

VA Research Currents

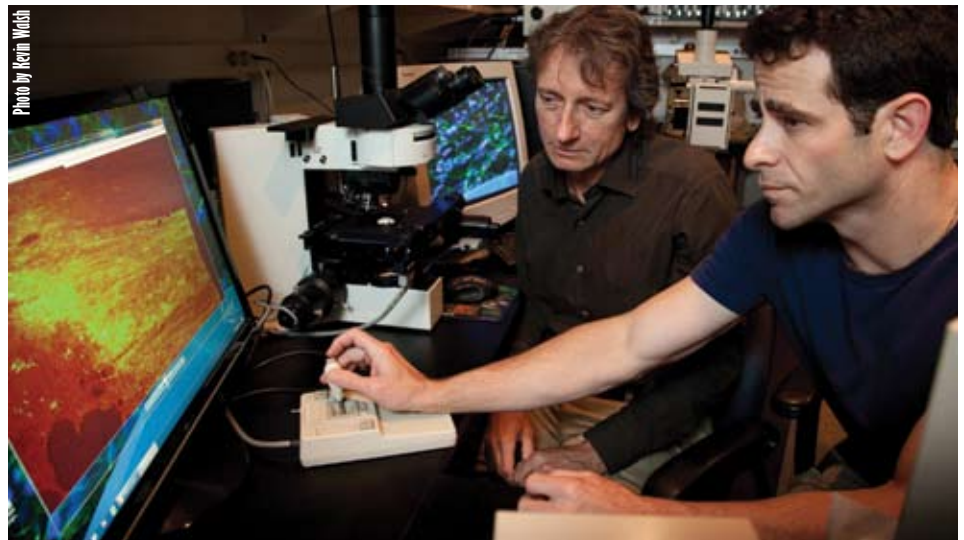
RESEARCH NEWS FROM THE U.S. DEPT. OF VETERANS AFFAIRS

Consortium aims to ramp up research on spinal cord injury New VA initiative will bring together key groups working toward a cure

When physician-researcher Mark Tuszynski, MD, PhD, talks with patients who have spinal cord injury, he advises them to “have a positive outlook and keep their bodies in the best shape possible. With much hard work and some luck, we hope to have truly promising therapies to deliver in the future.”

A new VA initiative aims to put researchers on the fast track toward that future. The VA Spinal Cord Injury Collaborative Translational Consortium is building teams of leading investigators—almost a “Who’s Who” of spinal cord research in the U.S. today—to nurture high-risk, high-return ideas that would likely not get funded through other programs, and to create synergy among scientists who are in hot pursuit of the same goal.

One lead group in West Haven, Conn., and another in San Diego have already



Dr. Mark Tuszynski of VA and the University of California, San Diego (left), seen here with associate Dr. Ephron Rosenzweig, is seeking ways to regenerate injured spinal cord tissue.

begun a dialog that will have them sharing data, techniques and experimental therapies; replicating each other’s results; and propelling the research forward at a pace that would otherwise be hard to attain.

“Right now we are still working in animal models,” says Audrey Kusiak, PhD, the scientific program manager for VA who designed the consortium and

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Study participant John Stoffel of Kenosha, Wisc., used a self-testing device at home to help ensure the right dose of warfarin.

Results in from comparison of home, clinic monitoring of blood thinner

Patients taking warfarin, a widely used blood-thinning pill that requires careful monitoring to ensure the right dose, achieve similar outcomes whether they come into a clinic or use a self-testing device at home, according to a VA trial involving nearly 3,000 Veterans at 28 sites. The study results, published in the Oct. 21 *New England Journal of Medicine*, are good news for heart patients who live far from clinics or are homebound.

“This study helps answer an important question for cardiologists, primary care physicians and other health providers, and will lead to

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Altitude may figure in U.S. West's high suicide rate

Parts of the Western U.S. are renowned for majestic mountains and high deserts. But according to new research from VA and the University of Utah Brain Institute, the region's lofty altitudes may play a role in a deadly problem: a higher prevalence of suicides.

A report in the Sept. 15 online edition of the *American Journal of Psychiatry* shows that the risk for suicide increases by nearly one-third at an altitude of 2,000 meters, or about 6,500 feet above sea level.

