Report on the 1st International Research Meeting

On the theme of Neurosciences

Paris, 5 June 2009

under the aegis of the President of the Republic of France,

under the esteemed patronage and in the presence of

Nicolas Sarkozy, President of the Republic of France
Christine Lagarde, Minister of the Economy, Industry and Employment, and
Valérie Pécresse, Minister of Higher Education and Research

Foreword

The commitment of the French state to this 1st International Medical Research Meeting provides clear evidence of France's determination to increase its attractiveness to investors in this domain.

In his speech, the French President personally embodied France's ambition to make the health care industry a centrepiece of its industrial competitiveness. Nicolas Sarkozy stressed the reorganisation of public research and the independence of the universities as two keys to the country's new capacity to organise sound cooperation between public and private research bodies. He emphasised France's aim of becoming the world's most attractive country for French and foreign drug companies, and for the creation of joint research programmes and clinical trials.

The President also reiterated the importance of the CSIS (Healthcare Industries Strategic Committee) and confirmed that a further meeting has been scheduled in 2009; he insisted on the need to make such International Medical Research Meetings an annual event at which the public and private bodies attending can discuss their collaboration and undertakings.

The LIR (International Research Laboratories) subscribes fully to the priority accorded to greater competitiveness in French research by public bodies and private companies alike.
The need for closer cooperation between public and private research bodies has long been recognised: structuring, promoting and developing the life sciences is a major challenge to ensure that all patients can enjoy rapid and unhindered access to scientific progress and the new medical technologies.
With its profound conviction that international research laboratories can provide France with added weight, the LIR intends to support and contribute to all initiatives aimed at stimulating national research, in particular the conduct of clinical research as well as collaboration between public research bodies and industry (through public-private partnership agreements).

The aim of these annual R&D Meetings ("R&D Datings") proposed by LIR and initiated in 2009 in the field of neurosciences is to allow public and private players in research to exchange views, increase mutual confidence and multiply opportunities for working together.

A meeting in 4 parts

- presentation of the new organisation of public research and of the National Life Science and Health Alliance with the creation of 10 theme-based institutes, including the institute of neurosciences, cognitive sciences, neurology and psychiatry,
- presentation of 4 technological platforms at the cutting edge of innovation in the field of neurosciences, representing 4 of the 500 research teams currently active in this field in France,
- exchanges between researchers with these 4 technology platforms and researchers from some 20 drug companies attending this novel “R&D Datings” meeting,
- identification and allocation of areas for joint exploration.

This document provides an overview of the presentation made by LIR president Dominique Amory with details of the key points of the presentations and of questions raised by attending researchers.

OVERVIEW

Ensuring dialogue between public and private research bodies

Dominique Amory

The key objective of this meeting was to ensure a paradigm shift and to reshape the way research is envisioned and performed in the public and private sectors.

1st paradigm: Separation of the public and private sectors

Today, this concept is nothing more than a hypothesis that no longer accurately reflects the reality of modern research. There have always been strong links between the public and private sectors, if only because many R&D directors of pharmaceutical companies initially came from the public sector. Cooperation between these two worlds is primarily a human rather than an abstract principle, and nothing can replace actual meetings to promote contact, initiate confidence and engender new projects. The overriding aim of the meeting on 5 June is to create such a link and strengthen it over time. Our companies are already convinced of the importance of such a link and are all too well aware that their own R&D efforts, however excellent, are no longer adequate, and that the need for cooperation can only increase. Network-type collaboration (e.g. FIPNET) has become vital to ensure renewal of the product pipeline; the choice is between succeeding together or failing individually.

2nd paradigm: Protecting research and intellectual property

While partnership is now a cornerstone of our R&D strategy, it is necessary to open research upstream (the "open innovation" concept) in order to avoid companies working individually in silos. It will thus be necessary to establish collaborations with clearly defined intellectual property rules between the public and private sectors in order to allow companies to team up with players in the public sector on joint technological platforms, as exemplified at the European level by the IMI (Innovative Medicines Initiative), research in the biomarker field and in the definition of targets well upstream. The NIH (National Institutes of Health) model created in the US may perhaps provide useful insights.

