“THE GENETIC TOOL-KIT”: THE LIFE-HISTORY OF AN IMPORTANT METAPHOR

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INTRODUCTION

The expression “the genetic tool-kit” denotes a central idea in evolutionary developmental biology: that there is a relatively small set of key regulatory genes for conserved developmental patterning functions—for tissues, organs, and body axial patterning—throughout the diverse phyla of bilaterally symmetrical animals, despite the tremendous morphological and developmental differences among those phyla. These genes comprise the basic “tools,” denoted by the term, that are essential for the developmental construction of these animals. This chapter will attempt to describe the historical background, genesis, significance—and limitations—of the term. Yet, before launching into the topic itself, it might be helpful to begin with a look at how new terms, in general, first promote and enlarge understanding and then, with time, often come to constrain it.

We understand things only in relationship to other things, whether objects or ideas. Though preverbal infants undoubtedly have some mental capacity for making comparisons, language is essential for making clear such conceptual linkages. The two essential linguistic forms for doing so are similes (“X is like Y”) and metaphors (“X is a Y”). Both are indispensable instruments (itself a metaphor) for making sense of the world but, in general, metaphors are more powerful, hence more effective than similes. Every simile raises an implicit question about the degree of resemblance (“How much is X really like Y?”), hence raising a doubt about its aptness while, in
"THE GENETIC TOOL-KIT": THE LIFE-HISTORY OF AN IMPORTANT METAPHOR

contrast, metaphors stress the essential identity between the term of the metaphor and the object/process to which it refers. A good metaphor captures something fundamental and thereby sharpens understanding. This is as true of metaphors used in science as those employed in ordinary speech. Within evolutionary biology, in particular, metaphors have been a particularly important aid in understanding. Indeed, the field was built upon a metaphor, one coined by Charles Darwin, that of “natural selection.” Though it was based on a simile to artificial (human-directed) selection as practiced by the plant and animal breeders, it is a metaphor. Evolutionary biology is, in fact, rife with metaphors. Some examples are “evolutionary tinkering,” “the selfish gene,” “the adaptive landscape,” “phylogenetic trees,” “genetic drift,” “inbreeding depression,” “hybrid vigor,” “life history studies,” “developmental plasticity,” “canalization,” “evolutionary entropy.”

Within evolutionary developmental biology specifically, there has been no metaphor more important than the genetic tool-kit. It captures the essence of the phenomenon that launched the contemporary field. It was based on the discovery that there is a rather limited set of regulator genes that play conserved functional roles in organizing the “body plans” (another metaphor) of the bilaterian animal phyla (the bilaterally symmetric animals which comprise the great majority of animal species). Though coined relatively late, with respect to the findings it sums up, the term crystallized understanding of the phenomenon it denotes.

In the first part of this article, the history and importance of this concept, and the origins of its designating term, will be set out. I will then discuss why a continued focus on the concept and use of the term may retard the further maturation of evolutionary developmental biology. Such a history of rise-and-fall of the usefulness of an expression is not atypical for metaphors in science. At first, they can be invaluable aids to understanding but, with repeated use, they inevitably lose their freshness and as new findings appear, they begin to seem less apt. The long-standing characterization of clichés, that “a cliché is a dead metaphor,” sums up this trajectory.

