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To solve old problems, study new research organisms

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The ability of animals to restore missing body parts has been a source of human fascination for millennia (Aristotle, 350 BC). We are amazed without fail when we witness such occurrences, as evidenced by how much has been written about regeneration by generations of biologists including Spallanzani (1768), Trembley (Lenhoff and Lenhoff, 1986), Haeckel (1869), Darwin (1844, 1936), Weissman (1893), Morgan (1901) and many other researchers in the 20th and 21st century (Maienschein, 2011). That many animals can regenerate arms, heads and organs is hardly a secret (Sánchez Alvarado and Tsonis, 2006). Yet, given such persistent interest, why is it that regeneration remains today as one of the last wild frontiers in Developmental Biology?

From the vantage point of our 21st century biological laboratories, we have seen many mysteries of life illuminated by understanding. We get the sense that after many centuries of biological research, we are making inroads into understanding some of the most fundamental principles of Life. Our collective optimism is reflected by the growth of biotechnology across the world striving to use scientific knowledge to cure human diseases. In fact, utter dismay that our own biology does not conform to our preferences drives much of biomedical research today: cancer, aging, and degeneration are but a few of the undesirables we wish to tame. Our strategy thus far, has been to focus on a handful of animal species that have yielded compliantly to their laboratory domestication: fruitflies, nematodes, frogs, zebrafish, chickens, mice, rats and, in a sense, humans as well. If one assumes the existence of ~9 million different species on our planet (Mora et al., 2011), then we have selected 0.00009% of these to invest the brunt of our research effort. Given the syncopated rhythm of evolution, and the complex and contingent histories that have shaped the biological attributes of each and every one of the species on our planet, the likelihood that the study of basically seven species will uncover all of the principles necessary to understand the underpinnings of Life is essentially zero.

Consider for example that as recently as 2012, we in the USA spent ~$840 billion in care for major diseases like Alzheimer's, cancer, hypertension, diabetes, obesity, heart disease, stroke and Parkinson's disease, but only ~$10 billion (or 1.2%) to study the fundamental basis of these diseases (Research!America, 2012). Also, consider that fundamental, curiosity-driven research has been, is and will continue to be the fountainhead of innovation and that the brunt of its funding in the US has -for the past 55 years- come from the National Institute of General Medical Sciences (NIGMS). Since its establishment in 1962, the NIGMS has supported the Nobel Prize winning work of 83 Nobelists. In 2016, the NIGMS funded 3987 research project grants at ~$391,000 each or ~$1.6 billion (NIGMS, 2016). At first blush, this figure sounds respectable, until one considers that people in the United States spent $2.5 Billion dollars on Halloween candy alone (NRF, 2016), *i.e.*, almost a billion more than the entire national budget aimed at spurring fundamental, life-changing and industry-birthing biomedical innovation. The relatively insignificant spending for investment (*i.e.*, fundamental research) compared to the vast amounts spent for consumption (*i.e.*, cost of disease care), and the present pressure on biologists to specialize and produce practical outcomes combine to restrict our way of interrogating Life to unacceptably narrow confines and unsatisfactory depths. We are measuring an astonishingly limited range of life with very limited resources, hoping that those numbers can save all of our lives.

And though there may be other reasons, I suspect that the time it has taken for regenerative biology to occupy its proper place at the table of biomedical research has been due to the fact that its flagship organisms (Fig. 1) have neither received much attention by the broad community, nor received funding comparable to that received by the workhorses of biomedical research (*e.g.*, mice, chicken, frogs, fruitflies, nematodes). These animals are usually referred to as “non-model organisms” or “emerging model organisms” or some other similar name, as if only some animals can be models. This is, of course, wrong because in biology all animals model some aspect of Life in all of its manifestations, the central subject of our discipline. By focusing on a few, essentially randomly selected organisms, biology and developmental biology have both become highly specialized endeavors promising mechanistic understanding to some of the most difficult questions in biomedical research today. And yet, we still find ourselves facing the same array of difficult problems as before, along with many new challenges. Our specialization may have begun to impede our progress at best, and at worst, to lead us astray.

