



DIRECTOR'S NOTE

In 2010, 1253 patients underwent brain tumor surgery at Barrow Neurological Institute—more than at any other brain tumor center in the United States. Though our volume is remarkable, it is also a poignant reminder of the work that remains: despite the efforts of 30 years of modern neuroscience research, patients with malignant brain tumors have gained only a few months in overall survival. This simply will not do.

Fortunately, a new era is dawning on brain tumor biology and therapy. In 2010, the Barrow Brain Tumor Research Center (BBTRC) was founded in an effort to synergize Barrow's neurosurgical and neuroscientific expertise and integrate the scientific assets of Phoenix and the state of Arizona. The blueprint for the BBTRC is innovative and streamlined: recruit the brightest young scientific minds in brain tumor biology nationwide, build a large-scale experimental ther-



Nader Sanai, MD

apeutics infrastructure designed to translate laboratory efforts into rapid-sequence clinical trials, and weave these elements into a coordinated system of clinical care. Our objective, simply put, is to offer an experimental therapy option for every patient with a brain tumor, irrespective of their diagnosis or stage of disease.

At the heart of the BBTRC is its scientific platform. We have begun to establish five new laboratories that approach brain tumor therapy through distinct but interconnected avenues of investigation. Each laboratory will be headed by a rising principal investigator with expertise in next-generation neuroscience areas like cancer stem cell biology, nanoparticle delivery, glioma immunotherapy, molecular neuro-oncology, and epigenetics. This is not science for the sake of science. Rather, it is a vertically-integrated system of translational neuroscience that will fuel a clinical trials infrastructure comprising world-class Barrow neurosurgical oncologists, neuro-oncologists, radiation oncologists, and neuroimaging specialists.

Without question, the BBTRC is one of the most ambitious and unconventional programs in the history of Barrow, but its objectives remain practical and achievable. Every design element, be it establishing a creative system for clinical-trans-

STRINGS ATTACHED

Ray Thurston's \$3-million gift to the BBTRC includes business guidance that is already paying big dividends

When Phoenix entrepreneur Ray Thurston decided to make a \$3-million gift to the new Barrow Brain Tumor Research Center, writing a check was only part of the equation. Just as important to the fledgling center is the business expertise that Thurston brings with him.

As part of his gift, Thurston—founder of SonicAir, a logistics company he sold to UPS in 1995—has been collaborating with Nader Sanai, MD, Director of the BBTRC. Thurston's goal is to help Dr. Sanai enhance efficiency, cut costs and focus the project's short- and long-term objectives.

"This is certainly the most detailed and thoughtful planning process I have ever been a part of. It increases our chances of success exponentially," says Dr. Sanai. "Ray pored over our timeline and said, 'Let's run all these processes in parallel. Cost is not an issue.' As a result, we have compressed an ambitious project from five to three years and reduced its expense, too."

In addition to improving the research process, Thurston built financial incentives into his gift agreement. "My donation requires that Dr. Sanai achieve certain goals on a quarterly basis, and if he achieves those goals, I write a check," Thurston says. "I think that

DIRECTORS MESSAGE

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lational collaboration, devising a rapid-sequence clinical trials program, or lending Barrow's fire and drive to the national and international brain tumor community, was conceived to impact brain tumor patients in the near-term.

Through this biannual newsletter, we hope to keep you apprised of our strides towards eradicating brain cancer. Our success will depend not only upon original science and investigation, but also the commitment of a select team of clinicians, scientists, nurses, and local advocates in Phoenix and beyond. On behalf of everyone at the Barrow Brain Tumor Research Center, I thank you for being part of our community.

Nader Sanai, MD

Director, Barrow Brain Tumor Research Center
Director, Division of Neurosurgical Oncology
Barrow Neurological Institute
nader.sanai@bnaneuro.net.

STRINGS ATTACHED

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today's benefactor is more interested in outcomes. Those organizations that can provide outcomes are going to attract more investments."

As for Dr. Sanai, he views Thurston as much more than a benefactor. "He's been a critical partner, really a genius innovator in terms of getting things done in the laboratory, and it has completely changed the way we approach and conduct our science."

Thurston's gift is funding research that uses spectroscopy to identify cancerous brain cells so that the cells can be better targeted during treatment.



