



- Research
- Finance & Funding
- Patents
- New Products
- Mergers & Acquisitions
- Law & Litigation

Volume 6, No. 16

December 17, 2008

In This Issue...

- ALS TDI, Asklepios To Develop Options For Treating ALS 1
- FDA Okays Phase III Trial Of Combination Therapy For Intrinsic Brainstem Glioma 2
- Recruitment Begins For Phase 2 Clinical Trial Of Advanced Heart Failure Treatment 3
- Gene Therapy Eliminates Brain Tumors Through Selective Recruitment Of Immune Cells.. 4
- Gene Therapy Reverses Damage In Heart Failure 5

Top of the News...

ALS TDI, Asklepios To Develop Options For Treating ALS

The ALS Therapy Development Institute (Cambridge, Mass.) and Asklepios BioPharmaceutical, Inc. (Chapel Hill, N.C.) said they would work together to develop a panel of viral vectors that could be used to deliver therapeutics based on targets identified by ALS TDI that slow or stop amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease).

The collaboration between the two research centers will focus on screening and characterization of optimal delivery vectors.

"This project is an aggressive and proactive effort to develop the safest alternative therapeutic delivery options available today," said ALS chief science officer Dr. Steve Perrin. "By focusing on developing therapeutic strategies while operating the largest discovery biology program for this disease, we are preparing to rapidly move potential therapeutics through the drug development process with today's patients in mind."

The custom-constructed Biological Nano Particle (BNP) vectors are designed using proprietary technology developed by Asklepios.

ALS TDI will evaluate the BNP vectors in a tightly-managed mouse colony that is based on mutations in a specific mutated protein, which is a cause of a genetic form of disease.

BNP vectors are of interest to drug development scientists because they generally do not elicit as aggressive an immune response often associated with other viruses, and have been clinically tested.

Samples from animals treated with BNP vectors will be analyzed by a variety of molecular and immunohistochemistry analysis techniques at ALS TDI to determine in which cell types each vector becomes localized in various tissue samples.

This project is seen as bolstering tools available as part of a

(Continued on page 2)

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(Continued from page 1)

key therapeutic strategy used by ALS TDI to develop effective therapeutics for ALS: viral gene therapy.

“There is a consensus that gene therapeutics are ideally suited to target the largely unmet medical needs of a variety of orphan diseases including ALS. I’m excited that AskBio has formed a partnership with ALS TDI, as it combines our experience in developing gene delivery technology with the expertise and capabilities that ALS TDI have in screening ALS therapeutic leads. Our main objective is to resolve issues that have limited successful gene delivery approaches to ALS in the past, and I look forward with a great deal of optimism to offering this initial step toward progress for the ALS community,” said Asklepios president Jude Samulski, Ph.D.

Funding for this project is made possible as part of a major, three-year, \$18 million funding and scientific collaboration between ALS TDI

and with the Muscular Dystrophy Association (MDA) and its Augie’s Quest Initiative, entered into at the beginning of 2007.

Asklepios BioPharmaceutical, Inc. also receives funding from MDA.

Contact: <http://www.askbio.com>

Contact: <http://www.als.net>

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FDA Okays Phase III Trial Of Combination Therapy For Intrinsic Brainstem Glioma

The Burzynski Research Institute, Inc. (Houston, Texas) said that it has reached an agreement with the U.S. Food and Drug Administration (FDA) that enables the company to move forward immediately with a pivotal Phase III clinical trial of combination antineoplaston therapy plus radiation therapy in patients with newly-diagnosed, diffuse, intrinsic brainstem glioma.

Antineoplaston therapy (ANP) uses a synthetic version of naturally occurring peptides and amino acid derivatives found in the human body to target and control cancer cells without destroying normal cells.

The agreement was made under the FDA’s Special Protocol Assessment (SPA) procedure and means that the design and planned analysis of the Phase III study is acceptable to support a regulatory submission seeking new drug approval.

