

MEETING REVIEW

Repair, regenerate and reconstruct: meeting the state-of-the-art

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ABSTRACT

The seventh EMBO meeting on the Molecular and Cellular Basis of Regeneration and Tissue Repair took place in Valletta, Malta, in September 2018. Researchers from all over the world gathered together with the aim of sharing the latest advances in wound healing, repair and regeneration. The meeting covered a wide range of regeneration models and tissues, identification of regulatory genes and signals, and striking advances toward regenerative therapies. Here, we report some of the exciting topics discussed during this conference, highlighting important discoveries in regeneration and the perspectives for regenerative medicine.

KEY WORDS: Cell plasticity, Progenitor cell, Regeneration, Reprogramming, Tissue repair, Wound healing

Introduction

One of the most stimulating forums for discussing advances and future perspectives in regeneration is the EMBO conference on the Molecular and Cellular Basis of Regeneration and Tissue Repair. In 2018, the 7th edition of this conference series was held in Valletta (Malta) and was organized by James Godwin (Jackson Laboratory/MDI Biological Laboratory, Bar Harbor, ME, USA), Kerstin Bartscherer (Hubrecht Institute, Utrecht, The Netherlands), Catherina Becker (University of Edinburgh, UK), Leonor Saúde (Instituto de Medicina Molecular, Lisbon, Portugal) and Nadia Rosenthal (Jackson Laboratory, Bar Harbor, ME, USA).

What makes this meeting series special is its evolutionary perspective and the variety of regeneration models presented throughout the phylogenetic tree (Fig. 1). This comparative approach is necessary to understand why some animals regenerate, whereas others do not, and to unravel the genetic tools required for enhancing regeneration. The spirit of this conference confers a unique atmosphere where the results from a variety of animal models are pushing the field ahead. Essentially, the main goal of the meeting is to unravel the fundamental mechanisms that drive regeneration and identify the advances that will be relevant for regenerative medicine.

Given the amount of work presented, it is impossible to include here all the issues discussed during the meeting. Instead, we aim to cover the most relevant aspects of each talk to give a flavour of how the field is moving forward.

The ignition session: progenitors stream onto the scene

The plenary lecture given by Thomas Rando (Stanford University, CA, USA) set the bar for the meeting. His talk covered several aspects

of muscle stem cell quiescence and muscle regeneration, particularly in the context of aging. He highlighted a cyclin D1-TGF β axis that influences cell cycle progression and demonstrated that this axis is involved in the beneficial effects of exercise during aged muscle regeneration. Additionally, he discussed the roles of *miR206* and *Runx1*, which suppress and promote, respectively, the level of fibro-adipogenic progenitors towards adipogenesis, with potential consequences in muscular dystrophy and regeneration capacity.

The first keynote lecture was given by Nancy Papalopulu (University of Manchester, UK), who also discussed progenitor differentiation, showing that the transition from proliferating progenitors to differentiated neural cells in mouse and zebrafish involves a dynamic mechanism of oscillations in gene expression. Oscillations in mouse *Hes5* gene expression are generated by the combined action of transcriptional repression, time delay, and protein and mRNA instability, with the microRNA *miR-9* a key component. Interestingly, oscillations in progenitor cells are aperiodic and noisy, whereas oscillations in differentiating cells are periodic and associated with a decline in *Hes5* expression. Moreover, the mutated *miR-9*-binding site of *Her6*, a zebrafish *Hes*-related gene, locks the cell in a transitory progenitor state that prevents neural differentiation. This observation points to *miR-9* as a factor involved in preserving the pool of neural progenitors.

Beating hearts get stronger: how to regenerate the heart

It immediately became evident that zebrafish would occupy a central position in the meeting, in particular zebrafish heart regeneration. The capacity for heart regeneration is known to vary among fish species. In his keynote lecture, Didier Stainier (Max Planck Institute for Heart and Lung Research, Bad Nauheim, Germany) reported that an acute immune response through Toll-like receptor signalling in zebrafish promotes heart regeneration but is defective in medaka, a species unable to regenerate its heart (Lai et al., 2017). This lack of regenerative capacity in medaka is associated with poor recruitment of macrophages and a suppressed immune response after physical injury. In addition, Mohankrishna Dalvoy (Weidinger Laboratory, Ulm University, Germany) reported that mTORC1 signalling is required in macrophages, cardiomyocytes and endothelial cells during early zebrafish heart regeneration.

