VA RESEARCH CURRENTS

RESEARCH NEWS FROM THE U.S. DEPARTMENT OF VETERANS AFFAIRS • JULY 2007

New model agreement will ease VA-industry drug trials

This summer, a clinical trial is getting under way at several VA sites to test a new drug that promises to boost the activity and lower the toxicity of 5-FU, a drug used to treat metastatic colon cancer. The study will be one of the first to take advantage of a newly revised template agreement for clinical trials between VA and pharmaceutical companies.

The contract, known as a Cooperative Research and Development Agreement (CRADA), is the same tool used by all federal agencies that conduct research with non-federal partners. VA has used CRADAs since they were legislated into use in the 1980s, but the agency's model form needed updating. That process,

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Durham study to probe benefits of guided imagery for PTSD

Guided imagery—a relaxation and mental-visualization technique aimed at promoting relaxation and well-being—has been clinically shown to help headaches, post-surgery pain, nausea from chemotherapy, and other conditions. Can it also ease the symptoms of posttraumatic stress disorder (PTSD)?

That question is at the core of a new VA study involving up to 36 women veterans who developed PTSD as the result of sexual trauma in the military. Some studies show that as many as 4 in 10 women were raped or otherwise

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Photo by Mitch Martin

Healing the injured brain: How can research help?

"Your skull gets pounded against your Kevlar [helmet]. Your brain gets tossed around like an egg in a bucket of water," is how Retired Army Pfc. Chris Lynch, who suffered a brain injury during training in 2000, explained his injury in a recent interview with the American Forces Press Service. Through intensive therapy, Lynch has recovered much of his ability to do everyday tasks, and now reaches out to newly brain-injured troops to offer support.

Traumatic brain injury (TBI) has been called the "signature injury" of the current U.S. military deployment. More than 26,000 troops have been wounded in Iraq alone, the majority of them from blasts. It is estimated that more than 60 percent of these blast injuries—such as from roadside bombs, mortars, or rocket-propelled grenades—result in TBI.

Neurologist Michael E. Selzer, MD, PhD, is the director of Rehabilitation Research and Development for VA.

How can research help meet the challenge of caring for veterans with TBI, and what clinical issues are driving VA research in this area? *Research Currents* discussed these issues with Michael Selzer, MD, PhD, VA's director of Rehabilitation Research and Development and a neurologist who studies regeneration of the central nervous system. (For the full text of the interview, along with additional background on TBI care in VA, visit *www.research.va.gov.)*

RC: Is TBI difficult to diagnose?

Selzer: Yes, because it's a complex and varied phenomenon—not only in severity, but in terms of where in the brain the inju-

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Career milestones

Laura Petersen, MD, MPH, was named director of VA's Houston Center for Quality of Care and Utilization Studies. The center is one of 15 VA-funded centers of excellence for health-services research. Petersen's work on financial incentives to improve health-care was cited extensively in the Institute of Medicine 2006 report titled "Provider Performance: Aligning Incentives in Medicine." She has also conducted several studies to benchmark and evaluate VA care, especially in comparison with non-VA care.

Robert H. Carter, MD, a physician-researcher at the Birmingham VA who studies the role of B lymphocytes in autoimmune disease, has been elected to membership in the prestigious Association of American Physicians.

Peter W. Groeneveld, MD, MS, received a Young Investigator Award at the American Heart Association's 2007 conference on Quality of Care and Outcomes Research in Cardiovascular Disease and Stroke. The Young Investigator Award recognizes the top-ranked abstracts submitted by investigators who are in the first five years of their faculty appointment. A physician at the Philadelphia VA and investigator with VA's Center for Health Equity Research and Promotion, Groeneveld was cited for his research on the cost-effectiveness of drug-eluting cardiac stents. ■

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Arthur Vandenbark, PhD, of the Portland VA Medical Center, has developed a multiple sclerosis drug called RTL1000.

