Research in the European Union

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European Union (EU) research policy and funding for brain research

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For European scientists, insufficient research funding may seem the largest handicap in their endeavour to successfully compete worldwide. However, lack of funding is not the only hurdle to overcome in European research. Recently, the EU presented the European Research Area (ERA), an ambitious new concept to create a Europe of knowledge that fosters more research and better organises research at the European level with more researchers taking part and improved funding schemes. Ultimately, this should lead to the creation of an "internal market" in research, the restructuring of the European research fabric, and the development of a common European research policy. This certainly applies to brain research as well, and a primary objective for the realisation of the ERA in this subject is to overcome the fragmentation in neuroscience research in Europe.

With Integrated Projects and Networks of Excellence the European Union provides two new types of instruments for the implementation of large-scale research activities. Integrated projects are primarily aimed at the generation and delivery of new knowledge through activities with ambitious, clearly defined scientific and technological objectives. A multidisciplinary approach involving academic as well as private sectors and the incorporation of the full spectrum from basic to applied research are the key issues here. Networks of Excellence, by contrast, are designed to support integration and structuring of the European research landscape with a more durable effect. Both initiatives, together with smaller traditional methods, will mobilise the available critical mass of excellence in brain research in Europe to overcome underfunding and fragmentation, which may finally also lead to improved or new therapeutic approaches to brain diseases.

Brain research, or—in a broader sense—neuroscience, has an important role in the improvement of health and quality of life. The driving forces behind the European effort in neuroscience research are the desire to gain new insights into mental processes in general and the need to develop new and better means for diagnosis and therapy of neurological and psychiatric disorders and diseases. The relevance of the latter issue is growing as the ageing of society enters public debate. Furthermore, based on a WHO study, about one third of all disease burden in Europe is caused by brain diseases (neurological, neurosurgical, and psychiatric diseases together), and this proportion will increase in the next 10–20 years.[1] Therefore, European research needs to take into account this important societal as well as political feature.

From the early Framework Programmes (FPs) of the EU onwards, research and technological development in biomedicine received continuous support. Thus, the brain research area of the BIOMED 2 and BIOTECH 2 programmes in FP4 (1994–98) received a budget of €85 million (£63 million) spent on 114 small-scale research projects. This effort catalysed the coordination of research in the scientific community.

In FP5 (1998–2002) the neuroscience budget has already increased to €85 million (£63 million) for a total of 86 medium-sized brain research projects. Although most FP5 projects in this area are still ongoing, it is already evident that these display strengthened networking and further mobilisation of high level European research teams.[2] (European Commission, 2003).

For brain research in FP6, "Genomics and biotechnology for health" is one of seven priority themes. This prioritisation sets the frame for a number of focused topics under the subheading "Studying the brain and combating diseases of the nervous system". In addition, the subpriority "Advanced genomics and its applications for health", which is divided into the two sections "Fundamental knowledge and basic tools for functional genomics in all organisms" and "Application of knowledge and technologies in the field of genomics and biotechnology for health", will offer several possibilities for brain research related topics, and thus draw additional funds to this area.

