

# ADVANCES IN NEUROLOGY AND NEUROSURGERY

**Matthew E. Fink, MD**  
Neurologist-in-Chief  
NewYork-Presbyterian/  
Weill Cornell Medical Center  
mfink@med.cornell.edu

**Richard P. Mayeux, MD, MSc**  
Neurologist-in-Chief  
NewYork-Presbyterian/  
Columbia University Medical Center  
rpm2@cumc.columbia.edu

**Robert A. Solomon, MD**  
Neurosurgeon-in-Chief  
NewYork-Presbyterian/  
Columbia University Medical Center  
ras5@cumc.columbia.edu

**Philip E. Stieg, PhD, MD**  
Neurosurgeon-in-Chief  
NewYork-Presbyterian/  
Weill Cornell Medical Center  
pes2008@med.cornell.edu

## Targeting Endosomal Trafficking in Alzheimer’s Disease

Recent breakthroughs in Alzheimer’s disease research may be leading scientists down a new pathway for drug discovery. **Scott A. Small, MD**, Director of the Alzheimer’s Disease Research Center at NewYork-Presbyterian/Columbia



Dr. Scott A. Small

University Irving Medical Center, believes the key may be in targeting a biological mechanism in the cell called retromer endosomal dysfunction. Conceptually, this represents quite a different model than the amyloid hypothesis, the long-standing theory of Alzheimer’s disease pathology.

A recent spate of large-scale clinical trials targeting amyloid has seen lukewarm results, with major pharmaceutical companies discontinuing studies of highly anticipated Alzheimer’s drugs. All of this has left scientists in something of a quandary. Are they intervening too late in the Alzheimer’s disease process? Is amyloid the wrong target?

The answers may reside in the work of Dr. Small and his colleagues in the Alzheimer’s Disease Research Center. Most recently, Dr. Small, **Richard P. Mayeux, MD, MSc**, Neurologist-in-Chief at NewYork-Presbyterian/Columbia, and members of their research team constructed a model based on the latest genetic and cellular findings, proposing

*(continued on page 2)*

### INSIDE THIS ISSUE

- 5 NeuroNEXT:**
- Fragile X Syndrome
  - Cryptogenic Sensory Peripheral Neuropathy
  - Glioblastoma Multiforme



NewYork-Presbyterian  
Neurology and Neurosurgery  
ranks #4 in the nation.

## Alzheimer’s and Prevention: Who Would Have Thought?

It is estimated that 47 million Americans have preclinical Alzheimer’s disease and are not yet exhibiting symptoms. This offers specialists such as **Richard S. Isaacson, MD**, Director of the Alzheimer’s Prevention Clinic at NewYork-Presbyterian/Weill Cornell Medical Center, a unique opportunity to intervene early on in the process.

Dr. Isaacson has four family members with Alzheimer’s disease. While his family history led to the decision to specialize in the treatment of Alzheimer’s, it also informed the way that he approached the overall management of the disease. Is Alzheimer’s primed to join other chronic diseases like heart disease and diabetes, which have modifiable risk factors? Research from population attributable risk models indicates that one out of three cases of Alzheimer’s may be preventable, and Dr. Isaacson wholeheartedly agrees.

**“In 2018, we can feel more comfortable using Alzheimer’s and prevention in the same sentence because the totality of evidence demonstrates that we can reduce risk.”**

— Dr. Richard S. Isaacson

“We know that Alzheimer’s disease starts in the brain 20 to 30 years before the onset of symptoms, giving physicians ample time to intervene in an individualized fashion for those at risk,” says Dr. Isaacson, who established the Alzheimer’s Prevention Clinic in 2013. “Having a few FDA approved drugs on the market is marginally helpful, but what about addressing vascular risk factors, lifestyle changes, exercise, nutrition, sleep,

*(continued on page 3)*

## Targeting Endosomal Trafficking in Alzheimer's Disease (continued from page 1)

that traffic jams in the early endosome can act as a pathogenic hub in Alzheimer's disease. They found that these congested pathways occur early in the disease and may develop independently of amyloid, further suggesting that retromer plays a key role in this process.

