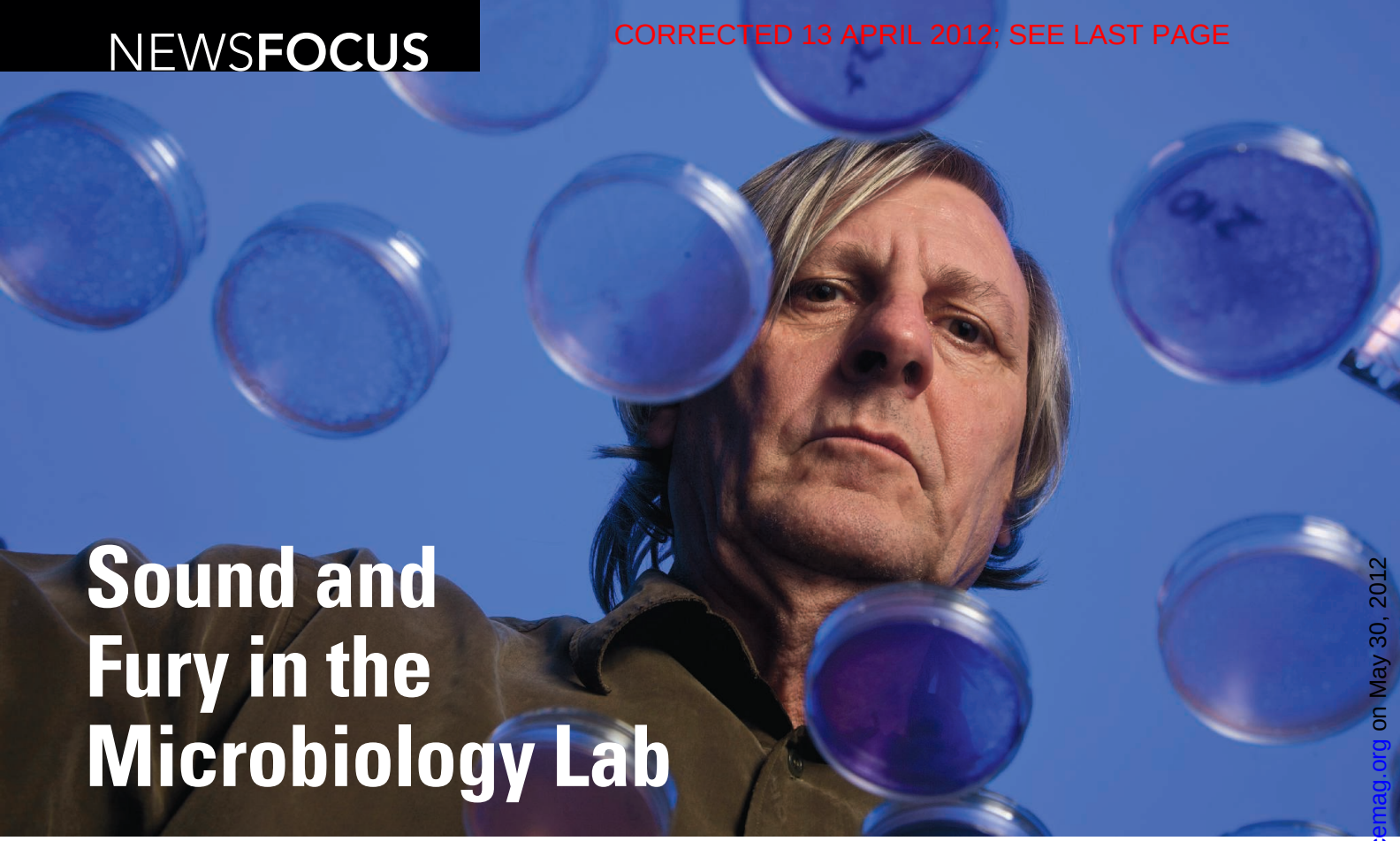
CORRECTED 13 APRIL 2012; SEE LAST PAGE



Sound and Fury in the Microbiology Lab

He's imaginative, rebellious, and often disdainful. Above all, France's most productive microbiologist loves a good fight

