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CHRISTIANE NÜSSLEIN-VOLHARD: FROM *DROSOPHILA* GENETICS TO THE DISCOVERY OF GENETIC CONTROL OF EMBRYONIC DEVELOPMENT

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"Creativity is combining facts
no one else has connected before".
Christiane Nüsslein-Volhard

The article presents Christiane Nüsslein-Volhard – a distinguished researcher in genetics and developmental biology whose studies have profoundly advanced our understanding of how genes in a fertilized egg determine the formation of the embryo. When Nüsslein-Volhard and her colleagues began their experiments with Drosophila melanogaster, this model organism was already widely used in genetic research. However, her approach was innovative: instead of merely observing mutations, she systematically induced thousands of them to identify the genes controlling the earliest stages of development. Her research demonstrated that the development of living organisms is governed by specific genes that can be identified, studied, and even modified. In 1995, she was awarded the Nobel Prize in Physiology or Medicine, together with Eric Wieschaus and Edward B. Lewis, for the discovery of the genetic mechanisms controlling embryonic development. This became a turning point in developmental biology: similar genes were later found in frogs, fish, mice – and even in humans – convincingly demonstrating the evolutionary commonality of the genetic pathways that determine morphogenesis.

K e y w o r d s: Christiane Nüsslein-Volhard, embryogenesis, genetic screens, morphogen, mutagenesis, Nobel Prize.

On October 9, 1995, the Nobel Assembly at the Karolinska Institute awarded the Nobel Prize in Physiology or Medicine to Edward B. Lewis, Christiane Nüsslein-Volhard, and Eric Wieschaus for their discoveries concerning "the genetic control of early embryonic development" [1].

In this article, we focus on Christiane Nüsslein-Volhard – a scientist whose ideas and experiments transformed our understanding of the mechanisms underlying the development of living organisms.

Christiane Nüsslein-Volhard was born on October 20, 1942, in the German city of Magdeburg. Her father, Rolf Volhard, was an architect – the eighth of ten children of Franz Volhard, a professor of medicine in Frankfurt and a specialist in cardiovascular diseases. Her maternal grandmother, Lise Haas-Mellmann, was an artist who gave up her career for the family. Christiane's mother had a great social gift and a natural talent for caring for children and people in need. Both parents were skilled musicians and talented in drawing, and they passed these skills to their children, who enjoyed these pursuits with full parental support. Christiane learned to play the flute but, as she recalled, despite her efforts, she "never drew as well as [her] sisters and brother" [1].

From an early age, however, she was fascinated by the natural sciences. She later wrote:

"I loved our garden and kept pets, but there was no one around who really knew about plants and animals and could explain them to me, so I

tried to find out as much as I could on my own and from books. In our family, I was the only one with a lasting interest in science. My parents supported me by providing the right books, and my brother and sisters listened to my stories and theories" [2].

This natural curiosity and independence eventually led her to biology. From 1962 to 1964, she studied biology, physics, and chemistry at the Johann Wolfgang Goethe University in Frankfurt am Main. In 1964, when the University of Tübingen launched a new program in biochemistry – the only one of its kind in Germany at the time – Christiane decided without hesitation to continue her studies there.

The student life in the old university town of Tübingen, as she later recalled, was romantic though rather modest. She viewed the biochemistry program itself as somewhat mixed: too much organic chemistry and too little biology. At the same time, she particularly enjoyed courses in physical chemistry, thermodynamics, and stereochemistry. The most valuable period came during her final year, when new faculty introduced courses in microbiology and genetics, and she had the opportunity to attend lectures by leading scientists from the Max Planck Institute for Virus Research, directed by Heinz Schaller. Later, in 1969, Christiane Nüsslein-Volhard began working at this institute [2].

In the early 1970s, biochemistry and molecular biology were entering a period of rapid expansion. Scientists were actively exploring the mechanisms regulating gene expression, the processes of protein synthesis, and the role of ribosomes. This wave of breakthroughs was reflected in a series of Nobel Prizes in Physiology or Medicine: in 1965, awarded to François Jacob, Jacques Monod, and André Lwoff for their discoveries concerning the regulation of genes [4, 5]; in 1968, to Robert Holley, Har Gobind Khorana, and Marshall Nirenberg for deciphering the genetic code [6, 7]; and in 1975, to Howard Temin, David Baltimore, and Renato Dulbecco for the discovery of reverse transcriptase and the interactio between oncogenic viruses and the cellular genome [8].

While pursuing her doctoral degree, Nüsslein-Volhard contributed to improving Schaller's methods for purifying RNA polymerase, an essential enzyme that initiates the transcription of RNA from DNA. In 1974, she earned her PhD for research on protein–DNA interactions and RNA polymerase binding in *Escherichia coli*.

