

# Cardiovascular Therapeutic Discovery

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Cardiovascular disease remains the leading cause of death in the United States and in much of the world [1–3]. With obesity, diabetes, and the aging population on the rise both here and abroad, there is urgent need for development of improved cardiovascular therapeutics.

Despite the increasing societal need and a nearly \$110 billion global market for new cardiovascular treatments, some major pharmaceutical companies have recently abandoned cardiovascular research and development, including Pfizer, manufacturer of some of the most successful (and lucrative) drug treatments [4]. In a recent review on this topic [5], Dr. Alan M. Garber offered his perspective and possible explanations for corporate abandonment of cardiovascular therapeutic development, as well as for the dearth of new cardiovascular therapeutics successfully exiting the development pipeline. Among many possible reasons, he highlighted the escalating costs and duration of comparative effectiveness trials, where enhanced efficacy compared to extant (and possibly low-cost generic) treatments, and not to placebo, are required. Newly surfacing safety concerns with new and currently approved therapeutics for cardiovascular disease, or comorbid diseases such as diabetes mellitus, may also dampen enthusiasm and increase cost.

Although corporate research and development is being partially directed away from cardiovascular therapeutic development, there is a tremendous and growing need for improved therapies. Increasingly, academia and academic–corporate partnerships are leading the charge for discovery. The purpose of this issue of the *Journal of Cardiovascular Translational Research* is to highlight a selection of novel and innovative approaches to develop improved therapies across the cardiovascular spectrum. While the methods highlighted in this issue by no means constitute a comprehensive list of all novel approaches, we sought to provide a broad array of ongoing research and development to highlight the breadth of thoughtful approaches being pursued to combat cardiovascular disease.

Traditionally, we think of pharmacologic approaches as the mainstay of therapy for most diseases. Several such approaches are highlighted herein, including development of hydrogen sulfide-based therapeutics, as well as drug targeting of cyclic nucleotide phosphodiesterases, TRPC channels, G-proteins, and platelet function. Beyond traditional pharmacologic approaches, we have also sought to highlight “biologic” therapeutic approaches, such as gene therapy or peptide targeting for heart failure with  $\beta$ ARKct or S100A1. The modulation of cardiac stem cell regenerative capacity by use of in vitro or in vivo peptide therapeutics, as well as novel drug/cell delivery modalities, is also highlighted. Maintenance and repair of cardiac structure and function with injectable matrices, which may also be useful for drug/peptide/cell delivery, is summarized. An overview of reversible RNA aptamer technology, which recently completed phase 2B clinical trials for anticoagulation therapy, is also included.

Finally, a possible explanation for the limited approval of new cardiovascular therapeutics could be that the pipeline fed by current discovery methods may be running dry.

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New ideas for unbiased discovery and validation of novel therapeutic and diagnostic approaches are also presented, including: zebrafish as a screening tool, a systems biology-based multidimensional approach, and a phenotypic high-throughput screening methodology.

The challenges of identifying, validating, and obtaining approval for new cardiovascular therapeutics are indeed daunting. However, with this issue of the *Journal of Cardiovascular Translational Research*, we wish to highlight hope for the discovery and development of new and effective treatments for this devastating disease.

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