**INSIDE WINTER 2011**

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**Gene Vital to Brain’s Stem Cells Implicated in Deadly Brain Cancer**

Protein identified that may cause brain cancer in humans.

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**ADVANCES IN NEUROSCIENCE**

**PSYCHIATRY, NEUROLOGY AND NEUROSURGERY**

**Functional Connection Between Brain Areas Impaired in Schizophrenia, Study Finds**

Contributing faculty for this article: Joseph A. Gogos, MD, PhD, and Maria Karayiorgou, MD

Patients with schizophrenia may have any of an array of symptoms, including delusions, hallucinations, thought disorder, flat affect, poverty of speech (alogia), asociality, and lack of motivation. Patients also invariably have cognitive symptoms, including poor executive functioning, an inability to sustain attention, and deficits in working memory—and these cognitive symptoms are better predictors of a patient’s functional outcome than the severity of other symptoms, according to Columbia University researchers Joseph A. Gogos, MD, PhD, Associate Professor of Physiology and Cellular Biophysics, Neuroscience, and Maria Karayiorgou, MD, Professor of Psychiatry in Genetics and Physiology and Acting Chief of the Division of Medical Genetics in the Department of Psychiatry.

In what may provide the most compelling evidence to date, the researchers have illuminated how a genetic variant may lead to schizophrenia by causing a disruption in communication between the hippocampus and prefrontal cortex regions of the brain, areas believed to be responsible for carrying out working memory.

Though schizophrenia is best known for its delusions and hallucinations, it is the disease’s impact on such cognitive abilities like working memory — a key element of executive functioning — that best predict how well a person will function in society.

In a recently published study, Drs. Karayiorgou and Gogos and their colleagues, Joshua A. Gordon, MD, PhD, and Torfi Sigurdsson, PhD, demonstrated that a key physiological problem underlying cognitive symptoms of schizophrenia, in particular a deficit in working

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**A Promising Approach for Pontine Gliomas**

Contributing faculty for this article: Mark M. Souweidane, MD

Diffuse pontine gliomas make up just 10 to 15 percent of pediatric brain tumors. But their progress is swift, and they are uniformly fatal. NewYork-Presbyterian Hospital/Weill Cornell Medical Center investigators are now assessing an innovative means of delivering radioimmunotherapy to these difficult-to-treat inoperable brain-stem tumors, which most commonly strike children between the ages of 6 and 10.

"Among parents and physicians, there is a lot of desperation, a lot of anticipation, and a lot of hope with regard to these tumors," said Mark M. Souweidane, MD, who is leading the research. Dr. Souweidane is Professor of Neurological Surgery at Weill Cornell Medical College, Vice Chairman of the Department of Neurological Surgery, and Director of Pediatric Neurological Surgery, NewYork-Presbyterian Phyllis and David Kornansky Center for Children’s Health.

Children with diffuse pontine gliomas may appear otherwise quite healthy except for the symptoms associated with the tumor — including altered eye movements and facial expressions, headaches, vomiting, and fatigue. “Their hearts are healthy, their kidneys are healthy. There’s nothing short of this one-and-a-half to two-inch tumor in the brain stem that we need to cure, which is very frustrating,” noted Dr. Souweidane.

The tumor remains localized in the brain stem, eventually interfering with such vital functions as heart rate, respiration, swallowing, and clearing of the throat. Surgery and chemotherapy are ineffective. The standard of care is temporizing external beam radiation therapy. But even with this approach, all patients recur, and the median survival time is only 9 to 12 months.

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**Top Ranked Hospital in New York. Ten Years Running.**
Reduced hippocampal–prefrontal synchrony correlates with behavioural performance in Df(16)A+/- mice. A, Coherence between the prefrontal cortex and the hippocampus during habituation sessions before training on the spatial working memory task. B, Days taken to reach criterion performance on the spatial working memory task. C, Days taken to reach criterion versus theta coherence during habituation sessions for each animal. Animals with lower theta coherence before training take longer to learn the spatial working memory task. Green line, linear regression of data from Df(16)A+/- mice. D, Development of hippocampal–prefrontal coherence during acquisition of the working memory task: theta coherence (top) and choice accuracy (bottom) during early (trials 1–5), middle (trials 26–30) and late (session in which criterion was reached) stages of training in wild-type (left) and Df(16)A+/- (right) mice. *P<0.05, **P<0.01. Data shown, mean +/- s.e.m.

memory, results from an abnormal connection between the hippocampus and prefrontal cortex (Nature Vol 464; April 1, 2010; p. 763-768). The researchers studied working memory in a population of mice genetically engineered to carry the equivalent of a microdeletion on human chromosome 22 (22q11.2), one of the main known genetic risk factors for schizophrenia, which was discovered by Dr. Karayiorgou 15 years ago. The mice (Df(16)A mice) have several abnormalities analogous to those in people with schizophrenia. According to Dr. Gogos, the Columbia team focused their research on the physiology underlying working memory normal, wild-type mice and Df(16)A mice performed a T-maze task in which they were first directed to enter one of two arms, then had to remember the arm visited during the previous phase and enter the opposite arm.