However, in a later interview, Nüsslein-Volhard noted that although she had earned a PhD in molecular biology, she did not consider herself a molecular biologist or a biochemist [9]. Eventually, she realized that she was no longer interested in developing new methods for DNA sequencing but was instead drawn to organismal biology.

Christiane Nüsslein-Volhard explaining Drosophila embryonic development [3]

At that time, a research group led by Alfred Gierer at the Max Planck Institute was studying regeneration processes in *Hydra*. After learning about this work, Christiane became fascinated by the concept of morphogens and the broader question of how structures are formed. She submitted a proposal for an EMBO fellowship, in which she argued that identifying morphogens would require combining genetics with developmental biology: if one could induce a mutation in a gene encoding a gradient and observe the consequences of its loss, the responsible genes could be identified [9].

In early 1975, Christiane began working with *Drosophila* (fruit fly) in Walter Gehring's laboratory in Basel. As she later recalled about her favorite research subject: *"I immediately loved working with flies. They fascinated me, and followed me around in my dreams*". The fruit fly proved to be an ideal model organism: after fertilization, the egg developed into an embryo, then into a larva, and finally into a mature fly within just nine days. Christiane started to investigate the bicaudal process in *Drosophila* mutants – the most complex mutants she had ever worked with [9].

At that time, studying embryonic mutants was particularly challenging, since the available methods for collecting eggs and analyzing embryos were both laborious and unsatisfactory. In a living embryo, it was difficult to observe structures, segment bounda-

ries, and polarity, while suitable fixation and clearing techniques were lacking. With the help of geneticist Jeannette Goldent and postdoctoral researcher David Ish-Horowicz, Christiane developed her own method for assessing mutant embryos from numerous lines.

Soon afterward, Christiane received a job offer from John Kendrew, the Director General of the newly established European Molecular Biology Laboratory (EMBL) in Heidelberg, which was recruiting scientists in multiple disciplines. The same offer was extended to her colleague Eric Wieschaus, who was engaged in several original projects at the time – including studies on germline development, cell line determination, and sex determination, all considered pioneering directions.

Although they worked in different cities – Christiane in Basel and later in Freiburg, and Eric Wieschaus in Zurich – they kept in close contact. Beyond discussing their experiments, they shared a common goal: to understand how a newly fertilized *Drosophila* egg develops into a segmented embryo.

Thus, both Christiane and Eric accepted John Kendrew's offer and spent three years, from 1978 to 1980, working together at EMBL in Heidelberg. No one before them had identified the genes controlling the earliest stages of embryonic development, but this did not deter them from designing an ambitious experimental strategy. They treated flies with mutagenic agents to randomly mutate roughly half of the *Drosophila* genome and then searched for mutations that disrupted body-axis formation or segmentation patterns.

Christiane and Eric were young, determined, and, as she later said, "*the only people who saw the potential in mutant screening*" – those who "*were far ahead of everyone else, who thought that screening was too much work, might not succeed, or would only yield messy results*" [9].

Christiane Nüsslein-Volhard and Eric Wieschaus in their shared office at the European Molecular Biology Laboratory in Heidelberg [10]

Christiana in the lab during experiments with Drosophila [11]

It is known that *Drosophila* has about 5,000 genes, and only a very small fraction of them, when mutated, lead to changes in the larval segmentation pattern. After a year of systematic screening for mutations, Nüsslein-Volhard and Wieschaus succeeded in identifying 15 different genes whose mutations caused segmentation defects. They took advantage of the segmented structure of the *Drosophil*a larva to analyze how genes control development. The genes were classified according to their order of action during embryogenesis and the way their mutations affected segmentation.

This work demonstrated that, in *Drosophila*, it was, in principle, possible to identify all the genetic components involved in the complex process of embryonic pattern formation [1].

Nüsslein-Volhard and Wieschaus showed (Fig.) that gap genes control the overall body plan along the head–tail axis and begin to act at a very early stage of embryonic development (Fig., *A*), defining the initial segmentation pattern (Fig., *B*). Loss of a gap gene function results in a reduction in the number of body segments. Pair-rule genes, acting downstream of gap genes, establish the pattern of 14 final segments (Fig., *C*). These segments subsequently acquire head–tail polarity through the action of segment polarity genes (Fig., *D*), which define polarity within each segment. Once the segments are established (Fig., *E*), homeotic genes determine the identity of each segment – that is, they specify which structures (e.g., wings, legs, antennae) will develop in each segment.