Several talks presented approaches to identify beneficial molecules for heart regeneration. Thomas Bise (Jazwinska Laboratory, University of Fribourg, Switzerland), identified ciliary neurotrophic factor (CNTF) as a molecule that stimulates cardioprotection and proliferation in regenerating zebrafish hearts (Bise et al., 2019), while, through a chemical screen for molecules that promote cardiomyocyte proliferation, Kenneth Poss (Duke University Medical Center, Durham, NC, USA) found that vitamin D analogues activate heart muscle cell division in embryonic zebrafish. A dominant-negative form of the vitamin D receptor reduces cardiomyocyte proliferation, whereas an activated form of this receptor causes massive cardiac hyperplasia (Han et al., 2019). This role of vitamin D requires the action of the proto-oncogene *ErbB2*. Its pro-proliferative action is not exclusive to cardiomyocytes, but also occurs in multiple cell types, such as hepatocytes, epicardial cells, retinal progenitors and

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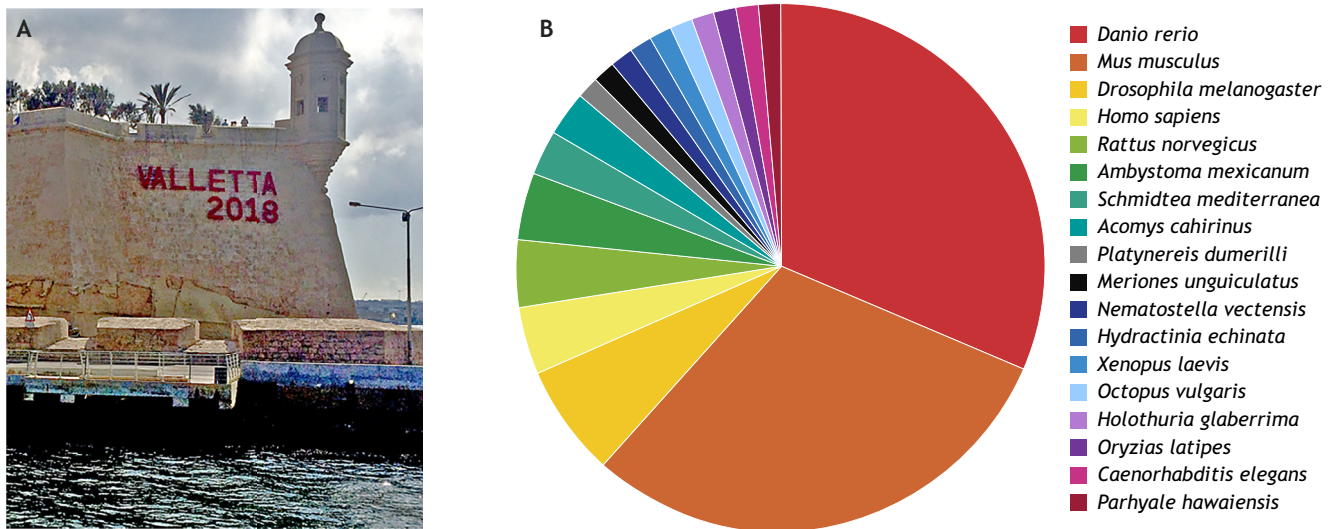


Fig. 1. The 7th EMBO conference on the Molecular and Cellular Basis of Regeneration and Tissue Repair. (A) La Guardiola in the bastion of Sanglea in Valletta (Malta). (B) Distribution of talks by animal model. Remarkably, 32% of talks featured more than one model species.

epidermis. Voot Yin (MDI Biological Laboratory, Bar Harbor, ME, USA) created a zebrafish-screening platform for novel molecules involved in regeneration. His team identified MSI-1436, an inhibitor of the protein tyrosine phosphatase 1B, as a potent regeneration-stimulating molecule (Smith et al., 2017), including heart regeneration. Moreover, MSI-1436 administration to adult mice post myocardial infarction stimulates cardiomyocyte proliferation and recovery.

