MAYO CLINIC

NeurosciencesUpdate

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INSIDE THIS ISSUE

The Mayo Clinic SPORE in Brain Cancer: Attacking Glioblastoma on More Than One Front

The Specialized Program of Research Excellence (SPORE) grant, awarded by the National Cancer Institute (NCI), focuses on integrating basic and applied science into clinical application. With high patient volumes, interdisciplinary collaborations, and the necessary infrastructure and institutional support, Mayo Clinic is uniquely positioned to translate discoveries into treatment. In 2004, Mayo received one of four SPORE awards in brain cancer research, and in 2011 the award was competitively renewed.

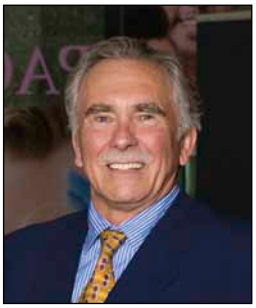
The brain cancer SPORE is a part of the Mayo Clinic Cancer Center, one of the largest NCI-funded cancer centers in the country and the only one to span three geographic locations. The SPORE grant supports major programmatic research by both seasoned and new investigators. Its activities are coordinated with Mayo's National Institutes of Health–funded Center for Translational Science Activities and the North Central Cancer Treatment Group (NCCTG). The NCCTG is a cooperative clinical research group for the development and execution of high-priority NCI-funded trials in a community setting. It is now part of the Alliance for Clinical Trials in Oncology, a group that integrates the scientific and operational activities of the Cancer and Leukemia Group B and the American College of Surgeons Oncology Group.

The focus of Mayo's brain cancer SPORE is primary brain tumors, particularly glioblastoma multiforme (GBM). Mayo's clinical researchers and basic scientists in molecular and stem cell biology, neuroimmunology, imaging science, pharmacology, epidemiology, neuropathology, and radiology collaborate across Mayo's three sites in Arizona, Florida, and Minnesota and with investigators at other institutions. Their investigations focus on:

- Identifying mechanisms of glioma initiation and progression
- Identifying diagnostic, prognostic, and predictive biomarkers for primary brain tumors
- Identifying targets for intervention and germline regions associated with brain tumor susceptibility
- Developing novel therapies and transitioning them into clinical trials

Previous Accomplishments From Mayo's Brain Cancer SPORE Grant

- Discovery of a critical difference between brain tumor stem cells and neural stem cells that render tumor cells less sensitive to the effects of ionizing radiation
- Demonstration that when normal monocytes are exposed to glioma cells, they assume immunosuppressive, myeloid-derived suppressor cell properties and that this type of cell alteration is increased in glioblastoma multiforme (GBM) tumors
- Characterization and validation of a putative tumor suppressor gene in primary central nervous system lymphoma
- Demonstration of specific SNP (single nucleotide polymorphism) sites that are associated with high-grade glioma susceptibility
- Identification of subtypes of GBM tumors that are and are not sensitive to a class of drugs that inhibit production of poly(ADP-ribose) polymerase (PARP) and which may be able to enhance chemotherapy benefit from temozolomide



Brian Patrick O'Neill, MD

Robert B. Jenkins, MD, PhD

Neurologist Brian Patrick O'Neill, MD, and clinical pathologist Robert B. Jenkins, MD, PhD, serve as the principal investigator and principal coinvestigator, respectively. Dr O'Neill leads the SPORE's Administrative Core, coordinating its operational structure and research programs among the other four SPORE cores. The Biostatistics Core, led by Karla V. Ballman, PhD, provides statistical collaboration for epidemiologic studies, basic science and clinical trials, and database management.

The Clinical Research Core is led by Jan C. Buckner, MD, who coordinates the core's patient recruitment, specimen acquisition, and protocol consents. Under the current SPORE, every patient with brain cancer across Mayo's three main campuses will be electronically entered into Mayo's Neuro-Oncology Registry, an invaluable database for present and future projects within Mayo's SPORE and other brain cancer SPORE programs in the United States.

The Pathology and Tissue Procurement Core, led by Caterina Giannini, MD, PhD, acquires tissue specimens from nearly every patient with newly diagnosed or relapsed glioma seen at Mayo Clinic and from all patients entered into SPORE protocols. This core is a centralized resource dedicated to processing glioma tissue specimens for culture, xenograft modeling, or frozen storage to provide investigators with the DNA and RNA needed for molecular research.

