# Laudatio to Christiane Nüsslein-Volhard as doctor honoris causa,

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It is a real pleasure and a great honor for me to introduce Prof Christiane Nüsslein-Volhard in the context of her nomination as Doctor Honoris Causa by the University Pompeu Fabra. Christiane Nüsslein-Volhard does not need much of an introduction —she is one of the best-known scientists in Developmental Biology and Genetics and biology in general. She pioneered a scientific approach with molecular studies in the fruit fly Drosophila, which constituted a revolution in biology and was recognized with a Nobel prize. To convey the importance of Professor Nüsslein-Volhard's achievements during her professional career is a difficult task, and I decided to do so by giving you my vision of her pillar contributions to this revolution in Biology, specifically to Developmental Biology, and to comment on her broader contributions to the scientific community.

Before entering into the **scientific accomplishments**, I will briefly summarize the field of developmental biology, which basically aims at understanding how a whole fully-differentiated organism is generated from a single multipotent cell, the zygote. Embryonic development involves an exquisite balance between cell proliferation and cell differentiation that results in an enormous number of different cell types that must occur in their correct proportions and locations. The cartography and final shape of the organisms are established by sequential processes that convert initially very simple patterns into others of increasing complexity. Thus, the building of a new organism involves the precise coordination of growth, spatial patterning and morphogenesis. The result is the generation of an individual with many different specialised organs, each with specific shape and function. You may take this as a brilliant triumph of evolution. Understanding the mechanisms that control the embryonic development in different animal species, and the roadmap that allows this to be highly reproducible in every individual, must be based on solid mechanisms selected throughout evolution. Getting deep knowledge about these mechanisms is a crucial key for tissue biology, regenerative medicine and biomedical engineering that aim at the therapeutic reconstruction of tissues and organs.

These fundamental questions about how an embryo develops into a new individual were posed long ago by the ancient Greek scientists and philosophers. In the last century, advances in experimental embryology, the tradition of watching and manipulating embryos that started in the late XIX century, joined the application of genetics and gene manipulation. With the birth of molecular biology, and its development into a fully developed discipline, these fundamental questions became addressable. Much of the excitement in developmental biology nowadays comes from our growing understanding of how genes direct these developmental processes. And it was at this crucial crossroad, envisaging the importance of placing genetics at the central stage of embryonic development, where Prof Nüsslein-Volhard played such a crucial role.

Prof Nüsslein-Volhard has been interested for many years in how complexity arises from basic patterns, and she did not fear in undertaking immense challenges to pursue this question. She begun by studying gene transcription —how genes are switched on. During her PhD in the University of Tübingen, she worked in the structure of gene promoters and isolated RNA polymerase binding sites from a phage –a bacterial virus. At that time, techniques were still developing and were far less powerful or as fast as today. However, Prof Nüsslein-Volhard saw the potential of **molecular biology for understanding the complex mechanisms underlying embryonic development**, one of the pillars of her scientific contributions.

This was how after her PhD, she transitioned to developmental genetics. In those years, it was recognized that the steps producing morphological complexity in the different organisms were reproducible from one embryo to the next, and that genes and cell interactions were important in embryonic development —but the underlying mechanisms were largely unknown and somehow, if not, enigmatic. Prof Nüsslein-Volhard predicted that **developmental mechanisms were so basic that they had to be evolutionary conserved**, and that **genetics would lead the path to the logics of the biological systems**. This is, in my opinion, one of the most revolutionary ideas in biology, and another of the scientific pillars that paved the future road to travel. Prof Nüsslein-Volhard wanted to go beyond the evident and thus investigated the logics of constructing the embryo. For this purpose, she aimed at combining genetics and developmental biology. The rationale was that **the function of a gene can be deduced from the effects produced by its deletion**, a simple but powerful concept. Genes whose mutations result in similar phenotypes are predicted to have similar functions, and their products are likely to cooperate. And brilliantly, she foresaw that knowing how simple organisms form would help us to better understand how complex organisms develop. This is how in 1973, she moved for a postdoctoral stay to the laboratory of Walter Gehring at the Biozentrum in Basel, who had just published the first set of early mutants in *Drosophila melanogaster*. No doubt that the Biozentrum and the Gehring's lab was one of the places to be if you wanted to understand genes and development. Developmental Biology was flourishing in new concepts, such as tissue patterning, morphogen gradients, positional information, … and *Drosophila* was a fantastic and rather simple and non-expensive model system to work with. As she stated in her Nobel Prize biography, *It was difficult to be a beginner in everything, after having been an expert in almost everything in the previous lab*. With a whole new set of techniques being established, and surrounded with talented colleagues, she studied the *bicaudal* gene, which is today one of the best-known genes. While there, she developed new methods to generate her own mutants. It was then that she met Eric Wieschaus who just had finished his PhD thesis, with whom she would share the Nobel prize (together with Ed Lewis) years later.

