

**CONNECTICUT  
PARKINSON  
WORKING  
GROUP  
NEWSLETTER  
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There is so much happening within CPWG and the PD community that it would be possible to scratch the surface only. To give you some idea: within CPWG we are having a MOTM (Meeting on the Move) in October at Yale, Tom Sullivan, Jeff Lincoln, Dick Montross, Steve Holahan, and a few others have started a golf get together once or twice a week; they caught the eye of a local news reporting team; there was extensive write-up in the local paper (more on this in the next issue) We are all ready with three eminent researchers in PD who will address the question: *Where are we now as regards a cure for PD?* They present their thoughts at a symposium on 3 May 2008. A small team is preparing to put out a new member list with the capability to access it in ways we have so far only wished for. Jeff has at least one new interview with the new neurologist at IND, David Russell M.D., Ph.D.

There is a similar burst of news on the PD front, from gene therapy to continuous dosing of Sinemet to PDF50. So expect several issues of this newsletter (given that we don't run out of steam (in our case, L-dopa) in the near future.

**PARKINSON DISEASE RESEARCH IN THE 21ST CENTURY - IN SEARCH  
OF THE CURE**

*Connecticut Parkinson's Working Group Sponsored Symposium*

On 3 March 2007 the CPWG sponsored its first scientific forum for its membership and others interested in PD. The topic was "Clinical Trials in Connecticut," and the invited researchers were among the foremost in the State. Nearly 250 people showed up; many came away asking for a repeat performance. The success in accomplishing our goal and the myriad requests for a sequel gave us the impetus to plan just that. This Symposium is the result.

On Saturday 3 May 2008, the CPWG is sponsoring its second scientific symposium and all are invited. We continue the formula of inviting the most respected PD experts as panelists. This year we ask the question that is paramount in many people's minds - "Will we find the cure?"

To respond to this question, we have asked three leading researchers in fields that are presently thought to be the most promising for a breakthrough in potential PD modifying

trials - neuroprotection, stem cell implantation, and gene therapy.

**Ira Shoulson, M.D.** is considered THE expert to whom all other clinical researchers turn to for guidance when attempting to design or decipher a reasonable neuroprotective study. He has been conducting clinical research in PD since the 1970s.

**Dr. Shoulson** is Professor of Neurology, Pharmacology and Medicine of the University of Rochester Medical Center, Director of Experimental Therapeutics (ETH), Louis C. Lasagna Professor of ETH, and long time Chair of the Parkinson Study Group (PSG). He has been the mentor of mentors in his dual role as Director of the Movement Disorders and ETH fellowship program at Strong Memorial Hospital, and as long-term chair of the PSG, a cooperative group of PD experts from medical centers across the United States and Canada who are dedicated to conducting the highest quality clinical research studies to improve treatment for patients with PD. He has been the Principal Investigator for countless multi-center clinical trials examining the symptomatic and neuroprotective effects of experimental interventions in PD. He will discuss clinical research today in neuroprotective or disease modifying trials.

**Xiangzhong "Jerry" Yang, M.D., Ph.D.** is at the University of Connecticut; he is widely known and internationally respected for his research in stem cells.

**Dr. Yang** (native Nutmegger) is Professor of Animal Science and founding director of UConn's Center for Regenerative Biology. His pre-eminent position in embryonic stem cell research and the therapeutic applications of cloning has made him the natural leader of the excellent faculty at the University performing research in basic science in the field of regenerative biology and medicine. Collectively, they are actively pursuing areas of basic science that might lead to therapeutic production of new cell types, tissues or organs as potential replacements for diseased tissues commonly found in such disorders as PD, multiple sclerosis, diabetes, muscular dystrophy and cancer. Dr. Yang produced the first clone of an adult cow in the United States in 1999. At our forum, he will discuss the potential of Stem Cell research in PD.

