Dankesrede

von

Prof. Dr. Dennis L. Kasper

anlässlich der Verleihung des Paul Ehrlich- und Ludwig Darmstaedter-Preises 2024

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Es gilt das gesprochene Wort!

Anrede,

It is indeed an enormous honor to receive this year's Paul Ehrlich and Ludwig Darmstaedter Prize. I am deeply thankful to the Foundation for awarding me this prestigious prize. I would like to thank the Members of the Scientific Council of the Paul Ehrlich Foundation and Prof. Thomas Boehm, the Chairman of the Council, for bestowing on me this highly esteemed award.

In thinking about what this award represents, I must start with Paul Ehrlich himself because I find many similarities in our interests, although the magnitude of his discoveries humbles me. Like me, Ehrlich was a microbiologist who dared to leap into the fields of immunology and chemistry. In working with antitoxins, he hypothesized that bacterial toxins bind to antibodies in the blood and that these antibodies, which he called side chains (and later he called receptors), bound to antigens in a lock-and-key fashion. Ehrlich hypothesized that these side chains were receptors on white blood cells in the blood that broke off and became circulating antibodies. These antibodies were called Ehrlich's first "magic bullet." It is astounding that this scientific genius predicted the existence and—to a significant degree—the function of B cells 50 years before Max Cooper and others discovered the bursa of Fabritius and the thymus and taught us about two types of lymphocytes—B cells and T cells.

This interface between immunology and microbiology is a challenging space to work, but very important and rewarding, nonetheless. It requires experimental techniques and scientific knowledge in two fields, and, as a result, the remarkable opportunities that scientifically exist to understand natural functions of the immune system are experimentally challenging. In microbiology related to medicine, many investigators in the field have done fabulous work on how microbes cause disease—including the discoveries of virulence factors, microbial survival factors, and how the immune system signals and responds to pathogens and vaccines. Although pathogens have certainly been an interest of mine, with regard to the microbiome, my lab has taken a different approach—studying how microbes shape our immune system to keep us healthy.

How did I get into this field? I went to medical school in Chicago and realized quite early that I loved doing research. I was given the opportunity as a 1st -year student to work in the research lab of Dr. William Moressi, and I found that, as a student, I spent many of my most exciting hours doing experiments. When I graduated and

did my clinical residency training at Cornell Medical Center/New York Hospital, I longed to return to the lab. At that time, all physicians needed to serve in the United States Army because of the war in Vietnam. I was fortunate enough to be assigned to the Walter Reed Army Institute of Research and to the Bacteriology group headed by Dr. Malcolm Artenstein. I worked on meningitis vaccines in the same lab that had developed groups A and C meningococcal polysaccharide vaccines. I aimed to develop a vaccine for group B meningococcus, an organism with a non-immunogenic polysaccharide. I was unsuccessful, but many years later, I am happy to report that Professor Rino Rappuoli, a prior recipient of the Ehrlich Prize, successfully deconstructed the proteome of the organism and determined which proteins should go into a successful vaccine. This vaccine is now being used clinically. After finishing my army service, I completed my internal medicine and infectious diseases training to join the faculty at Harvard Medical School.

I decided at that point to focus on organisms residing in the intestine that were normally not pathogens but, under special circumstances, caused disease. My work began on group B *Streptococcus* (GBS) and the gut anaerobe *Bacteroides fragilis*. However, I realized that to approach questions I was interested in, I needed additional training in chemistry. I did a memorable sabbatical in Stockholm at Karolinska Institute with Professor Alf Lindberg and learned some of the basics of carbohydrate chemistry.

My early work on *B. fragilis* was related to its role as a pathogen. Initially, I chose this organism, which is part of the normal colonic microbiota in 80% of humans, because when the microbe got into normally sterile sites like the peritoneum (e.g., ruptured appendix, trauma, cancer, etc.), it caused disease, especially abscesses. We found that *B. fragilis* was encapsulated, but remarkably, when the genome was sequenced early in this century, we found it had the genetic capability of making at least 8 capsular polysaccharides, which we named PSA through PSH. We discovered a unique genetic mechanism for regulating polysaccharide expression and determined that the most abundant polysaccharide was PSA.

Around the year 2000, it became evident to me that many of the immunological activities we were discovering related to PSA were unlikely to contribute to abscess formation and pathogenesis of disease; as such, we turned our attention to where these organisms reside for nearly their entire lives—the gut—and studied the relationship of the organism and its structural molecules to the immune system. At this juncture in my career, we began working with gnotobiotic and germ-free mice.

Working with and studying gnotobiotic animals started in the late 19th century. At that time, scientists were confronted with two opposing hypotheses proposed by Louis Pasteur and Marceli Nencki, the Polish chemist. Pasteur hypothesized that life is impossible without commensal bacteria, whereas Nencki suggested that the absence of germs would prolong life and health. This controversy led to the development of techniques and equipment to isolate living animals from their environments as much as possible. Nuttall and Thierfelder at the University of Berlin did pioneering work in this same period. These scientists delivered germ-free guinea pigs by Caesarean section and fed them sterile milk. This accomplishment demonstrated that life without bacteria is possible. In the mid-20th century, several institutions dedicated to gnotobiotic work were opened.