Thus, in seeking to answer the question "How do genes determine the body plan of *Drosophila*?",

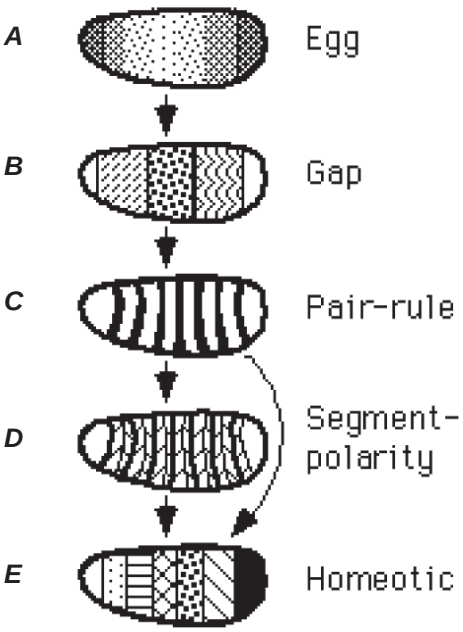

Fig. Regions of activity in the embryo for the genes belonging to the gap, pair-rule, and segment-polarity groups [1]

Nüsslein-Volhard and Wieschaus concluded that, first, developmental control genes can be systematically identified; and second, that a relatively limited number of such genes can be grouped into distinct functional classes. The results of these studies were first published in the scientific journal Nature in the autumn of 1980 [12].

Looking ahead, it should be noted that the research on "segmentation genes", which are key to determining body plan and the formation of body segments, later earned Christiane Nüsslein-Volhard the Nobel Prize in Physiology or Medicine in 1995, shared with Eric Wieschaus and Edward Lewis. This recognition not only underscored the significance of their discoveries but also marked a turning point in developmental biology, illustrating how genetic pathways can shape morphological development.

In the spring of 1981, Christiane Nüsslein-Volhard received an offer for a junior position at the Friedrich Miescher Laboratory (FML) of the Max Planck Society in Tübingen and moved there. According to Christiane, the FML offered "excellent conditions and a great challenge." She was fortunate to work with outstanding geneticists – Gerd Jürgens and Kathryn Anderson. Together, they carried out a large-scale screen for maternal mutants, identifying many genes involved in axis determination, including *bicoid* and *oskar*, as well as most of the dorsal group genes [2]. However, the newly identified genes, like the previously discovered pair-rule and gap genes, were not conserved outside insects.

Meanwhile, in 1985, Christiane was appointed director of an independent department at the Max Planck Institute for Developmental Biology, a position she held until her retirement in 2014. Her group expanded, allowing her to pursue molecular studies, including analyses of *bicoid* RNA localization (which had been cloned in Markus Noll's laboratory in Basel). Her PhD student, Wolfgang Driever, generated an antibody against the bicoid protein and discovered the bicoid gradient, which, depending on its concentration, determines the expression pattern of other segmentation genes [13, 14].

Christiane recalled: "Wolfgang established many molecular methods in my laboratory; later, Frank Sprenger and Leslie Stevens cloned *torso*, then Daniel St Johnston cloned *staufen*, and Robert Geisler cloned *cactus*. Improvements in visualizing gene products using *in situ* hybridization and antibody staining complemented earlier transplantation studies, leading to several exciting discoveries by Dave Stein and Siegfried Roth on the establishment of extracellular gradients and nuclear localization" [2].

Having uncovered the genetic logic behind the segmentation of *Drosophila*, Christiane turned her attention to understanding whether the same principles might also govern the development of vertebrates. She focused on the zebrafish (*Danio rerio*) as a new model organism. Exploring this unfamiliar system required creating an entire toolkit from scratch: new instruments, new methods, and, once again, a great deal of persistence and patience in

Christiane Nüsslein-Volhard with zebrafish at the Max-Planck Institute [15]

Christiane Nüsslein-Volhard [20]

searching for an answer to the central question – is embryogenesis in *Drosophila* in any way comparable to that in vertebrates?

When the zebrafish gene screen began, it was still unclear how much of what had been learned from *Drosophila* could be applied to vertebrates. Their modes of development seemed so different that many believed no common ground could exist. Only with time did the homology between invertebrates and vertebrates slowly emerge. At that time, several research groups were already working with mutant fish, but they were unable to raise them efficiently. Christiane's team spent nearly four years perfecting large-scale zebrafish breeding methods. The screen eventually revealed many of the same genes already known as key developmental regulators in frogs. As Christiane later said, when they "identified and cloned the equivalent mutants in fish, they were not a big surprise" [16].

In 1996, a special issue of Development was published, bringing together the results of two major zebrafish mutant screens carried out in Tübingen and Boston. The 37 papers in that issue described around 1,500 mutations in more than 400 previously unknown genes involved in a wide range of processes that govern development and organogenesis [17].

