ConvergenceRI

Rhode Island emerges as a key hub of Alzheimers research

By Richard Asinof

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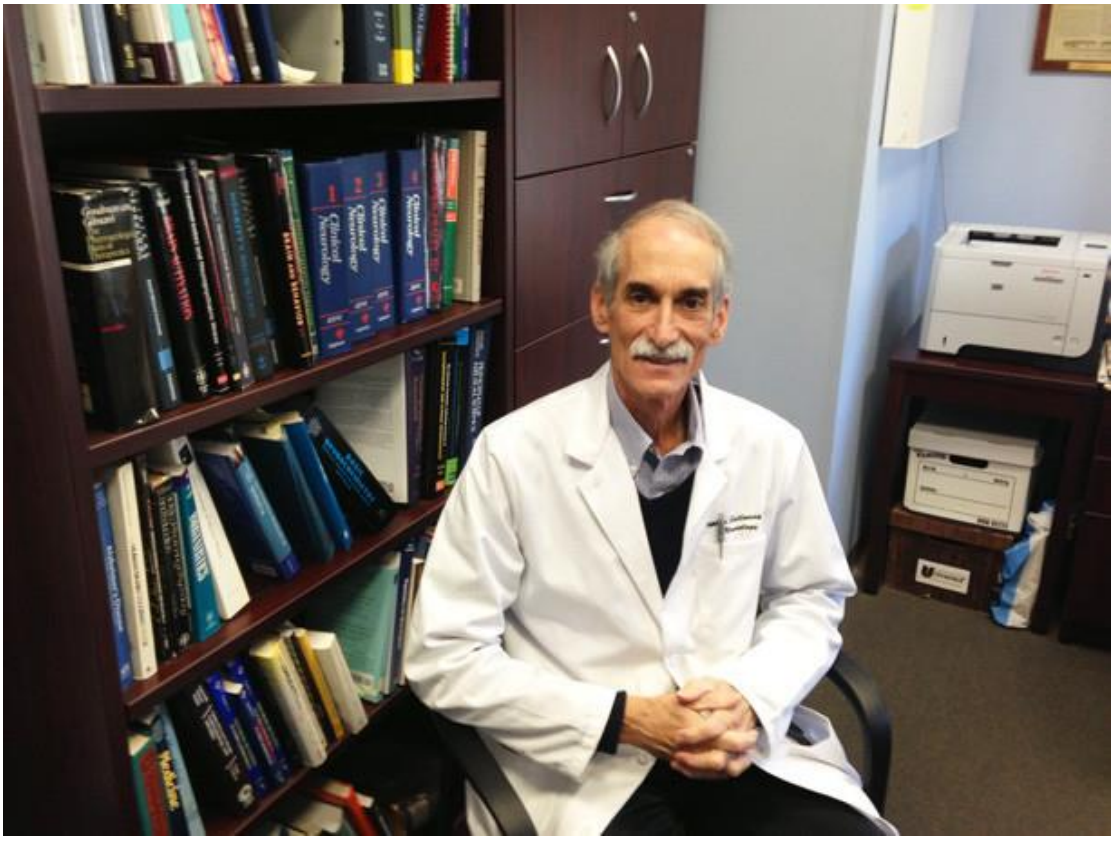

Dr. Stephen Salloway, director of Neurology and the Memory and Aging Program at Butler Hospital and professor of Clinical Neurosciences and Psychiatry at the Alpert Medical School at Brown University, is collaborating with two new national initiatives to develop brain health registries to advance clinical trial research targeting treatment and prevention.

PROVIDENCE – There are numerous surveys that attempt to benchmark Rhode Island according to all kinds of data sources – from density of restaurants to the size of tips, from business environment to tax burdens, from the number of new startups to the severity of snowstorms.

These statistical snapshots tend to become blurred over time, much like our own ability to recall the names of people in older photographs taken by our parents.

But the work of Dr. Stephen Salloway and his team at Butler Hospital, as reflected in two new public-private partnerships to speed the development of new approaches in treating and preventing Alzheimer's disease, offer a different kind of benchmark for Rhode Island – its emergence as a key nodal point and national hub in ongoing research on Alzheimer's.

It's a benchmark that has meaning for Rhode Island's aging demographic as well as potentially for the state's research engine and economic future – one that could have staying power and not fade away.

Salloway is the director of Neurology and the Memory and Aging Program at Butler Hospital and professor of Clinical Neurosciences and Psychiatry at the Alpert Medical School at Brown University.

