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**Background information on the award of the  
2024 Paul Ehrlich and Ludwig Darmstaedter Prize  
to Prof. Dr. Dennis L. Kasper**

## **Lessons from the gut**

**Immediately after a sterile birth, we humans, like all mammals, are colonized by microorganisms. These are mostly bacteria. This colonization lasts a lifetime. It covers our skin and our body cavities with a number of microbes that far exceeds that of all the cells in our body. The great majority of members of this microbiome are not pathogens. In fact, most are guarantors of our health, since, in the course of evolution, relationships have developed between bacteria and their host organisms from which both benefit. Our colon, for example, provides a warm and nutrient-rich habitat for ten trillion bacteria. In return, many of these tiny inhabitants defend us against their pathogenic relatives, provide us with essential vitamins and nutrients, or help us digest complex carbohydrates. This symbiosis can only succeed if our immune system reliably distinguishes between beneficial and harmful bacteria, and attacks only the latter. Doing so requires continuous communication between the symbionts and the immune system. Prof. Dr. Dennis Kasper, this year's Paul Ehrlich and Ludwig Darmstaedter Prize winner, has deciphered the first words and grammatical rules of the language in which this communication between guest microbes and host takes place. In the process, he made the astonishing discovery that certain archetypal bacterial molecules act as educators of the immune system, teaching it to maintain a healthy balance between inflammation and tolerance. This discovery has led to previously unknown therapeutic options.**

After having completed his medical studies in 1967 and worked as a resident for two years in New York, Dennis Kasper was assigned by the U.S. Department of Defense to the Walter Reed Army Institute of Research, where he completed his military service and was employed as a specialist in bacterial diseases. He began working on the development of vaccines whose effect was directed against the polysaccharides on the capsule of meningococci, the bacteria that can cause meningitis. This work established his interest in the chemistry of carbohydrates, a field in which he later pursued further training during a fellowship at Stockholm's Karolinska Institute and Arrhenius Laboratory. During the 1970s, while researching infections that occurred after internal injuries or surgery, he noticed an anaerobic bacterial species that was particularly frequently involved: *Bacteroides fragilis*. This was remarkable because these rod-shaped germs are normally found among the peaceful symbionts that colonize the colon. Apparently, they became dangerous only when they invaded the sterile space of the

abdominal cavity, especially since they are resistant to penicillin. Curiously, the germ's capsule displayed different chemical behaviors almost every time Kasper extracted it. To get to the bottom of this, he characterized the capsule immunochemically and morphologically in 1976, using the methods available at the time. The result: His first publication on the intestinal microbe *B. fragilis*, which from then on became a focus of his research.<sup>1</sup>

### **How and why does symbiosis succeed?**

Since then, Kasper has been using this microbe to answer the fundamental biological question of how and why a multitude of foreign organisms coexist peacefully with our own bodies in the immunocompetent environment of the gut. The award of the Paul Ehrlich and Ludwig Darmstaedter Prize recognizes this work. Long before the term microbiome was first defined in 1988 and prominently coined in 2001 by the doyen of microbiology, Nobel Prize winner Joshua Lederberg<sup>2</sup>, Dennis Kasper had already set out to explore this microbiome. Two special features set his research apart: For one, he uses the latest technologies from each of the four disciplines of chemistry, genomics, immunology and microbiology. And, in adopting this multidisciplinary approach, he does not primarily search for associative links between our microbiome and our health, which can easily be established today by metagenomic high-throughput methods – similar to a statistical survey. Rather, he searches for causal relationships. In other words, he is on the trail of the molecules with which intestinal bacteria act on and regulate our immune system. In this way, he has discovered how *B. fragilis* and other microbes in the intestine modulate the host's immune system. Many groundbreaking discoveries on microbial molecular modulation of the immune system are owed to this research, the most important of which are expanded upon below.

### **Hide and seek with eight variables**

Solving the question of how gut microbes coexist peacefully with us occupied Kasper for a quarter of a century and required the sequencing of the *B. fragilis* genome. Together with his colleague Laurie Comstock, he published his findings in a sensational paper that *Nature* featured as its cover story in 2001 with the headline "How gut flora 'hide'"<sup>3</sup>. While many bacteria equip their protective capsule with only one form of a complex sugar molecule (polysaccharide), if they carry one at all, *B. fragilis* is in fact capable of producing eight different polysaccharides (PS), which Kasper had previously labeled with the names PSA to PSH. By switching the genes responsible for synthesis on or off at will, the bacterium regulates which of these it produces when. In this way, it covers itself with ever new patterns of polysaccharides and presents itself to the immune system with constantly changing camouflage caps, thereby evading attention. Like a chameleon, the bacterium thus ensures that it is overlooked and tolerated by the immune system.

