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BEST HOSPITALS U.S.News & WORLD REPORT NEUROLOGY & NEUROSURGERY 2015-16

Clinician-Scientist Seeks to Personalize Brain Tumor Treatment

Brain tumors beware – if **Adam M. Sonabend, MD,** has his way, your days are numbered. In 2015, Dr. Sonabend, a neurosurgeon specializing in brain tumors, joined the Department of Neurosurgery at NewYork-Presbyterian/Columbia University Medical Center. A skilled neurosurgeon specializing in brain and skull base tumors, Dr. Sonabend is also a cancer researcher and leads the Translational Brain Tumor Laboratory at the Herbert Irving Comprehensive Cancer Center at Columbia University.

Dr. Sonabend earned his medical degree at the National Autonomous University of Mexico, where he graduated obtaining the Gabino Barreda Medal for the Highest Academic Achievement. Dr. Sonabend next served as a research associate at the University of Chicago Brain Tumor Laboratory, where he pioneered the use of stem cells for adenoviral gene therapy for glioblastoma. He then came to NewYork-Presbyterian/Columbia for residency training in neurological surgery, becoming Chief Resident. During his training, he continued his research pursuits, working closely with mentors that included **Jeffrey N. Bruce, MD,** Director of the Bartoli Brain Tumor Research Laboratory and Co-Director of the Brain Tumor Center at Columbia University.

Dr. Sonabend's drive to pursue neuro-oncology developed during medical school in his homeland. "Mexico is a very poor country and a lot of families are in strenuous circumstances," he says. "I saw terrible pathology – really desperate situations – and I was trained as a doctor in that setting. I was also able to do basic science research in the lab one full day a week throughout medical school. It was phenomenal. So with that exposure, I came to the United States very enthusiastic about pursuing a career in brain tumor research."

"Adam is one of the most outstanding residents that we have trained in recent years," says **Robert A. Solomon, MD**, Neurosurgeon-in-Chief, NewYork-Presbyterian/Columbia. "Besides achieving technical

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Less is More: The Benefits of Minimal Access Spine Surgery

Roger Härtl, MD, Director of Spinal Surgery and Neurotrauma at the Weill Cornell Brain and Spine Center and founder and Co-Director of the Weill Cornell Spine Center in the Department of Neurological Surgery, has long favored minimally invasive surgical techniques and technologies, dating back to his neurosurgical residency at Weill Cornell. "That is how I was trained, what I pursued as an attending, and which has been a continual part of my research efforts," says Dr. Härtl, whose clinical expertise includes simple and complex spine surgery, minimally invasive spinal surgery, and computer-assisted spinal navigation surgery. Today he treats 70 percent of his patients with some type of minimally invasive surgery.

Dr. Roger Härtl

Experience, Selection, Technique, Technology

According to Dr. Härtl, the increase in the number of minimally invasive spine surgeries he performs is due to several reasons. "Part of it is because I'm getting better at it. The more you do, the more proficient you become," he says. "My decision-making process has also improved, enabling me to better select the patients I think will do well with minimally invasive spinal surgery.

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Clinician-Scientist Seeks to Personalize Brain Tumor Treatment *(continued from page 1)*

mastery of neurological surgical operations, he has proven to be a gifted research scientist. At this young stage in his career, he has garnered numerous grants, awards, and honors. We look forward to a brilliant career treating patients with brain tumors and leading future innovative approaches to solving the mysteries of malignant gliomas."

To aid in Dr. Sonabend's research endeavors, in 2015 he received the National Institutes of Health Early Independence Award from the office of the NIH Director – one of only 16 young researchers to be so honored. This prestigious award provides an opportunity for exceptional junior scientists who have recently received their doctoral degree or finished their clinical residency to bypass traditional postdoctoral training and move immediately into independent research positions.

Dr. Adam M. Sonabend

"This is an amazing opportunity," says Dr. Sonabend. "I am extremely grateful as the award will allow my lab to move full steam ahead on the study of what makes brain tumors different from each other and identify unique susceptibilities that can be exploited for effective personalized treatments for this cancer."

