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Conferment of the Robert Koch Prize

and the Robert Koch Medal in Gold

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Laudatio

for

Prof. Dr. Jorge E. Galán

by Prof. Dr. Dr. Jürgen Heesemann

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By awarding the Robert Koch Prize to Prof. Jorge Galán, Head of the Department of Microbial Pathogenesis at the Boyer Center of Molecular Medicine at Yale University, New Haven, USA, the Robert Koch Foundation honours one of the pioneers of molecular and cell biology of infections. For over 25 years, Jorge Galán has been producing groundbreaking results which help us understand the molecular mechanisms involved in the pathogenicity of enteric pathogen salmonella. Particularly noteworthy were his analyses on the structure and functions of a new protein injection system/type 3 secretion system (T3SS) and the molecular effects of the effector proteins injected by salmonella into host cells (T3SS substrates), which reprogram the host cells to promote growth of the salmonella. J. Galán‘s work is of universal importance for infection biology, as most gram-negative bacteria in flora and fauna use protein injection systems homologous to salmonella T3SS.

Salmonellae include the highly pathogenic group of typhus pathogens (Salmonella typhi and paratyphi) and the less pathogenic group of typical enteritis/diarrhoea pathogens (enteritic salmonellosis). In countries with low hygiene standards, 500,000 people die every year from infections with typhus salmonellae, while in Germany 60-70 typhus cases are reported each year. By contrast, enteritic salmonellae were among the most common bacterial diarrhoea pathogens after Campylobacter jejuni (500,000 / 700,000 per year in Germany).

Salmonella were first isolated and characterised in Germany by Georg Gaffky in 1884 (Typhus bacillus) and August Gärtner 1899 (Bacillus enteritidis) and by Daniel Salmon in 1887 in the USA (Salmonella cholerae-suis). Friedrich Löffler, like August Gärtner a student of Robert Koch, observed mass mortality in his laboratory mouse unit in 1889/90 at the University of Greifswald, and also isolated the pathogen. As the infection of the mice was similar to human typhus symptoms, he called the pathogen Bacillus typhi-murium. He later used this pathogen as a biological weapon to combat the plague of mice on farms.

Today, in the age of genomics, all human pathogenic salmonellae are attributed to one type of bacteria, Salmonella enterica, and the pathogenic differences in the infectious diseases are marked by serotypes/pathotypes, e.g. Salmonella typhi or Salmonella typhi murium.
In his over 25 years of research, Jorge Galán has discovered the most important principles of these two pathogens. Why the fascination with Salmonellae?

Jorge Galán was born 54 years ago in Argentina, where he completed his veterinary studies in 1990 at La Plata University. We Europeans associate Argentina with huge herds of cows and steaks. Salmonellae are zoonotic pathogens, both cattle and poultry are also susceptible. In 1986, he left for the laboratory of Roy Curtis III in St. Louis, USA, probably with a missionary assignment to combat Salmonella. After just two years there, he published his first major paper on cell invasion by Salmonella typhi murium. This was followed by further publications on the development of salmonella vaccines. In 1990, these successes brought him a professorship at Stoney Brook University. In 1991/92, the first quantum leap in salmonella research was made: Salmonellae force absorption via host cells by contact and cause cytoskeleton shifts with their effector proteins. This discovery was a new paradigm, as until then, pathogenic bacteria had been considered passive microbes, under the control of host cells and it was believed that they could only damage the host cell via toxins. This discovery was followed by initial indications of a protein injection system similar to the flagella system and also occurring in Shigella and Yersinia.

In collaboration with a Japanese group, J. Galán succeeded in displaying the structure of the T3SS injection needle of Salmonellae using an electron microscope in 1998. Surprisingly, these needles are very similar to medical syringes. This scientific breakthrough earned him the appointment as Lucille P. Markey Professor of Microbiology at the Boyer Center of Molecular Medicine at Yale University.

