By Scott LaFee
UC San Diego Health Sciences Communication

Though one might think the brains of people who develop Alzheimer's disease (AD) possess building blocks of the disease absent in healthy brains, for most sufferers, this is not true. Every human brain contains the ingredients necessary to spark AD, but while an estimated 5 million Americans have AD – a number projected to triple by 2050 – the vast majority of people do not and will not develop the devastating neurological condition.

For researchers like Subhojit Roy, MD, PhD, associate professor in the Departments of Pathology and Neurosciences at the University of California, San Diego School of Medicine, these facts produce a singular question: Why don’t we all get Alzheimer’s disease?

In a paper published in the August 7 issue of the journal Neuron, Roy and colleagues offer an explanation – a trick of nature that, in most people, maintains critical separation between a protein and an enzyme that, when combined, trigger the progressive cell degeneration and death characteristic of AD.

“It’s like physically separating gunpowder and match so that the inevitable explosion is avoided,” said principal investigator Roy, a cell biologist and neuropathologist in the Shiley-Marcos Alzheimer’s Disease Research Center at UC San Diego. “Knowing how the gunpowder and match are separated may give us new insights into possibly stopping the disease.”

The severity of AD is measured in the loss of functioning neurons. In pathological terms, there are two tell-tale signs of AD: clumps of a protein called beta-amyloid “plaques” that accumulate outside neurons and threads or “tangles” of another protein, called tau, found inside neurons. Most neuroscientists believe AD is caused by the accumulating assemblies of beta-amyloid protein triggering a sequence of events that leads to impaired cell function and death. This so-called “amyloid cascade hypothesis” puts beta-amyloid protein at the center of AD pathology.

Creating beta-amyloid requires the convergence of a protein called amyloid precursor protein (APP) and an enzyme that cleaves APP into smaller toxic fragments called beta-secretase or BACE.

“Both of these proteins are highly expressed in the brain,” said Roy, “and if they were allowed to combine continuously, we would all have AD.”

Continued on next page...
Why Don’t We All Get Alzheimer’s Disease continued...

But that doesn’t happen. Using cultured hippocampal neurons and tissue from human and mouse brains, Roy – along with first author Utpal Das, a postdoctoral fellow in Roy’s lab, and colleagues – discovered that healthy brain cells largely segregate APP and BACE-1 into distinct compartments as soon as they are manufactured, ensuring the two proteins do not have much contact with each other.

“Nature seems to have come up with an interesting trick to separate co-conspirators,” said Roy.

The scientists also found that the conditions promoting greater production of beta-amyloid protein boost the convergence of APP and BACE. Specifically, an increase in neuronal electrical activity – known to increase the production of beta-amyloid – also led to an increase in APP-BACE convergence. Post-mortem examinations of AD patients revealed increased physical proximity of the proteins as well, adding support to the pathophysiological significance of this phenomenon in human disease.

Das said the findings are fundamentally important because they elucidate some of the earliest molecular events triggering AD and show how a healthy brain naturally avoids them. In clinical terms, they point to a possible new avenue for ultimately treating or even preventing the disease.

“An exciting aspect is that we can perhaps screen for molecules that can physically keep APP and BACE-1 apart,” said Das. “It’s a somewhat unconventional approach.”

Co-authors are David Scott, Archan Ganguly and Yong Tang, UCSD Departments of Pathology and Neurosciences; and Edward H. Koo, UCSD Department of Neurosciences. Roy and Koo are also members of the Shiley-Marcos Alzheimer’s Disease Research Center (ADRC) at UC San Diego.

Funding for this research came from the American Federation for Aging Research, National Institutes of Health grant P50AG005131 and a gift from Darlene Shiley to the ADRC.

Vesicles containing APP (green) and BACE (red) are normally segregated in neurons. Bottom: After neuronal stimulation, known to produce more beta-amyloid, APP and BACE converge in common vesicles, depicted in yellow.
Copper Identified As Culprit In Alzheimer’s Disease

By Mark Michaud
University of Rochester Medical Center

Copper appears to be one of the main environmental factors that trigger the onset and enhance the progression of Alzheimer’s disease by preventing the clearance and accelerating the accumulation of toxic proteins in the brain. That is the conclusion of a study appearing today in the journal Proceedings of the National Academy of Sciences.

