Iron seen in brain immune cells of Alzheimer’s disease patients

By Bruce Goldman

Examining postmortem brain tissue from Alzheimer’s disease patients, School of Medicine investigators identified what appears to be iron-containing microglia — specialized scavenger cells that sometimes become inflammatory — in a particular part of the hippocampus, a key brain structure whose integrity is critical to memory formation.

In postmortem brain tissue from people not diagnosed with Alzheimer’s, neither the iron deposits nor the scavenger cells engulfing them were present in that brain region.

The findings, recounted in a study now available online in *Neurobiology of Aging*, suggest that high-field magnetic resonance imaging, in particular an advanced version called 7T MRI that uses a powerful 7-Tesla magnet, could someday be used to diagnose and monitor Alzheimer’s patients earlier than is currently possible.

The findings also add a new suspect to the Alzheimer’s disease lineup. A long-held hypothesis holds that the most notorious feature of Alzheimer’s disease, amyloid plaques, is the main cause of the disorder. These plaques are extracellular aggregations of a small protein called beta-amyloid that are prominent in diseased patients’ brains, as well as in mouse models of the disease. The other most cited key player is tau, another Alzheimer’s-associated protein that abnormally aggregates into threadlike tangles inside nerve cells. Surprisingly, in the brain region of interest there was no consistent overlap between the iron-laden microglia and the amyloid plaques or tau.

“Microglia are the brain’s immune cells,” said Michael Zeineh, MD, PhD, assistant professor of neuroradiology and the study’s lead author. In their resting state, they’re like police officers in the doughnut shop, sitting down and relaxing, their guns holstered, but keeping their eyes open while placidly munching on whatever cellular debris or stray cell necrotic bits they come in contact with. “We now know that even exposure to small amounts of radiation from computed tomography scanning is associated with cellular damage,” said Patricia Nguyen, MD, one of the lead authors of the study and an assistant professor of cardiovascular medicine at Stanford.

“Whether or not this causes cancer or any negative effect to the patient is still not clear, but these results should encourage physicians toward adhering to dose-reduction strategies.”

The study was published online July 22 in the *Journal of the American College of Cardiology: Cardiac Imaging*, Won Hee Lee, PhD, and Yong Fuga Li, PhD, both postdoctoral scholars, are the study’s other lead authors.

“The use of medical imaging for heart disease has exploded in the past decade,” said Joseph Wu, MD, senior author of the study. Wu, a professor of medicine and of radiology, is director of the Stanford Cardiovascular Institute. “These tests expose patients to a nontrivial amount of low-dose radiation. But nobody really knows exactly what this low-dose radiation does to the patient. We now have the technology that allows us to look at very subtle, cell-level changes.”

Along with the burgeoning use of advanced medical imaging tests over the past decade have come rising public health concerns about possible links between low-dose radiation and cancer. The worry is that in some instances, cell-level changes may spur cells to grow into tumors.

“Legitimate concerns” But there has been limited scientific evidence to date that shows the effects of this low-dose radiation on the body, according to the study. Currently, there is a bill winding its way through Congress to fund more research on the health effects of low doses of radiation from CT scans, which expose the body to low-dose X-ray beams, can damage DNA and create mutations that spur cells to grow into tumors.

Juvenile inmates hospitalized more for mental health

By Erin Digitale

Juvenile inmates are much more likely to be hospitalized for mental health problems than children and teenagers who are not incarcerated, according to a new study from the School of Medicine.

In addition, the hospital stays of these inmates are longer, suggesting that their underlying mental health problems are worse.

The new study, which was published online July 21 in the *Journal of Adolescent Health*, examined almost 2 million hospitalizations of California boys and girls over a 15-year period. Mental health diagnoses were responsible for 63 percent of hospital stays by young people in the juvenile justice system, compared to 19 percent for those not in the system.

Although mental health problems have been previously documented in juvenile inmates, the study’s large size and assessment of hospital stays gives new insight into the widespread nature and severity of their mental health diagnoses.

“We know young people in the juvenile justice system have a disproportionate burden of mental illness,” said Michael Zeineh, MD, PhD, assistant professor of neuroradiology and the study’s lead author. “Whether or not this causes cancer or any negative effect to the patient is still not clear, but these results should encourage physicians toward adhering to dose-reduction strategies.”

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Antioxidants help treat skin-picking disorder in mice, researcher says

By Ruthann Richter

Two antioxidant supplements are effective in treating skin-picking disorder in mice, according to a study led by a School of Medicine researcher.

The findings suggest that people with the potentially serious disorder might benefit from this therapy.