MARSEILLE, FRANCE—Didier Raoult has come a long way, even though he hasn't really strayed far from home. As an unruly, rebellious teenager in this port city with a reputation for toughness, Raoult was suspended from high school several times. But today, at 59, he's the most productive and influential microbiologist in France, leading a team of 200 scientists and students at the University of Aix-Marseille, here in the city where he came of age. He has discovered or co-discovered dozens of new bacteria, and in 2003, he stunned colleagues with a virus of record size, dubbed *Mimivirus*, the first member of a family that sheds an intriguing new light on the evolution of viruses and the tree of life.

But Raoult hasn't lost his edge. Long-haired and tall, his piercing eaglelike eyes sometimes cloud over in an expression of apparent fear, and he has a sense of provocation that many find irritating. Controversial and outspoken, Raoult last year published a popular science book that flat-out declares that Darwin's theory of evolution is wrong. And in an episode reminiscent of his teenage days, he was temporarily banned from publishing in a dozen leading microbiology journals in 2006, an episode that still enrages him. Raoult likes to say that "life is full of sound and fury," in a reference to the novel by William Faulkner—and in his case, it's true. "If my wife hadn't been a psychiatrist, I would be even crazier," he says.

Raoult's craziness may be a key element to his success. "He's very imaginative, a very hard worker, and very enthusiastic," says Jérôme Etienne, dean of the medical faculty at the University of Lyon and a longtime collaborator and friend. Despite its mammoth size, scientists at Raoult's lab say they wouldn't want to work anywhere else. "He's my boss because he's one of the greatest microbiologists in the world," says Philippe Brouqui, who has conducted research under Raoult for more than 20 years.

Yet Raoult is also known for his enmities and his disdain for those who disagree with him. "People don't like to talk about him because he has a lot of influence. He can make life hard for you," says one of several French researchers contacted by *Science* who would only talk about Raoult if they could remain anonymous. "Few of his science colleagues will find the thought of another profile story about him particularly appealing," geneticist Jean-Michel Claverie of Aix-Marseille University—who severed ties with Raoult in 2006 after a 5-year collaboration—wrote in an e-mail to *Science*.

A magical period

Raoult's career has always been tightly linked to Marseille, a city where his family settled when he was 8 and whose rough-and-tumble reputation matches his character. He trained as a physician and obtained a Ph.D. in human biology here; in 2004, he would name a rickettsia species, *Afipia quartiernordensis,* in honor of Quartiers Nord, a local neighborhood of ill repute.

Rickettsias, intracellular Gram-negative bacteria transmitted by ticks, fleas, lice, and acarids, have become Raoult's specialty. He worked on a disease called Mediterranean spotted fever, or Marseille fever, and studied typhus for 6 months at the National Naval Medical Center in Bethesda, Maryland. When he came back to Marseille in 1984, the university president offered him an assistant professorship. He combined his work as a physician with basic research and the development of new diagnostic methods. In 1987, Raoult's lab became France's national reference center for rickettsias, and in 1988, a collaborating center for the World Health Organization for arthropod-transmitted bacteria.

He owes many of his discoveries to well-chosen collaborations. From heart valve

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samples provided by cardiologists in Lyon, for instance, he managed to isolate *Coxiella burnetii*, a bacterium already known to cause a zoonosis transmitted by cattle, goats, and sheep called Q fever. He showed that *C. burnetii* was also involved in endocarditis, an inflammation of the inner layer of the heart. He went on to discover several other microbes that cause endocarditis. "One of the keys to Raoult's success is his ability to make bacteria grow where others fail," says Michel Drancourt, who has worked in Raoult's group since 1984.

When the genomics revolution arrived, Raoult jumped to apply it in microbiology. In 1992, he bought his first DNA sequencing machine and started to fish for typical bacterial sequences in various samples with the aim of identifying new species. He sees "metagenomics," the analysis of microbial DNA in environmental samples such as seawater or soil, as a window on entirely new worlds in microbiology. "We're in a magical scientific period, an era of discoverers," he says.

