

# Stereotactic and Functional NEUROSURGERY NEWS



Fall 2006

## AANS/CNS Section on Stereotactic and Functional Neurosurgery and American Society for Stereotactic and Functional Neurosurgery

Editor: Konstantin Slavin, MD

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Michael Schulner, MD

#### The Future Is Now

The mission of the American Society for Stereotactic and Functional Neurosurgery is: To foster the use of stereotactic and functional neurological methods for the treatment of diseases of the nervous system.

The ASSFN goal is to:

Advance stereotactic and functional neurosurgery and related sciences, to improve patient care, to support meaningful basic and clinical research, to provide leadership in undergraduate and graduate education and continuing education, and to provide administrative facilities necessary to meet these goals.

(See <http://assfn.org/constitution/default.asp>.)

Accordingly, the ASSFN is a “big tent.” Our members are a diverse group, representing expertise that may seem divergent in a world of increasing subspecialization. Do neurosurgeons interested in movement disorders, radiosurgery, pain, and image guidance really have anything in common?

The answer is, undoubtedly, a resounding yes. There remains a strong clinical and intellectual overlap among these and other areas. For instance, the neurosurgeon doing tumor radiosurgery today may find that this technique has exciting applications for patients with tremor or pain. New refinements in image guidance and functional imaging will find their way into the operating room for all functional surgical indications.

History also sends us a warning against an overly narrow definition of stereotactic surgery. Medical advances of the kind that in the past led to a near-disappearance of our field can only be welcomed if they are of value to our

patients. That is why our journal, Stereotactic and Functional Neurosurgery, and our meetings will continue to demonstrate an inclusive definition of stereotaxis. As was made clear at our recent meeting in Boston, there are whole new therapeutic avenues and pathologies awaiting neurosurgical solutions. The ASSFN will be at the forefront of these efforts as neurosurgery tackles such problems as depression, tinnitus, and Alzheimer disease.

Being named president of the ASSFN at this time is truly an honor. We still are riding a wave of great innovation in our understanding of brain function and our ability to manipulate it for patient benefit. This has also been a time of great innovation in our society. The move to a biennial meeting schedule is complete and has greatly energized us all, as have the improvements introduced to our journal. We have opened up leadership positions to a wider representation of the membership. One and all are invited to step up and help us meet our mission.

As George Allen, the great American football coach, was fond of saying, The future is now. Never was this truer than in the field of stereotactic and functional neurosurgery, today.

#### ASSFN Business Update

The business meeting of the ASSFN took place on June 3 during the society’s biennial meeting in Boston. Among other business, new officers of the society were approved by the membership. Officers are: Michael Schulner, MD, president; Philip Starr, MD, vice-president; and Ali Rezai, MD, secretary and treasurer. For executive council, five new members were elected by closed ballot from a field of eight candidates. Executive council members for the 2006–2010 term are: Kelly Foote, MD, Kathryn Holloway, MD, Paul Larson, MD, Michael Kaplitt, MD, and Joshua Rosenow, MD.

# A Complete Success: Boston Meeting in Review



Konstantin Slavin, MD

Even with overwhelming support for making ASSFN meetings twice as frequent, there was a concern that this change would result in lower meeting attendance and insufficient new data for quality scientific presentations. Both of these concerns were proven wrong by the recent ASSFN meeting in Boston. The conference was a complete success with abundant new clinical and research data, a full conference room throughout the meeting, and an outstanding social program.

Below is a brief review of the meeting. I wanted to share the exciting atmosphere of the conference by mentioning some of its highlights and showing a few images (expertly taken by the meeting's coordinator, Martha Tobin).

The meeting took place in Boston Copley Plaza June 1–4, 2006. This was the first meeting of our new biennial schedule after the transition that our society adopted several years ago (the previous two meetings were in New York the summer of 2003 and in Cleveland the fall of 2004). There were more than 300 participants, with 261 medical registrants representing 19 countries, and more than 50 exhibitors from 15 different companies.