At that time, gnotobiotic studies pursued two goals—providing a nucleus of pathogen-free animals for biomedical research and studying anatomical and physiological particularities in germ-free animals. In the late 20th century, Jeff Gordon's group published a series of elegant studies describing the ability of components of the commensal microbiota of the gut to induce specific responses in the host intestinal epithelium.

With respect to the immune system, it had been previously noted that the presence of intestinal microbes was significant in defense against colonization by opportunistic pathogens. Researchers proposed that certain bacteria could be used as a probiotic to aid health. Notably, the hygiene hypothesis suggested that bacterial constitution of the microbiota were critical in protecting against allergy, asthma, and other immune-mediated diseases. By the early 2000s, an intimate relationship between commensals and the immune system was becoming evident. Several groups recognized the microbiome's potential to modulate the mammalian immune system—both in the innate and adaptive immunity spheres.

It was known that bacteria in the gut had some interactions with the gut immune system. However, there was no insight into the importance or mechanisms underlying this symbiotic relationship with the gut or systemic immune system. Sarkis Mazmanian, a postdoc in my lab, found that during the colonization of animals with *Bacteroides fragilis*, PSA directed the physical and cellular maturation of the developing immune system. Comparison of germ-free vs. *B. fragilis*-monocolonized mice revealed that the immunomodulatory activities of PSA during *B. fragilis* colonization corrected systemic T cell deficiencies and Th1/Th2 imbalances and directed lymphoid organogenesis. Surprisingly, PSA presented by dendritic cells

activated CD4+T cells and elicited appropriate cytokine responses. This was the first example of a molecular basis for host-bacterial symbiosis and revealed the archetypal molecule of commensal bacteria that mediates development of the host systemic immune system.

The adaptive immune system functions through the combined action of antigen-presenting cells and T cells and depends upon the innate immune system to guide adaptive immune responses. Before our work, the MHCII endocytic pathway was canonically thought to present only proteolytic peptides from extracellular pathogens to CD4+ T cells. Carbohydrates were thought to be unable to promote T-cell-mediated immune responses. In fact, our work proved that carbohydrates could be recognized by the ab-T cell receptor if the carbohydrate was presented by the MHCII molecule. We found that negatively or uncharged polysaccharides failed to bind to MHCII. However, PSA activated both the innate and adaptive immune systems. PSA initially activates antigen-presenting cells, such as a dendritic cell, through collaboration between innate immune receptors (TLR2/TLR1/dectin). Studies in my lab done by Brian Cobb, Wiltrud Kalka Moll, Surya Dasgupta and Deniz Erturk-Hasdimir showed the mechanisms by which PSA activated T cells to produce anti-inflammatory cytokines.

We developed further insight into the mechanistic interactions of PSA with the host by showing that MHCII presentation of depolymerized PSA stimulated CD4+Treg cells to produce IL-10, a potent anti-inflammatory cytokine. These studies demonstrated that bacterial molecules from the microbiota mediate the critical balance between health and disease and opened the door for endobiotic metabolites to become therapeutics for inflammatory diseases based on entirely novel biological principles.

We expanded the concept of microbiome-mediated immune system education developed in our PSA studies by discovering a second molecule and a different set of T cells requiring the microbiome for development. This discovery was of a glycosphingolipid—an alpha-galactoceramide made by *B. fragilis* (BfaGC)—having a powerful and vital impact on immune system development. The immunologic effects of BfaGC was on mucosal invariant natural killer T cells (iNKT). Work was done in my lab by Sungwhan Oh and Dingding An and collaboratively with Rick Blumberg, Jamie Rossjohn, and Seung Bum Park. Unlike PSA, which could modify CD4+T cell populations when administered to mice of any age, the mucosal iNKT cell modulation by BfaGC only occurred at a very early host age, but its impact (or

lack thereof in the absence of BfaGC) lasted throughout life. These experiments demonstrated a critical host developmental stage where exposure to certain microbial molecules had a profound and lifelong impact on the host immune system.

I hope this talk has given you a basic understanding of my science. Our work over the years has been the result of enormous insights and efforts on behalf of over 100 brilliant students and postdocs as well as fantastic collaborators both at Harvard and elsewhere. I have had the amazing good fortune of having many currently great and future great scientists working with me. I often feel as if I am a coach, and they are the all-stars making the great shots and plays.

Finally, I want to make clear that my work has been a 30-year partnership with my wife Marie. She has been the bastion of my support, and her work and encouragement have been a constant source of inspiration by providing me with her dynamic energy that has kept our scientific work (and me) going. Even beyond that, she has provided major insights experimentally and done superb editing on everything written from my lab. As far as I am concerned, this prize is given for us to share.

Again, I wish to thank the Ehrlich Foundation for bestowing this wonderful honor upon me and I want to give my heartfelt thanks to Professor Boehm, the selection jury, and all of my former students, post-docs, and colleagues. I am deeply honored, humbled by the magnitude of this recognition and deeply grateful for this prize.