There are notable differences in regenerative capacity across phylogenies. In contrast to zebrafish, murine cardiomyocytes lose their regenerative capacity soon after birth due to cell cycle withdrawal and onset of polyploidy. Guo Huang (University of California, San Francisco, CA, USA), however, observed that some mammals have diploid cardiomyocytes, and identified an inverse correlation throughout the mammalian phylogeny between the proportion of diploid cardiomyocytes and body temperature, metabolic rate and levels of thyroid hormone (Hirose et al., 2019). Inactivation of thyroid hormone signalling in newborn mice results in low temperatures similar to those of primitive mammals, and increases cardiac regeneration even in adults. Different areas of injured murine and zebrafish hearts were transcriptionally characterized by Dennis de Bakker (Hubrecht Institute, Utrecht, The Netherlands), who identified a transcriptionally distinct border zone common to both species, but found that these differ in that only zebrafish shows Wnt-pathway activation in that zone, which might be key for heart regeneration. Another example was presented by Yadong Wang (Cornell University, Ithaca, NY, USA), who investigated the potential of zebrafish extracellular matrix as an enabler of regeneration in non-regenerating rodents (Chen et al., 2016). Evidence was provided that mammalian hearts and axons can regenerate upon exposure to zebrafish extracellular matrix.

Heart re-vascularization has been investigated in mice by Paul Riley (University of Oxford, UK). He showed that VEGFC, a growth factor involved in coronary vessel development, induces lymphatic vasculature near to the infarction zone. These new lymphatic vessels function to traffic immune cells, a process dependent upon the LYVE1 receptor, which when mutated results in cardiac deterioration (Vieira et al., 2018).

Several laboratories are focusing on developing therapeutic strategies to improve heart regeneration capacity in mammals.

Francisco Azuaje (Luxembourg Institute of Health, Luxembourg) linked the expression signatures of different zebrafish heart regeneration stages to drug response profiles in human cells. His team identified a flavonoid that induces proliferation and reduces death of rat cardiomyocytes under hypoxia. Gioacchin Iannolo (ISMETT, Palermo, Italy) presented data on the role of non-coding small RNAs in heart regeneration. He studied miRNAs in human cardiomyocytes from biopsies and found that *miR34* blocks proliferation (Iannolo et al., 2018). *miR34* represses target genes associated with stemness and proliferation, such as Notch. Activation of the Notch target Numb in cardiac progenitors endows the capacity to proliferate. Together, these talks demonstrate how conditions and factors discovered in model systems for heart regeneration are now emerging as potential heart regenerators in mammals.

Re-wiring the nervous system

Regeneration of the central nervous system is poor in mammals. The hope is that by studying regenerative models, we can identify the genetic tools used for repair after injury or neurodegeneration. Spinal cord injury in mammals forms an astrocyte-rich fibrotic scar that prevents axonal re-growth. In contrast, zebrafish are capable of repairing the spinal cord and recovering motor and sensory neuronal function. Jan Kaslin (Australian Regenerative Medicine Institute, Clayton, Victoria, Australia) showed that migration of neural precursors to the lesion site and activation of neural stem cells are necessary to re-wire the spinal cord of zebrafish larvae (Lindsey et al., 2018). Leonor Saude (Instituto de Medicina Molecular, Lisbon, Portugal) found that zebrafish *foxfj1a*-expressing ependymal cells actively proliferated and contributed to spinal cord regeneration (Ribeiro et al., 2017). Moreover, in contrast to mammals, vascularization is restored and pericyte recruitment is associated with the new vessels that eventually re-establish the brain-spinal cord barrier.

The neonatal cerebellum can regenerate by reprogramming of nestin-expressing progenitors (NEPs). N. Sumru Bayin (Joyner Laboratory; Memorial Sloan Kettering Cancer Center, New York, NY, USA) hypothesized that activating developmental signals in the adult cerebellum after injury could enhance regeneration. Remarkably, activation of Hedgehog signalling after injury in the adult cerebellum increases the number of responsive NEPs (Wojcinski et al., 2017).

Hearing loss due to accidents, disease or aging affects millions of people worldwide. It is primarily caused by permanent loss of the mechanosensory receptors in the inner ear and their associated neurons. Using otic progenitors derived from human embryonic stem cells (Chen et al., 2012), Marcello Rivolta (University of Sheffield, UK) showed that injecting these in the base of the cochlea (either alone or in combination with cochlear implants) yields functional auditory improvement in gerbils, a mammalian model for auditory neuropathies. Mechanosensory receptors in the zebrafish lateral line are capable of complete regeneration after injury. In a genetic screen using retroviral insertion of CRISPR/Cas9 mutations, Wuhong Pei (Burgess Laboratory; NHGRI, NIH, Bethesda, MD, USA) identified genes encoding RNA splicing factors that are essential for regeneration but not for development (Pei et al., 2018).