Promising multiple sclerosis therapy in clinical trial

A multiple sclerosis drug developed at the Portland VA and Oregon Health & Science University is being tested in a phase I trial involving 30 patients at six sites nationwide. The drug, RTL1000, is designed to target only the pathogenic cells that play a role in the disease, and as such is expected to have fewer side effects than current therapies. It was given orphan-drug status by the Food and Drug Administration in 2003.

The research team is led by VA research career scientist and OHSU professor Arthur Vandenbark, PhD. With VA since 1974, he has been working more than 20 years to develop treatments to fight MS, a disease in which the body's own white blood cells attack the protective myelin insulation that surrounds nerves and enables them to relay messages from the brain to the muscles.

RTL1000 is based on a new type of molecule known as a "recombinant T-cell receptor ligand" (RTL) that binds to the immune cells involved in MS and neutralizes them. Vandenbark says the molecule represents a platform technology that can eventually be tailored for use against other autoimmune diseases. The technology is being developed further by Artielle ImmunoTherapeutics, which is sponsoring the RTL1000 trial.

So far, one group of six volunteers has taken part in the study. Four of them received low intravenous doses of the drug—2 milligrams—and two received placebo. Once the results have been analyzed for safety, four successive groups of patients will receive progressively higher doses of the drug or placebo.

"If everything looks good in this first cohort, the second cohort will receive 6 milligrams, the third 20 milligrams, the fourth 60 milligrams, and the fifth, 200 milligrams," explained Vandenbark. "The drug is very selective for a small subpopulation of myelin

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sexually assaulted during their service, and to date more than 25,000 women in the U.S. with military sexual trauma have been identified, says principal investigator Jennifer Strauss, PhD, a psychologist and health-services researcher at the Durham VA Medical Center and Duke University.

The Durham study has already enrolled about 20 women, most of whom served in the Vietnam era and have been receiving some form of therapy—medication, counseling, or both—for decades, but without substantial improvement. "They're treatment-resistant. They've been through individual and group therapy, they're on medication, and they still have symptoms," said Strauss.

Social workers will aid home-based intervention

Volunteers in the study will use personal digital assistants (PDAs) at home to listen to audio instructions and soothing music designed to help them relax and tap into their innate capacity for healing and growth. A control group will listen to the music but not the narrative, which was specially produced to target PTSD. Both groups will meet with a clinical social worker twice during the 12-week study. They'll also receive weekly 10-minute "coaching" calls from the social worker.

Regarding the audio narrative, Strauss said: "It's a metaphor—it has to be generic enough to appeal to everybody in this group. It takes them through experiencing how [the trauma] is affecting them now. It focuses on the present, and moving forward. What are some of the strengths you can derive from this experience? How can you grow from it? It's designed to increase self-confidence, motivation and hope. In essence, it's designed to move them from victim to survivor."

The approach is different from prolonged exposure therapy, a well-established PTSD treatment in which counselors help patients safely and gradually recall their traumas and work on changing the thoughts, feelings and behaviors surrounding the memories. Despite—or perhaps because of—the contrasts between the two approaches, Strauss believes guided imagery may prove an effective adjunct for exposure therapy. "I actually think the two can work very well together." She adds that the guided-imagery intervention she is testing is, to a large extent, rooted in cognitive behavioral therapy.

"It's very much grounded in cognitive behavioral techniques and principles of change. It's not that dissimilar to what I was taught to do in individual therapy. By completing the exercises, women learn that they can replace trauma-related emotions with positive imagery and healthier emotions, thereby reducing PTSD symptoms and negative emotions."

Jennifer Strauss, PhD, is leading a study in which women with PTSD will use PDAs—personal digital assistants—to listen to audio featuring guided imagery.

Functional MRIs, blood tests to help measure results

While guided imagery might sound "touchy feely" to some, the new VA study will take advantage of medical technology to help provide hard data on outcomes. Participants will undergo functional MRIs before and after treatment to document how their brains react to stress. The fMRI protocols were developed by study collaborator Rajendra Morey, MD, director of the Neuroimaging Core at VA's Durham-based Mid-Atlantic Mental Illness Research and Clinical Center.

