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# In Memoriam Walter J. Gehring (1939–2014)

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Earlier this summer, the scientific community was deeply saddened by the passing of Walter Gehring, who died on May 29th from the injuries caused by a tragic car accident. With his passing the scientific community lost an eminent scientist, an influential mentor who inspired generations of young scientists, and a great human being.

Walter Gehring was an eminent figure and renowned developmental biologist with a passionate curiosity, an infectious enthusiasm for all aspects of biology, a deep drive to discover fundamental concepts, and visionary ideas that inspired young and old across disciplines. Walter is probably best known for the discovery of the Homeobox in 1984, a gene segment coding for the evolutionarily conserved DNA binding Homeodomain, which is present in many related transcription factors such as the homeotic or Hox proteins that specify different regions along the anterior-posterior body axis in animals throughout the animal kingdom. His second major impact was the discovery of the conserved function of the Eyeless/Pax6 gene family in eye development, leading to the pioneering concept that corresponding organs in different animals are specified by conserved transcription factors. Both these discoveries had immense impact in biology and changed how developmental biology was approached, both at the experimental level, where suddenly interesting genes were easily cloned through their homology to other patterning genes, and at the level of

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perception as developmental studies in model organisms immediately became paradigmatic for human organogenesis and disease.

Walter was born in Zurich, Switzerland, and he was fascinated with biology from a young age, when his uncle presented him with a box full of caterpillars, which he then observed as they proceeded through metamorphosis. He studied Zoology at the University of Zurich and obtained his Ph.D. under the guidance of Ernst Hadorn. His model organism of choice has been from his PhD thesis onward the fruit fly Drosophila melanogaster. His thesis work focused on “transdetermination” of imaginal discs, in today’s world maybe a somewhat esoteric phenomenon, but back then in the pre-molecular days, a highly modern approach. Transdetermination describes the observation that imaginal discs, epithelial sacs that are the precursors of adult external structures and that differentiate into the adult body plan during metamorphosis, can change their fate. For example, an imaginal disc that normally gives rise to an antenna can get transformed into one that gives rise to a leg or a wing, after culturing it in adult hosts (Gehring, 1966b). In current terminology and thinking, such a transformation would be equivalent to the reprogramming of a tissue specific stem or progenitor cell, for example one that normally gives rise to the liver into one that produces lung tissue. Decades ahead of today’s ideas, Walter realized that understanding transdetermination would reveal processes that underlie the specification of different body parts, hence the analogy to “pluripotent precursors” or stem cells. During his PhD thesis work he also discovered an allele of the homeotic gene Antennapedia, a genetic lesion that transforms antennae into legs in Drosophila (Gehring, 1966a). Walter named the mutation “Nasobemia”, for an animal that can walk on his nose (from a poem by C. Morgenstern), and recognized the importance of the Antennapedia mutation, as it provided an entry point to decipher the molecular identity and the biochemical and genetic functions of genes that program cells into their tissue fates. Indeed, Antennapedia has been a “fil rouge” or central theme throughout his career, which is characterized by a continued and deepening investigation of the biology and mechanism of Anten-napedia function and related genes. After his Ph.D. thesis work, he moved to Yale University in 1965, where he first worked as a postdoctoral fellow with Alan Garen and was then quickly promoted to Assistant and Associate Professor of Developmental Biology. In 1972, Walter returned to Switzerland as a founding member of the Biozentrum of the University of Basel, where he served as Professor and Chair of Cell Biology until his retirement in 2009. It was at the Biozentrum, where his research group made the seminal discoveries that transformed developmental biology.

Walter’s research interests centered on the mechanisms by which cells and organs of a developing embryo are programmed to acquire their fate and are specified in the correct place to produce properly formed organs in the adult organism. Although Walter worked with worms, squids, ascidians and other animals, Drosophila remained his favorite experimental organism and he skillfully tailored his experimental strategies to take full advantage of the ever evolving molecular, genetic, and genomic arsenal to dissect and elucidate fundamental questions in biology. Indeed, he was one of the first developmental biologists who embraced the molecular cloning revolution and he immediately implemented these techniques for the study of development. He even briefly dropped the focus on development of organisms to incorporate the molecular biology approaches into his toolbox and was involved in the cloning of some of the first genes in Drosophila, like the 5S RNA or

heat-shock genes (Artavanis-Tsakonas et al., 1977; Ish-Horowicz et al., 1977; Schedl et al., 1978). As soon as it became practical, he returned to developmental biology questions, applying the molecular biology tools to its fullest extent.