“It is clear that, over time, copper’s cumulative effect is to impair the systems by which amyloid beta is removed from the brain,” said Rashid Deane, Ph.D., a research professor in the University of Rochester Medical Center (URMC) Department of Neurosurgery, member of the Center for Translational Neuromedicine, and the lead author of the study. “This impairment is one of the key factors that cause the protein to accumulate in the brain and form the plaques that are the hallmark of Alzheimer’s disease.”

Copper’s presence in the food supply is ubiquitous. It is found in drinking water carried by copper pipes, nutritional supplements, and in certain foods such as red meats, shellfish, nuts, and many fruits and vegetables. The mineral plays an important and beneficial role in nerve conduction, bone growth, the formation of connective tissue, and hormone secretion.

However, the new study shows that copper can also accumulate in the brain and cause the blood brain barrier – the system that controls what enters and exits the brain – to break down, resulting in the toxic accumulation of the protein amyloid beta, a by-product of cellular activity. Using both mice and human brain cells Deane and his colleagues conducted a series of experiments that have pinpointed the molecular mechanisms by which copper accelerates the pathology of Alzheimer’s disease.

Under normal circumstances, amyloid beta is removed from the brain by a protein called lipoprotein receptor-related protein 1 (LRP1). These proteins – which line the capillaries that supply the brain with blood – bind with the amyloid beta found in the brain tissue and escort them into the blood vessels where they are removed from the brain.

The research team “dosed” normal mice with copper over a three month period. The exposure consisted of trace amounts of the metal in drinking water and was one-tenth of the water quality standards for copper established by the Environmental Protection Agency.

“These are very low levels of copper, equivalent to what people would consume in a normal diet.” said Deane.

The researchers found that the copper made its way into the blood system and accumulated in the vessels that feed blood to the brain, specifically in the cellular “walls” of the capillaries. These cells are a critical part of the brain’s defense system and help regulate the passage of molecules to and from brain tissue. In this instance, the capillary cells prevent the copper from entering the brain. However, over time the metal can accumulate in these cells with toxic effect.
The researchers observed that the copper disrupted the function of LRP1 through a process called oxidation which, in turn, inhibited the removal of amyloid beta from the brain. They observed this phenomenon in both mouse and human brain cells.

The researchers then looked at the impact of copper exposure on mouse models of Alzheimer’s disease. In these mice, the cells that form the blood brain barrier have broken down and become “leaky” – a likely combination of aging and the cumulative effect of toxic assaults – allowing elements such as copper to pass unimpeded into the brain tissue. They observed that the copper stimulated activity in neurons that increased the production of amyloid beta. The copper also interacted with amyloid beta in a manner that caused the proteins to bind together in larger complexes creating logjams of the protein that the brain’s waste disposal system cannot clear.

This one-two punch, inhibiting the clearance and stimulating the production of amyloid beta, provides strong evidence that copper is a key player in Alzheimer’s disease. In addition, the researchers observed that copper provoked inflammation of brain tissue which may further promote the breakdown of the blood brain barrier and the accumulation of Alzheimer’s-related toxins.

However, because metal is essential to so many other functions in the body, the researchers say that these results must be interpreted with caution.

“Copper is an essential metal and it is clear that these effects are due to exposure over a long period of time,” said Deane. “The key will be striking the right balance between too little and too much copper consumption. Right now we cannot say what the right level will be, but diet may ultimately play an important role in regulating this process.”

