By Scott LaFee and Jackie Carr

Howard Feldman, MD, FRCP(C), a renowned Canadian neurologist noted for his original research in geriatric cognitive disorders and expertise in large-scale clinical trials, has been named the new director of the Alzheimer’s Disease Cooperative Study (ADCS) at University of California, San Diego, pending approval from the National Institute on Aging (NIA). He will also serve as dean for Alzheimer’s and Related Neurodegenerative Research at UC San Diego School of Medicine.

“Dr. Feldman is an extraordinarily accomplished physician and scientist, a thought leader in Alzheimer’s disease clinical research,” said Pradeep K. Khosla, chancellor of UC San Diego. “His research – and the many trials he has led – has been vastly influential in the field. His leadership will take ADCS to new levels, and further elevate UC San Diego’s standing as a pioneering institution in Alzheimer’s research and treatment.”

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Feldman cont’d…..

Feldman’s arrival coincides with the launch of a University of California (UC) program to accelerate the most promising Alzheimer’s disease research into early proof-of-concept clinical trials. Sponsored by the UC Office of the President with a foundational grant of $4 million, the UC Cures for Alzheimer’s Disease Initiative invites hundreds of laboratories throughout the 10-campus system to find new answers to Alzheimer’s disease and related disorders. The clinical trials will be coordinated at ADCS.

“Alzheimer’s disease is a growing and unprecedented public health threat,” said UC president Janet Napolitano. “Many of the world’s best scientists and physicians dedicated to understanding and ultimately conquering Alzheimer’s work at UC. This initiative and the important work done – and still-to-be-done – at ADCS under the leadership of Dr. Feldman is intended to more speedily translate some of their best ideas into new treatments and, hopefully, an eventual cure.”

Feldman, a professor of neurology and executive associate dean of research at the University of British Columbia Faculty of Medicine in Vancouver, is a prolific physician-scientist credited with several key contributions in geriatric cognitive disorders, Alzheimer’s disease (AD) and other dementias including frontotemporal dementia. He has published more than 150 peer reviewed scholarly papers in epidemiology, genetics, biomarker development and experimental therapeutics.

In a 2007 profile, the journal *Lancet Neurology* called him the “master of dementia.” In 2014, the media and information conglomerate Thomas Reuters named Feldman among the “World’s Most Influential Scientific Minds” (2002-2012) and one of the “Most Highly Cited Researchers in Neuroscience and Behavior” (2002-2012).

The ADCS was founded in 1991 by the late Leon Thal, MD, Distinguished Professor and Chair of Neurosciences at UC San Diego School of Medicine, with support from the National Institute on Aging. Currently, the ADCS administers multiple clinical trials at test sites across the country.

Feldman has long been active in translating basic research into treatments that benefit patients. In 1991, the same year the ADCS was founded, Feldman established the Alzheimer Clinical Trials Program at the University of British Columbia (UBC). He has also served as director of UBC Hospital’s Clinic for Alzheimer’s Disease & Related Disorders. He led a national cohort study of disorders of Mild Cognitive Impairment (ACCORD study, 1997-2005) and contributed to the Canadian Study of Health and Aging, a highly influential project that followed 10,000 elderly Canadians over a ten-year period from 1991 to 2001, chronicling their changing health status.

He has been a lead principal investigator on a number of clinical trials exploring the use of cholinesterase inhibitors for AD and Mild Cognitive Impairment, a condition that often precedes AD. In addition, Feldman and colleagues have identified two causal genes of frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS), disorders which severely affect language behavior and motor function. These discoveries have provided important, new areas of interest in the development of treatment targets and biomarkers.

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“I think dementia research has entered a new stage,” said Feldman. “Over the past two decades, we’ve learned an enormous amount about the biology of disease, and have advanced our ability for the first time to visualize the pathology of the dementias in the living brain. This heralds a new era in being able to mark the impact of treatment as we seek the elusive goal of slowing or preventing these dementias. Though progress has been slow, the urgency and scale of AD is great within our aging society, and I am optimistic that with a focused global effort we will succeed at improving the quality of life of those at risk or with dementia.”

In a 2014 paper published in the *Annals of the New York Academy of Sciences*, Feldman and colleagues called for “a new research roadmap, one that pulls together government, regulators, industry, academia and the community in an unprecedented collaboration focusing on four key priorities: the fundamental mechanisms of disease; new translational research to speed basic research to clinical testing; innovative partnerships; and preventing AD.”

“We also have to emphasize the mantra of prevention,” Feldman said. “It has been projected that if in the coming three decades we can delay the onset of dementia by one year, we will be able to reduce the prevalence by 10 percent. Furthermore, if we delay it by five years, we can reduce the prevalence by 50 percent. Any scientific or medical advances that slow or prevent disease progression can exponentially benefit every aspect of society.”

