People & Ideas

Joan Brugge: Running rings around cancer

Brugge has devoted her career to uncovering how perturbations in normal cellular processes give rise to cancer.

Joan Brugge was an undergraduate at Northwestern University when her sister was diagnosed with a brain tumor. Her sister's doctors couldn't say what caused the disease; they speculated that a virus might be involved. This spurred Brugge's lifelong quest to learn about the causes of cancer, starting with the study of tumor viruses (1).

Brugge identified the protein encoded by the *src* transforming gene of Rous sarcoma virus and its cellular homologue as a postdoc in Ray Erikson's lab at the University of Colorado (2). She further characterized the cellular Src protein during her time as a group leader at Stonybrook and the University of Pennsylvania (3). Later, following a brief stint in the private sector, she set up shop at Harvard Medical School to study the cellular processes that drive the striking morphological and phenotypic changes that accompany cancerous transformation in humans (4–6).

A leader in the field of cancer biology, Brugge manages a vibrant research program while meeting the demands of chairing the Department of Cell Biology. But, she took time out to chat with us about her career—past, present, and future.

STARTING LINE

When you first started working on cancer, what did people think caused the disease?

At the time, the causes of human cancer were elusive. There were only a few inducible tumor virus models available besides those using chemical carcinogens. There were a few "RNA tumor virus" models in chickens and mice as well as some DNA tumor viruses, with SV40 as a prototype. As a graduate student, I worked on the tumor antigen of SV40. It was very difficult to study the mechanisms of transformation because SV40 transformation was inefficient and slow; while SV40 tumor antigen is required to maintain the transformed state, additional hits are required in order to induce transformation. So, as a postdoc I switched to studying Rous sarcoma virus (RSV), which could transform cells in just two days. It seemed clear that the viral gene product—which by that time was known to be Src—could transform cells on its own. Shortly after I started my postdoc in 1975, Harold Varmus, Michael Bishop, and colleagues identified the viral Src gene of RSV as an adopted and dysregulated cellular gene.

We and many other labs around the country were trying to identify the cellular Src protein. We spent two years trying endless approaches to do it. I was almost at the point of giving up when we finally detected it on a gel! Then another postdoc in the lab, Marc Collette, identified Src as a protein kinase (in parallel with Art Levinson in Mike Bishop's and Harold Varmus' lab). That provided a major clue as to the nature of cellular activities that could contribute to transformation.

CHICANE FOR CANCER

How did the discovery of c-Src change your thoughts about cancer?

If you follow the papers from when I first started my own lab, we set out on an uncharted path pursuing the cellular functions of Src. There was an assumption that it was going to be involved in regulating normal cell proliferation, and that the virus' mutated version would constitutively stimulate cell proliferation. But, we gained a much broader view of Src over time when we realized that it is activated by many receptors and controls many different cellular proteins. This is one of many examples of how nature is very conservative in its use of proteins. Other key regulatory proteins associated with tumor viruses—Ras, Myc, Fos—were also found to regulate a really wide assortment of cellular activities controlled by diverse receptors. Scientists typically focused on the products of individual proto-oncogenes, and in the process discovered that these proteins regulate activities that go well beyond cell proliferation. That led to the realization that tumor development involves the dysregulation of multiple cellular functions besides just proliferation—things like adhesion, polarity, metabolism, and apoptosis.

> "Nature is very conservative in its use of proteins."

Joan Brugge

What guides your thinking about cancer today?

For the past several years my lab at Harvard has been trying to understand what cellular processes and pathways are responsible for the really significant changes in the organization of normal tissues that are associated with cancer. For instance, the glandular unit of the breast, the acinus, is a hollow sphere. In breast cancer, tumors demonstrate a whole spectrum of architectural changes in this structure: the spheres can be hollow or filled with cells; they can lose cellular polarity, or not; they can be invasive, or not. We've been working on understanding the processes that drive these different phenotypic histologies,

Text by Caitlin Sedwick
csedwick@gmail.com

using a breast cancer model system we adapted from Mina Bissell's 3D cell culture work.

Most recently, we've been studying the mechanisms that are responsible for the ability of tumor cells to survive without attachment to the extracellular matrix. Our 3D model system had shown us that acini start out as a solid sphere of cells. The hollow lumen is generated during morphogenesis through selective apoptosis of the inner cells. But we noticed that if you blocked apoptosis in these cells, they still died.

