5. Scientific understanding of the genetic regulation of vertebrate development and how zebrafish made it possible

So far, I argued that scientific understanding requires explanation and that understanding should be conceived as an ability that is manifested in grasping relations of the phenomenon to be understood and articulating these relations in the form of explanations. While my argumentation has hopefully convinced at least some readers, a central and justified question remains: does my view capture actual cases of understanding in scientific practice? This issue becomes even more pressing in light of the fact that I do not necessarily limit my analysis in the previous two chapters to scientific understanding. Especially in chapter four, I argued that understanding generally should be conceived as an ability. And in chapter three, I addressed several arguments concerning the relation between understanding and explanation without exclusive reference to scientific understanding. Although I do not argue that all kinds of understanding necessarily require explanation, I do claim that scientific understanding does. The basic worry that arises is that, while my arguments might in principle be convincing, they might miss important features or characteristics of scientific understanding and, hence, might not accommodate understanding actually gained by scientists. Even the examples from science that I give in the previous two chapters cannot completely dispel this concern. This is because the function of the examples is to illustrate and substantiate certain philosophical claims, but not to provide important insights into scientific practice. To address the concern that my arguments might not account for understanding that scientists actually achieve in practice or that I might miss important factors or characteristics of understanding, I turn to a concrete and detailed episode from scientific practice in this chapter.

Nowadays it is known that the physiological development of organisms is caused and regulated by genes (amongst other factors). But a genetic understanding of developmental processes is relatively novel and became broadly established only in the 1990s. Understanding developmental and embryological processes as genetically regulated was made possible by the combination of molecular genetics and developmental biology in the late 1960s. Before this rapprochement, scientists working in

these two disciplines were interested in and investigating completely different phenomena and did not cooperate. The vision of a better understanding of physiological and embryological processes as well as of genetic functions could only arise due to the specific circumstances in the '60s. From then on, the realization of that vision took 30 years and it relied crucially on one specific model organism: the zebrafish.

In section 5.1, I will briefly present the history of the research around zebrafish in order to understand the genetic regulation of developmental and embryological processes in vertebrates. In doing so, I rely heavily on Robert Meunier's depiction of the development of zebrafish as a model organism. Whereas Meunier is interested in the sense in which model organisms are models, I am using his case study as a basis to trace how the scientists actually gained the understanding of biological phenomena to which they aspired. While the analysis of the research episode will take place in section 5.2, I highly recommend to all readers to not skip section 5.1. I am aware of the potential worry of some readers that they will not understand everything I describe in section 5.1, especially if they do not have a background in biology, or that it would be a waste of time, as I will refer to the most important information again in section 5.2. Although both may be the case, I nevertheless strongly encourage all readers to read both sections in the given order. Having an idea of what happened in the course of this research episode when, in which order and why will make it more easy to then follow the philosophical analysis in section 5.2, and to understand why I emphasize certain details of the research episode in relation to specific philosophical claims. I argue in section 5.2 that the episode from biological research not only supports my arguments from the previous two chapters, that scientific understanding should be conceived of as an ability and requires explanation, but also reveals characteristic features of scientific understanding. In particular, the episode shows that, in order to scientifically understand a specific phenomenon, scientists need to possess relevant pieces of knowledge, research skills and equipment, as well as being situated in an appropriate research infrastructure that ensures functioning communication among scientists and the distribution of resources. Furthermore, the episode also reveals the iterative nature of the manifestation of scientific understanding. That is, scientific understanding does not manifest in a two-step process, consisting of first grasping relations and then articulating explanation. Rather, these two aspects of the manifestation are interwoven and interdependent.

But before turning to these characteristics of scientific understanding, one might wonder why I chose this particular scientific episode.[1] My main motivation

1 In using the term 'episode' instead of 'case study', I follow Hasok Chang in his attempt to address issues in the field of Integrated History and Philosophy of Science. According to Chang, "it is instructive to try seeing the history-philosophy relation as one between the *concrete* and the *abstract*, instead of one between the particular and the general. Abstract ideas are needed for the understanding of *any* concrete episode, so we could not avoid them even if we only

when I started looking for an episode from scientific practice was to find a candidate that is not from physics. Episodes from physics dominate in the philosophical literature on scientific understanding at least so far. All the extensive case studies I am aware of are from physics, and many other authors focus on physics, too, when they present shorter examples in their philosophical texts. Henk de Regt, Kareem Khalifa, and Finnur Dellsén, whose accounts I present in chapter two, all refer mainly to episodes from physics. While other (and often shorter) examples from different disciplines like biology or climate science occasionally appear in the debate on understanding, my impression is that physics still occupies a special status.

This dominance of physics is problematic. If the topic of philosophical analysis is *scientific* understanding, and this topic is approached mainly on the basis of episodes from *physics*, this procedure might lead to biases concerning the nature or acquisition of understanding in various different scientific disciplines. Relying mainly on episodes from physics might result in views or accounts of scientific understanding that suits understanding gained in physics very well, but that, by closer examination, might not accommodate understanding gained in the various branches of biology, climate science, psychology, or the social sciences and so on. I am not denying that understanding gained in various scientific disciplines might not share some fundamental characteristics. After all, I develop an account of *scientific* understanding, understanding gained in science in general. However, in order to identify the fundamental common characteristics of understanding gained in diverse scientific disciplines, philosophers of science should also pay attention to this diversity. And we have the resources to do this. Sub-fields like philosophy of the life sciences, of climate science, and of the social sciences developed in part because of the recognition of the diversity of different scientific disciplines. Philosophers of science interested in scientific understanding should of course also look at physics, but given the attention to physics in the literature on scientific understanding so far, I prioritize increasing the focus on other scientific disciplines. I contribute to this development with the episode from biology I engage with here.

The second reason why I find this scientific episode about zebrafish particularly interesting is the possibility to directly engage with the phenomenon that shall be understood. I will clarify in the course of section 5.1 what exactly I mean by this. In a nutshell, and in contrast to most other episodes or examples from science found

---

ever had one episode to deal with. […] Any concrete account requires abstract notions in the characterization of the relevant events, characters, circumstances and decisions. If we extract abstract insights from the account of a specific concrete episode that we have produced ourselves, that is not so much a process of *generalization*, as an *articulation* of what we already put into it. To highlight this change of perspective, I prefer to speak of historical "episodes" rather than "cases"." Chang, H. (2012), "Beyond Case-Studies: History as Philosophy." In Schmaltz, T. & Mauskopf, S. (eds.), *Integrating History and Philosophy of Science: Problems and Prospects*, pp. 109–124, Dordrecht, Springer, DOI: 10.1007/978-94-007-1745-9_8, p. 110, original emphasis.

in the philosophical literature on scientific understanding, scientists in the episode about zebrafish actually manipulated *real* instances of the phenomenon they wanted to understand in *real* fish that exhibit this phenomenon. That is, scientists were able to do things that are impossible to do when only theoretical models like mathematical equations or computer simulations are used in research. In such cases, scientists can manipulate the models and make inferences to the phenomena these models represent, but they cannot manipulate the phenomena themselves. This feature of the research on model organisms, the possibility to literally operate on the phenomenon under investigation, really made me interested in how biologists work with zebrafish. So, let us take a look at the episode from science itself and see what happened with and around zebrafish in biology.

5.1 How zebrafish became a model organism: the integration of molecular genetics and developmental biology

In the history of zebrafish as a model organism, Meunier identifies three stages that seem to apply to the development of most model organisms. I adopt this partition for my analysis. Meunier characterizes these stages in the following way:

> 1. The choice and introduction of the organism into research […] and its stabilization in research programmes like neuro-physiology, developmental or cell biology, which are integrative in the sense that they deal with phenomena on many different levels of biological organization and therefore recruit practices from a variety of fields. This stage includes the development of core descriptive and manipulative tools.
>
> 2. The accumulation of large collections of mutant strains and genomic data, and the construction of an infrastructure to maintain and share data and material resources.
>
> 3. The actual use of the model organism to construct models of mechanisms and the generalization of the mechanism by remodelling them in other organisms and constructing abstract mechanism schemata.[2]

2 Meunier, R. (2012), "Stages in the development of a model organism as a platform for mechanistic models in developmental biology: Zebrafish, 1970–2000." *Studies in History and Philosophy of Biological and Biomedical Sciences*, 43, pp. 522–531, DOI: 10.1016/j.shpsc.2011.11.013, p. 523. Over the past decades, a mechanistic explanation paradigm has been established in biology. Biological phenomena are explained in terms of mechanisms that specify, for example, underlying parts of the phenomenon, their organization, or their interaction. The case discussed here is an instance of this paradigm. I accept this paradigm and will not analyze or criticize it. For more information concerning the mechanistic explanation paradigm

5.1.1 Choosing, introducing, and stabilizing zebrafish in research

Meunier discusses all the three stages in more detail. To begin with, it was probably an influential factor that zebrafish had already been introduced as a research organism (but not a model organism) in the 1930s at the latest.[3] This distinction between research and model organism matters, because these two different types of organisms are used to study and understand different phenomena. Rachel Ankeny & Sabina Leonelli present the following differentiation between research or experimental organisms and model organisms:

> In short, although both experimental and model organisms are models in the sense of being representative of a larger class of organisms, they are distinct types of models because of the fundamental difference in the breadth of their representational scope and, most importantly, their intended representational target. Experimental organisms tend to be models for particular phenomena, while *model organisms are models for organisms as wholes*, used not just to explore specific phenomena, but *aimed at developing an integrative understanding of intact organisms* in terms of their genetics, development, and physiology, and in the longer run of evolution and ecology, among other processes.[4]

So, according to Ankeny & Leonelli, the zebrafish was introduced as a model organism because scientists wanted to understand intact organisms. If this were not the

---

in biology, see Machamer, P., Darden, L. & Craver, C. F. (2000), "Thinking about Mechanisms." *Philosophy of Science*, 67 (1), pp. 1–25, DOI: 10.1086/392759; or Bechtel, W. & Abrahamsen, A. (2005), "Explanation: a mechanist alternative." *Studies in History and Philosophy of Biological and Biomedical Sciences*, 36, pp. 421–441, DOI: 10.1016/j.shpsc.2005.03.010; or Darden, L., (2008), "Thinking Again about Biological Mechanisms." *Philosophy of Science*, 75 (5), pp. 958–969, DOI: 10.1086/594538; among others.

