

CenterPiece

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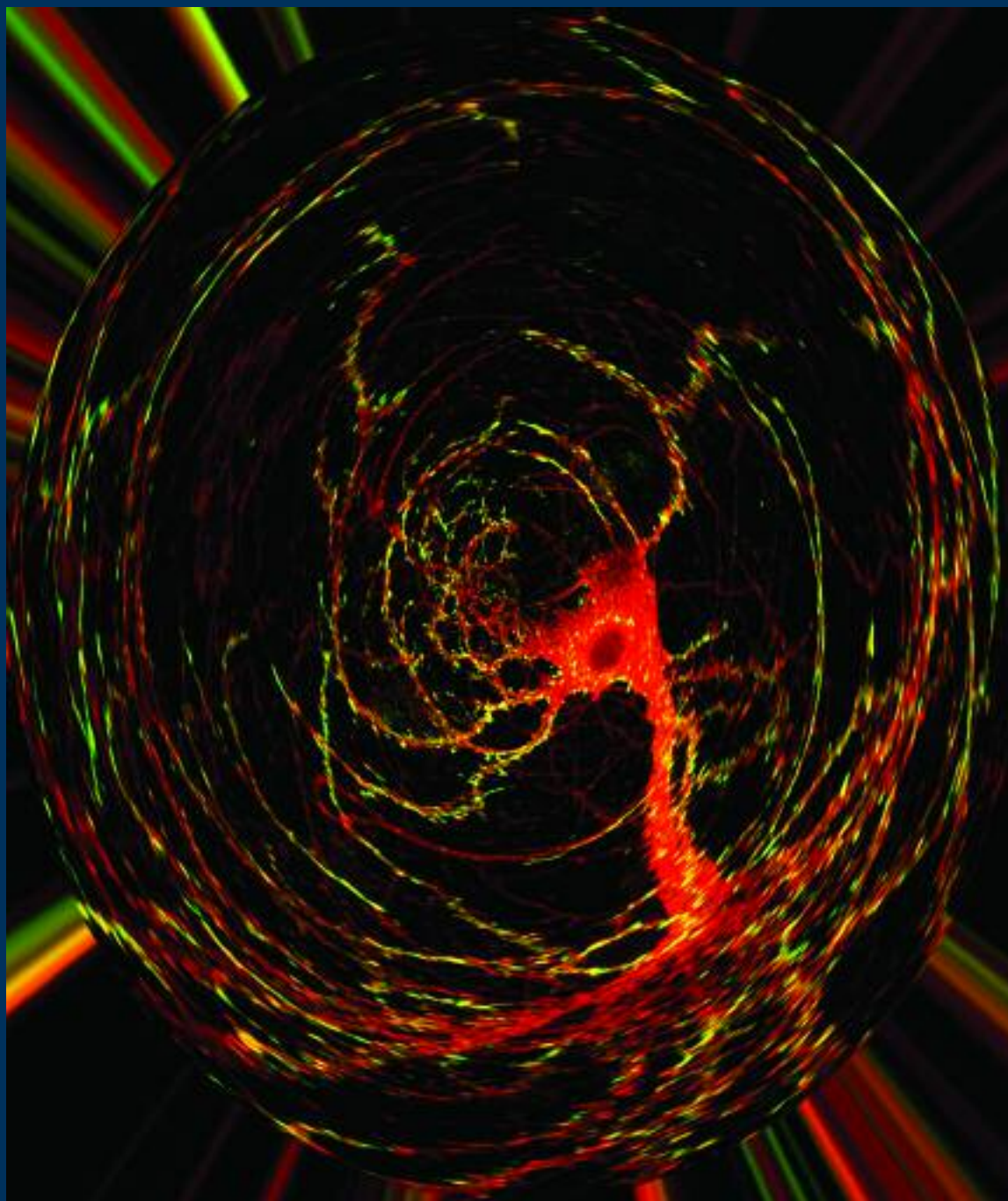
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Memory loss in Alzheimer's disease is reflected in this artist's rendering of a neuron being attacked by amyloid β -derived diffusible ligands (ADDLs), small neurotoxins discovered by researchers at Northwestern. ADDLs specifically target synapses and disrupt molecular mechanisms essential for long-term memory formation.

This attack on synapses may be the first step in Alzheimer's pathology. See related article on p. 6. 

(The image above by Pascale Lacor, neurobiology and physiology, won last year's Neuro-Art Display competition at the tenth annual Alzheimer's Day hosted by Northwestern's Cognitive Neurology and Alzheimer's Disease Center.)

Cognitive Neurology and Alzheimer's Disease Center

When asked how the field of Alzheimer's disease has changed over the past 30 years, Marsel Mesulam, director of the Cognitive Neurology and Alzheimer's Disease Center (CNADC), is quick to reply that "the study of Alzheimer's disease has changed from a torpid and esoteric field at the fringes of neuroscience to one which is vibrant with excitement and which holds the key to fundamental questions related to aging and cognition." Without hesitating, he adds, "I routinely advise young investigators or graduate students in the field of Alzheimer's disease research that the best is yet to come."



Image courtesy of Darren Gitelman, Cognitive Neurology and Alzheimer's Disease Center

Marsel Mesulam, director, Cognitive Neurology and Alzheimer's Disease Center

CNADC investigators and clinicians are at the cutting edge of this vital field. A multidisciplinary entity, CNADC has as its mission to investigate the neurological basis of cognitive function, elucidate the causes of dementias, and ensure that patients and their families are the beneficiaries of resultant discoveries.

The Center is based in the Feinberg School of Medicine, but current core and affiliated CNADC faculty represent more than 15 departments in four schools on both campuses, three university centers, Northwestern Memorial

Hospital, Rehabilitation Institute of Chicago, Evanston Northwestern Healthcare, and Children's Memorial Hospital. In 2004, CNADC faculty received \$7.4 million in research funding, published 124 papers on dementia and aging, and delivered 96 lectures in the U.S. and abroad.

CNADC's first decade

The groundwork for CNADC was laid in 1994, when the Northwestern medical school successfully recruited the Mesulam group from Harvard Medical School to enhance its programs on Alzheimer's disease. Two years later, Mesulam and colleagues Sandra Weintraub, psychiatry and behavioral sciences, and Linda Van Eldik, cell and molecular biology, submitted an application to the National Institutes of Health (NIH) to establish a federally funded Alzheimer's Disease Center in the Northwestern medical school.

The application was successful at its first submission, and a five-year award of over \$4 million was received to establish an infrastructure for clinical and basic research on Alzheimer's disease and related conditions. The following year the Center was designated as one of three statewide Alzheimer's disease centers by the State of Illinois.

Based on the Center's achievements during its first few years of activity, the renewal application to NIH was ranked number 1 among 16 other applications from centers throughout the United States, and a second five-year award, \$5 million, was received.

The four components of CNADC

Mesulam explains that CNADC conducts its work through four principal components.

- One of the 29 Alzheimer's Disease Centers in the U.S. designated and funded by the NIH National Institute on Aging (NIA).

- An Illinois Alzheimer's Disease Center that offers diagnosis, treatment, education, and research, including clinical trials.
- The Neurobehavior and Memory Health Clinical Service, the component through which CNADC serves its patients and caregivers and conducts drug trials.
- The Cognitive Brain Mapping Group, which focuses on functional magnetic resonance imaging.