3rd paradigm: "science for its own sake"

The need for results affects us all; the field of neurosciences is of immense importance for our ageing populations. The patient must once again become the centre of our attention, reminding us of the urgent need to discover appropriate solutions. Patients will serve as the catalyst of our cooperation.

There is a new economic model in the making based on closer collaboration and partnerships between the public and private sectors since a real need exists on both sides:

- the public sector requires funding,
- the private sector needs to fill in gaps (in terms of technologies and or skills, e.g. imaging equipment, access to primates, immunology).

The entire approach we advocate, constructed around patients and unfulfilled medical needs, is based on a new approach emphasising

- A sense of urgency (we must eliminate bureaucratic barriers such as excessive delays in signing contracts and diffusion of patent ownership).
- A business-oriented approach, i.e. pragmatism and insistence on tangible results.
- Mutual respect and confidence based on faultless ethical conduct on both sides. Industry is seeking to become an authentic partner rather than simply a banker or financier.

This new economic model perfectly reflects the attitude of the members of LIR regarding their commitment to improving therapeutic progress in favour of the patient as well as our major priority of catering for as yet unmet medical needs. To this end, it is our aim to organise further meetings based on the same conviction in the fields of diabetes, obesity and oncology.

Making France the priority destination for foreign investment in medical research

Christine Lagarde

The attraction of France as a country for medical research investment is based on three key elements:

- **Continual renewal of economic dynamism**
    - France is the second most economically attractive European country after the United Kingdom
    - It is Europe's third most attractive centre of biotechnology, after the UK and Germany, with 400 companies to date.

- **A strong public research sector**

  with scientific excellence of the highest order and strong connections with other European public research centres and with industry.

- **Promulgation of a partnership approach at the highest state level**
    - of which three strong indicators are: research tax credit, development of life-science clusters, individual taxation arrangements;
    - more particularly in the healthcare field: priority status for partnerships between public research units and private companies, the creation of biotechnology clusters and affirmation of the CSIS as a catalyst for dialogue between the government and pharmaceutical industry, with the next meeting confirmed for 2009.

A national life sciences and healthcare alliance

André Syrota

France enjoys a number of major advantages in the neuroscience field

with a long history of committed research in this domain, excellent facilities (550 research teams comprising 3300 researchers, engineers and students, 18 clinical research centres), a high number of publications (4200 per year), and a budget of EUR 220 m (excluding salaries).

The neuroscience domain comprises 5 major research areas

- central nervous system diseases,
- neurological development,
- cellular and molecular neurobiology,
- cognitive neuroscience and neurophysiology,
- neuropharmacology.

Scientific cooperation has been reinforced through a number of foundations

- the *Foundation for Alzheimer's Disease and Related Diseases*, a stakeholder in the presidential plan,
- FondaMental, active in the psychiatry field,

- *Voir et Entendre* (Seeing and Hearing), active in the field of sensory organs,
- *NeuroDis*, working on neurological deficits,
- The Paris School of Neuroscience, working in fundamental research.

France: opening new vistas in the public medical research arena

- in national terms, this has resulted in the creation of the Alliance Nationale pour les Sciences de la Vie et de la Santé (*National Life Science and Healthcare Alliance*)
- in European terms, France has set up partnerships to increase investment and strengthen synergy, particularly in the field of translational research (EATRIS, the European Advanced Translational Research Infrastructures in Medicine, brings together 5 cutting-edge European technology platforms in the field of translational research, four of which attended the Meeting of 5 June.)

Action plan against Alzheimer's disease

Alzheimer's disease affects 860 000 people in France, with annual treatment costs throughout Europe in the region of EUR 55 bn.

The action plan was made public on 1 February 2008 and will remain in place until 2012. It comprises 3 principle axes, 11 objectives and 44 measures, and it involves the investment of EUR 1.6 bn over this 5-year period (EUR 1.2 bn for the medical-social aspects, EUR 200 m for therapy and EUR 200 m for research).

5 key factors for the creation of partnerships

Ensuring that researchers and clinicians speak the same language
Yves Agid

These first International Medical Research Meetings constitute a strong reminder that the public research sector and private companies are now ready and willing to work hand-in-hand.