In 1978, Prof Nüsslein-Volhard and Dr Wieschaus got a job offer from the director general of the European Molecular Biology Laboratory, EMBL, to establish a joint lab. Together, they started a new project, conceptually very simple, extremely powerful, and technically not so obvious. The idea was to identify all genes involved in embryonic development by mutating them at a large-scale; in other words, to mutate all the genes of the genome in such a manner that not more than a single gene would be mutated in each individual, and then to look for specific developmental defects and trace back their function —what we now call reverse genetics. That was the first large-scale mutagenesis genetic screen in *Drosophila* embryos —*the Heidelberg screen*— performed between 1979 and 1980 at the EMBL in Heidelberg. Let me give you a flavor of it.

Since they wanted to understand the logics behind cell determination and differentiation, as well as to trace back the decisions made by cells and tissues during early development, it was necessary to find out: i) how many genes were involved in embryonic pattern formation, ii) whether each of these genes was unique, and iii) what types of changes and alterations can be traced back to a mutation in a single gene. Large-scale mutagenesis experiments would allow the identification of most, if not all, genes affecting embryonic developmental decisions on the basis of visible mutant phenotypes in the larva. With this in mind, they generated a collection of six hundred Drosophila embryonic mutants that corresponded to one hundred and twenty genes. They shared this mutant collection with the scientific community, pioneering the exchange of materials and data among different "fly laboratories". That work was published in the journal Nature in October 1980 and set up a turning point in the field, beautifully demonstrating that **genes controlled the logics of embryonic development**, and that **there was a sequential gene hierarchy**. Those mutants subsequently provided a very rich resource for understanding many fundamental processes in development and disease. Most of the "Heidelberg genes" are now molecularly characterized, and many of them are shown to be conserved in other animal species, including humans.

Although the screens were initially driven entirely by curiosity, the mutants now serve as models for many human diseases, showing once more the importance of fundamental scientific research for health sciences. After few years, Prof Nüsslein-Volhard was appointed to the Friedrich-Miescher-Laboratory of the Max-Planck-Society in Tübingen, where she moved in 1981, while Dr Wieschaus moved to Princeton University. But they maintained their ongoing scientific collaboration, which resulted in exciting discoveries and impressive breakthroughs, such as the discovery of the genes involved in the establishment of the fly body axes or the role of morphogens in development. These investigations gradually evolved to a far more comprehensive understanding of the principles of axis determination in animals. Overall, this innovative work led to the award in 1995 of the Nobel Prize in Physiology and Medicine to Prof Nüsslein-Volhard and Dr Wieschaus ***For the discoveries concerning the genetic control of early embryonic development***, together with Dr Lewis, and revealed that embryonic development was actually controlled by a relatively small fraction of genes within the genome, the so called *developmental genes*.

**From flies to fish**

Although impressive, this is only half of the story. One big question emerged after the fly work: were those genes and mechanisms extensive to other animal species? In particular, do vertebrates use similar strategies? Around that time, a high degree of gene homology among the metazoans slowly became apparent. As Stephen J Gould stated in 1977 "*I also believe that an understanding of the regulation must lie at the center of any rapprochement between molecular and evolutionary biology; for a synthesis of these two biologies will surely take place, if it occurs at all, on the common ground of development*". Thus, in the middle of her success in the discovery of the molecular mechanisms governing *Drosophila* embryonic development, Prof Nüsslein-Volhard went a step further and moved out of what now we may call *"the comfort zone"*. She explored whether a fish, such as a zebrafish, could eventually be exploited like the fly for the genetic analysis of vertebrate developmental genes and decided to test whether it could be used for the same strategy as for Drosophila —a large-scale genetic screen. In doing so, she anticipated zebrafish as one powerful vertebrate model organism for genetics. For those not familiar with what a "wet lab" is, let me tell you that such decision implies an enormous scaling-up in your facilities and another level in managing complexity. Shortly, a big enterprise. But she took it as a fascinating challenge that resulted in the beginning of the zebrafish large-scale screening, or the *Tübingen screen*, in 1992. There were only two other places in the world setting up this model system, in Eugene and Boston.

The screening turned out to be much more complex than in *Drosophila*, as the fly has in total five chromosomes while the fish has twenty-five. Moreover, to reach mutation saturation, in practical terms, it was needed to screen at least three thousand inbreed families. This was indeed a titanic project and required commitment and cooperativity to a degree that was exceptional for scientists normally used to work independently on their specific projects.

After working during almost two entire years, the Tübingen team was able to analyze one thousand one hundred and sixty-three fish mutants that displayed a specific phenotype. This vast enterprise was published in an issue of the journal Development in 1996, which was fully devoted to zebrafish. Twenty two out of thirty-seven articles came from the Tübingen screen. I still remember attending a seminar at Harvard Medical School in the 90s, in which there were two speakers, Prof Nüsslein-Volhard and Dr Nancy Hopkins —from Boston. They were sharing their new screening adventures with the scientific community. I was fascinated, not only because it was completely uncommon to see two women scientists as speakers at that time, but because I had never seen before a seminar with two so smart and well experienced co-speakers talking about those kinds of challenges. Theirs resulted in a very fruitful enterprise, not only for them but for all of us. Many labs around the world are using today zebrafish as a model system to study not only vertebrate development, but as patient avatars for cancer biology and precision therapy. And further, they demonstrated that the ***basic mechanisms in the construction of an organism are pretty much conserved among species***. Despite our pretenses, we humans are not so singular in this matter — and probably also not in others. As you may anticipate the impact of this work has been enormous. Now, we use simpler vertebrate organisms to study fundamental questions and from there we can better understand human's health and disease. Again, pioneering studies in basic research leading to a dramatic impact in biomedicine.

