



VA Research Currents

Antioxidants show promise in animal research as therapy for pancreatic cancer

Pancreatic cancer is one of the deadliest cancers, with patients rarely surviving beyond five years. The disease responds poorly to chemotherapy and radiation, and surgical removal of the pancreas is a risky, difficult procedure that works for only a small percentage of patients.

Now, research by an Iowa City team including VA surgeon Joseph Cullen, MD, suggests that antioxidant therapy may pose a potent yet non-toxic therapy that one day could brighten the outlook for veterans and others with the disease.

In a study published in *Human Gene Therapy* in Jan. 2006, Cullen and colleagues used an adenovirus vector to deliver a form of glutathione peroxidase—an antioxidant—directly into pancreatic tumors in mice. A

single injection resulted in about a 30-percent total cure rate. In cultures of pancreatic cancer cells, the treatment resulted in up to 95-percent inhibition of tumor growth.

By injecting the adenovirus directly into the tumor—an approach that is relatively novel in medical oncology, said Cullen—the toxic effects of the adenovirus are limited. Adenoviruses or other viruses are often combined with therapeutic molecules and used as transporters because of their ability to invade other cells and express their genetic material.

“The limitation of treatments of this type is toxicity to the surrounding normal tissue—and we’ve seen none of that with these medications,” said

see **PANCREATIC** on next page

Major NIH-VA arthritis study yields mixed findings on popular dietary supplements

A nationwide clinical trial led by a VA investigator and involving nearly 1,600 patients with osteoarthritis of the knee found little benefit overall for the widely used nutritional supplements glucosamine and chondroitin sulfate. The findings, reported in the Feb. 23 *New England Journal of Medicine*, did suggest, however that the supplements may help those with more severe pain.

“The dietary supplements were not effective in treating knee pain due to osteoarthritis in the general study population, but the combination of glucosamine and chondroitin appears to be effective in the subgroup with moderate to severe pain,” said lead investigator Daniel Clegg, MD, chief of rheumatology at the University of Utah and the George E. Wahlen VA Medical Center in Salt Lake City.

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HSR&D is partner in new open-access journal

Implementation Science (www.implementationscience.com) is a new online, open-access journal supported in part by VA’s Health Services Research and Development Service. The journal is published by BioMed Central, which publishes more than 140 open-access journals on the Web. More than half these journals, including *Implementation Science*, are “independent,” in that the researchers who launch them have editorial control. *Research Currents* interviewed Brian Mittman, PhD, of the VA Greater Los Angeles Healthcare System, who is co-editor-in-chief of the new journal along with Martin Eccles, PhD, a British health-services investigator. An excerpt from the interview appears below. For the full text, go to www.research.va.gov/news/research_highlights/mittman-06.cfm.

RC: Why is there a need for a new health-services research journal?

BM: Many of our [planning] discussions surrounded the fact that there are existing journals that publish this kind of work, but for those journals it is a secondary field. The traditional, or conventional, health-services journals cover a very broad range of topics, and implementation science, or quality-improvement research, is only one of them. There’s also a set of journals

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ARTHRITIS (cont. from pg. 1)

The Glucosamine/Chondroitin Intervention Trial (GAIT)—funded by the National Institutes of Health and conducted at 16 clinical sites—was the most rigorous trial to date of the dietary supplements, which are taken either alone or in combination by millions of arthritis sufferers in the United States, Europe and elsewhere. Several studies have shown benefits for the supplements, but according to a major analysis published in the *Journal of the American Medical Association* in 2000, some of those results may have been affected by bias or poor methodology. Questions also exist as to which specific forms of the supplements are best.

One control group in the study received placebo, while another received 200 mg per day of the pain-reliever celecoxib. Three intervention groups received either glucosamine, chondroitin sulfate, or both supplements together. After six months, the study team checked how many patients in each group reported a 20-percent or greater reduction in pain, using a well-established arthritis-pain questionnaire.

Two-thirds (66.6 percent) of the patients on the supplement combination showed a 20-percent or greater improvement. But this result was almost matched by placebo, which had

a response rate of 60.1 percent. The difference was not statistically significant. The individual supplements were slightly less effective than the combination. Celecoxib, on the other hand, yielded a response rate of 70.1 percent, a statistically significant improvement over placebo.