Last week, ConvergenceRI sat down with Salloway in his office at Butler Hospital to discuss one of the latest initiatives: the partnership between Global Alzheimer's Platform, or GAP, and the Brain Health Registry, seeking to enroll some 40,000 new members in a clinical trial registry before the end of the third quarter of 2016, using social media and an online presence to do so.

The long-term goal of the enrollment push, as described in a Jan. 19 news release, is to accelerate the momentum in finding a treatment for Alzheimer's by 2025.

In the course of the conversation, Salloway also talked about a second new public-private initiative, known as the Generations trial, a new prevention trial for Alzheimer's for people who are at high risk of developing Alzheimer's because they carry two copies of a gene.

If a person carries two copies of that gene, the risk of developing Alzheimer's is highly predictive, about 90 percent, according to Salloway. The onset occurs at about age 68, compared to those not having the genes, where the average age of onset is about 84.

The clinical trial will focus on two approaches – an active vaccine, developed from toxic amyloid plaque, to help a person develop antibodies against such plaque, as well as the use of a monoclonal antibody.

Butler Hospital and Salloway and his team are planning to be one of the sites for the clinical trial.

Because only about 2-3 percent of the population carries this risk gene, the process of identifying those who may have it can be a daunting task, according to Salloway.

In an approach similar to that of the new partnership between the Global Alzheimer Platform and Brain Health Registry, potential participants will be encouraged to enroll online if they have an interest in finding out their potential genetic risk.

The tests for the risk gene can be conducted with a blood test, or a cheek swab, so those interested in finding out their genetic risk can be sent a kit.

The two new initiatives complement the ongoing Phase III clinical trial, known as the Anti-Amyloid Treatment in Asymptomatic Alzheimer's study, or the A4 study, for which Butler Hospital has been one of the clinical sites, beginning in June of 2014. The study is testing where an antibody treatment can slow memory loss associated with Alzheimer's.

The urgency of the work on Alzheimer's is being driven by what Salloway called a "demographic"

imperative: the fact that for the first time, people 65 years and older will outnumber those under five years of age, with the divergence growing dramatically.

Alzheimer's is also a growing major public health problem, ranked at number-three behind heart disease and cancer, according to Salloway.

The promise of new developments in treatment and prevention of Alzheimer's are related in part to advancements in neuroimaging and genetics. "Before we had to wait until there was cognitive impairment and decline," Salloway said. "Now we can test people 20 years before cognitive decline and, hopefully, delay the cognitive impairment."

Here, then, is the ConvergenceRI interview with Dr. Stephen Salloway:

ConvergenceRI: How does the new partnership announced this week with Global Alzheimer's Partnership and the Brain Health Registry fit with the ongoing work of you and your team at Butler?
SALLOWAY: It supports clinical trials for potential treatments and preventions, building the infrastructure for clinical trials.

As you know, Alzheimer's is a major health problem, one that we face globally.

The reason is that that the rate of Alzheimer's will increase as the population ages.

And the population is aging. Probably the most dramatic indication of this is that we are facing a demographic imperative, where, for the first time, people [who are] 65 and older will outnumber those under five [years of age.]

That divergence is going to grow dramatically over the next 30 years. The bottom line is that we're going to have a lot of older people.

The major risk factor for Alzheimer's is age, so the risk pool is growing dramatically. [That's why] the U.S. Congress [and others] have made finding a treatment breakthrough for Alzheimer's by 2025 a top priority.

We're working toward a goal in treatment breakthroughs. One thing that's happening in response to this is building the global infrastructure to fight Alzheimer's to achieve these breakthroughs.

We are part of a new network, called the Global Alzheimer's Platform, or GAP, and that's basically a consortium or network of high productive Alzheimer's [research] centers.

The goal is to accelerate drug development. Right now, there are a lot of redundancies and silos; there are a lot of impediments to being more efficient.

Clinical trials are very costly, and we're trying to streamline the whole process. One thing that this new collaboration is going to accomplish is a partnership between the new GAP network and a project called the Brain Health Registry, which is being run out of the University of California at San Francisco by Dr. Michael Weiner, one of the pioneers in building this kind of research infrastructure.

Weiner led the Alzheimer's Disease Neuroimaging Initiative, or ADNI. That is a really terrific public-

private partnership, with funding from the National Institutes of Health, Pharma and [advocacy] groups.

That study is looking at how to predict if an older person is going to go on and develop Alzheimer's, and what tests we can do [to identify] what are the predictive factors. It's been very successful, with more than 1,000 publications; it has helped to re-engineer how we do Alzheimer's trials.

ConvergenceRI: How has brain imaging become a key factor in this work?
SALLOWAY: Let me come back to that shortly, and continue talking about this new, specific partnership.

