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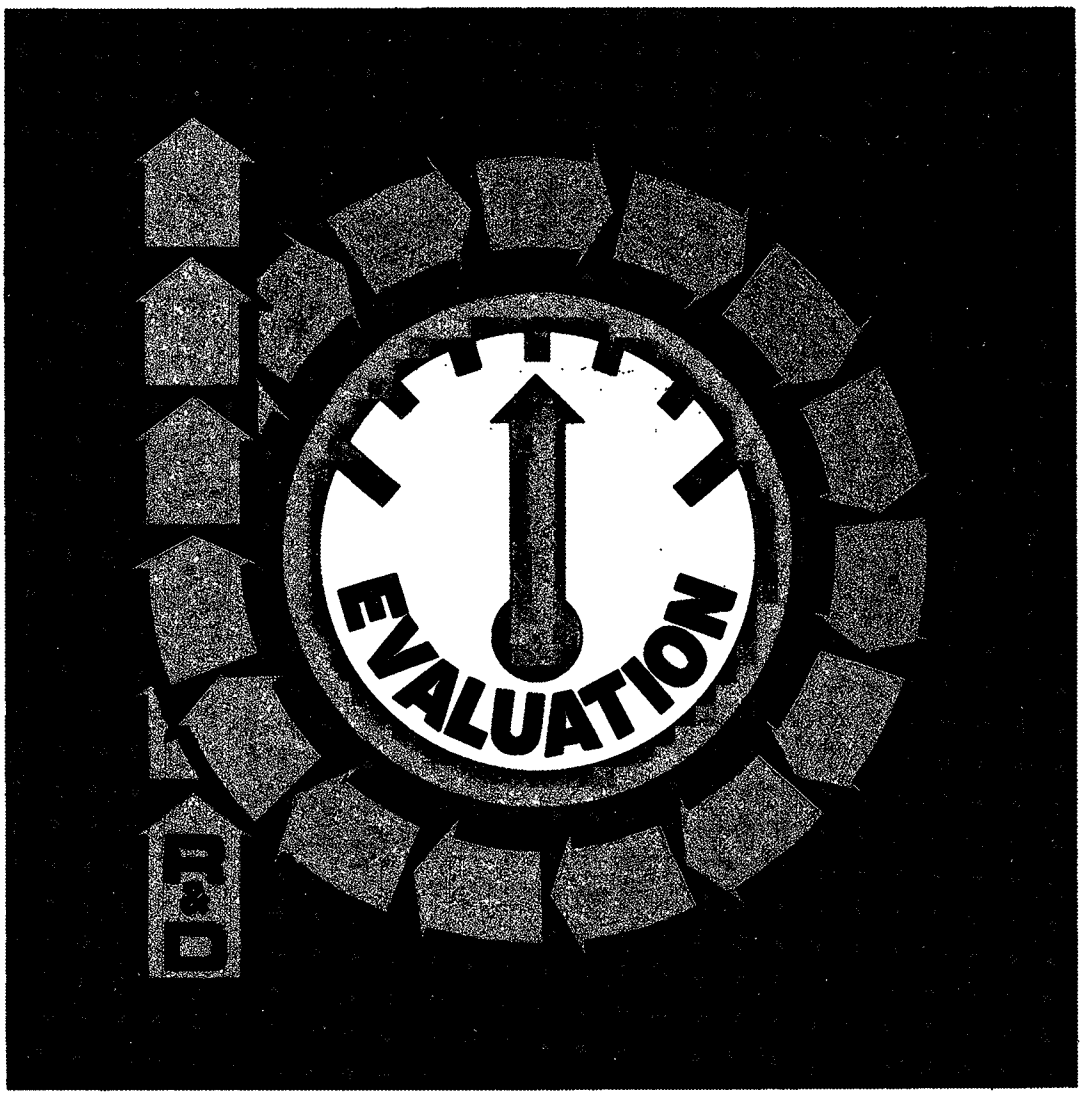
Evaluation of the Programme "Human Genome Analysis" (1990-1991)



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European Commission

Evaluation of the Programme "Human Genome Analysis" (1990-1991)

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EXECUTIVE SUMMARY

1. The Human Genome Analysis Programme (HGAP) is part of the Second Framework Programme of Community activities in research and technological development. This programme was set up under the heading "Health"of the "Quality of Life" section for:

   - using and improving new bioltechneogies in the study of the human genome for a better understanding of the mechanism of genetic functions as well as the prevention and treatment of human diseases;

   - developing an integrated approach to the ethical, social and legal aspects of possible applications of the results obtained.

2. As part of its regular evaluation exercise, the Commission appointed in December 1992 a panel of independent experts to carry out the evaluation of the HGAP. The authority for the Evaluation Panel is laid down in Article 4 (3) of the Council Decision adopting this programme (O.J. N° L196 of 29.6.1990,p.8). The same article specifies that the evaluation should be carried out having regard to the scientific and technical achievements of the programme, the quality and practical relevance of its results, the effectiveness of its management, its ethical, social and legal aspects, and its impact and benefits on national research programmes.
   In carrying out this evaluation the Panel visited four centres involved in the programme and interviewed over thirty people : Commission and national officials, participants in the HGAP and users.

3. The total funds committed to this programme were 15.6 MECU. The distribution of funds was as follows : Genetic Maps 21%, Physical Maps 27.6 %, Data Handling and Databases 15%, Advanced Genetic Technologies 18%, Training Activities 12 %, Administration 6.4%.

   HGAP involved approximately 100 EC institutes.

CONCLUSIONS

The panel finds that the HGAP has largely become a success and is an important driving force in the field of European human genome research. Genome research is, for the moment, advancing at an extremely rapid pace. In recent years the progress has been particularly striking in Europe, with the success of enterprises such as yeast whole-chromosome sequencing, whole genome physical maps and refined genetic maps. It is clear that HGAP has played an important role to establish a more balanced relationship with the US. It is, however, also clear that strong programs such as the one supported by AFM in France have been an important driving force. The HGAP was approved with a two year budget of 15.6 MECU. The amount of money devoted to genome research by the EC is very small compared to the budgets of the genome programs in the U.S. and Japan. The HGAP has therefore only supplemented ongoing national efforts and the weight of EC funding on individual programs greatly depends on the strength of the national programs. The EC has given very minor support to large French groups (less than 10%), while it has been quite

important for Great Britain, Germany, Italy and other European countries. The EC support would range from <5% to 50% of the total funding of each project. For the transnational projects, this kind of support can, in most cases, only have a modest impact and the potential for less well advanced countries to benefit from the transnational programs is limited.

The establishment of the resource centres, and training programs is of great help to organised scientific laboratories as well as less advanced ones or less established groups. This is a very important aspect of the HGAP and in general in today's science, since organisation and availability of resources are major issues. In this respect the HGAP has been very useful to the European genome research community, and this aspect should be stressed in the design of the future programs.

The cDNA program in the current HGAP has not developed as fast as was hoped although quite a number of partial cDNA sequences have been generated. There will clearly be a great need for large collections of high quality cDNA libraries in the future.

The ultimate goal of the global human genome project is the sequencing of the whole human genome. Large sequencing programs are presently not included in the HGAP. This situation should be rectified in a future HGAP.

The transnational projects have been of importance for promotion of European collaborations. They have also provided means for small laboratories, particularly in less developed countries to gain access to sophisticated technologies.

The fellowship program is a very essential component of the HGAP. It appears to have been implemented in a satisfactory way.

It was recognized that the activities undertaken within the ESLA program had justification. However, the evaluation panel debated whether the program should be financed to the same extent as done in the past simply because there are limited resources and many pressing questions to be investigated.
The already completed ESLA program can be regarded as a promising pilot study. The panel woulld like to emphasize that Europe offers unique possibilities for these kinds of studies due to the diversity in the health care and social programs that operate in the different countries.

The workshop support has in the past been taken from the administration budget. Although CAN-HUG and the ESLA working group provided input into the program it seems to some extent to have been adminstrated in an ad hoc manner.

RECOMMENDATIONS

1. It is the opinion of the panel that a third HGAP should be launched. Modifications in the project plan are, however, necessary due to the remarkable progress that has been made during the last year. It seems very likely that a high resolution genetic map and also a complete YAC- based physical map of the human genome will be completed within another year.

2. It is necessary to make a new strategic plan for the HGAP. This strategic plan should also consider the possibility of approaching sequencing of the entire genome by a "shot gun approach". Such an effect would require a drastic increase in funding.

3. A key feature of HGAP are the resource centers and it is essential to ascertain their continued existence. Making the results of whole genome physical mapping readily available to the community will be an extensive but necessary task; it must be tackled by informatic means including an accessible, complete and user-friendly database, but also at the level of the distribution of YAC- and cosmid clones, a very labour-intensive task. Making these reagents readily accessible to all European scientists, for instance by wide distribution of "polytene filters" containing ordered YACs for all human chromosomes would be an essential step. In general a wider range of ordered libraries is required, to serve the most diverse needs of genome research, once the first physical map will be completed.

4. In the future ordered collections of full length cDNAs will be required from all different tissues of the body. Resource centers providing ordered cDNA libraries as a service to the scientific community should be given high priority in a future HGAP.

5. Allocation of resources to megascale cDNA sequencing projects should be considered. The concept of cDNA sequencing to obtain a complete catalogue of the human genes was after all a European idea.

6. Mega-scale genomic sequencing which was not a component of the original HGAP needs to be considered in a future HGAP. It will be necessary to carry out some pilot projects involving megabase-sequencing to assess the future possibilities to approch sequencing of whole human chromosomes. Also, the possibility of sequencing the entire genome by a "shot gun approach" needs careful consideration. It is suggested that an ad hoc group is assembled to look into this problem. If the EC intends to participate in such a project it will have to greatly expand the program budget to faster reach the ultimate goal of the global genome program, the complete nucleotide sequence of the human genome.

7. EUROGEM, on the other hand, will soon have completed its mission once the high resolution genetic map has been finished.

8. Bioinformatics is a field that is likely to develop very rapidly in the near future. The design of user-friendly software for analysis of massive amounts of data will undoubtedly be an important aspect of a future HGAP. In view of the very widespread criticism directed to GDB, it becomes useful to envision alternative databases or at least different database access system : in this respect, the progress of the Heidelber IGD (Integrated Genome Database) appears promising and the distribution model advocated by this group, using a locally running ACeDB system fed with data from the other genome databases, appears particularly promising.
Communication between biologists and computer scientists remains imperfect : they still belong largely to two quite different cultures. Both fields have been evolving very quickly in recent years, and few individuals possess competence in both fields. An increase in their numbers, through attractive fellowships and positions, is probably

the only way of easing this difficulty.
Moreover attention, and some funding, should be devoted to improving interfaces between the "genome world" and the general biology community, including not only medical genetics but also, for example, groups performing functional research in the mouse system so that structure and function are brought closer together.

9. The transnational projects should be continued although they must be selected with great care. In supporting research and formulating suggestions on how to distribute research funds, it will be cogent to remember that collaborations, which are undoubtedly very important, cannot be organized by anyone, but must and will develop spontaneously. In that respect, it cannot be wise to stipulate collaborations between scientists from certain areas in Europe or even make the assignment of funds dependent on such collaborations. Such ideas are counterproductive. It would be preferable to rather start a special program of a limited extent for the support of deserving scientists in the bio-medical field working in those countries of Europe which are presently still weaker in melecular biology but are capable of catching up rapidly.

10. The training program appears largely to have been a success and a continuation of the program is recommended. It may, however, be necessary to find new means to spread information about the program since the number of applications was much smaller than anticipated. It should also be kept in mind that some modifications of the program might be very beneficial for young scientist working in the field of human genome analysis. There is one problem, which all European countries seem to share, i.e., the support and independence of young investigators who have proven themselves in their own or in other countries as first rate scientists. There is a very considerable lure by laboratories in the Unite States with its very flexible administrative structure at most universities and, above all, with an impressive number of top research centers at many U.S. universities. It will be increasingly attractive for young Europeans to seek to associate themselves with laboratories at such centers for longer or shorter periods of time, but usually during their years most productive for original research. Biomedical research, nowadays, can best be perfomed at centers of a critical size. It is necessary to recognize that it is one of the important tasks for science funding and organization in Europe to create a counterbalance to these very powerful centers for basic biomedical research in the U.S. A suggestion along these lines is to create positions for young independent researchers in the biomedical research areas which would allow highly qualified young scientists to pursue research of their own choice at one of the European universities, but uninhibited by their often very "traditional" administrative structures. In addition to positions, funds for consumable supplies, equipment and research personel should be attached to these positions. It is proposed that such structures would help very considerably in attracting or re-attracting many of the most productive young researchers from abroad to European countries.

11. ESLA programs are essential components of genome prorgrams. The panel recommends, although not unanimously, that the ESLA Program is continued and that long range support is provided. It is important that the program is announced as extensively as possible and that the contractors receive the proper information about the expected output of the program. An urgent component in future ESLA programs

will be to provide means for the participating groups to cooperate, interact and exchange ideas and results.
Special efforts should also be made to include economics of technical change, science policy and science studies in the program. The geographical inbalance is another problem that needs attention.

12. Support to workshops and meetings is clearly an essential component of HGAP and continuation of the program is recommended. However, some administrative changes are recommended. It is, for instance suggested that a scientific advisory board is established to advice on the policy of the program and to screen applications. Efforts should be made to obtain a better balance with regard to topics among the workshops that are supported. The support via HUGO to single chromosme workshops is essential and should be continued. In general, support should be given to chromosome workshops taking place in Europe as a contribution to the organization. Support should also be given as travel grants to European participants in workshops taking place outside of Europe. It seems also worthwile to support workshops which bring together scientists working within the HGAP on similar topics (as has been done to same extent in the past), for instance those working in EUROGEM or with cDNA libraires. This would obviously stimulate contacts between groups in different European countries.

13. Another welcome addition to the program would be education of practising physicians all over Europe. With the rapid progress in Medical Genetics our practising colleagues are already in a difficult position vis-à-vis their patients who will ask pressing questions. Specialized training programs might al least provide a partial solution to the problem.

RESUMÉ

1. Programmet vedrørende analyse af det humane genom (HGAP) hører under det andet rammeprogram for EF's aktioner inden for forskning og teknologisk udvikling. Programmet blev oprettet under punktet "Sundhed" i rubrikken "Livskvalitet" med henblik på:

   - Udnyttelse og forbedring af den nye bioteknologi til studiet af det humane genom med henblik på en bedre forståelse af mekanismerne i genernes funktion samt forebyggelse og behandling af sygdomme.;

   - udvikling af en integreret vurdering af de etiske, sociale og juridiske aspekter ved de mulige anvendelser af de resultater, der opnås.

2. Som et led i Kommissionens almindelige evalueringsaktiviteter blev der i december 1992 udpeget en gruppe uafhængige eksperter, som skulle foretage evalueringen af resultaterne. Bemyndigelsen af evalueringsgruppen er fastlagt i artikel 4, stk. 3, i Rådets beslutning om vedtagelse af programmet (EFT nr. L 196 af 29. juni 1990, s. 8). I samme artikel bestemmes det, at evalueringen skal gennemføres under hensyntagen til de opnåede videnskabelige og tekniske resultater, deres kvalitet og praktiske relevans, de etiske, sociale og juridiske aspekter og programmets betydning for nationale forskningsprogrammer.

   I forbindelse med evalueringen besøgte gruppen fire centre, der er involveret i programmet, og interviewede mere end 30 personer. Der var tale om tjenestemænd i Kommissionen og fra medlemsstaterne, deltagere i programmet og brugere.

3. Der er i alt afsat 15.6 mio. ECU til programmet. Dette beløb er fordelt med 21% til genetisk kortlægning, 27,6% til fysisk kortlægning, 15% til databehandling og databaser, 18% til avanceret genteknologi, 12% til uddannelse og 6,4% til forvaltning.

Ca. 100 institutter i EF var involveret i programmet.

KONKLUSIONER

Evalueringsgruppen mener, at programmet i det store og hele er en succes, og at det fungerer som en vigtig drivkraft for forskningen i det humane genom. Genomforskningen gør for tiden meget hurtige fremskridt. I de seneste år har fremskridtene især været bemærkelsesværdige i Europa, hvor man har haft held med sekvensering af hele gærkromosomer, fysisk kortlægning af hele genomer og nøjagtige genkort. Programmet har klart spillet et vigtig rolle for opnåelsen af et mere ligevægtigt forhold mellem Europa og USA. Det står imidlertid også klart, at vægtige programmer som det, der støttes af AFM i Frankrig, har været en vigtig drivkraft. HGAP-programmet blev vedtaget for en periode på to år med et budget på 16.6 mio. ECU. I forhold til USA og Japan anvender EF meget små beløb på genforskning. Programmet har derfor kun været et supplement til de aktiviteter, der gennemføres på nationalt plan, og EF-finansieringens vægt i de enkelte programmer afhænger i stort omfang af de nationale programmers styrke. EF har kun i meget begrænset omfang støttet større franske grupper (mindre end 10%), hvorimod støtten til det Forenede Kongerige, Tyskland, Italien og andre europæiske lande har været ganske betydelig. EF kan bidrage med 5% til 50% af hvert projekts samlede udgifter. Med hensyn til de transnationale

(3)

projekter vil denne type støtte i de fleste tilfælde kun have en beskeden betydning, og mindre udviklede lande har kun begrænsede muligheder for at få gavn af de transnationale programmer.

Oprettelsen af ressourcecentre og uddannelsesprogrammer er en stor hjælp for både velfungerende videnskabelige laboratorier og for mindre udviklede eller mindre veletablerede grupper. Dette område er et vigtigt aspekt ved programmet og ved moderne videnskab i almindelighed, eftersom organisering og rådighed over ressourcer er af stor betydning. Programmet har i den henseende været meget nyttigt for den europæiske genomforskning, og denne omstændighed bør der lægges vægt på ved tilrettelæggelsen af nye programmer.

cDNA-programmet under HGAP har ikke gjort så hurtige fremskridt, som man havde håbet, selvom der er udviklet delvise cDNA-sekvenser. Der vil bestemt være et stort behov for store cDNA-biblioteker af høj kvalitet fremover.

Det endelige mål for det verdensomspændende projekt vedrørende det humane genom er sekvensering af hele det humane genom. HGAP omfatter ikke i øjeblikket større sekvenserings-programmer. Dette bør der rådes bod på i fremtidige programmer.

De transnationale projekter har haft betydning for det europæiske samarbejde på området. De har også gjort det muligt for små laboratorier, især i mindre udviklede lande, at få adgang til avanceret teknologi.

Fellowship-programmet er en meget vigtig del af HGAP, og dets gennemførelse har tilsyneladende været tilfredsstillende.

Det anerkendes, at aktiviteterne under ESLA-programmet (etiske, sociale og juridiske aspekter), var berettigede. Eftersom ressourcerne er begrænsede, og der er mange områder, der snarest skal undersøges, har evalueringsgruppen dog diskuteret, om der fortsat skal ydes støtte til ESLA-programmet i samme omfang. Det allerede gennemførte ESLA-program kan betragtes som en lovende pilotundersøgelse. Evalueringsgruppen vil gerne understrege, at der i Europa er enestående gode muligheder for at gennemføre denne type undersøgelser på grund af den mangfoldighed af social- og sundhedsordninger, der gælder i de forskellige lande.

Støtten til workshop-arbejdet er hidtil taget fra administrationsbudgettet. Selv om CAN-HUG og ESLA arbejdsgruppen har medvirket i programmet, har ledelsen af det tilsyneladende i et vist omfang været ad hoc-præget.

HENSTILLINGER

1. Evalueringsgruppen mener, at der bør iværksættes et tredje program vedrørende analyse af det humane genom. På grund af det seneste års bemærkelsesværdige fremskridt er det imidlertid nødvendigt at indføre ændringer i programmet. I løbet af endnu et år vil man højst sandsynligt kunne færdiggøre et detaljeret genkort og et fuldstændigt, YAC-baseret fysisk kort af det humane genom.

2. Det er nødvendigt at fastlægge en ny strategisk plan for programmet. I forbindelse hermed kunne man overveje muligheden for at anvende haglgeværkloning ved sekvenseringen af hele genomet. Dette kræver, at støtten øges væsentligt.

3. Et af programmets nøgleelementer er ressourcecentrene, og det er yderst vigtigt, at deres fortsatte eksistens sikres. En stor, men nødvendig opgave er at gøre resultaterne af hele den fysiske genomkortlægning let tilgængelige. Dette skal gøres ved hjælp af edb-hjælpemidler, herunder en åben, fuldstændig og brugervenlig database, men også gennem

distribution af YAC - og cosmidkloner - en meget arbejdskrævende opgave. Det vil være et stort skridt i den rigtige retning at gøre disse tilgængelige for alle europæiske forskere, f.eks. ved en omfattende distribution af "polyten filtre", der indeholder ordnede YAC'er for alle menneskelige kromosomer. Der er generelt brug for et større antal ordnede biblioteker for at kunne dække genomforskningens forskellige behov, når det første fysiske kort er færdigt.

4. Der vil i fremtiden være behov for ordnede samlinger af cDNA'er i fuld længde fra alle de forskellige dele af kroppens væv. Ressourcecentre, der kan stille ordnede cDNA-biblioteker til rådighed for forskersamfundet, bør derfor prioriteres højt i det næste program.

5. Det bør overvejes at yde støtte til megaprojekter for sekvensering af cDNA. Ideen om sekvensering af cDNA for at få et fuldstændigt katalog over de menneskelige gener opstod trods alt i Europa.

6. I det næste program for analyse af det humane genom bør man inddrage storstilet genomsekvensering, der ikke indgik i det første program. Det vil blive nødvendigt at gennemføre nogle pilotprojekter, hvori der indgår megabase-sekvensering for at vurdere mulighederne for en fremtidig sekvensering af fuldstændige humane kromosomer. Muligheden for at sekvensere hele genomet ved hjælp af haglgeværkloning bør også nøje overvejes. Det foreslås, at der dannes en ad hoc-gruppe, som skal undersøge dette problem. Hvis EF agter at deltage i et sådant projekt, skal programmets budget øges væsentligt, for at man hurtigere kan nå det endelige mål for det verdensomspændende genomprogram - en fuldstændig nukleotidsekvensering af det humane genom.

7. EUROGEM vil på sin side have fuldført sin opgave, så snart det detaljerede genkort er færdigt.

8. Bioinformatik er et område, der sikkert vil undergå en meget hurtig udvikling i den nærmeste fremtid. Udviklingen af brugervenligt software til analyse af store mængder data vil uden tvivl udgøre en vigtig del af det næste HGAP. I betragtning af den meget udbredte kritik af GDB er det en god idé at overveje mulighederne for andre databaser eller om ikke andet forskellige systemer for adgang til databaser. Heidelber IGD (Integrated Genome Database) ser i den forbindelse lovende ud, og der er især store forventninger til denne gruppes distributionsmetode, der indebærer brug af et lokalt ACeDB-system med data fra de andre genomdatabaser. Kommunikationen mellem biologer og dataloger er endnu ikke tilfredsstillende. De to grupper tilhører stadig i høj grad to forskellige kulturer. Der er inden for begge områder foregået en meget hurtig udvikling i de senere år, og kun få har kompetence inden for begge fag.Dette problem kan sandsynligvis kun løses ved at øge antallet af sådanne tværfaglige eksperter ved at tilbyde attraktive udvekslingsordninger og stillinger.

   Der bør desuden ofres opmærksomhed og midler på at forbedre kontakten mellem den genteknologiske forskerverden og de almenbiologiske forskere, herunder ikke blot inden for lægevidenskabelig genetik, men også grupper, der udfører funktionel forskning i musesystemet så der kan skabes en tættere forbindelse mellem struktur og funktion.

9. De transnationale projekter bør fortsættes, men de skal udvælges med stor omhu. I forbindelse med støtte til forskning og forslag til, hvordan midlerne skal fordeles, bør det erindres, at samarbejde, der uden tvivl er meget vigtigt, ikke kan planlægges. Samarbejde skal og vil derimod opstå spontant. Det er derfor ikke hensigtsmæssigt at kræve samarbejde mellem forskere fra bestemte egne i Europa eller lade tildelingen af midler være betinget af dette samarbejde. En sådan fremgangsmåde virker mod hensigten. En

bedre løsning er at iværksætte et særligt program af begrænset omfang for at støtte kvalificerede forskere inden for biomedicin, der arbejder i de europæiske lande, som endnu har en svag stilling inden for molekylærbiologi, men som er i stand til hurtigt at råde bod på dette.

10. Uddannelsesprogrammet har i det store og hele været en succes, og det bør derfor fortsættes. Dog er det måske nødvendigt at finde nye måder at formidle oplysninger om programmet på, eftersom der blev indgivet langt færre ansøgninger end forventet. Det bør også tages i betragtning, at visse ændringer i programmet kunne være til stor gavn for unge forskere, der arbejder med analyse af det humane genom. Alle europæiske lande har tilsyneladende ét problem til fælles, nemlig hvordan man sikrer underhold og uafhængighed for unge forskere, der i deres eget eller andre lande har vist, at de er videnskabsmænd af højeste klasse. For disse forskere har laboratorier i USA, der har en meget fleksibel administrativ struktur, og frem for alt de imponerende mange fremragende forskningscentre ved de amerikanske universiteter stor tiltrækningskraft. Det vil blive stadigt mere attraktivt for unge europæere at blive tilknyttet laboratorier i disse centre for kortere eller længere tid, men typisk i de år, hvor de er mest produktive inden for grundforskning. Biomedicinsk forskning kan kun udføres på centre, der har en vis størrelse. Man må gøre sig klart, at en af de vigtigste opgaver i forbindelse med støtte og organisering af forskningen i Europa er at skabe et modstykke til disse meget magtfulde centre for biomedicinsk grundforskning i USA. Et skridt i denne retning kunne være at oprette stillinger for unge, uafhængige forskere inden for biomedicinsk forskning, der ville gøre det muligt for unge, højt kvalificerede videnskabsmænd at beskæftige sig med den forskning, de ønsker, ved et af de europæiske universiteter, uden at de bliver begrænset af de ofte meget "traditionelle" administrative strukturer, der hersker her. I forbindelse med disse stillinger bør der også gives midler til materialer, udstyr og forskningspersonale. Det forventes, at de nævnte foranstaltninger i væsentligt omfang vil kunne medvirke til at tiltrække eller lokke mange af de mest produktive unge forskere tilbage til de europæiske lande.

11. ESLA-programmer er en yderst vigtig del af genomprogrammer. Evalueringsgruppen foreslår - omend ikke samstemmende - at ESLA-programmet fortsættes, og at det støttes på lang sigt. Det er vigtigt, at kendskabet til programmet udbredes så meget som muligt, og at kontrahenterne bliver ordentligt informeret om det forventede resultat af programmet. Det er absolut nødvendigt, at nye ESLA-programmer giver de deltagende grupper mulighed for at samarbejde, påvirke hinanden og udveksle ideer og resultater.

    Der bør også ydes en særlig indsats for, at de økonomiske aspekter ved den tekniske udvikling, forskningspolitikken og de videnskabelige undersøgelser inddrages i programmet. Et andet problem, der bør tages op, er den geografiske uligevægt.