Alzheimer's Disease Centers

Alzheimer's disease, a neurodegenerative condition affecting over 15 million people worldwide, causes memory loss and, ultimately, dementia. The causes of Alzheimer's disease are not yet fully understood, and many studies are exploring possible factors that may be involved in its cause and development. Researchers at NIA-funded Alzheimer's Disease Centers are working to translate research advances into improved diagnosis and care for Alzheimer's disease patients while, at the same time, focusing on the program's long-term goal – finding a way to cure, and possibly prevent, Alzheimer's disease.

As evidenced by the 124 papers on dementia and aging published by CNADC faculty during 2004, the Center boasts an active research agenda. Even a few examples of ongoing CNADC research clearly demonstrate the diversity of investigational approaches encouraged by the Center.

Cholinergic neurons

Cholinergic nerve fibers of the cerebral cortex use acetylcholine as a chemical messenger and play a critical role in memory function. "Many years ago, we identified the nucleus basalis as the source of these fibers," recalls Mesulam. "Since then, Alzheimer's disease was shown to cause a severe destruction of

the nucleus basalis and its cholinergic fibers,” he continues. “Most of the currently available drugs for Alzheimer’s disease work by replenishing acetylcholine in the brain.”

An unresolved question for Mesulam and his colleagues was whether the cholinergic destruction occurs early in the disease or, as some investigators recently contended, only in the advanced stages. To address this question, Mesulam and CNADC colleagues Weintraub and Pamela Shaw, research technologist, turned to a longitudinal study, conducted in collaboration with Deborah Mash at the University of Miami.

Study members were elderly volunteers who had agreed to periodic testing of cognitive function and an autopsy at death. Some members of the group showed only age-related changes of memory during their participation in the study, whereas others developed the earliest signs of Alzheimer’s disease.

Abnormalities in the protein tau

The brains of study members who had died were examined with sensitive antibodies that recognize abnormalities in the shape and phosphorylation of the protein tau. “We found that these abnormalities, indicative of neural degeneration, emerged in the nucleus basalis during normal aging,” Mesulam reports, “and that they became much more prominent at the earliest stages of Alzheimer’s disease. The number of neurons containing abnormal tau was correlated with memory scores, not only in early Alzheimer’s disease, but also in the course of normal aging.

“These experiments demonstrated that cholinergic abnormalities are present at the earliest stages of Alzheimer’s disease, and that they may contribute to the memory changes seen not only in Alzheimer’s disease, but also in the course of normal aging,” Mesulam concludes. [M. Mesulam, et al. *Annals of Neurology*, 55:815-828 (2004).]

Vitamin study

CNADC researchers just completed their recruitment of volunteers to participate in a nationwide clinical trial to test whether taking high-dose supplements of vitamins B6, B12, and folate will slow the progression of Alzheimer’s disease.

People with Alzheimer’s disease have elevated levels of the amino acid homocysteine in their blood. In a pilot study published in the March/April 2004 issue of the *American Journal of Geriatric Psychiatry*, researchers found that high dose vitamins reduce levels of homocysteine in individuals with Alzheimer’s disease. The 40-center, NIA-funded vitamin study – known as VITAL (VITamins to Slow ALzheimer’s Disease) – recruited 400 participants across the country with moderate to mild Alzheimer’s disease.

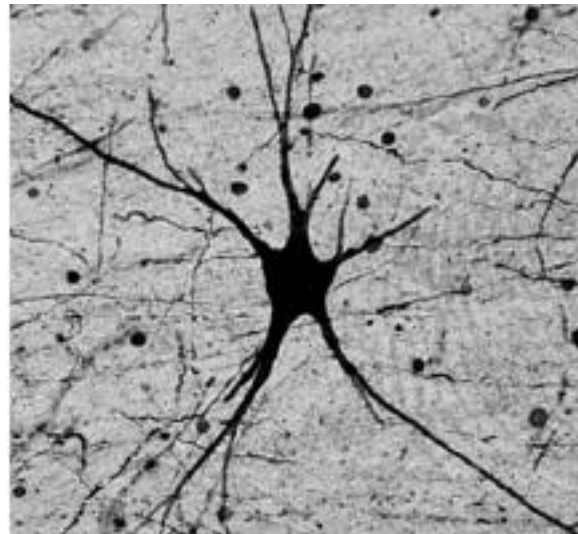
Mesulam, who together with Nancy Johnson, psychiatry and behavioral sciences, is a principal investigator on the arm of the study conducted at Northwestern, explains that “this study may lead to the development of a potentially important way of slowing the course of Alzheimer’s disease. However,” he hastens to caution, “people should not begin taking high doses of these vitamins on their own, since the safety and effectiveness of this treatment has not yet been demonstrated.”

Primary progressive aphasia (Mesulam’s syndrome)

Alzheimer’s disease is the single most common cause of dementia, and its high prevalence – over four million Americans have Alzheimer’s disease – may lead to the belief that dementia is always due to Alzheimer’s disease and that memory loss is a feature of all dementias. “It’s important to understand,” Mesulam points out, “that nearly a quarter of all dementias, especially those of presenile onset, may be caused by diseases other than Alzheimer’s

disease. Further,” he continues, “some of these so-called atypical dementias involve cognitive abnormalities in areas other than memory.”

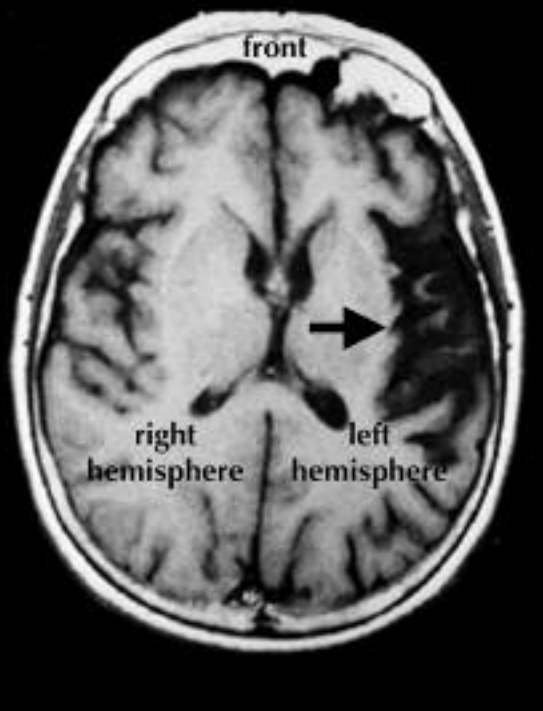
Primary progressive aphasia (PPA), for example, is an unusual dementia of unknown cause that is characterized by a relentless loss of language, but with memory relatively preserved. Also known as Mesulam’s syndrome because it was defined by Mesulam and colleagues, PPA was once considered a rare condition but is now commonly included among dementia syndromes and has been reported in several hundred individuals.



This nerve cell in the human nucleus basalis has been stained with an antibody that binds to choline acetyltransferase. These are the nerve cells that produce acetylcholine, a chemical messenger that helps form memories and that is depleted in Alzheimer’s disease.

