A team of engineers has developed a way to turn organs from mammals, such as lab mice or human bodies donated to science, transparent. Once transparent, scientists can add chemicals to the organs that attach to and highlight specific features, such as different cell types. The result is an intact organ that scientists can see inside and study.

The techniques, called CLARITY, involves a series of chemical treatments that replaces the fatty lipid membranes surrounding cells with a chemical mesh that keeps microscopic details intact without scattering light like lipid membranes do. Neurotransmitters and other important molecules remain in place and can be visualized with a rainbow palette of fluorescent dyes.

Until now, neuroscientists typically had to cut a brain into ultra-thin slices to visualize such features. But that destroys one of the things they’re most interested in studying: the cable-like axons that carry signals from one part of the brain to another. The scientists reported last week in the journal Nature, that the new method makes it possible to visualize these long-range connections as well as the fine-scale anatomy and molecular make up of neurons. This is probably one of the most important advances in decades for understanding the structure of the brain in decades.

Although they developed the method in mouse brains, the team shows that it works on human post-mortem brain tissue too. In the Nature paper, they describe abnormal neural connections in an autistic boy whose brain had been stored in formalin for more than 6 years.

With this breakthrough, researchers plan to compare circuitry in banked tissue from people with other neurological diseases, including Alzheimer’s disease, and from controls whose brains were healthy. Such studies in living people are impossible, because most neuron-tracing methods require genetic engineering or injection of dye in living animals. Scientists might also revisit the many specimens in repositories that have been difficult to analyze because human brains are so large.

Chung et al, Structural and molecular interrogation of intact biological systems, Nature 2013
New Alzheimer's Prevention Registry Recruiting 250,000 Volunteers

About the Alzheimer's Prevention Initiative

*We are launching a new era of Alzheimer's prevention research.*

People who have been touched by Alzheimer’s—a parent, partner, grandparent, or friend—know the challenges and sadness of this devastating disease. Many also wish to take action in the fight against the disease. Now, a new initiative offers a way for this group of family members, friends, and others to help combat Alzheimer’s in a direct and meaningful way.

The Alzheimer’s Prevention Registry (www.endalznow.org), launched in October 2012 by the Banner Alzheimer’s Institute, is a new online community of people who want to help scientists find treatments to slow, halt, or prevent the memory-robbing disorder.

Like the innovative Army of Women initiative launched by the Dr. Susan Love Research Foundation to invigorate breast cancer research, the Alzheimer’s Prevention Registry hopes to engage thousands of people across the United States who want to learn about and possibly participate in medical research studies for Alzheimer’s prevention. Ultimately, Banner and its partners hope to enroll 250,000 people in the Registry by June 2015.

“We are heading into a new phase of Alzheimer’s research, and we will need thousands of volunteers to test treatments to prevent the disease,” says Dr. Laurie Ryan, director of NIA’s Alzheimer’s Clinical Trials Program. “The Registry should help connect researchers to a community of people who are passionate about combating Alzheimer’s.”

The Alzheimer’s Prevention Registry is a shared resource that draws on the support of the Geoffrey Beene Gives Back Alzheimer’s Initiative and Alzheimer’s Research Forum. The Phoenix, Arizona-based Banner Alzheimer’s Institute, one of 27 NIA-funded Alzheimer’s Disease Centers, is a key partner in the Alzheimer’s Prevention Initiative, an international collaboration funded in part by NIA that will test treatments in people at high genetic risk for Alzheimer’s.

A growing community

Just six months in, more than 9,300 members have already joined the effort. Most are cognitively normal adults age 50 or older—the Registry’s target population—and 60 percent report a family history of Alzheimer’s disease, says Dr. Jessica Langbaum, a principal scientist at Banner.

“Enrollees see Alzheimer’s as a significant health issue and believe more must be done to stop it,” she says.

Anyone 18 and older can join the Registry by providing basic information and answering a few questions about their cognitive health, family history, and caregiving status. The Registry will then serve as a go-between, assessing trials submitted by researchers for inclusion in the Registry and e-mailing enrollees about studies for which they might qualify. All personal information submitted by volunteers remains private and will be used only to inform a registrant about research studies of possible interest. Registry members are under no obligation to participate in any clinical trials or studies.

