

THE FUTURE OF CARDIOVASCULAR GENE THERAPY –

advances in regenerative medicine go hand in hand with new perspectives and insights into potential treatments for heart disease

After a decade of pre-clinical and early Phase 1 and 2 clinical studies, gene therapy is now emerging as a genuine therapeutic option with the potential to alter the manner in which cardiologists manage heart disease¹. This article focuses on the progression of cardiovascular gene therapy and the continuing need to find less invasive and more cost-effective treatment options, with a specific focus on stable angina due to coronary artery disease, which may likely be the first indication served by cardiovascular gene therapy.

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Medical and surgical advances in cardiovascular intervention and treatment in the past 30 years have been monumental. Millions of lives have been improved and often saved. Despite this progress, cardiovascular disease is still the leading cause of death in the industrialised world. Globally, some 16 million people die each year of cardiovascular disease. In the United States alone, 12.4 million people have coronary artery disease. Among these, 7.3 million people aged 20 and older have had a heart attack and 1.5 million will have a new or recurrent heart attack this year. Coronary artery disease is the leading cause of death in the US, accounting for approximately 460,000 deaths annually. Once thought of as a men's health issue, heart disease is quickly being recognised as the silent killer of women. Compared to 46,000 deaths per year from breast cancer, 250,000 women die each year of coronary artery disease. Approximately five million people

in the US have congestive heart failure (CHF) and 300,000 of them will die this year².

Recognising these facts, it is clear that despite the rapid advances in cardiovascular therapy over the past 30 years, present therapies are still inadequate to treat the most prevalent and debilitating disease of our time. The grim statistics, however, may be about to change. The completion of the Human Genome Project has uncovered a new range of genes and genomic information that has begun to advance the field of regenerative medicine and revolutionise the cardiovascular gene therapy industry. The demand for cardiac-specific therapy, not directed merely at the symptoms, but at the correction of the underlying altered physiology that creates disease, is increasing every day³. Gene therapy for cardiovascular disease is aimed at providing a non-surgical alternative that will target the disease at its physiological roots and take advantage of nature's own mechanisms as therapeutic