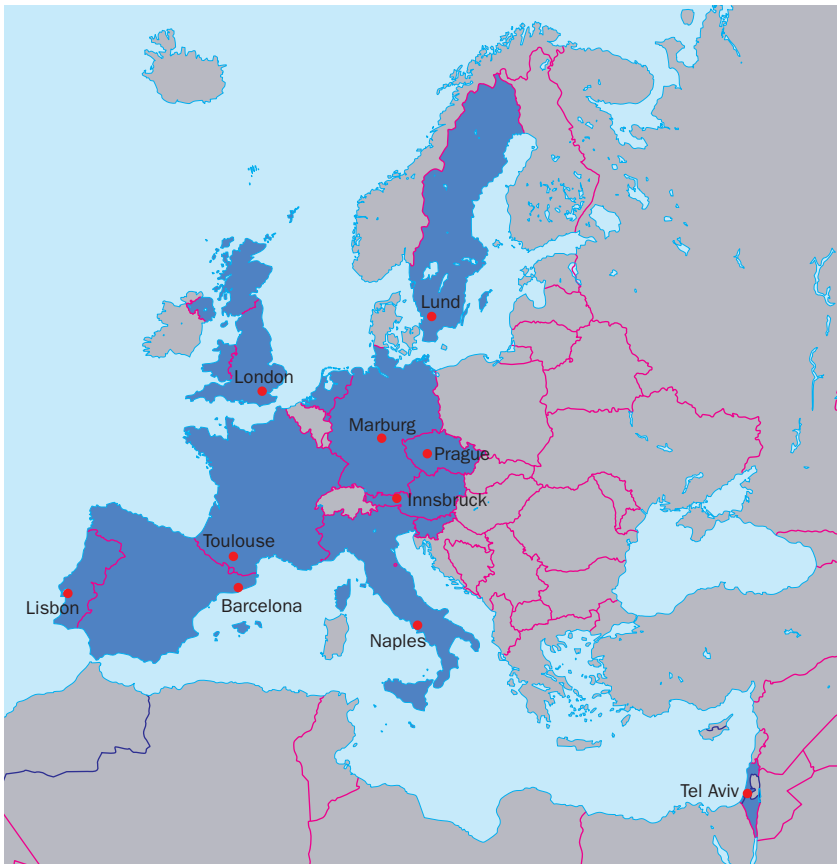
To determine those areas on which to focus research the Commission launched an invitation to submit Expressions of Interest during the summer of 2002. This exercise could also be a response to criticism of the lack of transparency for the choice of fund allocation. Mostly welcomed and appreciated by the scientific community,[3] the call for Expressions of Interest elicited an overwhelming response and provided the European Commission with a bottom-up approach to define the most relevant European research topics ready to be implemented.

In addition, neuroscience research in FP6 (and biomedical research in general) builds on two key issues. First, it will focus on the integration of postgenomic research, and second, it will emphasise the "translational" approach, which means research aimed at bringing basic knowledge through to the application stage, to enable consistent and coordinated progress at European level in medicine and to improve quality of life. For neuroscience

research, this approach should not only meet the hope of the many patients with brain diseases that new developments rapidly make it from "bench to bedside", but also increase Europe's competitiveness with the USA and Japan. Strong efforts by the EU to encourage participation and involvement of small and medium sized enterprises complement this approach.

The first contracts for FP6 brain research projects are currently being negotiated as a result of the first call for proposals, and it is expected that about €46 million (£34 million) will be funded in the first year (2003). In subsequent calls a multiple of this amount is expected for more large research projects. With the implementation of the first Integrated Projects and Networks of Excellences in brain research expected towards the end of this year, an important step will be taken to improve European research coordination and cooperation, especially through better networking.

Brain Research in Europe—Structuring European Neuroscience, a conference organised by the European Commission in collaboration with the European Parliament (September 18, 2003)[4] was an important opportunity to review these first steps into the European Research Area, to outline future perspectives for neuroscience research, and to increase the awareness of neuroscience in the general public and especially in decision-makers and other relevant stakeholders.



Participating units in the EuroPa research network.

EuroPa: European movement-disorders specialists form network to boost clinical research on Parkinson's disease (PD)

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Neurologists with long-term expertise in movement disorders from 11 European countries have created a cooperative network for clinical research in PD (figure). The project has a grant from the European Commission until December 2004. Clinical centres from Austria, the Czech Republic, France, Germany, Israel, Italy, the Netherlands, Portugal, Spain, Sweden, and the UK are members of the European Cooperative Network for Research, Diagnosis and Therapy of Parkinson's Disease (EuroPa). A German company, interActive Systems, also belongs to the project consortium (panel).

The aim of the EuroPa network is to establish a European clinical research organisation that will initiate, plan and conduct multicentre clinical trials and studies in PD. These will include projects driven both by members and by industry. All participants are already experienced clinical researchers. By bringing together their expertise and resources and setting up a common infrastructure and administration they intend to strengthen their research capacity and market position. As a result, Europe's significance for studies of movement disorders will grow and clinical research can be accelerated and improved.

A central database with internet-based data capture has been created to build a registry of patients with PD. The group has agreed on a common minimum data set to collect comparable clinical data from each patient included. Data entry and management is done via the internet.

Patients' data is transmitted and stored pseudonymised in accordance with data protection guidelines. Personal data is separated from clinical details and held by the responsible clinical centre. Only select personnel can identify a patient, for the purposes of inviting him or her for a clinical trial or a new visit. Participation by all patients is on a voluntary basis and they must give informed consent before data collection.

