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CREATING THE FUTURE: New Challenges in Biology and Medicine

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Boulogne-Billancourt

Under the High Patronage of

Mrs Roselyne **Bachelot-Narquin**
French Minister for Health, Youth, Sport and the Voluntary Sector

Mrs Valérie **Pécresse**
French Minister for Higher Education and Research

ABSTRACTS

MESSAGE FROM THE CHAIRMAN

Recent years have been marked by unprecedented growth and development in the life sciences in areas such as gene sequencing, protein interactions and molecular biology.

Research conducted during the last decade has resulted in important technological and conceptual advances, along with the development of treatments and early stage cures for diseases like cancer or neurodegenerative diseases.

The full sequencing of the human genome, and of a growing number of other living organisms, has heralded a new era in molecular biology and genetics for human medicine. Although these discoveries have opened an unprecedented path toward medical advances, they have also revealed that organic, physiological and genetic mechanisms are far more complex than initially believed.

I am therefore particularly honoured that such an impressive panel of scientists agreed to gather together at Ipsen's new corporate headquarters to lecture on the challenging and exciting perspectives of medical innovation.

Jean-Luc **Bélingard**,
Chairman and CEO of the Ipsen Group

Jean-Pierre **Changeux**
Chairperson

Professor at the *Collège de France* and the *Institut Pasteur*, he is a member of the French *Académie des Sciences*, the National Academy of Sciences US, the Institute of Medicine of the NAS. He discovered the allostery of proteins and isolated the nicotinic receptor of acetylcholine. Past president of the *Comité National d'Ethique*, he is the president of the *Commission des dations*, and the laureate of many scientific prizes: *médaille d'or du CNRS*, Balzan prize, Louis-Jeantet Prize, Biotechnology Study Center of the New York University school of Medicine award, Jean-Louis Signoret Prize of *la Fondation Ipsen*, the National Academy of Sciences award in neurociences (2007). He is also the author of several books including "*l'Homme neuronal*" and, recently, "*Du vrai, du beau, du bien. Une nouvelle approche neuronale*".

Nicole **Le Douarin**
Chairperson

Honorary professor at the *Collège de France, secrétaire perpétuelle* of the French *Académie des Sciences*, she is member of the National Academy of Sciences US, the Royal Society, the Pontifical Academy of Sciences. She received several awards including the *Médaille d'or du CNRS*. Her research area has been mainly on the development of neural crest cells using originally a Chicken-Quail chimera model she had developed. She wrote several books including "*Des chimères, des clones et des gènes*" and "*Les cellules souches porteuses d'immortalité*".

CAN WE WIN THE WAR ON CANCER?

J. Michael **Bishop**
University of California,
San Francisco

J. Michael Bishop is Chancellor, Arthur and Toni Rembe Rock Distinguished Professor, University Professor, and Director of the G.W. Hooper Research Foundation at the University of California, San Francisco. Soon after arriving in San Francisco in 1968, he shifted his attention to Rous sarcoma virus, hoping to explore the fundamental mechanisms of tumorigenesis. In 1970, he was joined by Dr. Harold Varmus. Together, they directed the research that led to the discovery of proto-oncogenes – normal genes that can be converted to cancer genes by genetic damage. This work eventually led to the recognition that all cancer probably arises from damage to normal genes, and has provided new strategies for the detection and treatment of cancer.
Drs. Bishop and Varmus have shared numerous awards for their work, including the 1989 Nobel Prize in Physiology or Medicine, and both have received the National Medal of Science.
Dr. Bishop has devoted his subsequent research to the study of proto-oncogenes – their functions in normal cells and their role in the genesis of cancer.
He is a member of the National Academy of Sciences, the Institute of Medicine, the American Academy of Arts & Sciences, the American Philosophical Society, and the Royal Society of London. He is the author of more than 300 research publications, and of the book "How to Win the Nobel Prize: An Unexpected Life in Science".