Fatherly spirit

One afternoon in August, during the ritual Friday meeting, a young Ph.D. student in Raoult's genomics group delivers a 10-minute talk about the sequence of a newly isolated bacterium. Raoult listens intently and then, in a warm voice, tells her how to proceed with the research. The Asian woman nods shyly. The other students of the group—many of them non-French as well—appear to be listening with deference.

"For foreign students, Raoult's lab is a springboard [to a career]," says microbiologist Patricia Renesto of Joseph Fourier University in Grenoble, who spent several years in Raoult's lab and admires him. "The flip side is that he controls everything. He can behave odiously," she adds. "Raoult has that fatherly family spirit, which some people don't understand," Brouqui says.

After the meeting, back at his office, Raoult boasts that the newly isolated microbe was one of 225 different bacterial species found in a single stool sample from Dakar. "The world record was 80 species. We beat it by a factor of two and a half," he says. "Half of those species have never been isolated from the gut before, and 21 are completely unknown."

Raoult's entire opus appears to be written in big numbers. A recent PubMed search showed him as an author on more than 1400 papers, including the description of more than 60 new bacterial species and one new bacterial genus, which Drancourt named *Raoultella*. But some scientists grumble that manuscripts out of Raoult's lab often contain errors, for instance, as a result of unchecked genetic sequences.

Indeed, problems in a paper about a mouse model for typhus got his lab in hot water in 2006. A reviewer for *Infection and Immunity*, a journal published by the American Society for Microbiology (ASM), discovered that four figures in a revised manuscript were identical to figures in the original manuscript, even though they were supposed to describe a different experiment.

In letters to ASM, made available by Raoult, second author Christian Capo and last author Jean-Louis Mège, a group leader, accepted "full responsibility" for the problem, which they said involved only two figures. Capo, in his letter, wrote that he had made an innocent mistake; Mège wrote that Capo had subsequently failed to show the

Big surprise. Raoult's team initially mistook the giant *Mimivirus* (illustration), discovered in a cooling tower, for a bacterium.

revised manuscript to other authors, who were on vacation, before resubmitting it. But after consulting its ethics panel, ASM banned all five authors, including Raoult, from publishing in its journals for a year. "We are not entirely comfortable with the explanation provided," ASM officials wrote to Mège. "Misrepresentation of data … is an affront to the ethical conduct of scientific inquiry."

Capo and Mège accepted the decision, but Raoult wrote ASM that he wasn't at fault and that the "collective punishment" was "very unfair." He appealed the ban, also on behalf of two other co-authors, but lost. Furious, he resigned from the editorial board of two other ASM journals, canceled his membership in the American Academy of Microbiology, ASM's honorific leadership group, and banned his lab from submitting to ASM journals, in which he had published more than 230 studies. His name has been on only two ASM journal papers since, both published in 2010. To clear his name, Raoult sent his ASM correspondence to French colleagues in 2007, along with a letter defending himself. "If I had been in the United States, I would have sued," he wrote.

Still, the affair does not appear to have dented Raoult's career. From 2013 onward, he will head a new government-funded academic medical center of excellence that will combine the expertise of various research and medical agencies in infectious and tropical diseases in Marseille.

Charlatans

Despite his long career in bacterial research, Raoult has become best known for the discovery of giant viruses. The story began in the late 1980s, when Timothy Rowbotham, a bacteriologist at the Public Health Laboratory in Leeds, U.K., isolated amoebae that had *Legionella* bacteria living inside them. In one amoeba, Rowbotham discovered another putative bacterium that he could not identify.