"The model predicts that interventions designed to unjam the endosome carry high therapeutic promise and that endosomal trafficking is a valid cell biological target for novel therapeutics," says Dr. Small. Their work on endosomal trafficking was featured as the cover story of the October 2017 issue of *Trends in Neuroscience*.

### The Path to Therapeutic Targets

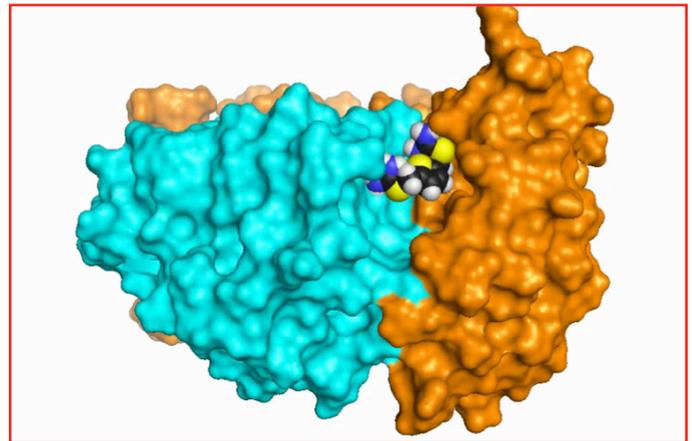
One of the Alzheimer's Disease Research Center's accomplishments early on was the design of a functional MRI (fMRI) imaging technique that could image the earliest signs of Alzheimer's disease, enabling the research team to obtain a very clear pattern of vulnerability for Alzheimer's in a region of the hippocampus called the entorhinal cortex.

"At the time, this was completely novel," says Dr. Small. "However, we still did not understand why one area was vulnerable and another resistant." Dr. Small continued to pursue this line of inquiry with other experts in the field, including **Karen E. Duff, PhD**, Deputy Director of the Taub Institute for Research on Alzheimer's Disease and the Aging Brain at Columbia and an expert in mouse models. Using fMRI to examine the entorhinal cortex both in mouse models and in patients with Alzheimer's disease, they were able to identify not only where the disease began, but also why it began, how it spread, and potential imaging opportunities for early detection. "This gave us a very clear pattern of vulnerability," says Dr. Small. Their findings, published in a seminal paper in *Nature Neuroscience* in 2014, helped take research in Alzheimer's disease to a new level.

Dr. Small, together with **Gregory A. Petsko, DPhil**, Director of the Robert and Helen Appel Alzheimer's Disease Research Institute at Weill Cornell Medicine, and research colleagues at Brandeis University, went on to identify a new class of compounds, called pharmacologic chaperones, which could bind to retromer's weak point and stabilize the protein molecules, thereby decreasing amyloid levels. "Our research demonstrated, what is to our knowledge the first time, that small molecules can act as pharmacological chaperones that can stabilize a multiprotein complex and enhance its function," says Dr. Small. Their groundbreaking work showing proof of principle for the efficacy of these retromer pharmacologic chaperones was published in 2014 in *Nature Chemical Biology*.

Dr. Small estimates that subsequently some 20 papers have been published validating the role that the retromer pathway plays in Alzheimer's disease. "If endosomal trafficking, in general, and the cellular pathway, retromer, in particular, play a role in Alzheimer's, could we target it for therapeutics? That is the ultimate finishing line." Dr. Small's lab is currently investigating novel therapies to help regulate this biological process, and the pharmaceutical industry is now taking an active interest in developing retromer drugs for Alzheimer's disease, as well as for Parkinson's.

