *Torpedo* AChE, and the enzyme structure when complexed to several ligands for which the enzyme-ligand X-ray structure is known. The results suggest that the ligand induced conformational changes are very small and limited primarily to loop regions.
- ⇒ Multiple copy molecular dynamics' simulations and continuum electrostatic calculations were used to map the entry and exit pathways of small cations, anions, and neutral ligands in the active enzyme gorge. The results suggest that the electrostatic potential varies little throughout the gorge region and is not influenced by the large macrodipole displayed by the enzyme as a whole.

PARTNERS

UNIVERSITÉ LIBRE DE BRUXELLES

Unité Conformation des Macromolécules Biologiques
Avenue Franklin Roosevelt 50
C.P. 160/16
1050 Bruxelles
Belgium

Shoshana Wodak

Tel.: +32-2-648 52 00

Fax: +32-2-648 89 54

E-mail: shosh@ucmb.ulb.ac.be

THE WEIZMANN INSTITUTE OF SCIENCE

Department of Structural Biology
76100 Rehovot
Israel

Joel L. Sussman

Tel.: +972-8-34 26 38

Fax: +972-8-34 41 59

BIOGENESIS AND STABILITY OF THE PHOTOSYNTHETIC APPARATUS IN GYMNOSPERMS UNDER NORMAL AND STRESS CONDITIONS

Co-ordinator: Université de Liège, Liège, Belgium (Fabrice Franck)

OBJECTIVES

- To examine chlorophyll synthesis in gymnosperms and define the "dark synthesis" pathway for evaluating the relative contribution of this pathway to chlorophyll synthesis in response to temperature variations and to atmospheric pollutants;
- To examine how chlorophyll synthesis is integrated with chlorophyll assimilation into photosynthetic complexes in gymnosperms compared to angiosperms. This will allow to understand how chlorophyll synthesis and the assembly of particular chlorophyll-protein complexes (light-harvesting and reaction centre complexes) are coupled;
- To characterise the photosynthetic physiology of gymnosperms at a molecular and biochemical level and make comparisons to other plants;
- To investigate at a molecular level the effects of environmental stress on photosynthetic apparatus of gymnosperms. This aims at determining the effects of environmental stresses (extreme temperatures and irradiances, sulphur dioxide) on the accumulation of free pigment that may cause photo-oxidative damage and at identifying how these factors interfere with the normal turn-over of photosynthetic components.

ACTIVITIES

- ◇ Pine (seedlings and needles from mature trees) is used as representative gymnosperm. The principal material for comparison (representative angiosperm) is barley. The green algae *Chlamydomonas reinhardtii* is used for specific purposes;
- ◇ Investigations on the mechanism of light-independent protochlorophyllide reduction in gymnosperms;
- ◇ Spectroscopic studies on protochlorophyllide forms in pine seedlings and their formation at normal or low temperature;
- ◇ Studies on the regulation of photosynthetic chlorophyll-protein complexes assembly in gymnosperms and angiosperms (free pigment accumulation, photochemical activities, polypeptide synthesis);
- ◇ Studies on the mechanism of photoinhibition and recovery processes in relation to chlorophyll turn-over;
- ◇ Investigations on the relationship between carotenoid synthesis and photosystem II assembly and turn-over;
- ◇ Study of pollutant effects (sulphur dioxide) on chlorophyll synthesis and integration into pigment-protein complexes.

RESULTS

- ⇒ Measurements of chlorophyllase activity in various plant materials including pine.
- ⇒ Evidence for a role of β -carotene in photoinhibition and rapid turn-over of the D1 protein of photosystem II reaction centre in *Chlamydomonas reinhardtii*.
- ⇒ Analysis of the characteristics of chlorophyll fluorescence lifetime during assembly of photosystems in darkness and further activation by continuous light in cotyledons of *Pinus brutia*.
- ⇒ Characterisation of the development of the photosynthetic apparatus in seedlings of *Pinus jeffreyi* and *Pinus brutia* by low temperature, steady-state fluorescence spectroscopy.
- ⇒ Determination of the influence of the photoactivation of photosystem II on the characteristics of constant and variable fluorescence of chlorophyll at room temperature in cotyledons of *Pinus jeffreyi* and *Pinus brutia*.
- ⇒ Mathematical analysis of spectroscopic characteristics of *in vivo* protochlorophyll(ide) forms during dark-growth of pine seedlings. Detection of three different forms of photo-inactive and two

- forms of photo-active protochlorophyll(ide). Evidence of an enhancement by low temperature treatments of the light-dependent pathway of chlorophyll synthesis in *Pinus jeffreyi*.
- ⇒ Determination by high performance liquid chromatography of the pigment composition (carotenoids and chlorophyll's) in cotyledons and needles of dark-grown seedlings of *Pinus jeffreyi* and *Pinus sylvestris*.

PARTNERS

UNIVERSITÉ DE LIÈGE

Département de Botanique, B22
Laboratoire de Photobiologie
Sart-Tilman
4000 Liège
Belgium

Fabrice Franck
Tel.: +32-4-366 39 04
Fax: +32-4-366 29 26
E-mail: u215501@vm1.ulg.ac.be

HEBREW UNIVERSITY OF JERUSALEM

Faculty of Agriculture
Agricultural Botany Department
76100 Rehovot
Israel

Jonathan B. Marder
Tel.: +972-8-48 19 18
Fax: +972-8-46 77 63

RUHR-UNIVERSITÄT BOCHUM

Plant Biochemistry Department
P.O. Box 10 21 48
4630 Bochum
Germany

Achim Trebst
Tel.: +49-234-700 36 34
Fax: +49-234-709 43 21

**MOLECULAR ANALYSIS OF THE GIBBERELLIN-REGULATED GENE
EXPRESSION IN PETUNIA FLOWERS**

Co-ordinator: Free University of Amsterdam, Amsterdam, The Netherlands (J.N.M. Mol)

OBJECTIVES

- The growth regulator gibberellic acid (GA) affects several processes in plants, most notably seed germination, floral induction, and elongation of various tissues and organs. Mutants that are unable to synthesise GAs or unable to respond to GA, have a dwarf phenotype and usually do not flower. In normal plants, GA is also required for the elongation of corollas and the synthesis of anthocyanin pigments, which give the flower its characteristic colour. The long-term objective of this project is to understand the molecular mechanism by which gibberellins control these processes.

ACTIVITIES

- ◇ Little is known about the perception of GA, and GA-receptors have not been cloned yet. Since a number of genes that are specifically expressed in corollas have been cloned and characterised, we have taken the approach to study if and how these genes are regulated by GA. In this bottom-up approach we examine the last step in the GA signalling cascade, which is the transcriptional activation of specific genes. By analysing the promoters of these genes and the corresponding transcription factors, we intend to move up into the GA signalling pathway thereby being able to characterise the protein factors and signalling molecules involved. GA is only active in the presence of metabolic sugars. Therefore, at the physiological level, the GA-signalling is examined with respect to the role of these sugars. As GA may not be the only stimulus activating gene expression, other stimuli have also been examined, such as wounding and jasmonic acid. This may provide insight in how different signalling pathways are connected and share similar components.

RESULTS

GA-activation of anthocyanin regulatory genes

- ⇒ GA induces expression of pigmentation genes in the corolla at the transcriptional level that can be considered an end point of the GA signalling pathway. We demonstrated this by using an in vitro culture system of excised floral buds. In this system, expression of pigmentation genes can be repressed by an incubation in sucrose medium. Expression can be reactivated by adding GA. The re-induction kinetics of all the structural pigmentation genes tested is about the same; mRNA accumulation is detectable among 4 and 6 hours after the application of GA. These genes are however not the primary GA-response genes but are activated by regulatory proteins whose genes are more directly controlled by GA-generated signals. Several of these regulatory genes have been cloned from petunia, among which An1, An2 and An11. The proteins of these three genes are all required for the transcriptional activation of the pigmentation genes of the second half of the anthocyanin pathway, beginning with dihydroflavonol 4-reductase. As expected, in the in vitro flower bud assay, activation of these An regulators by GA occurs earlier than that of the structural genes. Thus, the promoters of these genes are excellent tools to move one step up in the GA-signalling pathway.

GA-induced MYB-type transcription factor genes

- ⇒ Apart from An2, which encodes a MYB transcription factor, a number of other Myb genes have been cloned from corollas, by means of homology between the DNA-binding domains. The expression of the Myb27, Myb92, and Myb.Ph1 genes in petals requires the presence of GA3. However, examining the expression of Myb27 yielded a surprise. Myb27 is expressed in leaves and in almost all organs of the flower but mostly in corollas. By examining mutants and transgenic plants carrying a Myb27 promoter driven reporter gene we found that Myb27

expression is controlled by the same An1, An2, and An11 regulatory genes that control the pigmentation genes. Thus, the GA-activated expression of the regulator Myb27 may turn out to be very similar to that of the structural genes. The function and the target genes of the MYB27 protein are not yet known, despite the identification of more than 10 different transposon insertion alleles. All transposon insertions were found in one of the two introns or in the 3'UTR and which had no effect on mRNA synthesis. Although Myb27 is regulated by the An1, An2, and An1 gene products, which already act in young corollas, the level of Myb27 mRNA is the highest in relatively old corollas. How the differential effect on the An-target genes, myb27 and the pigmentation genes, is achieved by the same regulators is unknown. MYB27 seems not to be involved in transcriptional activation as it lacks a clear transcription activation domain in the C-terminal part of the protein. The C-terminal region is actually very short, so it might very well act as a repressor protein.

- ⇒ MYB92, which contains a putative transcription activation domain, is expressed in almost all organs of the flower. However, its function remains to be determined as a plant carrying a Myb92 knock-out allele did not show an altered visible phenotype. As petunia contains several Myb92 homologues, this might be due to functional redundancy.
- ⇒ The strongly GA-inducible Myb.Ph1 gene encodes for a protein that is required for the formation of the conical shape of epidermal cells of the corolla. The cells of a mutant in which the Myb.Ph1 gene was disrupted by a transposon were flat. This phenotype has been described before in Snapdragon and shown to be caused by a mutation in a MYB protein called mixta. Myb.Ph1 is therefore the petunia mixta homologue. The proteins are very homologous especially in the DNA binding domain. Myb.Ph1 expression in petals begins very early and is already at its maximum level in small yet unpigmented buds. At later stages the mRNA level declines. This indicates that GA activation of this gene is much earlier than that of the flavonoid genes. The promoter of Myb.Ph1 is therefore very interesting with respect to its mode of GA activation, because the response of this promoter to GA seems the highest of all GA-inducible Myb genes tested.

GIP1: a GA-induced cysteine-rich protein from elongating tissues

- ⇒ A GAST homologue from petunia, Gip1, was isolated. This gene is strongly induced by GA in petals, in stem and in leaves. Induction of this gene depends much less on the presence of sucrose than other GA-responsive genes GIP1 is a cysteine-rich protein of which the function is yet unknown. By examining a petunia seed library for transposon insertions in the Gip1 gene, one mutant allele was found to have a dTph1 insertion into the first intron. As it is located 21 bp from the 3' splice site it seems to affect pre-mRNA splicing because the mRNA level in this Gip1 mutant is severely reduced as compared to wild-type. Preliminary results suggest that this reduction leads to male sterility. No other phenotypes are visible that might be due to the partial inactivation of the gene.

GA-induced 'housekeeping' genes

- ⇒ The effect of GA on plant tissues is very dramatic. There is usually an extensive elongation and it is conceivable that many cellular processes are up-regulated. It was therefore of interest to look at the response of various, so called 'housekeeping' genes, to GA. By different approaches several of these genes from petunia were isolated: glyceraldehyde 3-phosphate dehydrogenase (GAPDH) and triose phosphate isomerase (TPI), which are involved in glycolysis, 5 enolpyruvyl shikimate-3-phosphate synthase (EPSPS) of the shikimate pathway, and S-adenosylmethionine synthase (SAM-S), which is required for the synthesis of SAM, a general methyl donor. In corollas, all these genes, except GAPDH, are up-regulated by GA. The pattern of this induction is very similar to that of the pigmentation genes. These first experiments, just by following mRNA levels, indeed suggest that several cellular processes are geared up by GA. However, the finding that several distinct genes are up-regulated in a comparable manner raises the question about the specificity of gene activation by GA. Since GA induces gene expression only in the presence of sucrose it was therefore of interest to examine the role sucrose as a possible, more general, signal molecule. The idea being that GA simply facilitates the uptake of sucrose. Sucrose uptake studies were done using ¹⁴C-sucrose as a tracer. This revealed that although GA stimulated sucrose uptake by 20-30%, GA was still needed as a specific stimulus. By inhibiting sucrose uptake by 40%, using the inhibitors PCMBs or vanadate, GA was still able to activate gene expression despite the much

lower sucrose uptake. In the samples that had taken up much more sucrose, the examined genes remained unexpressed. These results indicate that genes are not simply activated by a high intracellular sucrose concentration. It clearly requires a specific GA generated signal.

FOLLOW-UP

- ▶ Up to now, the results of this project show that actually many genes in plants are up-regulated by GA. Expression of several housekeeping genes is enhanced above a certain basal level, whereas the expression of several of the transcription factor genes analysed and of *gip1* appears to depend entirely on GA. The picture that is beginning to emerge is that GA may regulate genes in different ways, meaning that there is not a single linear pathway from GA-perception leading to promoter activation and gene expression. To get more insight into these different modes of activation, it will be necessary to examine in depth the steps that occur at the promoter of a primary GA-response gene in combination with the identification of second messenger signals that trigger these events in GA-stimulated cells.

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PARTNERS

FREE UNIVERSITY OF AMSTERDAM

Faculty of Biology
Department of Genetics
1081 HV Amsterdam
The Netherlands

J.N.V. Mol
Tel.: +31-20-525 78 26
Fax : +31-20-525 77 15

HEBREW UNIVERSITY OF JERUSALEM

Faculty of Horticulture and Agriculture
P.O. Box 12
76100 Rehovot
Israel

A. Halevy
Tel.: +972-8-48 13 57
Fax: +972-8-46 82 63

**NEW ELECTRICALLY CONDUCTING ORGANIC MATERIALS: DESIGN,
SYNTHESIS AND CHARACTERISATION**

Co-ordinator: Universität Tübingen, Tübingen, Germany (Michael Hanack)

OBJECTIVES

The research program involves the synthesis and properties of new types of organic conducting materials. Two main synthetic approaches will be undertaken:

- The synthesis of novel mixed donor (D)/acceptor (A) molecules capable of intramolecular charge transfer (CT);
- The synthesis of molecules containing two units, which after one-electron oxidation give rise to intramolecular CT between the resulting cation-radical moiety (now as an acceptor) and the remaining neutral donor moiety;
- The synthesis of new organofullerenes as strong acceptors.

ACTIVITIES

- ◇ Preparation of starting quinine derivatives containing nitrogen in the ring as precursors of new D-A, A-D-A and D-A-D systems and their conversion to N,N' dicyanoquinodiimines;
- ◇ Synthesis of donors with multiple TTF units and halogenated tetrathiafulvalenes;
- ◇ Synthesis of novel donor-acceptor molecules containing efficient donor TTF linked to an efficient acceptor moiety;
- ◇ Reaction of fullerene C₆₀ with functionalized o-quinodimethanes to form C₆₀-adducts as strong acceptors.

RESULTS

- ⇒ New donor and acceptor systems containing nitrogen in the ring have been prepared (1,4-benzoxazine system as the donor fragment) and converted to benzo-TCNQ and benzo-DCNQI adducts. Their electronic spectra and cyclic voltammetry were measured to study their behaviour towards formation new conducting materials.
- ⇒ The synthesis of the first intramolecular donor-acceptor system that includes a TTF moiety has been carried out. The electrochemical and spectroelectrochemical studies of this new system show that both donor and acceptor moieties keep their identity inside the intramolecular system.
- ⇒ Fullerene C₆₀ was reacted with functionalized o-quinodimethans (i.e. sultines) to form novel organofullerenes bearing quinone type adducts as precursors for synthetic metals. Their electrochemistry has been studied which shows them to be potentially electroactive materials that can be used for the preparation of new materials.
- ⇒ Several novel types of donors with multiple TTF units and halogenated tetrathiafulvalenes were synthesised. Single crystal structures of some of them were determined and their electrochemistry studied. A charge transfer complex of a multiple TTF-unit with TCNQ was prepared and its X-ray structure studied, which revealed a number of unusual features favourable for obtaining high electrical conductivity.

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PARTNERS

UNIVERSITÄT TÜBINGEN

Institut für Organische Chemie
Auf der Morgenstelle 18
72076 Tübingen
Germany

Michael Hanack
Tel.: +49-7071-292 43 42
Fax: +49-7071-295 244

UNIVERSIDAD COMPLUTENSE DE MADRID

Facultad de Química Orgánica
Ciudad Universitaria
28040 Madrid
Spain

Carlos Seoane-Prado
Tel.: +34-1-394 42 18
Fax: +34-1-394 34 72

BEN-GURION UNIVERSITY OF THE NEGEV

P.O. Box 653
84105 Beer-Sheva
Israel

James Becker & Joel Bernstein
Tel.: +972-7-46 11 87
Fax: +972-7-74 539

DEVELOPMENT OF A PACKED BED BIOREACTOR USING TWISTED RIBBONS OF POLYSTYRENE FOR THE CULTIVATION OF MAMMALIAN CELLS

Co-ordinator: Weizmann Institute of Science, Rehovot, Israel (Avinoam Kadouri)

OBJECTIVES

- To study in depth the advantages of packed bed over conventional stirred microcarrier bioreactors for the cultivation of those mammalian cells that require a surface for their adherence and growth and for the production of biologically active macromolecules from such cells.

ACTIVITIES

- ◇ Having examined a number of possible packing materials, such as treated polystyrene twisted ribbons, for the medium for the packed-bed, we decided to focus on the Fibra-cel non woven matrix of treated polystyrene fibres held in place by a coarse web of polypropylene filaments in the physical form of 6 mm diameter discs of about 1 mm in depth;
- ◇ We designed, built and evaluated a number of bioreactor configurations in which the Fibra-cel carrier was used as the support substratum or capturing medium for the animal cells; we focused our attention on both a rotating sheet of the Fibra-cel held against the vertical end wall of a standard roller bottle and also a rotating basket of Fibra-cel discs which can be scaled-up to commercial levels;
- ◇ We demonstrated the utility of the Fibra-cel system of cell cultivation for the production of tissue-Plasminogen Activator from an anchorage dependent normal human diploid fibroblast and a monoclonal antibody from a manufactured mouse cell hybridoma; in both of the latter cases, cultures were run in the continuous mode of operation and steady state productivities were obtained;
- ◇ To bridge the gap between bench-scale systems based on roller bottles in which processes for the production of materials from animal cells are developed and the large-scale commercial operations, which could be over 100 litres in size and based on a rotating basket of Fibra-cel discs, we demonstrated, that by making a small modification to the standard roller bottle (by adding to it a sheet of Fibra-cel in which all the cells grew as the walls of the bottle were presiliconised) we could obtain the same kind of biological activity (as measured by cell growth and physicochemical parameters such as glucose utilisation, pH changes and lactic acid production) that would be obtained in a standard unsiliconised, unmodified roller bottle; and moreover it was possible to show, in a geometrically and volumetrically equivalent version of the Fibra-cel containing roller bottle, that similar kinds of productivities and physicochemical parameter changes could be obtained in a scaled-down version of the rotating basket system.

RESULTS

- ⇒ There are a large number of alternative systems for the productive and commercial use of anchorage dependent animal cells in culture. We have reviewed such systems, and have concluded that the packed bed of Fibra-cel offers the most potential for future developments. The studies we have undertaken with the Fibra-cel non-woven polyester material have demonstrated the feasibility of this system for the propagation of a number of cell types (BHKC13, Mouse Hybridoma, normal human fibroblasts and genetically engineered CHO cells). It also found to be suitable for the generation of product materials from such cells such as tissue-Plasminogen Activator, monoclonal antibodies and a genetically engineered cell producing Blood Factor VIII.
- ⇒ In producing antibody from a Hybridoma cell culture we have shown that the cells remain attached to the carrier when this is held in a rotating basket on the spinning shaft of a bioreactor. Furthermore the extended productivity of the antibody by the cells indicates that they retain their viability and physiological capabilities after an extensive habitation of the polyester matrix of the Fibra-cel material. A similar message may be obtained from the examination of normal human diploid fibroblasts secreting t-Plasminogen Activator. Such cells were maintained in their

secreting mode for up to 40 days in a serum free medium while remaining attached to the Fibracel carrier. These latter cultures were more productive than other microcarrier controls.

- ⇒ When cells produced on the carrier were compared with their controls grown on either glass or treated polystyrene, it was shown that it was not possible to obtain significant differences in either cell yield and viabilities or in those physiological parameters which were studied during the initial experimentation with the exception of the amount of lactic acid produced in treated polystyrene flask cultures that differed from both the Fibracel and the standard Roller Bottle systems; the latter two systems, however, were not significantly different in any of the parameters' measures to date. Recent experiments are showing that it is possible to produce in a rotating basket packed bed system, which is geometrically equivalent system to the Fibracel containing roller bottle, results that are similar to those generated in the modified roller bottle. This result bridges the gap between what can be achieved under bench-scale conditions and the scaled-up systems that are commonly used in commercial operations.

FOLLOW-UP

- ▶ As the Fibracel system can be scaled-down to a 50 ml medium volume culture system held in a 120 ml roller bottle the development work on a new project may be conducted with considerable ease and efficiency in such a system. This will have the advantageous effect of scaling up to a unit process system based on over 100 litres of medium (a 2000 fold scale-up) without changing the substratum with which the cells interact. This facility should obviate the need to produce materials for the commercial market in systems based on the use of thousands of roller bottles (Erythropoietin) rather than in a scaled-up bioreactor containing a rotating basket of Fibracel discs;
- ▶ There is also little doubt that the three-dimensional nature of the cell growth can be likened to that which occurs in the organs of animal bodies. It has therefore become clear to us that this system will not only provide a cost-effective way of producing products on the industrial scale from animal cells grown in culture but that it may also be used for the creation of artificial organs. Such a facility might be applied in both the further studies of the way cells interact with one another in the close confines of a three-dimensional structure but there may be further opportunities for exploiting such systems to process blood *ex vivo* as either an artificial liver or kidney. The practicability of replacing different organs *in vivo* remains to be determined as it is unlikely that the polyester/polypropylene material of the Fibracel would dissolve *in vivo*. Nevertheless, it is also unlikely that these materials will cause immunological problems. In addition to these potential uses of Fibracel based artificial organs, there is a present need to replace animals in test systems for new products and quality control procedures. The development of organ mimics which can be stored and transported easily would obviate the need for expensive, unreliable and unethical animal experimentation.

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PARTNERS

THE WEIZMANN INSTITUTE OF SCIENCE
Department of Membrane Research and Biophysics
76100 Rehovot
Israel

university of surrey, guildford
Department of Microbiology
School of Biological Sciences
Surrey GU2 5X11
United Kingdom

Avinoam Kadouri
Tel.: +972-8-34 21 38
Fax: +972-8-46 69 66
Other contact (same tel/fax):
Meir Wilchek
Ray Spier
Tel.: +44-1483-30 08 00
Fax: +44-1483-30 03 74

PROTEIN COMPONENTS OF CHEMORECEPTOR ORGANELLES AND OF THE CUTICLE OF NEMATODES : IDENTIFICATION AND CLONING OF THE GENES, PRODUCTION AS RECOMBINANT PROTEINS AND ANALYSIS OF THE IMMUNE RESPONSE ELICITED

Co-ordinator: Istituto Internazionale de Genetica e Biofisica, Napoli, Italy (Paolo Bazzicalupo)

OBJECTIVES

- To increase our knowledge and understanding, at the cellular and molecular level, of the ontogenesis, structure and physiology of chemoreception and of the cuticle of nematodes;
- To clone and study parasite molecules, components of the chemoreception system and of the cuticle, as potential target for drug and/or vaccine development;
- To study the immune response toward molecularly defined antigens of nematodes;
- To perform pilot epidemiological studies to identify, in the Northern region of Morocco, special communities or situations where nematode infections are more frequent and/or severe;
- To train scientists from European and developing countries in the field of biotechnology as applied to the control of nematode infections.