12. Støtte til workshops og møder er helt klart en vigtig side af HGAP, og det anbefales, at programmet fortsættes. Der bør dog foretages nogle administrative ændringer. Det foreslås, at der f.eks. oprettes et videnskabeligt konsulentråd, der skal rådgive om programmet og sortere ansøgningerne. Der bør ydes en indsats for at skabe en bedre emnemæssig balance mellem de workshops, der modtager støtte. Den støtte, der via HUGO gives til workshops for enkelt-kromosomer, er af stor betydning og bør fortsættes. Der bør i almindelighed ydes støtte til kromosomworkshops i Europa som et bidrag til HUGO. Der bør ligeledes gives rejsestipendier til europæiske deltagere i workshops, der afholdes uden for Europa. Det vil nok også kunne betale sig at støtte workshops, hvor forskere, der arbejder med beslægtede områder, kan mødes (som man tidligere i et vist omfang har gjort). Der kan f.eks. være tale om forskere, der arbejder i EUROGEM eller med cDNA-biblioteker. Dette vil klart kunne forbedre kontakten mellem grupper i forskellige europæiske lande.

13. Videreuddannelse af praktiserende læger over hele Europa ville være en anden velkommen udvidelse af programmet. For mange praktiserende læger kan genetik vække traumatiske minder om deres lægeeksaminer. Med de hurtige fremskridt inden for lægevidenskabelig genetik står vore praktiserende kollegaer allerede i en vanskelig situation over for deres patienter, der stiller indgående spørgsmål. Specialiserede uddannelsesprogrammer kunne i det mindste være en delvis løsning på problemet.

ZUSAMMENFASSUNG

1. Das Programm Analyse des menschlichen Genoms (Genomprogramm) ist Teil des zweiten Rahmenprogrammes der Gemeinschaft für Forschung und technologische Entwicklung. Dieses Programm wurde unter dem Abschnitt "Gesundheit" des Kapitels "Lebensqualität" mit folgendem Ziele ausgearbeitet:

   - Nutzung und Verbesserung neuer Biotechnologien zur Untersuchung des menschlichen Genoms im Hinblick auf ein besseres Verständnis des Mechanismus der Genfunktionen sowie die Verhütung und Behandlung menschlicher Krankheiten

   - Erarbeitung einer integrierten Konzeption, die die thischen, sozialen und rechtlichen Aspekte im Zusammenhang mit möglichen Anwendungen der erzielten Ergebnisse berücksichtigt.

2. Im Rahmen ihrer regelmäßigen Bewertungstätigkeiten beauftragte die Kommission im Dezember 1992 einen Ausschuß unabhängiger Sachverständiger mit der Bewertung des Genomprogrammes. Die Zuständigkeit des Bewertungsausschusses wurde nach Artikel 4 Absatz 3 der Entscheidung des Rates zur Annahme dieses Programmes (ABl. Nr. L 196 vom 29.6.1990, S. 8) festgelegt. In diesem Artikel heißt es ferner, daß die Bewertung unter Berücksichtigung der wissenschaftlichen und technischen Ergebnisse des Programmes, der Qualität und praktischen Bedeutung dieser Ergebnisse, der Wirksamkeit seiner Abwicklung, seiner ethischen, sozialen und rechtlichen Aspekte sowie seiner Auswirkungen auf die einzelstaatlichen Forschungsprogramme und ihres Nutzens für diese zu erfolgen hat. Im Laufe der Bewertung besuchte der Ausschuß vier am Programm beteiligte Stellen und befragte über dreißig Personen, darunter Beamte der Kommission sowie der Mitgliedstaaten, am Programm zur Analyse des menschlichen Genoms Beteiligte und Anwender.

3. Für dieses Programm wurden insgesamt 15.6 Mio. ECU bereitgestellt. Dieser Betrag wurde wie folgt aufgeteilt: Genkarten 21 %, physikalische Karten 27,6 %, Datenbehandlung und Datenbasen 15 %, fortgeschrittende Gentechnologien 18 %, Ausbildung 12 %, Verwaltungsausgaben 6,4 %.

   Am Genomprogramm beteiligten sich rund 100 EG-Institute.

SCHLUSSFOLGERUNGEN

Der Ausschuß hält das Genomprogramm für einen Erfolg und für ein bedeutendes Anspornmoment auf dem Gebiet der Erforschung des menschlichen Genoms. In der Genomforschung werden zur Zeit rasche Fortschritte erzielt. In den letzten Jahren war der Fortschritt in Europa besonders deutlich; Erfolge wurden unter anderem auf dem Gebiet der Sequenzierung von ganzen Hefechromosomen, ganzer physikalischer Genomkarten und verbesserter genetischer Karten erzielt. Das Genomprogramm hat eindeutig bei der Wiederherstellung des Gleichgewichts in den Beziehungen du den Vereinigten Staaten eine wichtige Rolle gespielt. Sicherlich haben jedoch auch wichtige Programme wie AFM in Frankreich als bedeutendes Antriebsmoment gewirkt. Das Genomprogramm wurde mit einem Zweijahresetat von 15.6 Mio. ECU verabschiedet. In der EG wird im Vergleich zu den Vereinigten Staaten und Japan für Genomforschung sehr wenig Geld aufgewendet. Das Genomprogramm

diente somit nur der Stützung bereits angelaufener einzelstaatlicher Tätigkeiten, und der Einfluß der EG-Mittel auf die einzelnen Programme hängt weitgehend von der Qualität der einzelstaatlichen Programme ab. Die EG hat die französischen Gruppen in geringerem Maße (weniger als 10 %) unterstützt, weit mehr dagegen die britischen, deutschen, italienischen und diejenigen anderer europäischer Länder. Die EG-Hilfe belief sich auf 5 - 50 % der Gesamtausgaben der einzelnen Projekte. Auf internationale Projekte wirkt sich diese Unterstützung in den meisten Fällen nur in bescheidenem Maße aus, und die weniger fortgeschrittenen Länder können aus den internationalen Programmen nur beschränkten Nutzen ziehen.

Die Errichtung von "resource centres" und die Ausarbeitung von Ausbildungsprogrammen ist zur Unterstützung gut organisierter wissenschaftlicher Laboratorien oder auch weniger fortgeschrittener oder weniger bekannter Stellen sehr nützlich. Dies ist ein bedeutender Aspekt des Genomprogramms und der heutigen Wissenschaft allgemein, da Organisation und Mittel wesentliche Faktoren darstellen. In dieser Hinsicht war das Genomprogramm für die in Europa auf diesem Gebiet tätigen Wissenschaftskreise sehr nützlich, und dieser Aspekt ist bei der Ausarbeitung künftiger Programme hervorzuheben.

Mit dem cDNA-Programm wurden im Rahmen des Genomprogrammes nicht so rasche Fortschritte erzielt wie erwartet, obwohl eine ganze Anzahl cDNA-Sequenzen erarbeitet worden sind. Für die Zukunft ist eindeutig ein hoher Bedarf an umfassenden Sammlungen von cDNA-Bibliotheken von hoher Qualität zu erwarten.

Das Endziel des umfassenden menschlichen Genomprojekts besteht in der Sequenzierung des gesamten menschlichen Genoms. Das Genomprogramm umfaßt zur Zeit keine umfassenden Sequenzierungsprogramme. Dies ist in einem künftigen Genomprogramm zu ändern.

Die überstaatlichen Projekte haben die Zusammenarbeit in Europa gefördert. Sie stellten auch kleinen Laboratorien Mittel zur Verfügung, insbesondere in weniger entwickelten Ländern, um diesen den Zugang zu hochentwickelten Technologien zu ermöglichen.

Das Stipendienprogramm ist ein sehr wichtiger Teil des Genomprogramms. Es scheint bisher befriedigend durchgeführt worden zu sein.

Die Tätigkeiten im Rahmen des ESLA-Programmes wurden für gerechtfertigt erachtet. Der Bewertungsausschuß erörterte jedoch die Frage, ob das Programm im gleichen Maße wie bisher zu finanzieren sei, weil die verfügbaren Mittel beschränkt sind und zahlreiche dringende Fragen zu erörtern sind. Das bereits abgeschlossene ESLA-Programm kann als vielversprechende Pilotstudie betrachtet werden. Der Ausschuß unterstreicht, daß Europa wegen der vielseitigen Programme der einzelnen Staaten auf dem Gebiet des Gesundheits- und Sozialwesens einzigartige Möglichkeiten für solche Studien bietet.

Die Workshops wurden bisher aus Verwaltungsmitteln unterstützt. Trotz der Beiträge von CAN-HUG und der ESLA-Arbeitsgruppe scheint das Programm in einem gewissen Maße ad hoc verwaltet worden zu sein.

EMPFEHLUNGEN

Der Ausschuß ist der Ansicht, daß ein drittes Genomprogramm in die Wege geleitet werden sollte. Angesichts der im vergangenen Jahr erzielten, beachtlichen Fortschritte sind jedoch Änderungen des Projektplanes erforderlich. Mit großer Wahrscheinlichkeit dürfte binnen einem weiteren Jahr eine hochauflösende Genkarte sowie eine vollständige physikalische Karte

(auf YAC-Grundlage) des menschlichen Genoms ferteiggestellt werden.

2. Ein neuer strategischer Plan für das Genomprogramm ist festzulegen. Darin sollte auch die Möglichkeit eines "shot gun"-Ansatzes für die Sequenzierung des gesamten menschlichen Genoms in Erwägung gezogen werden. Dies würde eine beträchtliche Erhöhung des Mitteleinsatzes bedingen.

3. Die "ressource centres" bilden einen entscheidenden Aspekt des Genomprogramms, ihr Fortbestehen muß unbedingt gewährleistet sein. Eine umfangreiche, jedoch notwendige Aufgabe besteht darin, die Ergebnisse der physikalischen Genkartierung jederzeit gemeinschaftsweit verfügbar zu machen. Sie sollte mit Hilfe der Informatik einschließlich einer zugänglichen, vollständigen und anwenderfreundlichen Datenbasis gelöst werden, jedoch auch die Verteilung von YAC- und Cosmid-Klonen umfassen, was viel Arbeit verursacht. Ein wesentlicher Schritt würde darin bestehen, diese Reagentien den europäischen Wissenschaftlern jederzeit zur Verfügung zu halten, z.B. durch eine ausgedehnte Verteilung von Polytenfiltern, die geordnete YACs für alle menschlichen Chromosomen enthalten. Allgemein ist ein größerer Bereich von geordneten Bibliotheken erforderlich, um den diversifiziertesten Bedarf an Genomforschung nach Erstellung der ersten physikalischen Karte zu decken.

4. In Zukunft werden geordnete Sammlungen von (einem Gen entsprechenden) vollständig sequenzierten cDNAs von allen Gewebetypen des Körpers erforderlich sein. Den "resource-centres", die geordnete cDNA-Bibliotheken als Dienstleistung an die wissenschaftliche Gemeinschaft liefern, sollte in einem künftigen Programmen eine hohe Priorität eingeräumt werden.

5. Die Bereitstellung von Mitteln für cDNA-Sequenzierung in sehr großem Maßstab ist in Betracht zu ziehen. Die Erstellung eines vollständigen Katalogs menschlicher Gene durch die cDNA-Sequenzierung war bekanntlich eine europäische Idee;

6. Die Genomsequenzierung in sehr großem Maßstab, die im ursprünglichen Genomprogramm nicht vorgesehen war, sollte in einem künftigen Programm berücksichtigt werden. Einige Pilotprojekte mit "Megabasis"-Sequenzierung zur Bewertung der künftigen Möglichkeiten der Sequenzierung ganzer menschlicher Chromosomen werden durchgeführt werden müssen. Ernsthaft in Betracht zu ziehen ist ferner die Möglichkeit der Sequenzierung des gesamten Genoms nach dem "shotgun"-Verfahren. Es wird vorgeschlagen, zur Prüfung dieser Frage einen Ad-hoc-Ausschuß einzusetzen. Beabsichtigt die EG, sich an einem solchen Projekt zu beteiligen, so muß sie ihre Programmittel beträchtlich aufstocken, um das Endziel des umfassenden Genomprogrammes - die vollständige Nukleotidsequenz des menschlichen Genoms - rascher zu erreichen.

7. Der Auftrag von **EUROGEM** wird nach Erarbeitung der hochauflösenden Genkarte rasch beendet sein .

8. Das Gebiet der Bioinformatik dürfte sich in nächster Zeit stark fortentwickeln. Die Entwicklung einer anwenderfreundlichen Software zur Analyse der großen Masse an Daten ist sicherlich ein wichtiger Aspekt eines zukünftigen Genomprogramms. Wegen der häufigen Kritik an GDB sollten nunmehr alternative Datenbasen oder zumindest ein anderer Zugang zu den Datenbasen ins Auge gefaßt werden; in dieser Hinsicht

ist auf die mit der Heidelberger IGD (Integrierte Genom-Dantenbank) erzielten Fortschritte hinzuweisen. Besonders erfolgversprechend erscheint das von dieser Gruppe empfohlene Verteilungsmodell - ein auf örtlicher Ebene betriebenes ACeDB-System, in das auch Daten aus anderen Genom-Datenbasen eingespeist werden. Die Kommunikation zwischen Biologen und Datenverarbeitungswissenschaftlern ist weiterhin mangelhaft - beide gehören weiterhin einem verschiedenen Kulturkreis an. Beide Gebiete haben sich in den letzten Jahren rasch fortentwickelt, und Leute mit Fachkenntnissen auf beiden Gebieten sind selten. Der einzige Weg zur Minderung dieses Problems besteht vermutlich darin, die Zahl solcher Fachleute durch attraktive Stipendien und Stellungen zu erhöhen.
Ferner ist der Verbesserung der Kontakte zwischen Genomspezialisten und den übrigen Biologen einschließlich nicht nur der medizinischen Genetik, sondern z. B. auch der Gruppen, die funktionelle Untersuchungen an Mäusen durchführen, vermehrte Aufmerksamkeit zu schenken, und diesbezügliche Bemühungen sind finanziell zu unterstützen, um eine Annäherung von Struktur und Funktion zu ermöglichen.

9. Die mehrstaatlichen Projekte sind fortzusetzen, wenn sie auch sehr sorgsam auszuwählen sind. Bei der Unterstützung von Forschungstätigkeiten und der Abgabe von Empfehlungen ist unbedingt daran zu erinnern, daß Zusammenarbeitstätigkeiten ungeachtet ihrer großen Bedeutung nicht von irgendjemandem in die Wege geleitet werden können, sondern sich spontan ergeben müssen und es auch werden. Es ist somit nicht sinnvoll, Zusammenarbeitsvorhaben zwischen Wissenschaftlern bestimmter Gebiete in Europa vorzuschlagen oder sogar Mittel dafür bereitzustellen, dies wäre geradezu kontraproduktiv. Vorzuziehen wäre ein Sonderprogramm beschränkten Ausmasses zur Unterstützung von Wissenschaftlern mit Verdiensten auf dem Gebiet der Biomedizin in europäischen Ländern, in denen die Molekularbiologie zur Zeit weniger fortgeschritten ist, die den Abstand jedoch rasch aufholen könnten.

10. Das Ausbildungsprogramm scheint weitgehend erfolgreich gewesen zu sein; seine Fortsetzung wird empfohlen. Vielleichrt sollten jedoch neue Mittel zur Verbreitung der Informationen über das Programm gefunden werden, da die Zahl der Anwendungen weit niedriger war als erwartet. Nicht zu vergessen ist ferner, daß bestimmte Änderungen des Programmes für auf dem Gebiet der Analyse des menschlichen Genoms tätige junge Wissenschaftler sehr nützlich sein könnten. Ein Problem scheint in allen europäischen Ländern aufzutreten, d. h. die Unterstützung und Unabhängigkeit junger Forscher, die sich im In- oder Ausland als hervorragend erwiesen haben. Die sehr flexible Struktur der Laboratorien an den meisten amerikanischen Hochschulen und vor allem die beachtliche Zahl von Spitzenforschungszentren an vielen dieser Hochschulen üben eine starke Anziehungskraft aus. Eine längere oder kürzere Assoziierung mit Laboratorien solcher Stellen wird für junge Europäer zunehmend vorteilhafter, in der Regel gerade in den produktivsten Jahren ihrer Forschertätigkeit. Die biomedizinische Forschung läßt sich zur Zeit am besten in Forschungsstellen von kritischer Größe durchführen. Es muß anerkannt werden, daß eine der ersten Aufgaben der Finanzierung und Organisation der Wissenschaft in Europa darin bestehen muß, ein Gegengewicht zu diesen sehr attraktiven biomedizinischen Forschungsstellen in den USA zu schaffen. In diesem Zusammenhang wird u. a. angeregt, Stellen für unabhängige junge Forscher auf biomedizinischen Gebieten zu schaffen, wodurch hochqualifizierte

junge Wissenschaftler selbstgewählte Forschungen an einer europäischen Hochschule fortführen könnten, ohne durch die oftmals sehr "traditionellen" Verwaltungsstrukturen gehemmt zu sein. Außerdem sollten Mittel zur Deckung der Materialverbrauchskosten, Geräte und Forschungspersonal für diese Posten zur Verfügung gestellt werden. Es wird die Meinung vertreten, daß solche Strukturen viele der produktivsten jungen Forschungskräfte aus dem Ausland nach Europa anziehen oder zurückholen könnten.

11. ESLA-Programme sind wesentliche Elemente der Genomprogramme. Der Ausschuß empfiehlt - wenn auch nicht einstimmig - das ESLA-Programm fortzusetzen und langfristig zu unterstützen. Das Programm muß möglichst eingehend angekündigt werden, und die Vertragnehmer müssen die erforderlichen Informationen über die erwarteten Programmergebnisse erhalten. Wichtig für künftige ESLA-Programme sind die Zurverfügungstellung von Mitteln für eine Zusammenarbeit, gegenseitige Beeinflussung und einen Austausch von Ideen und Ergebnissen an die beteiligten Gruppen.
Besondere Anstrengungen sind ferner notwendig, um die wirtschaftlichen Aspekte der technischen Veränderung, der Wissenschaftspolitik und wissenschaftlicher Untersuchungen in das Programm aufzunehmen.

12. Die Unterstützung von Arbeitstreffen und Sitzungen ist eindeutig ein wesentlicher Faktor des Genomprogramms; die Fortsetzung des Programmes wird empfohlen. Einige administrative Änderungen werden jedoch vorgeschlagen. So wird angeregt, zur Beratung in programmpolitischen Fragen und zur Auswahl der Anträge eine wissenschaftliche Gruppe einzusetzen. Die Unterstützung von Workshops über einzelne Chromosomen durch HUGO ist wesentlich und sollte fortgesetzt werden. Allgemein sind Workshops über Chromosomen in Europa als Beitrag zur Organisation zu unterstützen. Ferner sind Europäische Teilnehmer an Arbeitstreffen außerhalb Europas durch Reisevergütungen zu unterstützen. Sodann sollten Workshops von Wissenschaftlern unterstützt werden, die sich im Rahmen des Genomprogrammes mit ähnlichen Themen befassen (wie dies bisher in einem gewissen Maße bereits der Fall war), z. B. EUROGEM oder cDNA-Bibliotheken. Dies wäre der Kontaktaufnahme zwischen den in verschiedenen europäischen Ländern auf diesem Gebiet tätigen Gruppen sicher förderlich.

13. Eine weitere begrüßenswerte Erweiterung des Programmnes wäre die Fortbildung praktizierender Ärzte in ganz Europa. Für viele praktische Ärzte ist die Genetik vielleicht eine traumatisierende Erinnerung an die Zeit ihres Studienabschlusses an der medizinischen Fakultät. Angesichts des raschen Fortschrittes auf dem Gebiet der medizinischen Genetik geraten die praktizierenden Ärzte oftmals in Schwierigkeiten, wenn ihnen ihre Patienten heikle Fragen stellen. Spezialisierte Fortbildungsprogramme könnten das Problem zumindest teilweise lösen.

ΠΕΡΙΛΗΨΗ

1. Το Πρόγραμμα Ανάλυσης του Ανθρώπινου Γονιδιώματος (ΠΑΑΓ) αποτελεί μέρος του δευτέρου προγράμματος-πλαισίου των δραστηριοτήτων της Κοινότητας στον τομέα της έρευνας και τεχνολογικής ανάπτυξης. Το πρόγραμμα αυτό καταρτίστηκε με βάση το κεφάλαιο "Υγεία" του τμήματος της Ποιότητας Ζωής, με σκοπό:

- τη χρησιμοποίηση και βελτίωση νέων τεχνολογιών στη μελέτη του ανθρώπινου γονιδιώματος, για την καλύτερη κατανόηση του μηχανισμού των γενετικών λειτουργιών καθώς και για την πρόληψη και θεραπεία των ανθρώπινων ασθενειών,

- την ανάπτυξη μιας ολοκληρωμένης προσέγγισης στη δεοντολογική, κοινωνική και νομική πτυχή των ενδεχόμενων εφαρμογών από τα αποτελέσματα που επιτυγχάνονται.

2. Ως μέρος του έργου της τακτικής αξιολόγησης, η Επιτροπή διόρισε τον Δεκέμβριο 1992, μία ομάδα ανεξάρτητων εμπειρογνωμόνων για να προβούν στην αξιολόγηση του ΠΑΑΓ. Τα καθήκοντα της Ομάδας Αξιολόγησης ορίζονται στο άρθρο 4 (3) της απόφασης του Συμβουλίου για τη θέσπιση αυτού του προγράμματος (ΕΕ αριθ. L 196 της 29ης Ιουνίου 1990, σελ. 8). Το ίδιο άρθρο ορίζει ότι η αξιολόγηση πρέπει να επιτευχθεί αφού ληφθούν υπόψη τα επιστημονικά και τεχνικά επιτεύγματα του προγράμματος, η ποιότητα και η πρακτική σημασία των αποτελεσμάτων του, η αποτελεσματικότητα της διαχείρισής του, η δεοντολογική, κοινωνική και νομική πτυχή, καθώς και η επίδραση και τα οφέλη του στα εθνικά ερευνητικά προγράμματα.
Για την πραγματοποίηση της αξιολόγησης, η Ομάδα επισκέφθηκε τέσσερα κέντρα που συμμετέχουν στο πρόγραμμα και εξέτασε περισσότερα από τριάντα άτομα: αξιωματούχους της Επιτροπής και των εθνικών αρχών, συμμετέχοντες στο ΠΑΑΓ και χρήστες.

3. Οι συνολικές πιστώσεις που διετέθησαν για το πρόγραμμα αυτό, ανέρχονταν σε 15,6 MECU. Η κατανομή των πιστώσεων είχε ως εξής: γενετικοί χάρτες 21%, φυσικοί χάρτες 27,6%, επεξεργασία δεδομένων και τράπεζες δεδομένων 15%, προηγμένη γενετική τεχνολογία 18%, δραστηριότητες κατάρτισης 12%, διοίκηση 6,4%.

Στο ΠΑΑΓ συμμετείχαν περίπου 100 ιδρύματα από τον χώρο των Κοινοτήτων.

ΣΥΜΠΕΡΑΣΜΑΤΑ

Η ομάδα θεωρεί ότι το ΠΑΑΓ σημείωσε μεγάλη επιτυχία και αποτελεί μία σημαντική κινητήρια δύναμη στον τομέα της ευρωπαϊκής έρευνας για το ανθρώπινο γονιδίωμα. Προς το παρόν, η έρευνα για τα γονιδιώματα προχωρεί με έναν υπερβολικά ταχύ ρυθμό. Κατά τα τελευταία χρόνια, η πρόοδος ήταν ιδιαίτερα εντυπωσιακή στην Ευρώπη, και σημειώθηκε επιτυχία σε τομείς, όπως στον προσδιορισμό της νουκλεοτιδικής αλληλουχίας ολόκληρων των χρωμοσωμάτων ζυμομηκύτων, σε φυσικούς χάρτες ολόκληρων γονιδιωμάτων καθώς και σε λεπτομερείς γενετικούς χάρτες. Είναι σαφές, ότι το ΠΑΑΓ έχει διαδραματίσει σημαντικό ρόλο στην καθιέρωση πιο ισορροπημένων σχέσεων με τις Η.Π.Α. Είναι όμως εξίσου σαφές ότι προγράμματα όπως εκείνα που έχουν υποστηριχθεί από την AFM στη Γαλλία αποτελούν μία σημαντική κινητήρια δύναμη. Το ΠΑΑΓ εγκρίθηκε με προϋπολογισμό δύο ετών, της τάξεως των 15,6 MECU. Το ποσό που διέθεσαν οι ΕΚ στην έρευνα για τα γονιδιώματα είναι πολύ μικρό σε σχέση με τα κονδύλια της έρευνας για τα γονιδιώματα στις Η.Π.Α. και στην Ιαπωνία. Για τον λόγο αυτό, το ΠΑΑΓ απλώς συμπλήρωσε τρέχουσες εθνικές πρωτοβουλίες, και το ύψος της κοινοτικής χρηματοδότησης μεμονωμένων προγραμμάτων εξαρτάται σε μεγάλο βαθμό από την ισχύ των εθνικών προγραμμάτων. Οι ΕΚ έχουν υποστηρίξει ελάχιστα μεγάλες γαλλικές ομάδες (σε ποσοστό μικρότερο από 10%), ενώ η υποστήριξη

ήταν αρκετά σημαντική για τη Μεγάλη Βρετανία, την Ιταλία και άλλες Ευρωπαϊκές χώρες. Η κοινοτική χρηματοδοτική ενίσχυση κυμαίνεται από < 5% έως 50% της συνολικής χρηματοδότησης κάθε έργου. Για τα διακρατικά έργα, αυτός ο τρόπος χρηματοδότησης μπορεί να έχει τις περισσότερες φορές μικρή μόνο επιρροή, το δε ενδεχόμενο όφελος από τα διακρατικά προγράμματα για τις λιγότερο προηγμένες χώρες είναι περιορισμένο.

Η εγκατάσταση κέντρων γενετικών πόρων και η οργάνωση προγραμμάτων κατάρτισης αποτελεί μεγάλη βοήθεια για τα οργανωμένα επιστημονικά εργαστήρια αλλά και για λιγότερο προηγμένα ή για λιγότερο καταξιωμένες ομάδες. Πρόκειται για μια πολύ σημαντική πτυχή του ΠΑΑΓ και γενικά της σύγχρονης επιστήμης, επειδή η οργάνωση και η διάθεση των πόρων αποτελούν βασικά θέματα. Στο σημείο αυτό, το ΠΑΑΓ ήταν πολύ χρήσιμο για την κοινοτική έρευνα επί των γονιδιωμάτων, και η πτυχή αυτή πρέπει να τονιστεί κατά τον σχεδιασμό των μελλοντικών προγραμμάτων.

Το πρόγραμμα cDNA στο υφιστάμενο ΠΑΑΓ δεν αναπτύχθηκε τόσο γρήγορα όσο αναμενόταν, μολονότι προέκυψαν μερικές νουκλεοτιδικές αλληλουχίες cDNA. Είναι σαφές, ότι στο μέλλον θα υπάρξει πολύ μεγάλη ανάγκη για σημαντικές τράπεζες συλλογής υψηλής ποιότητας cDNA.

Ο τελικός στόχος όλου του προγράμματος για το ανθρώπινο γονιδίωμα, είναι η ανεύρεση της νουκλεοτιδικής αλληλουχίας ολοκλήρου του ανθρώπινου γονιδιώματος. Μεγάλα προγράμματα που ασχολούνται με την νουκλεοτιδική αλληλουχία δεν συμπεριλαμβάνονται στο παρόν ΠΑΑΓ. Η κατάσταση αυτή επιβάλλεται να διορθωθεί σε μελλοντικό ΠΑΑΓ.

Τα διακρατικά έργα είχαν μεγάλη σημασία για την προώθηση της ευρωπαϊκής συνεργασίας. Παρείχαν επίσης τα μέσα σε μικρά εργαστήρια, ιδιαίτερα σε λιγότερο ανεπτυγμένες χώρες, για πρόσβαση σε υπερσύγχρονες τεχνολογίες.