The Western states have some of the highest average elevations in the nation—and the highest suicide rates. In 2006, the latest year for which national data were available, Montana, Idaho, Wyoming, Utah, Colorado, Nevada, New Mexico, Arizona and Oregon accounted for 9 of the 10 highest suicide rates in the country. Alaska also was in the top 10 in suicide rates.

After analyzing nationwide data from the U.S. Centers for Disease Control and Prevention, Perry Renshaw, MD, PhD, MBA, and colleagues concluded that altitude is an independent risk factor for suicide, and that “this association may have

High risk—A team led by Dr. Perry Renshaw, with the Salt Lake City VA Medical Center and the University of Utah Brain Institute, found that people who live at higher altitudes may be at increased risk for suicide.



arisen from the effects of metabolic stress associated with mild hypoxia [inadequate oxygen intake]” in people with mood disorders. In other words, people with problems such as depression might be at greater risk for suicide if they live at higher altitudes.

Other factors include gun ownership, sparse population

The researchers also concluded that the West's higher rates of gun ownership, a well-recognized factor in suicide, and lower population density—suicide is generally more prevalent in rural areas—may combine with altitude to influence suicide rates. The study suggests, though, that gun ownership and low population density by themselves cannot sufficiently explain the prevalence of suicides at higher altitudes.

To verify the study conclusions, lead author Namkug Kim, PhD, a former postdoctoral fellow under Renshaw, conducted a similar study in South Korea and found that the suicide rate in areas at 2,000 meters increases by 125 percent in that country.

Along with gun ownership and low population density, mental illness is a well-established risk factor for suicide. According to the American Foundation for Suicide Prevention, more than 6 in 10 people who take their own lives have major depression when they complete the act. Interestingly, past research has suggested a link between altitude and low mood, at least in the short term. Some research indicates that the decline in oxygen at higher altitudes is associated with worsening mood that can last for up to 90 days.

Understanding the full relationship between altitude and suicide will require much more study, according to Renshaw, who'd like to see epidemiologists examine the issue. “If altitude is related to suicide, then perhaps we could look with greater urgency at why this is true and what we can do to prevent it.” —

Adapted from a news release from the University of Utah

Nurse practitioner study amended

Earlier this year, *VA Research Currents* reported on a study in the March 2010 issue of the *American Journal of Nurse Practitioners* that had concluded that a majority of VA primary care patients “prefer to see nurse practitioners [NPs] as compared with physician assistants [PAs] and physicians.” In April, however, the journal published several amendments by the study authors. From the revised abstract: “The VHA is the largest healthcare system in the United States and the single largest employer of NPs and PAs. This study suggests that patients are satisfied with their providers of care for the most part. In 3 of the 21 regions of the VA system, satisfaction was slightly higher for NPs than doctors or PAs during one year of observation. The clinical implications of these observations require further exploration.”

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oversees it. “The hope is that after 10 years of research and funding, the consortium will have the data and expertise to translate the methods and results to humans. Toward that goal, I have already started talking with the Food and Drug Administration so they can help us design the experiments to make the data more meaningful during the preclinical phase.”

Academia, private sector to help guide effort

Tuszynski, with VA and the University of California, is at the helm of the San Diego team. The West Haven group is led by Jeffery Kocsis, PhD, of VA and Yale University. As the two groups build their partnership, they will also reach out to other collaborators—both in and outside VA—to bring additional expertise into the consortium. Kusiak says VA’s Rehabilitation Research and Development Service also expects to fund pilot studies by other VA investigators who can become part of the consortium by contributing tools to further its work. Examples include cells for transplantation or new drug-delivery methods.

Two advisory committees and a central advisory board that includes top names in spinal cord research from academia, government, private industry and the Veteran community will help guide the overall effort.

Much of the work in Tuszynski’s lab will focus on pinpointing networks of genes that trigger nerve regrowth. “We can then isolate these genes and introduce them into a non-regenerating cell to convert it into a regenerating cell,” explains Tuszynski. Another area of interest is using proteins called growth factors, namely BDNF and



Photo by Nick Lumester

Racing toward a cure—Champion wheelchair athlete and Navy Veteran Mike Savicki, who suffered a spinal cord injury in 1990, says he appreciates the “passionate work” of SCI researchers and believes their efforts may eventually lead to a cure. Savicki is on the board of the nonprofit No Barriers.

