Walter Gehring

2002 Balzan Prize for Developmental Biology
For his seminal contribution to the discovery of a universal principle underlying the body plan and eye development in metazoans.

Genomic Analysis of Eye Development

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The second half of the Balzan Prize was used by Walter Gehring to support the young postdoctoral fellow Lydia Michaut at the start of her academic career. She has become an expert in the genomic analysis of DNA chips (microarrays) applying her expertise to study eye development and eye diseases.
Insects have complex compound eyes and vertebrates have inverse lens eyes. Although these types of eye are different, the same genes are used in the early stages of development. The project has lead to distinct conclusions primarily due to the large volume of data that it produced. A special model system was used to conduct a total of 154,000 individual measurements of genetic activities. This system is based on the fact that there is only a single gene – PAX-6 – at the outset of eye development and that insects can, in certain instances, form eyes on extremities such as legs or antennae. By introducing and activating PAX-6 in certain cells of the fly, Gehring's team was able to initiate the development of eyes in places where they would not normally be expected to grow. This is an ideal system for identifying the genes that only occur in relation to eye development. Comparing the differences in gene activity patterns between normal fly legs and those with PAX-6 induced eyes reveals which genes are involved in eye development. To understand how the activity of identical genes can lead to the development of different eye types, it is essential to know how the relevant genes behave.
Lydia Michaut completed the first round of genomic analysis of Drosophila eye development, performing whole genome profiling in the eye primordia of larva, pupae and adults, followed by an evolutionary comparison of gene expression in the eyes of fruit flies and mice. Large-scale analysis of gene expression has shown that the number of genes activated in the eye increases dramatically as an insect develops. During the larval stage, 98 genes are specially activated for this purpose. The figure rises to 409 during the pupal stage, and 474 in the fully grown insect. However, the functions of the activated genes vary considerably (Michaut et al., 2003).

In collaboration with the Institute of Ophthalmologic Research, in Sion, she has also analyzed the gene response in the retina of a mouse model of Leber's congenital *amaurosis*, an early onset form of *retinitis pigmentosa* that results in blindness or severely impaired vision in children. Mutations in seven different genes, one of which is called RPE 65, have been associated with this disease. Lydia Michaut and Sandra Cottet have studied mice mutants lacking RPE 65, using high density microarrays to compare gene expression in the retina of normal and RPE 65-deficient mice, and identified the secondary defects which lead to the death of the photoreceptor cells in the retina. These gene products can serve as potential targets to screen for protective drugs or compounds which limit cell death in the retina (Cottet et al., 2006).
To allow general and easy access of these expression data in mouse and fly eyes, Lydia Michaut has set up a searchable database where Drosophila and mouse gene expression profiles in the eye can be easily queried and visualized (Eyebase), thereby fulfilling the main aim of the International Balzan Prize Foundation – to promote science and culture around the world.

Dedicated website: http://eyes-on-chips.webiro.ch

Publications:
- Cottet, S., Michaut, L., Boisset, G., Schlecht, U., Gehring, W.J. and Schorderet D.F., *Biological characterization of gene response in Rpe65-/- mouse model of Leber's congenital amaurosis during progression of the disease*. "The FASEB Journal", 20, 2036-2049, 2006.
- Kobayashi, M., Michaut, L., Ino. A., Honjo K., Nakajima, T., Maruyama, Y., Mochizuki, H., Ando, M., Ghangrekar, I., Takahashi, K., Saigo, K., Ueda, R., Gehring, W.J., Furukubo-Tokunaga, K., *Differential microarray analysis of Drosophila mushroom body transcripts using chemical ablation*, "Proceedings of the National Academy of Science", 103, 14417-14422, 2006.
- Michaut, L., Flister, S., Neeb, M., White, K., Certa, U. and Gehring, W.J., *Analysis of the eye developmental pathway in Drosophila using DNA microarrays*. "Proceedings of the National Academy of Science", 100, 4024-4029, 2003.

Statements by the Prizewinner and by Lydia Michaut:
I would like to use the funds of the Prize to carry out an ambitious project to apply our knowledge obtained in basic science to the prevention of retinal degeneration in elderly people. Walter Gehring (Rome, 13.11.2002)

The financial support of the Balzan Prize to Walter Gehring and Lydia Michaut is acknowledged on the Eyebase (http://eyes-on-chips.webiro.ch/), which also provides a direct link to the International Balzan Foundation internet site, hence promoting awareness of the Balzan Prize among the scientific community. In summary, the Balzan Prize has been invested successfully in a promising young investigator to enter an academic career in biomedical research. Her scientific progress has been quite substantial and she has also contributed to the fruitful collaboration between basic biologists and clinical ophthalmologists. Walter Gehring (2007)

During the larval stage, 25 percent of the genes activated for eye development are used to regulate other genes. You could say that they initiate the next stage in eye development. During the pupal stage, most of the genes are used to control the creation of the eye structure and, when the insect is fully grown, gene activity is very definitely geared towards receiving and transmitting light stimuli. Lydia Michaut (2008)