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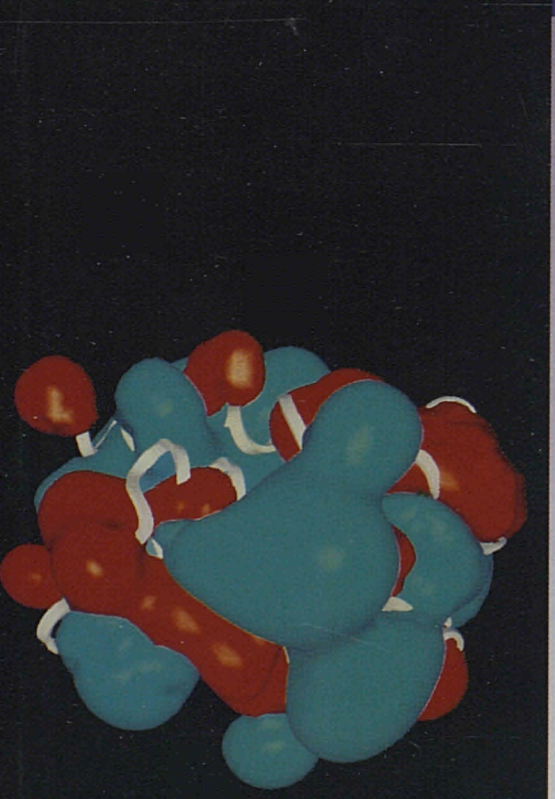

Biotechnology

1994 Report on Protein Engineering R&D Programmes in Europe

Report
EUR 16154 EN

Front cover

***Fusarium* cutinase at pH 4.5 with positive and negative isopotential surfaces represented as solid surfaces**

Parts of the backbone here represented as a ribbon can be seen to penetrate the isopotential surface at several locations. The potential surfaces have been calculated using TITRA (Petersen and Martel) and DelPhi (Biosym Technologies). The image was prepared as part of a study carried out by M. Sebastiao, P. Martel, A. Baptista and S.B. Petersen. Courtesy of the MR Center, SINTEF-UNIMED.

European Commission
Directorate - General XII
Science, Research and Development

BIOTECHNOLOGY

1994 REPORT ON PROTEIN ENGINEERING R&D PROGRAMMES

. CONTACT PERSON . FINANCIAL ASPECTS
. R&D PROGRAMME . SCIENCE & TECHNOLOGY ASPECTS
. POLICY ASPECTS . FUTURE DEVELOPMENTS

IN:

. BELGIUM . DENMARK . GERMANY . GREECE . SPAIN . FRANCE
. IRELAND . ITALY . THE NETHERLANDS . PORTUGAL
. UNITED KINGDOM . AUSTRIA . FINLAND . ICELAND . NORWAY
. SWEDEN . EMBL . EUROPEAN COMMISSION

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EXECUTIVE SUMMARY

Executive Summary

The recent Communication -COM(94) 438 final- from the Commission "*Research and Technological Development (RTD): achieving coordination through cooperation*" concerns the implementation of Art. 130H of the Treaty on European Union (which requires the Community and the Member States to coordinate their activities so as to ensure that national policies and Community policy are mutually consistent). This represents a logical follow-up of the White Paper on growth, competitiveness and employment, as much as it addresses one of the major weaknesses of the Community - the fragmentation of the research activities of the Member States.

The approach which has been followed for the sector described as Protein Engineering was to suggest that it might be a typical subject area (being relatively new and consisting of a combination of several disciplines and techniques) for review at national and Community levels to achieve an improved level of coordination.
A 3-step approach has been taken :
(1) to collect information on the national protein engineering programmes,
(2) to share and analyze this information and find a common presentation "format" and,
(3) to list topics for further action on the basis of this rigorous analysis of available data.

This work was carried out for 16 countries, the EMBL and the European Commission, with the crucial help of the "Protein Engineering Contact Group" made up of contact persons nominated by each country. The outcome of this work is the present 1994 report on protein engineering programmes which should be considered as the first step in a continuous approach towards the provision of better information to the scientific community, programme managers and policy makers involved in protein engineering R&D in Europe.

With further improvements (such as an extension of scope towards structural biology and more information on industrial activities), and with the methodology developed, the "Contact Group" could form, together with the European Commission services, a crucial network to share information, as well as to improve its quality and accuracy. This mechanism for the coordination of research effort in Europe may become a model for other subjects and sectors.

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INTRODUCTION

Introduction

- The principle of subsidiarity

The "*Second Commission working document concerning RTD policy in the Community and the 4th Framework Programme (1994-1998) of Community RTD activities*"[1] contains the following passage related to closer integration of research and technological development in Europe:
"*The principle of subsidiarity dictates that the Community should take action on research, only if the objectives can be better achieved by the Community than by the Member States acting on their own. Article 130h of the Treaty on European Union also requires the Community and the Member States to coordinate their activities so as to ensure that national policies and Community policy are mutually consistent. It must be acknowledged that not enough has been done on this point so far. A new approach is needed, with the detailed procedures tailored to each research area.*"

Whatever area is chosen, an inventory would be required to identify which national and Community activities would best come under the scope of an harmonization of relevant S&T policies. In producing such an inventory, difficulties as well as opportunities would have to be pragmatically understood and exploited, as they would suggest which implementation mechanisms would allow the desired form of coordination in the area in question.

- The European Commission White Paper

The European Commission White Paper entitled "*Growth, Competitiveness, Employment, the challenges and ways forward into the 21st century*"[2] states that Europe's research and industrial base suffers from a series of weaknesses: the level of financial resources and the application of research results are two of them. The following passage concerns the coordination of research:
"*A second weakness is the lack of coordination at various levels of the research and technological development activities, programmes and strategies in Europe. First, there is a lack of coordination between the national research policies. The Community's research budget accounts for only 4% of research spending by the 12 Member States. Even adding the resources allocated to joint European RTD activities in other frameworks (e.g. under Eureka, ESA, CERN, EMBL, etc.), the budget amounts to only 10% or so of the total. Despite the coordination called for by the existence of these activities and the need for the Member States to take them into account when defining their own policies, the national policies are still developed largely without reference to one another.*"

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[1] COM(93)158 final, 22 April 1993

[2] European Commision, Brussels - Luxembourg, 1994

• "*Research and Technological Development: achieving coordination through cooperation*"

The recent Communication[3] from the Commission "*Research and Technological Development (RTD) achieving coordination through cooperation*" concerns the implementation of Art. 130 H of the Treaty on European Union and represents a logical follow-up of the White Paper on growth, competitiveness and employment as much as it addresses one of the major weaknesses of the Community - the fragmentation of RTD activities in its Member States. The Communication mentions in particular that:
"*A distinction must be drawn between two concepts: (i) cooperation, which is now accepted by everyone as the usual mechanism for the Community action, with the obvious advantages of voluntary pooling of efforts and skills on a case-by-case basis; (ii) coordination, a mechanism which promises major advantages for increasing the efficiency of all RTD activities but which also imposes greater constraints and, hence, is harder to accept. For this reason, the Commission proposes a progressive approach to achieve better coordination by intensifying cooperation at the various stages of drafting and implementaiong RTD policy*".
The proposed approach is presented as:
"*The approach taken must be multifaceted and flexible, but also practical. Different types of activity will be undertaken at different levels:*
- on determination of RTD policies, with the objective of providing ministers in the Union with a forum for discussion with systematic preparatory work to supply the information which they all need;
- on implementation of research activities, including not only those covered by the Framework Programme for implementing Articles 130K and 130 L but also the activities under the national programmes in order to make all efforts more consistent;
- on international cooperation, where a stronger presence on the part of the European Union is both desirable and attainable, without impinging on the Member States' prerogatives".

• The approach for Protein Engineering

The approach followed here was to suggest that Protein Engineering might be a typical area for review at national and Community levels to achieve a good level of coordination. The field of protein engineering was felt appropriate, as being relatively new, and consisting of the combination of several disciplines and techniques.

A 3-step approach has been taken :
(1) to collect information on the national protein engineering programmes
(2) to share and analyze this information and find a common presentation "format" and,
(3) to list topics for further action on the basis of a rigorous analysis of the available data (gaps, duplications of effort, possible synergies, etc...).

In the first part of the report, the essential facts are presented in a summary with a common format, including the following parts for each country:

- **Contact person**
  (from whom additional information can be obtained)

[3] COM (94) 438 final, 19 October 1994

- **National programme**
  (or, if there is no programme in the strict sense of the word, the way PE R&D is organized at the national level)
- **Policy aspects**
  (including the strategic approach and priorities)
- **Financial aspects**
  (appropriate caveats are given for the figures presented)
- **Science & Technology aspects**
  (including the main R&D centers and S&T activities)
- **Future developments**
  (programmes or initiatives in preparation)

• Collection and analysis of information

The crucial first step of collecting information from the different countries as well as improving and validating the quality and accuracy of the data was carried out with the key contributions from the Protein Engineering Contact Group which consists of one contact person (see table page 13) per country, nominated by the national delegates (see table page 17) of the sub-group for horizontal activities of the CRN-BIOTECH (Committee of Regulatory Nature of the EC RTD Biotechnology programme).

The second part of the report concerns the analysis of the information collected. It was prepared following intensive discussions and consultations with the Contact Group. It highlights the organisational and technological aspects that have contributed to the research programmes in protein engineering and is, to a large part, based upon cautious analysis of the factual data that has been provided. Common trends rather than individual exceptions are highlighted, except when the nature of such exceptions contains an important message for the report as a whole.

P. de Taxis du Poët and E. Magnien
8 December 1994

DEFINITION OF PROTEIN ENGINEERING

Definition of Protein Engineering (PE)

One of the main objectives of this report is to offer to the reader (in particular, the scientists and policy makers) a précis of the national programmes / centers / activities in Europe, which could facilitate scientific collaboration as well as the coordination of research activities in Europe. Therefore, in view of these objectives, there are two risks in defining protein engineering: a too rigid definition would ignore important elements of what is considered as protein engineering in some countries and, a too flexible definition would include almost all biotechnological activities.

To limit these risks, the PE Contact Group proposed a definition which focuses on the objective of PE, rather than on the diverse components / tools / disciplines necessary to reach this objective: ***The term Protein Engineering applies to any deliberate modification of a protein structure which brings about a change in its functional properties.***

It is clear that PE requires the integration of competences in various domains (molecular biology, biochemistry, computer science, techniques of 3-D determination, etc). Therefore, anyone of these disciplines could not be considered under the umbrella of protein engineering, if it was not integrated with the others. Thus, PE is defined as the integration of various disciplines and techniques to reach the above mentioned specific objective.

Concerning how far we should go in each of these integrated disciplines composing Protein Engineering for the purposes of this report, a reasonable flexibility is allowed. Indeed, this diversity may reflect the different views on how important any particular discipline of protein engineering is considered. This additional information could be of interest to the reader, keeping in mind that the objective of this report is to describe the various ways the field of protein engineering is covered in each country.

PROTEIN ENGINEERING CONTACT PERSONS

"Contact Group"
for
Protein Engineering R & D Programmes in Europe

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CNR-BIOTECH
Sub-Group for
Horizontal Activities

Members of the sub-group for horizontal activities of the Regulatory Committee for the EC RTD programme in the field of Biotechnology (1990-94)

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GERMANY
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GREECE
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SPAIN
A. Albert

FRANCE
P. Printz

IRELAND
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Chairman : E. Magnien ; **Secretariat** : P. de Taxis du Poët

BELGIUM

BELGIUM

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NATIONAL PROGRAMMES

R&D policy has been progressively partially decentralized in Belgium. Therefore support for protein engineering is organized at the federal and regional levels, under the following programmes:

- Incentive programme for fundamental research in life sciences (federal)
- Inter-university poles of attraction (federal)
- Flemish action programme on biotechnology (regional)
- 3 Walloon programmes related to biotechnology (regional)
- French community programme
- Fonds National de la Recherche Scientifique (FNRS)

POLICY ASPECTS

- To underpin the growth of different fields in the biosciences and to create inter-university poles of attractions or networks in basic research (federal level)
- To stimulate R&D initiatives in specific fields of biotechnology and the transfer of existing knowledge and technology from universities to industry (Flemish region)
- To allow young researchers to acquire a complementary S&T training in university and industry, and to stimulate the collaboration between universities and industries (Wallonian region)

FINANCIAL ASPECTS

The amounts indicated include salaries, equipment, consumables, travel costs and overheads.

