Into the deep: Refocusing on 3D

Joan S. Brugge

Over the past 40 years my scientific pursuits have evolved along uncharted paths, guided by personal experiences, unexpected research findings and serendipity. The most recent turning point in my research interests was shaped by three converging events: a mid-life career move, an investment from Harvard Medical School, and the inspiration and guidance of Mina Bissell.

First, some background details to put the events surrounding this turning point in perspective. In the 1960s, the acceptable path for an academically inclined high-school girl was teaching, so I started my undergraduate studies at Northwestern University, Illinois, aiming to become a high school mathematics teacher. In the autumn of my second year, however, my sister developed a brain tumour and I set out to understand how such a young person could develop this deadly disease. My sister's neurosurgeon led me to research articles on tumour viruses — this was the first turning point of my life. Perusing these articles opened my eyes to the world of experimental research. I was immediately captivated, switched to biology and chemistry studies and headed to graduate school.

Although I started my graduate studies on DNA tumour viruses in the lab of Janet Butel at Baylor College of Medicine, Texas, I changed to investigating RNA tumour viruses with Ray Erikson when my husband matched at the University of Colorado Health Sciences Center for his medical residency. In Ray's lab, I joined an effort that was ongoing in many research groups around the world: to identify the elusive protein product of the Rous sarcoma virus oncogene, Src. After two frustrating and fruitless years, a band of molecular mass 60 K, fitting the criteria for the Src gene product, appeared on one of my gels. This provided a focus for the next 15 years of my research career; after leaving Ray Erikson's lab, I chose to investigate c-Src, the cellular homologue of the viral Src protein.

This choice was guided by my belief that understanding the normal function of c-Src would provide clues to the potent tumorigenic activity of its viral counterpart. This type of approach, focusing on understanding the function of a specific gene rather than a biological or pathological process, eventually became quite common in the 1980s, spurred by research on cellular homologues of viral oncogenes and technological advances in gene identification. Although my studies during this time led me astray from my focus on cancer, they provided many interesting insights into the functional activities of Src in multiple cellular processes.

Years later, in 1992, I was lured away from Src and academia to help start a biotechnology company. This venture was focused on structure-based drug design to target intracellular protein–protein interactions, which were emerging at the time as critical components of signalling pathways involved in disease. Being its Scientific Director was very exciting and an incredible learning experience. However, as the company grew, I was pulled further away from being a 'player-coach' orchestrating research programmes, to being more involved in the scientific strategic planning of the company in seeking critical partnerships for drug discovery projects. I greatly missed being part of the design and interpretation of experiments and made the decision to return to academia after five years.

The Department of Cell Biology (chaired by Marc Kirschner) and Harvard Medical School took a gamble on my ability to rebuild a laboratory up to par with those of my colleagues and offered me a Professorship. As I was not 'burdened' by the specific aims of previously awarded grants, this was a great opportunity to refocus my scientific interests. After much thought, I decided to forego protein- and pathway-directed studies, to address more fundamental questions in cancer biology *per se*, with a particular focus on developing culture models to investigate the pathways and processes underlying the marked changes in tissue architecture that are associated with human tumours.

Standard monolayer cultures were not amenable to addressing such questions, but luckily, before moving to Harvard Medical School, I ran into Mina Bissell. She described her elegant studies with Valerie Weaver on the reversion of aggressive breast tumour cells into growth-arrested structures with a normal acinar architecture by modulating the engagement of β1 integrin, an extracellular matrix receptor. This remarkable work not only demonstrated how cell–matrix interactions could suppress the activity of oncogenic alterations, but also highlighted the value of three-dimensional structures for investigating the processes that influence tissue architecture. This was exactly what I was looking for, and Mina generously arranged for me and Senthil Muthuswamy, then a post-doctoral researcher in my group, to learn the intricacies of 3D culture in her laboratory.

Over the past decade, studies using such 3D cultures have furthered our understanding of normal morphogenesis, cancer initiation and progression, and more recently, drug resistance. In 1998, I had no perception that my decision to switch to 3D cultures — and, as Mina likes to say, "to be reprogrammed" to a different way of interpreting biological findings — would turn out to be so valuable. I feel lucky to have had the opportunity to 'restart' my academic career and change the course of my scientific path.

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.

Joan S. Brugge is at the Department of Cell Biology, Harvard Medical School, 240 Longwood Avenue, Boston, Massachusetts 02115, USA.
e-mail: joan_brugge@hms.harvard.edu