Registry members will also receive regular updates about Alzheimer’s prevention research and clinical trials, as well as information about brain health. In addition to its website, the Registry is spreading the word about Alzheimer’s prevention research through Facebook and Twitter.

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Tackling the recruitment challenge

More than 300 Alzheimer’s-related clinical trials and studies are actively recruiting in the United States, each looking for anywhere from a few dozen to a few thousand participants. Typically, a trial must screen 10 or more people for each one who actually enrolls, a process that may take a few months to a year or more. The Registry aims to speed up that process by creating a ready-made pool of thousands of potential volunteers.

Dr. Langbaum explains that the Registry complements local recruitment efforts such as advertising and brochures. “Local recruitment efforts will still be very important. The Registry is not meant to replace them,” she says.

Prevention trials on the horizon

The Registry comes as scientists are gearing up for clinical trials that will test drugs and other promising treatments to prevent dementia. New trials will focus on “preclinical or asymptomatic” populations—people with Alzheimer’s-related brain changes who have no memory loss or other symptoms of the disease.

Many researchers believe that possible therapies may be successful if given early in the disease process, before the onset of memory and other thinking problems. Past trials in people who already have Alzheimer’s dementia have had disappointing results.

The first clinical trial to benefit from the Registry will be the NIA-sponsored A4 (Anti-Amyloid Treatment in Asymptomatic Alzheimer’s Disease) Trial, which expects to begin recruitment in late 2013. It will test the drug solanezumab in 1,000 symptom-free older volunteers whose brain imaging results show abnormal levels of amyloid, a protein whose sticky deposits are a hallmark of Alzheimer’s. Cognitive tests given over 3 years will determine if the drug helps maintain cognitive health, and imaging tests will track structural and functional brain changes.
ABCA7, a minor gene variant in whites, is major player in African-Americans

African-Americans with a variant of the ABCA7 gene have almost double the risk of developing late-onset Alzheimer’s disease compared with African-Americans who lack the variant. The largest genome-wide search for Alzheimer’s genes in the African-American community, the study was undertaken by the Alzheimer’s Disease Genetics Consortium and led by neurologists from Columbia University Medical Center. It was published in the April 10 issue of the Journal of the American Medical Association. The study was primarily funded by the National Institutes of Health (NIH).

“Our findings strongly suggest that ABCA7 is a definitive genetic risk factor for Alzheimer’s disease among African-Americans,” said study senior author, Richard Mayeux, MD, MS, professor and chair of Neurology at CUMC. “Until now, data on the genetics of Alzheimer’s in this patient population have been extremely limited.”

The ABCA7 gene is involved in the production of cholesterol and lipids, which suggests that lipid metabolism may be a more important pathway in Alzheimer’s disease in African-Americans than in whites. Because cholesterol and lipid imbalances (which eventually lead to vascular disease and heart attacks and strokes) are more common in African-Americans, treatments that reduce cholesterol and vascular disease may potentially be an effective way to reduce or delay Alzheimer’s in this population.

“While we need to conduct research to determine whether reducing cholesterol will lower the chance of Alzheimer’s in African-Americans, maintaining healthy cholesterol levels always has the benefit of lowering one’s risk of heart attack and stroke,” said Dr. Mayeux.

The study involved nearly 6,000 African-American participants, most of whom are volunteers from 18 NIH-funded Alzheimer’s Disease Centers. The Centers and other researchers contributed samples to the Alzheimer’s Disease Genetics Consortium, an NIH-supported research program led by Gerard D. Schellenberg, PhD, at the University of Pennsylvania. Approximately 2,000 of the volunteers were diagnosed with probable Alzheimer’s disease and 4,000 were cognitively normal. The purpose of the study was to look for genetic variants among African-Americans, who are known to have a higher incidence of late-onset Alzheimer’s than whites living in the same community. Ninety percent of all cases of Alzheimer’s, which affect an estimated 5 million Americans aged 65 and older, are described as having the late-onset form of the disease.

“ABCA7 is the first major gene implicated in late-onset Alzheimer’s among African Americans, and it has an effect on disease risk comparable to that of ApoE4—which has been known for two decades to be a major genetic risk factor in whites,” said Christiane Reitz, MD, PhD, assistant professor of neurology, who conducted the study’s genetic analyses as first author on the paper. “Both genes raise the risk of Alzheimer’s in this population twofold.” The extent of the role of ApoE4 in African-Americans had been uncertain because of inconsistent results from previous, smaller studies.