“We are very pleased by our agreement with the FDA to move forward with a confirmatory study on a type of tumor that has shown itself to be highly treatment resistant and challenged further by severely limited treatment options and clinical trials that could expand and discover new, efficacious therapies,” said Stanislaw R. Burzynski, M.D., Ph.D. “The SPA agreement puts antineoplaston therapy further down a straight path to regulatory approval, enabling the kind of study that should prove its merits as another option to cancer management.”

“BRI has reached this important milestone

(Continued on page 3)

gene therapy research news

Research: Krishna Patel
Marketing: Carla Kosovsky
Subscriber Services Manager: Sarah Dufour
Special Projects: Leila McGee
Production Assistant: Ben Levin

Published 24 times a year by
 DataTrends Publications, Inc.
 614 Jacob Ct. SW
 Leesburg VA 20175 USA
 Phone: 703-779-0574
 Fax: 703-779-2267

Corporate subscription: US\$295.00
info@datatrendspublications.com

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independently without financial backing from the government, and without a major pharmaceutical partner--a unique accomplishment in the oncology field. From inception, we have been committed to developing a targeted gene therapy option that is less aggressive on the body than conventional therapies and have made considerable progress on the steps mandated by the FDA to bring a new drug to a patient community and cancer type that has unmet needs."

The primary objective of this randomized study is to compare overall survival of children with newly-diagnosed diffuse intrinsic brainstem glioma (DBSG) who receive combination anti-neoplaston therapy [Antineoplastons A10 (Atengenal) and AS2-1 (Astugenal)] plus radiation therapy (RT) versus RT alone.

DBSG are considered to be one of the most difficult types of cancer to treat. It combines highly malignant characteristics with the very difficult location of the brainstem.

DBSG are inoperable because they involve most of the brainstem (diffuse and intrinsic).

The number of children in the U.S. with brainstem gliomas is approximately 660. Absent treatment, the survival rate from time of diagnosis is six months or less.

At present, there are no standard curative treatments for the disease. RT is the only treatment that may slow its progress, but at two years 93 percent of children with this type of cancer die, and none of them survive for five years.

Other conventional treatments such as chemotherapy have generally been tried in clinical trials but are shown to be ineffective. There are no pharmacological treatments approved for DBSG at this time.

Contact: <http://www.burzynskiclinic.com>

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Recruitment Begins For Phase 2 Clinical Trial Of Advanced Heart Failure Treatment

The Cardiopulmonary Research Science and Technology Institute (CRSTI), and Medical City Hospital (Dallas, Texas), have begun enrolling patients for a Phase 2 clinical trial for advanced heart failure.

Initial data for the so-called CUPID trial ("Calcium Up-Regulation by Percutaneous Administration of Gene Therapy in Cardiac Disease") were reported recently at the American Heart Association scientific sessions 2008.

The study is evaluating MYDICAR, a genetically-targeted enzyme replacement therapy for advanced heart failure.

"The CUPID trial is designed to rescue a failing heart by replacing an enzyme known to play a critical role in normal cardiac muscle cell activity. Our goal is not only to improve the symptoms of heart failure, but restore physiologic function and reverse the severity of the disease," said Eric J. Eichhorn, MD, FACC, an interventional cardiologist with The Dallas Heart Group. "The recent data reported from the study demonstrate the safety of MYDICAR, and improvements in cardiac function and overall condition observed in some patients further validate our target and approach. Given these early encouraging results, we have begun enrollment of phase 2 clinical testing to evaluate the ability of MYDICAR to improve heart function in more patients."

The Phase 2 portion is a randomized, double-blind, placebo-controlled, parallel-group, dose ranging trial that compares the use of MYDICAR at two or three dose levels with placebo.

CUPID is expected to enroll 46 patients with advanced heart failure at 15 U.S. medical centers.

MYDICAR is delivered in a single dose directly to the heart muscle during a short outpatient procedure, performed in a standard cardiac catheterization laboratory via a small incision in the upper leg.