Additional contributors include first author Itender Singh and Abhay Sagare, Mireia Coma, David Perimutter, Robert Gelein, Robert Bell, Richard Deane, Elaine Zhong, Margaret Parisi, Joseph Ciszewski, and R. Tristan Kasper, all with URMC. The study was funded by the Alzheimer’s Association, the National Institutes of Aging, and a pilot grant from the National Institute of Environmental Health Sciences.
A leading group of Alzheimer’s researchers contends that, as biomarkers to detect signals of the disease improve at providing clinically meaningful information, researchers will need guidance on how to constructively disclose test results and track how disclosure impacts both patients and the data collected in research studies. A survey conducted by a group including experts from the Perelman School of Medicine at the University of Pennsylvania found that a majority of Alzheimer’s researchers supported disclosure of results to study participants. The study is published online in Neurology.

“While this is not a call to immediately tell subjects their biomarker results, it does show that the field is moving to a point where experts want to share valid and meaningful results with participants,” said co-senior author Jason Karlawish, MD, professor of Medicine and Medical Ethics and Health Policy. “As we gain more data on the predictive abilities of these measurements, we will need models and methods to effectively reveal results.”

The study surveyed 139 Alzheimer’s clinical trial leaders and coordinators from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) in April 2012, just before the U.S. Food and Drug Administration approved the amyloid-binding radiotracer known as Amyvid (florbetapir). 73 percent of respondents supported disclosing amyloid imaging results to study participants with mild cognitive impairment, whereas 58 percent supported giving amyloid imaging results to those with normal cognition.

Six themes emerged from the survey, regarding participant preferences and cognition levels, researchers’ requests to develop standardized counseling procedures, participant education, and standardization of data-gathering, and concerns regarding potential harms and benefits to participants, as well as the ways disclosure could impact study results.

Currently, ADNI has a policy to not disclose results to participants, but the survey showed a growing trend of experts who would favor revising this policy. In addition to finding amyloid imaging results valuable, Alzheimer’s experts also valued other biomarker data collected in ADNI, such as spinal fluid tests, PET imaging, and other psychometric tests, suggesting that if amyloid imaging results were allowed to be disclosed, it would likely lead to disclosure of other test results.

The study was conducted by a team of researchers, including Dr. Karlawish, co-senior author Robert Green, MD, MPH, Division of Genetics and Department of Medicine at Brigham and Women’s Hospital and Harvard Medical School, Melanie Shulman, MD, from New York University Langone Medical Center and Kristin Harkins from Penn’s Alzheimer’s Disease Center.

The study was supported by the Marian S. Ware Alzheimer’s Program, Robert Wood Johnson Foundation, and the National Institutes of Health (HG02213, AG027841).
In patients with early Alzheimer’s disease, disruptions in brain networks emerge about the same time as chemical markers of the disease appear in the spinal fluid, researchers at Washington University School of Medicine in St. Louis have shown.

While two chemical markers in the spinal fluid are regarded as reliable indicators of early disease, the new study, published in JAMA Neurology, is among the first to show that scans of brain networks may be an equally effective and less invasive way to detect early disease.

“Tracking damage to these brain networks may also help us formulate a more detailed understanding of what happens to the brain before the onset of dementia,” said senior author Beau Ances, MD, PhD, associate professor of neurology and of biomedical engineering.

Diagnosing Alzheimer’s early is a top priority for physicians, many of whom believe that treating patients long before dementia starts greatly improves the chances of success.

Ances and his colleagues studied 207 older but cognitively normal research volunteers at the Charles F. and Joanne Knight Alzheimer’s Disease Research Center at Washington University. Over several years, spinal fluids from the volunteers were sampled multiple times and analyzed for two markers of early Alzheimer’s: changes in amyloid beta, the principal ingredient of Alzheimer’s brain plaques, and in tau protein, a structural component of nerve cells.

The volunteers were also scanned repeatedly using a technique called resting state functional magnetic resonance imaging (fMRI). This scan tracks the rise and fall of blood flow in different brain regions as patients rest in the scanner. Scientists use the resulting data to assess the integrity of the default mode network, a set of connections between different brain regions that becomes active when the mind is at rest.

Earlier studies by Ances and other researchers have shown that Alzheimer’s damages connections in the default mode network and other brain networks.

The new study revealed that this damage became detectable at about the same time that amyloid beta levels began to fall and tau levels started to rise in spinal fluid. The part of the default mode network most harmed by the onset of Alzheimer’s disease was the connection between two brain areas associated with memory, the posterior cingulate and medial temporal regions.