Explaining how the hippocampus and the prefrontal cortex synchronize, Dr. Karayiorgou noted, “The coordinated, rhythmic activity of neuronal populations in the brain gives rise to oscillations at a broad range of frequencies, which synchronize neural firing of interconnected cells in and between brain areas. For example, prefrontal cortex neuron firing is modulated by hippocampus theta-frequency.”

“It’s possible that imaging approaches such as fMRI could be used to examine the pattern of connectivity among brain regions and facilitate diagnosis of specific subtypes of schizophrenia in patients.”

— Maria Karayiorgou, MD

because it is easier to study in animal models than symptoms such as psychosis and asociality.

“We hypothesized that cognitive deficits are likely to be mediated by the same abnormal physiological processes as other symptoms,” added Dr. Gogos, “and that by studying cognition in mutant models we can offer some more general insights into the pathophysiology of the disease.”

Previous research with animal models has shown that neural activity in the hippocampus and prefrontal cortex becomes synchronized during the performance of a spatial working memory task. In this study, the Columbia team measured the synchronization of neural activity between these brain areas while both models allow us to use higher resolution techniques that provide information on the behavior of individual neurons.”

“While dysconnectivity between the prefrontal lobe and hippocampus contributes to cognitive deficits in patients with schizophrenia, it is less clear how this dysconnectivity can lead to psychosis,” she added. “It’s possible that dysconnectivity resulting from the 22q11.2 microdeletion may be more pervasive and affect connections between the prefrontal lobe and other cortical and subcortical areas. So it is very likely that other symptoms result when abnormal dysconnectivity causes...
Slowing the Rate of Brain Volume Loss in Alzheimer’s Disease

Contributing faculty for this article: Norman R. Relkin, MD, PhD, Dana Moore, PhD, and Diamanto Tsakanikas, PhD

Around age 30 our brains begin to shrink at a well-defined rate of about .5 percent per year, and the changes become conspicuous after age 60. In patients with Alzheimer’s disease (AD) these changes occur at two to four times the normal rate, providing neurologists with a concrete measure of brain degeneration, which correlates with declines in areas such as cognition, global outcome, behavior, and daily function.

Several years ago, building on findings in animal models that vaccines can generate anti-amyloid antibodies with a potent effect on the underlying pathology of Alzheimer’s disease, researchers in the Memory Disorders Program at NewYork-Presbyterian/Weill Cornell began evaluating the effectiveness of intravenous immune globulin (IVIG). At the April 2010 meeting of the American Academy of Neurology, Norman R. Relkin, MD, PhD, Director, reported the results of a recently concluded phase II study showing that Alzheimer’s patients who received IVIG for 18 months had significantly lower rates of brain shrinkage (6.7 percent versus 12.7 percent per year) and less whole-brain atrophy (1.6 percent versus 2.2 percent per year) than subjects in the control arm, who received a placebo during the first six months.

IVIG, a plasma protein replacement therapy, is prepared from the plasma of approximately 10,000 healthy human donors, and contains all four subgroups of IgG antibodies. IVIG is FDA-approved for immune deficiency and autoimmune disorders and some types of cancer.

In the phase II study, Dr. Relkin and colleagues enrolled 24 patients with mild to moderate AD whose symptoms had progressed on currently available medications. For the first six months, they compared four different doses of IVIG, from 0.2 g/kg every 2 weeks to 0.8 g/kg every 4 weeks, to saline placebo. For the next 12 months those in the placebo group were assigned to receive one of the four IVIG doses and the rest of the patients continued on their previous dose. “On our primary and several secondary outcome measures those who received continuous IVIG treatment over 18 months did significantly better than those who had gotten a delayed start,” said Dr. Relkin. The protective effect of IVIG was even more clear in the group that received the dose determined to be optimal in an earlier phase I study (0.4 g/kg every 2 weeks).

“There was about a 50 percent reduction in brain shrinkage in the continuously IVIG-treated group as a whole,” noted Dr. Relkin, “but we found that the effect was dose dependent and in the dose group that had the best clinical outcome. The rate of brain volume loss as measured by ventricular enlargement was just 3 percent, the same as is reported in normal adults.”