An estimated 4 percent of the population — or about 1 in 25 — suffer from skin-picking disorder, in which repeated, compulsive picking or scratching of the skin can lead to severe disfigurement and life-threatening infection. Skin picking is also common among laboratory mice, which may develop potentially fatal ulcerative dermatitis, skin lesions, caused by excessive grooming.

The condition is the single leading avoidable cause of hospital stays by young people in the juvenile justice system, compared to 19 percent for those not in the system.

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Low levels of hormone linked to social deficit in kids with autism

By Erin Digitale

A brain-chemistry deficit in children with autism may help to explain their social difficulties, according to a new finding from the School of Medicine.

The research team found a correlation between low levels of vasopressin, a hormone involved in social behavior, and the inability of autistic children to understand that other people’s thoughts and motivations can differ from their own.

The research was published July 22 in PLOS ONE.

“Autistic children who had the lowest vasopressin levels in their blood also had the greatest social impairment,” said the study’s senior author, Karen Parker, PhD, associate professor of psychiatry and behavioral sciences.

The findings raise the possibility that treatment with vasopressin might reduce social problems for autistic children who have low vasopressin levels, a hypothesis that Parker and her team are now testing in a clinical trial. However, the new research also showed that children without autism can have low vasopressin levels without displaying social impairment, Parker noted; in other words, autism is not explained by a vasopressin deficit alone.

Investigating vasopressin

Autism is a developmental disorder that affects 1 out of every 68 children in the United States. It is characterized by social and communication deficits and repetitive behaviors. The new study examined a social trait that psychologists call “theory of mind”: the ability to understand that others have different perspectives. Poor “theory of mind” makes it harder for people with autism to empathize and form relationships with others. Vasopressin is a small-protein hormone that is structurally similar to oxytocin. Like oxytocin, it has roles in social behavior. Vasopressin also helps regulate blood pressure.

In the new study, the researchers first verified that vasopressin levels accurately reflected vasopressin levels in the brain by measuring the hormone’s levels simultaneously in the brain and cerebrospinal fluid of 28 people who were having the fluid collected for medical reasons.

They then recruited 159 children ages 3-12 for behavioral testing. Of these children, 77 had autism, 47 did not have autism but had a sibling who did, and 35 were typically developing children with no autistic siblings. All of the children completed standardized psychiatric assessments of their neurocognitive abilities, social responsiveness, theory of mind, and ability to recognize other people’s emotions, which is known as affect recognition. All children gave blood samples that were measured for vasopressin.

In all three groups, children had a wide range of vasopressin levels, with some children in each group having low, medium, and high levels. Being socially withdrawn, however, had similar scores on theory of mind tests regardless of their blood vasopressin level, but in children with autism, low blood vasopressin was a marker of low theory of mind ability.

Testing the hormone’s effects

Parker and her collaborator, Antonio Hardan, MD, professor of psychiatry and behavioral sciences, are now investigating whether vasopressin treatment improves social abilities in children with autism. In some cases, vasopressin was found to be beneficial, but in others, the hormone is beneficial only for autistic children who start with low vasopressin levels or whether it might benefit all children with autism.
Women's immune system genes operate differently than men's, study finds

By Jennie Dusheck

A new technology for studying the human body's vast system for toggling genes on and off reveals that genes associated with the immune system toggle more frequently, and those same genes operate differently in women and men.

"The immune system is the complete set of all the switches that turn genes on and off in real time," said Chang. "We asked, 'How different or similar are people? This is different information than the measure of just how many genes they have acted on right now.' Even in identical twins, he said, one twin could have an autoimmune disease and the other could be perfectly well. And, indeed, the team reported that over a third of the variation in gene activity was not connected to a genetic difference, but rather to the different settings they have for the same gene.

The sex factor

Across the 12 volunteers, 7 percent of the genes were switched on in different patterns from person to person. For each person, these patterns persisted over time, like a unique fingerprint. "But the single greatest predictor for genes' tendency to turn on and off was the sex of the person," said Chang. "sex was far more important than all the other things we looked at, perhaps even combined."

When the team measured gene activity levels from 30 of the top 500 genes the researchers expected would show that turn genes on and off in real time. Other Stanford-affiliated authors of the paper are Kun Qu, PhD, senior research associate; Lisa Zaba, MD, PhD, instructor of dermatology; Paul Giresi, PhD, former postdoctoral scholar; Rui Li, life science research assistant; Michelle Longmire, MD, clinical instructor of dermatology; Youn Kim, MD, the Joanne and Peter Haas Jr., Professor for Cutaneous Lymphoma Research; and William Greensfeld, PhD, assistant professor of genetics.