Ray Thurston

BBTRC STEERING COMMITTEE

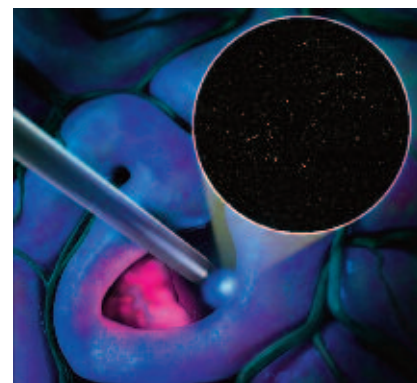
The BBTRC Steering Committee is a group of community volunteers who are working to raise \$17 million for the new center—\$8 million to endow the BBTRC and \$9 million to support initial laboratory start-up during the center's first eight years of operation. The goal of the committee is to assist in the quest to cure brain tumors by raising funds and awareness of this devastating disease.

Barrow Neurological Foundation recruited the first members of the BBTRC Steering Committee more than a year ago. Each had some kind of personal experience with brain tumors. The original members recruited others with a similar passion for finding innovative treatments for brain tumors, and today the committee is nearly 20 members strong.

For information about how you can contribute to the Steering Committee's efforts, please visit www.SupportBBTRC.org, e-mail Kathleen.Norton@chw.edu, or call Barrow Neurological Foundation (BNF) at 602-406-3041, Monday through Friday, 8:00 a.m. to 5:00 p.m. Gifts to BNF are tax-deductible in accordance with state and federal regulations.

BALANCE TRIAL

The Barrow 5-ALA Intraoperative Confocal Evaluation (BALANCE) study is a randomized Phase IIIa clinical trial being conducted at the Barrow Brain Tumor Research Center (BBTRC) that uses fluorescent technology to target invasive glioma tumor cells. Led by principal investigator Nader Sanai, MD, the protocol is being used to examine the efficacy of 5-ALA tumor fluorescence for identifying infiltrating gliomas intraoperatively and improving the extent of resection. It is the first randomized trial of its kind in the United States.



In the study, adult patients with a newly diagnosed or recurrent glioma are randomized to receive a placebo or an oral dose of 5-ALA, an amino acid compound that is metabolized by glioma cells into a fluorescent byproduct. This dose will be administered two hours before surgery to resect the patient's glioma. For some cases, use of an intraoperative confocal microscope that emits ultraviolet light onto the brain tissue permits additional visualization of individual tumor cells infiltrating normal brain, allowing for more accurate delineation of tumor margins and identification of errant tumor cells.

The BALANCE trial marks the first time an intraoperative confocal microscope will be tested in a randomized clinical trial for brain tumors and the first time the device will be used in conjunction with 5-ALA. Ultimately, the study's results may change the current management of malignant gliomas, establishing 5-ALA as a standard intraoperative adjunct in the United States.

BEER FOR BRAINS

The Beer for Brains Foundation has announced its second major fundraiser for the Barrow Brain Tumor Research Center (BBTRC). *Rare Affair* will be held Saturday, Nov. 5, 2011, from 6:30 to 10:30 p.m. at Talking Stick Resort in Scottsdale, Arizona. The fine food and beverage extravaganza will feature:

- over 75 rare craft beers
- exclusive wines
- select spirits and cigars
- gourmet cuisine
- a live band and entertainment
- silent auction, raffles and door prizes

Proceeds will benefit the BBTRC. General admission is \$75 and VIP tickets are \$175 each. VIP admission includes access to early VIP entrance (5:30 p.m.), VIP check-in, VIP area access, full dinner and deserts catered by Talking Stick Resort, exclusive craft-beers, wines and spirits, select cigars, and a Beer for Brains Foundation handmade stoneware stein.



For more information, visit www.theBeerForBrainsFoundation.org.

The Beer for Brains Foundation is a national, non-profit organization of craft-beer lovers, distributors and brewers committed to raising public awareness about brain cancer, engendering compassion for its victims and helping fund groundbreaking research. The Peoria, Arizona-based organization was founded by Louis Dolgoff, whose wife, Laurie, died of a brain tumor in August 2009. She received care at Barrow Neurological Institute.

