Beatrice Mintz, PhD, Pioneering Researcher at Fox Chase Cancer Center, Dies at 100

On January 3, 2022, a few weeks shy of her 101st birthday, my friend, colleague, and mentor Beatrice Mintz passed away after a long illness. Following a brief period at the University of Chicago, at age forty she joined the Institute for Cancer Research at the Fox Chase Cancer Center in Philadelphia. She went on working at Fox Chase for an amazing 60 years, a record that is unlikely to be broken. During that time, she made foundational scientific contributions that have influenced our thinking about the relationship between stem cells, embryonic development, and adult tumorigenesis.

Never shy of taking on big questions — "the only ones worth considering," as she was fond of saying—Bea began her career with an inquiry into one of the biggest and most fascinating questions of them all: how does a complex organism, with its diverse tissues and structures, arise from a single fertilized egg? To begin to address this problem, she combined early embryo cells of two genetically different mouse strains, creating "allophenic" mice which contained multiple, genetically identifiable populations of cells. Using this approach, Bea demonstrated that just a handful of embryonic stem cells were able to generate a fully developed animal. These experiments also revealed that normal development is a hierarchical process, with ever-more specialized clusters of stem cells expanding clonally, proliferating and differentiating in an orderly manner. Regarding this aspect of her career, Bea enjoyed telling the story about how, during the early 1970s, site visitors from National Institutes of Health were taken to Bea's mouse room, and upon seeing an oddly striped mouse that resulted from her allophenic approach, awarded her the grant on the spot. It was a classic Bea moment.

Her second big question involved the role of stem cells in cancer. At that time, few believed that cancer was the result of clonal expansion, positing instead that cancers develop from a combination of mutant cells. Using her allophenic, mix-and-match approach to create hybrid embryos, she showed that cancers could arise from single, developmentally arrested stem cells. "Observing that cancers develop from a single cell rather than a combination, she established clonal regulation as cancer's fundamental unit of development," Margaret Foti, MD, PhD, CEO of the American Association for Cancer Research, said in a story about Bea that appeared in *Temple Health Magazine*.

The manipulation of mouse embryos led Bea to address a third major question, namely, does the tumor microenvironment affect the growth of cancer cells? In a now classic experiment, she showed that tumorigenic teratoma cells, when placed within a normal mouse blastocyst, became somehow gentled by the neighboring embryonic cells, giving rise to perfectly normal mice. This result was and is astounding, and is the basis for her much repeated quote about the mouse whose father was a tumor. This experiment was among the first to demonstrate that cancer cells are not completely autonomous and free from restraint, giving rise to a new branch of cancer biology that is actively studied to this day. This work also had a powerful impact on the thinking of Bea's colleague at Fox Chase, Al Knudson, who was deep in consideration of mechanisms for tumor suppression.

It should also not be forgotten that Bea, along with Ralph Brinster at the University of Pennsylvania, showed that it was possible to introduce new genetic material into "transgenic" mice. This technical feat opened the gateways to the production of mouse models of development and cancer. For many scientists, such an achievement would have been the capstone of a career; for Bea, it was, as it were, just another day at the office.

For her many big discoveries, she won many big prizes, including being elected to the National Academy of Sciences as well as the American Academy of Arts and Sciences, receiving the first Ernst Jung Gold Medal for Medicine, the National Medal of Honor for Basic Research by the American Cancer Society, the Szent-Györgyi Prize for Progress in Cancer Research, and a Lifetime Achievement Award from the American Association for Cancer Research. More than any of these honors, she was proudest of having been chosen for the Pontifical Academy of Science, where she advised Pope John Paul II about human embryonic stem cells.

Bea worked alone for most of her career. This was a matter of choice, as she had no end of candidates eager to train under her mentorship. When she did take on a postdoctoral fellow, it was always someone of the highest caliber (Rudy Jaenisch, Michael Karin, and Lionel LaRue were among the chosen few) and even they usually didn't last too long in her lab. Her standards were exacting and she could be tough on people, herself most of all. She was a front-row sitter at seminars, usually asking a single question, but it was invariably the simplest yet toughest one you'd face.

On the other hand, she also had a softer side that was manifest in her sly sense of humor and her love of the visual and spoken arts. She wrote amusing poems, often featuring mice, but, as they didn't meet her high standards, would only show them fleetingly to trusted friends, then tuck them back in her desk drawer. This drawer was also home to the world's first transgenic mouse, which Bea later had stuffed by a taxidermist. Not satisfied with the mouse's unnatural predatory pose, she put it away along with the poems and rarely showed it to anyone.

When I came to Fox Chase, Bea was already past seventy and could easily have rested on her laurels, but she wanted to take on one more big challenge. After having done so much in developmental and stem cell biology, it was time, she said, to cure cancer. She had long been fascinated with the migration of melanocytes from the neural crest, which took a far longer and more circuitous route than most other cells. She suspected that aberrant, incompletely migrated melanocytes might become trapped in undifferentiated stem-like nests that could later contribute to melanoma.

To probe this model, she devised a typical 'Mintzian' experiment that married old and new techniques. The old involved grafting melanoma-containing skin to normal mice and watching what happened at the graft margins. The new was that the source of the graft was a transgenic mouse of her devising that developed melanoma due to SV40-T antigen expression in melanocytes.

At grant study sections, reviewers sometimes like to talk about the subtraction test: if the applicant did not exist, would the field of study suffer or be compromised in some significant way? With Bea Mintz, the answer is a resounding yes. I, and my colleagues at Fox Chase, were

privileged to know her. She was truly one of a kind, one of the key scientific figures of the last fifty years.

Jon Chernoff