

## REPORT

## Biotechnology &amp; The Future of Medicine



We are on the threshold of a new era in medicine. Cell therapy, the manipulation of immature stem cells to combat disease, is the latest revolutionary breakthrough in biological research. Not since Robert Hooke first peered through a piece of glass and called what he found a "cell" has science made such a giant leap in its understanding of this most basic-and eloquent-of structures.

One company at the forefront of this compelling and burgeoning field is Celmed Biotechnologies.

Celmed Biotechnologies was created in June 2001 to pursue work in the realm of autologous stem cell therapy for neurological diseases, including Alzheimer's, Parkinson's and Huntington's. In autologous stem cell therapy, stem cells drawn from the patient are later implanted back into the patient's body. This type of therapy has distinct advantages over heterologous stem cell therapy, where cells from matched donors are used.

Additional programs are focused towards the application of photodynamic therapy to restore bone marrow function in patients who have undergone chemotherapy for chronic myeloid leukemia (CML) and non-Hodgkins' lymphoma (NHL). This therapy also reduces the risk of life-threatening complications common with traditional bone marrow transplant procedures.

## Peptide research

Peptides are short chains of 20 or fewer amino acids-shorter than proteins, which range from 50 to over 300 amino acids in length. Natural processes of cellular and tissue regeneration involve peptide chains; they can either induce or inhibit biological effects, acting as agonists or antagonists in physiological systems. When used therapeutically, peptides are highly specific in their activity and effective at low doses. Unfortunately, there is one significant problem with the use of peptides as medicine: they are unstable and quickly lose activity once introduced into the body. The solution has been to develop long acting peptides, or LAP1, which are biochemically altered in a manner that stabilizes and preserves the peptide's unique sequence of amino acids.

## A novel peptide that increases growth hormone activity

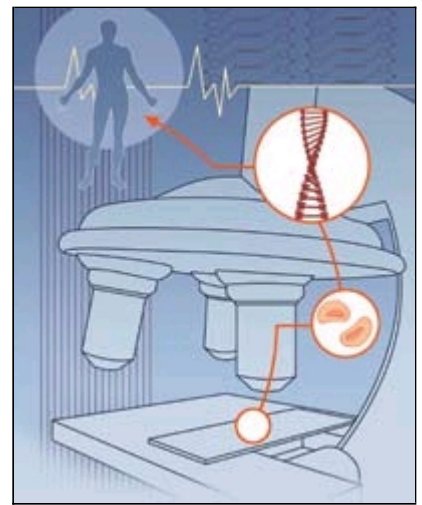
One of the most important therapeutic developments is a peptide that duplicates the activity of growth hormone releasing hormone (GHRH)-also known as growth hormone releasing factor (GRF)-in the body. In youth, a part of the brain called the hypothalamus makes plenty of GHRH, which stimulates the pituitary gland to release growth hormone (GH). Growth hormone, in turn, stimulates the production of insulin-like growth factor 1 (IGF-1) in the liver. The majority of growth hormone's youth-preserving, disease-preventative effects spring from the effects of IGF-1, which is also known as anabolic tissue growth factor. IGF-1 enhances immune function and preserves muscle tissue both structurally and functionally. Growth hormone acts directly to decrease the amount of fat stored in fat cells, helping to maintain youthful body composition.

Growth hormone and IGF-1 production decline by about 14% every 10 years. Muscle loss, fat gain, skin thinning, immune dysfunction and bone demineralization increase as GH and IGF-1 production declines. To date, growth hormone replacement is one of the most potent known therapies for slowing the onset of physical signs of aging. Unfortunately, it's prohibitively expensive, and its safety has not been conclusively proven. The therapeutic peptide ThGRF (TH 9507) is a growth hormone releasing factor analogue: it behaves like GRF in the body, leading to an increase in levels of both growth hormone and IGF-1.

## ThGRF research: selected studies

Research is bearing out the clinical value of ThGRF.2 It has been shown to have a longer duration of activity when compared with endogenous (made in the body) GRF. It reliably raises GH levels, and closely mimics the body's natural GH secretion pattern.