The registry will allow access to patients who fulfil particular diagnostic criteria and are interested in clinical trial participation. The internet-based infrastructure will facilitate efficient and cost-effective recruitment for future studies and support other joint research projects.

In contrast to national networks and organisations, this European-wide network has faced difficulties that are

determined by multinationality and heterogeneity. In order to collect and transfer data to the central database, for example, various national and even local data protection and ethical requirements had to be taken into account. Documents had to be translated into ten different languages.

The time required for data entry is about 20 min per patient. In most cases data can not be entered into the computer during the examination. Because the funding strategy of the European Commission has primarily focused on the network infrastructure, little provision has been made for personnel involved in recruitment of patients. Because of the typically heavy time pressure during outpatient visits, motivation is needed in order to take on the extra burden. In the long run additional resources are needed at all participating centres. The group has decided to minimise the initial number of patients to be recruited for the registry to a representative percentage of the entire outpatient population. Patients will be selected by use of a randomised sampling procedure.

Registry data entry started in May 2003. Some centres are still awaiting approval by either data protection authorities or ethical committees. The working structure of the clinical research organisation will continue to be developed during the second half of the funding period. EuroPa plans to select the first study by the end of 2003.

A further aim of the EuroPa project is a comparative health economic survey. PD affects a growing number of patients. With the rising cost of health care it is likely that research into the economics of health will increasingly provide a decision-making framework. For PD, there is little information on optimal strategies for resource allocation. A descriptive analysis of how care for PD is organised in Europe has already been finalised and will be followed by a comparative analysis of burden-of-disease, health-related quality of life, and patients' preferences in various European countries.

A significant challenge for the project team is to identify effective measures to ensure EuroPa's sustainability beyond the funding period. When this is achieved EuroPa will be open for new members. The EuroPa concept aims to establish national PD networks in participating countries. In each case this will require a sound legal basis. Potential options are being assessed. The expansion of EuroPa offers an opportunity not just to increase the number of patients and research projects but also to support the spread of evidence-based medicine for PD in all participating countries.

More information on the EuroPa project is available at http://www.europarkinson.net.

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The EC-funded DIADEM project

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Alzheimer's disease (AD) and related dementia are irreversible, degenerative disorders of the brain characterised by progressive cognitive decline, the loss of personality, and eventually death. Disease progression may last up to 20 years. Because of the effect on affected individuals and due to the enormous healthcare costs, these disorders present a major health problem. Within the last decade of research into AD, great progress—especially in the USA—has been accomplished and, as a consequence, the outlook for a potential medical treatment for these so far untreatable diseases has greatly improved. A crucial prerequisite is the development of diagnostic tests that identify patients at an early, presymptomatic stage.

The Foundation for Behaviour and Environment (VERUM), a not-for-profit organisation in Munich, Germany, has initiated the formation of a consortium to promote and coordinate European research in this highly competitive area. This research group includes 16 European research groups, two from the United States including the leading scientists in the subject, and a biotechnological company. The still scattered European resources are to be combined, thus increasing the European industry's competitiveness. This is because no single EU member state is able to provide sufficient resources and appropriate infrastructures, which are both necessary for successful competition, especially with the USA. There is no doubt that most of the work in AD research during the last decade has been done in laboratories in the USA, probably promoted by the former President Ronald Reagan's suffering from AD. European scientists contributed to this development mainly through their training in the US laboratories. Prominent alumni from these laboratories recently returned to Europe and set up very successful research programmes of their own in Spain, Portugal, Greece, Belgium, Germany, and Switzerland. Our research consortium should thus foster the integration of these high-profile European research talents and establish synergies by cooperation. In order to stay in close contact with research efforts in the US, two eminent researchers from Harvard Medical School and from the National Institute of Health have been included in the consortium.

