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November '09 | Vol.22 • No. 4

FEATURES

LETTER FROM ROBERT TJIAN

CENTRIFUGE

UPFRONT

[Piecing Together Rotavirus's Unique Approach](#)

[Seeing Spots](#)

[Dangerous Agent](#)

CHRONICLE

PERSPECTIVES & OPINIONS

LETTER TO THE EDITOR

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UPFRONT: Dangerous Agent

PAGE 1 OF 2

Dangerous Agent

by Laura Spinney



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Pascale F. Cossart

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A MODEL BACTERIUM IS SHOWING SCIENTISTS HOW PATHOGENS go from harmless to deadly.

In the early 1980s, scientists needed a model microbe they could use in the fight against infectious bacteria. Tuberculosis was re-emerging as a global health problem and a similar bacterium—one that also invades host cells—had been identified as the cause of Legionnaire's disease.

Enter Pascale Cossart. Then a young postdoc at the Pasteur Institute in Paris, Cossart was encouraged by her mentor, molecular biologist Maxime Schwartz (who would later become director of the institute), to leave her comfort zone—the study of gene-protein interactions—and investigate the more “pasteurian” theme of infection. It was

a big jump for Cossart, a biochemist by training, but she soon realized that the infectious agent she had chosen to study, *Listeria monocytogenes*, could be the model everyone was seeking.

Listeria grows quickly and has both benign and disease-causing varieties, so she could study virulence by comparing the two. It also behaves similarly to other disease-causing, intracellular bacteria, such as *Chlamydia* and *Rickettsia*, as well as *Legionella* and *Mycobacterium tuberculosis*.

Over the last two decades, Cossart, an HHMI international research scholar who heads the Pasteur Institute's Unit of Bacteria-Cell Interactions, has helped make *Listeria* one of the best understood bacterial pathogens. In 1996, for example, with Jérôme Mengaud, also at the Pasteur Institute, she identified the human protein E-cadherin as the receptor that *Listeria* latches onto, allowing it to enter host cells. *Listeria's* genome sequence was completed in 2006 thanks to an international consortium that Cossart coordinated. The methods her group has developed for studying *Listeria* are being applied more widely—for instance, their transgenic mouse model of *Listeria* infection is now also regarded as a model for viral and parasitic infections.

Most recently, Cossart's group has created a map showing how the transcriptional products of *Listeria's* genome change when the bacterium exists under different environmental conditions. The work appeared in *Nature* on June 18, 2009.

When ingested in contaminated food, *Listeria* can trigger miscarriage and kill people with weakened immune systems. It has the unique ability to invade three internal barriers: the intestinal lining, the placenta, and the blood-brain barrier. Cossart's latest findings may begin to explain how it transforms from a benign, free-living microbe into a dangerous agent of disease.

As a basic scientist, Cossart also wonders if the new map might give insight into how other opportunistic pathogens make that switch too. "For me, [*Listeria*] is a platform on which I establish concepts that I can then investigate in other pathogens, to see if they behave like it," she says.

Illustration: Ritchie Stirling / Hulton Archive / Getty Images

PAGE 1 OF 2

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[Back to Top](#) 📄

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- ⌘ [CURRENT ISSUE](#)
- ⌘ [SUBSCRIBE](#)
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- ⌘ [ABOUT THE BULLETIN](#)

November '09 | Vol.22 • No. 4

⌘ [FEATURES](#)

⌘ [LETTER FROM ROBERT TJIAN](#)

⌘ [CENTRIFUGE](#)

⌘ [UPFRONT](#)

[Piecing Together Rotavirus's Unique Approach](#)

[Seeing Spots](#)

[Dangerous Agent](#)

⌘ [CHRONICLE](#)

⌘ [PERSPECTIVES & OPINIONS](#)

⌘ [LETTER TO THE EDITOR](#)

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UPFRONT: Dangerous Agent

PAGE 2 OF 2

Typically, the DNA that makes up an organism's genome is transcribed into RNA, which is then translated into protein. Not all RNA is translated into protein, but research in recent decades has shown that even untranslated, or noncoding, RNA can play an important regulatory role. Cossart's group previously identified pieces of noncoding RNA that regulate *Listeria's* virulence. Suspecting that such a system of regulation might be widespread in the bacterial world, they set out to investigate *Listeria's* transcriptional program more systematically.

The gene chip company Affymetrix built them a set of tiling arrays, or arrays of DNA probes that correspond to overlapping stretches of the *Listeria* genome. Led by postdoc Alejandro Toledo-Arana, researchers from Cossart's lab and the labs of Jörgen Johansson (Umeå University, Sweden) and Marc Lecuit (Pasteur) used these arrays to analyze RNA extracted from *Listeria* that had been grown under different conditions. Specifically, they compared bacteria grown in broth with bacteria extracted from the intestine of *Listeria*-inoculated mice and with bacteria from inoculated samples of human blood. They also compared wild-type bacteria with bacteria genetically altered to lack known virulence factors.

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They identified several previously unknown regulatory mechanisms, including two noncoding RNAs that contribute

to *Listeria's* virulence and around 40 riboswitches—RNA structures that regulate protein production. Their work also revealed that *Listeria's* transcriptional program changes dramatically between its soil-dwelling and intestinal modes. As it arrives in the gut, some gene activity is turned up while other gene activity is turned down. For example, one protein, SigB, switches on a series of genes needed for *Listeria* to adapt to the mouse gut, whereas a different protein, PrfA, switches on genes needed for survival and replication in human blood.

Similar regulatory mechanisms will almost certainly turn up in other bacteria, Cossart says. While researchers go hunting for them, she has gone back to her model to fill in more gaps in knowledge. For example, with Lecuit and others, she has largely worked out the mechanisms *Listeria* uses to cross two of three internal barriers. Now she wants to nail the third: how it penetrates the bloodâ€”brain barrier. The more she knows about her model, she reasons, the more useful it will be—not only in the perpetual war against bacteria that make humans sick, but against all agents of infectious disease. ■

PAGE 2 OF 2

[↩ Back](#)

[Back to Top](#) ▲[Home](#) | [About HHMI](#) | [Press Room](#) | [Employment](#) | [Contact](#)

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