Cori Bargmann Autobiography

My parents grew up in Berlin and met in Nuremburg after World War II, where my father was a translator at the Nuremburg trials, and my mother, also a translator, worked for the Americans. My father went to the United States for graduate school, and my mother and older sisters came a few years later. After a few years at IBM my father became a Professor of Statistics and Computer Science at the University of Georgia. My mother's humanistic and artistic passions mirrored my father's love of math. It was an academic household; we all read, we all played the piano, we all sang. My most pleasant memories of my childhood are of falling asleep listening to my father play Beethoven sonatas far into the night.

We moved to Athens, Georgia when I was five. I went to public schools, which were integrated when I was in the sixth grade. My favorite teachers in high school were Dr. Hughes, the Latin teacher, and Mr. Clark, the chemistry teacher. I hid in the chemistry lab when I was supposed to be at pep rallies. As an undergraduate at the University of Georgia in Athens, I worked with the bacterial geneticist Sidney Kushner. I loved the lab and the intensity and the intellectual companionship of my fellow researchers.

I went to graduate school at MIT in 1981, as molecular genetics was exploding. Molecular genetics is an incredibly powerful discipline, in neuroscience as in other aspects of biology. First, genetics makes it possible to identify the essential molecular components of any biological system, including the brain. Second, the ability to manipulate gene function in particular cells makes it possible to map the flow of information in multicellular systems like the brain, and increasingly to modify that flow of information. Third, the genome represents both a complete set of instructions and a record of evolutionary history for an animal, and decoding it provides answers to questions you hadn't even realized you were asking.

As a graduate student I studied mutations that convert normal cells into cancer cells, in Bob Weinberg's lab at MIT. The year that I joined, Weinberg's lab identified the first oncogenic mutations in human ras genes, a landmark in the field. I studied an oncogene mutated in an unusual class of rat neuroblastomas and glioblastomas, a receptor called neu/Her2, and found the mutations that activated it in tumors. Later, other groups found that neu/Her2 was amplified in aggressive human breast cancers. Genentech then developed a rational therapeutic antibody against neu/Her2 called Herceptin, which is currently used to treat breast cancers. It's been a rewarding experience to see a discovery move from the lab to patients, and to have been one of many people who made that possible. You never know in advance where progress will come from: in the Weinberg lab, everyone thought that human oncogenes, not rat oncogenes, would lead to the first human treatments.

Weinberg was a terrific mentor, extremely creative and always focused on asking the most important questions. At the same time, he had a deep attachment to his family, and showed by example that you don't have to compromise as a scientist to

be a person. In that respect, he was a role model for women in science, but really a role model for everyone in science.

A longstanding curiosity about the biology of behavior led me to my postdoctoral field. The neuroethologists of the early 20th century had demonstrated the existence of innate, species-specific behaviors, but the brain and genes were mysteries to them. In the late 1980s, it began to seem possible to link the biology of behavior to its neuronal and molecular underpinnings, and find the relationships between genes and innate behaviors. Genetics and neuroscience were barely connected fields at that point, so there was an opportunity -- neuroanatomy and neurophysiology were powerful existing tools, but it seemed that taking a different approach could lead to different insights.

My decision of which system to study was inspired by the publication, in 1986, of the complete wiring diagram of the *C. elegans* nervous system by John White and Sydney Brenner. To explore any new country, you need a map, and no brain had ever been mapped with the extraordinary level of detail that White brought to *C. elegans*. I joined Bob Horvitz's *C. elegans* lab at MIT. Bob Horvitz has an incisive mind and the view that any biological problem of any sort can be studied with *C. elegans* genetics. The breadth of his own work certainly supports that view: he's made key insights into many areas, including cell signaling, apoptosis, and developmental timing. Armed with the new wiring diagram, Horvitz's encouragement, and reports from the 1970s that worms could chemotax to attractive chemicals, I started to map sensory neurons and behavior, and to learn more about how the worm responded to its environment.

In 1991 I moved to the University of California, San Francisco, to start a lab in the Department of Anatomy. The fact that a medical school anatomy department would recruit me was a sign of the unified vision of UCSF, which saw all of basic and translational science as an organic whole. The Neuroscience program in particular saw itself as a single discipline, spanning the range from Biophysics to Neurology and Psychiatry. UCSF is where I learned neuroscience (especially from my new lab neighbor, Marc Tessier-Lavigne).