Diamanto Tsakanikas, PhD, a neuropsychologist in the Weill Cornell Memory Disorders Program, performed cognitive and behavioral testing on the study subjects. She found that brain volume changes closely paralleled positive outcomes on the Clinical Global Impressions of Change scale, the Alzheimer’s Disease Assessment Scale-Cognitive Subscale (ADAS-cog), and the Neuropsychiatric Inventory. Patients in the uninterrupted IVIG-treatment group scored better than those in the delayed start of treatment or suboptimal dosing groups, she reported.

The hallmark of AD is an accumulation of amyloid in the brain, which begins long before symptoms become evident. Many AD researchers now believe that these deposits are a kind of “tombstone” of amyloid pathology rather than the culprits behind the disease. Instead, Dr. Relkin, says, “It is the aggregated soluble forms of amyloid – amyloid oligomers and higher order aggregates generated in the process of misfolding – that are highly toxic to brain cells and ultimately lead to neurodegeneration.”

“Aggregated forms of amyloid bind to receptors involved in neurotransmission and generate abnormal currents that disrupt neuronal integrity, thereby initiating a series of other events that actually mediate the cell death. These include inflammation, disordering of the neuronal cytoskeleton, reactive oxygen species attacking cell membranes, and a host of other things,” explained Dr. Relkin.

“The antibodies in IVIG, which are naturally produced by humans, recognize the misfolded, aggregated, pathologic forms of amyloid, but largely ignore the physiologic molecules that we all produce from birth,” according to Dr. Relkin. “They only respond when the molecules start to aggregate to the toxic oligomers and fibrils that we find in the brain of Alzheimer’s disease patients.

“Our multi-center phase III study of IVIG in AD, co-sponsored by the NIH and Baxter, is currently underway,” says Dr. Relkin. Participating researchers at 38 sites in North American are enrolling a total of 360 patients to examine the effects of two different doses of IVIG compared to placebo over an 18-month period. “It’s been seven years since a new medication was approved for treating Alzheimer’s disease,” Dr Relkin pointed out, “and it will be at least another two years before the phase III IVIG study is completed. But if the results of the phase III study are at all similar to those of phase I and II, it will well be worth the wait.”
Gene Vital to Brain’s Stem Cells Implicated in Deadly Brain Cancer

Contributing faculty for this article: Antonio Iavarone, MD, and Anna Lasorella, MD

A study co-led by Antonio Iavarone, MD, Associate Professor of Neurology and Pathology and Cell Biology, and Anna Lasorella, MD, Assistant Professor of Pediatrics and Pathology and Cell Biology, both of Columbia’s Institute for Cancer Genetics at the Herbert Irving Comprehensive Cancer Center, has identified a protein that activates brain stem cells to make new neurons during brain development, but that may be hijacked later in life to cause brain cancer in humans. The protein called Huwe1 normally functions to eliminate other unnecessary proteins and was found to act as a potential tumor suppressor in brain cancer. The findings were published in the August 18, 2009 issue of Developmental Cell and the paper was selected as the feature cover story.

“By identifying the normal function of Huwe1, we were able to learn that deregulation of Huwe1 function is involved in tumor development,” says Dr. Iavarone. Adds Dr. Lasorella, “This demonstrates that a gene’s basic function must be understood before we can learn how it also plays a role in the development of cancer.”

The research demonstrated that Huwe1 is responsible for “crowd control” for the mechanism that regulates the stem cell mass in the developing brain – effectively weeding out unnecessary stem cell-specific proteins ... and promoting neurogenesis.

To understand how brain tumors develop, Drs. Iavarone’s and Lasorella’s teams decided that they needed to understand the development of normal neural stem cells. During normal brain development, neural stem cells grow and divide rapidly before developing into neurons. To successfully change into neurons, proteins that keep the cells in an immature, stem cell state must be eliminated. By conditionally deleting the Huwe1 gene in the mouse brain, the researchers demonstrated that this enzyme is essential for the transition from self-renewing and proliferating neural stem/progenitor cells to differentiated neurons. Drs. Iavarone’s and Lasorella’s research demonstrated that Huwe1 is responsible for “crowd control,” for the mechanism that regulates the stem cell mass in the developing brain – effectively weeding out unnecessary stem cell-specific proteins and protooncogene N-Myc and promoting neurogenesis. Without Huwe1, Dr. Lasorella discovered that in mice, the N-Myc protein remains elevated and too few mature neurons form in the brain, resulting in the brain failing to properly develop.

Because stem cells and cancer cells share the capacity for rapid proliferation, but cancer cells have lost crowd control, Dr. Iavarone then looked for Huwe1 alterations in human brain tumors. Compared to normal brain tissue, he found that Huwe1 activity in tumors was significantly lower than in normal brain tissue.

