



Synaptic Dysfunction in Intellectual Disability Caused by SYNGAP1. Translational Research to Develop Human Models and Advance Pharmacological Treatments (TREAT-SNGAP)

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Synapses allow communication between neurons and are also the site for storing sensorial information. It is for this reason that synapses are very important in learning and memory. Recent biomedical research has shown that synaptic dysfunction is at the centre of many brain disorders, especially in conditions where cognitive abilities are impaired, such as intellectual disability (ID) or autism spectrum disorders. The human *SYNGAP1* gene encodes a protein that is highly enriched at brain synapses. Recent genetic studies have shown that mutations in *SYNGAP1* cause ID. Actually, *SYNGAP1* mutations could account for up to 1% of all ID cases, affecting thousands of people worldwide. Basic research studies using mice deficient for *SYNGAP1* have shown that, indeed, a synaptic dysfunction is importantly contributing to ID. Nevertheless, there is still no efficient treatment for kids with this disorder. It is thus necessary that we understand in great level of detail the alterations occurring at the synapse if we want to develop *SYNGAP1* deficiency treatments. Using mouse models we have studied proteomic alterations found at the synapse of *SYNGAP1* deficient animals. This research has allowed us to propose four candidate drugs that we think might correct synaptic alterations, potentially improving this condition. Now we want to actively investigate the effect of these drugs in *SYNGAP1* deficiency. As nowadays we have the capacity to develop neurons from human skin or blood cells, we will, for the first time, directly study human neurons obtained from *SYNGAP1* patients. These human neurons will also be used to investigate the validity of mouse findings in a human research system. The ultimate goal of TREAT-SNGAP is to identify new strategies to treat ID caused by *SYNGAP1*.