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Top of the News...

Gene Therapy Clinical Trial Yields Promising Results For Batten Disease

Promising results from a team of New York-Presbyterian Hospital/Weill Cornell Medical Center physician-scientists show that gene therapy is both safe and effective at slowing the progression of Batten disease, or late infantile neuronal ceroid lipofuscinosis (LINCL), a rare, genetic, degenerative neurological disorder that usually becomes fatal in children by the age of 8 to 12.

The clinical trial found that injecting a harmless gene-bearing virus into the brain was not only safe, but on the average significantly slowed the disease progression of the subjects tested.

Neurological function was assessed using a rating scale throughout an 18-month follow-up period.

“The virus is used as a Trojan horse that houses and then delivers a healthy, functional gene into the cells of the brain,” said lead author Dr. Ronald Crystal, chairman of the Department of Genetic Medicine and chief of the Division of Pulmonary and Critical Care Medicine at New York-Presbyterian Hospital/Weill Cornell Medical Center. “The genes are incorporated within the genetic material of the cells, which are then able to produce a protein that is deficient in Batten disease.”

Crystal is a world leader and pioneer in the use of gene therapy to treat a number of genetic disorders and diseases.

The results are published in the May 13 online issue of *Human Gene Therapy*. The gene in question – CLN2 – is mutated in children with the disease, causing a deficiency in the enzyme TPP-1, which is responsible for ridding cells of the central nervous system of waste materials.

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Small organelles within the cell, called lysosomes, become clogged with toxic material within the neurons of the brain.

“It’s like the garbage man of the cell is not able to do its job,” said Crystal. “The trash keeps getting backed up inside the cell until the cells can no longer function properly and then eventually die throughout the entire brain.”

When this happens, children with the disease begin exhibiting neurological symptoms, starting around age 4, including impaired muscle coordination (ataxia), involuntary twitching (myoclonus), and speech and developmental disorders.

A gradual decline in visual ability follows. Affected children generally become wheelchair-bound by the ages of 4 to 6 years and eventually become bedridden.

Because the disease is fatal early in life, there are only about 200 cases of the disease in

the world at a given time.

Subjects from around the world were carefully selected to take part in the trial.

Neurological surgeons from New York-Presbyterian Hospital/Weill Cornell Medical Center, led by Drs. Mark Souweidane and Michael Kaplitt, performed the gene therapy procedure.

Six tiny holes were made in the skull of each subject, and then a liquid containing the healthy CLN2 gene, within the harmless adeno-associated virus (AAV), was injected into the brain.

“Before now, we had no hope of a therapy for Batten disease, but today we can say that there is some hope,” Crystal said. “These results are not just promising for sufferers of the disease, but suggest that gene therapy can work and should be studied for other neurological disorders. Each gene in our body has the potential to become a target to study for human disease.”

Co-researchers include Dr. Stefan Worgall, Dr. Dolan Sondhi, Dr. Neil R. Hackett, Dr. Barry Kosofsky, Dr. Minal V. Kekatpure, Dr. Nurunisa Neyzi, Dr. Jonathan P. Dyke, Dr. Douglas Ballon, Dr. Linda Heier, Dr. Bruce M. Greenwald, Dr. Paul Christos, Dr. Madhu Mazumdar, Dr. Mark M. Souweidane and Dr. Michael G. Kaplitt – all from New York-Presbyterian/Weill Cornell.

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Gene Therapy Improves Vision In Patients With Congenital Retinal Disease

Patients’ vision improved from detecting hand movements to reading lines on eye chart. In a clinical trial at the Children’s Hospital of Philadelphia, researchers from the University of Pennsylvania have used gene therapy to safely re-

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gene therapy research news

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Published 24 times a year by

DataTrends Publications, Inc.

P.O. Box 4460

Leesburg VA 20177-8541 USA

Phone: 703-779-0574

Fax: 703-779-2267

Corporate subscription: US\$295.00

info@datatrendspublications.com

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store vision in three young adults with a rare form of congenital blindness.

Although the patients have not achieved normal eyesight, the preliminary results set the stage for further studies of an innovative treatment for this and possibly other retinal diseases.

An international team led by the University of Pennsylvania, the Children's Hospital of Philadelphia, the Second University of Naples and the Telethon Institute of Genetics and Medicine (both in Italy), and several other American institutions reported their findings today in an online article in the *New England Journal of Medicine*.

"This is the first gene therapy trial for a nonlethal pediatric condition," said Albert M. Maguire, M.D., associate professor, department of ophthalmology, University of Pennsylvania School of Medicine.

Maguire, together with his wife, Jean Bennett, M.D., Ph.D., professor of ophthalmology at Penn, have been researching inherited retinal degenerations such as Leber congenital amaurosis (LCA), for 18 years.

LCA is a group of inherited blinding diseases that damages light receptors in the retina. It usually begins stealing sight in early childhood and causes total blindness during a patient's twenties or thirties.

There is no treatment for LCA.