In the year 2000, the consortium submitted a research proposal to the European Commission called "Early Diagnosis of Alzheimer's Disease and Related Dementia (DIADEM)". The research plan is based on the conviction that increased knowledge of the neurobiology and the pathophysiology of genes and proteins associated with dementia will yield candidate molecules for the

development of new diagnostic tests and therapeutic targets. The research proposal was reviewed by an independent panel of scientists selected by the EU, and funding of the project was promised for 3 years. The European Commission will contribute €3·8 million (£2·8 million) to DIADEM; Switzerland, which is not a member of the EU, will provide another €1·3 million (£0·9 million), thus enabling Swiss scientists to participate in an EU-funded project; finally the VERUM Foundation will add a further €400 000 (£290 000). The funds are distributed among the members of the DIADEM consortium in annual instalments depending on the estimated costs of the work proposed and on the progress made. The VERUM Foundation, the coordinator of DIADEM, will make sure that the funds are used for research work as described in the contract with the European Commission. The VERUM Foundation is supported by an external advisory committee, which is knowledgeable about the science and is responsible for quality control, but independent of the investigators involved. The overall goal of this committee is to provide advice and guidance to the investigators. Regularly scheduled reviews on research progress, whether critical or laudatory, will help shape the direction and pace of research. Further control mechanisms are site visits, biannual workshops, in which all participants present and discuss their research work, and annual reports from all members of the consortium, which have to be submitted to the European Commission. The final decision whether or not funding will be continued will then be made by the European Commission.

The overall goal of the DIADEM project is to study dementia risk patterns. To achieve this goal, a high-throughput assay device will be developed, which can simultaneously probe for several biomarkers for dementia. Clinically identified molecules related to the genetics and pathogenesis of AD should be analysed for their neurobiological function in model organisms and cell culture assays. And molecules identified in basic research studies should be tested in clinical settings for their pathophysiological relevance in the diagnosis and, possibly, therapy of dementia. The combination of this approach with powerful developments in high-throughput screening, chip technology, and combinatorial chemistry should lead to products that are useful in the diagnosis, prevention, and—with newly identified therapeutic principles—treatment of dementia. To achieve the goals of this integrated basic, clinical, and biotechnological research programme, three methods have been designed to detect early pathophysiological events from three distinct but complementary angles: genetically modified model organisms that have pathological features of the human disease; tissue culture systems that can be used to address the cell biology of early pathophysiological events; and human patients along with healthy control individuals to supply this consortium with biological samples such as body fluids and DNA. Within the consortium it will be the task of the biotechnology company to develop a microarray-based assay device that can simultaneously test many biomarkers for dementia and drugs for disease prevention (DIADEM Chip).

For many years now the European Commission has supported European research within the so-called FPs in many different areas, including life sciences. The DIADEM project is funded under FP5 spanning from 1998–2002. FP6 was started in 2002 and runs through 2006. In FP5 only 16% of an overall budget of nearly €15 billion (£11 billion) were provided for research in the life sciences; similarly, in FP6 only 13% out of €17·5 billion (£13 billion) are allocated to this research area. The European Commission does not seem to consider neuroscience research to be of particular interest within the life sciences, as shown by their funding policy in both FP5 and FP6. If one bears in mind the already disastrous effect that neurodegenerative diseases exert on our societies, neuroscience is, compared with cancer research, rather poorly funded. To receive funds from the European Commission for projects such as DIADEM is by no means an easy task—mainly due to the Europe-wide competition for a small amount of money but also due to the enormous bureaucratic burden for the fulfilment of all the prerequisites. Despite the many hurdles to be overcome, the DIADEM project is well worth the effort: without funding by the European Commission the project would never have been realised. In the meantime, the DIADEM consortium has published more than 100 articles in leading scientific journals. In order to continue this successful work under FP6, a research proposal building on and extending DIADEM has already been submitted after the European Commission's first call. In the meantime, the consortium has been invited for contract negotiations.

The importance of partnerships with patients

Mary G Baker, president of the European Federation of Neurological Associations and European Parkinson's Disease Association

During the past 30 years, a model that seeks a partnership between doctors and other caregivers on the one hand, and patients and their families on the other has replaced paternalism in medical care. This trend has been of special interest and importance for patients with brain illnesses. First, there is abundant evidence that the worldwide challenge of brain disorders will continue to increase during the next two decades. Second, the stigma associated with brain disorders, inclusive of those disorders treated by psychiatrists and neurologists, cannot be effectively treated without the active participation of patients as well as their caregivers. And thirdly, patients now have access to medical information in cyberspace that lessens greatly the traditional imbalance between the knowledge possessed by doctors and that of their patients. The concept of partnership does not imply a level playing field in which the knowledge and skills of doctors is unrecognised, but rather mutual respect, mutual trust, and mutual collaboration in the design of patients' care protocols.