3 See Meunier (2012), p. 524. For more information, see Creaser, C. W. (1934), "The technic of handling the zebra fish (Brachydanio rerio) for the production of eggs which are favorable for embryological research and are available at any specified time throughout the year." *Copeia*, 4, pp. 159–161, DOI: 10.2307/1435845. For an overview on the use of zebrafish in science before its establishment as a model organism, see Laale, H. W. (1977), "The biology and use of zebrafish, Brachydanio rerio in fisheries research. A literature review." *Journal of Fish Biology*, 10, pp. 121–173, DOI: 10.1111/j.1095-8649.1977.tb04049.x.

4 Ankeny, R. A., & Leonelli, S. (2011), "What's so special about model organisms?" *Studies in History and Philosophy of Science*, 42 (2), pp. 313–323, DOI: 10.1016/j.shpsa.2010.11.039, p. 319, my emphasis. For more detailed information about the difference between experimental and model organisms see ibid. Although the authors put quite a lot of emphasize on understanding, they do not analyze this concept further. Still, their statement serves as supporting evidence that there is something epistemically interesting and important about the understanding of intact organisms via model organisms and that this subject should be analyzed in more detail.

case, zebrafish would not be appropriately viewed as a model organism. Let's keep this in mind and see what the scientists involved in the research on zebrafish actually wanted to achieve with this organism.

The person said to have initiated the development of zebrafish as a model organism was George Streisinger (1927–1984), a phage geneticist. Together with some colleagues, he was at the heart of phage genetics and involved in the emergence of the new field of molecular biology in the 1960s. Streisinger started to work with zebrafish with the goal to "establish zebrafish as a system that would allow him to relate the knowledge of molecular genetics that he had helped to establish to complex organismic properties."[5] Why did he choose zebrafish, and not some other experimental organism? Looking at the history of different model organisms, a sound list of appropriate features that facilitate the intended research can be identified: small size, short generation time, large amounts of eggs every week throughout the year, rapid development outside of the mother, and robustness to environmental influences, among others. These are instrumental traits, traits that make it easier for scientists to conduct their studies, some of which are shared by zebrafish and other organisms. The crucial feature that makes zebrafish especially suitable for developmental studies is that, during the first stages of development, the embryos and larvae are transparent. For that reason, it is relatively easy to study organogenesis, the phase of embryonic development during which the internal organs of an organism are formed from the three germ layers, with a simple dissection microscope. An additional important factor for Streisinger in choosing zebrafish was that fish seemed to be a good compromise. Since Streisinger wanted to conduct research on vertebrates, he needed a model organism closer to larger vertebrates but that is still small enough and reproduces quickly and in sufficiently large numbers to apply genetic strategies. Zebrafish is gigantic in comparison to, for example, fruit flies, but small for a vertebrate. But why zebrafish, since many fish share the important features of external fertilization and development? What made Streisinger ultimately decide on zebrafish and not another fish species is unknown. Maybe it was just a matter of chance and maybe other fish would have served the purpose just as well. The more important and crucial question is: why did Streisinger move from phage genetics to multicellular organisms in the first place?[6]

---

5 Meunier (2012), p. 524. For more biographical information about Streisinger see Stahl, F. W. (1995), "George Streisinger—December 27, 1927—September 5, 1984." *Biographical Memoirs. National Academy of Sciences (U.S.)*, 68, pp. 353–361; and Endersby, J. (2007), *A guinea pig's history of biology*. London, William Heinemann Ltd, chapter 11. For more details about the history of molecular biology, see Cairns, J., Stent, G. S. & Watson, J. D. (eds.) (1966), *Phage and the origins of molecular biology*. Cold Spring Harbor (NY), Cold Spring Harbor Laboratory Press.

6 See Meunier (2012), p. 524.

The reason for Streisinger's new interest was the view of bacteria and phage geneticists in the 1960s of having arrived at a dead end. No one expected any new groundbreaking findings in the discipline of molecular biology after the structure of DNA and the genetic code had been established. Molecular biology has turned into a normal science in which details are sorted out under a given paradigm.[7] Many bacteria and phage geneticists saw only one option, which Sidney Brenner characterized as "the extension of research to other fields of biology, notably development and the nervous system."[8] Therefore, many molecular biologists, Streisinger among them, started to work on more complex organisms, like mice, *Drosophila* or *C. elegans*, in order to extend the scope of their discipline. There was great optimism among the contemporaries about establishing this new research program of developmental or neuro-genetics.[9] For example, Brenner stated that "in principle, it should be possible to *dissect* the genetic specification of a nervous system in much the same way as was done for biosynthetic pathways in bacteria or for bacteriophage assembly."[10] Seymour Benzer described his vision in even more detail:

> Once assembled, the functioning nervous system embodies a complex of interacting electrical and biochemical events to generate behaviour. The fine structure and interlacing of even the simplest nervous systems are such that to *dissect* them requires a very fine scalpel indeed. *Gene mutation* can provide such a *microsurgical tool*; with it one might hope to analyse the system in a manner *analogous* to the one which has proven so successful in unravelling *biochemical pathways* and control *mechanisms at the molecular level*. [...] Among a collection of such non-phototactic mutants, one might expect to find defects affecting the *various elements of the system*. [...] This search for defects in non-phototactic mutants describes the outline of *a research program to attack the mechanisms underlying behaviour by genetic methods*.[11]

---

7 The situation in late 19th century physics, before the emergence of quantum and relativity theory, was comparable to the situation in molecular genetics in the 1960s. Late 19th century physicists also thought that they knew everything about the physical world that there is to know and that the future task of physicist will be limited to the more detailed specification of natural constants. As things turned out, this expectation was wrong.

8 Brenner, S. (1998), "Letter to Perutz." In Wood, W. B. (ed.), *The nematode Caenorhabditis elegans*, pp. x-xi, Cold Spring Harbor (NY), Cold Spring Harbor Laboratory Press, p. x.

9 See Meunier (2012), pp. 524f. I am adopting the term research program from Meunier as well as from some molecular biologists, but I am not advocating a Lakatosian theory of science. Occasionally, I refer to the new emerging scientific research as a discipline. It does not make a difference for my point about scientific understanding whether the integration of molecular genetics with developmental biology is labelled research program, discipline, or otherwise.

10 Brenner, S. (1974), "The genetics of Caenorhabditis elegans." *Genetics*, 77 (1), pp. 71–94, DOI: 10.1093/genetics/77.1.71, p. 72, my emphasis.

11 Benzer, S. (1968), "Genes and behavior." *Engineering and Science*, 32, pp. 50–52, my emphasis.

Meunier emphasizes that the important methodological metaphors used by the molecular geneticists were 'dissection' and 'surgery', while the metaphors 'pathway', 'circuit' and 'mechanism' designated the phenomena to be investigated by the methodology. These metaphors represent the vision that molecular geneticists had of their new research program. And most importantly, both Brenner and Benzer already pointed towards the goal of dissecting not only molecular mechanisms that underly organismic phenomena, but also processes on a higher physiological level, especially related to the nervous system.[12]

However, the realization of that vision was not as easy as molecular geneticists had hoped. The attempts to apply molecular knowledge to more complex organisms like mice, *C. elegans* or zebrafish were at first disenchanting. The successful establishment of the new research program of developmental and neuro-genetics, together with the establishment of model organisms like zebrafish within this program, was due in the end to an integration of molecular genetics with classical embryology and neuro-physiology. Importantly, embryologists and classical geneticists working on development also broadened their view and started to investigate molecular processes *independently* of molecular geneticists. Already since the 1950s, the term 'developmental biology' was used to refer to "the broadening of interests and the integration of different biological disciplines, in particular genetics, biochemistry, classical experimental embryology and molecular biology."[13] When molecular geneticists became interested in higher organisms, they relied heavily on the traditional practices, questions, and expertise of embryologists and physiologists, since the concepts and orientation of molecular biology had changed. Conventionally, molecular biology was interested in the structural and informational basis of replication and the synthesis of cellular molecules, for which specific practices were required. With the emergence of the new research program of developmental and neuro-genetics, the descriptive level moved from molecules to cells. Cell activities were the new explananda at which research on molecular activity was aiming. Instead of merely asking how DNA replicates, how proteins are synthesized and how they interact in metabolic reactions, molecular geneticists aimed to understand these activities in the context of complex phenotypes. As yet, these chemical activities were only related to phenotypes of bacteria and phages. These phenotypes are often defined as the growth of a bacterial colony under specific

12 See Meunier (2012), p. 525.

13 Fantini, B. (2000), "Molecularizing embryology: Alberto Monroy and the origins of developmental biology in Italy." *The International Journal of Developmental Biology*, 44 (6), pp. 537–553, p. 548. Alfred Kühn, Joseph Needham and Conrad Waddington, or Jean Brachet were among those early developmental biologists who were interested in molecular processes before the fields of molecular genetics and developmental biology merged.

circumstances, and the relation between these phenotypes and chemical activities is relatively straightforward. In the case of multicellular organisms, however, molecular geneticists had to handle phenotypes at many levels of organization, from cellular, tissue and organ properties up to the behavior of the organism as a whole. Molecular geneticists needed the expertise from embryologists and neurophysiologists in order to manage the new phenotypes with which they had not previously been concerned.[14]