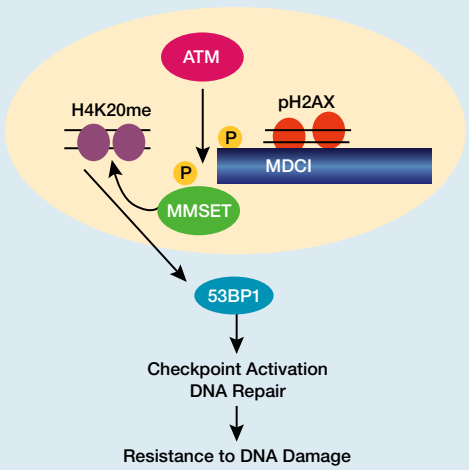


Figure. *The role of* MMSET *in GBM predisposition.* MMSET *is recruited to the sites of DNA damage and methylates histone H4K20, which in turn recruits the 53BP1 and facilitates DNA repair. Overexpression of* MMSET *in glioblastoma might render cancer cells more resistant to irradiation and chemotherapy because of enhanced DNA repair capability.*

The Animal Core, led by Jann N. Sarkaria, MD, provides mouse models that recapitulate the morphologic, molecular, and histopathologic features of primary human tumors in living tissue (see pages 5-6 in this issue). The current Mayo GBM xenograft model has been called the best model for developmental therapeutics currently available to brain cancer investigators. Mayo has shared cell lines and animals with investigators at institutions around the world.

The tight links between these four research cores enable rapid translation of basic science to human application. As an example, discoveries at Mayo Clinic on the application of the vaccine strain of the measles virus brought this novel therapy from the laboratory to a phase 1 clinical trial in just three years (see pages 3-4 and 6 in this issue).

Current SPORE Projects

SPORE project 1 is investigating mechanisms of resistance to temozolomide (TMZ), the standard chemotherapy for GBM, to advance understanding of why it fails to provide sustained benefit. Dr Sarkaria and Nadia N. Laack, MD, a radiation oncologist, will use the xenograft model to explore the influence of DNA repair on poly(ADP-ribose) polymerase (PARP) inhibitor efficacy and to identify discrete molecular signatures of tumors that signal PARP sensitivity or resistance.

SPORE project 2 is focused on the measles virus treatment alluded to earlier, optimizing it as a therapy for GBM, with the goal of augmenting its efficacy and safety for a subsequent phase 1 clinical trial. This study is led by medical oncologist Evanthia Galanis, MD, and Ian F. Parney, MD, PhD, a neurosurgeon (see pages 3-4 and 6 in this issue).

SPORE project 3 interrogates DNA pathways that sustain genetic mutations responsible for GBM predisposition. This year, Mayo Clinic scientists, led by pharmacologist Zhenkun Lou, PhD, discovered a critical role in the process played by a little-studied gene called *MMSET*. They found that *MMSET* helps to maintain DNA stability by enlisting proteins, such as the p53 binding protein 1, to repair damage that occurs. If *MMSET* is damaged, its restorative capacity fails and mutations leading to disease occur. This SPORE project will investigate whether levels of *MMSET* expression can be considered a biomarker for treatment resistance and ways of inhibiting the gene to make such therapies more effective.

In addition, Dr Jenkins and genetic epidemiologist PingYang, MD, PhD, are combining molecular genetics with epidemiologic studies to investigate the clinical relevance of chromosomal alterations in glioma formation. With collaborators at the University of California, San Francisco, they have found specific germline alterations that may be involved in gliomas. Their continued work will advance basic understanding of brain tumorigenesis, improve family counseling, and help inform future studies that could identify new therapeutic targets.

Taken together, these projects are aimed at improving the survival rate and the lives of patients with brain cancer through identification of genetic risk factors, improved understanding of the tumor pathogenesis and resistance to treatment, the generation of novel therapies, and the enhancement of traditional ones.

Update on the Measles Virus, a Novel Therapy for Glioblastoma

In the 1970s, it was reported that natural infection with the measles virus (MV) led to spontaneous regression of hematologic cancers in African children. This and other, similar reports led to investigations of the oncolytic, or cancer-fighting, properties of MV and other viruses and their potential in cancer treatment. Although approved in Asian countries, virotherapy drugs have not yet been approved in the United States.

