On the trail of a cure for cancer

Joan Massagué has discovered secrets that can save lives. An expert in cell division and the spread of cancer, he is one of the 50 most quoted researchers in all scientific fields. He speaks to **Sarah Sherwood** about his recent work on metastasis and his hopes for a cure for cancer.

Image courtesy of IRB Barcelona

Joan Massagué

What got you started in science?

Nature and collecting things have always fascinated me. I remember the day we studied minerals in elementary school. The simple concept that metals could be extracted from mineral ores was like an epiphany for me. I was certainly curious about how things in the natural world worked, and I was fortunate enough to have parents who understood and cultivated this. They stimulated me and facilitated my learning – but never forced me. I think this instilled in me a true desire to learn more about things. On top of curiosity, family tradition certainly played a role. I come from a family of three generations of phar-

macists – my grandfather, uncle, father and mother were all pharmacists.

Naturally when it was time to decide what to study at university, I chose pharmacy. My studies went well, and I went from exam to exam, but it wasn't until the fourth year of the five-year programme that I realised that my true love was biochemistry. It seemed to me to be a boiling pot for ideas. The structure of DNA had been solved some years before, and provided a cornerstone on which many principles of biochemistry were based. Concepts like hormones acting on cells – and the possibility of understanding what exactly they were and what they did – intrigued me. So I decided to switch and do a doctorate in biochemistry.

My PhD thesis focused on the metabolism of glycogen and its control by insulin, a molecule that is involved in diabetes. One day the director of the department asked me, "Well, what is it you want to do?" I replied, "Find a cure for diabetes, of course." A good answer, he said, but too ambitious. Diseases need to be solved step-by-step and they would find a good enough project for me to work on. I remember nodding and giving him a vague answer, but thinking inside, "But what I really want to do is find a cure for diabetes."

From 1976 to 1979, my research thesis and early development as a scientist flourished under the inspiring guidance of my doctoral mentor, Professor Joan Guinovart. At the same time, however, I witnessed the limited prospects that academic scientists had for a future career in Spain. Decades of negligence by the government, meagre resources and poor leadership had made the prospect of research most unattractive. So in 1979 I left for a period of postdoctoral training at Brown University in the United States, convinced that those were going to be my final years as a research scientist.

I envisioned returning to Spain to pursue a career as a pharmacist or in the local pharmaceutical industry. Instead, one thing led to the next in the USA, and after a productive postdoctoral period with Professor Michael Czech, I found myself in 1982 as the head of an independent laboratory group at the University of Massachusetts. At that time, I switched from the study of diabetes to the study of cell and tissue growth, which is of relevance to cancer. In 1989, I was offered a department chair at the Memorial Sloan-Kettering Cancer Center in New York and I have remained there ever since.

Your recent research focuses on the study of metastasis – the process by which a tumour spreads from one organ to another, and which causes 90% of all cancer deaths. How does this happen?

Until recently, metastasis was thought to be such a complex process that we didn't even know where to begin. In recent years, however, we have begun slowly but surely to uncover its secrets. It was impossible to say, for example, what made a cancer cell release itself from one tissue and what made it stick to another. We know, for example, that in order for normal tumour cells to metastasise, they must undergo certain genetic changes, and also that the tissues that these cells will colonise must have certain characteristics that favour the invasion and growth of the tumour cell. Many people don't know, for example, that cancer cells that originate in the breast tend to colonise the bones, lungs, liver or brain. Tumours in the colon, however, usually metastasise to the liver or lungs, but rarely to the bones or brain. We're not only uncovering the genes that permit these specific migrations to happen, but also getting a step-by-step look at the process.

Recent work from my laboratory, for example, shows that the combined activity of four genes allows a tumour cell to escape from its natural habitat, and invade a distant organ. This is what happens when a breast tumour cell metastasises to the lungs. But what happens in one type of tumour does not always happen in another. We are now studying whether the same genes are involved, for example, in breast cancers that spread to the brain or to bones. Hopefully, if we can identify and understand the role of the genes involved in the spread of different types of cancer, we will be able to design drugs to deactivate these genes and halt the process.

Are you hopeful that a cure for cancer will be found in your lifetime? What do you think is needed to achieve this?