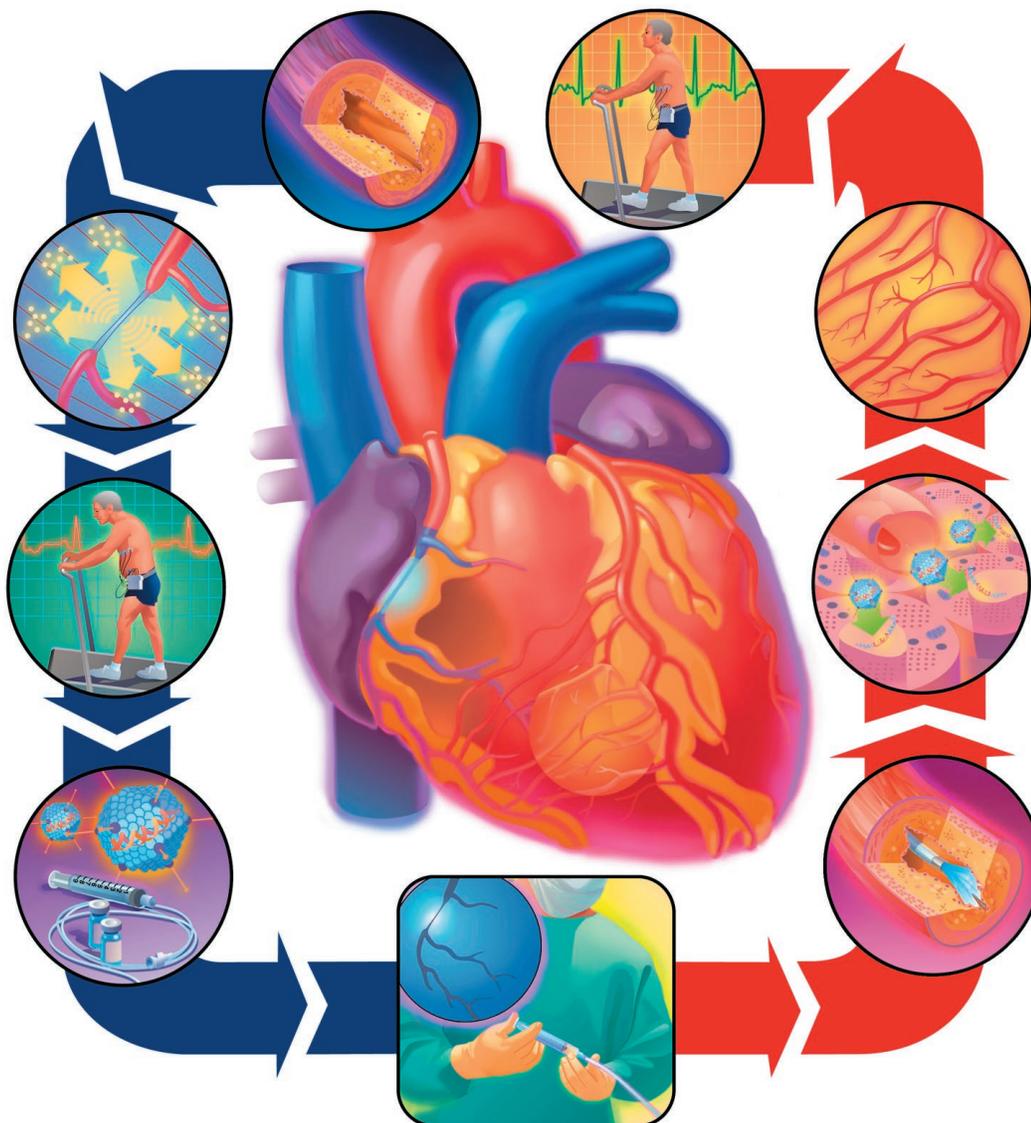


Figure 1
Potential angiogenic healing process

- 1** Blocked artery due to build-up of fatty and plaque deposits inside the lining of arterial wall
- 2** Signal of ischemic injury
- 3** Clinical diagnosis of myocardial ischemia due to coronary artery disease
- 4** Collateral Therapeutics' non-surgical catheter-based proprietary gene therapy approach
- 5 & 6** Intra-arterial administration of gene therapy product through cardiac catheter by an interventional cardiologist
- 7** Transfection of angiogenic growth factor genes into heart cells
- 8** The growth of collateral circulation following angiogenic gene therapy
- 9** Improved blood flow and heart function following angiogenic gene therapy

approaches. The advancement of cardiovascular gene therapy into large-scale clinical trials and potential regulatory approval could offer a much-desired solution to this unmet medical need for a large patient population worldwide.

Regenerative medicine goes hand-in-hand with the angiogenic healing process and with it, cardiovascular gene therapy. Angiogenesis is the term used to describe the body's natural ability to grow new blood vessels to sustain healthy tissue. A central premise of regenerative medicine is the stimulation of the body's cells to create new cells, which can lead to the growth of tissues, organs and even systems. The cardiovascular system is one of these. Reduced blood flow to the heart muscle (ischemia) causes injury to the heart muscle cells and stimulates the release of ischemic injury signals. In response to these signals in the heart, the human

body's natural angiogenic healing process is initiated and there is a natural attempt to grow new blood vessels to restore blood flow to the ischemic tissue. Unfortunately, this response is usually inadequate to keep up with the progressive nature of coronary artery disease, and ultimately progressive areas of the heart muscle are left without enough blood supply to accommodate increased stress or exercise. This is the cause of chest pain called angina pectoris. A cardiovascular gene therapy approach to amplify this natural angiogenic healing process has the potential to overcome nature's limited angiogenic response. Research and clinical trials have begun to provide insights into this potential approach by employing an innovative, non-surgical angiogenic gene therapy as illustrated in **Figure 1**.