Incentive programme for fundamental research in life sciences	3.6 MECU (6 projects, 1988-1993)

Inter-university poles of attraction	5.08 MECU (2 projects, 1990-1995)
Flemish action programme on biotechnology	Total of 22 MECU (1990-1995): A portion (3.5 MECU) is devoted to protein engineering (3 projects) and there is one centre for emerging technology (3.8 MECU, 1990-1997)
French community programme	1 MECU / 5 years
Walloon programmes related to biotechnology	0.72 MECU over a period of 2 to 3 years depending on the project

SCIENCE &TECHNOLOGY ASPECTS	
Incentive programme for fundamental research in life sciences	- structure-function relationships of a cell growth factor - NMR technology - membranes proteins in yeasts and plants - Enzyme solution dynamics - peptide-protein interactions - High-sensitive sequence analysis of proteins
Inter-university poles of attraction	- penicillin binding proteins - Development of new anti-cancer therapeutics (TNF and IFN)
Flemish action programme on biotechnology	- Molecular farming: the production of bioactive peptides in the seeds of transgenic plants by engineering the 2S-albumine stock proteins - Cloning and expression of human receptor genes - Molecular modelling of human lymphocyte dipeptidyl peptidase IV - antibody engineering - protein-carbohydrate interactions
French community programme	Concerted actions on the enzymes of organisms living at low temperatures (trypsines, subtilisines, amylase and lactamase)

Walloon programmes related to biotechnology	- Membrane protein of *Schistosoma mansoni* - Neuronal proteins - Lipase - Adrenergic receptors - Neuropeptides - Human receptors - Antigens of *Varicella zoster* virus, paramyxovirus and Toxoplasma gondii - Apolipoprotein A1 - Prolactins - Selection methods for enzymes with new properties

FUTURE DEVELOPMENTS
No information available

DENMARK

DENMARK

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NATIONAL PROGRAMME

The Danish protein engineering research centre (PERC) was established as a formal collaboration, within the context of the Danish biotechnological R&D programme 1991-1995 (Biotek II), between 4 groups:
- Odense university, protein structure and function unit
- Aarhus university, laboratory for macromolecular structure
- Aarhus university, laboratory for recombinant protein chemistry
- Carlsberg laboratory, protein structure and NMR group

POLICY ASPECTS

The idea is to combine scientific and methodological expertise into a common endeavour aimed at an increased understanding of the structure-function relationships, and ultimately to the elucidation of general principles which allow prediction of the structural change needed to obtain a desired functional alteration. Achievement of this general goal is planned through a common project entitled: "Systematic protein engineering studies of protein domains in single and multi-domain proteins"

FINANCIAL ASPECTS

A total of 4.5 MECU (1991-1993) with approximately 60% from the BIOTEK programme, and 40% from other sources. (This does not include salaries for permanent staff and infrastructure costs).

SCIENCE & TECHNOLOGY ASPECTS

The 4 PERC participants have developed interactions between the groups and nearly all national and many international research groups involved in protein engineering. PERC was invited to become a founding member of the international network of protein engineering centres (INPEC) in 1991. The 4 main research groups are:

-Odense university, protein structure and function unit Coordinator: P. Roepstorff (also PERC leader)	-Development of mass spectrometric methods for protein analysis and structure/function studies of acyl coenzyme A binding protein (ACBP)
-Aarhus university, laboratory for macromolecular structure Coordinator: B.F.C. Clark	-The explanation of the function of elongation factor (EF-Tu) arising from structural determination of its different conformational states and mutants
-Aarhus university, laboratory for recombinant protein chemistry Coordinator: H.C. Thøgersen	-Folding, structure and function of domains from multi-functional proteins
-Carlsberg laboratory, protein structure and NMR group Coordinator: F.M. Poulsen	-Protein structure NMR spectroscopy and protein engineering

Supporting technology: BioBase - The Danish EMBnet Node
E-mail contact: hum@biobase.dk
Contact person: Hans Ullitz Møller, BioBase, Ole Worms Allé, Bld. 170, Aarhus University, 8000 Aarhus C, DK, Tel. +45 8942 2846, Fax. +45 8613 1160

BioBase is a comprehensive service facility established for the Danish biotechnological research community that offers a large set of updated databases and a broad spectrum of sequence analysis programmes. These features, in connection with the European EMBnet nodes, offer opportunities that are essential for the modern researcher. Thus, it is possible to investigate if a new sequence contains elements that are either identical, or have a certain similarity, to elements of already known sequences. National funding for BioBase is 0.26 MECU per year.

FUTURE DEVELOPMENTS

The projects will be continued as planned, taking into account development in the international scientific society. A very important effect of the PERC collaboration is that all participants have widened their horizons, through the contacts and collaborations, and have been inspired to plan the next generation of projects to be initiated and problems to be solved.

GERMANY

GERMANY

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NATIONAL PROGRAMME

- There is no specific protein engineering programme but this sector is covered by the biotechnology programme "Biotechnology 2000"
- The national funding programme (BMFT) on "Molecular Bioinformatics" partly concerns (theoretical) protein engineering related activities

POLICY ASPECTS

Biotechnology 2000 states that the main focus of support is on projects dealing with the development of methods of protein structural analysis and molecular modelling. Also, a priority are methods for the simulation of structure and dynamics of complex molecules and methods for the design of proteins with new properties.

FINANCIAL ASPECTS

- A total of 16 MECU is dedicated to the protein engineering sector (66 % from the federal government), which includes 18 research projects (from 1 to 5 years) covering the 1987-1992 period. Six new projects (1.5 MECU) were launched in 1992
- In the "Molecular Bioinformatics" programme (11.4 MECU in three years), 40 % (4.56 MECU) is for protein engineering

The amounts given above are additional costs directly related to the research projects (including salaries, investments, consumables, travels, etc.). This is "project money" spent by the central federal government. Details of the money spent on protein engineering projects by the research institutes, Max-Planck Institutes and universities from their institutional money or by the "Deutsche Forschungsgemeinschaft", are not available.

SCIENCE &TECHNOLOGY ASPECTS	
National Centres	- GBF (Gesellschaft für Biotechnologische Forshung) houses the "Centre of Applied Protein Engineering", CAPE, Prof. D. Schomburg, Braunschweig - Institut für Molekulare Biotechnologie, Jena, Prof. Schuster
Protein X-ray Groups	- MPI für Medizinnische Forshung, Prof. K. Holmes, Heidelberg - Max-Planck Institut für Biochemie, Prof. R. Huber, Martinsried - FU Berlin, Institut für Kristallografie, Prof. W. Saenger, Berlin - Universität Freiburg, Institut für Biochemie, Prof. G. Schultz, Freiburg - GBF, Molecular structure research, Prof. D. Schomburg, Braunschweig *Two new groups to be installed*: - Max-Delbrück Zentrum, Dr. U. Heinemann, Berlin-Buch - Institut für Molekulare Biotechnologie, Dr. R. Hilgenfeld, Jena
Protein NMR Groups	- Max-Planck Institut für Biochemie, Dr. T. Holak, Martinsried - Universität Frankfurt, Institut für Organische Chemie, Prof. Griesinger, Frankfurt/main - Technische Universität München, Institut für Organische Chemie, Garching - Universität Frankfurt, Institut für Biophysikalische Chemie, Prof. Rüterans, Frankfurt/main - Universität Bayreuth, Lehrstuhl für Struktur der Biopolymere, Prof. Roesch, Bayreuth - GBF, Molecular structure research, Prof. D. Schomburg, Braunschweig

Protein Modelling Sofware and method development	- GBF, Molecular structure research, Prof. D. Schomburg, Braunschweig - GMD I1, Prof. T. Lengauer, St. Augustin
Development of Protein Data Banks	Protein Sequences: - MIPS, Dr. W. Mewes, Martinsried Enzyme information: - GBF, Molecular structure research, Prof. D. Schomburg, Braunschweig

FUTURE DEVELOPMENTS

There is a new programme: "Techniques for the decoding and use of biological design".

GREECE

GREECE

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NATIONAL PROGRAMME

There is no specific protein engineering programme but related projects receive support from the Greek Ministry of Research and Technology

POLICY ASPECTS

No information available.

FINANCIAL ASPECTS

The financial support obtained from National Sources is very small, and therefore much depends on European collaborations and funding from the EEC, which are both very limited. Support from industry is almost non-existent.

SCIENCE &TECHNOLOGY ASPECTS

The most relevant research group are:

Dept. of Biochemistry University of Athens Dr. Moudrianadis Dr. Hamodrakas	- Protein folding and prediction - Bioinformatics - Structural studies of protein-carbohydrate interactions - Metalloproteins, enzymes, and fibrous proteins. - Nucleosome structure
National Science Foundation Athens Dr. Oikonomakos Dr. Kolisis	- Carbohydrate active enzymes (glycogen phosphorylase). - Lipases

Institute Pasteur Athens Dr. Tzartos	- Antibody-antigen interactions - Receptors
Agricultural University of Athens Dr. Eliopoulos	- Bioinformatics, Data Bases
Dept. of Biochemistry University of Ioannina Dr. Sakarellos Dr. Gerothanasis	- NMR studies of pharmacological peptides, heme proteins and enzymes
Department of Biologya IMBB, Heraclion, Crete Dr. Kokkinidis Dr. Petratos	- α-helical bundle proteins - DNA bindingproteins - Metalloproteins
National Research Centre Demokritos Dr. Petrouleas Dr. Stassinopoulou	- ESR studies of photosystem II - NMR studies of carbohydrate binding proteins

FUTURE DEVELOPMENTS
No information available

SPAIN

SPAIN

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NATIONAL PROGRAMME

There is no specific programme on protein engineering, but related projects receive support from 2 main sources:

- The general programme for the Enlargement of Science, GPES (fundamental research)
- The national Programme of Biotechnology (oriented research)

POLICY ASPECTS

The principal gaps or problems to be solved are the limited number of research groups working on crystallography (2), protein design (2), NMR (2) and the lack of integrated work or the dispersion of scientific aims.

FINANCIAL ASPECTS

During the period 1990-94, the National Programme if Biotechnology has financed research projects on protein sciences for about 5 MECU. However, considering that other research projects in this field have been financed in other programmes, mainly in the Programme for General Promotion of Knowledge (basic science), we estimate that Spain has supported, during the period 1990-94, research projects on protein sciences for about 10 MECU.
This amount does not include infrastructure costs. To calculate this amount, we have considered as projects related to protein science, those ones which concern the production, utilization or characterisation of proteins or polypeptides, and not only those related to protein engineering.

SCIENCE &TECHNOLOGY ASPECTS

The national R&D Plan has created 2 national networks on:

- Protein structure, folding and stability (coordinated by Prof. M. Rico)
- Computational analysis of structure and evolution of biological macromolecules (coordinated by Prof. J.M. Carazo, Centro Nacional de Biotecnologia, Madrid):
  - Possible evolutive relationships in protein sequences
  - Useful models for system operations
  - Three-dimensional structures at different levels of resolution
  - New generation of parallel computer algorithms

The main centres, in which several groups work on protein engineering, are located in Madrid and Barcelona:

Madrid	
- Centro Nacional de Biotecnologia,	- Electron microscopy
- Centro de Biologia Molecular	- Database & Bioinformatics
- Centro de Investigaciones Biologicas,	
- Instituto de Quimica Fisica	- X-ray diffraction
- Instituto de la Estructura de la Materia,	- NMR 600 MHz
- Instituto de Catalisis y Petroquimica,	- Electron microscopy
- Depart. de Bioquimica y Biologia Molecular, Univ. Complutenses of Madrid	- Electron microscopy
- Depart. de Bioquimica y Biologia molecular, Autonomous Univ. of Madrid	- Electron microscopy - NMR 600 MHz
- Centro Pluridisciplinar UCM	
Barcelona	
- Instituto de Biologia Fundamental,	- X-ray diffraction, NMR
- Centro de Investigacion y Desarrollo	- Mass spectrometry
- Depart. de Bioquimica y Biologia Molecular, Autonomous University of Barcelona	
- Depart. de Ingenieria Quimica, Politecnica University of Barcelona	- X-ray diffraction
- Dept. Ingeneria Quimica, Autonomous University of Barcelona	

FUTURE DEVELOPMENTS

- The Higher Council of Scientific Research (CSIC) is currently drawing up a special programme on protein engineering

FRANCE

FRANCE

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NATIONAL PROGRAMMES

Three national programmes were launched in the early nineties. Two of them are now completed:

.IMABIO (Ingénierie des Macromolécules Biologiques) was launched by the CNRS (Centre National de la Recherche Scientifique) in 1990 for a four year period which ended in 1994.

