NEWS

Going on Trial: Gene therapy for Rett; return to arbaclofen

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Welcome to the June issue of Going on Trial, a monthly newsletter covering clinical trials and drug development for autism and related conditions. This month we preview early safety data from the first gene therapy trial for Rett syndrome, and we explore why it's so hard to design trials of drugs for autism.

I'm Calli McMurray, *Spectrum*'s summer intern. I've taken over Going on Trial from Peter Hess, the original author of the newsletter. I'd love to hear your thoughts and tips on what this newsletter should cover. Feel free to email me: **calli@spectrumnews.org**. Thank you for reading!

Rett's new frontier:

On 5 June, a woman in Canada with Rett syndrome received her first injection of an experimental gene therapy for the condition, the biotech company **Taysha Gene Therapies announced**. Her treatment represents the first-ever test of a Rett gene therapy in humans.

The woman is doing well and shows no adverse effects so far following her dose of TSHA-102, according to an update from the company yesterday.

"This is very exciting," says **Walter Kaufmann**, chief scientific officer at Anavex Life Sciences and adjunct professor of human genetics at Emory University School of Medicine. Kaufmann was not involved in this trial; Anavex is currently testing its own treatment for Rett. "The patient and the family who are doing this are pioneers."

The therapy was administered through a single injection into the cerebrospinal fluid surrounding the spinal cord. Six weeks after the initial dosing, an independent data monitoring committee is expected to decide if it's safe for a second patient to begin her dosing regimen.

The open-label, **phase 1/2 trial** is expected to eventually expand to 12 women: the first cohort will receive a smaller dose, and if all goes well, the second cohort of women will receive a larger one.

Rett syndrome, which mainly affects girls and women, is characterized by communication difficulties, intellectual disability and motor problems. It is caused by mutations in the gene that encodes methylcytosine-binding protein 2 (MECP2). This protein regulates other genes involved in development.

Gene therapy has the potential to treat or even reverse several aspects of Rett syndrome by restoring the production of MECP2. But MECP2 levels must stay within a 'Goldilocks' zone — not too high, not too low — because too much of it leads to **MECP2 duplication syndrome**, which mainly affects boys and men and involves similar features.

TSHA-102 delivers a functional copy of the MECP2 gene to cells as well as an additional untranslated sequence that uses microRNAs (short strands of genetic material) to keep protein production in check.

Taysha hopes to submit an investigational new drug application to the U.S. Food and Drug Administration (FDA) later this year, according to a company spokesperson.

And there is another gene therapy in the works: Earlier this month, genetic medicine company Neurogene **began recruiting** girls ages 4-10 for an open-label, **phase 1/2 trial** of their own therapy. Participants will be followed for five years after the one-time treatment.

Drug samples:

- In other Rett news: The results from the phase 3 trial of trofinetide — which **earned approval** from the FDA for the treatment of Rett syndrome in March — were **published** in *Nature Medicine* on 8 June.
- And yet another Rett drug could be on the horizon: Anavex Life Sciences has finished its **phase 2/3 trial** of the experimental drug blarcamesine, *Rett Syndrome News* **reported**. The trial included 92 girls with the syndrome aged 5-17 years. The company has already completed **phase 2** and **phase 3** trials of the drug, also called Anavex 2-73, in women with Rett syndrome. Both of those studies showed Anavex 2-73 is safe, eases behavioral challenges and improves quality of life compared with a placebo. The results of the new trial are expected later this year.
- A new phase 3 trial of the drug arbaclofen for fragile X syndrome is in the works. Allos Pharma met with the FDA earlier this month to discuss the trial's design, *Fragile X News Today* **reported**. The motivation for the trial stems from a **re-examination of data** from a 2011 phase 3 trial that failed to show improvements in social avoidance among children with the syndrome who received the drug compared with those who took a placebo. Per FDA guidance, Allos Pharma **reanalyzed the results** and found clinically meaningful

improvements in irritability, social responsiveness and social avoidance.

- The Swiss drug company Roche has discontinued its work on rugonersen, a gene therapy for Angelman syndrome, after disappointing results from **a phase 1** clinical trial, **reported** *FAST*. *Spectrum* covered **preclinical data** on the therapy in August.
- The U.S. National Institutes of Health (NIH) spends about as much as the pharmaceutical industry does on new drug approvals, according to an **analysis published** in *JAMA Health Forum* in April. NIH funding contributed to all but two of 356 drugs approved by the FDA from 2010 to 2019, to the tune of $1.44 billion per drug, on average; industry spending during a similar period amounted to a mean of $1.6 billion per drug, **a previous analysis found**.
- The FDA has published a draft of **updated recommendations** for good clinical practices. The updates “aimed at modernizing the design and conduct of clinical trials, making them more agile without compromising data integrity or participant protections,” according to a 6 June **press release**. The agency is **accepting comments** for 60 days.
- Plus, psychedelic drugs get their own guidance: The FDA issued its first **guidelines for clinical trials** of drugs such as psilocybin, LSD and MDMA as treatments for psychiatric disorders and other medical conditions. Psychedelics must meet the same effectiveness standards as other drugs, but the psychoactive effects require unique considerations to ensure safety and rigor, according to a 23 June **press release**.
- Researchers seeking FDA approval for autism drugs face three main challenges, according to a panel discussion held at a medical conference last year: a dearth of data on the tools that are most sensitive to short-term changes in autism traits; uncertainty about the endpoints the FDA would accept besides irritability; and the lack of validated biomarkers for autism. A **summary** of the discussion was published in the *Journal of Personalized Medicine* in April.

That’s all for June! **Make sure you subscribe** so you can receive this newsletter in your inbox every month.

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