“While Alzheimer’s disease patients have forgetfulness – they misplace personal objects, repeat questions, and forget recent events – patients with PPA come to medical attention because of the onset of word-finding difficulties, abnormal speech patterns, and glaring spelling errors,” Mesulam clarifies. “Some patients cannot find the right words to express their thoughts, while others cannot understand the meaning of words either heard or seen. Still others cannot name objects in their environment.”

—see CNADC, continued on p. 4



Patient with PPA. The arrow points to the language areas in the left hemisphere. The area has shrunk and has been replaced by the dark cerebrospinal fluid.

—CNADC, *continued from p. 3*

PPA program

CNADC's PPA Program – a 3-4 day, comprehensive, multidisciplinary approach to evaluation, diagnosis, and treatment – consists of four main components:

- clinical – state-of-the-art medical evaluation to establish the diagnosis;
- research – voluntary participation in ongoing research studies of PPA;
- education – instruction to address individual needs for information/resources; and
- treatment – clinical evaluation of the language deficits and a treatment plan.

Frontotemporal dementia

Frontotemporal dementia (FTD) is a degenerative condition of the front (anterior) part of the brain. In the early stages of this type of dementia, there is no true memory loss of the type seen in Alzheimer's disease. The areas of the brain affected by FTD – the frontal and anterior temporal lobes – control

reasoning, personality, movement, speech, social graces, language, and some aspects of memory.

FTD is marked by dramatic changes in personality, ability to concentrate, social skills, motivation, and reasoning. Symptoms such as loss of inhibition, apathy, and social withdrawal may lead to misdiagnosis as a psychological or emotionally based problem, or, in the elderly, be mistaken for withdrawal or eccentricity. FTD progresses to immobility and loss of speech and expression. Structural changes in the FTD patient's brain can be seen via scans or neuroimaging.

“Compared to Alzheimer's disease, patients with PPA and FTD are underserved when it comes to assistance and educational resources,” Mesulam notes. “Last fall CNADC held the first session of a three-part program aimed at FTD and PPA caregivers. The event attracted 55 attendees and elicited enthusiastic reviews, so we know we're meeting a need for these patient groups,” he concludes.

Cognitive brain mapping program

Recognizing the importance of functional magnetic resonance imaging (MRI), Mesulam and Darren Gitelman, neurology and radiology, were instrumental in establishing functional imaging resources at Northwestern (see top image on back cover).

“Modern technology based on computerized testing procedures, eye movement recordings, and functional brain imaging allows us to visualize the parts of the brain that become activated during mental activity and to determine how these patterns change in brain diseases,” Mesulam observes. “Dramatic technological advances in understanding how the brain works are occurring in the field of functional MRI,” he continues. “Imaging will play an increasingly more important role in the

early detection of dementias and also in exploring the complex relationship between brain and mental state.”

The cognitive brain mapping program, funded by NIH and private foundations, conducts research in:

- exploring the neural networks that support cognition;
- detecting changes in spatial awareness in stroke patients;
- mapping brain activations related to language, memory, emotion, and attention; and
- imaging in patients with memory loss, Alzheimer's disease, and PPA.

Pilot grant program

To encourage creative and innovative research, the Alzheimer's Disease Center of CNADC funds an Alzheimer's Disease Pilot Grant program as part of its activities.

This program, under the direction of John Disterhoft, physiology, targets junior investigators with interest in Alzheimer's disease who require initial support in order to obtain feasibility data for future R01-type applications; established investigators in Alzheimer's research who are testing a new hypothesis or methodology that is not an extension of ongoing research or is a high-risk new project not supported by current grants; and established investigators in non-Alzheimer's disease fields who wish to bring novel approaches to Alzheimer's disease research.

Educational seminars and conferences

The Center runs Thursday noon seminars on the Chicago campus on Alzheimer's disease and cognitive neuroscience. Local and national speakers conducting research in Alzheimer's disease, related dementias, and cognitive neuroscience are invited to speak, and attendance from the local community is welcome. Always “standing room only,” these seminars

attract both clinicians and basic scientists, offering opportunities for creating unique syntheses.

Once a year, the Center organizes an Alzheimer's Day, which features an external guest keynote speaker and posters based on the research of Northwestern investigators from the Chicago and Evanston campuses. The 2005 Alzheimer's Day is scheduled for May 6, and the keynote speaker will be Marilyn Albert, director of the Division of Cognitive Neuroscience in the Department of Neurology at Johns Hopkins University School of Medicine and co-director of the Johns Hopkins Alzheimer's Disease Research Center.

Outreach

Under the leadership of Darby Morhardt, director of education and outreach, CNADC sponsors a number of outreach programs.

- The Buddy Program, developed by CNADC in 1998, is a unique program matching first year Northwestern medical students with patients diagnosed with early Alzheimer's disease or a related illness. This program – which was recently expanded to include graduate students in basic science laboratories – allows both students and the diagnosed person to get to know each other on a more personal, rather than a clinical, level and to enjoy just being together. Last year the Buddy Program was honored by the American Society on Aging, receiving its 2004 MindAlert Award in the Early-Stage Dementia Program category.
- The Early Stage Support Group, a collaborative effort between Northwestern and the Alzheimer's Association,


Greater Illinois Chapter, serves both persons in the early stages of memory impairment and their family members or friends. A variety of topics pertinent to Alzheimer's disease and related dementias are covered throughout the course of these groups.

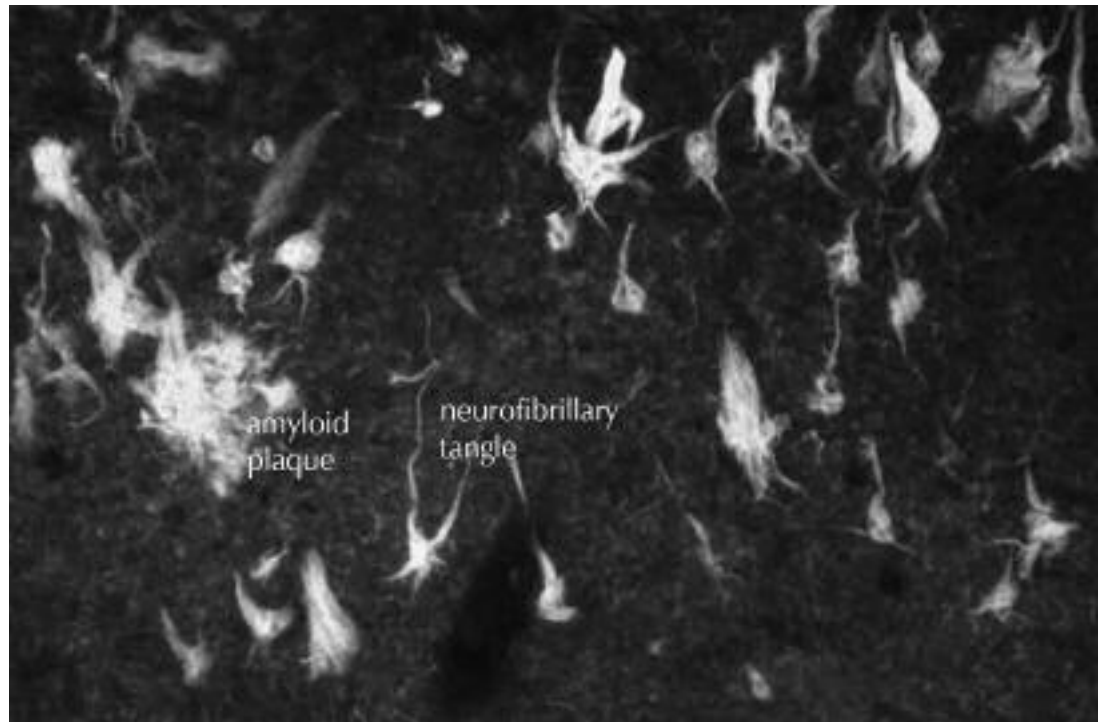
- The Culture Bus is a collaboration between CNADC and the Council for Jewish Elderly. Initiated fall 2002, the program is designed to take members on cultural excursions throughout the city, one day a week.
- A research recruitment video, "Participating in Research: A Legacy of Hope," was produced by CNADC with the help of research and community volunteers and agencies. Many of the common myths about research are addressed with the aim of reassuring seniors, particularly those from minority communities which are under-represented in research studies,

