

THE UNINTENTIONAL SCIENTIST

JOAN MASSAGUÉ
WAS HAVING
TOO MUCH FUN
TO NOTICE HE
WAS BUILDING
A CAREER—
AND SOLVING
PROBLEMS OF
CELL SIGNALING
AND CANCER
METASTASIS.



JOAN MASSAGUÉ SITS IN HIS 13TH-FLOOR OFFICE

at Memorial Sloan-Kettering Cancer Center's new high-rise research building and spreads his hands to indicate both what is visible—the modern decor, the large chunk of quartz on the windowsill, the sepia drawing of two greyhounds racing—and what is not—the unlikely start of his career. He shakes his head with amusement. “Through the smallest of back doors,” he says.

It's a good story, and he knows it. In fact, the trim, dark-haired man with the genteel manner, musical Catalan accent, and keen memory for Eric Clapton and Bob Dylan lyrics, still seems surprised by where he's landed.

When Joan (Joe-ahn) Massagué came here from his native Barcelona in 1979, it was supposed to be for two years, max. The plan: do a postdoctoral fellowship at Brown University, publish one paper in the *Journal of Biological Chemistry* (literary mecca for young biochemists), have a great time, and go back to Spain. He had no intention of making a career of science. That, he says, was not really a possibility in the Spain of 30 years ago, where the handful of science positions were occupied by older scientists who didn't make room for the next generation.

Instead, when he returned, he would likely settle down at a pharmacy, perhaps the one owned by his parents, both phar-

macists. He'd get his science “fix” other ways—studying geology, for instance, collecting rocks and crystals, a favorite hobby since his father bought him his first rock collection for his 13th birthday.

In 1970s Spain, says Massagué, a bachelor's degree was considered the career-defining degree. Few bothered to pursue an education further. “The Ph.D. was extra,” he says. “It was an activity almost to self-cultivate.”

And the postdoc in the United States? “I did it because I liked the Ph.D. so much, I said, ‘What the heck? Let's enjoy another two years.’” After earning a Ph.D. at the University of Barcelona, he searched out a postdoc position overseas and signed on in the lab of a young investigator named Mike Czech at Brown University, who was studying insulin receptors.

Two years in the United States came and went and over the next decade Massagué's drive took over (“I am determined and intense by nature”), and two things happened. He became known as the man who cracked the TGF-beta pathway—a complex molecular “conversation” by which cells tell their neighbors to stop dividing, among other things. And Massagué began to realize just how critical that message might be in cancer, a disease in which cells' primary mission is to divide and divide and divide.

The cancer community realized the importance of these signals, too. By 1989, Memorial Sloan-Kettering Cancer Center

had installed Massagué as chair of its cell biology program. In 1990, he became an HHMI investigator. When the Cancer Center created a cancer biology and genetics program in 2003, Massagué became its chair. Just before, in 2000, as a run-up to his 50th birthday, Massagué and his lab had switched their focus to metastasis and quickly began electrifying that field, identifying different sets of genes that drive the spread of breast cancer cells to the bone or the lungs. That work, says Larry Norton, Memorial Sloan-Kettering deputy physician-in-chief for breast cancer programs, “is hot as a pistol.”

A COMPETITIVE STREAK

“It was obvious, right off the bat, that [Massagué] had extraordinary talent,” says Czech. “He was a dream postdoc, someone who really went after the science, and who was dedicated to the sheer fun of discovery.” And unlike many postdocs, Massagué didn't have the distraction of wondering what he was going to do next, or how he was going to make a name for himself.

At the end of the two-year postdoc, Czech offered Massagué a non-tenure-track assistant professorship, with the option of spending 50 percent of his time on whatever he wanted, at the University of Massachusetts Medical School, where he had relocated his lab. It was an unusual offer. “We, in academia, don't usually retain people who've trained in our depart-

ment,” says Czech. “It’s an extraordinary breach of the way we operate. Joan was one of only two exceptions I can think of in 30 years.”

But the honor was lost on Massagué, who didn’t really see the point. He was going back to Spain with his wife, Roser Salavert, whom he’d met in Barcelona and married shortly after starting his postdoc. Massagué asked what gain there would be in it, to which Czech, among other persuasives, answered that there’d be a few thousand extra dollars in his paycheck. “That I understood,” says Massagué. He had only one more question. What, he asked Czech, was tenure?

