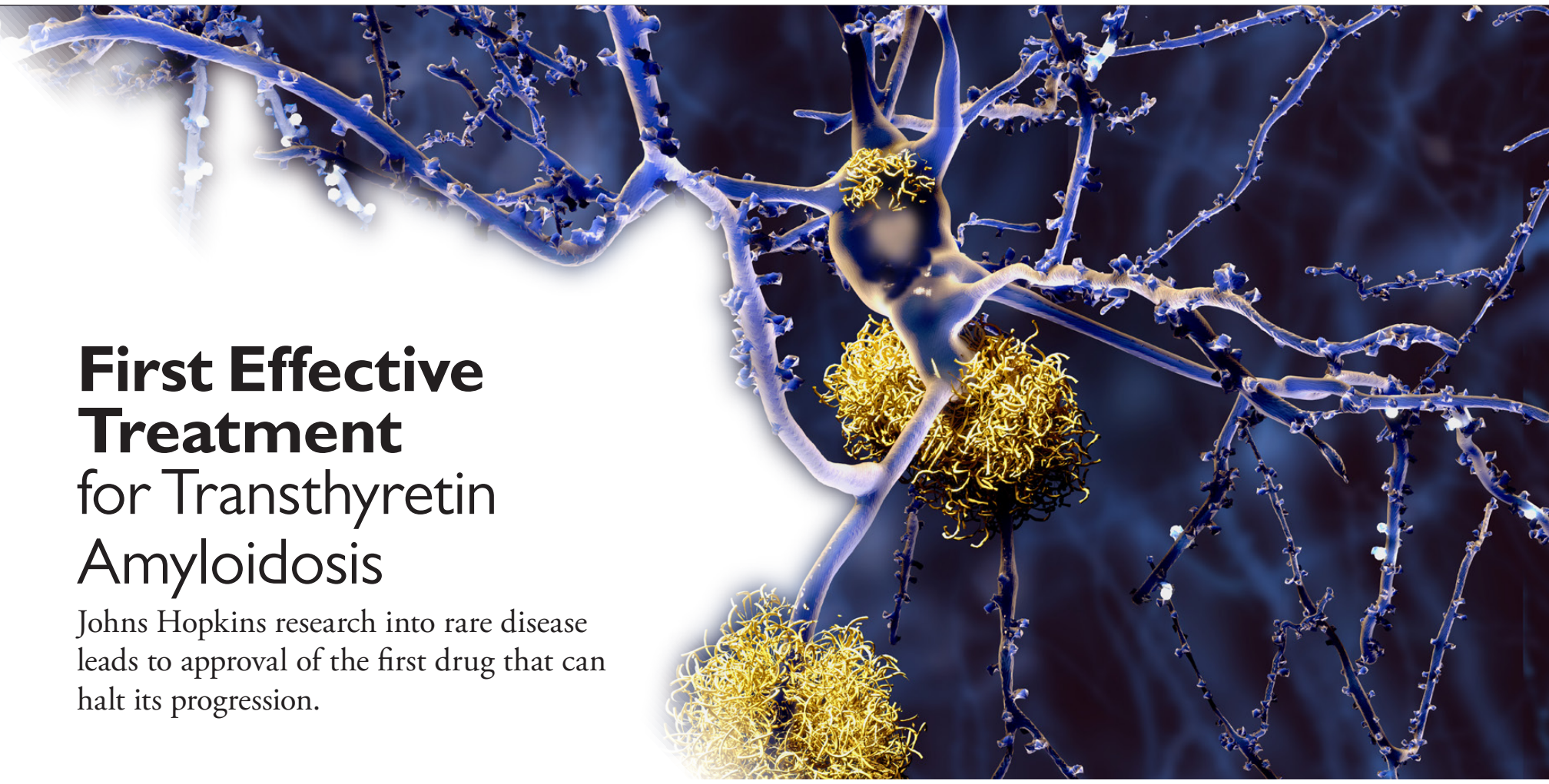
JOHNS HOPKINS MEDICINE

Physician Update

NEWS FOR PHYSICIANS FROM JOHNS HOPKINS MEDICINE

WINTER 2019



First Effective Treatment for Transthyretin Amyloidosis

Johns Hopkins research into rare disease leads to approval of the first drug that can halt its progression.

