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Massagué Selected to Receive Frontiers of Knowledge Award

The BBVA Foundation announced today that Joan Massagué, a Howard Hughes Medical Institute investigator at Memorial Sloan-Kettering Cancer Center, has won the inaugural Frontiers of Knowledge Award in Biomedicine.

According to the foundation, Massagué was honored for elucidating one of the fundamental processes that control cell division. The foundation said in its citation that Massagué's studies have considerably increased our understanding of the genetic and cellular bases of metastasis and have great potential for clinical application.

The BBVA Foundation, which has its headquarters in Madrid, is the philanthropic arm of the Banco Bilbao Vizcaya Argentaria – Spain's second largest bank. The Frontiers of Knowledge Awards consist of prizes in eight categories: Basic Sciences (Physics, Chemistry, Mathematics), Biomedicine, Ecology and Conservation Biology, Information and Communication Technologies, Economics, Finance and Management, Contemporary Music, Climate Change and Development Cooperation. The awards were established to recognize and promote research of excellence.

Massagué will receive the 400,000 euro (approx. \$550,000) prize at a ceremony in Madrid on June 18.

Over the past 30 years, our understanding of the birth and growth of tumor cells has expanded dramatically. Much less is known about metastasis, which enables cells to leave the primary tumor and spawn new tumors elsewhere. What surprises Joan Massagué is the length to which tumor cells go to take over the body.

Massagué became interested in human health while growing up in Barcelona. "But I didn't see myself as a physician," he says, "but as someone who wants to understand how diseases occur based on mishaps in physiology."

While studying insulin's action at the University of Barcelona and, later, at the University of Massachusetts, Massagué's interest strayed to a class of growth factors called transforming growth factor-betas. "These factors have a

profound influence on how cells go about the business of organizing themselves into tissues and organs," he says, adding that failure to obey their commands can transform normal cells into cancer.

Massagué emigrated to the United States in 1979, and by 1983 he had isolated TGF-beta from tumor cells. He then began to document that factor's many effects on cells, and identified and purified its multipart receptor.

By 1994, his group had discovered how TGF-beta activates that receptor. The same year, he and his collaborators showed that activating one arm of the TGF-beta pathway keeps cells from dividing. This explained why cells can become malignant when that arm of the pathway stops working, because tumors arise when cells proliferate unrestrainedly.

The researchers soon filled in the blanks between the beginning and end of the TGF-beta pathway and discovered proteins that commute into the nucleus to convey its inhibitory signal. Massagué derived a lot of satisfaction from this project because it usually takes many groups to accomplish such an undertaking. "Although I was trained as a biochemist," he says, "what really interests me is how a biological process works in its entirety."

The researchers later showed that cancer cells use various tricks to disable the TGF pathway's growth-inhibiting arm. But why go to the trouble when it would be simpler to disable the receptor, as colon cancer cells do? Further experiments showed that cancer cells that keep the receptor intact and just rid themselves of the pathway's growth-inhibitory arm are free to co-opt other arms to do their dirty work. "This was a wild moment for me," Massagué recalls. "It inspired me to study metastasis as a whole."

It was known that another arm of the TGF pathway boosts the production of a protein called interleukin-11 in mammary cells. When such cells are transformed and metastasize to bone, they are hemmed in by hard tissue. But bone is awash with TGF-beta, which can no longer keep these breast cells under control. Massagué found that the cancer cells use TGF to their own advantage because the interleukin-11 it helps them secrete recruits osteoclasts—the cells that chew up bone. By riddling bone with holes, the cancer cells create living space for themselves. "That was a real eye opener in terms of how complex and perverse the problem of metastasis really is," Massagué says.

In 2005, the researchers reported that a quartet of genes causes primary breast tumors to grow more blood vessels, which in turn promote tumor growth. The vessels, being highly permeable, also provide an easy escape route for the tumor cells. When the emigrants arrive in the lungs, they use the same four genes to pass from blood capillaries into lung tissue, where they spawn new tumors. "So a set of four genes has been selected for being very useful at three very important and very limiting steps of the metastatic process," Massagué says.

In studies reported earlier this year in the journal *Nature*, Massagué and his colleagues uncovered the first genetic clues that suggest how invasive breast cancer cells pry their way into the tightly protected interior of the brain, where they can grow into new and lethal tumors.

Massagué's team identified three genes that work together to fuel the spread of breast cancer to the brain. Their studies indicate that those renegade cancer cells use some of the same strategies that other breast cancer cells rely on to invade the lungs – but also need more specialized molecular tools to infiltrate the brain.

“This is the first paper of its kind that opens up a window into what it takes for cancer cells to attack the brain,” Massagué said. “It shows that is possible to start deconstructing this problem. Until now we knew almost nothing about it.”