Christiane Nusslein-Volhard (1942-) [1]

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Christiane Nüsslein-Volhard [7] studied how genes [8] control embryonic development in flies and in fish [9] in Europe during the twentieth and twenty-first centuries. In the 1970s, Nüsslein-Volhard focused her career on studying the genetic control of development in the fruit fly *Drosophila melanogaster* [10]. In 1988, Nüsslein-Volhard identified the first described morphogen, a protein coded by the gene *bicoid* [11] in flies. In 1995, along with Eric F. Wieschaus and Edward B. Lewis [12], she received the Nobel Prize in Physiology or Medicine [13] for the discovery of genes [8] that establish the body plan and segmentation [14] in *Drosophila* [15]. Nüsslein-Volhard also investigated the genetic control of embryonic development to zebrafish, further generalizing her findings and helping establishing zebrafish as a model organism [16] for studies of vertebrate development.

Nüsslein-Volhard was born in Magdeburg, Germany, on 20 October 1942, in the midst of World War II. Her mother, Brigitte Volhard, was an artist and musician and her father, Rolf Volhard, was an architect. Early in her life Nüsslein-Volhard vacationed at a farm where she became studied plants and animals, and by the age of twelve she worked to become a biologist. She attended primary school in Germany and she later recalled often neglecting subjects not related to her interests, resulting in mediocre grades overall.

Nüsslein-Volhard began attending Goethe Frankfurt University in Frankfurt, Germany, in 1962. Nüsslein-Volhard later said that the transition to university was difficult for her as she missed her friends and wasn't challenged by the biology program. Seeking more interesting classes, Nüsslein-Volhard broadened her studies to include physics and mathematics. In the summer of 1964, Nüsslein-Volhard left Frankfurt to study at the University of Tübingen in Tübingen, Germany, where a new biochemistry program had been established. Although she said that her accommodations in Tübingen were sparse—no central heating or warm water—she also said that she enjoyed the curriculum, especially genetics and microbiology. Furthermore, Tübingen housed the Max Planck Institute for Virus Research, which gave Nüsslein-Volhard the opportunity to attend lectures by many leading scientists such as Gerhard Schramm, and Heinz Schaller. She said that these lectures shaped her understanding of science. During this time she married briefly, resulting in her hyphenated last name. When she divorced she decided to retain her hyphenated name as it had begun to be associated with her scientific publications. In 1968, Nüsslein-Volhard graduated from University of Tübingen with a degree in biochemistry.

In 1969 Nüsslein-Volhard began her doctoral work in Heinz Schaller's Laboratory at the Max Planck Institute for Virus Research. She launched her thesis work on phage RNA-DNA interactions, but quickly discovered limitations with the tools available for experimentation. Subsequently, she developed a technique for purifying RNA polymerase, the molecule that transcribes RNA from DNA. By capturing the molecule where it binds to DNA at specific regions called promoters, she characterized promoter regions and described the molecular mechanisms that activate the process of transcription.

When Nüsslein-Volhard finished her PhD in 1973, she said that molecular biology work had lost much of its appeal to her. Interested to apply genetics to more complex phenomenon than those in viruses, she studied cellular biology, pattern formation [17], and regeneration in the hydra [18], a genus of freshwater polyps. In 1973 Nüsslein-Volhard met Walter Gehring, who had just published a paper on the gene *bicaudal* in *Drosophila* [15]. Interested in genes [8] like *bicaudal* that controlled the establishment of polarity [19] in embryos, Nüsslein-Volhard asked to join his lab at the University of Basel [20] in Basel, Switzerland. Gehring agreed, and in 1975 she moved to Switzerland.

Supported by a fellowship from the European Molecular Biology Organization (EMBO) in Heidelberg, Germany, Nüsslein-Volhard began postdoctoral work at the Biozenstrum, a research institute within the University of Basel [20]. She began large-scale genetic screens [21] of mutant *Drosophila* [15] embryos that lacked the *bicaudal* gene. Nüsslein-Volhard performed a type of genetic screen called a saturation screen, in which researchers work to identify all the genes [8] involved in a particular phenotype by exposing flies to mutagens and finding the genetic mutation that caused phenotypic abnormalities. By examining a cohort of flies missing the *bicaudal* gene, she could determine all the other genes [8] involved in the mutant bicaudal phenotype. Due to the tedious task of collecting and harvesting embryos, the large number of mutants needed for the screens, and the difficulties associated with identifying mutant phenotypes, Nüsslein-Volhard later reported that *bicaudal* was the most challenging gene she ever researched. However, after developing several techniques to facilitate her work, she identified a second gene which appeared to influence pattern formation [17] in fly embryos, a gene later called *dorsal*. Her work on *bicaudal* culminated in the 1977 paper "Genetic analysis of pattern-formation in the embryo of *Drosophila* [15] *melanogaster*".

In 1978, Nüsslein-Volhard accepted a position at the European Molecular Biology Laboratory [22] (EMBL) in Heidelberg, Germany. The offer coincided with the hiring of another *Drosophila* [15] researcher, Eric Wieschaus [23], who had finished his thesis in Walter Gehring's lab just as Nüsslein-Volhard had entered. Although the two had corresponded since those days, they

had never worked together until the EMBL approached them to jointly lead a group of researchers focusing on flies. Nüsslein-Volhard and Wieschaus undertook a project to discover the genetic mechanisms of how a fertilized *Drosophila* [15] egg [24] became a segmented embryo. *Drosophila* [15] larvae begin segmentation [14] shortly after fertilization [25], as the cells organize into fourteen distinct body segments. To investigate this process, Nüsslein-Volhard and Wieschaus exposed fly embryos to mutagens, and systematically characterized their phenotypic mutations. They screened mutated embryos that exhibited abnormal development of the body axis or segmentation [14] to identify which genes [8] had gone awry.