.PROTEINE 2000 was launched in January 1989 by the CEA (Commissariat à l'Energie Atomique).

.CM2AO (1991-1993) (Conception et Modélisation des Macromolécules) consists of 5 companies (BSN, Limagrain, Orsan, Rhône-Poulenc and Roussel UCLAF) and aims at the development of generic methods necessary for the creation and modelisation of biological macromolecules.

POLICY ASPECTS

.A priority: Protein engineering is considered a priority by the Ministry of Research, the main national research organisations, and the industry, particularly in the pharmaceutical sector.

.Integration: The first national initiative began with the 1982-1988 period of the biotechnology programme, aiming at integrating the different skills required.

.Limited number of centres: In 1990, the relay was taken up by national institutions (in particular CNRS and CEA). A limited number of centres were created, bringing together all necessary technical tools and aiming at technological applications.

.An industrial initiative: Industry has launched the CM2AO programme in which 5 companies are involved. The public services are supporting this initiative (50% from industry).

FINANCIAL ASPECTS	
IMABIO	26.7 MECU (1990-1994) equally distributed between equipment and construction cost for the 4-year programme
PROTEINE 2000	17.1 MECU (for 1994), salaries and running expenses included
CM2AO	2.4 MECU (1991-1993), salaries and running expenses included

SCIENCE &TECHNOLOGY ASPECTS

• IMABIO investment was concentrated in 7 centers, one of them (IBS, in Genoble) in partnership with the CEA. Each center has its own scientific character. The manpower of these research centers amounts to 359 staff scientists, 207 from CNRS , 15 from INSERM and 137 from the universities.

• PROTEINE 2000 involves 4 scientific departments of CEA, 3 in Saclay and one in Grenoble, and the Institut de Biologie Stucturale (IBS, Grenoble). All together, 155 scientists from CEA are involved. All the classical aspects of protein engineering are covered. An interesting and unique feature of the programme is the large investment in the field of molecular labelling using tritium, stable and radioactive isotopes or chemicals.

• The main research centres are:

Institut de Biologie Structurale, Grenoble	Access to the European synchroton (ESRF) Protein-protein and protein-nucleic acid interactions Structural enzymology, protein folding Molecular modelisation
Saclay	Molecular labelling: national units and/or facilities for labelling of biomolecules with isotopes. Engineering of receptor-ligands, enzymes inhibitors and chimeric antibodies. Drug delivery and targeting Structure-function of proteins, protein foding

Gif - Orsay	Access to electro-magnetic radiation sources (LURE) Structure of peptides and proteins Macromolecular interaction Structural enzymology and immunology
Centre de Biochimie Structurale, Montpellier	Structure and interaction of proteins Protein crystallisation
Institut de Biologie et Chimie des Protéines, Lyon	Structure-function of proteins and protein chaperons Post-translational modifications structure and engineering of collagen
Strasbourg	Structure of macromolecules involved in gene expression
Marseille	Production of recombinant proteins, purification and structural analysis of lipolytic enzymes
Toulouse	Structure-function of macromolecules, with regards to pharmaceuticals
Bioinformatics support is provided by the CNRS research group on "genomes et informatique" which includes 16 laboratories and involves 50 researchers.	

FUTURE DEVELOPMENTS

The CNRS is presently considering a continuation of IMABIO long term goals, through a new programme at the interface between chemistry and biology.

The CEA has just approved the scientific orientation of PROTEIN 2000 in three directions:
- Structural analysis of proteins and their interactions,
- New developments in the field of labelling of biomolecules using chemical, enzymatic and genetic approaches,
- Structure-function of proteins and design of new biomolecules

IRELAND

IRELAND

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NATIONAL PROGRAMME

There is no programme for protein engineering specifically. The State agency Forbairt administers:
- the National Scientific programme and,
- the Strategic Research programme.

The State also funds many relevant projects through:
- Bio Research Ireland,
- Teagasc (agriculture) and the
- Health Research Board.

POLICY ASPECTS

•The Scientific and Strategic Research programmes were relaunched in 1994. Very few new projects were funded in 1993. The Strategic scheme is targeted at particular sectors with commercial potential and helped set up the Irish National Centre for Bio-Informatics (INCBI) in 1993.

•There is also a Collaborative Research fund for industry/third level joint projects. Forbairt, the State agency for indigenous industrial development, administers these programmes.

•Bio Research Ireland was set up in 1987 to implement the National Biotechnology Programme and is now a division of Forbairt. It engages in commercial research on 5 campuses in specific areas (cell culture, diagnostics, pharmaceuticals, food and veterinary sciences).

•Teagasc is the State body for agricultural R&D.

•The Health Research Board is entirely State funded

•Industrial policy has targeted pharmaceuticals and fine chemicals; R&D grants are made directly to firms making protein products.

•Political responsibility rests with the junior minister for commerce and technology.

FINANCIAL ASPECTS	
The amounts mentioned below do not include salaries or infrastructure costs. These funds cover projects of 2 years' duration. No amount is specifically set aside for protein engineering.	
- Scientific Research Programme (1990-94)	- 0.35 MECU per year (40% of total funding) for biotech./life sciences
- Strategic Research Programme (1990-94)	- 0.12 MECU per year (12.5% of total funding) for biotech./life sciences
- Bio Research Ireland	- 0.25 MECU per year on protein projects
- Teagasc	- 0.39 MECU per year on food protein projects

SCIENCE &TECHNOLOGY ASPECTS	
- Protein crystallography group (T. Higgins)	- University College Galway
- Site-directed mutagenesis (S.G. Mayhew, M. Worral, J.P.G. Malthouse and P.C. Engel) - Serpin structure/function (M. Worrall) - Molecular modelling (G. Grant) - Receptor cloning (F. Martin)	- University College Dublin
- Antibody engineering (R. O'Kennedy) - Protein stability and modification (C. Fagan)	- Dublin City University
- Site-directed mutagenesis of *Staphylococcus aureus* epidermolytic toxin (C. Bailey) - Irish National Center for BioInformatics (INCBI), (A. Lloyd) - Membrane proteins as vaccine antigens - Cloning of fibrinogen binding protein and a metalloprotein (D.C. Williams)	- Trinity College Dublin
- Homology modelling research (D. Sheehan)	University College Cork.

FUTURE DEVELOPMENTS

Academics lobbied successfully for a restoration of science funding following drastic cuts in 1993. The junior minister for commerce and technology has appointed a 19-member committee of scientists, industrialists and public servants to review national policy. Its report is due by 31/12/1994. This will lead to a White Paper (government policy document).

ITALY

ITALY

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NATIONAL PROGRAMME

There is no specific programme in protein engineering but there are two initiatives partly supporting the protein engineering sector:
- Target project "Biotechnology and Bioinstrumentation" - BTBS -, 1988-1992
- Advanced biotechnology, 1989- 1993
- Neurobiology, 1992-1996

POLICY ASPECTS

The protein engineering sector is split into several programmes containing a wide range of areas with basic or applied oriented tasks

FINANCIAL ASPECTS

Target project "Biotechnology and Bioinstrumentation", 1988-1992	5.3 MECU (12 % of the total budget) is dedicated to protein engineering
Advanced biotechnology, 1989- 1993	24.8 MECU (22.5 % of the total budget) is dedicated to areas related to protein engineering
Neurobiology, 1992-1996	A fraction of the total budget (56.4 MECU) is dedicated to protein engineering

SCIENCE &TECHNOLOGY ASPECTS	
The three national programmes developing activities related to protein engineering are:	
Target project "Biotechnology and Bioinstrumentation"	Molecular and cellular engineering project including: - Protein engineering of polyfunctional enzymes, chimeric recombinant proteins - Characterization of enzymes and of the metabolism of organisms living in extreme conditions - Metabolic engineering, with particular emphasis on design of cytotoxic tissue-specific drugs - Research into natural factors having potential pharmacological activity
Advanced biotechnology	Specific projects on: - Innovative enzymes - Enzymes for food industry - Pharmacological peptides
Neurobiology	Some of the research projects are oriented to protein engineering because the programme approach is at molecular level

FUTURE DEVELOPMENTS
No information available.

THE NETHERLANDS

THE NETHERLANDS

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NATIONAL PROGRAMME

The first national protein engineering programme ran from 1986-1992 and was followed by a small interim programme from 1992-1994 to bridge the gap with a new programme which began in the second half of 1994. This is a separate programme which is part of a much larger national Biotechnology programme.

POLICY ASPECTS

An industrial lobby representing all of the major biotechnology companies in The Netherlands has produced an assessment of expected developments through to the year 2000 and the initiatives needed in fundamental research to ensure these developments. Four themes were indicated, one being fundamental research in the structure and function of proteins via protein engineering.
GBB has been selected to coordinate this programme because of Groningen's long tradition in protein structure research and because it was the center of previous protein engineering programmes.

FINANCIAL ASPECTS

4.6 MECU has been allocated to protein engineering research for the period 1994-1998. The funding is allocated for salaries for 25 graduates students and/or post-docs who will be carrying out the protein engineering projects and for consumables for this research. 50% of the funding originates from the Ministry of Economic Affairs and 50% from the universities and institutes already involved in protein engineering research

The Netherlands has invested heavily in all major areas of protein structure research. At the GBB (Groningen) alone, there is a full range of protein structure determination research facilities with each facility being incorporated in an active research group. These facilities include X-ray, electron microscopy, NMR, and molecular dynamics simulations.
Other centers in the country are also equipped with NMR for protein structure determination, including a 750 MHz NMR spectrometer at the Bijvoet Institute in Utrecht. Two other facilities are also being established for X-ray diffraction protein structure determination

SCIENCE &TECHNOLOGY ASPECTS

• Major principal protein engineering investigators:
- Prof. G. Canters, University of Leiden
- Prof. L. Dijkhuizen, GBB
- Prof. B. Dijkstra, GBB
- Prof. D. Janssen, GBB
- Prof. W. Konings, GBB
- Prof. A. de Kok, Agricultural University Wageningen
- Prof. G. Robillard, GBB
- Prof. G. Venema, GBB
- Prof. H. Verheij, University of Utrecht

• The first protein engineering activities were centred at the university of Groningen. Groups from the departments of biochemistry, biophysics, microbiology and genetics covered the whole cycle of protein engineering:
- cloning, sequencing and mutagenesis
- protein over expression, purification and characterization
- structure determination, X-ray diffraction and NMR
- molecular dynamics calculations and predictions

• The main areas were:
- engineering of penicillin binding proteins
- engineering of neutral protease
- engineering of cyclodextrin glycosyl transferase
- engineering of dehalogenase
- engineering of the alkane oxidase system
- engineering of membrane bound transport proteins

FUTURE DEVELOPMENTS

• The new programme will cover the following themes:
- engineering of enzymes of importance as industrial biocatalysts
- engineering of antibiotic proteins for the food and feed sector
- protein folding and export
- protein engineering of medically important transport and receptor proteins
- *de novo* protein design

• In addition to this national programme in preparation, two new activities are initiated in GBB:
- a protein engineering facility for the purpose of doing pre-competitive and contract research. The facility brings in additional scientific and support personnel plus the extra research facilities necessary to complete the entire protein engineering cycle in house
- a program in molecular nanostructure engineering. This project aims to build on the current expertise and develop technologies not yet available to achieve the goals of molecular nanostructure engineering -the making of entirely new macromolecular and supramolecular structures from small building blocks and being able to control their activities or function by electrical or optical signals and corresponding switching devices. Protein engineers, material science engineers and organic chemists are collaborating in this project.

PORTUGAL

PORTUGAL

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NATIONAL PROGRAMME

There is no specific programme for protein engineering. However, the topic is included in the 4-year general Science Programme (PRAXIS XXI) that will begin in 1995, under the title *Applied Biology and Biotechnology*.

