

## COMMENT

us some insights into the *in vivo* relationships between these factors and provide tools for the further analysis of their biological functions.

### Acknowledgement

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## MEETING REPORTS

### We are devo-evo

WORKSHOP: NOVARTIS FOUNDATION SYMPOSIUM NO. 222: HOMOLOGY, LONDON, UK, 21–23 JULY 1998. FOLLOWED BY AN OPEN MEETING: HOMOLOGY, WELCOME TRUST, LONDON, UK, 24 JULY 1998.

This workshop was suggested to the Novartis Foundation by Adam Wilkins, editor of *BioEssays* (Cambridge, UK) and was chaired by Brian Hall (Dalhousie, Canada). The reason for feeling that the workshop was timely is the accumulation of novel, important information from the emerging field of developmental evolutionary biology. Devo-evo raises new questions about the traditional concept of homology.

Most biologists agree that homology describes an inevitable evolutionary phenomenon – the similarity of structures among different organisms that is due to common descent, that is, the continuity of information in evolutionary lineages in terms of the genetics and developmental mechanisms. On the other hand, analogous sameness is due to independent, convergent evolution, and also demands similarity of function, which is not a necessary condition for homologous structures.

The typical, but not completely agreed-upon, four criteria for homologous structures are: (1) common descent; (2) structural similarity; (3) relative position to other structures; and (4) similar developmental mechanisms.

This last criterion is not universally accepted because it is known that different developmental mechanisms can produce otherwise clearly homologous structures. At issue is the question of whether structures whose development is controlled by homologous genes can, could or even should be considered homologous structures, even if none of the other homology criteria appear to be met<sup>1</sup>.



**Mis-expression of *Pax6* in flies can lead to ectopic eyes. Image kindly supplied by Walter Gehring.**

There are several prominent studies, most notably comparative developmental data<sup>2</sup> on the expression of *Pax6* from various phyla of metazoans. This gene is switched on in many light-detecting morphological

structures that, based on evolutionary, structural and developmental criteria, would not be considered to be homologous by most biologists. Nonetheless, these structures were categorized by W.J. Gehring and his colleagues as homologous on the basis of their *Pax6* data<sup>2</sup>. Conversely, *distalless* is a gene that is ubiquitously expressed in developing elongated structures, such as legs in chordates, wings in insects and tube feet in echinoderms that are arranged perpendicular to the anterior–posterior axis of animals. These structures do not fulfill the same function and they have not been considered to be homologous<sup>3</sup>.

Should the notion of homologous structures be altered, based on the discovery of ancient and homologous master control genes that regulate the workings of probably large cascades of downstream effector genes in animals from distant phyla? If the function of these structures were not similar, the issue of homology would probably not have been raised. But it is crucial to make it clear that the function of a structure or of a gene has never been a defining characteristic of homology. The concept of ‘functional homology’ is clearly

TIG DECEMBER 1998 VOL. 14 No. 12

## MEETING REPORTS

nonsensical in cases where the term is used to infer that similar functions of genes imply a phylogenetically based, but untested, relationship of homology that is responsible for this similarity of function. It is obvious that the function of homologous genes and homologous structures can change over time without changing their homology relationship<sup>4</sup>.

But does it really matter whether we call eyes in different phyla homologous or partially homologous only because a homologous gene is expressed in the cells that will make that structure? It is known that different developmental mechanisms can make homologous structures (e.g. during regeneration), so why shouldn't the same genes or mechanisms also make non-homologous structures? It is obvious now that homology can no longer be considered to be an all-or-nothing concept. If there is something like partial homology it occurs at the gene level, the network level, the developmental mechanisms level and the structural level.

Rather than to quibble about the degree or definition of homology is it not more important to focus our attention on more fruitful areas: novel data in comparative development (Richard Hinchliffe, Aberystwyth, UK; Guenter Wagner, New Haven, USA); how are genes and genetic networks maintained for eons of time (Frietson Galis, Leiden, The Netherlands; Axel Meyer, Konstanz, Germany; Greg Wray, Stony Brook, USA); why is development sometimes so variable, even among closely related species (Rudy Raff, Indiana, USA); how do gene networks

evolve; do single components of cascades stay the same, and are some segments of pathways more resilient to evolutionary change than others (Ehab Abouheif, Stony Brook, USA)?

This workshop did not get closer to finding a universally agreed-upon definition of homology and hardly anyone seemed to think that it was worthwhile even to try. It might be more important to focus our attention on more fruitful questions, such as to seek biological explanations for the phenomena of stasis, modularity, preservation of design, latent homology and directionality of evolution (David Wake, Berkeley, USA). The significant progress that came about at this meeting derived from the genuinely open-minded approach of all 25 invited participants. Every argument from the level of gene to that of paleontology or behavior was considered equally. It was realized that previous confusion resulted from the use of different homology criteria, which, when not clearly stated at the onset, will lead to conflicting inferences and results. Two major outcomes in particular of this meeting seem worth mentioning. The formerly controversial concept of 'partial homology' seems now to be a generally accepted and useful paradigm. Furthermore, because homology is no longer seen as an all-or-nothing phenomenon it is clear that it is necessary to specify at what level of the organismal hierarchy homology is claimed; for instance, the partial homology of genetic networks is probably the basis for the putative homology among the light receptors of different metazoan phyla.

The modern synthesis of evolutionary biology was based on biological sub-disciplines such as natural history, paleontology, systematics and population genetics. Developmental biology was not part of the modern synthesis. However, developmental mechanisms are clearly an important determinant of some macro-evolutionary phenomena and need to be incorporated into an extended modern synthesis. Only more comparative developmental data, when analysed in a phylogenetic context, will be able to allow us to improve the detection of patterns in the diversification of life and to determine which of the many potential developmental mechanisms are major ones and which don't seem to matter all that much. A symposium volume with papers and edited discussion (edited by Greg Bock and Gail Cardew) will be published in January 1999 by Wiley & Sons.

### Further reading

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## Turning over the pieces of the post-genomic jigsaw puzzle

NMHCC SECOND INTERNATIONAL CONFERENCE: **POST-GENOMIC ANALYSIS OF THERAPEUTIC TARGETS** PRECEDED BY A PRECONFERENCE SYMPOSIUM: **GENOMIC DISEASE MODELING AND TARGETING**, SAN DIEGO, CA, USA, 3–4 AUGUST 1998.

This conference showcased a pot-pourri of results and approaches from laboratories that are grappling with the opportunities and the pitfalls of drug discovery in the 'post-genomic' world. Participants at the meeting, most of whom were from the pharmaceutical industry, highlighted the key conundrums: 'Too much data and too little knowledge'; 'Of all putative targets, which ones are valid?'; and

'Of all valid targets, which ones should we be working on?'

Talks mostly dealt with four main themes: single nucleotide polymorphisms (SNPs) in gene discovery and pharmacogenetics; positional cloning and message profiling approaches; yeast-based systems for characterizing novel bioactive compounds and/or targets; and protein three-dimensional (3D) structure-based functional

genomics. A brief synopsis of each of these areas is given below.

The potential of SNP genotyping as a prognostic tool for assessing drug responsiveness (and potential side-effects) in patients was addressed by Patrice Rioux (Variagenics, Cambridge, MA, USA) and Jörgen Lönngrén (Professional Genetics Laboratory, Uppsala, Sweden). Such pharmacogenetic profiling of patients will

TIG DECEMBER 1998 VOL. 14 NO. 12