Weiner has moved on; he's still a leading principal investigator with ADNI, but he's started the Brain Health Registry.

The registry is an opportunity for people, from a wide age range, to sign up, online, provide some demographic information, and take a cognitive test.

You can take these cognitive tests online to find out how your performance compares to other people your age and if they show signs of any cognitive difficulty. The participant can also indicate a willingness to participate in clinical trials.

Then you can take tests, or do brain training, over a period of months, and see if you can improve your performance. I think they have something like 40,000 people signed up so far.

They have advertised online about it, mostly in the Bay area, and now it's becoming more of a national program.

This is what the rollout of the new partnership is about, with us here at Butler and Brown, and with the Brigham and Harvard, and with a private memory program down in Florida. [There are 11 sites nationwide all together.]

They're going to be doing online advertising to spread the word that people can do the testing. The goal is then to refer people who are interested in participating in clinical studies, and who might be eligible at sites like ours, to be part of either prevention trials or early treatment trials, depending on their level of cognitive performance.

This will feed the whole Alzheimer's research infrastructure.

ConvergenceRI: So, what role does brain imagining play as part of these new partnerships?
SALLOWAY: To answer your question about imaging, the major advances in Alzheimer's research so far have come in molecular brain imaging, and also in genetics.

Previously, we couldn't see the pathology of Alzheimer's and the plaques made up of amyloid protein, or the tangles made up of tau protein, until someone passed away.

Then, you [could view it] under the microscope, with special stains; that is what Dr. Alzheimer did.

And that is, obviously, too late for that person.

What we've done is taken some of those same stains, and then figured out a way to modify them a little

bit, and then use them in PET scanning, and they bind to the plaques.

We now have three tracers safely approved for use by the FDA to see the plaques, and we can tell who's at high risk for developing Alzheimer's.

Before, we had to wait until there was cognitive impairment and decline; now we can test people 20 years before the cognitive decline and, hopefully, delay the cognitive impairment.

ConvergenceRI: How does this relate, if at all, the work of Dr. Henry Querfurth and his work on insulin production in the brain?
SALLOWAY: He's moved on from Rhode Island Hospital; he's now at Beth Israel in Boston; he left about nine months ago. He's now running a memory program at Beth Israel.

ConvergenceRI: He seemed to have developed some promising research related to the role that insulin plays in the formation of plaque. [See link below to ConvergenceRI article.]
SALLOWAY: There are many factors that could go into modifying amyloid plaque deposits, and insulin processing is one of them. You may want to interview Dr. Suzanne de la Monte, a neuropathologist [at Rhode Island Hospital and a professor of Pathology at Brown Medical School].

She has piloted the idea of Type 3 diabetes, with insulin processing in the brain contributing to amyloid plaque development.

There is a trial going on at Rhode Island Hospital in terms of intranasal insulin that Henry [Querfurth] was involved with, to try and improve memory function.

ConvergenceRI: Back to brain imaging.
SALLOWAY: There are two ways we have now to determine who's at highest risk of developing Alzheimer's. One is with brain scans, [such as] an amyloid PET scan.

We're involved with a clinical Phase III study called the A-4 trial, or the Anti-Amyloid Treatment in Asymptomatic Alzheimer's study, for people 65-85 years old with normal cognitive functions. We do memory tests, and we do a PET scan.

Those [identified] as building up amyloid plaque can receive a monoclonal antibody [to fight against the development of amyloid] for three years, to try and delay cognitive decline. Participants have a 50 percent chance of getting the drug, and a 50 percent chance of getting the placebo.

One good thing about the study, especially for a neurologist, is that we get to give good news about 70 percent of the time – 70 percent of the people are not building up plaque and are at a lower risk of developing Alzheimer's.

ConvergenceRI: How does this work?
SALLOWAY: We go over to Rhode Island [Hospital] for the PET scan. They get an infusion of this tracer that has a low dose of radiation that's picked up by the PET camera; it binds to the amyloid plaque.

ConvergenceRI: You're using an antibody, a biologic, for treatment?
SALLOWAY: Yes, it's a relatively small molecule. It's an antibody that's targeted to different parts of the toxic forms of amyloid.

ConvergenceRI: Can you describe the stage of the clinical trial?
SALLOWAY: We're in Phase III trials for mild Alzheimer's, this is a prevention trial, working with solanezumab, a monoclonal antibody.

It's an exciting, whole new approach for us. We're now reaching out to the public, and that's why the media plays such an important role here.

[We need people] to volunteer and participate in this type of research, to see if they are at an increased risk and to modify that risk.

ConvergenceRI: And, the second way you mentioned?
SALLOWAY: Another way [to determine people who are at the highest risk] is to talk about genetics.

