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The use of biologics in the management of cardiovascular diseases

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The use of biologic agents including monoclonal antibodies, recombinant proteins, non-coding RNAs (miRNAs), gene therapy and, especially, stem cell therapy have revolutionized the treatment of a variety of diseases. Most notably, success in treating cancers have been achieved using hematopoietic stem cell therapy. Use of these agents in the treatment of cardiovascular disease is still in its infancy but recent advances have identified several new biologic agents. Current clinical trials are evaluating the success of stem cell therapy and fibroblast therapy as well as agents that either mimic or inhibit non-coding RNAs (miRNAs) as possible treatments for a several cardiac pathologies including heart failure, myocardial infarction, arrhythmias, coronary artery disease and ischemic heart disease. This review will focus on the use of stem cells and miRNA agents to characterize the current status of these agents and describe some of the nuances that have led to the extraordinary interest in them as therapeutic agents.

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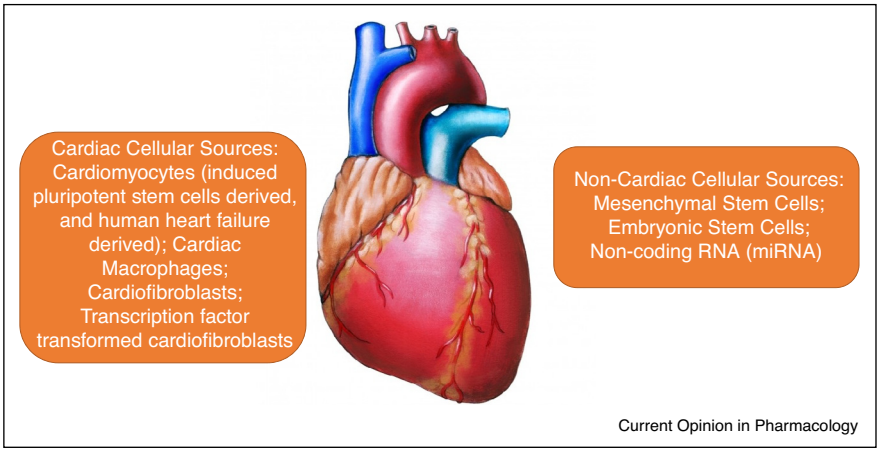
Introduction

The molecular biology revolution has greatly transformed our understanding of the multitude of processes which the body employs to function properly. In addition, it has dramatically altered the method and directions used to develop new molecular entities (NME) for therapeutic use through the identification of new targets. In particular, the expansion of biotechnology has focused considerable attention on the development of novel biologic agents from the theoretical perspective of developing new therapeutic agents with the highest degree of specificity possible. Biologics are defined as commercial products derived from biotechnology and from a pharmacological perspective are limited to substances derived from animal products of other biological sources that are used to treat or prevent disease. The hope that such targeted therapies would provide maximum benefit with the least harm has been observed to some extent in the management of autoimmune diseases (*e.g.*, Rheumatoid Arthritis) and cancers. Santos *et al.* [1] evaluated the development of NME per therapeutic area and the evidence clearly indicated that the development of biologics directed toward cardiovascular disease compared to small molecules lagged substantially behind other therapeutic areas, most notably blood and blood-forming organs and antineoplastic and immunomodulating agents (Figure 1).

As illustrated in Table 1, biologics being evaluated for use in cardiovascular diseases come from a variety of sources that include: monoclonal antibodies; recombinant proteins, RNA interference, fibroblast and growth factors, gene therapy and stem cell therapy. Information provided by the Pharmaceutical Manufacturer's Association (PhRMA) from 2013 identified 58 biologics being evaluated in various stages of clinical trials (Phase I, II or III) specifically related to cardiovascular disease of which nearly 50% were some form of stem cell therapy. Furthermore, the recognition that many biologics used for the treatment of inflammatory diseases such as rheumatoid arthritis target-specific cytokines and signaling molecules that have been implicated in the development of particular cardiovascular diseases (*e.g.*, heart failure and vasculitides) that make them especially attractive as targets for the future [2]. Examination of the ClinicalTrials.gov website listed 594 clinical trials being conducted in 2016 employing biologic agents (generally some form of cardiac stem cells (CSCs) alone or in combination) for therapeutic efficacy in a wide array of adverse cardiac events ranging from coronary artery disease to heart failure. Most of these studies are early Phase I and Phase II trials exploring the safety and efficacy and many have been completed but a significant number were either terminated or withdrawn for various reasons. Several trials are also evaluating the combination of pharmacological agents with CSC administration as a potential therapeutic intervention in acute and chronic cardiac adverse events. Monoclonal antibodies were the next largest group with most of the attention directed toward controlling hypercholesterolemia (please see Li and Robidoux, this volume) and in inhibiting VEGF. Antibodies directed against VEGF have found good therapeutic potential in the management of Age-Related

Figure 1



Schematic representation of the sources of potential biologic agents being considered in the treatment of cardiac disease.

Macular Degeneration. These agents include bevacizumab and ranibizumab. In addition, these agents have clear clinical utility in the management of a wide array of cancers. The development of novel agents through stem cell harvesting and differentiation has presented the greatest potential for therapeutic advances. A primary initial goal of these therapies was to regenerate cardiac muscle to replace any scarring that might contribute to future cardiomyopathy and/or arrhythmia development. A recent addition to the library of potential targets for biologics has been the identification of non-coding RNA (miRNA) that plays an important role in cellular differentiation and homeostasis. Since these families of agents are currently undergoing scrutiny in clinical trials and many have not yet been approved for use in cardiovascular diseases, this discussion will focus on two primary targets: Stem Cell Therapy and non-coding RNA (miRNA).

Stem cell therapy

Mesenchymal stem cells

The positive experience obtained in the treatment of many blood cancers using hematopoietic stem cell treatment has now been extended to the cardiovascular system using a variety of sources of cells. As described by Wegener *et al.* [3••] the original goal of this type of therapy was to generate new cardiac myocytes through differentiation of adult stem cells or induced pluripotent stem cells (iPSCs) to replace damaged cardiac muscle. However, the available evidence of success has not been compelling to date, primarily due to the low number of patients in which such studies have been conducted. The foundation of the studies has been to reprogram differentiated human cells (*e.g.*, embryonic stem cells) into an undifferentiated state for administration. There has been evidence of improved cardiac contractility and function in animal studies in which the undifferentiated cells actually become phenotypically cardiac myocytes. Some success has also been achieved using human stem cells handled in a similar fashion obtained from patients in heart failure.

However, a relatively recent shift in philosophy has developed regarding the use of stem cell treatment from one of regeneration to one aimed at promoting myocardial protection. Stem cells for use in this application can be

Table 1

Sources of biologic products for therapeutic use in vascular and cardiovascular diseases

Biologic product source	Therapeutic targets
Monoclonal antibodies	Age-related macular degeneration, hypercholesterolemia, diagnosis of deep vein thrombosis, stroke, cardiovascular disease
Stem cell transplantation	Critical limb ischemia, ischemic stroke, ischemic heart failure, myocardial ischemia, chronic coronary ischemia, myocardial infarction, congestive heart failure
miRNA inhibitors and activators and gene therapy	Heart failure, ischemic heart disorders, peripheral arterial disease, myocardial ischemia, coronary artery disease, atrial fibrillation, advanced heart failure, hypercholesterolemia
Recombinant proteins	Essential hypertension, stroke, atherosclerosis, coronary artery disease, ischemic stroke, thrombosis, peripheral vascular disease
Growth factors	Congestive heart failure, severe coronary heart disease