NEUROSURGERY'S Science Times

CHRONICLING THE TIMES IN THE INFORMATION AGE

The Science and Controversy of Spinal Fusion

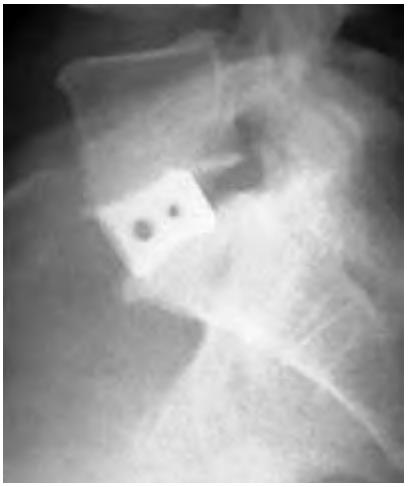
Science Times Editorial

The rapidly increasing use of spinal fusion operations in the United States has begun to generate concerns about the cost and cost-effectiveness of these procedures (1). Deyo, Nachemson, and Mirza present a concise review of this complex topic in the *Sounding Board* portion of the February 2004 issue of The **New Engl J Med** (350: 722-726, 2004). The article offers no new findings but because of the great importance of spine surgery for neurosurgical practice and clinical research this article deserves editorial comments in ***Neurosurgery's Science Times***.

The annual number of spinal fusion operations in the United States increased more than 75% between 1996 and 2001 and the great majority of these procedures were performed for degenerative spine disease. More than 300,000 procedures per year are now being done, with a mean hospital charge of $34,000, excluding professional fees. There is wide geographic disparity in the rate of spinal fusion surgery suggesting that there is little consensus on the appropriate indications for surgery.

Financial incentives to perform spinal fusion surgery exist for device manufacturers (the market for spinal implants and devices is $2 billion per year with an annual growth rate of 18-20%) and for neurosurgeons (reimbursement for spinal fusion surgery is better than is the case for many neurosurgical procedures). Some have suggested that the increase in spinal fusion surgery has been motivated primarily by remuneration (1). The authors do not ignore this possibility but point out that a number of other factors (an aging population, improved axial imaging technology, technological improvements in spinal fixation devices, and refinements in spinal surgical procedures) have contributed to the rapid increase in the number of spinal fusions.

The authors do an admirable job of reviewing the literature on the effectiveness of spinal fusion for degenerative conditions and the value and risks of surgical implants for spinal fusion. In brief, the data on the effectiveness of spinal fusion surgery with or without instrumentation, for degenerative disease of the spine is mixed. Some studies have demonstrated improved outcomes with spinal fusion compared to spinal surgery without fusion or to medical management. Similar studies reached the opposite conclusion and complication rates from spinal fusion surgery appear to be higher than complication rates for other spinal surgery, even though patients undergoing fusion are younger and less likely to have medical co-morbidities. Randomized trials, cohort studies and clinical series can be quoted to support both pro and con positions on the use of spinal fusion surgery and spinal instrumentation. Perhaps the best conclusion that can be reached from the presently available data is that reasonable people can legitimately disagree on the use of spinal fusion surgery and spinal instrumentation.



The authors favor a very cautious approach to spinal fusion and instrumentation. They recommend that the focus of research should shift from how to perform fusion procedures to how to select appropriate patients for fusion. I heartily agree, but there are several very basic problems that will continue to bedevil any attempts to reach a consensus on who will benefit from spinal fusion surgery. First, the data indicating a tight correlation between achieving a solid fusion and achieving pain relief and functional improvement are scant. Without such a correlation, studies reporting fusion rates are nearly meaningless as the purpose of spinal surgery is pain relief and functional improvement rather than a radiographic endpoint. Even if a correlation between fusion and patient outcome could be documented there is still no definitive method to determine that a solid fusion exists. In addition, it is arguable that psychosocial factors may be more important than anatomical factors in determining which patients with degenerative spine disease will improve with surgical (or non-surgical) therapy.

