Int. J. Dev. Biol. 46: 29-37 (2002)

From Transdetermination to the Homeodomain at Atomic Resolution

An interview with Walter J. Gehring*

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Since the Swiss zoologist Ernst Hadorn first realized in the late 1940s that genes are crucial to the development of the fruit fly *Drosophila* melanogaster (and any other organism, that is), the field of developmental biology has undergone some dramatic changes. Before Hadorn's revelation, genes were thought to be responsible only for traits such as eye colour or wing shape. In the early 1970s, the advent of the cloning technique revolutionized developmental biology once again. And today, the genomic revolution once more is about to push developmental biology to the next level.

One scientist who has witnessed many of these exciting developments first hand, and who has himself made several major contributions to the field, is Walter Gehring. In his lab at the Biozentrum in Basel, Switzerland, such major breakthroughs as the discovery of the homeobox, the development of a revolutionary method to detect gene enhancers, and the discovery of a master control gene of eye development, *eyeless*, took place.

Gehring, who was born 1939 and raised in Zurich, is a student of Ernst Hadorn. In Hadorn's lab Gehring witnessed, when he was a diploma student, the discovery of transdetermination. Gehring himself focused on a strange mutant that sported legs where antennae were supposed to grow. As it turned out later, "Nasobemia", as he called the mutation, was allelic to several Antennapedia mutants. Gehring set out to clone the respective gene. In 1983, he and his team finally succeeded, and shortly after that they discovered the homeobox. Gehring then went even one step further; in collaboration with Kurt Wüthrich of the ETH Zurich (The Swiss Federal Institute of Technology, Ed.), he resolved the atomic structure of the homeodomain of Antennapedia. In other words, with his extraordinary stamina, Walter Gehring went all the way from a humble mutant down to the atomic level of the very protein - an achievement not many other scientists can claim for themselves.

Today, the 63-year old molecular biologist is still bubbling over with ideas for new projects. In the last years of his career, he wants to shift his focus more towards applied research. One of his goals is to find a preventive measure for "macular degeneration", a degenerative disease of the retina that affects 50 percent of 85-year olds.

The interview was held in Walter Gehring's office at the Biozentrum in Basel, on June 6, 2001.

In 1999, you celebrated your 60th birthday. Would you have imagined 40 years earlier, when you started studying biology, that one day you would become such a successful and influential scientist?

Abbreviations used in this paper: Indy, "I'm not dead yet" gene; NIH, National Institutes of Health; SNF, Swiss National Science Foundation.

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0214-6282/2002/$25.00
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Printed in Spain
www.ijdb.ehu.es

No, I always say we start out as a small egg cell 100 microns in diameter. This should make us modest and I have always tried to be modest. One should not underestimate oneself either, one should always put the bar a little higher.

When did you first realize that you could become a successful scientist?

This was when I was a postdoc, facing the international competition at Yale University. Yale was an extremely good place and I could compete favourably with the American and Japanese postdocs. I realized the potential is there, my self-confidence grew, but I was still trying to learn molecular biology at that time.

What was the incentive for you to study biology?

It goes back to the time when I was a little boy. My uncle, who was doing military service at that time, sent me a box full of butterfly pupae. The letter said I should put it in the attic and then the butterflies would emerge. They were brownish and didn't look like much. I forgot them over the winter, and then in Spring I accidentally went to the attic and opened up the box, and there the butterflies had just emerged and showed their incredible beauty. This got me into biology. I wanted to find out what happens during metamorphosis. What turns an ugly caterpillar into a beautiful butterfly? Later, in "gymnasium" (i.e. high school / junior college), it turned out that biology became my favorite topic.

What role did Ernst Hadorn play for you at that time?

He didn't play any role at that time. I came to zoology through professor Chen. My father had a long-standing relationship with Chinese friends in Zürich. Later on Chen joined that social group. When I told my father I was going to study zoology, he was quite reserved because he thought I would never make any money. At that time it was very difficult to become a professor. So he sent me to Chen, and Chen showed me for the first time *Drosophila* bottles. I mostly remember that the fly rooms smelled awful but the flies were quite interesting. They had nice red eyes.

You were in gymnasium at that time?

Yes, and at about the same time, I joined Ernst Suter, who was doing radar studies of bird migration. He was looking for gymnasium students to help him. We had to film and photograph the radar screen 24 hours a day. So I got interested in bird migration, and I became a hobby bird watcher. At that time, Ernst Hadorn was by far the most prominent teacher at the University of Zurich, and he became my mentor. I finally asked him whether I could do my diploma thesis on bird migration, wrapping up the studies I had done with Ernst Suter. Hadorn agreed under the condition that I would later on switch to *Drosophila* - which was a very wise choice. Already during the analysis of the radar photographs I witnessed the discovery of transdetermination …

