Book review

Development/Zebrafish Issue. Volume 123. Edited by Chris Wylie. Company of Biologists, Cambridge, UK, 481 pp, 1996, ISBN: 0948601 46 9.

The December 1996 issue of Development, being a separate volume of the journal, is unusual in that it is entirely dedicated to developmental studies in the zebrafish (*Danio rerio*). It contains original research articles documenting the results of international research efforts to identify and functionally describe genes that regulate development in zebrafish. The majority of research contributions to this volume are from the research groups at the Cardiovascular Research Center, Massachusetts General Hospital and Harvard Medical School, USA and the Max-Planck Institute for Developmental Biology in Tübingen, Germany. However, these two groups also collaborated heavily with some of the most renowned centers in this particular field of developmental research throughout the world (e.g., Institute of Neuroscience, University of Oregon, USA; ICRF Developmental Biology Unit, Oxford, UK; Department of Biology, University of California, La Jolla, USA; Institute of Zoology, University of Basel, Switzerland; Institute of Neurobiology, University of Heidelberg).

This volume represents a highly organized and valuable description of the genes that play major roles in the succinct steps during the early stages of zebrafish development. The arrangement of this volume is veritable proof that science is not only challenging and interesting but rather that it can be a lot of fun. Indeed, the articles follow the steps in zebrafish development, while the top right edge of every page displays a small picture of a minute sequence in zebrafish development leading to a flipbook of zebrafish embryogenesis. This flipbook animation of zebrafish embryogenesis is explained in more detail at the end of the volume by Karlstrom and Kane. Furthermore, giving specific mutant phenotypes rather distinct names (e.g. van gogh, obelix, dackel, ding, crocodile, goosepimples, kurzschluss, quasimodo, zombie), facilitates the association of mutants with a given stage or function during embryogenesis. This volume will permit even the non-developmental scientist a good understanding of the matter at hand, while supplying the expert in the field with an array of cutting edge technology and in-depth information.

The first article in this volume by P. Haffter et al. discusses use of a large-scale genetic screen (Tübingen-screen; Max-Planck Institute) using ethylnitrosourea (ENU) to induce point-mutations in male zebrafish. The article further describes subsequent mating with wildtype females and ensuing mating of the F1 males with wild-type females, and finally inbreeding with the F2 siblings. These crosses provided the identification of genes with unique and essential functions in the development of zebrafish. Throughout the article, the reader is imparted with an important morphological understanding of the various stages of zebrafish development, which serves as an excellent basis for understanding the subsequent, more detailed research articles. Using ENU treatment a total of 4264 mutants were identified of which 1163 mutants were kept for characterization, and with complementation crosses between mutants of similar phenotype, 894 mutants were assigned to 372 genes. The Appendix to this first article lists all of the 372 genes in the Tübingen-screen, their respective alleles and phenotypes, as well as function/stage-association during development.

The second article by Driever et al. describes a similar large-scale genetic screen with ENU that was carried out at the Cardiovascular Research Center, Massachusetts General Hospital and Harvard Medical School, USA (Boston-screen). This screen, carried out in parallel and independently to the Tübingen-screen, identified 2383 mutations of which 1432 were discarded as they did not appear to affect specific aspects of development. Of the remaining 951 mutations 370 mutations were either lost during characterization or belonged to the following groups which were not further characterized: (1) abnormal body curvature; (2) subtle deviations from normal pigmentation; or (3) mutations that were lost after the phenotype had been confirmed. The 331 mutations were characterized via complementation analysis within phenotypic classes and were then assigned to 220 genes (loci) and their respective alleles. Although the Boston-screen is well described in the Zebrafish Issue of Development, it would have been extremely useful if Driever et al. had supplied an appendix to their research paper in a similar layout as had been supplied for the Tübingen-screen. Such an appendix would have allowed to compare the mutations identified in the Tübingen-screen with those of the Boston-screen directly within the volume of Development and certainly would have increased the usefulness of this compact volume. Nonetheless, information on the mutations and corresponding genes identified with both large screens described in volume 123 of Development, as well as other mutations (genes) identified in earlier work by these research groups, is available on the internet at several sites: http://zfishstix.cs.uoregon.edu; http://zebrafish.mhg.harvard.edu; http://zebrafish.uni-freiburg.de. In addition, all mutations reported by allele designation in this volume are available from the mutant stocks kept at the same academic sites cited above on request, therefore. providing accessibility to the information and working tools for anyone interested in a specific mutation. The mutations identified with both large-scale screens, in addition to excellent illustrations and photographs, form the working basis for all subsequent research papers in this volume of Development.

