Laudatio for Alain Fischer
by Prof. Dr. Jules A. Hoffmann
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Alain Fischer, MD and PhD, is the Director of the Research Institute of Genetic Diseases at the Necker Hospital in Paris. He is a Professor of the Paris Descartes University and has recently been elected to a Professorship at the prestigious Collège de France, also in Paris. An author of more than 600 papers in mostly prestigious journals, Professor Fischer has received many scientific awards (such as the Louis-Jeantet Prize for medicine). He has been elected to several national and international Academies and serves on many high profile Advisory or Editorial Boards.

Professor Fischer's main areas of research are the development of the lymphoid system, primary immunodeficiencies, the genetics of immunological disorders and most importantly in recent years, gene therapy.

Alain Fischer's interests initially focused on characterizing a series of primary immunodeficiencies in children who were directed to his hospital from various institutions in France and other countries. There exists a relatively large series of rare, or even exceptional, diseases in which the immune system is altered, leading to vulnerability to some infections, to autoimmune conditions, to autoinflammatory symptoms, to allergies and sometimes to cancer. It is estimated that this type of pathology affects 1 individual in 5000 in human populations and up to 250 distinct types of pathologies have been described in the field. The underlying cause in most of these conditions has been pinned down to a unique event, that is, to a single mutation in a gene leading to a loss of function of the encoded protein (more rarely to a gain of function).

In groundbreaking studies over the last 25 years, Fischer and colleagues have identified some 30 unique genetic defects each of which accounts for an immunodeficiency phenotype in these children. These studies have significantly contributed to unravelling the cellular and molecular basis of the corresponding immune pathologies and shed important light on immune pathways. To quote but a few examples, the studies have illustrated the roles of two defined genes in the development of T and B lymphocytes, of several other genes in the activation and proliferation of both types of lymphocytes, of still others in the control of

immunoglobulin class switching. Significantly also, these studies have unraveled novel genes which play a role in the control of autoimmunity and inflammation.

After defining the molecular parameters associated with these immune-deficient conditions, Alain Fischer and his associates have oriented their efforts to reverse or eliminate the molecular defects.
The Fischer group presently focusses on the therapeutic correction of hereditary combined severe X-linked deficiencies as a disease model .The strategy consists of injecting hematopoietic progenitors transfected with a modified virus carrying a functional copy of the gene affected by a mutation in the recipient. The viruses have been further modified to integrate into the recipient genome resulting in replication of the corrected copy at every cell division.

The first trial was performed more than 15 years ago, providing the first evidence that an inherited disease can be corrected by gene therapy. Although results are sustained over time, usage the first generation of vector led to insertional mutagenesis. Therefore, safer vectors were designed and transferred to the clinic. The new trials, that involve an international collaboration with scientists in Boston and London, have now provided extremely encouraging results, establishing both the safety of the procedure and the correction of the immune deficit. This remarkable progress in tightly-controlled gene therapy is at present being extended to larger numbers of patients and to other forms of immune deficiencies and inherited disorders. Although the viral vector strategy appears to be validated in these pioneering experiments, Alain Fischer and his associates are exploring the potentials of replacing the mutated gene of a given immunodeficient patient by the in situ correction of the mutation through homologous recombination.

Alain Fischer is one of the world leaders in the field of primary immunodeficiencies through the characterization of the genetic defects underlying many of these diseases. Most remarkably, he has spearheaded successful attempts to cure such deficiencies by gene therapy. He and his colleagues and associates have provided the first proof of concept of gene therapy of inborn errors in human patients, an outstanding example of a progression from basic research to clinical applications in life-threatening diseases.