He later sent the amoeba collection to Richard Birtles, a Ph.D. student in the United Kingdom. Always interested in new microbes, Raoult invited Birtles to come work in Marseille. Even there, the unknown amoeba resident initially defied identification—until the team looked at it using an electron microscope. It was not a bacterium at all but a novel virus bigger than any known virus. With a diameter of 700 nm—including its hairy crown—*Mimivirus* was also stuffed with a genome of 1.2 million DNA base pairs, six times bigger than any known DNA virus and bigger than some bacteria. Genetic comparisons showed that the unusual virus belonged to the group of nucleocytoplasmic large DNA viruses, which also includes the poxviruses. Raoult baptized it *Mimivirus*, short for "mimicking microbe," and the new family Mimiviridae.

Mimivirus turned out to have an interesting genome. An analysis performed with Claverie's team showed that it includes genes involved in DNA processing and protein production that were until then considered to be unique to living organisms. The finding revived the old debate about viruses' place in the tree of life, and Raoult has now staked out a strong position (see sidebar, p. 1035). But David Moreira of the University of Paris-Sud in Orsay says Raoult is out of his depth: "He has a tendency to throw himself into a field he doesn't know well."

Some scientists argue that the same is true for epidemic modeling, a field that has seen tremendous growth but which Raoult

Giant Viruses Revive Old Questions About Viral Origins

Where did viruses come from? And are they alive? Didier Raoult's 2004 discovery of the *Mimivirus*—and several other giant viruses identified since then—has brought those questions, debated for a century, back to the scientific fore.

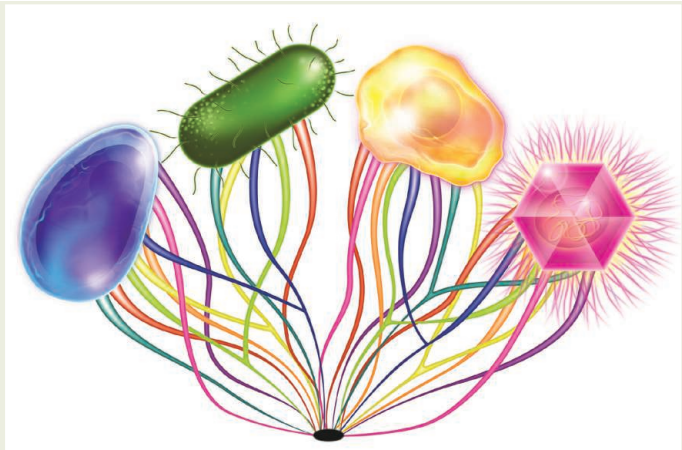
When viruses were discovered in the early 20th century, some scientists saw them as the missing link between the inanimate world and living organisms—a group that predated and perhaps gave rise to cells. But genetic data collected later supported an opposing view, in which viruses emerged from pieces of genetic material and other molecules broken out of cells; they would evolve further by stealing more genes from cellular organisms. This view suggests that viruses aren't part of the tree of life but are an ever-changing sideshow to its three domains: the Archaea, Bacteria, and Eukarya. In 2000, the International Committee on Taxonomy of Viruses officially declared that viruses are not alive.

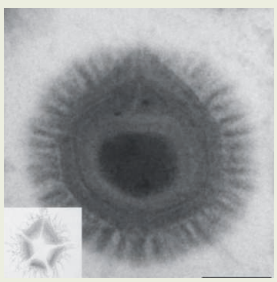
The genetic makeup of the *Mimivirus* has challenged this view. The viral giant is endowed with many genes encoding the enzymes that repair DNA, correct errors occurring during its replication, produce mRNA transcripts from genes, and translate those mRNAs into proteins. These so-called informational genes had so far been considered hallmarks of living things. Known viruses hijack the products of these genes from the cells they infect to replicate; the *Mimivirus* genes had never been found in viruses before. Based on the genome, Raoult and others have concluded that this class of virus has likely inherited its giant genome from an ancient viral ancestor endowed with the entire protein-translation machinery rather than picking up the genes piece by piece.

Not everybody was convinced. In 2008, David Moreira of the University of Paris-Sud in Orsay and his colleagues published an analysis showing that 126 *Mimivirus* genes have counterparts in cellular organisms, which they said supported the view that, despite its extreme size, *Mimivirus* has evolved by picking up genes here and there.