HISTORICAL BACKGROUND TO THE TERM

Though the expression “the genetic tool-kit” did not achieve currency until the late 1990s, it had a century-old antecedent in a prior idea. This is the concept that, in animal development and evolution, “some genes are more important than others.” That was, in essence, if not in those words (the word “gene” had not yet been coined), the key implication of a classic work, published in 1894, titled *Materials for the Study of Variation, Treated with Especial Regard to the Discontinuity in the Origin of Species*. The author was William Bateson (Figure 1.1), who would later give the science of genetics its name and who was one of its foremost practitioners in the first decades of the 20th century. The thesis of Bateson’s book was that it is hereditary variations of major observable phenotypic effect that are the source material for evolutionary change (Bateson 1894). It was thus a direct challenge to Darwin’s belief that all evolution proceeds via the accumulation of variations of small effect, as the subtitle itself rather aggressively suggests. As pointed out by Gould (1992), Darwin’s view had been, in a sense, a democratic one: it implicitly assigned equal potential importance to all genes affecting morphology in the evolution of traits and to all mutations that create changes of small phenotypic effect in those genes. Bateson intended to refute that idea by placing known mutations of major phenotypic effect at the center of evolutionary thought.
Central to the evidence he marshaled was the existence of what we now term “homeotic mutants,” those mutants that cause the development of one body part in a new location, replacing another body part, such as the mutants found in a number of insects that replace part or all of an antenna with a leg. Bateson named the phenomenon “homeosis,” but the expression “homeotic mutant” would come much later. To both Darwin and his 20th-century intellectual descendants who created NeoDarwinian evolutionary theory (reviewed in Mayr and Provine 1980; Wilkins 2008), the view championed by Bateson was anathema. They regarded such mutations as “sports,” that is freaks, that would inevitably quickly die out in a state of Nature, leaving no descendants, and which, therefore, could not have any evolutionary impact.

Although thus downgraded by most 20th-century evolutionary biologists, homeotic mutations continued to exert a fascination for a small group of geneticists interested in both developmental mechanisms and evolution. Among these, none was more important than Edward (“Ed”) B. Lewis (Figure 1.2), who worked on a group of homeotic mutations in Drosophila that transformed different segments of the thorax and abdomen of the fly into phenotypic facsimiles of other segments. A feature that particularly intrigued Lewis was that these mutations were all closely linked within one small region of the fruit fly’s third chromosome. Naming this cluster of genes for the prototypic, original mutation—which partially transformed the metathorax into a second mesothorax, creating a double-mesothorax fly—Lewis called it “the bithorax complex” (Lewis 1964, 1978). Though the importance of Lewis’ work was, by the late 1970s, universally recognized for its significance within developmental genetics, it is of historical interest that he began this work in the 1940s to solve an evolutionary (not a developmental) question: do new genes arise by duplication of old ones with one of the duplicates taking on a new function? (see Lewis 1996). This idea had been suggested by Calvin Bridges, based on his finding of duplicate bands in Drosophila salivary gland chromosomes (Bridges 1935). It had, however, been previously suggested, as a purely theoretical speculation, by J. B. S Haldane (1932) in his book, The Causes of Evolution, while its full significance would only become apparent in the 1970s, with Susumo Ohno’s book, Evolution by Gene Duplication (Ohno, 1970).
Fittingly, given their historical importance, it was genes of the bithorax complex that provided the initial evidence in support of the existence of genes of special general importance for animal “body plans” and which provided the first observations that laid the foundations for the concept of the “genetic tool-kit.”

**FROM “HOMEOTIC GENES” (AND “HOMEOBOXES”) TO THE GENERAL IDEA OF KEY REGULATORY GENES WITH CONSERVED DEVELOPMENTAL FUNCTIONS**

The experimental breakthrough from Lewis’ more abstract and generic ideas about developmental control to the beginnings of modern evolutionary developmental biology was provided by the cloning of the genes of the bithorax complex (Bender et al. 1983). The sequence analysis of these genes, along with those of the so-called Antennapedia complex (Laughan and Scott 1984; McGinniss et al. 1984), led to the realization that while the homeotic genes of both these *Drosophila* gene clusters—which were soon recognized as split parts of an original single gene complex—were no longer directly recognizable duplicates of one another, they shared a 180 bp coding region homologous to DNA binding regions of certain prokaryotic regulator genes, evidence of ancient gene duplication events, as predicted by Lewis. The genes were named Hox genes, and their encoded 60 amino acid polypeptides were termed “homeodomains.” Most homeobox sequences between different Hox genes themselves differ, and some of the sequence differences were soon shown to have major functional significance, but the homeobox family of sequences clearly marked a set of genes that had special importance for development in *Drosophila*. Indeed, the homeobox, as revealed in these first discoveries, was hailed in one commentary as a potential “Rosetta Stone” of biological development (Slack 1984), a special sequence that would help decode the complex “language” of DNA instructions underlying development.
Such hopes were both encouraged and dampened by the discovery that homeobox sequences were not peculiar to *Drosophila* but were found in abundance in other animals, by means of so-called “zoo blots” which detected them by means of DNA homology (McGinniss et al. 1984). The fact that they were numerous and probably universally used in the development of complex animals encouraged the view that these genes were of general and widespread significance. Yet, their sheer abundance within genomes and the fact that many were associated with genes whose expression pattern indicated no relationship to the phenomena of segment identity or segment specification, the functions originally associated with the genes of the Hox complex(es), reduced the chances that the homeobox-containing genes would provide some kind of Rosetta Stone for development. What remained was the original realization that genes containing the homeobox were all involved in development and that they specified positive regulators of gene transcription.

