Acceptance Speech by Jeffrey V. Ravetch
[Check against delivery.]

Since the description of the first antibodies, anti-toxins to diphtheria and tetanus, by von Behring and Kitasato in 1890, these remarkable molecules have preoccupied generations of immunologists and microbiologists and have resulted in fundamental advances in basic and applied research. Among the scientific breakthroughs that emerged from the characterization of antibodies were the discovery of mechanisms of somatic diversification, technologies for the development of monoclonal antibodies and the application of antibody therapy to the treatment of infectious, neoplastic and inflammatory diseases. The fundamental questions of how antibodies can mediate this dizzying array of functions rightly focused on the essentially unlimited capacity of antibodies to recognize their targets, elegantly elucidated by the three dimensional structure of the antibody in which recognition is mediated through the variable, antigen binding (Fab) domain and effector activity through the conserved, Fc domain.

It was my good fortune to be working in Phil Leder's laboratory in the late 1970s when these biochemical and genetic advances were being made, contributing as a fellow to the story of somatic recombination and class switching. It was a time when every experiment seemed to reveal something unexpected and the pace of the work was dizzying. Moving back to NY to set up my own lab in 1982 I made the decision to continue working on antibodies and to focus on the Fc region of the antibody and, in particular, to a class of molecules that bound to the Fc, the Fc receptors.

Why the Fc and Fc receptors? Progress in elucidating the effector pathways involved in antibody function began in the late 19th century with the work of Bordet and then Ehrlich who identified the complement proteins, so named because they complemented the ability of anti-toxins to mediate bacteriocidal activity. The classical complement pathway, which is activated by complexes of antibodies and antigens, dominated thinking about antibody effector paradigms, and appeared to answer the question of how antibodies interacted with and directed the cellular immune response. It would appear that the problem had been solved.

The first indication that alternative effector pathways might exist was the discovery by Berken and Benacerraf in 1965 that macrophages could bind to the Fc region of IgG. Biochemical studies in the ensuing decades suggested that Fc receptors were ubiquitously expressed on cells of the immune system, and could both inhibit or stimulate immune cell responses by their crosslinking.

How and if they contributed to the mechanisms by which antibodies mediated their activity in vivo was unknown when we started our studies in 1982.

We set out to define the molecules that we now recognize as the family of Fc receptors for IgG by cloning the genes for these receptors, adding new members to the growing family of molecules that shared Fc binding activity as we went along. Using gene knockout technology we demonstrated that Fc receptors, and not the complement components, were responsible for the in vivo effector activity of IgGs, both as pathogenic triggers of inflammation and protective mediators of pathogen clearance and anti-tumor responses. We demonstrated that the therapeutic activity of anti-tumor antibodies, first introduced in 2000, resulted from Fc receptor engagement and that antibody mediated protection from microbial pathogens, such as flu, HIV, ebola and anthrax required FcR engagement for their full in vivo potency. All of these studies highlighted what might seem obvious today - that both ends of the antibody are critical to its in vivo function and coupling to Fc receptors was a critical aspect of the biological function of the antibody in vivo. Engineering of the Fc domain to selectively enhance Fc receptor engagement is now a routine aspect of therapeutic antibody development. Thanks to the efforts of many talented students and fellows, some of whom are here tonight, our work 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.

And, it turned out just as Robert Huber envisioned back in 1976 when he solved the structure of the Fc domain, that the Fc is structurally diverse, its three dimensional conformation modulated by a complex, biantennary glycan found on the Fc domain. Changes in this glycan modulate the tertiary structure of the Fc, and in doing so, allow for the selective engagement of different members of the Fc receptor family. For example, the anti-inflammatory activity of high dose IVIG used to treat autoimmune diseases, resulted from IgG with 2,6 sialic acid linked to the complex biantennary glycan integral to the IgG Fc structure, driving the binding of Type II Fc receptors. Thus, for any one variable region, many hundreds of discrete Fc domains can be associated, translating the specificity of the variable region into distinct effector pathways through different Fc receptors.

And what is most satisfying to me are the questions that the work has generated. How is the glycan composition on the Fc regulated? What roles do Fc receptors play in feeding back on the antibody response, shaping the germinal center reaction and affinity maturation? How does the antibody response drive T cell memory? All of which comes down to the big question – how do

vaccines work and how can we manipulate them to make them better? The answer brings us back to von Behring and his diphtheria vaccine, composed of an immune complex of toxin and anti-toxin. Back in the lab we're revisiting this approach, using our knowledge of targeting the Fc to specific Fc receptors to develop approaches for universal flu protection, anti-tumor vaccines and other challenges. We may have known about antibodies for 130 years but we have yet to discover all that they can do.

I would like to end by thanking the hard-working and talented students and fellows I've had the privileged of working with over the years, the colleagues I've collaborated with and learned from, my friends and most of all my wife Wendy and my sons Jared and Ethan, who have been a source of joy and pride for all these years.