The establishment of zebrafish as a model organism is a case of this integration between molecular genetics and developmental biology. Streisinger's lab at the University of Oregon first developed ways to reliably maintain the zebrafish colonies. After this was achieved, the main goal of the lab was to establish tools for the genetic analysis of zebrafish. The first great success was the development of a technique that enabled the scientists to use artificial parthenogenesis to produce homozygous diploid animals. With this technique, clonal strains for later mutational analysis could be generated. These clonal strains were free of lethal mutations. The next tasks were to introduce mutations in the zebrafish strains and to devise mapping strategies for the zebrafish mutations. The main reason for Streisinger to develop all these new techniques was the "dissection of neuronal development by the use of mutant strains."[15] This objective was realized in the mid-80s, in form of γ-ray mutagenesis experiments, which was used to analyze a neuronal necrosis mutant. The results were published in 1988. Importantly, this analysis was a cooperation between Streisinger's lab at the Institute of Molecular Biology and the Institute of Neuroscience, both located at the University of Oregon. Monte Westerfield and Charles Kimmel were the members from the Institute of Neuroscience who participated in the γ-ray mutagenesis experiment together with the molecular geneticists. Notably, Kimmel has been trained as a developmental biologist. The molecular geneticists working in Streisinger's team did not reach their goal of the dissection of neuronal development on their own.[16] Meunier very nicely summarizes the integrative character of this research endeavor:

> Whereas Streisinger's lab brought in the expertise needed for the generation and genetic characterization of the mutation (segregation analysis, karyotype analysis), the description of the phenotypic effects of the mutation was based on

14 See Meunier (2012), p. 525.

15 Streisinger, G., Walker, C., Dower, N., Knauber, D. & Singer, F. (1981), "Production of clones of homozygous diploid zebra fish (Brachydanio rerio)." *Nature*, 291 (5813), pp. 293–296, DOI: 10.1038/291293a0, p. 293.

16 See Meunier (2012), pp. 525f. For more details concerning this series of experiments, see Grunwald, D. J., Kimmel, C. B., Westerfield, M., Walker, C. & Streisinger, G. (1988), "A neural degeneration mutation that spares primary neurons in the zebrafish." *Developmental Biology*, 126 (1), pp. 115–128, DOI: 10.1016/0012-1606(88)90245-x.

> the knowledge that Westerfield and especially Kimmel had accumulated over the preceding 15 years. They provided the descriptive knowledge and methods to behaviourally and physiologically characterize the specific effect of the mutation (fixing the embryos, measuring neuromuscular activity, staining sections, conducting behavioural response tests). The articulation of the main result — that the mutation selectively affected the central nervous system by causing necrosis in most cells, but sparing a particular class of neurons, namely primary neurons — required detailed knowledge of the neuro-anatomy of the fish, which Kimmel and Westerfield did […] posses.[17]

Molecular geneticists, who moved to multicellular organisms, needed the knowledge and practices from classical embryology and physiology, as without the descriptive work and knowledge provided by these disciplines, mutation-based studies would not have been possible. The reason is that descriptive devices like cellular fate maps, neural wiring diagrams or staging series[18] define the normal or wild-type organism, which refers to a non-manipulated member of the strain from which the manipulated members are also derived. Thus, the wild-type is a standardized strain. Without these sources, scientists would not have a contrastive foil that makes the mutation actually visible through comparison. Kimmel and his colleagues provided a first fate map for zebrafish in 1990 and published a staging series for zebrafish in 1995.[19] However, not only did the molecular geneticists rely on the descriptive practice of embryologists and physiologists in order to study the function of genes, but also embryologists and physiologists took on the methodology of mutational analysis in their research. For example, Kimmel and Westerfield continued to use mutational analysis after the publication of the neural degeneration mutant in 1988. Mutational analysis enabled explanations in terms of molecular genetics, which opened up new ways of research and were helpful in identifying structures, processes and functions on higher levels of organization. Among other things, the analysis of differential effects of a mutation made a more fine-grained classification of cell types

17 Meunier (2012), p. 526.

18 Cellular fate maps are representations that trace the history of each cell in development, neural wiring diagrams are descriptions of a nervous system and staging series define steps in the continuous process of development in embryos. For more details concerning descriptive models and descriptive devices in biological research, see Ankeny, R. A. (2000), "Fashioning descriptive models in biology: of worms and wiring diagrams." *Philosophy of Science*, 67, pp. 260–272, DOI: 10.1086/392824.

19 See Kimmel, C. B., Warga, R. M. & Schilling, T. F. (1990), "Origin and organization of the zebrafish fate map." *Development*, 108 (4), pp. 581–594, DOI: 10.1242/dev.108.4.581; and Kimmel, C. B., Ballard, W. W., Kimmel, S. R., Ullmann, B. & Schilling, T. F. (1995), "Stages of embryonic development of the zebrafish." *Developmental Dynamics: An Official Publication of the American Association of Anatomists*, 203 (3), pp. 253–310, DOI: 10.1002/aja.1002030302.

possible. Furthermore, mutation based analysis have become mainstream in developmental biology after the successful molecularization of *Drosophila* and *C. elegans* embryology. Therefore, it was probably easier to publish mutation-based studies than classical physiological studies by the 1990s.

At this point, the first stage of the development of zebrafish as a model organism, the choice and introduction of the organism into research and its stabilization in research programs was completed. Zebrafish was a model system for mutational analysis of development and physiological processes. For the next stage, the accumulation of more data, the material resources and the necessary infrastructure to maintain data and resources had to be developed.[20]

5.1.2 Building and establishing a research infrastructure

This happened in the mid-1990s through two coordinated large-scale mutagenesis screens, called *The Big Screen* in the zebrafish community. However, *The Big Screen* required some more preparative work. At the core of the integration of molecular genetics with embryology, right from the start, was the technique of mutational dissection. Mutational dissection enabled scientists to identify single genes that participate in the development of certain traits and the molecular characterization of these genes. Yet mutational dissection was crucially limited in the sense that scientists aimed at molecular explanations of development that include *interactions* between molecules that result in certain cellular behavior. These explanations only became available in late 1970s and Christiane Nüsslein-Volhard and Eric Wieschaus made a huge contribution to this breakthrough. They conducted a systematic search for mutations that affect embryonic patterning in *Drosophila* by a large-scale screen for mutants. Nüsslein-Volhard and Wieschaus selected only those mutants that showed an effect in embryonic patterning in order to detect the relevant genes for that process. Both researchers did not rely on any preceding ideas about which genes might be involved or how they influence embryonic patterning. This is called a saturation screen for specific phenomena, embryonic patterning in this case, and resulted in collections of different mutant strains. The identification of genes that affect the phenomenon when mutated enabled the scientists to hypothesize interactions among genes and molecular level explanations.[21] The hypothesized interactions with regard to regulatory pathways and mechanistic explanations on a molecular level were investigated in subsequent studies by using different collec-

20 See Meunier (2012), p. 526.

21 For more information concerning the experiments conducted by Nüsslein-Volhard and Wieschaus, see Nüsslein-Volhard, C. & Wieschaus, E. (1980), "Mutations affecting segment number and polarity in Drosophila." *Nature*, 287 (5785), pp. 795–801, DOI: 10.1038/287795a0.

tions of mutant strains.[22] The first project from Nüsslein-Volhard and Wieschaus achieved explanation in terms of molecular regulatory mechanisms at a depth that had not previously been achieved.[23]

Why was this study on *Drosophila* conducted by Nüsslein-Volhard and Wieschaus important for the research on zebrafish and how was it connected to *The Big Screen*? By the early 1990s, the required genetic and descriptive tools for the envisioned research had been implemented, but only a small number of zebrafish mutants was available. It was Nüsslein-Volhard who had the idea that a project very similar to the *Drosophila* screens could be used to obtain more zebrafish mutants when she read Streisinger's 1981 paper. Nüsslein-Volhard subsequently started to develop the infrastructure for a large-scale mutagenesis screen in zebrafish at the beginning of the 1990s. This included, among other things, the construction of new aquaria systems. Nüsslein-Volhard and her colleagues invested an extensive amount of creativity in this research infrastructure and published their results of a first pilot screen together with the specifications of the screen in 1994.[24] Thereby, *The Big Screen* was initiated in Tübingen in 1993 under the supervision of Nüsslein-Volhard. A very similar project was launched at the Massachusetts General Hospital in Boston under the direction of Wolfgang Driever, a former student of Nüsslein-Volhard who had worked with her on *Drosophila*. These two coordinated large-scale mutagenesis screens in Tübingen and Boston are the research projects labelled *The Big Screen*.[25]

In order to detect mutants, scientists involved in *The Big Screen* first observed standard anatomical features of the fish under a dissection microscope. The standard anatomical features were defined with a descriptive device, a check list that showed a simple anatomic map of zebrafish. The observed anatomical features of mutants were compared to wild-type animals that were raised under the exact same conditions as the mutants. Various stains were used in the subsequent steps to determine more fine-grained differences among similar phenotypes. The guiding heuristic assumption was that genes, which produce related phenotypes when mutated, might react with each other under normal conditions. Therefore, mutations with similar phenotypes or those with an effect on the same structures were grouped together, resulting in a large number of zebrafish mutant strains. The results from both screens were published together in 1996.[26] The crucial im-

22 For more information about follow up studies, see Driever, W. & Nüsslein-Volhard, C. (1989), "The bicoid protein is a positive regulator of hunchback transcription in the early Drosophila embryo." *Nature*, 337 (6203), pp. 138–143, DOI: 10.1038/337138a0.

23 See Meunier (2012), p. 527.

24 For more details, see Mullins, M. C., Hammerschmidt, M., Haffter, P. & Nüsslein-Volhard, C. (1994), "Large-scale mutagenesis in the zebrafish: in search of genes controlling development in a vertebrate." *Current Biology*, 4 (3), pp. 189–202, DOI: 10.1016/s0960-9822(00)00048-8.

25 See Meunier (2012), p. 527.

26 See ibid. p. 527.

portance of the availability of the mutant strains was expressed, among others, by Philip Ingham, who said that "the identification of so many mutations affecting zebrafish embryogenesis represents a quantum leap in our capacity to unravel the mechanisms underlying vertebrate development."[27] From then on, scientists could simply choose those mutations that affect the developmental process of interest. As a result, many postdocs who worked on the two mutagenesis screen projects took a set of related mutations and founded new labs, where they used the zebrafish mutants to investigate the mechanisms in which certain genes interact.[28] Hence, by the late 1990s the second stage in the development of zebrafish as a model organism, the accumulation of large collections of mutant strains and the construction of a research infrastructure, had been completed.