### **A bacterial sugar as a health signal**

To clarify the question of why the presence of *B. fragilis* in the intestine is important, Kasper and his team then went on to study its effect on mice that are born and grow up in a germ-free environment. These animals cannot be colonized by bacteria and therefore have no microbiome. Surprisingly, their defenses are weaker than those of normally raised mice because they lack certain T cells. Dennis Kasper and his team found that by colonizing the mice's intestines only with *B. fragilis*, and no other bacterial

species, they were able to correct the mice's T-cell deficiency and normalize their defenses. This effect did not occur when the mice were colonized with *B. fragilis* that did not contain polysaccharide A (PSA). Thus, without PSA, the bacterium was unable to correct the immune defect. What's more, Dennis Kasper also demonstrated that the bacterium is not even necessary to stimulate the production of T cells in its host organism – all it takes is the administration of highly purified PSA. It thus appears that PSA is a signal molecule that the hosts of the bacterium need for their immune system to mature. It protects them from chronic intestinal inflammation and helps in the healthy development of their lymphoid organs, such as the spleen.<sup>4</sup>

### **Break with a dogma**

Kasper was able to explain the biochemical basis for this immunocompetence of PSA, which is a large polymer of about 150 kilodaltons and consists of about 200 identical building blocks. It is located in the bacterium's capsule and attached to its membrane by a lipid anchor. Each of its building blocks consists of four different sugars and has both positive and negative charges. Much like proteins, PSA is thus zwitterionic in nature, which is why – although it is a sugar – it can be taken up by the host's antigen-presenting cells, processed and displayed on the surface of these dendritic cells in the major histocompatibility complex (MHC), thereby stimulating the production of regulatory T cells, and providing a balance between type 1 and type 2 T helper cells. Traditionally, the rule for this so-called MHC-II pathway in immunology was that it was reserved for the presentation of protein invaders. With his fundamental discovery that PSA also activates the immune system via this pathway, Kasper broke this dogma.<sup>5</sup>

### **Stimulation for the production of interleukin-10**

At the beginning of the millennium – spurred on by groundbreaking research and technological innovations by a number of colleagues<sup>6</sup> – Kasper's findings suddenly thrust the microbiome into the spotlight of biomedicine, making it an increasingly popular field of research. Over the past two decades, Kasper has succeeded in pinpointing the exact signaling pathways through which PSA acts on dendritic cells.<sup>7</sup> The zwitterionic nature of the sugar is as indispensable for this as its lipid anchor. PSA docks on to pattern recognition receptors (PPRs), such as the Toll-like receptor (TLR) 2, located on the surface of dendritic cells, where the PPRs assume the function of alerting the innate immune system when they recognize typical molecular patterns of foreign bodies, allowing it to trigger an inflammatory response. Surprisingly, however, the presence of PSA results in a balanced modulation of T cell activity that ultimately leads to the production of the molecule IL-10, one of the immune system's most important anti-inflammatory messengers. Its deficiency can promote the development of diseases such as asthma, ulcerative colitis, and multiple sclerosis. In other words, a healthy microbiome can counteract these diseases. It is likely that PSA-like molecules are produced not only by *B. fragilis*, but also by a number of other intestinal bacteria.

### **Early protection against later inflammation**

PSA is not the only signal molecule Dennis Kasper discovered in *B. fragilis*. The second is a glycosphingolipid designated by the abbreviation GSL-Bf717. While *B. fragilis* uses PSA to control the maturation of a balanced regulatory T cell population in the organism it inhabits throughout its life, it uses GSL-Bf717 to intervene in the

development of the immune system only during a short period of time, namely in the weeks and months after our birth. During this timeframe, this lipid from the intestinal bacterial membrane inhibits the proliferation of natural killer T cells (NKT cells), which combine elements of innate and acquired immunity, and can trigger the immune system to overreact to inflammation and attack its own body. Because it bears structural similarity to molecules that promote NKT proliferation, the bacterial lipid displaces many of these molecules from their binding sites, preventing the development of an oversized NKT pool. Adult mice who were exposed to bacterial glycosphingolipids as newborns have a significantly lower risk of developing autoimmune disease. This is an important argument for the careful administration of antibiotics in neonates.<sup>8</sup> To elucidate the structural determinants directing the host's immunomodulatory responses, Dennis Kasper's working group and colleagues chemically synthesized molecules and determined how structural alterations in bacterial glycosphingolipids modulate host NKT cells.<sup>9</sup>