POLICY ASPECTS

The aims of this general science programme are:
- to increase Portugese participation and involvement in EC projects;
- to increase the number of young Ph.D students, as well as post-doctoral positions;
- to consolidate the relationships between universities and industry and;
- to allow the insertion of researchers into the field of production.

FINANCIAL ASPECTS

Under the PRAXIS XXI Programme, the area *Applied Biology and Biotechnology* will receive 1.3 MECU per year over a period of 4 years (1994-1999). Approximately 40% of this budget will be devoted to protein science and engineering.

SCIENCE &TECHNOLOGY ASPECTS	
The most relevant research groups and projects are:	
Instituto de Ciências Biomédicas Abel Salazar, Porto - P.M. Ferreira - M.J. Saraiva - C.E. Sunkel - A.M. Damas	- Molecular characterization of proteins of the yeast cell wall - Recombinant proteins from Fasciola hepatica - Molecular studies of transthyretin variants - Molecular studies on protein kinases required during mitosis in higher eucaryotes - Structural and functional studies of mutants transthyretin proteins - 3-D structural studies of some proteins of the yeast cell wall
Faculdade de Ciências, Universidade do Porto, Porto - J.A.N. Ferreira Gomes - M.J. Ramos	- Structural and functional studies of serine proteases - Quantitative studies of enzyme-inhibitor binding interaction - Drug design
Instituto Tecnologia Química e Biológica, Oeiras - A.V. Xavier - M. H. Santos - M.A. Carrondo - M. Carrondo - M. Teixeira	- Novel haem-based catalysts - Biotechnology of extremophyles - Lactic acid biotechnology - X-ray 3-D structures of cytochromes and iron-sulphur proteins
Departamento Bioquimica, Universidade de Coimbra, Coimbra - C.F. Geraldes - E. Pires - R. Brito - C. Faro	- Structure and function of proteases - Structure and function of cell receptors - Studies on proteins surfaces (Lysozyme and Cytochrome *c*) - Studies on protein unfolding
Instituto Superior Técnico, Lisboa - J.S. Cabral - R.A. Barros	- Stability and behaviour of recombinant lipolytic enzymes in organic solvents - Lipases

Faculdade Ciências e Tecnologia, Universidade Nova de Lisboa, 2825 Monte da Caparica - J. J. G. Moura - I. Moura - J. Lampreia - P. Mata	- Dinuclear and polynuclear metal centres in biology - Transition metals in supra-molecular chemistry - Molecular graphics and *Ab initio* calculations on iron-sulphur proteins - Molecular recognition and protein/protein interactions - Development of mimetics on fundamental biological processes - protein sequencing and homology of haem and iron-sulphur proteins - Automatic 3-D generation of molecules of pharmaceutical interest.

FUTURE DEVELOPMENTS

The PRAXIS XXI programme, from which the whole area of biotechnology will receive a major boost, will end in 1999.

UNITED KINGDOM

UNITED KINGDOM

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NATIONAL PROGRAMME/CENTRES

Programmes	
-LINK Protein Engineering Programme	- BBSRC[1], DTI[2], MRC[3]
-Directed Programme in Advanced Biomolecule Design	- BBSRC
Centres	
-Molecular Database (SEQNET) Daresbury Laboratory	- BBSRC & EPSRC[4]
-Oxford Centre for Molecular Sciences Interdisciplinary Research Centre	- BBSRC & MRC
-Cambridge Centre for Protein Engineering Multidisciplinary Research Centre & the Unit for Protein Function and Design	- MRC
-Institute of Virology & Environmental microbiology	- NERC[5]

[1]BBSRC: Biotechnology and Biological Sciences Research Council, [2]DTI: Department of Trade and Industry, [3]MRC: Medical Research Council, [4]EPSRC: Engineering and Physical Sciences Research Council, [5]NERC: Natural Environment Research Council

POLICY ASPECTS

LINK Protein Engineering Programme

This programme is a part of a government wide initiative (LINK) which aims to stimulate more investment by industry in research and development, to develop priority areas of potential benefit to the economy and develop technologies which cross boundaries in industrial sectors and scientific disciplines. The Programme is led by the Office of Science and Technology (OST). Funding is 50:50 public sector:private industries. Research must involve the design, production or application of proteins with novel propoerties, the discovery of protein structure/function relationships or development of enabling technologies.

BBSRC support for Protein Engineering

The recent amalgamation of the Biological Sciences Committee and the Biotechnology Directorate, both of the former Science and Engineering Research Council (SERC) with the Agriculture and Food Research Council (AFRC) offers a great opportunity for a united approach to future Protein Engineering Strategy. The BBSRC is currently reviewing its strategy in Protein Science and bioinformatics as a whole. BBSRC will support both fundamental and strategic protein engineering. Protein engineering is a major theme at three BBSRC Research Institutes: Food Research (Reading), Babraham (Cambridge) and Nitrogen Fixation (Sussex). BBSRC also contributes to a national resource for users of molecular sequence and structure information and software tools to exploit these informatics resources at the Daresbury Laboratory (SEQNET). In addition instrumentation and facilities needed to advance protein engineering are supported. **Contact Person**: Dr. D. Yarrow BBSRC Polaris House North Star Avenue SWINDON SN2 1UH, UK, Tel +44 793 413200 Fax +44 793 413201.

MRC support for Protein Engineering

The MRC supports research across the spectrum of biological and medical sciences at its own establishments and universities. Its policy is to support basic research aimed at probing what can be discovered using the increasing power of protein engineering as well as research aimed at understanding particular molecules, whether involved in basic cellular processes or of potential practical importance to healthcare. Relevant areas supported are: high field NMR, protein crystallography, electron diffraction and molecular modelling for more effective design of drugs and vaccines. Relevant Centres are the MRC Centre for protein engineering (Directors A. Fersht and G. Winter) and The Cambridge University Protein Function and Design Unit (Hon. director A. Fersht). **Contact Person**: Dr. C. Moody, Research Management Group MRC 20 Park Crescent London W1N 4Al UK, Tel +44 716365422, Fax +44 714366179.

NERC support for protein Engineering

The NERC supports basic strategic and applied research in the physical and biological aspects of the environment. This is aimed at understanding the processes within the natural environment which allow the substancial exploitation of natural resources. The NERC utilises the molecular biology experience of its Institute for Virology and Environmental Microbiology at Oxford for research on baculovirus expression vectors to produce proteins for diagnostics and candidate vaccines. This is basic and strategic research in support of the agrochemical, veterinary and healthcare industries. **Contact Person**: Dr. M. G. Schultz, NERC, Polaris House, Swindon SN2 1EU, UK, Tel +44 793411800, Fax +44 793411502.

FINANCIAL ASPECTS	
The average Protein Engineering Programme and Centre expenditure per annum is 12 MECU (Period 1989-1994).	
Link Protein Engineering Programme	15.6 MECU (1989-1996) 18 projects
BBSRC Funding Oxford Centre for Molecular Sciences (IRC) Institute Research Standard Research Grants Directed Research Grants	 3.0 MECU per annum 2.5 MECU per annum 2.5 MECU per annum 0.9 MECU per annum
MRC Funding Cambridge centre for Protein Engineering	 3.0 MECU per annum
NERC funding Institute of virology	 0.34 MECU (incl. CEC & private sector funds)

SCIENCE &TECHNOLOGY ASPECTS	
Principal Investigator	**Link Programme Projects:**
- Lowe/Sussex	-ENDOR of Mn^{2+} ions in plants
- Rees/Bath	-Computer aided design and production of antibodies
- Henderson/Cambridge	-Overexpression and structure determination of membrane proteins
- Findlay/Leeds	-Mechanism of G-protein linked receptors
- Campbell, Baldwin, Johnson/Oxford	-750MHz NMR; structures of oxygenases, SH2/3 domains, protein phosphatases and kinases
- Fersht/cambridge	-Protein structure and design
- Jackson/Nottingham	-Development of STM for biomolecules
- Thornton/UCL (London)	-Conformationally restricted peptide design (based on predicted folds)
- Taussig/Babraham	-Design of anti-steroid antibodies
- Goodenough/Reading	-"Minimalisation" of an enzyme of commercial significance; Modifying the specificity of phospholipase A2
- Thornaly/Sussex	-Structure and mechanism of chorismate synthase
- North, Finlay/Leeds	-Further development of a protein database resource
- Sayers/Scheffield	-Bacterial display of rec-protein using endigenous export system
- Begent/London	-Understanding the immunogenicity of engineered antibodies
- Hubbard/York	-New molecular modelling interfaces (including virtual reality)

FUTURE DEVELOPMENTS

LINK Programmes

The Programme will end on or before 1996 and is 80% allocated. There is felt to be a need for a comparable programme to continue. Successor programmes are under discussion. One possibility is "Advanced biomolecular design", which would consider the engineering of other biopolymers (such as polysaccharides). **Contact Person:** Dr. M.J. Geisow (address above)

BBSRC

Genome research and advanced biophysical methods have provided the basis for rapid advances in understanding of biological function at the molecular level. This knowledge can now be exploited through the "rational" design of biomolecules. A greater understanding of biomolecules will provide many opportunities for industrial exploitation by the BBSRC user community in areas such as enzymes for industrial use, novel drug and pesticide design, the production of novel materials and the enhancement of food quality. Research in protein science supported by the BBSRC will include: folding modelling and design, molecular recognition and signalling, enzymes and catalysis, structural and storage proteins and production and degradation.

MRC

Genetic research is revolutionising studies in human biology, by leading directly to an increased understanding of disease and opening new routes to diagnosis and treatment across a wide range of conditions. As more sequence data becomes available (for example from the MRC Human Genome Mapping Project) it will be possible to extend the range of structure prediction and compare models with the experimental results of structures within the same protein family. Studies of molecular structure and function, including work on structure prediction, are central to industrial programmes to identify novel targets and develop more selective agents through the rational design of new ligands for key cellular proteins MRC will continue to provide training in protein engineering through state-of-the-art centres in order to meet the needs of both academic and industrial research.

NERC

NERC Protein Engineering using baculovirus expression vector systems offers new opportunities in the development of viral insecticides and vaccines; the study of viral morphogenesis; new diagnostics and more general studies of protein structure - function relationships. These activities will received continued support through the Institute of Virology.

AUSTRIA

AUSTRIA

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NATIONAL PROGRAMME

- There is no specific programme, but related projects are financed by the Austrian Science Foundation (FWF - Fonds zur Förderung der Wissenschaftlichen Forschung-)
- At the moment the FWF is evaluating two applications for the getting-up of special research programmes on "Computational structural biology" and "Determination of 3-dimensional structure to atomic resolution of biomolecules"

POLICY ASPECTS

In 1991, the FWF, in cooperation with the Austrian conference of university presidents and the Federal Ministry of Science and Research, laid the foundation for special areas of research similar to the special research programmes in Germany ("Spezialforschungbereiche"), thus clearly setting the stage for research priorities in Austria.
This funding initiative has been intended to promote interdisciplinary long-term fundamental research (via bottom-up principle) by assembling scientists from designated disciplines at selected university centres and providing them with the necessary research apparatus thus improving the international competitivity. After a most rigorous international review process, the FWF board of trustees can approve such a special research programme

FINANCIAL ASPECTS

Approximately 2 MECU are allocated for the current projects related to protein engineering.
The amount of future targeted national funding will depend on the decision of the FWF after the evaluation of the proposed special research programmes on "Computational structural biology" and "Determination of 3-dimensional structure to atomic resolution of biomolecules".