The work of his group then quickly culminated in several seminal discoveries. His group cloned the Antennapedia gene (via the technique of choice “molecular walking along a chromosome”) (Garber et al., 1983), which served as an entry point to decipher the molecular mechanisms of homeotic gene function and homeotic transformation (see below). In a follow-up landmark experiment published in a paper entitled “Redesigning the body plan of Drosophila by ectopic expression of the homoeotic gene Antennapedia” Gehring and coworkers showed that misexpression of Antennapedia was sufficient to transform an antenna into a leg (Schneuwly et al., 1987). They had thus experimentally recreated the phenotype of the Antennapedia mutation and demonstrated that homeotic genes are not only required for patterning but indeed are “master control genes” of body structures as Walter liked to call them.

The cloning of the Antennapedia region (or Antennapedia complex/ANT-C as it is officially called) heralded a new era in biology. In quick succession the “molecular walk” in the Antennapedia gene complex (Garber et al., 1983) led to the identification and functional analysis of several homeotic genes and the segmentation gene *fushi tarazu*. These studies and the coincident establishment of in situ hybridization to detect the spatial localization of the mRNA of the genes of interest in vivo led to striking discoveries of the organization of the body plan (Hafen et al., 1984; Kuroiwa et al., 1984; Kuroiwa et al., 1985; Levine et al., 1983). For example, it was observed that the homeotic genes are expressed in spatial domains overlapping with the body region that they specify and that the segmentation gene *fushi tarazu* is expressed in seven stripes, producing stunning images that were displayed on the covers of journals and textbooks. The cloning of Antenna-pedia and other homeotic genes within the ANT-C led directly to the most striking discovery, the identification of the homeobox as a common feature of homeotic genes (McGinnis et al., 1984c). Bill McGinnis and colleagues in Walter Gehring’s lab showed not only that the homeobox is a gene segment that is conserved among all homeotic genes in Drosophila, but also that it was conserved and present in many patterning genes across the animal kingdom (McGinnis et al., 1984a; McGinnis et al., 1984b). Walter and his collaborators could then quickly identify many related genes (in Drosophila and elsewhere) and get insight into their function via their spatial expression patterns (e.g. Fjose et al., 1985; Kuroiwa et al., 1985; Mlodzik et al., 1985). The discovery of a conserved DNA element, the Homeobox, in several body axis-patterning genes, was a quantum leap in molecular developmental biology, as it suddenly made cloning of additional such genes in Drosophila and other animal species easy via homology DNA hybridization. All the subsequent discoveries of the Hox complexes in vertebrates and associated antero-posterior body patterning functions were thus made possible with the discovery of the Homeobox. Importantly, Walter Gehring followed through on the Homeobox discovery with many functional studies, defining the Homeobox/domain as a DNA binding domain, and later described the structure of the Homeodomain and how it binds to DNA (e.g. Müller et al., 1988; Qian et al., 1989; Schier and Gehring, 1992).

Most notable is also Walter's discovery of the evolutionarily conserved, organogenesis-regulating genes of the Eyeless/PAX-6 family, which act as master control genes for eye development across the animal kingdom, directing the development of very different types of eyes such as the single lens eyes of vertebrates and the facet eyes of insects (Halder et al., 1995; Quiring et al., 1994). Gehring and collaborators found that the Pax6 gene was conserved in many different animal groups, that it is expressed during eye development in many species, and that ectopic expression of Drosophila Pax6 or Pax6 from other species, was sufficient to trigger the formation of extra eyes on legs, antennae and wings of adult flies (Halder et al., 1995). He interpreted this astonishing discovery to indicate that the various eyes found in the animal kingdom evolved from a single ancestral eye. The notion that eyes have a common evolutionary origin transformed the way we think about the evolution of organs and body plans and his recent work addressed the conundrum of how the morphologically distinct eyes of insects, octopi, and vertebrates evolved from a common ancestor. All these discoveries opened up new fields of research and others later found that these concepts hold true for many other organs and developmental processes.