Raoult stuck to his guns, and in a paper published in 2010 proposed a theory that went further: Not only does *Mimivirus* belong in the tree of life, but nucleocytoplasmic large DNA viruses (NCLDVs), the class to which it belongs, trace their origin to the very beginning of life on Earth, forming a fourth domain alongside the three well-established ones. His view was based on a phylogenetic analysis of eight DNA-processing genes shared by NCLDVs and the three known branches of life, in which the NCLDVs' versions seemed to form a separate cluster.

But constructing such phylogenies reaching back eons is tricky business, because similarities in genes don't always reflect shared ancestry; the same DNA sequence may have arisen independently in genes of different origins, a process called convergent evolution. In a paper published in June 2011, a team led by Eva Heinz of Newcastle University in the United Kingdom repeated Raoult's analysis but used different models of evolution that take this phenomenon into account. In their phylogenetic trees, the fourth domain evaporated, and the NCLDV genes were spread out over the other branches of life.





Even bigger. *Megavirus chilensis* (*left*) strengthened the case that giant viruses share a common ancestor. Didier Raoult believes they form a fourth domain, pictured here in magenta in a drawing from his lab.

For now, Raoult's position in this debate has few supporters. But the idea that giant viruses share ancient common ancestors was bolstered by a paper published in the *Proceedings of the National Academy of Sciences* last October by Jean-Michel Claverie of the University of Aix-Marseille—once Raoult's collaborator but no longer on speaking terms with him. Claverie recently isolated *Megavirus chilensis*, a virus distantly related to *Mimivirus* but even bigger, off the coast of Chile. In the paper, he reported that *Megavirus* shares 53% of its genes with *Mimivirus*; of seven genes encoding key steps in protein translation, four have a homolog in *Mimivirus* and had never been found in a virus before. "This rules out the scenario whereby those genes were acquired independently by both viruses," Claverie says. Even Moreira says the paper won him over for a common viral ancestor between the two viruses.

Edward Holmes, a virus evolution specialist at Pennsylvania State University, University Park, notes that ongoing fishing expeditions for new viruses—not just the giant ones—are likely to resolve the origins of these infectious agents. "It's naïve to say that we understand the history of the evolution of viruses based on current samples," Holmes says. "There may be undiscovered viruses on our planet, some completely novel." **–C.M.**

has repeatedly attacked as useless. Epidemic modelers are "charlatans," he says. "There are zero examples in infectious diseases of something that has been predicted by a model."

And then there is his popular science book *Dépasser Darwin* (*Beyond Darwin*). "Darwin was a priest," Raoult says, claiming that the image of the tree of life that Darwin proposed is inspired from the Bible. "It also is too simplistic." Raoult questions several other tenets of modern evolutionary theory, including the importance of natural selection. He says recent discoveries in genetics show how frequently genes are exchanged not just between different microbial species but also between microbes and complex organisms, for instance, in the human gut. That means de novo creation of entirely new species is possible, Raoult argues, and Darwin's branching tree of life should be replaced by a network of interconnected species.

"It's dangerous to say those things," says Moreira, who worries that Raoult is providing creationist groups with ammunition. "He goes a bit too far," says Eugene Koonin, an evolutionary biologist at the National Center for Biotechnology Information in Bethesda. "Darwin's theory is relevant but is incomplete. It does not apply to the evolution of microorganisms."

Raoult says he doesn't really care what other people think, and he relishes the constant storm around him. "An amazing thing I discovered when I arrived in Marseille was that the people there are fighters," he recalls. It's why he feels at home here. For Raoult, the fights never stop. **–CATHERINE MARY**

Catherine Mary is a writer in Caluire, France.

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News Focus: "Sound and fury in the microbiology lab" by C. Mary (2 March, p. 1033). The article said that a reviewer for *Infection and Immunity* raised concerns about four figures in a revised manuscript by Raoult and colleagues. The article should have made clear that at issue were panels within a single figure of the revised manuscript. As the article stated, one author acknowledged he had made a mistake, but only two panels were in error.