SCIENCE &TECHNOLOGY ASPECTS	
The 2 proposed special research programmes are:	
Computational structural biology University of Vienna, 5 institutes - A. Beyer - D. Blaas - G. Buchbauer - G. Köhler - P. Wolschann - M. Neumann - P. Schuster - P. Stadler - O. Steinhauser	- Sequence structure relationships (Inverse folding of biopolymers, application of statistically derived potentials to protein folding problems) - Simulation methods (Efficient algorithms for handling electrostatic interactions in biomolecules, biomolecular hydration, continuum models and atomistics simulations, molecular dynamics, simulation of protein unfolding) - Applications (Kinetic and dynamic properties of host-guest systems, influence of ligand binding on the structure and dynamics of HIV-protease, surface accessability, energetics and conformation of peptides complexed to virus-neutralizing antibodies) - Data analysis (Molecular similarity and molecular surfaces)
Determination of 3-dimensional structure to atomic resolution of biomolecules 3 universities: - Salzburg (M. Sippl) - Graz (C. Kratky, U. Wagner) - Innsbruck (B. Kräutler, R. Konrat)	-Experimental determination of protein structures and other biological macromolecules -Development and application of knowledge based energy functions for protein modelling, fold recognition, prediction and simulation -Combination of experimental and computational methods in determination and engineering of structures of biological macromolecules
University of Agriculture Vienna, Institute of applied microbiology (F. Rüker) - X-ray crystallographic structure determination, computer aided molecular modeling, and engineering of antibody-antigen complexes	

FUTURE DEVELOPMENTS

Future national funding will depend on the evaluation of the 2 proposed special research programmes and the decision from the Austrian Science Foundation (FWF), (decision at the beginning of 1995)

FINLAND

FINLAND

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NATIONAL PROGRAMME

•TEKES (Technology Development Center of Finland) funded 2 national research programmes involving aspects of protein engineering: Gene Technology in 1984-1987, and Biotechnology in 1988-92

•VTT (Technical research Center of Finland) funded an internal research programme of computer-aided molecular modelling in 1991-93

•VTT carried out also part of the Protein Engineering Programme of the Nordic Industrial Foundation in 1989-93

• The work initiated in the TEKES Biotechnology programme continues in closer industrial collaboration at both VTT and the University of Turku

POLICY ASPECTS

•Site-directed mutagenesis and the construction of fusion proteins are used as basic research tools in many academic institutes, research laboratories and R&TD laboratories in Finland. Protein engineering aiming to improve protein properties of immediate practical value is carried out at the VTT Biotechnology and Food Research Institute and at the Center for Biotechnology of the University of Turku which operate in close collaboration.

•Supporting technologies include protein structure determination by X-ray crystallography (Universities of Turku and Joensuu) and multidimensional NMR (VTT Chemical Engineering and Institute of Biotechnology, University of Helsinki). VTT has a large molecular modelling group focussed on macromolecular modelling.

•Two bulk enzyme producers, Genencor International Inc. and ALKO Ab, have significant interest in improving enzymes of industrial value. In addition, the diagnostic and pharmaceutical companies in Finland are actively engaged in protein engineering research aiming at improved diagnostic antibodies or drug design. These include eg. the Orion Corporation, Wallac Inc., Labsystems Inc. and Medix Biochemica.

FINANCIAL ASPECTS

The amounts mentioned below include only grants for PhD students, post-docs, etc, and consumables (no equipment) and are estimations:

- Biotechnology, TEKES, 1988-92: 1 MECU for protein engineering
- Molecular Modelling, VTT, 1991-1993: 0.5 MECU for protein engineering
- Nordic Industrial Foundation, 1989-1993: 0.2 MECU (Finland)

Individual research projects have received approximately 0.5 MECU /year from different governments bodies and industrial partners

SCIENCE &TECHNOLOGY ASPECTS

The major facilities and projects concerned with protein engineering are listed below:

VTT Biotechnology and Food Research, Espoo
Projects on: cellulolytic enzymes, recombinant diagnostic and catalytic antibodies, ion channel receptors
Relevant major equipment: two Silicon Graphics work stations (4D/35, Personal Iris), two IBM RISC6000 work stations (6000-32H, 6000-340)
Local contact: Dr. Tuula Teeri
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VTT Chemical Engineering, Espoo
Relevant major equipment: A Varian Unity 600 MHz spectrometer equipped with two channels, two Silicon Graphics workstations (Indigo, Indigo 2)
Local contact: Prof. Tor-Björn Drakenberg, tel. +35804565234, fax. +3580460041

University of Turku
Projects on: diagnostic antibodies, a-adrenergic receptors, inorganic pyrophophatases)
Relevant major equipment: A RAXIS-IIC area detector mounted on a Rigaku RU-200 x-ray generator with cryogenic cooling system for "flash-freezing", a small VAXcluster (DEC 3000AXP model 500, 2 VAX station 4000/60s, VAX station4000VLC), modelling work stations (Evans&Sutherland PS390, and ESV model30, Silicon Graphics Crimson with Elan Graphics)
Local contact: Prof. Markku Jalkanen, tel. +358216338601, fax. +358216338000

University of Helsinki, Institute of Biotechnology
Relevant major equipment: Varian Unity 500 MHz spectrometer equipped with two channels, two Sun Sparcstation 2s, a silicon Graphics workstation (Indigo)
Local contact: Dr. Ilkka Kilpeläinen
tel. +35804346089, fax. +35804346028, e-mail: Ikilpela@introni.helsinki.fi

University of Joensuu

Projects on: Carbohydrate degrading enzymes.
Relevant major equipment: X-ray diffractometer equipped with R-AXIS IIC area detector and RU200HB rotating anode. Several computers/workstations including EVand&Sutherland ESV3 and three Silicon Graphics Indigos
Local contact: Dr. Juha Rouvinen, tel. +358731513318, fax. +358731513390

FUTURE DEVELOPMENTS

•Presently protein engineering research is not gathered under a national framework programme, but is integrated into different basic and applied projects many of which are carried out as a joint effort of several academic and industrial laboratories. These projects are primarily funded by TEKES, the Academy of Finland, and major industrial partners.
Currently, major concerted projects involving protein engineering are in preparation under the framework of the "Graduate School" programme of the Academy of Finland (1994-1998). Upon the call for proposals of this programme (deadline August 15, 1994), at least three large proposals focussed of protein structure, funciton and engineering and applied biotechnology will be submitted.

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ICELAND

ICELAND

CONTACT PERSON

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NATIONAL PROGRAMME

•There is no current specific National protein engineering research programm in Iceland. However, such activities have been funded within:
- the basic science and biotechnology sectors of The Icelandic Council of Science,
- the National Research Council of Iceland and,
- the University of Iceland Research Foundation.

(The Icelandic Council of Science and the National Research Council of Iceland have now been merged. The new council is the Research Council of Iceland)

•Furthermore, Protein Engineering in Iceland was funded by the Nordic Industrial Fund, Umbrella Research Programmes during the period of 1990-1993

POLICY ASPECTS

Three institutes in Iceland are involved in protein engineering activities. These are:

•The Science Institute, University of Iceland,

•The Institute of Molecular Biology, Biology Institute, University of Iceland in collaboration with the Technical Institute of Iceland and,

•The Institute for Experimental Pathology, University of Iceland, Keldur

FINANCIAL ASPECTS

The funding for the 3 above institutes is approximately 0.88 MECU for 3 years (1990-1993). This includes the salaries of research associates but does not include infrastructure costs.

SCIENCE &TECHNOLOGY ASPECTS	
Three institutes are involved in protein engineering:	
Science Institute, University of Iceland, Dunhaga 3,IS-107 Reykjavik, Iceland Fax: 354-1-28911 - J.B. Bjarnason - A. Gudmundsdottir	-Molecular mechanisms underlying the psychrophilicity (cold-adaptation) of serine proteases from Atlantic cod
Laboratory of Molecular Biology, Institute of Biology, University of Iceland, Grensasvegur 12, IS-108 Reykjavik, Iceland Fax: 354-1-694069 - A. Palsdottir - S. Thorbjarnardottir	-Thermostable polysaccharide degrading enzymes from thermophiles -Thermostable DNA polymerases from thermophiles -Thermostable DNA ligases form thermophiles.
Institute for experimental Pathology, University of Iceland , Keldur v/Vesturlandsveg, IS-112 Reykjavik, Iceland Fax: 354-1-673979 - B. Magnadottir - B. Gudmundsdottir - E. Gunnarsson, - O. Andresson - V. Andresdottir, - V. Steinþorsdottir	-Clostridial beta-toxin for diagnostic and vaccines. -Molecular mechanisms underlying the virulence and antigenicity of an extracellular metallo-protease produced by a group of atypical strains of the bacterium *Aeromonas salmonicida* infecting various fish species. -Molecular clones of visna virus for diagnostic and vaccines.

FUTURE DEVELOPMENTS

A major reorganization of the Icelandic research councils is presently under way. The Icelandic Council of Science and the National Research Council have been merged and a new council formed named The Research Council of Iceland. Information regarding policy aspects of biotechnology and protein engineering programmes within the new Research Council of Iceland will be available by the end of 1994.

NORWAY

NORWAY

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NATIONAL PROGRAMME

There is none, but protein engineering is covered through biotechnology funding schemes directed by the Research Council.

POLICY ASPECTS

No national policy has yet been formulated, but a clear emphasis has been put by the Research Council on genetic engineering and, more recently, protein structure-function relationships.

FINANCIAL ASPECTS

Approximately 4 MECU have been allocated to protein engineering related activities since 1990. This sum also includes salaries for stipends and its has not been possible to separate the different cost contributions in the present analysis.

SCIENCE &TECHNOLOGY ASPECTS

All technological aspects of the protein engineering science are represented in Norway (18 projects were reported in 10 laboratories):

- X-ray	- Tromsø
- Genetic Engineering	- Tromsø, Trondheim, Bergen, Oslo
- Molecular Modelling	- Trondheim, Tromsø, Oslo, Bergen
- NMR	- Trondheim, Oslo, Bergen
- Sequence Analysis	- Trondheim
- Electrostatics	- Trondheim
Several groups are active:	
- Smalås/Hough, Univ. of Tromsø	- X-Ray
- Prydz, Biotechnology Center of Oslo	- TF/FACT VIII
- Krokan/Valla, Univ. of Trondheim	- U-DNA-Glyc./PGM
- Martinez/Flatmark, Univ. of Bergen	- Tyrosine Hydroxylase
- Helland, Univ. of Bergen	- HIV reverse transcriptase
- Skjeldal, Univ. of Ås	- Structure-function
- Petersen/Drabløs, SINTEF UNIMED, Trondheim	- Electrostatics, sequence analysis, NMR
- Smidsrød, Univ. of Trondheim	- Carbohydrate active enzymes
- Lindqvist, Univ. of Oslo	- Phage display

FUTURE DEVELOPMENTS

The Norwegian Research Councils have recently been reorganized and new strategies and policies are expected to be formulated in the near future.

SWEDEN

SWEDEN

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NATIONAL PROGRAMME

There is one programme funded by the Swedish National Board for Industrial and Technical Development (NUTEK). In addition projects in the area receive support from several research councils. A few companies are actively engaged in protein engineering research.

POLICY ASPECTS

Protein engineering is considered to be an area of high priority. Some projects are mainly problem oriented while in others the problem oriented research is combined with technology development. In the NUTEK programme an active involvement of companies is desired.

FINANCIAL ASPECTS

The annual public funding (excluding permanent positions and infrastructure costs) during the period 1992-1994 is about 2.5 MECU. In addition companies like Pharmacia, Symbicom and KaroBio are active in the field. Private funds are available for heavy equipment.

SCIENCE &TECHNOLOGY ASPECTS

The research covers all aspects of research related to protein engineering such as:
- cloning, sequencing and mutagenesis
- expression systems and purification methods
- X-ray diffraction and NMR spectroscopy
- molecular modelling and soft-ware development

The most important centers are:
- The Biomedical Center of Uppsala
(Prof. H. Eklund and A. Jones)
- The Royal Institute of Technology in Stockholm
(Prof. M. Uhlen)
- The University of Lund
(Prof. S. Forsen and A. Liljas)
- The Center for Structural Biochemistry at NOVUM Karolinska Institute
(Prof. T. Härd and R. Ladenstein)
- Pharmacia Bioscience Center
(Prof. B. Nilsson)

Among the current research areas, we can mention the engineering of $Ca2+$ binding proteins, IgG-binding proteins, lipases, cellulases, RUBISCO, antibodies, peptide hormones and hormone receptors. The folding of several proteins is studied as well as the orientation of membrane proteins.

FUTURE DEVELOPMENTS

In the near future the area will most probably be strengthened by funding from the new "Fund for strategic research".