Mayo Clinic is the first institution to use MV as a cancer therapy, including treatment of glioblastoma multiforme (GBM), the most lethal brain tumor. Under Mayo's previous Specialized Program of Research Excellence (SPORE) grant, medical oncologist Evanthia Galanis, MD, and colleagues brought MV from animal models to human testing in just three years. The phase 1 clinical trial used a modified MV strain in patients and found it safe and well tolerated. Under a new SPORE grant, Dr Galanis and neurosurgeon Ian F. Parney, MD, PhD, the project's codirectors, plan to develop a new phase 1 trial, focusing on reengineered versions of MV to optimize its therapeutic impact and the ability to track the propagation of the virus.

MV Advantages

Although wild-type MV can pose a serious health risk, millions of doses of vaccine strains of the virus, derived from the Edmonston vaccine lineage, have been administered worldwide with proven safety. Oncolytic viruses show selective preference for tumors because they can readily enter the tumor by exploiting either the molecular pathways associated with the malignant transformation or the specific receptors that are overexpressed by tumor cells. Building on identified mechanisms of MV entry and propagation in particular, Dr Galanis and her coinvestigators discovered that a vaccine strain of MV causes glioma cells to fuse, forming multinuclear cell aggregates that trigger apoptosis (Figure 1). Each cell infected by the virus causes another 50 to 100 cells to fuse and die. This cell death recruitment, called the *bystander effect*, suggests that MV could be a particularly potent therapeutic agent.

The four subtypes of GBM tumors are based on variations in gene signatures, which result in protein differences across the subtypes. Some of these expressed proteins migrate to the surface of cells. Reengineering the molecular characteristics of MV, a process called *retargeting*, enables the virus to more efficiently recognize tumor subtype receptor proteins and to enter cells through them (Figure 2). In addition, the Mayo research team has been able to modify the virus through genetic engineering so that it carries therapeutic transgenes and thus is even more effective.

Evanthia Galanis, MD

Ian F. Parney, MD, PhD

Addressing the Challenges of MV Therapy

Animal Model Testing

Rodents are not susceptible to MV because they do not express MV receptors. For that reason, mice have been genetically engineered to produce MV receptors that mimic those in humans. Collaborating with Jann N. Sarkaria, MD, a radiation oncologist and the head of the Animal Core facility of Mayo's brain cancer SPORE program, Dr Galanis's team tested the virus in 10 different xenograft models (see pages 5-6 in this issue). There was significant antitumor efficacy in each of these tumor models and no toxicity. Before testing MV therapy in human clinical trials, however, additional toxicology studies were conducted, and the virus was found safe in measles-susceptible rhesus macaques, a primate species considered to be the gold standard of animal models for measles neurotoxicity. Of note,

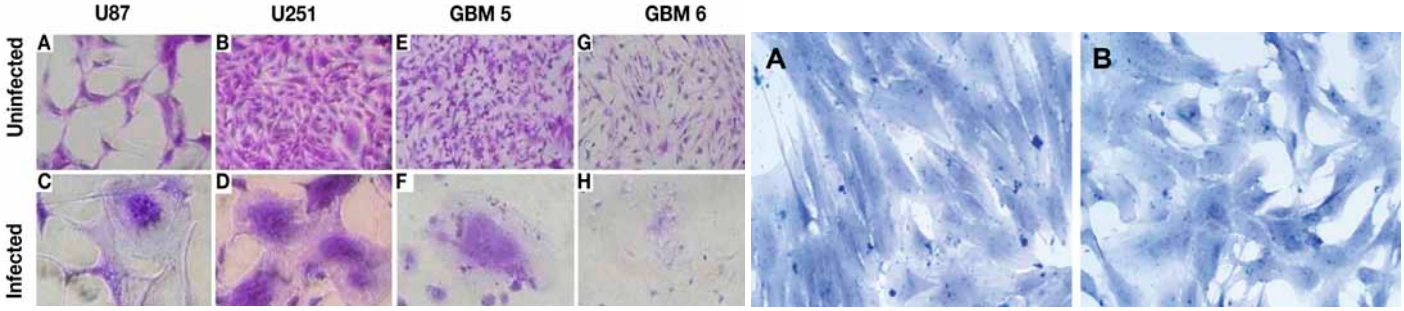


Figure 1. *Glioma cells (U87, U251, GBM 5, and GBM 6) infected with measles virus fuse to form multinuclear cell aggregates (syncytia), followed by cell death and eradication of monolayer cultures (left panel). In contrast, the virus causes no harm against normal cells such as astrocytes (A and B, right panel).*

brain tissue adjacent to tumors also expresses MV receptors, but at such low levels that the virus cannot propagate enough to harm normal brain cells.