The time has come to dispose of the terms “model” and “non-model” systems and adopt instead the more accurate term “research organism”. Our remarkable advances in genome editing, imaging, bioinformatics, high throughput assays and automation demands it. Adopting the term research organism allows us to bring our technological armamentarium to explore the wealth of Life on Earth and expand the boundaries of biological knowledge in the decades ahead. Organisms and entire ecosystems previously inaccessible to effective interrogation are no longer so, and

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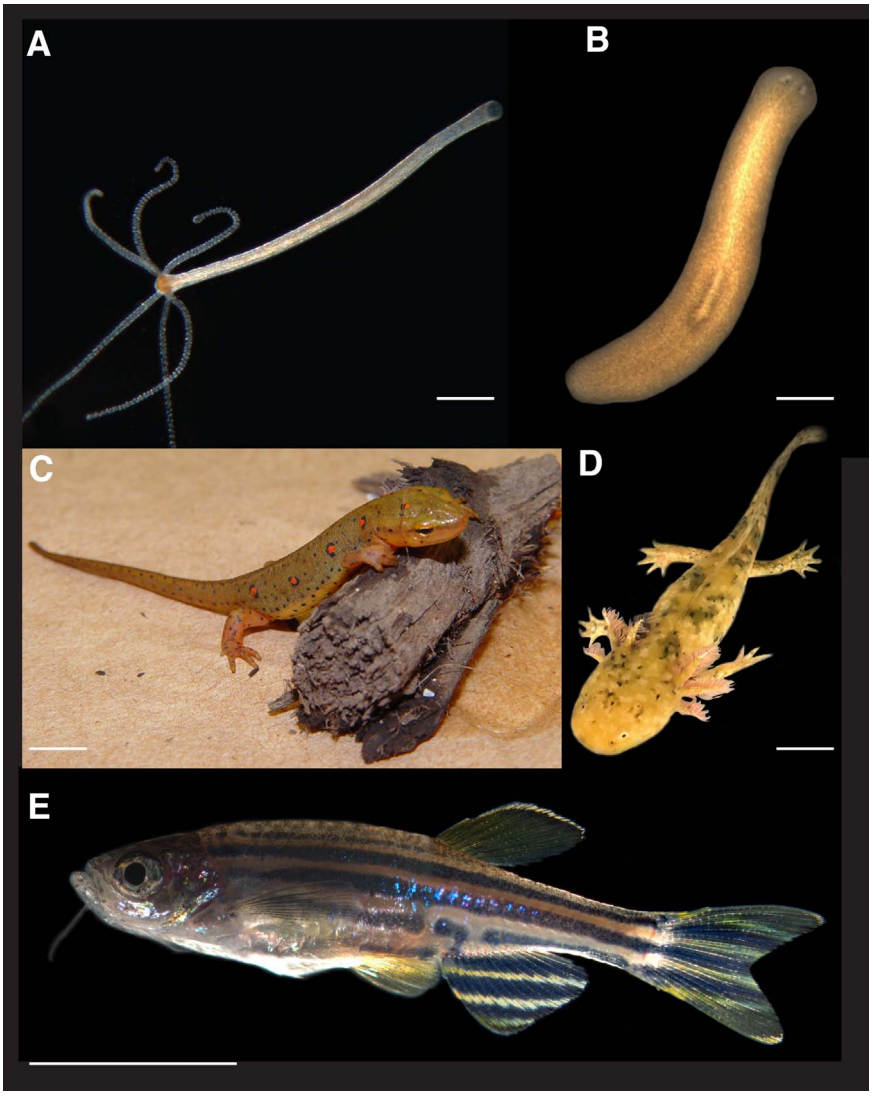

Fig. 1. Examples of commonly studied regeneration research organisms. A. *Hydra vulgaris*. Scale bar: 1 mm. B. The planarian *Schmidtea mediterranea*. Scale bar: 2 mm. C. The newt *Notophthalmus viridescens*. Scale Bar: 2 cm. Modified from (Sánchez Alvarado and Tsonis, 2006) Photograph by Panagiotis Tsonis. D. The neotenous salamander *Ambystoma mexicanum* or Axolotl. Scale bar: 2 cm. E. The teleost zebrafish *Danio rerio*. Scale bar: 2 cm. Except where noted all other photographs by the author.

the organisms inhabiting these, as of yet unexplored continents of knowledge may hold answers to some of the most vexing questions in biology. Because of the remarkable diversity of research organisms being used to unravel the secrets of regeneration (Figs. 1 and 2), I anticipate that regenerative biology will lead the charge in the discovery of new biology and thus expand our knowledge and understanding of biological properties to levels barely imagined today. The questions, findings and diverse array of organisms represented in this current issue of *Developmental Biology* are an example of the biology we all need to decipher and thoroughly comprehend. It is by studying a much broader representation of research organisms that we increase our chances of uncovering what is already possible in biology. It is such efforts that will ultimately help us better understand the successful biological experiments already carried out by Nature for millions of years. The study of new species and the mechanistic dissection of their respective biological properties is indispensable if we want to transform our limited understanding of Life and radically change the way in which biomedical research is currently practiced. Our next conceptual leap in biological research, therefore, will most likely come from those places where fundamental, curiosity-driven, discovery research is celebrated, supported and rigorously practiced, and many of those places are looking to regenerating organisms for such answers.