The collaborator: NOMIS researcher Eric Reiman is on a quest to prevent Alzheimer's disease by sharing big data

Asked whether collaboration has played a role in his success, Eric Reiman admits he has "an acute awareness of [his] own limitations," which may have something to do with his keenness to collaborate. New collaborative models and data-sharing programs have enabled Reiman and his colleagues to develop highly productive research programs, profoundly impacting the fight against Alzheimer's disease. "We are living in an age in which no single person, laboratory or discipline has the resources and skills to do everything that's needed on one's own," says Reiman.

Eric Reiman is leading the Platform for the Discovery of Alzheimer's Disease Mechanisms and Treatments project, which will make the genetic data from the brain tissue of 100 donors publicly available. The platform will provide a foundation to develop one of the largest basic and translational neuroscience programs for the fight against Alzheimer's disease (AD) and other neurodegenerative diseases. Emerging big-data analysis techniques will be used to discover molecular networks involved in the disease and molecular drivers of these networks, including those that could be targeted by new or repurposed treatments.

We spoke with Dr. Reiman about his work and his thoughts on collaboration on the eve of the NOMIS Distinguished Scientist Award 2017 ceremony in Zurich.

NOMIS: You began your career as a psychiatrist and brain imaging researcher. What motivated you to turn your focus to Alzheimer's disease research?

ER: After moving to Arizona, I had been asked to join the local chapter of the Alzheimer's Association, and I thought it would be nice to invest in an area of the community that had absolutely nothing to do with my work — I was interested in using brain imaging techniques to investigate regions of the brain that are involved in anxiety, emotion and other normal behaviors, as well as those that conspire to produce anxiety disorders. Even though I would occasionally evaluate patients with memory and thinking problems, it was only as a board member on that chapter that I fully developed an appreciation for the terrible toll that Alzheimer's disease takes on affected persons and their families. So I decided to explore ways to help make a difference through my research on the brain.

In 1993, I read a Wall Street Journal article noting the discovery of what turned out to be the major genetic risk factor for developing Alzheimer's disease. Persons with one copy of the

APOE4 gene had a higher risk, and persons with two copies had an even higher risk of developing the disease. I wondered, 'What if there was a promising way to postpone, reduce, or prevent the clinical onset of Alzheimer's disease?' It would take too many healthy volunteers and too many years to evaluate these treatments in prevention trials, waiting for the onset of memory and thinking problems. I then thought, 'What if we could detect and track the brain imaging changes associated with Alzheimer's disease in middle-aged persons with two, one or no copies of this gene (i.e., in persons at three levels of genetic risk); meaning detect and track Alzheimer's long before the onset of memory and thinking problems; and set the stage to use these and other methods to rapidly test prevention therapies and find ones that work, as soon as possible?' It was kind of a novel idea at the time. But our findings helped kindle interest in the study of what we now call "preclinical Alzheimer's disease" and ultimately set the stage for Alzheimer's prevention trials. It would be a dream come true if we could find and support the approval of Alzheimer's disease prevention therapies by 2025, and that dream motivates me each and every day.

Along the way, I have been interested in helping my colleagues to clarify genetic risk factors, disease mechanisms and molecular targets at which to aim new treatments, and develop a more diverse portfolio of promising treatments. We introduced the idea of establishing the Alzheimer's Genetics Consortium to access and analyze DNA from tens of thousands of well-characterized cases and controls, provide a public resource of genetic data, and help to characterize and confirm new Alzheimer's susceptibility genes. Data from this and other programs around the world have led to the discovery of many new susceptibility genes. Starting in 2007, we have provided widely used public resources of genetic and neuronal gene expression data from clinically and neuropathologically characterized Alzheimer's disease cases and controls to help researchers clarify the relevance of genetic risk factors and molecular mechanisms.

We also want to address a woefully inadequate standard of dementia care of for affected persons and family caregivers. In the U.S., more than half of people with disabling memory and thinking problems never have an evaluation, some of whom have potentially reversible contributors to their problem. And in most cases, affected persons and families do not have access to the information, coping strategies, and programs needed to address their nonmedical needs. I believe there is a chance to establish a new national model of dementia care that better addresses both the medical and nonmedical needs of patients and family caregivers throughout the course of their illness and do so in demonstrably affordable ways.

We established the Banner Alzheimer's Institute to help find effective prevention therapies as soon as possible, help establish the kind of dementia care model that every patient and family caregiver deserves, and forge new models of collaboration to help in that endeavor. What could be better than that?

NOMIS: What skills have helped you achieve success in your research? Has collaboration been an influencing factor?

ER: I think I have a knack for identifying good questions and finding new ways to work together with others to have the greatest impact. Why is collaboration so important to everything I do? Perhaps it's an acute awareness of my own limitations [laughs]. In my opinion, advances in 21st century science and medicine will depend on new models of

collaboration and data sharing. We are living in an age in which no single person, laboratory or discipline has the resources and skills to do everything that's needed on one's own.

I'm often asked how we could get different organizations to work together so well in the Arizona Alzheimer's Consortium. The key to our success has been a heightened sense of "scientific desperation." With newer, smaller and growing programs in Arizona's universities, research institutes and academic medical centers, we do not have illusions of self-sufficiency. We are motivated to reach out to partners from different disciplines and organizations to address shared goals and respective interests in more effective ways than we can do on our own. We have used state and private funds to conduct collaborative pilot studies, to foster push-pull relationships involving the development and use of new methods, and to find out which collaborations work. We then use the resulting data in publications and grant applications to support long-standing research programs.