that research need not be invasive or threatening. Recognizing its value to research centers, medical facilities, and other health professionals trying to recruit older patients, NIA chose this video for national distribution.

Team approach required

"The fight against Alzheimer's disease requires a team approach by a coalition of scientists and clinicians," Mesulam emphasizes. "This multidisciplinary setting allows us to combine patient service with scientific inquiry. The science is truly exciting and has already led to numerous discoveries on the organization of thought, memory, and language in the brain. A major goal," he concludes, "is to understand why these parts of the brain are vulnerable to diseases that cause dementia and what we can do for prevention and treatment."

Additional information on CNADC and its programs may be found at www.brain.northwestern.edu. 



Alzheimer's disease. The bright objects are abnormal and cause a destruction of brain areas that control memory.

Scientific breakthrough – a biomarker for Alzheimer’s disease

As many as four million Americans may suffer from Alzheimer’s disease, but the diagnosis is never really certain until brain tissue is examined at autopsy. No clinical laboratory tests currently exist, and other diseases give symptoms that resemble Alzheimer’s disease. Recently, however, a team of Northwestern researchers – headed by Chad Mirkin, chemistry and director of the Institute for Nanotechnology, and William Klein, neurobiology and physiology and a member of the Cognitive Neurology and Alzheimer’s Disease Center – became the first to identify in samples from living humans a biomarker associated with Alzheimer’s disease.

Discovery of ADDLs

In 1998, Klein and his colleagues discovered the existence of small neurotoxic proteins called “amyloid β -derived diffusible ligands” (ADDLs) in laboratory-bench experiments. In 2003, they proved that ADDLs accumulate in brain tissue of individuals with Alzheimer’s disease, with levels up to

70 times more than found in healthy individuals. [Y. Gong, et al. *Proceedings of the National Academy of Science*, 100:10417-10422 (2003).] Researchers now think it is likely that ADDLs cause Alzheimer’s disease memory loss, making them an ideal biomarker for diagnostics, as well as a target for therapeutics.

ADDLs disrupt synapses

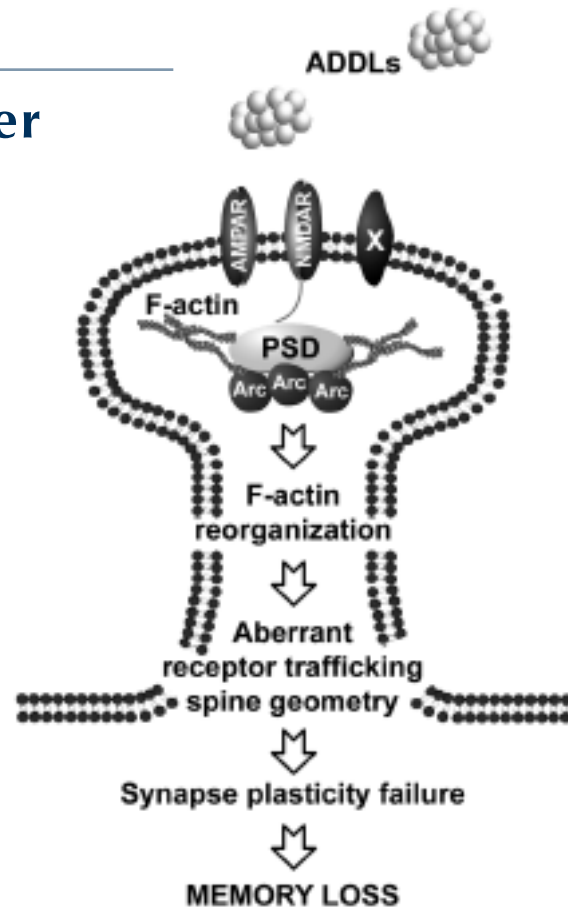
ADDLs specifically attack and disrupt synapses, the nerve cell sites responsible for information processing and memory formation. “Memory starts at synapses, so it was probable that Alzheimer’s disease would be a synapse failure,” Klein points out.

“Why is the damage so specific to memory?” he continues. “First, ADDLs bind to some synapses and not others – a very specific attack. Second, at the vulnerable synapses there is a gene linked to memory that needs to be expressed properly. When ADDLs attack those synapses, they disrupt normal expression of that gene, called *Arc*, and we think that causes memory loss.” [P. Lacor, et al. *Journal of Neuroscience*, 24:10191-10200 (2004).]

ADDLs were predicted to leak into the cerebrospinal fluid. However, the nanometer size of the ADDL biomarkers and their extremely low concentration in cerebrospinal fluid made detection impossible with conventional tools.

New analytical tool

In 2003, the invention of the ultra-sensitive bio-barcode amplification (BCA) technology by Mirkin and his research group provided a powerful new analytical tool 5,000 times more sensitive than available methods for the detection of both protein and nucleic acid targets. [J.-M. Nam, et al. *Science*, 301:1884-1886 (2003);



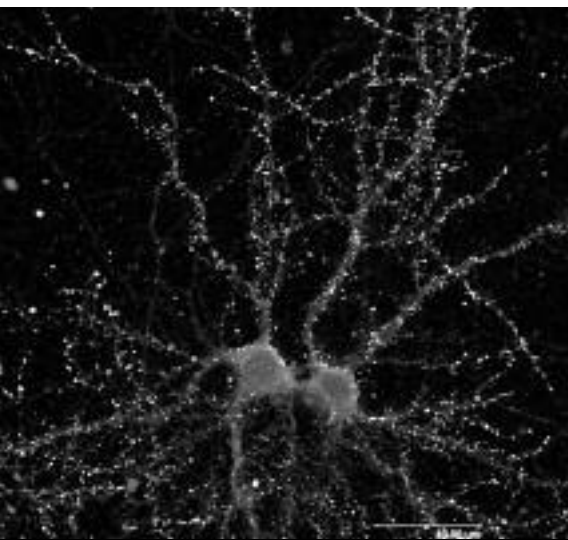
How ADDLs are thought to cause memory loss. As illustrated by this diagram, ADDLs are pathological ligands that bind with specificity to particular synaptic proteins (e.g., glutamate receptor subtypes), triggering expression of the memory-linked protein known as *Arc*. Ectopic *Arc* expression disrupts receptor trafficking and spine structure, likely through effects on f-actin. The consequence is failed synaptic information storage and lost capacity for long-term memory formation. Diagram by Kirsten Viola.