"Patients' vision improved from detecting hand movements to reading lines on an eye chart," Maguire said.

In 2001, Bennett and Maguire were part of a team which reported successfully reversing blindness using gene therapy on dogs affected by the same naturally occurring form of congenital blindness.

The current study is sponsored by the Center for Cellular and Molecular Therapeutics at The Children's Hospital of Philadelphia, directed by Katherine A. High, M.D.

High, a study leader and an Investigator of the Howard Hughes Medical Institute, has been a pioneer in translational and clinical studies of gene therapy for genetic disease, and in 2005 initiated a collaboration with Bennett and her group to translate their exciting animal findings into a clinical study.

The scientists used a vector, a genetically engineered adeno-associated virus, to carry a normal version of the gene, called RPE65, that is mutated in one form of LCA.

Three patients, ages 19, 26 and 26, received the gene therapy via a surgical procedure performed by Maguire between October 2007 and January 2008 at the Children's Hospital of Philadelphia, where the gene vector was manufactured at the hospital's Center for Cellular and Molecular Therapeutics (CCMT).

Starting two weeks after the injections, all three patients reported improved vision in the injected eye.

"Standard vision tests showed significantly improved vision in the patients," said Alberto Auricchio, M.D., a study leader from the Telethon Institute of Genetics and Medicine and University of Naples Federico II.

The researchers also reported that each injected eye became approximately three times more sensitive to light, and each was improved compared to the uninjected, previously better functioning eye.

The LCA gene therapy vector showed no signs of causing inflammation in the retina or other toxic side effects.

One of the three patients had an adverse event, a hole in the retina that did not affect eyesight and may have been surgery-related, rather than related to biological effects of the therapeutic gene or the vector used to carry it.

The patients enrolled in the study to date were identified at the Department of Ophthalmology at the Second University of Naples, an institution with long-standing experience in collecting and studying patients with inherited retinal diseases, under the supervision of Francesca Simonelli, M.D.

Testing continued over a period of six months following the gene therapy vector administration.

One patient was better able to navigate an obstacle course compared to before the injection.

The patients also had less nystagmus, an involuntary movement of the eyes that is common in LCA.

In the patient who experienced better vi-

(Continued on page 4)

sion even in the uninjected eye, the researchers suggest that the reduced nystagmus benefited both eyes.

“The current clinical trial will continue with more patients and with ongoing follow-up to monitor results,” said Bennett. “We expect improvements to be more pronounced if treatment occurs in childhood, before the disease progresses.”

“This result is important for the entire field of gene therapy,” said High. “Gene transfer has been in clinical trials for over 15 years now, and although it has an excellent safety record, examples of therapeutic effect are still relatively few. The results in this study provide objective evidence of improvement in the ability to perceive light, and thus lay the groundwork for future studies in this and other retinal disorders.”

The pace of moving from pre-clinical discoveries into clinical trials has typically been slow in the field of gene therapy due to the breadth of expertise required, ranging from in-depth knowledge of the disorder to detailed understanding of vector design, manufacture, and pre-clinical evaluation.

The complexities of regulatory oversight at both the federal and local levels also present challenges.

Through the Center for Cellular and Molecular Therapeutics, the Children’s Hospital of Philadelphia has developed concentrated expertise and substantial resources to facilitate the “bench to bedside” translation of gene therapy.

The clinical trial was sponsored and primarily funded by the Center for Cellular and Molecular Therapeutics at the Children’s Hospital of Philadelphia.

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Magnets Offer Breakthrough In Gene Therapy For Cancer

A revolutionary cancer treatment using microscopic magnets to enable “armed” human cells to target tumors has been developed by researchers funded by the UK’s Biotechnology and Biological Sciences Research Council (BBSRC).

Research published online April 17 in the journal *Gene Therapy* showed that inserting these nanomagnets into cells carrying genes to fight tumors, results in many more cells successfully reaching and invading malignant tumors.

Using human cells as delivery vehicles for anti-cancer gene therapy has long been an attractive approach for treating tumors, but these cells usually reach tumors in insufficient numbers to effectively attack them.

Now, a new “magnetic targeting” method has been developed to overcome this problem by Prof. Claire Lewis at the University of Sheffield, Prof. Jon Dobson at the University of Keele, and Prof. Helen Byrne and Dr. Giles Richardson at the University of Nottingham.

The technique involves inserting nanomagnets into monocytes, a type of white blood cell used to carry gene therapy, and injecting the cells into the bloodstream.

The researchers then placed a small magnet over the tumor to create a magnetic field and found that this attracted many more monocytes into the tumor.

“The use of nanoparticles to enhance the uptake of therapeutically armed cells by tumors could herald a new era in gene therapy - one in which delivery of the gene therapy vector to the diseased site is much more effective,” said Lewis, the head of the laboratory in which the work was done. “This new technique could also be used to help deliver therapeutic genes in other diseases like arthritic joints or ischemic heart tissue.”

