Acceptance Speech by Rafi Ahmed
[Check against delivery.]

I would like to thank the Board of Directors and the Scientific Advisory Committee of the Robert-Koch-Stiftung for recognizing our work on immunological memory for the Koch Award in 2017. This is a very special honor and I am pleased to share this award with Professor Antonio Lanzavecchia who has been a friend and colleague for many years.

I trained as a virologist but got fascinated by a very fundamental immunological question; *how does our immune system remember the pathogens we have encountered in the past?* Quite remarkably, this immunological memory can last for decades and even for a lifetime. Defining the underlying mechanisms of immune memory became the focus of my research when I started my lab in 1984. The prevailing dogma at that time was that antigen, in the form of antigen depots or coming from low-grade persistence of the pathogen, was the main driver of long-term immunity. The notion was that this antigen was required to stimulate memory B cells so they could produce antibody and that antigen was also essential for tickling T cells to maintain their numbers and to keep them ready to attack the pathogen. While antigen can certainly enhance immunity, we showed that long-term T cell immunity is an inherent property of the memory cells themselves; these cells could not only persist for extended periods without antigen but they also remained poised to rapidly elaborate effector function upon re-exposure to the pathogen. Along with Andreas Radbruch, we then showed that long-lived plasma cells that reside in the bone marrow are responsible for maintaining antibody responses after infection or vaccination. These studies defined the cellular basis of both T and B cell immunological memory and have provided the framework for developing vaccines that will confer long-term protective immunity against new and emerging infectious diseases and also against old diseases for which effective vaccines don't exist.

It had long been recognized that while acute viral infections resulted in highly effective T cell responses, chronic viral infections were often associated with decreased T cell immunity. It was assumed that either the T cell responses were never induced due to some viral immunosuppressive mechanisms or the virus specific T cells had been deleted in the thymus (clonal deletion) or in the periphery due to over-stimulation by antigen. However, we found that virus specific CD8 T cells were actually present during chronic viral infections, often in abundant amounts, but their function was compromised. The discovery of T cell exhaustion during chronic

viral infection immediately raised two important questions; *first, what is the mechanism of this dysfunction*? and *second, whether one could restore function back into these exhausted T cells?* We then showed that the PD-1 inhibitory receptor was the major brake on these exhausted CD8 T cells and that in vivo blockade of this inhibitory pathway restores function of these cells and results in viral control. This linking of T cell exhaustion with PD-1 has had a significant impact on the development of PD-1 directed immunotherapy for chronic infections and cancer and PD-1 inhibitors are now licensed for treatment of several different cancers.

I would like to end by thanking the many outstanding graduate students and post-doctoral fellows who have worked in my lab. The training of these young scientists has been one of the most rewarding aspects of my research career. Finally, I am most grateful to my family for their support and for allowing me to have so much fun for so long. How lucky one is to end up doing something you enjoy and even get prizes for it.