Το πρόγραμμα μεταδιδακτορικών σπουδών αποτελεί μία πολύ σημαντική πτυχή του ΠΑΑΓ. Φαίνεται ότι κατά το παρελθόν εφαρμόστηκε κατά τρόπο ικανοποιητικό.

Αναγνωρίστηκε ότι οι δραστηριότητες που ανελήφθησαν στα πλαίσια του προγράμματος ESLA ήταν δικαιολογημένες. Εντούτοις, η ομάδα αξιολόγησης εξέτασε κατά πόσο το ύψος της χρηματοδότησης του προγράμματος πρέπει να είναι το ίδιο όπως και κατά το παρελθόν, επειδή οι πόροι είναι περιορισμένοι και πρέπει να διερευνηθούν πολλά επείγοντα θέματα. Το ήδη ολοκληρωμένο πρόγραμμα ESLA θεωρήθηκε ως μία ενθαρρυντική πρότυπη μελέτη. Η ομάδα επιθυμεί να υπογραμμίσει ότι η Ευρώπη προσφέρει μοναδικές δυνατότητες για μελέτες αυτού του είδους, λόγω των υφισταμένων αποκλίσεων στον τομέα της υγειονομικής περίθαλψης και των κοινωνικών προγραμμάτων μεταξύ των διαφόρων χωρών.

Η χρηματοδοτική ενίσχυση των συναντήσεων πρακτικής εργασίας γινόταν κατά το παρελθόν από τον προϋπολογισμό της διοίκησης. Μολονότι το CAN-HUG και η ομάδα εργασίας ESLA εισήγαγαν στοιχεία στο πρόγραμμα, φαίνεται ότι σε ορισμένο βαθμό υπήρξε μία ad hoc διαχείριση.

ΣΥΣΤΑΣΕΙΣ

1. Κατά την άποψη της ομάδας θα πρέπει να τεθεί σε εφαρμογή ένα τρίτο ΠΑΑΓ. Εντούτοις, είναι απαραίτητες ορισμένες τροποποιήσεις στο σχέδιο του προγράμματος, λόγω της εξαιρετικής προόδου που έχει σημειωθεί κατά τα τελευταία χρόνια. Φαίνεται πολύ πιθανό, ότι μέσα σε ένα έτος θα έχει ολοκληρωθεί ένας πολύ ακριβής γενετικός χάρτης καθώς και ένας πλήρης φυσικός χάρτης του ανθρώπινου γονιδιώματος, βασισμένος στα YAC (τεχνητά χρωμοσώματα ζυμομυκήτων).

2. Είναι απαραίτητο να καταρτισθεί νέο στρατηγικό σχέδιο για το ΠΑΑΓ. Το στρατηγικό αυτό σχέδιο πρέπει επίσης να λαμβάνει υπόψη τη δυνατότητα προσέγγισης της νουκλεοτιδικής αλληλουχίας ολοκλήρου του γονιδιώματος, μέσω της τυχαίας κλώνωσης (μέθοδος shot gun). Μία τέτοια ενέργεια απαιτεί πολύ σημαντική αύξηση της χρηματοδότησης.

3. Τα κέντρα γενετικών πόρων αποτελούν ένα σημαντικό στοιχείο του ΠΑΑΓ και είναι απαραίτητο να διασφαλισθεί η συνεχής ύπαρξή τους. Η άμεση διαθεσιμότητα για τους ερευνητές των αποτελεσμάτων της φυσικής χαρτογράφησης ολοκλήρου του γονιδιώματος, είναι ένα μεγάλο αλλά απαραίτητο έργο. Το έργο αυτό πρέπει να υλοποιηθεί με μέσα που προέρχονται από την Πληροφορική, συμπεριλαμβανομένων προσιτών, ολοκληρωμένων και φιλικών προς τον χρήστη τραπεζών δεδομένων, αλλά και σε επίπεδο διανομής των κλώνων YAK καθώς και των κοσμιδιακών κλώνων, έργο που απαιτεί ένταση εργασίας. Το να καταστούν τα αντιδραστήρια αυτά προσιτά σε όλους τους ευρωπαίους επιστήμονες, π.χ. μέσω της ευρείας διανομής "πολυτενικών φίλτρων" που περιέχουν διατεταγμένα YAC για όλα τα ανθρώπινα χρωματοσώματα, θα μπορούσε να αποτελέσει ένα ουσιαστικό βήμα. Γενικά, απαιτείται ένα ευρύτερο φάσμα διατεταγμένων βιβλιοθηκών για να εξυπηρετήσουν τις πλέον διαφορετικές ανάγκες στην έρευνα του γονιδιώματος, από τη στιγμή που θα έχει ολοκληρωθεί ο πρώτος φυσικός χάρτης.

4. Στο μέλλον, θα απαιτηθούν διατεταγμένες συλλογές ολοκλήρου του μήκους του cDNA, από όλους τους διαφορετικούς ιστούς του σώματος. Θα πρέπει να δοθεί μεγάλη προτεραιότητα, σε ένα μελλοντικό ΠΑΑΓ, στα κέντρα γενετικών πόρων που θα παρέχουν διατεταγμένες βιβλιοθήκες cDNA, ως υπηρεσία προς την επιστημονική κοινότητα.

5. Θα πρέπει να ληφθεί υπόψη η διάθεση πόρων σε έργα που αφορούν τον μεγάλης κλίμακας προσδιορισμό της νουκλεοτιδικής αλληλουχίας του cDNA. Άλλωστε, ο προσδιορισμός της νουκλεοτιδικής αλληλουχίας του cDNA με σκοπό να καταρτισθεί πλήρης κατάλογος των ανθρωπίνων γονιδίων ήταν ευρωπαϊκή ιδέα.

6. Ο προσδιορισμός της νουκλεοτιδικής αλληλουχίας σε μεγα-κλίμακα, που δεν αποτελούσε τμήμα του αρχικού ΠΑΑΓ, πρέπει να ληφθεί υπόψη στο μελλοντικό ΠΑΑΓ. Είναι απαραίτητο να εκτελεσθούν ορισμένα πρότυπα έργα που θα συμπεριλαμβάνουν προσδιορισμό της νουκλεοτιδικής αλληλουχίας σε επίπεδο μεγα-βάσης, για να εκτιμηθούν οι μελλοντικές δυνατότητες προσέγγισης στην αλληλουχία των ολοκλήρων ανθρώπινων χρωματοσωμάτων. Επίσης, πρέπει να ληφθεί πολύ προσεκτικά υπόψη η δυνατότητα προσδιορισμού της αλληλουχίας ολοκλήρου του χρωματοσώματος με τυχαία κλώνωση. Προτείνεται η σύσταση ομάδας ad hoc για να εξετάσει το πρόβλημα αυτό. Εάν η ΕΚ προτίθεται να συμμετάσχει σε ένα τέτοιο έργο, θα πρέπει να αυξήσει σε μεγάλο βαθμό τον προϋπολογισμό του προγράμματος, ώστε να επιτευχθεί με ταχύτερο ρυθμό ο τελικός στόχος ολοκλήρου του προγράμματος για τα γονιδιώματα, δηλαδή, η ανεύρεση της πλήρους αλληλουχίας των νουκλεοτιδίων του ανθρώπινου γονιδιώματος.

7. Από την άλλη πλευρά, το EUROGEM θα έχει σύντομα ολοκληρώσει την αποστολή του, από τη στιγμή που θα έχει ολοκληρωθεί ο ακριβής γενετικός χάρτης.

8. Η βιοπληροφορική είναι ένας τομέας που ενδέχεται να αναπτυχθεί με πολύ ταχύ ρυθμό στο εγγύς μέλλον. Ο σχεδιασμός λογισμικών, φιλικών προς τους χρήστες, για την ανάλυση τεράστιου αριθμού δεδομένων θα αποτελέσει αναμφίβολα μία σημαντική πτυχή του μελλοντικού ΠΑΑΓ. Κατόπιν της πολύ έντονης κριτικής που ασκήθηκε προς την τράπεζα δεδομένων για το ανθρώπινο γονιδίωμα (GDB), είναι χρήσιμο να προβλεφθούν εναλλακτικές τράπεζες δεδομένων ή τουλάχιστον ένα διαφορετικό σύστημα πρόσβασης στις τράπεζες δεδομένων: στο σημείο αυτό, η πρόοδος του προγράμματος της Χαϊδελβέργης IGD (Integrated Genome Database - Ολοκληρωμένη Τράπεζα Δεδομένων για τα Γονιδιώματα) φαίνεται ενθαρρυντική, ενώ το πρότυπο διανομής που προτείνεται από την ομάδα αυτή, η οποία χρησιμοποιεί ένα τοπικό σύστημα ACeDB, που τροφοδοτείται με στοιχεία από άλλες τράπεζες δεδομένων, φαίνεται ιδιαίτερα ενθαρρυντικό.
Παραμένει ελλιπής η επικοινωνία μεταξύ βιολόγων και επιστημόνων της πληροφορικής: ανήκουν ακόμα, σε μεγάλο βαθμό, σε δύο εντελώς διαφορετικούς τομείς. Τα τελευταία χρόνια και οι δύο τομείς εξελίχθηκαν πολύ γρήγορα, και λίγα άτομα έχουν γνώσεις και στους δύο αυτούς τομείς.

Η αύξηση του αριθμού των επιστημόνων αυτών, μέσω ελκυστικών μεταδιδακτορικών υποτροφιών και θέσεων, είναι ενδεχομένως ο μοναδικός τρόπος για να ξεπερασθεί η δυσκολία αυτή. Επιπλέον, θα πρέπει να δοθεί προσοχή, καθώς και χρηματοδοτήσεις, για να βελτιωθούν τα σημεία επαφής μεταξύ του "κόσμου του γονιδιώματος" και του τομέα της γενικής βιολογίας, συμπεριλαμβανομένης όχι μόνο της γενετικής ιατρικής, αλλά και για παράδειγμα, των ομάδων που διεξάγουν έρευνα για τις λειτουργίες στο σύστημα των ποντικών, ώστε οι δομές και η λειτουργία να συσχετιστούν περισσότερο.

9. Επιβάλλεται να συνεχισθούν τα διακρατικά έργα, πρέπει όμως να επιλέγονται με μεγάλη προσοχή. Σε ό,τι αφορά την ενίσχυση της έρευνας και τη διατύπωση προτάσεων σχετικά με τον τρόπο κατανομής των πιστώσεων που προορίζονται για την έρευνα, είναι απαραίτητο να υπενθυμισθεί ότι οι συνεργασίες, που είναι αναμφίβολα πολύ σημαντικές, δεν μπορεί να οργανώνονται από κανένα, αλλά πρέπει να αναπτύσσονται και θα αναπτύσσονται αυθόρμητα. Στο σημείο αυτό, δεν είναι σκόπιμο να καθορίζονται οι συνεργασίες μεταξύ επιστημόνων από ορισμένες περιοχές της Ευρώπης, ή ακόμα να κατανέμονται οι πιστώσεις ανάλογα με τις συνεργασίες αυτές. Τέτοιες ιδέες είναι αντιπαραγωγικές. Θα ήταν προτιμότερο να τεθεί σε εφαρμογή ένα εξειδικευμένο πρόγραμμα περιορισμένου εύρους για την ενίσχυση αξιόλογων επιστημόνων στον τομέα της βιο-ιατρικής, οι οποίοι εργάζονται στις χώρες της Ευρώπης που παρουσιάζουν προς το παρόν μεγαλύτερες αδυναμίες στη μοριακή βιολογία αλλά είναι ικανές να συμπληρώσουν γρήγορα τα κενά.

10. Το πρόγραμμα κατάρτισης φαίνεται ότι αποτέλεσε μεγάλη επιτυχία και για τον λόγο αυτό προτείνεται η συνέχισή του. Ενδέχεται εντούτοις να αποδειχθεί απαραίτητη η ανεύρεση νέων τρόπων για τη διάδοση πληροφοριών σχετικά με το πρόγραμμα, αφού ο αριθμός των αιτήσεων συμμετοχής ήταν μικρότερος από ό,τι είχε προβλεφθεί. Θα πρέπει επίσης να ληφθεί υπόψη, ότι ορισμένες τροποποιήσεις στο πρόγραμμα θα ήταν πολύ χρήσιμες για τους νέους επιστήμονες που εργάζονται στον τομέα της ανάλυσης του ανθρώπινου γονιδιώματος. Υπάρχει ένα πρόβλημα, το οποίο φαίνεται να είναι κοινό σε όλες τις Ευρωπαϊκές χώρες, το πρόβλημα δηλαδή της υποστήριξης και της ανεξαρτησίας των νέων ερευνητών που έχουν αποδείξει στη χώρα τους, ή σε άλλες χώρες, ότι είναι διακεκριμένοι επιστήμονες. Τα εργαστήρια των Η.Π.Α αποτελούν σημαντικό σημείο έλξης, λόγω της ιδιαίτερα ευέλικτης διοικητικής δομής των περισσότερων πανεπιστημίων και, κυρίως, λόγω του εντυπωσιακού αριθμού κορυφαίων ερευνητικών κέντρων που λειτουργούν σε πολλά πανεπιστήμια των Η.Π.Α. Θα είναι ολοένα πιο ελκυστικό για τους νέους Ευρωπαίους να επιδιώκουν να συνεργάζονται με εργαστήρια τέτοιων κέντρων για μακροπρόθεσμες ή βραχυπρόθεσμες χρονικές περιόδους αλλά κυρίως κατά τη διάρκεια των πιο παραγωγικών τους χρόνων όσον αφορά τη διεξαγωγή πρωτογενούς έρευνας. Σήμερα, η έρευνα στον τομέα της βιο-ιατρικής μπορεί να διεξαχθεί με τον καλύτερο δυνατό τρόπο σε πολύ μεγάλα κέντρα. Είναι αναγκαίο να αναγνωρισθεί, ότι ένα από τα πιο σημαντικά καθήκοντα, σε ό,τι αφορά τη χρηματοδότηση και την οργάνωση της επιστήμης στην Ευρώπη, είναι η δημιουργία ενός αντίβαρου σε αυτά τα πολύ ισχυρά κέντρα βασικής βιο-ιατρικής έρευνας των Η.Π.Α. Προτείνεται στο σημείο αυτό, η δημιουργία θέσεων για νέους, ανεξάρτητους ερευνητές στα πεδία εκείνα της βιο-ιατρικής έρευνας, που επιτρέπουν σε εξαιρετικά ειδικευμένους νέους επιστήμονες να διεξαγάγουν έρευνα της επιλογής τους σε ένα από τα ευρωπαϊκά πανεπιστήμια, απελευθερωμένοι από τις συχνά πολύ "παραδοσιακές" διοικητικές τους δομές. Στη δημιουργία θέσεων, θα πρέπει να προστεθεί η διάθεση πιστώσεων για την προμήθεια αναλώσιμων υλικών και εξοπλισμού καθώς και για την πρόσληψη ερευνητικού προσωπικού. Υπολογίζεται ότι τέτοιες δομές θα βοηθήσουν πολύ σημαντικά στην προσέλευση ή επαναπροσέλευση πολλών από τους πιο παραγωγικούς νέους ερευνητές από το εξωτερικό στις ευρωπαϊκές χώρες.

11. Τα προγράμματα ESLA αποτελούν βασικές συνιστώσες των προγραμμάτων για τα γονιδιώματα. Η ομάδα προτείνει, αν και όχι ομόφωνα, τη συνέχιση του προγράμματος ESLA και την παροχή μακροπρόθεσμης ενίσχυσης. Είναι σημαντικό να γίνει το πρόγραμμα όσο το δυνατόν ευρύτερα

γνωστό, και οι ανάδοχοι να λάβουν τις κατάλληλες πληροφορίες για το αναμενόμενο αποτέλεσμά του. Ένα σημαντικό στοιχείο των μελλοντικών προγραμμάτων ESLA θα αφορά την παροχή μέσων στις συμμετέχουσες ομάδες με σκοπό τη συνεργασία, την αλληλεπίδραση και την ανταλλαγή ιδεών και αποτελεσμάτων.
Θα πρέπει επίσης να καταβληθούν ιδιαίτερες προσπάθειες για να συμπεριληφθούν στο πρόγραμμα η οικονομική των τεχνικών αλλαγών καθώς και η πολιτική και οι μελέτες για την επιστήμη. Η έλλειψη γεωγραφικής ισορροπίας αποτελεί ένα άλλο πρόβλημα στο οποίο πρέπει να δοθεί προσοχή.

12. Η ενίσχυση των συναντήσεων πρακτικής εργασίας και των συνεδριάσεων αποτελεί σαφώς μία βασική συνιστώσα του ΠΑΑΓ και προτείνεται η συνέχιση του προγράμματος αυτού. Εντούτοις, συνιστώνται ορισμένες διοικητικές αλλαγές. Προτείνεται για παράδειγμα η σύσταση μιας επιστημονικής συμβουλευτικής επιτροπής με σκοπό να γνωμοδοτεί για την πολιτική του προγράμματος και να εξετάζει τις αιτήσεις. Πρέπει να καταβληθούν προσπάθειες για να επιτευχθεί καλύτερη ισορροπία σε ό,τι αφορά τα θέματα μεταξύ των συναντήσεων πρακτικής εργασίας που χρηματοδοτούνται. Η χρηματοδοτική ενίσχυση, μέσω του οργανισμού HUGO, συναντήσεων πρακτικής εργασίας με αντικείμενο ένα κάθε φορά χρωμόσωμα έχει ουσιαστική σημασία και πρέπει να συνεχισθεί. Γενικά, πρέπει να δοθούν ενισχύσεις στις συναντήσεις πρακτικής εργασίας με αντικείμενο τα χρωματοσώματα που διοργανώνονται στην Ευρώπη, ως συνεισφορά στον παραπάνω οργανισμό. Θα πρέπει επίσης να δοθούν ενισχύσεις, με τη μορφή κάλυψης των δαπανών ταξιδίου, σε ευρωπαίους ερευνητές που συμμετέχουν σε συναντήσεις πρακτικής εργασίας εκτός Ευρώπης. Αξίζει επίσης να ενισχυθούν οι συναντήσεις πρακτικής εργασίας οι οποίες συγκεντρώνουν επιστήμονες που εργάζονται στα πλαίσια του ΠΑΑΓ σε ανάλογα θέματα (όπως έγινε ως ένα βαθμό κατά το παρελθόν), για παράδειγμα τους επιστήμονες εκείνους που εργάζονται στο EUROGEM ή με βιβλιοθήκες cDNA. Είναι προφανές ότι με τον τρόπο αυτό θα προωθηθούν οι επαφές μεταξύ ομάδων σε διαφορετικές ευρωπαϊκές χώρες.

13. Μία άλλη ευπρόσδεκτη προσθήκη στο πρόγραμμα είναι η κατάρτιση κλινικών ιατρών σε όλη την Ευρώπη. Για πολλούς κλινικούς ιατρούς, η γενετική αποτελεί ίσως μία τραυματική εμπειρία της εποχής που έδιναν εξετάσεις στην Ιατρική Σχολή. Με την ταχεία πρόοδο στην γενετική ιατρική, οι κλινικοί συνάδελφοί μας βρίσκονται ήδη σε δύσκολη θέση έναντι των ασθενών τους που θα τους θέτουν πιεστικές ερωτήσεις. Τα εξειδικευμένα προγράμματα κατάρτισης μπορούν τουλάχιστον να αποτελέσουν μία μερική λύση στο πρόβλημα.

RESUMEN

1. El Programa de Análisis del Genoma Humano (HGAP) forma parte del Segundo Programa marco de Acciones Comunitarias de Investigación y Desarrollo Tecnológico, y se incluye en el apartado "Salud" del capítulo "Calidad de Vida". El programa tiene por objetivo:

   - utilizar y perfeccionar nuevas biotecnologías para el estudio del genoma humano, a fin de comprender mejor los mecanismos de las funciones genéticas y prevenir y tratar las enfermedades humanas;

   - elaborar un enfoque integrado de los aspectos éticos, sociales y jurídicos que planteen las posibles aplicaciones de los resultados obtenidos.

2. En el marco de sus tareas de supervisión periódica y en virtud del apartado 3 del artículo 4 de la Decisión del Consejo por la que se adopta el HGAP (D.O. nº L196 de 29.06.1990, p.8), la Comisión designó en diciembre de 1992 un grupo de expertos independientes para que evaluaran dicho programa. En ese mismo artículo se especifica que la evaluación ha de llevarse a cabo teniendo en cuenta los logros científicos y técnicos del programa, la calidad y la importancia práctica de los resultados, la eficacia de la gestión, los aspectos éticos sociales y jurídicos, y las aportaciones y repercusiones en los programas nacionales de investigación.
   Durante la evaluación el grupo de expertos visitó cuatro centros que participaban en el programa y consultaron a más de trenta personas (funcionarios nacionales y comunitarios, participantes en el HGAP y usuarios).

3. El importe total asignado al programa ascendió a 15,6 millones de ecus, distribuidos de la siguiente manera: mapas genéticos 21%, cartografía física 27,6%, tratamiento de datos y bases de datos 15%, tecnologías genéticas avanzadas 18%, formación 12% y gestión 6,4%.

   En el HGAP intervinieron aproximadamente 100 centros comunitarios.

CONCLUSIONES

El grupo de trabajo piensa que el HGAP ha conseguido un gran éxito y es una importante fuerza motriz en el panorama de la investigación europea sobre genoma humano. Actualmente, la investigación sobre el genoma está avanzando a un ritmo extremadamente rápido. El progreso ha sido especialmente espectacular en Europa durante los últimos años, con el éxito de empresas como la secuenciación de un cromosoma completo de levadura, mapas físicos de genomas completos y mapas genéticos perfeccionados. Está claro que el HGAP ha desempeñado un papel importante en el establecimiento de relaciones más equilibradas con los Estados Unidos. No obstante, también está claro que ciertos programas, como el apoyado por la AFM en Francia han sido también un elemento importante. El HGAP fue aprobado con un presupuesto bianual de 15,6 millones de ecus. El importe dedicado a la investigación del genoma en la CE es muy pequeño comparado con los presupuestos de los programas sobre genoma de los Estados Unidos y de Japón. Por tanto, el HGAP se ha limitado a complementar actividades nacionales existentes, y la importancia de la financiación comunitaria de los distintos programas depende en gran medida del peso de los programas nacionales. La CE ha concedido apoyo muy escaso a grandes grupos franceses (menos del 10%), mientras que ha sido importante en el caso de Gran Bretaña, Alemania, Italia y otros países europeos. El apoyo comunitario varía entre <5% al 50% del coste

total de cada proyecto. En el caso de proyectos transnacionales, este tipo de apoyo, en la mayoría de los casos, sólo supone una modesta influencia, y la posibilidad de que los países menos avanzados se beneficien de los programas transnacionales es limitado.

El establecimiento de los centros de recursos y los programas de formación son de gran ayuda para los laboratorios científicos organizados, así como para los grupos menos avanzados o menos establecidos. Éste es un aspecto muy importante del HGAP y de la ciencia actual en general, ya que la organización y la disponibilidad de los recursos son temas fundamentales. A este respecto, el HGAP ha sido muy útil a la Comunidad europea de investigación sobre el genoma, aspecto que debe acentuarse cuando se elaboren futuros programas.

El programa sobre ADNc del HGAP actual no se ha desarrollado con la rapidez que se esperaba, aunque se han producido bastantes secuencias parciales de ADNc. Está claro que, en el futuro, se dejará sentir la necesidad de disponer de grandes colecciones de bibliotecas de ADNc de elevada calidad.

El objetivo final del proyecto global sobre el genoma humano es la secuenciación de todo genoma humano. Actualmente no se incluyen en el HGAP grandes programas de secuenciación. Esta situación deberá corregirse en un futuro HGAP.

Los proyectos transnacionales han sido importantes para fomentar la colaboración europea y también han proporcionado medios a los pequeños laboratorios, especialmente en países menos desarrollados, para acceder a tecnologías complejas.

El programa de asociación es un componente fundamental del HGAP y parece que se ha llevado a cabo de forma satisfactoria.

Se admite que las actividades emprendidas dentro del programa ESLA estaban justificadas. No obstante, el grupo de evaluación debatió si el programa debería financiarse con la misma amplitud que en el pasado, dado el carácter limitado de los recursos y la amplitud de la gama de cuestiones urgentes que deben investigarse.
El programa ESLA ya completado puede considerarse como estudio piloto prometedor. El grupo de trabajo desea llamar la atención sobre el hecho de que Europa ofrece posibilidades únicas para este tipo de estudios, debido a la diversidad de los sistemas sociales y de atención sanitaria que funcionan en los distintos países.

El apoyo económico a los seminarios se ha tomado en el pasado del presupuesto de gestión. Aunque el grupo de trabajo de ESLA y CAN-HUG han colaborado con el programa, parece que se ha administrado de manera ad hoc.

RECOMENDACIONES

1. El grupo de evaluación considera que debe organizarse un tercer HGAP. No obstante, es necesario introducir modificaciones en el plan del proyecto debido al importante progreso que se ha observado durante el último año. Parece muy probable que en el plazo de otro año se complete un mapa genético de alta resolución y también un mapa físico completo del genoma humano basado en el CAL (Cromosoma artificial de levadura).

2. Es necesario elaborar una nueva estrategia de HGAP. Esta estrategia debe considerar también la posibilidad de enfocar la secuenciación del genoma completo mediante un "enfoque de tiro de escopeta". Esto exigiría un aumento importantísimo de la financiación.

3. Un rasgo clave del HGAP lo constituyen los centros de recursos y es fundamental asegurar la continuación de su existencia. La tarea de poner los resultados de toda la cartografía física del genoma rápidamente a disposición de la Comunidad será vasta pero necesaria; debe apoyarse en medios informáticos, con inclusión de una base de datos accesible, completa y de fácil uso, pero también a nivel de la distribución de clones de cósmidos y de CAL, tarea que exige la dedicación de mucho trabajo. Constituiría un paso fundamental el poner estos reactivos rápidamente al alcance de todos los científicos europeos, por ejemplo mediante la amplia distribución de "filtros de politeno" con CAL ordenados para todos los cromosomas humanos. En general, se requiere una gama más amplia de bibliotecas ordenadas para satisfacer las más diversas necesidades de la investigación sobre el genoma, una vez se haya completado el primer mapa físico.

4. En el futuro, se necesitarán colecciones ordenadas de ADNc de longitud completa procedentes de todos los tejidos del organismo. Los centros de recursos que proporcionen bibliotecas ordenadas de ADNc como servicio a la comunidad científica deberán tratarse con prioridad en un futuro HGAP.

5. Debe considerarse la asignación de recursos a proyectos de secuenciación de ADNc a gran escala. Después de todo, la idea de secuenciar el ADNc para obtener un catálogo completo de los genes humanos es de origen europeo.

6. En un futuro HGAP debe considerarse la inclusión de la secuenciación genómica a gran escala, que no formaba parte del HGAP original. Será necesario realizar algunos proyectos piloto con secuenciación de megabases para evaluar las posibilidades futuras de tratar la secuenciación de cromosomas humanos completos. Asimismo debe considerarse cuidadosamente la posibilidad de secuenciar el genoma completo mediante un "enfoque de perdigonada". Se sugiere la creación de un grupo específico para tratar este problema. Si la CE tiene intención de participar en un proyecto de este tipo, tendrá que ampliar en gran medida el presupuesto del programa para conseguir más rápidamente el objetivo final del programa sobre el genoma global, la secuencia núcleotidica completa del genoma humano.