“Based on these results, we now know that both ApoE4 and ABCA7 are major genetic risk factors for African-Americans, whereas for whites, only one of the two—ApoE4—confers a similar degree of risk,” said Dr. Mayeux, who is also co-director of the Taub Institute for Research on Alzheimer’s Disease and the Aging Brain and the Gertrude H. Sergievsky Center at CUMC. He is the Gertrude H. Sergievsky Professor of Neurology, Psychiatry and Epidemiology.
Several other genes that had recently been linked to Alzheimer’s in white populations were also confirmed in the current study to play a role in African-Americans. “Because they cross ethnic groups, the likelihood increases that these genes are very important in the development of Alzheimer’s,” said Dr. Reitz, who is a member of both the Sergievsky Center and the Taub Institute. “And that gives us clues in our search for the cellular pathways associated with the disease.”

“These findings suggest that the genetic underpinnings of Alzheimer’s disease may vary among different populations—and so should not be treated homogeneously,” said Dr. Reitz.

“One of the key research goals set forth in the National Alzheimer’s Project Act of 2011 is to improve outcomes for ethnic and racial minority populations that are at higher risk for this devastating disease,” said Neil Buckholtz, PhD, of the National Institute on Aging, which leads the NIH effort to find ways to treat, delay or prevent Alzheimer’s. “These findings advance our understanding of genetic underpinnings that may play a role in disease onset and progression in African-Americans and suggest a novel target for therapeutic development.”

ABCA7 also affects the transport of several important proteins, including amyloid precursor protein, which is involved in the production of amyloid—the major source of the plaques that develop in the brains of Alzheimer’s patients. Thus, there are multiple ways that ABCA7 might contribute to an increased risk of late-onset Alzheimer’s disease among African-Americans.

The most immediate impact of the new findings will be for scientists studying the causes of Alzheimer’s and ways to prevent the disease. “Our next step is to do more lab work and more genetic sequencing, to understand the biological reasons for the increased risk seen with ABCA7 and other genes implicated in late-onset Alzheimer’s disease,” said Dr. Mayeux.

While the study’s discoveries may eventually lead to the development of genetic risk estimates specific to African-Americans, Dr. Mayeux cautions that the utility of genetic testing for Alzheimer’s is still years away. “We are not yet at the point where we can take what we know about Alzheimer’s and come up with an accurate risk assessment,” he said.

The study’s findings also must be replicated in independent groups of African-Americans.

“The participant data pooled together for this analysis basically represented all of the African-American samples from well-characterized individuals in the United States,” said Dr. Buckholtz. “Because large sample sizes are needed to conduct reliable genetic analyses, it is vitally important that African-Americans and people of other racial/ethnic groups participate in genetic studies supported by NIA.” He noted that broad collaboration and data-sharing efforts among researchers make such studies possible.

The paper is titled, “Variants in the ATP-Binding Cassette Transporter (ABCA7), Apolipoprotein E E4, and the Risk of Late-Onset Alzheimer Disease in African Americans.” The other contributors are: Jennifer L. Manly (CUMC); Gyungah Jun, Badri Narayan Vardarajan, Mark Logue, Clinton T. Baldwin, Lindsay A. Farrer, Kathryn L. Lunetta (Boston University); Adam Naj, Margaret A. Pericak-Vance, Ruchita Rajbhandary (University of Miami); Li-San Wang, Chiao-Feng Lin, Gerard D. Schellenberg, Otto Valladares, Laura B. Cantwell (University of Pennsylvania); Eric B. Larson, Paul K. Crane, Walter A. Kukull (University of Washington); Neill R. Graff-Radford, Nilufer Ertekin-Taner (Mayo Clinic); Denis Evans, Lisa L. Barnes, David A. Bennett (Rush University); Philip L. De Jager, Towfiqube Raj, Robert C. Green (Harvard University); Jill R. Murrell, Tatiana M. Foroud, Hugh Hendrie, Kathleen Hall (Indiana University); Joseph D. Buxbaum (Mount Sinai Medical Center); Daniele Fallin (Johns Hopkins University); C. P. Go (University of Alabama); Patrick Griffith (Meharry Medical College); Thomas O. Obisesan (Howard University); M. Ilyas Kamboh, Oscar L. Lopez (University of Pittsburgh); Alison M. Goate (Washington University); Goldie S. Byrd (North Carolina A & T University); and Jonathan L. Haines (Vanderbilt University).

