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Drug and cell delivery for cardiac regeneration☆

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ABSTRACT

The spectrum of ischaemic cardiomyopathy, encompassing acute myocardial infarction to congestive heart failure is a significant clinical issue in the modern era. This group of diseases is an enormous source of morbidity and mortality and underlies significant healthcare costs worldwide. Cardiac regenerative therapy, whereby pro-regenerative cells, drugs or growth factors are administered to damaged and ischaemic myocardium has demonstrated significant potential, especially preclinically. While some of these strategies have demonstrated a measure of success in clinical trials, tangible clinical translation has been slow. To date, the majority of clinical studies and a significant number of preclinical studies have utilised relatively simple delivery methods for regenerative therapeutics, such as simple systemic administration or local injection in saline carrier vehicles. Here, we review cardiac regenerative strategies with a particular focus on advanced delivery concepts as a potential means to enhance treatment efficacy and tolerability and ultimately, clinical translation. These include (i) delivery of therapeutic agents in biomaterial carriers, (ii) nanoparticulate encapsulation, (iii) multimodal therapeutic strategies and (iv) localised, minimally invasive delivery *via* percutaneous transcatheter systems.

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Abbreviations: MI, myocardial infarction; CHF, congestive heart failure; CSCs, cardiac stem cells; BMMNCs, bone marrow derived mononuclear cells; MSCs, human mesenchymal stem cells; VEGF, vascular endothelial growth factor; GCSF, granulocyte colony stimulating factor; ADSCs, adipose derived stem cells; HGF, hepatocyte growth factor; β-GP, β-glycerophosphate; HEC, hydroxy-ethyl cellulose; PEG, poly(ethylene glycol); PCL, polycaprolactone; ECM, extracellular matrix; RGD, Arg-Gly-Asp; PG, poly(e-caprolactone)/gelatin; LVEDVI, left ventricular end diastolic volume index; LVR, left ventricular restraint; BCM, bioabsorbable cardiac matrix; PGE2, prostaglandin E2; PGI2, prostaglandin I2; PLGA, polylactic-co-glycolic acid; PP, pyrvinium pamoate; NADH, nicotinamide adenine dinucleotide; DPP-IV, dipeptidylpeptidase IV; miR, microRNA; modRNA, modified RNA; LVEF, left ventricular ejection fraction; PEI, polyethylenimine; APOSEC, apoptotic peripheral blood cells; SDF-1, stromal cell derived factor-1; NRG-1, neuregulin-1; IGF-1, insulin-like growth factor-1; FGF-1, fibroblast growth factor-1; Shh, Sonic hedgehog morphogen; Ang-1, angiopoietin-1; CPC, cardiac progenitor cell; CDC, cardiosphere derived cell; VRD, ventricular restraint device; PTCA, percutaneous transluminal coronary angioplasty.

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1. Introduction

This review encompasses drug and cell delivery for cardiac regeneration. This treatment can be cardioprotective; to protect heart muscle tissue after an acute myocardial infarction (MI), or cardiorestorative; to regenerate tissue in patients with chronic ischaemic heart failure. Acute myocardial infarction occurs upon occlusion of one of the coronary vessels, most commonly due to atherosclerotic plaque, resulting in an ischaemic region of myocardium which, even if reperfused, can produce lasting tissue damage with associated symptoms. Initially, MI produces an inflammatory response and extensive ischaemic death of cardiomyocytes within the affected area, resulting in a partial loss of ventricular function. Over time, especially if the affected area is expansive and transmural, complex alterations occur in the myocardium, a phenomenon known as ventricular remodelling [1]. These adaptations are an attempt to compensate for ventricular malfunction. However, the heart possesses only a limited regenerative capacity. Remodelling encompasses the creation of collagenous, non-contractile scar tissue, thinning of the myocardial wall and progressive enlargement and dilation of the ventricle. This ultimately contributes to a decrease in ventricular contractile function and output. This can progress to congestive heart failure (CHF), where the heart is unable to pump enough blood to meet the metabolic demands of the body [2–4].

