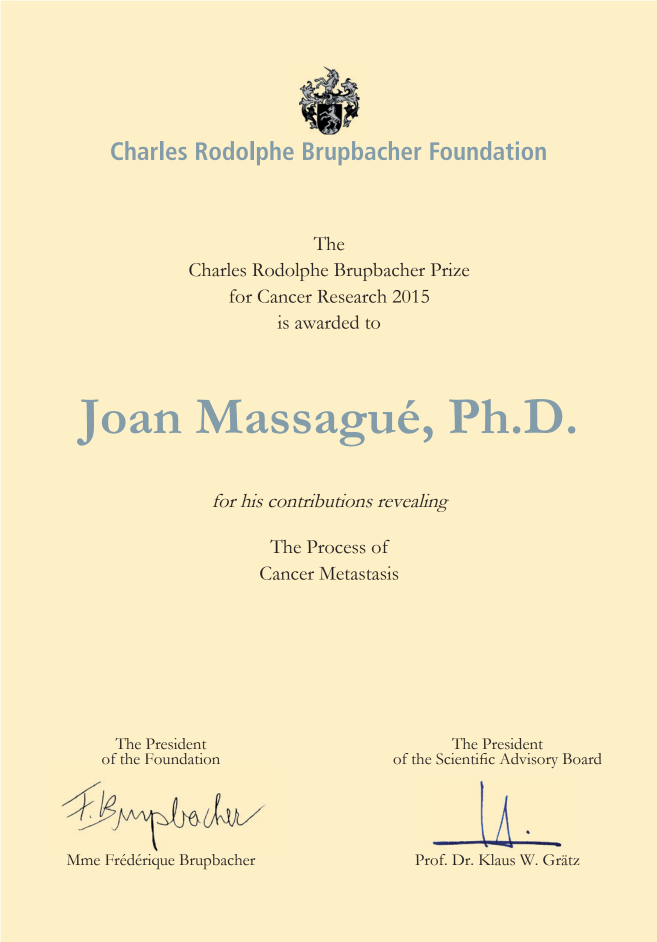
Charles Rodolphe Brupbacher Foundation

The
Charles Rodolphe Brupbacher Prize
for Cancer Research 2015
is awarded to

Joan Massagué, Ph.D.

for his contributions revealing

The Process of
Cancer Metastasis

The President
of the Foundation

Mme Frédérique Brupbacher

The President
of the Scientific Advisory Board

Prof. Dr. Klaus W. Grätz

Laudatio

Paul Kleihues

Metastatic spread to distant organs is generally the worst prognostic factor for the survival of cancer patients. Owing to their critical clinical significance, the mechanism and targeting of metastasis have been studied for a long time, but are not well understood. Glioblastoma, the most malignant tumour of the nervous system, infiltrates the brain so diffusely that successful surgical resection is not possible. Nevertheless, glioblastoma cells are unable to cross the pia mater into the subarachnoidal space, neither do they manage to cross the blood-brain barrier and spread to other organs. Paradoxically, some tumour types readily metastasize to the nervous system, particularly breast and lung cancer, but also including the less frequently-occurring clear cell renal cell carcinoma and melanoma. Circulating breast and prostate cancer cells preferentially target bones, but prostate cancer does not spread to the nervous system. While some metastatic patterns reflect lymphatic and blood circulatory pathways, most of them do not.

Enter Dr. Juan Massagué, who used elaborate genetic and epigenetic analyses to understand some of these patterns of enigmatic site-specific metastasis.

As early as 2003, he reported that human breast cancer cell lines which generate osteolytic bone metastases with high efficiency are characterized by expression of three cooperating genes. These encode osteolytic and angiogeneic factors, and the pro-metastatic transforming growth factor beta. This key publication, cited by other authors more than one thousand times, also showed that the metastatic process requires the involvement of genes that may not have been essential in the development of the primary tumour. More recently, Dr Massagué and his team showed that the stroma of primary tumours can be a determining factor in the context of metastatic targeting. The proteins fCXCL12 and IGF1, derived from cancer-associated fibroblasts, can drive triple-negative breast carcinoma cell populations toward enrichment for clones that have a constitutively high level of Src activity and a propensity for metastatic growth in bone.

In his laboratory, by comparing the pattern of gene expression in human breast cancer cell lines with low and high potential to generate lung metastases, Dr. Massagué clearly identified a set of genes which mediate metastasis to the lung, and at the same time promote growth of the primary breast carcinoma. The lung metastasis expression signature in breast carcinomas appeared to independently predict spread to the lung and a poor prognosis overall.