Successful cooperation will involve providing solutions in three distinct areas:

- knowledge and regulation of intellectual property,
- results, based on the desire to place patients at the heart of research activities,
- organisation of modes of co-operation: who, what, when, how?

The presentation of the four innovative technological platforms selected for this meeting (ICM, Clinatec, MIRCen and Neurospin) highlights 5 common characteristics that will be of paramount importance for the creation of partnerships:

1. **scientific excellence** of research staff, resources and processes; this element forms the cornerstone of the partnership project but must be complemented by other elements in order to create an authentic edge in terms of competitiveness or attractiveness;

2. **openness** typified by the interconnections between the various French innovative technological platforms on the one hand, and between these platforms and the major French research institutes on the other, and ultimately with other innovative European platforms;

3. **a multidisciplinary approach and coordination of complementary technologies**;

4. **a translational approach** and the ability to intervene at different stages of research, from fundamental research through to clinical experimentation;

5. **provision of services to drug companies** as illustrated by the transfer of knowledge and skills to industry (Clinatec) and the provision of infrastructures to allow large-scale data processing.

Benefits of each individual technological platform in terms of public-private sector partnerships

The Brain and Spinal Cord Institute (*Institut du cerveau et de la moelle épinière*)

- priority status for clinical research and the national network will ensure optimal patient recruitment,
- clinical and biological resources in neurology, psychiatry and ophthalmology (e.g. patient cohorts, DNA samples, Europe's largest brain bank, etc.),
- grouping at a single site of a clinical research centre and a project incubator, at the Salpêtrière hospital site and direct relations with the University of Paris VI,
- "private foundation of general interest" status seeking private funding of more than 25% of its operating budget.

The Brain and Spinal Cord Institute (ICM) is a neuroscience research foundation built at the site of the Pitié-Salpêtrière University Hospital, the largest Paris public hospital at which some 100 000 patients presenting nervous diseases (neurology, psychiatry, neurosurgery, rehabilitation) are seen each year. The ICM, due to be opened in the autumn of 2010, comprises a building with floors pace of 22 500 m² housing over 600 researchers, engineers and technicians, working closely with the clinical departments (neurology, psychiatry, neurosurgery, rehabilitation) that together form the "Nervous System Diseases Centre". Healthcare is based on scientific research, with a multidisciplinary approach to behavioural genes and to gene behaviour. The ultimate objective is scientific excellence, but "at the service of patients", hence the creation within the ICM of a clinical investigation centre and the close collaboration with a Biological Resources Centre. Located within the Ile-de-France biocluster, the ICM will have a "company incubator" on its doorstep. Finally, it is a private foundation of recognised public utility, thus facilitating the intellectual and financial management of some 40 independent research teams.
The institute's scientific programme remains open-ended and will align with the objectives of the actual teams recruited, provided that they are working in one of the following major scientific areas:

- aging and new regenerative diseases; mechanisms of cell death,
- neurodevelopment and glial cells, multiple sclerosis and related diseases,
- neural code, synaptic excitability; epilepsy,
- the neuronal basis of cognitive and emotional motor behaviour; diseases motor system, intellect and psyche.

Clinatec

- a biomedical research centre dedicated to microtechnology and nanotechnology health applications,
- organised collaboration between clinicians, neuroscience researchers and biologists on the one hand, and on the other between microtechnology and nanotechnology experts from Minatec and the CEA-LETI (*Atomic Energy Commission-Laboratory for Electronic and Information Technologies*) facility in Grenoble.
- the development of technical devices capable of providing therapeutic solutions in neurodegenerative diseases (e.g. Parkinson's disease, brain cancers, etc.) and for motor and sensory handicaps. These solutions target specific parts of the brain.
- Validation of these devices comprises three phases:
- implantation in animals,
- clinical testing and validation in patients meeting the requisite inclusion criteria under the sole supervision of partner university hospitals
- large-scale clinical trials at the Grenoble University Hospital, or other partner university hospitals, governed by agreements that are currently being finalised.