Tracking Virus Propagation

Monitoring the propagation of MV is critical to determining its efficacy as a cancer treatment. A researcher cannot conduct multiple biopsies in treated patients for obvious safety considerations. Under the SPORE grant, Dr Galanis and colleagues are testing two approaches for tracking viral replication—one through peripheral blood sampling and the other through radiographic imaging. The first approach involves engineering strains of MV to carry the soluble marker human carcinoembryonic antigen (CEA), which led to the construction of the viral strain MV-CEA. This antigen is not expressed by glioma cells but can be measured in the blood. Such a blood test would demonstrate propagation but would not be location specific.

The second approach is to introduce into the virus a gene called *sodium iodine symporter* (*NIS*), which traps radioactive iodine and thus could be imaged by CT SPECT. The additional advantage of this approach, notes Dr Galanis, is that "targeted imaging of MV activity would allow us to both determine viral localization and target radiation, in the form of therapeutic iodine radioisotopes, to the tumor. What we have found in animal models is that viral replication actually increases in irradiated cells. The combination of virus and radiation creates a strong synergistic effect."

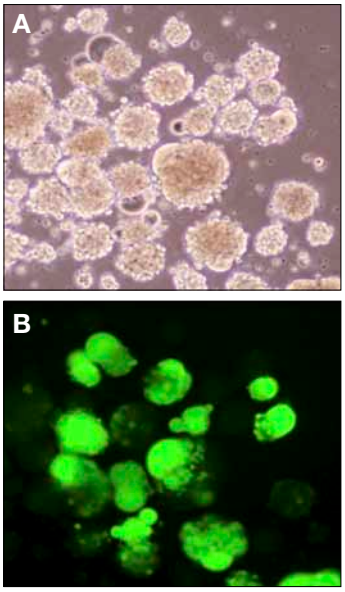


Figure 2. *Measles virus strains also effectively infect and kill glioma stem cells (Panel A). A virus strain coding for a green fluorescent protein (MV-GFP) was used in research described earlier, to help visualize the infected cells (Panel B).*

Human Antimeasles Immunity

Another challenge to using MV therapeutically is the fact that most patients have been immunized against MV. This immunization is less of a challenge when MV is injected directly into the tumor during a neurosurgical procedure, as it is in GBM, than its systemic administration for other forms of cancer. Targeted tumor injection of MV also overcomes the effects of the blood-brain barrier.

Independent of the route of viral administration, blocking the innate immune response within the tumor itself can promote viral spread in the tumor. This modification of the innate immune response can be accomplished by using the immunosuppressant cyclophosphamide. Its effectiveness as an additive to MV for GBM has been demonstrated in mice bearing human tumor xenografts.

Figure 3. *Virus for human studies is prepared at the Mayo Clinic Viral Vector Production Laboratory, directed by Mark J. Federspiel, PhD.*

Furthermore, administration of the MV-NIS strain of the virus in combination with cyclophosphamide has been found to reduce the primary immune response and prolong viral gene expression in squirrel monkeys.

Another strategy that Dr Galanis and colleagues are investigating is the use of mesenchymal stem cells, which may not only aid in circumventing antimeasles immunity, but may also facilitate the systemic delivery of the viral treatment. This strategy can be important in cancers such as ovarian cancer, for which Dr Galanis is developing a human safety trial.

Phase 1 GBM Clinical Trial Extension

Drs Galanis and Parney and their colleagues look forward to Mayo's SPORE-funded development of the follow-up phase 1 clinical trial using new strains of engineered MV, such as MV-NIS. Dr Galanis notes that the rapid translation from laboratory to human testing in the previous trial was greatly expedited by the SPORE grant, which facilitates teamwork. The grant helped in the acquisition of human tumor tissue samples, for example, and supported in vivo testing in animal models, as opposed to testing established cell lines in vitro. Thus, preclinical efficacy studies were conducted in tumor models that more closely mimic human tumor morphologic and histopathologic features.