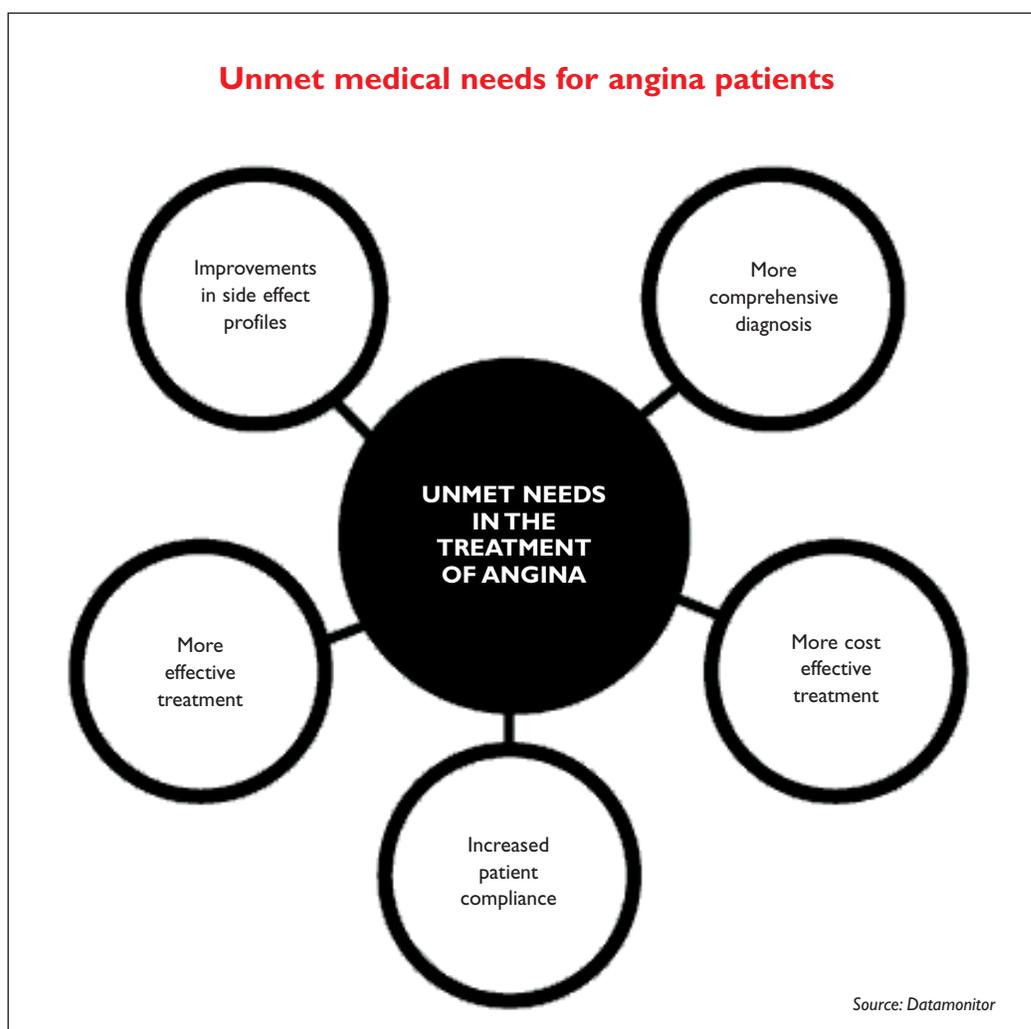
Optimising gene delivery was initially a prime focus in the field of gene therapy. The development

of viral vectors to deliver therapeutic genes into cells followed by the development of non-viral systems presented considerable opportunities for gene therapy in treating cardiovascular disease. A major shortcoming of viral vectors is their inability to induce sustained long-term expression. Some disease areas require a sustained level of gene expression to provide a therapeutic response. The lack of an appropriate expression-specific, target specific vector has slowed the advancement of gene therapy treatments for some clinical indications. Cardiovascular angiogenic gene therapy, however, requires only a limited transient therapeutic gene expression. Limited gene expression has been shown to be adequate for the delivery of growth factors that can induce and augment angiogenesis, and once the angiogenic process is complete, sustained expression may not be necessary. As a result, a new safety profile is being established for this technology, and the earlier concerns regarding the use of viral vectors for longer-term expression has lessened. To that end, cardiovascular

disease demonstrates the potential of gene therapy perhaps better than any other indication⁴.

