



*We are trying to develop something akin to a flu shot, but for Alzheimer's disease. The hope is that everybody over the age of 55 or anybody who has susceptibility for early onset Alzheimer's would receive the vaccine.*

## USING MONOCLONAL ANTIBODIES

*What are the opportunities for using monoclonal antibodies to treat Alzheimer's disease?*

**CHAIN:** It took a long time to understand the hallmarks of Alzheimer's disease. The beta amyloid plaques that appear in the brains of patients with Alzheimer's are just a sign of what has happened. The soluble, floating toxins, amyloid precursors, that accumulate in the fluids and that float around in the fluids of the brain are what cause the damage. It's these floating toxins that eventually form the plaques. Amyloid precursors, for reasons that we don't fully understand, are metabolized and broken down by two different enzymes to release smaller fragments.

Our technology uses monoclonal antibodies that are selected for their ability to bind to either end of these fragments but do not bind to the larger protein. The beauty of using monoclonal antibodies is that they can be selected for use on any target with exquisite high specificity. Only a small amount, about 1%, of the antibody reaches the brain, but that 1% may be sufficient. Some of that antibody would be expected to bind to some of the floating toxins in the fluids and help shuttle them away.

Some antibodies may bind to the plaques and help to stimulate an inflammatory immune reaction that helps to clear fluid away. Some of the antibodies that don't get into the brain act like a sponge outside of the brain to absorb beta amyloid. There are about five different theories as to how the monoclonal antibodies work, and they all probably play a role.

## HUGE POTENTIAL

*What is the market potential for Alzheimer's drugs?*

**CHAIN:** It's a massive market because there really isn't anything available to prevent Alzheimer's disease. Once these drugs have been shown to be suc-

## DR. DANIEL CHAIN discusses the development of monoclonal antibodies as Alzheimer's therapeutics.

Dr. Chain founded a company, Intellect Neurosciences, to advance the platform he developed to create monoclonal antibodies that clear away the beta amyloid proteins that accumulate in the brains of Alzheimer's patients. This work has the potential to lead to an active vaccine that could prevent the onset of this brain-damaging disease.

### ALZHEIMER'S FACTS

- Alzheimer's disease (AD) affects 5.3 million Americans and 35 million individuals worldwide.
- AD accounts for 50% to 80% of dementia cases.
- AD is the seventh-leading cause of death in the United States.
- Four drugs are available to treat Alzheimer's: Aricept, Exelon, and Razadyne for people with mild or moderate AD and Namenda for moderate to severe AD. These drugs work by regulating neurotransmitters. They may help maintain thinking, memory, and speaking skills, and help with certain behavioral problems, but they don't change the underlying disease process.

Sources: Alzheimer's Association. For more information, visit [alz.org](http://alz.org). National Institute on Aging. For more information, visit [nia.nih.gov](http://nia.nih.gov).

cessful, the sky's the limit because there is a huge unmet medical need in this area.

The Holy Grail for Alzheimer's disease is an active vaccine rather than administering a monoclonal antibody. With an active vaccine, we stimulate the immune system of the patient so that the immune system will develop antibodies that would target the amyloid toxin.

A vaccine would have broad potential, much larger than monoclonal antibodies, because it is expensive to produce monoclonal antibodies.

### VACCINATING AGAINST ALZHEIMER'S

*How can this work lead to the development of an active vaccine, and what are the challenges?*

**CHAIN:** Our company's Recall-Vax program has two candidates, RV-01 and RV-02, which try to reproduce the specificity using an active vaccine that we are able to achieve with monoclonal antibodies. This is in early-stage development, but we think it has a lot of promise in terms of safety and range of use. It could be used to treat people with the disease and potentially as a prophylactic to delay or prevent onset.

We are trying to develop something akin to a flu shot, but for Alzheimer's disease. The hope is that

## CAREER Highlights

Daniel G. Chain, Ph.D., is Founder, CEO, and Chairman of Intellect Neurosciences, a development-stage biopharmaceutical company engaged in the discovery and development of disease-modifying therapeutic agents for the treatment and prevention of Alzheimer's disease.

After graduating with a degree in biochemistry in London, he moved to Israel, where he earned his Ph.D. in biochemistry from the Weizmann Institute of Science. Dr. Chain then joined the Center for Neurobiology and Behavior at Columbia University College of Physicians and Surgeons, which was under the direction of Dr. Eric Kandel who later was awarded a Nobel Prize for his research exploring the workings of memory.

Dr. Chain is a third-generation biochemical researcher. His father, Ernst Chain, M.D., discovered how penicillin could be used as an antibiotic. For his work, the elder Dr. Chain in the 1940s shared the Nobel Prize with Dr. Alexander Fleming.

everybody over the age of 55 or anybody who has susceptibility for early onset Alzheimer's will receive the vaccine. Ultimately, if we could immunize people once a year and delay Alzheimer's indefinitely that has a huge market potential.

Trials studying Alzheimer's are very difficult, and they take a long time to complete. There are no biomarkers that have been accepted by the FDA. The only clinical outcome that the FDA will accept is improved cognition according to standard measures of cognition, which is a slightly subjective way of assessing the success of a drug.