Clinatec is a biomedical research centre dedicated to microtechnology and nanotechnology health applications. It brings together clinicians, neuroscience researchers and biologists working together at a single facility with microtechnology and nanotechnology experts from Minatec and the CEA-LETI (*Atomic Energy Commission-Laboratory for Electronic and Information Technologies*) facility in Grenoble. The aim is to harness the technical know-how and expertise of the CEA engineers in the development of devices able to meet medical needs expressed by doctors.

Clinatec's research efforts are focused on neurodegenerative diseases (e.g. Parkinson's disease, brain cancers) and motor and sensory handicaps. The company is developing technical devices to provide therapeutic solutions in these disease areas. The devices are tested by implantation in animal models in order to investigate their biocompatibility, toxicity and technical performance.

Following validation of the devices and their passage to the prototype stage, they undergo clinical validation and testing in patients meeting the requisite study inclusion criteria. This phase is conducted under the sole supervision of affiliated teaching hospitals. At the end of these preclinical studies, and following validation of the prototypes, which in some cases are adapted and improved, final validation is undertaken through larger-scale clinical trials performed at the Grenoble teaching hospital or other affiliated teaching hospitals, for which the relevant agreements are currently being finalised.

Clinatec thus represents a coherent translational production chain, spanning the design stage at the Minatec microtechnology and nanotechnology centre through to standard clinical research facilities within university teaching hospitals.

MIRCen: pre-clinical imaging technology

- Provision of exceptional resources using a single technological plateau, currently unrivalled in France and Europe: radioisotopic functional and anatomical imaging, molecular and cellular biology expertise, laboratories and animal houses of microbiological safety levels 2 and 3 used exclusively for behavioural, anatomical and electrophysiological studies.
- Use of primate models of diseases: a key tool for the development of new therapeutic solutions.
- Two types of creation: design of new animal models by means of gene transfer and identification of new biomarkers in Huntington's chorea.

Created in December 2008, MIRCen is a preclinical imaging platform devoted to the design, implementation and validation of innovative therapies for neurodegenerative diseases (e.g. Parkinson's disease, Huntington's chorea, Alzheimer's disease, multiple sclerosis, etc), liver diseases, heart diseases and infectious diseases.
Thanks to its multidisciplinary format, MIRCen is able to provide the researchers assembled under its banner with exceptional resources, currently unrivalled in France and Europe, comprising the expertise of doctors, physicians and neurobiologists, virologists and medical imaging specialists. MIRCen in fact has access at a single site to radioisotopic functional and anatomical imaging, expertise on molecular and cellular biology, and laboratories and animal houses of microbiological safety levels 2 and 3 for use exclusively in behavioural, anatomical and electrophysiological studies. The fruit of a partnership between Inserm, the French Atomic Energy Commission (CEA), MIRCen is located at the CEA centre in Fontenay-aux-Roses, near major hospital centres and pharmaceutical industry research centres, and at the heart of the biomedical research facilities of the Ile-de-France region.

NeuroSpin

- A novel, multiple-scale and multimodal imaging platform.
- An exceptional technical platform uniting MRI (magnetic resonance imaging) scanners for human subjects operating at power levels of 3 and 7 T (tesla), an MEG (magnetoencephalograph), an EEG (electroencephalograph), analytical tools and image processing software.
- Collaboration with the CEA to ensure the creation by 2012 of a magnet with the hitherto unmatched power of 11.7 T, thanks to the entirely unique approach of NeuroSpin, which brings together under a single roof methodological creators and neurobiologists of the very highest order.
- Research topics of key importance for public health: NeuroSpin is effectively concerned with the working of the healthy brain, how it performs calculations, how it learns to read and how it processes different types of information, as well as the working of the dysfunctional brain, e.g. addictions, neurodegenerative diseases, schizophrenia, epilepsy, stroke and cancer.
- Advances in methodology of immediate industrial interest: *in vivo* and *in situ* studies of the mechanism of action of drugs, diagnosis and monitoring of drug efficacy.

NeuroSpin, a major research platform set up in 2006, aims to push back to current frontiers of brain imaging. The goal of the centre is to understand above the normal brain and cerebral dysfunctions through original multi-scale and multimodal imaging techniques.