ACTIVITIES & RESULTS

Chemoreception

- ⇒ We have completely characterised a chemoreception mutant identifying a new gene *dyf-1* and have shown that it affects the structure of the amphids, the main chemosensory organs of nematodes.

Avoidance mutants

- ⇒ We have designed a completely new test for the chemical avoidance response. The test is relatively easy to perform, fast and unambiguous and has enabled us to screen over 150 different chemicals for the ability to trigger the avoidance reflex in *C. elegans*. Among the newly identified repellents are copper ions, quinine and other antimalarial drugs. Using the assay described above, we have isolated 13 new mutants unable to avoid quinine. Some of these mutants are particularly interesting in that they apparently have normal cilia and amphidial channels. Two of these mutants do not complement and define a new gene *qui-1* that we have mapped genetically on chromosome IV near the gene *tra-2*. The mutants fail to avoid quinine but are still able to avoid other repellents, including copper ions and garlic extracts. This finding, together with the apparent normal architecture of the cilia, suggests that the two mutations are likely to affect the receptors directly and not the general functioning of chemosensory neurones.

Cuticle

- ⇒ We have identified and cloned three homologues of *cut-1* in *Ascaris lumbricoides* and at least two in *Brugia pahangi*. Southern blots with conserved regions have shown that genes homologous to *cut-1* are conserved in all other nematode species tried. Together with several *cut-1* like genes that have been discovered in *C. elegans* by the genome sequencing project they represent a new gene family with an important role in making up the protective layers of nematodes. One *Ascaris* gene has been studied more completely and the whole genomic and cDNA sequences determined. The homology with *C. elegans cut-1* is higher than 85% at the amino acid level and like in *C. elegans* the protein begins with a signal peptide.
- ⇒ Recombinant *Ascaris* CUT-1 has been obtained from *E. coli* expression vectors and used to raise specific antisera in rabbits. Immuno-electron-microscopy has been used to localise CUT-1 and CUT-2 epitopes in nematode cuticles. Determination of the genomic sequences and identification of cDNA clones from *Brugia pahangi* are in progress in Glasgow.
- ⇒ Using recombinant CUT-2 produced in *E. coli* we have studied CUT-2 cross-linking *in vitro* and demonstrated the importance of hydrophobic interactions in this process, which occurs during

cuticle assembly *in vivo*, and involves the formation of dityrosine bridges between different CUT-2 molecules.

Immune response to gp 30 and filarial antigens

- ⇒ We performed a series of experiments to establish the cellular and immune response of mice to native gp30 and to a synthetic gp30 peptide that corresponds to a T cell epitope. A variety of immunisation protocols was used:
- mice immunised and boosted with L3 of *Brugia pahangi*;
 - mice immunised sub-cutaneously with 100 micrograms of the synthetic gp30 peptide or with 100 micrograms of native *Brugia* antigen;
 - mice infected with adult *B. pahangi* by transplantation into the peritoneal cavity;
 - mice immunised by footpad injection with the peptide and or the adjuvant alone.
- ⇒ Sera and lymphocytes from these animals were then analysed for presence of specific antibodies, for proliferation for cytokine production. Sparingly, peptide immunised animals had no detectable antibody response to *Brugia* antigen, while animals immunised with the native antigen or with worms did. Similarly, lymphocytes from native antigen immunised animals proliferated in response to *Brugia* antigen but not to peptide while cells from peptide immunised animals did not proliferate in response to native antigen but there was a modest stimulation with peptide. Finally no differences were observed in the expression of any cytokine mRNA from lymphnodes of peptide immunised animals compared to adjuvant only controls.

PARTNERS

ISTITUTO INTERNAZIONALE DE GENETICA E BIOFISICA

Centro Interuniversita Ricerca Paese in via di Sviluppo
Via Guglielmo Marconi 10
80125 Napoli
Italy

Paolo Bazzicalupo
Tel.: +39-81-725 72 81
Fax: +39-81-593 61 23

UNIVERSITY OF GLASGOW

Department of Veterinary Parasitology
Glasgow
United Kingdom

Eileen Devaney
Tel.: +44-151-708 93 93
Fax: +44-151-708 87 33

INSTITUT PASTEUR DU MAROC

Place Charles Nicolle 1
Casablanca
Morocco

Abdellah Benslimane
Tel.: +212-2-80 44 07
Fax: +212-2-609 57

DISTRIBUTION COMPARISON BETWEEN COLIPHAGES AND ANAEROBIC BACTERIA PHAGES IN WATER SOURCES

Co-ordinator: University of Barcelona, Barcelona, Spain (Joan Jofre)

OBJECTIVES

- To evaluate the usefulness of bacteriophages as indicators of human viruses in drinking waters;
- To determine which of the three groups of phage, somatic coliphages, F-specific bacteriophages or bacteriophages infecting *Bacteroides fragilis*, at present being considered as potential indicators of enteric viruses, best fulfils the indicator function;
- To determine the validity of the results in different geographical areas.

ACTIVITIES

- ◇ To improve the methods for the detection of small amounts of bacteriophages in waters, either by presence/absence tests or concentration of bacteriophages from water samples;
- ◇ To determine the levels of somatic coliphages, F-specific bacteriophages or bacteriophages infecting *Bacteroides fragilis* in sewage-polluted water samples in Spain and Israel;
- ◇ To determine the presence of the three groups of bacteriophages in a great number of drinking water samples in Spain and Israel;
- ◇ Collection of comparative data on the presence of bacteriophages and faecal coliforms, used at present as bacterial indicators in drinking water samples;
- ◇ Collection of comparative data on the presence of bacteriophages and enteroviruses in a fraction of the water samples tested.

RESULTS

- ⇒ Methods for the detection of small amounts of phages in drinking water had been either developed or improved. Presence/absence methods for the detection of bacteriophages in 100 mL of drinking water had been improved for the three groups of bacteriophages. A simple method, based in the retention of phages by a membrane of inorganic material with a honeycomb pore structure, which a recovery of about 50 % was developed for concentration of bacteriophages from 1 litre of water.
- ⇒ The levels of somatic coliphages, F-specific coliphages and bacteriophages infecting *Bacteroides fragilis* were determined in domestic sewage of Israel and Spain. Results allowed to verify that the three groups of phages were present in similar quantities and proportions in sewage samples from the two countries. In domestic sewage somatic coliphages, which were the most abundant, and F-specific bacteriophages outnumbered significantly *Bacteroides fragilis* phages. Levels of the different groups of phages per 100 mL of raw sewage are the following : somatic coliphages between 10⁵ and 5x10⁶, F-specific coliphages between 5x10⁴ and 10⁶, and bacteriophages infecting *B. fragilis* between 10³ and 5x10⁴.
- ⇒ The comparison of the microbial levels in raw sewage, non disinfected groundwater and disinfected drinking water, indicates that phages are more resistant to natural inactivation and to water treatments than faecal coliforms. Thus, in this respect bacteriophages behave more similarly to viruses than bacteria do.
- ⇒ The relative frequencies of isolation of faecal coliforms and phages in disinfected waters show some differences in data from Spain and Israel. In Spain, bacteriophages infecting *Bacteroides fragilis* were always the most frequently isolated. Considering the period 1993-1994, the frequencies of isolation were : somatic coliphages 2.4%, F-specific phages 4.9% and phages infecting *B. fragilis* 13.7%. In Israel, considering the period 1992-1994, the frequencies were : somatic coliphages 5.6%, F-specific coliphages 6.6% and phages infecting *B. fragilis* 5.1. However, considering only values from 1994, when stronger disinfection was implemented in Israel, the distribution of frequencies was : somatic coliphages 2.1%, F-specific bacteriophages 3.1% and *B. fragilis* phages 12.9%, which are not significantly different from the frequencies found in disinfected water in Spain. These values and the levels of the three groups of

- bacteriophages in raw sewage strongly suggest that bacteriophages infecting *B. fragilis* rank first in resistance to natural inactivation and to disinfection, followed by F-specific bacteriophages.
- ⇒ The studies on the correlation between the presence of bacteriophages and the presence of enteroviruses are not conclusive, mainly because of the extremely low frequency of isolation of viruses. No enteroviruses were isolated in the samples tested in Spain. On the contrary they were isolated in three of the samples analysed in Israel. Two of the three samples were also positive for F-specific bacteriophages and none for either somatic coliphages or phages infecting *Bacteroides fragilis*. However the used concentration technique requires to bring the pH of the sample to low pHs, to which most *B. fragilis* bacteriophages and many somatic coliphages are very sensitive.
 - ⇒ The study performed in Spain reveals that at least bacteriophages infecting *B. fragilis* are as resistant as enteroviruses to complete water treatments, as can be inferred from the values found in the source water and in the treated water.
 - ⇒ For the moment it has not been possible to show any clear periodic distribution of the three groups of bacteriophages studied. However some data suggest that the frequencies of isolation increase during the rainy periods. The same fact has been described for enteroviruses.
 - ⇒ In conclusion, the results obtained indicate that bacteriophages are found in water samples that do not contain bacterial indicators as for example faecal coliforms, despite the fact that faecal pollution, in their origin, contains more faecal coliforms than bacteriophages. Therefore, phages cross more successfully than bacteria do the multiple barriers that faecal micro-organisms found in their way from sewage to drinking water. In this respect they behave like viruses. This successful crossing of the barriers has been observed in the two areas studied, and is more evident for phages of *B. fragilis*, and to a minor extent for F-specific bacteriophages. Results obtained in this project are promising regarding the potential utility of bacteriophages as indicators of human viruses in drinking water.

FOLLOW-UP

- ▶ Although the results obtained in this project are very promising, extensive research needs to be done before decisions may be taken regarding the potential use of bacteriophages as indicators of human viruses in drinking water. Some aspects that need to be further investigated are described below. A few of them are already being investigated by either the research groups participating in the project or other groups;
- ▶ Further determine the resistance of the different groups of phages to inactivation in their way from faeces to drinking water and when possible compare that resistance to the resistance of those groups of human enteric viruses known to be more resistant to inactivation as for example the hepatitis A viruses. This will include :
 - die off rates affecting different bacteriophages in nature;
 - removal of bacteriophages in all types of water treatments;
 - sensitivity/resistance of bacteriophages to different disinfectants.
- ▶ Study the correlation between the presence of viruses and the presence of bacteriophages in drinking water samples. This study is difficult because of the very low frequencies of detection of human enteric viruses in drinking water samples;
- ▶ Perform epidemiological studies in order to determine whether correlation exists between the presence of bacteriophages in drinking water with the incidence of gastrointestinal diseases caused by viruses transmitted through water.

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PARTNERS

UNIVERSITY OF BARCELONA

Department of Microbiology

Avenida Diagonal 645

08028 Barcelona

Spain

Joan Jofre

Tel.: +34-402 11 00

Fax: +34-411 05 92

TECHNION - ISRAEL INSTITUTE OF TECHNOLOGY

Department of Civil Engineering

Environment & Water Resources Engineering

Technion City

32000 Haifa

Israel

Robert Armon

Tel.: +972-4-29 21 11

Fax: +972-4-22 01 33

4. Additional fields of mutual interest

4.3. Materials and production technologies

INTEGRATED GAS FLOW AND GAS SENSORS BY USING POROUS SILICON MICROMACHINING

Co-ordinator: Institute of Microelectronics, Athens, Greece (Androula G. Nassiopoulou)

OBJECTIVES

- To further explore porous silicon technology capability to silicon micromachining applications for sensor fabrication, compatible with C-MOS processing;
- To produce a prototype of a gas flow sensor of a thermopile type, with integrated thermopiles on a polysilicon bridge covered with an isolated SiO₂ overlayer. The use of the fabricated sensors as calorimetric sensors for combustible gases is also going to be tested. The main specifications of the sensor will be :
 - full compatibility with C-MOS technology;
 - high sensitivity;
 - low cost;
 - low power consumption;
 - protection of the active elements against chemical and mechanical contaminations;
 - possibility to combine flow and concentration measurements.

ACTIVITIES

- ◇ Micromachining applications of porous silicon
Porous silicon, besides its exciting optical and electro-optical properties, it offers important advantages for bulk silicon micromachining:
 - by the possibility of producing thick sacrificial layers (100 μm thick and above) which lead, after their dissolution, to bridges and membranes with high distance to bulk silicon;
 - it is fully compatible with C-MOS technology;
 - front side lithography is only needed and expensive equipment for double-side lithography is avoided.The above possibilities are fully investigated with the aim to optimise materials and processes.
- ◇ Fabrication of two prototypes: an integrated gas flow sensor and a gas sensor
 - The gas flow sensor will be of the thermopile type. An integrated thermopile will be fabricated on a polysilicon bridge covered with SiO₂. A thermally isolated resistor will also be integrated on the bridge, whose temperature will be measured by the thermopile;
 - The produced flow sensor will be converted into a gas sensor by evaporating metals like platinum and palladium on top of or instead of the resistor.
- ◇ Process characterisation will be done at each step for process optimisation
- ◇ Sensor testing will be divided into three parts:
 - design and construction of the testing apparatus;
 - testing of the devices under various conditions, including study of their sensitivity, response and recovery times, reproducibility and reversibility, study at any environmental interference of the device and make suggestions for their elimination;
 - study of the fundamental physical properties involved in order to interpret the operating mechanisms of the device with high accuracy. As a result of this study, certain conclusions and future directions will be defined.

RESULTS SO FAR

- ⇒ Porous silicon technology has been successfully used for front side silicon micromachining in a process that is fully C-MOS compatible. Porous silicon is used as a sacrificial layer and is removed by C-MOS compatible chemicals, leaving a very smooth bottom surface and sidewalls. Deep trenches, bridges with suspended membranes and cantilevers are formed, which open new possibilities in monolithic integration of sensors with electronics. Cavities as deep as ~ 120 μm

and suspended polysilicon membranes with a flat surface as large as 230 x 550 μm^2 were fabricated by this process. Also other micromechanical structures as for example very flat polysilicon cantilevers of dimensions 150 μm x 2 μm x 2 μm were easily obtained after optimisation of the process in order to minimise the strain within the polysilicon films. Process steps for sensor fabrication are under testing.

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PARTNERS

INSTITUTE OF MICROELECTRONICS

NCSR Demokritos
P.O. Box 60228
153 10 Aghia Paraskevi Attikis
Athens
Greece

Androula G. Nassiopoulou
Tel.: +30-1-654 27 83
Fax: +30-1-651 17 23

LINKOPING UNIVERSITY

Laboratory of Applied Physics
58183 Linkoping
Sweden

Anita Lloyd Spetz
Tel.: +46-13 28 17 10
Fax: +46-13 13 75 68

UNIVERSITY OF CYPRUS

Natural Sciences Department
P.O. Box 537
1678 Nicosia
Cyprus

Constantinos Christofides
Tel.: +357-2-33 86 71
Fax: +357-2-33 90 60

AIN-SHAMS UNIVERSITY

Faculty of Science
Physics Department
Abbasia - Cairo
Egypt

Hassan Talaat
Tel.: +20-2-284 21 23
Fax: +20-2-66 40 51

QUALITY CONTROL IN THE MIDDLE EAST (QCIME)

Co-ordinator: IT Consult GmbH, Lilienthal, Germany (Thies Wittig)

Industrial manufacturing in Egypt is rapidly expanding but what currently exists is still far behind Europe and the Western World, both in quantity and quality. Despite the tremendous market potential in the Middle East - an area of several hundred million inhabitants - local industry will continue to fight a losing battle against imports as long as it does not bring its quality standards to an equal, international level. The advantageous labour rates of the local industry will only bear fruits on the competitive global markets if no doubt remains about the quality of the goods produced. Stable quality of products can only be achieved through rigid adherence to well-defined control procedures, covering the entire life-cycle of products, from raw material to after-sales services. While the introduction of overall Quality Management is a first step that has to be followed by an integrated control system for the production processes, the success of Quality Management depends on its acceptance by the work force. To bring such changes in the working culture about requires intensive creation of awareness and training.

OBJECTIVES

→ QCiME has set itself the goal to achieve the introduction of Quality Management, both in technical terms and in creating the awareness and paving the path to the necessary changes in the working culture. Naturally, with its small size QCiME cannot address the whole Middle East industry, but what it can set an example that can be used not only to show that Quality Control works in a technical sense but that it can be integrated in the business and production process and accepted by the work force and thus actively supported.

In order to be effective in this exercise, the project will concentrate on Egypt as a country with a relatively high standard of industrialisation. Not only are the chances of success higher in such environment but also the uptake of these techniques by other industrial sectors is expected to be quite rapid in Egypt;

→ QCiME concentrates on Quality Management and Control in manufacturing with the emphasis on:

- the integration of Quality Control Management in the business process;
- the extension of QC Software from discrete to continuous processes;
- the introduction of QC Software in the production process;
- raising general awareness through dissemination and training actions such as workshops and seminars, based on locally implemented working solutions;
- the baseline of this project is the software tool UNIQUE that was developed in ESPRIT Project 6559.

The envisaged demonstration will be at a paper production factory situated in one of the new industrial areas near Cairo. The nature of the end product, the production process and the location of the demonstration site aim at promoting as much as possible the dissemination objective.

→ The specific aims of QCiME are :

- to demonstrate that the state-of-the-art customisable software system can be successfully applied to developing countries' industry and with significant tangible benefits. The UNIQUE software includes comprehensive system guidance, help and tutorials. This is of major benefit to geographical areas where consultants and trainers in technological subjects are not in great supply;
- to customise and install the UNIQUE software modules for the user's system. This will involve modelling the process that will serve as a graphical aid to the understanding of the process by the user and also as a core part of the Quality Control Management system. The knowledge of the operators and engineers of the paper production will be captured into the diagnosis system that is then to be used for troubleshooting any potential quality problems. Quality tools (such as SPC), Reporting and Archiving functions will be customised to the requirements of PPM;

- to translate the software and user guides into Arabic which will be undertaken by the participating Egyptian software house who are experts in this field;
- the results of the project will be promoted and disseminated across Europe, Egypt and neighbouring countries using trade journals, exhibitions, conferences, workshops and seminars.

ACTIVITIES

- ◇ User Requirements and System Specification, consisting of the definition and implementation of the paper production process model. Training for the quality control concepts and the software framework for the partners. This includes also the introduction of the general Quality Management of ISO 9000. Translation of the existing system software and the tutorial into Arabic for use at the factory operator level. Installation of the quality system for the production facilities of the paper production company. Public workshops for related industries in Egypt. These will cover both QCiME specific issues as well as quality control questions in general.

RESULTS SO FAR

- ⇒ Definition and implementation of the quality control model of the paper production process.
- ⇒ Translation of the Tutorial into Arabic.
- ⇒ First public workshop with invited industries in Egypt.

Exploitation Plans

- ⇒ UNIQUE is a result of an already completed ESPRIT project. Thus the software as it was defined in that project and developed to a prototype stage is at the beginning of the industrialisation phase, targeted to the 'western' markets, in particular Europe. With the development resulting from QCiME the market potential is directed to the Arabic world, where Quality Control in general and related software systems in particular are still in an early stage. By extending UNIQUE that already incorporates most advanced concepts for QC for discrete processes the partners of QCiME will gain a substantial advantage over their competitors. Involving an end user right from the beginning of the development, QCiME is user driven ensuring that the results will meet the user needs of other applications as well.
- ⇒ A self-contained tutorial system is being developed that will not only assist the user of the software in the daily operation but that will also be used as a marketing instrument. A special licence-free demo-version will be created that can be given to potential customers to help them assess the advantages of the complete software system through extensive and detailed examples.
- ⇒ The key points of the Exploitation Strategy are the followings :
 - licensing of the full UNIQUE software to the Egyptian partners for exploitation in the Middle East;
 - concerted marketing activities to gain new markets. The planned joint activities aim not only at extensions to the Middle East but also to other European countries, in particular UK, Greece and Germany;
 - adapting the additions that were made for continuous processes to the “European” versions of UNIQUE and exploitation by the software partners;
 - arabization of the final software;
 - packaging the tool to be extended in the wider context of consultancy in QC, which is in rapidly growing demand throughout the region.

PARTNERS

IT CONSULT GMBH

Klosterstraße 33
28865 Lilienthal
Germany

Thies Wittig
Tel.: +49-429-884 66
Fax: +49-429-884 48
E-mail: 100543.3455@Compuserve.com

KEY INDUSTRIAL SOFTWARE SYSTEMS LTD

Albans Road Street 17
Portsmouth Hants P04 9AU
United Kingdom

Ebrahim Mazharsolook
Tel.: +44-1705-83 16 70
Fax: +44-1705-83 16 70
E-mail: mazhar@ee.port.ac.uk

INTELLTECH S.A.

AG. Konstantinoy Street 40
151 24 Maroussi
Athens
Greece

Kostas Seferis
Tel.: +30-1-680 52 84 / 52 85 / 51 31
Fax: +30-1-680 51 98
E-mail: kse@rho.forthnet.gr

STANDARDATA EGYPT

Ahmed Orabi Street 13
Mohandessin Cairo
Egypt

Adel Danish
Tel.: +20-2-302 83 13/344 53 94 (346 11 22)
Fax: +20-2-346 06 52
E-mail: adanish@ritsecl.com.eg

PYRAMID PAPER MILLS S.A.E.

P.O. Box 17
6TH October City
Egypt

Christos Cavallis
Tel.: +20-11-33 10 70
Fax: +20-11-331 01 01

STRUCTURE AND CHEMISTRY OF AIR POLLUTANTS ON METAL SURFACES

Co-ordinator: University of Cambridge, Cambridge, United Kingdom (David A. King)

OBJECTIVES

- To study the structure and reactivity of small pollutant molecules (CO_2 , NO , NO_2 and SO_2) over well defined metal single crystal surfaces;
- To study in particular the least active, most abundant molecule CO_2 , attempting to define ways to effectively activate it;
- Comparing studies on clean surface to partially alkali metal covered surfaces, as a function of its coverage. Other surface sensitive, nondestructive methods such as work function change measurements and optical second harmonic generation (SHG) were planned to be employed in cases where in situ coverage changes may be crucial to extract the kinetics of intermediate formation;
- To widen the basic understanding of the surface chemistry of small molecules of ecological importance.

ACTIVITIES

Different crystals were investigated in the three laboratories. The project started with smooth basal planes (0001) of the three hexagonal closed packed metals Re, Ru, and Co and investigated more corrugated planes like the (1010) and more inert substrates later. Towards the end of the project experiments were performed in the Cambridge laboratory trying to control surface chemistry of small molecules by surface acoustic waves.