This enabled him to expand his working group and utilise the exceptional scientific environment at Yale University for his new research ideas. He intensified his analyses of the biological structure of the T3SS injection system and the many effector proteins. He succeeded in determining a spatial arrangement and function of the various T3SS proteins, thus revealing the structure and effects of this nanomachine. He was also the first to identify the structure of effector proteins and their chaperones (proteins which accompany the effectors). Finally, he also succeeded in proving that the effector proteins must be deployed by an ATPase for insertion into the injection needle. His latest research investigates how T3SS specifies the sequence of the effector proteins to be secreted (sorting platform). These results on the structure and function of salmonella T3SS provide vital information on the T3SS of other human pathogenic bacteria such as Shigella, Yersinia, Chlamydia etc. and plant pathogens such as Pseudomonads or Xanthomonads. His studies are also the basis for developing virulence blockers which inhibit the function of T3SS. This would enable us to use anti-infectives to target pathogenic bacteria specifically, while preserving the protective normal flora, which is not possible with conventional broad-spectrum antibiotics.

J. Galán has also researched another application-oriented aspect of Salmonella T3SS, by using the injection system as a bacterial vaccination gun. Salmonella can produce antigens of the influenza virus or cancer cells and inject them into cells presenting antigens via T3SS, thus triggering a protective CD8 T-cell immune response. This technology creates a new field for the development of a polyvalent live vaccine.

His work towards understanding the cellular effects of salmonella T3SS-injected effector proteins, which revolutionised the concept of pathogenicity of bacteria, is no less important. There are few host proteins with signalling transduction or cytoskeleton functions which cannot be imitated by salmonella effector proteins. This mimicry by bacterial effector proteins injected into host cells via T3SS not only applies to salmonella, but also for Shigellae, Yersinia, Pseudomonads and plant pathogenic bacteria. They determine whether a pathogen multiplies intracellularly or extracellularly. Some of these effector proteins are evolutionarily related to host proteins, but most appear to be inventions of the microbe world. Only the co-evolution of pathogens and hosts optimised the function of these proteins. J. Galán identified effector proteins in salmonellae which act as protein tyrosine phosphatase, Rho GTPase activator, Rho GTPase inactivator, ubiquitin ligases etc. in the host cell, and thus allow the salmonellae to survive and multiply intracellularly. With this pioneering work, he established the new research area of Cellular Microbiology together with two former Robert Koch Prize winners, Philippe Sansonetti and Pascal Cossart. The cell biology of the host together with the molecular biology of the pathogen are the two sides of infection biology, as J. Galán drummed into his doctoral students and post-docs.

His scientific curiosity allowed him to go beyond the borders of his salmonella project and led him to analyse the pathogenicity of the most common causes of enteritis in Europe, Campylobacter jejuni. In this context, I wish to mention the discovery of the effect of the Campylobacter toxin CDT, which is associated with stopping the host cell cycle, and his work on the importance of the metabolic features of the pathogen which codetermines the pathogenesis. Investigation of the adaptation of the pathogen metabolism to the host is therefore the third key area, besides cell biology and bacterial modulin, which ensures that J. Galán has an important place in biological research of infections.

For an overview of Galán‘s research work, all you have to do is look at Cell, Nature, Science, Cell Host Microbe and PNAS and take the time to read the many articles. To compete in the fields of molecular biology, cell biology, immunology, biochemistry and structural biology as a veterinarian requires outstanding talent for biological research of infections and demands self-discipline, ambition, critical thinking, creativity, and above all, dauntlessness. These characteristics as a researcher, as well as geniality and fairness made J. Galen an extremely popular mentor, especially with German post-docs, who now hold professorships not only in Germany, but also in Switzerland and Austria. And when these students talk about their “great master”, it sounds like what August Gärtner, who discovered Salmonella enteritidis, wrote about his two-year post-doc (1884-1886) with Robert Koch: “I can summarise life under Robert Koch in one word - it was competitive work, no-one took holidays. Sundays did not exist. It was a tough but great time.”

By presenting this year’s prize to Jorge Galán, the Robert Koch Foundation honours an exceptional scientist, who made a key pioneering contribution to understanding the molecular mechanisms of the complex pathogenicity of salmonella. It is already clear that his discoveries will have consequences for the treatment of infectious diseases. The Robert Koch Foundation and all of us wish you, dear Jorge, and your wife continued success and happiness in your research into the pathomechanisms of infectious pathogens.