Dr. Sonabend's research focuses on TOP2A effects on transcription in gliomas and the related therapeutic implications for personalized therapy. He is also investigating novel means of delivery of chemotherapy into the brain that overcomes the blood-brain barrier and is involved in several clinical trials to test novel and promising therapies for patients with brain tumors. He is a principal investigator on one such trial that will be using gene therapy in retroviruses injected into the brain in order to kill brain tumor cells.

"Our Translational Brain Tumor Lab has the ultimate goal of figuring out the molecular features of brain tumors in order to treat a patient with a particular drug," says Dr. Sonabend. "Brain tumors are heterogeneous and very complex. There aren't even two brain tumors that look like each other. Yet the way we have dealt with these brain tumors has been to try a treatment, like chemotherapy, and take the average response for hundreds of patients for this particular treatment and see if there is some mild survival benefit. Sometimes it boils down to surviving two or three months longer when you have the treatment than when you don't. Then the treatment gets approval by the FDA and everybody starts getting that treatment. It turns out that those two or three months of survival are really the result of an average of very different responses. There is a spectrum: There are patients who never respond at all and there are patients who survive for years. So you are treating a lot of patients who are not going to benefit from these treatments.

"Gliomas are complex and have many different molecular features. Even within the same tumor, there are changes depending on the area of the tumor," continues Dr. Sonabend. "Our thought is that if we take this molecular information and see what's different between tumors we can start making smart decisions about what treatments to offer to which patients. Another aspect of our research is to understand how genes are turned on or off across different brain tumors, which might contribute to unique susceptibilities.

"We often find drugs that might actually kill tumor cells, but the problem is that the brain is a very difficult area to target. You can't get through the blood-brain barrier," explains Dr. Sonabend. "Even with drugs that permeate and get into the brain – the blood-brain barrier is so sophisticated that it actually has pumps that return the drugs back to the blood. Figuring out ways to get these drugs into the brain is a key part of our research."

As one strategy, Dr. Sonabend and Dr. Bruce are researching a convection-enhanced delivery system in which a drug is infused directly into the brain, achieving a high concentration in the tumor and minimizing side effects for the patient. "This technique involves placing a catheter directly into the brain and very slowly infusing chemotherapy using a subcutaneous pump," says Dr. Sonabend. "This allows concentrations for these drugs hundreds or thousand-folds higher than what you would achieve through the systemic circulation in the blood. Most side effects of chemotherapy are systemic. With this approach, you achieve an extremely high concentration in the brain, but the concentration elsewhere is so low that it appears to be very well tolerated, as previously proven by Dr. Bruce and others in a series of clinical trials."

Dr. Bruce and Dr. Sonabend have implemented a strategy to prolong the convection of these drugs into the brain. To do this, they have used a pump that can be implanted underneath the skin. If this system works well, patients will actually go home and get chemotherapy delivered into their brain for as long as needed. If the pump runs out of medication, it can be refilled with a needle without having to do another surgery. This is an effective way of achieving prolonged convection of drugs into the brain.

Staying the Course

First and foremost, Dr. Sonabend's practice is focused on caring for patients with brain tumors. "I find the most appropriate and innovative therapy for these patients sometimes involves using the standard of care," he says. "But sometimes it involves enrolling patients in clinical trials. There are some very promising experimental therapies here where we are really thinking outside of the box. These therapies can only be achieved within a very regulated research framework that will enable us to learn whether this new treatment is helping the patient or not. And, of course, these novel treatments don't become available right away – they first need to be tested."

Dr. Sonabend participates in Columbia's Tumor Board to evaluate the diagnosis and treatment of each patient. "We all come together – neurosurgeons, oncologists, neuro-oncologists, radiologists, pathologists – to discuss every case," he says. "The multidisciplinary expertise of the clinicians and scientists here affords patients with brain cancer the greatest opportunities for treatment and survival."

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Less is More: The Benefits of Minimal Access Spine Surgery *(continued from page 1)*

"Another factor is the technique and the technologies that we have available now," adds Dr. Härtl. "I use a lot of navigation, such as an intraoperative CT scanner and the GPS system, which allows you to work through very small incisions – you see everything in virtual reality on a screen. When I put in a screw I know exactly where it goes. I don't have to open up the skin to see what's going on in the spine. Navigation technology makes the surgery easier, faster, and safer."