MI represents an enormous source of morbidity and mortality on a global scale. Coronary artery diseases such as MI and CHF are the main cause of death in developed countries, and pose a substantial healthcare burden [3]. According to the European Society of Cardiology one in six men and one in seven women in Europe will die from myocardial infarction [5]. The American Heart Association reports that 635,000 Americans have a new myocardial infarction each year and that the number of deaths attributable to heart failure in the US in 2009 was 275,000 [6]. Current therapies for the treatment of MI and CHF include pharmacological intervention, surgical procedures such as ventricular resection, coronary artery bypass or mechanical aids such as left ventricular assist devices. Such approaches serve to restore function or limit disease progression to some degree, but are not always effective long-term [7]. Reperfusion of the culprit artery (with coronary angioplasty and/or stent placement) can have a profound effect on limiting infarct

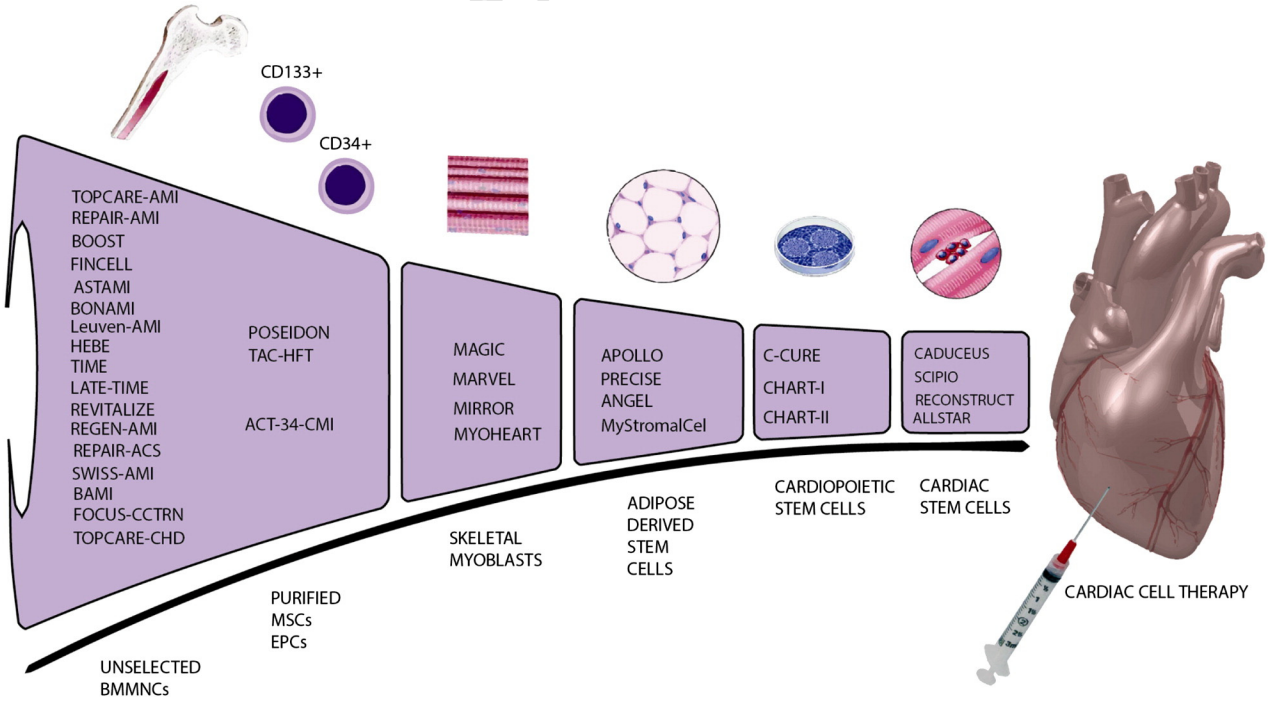

Fig. 1. Clinical trials in cell therapy: This figure shows the range and progression of cardiac cell therapy trials, with cell type underneath (graphically represented above) and depicts the trend of moving from unselected cell populations and different cell types towards cardiopoietic and cardiac stem cells.

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