(Continued on page 4)

Data from the Phase I in advanced heart failure was presented, and demonstrated that MY-DICAR had an acceptable safety profile in these first nine patients, as determined by study investigators and an independent safety committee.

In addition, improvements from baseline to six months across a number of parameters important in assessing heart failure status were observed, including symptomatic (5 patients), functional (4 patients), biomarker (2 patients) and left ventricular function/remodeling (6 patients).

Of the nine patients treated, two with low levels of pre-existing antibodies to the AAV vector did not show improvement in these parameters.

The data are consistent with safety established for other AAV vectors, which has been demonstrated in clinical studies of more than 500 patients.

AAV vectors are the product of decades of research focused on the safety of gene transfer agents, and are derived from components of a non-replicating, non-pathogenic, commonly occurring human virus.

AAV vectors do not integrate into the chromosome and are considered non-mutagenic. In addition, they have not been associated with the types of inflammatory reactions observed in trials involving adenoviral vectors, which are known to induce acute inflammation of tissues due to activation of the body's immune system.

Heart failure is the leading medical cause of hospitalization and is expected to result in estimated direct and indirect costs to the healthcare system in 2008 of \$35 billion.

Despite important therapeutic advances in pharmacologic and device therapies, the prognosis of heart failure patients remains poor.

Access to nonpharmacologic therapies, such as heart transplantation and the use of mechanical assist devices, is restricted to a fraction of patients who need them.

About 5 million people in the United States have heart failure, and another 550,000 new cases are diagnosed each year. Heart failure contributes to or causes about 280,000 deaths annually.

The most common symptoms of heart failure are shortness of breath, feeling tired, and

swelling in the ankles, feet, legs, and sometimes the abdomen. There is no cure for heart failure.

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Gene Therapy Eliminates Brain Tumors Through Selective Recruitment Of Immune Cells

Scientists seeking to harness the power of the immune system to eradicate brain tumors face two major hurdles: recruiting key immune cells called dendritic cells into areas of the brain where they are not naturally found and helping them recognize tumor cells as targets for attack.

Researchers doing laboratory and animal studies at Cedars-Sinai Medical Center, however, have identified a sequence of molecular events that accomplish both objectives.

The Cedars-Sinai team discovered that a protein – HMGB1 – released from dying tumor cells activates dendritic cells and stimulates a strong and effective anti-tumor immune response.

HMGB1 does so by binding to an inflammatory receptor called toll-like receptor 2, or TLR2, found on the surface of dendritic cells.

“Toll receptors play a major role in the immune system's recognition of bacterial and viral components, but now we have shown that they also trigger an immune response against tumors,” said Maria G. Castro, Ph.D., co-director of Cedars-Sinai's Board of Governors Gene Therapeutics Research Institute and one of the article's senior authors. “Activation of Toll receptors was essential for two key stages in initiating immune responses against the tumor – the migration of peripheral dendritic cells into the brain tumor and the subsequent activation of dendritic cells and stimulation of a specific anti-tumor cytotoxic T-cell mediated response.”

Building on more than 10 years of research in this area, the researchers used a combined gene therapeutic approach, using one protein (Flt3L) to draw dendritic cells from bone marrow into the brain tumors, and a second pro-

(Continued on page 5)

tein (Herpes Symplex type I Thymidine Kinase, or TK), combined with the antiviral gancyclovir to kill tumor cells and elicit long-term survival.

In this paper, they uncovered a novel mechanism by which tumor cell death in response to the treatment leads to the release of an endogenous tumor protein, HMGB1, which is essential to trigger the anti-tumor immunological cascade.

The study showed for the first time that HMGB1 released from dying brain cancer cells activates TLR2 signaling on tumor infiltrating dendritic cells, resulting in the activation and expansion of tumor-antigen specific T cells.

This caused the regression of the brain tumors and increased survival time by six months in experimental brain tumor models.

Glioblastoma multiforme is the most aggressive type of brain tumor, with only five percent of patients surviving five years following diagnosis.