This work was supported by the National Institutes of Health, the Howard Hughes Medical Institute, the Stanford Cancer Center, the Scleroderma Research Foundation and the Haas Family Foundation.

Stanford's Department of Genetics also supported the work.  

Heart-health app launches in UK, Hong Kong

By Tracie White

The MyHeart Counts app, an iPhone app that allows users to learn about their own heart health while also participating in a large-scale study designed by cardiologists at the School of Medicine, became available in Hong Kong on Aug. 6. Those participating in the fitness test, as well as a newsfeed section that provides updates on heart health news. The new version of the app will include a single study. The new version of the app will include a newsfeed section that provides updates on heart health news. The new version of the app will include a newsfeed section that provides updates on heart health news. "We would like millions of participants," said McConnell. "We would like millions of participants."

The new version of the app focuses on empowering participants with more feedback about their individual behaviors and risk, based on the American Heart Association's "Life’s Simple 7" recommendations. "We'll now be providing feedback about physical activity, diet, blood pressure and cholesterol levels," said Michael McConnell, MD, professor of cardiovascular medicine and principal investigator for the study. Researchers are reporting that they have collected the most data ever on the 6-minute walk fitness test for a single study. The new version of the app will include information comparing the user's data to others participating in the fitness test, as well as a newsfeed section that provides updates on heart health news. The researchers expect the new version of the app to be released in late summer. For more information about the app, visit https://myheartcounts.stanford.edu.  

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continued from page 2

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The MyHeart Counts app has garnered more than 41,000 users who have agreed to participate in a study of cardiovascular health.

Howard Chang is the senior author of a study revealing that immune system genes switch on and off differently in women and men, and that the source of that variation is not primarily in the DNA.

The new study, which was published July 29 in the new journal Cell Systems, took ordinary blood samples from 12 healthy volunteers to measure how certain genes are switched on and off, and how that measure varied from individual to individual. Chang's team also looked at regulatory elements that control gene-switching activity at different times in the same volunteers. The researchers looked exclusively at specialized immune cells called T cells, which are easy to isolate from a standard blood sample and easy for volunteers to supply and which are an important component of the immune system.

One goal of the study was to establish a baseline measure of how much genetic activity varies among healthy people. That way, when other researchers make similar measures in people who are ill, they’ll have an idea of what is normal. Another goal was to refine the new technique for measuring gene activity, "In the past," he said, "people needed a huge number of cells to do this kind of measurement. You’d actually need a pound of flesh to get certain rare cell types. So you can’t get that out of a live person — and certainly not one that’s right here.

Examining the source

Researchers probed by growing cells in the lab so they had enough cells to study. "But, continued Chang, "you are studying copies of copies; you aren’t studying the original cells anymore. Those months of being grown in the lab completely changes how the cells are behaving and so you are no longer looking at the person. How the laboratory cells behave has nothing to do with what the person just ate, whether they had a fight with their girlfriend or whether they had an infection," said Chang. With lab-grown cells, the cells haven’t experienced any of those things, all of which can alter the regulation of individual genes.

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Researchers at the School of Medicine have identified a cell type in the liver of mice that can both self-renew and make new liver cells. The discovery solves a long-standing mystery as to how the organ, which is responsible for many metabolic processes, maintains itself when liver cells, most of which are called hepatocytes, grow old and die.

“There’s always been a question as to how the liver replaces dying hepatocytes,” said professor of developmental biology Roel Nusse, PhD. “Most other tissues have a dedicated population of cells that can divide to make a copy of themselves, which we call self-renewal, and can also give rise to the more specialized cells that make up that tissue. But there never was any evidence for a stem cell in the liver.”

Researchers have assumed instead that mature hepatocytes would themselves divide to replace a dying neighbor. However, these cells have an abnormal make up that tissue. But there never was any evidence for a stem cell in the liver.

Wang and Nusse are found adjacent to the central vein and, as such, must have access to the blood supply. Wang and Nusse identified these cells when they observed that a large population of cells approximately 300 times larger than the normal cell population was situated adjacent to the central vein in the liver of mice, the possibility that there is more than one kind of hepatocyte in the liver could be the enhanced ability to quickly grow old and die.

“People in the field have always thought of hepatocytes as a single cell type,” said Wang. “And yet the cell we identified is clearly different from other cells in the liver. Maybe we should accept that there may be several subtypes of hepatocytes, potentially with different functions.”

