

 PROFILE

# Profile of Dennis L. Kasper

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"I was working on the microbiome before it was called the microbiome," says Harvard microbiologist and immunobiologist Dennis L. Kasper, who for over 4 decades has delineated the central role of the mammalian microbiota in immune system development, maturation, and regulation. His achievements, including identification of immunomodulatory molecules from the microbiome and demonstration of their potential to treat certain immune-mediated diseases, contributed to the foundation of a dynamic new research field. Elected to the National Academy of Sciences in 2018, Kasper reports in his Inaugural Article (1) the discovery of a bacterial lipid anchor to a polysaccharide capsule that is required for host antiinflammatory responses. He and his colleagues also elucidate the immunologic mechanisms underlying these responses, which could facilitate the development of therapeutic agents derived from symbiotic microbes.

## First to Attend College

Kasper was born in Chicago to first-generation American parents. His father was an airplane mechanic during World War II, who later founded a chain of successful sporting goods stores. "My father was a great solver of mechanical problems," says Kasper. "His way of thinking influenced me." Kasper's grandfathers were also early influences. Despite having no formal education, both were successful businessmen who valued academia. Kasper's grandfather encouraged him to become a professor, but when Kasper became the first in his family to attend college he initially did not follow this advice. He instead chose to be a premed student at the University of Illinois, Urbana. While attending medical school, Kasper developed a passion for research in the laboratory of friend and mentor William Moressi, an assistant professor of physiology. Kasper received his medical doctoral degree from the university in 1967.

## Twist of Fate

Kasper completed an internship in internal medicine at New York Hospital–Cornell University Medical Center before obtaining a 1-year deferment from the Vietnam War draft to complete his first year of residency at the hospital. Kasper then received orders to



Dennis L. Kasper. Image courtesy of Richard Groleau (Harvard Medical School, Boston, MA).

go to Vietnam as a preventive medicine officer. In an interview at the Office of the Surgeon General in Washington, DC, he was asked if he wanted to be a virologist or a bacteriologist. Kasper says, "I knew what bacteria looked like, but not a virus, so my orders were changed, and I was assigned to the Department of Bacterial Diseases at the Walter Reed Army Institute of Research."

This "twist of fate," as he calls it, influenced Kasper's career. Immunologist and microbiologist Malcolm Artenstein was the chief of the department and gave his new mentee freedom to select projects. Kasper elected to continue the work of microbiologist Emil Gotschlich, who in 1970 developed the first polysaccharide vaccine for meningitis. Kasper investigated proteins as candidate immunogens to protect against group B meningococcus (2).

## Group B *Streptococcus* Vaccines

After leaving Walter Reed in 1972, Kasper completed the second year of his residency at what is now Brigham and Women's Hospital in Boston. He accepted a fellowship at Harvard's Channing Laboratory based at Boston City Hospital. Director Edward Kass was impressed by the young post-doctorate and had Kasper appointed as an instructor in medicine at Harvard Medical School. Kasper says of Kass, "He taught me how to conduct a successful academic life."

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Kasper was promoted to an assistant professorship at Harvard, followed by an associate professorship and full professorship. His active research program was initially supported, in part, by a Research Career Development Award from the National Institutes of Health. In 1985 he also received the prestigious Squibb Award from the Infectious Diseases Society of America.

For decades, Kasper worked with pediatrician Carol Baker, whom he first met at the Channing Laboratory. Kasper and his group created conjugate vaccines for 5 major serotypes of group B *Streptococcus*, a serious infection of newborns, for human use, and Baker successfully tested them in phase 1 and phase 2 human clinical trials (3). Although the vaccines produced good results in the trials, pharmaceutical companies were averse to proceeding with development because the target recipients were pregnant women. Over the past 5 years, however, industry interest in the vaccines has grown.

### Immunomodulatory Molecule from Microbiome

Kasper's research in the 1970s on infectious diseases led to investigations of infections due to the normally commensal microbiota. Of the hundreds of microbial species colonizing the human intestine, *Bacteroides fragilis*, which is resistant to penicillin, was the most commonly isolated microbe from sites of infection. In 1976 Kasper reported an immunochemical characterization of the bacterium's polysaccharide capsule (4). Later, he and his team determined that the microbe produces at least 8 distinct capsular polysaccharides (PSA-H), yielding a diversity that allows the organism to modulate its surface antigenicity (5).

Scientific dogma held that carbohydrates are T cell-independent, but in a landmark 2004 study, Kasper and his colleagues found that the zwitterionic (both positively and negatively charged) PSA of *B. fragilis* activates regulatory T cells that make interleukin 10 (IL-10), a potent antiinflammatory cytokine (6, 7). The identification of a microbiota-derived molecule capable of stimulating the innate immune system suggested that many gut organisms might also be central to disease susceptibility and resistance. For this and prior achievements, Kasper was elected as a member of the National Academy of Medicine (2001) and the American Academy of Microbiology (2005).