In 1971, the United States President Richard Nixon called for a concentrated research initiative to conquer cancer, which was soon dubbed the War on Cancer.
The Federal investment in cancer research rose dramatically and has been sustained throughout the ensuing decades. Yet thirty-seven years later, as deaths from cardiovascular disease are declining, cancer threatens to become the leading killer in developed nations. Some critics claim that we have literally lost the war on cancer, blaming the research community for failing to focus on curing the disease, instead indulging itself in molecular minutiae[1].
But these Cassandras have it all wrong. By achieving a molecular understanding of how cancer originates and why it often resists our best antidotes, we are poised to attack the disease in ways that could not have been imagined twenty years ago. We have reduced malignant behavior to a relatively limited number of phenotypic perturbations of the cell[2]. And we have uncovered the fundamental malady that underlies those perturbations - a disturbance of two sorts of genes: proto-oncogenes, which are accelerators in the cell; and tumor suppressor genes, which are brakes[3]. The many and varied causes of cancer all somehow lead to jamming the accelerators and disabling the brakes.
This fundamental simplification can now be applied to every aspect of the cancer problem, including: determination of cause; elucidation of genetic predisposition; early detection; stratification of disease; prediction of outcome; "magic bullet" therapies; personalization of therapy; and early prediction of therapeutic response. The prospects for success in most of these applications rest in large measure on remarkable advances in genomic science. Efforts are underway to create inventories of all the relevant genomic abnormalities in every form of human cancer[4]. And the discovery that the growth of cancers is probably fueled by outlaw stem cells has uncovered a previously unknown "tap root" of cancer, offering new hope of cures by targeting therapy to the outlaws[5]. We have not closed the book on cancer for all time, but we are turning the pages very rapidly. We can win the war on cancer: in the short term, with more effective therapies; and in the longer term, by interdicting the causes of cancer to prevent the disease[6].

References

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Jules **Hoffmann**

Institut de Biologie Moléculaire et Cellulaire, Strasbourg

J. Hoffmann is a Research Professor with CNRS at Strasbourg and currently the President of the French *Académie des Sciences*. He is also a Member of the National Academy of Sciences USA and of several European Academies and a recipient of the Cooley, Koch and Balzan Prices. He has devoted his scientific career to the study of innate immunity with Drosophila as a model system. J. Hoffmann and his colleagues are credited with the discovery of the role of Toll receptors in innate immune defenses and the deciphering of the signaling cascades activated during fungal, bacterial, viral and parasitic infections in model systems.

PHYLOGENETIC PERSPECTIVES OF INNATE IMMUNITY

Innate immunity is a first line defense mechanism against infections which is shared by all metazoans (and metaphyta). Adaptive immunity has appeared in the ancestors of cartilagenous fish, probably some 450 millions years ago, and contributes to the host defense solely in Vertebrates, which represent some 5 % of all existant animal species. In these species, innate immunity, in addition to its direct roles against microorganisms, activates and orients the adaptive responses. Studies in model organisms, such as Drosophila melanogaster, have led in recent years to a basic understanding of innate immunity in the absence of adaptive defenses. The receptors for bacterial and fungal cell wall components (essentially peptidoglycans and glucans) have been identified. Two prominent intracellular signaling cascades are activated downstream of these receptors: the Toll pathway during fungal and Gram-positive bacterial infections, and the immune deficiency (IMD) pathway during Gram-negative bacterial infection. These cascades act upon transcription factors of the NF-kappaB family which ultimately control the expression of hundreds of immune genes the products of which concur to fight off the infections.

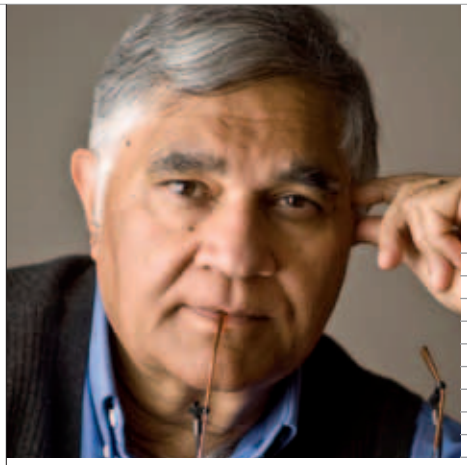
Genome sequencing has recently revealed that most of the players (genes) of the innate response of Drosophila are already present in as ancient animal forms as sponges and cnidaria, suggesting that the innate immune response as we now see it in Drosophila has appeared with multicellularity. Importantly, all the genes involved in the host defense of the fly, have homologues (or very similar counterparts) in the immune response of mammals: this is in particular the case for the Toll receptors initially discovered in flies.

NEUROENDOCRINE REGULATION: A VIEW FROM THE PORTAL

Iain C.A.F. **Robinson**
MRC, National Institute for Medical Research, London

After postgraduate training in Oxford and Denmark, Iain Robinson joined MRC's National Institute for Medical Research (NIMR) at Mill Hill, London, where he is Head of the Division of Molecular Neuroendocrinology, and Director of NIMR. He is a Visiting Professor at University College, London and Fellow of the Academy of Medical Sciences.
He has also worked in the pharmaceutical industry and co-founded a Biotech company.
His research interests are in development, growth and metabolism in health and disease.