**THE GENETIC TOOL-KIT: THE SEMINAL FINDINGS THAT LED TO ITS COINAGE AND THE KEY IDEA**

It was, however, two reports on Hox genes in 1989, from two separate labs (Duboule and Dolle 1989; Graham et al. 1989), that regalvanized the whole field of homeobox gene research and which provided the cornerstone of the idea of the “genetic tool-kit.” These papers reported that not only did mice possess Hox genes homologous to those of the fruit fly but, as in the fruit fly, these existed as clusters of such genes, in fact four such clusters in the genome, compared to *Drosophila*’s single (though split) cluster. Furthermore, there was a clear relationship between the mammalian Hox gene clusters and those of *Drosophila*, in terms of both the order of the homologous genes along the chromosome and the respective regions of the embryos of the two animals in which they were expressed.

Thus, for example, the most anteriorly expressed genes of the Antennapedia complex in the fruit fly had matching homologues in the most anteriorly expressed genes of the four Hox gene clusters in the mouse.

These findings could hardly have been more exciting or surprising. They indicated that beneath the dramatic surface differences of development exhibited by an insect and a mammal, the two animals shared some underlying form of genetic specification of the antero-posterior (a-p) body axis. Nor were the similarities of Hox clusters in fruit fly and mouse some kind of fluke or amazing coincidence: within five years or so, Hox gene clusters with the same general features, were found throughout the bilaterian animal phyla. The findings blew apart the conventional wisdom of preceding decades, that different morphologies of structures of comparable function between different animal groups must reflect comparable differences in their genetic specification (Mayr 1963; Salvini-Plawen and Mayr 1977).

These discoveries, from the labs of Krumlauf and Duboule, set off a gold rush in many laboratories to see if other important regulator genes first identified in one organism, usually *Drosophila*, might have similar expression patterns in other, often quite different, animals. Such resemblances, if found, would provide preliminary indications of similar roles in both invertebrate animals and the far more complex vertebrates. The prospectors were not disappointed: gold was soon struck.

Within the space of half a dozen years, a panoply of genes identified in *Drosophila* as essential for the development of various specific organs and tissues in the fruit fly, and
all encoding transcription factors, were discovered to be expressed in the developing rudiments of the comparable organs and tissues of mammals. For instance, to take the most famous example, a gene (Pax6) crucial for eye formation in Drosophila, which was first identified by Thomas Hunt Morgan and his colleagues in the 1920s, as the gene eyeless, is required comparably for mouse and human eye development. Or, to take a second example, the fruit fly gene tinman, required for mesoderm and specifically heart development, was found to be represented by a small family of homologous genes in vertebrates which are similarly required for mesoderm and heart development. Furthermore, these genes were not only expressed in comparable organ sites but, as shown by knockout mutations in mice, found to be required for development of the respective murine organs and tissues. Other genetic findings involved replacement of Drosophila genes by their mouse homologues, with the discovery of retained developmental function. Still other findings involved overexpression of particular key regulator genes with the resulting production of small versions of the respective organs that they controlled. The most dramatic of these involved the ectopic production of eyes in Drosophila following overexpression of the mouse version of the Pax6 gene (Halder et al. 1995). The ensemble of findings of conserved gene functions for development throughout the bilateria have been reviewed in Carroll et al. (2001) and Wilkins (2002).