… tell me more about that …

Hadorn was transplanting imaginal discs. Usually you transplant the discs from one larva into another and then you try to find out what a particular fragment could do if put into a larva of the same age or into a larva of younger age, where it still had time to grow before metamorphosis. Sometimes he was really playful and stuck some discs into adult flies. That turned out to be very interesting because in the adult females the discs grew but did not differentiate. So you could separate the growth phase from metamorphosis. Then he pushed this to the extreme; he kept transplanting imaginal discs from one generation of adult flies to the next, and at every generation he took out a sample of the tissue and injected it back into a larva to see what the cells were still capable of forming. Among the very first experiments, he tried genital discs. He cultured them for generations, and they first formed genitalia, as they were supposed to. But all of a sudden, they switched to making legs and antennae next to genital structures. At the same time he gave his graduate student Theo Schläpfer the eye disc to work on. Now, this is a very funny story. Rolf Nöthiger helped Schläpfer doing the transplantations and when Schläpfer analysed the metamorphosed tissue, he discovered huge pieces of wing tissue. At first he was absolutely furious at Nöthiger because he thought he had smuggled in some wing discs. We both went upstairs, but Rolf swore by his mother that he had not done anything wrong. So Schläpfer after a week took all of his courage and told Hadorn that

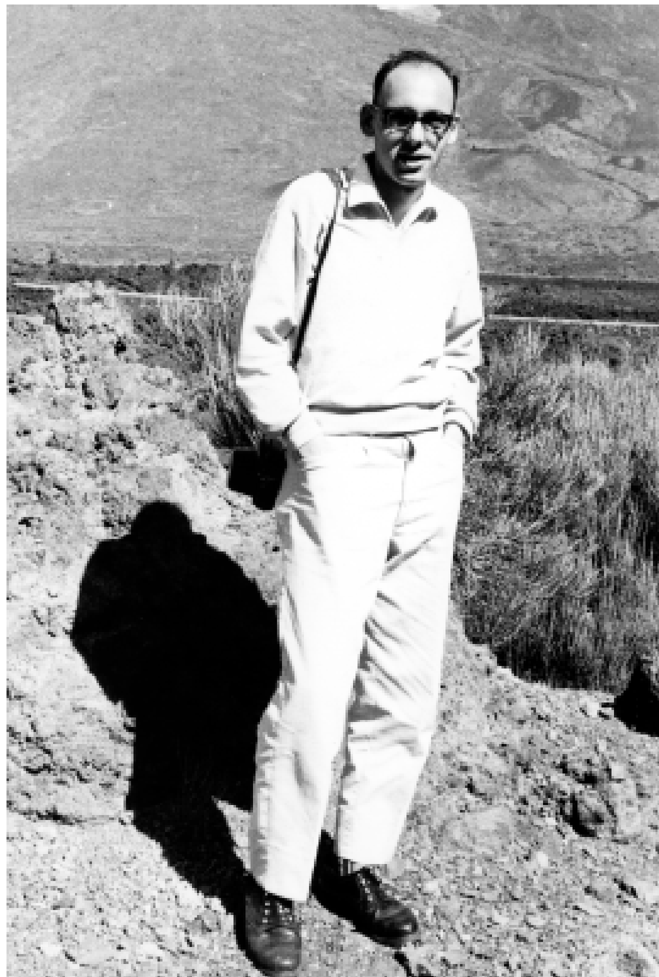

Fig. 1. Walter Gehring *as a graduate student in 1964.*

he had found wing tissue derived from eye discs. Then Hadorn said *"The same happened to me with genital discs, I got antennal tissue out of it".* That was the discovery of transdetermination.

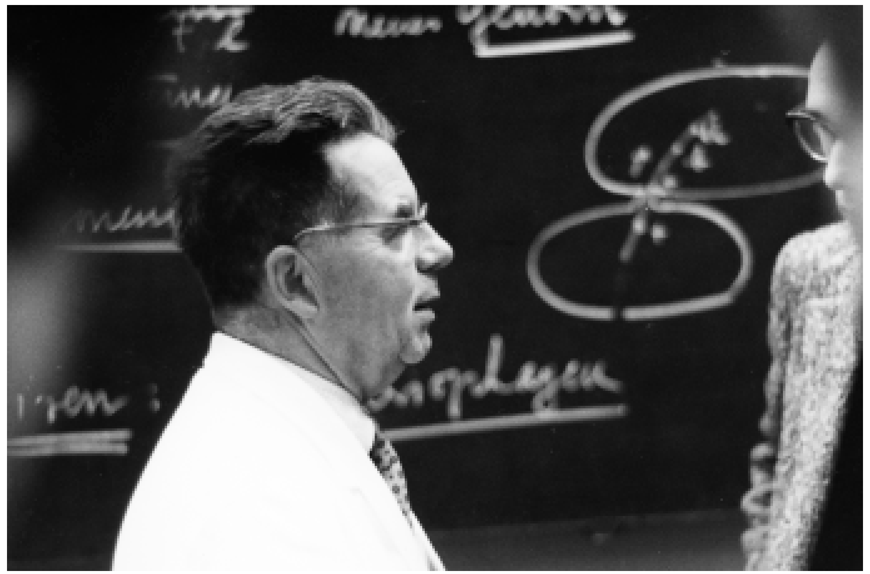

Fig. 2. A discussion with Ernst Hadorn after a lecture.

