Walter Jakob Gehring (1939–2014)

Walter J. Gehring died in Basel, Switzerland on May 29, 2014 from the injuries of a car accident on May 1 in Lesbos, Greece. With his passing, the scientific community loses one of the pioneers in the field of molecular developmental biology and a mentor of many scientists working in this and in related fields.

Walter J. Gehring
Walter J. Gehring talking about eye evolution during a birthday anniversary symposium organized at the Biozentrum in Basel in March 2014. Photograph courtesy of the Biozentrum.

Walter started his scientific career in the laboratory of Ernst Hadorn, an eminent developmental biologist working at the University of Zürich. He worked on a phenomenon known as transdetermination, the occasional respecification of *Drosophila* imaginal disc tissue upon growth in the abdomen of adult flies. At some point during Walter's PhD, Hadorn's secretary showed Walter a funny-looking fly, which, upon closer inspection, had a leg in place of the antenna on the head. Walter called the mutation causing this phenotype "Nasobemia," and this was the beginning of a lifelong connection to master regulators in development.

For his postdoctorate, Walter joined Alan Garen's lab at Yale, where he wanted to learn more about the novel, emerging techniques of DNA cloning. After his appointment to the Biozentrum in Basel in 1972, Walter's lab established the first European DNA bank of *Drosophila* (instead of calling it a gene "library," the term used in the US, Walter insisted with a big smile that, being in Switzerland, it would be much better to call it a gene "bank"!). In a fruitful collaboration with Alfred Tissière's lab in Geneva, the heat shock genes were cloned (Schedl et al., 1978) and subsequently analyzed, putting the lab in the spotlight for establishing a proof of principle for gene identification from the gene bank.

Identifying developmental control genes in the bank was the ultimate goal for Walter. This remained a difficult task, however, because there were no probes available for these genes. David Hogness's lab at Stanford had established "chromosomal walking" as a new concept to isolate genes. The identification of desired DNA clones relied on the availability of genetically and cytologically well-defined chromosomal rearrangements with a breakpoint in the gene of interest. Using this technique, it took 3.5 years to identify the *Antennapedia* (*Antp*) gene, which was finally published in 1983 (Garber et al., 1983), concomitantly with similar studies from Thom Kaufmann's lab (Scott et al., 1983).

The molecular characterization of *Antp* changed the field of molecular developmental biology in a most dramatic manner. Not only were sequence homologies identified between *Antp* and other homeotic loci (called H-box homology; McGinnis et al., 1984a), but the Gehring lab also identified short stretches of sequence homology (180 bp) in genomic DNA from many different animal species (McGinnis et al., 1984b). Walter insisted that the H-box, due to its importance, be renamed the "homeobox," a term still used today. The unexpected finding that invertebrates and vertebrates share similar developmental control genes was startling, and subsequent studies even showed that similar cell types use similar transcriptional regulators in very different organisms.

Beyond these important implications for the field, the homeobox also provided a probe to clone numerous genes from any given organism without the requirement of prior information or molecular tools such as probes or antibodies. DNA hybridization turned out to be the perfect discovery tool for developmental control genes harboring highly conserved DNA-binding domains. Within a few months, the number of cloned homeobox genes exceeded by far the number of labs working in the field. A new area in molecular developmental biology was born!

Of course, the significance of the homeobox did not escape the attention of Ed Lewis, who pioneered the genetic analysis of the homeotic genes in *Drosophila*. As Lewis mentioned in a note he added to a shipment of flies to Basel: "Dear Walter, you made the homeobox our flying carpet."

The next big step that Walter wanted to undertake was to "redesign" the body plan of the fruit fly by the inappropriate expression of the *Antp* gene in head tissue, more precisely in the antennal disc. Although there was ample indirect evidence that *Antp* did specify the second thoracic leg in flies and that inappropriate expression might lead to antenna-toward-leg transformation (such as in the dominant Nasobemia mutant), Walter wanted to do the key experiment and directly demonstrate that a single gene could transform a tissue to a large degree (Schneuwly et al., 1987). As Walter mentioned in his correspondence with

the *Nature* editors during the publication procedure, "I want to see molecular evidence," in addition to genetic evidence. It is fair to say that this statement reflects one of the major driving forces in Walter's scientific approach and vision: the quest for molecular evidence of biological observations.