In order to target retromer and endosomal trafficking, Dr. Small and his colleagues are still trying to understand why retromer dysfunction affects the entorhinal cortex. "We have relied on these patterns of regional vulnerability to get to retromer. But that



Three-dimensional image showing how drug compounds target retromer to improve endosomal trafficking defects (Source: *Nature Chemical Biology*. June 2014)

doesn't explain at a basic science level why the entorhinal cortex is vulnerable to retromer dysfunction," says Dr. Small.

One way to confirm the retromer pathway is to look at genetics. Dr. Richard Mayeux has led a population-based Alzheimer's disease study since 1989 and was one of the first to link genetic risk factors and biomarkers to vulnerability. He and his research team have identified a number of retromer-related genes that have been strongly linked to Alzheimer's, thereby showing a pathogenic role.

Looking ahead, Dr. Small talks of incorporating precision medicine into the equation. "We want to make sure that patients who enroll in clinical trials have evidence of retromer dysfunction so that we can track them," he says. Progress has already been made by Dr. Small's lab, which has identified biomarkers of retromer dysfunction in a mouse model that are now going on to be tested in human subjects.

Such progress emanates from years of research in the Alzheimer's Disease Research Center and collaborations with some of the most brilliant minds in dementia and aging research – among them Dr. Mayeux, and **Lawrence S. Honig, MD, PhD**, Director of the Center's Clinical Core. "The early days were difficult," says Dr. Small. "It took a lot of work, collaborations, and papers. The cliché is that it takes a village. It actually takes a great university."

### Reference Articles

Small SA, Simoes-Apassov S, Mayeux R, Petsko GA. Endosomal traffic jams represent a pathogenic hub and therapeutic target in Alzheimer's disease. *Trends in Neuroscience*. 2017 Oct;40(10):592-602.

Mecozzi VJ, Berman DE, Simoes S, Vetanovetz C, Awal MR, Patel VM, Schneider RT, Petsko GA, Ringe D, Small SA. Pharmacological chaperones stabilize retromer to limit APP processing. *Nature Chemical Biology*. 2014 Jun;10(6):443-49.

Kahn UA, Liu L, Provenzano FA, Berman DE, Profaci CP, Sloan R, Mayeux R, Duff KE, Small SA. Molecular drivers and cortical spread of lateral entorhinal cortex dysfunction in preclinical Alzheimer's disease. *Nature Neuroscience*. 2014 Feb;17(2):304-11.

### For More Information

Dr. Scott A. Small • sas68@cumc.columbia.edu

## Alzheimer's and Prevention: Who Would Have Thought? *(continued from page 1)*

and stress management? There is a saying: Once you have seen one person with Alzheimer's, well, you have seen one person with Alzheimer's. What this means is that from a clinical perspective, Alzheimer's is a very heterogeneous disease. I believe that different people can take different roads to Alzheimer's. Some may have insulin resistance and fast-forward amyloid production. Others may have a genetic link. We need to figure out what road they're on and get them off that road. I didn't feel comfortable with a one-size-fits-all approach and started looking deeper, considering genetic variations and the person's individual biology, in crafting a targeted plan."

### A Multimodal Prevention Strategy

While there is no disease-modifying therapy currently available for treatment, Dr. Isaacson believes combining a variety of evidence-based low-risk interventions along with lifestyle modifications may help to delay, or in some cases, possibly prevent the progression toward dementia. He is not alone in this thinking. Observational studies have shown that modifiable vascular, metabolic, and lifestyle-related factors have been associated with dementia risk. Findings from the 2015 Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), a groundbreaking two-year proof-of-concept randomized controlled trial of over 1,200 people, suggest that a multidomain intervention – diet, exercise, cognitive training, and vascular risk monitoring – could improve or maintain cognitive functioning in at-risk elderly over time.

"These interventions were found to be as effective in individuals who have the most common gene for late-onset Alzheimer's disease," notes Dr. Isaacson. "So, not only do we have some control over our destiny, it may even be possible to win the tug-of-war against our genes."

