Laudatory speech for Jeffrey Ravetch

[Check against delivery.]

Jeffrey Ravetch, a native from New York, trained as an undergraduate in molecular biophysics and biochemistry at Yale University where in 1973 he got his bachelor of sciences centered on thermodynamic and kinetic properties of synthetic oligonucleotides. He then left for the MD/PhD joined program of the Rockefeller University/Cornell Medical School and defended his PhD thesis in 1978 on the genetics of virus replication and gene expression for single stranded bacteriophage. One year later, he earned his MD from Cornell University Medical School. After this initiation into state-of-the-art molecular genetics in the best imagineable scientific environment, J.Ravetch was accepted in the laboratory of Phil Leder at the Department of Genetics of Harvard University. Leder, a Lasker award winner who initially had worked with Marshall Nirenberg on the genetic code and the genetic basis of protein production, conducted at that time pioneering studies in mouse models of cancer. He was also one of the pioneers in the studies on antibody diversity and the underlying mechanisms leading to this diversity.

We can easily imagine how exciting this breakthrough period was in the biomedical field and the myriads of possibilities which all of sudden opened for research. It was fully understood at that time that antibodies consisted of a variable antigen binding region, referred to as Fab, and a constant region, called Fc (F standing for fragment). Whereas most laboratories were focusing on the structures and roles of the highly variable Fab fragment as the basis of the immune repertoire of antigen recognition modules, relatively few studies centered on the invariant Fc domain which interacts with the cell surface on many immune cells. Jeff Ravetch made the courageous decision to address the central question of how antibodies mediate diverse effector activities through an invariant Fc domain. During the following years, first at the Memorial Sloan Kettering Cancer Center and the Cornell Medical College and, after 1996 at the Rockefeller University, Jeff made rapid and considerable progress. He defined a family of cell surface receptors that bind the IgG antibody through its Fc domain. These receptors were hence forward referred to as Fc receptors and in the case of binding IgG, FcγR. These receptors were predominantly expressed on immune cells. Through knock out experiments in mice, Ravetch and associates then showed that this binding selectively mediated activation, respectively inhibition signals. Their studies demonstrated that activation of Fc receptors was necessary and sufficient to mediate pro-inflammatory activity of pathogenic antibodies in autoimmune diseases, and that tolerance to self antigens was under the genetic control of the inhibitory Fc receptor on B lymphocytes. The studies also revealed that the therapeutic activity

of anti-tumor antibodies was mediated by the Fc receptors and that in vivo, antibody protection from microbes, such as flu or HIV, required FcR engagement.
As Jeff Ravetch concluded from these and a plethora of other experiments, « the dogma that antibodies mediated their in vivo pro-inflammatory activity by the classical pathway of complement activation was thus challenged by this discovery that these reactions were dependent on Fc receptors and independent of the complement cascade ». The studies of Ravetch and associates thus established a novel pathway for the effector activity of antibodies that applied to inflammatory responses as well as to the classical neutralizing antibodies for bacterial toxins and viruses.

Another hallmark of the Ravetch laboratory was the demonstration that the Fc domains are structurally diverse resulting from both amino acid and glycan heterogeneity, which translates into functional diversity through the ability to engage disparate types of Fc receptors. The important and totally novel conclusions of these studies is that for any variable region of an antibody, many hundreds of discrete Fc domains can be associated, thus translating the specificity of the variable region of the antibody into distinct effector pathways through different Fc receptors.

The studies of Ravetch and his associates represent a paradigm shift in the way we view antibodies. In particular, the discovery of the functional diversification of antibodies based on the modulation of the Fc structure and its coupled effector pathways has opened new and multiple possibilities in therapy against autoimmune diseases and for cancer immunotherapy.

Jeff Ravetch is considered as one of the central players in modern immunology, both in the field of basic research and more recently in clinical immunology. He has been distinguished by several prominent prices, namely by the William Coley Award of the Cancer Research Institute in New York in 2007, the Sanofi-Pasteur Award for Biomedical Sciences in Paris in 2012, the Gairdner International Award for Medical Sciences in Toronto, Canada, in 2012, and most recently by the Wolf Price in Medicine in Israel. He is a member of many prestigious Academies, namely of the US National Academy of Sciences and of the National Academy of Medicine. He is also a member of the American Academy of Arts and Sciences.

I will finish on a personal note in this austere scientific setting : of all the scientists whom I have had the privilege to come to know, Jeff Ravetch is the finest gastronomist and is a friend to many distinguished Chefs of 3-star restaurants, namely, although not exclusively in France, and particularly in Paris and in Alsace.