Over the course of her career, Christiane has authored and co-authored 75 scientific papers listed in PubMed, 54 of which are devoted to *Danio rerio.* Continuing her research, she demonstrated that similar, and in some cases identical, genes exist in higher organisms. One of her papers [18] described a specific signaling pathway (CSF1R) in zebrafish. Understanding such signaling networks provides the basis for identifying new therapeutic targets linked related to human diseases, including cancer and neurological disorders.

In the same year, 2022, another article was published discussing the origins, importance, and usefulness of genetic model organisms. The universality of developmental mechanisms shared across species was illustrated through these genetic model systems, each offering unique advantages for exploring different aspects of developmental biology: *Drosophila melanogaster* – for analyzing morphogenetic mechanisms; *Danio rerio* – for observing organogenesis in vertebrates; *Caenorhabditis elegans* – for studying cell–cell interactions; and the mouse (*Mus musculus*) – for modeling physiological processes and human diseases [19].

The strategy proposed by Christiane Nüsslein-Volhard became fundamental to modern concepts of the genetic control of embryonic development. It provided a framework for understanding how genetic information is translated into the complex anatomical structure of a multicellular organism. Without doubt, Nüsslein-Volhard's pioneering work inspired an entire generation of scientists to explore the intricate functions of genes and their significance for evolutionary biology.

Beyond her discoveries, C. Nüsslein-Volhard has played a crucial role in promoting scientific collaboration and education. Through her leadership, she developed training programs for young researchers, emphasizing the importance of interdisciplinary approaches in developmental biology [21]. Her laboratory continues to serve as a beacon for aspiring scientists, fostering a culture of curiosity and innovation that resonates across the scientific community.

Christiane Nüsslein-Volhard's contributions to developmental biology have earned her numerous prestigious awards, including, in addition to the Nobel Prize in Physiology or Medicine (1995), the Albert Lasker Award for Basic Medical Research (1991). She is a member of several leading scientific academies, among them the Royal Society (London) and the U.S. National Academy of Sciences.

Nüsslein-Volhard C. also authored a cookbook, published in 2006 and still available today. She enjoys cooking and sees parallels between culinary work and laboratory science – both require organization, manual skill, and attention to detail. She is also passionate about music: she plays the flute, sings, and occasionally performs for her friends.

In an interview, when asked, “Do you have any advice for young scientists?”, she replied that one should be genuinely curious about science and take joy in discovery. “Research depends on achievement – on making discoveries and publishing them. It means hard work, and if you are not rewarded by success, it can be very frustrating. Don’t listen too much to mentors and teachers – they may not be honest, only polite. So it’s important to evaluate your own abilities critically, in comparison with others. This is your own responsibility” [22].

In summary, Christiane Nüsslein-Volhard’s contribution to developmental biology is far-reaching and continues to shape future research aimed at uncovering the genetic mechanisms and processes that drive development.

КРІСТІАНА НЮССЛЯЙН-ФОЛЬХАРД: ВІД ГЕНЕТИКИ ДРОЗОФІЛИ ДО ВІДКРИТТЯ ГЕНЕТИЧНОГО КОНТРОЛЮ ЕМБРІОНАЛЬНОГО РОЗВИТКУ

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У статті представлено Крістіану Нюссляйн-Фольхард – видатну дослідницю в галузі генетики та біології розвитку, чиї роботи допомогли зрозуміти, як гени в заплідненій яйцеклітині формують ембріон. Коли Нюссляйн-Фольхард і її колеги розпочали експерименти з *Drosophila melanogaster*, ця модельна система вже широко використовувалася в генетичних дослідженнях. Проте її підхід був інноваційним: вона не просто спостерігала за мутаціями, а систематично індукувала їх тисячі, щоб визначити, які гени контролюють розвиток організму на найраніших етапах. Дослідження Крістіани Нюссляйн-Фольхард показали, що розвиток живих організмів визначається конкретними генами, які можна ідентифікувати, вивчати й навіть модифікувати. У 1995 році вона отримала Нобелівську премію з фізіології або медицини разом з Еріком Вішаусом та Едвардом Б. Льюїсом за відкриття генетичних механізмів контролю ембріонального розвитку. Це стало поворотним моментом у біології розвитку: згодом подібні гени були знайдені у жаб, риб, мишей – і навіть у людини, що переконливо продемонструвало еволюційну спільність генетичних шляхів, які визначають морфогенез.

Ключові слова: Крістіана Нюссляйн-Фольхард, ембріогенез, генетичний скринінг, морфоген, мутагенез, Нобелівська премія.

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