In that study, we are targeting a gene mutation. Some people have the mutation, some fail to carry a mutation.

The mutation appears to cause the early onset of Alzheimers when someone is in their 40s or early 50s.

There is a 50 percent chance that anyone in the family who has that mutation will develop Alzheimer's at a predictable age of onset. That mutation can be determined through a blood test.

This is called the Dominantly Inherited Alzheimer's Network, or DIAN trial. We're doing a prevention trial for people whose families carry this form of mutation, and we're testing two different drugs, including solanezumab, to try and delay cognitive decline in those people at risk.

ConvergenceRI: Did you help to develop the antibody yourself? Did it come from Brown or another academic research center?
SALLOWAY: It's a Lilly antibody. So, Lilly is a co-sponsor of the NIH trial, with the Alzheimer's Association as a partner.

These new type of private-public partnerships are critical to move the field forward. Almost all of the big clinical trials are now done in a partnership, because it's the only way to be able to afford doing them.

The new antibodies could have been developed in an academic research center and then licensed to a lab, but, usually, they are developed in Pharma.

ConvergenceRI: In the Brookings Institute's report released this week, called "Rhode Island Innovates," one of the focal points was the need to develop public-private partnerships to drive the innovation economy forward in Rhode Island. One of needs identified was the development of new funding mechanisms for research. Does this tie into your work on developing treatments and prevention for Alzheimer's?
SALLOWAY: It's essential. The big projects, such as if you do a Phase III clinical trial, we're talking more than $500 million to run a trial like that.

These big prevention trials which last for three to five years, it's a major undertaking, and the investment has to come from new types of public-private arrangements.

I'm not kidding; it's essential.

ConvergenceRI: Can you describe how you might create such a fund here in Rhode Island? What would it look like?
SALLOWAY: This is where innovation would come in, and some creativity. The funding side, this is not my area of expertise.

Right now, there's been a fair amount of advocacy around Alzheimer's care. It costs more than heart disease and cancer, if you look at both the formal and informal care costs.

It's a major burden on our health care system, especially if the numbers are going to increase over time.

Right now, we've been spending [up until this past month], about $400 million a year for Alzheimer's research and more than $6 billion for cancer research. You can see that it's way out of whack in terms of the proportion of health care costs.

Alzheimer's is apparently one of the things that Congress does agree on; it's a bipartisan issue. People in Congress don't want to get Alzheimer's. This year, [in the budget], they voted for an additional $350-$400 million, doubling the Alzheimer's research budget.

I've heard that Hillary Clinton has called for a billion or $2 billion more.

It will take a lot more investment on the federal and the public side – in partnership with the private sector.

ConvergenceRI: Can you explain further?
SALLOWAY: Now that we're getting the additional money, there's another new project, I just got the newsletter today, that's rolling out soon [that exemplifies the new kinds of public-private partnerships we need]. We're going to an investigator's meeting next week.

It's called the "Generations" trial. It's for people who are at high risk for developing Alzheimer's because they carry two copies of a risk gene.

If you carry two copies of that gene, your risk of developing Alzheimer's is about 90 percent, that's highly predictive.

The onset of Alzheimer's [occurs around] the age of 68 [for those people who possess the two copies of the risk gene], compared to people who do not have that gene, the average age of onset of Alzheimer's is 84.

[The presence of the risk gene] can be identified with a blood test, or a cheek swab, so that's what we will be doing.

The Generations trial is being funded with the largest grant by the NIH, so far, for the prevention of Alzheimer's research. NIH is providing the cornerstone for the study.

The Alzheimer's Association is also pitching in, as is the Banner Alzheimer's Institute, which is in Phoenix, Ariz., they're contributing tens of millions to this effort.

The Pharma partner is Novartis; they are contributing two compounds that are going to be tested.

One is an active vaccine, which is different from an antibody. It was developed from a piece of amyloid, [similar] to the way that vaccines are developed for an infectious disease. Then the person mounts antibodies against the toxic amyloid, to try and clear it.

Another drug will also be tested, a beta secretase inhibitor, which seeks to inhibit the enzyme that causes the toxic form of amyloid to develop.

So, in this public-private partnership, you have philanthropy, you have a patient advocacy group, the NIH and a Pharma partner.

And, the GAP network is that same type of collaboration.

I think it's going to take creative financing, and I think the public has to be involved.

This is, again, a place where I'm totally outside my league of expertise. I can tell you much more about the antibodies and the clinical trials.

It may require a new kind of social investment, something like Alzheimer's bonds, similar to what the government has done in the past for war bonds.

We need to figure out how to do this; it's going to take a lot of money, and it's going to take a sustained commitment.