For more information, visit cumc.columbia.edu or columbiadoctors.org.
Genetic Markers ID Second Alzheimer’s Pathway

By Jim Dryden
Washington University School of Medicine

Researchers at Washington University School of Medicine in St. Louis have identified a new set of genetic markers for Alzheimer’s that point to a second pathway through which the disease develops.

Both a tangle (top left) and a plaque (bottom right) can be seen in the brain of a patient with Alzheimer’s disease.

Much of the genetic research on Alzheimer’s centers on amyloid-beta, a key component of brain plaques that build up in the brains of people with the disease.

In the new study, the scientists identified several genes linked to the tau protein, which is found in the tangles that develop in the brain as Alzheimer’s progresses and patients develop dementia. The findings may help provide targets for a different class of drugs that could be used for treatment.

The researchers reported their findings online April 24 in the journal *Neuron*.

“We measured the tau protein in the cerebrospinal fluid and identified several genes that are related to high levels of tau and also affect risk for Alzheimer’s disease,” says senior investigator Alison M. Goate, DPhil, the Samuel and Mae S. Ludwig Professor of Genetics in Psychiatry. “As far as we’re aware, three of these genes have no effect on amyloid-beta, suggesting that they are operating through a completely different pathway.”

A fourth gene in the mix, *APOE*, had been identified long ago as a risk factor for Alzheimer’s. It has been linked to amyloid-beta, but in the new study, *APOE* appears to be connected to elevated levels of tau. Finding that *APOE* is influencing more than one pathway could help explain why the gene has such a big effect on Alzheimer’s disease risk, the researchers say.

“It appears *APOE* influences risk in more than one way,” says Goate, also a professor of genetics and co-director of the Hope Center for Neurological Disorders. “Some of the effects are mediated through amyloid-beta and others by tau. That suggests there are at least two ways in which the gene can influence our risk for Alzheimer’s disease.”

The new research by Goate and her colleagues is the largest genome-wide association study (GWAS) yet on tau in cerebrospinal fluid. The scientists analyzed points along the genomes of 1,269 individuals who had undergone spinal taps as part of ongoing Alzheimer’s research.

Whereas amyloid is known to collect in the brain and affect brain cells from the outside, the tau protein usually is stored inside cells. So tau usually moves into the spinal fluid when cells are damaged or die. Elevated tau has been linked to several forms of non-Alzheimer’s dementia, and first author Carlos Cruchaga, PhD, says that although amyloid plaques are a key feature of Alzheimer’s disease, it’s possible that excess tau has more to do with the dementia than plaques.

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Genetic Markers ID second Alzheimer’s Pathway continued...

“We know there are some individuals with high levels of amyloid-beta who don’t develop Alzheimer's disease,” says Cruchaga, an assistant professor of psychiatry. “We don’t know why that is, but perhaps it could be related to the fact that they don’t have elevated tau levels.”

In addition to APOE, the researchers found that a gene called GLIS3, and the genes TREM2 and TREML2 also affect both tau levels and Alzheimer’s risk.

Goate says she suspects changes in tau may be good predictors of advancing disease. As tau levels rise, she says people may be more likely to develop dementia. If drugs could be developed to target tau, they may prevent much of the neurodegeneration that characterizes Alzheimer's disease and, in that way, help prevent or delay dementia.

The new research also suggests it may one day be possible to reduce Alzheimer’s risk by targeting both pathways.

“Since two mechanisms apparently exist, identifying potential drug targets along these pathways could be very useful,” she says. “If drugs that influence tau could be added to those that affect amyloid, we could potentially reduce risk through two different pathways.”