Feldman’s understanding and vision for the future of AD treatment made him a compelling choice for the ADCS directorship, said David Brenner, MD, vice chancellor, UC San Diego Health Sciences and dean of UC San Diego School of Medicine. “Not to mention the extraordinary scope of his work and achievements. Dr. Feldman has rare and deep experience in both academia and in industry, a crucial combination. He understands how things work in both the lab and the clinic, and the needs of scientists, doctors and patients.”

From 2009 to 2011, Feldman took an unpaid leave from academia to work as vice-president and therapeutic area head of neuroscience for Global Clinical Research and Development at Bristol-Myers Squibb, a Connecticut-based pharmaceutical company. He was responsible for drug development related to AD, neuropathic pain, autism, depression, schizophrenia and migraine.

Feldman is a fellow of the Canadian Academy of Health Sciences, the American Academy of Neurology and the Royal College of Physicians & Surgeons. He is a member of the editorial board for a number of journals, serves on the scientific advisory board for several international conferences on AD and related disorders and is frequently called upon as a member of peer reviewed scientific panels. His research has been foundational to the Djavad Mowafaghian Center for Brain Health, a clinical and research collaboration between UBC Faculty of Medicine and Vancouver Coastal Health.
Cancer Drug Clears Plaque, Improves Mouse Memory

Could an FDA-approved drug that trains the immune system on tumors benefit the brain? According to a report in the January 18 Nature Medicine, an antibody that boosts the cancer-fighting ability of T cells also prods them to issue a rallying cry that calls peripheral macrophages to the central nervous system. Scientists led by Michal Schwartz, Weizmann Institute of Science, Rehovot, Israel, report that these immune cells then clear Aβ plaques and improve memory in mouse models of Alzheimer’s.”

“These data add to the growing body of evidence suggesting that peripheral adaptive immunity plays a role in the pathophysiology of Alzheimer’s disease,” said Guillaume Dorothy, INSERM, Paris, who was not involved in the work.

“Inline with other recent studies, this suggests that immunomodulatory strategies in the periphery may have therapeutic potential in AD. “

The ideal immune target and strategy still remain to be determined, he said.

Previously, Schwartz and colleagues reported essentially the same outcomes in mouse models when they used genetic methods to temporarily deplete regulatory T cells in the periphery—effectively easing the brakes on the immune system. This response depended on a burst of interferon-γ (IFN-γ) from circulating effector T cells. The cytokine stimulated the choroid plexus to recruit monocyte-derived macrophages from the periphery to the brain. There, the myeloid cells surrounded and cleared Aβ plaques. In the current study, the group wanted to test a more clinically relevant strategy for eliciting an IFN-γ response from effector T cells.

The FDA-approved melanoma drug pembrolizumab from Merck elicits a similar IFN-γ response. Known as KEYTRUDA, this antibody neutralizes the programmed T cell death 1 (PD-1) receptor on effector T cells. PD-1 normally keeps T cell activity in check and suppresses tumor-fighting activity. It is known as an immune checkpoint. Without PD-1, these cells release IFN-γ and can once again kill tumors (Mamalis et al., 2014). In this paper, the research group tested a similar anti-PD-1 antibody, specifically for use in animals.

To investigate, first author Kuti Baruch from Schwartz's group, collaborating with Ido Amit's immunogenomics group, tested the effects of the anti-PD-1 antibody in 10-month-old 5XFAD mice, which had accumulated significant cerebral Aβ plaques. The researchers injected the mice intraperitoneally twice, three days apart, with either the PD-1 antibody or an IgG control. Some animals got a second round of treatment a month later.

The anti-PD-1 antibody appeared to elicit a robust IFN-γ response. A week after the first injection, more CD4+ T cells from the treated mice were producing IFN-γ and RNA sequencing revealed an IFN-γ-associated expression profile at the choroid plexus.

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Cancer drug cont’d……

The researchers isolated the choroid plexus from the mouse brain and analyzed it, but did not compare it to other tissues. More myeloid cells infiltrated the brains of treated mice, while astrogliosis and Aβ plaque load in the hippocampi and cerebral cortices fell by half. Mice that got a second round of injections wound up with even less Aβ.

These pathology benefits seemed to translate to behavior, the scientists reported. A month after the first round of injections, treated mice remembered the location of a hidden platform in a radial arm water maze better than untreated controls. Mice given a second round of treatment performed almost as well as wild types. Cognitive deficits returned in mice that got only one set of injections, suggesting that repeat dosing is needed to maintain benefits.

