# Laudatio
# von
# Prof. Dr. Pascale Cossart

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

# an
# Prof. Dr. Dennis L. Kasper

# Paulskirche, Frankfurt am Main
# 14. März 2024

# Es gilt das gesprochene Wort

Anrede,

The scientist honored today, and honored alone, by the Paul Ehrlich-and Ludwig Darmstaedter-Prize 2024 Professor Dennis Kasper is a pioneer. He has discovered the two first chemicals produced by microbes present in the gut that play an essential role in the development and the regulation of the gut immune system, thereby influencing infectious diseases as well as autoimmune diseases.
Everybody knows now that our gut is full of microbes which are absolutely necessary for our health. I am talking of what used to be called the intestinal flora, the commensal microorganisms that populate our gut and which you know, are now called the gut microbiota or the gut microbiome. We have one thousand billion of microbes in our gut, as many as we have cells in our body. What do these microbes do? And how?
They are fulfilling many functions. And this is the area in which our today laureate has been a pioneer!
The most well-known function of the gut microbiome is that the microbes that reside in the gut terminate the digestion by reducing the food products into simple molecules that can diffuse to the blood and via the blood to the different tissues where they are needed. In addition, some microbes produce vitamins which are not brought by the food.
Second function: From experiments performed in animals, more precisely in mice that have no microbes in the gut which are so called “germ-free”, we know that the microbes are critical to protect against infections as germ-free animals are highly susceptible to infections.

There are many ways for microbes to protect against infectious agents, one being to be present all along the intestinal tract and prevent infectious agents to colonize, establish a niche and reach the intestinal epithelial cell layer and cross the intestinal barrier. Another way used by commensal microbes to prevent access of pathogens to the intestinal cells is to stimulate the production of mucus which cover all the intestinal cells and act as a thick barrier. The third way used by commensals microbes to protect individuals against infections is to permanently stimulate the immune cells so that in a healthy gut, pathogens cannot produce an infection. And this is where Dennis Kasper has played a key

role and has made important discoveries in a field which started to explode 25 five years ago thanks to advances in genomics and metagenomics.
As written by Jeff Gordon, another scientist who started early to work in the field of microbiomes
"The importance of the gut microbiota has been recognized since the days of Pasteur and Mechnikoff. What makes today different from yesterday, and tomorrow so exciting, is that we now have the tools to identify the molecular mechanisms that regulate assembly of the microbiota and determine how its components affect postnatal mammalian development and adult physiology."

While Jeff Gordon has been playing a role in the field by identifying how diversity and composition of microbiomes varies according to age, nutrition, environment, genetics etc., what is unique with Kasper's work is that he was the first to identify molecules of one bacterium of the microbiota, which play a critical role in the development and regulation of the immune system. I will focus today on these two molecules, but Dennis Kasper has made many other important contributions as both an immunologist and a microbiologist.

The immune system is an ensemble of cells and components which collaborate to fight infections. What is important to know is that the immune response to a pathogen occurs in several steps, the first occurring immediately after contact with a pathogen and being nonspecific, it is called the innate immune response. The second occurs later. It is induced by some components of the pathogen and therefore is specific to the pathogen. It is called the adaptive immune response.

Dennis Kasper discovered two molecules of the gut microbe *Bacteroides fragilis* which significantly affect the immune system itself.
**The first molecule is PSA,** a polysaccharide (a big sugar!), shown by Dennis Kasper to stimulate both innate immunity and adaptive immunity. This pioneering work was published in Cell in 2003 with Sarkis Mazmanian as first author. (Sarkis is still in the microbiome field and successful, highlighting that Dennis Kasper has launched important people). In fact Kasper showed that after interaction with dendritic cells PSA stimulates the PI3 kinase pathway, whereby it is modified and presented to T cells.

Polysaccharides were previously thought not to influence the T cell response. The presentation to T cells seemed to be reserved for proteins only. **Kasper changed this paradigm** by showing that orally administered PSA changes the Th1/Th2 balance of the systemic immune system and directs lymphoid organogenesis. The corresponding papers were the first reports bringing a molecular demonstration of the host immune system– gut bacteria functional relationship.
Kasper then showed that dendritic presentation of modified PSA stimulates the production of Interleukin 10, a potent anti-inflammatory cytokine, and could demonstrate in mouse models of inflammatory bowel diseases (IBD) that PSA suppresses the production of proinflammatory Interleukin 17. **These results opened the door for PSA like factors becoming new therapeutics for inflammatory diseases based on new principles**.

**The second molecule** originating from commensals and having a key immune regulatory role is a glycoplipid in the membrane of *B. fragilis, which* Kasper called GSL-Bf717. He showed that this molecule inhibits the proliferation of natural killer T cells in the colon, which if too numerous can result in immune-related colitis. In particular this molecule protects adults when present shortly after their birth. Kasper also showed that the lipids are modified by dietary branched chain amino acids taken up in the host gut by *B. fragilis* . As shown in his nature paper of 2021, a *B. fragilis* knockout strain that cannot metabolize branched-chain amino acids showed reduced branching in the respective glycolipids, and mice monocolonized with this mutant strain had impaired colonic natural killer T cell regulation, implying an immunomodulatory activity which is structure-specific. Kasper has really come to a detailed analysis of the metabolites produced by a commensal to control the immune status of the host.

These discoveries were reported in the most prestigious journals, in whom Dennis Kasper continues to publish. While already well advanced in his career, Kasper has an impressive productivity which does not seem to have been impeded by the pandemic. His list of recent publications is impressive.

In summary, Dennis Kasper has in the last twenty years performed an amazingly detailed analysis of the role of commensals for the host. The jury was really impressed by Kasper ‘s achievements.

He is among the pioneers and really deserves the Paul Ehrlich-and Ludwig Darmstaedter-Prize 2024 for mechanistic key advances in a field which is dominated by correlative analysis, as he discussed in his paper entitled "Moving beyond microbiome-wide associations to identifying causal microbes".

As I already said I have focused here on one aspect of D Kasper activity, but he has had and still has a broad activity. He has, for example, published last month in Cell an amazing paper with John Mekalanos and Christophe Benoist in which he showed that intestinal cells produce unexpectedly a component thought so far only present in the blood, the complement component C3. Another great finding that reveals another way used by gut bacteria to protect against enteric infections.

Dear Dennis Kasper, we are really happy to see you here as the laureate of the Paul Ehrlich-and Ludwig Darmstaeder-Prize 2024**. Please receive on behalf of the whole jury my sincere congratulations.**