Along with this, co-investigator Christine Marx, MD, MA, will run sophisticated blood tests before and after treatment to check the

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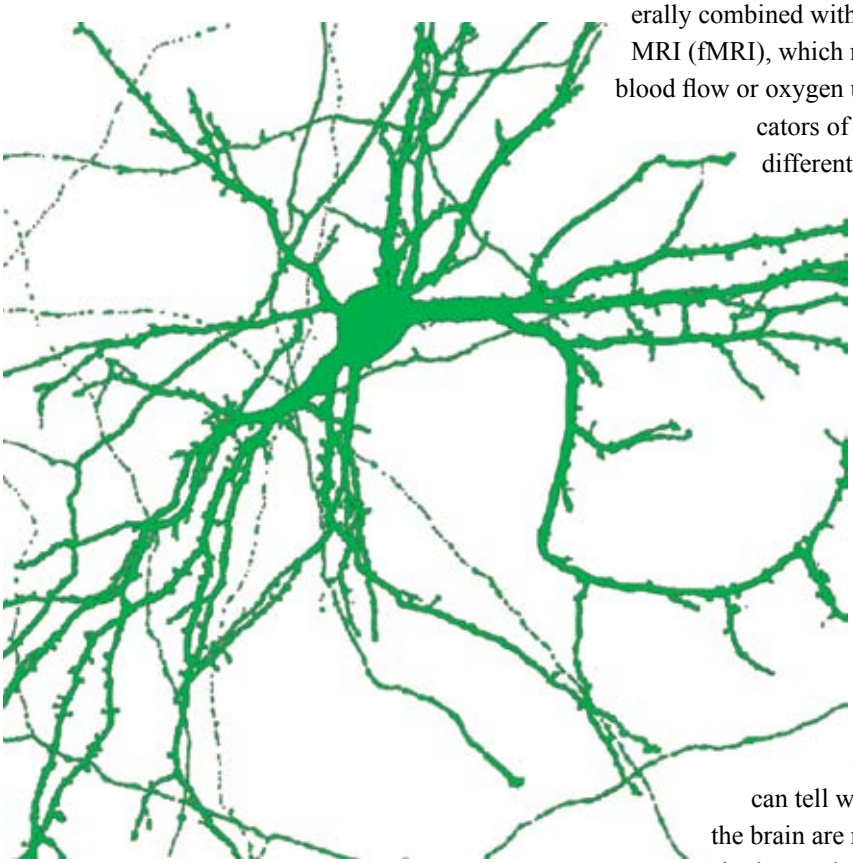
ries occur. Symptoms vary greatly depending on what nerve pathways are interrupted. When we evaluate people with TBI, we need to find out not only about the obvious deficits—like weakness on one side, which often happens with more severe injuries—but even subtle things, like loss of attention. A good example would be a secretary who had been functioning at a high level and could take notes at meetings where six people were talking back and forth to each other. Now, after even a relatively mild brain injury, she finds she can't take in all this information anymore, because it's coming from too many directions at one time.

It's important to remember that even mild TBI can have a very serious impact on a person's life. For example, if you lose those subtle intellectual capacities that made you an effective worker in the modern workforce, that can be very disabling.



Neuron image courtesy of Vanderbilt University

RC: Do brain scans help in diagnosis?

In TBI, the structural damage is not as easy to see as it with stroke, because the damage is not all in once place—it's scattered. But as imaging technology continues to evolve, we're able to do more. Conventional magnetic resonance imaging (MRI) is useful to a large extent because it can show damage to many—but not all—of the brain's structures. Diffusion tensor imaging (DTI), a newer type of MRI, is particularly valuable because it shows damage to nerve fibers, which is an important factor in TBI.

Still, the only way an MRI can tell you about an injury's effect on brain function is if you've done studies to correlate certain parts of the brain and certain nerve-fiber pathways with certain functions. More research is needed to determine all those correlations, especially when the damage is more subtle or scattered.

