Acceptance Speech by Antonio Lanzavecchia

I am deeply honoured and humbled by receiving this prestigious prize from the Robert Koch Foundation and I am especially happy to share it with my friend and colleague Rafi Ahmed. When I trained in infectious diseases at the University of Pavia, I never dreamed that I would be standing here at this ceremony, which honours the legacy of one of the Founders of this field. This award recognizes the work performed over many years with a fantastic group of talented scientists with whom I have had the opportunity to interact.

There are many to acknowledge and thank, in particular those who fostered the start of my career, Franco Celada who offered me my first laboratory bench in Genova as well as advice for my transition from the clinic to basic research and Fritz Melchers who offered me the possibility to work at the Basel Institute on a project focusing on human immunology. I remember that there was not a general consensus around this concept and Fritz asked me to explain why I wanted to study the immune system in humans. This was indeed the title of my promotion seminar at the Basel Institute, which luckily was successful. This experience has taught me the importance to give freedom and space to young fellows that want to pursue their own ideas.

I started to work with cells with the notion that looking at lymphocyte behaviour in vitro might illuminate on certain aspects of their function in vivo. I was looking at T cells growing in culture very much like Robert Koch was looking at bacteria growing in hanging-drops. The three main components of the immune system, T cells, B cells and antigen-presenting cells, can be easily obtained from blood and I quickly found ways to isolate clones of antigen-specific T and B cells in order to study their function. This reductionist approach eventually paid off and I was able to address specific questions.

I was interested to understand the link between T cell specificity and function, which at the time was still debated. Based on in vitro experiments, I concluded that the enigmatic T cell receptor was required for triggering, but not for delivering the effector function, be it help or cytotoxicity. The same approach was used to dissect the mechanisms that underline T-B cognate interaction, namely the efficient capture and internalization of antigen by B cells through membrane immunoglobulins, followed by processing and presentation to antigen-specific T cells. Other in vitro studies dealt with the mechanisms of antigen capture, the identification of universally immunogenic peptides and the role of HLA molecules as disposable receptors for peptides.

The in vitro cell culture approach worked well and was facilitated by the fact that human cells are easier to culture than mouse cells (or perhaps mouse immunologists paid less attention to in vitro cultures). For instance, in the early Nineties, it was clear that the dendritic cells discovered by Ralph Steinman were essential for initiating T cell responses, but the difficulty of obtaining these cells in their resting, so-called “immature” state was the bottleneck to study their physiology. We discovered that large numbers of immature dendritic cells could be generated by culturing human monocytes with GM-CSF and IL-4. Using this method, we were finally able to study the mechanisms of antigen uptake and presentation by dendritic cells and to identify the microbial and endogenous stimuli that trigger their maturation into the most potent immune-stimulatory cells. The method contributed in the Nineties to the explosion of research on dendritic cells and to the understanding of how these cells link innate and adaptive immunity.

The possibility to work with well-controlled cellular systems was also instrumental to investigate the mechanisms of TCR engagement and revealed for the first time the role of cytoskeleton-driven motility in T cell activation. Using the cell-based approach we could demonstrate that signalling at the immunological synapse is sustained by a TCR serial triggering mechanism and that costimulatory molecules act as signal amplifiers impacting on T cell activation and differentiation. At the time, I was so satisfied by these results that I decided to drop this line of research (another reason was that the field was moving into a highly sophisticated imaging analysis that were outside my reach).

At the end of the nineties the reductionist approach of cellular immunology fell short following development of powerful methods to study T and B cell development using receptor transgenic mice (as pioneered by Harald von Boehmer and David Nemazee at the Basel Institute) and of methods to conditionally alter gene expression in mice (developed by Klaus Rajewsky in Cologne). It was time to explore another aspect where the human immune system offers a great advantage: the cellular basis of immunological memory.

With my colleague Federica Sallusto, we started to dissect the phenotype, specificity and function of human memory T cells and came to the conclusion that there are two main functional subsets: central memory T cells characterized by lymph-node homing receptors, limited effector function but high proliferative capacity and effector memory T cells characterized by tissue homing capacity, immediate effector function but limited proliferative capacity. In the same study, we showed that central memory cells are differentiation intermediates, while effector memory represent terminally differentiated cells. This functional division is also evident in the B cell system, where the long-lived plasma cells first described

in the mouse by Andreas Radbruch and Rafi Ahmed represent the terminally differentiated cells.

