AD vaccine redux

By Lev Osherovich, Senior Writer

Researchers at **Harvard Medical School** have teamed up with vaccine maker **Mercia Pharma Inc.** to design a next-generation Alzheimer's disease vaccine with an adjuvant that promotes a beneficial anti-inflammatory response that the team hopes will enhance β -amyloid clearance without triggering neuroinflammation.¹

AD is caused by accumulation of β -amyloid ($A\beta$), an extracellular protein fragment that forms deposits around neurons. Those deposits, or plaques, trigger neuronal degeneration and attract inflammatory microglia, which further accelerate neuron death. Preventing the formation of $A\beta$ plaques or clearing away $A\beta$ before it reaches toxic levels is the central focus of AD therapeutic development.

In principle, $A\beta$ can be targeted with injected antibodies, but this passive immunotherapy approach has thus far met with failure. Two $A\beta$ -binding mAbs—bapineuzumab (AAB-001) from **Johnson & Johnson** and **Pfizer Inc.** and solanezumab (LY2062430) from **Eli Lilly and Co.**—failed in Phase III testing to prevent AD progression in patients with mild to moderate disease.

The most recent casualty is Gammagard Liquid 10%, a polyclonal mixture of antibodies from **Baxter International Inc.** that failed in a Phase III trial in a population of patients with mild to moderate AD.

An alternative approach consists of building up a patient's natural immune response against $A\beta$ before the onset of disease. The simplest way to do so is with active immunotherapy or vaccination, in which $A\beta$ is introduced to the peripheral immune system in a nontoxic form that stimulates a robust antibody-based response.

This was the idea behind the AN-1792 AD vaccine candidate from **Elan Corp. plc** and Wyeth (now Pfizer). However, that product failed to prevent AD progression in Phase II testing in 2002, partly because of a poor antibody response in the majority of patients. Moreover, about 6% of patients developed meningoencephalitis, a neuroinflammatory condition thought to be caused by T cell activity in the brain.

Since then, academic researchers and companies have pursued a range of strategies to increase antibody production and decrease inflammatory T cell activity in second-generation AD vaccine candidates (see Table 1, "Alzheimer's disease vaccine pipeline").

Now, a team lead by Cynthia Lemere, associate professor of neurology at **Brigham and Women's Hospital** and Harvard Medical School, has designed a new AD vaccine that appears to achieve both goals.

"This is the third-generation vaccine since the AN-1792 trial concluded," said Lemere. "Since that trial halted, there has been a strong interest in developing an AD vaccine that would avoid a T cell response."

Lemere said second-generation vaccines are designed to avoid interacting with T cells entirely, but such an approach limits the robustness of the B cell-mediated antibody response, which requires assistance from T cells.

Rather than completely avoiding T cells, Lemere's vaccine skews T cell activity away from the proinflammatory T helper type 1 (Th1) cell response and promotes an anti-inflammatory Th2 cell-type response. The Th2 cell response enhances the activity of B cells and provides anti-inflammatory cytokines that promote $A\beta$ clearance.

"This vaccine initiates a Th2 anti-inflammatory response, so it's a two-pronged approach with a strong humoral response as well as a protective cellular response," said Lemere.

Antibodies vs. plaques

Lemere's vaccine, termed MER5101, consists of the first 15 amino acids of $A\beta$ attached by a flexible covalent linker to diphtheria toxoid, a carrier

Table 1. Alzheimer's disease vaccine pipeline. At least seven vaccines against β -amyloid ($A\beta$) are in preclinical through Phase II testing to prevent AD.

Source: BCIQ: BioCentury Online Intelligence

Company	Product	Description	Status
Johnson & Johnson (NYSE:JNJ)/ Pfizer Inc. (NYSE:PFE)	PF-5236806 (ACC-001)	$A\beta$ -related immunotherapeutic conjugate	Phase II
Affiris AG/GlaxoSmithKline plc (LSE:GSK; NYSE:GSK)	AD02	Vaccine against a peptide mimic of $A\beta$	Phase II
Cytos Biotechnology AG (SIX:CYTN)/ Novartis AG (NYSE:NVS; SIX:NOVN)	CAD106	Vaccine against $A\beta$	Phase II
AC Immune S.A.	ACI-24	Vaccine that stimulates the production of β -sheet conformation-specific antibodies	Phase I/II
Affiris/GlaxoSmithKline	AD03	Vaccine against a peptide mimic of $A\beta$	Phase I
Intellect Neurosciences Inc. (OTCBB:ILNS)	RV-01	Four-amino-acid amino-terminal fragment of $A\beta$ conjugated to tetanus toxoid	Preclinical
Mercia Pharma Inc.	MER5101	Fifteen-amino-acid amino-terminal fragment of $A\beta$ conjugated to diphtheria toxoid in an anti-inflammatory oil-based adjuvant	Preclinical