NT-3, to coax nerve cells to sprout new axons. Axons are the long, spindly part of the neuron that connects with other neurons to transmit impulses from the brain.

Combination therapy nets strong results in lab studies

The San Diego lab is also exploring the use of scaffolds made of a natural sugar-based substance called agarose. A damaged spinal cord has gaps above and below the injury that prevent nerve impulses from traveling through. The implanted scaffold acts like a bridge for regenerating axons to grow across the injury site.

Tuszynski believes in a combination approach, and his lab has had a string of successes along that line. Kusiak notes that

recent studies from the San Diego team “have shown that combinations of cells, drugs and growth factors result in regrowth of nerve fibers past the site of injury twelve months after the injury. Similar combinations have resulted in recovery of function in rodents as well as non-human primates.”

Some experimental therapies for spinal cord regeneration must be used within hours of the initial injury. Others, targeted to “subacute” injuries, must be used within a week or two. That’s the case with a therapy now being tested in a small safety-and-tolerability trial just begun by Geron Corporation, whose medical director sits on the advisory board of the VA consortium. In that trial, for the first time ever, human

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Greater medical burden seen in Veterans with PTSD

A large study by a VA and Stanford University team shows that among the newest generation of Veterans enrolled in VA health care, those with a mental health condition—especially posttraumatic stress disorder (PTSD)—tend to have more physical ailments.

The results, published online Sept. 18 in the *Journal of General Internal Medicine*, are not surprising in light of past research on the link between emotional stress and physical illness. But the findings may help guide VA as it continues expanding services to care for returning Veterans.

“In caring for Veterans returning with PTSD, we should account not only for their mental health needs, but also for their increased medical needs,” says lead author Susan Frayne, MD, MPH, with the VA Palo Alto Health Care System and Stanford University.

She says examples of areas where VA needs to assure ample capacity, based on the study results, include physical therapy and pain clinics to address high levels of musculoskeletal conditions; behavioral medicine and nutrition services to help with common conditions such as obesity; and clinics that specialize in women’s health care to respond to the particularly heavy burden of medical illness seen in women with PTSD.

Findings based on 90,000 VA patients

The researchers examined the records of more than 90,000 Iraq and Afghanistan Veterans who used VA outpatient care in fiscal year 2006–2007. The majority had received a diagnosis of at least one mental health condition. About 35 percent of men and 27 percent of women had PTSD.

The link between PTSD and medical (non-mental) illness was stronger among women than among men. Women with PTSD had a median of 7 medical conditions, versus 4.5 for women with no mental health diagnosis. The most common physical ailments for women were lower-back problems, headaches and lower-extremity joint disorders. Men with PTSD had a median of 5 medical conditions, versus 4 for men with no mental health diagnosis. The most common complaints for men were similar to those of women—for example, back and knee problems—but also included hearing loss.

Frayne, who conducts research for VA’s Center for Health Care Evaluation and Women’s Health Center of Excellence, both based in Palo Alto, says her team’s study is among the first to provide a



Photo by Staff Sgt. Ali E. Fraz/USAF

Tight spot—A U.S. Army soldier with the 25th Infantry Division patrols an alleyway in Diyala province, Iraq, in May 2009.

broad overview of the significant medical burden among newly returned Veterans with PTSD. The study checked for 222 specific medical conditions, from cancer to digestive trouble.

Related research by a team at the San Francisco VA Medical Center, published in January 2010, also in the *Journal of General Internal Medicine*, yielded similar findings: Iraq and Afghanistan Veterans with mental health conditions, particularly PTSD, used significantly more non-mental health services than those with no mental health diagnosis. The study was based on the records of nearly 250,000 Veterans who used VA care for the first time between 2001 and 2007.