**Andrew Feigin, M.D.** is Associate Professor of Neurology and Associate Director of the Movement Disorders Center of North Shore Long Island Jewish. He heads the Neuroscience Experimental Therapeutics Division of the Feinstein Institute for Medical Research with specific interest in using state-of-the-art imaging methods to develop new therapies for PD, Huntington disease, and other Movement Disorders. He is a leading investigator on many clinical trials of new treatments for PD, and was one of the leading authors of the recent article in the Lancet Neurology reporting what is considered a major breakthrough in the treatment of PD using gene therapy. **Dr. Feigin** will discuss the exciting news about gene therapy that was published in this article

With such a distinguished panel discussing the ultimate question in our minds, the CPWG is proud to present its second effort in two years to inform and educate. Save May 3, 2008 from 10 am to 1 pm for this symposium at Central Connecticut State University in New Britain. We will be providing more details in the near future, including registration procedures.

*{The following article is taken from a report that appeared in the 6/23/07 issue of The Lancet, recounting the first gene therapy clinical trial for PD, which may offer a promising approach to all neuro-degenerative diseases. Deb}*

### **Patients' Motor Skills Improved with No Major Side Effects, Weill Cornell Team Reports**

**NEW YORK (June 21, 2007)** - A team of physician-scientists at New York-Presbyterian Hospital/Weill Cornell Medical Center (NYPH/WCMC) has completed the first-ever phase 1 clinical trial of a breakthrough treatment using gene therapy to battle PD. The procedure, in

which surgeons inject a harmless gene-bearing virus into the brain, was found to be both safe and effective in improving motor function for the eleven men and one woman over the course of one year.

"These exciting results need to be validated in a larger trial, but we believe this is a milestone not only for the treatment of PD, but for the use of gene-based therapies against neurological conditions," says lead researcher Dr. Michael Kaplitt, associate professor of neurological surgery and the Victor and Tara Menezes Clinical Scholar in Neurological Surgery at WCMC, and director of Movement Disorders Surgery at NYPH/WCMC. Thirteen years ago, he and Dr. Matthew During pioneered a now widely used gene-delivery technique for the brain using an altered, harmless form of adeno-associated virus (AAV). In 2003, Dr. Kaplitt performed the worlds' first gene therapy surgery for PD.

"Viruses exist in nature mainly to transfer their own genes to the host cell," he explains. "So, we modify the AAV in such a way that the only gene it carries is the one we want to deliver to the therapeutic site."

In this case, the 'gene of interest' is the glutamic acid decarboxylase (GAD) gene. "GAD makes a chemical called GABA, a major inhibitory neurotransmitter in the brain that helps 'quiet' excessive neuronal firing," but which is substantially reduced in activity and amount in PWP, explains Dr. During, professor of molecular biology and cancer genetics at Ohio State University and the senior author of the current study. Combined with the loss of many dopamine-producing brain cells, the diminished GABA results in a "dysfunction in brain circuitry responsible for coordinating movement."

The researchers' bold idea: to insert GAD back into the subthalamic nucleus, a key regulatory center within this motor circuit of the brain to boost GABA production and thereby normalize the function of the entire circuit. "Not only would this alter the chemical balance in the subthalamic nucleus; it should also provide GABA to other parts of the network that weren't getting enough of the neurotransmitter."

To test that theory, the investigators injected the GAD-bearing AAV vector into the subthalamic nucleus of each of the 12 PWP. Although symptomatic on both sides of the brain, they injected only one side for safety reasons and for comparison with the untreated side. They used the standard UPDRS to track changes in patients' symptoms over the next 12 months and PET scans to observe changes in brain activity. These were both performed by the other two principal authors, Drs. Andrew Feigin and David Eidelberg of the Feinstein Institute for Medical Research at North Shore-Long Island Jewish Health System.

Like all phase 1 studies, the primary purpose was to gauge the safety of the technique; it succeeded brilliantly: they saw no adverse events related to the treatment, no immunological changes or infections over the year of the study, no imaging evidence of toxicity whatsoever. The results in terms of clinical and neurological efficacy were also encouraging, with UPDRS scores measuring motor function at three months post-treatment improving 25 – 30% in the 'off-state' phase, and similarly in the on-medication phase. Several individual patients showed impressive improvements of between 40% and 65%. "That was surprising and heartening, because traditional PD surgeries improve patients in the off-state but not as frequently in the on-medication state," Dr. Kaplitt continued.