The scientific program was put together by Ron Alterman, MD, and Robert Maciunas, MD. It included 79 oral presentations and 32 posters. There were no concurrent sessions, a format that had been a great success at our previous meeting in Cleveland. The entire program took place in a large auditorium, allowing each attendee to hear about progress in all areas of stereotactic and functional neurosurgery, instead of having to choose between two or more equally interesting sessions. In addition to pure neurosurgical presentations, participants enjoyed multiple in-depth reviews and updates from our colleagues in basic sciences, psychiatry, radiology, and many other fields. The conference followed a new format in which the talks themselves were limited to five minutes but were followed by a few minutes of lively discussion. This format was popular with the audience, based on the liveliness and number of frank discussions after the oral presentations.

Every morning of the conference started with superb seminars, which focused on intraoperative monitoring, extracranial



Breakfast seminars combined expert opinions and audience participation.



The exhibition hall was a place for informal discussions and interaction with partners from industry.

radiosurgery and the future of neuronavigation. These sessions provided state-of-the-art overviews of current and future trends in each of the topics. During lunch on the first full day of the meeting, our honored guest Ronald R. Tasker, MD, shared some unique personal recollections and images from his years as a stereotactic pioneer. We also heard from Jack El-Hai, author of the bestselling book *The Lobotomist*, a biography of neurologist and psychiatrist Walter Freeman. This presentation included some fascinating and rare video footage of the early days of psychosurgery. And to make the entire event even more memorable, the social program included a gala reception at the John F. Kennedy Presidential Library and Museum.

For those of you who were at the meeting, here are some images to refresh pleasant memories. For those who missed it, perhaps these photos will give you another reason to join us for our next meeting in Vancouver in June 2008!



The gala reception in the JFK Presidential Library and Museum was a highlight of the conference.



The presentation by Honored Guest Ronald Tasker, MD, was a top highlight of the meeting.



Conference Chair Rees Cosgrove, MD, (right) introduces Jack El-Hai, author of *The Lobotomist*, a biography of neurologist and psychiatrist Walter Freeman.



Society President Andres Lozano, MD, (left) presents Ziv Williams, MD, with the award for best oral presentation.

# Deep Brain Stimulation for Parkinson Disease: A Consensus Report



Brian H. Kopell, MD



Ali R. Rezai, MD

With over 35,000 deep brain stimulation implants worldwide to date, DBS has become the surgical gold standard for the treatment of movement disorders. Indeed, the past decade has witnessed a renaissance for the surgical treatment of intractable

disorders. Several factors have driven the growth of this therapy including better understanding of pathophysiology, improved imaging, and innovations in stereotactic surgical technology.

Perhaps the most important development has been the application of the multidisciplinary approach to clinical neuroscience. Integral to DBS success is the close collaboration of movement disorder specialists with functional neurosurgeons. This synergistic approach has proven vital in the development of this complex and multifaceted therapy. In 2003, the Executive Committee of the Congress of Neurological Surgeons called for an effort to develop literature-based “guidelines” for the treatment of Parkinson disease by DBS. This call was quickly echoed by the International Executive Committee of the Movement Disorder Society.

The success of any surgical therapy entails a detailed understanding of patient selection, surgical technique, and postoperative management. With more than 500 centers worldwide performing DBS for movement disorders, a vast body of knowledge has been attained. Yet, to date there has not been a central document that harnesses the experience and knowledge of experts in this field in critically and comprehensively reviewing the current status of DBS for PD. Toward this end, the DBS Consensus for PD was formed.

## DBS Consensus for PD

The goal of DBS Consensus for PD was to develop a comprehensive document based on a thorough search, review and evaluation of the existing literature that covers the present status of DBS treatment for PD. Sponsorship for this project was provided by the CNS, MDS and the ASSFN. In addition, Medtronic Neurological, a worldwide manufacturer of DBS hardware, provided additional financial support for this process in the form of an unrestricted educational grant. Medtronic had no involvement or input into the process, content, organization, composition of or participants in the final document.