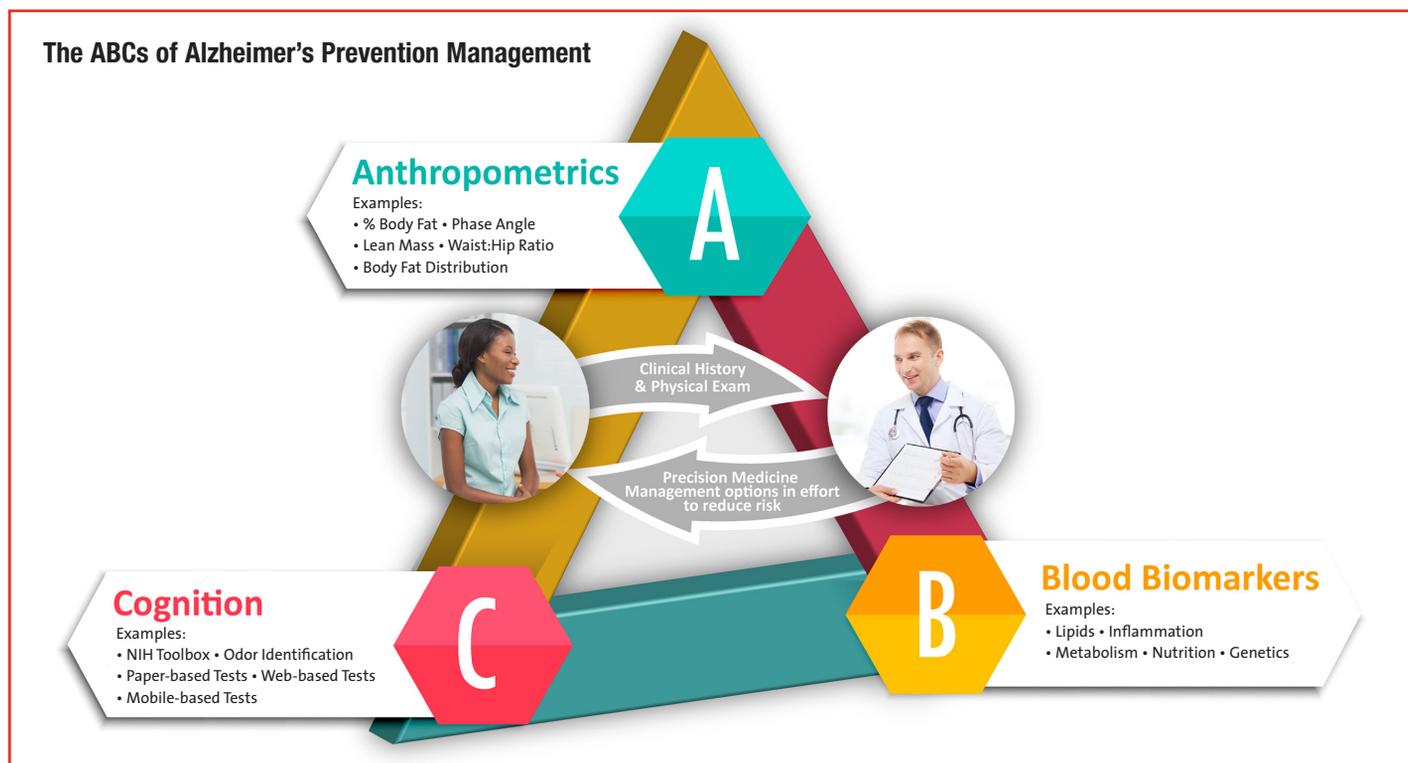
The Alzheimer's Prevention Clinic at Weill Cornell focuses on promoting brain health and reducing risk through a series of multidisciplinary interventions that target lifestyle behavior modifications. Because Alzheimer's prevention is a nascent field with a paucity of literature, the Clinic's methods are being rigorously tested in an ongoing clinical research study. The work of Dr. Isaacson and his team has helped establish that proactively managing Alzheimer's risk factors is a feasible endeavor, and the Clinic has drawn an increasing number of people who seek to lower their Alzheimer's risk.