7. Por otra parte, EUROGEM habrá completado su misión una vez terminado el mapa genético de alta resolución.

8. La bioinformática es un campo que probablemente se desarrollará muy rápidamente en el futuro próximo. El diseño de programas de uso fácil para el análisis de grandes cantidades de datos constituirá indudablemente un aspecto importante de un futuro HGAP. A la vista de las críticas generales de que es objeto GDB, parece útil prever bases alternativas de datos o, al menos, un sistema diferente de acceso a las bases de datos: a este respecto, parece prometedor el avance de la IGD (Integrated Genome Database) de Heidelberg y el modelo de distribución preconizado por este grupo, con un sistema ACeDB que funciona localmente y se alimenta con datos procedentes de otras bases de datos sobre genoma, parece particularmente prometedor. Sigue dejando que desear la comunicación entre biólogos y científicos de la informática: siguen perteneciendo en gran medida a dos culturas bastante diferentes. Los dos sectores han evolucionado muy

rápidamente en los últimos años, y pocas personas son competentes simultáneamente en los dos.
Probablemente, la única forma de eliminar esta dificultad es aumentar el número de estas personas mediante puestos y becas atractivas.
Por otra parte, debe dedicarse atención, y cierta financiación, a la mejora de la interface entre el "mundo del genoma" y la comunidad de biología general, con inclusión no sólo de la genética médica sino también, por ejemplo, de grupos que realicen investigación funcional en el sistema del ratón, de forma que puedan aproximarse estructura y función.

9. Deben continuarse los proyectos transnacionales, aunque tengan que seleccionarse muy cuidadosamente. Al prestar apoyo a la investigación y formular sugerencias sobre como distribuir los fondos de investigación, deberá recordarse que las colaboraciones, que son indudablemente muy importantes, no pueden ser organizadas por nadie, sino que deben desarrollarse espontáneamente. A este respecto, no es prudente estipular la colaboración entre científicos procedentes de determinadas zonas de Europa o incluso condicionar la atribución de fondos a dichas colaboraciones. Tales ideas son contraproductivas. Sería preferible iniciar un programa especial de extensión limitada para apoyar a los científicos que lo merezcan en el campo biomédico que trabajen en los países de Europa que siguen presentando un bajo nivel en biología molecular pero son capaces de elevarlo rápidamente.

10. El programa de formación ha sido en gran medida todo un éxito, por lo que se recomienda continuarlo. No obstante, puede ser necesario encontrar nuevos medios de difusión de información sobre el programa, ya que el número de solicitudes fue muy inferior al previsto. Debe tenerse en cuenta también que la modificación de ciertos aspectos del programa podría ser muy beneficiosa para jóvenes científicos que trabajen en el campo del análisis del genoma humano. Existe un problema que parecen compartir todos los países europeos, que es el del apoyo y la independencia de jóvenes investigadores que se han revelado como científicos de primer orden en su propio país o en otro distinto. Existe una atracción muy importante por parte de los laboratorios de los Estados Unidos, con su flexibilísima estructura administrativa de la mayoría de las universidades y, sobre todo, con un número impresionante de centros de investigación de máximo nivel en muchas universidades. Cada vez será más atractivo para los jóvenes europeos intentar asociarse con los laboratorios de tales centros durante más o menos tiempo, pero generalmente durante sus años más productivos para la investigación original. Actualmente, la investigación biomédica se realiza de forma óptima en los centros que han alcanzado un tamaño crítico. Es necesario reconocer que una de las importantes tareas de la organización y financiación de la ciencia en Europa es crear un contrapeso frente a estos poderosos centros de investigación biomédica fundamental de los Estados unidos. Desde aquí se sugiere la creación de puestos para jóvenes investigadores independientes en las áreas de investigación biomédica que permitirían a jóvenes científicos de elevada cualificación proseguir las investigaciones que ellos mismos eligieran en algunas de las universidades europeas, pero al margen de sus, frecuentemente muy "tradicionales", estructuras administrativas. Además, a estos puestos deberían asignarse fondos para adquirir material fungible, equipo y personal de investigación. Se supone que tales estructuras ayudarían muy considerablemente a los países europeos a retener o volver a atraer a muchos de los jóvenes investigadores más productivos, que de otra forma saldrían de Europa.

11. Los programas ESLA son componentes básicos de los programas sobre el genoma. El grupo de trabajo recomienda, aunque sin unanimidad, que se continúe con el programa ESLA y que se le proporcione apoyo de largo alcance. Es importante que el programa se anuncie lo más ampliamente posible y que los contratistas reciban información adecuada sobre los resultados que se esperan del programa. Un componente urgente de los futuros programas ESLA consistirá en proporcionar medios para que los grupos participantes cooperen, interactúen e intercambien ideas y resultados.
También debe procurarse incluir la economía del cambio técnico, la política científica y los estudios de la ciencia en el programa. Otro aspecto que exige atención es el desequilibrio geográfico.

12. El apoyo a seminarios y reuniones constituye claramente un componente fundamental del HGAP, por lo que se recomienda continuar con este programa. No obstante, se recomiendan ciertos cambios administrativos. Por ejemplo, se sugiere la creación de un grupo consultivo científico, encargado de emitir dictámenes sobre la política del programa y de seleccionar las solicitudes. Debe intentarse obtener un mejor equilibrio respecto a los temas tratados en los seminarios objeto del apoyo. El apoyo a través de HUGO a seminarios sobre cromosomas sencillos es fundamental y debe continuar. En general, debe prestarse apoyo a los seminarios sobre cromosomas que se celebren en Europa como contribución a la organización. También debe darse apoyo en forma de bolsas de viaje a europeos que participen en seminarios celebrados fuera de Europa. También parece conveniente apoyar seminarios en que se reúnen científicos que trabajan dentro del HGAP sobre temas similares (como se ha hecho en el pasado en cierta medida), por ejemplo los que trabajen con bibliotecas de ADNc o EUROGEM. Evidentemente, así se fomentarían los contactos entre grupos de distintos países europeos.

13. También sería una adición positiva la inclusión en el programa de la educación de médicos en ejercicio en toda Europa. Para muchos médicos en ejercicio, la genética puede ser un recuerdo traumático de la época en que se examinaban en la facultad de medicina. Con el rápido progreso de la genética médica, nuestros colegas en ejercicio ya encuentran dificultades cuando sus pacientes les plantean preguntas urgentes. El problema podría resolverse, al menos parcialmente, mediante programas especializados de formación.

RESUME

1. Le programme "Analyse du génome humain" appartient au deuxième programme cadre pour des actions communautaires de recherche et de développement technologique. Il a été fixé au paragraphe "Santé" du chapitre "Qualité de la vie", avec les objectifs suivants:

   utiliser et améliorer les nouvelles biotechnologies pour l'étude du génome humain en vue d'une meilleure compréhension des mécanismes des fonctions génétiques, ainsi que de la prévention et du traitement de maladies humaines;

   élaborer une approche intégrée des aspects éthiques, sociaux et juridiques des applications possibles des résultats obtenus.

2. Dans le cadre de ses responsabilités en matière d'évaluation, la Commission a nommé en décembre 1992 un groupe d'experts indépendants chargés d'évaluer le programme "Génome humain". Le mandat de ce groupe est fixé à l'article 4 paragraphe 3 de la décision du Conseil arrêtant le programme en question (JO L 196 du 29.6.1990, p. 8). Le même article précise que l'évaluation doit prendre en compte les résultats scientifiques et techniques du programme, leur qualité et leur valeur pratique, l'efficacité de la gestion du programme, ses aspects éthiques, sociaux et juridiques ainsi que son incidence sur les programmes nationaux de recherche et les avantages que ceux-ci en ont tirés.

   Au cours de son évaluation, le groupe d'experts a visité quatre centres participant au programme et a rencontré plus de trente personnes - fonctionnaires de la Commission et fonctionnaires nationaux, participants et utilisateurs.

3. La somme des fonds alloués au programme s'élevait à 15,6 millions d'écus, répartis comme suit: cartes génétiques 21%, cartographie physique 27,6%, traitement des données et bases de données 15%, technologies génétiques avancées 18%, formation 12%, administration 6,4%.

   Une centaine d'instituts de la Communauté ont participé au programme.

CONCLUSIONS

Le groupe d'experts estime que le programme "Génome humain" est une réussite et qu'il joue un rôle moteur dans la recherche européenne sur le génome humain. Les recherches actuelles dans ce domaine progressent avec une extrême rapidité. Au cours de ces dernières années les progrès ont été particulièrement sensibles en Europe, marqués par le succès d'entreprises telles que le séquençage du chromosome de levure entier, la cartographie physique de génomes entiers et des cartes génétiques affinées. Il est évident que le programme a joué un rôle important dans l'établissement de relations plus équilibrées avec les Etats-Unis. Cependant, il est tout aussi évident que des programmes de grande ampleur comme celui que subventionne l'AFM en France ont stimulé la recherche. Le programme "Génome humain" a été adopté avec un budget de 15,6 millions d'écus sur deux ans. Les sommes allouées par la Communauté européenne à la recherche sur le génome sont très modestes comparées aux budgets des programmes américains et japonais dans ce domaine. Le programme "Génome humain" n'a donc fait que compléter les actions nationales en cours et le poids des subventions communautaires dans les différents programmes dépend largement de l'ampleur des programmes nationaux. La contribution communautaire accordée à des groupes français importants est mineure (moins de 10%), alors qu'elle est substantielle au Royaume-Uni, en Allemagne, en Italie et dans d'autres pays européens. L'aide communautaire varie de moins de 5% à 50% du budget total de chaque projet. En ce qui concerne les projets transnationaux, ce type d'aide ne peut avoir, dans la plupart des cas, qu'une

(7)

incidence modeste, et les possibilités pour les pays moins avancés de bénéficier de ces programmes sont limitées.

La mise en place de centres d'approvisionnement et de programmes de formation est très utile aux laboratoires scientifiques bien organisés aussi bien qu'aux laboratoires moins avancés ou aux groupes moins structurés. Il s'agit là d'un élément important du programme, et des activités scientifiques actuelles en général, car l'organisation et la disponibilité des ressources sont des questions essentielles. Sur ce point, le programme a été précieux pour les chercheurs européens dans le domaine du génome, et cet élément doit être souligné dans l'élaboration de programmes futurs.

Le programme sur l'ADN c dans le programme "Génome humain" actuel n'a pas été développé aussi rapidement qu'on l'espérait, bien qu'un grand nombre de séquences partielles d'ADN c aient été établies. Il est clair qu'à l'avenir un grand nombre de bibliothèques d'ADN c de haute qualité seront nécessaires.
L'objectif du projet "Génome humain" dans son ensemble est le séquençage du génome humain entier. Le programme ne contient pas actuellement de programmes de séquençage de grande ampleur. Cela devrait être le cas dans le futur.

Les projets transnationaux ont sensiblement contribué à la promotion de la collaboration au niveau européen. Ils ont aussi permis à de petits laboratoires, notamment dans des pays moins développés, d'accéder à des technologies avancées.

Le programme de bourses d'études est une composante essentielle du programme "Génome humain". Il semble avoir été réalisé de manière satisfaisante dans le passé.

Les experts reconnaissent que les activités ESLA sont justifiées. Cependant, ils se demandent si ces elles doivent bénéficier du même financement que par le passé, tout simplement parce que les ressources sont limitées et que de nombreuses questions doivent être étudiées d'urgence.

Les activités ESLA déjà terminées peuvent être considérées comme une étude pilote prometteuse. Le groupe d'experts désire faire remarquer que l'Europe, par la diversité des programmes appliqués dans les différents pays en matière de soins de santé et de protection sociale, offre des possibilités uniques pour ce type d'études.

Les séminaires ont été, dans le passé, financés par le budget administratif. Bien que le CAN Analyse génome humain et le groupe de travail ESLA aient contribué à l'organisation du programme, il semble que celui-ci a été administré assez convenablement.

RECOMMANDATIONS

1. Le groupe d'experts estime qu'il convient de lancer un troisième programme "Génome humain". Le plan du projet doit cependant être modifié, compte tenu des progrès remarquables réalisés au cours de la dernière année. Il est très probable qu'une carte génétique à haute résolution ainsi qu'une carte physique complète du génome humain sur la base du chromosome artificiel de levure pourront être établies en un an.

2. Il convient d'élaborer un nouveau plan stratégique pour le programme. Ce plan doit aussi envisager la possibilité d'aborder le séquençage du génome entier selon une "approche en aveugle". Cette approche nécessiterait un financement beaucoup plus important.

3. L 'existence de centres d'approvisionnement est une caractéristique essentielle du programme. Mettre à la disposition des chercheurs les résultats de la cartographie physique du génome entier sera une tâche de longue haleine mais nécessaire; elle doit être entreprise avec des moyens informatiques, notamment une base de données accessible, complète et conviviale; il convient aussi d'assurer la distribution de clones de chromosomes artificiels de levure et de cosmides, ce qui requiert un personnel important. Il sera essentiel de rendre ces réactifs aisément accessibles à tous les scientifiques européens, par exemple en diffusant largement des "filtres de polytène" contenant les chromosomes de levure ordonnés pour tous les chromosomes humains. De manière générale, une gamme plus étendue de bibliothèques ordonnées sera requise pour répondre aux besoins les plus divers de la recherche sur le génome, une fois que la première carte physique sera établie.

4. A l'avenir, des collections ordonnées d'ADN c entiers de tous les types de tissus corporels seront nécessaires. Les centres d'approvisionnement mettant des bibliothèques ordonnées d'ADN c à la disposition de la communauté scientifique doivent avoir une priorité élevée dans un futur programme "Génome humain".

5. Il convient d'envisager l'attribution de ressources à des projets de séquençage de l'ADN c à très grande échelle. Le principe du séquençage de l'ADN pour obtenir un catalogue complet des gènes humains était, après tout, une idée européenne.

6. Le séquençage génomique à très grande échelle, qui n'était pas prévu dans le premier programme, doit être envisagé dans un programme futur. Il faudra réaliser des projets pilotes incluant le séquençage d'une très grande base afin d'évaluer les possibilités d'aborder le séquençage de chromosomes humains entiers. La possibilité de séquencer le génome entier grâce à une "approche à l'aveugle" doit elle aussi être étudiée avec attention. Il est proposé de créer un groupe ad hoc pour étudier ce problème. Si la Communauté européenne veut participer à un tel projet, elle devra augmenter considérablement le budget du programme pour atteindre plus rapidement le but final du programme global sur le génome, à savoir réaliser la séquence complète des nucléotides du génome humain.

7. Par ailleurs, EUROGEM aura bientôt terminé sa mission avec la réalisation de la carte génétique à haute résolution.

8. La bioinformatique est un domaine qui se développera sans doute très rapidement dans un avenir proche. La conception de logiciels conviviaux destinés à l'analyse de grandes masses de données représentera indubitablement un élément important d'un futur programme "Génome humain". Etant donné les nombreuses critiques émises contre la BDG, il devient utile d'envisager des solutions de remplacement à cette base de données, ou du moins un système différent d'accès à la base: sur ce point, les progrès de l'IGD d'Heidelberg ("Integrated Genome Database", base de données intégrée sur le génome) semblent prometteurs et le modèle de distribution défendu par ce groupe, qui utilise un système ACeDB local alimenté par des données provenant des autres bases de données sur le génome est particulièrement intéressant.

La communication entre biologistes et informaticiens reste imparfaite: les deux groupes appartiennent encore à des cultures très différentes. Leurs deux domaines ont évolué très rapidement au cours des dernières années, et peu d'individus possèdent des compétences dans les deux secteurs. La seule solution est probablement d'en accroître le nombre, grâce à des bourses d'études et à des postes attrayants.

En outre, il convient de prendre en considération et de financer l'amélioration des "interfaces" entre le "monde du génome" et la communauté de la biologie générale, qui incluent non seulement la génétique médicale mais aussi, par exemple, des groupes réalisant des recherches fonctionnelles sur le système de la souris, de manière à rapprocher structure et fonction.

9. Les projets transnationaux doivent être poursuivis, bien qu'il faille les sélectionner soigneusement. En accordant des aides à la recherche et en formulant des suggestions sur la répartition des fonds destinés à la recherche, il convient de se rappeler que la collaboration - indubitablement essentielle - ne peut être planifiée, mais doit s'établir spontanément. C'est pourquoi il n'est pas judicieux de prévoir une collaboration entre scientifiques venant de certaines régions d'Europe, ou même de subordonner l'attribution de fonds à une telle collaboration. Ces idées vont à l'encontre du but recherché. Il vaudrait mieux lancer un programme spécial, d'ampleur limitée, pour venir en aide à des scientifiques méritants du secteur biomédical dans les pays d'Europe qui accusent actuellement un retard en biologie moléculaire mais sont capables de le rattraper rapidement.

10. Le programme de formation paraît, dans l'ensemble, avoir atteint ses objectifs, et sa poursuite est recommandée. Il faudra cependant peut-être trouver de nouveaux moyens de diffuser les informations le concernant, car le nombre des demandes a été beaucoup plus faible que prévu. Il faut également garder à l'esprit le fait que des modifications du programme pourraient être très utiles à de jeunes scientifiques travaillant dans le domaine de l'analyse du génome humain. Tous les pays d'Europe semblent être confrontés au même problème, celui d'assurer aide et indépendance à de jeunes chercheurs qui se sont révélés des scientifiques éminents dans leur propre pays ou à l'étranger. Une forte attraction est exercée par les laboratoires des Etats-Unis, dont la plupart des universités possèdent une structure administrative très souple et, surtout, un nombre impressionnant de centres de recherche de haut niveau. Il sera de plus en plus intéressant pour les jeunes Européens de collaborer avec les laboratoires de ces centres pour des périodes plus ou moins longues, mais généralement pendant leurs années les plus productives pour la recherche originale. De nos jours, les meilleurs endroits où poursuivre des travaux de recherche biomédicale sont des centres de taille critique. Il faut reconnaître que l'un des rôles fondamentaux du financement et de l'organisation de la science en Europe est de créer un contrepoids à ces très grands centres de recherche biomédicale fondamentale aux Etats-Unis. Dans ce sens, on peut proposer de créer des postes pour de jeunes chercheurs indépendants dans des domaines de recherche biomédicale, qui permettraient à de jeunes scientifiques hautement qualifiés de poursuivre les recherches de leur choix dans l'une des universités européennes, sans cependant se trouver soumis aux contraintes de leurs structures administratives souvent très "traditionnelles". Des fonds destinés aux fournitures consommables, aux équipements et au personnel de recherche seraient en outre attachés à ces postes. De telles structures contribueraient considérablement à attirer ou à faire revenir dans les pays européens un grand nombre des jeunes chercheurs les plus féconds.

11. Les activités ESLA sont une composante essentielle des programmes sur le génome. Le groupe d'experts recommande, bien que sans unanimité, la poursuite de ces activités et l'octroi d'une aide à long terme. Il importe que le programme soit publié le plus largement possible, et que les contractants reçoivent les informations adéquates concernant les résultats attendus. Fournir aux groupes de participants les moyens de coopérer, d'entrer en interaction et d'échanger des idées sera une priorité pour les futures activités ESLA.

Des efforts particuliers devront également être fournis pour inclure dans le programme du comité les aspects économiques des changements techniques, la politique de la science et les études scientifiques. Le déséquilibre géographique représente aussi un problème à étudier.

12. L'aide apportée à l'organisation de séminaires et de réunions est visiblement un élément essentiel du programme "Génome humain", et la poursuite de cette action est recommandée. Cependant, des changements sont proposés dans l'administration. Il est par exemple suggéré d'établir un comité scientifique consultatif chargé d'émettre des avis sur la politique du programme et de filtrer les candidatures. Il faut s'efforcer d'obtenir un meilleur équilibre dans les sujets traités par les séminaires subventionnés. L'aide apportée grâce au programme HUGO aux séminaires sur le chromosome unique est essentielle et doit être poursuivie. D'une manière générale, il convient de soutenir par une contribution à leur organisation les séminaires sur les chromosomes qui ont lieu en Europe. Le soutien peut également prendre la forme de subventions couvrant les frais de voyage des Européens participant à des séminaires organisés dans des pays non européens. Il semble également opportun de soutenir les séminaires qui rassemblent des scientifiques travaillant sur des sujets similaires au sein du programme "Génome humain" (comme cela a été fait auparavant dans certains cas), par exemple les chercheurs qui travaillent au sein d'EUROGEM ou avec des bibliothèques d'ADN c. Cela stimulerait bien sûr les contacts entre groupes situés dans des pays d'Europe différents.

13. Un autre complément intéressant au programme serait la formation de médecins exerçant dans toute l'Europe. Pour beaucoup de praticiens, la génétique n'est qu'un mauvais souvenir du temps de leurs examens. Les progrès rapides de la génétique médicale mettent nos collègues praticiens dans une position difficile vis-à-vis de patients qui les pressent de questions. Des programmes de formation spécialisés pourraient apporter une solution au moins partielle à ce problème.

SINTESI

1. Il programma di analisi del genoma umano (PAGU) fa parte del secondo programma quadro delle attività comunitarie di ricerca e sviluppo tecnologico. Questo programma è stato creato sotto la voce "Sanità" del settore "Qualità della vita" con il fine di:

   - sviluppare e diffondere le nuove biotecnologie riguardanti lo studio del genoma umano allo scopo di approfondire la conoscenza del meccanismo delle funzioni genetiche per la prevenzione e la lotta contro le malattie dell'uomo;

   - elaborare un approccio integrato che tenga conto degli aspetti etici, sociali e giuridici delle eventuali applicazioni dei risultati ottenuti.

2. Nel dicembre 1992 la Commissione ha designato, in quanto parte integrante di un regolare esercizo di valutazione, un gruppo di esperti indipendenti per attuare la valutazione del suddetto programma. Il gruppo di esperti è previsto dall'articolo 4, paragrafo 3, della decisione del Consiglio che addotta il suddetto programma (GU L 196 del 29.6.1990, pag. 8). Lo stesso articolo specifica che la valutazione dev'essere effettuata tenendo conto dei progressi scientifici e tecnici del programma, la qualità e l'importanza pratica dei suoi risultati, l'efficacia della sua gestione, i suoi aspetti etici, sociali e giuridici e il suo impatto e benefici sui programmi di ricerca nazionali.
   Nell'effettuare la valutazione, il gruppo ha visitato quattro centri partecipanti nel programma ed ha intervistato più di 30 persone tra cui funzionari della Commissione e funzionari nazionali, partecipanti al programma e utilizzatori.

3. L'importo totale assegnato a questo programma ammontava a 15,6 Mio di ECU. I fondi erano suddivisi come segue: mappe genetiche 21%, mappe fisiche 27,6%, elaborazione di dati e basi di dati 15%, tecnologie genetiche avanzate 18%, attività di formazione 12%, amministrazione 6,4%.

   Hanno partecipato al programma circa 100 istituti della Comunità europea.

CONCLUSIONI

Il gruppo di valutazione è del parere che il PAGU stia riscuotendo un gran successo e sia una importante forza trainante nel settore della ricerca europea del genoma umano. La ricerca sul genoma, attualmente, avanza a velocità rapidissima. Negli ultimi anni il progresso è stato particolarmente evidente in Europa, con il successo dei progetti quali la sequenziazione dell'intero cromosoma del lievito, le mappe fisiche del genoma completo e sofisticate mappe genetiche. E' chiaro che il PAGU ha rivestito un ruolo importante per determinare una relazione più equilibrata con gli Stati Uniti. Tuttavia, è chiaro che i programmi di una certa importanza come quello finanziato dalla AFM in Francia sono stati un importante incentivo. Il PAGU è stato approvato con un bilancio biennale di 15,6 Mio di ECU. L'importo finanziario riservato dalla Comunità europea alla ricerca sul genoma è molto esiguo se comparato con i bilanci dei programmi sul genoma negli Stati Uniti e in Giappone. Il PAGU ha quindi sovvenzionato solo programmi a livello nazionale già in corso e la percentuale dell'aiuto comunitario per i programmi individuali dipende in gran parte dal peso dei programmi nazionali.La Comunità

(8)

europea ha dato un aiuto assai esiguo a grossi gruppi francesi (meno del 10%) mentre è stato assai importante per il Regno Unito, la Germania, l'Italia ed altri paesi europei. L'aiuto comunitario varia dal < 5% al 50% del finanziamento totale di ogni progetto. Per i progetti transnazionali, nella maggior parte dei casi, questo aiuto è solo di modesta portata e, per i paesi meno sviluppati, la possibilità di beneficiare dei programmi transnazionali è limitata.

L'istituzione di centri di risorse e dei programmi di formazione è di grande aiuto sia per i laboratori scientifici organizzati, sia per i gruppi meno progrediti o meno organizzati. Questo aspetto è molto importante per il PAGU e in generale per la scienza odierna, visto che l'organizzazione e la disponibilità delle risorse sono i problemi di maggiore importanza. A questo riguardo il PAGU è stato di grande utilità per la ricerca del genoma nella Comunità europea e si deve tener conto di questo aspetto nella progettazione dei futuri programmi.

Il programma del cDNA nell'attuale PAGU non si è sviluppato così velocemente come si sperava sebbene si siano generate un gran numero di sequenze parziali del cDNA. In futuro saranno necessarie sempre più grandi raccolte di librerie del cDNA di ottima qualità.

L'obiettivo finale del progetto del genoma umano completo è il sequenziamento dell'intero genoma umano. Non sono inclusi nel PAGU, attualmente, programmi di sequenziamento estesi. Si deve modificare questa situazione in un PAGU futuro.

I progetti transnazionali hanno rivestito una certa importanza per la promozione di collaborazioni europee. Inoltre, hanno fornito a piccoli laboratori, soprattutto dei paesi meno sviluppati, i mezzi di accesso alle tecnologie sofisticate.

Il programma di scambio dei ricercatori è una componente assolutamente essenziale del PAGU e sembra che in passato abbia funzionato in modo soddisfacente.

Si è riconosciuto che le attività intraprese nell'ambito del programma ESLA erano giustificate. Tuttavia, il gruppo di valutazione ha discusso per vedere se il programma debba essere finanziato nella stessa misura del passato poiché ci sono risorse limitate e molti problemi incalzanti devono essere analizzati. Il programma ESLA già completato può essere considerato come uno studio pilota promettente. Il gruppo di esperti tiene a sottolineare il fatto che l'Europa offre possibilità uniche al mondo per questo tipo di studi, vista la diversità dell'organizzazione sanitaria e dei programmi sociali che operano nei vari paesi.

In passato il finanziamento per il workshop è stato ricavato dal bilancio amministrativo. Sebbene il comitato HUG ed il gruppo di lavoro ESLA abbiano dato una partecipazione attiva al programma, sembra che in certa misura siano stati amministrati ad hoc.

RACCOMANDAZIONI

1. Il gruppo di valutazione ritiene che si possa lanciare un terzo PAGU. Sono necessarie, comunque, alcune modifiche al piano del progetto, visti gli incredibili progressi realizzati durante l'anno passato. Sembra assai probabile che una mappa genetica ad alta risoluzione e inoltre una mappa fisica completa basata sullo YAC (cromosoma artificiale del lievito) del genoma umano verrà completata nell'arco di un anno.

2. E' necessario creare un nuovo piano strategico per il PAGU. Tale piano deve prendere in considerazione anche la possibilità di attuare il sequenziamento del genoma intero con un approccio casuale. Tale procedura richiederebbe un drastico aumento di fondi.

3. Una caratteristica tipica del PAGU sono i centri informatici ed è importante assicurare la loro esistenza ininterrotta. Per quanto riguarda l'intera mappa fisica del genoma, sarà un'impresa ardua

ma necessaria rendere disponibili alla comunità dei ricercatori i risultati già ottenuti; tale difficile compito va affrontato con mezzi informatici comprendendo una base di dati accessibile, completa e di facile impiego per l'utente, ma anche a livello della distribuzione di cloni e cosmidi e YAC. Un passo essenziale verso l'obiettivo consisterebbe anche nel rendere accessibili questi reagenti a tutti gli scienziati europei, per esempio distribuendo su larga scala "filtri politene" che contengono YAC ordinati per tutti i cromosomi umani. In generale sono necessarie serie di librerie ordinate più estese che servano agli scopi più svariati della ricerca sul genoma, una volta che la prima mappa fisica sarà completata.

