Aβ's dry (AMD) humor

By Lev Osherovich, Senior Writer

A collaborative effort by **Pfizer Inc.** and U.S. academics has found that immunotherapy against β-amyloid can reverse the retinal protein deposition that leads to dry age-related macular degeneration. The finding could open up a repurposing opportunity for mAbs in development for Alzheimer's disease.¹

"We've established β-amyloid as a therapeutic target for dry AMD," a thus far untreatable form of the disease, said team leader Catherine Bowes Rickman, associate professor of ophthalmology and cell biology at **Duke University**.

Bowes Rickman's team built on prior observations by coauthor Lincoln Johnson that β-amyloid (Aβ) accumulated in drusen, the proteinaceous deposits that lead to age-related macular degeneration (AMD) over time.² Johnson is associate director of the Center for the Study of Macular Degeneration at the **University of California, Santa Barbara**.

Previously, Johnson's team "looked at the components of drusen and found that there was amyloid there," said Bowes Rickman. "Studies have found higher amounts of amyloid in the drusen of AMD patients than in controls" who had drusen but hadn't yet developed clinical AMD.

In the new study, Bowes Rickman's team extended those findings by introducing anti-Aβ antibodies into a new mouse model of AMD. The result was a therapeutic effect on retinal pathology and visual acuity.

Eyemyloid

Because good animal models for AMD are scarce, the team designed a mouse overexpressing the human form of the cholesterol transport protein apolipoprotein E4 (APOE4), which causes accumulation of Aβ and increases AD risk. To speed up the disease process, the researchers overfed the animals a high-cholesterol diet.

Indeed, excess APOE4 caused retinal pathology that resembled AMD. Bowes Rickman's team found that the overfed APOE4 mice had retinal Aβ deposits and abnormally large retinal cells, and had poorer visual function than wild-type controls.

The changes in cell size were similar to what is seen in the retinas of cadavers with dry AMD, thus corroborating the mouse model's validity.

"There is a blood eye barrier in the back of the eye, but we don't have to cross this barrier to get a therapeutic effect."

—Catherine Bowes Rickman,
Duke University

Intraperitoneal injection of anti-Aβ mAbs engineered to bind the C-terminal region of Aβ decreased AMD-like pathology and increased visual acuity in mice compared with no treatment.

Among the antibodies the team tested was Pfizer's ponezumab (PF-04360365), which is in Phase II testing for AD.

Notably, anti-Aβ mAbs do not penetrate the eye but remain in the periphery. Thus, Bowes Rickman thinks the mAbs work through the so-called sink effect, in which antibodies in the periphery soak up blood-borne Aβ. Depleting peripheral Aβ is thought to shift the misfolded protein's equilibrium and drive it out of immunologically privileged areas like the brain and retina.

"There is a blood eye barrier in the back of the eye, but we don't have to cross this barrier to get a therapeutic effect," said Bowes Rickman.

Bowes Rickman suspects that keeping Aβ out of the eye may lower the chronic activity of the complement system, an innate immune mechanism recently shown to contribute to dry AMD.³

Her team is now testing whether anti-Aβ mAbs can alleviate disease in a mouse model of AMD caused by excessive complement activity.

ADded value

At least seven companies have anti-Aβ mAbs in preclinical through Phase III testing for AD. The Phase III compounds include bapineuzumab (AAB-001) from **Johnson & Johnson** and

Pfizer and solanezumab (LY2062430) from **Eli Lilly and Co.**

Bowes Rickman thinks ponezumab may be especially suitable as an AMD therapeutic because, unlike other anti-Aβ mAbs, it has been engineered to evade the complement system. Ordinary mAbs can activate complement and potentially exacerbate AMD.

The team has yet to test these other anti-Aβ mAbs in its APOE4 model.

Ryo Kubota, chairman, president and CEO of ophthalmic company **Acucela Inc.**, said that although Bowes Rickman's "data seem solid," it may be better to go further upstream and prevent the conditions that lead to Aβ deposition.

Acucela is developing compounds to block the formation of *N*-retinylidene-*N*-retinyl-ethanolamine (A2E), a toxic metabolite whose accumulation is associated with dry AMD. The company's ACU-4429 is in Phase II testing for the indication.

Kubota thinks A2E may act upstream of Aβ. He said A2E, which prevents normal protein turnover by lysosomes, may lead to the deposition of Aβ in the back of the eye, leading to AMD.

"Inhibition of lysosomal function by A2E is believed to be the cause of drusen formation," said Kubota. "Drusen may be functioning like a magnet to attract Aβ. Targeting the pathological event—A2E itself—earlier in the disease process is a logical approach, represents an ideal target and addresses the root cause of AMD."

Osherovich, L. *SciBX* 4(26); doi:10.1038/scibx.2011.727
Published online June 30, 2011

REFERENCES

1. Ding, J.-D. *et al. Proc. Natl. Acad. Sci. USA*; published online June 20, 2011; doi:10.1073/pnas.1100901108
Contact: Catherine Bowes Rickman, Duke University, Durham, N.C.
e-mail: bowes007@duke.edu
Contact: John C. Lin, Pfizer Inc., South San Francisco, Calif.
e-mail: john.lin@pfizer.com
2. Johnson, L.V. *et al. Proc. Natl. Acad. Sci. USA* **99**, 11830–11835 (2002)
3. Bradley, D.T. *et al. Eye (Lond.)* **25**, 683–693 (2011)

COMPANIES AND INSTITUTIONS MENTIONED

Acucela Inc., Seattle, Wash.
Duke University, Durham, N.C.
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Pfizer Inc. (NYSE:PFE), New York, N.Y.
University of California, Santa Barbara, Calif.