

## Pascale Cossart



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“At the borderline between microbiology and cell biology,” is Pascale Cossart’s description of her laboratory at the Pasteur Institute in Paris. Over the last 20 years, the Cossart lab has turned that border zone into an extraordinary vantage point for viewing the ancient struggle of host v. pathogen. The conflict can be seen for the first time from both sides.

Cossart’s pathogen is *Listeria monocytogenes*, a wily food-borne bacterium that can survive freezing and even grow at four degrees. *Listeria*’s impact on the immune-compromised and on pregnant women can be devastating. But Cossart was also drawn to *Listeria*’s sheer resilience as a paradigm for bacterial infection.

### From Both Sides Now

By screening *Listeria* mutants, Cossart and Jean-Louis Gaillard found in 1991 that the gene for the cell surface protein, internalin, was required for the pathogen to gain entry to host epithelial cells. Working with Christine Kocks, Cossart identified ActA, the protein responsible for actin-based motility, as a key factor for bacterial dissemination into the host and also a great tool for cell biologists. In 1996, the focus shifted to the other side of the equation when Cossart and Jérôme Mengaud identified human E-cadherin as the receptor molecule and *Listeria*’s prime target for entry. In 1999, Cossart and Marc Lecuit turned an experimental glitch into a breakthrough when they realized why their mouse model for *Listeria* infection wasn’t working: a single amino acid difference between mouse and human E-cadherin. That led them to a transgenic “humanized” mouse model for *Listeria* infection. This pinpoint approach to species specificity could also have implications in host resistance and for the evolution of trans-species pathogens.

In recent work, the Cossart lab has widened its border zone approach to identify new virulence factors and new regulatory mechanisms in *Listeria*, including an RNA

thermosensor, to find new host receptors, and to explore the cooption of the host’s cytoskeleton and also the clathrin-dependent system of endocytosis. The lab has also puzzled out how *Listeria* uses internalin to cross the human maternofetal barrier. In addition, Cossart promoted and coordinated the complete sequencing of the *Listeria* genome.

The lab’s interdisciplinary nature was one of the attractions for H el ene Bienne, a microbiologist who joined the Cossart lab at the Pasteur nine years ago and remains on loan from the French national agronomics research institute, INRA. Bienne says she fits right in a lab marked by its diversity of personnel and methodology. “In Pascale’s lab, you are covering a lot of different topics from the cell invasion process to signaling pathways to the manipulation of the host’s cytoskeleton. The

new virulence factor that I am studying was discovered through post genomics. Here you are doing everything from classic genetics to genomics,” says Bienne.

### Getting the Point

It was clear by the late 1980s that cell biology had much to offer to microbiology, recalls Daniel Louvard, who is now the Research Director of the Curie Institute in Paris. He was Cossart’s colleague at the Pasteur at a time when he was trying to persuade researchers

to merge the power of bacterial genetics with the breakthroughs in actin dynamics and filament function. “Pascale was one of the few at the Pasteur who got the point,” Louvard recalls. “In less than a decade, Pascale became an outstanding cell biologist and has done all this beautiful work on how intracellular bacteria manage to invade cells, manage to escape the cell’s immune system, and go from one cell to another. Of course, I only contributed to the beginning and not for her subsequent triumphs,” says Louvard.

Since his move to the Curie, Louvard reports that, “We have remained extremely good colleagues. Pascale is a very easy person to

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interact with and very direct. But she can be a tough cookie and I like that about her. To do what she has done, especially as a woman, and to reach this level in science in France, she has to be tough. Pascale has my admiration.”

Cossart is indeed a prominent figure in French science. She directs one of the Pasteur’s 10 research departments. Her honors include membership in “L’Institut de France, Academie des Sciences” and the title of “Chevalier de la Legion d’Honneur.” Outside France, Cossart was renewed last year as an HHMI International Research Scholar. In 1998, she won the L’Oreal/UNESCO Award for Women in Science and in 2000, the Swedish Society of Medicine’s Louis Pasteur Gold Medal.

### A Short Walk to Montparnasse

Although her life centers on her science, Cossart is fiercely proud of her three grown daughters, Marie-Hortense, Josephine, and Eugenie who are, respectively, a psychologist, an organ transplant unit coordinator, and a lawyer. Cossart lives in Paris, 15 minutes on foot from her lab at the Institut Pasteur in Montparnasse, but the family has a country house in the Loire Valley. There, Cossart loves to garden and entertain. She brushes off any suggestion

that she has a secret for keeping all her various responsibilities going, other than, “I work like crazy and I do the best I can. I also like to finish things.”