Mayo's vector production laboratory (Figure 3) has developed improved production methods so that increased doses of the virus can be delivered in small volumes—an important consideration when injecting the brain. The efficient collaboration between researchers in Mayo's Molecular Medicine laboratories and its Toxicology and Biodistribution laboratory also helped validate the safety of MV therapy in

Continued on page 6

Beyond the Petri Dish: The Mayo Clinic Glioblastoma Xenograft Model

For many years, investigations of tumor formation, growth, and response to treatment have relied on tumor cell lines established in the late 1960s and cultured in vitro. It is now known that prolonged tissue culturing can alter cellular genetic and morphologic characteristics. As a result, such cell cultures do not accurately reflect key features of human tumors. For example, established glioblastoma multiforme (GBM) cell lines cultured in a petri dish lack a growth factor receptor found in more than 40% of human primary GBM tumors. Prolonged cell culturing can also lead to hypermethylation of specific genes, a DNA modification present in twice the number of cultured versus human GBM tumors.

Mayo's Xenograft Model

Xenografting, a means of introducing foreign tissue into an organism, can be used to generate in vivo cell lines by implanting human tumor specimens directly into animal models. One of the first laboratories to do so was at Mayo Clinic under the direction of Jann N. Sarkaria, MD, a radiation oncologist and head of the Animal Core of the Specialized Program of Research Excellence (SPORE) program, where investigators have developed more than 50 glioblastoma xenograft models since 2002. Tissue specimens from human tumors are implanted into the mouse flank and, if growth occurs, can subsequently be implanted into mouse brains. Serial transplantation into further generations of mice continues the maintenance of in vivo xenograft cell lines.

The singular advantage of xenografting for basic and translational research is that xenografted cells generate tumors that maintain the important morphologic, molecular, and histopathologic features of primary human tumors, including, for example, the invasive features of GBM. Different subtypes of GBM tumors can be observed to see how quickly they grow in mice, how invasive they are, and what their individual pathologic features are. When phenotyping is concluded, the molecular mechanisms can be examined and manipulated.

Currently, Mayo has 52 cell lines that represent four of the five subtypes of GBMs. Of those cell lines, 35 have been implanted in mouse brains and later dissected out for gene-expression profiling, measurement of messenger RNA globally, and detection of chromosomal deletions or amplifications. The laboratory is about to begin whole-exome sequencing. It is exacting, painstaking, and labor-intensive work.

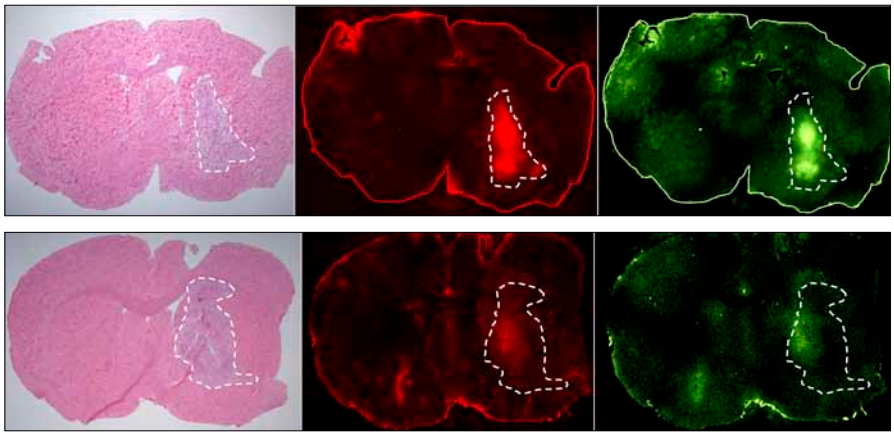


Figure. *Testing the integrity of the blood-brain barrier (BBB) in the Mayo Clinic xenograft model. Micrograph shows a pathologic mouse brain section with tumor (outlined in white) in a mouse pretreated with placebo (top panel) or bevacizumab (bottom panel). Penetration of the BBB with injection of Texas Red dextran (middle column, both panels) and fluorescein (right column, both panels) showed significantly less BBB penetration in a mouse pretreated with bevacizumab.*

Because of its scope relative to the number of cell lines and the degree of phenotyping and genetic characterization, Mayo's xenograft model is considered a premier, state-of-the-art model. Research grant applicants to the National Institutes of Health are often told they need a model that is similarly characterized, and Mayo has shared its cell lines with researchers around the world—55 to date. The SPORE grant (see pages 1-2 in this issue) provides financial support for this type of distribution.