NeuroSpin has an exceptional technical platform at its disposal: MRI (magnetic resonance imaging) scanners for human subjects operating at power levels of 3 and 7 T (tesla), an MEG (magnetoencephalograph), an EEG (electroencephalograph), analytical tools and image processing software.
By 2012, the NeuroSpin and CEA research teams will have designed and implemented a magnet with the currently unrivalled power of 11.7 T, thanks to the entirely unique approach of NeuroSpin, which brings together under a single roof methodological creators and neurobiologists of the very highest order.
NeuroSpin has some ten teams comprising around 100 researchers active on topics of key importance for public health and is effectively concerned with the working of the healthy brain, how it performs calculations, how it learns to read and how it processes different types of information, as well as the working of the dysfunctional brain, e.g. addictions, neurodegenerative diseases, schizophrenia, epilepsy, stroke and cancer.

NeuroSpin's research efforts are underpinned by specific methodological developments:
- experimental use of contrast media, biological markers for molecular imaging,
- *in vivo* and *in situ* studies of drug mechanisms of action,
- diagnosis and monitoring of drug efficacy,
- development of a new generation of extremely powerful (11.7 T) clinical MRI scanners,
- multimodal imaging (the MEG-MRI project),
- development of instrumentation associated with MRI systems (3, 7 and 17.65 T),
- development of neuroimaging software (BrainVISA).

The presentation by Luc Rousseau, who was represented on 5 June by Jean-Marc Grognet, underscored the importance of developing public sector-private sector partnerships in pharmaceutical research

3 key themes ran through the presentation:

- A country's investment in the healthcare industries forms core part of its future.
- France is seeking to provide a more attractive environment than ever before (tax incentives, research, centres of excellence).
- More than any country, it is actively seeking to encourage partnerships between the public and private sectors.

The pharmaceutical industry one of the key factors behind growth in the French economy, with a turnover of EUR 45 bn (of which more than 15% is invested in R&D) and 100 000 qualified staff; thanks to its long-standing history of pharmaceutical production, France is the European leader in this field and the third most important country worldwide with a trade balance of EUR 5 bn.

This excellent position is further reinforced by the quality of the country's health system and its willingness to rapidly embrace innovation.

More R&D challenges ahead

The cost of developing a new drug is rising (between EUR 800 m and EUR 1 bn) while the failure rate too continues to increase. This context favours opportunities that capitalise on innovation, wherever it may be found: externally, through partnerships or the type of corporation specific to clusters. In this regard, biotherapies and medical devices are especially promising areas.

Against this background, France must preserve and indeed strengthen its attractiveness in medical research, thanks mainly to the following key mechanisms:

1. Research tax credits: a key factor in France's bid for fiscal attractiveness

Following fiscal reform in 2008, research tax credit is applied pro rata based on the R&D costs declared by drug companies and represents 30% of total spending up to a ceiling of EUR 100 m and 5% thereafter. For companies benefiting for the first time from this credit, the ceiling is 50% for the first year and 40% for the second year, with an additional credit of 60% up to EUR 12 m being granted to companies for research spending on contracts signed with state-run laboratories.

The state research tax credit budget doubled from EUR 1.4 bn in 2007 to EUR 3 bn in 2008.

2. The innovative young companies measure

This measure concerns independent SMEs founded within the last 8 years and engaged in authentically innovative activity (at least 15% of spending on R&D). It consists of a reduction of employment contributions with company tax being waived during the first three years of the company's existence and a 50% reduction for the following two years.

In 2008, the measure was applied for 2000 innovative young companies and the budget totalled EUR 112 m.

3. Development of the biotechnology sector

There are currently 400 biotechnology companies in France employing 6000 staff.

4. Reorganisation of public research through reforms in 10 major universities at a cost of EUR 5 bn and the creation of the National Life Sciences Alliance bringing together the CEA, the CNRS, Inra, Inria, Inserm, the Institut Pasteur and university presidents

5. Centres of excellence for healthcare companies

The aim of the centres is to create geographical zones uniting companies, research centres and universities to collaborate in a joint development strategy, enabling sufficient critical mass to be attained to ensure an international presence.