"We are offering a clinical precision medicine approach for normal patients at risk, those with preclinical Alzheimer's, and those who have mild cognitive impairment due to Alzheimer's," says Dr. Isaacson. "Each patient undergoes what we call the ABCs of Alzheimer's prevention management. A is for anthropometrics, or body composition. B represents blood-based biomarkers related to genetics, lipids, metabolism, inflammation, and nutrition. C stands for cognition. In addition to blood draws, genetic testing, and biometric measurements, patients undergo extensive cognitive assessments. We paint a very fine-tuned picture and reassess these measures every six months. If the initial behavior modifications we recommend are not helping, the multidisciplinary team will suggest alternatives."

Dr. Isaacson puts his beliefs into practice for himself as well. "Essentially, everything I tell my patients to do in terms of making the right lifestyle choices, I do myself," he says. "I firmly believe that these changes can reduce my own personal risk, as well as my patients' risk, while also benefiting overall health."

Technology also has a major presence in their approach. Clinicians use wrist biosensor devices to measure patients' exercise frequency and intensity, average pulse rate, maximum pulse rate, as well as

*(continued on page 4)*





Dr. Richard S. Isaacson

REM, deep and total sleep. “Think of it as a Fitbit on steroids,” says Dr. Isaacson, who is conducting a pilot study of the tool with 40 patients aged 25 to 75 years. “We are committed to using technology to facilitate diagnosis, ongoing monitoring, and optimizing personalized therapeutic management.”

The Clinic’s technology team, which includes a bioinformatics neurology fellow and a previous IBM Watson team member who is now developing artificial neural networks for use in the Alzheimer’s Prevention Clinic dataset, has also created mobile phone-based cognitive tests to predict whether patients have the earliest signs of memory loss due to Alzheimer’s. They have collaborated with faculty at Harvard to develop a cognitive assessment that can be done via cell phone, computer, or tablet, that can predict whether amyloid is present in the brain.

“Based on prevailing evidence, one out of three cases of Alzheimer’s disease may be preventable if we do everything right. Even if we can tell a patient ‘we are not 100 percent sure this approach works, but it’s low risk,’ that’s a big step forward,” says Dr. Isaacson. “From the volume of patients we are seeing in our clinic, we have learned that there is definitely a need for this service. And our preliminary evidence – published in a peer-reviewed publication and presented at professional meetings – shows measurable improvements in cognitive function at baseline and at six-month follow-up, as well as improvement in blood biomarkers of Alzheimer’s disease risk. We have been able in the

short term to improve brain health. The tricky part is, are we really preventing Alzheimer’s or just improving brain health? That’s where we need to go next.”

### Moving Forward

Dr. Isaacson and his team have developed a framework for practice for neurologists in the field of Alzheimer’s prevention. Not surprisingly, their model has attracted visiting neurologists from all over the world seeking to replicate it at their own institution, and there are now several prevention clinics in the U.S. and globally that have created, or plan to create, similar programs based on the Weill Cornell approach.

Recognizing the demand for information by patients and practitioners alike, the Alzheimer’s Prevention Clinic team launched an educational website, Alzheimer’s Universe (AlzU.org). The site, which offers an Alzheimer’s prevention education course for patients, as well as a free CME-accredited course on prevention for neurologists and other physicians, has drawn one million visitors since its inception only four years ago.

“In terms of the ‘textbook’ of Alzheimer’s prevention, the first chapter is written and we are making progress on chapter two, but we still have a long way to go,” continues Dr. Isaacson. “We need to define what Alzheimer’s prevention is and isn’t, and legitimize the evidence-based approach to prevention based on science, determining what is and what is not in our control.”