In 1980 Nüsslein-Volhard and Wieschaus published "Mutations Affecting Segment Number and Polarity in *Drosophila* [15]". They reported fifteen genes [8] that, when mutated, caused defects in the fourteen segments of fly embryos. They further classified the genes [8] into groups based on how, and in what order, they affected segmentation [14]. First, they identified three gap genes [8], each of which help determine the identities of each segment of the embryo. Second, they identified six pair-ruled genes [8] which affected alternating segments. Finally, the group identified six segment polarity [19] genes [8], genes [8] that helped establish the anteroposterior axis of each segment. For their work on segmentation [14] in *Drosophila* [15], Nüsslein-Volhard and Wieschaus shared the 1995 Nobel Prize in Physiology or Medicine [13] with Edward B. Lewis [12]. Lewis helped identify the Hox genes [26] of the bithorax complex [27] in *Drosophila* [15], and he demonstrated the extreme phenotypes of flies that had homeotic mutations.

Before their 1980 research was published, Wieschaus had started looking for a new job. Although the EMBL extended Nüsslein-Volhard's contract for another three years, she did not feel comfortable working there without Wieschaus, who in 1981 had been hired at Princeton University [28] in Princeton, New Jersey. Later that year Nüsslein-Volhard accepted a position as a junior investigator at the Friedrich Miescher Laboratory (FML) and moved back to Tübingen. At the FML, Nüsslein-Volhard continued to study several of the genes [8] identified in her 1980 paper.

In 1986, Nüsslein-Volhard became director of the Max Planck Institute for Developmental Biology [29] in Tübingen, Germany, a position that she held into the early twenty-first century. In 1988, Nüsslein-Volhard and her student Wolfgang Driever [30] isolated the protein coded by the gene *bicoid* [11]. A pregnant fly deposits in her eggs some bicoid [11] protein, which collects in the anterior portion of the egg [24] when sperm [31] fertilizes it and it becomes an embryo. Nüsslein-Volhard and Driever identified the bicoid [11] protein as a transcription factor that regulated the expression levels of some of the segmentation [14] genes [8]. Furthermore, originating in the anterior region of the embryo, the bicoid [11] protein acted as a morphogen, diffusing posteriorly across the embryo and impacting development in a concentration dependent manner. While scientists in the twentieth century like Alan Turing, Lewis Wolpert [32], and Francis Crick [33] had hypothesized the existence of morphogens [34], bicoid [11] was the first protein that demonstrably met the definition of a morphogen.

While she continued her work on the genetic control of development and morphogen gradients, Nüsslein-Volhard began to test if her methods used on *Drosophila* [15] could be extended to vertebrates. She pursued the same sort of mutation experiments that she had used in *Drosophila* [15] in the zebrafish *Danio rerio* [35]. Although some funding agencies questioned the work due to the scant genetic information about zebrafish compared to *Drosophila* [15], Nüsslein-Volhard said that the fish [9] were ideal for genetic and developmental studies due to their rudimentary spinal cords and transparent embryos. Furthermore, as the zebrafish is a vertebrate, it is more help than is *Drosophila* [15] for scientists as they study similar processes of development in humans [36].

In 1986 Nüsslein-Volhard began working with the fish [9] in her lab at the Max Planck Institute. By 1993 Nüsslein-Volhard constructed a fish [9] lab run by 16 researchers and housing nearly 7000 aquaria. Three years later her lab published manuscripts describing 1200 zebrafish mutants showing that, like *Drosophila* [15], large numbers of developmental mutants could be obtained in a vertebrate species. Analysis of the genes [8] that caused mutant phenotypes contributed to many developmental theories in vertebrates such as somitogenesis [37], segmentation [14] and pair-rule patterning, hematopoeisis [38], limb formation, and neurogenesis. Her work with zebrafish eventually led her to publish *Zebrafish: A Practical Approach* in 2002, a laboratory manual outlining practical principles in working with the species. Afterwards, zebrafish became a standard vertebrate research model due to their similarities with mammals, rapid embryonic development, and large transparent embryos.

Leading up the Nobel Prize in 1995, Nüsslein-Volhard received many awards. In 1986 she received the Leibniz Prize of the German Research Foundation. In 1989, she received the Carus Prize of the German Academy of Sciences [39] Medal. In the 1990's, Nüsslein-Volhard received the Rosenstiel Medal. In 1991 she was awarded with the Lasker Basic Medical Research Award. In 1994 a newly discovered asteroid in the main asteroid belt of our solar system was also named after her: 15811 Nüsslein-Volhard.

Nüsslein-Volhard's later career has focused on social, ethical and philosophical issues in the sciences. She served on the German National Ethics Council from 2001 to 2006. In 2004 Nüsslein-Volhard established the Christiane Nüsslein-Volhard [7] Foundation, which seeks to promote gender equality in science by providing support and resources to women scientists. Nüsslein-Volhard has no children, and she has said that the difficulty for women to balance research and family obligations is one of most prominent reasons women are underrepresented in leading scientific positions. When asked about her continued interest in developmental biology after over thirty years in the field, Nüsslein-Volhard stated that there are always new questions posed by science and new levels of understanding to be obtained.

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Subject

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