The researchers are continuing to study the connections between brain network damage and the progress of early Alzheimer’s disease in normal volunteers and in patients in the early stages of Alzheimer’s-associated dementia.
Study could help yield new drugs for brain disorders

The glutamate-binding segments (blue, yellow) of ionotropic glutamate receptors undergo a "rocking" motion during activation by glutamate (red). (The dotted line provides a point of reference.)

Johns Hopkins University School of Medicine

Johns Hopkins biophysicists have discovered that full activation of a protein ensemble essential for communication between nerve cells in the brain and spinal cord requires a lot of organized back-and-forth motion of some of the ensemble's segments. Their research, they say, may reveal multiple sites within the protein ensemble that could be used as drug targets to normalize its activity in such neurological disorders as epilepsy, schizophrenia, Parkinson's and Alzheimer's disease.

A summary of the results, published online in the journal *Neuron* on Aug. 7, shows that full activation of so-called ionotropic glutamate receptors is more complex than previously envisioned. In addition to the expected shape changes that occur when the receptor “receives” and clamps down on glutamate messenger molecules, the four segments of the protein ensemble also rock back and forth in relation to each other when fewer than four glutamates are bound.

“We believe that our study is the first to show the molecular architecture and behavior of a prominent neural receptor protein ensemble in a state of partial activation,” says Albert Lau, Ph.D., assistant professor of biophysics and biophysical chemistry at the Johns Hopkins University School of Medicine.

Glutamate receptors reside in the outer envelope of every nerve cell in the brain and spinal cord, Lau notes, and are responsible for changing chemical information — the release of glutamate molecules from a neighboring nerve cell — into electrical information, the flow of charged particles into the receiving nerve cell. There would be sharply reduced communication between nerve cells in our brains if these receptors were disabled, he added, and thought and normal brain function in general would be severely compromised. Malfunctioning receptors, says Lau, have been linked with numerous neurological disorders and are therefore potential targets for drug therapies.

Lau explained that each glutamate receptor is a united group of four protein segments that has a pocket for clamping down on glutamate like a Venus fly trap snaring a bug. Below the glutamate-binding segments are four other segments embedded in the cell’s outer envelope to form a channel for charged particles to flow through. When no glutamates are bound to the receptor, the channel is closed; full activation of the receptor and full opening of the channel occur when four glutamates are bound, each to a difference pocket.
‘Rocking’ Receptor: Crucial Brain-Signaling Molecule Requires Coordinated Motion To Turn On continued...

Previously, Lau says, investigators thought that the level of receptor activation simply corresponded to the degree to which each glutamate-binding segment changed shape during the glutamate-binding process. Using a combination of computer modeling, biophysical “imaging” of molecular structure, biochemical analysis and electrical monitoring of individual cells, the researchers teased apart some of the steps in between zero activation and full activation. They were able to show that the four glutamate-binding segments, in addition to clamping down on glutamate, also rock back and forth in pairs when fewer than four glutamates are bound.

“It isn’t clear yet how this rocking motion affects receptor function, but we now know that activation depends on more than how much each glutamate-binding segment clamps down,” says Lau. Previous development of drugs targeting the receptor focused on the four glutamate-binding pockets. “Our discovery of this molecular motion could aid the development of drugs by revealing additional drug-binding sites on the receptor,” he adds.

Other authors of the report include Héctor Salazar, Valentina Ghisi and Andrew Plested of the Leibniz-Institut für Molekulare Pharmakologie, and Lydia Blachowicz and Benoît Roux of the University of Chicago.

This work was supported by grants from the National Institute of General Medical Sciences (GM094495, GM062342), NeuroCure and the Human Frontier Science Program.
In *The New England Journal of Medicine* (NEJM), a team of scientists, including Paul Aisen, MD, professor of neuroscience and director of the Alzheimer’s Disease Cooperative Study, issued a sort of post-mortem on semagacestat, a small-molecule gamma-secretase inhibitor that drug developer Eli Lilly hoped would prove to be an effective treatment for Alzheimer’s disease (AD).