To this end, Dr. Isaacson’s team received NIH funding to undertake brain imaging in women ages 40 to 65 in a first-of-its-kind study aimed at defining the “critical window” for risk reduction. “Once a disease of old age, Alzheimer’s is beginning to be seen by neurologists as a disorder of younger and middle-aged people,” says Dr. Isaacson. “That is how our field is going to survive. We have to prevent the disease, not just treat it.”

Dr. Isaacson’s focus on prevention had its skeptics at first, but it seems like the tide is turning. In fact, the American Academy of Neurology has even applied the term “newrologists” to emphasize the move toward preventative, interventional, and regenerative care efforts, as well as novel therapies.

“In 2018, we can feel more comfortable using Alzheimer’s and prevention in the same sentence because the totality of evidence demonstrates that we can reduce risk,” says Dr. Isaacson.

### Reference Articles

Berti V, Walters M, Sterling J, Quinn CG, Logue M, Andrews R, Matthews DC, Osorio RS, Pupi A, Vallabhajosula S, Isaacson RS, de Leon MJ, Mosconi L. Mediterranean diet and 3-year Alzheimer brain biomarker changes in middle-aged adults. *Neurology*. 2018 May 15;90(20):e1789-e1798.

Schelke MW, Attia P, Palenchar DJ, Kaplan B, Mureb M, Ganzer CA, Scheyer O, Rahman A, Kachko R, Krikorian R, Mosconi L, Isaacson RS. Mechanisms of risk reduction in the clinical practice of Alzheimer’s disease prevention. *Frontiers in Aging Neuroscience*. 2018 Apr 10;10:96.

Mosconi L, Walters M, Sterling J, Quinn C, McHugh P, Andrews RE, Matthews DC, Ganzer C, Osorio RS, Isaacson RS, De Leon MJ, Convit A. Lifestyle and vascular risk effects on MRI-based biomarkers of Alzheimer’s disease: A cross-sectional study of middle-aged adults from the broader New York City area. *BMJ Open*. 2018 Mar 23;8(3):e019362.

Schelke MW, Hackett K, Chen JL, Shih C, Shum J, Montgomery ME, Chiang GC, Berkowitz C, Seifan A, Krikorian R, Isaacson RS. Nutritional interventions for Alzheimer’s prevention: A clinical precision medicine approach. *Annals of the New York Academy of Sciences*. 2016 Mar;1367(1): 50-66. Review.

Seifan A, Isaacson RS. The Alzheimer’s Prevention Clinic at Weill Cornell Medical College/NewYork-Presbyterian Hospital: Risk stratification and personalized early intervention. *The Journal of Prevention of Alzheimer’s Disease*. 2015 Oct 16; 2(4).

### For More Information

Dr. Richard S. Isaacson, MD • rii9004@med.cornell.edu  
Alzheimer’s Universe • AlzU.org

## NeuroNEXT

### NN107 FX-LEARN: A Study of AFQ056 in Fragile X Syndrome

Fragile X syndrome is a single-gene disorder and the most commonly inherited cause of intellectual disability. Effects range from learning disabilities to severe intellectual impairment. This study will examine if drug therapy with AFQ056 can improve communication and learning in children with Fragile X syndrome. The study will also determine the most effective dosing to improve neural plasticity, which is the core deficiency in Fragile X, as well as the safety of the therapy.

Participants between the ages of 32 months and six years of age will be randomized to either receive the drug therapy or a placebo for the initial period of about one year. All participants will be evaluated by speech language therapists, who will analyze and measure change in language skills in response to the intervention and deliver language therapy sessions to the family. In the study's extension phase, all participants will be treated with the active drug for a

period of about 8 months. The study is the first of its kind to evaluate whether a treatment aimed at improving a core deficit of brain connectivity can change the ability to learn in young children with Fragile X syndrome.