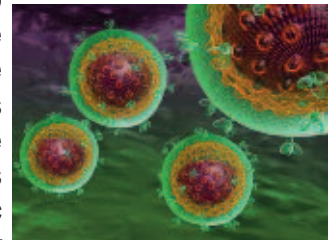
TOCA 511/5-FC ONCOLYTIC VIRUS TRIAL

During the fall of 2011, Barrow Neurological Institute will be the only center in North America to conduct a Phase I/II clinical trial implementing gene transfer therapy with Toca 511—a live replication-competent retrovirus that targets recurrent high-grade gliomas. Specifically, the Toca 511 trial will examine the safety and efficacy of administering the prodrug Flucytosine (5-FC) to patients who have had the gene therapy, enabling their tumor cells to activate the drug in vivo. All patients will have already undergone surgery, radiation, and chemotherapy for their recurrent tumors. The study will be divided into two separate protocols; one targeting the tumor resection bed following a reoperation, and the other targeting the tumor mass without reoperation.

The first clinical protocol will study increasing doses of Toca 511 administered into the walls of the resection cavity at the time of surgical tumor resection for recurrent high-grade glioma. Because the tumor will be debulked first, this approach will have the advantage of reducing the volume of tumor burden for the vector to transduce. Also, more Toca 511 can be administered into the cavity of a resected tumor than can be administered when the vector is administered intratumorally.

The second protocol will use stereotactic injection of Toca 511 into the recurrent tumor mass without repeat resection. This approach will be tailored for patients unable to undergo a second resection due to tumor location or medical comorbidities. In each protocol, an escalating dose strategy will be used to determine the optimal treatment regimen. All patients enrolled in this clinical trial will be eligible for a long-term continuation protocol that includes additional 5-FC treatment cycles.

Though other clinical trials have attempted to genetically modify tumors using inert viral vectors, the Toca 511 trial will be the first to take advantage of the biological capabilities of a live replication-competent virus that can widely invade proliferative tumor populations and deliver multiple genetic payloads. With the help of our biotechnology partners, we hope to harness the power of genetics to evaluate unconventional but promising strategies to treat malignant glioma patients.



EXTRAMURAL FUNDING AWARDED TO THE BBTRC

- American Association of Neurological Surgeons / National Research and Education Foundation Young Clinician Investigator Award
Principal Investigator: Nader Sanai, MD
Total Funding: \$40,000
- American Brain Tumor Association Discovery Grant
Principal Investigator: Nader Sanai, MD
Total Funding: \$50,000
- Arizona Biomedical Research Commission Category I Grant
Principal Investigator: Nader Sanai, MD
Total Funding: \$50,000
- Arizona Biomedical Research Commission Category III Grant
Principal Investigator: Nader Sanai, MD
Total Funding: \$1,050,000



**Rachael W.
Sirianni, PhD**

Photo credit: Henry Douglas, Yale Medical School

Dr. Sirianni will join the BBTRC as a principal investigator in the fall of 2011. Dr. Sirianni attended Arizona State University (ASU) where she earned her Bachelor of Science degree in Bioengineering. During her undergraduate studies at ASU, Dr. Sirianni worked in the laboratory of Brent Vernon, PhD, learning how to characterize "smart polymers" for stimuli-responsive drug delivery. She pursued an additional year of postgraduate research on this project while also teaching quantitative transport courses at ASU.

In 2004, Dr. Sirianni was recruited to Yale University to join the Biomedical Engineering PhD program, entering the laboratory of W. Mark Saltzman, PhD. For her thesis, Dr. Sirianni developed models to understand the factors that govern drug release and subsequent tissue distribution resulting from implantation of a drug-eluting vascular stent. She also applied controlled-release polymers in the central nervous system to better understand how delivery rate modulates the function of brain-derived neurotrophic factor in the brain.

After completing her PhD in 2008, Dr. Sirianni accepted a Postdoctoral Fellowship in Diagnostic Radiology at the Yale School of Medicine, where she worked in the laboratory of Richard Carson, PhD, at the Positron Emission Tomography (PET) Center. After being awarded a National Institutes of Health Postdoctoral Training Grant, Dr. Sirianni developed a new PET imaging technique to radiolabel polymer nanocarriers for direct and noninvasive quantification of drug delivery to the central nervous system. She also studied the biodistribution of polymer nanoparticles targeted for passage through the blood-brain barrier and collaborated with other researchers to characterize the distribution of polymer nanoparticles for the treatment of brain tumors in rats. These studies earned her several national accolades, including a first place award from the Society for Nuclear Medicine in 2010 and a travel fellowship at the 2011 Annual BrainPET Conference.

