Researchers propose minocycline as a promising drug for patients with Fragile X syndrome

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First row (left to right): Iryna Ethell, Tina Bilousova; second row (L to R): Jennifer Aye, Douglas Ethell, Lorraine Dansie, Jonathan Charles (Michelle Ngo, not shown). Iryna Ethell is holding the Breakthrough Award of the Year awarded to her by The FRAXA Research Foundation. Credit: Ethell lab, UC Riverside

A UC Riverside-led team of biomedical scientists has found that a readily available drug called minocycline, used widely to treat acne and skin infections, can be used to treat Fragile X syndrome, the most common inherited cause of mental impairment and the most common cause of autism.

The study's findings have already impacted future therapies, with the approval of a new clinical trial in Toronto, Canada, that will test minocycline in patients with Fragile X.

Neurons in the brain communicate with each other at specialized contact sites called synapses, with many of these synapses occurring on small mushroom-shaped structures called dendritic spines.

During early development dendritic spines have immature finger-like shapes. But learning stabilizes the synapses and dendritic spines take on a mature mushroom shape, which make them more efficient.

The brains of patients with Fragile X syndrome have an overabundance of immature dendritic spines.

In their report, the researchers, led by Iryna Ethell and Douglas Ethell, faculty members in UCR's Division of Biomedical Sciences, describe how dendritic spine development in mice with Fragile X is delayed by enzymes called matrix metalloproteinases (MMPs), which are involved in normal brain development and physiological processes. They report that high levels of certain MMPs keep the synapses immature and inefficient.

But minocycline, they found, reduces these MMP levels in the mice, allowing the synapses to mature and make more efficient contacts between neurons in the brain. The outcome: corrected brain abnormalities in dendritic spines, reduced anxiety and improved cognitive function.

Study results appear online, ahead of print, in the *Journal of Medical Genetics*.

In their experiments, the Ethells found that young Fragile X mice treated with minocycline showed an increase of dendritic spine maturation in the hippocampus, a brain area that is critical for learning and memory. Besides less anxiety, minocycline-treated mice showed better exploration skills as compared to untreated mice.

The Ethells are enthusiastic about how their discovery already is leading to a clinical trial.

"Clinical studies often quickly follow such basic science because once there is a solid understanding of how problems arise, it is much easier to come up with solutions," said Iryna Ethell, an associate professor of biomedical sciences.

The study was funded by a grant from the FRAXA Research Foundation. FRAXA was founded in 1994 by three parents of children with Fragile X to support scientific research aimed at finding a treatment and a cure for Fragile X.

Dr. Michael Tranfaglia, FRAXA's chief scientific officer, said of the UCR researchers, "This group has done something unique and incredibly valuable: They have identified an off-the-shelf treatment for Fragile X through their basic research. By bringing their unique perspective to Fragile X research, they have helped us to understand why neurons are malformed in this disorder, and more importantly, how we can treat it.

"We were so impressed with their work that we just awarded Dr. Iryna Ethell the FRAXA Breakthrough Award for 2008. This is easily the most important scientific breakthrough in the Fragile X field in many years."

According to Dr. Carl Paribello, president of Fragile X Research Foundation of Canada and the director of the clinical trial (scheduled for early 2009) at Surrey Place Centre Fragile X Clinic in Toronto, Canada, the UCR-led study "will go a long way towards dispelling the idea that mental impairment cannot be treated."

"The work could lead to the first treatment that actually targets the underlying defect in Fragile X syndrome and not just the symptoms," Dr.

Paribello said.

UCR's Douglas Ethell, an assistant professor of biomedical sciences, noted that effective therapies for Fragile X syndrome are few and far between. "This is a good time for identifying highly effective therapeutic strategies that might work in Fragile X patients," he said. "We are excited that our research has the potential to affect many lives."

Fragile X affects 1 in 4000 males and 1 in 6000 females of all races and ethnic groups. About 1 in 259 women carry Fragile X and could pass it to their children. About 1 in 800 men carry Fragile X; their daughters will also be carriers.

Minocycline belongs to a group of antibiotics that has been used in people for more than fifty years to treat Lyme disease, acne, and other skin infections.

Minocycline may have beneficial effects in other disorders where higher-than-normal brain levels of MMP-9 are found. It is currently under study for treating rheumatoid arthritis, multiple sclerosis (MS), Parkinson's disease, and several other neurodegenerative conditions.

"In the future, new compounds that more specifically target MMP-9 can be developed and tested," Douglas Ethell said.

Next in their research, the Ethells and their colleagues plan to refine the therapeutic strategy in Fragile X mice to determine the optimal age, if any, to administer minocycline. They will also explore other MMP inhibitors that may be more effective than minocycline.

"We will investigate whether a combination of MMP inhibitors with other drugs, such as fenobam, can help mature the synapses in Fragile X mice," Iryna Ethell said.

Source: University of California - Riverside