Cardiovascular gene therapy as the next frontier of medicine has attracted attention from pharmaceutical and biotechnology companies. Today, a number of biotechnology companies including Collateral Therapeutics, Inc (San Diego, CA), GenVec, Inc (Gaithersburg, MD) and Valentis, Inc (Burlingame, CA) are focused on the development and commercialisation of cardiovascular gene therapy products. A number of larger biotechnology companies such as Genzyme BioSurgery have active gene therapy programmes as well. Collateral Therapeutics, however, is currently the only gene therapy company to focus entirely on developing a treatment for cardiovascular disease targeted to large therapeutic patient populations. Collateral Therapeutics, in collaboration with Schering AG, is a leader in the field of cardiovascular gene therapy with the advancement of its lead product candidate, GENERX™, in the first-ever, large-scale Phase 2b/3

Figure 2



clinical trials, which are now being conducted in the US and in Europe. GENERX is a non-surgical angiogenic gene therapy designed for the potential treatment of stable angina due to coronary artery disease (CAD). This technology and others in Collateral's pipeline are being developed to improve heart function in a non-surgical manner by amplifying the body's natural processes and augmenting its own healing potential. GenVec's BioBypass® is a direct injection product candidate, which is currently in Phase 2 trials for the potential treatment of CAD and peripheral vascular disease while Valentis is evaluating an intramuscular injection, del-1 GeneMedicine™, in Phase 1 clinical trials, under an agreement with ARK Therapeutics for peripheral artery disease. GenVec recently announced that its partnership with Pfizer for the development of BioBypass had ended. It has been reported that sometime in the future, GenVec intends to take BioBypass into Phase 3 trials.

The future success of this new gene therapy paradigm in cardiovascular disease treatment has significant economic implications. According to the American Heart Association, cardiovascular disease accounts for at least 300,000 Medicare hospitalisations annually amassing almost \$300 billion in direct and indirect costs. The population of patients over the age of 65 is expected to double by 2020, at which time the healthcare costs will approach \$1 trillion⁵. Simply put, people affected by cardiovascular disease continue the search for improved and more cost-effective ways to treat heart disease. Future therapy ideally must be less invasive, longer lasting, less expensive and most importantly directed at altering the disease process, not just treating the symptoms, and cardiovascular gene therapy has the potential to address these issues (Figure 2).

Stable angina market and conventional treatments

Angina pectoris is the medical term for chest pain due to coronary artery disease. During times of emotional stress or physical exertion, the heart muscle doesn't receive enough blood due to the blockages and narrowing in the coronary arteries, resulting in chest pain. Nearly seven million people suffer from angina in the United States alone⁶ (Figure 3).

Additionally, angina patients generally represent 2-3% of an industrialised country's total patient population, with an estimated 18 million angina patients in six leading industrialised countries. Despite this vast patient population, the stable angina market is poorly served with existing treatments⁷. These treatments include pharmaceuticals,

Figure 3
Prevalence of angina 2000-2005 (000s)

COUNTRY	2000	2005	GROWTH (%)	PROPORTION POPULATION OF (%) 2000**
Italy	1,755	1,824	3.93	3.06
Japan	3,878	4,078	5.16	3.06
Spain	1,142	1,199	4.99	2.88
UK	1,600	1,493	-6.70	2.72
Germany	1,927	1,836	-4.72	2.34
US	6,400*	6,791	6.11	2.30
France	1,313	1,240	-5.56	2.22

* American Heart Association's 2001 Statistical Update

** Figures calculated from World Population Prospective: 1998 Revision

Source: Datamonitor CardioVision

interventions such as percutaneous transluminal coronary angioplasties (PTCA) and stents, and surgical procedures such as coronary artery bypass graft (CABG) surgery.

The new revolution in cardiovascular gene therapy is developing as an alternative to the present conventional therapies for treating CAD and heart failure. Currently, there is no perfect treatment for angina. Angina has traditionally been treated with chronic drug therapy. Existing drug therapy for angina is recognised to have limited effect. Often associated side-effects such as fatigue and impotence further limit their efficacy. Moreover, many patients still have angina attacks despite taking multiple drugs. Even considering the significant cost, the use of balloon angioplasty and coronary stents has been, and will continue to be, an effective treatment modality for the angina market. But the long-term benefits of these coronary interventions like balloon angioplasty and the use of stents to wrestle with the problem of restenosis, which is the renarrowing or reclosure of the coronary artery following a dilatation, sometimes even within weeks to months. And obviously, CABG surgery, although effective, is still highly invasive and associated with significant morbidity and even mortality. Many patients and their physicians prefer to seek other treatment alternatives before undergoing major open-heart surgery. Furthermore, even when CABG surgery is effective, the progressive nature of coronary artery disease leads to further blockage of the coronary arteries and even the bypass grafts. Over five to 10 years, as