Stabilizing the spine, says Dr. Härtl, offers challenges not present in other surgical procedures, including skull base surgery, which often uses pre-existing channels to reach the brain through the nose or mouth. "With the spine, we have to create these pathways, and once you're in you may be faced with something unexpected. For example, instruments and screws may be needed to stabilize the spine," he says. "It took a long time to get to the point where we can do this less invasively…we've made a lot of advances."

Dr. Härtl continually seeks ways to use minimally invasive procedures to avoid fusion surgery and to circumvent the overall extent of surgery in general. "Do we have to do a five-level decompression with fusion to address the patient's problem or could we achieve the same result with a less invasive approach?" he questions. "Spine surgery is often used prophylactically to prevent symptoms from worsening. But decompression with open surgery can sometimes destroy stabilizing tissue and eliminate so much bone that a subsequent, more major operation is needed to fix a problem created by the original surgery."

To test their views, Dr. Härtl and his colleagues undertook a retrospective case series investigation of surgery for lumbar spinal stenosis (LSS). Surgical decompression is the intervention of choice for LSS when nonoperative treatment has failed. Standard open laminectomy is an effective procedure, but minimally invasive laminectomy through tubular retractors is an alternative. "Our aim was to evaluate the clinical and radiographic outcomes of this procedure in patients who underwent LSS and to compare outcomes in patients with and without preoperative spondylolisthesis," says Dr. Härtl.

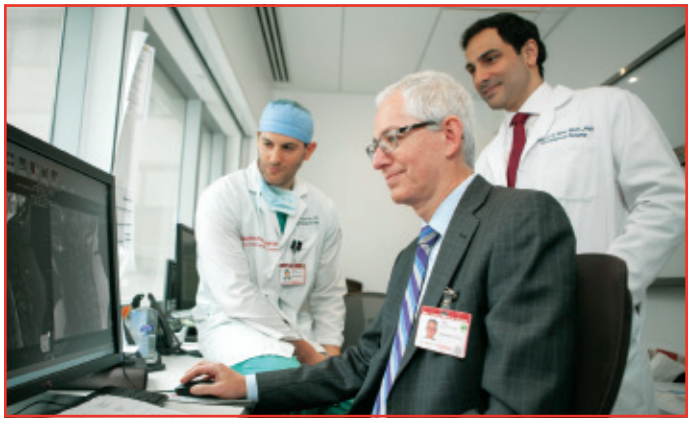
Their study, published in the *Journal of Neurosurgery: Spine,* analyzed the results of patients with LSS without spondylolisthesis and with stable Grade I spondylolisthesis who had undergone minimally invasive tubular laminectomy between 2004 and 2011. Among 110 patients, preoperative spondylolisthesis at the level of spinal stenosis was present in 52.5 percent.

The reoperation rate requiring fusion at the same level was 3.5 percent, indicating that patients with and without preoperative spondylolisthesis had no significant differences in their clinical outcome or reoperation rate. The study demonstrated that minimally invasive laminectomy is an effective procedure for the treatment of LSS and reoperation rates for instability are lower than those reported after open laminectomy. The researchers concluded that functional improvement is similar in patients with and without preoperative spondylolisthesis and that this procedure can be an alternative to open laminectomy. Routine fusion may not be indicated in all patients with LSS and spondylolisthesis.

Tracking Patient Outcomes

The Weill Cornell Brain and Spine Center, as well as the Neurological Institute at NewYork-Presbyterian/Columbia University Medical Center, participate in the Quality Outcomes Database (QOD), the largest continuous spine registry in North America with nearly 30,000 patients enrolled from 78 neurosurgical centers. The registry is segmented into four modules: lumbar, cervical spine, cerebrovascular, and spinal deformity.

"The most powerful registries are those that are inter-institutional," says **Eric H. Elowitz, MD**, a neurosurgeon specializing in minimally invasive spinal surgery at Weill Cornell. "This is where we can pool not only our numbers, but also numbers from centers across the country to give us a better idea of what works and what doesn't work for patients. There has not been a specific multicenter neurosurgery registry until this one."



