Genomic Analysis of Eye Development

Walter Gehring†

2002 Balzan Prize for Developmental Biology

Balzan GPC Adviser: Nicole Le Douarin
Project Directors or Main Researchers: Lydia Michaut, Sandra Cottet
Affiliated Institution: Biozentrum, Universität Basel
Period: 2002-2008
Website: http://eyes-on-chips.webiro.ch

Walter Gehring† was Emeritus Professor at the Biozentrum of the Universität Basel. The second half of his Balzan Prize was used for postdoctoral support for Lydia Michaut, now an expert in the genomic analysis of DNA chips (microarrays), to study eye development and eye diseases.

Insects and vertebrates have different types of eye, but the same genes are involved in the early stages of development. This project used a special model system based on the fact that there is only one gene, PAX-6, at the outset of eye development, and that in some cases insects can form eyes on extremities. A total of 154,000 individual measurements of genetic activities was conducted. By introducing and activating PAX-6 in certain cells of the fly, Professor Gehring's team was able to initiate the development of eyes in places where they would not normally be expected to grow, which 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.

Michaut's first round of genomic analysis of *Drosophila* eye showed that the number of genes activated in the eye increases dramatically as an insect develops, but that the functions of the activated genes vary considerably (Michaut *et al*., 2003). At a later stage, in collaboration with the Institut de Recherche en Ophtalmologie in Sion, she

then 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. Together with Sandra Cottet, Michaut 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 set up a searchable database where *Drosophila* and mouse gene expression profiles in the eye can be easily queried and visualized (Eyebase).

Publications

Cottet S, Michaut L, Boisset G, Schlecht U, Gehring WJ, Schorderet DF. 2006. 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.

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 WJ, Furukubo-Tokunaga K. 2006. Differential microarray analysis of *Drosophila* mushroom body transcripts using chemical ablation. Proceedings of the National Academy of Science. 103: 14417-14422.

Michaut L, Flister S, Neeb M, White K, Certa U, Gehring WJ. 2003. Analysis of the eye developmental pathway in *Drosophila* using DNA microarrays. Proceedings of the National Academy of Science. 100: 4024-4029.