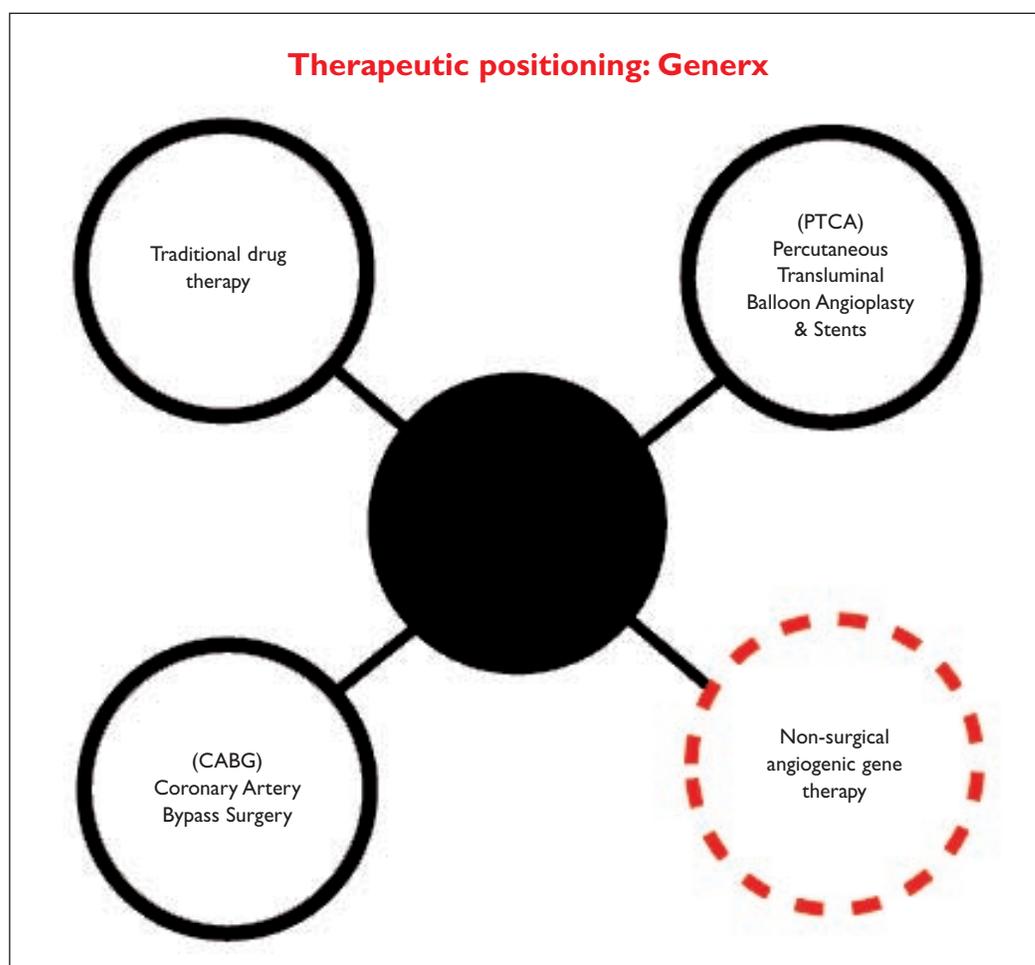
many as 50% of patients may need further intervention or repeat surgery. A more recent controversy centres on the short and long-term side effects, including neurological and cognitive dysfunction, related to the use of the cardiopulmonary bypass pump (heart-lung machine). Even with the advent of 'off-pump' bypass surgery to perform CABG surgery without the use of cardiopulmonary bypass, at present less than 20% of patients have their surgery performed using this newer technique. Cardiovascular gene therapy, by inducing 'therapeutic angiogenesis', might obviate the need for bypass surgery, with or without the use of the heart-lung machine. Cardiovascular gene therapy is designed to enhance the human body's natural, regenerative process of angiogenesis and restore blood supply to ischemic areas of the heart is a potential fourth alternative therapy in the toolbox of the interventional cardiologist for the treatment of angina pectoris and coronary artery disease (Figure 4).

