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Bench to bedside: Current advances in regenerative medicine

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Regenerative medicine is a diverse and rapidly evolving field, employing core expertise from biologists, engineers, and clinicians. Recently the field has made significant progress towards regenerating or replacing tissues lost to age, disease or injury. Current strategies include transplantation of adult or pluripotent stem cells to replace tissue or support tissue healing. Promising approaches for the future of regenerative medicine include stimulating endogenous stem cells for *in situ* repair, transplantation of organoids to repair minor tissue injury, and the use of interspecies chimerism to produce functional metabolic organs for transplantation. In our review we focus on these emerging strategies, paying particular attention to their current and prospective translational impacts and challenges.

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Introduction

Transplantation of adult stem cells is a well-established technology to treat disease, with hematopoietic stem cell transplantation in wide spread clinical use for over 50 years. Nevertheless, this technology continues to find new clinical applications. For example, recent results from an international clinical trial showed that high-dose immunosuppressive therapy and subsequent autologous hematopoietic stem cell (HSC) transplantation is effective in inducing long-term sustained remissions of active relapsing-remitting multiple sclerosis [NCT00273364] [1]. In this trial only 6% of patients treated with HSCs relapsed, compared to 60% in the untreated control group. Similarly, autologous cultured epidermis transplantation is a long-established approach. Notable progress has recently been made in the treatment of skin blistering disorders by gene correction of epidermal cells, followed by their expansion in culture and subsequent transplantation [2••]. In a recent world first, this graft technique was used to almost completely replace the skin of a child with epidermolysis bullosa (EB).

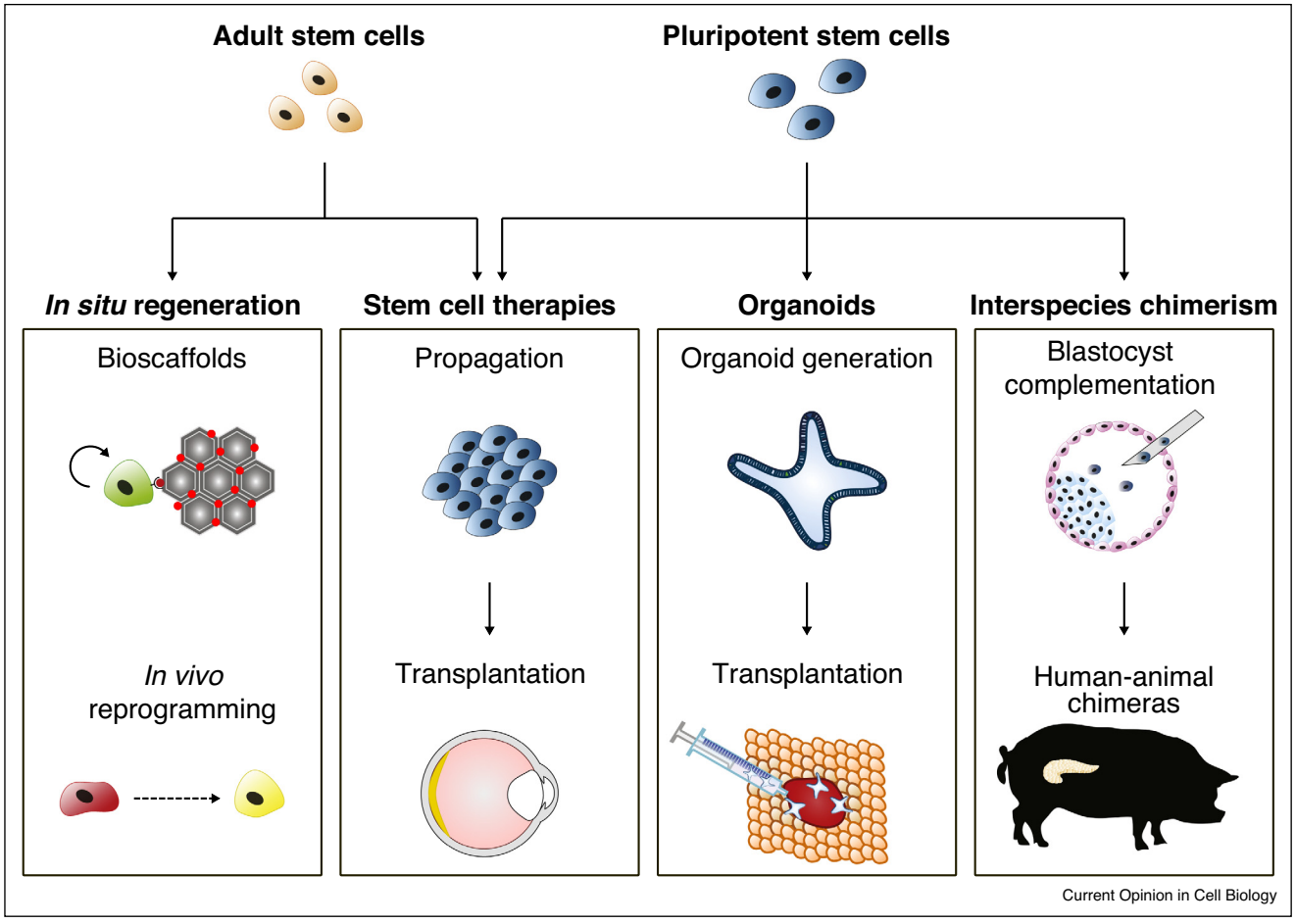
Allogeneic mesenchymal stem cell (MSC) transplantation has also been widely used in patients to treat a range of conditions [3]. However, evidence of efficacy has been lacking in many cases. Recent studies of patients with graft-versus-host disease (GvHD) suggest that successful treatment is determined by the state of the patient's immune system rather than by the state of the infused MSC. Galleu *et al.* (2017) found that patients who had high cytotoxic T cell activity against MSCs responded to MSC infusion, whereas those with low activity did not [4]. After infusion, host phagocytes engulfed apoptotic MSCs and produced indoleamine 2,3-dioxygenase, which was necessary for the immunosuppressive effect of MSCs. This suggests that patients should be stratified for MSC treatment according to their cytotoxic T cell activity, or, alternatively that patients could be treated with apoptotic MSCs.