5.1.3 Using zebrafish as a model organism

In the third and final stage, the model organism was used, finally, to construct models of mechanisms. This was possible only because the manipulative and descriptive tools had been developed at the first stage, and the large-scale mutagenesis screens had been performed at the second stage to identify and provide different mutant strains. To show how the third step was realized, Meunier presents the research on one of the mutants that was identified in the screen, *one-eyed pinhead* (*oep*).[29]

The research groups in Tübingen and Boston identified different alleles of the *oep* gene. Like most other mutants, the *oep* mutant was assigned to more than one class of mutant phenotypes due to the different processes or structures affected by *oep* at different stages in development. The next success following the identification of *oep* was achieved by the Driever's group in Boston. They could, on the one hand, specify how *oep* affects the formation of the three primary germ layers during gastrulation, a process taking place in the early embryogenesis. On the other hand, by creating a double mutant, they showed a genetic interaction between *oep* and the *no tail* (*ntl*)

27 Ingham, P. W. (1997), "Zebrafish genetics and its implications for understanding vertebrate development." *Human Molecular Genetics*, 6 (10), pp. 1755–1760, DOI: 10.1093/hmg/6.10.1755, p. 1759.

28 See Meunier (2012), p. 527.

29 Following the convention in the field, gene symbols are lower case and italicized, while protein symbols are the same as the corresponding gene symbols, but the first letter is uppercase and the protein symbols are non-italic, see (https://wiki.zfin.org/display/general/ZFIN+Zebrafish+Nomenclature+ConventionsZFINZebrafishNomenclatureConventions-2; last accessed April 12th, 2022).

gene.[30] Then, other researchers in New York achieved the molecular isolation of *oep* using positional cloning.[31] That was the first time that a Zebrafish gene was cloned by this approach.[32]

The cloned *oep* mutant embryos were lacking Oep activity, which leads to defective germ layer formation, organizer development, and positioning of the anterior-posterior axis that results in a cyclopic phenotype without endoderm, prechordal plate, and ventral neuroectoderm.[33] Meunier describes the importance of the molecular isolation of *oep* as follows:

> This allowed comparing the sequence of the Oep protein to other known proteins, which suggested that it had a signalling and a membrane binding sequence. At the same time it allowed applying many molecular strategies, like injection of the mRNA for rescue or overexpression, or fusion mRNA's coding for markers, detectable by immunostaining or otherwise, as well as *in situ* hybridization to observe expression patterns. These techniques were immediately used to localize the protein on the cellular level and the expression of the gene in the embryo.[34]

In the course of subsequent research, it was discovered that Oep is an essential component of the Nodal signaling pathway. The signaling molecule Nodal plays an important role in early embryonic patterning and has been discovered for the first time in mice. In zebrafish, two orthologs[35] of *nodal*, *cyclops (cyc)* and *squint (sqt)*, were found. The products of *cyc* and *sqt* are collectively called Nodal signal. The crucial observation in these experiments was that the phenotype of the double mutant for the *cyc* and *sqt* genes and the *oep* mutant phenotype are very similar. This observed similarity, together with the fact that embryonic processes associated with Nodal signaling are affected by the *oep* mutation, and with the knowledge that Oep is membrane-associated while acting cell-autonomously[36], resulted in the hypothesis

30 For more information, see Schier, A. F., Neuhauss, S. C., Helde, K. A., Talbot, W. S. & Driever, W. (1997), "The one-eyed pinhead gene functions in mesoderm and endoderm formation in zebrafish and interacts with no tail." *Development*, 124 (2), pp. 327–342, DOI: 10.1242/dev.124.2.327.

31 For more detailed information, see Zhang, J., Talbot, W. S. & Schier, A. F. (1998), "Positional cloning identifies zebrafish one-eyed pinhead as a permissive EGF-related ligand required during gastrulation." *Cell*, 92 (2), pp. 241–251, DOI: 10.1016/S0092-8674(00)80918-6.

32 See Meunier (2012), p. 528.

33 See Gritsman, K., Zhang, J., Cheng, S., Heckscher, E., Talbot, W. S. & Schier, A. F. (1999), "The EGF-CFC protein one-eyed pinhead is essential for nodal signaling." *Cell*, 97 (1), pp. 121–132, DOI: 10.1016/s0092-8674(00)80720-5, p. 121.

34 Meunier (2012), p. 528.

35 Genes in different species, which originated from a single gene from the last common ancestor of these species by vertical descent, are termed orthologs or orthologous genes.

36 This knowledge had been established by other studies, see for example Schier et al. (1997).

that "Oep is required for cells to receive Nodal signals."[37] In order to arrive at this hypothesis, it was necessary to carefully compare and relate different mutants from the large collection available. However, to understand how exactly Oep affects Nodal signaling, the scientists wanted to figure out whether Oep is necessary for Nodal signaling, or whether it merely has an amplifying function, and where exactly it is located in the biochemical pathway. Two experiments were performed to obtain insights about this process.[38]

First, to test whether Oep is necessary or merely an amplifier for Nodal signaling, an overexpression of the Nodal signal was induced through the injection of *cyc* and *sqt* mRNA. If Oep is an amplifier, this overexpression would lead to development of the *oep* mutant such that its phenotype would be closer to the wild type, or even lead to dorsalization.[39] In other words, the idea was that the injected *cyc* and *sqt* mRNAs would replace the function of *oep*, which is absent in the *oep* mutants, and, therefore, the defects in the *oep* mutant embryos due to the absence of *oep* would be corrected and normal, wild-type phenotypes would develop. However, no effect was observed in *oep* mutants, which led to the conclusion that, during embryogenesis, Oep is indeed essential for Nodal signaling and not merely an amplifier. Sqt/Cyc do not replace the function of Oep. For the second experiment, the scientists already had evidence for the transmission of Nodal signaling in the cell by a pathway that involves the ActRIB receptor and the Smad2 transcription factor. The goal was to determine whether this evidence was correct, whether Oep is indeed essential for the response to these two factors. Therefore, mRNAs of the genes that code for these factors (already activated versions of ActRIB and Smad2) were injected in *oep* mutants. The activation of this pathway by Oep was simulated by the injection of the activated factors. In this case, the mutant phenotypes became more similar to the wild type. The hypothesis that Nodal signals are transmitted by this pathway was confirmed and the experiment showed that Oep acts upstream of these components. Hence, "Oep [is identified] as a novel and specific component of the Nodal signalling pathway"[40] and Oep was localized as an extracellular co-factor, which is necessary for the Nodal signal to activate the downstream elements in the pathway. In follow-up studies that used further mutants and reagents, further elements of the pathway

37 Gritsman et al. (1999), p. 125.

38 See Meunier (2012), p. 529. The whole study consisted of more experiments, which are all presented in Gritsman et. al. (1999). However, the two experiments presented here were the most crucial ones.

39 Dorsalization refers to the formation of dorsal cell types, one class of primary sensory neurons in the lamprey spinal cord, and the organization of tissues along the dorsoventral (from back to belly) axis.

40 Gritsman et. al. (1999), p. 128.

were added.[41] However, to achieve the bigger goal of explaining organizer function in early embryonic patterning, the investigation on the Nodal signaling pathway was only one step. To relate such pathways to cellular phenotypes and to explain broader developmental or physiological processes on that basis, the same material models, i.e. the same sets of mutants and reagents, could be used in varying combinations with other components, like appropriate cameras, for the respective level of biological organization.[42]

Importantly, in the two experiments on the *oep* mutants situations were observed in which an abnormal phenotype is a result of the absence (loss of function) of the respective genes. On the basis of that observation, scientists established a causal relation between a gene and an aspect of the normal phenotype. But the aim of the experiments was to establish causal relations not between genes and partial phenotypes, but instead among genes. The identified causal relations between genes and phenotypes have an instrumental purpose, because the causal relations among genes can be inferred from the causal relations between genes and phenotypes.[43] For instance, Meunier reconstructs the inference made in the second experiment on *oep* mentioned above:

> "Oep, and everything that comes downstream in the causal chain, cause an aspect of the phenotype (in the precise sense that the absence of Oep and therefore of the activity of downstream elements results in an aberration). Whatever is downstream of Oep in the causal chain is not active if Oep is absent. If the normal phenotype is present if ActRIB and Smad2 are present (enforced, independently of Oep), in the absence of Oep, then they should act downstream of Oep in the causal pathway."[44]

The causal relations between genes and partial phenotypes provide the basis for abductive inferences about the causal interactions among proteins produced by certain genes. These interactions are the regulatory events that allow for cell differentiation. Achieving the goal of identifying and establishing causal relations among genes, therefore, requires counterfactual reasoning, abductive inference and the paradigm

41 For more information, see Bisgrove, B. W., Essner, J. J. & Yost, H. J. (1999), "Regulation of midline development by antagonism of lefty and nodal signaling." *Development*, 126 (14), pp. 3253–3262, DOI: 10.1242/dev.126.14.3253.

42 See Meunier (2012), p. 529. Such a study that involved *oep* mutants and other components of the zebrafish Nodal signaling model has been conducted, for example, by de Campos-Baptista, M. I., Holtzman, N. G., Yelon, D. & Schier, A. F. (2008), "Nodal signaling promotes the speed and directional movement of cardiomyocytes in zebrafish." *Developmental Dynamics: An Official Publication of the American Association of Anatomists*, 237 (12), pp. 3624–3633, DOI: 10.1002/dvdy.21777.