The authors also recommend that randomized trials be required before FDA approval is granted for spinal implants. I must point out that such a requirement will make it impossible to accomplish their other objective of determining who will benefit from surgery. A "definitive" randomized trial will give us an either/or answer as to the value of spinal fusion and instrumentation. If the trial is negative, patients who would actually benefit from fusion will be denied this option for financial and medico-legal reasons, as occurred following the EC-IC bypass trial (2, 5). If the trial is positive, spinal fusion will be applied promiscuously to patients who fall outside the constraints of the trial, by surgeons with higher morbidity and mortality than trial surgeons, as occurred following the NASCET and ACAS trials (3, 4, 6).

Faith in the power of randomized trials to determine the appropriateness of surgical intervention is touching, but the results of applying the conclusions of such trials has not been encouraging. Surgeon-specific, meticulous, prospective registries with clinically relevant outcomes documented by unbiased adjudicators are far more likely to give us the data we need to determine what combination of factors predict a favorable result in from spinal fusion surgery (4).

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OUTCOMES & POPULATION SCIENCE

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New Initiative for Orofacial Pain Research

Contributing to the goals of the NIH Pain Consortium, the National Institute of Dental and Craniofacial Research (NIDCR) and the National institute of Neurological disorders and Stroke (NINDS) have jointly announced an invitation for applications to stimulate and support innovative interdisciplinary research studies to elucidate the molecular mechanisms underlying orofacial pain, particularly the discovery of proteins and protein networks critical to processing nociceptive information (RFA-DE-05-004).

It is estimated that the economic burden of chronic pain on the population is on the order of $100 billion annually. A number of orofacial disorders treated by neurosurgeons such as trigeminal neuralgia are associated with chronic pain. An examination of the pain experience at all levels of basic and clinical research will help elucidate the pathophysiology of pain disorders. With this request for Applications (RFA), the NINDS and NIDCR hope to gain a better fundamental understating of the molecular mechanisms involved in orofacial pain disorders which, coupled with molecular imaging and biocomputational technologies, will provide a basis for gene-based diagnostic criteria and insights for developing novel prevention and therapeutic strategies that are case and patient specific. It is envisioned that interdisciplinary teams of investigators with expertise in biology, genomics, proteomics, imaging, as well as clinical and computational sciences will be established through this program. The treatment of pain syndromes falls well within the scope of neurosurgical practice and research. This RFA may provide an excellent funding opportunity for neurosurgeons as members of these interdisciplinary research teams. More information about this RFA can be found at http://grants.nih.gov/grants/guide/rfa-files/RFA-DE-05-004.html.

CHARLES LIU, M.D., PH.D.
CONTRACTS AND GRANTS

"Leaching RNA": A New Model of Disease Pathogenesis

Junghans et al. at the Harvard Institute of Human Genetics in Boston, MA recently demonstrated (**Science** 303; 383-7, 2004) that the monoallelic expansion by the trinucleotide repeat (CUGn) associated with myotonic dystrophy type 1 (DM1) results in the production of mutant RNA with the capacity to disrupt specific transcription factors that produce the disease phenotype. The CUGn expansion is located on the 3' untranslated region of the myotonic dystrophy protein kinase gene (DMPK) and appears to produce a mutant RNA which can directly bind various transcription factors that will then coalesce into bundles of inert ribonucleic protein (RNP) which are confined to the nucleus. The investigators used cultured myocytes from normal and DM1 subjects to show that that DMPK mutant RNA coprecipitates specificity protein 1 (Sp1) and retinoic acid receptor gamma (RARgamma). They then showed that the sequestration of these transcription factors led to an overall decrease in the ratio of transcription factors found in the chromatin versus that which was bundled in the RNP of the nucleus *(Fig. 1)*. Multiplex reverse transcriptase polymerase chain reaction (RT-PCR) was used to demonstrate a quantifiable decrease in RNA levels of genes that included CLCN1 which encodes the skeletal muscle chloride channel whose disruption has been implicated in DM1 myotonia. Finally, the investigators revealed that when DM1 myocytes were transduced with a high-expressing Sp1 plasmid, the depressed CLCN1 mRNA levels were increased (by 280%) to normal levels.