Existing drugs used to treat AD (and most of those in development) attempt only to slow progression of the neurodegenerative disease, and often with barely perceptible benefit. Actually curing or preventing AD, which afflicts roughly one in eight Americans over the age of 65, remains but a distant hope.

Semagacestat was never deemed a cure, but it had promise, based upon animal models that suggested the drug might effectively block the proteolysis or breakdown of amyloid precursor protein, a necessary ingredient of the neuron-killing plaques that characterize AD.

But the drug proved problematic in clinical test and, in the *NEJM* paper, Aisen and colleagues describe in great detail why semagacestat’s phase 3 clinical trial (typically the final stage before market approval) was halted in 2010.

Rather than improve the condition of Alzheimer’s patients, semagacestat seemed to make things worse. In comparisons of cognitive status, patients taking semagacestat fared no better than those taking a placebo. Patients who took higher doses of semagacestat experienced significant worsening of their functional abilities. They also lost more weight and had higher rates of skin cancer and infection.

For Alzheimer’s patients and their caregivers, the demise of semagacestat was a blow, further evidence of the frustrating complexities and difficulties of AD. It has been more than a decade since memantine, the last AD drug to be successfully tested and approved.

But hope endures, and a battle lost can still help win the war.

Aisen said efforts to develop semagacestat helped further collaboration between industry and academia, a partnership that will be vital to any eventual success. More to the point, lessons were learned.

“Additional papers on the semagacestat study will follow,” Aisen said, “advancing our understanding of biomarkers and their relationship to drug mechanisms.”

Elsewhere, prospects look brighter.

“We are now launching a new paradigm of AD drug development: testing anti-amyloid therapies at the asymptomatic stage of AD,” Aisen said. “The first such trial, the ADCS A4 study (Anti-Amyloid treatment in Asymptomatic Alzheimer’s) will begin by the end of this year. This new approach, enthusiastically endorsed by the FDA, is a big step toward achieving effective therapy.”

Paul Aisen, MD

Oprah’s And Einstein’s Faces Help Spot Dementia

By Marla Paul
Northwestern University

Simple tests that measure the ability to recognize and name famous people such as Albert Einstein, Bill Gates or Oprah Winfrey may help doctors identify early dementia in those 40 to 65 years of age, according to new Northwestern Medicine research.

The research appears in the August 13, 2013, print issue of Neurology, the medical journal of the American Academy of Neurology.

“These tests also differentiate between recognizing a face and actually naming it, which can help identify the specific type of cognitive impairment a person has,” said study lead author Tamar Gefen, a doctoral candidate in neuropsychology at the Cognitive Neurology and Alzheimer’s Disease Center at Northwestern University Feinberg School of Medicine.

Gefen did the research in the lab of senior author Emily Rogalski, assistant research professor at Northwestern’s Cognitive Neurology and Alzheimer’s Disease Center.

Face recognition tests exist to help identify dementia, but they are outdated and more suitable for an older generation.

“The famous faces for this study were specifically chosen for their relevance to individuals under age 65, so that the test may be useful for diagnosing dementia in younger individuals,” Rogalski said. An important component of the test is that it distinguishes deficits in remembering the name of a famous person from that of recognizing the same individual, she noted.

The study also used quantitative software to analyze MRI scans of the brains of the individuals who completed the test to understand the brain areas important for naming and recognition of famous faces.

For the study, 30 people with primary progressive aphasia, a type of early onset dementia that mainly affects language, and 27 people without dementia, all an average age of 62, were given a test. The test includes 20 famous faces printed in black and white, including John F. Kennedy, Lucille Ball, Princess Diana, Martin Luther King Jr. and Elvis Presley.

Participants were given points for each face they could name. If the subject could not name the face, he or she was asked to identify the famous person through description. Participants gained more points by providing at least two relevant details about the person. The two groups also underwent MRI brain scans.