Conventional MRI, which can show the structure of the brain in high detail, is generally combined with functional MRI (fMRI), which measures blood flow or oxygen use—indicators of activity—in different parts of the brain as the person performs a task. If you correlate fMRI with structural MRI—that is, actually superimpose one scan on the other—you can tell what parts of the brain are not functioning as the person performs a task that is now difficult for him because of the injury. With this approach, we may eventually be able to predict the deficits in mental ability that are easily missed in the field. This type of correlation is done routinely in research nowadays, but we haven't yet employed it on a large scale for clinical diagnosis.

RC: What is considered state-of-the-art treatment for TBI?

It's basically a mix of therapies—cognitive, speech, occupational—plus medication to control specific symptoms, such as anxiety or pain. The therapies are based on practicing and finding strategies to compensate for lost skills. They can be very helpful in improving the quality of life of those with TBI, but the amount of improvement you can get is limited. We don't yet have a real way of reversing the deficits.

RC: Do current therapies take advantage of brain "plasticity"—the innate ability of the brain to rewire itself to compensate for damaged nerve cells and lost function?

Yes. As patients go through therapy and relearn and practice skills, nerve cells in their brain may change their shape to a limited extent. For example, a nerve cell has a fiber—axon—that it uses to talk with other nerve cells. These axons can sprout new branches, and these branches can travel for very short distances—generally, less than one millimeter. As long as the nerve cells haven't been killed, the brain can rewire its connections, to some degree, over short distances.

Along with this, synapses—the junctions where nerve cells talk with each other—become stronger with use. So through a combination of increased strength of the synapses plus local sprouting, we can regain some of the local connections. That means a nerve can now activate not just the neighboring nerve it used to activate, but

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CRADA (from pg. 1)

which required extensive legwork and other consulting, took about two years, culminating last month with the finalization of VA's new clinical trial CRADA. Model CRADAs for other types of VA research—for example, studies involving medical devices—will follow over the next few weeks. All the CRADAs will eventually be mandated throughout the VA system.

Prior to the advent of the new CRADA, agreements for drug trials involving VA and industry were based on contracts provided by the drug company. Negotiation on VA's behalf was usually handled by staff at the nonprofit corporations that help support VA research, or by administrative officers at local VA research offices. The same nonprofit and VA staff will still be involved in clinical-trial negotiations, but now the CRADA will serve as the uniform contract, and should make for smoother, faster negotiations.

New document is 'easy, flexible'

"Now, when a drug company wants to deal with VA, they'll have to use the CRADA," said Amy Centanni, director of VA's Technology Transfer Program, which worked with VA's Office of General Counsel in updating the clinical trial CRADA. Referring to the nonprofit and VA administrative staff, she said, "I think people will be pretty happy once they see how the document works and understand how easy and flexible it is."

Jeffrey Moore, PhD, a Tech Transfer analyst, said the new model agreement protects the interests of VA and veterans, and also poses advantages to industry.

"It reads much more clearly and has been significantly streamlined. We think it will reduce the negotiation time and allow veterans to participate in clinical trials, should they choose to do so, in a more timely manner." Citing the new colorectal-cancer trial in which VA is partnering with San Diego-based Adventrx, Moore said: "The negotiations would have taken far longer. The process would have been much more difficult."

Photo by Art Gardiner

Dr. Jeffrey Moore and Amy Centanni spearheaded the effort to update VA's Cooperative Research and Development Agreement.

Centanni stressed that CRADAs—for clinical trials as well as other types of research—"will give veterans access to cutting-edge technology, drugs and devices that they might not otherwise have." She noted in particular that CRADAs will expand access to experimental treatments for VA patients for whom standard therapies have failed.

The drug companies are pleased, she said, because "we've come up with something that ties all the VA sites together. We've addressed the majority of the issues that were of concern to them, and they understand what we're doing and why we're doing it." She said issues such as intellectual property, data rights and liability took considerable time to iron out in the new model CRADA in a way that was satisfactory to VA and industry, but all parties stand to benefit now from a standardized contract and streamlined negotiations.