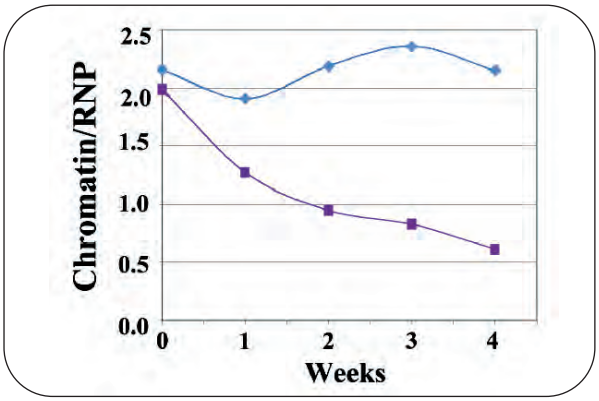

FIGURE 1. *Redistribution of RARγ over time. Cells were induced for DMPK expression and assayed at times specified for RARγ derived from Western blot data.*

This study supports a disease model whereby RNA leaching by the nucleotide repeats of a mutant gene results in the binding and sequestration of nuclear transcription factors that disrupt gene expression patterns. This hypothesis has considerable implications for numerous genetic disorders, including Huntington's Disease as well as potentially CNS neoplasia, in which transcriptional dysregulation appears to play an important functional role.

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BASIC SCIENCES RESEARCH

Ischemic Preconditioning Awakens Hibernation State

In an article published in the **Lancet** (362: 1028-1037, 2003), Stenzel-Poore and colleagues from Portland, Oregon discuss the effect of ischemic preconditioning on the genomic response to cerebral ischemia. They note a similarity to neuroprotective strategies in hibernation and hypoxia tolerant states. The researchers add considerable information to the question of brain tolerance to ischemia by looking at the gene expression and cellular mechanisms altered by preconditioning. Preconditioning is an interesting laboratory phenomenon, which observes a significant dimunition in the damage from a stroke in animals which had previously been preconditioned with a fifteen minute event of ischemia or TIA.

Researchers have recognized this phenomenon for sometime without well understanding the mechanism of such protection. In this latest report, gene expression and cellular mechanisms were compared between normal mice and mice which had been preconditioned by a prior brief period of ischemia. The preconditioned mice showed a 70 percent decrease in brain damage with the experimental stroke. The most striking changes were that the gene profiles of the preconditioned animals showed a hardwired response to slow metabolism, conserved energy usage and prevent blood clotting. The authors see a striking similarity between those changes which limit blood flow and oxygen and glucose uptake to those seen in hibernating animals. This suggests that there may be an evolutionary and genetic response to initial ischemic injury, which suggests a naturally occurring protective strategy and therefore, a likely route for future treatments that target certain protective genes in high risk patients. Additionally, by understanding the proteins expressed in natural states such as hibernation or cold tolerance, treatment modalities which slow metabolism in the face of an ischemic challenge may result in decreased morbidity and mortality of ischemia.

The implications of such studies are several fold. The first and most important is that genetic analysis may allow rapid understanding of mechanisms which have been long observed, but poorly understood. Second is that the response to threat and injury may often recapitulate a natural state such as hibernation with its protective effects and understanding of one may help the understanding of the other. Finally, by taking genetic analysis to the protein level, treatment strategies may be more rapidly available.

ROBERT J. DEMPSEY, M.D.
NATIONAL INSTITUTES OF HEALTH NEWS

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Surgical Trial in Intracerebral Hemorrhage (STICH)

The long awaited results of the internatioal Surigcal Trial for Intracerebral hemorrhage (STICH) are finally in. A preliminary report was presented by Professor A. D. Mendelow, STICH Principal Investigator, at the Joint Annual Meeting of the AANS/CNS Section on Cerebrovascular Surgery and the American Society of Interventional and Therapeutic Neuroradiology in San Diego, February 3, 2004, pending anticipated publication of the results in the *Lancet*.