Dr. Eric H. Elowitz (center) with Dr. Jared Knopman and Dr. Michael S. Virk

What makes a spine surgery registry unique compared to other registries, says Dr. Elowitz, is that it looks at patient health-assessed outcomes. "For example, most registries just look at the complications, such as if the patient was readmitted to the hospital, if they had to go back to surgery, infection rates, and any blood loss," he says. "However, in spine surgery we need to measure how we are improving the patient's quality of life, not just at 30 days, but for a longer period of time." In the practice of Drs. Härtl and Elowitz, a staff member calls each patient before surgery to conduct a questionnaire measuring preoperative scores for pain and quality of life; the call is then repeated at three months and at one year post-surgery.

QOD provides a detailed quarterly report to participating centers. "The report shows our results, but also puts them into perspective benchmarked against other centers," says Dr. Elowitz. "These outcomes are risk-adjusted for different types of surgeries, so it gives us some very powerful information."

"Going forward, we need additional data telling us exactly how patients do after different types of procedures," says Dr. Härtl. "There is a tremendous heterogeneity right now. More than any other surgery, if you ask different spine surgeons you get many different opinions – even different opinions from the same surgeon."

Reference Article

Alimi M, Hofstetter CP, Pyo SY, Paulo D, Härtl R. Minimally invasive laminectomy for lumbar spinal stenosis in patients with and without preoperative spondylolisthesis: clinical outcome and reoperation rates. *Journal of Neurosurgery: Spine.* 2015 Apr;22(4):339-52.

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Clinical Trials Update: NeuroNEXT

The Network for Excellence in Neuroscience Clinical Trials, NeuroNEXT, was created to conduct studies of treatments for neurological diseases through partnerships with academia, private foundations, and industry. The network is designed to expand the capability of the National Institute of Neurological Disorders and Stroke to test potential new therapies, increase the efficiency of clinical trials, and respond quickly as new opportunities arise to test promising treatments. **Karen Marder, MD, MPH**, and **Claudia Chiriboga, MD, MPH**, are co-principal investigators, and **Claire Henchcliffe, MD, DPhil**, is site PI at Weill Cornell. **Joyce Moran, CCRC**, is NeuroNEXT Project Manager.

NN104 – RHAPSODY: A Multicenter, Phase II Study of 3K3A-APC with tPA in Ischemic Stroke

Currently, the only approved treatment in the U.S. for ischemic stroke is a drug called recombinant tissue plasminogen activator (rtPA or tPA), indicated for intravenous administration within three hours of onset of the stroke. The drug is designed to break down blood clots to restore blood flow to the brain. In some patients, however, tPA can cause internal bleeding and other complications.

This multicenter, Phase II study uses a continual reassessment method to determine the safety, tolerability, and activity of 3K3A-APC, a recombinant variant of human activated protein C (APC), in combination with tissue plasminogen activator (tPA), in subjects with moderately severe acute hemispheric ischemic stroke. The cytoprotective properties of 3K3A-APC may be useful in protecting ischemic brain tissue from further damage, while avoiding an increase in the chance of treatment-related bleeding.

The study intervention will be administered as a 15-minute infusion every 12 hours for up to 5 infusions. Four dose levels will be considered for this trial. Approximately 100 participants, ages 18 to 80 years old, will be enrolled and followed for 90 days.

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NN105 – STAIR: An Exploratory Phase II Study of a Novel Vasopressin 1a Receptor Antagonist in Irritable Subjects with Huntington's Disease

Huntington's disease (HD) is an inherited disease that results from expansion of a trinucleotide (CAG, cytosine/adenine/guanine) repeat that encodes a polyglutamine tract in the huntingtin gene and gradually damages neurons. Over time this cellular loss affects voluntary motor control, results in involuntary movements, and causes cognitive decline. Psychiatric symptoms, including irritability, are commonly seen in HD, and are quite distressing for patients and their family. Preclinical pharmacology studies suggest that SRX246, a first-in-class vasopressin 1a (V1a) receptor antagonist, has potential as a novel therapeutic agent for major neuropsychiatric symptoms seen in HD patients.

This research study is being conducted to test the tolerability and further examine the safety of SRX246 in irritable subjects with early symptomatic HD when it is given orally at doses up to 160 mg twice daily compared to placebo. Approximately 150 HD patients will be screened to enroll 108 subjects at NeuroNEXT sites across the United States.

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