Her team is now working on crafting master agreements between VA and some of the larger pharmaceutical companies.

"The idea is that we'd sign one master, and that is what would be used throughout the entire VA system. So if a group in San Diego and one in Nashville wanted to do a study with Novartis, for example, they would just go to their file cabinet and pull out the Novartis agreement, and all they'd have to negotiate locally was their budget and 'statement of work.'"

Centanni said she expects close to 1,000 clinical trial CRADAs to be signed between VA and commercial partners each year, basing her estimate on the actual number of trials that VA already conducts. ■

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peptide-reactive T cells. Weight-equivalent doses in mice do not have any side effects, so we are hopeful there won't be any problems in MS subjects."

In animal studies, said Vandenbark, "A large single dose [of RTL] given after the onset of paralysis was able to reduce clinical signs, demyelination and axonal damage very significantly for weeks to months." He said a large single intravenous dose might conceivably have long-lasting effects in patients, but for now the plan is to administer the drug monthly. He said an oral form would be desirable, but so far that approach has not worked in mice.

Because of the highly specific nature of RTL1000's design, only patients with a certain gene—DR2—are enrolled in the trial. Currently, there are about 24,000 MS patients in the U.S. with this genetic profile who would be eligible for the drug.

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levels of brain hormones related to stress, such as allopregnanolone and pregnenolone. Marx says preliminary data have linked several neurosteroids to PTSD symptoms. Besides evaluating the effects of guided imagery, she thinks her analysis may help identify promising new targets for drug interventions for PTSD.

This phase of the work is supported by the Samueli Institute, a Virginia-based nonprofit that aims to "transform healthcare through the scientific exploration of healing," and that partners with researchers from academia, health systems and government agencies—including VA and the Department of Defense—on studies of alternative treatments.

Posttraumatic stress disorder among women veterans, particularly stemming from sexual harassment or assault during their military service, has increasingly been a topic of study for VA researchers.

Besides the brain scans and blood tests, outcomes of the study will be measured through standardized assessments for PTSD.

Later this summer, Strauss will begin piloting the guided-imagery audios with 20 combat veterans, mostly men. She cites prior work by Leslie Root, PhD, formerly with the VA in Biloxi, Miss., who had begun exploring guided imagery for PTSD in combat veterans and found it effective. Strauss admits that even she still tends to instinctively associate this gentle therapy more with women than with men, but she is quick to point out that Root's data and her own don't support this notion. Her preliminary surveys among patients at the Durham VA—a mostly male population—showed that about 85 percent had used some form of complementary and alternative medicine, and that most were open to the idea of using guided imagery.

"When we described what the therapy involves and asked them if they would use the audio, most said yes. They seemed very receptive." ■

Research mentor had used guided imagery in battle with cancer

Jennifer Strauss' research mentor, Mimi Butterfield, MD, MPH, a VA psychiatrist and health-services researcher, had discovered the benefits of guided imagery while battling an aggressive form of breast cancer, to which she ultimately succumbed last year.

Butterfield wrote to guided-imagery pioneer Belleruth Naparstek to thank her for her tapes, which Butterfield had found useful for reducing pain and discomfort and helping her cope emotionally. The VA researcher also offered her services to help formally evaluate the therapy. Naparstek took her up on the offer, and this led to the development—with Strauss' involvement—of the audio intervention now being tested.

Strauss: "Mimi was a die-hard empiricist, but also a very creative and open-minded woman."

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"We expect a therapeutic effect only in this subset of MS patients," said Vandenbark, "but the effects should be much more pronounced than what we see with current therapies."

Another MS treatment developed by Vandenbark's team, NeuroVax, is now in a proof-of-principle trial with 200 patients in Eastern Europe. "There's faster enrollment there because the current therapies for MS are too expensive for patients or the health systems," noted Vandenbark.

He said that potentially, NeuroVax and RTL1000 could be combined for an effective one-two punch against MS. "The two drugs have different but very compatible mechanisms of action and I believe they would be fantastic if used together."