Researchers found that the people who had primary progressive aphasia, a form of early onset dementia, performed significantly worse on the test, scoring an average of 79 percent in recognition of famous faces and 46 percent in naming the faces, compared to 97 percent in recognition and 93 percent on naming for those free of dementia.

The study also found that people who had trouble putting names to the faces were more likely to have a loss of brain tissue in the left temporal lobe of the brain, while those with trouble recognizing the faces had tissue loss on both the left and right temporal lobe.

“In addition to its practical value in helping us identify people with early dementia, this test also may help us understand how the brain works to remember and retrieve its knowledge of words and objects,” Gefen said.

Commentary offers insight into Swedish study that identifies risk factors in late adolescence that may predict dementia diagnosis before age 65

A University of Michigan expert says a new study by Swedish researchers opens the door to better understanding early predictors of developing dementia before age 65 while raising new questions about risks tied to the devastating memory disorder.

Commentary “Young-Onset Dementia, Unanswered Questions and Unmet Needs” by Deborah Levine, M.D., M.P.H., assistant professor of medicine in the division of general medicine in the U-M Medical School, appears in the Journal of the American Medical Association (JAMA) Internal Medicine. The piece corresponds with a study led by Peter Nordstrom, Ph.D., of Umea University in Sweden. Nordstrom’s study identified risk factors in late adolescence that predicted dementia before age 65 (characterized as young-onset dementia or YOD) among Swedish men in mandatory military service.

One of the most significant findings by Nordstrom and colleagues, Levine says, is that high blood pressure in late adolescence increased the likelihood of developing dementia in middle age. Even after accounting for whether an individual had a stroke, high blood pressure still was associated with a higher risk of developing YOD.

“The finding that high systolic blood pressure in late adolescence is associated with an increased risk of young-onset dementia, if confirmed, provides a potential target for intervention studies to prevent young-onset dementia and possibly late-onset dementia,” says Levine, also a research scientist with the Center for Clinical Management Research, VA Ann Arbor Healthcare System and assistant professor of medicine in the departments of internal medicine and neurology at U-M.

Levine cautions that the observational study by Nordstrom was unable to prove that having a risk factor, like high blood pressure, causes YOD or that treating a risk factor will prevent YOD.

Still, these are potential implications of the study.

“Rather than being unavoidable, young-onset dementia may be preventable,” Levine says, “In addition to avoiding head trauma, drug and alcohol intoxication, the study by Nordstrom and colleagues raises the possibility that detecting and treating high blood pressure in adolescents and young adults may prevent young-onset dementia and perhaps late-onset dementia.”

The study is especially timely, Levine says, as more Americans may develop YOD because of increases in traumatic brain injury among young veterans and stroke among young African Americans and middle-aged adults.

Unfortunately, Levine says, many patients and families experiencing YOD have unmet needs.

“Young-onset dementia causes major health, social, and financial problems for patients and their families,” she says. “Adults with young-onset dementia often become unable to parent young children or hold a job. They frequently lose health insurance. Although adults with young-onset dementia have high caregiving needs, many lack access to health care and adult caregivers.”

“One priority is to do research that identifies ways to prevent young-onset dementia. Treating high blood pressure in adolescents and young adults may be one way to prevent young-onset dementia,” Levine adds. “Another priority is to improve care and access to long-term services for adults with young-onset dementia. This is urgent because adults with young-onset dementia and their families really need our help.”
What if we could pinpoint a hereditary cause for Alzheimer's, and intervene to reduce the risk of the disease? We may be closer to that goal, thanks to a team at the University of Kentucky. Researchers affiliated with the UK Sanders-Brown Center on Aging have completed new work in Alzheimer's genetics; the research is detailed in a paper published today in the Journal of Neuroscience.

Emerging evidence indicates that, much like in the case of high cholesterol, some Alzheimer's disease risk is inherited while the remainder is environmental. Family and twin studies suggest that about 70 percent of total Alzheimer's risk is hereditary.