EMBL
(European Molecular Biology Laboratory)

EUROPEAN MOLECULAR BIOLOGY LABORATORY

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PROGRAMME

A European network of laboratories:
All four EMBL laboratories are involved in aspects of protein engineering. The main laboratory in Heidelberg (DE) has several research groups in protein design, folding and engineering. The Hamburg (DE) and Grenoble (FR) Oustations specialize in the use of synchroton radiation for the solution of high resolution crystal structural and macromolecular complexes. The Cambridge (GB) Oustation is a European center of protein databases and will have research activities in computational protein design. Research groups at each laboratory are multinational and aim to spread expertise to European member countries through intensive training and carrier development of predocs, postdocs and relatively junior group leaders that may embark on careers in their national institutions after several years at an EMBL laboratory.

POLICY ASPECTS

- Access to larger scale facilities

One of the aims of EMBL is the provision of access to European large facilities. In the area of protein engineering, visitors' and fellowship programmes are in place to provide access to beam lines at the two synchroton facilities used primarily for protein X-ray crystallography, the older Hamburg installation at DESY and the modern ESRF in Grenoble. In addition, EMBL will provide general access to structure refinement computer calculations on a multiprocessor machine in Heidelberg.

- Integration of structure determination and genetic engineering

Increasingly, single research groups integrate techniques such as X-ray crystallography and molecular genetics in support of protein engineering. This stems in part from technological developments easing the adoption of new techniques and in part from the wish to closely supervise all aspects of the protein engineering cycle under single leadership.

FINANCIAL ASPECTS

• Support from EMBL member countries

Total expenditure of the EMBL laboratories in protein engineering is estimated to be about 0.8-0.9 MECU per year (not including group leader salaries). The precise amount is not known as the relevant research groups are also active to varying degrees in related disciplines, e.g., structure determination or mass spectrometry analysis of naturally occurring proteins.

• External funding

EMBL funding in protein engineering has been supplemented by grants from the European Commission under the BRIDGE and BIOTECH programmes, as well as from the German DFT and BMFT, and from specific collaborative arrangements with individual pharmaceutical companies. External support has amounted to approximately 0.4 MECU per year. EMBL scientists have on several occasions acted as coordinators of collaborating European research networks funded by the European Commission.

• Access to large scale facilities

Recently, access to synchroton and high performance computing facilities has been supported by grants under the Human Capital and Mobility Access to Large Scale Installations programme of the European Commission.

SCIENCE &TECHNOLOGY ASPECTS

Particular projects are chosen independently by the individual research groups. Intergroup collaborative projects combining complementary expertise are common.

• Groups involved in aspects of protein engineering:

Tom Creighton (US,) Stephen Cusak (GB), Werner Kühlbranst (DE) Matthias Mann (DE), Hartmut Oschkinat (DE) Chris Sander (DE), Matti Saraste (FI), Luis Serrano (ES) Dietrich Suck (DE), Rebecca Wade (GB), Rik Wierenga (NL), Keith Wilson (GB)

• Current protein engineering research areas:

- redesign to elucidate the structural basis of function
- redesign to understand the basic principles of protein folding
- design and grafting of active sites
- design of ligands for therapeutic use
- *de novo* design to develop constructive principles of protein design

• Advanced instrumentation used in protein engineering:

- X-ray crystallography, synchotron beam lines, 2-D detectors
- Computing: multi-processor computers, computer graphics
- NMR spectroscopy: 500 and 600 MHz spectrometers
- Electron microscopy: two 200 kV instruments
- Mass spectrometry: Electrospray triple quadrupole (ES MS/MS) and matrix assisted laser desorption/ionization MS with reflector time of flight analyzer

• Proteins in engineering projects:

These include: chemotactic protein cheY, triose phosphate isomerase, lipase, subtilisin-type protease, actin, DNAse, S1 end P1 nuclease, plant light harvesting complex LHC II, interleukin-4, trypsin inhibitor BPTI, alpha-lactalbumin, cytochrome oxidase, SH3 domains, rop, cytochrome P450, and serine tRNA synthetase.

FUTURE DEVELOPMENTS

• Protein structure research at EMBL Grenoble

As a provider of access to high intensity X-ray beams for protein structure research at the ESRF, the Grenoble Outstation of EMBL will in the future take on increasing importance in structural biology research. Accordingly, the EMBL has committed significant financial resources to an expansion of the Grenoble Outstation in 1994/95.

• Macromolecular Structure Database

The new Cambridge Outstation of EMBL, the European Bioinformatics Institute, will in 1995 begin building up the European component of the new Macromolecular Structure Database (MSD) that with its US partners will continue and extend the work of the Protein Data Bank. This database of protein and nucleic acid three-dimensional structures will be an important resource for protein engineering. Usefulness of the database will be increased through links to sequence and enzyme function databases and through the development of network information services related to protein structure and function.

• New techniques and new applications

-Engineering membrane proteins: As techniques of structure determination improve, protein engineering at the EMBL is likely to expand into the reengineering of membrane proteins in the near future.

-Emerging physical techniques: EMBL groups are making increasing use of mass spectrometry for protein engineering applications and are currently investigating the use of atomic force microscopy.

-Structure-based design of molecular evolution experiments: In the next few years a major new contribution to protein engineering is likely to come from combining insight into D protein structures with the power of molecular diversity. In this emerging approach, proteins with novel function are developed in selection experiments in which the protein's genetic information is varied (randomized) at well-defined positions, followed by cell growth under stringently selective conditions. Groups at EMBL are currently involved in planning projects in the new area of designed molecular evolution.

EUROPEAN COMMISSION

EUROPEAN COMMISSION

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PROGRAMMES

The ongoing BRIDGE (1990-1993) and BIOTECH (1992-1994) biotechnology programmes cover the protein engineering sector. The next biotechnology programme in the 4th Framework Programme (1994-1998) will include Stuctural Biology.

POLICY ASPECTS

.To strengthen the scientific and technological bases of Community industry and encouraging it to become more competitive at international level (article 130f of the treaty on European Union)

.To coordinate the Community and the Member States research and technological development activities so as to ensure that national policies and Community policy are mutually consistent (article 130h of the treaty on European Union)

.There are 2 types of protein engineering research projects:

- basic research projects (or N projects) which are carried out for the integration of research efforts for tasks where the main bottlenecks result from gaps in basic knowledge
- generic research projects (or T projects) which benefit from the combined contributions of different disciplines and techniques through efforts intended to remove important bottlenecks resulting from structural and scale constraints

FINANCIAL ASPECTS

The EC contribution for the protein engineering sector in the BRIDGE (1990-1993) and BIOTECH (1992-1994) programmes (not taking into account the BIOTECH 3rd call for proposals yet) is approximately 32 MECU*, corresponding to:

36 projects including 180 laboratories

BRIDGE (3-year projects)	3.28 MECU (4 N-projects, 21 labs.) 4.34 MECU (5 T-project, 23 labs.)
BIOTECH (2 or 3-year projects)	17.39 MECU (20 basic projects, 107 labs.) 4.92 MECU (7 generic projects, 44 labs.)
*Including the contribution for projects on information infrastructures (protein sequence database, etc...): - 2 N-projects in BRIDGE (1.17 MECU, 7 labs.) - 1 project in BIOTECH (1.2 MECU, 6 labs.)	

SCIENCE &TECHNOLOGY ASPECTS

The following protein engineering topics are covered in the BRIDGE and BIOTECH programmes:

BRIDGE	- Protein sequence databank, 1project / 1 lab. - Integrated Europ. prot. struct. database, 1 project / 6 labs. - Peptide lantibiotics, 1 project / 4 labs. - Enzyme catalysis, protein stability and folding, 1 project / 4 labs. - Triosephosphate isomerases, 1 project / 6 labs. - Alpha-helical bundle proteins, 1 project, 7 labs. - Lipases 3-D structure and catalytic mechanism, 5 projects / 23 lab.
BIOTECH	- Validation of results of 3-D structural studies, 1 project / 6 labs. - Enzymes associated with membranes, 6 projects / 32 labs. - Antibodies-antigens interactions, 3 projects / 15 labs. - Receptors, 6 projects / 30 labs. - Metalloproteins, 3 projects / 18 labs. - Protein engineering of lipases, (4 projects / 26 labs.) - Carbohydrate active enzymes (5 projects / 30 labs.)

FUTURE DEVELOPMENTS

Protein engineering activities are included, in particular, in the area 6 ("Structural Biology"), which is one of the 8 scientific areas of the Biotechnology programme of the 4th Framework Programme (1994-1998).
Projects proposals will be invited in the area of Structural Biology which is described in the Workprogramme as followed (the complete information package is available on request from the Commission services):

Area 6 - Structural Biology

6.1 Structure-function relationships

Objectives

The primary scientific and technological objective is the understanding of how the function of biological macromolecules is related to their structure and spatial organisation, and the design of improved biomolecules with the desired properties. Towards this long-term objective, the approach followed in this area will focus on technological means irrespective of the types of molecules or subjects those means will be applicable to.

Flexibility on subjects: a reasonable flexibility will be applied to the choice of biological macromolecules for these investigations, and to the subjects under study. They could, for example, cover protein folding, biocatalysis, membrane proteins, nucleic acids, carbohydrates, RNA, etc. This flexibility aims at mobilizing the scientific community of structural biologists , inviting the most promising and innovative research, and being capable of responding rapidly to the evolution of concepts.

Technological requirements: The following constraints aim at enforcing synergies between different novel aspects of research in structural biology. The invited contributions should be multidisciplinary and systematically combine the three following facets of structural biology:
- experimental determination of three-dimensional structures,
- improvement of structure determination techniques and,
- development of biochemical entities with the desired functions.

Research tasks

In view of the flexibility on subjects, and the requirements for technological inputs presented above, the proposals could address a wide spectrum of targets, provided they would address all three following topics to variable degrees (although one topic should become prominent in each proposal):

6.1.1 Three-dimensional structure determination

As the life sciences experts wished to stress, the systematic experimental determination of many more three-dimensional structures of biological macromolecules and complexes of macromolecules (such as proteins, DNA, RNA, carbohydrates or lipids) will form the basis of our developing knowledge of the relationships between primary structures and the tertiary structures of biologically active macromolecules and, even more so, the quaternary structures of the multi-subunit complexes which mediate most biological activities. The complementary need to store, retrieve and analyze the rapidly accumulating biomolecule structural information is taken into account in Area 8 (Infrastructures).

6.1.2 Improvement of techniques

The improvement of techniques, such as X-ray diffraction, NMR, mass spectrometry, etc, for experimental 3-D structure determination of biological macromolecules and the growing size of structures that they can assess will allow, for example, better resolution, and work on subcellular structures, with further implications for an understanding of biological functions within the cell. Synergies and complementarities between the different techniques are invited in the proposals. Of particular importance for the improvement of techniques is synchrotron radiation for macromolecular crystallographers which allows more accurate data to be obtained. Because synchrotron radiation facilities are particularly suited to serve multinational interests through collaborative projects, proposals including the cost of operating such facilities would be welcome, particularly when this leads to novel and challenging experiments (e.g. very small crystals and rapid data collection).

6.1.3 Biomolecules with the desired functions

The discovery and refinement of new biochemical entities with desired functions will consider both terms of the following alternatives :
-rational design, including *de novo* design, of biomolecules with specific structural,chemical or catalytic properties, which requires a detailed understanding of and control over biomolecular conformation and reactivity.
-*in vitro* selection technologies of natural or *de novo* designed structures by their binding or catalytic activities, consisting in a large, heterogeneous pool of biomolecules subjected to multiple rounds of selection and mutation. This includes, for example, display of proteins on the surface of filamentous phage, or *in vitro* directed molecular evolution to select RNAs with catalytic or affinity properties.

6.2 Interface of structural biology with electronics

Objectives

The emerging interface of biology and electronics will be explored with a view to allow the interplay of competencies in structural biology and micro- and nano-scale engineering towards new possibilities of designing functional units which could incorporate modifications at the scale of the nanometre. In this domain, the invited contributions should in priority reduce the huge gaps which still exist between groups which deal with:
- micro or nano device fabrication in materials and,
- biological systems where structural biology is of key importance.

Research tasks

The systematic combination of groups of material engineers which deal with micro or nano device fabrication, and groups of "bioengineers" which deal with biological molecules is requested in the invited contributions for this research task. Priority will be given to the study of the interface of man-made structures and biological molecules, including the following scientific and technological topics:

6.2.1 Signal transduction

The signal transduction, in particular, electrical and optical signals, between biomolecular functional units and man-made substrate structures, including, for example, direct electron transfer between metals and redox enzymes.