Many hormones and neurotransmitters are released in pulses, with levels rising and falling slightly in a regular pattern. It's difficult to mimic this natural pulsatility with growth hormone replacement therapy, and with the lack of natural ups and downs come adverse effects, including fluid retention, carpal tunnel syndrome and insulin resistance. While some clinicians have managed to achieve some level of pulsatility by giving frequent subcutaneous injections of growth hormone, the use of ThGRF has thus far proven to be safer, more convenient and more conducive to a pulsatile pattern resembling the natural physiological release of GH and IGF-1. To date, some of the applications include: ThGRF, growth hormone and IGF-1 levels. In a study of men aged 50 to 60 years, ThGRF administration caused IGF-1 levels to rise by 90% to 106% in a matter of only a few days-to levels comparable to those of a young adult.<sup>3</sup> The 39 men involved all had similar IGF-1 levels when the study began. Other hormones were not adversely affected, which implies that ThGRF had highly specific effects on the body. Side effects were comparable to those seen with placebo. All told, this study found that ThGRF therapy could successfully and safely restore growth hormone secretion to youthful levels.



*Sleep.* In aging people, insomnia is a common complaint. Current treatments for insomnia are effective for those who have trouble falling asleep, but do little to help decrease frequent wakeful episodes during the night. Sleep-inducing medications have some drawbacks: they can be addicting, and they usually impair rather than improve daytime alertness and increase the risk of accidents. ThGRF has been assessed as a therapy for sleep maintenance insomnia in a Phase II trial involving 12 healthy subjects between 50 and 65 years of age. The peptide slightly increased restful slow wave sleep and increased alertness during the day, especially during the hours of late afternoon and early evening.

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Chronic obstructive pulmonary disease (COPD). COPD patients often experience dramatic loss of muscle function and decreases in exercise tolerance. With 16 million Americans afflicted by COPD-the fourth leading cause of death in the U.S.-much use exists for therapies that can improve quality of life in these patients. A clinical trial is underway to measure positive effects of ThGRF therapy on endurance, muscle function, and overall quality of life in people with COPD.

Hip fracture. Each year, 754,000 people in North America, Japan and the U.S. suffer a hip fracture. During recovery from the fracture and surgery to repair it, these individuals often suffer significant loss of strength and muscle mass. Currently under investigation is an examination of the benefits of ThGRF measuring hip fracture patients' ability to perform daily activities and regain their strength and balance. This study also will measure patient independence and level of consumption of health care services following surgery.

#### Novel delivery systems for therapeutic peptides



Therapeutic drug delivery is a particularly difficult issue with regard to peptides as they cannot be taken orally. Studies have found that compliance is likely to be poor if subcutaneous injections are the only drug delivery method that works. One potential option is the development of a new transdermal peptide delivery system that features a skin patch lined with a titanium microprojection array, which opens up miniscule pathways through the skin. These pathways allow the painless and direct introduction of peptides, drugs or vaccines.<sup>4,5</sup> The transdermal patch is coated with whatever drug is being used, and when applied the patch can introduce the necessary amount of drug in a short time span. Animal studies have shown that the potency of the dose given increases with this delivery system. This means that lower dosages can be effectively given. There is decreased likelihood of skin irritation compared to traditional drug delivery patches.

#### Autologous stem cells

One of the most promising areas of medical exploration is in the area of stem cell research. Stem cells are immature, undifferentiated cells that can mature into any type of cell that exists in the body. Modern stem cell technology enables scientists to direct the maturation of these stem cells, encouraging them to develop into a specific type of cell. The potential use of stem cells taken from embryos has aroused a significant amount of controversy because of ethical concerns. There are now ways around this issue by utilizing autologous stem cell transplantation. Stem cells from the patient's own body are extracted and cultured or treated for eventual reimplantation into the patient. This technique also circumvents the common problem, where the patient's immune system reacts strongly against the implantation of foreign-cells or organs.

Cultured and implanted stem cells could restore the function of organs or tissues destroyed by disease. Autologous stem cell therapy holds huge promise in the treatment of disorders that are now incurable, including Parkinson's disease, Huntington's disease, Alzheimer's disease, juvenile diabetes, spinal cord injury and the neurological damage caused by stroke and brain tumors.