At participating medical centers, surgeons randomized patients presenting with ICH to receive either early clot evacuation (within 72 hours post-insult) or initial conservative treatment. Patients were included in the study if clinical equipoise existed regarding the utility of early surgery according to the treating physicians. Hence, patients thought strongly to benefit from surgery (eg. a young patient herniating from lobar hematoma), and those where surgery is thought to be futile (eg. a deeply comatose older patient with thalamic bleed) were not randomized. Most commonly randomized patients were those with GCS equal to or greater than 5, minimum clot diameter of at least 10 ml on initial head computed tomography (CT), and age greater than 14. Exclusion criteria included clear evidence that the hemorrhage was due to an aneurysm, AVM, neoplasm, or trauma; ICH within the posterior fossa; severe pre-existing mental or physical illness causing significant disability prior to the insult; and cases where surgery could not be performed within 72 hours of the initial insult. Outcome was assessed based on prognosis at time of randomization. Prognosis was determined using the following equation: prognostic score = (10 x admission GCS) – age (yr) – (0.64 x clot volume (ml)). For those patients with a poor prognosis a favorable outcome included a good recovery, moderate disability, and the upper severe disability categories of the extended Glasgow outcome score. For those patients with a good prognosis a favorable outcome included a good recovery and moderate disability.

The authors concluded based on over 1000 randomized patients that there was no difference in outcome between the cohort of patients undergoing early surgical intervention and those that were treated conservatively. Subgroup analyses are not complete, but there does not appear to be a clear advantage of surgery in any group analyzed. Clots that track to within 1 cm of the cortical surface may represent an exception.

The ICH accounts for only 10-15% of all strokes, but has the highest mortality of any stroke subtype. Despite our evolution in medical knowledge and demand for evidence-based medicine, the current treatment of ICH remains anecdotal and inconsistent. The authors designed and completed a large multicenter trial evaluating the appropriate treatment for supratentorial ICH in an attempt to establish guidelines. The conclusion reached was that in cases where surgical intervention is not heavily favored by current clinical judgement, early clot evacuation does not offer clinical benefit over conservative management. The trial sadly could not confirm current practice guidelines, nor support new ones. Based on these findings, there continues to be no scientific standard of care for ICH. It is currently unknown whether any intervention can ameliorate the morbidity and mortality of this illness, as there is no convincing evidence of benefit from any medical treatment, while the role of surgery remains controversial. Therefore, without defined indications for clot evacuation, therapeutic protocols for ICH will continue to be determined based on clinical judgment and individual case circumstances. Science sadly awaits new breakthroughs that shatter the current nihilism for this illness.

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TECHNOLOGY & CLINICAL RESEARCH

More Effective Targeting of Tumor Angiogenesis

Laboratory investigations have shown that tumor progression depends upon three fundamental processes: 1) proliferation, 2) invasion, and 3) angiogenesis. Each of these elements has been targeted by therapies with variable efficacy and some toxicity. In most cases the toxicity associated with the therapeutic intervention is due to a lack of specificity. Normal cells depend on many of the same elements during growth and differentiation

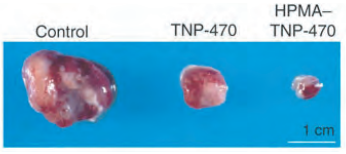

FIGURE 1. *Excised tumors: TNP-470, HPMA copolymer–TNP-470 conjungate and saline on male SCID mice bearing A2058 human melanoma (n=5 mice per group) on day 8 of treatment.*

that contribute to tumor progression. Angiogenesis in particular has been difficult to target specifically because the process of new blood vessel formation is such a critical component of normal physiology. Currently there are over 60 angiogenesis inhibitors in clinical trial for a variety of malignancies. One of the most effective of these angiogenesis inhibitors is a low molecular weight synthetic analogue of fumagillin designated "TNP-470" *(Fig. 1)*. This drug is a potent endothelial cell inhibitor in vitro and has the broadest anti-cancer effect of all the anti-angiogenic agents. In clinical trials TNP-470 has been remarkably effective, but with some concerning neurotoxicity attributable to drug crossing the normal blood brain barrier. Accordingly an important goal in anti-angiogenic therapy has been to modify TNP-470 in a manner that would retain its anti-angiogenic biological activity while minimizing the associated toxicity. Researchers at Harvard under the guidance of Judah Folkman may have achieved this goal.