- ◇ LEED and XPD intensity distribution measurements for several adsorbed molecules or complexes, of relevance to this project
- ◇ High resolution EELS investigation of SO_2 on Ru(001) and K/Ru(001)
- ◇ Studies of the adsorption of formic acid leading to formate on Ni(110) using XPD and model XPD calculations
- ◇ Structural characterisation of methoxy and carbon monoxide on Ni(110)
- ◇ Investigation on the diffusion of potassium on Re(001) by coverage grating-optical second harmonic diffraction
- ◇ Studies of the repulsive interaction of potassium on Re(001) using temperature programmed desorption, workfunction measurements, and optical second-harmonic generation
- ◇ A detailed RAIRS, LEED, and TDS investigation to characterise the different coverage dependent phases of CO on Co(1010)
- ◇ Study of the coadsorption of D_2O with preadsorbed K on Co(1010)
- ◇ Investigation into the effect of surface acoustic waves on Cooxidation over Pt single crystals using TPD, RAIRS, LEED and PEEM

OUTCOME

- ⇒ Substantial advances have been made from the point of view of instrumentation and research results
- ⇒ Deeper theoretical understanding of the adsorption of SO_2 and CO_2 on the Ru(001) and Ni(110) surface
- ⇒ Understanding of the influence of K coadsorption on SO_2 decomposition on Ru(001)
- ⇒ A structural model for CO and methoxy layers on Ni(110)
- ⇒ Information about the diffusion rate and repulsive interaction of K on Re(001)
- ⇒ Explanation for the change in work function as a function of alkali metal coverage on transition metals
- ⇒ Characterisation of different coverage dependent phases of CO on Co(1010)
- ⇒ Understanding of the adsorption of D_2O onto multilayer K on Co(1010)

⇒ Experimental proof for the influence of surface acoustic waves on catalytic reactions at the gas solid interface.

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PARTNERS

UNIVERSITY OF CAMBRIDGE

Department of Chemistry
Lensfield Road
Cambridge CB2 1EW
United Kingdom

David A. King
Tel: +44-1223-33 63 38
Fax: +44-1223-33 65 36

FORSCHUNGSZENTRUM

IGV
P.O. Box 1913
52425 Jülich
Germany

Hans Bonzel
Tel: +49-2461-61 32 70
Fax: +49-2461-61 39 07

HEBREW UNIVERSITY OF JERUSALEM

Department of Physical Chemistry
91904 Jerusalem
Israel

Micha Asscher
Tel: +972-2-58 57 42
Fax: +972-2-61 80 33

**MICROWAVE PROPERTIES OF HIGH TC THIN FILMS AND
SUPRACONDUCTOR-INSULATOR COMPOSITES**

Co-ordinator: Ecole Normale Supérieure, Paris, France (Nicole Bontemps)

OBJECTIVES

- A study of the frequency dependent surface resistance and/or transmission of high T_c thin films in a 10-500 GHz frequency range, in order to determine fundamental parameters such as the penetration depth, the scattering rate of the quasi-particles and possibly provide a proper description of the residual losses. The analysis will be implemented by applying an external field in order to identify the vortex induced resistance and the depinning frequency;
- A study of the microwave propagation through composite materials consisting of superconducting grains embedded in an insulating matrix, in the presence or in the absence of a magnetic field, mostly at 10 GHz. Special emphasis will be put on a basic understanding of the magnetic and dielectric losses as a function of the filling factor, in order to be able to define a composite with negligible reflection and attenuation of the electromagnetic waves.

ACTIVITIES

- ◇ Design and realisation of a transmission set-up in the range 100-500 GHz, with special emphasis on impedance matching in the range 120-180 GHz;
- ◇ Design and realisation of a near field mm wave microscope at 80GHz in order to investigate the local electromagnetic response at a 30 mm scale;
- ◇ Basic studies of thin films: measurement of the absolute value of the electromagnetic penetration depth. Study of the role of the various defects on the scattering rate and eventually on the superconducting order parameter;
- ◇ Preparation of YBCO and BSCCO based composites (achievement of high filling factors). Magnetic measurements and investigation of the static magnetic field distribution in these composites;
- ◇ Design and realisation of a transmission set-up in the range of 60-90 GHz and transmission measurements through the composites in the presence of a dc magnetic field.

RESULTS

- ⇒ The linear dependence of the penetration depth as a function of temperature has been observed for the first time in a thin film using the transmission set-up at various frequencies (100-500 GHz). The decrease of the scattering rate in the superconducting state can be observed and may be an important clue to the coupling mechanism.
- ⇒ A near field mm wave microscope with the optical control of the probe-sample separation has been developed and its capability demonstrated.
- ⇒ The linear surface resistance of YBCO thin films has been measured as a function of a dc magnetic field with a parallel plate resonator technique. The magnetic field was used as a diagnostic tool to detect the presence of weak links. The non-linear surface impedance of the films was also studied versus the dc magnetic field. The vortices and weak links contributions were discriminated.
- ⇒ The thorough study of the static magnetic field distribution in a set of YBCO and BSCCO based composites has been achieved, showing how the mean field and the width of the distribution depend on the filling factor;

FOLLOW-UP

The present research will be further developed along two main lines:

- Improvement of the transmission set-up in terms of impedance matching (to achieve a better accuracy) and of frequency range;
- Development of the near-field mm wave microscope in order to achieve sensitivity in terms of surface resistance, to work at cryogenic temperature and to achieve polarisation studies.

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PARTNERS

ECOLE NORMALE SUPÉRIEURE

Physique de la Matière Condensée
Rue Lhomond 24
75005 Paris
France

Nicole Bontemps
Tel.: +33-1-44 32 35 04
Fax: +33-1-44 32 38 40

HEBREW UNIVERSITY

Racah Institute for Physics
Givat Ram
91405 Jerusalem
Israel

Dan Davidov, Michael Golosovsky
Tel.: +972-2-58 511
Fax: +972-2-61 78 05

EPITAXIAL GROWTH OF WIDE GAP SEMICONDUCTORS (Al, Ga)N FOR OPTOELECTRONICS

Co-ordinator: Centre de Recherche sur l'Hétéroépitaxie et ses Applications (CRHEA-CNRS), Valbonne, France (Pierre Gibart)

OBJECTIVES

- Epitaxial growth by metalorganic vapour phase Epitaxy of device quality (Al,Ga)N alloy semiconductors
- Fabrication of an U.V. detector based on nitrides

ACTIVITIES

- ◇ Development of metalorganic vapour phase epitaxy (MOVPE) applied to the growth of nitrides in both Laboratories, test of new nitrogen precursors.
- ◇ Fabrication of UV detectors, photoconductive GaN and photovoltaic GaN.

OUTCOME

- ⇒ Implantation of a MOVPE facility for nitrides in Tunisia
- ⇒ Evaluation of new nitrogen precursors and new activation processes in the MOVPE growth of GaN
- ⇒ Growth of high quality GaN on sapphire
- ⇒ Achievement of p and n-doping of GaN
- ⇒ Fabrication of UV detectors based on photovoltaic GaN
- ⇒ Growth of AlGaN alloy semiconductors

FOLLOW UP:

- ▶ The expertise obtained on GaN at CRHEA and the University of Monastir will be used in further projects and co-operations. Presently, new developments in the field of UV detectors for the UV-B of the sun have started with the University of Madrid in the frame of EU contract "Environment and Climate" and the University of Casablanca in the frame of CNRS-CNR co-operation programme.

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PARTNERS

CENTRE DE RECHERCHE SUR L'HÉTÉROÉPITAXIE ET SES APPLICATIONS

(CRHEA-CNRS)

Sophia Antipolis

06560 Valbonne

France

Pierre Gibart

Tel.: +33-4-93 95 42 27

Fax: +33-4-93 95 83 61

E-mail: pg@crhea1.unice.fr

UNIVERSITÉ DE MONASTIR

Département de Physique

Route de Kérouan

5000 Monastir

Tunisia

B. el Jani

Tel.: +216-3-46 17 66

Fax: +216-3-4873

**DEVELOPMENT OF LARGE AREA GASEOUS IMAGING PHOTOMULTIPLIERS
FOR APPLICATIONS IN NUCLEAR MEDICINE**

Co-ordinator: Ecole Polytechnique, Palaiseau, France (Philippe Mine)

OBJECTIVES

- The objective of the present research is to develop a large area, fast, high resolution solid photocathode gaseous photomultiplier for photon imaging over a broad spectral range from visible to VUV;
- Main applications foreseen are :
 - UV and visible photon imaging for fast readout of solid scintillators in medical applications such as PET (positron emission tomography) and gamma cameras;
 - applications in industrial radiography for non-destructive evaluation;
 - applications in high energy particle physics, atomic physics and astrophysics.

ACTIVITIES

- ◇ Study of the characteristics of photocathodes materials such as the determination of the quantum efficiency and its dependence on wavelength and temperature;
- ◇ Photocathode compatibility with gaseous amplification media under various operating conditions;
- ◇ Matching of a chosen scintillator crystal with a suitable photocathode;
- ◇ Design and construction of a gaseous imaging photomultiplier;
- ◇ Various systematic tests of the photomultiplier and the scintillator-photomultiplier assembly;
- ◇ Possible incorporation in a PET scintillator system;
- ◇ Design and construction of a sealed photomultiplier and tests.

The first material studied is the well-known inorganic photo-emitter Cs1. Other materials currently investigated are the organometallic compounds having a low ionisation threshold.

EXPECTED OUTCOME

Following performance from the device:

- ⇒ High quantum efficiency in the spectral range of interest;
- ⇒ Stability with time in a relatively unpurified gaseous environment;
- ⇒ Sum-mm two-dimensional localisation accuracy over large surfaces, without parallax error;
- ⇒ Sub-nanosecond timing;
- ⇒ Efficient detection of photons due to the high single electron detection efficiency of the multistage electron multiplier;
- ⇒ High rate capability due to fast ion removal at low-pressures, the low charge density in the avalanche and the possibility of subdividing the readout electrodes into arrays of individual pixels;
- ⇒ Low ageing of the photocathode due to the multistage operation and the possibility to incorporate an electric gate, to stop back-drifting ions;
- ⇒ Possibility to use the device in a triggered mode with built-in-electronic delay (drift in gas), further increasing its high rate capability and immunity to background.

Besides the immediate application to PET and the large spectrum of possible applications of these devices, in basic and applied research, the study may provide new valuable physical data about the properties of new photosensitive and scintillation materials.

RESULTS

- ⇒ We performed a complete study of CsI as a photo-emitter. We realised that the discrepancies in the measured quantum efficiencies around the world were due to incorrectly referenced standards supplied by some manufacturers, or to the effect of the substrate. We have now agreed, in the framework of the RD26 collaboration, to a common data.
- ⇒ We have studied the effect of aging by radiation, by light and by current. We have determined that the gas used for amplification has no effect on the quantum efficiency, when the electric field is large enough.
- ⇒ We have measured the effect of the incident angle, which is of high interest for application as Cerenkov detectors. The quantum efficiency of amorphous silicon was measured, with different doping percentages. We found that the highest value is obtained for p- doped photocathodes. About twelve organics or organometallic compounds were studied.
- ⇒ We conclude that only the derivatives of ferrocenes exhibit potentially useful quantum efficiencies. Similar organometallic compounds, containing different metallic elements, are much worse than those containing iron. Our best choice is decamethylferrocene, that has some unique characteristic: it is solid, its quantum efficiency is high at 220nm and it is not air-sensitive.

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PARTNERS

ECOLE POLYTECHNIQUE

Laboratoire de Physique Nucléaire des Hautes
Energies
91128 Palaiseau
France

Philippe Mine
Tel.: +33-1-69 33 31 06
Fax: +33-1-69 33 30 02
E-mail: mine@polhp5.in2p3.fr

THE WEIZMANN INSTITUTE OF SCIENCE

Faculty of Physics
Department of Nuclear Physics
P.O. Box 26
76100 Rehovot
Israel

Amos Breskin
Tel.: +972-8-343 077
Fax: +972-8-466 966

VRIJE UNIVERSITEIT BRUSSEL

Faculty of Sciences
Inter-University Institute for High Energy Physics,
Radiation
Instrumentation Group
Pleinlaan 2
1050 Brussel
Belgium

Stefaan Tavernier
Tel.: +32-2-641 21 40
Fax: +32-2-641 22 82

**STRUCTURE AND PROPERTIES OF MULTICOMPONENT L1₀ INTERMETALLICS
AT AMBIENT AND HIGH TEMPERATURES**

Co-ordinator: Technion-Israel Institute of Technology, Haifa, Israel (Lev Arie Levin)

OBJECTIVES

- Investigation of the structure, the physical and mechanical properties of a ternary γ -titanium aluminide (with iron addition), after various multi-step heat treatments;
- Characterisation of phase composition and morphology after each treatment;
- Detailed investigation of the pseudo-binary and ternary phases formed.

ACTIVITIES

- ◇ Comprehensive characterisation of the ternary phase τ_2 (D8_a) : study of range of existence, changes in crystal structure and morphology due to variations in composition and thermomechanical history. The analysis of SE images and X-ray maps leads to the conclusion that τ_2 is enriched in iron;
- ◇ Characterisation of a newly discovered superlattice named "X-phase". The plates containing the X-phase are interlaced with γ , and have a characteristic non-uniform appearance. SAD pattern obtained from plates was indexed in terms of an orthorhombic unit cell. The result was confirmed by the transmission electron microscopy and X-ray diffraction analysis.

EXPECTED OUTCOME

- ⇒ Finding the specific features of an iron alloyed γ -TiAl. Finding the influence of the ternary phases on alloy's properties;
- ⇒ Establishing a methodology for the optimisation of the alloy's properties with regard to basic physico-chemical parameters of the components.

PARTNERS

TECHNION-ISRAEL INSTITUTE OF TECHNOLOGY Lev Arie Levin
Department of Materials Engineering Tel.: +972-4-29 45 83 / 29 45 95
Technion City Fax: +972-4-32 19 78
32000 Haifa
Israel

BEN GURION UNIVERSITY OF THE NEGEV Michael Talianker & Adin Stern
Department of Materials Engineering Tel.: +972-7-46 14 75
84015 Beer-Sheva Fax: +972-7-27 59 10
Israel

UNIVERSITA DEGLI STUDI DI ANCONA Enrico Evangelista
Dipartimento di Meccanica Tel.: +39-71-220 47 30
Via Breccie Bianche Fax: +39-71-220 48 01
60131 Ancona
Italy

MAX PLANK INSTITUTE FOR IRON RESEARCH Gerhard Sauthoff
Applied Physical Metallurgy Tel.: +49-211-67 92-1
Max-Plank-Straße 1 Fax: +49-211 67 92-313
Postfach 140260
40237 Düsseldorf
Germany

**ELECTROCHEMICAL CONTROL OF SILICON SURFACES FOR ELECTRONIC
AND SOLAR APPLICATIONS**

Co-ordinator: Centre National de la Recherche Scientifique, Meudon, France
(Mohamed Etman)

OBJECTIVES

The project gathers an international network of seven institutes to investigate the possibility of electrochemical control of silicon surfaces for electronic and solar applications. The main goal is the elucidation of the mechanisms governing the anodic oxidation and dissolution of silicon, and the influence of these processes on the surface characteristics. The work is organised around the three following objectives:

- Characterisation of the oxide films present at the silicon surface during electropolishing or after anodic oxidation;
- Identification of intermediate chemical products and determination of reaction pathways in the anodic dissolution of silicon;
- Assessment of the role of crystallographic orientation in the electrochemical properties of silicon.

ACTIVITIES

Study of the oxide film during silicon electropolishing. This includes the following activities

- ◇ Determination of the oxide nature as a function of formation potential using in-situ infrared spectroscopy (Palaiseau);
- ◇ Development of electrochemical techniques for measuring the silicon oxide thickness in fluoride media during the electropolishing regimes, and calibration of these measurements using in-situ infrared spectroscopy and ellipsometric techniques (Palaiseau, Bath);
- ◇ Characterisation of the charged species incorporated into the anodic oxides, and modelling of the published experimental results of "transient flat-band potential" (Palaiseau, Cairo).

Reaction mechanisms in the anodic dissolution of silicon

- ◇ Effect of electrolyte composition upon oxide formation: role of mass-transport and charge-transfer kinetics, effect of cations upon anodic dissolution (Meudon);
- ◇ Identification of chemical intermediates in the silicon dissolution reaction, using in-situ infrared spectroscopy (Palaiseau, Bath);
- ◇ Study of silicon stabilisation by redox reagents in a fluoride electrolyte. Organic dye materials may be adsorbed or grafted on the silicon surface (Meudon, Bath, Cairo);
- ◇ Determination of the conditions for oxide control in a non-aqueous electrolyte (Constantine, Meudon).

Crystallographic-orientation-dependent electrochemical effects

- ◇ Electrochemical determination of the orientation of the electrode surface (Meudon, Constantine);
- ◇ Study of the facetting trends of the silicon surface in the electropolishing regime (Meudon, Constantine).

RESULTS

Study of the oxide film during silicon electropolishing

- ⇒ An active collaboration between Palaiseau and Bath has led to a definition of identical experimental conditions in the two groups (electrolyte composition, design of a circulation cell for an appropriate control of mass-transport conditions). The infrared experiments have been performed in Palaiseau, and the ellipsometric measurements have been performed by Bath in co-operation with Southampton.

- ⇒ Systematic measurements of the infrared spectra have been carried out in different electrolytes as a function of potential. The polarisation of the infrared beam has been changed, and the spectra have been analysed quantitatively. In the n-SiO spectral region, the s-spectra consist of a main line at around 1065 cm^{-1} , corresponding to the TO component of the asymmetric stretching mode of a SiOSi group (vibration of the oxygen atom parallel to the Si-Si axis), plus two lines ascribed to defects and disorder. The p-spectra exhibit two extra lines, representing the LO counterparts of the main line and disorder mode. A quantitative analysis of these spectra has allowed to derive information on oxide thickness (from the magnitude of the signals), on oxide perfection (from the relative amount of signal associated with defects), and on oxide density (the density of Si-O vibrators is directly related to the LO-TO splitting). Oxide thickness is found to increase monotonically with potential with a more or less constant slope of 9 \AA/V . This slope is somewhat larger in the region of the second current peak and near the end of the second current plateau in the typical voltammogram. The oxide thickness is found to depend little upon the electrolyte. The perfection and density of the oxides appear to be optimum near the middle of the second current plateau. This is consistent with the idea that the oxide is strongly hydrated in the first-plateau region, and possibly also near the end of the second-current plateau, where hydration is probably associated with an increase in porosity.
- ⇒ In-situ ellipsometric measurements have been performed for the same electrolytes as used for the infrared measurements. The infrared and ellipsometric oxide thickness are generally in agreement within 50%. However, some deviations are present, especially at potentials more positive than 5 V vs SCE, where the thickness as derived from ellipsometry appears systematically larger. In this potential range, however, SEM indicates that substantial surface roughening occurs. One may infer those localised dielectric breakdown causes pitting and roughening of the surface, hence a rise in the dissolution rate, in the observed anodic current, and in the amount of hydrated oxide, in agreement with the infrared results. Ellipsometric measurements show that the roughening is far more severe for (100) samples than for (111) samples.
- ⇒ The thickness derived from electrochemical measurements have been compared with those derived from infrared spectroscopy and ellipsometry. Coulometric measurements appear to give the correct variation of oxide thickness as a function of potential, except that the deduced values appear systematically larger by a factor of ~ 1.5 than those derived from infrared spectroscopy and ellipsometry. On the other hand, high-frequency capacitance measurements appear to yield an underestimated oxide thickness. The most striking fact is that the thickness derived from such measurements remains almost constant over a wide range of potential. The evident failure of the three methods to give identical values of the oxide thickness is not surprising because each method actually measures different properties of the oxide. The electrode capacitance corresponds, in principle at least, to the presence of a continuous insulating dielectric film. The results suggest that such a film is very thin and that its thickness varies only weakly with potential. Infrared spectroscopy measures the integrated intensity of the Si-O absorbency corresponding to a layer of unhydrated oxide (the dry oxide). However, it is not necessary for this layer to be continuous or insulating. A defective or porous layer of oxide is also detected. Finally, ellipsometry measures the total oxide thickness and is relatively insensitive to factors such as porosity or partial hydration.
- ⇒ The defective and hydrated nature of the oxide accounts for the very high dissolution rates calculated from the current densities by assuming that the dissolution and growth rates are equal. Typically, the dissolution rate for the anodic oxides is up to two orders of magnitude higher than for the thermal oxide. This suggests that the attack of the anodic oxide by fluoride species is effectively enhanced by a large internal area, with the reaction taking place within the hydrated surface layer rather than exclusively at the surface as in the case of thermal oxide.

When a silicon electrode has been polarised for a while at anodic potential, electric charges are stored inside the interface oxide film. When the polarisation is released, some of these charges are swept back to the electrode, resulting in a transient current and a change in the interface dipole, which is experimentally accessed through flat-band potential measurements. Some other charges will disappear only upon dissolution of the oxide film. This charge decays have been modelled in Cairo. The transient currents and flat-band potentials can now be calculated and compared with experimental data.

Preliminary results support the idea of a layer of positive charges close to the silicon surface, and a distribution of negative charges through the oxide. Systematic measurements are presently underway.

Reaction mechanisms in the anodic dissolution of silicon

- ⇒ A systematic study of mass transport and charge-transfer kinetics in different electrolytes has been performed at Meudon, using voltammetry in a rotating-disk-electrode arrangement. Silicon dissolution appears to be limited by interface kinetics in electrolytes of low fluoride concentration, and by mass-transport in electrolytes of high fluoride concentration. The critical concentration c_F^* between the two regimes is of the order of 0.1 M. The values of the mass-transport-limited current are consistent with a limitation by the supply of fluoride species to the electrode.
- ⇒ A striking effect of the cations present in the electrolyte has been noticed. Whilst the presence of different anions (except for F⁻) appears of minor importance, addition of alkali-metal ions to the electrolyte has been found to increase the anodic dissolution current, with an increasing effect upon adding heavier ions: the effect of Li⁺ is negligible, but an increasing current is observed in the sequence Li⁺ < Na⁺ < K⁺ < Rb⁺ ≈ Cs⁺. In some instances, the picture may be complicated by the low solubility of the fluoride (Li⁺) or of the fluosilicide (Rb⁺, Cs⁺). When these side effects are avoided, the major effect of the cations may consist in either a change in the nature of the oxide or in its dissolution rate. Specific experiments have demonstrated that the effect is essentially a catalytic effect acting over the dissolution rate. Adsorbing cations may act as catalysts in either the hydrolysis of SiOSi bridges, or in the attack of SiOH groups by fluoride ions. The various dependencies observed may be qualitatively understood in terms of such a two-step process.

The effect of addition of complexes to the electrolyte has been investigated in Cairo. Ruthenium-bipyridine complexes have been found to lead to remarkable enhancement of the photocurrent at an n-Si/fluoride-electrolyte interface, providing significant stabilisation of the photoelectrode. This shows that a strong interaction between the reducing species and the photoelectrode is achieved in this system. The current oscillations that are normally present in the anodic potential range disappear in the presence of the ruthenium-bipyridine complex. Subsequent implications for the mechanism responsible for the current oscillations are presently being worked out.

Crystallographic-orientation-dependent electrochemical effects

- ⇒ A systematic study of the n-Si/fluoride interface has been undertaken at Meudon in collaboration with Constantine. The advantage of n-Si over p-Si is that the flat-band potential is determined with a better accuracy, and the effect of illumination may be studied. The effect of alkali-metal ions in the electrolyte has been investigated and (100), (111) and (110) crystallographic orientations have been studied. Preliminary results confirm that the flat-band potential and interface current are affected by both factors. Especially, these results demonstrate the possibility of determining electrode orientation from electrochemical measurements.

FOLLOW UP

- ⇒ Further investigations of the electropolishing regime are in progress, using AFM and SEM for a characterisation of surface morphology. Oxide characterisation is pursued in the regime where the interface current exhibits a damped oscillating behaviour. Infrared spectra have been recorded as a function of time, during the oscillation. This gives a clear-cut indication for an oscillation of the characteristics of the oxide film (thickness, density, defectivity). The dissolution rate of the oxide film at different stages during the oscillation has also been investigated. Similar experiments are in progress using a different control of the interface (from potentiostatic to galvanostatic). The same approach is also underway using in-situ ellipsometry. In parallel, the high-frequency capacitance will be measured. We also plan experiments using microwave reflectivity to follow the changes in surface hole density (preliminary measurements have already been completed). Finally, the modelisation of the charge stored in the oxide will be tested against the measured current-time characteristics when the experiments are completed;
- ⇒ Regarding the reaction mechanisms, now the mass-transport effects are well understood, and focus will be put on the kinetic aspects. The in-situ infrared experiments, which up to now have been unable to provide information on the chemical intermediates in the silicon dissolution reaction, will be pursued using a potential-modulation technique. The effect of the presence of

some cations on p-Si/F⁻ interfaces and of some dyes on n-Si/F⁻ interfaces under illumination in aqueous electrolytes is still under investigation. Impedance of the illuminated n-Si/F⁻ interface in non-aqueous electrolytes is presently being explored;

- ⇒ Regarding the effects of crystallographic orientation, n-Si/F⁻ interfaces of different orientations have been studied in darkness and under illumination in aqueous and in non-aqueous electrolytes. Impedance measurements have been performed and modelisation is in progress.