We have also capitalized on new public-private partnerships in the Alzheimer's Prevention Initiative. Using NIH (National Institutes of Health), philanthropic and industry funds, we have launched prevention trials in cognitively unimpaired persons at increased genetic and/or biomarker risk for Alzheimer's disease. We have capitalized on complementary resources and skills to overcome challenges to prevention research that academic or industry stakeholders could not have accomplished on their own. We have included expensive biomarkers, data and biological-fluid-sample-sharing agreements to conduct these trials in ways that would have the greatest public benefit.

None of what we have done or hope to do would be possible in the absence of strategically informed collaborations, a track record of productivity in these collaborations and a genuine interest among each of the stakeholders to value their partners and address both their shared and mutual goals.

NOMIS: Collaboration has certainly been a cornerstone of your work. What qualities do you look for in fellow collaborators?

ER: I am always interested in working with outstanding people — investigators with interesting ideas, a track record of productivity, methodological strength and scientific rigor, as well as young investigators who are committed to developing those skills and using them in impactful ways. I look for people with complementary strengths, a collaborative spirit and shared values. And I look for that gleam in the eye during initial discussions about collaborative possibilities. The opportunity to learn from, assist and work with colleagues from other disciplines and organizations has been one of the joys of my work.

NOMIS: The Alzheimer's platform project will generate a public resource of detailed gene expression data in an effort to galvanize the discovery of Alzheimer's disease mechanisms, risk factors and treatments. How will this platform change Alzheimer's disease research?

ER: In previous work, we generated a widely used public resource of neuronal gene expression data in 20 brain donors with and without the clinical and neuropathological features of Alzheimer's disease. Those data have been used in hundreds of published

studies to support the discovery of new Alzheimer's disease susceptibility genes and possible disease mechanisms.

With the advent of new technologies and big-data analysis methods, we can now generate detailed information about genes that are differentially expressed in individual brain cells and their relationship to inherited genes; use these data to explore the molecular networks involved in the development of Alzheimer's disease; and provide molecular targets at which to aim new treatments. Moreover, we can provide an invaluable public resource of data to the field to further clarify risk factors and disease mechanisms, develop a more diverse portfolio of promising treatments, and do so in ways that might be particularly relevant to this fundamentally human disease.

We are excited about the opportunity to use extremely high-quality tissue from 100 clinically, longitudinally and neuropathologically assessed brain donors with and without Alzheimer's disease; sequence RNA from several brain cell types and regions that differ in their vulnerability or resilience to Alzheimer's disease and sequence their inherited genes; capitalize on our big-data analysis strengths to characterize targets at which to aim new treatments; and provide a public resource of data and findings. We anticipate that this project will provide one of the most valuable and widely used data resources in the scientific fight against Alzheimer's disease and a foundation for future studies. We're excited about the chance to provide a bridge between these correlational data from people with experimental studies in laboratory models. It will enable us to find better ways to address Alzheimer's disease than studies in people or laboratory models alone.

To date, the investigational disease-modifying treatments that have been tested in clinically affected patients have failed to work. It's possible that some of these treatments need to be started before the onset of symptoms, when the disease has already ravaged the brain — a possibility we are now testing in our prevention trials. But it's also possible that cellular and animal models of Alzheimer's disease fail to account for critical elements of the human disease and that human data would help to provide information that would lead to more successful drug development. We believe that detailed molecular data from brain cells, cell types and regions that differ in their vulnerability or resilience to the pathological features of Alzheimer's disease — for example, those related to the development of amyloid plaques, tangles, inflammation, and the loss of brain cells and their connections — will provide complementary and critically important information about the actual disease.

With advances in computational power, increasingly sophisticated big-data analysis techniques can be deployed to interrogate these and other datasets, generate molecular networks of interest, and discover molecular drivers of the proposed networks. Those drivers could then be targeted by new or repurposed drugs and put to the test in different cellular and animal models to help clarify causal connections and discover treatments that might have the best chance to work.

NOMIS: How will the platform change the way researchers collaborate?

ER: We are interested in promoting active "push-pull relationships" among researchers who conduct studies in expired brain donors, living people and laboratory models, helping them to capitalize on complementary approaches and converge findings to fulfill their respective

and shared goals. We want to embed our big-data specialists in our basic science labs to help foster those collaborations and further clarify disease mechanisms. Once researchers see the added value of these kind of collaborative relationships, they will embrace the approach more fully in their own work. We are also interested in finding ways to share data and biological samples (for example, brain tissue) with researchers around the world, such that they can capitalize on their own expertise, resources and time to advance the scientific effort.

When it comes to the fight against Alzheimer's disease — and to the advancement of science and medicine more generally — we're all in this together. ♦

This interview was conducted by Sarah Stoeter and Cosima Crawford on Oct. 18, 2017 at ETH Zurich.

Eric Reiman is executive director of the Banner Alzheimer's Institute and chief executive officer for Banner Research. He is also professor of psychiatry at the University of Arizona, university professor of neuroscience at Arizona State University, clinical director of neurogenomics at the Translational Genomics Research Institute (TGen) and director of the Arizona Alzheimer's Consortium. He is a recipient of the Potamkin Prize for his contributions to Alzheimer's disease research.