PNAS RETROSPECTIVE

Beatrice Mintz, a giant in mammalian development

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Beatrice Mintz died on January 3, 2022, at the age of 100. She started her scientific career in the early 1950s at a time when only a small number of women chose a path in science. She was a professor of biological science at the University of Chicago before joining the Fox Chase Cancer Institute of Philadelphia in 1960.

Beatrice Mintz, known as "Bea" to her friends, was a developmental geneticist. Her approach to science has been deemed as "innovative, unprecedented, extraordinary, unequaled" (1). Her pioneering work had a major impact on many different areas of science. She began her career addressing one of the most complex and fascinating questions of development: how the many different and diverse tissues in an organism are initiated and develop from a single fertilized egg. In the early 1960s Bea—at about the same time as Andrzej Tarkowski in Poland and Ralph Brinster in Philadelphia—generated the first chimeric mice by combining early, genetically distinct, mouse embryos. She had contemplated this experiment for many years at the University of Chicago and began to work seriously on it after moving to Fox Chase (discussing the project with her colleagues) (Fig. 1). And indeed, this manipulation of embryos was a breakthrough to a new era of experimental work in mammalian development. (Bea did not like the designation "chimera" because of its association with "monsters" in Greek mythology; she described these mice as "allophenic.")

Bea experimented on mouse embryos to explore how they form complex organs during development. She established the clonal origin of lineages as diverse as the pigment system (2), the somite, muscle, vertebrate and skull (3, 4), and the hematopoietic lineage (5). In addition, her laboratory generated transgenic mice, initially by injection of DNA into blastocysts (6) and later into the pronucleus (7).

The embryo manipulations used to generate chimeric mice also led Bea to address another major question in biology: how the proliferation of a cancer cell is affected by its microenvironment. In a brilliant experiment, she placed tumorigenic teratoma cells into a normal mouse blastocyst and showed that the tumor cells became "normalized" by the embryonic environment and were able to generate normal, tumor-free mice (8, 9). This finding was and remains an astounding result and argues that cancer is not only caused by (irreversible) genetic changes, but also by reversible epigenetic alterations, a branch of cancer biology that is actively studied today.

In later years, Bea turned her attention to a different challenge and created a new model for melanoma research. Her transgenic mouse model showed that the tumor cells metastasized into skin and eye (10). Her contributions proved essential to understanding some of the complexities of development of melanoma.

On a more personal note, Bea had a decisive influence on my career. I was a young and naïve postdoc in Arnold Levine's laboratory at Princeton, working on SV40 DNA replication. I was puzzled as to why this virus causes only sarcomas in mice, not liver or brain tumors. Was the virus unable to infect the liver and brain cells but could infect skin cells, or could it infect all cells but could only transform skin cells? Thus, the question concerned the tropism of the virus. Was there an experimental setup to distinguish between these possibilities?

Fig. 1. Perry, Blumberg, Knudson, Rose, and Mintz, early 1960s. Image credit: Fox Chase Cancer Center Archives.

At that point, I happened to come across Bea's 1967 paper, published in PNAS (2). She had generated striped mice by aggregating embryos derived from pigmented and albino mice. This publication became the most influential paper that I ever read: It fundamentally shaped my future science career. Bea argued from the number of stripes in the chimeras that the pigment system is derived from 17 primordial "founder" melanoblasts on each side of the midline. It is an amazing paper, easy to read but difficult to understand. How could she get a "standard" mouse with 17 stripes if cells of the two donors were randomly chosen to contribute to a given stripe? The paper was controversial at the time: If albino and pigmented melanoblasts were randomly contributing to the respective coat color area, as Bea argued, only a small fraction of the chimeras should display the standard pattern with 17 stripes (to be exact: 1 in 2^{17} mice), unless like-cells aggregated and would form a wider stripe (11, 12). A key hypothesis of the

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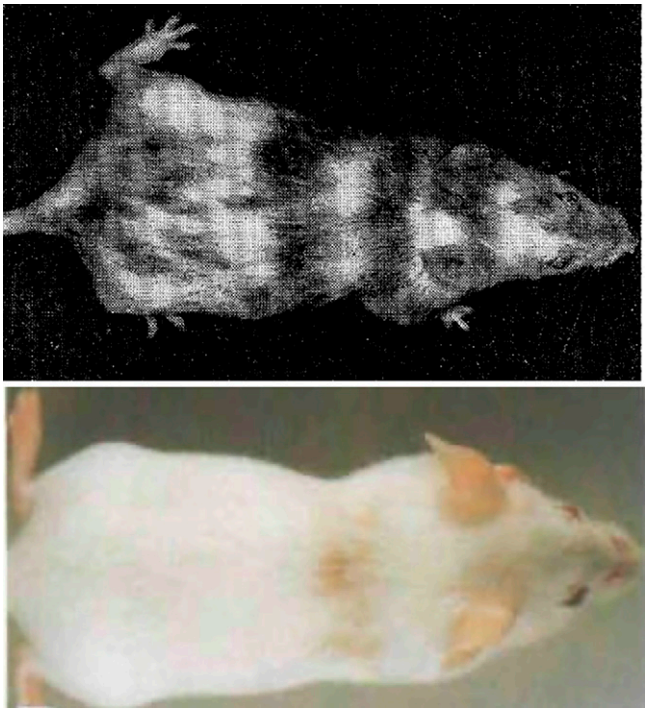
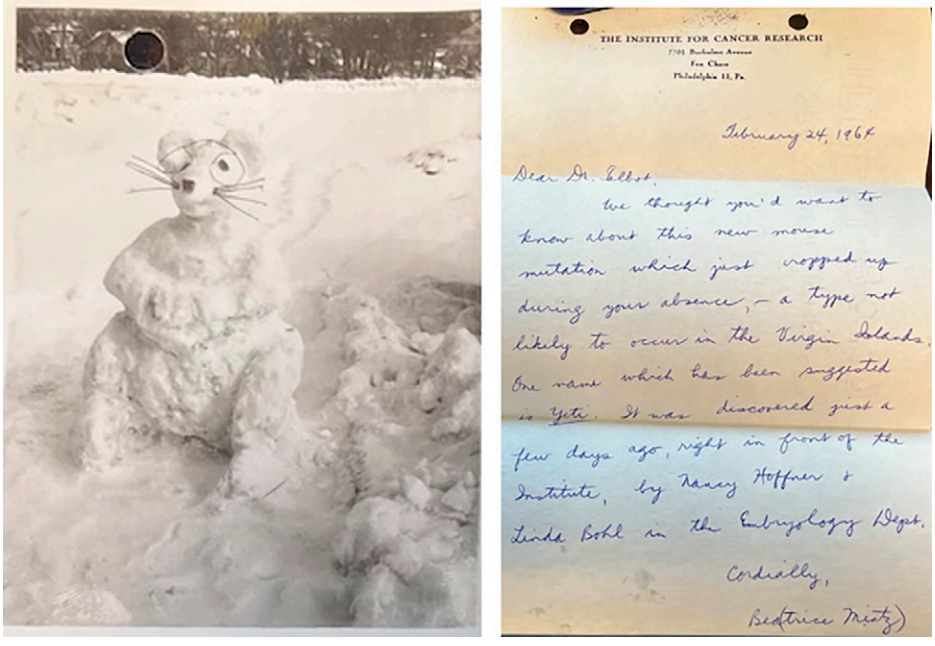