Regenerating limbs: from amphibians to mammals

Unlike mammals, many amphibia can regenerate the complete limb upon amputation. James Monaghan (Northeastern University, Boston, MA, USA) found that nascent RNA synthesis increases dramatically in regenerating amphibian limbs, annelid segments and mouse digit tips. He concluded that blastema cells are in a state of hypertranscription, which, at least in amphibians, requires signalling through the YAP transcription factor and the presence of intact nerves. However, unlike other vertebrate models, digit tip regeneration in mice occurs after denervation, as found by Connor Dolan (Muneoka Laboratory; Texas A&M University, College Station, TX, USA).

Factors that prevent limb regeneration have been identified by repeated amputation of the axolotl limb, which ultimately diminishes its regenerative capacity (Bryant et al., 2017). This strategy enabled Jessica Whited (Harvard Medical School, Boston, MA, USA) to identify genes that block regeneration, such as *amphiregulin*, and genes that promote regeneration, like *eyes absent 2*. The search for molecules that enhance limb regeneration was also the topic of Nirosha Murugan's talk (Levin Laboratory; Tufts University, Medford, MA, USA). She has identified five pro-regenerative drugs that, when applied in a special silk-hydrogel bioreactor to amputated limbs, promote wound closure, bone growth, vascularization and re-patterning resembling early digit identity.

The trigger: early signals, wound repair and scarring

In mammals, injury often induces scarring rather than regenerative repair; understanding the mechanisms underlying these divergent responses to wound repair is therefore crucial. Some of the earliest events that occur during the wound response are poorly understood, mainly because they are local and transient. To tackle this issue, Philipp Niethammer (Memorial Sloan Kettering Cancer Center, New York, NY, USA) used advanced *in vivo* imaging to show that early wound responses involve an osmotic surveillance mechanism led by neutrophils sensitive to the hypotonic environment generated by the wound (Huang and Niethammer, 2018). He also found that oxidized lipid species link redox regulation to lipid metabolism at damaged sites. Furthermore, Anna Huttenlocher (University of Wisconsin-Madison, USA) found that tissue injury leads to ROS-dependent vimentin production near the wound edges. ROS and vimentin are required for collagen expression and organization at the wound edges during repair (LeBert et al., 2018).

MAP kinases operate as regulators of regeneration in many tissues and organisms. Blocking the MAPK/ERK signalling pathway in fragmented planaria impairs regenerative growth, while allowing wound healing (Owlarn et al., 2017). By studying

the downstream response to ERK-mediated injury signals using phosphoproteomics and ribosome profiling, Kerstin Bartscherer (Hubrecht Institute, Utrecht, The Netherlands) identified translational regulation as an integral part of the response to damage.

Several laboratories are exploring the emergence of scars in mammalian skin and its reversion to scarless regenerated tissue. Yuval Rinkevich (Helmholtz Center, Munich, Germany) showed that the shift from scarring to scarless regeneration is caused by a change in fibroblast compositions in the skin (Jiang et al., 2018). The dermal lattice in developing skin originates from engrailed-negative fibroblasts, whereas it is later colonized by engrailed-positive cells that promote fibrotic scar formation. Remarkably, this response can be reverted by locally transplanting engrailed-negative fibroblasts, which mediate scarless repair.

The MRL (Murphy Roths Large) mouse provides a model for regeneration in mammals, as complete healing occurs in the absence of scarring. Ellen Heber Katz (Lankenau Institute for Medical Research, Wynnewood, PA, USA) showed that in MRL mice, the scarless wound and the entry into the cell cycle (epimorphic regeneration) is due to the lack of expression of the cell cycle inhibitor *p21^{cip/waf1}*. In addition, MRL mice are characterized by a systemic, but transient, upregulation of *Hif1a* after injury. Moreover, drug-induced transient stabilization of *Hif1a* in non-regenerating mice induces regeneration.

As a model of the non-fibrotic scarless repair mechanism, Phoebe Kirkwood (Saunders Laboratory; University of Edinburgh, UK) showed that pericytes, cells that are associated with the capillaries of the endothelium, are mobilized to undergo mesenchymal-to-epithelial transition for endometrial recovery following menstrual cycle disruption.

