Cornelia Isabella Bargmann (1961-) [1]

By: Garcia, Dasia Keywords: C. elegans [2] Neuroscience [3]

Cornelia Isabella Bargmann studied the relationship between genes [4], neural circuits, and behavior in the roundworm *Caenorhabditis elegans* [5] (*C. elegans*) during the twentieth and twenty-first centuries in the US. Bargmann's research focused on how the sense of smell (olfaction) in the nematode word *Caenorhabditis elegans* [6]. She provided a model to study how neural circuits develop and function in the human brain, as the genetic regulatory pathways are similar. She also studied how neurons develop and form connections to influence sensory abilities, and how chemicals called neuropeptides influence reproductive behavior in *C. elegans*. Such studies enabled researchers to make inferences about similar processes in other organisms, such as humans [7].

Bargmann said her interest in science arose from a prank conducted in the eighth grade. An earth science teacher told her that sodium was a metal and that it would burn if exposed to water. Bargmann and accomplices stole the sodium from the school lab and flushed it down the toilet in the boys' locker room. The toilet blew off the wall from the explosive reaction between sodium and water, and Bargmann later recalled that as the moment science struck her as being fun and exciting.

Bargmann enrolled at the University of Georgia in 1977, and she worked in Wyatt Anderson's population biology lab. She prepared fly food to feed the *Drosophila melanogaster* [8] flies under experimentation. Bargmann transitioned to Sidney Kushner's laboratory during her junior and senior years to learn more about molecular biology, while conducting research involving RNA metabolism and genetics in bacteria. Bargmann graduated valedictorian from the University of Georgia in 1981 with a bachelor's degree in biochemistry.

Bargamann began her PhD studies in 1981 at the Massachusetts Institute of Technology, a private research facility in Cambridge, Massachusetts, under the guidance of Robert Weinberg. Bargmann studied mutations to genes [4], called oncogenes, which changed normal cells into cancer cells. Oncogenes are genes [4] that have the potential to cause cancer and do so when mutated or expressed at abnormally high levels. The year that Bargmann joined, Weinberg's lab identified the first oncogenic [9] mutations in human RAS genes [4]. RAS genes [4], which code for RAS proteins, help send a chemical signal to cells to divide and grow at appropriate times. When the RAS gene has been damaged or mutated, an incorrect RAS protein is created causing improper signaling to the cells, which divide and grow uncontrollably. This uncontrolled growth leads to cancer.

Building her research in Weinberg's lab of the discovery of the RAS oncogene [10], Bargmann focused her doctoral research on the oncogene [10] called *neu* to determine its role in tumor formation. *Neu* is a gene that codes for the protein p185, and once mutated, the oncogene [10] causes cancer. Bargmann's research focused on two types of cancer, one called neuroblastomas that develops from immature nerve cells [11] found in an embryo or fetus [12], and another called glioblastomas found in the brain. Bargmann studied *neu* oncogene [10] in rodents. To study how oncogenes begin to produce proteins, she introduced a chemical called ethylnitrosourea, which induces neuroblastomas and glioblastomas, to pregnant rats to observe the effect on the fetuses. The chemical induced mutations and emabled Bargmann to study the expression of the p185 protein.

The p185 protein delivers a signal to an enzyme that activates or deactivates other proteins called tyrosine kinase. In some forms of cancer, those uncontrolled kinases cause tumors to grow. Bargmann observed that tyrosine kinases were abnormally active when oncogenes activated. She inferred that the normal product of the *neu* gene was a protein that received (receptor) an unidentified cancer-causing factor. That oncogenic [9] mutation of *neu* led to the discovery that the *neu* protein was a novel epidermal growth factor receptor. The epidermal growth factor receptor controls cell growth. An active growth factor receptor signals to the cell to grow and reproduce continuously (proliferate), resulting in a cancerous tumor.

The discovery of the oncogenic [9] mutation in the *neu* gene in rats led other researchers to discover that the human equivalent of the *neu* receptor, called HER2, existed in abnormally large amounts in aggressive human breast cancers. As a result of her work, Bargmann received her doctorate in biology in 1987.

Bargmann transitioned to postdoctoral studies in 1991 at another lab at the Masachussettes Institute of Technology led by Robert Horvitz, who also studied the *Caenorhabditis elegans* (*C. elegans*) worm. Many researchers had begun to use *C. elegans*as a commonly used model organism [13] in studies related to molecular biology, developmental biology, and neurobiology, because many genes [4] are similar between *C. elegans*and humans [7]. Bargmann focused on finding the relationships between genes [4] and behaviors in the *C. elegans*. Bargmann selectively removed specific neurons in the worm with a laser to observe the impact

on the worm's reaction to chemicals. She found that different neurons responded to different stimuli, and the combined activity of several neurons affected how well the worm was attracted or repelled by the chemicals introduced to its environment.

Bargmann's next tested four classes of chemical sensing neurons, chemosensory neurons, and their responses to different environmental conditions required for larvae to develop into adults. She concluded that to develop, larvae needed both food and a dauer pheromone. The dauer pheromone senses other worms [14], and it induces larvae to enter into the stress-resistant dauer larval stage, during which the worm does not eat or reproduce. When the chemosensory neurons that detect dauer pheromone are destroyed, the neurons lack the ability to signal for normal development.

