

## Howard J. Worman

When Howard Worman's scientific ship finally came in, it arrived via France. In 1999, Worman, who is at Columbia University Medical Center, heard from his longtime collaborator Jean-Claude Courvalin in Paris. Courvalin had startling news from two colleagues at INSERM, the French national biomedical research arm. "They told me that they had a patient with a myodystrophy who had a mutation in the lamin A/C gene. I was stunned," Courvalin recalls. Geneticist Ketty Schwartz and her postdoc, Gisèle Bonne, had linked autosomal dominant Emery–Dreifuss muscular dystrophy (EDMD) to the lamin gene, *LMNA*. Courvalin told them that this was a major discovery, a major paper surely, and great news for his friend Howard Worman in New York, who had cloned *LMNA* in 1993. "But first they asked me, 'What is a lamin?'"

At the time, Worman and Courvalin were among the few cell biologists who could answer that question in any detail. Lamins are the nuts and bolts of the nuclear envelope: intermediate filaments that keep chromatin safe inside, anchor the nuclear pore complexes that gate the nucleus, and form the nucleus's meshlike inner casing. Courvalin explains, "Until this [EDMD] connection turned up, it was just science—cell cycle and fundamental cell biology. Suddenly it became disease—cardiomyopathy, premature senescence, lipodystrophy. Suddenly it was really hot stuff."

Lamins are still hot stuff. Defects in lamins and other nuclear envelope proteins are now linked to a wide range of disorders involving skeletal muscle, heart muscle, the peripheral nerves, adipose tissue, bone, neutrophils, and the liver. Defective lamins are implicated in an accelerated aging syndrome called progeria (Hutchinson–Gilford progeria syndrome) and even in normal aging. For lamin researchers like Worman, it's been a heady time in the scientific spotlight after years of quiet slogging.

### Mapping Lamin Genes

"Howard is one of the original nuclear lamina people" and deserves the attention, says Kathy L. Wilson of the Johns Hopkins School of Medicine, who counts herself among "the crazy few" who took an early interest in nuclear lamins. "Howard helped discover the field and kept it going. He mapped lamin genes before anyone cared where lamin genes would map."

Wilson says that as a practicing physician and a bench scientist, Worman brought something else to the lamin field. "Howard was unique in the field because he's always had his finger on the pulse of medical relevance." According to Wilson, only after the EDMD connection was made did physicians and geneticists take any special notice of the nuclear lamina genes. "I've heard Howard call it 'the invasion of the positional cloners,'" she says. "Suddenly they were able to map diseases, and every other one was related to lamins."

Being a doctor and a cell biologist has always been important to Worman. Worman says that, ironically, his clinical specialty, liver disease, has had only limited relevance to his bench expertise with lamins, at least until now. In any case, lamin seminars have changed, says Worman. "For years I used to go to meetings with the same three cell biologists. All of a sudden this connection is made to disease and I'm going to meetings with neurologists, cardiologists, endocrinologists, geneticists, and pediatricians."

Worman's own lab has certainly spread out to study the class of disorders that are now called "laminopathies." Worman is looking at the effect of abnormalities in lamins and associated nuclear envelope proteins on keratinocytes, in familial partial lipodystrophy, and on activation of the mitogen-activated protein kinase pathway in X-linked and autosomal dominant EDMD. His training in cell biology and his practice in internal medicine are coming together. The good thing about doing internal medicine is that

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he can understand all these diseases, he says. “It’s a great advantage now to have had solid training as a general internist. If I had trained in a more limited specialty, I might not understand the wide range of disease connections to lamins.”

### Next Slide, Please

Worman clearly remembers why he became a physician. His parents, who were not doctors, thought that it was the perfect job. “Back in those days, it may have been, but the practice of medicine has changed a lot since the 1960s,” he adds—and not for the best. He has a harder time explaining why he became a cell biologist. Medical school was his goal as a Cornell undergraduate, but he was always drawn to the lab life. At Cornell, he worked in several labs and completed a senior honors project in biochemistry. Perhaps it was his work–study job that led him to cell biology. “I was the projectionist for the chemistry department seminars. So every week I was forced to listen to esoteric seminars that were way over my head. I think that may have had some impact.”

Worman chose the University of Chicago Medical School, partly because it had a reputation for encouraging medical students who were interested in research. At Chicago, he was first author on two reports about vesicle membrane transport under physiologist Michael Field. For his internal medicine residency, Worman chose New York Hospital (now part of Cornell-Weill), partly because it was down the street from the Rockefeller University. In 1987, he interviewed with Günter Blobel at Rockefeller to see if he could do research in Blobel’s lab during his “short track” residency as a postdoc. He stayed a little more than three years. As Worman recalls it, Blobel said, “You know, somebody like you comes to me; you’re

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Blobel promptly steered him into nuclear

lamins, which had just been identified as intermediate filaments, the largely overlooked third component of the cytoskeleton. “Günter told me, ‘You should work on the nuclear envelope. There is very little known about it so it’s wide open.’ I’d never thought about the nuclear envelope much except the one half-lecture we had in medical school.”