protein. The team collaborated with Mercia to formulate the vaccine in the company's MAS-1 adjuvant, an oil-and-water nanoparticle emulsion.

Peter Blackburn, cofounder and president of Mercia, said MAS-1 had previously been used in Aphton Corp.'s Insegia (G17DT), a cancer vaccine against gastrin-17 that failed in Phase III testing for pancreatic cancer. Aphton's cancer vaccine program was acquired by Receptor BioLogix Inc., now a part of **Symphogen A/S**.

Mercia acquired rights to MAS-1 as part of Aphton's Chapter 11 bankruptcy sale in 2006.

In a mouse model for AD, animals receiving MER5101 had higher levels of A β -specific antibodies than untreated controls. The elicited antibodies were predominantly of the IgG2b isotype, which is associated with Th2 cell responses.

In samples from human brains with AD, IgG2b antibodies from MER5101-immunized mice readily stained amyloid plaques, whereas proinflammatory IgG2a antibodies did not.

Immunized mice also had a robust anti-inflammatory T cell response to the vaccine. Cultured splenocytes from immunized mice responded to re-stimulation

with the original A β -diphtheria toxoid conjugate by proliferating and secreting a range of anti-inflammatory cytokines.

The result of the combination of antibody production and anti-inflammatory T cell activity was prevention of AD progression in immunized mice. Animals immunized with MER5101 had lower A β levels in the brain and performed better in cognitive tests than unvaccinated controls. Additionally, brain slices from vaccinated mice showed fewer proinflammatory microglia than slices from untreated controls.

Results were published in *The Journal of Neuroscience*.

AD infinitum

Although prior vaccine candidates have not shown the anti-inflammatory Th2 cell profile seen with MER5101, it remains to be seen whether the new vaccine's anti-inflammatory effects will improve efficacy in the clinic.

"Whether this would translate into a sustained Th2 response in humans is an open question," said Lemere. "What you see in the mouse is more or less irrelevant to what you see in humans. You can certainly ask questions about what's happening to A β , but there's no animal model for the human immune system."

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Harvard Medical School

Daniel Chain, chairman and CEO of **Intellect Neurosciences Inc.**, said Lemere's findings are a step toward eliciting a potent but safe immune response in AD.

"I think the challenge for an AD vaccine is to get a strong humoral response as well as a Th2 response," said Chain. "The 1–15 fragment and diphtheria toxoid fragment are used in the second-generation vaccines, but the adjuvant they use here is novel and gives a strong Th2 response."

Intellect's RV-01 vaccine against A β is in preclinical development for AD.

The next challenge, said Chain, is "to get a strong antibody response and have it be sustained over time." He recommended a long-term study of antibody responses to MER5101.

Another question is whether the anti-inflammatory effects of MER5101 in the periphery will translate to an effect on antibody activity in the brain. It is not yet clear whether A β antibodies penetrate into the brain to directly clear up plaques or act primarily in the brain's vasculature to neutralize loose A β and thus prevent plaque growth.

Thus, further mouse studies are needed to see whether the antibodies and Th2 cells induced by MER5101 act in the brain or in the periphery.

"You get anti-inflammatory activation in the periphery, but you also get a bystander or passive effect from the secretion of anti-inflammatory cytokines that do get into the brain," said Blackburn.

Blackburn said Mercia is conducting toxicology studies of MER5101 in preparation for an IND submission. He did not disclose a timeline.

MER5101 and the MAS-1 adjuvant are covered by patents owned by Mercia. The company, founded in 2004, has raised about \$6 million from private investors and from grants. It hopes to partner the MER5101 project to advance it.

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Intellect Neurosciences Inc. (OTCBB:ILNS), New York, N.Y.
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