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PARTNERS

CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE

Laboratoire d'Electrochimie des Interfaces
Place Aristide Briand 1
92195 Meudon/Bellevue
France

Mohamed Etman
Tel.: +33-1-45 07 55 23
Fax: +33-1-45 07 58 58

ECOLE POLYTECHNIQUE PALAISEAU

Laboratoire de Physique de la Matière Condensée
Route Saclay
91128 Palaiseau Cedex
France

J.N. Chazalviel
Tel.: +33-1-69 33 46 63
Fax: +33-1-69 33 30 04

CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE

Laboratoire de Physique des Solides
Place Aristide Briand 1
92195 Meudon/Bellevue
France

Ouri Gorochov
Tel.: +33-1-45 07 53 79
Fax: +33-1-45 07 58 41

UNIVERSITY OF BATH

School of Chemistry
Claverton Down
Bath Ba2 7AY
United Kingdom

L. Peter
Tel.: +44-1225-82 61 30
Fax: +44-1225-82 62 31

UNIVERSITY OF CONSTANTINE

Institut de Physique
Département d'Energétique
Constantine
Algeria

Abdel Hamid Chari
Tel.: +213-469 20 62
Fax: +213-469 60 81

UNIVERSITY OF AIN-SHAMS

Faculty of Sciences
Photoenergy Unit
Abbasia - Cairo
Egypt

Abdel Mottaleb
Tel/Fax: +20-2-244 76 83

UNIVERSITY OF AIN-SHAMS

Faculty of Engineering, Electronics and
Communications Engineering
Abbasia - Cairo
Egypt

H.F. Ragaie
Tel.: +20-2-282 66 36
Fax: +20-2-285 06 17

ENVIRONMENTAL CHALLENGES ADDRESSED WITH NEW ELECTRODE MATERIALS: DIAMOND AND DIAMOND-LIKE CARBON FILMS

Co-ordinator: Centre National de la Recherche Scientifique, Meudon, France
(Claude Levy-Clement)

OBJECTIVES

- With their unique chemical stability, high electron mobility and negative electron activity, boron doped diamond thin films are likely to have favorable properties for a number of electrochemical applications. Such electrodes have demonstrated very efficient reduction of nitrate (nitrite) into ammonia and they can be polarized to large negative potentials without suffering damage. Furthermore, these electrodes are shown to be dimensionally stable even in the most corrosive conditions, such as in fluoride solutions. Added to that, both its hardness and its resistance against radiation damage make diamond film a very appropriate material for work under especially harsh environmental conditions, such as reduction of nuclear wastes (nitrate in basic solutions), electrowinning of metals from cyanide solutions for example, and high temperature molten salt electrolysis. Electrodeposition of various metals (Au, Pt, Pb and Hg) on diamond electrodes has been demonstrated.
- Depending on the deposition technique and conditions used for the preparation carbon-based films are either graphite-like consisting entirely of sp^2 -bonded carbon (a-C or graphite) or contain both sp^2 - and sp^3 -hybridized carbon (« diamond-like carbon »: DLC) or are very rich in Sp^3 phase (diamond). Although inferior to diamond in many respects DLC films may be of greater importance in some specific electronic such as flat panel display (FDP) and electrochemical applications at very negative potentials.
- The objectives of this collaborative project were the growth and development of new materials such as boron-doped polycrystalline diamond thin films and DLC films capable of forming electrodes for electrochemical reduction of compounds at very negative potentials or very cathodic reactions such as ozone fixation, electrochemical reduction of nitrate-nitrite ions and affluent gasses including NO_x (and N_2), SO_2 , CO_2 , and the electrodeposition of very negative metals.

ACTIVITIES

- ◇ Throughout the project the synthesis of the diamond and DLC thin films has been developed and continuously improved. The CVD (chemical vapor deposition) diamond films containing different amounts of boron (B) were grown in a hot filament and a microwave reactors. The DLC thin films both undoped and B-doped were grown in a UHV-PLD (ultra high vacuum-pulse laser deposition) chamber. The best samples were exchanged among the partners. Their chemical properties were investigated in order to correlate them with their electrochemical and electrocatalytic properties in particular to reduce the nitrate and nitrite ions. Deposition of copper and II-VI alloys was studied to develop the technology of metallic or semiconductor thin film on diamond thin films as this technology may have impact on various applications such as detector, solar cells etc.

RESULTS

- ⇒ Throughout the project the boron doping procedure has been developed and continuously improved, hence good highly conductive diamond coated samples could be produced for electrochemical experiments It has now reach the stage where good control on B doping has been achieved on diamond thin films. The diamond thin films were deposited on various substrates such like silicon, molybdenum or tungsten.
- ⇒ In order to obtain conductive DLC thin films, the BAM group had to realise the boron doping of hydrogenfree amorphous carbon (a-C) films. In analogy to successful doping experiments with crystalline diamond films produced by CVD, doping of the amorphous counterpart during the

deposition process had to be demonstrated. The BAM group established a new UHV-PLD chamber. Mixing of carbon and boron was done by scanning the two splitted beams of the XeCl excimer laser along the edges of two coplanar target sections (carbon and boron carbide). It can be concluded from the density and elasticity measurements that 308 nm excimer radiation with fluences of the order of 20 J cm⁻² and intensities of the order of 1 GW cm⁻² can only produce amorphous carbon films with sp³ (diamond) contents of less than 50%. The boron was homogeneously distributed throughout the film with an atomic concentration of 20%.

- ⇒ In this work we correlated the ability to reduce nitrates and deposit metal on different diamond doped thin films with the physical properties of these films that depend on the growth process. The diamond thin films were grown by (HF)CVD (Hot Filament Chemical Vapour Deposition) and μ WCVD (Microwave Plasma CVD) on silicon and tungsten substrates and they were boron doped in situ. Two kinds of films were made by laser ablation (one undoped and the other containing Boron).
- ⇒ To characterise the structure of the films we carried out Near Edge X-ray Absorption Spectroscopy (NEXAFS). The nature of the surface was analysed by XPS and its morphology by SEM. (HF)CVD and μ WCVD methods gave well-crystallised films, while those made by laser ablation were amorphous.
- ⇒ The electrochemical behaviour of boron doped diamond films was investigated, in a number of neutral and alkaline solutions with and without nitrate ions. Two kinds of diamond electrodes were studied : self supported films (100 μ m) and diamond films supported on a silicon substrate. It was found that water oxidation and reduction appear at much larger polarisations for diamond electrodes, as compared to platinum and platinized platinum electrodes. In particular, the higher (cathodic) overpotential for hydrogen reduction permits efficient nitrate to ammonia reduction. The underlying Si substrate is shown to take part in the electrochemistry of the diamond electrodes. In the case of the Si supported electrode, the reaction with the Si substrate was imminent. For the free standing diamond electrode, various impurities in the grain boundaries and at the back of the electrode, including back metallic contact, intervened with the electrochemistry of the diamond electrode, but to a much lesser extent than with the supported sample. Meticulous cleaning and a careful working practice permitted this interference to be excluded altogether in the self supported diamond film. Because this kind of film is very long and expensive to produce CVD diamond films were grown on molybdenum and tungsten substrates. Their reflectance properties were studied using FTIR measurements, whereas their electrochemical properties are now under investigation.
- ⇒ The reduction of nitrates in alkaline (KOH 1M) and neutral solutions (KCl 0.1 M) were performed at - 2 V/SCE. At this potential there was a clear competition between the reduction of water and nitrates. Ammonia was detected as one product of the reaction. Under potential deposition (UPD) of copper in 0.1M sulphuric acid was observed at 0.1 V before the reversible Nernst potential. But the extent of UPD was surprisingly weak as it was calculated that only a few percentages of the electrode surface could be covered by one monolayer. However the UPD phenomenon is more important on well-crystallised films compared to amorphous ones and it is enhanced by an electrochemical activation of the electrodes at negative potentials.
- ⇒ Currently, the reduction of bicarbonate solutions, which are a model system for CO₂ reduction, using diamond electrodes is investigated. Although, only one (formaldehyde) organic species was being analysed, the results of the work were quite astonishing. Exceedingly high Faradaic efficiencies of 2-3 were found for this process, i.e. for each electron delivered by the diamond electrode, two electrons were produced spontaneously by the redox reaction and were injected to the diamond electrodes.

FOLLOW UP

- ▶ We will try to carry-out a few studies using surface modified diamond electrodes. Thus, shallow (superficial) ion implantation of diamond samples by transition metal atoms, such as Ni, Fe, Cu etc., will be attempted, and the influence of this "surface" modification, on the rate of reduction of effluent gases, will be investigated. Even more superficial modification, like binding metal atoms to the surface, chemically, will be attempted;
- ▶ Doping of the CVD diamond with Ni will also be tried;
- ▶ Better boron doped DLC films will be grown by optimising the parameters of deposition and using a completely new contacting procedure. Also titanium doping will be tested. Because of the extreme thinness of the films spectroscopic ellipsometry measurements will be carried out to study the electronic properties of the thin films;
- ▶ A comparative study of the electrochemical properties of various p-type boron doped CVD diamond films deposited on silicon and non silicon substrates such like molybdenum and tungsten and insulating substrates such as quartz or on undoped CVD diamond films will be undertaken. The purpose is to evaluate the effect of the deposition parameters on the electrochemical properties of the various electrodes. This study will include the DLC thin films;
- ▶ The investigation of the reduction of bicarbonate solutions (which are a model system for CO₂ reduction) using diamond electrodes will continue during the next period of research, in order to produce some basic understanding of the reaction mechanism of formaldehyde species. Formation of other products, such as formate ion, or even methanol, will also be studied. Furthermore, this work is being extended to other products, using mixtures of precursors (nitrate and bicarbonate) with the aim to study the formation of urea.

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PARTNERS

CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE

Laboratoire de Physique des Solides de Bellevue
Place Aristide Briand 1
92195 Meudon
France

Claude Lévy-Clément
Tel.: +33-1-45 07 52 79
Fax: +33-1-45 07 58 41
E-mail: levy@cnsr-bellevue.fr

FEDERAL INSTITUTE FOR MATERIALS RESEARCH AND TESTING

(BAM) Laboratory for Laser and Chemical Thin
Film Technology (5.32)
Unter den Eichen 87
12205 Berlin
Germany

Wolfgang Kautek
Tel.: +49-30-8104-1822
Fax: +49-30-8104-1822 (or -1827)
E-mail: Wolfgang.Kautek@bam-berlin.de

WEIZMANN INSTITUTE OF SCIENCES

Department of Materials and Interfaces
76100 Rehovot
Israel

Reshef Tenne
Tel.: +972-08-934 23 94
Fax: +972-08-934 41 37
E-mail: cpreshef@weizmann.weizman.ac.il

TECHNION - INSTITUTE OF TECHNOLOGY

Solid State Institute and Physics Department
32000 Haifa
Israel

Rafi Kalish
Tel.: +972-4-29 39 06 (630)
Fax: +972-4-23 51 07
E-mail: Kalish@ssrc.technion.ac.il

**THE CONFLUENCE OF CONFOCAL NEAR-FIELD MICROSCOPY: ZOOMING
WITH LIGHT TO 50 NM RESOLUTION**

Co-ordinator: University of Amsterdam, Amsterdam, The Netherlands (G.J. Brakenhoff)

OBJECTIVES

- A concept was developed of combining high resolution 3 D confocal imaging techniques with near-field microscopy in order to build a light microscope that will be able to magnify from a few hundred times to hundreds of thousands of times.

ACTIVITIES AND RESULTS

- ⇒ With confocal scanning optical microscopy and near-field scanning optical microscopy being both leading edge of light microscopy techniques, the advantages are brought together in a combined confocal/near-field scanning microscope. A unique instrument then results, able to zoom from the resolution normally associated with a conventional light microscope to the limits of resolution of a confocal scanning microscope, to the resolutions normally associated with the electron microscope.
- ⇒ For this combined imaging, a special optical layout was developed with the specific advantage that for the image collection in the near-field mode as well as in the confocal mode one and the same cooled CCD detector can be employed for data collection. This has been made possible by choosing for the confocal imaging in the combination concept, the so-called bilateral scanning mode as recently developed by Brakenhoff.
- ⇒ The ability to fully integrate far-field confocal optical techniques with near-field methodologies leads to a synergistic interplay providing beneficial improvements in far-field resolution while expanding the view of the near-field into the depth of the sample;

PARTNERS

UNIVERSITY OF AMSTERDAM
Faculty of Biology
Section Molecular Cytology
Kruislaan 316
1098 SM Amsterdam
The Netherlands

G.J. Brakenhoff
Tel.: +31-20-525 51 89 / 7
Fax: +31-20-525 62 71

**THE HEBREW UNIVERSITY OF JERUSALEM-
REHOVOT**
Division of Applied Physics
76100 Rehovot
Israel

A. Lewis
Tel.: +972-2-679 82 43
Fax: +972-2-679 80 74

THE DEVELOPMENT OF ENVIRONMENTAL EMISSION CONTROL CATALYSTS

Co-ordinator: Brunel University, Middlesex, United Kingdom (Carole C. Perry)

OBJECTIVES

- To study in detail the formation, constitution and performance of a novel family of cheaper, non-noble metal emission control catalysts based on promoted ceria;
- To elucidate the fundamental science of their operation as well as deleterious processes such as aging and poisoning.

ACTIVITIES

- ◇ Catalyst preparation will be studied in order to understand the relationship between preparation methodology and catalyst characteristic such as activity and longevity;
- ◇ Catalyst characterisation will be addressed by rather fundamental studies of the solid-state chemistry of the prepared catalysts;
- ◇ Study of the behaviour of the prepared catalysts under catalytic running conditions at laboratory scale;
- ◇ Surface mechanistic studies applied to the best performing catalysts in order to link their constitutional nature and their redox behaviour to their reaction chemistry;
- ◇ Dispersion on support media;
- ◇ Catalyst longevity and deactivation will be evaluated by analysing used catalyst samples from the project.

EXPECTED OUTCOME

- ⇒ A novel family of cheaper, non-noble metal emission control catalysts based on promoted ceria will be developed and tested;
- ⇒ The understanding of their operation as well as deleterious processes such as aging and poisoning will be increased allowing for further progress in catalyst preparation.

PARTNERS

BRUNEL UNIVERSITY

Uxbridge
Middlesex UB8 3PH
United Kingdom

Carole C. Perry
Tel.: +44-1895-27 40 00
Fax: +44-1895-25 68 44

THE WEIZMANN INSTITUTE OF SCIENCE

Office of Research Contract and Projects
76100 Rehovot
Israel

Nurit Guter & D. Goldfarb
Tel.: +972-8-34 21 11
Fax: +972-8-46 69 66

UNIVERSITY OF CYPRUS

Department of Natural Sciences
P.O. Box 537
Nicosia
Cyprus

C.R. Theocharis
Tel.: +357-2-42 32 50
Fax: +357-2-36 61 98

UNIVERSITY OF NOTTINGHAM

University Park
Nottingham NG7 2RD
United Kingdom

P.G. Harrison
Tel.: +44-1602-51 51 51
Fax: +44-1602-51 35 55

IRRADIATION-INDUCED ENHANCEMENT OF CRITICAL CURRENTS IN HIGH-T_c SUPERCONDUCTORS

Co-ordinator: Centre National de la Recherche Scientifique, Palaiseau, France (Marcin Konczykowski)

OBJECTIVES

- Identification of the elementary pinning interactions in high T_c single crystals and films with controlled irradiation-induced defects;
- Determination of the mechanisms of flux motion in the presence of point defects and certain types of extended defects;
- Determination of the conditions under which flux motion can be reduced and the current-carrying capability enhanced at high temperatures;
- Determination of the stabilising effects of (heavy-ion induced) columnar defects on vortex lines, in relation with the intrinsic material anisotropy;
- Identification of the destabilising effects of disorder on vortex lattice structure, and the role of vortex lattice dislocations in determining the bulk pinning current density;
- Determination of the optimum repartition of vortices over columnar defect sites in relation to the matching field, and the role of vortex interstitials;
- To probe the vortex response and the robustness of different vortex phases to different kinds of disorder.

ACTIVITIES

- ◇ Growth of Bi₂Sr₂CaCu₂O₈ and La_{2-x}Sr_xCuO₄ single crystals using the travelling-solvent floating zone technique;
- ◇ Irradiation with swift heavy ions at GANIL;
- ◇ Low-temperature electron irradiation using the van der Graaf accelerator;
- ◇ Characterisation of irradiation damage using SEM techniques;
- ◇ Measurements of magnetisation (current density) as function of temperature, field (up to 16 T), and field angle, using microscopic Hall probes, Hall arrays, and vibrating sample magnetometer;
- ◇ Measurements of magnetic torque in order to characterise material anisotropy;
- ◇ Ac transitivity ("local susceptibility") and magnetic relaxation measurements using microscopic Hall probes. In superconductors, these are equivalent to contact less transport measurements at extremely low voltage.

RESULTS

- ⇒ A remarkable enhancement of the current-carrying capacity of high T_c materials can be achieved by the introduction of linear columnar defects through heavy-ion irradiation.
- ⇒ Strong linear defects partially undo the detrimental effects of large material anisotropy. Columnar defect induces the alignment of 2D vortex segments, whereby the vortex line tension, which in the unirradiated material is practically zero at high temperatures and fields, is re-established. The effect is present up to fields close to the matching field B_f, at which the number of columnar defects is nominally equal to the number of vortex lines.
- ⇒ The temperature region in which vortices are effectively pinned in Bi₂Sr₂CaCu₂O₈ increases with progressive irradiation dose, until saturation occurs at a B_f of several kG. The latter effect has also been found in less anisotropy YBa₂Cu₃O₇, where pinning enhancement saturates at B_f 4 T.
- ⇒ The introduction of strong disorder lowers the thermodynamic magnetisation of high T_c superconductors in an amount proportional to the pinning energy, which at zero field equals 1000 K per 2D vortex segment.
- ⇒ The creation of extra point defects by low temperature electron irradiation does not increase pinning under all circumstances. Rather, it destabilises the low temperature, low field crystalline vortex state and promotes the formation of very mobile vortex dislocations.

⇒ Vortex lattice dislocations were shown to be responsible for the decrease of the current-carrying capacity of $\text{YBa}_2\text{Cu}_3\text{O}_7$ single crystals at high field.

PARTNERS

CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE

Ecole Polytechnique
Laboratoire des Solides Irradiés, URA 1380
Route de Saclay
91128 Palaiseau
France

Marcin Konczykowski & Kees van der Beek

Tel.: +33-1-69 33 45 03

Fax: +33-1-69 33 30 22

E-mail: beek@hplsesi.polytechnique.fr

LEIDEN UNIVERSITY

Faculty of Astronomy and Physics
Kamerlingh Onnes Laboratorium
Nieuwsteeg 18
2311 SB Leiden
The Netherlands

Pieter Hendrik Kes

Tel.: +31-71-527 54 72

Fax: +31-71-527 54 04

BAR-ILAN UNIVERSITY

Department of Physics
Ramat Gan
Israel

Yosef Yeshurun

Tel.: +972-3-531 84 34

Fax: +972-3-534 20 19

**SPATIAL LIGHT MODULATORS FOR ANALOG OPTICAL COMPUTING, IN
PARTICULAR CONOSCOPIC HOLOGRAPHY**

Co-ordinator: Hebrew University of Jerusalem, Jerusalem, Israel (Aharon J. Agranat)

OBJECTIVES

- To develop a generic family of spatial light modulators (SLM), based on the concept of electroholography (EH). The SLMs will be constructed of paraelectric photorefractive crystals, in particular potassium lithium tantalate niobate (KLTN). The SLMs are tailored to be used in holographic memory systems, and conoscopic holography metric systems.

ACTIVITIES

- ◇ Growth of doped KLTN crystal that are suitable for the EH SLMs
A crystal growth system was designed and built. The system that implements the "top seeded solution growth" method has been completed and was used so far to grow approximately 32 crystals. These first samples were used primarily to investigate the photorefractive (PR) effect in KLTN crystals, in particular the voltage controlled PR effect and the fixing processes, both of paramount importance for the SLMs. Finally, a new KLTN sample was grown with high photorefractive sensitivity at 690 nm.
- ◇ Construction of EH SLM prototypes
The group in Jerusalem tested a new architecture for an SLM based on paraelectric photorefractive crystals - the electroholographic SLM that is based on the voltage controlled PR effect in paraelectric PR crystals. In addition, initial efforts to realise the Fabry-Perot SLM were launched. Construction of the basic EH pixel.
- ◇ Incorporation of the SLM prototypes in holographic systems
The French group at Orsay devoted its efforts to the development of a generic method for phase multiplexing volume holograms that will enable real time updating and refresh of the stored information, and will eventually serve as a test ground for the SLMs.

RESULTS

- ⇒ Growth and characterisation of KLTN crystals operating at room temperature with very high diffraction efficiency, crystals with photorefractive sensitivity at 690 nm, and the development of fixing processes in these crystals.
- ⇒ Construction of the first EH pixels using the KLTN crystals.

PARTNERS

HEBREW UNIVERSITY OF JERUSALEM
Department of Applied Physics
91904 Jerusalem
Israel

Aharon J. Agranat
Tel.: +972-2-658 45 26
Fax: +972-2-658 61 67

**ECOLE NATIONALE SUPERIEURE DE
TELECOMMUNICATION**
France

Gabries Sirat

**EFFECTS OF IMPLANTATION ON GROWTH, DEFECT FORMATION AND
DOPING OF DIAMOND**

Co-ordinator: Technion-Solid State Institute, Haifa, Israel (Rafi Kalish)

OBJECTIVES

- To understand the way diamond damages as a result of ion implantation;
- To study the role that temperature during or following the implantation has on the nature of the damage;
- To investigate the role that defects introduced into diamond in a controlled way by ion implantation have on subsequent homoepitaxial diamond growth;
- To devise ways of doping diamond p-type by implantation of boron ions and the search for suitable n-type dopants introduced into diamond by implantation.

ACTIVITIES

- ◇ Well-characterised diamond crystals or CVD diamond films are damaged by implantation of inert ions (C and Xe) at different temperatures;
- ◇ The outcome of the implantation is studied by various electrical and optical methods;
- ◇ Overgrow the damaged diamond surfaces with a homoepitaxial diamond layer (including ¹³C enriched layers) and characterise their properties;
- ◇ Utilise the knowledge gained from the above on damaging and annealing diamond for doping diamond by implanting potential dopant atoms (B for p-type and Li, Na, P... for n-type);
- ◇ Make use of graphitization of diamond and CVD diamond overgrowth for the realisation of thin single crystal diamond membranes by lift off techniques.