At the BBTRC, the Sirianni Laboratory will develop custom-engineered biopolymers for intraparenchymal drug delivery, as well as devise PET imaging methods that enable real-time quantification of drug elution into gliomas.

Selected Publications

1. Sirianni RW, Jang EH, Miller KM, Saltzman WM. Parameter estimation methodology in a model of hydrophobic drug release from a polymer coating. *J Control Release*. Mar 19 2010;142(3):474-482.
2. Sirianni RW, Olausson P, Chiu AS, Taylor JR, Saltzman WM. The behavioral and biochemical effects of BDNF containing polymers implanted in the hippocampus of rats. *Brain Res*. Mar 19 2010;1321:40-50.
3. Sirianni RW, Zheng MQ, Huang Y, Saltzman WM, Carson RE. Development of dPET, a non-invasive imaging technique to measure the distribution of drugs after direct delivery to the brain. *Journal of Nuclear Medicine*. 2010;51(Suppl 1).
4. Sirianni RW, Kremer J, Guler I, Chen YL, Keeley FW, Saltzman WM. Effect of extracellular matrix elements on the transport of paclitaxel through an arterial wall tissue mimic. *Biomacromolecules*. Oct 2008;9(10):2792-2798.
5. Solis FJ, Weiss-Malik RA*, Vernon B. Local monomer activation model for phase behavior and calorimetric properties of LCST gel-forming polymers. *Macromolecules*. 2005;38(10):4456-4464.

*Rachael A. Weiss-Malik



Mark E. Oppenlander, MD

Dr. Oppenlander was born and raised in Lansing, Michigan. He attended the University of Michigan, where he majored in cellular and molecular biology and graduated with highest distinction. While an undergraduate, Dr. Oppenlander was awarded the Endocrine Society Research Fellowship and conducted research in the Department of Human Genetics at the University of Michigan. Subsequently, at the University of Michigan School of Medicine, he was awarded a student biomedical research fellowship to study human genetics in Germany at the University of Heidelberg. Dr.

Oppenlander's passion for the clinical neurosciences led him to the field of neurological surgery. At the University of Michigan Department of Neurosurgery, he evaluated the functional coherence of EEG data to localize epileptogenic foci under the guidance of Oren Sagher, MD. Also during medical school, Dr. Oppenlander examined the neurological correlates of cranial neuropathy with cervical spine disease.

In 2008, Dr. Oppenlander joined Barrow Neurological Institute as a resident in neurological surgery. Presently in his fourth year of training, Dr. Oppenlander is developing his clinical and research interests in adult and pediatric neurosurgical oncology. Among several ongoing clinical research projects, he is investigating the value of extent of resection for recurrent glioblastoma, a study he will present at the 2011 Society for Neuro-Oncology Annual Meeting.

Selected Publications

1. Oppenlander ME, Wolf A, Porter RW, Nakaji P, Smith KA, Spetzler RF, Sanai N. An extent of resection threshold for recurrent glioblastomas. In Submission.
2. Oppenlander ME, Spetzler RF. Advances in spinal hemangioblastoma surgery. *World Neurosurg.* Jul 2010;74(1):116-117.
3. Oppenlander ME, ReKate HL. Use of adipose tissue to ease compatibility of a stylet with its sheath during ventriculoperitoneal shunt placement: technical note. *Neurosurgery.* Jun 2010;66(6 Suppl Operative):333.
4. Oppenlander ME, Orringer DA, La Marca F, McGillicuddy JE, Sullivan SE, Chandler WF, Park P. Dysphagia due to anterior cervical hyperosteozytosis. *Surg Neurol. Sep 2009;72(3):266-270; discussion 270-261.*
5. Tozum TF, Oppenlander ME, Koh-Paige AJ, Robins DM, McCauley LK. Effects of sex steroid receptor specificity in the regulation of skeletal metabolism. *Calcif Tissue Int.* Jul 2004;75(1):60-70.

NURSING SPOTLIGHT

Gracia Nicolaescu joins the BBTRC team as our Neurosurgical Oncology Nurse Navigator. Originally from the Detroit area, Gracia attended the University of Michigan where she earned her Bachelor of Science degree in Nursing. She began her nursing career as a neurosurgery team member in the operating rooms at the University of Michigan Hospital. While there, she developed an interest in the care of neurosurgical patients.

