DRUG DISCOVERY& DEVELOPMENT Strategies & Technologies Driving Drug Discovery to Market

Feed Your Heart

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For more than a decade we have lived with the promise that therapeutic angiogenesis—the growth of new blood vessels in damaged tissues and organs—would provide a lasting clinical benefit to patients suffering from coronary artery disease, the leading cause of death in the Western world. However, numerous successful protein-, gene- and cell-based angiogenesis studies in animals with experimentally-induced cardiac ischemia have not been followed by positive efficacy data in human trials. Is there still hope that therapeutic angiogenesis in the diseased heart can be achieved?

There is no doubt that angiogenesis offers promise for the treatment of cardiovascular disease. This potent physiological process is stimulated by a diminution of blood supply to vital organs, and results in the production of new collateral vessels to overcome the ischemic insult. Early studies with protein-based therapeutics focused largely on the intravenous or intracoronary administration of a particular growth factor to stimulate angiogenesis in the heart. Although the therapy was deemed safe, statistically significant efficacy could not be demonstrated.

The advent of gene therapy quickly found its way into gene-based angiogenesis trials in humans. Numerous trials demonstrated the safety of gene-based products, but as they progressed to more tightly controlled, blinded clinical trials, efficacy could not be demonstrated.

Cell-based angiogenesis therapy, which has proven successful in animals, is still years away from large-scale clinical trials. The approach is to transplant progenitor endothelial cells into the damaged heart, leading to the proliferation and remodelling of the endothelial cells into functioning blood vessels. However, views that such therapy could lead to infections, arrhythmias, or possible nascent tumor sites will have to be answered by well-designed safety studies in animals.

Where does this leave the field of angiogenesis? Recently, there has been a resurgence of interest in returning to protein-based therapy to stimulate angiogenesis in the ischemic heart. Because earlier studies indicated that an intravenous or intracoronary delivery of the protein was not efficacious, more recent clinical studies have relied on direct injections into the ischemic heart muscle. Such localized administration of the potent angiogenic growth factor, human fibroblast growth factor-1 (FGF-1), has given statistically-significant improvement in work capacity and blood perfusion in no-option heart patients. With protein therapy, relatively large amounts of the therapeutic agent can be injected into the ischemic muscle, to pharmacologically "jump start" the process of collateral artery formation. As proteins such as FGF-1 are cleared in less than three hours from the body, this type of therapy does not portend serious side effects, and no serious adverse events have yet been noted in the ongoing clinical trials with FGF-1.

The goal of angiogenesis therapy is to safely and efficiently form new blood vessels to nurture and replenish tissues that have been damaged by underperfusion and ischemia. Numerous lines of evidence indicate that by supplying tissues with angiogenic protein(s), the natural neovascularization process is stimulated. Given the current real and imagined limitations of gene and cell-based angiogenic therapy, protein-based therapy is likely to become a dominant treatment option for patients with coronary artery disease in the not too distant future.

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