Putting a cap on AD

By Lev Osherovich, Senior Writer

In the wake of recent Phase III failures of antibodies against β -amyloid to treat Alzheimer's disease, **AC Immune S.A.** and **Swiss Federal Institute of Technology Lausanne** researchers have unveiled an alternative—a class of small molecules that directly block amyloid fibril growth.¹ If the compounds can be made to enter the brain, the approach could arrest the growth of amyloid plaques upstream of the usual target points for antibodies.

Amyloid fibrils are repetitively structured polymers of β -amyloid ($A\beta$), a protein fragment produced in the brains of patients with AD, and are thought to trigger inflammatory activity and neuronal death. Fibrils grow by trapping monomers of $A\beta$ at their ends, eventually forming the large amyloid plaques that are the hallmark of AD histopathology.

Numerous therapeutics have aimed to either block production or aggregation of $A\beta$ and thus prevent the growth of fibrils. Previously, academic researchers had screened for small molecule modulators of $A\beta$ polymerization, but those screens yielded only nonselective compounds like metal chelators and fibril-binding dyes.²

The AC Immune team had sought an alternative to these nonspecific amyloid-binding compounds and used insights into the structure of $A\beta$ fibrils to rationally design a class of molecules that cap off the ends of fibrils.

"These are rationally designed nondye compounds that are optimized for β -sheet-containing aggregates," said CTO and R&D head Andreas Muhs, who led the team. "These compounds bind to the ends of fibrillar structures and prevent growth."

Muhs' team used an *in vitro* assay to screen a family of 3-aminopyrazole compounds for the ability to bind to fibril ends and arrest their growth.

The best hits were dimeric 3-aminopyrazoles with aromatic substituents. Muhs suspected that this type of compound fits tightly into the β -sheet pocket at the ends of each fibril and blocks the recruitment of further monomers.

Consistent with this prediction, electron microscopy of fibrils grown *in vitro* in the presence of the top hits of the series revealed stunted and amorphous aggregates, whereas fibrils grown in the presence of vehicle were highly regular.

The best of the compounds also prevented *in vitro* growth of smaller, oligomeric aggregates of $A\beta$ that some researchers think are the true causal agents in AD. Indeed, oligomers cause acute neurotoxicity in cell culture models of AD, but the relevance of oligomers in clinical AD remains controversial.³

The best compounds from the AC Immune team lowered the extent of oligomer-mediated cell killing compared with vehicle, thus suggesting the compounds can act on both fibrils and oligomers.

Results were published in *The Journal of Biological Chemistry*.

Avoid the amyloid

The AC Immune team's findings suggest a model in which capping the ends of oligomers or fibrils prevents amyloid growth and subsequent toxicity (see **Figure 1, "Blocking amyloid growth"**). Muhs said the company is developing an unnamed member of the 3-aminopyrazole family as a lead compound in a preclinical small molecule program in AD.

Although the compounds work well *in vitro*, how putting a cap on amyloid fibrils would affect AD pathology *in vivo* remains unclear.

Jonathan Weissman, professor of biochemistry and cellular and molecular pharmacology at the **University of California, San Francisco**, said he was "pretty skeptical that capping approaches represent a viable therapeutic option. It's not clear that amyloids are the toxic agent, and even if you did cap them they would probably break and generate new ends."

Muhs acknowledged that the breakdown of amyloid fibrils into smaller fragments could be a concern.

"You don't want to cut the fibril in the middle and make more ends,"

Figure 1. Blocking amyloid growth. Kroth *et al.* have designed small molecules to block the formation and growth of amyloid, an aberrant protein thought to cause Alzheimer's disease (AD).

In AD, amyloid precursor protein (APP) is proteolytically cleaved to produce the β -amyloid ($A\beta$) fragment [a]. This fragment is thought to spontaneously fold into an aberrant structural form [b] prone to clumping together in other misfolded molecules of its type [c]. Over time, this oligomeric aggregate grows into a large, structurally repetitive amyloid fibril [d].

AC Immune S.A.'s small molecules bind to the ends of amyloid oligomers and fibrils, blocking their growth [e] and thus preventing AD progression [f].

he said. “You have to make sure that you don’t break the fibrils into something smaller that is more toxic.”

Another concern is whether the amyloid-capping compounds can readily penetrate the brain, as the molecules tended to be hydrophobic and thus would be excluded by the blood brain barrier.

AC Immune’s most advanced AD therapeutic is the amyloid-binding mAb crenezumab (MABT5102). The compound is partnered with Roche’s Genentech Inc. unit and is in Phase II testing

to prevent progression of an aggressive hereditary form of AD. In June, AC Immune partnered with Genentech to develop antibodies against another AD target, microtubule-associated protein- τ (MAPT; TAU; FTDP-17).

Muhs said the rational design approach to amyloid-end capping eventually could be applied to other neurodegenerative diseases such as Parkinson’s disease (PD). In PD, the intracellular protein α -synuclein (SNCA) forms amyloid deposits within Lewy bodies, which are among the cellular characteristics of the disease.

“These are rationally designed nondye compounds that are optimized for β -sheet-containing aggregates. These compounds bind to the ends of fibrillar structures and prevent growth.”

**—Andreas Muhs,
AC Immune S.A.**

“The compounds we have described here are quite specific for A β , but there are other molecules that have amyloid-like structures, such as α -synuclein,” said Muhs. “We could use our knowledge of amyloid structure to design other compounds” that block the growth of other types of amyloids.

AC Immune has filed for patents covering the compounds used in the study, and the IP is available for licensing or partnering.

Osherovich, L. *SciBX* 5(35); doi:10.1038/scibx.2012.916

Published online Sept. 6, 2012

REFERENCES

1. Kroth, H. *et al. J. Biol. Chem.*; published online Aug. 13, 2012; doi:10.1074/jbc.M112.357665
Contact: Andreas Muhs, AC Immune S.A., Lausanne, Switzerland
e-mail: andreas.muhs@acimmune.com
2. Bieschke, J. *et al. Nat. Chem. Biol.* **8**, 93–101 (2012)
3. Benilova, I. *et al. Nat. Neurosci.* **15**, 349–357 (2012)

COMPANIES AND INSTITUTIONS MENTIONED

AC Immune S.A., Lausanne, Switzerland
Genentech Inc., South San Francisco, Calif.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Swiss Federal Institute of Technology Lausanne, Lausanne, Switzerland
University of California, San Francisco, Calif.