Using mouse xenograft models, his team recently showed that high expression of the lysosomal enzyme cathepsin S greatly facilitates breast-to-brain metastasis. However, only about one in a thousand circulating breast or lung cancer cells that managed to enter the brain were able to survive. The others were killed by astrocytes that secrete Fas ligand and the protease plasmin converts membrane-bound Fas ligand into a paracrine signal which triggers apoptosis, an internal suicide program. Dr. Massagué and his colleagues were also able to identify a survival mechanism: the few carcinoma cells escaping apoptosis over-expressed serpin proteins, which counteract plasmin.

Clear cell renal cell carcinomas are the most common malignant neoplasm of the kidney in adults. They typically spread to the lung via the vena cava, but they also spread to unusual sites, including the brain, sometimes several years after resection of the primary neoplasm. Up to 70% of these tumours are attributable to inactivation of the von-Hippel-Lindau gene by mutation, allelic deletion or epigenetic silencing. The von-Hippel-Lindau gene product, normally specified as VHL, causes degradation of the hypoxia inducible factor HIF2 α that activates the expression of several genes with tumorigenic and pro-metastatic functions. Dr. Massagué has shown that DNA methylation restricts expression of the metastasis-associated VHL-HIF target genes and thereby reduces the capacity of affected cells to spread to other organs. This demonstrates that in some cancers, including clear cell renal cell carcinoma, development of the capacity to metastasize becomes operative during progression along the tumour-initiating pathway. Hence the metastatic cascade may be less dependent on metastasis-promoting driver mutations in the primary tumour than on epigenetic stimulation of cell survival and self-renewal mechanisms.

These are just a few of the many examples of Dr. Massagué's scientific discoveries that have greatly influenced the field of organ-specific metastatic spread. Identifying the genes responsible for initiation and completion of the metastatic process may allow development of strategies to decrease or abolish the capacity of circulating tumour cells to form metastases in distant organs.

In recent years, evidence has emerged that the two main themes of this year's Symposium – cancer stem cells and mechanisms of metastasis – are tightly linked biologically. Dr. Massagué and colleagues have emphatically shown that phenotypic properties and signalling pathways of disseminated cancer cells that enable metastatic growth in distant organs overlap significantly with those of normal stem cells. The chance that a cancer cell will emigrate from a primary neoplasm to form a metastasis is incredibly low. There are, however, shelters in which these cells may survive. One such place is the bone marrow, a classical site where tumour stem cells can hide and from which they may eventually migrate and successfully colonize other tissues. In very elegant studies, Dr. Massagués team showed that in the brain there is a perivascular niche that greatly facilitates colonization. Metastasis-initiating cancer cells, after overcoming the blood-brain barrier, stick to and grow on the surface of blood capillaries. This interaction with capillaries ensures a generous supply of oxygen and glucose, which enables the formation of a multi-layered perivascular sheath from which surviving cells eventually form a metastasis.

Throughout his scientific career, Dr. Massagué has been scientifically productive and innovative. His work on mechanisms of metastasis has finally opened the door to a better understanding of the fundamentals of the metastatic process and we look forward to more discoveries from his laboratory, which we hope will lead to metastasis-preventing treatments. On behalf of the Charles Rodolphe Brupbacher Foundation and all of us at this exciting symposium, sincere congratulations to Dr. Massagué as recipient of the Brupbacher Award 2015 !

Joan Massagué

Summary Curriculum vitae

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Date of Birth April 30, 1953.

Education

1975 B.S., University of Barcelona
1978 PhD, Biochemistry, University of Barcelona.

Professional Appointments

1979–82 Research Fellow, Brown University.
1982–85 Assistant Professor of Biochemistry, U. Massachusetts Medical School
1985–89 Associate Professor of Biochemistry, U. Massachusetts Medical School
1989– Alfred P. Sloan Chair, Memorial Sloan Kettering Cancer Center
1989–13 Chairman, Cell Biology and Cancer Biology Programs, MSKCC
1990–13 Investigator, Howard Hughes Medical Institute
2014– Director, Sloan Kettering Institute
2014– Provost, Gerstner Sloan Kettering Graduate School of Biomedical Sciences

Advisory Boards (partial list)

1996–00 Board of Scientific Advisors, National Cancer Institute
1998–10 External Advisory Board, MD Anderson Cancer Center
2000–14 Member and Chair, Scientific Advisory Board, CNIO, Madrid
2009–12 Board of Directors, American Association for Cancer Research
2006– Adjunct Director; External Advisory Board Institute for Research in Biomedicine Barcelona
2010– Board of Trustees, The Vilcek Foundation
2014– Chair, External Advisory Board, Institute for Research in Biomedicine Barcelona
2015– Scientific Review Board, Howard Hughes Medical Institute

Editorial Boards (partial list)

Proceedings of the National Academy of Sciences USA;
Cell; Genes & Development; EMBO Journal;
EMBO Molecular Medicine; Journal of Clinical Investigation;
Journal of Cell Biology; Cancer Discovery; eLife