He took the offer and, with characteristic fearlessness, decided to try to identify the receptor for transforming growth factor

beta—i.e. TGF beta. Growth factors are chemical telegrams that cells release into the space between one another. The growth factors then make their way to nearby cells, latch on to them via a receptor on the surface of the cell, and deliver their message. Only that’s just the start, because the message actually needs to be passed to a number of different players before it’s received and acted upon.

Little was understood about TGF beta, its receptor, the details of how its message got relayed, what the message said, and what happened as a result. It was so complicated, even people in the field kept their distance.

“I was told that it was very difficult, that I might fail,” says Massagué. “I said, ‘I don’t care, I’m going back to Spain. This

is just to kill some extra time.’” He’d already done more than he’d set out to do in the United States. He had nothing left to prove to himself. “I thought I was already enough of a success,” he says. “Had I been a little more sophisticated and engaged in the career mode,” he says, “I would have been petrified to realize where I stood.”

Massagué told Czech he needed 100 percent of his time for TGF beta, obtained an independent investigator (R01) grant from the National Cancer Institute, and identified the receptor for TGF beta. In fact, somewhat to his dismay, he identified three of them, which meant triple the work figuring out what they all did. But his curiosity was piqued. He wanted to know what

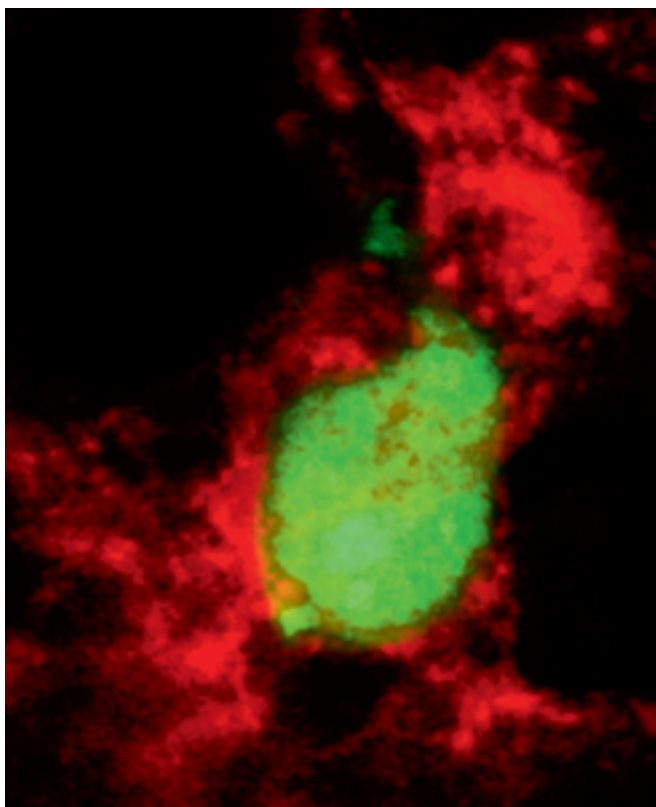


Image: David Padua / Massagué lab Photo: Mark Mahaney

A HUMAN BREAST CANCER CELL (GREEN) LODGED IN A MOUSE LUNG CAPILLARY IS SURROUNDED BY A RED DISRUPTION OF THE VASCULAR ENDOTHELIAL CELLS, CAUSED BY THE CYTOKINE ANGIOPOIETIN-LIKE 4, WHICH, ACCORDING TO STUDIES IN MASSAGUÉ'S LAB, IS INDUCED BY TGF-BETA. THE WEAKENED ENDOTHELIUM ENABLES THE SEEDING OF PULMONARY METASTASES.

happened next. What chemical did that receptor make once TGF beta activated it? What gene did that chemical touch? What did the gene do as a result? Each answer only made him want to go further. “I didn’t anticipate working on the entire pathway,” he says. But Massagué felt driven to know the whole story. Eventually, he says, the TGF-beta pathway became his “playground.”

During the next six years, he mapped out most of the molecular minutiae of the pathway. By then, he was working at a feverish pace—and starting to look over his shoulder a bit. “At that point, I was not easygoing about it anymore,” he says. “I had something I really wanted. I saw that I could crack this problem and I wanted to do it.” That’s when a friend gave him the drawing of racing greyhounds. “As naïve as I was, I’m a pretty competitive guy,” he says. “I’m happy not to race, but when I race, I like to win.”

His biggest fear, he says, was that he would be foiled somehow in finishing his project. If someone else got there first, it might cut off support or funding. “It was like I was sitting in front of a canvas and I had conceived of a painting. And I *had* to paint it,” he says. “And I didn’t just want to paint the arm, or the head. I had to paint the whole thing. I was happy to have other greatly talented people right next to me painting the same view. But I had to do my own whole portrait of it.”