It was not, however, just transcription factors and their roles that were found to be conserved. All the major signal transduction families were found to be similarly conserved across the bilateria, and often their roles in particular developmental processes were similarly conserved. These included the Wnt, Fgf, Bmp, and Shh signaling pathways. Some of these uses might involve convergent gene/module recruitment processes, but for the most part, it appears that there has been true conservation of these usages, or “deep homology” to use the phrase of Shubin et al. (1997).

The evolutionary implications were both clear and startling: this shared genetic machinery must go back to the ancestor of all bilaterian animals, dubbed the “Urbilatertian,” which must have lived before the start of the Cambrian period (based on the discovery of a few such in the late Proterozoic), more than 540 million years ago. Evidently, their essential roles had been retained even as the organs and tissues that they helped specify evolved, often dramatically, into very different forms. Thus, beneath the tremendous visible phenotypic diversity of animals lay a previously wholly unexpected set of shared genetic “instructions.”

It is this idea that is encapsulated in the term “the genetic tool-kit,” referring specifically to the genes required for the development of bilaterian animal forms. (There had been several earlier usages of this term but in different contexts and with different referents.) Interestingly, however, it is not clear who coined the term. I have asked several major figures in the field and no one seems to know who used the term first. One of the earliest published uses of the term, though simply stated, as if self-explanatory, is in Knoll and Carroll (1999). In that same year, Michael Akam was using the term in his lectures at the University of Cambridge (M. Akam, pers. comm.). Furthermore, in subsequent published papers, the term is almost always used without explanation or careful definition, as if it needs no such clarification. It seems probable that the publication that gave the term its real currency was the book by Sean Carroll (Figure 1.3) and two colleagues, From DNA to Diversity: Molecular Genetics and the Evolution of Animal Design (2001).

It is also interesting that no one has tried to put a number to the components of the genetic tool-kit. But if one adds up all the conserved transcription factor and signal transduction genes, one is probably looking at a set of a few hundred genes, perhaps no more
than 200–300, not counting paralogues, and perhaps considerably less, yet whatever the precise number, this set is clearly only a small fraction of the total number of genes in animal genomes, which range, roughly, from 12,000 to 25,000. (That range of gene numbers seems small in comparison to earlier estimates (Fields et al. 1994), but the estimated sum of “tool-kit” genes remains a small part of the total.)

In effect, it appears that the idea was so well established by the late 1990s that the function of the term seems to have been to crystallize the concept rather than initiate a new way of thinking. In this, it differs from other comparable metaphors, whose origination helped give clear definition to the respective ideas designated. Phrases such as “the adaptive landscape,” “the selfish gene,” “the genetic program” are all in the latter category. Yet, the genetic tool-kit (for animal development) provided a wonderful shorthand description for what was, and remains, the most surprising phenomenon in the field of evolutionary developmental biology and, indeed, one of the most unexpected in 20th-century evolutionary biology as a whole.

In using the term, it should be noted that elements of the tool-kit need not be single genes. They can be small groups of conserved interacting genes. Such co-operating tool-kit elements were termed, tongue-in-cheek, a “junta” by Claude Desplan (Desplan 1997), in deliberate contrast to the earlier concept of (single) “master genes” (Halder et al. 1995), the latter presumably individually governing a particular developmental process. The need to move away from the master gene concept became evident with discoveries that it is not $Pax6$ alone that governs eye development but a group of interacting genes of which $Pax6$ is but one (reviewed in Pappu and Mardon, 2004 and Treisman 1999). Formulations preferable to junta, for such conserved interacting cohorts of genes, are “module” or “kernel”
(Davidson 2006). Such interacting gene groups can themselves be co-opted in evolution for other developmental processes. Thus, for instance, the eye development kernel, though using different paralogues, is used in vertebrate muscle (Kardon et al. 2002). It is not clear, however, which biological usage came first.