Awards And Honors (partial list)

1979 Fulbright Foundation Postdoctoral Fellowship
1993 King Juan Carlos I Research Prize
1998 Member, European Molecular Biology Organization
1999 Member, American Academy of Arts and Sciences
2000 Member, National Academy of Sciences, USA
2004 Member, Royal Academy of Medicine of Spain
2004 Prince of Asturias Award in Science and Technology
2005 Member, Royal Academy of Pharmacy of Spain

2006	Member, Institute of Medicine, USA
2006	Vilcek Prize
2007	Passano Laureate Prize
2008	Frontiers Prize in Biomedicine, BBVA Foundation
2009	G.H.A. Clowes Memorial Award, American Association for Cancer Research
2010	Feodor Lynen Medal, Nature-Miami Winter Symposia
2011	Robert J. and Claire Pasarow Prize in Cancer Research
2011	Breast Cancer Innovator Award, Department of Defense
2014	National Prize of Culture, Catalonia
2014	National Prize for Research, Spain

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Molecular Basis of Metastasis

Joan Massagué

Metastasis, the process by which cancer cells from a primary tumor infiltrate and overtake distant organs, is a central obstacle in oncology today. It would be difficult to overstate the medical and societal importance of this problem. Approximately 90% of deaths from cancer are directly caused by metastasis, not by the primary tumor. A diagnosis of cancer is typically followed by resection of the primary tumor, but by then spread of cancer cells to distant organs may already have occurred. Despite treatment advances to eradicate the residual disease, current clinical management of overt metastasis rarely results in a cure. The mechanisms underlying metastasis must therefore be understood and mined for effective therapies to advance cancer treatment beyond this roadblock.

Metastasis is an old problem. The spreading capacity of malignant tumors earned this disease its name over two millennia ago. Hippocrates called it karkinos (crab, in Greek) in reference to the projections spreading from the tumor like legs from a crab's body. By the 19th century metastasis was recognized as the result of tumor seeds that spread cancer to other organs. In the 1970s Isaiah Fidler and others described many of the basic features of metastasis, including the different profile of affected organs in different types of cancer, the role of the circulation in metastatic dissemination, and the varying metastatic capacity of cancer cells in a heterogeneous tumor. Up until the late 1990s, however, our knowledge about the molecular basis of metastasis remained descriptive in nature. Mechanistic insights were limited to how cancer cells migrate and invade surrounding tissues. While invasion and migration are necessary early steps for tumor dissemination, the vast majority of cancer cells that leave a tumor perish. The mechanisms allowing cancer cells to survive as metastatic seeds and colonize distant organs remained a mystery. The daunting complexity of the metastasis and the lack of appropriate research tools deterred work on the problem.

Three developments at the turn of this millennium paved the way for more research: One was the epic success pioneered by Michael Bishop and Harold Varmus in the 1970s, and joined by many others, to identify genes and molecular pathways that initiate tumor formation. This progress suggested that metastasis eventually could also be dissected and understood at the molecular level. The second was the recognition, eloquently highlighted by Robert Weinberg and Douglas Hanahan, that primary tumors contain a large presence of non-cancerous stromal cells that supports the growth of the tumor. This suggested that the tumor microenvironment could also play a role in selecting for metastatic traits during the clonal evolution of tumor cell populations. The third development was the advent of new technologies, including genome sequencing, gene expression analysis, and in vivo cell imaging that provided key tools to investigate metastasis. These three advances converged to make a mechanistic assault on metastasis possible.

Within this context, lessons learned from dissecting the TGFβ signal transduction pathway turned my attention to metastasis. The transforming growth factor β (TGFβ) pathway plays crucial roles in embryonic development, tissue regeneration, and immunity. Its malfunctions cause congenital disorders, chronic inflammation, fibrotic diseases, and cancer. Earlier, we identified the TGFβ receptors, their signaling mechanism, and the central concept of how this pathway regulates gene expression to control cell proliferation and fate. Of particular interest to us was the paradoxical role of TGFβ in cancer. TGFβ acts as both a suppressor of tumor initiation and a promoter of metastasis. To form tumors, cancer cells must avoid the anti-tumor effect of TGFβ by losing cell death responses to this factor. With this done, cancer cells are free to use TGFβ for metastasis. Asking how so, we found that in breast tumors TGFβ from the stroma stimulates cancer cells to produce angiopoietin-like 4. Educated in this manner, cancer cells can leave the tumor, lodge in lung capillaries and use angiopoietin-like 4 to break out of blood vessels into the tissue. The resulting accumulation of metastatic seeds in the lungs increases the risk of metastasis. These observations taught us that metastatic cells are selected to make use of anything that helps them pass through barriers. We postulated that metastatic cells must have organ-specific traits that are selected during the colonization of different organs. Based on this notion, and using mice as cell sorters, we isolated cancer cells with different organ tropisms from heterogeneous tumor populations of the same patient. These experimental models combined with data from large sets of human clinical samples led to the identification of many genes in breast, lung, and renal cancers that promote or suppress metastasis to the bones, the lungs, or the brain. Some of these genes encode proteins, others micro-RNAs. Their analysis in model systems uncovered unsuspected mechanisms of cancer cell infiltration of distinct organs, survival in the new host tissue, and unbridled outgrowth of metastatic colonies. Notably, these genes not only mediated organ-specific metastasis in experimental models but predicted relapse to these organs in patients.