Many lines of evidence from our laboratory supported the idea that the cells in the center are stressed by loss of attachment to matrix. We found that matrix detachment was associated with a block in glucose uptake that causes a dramatic drop in cellular ATP levels. And then we got this really surprising result: we could rescue the ATP levels and prevent cell death if we added antioxidants. We found that antioxidants allow the use of an alternate energy pathway, fatty acid oxidation. Antioxidants are up-regulated in a reasonable number of tumors, so now we'd like to understand to what extent they might actually contribute to tumor progression.

CLEARING HURDLES

What are the major hurdles you've faced in your career?

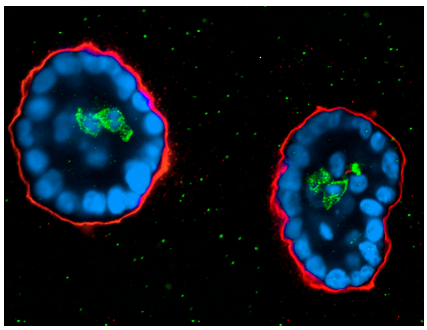
Just deciding to pursue research as a career was one hurdle. When I was in high school, the women who had careers around me were either nurses or teachers. I loved problem solving and was good at math, so I thought I might be a high school math teacher. Later on, when I decided to go to graduate school, I didn't have a lot of guidance because a research career wasn't a common choice. I picked my graduate school, Baylor College of Medicine, out of a Peterson's Guide. [laughs] Undergraduates are so much more sophisticated today.

Later, as a graduate student, I had decided that I could not handle an independent faculty position and have a family as well; so I planned to be a research associate in someone else's lab. So, one of my largest hurdles happened after my son Shawn was born, when I was a postdoc at the University of Colorado. It was really emotionally difficult for me to go back to work. I was very reluctant to leave his care to anyone else. However, I was also excited to get back to my studies of the Src protein, which we'd finally discovered just a few months before Shawn was born. It took a few tries before I eventually found some wonderful people I felt I could trust to help care for him in a warm and loving environment. That really helped me succeed in my career, but it wasn't effortless. My postdocs know I appreciate the challenges of trying to balance a career in science with the demands of parenthood. Both my husband and my son have been incredibly supportive of me in my career, so having a family is not something I take for granted.

The extended family of the Brugge lab.

Do you have advice for young scientists?

One thing I think is important for young scientists to know is that you really can't predict what your potential is going to be. Too often I hear postdocs and junior faculty—especially women—say, "I could never handle doing what you're doing." They're afraid they won't be able to balance having a career with the demands of having a family. Or, maybe they just feel overwhelmed when they look at the breadth of responsibilities that senior faculty have to manage.



A breast cancer cell line forms hollow spheres when grown in 3D culture.

But it's important to understand that you don't have to tackle those kinds of responsibilities right away. You will take on new responsibilities as your career evolves and you gather the resources to handle them; you don't have to do it all at once.

> "When something unexpected happens, it might shine a light in the black box of biology."

My message to junior faculty and postdocs, then, is that it's important to take baby steps in your career. At each step, assess whether you feel comfortable and whether you still enjoy what you're doing. Don't make assumptions about what your capabilities are. Just try it and see how it goes.

Also, when it comes to your experiments, don't be afraid to chase down a strange result. Recently, a postdoc in my lab, Michael Overholtzer, made a puzzling observation that he decided to investigate. In the process, he discovered a phenomenon we called entosis—when cells internalize into neighboring cells—that could be involved in either preventing or promoting cancer. He's now investigating that in his own lab. So remember that when something unexpected happens, it might shine a light in the black box of biology.

1. Brugge, J.S., and J.S. Butel. 1975. *J. Virol.* 15:619–635.
2. Brugge, J.S., and R.L. Erikson. 1977. *Nature.* 269:346–348.
3. Lynch, S.A., et al. 1986. *Science.* 234:873–876.
4. Debnath, J., et al. 2002. *Cell.* 111:29–40.
5. Overholtzer, M., et al. 2007. *Cell.* 131:966–979.
6. Schafer, Z.T., et al. 2009. *Nature.* 461:109–113.