Furthermore, these improvements in motor function occurred on the side of the body controlled by the treated brain hemisphere. Also, AAV tends to require several weeks to maximize and stabilize production of a therapeutic gene, and since they did not see significant clinical changes until more than 1 month after surgery, it would suggest that it was the gene therapy driving the improvement. There were also strong trends toward reductions in medication-linked dyskinesia (movement difficulties) and improved activities of daily living but not of statistical significance.

Finally, PET scans revealed a more normal level of activity in the treated half of the brain up to 1 year following surgery. Animal studies suggest that the transplanted gene remains active for years but only longer follow-ups will tell whether the improvements persist.

The next step would be a larger, more definitive efficacy-centered study.

This work was funded by Neurologix, of Fort Lee, N.J., which is developing the adeno-associated virus-borne GAD (AAV-GAD) agent. Drs. Kaplitt and Doring are co-founders of the company and consultants. For more information, visit [www.nyp.org](http://www.nyp.org).

***Editorial Comment:*** Growth factor therapy has followed a bumpy road over the last two decades: there was great hope for it when it was so successful in trials with primates. Broadly speaking, they were "made" to have PD by selectively destroying their substantia nigra with MTPT and then given GDNF, which returned them to the condition they were in before MTPT - that is, they were cured. It turned out that delivery and utilization of GDNF to humans did not follow the primate model. There have been no successful trials for GDNF in humans (Amgen notwithstanding). Now, using genetic modification to deliver what is essentially GDNF (Amgen "owns" the patent on GDNF so other companies have to become pretzels and develop something else which behaves like GDNF) to the right place in the brain, we have reports - the next two articles - of at least the safety of the therapy (Phase I) and strong indication that the methods used decrease off-time and improve the quality of on-time. Phase II trials are underway for this. If we were able to continue to improve the treatment we get off time is zero and on-time is improved to the point of normalcy. Call this whatever you like, but I think we already have a word for it. **DO NOT USE THIS WORD!** In the next newsletter I hope we can explain why I say that - we may need the help of some of our PD researchers.

One big fly in the ointment right now is the Placebo Effect (PE), which seems to play a major role in PD trials. There are documented cases of PWP going off all meds and being "normal" for as long as a year after participating in a trial in which NOTHING was done to her/him except to make her/him part of the trial. No drug administered, no procedure done! Hard to believe, but true. With the Phase II trials, we will see if the PE is making things seem better than they are. **Stan}**

## **Ceregene Presents Long Term Follow-Up Data From Phase 1 Trial of CERE-120 Demonstrating Improved Motor Function in Parkinson's Patients**

*Encouraging Results Prompted Phase 2 Study Now Underway at Nine Centers*

SAN DIEGO, Calif., April 16, 2007 /PRNewswire/ -- Ceregene, Inc., a biopharmaceutical company, today presented long term follow-up data from a Phase 1 clinical trial of CERE-120, a gene therapy product in development for the treatment of PD. One year after the stereotactic neurosurgery to deliver CERE-120 into their putamen, a region of the brain affected by the degeneration of neurons in PD, all 12 patients with advanced PD demonstrated a 36 percent ( $p < 0.001$ ) reduction in PD symptoms as measured by the UPDRS motor "off" score ("motor off" meaning patients were off PD medication at evaluation time). Results presented today by Philip Starr, M.D., Ph.D., associate professor of neurosurgery at the University of California, San Francisco, at the American Association of Neurological Surgeons' (AANS) annual meeting in Washington D.C., also show CERE-120 to be well tolerated. The Phase 1 trial was an open-label study conducted at two sites - UCSF and Rush University Medical Center in Chicago.

CERE-120 was delivered at two different doses; the patients receiving the lower dose took longer than those with the higher dose to reach the 36 percent improvement in UPDRS motor "off" scores. Both groups had maintained the improvement at 12-months, the final follow-up time point in the study. Patients also demonstrated a 50 percent reduction in hours of "off" time and a doubling of good quality "on" time without dyskinesias, according to self-reported diaries.

