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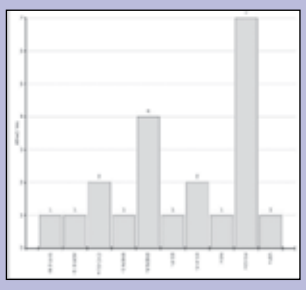
Pipeline Watch

Worldwide Late-Stage Clinical Developments *Page 8*



Each month, *Drug & Market Development* tabulates the most recently reported late-stage clinical developments from the more than 7,000 drug candidates currently under active research worldwide, to help ensure you keep fully up-to-date with competitor R&D activity. In this issue, we highlight 119 events in therapeutic categories including:

- **Cancer**
- **Dermatology**
- **Infectious Diseases**
- **Nervous System**
- **Reproductive Health**

Bright light on the prostate cancer horizon

With alarming statistics that one in every six men will be diagnosed with prostate cancer it may come as a surprise that no treatments exist for patients with advanced cases of the disease. All that could soon change as the FDA reviews Dendreon's new active cellular immunotherapy treatment, Provenge. If approved, the drug will be the first immunotherapeutic to ever reach the market and will signal a significant change in the treatment options available for many cancer patients. **Page 4**

Anorexia and bulimia: Dying to be slim

Sadly, eating disorders rank as the third most common chronic illness in adolescent females. Yet these highly prevalent syndromes historically have been overlooked by the pharmaceutical industry and few therapies exist to treat the complex mental illnesses. New research is focusing on disturbances in brain neurotransmitter pathways and several drugs are now in development, including Daiichi Sankyo's ghrelin agonist, and Pfizer's sertraline. **Page 16**

Protein promise in heart disease

Historically, protein therapies have been used as treatments for cancer and other disorders, but new research suggest that they could also play a role in treating cardiovascular disease. The most promising proteins demonstrating angiogenic properties include FGF-1 and VEGF-1 and at least 29 trials are underway with early data looking promising. If the cardiovascular study results can be reproduced in other therapeutic domains, then protein therapy could become the treatment modality of choice for many disorders. **Page 19**

New leads on spinal cord regeneration

Around 250,000 people live with spinal cord injuries in the US. Patients suffer sensorimotor loss and damage to the central nervous system. Unfortunately, the regenerative capacity of axons in the central nervous system is poor relative to other tissues in the body such as skin and bone. But research has suggested that a particular compound, Sema3A, could be responsible for inhibiting axonal regeneration in the CNS. Thus scientists are now evaluating whether a small-molecule inhibitor of Sema3A could promote axonal regeneration. **Page 22**

Inter-agency co-operation on the rise

Many international regulatory agencies have struck up agreements between themselves in recent years to share confidential information about pharmaceutical products. Such agreements are designed to facilitate information on the safety of medicines and help in preventing technical barriers to trade. The US FDA is the most active in this area with more than 40 agreements in place and the Heads of the Medicines Agencies view such alliances as the backbone of the entire regulatory network. **Page 24**

Muscular Dystrophy: New treatments

Muscular dystrophy is the common name for several progressive hereditary diseases. It affects one in 3,500 children, many of whom will die early in life. There are more than 30 known variants of the disease yet there are no effective treatments available. Researchers are focusing on a range of different approaches to treatment including RNAi inhibitors, stem cells, myostatin inhibitors and gene therapy. While much research is in the early stages, several drugs are showing promise. **Page 28**

D&MD PUBLICATIONS

Protein Promise in Heart Disease

- Protein therapies are usually associated with anticancer regimens, however, some initial clinical trials indicate that they could play a significant role in treating cardiovascular disease, based on their angiogenic properties.
- The best-known growth factors with proven angiogenic potency are fibroblast growth factor-1 (FGF-1) and vascular endothelial growth factor-1 or -A (VEGF-1).
- Although most of the 866 ongoing US FDA-authorized studies investigating protein therapy are cancer trials, 29 studies are focusing on protein therapy for cardiovascular disease (CVD). So far, the results look promising.
- If the cardiovascular study results can be reproduced in other therapeutic domains, then protein therapy could well become the treatment modality of choice for many disorders.
- This article was written by Dr Thomas Stegmann, chief medical officer and co-president, Cardiovascular Biotherapeutics. He can be contacted on email: tstegmann@cvbt.com

Cardiovascular disease is the number one killer in the US, claiming around 2,500 lives a day, or one death every 35 seconds, according to the American Heart Association. This is more than the next four leading causes of death combined – cancer, chronic lower respiratory diseases, accidents and diabetes mellitus.