Recently published studies identified several variations in DNA sequence that each modify Alzheimer's risk. In their work, the UK researchers investigated how one of these sequence variations may act. They found that a "protective" genetic variation near a gene called CD33 correlated strongly with how the CD33 mRNA was assembled in the human brain. The authors found that a form of CD33 that lacked a critical functional domain correlates with reduced risk of Alzheimer's disease. CD33 is thought to inhibit clearance of amyloid beta, a hallmark of Alzheimer's disease.

The results obtained by the UK scientists indicate that inhibiting CD33 may reduce Alzheimer's risk. A drug tested for acute myeloid leukemia targets CD33, suggesting the potential for treatments based on CD33 to mitigate the risk for Alzheimer's disease. Additional studies must be conducted before this treatment approach could be tested in humans.

Authors on the paper, titled "CD33 Alzheimer's Risk-Altering Polymorphism, CD33 Expression, and Exon 2 Splicing" are Manasi Malik (lead author), Steven Estus, James F. Simpson, and Ishiti Parikh, all of the UK Department of Physiology; Bernard R. Wilfred and Peter Nelson of the UK Department of Pathology, and David W. Fardo of the UK Department of Biostatistics.
In vitro discovery opens new avenues for future chromosome therapy

Jun Jiang, PhD (left) and Jeanne Lawrence, PhD are among the authors of a study in Nature finding that the extra chromosome in trisomy 21, better known as Down syndrome, can be silenced in a cell culture.

University of Massachusetts Medical School Office of Communications

Scientists at UMass Medical School are the first to establish that a naturally occurring X chromosome “off switch” can be rerouted to neutralize the extra chromosome responsible for trisomy 21, also known as Down syndrome, a genetic disorder characterized by cognitive impairment.

The discovery provides the first evidence that the underlying genetic defect responsible for Down syndrome can be suppressed in cells in culture (in vitro). This paves the way for researchers to study the cell pathologies and identify genome-wide pathways implicated in the disorder, a goal that has so far proven elusive. Doing so will improve scientists’ understanding of the basic biology underlying Down syndrome and may one day help establish potential therapeutic targets for future therapies. Details of the study by Jiang et al. were published online in Nature.

“The last decade has seen great advances in efforts to correct single-gene disorders, beginning with cells in vitro and in several cases advancing to in vivo and clinical trials,” said lead author Jeanne B. Lawrence, PhD, professor of cell & developmental biology. “By contrast, genetic correction of hundreds of genes across an entire extra chromosome has remained outside the realm of possibility. Our hope is that for individuals living with Down syndrome, this proof-of-principal opens up multiple exciting new avenues for studying the disorder now, and brings into the realm of consideration research on the concept of ‘chromosome therapy’ in the future.”

Humans are born with 23 pairs of chromosomes, including two sex chromosomes, for a total of 46 in each cell. People with Down syndrome are born with three (rather than two) copies of chromosome 21, and this “trisomy 21” causes cognitive disability, early-onset Alzheimer’s disease; and a greater risk of childhood leukemia, heart defects and immune and endocrine system dysfunction. Unlike for genetic disorders caused by a single gene, genetic correction of a whole chromosome in trisomic cells has been beyond the realm of possibility, even in cultured cells.

Harnessing the power of the RNA gene called XIST, which is normally responsible for turning off one of the two X chromosomes found in female mammals, UMMS scientists have shown that the extra copy of chromosomes 21 responsible for Down syndrome can be silenced in the laboratory using patient-derived stem cells.
The natural function of the XIST gene, located on the X chromosome, is to effectively silence one of the two X chromosomes in female cells, making expression of X-linked genes similar to that of men, who have just one X chromosome. The large XIST RNA is produced early in development from one of the female’s two X chromosomes, and this unique RNA then “paints” the X chromosome and modifies its structure so that its DNA can’t be expressed to produce proteins and other components. This effectively renders most of the genes on the extra chromosome inactive.