The results appeared to extend to other mouse models of Alzheimer’s. In eight- or 11-month-old APP/PS1 mice, the anti-PD-1 antibody reduced Aβ plaque area and number by at least half. No behavioral assays were reported for these mice.

“This is the first time immune checkpoint text of a neurodegen-
Alzforum, adding, “Since it is based on an existing FDA-approved therapy for cancer, it can potentially be immediately tested in patients suffering from Alzheimer’s disease.” She pointed out that the therapy is not directed against any specific disease pathology, but rather helps the immune system “cleanse” the brain of toxic materials, including Aβ. She plans to explore whether blocking other immune checkpoints treats AD mouse models. A Merck representative said the company has no current plans to test pembrolizumab in AD.

Though Schwartz’ data imply that boosting systemic immunity could help clear Aβ when a full load of amyloid pathology is present in the brain, Dorothee found a different result at an earlier stage of pathogenesis in mice, when plaques first appeared. In that soon-to-be-published study, microgliosis rose and performance on behavioral outcomes improved when regulatory T cells were stimulated, not inhibited. Disease worsened in their absence. “To me this suggests a complex and dynamic process that involves multiple immune effectors, with changes depending on the state of neuroinflammation and the stage of disease progression,” Dorothee said.

Gabriela Constantin, University of Verona, Italy, agreed that PD-1 inhibition should be studied at earlier stages of AD in models. Constantin and Dorothee noted that removal of β-amyloid by any means has yet to show a clinical benefit in human trials. They proposed testing PD-1 therapy in tau models, which Schwartz is currently doing. In addition, Constantin said that PD-1 blockade exaggerates inflammatory disease in animal models. Researchers should investigate how such outcomes will affect AD, she cautioned. Side effects of pembrolizumab include inflammatory reactions in the lung, liver, and other organs.—Gwyneth Dickey Zakaib

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Exposure to Environmental Toxin May Increase Risk of Alzheimer’s and Other Neurodegenerative Diseases

A new study published January 25, 2016 in the science journal Proceedings of the Royal Society B indicates that chronic exposure to an environmental toxin may increase risk of neurodegenerative illness. Conducted by scientists at the Institute for EthnoMedicine, a non-profit medical research organization, and the University of Miami Brain Endowment Bank, the study provides a foundation for future research in Alzheimer’s disease, ALS and Parkinson’s disease.

Brain tangles and amyloid deposits are the hallmarks of both Alzheimer's disease and an unusual illness suffered by Chamorro villagers on the Pacific Island of Guam, whose diet is contaminated by the environmental toxin BMAA. Pacific Islanders with this unusual condition also suffer from dementia and symptoms similar to Alzheimer’s disease, ALS and Parkinson’s disease.

The cause of neurodegenerative disease remains largely unknown, and the role of environmental factors in these illnesses is poorly understood. However, scientists have suspected a link between BMAA, a neurotoxin found in some harmful algal blooms, and neurodegenerative illness.

“Our findings show that chronic exposure to BMAA can trigger Alzheimer’s-like brain tangles and amyloid deposits,” said Paul Alan Cox, Ph.D., an ethnobotanist at the Institute for EthnoMedicine and lead author of the study. “As far as we are aware, this is the first time researchers have been able to successfully produce brain tangles and amyloid deposits in an animal model through exposure to an environmental toxin.”

After 140 days, tangles and amyloid deposits were found in the brain tissues of all of the vervets who consumed BMAA. However, there was a significant reduction in the density of tangles in those that consumed equal amounts of L-serine.

Cox does not advocate patients taking L-serine at this time. “The FDA has not approved its use for the treatment of neurodegenerative illness, and much more research is needed,” he said. “However, this new animal model may prove useful in evaluating other potential new Alzheimer’s drugs.”

The Institute has sponsored FDA-approved human clinical trials to study the effects of the naturally-occurring amino acid L-serine in people with ALS, and is working with Dartmouth Medical School to begin a Phase I human clinical trial of L-serine for patients diagnosed with mild cognitive impairment or early stage Alzheimer’s disease.

Original article appeared in Neuroscience News.
A University of Southampton-led study has found that blocking a receptor in the brain responsible for regulating immune cells could protect against the memory and behavior changes seen in the progression of Alzheimer's disease.

The research, published Jan 7, 2016 in the journal *Brain*, was jointly funded by the MRC (Medical Research Council) and Alzheimer's Research UK.

It was originally thought that Alzheimer's disease disturbs the brain's immune response, but this latest study adds to evidence that inflammation in the brain can in fact drive the development of the disease. The findings suggest that by reducing this inflammation, progression of the disease could be halted.

The team hope the discovery will lead to an effective new treatment for the disease, for which there is currently no cure.