Over the past two decades, Johns Hopkins neurologist **Michael Polydefkis** has cared for hundreds of patients with transthyretin (TTR) amyloidosis. This inherited disease, affecting an estimated one in 100,000 people in the U.S., causes the abnormal proteinacious deposits known as amyloid to accumulate in the nerves, heart and other locations—leading to neuropathy, heart failure and eventually death.

"It was a disease that I dreaded diagnosing in patients because I knew what they had in store," Polydefkis says.

Now, research conducted in Polydefkis' lab and elsewhere is providing new hope for patients, paving the way for drugs that have the potential to reverse this disease's progression for the first time.

Polydefkis explains that this disease stems from TTR, a protein produced mainly in the liver that ferries thyroid hormone and retinol elsewhere in the body. This protein is usually bound in a tetramer form that dissociates into four individual pieces. In some people, these pieces misfold into a square-like shape that agglomerates, leading to amyloid deposits.

Although a subset of patients can be cured with liver transplants, and a drug that could slow the disease somewhat was approved in Europe, there were no truly effective treatments for the majority of patients with this disease in the United States.

"We'd watch patients who rode horses or go square dancing or do needlework lose the ability to do those things," says Johns Hopkins neurology nurse practitioner **Kathleen Burks**. "This disease doesn't cause any cognitive decline, so these patients were just trapped in bodies that were turning on them."

However, several years ago, researchers devised a couple new approaches to this disease. Both centered on knocking down the levels of this protein using either an antisense oligonucleotide or RNA interference (RNAi). Polydefkis says that he, Burks, and their colleagues at Johns Hopkins leaped at the opportunity for Johns Hopkins patients to join these trials. As an aid to track patients' prognoses, Polydefkis' lab developed a protocol to test for amyloid using punch skin biopsies, a method that Polydefkis pioneered years ago to diagnose and follow various forms of neuropathy.

The results from both trials were overwhelmingly positive, says Burks. Although the first part of each trial was double-blind, it was often clear who was taking the oligonucleotide (inotersen) or the RNAi drug (patisiran) and who was taking the placebo: the disease process of those taking either of these drugs stopped progressing. Some of those on the RNAi drug even showed small degrees of improvement.