The pituitary gland is the master regulator of the endocrine systems of the body, secreting hormones that regulate many important body functions such as growth and metabolism, reproduction and lactation, and responses to stress. The pituitary is itself controlled by specialized neurons in a region of the brain called the hypothalamus. These neuroendocrine neurons release their products into a "private" blood supply, the hypophysial portal system, which carries them from the brain to the pituitary gland. In this way, the brain controls our hormone systems to maintain normal homeostasis and to respond to changing demands throughout life. New developments in physiological transgenesis and imaging make it possible to view and manipulate neuroendocrine systems in living animals, looking both "up" and "down" this system. Looking towards the brain gives insights into the secretions and activities of these specialized neurons, how they act together to integrate signals from different regions of the brain and from the periphery, and to find out what their command outputs are, reaching their pituitary target cells, and beyond. Looking towards the pituitary reveals a complex organization of cell networks that respond to incoming signals by secreting their hormone products in coordinated patterns. The pituitary gland is remarkably plastic, with resident stem cells in the adult gland that can replenish all of the different cell types according to changing physiological demands. Thus the portal system carries neuroendocrine cascades of signals that amplify and convert small neuronal messages to large hormonal signals, coded in both frequency and amplitude of their sounds and silences, to which the rest of the body is listening.



Inder **Verma**

Laboratory of Genetics,
The Salk Institute,
La Jolla, California

Inder Verma, American Cancer Society Professor of Molecular Biology in the Laboratory of Genetics at The Salk Institute is one of the world's leading authorities on the development and use of engineered viruses for gene therapy. He received a master's degree from Lucknow University, India, and a PhD from The Weizmann Institute of Science in Rehovoth, Israel. Dr. Verma was elected to the National Academy of Sciences, American Academy of Arts and Sciences, and the American Philosophical Society.

GENE THERAPY: 25 YEARS OF UPS AND DOWNS

At the beginning of the third millennium, man has an opportunity to fulfill the cherished goal of improving the lot of humankind. Newer modalities of medicine are being practiced and daily new breakthroughs are being reported. I would like to talk about gene therapy, a form of molecular medicine, which will have a major impact on human health. At present, gene therapy is being contemplated for both genetic and acquired diseases. These include hemophilia, cystic fibrosis, diabetes, cancer, Parkinson's, Alzheimer's, etc. A prime requirement for successful gene therapy is the sustained expression of the therapeutic gene without any adverse effect on the recipient. A highly desirable delivery vehicle will be the one that can be generated at high amounts, integrate in non dividing cells and have little or no associated immune problems. We have generated third generation lentiviral vectors with expanded host range that can introduce genes in a variety of cells. Thus our current lentiviral vectors are devoid of six viral genes and therefore we consider them to be safe vectors. By using third generation lentiviral vectors we can introduce genes directly into brain, liver, muscle, hematopoietic stem cells, and more recently retina and a number of tumor cells. Our data shows that lentiviral vectors cannot only efficiently deliver genes, but also have long term sustained production of the foreign protein. We have not observed any untoward immunological consequences due to the vector.

My talk will discuss in detail the use of vectors for a wide variety of genetic and acquired diseases. Additionally I will discuss the use of lentiviral vectors for transgenesis, studying complex biological systems. I will also discuss the use in reprogramming somatic cells.

GENERATING BRAIN CELLS FROM STEM CELLS

Fred H. **Gage**
Laboratory of Genetics, The Salk Institute,
La Jolla, California

Fred H. Gage, Ph.D., a Professor in the Laboratory of Genetics, joined The Salk Institute in 1995. He received his Ph.D. in 1976 from The Johns Hopkins University. Dr. Gage's work concentrates on the adult central nervous system and unexpected plasticity and adaptability to environmental stimulation that remains throughout the life of all mammals. In addition, his studies focus on the cellular, molecular, as well as environmental influences that regulate neurogenesis in the adult brain and spinal cord.
Prior to joining Salk, Dr. Gage was a Professor of Neuroscience at the University of California, San Diego. He has won numerous prizes and awards for his work including *La Fondation Ipsen* Prize for Neuroplasticity and recently the Keio Medical Science Prize; serves on many health related boards, and was President of the Society for Neuroscience. He is a Fellow of the American Association for the Advancement of Science, a Member of the National Academy of Sciences and the Institute of Medicine, and a Member of the American Academy of Arts and Sciences.