However, when the researchers looked at the results based on patients' pain levels—1,229 patients had been classified at the study's outset as having mild knee pain, and 354 patients as having moderate to severe pain—the treatment outcome was different. Among those with moderate to severe pain, the supplement combo had a response rate of 79.2 percent, compared to 54.3 percent for placebo. The supplements statistically outperformed celecoxib, which had a response rate of 69.4 percent for this subgroup. For those with mild to moderate pain, celecoxib retained its edge, with a response rate of 70.3 percent, versus 62.9 percent for the supplement combo and 61.7 percent for placebo.

Study coauthor Domenic Reda, PhD, acting director of VA's Cooperative Studies Program Coordinating Center in Hines, Ill., says further research may help sort out the real benefits of glucosamine and chondroitin sulfate.

“For the moderate to severe group, the combination was quite effective, both clinically and statistically,” he noted. “However, only 20 percent of the patients had moderate to severe pain, so we believe the results need to be replicated in a larger trial.” ■

PANCREATIC (cont. from pg. 1)

Cullen, chief of the Surgical Service at the Iowa City VA Medical Center.

Glutathione peroxidase, like vitamins C or E and other antioxidants, breaks down lipid hydroperoxides, or rancid fats. These free radicals are thought to play a role in tumor growth, and Cullen's recent findings confirm that they are indeed critical in pancreatic cancer. Since publishing their findings on glutathione peroxidase and another molecule, manganese superoxide dismutase, Cullen and his team have gone on to experiment with other antioxidants that appear to be even more effective.

“Some of our newer results are even more promising,” said the VA investigator. He explained that different antioxidants target different parts of cancer cells, and it's a question of finding which compound has the greatest inhibitory effect.

“The antioxidants work in different parts of the cells, and as a result, some antioxidants work better in some cancers versus others,” he said. “We're homing in on which antioxidant is going to be most effective in pancreatic cancer.”

Lead author on the *Human Gene Therapy* paper was Dr. Jingru Liu of the University of Iowa College of Medicine, where Cullen is a professor. The work was funded by VA, the National Institutes of Health, and the Susan L. Bader Pancreatic Cancer Research Fund. ■

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Seattle ERIC offering research methodology courses

The next Summer Session of the Seattle Epidemiology, Research and Information Center will take place June 26 – 30, 2006, featuring courses in epidemiology, biostatistics and clinical research methods. Tuition is waived for VA employees. For details visit www.eric.seattle.med.va.gov or contact program manager Nancy Aziz at (206) 277-4376 or nancy.aziz@va.gov.

Neuromuscular stimulation helps restore walking ability in chronic stroke patients

Functional neuromuscular stimulation (FNS)—a method of electrical stimulation that uses electrodes implanted in weak or paralyzed muscles and connected to an external controller worn on a belt—can significantly enhance the walking ability of chronic stroke patients, reported VA researchers and colleagues in the January issue of *Stroke*.

Senior author Janis J. Daly, PhD, MS, and her team at the Cleveland VA Medical Center and Case Western Reserve University studied 32 men and women who had suffered a stroke more than a year earlier. One group was treated four times weekly with a regimen of what are considered the best available stroke therapies: body-weight-support treadmill training, overground walking, and coordination exercises. The therapies were individualized for each patient.

The other group received the same treatment, but with the addition of

FNS, applied to eight electrodes implanted at key points in weak or paralyzed leg muscles. The electrodes are placed during a half-day outpatient procedure, with patients under conscious sedation. The electrodes are removed when the course of FNS therapy has ended.

After 12 weeks, the 29 patients remaining in the trial were assessed primarily with the Tinetti gait scale, which measures components such as gait initiation, trunk alignment, step continuity and swing-limb floor clearance. Nine of those in the FNS group had gains of 2 to 6 points, while only two participants in the non-FNS group had a gain of 2 or more points. There were 53 reports of functional milestones for the FNS group—such as being able to walk a mile or do errands—compared to only 11 in the non-FNS group.

“We showed that coordinated gait components can be regained in re-

sponse to FNS by chronic stroke survivors with otherwise persistent gait deficits,” said Daly, director of VA’s Stroke Motor Control and Motor Learning Laboratory; associate director of education at the Cleveland FES Center; and an associate-rank professor in the department of neurology at Case Western Reserve University School of Medicine.