Several social and cultural changes in the last three decades have had implications for people and their families living with neurological illnesses.

To ask people with neurological illness and their carers what they need is a key step towards improved quality of

service provision, but one which is generally forgotten by healthcare planners. There have been enormous shifts in patterns of care for chronic diseases over the past few decades, in part because most people over age 70 have one or more comorbidity, regardless of the chief complaint or primary diagnosis.

Demographic changes mean that neurological illnesses generally will become more common with the rise in the number of elderly people, especially people older than 80 years, and this change will put even more pressure on carers. Unfortunately, this increase in need coincides with a decrease in the availability of informal carers. This latter trend is due to falling birth rates, changes in family structure, and changes in the role of women in society who now opt for a career in the workforce in ever-greater numbers.

Voluntary organisations can help build bridges to the power bases of central government and medical and social services, provided that such groups are given sufficient resources to get the job done. No patients' organisation can exist in a vacuum; they all need to be flexible and responsive to outside influences. A robust voluntary organisation can conflate the knowledge and clinical observations of the doctors with the experiences of those people living with, and families affected by, chronic brain illnesses on a daily basis.

People want to participate in the management of their illness. With the changing demographics and the repercussions that this attitude will have upon all our societies, never before have voluntary organisations been such critical components to ensure effective delivery of services. Service delivery should meet the perceived needs of patients, and patients should have the opportunity to make their care requirements and preferences known to their doctors and health ministries. In order for the providers of service to deliver appropriate and cost-effective care, they must listen to the voices of the voluntary organisations and recognise the necessity for a climate of partnership. Voluntary groups can also help carers to focus more sharply on the families of people affected by brain disorders, so that their needs, too, can be met.

To meet the needs of patients, doctors, and carers, strategic alliances become increasingly important. During the last few years, close partnerships have been forged among the members of the European Federation of Neurological Associations (EFNA), and with other organisations. As these strategic alliances have emerged, and the linking of healthcare professionals, the pharmaceutical and biotech industries, and other groups into the equation of care has become easier.

EFNA's membership brings together the European umbrella organisations of neurological and psychiatric patient advocacy groups and aims to raise public awareness of brain disorders, while eliminating the prejudice and stigma associated with them. Other objectives are: to promote better diagnosis, treatment, rehabilitation and care; to provide better access to better information; and to increase the priority given to brain illness by policy and decision makers and healthcare providers.

EFNA works closely with the European Federation of Neurological Societies, WHO, and pharmaceutical and other industries in a "Partnership for Progress". It has also played a central part in creating the recently formed European Brain Council, which promotes brain research. It is EFNA's hope to improve the quality of life of those living with brain conditions and to provide a powerful and responsible voice for patients and their carers at a European level.

There are good examples of what can be achieved by collaboration and partnership—for example, the successful Global Campaign for Epilepsy, "Out of the Shadows", in 2001. Another ongoing collaboration that must be highlighted in this discussion is the Working Group on Parkinson's Disease formed by the WHO and linked to non-governmental organisations within several WHO regions. By working together, they have now developed a Global Declaration that will be launched at the seventh World Parkinson's Day International Symposium in Mumbai, India, in December 2003.

Clearly, the global disease burden of brain illness in developing countries must be a priority for health ministries; in part, because people and their families living in poverty have an almost insurmountable obstacle of accessing the care they need so badly. Neurologists and psychiatrists would help immeasurably to improve this widespread problem if they joined forces to highlight the momentous and very positive evolution of partnership with patients, which is already moving so successfully from aspiration to accomplishment on a global scale.

On 10 June 2003, in the European Parliament, the European Brain Council was launched with the full support of Commissioner Busquin, who endorsed the importance of the role of patients in its creation and management. This event highlights what can be achieved by real collaboration. This council has brought together scientists, clinicians, patient groups, the health insurance, pharmaceutical, and biotech industries, media, and the ultimate partnership, Members of the European Parliament. This does reflect a dialogue between the needs of society and science, and fully substantiates the principles behind EFNA's motto "Partnership for Progress".

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