While adult stem cell therapies continue to find new and exciting clinical applications, adult stem cells can only give rise to a limited number of cell types and can be hard to scale. This has driven the development of many next-generation regenerative strategies. The new approaches include methods to promote endogenous tissue repair, through the use of pharmacological bio-scaffolds [5], *in vivo* cell reprogramming [[8•]], senolytics [7], methods to produce novel autologous cell therapies using induced pluripotent stem cells (iPSCs) [8•], and techniques aimed at engineering functional human tissues and organs through *in vitro* tissue engineering [9••] and interspecies chimerism [10••]. In this review we will focus on these emerging strategies in the field of regenerative medicine and discuss the technical and translational challenges they pose (Figure 1).

In situ regeneration

An attractive strategy for regenerative medicine is to target endogenous repair mechanisms in resident cell populations. A promising approach for this is through the recruitment of tissue-resident stem populations

Figure 1



Current strategies in regenerative medicine. Somatic stem cells can be targeted *in situ*, through the application of bioscaffolds seeded with pro-regenerative agents, to activate endogenous repair mechanisms [5]. Alternatively, tissue resident cells can be reprogrammed from a pathophysiological state [15,16] or to an alternative functional state [14,58] to alleviate disease. Adult, embryonic or induced pluripotent stem cells can also be transplanted to enhance regeneration. This may include *ex vivo* expansion and gene editing to correct pathogenic mutations. Transplantation of organoids shows promise as a strategy to improve regeneration [9••]. Finally, the generation of human-animal chimeras could facilitate the production of entire human organs. Bioscaffolds, biological scaffolds.

following trauma. Implanted biological scaffolds (bioscaffolds) provide structural support for functional tissue regrowth and facilitate localised delivery of pro-regenerative agents [11]. A recent advance has been the use of a clinically-approved degradable collagen sponge seeded with a GSK3 inhibitor to promote mesenchymal stem cell (MSC)-based dentine regeneration in a rodent model. While this represents a new approach to tooth repair [5], significant concerns are the off-target effects of broad stimulation of pro-regenerative pathways and the possibility that continued activation of somatic stem cells might lead to their depletion and loss of regenerative capacity.

An alternative *in situ* approach for regenerative medicine is reprogramming of terminally differentiated cells. One current strategy for *in vivo* reprogramming involves enforcing expression of key regulatory transcription factors (TFs) to convert cells to an alternative mature state [6]. This strategy can be employed to generate functional cells to replace those lost through disease. Insulin positive pancreatic β-like cells have been successfully generated in mice from pancreatic exocrine [12], hepatic [13] and gastrointestinal [14] cells following virus-mediated delivery or transgenic expression of a combination of pancreatic TFs. This partially alleviates hyperglycaemia in diabetic murine models. Alternatively pathological cells can be reprogrammed to ameliorate disease, as with the conversion of myofibroblasts to hepatic-like cells in induced murine models of liver damage, through adenovirus-mediated induction of a combination of hepatic TFs [15,16]. Nevertheless, the efficiency of reprogramming cells *in vivo* is generally low, which may limit translation of this approach into the clinic.