J.-M. Nam, et al. *Journal of the American Chemical Society*, 126:5932-5933 (2004).]

The marriage of Klein’s discovery and Mirkin’s technology has provided the first critical step in the early detection of Alzheimer’s disease.

How BCA works

In the BCA process, a magnetic microparticle and a gold nanoparticle are each outfitted with an antibody specific to the antigen – in this case, ADDLs. In solution, the antibodies “recognize” and bind to the ADDL, sandwiching the protein between the two particles. Also attached to each tiny gold nanoparticle (just 30 nanometers in diameter) are hundreds to thousands of identical strands of DNA. Mirkin calls this “barcode



ADDL-targeted neurons. Neurotoxins that accumulate in Alzheimer’s disease-afflicted brains have an unusual ability to bind to synapses, the parts of nerve cells where memory formation begins. These neurotoxins, called “ADDLs,” are shown in this image as bright spots coincident with synapses. Image courtesy of Pascale Lacor.

DNA” because it has been designed as a unique label specific to the target.

After the “particle-ADDL-particle” sandwich is removed magnetically from solution, the barcode DNA is removed from the sandwich and read using standard DNA detection methodologies.

Groups differentiated

ADDL concentrations in the cerebrospinal fluid of patients who had been evaluated and determined to have Alzheimer’s disease were consistently higher than the levels found in the control group of healthy individuals who were not demented; the two groups were easily differentiated.

“Before this assay can be used clinically, however,” Mirkin emphasizes, “it needs to be statistically validated with a patient pool larger than the 30 individuals we tested.”


The ability to discriminate patients with Alzheimer’s disease from healthy individuals could help advance discovery of new therapeutics by determining who should participate in clinical trials and by providing readouts to assess efficacy.

The researchers would next like to develop the technology so that the test could be done using a blood or urine sample instead of cerebrospinal fluid, which is more difficult to obtain.

Looking ahead

Since its invention, BCA technology has also been used to detect trace amounts of anthrax lethal factor and prostate specific antigen.

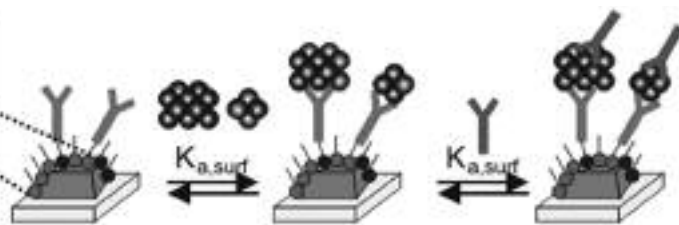
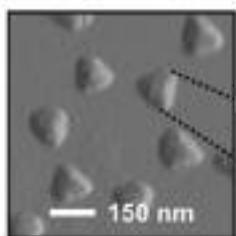
Looking ahead, the extraordinary sensitivity and selectivity of the test could be used to target known biomarkers for a wide variety of

diseases – such as HIV infection, various cancers, and Creutzfeldt-Jakob disease – enabling early diagnosis that would be impossible with conventional technology. 

The Mirkin and Klein findings were published online in January 2005 by the *Proceedings of the National Academy of Sciences (PNAS)* and appeared in the February 15, 2005, issue of *PNAS*, 102:2273-2276. In addition to Mirkin and Klein, other authors on the *PNAS* paper are lead author Dimitra G. Georganopoulou, post-doctoral fellow, Lei Chang, research associate in neurobiology and physiology, and C. Shad Thaxton, graduate student, all from Northwestern University; Jwa-Min Nam, former graduate student at Northwestern; and Elliott J. Mufson, Rush University Medical Center, Chicago.

The research was supported by the National Science Foundation (NSF), NSF Nanoscale Science and Engineering Center, Department of Defense, National Institutes of Health, and Boothroyd Foundation.

Nanoscale optical biosensor technology



Northwestern researchers William Klein, neurobiology and physiology, and Richard Van Duyne, chemistry, collaborated to develop another test that detects amyloid β -derived diffusible ligands (ADDLs) in cerebrospinal fluid.

In this work, a nanoscale optical biosensor based on the localized surface plasmon resonance (LSPR) of silver nanoparticles was used to study the interactions between the antigen ADDLs, and specific anti-ADDL antibodies. Using the sandwich assay format, the LSPR nanosensor provided quantitative binding information for both antigen and second antibody detection that permits the determination of ADDL concentration at the 50 femtomolar level.


This unique capability offers the possibility of measuring the tendency of ADDLs to stick to one another, ultimately forming the fiber-like aggregates that are associated with neuron death. Furthermore, this study demonstrated, for the first time, that the LSPR nanosensor was successful at analyzing human brain extract and cerebrospinal fluid samples.

Examination of these results from both Alzheimer’s disease and control patients reveals that the LSPR nanosensor provides new information relevant to the understanding and possible diagnosis of Alzheimer’s disease. This important advance is one of the first results from studies in which nanotechnology has been

AT LEFT: Schematic representation of LSPR immunoassay for an Alzheimer’s disease biomarker.

The usefulness of LSPR nanosensor technology for the screening of human samples for disease diagnosis has been demonstrated for the first time. These results suggest that a more general approach to the understanding of diseases and drug-target interactions may be at hand. Figure reprinted with permission from “Detection of a Biomarker for Alzheimer’s Disease from Synthetic and Clinical Samples Using a Nanoscale Optical Biosensor,” A.J. Haes, L. Chang, W.L. Klein, and R.P. Van Duyne. *Journal of the American Chemical Society*, 127:2264-2271. ©2005 American Chemical Society.

applied to clinical materials for biomolecular diagnostics.

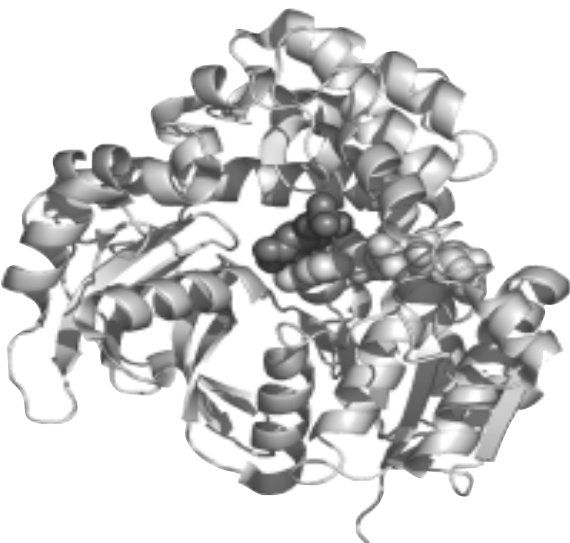
The LSPR method and the barcode amplification (BCA) technology differ in the way they measure ADDLs. The BCA technology can detect the proteins even if they are present in very small amounts, while the LSPR method is able to determine quantitatively the binding strength of ADDLs to their antibodies and measure the size of the proteins it detects. 

