2002 Hans Sigrist Prize

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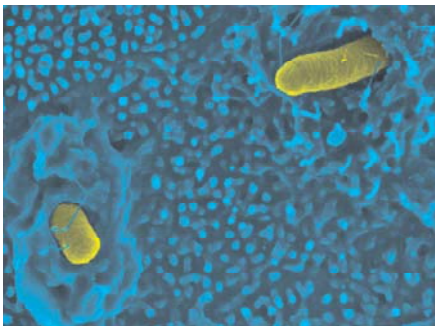
Microbial pathogens have evolved unique ways to interact with their hosts. In many instances the terms of this interaction reflect the co-evolutionary balance that the host and pathogen must reach in order to secure their survival. It is therefore not surprising that bacterial pathogens have evolved a large array of virulence factors well suited to interfere with or stimulate a variety of host-cell responses in order to invade, survive and replicate within their hosts. The identification and characterization of these virulence factors is proving to be a fruitful area of research in more ways than expected. The understanding of how pathogens interact with their hosts is not only providing the basis for the development of novel therapeutic approaches but also a number of very sophisticated tools for probing basic aspects of cellular physiology and immunology. Our laboratory studies the pathogenesis of two intestinal pathogens, Salmonella enterica and Campylobacter jejuni. Combined, these two pathogens account for the vast majority of cases of infectious diarrhea worldwide leading to an estimated 2,000,000 deaths. We are interested in characterizing the bacterial determinants involved in the pathogenesis of these bacteria, as well as the host responses that they stimulate. We



Scanning electron micrograph showing the interaction of Salmonella typhimurium with cells of the intestinal epithelium

take a multidisciplinary approach in our studies involving bacterial genetics, biochemistry, cell biology, immunology as well as structural biology. As a result, we are beginning to define not only the molecular details of the host pathogen interactions but also the atomic interface between these pathogens and the host.

One of the bacterial determinants of virulence that we have been studying during the last few years is a remarkable organelle, the type III secretion system, which has specifically evolved to «inject» bacterial proteins into the host cell. These bacterial proteins have the capacity to modulate or interfere with a variety of normal cellular functions for the pathogen's benefit. Work in our laboratory supported by the funds provided by the Hans Sigrist Prize are characterizing the function of this remarkable bacterial device. In addition, we have been able to harness this bacterial device as means to deliver other proteins into host cells, whose production by Salmonella we have engineered by genetic engineering approaches. We have constructed strains of Salmonella unable to cause disease but able to produce proteins from other pathogenic microorganisms such as the Human Immune Deficiency virus (HIV) that are currently being tested for their potential use as an AIDS vaccine.

It has a great honor for me to receive the Hans Sigrist Prize. The availability of the significant funds associated with the Award have provided our laboratory with additional flexibility to pursue high-risk but potentially high-impact projects that would otherwise we would have been unable to carry out.

Selected Recent Publications:

Lara-Tejero, M. and J. E. Galán. 2000. A bacterial toxin that controls cell cycle progression as a deoxyribonuclease I-like protein. Science 290: 354-355.

Stebbins, C. E. and J. E. Galán. 2001. Structural mimicry in bacterial virulence. Nature. 412:701-5.

Stebbins, C. E. and J. E. Galán. 2001. Maintenance of an unfolded polypeptide by a cognate chaperone in type III secretion of a bacterial virulence factor. Nature. 414:77-81.

Kubori, T. and J. E. Galán. 2003. Temporal regulation of Salmonella virulence effector function by proteasome-dependent protein degradation. Cell 115:333-342.

Hernandez, L. D., K. Hueffer, M. R. Wenk, and J. E. Galán. 2004. Salmonella modulates vesicular traffic by altering phosphoinositide metabolism. Science 304:1805-7.

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