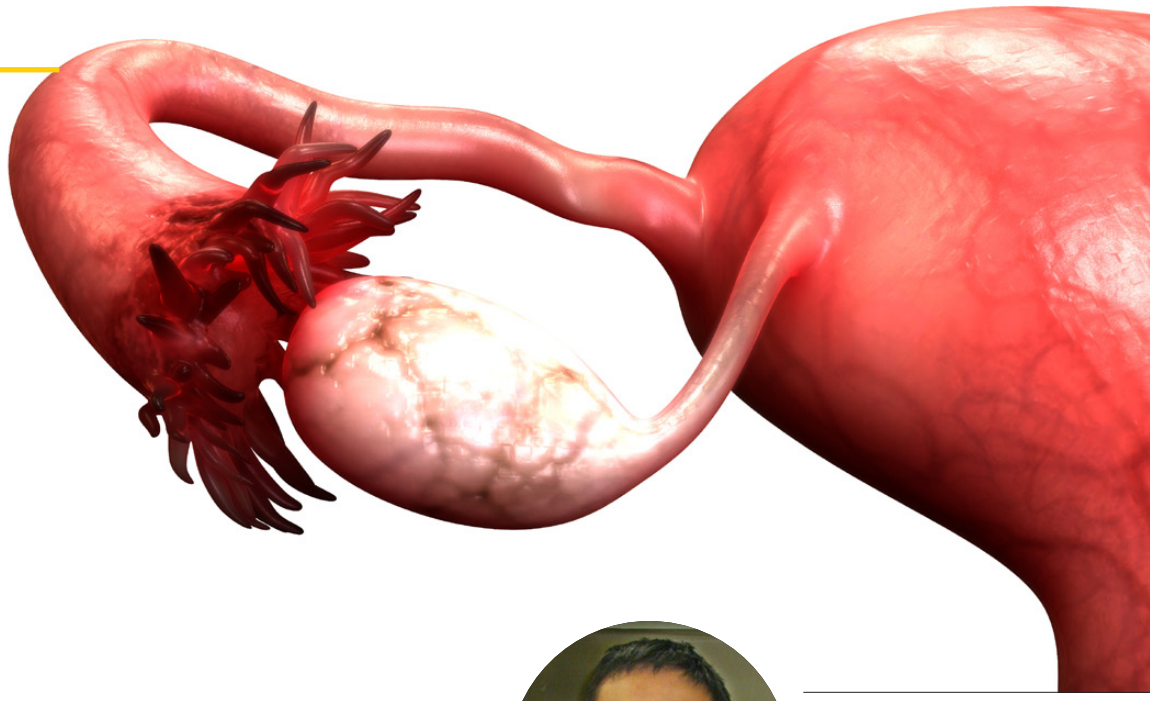
"To stay the same or improve in this disease is unheard of," Polydefkis says.

Patisiran was recently FDA approved, and inotersen is expected to follow shortly.

"This is a game-changer for a disease we've been completely defenseless against," Polydefkis says. "Now, when I have to deliver this diagnosis, I can be optimistic with patients for the first time." ■

To learn more, call 410-614-1522

Although a subset of patients can be cured with liver transplants, and a drug that could slow the disease somewhat was approved in Europe, there were no truly effective treatments for the majority of patients with this disease in the United States. Image shows 3D representation of abnormal amyloid buildup in nerves.



Uniting Basic and Applied Science **for Ovarian Cancer**

New Johns Hopkins-led SPORE helps speed translation from the lab to the clinic.

Despite many research efforts, ovarian cancer survival has improved only slightly over the past half-century. However, a federally funded research model combining basic and clinical work could help speed discoveries that lead to earlier detection and more effective interventions to fight ovarian cancer.

Johns Hopkins, in collaboration with the University of Pennsylvania, has recently became one of four Specialized Programs of Research Excellence (SPOREs) in the nation for this disease, joining the Mayo Clinic, Roswell Park Cancer Institute, and University of Texas/MD Anderson.

Each project funded by the SPORE, which provides $12.5 million over five years, is uniquely headed by both basic and applied scientists. The program requires that each of these projects produces a human end point within the five-year funding period.

Johns Hopkins physician-scientist **Ie-Ming Shih**, the principal investigator of the new SPORE, explains that late detection and a lack of effective treatments for late-stage disease are the two biggest hurdles to improving survival.

"To accelerate the discoveries and to deliver tools and new therapy critical for our patients, we need to integrate basic and clinical scientists together," says Shih.

Shih and colleagues are partnering to translate recent discoveries in ovarian high-grade serous cancer (HGSC) into clinical tools for early detection and more effective interventions through four projects. The specific aims of each project include:

1. Apply PapGene test for early ovarian cancer detection, using routinely collected liquid based cervical cytology specimens.
2. Modulate the ovarian tumor microenvironment with listeria-based vaccination.
3. Introduce epigenetic therapy to augment immune signaling and sensitize ovarian cancer to immune checkpoint inhibitors.
4. Explore the potential of SYK inhibitors to sensitize ovarian cancer to the anti-tumor effects of paclitaxel.

Amanda Fader, a clinical researcher leading the first SPORE project, is applying a specialized Pap smear test to detect ovarian cancer in its earliest stages, when it can be treated more easily. This test, when combined with an accompanying blood test, could help identify the presence of tumor DNA. "The work coming out of this SPORE has the potential for immediate or near-term impacts on patient care and patient outcomes," says Fader.