Neurosurgeons Ali Rezai and Alim Benabid, neurologists Günther Deuschl and Anthony Lang and clinical neuroscientist Kelly Lyons comprised the project’s steering committee. The steering committee invited neurologists, neurosurgeons, neuropsychologists, neuropsychiatrists and researchers with experience and expertise in DBS for PD from all of the major international centers involved in this treatment to create a writing committee. This committee, which consisted of 30 specialists in movement disorder surgery, critically reviewed close to 700 of

the published articles on DBS for PD and had numerous phone conferences and meetings including a three-day meeting.

Initially, the goal of this project was critical review of the body of literature to provide evidence-based guidelines for DBS surgery for PD. However, it quickly became evident that there was very little published Class I data in the currently available literature to formulate definitive recommendations and conclusions for most of the questions and issues proposed. It was decided that the outcome would be categorized into the three major overarching areas of preoperative issues, surgical issues, and postoperative issues that were addressed by answering a comprehensive list of standardized questions related to these areas.

In this context, it was decided to organize responses to the questions into four parts in order to achieve the goals of the project. The first part, entitled “Available Data,” covers the available knowledge as published. The second part, entitled “Conclusions,” is a statement of how the entire group interpreted the available knowledge. The third part, “Pragmatic Recommendations,” covers the experience and knowledge of the entire working group. The final section, “Points to Be Further Addressed,” summarizes important questions to be addressed in future studies.

By discussing opposing or conflicting opinions, the committee was able to reach a consensus and to provide pragmatic recommendations based upon the experience and knowledge of the entire working group as well as the published literature. In addition to the three seminal papers on preoperative, surgical and postoperative issues, the group authored six more papers to provide additional background information necessary for the reader: “Functional Anatomy and Physiology of the Basal Ganglia,” “DBS Surgical Technique,” “Intraoperative Physiological Mapping and Confirmation,” “Postoperative DBS Programming,” “DBS Treatment Outcomes,” and “Neuropsychological and Neuropsychiatric Considerations.” All papers underwent formal peer review with appropriate revision. The three lead papers were subsequently reviewed and endorsed by the Scientific Issues Committee of the MDS and ASSFN.

This compiled work was recently published in a special issue of the journal *Movement Disorders* in the summer of 2006. The articles will also be posted on the official Web sites of the CNS and ASSFN.

One of the most important results of this complex and challenging task was the identification of further points to be addressed by future investigations. A study addressing any one of these points would provide an important and useful contribution to this rapidly growing field. For example, the general lack of Class I data in this field is a unique and rich opportunity for clinical neuroscientists.

DBS for PD, of course, is a “moving target” as the field continues to evolve. However this consensus report is invaluable to understanding the state of the art and provides a starting point for future endeavors as DBS is applied to other arenas in neurological and psychiatric disorders.

# Stereotactic Gene Therapy For Parkinson Disease



Nicholas M. Boulis, MD

Current surgical therapy for medically refractory Parkinson disease has provided a means for durable symptomatic relief. Nonetheless, deep brain stimulation remains far from optimal. Implantable devices remain vulnerable to malfunction and infection and require battery changes. More importantly, the therapy allows compensation for the loss of striatonigral transmission, but fails to replace lost dopamine and lacks specificity with respect to neuronal subtypes and neurotransmitter

systems. Most of all, DBS provides symptomatic relief but does nothing to slow or reverse the underlying neurodegenerative process. The evolution of gene therapy has supplied us with several new strategies that may serve to augment or replace DBS.

The realization of goals for Parkinson gene therapy depends on the development of two separate technologies within the broader field of molecular therapy. First, successive improvements in the means to deliver genes to the nervous system have been critical to the potential for success of ongoing trials and promise to provide improvements in these individual approaches. Second, the choice of which genes to deliver underlies the critical differences in current strategies.

Broadly, gene delivery can be achieved through both viral and nonviral vector systems. While nonviral systems eliminate many concerns about the immune response to vectors, to date they have proven to be neither efficient nor durable. Thus, the focus of efforts has remained on viral vectors. Viral vectors consist of viruses whose genomes have been modified to remove genes necessary for replication and hence self-sustaining and amplifying infection. Over the last decade, this process of "viral attenuation" has proven insufficient because residual viral gene products can still be recognized by the immune system. Therefore, vector systems have been "gutted," removing all functioning viral genes and hence denuding the vectors of viral gene products. This effort, together with the ability of advanced generation vector systems to deliver their genetic payload into the genome of host cells, allows transgene expression to occur in a safe and durable fashion. The leading vector systems for stereotactic application are adeno-associated virus and lentivirus.