The clinical spectrum of cardiovascular disease comprises: coronary heart disease (CHD), congenital cardiovascular defects, heart failure, stroke, high blood pressure and peripheral arterial disease. Of the 71.3 million American adults with one or more types of CVD, 27.4 million are estimated to be aged 65 or older. Preliminary mortality data show that CVD was the underlying cause of death in 37.3% of all deaths, or one in every 2.7, in the US in 2003. CVD as an underlying or contributing cause of death (1.4 million deaths) made up 58% of deaths in 2002. The estimated direct and indirect cost of CVD for 2006 is US$403.1 billion.[1]

In Europe, the numbers are similar: CVD causes nearly half of all deaths in Europe (49%) and in the EU (42%).[2] Each year, CVD causes more than 4.35 million deaths in Europe and over 1.9 million deaths in the EU. CVD is the main cause of death in women in all countries of Europe and is the main cause of death in men in all countries except France and San Marino. CHD by itself is the single most common cause of death in Europe, accounting for 1.95 million deaths a year. Overall, CVD is estimated to cost the EU economy US$169 billion a year.[2]

Methods of treating patients with severe medically refractory CHD include various catheter-based techniques (percutaneous coronary intervention or PCI) and such modifications as laser angioplasty, rotablator techniques and stent implantation; also surgical procedures, particularly coronary artery bypass grafting (CABG). An estimated 664,000 PCI procedures and 467,000 CABG operations were performed in 2003 in the US.[1]

A significant number (estimated at 150,000 a year) of these patients, however, present with diffuse coronary artery disease, proximal stenosis and additional peripheral stenoses/occlusions of the coronary artery branches, small vessels, or severe general co-morbidities, which makes them unsuitable both for PCI and for CABG ('no-option' heart patients). Owing to hereditary factors, Asian Indians in particular show this unfavorable pattern of CHD.

Thus, despite several treatment options across the clinical spectrum of cardiovascular disease, a significant proportion of patients are unsuitable for many of the regimens on offer.[1–3] To combat this unmet need, protein therapy is being explored as a potential treatment. Although most of the 866 ongoing US FDA-authorized studies investigating protein therapy are cancer trials, 29 studies are focusing on protein therapy for cardiovascular disease (CVD). So far, the results look promising.

Magic molecules

Proteins are the most important molecules inside every living cell, tissue and organ, and perform all functions necessary for life: they regulate all our physiological reactions, they metabolize carbohydrates and fats, they defend our bodies against bacteria and viruses, they work as enzymes, exquisitely potent hormones, antibodies, cytokines and signaling peptides that transmit information into cells – they do everything. Most human diseases are related to the malfunctioning of particular proteins, either systemically or locally. Today, a variety of human proteins can be produced with relative ease by means of genetic engineering and recombinant DNA technology. Large quantities of the desired protein can be made in mammalian cells, yeast or bacteria. Novel protein expression systems, including the newly introduced phage technology process, allow biologically active, properly folded, engineered proteins to be manufactured and purified in high yield at a very reasonable cost.

Therapeutic proteins can be used as highly effective medical treatments – protein therapy – for a wide array of diseases in which the protein is either lacking or deficient (for example, growth hormone and insulin), or the therapeutic protein is used to inhibit a biological process (eg, antibodies that block blood supply to tumors). A range of proteins and protein- based therapies are accepted treatments and have already been introduced into the market: for example, Interleukin-2 for the treatment of HIV infection and advanced tumor stages; Interferon (IFN) alfa-2b and IFN alfa-2a (today most commonly used as pegylated form) for the treatment of hepatitis B and C; granulocyte colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-GSF) for the treatment of HIV infection, hematological diseases and cancer; mycophenol for the treatment of chronic organ rejection and immunosuppression, or tumor necrosis factor (TNF) inhibitors for the treatment of rheumatoid arthritis. However, as yet no angiogenic protein-based therapy has been approved by the US FDA for the treatment of CVD.

Angiogenesis and CVD

To understand the implications of protein therapy in CVD, it is worth looking at the process of angiogenesis (the formation of new blood vessels) and its role in both disease and potential treatment. Research into angiogenesis started nearly 30 years ago and focused mainly on the inhibition of

angiogenesis to limit tumor growth. In the 1980s, the isolation, characterization and purification of the first angiogenic growth factors were reported; subsequently, inhibitors of angiogenesis were developed. Examples include angiostatin, endostatin, and tumstatin. In 2004, the US FDA approved the first anti-angiogenic protein therapy for cancer, Avastin (bevacizumab, rhuMAb-VEGF) to treat metastatic colorectal cancer in combination with established chemotherapy. Research into angiogenesis and heart disease established that in blood vessels of mature organisms, the endothelial cells remain in a quiescent, non-proliferate state until they are stimulated by conditions, such as wounding, inflammation, hypoxia or ischemia. The development of new vessels can be considered as the result of several processes:

- Dissolution of the matrix underlying the endothelial cell layer;
- Migration, adhesion and proliferation of endothelial cells;
- Formation of a new three-dimensional tube, which then lengthens from its tip as circulation is re-established;
- In larger vessels, vascular smooth muscle cells also migrate and adhere to the newly deposited matrix of the nascent vessel.

Angiogenic growth factors (proteins) induce, promote and/or interfere with all these steps of angiogenesis.