Transdetermination reflects an artificial situation. What does it tell us for normal development?

You're right. We still don't understand the mechanism of transdetermination. It involves the activation or inactivation of certain homeotic genes, but it is still not known what the real genetic mechanism is.

Is it a relevant mechanism in normal development?

No, it does not happen normally. But it shows a number of very interesting things. First of all it shows that those cells, if grown in culture, don't have a limited lifespan. We can culture imaginal discs for up to five years. The other discovery was that the transdetermination sequences, for example from genital to leg to antenna, were reproducible. They mostly, but not always, correspond to a homeotic mutation. We think that by random cutting and proliferation of the imaginal discs we bring cells of different determination into close contact, and you generate interactions that lead to the changes in determination, in a more or less predictable fashion.

Is anybody still working on that?

Yes, Gerold Schubiger is, and I am still working a little bit on that. I think now the time is right. And this is one of the corpses in my cellar that I still have to dig up.

Coming back to Ernst Hadorn. Is it fair to say that he was the person who launched developmental biology in Switzerland?

Yes. He was the major figure. My intellectual pedigree goes back to Theodor Boveri. He had a student named Fritz Baltzer, and Baltzer had Hadorn as a student, and I'm a student of Hadorn. Boveri made major contributions in the chromosomal theory of inheritance, and Hadorn realized that one could understand development only on the basis of genetics. That was his major achievement. Thanks to Hadorn, *Drosophila* became really popular in developmental biology. He started out working on newts, trying to figure out what is the contribution of the nucleus and the cytoplasm to early development. But then Hadorn realized that you had to use genetic methods to study development. He went to the US, and there he got the first lethal mutant, *lethal giant larvae.* Hadorn began to analyse this and other lethal mutants, and that actually provided the key to understanding the genetic control of development and that development is basically a question of genetics. Then, he did one more remarkable thing: he founded, together with the biochemist Jean Brachet and the cell biologist Paul Weiss, the "Journal of Developmental Biology". Before that the discipline was called "embryology" or "Entwicklungsmechanik" in German. The old embryologists at that time didn't believe in genes; Hans Spemann for instance didn't think that the genes were of any importance for development. But Hadorn's lethal mutations proved that genes were crucial for normal development. This was a major accomplishment.

Who else besides Hadorn was important for developmental biology in Switzerland?

At the beginning of the century, Rudolf Geigy did a nice experiment on *Drosophila*, but he didn't follow up. Then there was Rudolf Weber, a student of Portmann, who established an excellent group of developmental biologists in Bern. They worked mostly on frogs. Of course later, Max Birnstiel was an important figure. He was one of the pioneers in gene isolation. He isolated the first ribosomal genes with a graduate student, but has never been given enough credit for that. I still remember, when I was a young postdoc in 1966, Max showed that you could isolate genes in a test tube. That was a totally new concept. We always thought of a gene as something mysterious sitting on a chromosome. This was a revelation for me.

Where does developmental biology in Switzerland stand today internationally?

For a small country, we are doing remarkably well. There are some good developmental biology groups at the universities of Basel, Fribourg, Geneva, Lausanne and Zürich.

Can you compare science today with science in Hadorn's times? What changed most?

The means we had at that time were very modest. A few glass petri dishes, a few bottles, and a few vials, and hardly any chemicals. Nowadays you have all sorts of kits and complicated equipment. Essentially, what we are doing today has nothing to do with what we did in those early days, except for crossing flies of course, and sometimes a transplantation of imaginal discs. All the techniques have changed completely. And things have been scaled down dramatically.

Fig. 3. Looking at barnacles with David Hogness *(right) in Northern California (ca. 1991).*

How did you first become interested in homeotic mutations?

That is a very funny story. In 1964, the secretary of Ernst Hadorn, Züsi Blankart, gave me some flies with strange heads. It turned out they had legs on their heads. I started to map the gene for this mutant by recombination. It turned out it was different from *aristapedia*, which is a recessive mutation that only transforms the tip of the antenna into a tarsus. My mutation instead gave a complete middle leg. That's why I named it *Nasobemia*. Christian Morgenstern made this funny poem about an imaginary animal that can walk on its nose. Later on we gave crazier and crazier names to mutations. I was able to map *Nasobemia* to 84; then I tested it against various *Antennapedia* alleles that were until then assigned to the wrong locus. They all shared one chromosomal breakpoint at the *Nasobemia* locus. Later on, using molecular biology, we proved that they were all alleles of the same gene.

When did you realize that this is a really important mutation?