6.2.2 Improvement of experimental tools

The improvement of non-destructive techniques with high spatial and time resolution which, for example, characterise bio-active interfaces (structure, function, stability) and, the design of miniaturized transducers for devices based on biological function.

6.2.3 Research on new applications

The molecular nanostructure engineering, combining nanotechnology and biosystems, will be explored in order to lead to new generations of applications. Here, the task is not to develop a specific application or product but rather to acquire the basic understanding necessary to detect and highlight new opportunities for applications which can emerge from the following symbiosis between biosystems and nanotechnology:
-biological molecules present properties (for example, the tendency to self-assemble into highly organized two- and three-dimensional structures) which are highly attractive in today's drive for new engineering materials and,
-nanotechnology offers new tools to study biological molecules, to perform micro-scale biochemistry, to manipulate cell components and to render macromolecular structures able to controlling their activities or function (for example, in the field of biosensors).

ANALYSIS OF PROTEIN ENGINEERING R&D PROGRAMMES IN EUROPE

Analysis of European Protein Engineering R&D Programmes

Abstract

The European Commission has asked nationally appointed experts in the area of Protein Engineering (PE), from 16 European countries that are fullparticipants in the European research programmes, to analyse the current organisational status of PE in Europe. The Commission has specifically stated that it wants to describe those organisational and technological aspects of the various research programmes involving PE. The present consensus document is, to a large part, based upon cautious analysis of data that has been provided by the individual experts. The nature of the present task requires that common trends rather than individual exceptions are highlighted, except when the nature of such exceptions may contain an important message for the report as a whole.

- The organisation of Protein Engineering

Only a minor proportion of European countries have dedicated protein engineering programmes (Denmark, France, The Netherlands, Sweden and United Kingdom). Two countries (Germany and Japan) and the European Commission have programmes which, in effect, include applied protein engineering or underpinning technologies (i.e. projects in BAP, BRIDGE and BIOTECH). Belgium, Finland and Spain have national programmes, which include protein engineering. Six countries (Denmark, France, Germany, the Netherlands, Norway and United Kingdom) have allocated funding for specific topics in protein engineering to selected centres. Finally the European Molecular Biology Laboratory and its outstations have received funding that has allowed some scientific groups to pursue protein engineering research. From 1989-1993 the Nordic Industrial Foundation (Denmark, Finland, Iceland, Norway and Sweden) carried out a specific programme for Protein Engineering. This information is summarized in Table 1.

- Policy aspects

PE is clearly being worked on in all the countries surveyed, whether or not a specific national programme or centres for PE can be identified. The setting up of special initiatives or centres of excellence (in those countries which have them) probably resulted from policy-makers recognising the strategic relevance of PE as well as the medium- to long-term importance of modified proteins in the biotechnology and pharmaceutical markets. Industries have been very influential in those countries that do have national programmes and centres for PE.

- Financial aspects

In each of the 16 countries, substantial funding has been made available for PE activities, both for capital equipment, infrastructure costs and research programme grants. The funding schemes are all of finite length, in many cases consisting of 5-year programmes. Some of these are actually ending or will end within 1-2 years.

Due to seemingly very different methods of accounting for PE funds, an accurate comparison of national and international financial committments is very difficult to obtain. The total national annual spending has been estimated by the national representatives. When the numbers are analysed per head of national population, a baseline figure of 0.2-0.3 ECU

per capita appears as a plausible average figure, in particular in the countries that have recognised national PE programmes. The level of funding broadly reflects the size of the economies as one would expect. However, in countries where funding is very low, this may also reflect a lack of government awareness of the strategic importance of PE. Further support for this view comes from our observation that the development of national programmes correlates with countries that already have a substantial established biotechnological or pharmaceutical industry.
As is evident from the BRIDGE and BIOTECHNOLOGY programmes, countries with no national programmes or centres relay heavily on their European partners for access to resources unavailable or in short supply in their own countries. Such a lack of local provision of resources seriously inhibits progress.

- Complex funding routing

There is evidence of a wide variation of coordination of PE activities within countries, without even considering the question of transnational coordination. This variation seems to arise from factors related to the different sources of funding: governmental (Federal vs. State difference); sectoral (public sector bodies, research councils, charities) and traditional (trade, chemistry, biology, medicine, food and agriculture). In essence, the links and communications between these different communities have always been relatively weak. This makes the coordination of a multidisciplinary, cross-sectoral field of endeavour like PE quite difficult in some countries. It also makes it unnecessarily difficult for the individual researcher to obtain grants, since PE does not have any obvious single association with a particular granting body - thus applications are often deferred to other bodies.

- The industrial interest and activities in PE

Many industries do not have in-house protein structure determination or macromolecular modelling facilities whereas national PE programmes and centres all have a strong emphasis on instrumental and computational methods as well as integrating the necessary molecular biology, protein purification and production. Many small and medium sized industries (SMEs) rely upon publications by or collaborations with universities or research institutes. The largest biotechnological and pharmaceutical industries have indeed set up most or all such facilities in-house. Shortage of time has prevented a thorough review of the industrial contribution to PE in Europe - this will be addressed in the next report to be published by the European Communities.

- Science and technology towards future developments

The methodologies involved in Protein Engineering are viewed as a group of enabling technologies for the future of European Biotechnological and Pharmaceutical sciences. Thus, the panel recommends that further strengthening and consolidation of the European part of these methodologies is secured through the EC as well as national funding. The necessary research is of a fundamental nature, and there is a clear need for long term programmes funding such research.
Protein Engineering is essentially a complex science that encompasses several recent technological achievements. Our understanding of structure-function relationships of proteins is not advanced enough to enable us to rationally design proteins with the function required.

In order to increase this understanding, the panel favours an overall approach, widely open to a large spectrum of methodologies, biomolecules, types of interaction, etc, from which a variety of inputs could be obtained.
Future achievements will depend on a concerted development of the component technologies of protein engineering. In this context, it should be stressed that the importance of the individual technologies may change since new technologies are constantly emerging. Particular attention should be given to the emergence of the growing alternative to rational design, consisting of selection technologies, such as protein phage display or *in vitro* directed molecular evolution which mimics Darwinian evolution at the molecular level. The complementarity and synergy between rational design and these selection technologies are stressed.
The area of protein engineering should therefore be monitored continuously by the European Commission. In order to facilitate a continuous monitoring, the panel suggests that a European Organisation of Protein Engineering Centres (EPEC) should be established, with support from the Commission.

The Group identified several technologies that should be considered. Below is a non-prioritized list:

- *Mass spectrometry should be recognized as an emerging technology for Protein Engineering*

- *Technologies for studying structure of membrane and other non-soluble proteins. These inclide 2D Cryoelectron microscopy, atomic force microscopy and related techniques for the study of shape and actions of proteins*

- *System level nanostructure engineering. Clear possibilities for industrial interest in the integration of micro electronics and biological systems are emerging. Active communication links with R & D activities in the electronics industry should be established.*

- *Studies of molecular recognition should be given high priority. Techniques for the characterization and monitoring of protein surfaces are important. The intrinsic role of electrostatic interactions between a protein and its substrate should be studied.*

- *Technologies should be developed for the incorporation of non-natural amino acids which would enhance the abilities of PE to develop totally new structures with novel functional properties.*

Table 1: *Protein engineering programmes and specific funding for selected centres in Europe 1985-1994. INPEC is International Protein Engineering Centres and NI programme is Nordisk Industrifonds Protein Engineering Programme (1989-1993).*

Countries	National Protein Engineering Programmes	Specific Protein engineering funding for selected centres
Austria		
Belgium		
Denmark	YES	YES - INPEC member, NI programme
Finland		NI programme
France	YES	YES - INPEC member
Germany		YES - INPEC member
Greece		
Iceland		NI programme
Ireland		
Italy		
The Netherlands	YES	YES - INPEC member
Norway		NI programme
Portugal		
Sweden	YES	NI programme
United Kingdom	YES	YES - INPEC member
EC		
EMBL		

OVERVIEW IN OTHER COUNTRIES (USA, JAPAN, CANADA)

Overviews in other countries (USA, Canada and Japan)

The following information has been obtained through the "EC-US Task Force in Biotechnology", in particular following the fourth meeting of the task force on 18-19 October 1994, and from INPEC (International Network of Protein Engineering Centres).

• Support of Structural Biology and Protein Engineering research in the USA

The US Federal Biotechnology Research Initiative does not treat structural biology or protein engineering as separate sectors. Instead, they are embedded in the principal biotechnology research areas:
-Agriculture;
-Energy;
-Environment;
-Healthcare;
-Manufacturing/Bioprocessing (*Relevant major themes are: understanding enzyme structure-function relationships to tailor proteins for particular purposes; employing remodelling techniques to improve product design; molecular simulations and stable biosensors for in-process use*)
-General Foundations (Underpinning research) *(Relevant themes are: biochemical and biophysical technique development (new methods for identifying, synthesizing, purifying, characterizing and manipulating nucleic acids, proteins and other biomolecules; instrument development, especially for studying macromolecular conformation and chemical structure; information research and development (methods for storing, processing and analyzing biological data).*

Current priority areas are: Health (therapeutic agents developed through recombinant DNA technology; vaccines and molecular nuclear medicine) and the Environment (Bioremediation, monitoring/biosensors and environmentally friendly pesticides).
Support for protein engineering and structural biology is also derived from the budget for infrastructure *(Relevant themes are the provision and maintenance of databases of DNA and amino acid sequences and the 3-dimensional structure of proteins)*: Facilities; Training; Instrumentation; Repositories and Databases/Reference Standards.

Structural Biology is a major emphasis for at least three federal agencies, the National Institutes of Health (NIH)* the National Science Foundation (NSF) and the Department of Energy (DOE). The Howard Hughes Medical Institute (HHMI) is also a major source of funding for research in the area of structural biology. The National Institute for Standards and Technology (NIST) at the Department of Commerce (DOC) supports a major structural biology programme through its Centre for Advanced Research in Biotechnology (CARB). CARB is the USA member of the International Network of Protein Engineering Centres (INPEC). The multiplicity of agencies with various missions ensures coverage of the many aspects of structural biology needed for an effective programme.

**There are approximately 20 independent institutes that comprise the National Institutes of Health. Each has its own independent budget and distinct mission. Those institutes with a significant interest in Structural Biology include: the National Centre of General Medical*

Sciences (NIGMS), the National Centre for Research Resources (NCRR), the National Cancer Institute (NCI), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute of Allergy and Infectious Diseases (NIAID), the National Library of Medicine (NLM) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS).

Research: All of the federal agencies cited above fund grants to individuals within institutions to do research in the area of structural biology. Funds are made available on application and a favourable peer review of the grant application. Individual research grants are favoured in most of the Institutes within NIH and NSF. The bulk of HHMI research support is given to HHMI investigators. These investigators are selected and are actually employees of HHMI. At least for NIH, applications from foreign institutions are accepted.

Infrastructures: The vitality of Structural Biology is dependent on the health of shared facilities, for example, such synchotron facilities and databases as the Protein Data Bank. Funding for synchotron beam lines comes primarily from DOE. Funding for the individual stations is available from DOE, NSF, NCRR (of the NIH) and HHMI. Funding for the Protein Data Bank comes primarily from NSF with significant cofunding from NIH (NLM and NIGMS) and DOE. The development of validation software is funded by the EC.

Training: The National Institute of General Medical Sciences has an Institutional Predoctoral Training programme in the area of Molecular Biophysics funded by the Office of Aids Research, NIH. Individual postdoctoral fellowships are also funded. By legislation these are available only to US citizens and resident aliens. Special programmes for foreign visitors are available through the Fogarty International Centre (contact Dr. David Wolff, +1.301.496.1653.) NSF funds institutional predoctoral training grants, individual predoctoral fellowships and individual postdoctoral fellowships. There are special programmes available for foreign visitors. (Information about NSF programmes is conveniently available from the NSF gopher hole). In addition to formal training programmes, significant numbers of predoctoral and postdoctoral trainees are supported on individual NSF and NIH research grants.

Instrumentation: Shared instrumentation is funded through special programmes at NSF and NCRR. Dedicated instrumentation is funded through individual research grants. A particular problem exists with the funding of very expensive pieces of equipment, especially if it cannot be shared among several laboratories.

