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Regeneration: From cells to tissues to organisms

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The remarkable ability of some animals to replace body parts following injury has captured the imagination of humans for millennia, and has attracted scientists to explore regeneration phenomena for centuries (Dinsmore, 1991; Goss, 1969). Technological and interdisciplinary approaches have morphed regeneration science into a formidable collaborative effort aimed at understanding how cell-based strategies can be used to restore damaged or diseased tissues and organs (Stocum, 2001). The idea for a Special Issue on regeneration was conceived following a satellite symposium held at the 75th Annual Meeting of the Society for Developmental Biology in Boston, MA, titled: “Evolution of regenerative abilities: recapitulation of development or novel mechanisms?” The symposium brought together prominent senior scientists and new investigators in the field of regenerative biology, who highlighted how broad application of new transgenic technologies and the accessibility of comparative genomics are opening frontiers in stem cell and regenerative biology research using classic and emerging models (Chen and Poss, 2017; Sánchez Alvarado and Tsonis, 2006). Much of the discussion centered on how the study of regeneration, at its core, shares fundamental similarities with the goal of understanding the basic principles underlying organismal development (e.g., cell differentiation, morphogenesis, and tissue patterning) (Brockes and Kumar, 2008; King and Newmark, 2012; Tanaka and Reddien, 2011). However, unraveling the molecular differences that confer regenerative abilities in post-embryonic organisms, such as scarless wounding, adult stem cell regulation in vivo, and the formation of the regeneration blastema, continues to attract the collective efforts of the regeneration community.

The reviews and research articles in this issue tackle topics on the evolution and divergence of regenerative abilities. For example, *Erickson* and *Echeverri* discuss lessons learned on the molecular logic underlying scarless wound healing, an ability that is a crucial step in regenerative organisms (Erickson and Echeverri, 2018). Moreover, *Seifert* and *Muneoka* assess the parallels between the formation of a blastema in classical regeneration organisms like the axolotl versus recent mammalian models like the lab mouse digit tip and the African Spiny mouse ear regeneration model (Seifert and Muneoka, 2018). In contrast to vertebrates, invertebrates can display a prodigious capacity for whole-animal regeneration that is highly variable even amongst members of the same phylum, such as annelids or planarians; the review by *Lai* and *Aboobaker* discusses emergent concepts on the evolution of stem cell-based regeneration within invertebrates. Of course, a major driver of regeneration research is understanding why humans have such a limited regenerative capacity (Tanaka, 2003). In

their review, *Baghdadi* and *Tajbakhsh* discuss the evolution of skeletal muscle regeneration (Baghdadi and Tajbakhsh, 2018). The articles by *Llonch, Carido* and *Ader*, and *Lee* and *Rawlins*, provide insights into why humans fail to regenerate retinal tissue, or the lung, respectively; these reviews also offer an overview of how regenerative medicine research is making inroads into developing novel therapies, often based on understanding key principles of how these organs develop and how stem cells can be controlled to divide and differentiate without adverse effects (Llonch, Carido and Ader, 2018, Lee and Rawlins, 2018). The remaining reviews focus on the involvement of biophysical mechanisms in regenerative processes: *McLaughlin* and *Levin* discuss emerging concepts on the role of ionic mechanisms associated with tissue growth, and *Chiou* and *Collins* cover how the mechanical environment influences cell differentiation and morphogenesis in animal regeneration (McLaughlin and Levin, 2018, Chiou and Collins, 2018).

An editorial by *Sánchez Alvarado* argues that understanding the classic problem of regeneration and its potential applications will require us to think outside the confines of existing research organisms and to explore new and yet to be discovered animals (Sánchez Alvarado, 2018). His commentary serves as a preamble for the research papers contributed to this issue, which are collectively focused on dissecting cellular and molecular underpinnings of regeneration in hydrozoans, echinoderms, flatworms, flies, tunicates, fish, lizards, frogs, and salamanders. These research papers give an unique insight into many of the animals that have given us clues about how the ability to regenerate is executed at a molecular level and also raise interesting questions for future investigation, such as why do closely related species use different mechanisms to regenerate the same tissue types and how they evolve these different mechanisms? And, how are genes that are used during development re-activated in response to injury?

The field of regeneration has a long and winding history due to the lack of tools to address mechanistic questions in most classic animal models capable of replacing lost tissues. With the development of molecular and genomic tools that have been successfully applied to diverse research organisms, the last two decades have ushered a renaissance in the regeneration field. This renaissance was not only dependent on new technologies, but also built upon the seminal work of dedicated individuals who pushed the field forward driven by a passion for understanding the mysteries of regeneration. Sadly, in 2016 we lost an advocate of the regeneration field, Dr. Panagiotis “Takis” Tsonis, who loved salamanders and spent his career working to elucidate the mysteries of newt limb and lens regeneration. We pay tribute to Dr. Tsonis in this *Developmental Biology* issue by including an *In memoriam* piece written by *Voss*, *Simon* and *Sánchez Alvarado*, who honor Takis’ contributions to regenerative biology (Voss, Simon and Sánchez Alvarado, 2018).

The combination of review articles and primary research articles in this Special Issue on Regeneration cover a wide range of diverse aspects of how tissue regeneration is orchestrated at a cell and molecular level. In addition, they pose interesting questions that hopefully will attract many more inquisitive minds to the exciting field of regeneration.

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