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Doubts about Targretin in AD

By Lev Osherovich, Senior Writer

Four independent academic teams have called into question[1–4] some conclusions from a 2012 paper by **Case Western Reserve University School of Medicine** researchers that suggested the cancer drug Targretin bexarotene could be useful for treating Alzheimer's disease.[5] The new studies failed to replicate some aspects of the original work, but the main conclusions—that Targretin reduces levels of soluble β-amyloid and improves cognitive function in mice—appear to stand.

A clearer picture should emerge in early 2014, when researchers from the **Cleveland Clinic Lou Ruvo Center for Brain Health** are expected to report findings from a Phase II trial of bexarotene to treat AD.

Targretin is marketed by **Eisai Co. Ltd.** to treat cutaneous T cell lymphoma (CTCL) and went off patent last year. The compound is an agonist of retinoid X receptor (RXR), a transcription factor that controls expression of proteins involved in lipid transport in the brain. Defects in lipid transport contribute to AD.

In the original study, a team led by Case Western professor of neurosciences and neurology Gary Landreth examined the effect of agonizing RXR on β-amyloid (Aβ) clearance and cognition in a mouse model for AD.

In one commonly used mouse model for AD, Targretin led to higher levels of apolipoprotein E (ApoE), a lipid-ferrying protein that counteracts Aβ accumulation, than did vehicle. Targretin-treated mice also had lower levels of soluble Aβ and Aβ plaques in the brain and performed better in tests of cognition and memory than vehicle-treated controls.

Because of the striking effect of Targretin on Aβ plaques—about a 75% decrease compared with controls—independent academic teams at the **University of Pittsburgh**, the **University of Florida College of Medicine**, the **Catholic University Leuven** and a consortium of researchers at **The University of Chicago**, **Harvard Medical School**, the **University of Tuebingen**, the **Northwestern University Feinberg School of Medicine** and the **Washington University in St. Louis School of Medicine** tried to replicate Landreth's study.

In each case, the teams examined the effects of Targretin or generic formulations of bexarotene in a wide range of mouse models for AD as well as in dogs.

None of the four teams saw a statistically significant decrease in Aβ plaque levels after treatment. Two of the four teams found that bexarotene decreased levels of soluble Aβ in cerebrospinal fluid or interstitial fluid compared with vehicle, whereas the other two teams saw no statistically significant change in soluble Aβ.

The Leuven team, headed by Bart De Strooper, professor of human genetics, tested the effects of bexarotene on cognition and memory and saw that treated animals had modestly better performance in an assay of social memory compared with animals given vehicle.

De Strooper noted in his technical comment in *Science* that the drug's toxicity led to behavioral abnormalities that made cognitive assays difficult to interpret.

In contrast, a team co-led by Radosveta Koldamova and Iliya Lefterov, both associate professors of environmental and occupational health at the University of Pittsburgh, showed that bexarotene improved memory and cognition in line with Landreth's findings.

Results from all four studies were reported as non–peer reviewed technical comments in *Science*.

Formulation fulmination

In a published response to the four technical comments,[6] Landreth's team suggested that differences in drug formulation could explain the discrepancy between the original study and the efforts to replicate it.

For example, Landreth's team noted that the toxicity and lack of efficacy seen by De Strooper's team could be due to the use of a different vehicle. Landreth's team used off-the-shelf Targretin capsules solubilized in water. De Strooper's team used cyclodextrin-based solvents.

Of the four groups, the University of Pittsburgh team used the closest formulation to the one in Landreth's original paper. That team saw the most pronounced results with the drug.

The findings highlight the difficulty in consistently conducting seemingly similar assays in different laboratories. For example, the fact that two of the new teams saw reductions in soluble Aβ and the other two teams did not suggests that subtle methodological differences can lead to highly varied results.

There is little consensus about how changes in biomarkers such as soluble Aβ or plaque levels in mice relate to human disease. Likewise, it is unclear whether improving mouse learning and memory would lead to meaningful improvements in functional and cognitive endpoints in humans, the clinical standard for AD therapy.

Landreth cofounded **ReXceptor Inc.** to develop brain-penetrating formulations of bexarotene to treat AD. The company plans to start a Phase Ib trial in healthy volunteers.

"The trial will use the FDA-approved dose of the drug, administered exactly as described on the Eisai label," said Landreth.

The Cleveland Clinic is running a Phase II trial of bexarotene. It has not been disclosed how that formulation differs from ReXceptor's.

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