The three other projects listed above, says Shih, are aimed at overcoming ovarian cancer's ability to evade treatment or become resistant to chemotherapies. One of these aims to exploit a vulnerability in ovarian cancer cells by combining therapeutics; another seeks to overcome resistance to platinum chemotherapies through a different class of drugs known as BET inhibitors; the third seeks to make ovarian cancer cells more sensitive to paclitaxel by inhibiting a cancer protein called spleen tyrosine kinase.

IE-MING SHIH WORKS TO TRANSLATE DISCOVERIES IN HGSC INTO TOOLS FOR EARLY DETECTION AND EFFECTIVE INTERVENTIONS.

To accomplish the goals of each of these four projects, the new SPORE will have three cores (Administration, Biorepository/Pathology, Biostatistics) and two programs for Developmental Research and Career Enhancement, mechanisms that can bring new ideas and new investigators into ovarian cancer research. ■

Reducing Inflammation After Heart Attacks May Prevent Secondary Events

Trying to reduce inflammation in patients following a heart attack, **Thorsten Leucker** is employing a newer drug normally reserved for patients with stubbornly high low-density lipoprotein (LDL) cholesterol.

Drugs that inhibit the action of a protein called proprotein convertase subtilisin/kexin type 9 (PCSK9) are used for patients whose cholesterol remains high, despite treatment with statins. But studies by Leucker, a cardiac critical care physician and director of basic and translational vascular biology research at the Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, and others suggest that PCSK9, beyond raising cholesterol, mediates inflammation in a variety of tissues, including the endothelial cells lining blood vessels. Knowing that heart attacks bring a huge wave of inflammation, Leucker proposed giving heart attack patients a PCSK9 inhibitor in addition to standard therapies.

Thorsten Leucker

In a small clinical trial called EVACS (Evolocumab in Acute Coronary Syndrome), Leucker and his cardiology colleagues **Steven Schulman**, **Gary Gerstenblith**, **Steven Jones**, **Michael Blaha** and **Thomas Schindler**, and research program coordinators **Frances Kirkland** and **Christine McLeod**, are evaluating the effects of administering one dose of the PCSK9 inhibitor evolocumab during hospital admission for a heart attack on outcomes such as cholesterol, heart and blood vessel inflammation, and serum markers of endothelial cell function in the hospital and 30 days later, as well as the heart's function. The double-blind, placebo-controlled study of 60 patients is the first to investigate evolocumab in this setting.

"Our idea is that by giving the patients a PCSK9 inhibitor, we can limit the degree of inflammation and thereby improve healing of the injured heart muscle, stabilize plaques and prevent any new heart attacks during the high-risk, 30-day period following a heart attack," Leucker says.

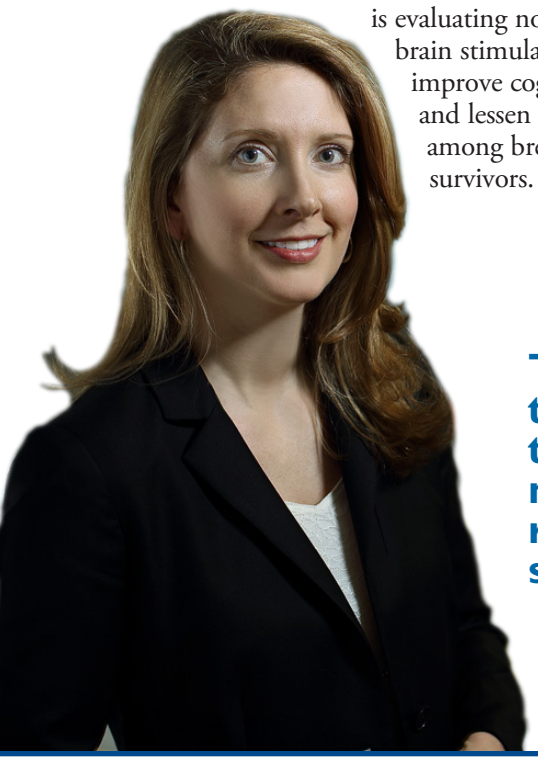
The trial emerged from a friendly discussion while walking down the halls when Leucker was a fellow, says Jones, director of inpatient cardiology.