THE GENETIC TOOL-KIT AS A NON-ANSWER TO THE QUESTION OF EVOLUTIONARY DIVERSIFICATION WITHIN THE ANIMAL KINGDOM

Though the word “evolution” immediately connotes orderly, though not necessarily “gradual,” change, biological evolution is as much about what is retained (conserved) as that which changes with time. Without a large measure of hereditary and evolutionary stability/conservation, one would not have evolution, only chaos. Since evolutionary biology revolves around these two properties of change and continuity, correspondingly, nearly every one of its terms refers directly or implicitly to either stability-conservation or change, whether of genes or gene networks, phenotypic properties or species.

The genetic tool-kit is intrinsically about what has been retained in animal evolution among the bilaterian animal phyla, all descendants of the presumptive “Urbilaterial,” in more than 520 million years of animal evolution and diversification (Carroll et al. 2001; De Robertis 2008). Yet, the singular fact about animal evolution is that there has been a huge diversification of animal forms since the Cambrian period. That diversification transformed the world of living things, and along with the evolution and diversification of plant forms, correspondingly transformed the look and the chemistry of the land surfaces of the planet itself and of the oceans. Furthermore, there must have been substantial diversification of animal forms during the key 10–20 million years of the so-called Cambrian explosion, when most of the animal phyla either originated or expanded substantially from earlier pre-Cambrian beginnings. Correspondingly, at the genetic level, something must have been changing and evolving in these different animal lineages, even as the genetic tool-kit was being retained and employed in the specification of very different bilaterian body plans.

The concept of the genetic tool-kit is completely silent on both what that something is and how those changes came about. Indeed, a heavy emphasis on the genetic tool-kit as the central discovery in the field of “evo-devo,” as seen in some publications, implicitly tends to reduce the nature of those changes to matters of “variation” on basic themes, whose explanation can be addressed in the form of a general cataloging of the different kinds of genetic change that could have contributed to post-urbilaterial evolution (e.g., De Robertis 2008). Yet, to relegate—however unintentionally—the greatest part of animal evolution, including the origination of the major phyla to the status of an epiphenomenon that postdates the assembly of the genetic tool-kit, must be a mistake. A more productive stance involves moving on from the concept of the genetic tool-kit to understanding how the genetic foundations underlying animal development have evolved while retaining the elements of the genetic tool-kit.

As Knoll and Carroll (1999) pointed out, in the same article in which (perhaps) the term was used in print for the first time, the situation must involve the evolution of the genetic networks within which the elements of the tool-kit are embedded. In effect, the elements of the genetic tool-kit need to be seen as parts of larger genetic regulatory networks or GRNs (Davidson 2001). A simple way to put this is that the evolution of different genetic architectures involves the “rewiring” of GRNs (Davidson 2001; Peter and David-
son 2011; Wilkins 2002, 2005, 2007a, 2007b), and that for major changes in development, this involves new connections between elements of the genetic tool-kit with genes upstream or downstream of them. Nevertheless, such reconfiguring of GRNs for different organs or tissues, in diverging evolution, must leave the essential elements of the genetic tool-kit in place. How is this combination of change and conservation within GRNs achieved?