I wrote a little paper in German about *Nasobemia* (Gehring W., 1966). I made some very bold predictions in the Discussion, such as *This must be a controlling gene, which activates all genes needed to make a leg.* This prediction was entirely correct. On the other hand, I didn't realize that it had to turn off all the antennal genes in order to turn on the leg genes. I realized this only later. At that time, I told my lab mate Theo Schläpfer, I wanted to find out about the molecular basis of this mutation. He thought I was crazy and told me that I would never succeed – and he was not the only one. When I told "old embryologists" I wanted to find out what these genes do, they felt that molecular biologists were not asking the right questions. And when I talked to molecular biologists, they also discouraged me because in their view it was difficult enough to find out about the lac operon; a gene that controls hundreds of other genes would be hopeless anyway. Others predicted it would be a simple enzyme.

What happened then?

Alan Garen came to Zurich to learn about transdetermination. Because Hadorn was very busy, I was in charge of talking to him, and at the end of the day, instead of Alan Garen coming to Zurich, he invited me to come to Yale to learn about molecular biology. When I arrived at Yale, Walter Gilbert and Benno Mullerhill had just purified the lac repressor by brute force biochemistry. That ended a long debate over whether it was an RNA or a protein. At this point, we decided to start working on DNA binding proteins.

Did you have any idea at that time that your protein might also be a DNA binding protein?

Yes, I always thought it was a lac-repressor-like molecule, but presumably an activator. It was clear by then that there were both activators and repressors. But there was also the myth at that time that they were present only in minute quantities. This was true for the lac repressor, but not for higher organisms. Higher organisms show a different mode. Instead of making proteins with extremely high binding constants they just produce much more of a low affinity protein.

When did you start cloning the *Antennapedia* gene?

That was back in Basel in 1972. I returned to Basel with my first graduate student, Eric Wieschaus. He later got the Nobel prize with another postdoc of mine, Christiane Nüsslein-Volhard. When gene cloning became available, I immediately realized that this was the way to go. It was an absolute breakthrough. The first *Drosophila* clones were made by my friend David Hogness in 1973/74. Then David came to the Biozentrum where he discovered the Hogness box. At the Biozentrum, we still have a room named after him. He and Welcome Bender had the ingenious idea how to clone a gene for which you had no idea what its biochemical nature was. This technique was called "walking along the chromosome". David Hogness began to walk towards the *Bithorax* complex (Bender *et al.,* 1983). We started immediately to clone the *Antennapedia* gene, actually it was mostly Rick Garber, an American postdoc and Atsushi Kuroiwa, a Japanese postdoc. This was really hard work for 3.5 years. Finally this all paid off (Garber *et al.,* 1983).

How?

First of all, we were able to find out that it was indeed a DNA binding protein. It was a transcription factor, an activator and a repressor, depending on the context. And then it led to the discovery of the homeobox. That's where we caught up with David and actually passed him. The idea came originally from Ed Lewis that these genes have arisen by tandem duplications. When he started to analyze the *Bithorax* genes closer, he came up with this model that all the thoracic and abdominal segments were specified by a set of genes in the *Bithorax* complex. In principle, the model was right, but it turned out that it had to be modified. There were only three genes instead of nine, and instead of one gene for each segment there were segment specific enhancers. So the idea was around that the genes arose by duplication, and therefore the genes should share some sequences. That's why we were looking for homologies among various homeotic genes. Once we had cloned the *Antennapedia*

region and tried to map the gene on this piece of DNA, we first of all found that the gene was gigantic and that almost all of the mutations were in introns. When we mapped the exons by hybridising cDNAs, we found that it hybridised not only to what was defined as *Antennapedia* by chromosomal deletion, but we found one site of hybridisation outside. That was a neighbouring gene, *fushi tarazu*. I asked David Hogness to send us the *Bithorax* gene, and we also found it there. That's when we coined the term homeobox.

The editors of "Nature" didn't like the term "homeobox". Is this true?

They didn't like it at all. If you read our first paper (McGinnis *et al.,* 1984), they changed it when we first mentioned the word homeobox and replaced it by the words "homeotic sequence". We wanted to call it a box because it is a short sequence of DNA that we were used to boxing-in with a rectangle. But they felt it was a slang type term. They took it out in the first place, but they forgot to take it out in the second place, so the word is still in the paper. This anecdote shows you how much influence editors have - honestly, that's not good. Anyway, the homeobox caught on.

Did you known at that time about the work in Tom Kaufmann's lab?

We knew that they were also cloning Antennapedia.

But you didn't know how quickly they were progressing…

Well, we definitely were first. I reported the homeobox discovery at a meeting in Southampton before there was any news from Kaufmann´s or Matthew Scott's lab, and we also coined the term. Matt found the same homologies as we did. But we used the homeobox as a probe to fish out *Deformed* immediately and *abdominal-A* and then (and this was even more important, since if it had been confined to *Drosophila* nobody would have talked about it) we found it also in vertebrates. At this point it became clear that it was something very important because it was universal. We had been looking so long for a universal principle of development in spite of the fact that a mouse, a fly and a frog develop so differently - and here it was.

