Eric Davidson, California Institute of Technology: *"Causality of Gene Regulation in Animal Biology"*

In terms of process and mechanism there are three great conceptual domains within which the biology of any given animal can be understood: where the animal and its functional capabilities came from, in terms of development during its life cycle; where the animal came from in terms of its evolutionary antecedents; and how the animal works during its post- developmental life, that is, how it executes its reversible physiological responses to the environment it lives in, aside from the innumerable organ specific functions with which it was endowed in the later stages of its development. All three, development, evolution, and physiological response are causally all the output of genomic sequence. All three depend directly on regulatory deployment of continuous gene expression, and underlying all three classes of process are genomically encoded networks of regulatory gene interactions.

I shall discuss mainly development and evolution here, but begin with two examples of gene regulatory networks (GRNs) that control reversible physiological processes. One of these controls responses of certain innate immune cells to pathological challenge; the other healing of integumentary wounds.

Development is directly a process in which spatial regulatory states are formulated which determine gene expression at every time and at every place in the organism. This fundamental function is organized by species specific, genomically encoded GRNs, which consist of regulatory genes that make the spatial regulatory states, and their interactions. As I shall show by example, we now can prove that, if complete, GRNs per se can suffice to explain the developmental process of embryogenesis, both directly and indirectly.

Evolution of the animal body plan means evolution of the GRNs controlling animal development, since change in developmental GRNs is what causes change in the body plan. Thus evolution can be regarded as the deep time derivative of encoded GRN structure. Since the dawn of the Cambrian, animal lineages have

undergone large evolutionary changes and we can now begin to understand how this happened by considering the process through the lens of GRN structure.

It is necessary to think carefully to distinguish what is directly controlled by the regulatory genome from what is downstream apparatus or is not genetically specified. We must carefully note what is biochemical machinery deployed in response to genomic regulatory events; recognize those typically late developmental events which are left to stochastic processes; and be aware of those features of the organism in which the hardwired template with which it is developmentally endowed is modified for a given organism by the events of its life. From the point of view of the basic processes of animal biology, however, the essential control functions are genomically encoded; these are the functions which determine which way the process will go, and qualitatively how it will come out.