Center for Drug Discovery and Chemical Biology

“The newest University research center, the Center for Drug Discovery and Chemical Biology (CDDCB), actually needs no introduction,” remark Center co-directors Martin Watterson, molecular pharmacology and biological chemistry, and Linda Van Eldik, cell and molecular biology. “It evolved from the faculty-initiated Drug Discovery Program that was established in 1996 to facilitate interdisciplinary research and educational activities,” they explain. “The Drug Discovery Program was one of the first academic-based drug discovery programs in the United States and is recognized as a national and international center of excellence.”

What is drug discovery?

Drug discovery, as its name implies, is the early, more exploratory phase of the drug discovery/drug development continuum. Interdisciplinary research in this early phase is much like other scientific research in the basic and clinical disciplines, except that drug discovery research focuses on the implications for later therapeutic intervention. The goal is to move beyond description into knowledge of mechanism that will facilitate rational intervention.



Three-dimensional structure of an enzyme with a bound product and co-factor shown as dark and light grey spheres. In addition to providing insight into mechanisms of enzyme catalysis, the high-resolution structure provides the starting point for structure-assisted design of enzyme inhibitors. Image courtesy of CDDCB investigator Wayne Anderson.

“Drug discovery research seeks to use new insights regarding a macro-molecular structure or biological pathway as a starting point for identification and validation of targets that can potentially be manipulated by compounds,” Van Eldik observes.

“Which means,” she continues, “we ask whether it is possible to intervene in a biological process to inhibit development or progression of disease. Important next steps for success in later stage drug development are considerations of the ability of compounds to get to the drug discovery target, to modulate selectively the function of the target, and to have biological endpoints of preclinical research that are translatable to the clinic.”

What is chemical biology?

Chemical biology focuses on the design, identification, and application of small molecules to investigate the multifaceted functions of living cells and organisms. Integrated biology seeks to place the knowledge of both molecular and cellular processes into a broader context. The marriage of these two fields generates integrative chemical biology investigations that emphasize the *in vivo* administration of compounds and measurement of the subsequent functional effects on the entire biological system.

“The resulting basic science knowledge from integrative chemical biology investigations has the potential to provide information for future drug discovery efforts because small molecule perturbations are used as a foundation,” Watterson says. “This interdisciplinary research from atom to animal allows small-molecule modulation of pathways and processes to investigate a central drug discovery question: is a molecular target or pathway ‘druggable?’”

CDDCB promotes interdisciplinary research

CDDCB provides an umbrella under which faculty with diverse research expertise collaborate in synergistic, interdisciplinary subgroups, leading to coordinated investigations and

educational opportunities that enhance the overall quality of drug discovery and chemical biology research. In addition to providing a critical link between fundamental research and discovery of new therapies and diagnostics for diverse disorders, the Center also serves as an interface for discipline-based research in biology, chemistry, and molecular biophysics. The Center’s objective is to facilitate innovative investigator-initiated research and to minimize barriers to academic research in the areas of integrative chemical biology and drug discovery.

CDDCB now includes more than 35 clinical and basic science faculty from the Feinberg School of Medicine, Weinberg College of Arts and Sciences, Children’s Memorial Hospital, and University of Chicago, as well as the directors of the Robert H. Lurie Comprehensive Cancer Center, Cognitive Neurology and Alzheimer’s Disease Center, and Institute for BioNanotechnology in Medicine. Compared to other academic chemical biology or drug discovery programs, CDDCB is in an advantageous position because of the existence within a single center of the requisite expertise in synthetic organic and medicinal chemistry, structural biology, pathophysiology, animal models of disease, and translational research.

“Some examples of the types of research pursued by CDDCB faculty provide insights into the interdisciplinary nature of the research carried out by Center investigators,” Watterson comments. “Richard Silverman’s chemical biology research that led to development of a new drug which fills a major unmet need – and may be a new ‘blockbuster’ for Pfizer, Inc., under the tradename of Lyrica – is a good example that has gone from testing hypotheses in basic science to the bedside.”

Planning for serendipity: from bench to bedside

Silverman and his colleagues try to understand how to interfere with the

enzymes involved in neurological diseases by the design of small organic molecules as potential selective inhibitors of the enzymes. In some cases they have developed molecules that do precisely what they are targeting, and in other cases they have developed molecules that are biologically effective, but for unexpected reasons.

The latter is the case with Lyrica. “If we had not started by studying a particular biological system,” Silverman says, “we would never have made serendipitous discoveries.”

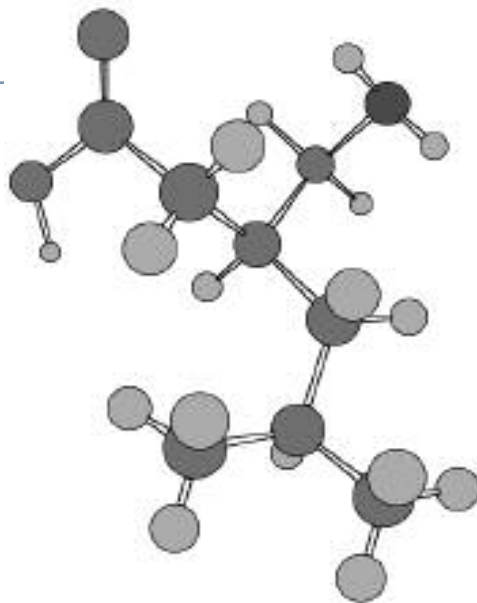
Interest in the enzyme GABA aminotransferase

The story of Lyrica, formerly called pregabalin, started with Silverman’s interest in the enzyme GABA aminotransferase, the enzyme that degrades the inhibitory neurotransmitter GABA. Certain diseases, such as some epilepsies, are characterized by a decrease in the concentration of this inhibitory neurotransmitter in the brain. The concentration of GABA can be raised by inhibition of its degrading enzyme, GABA aminotransferase, and Silverman was interested in finding selective GABA aminotransferase inhibitors.

Unfortunately, the enzyme that makes GABA, glutamate decarboxylase, is similar to GABA aminotransferase, and a molecule that inhibits both of these enzymes would clearly be counter-productive. Fortunately, Silverman and his colleagues serendipitously discovered compounds that activated glutamate decarboxylase, rather than inhibiting it, raising the possibility of producing more GABA by activation of the enzyme that makes it. As this discovery would be a new mechanism for increasing GABA levels in the brain, they had potentially reached their scientific goal via an unexpected route.

Lyrica

Eventually, Lyrica, the name for the lead compound chosen for later drug development, was quite effective in clinical trials for three different indications: epilepsy, neuropathic pain, and anxiety. “Lyrica was not designed as a therapeutic for



The structure of Lyrica, a new FDA-approved drug synthesized at Northwestern University by CDDCB investigator Richard Silverman.

neuropathic pain, but if I had not been interested in studying effects of small molecules on brain enzymes, this would not have been discovered,” Silverman affirms. “I should also say that the mechanism of action of this drug as an anticonvulsant agent turns out to be unrelated to activation of glutamate decarboxylase. There is a calcium channel to which it binds as well, which is the ultimate cause for its effect.”

In terms of the linkage between chemical biology and drug discovery, Silverman notes that he is a strong believer in rational design of small molecules as potential therapeutics – as is every drug company. “One of the goals of CDDCB,” he adds, “is to foster an intellectual and collegial environment that facilitates the translation of research at the chemistry-biology interface and the ready pursuit of its associated serendipitous discoveries.”