Wang and Nusse identified these cells around the central veins by looking in mice for cells anywhere in the organ that expressed a protein called Aix2. The protein is produced by cells in response to Wnt signaling, and its presence is a hallmark of the Wnt signaling pathway. These cells were also characterized by their expression of the KLRB1 gene, which regulates the activity of immune cells.

Nusse is the senior author of the work, which was published Aug. 5 in *Nature*. He is also a member of the Stanford Cancer Institute, a Howard Hughes Medical Institute investigator. First author Ash Alizadeh, MD, an assistant professor of gastroenterology and hepatology at the University of California-San Francisco, led the research as a visiting scholar in Nusse’s lab.

The liver is a large, multi-lobed organ that plays a vital role in filtering toxins from the blood. It also makes digestive enzymes and is involved in many important metabolic processes. A central vein carries blood from one side of the liver to the other, and the stem cells identified by Wang and Nusse are found adjacent to these veins.

**Abundance of chromosomes**

Until now, it’s been thought that there was just one class of hepatocytes in the liver. Most of these mature cells are diploid, meaning they have more than the normal two copies of each chromosome. Although these cells divide and maintain the capacity to divide, it can do whatever it wants with its genome, said Nusse. “Red blood cells, for instance, have no DNA. Muscle cells have many copies of each chromosome.” An advantage of making extra copies of chromosomes could be the enhanced ability to quickly make large amounts of particular proteins, for example.

A database compiled by Ash Alizadeh and his team links gene expression patterns and immune system response to patient survival rates in nearly 18,000 cases of 39 types of cancers.

By Krista Conger

Physicians have long sought a way to accurately predict cancer patients’ survival outcomes by looking at biological details of the specific cancers they have. But despite concerted efforts, no such clinical crystal ball exists for the majority of cancers.

Now, researchers at the School of Medicine have compiled a database that integrates gene expression patterns from 39 types of cancer from nearly 18,000 patients with data about how long those patients lived.

Combining the data from so many people and cancers allowed the researchers to overcome reproducibility issues inherent in smaller studies. As a result, the researchers were able to clearly see broad patterns that correlate with poor or good survival outcomes. This information could help them pinpoint potential therapeutic targets.

“We were able to identify key pathways that can dramatically stratify survival across diverse cancer types,” said Ash Alizadeh, MD, PhD, an assistant professor of medicine and a member of the Stanford Cancer Institute. “The patterns were very striking, especially because few such examples are currently available for the use of genes or immune cells for cancer prognosis.”

In particular, the researchers found that high expression of a gene called FOXM1, which is involved in cell growth, was associated with a poor outcome in many of the cancers. In addition, the expression of the KLRB1 gene was upregulated in the tumor, which modulates the body’s immune response to cancer, and seemed to confer a protective effect.

A paper describing the research was published online July 20 in *Nature Medicine*. Alizadeh shares senior authorship with Ludan Zhao and research assistant Andrew Gentles, PhD, share lead authorship of the paper.

The new database, which will be available to physicians and researchers, is called PRECOG, an abbreviation for “prediction of cancer outcomes from genomic profiles.”

In addition to identifying potentially useful gene expression patterns in cancers, the researchers also used Cibersort, a recently published technique developed by Newman in Alizadeh’s laboratory, to determine the composition of white blood cells that differ between cancer and normal cells and deduces the cell types from genes expressed in the bulk tumor — a process that Newman likens to analyzing a smoothie to identify which fruits and vegetables are present or absent in individual component fruits and vegetables.

“We were able to infer which immune cells are present or absent in individual solid tumors, to estimate the prevalence and to correlate that information with patient survival,” said Newman. “We found you can even broadly distinguish cancer types just based on what kind of immune cells have infiltrated the tumor.”

**Putting it all together**

Researchers have tried for years to identify specific patterns of gene expression in cancer that could predict outcomes that differ from those in normal tissue. By doing so, physicians would be enabled to develop drugs to reduce the risk of cancer or to personalize antibody treatments for patients who have a high risk of recurrence.

To this end, the researchers developed a new tool that can be applied to a broad range of cancers and can be used to determine the metabolic processes that are altered in cancer cells. The tool, called Cibersort, allows researchers to quickly assess the metabolic functions of the liver, allowing them to identify potential new treatments for liver disease.

A new database, which researchers at the School of Medicine have compiled, is called PRECOG. It links gene expression patterns and immune system response to patient survival rates in nearly 18,000 cases of 39 types of cancers.

**Team links gene expression, immune system with cancer survival rates**

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A paper describing the research was published online July 20 in *Nature Medicine*. Alizadeh shares senior authorship with Ludan Zhao and research assistant Andrew Gentles, PhD, share lead authorship of the paper.