Because Alzheimer's is a tough disease to get traction on.

We've gotten traction on the imaging side, and on the genetics side, and we need one or two breakthroughs on the therapeutic side to give us more encouragement.

We're going to have to have a lot of stay-put power to be successful, and that's going to take money.

To be successful, and that's going to take money.

ConvergenceRI: How important is the new Generations trial?
SALLOWAY: All of the clinical studies are great, but the Generations study is going to be a game-changer.

Only 2-3 percent of the population carry this risk gene, so you have to screen some 50,000 to 100,000 people to find the 1,300 participants for the study that meet the criteria.

It fits in with the Brain Health Registry strategy, to build a registry using online media to reach people and to engage with people, to find out about their potential risk and encourage them to volunteer.

This is another major study that's going to use the same approach. Banner has already set up an Alzheimer's prevention registry.

People can sign up online and indicate their interest in finding out more about the Alzheimer's trials. They also have this new component called gene match, for people who are between the ages of 55-75, who express an interest in finding out their genetic risk.

They are then sent a kit with a cheek swab, people send it back in, and some of them, not everyone, may be invited to join programs such as ours here in Rhode Island to become a participant in the study.

ConvergenceRI: What are the number of sites, nationwide, for the Generations study, and for the GAP program?
SALLOWAY: For the GAP program, we're one of 11 sites nationwide. For the new Generations study, I'm guessing it's about 20 sites; I'm not sure.

ConvergenceRI: Is Rhode Island creating a talent hub for Alzheimer's research?
SALLOWAY: Recruiting people is very important; we have an excellent staff. Our program has grown from an initial four people to 30 people, over the last 19 years, but the growth has been greatest in the last five years. It's accelerated.

And, we're continuing to grow; as we gain more success, the program could grow substantially.

If one of these drugs proves to be effective, then you have to figure out how to administer it to millions of people.

ConvergenceRI: That's a game-changer. It also raises questions about who's going to control the drug and how much it is going to cost, given the public-private partnerships.
SALLOWAY: That's a whole other topic of conversation.

We're one of the leading centers in this Alzheimer's research enterprise. One of the things that we're really advocating for, as we develop the infrastructure, is a new model of funding, to make sure that we have the staff we need to carry it to scale.

The biggest thing is scaling up. Up to now, we've been doing studies of people who already have dementia or the signs of cognitive impairment.

When it comes to those eligible for [potential] repair and prevention, you have to go out and find the people who are at risk. These people don't know that they are at risk.

It's a whole new endeavor. Sites like ours, we need to have stable money for staffing that's related to the volume of work.

That's not how studies have been funded in the past, in per patient projects: you get so much for performing procedures for each participant.

That doesn't take into account what the staffing needs might need to be.

With our ongoing studies with cognitive impairment, we're pretty good; we know who the patients that are likely to be eligible and pass all the biomarkers. I'd say we're one of the best in the world at that.

But, when you go out to screen people in the larger community, 70 percent of the people are going to

be negative for an amyloid scan, or cognitively normal.

One of the goals of the GAP program is to develop a paradigm or an algorithm that can tell us who's more likely to develop Alzheimer's.

In our A-4 study, about 80 percent of the people that we screen will not be eligible for the medication part of the trial. That's a lot of effort.

ConvergenceRI: One of the concepts introduced by the Brookings Institute report was the development of collaborative research innovation centers that could focus on proof-of-concept work. Is that the kind of public-private venture that would be appealing for your Alzheimer's work here in Rhode Island?
SALLOWAY: Early proof of concept is an important goal for the field and a new research focus. If the drugs are going to fail, we want them to fail early, better than in later, Phase III trials, after a big investment in capital.

We need to have biomarkers in order to get an early readout. We're trying to develop those, like in the DIAN study, where one of the main outcomes is a biomarker readout to see if we're moving our target sufficiently and likely to get clinical benefits.

Proof of concept is extremely important.

ConvergenceRI: What haven't I asked that I should have asked? Are there other topics that you would like to discuss?
SALLOWAY: One of the things that really amazing, is that in order for the FDA to approve new tracers, what's required is for people who are terminally ill to agree to have an amyloid scan, is to then donate their brain after they pass away.

So that we can then compare what we saw, pre-mortem, to post-mortem results.

That, to me, is a huge contribution for a terminally ill person and their family to agree to go through that, because it won't be of any direct benefit to them, other than getting an autopsy report.

That's the high level of evidence that the FDA requires to approve a new diagnostic test.

I am moved by their altruism. That's what we are going to need, that spirit of altruism, in order to make progress against Alzheimer's.