4. In futuro si richiederanno raccolte ordinate di frammenti di cDNA in tutta la lunghezza provenienti da tutti i tessuti del corpo. Data l'utilità che rivestono per la comunità scientifica i centri che forniscono librerie ordinate di cDNA, devono avere l'assoluta priorità in un futuro PAGU.

5. Si dovrebbe prendere in considerazione l'assegnamento di risorse a progetti di sequenziamento del cDNA su larghissima scala. Dopo tutto, il concetto del sequenziamento del cDNA per ottenere un catalogo completo dei geni umani, è un'idea europea.

6. In un futuro PAGU si deve prendere in considerazione la necessità di creare una sequenziazione genomica su larghissima scala, fattore che non è stato preso in considerazione nel PAGU originale. Sarà necessario realizzare alcuni progetti pilota che comprendano il sequenziamento di alcuni milioni di basi per valutare le possibilità future relative ad una politica di sequenziamento dei cromosomi umani completi. Inoltre, si deve soppesare attentamente la possibilità relativa al sequenziamento dell'intero genoma con un approccio casuale e si suggerisce la creazione di un gruppo ad hoc per analizzare questo problema. Se la Comunità europea intende partecipare a tale progetto, deve però incrementare di molto il bilancio del programma per accelerare l'obiettivo del programma globale sul genoma e cioè il sequenziamento completo del nucleotide del genoma umano.

7. D'altra parte, l'EUROGEM, avrà completato presto la sua missione, una volta che la mappa genetica ad alta risoluzone sarà terminata.

8. Probabilmente il settore della bioinformatica si svilupperà molto rapidamente in un prossimo futuro. Il progetto di un software di facile utilizzazione per l'analisi di grossi quantitativi di dati avrà senz'altro un peso importante in un futuro PAGU. Vista la critica estesa diretta al GDB, è utile prevedere basi di dati alternative o perlomeno un diverso sistema di accesso alla base di dati: a questo riguardo, il progresso dell'IGD di Heidelberg sembra promettente e altrettanto promettente sembra il modello di distribuzione nominato da questo gruppo, che usa un sistema locale ACeDB gestito localmente e alimentato con i dati di altre basi di dati del genoma.

   Lascia a desiderare la comunicazione tra i biologi e gli esperti di computer: essi appartengono tuttora a due culture totalmente differenti. Entrambi i settori hanno avuto un'evoluzione rapidissima negli ultimi anni e sono poche le persone competenti contemporaneamente in entrambi i settori.

   Un loro aumento numerico mediante borse di studio e posti attraenti, è probabilmente l'unico modo per ovviare a questa difficoltà.

   Inoltre, si deve dedicare una maggiore attenzione e provvedere ad un finanziamento per migliorare l'interfaccia tra il "mondo del genoma" e la comunità della biologia generale, comprendendo non solo la genetica medica, ma anche, per esempio, gruppi che attuino una ricerca funzionale nel sistema del topo cosicché la struttura e la funzione vengano maggiormente avvicinate.

9. I progetti transnazionali devono continuare anche se la loro selezione dev'esser fatta con grande cura. Nel sostenere la ricerca e formulare suggerimenti su come distribuire i fondi, è bene

ricordare che le collaborazioni, senz'altro assai importanti, non possono essere organizzate da chiunque, ma devono svilupparsi e si svilupperanno spontaneamente. A questo riguardo non è bene impegnarsi con collaborazioni tra scienziati di certe zone in Europa e neanche fare affidamento sui fondi che dipendono da tali collaborazioni. Tali idee sono controproducenti. É preferibile, piuttosto, cominciare un programma speciale di un'ampiezza limitata per sostenere scienziati promettenti nel settore biomedico che lavorano in quei paesi europei che, per il momento, sono ancora deboli per quanto riguarda la biologia molecolare, ma sono in grado di recuperare il ritardo rapidamente.

10. Il programma di formazione ha avuto un grande successo e si raccomanda una continuazione dello stesso. Può essere necessario, tuttavia, trovare nuovi mezzi per diffondere l'informazione relativa al programma, visto che il numero delle candidature era molto più limitato di quanto si prospettava. Bisogna anche tenere a mente che alcune modifiche del programma possono essere di gran beneficio per giovani scienziati che lavorano nel settore dell'analisi del genoma umano. Sussiste un problema che sembra comune a tutti i paesi europei, vale a dire il sostegno e l'indipendenza di giovani ricercatori che si sono rivelati scienziati di alto livello nei loro o in altri paesi. C'è un richiamo considerevole dai laboratori degli Stati Uniti con la loro struttura amministrativa assai flessibile nella maggior parte delle università e, soprattutto, con un numero impressionante di centri di ricerca all'avanguardia in molte università americane. Per i giovani europei è sempre più attraente cercare di associarsi ai laboratori nei suddetti centri per periodi più lunghi o più corti ma, generalmente, negli anni più produttivi per la ricerca. La ricerca biomedica, oggigiorno, può essere attuata al meglio nei centri che abbiano raggiunto la massa critica. E' necessario riconoscere che uno dei compiti principali per il finanziamento e l'organizzazione scientifica in Europa sta nel fatto di creare un contrappeso a questi centri così potenti per la ricerca biomedica di base negli Stati Uniti. A questo riguardo si suggerisce di creare posti per giovani ricercatori indipendenti nei settori della ricerca biomedica che permettano ai giovani scienziati altamente qualificati di continuare la ricerca che hanno scelto in una delle università europee, ma, non dovendo sottostare alle strutture amministrative, molto spesso troppo "tradizionali". Oltre ai posti si dovrebbero abbinare fondi per beni di consumo, attrezzature e personale di ricerca. In questo modo tali strutture aiuterebbero in modo considerevole ad attrarre o a far tornare dall'estero molti dei giovani ricercatori più dotati nei paesi europei.

11. I programmi ESLA sono componenti essenziali dei programmi relativi al genoma. Il gruppo di valutazione raccomanda, anche se non all'unanimità, che il programma ESLA continui e che si fornisca un sostegno a lungo raggio. E' importante che il programma sia esteso il più possibile e che i contraenti ricevano informazioni adeguate relativamente all'obiettivo previsto del programma. E' urgente per i futuri programmi ESLA fornire mezzi di cooperazione, azioni incrociate e scambi di idee e risultati ai gruppi partecipanti.
Si devono fare notevoli sforzi per includere gli aspetti economici dei cambiamenti tecnologici, della politica scientifica e degli studi scientifici nel programma. La disparità geografica crea un altro problema di cui ci si deve occupare.

12. Si devono finanziare i seminari e le riunioni, componenti essenziali del PAGU e si raccomanda una continuazione del programma. Tuttavia, si raccomandano alcuni cambiamenti amministrativi. Si suggerisce, per esempio, la creazione di un gruppo scientifico consultivo per dare pareri sulla politica del programma e per analizzare le candidature. Vanno fatti sforzi per ottenere un maggiore equilibrio tra gli argomenti trattati nei seminari finanziati. Il finanziamento tramite HUGO per i singoli seminari sui cromosomi è essenziale e deve continuare. In generale, i seminari europei sui cromosomi devono ricevere un finanziamento come contributo all'organizzazione. Per i seminari al di fuori dell'Europa, si devono accordare agevolazioni ai partecipanti europei. Sembra importante anche sostenere i seminari in cui si trovano radunati gli scienziati che lavorano all'interno del PAGU su argomenti simili (come si è fatto in parte in passato), per esempio per coloro che hanno collaborato a EUROGEM o alle librerie del cDNA. Ovviamente tutto ciò stimolerebbe i contatti tra i gruppi dei vari paesi europei.

13. La formazione dei medici di tutta Europa va considerata come un elmento positivo da inserire nel programma. Per molti medici la genetica è un ricordo traumatico dei loro esami universitari. Con il rapido progresso nella genetica medica, i nostri colleghi medici sono già in una posizione difficile di fornte ai loro pazienti che pongono domande incalzanti. Una soluzione almeno parziale al problema può essere la creazione di programmi di formazione specializzati.

SAMENVATTING

1. Het Programma Analyse van het Menselijk Genoom (PAMG) is een onderdeel van het tweede kaderprogramma van communautaire werkzaamheden op het gebied van onderzoek en technologische ontwikkeling. Het programma is in het raam van de actie "Kwaliteit van het bestaan", onder het punt "Gezondheid", opgezet met als doel :

   - nieuwe biotechnologieën toe te passen en te verfijnen bij de studie van het menselijk genoom, met het oog op het verwerven van een beter inzicht in de genetische mechanismen enerzijds en de preventie en behandeling van menselijke ziekten anderzijds ;

   - een geïntegreerde benadering tot stand te brengen van de ethische, sociale en juridische aspecten van eventuele toepassingen van de resultaten van dit programma.

2. In het kader van de standaard-evaluatieprocedure heeft de Commissie in december 1992 een panel van onafhankelijke deskundigen belast met de evaluatie van het PAMG. De basis voor de activiteiten van het evaluatiepanel is artikel 4, lid 3, van de beschikking van de Raad waarbij dit programma is vastgesteld (PB L 196 van 29.6.1990, blz. 8). In het bedoelde artikel is bepaald dat bij de evaluatie rekening moet worden gehouden met de wetenschappelijke en technische resultaten van het programma, de kwaliteit en de praktische toepasbaarheid van die resultaten, de doeltreffendheid van het beheer, de ethische, sociale en juridische aspecten en de consequenties en voordelen voor de nationale onderzoekprogramma's.
   In het kader van deze evaluatie heeft het panel vier bij het programma betrokken centra gevisiteerd en meer dan dertig betrokkenen (ambtenaren van de Commissie en van de Lid-Staten, deelnemers aan het PAMG en gebruikers) geïnterviewd.

3. Voor dit programma is een totaalbedrag van 15,6 miljoen ecu uitgetrokken. Deze middelen zijn als volgt verdeeld : genetische kartering 21 %, fysische kartering 27,6 %, gegevensverwerking en databanken 15 %, geavanceerde genetische technologieën 18 %, opleidingsactiviteiten 12 %, administratie 6,4 %.

   Bij het PAMG waren een honderdtal instituten in de EG betrokken.

CONCLUSIES

Het panel heeft vastgesteld dat het PAMG grotendeels een succes is geworden en dat het een belangrijke impuls heeft gegeven aan het Europese onderzoek van het menselijk genoom. Het genoomonderzoek vordert momenteel met reuzenschreden. De jongste jaren is met name in Europa grote vooruitgang geboekt en zijn projecten als de sequentiebepaling van volledige gistchromosomen, de fysische kartering van het hele genoom en het opstellen van gedetailleerde genetische kaarten met succes bekroond. Het laat geen twijfel dat het PAMG een belangrijke rol heeft gespeeld bij het herstel van een zeker evenwicht met de Verenigde Staten. Evenzeer is echter duidelijk dat ook van grootschalige initiatieven zoals het onderzoekprogramma dat door het Franse AFM wordt gesteund, belangrijke impulsen zijn uitgegaan. Bij de vaststelling van het PAMG is voor de hele tweejarige looptijd van het programma een budget van 15,6 miljoen ecu ter beschikking gesteld. De bedragen die door de EG voor genoomonderzoek worden uitgetrokken zijn erg klein in vergelijking met de financiële middelen waarover de genoomprogramma's in de VS en Japan beschikken. Het PAMG kon daarom slechts een aanvulling zijn van de bestaande inspanningen op nationaal niveau ; het effect van EG-financiering op individuele programma's hangt in hoge mate af van de sterkte van de nationale programma's. Aan de grote Franse onderzoekgroepen heeft de EG bijzonder weinig steun verleend (minder dan 10 %) terwijl de steun voor Groot-Brittannië, Duitsland, Italië en andere Europese landen zeer belangrijk is geweest. De financiering door de EG varieert van minder dan 5 % tot 50 % van het totale budget van elk project. Voor transnationale projecten sorteert deze vorm van ondersteuning in de meeste gevallen een eerder gering effect. De minder geavanceerde landen halen uit deze transnationale programma's ook vrij weinig profijt.

Het opzetten van "resource centres" en opleidingsprogramma's betekent zowel voor gevestigde als voor minder geavanceerde wetenschappelijke laboratoria en minder gestructureerde groepen een belangrijke steun. Dit is een uiterst belangrijk aspect van het PAMG en van de hedendaagse wetenschap in het algemeen, aangezien aspecten als organisatie en de beschikbaarheid van hulpmiddelen van fundamenteel belang zijn. In dit opzicht heeft het PAMG het Europese genoomonderzoek een grote dienst bewezen. Aan dit aspect moet dan ook bij het opzetten van toekomstige programma's de nodige aandacht worden besteed.

Het cDNA-programma van het lopende PAMG is minder expansief gebleken dan verhoopt, hoewel heel wat partiële cDNA-sequenties zijn bepaald. Het is duidelijk dat er in de toekomst een grote behoefte zal bestaan aan omvangrijke cDNA-bibliotheken van zeer goede kwaliteit.

Het einddoel van het mondiale "Human Genome Project" is de sequentiebepaling van het volledige menselijk genoom. Momenteel worden in het kader van het PAMG geen grootschalige sequencing-programma's uitgevoerd. Dit dient in een toekomstig PAMG te worden gecorrigeerd.

De transnationale projecten hebben goede diensten bewezen bij de bevordering van de Europese samenwerking. Ook hebben zij ervoor gezorgd dat kleinere laboratoria, met name in de minder ontwikkelde landen, toegang hebben gekregen tot geavanceerde technologieën.

Het beurzenprogramma is zeker een essentieel onderdeel van het PAMG. Het laat zich aanzien dat dit in het verleden naar behoren heeft gefunctioneerd.

Het evaluatiepanel erkent dat er goede gronden waren voor het uitvoeren van de in het kader van het programma Ethische, Sociale en Juridische Aspecten (ESJA) aangevatte activiteiten. Het vraagt zich echter af of dit programma nog in dezelfde mate als voorheen moet worden gefinancierd, aangezien de financiële middelen beperkt zijn en vele andere dringende vragen een antwoord eisen.
Het reeds voltooide ESJA-programma kan worden gezien als een veelbelovende verkennende studie. Het panel benadrukt dat Europa, in het licht van de grote verschillen tussen de stelsels voor gezondheidszorg en sociale zekerheid in de diverse landen, voor dit type onderzoek unieke kansen biedt.

Voor de ondersteuning van workshops is in het verleden de post "huishoudelijke uitgaven" aangesproken. De inbreng van CAN-HUG en de ESJA-werkgroep in het programma kan niet worden geloochend ; wel schijnt het op een enigszins willekeurige manier te zijn beheerd.

AANBEVELINGEN

1. Het panel is van menig dat er een derde PAMG moet worden opgezet. De aanzienlijke vooruitgang die het laatste jaar is geboekt, maakt evenwel bepaalde wijzigingen in de opzet van het project noodzakelijk. Het laat zich aanzien dat binnen het jaar een zeer gedetailleerde genetische kaart alsmede een volledige, op de YAC-technologie gebaseerde fysische kaart van het menselijk genoom zullen zijn voltooid.

2. Voor het PAMG moet een nieuw strategisch plan worden opgesteld. Daarbij moet rekening worden gehouden met de mogelijkheid om bij de sequencing van het volledige genoom uit te gaan van een "shotgun"-benadering. Deze optie vereist evenwel een drastische verruiming van de financiële middelen.

3. Een essentieel aspect van het PAMG zijn de "resource centres", waarvan het voortbestaan hoe dan ook moet worden gegarandeerd. De resultaten van de fysische kartering van het hele genoom in een gemakkelijk raadpleegbare vorm ter beschikking stellen van alle betrokken wetenschappers, is een taak waarvan noch de omvang, noch het belang mogen worden onderschat. Om deze tot een goed einde te brengen is niet alleen informatisering nodig (met name een vlot toegankelijke, complete en gebruiksvriendelijke databank) maar ook een distributiesysteem voor YAC- en cosmideclonen. Het opzetten daarvan wordt ongetwijfeld een zeer arbeidsintensieve onderneming. Door dit moleculaire alaam ter beschikking te stellen van alle Europese

wetenschappers, b.v. via de grootschalige verspreiding van "polytene filters" met geordende YAC's voor alle menselijke chromosomen, zou al een essentiële stap zijn gerealiseerd. In het algemeen is een breder spectrum van geordende bibliotheken vereist met behulp waarvan, na de voltooiing van de eerste fysische kaart, in de meest diverse behoeften van het genoomonderzoek kan worden voorzien.

4. In de toekomst zal er behoefte bestaan aan geordende collecties integrale cDNA's uit de verschillende weefsels van het lichaam. Resource centres die als dienstbetoon aan de wetenschappelijke gemeenschap geordende cDNA-bibliotheken ter beschikking stellen, dienen in een toekomstig PAMG een hoge prioriteit te krijgen.

5. Overwogen moet worden om middelen ter beschikking te stellen voor megaprojecten op het gebied van cDNA-sequencing. De idee om via sequencing van cDNA's een complete catalogus van menselijke genen op te stellen, is ten slotte in Europa geboren !

6. Aan sequentiebepaling op megaschaal, die in het oorspronkelijke PAMG niet aan de orde was, moet in een toekomstig PAMG de gepaste aandacht worden geschonken. Om de kansen inzake sequentiebepaling van volledige menselijke chromosomen voor de toekomst in te schatten, zal het nodig zijn enkele proefprojecten uit te voeren waarbij megabase-sequenties worden bepaald. Ook moet serieus de mogelijkheid worden onderzocht om de basensequentie van het hele genoom via een "shotgun"-benadering te achterhalen. Voorgesteld wordt, deze kwestie door een ad hoc werkgroep te laten onderzoeken. Indien de EG overweegt in een dergelijk project te participeren, zullen de voor het programma uitgetrokken financiële middelen aanzienlijk moeten worden uitgebreid om het uiteindelijke doel van het mondiale genoomprogramma - de kennis van de complete nucleotidensequentie van het menselijk genoom - sneller te bereiken.

7. Daar staat tegenover dat de taak van EUROGEM : het opstellen van een gedetailleerde genetische kaart, eerlang zal zijn volbracht.

8. Van de bio-informatica kan in de nabije toekomst een explosieve ontwikkeling worden verwacht. De ontwikkeling van gebruiksvriendelijke software voor het analyseren van kolossale hoeveelheden gegevens zal ongetwijfeld een belangrijk onderdeel vormen van het toekomstige PAMG. Met het oog op de alom geformuleerde bezwaren tegen de GDB verdient het aanbeveling het gebruik van andere databanken of ten minste andere toegangssystemen niet uit te sluiten : in dit verband is de met de Heidelberger "IGD" (Integrated Genome Database) geboekte vooruitgang veelbelovend en lijkt het door de betrokken groep bepleite distributiemodel - een lokaal ACeDB-systeem waarin gegevens uit de andere genoom-databanken worden ingevoerd - allerlei voordelen te bieden.
De communicatie tussen biologen en informatici laat nog te wensen over : zij leven nog steeds in grotendeels gescheiden werelden. Beide vakgebieden zijn de laatste jaren bijzonder snel geëvolueerd en maar weinigen beschikken over een uitgebreide vakkennis in beide specialismen.
Waarschijnlijk kan daaraan alleen iets worden gedaan door het creëren van aantrekkelijke beurzen en banen die ervoor moeten zorgen dat het aantal van deze "bruggenbouwers" toeneemt.
Bovendien moet werk worden gemaakt (en in enige financiering worden voorzien) van een verbeterde communicatie tussen de wereld van de genoomanalyse en de rest van de biologische wetenschap - niet alleen de medische genetica maar ook, bij voorbeeld, het functioneel onderzoek van het muizegenoom. Dit moet het mogelijk maken structuur en functie duidelijker aan elkaar te relateren.

9. De transnationale projecten moeten worden voortgezet, al dient bij de selectie daarvan de grootste zorg aan de dag te worden gelegd. Bij het steunen van onderzoek en het formuleren van suggesties betreffende de verdeling van financiële middelen dient men zich voor ogen te houden dat samenwerking, hoe belangrijk ook, niet van buitenaf kan worden opgedrongen maar alleen spontaan kan, en moet, tot stand komen. In dit verband lijkt het geen verstandige keuze om van de samenwerking tussen wetenschappers uit bepaalde regio's in Europa een spijkerharde eis te maken of de toekenning van financiële middelen van dit soort samenwerking afhankelijk te maken.

Een dergelijke aanpak sorteert alleen een averechts effect. Veeleer verdient het de voorkeur een speciaal programma van beperkte omvang op te zetten ter ondersteuning van verdienstelijke beoefenaren van de biomedische wetenschappen uit Europese landen die momenteel inzake moleculaire biologie een zekere achterstand vertonen maar in staat zijn deze snel in te lopen.

10. Het opleidingsprogramma lijkt goeddeels een succes te zijn geworden en het panel pleit voor de voortzetting daarvan. Wel moet misschien worden uitgekeken naar nieuwe mogelijkheden om de bekendheid van dit programma te vergroten, aangezien het aantal aanvragen veel kleiner is gebleven dan verwacht. Ook dient men zich te realiseren dat voor jonge, in de genoomanalyse actieve wetenschappers bepaalde aanpassingen van het programma een enorm pluspunt zouden betekenen. Er is namelijk een probleem waar álle Europese landen mee te kampen hebben : de ondersteuning van het zelfstandig onderzoek van jonge vorsers die zich in hun eigen of in een ander land als wetenschappers van topniveau hebben ontpopt. Op deze mensen oefenen de laboratoria in de Verenigde Staten een zeer grote aantrekkingskracht uit. De meeste universiteiten hebben daar immers een zeer soepele administratieve structuur, en bovenal telt het land een indrukwekkend aantal onderzoekcentra van topniveau, verspreid over de verschillende universiteiten. Voor jonge Europeanen wordt het steeds verleidelijker gedurende kortere of langere tijd in de laboratoria van deze centra te gaan gasteren - meestal gedurende de periode van hun carrière waarin zij de grootste werkkracht en wetenschappelijke creativiteit aan de dag leggen. Biomedisch onderzoek kan heden ten dage het best worden gedaan in centra met een bepaalde minimumomvang. Men dient zich te realiseren dat één van de belangrijke taken van de financiering en de organisatie van het wetenschappelijk onderzoek in Europa erin bestaat, een tegengewicht te vormen voor de enorme aantrekkingskracht van deze Amerikaanse centra voor fundamenteel biomedisch onderzoek. Daarom wordt hier voorgesteld om ten behoeve van jonge zelfstandige biomedische wetenschappers banen te scheppen waardoor hooggekwalificeerde jonge wetenschappers onderzoek naar eigen keuze zouden kunnen doen aan één van de Europese universiteiten, zonder daarbij gehinderd te worden door de vaak "traditionele" administratieve structuren van deze laatste. Naast deze banen zelf dient ook in (daaraan gekoppelde) financiële middelen voor klein materiaal, toestellen en laboratoriumpersoneel te worden voorzien. Dit soort voorzieningen kan er in niet geringe mate toe bijdragen een groot aantal produktieve jonge wetenschappers uit derde landen naar Europa te lokken c.q. terug te halen.

11. De ESJA-programma's zijn een essentieel onderdeel van de genoomprogramma's. Hoewel ter zake niet unaniem, beveelt het panel aan het bestaande ESJA-programma voort te zetten en ervoor te zorgen dat dit ook op langere termijn wordt ondersteund. Belangrijk is dat aan het programma de ruimst mogelijke bekendheid wordt gegeven en dat de contractanten terdege worden voorgelicht over de resultaten die van het programma worden verwacht. In het kader van toekomstige ESJA-programma's dient ook absoluut te worden voorzien in middelen die de deelnemende groepen in staat moeten stellen samen te werken, op elkaars activiteiten in te spelen en ideeën en resultaten uit te wisselen.
Er moet een extra inspanning worden gedaan om in het programma ook voor de economische aspecten van technologische evolutie, voor wetenschapsbeleid en voor "wetenschapsonderzoek" de nodige plaats in te ruimen. Ook aan de geografische onbalans moet dringend iets worden gedaan.

12. De ondersteuning van workshops en vergaderingen is duidelijk een essentieel onderdeel van het PAMG en de voortzetting van dit programma is zeker gewenst. Wel wordt gepleit voor enkele wijzigingen van administratieve aard. Zo lijkt het b.v. wenselijk een wetenschappelijke adviesraad op te zetten die de aanvragen screent en de verantwoordelijken voor het programma van advies dient inzake beleidskwesties. Er moet worden gestreefd naar een beter thematisch evenwicht tussen de ondersteunde workshops. De ondersteuning, via HUGO, van workshops over afzonderlijke chromosomen is van cruciaal belang en moet worden voortgezet. In het algemeen lijkt de ondersteuning van chromosoom-workshops in Europa als bijdrage aan deze organisatie een goed idee. Een andere noodzakelijke vorm van steun is het verstrekken

van reistoelagen aan Europese onderzoekers die aan buiten Europa gehouden workshops willen deelnemen. Ten slotte lijkt het verstandig om (zoals in het verleden tot op zekere hoogte is gebeurd) "ontmoetingsbijeenkomsten" te ondersteunen voor wetenschappers die in het kader van het PAMG op verwante thema's werken - b.v. de deelnemers aan EUROGEM of de samenstellers van cDNA-bibliotheken. Dit kan de contacten tussen de groepen in de verschillende Europese landen alleen maar ten goede komen.

13. Een laatste welkome aanvulling van het programma is de bijscholing van praktizerende artsen in heel Europa. Voor menig praktizerend arts is genetica niet méér dan een nare herinnering uit zijn/haar opleidingsperiode aan de universiteit. De snelle vooruitgang van de medische genetica heeft ervoor gezorgd dat menig praktizerend medicus zich ten aanzien van zijn patiënten reeds in een lastig parket voelt gebracht ; gespecialiseerde opleidingsprogramma's kunnen dit euvel althans gedeeltelijk verhelpen.

RESUMO

1. O Programa de Análise do Genoma Humano (PAGH) insere-se no segundo programa-quadro para acções comunitárias no domínio da investigação e do desenvolvimento tecnológico. Este programa, criado ao abrigo da rubrica "Saúde" do capítulo "Qualidade de vida", pretende:

- utilizar e melhorar novas biotecnologias no estudo do genoma humano para uma melhor compreensão do mecanismo das funções genéticas e para a prevenção e tratamento de doenças humanas;

- desenvolver uma abordagem integrada dos aspectos éticos, sociais e jurídicos das possíveis aplicações dos resultados obtidos.

2. Para o seu exercício de avaliação regular, a Comissão designou, em Dezembro de 1992, um grupo de peritos independentes para procederem à avaliação do PAGH. A competência do painel de avaliação foi estabelecida no nº 3 do artigo 4º da decisão do Conselho que adopta este programa (JO nº L 196 de 29.6.1990, p. 8). O mesmo artigo especifica que a avaliação deve ser efectuada em relação aos resultados científicos e técnicos do programa, à qualidade e importância prática desses resultados, à eficiência da sua gestão, aos seus aspectos éticos, sociais e jurídicos e ao seu impacto e benefícios para os programas de investigação nacionais.

Para essa avaliação, o painel visitou quatro centros associados ao programa e entrevistou mais de trinta pessoas: funcionários nacionais e da Comissão, participantes no PAGH e utilizadores.

3. O montante total dos fundos atribuídos ao programa foi de 15,6 milhões de ecus, com a seguinte distribuição - mapas genéticos: 21%, mapas físicos: 27,6%, tratamento de dados e bases de dados: 15%, tecnologias genéticas avançadas: 18%, actividades de formação: 12% e administração: 6,4%.