The high neurosurgical patient volume at Barrow Neurological Institute attracted Gracia, where she initially worked as an operating room nurse. While assisting neurosurgery faculty and residents with patient care, she developed a particular interest in the perioperative care of brain tumor patients. The opportunity to extend her impact beyond the operating room presented itself when she was recruited to the BBTRC in Summer 2011 as its Nurse Navigator. Gracia now serves as a central resource for all Barrow brain tumor patients, as well as a point of intersection for the neurosurgical oncology, radiation oncology, and neuro-oncology service lines. With this multidisciplinary focus, Gracia navigates brain tumor patients through their individual plans of care following surgery and also in the context of specific clinical trials. Ultimately, through Gracia's efforts, the BBTRC will set a new national standard for brain tumor patient care and clinical trial coordination.



Gracia Nicolaescu, RN, BSN



Kris A. Smith, MD

Dr. Smith is Director of the Gamma Knife Center at Barrow Neurological Institute and Co-Director of the Division of Neurosurgical Oncology. Dr. Smith specializes in microsurgical and radiosurgical treatment of brain tumors, and he also sees patients at the Barrow Acoustic Neuroma Center. His previous investigations have focused on glioblastoma radiosensitivity, as well as a Phase I/II clinical trial examining multimodal therapy for gliomas combining Gamma Knife radiosurgery and Gliadel wafer implantation. The initial reported experience with this treatment strategy suggested a survival benefit when compared to historical controls.

Dr. Smith received his Bachelor of Science degree from Brigham Young University and his Doctorate of Medicine from the University of Nevada School of Medicine. After medical school, he completed a 1-year general surgery internship before beginning his residency training at Barrow Neurological Institute. During his training, Dr. Smith was trained in radiosurgery at the Karolinska Gamma Knife Center in Stockholm, Sweden. He also completed a radiosurgery preceptorship under L. Dade Lunsford, MD, at the University of Pittsburgh Department of Neurological Surgery. Dr. Smith pursued another subspecialty interest in the microsurgical treatment of epilepsy, which led him to another preceptorship under Youssef Comaif, MD, at the Cleveland Clinic Surgical Epilepsy Program.

In 2008, Dr. Smith was awarded the Academy Cup for Best Scientific Presentation by the Rocky Mountain Neurosurgical Society for his work combining Gliadel wafer implantation with concomitant Gamma Knife radiosurgery following glioblastoma resection. Dr. Smith has treated approximately 1,000 glioblastoma patients over the course of his career and continues to strive to slow disease progression and preserve neurological function.

Selected Publications

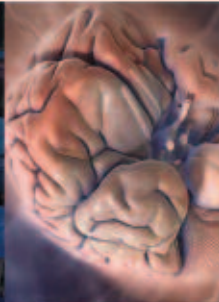
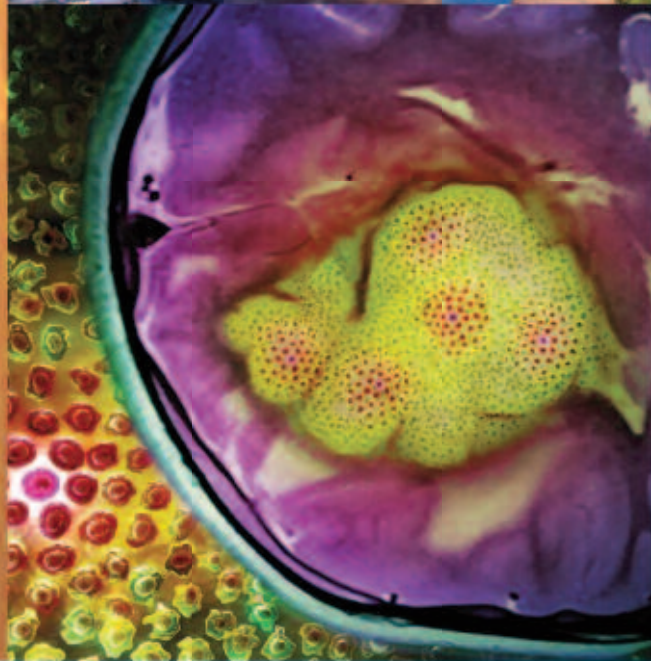
1. Smith KA, Ashby LS, Gonzalez LF, Brachman DG, Thomas T, Coons SW, Battaglia M, Scheck A. Prospective trial of gross-total resection with Gliadel wafers followed by early postoperative Gamma Knife radiosurgery and conformal fractionated radiotherapy as the initial treatment for patients with radiographically suspected, newly diagnosed glioblastoma multiforme. *J Neurosurg.* Dec 2008;109 Suppl:106-117.
2. Lekovic GP, Smith KA, Feiz-Erfan I, Porter RW, Biggs C, Shetter AG. Radiosurgery of jugular foramen tumors. *Operative Techniques in Neurosurgery.* 2005;8(1):54-60.
3. Deshmukh VR, Smith KA, Rekatte HL, Coons S, Spetzler RF. Diagnosis and management of pineocytomas. *Neurosurgery.* Aug 2004;55(2):349-355; discussion 355-347.
4. Javedan SP, Manwaring K, Smith KA. Treatment of posterior third ventricular central neurocytoma with endoscopic biopsy, endoscopic third ventriculostomy and stereotactic radiosurgery. *Minimally Invasive Neurosurgery.* 2003;46:129-192.
5. Rogers CL, Shetter AG, Fiedler JA, Smith KA, Han PP, Speiser BL. Gamma knife radiosurgery for trigeminal neuralgia: the initial experience of The Barrow Neurological Institute. *Int J Radiat Oncol Biol Phys.* Jul 1 2000;47(4):1013-1019.

