

Title: *Accelerating Therapies for GLUT1 Deficiency Syndrome with Small Molecule candidates*

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Research Theme/Topic: Biophysics, Engineering, Chemical and Molecular Biology.

Main Abstract:

GLUT1 Deficiency Syndrome (GLUT1-DS) is a genetic condition caused by abnormalities in the GLUT1 protein, which is crucial for moving glucose into the brain. This condition can lead to a range of neurological issues, including learning difficulties, movement disorders, and epilepsy. Currently, the main treatment is the ketogenic diet, but it does not work for every patient and in all the symptoms, and can be hard to follow. Our research is looking to develop new drug treatments specifically targeting GLUT1-DS. We have already found some chemical compounds that seem to help cells grow by improving how they take in glucose through GLUT1 protein. Now, we are working on confirming how these compounds interact with GLUT1 and checking if they are effective using cells from patients.

We have also found that the way GLUT1 protein works is altered in people with GLUT1-DS, and these changes might make these patients particularly likely to benefit from certain types of drugs that target GLUT1 protein. The project has two main goals:

- (1) Test these compounds to see if they could be used to treat GLUT1-DS. This includes detailed studies to understand how these molecules work with GLUT1 protein, particularly when GLUT1 is not working correctly.
- (2) Study the specific changes in GLUT1 in patients with GLUT1-DS and to see how effective our drugs are on cells taken from these patients. This will help us make sure that our treatments will work in real- world situations.

The doctoral student will focus on both aims. The first one will be conducted in the PI laboratory and it will include the use of advanced biophysical methods (binding assays, structure determination, compound screening, etc.) together with the use of well-known biochemical and molecular biology strategies. The student will learn how to purify protein samples to homogeneity and how to accurately determine the structure of the protein bound to activating molecules.

The second aim will be conducted in collaboration with the *IRCCS Mondino Foundation* to test the efficacy of the selected molecules using patient-derived fibroblasts.

Techniques: Electrophysiology, protein expression and purification, cell biology assays, computational methods (docking, molecular dynamics, protein engineering).