New therapeutic approach discovered

An integrative chemical biology collaboration between medicinal chemists in Watterson’s laboratory and biologists in Van Eldik’s laboratory resulted in the discovery of a new therapeutic approach in neurodegenerative diseases, such as Alzheimer’s disease, and has now evolved into a bona fide drug discovery project. With lead compound development

being done by the Watterson group and biological validation by Van Eldik’s group, this collaborative effort is moving toward filing of an Investigational New Drug Application in the near future.

Neurodegenerative disorders

Alzheimer’s disease and related neurodegenerative disorders are characterized by an excessive and chronic activation of glial cells that leads to a state called neuroinflammation. The normal role of the glial cells is to cooperate with the neurons to keep the brain operating smoothly. When an injury or change in the brain occurs, the glial cells mount an inflammation response to fight off the insult and restore the brain to its proper functioning.

Diseases such as Alzheimer’s, however, are characterized by over-activation of the glia, causing a dangerous level of neuroinflammation that can lead to nerve cell dysfunction which is manifest as dementia (see image, bottom right, on back cover). Although neuroinflammation appears to play a pivotal role in the development and progression of neurodegeneration, the molecular triggers and mechanisms underlying the process and the discovery of approaches to downregulate the neuroinflammation received little attention prior to the pioneering work of the CDDCB investigators.

Kinase inhibitors

Chemists in Watterson’s laboratory had developed a chemistry platform for the rapid design, production, and testing of bioavailable protein kinase inhibitors. Protein kinases – key regulators of cellular homeostasis and response to injury and disease – are an emerging class of therapeutic targets across multiple disease areas. For example, the first Food and Drug Administration (FDA) approval of a kinase inhibitor, the anti-cancer drug Gleevec, was a recent landmark event.

Protein kinase mediated pathways are known to control the expression of genes encoding proinflammatory and oxidative stress related proteins. The dampening of excessive production of these damaging

—see CDDCB, continued on p. 10

proteins by inhibition of protein kinase mediated pathways was, therefore, a logical hypothesis to test. A concern for all new therapeutics is the bioavailability of a drug, the drug's ability to be taken up efficiently by the tissue of interest. This concern is especially critical for passage across the blood brain barrier.

Promising compounds

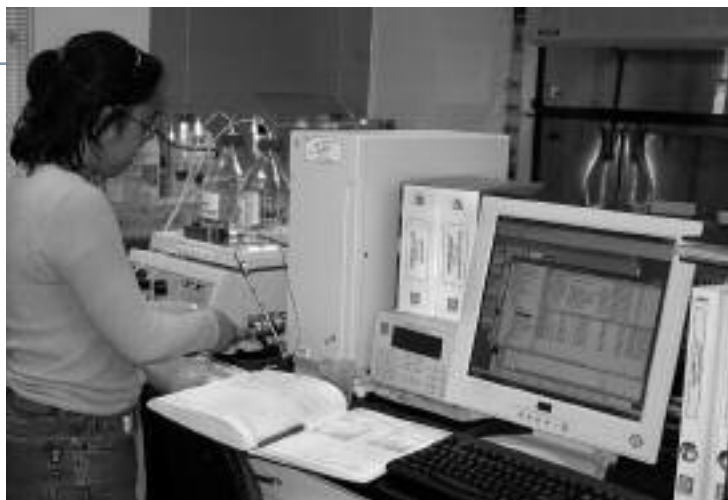
The synthetic protein kinase inhibitors made in the Watterson laboratory have a high potential for brain uptake and were assayed by Van Eldik's group for their ability to suppress selective glial activation responses and to attenuate associated brain dysfunction.

A set of promising compounds was shown to suppress disease onset and progression in an animal model of Alzheimer's disease, including the amelioration of behavioral deficits reflective of neuro-inflammatory injury to the hippocampus – the part of the brain whose functioning is linked to the cognitive decline seen in Alzheimer's and related disorders. These novel and exciting results provide the foundation for current development of lead compounds for future clinical investigations.

The ability to identify rapidly a druggable pathway in pathophysiology and to move immediately towards new therapeutic development demonstrates the capability of the interdisciplinary environment provided by CDDCB to facilitate testing of fundamental hypotheses in biology and to translate the findings towards the clinic.

From bedside to bench: explaining chemoprevention

While many of the Center investigators' research projects focus on translating basic science discoveries into clinical applications – bench to bedside – Raymond Bergan, hematology/oncology, is pursuing cancer-related work that could be described as moving from bedside to bench. To obtain insights into basic cancer biology, Bergan is using epidemiological information from human



Postdoctoral scholar Hantamalala Ranay-Ranaivo uses high performance liquid chromatography to study metabolism of new anti-cancer and anti-neurodegeneration drugs synthesized in the laboratory of CDDCB investigator Martin Watterson. Image courtesy of CDDCB.

population studies to identify potential therapeutics and then, at the bench, testing hypotheses about how those drugs work.

It has been known for a long time from epidemiological studies that populations, such as Southeast Asians, which consume high levels of dietary soy have about a ten-fold lower rate of occurrence of prostate cancer than non-soy consumers in the United States. There is also evidence that one component in dietary soy, called genistein, may be associated with these lower rates of metastatic prostate cancer. Genistein is active in preventing cancer in a number of preclinical model systems and is currently being tested by Bergan and others in human clinical trials as a chemoprevention agent. The mechanisms by which genistein may exert its anti-cancer activities are not known.

Studies of genistein

To explore potential cancer-related cellular pathways upon which genistein may be acting, Bergan is performing mechanistic studies with cancer cells in culture. To inform and guide the design of this bench research, data on such factors as dietary levels of genistein, clinically relevant drug concentrations, and efficacy after extended periods of administration are being gathered from the human studies. The mechanistic bench studies, in turn, are leading Bergan to new discoveries about how cancer preventive agents such

as genistein may work, discoveries which can then be translated back into clinical studies.

Educational initiatives

In providing training for the next generation of drug discovery and chemical biology scientists, CDDCB emphasizes the integration of

research and education, with a focus on interdisciplinary research training. The educational programs of the Center provide trainees with opportunities to develop a firm intellectual foundation and to acquire the skills needed to be independent scientists with an understanding of the multiple interdisciplinary experimental and technical strategies that can be used to address research questions.

In addition to appreciating the drug discovery and *in vivo* chemical biology process and its implications for future health care advances, trainees also gain a

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realistic perspective on how scientific discoveries can be translated most readily into applications. CDDCB provides opportunities for trainees to participate in courses and specialized workshops, present their work at regional and national meetings, and develop short-term projects or collaborative experiences in other academic institutions or in industry.

Fostering broad perspectives

Students and fellows also have the opportunity to participate in international exchange programs for the purposes of education and training in specific areas of complementary expertise. Two institutions participating in such exchange programs are Université Louis Pasteur in Strasbourg, France, and the Cardiology Institute in Moscow, Russia. The presence of international students and fellows in Chicago area laboratories and the visits of trainees to foreign laboratories provide a broader perspective for future career development.

Another defining feature of CDDCB's educational initiatives is the emphasis on diversity of both investigational methods and investigators. The summer undergraduate research program administered by the Center is particularly successful in the latter regard, with excellent representation of women and minorities from the quantitative sciences.