I'm very hopeful. Cancer treatment has seen incredible advances over the years and highly effective treatments now exist for certain types of tumours. Thanks to advances in research and the resulting drugs, some forms of childhood leukaemias, for example, have a remission rate of up to 90%, where patients show no signs or symptoms of the disease. However, there is still a long way to go. We need to discover new treatments that will be more effective, less toxic and less expensive than what we have at present.

It is clear that the best research, the kind that is really going to bring about important results, will require experts from many different fields working together – and for this we need better facilities and co-operation. Nowadays cancer research relies on sophisticated imaging techniques, high-resolution X-rays, genetics, gene transcription, computer science, molecular and cell biology, gene expression and biophysics – in addition to clinical expertise. This new culture of integrating clinical and experimental sciences creates real opportunities for productive interaction. The idea now is that within three decades we will know enough about

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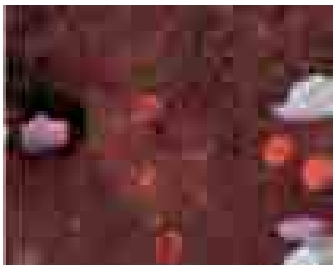
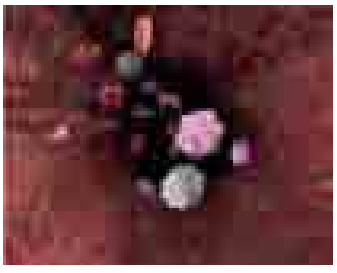
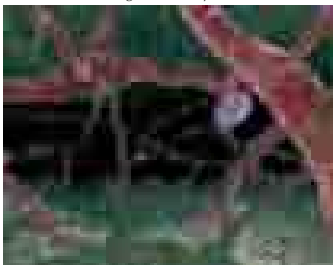




the biological and genetic basis of cancer to be able to make a difference.

How do results from research get out of the lab and into the hospitals where they can make a difference for patients with cancer?

Traditional therapies to treat cancer, including surgery, radiotherapy and chemotherapy, have made great strides in reducing the level of mortality caused by many types of cancer. But these strategies have generally focused on removing solid tumours, and then treating neighbouring cells with radiation and drugs to prevent the tumour from growing back. Often the main objective of this approach is to control the growth of the main tumour, when perhaps the problem also lies elsewhere – in secondary tumours that appear in other parts of the body when the cancer spreads or metastasises. Until recently, little research and few drug-discovery efforts have focused on this aspect. Knowing the genes that are involved in metastasis gives us some good targets for drugs that might work.

It is still early on, though, and the next step is to investigate these possibilities. First, potential drugs must be discovered and tested in the laboratory, in cell and animal studies. Once this process is finished and the potential drug proves to be promising, it must go through a series of clinical trials – developed by doctors – in which it is tested on a group of test patients with cancer to see how effective it is and whether it causes side effects. This is a long process, however, with no guarantees. In general, only very few potential drugs found in the laboratory reach the point of clinical trials, and it can take up to 15 years for a drug to be approved. It's a long process with an enormous investment in terms of time, effort and money, but well worth it in the end when we manage to find a treatment that saves lives.

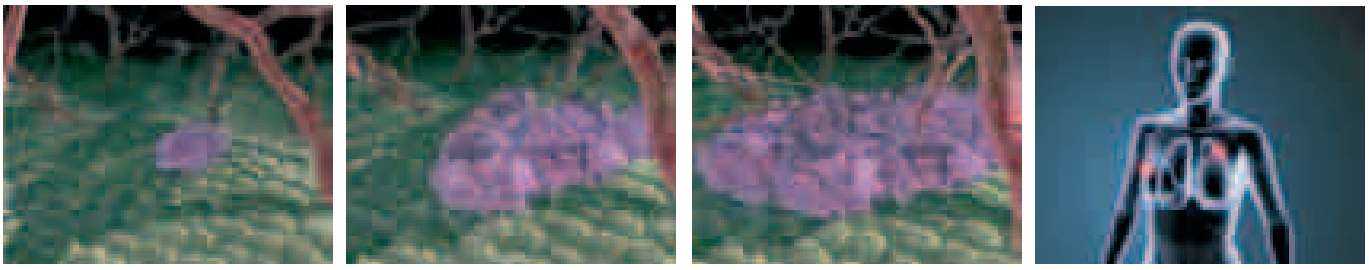
What would you say to a person with cancer, or someone with a loved one with cancer, who hears about your research and wants to know when a drug will be available to help them?

