ESCO Science Spotlight, Autumn 2025

Contributed by Dr. Bruria Benzeev head of the pediatric neurology unit and head of the Israeli Rett center at Safra pediatric hospital, Sheba medical center, Israel.

The last few months research published information in the field of STXBP1 related neurodevelopmental disorder, STXBP1 related translational and basic science research were interesting and will be summarized in the following report but we will have to start with the significant events related to gene therapy progress for the disorder based first on the information received from the press releases of Capsida Biotherapeutics.

On May 12 after long research by Capsida Biotherapeutics that covered all the required regulatory demands, the U.S. Food and Drug Administration (FDA) cleared for clinical trial the Investigational New Drug (IND) application for CAP-002 developed by the company. The construct is the first-in-class, intravenously (IV) administered gene therapy to enter clinical trials for syntaxin-binding protein 1 developmental and epileptic encephalopathy (STXBP1-DEE) and the first drug entering a human clinical trial utilizing an IV-administered, blood brain barrier-crossing engineered capsid that was constructed to " detarget" off-target tissues, like liver and dorsal root ganglia (DRG). This was followed soon after on May 14 by Capsida's presentation of new non-human primate (NHP) GLP toxicology data for CAP-002. The data included demonstration of dose-dependent brain-wide expression of STXBP1 and simultaneous detargeting of the liver and dorsal root ganglia (DRGs). The conclusion of this important experiment in the mouse model was that all doses of CAP-002 tested show the potential to fully correct seizures and meaningfully correct cognitive and motor dysfunction in patients and that in all dosages tried the "detargeting " of liver and DRG's was more efficient that the classical AAV9 vector used in genetic therapy trials of other neurodevelopmental disorders. In this press release the message was that CAP-002 was well tolerated with no adverse clinical pathology or histopathology findings throughout the central nervous system, DRGs, or peripheral organs, including the liver.

In addition on *May 29, 2025* — Capsida Biotherapeutics ("Capsida") announced the U.S. Food and Drug Administration (FDA) has granted Fast Track designation to its CAP-002 program. This track is designed to facilitate the development and expedite the review of drugs that are intended to treat serious or life-threatening conditions and have the potential to address an unmet medical need. A drug that receives Fast Track designation may be eligible for more frequent meetings and communications with the FDA and priority review of application for marketing approval if relevant criteria are met.

These very promising positive steps led to the opening of SYNRGY Phase 1/2a clinical trial in the US, with the first patient recruited in August? 2025.

But to our sorrow in Sep 10th 2025 Capsida shared with the STXBP1 community that the first patient to participate in the SYNRGY trial for STXBP1-Related Disorders passed away. So far there is no more available data published on the course of this devastating event. The company declares that they are working with urgency to gather information and find answers and are committed to share it with the community. Meanwhile the company alerted the FDA on the event and voluntarily decided to pause the CAP-002 SYNRGY study while further investigating the underlying root cause of the patient's death and will also inform the community on their future plans about the program .

But this is definitely not the end of the road for gene therapy research and hopefully clinical trials for STXBP1 DEE .

In a recent paper by R. Aeran et al, the Encoded therapeutic team (another company in the field of gene therapy development) are describing their progress in developing gene therapy construct for STXBP1. (**Ref: Neuron-targeted gene therapy rescues multiple phenotypes of STXBP1-related disorders in mice and is well tolerated in nonhuman primates R Aeran et al . Molecular Therapy 2025:33:8.)**

The researches are using the AAV9 vector which is currently the leading viral vector for central nervous system (CNS)-targeted gene therapies. They chose to use the brain intraventricular route to introduce their product . The two novel steps they took are:

(A) After thorough investigation, they engineered novel promoter cassettes that will promise efficient distribution and expression of the STXBP1 gene in both GABAERGIC and Glutamatergic neurons which is crucial for rescuing the neurological phenotype of STXBP1 deficiency with less expression in other non neuronal cells.

(B) They added a 3'UTR regulatory element (DT-A) that will be responsible to “detarget” expression in DRG (dorsal root ganglia) cells which is known to be a major element in the nervous system toxic effects of gene therapy.

In their mice models using very young mice bilateral intracerebroventricular (ICV) injection achieved robust neuronal expression of the STXBP1 gene and rescued key behavioural phenotypes in Stxbp1+/ -haploinsufficient mice. The treated mice showed significant improvement in motor, behavioural, cognitive functions as well as significant reduction in seizures and EEG hyerexctability patterns (better seizure control and correction of EEG abnormalities). In addition they completed a dose ranging mouse study to identify the optimal dose that will rescue the phenotype of the STXBP1 deficient mice.

The mice experiments were proceeded into safety and efficacy experiments in non human primates and showed widespread vector biodistribution in the central nervous system of the animals after unilateral ICV administration with good tolerance to the vectors . They also re-proved the benefit of the added component that is responsible for “detargeting” the DRG cells by performing both electrophysiological and histopathology studies which show much milder negative effect than the insult seen without this component. Transient elevations in serum liver enzymes were observed within 1–2 weeks post-dosing but these elevations resolved or remained only slightly elevated by day 30 post-dosing. In general the experiment in non human primates showed safety, tolerability, activity, and DRG detargeting as expected.