After this brief scientific profile, I would like to comment on the role played by Prof Nüsslein-Volhard **as a scientific mentor**. As a glimpse: the Nüsslein-Volhard lab style has always been that postdocs leaving the lab took their projects with them, and sometimes PhD students too. Her "people" may have left Nüsslein-Volhard's lab with some of the most interesting projects that anyone would die to keep for him or herself. This is named generosity. And it is also a bold declaration for the implementation of young scientists as group leaders.

For the Tübingen screen, she built a highly committed team of exceptional scientists to work in a communal project —for the greater good. She inspired experienced scientists and PhD students to work for the collectivity, instead as doing it as independent fellows. In the competitive environment of today's science, this requires to generate confidence among the members of the team, and to build up strong bonds between them and the group leader. Everybody needs to trust each other and the director. This bond is not easy to build. As she stated in an issue of the journal Development in 2012, where she described the Tübingen screen, *People had worked for several years on this communal project without any publication that it had to be ensured that they receive proper credit for their efforts. How to deal with the need of publishing the work of so many people and give justice to everybody? How to prevent a race with the labs in Boston, which had similar goals and approaches?* These questions are still present today in many laboratories. Science can be merciless and if you do not make the right decisions, you risk your work to be forgotten and eventually your career. But coming back to Tübingen, what happened there after the submission of the articles to Development was a wonderful party celebrating the successful end of an immense and unique enterprise. Prof Nüsslein-Volhard has mentored many leading scientists now running their own labs in Europe, United States or Japan. Those mutant fish provided a rich resource for many laboratories and made of Tübingen a landmark for developmental biologists.

We all know that doing science is not such an easy job nowadays. However, her example and advice for young scientists are, in my opinion, extremely valuable: change fields after your PhD, develop your independent profile, be self-critical, and assess your own abilities in comparison with others. Note that all the above relies on yourself.

Finally, I will not end without a brief note on the impact of Prof Nüsslein-Volhard's commitment to **closing the gender gap in science**. As we all know —or at least we should—, women are underrepresented in leading scientific or research positions when measured by their scientific potential. Prof Nüsslein-Volhard, as all pioneering women, worked in an environment where most of her peers were men. She experienced the difficulties of not belonging to the club, but thanks to her determination and intelligence, and the many scientific contributions mentioned above, she succeeded. It was witnessing and experiencing these gender inequalities that, in 2004, prompted her to initiate a foundation that gives support to talented young women scientists who have children, with the aim to increase the contribution of highly qualified women to edge science in Germany. This Foundation —the *Christiane Nüsslein-Volhard Stiftung* for the promotion of science and research— aims to help to prevent the loss of talent, by improving women opportunities in sciences. Her foundation targets specifically the problem of balancing family duties with the strong demand required to develop a career as an independent researcher, and focuses on PhD students and postdoctoral fellows in the fields of experimental natural sciences and medicine.

Prof Nüsslein-Volhard knows well that being a scientist is a very demanding professional decision, which very early on requires a high degree of independence, a great deal of engagement and motivation, as well as talent, originality, and intelligence. In order to gain an independent and permanent position, it is necessary a strong dedication. This may not be possible if family responsibilities are too big, or rely only on women's side. It is therefore not uncommon for a woman to subordinate her career to that of her partner, or to decide against having children. Such a decision is normally not demanded from men —it is usually inconsequential to their career whether they have a family with children or not. Prof Nüsslein-Volhard considered that these were weighty causes for few women in leading positions and for those who are, to more likely remain without children. The objective of the foundation was to provide funds intended to pay for assistance in household tasks and for additional childcare to relieve these young female scientists from household burden and gain time and flexibility for research activities. She was generous enough to start the Foundation with her own funds, that seeded for several institutions to join her initiative. I am happy to say that this foundation has inspired institutions among us, like the Center of Genomic Regulation, CRG, and our own Department of Medicine and Life Sciences, that pioneered in Spain the establishment of this kind of allowances for young female scientists. This path has been later followed by the Barcelona Institute of Science and Technology, BIST, and by the rest of the University Pompeu Fabra. These fellowships help, but clearly do not solve things. In other words, there is still a long road to travel and we ALL need to keep working with multiple actions and policies to help closing the gender gap.

I would like to finish by emphasizing the importance of Prof. Nüsslein-Volhard as one of the intellectual pillars of Developmental Biology, a pioneer scientist who explored and developed new concepts and intellectual frameworks, a leader who promoted long term projects of great value and mentored top scientists. And above all, an extraordinary woman who worked for making science a space for intellectual debate where all of us may stand.

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