Walter Gehring's group pioneered numerous molecular and genetic techniques, such as in situ hybridization, revealing segmental expression of Homeobox and other genes (Hafen et al., 1983), and enhancer trapping (enhancer detection in vivo) (Bellen et al., 1989; O'Kane and Gehring, 1987; Wilson et al., 1989), used to discover new genes and to dissect genetic regulatory interactions and networks (Hiromi and Gehring, 1987), to list just two such techniques. In general, he recognized the potential of novel techniques and implemented many of them before they became common practice, as mentioned above for example for DNA/gene cloning and associated molecular genetics.

Although Walter is mainly known for his work with Drosophila, he was passionate about zoology and developmental biology in general. As a manifest of that, every other summer he directed a marine biology course at the Laboratoire Arago (L'observatoire Océanologique) in Banyuls in the south of France, where a minilab was set up and participants performed experiments with sea urchins, ascidians and other sea animals that they collected from the Mediterranean [before indulging in dinners feasting on the same creatures, along these lines: Walter knew a good wine and a good meal as much as a good biology experiment]. His general broad interest and excellent understanding of zoology resurfaced in the later stages of his career, when he focused on the evolution of the eye, following the discovery of the conserved function of the Eyeless/Pax6 genes in eye development (Gehring, 2014; Gehring and Ikeo, 1999). He applied his interest in zoology and systematically investigated how seemingly diverse eyes from different animals could have the same underlying molecular and evolutionary origin. His course work in marine biology in Banyuls thus came full circle and it helped guide the molecular evolutionary questions and experiments (Gehring, 2014).

Walter's outstanding research contributions were recognized by many prestigious awards from around the world, including the Jeantet Prize for Medicine (1987), the March of Dimes Prize in Developmental Biology (1997), the Kyoto Prize for Basic Science (2000) and the Balzan Prize for Developmental Biology (2002). He was also honored with the "Grosses Bundesverdienstkreuz" of the Federal Republic of Germany in 2010, and he was elected to several national academies, including the Royal Society of London and the US National

Academy of Science. Walter acted as president of the International Society for Developmental Biologists (ISDB) and as secretary-general of the European Molecular Biology Organization (EMBO).

It is impossible to view Walter's impact on developmental biology only through his own work, as he inspired numerous researchers. Many of his trainees, postdocs and students alike (actually too many to list them here), became themselves accomplished leaders in various fields of biology. Indeed, Walter had a gift of recruiting highly talented and ambitious people and his laboratory was a buzzing group of researchers who were driven to make groundbreaking discoveries. Not only that, but Walter also had a sharp instinct and determination, combining a playful and a forceful approach to biological discovery, to push some initially crazy ideas of which several were eventually proven correct. Throughout his life, Walter kept close contact with his former trainees and collaborators around the world and he indeed founded a large and cohesive scientific family, spanning diverse disciplines and model organisms. Many of his former co-workers became life-long friends and keenly and frequently visited the Biozentrum and Basel. It was only a couple of months ago in March, when many of us attended a symposium in Basel to honor him on his 75$^{th}$ birthday, where Walter was in great spirits and full of energy and enthusiasm. This was the last of several such meetings, which exemplified his impact on biology, and where his former students and co-workers gathered to celebrate and exchange scientific ideas and social memories.

Also, at this year's Drosophila EMBO Conference in Crete (held every two years in June at the Greek Orthodox Academy in Kolymbari, a site Walter loved very much), his extraordinary mentorship and scientific impact was recognized at a special remembrance. Walter was one of the participants that attended the original meeting in 1978 and his absence leaves a big hole in the meeting. He will long be remembered for his drive, enthusiasm and encouragement, and although his legacy is being carried forward by his scientific descendants – many of his "scientific children", "grandchildren" and "great grandchildren" were major participants at this year's Kolymbari meeting, he was and will be deeply missed.

Walter Gehring was an extraordinary scientist and iconic figure. His impact on developmental biology was immense, and his lasting legacy will include future discoveries of his many trainees. He lives on in the fond memories of his colleagues, family, and friends.

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