These findings foster an intensely Darwinian view of the metastatic process. Metastasis appears as the end result of a selection process in which cancer cells progress through highly demanding steps. Although circulation patterns matter somewhat, cancer cells in the circulation can reach all the organs of the body. No organ microenvironment is favorable to incoming cancer cells. All organs are hostile, some just a little less so than others. Each step in the metastatic sequence is a narrow bottleneck that causes the demise of the vast majority (>99%) of the cancer cells engaged in the process. Each step selects for cells that, though epigenetic changes more than through specific mutations, have gained a higher probability of succeeding. No single gene mutation or deviant mechanism could help cancer cells navigate the entire ordeal. Rather, the selected cancer cells resort to different gene products that in combination increase the probability of successful passage through a particular step. The combination of these cell-autonomous and environmental determinants dictates the organ distribution and the efficacy of metastasis in a given cancer.

Three additional revelations punctuated our work on the molecular basis of metastasis. First, disseminated cancer cells depend on mechanisms that selectively amplify survival and stemness pathways in microenvironment-dependent manner. This phenomenon is manifest in the survival of VCAM1-positive breast cancer cells that profitably interact with leukocytes in the lung parenchyma, or the survival of SRC-positive breast cancer cells that interact with CXCL12-rich mesenchymal cells in the bone marrow. Similarly, breast cancer cells can support their tumor-initiating capacity by producing the extracellular matrix protein tenascin-C, a protein of stem cell niches that enhances Notch and Wnt signaling in metastasis-initiating cells. Moreover, cancer cells can resist the stresses of metastasis and chemotherapy alike by engaging myeloid cells via a TNF-CXCL1-S100A8/9 paracrine loop.

Another unexpected revelation was the phenomenon of tumor self-seeding, whereby previously disseminated metastatic cells can re-infiltrate the tumor of origin. Aggressive clones that leave a tumor and survive in distant organs can re-enter the circulation, re-infiltrate the tumor or origin and expand in this supportive microenvironment. A result of this dynamic cycle is the amplification of aggressive metastatic populations in the primary tumor or in the inflamed parenchyma after tumor removal. Tumor self-seeding provides a plausible explanation for various clinical manifestations of metastasis, response to therapy, or resistance to it. Therefore interference with this process provides an opportunity for therapy against tumor recurrence.

The diversity of metastatic mediators discovered over the past decade underscores the complex biology of this process and, at the same time, raises sobering questions about the possibility of developing drugs to combat metastasis in multiple organs and in different types of cancer. However, recent findings offer hope in this regard. We found that disseminated cancer cells need to adhere to the external surface of blood capillaries, coopting the vessels in order to survive and initiate metastatic growth. To this end, cancer cells express the cell adhesion molecule L1CAM. L1CAM is normally expressed in developing neurons for neurite extension and synapse formation during brain development. Prior reports noted the anomalous expression of L1CAM in different types of cancer as an indicator of poor prognosis. Our unexpected finding that L1CAM mediates vascular cooption by metastatic cells for colony outgrowth points at a general mediator of metastasis at a variety of sites that could be targeted therapeutically.

I hope that this brief review shows that the progress to date has debunked the old myth of metastasis being too difficult to dissect molecularly or deconstruct conceptually. Indeed, the field at large has now embraced the task of taking this problem to the next level of molecular definition, and towards more effective treatments. For example, we are now poised to make progress on the most ominous complication of cancer: brain metastasis. Brain metastasis is highly disruptive and lethal. It is estimated to affect nearly 400,000 people in the US and Europe alone, and is on the rise. Clearly more work on brain metastasis is in order. Finally, latent metastasis –the state of disseminated cancer cells that have not yet initiated aggressive outgrowth– represents a major untapped opportunity to prevent metastasis. By learning more about the mechanisms that sustain latent metastatic cells in hiding and oblivious to drugs that only kill growing cells, we should be able to increase the efficacy of adjuvant therapies to rid the patient's body of residual disease after the removal of a primary tumor. Given the recent rapid progress in our mechanistic understanding of metastasis, I have no doubt that problems such as the secrets of latent disease or the nature of brain metastasis will be conquered.

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