Bargmann then researched the effect of different odorants on *C. elegans*behavior, and her olfactory study provided evidence that *C. elegans*have a sense of smell. She discovered that chemosensory neurons detect chemicals at a range of concentrations that either attract or repel the nematode. Mutants that possess the odr gene showed defects in chemosensory neurons, and an inability to smell, so they failed to respond to chemical stimuli.

Bargmann accepted an assistant professor position in 1991 at the University of California, San Francisco, in San Francisco, California, where she started her own lab. She continued researching the sense of smell (olfactory) in *C. elegans*, identifying chemosensory neurons and receptor genes [4]. Bargmann identified fourteen types of chemosensory neurons and over 40 highly divergent types of G protein-coupled receptors, GPCRs, that detect chemical factors like attractants, repellants, and pheromones. GPCRs are essential for the worm to sense chemicals in its environment. A single type of chemosensory neuron [15] could make products from four different receptor genes [4], explaining the worm's diversity in sense of smell. In 1995 Bargmann became an affiliated investigator at the Howard Hughes Medical Institute.

Bargmann began to study how *C. elegans*detect, and she found that a specific odor-causing chemical caused a specific behavioral response. The odorant diacetyl, an organic chemical compound normally found in worm food, caused the worms [14] to move towards the compound. The *odr-10* gene produces a protein that senses diacetyl, an intense buttery flavor, and is responsible for the animal's sense of smell, as shown by its presence at the tip of the animal's nose in the sensory cilia. Bargmann found the *odr-10* gene to produce the membrane receptor, G protein-coupled receptor, or GPCRs. She found that the receptor helped the worms [14] detect a single kind of odorant. She continued to research how the worms [14] smelled and reacted to different odorant chemicals, which led to the discovery that an animal's behaviors such as attraction, avoidance, feeding, and mating are controlled by sensory neurons.

In 1998 Bargmann became a full professor at the University of California San Francisco and served as vice chair of the department from 1999 to 2004. Throughout that time, she studied solitary and social feeding behaviors. In 2004 she discovered that environmental conditions such as the presence of oxygen dictated social or solitary feeding behaviors. Bargmann found that *C. elegans*worms [14] prefer to eat alone, but an elevated presence of oxygen causes them to eat in groups.

In the early 2000s Bargmann researched nervous system development and cell recognition during larval stages in *C. elegans*. She discovered the SYG-1 protein, which directs neurons to form connections with each other during development. The existence of SYG-1 protein, found in *C. elegans*and in mammals, indicates future synapses will form during the development of the central nervous system [16]. Researchers hypothesized that the SYG-1 protein helps connect neurons to each other during the development of the central nervous system [16].

Bargmann also studied aging in *C. elegans*in the early 2000s. Bargmann showed how to manipulate cells to double the lifespan of *C. elegans*. The rate of ageing was influenced by an interaction between two proteins: a transcription factor, DAF-16, and an insulin growth factor 1, IGF-1. Transcription factors regulate the transcription of DNA to messenger RNA, which is later translated into proteins. Transcription factors regulate what proteins the cells will manufacture, and are important for the normal development of an organism, as well as cellular function and response to disease. The insulin growth factor 1 functions in larval development, reproduction, growth, and ageing.

Bargmann moved to Rockefeller University [17] in New York City, New York, in 2004. She later married Richard Axel, a neuroscientist at Columbia University [18] in New York, New York. While at Rockefeller University [17], Bargmann continued her work examining gene function and signaling systems.

Bargmann showed that a signaling system of two proteins, vasopressin and oxytocin, found in the brain, are used by neurons to communicate with each other, ultimately influencing reproductive behavior. The oxytocin/vasopressin signaling system exists in humans [7] and researchers associated it with trust and monogamous mating.

Bargmann received multiple awards including the 2004 Dargut and Milena Kemali International Prize for Research in the Field of Basic and Clinical Neurosciences, the 2009 Richard Lounsbery Award from the US and French National Academies of Sciences, the Kavli Prize awarded by a partnership between The Norwegian Academy of Science and Letters in neuroscience in

2012, the Dart/NYU Biotechnology Achievement Award, and the 2013 Breakthrough Prize in Life Sciences awarded by the Breakthrough Prize Board. She was elected to the US National Academy of Sciences, the American Philosophical Society [19], and the American Academy of Arts and Sciences. Bargmann continued her research on *C. elegans*into the early decades of the twentieth century as a Howard Hughes medical investigator at Rockefeller University.

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Subject

Bargmann, Cornelia I. [28] Drosophila melanogaster [29] Neural circuitry [30] Weinberg, Robert E. [31] Neurobiology [32] HER-2 gene [33] Howard Hughes Medical Institute [34] HER-2 protein [35] DNA [36] Oxytocin [37] Genes, ras [38]

Topic

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Publisher

Arizona State University. School of Life Sciences. Center for Biology and Society. Embryo Project Encyclopedia.

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Last Modified

Wednesday, July 4, 2018 - 04:40

DC Date

2017-06-19

DC Date Accessioned

Tuesday, June 20, 2017 - 04:13

DC Date Available

Tuesday, June 20, 2017 - 04:13

DC Date Created

2017-06-19

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