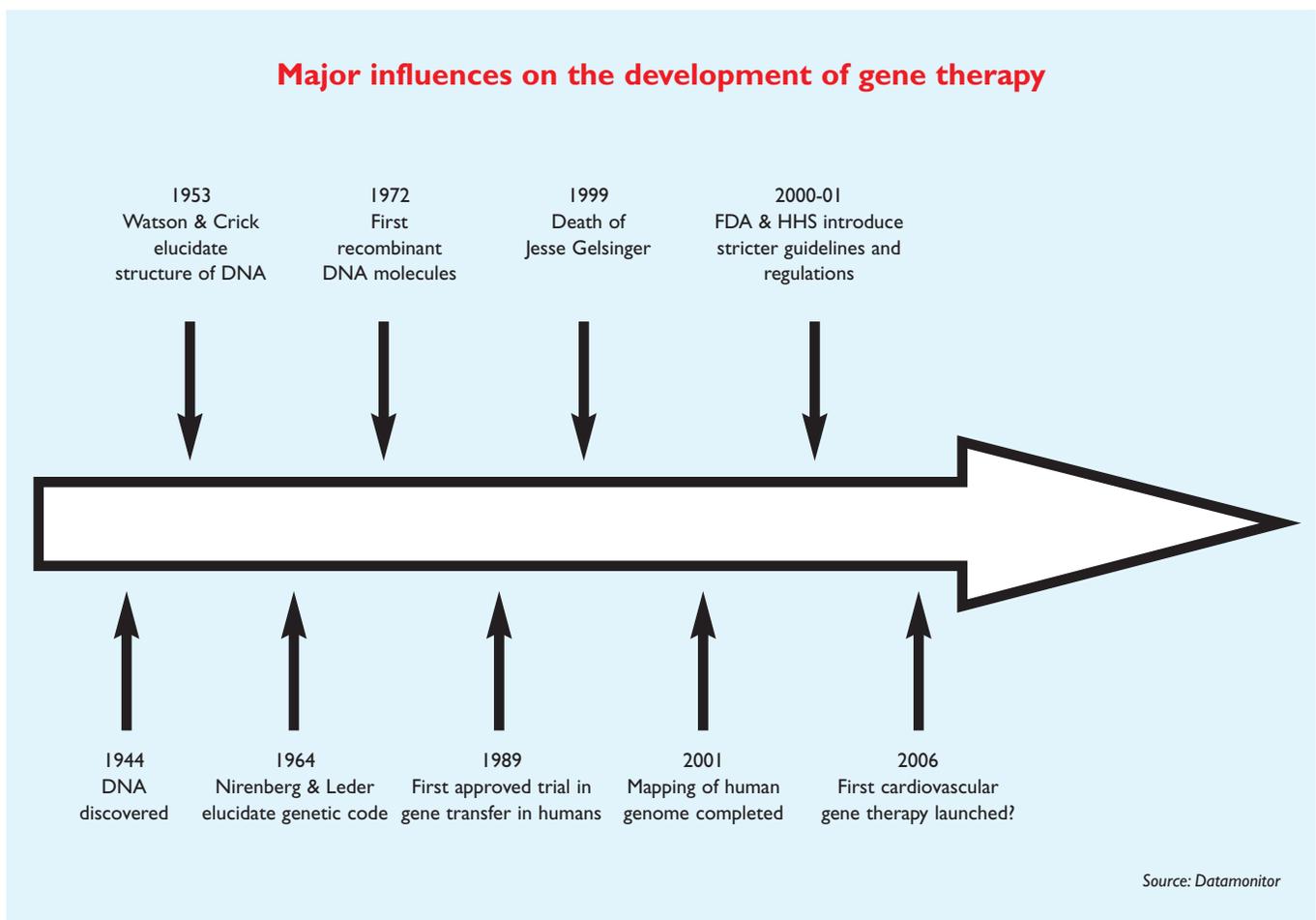
Cardiovascular gene therapy has the potential to offer more personalised treatment for stable angina. Stable angina due to coronary artery disease is