43 See Meunier (2012), p. 529.

44 Ibid. p. 529.

of differential gene expression.[45] In case of the *oep* mutant, a model of the Nodal signaling was successfully constructed. With that, the third and final stage of the development of zebrafish as a model organism was reached. If, in a next step, the knowledge gained by these experiments is to be generalized, such material models of mechanisms have to be instantiated in other species, which will require analogical reasoning. When the mechanism is successfully instantiated in different material models, it still demands inductive inference to arrive at a generalization of the respective molecular mechanism.[46]

5.1.4 Explaining physiological phenomena through molecular regulation

Let me summarize this episode from scientific research as it is presented by Meunier. Around 1970 a new research program developed as a combination of developmental biology and molecular genetics with the aim of constructing, through mutational dissection of molecular pathways, models of the genetic regulation of processes in the development, physiology, and behavior of multicellular organisms. Zebrafish was introduced as a new model organism that served this purpose, as illustrated by the example of *oep* mutants to model the Nodal signaling pathway. The new research program included genetic and physiological techniques and the skills to employ them, descriptive devices and nomenclature, collections of mutant strains and sequence data, and the infrastructure to share these resources. In order to determine causal relations among genes, a whole arrangement of mutants, mRNAs and other reagents, and instruments such as microscopes was necessary. The vision of Benzer, Brenner and Streisinger to achieve explanations of physiological phenomena in terms of molecular regulation gained by mutational analysis was fulfilled. The new research community developed manipulative and descriptive tools, generated mutants in various mutagenesis experiments and shared these mutants as well as the available information.[47] Meunier himself concludes:

> Material models of mechanisms are different from the mechanisms themselves [that] occur in the fish, in that the former consist of various objects, animals and

45 This paradigm "implies that gene expression is regulated through gene activity in complex regulatory loops." Ibid. p. 523.

46 See ibid. p. 529. Remember that this is the claim Meunier argues for in his paper. He uses the case study of the development of zebrafish as a model organism to argue that organisms are model organisms in virtue of their use in the construction of models of particular mechanisms, and not in virtue of being models for a higher class of organisms. Again, since my analysis focuses on what scientific understanding is and how it is achieved, I am leaving the question in which sense organisms are model organisms aside and will not discuss Meunier's argument.

47 See ibid. pp. 529f.

> others, that by virtue of their combination and arrangement, carve out the mechanism from the whole of causal interactions taking place in a fish and thus represent them. *But, in contrast to other material models, like plastic ball and stick models of molecules for instance, the fact that these models are built using the organisms that actually exhibit the mechanisms modelled enables researchers to literally operate the mechanism in order to manipulate the developmental process and thereby understand it better.* […] In this way they generate knowledge about the entities that make up the mechanism (e.g. their activities, their position relative to each other, quantitative characteristics etc.). New entities or activities involved in the mechanism can be added to the model by adding new mutant strains or reagents. *A generative material model as it is described here thus establishes new knowledge through stepwise combination of interventions in the system modelled.* In describing the mechanism as represented in the material model, theoretical models are constructed through text or diagrams.[48]

This quote clarifies two characteristics of model organisms that I mentioned at the beginning of this chapter. First, I claimed that model organisms enable scientists to directly engage with the phenomenon that shall be understood. Scientists do that through manipulating genetic mechanisms that underling embryonic development of real vertebrates. Furthermore, at the beginning of section 5.1.1, I referred to a characterization of model organism proposed by Ankeny & Leonelli. According to them, model organisms are not models for particular phenomena, but rather for organisms as wholes that serve the aim of gaining an integrative understanding of intact organisms. This is exactly what zebrafish was used for in the case of the research on *oep*. Ultimately, biologists were not interested in particular phenomena, such as the effects that the injection of certain mRNA has on some mutant. Instead, researchers wanted to understand the regulatory genetic mechanism underlying developmental, physiological, and behavioral processes *in normal organisms*. They aimed precisely at the integrative understanding of intact organisms that Ankeny & Leonelli demand for model organisms in contrast to experimental organisms. Hence, Meunier's characterization of model organism is in line with the view of Ankeny & Leonelli and it is plausible to regard zebrafish as a new model organism, and not merely an experimental organism.

So much for the historical part. Again, the research question Meunier wants to answer with this episode from scientific practice concerns how model organisms are models or, to put it differently, what 'model' in the term 'model organism' means. While I do not further discuss the concept of model organisms, I use this episode to address a different question: how did the biologists involved in the establishment of the new research program around zebrafish understand the phenomena they wanted to understand and explain? I answer this question in the next section.

48 Ibid. p. 530, my emphasis.

5.2 How is this a case of scientific understanding?

What can this episode from scientific research reveal about scientific understanding and the way scientists achieve it? My analysis of the episode around zebrafish serves two goals. First, it serves to examine whether my claims from the two previous chapters, that understanding requires explanation and that understanding is an ability that manifests in the process of grasping relations of a phenomenon and articulating these relations in the form of explanations, are supported or rebutted by the episode from biology. Second, the episode helps to identify characteristics of understanding achieved in science by scientists *qua* scientists that did not become apparent in the preceding chapters, since they did not address scientific understanding specifically. Let's look at the three stages of the establishment of zebrafish as a model organism that Meunier distinguishes and their respective contribution to the possibility of scientific understanding of the genetic regulation of vertebrate development.

5.2.1 Gaining necessary knowledge, research skills and tools

The empirical phenomenon that scientists wanted to understand in this case is the genetic regulation of embryonic development of complex organisms like vertebrates. Molecular biologists viewed this phenomenon as a developmental mechanism. The relations that are grasped in this case are causal relations. The genetic activities that take place within a cell cause the development of a specific phenotype of a differentiated cell, and various cell behaviors cause physiological phenotypes.[49] In order to grasp, that is, to get epistemic access to, the causal relations involved in the developmental mechanism, scientists first needed to have the knowledge and skills required for this phenomenon. Recall that I do not see a conceptual difference between the terms 'ability' and 'skill', only a terminological one. However, for the sake of clarity, I will use the term 'ability' to refer to understanding, and the term 'skill' when I refer to any other type of knowing-how that is involved in or serves the goal of understanding.

The availability of the necessary knowledge and skills was only possible because of the integration of molecular genetics with classical embryology and neurophysiology. Molecular geneticists in the 1960s, like Streisinger, Benzer and Brenner, wanted to understand the development of complex organisms, but they were not able to achieve this understanding with the knowledge and skills from their

49 I stay agnostic at this point whether the relations in this case should be seen as causal, mechanistic, or functional relations, since this differentiation does not affect the acquisition of scientific understanding, which requires the grasp of any type of relation. For the sake of convenience, I follow Meunier in taking the grasped relations in this case of scientific research to be causal.

field alone. Molecular geneticists needed the knowledge from embryologists and neurophysiologists as well as the skills to apply research techniques from these disciplines. On the other hand, embryologists and neurophysiologists also had the goal of understanding molecular processes underlying development, yet were similarly not in a position to achieve this goal merely with their own knowledge and skills. Knowledge and skills from both disciplines had to be merged.

This process can be seen clearly in the research conducted during the 1980s by Streisinger's lab. Streisinger's knowledge and skills, which he acquired through his work on phage, were sufficient to find ways of reliably maintaining the zebrafish colonies and establishing techniques for their genetic analysis. He was able to produce homozygous diploid animals through artificial parthenogenesis and to generate clonal strains free of lethal mutations, which could be used for later mutational analysis. In short, the knowledge and skills from his discipline enabled Streisinger to handle a new organism within the boundaries of his discipline. However, Streisinger and his colleagues were not able to make sense of the effects of the mutations they were able to induce and map in zebrafish, since they had never dealt with multicellular organisms before. They could not grasp any phenotypic effects caused by mutation. The molecular geneticists were restricted to the generation and genetic characterization of the mutation, but they could not identify and describe any phenotypic effects. Since the embryos and larvae of zebrafish are transparent, the visual access to the phenotypic effects of a mutation facilitates grasping of the causal relations underlying development. However, while the geneticists literally saw the developmental processes within the transparent embryos, they did not "see" the effects of the induced mutation, as they did not know how normal, non-mutated zebrafish embryos develop and look. Hence, they did not and could not grasp any significant or relevant effect of the mutation during early embryogenesis. And even if the molecular geneticists learned and then knew what the normal embryo looks like from textbooks, the mutant embryo would have to be observed or maybe even dissected carefully to detect the phenotypic differences. These skills, identifying and characterizing phenotypic effects and noticing significant differences through observation or dissection, needed to be learned and trained by molecular geneticists to understand genetic functions on more complex levels of biological organization.

At this point, the knowledge and skills from embryologists and neurophysiologists entered the scene. They were able to behaviorally and physiologically describe the effects of a mutation through, for example, the fixation of embryos, measurements of neuro-muscular activities, staining sections or the execution of behavioral response tests. Without the descriptive knowledge and usage of the descriptive devices like cellular fate maps, neural wiring diagrams or staging series, the phenotypic effects of mutations could not be recognized. In other words, while the molecular geneticists were able to induce and map genetic mutations but were not able to relate this knowledge to any phenotypic effects, embryologists and neurophysi-

ologists could identify phenotypic effects, but had no idea how genetic regulation is related to these effects or what is happening at the genetic level at all. Because of the lack of specific knowledge and skills on both sides, all the scientists involved in this new research endeavor, molecular geneticists as well as embryologists and neurophysiologists, could not grasp the relations involved in the phenomenon that they all wanted to understand. Only through the integration and combined use of the knowledge and skills from both biological disciplines were the scientists able to grasp a relation between a specific mutation and its phenotypic effect in the development of an embryo. By using mutational analysis, the scientists could determine which genetic mutation is present in a mutant, and with the skillful use of descriptive devices from embryology and neurophysiology they could literally see the phenotypic effects, and hence could grasp a relation between a mutation and a phenotypic effect. The specificities of the grasped relation, its components and structures, can be investigated by using further knowledge and skills and articulating the insights gained in the form of a new explanation. After grasping a relation between a mutation and a phenotypic effect, this relation can only be articulated if the knowledge necessary to make sense of the grasped relation is available. In the case of the neuronal necrosis mutant, the biologists could explain that the *ned-1* gene, at which the mutation was targeted, is essential to some, but not all cells of the central nervous system, because some neurons develop normally despite the mutation.[50] In order to articulate this explanation, scientists had to have the skills and tools to conduct the experiments and the necessary knowledge from genetics and neurophysiology to identify significant effects, grasp the relation between the *ned-1* gene and different groups of cells, and combine the relevant pieces of knowledge in such a way that the experimental results make sense. That is, Streisinger, Kimmel and their colleagues scientifically (and partially) understood the function of the *ned-1* gene in the early embryonic development of zebrafish.