The researchers at the University of Southampton used tissue samples from healthy brains and those with Alzheimer's, both of the same age. The researchers counted the numbers of a particular type of immune cell, known as microglia, in the samples and found that these were more numerous in the brains with Alzheimer's disease. In addition, the activity of the molecules regulating the numbers of microglia correlated with the severity of the disease.

The researchers then studied these same immune cells in mice which had been bred to develop features of Alzheimer's. They wanted to find out whether blocking the receptor responsible for regulating microglia, known as CSF1R, could improve cognitive skills. They gave the mice oral doses of an inhibitor that blocks CSF1R and found that it could prevent the rise in microglia numbers seen in untreated mice as the disease progressed. In addition, the inhibitor prevented the loss of communication points between the nerve cells in the brain associated with Alzheimer's, and the treated mice demonstrated fewer memory and behavioral problems compared with the untreated mice.

Importantly, the team found the healthy number of microglia needed to maintain normal immune function in the brain was maintained, suggesting the blocking of CSF1R only reduces excess microglia.

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What the study did not find is a correlated reduction of the number of amyloid plaques in the brain, a characteristic feature of Alzheimer's disease. This supports previous studies that argue other factors may play more of a role in cognitive decline.

Dr. Diego Gomez-Nicola, lead author of the study and an MRC New Investigator Research Grant (NIRG) fellow at the University of Southampton, said: "These findings are as close to evidence as we can get to show that this particular pathway is active in the development of Alzheimer's disease. The next step is to work closely with our partners in industry to find a safe and suitable drug that can be tested to see if it works in humans."

Dr. Rob Buckle, director of science programmes at the MRC, added: "It is increasingly clear that inflammation is a key player in a number of neurodegenerative conditions and this study is beginning to unravel the biological processes behind this link. The study is an excellent example of how basic research can lead to promising partnerships with industry that could be of real benefit for those with dementia."

Dr. Simon Ridley, Director of Research at Alzheimer's Research UK, said: "This work, looking at the role of the immune system in Alzheimer's disease, suggests that blocking the action of the CSF1R protein in mice could help limit the damaging effects of inflammation and protect against symptoms like memory loss. In the last few years, scientists in Southampton have been at the forefront of research into the role of the immune system in Alzheimer's, so it is encouraging to see this study taking these ideas forward by identifying a specific mechanism that could be a target for future treatments."

Dr. Gomez-Nicola and his colleagues at the University of Southampton will continue their work with funding from the Dementia Consortium - a collaboration between Alzheimer's Research UK, MRC Technology and pharmaceutical companies, Eisai and Lilly.
Singing is Beneficial for Memory and Mood Especially in Early Dementia

Researchers led by Dr. Teppo Särkämö at University of Helsinki, Finland have revealed that caregiver-implemented musical leisure activities, particularly singing, are cognitively and emotionally beneficial especially in the early stages of dementia. The findings could help improve dementia care and better target the use of music in different stages of dementia. The research was published December 2015 in the *Journal of Alzheimer's Disease*.

Initially, the researchers recruited 89 dyads of persons with mild to moderate dementia and their caregivers to a single-blind randomized controlled trial in which they received a 10-week music coaching intervention involving either regular singing or listening to familiar songs or standard care. Previously, the results from a 9-month longitudinal follow-up with neuropsychological tests and mood questionnaires showed that the musical activities were able to enhance various cognitive skills, such as working memory, executive functions, and orientation, and alleviate depression compared to standard care.

Here, the focus of the researchers was to uncover how different clinical and demographic factors influence the specific cognitive and emotional effects of the two music interventions and, thereby, determine who benefits most from music. Looking at the backgrounds of the dementia patients, the researchers systematically evaluated the impact of dementia severity, etiology, age, care situation, and previous musical hobbies on the efficacy of the music interventions.

Singing was found to be beneficial for working memory, executive function, and orientation especially in persons with mild dementia and younger (< 80 years) age, whereas music listening was associated with cognitive benefits only in persons with a more advanced level of dementia. Both singing and music listening were more effective in alleviating depression especially in persons with mild, Alzheimer-type dementia. Importantly, the musical background of the persons with dementia (whether they had sung or played an instrument before) did not influence the efficacy of the music interventions.

"Given the increasing global prevalence and burden of dementia and the limited resources in public health care for persons with dementia and their family caregivers, it is important to find alternative ways to maintain and stimulate cognitive, emotional, and social well-being in this population. Our findings suggest that musical leisure activities could be easily applied and widely used in dementia care and rehabilitation. Especially stimulating and engaging activities, such as singing, seem to be very promising for maintaining memory functioning in the early stages of dementia," Särkämö concluded.
The following studies will be enrolling in 2016. For information on these studies in early 2016 please visit :

http://www.adcs.org/Studies/clinicalResearchStudy.aspx