All articles subsequent to the first two are organized with respect to the different stages of embryogenesis and the functional appearance of genes in the respective stages. Thus, the third and fourth articles deal with the mutants affecting epiboly and early arrest, while the fifth article investigates mutations affecting cell fates and rearrangements during gastrulation. The further embryogenesis proceeds the more complex, detailed and refined are the endpoints which are being inspected for mutational effects in the respective ensuing research articles. For example, Schier et al., Brand et al., Heisenberg et al. and Jiang et al., investigate mutations and genes that affect or are involved in the development of the embryonic brain, the formation of the boundary between midbrain and hindbrain, forebrain development or neurogenesis and brain morphology, respectively, and thus promote the basic understanding of zebrafish brain development. Immediate to the latter articles, however, are research reports by Abdelilah et al. and Furutani-Seiki et al. which discuss mutations and genes affecting neural survival (altered rate of apoptosis) and neural degeneration, respectively. The information from the latter research articles have meanings and ramifications that go beyond developmental biology i.e. have great importance in toxicology (i.e. teratology and developmental toxicology), human genetics, neuromedicine and pathology (e.g. in diseases such as Alzheimer's, Parkinson's and amyotrophic lateral sclerosis (ALS) disease).

For the more applied aquatic toxicologist the results of these two large-scale genetic screens are of a more limited utility. At fist sight it would appear as if many of the malformations observed in routine zebrafish development tests (also with non-genotoxic compounds) seem comparable to some specific phenotypes described in this volume of Development. However, when screening for mutations in the large-scale genetic screens it was impossible for the research groups to keep all identified mutants. Therefore, Haffter et al. classified the mutants in Class A, Class B and Class C, Class D mutants. (A) General abnormality: degeneration, retardation, necrosis; (B) well defined specific deviation from normal morphology; (C) abnormal motility, or touch response; and (D) abnormal retinotectal projection. Class A, which was discarded from further evaluation, contained mutants which displayed any of the four phenotypes (degeneration of the entire body during hatching; degeneration of the brain followed by whole-body necrosis; degeneration associated with an enlarged heart cavity and reduced circulation during hatching; retardation, judged by underdevelopment of the jaw, the liver and gut, small eyes, and the presence of unconsumed yolk on day 6 of development), occurring with approximately equal frequency. Unfortunately, in routine developmental toxicity assays with zebrafish, rather few compounds induce Class B, C or D responses, while the predominant number of compounds having any effect would be classified as Class A. The lacking knowledge on what genes are involved in the Class A mutants prevent elucidating potential compound specific mechanism(s) involved in the genesis of an compound exposure associated phenotype. Although a lot more elaborate and complex, it would be of great value if Class A mutants could be characterized in the future.

Having the enormous amount of genetic information on zebrafish development and the mutations that produce specific phenotypes is of great advantage as it yields

an important information basis for the elucidation of zebrafish-specific genetic functions and for genetic functions in vertebrates in general. Indeed, all authors in this volume of Development strive to make comparisons with other species (*Drosophila*, *Xenopus*, *C. elegans*, mice) and excel in pointing out those genes in other species that have either identical or comparable functions or phenotypes. To date, however, this is successful in only a small number of cases. In the future it will be important to link the mutant loci isolated in zebrafish to the repertoire of genes isolated and characterized at a molecular level in other vertebrate systems. This will require good genetic maps of zebrafish as well as of the other vertebrates (*Xenopus*, mouse, human). In this context it must be stressed that the identification of a phenotype and the corresponding gene (mutation) is only a first step in elucidating the mechanism(s) that is involved in the genesis of the respective phenotype. However, for the molecular biologist, biochemist, geneticist or toxicologist interested in determining how a given phenotype is produced this volume of Development certainly provides a good starting point. This pertains especially to aquatic and genetic toxicologists who aim to understand the effects of genotoxins in general and of those compounds that produce single point mutations in particular. Despite the minor fact that this volume of Development is not a ready help for the more routine-oriented aquatic toxicologist, the detailed description of the methods used for the assessment of effects, the beautiful and elaborate illustrations and photographs, the excellent subject index and cross references, as well as the highly organized structure make the Zebrafish Issue of Development (Volume 123, December Issue 1996) of inestimable value.

Daniel R. Dietrich
Environmental Toxicology
University of Konstanz
D-78457 Konstanz, Germany

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