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In addition to identifying potentially useful gene expression patterns in cancers, the researchers also used Cibersort, a recently published technique developed by Newman in Alizadeh’s laboratory, to determine the composition of white blood cells that differ between cancer and normal cells and deduces the cell types from genes expressed in the bulk tumor — a process that Newman likens to analyzing a smoothie to identify which fruits and vegetables are present or absent in individual component fruits and vegetables.

“We were able to infer which immune cells are present or absent in individual solid tumors, to estimate the prevalence and to correlate that information with patient survival,” said Newman. “We found you can even broadly distinguish cancer types just based on what kind of immune cells have infiltrated the tumor.”

**Putting it all together**

Researchers have tried for years to identify specific patterns of gene expression in cancer that could predict outcomes that differ from those in normal tissue. By doing so, physicians would be enabled to develop drugs to reduce the risk of cancer or to personalize antibody treatments for patients who have a high risk of recurrence.

To this end, the researchers developed a new tool that can be applied to a broad range of cancers and can be used to determine the metabolic functions of the liver, allowing them to identify potential new treatments for liver disease.

A new database, which researchers at the School of Medicine have compiled, is called PRECOG. It links gene expression patterns and immune system response to patient survival rates in nearly 18,000 cases of 39 types of cancers.
Researchers link HIV susceptibility to class of immune cells

By Bruce Goldman

High diversity among certain cells that help fight viruses and tumors is strongly associated with the likelihood of survival of patients infected with HIV, School of Medicine researchers have found.

“The diversity of these cells, which secrete large amounts of an array of cytokines and granulocytes, is highly predictive of survival across many different types of solid cancers,” said Alizadeh. “We wanted to be able to connect gene expression data with patient outcome for thousands of people at once.”

The research, known as PRECOG, is a machine-learning tool that identifies genes associated with positive or negative clinical outcomes by comparing gene expression profiles of tumor and healthy cells from the same patients. The tool can predict treatment responses for new therapies for patients with advanced cancer.

“If a group of patients respond well to treatment, we can use the tool to identify gene signatures that may be associated with that response,” said Alizadeh. “This allows us to develop targeted therapies for patients who are not responding to standard cancer treatments.”

Additional support for the tool came from a study published in the Journal of Clinical Oncology, which showed that PRECOG could accurately predict treatment responses for patients with melanoma.

“By using machine learning to connect gene expression data with patient outcome, we can identify new therapeutic targets and improve patient outcomes,” said Alizadeh.

The researchers plan to continue developing PRECOG to improve its accuracy and to test its performance in larger patient populations.

“This opens up a new field of research that could lead to significant improvements in cancer care,” said Alizadeh. “We are excited about the potential of this tool to transform the way we approach cancer treatment.”

The research was supported by the National Cancer Institute, the American Cancer Society, the American Society for Clinical Oncology, and the American Society of Clinical Oncology Foundation.

For more information, please visit the PRECOG website at http://pre cog.ca.

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radiation, Wu said. This study’s findings point to the need for more research, he said.

The study isn’t the final word on the risks, because scientists have serious concerns about the exposure to low-dose radiation, but the problem is that it is difficult to prove a causal relationship with cancer, Nguyen said. Even though there are some data suggesting that there is damage occurring at a cellular level, this damage is being repaired. It is the damage that escapes repair, or the cells that are too damaged to repair, that can go on and produce cancer. We can’t track those cells with current technology.

In this study, researchers examined the effects on human participants of low-dose radiation from a wide range of cardiac and vascular CT scans. These imaging procedures are commonly used for a number of reasons, including making sure that patients are not having obstructive coronary artery disease, and for those with aortic stenosis in preparation of transcatheter aortic valve replacement. A CT scan, which is used for imaging and diagnostic procedures throughout the body, exposes patients to at least 150 times the amount of radiation from a single chest X-ray, the study said.

In 2007, the National Cancer Institute estimated that 29,000 future cancer cases could be attributed to the 72 million CT scans performed in the country that year. Increase in DNA damage, cell death

But the reliability of such predictions depends on how scientists measure the underlying link between radiation and cancer in the first place. Nguyen said.

The risk of developing cancer grows with the effects of low-dose radiation — all we know is about high doses from atomic bomb blast survivors — we just assume it’s directly proportional to the dose,” said Nguyen. “We wanted to see if radiation can accidentally happen at the cellular level.... Researchers examined the blood of 67 patients undergoing cardiac CT angiograms. Using such techniques as whole-genome sequencing and flow cytometry to measure biomarkers of DNA damage, researchers examined the blood of patients both before and after undergoing the procedure. Results showed an increase in DNA damage and cell death, as well as a decrease in expression of genes involved in cell repair and death, the study said.

