Press release

The 20th *Colloque Médecine et Recherche* of the *Fondation Ipsen* in the Neurosciences series:

"Programmed cells: from basic neuroscience to therapy"

Paris (France), April 3rd, 2012 – Embryonic stem cells have the potential to become any type of cells found in the body, including various types of nerve cells, but they have several drawbacks, both ethical and practical. Recently developed methods for producing patient-specific nerve cells by reprogramming skin cells overcome most of these disadvantages and offer a rich palette of opportunities for research into the nervous system. The production of these programmed cells, their applications in basic neuroscience and their potential for the development of new therapies for nervous system disorders have been explored by an international panel of experts at the 20th Neuroscience colloquium hosted by Fondation IPSEN. The meeting, hold in Paris on April 2nd, was organised by Fred H. Gage (The Salk Institute for Biological Studies, La Jolla, USA) and Yves Christen (Fondation IPSEN, Paris, France).

Over fifty years ago, in ground-breaking research that was also a technical tour-de-force, **John Gurdon** (Wellcome Trust Cancer Research UK, Cambridge, UK) showed that the nucleus of any cell in the body contained all the information needed for the development of an embryo. This demonstration laid the basis for the cloning of embryos that was to give rise to 'Dolly the sheep'. A further step was the identification in the early 1980s of embryonic stem cells, cells in the early embryo that are pluripotent: they retain the ability to become any cell type. By the late 1990s, techniques for transforming embryonic stem cells in culture into cells with the specific characteristics of particular body cells, such as nerve cells were developed. In principle these could be used to repair damaged human organs, which led to a wave of excitement about their potential for restorative medicine. Ethical considerations hampered progress, particularly as harvesting human embryonic stem cells, which come from extra embryos created for in vitro fertilisation, means destroying the embryo. Cells derived from embryonic stem cells also carry the risk that, as they are foreign tissue, the recipient's immune system will react adversely.

Recent technical advances promise a way out of both these dilemmas. Pluripotent cells have been induced directly by treating human body cells (somatic cells) with a cocktail of gene transcription factors and specific cell types have been produced from them (**Rudolf Jaenisch,** Massachusetts Institute of Technology, Boston, USA). The reprogramming of cells requires changing the state of the chromatin, the complex structure that regulates which parts of the DNA are available for transcription into proteins at any time. In the early experiments this was achieved by placing the nucleus from a somatic cell in a permissive environment, such as a fertilized egg cell from which the nucleus had been removed. Now the specific biochemical mechanisms involved are being identified, both for overall reprogramming of a nucleus and even for regulating specific genes (**Gurdon**; **Jaenisch**). A further step is the discovery that fibroblasts from the skin can be directly converted into neurons without having to go through the pluripotent stage (**Marius Wernig** , Stanford University School of Medicine, Stanford, USA).

Another advantage of both induced pluripotent cells and direct reprogramming of fibroblasts to neurons is that the donor cells can come from individual patients, so the cells that are generated have the same constellation of gene polymorphisms. This is being put to good use in experiments investigating the basic mechanisms of various diseases of the nervous system, as well as testing for potential therapeutic compounds. Cells taken from patients with familial Alzheimer's disease are being used to probe the effects of specific mutations on neuron function (**Lawrence Goldstein,** Howard Hughes Medical Institute, La Jolla, USA). By comparing such cells with those from patients with the

non-genetic form of the disease, common disease mechanisms may be discovered. Gene mutations linked to specific diseases are also identified in embryonic stem cells during pre-implantation genetic screening: a collection of 30 cell lines from 15 diseases is now available to researchers for the production of specific pluripotent cells (**Marc Peschanski,** Inserm/UEVE UMR U861, Evry, France).

By the time patients present with a neurodegenerative disease, their condition is already very advanced. Neurons derived from pluripotent stem cells offer the opportunity to study the early stages of disease in vitro, a method being used for Alzheimer's as well as spino-cerebellar ataxia (**Oliver Brüstle,** Institute of Reconstructive Neurobiology, Life & Brain Center, University of Bonn, Bonn, Germany). In amyotrophic lateral sclerosis (motor neuron disease), a specific type of motor neuron degenerates and techniques are being developed to reproduce these cells to determine what goes wrong and how it might be prevented or ameliorated (**Christopher Henderson**, Columbia University, NY, USA). Screens for gene expression are identifying specific differences between cells from patients and healthy controls, an approach that has also led to the identification of a malfunctioning protein with a central role in myotonic dystrophy type 1 and drugs targeting it (**Peschanski**).

This concept of a 'disease-in-a-dish' is also being applied to neural development and its relationship to disease (**Lorenz Studer,** Memorial Sloan-Kettering Cancer Center, New York, USA). In the neurodevelopmental conditions of the autistic spectrum, various subtypes of the disorder are being characterised by making neurons from fibroblasts of autistic children, (**Alysson Muotri,** University of California San Diego, La Jolla, USA). The approach has already been usefully applied to Rett syndrome, a rare genetic disorder that shares some behavioural characteristics with autism.

Stem cells populations are maintained in adulthood for renewing tissues as cells wear out and die. Aging has been linked to functional deterioration in adult stem cells and so may also contribute to late-onset diseases (**Juan Carlos Izpisua Belmonte,** The Salk Institute for Biological Studies, La Jolla, USA). One example is Parkinson's disease, where the structure and physiology of neural stem cells are affected by a gene mutation linked to one form of the disease. Neurons derived from patient's fibroblasts are also being used experimentally for promoting repair in Parkinson's disease and, more promising, in stroke, where restoration of movement has been demonstrated in a rodent model. One problem with the use of patients' fibroblasts is that the cells will carry any causal mutations, which could contribute further to the disease process.

While many of the speakers will be focusing on the potential of programmed cells for identifying and testing therapeutics, stem cell technology also offers a novel way of investigating what makes us human – or rather what distinguishes our brains from those of chimpanzees (**Gage**). Gene expression and the behaviour of neuron progenitor cells are being compared in neuron cell lines made from induced pluripotent stem cells from humans and chimps. The applications of this young technology are clearly hugely diverse and this meeting has illuminated some of the important ways that this potential is currently being explored.

About the Fondation Ipsen

Established in 1983 under the aegis of the Fondation de France, the mission of the Fondation Ipsen is to contribute to the development and dissemination of scientific knowledge. The long-standing action of the Fondation Ipsen aims at fostering the interaction between researchers and clinical practitioners, which is indispensable due to the extreme specialisation of these professions. The ambition of the Fondation Ipsen is to initiate a reflection about the major scientific issues of the forthcoming years. It has developed an important international network of scientific experts who meet regularly at meetings known as Colloques Médecine et Recherche, dedicated to six main themes: Alzheimer's disease, neurosciences, longevity, endocrinology, the vascular system and cancer science. Moreover the Fondation Ipsen has started since 2007 several meetings in partnership with the Salk Institute, the Karolinska Institutet, the Massachusetts General Hospital, the Days of Molecular Medicine Global Foundation as well as with the science journals Nature, Cell and Science. The Fondation Ipsen produced several hundreds publications; more than 250 scientists and biomedical researchers have been awarded prizes and research grants.

For further information, please contact:
Isabelle de Segonzac, Image Sept
E-mail : isegonzac@image7.fr
Tel. : +33 (0)1 53 70 74 70