Overall, CDDCB provides educational innovation across disciplinary lines and a training environment that promotes confidence in self-directed learning, a life-long intellectual skill needed for continued success and productivity.

Additional information on CDDCB and its programs may be found at www.northwestern.edu/research/cddcb. 



Chemists synthesizing new anti-cancer and anti-neurodegeneration drugs in the Watterson laboratory. From left to right: Postdoctoral scholar Heather Behanna, senior chemist Sakti Roy, and predoctoral scholar Laurie McNamara. Image courtesy of CDDCB.

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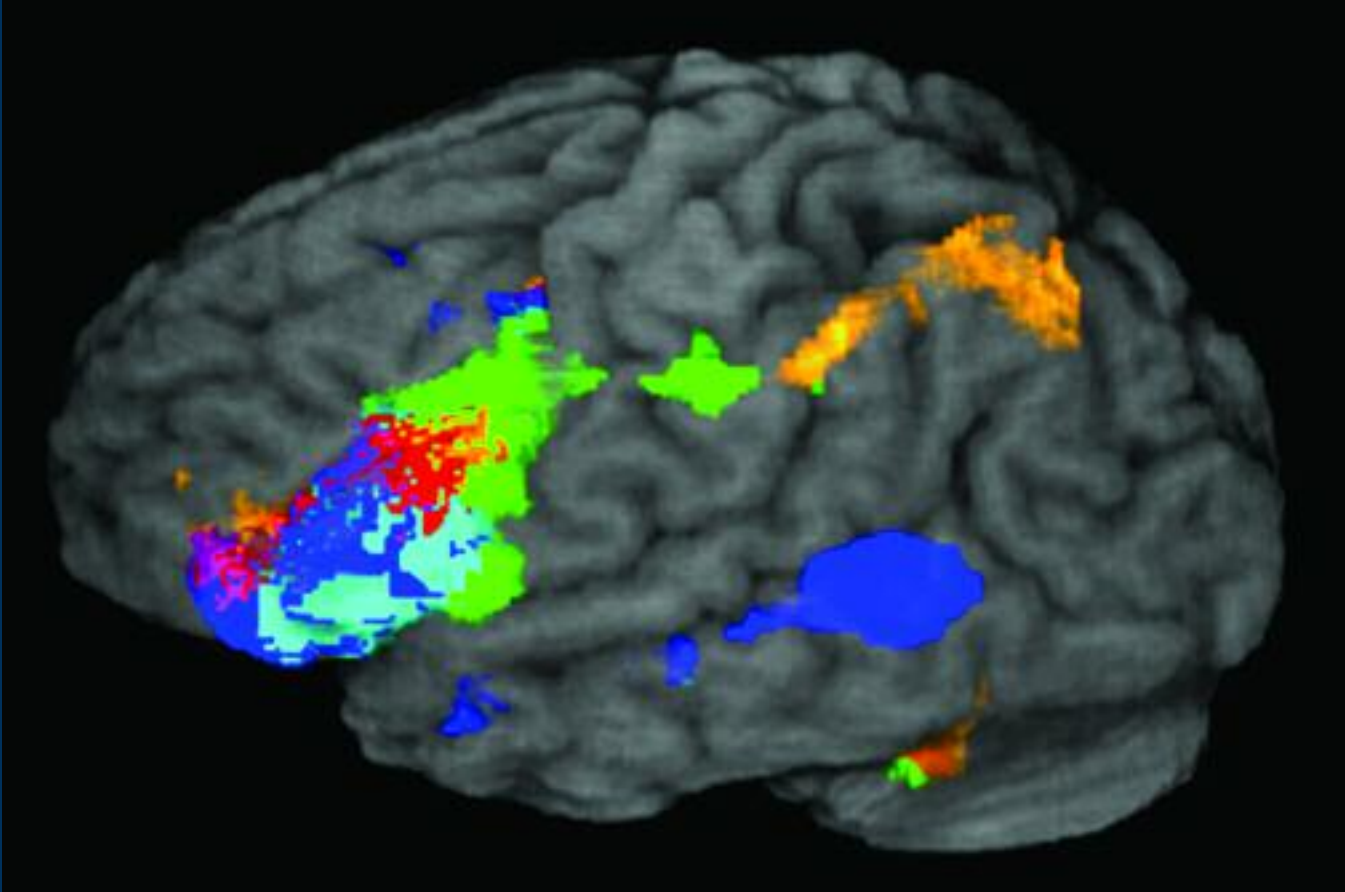
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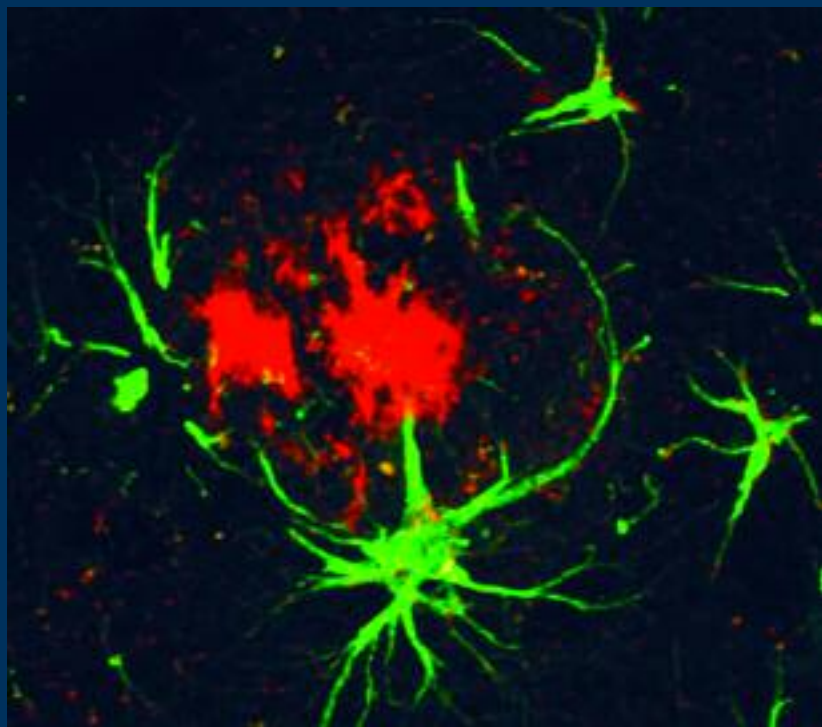
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Images from Northwestern research centers

ABOVE: Functional imaging during language tasks. Image of the left hemisphere, human brain. Different brain areas are involved in specific aspects of language: blue, word meaning; orange, spelling; and green, phonology. This image is from work at the Cognitive Neurology and Alzheimer's Disease Center by Darren Gitelman, Cynthia Thompson, Anna Nobre, Todd Parrish, and Marsel Mesulam of the Cognitive Brain Mapping Group. See related article on p. 2.

RIGHT: Inflammation response. Neuroinflammation as seen by increased size and number of glial cells (green) surrounding an amyloid plaque (red) in the brain of a mouse model of Alzheimer's disease. This image is from work at the Center for Drug Discovery and Chemical Biology by Holly Oakley and Robert Vassar. See related article on p. 8.



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