Although most cells damaged by the scan were repaired, a small percentage of the cells died, the study said.

“These findings raise the possibility that radiation exposure from cardiac CT angiography may cause DNA damage to human blood and arteries if damaged cells are not repaired or eliminated properly,” the study said. “Cumulative cell death after repeated exposures may also be problematic.”

A person or an animal should learn more because it’s not a benign effect even at these low dosages,” Nguyen said. “Our research supports the idea that maybe physicians shouldn’t just use these scans. We should eliminate CT scans because they’re obviously important, but you can make it safer by reducing the doses, by getting better machines and technology, and by giving patients something to protect them.”

Nguyen added: “It is important to note that we did not detect any DNA damage in patients receiving the lowest doses of radiation and who were of average weight and had regular heart rates.”

Other Stanford authors are postdoctoral scholars Shawn von der Porten, MD, PhD, Jedd Chamberlain, PhD, and Sang-Ging Ong, PhD; medical student Wan Xiong Hong; research associates Grace Liang and Ivy Nguyen, MD; graduate students Ewen Wang, MD, and Dominik Fleischmann, MD, PhD, professor of bioengineering, of genetics and of medicine; and Lynne Huffman, MD, associate professor of pediatrics; and Paul Wise, MD, professor of pediatrics.

The work was funded by an early career investigator award from Stanford’s Child Health Research Institute, of which Chamberlain, Huffman and Wise are members.

Stanford’s Department of Pediatrics also supported the work.

Study methods

For the study, the researchers selected mice with lesions on the face and limbs — signs of skin picking. Because the condition is painful and potentially fatal, the researchers treated all the mice with a thin film of topical antibiotic and steroidal ointment to relieve their discomfort. A third of the mice received a high dose of NAC in their drinking water. Another third were given drops of glutathione on the nose. (Because mice are nose breathers, they easily inhale the compound.) A control group was given neither of the compounds.

Almost all the animals treated with NAC showed some improvement, though the improvement was slow. By the end of the study, 40 percent were fully cured. Among the animals treated with glutathione, results were more rapid: Within two to four weeks, about half were cured; the other half did not respond. There was no change among the control animals.

Garner believes that NAC works by combating oxidative stress that causes certain cells in the brain to die or become inactive. “Our thought is maybe NAC works because in the brain it is the precursor to glutathione, and the brain has to make glutathione to protect itself against oxidative stress,” he said.

NAC, however, isn’t easily tolerated by many people, causing gastrointestinal distress, he said. Intra-nasal glutathione, on the other hand, may avoid these potential side effects by bypassing the gut and liver delivering the compound directly to the brain. He first presented the results in April to a patient advocacy group.

The sense of excitement from patients, advocates and researchers was palpable,” he said. “This is the first new potential drug for this disorder in years.”

Garner said his next step is to plan a clinical trial in mice to test the theory.

Another Stanford co-author of the study is research associate Jerome Geronimo. The experiments were conducted by researchers at the University of North Carolina Chapel Hill.

The study was funded by the Timothy Foundation, a private nonprofit supporting research in body-focused repetitive behaviors, and by the Division of Laboratory Animal Medicine at UNC-Chapel Hill.

Stanford’s Department of Comparative Medicine also supported the work.

Joseph Garner

The study was supported by the American Heart Association, the National Institutes of Health and the Society of Cardiac and Vascular Radiology.

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substances might come their way. If they encounter something alarming, they whir to action. Activated microglia are like officers with their guns out, they speculates.

Microglia inflamed

The bulk of microglia found in association with iron in the study were in an activated, inflammatory state. Alzheimer’s is increasingly understood to involve brain inflammation, and groups led by Stanford researchers such as neurologists Katrin Andreasson, MD, and Tony Wyss-Coray, PhD; and immunologists Ben Barres, MD, PhD, have previously fingered microglia as potential suspects in the early inflammatory pathology of the disease.

This study adds the new finding that inflamed, iron-associated microglia are present in the hippocampus in Alzheimer’s and are observable by 7T MRI, which could advance the scientific community’s understanding of the disease.

The researchers noted that this was a preliminary study performed on a small number of human brain specimens, which is not typical for brain research. In this case, the specimens were supplied by the study’s senior author, Brian Rutt, PhD.