Daly described other functional and quality-of-life milestones for FNS patients that were reported in the recent *Stroke* article.

“One patient was able to return to work as a fifth-grade elementary teacher,” she said. “Prior to our study, she had not been able to do that. Conventional therapies had failed her in that regard.” Daly cited another patient who progressed from being wheelchair-dependent in an assisted-living environment to being ambulatory in his own home and community.

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HSR&D is partner in new online, open-access journal (cont. from pg. 1)

that we label the “quality and safety” journals, but these have a more applied orientation and target a different audience. The highly technical, theoretical, methodological papers that any field needs did not have a home.

RC: What is VA’s role in the project?

BM: HSR&D is providing in-kind support, and many of the planning- committee and editorial-board members are HSR&D investigators. CIDER [VA’s Center for Information Dissemination and Education Resources] in Boston serves as the editorial office for the journal. This in an international journal without any formal sponsor, but VA is recognized as the primary supporting organization.

RC: Why an online, open-access journal?

BM: We’ve seen evidence of a vicious cycle in journal publishing—as print subscription fees for institutions go up, libraries will review their subscriptions and identify a few where the readership and use of the print version are too

small to justify the subscription. As they begin to pull out, publishers find it more difficult to support the print version and they move to online-only. BioMed Central has been attracting a number of professional associations that have moved away from a print publisher to online-only because of the economics.

It makes economic sense for our readers, too. This field, perhaps more than others, is international in scope, and we expect a significant number of readers from developing countries where the library budgets just don’t allow for a costly print journal. That was one of our considerations. Another advantage to an online journal is that the amount of space needed to fully document our interventions is typically greater than that required to document a new drug or surgical procedure. Some of the management and quality-improvement programs we design are multifaceted and require a lot of space to describe. Traditional print journals do not allow for that level of documentation. ■

Career milestones

Eugene Oddone, MD, received VA's Undersecretary's Award for Outstanding Achievement in Health Services Research at last month's VA Health Services Research and Development national meeting in Washington, DC. Oddone, director of the Durham-based VA Center of Excellence for Health Services Research in Primary Care, was cited for his innovative studies aimed at improving quality of care; reducing racial disparities in health care; and promoting self-management among chronic disease patients. He is credited with developing one of VA's most successful interdisciplinary research groups and increasing research collaboration between the Durham VA Medical Center, the University of North Carolina at Chapel Hill, and Duke University.

David J. Casarett, MD, MA, is the first recipient of the William A. Nelson Award for Excellence in Health Care Ethics, from VHA's

National Center for Ethics in Health Care. Casarett, a physician at the Philadelphia VA medical center and researcher at the Center for Health Equity Research and Promotion, is widely known for his studies on how patients make healthcare decisions at the end of life, and has been a vocal advocate for veterans' access to hospice care.

Michael E. Charness, MD, chief of staff at the Boston VA Healthcare System, was named to a four-year term on the National Advisory Council of the National Institute on Alcohol Abuse and Alcoholism.

STROKE (cont. from pg. 3)

Studies such as Daly's are increasingly challenging the notion that stroke survivors are unable to recover movement or coordination after more than six months or so. Scientists believe therapies such as FNS may help the brain "rewire" itself, even up to more than a year after stroke, with undamaged neurons taking over functions that had previously been handled by other parts of the brain and

nervous system. Previous research by Daly's group has shown that such gains can be maintained for at least six months after treatment. She hopes to conduct further studies to document longer-term benefits, which she said she has seen often in former FNS patients who visit her clinic.

According to Daly, the potential benefits of FNS outweigh the expense—about \$4,960 in incremental costs per patient—and the system could be feasible in the future for routine use in rehabilitation settings.

"Any experienced therapist could learn how to use the system," said the researcher, who has designed templates to guide clinicians in tailoring the stimulation pattern for each muscle.

A second senior author on the study was Robert L. Ruff, MD, PhD, chief of neurology for VA and acting director of VA's Rehabilitation Research and Development (RR&D) Service. The work was funded by RR&D. ■

VA Research Week

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