THINKING ABOUT HOW GRNS ARE “REWIRED”: TWO APPROACHES

There have been two major approaches to understanding how the genetic networks that underlie development have evolved. The first stresses the way that whole chunks of already-evolved GRNs, so-called modules, can be brought into play via new genetic linkages, to create new composite GRNs that, in turn, possess new developmental properties (Davidson 2001, 2006; Davidson and Erwin 2006; Wilkins 2007b; Peter and Davidson 2011). The second emphasizes the molecular-genetic events and selective processes that create individual new gene regulatory linkages; these include the steps that create the modules or extend and modify existing genetic pathways within these modules (Gehring and Ikeo 1999; Pomiankowski et al. 2004; Wilkins 1995, 2007a). These two ways of looking at the evolution of genetic networks are neither competitive nor mutually exclusive but, by emphasizing different aspects, have different kinds of relevance for thinking about the genetic tool-kit. The first approach, which we may term the “module-centric” perspective, largely takes the elements of the genetic tool-kit as preexisting givens and has had little to say about either how the tool-kit elements initially acquired their roles or how linkages within tool-kit modules evolved. One of the few treatments of such questions from this school is Davidson’s discussion of how regulatory genes, including members of the genetic tool-kit, may capture or lose new downstream, differentiation genes, creating different “batteries” of such genes under single regulatory gene control (Davidson 2001, p. 191). The module-centric school has, however, made one large claim about the nature of the new linkages underlying developmental evolution: that they involve, overwhelmingly, mutations in cis-regulatory elements of regulatory changes (Akam 1998; Carroll 2005; Davidson 2001; Peter and Davidson 2011; Stern 2000; Stern and Orgogozo 2008; Wray et al. 2003). Despite its repeated and vigorous assertion, this claim is controversial to say the least, with there being many good arguments against it (Alonso and Wilkins 2005; Hoekstra and Coyne 2008; Wagner and Lynch 2008). In particular, the evolution of different gene families, each specifying groups of related proteins, has, without question, contributed to organismal evolution generally and developmental evolution specifically. This issue, namely the kinds of mutations involved in GRN alteration is, however, ancillary to the subject of the genetic tool-kit, the focus of this chapter.

The second approach to genetic network evolution, which might be termed the “linkage-centric” perspective, stresses the processes and the kinds of selective pressures that first initiate and expand genetic pathways and modules, step-by-step, gene-by-gene. It has principally employed the evolution of sex determination pathways as a model of how genetic regulatory structures evolve and expand, as a result of selective pressures (Pomiankowski et al. 2004; Wilkins 1995, 2002). A key conclusion of this analytical work is that the evolution of both pathways and networks is from the bottom-up, so-called “retrograde addition.” Yet, clearly, retrograde addition cannot be the whole story of
pathway and network growth: there is much circumstantial evidence for the insertion of new regulatory elements within pathways (and networks), a process that has been dubbed “intercalary addition” (Gehring and Ikeo 1999). The processes by which such insertion takes place to create new functional linkages, however, remain mysterious. In particular, it is unclear whether intercalary addition can happen in single steps—which seems unlikely—or involves sequential steps. This matter has received remarkably little theoretical or experimental attention, with respect to either the molecular processes or the evolutionary-selective pressures that would be involved.

Yet, somewhere within such processes must lie the answer to the question of how the elements of the genetic tool-kit have remained in place while the developmental processes which they help to regulate have evolved and diversified so greatly. The longest extended discussion of this problem, to date, can be found in Wilkins (2002, pp. 161–169). It was couched in general terms and followed the predominant thinking of the times, focusing on evolution via changes in cis-regulatory elements. Furthermore, it was formulated in terms of single regulatory genes. It would, however, apply to small groups of interacting elements of the tool-kit, modules or kernels.

The argument is straightforward. One can readily imagine, for instance, how individual genes downstream of either particular tool-kit genes or tool-kit modules, in particular differentiation genes, can be added or subtracted by mutation and then put to the test of selection. (The argument of Eric Davidson, mentioned earlier, about the growth of batteries of differentiation genes under a key transcription factor’s control concerns just that process.) Similarly, mutations in genes upstream of the tool-kit elements might alter the timing or placement of activation of those elements (and everything downstream of them). A lot of developmental evolution involves just such alteration of timing and spatial deployment. Although many such mutations would be lethal, some fraction would be viable and could lead to developmental alteration and consequent evolution within a population. In contrast, mutations that eliminate or greatly affect the central element(s) (i.e., the members of the genetic tool-kit) would be expected to have highly deleterious, and often lethal, effects. Hence, there should be continual, strong, selective pressure to maintain those key central, coordinating genetic control elements, even as the cast of genes they control downstream may be changing during evolution, or their upstream controls—regulating when and where they are activated—are altered.