According to the researchers, human high-grade gliomas carry focal hemizygous deletions of the X-linked Huwe1 gene in association with amplification of the N-Myc locus. Their results indicate that Huwe1 balances proliferation and neurogenesis in the developing brain and that this pathway is subverted in malignant brain tumors.

“The loss of Huwe1 may be an important factor in the development of brain cancer, suggesting that Huwe1 protein function may be used for new therapeutic targets to fight deadly brain cancer,” says Dr. Lasorella.

“Our next step will be to analyze the structural changes in Huwe1 and research ways to restore this gene in brain tumor patients,” says Dr. Iavarone. “In mice, giving Huwe1 back blocks the ability of normal stem cells to proliferate and develop tumors. We are hopeful that if we can restore Huwe1 activity in brain tumor cells resulting from Huwe1 deletion, then we can stop the tumor growth.”
In collaboration with investigators at other institutions, Dr. Souweidane and his colleagues sampled pontine glioma tissue from patients to identify receptors for a monoclonal antibody called 8H9, which is very adept at distinguishing between tumor cells and normal brain cells. The researchers attached the antibody to radioactive iodine ($^{124}$I) and validated its safety and tissue perfusion in animal studies.

Using convection-enhanced delivery (CED), the therapy is administered via a catheter to the tumor. The catheter is connected to a low-flow pump that administers just a few drops of the chemotherapy agent each hour. This approach pushes the drug through the space between the tumor cells, thereby avoiding toxicity, bypassing the blood-brain barrier, and delivering high concentrations of the drug directly to the tumor.

Diffuse pontine gliomas are ideally suited for this delivery system because they are small and localized. "The clinical features of this tumor make it very appealing for this form of local delivery," explained Dr. Souweidane. The researchers are now planning a phase I study in children with diffuse pontine glioma, in collaboration with Memorial Sloan-Kettering Cancer Center. The research, which is funded by The Cure Starts Now Foundation, seeks to establish the safety parameters of $^{124}$I-8H9 using CED.

Another key feature of the $^{124}$I-labeled 8H9 therapy is its ability to be tracked using positron emission tomography. Until now, surrogate tracers such as MRI contrast agents were the only way to track where a molecule travelled once it was infused into the body. But this methodology is unable to track where the molecule resides hours, days, or weeks following infusion. Dr. Souweidane and his colleagues plan to use PET imaging to track the presence of $^{124}$I-labeled 8H9 therapy once infused into a patient.

"For the first time, we’ll have proof-of-principle that we can image with accuracy where these molecules are going," he said. "It’s senseless to think we can provide patients with adequate therapy if we can’t get the agent into the tumor bed."

Convection-enhanced delivery... pushes the drug through the space between the tumor cells, thereby avoiding toxicity, bypassing the blood-brain barrier, and delivering high concentrations of the drug directly to the tumor.

With diffuse pontine glioma remaining such a formidable clinical challenge, Dr. Souweidane noted, "This approach is the most exciting thing in pediatric neuro-oncology right now. I’m convinced we can learn how to cure this cancer if we can find the right agent and the right delivery scheme."

For more information about this research, visit The Cure Starts Now Foundation Web site at www.thecurestartsnow.org/research/grants/.

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continued from Pontine Gliomas, page 1

abnormal information flow and an inability to accurately interpret incoming sensory input."

Drs. Gogos and Karayiorgou plan to continue their exploration of the physiologic consequences of the 22q11.2 microdeletion. "We want to find out which molecular and synaptic deficits underlie the impaired functional connectivity between the hippocampus and prefrontal cortex, and whether similar alterations in communication are present among other brain areas and in other disease-associated mutations," noted Dr. Gogos.

"Whether this research will inform the development of new diagnostic tools and treatments for schizophrenia across the board (i.e. beyond the genetic subtype associated with the 22q11.2 microdeletion) is still not clear," said Dr. Karayiorgou. "It’s possible that imaging approaches such as fMRI could be used to examine the pattern of connectivity among brain regions and facilitate diagnosis of specific subtypes of schizophrenia in patients. It might also be possible to use our understanding of the causes of the impaired functional connectivity studies in animal models and then humans to identify drugs that can restore impaired connectivity to physiological levels."

continued from Brain Areas Impaired in Schizophrenia, page 2

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mean resultant length
Hippocampal theta
Prefrontal theta

**Selectivity of hippocampal–prefrontal synchrony deficits in Df(16)A+/- mice.** a, Comparison of phase-locking to theta oscillations in prefrontal cortex and hippocampus across the two genotypes. Phase-locking to prefrontal theta oscillations is intact.
Important news from the Neuroscience Centers and the Departments of Psychiatry of NewYork-Presbyterian Hospital. Current research projects, clinical trials, and advances in the diagnosis and treatment of patients with neurological and psychiatric diseases.

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