Fig. 2. Chimera with "standard stipe" pattern (2) and single stripe from retrovirus vector labeling at gastrulation with similar width as in chimeras. Used with permission of The Company of Biologists, from ref. 13; permission conveyed through Copyright Clearance Center, Inc.

paper (2) was that a given stripe was clonally derived from one founder cell and not from several. This indeed was verified in a later study that introduced a lineage label (a retroviral vector transducing the tyrosinase gene, which is mutated in albino mice) into the gastrulating albino embryo at a stage when the neural crest cells migrate out of the neural tube (13). The idea was that if a single vector infected a founder cell, the cell would clonally expand and the pigmentation stripe should cover the area occupied by the daughter cells of the labeled founder cell. The key question was whether the width of the stripes in the mosaic animals would be similar or smaller, as compared to those in the chimeras, as the latter would indicate a larger number of founder cells of the pigment system. Indeed, the mosaic mice, on average, contained one stripe with a similar width as seen in Bea's chimeras (Fig. 2), supporting the clonal origin of stripes in the chimeras. Thus, these results were entirely consistent with Bea's conclusion.

While, as an inexperienced biologist, I did not comprehend the developmental implications of the paper (2) at the time, I was awestruck by the possibility of generating a live mouse from cultured embryos. If one could introduce the viral DNA into an early cleavage embryo and generate a mouse, the DNA would be in liver and brain and skin, and this could answer my questions. Bea, after some initial hesitation, agreed that I could, as a visiting scientist, attempt this experiment. I prepared the SV40 DNA in Princeton and commuted to Philadelphia, where I learned from her how to manipulate mouse embryos and to generate mice. To my surprise, the experiment worked and we produced the first transgenic animals that carried foreign DNA in their genome (6). Unexpectedly, the animals, despite carrying the SV40 DNA in their genome, did not develop any tumors, presumably because the SV40 DNA had been silenced by methylation.

Bea was one of the most distinguished developmental geneticists of the last century and was a generous and inspiring mentor. All that I know about mouse embryogenesis, about the genetics of mouse development and of coat color, about the manipulation of mouse embryos and the use of genetics for solving problems of mouse biology, I learned from her. It is fair to state that Bea's mentorship decisively affected my thinking and shaped my whole scientific life.


THE INSTITUTE FOR CANCER RESEARCH
7701 Burholme Avenue
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Philadelphia 11, Pa.

February 24, 1964

Dear Dr. Talbot,

We thought you'd want to know about this new mouse mutation which just cropped up during your absence, - a type not likely to occur in the Virgin Islands. One name which has been suggested is Yeti. It was discovered just a few days ago, right in front of the Institute, by Nancy Hoffner & Linda Bohl in the Embryology Dept.

Cordially,

Beatrice Mintz

Fig. 3. Mouse made of snow by Mintz and described in a letter to Tim Talbot, then the director of the Institute (1964). Image credit: Fox Chase Cancer Center Archives.

I have described my time in Bea Mintz's laboratory in some detail, as the time with her was the most influential time in my training. She was an exceptional mentor who made me aware of the most exciting and challenging problems in mammalian developmental biology and how to approach such problems without being intimidated by daunting experimental obstacles. Her laboratory was organized in a very efficient way, reflecting her style of doing science. She did everything herself: building her own equipment, producing the microinstruments for handling and manipulating embryos, and checking daily on the mice of the colony. I religiously copied all this infrastructure and this enabled me to establish my own laboratory focused on mouse development.

Bea was legendary for setting high standards for members in her laboratory. But Bea also had a softer and a humorous side. She wrote poems featuring mice (according to Jon Chernoff in a personal communication) and built a snow mouse (Fig. 3) that she described to Tim Talbot, then the director of the Institute. She will be remembered as a giant in mammalian embryogenesis and developmental genetics who laid the foundation for our present understanding of mammalian development.

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