Inflammation takes the lead

As has already been discussed above, the role of the immune response in regeneration is fundamental to understand the distinction between scarless regeneration and non-regenerating scar-producing scenarios. James Godwin (MDI Biological Laboratory/Jackson Laboratory, Bar Harbor, ME, USA) analysed the inflammatory response to injury in regenerating limbs of salamander and found macrophage recruitment near the wound. Macrophage depletion before amputation interrupts the progression from wound healing to regeneration. A comparative analysis of different transcriptional responses to Toll-like receptor signalling upon different triggers in mammals and salamanders revealed that, although the response to infection is conserved, the response to amputation is specific to salamanders. Analyses of the genes involved in this signature might provide potential therapeutic strategies to foster tissue regeneration in mammals.

Catherina Becker (University of Edinburgh, UK) has been exploring the involvement of innate immune cells in spinal cord regeneration in zebrafish larvae. Upon injury in *irf8* mutants, which lack macrophages, inflammation and IL1 β production increase and regeneration is impaired (Tsarouchas et al., 2018). Reducing IL1 β or IL1 β -producing neutrophils rescues regeneration in *irf8* mutants. However, IL1 β is required for the early steps of regeneration. Thus, inflammatory responses must be tightly controlled by macrophages to foster regeneration of the spinal cord. Will Wood (University of Edinburgh, UK) examined the inflammatory response in laser-damaged *Drosophila* embryos, and found that macrophage migration to the lesion sites is mediated by Ca²⁺-dependent JNK signalling, which leads to upregulation of the damage receptor Draper. In addition, adipocytes migrate to wounds inflicted in late pupal stages using an unusual peristaltic mode of motility, and can drive wound healing (Franz et al., 2018).

Comparing the regenerative potential of the spiny mouse (*Acomys*) with the non-regenerating house mouse, Jennifer Simkin (Seifert Laboratory; University of Kentucky, Lexington, KY, USA) found differences in spatiotemporal localization of macrophage subtypes and uncovered a distinct pro-inflammatory macrophage type present during *Acomys* scarless regeneration (Simkin et al., 2017).

A declining capacity for repair and proliferation is a hallmark of aging. However, modulation of the immune environment can improve plasticity and repair. In a search for factors with immunomodulatory activity, Joana Neves (Jasper Laboratory; Buck Institute for Research on Aging, Novato, CA, USA) found that the mesencephalic astrocyte-derived neurotrophic factor (MANF) stimulates repair in *Drosophila* and mouse retina, and that this capacity decreases with age (Neves et al., 2016). Nikolay Ninov (Center for Regenerative Therapies, Dresden, Germany) studied the relationship between inflammation of pancreatic β -cells and their proliferation in aging. NF- κ B signalling is upregulated with age, which correlates with a decline in proliferation. He found that NF- κ B activity in aging cells coincides with elevated expression of *socs2*, an inhibitor of proliferation (Janjuha et al., 2018).

Insulin signalling in regeneration and plasticity

The link between nutrition control and early regeneration has been examined by Maria Leptin (University of Cologne and the European Molecular Biology Laboratory, Germany). She showed that signalling through the insulin receptor (InR) and TOR is necessary for epithelial organization during wound healing in *Drosophila* (Kakanj et al., 2016). The insulin pathway activates Pi3K and FOXO, whereas the TOR pathway operates through the Atg1/Atg13 autophagy machinery. TOR and insulin signalling have also been found to regulate plasticity. Sarah Becker (Jarriault Laboratory; IGBMC, Strasbourg, France) reported that nutrient signals mediated by InR and TOR are crucial for cellular plasticity in the context of Y epithelial cell to PDA motor neuron transdifferentiation in *Caenorhabditis elegans*. Michael Gallo (The University of Texas MD Anderson Cancer Center, Houston, TX, USA) also focused on InR signalling, looking at a *Drosophila* model for diabetes-associated pain hypersensitivity. He found that injury-associated pain sensitivity could be reverted by ectopically expressing InR in nociceptive sensory neurons (Im et al., 2018).

Plasticity

The YAP/TAZ transcription factors, the principal effectors of the Hippo pathway, are crucial for inducing cell-fate plasticity (Totaro et al., 2018). Stefano Piccolo (University of Padua, Italy) showed that YAP/TAZ is required during physiological regeneration of gut, mammary gland differentiation and upon disease in pancreas. YAP/TAZ are dispensable during homeostasis but are required for the expansion of progenitors during repair and disease, and for *in vitro* organoid formation.