Jun Jiang, PhD, instructor of cell and developmental biology at UMMS, came to work with Dr. Lawrence in 2009 and began a research project to insert the XIST gene into one chromosome 21 – supported by NIH funding for high-risk, high-impact work. The concept grew out of earlier studies by Lawrence and colleague Lisa Hall, PhD, research assistant professor of cell and developmental biology, that suggested the possibility that the chromosome-silencing effect of XIST might be replicated in an extra chromosome 21 in trisomic cells. They worked to do this in induced pluripotent stem cells derived from fibroblast cells donated by a Down syndrome patient because stem cells have the special capacity to form different cell types of the body. Their work showed that the large XIST gene could be inserted at a specified location in the chromosome using zinc finger nuclease (ZFN) technology, a key tool provided by collaborators at Sangamo BioSciences, Inc., a biotechnology company based in Richmond, California. Furthermore, RNA from the inserted XIST gene effectively repressed genes across the extra chromosome, returning gene expression levels to near normal levels and effectively silencing the chromosome.

This finding opens multiple new avenues for translational scientists to study Down syndrome in ways not previously possible. Determining the underlying cell pathologies and gene pathways responsible for the syndrome has previously proven difficult, because of the complexity of the disorder and the normal genetic and epigenetic variation between people and cells. For example, some prior studies suggested that cell proliferation in Down syndrome patients may be impaired, but differences between people and cell lines made it difficult to conclude this definitively. By controlling expression of the XIST gene, Lawrence and colleagues were able to compare otherwise identical cultures of the Down syndrome cells, with and without expression of the extra chromosome. What they showed is that the Down syndrome cells have defects in cell proliferation and in neural cell differentiation, both of which are reversed by silencing one chromosome 21 by XIST.

“This highlights the potential of this new experimental model to study a host of different questions in different human cell-types, and in Down syndrome mouse models,” said Lawrence. “We now have a powerful tool for identifying and studying the cellular pathologies and pathways impacted directly due to over-expression of chromosome 21.”

“Dr. Lawrence has harnessed the power of a natural process to target abnormal gene expression in cells that have an aberrant number of chromosomes,” said Anthony Carter, PhD, of the National Institutes of Health’s National Institute of General Medical Sciences, which partly supported the study. “Her work provides a new tool that could yield novel insights into how genes are silenced on a chromosomal scale, and into the pathological processes associated with chromosome disorders such as Down syndrome.”

New discoveries made using this approach could one day identify new therapeutics for chromosome disorders like Down syndrome.

“In the short term the correction of Down syndrome cells in culture accelerates the study of cell pathology and translational research into therapeutics, but also for the longer-term, potential development of ‘chromosome therapies,’ which utilize epigenetic strategies to regulate chromosomes, is now at least conceivable. Since therapeutic strategies for common chromosomal abnormalities like Down syndrome have received too little attention for too long, for the sake of millions of patients and their families across the U.S. and the world, we ought to try,” said Lawrence.

Lawrence and colleagues will now use this technology to test whether chromosome therapy can correct the pathologies seen in mouse models of Down syndrome.
Studies That Will Be Open for Enrollment Soon

For Information: http://www.adcs.org/Studies/clinalResearchStudy.aspx

A4 – Anti Amyloid in Asymptomatic Alzheimer’s Disease

SNIFF – the Study of Nasal Insulin to Fight Forgetfulness

The Dominantly Inherited Alzheimer Network (DIAN). DIAN is an international research partnership of leading scientists determined to understand a rare form of Alzheimer’s disease that is caused by a gene mutation. Understanding of this form of Alzheimer’s disease may provide clues to decoding other dementias and developing dementia treatments.

Funded by a multiple-year research grant from the National Institute on Aging, DIAN currently involves thirteen outstanding research institutions in the United States, United Kingdom, Germany and Australia. John C. Morris, M.D., Friedman Distinguished Professor of Neurology at Washington University School of Medicine in St. Louis, is the project’s principal investigator.

DIAN is currently enrolling study participants who are biological adult children of a parent with a mutated gene known to cause dominantly inherited Alzheimer’s disease. Such individuals may or may not carry the gene themselves and may or may not have disease symptoms (click here for information about genetic testing).

To register for DIAN drug trials or DIAN, visit www.DIANExpandedRegistry.org.

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