RESULTS

- ⇒ A comprehensive picture of the ion-beam induced transformation of diamond to graphite has been obtained, and a model for this transformation, based on a consideration of the damage produced around each ion track and the dependence of this damage on implantation temperature has been proposed.
- ⇒ Good p-type doping of diamond has been achieved by Boron ion implantation followed by a proper annealing procedure, yielding record high hole mobilities of 385 cm²/V.sec (at RT) and the lowest compensation ratio of 0.05 ever reported for ion-implantation doped diamond.
- ⇒ P-type activities, though with inferior electrical properties, have been obtained by B ion implantation of CVD (highly textured and non oriented polycrystalline) diamond films following the implantation - annealing procedures employed to Type IIa diamond (see above).
- ⇒ Attempts to achieve n-type semiconductivity of diamond by Li, Na and P ion implantations, along the lines that have yielded good p-type conductivities in B implanted diamond have been, so far, fruitless. No useful conductivities could be measured. However some indications that P may act as a donor in diamond were obtained.
- ⇒ Bias enhanced nucleation was applied to grow oriented diamond films on untreated silicon substrates leading to heteroepitaxially oriented diamond films.
- ⇒ Homoepitaxial diamond films were grown on (100) natural diamond substrates to study the effect of ion implantation on diamond growth. In some cases isotopic ¹³CH₄ was used for the deposition of isotopically labelled ¹³C-diamond. The substrate and film can thus be distinguished by their Raman spectra.

- ⇒ The structural and morphological effects caused by the addition of boron or nitrogen to the gas mixture during CVD diamond growth were studied and are attributed to the influence of these dopants on the growth velocities in the <100> and the <111> direction respectively.
- ⇒ Deep ion implantation was used to create an etchable graphitic layer that was either directly “lifted off” or has been lifted-off after overgrowth of the top, annealed, layer.

FOLLOW-UP

- ▶ Research in many of the above fields continues, though without the support of the EC. In particular the quest for n-type doping of diamond still requires much work, which is indeed ongoing in Israel;
- ▶ Growth of highly oriented thick diamond films, mainly for optical and thermal applications continues in Germany.

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PARTNERS

TECHNION - SOLID STATE INSTITUTE

Physics Department
Technion City
32000 Haifa
Israel

Rafael Kalish
Tel.: +972-4-829 39 06
Fax: +972-4-823 51 07
E-mail: kalish@ssrc.technion.ac.il

FRAUNHOFER INSTITUTE IAF

Tullastraße 72
79108 Freiburg
Germany

Peter Koidl
Tel.: +49-761-515 93 50
Fax: +49-761-515 94 00

STUDY OF SIGE LAYERS EPITAXIALLY GROWN ON SI BY ION BEAM SPUTTER DEPOSITION

Co-ordinator: Université Paris XI, Orsay, France (Françoise Meyer)

OBJECTIVES

- To study SiGe alloy films epitaxially grown on silicon by ion beam sputter deposition (IBSD);
- To determine the influence of the growth technique on the SiGe films properties, such as stress and roughness;
- To find optimal deposition parameters;
- To determine the thermal stability of the film stress after annealing.

ACTIVITIES

The research project integrates a large number of techniques of characterisation:

- ◇ Growth mode was studied in situ by Auger electron spectroscopy;
- ◇ Topology was studied ex-situ by atomic force microscopy;
- ◇ Strain was investigated by X-ray diffraction and Raman spectroscopy;
- ◇ Stress was determined from the measurement of the substrate curvature after deposition;
- ◇ Composition was determined by secondary ion mass spectroscopy, electron dispersive spectroscopy and Rutherford backscattering spectroscopy;
- ◇ Crystal defects were studied by transmission electron microscopy;
- ◇ Rapid thermal annealing and conventional annealing were performed under nitrogen or vacuum.

EXPECTED OUTCOME

- ▶ Evaluation of the potentialities of IBSD to grow SiGe films;
- ▶ Identification of the defects which lead to compressive strain;
- ▶ Strain relaxation in IBSD SiGe films.

RESULTS

- ⇒ The optimal growth temperature for a Ge-content of 20-25 % is found to be close to 550°C - 625°C.
- ⇒ IBSD leads to more abrupt interfaces and smoother films than molecular beam epitaxy. This result is related to the energetic bombardment of the growing films.
- ⇒ The samples grown at low (< 550°C) temperatures reveal point-like defects due to the bombardment of the growing film with high energetic Si and Ge atoms. These defects are parallel to {113} and {001} lattice planes and lead to an additional compressive stress ($\sigma = -1$ GPa) in the films.
- ⇒ Point-like defects are missing in the layers grown at 700°C. The films are then characterised by the presence of extended dislocations in the bulk of the layer as well as in the SiGe/Si interface and the Si substrate.
- ⇒ These defects are distributed across the entire SiGe film. This more or less random distribution of defects leads to local fluctuations of the interplane distance. The average magnitude of the fluctuations was derived from high-resolution X-ray diffraction spectra using a novel simulation procedure.
- ⇒ A detail study of strain relaxation kinetics in IBSD SiGe films clearly demonstrated that the strain relaxation is not a one-step thermally activated process but is governed by different mechanisms with various relaxation times.

⇒ These defects are distributed across the entire SiGe film. This more or less random distribution of defects leads to local fluctuations of the interplane distance. The average magnitude of the fluctuations was derived from high-resolution X-ray diffraction spectra using a novel simulation procedure.

FOLLOW-UP

Both groups are continuously co-operating on :

- ▶ Electrical properties of Schottky diodes on SiGe films;
- ▶ Properties of ternary alloy SiGeC, local order in particular.

This collaboration is supported through an Arc en Ciel program.

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PARTNERS

UNIVERSITÉ PARIS XI

Institut d'Electronique Fondamentale
Centre d'Orsay
Bâtiment 220
91405 Orsay
France

Françoise Meyer
Tel.: +33-1-69 15 40 24
Fax: +33-1-69 15 40 20
E-mail: francoise.meyer@ief.u-psud.fr

TECHNION - INSTITUTE FOR TECHNOLOGY

Department of Materials Engineering
32000 Haifa
Israel

Moshe Eizenberg
Tel/Fax: +972-4-829 45 85

**QUANTITATIVE RADIOGRAPHIC, TOMOGRAPHIC, HOLOGRAPHIC METHODS
FOR NONDESTRUCTIVE MEASUREMENTS OF STRUCTURAL INTEGRITY OF
HIGH STRENGTH ENGINEERING CERAMICS**

Co-ordinator: Technical University of Denmark, Lyngby, Denmark (Asger Lindegaard-Andersen)

OBJECTIVES

- To develop film-based radiographic, tomographic and holographic methods for quantitative nondestructive evaluation of high strength ceramics;
- To combine X-ray and optical techniques to obtain information about correlation among the structural integrity of ceramic samples and the distribution of deformations during load tests;
- To develop digital image processing software to maximise the amount of information that can be extracted from X-ray and holographic recordings.

ACTIVITIES

- ◇ Important material and process parameters will be varied in the production of samples in order to optimise the properties of the resulting ceramic samples;
- ◇ The samples will be tested by 4-points bending. X-ray radiography will be performed on all samples and few will be subject to more extensive study by tomographic methods;
- ◇ Holographic interferometry with the double exposure technique will be applied to select ceramic plates. Anomalies in the resulting deformation or stress pattern will be related to defects revealed by the X-ray investigations.

EXPECTED OUTCOME

- ▶ Quantitative interpretation of film-based X-ray radiographic and tomographic recordings and of holographic recordings is complicated. The results of the project are expected to contribute to the knowledge and application of the fundamental science of measurements and image science;
- ▶ Quantitative nondestructive evaluation methods will provide researchers involved in the development of ceramic and composite materials with a useful tool to characterise the material during successive stages of production. This will make it possible to optimise materials and process parameters;
- ▶ A new apparatus, based on the experimental set-ups of the project, may be of interest to producers of X-ray and/or holographic equipment.

RESULTS

X-ray radiography

- ⇒ X-ray radiographic results were compared with the results obtained by surface analysis, 4-point bending tests, optical microscopy, scanning electron microscopy and density measurements on samples of high strength engineering alumina and alumina zirconia ceramics. A strong correlation was found between these results, implying that X-ray radiography may be used in combination with i.e. surface flaw analysis for nondestructive assessment of the sample strength.
- ⇒ Another major conclusion is that X-ray radiographic NDT is a useful tool for quality assurance even at the very early stage of the manufacturing process.

X-ray tomography

- ⇒ A film-based tomographic system was developed. Film and object rotate synchronously around parallel axes carefully aligned in a vertical plane through the X-ray source, which was a micro-focus with focal spot size about 10 μm . The resolution which could be obtained was not better than 50 μm . The contrast resolution was limited to about 2%. Evidently, the spatial resolution sets a lower limit for achievable contrast resolution. Therefore, taking into account also the speed of

investigation, especially the very time consuming alignment procedures, film-based X-ray tomography is rather to be considered as a specialised research method than a method suitable for industrial ceramic quality and process control.

Holographic interferometry

- ⇒ Bars of ceramic samples were loaded in a three-line loading system with 50 mm separation among lines of contact and holographic interferograms were recorded. The results indicated that hidden defects could be detected by using holographic interferometric evaluation of the strain distribution under nondestructive load. Moreover, the location and the size of the defect could be estimated fairly well.

FOLLOW-UP

- Industrial CT-scanner: toward the end of the project a real-time X-ray system was installed. The system consists of a micro-focus tube (160 kVp, focal spot size $\sim 10 \mu\text{m}$), an X-ray image intensifier tube, a CCD video camera and a frame grabber for digitising the video signal. Based on this system, a computer-assisted X-ray tomograph (a CT-scanner) for industrial use has been developed. In order to achieve this, a computer-controlled step-wise rotating object table has been constructed and a Windows program for data collection and tomographic reconstruction on a PC has been developed.

PARTNERS

TECHNICAL UNIVERSITY OF DENMARK

Laboratory of Applied Physics
Building 307
2800 Lyngby
Denmark

Asger Lindegaard-Andersen

Tel.: +45-42 88 24 88
Fax: +45-45 93 12 22

TECHNICAL UNIVERSITY OF DENMARK

Institute of Mineral Industry
DTH, Building 204
2800 Lyngby
Denmark

John Engell

Tel.: +45-45 93 41 17
Fax: +45-45 93 48 86

TECHNION-ISRAEL INSTITUTE OF TECHNOLOGY

Department of Electrical Engineering
Technion City
32000 Haifa
Israel

Joseph Shamir

Tel.: +972-4-29 32 73
Fax: +972-4-22 15 81

**IMPROVEMENT OF COMBUSTION PROCESSES BY SWIRLING FLOWS AND
TURBULENT RECIRCULATING FLAMES**

Co-ordinator: Tel Aviv University, Tel Aviv, Israel (Shmuel Einav)

OBJECTIVES

- The project is aimed at improving understanding of swirling flows with applications to practical combusting flows. A range of instrumentation based upon laser-light scattering techniques complemented by probe methods has been developed and used to quantify the turbulent nature of swirling jet flows, including those with a dispersed liquid phase, and to extend the knowledge of turbulent transport processes in combustor-related flows. Attention was focused on the atomisation of liquids in swirling jets, with application on the development of low-emission combustion technologies;
- The advanced instrumentation used throughout the work has included the development of a new hot-wire probe and system capable of yielding three instantaneous velocity components at a point in a 3-D flowfield. In addition, the work considered techniques such as flow visualisation, and forms of laser-Doppler and phase-Doppler velocimetry, as well as sampling probes for gas species concentrations;
- In particular, the use of phase-Doppler velocimetry to study two-phase flows with practical relevance was evaluated in a purpose-built rig in terms of the mechanisms of polydispersion in regions of large variations of flow time scales.

ACTIVITIES

The work programme over the reporting period comprised several tasks, which can be conveniently summarised as follows:

- ◇ Development and evaluation of instrumentation
 - A new hot-wire probe was developed, together with a data processing system, in order to measure instantaneously these velocity components at a point in a three-dimensional flowfield. The technique was tested in a well-defined turbulent pipe flow and then, applied to the swirling jet flow issuing into a coflowing stream reported previously;
 - A dedicated optical system for the visualisation of the processes of liquid atomisation in swirling jets was developed including three basic techniques, namely :
 - direct visualisation, making use of laser light sheet illumination;
 - laser shadowgraphy;
 - white lighting of the flow, with sequential images acquired by a fast CCD camera.
 - A phase-Doppler velocimeter was assembled to measure simultaneously the velocity, size and mass flux of the air and particle phases in dispersed jets. The velocimeter was tested in a polydisperse particle laden turbulent jet ($Re = 15.000$) making use of glass beads with a size distribution centred at $50\mu\text{m}$ and with a standard deviation of $15\mu\text{m}$. The results quantify the extent to which the system is able to detect the effects of particle polydispersion in flow regions of large variation of the flow time scales.
- ◇ Measurement programme
 - A turbulent swirling jet issuing into a co-flowing steam was experimentally investigated following the previously reported results. It is shown that the concept of flow similarity does not apply when the distance from the jet exit plane is less than 30 nozzle diameters. In this zone, the effect of swirl on the Reynolds stress is shown to be small;
 - The atomisation processes and spray quality typical of the swirling flows found in practical combustors was studied in detail making use of a laboratory model of a prefilming airblast atomiser. The tests were carried out at atmospheric pressure and using water for a liquid film

thickness among 0.2 and 0.7mm, a liquid mass flow rate up to 11g/s. primary air velocities up to 200m/s and swirl numbers in the range $0 < S < 2.5$. The results quantify the various atomisation regimes, from the Rayleigh mode up to prompt atomisation, and show that the disintegration of the liquid film close to the atomising edge of the nozzle is associated with a periodic process mainly dependant on the primary air velocity. The Sauter mean diameter of the liquid phase is shown to be independent of the liquid film velocity for coaxial swirling flows, providing that the primary air velocity is kept above 120m/s. The related drop size velocity distribution is shown to contribute to the optimisation of combustion efficiency in practical combustors;

- The efficiency of the concept of lean-premixed-prevaporised, LPP, combustion technology was studied in two laboratory combustors. An axisymmetric combustion chamber was used downstream of a premixing duct, where liquid gasoline was prevaporized and mixed with a swirling air stream. Measurements of pollutant emissions at the exit of the combustion chamber quantify the performance of the technology in terms of the combustion of gaseous propane. In addition, the results were extended through the use of a rectangular sector combustor, which have allowed the analysis of flame interaction , as in annular combustion chambers.

RESULTS

⇒ The results obtained in swirling jets issuing into a coflowing stream provide evidence of the lack of flow similarities in near-nozzle regions and are important to assess physical models to be used to extrapolate the experimentally-acquired information. In addition, the atomisation of a liquid film in co-axial swirling jets was studied in detail and showed that the disintegration of the liquid film close to the atomising edge of the nozzle is associated with a periodic process. The importance of the atomisation process in the development of low-emission combustor technologies was assessed in a combusting laboratory environment, based on detailed measurement of pollutant emissions.

⇒ Main innovative aspects of the work performed in the reporting period :

- development of a new hot-wire probe for simultaneous measurements of the three velocity components in swirling jets;
- analysis of the response of a phase-Doppler velocimeter in polydisperse, two phase jet flows;
- detailed analysis of the break-up of an annular liquid sheet downstream of an air-blast atomiser, as a function of the swirling level of the flow and of the liquid film characteristics.

PARTNERS

TEL AVIV UNIVERSITY
Department of Fluid Mechanics
Heat Transfer 2
P.O. Box 39040
69978 Tel Aviv
Israel

Shmuel Einav
Tel.: +972-3-640 94 18
Fax: +972-3-640 79 39

INSTITUTO SUPERIOR TÉCNICO
Departamento de Engenharia Mecânica
Pavilhão de Máquinas, 1º Avidar
Avenida Rovisco Pais
1096 Lisboa Codex
Portugal

Manuel V. Heitor
Tel.: +351-1-841 73 79 / 841 71 94
Fax: +351-1-849 61 56

ELECTRO-OPTICAL STUDIES OF FERROELECTRIC LIQUID CRYSTALS

Co-ordinator: Technische Hochschule Darmstadt, Darmstadt, Germany (W. Haase)

OBJECTIVES

- To understand the switching behaviour in ferroelectric liquid crystals compared to ferroelectric liquid crystalline polymers;
- Determination of the physical parameters (i.e. spontaneous polarisation, rotational viscosity's, tilt angle) of the FLC's under investigation;
- To understand the influence of high spontaneous polarisation and dislocation domain formation on the structural parameters of ferroelectric liquid crystals;
- The tilt angle measurements by X-ray and optical methods should be compared, the dielectric data must be evaluated;
- To study thin and ultrathin smectic C* films by X-ray reflectivity.

ACTIVITIES

- ◇ Analysing the fast switching behaviour (S) in low molar mass FLC's and the switching properties (mS) in side chain polymers by triangular wave methods;
- ◇ Determination of the spontaneous polarisation with different techniques (Hysteresis method and reversal current method), tilt angle (X-ray and electrooptic technique, and rotational viscosity's from dielectric and electrooptic measurements;
- ◇ Mixtures of FLC's showing up different values of spontaneous polarisation were investigated by polarising microscopy light diffraction and dielectric spectroscopy. A relation between the value of the spontaneous polarisation and the domain periodicity was established;
- ◇ The zigzag defects and the microdomains in surface stabilised liquid crystal cells were carefully analysed by means of light scattering method. The tilt angle as function of temperature obtained by different techniques was analysed. The dielectric relaxation spectroscopy in a broad frequency region allowed to detect molecular and collective relaxation processes;
- ◇ X-ray reflections on ultrathin film allowed to study the layer thickness properties and interfaces properties.

RESULTS

⇒ The objectives to the five points in question could be answered with detailed, specific results.

FOLLOW UP

Both groups are continuously co-operating by:

- ▶ Dielectric relaxation spectroscopy on low molar mass and polymeric FLC's;
- ▶ Pyroelectric investigations on FLC's;
- ▶ Development of devices for application as spatial light modulators based on FLC's;
- ▶ Using both capabilities in solving questions related to EPR and magnetic properties of exchange coupled systems.

PARTNERS

TECHNISCHE HOCHSCHULE DARMSTADT

Institut für Physikalische Chemie

Petersenstraße 20

64287 Darmstadt

Germany

W. Haase

Tel.: +49-6151-16 33 98

Fax: +49-6151-16 42 98

E-mail: d54d@hrzpub.th-darmstadt.de

HEBREW UNIVERSITY OF JERUSALEM

Faculty of Sciences

Racah Institute of Physics

Givat Ram

91904 Jerusalem

Israel

D. Davidov

OPTICAL BISTABILITY IN MOLECULAR SYSTEMS

Co-ordinator: Universität Regensburg, Regensburg, Germany (A. Penzkofer)

OBJECTIVES

- To find a suitable organic dye for optical bistability and fast optical switching involving the triplet state;
- To develop spectroscopic techniques to measure the triplet state quantum yield and the triplet-triplet absorption dynamics;
- To analyse in detail the singlet and triplet absorption and emission dynamics of a selected organic dye of high triplet quantum yield.

ACTIVITIES

- ◇ Measurement of linear absorption and emission spectra of eosin Y;
- ◇ Measurement of absolute S_1 -state excited-state absorption cross-section spectrum of eosin Y in methanol by picosecond laser pulse excitation and time-delayed picosecond light continuum probing;
- ◇ Measurement of triplet quantum yield and intersystem-crossing rate of eosin Y in methanol and water by picosecond double pulse transient absorption measurements;
- ◇ Measurement of triplet-triplet absorption of methanol using nanosecond excimer laser triplet population and picosecond light continuum absorption probing in the triplet state.

RESULTS

- ⇒ A good understanding of the singlet and triplet absorption spectroscopic behaviour of eosin Y was obtained. Absolute singlet excited state absorption cross-section spectra and triplet-triplet absorption cross-section spectra were determined. A new technique for triplet quantum yield measurement and intersystem-crossing rate determination was developed and was applied to the measurement of the intersystem-crossing rate of eosin Y in methanol and eosin Y in water.

FOLLOW-UP

- The project started our interest in the triplet spectroscopy of organic dyes. We continued to study intersystem crossing. We studied the higher excited-state triplet to singlet intersystem crossing by double-pulse picosecond excitation and fluorescence detection. A fluorescence detection technique was developed to determine the quantum yield of triplet formation by S_1 - T_1 intersystem crossing. The intersystem crossing rate of some organic dyes has been determined.

SELECTED PUBLICATION

REINDL, S., PENZKOFER, A. 1996. Higher excited-state triplet-singlet intersystem crossing of some organic dyes, Chem. Phys. 211: 431.

PARTNERS

UNIVERSITÄT REGENSBURG

Naturwissenschaftliche Fakultät II
93040 Regensburg
Germany

A. Penzkofer

Tel.: +49-941-943 21 07

Fax: +49-941-943 27 54

E-mail: alfons.penzkofer@physik.uni-regensburg.de

TECHNION-ISRAEL INSTITUTE OF TECHNOLOGY

32000 Haifa
Israel

Shammai Splizer & Jacob Katriel

4. Additional fields of mutual interest

4.4. Cultural heritage

**EURO-MED-GLACURES: ETUDE PHYSIQUE ET PRESERVATION DES
CERAMIQUES GLACUREES DE L'ESPACE MEDITERRANEN ARCHITECTURE-
ARCHEOLOGIE**

Coordinateur: Université Michel De Montaigne – Bordeaux III, France (Françoise Bechtel)

OBJECTIFS

Caractériser le matériel céramique glaçuré recueilli soit sur des lieux de production attestés en utilisant les ressources naturelles minéralogiques, locales ou non (on étudiera des cas précis pour les pays suivants: Tunisie, Égypte, Syrie, ...), soit sur des lieux d'utilisation (France, Italie, Espagne).

- Identifier les matériaux utilisés et retrouver les techniques de production et de décoration des céramiques glaçurées de l'espace méditerranéen : on traitera divers cas d'étude, en particulier la céramique glaçurée à décor de lustre métallique; on étudiera de manière très approfondie du matériel provenant de Tunisie et de Syrie.
- Déterminer l'état de conservation/altération de la glaçure et de son support en donnant une description fine des régions altérées, en précisant la nature des produits d'altération et en interprétant les figures d'altération mises en évidence.

ACTIVITES

- ◇ Afin d'atteindre les objectifs visés avec ces céramiques glaçurées, qui sont au sens moderne du terme des matériaux composites, on va mettre en oeuvre des méthodes physiques de caractérisation des solides, plus particulièrement des archéomatériaux. Citons notamment les micro-observations de textures et les analyses élémentaires locales (par exemple : microscopie électronique à balayage, spectroscopie Auger, spectroscopie de photoélectrons, cathodoluminescence, etc...).
- ◇ Parallèlement, des expériences systématiques de re-création ou de simulation seront menées avec des artisans céramistes et des Centres de recherche industrielle, selon une démarche pluridisciplinaire. En amont et en aval du travail des physiciens, elle impliquera également des architectes, des archéologues et des historiens de l'art. C'est en cela que ce programme est pour ce matériau, et à l'échelle envisagée, particulièrement innovant.

RESULTATS ESCOMPTEES

- ⇒ Connaissances pratiques sur la production de la céramique glaçurée et de sa décoration, en fonction des ressources naturelles locales ou importées (argile, fondants, matières colorantes) et des ressources technologiques spécifiques d'une culture, d'une région déterminées. Transposition à la production artisanale et industrielle contemporaine.
- ⇒ Mise au point de protocoles expérimentaux permettant de déterminer avec précision l'état de conservation des glaçures ainsi que de leur support, et création d'un réseau de compétence pluridisciplinaire entre des Centres de recherche de pays différents, acteurs d'une coopération nord-sud et est-ouest dans l'espace méditerranéen.
- ⇒ Constitution progressive d'une base de données analytiques sur les constituants et la texture des céramiques glaçurées de l'architecture et de l'archéologie pour des régions, des périodes et des lieux de production attestés.