In light of the trend seen across both studies, Frayne notes that early intervention for both physical and mental illness will be

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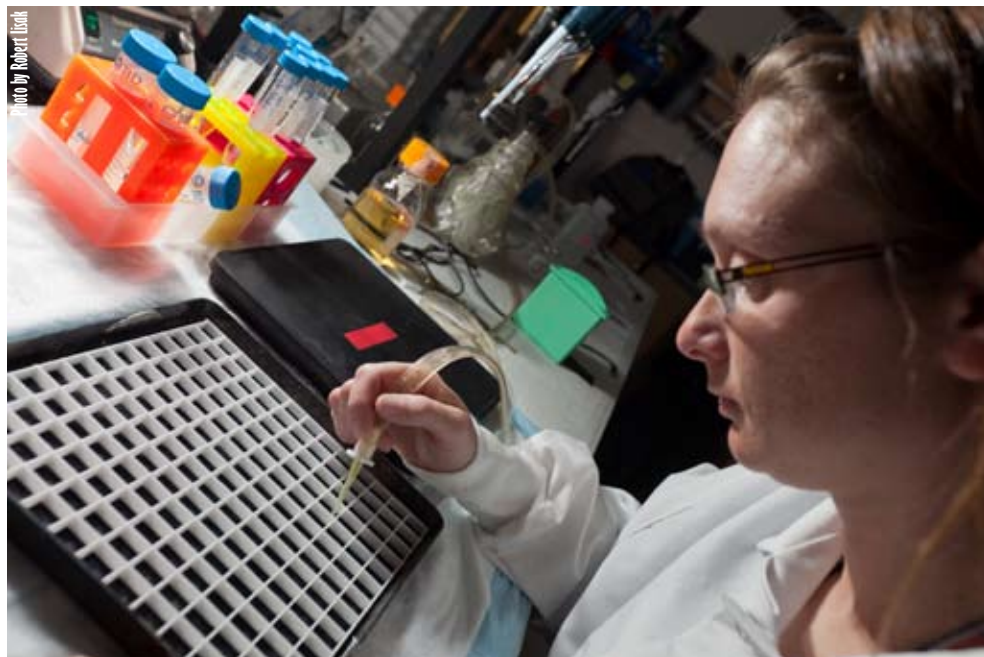
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patients are being injected with human embryonic stem cells, which are still highly controversial. The VA consortium, though, will seek to develop therapies that will work even months after an injury. “That’s more relevant to our Veteran population than acute or subacute therapies,” says Kusiak.

Kocsis, who for many years has partnered with well-known VA-Yale neurology researcher Stephen Waxman, MD, PhD, is working on methods that will complement those of the San Diego group. One area is the development of imaging techniques to track the survival of transplanted cells and to show how nerve fibers are growing inside the live organism. Currently, researchers rely on examining tissue under a microscope to gauge the success of a therapy. Kocsis’ team is now working with a commercially available system that had previously been used mainly by cancer researchers to view tumor progression. “The resolution is not great, but it gives us good correlation with cell survival,” he says. His team is also looking to take advantage of sophisticated scanning tools such as positron emission tomography and diffusion tensor imaging.

Adult stem cells show promise

The West Haven group has also been testing adult stem cells for spinal cord regeneration. In one recent study, they and Japanese collaborators infused mesenchymal stem cells—which can be derived from bone marrow or umbilical cords—into the bloodstream of rats with damaged spinal cords. The stem cells turned into neurons at a significant rate. The result was improved movement in the animals. Because the delivery method was non-invasive—it involved no surgery—Kocsis



Chemical clues—Heather Mallozzi, a research associate at the West Haven VA Medical Center, performs immunohistochemistry to look for specific proteins in injured spinal cord tissue.

believes it holds promise for eventual human trials. A twist on this approach is now in the works in the West Haven lab: genetically engineering the stem cells to produce “trophic factors,” or growth-stimulating proteins, which should further boost regeneration.

Through consortium funding, Kocsis and colleagues are also continuing their longstanding work on remyelination—restoring the waxy insulation around damaged axons so they can once again conduct electrical impulses. The team is one of many worldwide that are experimenting with olfactory ensheathing cells, which can be harvested from the lining of the nose. Transplanted into the spinal cord of rats, the cells have triggered remyelination and axon regrowth in several experiments.

It’s hard to predict right now which therapies will emerge as the most practical for human trials, but Kusiak believes the

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Veterans and SCI

- Between 225,000 and 296,000 people in the U.S. have a spinal cord injury or disorder that significantly affects their daily lives. Of these, more than 25,000 are Veterans who receive care in VA, making VA the largest integrated health care system in the world for spinal cord care.
- Pending the development of effective regenerative therapies, spinal cord injury is a lifelong, incurable condition that requires ongoing management and preventive care to minimize complications such as pressure ulcers, obesity and respiratory problems.
- Most spinal cord injuries occur well before retirement age—average age at onset is 39 years. More than half of Veterans with spinal cord injury have been injured for more than 20 years, and about 80 percent are 50 years of age and older.