RECENT PUBLICATIONS BY BBTRC INVESTIGATORS

1. Turner JD, Sanai N. A brain tumor stem cell origin for glioblastoma endothelium. *World Neurosurg.* May-Jun 2011;75(5-6):574-575.
2. Sanai N, Polley MY, McDermott MW, Parsa AT, Berger MS. An extent of resection threshold for newly diagnosed glioblastomas. *J Neurosurg.* Jul 2011;115(1):3-8.
3. Sanai N, Eschbacher J, Hattendorf G, Coons SW, Preul MC, Smith KA, Nakaji P, Spetzler RF. Intraoperative Confocal Microscopy for Brain Tumors: A Feasibility Analysis in Humans. *Neurosurgery.* Feb 16 2011.
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5. Chen L, White WL, Spetzler RF, Xu B. A prospective study of nonfunctioning pituitary adenomas: presentation, management, and clinical outcome. *J Neurooncol.* Mar 2011;102(1):129-138.
6. Sughrue ME, Sanai N, Shangari G, Parsa AT, Berger MS, McDermott MW. Outcome and survival following primary and repeat surgery for World Health Organization Grade III meningiomas. *J Neurosurg.* Aug 2010;113(2):202-209.
7. Sanai N, Berger MS. Intraoperative stimulation techniques for functional pathway preservation and glioma resection. *Neurosurg Focus.* Feb 2010;28(2):E1.
8. Sanai N. Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma. *World Neurosurg.* Jul 2010;74(1):4-5.
9. Pallud J, Fontaine D, Duffau H, Mandonnet E, Sanai N, Taillandier L, Peruzzi P, Guillevin R, Bauchet L, Bernier V, Baron MH, Guyotat J, Capelle L. Natural history of incidental World Health Organization grade II gliomas. *Ann Neurol.* Nov 2010;68(5):727-733.
10. Mahmood U, Kwok Y, Regine WF, Patchell RA. Whole-brain irradiation for patients with brain metastases: still the standard of care. *Lancet Oncol.* Mar 2010;11(3):221-222; author reply 223.
11. Kalani MY, Filippidis AS, Kalani MA, Sanai N, Brachman D, McBride HL, Shetter AG, Smith KA. Gamma Knife surgery combined with resection for treatment of a single brain metastasis: preliminary results. *J Neurosurg.* Dec 2010;113 Suppl:90-96.

2011

**BARROW NEUROLOGICAL INSTITUTE
BRAIN TUMOR SYMPOSIUM**



THURSDAY-SATURDAY, NOVEMBER 3-5, 2011

SYMPOSIUM LOCATION:

**Royal Palms Resort
Scottsdale, Arizona**

5200 East Camelback Road, Phoenix, AZ 85018

**SAVE THE DATE!
NOVEMBER 3-5, 2011**



BBTRC
Barrow Brain Tumor Research Center
350 W. Thomas Rd.
Phoenix, Arizona 85013