PARTENAIRES

UNIVERSITE MICHEL DE MONTAIGNE – BORDEAUX III

Cnrs Maison De L'archeologie
Domaine Universitaire
33405 Talence

France

Pr Françoise Bechtel
Tel.: 33-5-5684.5153
Fax: 33-5-5684.5157
E-mail: Crpaa@Montaigne.U-Bo

Agence Nationale Architecture Sites Et Monuments
2 Place Ben Badis
Alger
Algerie

Mr Mohamed Debieche
Tel.: 213-271.02.58
Fax: 213-271.18.20

INSTITUT FRANCAIS D'ARCHEOLOGIE ORIENTALE(LE CAIRE-EGYPTE)

C/O Rue De L'universite 128 Bis
75351 07sp Paris

France

Dr Roland-Pierre Gayraud
Tel.: 33-4-4252.4309
Fax: 33-4-4252.4378
E-mail: Lamm@Aixup.Univ-Aix.Fr

UNIVERSITA DEGLI STUDI DI SALERNO

Centro "N.Cilento" Per L'archeologia Medievale
Via Dei Due Principati 42
84100 Salerno

Italia

Pr Paolo Peduto
Tel.: 39-89-96.22.64
Fax: 39-89-96.22.62

UNIVERSITE DE FRIBOURG

Institut De Mineralogie
Perolles
1700 Fribourg
Suisse

Pr Marino Maggetti
Tel.: 41-26-300.89.20
Fax: 41-26-300.97.65
E-mail: Marino.Maggetti@Unifr.Ch

MUSEE NATIONAL DE DAMAS

General Directorate Of Antiques And Museums, Islamic Dept
Damas

Rep. Arab. Syrienne

Ms Mouna Moua'zen
Tel.: 963-11-221.99.38
Fax: 963-11-224.79.83

INSTITUT NATIONAL DU PATRIMOINE

Unite De Recherche Sur Le Patrimoine
4, Place Du Chateau
Tunis
Tunisie

Dr Abdelaziz Daoulati
Tel.: 216-1-26.16.22
Fax: 216-1-56.24.52

MIDDLE EAST TECHNICAL UNIVERSITY

Dept Of Physics - Dept Of Archaeometry
Inonu Bulvari
06531 Ankara
Turquie

Prdr Ay Melek Ozer
Tel.: 90-312-210.32.73
Fax: 90-312-210.12.81
E-mail: Aymelek@Rorqual.Cc.Metu.Edu.Tr

"DEMOKRITOS" NATIONAL CENTRE FOR SCIENTIFIC RESEARCH

Institute Of Materials Science Lab Of Archaeometry
Ag. Paraskevi
15310 Ag. Paraskevi
Greece

Dr Yannis Maniatis
Tel.: 30-1-652.28.72
Fax: 30-1-651.94.30
E-mail: Maniatis@Ims.Ariadne-T.Gr

**INTEGRATION OF TRADITIONAL AND NEW TECHNIQUES FOR THE PROTECTION
AND CONSERVATION OF HISTORICAL AND CULTURAL BUILT HERITAGE IN
EARTHQUAKE-PRONE AREAS.**

Co-ordinator: Istituto Di Ricerca Sul Rischio Sismico, Italia (Vincenzo Petrini)

OBJECTIVES

The main objectives are defined as follows:

- To contribute to increase the presently limited knowledge on the seismic behaviour of ancient constructions and to develop a consolidated practice of multi-disciplinary approaches including different aspects like the economic one, the limited consciousness of technical bodies of public administrations, the scarce attention paid to retrofitting and rehabilitation in the curricula of the university studies for civil engineers and architects.
- Verify the advantages of the integration of traditional and new techniques, particularly those involving the use of new materials.
- Reducing the cost of the practice of retrofitting when applied to the preservation and protection of the historical and cultural built heritage.
- Confront their respective experience and know-how, and seek for a concerted approach of the problems identified as 'to-be-solved'

ACTIVITIES

The key activities involve:

- ◇ Setting-up a "Euro-Mediterranean network for rehabilitation of ancient building stock in earthquake-prone areas".
- ◇ To establish the connection between different experiences. More precisely: compare the approaches typical of the European countries and of the southern Mediterranean countries; compare and, when possible, combine the way of looking to the preservation of vernacular historical buildings and of monuments; integrate modern and traditional strengthening techniques and old and new materials. To this purpose the common work of experts in the different field has been selected as a suitable tool.
- ◇ Tree field workshops organised once a year over a period of three years in "southern Mediterranean countries"; they will be attended by advanced students and young professionals, and "teaching staffs" from both "southern Mediterranean countries" and member-states of the European Union; attendance should be multi-national and multi-disciplinary, organised in small teams (5-8 teams of 5-7 participants each) dedicated to specific topics: a group of buildings; traditional coatings and colours; monumental buildings; typology of constructions; structural damages eventually caused by earthquakes; proposals for rehabilitation;

EXPECTED OUTCOME

- ⇒ It is expected that, within the three years duration, a multi-national network of young professionals, well acquainted to each other and well trained at working together, from various disciplines, will accumulate common material and experience, and will be ready to initiate co-operative research projects and to undertake major rehabilitation initiatives here and there. A by-product of the concerted action will be to implement or develop the teaching of rehabilitation in some architecture and civil engineering schools; this could prove to meet likely economic requirement in the near future.

PARTNERS

ISTITUTO DI RICERCA SUL RISCHIO SISMICO

Consiglio Nazionale Delle Ricerche
Via Bassini, 15
20133 Milano
Italia

Pr Vincenzo Petrini
Tel.: 39-02-2639.9280
Fax: 39-02-2668.0987
E-Mail: Petrini@Daphne.Irrs.Mi.Cnr.It

U.N.E.S.C.O.

Cairo Office
8, Abdel Rahman Fahmy St.
11511 Garden City - Cairo
Egypte

Dr Adnan Shihab-Eldin
Tel.: 20-2-354.55.99
Fax: 20-2-354.52.96
E-mail: Uhcai@Unesco.Org

FACULTE POLYTECHNIQUE DE MONS

Service D'architecture
9 Rue De Houdain
7000 Mons
Belgium

Pr Hugues Wilquin
Tel.: 32-65-37.45.01
Fax: 32-65-37.46.00
E-mail: Hugues.Wilquin@Fpms.Ac.Be

NATIONAL TECHNICAL UNIVERSITY OF ATHENS

Faculty Of Architecture Dept Of Architectural
Technology
42 Patisson Str.
10682 Athens
Greece

Pr Nikos Kalogeras
Tel.: 30-1-772.38.81
Fax: 30-1-772.38.98
E-mail: Nickalog@Central.Ntua.Gr

ECOLE D'ARCHITECTURE DE PARIS LA SEINE

14, Route Bonaparte
75006 Paris
France

Pr Patrick De Maisonneuve
Tel.: 33-1-4450.5608
Fax: 33-1-4450.5621
E-mail: Patrick.Demaisonneuve@Parislaseine.Archi.Fr

UNIVERSIDAD POLITECNICA DE VALENCIA

Depto De Composicion - Escuela Tecnica Superior De
Arquitectura
Camino De Vera S/N
46022 Valencia
Espana

Pr Fernando Vegas Lopez-Manzanares
Tel.: 34-96-387.74.40
Fax: 34-96-387.74.49
E-mail: Fvegas@Cpa.Upv.Es

JORDAN UNIVERSITY OF SCIENCE AND TECHNOLOGY

Architecture Engineering Dept
P.O. Box 3030
22110 Irbid
Jordanie

Pr Azm S. Al-Homoud
Tel.: 962-79-33064
Fax: 962-2-295123
E-mail: Jdc@Go.Com.Jo

INSTITUT NATIONAL DU PATRIMOINE

Laboratoire De Conservation Musee National Du Bardo
2000 Lebaro
Tunisie

Dr Slim Khosrof
Tel.: 216-1-51.36.50
Fax: 216-1-51.40.50

AGENCE NATIONALE ARCHITECTURE SITES ET MONUMENTS

Dept Restauration Et Conservation
2, Boulevard Amara Rachid, Bastion 23
Alger
Algerie

Dr Mohamed Debieche
Tel.: 213-2-71.02.58
Fax: 213-2-73.18.23

MINISTERE DE LA CULTURE

General Directorate Of Antiques And Museums,
Engineering Dept
St. Kasser Al Hier
Damascus
Rep. Arab. Syrienne

Dr Lina Kutiefan
Tel.: 963-11-222.85.66
Fax: 963-11-224.79.83

MINISTERE DES AFFAIRES CULTURELLES

Dr Abdelaziz Touri
Direction Du Patrimoine Culturel
17, Rue Michlifen Adgal Agdal
10 000 Rabat
Maroc

Tel.: 212-7-67.13.81
Fax: 212-7-67.13.97

**STUDY, CHARACTERIZATION AND ANALYSIS OF DEGRADATION
PHENOMENA OF ANCIENT, TRADITIONAL AND IMPROVED BUILDING
MATERIALS OF GEOLOGIC ORIGIN USED IN CONSTRUCTION OF HISTORICAL
MONUMENTS IN THE MEDITERRANEAN AREA.**

Co-ordinator: Universidad Autonoma De Barcelona, Espana (Jose Luis Brianso-Penalva)

OBJECTIVES

The main objectives are defined as follows:

- The co-ordination of various R.T.D. groups of the European Union (EU), and Third Countries (TC) in the Mediterranean Area, on preservation and restoration of Cultural Heritage;
- To allow synergy among the groups dealing with degradation and alteration of geologic materials (traditional or improved by technical process) used in construction and rehabilitation of the Cultural Heritage in the Mediterranean Area;
- Strengthening the partnership by promoting mobility and exchange of scientific and technical staff of the programs and teams.

ACTIVITIES

The key activities involve:

- ◇ Organisation of three Prospective Studies, based on different types of geologic materials, carried out in parallel in Third Countries of the Mediterranean Area;
- ◇ Organisation of two thematic Workshops focused on techniques and methodologies applied on sedimentary rocks, igneous and metamorphic rocks, and clay materials;
- ◇ Organisation of two Training Courses addressed to specialist of preservation of Monuments (both scientists and technicians).

EXPECTED OUTCOME

The expected outcomes are:

- ⇒ Prospective studies of materials and their alterations used in several monuments from the TC of the Mediterranean Area, as well as studies of socio-economic and environmental factors in the surrounding of these monuments;
- ⇒ Proposition of guidelines and models for rehabilitation of these monuments;
- ⇒ Joining of several groups from non-member states in order to use advanced technologies considered by CA and giving the opportunity to the EU partners to study determined monuments in TC;
- ⇒ Enabling the N-S, N-N and S-S mobility of the researchers within laboratories, as well as enabling the interchange of samples to be analysed in other laboratories;
- ⇒ Organisation of Training Courses under the auspices of the UNESCO Cairo Office;
- ⇒ Creation of a permanent network on the materials considered by this CA and used in Cultural Heritage;
- ⇒ Identification of Joint Research requirements as the basis for JRP-s proposed to EC within the V Framework Programme of INCO-MED.

PARTNERS

UNIVERSIDAD AUTONOMA DE BARCELONA

Dept Of Geology (Unit Crystallography) Faculty Of
Sciences
Edificio C
08193 Bellaterra (Barcelona)
Espana

Dr Jose Luis Brioso-Penalva
Tel.: 34-93-581.30.90
Fax: 34-93-581.12.63
E-mail: Joseluis.Brioso@Cc.Uab.Es

UNIVERSITE CADI AYYAD

Faculte Des Sciences Laboratoire De Geologie
Structurale
Bd Prince My Abdellah Bp S15
4000 Marrakech
Maroc

Pr Mohamed Bouabdelli
Tel.: 212-4-43.46.49
Fax: 212-4-43.67.69

UNIVERSITY OF MALTA

Institute For Masonry & Construction Research
Msd 06 Msida
Malte

Ms Joann Cassar
Tel.: 356-32.90.28.66
Fax: 356-33.64.50
E-mail: Saline@Dream.Vol.Net.Mt

UNIVERSITY OF SURREY

Dept Of Chemistry Thermochemistry Laboratory
Gu2 5xh Guilford
United Kingdom

Dr Angela Danil De Namor
Tel.: 44-1483-300.800
Fax: 44-1483-300.803

UNIVERSITY OF CAIRO

Pr Hassan Fahmi Imam
Engineering Centre For Archeology & Environment,
Rock Eng. - Mining Dept
Giza
Egypte

Tel.: 20-2-573.15.60
Fax: 20-2-573.15.60

INSTITUTO INVESTIGACAO CIENTIFICA TROPICAL

Centro De Cristalografia E Mineralogia
Almeda D. Afonso Henriques 41 - 4
1000 Lisboa
Portugal

Prdr Maria Ondina Figueiredo
Tel.: 351-1-847.65.96
Fax: 351-1-363.14.60
E-mail: Crist@Iict.Pt

RHEINISCH-WESTFAELISCHE TECHNISCHE

Hochschule Aachen
Geologisches Institut
Templergraben 55
52056 Aachen
Deutschland

Dr Bernd Fitzner
Tel.: 49-241-80.57.27
Fax: 49-241-88.88.34-6
E-mail: Fitzner@Geol.Rwth-Aachen.De

INSTITUT NATIONAL DU PATRIMOINE

Laboratoire De Conservation
Place Du Chateau 4
1008 Tunis
Tunisie

Dr Slim Khosrof
Tel.: 216-1-51.36.50
Fax: 216-1-51.40.50

UNIVERSITE DE LIMOGES

Inst. Universitaire De Technologie Departement De Genie
Civil
Bd. Robert Derche
19300 Egletons
France

Dr Jacques Rosier
Tel.: 33-5-5593.4509
Fax: 33-5-5593.4501
E-mail: Rosier@Unilim.Fr

INTERN. CENTRE FOR THE PRESERVATION & THE RESTORATION OF CULTURAL PROPERTY

Via Di San Michele 13
00153 Rome
Italia

Phd Ernesto Borelli
Tel.: 39-658.55.31
Fax: 39-658.55.53.34.9
E-mail: Eb@Iccrom.Org

U.N.E.S.C.O.

Cairo Office
Abdel Rahman Fahmy Street 8 Garden City
11511 Cairo
Egypte

Dr Adnan Shihab-Eldin
Tel.: 202-354.55.99
Fax: 202-354.52.96
E-mail: H.Helal@Unesco.Org

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Galili, G.	CI1*CT94-0087
Gao, Q.	IC18-CT96-0069
Garcia, F.	IC18-CT95-0809
Garcia, J.L.	CI1*CT92-0104
Garcia-Moreno, E.	IC18-CT96-0099
Gargouri, A.	CI1*CT92-0104
Gavach, C.	AVI*CT92-0014
Gayraud, R-P.	IC18-CT98-0386
Gedeon, R.	AVI*CT93-0005
Gherissi, S.	AVI2-CT93-054

Ghrabi, A.	AVI*CT94-0007 IC18-CT98-0267
Gibart, P.	CII*CT93-0313
Ginzburg, I.	CII*CT94-0130
Girardie, A.	TS3*CT93-0208
Girof, R.	TS3*CT93-0244
Gitelson, A.	AVI*CT93-143 IC18-CT97-0154
Glaser, I.	CII*CT93-0004
Glass, E.	IC18-CT95-0009 IC18-CT95-0004
Glekas, I.	AVI2-CT93-062 IC18-CT97-0142
Godbold, D.L.	IC18-CT96-0035
Goldfarb, D.	AVI*CT92-0012
Goldman, M.	IC18-CT96-0122
Golik, A.	AVI*CT92-0016
Golosovsky, M.	CII*CT93-2027
Gomes, A.	IC18-CT98-0346
González, I.	AVI*CT94-0013
González, M. M. L.	IC18-CT97-0198
Goossens, M.	AVI*CT93-0014
Göral, V.	AVI*CT93-0008
Gordon, A.	TS3*CT92-0093
Görgen, H.	TS3*CT92-0112
Gorman, A.	CII*CT94-0126
Gorochof, O.	CII*CT93-0070
Graber, E.	AVI*CT92-0006
Grandinetti, L.	IC18-CT95-1139
Grangaud, J.P.	TS3*CT92-0144
Granlund, G.	EC-ISR-93003
Granum, E.	EC-ISR-93003
Gray, J.	CII*CT93-0005
Gray, J.C.	CII*CT94-0080
Green, M.	AVI*CT94-0011
Gressel, J.	IC18-CT98-0391
Grego, S.	TS3*CT92-0047
Grimm, H.	AVI*CT94-0006
Gronenborn, B.	IC18-CT96-0121
Grouzis, M.	TS3*CT92-0047
Gryseels, B.	AVI*CT93-0004
Guariso, G.	IC18-CT95-0809
Guenoun, A.	AVI2-CT93-058
Gueye, A.	IC18-CT95-0009
Guizani, I.	AVI*CT92-0013
Gulcan, R.	IC18-CT98-0310
Gunay, G.	AVI2-CT93-072 IC18-CT97-0161
Gur, A.	AVI*CT94-0009
Gurria Gascon, J.L.	AVI2-CT93-126
Guter, N.	AVI*CT92-0012
Gutnick, D.L.	CII*CT94-0083
Haase, W.	CII*CT90-0542
Habela, M.A.	IC18-CT95-0009

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Haddouchi, B.	AVI2-CT93-073
Hadjichristophorou, M.	AVI2-CT93-123
Hajji, M.	IC18-CT96-0055
Halevy, A.	CII*CT93-0074
Halim Salem, M.	TS3*CT92-0061
Halim, A.A.	AVI*CT94-0003
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Hall, M.A.	IC18-CT96-0082
Hallak, H.	AVI*CT94-0008 IC18-CT97-0142
Hamad Wafa, A.A.	AVI*CT93-0004
Hamadi, R.	TS3*CT92-0119
Hamburger, J.	AVI*CT94-0001 IC18-CT98-0354
Hamdy, A.	IC18-CT96-0055 IC18-CT97-0163
Hamers, R.	AVI*CT92-0010
Hamidat, A.	AVI*CT94-0004
Hammami, N.	IC18-CT98-0289
Hammou, O.	TS3*CT92-0143
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Hamze, M.	IC18-CT97-0153
Hamza, A.	IC18-CT97-0147 IC18-CT97-0186
Hanack, M.	CII*CT93-0066
Harfouche, A.	IC18-CT97-0200
Harrison, P.G.	AVI*CT92-0012
Harrouni, S.	IC18-CT96-0055
Harpaz, S.	IC18-CT98-0333
Hashwa, F.	IC18-CT98-0136
Hegazi, N.	IC18-CT95-0905
Heitor, M.V.	CII*CT91-0923
Hejnen, H.	AVI2-CT93-020
Hermenegildo, M.	EC-ISR 90
Higgit, D.	IC18-CT98-0268
Himonas, C. A.	IC18-CT98-0354
Hoelmann, A.	IC18-CT96-0099
Homedan, M.	IC18-CT98-0308
Hötzl, H.	AVI2-CT93-072
Hours, B.	AVI*CT93-0011
Huang, J.	IC18-CT95-0809
Huchzermeyer, B.	IC18-CT96-0055
Huibers, F.	AVI*CT93-0004
Hüttermann, A.	IC18-CT97-0186
Ibrahimi, S.	AVI2-CT93-107
Icli, S.	AVI*CT94-0013
Ilana, B.	CII*CT94-0096
Iman, H. I.	IC18-CT98-0384
Inan, D.	AVI*CT94-0004

Inclan, U.	IC18-CT95-0809
Inel, Y.	AVI2-CT93-074
Inglebert, M.	IC18-CT95-0175
Ioannides, M.	KIT Nr. 204
Iordanou, G.	AVI*CT92-0017
Isik, F.	IC18-CT97-0200
Issa, M.	IC18-CT95-0175
Ita, E. O.	IC18-CT98-0331
Jackson, D.	IC18-CT97-0171
Jaffe, C.L.	IC18-CT95-0023
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Jiangxiong, M.	TS3*CT92-0093
Jimenez-Montealegre, R.	IC18-CT97-0202
Jofre, J.	CII*CT91-0907
Jongegan, F.	IC18-CT95-0009
	IC18-CT95-0003
Jordan, A.	IC18-CT95-0895
Jori, G.	IC18-CT96-0076
Jourdane, J.	AVI*CT94-0001
Jrad-Fantar, A.	AVI2-CT93-087
Kabariti, M.	IC18-CT96-0039
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Kabay, N.	AVI*CT94-0014
Kacem, R.B.	IC18-CT95-0175
Kachani, M.	IC18-CT95-0009
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Kadi, M.	AVI*CT93-0010
Kadouri, A.	CII*CT93-0003
Kafkafi, U.	IC18-CT98-0272
Kagan-Zur, V.	IC18-CT96-0035
Kakas, A.C.	KIT Nr. 12
Kaliakatsos, I.	IC18-CT96-0099
Kaliras, P.	IC18-CT98-0367
Kalish, R.	CII*CT93-0065
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Kallidromitou, D.	AVI*CT93-0006
Kallos, G.	AVI*CT92-0005
Kalogeras, N.	IC18-CT98-0385
Kandiyoti, R.	TS3*CT92-0093
Kassas, M.	AVI*CT94-0003
Katriel, J.	CII*CT89-0442
Katsaros, D.	TS3*CT92-0119
Katzir, A.	CII*CT93-0362
Kautek, W.	CII*CT93-0065
Kaya, Z.	IC18-CT97-0200
Kegels, G.	AVI*CT93-0011
Keller, U.	CII*CT94-0108
Kellner, R.	CII*CT93-0362
Kewny, L.	IC18-CT97-0177
Kerdjoudj, H.	AVI*CT92-0014
Kes, P.H.	CII*CT93-0069
Khallaayoune, K.	AVI*CT93-0004
Khamis, M.	IC18-CT98-0272

Khan, A.	IC18-CT96-0055
Kharrat, M.	IC18-CT98-0300
Khakee, A.	IC18-CT98-0268
Khatib, A.	AVI*CT94-0009
Khawlie, M.	IC18-CT97-0161
Khedr Fahmi, I.	IC18-CT98-0289
Kherbeche, A.	AVI2-CT93-083
Khlat, M.	IC18-CT96-0036
Khliat, H.	IC18-CT97-0198
Khogali, M.	AVI*CT93-0012
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Khouja, L.	IC18-CT97-0200
Khoury, J.	IC18-CT96-0091
Khosrof, S.	IC18-CT98-0385
	IC18-CT98-0384
Kimchie, S.	IC18-CT96-0099
Kinet, J.M.	TS3*CT94-0264
	IC18-CT98-0390
King, D.A.	CI1*CT94-0125
Kirsch, J.	CI1*CT94-0130
Kittler, J.	EC-ISR-93003
Kleinwächter, J.	AVI*CT94-0013
Kock, N.	IC18-CT95-0009
Koidl, P.	CI1*CT92-0063
Konczykowski, M.	CI1*CT93-0069
Koornneef, M.	CI1*CT91-0932
Köseoglu, G.	ICA-17
Kost, J.	CI1*CT94-0779
Kotea, N.	TS3*CT93-0244
Koudijs, A.	EC-MED-35
Kouklos, E.	IC18-CT97-0163
Kramvis, S.	IC18-CT96-0122
Krimai, Z.	IC18-CT97-0198
Krishnamoorthy, R.	TS3*CT93-0244
Kusel, J.	IC18-CT98-0367
Kutiefan, L.	IC18-CT98-0385
Kyritsis, S.	AVI*CT94-0002
Laabid, A.	TS3*CT92-0112
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Labat, M.	CI1*CT92-0104
Labed, L.	IC18-CT95-0175
Laborde, J.P.	AVI2-CT93-058
Laghezali, M.	IC18-CT98-0310
Lailhacar, S.	TS3*CT94-0264
Laouina, A.	IC18-CT98-0268
	IC18-CT97-0147
Lanarhs, T.	IC18-CT98-0293
Lapidot, A.	CI1*CT94-0108
Larbot, A.	AVI*CT92-0014
Latif, A.A.	IC18-CT95-0009
Lazarides, D.	IC18-CT96-0039
Leblebici, D.	ICA-17
Leenaerts, R.	AVI2-CT93-081
Lehucher, P.M.	AVI2-CT93-058