Ever since Walter had been in Alan Garen's lab, he was interested in DNA-binding proteins, suspecting that, similar to bacteria, such proteins would play key roles in developmental processes. Despite many attempts to purify such proteins from extracts, not much progress was made. To Walter's delight, it turned out that the homeobox indeed codes for the DNA-binding domain of Hox proteins, the homeodomain. Now Walter wanted to know more about the interaction of homeodomain proteins with DNA. At a Swiss meeting in 1986, he heard a talk by Kurt Wüthrich, from the ETH in Zürich, who had started to establish methods to determine the structure of proteins using NMR spectroscopy. Although these NMR studies were really just developing (a protein of the size of the homeodomain had not been structurally analyzed at that time) and several tens of milligrams of pure protein were required to start the collaboration (protein expression and purification were not as easy as they are today), Walter decided that this would be an interesting and promising way to go, and he put a PhD student on the project. After a bit more than 2 years of work, the three-dimensional structure of the Antennapedia homeodomain was solved by the Wüthrich group, first in the absence, and later in the presence, of DNA (Gehring et al., 1994). These studies revealed numerous molecular details about protein structure, folding, and interaction with DNA and allowed for interesting interpretations about the evolutionary conservation of specific amino acids within the homeodomain. Again, trying a somewhat different and risky approach and a new collaboration allowed the Gehring lab to make another big step forward.

What came next was neither anticipated nor predicted by Walter (and he loved to make predictions or to say that he predicted a specific outcome of an experiment!). In a control experiment, a cDNA clone was isolated that encoded a DNA-binding protein. Because the experimental side of the experiment did not advance, Walter decided that at least the control should be analyzed in detail to finish up the project. Upon sequencing, database analyses spat out homologies between this DNA fragment and the mouse gene small eye (*sey*), the human gene *Aniridia* (these genes were also referred to as PAX6), and some PAX genes in flies. Moreover, the cDNA clone hybridized to sequences on the fourth chromosome in flies, in a region where the *eyeless* (*ey*) mutation had been mapped. *Ey* mutant flies have little or no eye structures left on their head. Based on this analogy, the astounding hypothesis could be envisioned that facet eyes in flies and lens eyes in vertebrates could use the same transcription factor, PAX6, as a master regulator. It indeed turned out that this was the case (Quiring et al., 1994).

What followed this discovery was what Walter himself would claim as his most stimulating scientific period. Walter always had a somewhat simplistic idea of things. Although he knew about the complexity of life, he favored simple hypotheses, and he now wanted to demonstrate the role of PAX6 (*ey* in flies) in eye formation in the adult by inducing *ey* and subsequently eye formation in different tissues in the fly. The arguments in favor of such a result, which Walter used to keep the students handling the project on track, were the successful formation of antennal legs by misexpression of Antp (he called this the "Schneuwly" experiment) and the occurrence of transdetermination toward eye structure from several imaginal discs, as he and others had already observed in the Hadorn lab. After lots of negative results and numerous discussions in the lab on how to terminate this project for the sake of the involved researchers, the occurrence of red eye pigments first and then the observation of regions of incredibly perfect facets on different appendages indeed showed that ectopic expression of *ey* (and also of the vertebrate homolog PAX6) resulted in the formation of facetted eyes on different body parts (Halder et al., 1995). Walter was right (this time)! A simple hypothesis was worth being rigorously tested despite numerous well-grounded reasons for the experiment not to work.

From then on, Walter's interest turned to the field of molecular evolution, and he proposed that the different eye types originated monophyletically and subsequently diversified by divergent, parallel, or convergent evolution (Gehring, 2014). He still had a number of ongoing collaborations, and he wanted again to find molecular evidence for his hypotheses.

Walter was a passionate scientist. He put science in front of everything else in life. His enthusiasm was infectious and his talks were highly stimulating. Recently, at the hospital in Basel, his immediate concerns were for his collaborators; they needed to be alerted that he would not answer his email for a while but that the research efforts should continue during his absence. In addition, a manuscript to be published in *PNAS* had to be proofread, such that its publication could proceed quickly and without delay.

Walter was also an incredible mentor. For his 60th, 70th, and 75th birthday anniversaries, respectively, a symposium was organized in Basel, and all former collaborators were invited. More than 100 of them made their way again this year, when his 75th birthday was celebrated from March 21 to 22, and Walter concluded the symposium with a scientific lecture (see picture) and two dinner speeches in the evening. It was again a fantastic weekend, and all of the participants were shocked to hear only 10 weeks later the unbelievable news that Walter had passed away.