### **New approaches against many autoimmune diseases**

Research into the molecular language in which our microbiome and immune system communicate symbiotically for mutual benefit is still in its infancy. This year's Paul Ehrlich and Ludwig Darmstaedter Prize winner has succeeded in opening the door to this new field of research. Traditionally, interactions between microbes and their hosts had been studied from the perspective of infectious diseases, which meant that for a long time the focus was on pathogen signaling molecules. Dennis Kasper deserves credit for being the first to overcome this one-sidedness by focusing on the signaling molecules of symbionts. Through persistent work, he uncovered communication channels within the superorganism that our microbiome and we form with each other. In doing so, he discovered the first microbial signals that make us healthy, not sick. He has not only precisely described the causal action mechanism of these signals from the gut, showing new possibilities for preventive medicine, while at the same time bringing into focus targets and strategies for the development of drug therapies, which by no means concern only the intestine. In addition, he has defined multiple pathways by which the microbiota educate the immune system. The immunomodulatory anti-inflammatory effect of the bacterial signal molecules he discovered also unfolds systemically, giving rise to the concrete hope of being able to treat autoimmune diseases like inflammatory bowel disease and multiple sclerosis more effectively in the future.<sup>10</sup>

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<sup>1</sup>D. L. Kasper. The polysaccharide capsule of *Bacteroides fragilis* subspecies *fragilis*: immunochemical and morphologic definition. *J. Infect. Dis.* 133, 79-87 (1976).

<sup>2</sup> S. L. Prescott. History of medicine: Origin of the term microbiome and why it matters. *Human Microbiome Journal* 4 (2017) 24-25

<sup>3</sup> Krinos CM, Coyne MJ, Weinacht KG, Tzianabos AO, Kasper DL, Comstock LE. [Extensive surface diversity of a commensal microorganism by multiple DNA inversions](#). *Nature*. 2001 Nov 29;414(6863):555-8. doi: 10.1038/35107092. PubMed PMID: 11734857; NIHMSID:NIHMS33509.

<sup>4</sup> S. K. Mazmanian, C. H. Liu, A. O. Tzianabos, D. L. Kasper, An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. *Cell* 122, 107-118 (2005).

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<sup>5</sup> B. A. Cobb, Q. Wang, A. O. Tzianabos, D. L. Kasper, Polysaccharide processing and presentation by the MHCII pathway. *Cell* 117, 677-687 (2004).

<sup>6</sup> Jeffrey Gordon, Lora V. Hooper, and David Relman are especially noteworthy at this point.

<sup>7</sup> Erturk-Hasdemir D, Oh S, Okan N, Stefanetti G, Gazzaniga F, Seeberger P, Plevy S, Kasper D. Symbionts exploit complex signaling to educate the immune system. *Proceedings of the National Academy of Sciences*. 2019; 116(52):26157-26166.

<sup>8</sup> An D, Oh SF, Olszak T, Neves JF, Avci F, Erturk-Hasdemir D, Lu X, Zeissig S, Blumberg RS\*, Kasper DL\*(\*co-senior and corresponding authors). Sphingolipids from a symbiotic microbe regulate homeostasis of host intestinal natural killer T cells. *Cell* 2014; 156:1-11.

<sup>9</sup> Oh SF, Praveena T, Song HB, Yoo JS, Jung DJ, Erturk-Hasdemir D, Hwang YS, Lee CWC, Le Nours J, Kim H, Lee J, Blumberg RS, Rossjohn J, Park SB, Kasper DL. Host immunomodulatory lipids created by symbionts from dietary amino acids. *Nature* 2021; 600:302-307.

<sup>10</sup> Erturk-Hasdemir D, Ochoa-Repáraz J, Kasper DL, Kasper LH. Exploring the Gut-Brain Axis for the Control of CNS Inflammatory Demyelination: Immunomodulation by *Bacteroides fragilis*' Polysaccharide A. *Front Immunol*. 2021;12:662807.