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Lemonnier, D.	TS3*CT94-0282
Lerberge	
Letouze, R.	IC18-CT98-0308
Lettinga, G.	AVI*CT94-0009
Leupold, D.	CII*CT94-0126
Levanon, D.	CII*CT94-0086
Levi, G.	EC-ISR 90
Levi, M.	AVI*CT93-0001
Levin, L.A.	CII*CT93-0311
Levsen, K.	AVI*CT92-0004
Lévy-Clément, C.	CII*CT93-0065
Lewando-Hundt, G.	AVI2-CT93-031
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Lewis, A.	CII*CT92-0096
Liberti, L.	AVI*CT94-0010
Lieth, H.	IC18-CT96-0055
Lindegaard-Andersen, A.	CII*CT91-0927
Litz, N.	AVI*CT92-0006
Lloyd, D.H.	IC18-CT95-0009
Lluch, C.	IC18-CT96-0081
Lo Cicero Vaina, R.	IC18-CT96-0039
Lobo-Guerrero, J.	AVI*CT94-0004
Loizides, L.	AVI*CT92-0016
Loizidou, M.	AVI2-CT93-062
Lopez-Manzanares, F. V.	IC18-CT98-0385
Lorenz, N.	TS3*CT92-0112
Lounis, A.	AVI*CT92-0014
Luria, M.	AVI*CT92-0005
Luzzatto, L.	TS3*CT93-0244
Maass, E.	IC18-CT96-0035
Madkour, M.	IC18-CT96-0121
Madsen, H.	AVI*CT93-0004
Magan, N.	AVI*CT93-0067
Maggetti, M.	IC18-CT98-0386
Mahadin, K.	AVI2-CT93-020
Mahasneh, I.	IC18-CT95-0895
Mahjoub, Z.	ITDC 135-82159
Majali-Mahasneh, S.	AVI*CT94-0003
Makkouk, K.	IC18-CT96-0121
Malash, N.	IC18-CT98-0313
Malik, Z.	IC18-CT96-0076
Mameri, M.	AVI2-CT93-081
Mameri, N.	AVI2-CT93-081
Mammou, M. A.	IC18-CT98-0269
Manneback, P.	ITDC 94-201-82164
Maniatis, Y.	IC18-CT98-0386
Mannis, A.	IC18-CT95-0809
Mantell, S.	TS3*CT93-0221
	IC18-CT98-0308
Marcos, A.	TS3*CT94-0282
Marder, J.B.	CII*CT94-0085
Marecos Da Monte, H.	AVI*CT94-0012
Margaris, N.	IC18-CT96-0055

Marouf, B.	AVI2-CT93-019
Marschner, H.	CII*CT93-0006
Marques, J. C.	IC18-CT98-0270
Maselli, F.	IC18-CT97-0155
Martinez Beltran, J.	TS3*CT92-0061
Martinez, P.F.	IC18-CT96-0082
Martinez-Duart, J.M.	AVI*CT94-0008
Martinez-Pardo, R.	TS3*CT93-0208
Mata-Alvarez, J.	AVI-CT94-0011
Matthies, M.	IC18-CT96-0055
Maubois, J.L.	TS3*CT92-0119
Mavroyannopoulos, G.	IC18-CT98-0272
Mawajdeh, S.	AVI*CT94-0003
Mayer, O.	AVI*CT94-0004
Maza, J.A.	IC18-CT96-0069
Mazharsolook, E.	IC18-CT95-0410
Mbaye, A.	TS3*CT92-0126
Mc Lean, J.	ICA-17
McNeil, C.J.	AVI*CT93-0002
Mebrahtu, A.M.	TS3*CT92-0015
Mechergui, M.	AVI*CT93-0009
Megier, J.	IC18-CT97-0155
Mejdeddine Kraiem, M.	IC18-CT96-0029
Mellor, P.	TS3*CT92-0151
Menenti, M.	TS3*CT92-0061
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Meric, E.	AVI*CT92-0007
Merzouk, A.	IC18-CT96-0091
Messad, D.	AVI2-CT93-083
Meyer, F.	CII*CT91-0931
Micallef, A.	AVI*CT92-0015
Micallef, J.	ICA-17
Michaelidou, S.C.	AVI*CT92-0004
Michelozzi, M.	IC18-CT97-0200
Michel, B.	AVI2-CT93-099
Mignani, A.	IC18-CT97-0171
Millot, C.	AVI*CT93-0003
Mine, P.	CII*CT93-0312
Mirelman, D.	AVI*CT93-0008
Mlika, M.	IC18-CT98-0310
Moawad, H.	IC18-CT98-0313
Mokhtari, A.	AVI*CT92-0011
Mokssit, A.	AVI*CT93-0010
Mol, J.N.V.	CII*CT93-0074
Moletta, R.	AVI*CT94-0011
Monteiro Teixeira, J.L.	AVI*CT93-0009
Monteuuis, O.	TS3*CT94-0278
Moreno, J.	IC18-CT97-0154
Moreno-Lucas, F.	IC18-CT96-0091
Morgana, B.	IC18-CT98-0289
Mortier, L.	AVI*CT93-0003
Mosbaek, H.	AVI2-CT93-112
Moser, J.G.	CII*CT94-0126
Motosh, N.	IC18-CT95-0895

Mottaleb, A.	CII*CT93-0070
Moua'Zen, M.	IC18-CT98-0386
Moulla, A.	AVI*CT93-0015
Moumni, Y.	IC18-CT97-0134
Mounir, L.	IC18-CT96-0064
Mousain, D.	IC18-CT97-0197
Moussa, H. B.	IC18-CT98-0270
Moussaria, H.	AVI2-CT93-126
Mueller, W-R.	IC18-CT97-0167
Muguruza, I.	AVI*CT94-0013
Müller, W.E.G.	AVI*CT93-0001
	IC18-CT96-0034
Muñoz, A.H.	AVI*CT94-0015
Murli, A.	IC18-CT95-1139
Muszkat, L.	AVI2-CT93-074
Nadifi, S.	AVI*CT93-0014
Nafa, K.	TS3*CT93-0244
Narkis, N.	AVI2-CT93-092
Nassiopoulos, A.	IC18-CT95-0507
Nasr, H.	IC18-CT97-0197
Nativ, R.	AVI2-CT93-072
Neiland, A.	IC18-CT96-0064
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Neis, U.	AVI2-CT93-076
Neskakis, A.	IC18-CT96-0099
Nesme, X.	IC18-CT97-0198
Newton, C.	IC18-CT98-0311
Nicolaidis, A.	CII*CT94-0122
Nigim, K.A.	AVI*CT94-0004
Nitayarumphong, S.	IC18-CT98-0346
Njock, J. C.	IC18-CT98-0331
Nychas, S.G.	AVI*CT92-0017
Nzingoula, S.	TS3*CT92-0144
Oppenheim, A.	CII*CT94-0097
Orecchia, P.	AVI*CT92-0001
Oron, G.	AVI2-CT93-076
Orthofer, R.	IC18-CT97-0161
Ortiz Uribe, I.	AVI*CT94-0014
Ortiz, S.E.	AVI*CT94-0014
Oskam, L.	IC18-CT95-0023
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Othman, K.	TS3*CT93-0249
Ouassini, A.	IC18-CT98-0167
Ouassou, A.	IC18-CT97-0200
Ouazar, D.	AVI*CT93-143
Ouessar, M.	IC18-CT98-0269
Oueslati, A.	AVI2-CT93-019
Oussaid, F.	TS3*CT92-0106
Oweis, T.Y.	AVI2-CT93-080
Ozer, A. M.	IC18-CT98-0386
Ozbek, H.	IC18-CT98-0392
Özcel, A.	IC18-CT95-0023
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Ozturk, M.	IC18-CT97-0153

Paggi, L.	AVI*CT92-0001
Paiva, M.R.	TS3*CT93-0249
Paloscia, S.	IC18-CT97-0154
Papadopoulos, I.	AVI*CT94-0002
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Paperna, I.	AVI*CT92-0001
Paschaloudis, D.	IC18-CT96-0039
Patrick, S.	IC18-CT96-0029
Paul, R.	AVI*CT93-0007
Pavoni, B.	AVI2-CT93-087
Pearce, D.	KIT Nr. 12
Pease, C.	IC18-CT95-0905
Peduto, P.	IC18-CT98-0386
Pekmezci, M.	IC18-CT97-0177
Peleg, S.	EC-ISR-93003
Penzkofer, A.	CH1*CT89-0442
Pereira, L. S.	IC18-CT97-0169
Perry, C.C.	AVI*CT92-0012
Peter, L.	CH1*CT93-0070
Petrini, V.	IC18-CT98-0385
Pichat, P.	IC18-CT98-0267
Pinto de Lemos, E.E.	TS3*CT93-0221
Plomion, C.	IC18-CT97-0200
Preston, P.	IC18-CT95-0009
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Priefer, U. B.	IC18-CT98-0313
Prieto, M.R.	IC18-CT96-0069
Pritschow, G.	KIT Nr. 204
Protogeropoulos, C.	AVI*CT94-0004
Puglia, A. P.	IC18-CT98-0300
Quazar, D.	IC18-CT97-0154
Quelhas Dos Santos, J.	AVI*CT94-0002
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Quensiere, J.	IC18-CT98-0331
Quesada, A.	IC18-CT98-0293
Qunzhu, Z.	IC18-CT96-0069
Rafiq, M.	AVI*CT92-0014
Ragab, R.	IC18-CT96-0091
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Ragaie, H.F.	CH1*CT93-0070
Rahimy, C.	TS3*CT93-0244
Ramdani, M.	IC18-CT96-0029
Ramzy, R.	AVI*CT94-0001
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Rayyan, F.	AVI2-CT93-112
Razum, O.	AVI*CT93-0012
	IC18-CT98-0352
Ready, P.D.	TS3*CT93-0253
Rebella, C.M.	IC18-CT96-0069
Reichert, B.	AVI2-CT93-072
Remon, J.P.	CH1*CT94-0779
Reoulengar, G.	TS3*CT92-0112
Reysoo, F.	AVI*CT93-0013

Reysoo, H.P.	AVI*CT93-0013
Rietbrock, C.	ITDC 204-82166
Rinkevich, B.	AVI*CT93-0001
Rinkevich, B.	IC18-CT96-0034
Rishpon, J.	AVI*CT93-0002
Rodrigues Junior, C.J.	TS3*CT93-0221
Roig, B.J.	AVI*CT92-0009
Romana, J.	AVI2-CT93-126
Romana, L.A.	AVI2-CT93-087
Romano, D.	IC18-CT98-0268
Römheld, V.	CII*CT93-0006
Ronsmans, C.	IC18-CT98-0349
Rosenthal, H.	AVI2-CT93-123
Rosenwaks, S.	CII*CT94-0096
Rosier, J.	IC18-CT98-0384
Rossi, G.	IC18-CT97-0169
Rubinstein, A.	CII*CT94-0131
Ruppel, A.	AVI*CT94-0001
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Rusen, K.	IC18-CT98-0268
Sbay, H.	IC18-CT97-0200
Sadananda, R.	IC18-CT95-0809
Sadiki, M.	IC18-CT96-0081
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Safi, M.	AVI*CT94-0015
Sagiv, Y.	EC-ISR 90
Sahnoun, H.	IC18-CT97-0155
Sala, M.	IC18-CT97-0147
Salameh, E.	AVI2-CT93-080
	IC18-CT97-0143
Salch, F.	AVI*CT94-0007
Salgot De Marçay, M.	AVI2-CT93-076
Sall, P.N.	TS3*CT92-0047
Salleh, M.	IC18-CT98-0333
Salleo, S.	IC18-CT97-0153
Salomon, Y.	CII*CT94-0126
Salomons, W.	AVI*CT92-0016
Sammari, C.	AVI*CT93-0003
Samsunlu, A.	AVI*CT94-0015
San Roman, E.A.	IC18-CT96-0076
Sandini, G.	EC-ISR-93003
Sansur, M.	IC18-CT96-0036
Santiago, C.	IC18-CT98-0333
Sanchez Viesca, A. F.	IC18-CT98-0346
Sardo, V.	IC18-CT96-0055
Saubion, C.	AVI2-CT93-054
Sauthoff, G.	CII*CT93-0311
Savage, M.	IC18-CT97-0161
Savoure, A.	IC18-CT97-0200
Sayadi, S.	CII*CT92-0104
Sayed, S.	AVI*CT93-0013
Sayin, F.	TS3*CT92-0143
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Scapini, F.	IC18-CT98-0270

Scheer, H.	CI1*CT94-0126
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Wolftrum, J	CI1*CT94-0096
Xanthoulis, D.	AVI*CT94-0002
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Zodiatis, G.	AVI*CT92-0016
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ALGERIA

Agence Nationale Architecturale Sites et Monuments	IC18-CT98-0386
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Centre de Développement des Matériaux	AVI*CT92-0014
Centre de Développement des Techniques Nucléaires	AVI*CT93-0015
Centre de Développement des Techniques Nucléaires	AVI2-CT93-087
Centre de Développement des Technologies Avancées	AVI*CT92-0011
Centre Hospitalo-Universitaire Mustapha	TS3*CT93-0244
Ecole Nationale Polytechnique d'Alger	AVI2-CT93-081
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Hopital Parnet	AVI*CT92-0010
Hopital Parnet	AVI*CT92-0013
INRF	IC18-CT97-0200
Institut Algérien du Pétrole	AVI*CT94-0007
Institut National des Hydrocarbures & de la Chimie	AVI2-CT93-083
Institut National des Sciences de la Mer	AVI*CT93-0003
Institut National Agronomique	IC18-CT98-0300
Ministère de la Santé	TS3*CT92-0144
Office National de la Météorologie	AVI*CT93-0010
Société Algérienne de Canalisation d'Ouvrages et Charpentes	AVI2-CT93-081
Université de Constantine	CI1*CT93-0070
Université de Constantine	AVI*CT93-0007
Université des Sciences et de la Technologie Houari Boumediene	AVI*CT92-0014
Université des Sciences et Techniques Blida	TS3*CT94-0264
Université des Sciences et Techniques Blida	IC18-CT98-0390
Université de Tlemcen	AVI*CT93-0011

AUSTRIA

Environmental Software and Services	IC18-CT95-0809
University of Technology	CI1*CT93-0362

BELGIUM

Faculté des Sciences Agronomiques de Gembloux	AVI*CT93-0007
Faculté des Sciences Agronomiques de Gembloux	TS3*CT92-0126
Faculté des Sciences Agronomiques de Gembloux	AVI*CT94-0002
Faculté des Sciences Agronomiques de Gembloux	IC18-CT98-0272
Faculté Polytechnique de Mons	IC18-CT98-0385
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IMEC	ICA-17
Katholieke Universiteit Leuven	EC-ISR 90
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Universiteit Gent	CII*CT94-0779
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Université Libre de Bruxelles	CII*CT94-0105
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Universidade de Rio de Janeiro	IC18-CT98-0293
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CAMEROON

Ministere de L'Elevage, des Pêches et des Industries Animales	IC18-CT98-0331
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Chinese Academy of Agricultural Sciences	IC18-CT98-0391

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Agricultural Research Institute	AVI*CT94-0002
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Cyprus Institute of Neurology and Genetics	CII*CT94-0122
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DENMARK

Aalborg University
Danish Bilharziosis Laboratory
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Agricultural Genetic Engineering Research Institute
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Atomic Energy Authority
Central Laboratory for Food and Feed
Climate Water and Environment Research
Coastal Research Institute
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Drainage Research Institute
Egyptian Consulting and Trading Co
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Electronic Research Institute
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El-Hussein University Hospital
El Minia University
Environmental Quality International
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Université de Bordeaux I	IC18-CT98-0386
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Université de Nice - Sophia Antipolis	AVI2-CT93-099
Université de Limoges	IC18-CT98-0384
Université de Paris VII	IC18-CT95-0905
Université Paris XI	CII*CT91-0931
Université de Paris-Sud XI	TS3*CT94-0264
Université de Paris-Sud XI	IC18-CT98-0390
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Université de Provence	CII*CT92-0104
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Biologische Bundesanstalt für Land- und Forstwirtschaft	IC18-CT96-0121
Bomin Solar Research GmbH	AVI*CT94-0013
Bomin Solar Research GmbH	IC18-CT98-0267
Centrum Neue Technologien	AVI*CT94-0006
Deutsche Forschungsanstalt für Luft- und Raumfahrt e.V.	AVI*CT94-0013
DFKI - Compulog-Net	KIT Nr 12
Eberhard-Karls-Universität Tübingen	AVI*CT93-0008
European Molecular Biology Laboratory	CI1*CT94-0097
Fachhochschule Aachen	IC18-CT96-0099
Federal Institute for Materials Research & Testing	CI1*CT93-0065
Forschungsinstitut für Wasser und Abfallwirtschaft	AVI*CT94-0015
Forschungsinstitut Borstel	IC18-CT95-0004
Forschungszentrum	CI1*CT94-0125
Forschungszentrum Borstel	IC18-CT95-0009
Fraunhofer Institut IAF	CI1*CT92-0063
Fraunhofer Institut für Physikalische Messtechnik	CI1*CT93-0362
Fraunhofer Institut für Toxikologie und Aerosolforschung	AVI*CT92-0004
German Aerospace Research Establishment	AVI*CT94-0004
GTZ	TS3*CT92-0112
Hovelmann & Bidinger	IC18-CT96-0099
Institut für Kybernetik und Systemtheorie	EC-MED-35
Institut für Solarenergieforschung GmbH	AVI*CT94-0007
	IC18-CT98-0267
Institut für Wasser-, Boden- und Lufthygiene	AVI*CT92-0006
IT consult GmbH	IC18-CT95-0410
Johannes Gutenberg-Universität	AVI*CT93-0001
Johannes Gutenberg-Universität	IC18-CT96-0034
Max-Born-Institut für Nichtlineare Optik & Kurzzeitspektroskopie	CI1*CT94-0126
Max Planck Institut	IC18-CT96-0076
Max Planck Institut for Iron Research	CI1*CT93-0311
Max Planck Institut für Hirnforschung	CI1*CT94-0130
Parsytec Computer GmbH	ITDC 204-82166
Parsytec Computer GmbH	IC18-CT95-0895
Rheinisch-Westfälische Technische Hochschule Aachen	IC18-CT96-0099
Rheinisch-Westfälische Technische Hochschule Aachen	IC18-CT98-0313
Rheinisch-Westfälische Technische Hochschule Aachen	IC18-CT98-0384
Ruprecht-Karls-Universität Heidelberg	AVI*CT93-0012
Ruprecht-Karls-Universität Heidelberg	AVI*CT94-0001
Ruprecht-Karls-Universität Heidelberg	IC18-CT98-0352
Ruprecht-Karls-Universität Heidelberg	IC18-CT98-0367
Ruhr-Universität Bochum	CI1*CT94-0085
Technische Hochschule Darmstadt	CI1*CT90-0542
Technical University of Berlin	CI1*CT94-0108
Technische Universität Clausthal	AVI*CT94-0007
Technische Universität Clausthal	IC18-CT98-0267
Technische Universität Hamburg-Harburg	AVI2-CT93-076
Technische Universität Hamburg-Harburg	AVI*CT92-0016
Tieraerztliche Hochschule Hannover	IC18-CT96-0055
Türkisch-Deutsche Gesundheitsstiftung E.V.	AVI*CT93-0012
Türkisch-Deutsche Gesundheitsstiftung E.V.	IC18-CT98-0352
Universität Bremen	AVI2-CT93-074
Universität der Bundeswehr München	AVI*CT94-0004

Universität des Saarlandes	IC18-CT95-0905
Universität Düsseldorf	CI1*CT94-0126
Universität Goettingen	IC18-CT96-0035
Universität Goettingen	IC18-CT97-0186
Universität Hamburg	TS3*CT93-0249
Universität Hannover	TS3*CT93-0249
Universität Heidelberg	CI1*CT94-0096
Universität Hohenheim	TS3*CT92-0015
Universität Hohenheim	CI1*CT93-0006
Universität Hohenheim	TS3*CT93-0249
Universität Hohenheim	IC18-CT98-0333
Universität Karlsruhe	AVI2-CT93-072
Universität Karlsruhe	IC18-CT97-0167
Universität Kiel	AVI2-CT93-123
Universität München	CI1*CT94-0126
Universität Osnabrück	IC18-CT96-0055
Universität Regensburg	CI1*CT89-0442
Universität Stuttgart	KIT Nr 204
Universität Stuttgart	AVI*CT94-0005
Universität Stuttgart	IC18-CT97-0167
Universität Tübingen	CI1*CT94-0106
Universität Tübingen	CI1*CT93-0066
Universität Wurzburg	IC18-CT97-0143

GREECE

Agricultural University of Athens	AVI*CT94-0002
Agricultural University of Athens	IC18-CT98-0272
Aristotle University of Thessaloniki	AVI*CT92-0017
Aristotle University of Thessaloniki	IC18-CT96-0039
Aristotle University of Thessaloniki	IC18-CT98-0392
Aristotle University of Thessaloniki	IC18-CT98-0354
Centre for Renewable Energy Sources	AVI*CT94-0004
DEMOKRITOS National Centre for Research	IC18-CT98-0386
Dimman Consulting Ltd	IC18-CT96-0039
Engineering & Computer Applications S.A.	AVI*CT94-0006
Epsilon International S.A.	AVI*CT93-0006
Institute of Marine Biology of Crete	AVI*CT92-0001
Institute of Ghania	IC18-CT97-0153
Institute of Microelectronics	IC18-CT95-0507
Intelltech S.A.	IC18-CT95-0410
National & Kapodistrian University of Athens	AVI*CT92-0005
National Foundation Agricultural Research	AVI2-CT93-076
National Foundation Agricultural Research	IC18-CT98-0272
National Technical University of Athens	IC18-CT95-0895
National Technical University of Athens	AVI*CT93-0006
National Technical University of Athens	AVI2-CT93-062
National Technical University of Athens	IC18-CT97-0138
National Technical University of Athens	IC18-CT97-0163
National Technical University of Athens	IC18-CT98-0385
Onassis Cardiac Surgery Centre	CI1*CT94-0122
Research and Development	TS3*CT92-0119
Technological Education Institute	IC18-CT96-0099
University of Crete	AVI2-CT93-092
University of Patras	AVI*CT92-0016
University of the Aegean	IC18-CT96-0055
University of the Aegean	IC18-CT98-0268