Source: www.queri.research.va.gov/about/factsheets/sci_factsheet.pdf

Is chocolate good for your heart?

Go ahead, eat that chunk of dark chocolate—you may be doing your heart a favor.

That's the upshot of a new study by a group with VA, Brigham and Women's Hospital, and Harvard Medical School. Led by Luc Djoussé, MD, MPH, DSc, the researchers examined chocolate-eating habits and the prevalence of coronary heart disease among nearly 5,000 adults ranging in age from 25 to 93.

Those who reported eating chocolate five times per week or more were about half as likely to have heart disease, compared with those who didn't partake at all. For those who ate less chocolate, up to four servings a week, there was still a 26-percent reduction in heart disease. The researchers adjusted for various factors that could have influenced the results, such as age, smoking, exercise or hereditary heart risk.

The results appeared online in September in the journal *Clinical Nutrition*.

While the study didn't distinguish among different types of chocolate—dark chocolate versus more sugary types—it did find that eating non-chocolate candy was associated with an increase in heart disease.

Djoussé says dark chocolate is rich in beneficial natural chemicals called flavonoids, which act as antioxidants. The food has been shown in other research to help lower blood pressure, prevent excess blood clotting and lower inflammation. A related study published earlier this year by Djoussé's group found yet further cardiovascular benefits—less atherosclerotic plaque among those who ate more chocolate.

The VA-Harvard researcher notes that the health effects of chocolate are not due



solely to its antioxidant properties. He points out that red wine, also an antioxidant, does not lower blood pressure. So there are other chemical factors at play.

Even though the new study results would seem to suggest “the more the better” when it comes to chocolate, Djoussé urges moderation. “At this point, for cardiovascular benefits, moderate consumption of two to three servings per week would be reasonable,” he says.

A Harvard colleague of Djoussé's, Murray Mittleman, MD, DrPH, recently led a study of nearly 32,000 Swedish women that also showed a cardiovascular benefit to chocolate—specifically, in cutting the risk of heart failure. He, too, warns against excessive consumption: “You can't ignore that chocolate is a relatively calorie-dense food, and large amounts of habitual consumption are going to raise your risks for weight gain. But if you're going to have a treat, dark chocolate is probably a good choice, as long as it's in moderation.” —

Training course on colorectal cancer

Colorectal cancer (CRC) is the third most common cancer in the U.S. and the third leading cause of cancer-related deaths. In the VA health care system, there are some 4,000 new CRC cases each year.

Screening, diagnostic testing and early intervention can go a long way toward saving lives. To help ensure state-of-the-art care in this area, VA Research recently spearheaded a partnership with other VA offices and the National Coalition for Health Professional Education in Genetics (NCHPEG) to launch a computer-based training course for clinicians on genetics and colorectal cancer. The three-hour course is now in use in the VA system and will be posted on the NCHPEG website in spring 2011 for use by non-VA clinicians.

VA Chief Research and Development Officer Joel Kupersmith, MD, says the collaborative effort “has yielded an educational tool that enables clinicians to bring the benefits of genetic information to the bedside.”

As many as 35 percent of CRCs are related to family history, and up to 7 percent involve specific hereditary cancer syndromes. One example is Lynch Syndrome, named after Henry Lynch, MD, who collaborated with VA Research on the new training module.

According to Laurence Meyer, MD, PhD, associate chief of staff for research at the Salt Lake City VA Medical Center and national director of genomic medicine for VA Patient Care Services, “It will be very useful to have in-house VA materials to refer to” as VA hires more genetics counselors and expands its services in this area. He says the new training course will be part of a larger array of educational tools for clinicians—as well as for Veterans and their family members—on the role of genes in colorectal cancer and other diseases. —

Polytrauma conference—Researchers and other experts from VA, the Department of Defense, and the National Institutes of Health, along with other federal and academic partners, will meet in Bethesda, Md., on Dec. 7 and 8 for the “3rd Annual Traumatic Spectrum Conference: Emerging Evidence on Polytrauma for Warrior Recovery and Reintegration.” From March 2003 through March 2010—the latest period for which statistics are available—nearly 1,800 inpatients with severe multiple injuries were treated at VA’s four main polytrauma rehabilitation centers, which are the hub of a larger network of polytrauma care. To read about the polytrauma-care experience of Marine Lance Cpl. Kyle Anderson, seen in the photo with VA physical therapist Wendi Slattengren, visit www.va.gov/health/NewsFeatures/20100924a.asp. For more information about VA polytrauma care in general, visit <http://www.polytrauma.va.gov>.