HIS ARTISTIC VISION

The ability to imagine the big picture, and to visualize molecules and processes that are too small to see in literal terms is one of Massagué’s unique talents, according to colleagues. “The way he sees things is not always the way in which the conventional scientist sees things,” says Gaorav Gupta, a medical resident at Memorial Sloan-Kettering who was a graduate student in

Massagué’s lab. Only occasionally, says Gupta, does one get to see from his point of view, usually when all the experiments have been done and it’s time to write the paper summarizing the results.

“That’s when Joan shines,” says Gupta. “He’s able to craft the story as he saw it, probably from the very beginning.” And he’s able to draw it. His drawings of scientific processes, says Gupta, are as good as many professional artists’. “I think that’s how he’s made his career,” says Gupta.

“Mechanism on one side, artistic vision on the other.”

As the would-be pharmacist was deciphering the TGF-beta pathway, leading medical institutions in the United States and Europe courted him. He accepted the job at Memorial Sloan-Kettering, because he wanted to apply what he was learning to a cause—the understanding of cancer.

With the 1989 move to Manhattan, Massagué says, it became clear that he wasn’t going back to Barcelona. His



WITH ROOTS IN NEW YORK AND BARCELONA, MASSAGUÉ HAS SET OUT TO SOLVE PROBLEMS OF CANCER METASTASIS IN HIS U.S. LAB AND HELP HIS SPANISH HOMETOWN BUILD ITS RESEARCH INFRASTRUCTURE.

Mark Mahaney

“AS NAÏVE AS I WAS, I’M A PRETTY COMPETITIVE GUY. I’M HAPPY NOT TO RACE, BUT WHEN I RACE, I LIKE TO WIN.”

parents were going to have to find someone else to run the pharmacy. And his daughters, Laia and Marta, both born here, were going to be Americans of Catalan heritage. His wife, Roser Salavert, today a district community superintendent in Manhattan’s Department of Education, had the foresight to get her doctorate in education, just in case the United States became their permanent home. “We always kept a very open mind,” she says. Massagué had embraced the life of a U.S. scientist.

But he wasn’t about to cut his Catalan ties. Both of his parents grew up in villages. His paternal grandfather was the village pharmacist. His maternal grandfather was a farmer and the village ironsmith. Eventually, his father’s family moved to Barcelona. His mother was sent there to study to be a pharmacist—an unusual decision for a traditional family.

Unfortunately, her first year of school was 1936—the start of the Spanish Civil War. “She had a very hard time,” says Massagué. “She went back to her village to find her father and brother gone and did not know if they were alive.” She lived with her mother for a time, until her mother was jailed. After the war, the family reunited, and Massagué’s mother, with a doggedness she’d pass on to her son, returned to Barcelona and her studies.

That’s how she met Massagué’s father. They married and passed along their love of science and learning to Massagué, the

eldest of their six children. “I had a natural inclination for natural sciences as a kid,” says Massagué. “I loved butterflies. I fell in love with minerals. I like bird watching. Botany. Sociology. Everything.”

And when the opportunities came his way in the United States, his parents were supportive. “They never asked, ‘Why are you hanging so long in the U.S.? When are you coming back?’” he says. “It was, ‘Go for it. This is lovely. Don’t worry about the rest, the pharmacy, others can run it.’”

THE NEXT CHALLENGE

He could have spent the rest of his scientific days as the TGF beta guy. But around 2000, Massagué got the itch for a new problem to solve.

Going back to Spain was an option, but he was already back several times a year, to visit family and to help Barcelona expand its research capacity. Since 2005, he has been adjunct director of the new Institute for Research in Biomedicine in Barcelona, whose director is Joan J. Guinovart, Massagué’s Ph.D. thesis advisor. That, he says, allows him to cultivate his life “as a man from New York and Barcelona.”

Characteristically, the new problem he chose was the toughest in cancer biology: metastasis, the process by which cancer cells leave the tumor of origin and take root in other parts of the body.

Metastasis was recognized as far back as ancient Egypt. But it’s still a huge

problem, perhaps *the* problem of cancer. “All the chemotherapy, or the bulk of it, and the radiation, after the surgeon is done, is to prevent metastasis,” says Massagué. “If it were not for metastasis, cancer would be a minor fraction of the problem it is today. You’d just go to the O.R., have the lump taken out, and go home. It would be little more than going to the dentist.”