A large variety of very potent proteins and polypeptides, termed 'growth factors', exists in the human body. Growth factors are naturally occurring proteins capable of stimulating cellular proliferation, maturation, and differentiation; they typically act as signaling molecules between cells and bind to specific receptors on the surface of their target cells. The best-known growth factors with proven angiogenic potency are fibroblast growth factor-1 (FGF-1) and vascular endothelial growth factor-1 or -A (VEGF-1). FGF-1 stimulates the proliferation and differentiation of all cell types necessary for building an arterial vessel – endothelial cells, smooth muscle cells, and fibroblasts (adventitial cells) – whereas VEGF-1 mainly stimulates endothelial cells, and increases the permeability of the vessel wall.

Developing protein therapies

In contrast to the still very active research and development of anti-angiogenic proteins for the treatment of malignant tumors, research into the use of angiogenic proteins in promoting angiogenesis as a therapeutic option for CVD is still at an early stage – as reflected by the accordingly small number of clinical trials. In light of the importance, frequency and socio-economic impact of CVD in the Western world, however, and due to the limitations of conventional treatment modalities (PCI, CABG), especially for diffuse atherosclerotic diseases, the introduction of protein therapy as pro-angiogenic treatment could become the next important step in fighting CVD.[3]

In 1998, protein therapy was introduced for the first time in humans into the therapeutic arsenal of treatment modalities for CHD.[4,5] Because of the potency of FGF-1 (acidic FGF) in promoting angiogenesis with respect to proliferation of all cell types needed for vascular growth, FGF-1 was used as single protein therapy for patients suffering from diffuse CHD. In the context of the first-in-man clinical study, it should be noted that only the intramyocardial application of the growth factor appeared to be effective. This has the attractive feature of avoiding a systemic distribution and circulation of the protein, which would have potentially undesirable side-effects.[4]

The FGF family, with its prototype members, FGF-1 and FGF-2 (basic FGF), consists of at least 22 known members to date. They all are 16–18 kDa single chain peptides and display high affinity to heparin and heparin sulfate. FGFs stimulate a variety of cellular functions by binding to cell surface FGF-receptors (FGFR) in the presence of heparin proteoglycans. FGFRs are single chain receptor tyrosine kinases that become activated through autophosphorylation induced by a mechanism of FGF mediated receptor dimerisation. Receptor activation gives rise to a signal transduction cascade that leads to gene activation and diverse biological responses, including cell differentiation, proliferation and matrix dissolution, thus initiating a process of mitogenic activity critical for the growth of endothelial cells, fibroblasts, and smooth muscle cells.

These biological effects of FGF are established as a result of intracellular signal transduction initiated by the growth factor binding to and activating its receptors. The structure of the FGFRs includes an extracellular portion containing the ligand-binding domain, a transmembrane segment and a tyrosine kinase domain in the cytoplasm. FGF-1 is a monomeric single chain polypeptide consisting of 141 amino acids, and it binds to the second and third immunoglobulin like domains of all four FGFRs. FGF-1 contains no secretory leader sequence and is stabilized by binding to heparin.[6]

With patient safety being the primary endpoint, the first clinical trial was performed in 40 patients, who needed CABG primarily; additional diffuse CHD was simultaneously treated by local injection of FGF-1 intramyocardially as adjunct to bypass surgery (20 patients). The control group (20 patients) received heat-denatured FGF-1. No side-effects were seen and a three-fold increase in vascular density was observed within the treated myocardium group compared with the control group, over both the three-month and three-year periods. There was a strictly localized angiogenic effect in the treated myocardium; the angiogenic response to FGF-1 protein delivery in the myocardium persisted over years; there was also an improvement of the myocardium regarding perfusion and function.[5]

In a second clinical trial that included 20 patients with CHD and no option for PCI and/or CABG, the FGF-1 administration as sole therapy was accomplished through mini-thoracotomy.[7] That second study, completed in 2000, focused on both safety and the functional status of the patients after therapy. The results were as follows: improvement of myocardial perfusion demonstrated by SPECT scans, under rest as well as under stress conditions; improvement of maximum working capacity in 18 patients; improvement in CCS-classification of at least one class in all patients. Since then, a Phase I human clinical trial has been successfully performed in the US, confirming the results of the two German trials.[8]

Because atherosclerotic disease is a systemic disease, CV Biotherapeutics is also performing clinical trials in peripheral arte-

rial disease (PAD) and in patients suffering from diabetic ulcers (wound healing). A proof of concept trial is also underway in Russia in patients with chronic back pain – a disease which might also be related to a lack of perfusion (lumbar arteries).

This new type of treatment for severe CVD – using a human protein with no immunogenic response, no need for viral vectors, localized effect at the target tissue and predictability of dose – is just one example of the promise of protein therapy. If the CVD study results can be reproduced in other therapeutic domains, then protein therapy could well become the treatment modality of choice for many disorders.

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