Addressing Cognitive Problems That Arise from Cancer Treatment

As cancer treatments improve, the number of survivors is expected to reach 20 million by the year 2026, says neuropsychologist **Tracy Vannorsdall**. But cancer and its treatment can lead to changes in brain structure and function, resulting in reduced cognitive and mental health for survivors.

Vannorsdall, who studies cancer-related cognitive impairment, says many associate this with chemotherapy. But that's just one potential trigger. Radiation, endocrine treatments, pain medications and fatigue can also affect cancer patients' cognition. Rated by cancer survivors as one of the most problematic post-treatment symptoms, cognitive dysfunction can last for years, contributing to lower quality of life.

During a recent Grand Rounds talk at Johns Hopkins, Vannorsdall discussed two of her intervention studies. The first is evaluating noninvasive brain stimulation to improve cognition and lessen fatigue among breast cancer survivors.



This approach—using tDCS—will increase the likelihood that neurons will fire in response to cognitive stimulation.

—TRACY VANNORSDALL

Chemotherapy is associated with structural and functional changes in the brain's dorsolateral prefrontal cortex, an area that mediates complex cognitive function, says Vannorsdall. For this study, she is using transcranial direct current stimulation (tDCS)—a treatment that delivers a very low current via two electrodes placed on the scalp—while study participants complete a working memory task called a dual n-back test. Participants, seated at a computer, are presented with a series of shapes and sounds, then asked to determine if a shape or sound is identical to one presented one, two or three times back in the sequence. They complete five 30-minute sessions over a week.

"The notion is this will increase the likelihood that neurons underlying the electrodes will fire in response to cognitive stimulation," Vannorsdall says. "It's a very challenging task, but it's adaptive. If patients are having difficulty, the task gets simplified. Once they reach a level of success, it goes up a degree of difficulty." Prior studies have shown that tDCS improves working memory and reduces fatigue in multiple sclerosis patients.

In another study, Vannorsdall and radiation oncologist **Kristin Redmond** hoped to prevent cognitive deficits in patients with brain metastases. Prior studies indicated that sparing the hippocampus, which is involved in learning and memory, from radiation can help preserve memory. Vannorsdall and Redmond looked for other areas to be spared.

Redmond found that the genu, a "relay station" in the corpus callosum packed with neurofibers and involved in executive functioning, attention and processing speed, can be easily damaged by radiation. In a pilot study, Vannorsdall and Redmond are adapting radiation given to patients to shield the genu, and monitoring participants through cognitive testing; brain imaging to study their white matter; and questionnaires about participants' quality of life, moods and functioning.

Through this work, says Vannorsdall, "I think we have the possibility of helping preserve a wide array of cognitive skills." ■

