FONDATION LOUIS-JEANTET

25 years Jubilee Symposium
Geneva, October 7 - 9, 2008

ABSTRACTS OF THE CONFERENCES

OPENING CONFERENCE

Rolf M. ZINKERNAGEL *(Institut für Experimentelle Immunologie, Zürich)*

On medicine and science

For 25 years, the Louis-Jeantet Foundation has supported excellence in medical science in Europe and awarded prizes to an impressive group of laureates and projects including this year's two prize-winners.

Over these years, methods have improved enormously and we can measure almost everything. The more difficult question however is whether what we measure is important. Here medicine plays a key role because disease and death are important pathophysiological markers that tell us when something is worthwhile studying. Of course, should we one day know all the molecular details, then so called "systems biology" may become reality, i.e. the hope to be able to use all accumulated knowledge to explain structure, function, disease and death. One example illustrating this is the question about the role of maternal antibodies transferred to the offspring in serum and milk. Maternal antibodies attenuate epidemiologically important and acutely lethal infections to a low level, so that offspring survive the infection and get actively immunized. Therefore, the success of vaccines against childhood infection reflects host-parasite co-evolution. In contrast, chronic persistent infections by herpes viruses, tuberculosis, malaria or HIV cannot so far be controlled by vaccines. These infections kill the host slowly within 20 - 40 years of life and therefore exert little evolutionary pressure on the human species. Because their variability and persistence cannot (yet?) be imitated by vaccines, control of these infections must be performed via antibiotics, antivirals, vector control and prevention. These examples show that theoretical knowledge and research is best combined with medicine and should include evolutionary considerations. Therefore science is crucial for medicine and medicine is essential for science.

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HOST-PATHOGEN AND IMMUNITY: A TRIPARTITE ADVENTURE

PHILIPPE J. SANSONETTI *(Institut Pasteur, Paris)*

Bacterial pathogens: tool box to tinker the immune system, suggestion box to understand the immune system

Beyond the generic innate immune response elicited in tissues by infecting pathogens upon host perception of their prokaryotic-specific motifs (i.e. LPS lipoproteins, flagellin, peptidoglycan) by specific sensors (i.e. TLRs, NLRs, C-type lectins), it clearly appears that these pathogens have often evolved elegant strategies to subvert this response. Upon long co-evolution with their hosts, they have accumulated genes encoding effectors capable to hit straight at the heart of signalling cascades that are essential to elicit both innate and adaptive responses, thereby reaching a compromise that may be beneficial for both "partners". By collaboratively studying these regulatory mechanisms, and by letting bacteria "educate" them through their efforts to decipher these strategies, microbiologists and immunologists can hope to unravel new paradigms and to capitalize on them to foster the development of novel control strategies.

JULES A. HOFFMANN *(Institut de Biologie Moléculaire et Cellulaire, Strasbourg)*

The antimicrobial host defence of *Drosophila*: a paradigm for innate immunity

The fruitfly *Drosophila* mounts a potent defence reaction during fungal, bacterial and viral infections. We have investigated this defence and have asked three types of questions: (1) how does *Drosophila* recognize the invading micro-organisms; (2) how does recognition lead to activation of intracellular signalling cascades and gene reprogramming; (3) which effector molecules are produced to oppose the micro-organisms. Our results point to a sophisticated defence mechanism which is based on several circulating, transmembrane or cytosolic receptors of microbial ligands. Bound receptors trigger several distinct signalling cascades which culminate in the activation of NF-kB family members, which in turn control the expression of hundreds of immune-response genes, some of which have potent antimicrobial activities. Stringent parallels with innate immune mechanisms of mammals point to a common ancestry of this defence and will be discussed in the presentation.

WOLFGANG BAUMEISTER *(Max-Planck-Institut für Biochemie, Martinsried)*

From words to literature in structural biology

With the advent of computer-controlled electron microscopes and the automation of data acquisition, it became possible to obtain molecular-resolution tomograms of structures as large as whole cells. Noninvasive three-dimensional (3-D) imaging of vitrified cells is where cryoelectron tomography promises to make unique contributions by closing the gap between the cellular and the molecular worlds. Tomograms of cells at molecular resolution are essentially 3-D images of the cell's entire proteome, and they reveal the spatial relationships of macromolecules in the cytoplasm, the "interactome". To exploit the imposing amount of information contained in a cellular tomogram, pattern recognition techniques must be used that are capable of detecting and identifying molecules in tomograms with a low signal-to-noise ratio through their structural signature.

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CARDIOVASCULAR AND METABOLISM: WHEN METABOLIC ALTERATIONS MEET CARDIOVASCULAR DISORDERS

C. RONALD KAHN *(Joslin Diabetes Center, Harvard Medical School, Boston)*

Central role of insulin resistance in cardiovascular disease and the metabolic syndrome

The metabolic syndrome includes obesity, glucose intolerance, abnormalities in lipid metabolism, hypertension, hepatic steatosis and gallstones. The incidence of the metabolic syndrome and its various components is rising at epidemic rates. Using genetic and acquired animal models, we show that insulin resistance is central to the pathophysiology of the metabolic syndrome. For example, a mouse with pure hepatic insulin resistance created by knockout of the insulin receptor in liver develops hyperglycemia due to increased hepatic glucose output and a dyslipidemia characterized by low HDL cholesterol, small dense LDL cholesterol, and marked sensitivity to diet induced hypercholesterolemia with severe atherosclerosis. Insulin resistance in other tissues, like the beta cell and brain, also contribute to the syndrome, with decreased insulin secretion, increased appetite leading to obesity, and other disorders. Thus, insulin resistance is sufficient to produce most of the features of the metabolic syndrome and serves as the best site for therapy of this disorder.