He added: "This is a dream only partially realized. It's great to get this far—most drugs don't ever get into clinical trials—but the issue of efficacy for MS still needs to be established. I'm ecstatic we're in clinical trials, but we still have a long road ahead. One step at a time!" ■

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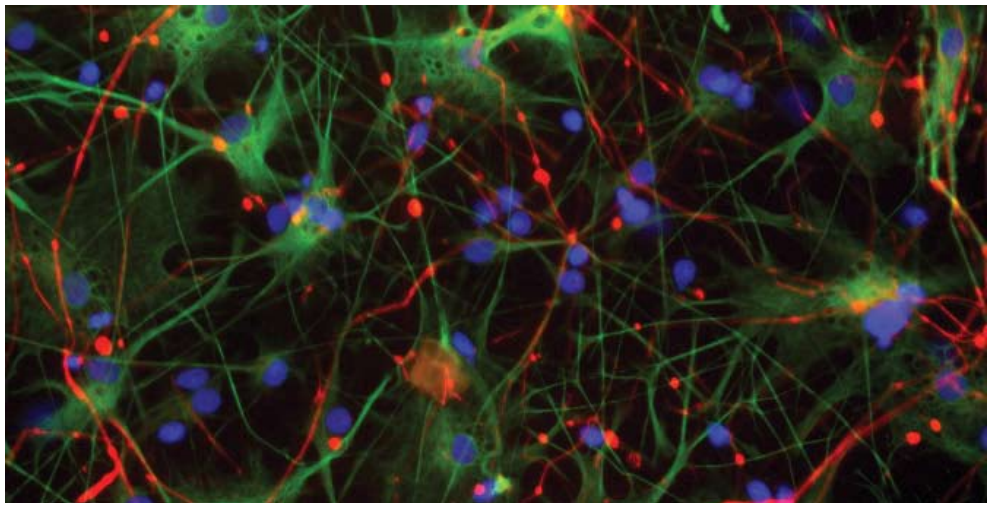
The image at the right, showing human neurons in culture, comes from the lab of Micheline McCarthy, MD, PhD, at the Miami VA Medical Center. Her team studies the impact of HIV on neuron development and survival.



also other nerves that had lost their inputs because of the injury. So the function in a finger could be regained, for example, if the nerves that activate the neighboring finger were spared and could assume the extra function. But those same intact nerves would not be able to activate a leg that had lost its nerve supply—the distance in the brain between where the hand is represented and the leg is represented is too great.

So the brain's intrinsic plasticity can allow for some improvements, but we can't get huge changes.

RC: How can research contribute to better treatments?

To go beyond the limits of the current therapies, you have to repair the nervous system. VA scientists and others are exploring various ways to do this.

There are brain chemicals that appear to block the re-growth of nerve cells. Some of the research involves neutralizing these chemicals. Along similar lines, it may be possible to provide drugs that enhance the natural ability of nerve cells to grow. Researchers are looking at proteins called trophic factors, which are present in the brain in very small amounts and are needed for nerve cells to be healthy and re-grow their fibers.

Another way to repair brain damage is to replace brain cells that have been killed or damaged. This could involve adult stem cells or other "nerve progenitors" that would be transplanted and develop into nerve cells to replace the lost ones.

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Current VA research on brain injury

In fiscal year 2006, VA spent $26.1 million for research on neurotrauma, which includes spinal cord injury and traumatic brain injury (TBI). Areas of focus in TBI research include the biology of neurotrauma; screening and diagnosis; efficacy of medications to control symptoms; the interplay between PTSD and TBI; and social and vocational reintegration. Other VA research, in areas such as prosthetics, stroke and neurodegenerative disease, also promises to yield knowledge that may have an impact on TBI treatment. Here are a few examples of research now in progress:

- The Defense and Veterans Brain Injury Center, a joint project of VA and the Department of Defense, is investigating the usefulness of drugs such as sertraline, citalopram and rivastigmine for treating TBI symptoms such as headaches, anxiety, mood swings. These drugs are effective for people without TBI, but their role in TBI treatment remains uncertain. For more information on this and other research at the center, visit www.dvbic.org.