They also demonstrated in their experiments that the inclusion of the two components (the specific promoter for selective neuronal expression and the component aimed to detarget DRG) to the STXBP1 normal gene construct work together in the same efficiency as the construct including only the specific promoters and the gene itself. Their publication concluded that these results give strong support for further clinical development of these candidate vectors to treat STXBP1-RD, and continued research to optimize targeted gene therapy candidates for a variety of therapeutic applications.

Accumulating new and more detailed clinical data on STXBP1 DEE patients is crucial both for understanding their symptoms and planning appropriate interventions and as a basis for further follow-up during more advanced therapies trials.

In August this year, a study on the extent of CVI (cortical visual impairment), its assessment and prognosis in a group of 85 patients with several distinct genetic related developmental disorders was published. It included children with STXBP1 mutations as well as children with SLC6A1, Ring 14, and 8p-related disorders. **(Ref: Cortical Visual Impairment Across a Range of Neurodevelopmental Disorders (NDD): Clinical Characterization, Diagnostic Tool Evaluation, and Association with Developmental Outcomes. M Abbott et al. J Child Neurol.)**

CVI is defined as visual impairment resulting from brain abnormalities, despite intact ocular structures and function, or visual deficits that are disproportionate to coexisting ocular conditions. Presence of CVI has been shown to negatively impact children's learning and behaviour in many aspects and its diagnosis is important in order to direct to appropriate treatment approach.

The work was retrospective and based on chart reviews of the patients but all patients reviewed had specific test used (CCSA- clinician- vision) evaluating their visual function with additional assessments of other developmental aspects and all went through full ophthalmologist examination.

Out of 85 patients included in the study, 42 had STXBP1 mutations. Fifty precent of them were diagnosed with CVI which is much more than previously reported in the literature. The study also showed that there was a direct correlation between CVI diagnosis and worse functioning on motor and communication scales and in addition worse VABS-3 scores indicating worse adaptive behaviour.

This study is of clinical importance emphasizing the need of CVI assessment possibly by using the CCSA-vision clinician scale after full ophthalmological examination in patients with STXBP1 as early as possible and intervening with the available therapies to try and improve this disability which hopefully will lead to some improvement in other developmental skills. If the authors estimation of up to 50% CVI in STXBP1 DEE patients turns to be true, CVI assessment can be added as additional marker for improvement in future advanced therapies trials.

In addition to papers related to STXBP1-DEE there are several publications on the STXBP1 gene and protein involvement in other body systems and pathophysiological processes which may be of importance for better understanding the role of its deficiency or overexpression in the STXBP1 population.

Many of the neurodevelopmental related gene products have a role in other body systems especially in the immune system and their overexpression or under expression locally in different tissues can interfere with various pathophysiological processes. In a recent paper published in NATURE (a major scientific journal) Ling hao et al (**Ref : Catechin suppresses HNSC via STXBP1 dependent inhibition of macrophage infiltration and CD47 mediated immune evasion Ling Hao et al . Nature Scientific Reports | (2025) 15:23968**), the researchers emphasize that higher expression of STXBP1 in epithelial tumours like head and neck squamous cell carcinoma is a bad prognostic sign. They found that overexpression of STXBP1 gene promotes tumor immune escape through dual pathways interfering with this tumour response to therapy and that the natural compound Catechin can specifically inhibit STXBP1 expression and significantly suppress tumour growth. Of course this study is not

directly relevant to our community but it makes us aware to the fact that in gene therapy planning there could be significant clinical meaning to “too much “ as well as to “too little.“

A comprehensive review related to the role of STXBP1 protein (Munc-18) in the pathogenesis of neurodegenerative disorders including Alzheimer and Lewy body disease was also published in August this year. (**Ref: Munc 18-1 is a multifaceted therapeutic target for Dementia Running title: Munc 18-1 is a master regulator of Dementia pathogenesis. KS Singh et al. Ageing Research Reviews Aug 2025)**

The review starts with reports of several previous studies that showed decreased STXBP1 protein levels in both human brain and CSF specimens in dementia and in its animal models.

In addition, based on the data presented they propose that STXBP1 (Munc18-1) serves as a master regulator in the multifactorial landscape of dementia, owing to its capacity to interface with several critical proteins and pathways implicated in various abnormal mechanisms leading to neurodegeneration and dementia.

In this review they explain why both the classical role of STXBP1 in synaptic vesicle formation and neurotransmitter release but also other less canonical roles of the protein related to neuroinflammation, amyloid precursor processing, Tau phosphorylation, chaperone effect on α-synuclein, BDNF regulation may take part in dementia related processes. The authors suggest that different approaches to increase STXBP1 levels can be a target for treatment in various neurodegenerative dementing processes. In addition, if even part of the mechanisms described are relevant to real life brain pathophysiology they can be involved in both the pathogenesis and clinical course of STXBP1 related neurodevelopmental disorder and should be further looked at.