To find the key controls for cancer’s spread, Massagué had to think up a novel way to collect the cells that had the knack both to metastasize and to successfully set up shop. Not easy; cells aren’t very efficient at the whole metastasis game. Primary tumors shed millions of cells into the bloodstream every day. “And yet,” says Massagué, “if we die of metastasis, we don’t die of millions of metastases.” Which cells were the right ones to study?

He used cells taken from the tumor of a woman who had died of breast cancer and injected them into immunodeficient mice. Then he collected those that traveled to the bone—a common site of metastasis for breast cancer—and injected them into yet another batch of mice. In those mice, bone tumors developed in half the time, indicating that Massagué has recruited the worst offenders.

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microscope beam, a cryogenic “plunge freezing” to fix a biological sample, and a motor-driven stage to tilt it, one degree at a time, through two axes while a charge-coupled device camera reels off still shots of the sample. This river of images and positional data flows to a tomographic computer program, which merges it all and calculates three-dimensional models. With those, Jensen makes moving pictures of things once invisible. It is visually startling, technically astounding work but is balanced by other interests in Jensen’s life. His highest priorities are his wife and their six children. “I am a family man,” he says simply. Jensen spends time each week driving to piano, violin, and dance lessons; coaching basketball and soccer; and camping with scouts. “At night, I read bedtime stories to kids and sometimes rock our baby to sleep,” says Jensen.

Most of all, scientists have no sense of wonder: Which brings us to HHMI investigator Mark Schnitzer, a physicist turned neuroscien-

tist at Stanford who has developed a range of optical “needles,” fiber optic filaments honed into microscope lenses from 350 micrometers to 1,000 micrometers in diameter (a human hair is about 85 micrometers across). These are the eyes of a “microendoscope” that can be inserted into the deep brain structure of a living, moving mouse. Using laser pulses and fluorescent dyes, Schnitzer focuses his microendoscope on individual neurons or up to a hundred brain cells at a time.

Schnitzer’s science goes far beyond gee-whiz technology. His insertable microscope is already moving toward human applications to guide surgeons to better placements of cochlear implants or give researchers the inside view of muscle contractions at the level of sarcomeres, the basic contractile unit in striated muscle. “In imaging science, the data can be both informative scientifically and beautiful to the eye,” he says. Schnitzer sees the wonder all right. ■

FOR MORE INFORMATION: To learn more about the new 56, see www.hhmi.org/news/20080527.html.

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Among the things he has discovered from those wrongdoers: cells both start out with the capacity to metastasize and acquire it later. (Previous theories had been in the either/or category.) His team also discovered that many of the genes that support metastasis need to work in concert to achieve their goal. Activating just one or two of them doesn’t do the trick. In 2003, he reported on the gene combination found in breast cancer cells that are prone to spread to the bone. More recent research by Massagué, published in 2007, has focused on four genes that regulate blood vessel growth and appear to be critical to the spread of breast cancer to the lungs.

Experiments in mice revealed that silencing these genes individually decreased tumor cells’ ability to set up house in the lungs and that silencing them all basically shut the tumor down.

What’s more, two drugs already on the market—Eribitux and Celebrex—can counteract the action of these genes in mouse studies. Clinical trials may begin as soon as a year from now, says Norton, who is collaborating with Massagué on this work. Meanwhile, Massagué’s team has also discovered that certain microRNAs—small nucleotides that suppress gene function—are in short supply in some metastatic cells, suggesting, again, that a brake has been turned off somewhere. Adding them back to cells appears to turn off genes involved in cell proliferation and migration, neutralizing the cells’ ability to spread.

“If you silence the genes with microRNA molecules, or you silence their products with drugs that work against them, you accomplish a synergistic slow down of metastasis,” Massagué says. “In the pharmaceutical armamentarium we have, there may already be many things that one can resort to while waiting the proverbial 10 to 15 years to develop a drug on a newly found target.”

Of what comes next, Massagué is circumspect. “I don’t know. I’m the guy who initially was thinking in terms of five more months,” he laughs. Then his ambition surfaces and he gets serious. “Right now we are in the thick of deconstructing genes to see how they are used in metastasis and how one can intervene. I see myself, for at least another five years, wholly pushing, painting this new canvas: metastasis.” TGF beta, he says, has recently been implicated in metastasis of breast cancer to the lung—a neat connection of his work that he intends to explore.

There are, he says, plenty of questions to be asked—and answered. Why, for example, do different types of breast cancer migrate to the same organs—but use different genes to do so? He’s finally thinking about career trajectories—but maybe someone else’s. “One could start a career studying metastasis in his or her thirties and retire having worked on nothing else.” ■



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