“Some imaging studies using mouse models of Alzheimer’s disease had revealed the presence in these mice’s brains of tiny, mysterious black dots that could signal the presence of iron, an element that when in the wrong place or in certain chemical forms, can be highly reactive and inflammation-inducing,” Rutt wrote.

Rutt and colleagues used these methods to test the possibility that this iron might be tightly associated with amyloid plaques.

Rutt teamed up with Zeineh to scrutinize the human brain specimens for iron particles. “We wanted to see if there was an association of iron with Alzheimer’s plaques in humans,” Rutt said.

In a series of experiments involving 7T MRI, computational analysis and painstaking laboratory staining techniques, the scientists probed slabs of tissue taken from several of the brains of patients with Alzheimer’s and five control patients. Those microglia were found in five of the patients’ brains — and, most severe ravages of Alzheimer’s.

The Stanford scientists then carefully sectioned the tissue slabs into several hundred ultra-thin sections; incubated the sections with a monoclonal antibody designed to recognize the human brain specimens for iron, which was produced by the study’s senior author, Brian Rutt, and other researchers. They used the resulting stain to illuminate the brain sections, then took images of the brain regions under study.

The researchers cautioned that the stains used in the study wouldn’t have been able to visualize soluble clusters of iron. “We didn’t look at those,” they speculates.

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“We didn’t consistently find the iron associated with plaques as we were expecting,” Rutt said. “We weren’t sure where to look,” Rutt said.

The brains of people who’ve died with Alzheimer’s and Tau is also found throughout the hippocampus, known to incur such swelling and tau; and analyzed the resulting stain sections using iron staining techniques.

“Past research has shown that many dentists do not participate in the program,” the study said. “Many patients seeking dental care except prescribe pain medications.”

The researchers said Medicaid dental care, such as fillings and minor extractions.

The study examined county-level rates of emergency room visits for dental problems: which generally can do little for patients seeking dental care except prescribe pain medications and antibiotics.

“Value of preventive care

As of January 2013, some 45 million Americans were living in regions with shortages of dental care providers, particularly in rural areas. In coming years, the national supply of dentists is expected to decrease further than many current dentists retire.

The large number of visits to emergency rooms for dental problems that could be treated in outpatient clinics, the researchers found, is indicative that our health-care system treats dental care differently than other preventive care when, in fact, dental care should be considered part of a patient’s overall health and well-being,” said Maria Raven, MD, MPH, associate professor of emergency medicine at UCSF and the study’s senior author.

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El-Sayed appointed associate dean for maternal and child health

By Erin Digitale

Maternal-fetal medicine expert Yasser El-Sayed, MD, has been appointed as an associate dean for maternal and child health at the School of Medicine, effective immediately. El-Sayed will focus on obstetrics and related women’s issues, ensuring that pre-conception and pregnancy-related care are fully integrated into the perinatal care at Lucile Packard Children’s Hospital Stanford and into the school’s strategic planning. He joins three other associate deans for maternal and child health who represent faculty affairs, research and global affairs.

“Yasser is known as balanced in his approach: He is good at considering both hospital administrative and School of Medicine perspectives,” said David Stevenson, MD, senior associate dean for maternal and child health, who appointed El-Sayed to the new role. “He is perceived as very responsive, and he’s a really good doctor, as well as a very strong and well-established clinical investigator.”

El-Sayed came to Stanford as an intern in 1990. He is the Charles B. and Ann L. Johnson Professor and director of the Division of Maternal-Fetal Medicine and Obstetrics at the School of Medicine. He is also co-director of the Johnson Center for Pregnancy and Newborn Services and obstetrician-in-chief at Lucile Packard Children’s Hospital Stanford. He will assume his new role with his existing positions. Over the course of his career, El-Sayed has been instrumental in developing and directing the division’s extensive clinical and research programs.

“I think the challenges we face for perinatal care are profound and exciting,” El-Sayed said. “The hospital and university have to work closely together to continue to prove that academic, tertiary medical centers are critical for providing excellent health care to the population. The new team of associate deans speaks to how faculty members in the medical school, with leadership roles at the hospital, can facilitate that kind of productive, visionary dynamic.”

Steven Asch, MD, MPH, and Sang-Ick Chang, MD, MPH, assumed leadership of the Division of General Medical Disciplines in the Department of Medicine, effective June 15. Asch, a professor of medicine, oversees research activities in the division. Chang, a clinical professor of medicine, oversees its clinical activities. Both oversee the division’s educational mission.

Marion Buckwalter, MD, PhD, was promoted to associate professor of neurology and neurological sciences, effective April 1. Her research focuses on genetics and treatment planning.