In a recent paper published in Nature Medicine, Satchi-Fainaro and colleagues attempted to minimize toxicity by using a water-soluable synthetic polymer to carry TNP-470 into tumor blood vessels (1). The polymer chosen for this study was N-(2-hydroxypropyl)methacrylamide (HPMA), which was attached to the TNP-470 by a Gly-Phe-Leu-Gly linker molecule. The new and improved drug was designated HPMA-TNP-470 and was tested against conventional preparations of TNP-470. In a series of well-controlled experiments the authors demonstrated that HPMA-TNP470 was more effective and less toxic than the unmodified drug. HPMA copolymer-TNP-470 substantially enhanced and prolonged the activity of TNP-470 in vivo in tumor and hepatectomy models. Polymer conjugation prevented TNP-470 from crossing the blood-brain barrier (BBB) and decreased its accumulation in normal organs, reducing drug-related toxicities. Treatment with TNP-470 caused weight loss and neurotoxic effects in mice, whereas HPMA-TNP470 did not.

The striking efficacy of the modification is almost certainly due to the increased specificity achieved by adding the water soluable polymer. The enhanced permeability and retention (EPR) effect is a physiological phenomenon that occurs in many tumors. Blood vessels that grow in response to oncogenic signaling are often immature and not completely formed. Passive diffusion through these vessels into the tumor tissue can occur easily; whereas passive diffusion is regulated at sites of normal vasculature such as the blood brain barrier. By linking the polymer to the drug, Folkman's group increased the likelihood that the drug would find its way into tumor vasculature, where it could mediate its effect. These scientific observations have yet to be translated into an effective clinical therapy. However the potential applications of the drug in CNS malignancies would be a logical extension of these results. High-grade intra-axial tumors that compromise the blood brain barrier might be ideal targets for a drug like HPMA-TNP-470. Prior neurotoxicity of the TNP-470 has precluded application to CNS lesions. With the innovation described by Folkman and colleagues a new era of anti-angiogenic therapy may be upon us.

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TRANSLATIONAL RESEARCH

Reference:

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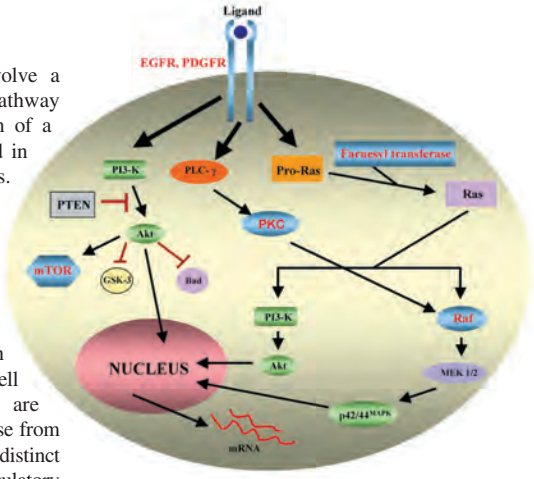
Targeted Molecular Therapy In Glial Tumors

Human gliomagenesis appears to involve a complex network of signaling pathway alterations, rather than the expression of a particular dominant oncogene, as is observed in certain leukemias or breast cancers. Glioblastomas (GBMs) can be grouped into at least two major categories, primary or "de novo" GBM and secondary GBMs, those tumors that arise and transform from precursor, lower-grade lesions. Primary GBMs tend to be observed in older patients and exhibit alterations of the Epidermal Growth Factor Receptor (EGFR) gene as well as cell cycle regulatory genes. Secondary GBMs are observed in younger patients and typically arise from lower-grade neoplasms. These tumors contain distinct molecular alterations, but also in cell cycle regulatory components, in this case the p53 gene, and growth factor receptors, such as the platelet-derived growth factor receptor (PDGF-R), and/or its ligand(s). A common theme is that there appears to be cooperativity between activation of oncogenic growth factors and perturbation of cell cycle regulatory components. The observed clinico-pathologic observations have generally been supported to date by mouse models of gliomagenesis. In this era of targeted molecular therapeutics, specific classification schemes will be of great use in clinical trial design and future treatment selection and will be continually refined as the use of genomics and proteomics is more widely applied to glioblastoma diagnosis.