While new drugs have had some impact on survival rates, the traditional approaches to cancer treatment – surgery, radiation and chemotherapy – have failed to provide major improvements in long-term survival.

Immunotherapy – eradicating brain cancer cells by harnessing the patient’s immune system – has been an attractive treatment approach, in theory.

An effective anti-tumor immune response initially depends on dendritic cells that constantly “sample” the environment and can recognize unusual proteins, such as those belonging to cancers or infectious pathogens.

However, since there are few dendritic cells in the brain, the immune responses in this organ are dampened when compared to those elicited in other parts of the body.

According to Pedro Lowenstein, M.D., Ph.D., director of the Board of Governors Gene Therapeutics Research Institute and co-senior author, “The discovery of a central role for HMGB1 and TLR2 in overcoming immune ignorance to brain tumor antigens provides a new therapeutic approach in the fight against brain tumors. Our conclusions relating to anti-glioma immune responses have also been extended to enhancing immune responses against a number of other metastatic brain cancers, such as melanoma.”

He stated that plans are underway to test this novel therapeutic approach in a human clinical trial for recurrent brain tumors in 2009.

The findings appear in the January 13 issue of *PLoS Medicine*, an open-access online journal.

Citation: PLoS Medicine, “HMGB1 mediates endogenous TLR2 activation and brain tumor regression,” Jan. 13, 2009.

Contact: Maria G. Castro,
castromg@cshs.org

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Gene Therapy Reverses Damage In Heart Failure

Long-term gene therapy resulted in improved cardiac function and reversed deterioration of the heart in rats with heart failure, according to a recent study.

The rats were treated with a gene that generates a peptide called ARKct, which was administered to hearts in combination with recombinant-adeno-associated virus serotype 6 (rAAV6).

ARKct works by inhibiting the activation of G protein-coupled receptor kinase 2 (GRK2).

GRK2 is a kinase that is increased in heart failure myocardium.

Enhanced GRK enzymatic activity contributes to the deterioration of the heart in heart failure, according to Walter J. Koch, Ph.D., director of the Center for Translational Medicine at Jefferson Medical College of Thomas Jefferson University.

Koch’s research team carried out the study, which was led by Giuseppe Rengo, M.D., a post-doctoral fellow.

“The theory is that by inhibiting this kinase, the heart will recover partially due to reversal of the desensitization of the adrenergic receptors,” Koch said. “The expression of ARKct leads to a negative neurohormonal feedback that prevents the heart from continuing on the downward slope during heart failure. This was one novel finding of the study.”

Koch and his colleagues used five groups

(Continued on page 6)

of rats in their study. Two groups received rAAV6 with the ARKct peptide, two groups received rAAV6 with green fluorescent protein (GFP), and the last group received a saline treatment. One of the ARKct groups and one of the GFP groups also received the beta blocker metoprolol concurrently.

Twelve weeks after receiving the treatment, the rats who received the ARKct had a significantly increased left ventricular ejection fraction.

The treatment also reversed the left ventricular deterioration and normalized the neurohormonal status.

Koch said that targeting the GRK2 enzyme with ARKct was sufficient to reverse heart failure even without concomitant metoprolol.

The rats that received GFP or saline alone experienced more deterioration of cardiac function during the course of the study. This deterioration was prevented, but not reversed, with the

concomitant metoprolol.

“Our data show that beta blockers and the ARKct peptide are compatible and can be given together,” Koch said. “Although beta blockers are effective at stopping the downward progression of the disease, they do not reverse the damage already done. That is where the ARKct gene therapy comes in.”

In future trials in humans, the ARKct peptide will be administered with beta blockers, which are the standard treatment.

However, Koch said that if a pharmaceutical inhibitor can be developed, then a new class of drugs to treat heart failure could possibly even replace beta blockers.

The study was published online in *Circulation*.

Contact: Walter J. Koch, Ph.D., 215-955-9982, walter.koch@jefferson.edu

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