Discovery of a novel drug candidate to develop effective treatments for brain disorders

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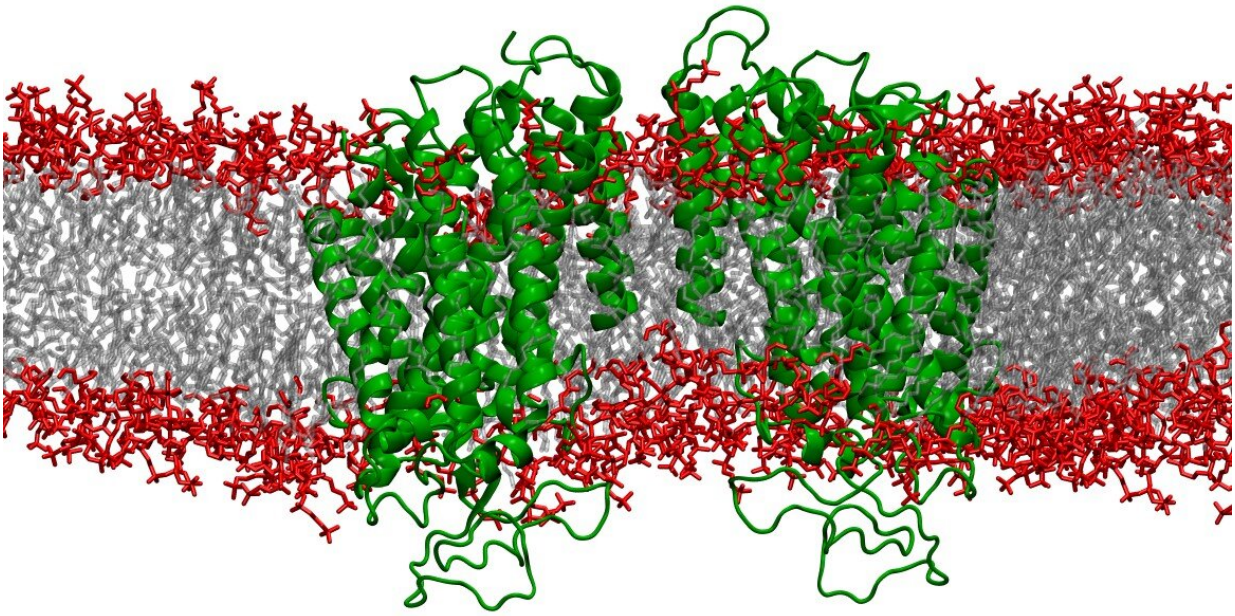

The Protein NKCC1 is a transporter of ions in the brain; their concentration is crucial for brain function. The newly discovered compounds can potently and

selectively block NKCC1, without undesired side effects. Credit: IIT-Istituto Italiano di Tecnologia

Researchers at IIT-Istituto Italiano di Tecnologia (Italian Institute of Technology) have discovered a novel chemical compound that has the potential to become a new drug for the treatment of core symptoms of brain disorders like Down syndrome and autism. These results were obtained in preclinical models where the new compound ameliorated difficulties in cognitive tasks, as well as social interactions and repetitive behaviors present in neurodevelopmental and possibly neurological disorders. The study has been published in the scientific journal *Chem*.

These breakthrough findings are the result of a joint effort of two Italian research teams guided by Laura Cancedda and Marco De Vivo, at the Istituto Italiano di Tecnologia in Genova (Italy). The two groups worked on complementary aspects of the research study: The De Vivo's group designed the new molecules with the aid of computational methods, and synthesized them, while Cancedda's lab focused on extensive biological tests of such compounds. The final result represents the development of a promising drug candidate with potential to become a clinical drug in forthcoming years.

Co-first authors of the research article are Annalisa Savardi (Cancedda's Lab) and Marco Borgogno (De Vivo's lab) who worked synergistically to identify the novel chemical compounds and investigate their biological consequences in the brains of preclinical models of neurodevelopmental disorders. Such models are the first experimental steps to verify the benefits and safety of the new drug.

The study published on Chem is the result of a joint effort of two Italian research teams guided by Laura Cancedda and Marco De Vivo, at the Istituto Italiano di Tecnologia in Genova (Italy). Co-first authors are Annalisa Savardi (Cancedda's Lab) and Marco Borgogno (De Vivo's lab). Credit: IIT-Istituto Italiano di Tecnologia

In particular, researchers focused on the effect of the molecules on the protein NKCC1, a very promising target for drugs to treat brain disorders. NKCC1 is a transporter of chlorine (and other) ions in the brain, and the correct concentration of such ions is crucial for brain function. In several brain disorders like Down syndrome, autism and epilepsy, the concentration of such ions in the brain is dysregulated due to NKCC1 abnormal function. These newly discovered compounds can potently and selectively block NKCC1, without undesired side effects (excessive diuresis) caused by other drugs that are non-selective NKCC1 inhibitors.

"This study and exciting results come at a time where neuroscience drug discovery in industry struggles to deliver novel breakthrough classes of effective molecules. As a matter of fact, therapeutic options for most of neurodevelopmental disorders have remained scant, or not highly effective over the last decades. This is mainly due to a poor understanding of the mechanisms underlying these challenging pathological conditions. This discovery follows several years of work on NKCC1 function and inhibition at IIT and will possibly bring us closer to the development of sustainable therapeutics for the treatment of a number of brain disorders," says Laura Cancedda.

"At this point, our most promising compound could enter into clinical tests in hospitals in less than two years from now. This additional step toward making of this compound an approved drug, however, requires further work and more funds. For this reason, we plan to launch a new start-up company dedicated to this project. It would be wonderful to see our discovery impacting on those in needs," says Marco De Vivo.

The newly discovered drug candidate is now undergoing advanced preclinical studies to move it forward and hopefully reach clinical studies. Additional studies will allow defining the overall safety profile of the molecule and other key parameters such as pharmacokinetics, formulation and dosing, necessary to fulfill the regulatory requirements to access clinical studies.

More information: Savardi, Borgogno, et al. *Chem* (2020). DOI: 10.1016/j.chempr.2020.06.017 , www.cell.com/chem/fulltext/S2451-9294(20)30298-9

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