Recent reports in Clinical Cancer Research illustrate many of the issues involved in translational application of molecular therapeutics to solid tumors, including glial tumors. Since many of the molecular targets, including the EGFR, are shared between gliomas and other cancers, neuro-oncologists have an opportunity to learn from preclinical studies and clinical trials conducted in other tumors. EGFR belongs to the ErbB family of receptor tyrosine kinases (RTKs), a family that also includes ErbB2, the target of the Herceptin monoclonal antibody (mAb) expressed in subtypes of breast cancer. Nyati and colleagues (**Clin Cancer Res** 10: 691-700, 2004) from the University of Michigan and Pfizer demonstrate that an irreversible pan-ErbB tyrosine kinase inhibitor, CI-1033, radiosensitized colon cancer cells in vitro and in vivo, a finding that has been observed for other EGFR inhibitors in multiple preclinical studies. Many basic and translational issues are raised by this observation. First, will ErbB inhibitors be more effective when used in combination with cytotoxic agents, such as chemotherapy and radiation? The preclinical data support combination treatment, but the available clinical trial data are less certain, as outlined by Harari and Huang (**Clin Cancer Res** 10: 428-432, 2004) in their commentary re: Nyati et al. Will irreversible blockade of ErbB receptors result in greater efficacy than reversible kinase inhibition resulting from treatment with Iressa (ZD1839) or Tarceva (OSI-774), two agents in clinical trial for adult gliomas in the North American Brain Tumor Consortium (NABTC).

Many practical issues come to mind regarding the clinical use of these newer agents in treatment of glial tumors. Particular inhibitors should be chosen only if the target is present in the tumor tissue. Stratification of cases has not yet been done in the majority of trials, including glioma trials conducted by the National Brain Tumor Consortia funded by the National Cancer Institute, NABTC and NABTT (New Approaches to Brain Tumor Therapy). But the early proteomic data sugeest the activation (e.g phosphorylation status) of a particular receptor or cellular kinase(s) may be more important than levels of expression. Moreover, there is preclinical evidence that tumor cells harboring mutations downstream of EGFR and PDGF-R will be resistant to receptor inhibitors. These issues will impact on trial design and require broader molecular analysis as part of the patient selection criteria. Timing and duration of administration of the newer agents will also be an issue since the preclinical data suggest that many of these drugs do not directly kill tumor cells. Clinical end-points will have to be reconsidered, since many of the agents are without any appreciable toxicity and could in theory be administered indefinitely. Integration with conventional anticancer therapies and other biologic approaches will be an important issue. Moreover, the brain will, as always, provide a challenge for delivery of many of these agents, although the data seem to suggest that small molecule kinase inhibitors are able to penetrate the blood-brain barrier. Lastly, advances in neuro-imaging will likely have and impact in clinical trial design. For example, MR spectroscopy and perfusion imaging may be valuable complements to anatomic imaging in determining extent of residual disease (a criterion for patient enrollment in the majority of trials conducted by NABTT and NABTC) and treatment response. There has clearly been a paradigm shift in the treatment of cancer that will impact on our management of glial tumors. The challenge for neurosurgical oncologists and neuro-oncologists will be to learn from these observations so that we can harness the power of genomics to improve the natural history of this formidable disease.



Potential molecular targets for glioma therapy. Inhibitors of molecules shaded in blue ( ) are currently in clinical trials for various cancers, including malignant gliomas. Inhibitors of molecules shaded in green ( ) are in preclinical laboratory testing and development.

DONALD M. O'ROURKE, M.D.