This argument was made 10 years ago and should be “revisited.” It needs to be revised beyond the framework of evolution-by-cis regulatory control mutations and in the light of new facts generally. It is, for example, now clear that within a tool-kit module, there can be alterations of both module membership and patterns of interaction among the elements. An instance involves the two somewhat different regulatory modules controlling determination of the eye development field in Drosophila and in the beetle, Tribolium (Yang et al. 2009a, 2009b) (Figure 1.4). Presumably both are derived from an ancestral module, one that was probably closer to the present-day Tribolium module than that of Drosophila, but the key point is that such evolution of linkages between “tool-kit” genes can take place without destroying developmental function.

Hence the central argument, earlier, that mutational alteration of the tool-kit elements or their connections would tend to be lethal needs modification. That selection pressure probably explains the relative stability and conservation of core genetic tool-kit roles, but it is not an absolute constraint. The phenomenon of “intercalary addition,” though still mysterious as to mechanism, almost certainly plays a part in such changes. Clearly, this phenomenon of changing interactions among core tool-kit members needs reexamination, both theoretically and experimentally.
CONCLUSIONS

The term the genetic tool-kit sums up a crucial fact that, initially, was regarded with astonishment: the existence of conserved developmental functions by key genes throughout all the bilaterian animal phyla. More than a decade old, it was coined well after the phenomenon it described had come to light. In so doing, it helped sharpen and solidify that understanding and constituted a real advance for the field.

The term, however, always carried a connotation that the genes of the tool-kit are the essential elements for constructing the bodies of animals, via the processes of development. In reality, they only play a part, however central that part is. The actual development of each kind of animal requires most of the genes in the genome, if one excludes the genes used exclusively for purely cellular functions, such as metabolism and the cell cycle. Even those latter functions, however, are essential for the creation of cells, and without cells, there is no development. Thus, it is not stretching things too far, to say that the real genetic tool-kit is essentially (close to) the entire set of genes in the genome. But, looked at that way, the term completely loses its usefulness. The genetic tool-kit, as the term is normally employed, refers to what might be called the core genetic functions of animal development. It is the nature of the relationships between those core genes and the rest of the genome, both in the functional interactions deployed and in the evolution of those functional relationships, that pose crucial questions for the field today.

One of these concerns how the members of the tool-kit came to occupy the place that they do. The only point that is really clear is that these genes evolved from closely related
genes present in prebilaterian early animals, perhaps cnidarian or cnidarian-like animals; these tool-kit precursor genes included both transcription factor genes (Plaza et al. 2003; Thomas-Chollier et al. 2010) and cell-signaling and cell-adhesion factor genes (Nichols et al. 2006). The crucial point of this observation is that the developmental functions of those ancestral genes must have been different in nonbilaterian ancestors. Despite some early perceptive comments on this issue (Davidson 2001; Scott 1994), this question, pertaining to events that occurred more than half a billion years ago, is clearly not amenable to definitive resolution. It should, however, receive more attention than it does. It is entirely conceivable that experimental simulation of the generation of new regulatory linkages could help illuminate this phenomenon. That question, in turn, raises the more general one of how the evolution of and diversification of GRNs around—both upstream and downstream of—the elements of the genetic tool-kit takes place, discussed earlier. In effect, the ways in which genetic networks underlying development evolve remain a major question, perhaps the major question at the level of genes and genomes, for evolutionary developmental biology.

I will end by returning to the general comments on metaphors and their usages with which this chapter began. The term the genetic tool-kit provides a good illustration of the history of successful metaphors in science: the process is not unlike that of organisms, involving birth, growth and maturation, then decline. When first coined, a good metaphor illuminates matters quickly and efficiently, like the switching on of a light in a dark room. But with time and frequent usage, its illuminating power dims somewhat. Part of that dimming involves the fact that the metaphor seems less apt, as new findings appear, complicating the picture. In the end, metaphors in science usually outlive their usefulness, with their final function being to highlight what they leave unexplained. A good metaphor, toward the end of its useful life, is rather like Moses at the end of his: it points the way toward a promised land of new questions, but it will not itself contribute to answering those questions.

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