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Statins for fragile X

By Lev Osherovich, Senior Writer

Researchers at the **Massachusetts Institute of Technology** have mouse data showing that the cholesterol drug lovastatin can correct fragile X syndrome.[1] The findings add to a growing list of unconventional strategies for treating this common form of mental retardation.

Fragile X syndrome is caused by trinucleotide repeat expansions in *fragile X mental retardation 1* (*FMR1*). The condition causes alterations in protein synthesis in neurons, leading to developmental delays, autism and epilepsy.

FMR1's normal function is to negatively regulate protein synthesis. Indeed, *Fmr1* knockout mice generally exhibit increased protein levels. Thus, therapeutic strategies for the condition have aimed to lower overall rates of protein synthesis by hitting translation factors and brain receptors that regulate translation.[2]

Three companies—**Novartis AG** and **Roche** and partner **Seaside Therapeutics Inc.**—have clinical-stage compounds for fragile X syndrome that target such brain receptors.

Now, a team led by Mark Bear, professor of neuroscience at MIT and an investigator at the **Howard Hughes Medical Institute**, has shown that lovastatin can lower protein synthesis in the brain and correct at least one mouse-specific manifestation of fragile X syndrome—epileptic seizures caused by loud noises.

Brain chilling

Bear's team strung together prior evidence to formulate the hypothesis that statins could help treat fragile X.

In the 1990s, several teams showed that statins reduced farnesylation of Ras and the activity of two downstream kinases, MAP kinase 3 (MAPK3; ERK-1) and MAPK1 (ERK-2), in cells.[3] In 2010, Bear's team showed that blocking Ras-ERK-1/ERK-2 signaling decreased overall protein synthesis in a mouse model of fragile X.[4]

"What made us pursue lovastatin was that this is a widely used drug in clinical practice with a well-known safety profile that is even used in children," said Bear.

His team found that brain tissue from *Fmr1* knockout mice treated with lovastatin had lower levels of active ERK-1 and ERK-2 and less protein synthesis than tissue from vehicle-treated controls. In cultured brain slices, lovastatin corrected the defective responsiveness to electrical stimulus found in *Fmr1* knockouts.

The team then tested the effects of lovastatin on electrophysiological excitability of brain tissue from *Fmr1* knockouts. Brain slices from the visual cortex of *Fmr1* knockout mice treated with lovastatin had a higher threshold of excitation than slices from vehicle-treated controls. Altogether, lovastatin made the brain slices of *Fmr1* knockouts behave similarly to those from wild-type mice.

Lovastatin's moderating effect on brain activity led to lower susceptibility to noise-induced seizures than vehicle.

"Lovastatin could correct the excess protein synthesis in our mouse model of fragile X and could correct the audiogenic seizure phenotype that's a robust feature of this model," said Bear.

The findings were reported in *Neuron*.

Statin' the case

The findings suggest statins could fit into to a treatment regimen for fragile X syndrome, but it is unclear whether the compounds could work as monotherapy or as adjuncts to other translation-lowering treatments.

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>
> ***—Mark Bear, Massachusetts Institute of Technology***

Statins inhibit HMG-CoA reductase, a biosynthetic enzyme that is several steps upstream of ERK-1 and ERK-2. Thus, the molecules are fairly indirect inhibitors of ERK-1 and ERK-2 activity. In contrast, brain receptor antagonists are thought to hit fragile X–related translational mechanisms more directly.

Seaside cofounder, president and CEO Randall Carpenter suggested statins could prove useful in a subset of patients with fragile X syndrome that have severe seizures. "This paper was largely focused on epileptogenesis and excitability in seizure models," noted Carpenter. "About 20%–30% of people with fragile X mutations also have a seizure disorder."

Seaside and Roche are developing the biotech's arbaclofen (STX-209), a $GABA_B$ receptor antagonist that is in two Phase III trials for fragile X syndrome and has completed a Phase II trial for autism spectrum disorder (ASD). Seaside will report the ASD data this year.

Seaside was cofounded by Bear and has not licensed his statin discoveries.

Carpenter said it is not clear why some patients with fragile X have epilepsy and others do not, but Bear's findings suggest statins could be an add-on therapy for patients in the former camp.

Seaside and Roche also are co-developing RG7090, an antagonist of metabotropic glutamate receptor subtype 5 (mGluR5; GRM5) that is in Phase II trials for fragile X syndrome. Seaside's STX-107, another mGluR5 antagonist, is in Phase II testing for fragile X.

Novartis' AFQ056, another mGlur5 antagonist, is in Phase III trials for fragile X.

Carpenter said $GABA_B$ and mGluR5 are well-validated targets that reduce the translation of a broad range of proteins and that it remains to be seen whether inhibiting Ras-ERK-1/ERK-2 signaling with statins would have a comparably protective effect.

Indeed, because lovastatin had a big effect on audiogenic seizure but only a modest effect on Ras-ERK-1/ERK-2 signaling, the compound could be working through other mechanisms.

"It's possible that lovastatin could be doing more than just inhibiting ERK-1 and ERK-2—it depletes farnesylation in the brain, so there may be other targets," said Bear.

He now plans to test lovastatin in other murine and tissue culture assays of fragile X syndrome to see whether the compound affects the cognitive aspects of the disease. He also plans to compare the efficacy of statins with that of mGlur5 antagonists.

Carpenter said that instead of statins, it might be more effective to develop compounds that directly hit translational regulatory kinases like ERK-1 and ERK-2.

Indeed, one such kinase—p21 protein (Cdc42 Rac)-activated kinase 1 (PAK1)—is the target of preclinical compounds from **Afraxis Inc.** for fragile X syndrome.

Carpenter said such strategies raise concerns about safety and selectivity because of the importance of these targets in the normal functioning of other tissues.

Afraxis CEO Jay Lichter said ERK-1 and ERK-2 are likely to be upstream of PAK1 in the kinase cascade that governs translation levels. He added that hitting this pathway indirectly with statins is an attractive option from a safety standpoint.

"I don't think an ethics board would have a problem giving this to kids," said Lichter.

Along those lines, a Canadian team has started a small open-label dose-ranging study of lovastatin in patients with fragile X who are 10–40 years old.

Lichter noted that besides fragile X syndrome, PAK1 is an attractive target in a range of inflammatory and cancer indications. Last month, Afraxis sold its portfolio of PAK1 inhibitors to Roche's **Genentech Inc.** unit. Genentech did not disclose its development plans for Afraxis' fragile X compounds.

There are patents pending on the findings reported in *Neuron*, and the findings are available for licensing.

Osherovich, L. *SciBX* 6(6); doi:10.1038/scibx.2013.129
Published online Feb. 14, 2013

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COMPANIES AND INSTITUTIONS MENTIONED

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