The successful integration of knowledge and skills from both disciplines is illustrated not only in the study on neuronal necrosis mutants that Streisinger together with Kimmel and others published in 1988, but also in the adoption of mutational analysis, a technique from molecular genetics, by embryologists and physiologists. From the late 1980s on, mutational analysis became a mainstream tool in developmental biology and mutation-based studies were much more popular than classical physiological studies. This trend shows that molecular geneticists and developmental biologists actually acquired knowledge and skills from each other. In the study on the neural degeneration mutant, the developmental biologists like Kimmel acquired knowledge and skills from molecular geneticists like Streisinger, and the other way around. Their research was not a two-step study where first the molecular geneticists did their thing, and in the second step the developmental biologists did theirs,

50 See Grunwald et al. (1988).

respectively. Instead, it was an instance of a real integration of two research disciplines, together with the knowledge and skills, that was necessary in order to gain understanding of the phenomenon that everyone was interested in, the genetic regulation of embryonic development of complex organisms. This was the situation at the end the first phase of the development of zebrafish as a model organism.

What did the first phase reveal about the characteristics of scientific understanding? It showed that specific knowledge, skills, and tools were required to understand the phenomenon in question. Without the relevant knowledge from genetics and neurophysiology, the skills to conduct experiments in such a way that they allow access to the phenomenon of interest, and the tools needed for this, the respective phenomenon could not be understood. As long as the biologists lacked the required knowledge, skills and tools to conduct the research in the appropriate way, they could neither grasp any relations involved nor articulate any explanation about aspects of the phenomenon. Since the skills that scientists need to understand phenomena in a scientific way are skills to conduct scientific research, I label these skills *research skills* from now on.[51] The acquisition of research skills is closely linked to the availability of specific tools to conduct research. I am using the term "tool" in a loose sense: any material or theoretical object that can facilitate research is a tool. Examples of tools include mathematical equations, software, dissection microscopes, or cellular fate maps. If you cannot use the fate map for *C. elegans*, you also will not be able to use a fate map for zebrafish. It is the acquisition of certain research skills that enables the use of certain objects as tools in the context of research. Once you acquire the skills to read and use a fate map for *C. elegans*, you will (probably) be able to use a fate map for zebrafish.

So, in order to understand phenomena scientifically, that is, through the scientific method, scientists first need to acquire the relevant knowledge, necessary research skills, and required tools to conduct research in a way that is appropriate to understand the phenomenon in question. It is important to explicitly take these resources into account in any analysis of understanding gained in specific episodes, as the presence or absence of any of these resources might explain why phenomena were understood in some cases, but not in others. However, this is not enough to achieve the aspired comprehensive understanding of the genetic regulation of vertebrate development. The second phase of the development of zebrafish as model organism was crucial as well.

---

51 The importance of specific skills for the acquisition of understanding in science has already been recognized by, for example, Sabina Leonelli and Henk de Regt. See Leonelli, S. (2009), "Understanding in Biology: The Impure Nature of Biological Knowledge." In de Regt, H. W., Leonelli, S. & Eigner, K. (eds.), *Understanding: Philosophical Perspectives*, pp. 189–209, Pittsburgh, University of Pittsburgh Press; and de Regt, H. W. (2017). While this insight is therefore not novel, the episode around zebrafish provides additional support for it.

5.2.2 Generating the required material equipment and developing a research infrastructure

In addition to establishing the necessary knowledge, descriptive and manipulative tools, and the research skills to use them, the infrastructure to generate and maintain these resources, data and results of studies was set up during the second phase. This happened for two reasons.

First, following the successful integration of both disciplines in the first phase, biologists joining this research program should be equipped with the necessary knowledge and research skills to conduct successful research in the new field. Without access to the newly established combination of knowledge and research skills, new researchers in the field would not have had the chance to gain understanding of the genetic regulation of vertebrate development. Any biologist who wanted to join the new research program around zebrafish needed to have the knowledge and the research skills from molecular genetics as well as embryology and neurophysiology. Otherwise, she would have the same problem that Streisinger in the first phase was facing, before Kimmel and Westerfield joined the research project. Moreover, in order to learn the required knowledge and train the necessary research skills, scientists needed supervisors or peers who could teach them, who already possessed the knowledge and research skills from both biological disciplines. It would not have helped scientists who wanted to join the new research program if they had been trained by "pure" molecular biologists or embryologists, as they could not teach all the knowledge and research skills required for this specific research. That is, in order to do successful research on and understand the genetic regulation of vertebrates, scientists needed to build up a new research community, later called developmental genetics, in which the required expertise is maintained and can be shared with new colleagues.

Yet there was a second and not less important reason for establishing a new research infrastructure. While the ultimate goal was to understand the genetic regulation of vertebrate development in general, individual studies focused only on specific genes, their interaction and the resulting phenotypes, like the study from Streisinger and Kimmel on the function of the *ned-1* gene for the development of the nervous system. This limitation of individual studies is due to the complexity of the phenomenon being studied. Different mutations affect various structures or processes at different stages during the development, and these various genetic activities cannot be studied in only a few experimental studies. In other words, if biologists really wanted to understand the genetic regulation of vertebrate development in general, they would have to study the effect of every gene at any stage during embryonic development on any structure of the embryo. Not only would this research require a lot of time and resources, but it could not be conducted at all after the first phase of the introduction of zebrafish. The reason was that no one knew which genes

are involved in developmental processes. Before one could study which effects a gene has on developmental processes, it would have been helpful to know which genes are involved in developmental processes at all. Some genes might not be involved in developmental processes; given the complexity of the envisioned research, some narrowing would have been helpful.

The Big Screen provided this guidance. By randomly inducing some mutations and only looking at the phenotypic effects, genes that participate in developmental processes could be identified. That is, biologists first randomly generated many different mutants and grouped them together according to similar or almost identical phenotypic traits. Only after the grouping did the biologists analyze the mutation that took place in the respective mutants. Through this method, it was possible to identify many mutations that somehow affect zebrafish embryogenesis. Now that researchers knew which genes are involved in developmental processes and had the mutant strains with identified mutations, they could start to study the actual function of the respective genes. Thus, the necessary infrastructure of the zebrafish community was established. Several new labs were founded that focused on specific mutant strains and associated developmental processes. Individual researchers conducting these specific experiments achieved understanding of the mechanisms investigated and shared their data and results with the whole community. Thus, colleagues could access the information from the individual studies and comprehend the results gained about the investigated mechanisms even though they did not conduct the experimental study themselves, and they could use the results from other studies in their own research if that seemed appropriate.[52] That is, without the generation of the various mutant strains in *The Big Screen*, the biologists working with zebrafish would have lacked the necessary material, the mutant strains, to analyze the genetic mechanisms underlying vertebrate development.

The second phase in the establishment of zebrafish as a model organism provides two further important aspects for scientific understanding. In order to understand specific phenomena, scientists need a functioning research infrastructure to share information and new insights as well as the necessary material equipment to conduct specific studies. Scientists use the knowledge that their colleagues generate and the methods they implement by applying them to understand the phenomenon

52 I explain in more detail in chapter six how it is possible to achieve understanding by receiving an explanation by testimony and not by conducting a certain experiment. Scientists are able to understand the phenomena their colleagues have researched by reading their publications or talking to them in person if they grasp the relations of the phenomenon presented in an explanation, construct relations between the information contained in the explanation and their knowledge, and draw further inferences, which have not been available to them before they received the explanation. Again, this is different from merely knowing an explanation, which does not enable scientists to put the results from other studies to use in their own research.

they themselves are researching. Additionally, results and insights gained in other studies can enable biologists to grasp new relations they might not have been aware of without the additional information from other experiments. Communication between scientists of a discipline is crucial for gaining scientific understanding and for making scientific progress. Therefore, it was essential to establish the necessary infrastructure to ensure communication among scientists and the availability of material necessary to conduct studies. You cannot understand a phenomenon if you have the necessary knowledge and relevant research skills and tools, but lack the material to work with, to actually conduct a study in which you apply and use the knowledge and research skills you possess. If you want to understand the function of a specific gene for the development of the nervous system, for example, but you do not have a mutant strain that lacks precisely this gene, you will not understand the function of this gene for the development of the nervous system.

So, the first phase showed that scientists need specific knowledge, research skills, and tools to understand a certain phenomenon scientifically. This finding is important, as it indicates that any analysis of individual cases of understanding has to consider the knowledge, research skills and equipment that was present or required for that specific case. Phase two highlighted that, additionally, scientists need an appropriate research infrastructure that ensures the distribution and maintenance of information and insights gained in individual studies as well as the required material equipment. The third phase, to which I now turn, demonstrates the importance identified in phase two of functioning communication among researchers and, furthermore, points to an additional feature of the manifestation of scientific understanding, its iterative nature.

5.2.3 The iterative manifestation of scientific understanding

In the context of the third and final stage of the development of zebrafish as a model organism, the study on the *oep* mutant is a further example of how biologists acquired understanding of a specific function of one gene in embryonic development. Before Gritsman and colleagues initiated their studies on Oep, some knowledge about the function of Nodal and Oep in embryonic development as well as phenotypic effects caused by respective mutations had already been established through other studies.[53] However, it was not clear with which receptors and pathways Oep interacts, and what exactly the relation is between Oep and phenotypic effects. Importantly, the research on Nodal on the one hand and Oep on the other was not yet related. Studies on the effects of Nodal and Oep in zebrafish, which revealed all the insights I just mentioned, had been conducted independently from each other.