Funding for this research comes from the National Institute on Neurological Diseases and Stroke (NINDS) and the National Institute on Aging (NIA) of the National Institutes of Health (NIH). Other funding was provided by AstraZeneca and the Barnes-Jewish Hospital Foundation. For a complete list of groups that funded portions of this study, please consult the “Acknowledgements” section of the paper. NIH grant numbers: P30 NS069329-01, R01 AG035083, R01 AG16208, P50 AG05681, P01 AG03991, P01 AG026276, AG05136, P01 AG05131, R01 AG17917, R01 AG15819, K08 AG034290, U01 AG024904, P30 AG010129 and K01 AG030514.

Researchers collaborate with the New York Stem Cell Foundation using skin samples and brain imaging to identify causes and cures.

Sam Gandy, MD, PhD, of the Icahn School of Medicine at Mount Sinai is leading an international team of researchers working to reprogram skin cells into brain cells to gain a better understanding of Alzheimer's disease (AD). As part of the consortium, Dr. Gandy is collaborating with Scott Noggle, PhD, the NYSCF – Charles Evans Senior Research Fellow for Alzheimer's Disease and Director of the New York Stem Cell Foundation’s (NYSCF) laboratory in Manhattan.

Dr. Gandy heads the Stem Cell Research Consortium funded by the Cure Alzheimer's Fund (CAF). The Consortium consists of six institutions that plan to directly investigate, for the first time, brain cells in petri dishes from individual patients who have the common form of AD.

Dr. Gandy is working with Dr. Noggle’s team to reprogram skin cells from AD patients into brain cells using stem-cell technology. The research team will obtain and monitor adult AD brain cells, providing not only a way to study the causes of the disease but also a system for discovering potentially effective drugs. The strategy has been nicknamed “the patient-specific disease in a dish” and enables studies on a time scale of minutes or hours, compared with mouse model testing, which routinely requires nine months to one year.

“This approach is one of our best shots at understanding common forms of Alzheimer’s. Once defects are identified, we can use these same brain cells to screen for new drugs,” said Dr. Gandy, Professor of Neurology and Psychiatry and Director of the Center for Cognitive Health at Mount Sinai. “This breakthrough technology will enable us to identify genetic and biochemical differences underlying the most common form of Alzheimer’s disease.”

In collaboration with Mary Sano, PhD, Professor of Psychiatry and Director of the Mount Sinai Alzheimer’s Disease Research Center (ADRC), Dr. Gandy plans to select carefully characterized patients and healthy participants from the ADRC who will have skin biopsies and will also undergo brain scans to detect the amount of amyloid plaque, the hallmark of AD, present in the brain. Samples will also be collected from a skin cell bank at the National Institutes of Health. The scans will be used to confirm AD, the risk for developing AD, and whether a brain is amyloid-free.

Dr. Noggle will reprogram these skin cells into the various cell types that make up the brain, employing the NYSCF Global Stem Cell Array, a breakthrough automated robotic technology that produces standardized stem cell lines. Results are specific to the patient’s genetic makeup, allowing researchers to uncover Alzheimer’s-related changes at an individual level and to track changes that might otherwise go undiscovered.

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“Having all the cell types together in the same dish enables us to mimic as closely as possible the normal and the diseased adult human brain,” said Dr. Gandy. “In these mixed cultures, we will study the roughly three-dozen genes that have been linked to AD to see if any are dysfunctional in such a way as to cause one or more known features of the disease.”

To encourage international collaboration in Alzheimer’s treatment, consortium researchers will create a stem cell bank that can be accessed globally to accelerate drug screening worldwide. This collaboration is an example of NYSCF’s commitment to work with global collaborators to advance research.

"We can, for the first time, test drugs across a large, diverse population of Alzheimer's patients, using only their cells. This stem cell resource will embolden scientific investigations and accelerate bench to bedside delivery of new treatments," said Dr. Noggle. "We’re incredibly excited to be working with Dr. Gandy and fellow collaborators to find a cure for Alzheimer’s disease."

Other organizations involved in the Consortium are Hadassah University Medical Center, Harvard Medical School and Massachusetts General Hospital, Harvard University Stem Cell Institute, and The Rockefeller University, who is pursuing related research separately funded by CAF.

For more information, visit http://www.mountsinai.org.
ADNI II Study

The goal of the Alzheimer's Disease Neuroimaging Initiative Study is to learn how to stop the progression of mild cognitive impairment (MCI) and Alzheimer's disease in future generations. Information from the study might, in the future, lead to new treatments.  

ADCS Trials Enrolling...

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.