Three separate strategies have entered clinical trials: subthalamic nucleus inhibition, striatal dopamine replacement and trophic factor gene delivery.

**Subthalamic Nucleus Inhibition** The first strategy, STN inhibition, is based upon the effect of STN DBS and lesioning in PD patients as well as work from Mahlon DeLong, MD, in primates, and Andres Lozano, MD, in humans, demonstrating benefit from STN infusion of GABA agonists. Matthew During, MD, in collaboration with Michael Kaplitt, MD, initially demonstrated that delivery of the

GAD gene using an AAV vector could improve the symptoms of dopamine deprivation in a rodent model of PD. They provided additional evidence that STN GAD expression might change the valence of STN pallidal output from excitatory to inhibitory.

This strategy has been brought to a clinical trial by Neurologix. Twelve patients greater than or equal to Hoehn and Yahr Grade III were enrolled, with the first patient treated in August 2003 and the final patient treated in May 2005. Each patient underwent MER-guided STN mapping followed by unilateral infusion of AAV vector by Michael Kaplitt, MD, at Cornell. Patients were divided into three groups of four, with the first group receiving a low dose ( $3.5 \times 10^9$ vg) and the last group receiving the highest dose ( $3.5 \times 10^{10}$ vg). All patients have now completed the required one-year follow-up in the study, with no significant adverse events related to the study treatment. Clinical and positron emission tomographic analysis by David Eidelberg, MD, and Andrew Feigin, MD, has revealed a statistically significant, time-dependent improvement in motor UPDRS with a corresponding significant reduction in abnormal basal ganglia metabolism only on the treated side. A complete analysis and reporting of the study results is anticipated in the late fall.

**Striatal Dopamine Replacement** The next strategy, striatal dopamine replacement, has been pursued seriously by two groups. The first trial was founded under the auspices of Avigen, but is now run by Genzyme since the closure of gene therapy efforts by Avigen. This trial employs an AAV vector to deliver the gene for aromatic amino acid L-dopa decarboxylase. Initial experiments by Krzysztof Bankiewicz, MD, demonstrated that AADC expression in the putamen could restore striatal dopamine when L-dopa was administered in animal models of PD. This strategy provides a potential means to control the amount of dopamine produced through the amount of L-dopa administered. The investigators hypothesized that this approach would prevent the development of runaway dyskinesias like those that complicated fetal mesencephalic transplants. This team conducted extensive preclinical studies including an examination of the role of convection-enhanced delivery in viral injection as well as testing of a silicon tubing injection cannula. The issue of ideal cannula design has emerged as important to prevent vector-cannula binding with a resulting drop in the titer delivered. In the ongoing clinical trial at the University of California, San Francisco, five patients have been treated with bilateral intrastriatal AAV-AADC injections. To date, there have been no serious adverse events. PET studies in the initial two patients have demonstrated a 15 percent increase in striatal AADC activity six months after injection.

A second trial has been pursued by Oxford Biomedica for stereotactic injection of a lentiviral vector carrying three separate transgenes: tyrosine hydroxylase, AADC, and GTP cyclohydrolase I. These three gene products are necessary for the production of L-dopa with subsequent dopamine production. Thus, unlike the Genzyme strategy, the Biomedica vector, named Prosavin, will drive dopamine production independent of L-dopa administration. An initial attempt was made by the company to launch a spinoff in southern California (San Diego Biomedica) with the goal of launching a trial of stereotactic putamenal Prosavin injection in the United States. However, vector production problems led to the closure of San

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Abbreviations: AADC, aromatic amino acid L-dopa decarboxylase; AAV, adeno-associated virus; ATP, adenosine triphosphate; DBS, deep brain stimulation; GABA,  $\gamma$ -aminobutyric acid; GDNF, glial cell line-derived neurotrophic factor; GFLs, GDNF-family ligands; GTP, guanosine triphosphate; MER, microelectrode recording; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PD, Parkinson disease; PET, positron emission tomography; STN, subthalamic nucleus; UPDRS, Unified Parkinson's Disease Rating Scale