Hebrew University of Jerusalem	CII*CT94-0097
Hebrew University of Jerusalem	IC18-CT95-0023
Hebrew University of Jerusalem	EC-ISR-93003
Hebrew University of Jerusalem	CII*CT93-2027
Hebrew University of Jerusalem	AVI*CT92-0005
Hebrew University of Jerusalem	CII*CT94-0131
Hebrew University of Jerusalem	IC18-CT98-0354
Hebrew University of Jerusalem	IC18-CT97-0186
Hebrew University of Jerusalem	IC18-CT97-0200
Hebrew University of Jerusalem	IC18-CT97-0142
Hebrew University of Jerusalem	IC18-CT98-0272
Israel Oceanographic & Limnological Research	AVI*CT92-0016
Israel Oceanographic & Limnological Research	AVI2-CT93-123
Israel Oceanographic & Limnological Research	IC18-CT98-0293
Migal-Galilee Technological Center	CII*CT94-0086
National Institute of Oceanography	IC18-CT96-0034
National Institute of Oceanography	AVI*CT93-0001
Technion-Israel Institute for Technology	CII*CT89-0442
Technion-Israel Institute for Technology	CII*CT91-0907
Technion-Israel Institute of Technology	CII*CT91-0927
Technion-Israel Institute of Technology	CII*CT93-0311
Technion-Israel Institute for Technology	CII*CT91-0931
Technion-Israel Institute of Technology	AVI2-CT93-092
Technion-Israel Institute of Technology	AVI*CT94-0011
Technion-Israel Institute of Technology	EC-ISR-93003
Technion-Israel Institute of Technology	IC18-CT95-1139
Technion-Israel Institute of Technology	IC18-CT96-0099
Technion-Israel Institute of Technology	CII*CT93-0065
Technion-Israel Institute of Technology	IC18-CT97-0202
Technion-Israel Institute of Technology	CII*CT92-0063
Technion-Solid State Institute	CII*CT94-0122
Tel Aviv University	IC18-CT95-0895
Tel Aviv University	AVI*CT92-0009
Tel Aviv University	EC-ISR-93003
Tel Aviv University	CII*CT91-0923
Tel Aviv University	CII*CT93-0362
Tel Aviv University	AVI*CT93-0002
Tel Aviv University	CII*CT94-0083
Tel Aviv University	CII*CT93-0005
Tel Aviv University	AVI*CT92-0007
Tel Aviv University	IC18-CT97-0171
Tel Aviv University	IC18-CT96-0122
The Institute for Petroleum Research & Geophysics	AVI2-CT93-074
The Volcani Center	AVI*CT92-0006
The Volcani Center	EC-ISR-93003
The Weizmann Institute of Science	CII*CT94-0126
The Weizmann Institute of Science	CII*CT94-0126
The Weizmann Institute of Science	AVI*CT92-0004
The Weizmann Institute of Science	AVI*CT94-0008
The Weizmann Institute of Science	CII*CT93-0003
The Weizmann Institute of Science	AVI*CT93-0008
The Weizmann Institute of Science	CII*CT94-0130
The Weizmann Institute of Science	CII*CT94-0108
The Weizmann Institute of Science	CII*CT91-0932
The Weizmann Institute of Science	CII*CT94-0087
The Weizmann Institute of Science	CII*CT94-0105
The Weizmann Institute of Science	CII*CT93-0004
The Weizmann Institute of Science	CII*CT93-0312

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The Weizmann Institute of Science
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The Weizmann Institute of Science

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CII*CT93-0065
AVI*CT92-0012
IC18-CT98-0391

ITALY

Istituto de Agrometeorologia e Analisi	IC18-CT97-0155
Beta Studio S.R.L.	AVI*CT93-0006
Centro Ricerche sur Calcolo Parallelo e Supercalcolatori	IC18-CT95-1139
CERFE	AVI2-CT93-020
Community of Mediterranean Universities	AVI*CT94-0010
Conphoebus Campo Prove	IC18-CT96-0039
CONPHOEBUS Istituto di Ricerche per le Energie Rinnovabili	IC18-CT98-0289
Consiglio Nazionale delle Ricerche	AVI*CT93-0003
Consiglio Nazionale delle Ricerche	IC18-CT98-0289
Joint Research Centre	IC18-CT97-0161
IROE-CNR	IC18-CT97-0171
Institut Agronomique Mediterranéen de Bari	IC18-CT96-0055
Istituto Centrale per la Ricerca Scientifica e Tecnologica Applicata al Mare	AVI2-CT93-087
Institute d'Appolonia S.P.A.	AVI2-CT93-099
Istituto Internazionale de Genetica e Biofisica	TS3*CT92-0096
Istituto per l'Infanzi	AVI*CT94-0003
Istituto per l'Infanzi	IC18-CT98-0349
Istituto Sperimentale Italiano "L. Spallanzani"	TS3*CT92-0119
Politecnico di Milano	IC18-CT95-0809
CÓNISMA	IC18-CT98-0270
Istituto di Ricerca sulle Ondi Elettromagnetichi	IC18-CT97-0154
Istituto Sperimentale per la Patologia Vegetale	IC18-CT98-0300
Istituto di Ricerca sul Rischio Sismico	IC18-CT98-0385
Intern Centre for Preservation	IC18-CT98-0384
Società di Ricerca e Servizi di Ingegneria	AVI2-CT93-091
Studio Sardo di Catania	IC18-CT96-0055
Universita degli studi della Tuscia	TS3*CT92-0047
Universita degli studi de Trieste	IC18-CT97-0153
Universita degli studi di Ancona	CII*CT93-0311
Universita degli studi di Bologna	IC18-CT98-0311
Universita degli studi di Firenze	IC18-CT98-0268
Universita degli studi di Milano	AVI*CT92-0007
Universita degli studi di Padova	IC18-CT96-0076
Universita degli studi di Padova	IC18-CT96-0069
Universita degli studi di Roma "La Sapienza"	AVI*CT92-0001
Universita degli studi di Roma "La Sapienza"	AVI2-CT93-107
Universita degli studi di Roma "Tor Vergata"	AVI*CT92-0001
Universita degli studi di Torino	IC18-CT96-0035
Universita della Calabria	IC18-CT95-1139
Universita di Cagliari	AVI2-CT93-073
Universita de Catania	IC18-CT97-0169
Universita di Napoli	IC18-CT95-1139
Universita di Pisa	EC-ISR 90
Universita di Pisa	IC18-CT98-0310
Universita di Sassari	IC18-CT98-0268
Universita di Udine	EC-ISR 90
Universita di Venezia	AVI2-CT93-087
Universita di Venezia	AVI*CT94-0011
University of Bergamo	IC18-CT95-1139
University of Cagliari	AVI*CT92-0002

University of Genova
University of Genova
University of Salerno

AVI2-CT93-080
EC-ISR-93003
IC18-CT98-0386

IVORY COAST

Centre Hospitalier Universitaire de Yopougon

IC18-CT98-CT98-
0349

JORDAN

Al Al-Bayt University
CEHA-WHO
Family Health Group
Jordan University of Science & Technology
Ministry of Water and Irrigation
Ministry of Water and Irrigation
Ministry of Water and Irrigation
Renewable Energy Research Centre
Royal Scientific Society Jordan
Royal Scientific Society Jordan
Royal Scientific Society Jordan
University of Jordan
University of Jordan
University of Jordan
University of Jordan
University of Jordan
University of Jordan
University of Jordan
University of Jordan
University of Jordan
Yarmouk University

IC18-CT95-0895
AVI*CT94-0009
AVI*CT94-0003
AVI*CT94-0003
AVI*CT93-0005
AVI*CT94-0012
IC18-CT97-0136
AVI*CT94-0004
IC18-CT96-0039
IC18-CT96-0099
IC18-CT98-0289
AVI2-CT93-020
AVI2-CT93-080
AVI2-CT93-112
AVI*CT94-0009
AVI*CT94-0003
IC18-CT98-0385
IC18-CT97-0143
IC18-CT97-0163
IC18-CT97-0169
IC18-CT98-0354

LEBANON

American University of Beirut
American University of Beirut
American University of Beirut
American University of Beirut
American University of Beirut
American University of Beirut
American University of Beirut
Conseil et Développement
Centre for Remote Sensing
Integro Middle East
Lebanese University – Ministry of Public Health

IC18-CT96-0036
AVI*CT94-0003
AVI*CT93-0012
AVI*CT94-0003
IC18-CT98-0352
IC18-CT97-0177
IC18-CT97-0136
IC18-CT97-0142
IC18-CT97-0161
IC18-CT95-0175
IC18-CT97-0153

MALAYSIA

University Putra Malaysia

IC18-CT98-0333

MALTA

Malta Council for Science & Technology
Euro-Mediterranean Centre in Marine Contamination Hazards
University of Malta

AVI*CT92-0015
AVI*CT92-0015
AVI*CT94-0010

Institut National d'Administration Sanitaire	TS3*CT92-0112
Institut National d'Administration Sanitaire	TS3*CT92-0144
Institut National d'Administration Sanitaire	AVI*CT93-0011
Institut National d'Administration Sanitaire	IC18-CT98-0349
Institut Pasteur	TS3*CT92-0096
Institut Pasteur	AVI*CT93-0014
Institut Pasteur	AVI2-CT93-107
Maroc-Météo	AVI*CT93-0010
Ministère de la Culture	IC18-CT98-0385
Ministry of Public Health	IC18-CT98-0346
Ministère de l'Agriculture et de la Mise en Valeur Agricole	TS3*CT92-0151
Office National de l'Eau Potable	AVI2-CT93-020
Office National de l'Eau Potable	IC18-CT97-0267
Université Abdelmalek Essaadi	AVI*CT94-0011
Université Abdelmalek Essaadi	AVI2-CT93-054
Université Abdelmalek Essaadi	IC18-CT97-0167
Université Cadi Ayyad	TS3*CT93-0249
Université Cadi Ayyad	IC18-CT98-0390
Université Cadi Ayyad	IC18-CT98-0384
Université de Fes	AVI*CT92-0014
Université de Kenitra	AVI2-CT93-081
Université Ibnou Zohr Agadir	IC18-CT98-0269
Université Mohammed I	AVI2-CT93-073
Université Mohammed I	ITDC-94-201-82164
Université Mohammed V	IC18-CT96-0029
Université Mohammed V	TS3*CT94-0278
Université Mohammed V	TS3*CT93-0208
Université Mohammed V	IC18-CT97-0147
Université Mohammed V	IC18-CT98-0270
Université Mohammed V	IC18-CT97-0134
Université Mohammed V	IC18-CT97-0154
Université Mohammed V	IC18-CT98-0313
Université Moulay Ismail	IC18-CT98-0293

MOZAMBIQUE

Centro de Investigacao para a Saude & Desenvolvimento	IC18-CT98-0346
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NIGERIA

National Institute of Freshwater Fisheries Research	IC18-CT98-0331
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NORWAY

University of Bergen	IC18-CT96-0029
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PHILIPPINES

Southeast Asian Fisheries Development Centre	IC18-CT98-0333
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PORTUGAL

Associação Terras Dentro	IC18-CT98-0268
AquaAmbiente S.A.	AVI*CT94-0015
Electricidade de Portugal	IC18-CT96-0039
Geografica Lda	AVI2-CT93-126

Instituto de Higiene e Medicina Tropical	AVI*CT92-0003
Instituto de Higiene e Medicina Tropical	TS3*CT93-0253
Instituto de Investigação Científica Tropical Quinta do Marqués	TS3*CT93-0221
Instituto Nacional de Saúde	TS3*CT92-0106
Instituto Investigação Científica Tropical	IC18-CT98-0384
Instituto Superior de Agronomia	AVI*CT94-0002
Instituto Superior de Agronomia	TS3*CT92-0126
Instituto Superior Técnico	CII*CT91-0923
Laboratorio Nacional de Engenharia Civil	AVI*CT94-0012
Laboratorio Nacional de Engenharia Civil	IC18-CT97-0136
Universidade da Madeira	TS3*CT92-0151
Universidade de Lisboa	IC18-CT96-0055
Universidade de Lisboa	TS3*CT92-0151
Universidade Nova de Lisboa	IC18-CT95-0009
Universidade Nova de Lisboa	TS3*CT93-0249
Universidade Nova de Lisboa	IC18-CT95-0023
Universidade Nova de Lisboa	IC18-CT97-0169
Universidade Nova de Lisboa	IC18-CT98-0346
Universidade do Algarve	AVI2-CT93-076
Universidade do Algarve	AVI2-CT93-008
Universidade do Algarve	IC18-CT98-0266
Universidade Technica de Lisboa	AVI*CT93-0009
Universidade de Aveiro	IC18-CT97-0147
Universidade de Coimbra	IC18-CT98-0270
Universidade de Coimbra	IC18-CT98-0392

SPAIN

Asociacion Centro Tecnologico	AVI*CT94-0013
Centro International Agronomicos Mediterraneo	IC18-CT97-0197
Centro de Investigaciones Biologicas	CII*CT94-0083
Centro de Investigaciones Energeticas Medioambientales y Tecnologicas	AVI*CT94-0013
Centro de Investigaciones Energeticas Medioambientales y Tecnologicas	IC18-CT98-0289
	IC18-CT97-0163
CIEMAT	AVI*CT94-0004
CIDA	IC18-CT98-0390
Consejo Superior de Investigaciones Cientificas	IC18-CT96-0091
Consejo Superior de Investigaciones Cientificas	IC18-CT98-0266
Consejo Superior de Investigaciones Cientificas	IC18-CT98-0392
Consejo Superior de Investigaciones Cientificas	IC18-CT98-0301
Dpt de Ordination del Territorio Urbanismo y Medio Ambiente Caminos Canales y Puertos	AVI*CT94-0015
Escuela Andaluza de Salud Publica	TS3*CT92-0088
Estacion Experimental "La Mayora"	AVI2-CT93-008
Estacion Experimental de Zonas Aridas	IC18-CT97-0134
Infocarta S.A.	AVI2-CT93-126
Instituto de Maquina Herramienta	AVI*CT94-0013
Instituto de Nutrición y Bromatología	TS3*CT94-0282
Institute for Prospective Technology	IC18-CT98-0289
Instituto de Salud Carlos III	AVI*CT92-0013
Instituto Nacional Reforma y Desarrollo Agrario	TS3*CT92-0061
Instituto Tecnologico de Canarias	IC18-CT96-0099
Instituto Valenciano de Investigaciones Agrarias	IC18-CT96-0082
Instituto Valenciano de Investigaciones Agrarias	IC18-CT98-0310
Instituto Zaragoza Agronomico	IC18-CT98-0310
Son Dureta Hospital	AVI*CT92-0009
Universidad Autonoma de Barcelona	AVI*CT94-0008
Universidad Autonoma de Barcelona	IC18-CT96-0076

Universidad Autonoma de Barcelona	AVI*CT94-0010
Universidad Autonoma de Barcelona	IC18-CT97-0147
Universidad Autonoma de Barcelona	IC18-CT98-0384
Universidad Complutense de Madrid	CII*CT93-0066
Universidad Complutense de Madrid	AVI*CT92-0011
Universidad Complutense de Madrid	IC18-CT97-0147
Universidad Complutense de Madrid	IC18-CT98-0293
Universidad de Barcelona	AVI*CT94-0011
Universidad de Barcelona	CII*CT91-0907
Universidad de Barcelona	AVI2-CT93-076
Universidad de Barcelona	IC18-CT98-0384
Universidad de Cantabria	AVI*CT94-0014
Universidad de Extremadura	AVI2-CT93-126
Universidad de Extremadura	IC18-CT95-0009
Universidad de Granada	IC18-CT96-0081
Universidad de las Islas Baleares	IC18-CT96-0099
Universidad de Murcia	AVI*CT92-0010
Universidad de Santiago de Compostela	CII*CT94-0086
Universidad de Santiago de Compostela	TS3*CT92-0106
Universidad de Valencia	TS3*CT93-0208
Universidad de Valencia	IC18-CT97-0154
Universidad de Valencia	IC18-CT97-0177
Universidad de Valencia	IC18-CT98-0385
Universidad de Valladolid	AVI*CT94-0009
Universidad Politécnica de Madrid	EC-ISR 90

SWEDEN

Korolinska Institute	IC18-CT98-0346
Linköping University	EC-ISR-93003
Linköping University	IC18-CT95-0507
Lunds Universitet	IC18-CT96-0091
Royal Institute of Technology	EC-ISR-93003
UMEAA Universitet	IC18-CT98-0268

SWITZERLAND

University of Fribourg	IC18-CT98-0386
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SYRIA

Ministère de la Culture	IC18-CT98-0385
Arab Center for the Studies of Arid Zone and Dry Land	IC18-CT96-0091
Damascus University	AVI*CT94-0007
Damascus University	AVI*CT94-0003
GOSM	IC18-CT98-0308
Higher Institute of Applied Science and Technology	AVI2-CT93-112
International Center for Agricultural Research in the Dry Area	AVI2-CT93-080
International Center for Agricultural Research in the Dry Area	IC18-CT96-0121
International Center for Agricultural Research in the Dry Area	IC18-CT98-0301
Ministry of Agriculture & Agrarian Reform	IC18-CT98-0301
Musée National de Damas	IC18-CT98-0386

THAILANDE

Ministry of Public Health	IC18-CT98-0346
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THE NETHERLANDS

Cap Volmac B.V.	EC-MED-35
Erasmus Center for Financial Research	IC18-CT95-1139
Erasmus Universiteit Rotterdam	IC18-CT95-1139
Free University of Amsterdam	CII*CT92-0096
Free University of Amsterdam	CII*CT93-0074
Free University of Amsterdam	IC18-CT97-0134
Koninklijk Instituut voor de Tropen	AVI*CT92-0003
Institute for Soil Fertility Research	AVI*CT92-0016
International Reference Centre for Community Water	AVI2-CT93-020
Nederlands Instituut voor Onderzoek der Zee	IC18-CT96-0034
Nederlands Meetinstituut	TS3*CT92-0093
Netherlands Energy Research Foundation	AVI*CT94-0004
Prof. H.C. Van Hall Institute	AVI*CT93-0013
Rijks Geologische Dienst	IC18-CT96-0122
Royal Tropical Institute	IC18-CT95-0023
Synoptics	AVI*CT93-143
Technische Universiteit Eindhoven	AVI*CT94-0004
University of Leiden	CII*CT93-0069
University of Leiden	AVI*CT93-0004
Utrecht University	TS3*CT91-0019
Utrecht University	IC18-CT95-0003
Utrecht University	IC18-CT95-0009
Wageningen Agricultural University	AVI*CT94-0009
Wageningen Agricultural University	AVI*CT93-0004
Wageningen Agricultural University	CII*CT91-0932
Wageningen Agricultural University	CII*CT94-0086
Wageningen Agricultural University	AVI*CT93-0009
Wageningen Agricultural University	IC18-CT98-0269
Wageningen Agricultural University	IC18-CT97-0202
Wagner Advies B.V.	AVI*CT93-0013
Winand Staring Centre of Integrated Land Soil & Water Research	IC18-CT96-0069
Winand Staring Centre of Integrated Land Soil & Water Research	TS3*CT92-0061

TUNISIA

Agence pour la Maîtrise de l'Energie	IC18-CT98-0289
Centre de Biotechnologie de Sfax	CII*CT92-0104
Centre de Recherche du Génie Rural	IC18-CT96-0076
Centre National de l'Informatique	TEDIPP
Centre National de Télédétection	IC18-CT97-0155
Centre National de Télédétection	AVI*CT92-0008
Compagnie Minière du Nord Ouest	AVI2-CT93-019
Département Etudes et Développement	AVI2-CT93-126
Direction Générale de la Production Agricole	IC18-CT96-0081
Ecole Nationale d'Ingénieurs de Monastir	IC18-CT95-0363
Ecole Nationale d'Ingénieurs de Tunis	IC18-CT97-0154
Ecole Nationale d'Ingénieurs de Tunis	AVI*CT94-0015
Ecole Nationale de Médecine Vétérinaire	IC18-CT95-0003
Ecole Nationale de Médecine Vétérinaire	IC18-CT95-0004
Ecole Nationale de Médecine Vétérinaire	IC18-CT95-0009
Ecole Nationale de Médecine Vétérinaire	TS3*CT91-0019
Ecole Normale Supérieure de l'Enseignement Technique	AVI2-CT93-054
Ecole Supérieure d'Agriculture	TS3*CT92-0119
Ecole Supérieure des Ingénieurs de l'Équipement Rural	AVI*CT94-0002
Faculté des Sciences de Tunis	ITDC 135-82159

Faculté des Sciences de Tunis	IC18-CT98-0270
Faculté des Sciences de Tunis	IC18-CT98-0390
Faculté des Sciences de Tunis	TS3*CT94-0264
Institut Agronomique de Tunisie	AVI*CT93-0009
Institut des Régions Arides Medenine	TS3*CT92-0047
Institut des Régions Arides Medenine	IC18-CT98-0269
Institut des Régions Arides Medenine	IC18-CT97-0134
Institut National Agronomique de Tunisie	AVI2-CT93-073
Institut National Agronomique de Tunisie	IC18-CT98-0310
Institut National d'Agriculture de Tunisie	TS3*CT93-0208
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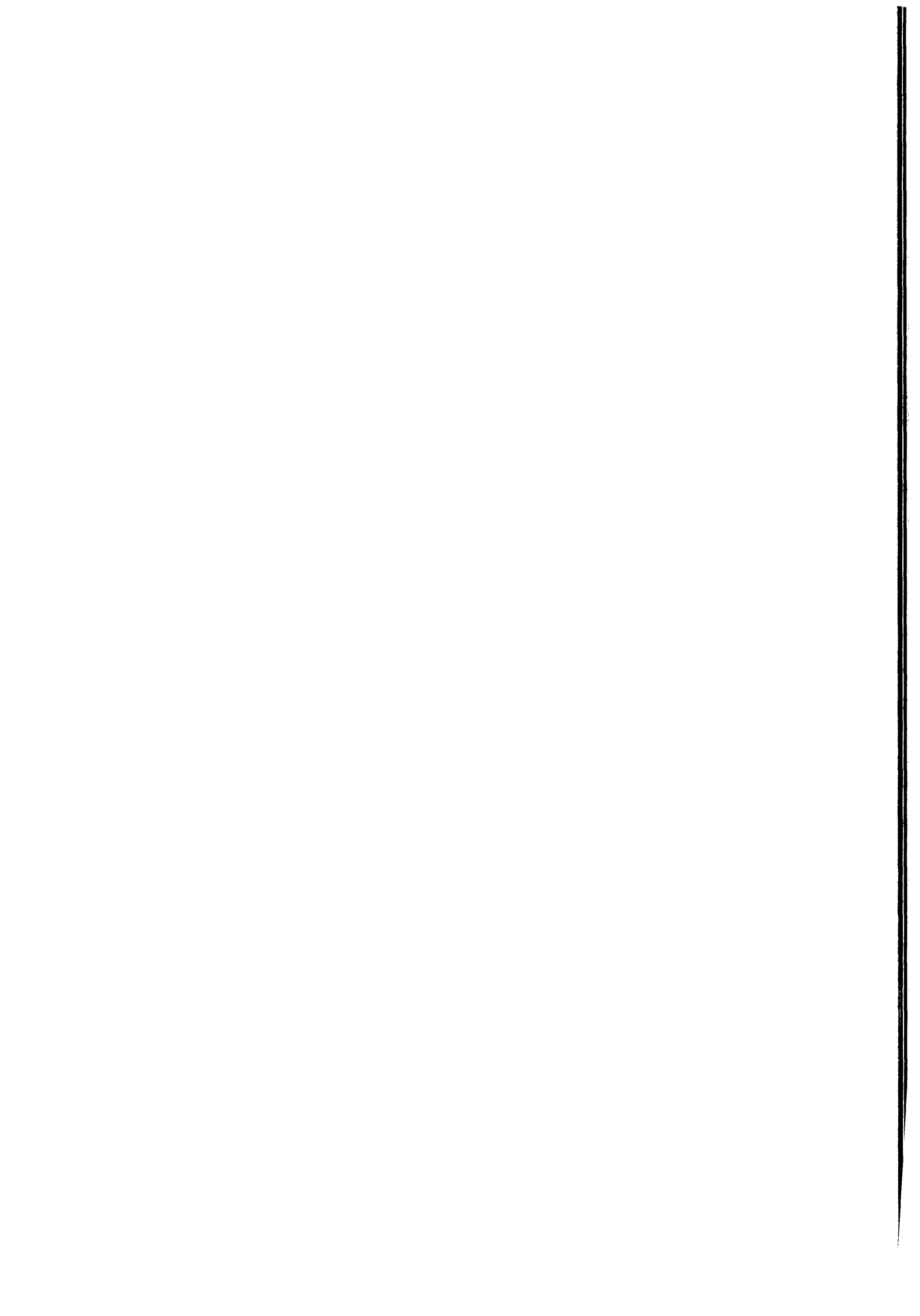
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**Euro-Mediterranean S&T Cooperation
Project Reports, edition 1998, volume 2**

Luxembourg: Office for Official Publications of the European Communities

1999 — 324 pp. — 21.0 x 29.7 cm

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