53 See Gritsmann et al., p. 121.

The studies by Gritsman and colleagues changed that. From the very beginning, they were interested in the role of *oep*. Since the *oep* gene is expressed maternally as well as zygotically, the researchers generated embryos that lack both maternal and zygotic Oep. These mutants were called MZ*oep* mutants. When these mutants were generated, the biologists recognized that "MZ*oep* mutant embryos are very similar to double mutants for *sqt* and *cyc*, two zebrafish *nodal* related genes."[54] Only due the observed similarity between the two mutants was it possible for the biologists to grasp the relation between Oep and the Nodal signaling pathway. Through this observation, the biologists had epistemic access to the relation between Oep and Nodal signaling. Only now did they have reasons to assume that there is a connection. Importantly, grasping a relation between the two genes is something more than and distinct from merely noticing the similarity of two mutant phenotypes. Seeing the similarity was necessary but not sufficient for grasping the relation between the genes. It might have happened that the biologists saw and recognized the similarity of the phenotypes, but were unable to grasp the relation between Oep and Nodal, for example if specific knowledge about characteristics of the two genes had been missing at that time. Evidently, Gritsman and her colleagues were able to grasp a relation between Oep and Nodal only because they possessed the necessary knowledge about Oep and Nodal that had been established in other studies, and the required research skills and tools to become aware of the relation. Without the necessary resources to generate the MZ*oep* mutants and then recognize the similarity between the different mutants, it would not have been possible to grasp the relation. That the biologists had the required knowledge, research skills and tools was only due to the development of zebrafish research community over the previous decades, grounded in the integration of molecular genetics and developmental biology.

Gritsman and colleagues grasped the relation between Oep and Nodal, but they did not yet understand it. To arrive at an understanding of the function of *oep* in embryonic development, they still needed to articulate the relation in the form of an explanation of the role of Oep in Nodal signaling. This was not possible on the basis of the available knowledge and the observed similarity of the two mutants. The biologists knew that something was going on between the proteins Oep and Nodal, but they did not know how the proteins interact. Therefore, the biologists could not yet explain why and how Oep and Nodal interact or why the MZ*oep* mutants and the double mutants for *sqt* and *cyc* look so similar, because they had no epistemic access to the details of the relation. To articulate the grasped relation in an explanation, further cognitive work was necessary. Based on the already available knowledge, the biologists reflected on the observed similarity of the different mutants and considered possible reasons for it by performing abductive reasoning. They were looking for the most likely explanation of the similarity and had the idea that Oep and Sqt/

54 Ibid. p. 122.

Cyc (Nodal) might act in a common pathway. If this is the case, it would explain why the same phenotypic effects can be observed when one of the two components is missing. In both cases, the pathway would not function properly and would lead to identical effects. In general, molecular signaling pathways refer to processes by which a chemical or physical signal is transmitted through a cell as a series of molecular events, which ultimately result in a cellular response.

Assuming that Oep and Sqt/Cyc (Nodal) do act in a common pathway, how and where in the pathway do they act? Here, knowledge generated by other studies came into play. Taken into account that "Oep acts cell autonomously […] whereas Nodal signals can act nonautonomously […] suggested that Oep is required for cells to receive Nodal signals."[55] Still, this was only a hypothesis for which the scientists wanted supporting evidence. Through further counterfactual reasoning, they had the idea that, if Oep is not required for Nodal signaling, MZ*oep* mutants would be rescued by injecting mRNAs encoding Sqt, Cyc, or mouse Nodal as replacement for Oep, and they devised the respective experiment. In other words, if the idea that Nodal signaling necessarily requires Oep is false, the injection of Nodal in the absence of Oep would lead to a normal development of the mutants. Since the mutants were not rescued through this procedure, the biologists obtained the evidence that Oep is indeed essential for Nodal signaling and that Nodal signaling does not take place without Oep, and they could explain the role of Oep during embryogenesis with this observation. The use of further available knowledge from other studies and research skills enabled the biologists to grasp and explain this crucial detail of the relation between Oep and Nodal, the necessity of Oep.

However, the biologists did not yet achieve the understanding of the function of Oep in the Nodal signaling pathway to which they aspired. It was still not understood exactly which step in the Nodal signaling pathway requires Oep. Again, results obtained by other research groups were crucial to understand this aspect. Since other studies suggested but did not definitively show that Nodal signaling is mediated by a pathway that might involve the ActRIB receptor and the Smad2 transcription factor, Gritsman and colleagues wanted to test whether "Oep is essential for the responses to these factors."[56] At this step, the counterfactual reasoning process was that if Nodal signaling is transmitted by the indicated pathway, and Oep is essential for Nodal signaling, the pathway will not be activated if Oep is absent. In other words, Oep activates this particular pathway and the ActRIB receptor as well as the Smad2 transcription factor act downstream of Oep in the causal pathway. If this is the case, it should be possible to activate the Nodal signaling pathway at a subsequent step, one that follows the activation by Oep, in the MZ*oep* mutants by

55 Ibid. p. 125.

56 Ibid. p. 125.

injecting already activated ActRIB and Smad2 in the mutants. The impossible activation of the Nodal signaling pathway by Oep in the mutants would be replaced by an activation of the downstream components outside of the mutants, which are then injected. Since the mutants were rescued as a result of this injection, the hypothesis could be confirmed and the biologists arrived at a new understanding of Oep "as an essential component of Nodal signaling […] that allows Nodal to activate its downstream signaling pathway."[57] They had grasped and articulated where in the pathway Oep executes its function, how Oep and Nodal are related.

This example, the process of understanding the function of Oep for Nodal signaling in vertebrate development, demonstrates the complexity of the manifestation of scientific understanding. Gritsman and colleagues had to have access to the required knowledge already generated by other studies, possess the relevant research skills and tools to conduct research that enabled them to grasp the relation between Oep and Nodal in the first place. Only subsequently could they detect the components and structure of the relation more precisely, like the exact role of Oep as an essential cofactor for Nodal signals and its position in the causal relation, as allowing for the activation of the downstream signaling pathway. Without the pieces of knowledge about *nodal* and *oep* gained in other studies, Gritsman and colleagues would not have been able to understand their relation. Even if they had recognized the similarity between the *oep* mutant and the other mutant lacking *nodal* and concluded that the genes must somehow be related, they would have had no chance to understand how the genes are related without some preexisting knowledge about these genes. If you do not know that Oep acts cell autonomously, while Nodal can act nonautonomously, you will never have the idea that Oep might be necessary for cells to receive Nodal signal, not to mention that this might actually be the case. Without some minimal or hypothetical knowledge about aspects of the phenomenon to be understood, scientists would not have any starting point for their research, would have no idea where to start or which hypothesis could be tested first. If scientists have some knowledge to start with, they then need the research skills, tools, and material to do the research that they hope will allow them to understand the phenomenon. In the case of the research on the *oep*-mutant, Gritsman and colleagues had knowledge about Oep and Nodal from other studies, had the research skills and tools to induce and map mutations in the *oep*-mutants as well as to identify significant phenotypic effects and, last but by far not least, they had the material, that is, the specific zebrafish mutant strain to work on.

All of these resources, the knowledge, research skills, tools, and material were provided from the established and functioning research infrastructure around zebrafish. If Gritsman and colleagues had not been trained in the research skills and

57 Ibid. p. 129.

the use of tools from the newly established field of developmental genetics, comprising the formerly separate fields of molecular genetics, embryology and neurophysiology, had not have access to the results gained in other studies on Oep and Nodal, and had not have the *oep*-mutant, which was identified in *The Big Screen*, they would not have been able to do the research they actually did and to gain the understanding of the function of *oep* for vertebrate development that they did acquire. The team around Gritsman needed the broader research infrastructure that provided them with all the resources they needed in order to acquire scientific understanding. It was *The Big Screen* that made the identification of the various mutations, the founding of new labs focusing on different mutants and hence parallel research on different mutations and their effects on embryonic development, which resulted in the discovery of novel insights published and made available for other scientists who might need these insights for their own research, possible. In order to get understanding of a specific phenomenon, scientists must be part of an appropriate infrastructure. In the example of the function of *oep* in vertebrate development, Gritsman and colleagues were part of an infrastructure appropriate for understanding this phenomenon.

So, the example of the research conducted by Gritsman and her team within the third phase of the establishment of zebrafish as a model organism corroborates my claims that the first and second phase of the episode and the resources established during these phases are necessary for the scientific understanding of the genetic regulation of vertebrate development. However, the studies on *oep* and *nodal* reveal an additional crucial aspect of the manifestation of understanding. I argue in chapter 4.3 that the ability to understand a phenomenon manifests in the process of grasping relations the phenomenon stands in and articulating these relations in the form of explanations. As the research on the *oep*-mutant shows, biologists did not grasp all details of the relation in question at once and then articulate an explanation of this relation. That is, the biologists did not first grasp everything there was to grasp and then articulate this in an explanation, as the characterization in chapter 4.3 might suggest. Rather, grasping relations and articulating explanations – manifesting understanding – is an iterative process. Grasping and explaining depend on each other. Let me elaborate this idea again with the research on *oep*.

When the scientists generated the *oep*-mutants, the process of understanding began with grasping the similarity relation between the phenotypes of the generated *oep*-mutants and the double mutant for *cyc* and *sqt*. Based on the knowledge of which genes the two mutant strains are lacking and the observation that both mutant strains have a similar phenotype, the biologists reasoned that the genes missing in one of each mutant type must be related. Only due the observed similarity of the different mutants was it possible for the biologists to grasp a relation of the respective genes. The biologists had reasons to assume that there is a relation, but they did not yet understand this relation. To gain understanding of what is going on and how

the genes interact, the biologists were looking for reasons for the observed similarity of the different mutants. They were looking for an explanation of the similarity and had the idea that the proteins encoded by the genes might act in a common molecular pathway. If this is the case, it would explain why the same phenotypic effects can be observed when one of the two components of the same pathway is missing. In both cases, the pathway would not function properly and would lead to identical effects. So, the biologists articulated a first hypothetical explanation: the zebrafish mutants that lack *oep* or *nodal* have a very similar phenotype because the proteins encoded by the two genes act in a common molecular pathway.