New Initiatives:
- Vaccine biotechnology (enhancement of immunogenicity)
- Novel computational tools for structural biology
- Microgravity crystal growth and separation processes
- Bioelectronics and Bionetworks
- Biomaterials

Financial Aspects: It is not possible here to single out funds allocated to Structural Biology from the FY 1994 allocation. However, the major agencies active in this area are: NIH; DoE; NSF. Funds allocated by these agencies in the area of Health, Manufacturing/Bioprocessing and Databases are: 1.7 $bn.

• JAPANESE Protein Engineering & Biomolecular Engineering

- Protein Engineering Research Centre (PERI)

PERI is the national protein engineering centre, endowed by the Japan Key Technology Centre in 1986 as the world's first exclusive, integrated centre for Protein Engineering. PERI is a joint venture of Japan Key-Tech and 14 industrial firms. The Centre recently learned that continuation of its funding (previously somewhat in doubt) has been approved to: 17.1 ¥bn (1986-1996).

PERI is organised into 5 research departments which reflect the progress of research from the isolation of a natural protein through to expression of engineered forms:

1. Structure analyses (X-ray, NMR, cryomicroscopy)
2. Structure-function correlation (Molecular graphics, protein design)
3. Protein modification and biosynthesis (DNA methods and intracellular transport).
4. Protein characterization (sequencing, post-translational modification analysis).
5. Databases (Protein modelling, structure prediction)

Current themes are: structure determination; molecular simulations; protein folding computational structural biology; protein design and synthesis; protein stabilization; high performance catalytic antibodies and structural analysis and application of membrane proteins. Technology transfer is arranged by six laboratory annexes of PERI which were created at the research institutes of participating firms. Work has also been initiated at PERI by seconded academics and industrial scientists.

Future developments include: more application in chemicals, electronics, environmental safety and pharmaceutical industries; downsizing of proteins by protein engineering and chemical synthesis of modified proteins.

- Biomolecular Engineering proposed initiative for 1994

The "Association for the Progress of New Chemistry" investigated the theme "Biomolecular Engineering" during FY 1993: "*Due to recent advances in proteins, nucleic acids, carbohydrate and lipid science, research should be initiated to construct a framework for research into the mechanisms of biomolecular function. An aim could be the downsizing of biomolecules to create more stable economic materials retaining functionality. Particular applications are in chemistry, environment, information, machine, electronics, food-agriculture, forestry, fishery and medicine*".

The BEP (Biomolecular Engineering programme, 1995-2005) will receive 26.4 bn yen net for: Preliminary research (-1995), Expression and structure-function analysis (1996-1998), and Downsizing & multi-functional protein assemblies (1999-2004).

The research targets are: low energy - loss production schemes, artificial (novel) enzymes, biodegradable polymers, means to degrade persistent materials (pollutants), stability towards solvent and heat, creation multiplicity (LSI) and polyfunctionality, novel medicines and diagnostics, biocomputers, and high sensitivity monitoring.

A major concept of the Biomolecular Engineering programme is that of "downsizing" functional protein units, stabilization of structures towards loss of function and assembly of engineered biomolecules into multi-functional assemblies (Large-Scale Integration LSI).

. The Protein Engineering Network of Centres of Excellence (PENCE) in CANADA

Support for protein engineering comes from a number of federal and provincial sources but mainly through a programme run by the Medical Research Council of Canada and the Natural Sciences and Engineering Research Council of Canada. Their programmes are available to other life science applicants.

Set up in 1990, the Protein Engineering Network (PENCE) is a multidisciplinary consortium of university, government laboratory and industrial scientists across Canada researching the relations between the molecular structure and function of proteins by chemical and molecular biological synthesis of systematically modified proteins.

Major Achievements:
- Leads for a potential drug against inflammation
- Developing method for automated synthesis of oligosaccharides (joint venture)
- Developing novel drug delivery technology using chemical crosslinking of proteins (joint venture)
- Developed improved engineered enzymes which reduce amount of chlorine used to bleach wood pulp

Description of research:
Protein Engineering is a multi-disciplinary science whose overall aim is to modify the structures of proteins. Initially, modifications are designed to reveal details of the relationship between structure and function in proteins. Thereafter, modifications are intended to improve the utility of proteins for commercial and therapeutic use. PENCE's programme covers all aspects of protein engineering, grouped into 7 major areas:

1 - Growth Factors, Receptors and Signal Transduction
Growth Factors are of enormous interest to the pharmaceutical industry because they represent targets for development of effective therapies for allergic diseases, tissue repair and cancer. PENCE researchers focus on 3 of 70 or so cellular growth factors as well as the SH-2 and SH-3 domains involved in intracellular signal transduction. Approaches to the study of IL-8, IL-5 and TGFα include the determination of their structures and synthesis of analogues, coupled with biological studies. This work is providing new insights into receptor-subunit interactions, receptor activation and sites of protein/protein interactions in downstream signal transduction molecules.

2 - Proteinases of Disease
Proteinases, enzymes which break down proteins, are involved in many diseases in which aberrant protein turnover occurs. These include muscular dystrophy, bacterial infections, stroke and myocardial infarction. PENCE researchers are developing a database of structural, enzymological, mechanistic and chemical knowledge on the cysteine proteases and are using this information to design non-peptidyk inhibitors and other lead compounds for therapeutic development.

3 - Vaccines and Immunological Products for the Treatment of Infectious Diseases
PENCE researchers are developing novel vaccines and therapeutics for the prevention of

significant viral and bacterial infections. A "rational design" approach based on extensive structure-function studies of key virulence factors is being used to generate technologies upon which development of new classes of vaccines and therapeutics will be based. It is anticipated that the technology will be generally applicable for the development of vaccines directed against a variety of pathogens.

4 - Carbohydrate-based technologies
A number of distinct projects, unified by their common basis in carbohydrate/protein interactions, are being pursued. These include the development of specific cellulose-binding proteins as affinity ligands for protein-based therapeutics, or as newspaper de-inking agents; the development of novel enzymatic approaches for synthesis of oligosaccharides and the development of glycosidase inhibitors as therapeutic agents.

5 - Metalloproteins for Industry and Medicine
Environmental concerns have focused attention on ways to remove lignin from woodpulp at the same time as reducing the use of potential environmentally damaging chlorinated compounds. PENCE researchers are studying a number of enzymes that share the ability to delignify wood. Other metalloproteins which ordinarily fulfill critical roles in ligand transport (haemoglobin and myoglobin) are being studied for possible use as drug delivery agents.

6 - Protein Design
PENCE researchers are studying how proteins fold into their biologically active conformations. This knowledge is applied to the design and synthesis of synthetic peptide vaccines and to the design of synthetic mini-globulins for diagnostic and therapeutic applications.

7 - Protein Structure and Function Technology Development
Central to the successful use of protein engineering is the use of a wide variety of rapidly developing and sophisticated technologies. The overall objective is to develop three of these technologies: automated approaches for the analysis of NMR spectra; NMR approaches to the characterization of protein dynamics; and peptide-based technologies.

Current Industrial Involvement: PENCE researchers are working with the following companies:
- Allelix Biopharmaceuticals
- Biomira Inc
- Connaught Lab. Ltd.
- GlycoDesign Inc.
- Hemosol Inc.
- Hypercube Inc.
- Merck Frosst Canada Inc.
- PAPRICAN
- Symphar Inc.
- Synthetic Peptides Inc.

CONCLUSION

Conclusion

The 1994 report on protein engineering programmes in Europe should be considered as the first step in a continuous approach towards providing better information for the scientific community, programme managers and policy makers involved in protein engineering R&D in Europe.
As a first step, this report has deliberately chosen to focus on a rather specific target (the national protein engineering programmes or the protein engineering parts of wider national programmes), therefore ignoring important aspects of the development of protein engineering such as the overall context (in particular, the industrial context) in which the national programmes are implemented.
The initial limited scope may be enlarged and modified for future reports (such as the 1995 one). Indeed, the contact group has already pointed out the need to take into account the four following aspects:

The nature of collected information did not lead, in the present report, to answer the question "What do we know about Protein Engineering ?" and thus a scientific "state of the art" report, but rather to answer the question "How is Protein Engineering research **organized** in each European country ?". These two aspects clearly depend on each other and a balance should be reached between them in the next report in terms of information collected and inputs received from the scientific community.

The "receivers" of information should not be limited to the European Commission services. Indeed, all policy makers and programme managers in European countries as well as the European scientific community are potentially interested. Reactions and suggestions are invited from this large potential audience and should be taken into account to improve the quality of the next report.

The scope of protein engineering seems to be too limited to efficiently address the various activities related to the basic problem of structure-function relationships. This problem is the same for all biological macromolecules and, very often, various types of biomolecules interact with each other as well, so the border lines between the different types of biomolecule become unclear (such as catalytic activities supported by enzymes and also abzymes). It is therefore suggested that the scope be extended to the wider area of structural biology, including types of biological macromolecules, other than proteins;

The industrial aspects of R&D activities should also be taken into account, both upstream, as an important element influencing R&D programmes and policies, and downstream, as a contribution to the improvement of competitivity.

Concurrently with the present report, the "Protein Engineering Contact Group" is now established, which has meant the emergence of a group of persons sharing information, discussing policies, etc, and therefore creating a "tool" that contributes to the coordination of research in Europe. The role of this "Contact Group" is crucial to the improvement of the quality and accuracy of information, and for the formation of a network, together with the European Commission services, so that it hopefully becomes an instrument of further and deeper coordination.

ANNEX 1
Publications and Reports

PUBLICATIONS AND REPORTS

The following publications and reports on protein engineering in Europe aim to reflect the general context, as well as reveal pre-existing relevant information or initiatives in the development of protein engineering in Europe.

International

The International Network of Protein Engineering Centres (INPEC) is an unofficial group of national centres concerned with protein engineering research, which was established on May 1991. The INPEC centres are the:

- *Cambridge centre for protein engineering, Cambridge,* *England*
- *Centre for advanced research in biotechnology, Rockville,* *USA*
- *Centre for applied protein engineering, Braunschweig,* *Germany*
- *Danish protein engineering research centre, Aarhus, Odense, Copenhagen,* *Denmark*
- *Laboratory for protein engineering (P-2000), Paris and Grenoble,* *France*
- *MR-centre for protein engineering, Trondheim,* *Norway*
- *NRC centre for protein structure and design, Montreal & Ottawa,* *Canada*
- *Protein engineering research institute, Osaka,* *Japan*

Each country may have up to one node within INPEC. Each node is encouraged to communicate its country's activities in protein engineering to INPEC and to disseminate information on INPEC's activities throughout the node's country.
The aims of INPEC are the:

- *Promotion of basic and applied research in the field of protein design*
- *Mutual cooperation and exchange of information to avoid duplication of research*
- *Organization of annual international protein engineering meetings*
- *Exchange of scientists*
- *International training at the post-doctoral level*

Europe

Protein Science & Engineering in Europe,
M. Geisow
Report & Position paper, Meeting at GBF, Braunschweig (DE), 4-5 May 1993

European Research Programmes in Protein Engineering: Past, Present and Future
P. Woolley and B.F.C. Clark
Biotec (Milan; publ. Clas International, Brescia), May 1989, pp. 35-41

Ingénierie des protéines: des stratégies nationales pour une recherche précompétitive
J-C. Pinon
Biofutur, February 1989, pp.6-10.

Europe's shining new light
N. Hall
New Scientist, 14 March 1992, pp. 30-33.

Nordic Countries
Nordic Programme for research and Dissemination of Technical Expertise in Protein Engineering
4th. annual report: May 1992-April 1993.

France
L'ingénierie des protéines: place de la France dans la compétition internationale
CADAS (Comité des Applications de l'Académie des Sciences)
Rapport n°12, juin 1991.

United Kingdom
Newsletters:
Peptide: Quaterly publication of the UK Protein & Peptide Science Group (Biodigm, Unit 5, the Hillside Centre, Upper Green St. High Wycombe Bucks HP11 2RB).

Perspective on protein engineering (Bi-annual publication of the LINK Protein Engineering Programme) address as above.

ANNEX 2
Coordinates of Protein Engineering Scientists mentioned in the report

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