Unique Astrocyte Ribbon in Adult Human Brain Contains Neural Stem Cells But Lacks Chain Migration

In rodents, the adult subventricular zone (SVZ) is a primarily neurogenic germinal zone under nonpathological conditions. Neuronal progenitors travel by chain migration rostrally within the SVZ along the wall of the lateral ventricle and then along the rostral migratory stream (RMS) to generate olfactory interneurons. Ependymal cells (E cells) produce noggin, inhibiting the gliogenic activity of bone morphogenic proteins, and creating a neurogenic niche within the adult SVZ. Recent work by Sanai and colleagues from the University of California at San Fransisco and from Valencia, Spain (**Nature** 427: 740 – 744, 20) suggests that the human adult SVZ differs from the rodent in that: 1) a subventricular "ribbon" of multipotential astrocytes was found to line the human lateral ventricles 2) no migrating neuroblasts were visualized in the human SVZ; 3) no RMS was seen in the human olfactory peduncle.

Sanai and colleagues examined human SVZ harvested during the course of 65 neurosurgical resections (41 tumor, 14 vascular, and 13 epilepsy) and 45 brain autopsy specimens. SVZ was harvested from various areas of the anterior horn, body, atrium, occipital horn and temporal horn of the lateral ventricular walls. The authors identified a band of cells ~50 µM deep to the lateral ependymal surface that stained with astrocyte intermediate filament markers GFAP and vimentin. A subpopulation of these astrocytes divided in vivo, and generated neurons, astrocytes, and oligodendrocytes in vitro, independent of exogenous growth factors.

This work emphasizes the need to study human tissue to learn about the human brain. It describes a novel population of potential neural and glial progenitor cells in the adult human brain. Although more than half of the SVZ regions studied were from patients with brain tumors, similar findings were seen in epilepsy and vascular surgical specimens and autopsy tissue. The potential contribution of this cell population to neuronal or glial replacement strategies or in the development of gliomas remains to be elucidated.

GUY MCKHANN II, M.D.
TECHNOLOGY & CLINICAL RESEARCH

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SCIENCE LEGISLATIVE NEWS

BY KATIE O. ORRICO, J.D. AND BARBARA E. PECK
RESEARCH LEGISLATION AND REGULATORY AFFAIRS

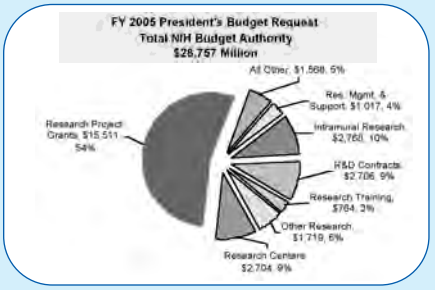
Washington News

President Bush Unveils his Budget for Fiscal Year 2005. On February 2, 2004, President Bush released his budget for fiscal year 2005. The proposed budget includes $580 billion in spending for Department of Health and Human Services programs, including nearly $29 billion in budget authority for the National Institutes of Health—which represents a 2.7 percent increase over FY 2004 funding levels.

Research Priorities in FY 2005. The President has identified several key funding priority areas for the upcoming fiscal year, including biodefense; implementing the NIH Roadmap for Medical Research; obesity research; and managing a research initiative on developing nuclear and radiological threat countermeasures. Additional support will be provided to continue progress in promising areas of science related to specific diseases such as cancer, HIV/AIDS, diabetes, Parkinson's disease and Alzheimer's disease.

NIH Roadmap for Medical Research. In an effort to target major opportunities and gaps in biomedical research that no single institute at NIH could tackle alone, the FY 2005 budget allocates a total of $237 million for the "Roadmap" initiative, an increase of $109 million over FY 2004. It is anticipated that the Roadmap will help transform new scientific knowledge that will result in tangible benefits for the American public of new treatments, prevention strategies, and diagnostics through overcoming barriers to rapid progress in biomedical research. The Roadmap is organized into three core themes: New Pathways to Discovery; Research Teams of the Future; and Re-engineering the Clinical Research Enterprise. Details about the Roadmap are available at: http://nihroadmap.nih.gov/.

Research Project Grants. The support of basic medical research through competitive, peer-reviewed, and investigator-initiated research project grants (RPGs) represents 54 percent of NIH's total budget request for FY 2005 and approximately 558 more grants are expected to be funded than in FY 2004. Of these, approximately 258 are for new and competing awards.