No PAGH participaram cerca de 100 institutos comunitários.

CONCLUSÕES

O painel considera que o PAGH obteve um êxito considerável e que constitui uma importante força motriz no domínio da investigação do genoma humano na Europa. Actualmente, a investigação sobre o genoma está a avançar muito rapidamente. Nos últimos anos, o progresso tem sido particularmente notório na Europa, com o êxito de trabalhos tais como a sequenciação completa do cromossoma de uma levedura, os mapas físicos de genomas completos e os mapas genéticos refinados. O PAGH desempenhou claramente um papel importante no estabelecimento de uma relação mais equilibrada com os EUA, sem esquecer a importante força motriz gerada por programas fortes tais como o apoiado pela AFM em França. O PAGH foi aprovado com um orçamento de 15,6 milhões de ecus para dois anos. O montante destinado pela Comunidade à investigação do genoma é muito reduzido, comparado com os orçamentos de programas sobre o genoma nos EUA e no Japão. O PAGH constitui, assim, apenas um suplemento dos

actuais esforços empreendidos a nível nacional e a importância do investimento comunitário em programas específicos depende em grande parte da importância dos programas nacionais. A Comunidade tem dado um importante apoio à Grã-Bretanha, Alemanha, Itália e outros países europeus, embora um apoio muito reduzido a grandes grupos franceses (menos de 10%). O apoio comunitário varia entre <5% e 50% do custo total de cada projecto. Quanto aos projectos transnacionais, este tipo de apoio tem, na maioria dos casos, apenas um impacto reduzido e a possibilidade de os países menos avançados beneficiarem dos programas transnacionais é limitada.

A criação de centros de recursos e de programas de formação constitui uma grande ajuda tanto para os laboratórios científicos organizados como para os grupos menos avançados ou menos bem estabelecidos. Este é um aspecto muito importante do PAGH e, em geral, da ciência actual, dada a importância da organização e da disponibilidade de recursos. Neste sentido, o PAGH tem sido de grande utilidade para a investigação do genoma na Europa, um aspecto que deverá ser salientado na concepção dos programas futuros.

O programa do ADNc no âmbito do actual PAGH não se desenvolveu com a rapidez esperada, embora tenham sido obtidas uma série de sequências parciais de ADNc. No futuro, haverá sem dúvida uma grande necessidade de grandes colecções de bibliotecas de ADNc de alta qualidade.

O objectivo final do projecto global do genoma humano é o de sequenciar o genoma humano na sua totalidade. Os grandes programas de sequenciação não estão actualmente incluídos no PAGH, o que deverá ser rectificado no futuro.

Os projectos transnacionais têm sido importantes para promover a colaboração europeia, para além de proporcionarem aos pequenos laboratórios, em especial nos países menos desenvolvidos, o acesso a tecnologias sofisticadas.

O programa de bolsas de investigação constitui uma componente essencial do PAGH e tem sido implementado de forma satisfatória no passado.

O painel de avaliação, embora reconhecendo que se justificam as actividades empreendidas no âmbito do programa ESLA, debateu a questão de o programa dever ou não ser financiado tal como anteriormente devido à limitação dos recursos e à quantidade de questões urgentes a investigar.
O programa ESLA já concluído pode ser considerado como um estudo-piloto prometedor. O painel salienta que a Europa oferece possibilidades únicas para este tipo de estudos, dada a diversidade dos programas de cuidados de saúde e sociais aplicados nos vários países.

As despesas do seminário foram, até agora, costeadas pelo orçamento da administração. Embora o CAN-HUG e o grupo de trabalho do ESLA tenham dado a sua contribuição, o programa tem sido, até certo ponto, administrado de uma forma ad-hoc.

RECOMENDAÇÕES

1. O painel considera que deve ser lançado um terceiro PAGH, embora seja necessário introduzir alterações no plano de projecto, dados os grandes progressos obtidos durante o último ano. É muito provável que, durante o próximo ano, se complete um mapa genético de alta resolução e um mapa

físico integral do genoma humano com base no YAC (*Yeast Artificial Chromosome*).

2. É necessário um novo plano estratégico para o PAGH, que deverá considerar a possibilidade de uma sequenciação do genoma inteiro pelo "*shot gun approach*", o que implica um grande aumento do financiamento.

3. Os centros de recursos são um factor-chave do PAGH e é essencial garantir a sua existência. Pôr à disposição da comunidade os resultados da cartografia física integral de um genoma constitui uma tarefa de grande envergadura mas necessária, que deve ser realizada com o apoio de meios informáticos, incluindo uma base de dados acessível, completa e de consulta fácil, mas também através da distribuição de clones de cosmídeos e de YAC, o que representa um trabalho intensivo. Permitir um acesso fácil destes reagentes a todos os cientistas europeus, por exemplo através de uma vasta distribuição de "filtros de politene" com YAC ordenados para todos os cromossomas humanos será um passo essencial. Em geral, é necessária uma gama mais vasta de bibliotecas ordenadas para responder às mais diversas necessidades da investigação sobre o genoma, uma vez completado o primeiro mapa físico.

4. No futuro, serão pedidas, para todos os tecidos do corpo, colecções ordenadas de ADNc no seu comprimento total. Num PAGH futuro deverá ser atribuída prioridade aos centros de recursos que fornecem bibliotecas ordenadas de ADNc como um serviço à comunidade científica.

5. Deve ser considerada a atribuição de recursos para projectos de sequenciação de ADNc em mega-escala, já que o conceito de sequenciação do ADNc para a obtenção de um catálogo completo dos genes humanos é uma ideia europeia.

6. Num futuro PAGH deverá se incluída a sequenciação genómica em mega-escala, que não fazia parte do programa original. Será necessário realizar alguns projectos-piloto que integrem a sequenciação de megabases para avaliar as futuras possibilidades de sequenciar os cromossomas humanos na sua totalidade. A possibilidade de sequenciação do genoma completo através do "*shot gun approach*" também merece uma consideração cuidada, sendo sugerido que se reúna um grupo ad-hoc para analisar este problema. Se a Comunidade pretende participar neste projecto, terá de prever um grande aumento do orçamento do programa para permitir atingir o objectivo final do programa global sobre o genoma, que consiste na sequência completa dos nucleótidos do genoma humano.

7. O EUROGEM, por outro lado, terá em breve cumprido a sua missão, uma vez completado o mapa genético de alta resolução.

8. A bio-informática é um domínio que se deverá desenvolver muito rapidamente num futuro próximo. A concepção de suporte lógico de fácil utilização para a análise de grandes quantidades de dados será, sem dúvida, um aspecto importante do futuro PAGH. Dadas as críticas generalizadas dirigidas ao GDB, é conveniente prever bases de dados alternativos ou, pelo menos, um sistema diferente de acesso às bases de dados: a este respeito, o progresso registado pelo Heidelber IGD (*Integrated Genome Database*) parece prometedor, em especial o modelo de distribuição, que este grupo propõe, através de um sistema ACeDB que funciona a nível local e é alimentado com

dados de outras bases sobre o genoma.
A comunicação entre biólogos e especialistas em informática continua a ser imperfeita: são ainda duas culturas muito diferentes. Trata-se de dois domínios que evoluiram muito rapidamente nos últimos anos e poucos indivíduos são competentes em ambos.
A aumento do seu número, através de bolsas de investigação e postos de trabalho interessantes, é provavelmente a única forma de ultrapassar esta dificuldade.
Além disso, deve ser atribuída alguma atenção e alguns fundos ao melhoramento da interface entre o "mundo do genoma" e a comunidade da biologia em geral, incluindo não só a genética médica mas também, por exemplo, grupos que se dedicam a estudos funcionais do sistema do rato, de forma a permitir a aproximação da estrutura e da função.

9. Os projectos transnacionais devem continuar a ser implementados, embora sujeitos a uma selecção cuidadosa. Ao ser dado o apoio à investigação e ao serem apresentadas sugestões sobre como distribuir os fundos de investigação, é necessário lembrar que as colaborações, sem dúvida muito importantes, não podem ser organizadas por alguém mas devem surgir de forma espontânea. A este respeito, não é aconselhável estipular colaborações entre cientistas de determinadas regiões da Europa ou mesmo atribuir fundos dependentes dessas colaborações. Estas ideias são contraproducentes. Será preferível lançar um programa especial de duração limitada para apoiar os cientistas merecedores no domínio da biomédica nos países da Europa que são actualmente mais fracos em biologia molecular mas que são capazes de recuperar rapidamente.

10. O programa de formação parece, em geral, ter sido bem sucedido, recomendando-se a sua continuação. Poderá, no entanto, ser necessário encontrar novos meios de divulgar as informações sobre o programa, uma vez que o número de candidaturas foi muito inferior ao previsto. Deve-se ainda ter em conta que algumas alterações do programa podem trazer grandes vantagens aos jovens cientistas que trabalham no domínio da análise do genoma humano. Um dos problemas que se verifica em todos os países europeus é o de dar apoio e independência aos jovens investigadores que mostraram ser cientistas de primeira categoria, no seu ou noutros países. Nos Estados Unidos, os laboratórios representam uma atracção considerável, dada a grande flexibilidade da estrutura administrativa da maioria das universidades e, sobretudo, o impressionante número de centros de investigação de primeira categoria em muitas delas. Torna-se cada vez mais interessante para jovens europeus procurarem associar-se a laboratórios nesses centros por períodos mais ou menos longos, normalmente durante os anos mais produtivos em termos de trabalho original. Hoje em dia, podem obter-se os melhores resultados da investigação em biomedicina em centros de pequenas dimensões. É necessário reconhecer que uma das importantes funções do financiamento e da organização da ciência na Europa é a de contrabalançar os poderosos centros de investigação de base em biomedicina nos EUA. Neste sentido, uma das sugestões é a de se criarem postos para jovens investigadores independentes nas áreas de investigação biomédica que permitam aos jovens cientistas altamente qualificados prosseguir o ramo da sua escolha numa universidade europeia sem estarem sujeitos às suas estruturas administrativas, muitas vezes demasiado "tradicionais". Juntamente com os postos de trabalho devem ser proporcionados fundos para material, equipamento e pessoal de investigação. Estas estruturas deverão contribuir para que muitos dos jovens investigadores mais produtivos que se

encontram no estrangeiro se voltem a interessar pela Europa.

11. Os programas do ESLA são componentes essenciais dos programas sobre o genoma. O painel recomenda, embora não por unanimidade, que se prossiga com o ESLA e que seja dado um apoio alargado. É importante fazer a máxima divulgação do programa e fornecer aos candidatos as informações necessárias sobre que resultados se esperam. Uma componente urgente dos futuros programas ESLA será a de criar meios para que os grupos de participantes cooperem, interajam e troquem ideias e resultados.
Devem igualmente ser feitos esforços para incluir no programa os aspectos económicos das alterações técnicas e da política e estudo da ciência. O desequilíbrio geográfico é outro dos problemas que carecem de atenção.

12. O apoio a seminários e reuniões é, sem dúvida, uma das principais componentes do PAGH, sendo recomendada a sua continuação. No entanto, recomendam-se algumas alterações na sua administração. Sugere-se, por exemplo, que seja criado um comité científico consultivo para dar pareceres sobre a política do programa e seleccionar as candidaturas. Deve-se procurar obter um melhor equilíbrio entre os temas que são tratados nos seminários apoiados pelo programa. O apoio dado, através do HUGO, a seminários sobre um único cromossoma é essencial e deve ser mantido. Em geral, deve ser dado apoio aos seminários sobre cromossomas realizados na Europa, como uma contribuição para a organização. Deve igualmente ser dado apoio, na forma de ajudas de custo, para as viagens de participantes europeus nos seminários que se realizam fora da Europa, bem como para os seminários que congregam cientistas que trabalham no âmbito do PAGH sobre temas semelhantes (tal como já se fez anteriormente), por exemplo os que trabalham no EUROGEM ou com bancos de ADNc, o que irá obviamente incentivar os contactos entre grupos de vários países europeus.

13. Outra vertente desejável do programa seria a formação dos médicos a nível de toda a Europa. Muitos deles guardam da genética uma lembrança traumática do tempo em que estudaram nas faculdades. Com o rápido avanço da genética médica, os nossos colegas encontram-se já numa posição difícil em relação aos seus pacientes, que lhes fazem perguntas difíceis. Os programas de formação especializada podem oferecer pelo menos uma solução parcial para o problema.

1. BACKGROUND

The idea of mapping and sequencing the human genome was widely discuss in the mid 1980s. These discussions culminated in proposals for human genome programmes in a number of European countries as well as in USA and Japan. The aims of most were identical: to produce detailed maps of all 23 chromosome pairs, in order to make it easier to find, sequence, and study the genes. There was a further commitment to support technology development, in order to address the long-term aim of sequencing the whole genome. It was also generally agreed that the Human Genome Project, as it is often called, should be a global collaborative effort.

2. HISTORY

In 1987 the Council of the European Communities decided [1]that, within the second Framework Programme for community activities in the field of research and technological development, there should be initiated, under the heading "Health in the "Quality of Life" section, new activities relating to the development of knowledge of human genome.
In July 1988 the Commission presented a "Proposal for a Council Decision on a specific research programme in the field of health protective medicine; Human genome Analysis[2]. This proposal was given its first reading in the European Parliament in February 1989. Thirty eight amendments were adopted by the Eruopean Parliament most of which dealt with the justification in the proposal and, to a great extent, with possible misuses of the long term results. In relation to the public concern expressed mainly in Germany but also by the European Parliament, Vice President Pandolfi, Commissioner responsible for research & Technology, introduced a delay at this stage. In November 1989 a modified proposal, incorporating 16 of the Parliament's amendments and accommodating to some extent another 10, was submitted by the Commission to the Parliament. With very minor modification, this text became the basis of the Council common position adopted in December 1989. Following the second reading in Parliament in May (at which a further 6 amendments were proposed), the programme was finally adopted by the Council on June 29, 1990[3].
The most notable change was in the title, "predictive medicine" being omitted.
The 2 years which had elapsed since the programme was first mooted had been put to good use by an ad hoc Working Party on Human Genome Analysis first chaired by Professor P Pearson (NL) and later by Professor M Ferguson-Smith (UK) (Appendix I) This Working Party set up 6 Study Groups (Appendix II).

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[1]Council Decision 87/516, Euratom, EEC of 28/09/1987
OJ N° C27, 2.2.1989, p. 6 and OJ N° C302, 12, 1989, p. 18
[3]Council Decision 90/395/EEC of 29/06/1990

(11)

i) Genetic mapping
Chairperson: Professor M Ferguson-Smith

ii) Physical mapping (ordered clone libraries)
Chairperson: Professor J-L Mandel

iii) Data handling and databases
Chairperson: Dr C Frontali

[3]Council Decision 90/395/EEC of 29/06/1990

iv) Advanced genetic technologies
Chairperson: Professor L Bolund

v) Training
Chairperson: Professor P Pinho de Costa

vi) Ethical, social and legal aspects
Chairperson: Professor E-L Winnacker (D) followed by Professor M Niermeijer (NL)

Based on the reports of the first five of these groups, the Working Party produced a work plan. Budget subdivisions were also suggested; a plea was made for a specific allocation to data-handling and data bases, which was taken up by the Commission and endorsed in the Council decision. A "final" report was submitted to the CG C in June 1989. It was expected that the programme was about to be adopted. However, the work then continued into the first half of 1990. During the latter phase, the Working Party conducted a survey of "resources" in Member States, in preparation of the setting up of the Resource centers and networks of laboratories foreseen in their report, with the following results:

-EUROGEM52 laboratories contacted
28 expressed interest

-YAC libraries 4 libraries offered
5 offered to screen libraries

-cosmid libraries 2 replies

-cDNA libraries3 groups expressed interest

-data resource 2 laboratories expressed interest

The 2 year programme came into being on June 29, 1990, with a budget allocation of 15 MECU, 3 of which for 1990. Under the system of annual budgets imposed by Parliament, this

3 MECU had to be allocated by December 1990 or would be lost from the programme. Given the difficulties encountered in the administration process, it would have been unwise to attempt to launch a call for proposals before the programme Advisory Committe (CAN-HUG) had met; this could not be arranged before September. The CAN and the Commission faced a dilemma; there was clearly insufficient time for an open call, peer review, contract negotiations etc. However, unless contracts could be concluded by December 3 MECU, amounting to more than 25% of the total sum available for the research contracts, would be irrevocably lost. The CAN and the Commission agreed that a limited call, restricted to the provision of resource centres and participation in the EUROGEM network, should be directed to those laboratories which had responded to the ad hoc Working Party's enquiries. This was done and, in the light of advice from experts and the CAN, contracts were signed for 8 Resource Centres and the participation of 23 laboratories in the EUROGEM network. The CAN agreed, in all cases, to err on the side of inclusion rather that exclusion.
The first task of the Advisory Committe (CAN/HUG) was to advise the Commission on the open call for proposals, which was launched in October 1990 (deadline for applications was January 10, 1991). Forty-eight proposals for transnational research projects were received and after peer review, and comprehensive discussion with CAN-HUG, 14 of these projects were funded. An indicative distribution of funds between the various areas of the programme was included in the Council decision. However, this was altered on the strong advice of CAN-HUG, recommending that none of the proposals for transnational research projects on data handling and databases should be supported, although they advised that the Data Resource should be supported and that the remaining funds should be transferred to physical mapping, where there had been a large number of good proposals. A reserve list was also established in the event a further 0.6 MECU was made available by the Parliament which would allow 3 more proposals to be funded. The final distribution of funds was as follows:

Genetic map3.3
Physical map4.3
Data handling and databases2.3
Advanced genetic technologies2.8
Training activities1.9
Ethical, social, legal aspects1.0
Administration1.0
TOTAL15.6
A separate, open Call for Proposals for studies on the ethical, social and legal aspects was launched on August 14, 1991 (deadline November 4, 1991). Forty-eight proposals were received and after peer review and discussions with CAN-HUG 18 were funded.

3. THE REQUIREMENT FOR EVALUATION

The requirement for evaluation is laid down in Article 4 of Council Decision 90/395/EEC of 29 June 1990 adopting a specific research and technological development programme in the

field of health: human genome analysis (1990 to 1991) The same Article specifies that the evaluation shall be carried out by independent experts and published in the form of a communication to the European Parliament and the Council. Further it indicates that this communication shall be established having regard to the objectives and evaluation criteria set out in Annex II of this Decision (Appendix III) and in accordance with Article 2 (2) of Decision 87/516/Euratom, EEC (Appendix IV)

4. COMPOSITION OF THE PANEL

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5. SOURCES OF INFORMATION

The panel received a number of documents from the Commission which covered the nature of the programme itself and the evaluation criteria. The list of all the documents submitted to the list the Panel is given in Appendix V. Giving the timing of evaluation, very few progress reports were available. The Panel then decided that in addition to the written information they would interview some of the contractors of the different projects as well as visit some centres involved in the programme. A list of the contractors interviewed and of the centres visited is given in Appendix VI.
Most of the leaders of the ESLA projects were interviewed by Dr Latour over the telephone. Dr Bertrand Jordan participated in some of the panel meetings and provided very valuable information about the worldwide ongoing genome efforts. The panel is grateful to Dr Jordan for useful discussions and for providing a very valuable report which was used in preparing this document.

6. HUMAN GENOME RESEARCH IN A WORLDWIDE PERSPECTIVE*

Below is a description of the present state of the four major components of genome programmes: genetic mapping, physical mapping, sequencing and informatics.

6.1 Genetic mapping

The concept of a general genetic map of the human genome based on DNA polymorphisms is only a little over ten years old, but the * construction of such a map has made tremendous progress since it was first proposed. Optimism was high in the mid to late eighties, with the publication in 1987 of the first comprehensive genetic map having an average spacing of 10 to 20 centimorgans. Prediction of, and planning for, a 2 centimorgan map by 1991 or 1992 was incorporated, for example, in the US genome programme. Progress turned to be slower than anticipated, both because of the amount of work required and because of the rather uninspiring nature of the day to day effort involved and of a certain lack of interest by funding agencies. It was also felt, in some circles, that large-scale physical maps based on pulsed field gel experiments and using "linking clones" were around the corner, and that they would make much of genetic mapping obsolete.
However, it was soon realized that physical maps would have to be based on contigs of cloned DNA segments to be really useful - and that this was not going to be easy. It also became apparent that in any case a complete and detailed genetic map with high quality

* extracted from the report "An assessment of progress in human genome programmes worldwide", written by Dr B. Jordan; see pp. 51-71 of this report

landmarks was, and would remain, essential to the positional cloning ("reverse genetics") approaches. More polymorphic markers were found, first minisatellites or VNTRs, later the microsatellites - so that by the time Southern blotting was more or less automated RFLPs were no longer the main genetic mapping tool. Generation of large numbers of microsatellites is going ahead in a number of laboratories, and the first whole-chromosome, and even whole-genome, genetic maps based solely on microsatellites have already been published. Data capture and analysis using this system remain too cumbersome, and ways are being found to efficiently multiplex the assay of microsatellitepolymorphisms and to call the results more or less automatically. Throughout this stage, as well as the preceding one, the general availability of the CEPH panel of families as DNA samples has played an important and very positive role.

Two general maps have been published late in 1992, the one produced by collaborating groups using the CEPH panel (NIH/CEPH collaborative mapping group, 1992) and a "pure" microsatellite map obtained by Jean Weissenbach's laboratory at Généthon. Although less detailed (814 markers instead of 1416), the Généthon map is both more reliable (being constructed by a single group rather than assembled from many different sets of data) and more useful since it is exclusively based on highly polymorphic markers.

The software available to perform genetic analysis has made good progress (aided of course by the very large increase in computing power per dollar) and is now able to tackle difficult problems including the search for genetic components in multifactorial diseases such as diabetes or hypertension. Input of data, however, remains a largely manual and error-prone procedure which should be automated if at all possible or at least made much more user-friendly.

It now appears quite feasible to generate a density of highly polymorphic markers equivalent to one per centimorgan. This does not mean that it will be easy to order all of them with respect to each other, since at such small recombination fractions the search for individuals with recombinations in the interval becomes the bottle neck. It may however not be necessary to do this by genetic means, since efficient cytogenetic methods (interphase mapping, or even in situ hybridization to highly decondensed chromosomes) may be able to do this much more quickly. A recent variant of "sperm mapping", in which the whole DNA of a single sperm is first amplified with random primers thus making it possible in later stages to assay many markers on the same haploid DNA complement, may also become very significant. Thus it seems very likely that a high-resolution genetic map of the human genome will be available in the near future

6.2 Physical mapping

At the beginning of genome programmes the concept of whole chromosome physical maps based on pulsed field gel analysis of Not I cut genomic DNA complemented by a complete set of the corresponding linking clones (segments of DNA containing the rare Not I sites and a few kilobases of DNA on either side) was entertained by several groups. It soon became clear that this approach suffered from serious technical difficulties and shortcomings, and that

a really reliable and useful map of a whole human chromosome had to based on a complete set of overlapping cloned DNA segments.
Contig building across human chromosomes was initiated, in particular for chromosomes 16 and 19 at Los Alamos and Lawrence Livermore. This rather heroic undertaking (it takes 5,000 to 10,000 cosmids to cover a chromosome) was pursued until coverage reached 60 to 70%, and benefited from the arrival of YACs which made closure possible, as has been the case for the nematode genome. The extensive investment in cosmids was not a complete loss since, in practice, it turns out to be very useful to have a "cosmid layer" underlying a YAC contig map; cosmids provide DNA in a form which is very amenable to further experiments such as looking for genes and sequencing.
Chromosome-specific YAC libraries are in principle an important resource for the construction of a physical map: alignment of the few hundred large YACs needed to cover an average-sized chromosome should be almost trivial compared to the equivalent endeavour with many thousands of cosmids. They can be obtained the hard way, by making a library from a suitable human-hamster hybrid cell line and subsequently screening for the few per cent of human-specific clones, as done in Saint-Louis for the Xq24 to Xq28 library. Attempts to make such libraries from sorted chromosomes have given some promising results but have so far failed to provide complete libraries. The alternative route of "extracting" chromosome-specific components from a whole-genome YAC library is much more appealing, and recently two groups have reported success in doing this using as a mixed probe sequences derived from a chromosome-specific cosmid library or from a somatic hybrid.
It is now generally accepted that the primary whole-chromosome physical maps will be based on YACs, in spite of the problems with chimeric clones, at least until some better vector comes along. Physical mapping of chromosomes 7 and X has been pursued in Saint-Louis, using "STS content mapping" and the whole genome YAC library. This approach relies on defining about one thousand STS per chromosome and then assaying YACs with the corresponding oligonucleotides. Positive YACs usually contain two or three such STS and can be overlapped with their neighbours by looking for the common STS. This very robust approach is work-intensive but reliable. Daniel Cohen's group at Généthon has used a somewhat similar STS content method to construct the complete chromosome 21 map, and a more adventurous fingerprinting technique to build contigs simultaneously over the whole genome. The latter project, which uses the high-capacity blotting machines installed at Généthon, appears well on the way to produce a nearly continuous contig map of the whole genome.
Thus YAC-based physical maps of many whole chromosomes will soon be obtained. These maps can be tremendously useful to the whole community, particularly if they together with the underlying reagents, are made available in a convenient format. In this respect, the example set by the nematode community is worth considering. The LMB laboratory provides so-called "polytene filters" which contain a complete set of YACs ordered as they occur along the six nematode chromosomes. A similar scheme could be used to make available maps and reagents for each of the human chromosomes.

6.3 Sequencing

When genome programs were first discussed in the mid-eighties, it was generally expected that sequencing technology would progress rapidly and that megabase sequencing at prices well below one dollar per base was just around the corner. Such progress has not occurred; instead several megabase sequencing projects initiated in the late eighties and aiming at obtaining one or several megabases of sequence have failed to deliver the expected results. The traditional sequencing method has been automated in part or (in Japan) in toto, but throughput in the latter case cannot yet be assessed; multiplex sequencing, a very rational approach, has run into serious difficulties with handling of the huge amounts of data produced. Exotic methods based on microscopy have generated much initial excitement but have not yet demonstrated feasibility; the same is true for very fast techniques based on single molecule degradation and extremely sensitive analysis of single bases. Sequencing by hybridization is closer to a real-life feasibility demonstration; it certainly holds a lot of promise for detection of mutations in known genes and may well develop into the megasequencing method of the late nineties. Efforts must be continued, since only radically new technologies are capable of bringing speed up, and cost down, by the one or two orders of magnitude necessary to make sequencing of whole genomes a realistic task.

Current results show that it is indeed feasible with present technology to sequence a few hundred kilobases, up to at least one megabase, at a cost in the order of one dollar per base. In this respect the model for near-future megabase sequencing appears to be the Nematode operation rather than the EEC yeast effort which has been useful and worthwhile but very expensive (i.e. close to ten dollars per base): sequencing will in the future have to be divided in larger chunks between a smaller number of centres. Sequencing at this cost is certainly worthwhile for model organisms with small genomes such as E. coli, Bacillus subtilis or even yeast. As genomes get larger and less densely populated with genes, the answer becomes less obvious. In the human system megabase-sequencing can only at this point be considered as a model experiment: sequencing a few 1-2 megabases long, particularly "interesting" regions, to find out how such sequencing produces results in a genome very rich in repetitive sequences, how efficient present algorithms are at finding genes in such DNA and whether anything unexpected comes out of such massive experiments. It will then be easier to decide whether, and how, to proceed.

