Highlights from the 2025 STXBP1 Researcher Roundtable

The 2025 STXBP1 Researcher Roundtable took place in October in Heidelberg, Germany. This yearly meeting switches between the US and Europe each year. Nearly forty scientists and doctors attended, spending three days sharing research updates, new ideas, and plans for the future. The main topics were: how STXBP1 works in the body, developments in therapy, and getting ready for clinical trials.

Biological Mechanisms

The STXBP1 protein helps control the release of signals between nerve cells in the brain, but scientists are still figuring out how changes (mutations) in the *STXBP1* gene affect this process. The meeting started with Matthijs Verhage explaining how problems in genes related to nerve cell communication can lead to different diseases. Other speakers—Niels Cornelisse, Thomas Opladen, and Jacqueline Burre—talked about genes besides *STXBP1* that also help with nerve cell activity, and how changes in these genes can cause problems that are sometimes like those seen in STXBP1-RD, but sometimes different. Then, Sylvia Korhorn, Caroline Pearson, Jean-Francois Perrier, and Matthew Vanheusden focused on what happens when there are mutations in the *STXBP1* gene itself and the problems these can cause.

One important discussion was about "dominant-negative" missense variants. This means some mutations might make a faulty protein that actually interferes with the normal one. Scientists—including those at this meeting—are studying if these harmful effects happen in any *STXBP1* variants. This is important because certain therapies, like antisense oligonucleotides (ASOs) and CRISPRa, try to increase STXBP1 from a person's own genes, but might not work for people with these specific gene variants. One of the main results from this meeting was that the group agreed it's really important to answer this question and more research is needed to sort this out.

Therapeutic Development

On the second day of the conference, experts talked about STXBP1-RD and new treatments. Ingo Helbig started by sharing updates about how STXBP1-RD affects patients. Merel Swinnen explained how walking is different for people with STXBP1-RD. Adrián Carbó talked about what they learned from patients in Madrid, Spain, and Matteo Lenge and Alice

Dainelli shared results from brain scans, showing about half of the 21 patients had changes in their brains. Francesca Furia discussed milder cases of STXBP1. These patients usually learn to walk and talk, even if it takes longer, and more than half have normal thinking skills without major brain problems. Most have epilepsy that can be controlled, but many still face challenges like autism or other behavior issues. Scientists say this group needs to be studied more in the future.

Bruria Ben-Zeev, Allan Bayat, Matias Wagner, and Andreas Zieglar talked about treatments and what they've learned from other brain disorders like Dravet syndrome, Lennox-Gastaut, SCN2A-related disorders, and muscle diseases. Ana Mascaro explained how scientists use human nerve cells to test new drugs. Efrat Ben-Zeev described how computers can help find new medicines for STXBP1-RD. Millie Stone and Hila Ben-Moshe showed results from using existing drugs, like Ravicti and beta-nicotinamide mononucleotide (β-NMN), to help STXBP1-RD patients. Mingshan Xue, Ben Prosser, Gad Vatine, and Nathan Henderson talked about treatments that involve the *STXBP1* gene itself, such as gene replacement (giving someone a working gene), ASOs, RNA editing, and CRISPRa, which are ways to fix or improve the gene.

The last talks raised an important question: How much more STXBP1 protein do brain cells need for treatments to work, and how many cells need this boost? Treatments like gene replacement, ASOs, CRISPRa, and RNA editing all try to raise STXBP1 protein, but no one knows the exact amount needed yet. Scientists showed that ASO and CRISPRa can increase STXBP1 by about 40% in cells from patients, but it's unclear if that's enough. In mice, giving a low dose of the gene helped stop seizures but didn't fix thinking, movement, or behavior problems. A higher dose helped with all these issues. The big takeaway was that figuring out how much STXBP1 needs to be increased is very important for future treatments.

Clinical Trial Readiness.

On the last day of the meeting, everyone focused on finding new ways to track STXBP1-RD and collect information about how the disease changes over time. Biomarkers—things in the body that can be measured to show how sick someone is—are important for checking if treatments are working in STXBP1. Scientists also talked about the "natural history" of the disease, which means how a disease moves forward in people and how to measure that. Hilgo Bruining, Additya Sharma, Shilpa Anand, and Jillian McKee gave talks about special brain wave patterns (EEG) that might help as biomarkers for STXBP1-RD. Laura Wetzel and

Jan Lui talked about finding signs of the disease in blood and spinal fluid. Andreas Brunklas explained how tracking the natural history helped with a gene therapy trial for Dravet Syndrome, which is similar to STXBP1-RD. Sam Pierce shared updates about the STARR natural history study in the US, and Elena Gardella and Hannah Stamberger talked about the ESCO natural history study and registry in Europe. The session ended with talks about different tools used to measure how someone with STXBP1-RD is doing. Sarah Tefft talked about a new rating scale to judge overall change; Andrea Miele discussed a child development test called the Bayley 4; and Megan Abbott introduced a new way to measure how severe STXBP1-RD is.

Looking Ahead

Overall, the meeting showed strong advances in research and getting ready for clinical trials. Studies like STARR and ESCO are providing helpful data, and the new tools will make it easier to track changes in future drug trials. Pharmaceutical companies have noticed and praised these efforts, setting up more progress for the future of STXBP1 research.