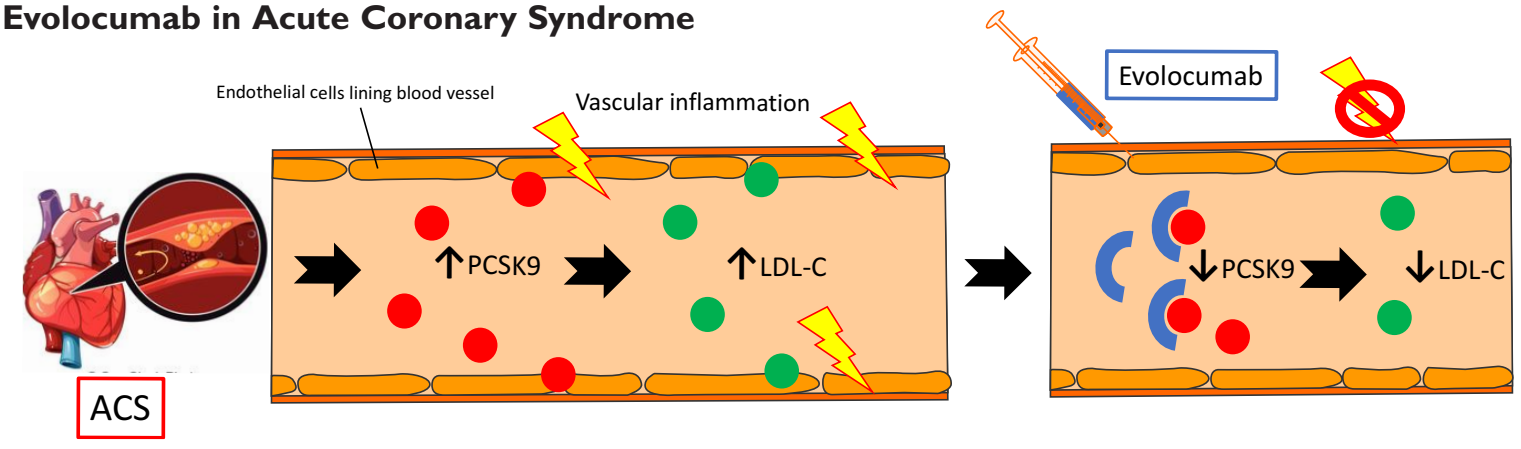
Learn more about cancer treatment and fuzzy thinking: **bit.ly/chemobrainhelp**.

The effort is supported by the psychiatry department's Venture Discovery Fund.

Cancer Treatments' Link to Cognition

- Poorer outcomes for patients with pre-existing mental illness
- Related to the development of mental health problems
- Associated with reduced cognitive functioning

Evolocumab in Acute Coronary Syndrome



"The implication of all this is rather large," he says. "If we find there is a striking improvement in outcome by giving both of these drugs early, this may become a new strategy to lower the early- and long-term risks and preserve heart function after a heart attack, which is a completely different philosophy regarding the use of these drugs."

Inflammation is one of several targets Leucker is studying in the vascular biology program. Others include evaluating high-density lipoprotein (HDL) in inflammation and monitoring lipoprotein(a) and its effects on conditions such as aortic stenosis. The researchers also are studying cells from other patients who are subject to inflammation, such as those with HIV and diabetes, in search of interventions that could protect against inflammatory insults.

"Our goal is to integrate the basic science and clinical components of the vascular biology program and develop bench-to-bedside projects to directly help our patients," Leucker says. ■

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Introducing the Johns Hopkins Doctor Referral App

This new app provides a simple way for health care providers to connect with and refer patients to physicians across Johns Hopkins Medicine in the departments of neurosurgery, orthopaedics, surgery and urology. Registration required.

Visit **bit.ly/hopkinsapp**

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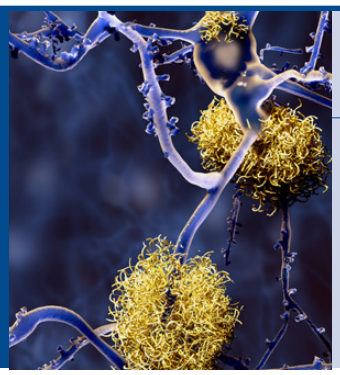
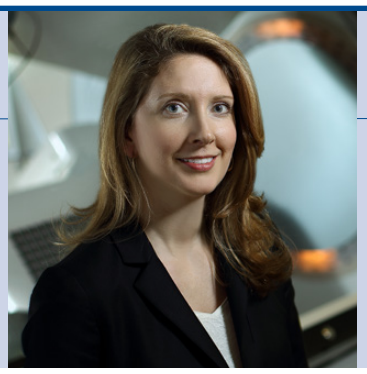
PhysicianUpdate

Inside





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