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From autism to Alzheimer's: Membrane transporters open new avenues for treating brain disorders

Solute carriers (SLCs) are specialized transport proteins that control the movement of nutrients, ions and neurotransmitters across cell membranes and are essential for brain metabolism and neuronal communication. While some SLCs have been targeted successfully by drugs for decades, most of this large protein family remains therapeutically unexplored. A new review in *Nature Reviews Drug Discovery* (DOI: 10.1038/s41573-026-01513-4; impact factor: 91), led by Giulio Superti-Furga, founding scientific director of the Austrian Academy of Sciences (OeAW) institutes CeMM and Cori, highlights the growing potential of SLC transporters as targets for drugs and gene therapies in central nervous system disorders, including epilepsy, autism spectrum disorders, Alzheimer's disease and Parkinson's disease.

SLCs act as both gatekeepers and workhorses at cell membranes. They determine what enters the cell and when: sugars that provide energy, amino acids that serve as building blocks, ions, vitamins, and even the chemical messengers that enable communication between nerve cells. In humans, 464 SLC transporters belonging to 70 families are currently known, collectively controlling a vast network of molecular traffic across the lipid bilayer surrounding every cell that is fundamental to its function.

Neurons have high energy demands and must tightly regulate the concentration and distribution of neurotransmitters. SLCs help ensure that the right molecules are available in the right place at the right time. If this transport system is disrupted, both neuronal metabolism and communication can be severely affected. This makes SLCs attractive therapeutic targets: manipulating the transport of key molecules could provide new ways to intervene in disease processes.

Established targets and untapped potential

A limited number of SLCs have long been established as effective drug targets. Some of the most widely used drugs in neurology and psychiatry act on these transporters. Selective serotonin reuptake inhibitors (SSRIs), for example, block the serotonin transporter, preventing serotonin from being taken back up into cells and thereby increasing its availability between neurons. This mechanism is widely used in the treatment of depression, anxiety disorders and other psychiatric conditions.

SLC transporters are also established targets in epilepsy. Tiagabine, for example, inhibits an SLC transporter for GABA, the brain's principal inhibitory neurotransmitter, increasing GABA availability and helping to reduce excessive neuronal activity. Other approved drugs target SLCs involved in the transport or storage of dopamine and other neurotransmitters. Yet these established medicines address only a small fraction of the SLC family. The new review points to a much broader therapeutic landscape that is now beginning to come into view.

Activating rather than blocking

Most drugs targeting SLCs work by inhibiting transporter activity. But in many disorders, the underlying problem is the opposite: a transporter may be insufficiently active, expressed at abnormally low levels or located in the wrong part of the cell. Researchers are therefore exploring new strategies to activate, stabilize or restore the function of SLC transporters. The first candidates are already in clinical development, including potential therapies for epilepsy, autism spectrum disorders and chronic pain. They act on transporters that regulate the balance between excitatory and inhibitory signals in the brain.

The therapeutic potential of SLCs also extends beyond neurotransmission. These transporters regulate the supply of energy and nutrients to neurons as well as the movement of glucose, ions and metabolic products. Disrupted energy metabolism is increasingly recognized as an important feature of neurodegenerative diseases such as Alzheimer's and Parkinson's disease. Transport pathways involved in cellular metabolism could therefore provide additional points of therapeutic intervention, although many of these approaches remain at an early stage of research.

For diseases caused directly by the loss of function of an SLC gene, research is already going a step further. Gene therapies aim to provide a functional copy of the affected gene and thereby correct the underlying transport defect. The first approaches are already being evaluated in clinical trials, including therapies for SLC6A1-related neurodevelopmental disorders, GLUT1 deficiency syndrome and a rare disorder caused by mutations in the SLC13A5 gene.

From the Human Transportome to New Medicines

Giulio Superti-Furga, founding director of CeMM and senior author of the review, was among the researchers who recognized the broader therapeutic potential of SLCs early on. For many years, his research has focused on the human "transportome" (the complete set of transport proteins in the human body). He also led RESOLUTE (https://re-solute.eu/), a major international initiative established to systematically investigate the biology of SLC transporters and make them more accessible for drug discovery.

To translate these findings into new medicines, he co-founded the biotechnology company Solgate together with Ariel Bensimon, Gaia Novarino, Stefan Kubicek and Georg Winter. Bensimon and Solgate's Chief Scientific Officer, Enrico Girardi, are also co-authors of the review. The first author is Yee Kwan Law, a PhD student in Superti-Furga's research group at CeMM.

Superti-Furga is now expanding this research in Graz as founding scientific director of the new Carl and Gerty Cori Institute of Molecular and Computational Metabolism (Cori) of the Austrian Academy of Sciences. Cori aims to systematically decipher human metabolism and its role in health and disease. SLCs are central to this effort because they determine which nutrients and metabolic products enter and leave cells. Understanding these fundamental transport processes could reveal new vulnerabilities in disease and, ultimately, new opportunities for therapeutic intervention.

A New Frontier for Drug Discovery

Despite their potential, SLCs remain challenging drug targets. The biology of many transporters remains poorly understood, while developing suitable assay systems and compounds is technically demanding. As a result, only a small fraction of this large protein family has so far made its way into drug development. At the same time, that landscape is beginning to change: Advances in structural biology, cryo-electron microscopy, computer-aided drug design and screening technologies are improving researchers' ability to selectively target transporters that have previously been difficult to access.

Rather than focusing exclusively on individual neurotransmitters or receptors, future therapies could specifically correct the molecular transport pathways that determine the metabolism and chemical balance of nerve cells. Whether this will ultimately lead to new treatments for epilepsy, autism, Alzheimer's or Parkinson's remains to be demonstrated in clinical trials. But with the first therapeutic candidates already in development, SLC transporters are moving from a relatively overlooked protein family toward the forefront of neuroscience drug discovery.

Pictures attached
Foto: First author Yee Kwan Law (left, © Wolfgang Däuble) and corresponding author Giulio Superti-Furga (right, © Franzi Kreis)
Graphic: Schematic representation of SLC membrane transporters © Bojan Vilagos
The Study "Solute carrier membrane transporters: emerging targets in CNS disorders" was published in *Nature Reviews Drug Discovery* on 1 September 2026. DOI: 10.1038/s41573-026-01513-4
Authors: Yee Kwan Law, Selene Glück, Enrico Girardi, Ariel Bensimon, S. Andreas Angermayr and Giulio Superti-Furga
Funding: This work was supported by Angelini Pharma.

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For further information please contact:

Wolfgang Däuble
Media Relations Manager / Science Writer
Phone +43-1/40160-70092
wdaeuble@cemm.at

CeMM
Research Center for Molecular Medicine
of the Austrian Academy of Sciences
Lazarettgasse 14, AKH BT 25.3
1090 Vienna, Austria
www.cemm.at