Celmed's stem cell work is progressing on two different platforms: the use of neural stem cells to treat neurodegenerative diseases, and the use of hematopoietic (bone marrow) stem cells in the treatment of cancers that involve blood cells-non-Hodgkin's lymphoma (NHL) and chronic myeloid leukemia (CML).

One key study in the realm of neural stem cell transplantation recently focused on a Parkinson's disease patient whose symptoms greatly decreased within a year of transplantation.<sup>6</sup> Researchers discovered that while many of the transplanted cells developed the ability to make dopamine-the neurotransmitter that is lacking in Parkinson's patients-the symptomatic improvement appeared to be due to some other variable. Symptoms continued to improve a year after the transplant, despite the fact that dopamine uptake in the brain declined to levels seen at the beginning of the study by that time. No other therapy has shown so much promise in the treatment of Parkinson's disease.

#### Photodynamic stem cell therapy

Bone marrow makes most of the components of blood and of the immune system, and when its function is compromised, life-

threatening infections and other problems can set in. Chemotherapy often results in a loss of bone marrow function. This is why bone marrow transplant is often a necessary part of cancer therapy. Unfortunately, about 70% of patients aren't able to receive a bone marrow transplant because a compatible donor cannot be found. Even when a match is found, graft vs. host disease (GvHD) is a distinct and dangerous possibility.



The oncology research community has explored the possibility of autologous bone marrow transplants-where the marrow is taken from the patient before chemotherapy and reintroduced post-chemotherapy-but there is always the possibility that cancerous cells will remain in the transplanted marrow, potentially reintroducing the cancer. Celmed has developed a new technology called Theralux™ that solves this problem, making autologous bone marrow transplants a viable option. Bone marrow is drawn from the patient and treated with a photosensitive molecule-a peptide called TH 9402. In studies performed in 1999, it was found that TH 9402 accumulates in cancerous cells and causes them to be destroyed when exposed to a specially designed light. When marrow is exposed to this light source, cancerous cells are eradicated and healthy ones preserved. The resulting marrow is ready for transplantation back into the patient after chemotherapy has ended. Animal studies suggest that Theralux™ circumvents the problems of graft vs. host disease and preserves the cancer-therapeutic and immune-stimulating effects of bone marrow transplantation.<sup>7-10</sup>

Chronic myelogenous leukemia (CML), characterized by uncontrolled proliferation of certain types of blood cells, and non-Hodgkin's lymphoma (NHL), where immune components become malignant and multiply, are also in advanced study phases. Both cancers are on the rise. CML is responsible for 10,000 new cases each year in Japan, Canada the U.S. and Europe, and 25,000 people dying from NHL each year in the U.S. alone. Sixteen CML patients have had autologous transplant of photodynamically treated bone marrow. Thus far, four of them have entered complete remission, with 82% survival rate at 15 months. In January 2001, researchers in Montreal, Canada began a trial of Theralux™ in the treatment of 28 NHL patients.

#### Future directions

Currently, ThGRF is undergoing several phase II human trials, and a series of Investigational New Drug (IND) applications for this unique product have been formally filed. Research has indicated that elements of the endocrine system, particularly growth hormone and IGF-1, are actively involved in the function of the immune system. Currently, a study is underway to determine whether ThGRF administration will improve immune response to the flu vaccine in 160 elderly people. The clinical usefulness of such a therapy is potentially enormous; influenza kills 40,000 people each year, and over 90% of those people are aged 65 or older. The study will measure improvement in levels and activity of T lymphocytes and antibodies, as well as any decline in common flu complications, such as pneumonia.

A second Phase II study of 90 men and women aged 35 to 50 is currently underway to further test the effectiveness and safety of ThGRF for the treatment of sleep maintenance insomnia. This study, involving seven different centers in Canada and Europe, will measure the effects of varying doses of ThGRF over a two-week period on daytime alertness, subjects' assessment of their sleep quality, and polysomnographic recordings taken during the night.

Type 2 diabetics have been warned against growth hormone replacement and GRF therapy because it exacerbates insulin resistance. Because so many aging people suffer from type 2 diabetes and prediabetes, researchers have now implemented a study designed to ascertain whether the drug is safe for this population.

The above studies and applications are at the forefront of the new applications that will surely emerge from cellular research. New products taming degenerative diseases will change the understanding of the human body as we now know it.

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