The capacity to switch between fates was presented by Olov Andersson (Karolinska Institutet, Stockholm, Sweden), who reported that mesodermal cells in zebrafish larvae can under certain circumstances transdifferentiate to regenerate a pool of β -cells. Meanwhile, Anne Grapin-Botton (Max Planck Institute, Dresden, Germany) demonstrated that cell ablation in embryonic pancreas induces compensatory proliferation. However, insulin production and β -cell mass are greater in regenerated than in normal undamaged tissue, which suggests an overcompensation after damage. Also focusing on compensatory proliferation, George Eisenhoffer (University of Texas MD Anderson Cancer Center, Houston, TX,

USA) analysed zebrafish epidermis and found that Wnt8a-containing apoptotic bodies are engulfed by basal stem cells to activate proliferation and replace dead cells (Brock et al., 2019). Another signal that favours regeneration is the Hedgehog pathway, the activation of which results in recovery of aged intervertebral discs in mice (Bonavita et al., 2018), as shown by Chitra Dahia (Hospital for Special Surgery, Weill Cornell Medical College, New York, NY, USA).

New approaches and perspectives

The capacity to regenerate relies not only on the presence/absence of certain genes but also on regulatory non-coding regions. By combining RNA-Seq and ATAC-Seq, Elena Vizcaya Molina (Corominas and Serras laboratory; University of Barcelona, Spain) identified the genomic map of damage-responsive enhancers that are active during *Drosophila* regeneration and showed that *Drosophila* imaginal discs, zebrafish heart and mouse liver share a core set of conserved genes required for regeneration (Vizcaya-Molina et al., 2018).

Two talks presented *in silico* models of cellular behaviour in regenerating systems. First, Torsten Thalheim (Computational Tissue Group; Interdisciplinary Centre for Bioinformatics, Leipzig University, Germany) reported a 3D multiscale individual cell-based model of mouse small intestinal crypts and organoid culture for tracking individual cell properties and predicting organoid growth behaviour (Thalheim et al., 2018). Second, Rajanikanth Vadigepalli (Thomas Jefferson University, Philadelphia, PA, USA) presented an *in silico* model for rat liver regeneration that, combined with experimental data, can provide insights into transcriptional states during regeneration.

Regeneration across the animal kingdom

Studies of less-common model systems can broaden our perspective of regeneration and its evolution, and enable discovery of new mechanisms. Peter Reddien (MIT, Whitehead Institute, Cambridge, MA, USA) showed that muscle cell signals are the clue to planarian whole-body regeneration. Follistatin, an antagonist of activin signalling expressed in muscle cells, is dispensable under homeostasis but required in injured planaria. Its downregulation induces an increase in *wnt1* expression, which negatively affects head regeneration.

A major issue in regeneration biology is the extent to which regeneration re-uses developmental cues. Using the cnidarian *Nematostella*, Eric Röttinger (CNRS, INSERM, University Côte d'Azur, Nice, France) proposed that regeneration deploys a re-wired gene regulatory network that integrates part of the embryonic program, as well as regeneration-specific genes/gene modules (Warner et al., 2018). In another cnidarian, *Hydractinia*, a somatic cell dedifferentiation mechanism is activated to regain stemness, as shown by Uri Frank (National University of Ireland, Galway, Ireland).

The sea cucumber eviscerates most of its digestive tract in response to stress and regenerates a pool of progenitors by dedifferentiation of mesenteric cells. José García-Arrarás (University of Puerto Rico, San Juan, Puerto Rico, USA) showed that Wnt signalling is crucial for dedifferentiation and regeneration of the lost tissues. Anabelle Planques (Vervoort Laboratory; Institut Jacques Monod, Paris, France) characterised posterior regeneration following amputation in the annelid *Platynereis*, showing that proliferating cells of the regenerating structure have a local origin, and that the process is rapid and reproducible (Planques et al., 2018). An alternative to axonal regeneration is the re-innervation after lesioning that occurs in the peripheral nervous system of the cephalopod *Octopus vulgaris* (Imperadore et al., 2017), as shown by Pamela Imperadore

(Association for Cephalopod Research-CephRes, Naples, Italy). Finally, Çağrı Çevrim (Averof Laboratory; Institut de Génomique Fonctionnelle, Montpellier, France) described a live-imaging approach to identify the progenitors of sensory organs during crustacean limb regeneration. These diverse models demonstrate both conserved and divergent principles operating during regeneration across evolution.

Conclusion

This conference provided a stimulating scenario for sharing the advances in different animal systems. It is extremely encouraging that the series has evolved into an inspirational forum to discuss the latest advances in regeneration and repair research. Therefore, it is essential to continue to consolidate the EMBO conference series in order to further basic regeneration research and build bridges between regeneration biology and regenerative medicine.

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Competing interests

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