This is a very difficult question, and one that comes up often. I normally explain to people with these types of questions that I am not a physician and am not qualified to treat patients. I work in a lab and focus on the research behind the processes involved in cancer, not on developing the drugs or applying them to patients. The responsibility for treating patients and starting clinical trials, for example, lies with the doctors in the hospitals. What's for sure, however, is that to beat cancer, scientists and doctors must work closely together. It is, however, extremely gratifying when we make discoveries that end up helping people.

You left Spain 28 years ago for the USA and eventually the Memorial Sloan-Kettering Cancer Center. Now you are helping to set up the new Institute for Research in Biomedicine (IRB) in your native city of Barcelona. How important is it to bridge the gaps between research done in different parts of the world?

Though my research laboratory is based in New York, I collaborate all the time with other institutes at the local, national and international levels, including IRB Barcelona. This is the way research has to be done. Scientists realise that they cannot work effectively in isolation. Though they may be very good at their jobs, they'll never reach the goal of being able to translate basic research results into medical applications if they work alone. The idea is to combine scientific, technological and medical expertise to create strong integrated nodes with an international presence that can work together with similar institutes and hospitals across the world to share their knowledge and expertise.

It's an exciting time to be working in science. Through these types of collaborations, scientists now have many opportunities to spend time working in labs in different countries. Talent and passion for science can come from anywhere. Some members of my lab come from large cities with famous universities (such as New York, Los Angeles, Chicago, Santiago, Mexico, Toronto, Vienna, Munich, Rome, Madrid, Barcelona, Beijing, Calcutta, Tokyo and Istanbul) but others come from smaller towns. One student grew up in a remote Himalayan valley in Nepal, another in a tiny island off the coast of Iceland, another in a small town in northern Greece, and another in a rural area in Argentina, for example. With a positive attitude and a bit of luck, people with talent and passion always find a way.



Cells from a breast cancer tumour release themselves from the tissue and migrate to form a metastasis in the lung

REVIEW

Joan Massagué is a well-known and respected international scientist. It is fascinating to read how he entered the research field. Like so many other scientists, he had ambitions to study other subjects and found an all-consuming passion along the way!

Professor Massagué is hopeful that therapies will be developed to block genes responsible for metastasis. In addition to providing an overview of current research, the interview could be used in several ways: to aid in comprehension; to complement lessons on cancer genetics; as a start for further research into leukaemia and solid tumours; to investigate the steps in drug development, from conception to clinical use; or to start a debate on government funding of cancer research and patient treatment.

Shelley Goodman, UK

As far as Spain is concerned, the situation is thankfully very different from when I left. There is a much better recognition on the part of the government of the need to create institutes and infrastructures that allow Spanish scientists to do really significant work. Spain has excellent cancer researchers who obtain very good results at the international level. However, their scientific results have traditionally encountered obstacles in being translated into tangible results. We will need to find a more efficient way to bring together the three main tools we have in the fight against cancer: basic, clinical and pharmaceutical research.

One thing is certain, however, and that is that the next generation of scientists stands a very good chance of making a real difference in the fight against cancer. Our job is to ensure that we nurture young talents and provide our biologists, geneticists, pharmacists and doctors with the training and resources they need to tackle the challenge head-on. My advice for future scientists? Show up at your local college or university and talk to graduate students and other scientists. Ask them how they got started and what opportunities they know of for someone like you. Get diverse opinions, and then go for it!

Web resources

To find out more about the research group of Joan Massagué, see at: www.mskcc.org/mskcc/html/10614.ctm

For more information on the IRB Barcelona, see: www.irbbarcelona.org

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Joan Massagué is Chair of the Cancer Biology and Genetics Program at the Memorial Sloan-Kettering Cancer Center in New York, USA, and Adjunct Director of the Institute for Research in Biomedicine in Barcelona, Spain.

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