“Though the concept of magnetic target-

(Continued on page 5)

ing for drug and gene delivery has been around for decades, major technical hurdles have prevented its translation into a clinical therapy," said Dobson.

"By harnessing and enhancing the monocytes' innate targeting abilities, this technique offers great potential to overcome some of these barriers and bring the technology closer to the clinic."

"This exciting work could have huge implications in healthcare," said Brown, BBSRC director of science and technology.

"Fundamental bioscience research may sometimes seem to have little relevance to everyday life, but understanding the basic workings of the human body and harnessing nanoscale technology has resulted in a process of great potential in tumor therapy."

The team are now looking at how effective magnetic targeting is at delivering a variety of different cancer-fighting genes, including ones which could stop the spread of tumors to other parts of the body.

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Update On Progress Of Rh-Apo2L Testing

Santa Monica, Calif.-based Aida Pharmaceuticals, Inc. (AIDA) said on April 28 that the company is compiling data for its Phase 2 testing results of Rh-Apo2L and expects to announce the findings within the next month.

The company previously announced that the target cancers for the drug have been determined and initial results are extremely positive.

The cancer targets that the company has chosen are ailments which Rh-Apo2L has shown the most efficacy and which have the most market potential.

Rh-Apo2L is a biotechnology gene therapy drug used to treat certain forms of cancer.

The biopharmaceutical drug has gained the attention of researchers and clinical professionals throughout the People's Republic of China who are observing the drug for potential replacement of surgery and radiation therapy for

cancer.

Potentially, more than eight million lives can be saved each year in the People's Republic of China by this drug, the company said.

The company previously announced that Rh-Apo2L testing results have shown strong efficacy in treating non-small cell lung cancer, non-Hodgkins lymphoma, stomach cancer, pancreatic cancer and kidney cancer.

The company intends to immediately file for Phase 3 clinical testing with the People's Republic of China's State Food and Drug Administration after the announcement of the findings from Phase 2 testing.

The company anticipates that the Chinese government will then allow for the commencement of Phase 3 testing within two to three months after the Phase 2 results are published.

Phase 3 testing will entail large-volume tests on over 300 patients and is the last step before it may be commercially sold in the People's Republic of China.

Aida Pharmaceuticals is a product-focused pharmaceuticals company engaged in the formulation, clinical testing, registration, manufacture, sales and marketing of advanced pharmaceutical and genetic products in mainland China.

The company's mission is to discover, develop and market meaningful new therapies that improve human health.

Aida Pharmaceuticals, in operation since March 1999, is headquartered in Hangzhou, China, with manufacturing, distribution and sales points throughout mainland China.

Aida is GMP certified in China and ISO9002 certified for quality assurance and ISO14000 certified for ecologically-friendly practices.

Contact: <http://en.aidapharma.com>

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Gene Transfer May Prove Effective For Erectile Dysfunction

Maxi-K gene therapy may be a safe and effective future option for men whose erectile dysfunction (ED) is not treatable with oral therapy.

Two studies presented May 15 at the annual meeting of the American Urological Association (AUA) may give hope to these individuals.

Maxi-K therapy is a unique, locally administered gene-transfer technology to treat erectile dysfunction (ED).

The safety and the restorative effects of the treatment have been shown by data from participants in a phase I trial.

In some men, the effect lasted up to six months.

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The gene therapy appears safe as no transfer-related adverse events were reported more than two years after the transfer in some subjects.

Unlike conventional oral therapies for men with ED, Maxi-K therapy does not require prior planning, fosters sexual spontaneity and can be used by men taking heart medication.

Researchers not only provided follow-up to previous studies on Maxi-K therapy in men, but also explored whether increased erectile function enhanced other areas of sexual behavior.

Male cynomolgus monkeys with ED were observed during their injection period and while in the presence of estrogen-implanted females.

Researchers observed and measured the monkeys' number of ejaculations, time to ejaculation, number of mounts, time to first mount, number of thrusts, number of sexual invitations by the female and number of erections achieved.

Researchers observed dramatic changes after gene transfer, including increases in the number of partial and full erections and a two-fold increase in erection duration.

An increase in intimacy was also seen.

The data imply that increased erectile function per se may lead to increased sexual function.

"This study gives hope to men who experience ED but have not responded to oral therapies," said Arnold Melman, M.D., one of the study's authors. The importance of these observations in clinical and pre-clinical trials is that it appears that gene transfer with the Maxi-K channel enhances both erectile capacity as well as other important measures of sexual behavior."

Researchers also presented updated data reaffirming that human patients being treated with hMaxi-K therapy for ED were not adversely affected.

The trial, conducted with 11 men between the ages of 18 and 65 with moderate to severe ED who received previous unsuccessful treatment, concluded that direct, organ-targeted, naked DNA gene transfer with hMax-K produced no treatment-related adverse events and the treatment is not associated other diseases or conditions.

These results open the door to further testing involving Maxi-K gene transfer and could lead to its effective use in treating the human population.

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