Norman LaCayo, MD, has been promoted to associate professor of pediatrics, effective April 1. His recent research focuses on gene and protein expression in the leukemia cells of children diagnosed with acute leukemia, with an aim to improve diagnosis and therapy for each patient.

Jason Lee, MD, was promoted to professor of surgery, effective April 1. His research focuses on the development of techniques and devices to repair complex aortic aneurysms. He is analyzing the performance of a variety of endovascular stents, which result in the best patient outcomes. He also teaches physicians worldwide how to use these devices.

Alison Marsden, PhD, was appointed associate professor of pediatrics and of bioengineering, effective July 1. Marsden specializes in pediatric and congenital heart disease, using simulations of blood flow to improve medical device design and imaging and to study the progression of heart disease. She also works with clinical researchers to develop tools for personalized medicine and treatment planning.

Marco Perez, MD, was appointed assistant professor of medicine, effective May 1. Perez is the director of the Stanford Inherited Arrhythmia Clinic, and his research, which focuses on rare and inherited arrhythmias, uses genetics and epidemiology to investigate the causes of cardiovascular diseases.

Maria Polyakova, PhD, assistant professor of health research and policy, has received the 2014 Geneva Association’s Ernst Meyer Prize. This award was given in recognition of her research on risk and health insurance economics. Based in Switzerland, the Geneva Association focuses on insurance economics. Assistant professor of biomedical engineering, was named a 2015 National Geographic Emerging Explorer. As one of 14 honorees, he will receive $10,000. Prakash specializes in developing low-cost scientific tools, such as the Foldscope microscope and a small-scale chemistry kit.

Laura Roberts, MD, the Katharine Dexter McCormick and Stanley McCormick Memorial Professor and chair of psychiatry and behavioral sciences, will be awarded $50,000 as the recipient of the 2015 MacLean Center Prize in Clinical Ethics from the MacLean Center for Clinical Medical Ethics at the University of Chicago. Roberts specializes in ethics, suicide prevention and careers and leadership in academic medicine and medical education.

Ivan Soltész, PhD, was appointed professor of neurosurgery, effective May 1. He is also the vice chair of neurosurgery. His research focuses on developing and utilizing a network of brain regions and the mechanisms of circuit dysfunction in epilepsy. His team has created virtual networks of brain regions using supercomputers, and developed methods for the control of epilepsy.

UNAID ZAMAN, MA, MBChB, MRCP, has received the UK-U.S. Fulbright British Heart Foundation Research Scholar Award. Zaman is a postdoctoral research fellow at Imperial College London and a postdoctoral scholar at the School of Medicine. He will receive about $109,000 to do research at Stanford for one year. He plans to examine treatments for sudden cardiac death.

OF NOTE

Researchers awarded $14 million from NIH for two precision-health projects

By Jennie Dushock

The National Institutes of Health has awarded School of Medicine researchers Teri Klein, PhD, and Russ Altman, PhD, $14 million in funding for two projects that will advance the practice of precision health.

Altman’s project, which is focusing on the development of methods for the control of epilepsy, was awarded $10 million grant from the National Institute of General Medical Sciences to expand the use of personalized medicine by incorporating genetic, genomic and chemical resource, PharmGKB knowledge base, now in its 15th year. PharmGKB provides comprehensive information about how genetics affects drug response in individuals.

“People can react very differently to the same drugs. For example, the enzyme CYP2D6 is involved in metabolizing hundreds of prescription drugs. One drug that CYP2D6 metabolizes is the opiate painkiller codeine, which converts into morphine — the active form of the painkiller. Most people have just two copies of the CYP2D6 gene, but some of us have more. Extra copies of this enzyme result in very fast metabolism, making us ‘poor metabolizers’,” said Klein. She is the Charles B. and Ann L. Johnson Professor and director of the Johnson Center for Pharmacogenomics.

“PharmGKB has organized genetic information derived from nearly 10,000 scientific papers and documented nearly 100 gene/drug associations, dosing guidelines and drug labels. This knowledge base includes, for example, gene/drug associations, dosing guidelines and drug labels. This knowledge base includes, for example, gene/drug associations, dosing guidelines and drug labels.”

The second grant is a three-year, $4 million grant from NIGMS and the National Human Genome Research Institute to Klein and co-principal investigator Yasser El-Sayed, PharmD, chair of pharmaceutical sciences at St. Jude Children’s Research Hospital, for the Clinical Pharmacogenetics Implementation Consortium.

The consortium publishes clinical guidelines that teach health-care providers how to use information about their patients’ genetics to guide and optimize drug prescriptions.