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Vaccine Trials and Other Therapies to Slow the Progression of Alzheimer's Disease

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"If we can slow progression of Alzheimer's by five years, we can cut the prevalence in half by 2050. There is a tremendous need to develop a therapy that slows progression," says Peter Snyder, PhD, senior vice president and chief research officer, Lifespan, and professor of neurology, The Warren Alpert Medical School of Brown University. The challenges posed by Alzheimer's disease are so vast and debilitating, with such far-reaching impact on millions of people worldwide, that finding solutions no longer can be handled in silos. It is through collaboration and sharing of resources and brainpower that a breakthrough on the horizon is promising. Not only will quality of life be improved for those affected and those who care for them, but the massive financial burden on our medical and social systems will also be significantly eased. In 2010, health care and academic institutions across Rhode Island created The Norman Prince Neurosciences Institute (NPNI), dedicated to advancing the neurosciences and treating nervous system disorders through world-class research, clinical care and education. Partners include Rhode Island Hospital and Bradley Hospital (part of Lifespan), Butler Hospital (part of Care New England), Brown University, and the Providence VA Medical Center. NPNI's three focus areas are neurodevelopmental diseases such as autism; neurorestoration and neurorehabilitation including assistive technologies and deep brain stimulation; and aging and dementia. Every project included in this profile falls under the umbrella of NPNI. At this point in time, attacking Alzheimer's disease at every point along its course is key. "We're knitting together strengths of multiple systems to advance novel diagnostics and therapeutics for dementia, with the goal of creating a combined Center for Clinical Research in Neurodegenerative Diseases," says Stephen Salloway, MD, director of Butler Hospital's Memory and Aging Program and a principal investigator at Lifespan. "We're working across the spectrum from clinical markers for early detection through to lifestyle interventions...from symptomatic therapies to vaccines. And there's a place for all of it."



From left, Stephen Salloway, MD, director of the Memory and Aging Program at Butler Hospital; Brian Ott, MD, director of the Alzheimer's Disease and Memory Disorders Center at Rhode Island Hospital; and Peter Snyder, PhD, senior vice president and chief research officer of Lifespan

According to Salloway, a big part of the equation is creating a risk profile similar to those for heart disease and cancer. To that end, Brian Ott, MD, director of Rhode Island Hospital's Alzheimer's Disease and Memory Disorders Center, has led the recent launch of **Prevent AD: The Rhode Island Alzheimer Prevention Registry** to find ways to delay early symptoms. Funded by the National Institute on Aging, and in collaboration with Butler Hospital and Memorial Hospital, the registry provides those at risk for developing Alzheimer's, but who show minimal or no symptoms, access to the most promising prevention trials. Snyder and Salloway are also centrally involved in a major international prevention trial called DIAN Dominantly Inherited Alzheimer Network —studying a rare form of Alzheimer's disease caused by three different gene

mutations. Funded by the National Institute on Aging and private sources, DIAN currently involves 13 research institutions in the United States, United Kingdom, Germany and Australia. Salloway leads a primary clinical site at Butler, and he will be a project leader testing two monoclonal antibody vaccines and a small-molecule treatment against amyloid plaque—a hallmark of Alzheimer's disease. Snyder is responsible for assessing cognitive changes in all study patients. A second major international trial for which Rhode Island Hospital and Butler Hospital are central sites is ADNI—The Alzheimer's Disease Neuroimaging Initiative. This \$100 million longitudinal study aims to determine the best biological markers of early Alzheimer's disease using cutting-edge brain imaging techniques and laboratory tests. Snyder was one of the original architects of ADNI, and a co-author of the project plan in 2001.

"Our goal is to move the intervention earlier to the mild cognitive impairment or preclinical stages of the disease," says Snyder. "The ADNI database, which is open to all, has allowed us to make important progress in the development of reliable biomarkers of early disease progression, allowing us also to model how many subjects we need for clinical trials. Investigators from around the world have published more than 250 articles from ADNI data." In collaboration with Snyder and Salloway, Ott leads Lifespan's involvement in the Alzheimer's Disease Cooperative Study, a consortium of Alzheimer's research centers that carries out clinical trials sponsored by the National Institutes of Health. The first upcoming trial, A4, is a multicenter prevention study using PET imaging to determine whether treating people in the preclinical phase can prevent cognitive decline. "A great advance in the field is our ability to see amyloid plaques in a living person safely," says Ott. "Seven years ago, someone had to pass away and then we looked at brain tissue under the microscope to make a definitive diagnosis."

A future direction includes a study of deep brain stimulation for Alzheimer's disease in which patients with mild symptoms will have electrodes implanted by neurosurgeon G. Rees Cosgrove, MD at Rhode Island Hospital, with follow-up treatment at Butler. "Half the patients will receive deep brain stimulation for the first year; the other half won't. We're hoping that those who do will have better cognitive performance," says Salloway. Extending Lifespan's expertise in preventing dementia are noninvasive lifestyle interventions that may alter a patient's risk profile. Lori Daiello, PharmD is studying the effectiveness of fish oil and other supplements, while Geoffrey Tremont, PhD is studying the impact of exercise, yoga, and relaxation therapies. Insulin resistance is another important piece of the puzzle. Rhode Island Hospital will soon participate in a clinical trial of intranasal insulin based on the work of Henry Querfurth, MD, Suzanne de la Monte, MD and others who have conducted basic laboratory research studying "type 3 diabetes" of the brain in Alzheimer's patients.

"I liken the Alzheimer's disease process to atherosclerosis, which also develops because of metabolic factors like diabetes and hypertension," says Ott. "After decades of the ravages of that process, plaques build up and close off your arteries—you get heart attacks and strokes that damage the heart or brain. You have to live with the aftermath; you can't turn that around. Similarly with Alzheimer's, we have to think about that model for how we approach the disease and intervene as early as possible."