# Application for New Membership

## American Society for Stereotactic and Functional Neurosurgery



Name \_\_\_\_\_

Office Address \_\_\_\_\_

City \_\_\_\_\_ State \_\_\_\_\_ Country \_\_\_\_\_

Phone \_\_\_\_\_ Fax \_\_\_\_\_ E-mail \_\_\_\_\_

Residency Training Program: \_\_\_\_\_ Years: \_\_\_\_\_

Medical School: \_\_\_\_\_

Specialty (circle): Neurosurgery Neurology Other: \_\_\_\_\_

AANS Member:  Yes  No CNS Member:  Yes  No

Interests in Stereotactic and Functional Neurosurgery: (please circle)

Movement Disorders Pain Epilepsy Psychosurgery Tumors Biomedical Engineering Radiosurgery

Determine and circle your membership category:

| Category        | Yearly Fee | Description   |
|-----------------|------------|---|
| Active          | \$325      | For practicing neurosurgeons in the United States or Canada who have completed residency/fellowship |
| Resident/Fellow | \$25       | One-time fee (not yearly). For neurosurgical trainees currently in residency or fellowship          |
| Senior          | Free       | For neurosurgeons who are retired and over 65 years old   |
| Associate       | \$50       | For non-neurosurgeons   |

The benefits of Active membership include:

- Membership in the AANS/CNS Section on Stereotactic and Functional Neurosurgery
- Membership in the World Society for Stereotactic and Functional Neurosurgery
- Reduced fees for the biennial ASSFN meetings
- Subscription to the journal Stereotactic and Functional Neurosurgery (including online access)

The benefits of all other membership categories are:

- Membership in the AANS/CNS Section on Stereotactic and Functional Neurosurgery

- Reduced fees for the biennial ASSFN meetings
- Eligibility to subscribe to the journal Stereotactic and Functional Neurosurgery (including online access) at the reduced rate of \$135. If you are joining the ASSFN as a Resident/Fellow, Associate, or Senior member and wish to have the journal subscription, a check for \$135 payable to the ASSFN with ASSFN journal referenced in the memo field can be sent to ASSFN c/o AANS, 5550 Meadowbrook Drive, Rolling Meadows, IL 60008, and check this box:  
 YES I would like to receive the society journal at the reduced rate and have separately sent my check to the ASSFN in care of the AANS as described above.

**There are two ways to become an ASSFN member:** Apply online at [www.MyAANS.org](http://www.MyAANS.org) (for Active member applications only), or mail this application form and check for appropriate fee (see table above) made out to ASSFN to:

ASSFN, c/o AANS, 5550 Meadowbrook Drive, Rolling Meadows, IL 60008. For questions or concerns, contact the current (2006–2008) ASSFN secretary-treasurer, Ali Rezaei at [rezaia@ccf.org](mailto:rezaia@ccf.org), or the membership chair, Nick Boulis, at [boulisn@ccf.org](mailto:boulisn@ccf.org).

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Diego Biomedica. The company is continuing to pursue a Prosvavin trial in Europe, with talk of the initial human injections occurring in either England or France. The company continues to entertain the possibility of a separate U.S. trial.

**Trophic Factor Gene Delivery** The final strategy, trophic factor gene delivery, evolved out of the success of a variety of growth factors in cell culture and animal models. In this class of proteins, the GDNF-family ligands, GFLs, have been recognized as having the most profound effects on dopamine neuron survival. The GFL family consists of GDNF, Neurturin, Artemin, and Persephin. The southern California biotech company Ceregene has taken the lead on stereotactic GFL gene therapy with its product Cere-120, an AAV vector for the delivery of the Neurturin gene. The basis for the Ceregene trial can be found in the primate studies of Jeffrey Kordower, PhD, on striatal GDNF gene delivery with lentiviral vectors, which demonstrated protection of striatal dopamine delivery with tyrosine hydroxylase staining, PET, and behavior studies in two different monkey models. Preclinical studies by Ceregene in collaboration with Dr. Kordower demonstrated that Cere-120 could similarly protect dopamine neurons in the MPTP

