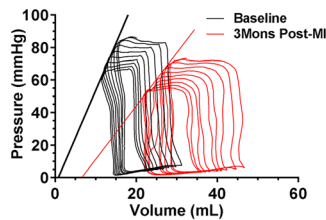


**P2Y<sub>2</sub>R Prompts Cardiac Progenitor Cell Activation (p 1224)**

**Khalafalla et al rejuvenate cardiac progenitor cells via nucleotide receptor signaling.**

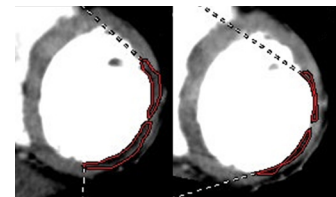
The use of autologous cardiac progenitor cells (CPCs) for repairing failing hearts has shown promising results in animal models, but trials in patients with heart failure have provided modest, if any, clinical benefits. One reason for the limited efficacy of CPCs may be that CPCs from patients carry genetic predispositions for heart failure, or have reduced regenerative capacity because of patient’s age or other characteristics. Boosting the potency of autologous CPCs may, therefore, improve their clinical performance. Regeneration in a variety of tissues has been shown to be promoted by the nucleotide receptor P2Y<sub>2</sub>R, which is activated by extracellular UTP. Now, Khalafalla and colleagues have discovered that P2Y<sub>2</sub>R is more abundantly expressed in healthy, fast-growing human CPCs than in slow-growing, more senescent cells. Furthermore, UTP treatment of human CPCs increased their regenerative potency (proliferation and migration rates) as did overexpression of P2Y<sub>2</sub>R. Knockdown of the receptor had the opposite effect. The team went on to show that CPC activation via UTP and P2Y<sub>2</sub>R was dependent on the downstream signaling factor YAP (Yes-associated protein). Together, these results indicate that rejuvenating CPCs by activating the UTP–P2Y<sub>2</sub>R–YAP pathway may improve outcomes of CPC therapy.



**CBSCs Preserve Structure and Function After MI (p 1263)**

**Sharp et al bring cortical bone stem cell therapy one step closer to the clinic.**

A variety of cell types have been tested in animals and patients for their potential to promote the regeneration of injured and failing hearts. Mesenchymal stem cells (MSCs) and cardiac-derived progenitor cells (CDCs), for example, are among the most commonly tested cells, but while these cells have given encouraging results in animals, clinical benefits in patients remain uncertain. Stem cells derived from the cortical region—the dense outer layer—of bone (CBSCs) have recently been shown to be more effective than CDCs at improving heart function and reducing scar size after myocardial infarction in mice. Now, Sharp and colleagues have tested these cells in a larger animal model, more comparable to human patients. After undergoing induced myocardial infarctions, a group of pigs was given transendocardial injections of allogenic CBSCs, while another group was given control injections. After 3 months, the hearts of the CBSC-treated pigs exhibited smaller infarct scars, less ventricular dilation, and better preservation of function than control pigs. Although the study did not compare CBSCs to other types of stem cells, the results warrant further investigations of CBSCs as a potential cell therapy option.



**Cell Dosing in Ischemic Cardiomyopathy (p 1279)**

**Stem cell dose is critical to cell therapy outcomes, say Florea et al.**

Many preclinical studies and clinical trials of cell therapies for heart disease have focused on identifying the best cell type to use, but few have focused on determining the optimal dose. Even the studies that have investigated cell dosage have given complicated and seemingly contradictory results. Given the importance of resolving questions of dosage, Florea and colleagues tested the safety and efficacy of 2 different doses of human allogenic mesenchymal stem cells (hMSCs) in 30 patients with chronic ischemic left ventricle dysfunction following myocardial infarction. Fifteen of the patients were given transendocardial injections of 20-million hMSCs, while the other 15 were dosed with 100-million cells. All patients were then followed for 12 months during which time none experienced serious adverse events. While the size of the infarct scars and the presence of systemic inflammation was shown to decrease similarly in both treatment groups, only patients in the 100-million cell group experienced improvements in left ventricle function. The results show that cell dosage is an important determinant of the clinical outcome of cell therapies and highlight the need for further trials aimed at evaluating optimal dosage.

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## In this Issue Ruth Williams

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