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improved care for their patients,” says VA Chief Research and Development Officer Joel Kupersmith, MD, himself a cardiologist. “The results are especially applicable for VA’s patient population.”

Traditionally, doctors, pharmacists or nurses monitor patients on warfarin, sold as Coumadin, over several clinic visits. They test how fast the blood clots and adjust the dose accordingly: Too low a dose won’t prevent clots, and blood flow to the heart, brain or other areas of the body could be blocked. Too high a dose could lead to dangerous internal bleeding.

Patients also have the option of tracking their own response at home using handy blood analyzers known as INR monitors. INR stands for international normalized ratio—a measure of how fast the blood clots. Patients do a finger-stick, apply a small amount of blood to a test strip, and feed the strip into the device. The procedure resembles the one used by people with diabetes to check their blood sugar. Patients can then call in the results to their provider and get advice on dosing without having to come into the clinic. In some cases, they can even set the proper dose of warfarin on their own.


The authors of the VA study expected home monitoring to work better than clinic monitoring. One reason is that self-testing can be done more frequently—say, weekly, as compared with the typical monthly schedule of even the best clinic-based monitoring. As a result, off-target INR values can be adjusted more quickly.

Somewhat surprisingly, the VA study found little difference between weekly self-testing and monthly “high-quality” INR testing by clinic-based care teams. The main outcome measures were strokes, major bleeding incidents, and death.

“The data show that any extra benefit of patient self-testing in terms of reducing major events would be modest at best,” says study co-leader David Matchar, MD, an internist with the Durham VA Medical Center, Duke University School of Medicine, and Duke-NUS Graduate Medical School.

The study found that self-testing at home, however, did pose some advantages in other areas: It boosted patients’ satisfaction with warfarin therapy and increased the amount of time they were in the appropriate dose range.

Study co-leader Alan Jacobson, MD, a cardiologist and researcher with VA and Loma Linda University School of Medicine, suggested that one take-home message of the study is that “patients who are being systematically monitored—no matter by what means—are likely to have good outcomes.” He said self-monitoring may be a good option for many patients, especially for those who live in rural areas or who otherwise have difficulty getting to a clinic.

The study was sponsored by VA’s Cooperative Studies Program (www.research.va.gov/programs/csp). 

Inside: Super-charging research on spinal cord injury

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critical in helping Veterans avoid long-term health problems.

As to the reasons underlying the connection between PTSD and medical illnesses, Frayne offers several theories.

“One possibility,” she says, “is that PTSD itself leads to increased risk of medical illness. One way this could happen is that PTSD can cause changes in the neuroendocrine system in the body, which might affect other biological processes.”

Another possibility is that “PTSD itself does not cause medical conditions, but that whatever caused the PTSD also simultaneously caused the medical condition.” An example would be a service member who was exposed to a blast that broke a bone and also caused emotional trauma.

Despite the trends seen in the study, Frayne emphasizes that not all Veterans with PTSD have a greater array of health problems.

“While it’s important to take medical conditions in patients with PTSD very seriously,” she says, “it’s also important not to assume that all returning Veterans have these conditions.”



Picture of progress—Dr. Jeffery Kocsis (left), Heather Mallozzi and Dr. Masanori Sasaki, with VA and Yale University, view in vivo images of neural repair that resulted from cell therapy.

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consortium will speed progress toward that goal. She says she’s gotten excellent feedback on the overall plan from her counterpart at the National Institutes of Health—particularly on the built-in checkpoints that require careful validation by collaborating groups before a potential therapy can advance from rodent to primate testing, and from primates to humans.

The field of spinal cord research is at a crossroads, says Kusiak, and aggressive, wide-reaching approaches are needed more than ever to move discoveries from labs to clinics. She hopes the new consortium will do just that. “It is truly unique to VA,” says Kusiak. “We think it’s a model system for translation.”