GBM Xenograft Modeling in Action

As Dr Sarkaria points out, the majority of clinical trials are launched with limited human or animal data. It is gradually becoming the standard to have animal data, but most preclinical drug trials use tumors that are cultured in vitro. The xenograft model allows evaluation of therapeutic drugs and combined drug and irradiation regimens in living tissue, using tumor lines that more closely replicate human tumor therapeutic sensitivity. Another advantage is that identical tumor subtypes can be implanted in mouse brains and the mice randomly assigned to a treatment or a no-treatment group. Dr Sarkaria notes that in this way,"you have a very robust understanding of how the drug works in a particular tumor with a particular gene signature and molecular characteristics. Human patients, on the other hand, may develop medical conditions, such as a blood clot, that can cloud the outcome."Some examples of recent studies using the xenograft model are discussed on page 6.

Jann N. Sarkaria, MD

Explanation of Variable Response to Epidermal Growth Factor Receptor Inhibitor Therapies

Increased signaling of epidermal growth factor receptor (EGFR) inhibitors is thought to contribute to the malignant characteristics of certain tumors, including GBM. Among these tumors, however, only subgroups within a given type are responsive to EGFR inhibitor therapy (eg, erlotinib, gefitinib). Several laboratory approaches have been used to determine the molecular factors that explain the varying response, but they have had mixed results.

The xenograft approach successfully replicated the clinical finding that mutations in certain molecular markers were a factor in EGFR inhibitor sensitivity and resistance. The model also demonstrated that an additional mutation contributed to sensitivity in two specific GBM subtypes (Sarkaria et al. *Mol Cancer Ther*. 2007;6[3]:1167-74).

New Mechanisms of Acquired Resistance to Temozolomide

Another validation of correlations between the animal model and human tumor mechanisms has come from an investigation into why gliomas develop chemoresistance to the commonly used drug temozolomide (TMZ). TMZ is known to induce cellular apoptosis. Although GBM is initially responsive, more than 90% of recurrent GBM tumors show no response to a second round of TMZ. Using TMZ-resistant GBM xenograft cell lines from Mayo, a research team at the University of Alabama found that both primary and recurrent human GBM biopsies and primary and TMZ-resistant GBM xenograft lines exhibit a similar, although unexpected, remodeling adaptation to TMZ. This finding not only helps explain the nature of TMZ resistance, but also will inform future drug development (Oliva et al. *J Biol Chem*. 2010;285[51];39759-67).

Do PARP Inhibitors Work? Evaluating Their In Vivo Effects on Tumor Sensitivity

PARP inhibitors are a class of drugs that inhibit production of an enzyme called *poly(ADP-ribose) polymerase*, or PARP. Several preclinical studies, using established cell lines, suggested that PARP inhibitors could enhance the efficacy of TMZ in both TMZ-sensitive and TMZ-resistant tumors and would also improve the effects of radiation therapy. In anticipation of a large clinical trial to evaluate a PARP inhibitor, Dr Sarkaria and his team tested it in a panel of glioblastoma xenografts. The results, unlike those predicted from established cell lines, showed that although the PARP inhibitor was effective in newly formed tumors, recurrent tumors remained resistant. The investigators also discovered that specific expression of a DNA repair protein, MGMT, makes tumors resistant to the sensitizing effects of PARP inhibitors.

A clinically significant finding was the fact that some PARP inhibitors were more effective in mouse flank tumors than tumors in the brain, a dissociation that could be demonstrated only by contrasting in vivo tumor sites using a xenograft model. The differences in sensitivity of brain versus flank tumors suggest a failure of these specific PARP inhibitors to penetrate the blood-brain barrier (Figure). This finding is in contrast to the commonly accepted paradigm that because portions of GBM tumors have an open blood-brain barrier, drugs will penetrate all of the tumor. Mayo's results suggest that failure of penetration is an important issue in designing novel treatments such as PARP inhibition.