#### For More Information

NewYork-Presbyterian/  
Columbia University Irving Medical Center  
Principal Investigator: Jeremy Veenstra-VanderWeele, MD  
Phone: (646) 774-5251  
Email: jv2511@cumc.columbia.edu

#### Study Location

Center for Autism and the Developing Brain  
NewYork-Presbyterian Westchester Division  
21 Bloomingdale Road  
White Plains, NY 10605

### NN108 TopCSPN: A Study of Oral Topiramate as a Therapy for Cryptogenic Sensory Peripheral Neuropathy

The TopCSPN trial is a 96-week, double blind, randomized, placebo-controlled trial of oral topiramate at a target dose of 100 mg daily (50 mg twice daily) as a potentially disease altering therapy for cryptogenic sensory peripheral neuropathy (CSPN). Adults, ages 18 to 75, diagnosed with CSPN who also have metabolic syndrome (defined by the ATP III criteria) and do not have an alternative cause for neuropathy are potentially eligible. Randomized participants will return to the clinic for follow-up visits every 16 weeks. The treatment phase will last 24 months.

Primary outcome measures are change in the Norfolk Quality of Life-Diabetic Neuropathy (NQOL-DN) Scale and intraepidermal nerve fiber density (IEFND) at the distal thigh.

#### For More Information

NewYork-Presbyterian/  
Columbia University Irving Medical Center  
Principal Investigator: Thomas Brannagan III, MD  
Phone: (212) 305-0405  
Email: tb2325@cumc.columbia.edu

### NN106 CYTO-C (Cytochrome c Oxidase Activity in Newly Diagnosed GBM)

Glioblastoma multiforme (GBM), a malignant form of astrocytoma, is the most common and most aggressive glioma. Subjects with newly diagnosed GBM who undergo standard of care treatments (maximal surgical resection, 60 Gy radiotherapy together with Temozolomide, followed by maintenance Temozolomide for 6 months) have been found to have a median survival time of 14.6 months. It is postulated that overall survival in patients with newly diagnosed GBM treated with standard of care measures is correlated with Cytochrome c Oxidase (CcO). The greater the CcO activity, the shorter the overall survival time. Thus, CcO activity as a biomarker could have valuable clinical implications in guiding patient therapy.

This research study is being conducted to determine the relationship between CcO activity in GBM tumors and

overall survival time (time from diagnosis to death) and to compare the usefulness of CcO as a biomarker to an already well-known biomarker, MGMT.

The study seeks to recruit 200 male and female subjects, aged 21 or older, with newly diagnosed GBM who are undergoing standard of care treatment as defined above and have a KPS score >60. Tumor tissue samples will be sent to assess CcO activity and brain imaging, and medical records will be utilized to assess disease progression.

#### For More Information

NewYork-Presbyterian/  
Columbia University Irving Medical Center  
Principal Investigator: Teri N. Kreisl, MD  
Phone: (212) 342-0571  
Email: tnk2109@cumc.columbia.edu

## ADVANCES IN NEUROLOGY AND NEUROSURGERY

NewYork-Presbyterian Hospital  
525 East 68th Street  
New York, NY 10065

[www.nyp.org](http://www.nyp.org)

NON-PROFIT ORG.  
US POSTAGE  
PAID  
STATEN ISLAND, NY  
PERMIT NO. 169

### **SAME DAY APPOINTMENT SERVICE FOR NEW PATIENTS**

For rapid access to a neurological specialist for patients requiring immediate evaluation, call:

**NewYork-Presbyterian/Columbia**  
(646) 426-3876

**NewYork-Presbyterian/Weill Cornell**  
(212) 746-2596

**Amazing Advances in Research,  
Technology, and Patient Care**  
NewYork-Presbyterian's new  
clinical innovations site for  
professionals  
[nyp.org/amazingadvances](http://nyp.org/amazingadvances)

 **NewYork-Presbyterian**



Amazing Advances in Research, Technology, and Patient Care

### **CLINICAL INNOVATIONS**