When did you come up with the idea to look for it in vertebrates? Has this been your idea?

Yes. Well, of course, several people in the lab had the idea at about the same time. I remember very vividly the seminars we had with Eddy de Robertis. When Bill McGinnis, Mike Levine, and Ernst Hafen first found the homeobox sequence and we discussed it, Eddy immediately realized this was very important. We made some zoo blots first and Eddy wanted to examine if it was present in frogs. It would have been unforgivable, if we had not taken this opportunity. But there was only one student who wanted to try this crazy experiment; others, who are quite famous today, didn't want to burn their fingers. It was Andres Carrasco, a student from Argentina, who cloned the first frog homeotic gene (Carrasco *et al.,* 1984). Bill McGinnis helped him considerably. When it was sequenced, it turned out that 59 out of 60 amino acids were identical to the homeobox of the Antennapedia protein.

Fig. 4. After the discovery of the homeobox: *Eddy De Robertis (with frog) and Walter Gehring (with "fushi tarazu" stripes) around 1984.*

That must have been one of the most amazing moments in your scientific life …

Oh yes. It was fantastic. Frank Ruddle was here on sabbatical. He was supposed to do some writing, but he couldn't stand it anymore, went back into the lab with Bill McGinnis and they cloned the first mouse homeobox gene. I didn't want them to clone the first human homeobox gene at that time, because there were too many ethical problems. So Mike Levine did the job in the US after he left my lab, and that was OK with me since we had enough problems at that time with the anti-gene technology movement here in Switzerland.

You have written down your version of the discovery of the homeobox in a remarkable book (Gehring, 1999a), but this recollection of the events has met with some harsh criticism. Was the criticism, especially the one by Bill McGinnis and Peter Lawrence (McGinnis and Lawrence, 1999; Desplan, 1999) justified?

I think it was very unfair the way they did it, and I have a hard time to forgive. I discussed it with Atsushi Kuroiwa, who was also involved in all the experiments. He confirms my point of view. Then I also wrote a reply (Gehring, 1999b), where I pointed out that the band on a gel they were criticizing was published already twice (Garber *et al.,* 1983; McGinnis *et al.,* 1984). Rick Garber really did, together with Atsushi

Kuroiwa, all the cloning. When Bill McGinnis and Mike Levine arrived at the lab, the gene was already there. I also asked Bill McGinnis at that time to find out what the mysterious band meant, which he did. Clearly, Bill played a major part in the discovery of the homeobox. On the other hand, Peter Lawrence doesn't understand molecular biology as far as I'm concerned; he didn't understand what this discovery meant. Claude Desplan´s criticism was much fairer.

One of your outstanding abilities has been, and probably still is, to attract brilliant young people to your lab. How do you do that?

Well, I always try to give good lectures and attractive courses and also to stimulate students. One of my secrets was that I never forced people to do things. I suggested several topics on which they could work and they could make their own choice. That also means that it was not my fault if they picked the wrong subject. By leaving them a lot of freedom I try to get the best out of my collaborators. That invariably works well with excellent people. However, with others it doesn't work all the time. In these cases I try to direct them and tell them what they should do and that may or may not work. I believe we reach the highest creativity when we have a lot of intellectual freedom.

Give us some names of people who have been working in your lab …

I mentioned Eric Wieschaus and Christiane Nüsslein-Volhard already. David Ish-Horowitz was here, too and also Paul Schedl, Spyros Artavanis-Tsakonas, Bill McGinnis, Mike Levine, Atsushi Kuroiwa, Yash Hiromi, Hugo Bellen, Ernst Hafen, Renato Paro, Marek Mlodzik, Alex Schier, Ueli Grossniklaus, Leslie Pick, Markus Affolter, Kahir O´Kane, just to name a few. There are about 120 in total.

Do you still have good ties with some of them?

Yes. For my 60th birthday, Ernst Hafen and Markus Affolter organized a symposium, actually a good scientific meeting, and about 120 people came. I was very much surprised.

Another hallmark of yours has been that you always adopted new technologies very quickly. Has this been part of your success?

Yes, you always have to adopt new technologies and new ideas to stay at the forefront. For example, it was a disappointment for me that my good friend Rolf Nöthiger, when he was in his thirties, was not willing to adopt molecular biology. I just learned whatever I needed in order to advance. Now we're in DNA chips and genome research.

Your second breakthrough after the homeobox was the eyeless gene …

I had one more breakthrough, which I consider quite important, and that was enhancer trapping. Here's the story: we finally realized that *fushi tarazu* had a very large control region, much larger than the coding region. So, controlling these genes is actually much more important than the structural part. We fused the *fushi tarazu* control region to a reporter gene, beta-galactosidase, and we showed that we could get the zebra stripes in the embryo. When I saw these stripes I thought, well, one could turn the idea around: take the reporter and look for zebra stripes. Then Cahir O'Kane, who had done a lot of bacterial work, came here from Ireland and we fused his ideas with mine. Finally we took a transposon with a very weak, ubiquitously active promoter, hooked it to the β-gal gene, and we used this construct as a probe to detect enhancers (O´Kane and Gehring, 1987).