The pharmaceutical industry has come to the realization that with Alzheimer's disease it's hard to know if a drug is working. Sometimes the results don't come clear until after a Phase III trial is finished, which is a costly and risky undertaking, even for the big companies. There have been some very unfortunate failures in this area. ♦

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# Intellect Neurosciences' Research of **ALZHEIMER'S DISEASE**

Research is pointing to a promising area of science: using monoclonal antibodies to stop the accumulation of the amyloid beta protein, which accumulates in the brains of Alzheimer's patients. But at the time Daniel Chain, Ph.D., conceived of the Antisenilin platform, researchers were not approaching any brain disease using monoclonal antibodies.

"No one had really thought about how to use antibodies to treat diseases that affect the brain," he says. "And there was a debate as to what the focal point of Alzheimer's disease was. It took a long time to understand the hallmark of Alzheimer's disease. The beta amyloid plaques in the brains of patients with Alzheimer's are just a sign of what has happened."

Dr. Chain's idea was to use a specific class of antibodies that would tag onto the ends of beta amyloid to help mobilize and clear the toxins away from sites of damage in the brain. Dr. Chain referred to these antibodies as Antisenilins because they could potentially be used to prevent senility in Alzheimer's disease patients — and because the name rhymes with penicillin, which was a tribute to his late father, a prominent researcher who shared the Nobel Prize for the discovery of penicillin.

Dr. Chain founded Intellect Neurosciences in 2005 to develop the technology portfolio. The company has three different programs, but the Antisenilin technology has garnered the most attention.

"There is a protein called the amyloid precursor, which is present in the body in various tissues and, for reasons that we don't fully understand, it is metabolized and broken down by two different enzymes to release smaller fragments," Dr. Chain says. "These fragments are relatively innocuous and float around, but under certain conditions, particularly in the aging brain, they accumulate in the fluids that surround the brain. They become sticky and start clumping together, which can be extremely toxic to nerves."

The company had licensed its Antisenilin technology to Wyeth, and now Pfizer, along with



*The beauty of monoclonal antibodies is that they can be selected for any target with exquisite high specificity, says Dr. Daniel Chain.*

Janssen, is conducting Phase III trials of a product developed from that technology. Bapineuzumab is a humanized monoclonal antibody to the beta-amyloid plaques that are theorized to contribute to Alzheimer's disease. The company also has licensed the technology to Elan Pharma.

Internally, the company is developing IN-N01, a humanized monoclonal antibody based on the Antisenilin monoclonal antibody technology. IN-N01 is being developed as a second-generation drug candidate with the aim of improving the overall safety and efficacy compared with other drug candidates in more advanced development. Dr. Chain says the product candidate is still in the discovery phase, and human trials are several years away.

The company's second program is Oxigon, which is a clinical stage small-molecule being developed as a potential disease-modifying drug for Alzheimer's disease. The drug has the potential to protect the brain and other tissues against oxidative stress, and appears to stabilize the less toxic soluble forms of beta amyloid.

Oxigon has been successfully tested for safety across animal species and in two human Phase I clinical trials conducted in a total of 90 healthy elderly volunteers. The company is planning to initiate clinical trials in Alzheimer's disease patients to test various doses of the drug to examine its effects on various relevant biological markers.

Additional studies are being conducted to explore the drug's potential utility to treat other diseases such as Parkinson's disease, Huntington's disease, motor neuron disease, glaucoma, cardiovascular disease, Friedrich ataxia, and protection against radiation injury.

## **AN ALZHEIMER'S VACCINE**

One of the company's more exciting programs is Recall-Vax, a vaccine platform that has the poten-

## **THE COST OF ALZHEIMER'S DISEASE**

Alzheimer's disease in U.S. adults older than 65 will cost \$1 trillion per year by 2050, for a total of \$20 trillion in the next 40 years, as the number of patients with AD jumps from its current level of 5.1 million to 13.5 million in 2050.

A new treatment that delays the onset of disease by five years would push back the growth of new cases, reducing the number of people with the disease by 43% and saving \$447 billion a year by 2050.

A treatment that slows the progression of AD by five years would reduce the number of people in the severe stage of the disease by more than 80% and save \$197 billion a year by 2050.

Source: Alzheimer's Association.  
For more information, visit [alz.org](http://alz.org).

tial not only to treat the disease but also to prevent the onset of Alzheimer's.

The vaccine would act by stimulating the immune system to produce antibodies that clear beta-amyloid peptides and prevent further accumulation. Studies in animal models have shown that active immunization can clear amyloid plaques, prevent accumulation of beta amyloid, and stop cognitive decline.

Dr. Chain says the active vaccine aims to stimulate the immune system of the patient so that the immune system will develop antibodies that would target the amyloid toxin.

"Our Recall-Vax program has two candidates, RV-01 and RV-02, which try to reproduce the specificity in an active vaccine format that we are able to achieve with monoclonal antibodies," he says. "Both of these vaccines are in the discovery phase." ♦





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