Mimicking human GBM tumor growth, the xenograft model has much to offer in understanding the fundamental biology of GBM tumors, their resistance to standard and experimental treatments, and the development of novel therapies.

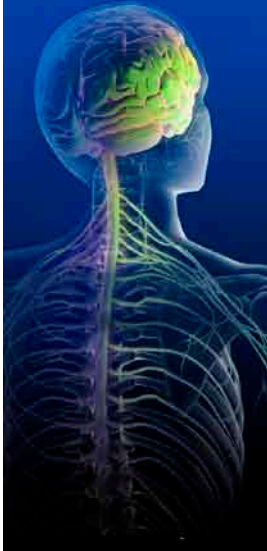
Update on the Measles Virus, a Novel Therapy for Glioblastoma

Continued from page 4

primates, a key consideration when introducing a novel therapeutic approach such as MV. The tight links between laboratories and the level of integration with patient care at Mayo hold promise for an equally efficient transition into the follow-up phase 1 clinical trial.

Of note, the high expression of MV receptors in human GBM tumors is a mechanism that tumor cells use to escape immune surveillance. It now appears that reengineered MV could be the Trojan horse that takes these receptors up on their invitation and delivers a much-needed and powerful weapon in the fight against GBM.

Research Highlights in Neurology and Neurologic Surgery



Neurosciences Research

Mayo Clinic Researchers Find Evidence of Inflammatory Cortical Demyelination in Early-Stage Multiple Sclerosis

In a major shift in the understanding of the origin and mechanisms of central nervous system inflammatory demyelinating disease, Mayo Clinic researchers, in collaboration with researchers at Cleveland Clinic, Medical University of Vienna, and Georg August University (Göttingen, Germany), found a surprising frequency of inflammatory cortical demyelinating lesions in patients with early-stage multiple sclerosis (MS). MS has traditionally been thought of as initiating in white matter and extending to cortical gray matter only in later stages of the disease. However, this study suggests that the disease may originate in the subarachnoid space and in the cortex. Cortical tissue was obtained as part of white matter tissue sampling in 536 patients, many of whom were thought to have possible tumor. Sufficient cortical tissue was available in 138 patients and assessed for cortical demyelination. Immunohistochemistry enabled the researchers to characterize demyelinating activity and inflammation and the associations between cortical demyelination and meningeal inflammation. In the subgroup of patients with confirmed early-stage MS, cortical demyelination was associated with meningeal inflammation. The findings have important implications for understanding the pathogenic mechanisms of MS and its treatment. The study was selected by the *Neurology Today* Editorial Advisory Board as one of the top 10 best manuscripts of 2011 and was published in the December 8, 2011, issue of *New England Journal of Medicine* (365[23]:2188-97). Authors: C. Lucchinetti, B. Popescu, R. Bunyan, N. Moll, S. Roemer, H. Lassmann, W. Brück, J. Parisi, B. Scheithauer, C. Giannini, S. Weigand, J. Mandrekar, and R. Ransohoff.

Estrogen and Risk of Stroke in Women With Premature or Early Menopause

Mayo Clinic researchers found that estrogen may prevent strokes in women with premature or early menopause. Their findings challenge the conventional wisdom that estrogen is invariably a risk factor for stroke, particularly ischemic stroke (IS). Researchers reviewed seven observational studies published between 2006 and 2010, including one from Mayo Clinic. Three cohort studies showed increased risk of stroke in women who underwent bilateral oophorectomy before age 50 years compared with those who did not. However, in one of the studies, hormone therapy was associated with reduced risk. Four other studies showed that early onset of menopause was associated with all types of stroke, including IS, regardless of whether menopause was induced or natural. The authors concluded that age of menopause onset was a critical factor for IS risk and that it is possible that estrogen protects against IS before age 50 years but may become a risk factor after age 50 or 60 years. These findings have implications for women who have premature or early menopause from natural causes or ovary removal. The study was published in *Menopause* in preprint form online on October 6, 2011. Authors: W. Rocca, B. Grossardt, V. Miller, L. Shuster, and R. Brown Jr.