In 2000, it became inevitable to leave the comfortable environment of the Basel Institute to move to a new institute in the Italian speaking part of Switzerland, the Institute for Research in Biomedicine in Bellinzona. Just after arriving in Bellinzona, I draw again my attention to B cells. By revisiting experiments done in the Eighties, we defined in more details the requirements for the activation of human naïve and memory B cells and the role of Toll like receptors. This work led us to the development of robust methods to immortalize human memory B cells and to preserve single plasma cells in culture. With this toolkit, we were finally able to isolate human monoclonal antibodies with an efficiency ranging from 30 to 100%. At this point my research took a new turn and from cells became totally focused on antibody molecules.

The use of antibodies for passive vaccination (or serotherapy) is one of the great contributions of German science to human health for which Emil von Behring received the first Nobel prize for Medicine and Physiology in 1901. However, it is fair to say that this approach was essentially lost in translation. For tetanus and diphtheria toxins we still use horse antisera that have well-known side effects and we have only one chimeric monoclonal antibody approved for prevention of RSV in premature newborns. One reason for this loss of translation was that methods available at the time, namely mouse monoclonal antibodies and display libraries, while effective for the isolation of antibodies to human antigens, were much less suited for anti-bacterial antibodies.

In the early 2000 Michel Nussenzweig (who received the Robert Koch award in 2016) developed a method to isolate single antigen-specific B cells with an antigen bait and rapidly clone the antibody genes to produce recombinant antibodies, a method that represented a real breakthrough in the HIV field. To develop a universal method that could be applied to any antigen we decided to take a different approach (that I will call “target-agnostic”) which consists in the direct screening, with a variety of assays including neutralization, the antibodies produced by immortalized memory B cells or plasma cells. Using these high-throughput cellular screens, we were able to rapidly isolate a plethora of potent neutralizing antibodies against emerging pathogens such as SARS and MERS coronaviruses, Rabies and Ebola virus. Using the same method, we isolated antibodies with unusual breadth, such as an antibody that neutralizes all influenza A viruses, and even an antibody that neutralizes 4 different paramyxoviruses. The target agnostic approach was particularly useful to find the “Achilles’ heel” of complex pathogens. In the case of human cytomegalovirus, we found that

the most potent neutralizing antibodies bind to a pentameric complex of viral proteins and showed that a recombinant pentamer vaccine can induce, in an animal model, neutralizing antibody titres at least 100-fold higher that those found after natural infection. There is growing hope that the new wave of potent and broadly neutralizing antibodies, together with the improved methods of antibody manufacturing, will finally reduce to practice after more than a century the great intuition of Behring and Kitasato.

Beyond the translational studies that I just mentioned, the B cell immortalization method was useful to address fundamental questions, such as the role of somatic mutations in affinity maturation and antibody diversification. By reconstructing the genealogy trees of antigen-specific B cell clones, we found that in most instances affinity maturation develops rapidly, through just a few mutations, but continuous redundant mutations accumulate leading to an extensive intraclonal diversification which was instrumental for the generation and selection of antibodies with broader reactivity to related viruses. The flip side of this process is the generation of certain autoantibodies.

Besides the useful antibodies and the basic insight into antigen driven selection, the target-agnostic approach brought us a very surprising finding. While studying the antibody response to plasmodium-infected erythrocytes we found a new type of antibodies that are generated by insertion of non-VDJ sequences in immunoglobulin genes. In approximately 10% of malaria infected individuals the insertion of a LAIR1 exon derived from chromosome 19 in the V-DJ junction or in the switch region generates clones of antibody producing B cells that display a mutated LAIR1 domain on the tip of the CDR3 or in the elbow between the VH and CH1 domains. I am sure that you realize how this mechanism resembles the Paul Ehrlich's side chain model of antibody production.

Looking back on almost 40 years, I realize that the choice to study the human immune system took me through a long trip that touched all aspects of adaptive immunity. This trip has also taken me from the comfort of hypothesis-driven research to the excitement of discovery-based research and has increased my motivation to find new ways to realize the full potential of vaccines and antibodies. This takes us back to the origin of our discipline, when scientists like Robert Koch found their drive in the need to fight infectious diseases.

In closing I would like to thank all the past and present members of my laboratory, my colleagues in Basel and Bellinzona, and the Robert Koch Foundation for this prestigious prize.