What did you find?

When we stuck the construct into the genome, we expected about 1 in 1000 or, optimistically, 1 in 100 of the transformed lines to find an enhancer. But then it turned out that we were all completely wrong. 60 or 70 percent of the lines showed some tissue-specific patterns. The genome is obviously full of enhancers. This idea then was combined with the GAL4-system which came from Andrea Brand and Norbert Perrimon at Harvard (Brand and Perrimon, 1993). She combined this idea with our enhancer trap idea, and so we could get targeted gene expression. This technique brought a completely new aspect into genetics. Now we can do gene hunting by expression patterns, look for genes which are expressed in the eye, for instance, and we can also detect redundant genes, which you could not detect using mutational analysis. We invented a method to detect redundant genes.

How proud are you of the *eyeless* gene?

I am very happy about this latest discovery, because there I was betting against everybody else. We discovered *eyeless* in a control experiment. Usually students don't want to do control experiments because they're dull, but sometimes control experiments can be more important than the experiments themselves. I had given a short 21 base pair long oligonucleotide sequence to Rebecca Quiring that she found to be present in the *caudal* and *fushi tarazu* promoter sequences. We thought this might be a common binding site for a regulatory DNA binding protein. As a positive control I gave her a homeobox binding site. She never fished anything with the 21 base pair probe, but in the first experiment she fished a protein which strongly bound to the homeodomain recognition site. And then she struggled with this protein. First, she did not find any homeobox. Of course, I got interested and asked her to clone the entire gene. It turned out that the clone contained multiple inserts from four different chromosomal regions, including rRNA sequences. Every thesis adviser would have said "stop here", but I did not. I insisted to sequence it from the other end, and there she found protein coding sequences. She fed this into the computer and sent it to Heidelberg for a database search. After lunch the computer was just spitting out homology after homology. I will never forget that. The first one that came out was mouse *Pax-6*, the second was human *Aniridia*, the third was *Drosophila paired*. They were all paired box containing genes. Then, I already knew that the gene might also have a homeobox, because *Pax-6* has a paired box and a homeobox. When she put the next 500 base pairs into the computer, all the homeoboxes poured out.

What was next?

When we looked at the region on the fourth chromosome, the nearest gene there was *eyeless*. Then I was convinced that we had discovered something very important. Of course, we hadn't proven any-

thing yet. But we knew at that time that *Pax-6* in the mouse was associated with the *Small eye* mutation. Uwe Walldorf helped Rebecca to sequence two mutants, and that's how we proved that the gene was indeed *eyeless* (Quiring *et al.,* 1994). When I saw that *eyeless*, *Small eye,* and *Aniridia* are homologous genes, it dawned on me: This could probably be the universal master control gene for eye development. I then had the crazy idea to express the gene ectopically to grow eyes on parts of the body where they're not supposed to grow. When I presented this idea at a *Drosophila* workshop in Crete, I got 20 different reasons from as many colleagues why this would not work. But other than my colleagues, I knew from my work on transdetermination that wing cells, for instance, can give rise to eyes. This made me hope that the experiment might work.

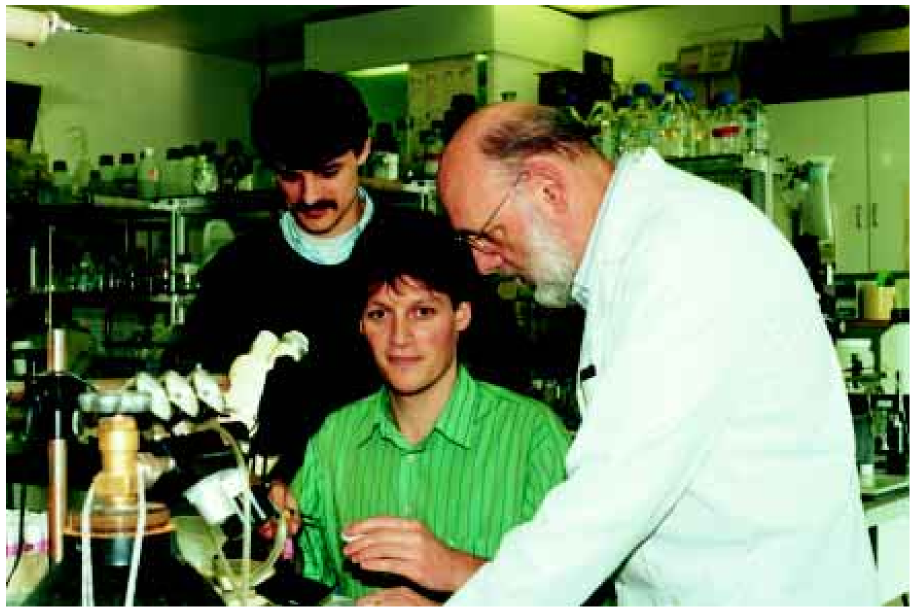

Fig. 5. After the successful induction of extra-eyes, *with Patrick Callaerts (left) and Georg Halder (center) in 1995.*

Who did the experiments?