monkey model. The Phase I Cere-120 trial set out to test the safety and tolerability of putamenal Cere-120 injection in 12 patients. Six patients were injected at UCSF by Philip Starr, MD, and six were injected at Rush University Medical Center by Roy Bakay, MD. Each site conducted four low dose ( $1.4 \times 10^{11}$  vg) and two high dose ( $5.7 \times 10^{11}$  vg) injections. All patients were treated between June of 2005 and March of 2006. All patients were greater than or equal to Hoehn and Yahr Grade III. Surgery consisted of four injections targeting the putamen on each side with two deposits at each injection site. Open label follow-up of this initial cohort for six months has shown no serious adverse events or decline in neurological condition. Efficacy data is expected from this group in the fall. On the basis of these results, a Phase II controlled, multicenter trial is planned to begin in late 2006.

Thus, stereotactic gene therapy for PD has moved into three separate Phase I clinical trials. To date there have been no serious adverse events. In late 2006 and 2007, Phase II trials are expected from both the Neurologix and Ceregene groups. Whether these approaches will replace DBS, provide an alternative, or augment the current techniques will depend on the outcomes of these trials. The current federal funding climate as well as the landscape for industry-sponsored gene therapy trials has created added challenges to clinical translation.

## ASSFN–AANS/CNS Section on Stereotactic and Functional Neurosurgery

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### ASSFN Officers and Executive Council

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Michael G. Kaplitt, MD, PhD (2006–2010)  
Paul Larson, MD (2006–2010)  
Joshua M. Rosenow, MD (2006–2010)

### Upcoming Meetings – Mark Your Calendars!

**European Society for Stereotactic and Functional Neurosurgery**—Montreux, Switzerland, Oct. 4–7, 2006 ([www.essfn2006.org](http://www.essfn2006.org))

**Latin-American Congress of Neurosurgery (CLAN)**—Buenos Aires, Argentina, October 21–26, 2006 ([www.clan2006.com.ar](http://www.clan2006.com.ar))

**Movement Disorder Society**—Kyoto, Japan, Oct. 28–Nov. 2, 2006 ([www.movementdisorders.org/congress/congress06](http://www.movementdisorders.org/congress/congress06))

**North American Neuromodulation Society**—Las Vegas, Nev., Dec. 7–9, 2006 ([www.neuromodulation.org/education.htm](http://www.neuromodulation.org/education.htm))

**CyberKnife Users' Meeting**—Palm Springs, Calif., Jan. 24–28, 2007 ([www.cksociety.org](http://www.cksociety.org))

**American Academy of Pain Medicine**—New Orleans, La., Feb. 7–10, 2007 ([www.painmed.org/annualmeeting](http://www.painmed.org/annualmeeting))

**Third Annual Symposium on Clinical Neurology and Neurophysiology**—Tel Aviv, Israel, Feb. 19–21, 2007 ([www.neurophysiology-symposium.com](http://www.neurophysiology-symposium.com))

**American Association of Neurological Surgeons**—Washington, D.C., April 14–19, 2007 ([www.aans.org/annual/2007/default.asp](http://www.aans.org/annual/2007/default.asp))

**Brazilian Society for Stereotactic and Functional Neurosurgery**—Rio Quente, Goias, Brazil, May 16–19, 2007 ([www.scripventos.net/bssfn2007](http://www.scripventos.net/bssfn2007))

**International Stereotactic Radiosurgery Society**—San Francisco, Calif., June 23–27, 2007 ([www.isrs2007.org](http://www.isrs2007.org))

**Congress of Neurological Surgeons**—San Diego, Calif., Sept. 15–20, 2007 ([www.neurosurgery.org](http://www.neurosurgery.org))

**And for 2008:**  
AANS—Chicago, Ill.  
Gamma Knife Society—Quebec City, Canada  
ASSFN—Vancouver, Canada  
CNS—Orlando, Fla.