Facilities Construction The budget document notes that during FY 2004, both the Mark O. Hatfield Clinical Research and part of the John E. Porter National Neurosciences Research Center are scheduled to open, which together will provide significant additional laboratory and patient research space at NIH's main campus in Bethesda, Maryland. These two new major research assets have been designed and will be managed specifically to allow the NIH Institutes and Centers to work more collaboratively to speed the pace of fundamental discoveries and their translation into effective therapies and prevention strategies.

Individual Institute Funding. The budget document does not outline in any detail the specific research priorities for the neurosciences, however budget authority (dollars in millions) for key institutes of interest to neurosurgeons and other neuroscientists are as follows:

Institute	FY 2004	FY 2005	% Change
National Cancer Institute	$4,736	$4,870	2.8
National Heart, Lung & Blood Institute	2,878	2,964	2.9
National Institute of Neurological Disorders and Stroke	1,501	1,546	2.9
National Institute of Arthritis & Musculoskeletal & Skin Diseases	501	515	2.8

More Details. The full text of the HHS and NIH budget documents are available at:
http://www.hhs.gov/budget/05budget/fy2005bibfinal.pdf
and
http://www.nih.gov/news/budget/FY2005presbudget.pdf.

Bioethics Panel Issues Report on Stem Cell Research; New Members Appointed

In January, the President's Council on Bioethics issued a report entitled, Monitoring Stem Cell Research. The report summarizes some of basic science and medical applications of stem cell research developments since August 2001. In addition, the report highlights ethical, legal and policy discussions related to stem cell research. The report is not a definitive or comprehensive study of the entire topic and contains no proposed guidelines, regulations or specific public policy recommendations.

A copy of the full report is available at: http://bioethics.gov/reports/stemcell/index.html.

In other Council news, three new members have been appointed to the Council on Bioethics: Johns Hopkins University pediatric neurosurgeon, Dr. Benjamin Carson, Peter Lawler, a government professor at Berry College in Mount Berry, Georgia, and political scientists Diana Schaub from Loyola College in Baltimore. These replacements were reportedly made when two former science advisors disagreed with White House policy on stem cell research and other scientific matters. Elizabeth Blackburn, a biologist at the University of California, San Francisco, and William F. May, a bioethicist at the University of Virginia, Charlottesville, were dismissed on February 27, 2004.

Congress Moving on Stroke Legislation

The United States Senate and House of Representatives are once again considering stroke related legislation. On March 3, 2004, the House Energy and Commerce Committee reported out of committee H.R. 3658, the Stroke Treatment and Ongoing Prevention Act, clearing the measure for consideration by the House of Representatives. The companion bill in the Senate, S. 1909, is currently pending before the Senate Health, Education, Labor and Pensions Committee. These bills would amend the Public Health Service Act and are designed to strengthen education, prevention, and treatment programs relating to stroke.

Each bill has three distinct areas and goals: (1) public education regarding the prevention and treatment of stroke through a national education campaign; (2) the education of medical professionals in the prevention, diagnosis and treatment of stroke; and (3) the establishment of a national stroke registry. Both bills allow grants to private organizations to assist in education the public or medical professionals. Provisions of the bills also call for the development of task forces to assist Health and Human Services in developing the necessary materials.

"Stroke is the third leading cause of death in the United States, but only 3% of patients get appropriate, timely treatment with clot-dissolving drugs. If these patients got proper treatment, we could reduce by more than one half the incidence of death and disability," Senator Edward Kennedy (D-MA), a co-sponsor of the Senate bill said. "We intend to introduce this bill which provides grants to set up systems of care and public education on symptoms of stroke and prompt treatment."

"The economic cost of stroke is staggering. The United States spends over $30 billion each year caring for stroke victims. This legislation seeks to prevent and more effectively treat strokes to save lives and lower health care costs," Chip Pickering, (R-MS), co-sponsor of the House bill, said.

Both the Senate and House passed similar stroke legislation in 2002, but failed to complete action before adjourning for the year. The full texts of these bills are available at http://thomas.loc.gov/.