- A team of VA researchers is studying "best practices" in polytrauma care—with a focus on TBI therapy—and aims to implement them across all VA polytrauma sites. The group is also establishing a registry of VA polytrauma patients to support research and future clinical care.

- Researchers at the Polytrauma Center in Palo Alto center have been exploring innovative rehabilitative techniques for brain-injured veterans, including robotic movement therapy and simulated driving assessments. Work here has been featured on "ABC Nightline."

- VA scientists are exploring the use of gene therapy, cell transplantation, tissue engineering and other cutting-edge strategies to help regenerate nerve cells in TBI as well as conditions such as spinal cord injury, multiple sclerosis and Alzheimer's disease. For example, at last year's American Academy of Neurology meeting, Cesario Borlongan, PhD, a neuroscientist at the August (Ga.) VA Medical Center, presented study results showing that a single dose of adult stem cells transplanted into the brain significantly improved recovery in an animal model of stroke. ■

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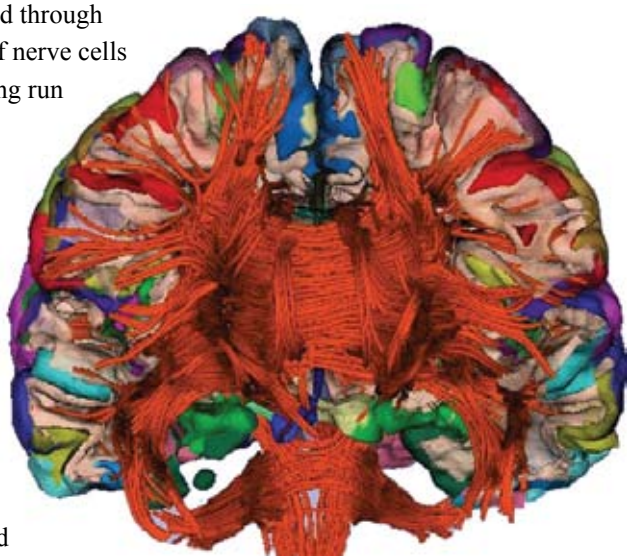
'We cannot afford to be confined by our current techniques. ...We must think outside the box.'

RC: How heavily should VA invest in these avenues of research ?

The Office of Research and Development has to be sure that it invests in research both to provide near-term benefits to our soldiers returning from OEF/OIF with TBI, and to give them hope for more profound improvements in the long term. TBI research should be balanced between these two essential goals.

At one end of the research spectrum, we have to do clinical studies that will find the optimal parameters—such as dose, frequency of treatment, duration of treatment—for therapies whose effectiveness is already partially established, based on preliminary studies in patients. At the other end of the spectrum, research on the cellular and molecular mechanisms by which the brain can be repaired through regeneration or replacement of nerve cells and nerve fibers may in the long run provide the potential for more profound functional improvement. But the chances of failure are greater, and the time it takes to develop a clinical treatment based on the findings is much longer. Lying somewhere between these two extremes is "translational research," in which studies on experimental animals have already produced strong reason to expect that a proposed therapy will prove safe and effective, and is therefore ready for preliminary studies in human patients. All three types of research are important.



This computerized visualization of data from a diffusion tensor image, from Dr. Martha Shenton's lab at the Boston VA, shows the human cortex. The red thread-like structures are neuron fibers.

Because of the enormous impact of TBI on our soldiers in OEF/OIF, the VA research community is accelerating its efforts at all three levels of investigation: fundamental science, translational research and clinical research. We cannot afford to be confined by our current techniques. Fine-tuning them is part of what we need to do, but that alone will not lead to the kind of big recovery we are seeking for our veterans with TBI. We must think outside the box, so that they can have the best available treatments as quickly as possible, and have hope for even greater improvements in the future. ■

For the full text of this interview with Dr. Selzer and more background on TBI care in VA,, visit www.research.va.gov.