### Second Opinion

Worman soon knew much more, eventually cloning the lamin B receptor that anchors the nuclear lamina and chromatin to the nuclear inner membrane. In 1990, Worman took his first faculty job at the Mount Sinai School of Medicine. He was still intent on combining science and medicine, so between grant writing and lab building, he served an “intensive apprenticeship” with Fenton Schaffner, a legendary specialist in liver disease. “He was *the* guy in the liver world,” Worman remembers. “Everyone went to see him, at least for a second opinion.”

Schaffner’s caseload was an encyclopedia of liver disease. In six months, Worman saw 150 patients with primary biliary cirrhosis, a rare condition anywhere else but in Schaffner’s Mount Sinai practice. Worman learned that patients with primary biliary cirrhosis often have antibodies against nuclear envelope proteins, a finding that he has doggedly pursued but not yet completely resolved.

In 1995, Worman was jointly recruited by the departments of medicine and of anatomy and cell biology at Columbia, where he remains today, running a large nuclear lamin lab and a small clinical practice in liver disorders. Worman was at Columbia in 1999 when he had word from Courvalin, his collaborator in Paris, that Worman’s *LMNA* gene had been linked to autosomal dominant EDMD. Soon afterward, mutations in *LMNA* were shown to cause several other very different diseases. It was an important discovery, according to Courvalin, but it came in the context of a lot of basic cell biology work, much of it done by his friend Worman.

### From Gene to Symptoms

Says Courvalin, “We could never have imagined that this protein could cause a myopathy. It’s a protein that is present in all cells, in the brain, everywhere—so why only a muscle disease?” But the genetic discovery would have been meaningless without the lamin protein background, Courvalin believes. “When you describe a new genetic disease, the link between the gene and the symptoms of the patients is often completely unknown. There are many

steps to analyze what happens at the organ level, then the tissue level, and then the molecular level. It can take 20 years of hard work to make the connection. In deciphering the cell biology of these steps, Howard was the pioneer.”

Even with the explosion in clinical relevance of his research, cell biology is still central to his approach, says Worman. So is membership in the ASCB, which Worman joined while a postdoc in the Blobel lab. “I think that the ASCB has the best science,” he says. “My lab training was in cell biology, and most of the things we do in the lab are still cell biology.” As one of the few M.D.s in the ASCB with a foot in both the basic research and clinical worlds, Worman says, “I’d like to see M.D.s and translational researchers get more involved in the Society. The ASCB is the world’s leading [cell biology] organization, and to tie cell biology more in with medicine would be a great thing to do.”

Outside the lab, Worman remains the quintessential New Yorker, even if he was born and raised across the Hudson River in suburban New Jersey. He lives in a co-op apartment on Manhattan’s Upper West Side with his

wife, Terry, a serious student of high cuisine and, by all reports, a formidable chef in her own right. Says Howard Reynolds, a medical colleague, former Worman postdoc, and old friend, “Terry is about as expert on that as Howard is on lamins.” The Wormans have two children, Max, 5, and Naomi, 4. Their father says that the children enjoy Thomas the Tank Engine, dressing up, and video games. “They are little kids, interested in little kids’ things.” Worman himself admits to an obsession with the Yankees (“I’m an above-average fan,” he says, “but not insane”) and the latest restaurants, an enthusiasm he shares with Terry. Their friend Reynolds parses it differently: “Terry really knows good food. Howard is a world-class eater.”

Then Reynolds quickly adds that Howard Worman knows his lamins, his clinical field, and his place in the future of medicine. Says Reynolds, “Back when we were young—when we were baby doctors—Howard always had this clear view of the balance in American medicine of basic research, of clinical research and teaching, and of clinical care. He still has it.” ■

—John Fleischman

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### Postdoc Position Available in Virginia

A postdoctoral position is available immediately at Eastern Virginia Medical School, Norfolk, in the Hampton Roads/Virginia Beach area. Position is in the Department of Microbiology and Molecular Cell Biology. Candidate must have experience with molecular biology techniques, and experience in protein purification is preferred. Project will focus on MCM8, new member of the MCM family of proteins. See *NAR*, 2003, Vol 31, 2915-2925 and *MRT*, 2008, Vol 71, 288-297. Candidate must be interested in chromatin analysis and cell cycles studies. Prefer candidate already within the USA. Interview preferred. Please direct CV to address below. EVMS is an Affirmative Action/Equal Opportunity Employer and Drug Free Workplace.

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