Walter loved Greece, its culture, and its cuisine. He attended all 18 previous EMBO conferences in Crete, at which every other year roughly 100 *Drosophila* researchers gather to discuss the newest results in the field. The 19th Crete conference, "The Molecular and Developmental Biology of *Drosophila*," took place in the same week as the memorial service organized by the University of Basel honoring Walter. His colleagues attending the conference in Greece sent the following message to be read during the service:

"Walter was one of the participants of the original meeting of the *Drosophila* Conference in 1978, which is held biennially in Crete for almost 40 years, and which is currently meeting at the Kolymbari site that he loved so much. His absence leaves a big hole in the meeting, but we will long remember his drive, enthusiasm, and encouragement. His legacy is being carried forward by his

scientific descendants; many of his children, grandchildren, and great-grandchildren are major participants at this year's meeting. His extraordinary mentorship and scientific impact was recognized at a special presentation this week by a former student. He is and will continue to be deeply missed.''

Walter was a wonderful colleague to be around at the Biozentrum. He always had an ear for everything, from research to politics and sports (Walter always mentioned that, early in his career, he had to decide whether he would want to become a professional football player or a scientist; who knows where Swiss soccer would have been with him as a forward player!). He was incredibly supportive of young scientists and, later in his career, of female scientists. He took special care of people outside academia; the ladies taking care of the glassware and the fly food called him ''papa natale,'' since he brought them a special present at Christmas every year. For us, Walter was the father of the ''second floor,'' always ready to make you laugh with a good joke, a new or an old story told with a sparkle in the eyes. He is and will be missed very much.

Markus Affolter[1]
and Martin Müller[1,*]
[1]Biozentrum der Universität Basel, Klingelbergstrasse 70, CH-4056 Basel, Switzerland
*Correspondence: markus.affolter@unibas.ch
http://dx.doi.org/10.1016/j.devcel.2014.07.011

REFERENCES

Garber, R.L., Kuroiwa, A., and Gehring, W.J. (1983). Genomic and cDNA clones of the homeotic locus Antennapedia in Drosophila. EMBO J. *2*, 2027–2036.

Gehring, W.J. (2014). The evolution of vision. WIREs Dev. Biol. *3*, 1–40.

Gehring, W.J., Qian, Y.Q., Billeter, M., Furukubo-Tokunaga, K., Schier, A.F., Resendez-Perez, D., Affolter, M., Otting, G., and Wüthrich, K. (1994). Homeodomain-DNA recognition. Cell *78*, 211–223.

Halder, G., Callaerts, P., and Gehring, W.J. (1995). Induction of ectopic eyes by targeted expression of the eyeless gene in Drosophila. Science *267*, 1788–1792.

McGinnis, W., Levine, M.S., Hafen, E., Kuroiwa, A., and Gehring, W.J. (1984a). A conserved DNA sequence in homoeotic genes of the Drosophila Antennapedia and bithorax complexes. Nature *308*, 428–433.

McGinnis, W., Garber, R.L., Wirz, J., Kuroiwa, A., and Gehring, W.J. (1984b). A homologous protein-coding sequence in Drosophila homeotic genes and its conservation in other metazoans. Cell *37*, 403–408.

Quiring, R., Walldorf, U., Kloter, U., and Gehring, W.J. (1994). Homology of the eyeless gene of Drosophila to the Small eye gene in mice and Aniridia in humans. Science *265*, 785–789.

Schedl, P., Artavanis-Tsakonas, S., Steward, R., Gehring, W.J., Mirault, M.E., Goldschmidt-Clermont, M., Moran, L., and Tissières, A. (1978). Two hybrid plasmids with D. melanogaster DNA sequences complementary to mRNA coding for the major heat shock protein. Cell *14*, 921–929.

Schneuwly, S., Klemenz, R., and Gehring, W.J. (1987). Redesigning the body plan of Drosophila by ectopic expression of the homoeotic gene Antennapedia. Nature *325*, 816–818.

Scott, M.P., Weiner, A.J., Hazelrigg, T.I., Polisky, B.A., Pirrotta, V., Scalenghe, F., and Kaufman, T.C. (1983). The molecular organization of the Antennapedia locus of Drosophila. Cell *35*, 763–776.