Acceptance Speech by Alain Fischer
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[Address]
I am deeply honoured by the award of this prestigious prize from the Robert Koch Foundation, together with my close colleague Jean-Laurent Casanova. This award comes as recognition of the work performed by a fantastic group of talented scientists and physicians with whom I have had the good fortune to interact on a daily basis for over 35 years now. Thank you, Professor Hoffmann, for your subtle, kind and somewhat embellished presentation of my career.

In the 1880s, Robert Koch and Louis Pasteur were engaged in a fierce bout of German-French rivalry, with roots in violent nationalism. Koch and Pasteur are the heroes of the germ theory, from which the modern fields of microbiology, immunology and infectious disease have all emerged. I am inclined to think that their achievements are unrelated to the antagonism that was prevailing at that time. Fortunately, 130 years later (and for 70 years now), Germany and France have become peaceful neighbours and, more importantly, key components of the European community that we (as scientists and citizens) wish to see taking a preponderant role in the future of our continent.

As a medical student in the early 1970s, I had the good fortune to meet Claude Griscelli, a paediatrician who had trained in immunology with Maxime Seligmann and Baruch Benacerraf. At that time, Claude was creating a small clinical unit at Necker Children's Hospital in Paris, in order to care for patients suffering from primary immunodeficiencies (PIDs). This was also the time when Robert Good in Minneapolis identified some of first phenotypes of inherited immune defects (such as chronic granulomatous disease, CGD) and also successfully transplanted (in 1968) bone marrow cells from a healthy donor to a young child with severe combined immunodeficiency – the first ever successful allogeneic hematopoietic stem cell transplantation. I became conscious that we knew very little about those conditions but that ongoing developments in immunology could provide concepts and tools to help characterize these PIDS and improve patient care. Accordingly, I went to London to work with Marc Feldmann and Peter Beverley, who gave me the opportunity to learn basics of immunology and to perform research on human T-B cell interactions.

What has since happened in the field has gone far beyond my expectations because advances in molecular biology and genomics have made it possible to identify the primary genetic causes of monogenic PIDS. A flurry of genes was identified: for example, Kunkel and
Segal independently discovered in the 1980s that the CYBB gene is mutated in the X-linked form of CGD. It then became possible not only to understand disease mechanisms, provide an accurate diagnosis but also to characterize key elements of the innate and adaptive immune system in view of their roles in PIDs. Furthermore, the study of PIDs showed how effector mechanisms in humans were involved in immunity against microorganisms and how regulatory pathways controlled self-reactivity in vivo. The dean of my faculty repeatedly told me that my clinical unit was like an animal house for knock-out mice! Well, that is something of an overstatement but it is not entirely wrong!

Most of our contributions have concerned the adaptive immune system. By studying a cohort of patients suffering from a form of severe combined immunodeficiency, Jean-Pierre de Villartay identified two components of the non-homologous end-joining repair pathway that are absolutely required in rearrangements of T cell and B cell antigen receptor genes. In collaboration with Tasuku Honjo (who was awarded the Robert Koch Prize in 2012), Anne Durandy discovered that activation-induced deaminase (AID) was the long-sought-after mutator that triggered the process of Ig class switch recombination and somatic mutation of the variable section of Ig genes. By studying a rare, inherited immunopathological condition (dreadfully named "hemophagocytic lymphohistiocytosis" in the 1950s), Geneviève de Saint Basile discovered key components of the exocytic machinery of cytotoxic secretory granules. We were quite surprised to see that this process mimics the molecular machinery that mediates the exocytosis of neurotransmitters at synapses, as was so elegantly described by the 2013 Nobel prize winners James E. Rothman, Randy Shekman and Thomas Sudhof. Frédéric Rieux-Laucat showed that inherited lymphoproliferation and auto-immunity in humans can emerge from failures of the FAS-mediated apoptotic pathway. He also showed that somatic mutations of the same gene have the same consequences, giving birth to a somatic gene theory of auto-immunity as also proposed by Chris Goodnow in Canberra.

These genetic studies also paved the way to new gene-based therapeutics. This had been in the air since the early 1970s, since pioneers like Ted Friedmann and others who had unravelled the biology of retroviruses. Once we had found that somatic revertant mutations causing a particular form of severe combined immunodeficiency (γc deficiency) generated multiple T cells and hence an attenuated disease phenotype, we reasoned that this “natural gene therapy” could be engineered appropriately to correct the T cell immunodeficiency phenotype. With Marina Cavazzana and Salima Hacein-Bey-Abina, clinical development was set up; the results indicated that the hypothesis was indeed correct, with sustained clinical benefit for over 15 years. However, 15 years ago, it was not anticipated that the use of gamma retroviruses would be associated with a high risk of insertional mutagenesis.
Progress by several groups over the last 10 years (notably those led by Christopher Baum and Luigi Naldini) has enabled the development of safer vectors that are now being successfully used to treat several immunodeficiencies, from severe combined immunodeficiencies to the Wiskott Aldrich syndrome and beyond. The range of medical applications is broadening progressively. Interestingly enough, research on transduced, marked T lymphocytes from treated patients is today generating surrogate information on the dynamics of lymphocyte populations.

Overall, these results confirm that (at least in the field of PID) the bench-to-bedside approach to medicine also works in the other direction - thus creating a kind of circular path or, to be more exact, a helical path to progress. This required an adaptation of organizational structure; despite the many criticisms of our system I can formulate, I have to say that this work was achievable in the setting of a Parisian university hospital. It has culminated in the foundation of the Imagine Institute, a research institute dedicated to genetic diseases.

I could not end this speech without mentioning the deep commitment of patients and families to this research. Over the years, they have demonstrated their enthusiasm, generosity, support and courage while participating in and promoting research on PIDs. We must not forget that patients are at the start of our journey and at the end. Lastly, I wish to thank my family for their constant support – even when I have not been physically or consciously present!