Pascale Cossart comes from the northern French city of Arras. Her father ran the family flour mill and animal feed business. Her mother raised their five children. Her parents supported her educational ambitions, Cossart recalls, but they soon realized that their daughter needed no pushing. The defining moment came in secondary school on the first day when chemistry textbooks were handed out. “I read it through and that was that.” Cossart sailed through her undergraduate degree in Chemistry at the University of Lille and started on a graduate program there before wandering into a biochemistry lecture. She was instantly hooked and restarted as a biochemistry undergraduate to pursue a double major.

In 1970, she took up a fellowship at Georgetown University, returning to France in

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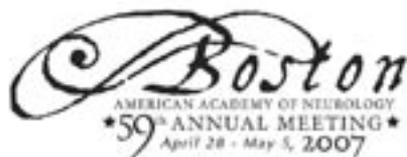
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1971 with a Masters in Biochemistry and lab experience in lipid protein interactions. She earned her doctorate from the University of Paris through work at the Pasteur with George Cohen on *E. coli* protein chemistry. The Pasteur system allows young postdocs a great deal of research independence, if limited lab space. Cossart was more or less on her own as an investigator from the early 1980s, working on gene expression in *E. coli*. But Cossart was discouraged by Pasteur administrators from competing against what she calls “the big elephant labs in the U.S.” and encouraged to switch to infectious diseases. Meanwhile, Louvard was beginning his campaign to link cell biology to host-pathogen studies.

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With an exclusively biochemical background, Cossart found the prospect of shifting both exciting and daunting. She recalls, “This would be going into a new field and my background was in chemistry and absolutely not in cell biology so I knew I would have to jump feet first into a subject about which I knew absolutely nothing. I didn’t even have any background in growing cells in culture. Cell adhesion? I knew nothing then.”

### Fast Actin Learning

Cossart began her cellular self-education with Pasteur colleagues and by recruiting newcomers with needed skills to her lab. Cossart also credits the ASCB. “When I started to work on actin-based motility, I went to Daniel and asked him, ‘where should I go to learn this?’ He said, ‘You should go to this Keystone meeting and then you should go to the ASCB meeting.’ I did both and I liked the ASCB from the very beginning. This is a very dynamic society and I was amazed at how well things are run. I go to the ASCB meeting regularly.” Cossart also served as a member of the 2006 Annual Meeting Program Committee.

Cossart’s eclectic approach to people and to methods is one reason that Marc Lecuit, an MD who was looking for a research placement in virology, ended up struggling with a mouse model of *Listeria* infection for Cossart. (Lecuit also ended up as an ASCB member.) “Pascale is always looking for people who share her enthusiasm for scientific questions and have the energy to go on,” he notes. Lecuit’s energy was quickly tested by experiments with mouse cells that didn’t work as predicted. “My work was

going nowhere,” Lecuit remembers. “We already had two systems in the lab and there were discussions with people who said that maybe I should use the system that works.

“This was a routine project and I probably could have done it using the other system. But Pascale was mostly interested in the science. She felt that we had a question to answer and if I was willing to go on, maybe I could find a way to answer it. In science, when you find out why something isn’t working, very often you find unexpected results.” The unexpected result for Lecuit was the discovery of the single amino acid variation between mouse and human E-cadherin that opened a new window on species specificity.

### High Impact and the Academy

Cossart also brings energy to her responsibilities outside the Pasteur, including her membership in the French academy, according to Lecuit. Last year, Cossart organized an unprecedented session at the academy. She invited six young researchers from around France whose work had recently appeared in high-impact journals, along with their PIs, to present. By all reports, it was a triumph of cutting-edge bioscience and time management. Each PI had five minutes to introduce the work and the young researcher. The young researcher had 15 minutes to speak. The academicians had 10 minutes for questions and discussions. The Institut de France’s building with its famous dome opposite the Pont des Arts is a landmark of central Paris, says Marc Lecuit. “For young people to be selected to present at the institute, well, let’s say that it’s better than the average guest seminar invitation.”

According to Bierne, the chief drawback in working with Cossart these days is her heavier travel schedule. “But when Pascale wants to discuss science with you, she won’t take you to have a sandwich,” says Bierne. “Pascale prefers to discuss things over good food and good wine. In that, you can say that she is very French.”

“Pascale gives you energy,” adds Bierne. “She pushes you when you want to try something new.” ■