They understood that the two genes are related, but they did not know whether the genes really act on a common molecular pathway and if so, how exactly they interact. To answer these questions, the biologists referred to the results and knowledge about features of these genes gained in other studies. At this stage, the biologists grasped that the insights from these other studies are related to the function of *oep* for embryonic development. The integration of this additional knowledge "suggested that Oep is required for cells to receive Nodal signals."[58] This is already a more concrete conception of the relation of the genes, more concrete than just saying the genes somehow act on some common pathway. The biologists arrived at the following hypothetical explanation: in normal, non-mutated fish, *oep* has an important function in embryonic development, because it activates the Nodal signaling pathway by which several early embryonic developmental processes are regulated.

However, this was still only a hypothetical explanation. The scientists wanted supporting evidence to ensure that they understood the function of *oep* correctly, that this explanation represents the relation of Oep and Nodal correctly. In a third step, the biologists designed and conducted several experiments to determine whether Oep is indeed necessary for Nodal signaling. These experiments did show that the scientists were right, that Oep is indeed essential for Nodal signaling. The biologists could confirm their hypothetical explanation. Nonetheless, before conducting the additional experiments in the third step, the biologists could not know whether their articulated hypothetical explanation was correct. That is, they could not know whether they already understood the function of *oep*, or rather misunderstood it. It could have happened that the experiments in which the biologists tested the hypothetical explanation falsified this explanation, instead of confirming it. You do not know this in advance, which is why you test your explanations. If the hypothetical explanation would have been falsified, the biologists would have realized that they had misunderstood the function of *oep*, that is, that their explanation did not represent relations of the phenomenon. When phenomenon and explanation conflict, this motivates scientists to work out and articulate an alternative explanation, to understand the phenomenon in a different way in which the conflict

58 Ibid. p. 125.

dissolves. This observation nicely fits Michael Polanyi's idea, presented in section 4.2, that understanding brings our language and the world in line, establishing coherence among language and perception.

Ultimately, the iterative process of grasping and explaining, of taking various pieces of knowledge into account by performing, in this case, abductive and counterfactual reasoning and testing generated hypothetical explanations by employing research skills for the intervention or manipulation in the model organism finally enabled the researchers to articulate the following explanation, to arrive at the following understanding, of the function of Oep in vertebrate development: Oep is required for vertebrate embryogenesis, because it activates the Nodal signaling pathway by which germ layer formation, organizer development, and the positioning of the anterior-posterior axis are regulated.

5.3 Understanding the genetic regulation of vertebrate development scientifically

How did the research on zebrafish allow for scientific understanding? Analyzing this episode from scientific practice revealed three important and related insights.

First, biologists could understand the genetic regulation of embryonic development of complex organisms because they had the necessary knowledge from molecular genetics as well as from developmental biology, viz. embryology and neurophysiology, as well as the research skills and tools from both disciplines. These resources enabled biologists to grasp relations between genetic activities and developed phenotypes in a given experiment. Material skills, like the skills to map and isolate genes or to fix and dissect embryos, to name just a few, were necessary for understanding, because their application enabled the scientists to carve out, to isolate, relations that are part of the phenomenon of interest. Without the possession and use of these material skills, scientists would not have been able to investigate any phenomenon they did not yet understand. They would never have gained epistemic access to the phenomenon of interest. When a relation was grasped, when scientists became aware of it after it had been isolated with the aid of research skills, they tried to make sense of that relation by figuring out its details. In the case presented here, abductive and counterfactual reasoning was used to hypothesize what this relation might look like, what its details are, and to articulate a tentative explanation on the basis of this reasoning process. The hypothesized explanation was then tested in subsequent studies, for which additional research skills as well as additional knowledge may have been required. Intervening in the grasped relation again allowed for epistemic access to more details of the relation. When the scientists conducting a specific study grasped no more details of a relation and articulated and tested all the aspects that were grasped, they formulated a final explanation – for the study in question – and

gained understanding of the phenomenon of interest to the extent that was possible in the setting of the study. The history and use of zebrafish as a model organism to understand the genetic regulation of vertebrate development shows that scientific understanding of empirical phenomena requires the availability and use of relevant knowledge, research skills and related tools.

Second, the episode demonstrates that achieving scientific understanding is an extremely complex and demanding process that requires and is influenced by an appropriate context or environment. All the participating scientists in this project had the goal of understanding the genetic regulation of vertebrate development, but realizing this goal required a huge community. Besides establishing and learning the necessary knowledge and research skills, an infrastructure to secure the communication and distribution of theoretical as well as material resources needed to be implemented. These resources cover zebrafish mutant strains, material tools to work on the mutants, as well as knowledge that was gained in individual studies. Since the genetic regulation of vertebrate development is a very complex phenomenon, single scientists or groups of scientists will never be able to understand this phenomenon without the results and support from other research groups. Because the research community working on zebrafish split up into several research groups working on specific genes or specific developmental processes, it was necessary to formulate what was understood about an aspect of the genetic regulation in the form of an explanation. The acquired knowledge or explanation could then be communicated to others, who can scrutinize or also use the shared knowledge for their own research. Each study contributes insights about parts of the phenomenon, but only as a community with a functioning infrastructure can the genetic regulation of vertebrate development be scientifically understood in its entirety.

The third important insight provided by this episode is the stepwise and iterative manifestation of scientific understanding. The scientists did not do their research, then grasp every relation or all the details of a relation of a phenomenon at once, and then articulate the one "final" explanation for the respective study. Instead, manifesting scientific understanding of a phenomenon is an iterative process of applying scientific methods, grasping relations that were carved out by the method, articulating the grasped relation in an explanation through reasoning or additional research, which again enables grasping further relations or details of an already grasped relation, the successive articulation of an additional or more precise explanation, and so on. This goes on until the scientists decide that, for some specific study, they have understood the phenomenon sufficiently for the time being and publish their results. And the iterative manifestation of scientific understanding parallels the stepwise combination of interventions in the model organism that Meunier emphasizes.

Generally, my analysis of this scientific episode matches the views from Ankeny & Leonelli and also from Meunier concerning model organisms and their use in

scientific practice. Recalling the quote from the beginning of this chapter, the characteristic feature of model organisms, according to Ankeny & Leonelli, is its use as a model for organisms as wholes and for gaining an integrative understanding of intact organisms with regard to their genetics, development and physiology. These are exactly the goals of the biologists working on zebrafish. They wanted to understand the genetic regulation of vertebrate development as a whole. Understanding the more particular phenomena involved, like the effect of injecting certain mRNAs in specific mutants, were necessary instrumental steps in the process of understanding the phenomenon that was ultimately of interest. In all the studies on the various zebrafish mutants identified in *The Big Screen* and numerous experiments within each study, the scientists operated the mechanism and thereby manipulated the development, as Meunier expresses in the quote I present in section 5.1.4. Through the stepwise combination of interventions, the mechanism was carved out and analyzed, and thereby understood. That the biologists could carve out the mechanism by intervention and manipulation was only possible because an appropriate research infrastructure was established. As I already said, this infrastructure secured the communication among scientists and the distribution of the necessary material equipment, research skills and tools and the knowledge acquired in the studies. Through carving out the genetic mechanism in the mutants, it could be grasped and articulated in an explanation, which can then serve as a basis for the construction of theoretical models of the mechanism in other organisms, according to Meunier. This is in line with the ultimate goal of Gritsman and colleagues in studying Oep. They did not want to understand the effects of the presence or absence of Oep in certain mutants, but rather the general function of Oep in normal, unmanipulated embryonic development.

In sum, the episode from the research around zebrafish supports my view developed in the previous two chapters. In chapter four, I argued that understanding is an ability to make sense of a phenomenon through aligning experience and the knowledge stored in the respective language an individual uses. Scientists working on zebrafish did exactly this, they made sense of the causes of embryonic development by bringing their "experience" (in the case of science, observations of embryos or genetic data) in line with what they already knew about genes and embryonic development. Since the scientists involved articulated and published explanations about aspects of the genetic regulation of vertebrate development that they understood, the episode also sustains the claim I defend in chapter three, namely that scientific understanding requires explanation. Beyond that, the analysis of this episode shows that, first, scientific understanding of some phenomenon requires relevant knowledge, specific research skills and tools. Second that an appropriate community ensuring the generation and distribution of needed (material) equipment is necessary. And finally, the episode highlights that the manifestation of understanding is an iterative process, consisting of several subsequent steps of grasping some relation or

aspects thereof and articulating what has been grasped in a (tentative) explanation. These are the three important findings I take into the next chapter.

So, I maintain that the episode analyzed here provides crucial insights about the nature of scientific understanding and the way scientists achieve scientific understanding of phenomena. Am I thereby making the same problematic move I accuse other philosophers of science of at the beginning of this chapter, generating claims about scientific understanding by looking at one particular discipline? Is it not the case that the episode about zebrafish can only reveal insights about understanding gained in biology, about "biological understanding", or even more narrowly, about understanding gained in developmental genetics, the discipline that developed together with the establishment of zebrafish as a model organism?

I hope not, as I follow Hasok Chang in

> "seeing the history-philosophy relation as one between the *concrete* and the *abstract*, instead of one between the particular and the general. Abstract ideas are needed for the understanding of *any* concrete episode, so we could not avoid them even if we only ever had one episode to deal with. […] Any concrete account requires abstract notions in the characterization of the relevant events, characters, circumstances and decisions. If we extract abstract insights from the account of a specific concrete episode that we have produced ourselves, that is not so much a process of *generalization*, as an *articulation* of what we already put into it."[59]

In this chapter, I looked at one concrete episode. In the next chapter, I abstract away from this concrete episode and develop my account of scientific understanding by taking the three insights gained from the concrete episode into account.

59 Chang (2012), p. 110. I used the exact same quote already in the first footnote of this chapter where I clarified my use of the term "episode".