one of the most advanced targets for cardiovascular gene therapy development. Angina may very well be the first cardiovascular indication for which gene therapy is launched, and the commercial development programme of GENERX has the potential to position Collateral Therapeutics as the first cardiovascular gene therapy company to reach the market⁸. With Collateral Therapeutics' lead product candidate, GENERX in Phase 2b/3 clinical studies, cardiovascular gene therapy is no longer an experimental therapy, but a potential treatment, poised to join mainstream therapeutics⁹.

Gene therapy researchers are now beginning to report encouraging Phase 1 and 2 clinical trials that support the safety and clinical benefits with gene therapy using angiogenic growth factors for cardiovascular disease. Now in 2002, with the advancement of GENERX, it is clear that the potential to offer patients this new, simpler, more cost-effective treatment for serious cardiovascular disease can be seen. Like the scientific revolution that started with the discovery of DNA and its double helix structure in 1953, like the surgical

Figure 4





revolution that led to the development of CABG and PTCA to treat coronary artery disease, cardiovascular gene therapy, almost a half century later, is now emerging as a potential therapeutic option to treat areas of cardiovascular disease.

State of gene therapy

It is important to understand the entire gene therapy industry to fully comprehend the potential to treat cardiovascular disease. Similar to other innovative technologies, such as monoclonal antibodies, that took many years to demonstrate their commercial potential, gene therapy still faces challenges before it can achieve full commercialisation. Nevertheless, the field has progressed remarkably since the early 1990s¹⁰. The final stage of clinical testing before FDA consideration for commercial use has begun for several leading gene therapy companies. As a whole, the gene therapy industry is much further along than currently believed. Companies in the industry are advancing in human clinical trials, with major clinical data coming out in the next one to two years across many disease

areas. Additionally, safety has been established in numerous Phase 1/2 studies, and large-scale Phase 2b/3 or Phase 3 clinical trials are now under way in four different gene therapy programmes across all disease areas.

The future implications of cardiovascular gene therapy

A major focus in early development of cardiovascular gene therapy was delivery optimisation, but with encouraging data from Phase 1 and 2 studies proving the utility of vector delivery and safe transient gene expression in the heart, the primary focus now in developing gene therapy for cardiovascular disease is on clinical, regulatory and manufacturing processes. As previously stated, the long-term financial implications of cardiovascular gene therapy should not be overlooked. Currently, long-term care is a major source of financial expense in chronic and incurable cardiovascular disease and gene therapy has the potential to reduce this expense¹¹.

The development of gene therapy for all disease

Figure 5

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areas has been subject to much attention by regulatory agencies as a result of an unfortunate setback in 1999. The tragic and high profile death of Jesse Gelsinger resulting directly from his participation in a gene therapy trial for the inherited disorder, Ornithine Transcarbamylase (OTC) deficiency, conducted by researchers at the University of Pennsylvania, for many good reasons has dramatically increased the involvement of governmental regulation. The revolutionary nature of this therapy, as well as many ethical and safety concerns, has prompted gene therapy clinical trials to be subject not only to the US FDA (Food And Drug Administration) review, but also to review and approval by the National Institutes of Health's (NIH) Recombinant Advisory Committee (RAC) and its human gene therapy subcommittee. It is important that gene therapy companies work in partnership with these regulatory agencies so that safe and effective products can be developed.

As commercialisation approaches reality, success of this industry will also depend on the intellectual property held by key players. The ability to obtain patent protection on the delivery systems and the therapeutic genes as well as the mode of delivery to the target cell and the disease indication both in the US and in other countries is of utmost importance.

The ability to defend patents, once obtained, and to operate without infringing upon the patents and proprietary rights of others is also a focus. From an intellectual property perspective gene therapy progress will require more than just composition of matter protection and in many cases, method patents will also be important (Figure 6).

Despite the challenges presented here, important regulatory pathways have been forged, which could lead to product registration with global health authorities and commercialisation of a cardiovascular gene therapy product that has the potential to offer new hope to patients and their families. **DDW**

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