### Therapeutic Potential and Mechanisms

In 2005 Kasper and his team determined that the PSA of *B. fragilis* stimulates a normal balance of T cells in the immune system of germ-free mice (8). The findings suggest that PSA helps to direct the cellular and physical maturation of the developing immune systems of mammals. The following year, Kasper's group identified Toll-like receptors crucial to the convergence of innate and adaptive responses stimulated by PSA (9). They subsequently demonstrated that PSA protects animals from experimental inflammatory bowel disease through the induction of IL-10 production by regulatory T cells (7).

Kasper's research supports the hygiene hypothesis, which holds that exposure to microbes at an early

age helps to build immunity. Microbial exposure during early life, for example, has a long-term effect on invariant natural killer T cells (iNKT) and their function in the lungs and colon (10). Colonization of germ-free mice with human or rat microbiota results in offspring that are immunologically similar to germ-free mice (11).

### Glycosphingolipids as Immunomodulatory Molecules

*Bacteroides* have unique sphingolipids—membrane components with roles in signal transduction—that are not found in other bacterial phyla. Kasper and his colleagues isolated and determined the structure of these sphingolipids before demonstrating that a particular one, known as Bf717, which is structurally defined as a glycosphingolipid, therapeutically blocks inflammation in the colon induced by iNKT cells (12). The number of iNKT cells in an individual is set during the neonatal period, with these cells being important to the pathogenesis of ulcerative colitis.

PSA and Bf717 are thus far the only identified immunomodulatory molecules from the microbiome. "Such molecules are hard to find," Kasper says. "It's because the technology required to do it requires bacteriology, immunology, chemistry, and genetics. Most [laboratories] specialize in one or the other. We do a little of everything to mechanistically understand how microbial molecules interact with the immune system."

### Microbiota's Immune System Effects

Working with Harvard immunologist Ulrich von Andrian, Kasper and his team used click chemistry to fluorescently label live anaerobic gut bacteria and observe them in real time in the gut using 2-photon microscopy (13). In another study, Kasper, along with Harvard colleagues Diane Mathis and Christophe Benoist, colonized previously germ-free mice with 63 microbial strains and immunoprofiled the changes that occurred in the rodents' immune systems (14). The study marked a systematic cataloging of the microbiota's effects on a mammalian immune system.

Another unique research approach employed microbe-phenotype triangulation to move beyond standard correlative microbiome studies in identifying microbial organisms that regulate responses to colitis (15). Kasper says, "The microbiota is very complex, with hundreds of bacterial species. We provided a roadmap for how to experimentally search through this complexity and find individual species that are responsible for a given host phenotype."

### Discovery of Lipid Structure on PSA

Kasper's Inaugural Article reports a lipid structure on PSA that is required for activation of antigen-presenting cells (1). Kasper says, "The lipid is less than 1% by weight of the PSA molecule. It was not obvious that the lipid was part of the PSA molecule, but certain results were not explainable by the polysaccharide alone. Therefore, we had to significantly 'energize' our chemical systems to find it."

Coauthor Scott Plevy of Pennsylvania-based Janssen Research and Development and his group previously found that mice with a defective PI3K intracellular signaling pathway were susceptible to colitis (16). Building on this research, Kasper and his colleagues (1), spearheaded by Deniz Erturk-Hasdemir, found that both the Toll-like receptor signaling pathway and C-type lectin pathway, through receptor Dectin-1 activation, are required to stimulate PI3K and activate downstream antiinflammatory signals. The outer membrane-associated lipid is required to initiate the process. Better understanding of the molecular mechanisms modulating immunity is essential to the development of symbiotic microbe-derived therapeutics. Kasper recently received a grant from the US Department of Defense to investigate the medicinal potential of the lipid.

### Continuing a Legacy

In addition to authoring more than 450 papers and serving in a variety of administrative positions at Harvard and elsewhere, Kasper has trained almost 100 young scientists, fulfilling his maternal grandfather's dream of his becoming a professor. His wife, Marie, is a Harvard Medical School administrator and editorial assistant on the medical textbook *Harrison's Principles of Internal Medicine* (17), of which Kasper is an editor. He has 3 children, 2 of whom are pursuing careers in the sciences, and 8 grandchildren.

"I came from a family without formal education, but they nonetheless held academics in very high esteem," Kasper says. "This passion for education has been passed on to our children and, I like to think, our grandchildren." He added, "I still love coming to work every day. There's nothing that I'd rather do."

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