Massive and partial cDNA sequencing was proposed several years ago, in particular by Sydney Brenner, but the most publicized implementation of this strategy occurred in USA. The approach has turned out to be quite effective at finding "new" genes, and provides partial sequence data on several thousands of hitherto unknown genes. It is practiced in a number of laboratories outside the USA, including the HGMP resource centre in Harrow, the Genethon, the Osaka Institute of Molecular and Cellular Biology and others. Some scientific questions remain open: how effective is the approach at finding all, or even a significant fraction, of the existing genes? For example, one may wonder how many of the 182 chromosome III genes in yeast would have escaped detection by this approach. Another issue is the localization of the "new" genes revealed by this approach: even simple chromosome assignment is, at this time, very cumbersome and new methods are badly needed. As these exercises continue, the

question of real time data availability becomes more and more important, to avoid duplication of effort. This has two aspects: data must be comparable, i.e. laboratories should agree to sequence the same region of cDNAs (5' or 3'), and it should be deposited and made accessible very quickly. Finally, of course, the vexing problem generated by attempts to patent these partial sequences should be resolved, ideally by a general decision not to indulge into such exercises. The recent negative ruling by the US patent office is a big step in the right direction although the issue is far from closed yet.
A problem with the cDNA approach is that it may be difficult to convince anyone to produce the complete sequence after the first "glamerous" discovery has been made.
Discussion on the relative merits of these two approaches are heavily dependent on the organism considered and on the cost of large-scale sequencing. Under present conditions (one to two dollars per base) sequencing of genomic DNA definitely makes sense for small genomes, up to a few megabases: a 5 megabase (E coli) or even 15 megabase (yeast) sequence is clearly feasible, and the wealth of information provided (as shown by the recent nematode and yeast results) justifies the relatively high price of the exercise. The high gene density found in these organisms reduces the saving which could be achieved by going the cDNA way.
For larger genomes with intron-containing genes (such as the 100 megabase nematode genome) the question becomes more debatable. For the human genome, if one takes the presently accepted upper limit for the number of genes of 100,000, and allows 1.5 Kilobases of coding sequence per gene, one ends up with an exon content of 5% - a figure which does make cDNA approaches attractive. So far large human DNA sequences do not appear to contradict current estimates of gene density - but the sample is too small to be representative. In any case, if cost can be brought down to below 0.1 dollars a base by new techniques or by very efficient implementation of present methods, a whole chromosome could be sequenced for a sum of the order of 10 million dollars, i.e. roughly the amount previously budgeted for the physical map of such an entity in the US genome programme: large-scale sequencing would become irresistible.
Informatics has been recognized from the start as a very important component of genome programmes, and has been funded accordingly, in particular in the USA. Significant progress has been made, but the situation is still far from satisfactory because of the exponential growth in the amount of data and the bewildering variety of tasks which need to be addressed.

6.4 Databases

Several genome databases have been established to cater to the growing needs of genome mappers. In addition to the familiar DNA sequence databases (EMBL and Genbank), there are systems storing all kinds of human mapping data (GDB), information on the mouse genome (GBASE), clinical description with mapping results (OMIM, GENATLAS) to name but a few. In principle these systems only store "public" data, either already published or adequately verified by expert inspection and released for general distribution. Thus the data is in most cases quite reliable, but often lags behind recent work. It would probably be very

useful to display provisional data (flagged as such), since such non-verified results often provide very useful hints to others.

Databases have been developed over the years using a variety of database structures: IRX for OMIM, SYBASE for GDB and GENATLAS, INGRESS for GBASE... Each of these systems has its own query structure and its particular quirks; their only standard feature is their lack of user friendliness, which makes it relatively difficult for the average biologist to use them. A rising star in this world of databases is the Nematode system, ACeDB ("A Cenorhabditis elegans Data Base) which is winning over scientists from other fields thanks to its performance and ease of use: the system is now used for the Arabidopsis programme (AAtDB), by some Drosophila groups, and it constitutes the front end of the Integrated Genome Database (IGD) being developed at the DKFZ in Heidelberg.

Because of the complex nature, of the variety of data stored and of the many ways in which links can be established between different kinds of information, these databases are normally used on-line. Accessing them requires not only a local computer (which is easy), but also a high-speed link to the database itself or to one of its secondary nodes, and sufficient local network expertise to actually establish the connection in a reliable way. While the high-speed link situation is relatively satisfactory in most of the US, it is definitely not so in the rest of the world. Using a database such as GDB with transmission speeds below 9600 baud is essentially hopeless.

The growing power and dropping price of microcomputers and Unix workstations, in conjunction with these transmission problems, is causing a shift towards systems in which a local, periodically updated version of the database is used.

Computerized laboratory notebook systems are often discussed, but few groups actually implement and use them. Yet the need is obvious: even partial automation leads to a large increase in the number of objects handled in the laboratory, thus rigourous and efficient data organization and storage become absolutely essential to avoid a disaster. But the development of such a system for the average group is not easy, as it makes great demands on flexibility and user friendliness, not to mention raw computing power and storage space. Only fairly large groups organized around a common task seem to succeed in this endeavour, for example the Lawrence Livermore group which has set up a sophisticated and relatively easy to use system to record and follow progress on its cosmid fingerprinting and contig building work, or the Généthon team for their whole-genome contig building task. Such large groups end up building local databases which must then be able to communicate with the "general" databases.

Comparing a sequence to all known sequences is a task whose complexity increases exponentially with the number of known sequences. In spite of the very rapid growth of computing power per dollar over the past decade, it is not certain that computers will keep up with the increasing flow of data. New algorithms are being perfected, and massively parallel machines, using dedicated hardware chips, may be the answer. Finding exons in a large genomic DNA sequence is still a vexing problem, as shown by the difficulties encountered in interpreting a recent 106 Kilobase genomic sequence from chromosome 19; the algorithm used found less than half of the exons subsequently detected by other methods. More work is clearly needed in this area.

Communication between biologists and computer scientists remains imperfect: they still belong, by and large, to two quite different cultures. Both fields have been evolving very quickly in recent years, and few individuals have real dual competence.

6.5 Instrumentation

Newcomers to recombinant DNA laboratories, and even to genome centres, are often appalled by the predominance of manual work. Most procedures are performed by hand, machines being used only for a few specific steps. Even DNA "sequencers" only automate a small - albeit vital - part of the sequencing procedure. In fact, even in most specialized genome centres, manual work still predominates. Few laboratories, for example, have completely automated cosmid preparations; construction of YAC libraries still involves lengthy and tedious hand picking of clones into microtiter plates; and apart from a few pipeting robots (in most cases the Beckman Biomek machine, originally developed for Elisa assays) there are very few commercially available robots around. Exceptions exist, the foremost being Hans Lehrach's operation at the ICRF, the "Genethon" centre set up near Paris. Another case, however not yet functional - is the HUGA "sequencing factory" in Tsukuba. But on the whole the penetration of instrumentation and robotics has been disappointingly slow in laboratories implementing human genome programmes.

This unfortunate state of affairs reflects some very real problems. Recombinant DNA technology is still in a state of flux: thus a manufacturer's decision to develop an instrument automating a certain procedure entails a very serious risk: the probability is high that by the time the instrument is ready to be marketed the procedure will have become obsolete. The "Labimap" Southern blotting machine has just been marketed, more than four years after the programme started, and by now PCR has replaced Southern blotting in most of its applications; likewise the HUGA set-up is based in part on obsolescent sequencing technology. In addition genome research, even today, is a relatively small sector: the market for a hypothetical high-throughput sequencing machine capable of reading 500,000 bases per working day is likely to be quite small - unless the resulting sequence is very affordable. Other, more "cultural" reasons hinder progress: most biologists are not very instrument-literate, and the race to a publishable result does not lend itself to careful investment in new technology; and communication between robotics specialists and biologists suffers some problems - as with informatics.

There are, however, some signs of progress. ABI has sold more than 1 000 sequencers world-wide, even though they are not all in actual use; semi-automated procedures based on the 96-well microtiter plate are becoming more common; and instrument literacy, as well as computer knowledge, is increasing among biologists. Genome programmes *have* had a positive effect, by providing both the incentive and the funds for at least partial automation; and the demonstrated success of some groups in performing some routines by machine is now tempting smaller, more conventional laboratories to do the same. Concurrent increases in computing power per dollar for small computers make it easier to automate complex procedures: mechanical precision can be substituted by software sophistication - an

increasingly available commodity. Numerous opportunities exist in this field, both for research groups to operate more effectively and for astute companies to generate profits.

7. EUROPEAN INVOLVEMENT IN HUMAN GENOME RESEARCH

It is difficult to draw conclusions in such a study at a time when events are moving so rapidly. Clearly the balance has shifted in recent time towards Europe, with the success of enterprises such as yeast whole-chromosome sequencing, whole genome physical maps and refined genetic maps. Agencies in the US have, as usual, been quick to assess the new situation and to launch new centers incorporating some of the features of Généthon and in attracting the CEPH MegaYAC library to the other side of the Atlantic. It is clear that HGAP has played an important role in capitalizing on this - possibly temporary - success to establish a more balanced relationship with the USA. It is, however, also clear that strong programs such as the one supported by AFM in France have been an important driving force.

The European engagement in various activities is summarized below:

Activity	European involvement
cDNA sequencing	moderate to significant
Genomic sequencing	low, although significant in model organisms
YAC-contig building	very high
Microsatellite-based genetic mapping	very high
Making genome data bases more user-friendly	important

8. EVALUATION OF EUROGEM AND THE RESOURCE CENTRES

The resource centres were established to improve the infrastructure of the HGAP in Europe, by delivering specialised services. The program included the following activities:

a) One resource centre included the CEPH in Paris and the ICRF unit in South Mimms,

UK. These comprise centralised facilities supplying 22 network laboratories with the resources for linkage studies (DNA, filters, probes and primers). The resource centres and the network laboratories are expected to produce new genetic markers and a high density linkage map of the human genome.

b) Resource centres were established to produce and distribute chromosome specific cosmid libraries and ordered YAC libraries to research groups interested in screening such libraries as well as to organise databases which will integrate information about the probes and clones obtained from these libraries. One resource centre for cosmid libraries and 5 for the screening and distribution of YAC clones have been established.

c) Resource centres for cDNA libraries were also established; a consortium of four laboratories was formed to provide normalised cDNA libraries and services.

d) A central facility for computing services was established in Heidelberg

e) A Danish family bank, comprising cells and information about 1000 families was established as an instrument for genetic analysis of normal traits.

The EUROGEM Network and Resource Centres seem to be fulfilling their commitment of positioning about 1000 genetic markers on human chromosomes in the 24 months the program has run. From the scientific report of the Probe Resource Centre it is not possible to establish how the remaining part of the program has run. A genetic map is not yet available but all the markers could be mapped within the remaining time of the program. The main drawback of the EUROGEM program seems to have been the decision to use RPLPs and filter hybridisation, failing to foresee that genetic maps can be constructed more quickly and efficiently using microsatellites. The project has thus been surpassed by other projects, microsatellite-based, mainly the Généthon project. The Resource Centres and the Network laboratories have now switched to use the microsatellites developed at Genethon and already mapped at Généthon using 8 CEPH families only. This seems a wise decision and will produce an informative and precise genetic map. Since many more (2-4000) microsatellites have been produced by Généthon and are being mapped on the CEPH families it may be useful to continue this collaboration to complete the human genetic map within the next one to two years. Once the first map will be completed, the remaining regions, where fewer markers have been localised by the random approach of Généthon, will have to be completed: this could be accomplished by ad hoc programs and this may be pursued in a future HGAP with open calls for proposals.

At the time of this report, cosmid, YAC and cDNA resource centres have all been working for some time. Cosmid libraries for chromosomes X and 21 were intially available for screening by filter hybridisation at the ICRF but have since been expanded to include other chromosomes. YAC libraries can be screened by PCR or by filter hybridisation at the screening centres. Not all the centres have all the available libraries: the St.Louis library has

not been aquired by the Pavia Centre, and the ICRF library is not available to other Centres. All Centres have the ICI library and all have now acquired the CEPH MegaYAC library which has been distributed recently.
A final decision on a common database has not been taken: at the ICRF, a data base already exists for cosmids and YACs screened in house and could also store data from other centres. An important role for the screening centres has been the technical support to laboratories without large experience in the specific field which in addition to the screening may obtain help in related techniques for yeast cultivation and analysis of clones. The YAC- and cosmid-library resource centers that have been sponsored by the current HGAP have been of immense value to European scientists, interested in gene mapping.

Less information has arrived to the panel on the cDNA resource centres: normalised libraries have been prepared for a number of tissues and a large numbr of cDNAs have been sequenced by some of the groups. The Généthon group seems to have sequenced the largest number of cDNAs from commercially avaialble libraries which unfortunately have been found to be contaminated with sequences from other organisms. However, EC funding has been a small percentage (less than 10%) of the support received by the group. Difficulties for the consortium may also have derived from the cDNA patenting issue. The services offered by the cDNA resource center may have been exploited less than other resources, but they are likely to become very relevant in the future, when many YACs and cosmids will be ordered in contigs. The experience obtained in the first HGAP may therefore be used profitably.

The data resource for human genome research in Heidelberg has operated as support for research as well as to develop new software for genome mapping. The EDR provides on-line access to major analysis tools and packages. This includes the HUSAR package, for sequence analysis, the LINKAGE package for genetic mapping, the ICRF package for physical mapping and others. An open software system was developed, IGD, to handle human genome data. As for other resource centres, among the activities was the organisation of training and workshops. The centre might have been more used if computer connection with Germany had been of better quality. This problem has probably discouraged potential users. It seems, however, that the computer connections with Germany are likely to improve in the near future.
The resource centres seem in general to be a very important and useful support for the HGAP.

9. EVALUATION OF TRANSNATIONAL RESEARCH PROJECTS

The program included 6 projects on physical mapping of regions from chromosomes X, Y, 21 and 22. The other 11 projects concerned the improvement of methods and basis for the study of the human genome.
The small number of transnational projects funded reflects to a large extent the human genome projects going on in Europe at the time of the call for proposals. The scientific qualifications of the groups which have received support are in general quite high and the results obtained

are therefore of good quality. It is, however, difficult to make an evaluation of individual projects due to the lack of progress reports. Some information could, however, be extracted through interviews with a limited number of the project leaders and from some reports that were avialble. Many of the projects are known from publications.
In addition to the scientific results several important goals have been obtained as a result of HGAP:

1) An important goal of the transnational project was to stimulate new collaborations among European laboratories. This seems to have happened in many cases. In addition, the availability of funds for a common goal may have strengthened already existing collaborations. It appears that collaborations based on previous scientific contacts were much more successful than those based on newly established links.

2) A second goal was the development of new technologies for genome research. Projects included mapping, sequencing, cDNA normalisation, in situ hybridisation etc.. Some interesting projects were included in this part of the HGAP and in many instances significant improvements of the existing technologies have been accomplished (e.g. sequencing, new mapping techniques based on chromosome deletions etc.)

10. EVALUATION OF THE TRAINING PROGRAM

Fellowship grants and specialised courses were regarded as an important instrument for the distribution and the utilisation of knowledge and technological applications stemming from human genome research training, i.e. fellowships and courses. A budget of 1.9
MECU was earmarked for this task.
The Commission services and the Advisory Committee (CAN-HUG) agreed that a prerequisite for a fair and equal selection of trainees was widely available information to young scientists. Therefore, prior to the first selection round opportunities for training were advertised in Nature.
There were three rounds for the selection of trainees:

Selection round 1 (July 1991): 15 applications
Accepted for support: 9 candidates (origin 2 D; 2 E; 2 F; 2 I; 1 NL)
Location of host laboratories: 2 B; 1 D; 2 F; 4 UK
Selection round 2 (October 1991): 18 applications

Accepted for support: 10 candidates (origin: 4 D; 1E; 2 F; 1 GR; 2 I)
Location of the host laboratories: 1D; 4 I; 5 UK

Selection round 3 (May 1992): 16 applications
Accepted for support: 8 candidates (origin:1 D;3 E;1 F;
1 GR; 1 I;1 P)
Location of host laboratories: 1D; 1 F; 6 UK

It was the opinion of the selection committee (Professors: Gannon (IRL), Hanoune (F; he did not participate in the last meeting), Maniatis (GR) and Dr. Rodriguez de Cordoba (E) that sufficient funds were available to give support in all cases where the candidates met the required high scientific standards and a good work programme relevant to the scope of the HGAP was presented. Indeed they were disappointed that more candidates had not applied, particularly from areas where the relevant techniques are less developed.
Selected candidates received a bursary for a maximum of two years to learn new techniques with a view to continue a scientific career. A bench fee was given to the host laboratory to provide for materials but could also be used for travelling in order to enable the trainees to participate in international scientific conferences.
A more targeted support, exclusive to candidates from countries in the Mediterranean (inclusive of Portugal) was provided through support for summer courses. Candidates were selected with the help of the same selection committee. However, only the Advanced Course on Molecular Genetics, (Leiden May 31 to June 5 1992) was considered for support. Travel expenditures and accomodation for 4 participants (two from Greece, one from Italy and one from Portugal) were reimbursed by the Commission. (Additional support to other courses was made available through Commission resources outside the programme).
In addition to the implementation of procedures as foreseen in the Council Decision two important modifications were discussed by CAN-HUG:
-The specific requirement to spread more sophisticated methods of
human genome analysis throughout Member States would justify a deviation from the general principle of awarding bursaries only to scientists. It was suggested that support also could be given for the training of technical staff.
-Well trained scientists would contribute significantly to the establishment of new technologies in their home countries. Therefore it was recommended that a bursary should be continued for up to 12 months after the two years spent abroad.
It is the opinion of the evaluation panel that the training program is an important aspect of the HGAP and that it has been implemented successfully. Given the general need for post-doctoral support it is surprising that the number of applicants was so small. In the future all possible efforts ought to be made to spread information about the fellowship program well in advance of the application deadline.
The idea of providing support to the fellows after returning to their home countries seems worthwile and is encouraged (see also below) and the panel likes the idea proposed by CAN-HUG that technical staff also could be included in the program.

11. EVALUATION OF THE WORKSHOP ACTIVITIES SPONSORED WITHIN THE HGAP

In the budget of the HGAP, 1 MECU were allocated for administration. Parts of this allocation have been utilised for the support of workshops. Alltogether 29 workshops were supported between 1990 and 1992. Of particular importance is the support that is awarded to HUGO for the the single chromosome workshops. A particularly urgent part of the support

is given to European scientists as travel support ascertaining strong European participation in distant workshops.
The panel was surprised that a very large fraction of the workshops dealt with ethical, social and legal aspects of HGAP. It also seems that the number of workshops that received support was very large and that the support given in each case usually was small (10 000 ECU or less) It may in the future be appropriate to be more selective and support the most urgent workshops to a greater extent. Lastly the panel was surprised to learn that decisions about workshop funding in some of the cases were made by the administrator of the program. It is recommended for the future that a peer review committe is established which makes decisions about policies regarding the future workshop program and which also screens the applications for support. Such a committe has, for instance, been established by EMBO which has a workshop program, similar to that of the HGAP.

12. EVALUATION OF THE PROGRAM ON ETHICAL, SOCIAL AND LEGAL ASPECTS

The ESLA program is a significant component of HGAP. It was unfortunate that the grants were only awarded for a period of one year. It is the opinion of the evaluation panel that the EC got a lot for its limited amount of money; the reports, even if they are somewhat unequal in quality represent a useful first attempt at the immense array of problems that the human genome initiative raises. By social science standards, the reports represent an impressive collection of information and research trails. Those first studies support the view that producing a genetic map of the genome is only one part of the initiative and that the biggest problems will be in transforming those technical possibilities into full scale medical practice. If the scientists involved in genome research believe they will be through once the technical problems have been solved they have to brace themselves from deep disappointments.
It is striking from the reports that there is no basic opposition to most of the aspects of the genome initiative from the general public; in other words, there is no major confrontation between technology on the one hand and ethics on the other; on the contrary the public seems sometimes to be more daring than the medical practitioners. This does not mean that the transformation from technical possibilities to medical practice will be easy.
The panel was surprised by the uneven geographical distribution of the ESLA projects. Particularly the almost complete absence of France from the program was unexpected. This might be due to lack of interest rather than poor advertising of the program. Another unexpected finding was the absence of projects dealing with economical issues.
The complete absence of questions related to science policy was another astonishing observation. This is unfortunate since science policy is one domain that should closely link the social and the natural sciences. Lastly the absence of the "science studies" which could provide us with first hand detailed empirical results on the practice of natural scientists and medical practitioners and on their way of handling the social, ethical, economical and philosophical aspects of their own technical work. Instead too much of the reports include bibliographic searches or purely philosophical surveys that lack empirical assesment of how

the scientists and physicians apply the knowledge generated within the human genome project.

13. INDUSTRY'S VIEW OF THE HUMAN GENOME ANALYSIS PROGRAMME

This section was solicited from Mr Pascal Brandys, President and Chief Executive Officer, Genset, Paris and is presented in Appendix VII

14. ADMINISTRATIVE ASPECTS

The HGAP has been managed by a small staff with limited resources. It was the impression of the panel that the program administrators had done their very best to implement the program and to establish good contacts with applicants and later with the contractors. There was nevertheless many complaints regarding the bureacracy associated with the program. It was the opinion of several of the scientists participating in the present program that the amount of paper work required to apply for and to maintain funding in the present program was very considerable and outright disturbing. There were also severe delays in distributing the money after decision had been made about the grants. Although, it is clear that the problems sometimes arose at the national level, for instance when signing subcontracts, it is clear to the panel that there is substance in the criticism. It would, therefore, be important to seriously consider that the administrative process be simplified and that adequate time is allowed between the announcement of a program and the deadline for applications. It would be a much appreciated service to the scientific community, if one were to rectify administrative matters at the EC.

Another administrative aspect that disturbed the panel was that the system of open applications and peer review was not always strictly practised. For instance, when funds were awaraded to the resource centers and the EUROGEM network a limited call for proposals was made. It is recognized that the time limit for the grant made it difficult to make an open call for proposals followed by evaluation by peer review. Nevertheless it was unfortunate that applications could not be selected in an open competition. It is to some extent understandable that such a selection procedure had to be employed, because the program was new, shackled somewhat by a tight and inflexible administrative structure and had suddenly to be launched within a very limited span of time. However, this procedure should not be repeated or serve as the model for future programs or planning. The panel must insist that, in the future, programs be generally announced in time and made available for application to the entire scientific community in the respective fields of research.

Similarly, both for the selection and the evaluation procedures, the proven system of critical peer review must be strictly adhered to.

An efficient peer review system, both during the screening of applications and in the evaluation of research accomplished, would safeguard against unjustified or exaggerated forms of critizism by fellow-scientists.

Lastly the panel was surprised to find that progress reports from many of the programs were

lacking when the evaluation started. From the interviews it became apparent that many of the investigators were unaware of the fact that the deadline for submitting the reports was since long passed. It is urgent that the program administration in the future enforces strict deadlines for reports in order to facilitate the evaluation of the program.

15. CONCLUSIONS

The panel finds that the HGAP has largely become a success and is an important driving force in the field of European human genome research. Genome research is for the moment advancing with an extremely rapid pace. In recent years the progress has been particularly striking in Europe, with the success of enterprises such as yeast whole-chromosome sequencing, whole genome physical maps and refined genetic maps. It is clear that HGAP has played an important role to establish a more balanced relationship with the US. It is, however, also clear that strong programs such as the one supported by AFM in France have been an important driving force. The HGAP was approved with a two year budget of 15 MECU. The amount of money devoted to genome research by the EC is very small compared to the budgets of the genome programs in the US and Japan. The HGAP has therefore only supplemented ongoing national efforts and the weight of EC funding on individual programs greatly depends on the strength of the national programs. The EC has given a very minor support to large French groups (less than 10%), while it has been quite important for British, German, Italian and other European countries. The EC support would range from <5% to 50% of the total funding of each project. For the transnational projects, this kind of support can in most cases only have a modest impact and the potential for less well advanced countries to benefit from the transnational programs is limited.

On the other hand, the establishment of the resource centres, and training programs is of great help to organised scientific laboratories as well as less advanced ones or less established groups. This is a very important aspect of the HGAP and in general in today's science since organisation and availability of resources are major issues. In this respect the HGAP has been very useful to the European genome research community, and this aspect should be stressed in the design of the future programs.

The cDNA program in the current HGAP has not developed as fast as was hoped although quite a number of partial cDNA sequences have been generated. There will clearly be a great need for large collections of high quality cDNA libraries in the future.

The ultimate goal of the global human genome project is the sequencing of the whole human genome. Large sequencing programs are presently not included in the HGAP. This situation should be rectified in a future HGAP.

The transnational projects have been of importance for promotion of European collaborations. They have also provided means for small laboratories, particularly in less developed countries

to gain access to sophisticated technologies.

The fellowship program is a very essential component of the HGAP. It appears to have been implemented in a satisfactory way in the past.

It was recognized that the activities undertaken within the ESLA program had justification. However, the evaluation panel debated whether the program should be financed to the same extent as done in the past simply because there are limited resources and many pressing questions to be investigated.
The already completed ESLA program can be regarded as a promising pilot study. The panel would like to emphasize that Europe offers unique possibilities for these kinds of studies due to the diversity in the health care and social programs that operate in the different countries.

The workshop support has in the past been taken from the administration budget. Although CAN-HUG and the ESLA working group provided input into the program it seems to some extent to have been administrated in an ad hoc manner.

16. RECOMMENDATIONS

(1) It is the opinion of the panel that a third HGAP should be launched. Modifications in the project plan are, however, necessary due to the remarkable progress that has been made during the last year. It seems very likely that a high resolution genetic map and also a complete YAC-based physical map of the human genome will be completed within another year.

(2) It is necessary to make a new strategic plan for the HGAP. This strategic plan should also consider the possibility of approaching sequencing of the entire genome by a "shot gun approach". Such an effect would require a drastic increase in funding.

(3) A key feature of HGAP are the resource centers and it is essential to ascertain their continued existence. Making the results of whole genome physical mapping readily available to the community will be an extensive but necessary task; it must be tackled by informatic means including an accessible, complete and user-friendly database, but also at the level of the distribution of YAC- and cosmid clones, a very labour-intensive task. Making these reagents readily accessible to all European scientists, for instance by wide distribution of "polytene filters" containing ordered YACs for all human chromosomes would be an essential step. In general a wider range of ordered libraries is required, to serve the most diverse needs of genome research, once the first physical map will be completed.

(4) In the future ordered collections of full length cDNAs will be required from all different tissues of the body. Resource centers providing ordered cDNA libraries as a

service to the scientific community should be given high priority in a future HGAP.

(5) Allocation of resources to megascale cDNA sequencing projects should be considered. The concept of cDNA sequencing to obtain a complete catalogue of the human genes was after all a European idea.

(6) Mega-scale genomic sequencing which was not a component of the original HGAP needs to be considered in a future HGAP. It will be necessary to carry out som pilot projects involving megabase-sequencing to assess the future possibilities to approch sequencing of whole human chromosomes. Also, the possibility of sequencing the entire genome by a "shot gun approach" needs careful consideration. It is suggested that an ad hoc group is assembled to look into this problem. If the EC intends to participate in such a project it will have to greatly expand the program budget to faster reach the ultimate goal of the global genome program, the complete nucleotide sequence of the human genome.

(7) EUROGEM, on the other hand, will soon have completed its mission once the high resolution genetic map has been finished.