HELEN H. HOBBS *(McDermott Center for Human Growth & Development, Dallas)*

Rare mutations in complex diseases: not so rare and not so complex

Helen H. Hobbs and Jonathan C. Cohen. Howard Hughes Medical Institute, University of Texas Southwestern Medical Center, Dallas

Coronary atherosclerosis is a complex disease that results from multiple factors, both genetic and non genetic. We have taken a variety of approaches to test the hypothesis that rare sequence variations cumulatively contribute to complex traits and diseases in the general population. We have found rare and low frequency DNA sequence variations that impact on multiple traits that confer susceptibility (and resistance) to coronary atherosclerosis, including plasma levels of HDL-cholesterol, LDL-cholesterol and triglycerides. Such sequence variations provide a particularly powerful handle with which to dissect the relationships between genes, risk factors, and disease.

RICHARD P. LIFTON *(Yale University School of Medicine, New Haven)*

Genes, genomes and the future of cardiovascular diseases

Hypertension affects 1 billion people and is a major risk factor for stroke, myocardial infarction, congestive heart failure and kidney failure. By investigation of families with extreme forms of high or low blood pressure we have identified mutations in 10 genes that cause very high blood pressure and 10 that cause life-threatening low blood pressure. Most interestingly, the genes at both ends of the distribution are involved in renal salt handling - mutations that increase net renal salt re-absorption raise blood pressure, while those that reduce salt re-absorption lower blood pressure. Investigations of these same genes in the general population have shown that rare mutations have substantial effect on blood pressure and that these collectively are present in at least 2% of the population. Finally, these studies have identified a novel family of protein kinases, the WNK kinases, that are involved in regulating the balance between salt re-absorption and potassium secretion. These findings support early combination therapies that target the salt handling pathway and secondary compensatory mechanisms, and identify new therapeutic targets likely to be of high efficacy.

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NEUROSCIENCE: FROM PATCH CLAMP TO COGNITIVE FUNCTIONS

BERT SAKMANN *(Max-Planck-Institut für Neurobiologie, Martinsried)*

Neurophysiology of decision making in the rodent brain

Decision making relies on sensory input, comparison with previous experience and motor action. A simple rodent behaviour is reward driven gap crossing. It can rely on the sensory input from a single vibrissa and exciting a single column in the barrel cortex. The major output emitted by a single column is by the thick-tufted pyramids in the infragranular layer that project to the pons. Possibly these pyramids establish the link between sensory input and motor action.

THOMAS J. JENTSCH *(Max-Delbrück-Centrum für Molekulare Medizin, Berlin)*

Acid and chloride in endosomes and lysosomes: surprising insights from sick mice and men, and from biophysics

Several CLC chloride transport proteins reside in membranes of endosomes and lysosomes. They are thought to facilitate their luminal acidification by neutralizing currents of the electrogenic proton pump. Loss-of-function mutations of vesicular CLC genes lead to diseases like kidney stones, osteopetrosis, and lysosomal storage disease in both men and mice. Whereas all CLC proteins were thought to be chloride channels like the founding member ClC-0 from the electric fish Torpedo, it is now clear that several, if not all vesicular CLCs are chloride/proton exchangers. These surprising new findings point to a previously unsuspected role of chloride in endosomes/lysosomes.

RIITTA HARI *(Helsinki University of Technology, Espoo)*

Do we need two-person neuroscience?

We are born into a social world constructed and interpreted by others. During our whole life, we interact with other people, constantly trying to figure out their intentions and actions. In this lecture I will argue that to properly study the social shaping of the human brain (and mind), we should progress from one-person neuroscience to two-person neuroscience. A great challenge is to build a new conceptual framework that incorporates neuroscience, psychophysiology, and social sciences. Novel methods are needed for online and time-synchronized monitoring of two individuals during real-life-like social interaction. To appreciate the bridge between brain and body, both brain signals and autonomic nervous activity should be recorded from the interacting partners.

The two-person neuroscience will have applications in characterizing and treating disorders of social interaction, as well as in monitoring and improving master-apprentice and patient-therapist relationships. It can also contribute to old philosophical questions, such as intersubjective understanding.

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PAUL NURSE *(The Rockefeller University, New York)*

Controlling the cell cycle

The growth and reproduction of all living organisms are dependent on the cell cycle, the process which leads to cell division. Uncontrolled division of cells is important for disease particularly cancer. Two events, S-phase and mitosis, are common to all cell cycles and are necessary for the two newly divided cells to receive a full complement of genes. The onset of S-phase and mitosis are controlled by cyclin dependent kinases in all eukaryotes studied from yeast to human beings. Checkpoints controls working through the CDKs block cell cycle progression if cells are too small or DNA incompletely replicated.