This Phase 1 clinical trial was partially supported by a grant from The Michael J. Fox Foundation for PD Research. Based on the results of the Phase 1 study, the Foundation has provided a \$1.9 million grant, which will partially fund Ceregene's ongoing Phase 2 trial, whose president stated that they "are pleased with the results of this early study which suggests that the majority of patients treated with CERE-120 may have exhibited significant and stable improvement for a full year" after treatment. He indicated that their goal for products such as CERE-120 is not only to improve symptoms but also to prevent progression of the disease. "Through stereotactic surgery, we are able to administer CERE-120 in a highly targeted fashion to one area of the brain that PD affects., and we were able to do this safely," he continued. "Given the encouraging data from the Phase 1 trial of CERE-120 in PD, we are conducting a follow-on Phase 2 trial that is currently enrolling patients at nine clinical trial sites in the United States," said Raymond T. Bartus, Ph.D., Ceregene's senior vice president of clinical and preclinical R&D and chief operating officer. "The data from the Phase 1 trial are reflective of the impressive results we gathered from preclinical studies, which demonstrated the ability of CERE-120 to stimulate the survival and improve the function of key neuronal cells affected by PD, as well as an excellent safety profile over a wide range of CERE-120 dose levels."

CERE-120 is composed of an adeno-associated virus (AAV) vector carrying the gene for neurturin (NTN), a naturally occurring protein known to repair damaged and dying dopamine-secreting neurons, keeping them alive and functioning normally. NTN is a member of the same protein family as glial cell-derived neurotrophic factor (GDNF). The two molecules have similar pharmacological properties, and both have been shown to benefit the midbrain dopamine neurons that degenerate in PD and are responsible for the major motor impairments.

A double blind, controlled Phase 2 clinical trial is now enrolling 51 patients with advanced PD at nine medical centers in the United States, with two thirds of patients being enrolled in the active treatment group and one-third in the control group. Patients will be followed for 12 months for safety and efficacy. ***{At the PDF50 meeting in NYC on 12 Oct 2007 Ceregene reported that they had fulfilled their enrollment and there were 56 enrollees at eight centers - Deb}.***

{4 September 2007 - from WE MOVE, which is an on-line publication of the eponymous organization that comes out monthly and has easily read articles on diseases leading to moving disorders. Why don't you send us your thoughts on the article? Stan}

### **Continuous Levodopa for the Treatment of PD**

**Background** When PWP start taking levodopa/carbidopa (L/C), their symptoms typically improve and are usually evenly controlled over a period of time. However, as PD progresses, the symptoms often become more difficult to



society is much like this. We each have a system we circulate in and make contact with other systems from time-to-time. These meeting places are called clubs, committees, offices, ...

In particular, the CPWG is a small system, which, as a group, interfaces with other groups (APDA, PDTrials, IND, the system of clinical neurologists). Each member is like a cell in the body, performing its job as dictated by the system it inhabits. So, Jackie is a facilitator cell and Steve a fiscal cell, Pat Sullivan an organizer cell, and so on, each representing the system that she belongs to. How about you? If you participate in meetings you are both an educator cell and a support cell. If your membership in CPWG makes no demands on your time you are a stem cell. That is, you are a cell that has the ability to become whatever you want! Pretty nifty. You can keep stem cell status or affiliate with some of the other cells doing a specific function and become one of them, for classification anyway.

Just as with the body, we need all our cell types - workers, nurturers, planners, and, yes, stem cells. I suppose we should say that you are a stem cell that can become another cell and, which is different than real stem cells, you may return to stem cell status whenever you want. I could take this analogy further but, like all analogies, eventually it would break down (or else it would not be an analogy, but the real thing).

A question you will likely ask is: What is the point? There is no point. I thought it was an interesting idea to find an analogy of stem cells in an obvious analogy to our societies' structure, the human body. And I am always looking for ways that enable formerly silent members to find a voice, if they want to. Maybe you can find a point by using this analogy in your own thinking about how you would like to be, perhaps, active in CPWG. We are an extremely open group - we will try almost anything (golf, large professional symposia, having almost all people who run the thing be PWP, put out a newsletter, NOT do a walkathon, ...) so if you want to try something, transform your stem cell-ness and let us hear about it.

***Stan Wertheimer***

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**DISCLAIMER: Articles in this newsletter are for information only.  
Any questions of treatment should be discussed with your physician.**

**WRITE! your representatives in congress.**

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