Stem cells are loosely defined as self-renewing progenitor cells that can generate one or more specialized cell types.
In vertebrates, stem cells are traditionally sub-divided into two groups. The first group consists exclusively of embryonic stem (ES) cells. These cells, which are derived from the inner cell mass of the blastocyst, are capable of generating all differentiated cell types in the body. ES cells, in turn, generate the second group, which are organ- or tissue-specific stem cells. An example of this second group is the neural stem cell, which generates all of the cell types of the nervous system. In most organs, stem cells are present through adulthood, albeit in small numbers. In some organs, like the brain, these stem cells can be isolated from tissues, grown in culture, and then induced to differentiate, either *in vitro* or after transplantation *in vivo*. However, it is not clear whether ES cells or tissue- specific cells, other than in the hematopoetic system, can be transplanted clinically to replace diseased or damaged human cells.
It has long been believed that organ-specific stem cells are restricted to making the differentiated cell types of the tissue in which they reside. In other words, these cells have irreversibly lost the capacity to generate other cell types in the body. This concept of restriction has recently been challenged, opening up the possibility that tissue-specific cells might be reprogrammable.
I will report on efforts to understand the molecular and cellular bases of cell fate determination of ES cells and of tissue-specific stem cells; in addition, I will address the issue of reprogramming adult cells. I will draw from results in the nervous system to illustrate the progress being made to reveal how stem cell biology can be valuable to the understanding of fundamental issues of brain function as well as to the modeling of human neurological disease.

Eric R. **Kandel**

Columbia University,
New York

Eric R. Kandel, M.D., is University Professor at Columbia, Fred Kavli Professor and Director, Kavli Institute for Brain Science and a Senior Investigator at the Howard Hughes Medical Institute. A graduate of Harvard College and N.Y.U. School of Medicine, E. Kandel trained in Neurobiology at the NIH and in Psychiatry at Harvard Medical School. He joined the faculty of the College of Physicians and Surgeons at Columbia University in 1974 as the founding director of the Center for Neurobiology and Behavior. Recipient of many awards, including the 1983 Lasker Prize, the 2000 Nobel Prize, the National medal of Science, and the Jean-Louis Signoret Prize of *La Fondation Ipsen*, he is a member of the National Academy of Sciences USA and the French *Académie des Sciences*. He recently published his autobiography: "In search of memory".

Eric Kandel's research has been concerned with the molecular mechanisms of memory storage in *Aplysia* and mice. More recently, he has studied animal models in mice of memory disorders and mental illness.

ON THE PERSISTENCE OF MEMORY STORAGE

I will consider a general molecular mechanism, which emerged from studies of *Aplysia* and mice whereby a transient short-term memory is converted into a stable, self-maintained, long-term memory. I will then consider cellular mechanisms in the mouse whereby a long-term explicit memory for space is perpetuated by means of selective attention during acquisition.

Finally I will consider a novel molecular mechanism for self-sustaining perpetuation of memory storage.

CAN WE UNDERSTAND HUMAN CONSCIOUSNESS?

Stanislas **Dehaene**
Collège de France, Paris
INSERM-CEA Cognitive Neuroimaging Unit
Saclay

Stanislas Dehaene is professor at the *Collège de France*, where he holds the chair of Experimental Cognitive Psychology. He is the head of the INSERM-CEA Cognitive Neuroimaging Unit at NeuroSpin in Saclay, just south of Paris - France's advanced neuroimaging research center. His research investigates the neural bases of human cognitive functions such as reading, calculation and language, with a particular interest for the differences between conscious and non-conscious processing. He is a member of the French *Académie des Sciences* and of the Pontifical Academy of sciences and the author of several books, including: *La bosse des maths* and *Les neurones de la lecture*. Laureate of the Jean-Louis Signoret prize of *La Fondation Ipsen* and the Louis D. prize of the *Institut de France*, the Heineken prize for cognitive science.

For many years, consciousness was considered outside of scientific investigation. Around the 1980s, however, under the impulsion of Larry Weiskrantz, Tim Shallice, Michael Posner, Francis Crick, Christoph Koch, or Bernard Baars, the cognitive and neural architectures of consciousness became a prominent focus of experimental investigation. Building upon this work, Jean-Pierre Changeux and I proposed a simple framework, the global neuronal workspace, which predicted that considerable cerebral processing was possible under non-conscious conditions, but that conscious access would correspond to the non-linear ignition of a distributed network, dominating in prefrontal and parietal cortices, which serves to broadcast information and make it reportable.
I will present a series of experiments, performed with Laurent Cohen, Antoine Del Cul, Raphaël Gaillard and Lionel Naccache, that use masking to test the model. We created minimal contrasts between subliminal and conscious processing of visual stimuli, and tracked the ensuing brain activation using event-related potentials and intracranial recordings. Non-conscious processing was observed in multiple cortical areas within an early time-window, accompanied by induced gamma-band activity, but without coherent long-distance neural activity, suggesting a quickly dissipating feed-forward wave. By contrast, conscious processing of unmasked words was characterized by four simultaneous neurophysiological markers: sustained voltage changes, particularly in prefrontal cortex, large spectral power increases in the gamma band, increases in long-distance phase synchrony within the beta range, and increases in long-range Granger causality. We argue that all of these measures provide distinct windows into the same "ignited" state of conscious processing. This knowledge is now being applied to the monitoring of non-conscious integrity and conscious states in non-communicating patients.

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