It was at UCSF that my lab began to work seriously on the molecular genetics of olfactory behavior in *C. elegans*. We did genetic screens for olfactory mutants, cloned the genes, and pored over the first bits of the *C. elegans* genome. These approaches led us to the molecular basis of odorant sensation. As had been shown by Buck and Axel in mice, the *C. elegans* olfactory system was composed of an enormous array of G protein-coupled receptors that were specifically expressed in subsets of olfactory neurons. About 2000 *C. elegans* genes encode receptors in these gene families (about 10% of its genes); to my knowledge, *C. elegans* still holds the record for the largest number of chemoreceptor genes in any animal. Happily, the fact that one gene emerged from a classical genetic screen meant that we knew what it detected: *odr-10,* an olfactory mutant identified by Piali Sengupta, was required for the behavioral response to the odor diacetyl.

The genetic screens yielded more than one gene, of course: these initial screens and later screens provided a broad view of the development and function of the *C. elegans* nervous system. Particularly interesting were sensory transduction pathways regulated by cGMP and TRPV channels; a gap junction/calcium channel pathway that linked neuronal development with early neuronal activity; and receptors that directed axon guidance and synapse formation.

The diacetyl receptor *odr-10* helped us to understand the molecular basis of odor sensation, and was also a wedge to drive into the behavior as a whole. Having the one-and-only-one diacetyl receptor in the worm genome gave us the ability to decide whether and how the worm was going to sense diacetyl. Emily Troemel genetically modified animals to move *odr-10* from its normal home in a neuron that senses attractants into an adjacent neuron that senses repellents. Worms with this molecular confusion could sense diacetyl, but they avoided it, the behavior appropriate for the host neuron, instead of approaching it as they normally would. This experiment suggests that the worm has dedicated sensory neurons for attraction or repulsion, forming a prepatterned template for its behavioral preferences.

The idea of a genetically hard-wired prepattern for taste and smell behavior may be a general principle. For example, Charles Zuker and Nick Ryba subsequently showed that sweet and bitter tastes in mice are detected by different taste cells that direct either acceptance or rejection behavior.

Having said that, the existence of an innate map does not preclude later modification based on experience. All animals learn, and *C. elegans* can learn about odors, touch, temperature, and taste. In addition, *C. elegans* behaviors are rapidly and reversibly remodeled depending on context and the animal's internal state. Variability and flexibility are at the heart of behavior.

An example of behavioral flexibility is *C. elegans*'s response to other members of its species. The decision to join or avoid other animals is made by a switch driven by neuromodulatory signaling that changes information flow through neural circuits. Both context cues and individual genetic differences contribute to the decision, converging on a neural circuit that integrates genes and the environment. As in our studies of olfaction, a gene (the neuropeptide receptor *npr-1)* provided a wedge to drive into this social decision. To understand it, we needed all of the tools at our disposal: the *C. elegans* wiring diagram, the *npr-1* gene, an understanding of context cues (environmental oxygen), an understanding of the animal's pheromones (happily, worked out by several excellent chemistry labs over the past few years), and even an understanding of how the lab is different from the worm's natural environment. A major step forward for understanding this circuit and others came from the development of genetically-encoded calcium indicators, beginning with Roger Tsien, Junichi Nakai, and (in *C. elegans)* Bill Schafer. Nikos Chronis in my lab combined this genetic technology with microfluidics to visualize the effects of

defined sensory stimuli and context on neural activity, providing a new mechanistic view of gene and circuit function.

It may seem a quirky choice to study the brains of worms. But from a genetic perspective, it was a smarter choice than anyone would have guessed at the time. Human biology, especially human neurobiology, is very complex, and our view of the human brain is fragmentary. However, the genomes of humans and worms share more genes than any of us expected, including most classes of genes that are important in the nervous system. (The complexity of the human nervous system comes from regulating the genes in different ways, and from deploying them in vastly larger numbers of neurons.) The basic functions of those genes are similar in all animals, so if we view one goal of biology as building a "dictionary" containing the meaning of each gene, we can assemble definitions in that dictionary from any animal, with a good chance that the definitions and grammar will apply across all animals and humans. Those of us who study worms hope to meet those who study human brains in the middle, using the universality of biology to translate understanding across organisms.

We are privileged to be scientists. The lab is an endlessly rewarding environment, full of smart, lively, and curious students and postdocs. Collaborations with other scientists let us branch out and explore new intellectual areas without sacrificing high standards. One of the greatest privileges of science is the company of other scientists, and the excitement that comes from other peoples' discoveries as well as your own. I am now at The Rockefeller University in New York, surrounded by colleagues of dazzling accomplishment. The lab is very fortunate to enjoy the intellectual freedom provided by the support of the Howard Hughes Medical Institute.

My sisters Monika, Eve, and Dorie are brilliant, witty, loving, and thoughtful. They grace the fields of English literature, medicine, and law, and I think they are the highest form of life on the planet. My husband, Richard Axel, is a neuroscientist at Columbia University with a passion for opera, art and literature. He makes me happy in ways that I had not thought possible.