I recruited two young scientists, Patrick Callaerts and Georg Halder, to conduct two of my dream experiments. One was to ectopically induce eyes, the other to prove universality. It didn't work in the beginning. The day before they wanted to give up, Georg and Patrick Halder found the first spots of red pigments in legs. This was the sign that it had worked. A few days later we had the first facets, and a few weeks later we had really nice eyes (Halder et al., 1995).

That made headlines around the world.

Yes, yes. On the front page of the New York Times, it said *"Scientists outdo Hollywood"*.

Have you been surprised how many headlines you got?

No, we were afraid of getting a lot of adverse reactions, which, in fact, we did get. I didn't understand, for instance, when it was just given as a fact in the newspaper: *"Here is Dr. Frankenstein who puts eyes on the legs and the wings of flies"*. Later, a picture of mine showing a fly with extra eyes was used as a *"negative example"* to raise money for the anti-gene technology campaign.

The publicity, it sounds, has not been positive for you?

No, generally not. But when you explained it to people, they would understand it. For example, when I gave lectures at the senior university, many people in the audience realized that I'm no Frankenstein and that this is the way science has to go.

How do you see the relationship between science and society today in Switzerland?

The communication, I think, has improved, but it can still become better. Nobel prize winner Rolf Zinkernagel, for instance, writes a weekly column about science in the leading tabloid "Blick". For scientists like me it was very useful that we had to fight against a referendum in 1997 which aimed at prohibiting gene technology to a large extent. That made us aware of the need to improve our communication with the public. Some of us cannot do that very well, some can do it better; and there are some journalists who help to bridge the gap between scientists and the public. It's dangerous, for example, in genetic engineering to promise too much and hold very little. Of course you have to be optimistic as a scientist and you have to try the impossible. Many times you fail, but sometimes you get this one breakthrough.

Well, you had many.

We forgot the NMR studies of the Antennapedia protein binding to DNA (Billeter *et al.,* 1993). That was a very fruitful collaboration with Kurt Wüthrich from the Federal Institute of Technology (Zurich). That was a great intellectual adventure. I could follow this gene from the antennal legs all the way down to the atomic level.

You have always been advocating interdisciplinary networks of scientists. Nowadays this becomes more and more popular. Have you been ahead of time?

You shouldn't make networks for the sake of networks. But you should always pick the best collaborators. With Kurt Wüthrich, for instance, I was very lucky. He was the best man in the field for NMR. And if two leaders get together, then you get rewarding results. I'm advocating this type of network, not some of these European networks that are just excuses to get funding. Unfortunately, they also favour some mediocre people.

What's the standing or reputation of science in Switzerland? How good is the funding?

The funding was quite good in the beginning of the seventies. But since then we have more or less been on the same level. In the US, the NIH budget has gone up by almost 50 percent during this period. Now Switzerland has to do something about that. The economy has

Fig. 6. The Kyoto Prize (2000) *being awarded by the Chairman of the Inamori Foundation.*

recovered largely, something more has to be invested. You cannot stand still, you always have to grow a little bit.

But in many disciplines such as physics or immunology, Switzerland is still a top player.

That's true. But that's our raw material. We have no oil, no coal, no gold, we have nothing but our education and our brains.

Is the leadership position in danger if the funding is not raised substantially?

Yes, absolutely. We could lose it rather rapidly.

When the evolutionary biologist Stephen Stearns left the University of Basel a year ago, he said that the Biozentrum, where you work, nowadays is only second-rate. Is this true?

That was a rather mean statement. It is true, however, in the sense that twelve faculty members of the original team have retired, and now a lot of young people are coming, and we have to give the young people a chance. I came here at the age of 32, they gave me a lot of credit. Some of the young are extremely good, the first prizes have already come in. For the first time we have two excellent women scientists in the faculty: Silvia Arber, the daughter of Nobel prize winner Werner Arber, and Anita Lüthi, two outstanding neurobiologists. We have a new generation here, and they need some time. I'm quite optimistic. The model of the Biozentrum, where we have different disciplines and institutes under one roof, is still a very good model. Stephen Stearns issued his criticism because he was angry at Basel; it was a personal thing.

Last year, a large, interdisciplinary research project on "organogenesis" that you are heading didn't get funding from the Swiss National Science Foundation (SNF) as a *"Nationaler Forschungsschwerpunkt"*. Were you disappointed?