(8) Bioinformatics is a field that is likely to develop very rapidly in the near future. The design of user-friendly software for analysis of massive amounts of data will undoubtedly be an important aspect of a future HGAP. In view of the very widespread criticism directed to GDB, it becomes useful to envision alternative databases or at least different database access systems: in this respect, the progress of the Heidelberg IGD (Integrated Genome Database) appears promising and the distribution model advocated by this group, using a locally running ACeDB system fed with data from the other genome databases, appears particularly promising.
Communication between biologists and computer scientists remains imperfect: they still belong largely to two quite different cultures. Both fields have been evolving very quickly in recent years, and few individuals possess competence in both fields. An increase in their numbers, through attractive fellowships and positions, is probably the only way of easing this difficulty.
Moreover attention, and some funding, should be devoted to improving interfaces between the "genome world" and the general biology community, including not only medical genetics but also, for example, groups performing functional research in the mouse system so that structure and function are brought closer together.

(9) The transnational projects should be continued although they must be selected with great care. In supporting research and formulating suggestions on how to distribute research funds, it will be cogent to remember that collaborations, which are undoubtedly very important, cannot be organized by anyone, but must and will develop spontaneously. In that respect, it cannot be wise to stipulate collaborations between scientists from certain areas in Europe or even make the assignment of funds

dependent on such collaborations. Such ideas are counterproductive. It would be preferable to rather start a special program of a limited extent for the support of deserving scientists in the bio-medical field working in those countries of Europe which are presently still weaker in molecular biology but are capable of catching up rapidly.

(10) The training program appears largely to have been a success and a continuation of the program is recommended. It may, however, be necessary to find new means to spread information about the program since the number of applications was much smaller than anticipated. It should also be kept in mind that some modifications of the program might be very beneficial for young scientist working in the field of human genome analysis. There is one problem, which all European countries seem to share, i.e., the support and independence of young investigators who have proven themselves in their own or in other countries as first rate scientists. There is a very considerable lure by laboratories in the United States with its very flexible administrative structure at most universities and, above all, with an impressive number of top research centers at many U.S. universities. It will be increasingly attractive for young Europeans to seek to associate themselves with laboratories at such centers for longer or shorter periods of time, but usually during their years most productive for original research. Biomedical research, nowadays, can best be performed at centers of a critical size. It is necessary to recognize that it is one of the important tasks for science funding and organization in Europe to create a counterbalance to these very powerful centers for basic biomedical research in the U.S. A suggestion along these lines is to create positions for young independent researchers in the biomedical research areas which would allow highly qualified young scientists to pursue research of their own choice at one of the European universities, but uninhibited by their often very "traditional" administrative structures. In addition to positions, funds for consumable supplies, equipment and research personel should be attached to these positions. It is proposed that such structures would help very considerably in attracting or re-attracting many of the most productive young researchers from abroad to European countries.

(11) ESLA pograms are essential components of genome programs. The panel recommends, although not unanimously, that the ESLA program is continued and that long range support is provided. It is important that the program is announced as extensively as possible and that the contractors receive the proper information about the expectd output of the program. An urgent component in future ESLA programs will be to provide means for the participating groups to cooperate, interact and exchange ideas and results.
Special efforts should also be made to include economics of technical change, science policy and science studies in the program. The geographical inbalance is another problem that needs attention.

(12) Support to workshops and meetings is clearly an essential component of HGAP and

continuation of the program is recommended. However, some administrative changes are recommended. It is, for instance suggested that a scientific advisory board is established to advice on the policy of the program and to screen applications. Efforts should be made to obtain a better balance with regard to topics among the workshops that are supported. The support via HUGO to single chromosme workshops is essential and should be continued. In general, support should be given to chromosome workshops taking place in Europe as a contribution to the organization. Support should also be given as travel grants to European participants in workshops taking place outside of Europe. It seems also worthwile to support workshops which bring together scientists working within the HGAP on similar topics (as has been done to same extent in the past), for instance those working in EUROGEM or with cDNA libraries. This would obviously stimulate contacts between groups in different European countries.

(13) Another welcome addition to the program would be education of practising physicians all over Europe. With the rapid progress in Medical Genetics our practising colleagues are already in a difficult position vis-a-vis their patients who will ask pressing questions. Specialized training programs might at least provide a partial solution to the problem.

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COUNCIL DECISION

of 29 June 1990

adopting a specific research and technological development programme in the field of health: human genome analysis (1990 to 1991)

(90/395/EEC)

THE COUNCIL OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community, and in particular Article 130q (2) thereof,

Having regard to the proposal from the Commission (1),

In cooperation with the European Parliament (2),

Having regard to the opinion of the Economic and Social Committee (3),

Whereas Article 130k of the Treaty provides that the framework programme is to be implemented through specific programmes developed within each activity;

Whereas, by its Decision 87/516/Euratom, EEC (4), as amended by Decision 88/193/EEC, Euratom (5), the Council adopted a framework programme for Community activities in the field of research and technological development (1987 to 1991), which defined activities to be undertaken in the field of health;

Whereas that Decision provides that Community action is justified where research contributes, *inter alia,* to the strengthening of the economic and social cohesion of the Community and to the promotion of its overall harmonious development, while being consistent with the pursuit of scientific and technical excellence;

Whereas two successive pluriannual programmes of research and training of the European Economic Community in the field of biotechnologies (6), the second of which is still in progress, have shown the possibility and usefulness of Community action promoting the utilization of modern biology for scientific, medical and industrial purposes;

Whereas the framework programme provides, under the heading 'Health' in the 'Quality of Life' section, for the initiation of new activities relating to the development of knowledge of the human genome;

Whereas, following the adoption of a third Community Framework Programme for activities in the field of research and technological development (1990 to 1994), it is necessary to continue the implementation of the second Framework Programme (1987 to 1991) by means of specific programmes for which the latter makes provision;

Whereas a specific programme to study the human genome is therefore necessary and, in particular, it is necessary to:

— develop and disseminate the basic technologies concerning the study of the human genome, with the intention of improving knowledge of matters of medical importance,

— increase the resolution of the human genetic map and improve the physical map by the creation of ordered clone libraries, as a basis for locating genes of medical importance on chromosomes and for a better general understanding of gene function, and

— organize networks and coordination, on a European and international scale, of researchers from all disciplines working in this field;

Whereas achievement of the abovementioned goals requires the undertaking at Community level of action aimed at:

— filling some existing gaps in scientific and technological knowledge, and

— encouraging cooperation between European research establishments with a view to furthering the development of existing technologies, while promoting all research sectors capable of generating new lines of research;

Whereas, simultaneously, measures must be taken to promote cooperation between the Community programme and similar ones developed in third countries or by international organizations;

Whereas the right to a genetic identity forms part of the integrity and the dignity of an individual and this principle is recognized in the constitutions and laws of Member States and in the Community legal system as forming part of the fundamental rights for which respect is ensured;

Whereas the results which can be achieved from human genome research require the development of an integrated

(1) OJ No C 27, 2. 2. 1989, p. 6 and OJ No C 303, 2. 12. 1989, p. 18.
(2) OJ No C 69, 20. 3. 1989, p. 85 and OJ No C 149, 18. 6. 1990.
(3) OJ No C 56, 6. 3. 1989, p. 7.
(4) OJ No L 302, 24. 10. 1987, p. 1.
(5) OJ No L 89, 6. 4. 1988, p. 35.
(6) OJ No L 375, 30. 12. 1981, p. 1 and OJ No L 83, 25. 3. 1985, p. 1.

approach, taking into account the medical, ethical, social and legal aspects of the possible applications of such results and the need to avoid any improper use thereof;

Whereas the development of an integrated approach was proposed by the European Parliament in its resolution of 16 March 1989 (1);

Whereas there are good grounds for guaranteeing the right of an individual to have an informed choice as to whether or not he should receive information concerning his genetic characteristics;

Whereas, in the absence of clear standards and provisions concerning possible developments in the field of genome analysis, there may be a risk, on the one hand, that attempts will be made to intervene in the human genome in order to make the modifications so obtained hereditary and, on the other, that genetic analyses will be carried out for monitoring purposes, which may have a profound effect on social life; whereas there are, accordingly, good grounds for taking the necessary steps to preclude unacceptable developments, particularly in terms of predictive medicine;

Whereas, furthermore, it is necessary to examine in detail, during the course of the programme, the prenormative aspects arising from human genome analysis by establishing a reliable scientific data set which could provide a basis for political authorities to establish sound, clear and responsible rules;

Whereas the Scientific and Technical Research Committee (Crest) has been consulted,

HAS ADOPTED THIS DECISION:

Article 1

A specific research and technological development programme for the European Economic Community in the field of human genome analysis, as defined in Annex II, is hereby adopted for a period of two years commencing on 29 June 1990.

Article 2

1. The funds estimated as necessary for the execution of the programme amount to ECU 14 million, including expenditure on a staff of two.

2. An indicative allocation of funds is set out in Annex I.

Article 3

Detailed rules for the implementation of the programme and the rates of the Community's financial participation are set out in Annex II.

Article 4

1. The Commission shall send the European Parliament and the Council an annual report on the progress of the programme.

2. In the second year of implementation of the programme, the Commission shall review it and send the results of its review to the European Parliament and the Council; the report shall be accompanied, where necessary, by proposals for amendment or extension of the programme.

3. An evaluation of the results achieved shall be carried out by independent experts and published in the form of a communication to the European Parliament and the Council.

4. The abovementioned reports shall be established having regard to the objectives and evaluation criteria set out in Annex II and in accordance with Article 2 (2) of Decision 87/516/Euratom, EEC.

Article 5

The Commission shall be responsible for the execution of the programme. It shall be assisted by a committee of an advisory nature, hereinafter referred to as 'the Committee', composed of the representatives of the Member States and chaired by the representative of the Commission.

Article 6

1. The representative of the Commission shall submit to the committee a draft of the measures to be taken. The committee shall deliver its opinion within a time limit which the chairman may lay down according to the urgency of the matter, if necessary by taking a vote.

2. The opinion shall be recorded in the minutes; in addition, each Member State shall have the right to ask to have its position recorded in the minutes.

3. The Commission shall take the utmost account of the opinion delivered by the committee. It shall inform the committee of the manner in which its opinion has been taken into account.

Article 7

The procedure laid down in Article 6 shall apply in particular to:

— the contents of the calls for proposals,

(1) OJ No C 96, 17. 5. 1989, p. 165.

— the assessment of the proposed projects and the estimated amount of the Community's contribution to them,

— departures from the general rules governing Community participation set out in Annex II,

— the participation in any project by third-country organizations and enterprises referred to in Article 8 (2),

— any adjustment to the indicative allocation of resources set out in Annex I,

— the measures to be undertaken to evaluate the programme,

— the arrangements for the dissemination, protection and exploitation of the results of research carried out under the programme.

Article 8

1. The Commission is authorized, in accordance with Article 130n of the Treaty, to negotiate agreements with third countries and international organizations, particularly with third countries participating in European Cooperation in the field of Scientific and Technical Research (COST) and with States which have concluded framework agreements for scientific and technical cooperation with the Community, with a view to associating them with the programme.

2. Where framework agreements for scientific and technical cooperation between third countries and the European Communities have been concluded, organizations and enterprises established in those countries may, on the basis of the criterion of mutual benefit, become partners in a project undertaken within this programme.

3. No contracting party based outside the Community and participating as a partner in a project undertaken under the programme may benefit from Community financing for this programme. Such contracting party shall contribute to the general administrative costs.

Article 9

This Decision is addressed to the Member States.

Done at Luxembourg, 29 June 1990.

For the Council
The President
M. SMITH

ANNEX I

INDICATIVE INTERNAL ALLOCATION OF RESOURCES

	ECU million
Improvement of the human genetic map	3,3
Physical mapping (ordered clone libraries)	3,4
Data processing and databases	2,2
Improvement of the methods and basis for the study of the human genome	2,2
Training	1,9
Ethical, social and legal aspects	1,0
Management and staff	1,0
TOTAL	15,0

ANNEX II

SPECIFIC RESEARCH PROGRAMME IN THE FIELD OF HEALTH: HUMAN GENOME ANALYSIS

1. OBJECTIVES

Use and improvement of new biotechnologies in the study of the human genome for a better understanding of the mechanisms of genetic functions, as well as the prevention and treatment of human diseases. In the pursuit of these objectives, optimal cooperation will be sought with the programmes of third States and international organizations.

At the same time, measures will be taken to draw up an integrated approach to the medical, ethical, social and legal aspects of possible applications of results obtained through the programme to ensure that they are not misused and also, with prenormative aspects in mind, to establish a set of bioethical principles to be followed in the developments to come.

Alteration of germ cells or any stage of embryo development with the aim of modifying human genetic characteristics in a hereditary manner is excluded from the programme objectives.

2. TECHNICAL CONTENT

Precompetitive Community research, setting up and reinforcement of networks of European laboratories, and training, intended to allow the use of modern technologies for the study and setting up of the human genetic map as well as possible medical applications of the knowledge gained.

The research described below will require the use of data-processing facilities for the handling of data and the setting up of integrated databases to serve European networks, in close cooperation with other Community research programmes.

2.1. Improvement of the human genetic map

Setting up a European network, extending worldwide, for the collection and mapping of the DNA of large families, in order to provide research scientists with well-characterized genetic material and sets of probes to determine the location of the relative positions of genes on the chromosomes.

2.2. Setting up of ordered clone libraries of human DNA

Setting up of a European network of laboratories working on establishing overlapping clone libraries and support for limited sequencing of cDNA.

2.3. Improvement of the methods and basis for the study of the human genome

New biochemical reagents (restriction enzymes, etc.). Improvement of methods for the detection and localization of genetic markers (techniques for labelling DNA probes, amplification of genes, etc.). Development of new vectors for the cloning of large DNA fragments and of procedures for the transfection of chromosomes.

Development of model systems for the reproducible and stable expression of medically important genes both *in vivo* and *in vitro*, aimed at the wellbeing of patients. Development of new computer software for the storage and manipulation of data from genome sequencing and mapping.

2.4. Training

Setting up of a training programme to assist with the technology transfer of molecular genetics methods, in particular to Member States in which these techniques are currently underdeveloped.

3. IMPLEMENTATION

3.1. The programme shall be implemented through entering into cost-shared or marginal cost contracts, support to centralized facilities and new or existing networks, entering into training contracts, issue of training grants, organization of courses, consultations with national experts, organization of

study-group meetings, participation in seminars and symposia, publications, studies, dissemination of results to all interested groups and organization of public presentations.

For shared-cost contracts, the Community participation will be up to 50 % of the total expenditure. However, in the case of universities and research institutes carrying out projects under this programme, the Community may bear up to 100 % of the additional expenditure involved. In other cases, Community participation could reach 100 %.

Participants may be research establishments, universities, private enterprises or combinations thereof located in Member States or in the third countries referred to in Article 8, or competent organizations in a position to make a significant contribution.

Projects must be carried out by participants from more than one country, and include at least two independent partners from two Member States.

Fellows coming from third countries will be accepted in the training programme, provided that they meet the required conditions and that their costs are covered from other sources, such as other Community programmes or actions which support fellows coming from developing countries.

The contracts concluded by the Commission will govern the rights and the obligations of each party, in particular the means of distribution, protection and exploitation of the results of the research.

3.2. The drawing up of research contracts can only take place if the contracting parties undertake to abstain in this programme from all research modifying, or seeking to modify, the genetic constitution of human beings by alteration of germ cells or of any stage of embryo development which may make these alterations hereditary.

The contracts shall regulate the granting of licences arising out of research projects and, in particular, there shall be no right to exploit on an exclusive basis any property rights in respect of human DNA. In addition, the Commission shall reserve the right to publish the results of the research performed within the scope of the contracts.

The contracts will guarantee that the members of the families participating in the studies referred to in paragraph 2.1 will be fully informed of, and have consented to the use and study of, their DNA. The contracts will also guarantee complete protection of the confidentiality and anonymity of the personal data obtained in the programme.

3.3. The Commission will ensure that during the execution of the programme there will be wide-ranging and in-depth discussion of the ethical, social and legal aspects of human genome analysis and that possible misuses will be identified regarding applications of the results obtained or of future developments of that research. It will ensure that the far-reaching consequences of the research will be evaluated in a responsible manner and will submit to the European Parliament, the Council and the Economic and Social Committee an annual report, possibly with legislative recommendations arising as much from the research policy angle as from the legal one. To this end, the Commission will obtain advice from experts in different fields of science, law, philosophy and ethics, together with representatives of patient's associations.

4. EVALUATION CRITERIA

The communication from the Commission to the Council on a Community action plan relating to the evaluation of Community research and development programmes [1] states that the objectives and milestones for each research programme have to be set out in verifiable and, where possible, quantitative form. These reference marks are listed below:

4.1. The long-term objective of this programme is to contribute to a better understanding of the mechanisms of genetic function as well as to the fight against human diseases arising from genetic variation (including genetic diseases *sensu stricto* and many common diseases with a genetic component, such as heart disease and cancer), through early diagnosis, prevention, and improvement of prognosis and therapy. The Commission proposes to achieve this objective by:

— the organization of networks of laboratories around European facilities for (a) the improvement of the human genetic map, and (b) the setting up of ordered clone libraries of human DNA, either of the complete genome or of selected chromosomes, together with cDNA sequencing,

[1] OJ No C 14, 20. 1. 1987, p. 5.

— the launching of a programme of prenormative research aiming at improvement of the methods and basis of the study of the human genome,

— the setting up of a programme of training to increase the distribution of modern genetic technologies in Europe and to improve technological know-how in European laboratories,

— the promotion of cooperation with third countries and international organizations.

4.2. The primary short-term objective is that the programme should succeed in establishing the abovementioned European networks of laboratories in the fields of:

— the human genetic map,

— ordered clone libraries of human DNA and cDNA sequencing,

— improvement of the methods and basis for the study of the human genome,

by using data-processing facilities for data-handling and by setting up integrated databases.

These objectives should be verifiable in 1991.

4.3. Particular objectives to be attained within two years of the programme's implementation are as follows:

1. Concerning the human genetic map:
   — the present total of 40 well-studied large families which form the basis for the genetic map should be increased to 60 families,
   — genetic material from these families, and DNA probes, should be made available to the European laboratories concerned, while respecting the individual rights of those families,
   — a central facility should be identified to pool the results and establish an improved genetic map at the one to five centimorgan level, and an integrated databank should be set up.

2. The strategies for setting up ordered clone libraries of human DNA should be compared and a better approach defined; facilities for maintaining the stocks of cloned DNA fragments should be established and the available clones dispatched to interested European laboratories.

3. Substantial improvements should be obtained in the following research fields to improve the methods and the basis for the study of the human genome:
   — new reagents, such as restriction enzymes,
   — methodology for cloning large DNA fragments and for the transfection of chromosomes,
   — gene vectors adapted to human somatic celles *in vitro*,
   — methodology for the detection of a particular gene in a cell,
   — localization, cloning and sequencing of new genes, especially those which are disease-related,
   — new computer software for processing of DNA sequence data.

4.4. In addition, the programme should ensure that the following general criteria are met:

1. That throughout the execution of the programme, the ethical, social and legal aspects of human genome analysis should be the subject of wide-ranging and in-depth discussions, and possible abuses of the results or later developments of the work should be identified; principles for their utilization and control should be proposed.

2. That the drawing up of research contracts should presuppose that the contracting parties undertake to abstain in this programme from all research modifying or seeking to modify the genetic constitution of human beings by alteration of germ cells or of any stage of embryo development which may make these alterations hereditary.

3. That the members of the families taking part in the studies mentioned in point 2.1 must have been informed and must have given their consent, and the confidentiality and anonymity of personal data must be ensured.

4. That the development and the application of somatic gene therapy are not provided for within the framework of the present programme.

5. That only somatic actual or potential medical applications should be facilitated.

6. That potential opportunities for industrial development should be explored.

7. That the overall scientific standard of the participating European laboratories must have been improved.

8. That, taking account of the results of Community, national or commercial research activities in human genetics, the evaluation panel should consider whether the human genome analysis has contributed to the transfer of knowledge and the development of the results of the said activities in regions of the Community other than those in which the research was conducted. The evaluation panel should also ascertain whether cooperation with third countries and international organizations has indeed been achieved and whether this cooperation has had positive results.

REQUIREMENTS FROM THE 2ND FRAMEWORK PROGRAMME

1 Article 2 of the Framework Programme Decision (87/516/EURATOM,EEC) states that each specific programme shall:

- state its precise objectives and provide for an evaluation of results achieved in relation to these objectives;

- be evaluated in the light of all selection criteria set out in Annex III, which include that of contributing to the strengthening of the economic and social cohesion of the Community.

2 The selection criteria set out in Annex III to the Framework Programme decision state that:

- "In general, Community R&TD actions should be selected on the basis of scientific and technical objectives, their scientific and technical quality and their contribution to the definition or implementation of Community policies.

  A particular aim of Community R&TD shall be to strengthen the scientific and technological basis of European industry - including that of SMEs - especially in strategic areas of high technology, and to encourage it to become more competitive at the international level.

  Community action can be justified where it presents advantages (added value) in the short, medium or long term from the point of view of efficiency and financing or from the scientific and technical point of view as compared with national and other international activities (public or private).

The following criteria in particular justify Community action:

- research which contributes to the strengthening of the economic and social cohesion of the Community and the promotion of its overall harmonious development, consistent with the pursuit of scientific and technical quality,

- research on a very large scale for which the individual Member States could not, or could only with difficulty, provide the necessary finance and personnel,

- research, the joint execution of which would offer obvious financial benefits, even after taking account of the extra costs inherent in all international cooperation,

- research which, because of the complementary nature of work being done nationally in part of a given field, enables significant results to be obtained in the Community as a whole for the case of problems whose solution requires research on a large scale, particularly geographical,

- research which contributes to the achievement of the common market and to the unification of the European scientific and technical area, and research leading, where the need is felt, to the establishment of uniform norms and standards."

LIST OF DOCUMENTS

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An Evaluation of the Human Genome Analysis Programme of the Commission of the European Communities from an industrial perspective

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The Human Genome Analysis Programme adopted by the Commission of the European Communities in 29 June 1990 is now completed. During this period of three years, there has been a dramatic evolution in the field which can be chraracterized by four main aspects :

- fast progress of genetic mapping, and to a lesser extent of physical mapping, with now evidence of the probable completion of the total mapping of the Human Genome before the end of the millenium;

- limited progress in basic technologies involved : YAC libraries, sequence tagged sites, cDNA libraries and Sanger sequencing still constitute the main tools currently used in laboratories;

- fast development of an industry serving genome research with instruments and reagents;

- involvement of private companies in human genome research and patenting of the results of this research, particularly in the U.S.A.

Human Genome Research is now a field of extremely active global competition with the support of massive private funding. Accordingly, it will be driven in the coming years by its potential applications in human diagnotics, prognostics and therapeutics.

In order to take advantage of the comparatively good level of human genome science in the European Community, the Commission should now focus on the following organizational issues :

- definition of activities between public and private laboratories;

- optimal use of the E.C. industry resources for the genome research;

- support of the E.C. industry seeking to exploit the results of human genome programmes.

With these goals in mind, the following comments can be made on the results of the current Human Genome Analysis Programme :

1) *Resource centres are necessary to organize and distribute libraries, not to provide reagents or perform routine experiments.*

The success of the CEPPH YAC libraries is a clear indication of the added-value of a well-organized resource centre. On the other hand, the use of academic laboratories for routine or production operations has proved to be a waste of resources.

First, the use of talented scientists for routine DNA sequencing, DNA synthesis or cloning operations slows down the progress of fundamental research which is the primary vocation of these laboratories.

Second, the academic laboratories are not organized to handle these activities efficiently. For instance, the dramatic economies of scale in DNA sequencing and synthesis can only be achieved in industrial organizations that focus on automation, engineering development, purchasing know-how, and industrial organization.

2) *Routine activities should be contracted to the industry with qualified bidding procedures and a preference for E.C. companies.*

The current E.C. industry counts a number of efficient companies ready to provide human genome research with quality products and services at competitive world prices. Contracts should be awarded to the lowest bidders among qualified E.C. companies. This contracting approach would allow substantial savings in global research budgets and put the E.C. industry on a par with its American counterpart with benefits from similar procedures.

This contracting approach would also favor the development of projects to exploit results of the programmes with the development of new products for research, human diagnostics or therapeutics.

3) *Academic biochemistry laboratories are not efficient to develop new instruments.*

All instrumentation currently used in human genome research laboratories has been developped by the industry. The only exceptions are found in the laboratories of biochemical instrumentation that tend to use their own equipment to perform their experiments. It is clear that the results of current instrumentation programmes are very disappointing, as the developped systems never reached the market.

The activity of instrument development bound on established technologies should be left to the industry. The investigations on new technologies for genome research can also be conducted with existing instruments. For example, it is possible to study DNA sequencing by mass spectometry on tunnel microscopy with existing commercial equipment.

4) *A network using UNIX workstations should be established between all European Community Human Genome laboratories.*

The handling of data and exchange of information between genome research laboratories will probably be the major challenge of the coming years. UNIX workstations are fast becoming the standard for software applications requiring large computing power and storage capacity. They also have the immense advantage to allow interactive communication on the Internet network. The Commission should support the establishment of a workstation network which will allow fast and efficient distribution of databases, communications between research laboratories and resource centers, and communication between research laboratories and industrial contractors for the supply of services and products. This network will be also a firm foundation for the launch of new databases which could complete effectively with the overwhelmingly dominant U.S. databases.

5) *Results of Human Genome Programmes supported by the European Commission should be patented.*

The current position of providing free access to the European results of Human Genome research is no longer tenable when the U.S. public institutions and private industries are engaged in a massive effort of patenting cDNAs, expressed tagged sites, genetic markers and complete genes. This evolution may lead to a huge dificit of intellectual property within the European Community, which in turn could essentially eliminate the E.C. industry from the applications in human diagnostics and therapeutics. The consequences could be estremely severe during the next millenium. The Commission should make compulsory the patenting of the key results of the programmes it supports by the contractors. In order to facilitate the transfer of property rights, an office should be established to organize licensing for the benefits of instrumentation, reagents, diagnostic and pharmaceutical companies. Exclusivity and preference rights should be established on the basis of the qualification and the origin of licensees.

It is suggested that the above comments could help in the definition of a new Framework Programme which could organize four main types of activities : i) resource centres dedicated to distributing libraries; ii) industrial contractors dedicated to providing services and reagents; ii) transnational contracts for the execution of master research projects, and iv) computer networks.

LIST OF ABBREVIATIONS

CAN-HUG	COMMITTEE OF THE ADVISORY NATURE ON HUMAN GENOME
CEPH	CENTRE D'ETUDES POLYMORPHISME HUMAINE
CGC	COORDINATION AND MANAGEMENT COMMITTEE
DKFZ	DEUTSCHES KREBSFORSCHUNGSZENTRUM
EMBL	EUROPEAN MOLECULAR BIOLOGY LABORATORY
ESLA	ETHIC, SOCIAL AND LEGAL ASPECTS OF HUMAN GENOME ANALYSIS
EUROGEM	EUROPEAN GENE MAPPING
HGAP	HUMAN GENOME ANALYSIS PROGRAMME
HUGO	HUMAN GENOME ORGANISATION
ICRF	IMPERIAL CANCER RESERACH FUND
NIH	NATIONAL INSTITUTE OF HEALTH

European Commission

EUR 15706 - Evaluation of the Programme Human Genome Analysis (1990-1991)

U. Pettersson, W. Doerfler, B. Latour, D. Toniolo, H. Vanden Berghe

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This is the evaluation report on the Human Genome Analysis Programme 1990-1991 presented by an independent Panel of external experts.

The Panel consisted of five experts under the chairmanship of Prof. U. Pettersson.

This report includes information based on an earlier report "Assessment of progress in Human Genome Programmes world wide" written by Dr. B. Jordan, also on documents provided by the programme managers, as well as on-site visits and interviews with selected projects contractors.

An executive summary highlights the main findings and recommendations of the Panel.

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