The creation of these centres will allow funding of projects of a value of between 1 and 10 m euros by means of twice-yearly calls for projects.

Between 2005 and 2008, thanks to the 8 healthcare and biotechnology centres of excellence*, funding totalling EUR 140 m was channelled into 80 R&D projects through public grants.

* Medicen Paris Région, Nutrition Santé Longévité, Alsace Biovalley, Lyon Biopôle, Euro Bio Med, Cancer BioSanté, Prod'Innov and Biothérapies Atlantiques

Working towards the future

Roundtable following the "R&D Datings" Meeting

How our different teams viewed France prior to the Meeting

Dominique Amory

Only 20% of our teams work with researchers in the public sector. Language is obviously the most important hurdle, and there is also some cultural reticence, with France having a reputation for being relatively closed to private funding.

There are also numerous administrative constraints and drawing up contracts is time-consuming.

There is also a degree of uncertainty about France: "you never know what to expect!"

Commentaire : une attitude de curiosité ???

We nevertheless remain convinced that we can no longer carry out research independently. We would like to work together with public research bodies, but we need tangible patient-oriented results.

Two types of collaboration are possible between innovative technological platforms and the industry (D. Le Bihan, NeuroSpin)

- co-operation on projects,

- utilisation by the industry of the specific services provided by these platforms.

Questions raised by drug companies during the round table

1. Maintaining dialogue about areas of research

It would be extremely useful to cooperate on areas of overlap between public and private research (Lilly), and, in particular, to explore potential synergy between drugs and medical devices (MSD).

France could underpin a European initiative in the development of new therapies for prodromal syndrome (Roche), and the granting of longer exclusivity periods for drugs designed to slow down progression of the disease would stimulate research in this field (Roche)

There are opportunities in the new therapeutic areas (gene therapy, cellular therapy) (GSK)

2. The implications for intellectual property rights

Care must be taken to avoid this common stumbling block of public-private partnerships (Boehringer Ingelheim).

The concept of "open innovation" is based on data sharing and joint access to technologies. In practice, it would be useful to examine framework rules or contracts for the various technology platforms presented (Boehringer Ingelheim). There is a need for simplification (Serono).

3. Ethical standards governing clinical practice (GSK)

4. Practical organisation of cooperation between public technology platforms and private drug companies

Particular emphasis was placed on the following points:

- the ability to identify the right partners as early as possible (Astra),
- the efficacy to be gained by creating special clinical research staff status, since most people working in this area do not work exclusively in clinical research (Roche),
- the advantages of collaborating to ensure optimal patient group recruitment (particularly in psychiatry, constituting the requisite subgroups) (J&J),
- the advantages of data sharing (from collection to analysis),
- the benefits of a joint technology platform for studies (Novartis).

5. Potential tax incentives other than research tax credit

While international research laboratories recognises the importance of research tax credit in making France more attractive for R&D investment, certain members propose the examination of additional measures such as recognition of the value of clinical research investment and reduction of taxation on innovative products.

Afterword

Valérie Pécresse

Each year, France continues to file twice as many patterns as other countries, noted the French Minister of Higher Education and Research in the presentation of the challenge of research in France. While the government seeks to create increased dynamism through its reforms of public research bodies and the universities, public research cannot accomplish everything on its own.

The objectives set out by the Member States in Lisbon in 2000 of raising R&D funding to 3% of GDP by 2010 can only be reached with the involvement of manufacturers. The French government's aim of tripling research tax credit provides a clear signal of its ambition and its willingness to ensure such cooperation. In this regard, the Minister reiterated that credits corresponding to subcontracting agreements with public laboratories would count double terms of research tax credit.

Valérie Pécresse outlined a number of concrete steps to enhance cooperation: a website presenting the best public teams on the basis of multiple criteria, the creation of support doctorates (i.e. the preparation of theses by students carrying out work on a specific theme for private companies).

The minister concluded with a reference to the prospective reflection launched as part of a strategy of research driven by the ministry in which health and biomedical research will occupy a key place.