Yes, of course. But I think this was largely a political decision. We had excellent people on the project. For the first time in my life I have been disappointed by the SNF. On the other hand they have been financing my personal grants at the maximum level. It's not catastrophic for me, I want to do this project anyway. I got already half a million Swiss francs from the university to get it started. We have started it and are full of enthusiasm. We collaborate with ophthalmologists in Zurich and Lausanne, and I think we have a very good eye project. For the rest of my career, I want to do something more applied.

Where will the project lead to?

Our goal is to find a preventive measure for age-related macular degeneration. This degeneration of the retina is very common in old people. More than 50 percent of people over 85 have macular degeneration and in the worst case you become completely blind. My mother has this, my grandmother had it. We think that we know the mechanism from work in flies and mice. Thanks to excellent genetic and genomic work done by a group in Lausanne, we have probably found the crucial gene. It produces an extracellular protein. This is important because we may be able to apply a medicine from the outside. We don't know yet whether we have to inject it into the eye or whether we can apply it as eye drops. That would be a preventive measure before the degeneration starts.

What's the role of functional genomics for developmental biology in the future?

So far, in developmental genetics we have worked with one gene after the other, but with the advent of DNA chips and micro arrays we can really look at the entire genome. And that offers entirely new aspects. For example, we think that at least 2000 genes are required to form a *Drosophila* eye, and that we may now be able to see them on the chips. We're just beginning with these experiments.

Is this the future of developmental biology?

Well, this is part of it. But I think the future of developmental biology will be a fusion with evolutionary biology. You cannot understand anything about development without understanding evolution. Organisms are not rationally designed like a human engineer would design a machine, but they are put together by tinkering. The DNA chips and micro arrays on the other hand are wonderful tools for diagnosing genes involved in human diseases. Most diseases have a genetic component, a predisposition. That will put medicine almost on a novel basis, a basis that emphasizes much more prevention and natural regeneration of parts.

You're thinking about stem cells.

Yes, somatic stem cells. Our friends in Lausanne, for instance, work on retinal stem cells. They can grow them in culture. Relatively soon, there will be organ engineering which will be able to more or less replace organ transplantation. For example, *Pax-6* not only makes eyes but also Langerhans islets in the pancreas, which is very important for Diabetes. There is already a small company which Peter Gruss has founded in Göttingen which plans to make pancreas islets.

Are you saying that basic research in developmental biology meets medicine?

Yes, it begins to. But I still favour basic research very strongly. We would never have found *Pax-6* without *Drosophila*. The nice thing is that we now can extrapolate much more from flies to humans - more than we ever dreamed of.

Recently, you received the prestigious Kyoto prize. What does it mean to you?

The Nobel prize is given for a particular discovery, but the Kyoto prize is given for a lifetime achievement, and that's very rewarding. It's only given to three people, one in advanced technology, one in science, and one in arts or philosophy. It's not only prestigious, it's a very large prize, too. As a scientist, you never know how to evaluate your own work, you always have to be slightly overoptimistic. So if your peers review you as an outstanding scientist, this is a great recognition.

Talking of achievements, I think we have forgotten one. In early 1990 you made headlines with a strain of flies that seems to live substantially longer than their peers (Shepherd *et al.,* 1989). What happened to them since?

We stopped the project. I gave it to a collaborator, Christine Brack, and she couldn't confirm our initial results, and then she gave it up. I'm still convinced that the initial results were correct. There are two lines of evidence that suggest that they were right. First, the same gene was found to be a longevity gene in fungi, and secondly, Seymour Benzer has isolated another gene that has a dramatic effect on lifespan called *methusalem*. I think these genes exist.

… Isn't there another gene called *Indy*, standing for "I'm not dead yet"?

Yes, that's a third one. In worms, they pushed it much further than in flies, and there is now ample evidence for genetic control of aging. That doesn't mean it is monogenic as it is true for the eye to some extent. The idea is that some genes have a very strong effect which might tell you about the mechanism of aging.

But you're not working on aging anymore?

You should understand that we had the homeobox genes, then we found *eyeless*. There was just no more room left for this project. Maybe some day I will come back to work on it. Anyway, personally I wouldn't wish to make people live longer at any price. But, for instance, retinal degeneration goes in the same direction. Once my grandmother lost her vision and her hearing, she didn't want to live anymore since her quality of life was miserable.

That means you want to improve the quality of life in old age, but not necessarily prolong the lifespan?

Yes, definitely. Although from a theoretical point of view, the mechanism of aging is interesting, I feel that life chooses to constantly renew itself. Death is part of the life program that starts with fertilization. I don't think we want to get 240 year old human beings, rather we want to improve the quality of life.

You still have a lot of ideas and projects. Retiring obviously is not among them?

I can work here until the age of 70 if I'm still healthy. If I'm no longer productive and run out of ideas, which I'm not afraid of, then I will immediately quit and let the young people take over. If I'm still in good shape at 70, I'll retire to Banyuls, France, where I have a little guest lab with a microscope. I still have many ideas that I want to pursue.

Good luck, Walter Gehring, for all your plans, and thanks a lot for this enlightening interview.

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