Mayo Clinic Research Improves Diagnosis and Potential Treatment of Neuromyelitis Optica

Mayo Clinic researchers have identified critical steps leading to myelin destruction in neuromyelitis optica (NMO), a debilitating, relapsing autoimmune central nervous system (CNS) disorder, which is commonly misdiagnosed as multiple sclerosis. The findings advance the understanding of the underlying molecular mechanisms of interactions between immunoglobulin G, the antibody specific for NMO, and aquaporin-4, the water channel that is the target of pathogenic antibodies in NMO. The findings provide pathophysiological insights into the evolution of CNS lesions. They also reinforce the concept of NMO as a spectrum disorder by helping to explain differences in the nature and anatomical distribution of NMO lesions and variation in the imaging and clinical findings among patients with NMO. These findings are important to the development of optimal treatment of NMO. The paper was published in preprint form online on November 29, 2011, in *Proceedings of the National Academy of Sciences.* Authors: S. Hinson, M. Romero, B. Popescu, C. Lucchinetti, J. Fryer, H. Wolburg, P. Fallier-Becker, S. Noell, and V. Lennon.

To read more about Mayo Clinic neurosciences research and patient care, visit www.mayoclinic.org/medicalprofs.

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Neurosciences Update

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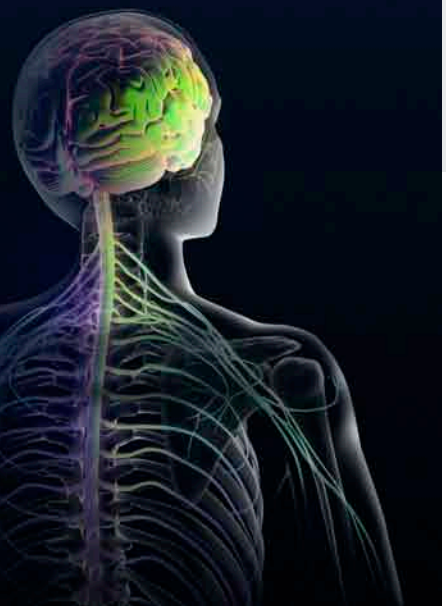


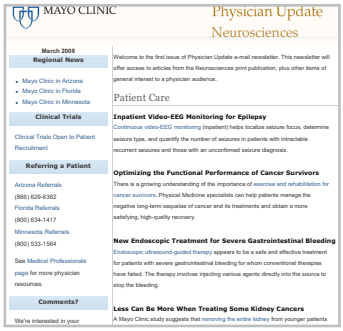
Education Opportunities

Please join the Mayo Clinic Neurology and Neurosurgery Continuing Medical Education (CME) Facebook group. To join, search Facebook for Mayo Clinic Neurology and Neurosurgery Continuing Medical Education (CME). This group provides CME course information and updates, along with short video interviews with speakers and course directors.

Clinical Trials Update

1. Study of Dichlorphenamide in Periodic Paralysis. Double-blind, placebo-controlled study of dichlorphenamide (Daranide) for treatment of hypo- or hyperkalemic periodic paralysis.
2. Study of Thymectomy in Acetylcholine Receptor–Positive Myasthenia Gravis. Patients with generalized myasthenia gravis with or without treatment with Mestinon and prednisone are randomly assigned to receive thymectomy or not and observed for three years.

For more information about other Mayo Clinic research studies, please visit the Research section on www.mayoclinic.org/medicalprofs.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March 2005

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We're interested in your

Welcome to the first issue of Physician Update e-mail newsletter. This newsletter will offer access to articles from the Neurosciences print publication, plus other items of general interest to a physician audience.

Patient Care

Inpatient Video-EEG Monitoring for Epilepsy

Continuous video-EEG monitoring (inpatient) helps localize seizure focus, determine seizure type, and quantify the number of seizures in patients with intractable recurrent seizures and those with an unconfirmed seizure diagnosis.

Optimizing the Functional Performance of Cancer Survivors

There is a growing understanding of the importance of exercise and rehabilitation for cancer survivors. Physical Medicine specialists can help patients manage the negative long-term sequelae of cancer and its treatments and obtain a more satisfying, high-quality recovery.

New Endoscopic Treatment for Severe Gastrointestinal Bleeding

Endoscopic ultrasound-guided therapy appears to be a safe and effective treatment for patients with severe gastrointestinal bleeding for whom conventional therapies have failed. The therapy involves injecting various agents directly into the source to stop the bleeding.

Less Can Be More When Treating Some Kidney Cancers

A Mayo Clinic study suggests that removing the entire kidney from younger patients

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