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Advances and challenges in rational drug design for SLCs

Rachel-Ann A Garibsingh¹, Avner Schlessinger^{1,*}

¹Department of Pharmacological Sciences, Icahn School of Medicine at Mount Sinai, New York, NY 10029

Abstract

There are over 420 human Solute Carrier transporters (SLCs) from 65 families that are expressed ubiquitously in the body. The SLCs mediate the movement of ions, drugs, and metabolites across membranes, and their dysfunction has been associated with a variety of diseases, such as diabetes, cancer, and central nervous system disorders. Thus, the SLCs are emerging as important targets for therapeutic intervention. Recent technological advancements in experimental and computational biology allow better characterization of SLC pharmacology. Here we describe recent approaches to modulate SLC transporter function, with an emphasis on the use of computational approaches and computer-aided drug design to study nutrient transporters. Finally, we discuss future perspectives in the rational design of SLC drugs.

Keywords

solute carrier; protein structure prediction; computer-aided drug design; structure-based drug discovery; membrane transporter

SLC pharmacology

Transport of solutes by Solute Carrier (SLC) transporters is essential for many of life's processes, such as importing nutrients into cells, generating electrical and chemical signals, regulating cell volume, as well as the delivery and excretion of drugs. In humans, there are over 420 SLCs that are grouped into 65 families based on their sequence, function, and number of transmembrane (TM) regions [1]. A large number of SLCs are implicated in a wide array of diseases, including central nervous system (CNS) and metabolic disorders, as well as diabetes and cancer [2]. For example, genetic variations in the norepinephrine transporter (NET, SLC6A2) are associated with attention-deficit hyperactivity disorder (ADHD) [3], and upregulation of the neutral amino acid transporter, alanine serine cysteine transporter 2 (ASCT2, SLC1A5) is linked to poor prognosis in non-small cell lung cancer (NSCLC) [4]. In addition, the majority of the SLCs are capable of being modulated by small molecules, such as their natural substrates (e.g., organic ions and cations, see Glossary), as

*Corresponding Author: Avner Schlessinger, One Gustave L. Levy Place, Box 1603, New York, NY 10029, (212) 241-3321, avner.schlessinger@mssm.edu.

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well as prescription drugs and phospholipids, which can bind in substrate or allosteric binding sites [5]. Thus, SLCs are emerging as important, druggable targets.

However, compared to other protein families of similar size, such as GPCRs or protein kinases, only few SLCs have been targeted with tool compounds or clinically approved drugs [6, 7]. Furthermore, most drugs targeting the SLCs focus on a small subset of proteins, such as neurotransmitter transporters belonging to the SLC6 family, including the γ -aminobutyric acid transporter (GAT1, SLC6A1), norepinephrine transporter (NET, SLC6A2), dopamine transporter (DAT, SLC6A3), and serotonin transporter (SERT, SLC6A4) for the treatment of CNS diseases and disorders [6]. Interestingly, from 2015 to 2018, out of 172 novel drug approvals by the U.S. Food and Drug Administration (FDA), four drugs target three SLCs including: the vesicular monoamine transporter 2 (VMAT2, SLC18A2), the uric acid transporter (URAT1, SLC22A12) and the sodium-glucose transporter (SGLT2, SLC5A2) (Table 1)^{i,ii} In addition, the Japanese Pharmaceuticals and Medical Devices agency (PMDA) has recently approved elobixibat, an inhibitor of the apical sodium bile acid transporter (ASBT, SLC10A2) for treating chronic idiopathic constipation [8] (Table 1). While the number of drugs targeting SLCs is still low, “drugging” previously unexplored SLCs suggests that there are other promising therapeutic SLC targets.

Most of drug discovery efforts toward the human SLCs have focused on high throughput [9] and phenotypic screens [10], optimization of known inhibitors with medicinal chemistry and molecular design [11], as well as ligand-based computational approaches such as quantitative structure-activity relationship (QSAR) and pharmacophore modeling (reviewed in [7, 12]). One weakness of ligand-based approaches is their limited ability to guide the design of unique chemical scaffolds [7]. Computer-aided structure-based drug design offers the advantages of an in-depth understanding of the three-dimensional (3D) protein binding site and possible insight into different conformational states; and when combined with virtual screening of large compound libraries, it can lead to the discovery of novel chemical scaffolds [13].

SLC structure and mechanism

An important step toward increasing the number of tool compounds and eventual drugs targeting the SLCs, requires the characterization of SLC structures in different conformational states in complex with their ligands. Technical limitations, such as the lack of inadequate biological reagents (e.g., antibodies) and poor protein expression by conventional techniques have hindered the development of pharmacological agents targeting SLCs [6]. Furthermore, only a small number of atomic-resolution structures of human SLCs have been determined [14], making it difficult to elucidate molecular interactions between small molecules and transporters, and to rationally design relevant chemical tools. Encouragingly, in recent years there has been a surge in the number of experimentally determined structures of SLCs and their homologs from other organisms [5]. For example, structures of important human SLCs, such as the electrogenic sodium bicarbonate cotransporter (NBCe1, SLC4A4) [15], as well as the amino acid transporters, ASCT2 [16] and large neutral amino acid transporter (LAT1, SLC7A5) [17] have been determined at near atomic-resolution using cryo-electron microscopy (cryo-EM). Although most cryo-EM SLC

structures are at insufficient resolution for describing the molecular interactions useful for rational drug design, this is anticipated to change in the near future due to various advances, such as those made in detector technology and data processing [18].

The recent structures have revealed that apart from their diverse functions, the SLC families cluster to evolutionarily unrelated structural classes or folds, where the most common folds are the major facilitator superfamily (MFS) and leucine transporter (LeuT) folds [19]. Notably, although the SLCs generally follow an ‘alternating access’ transport mechanism [20, 21], each structural class uses a distinct type of conformational changes to transport substrates (Figure 1). For example: (i) MFS proteins use a ‘rocker-switch’ mechanism (e.g. GLUT1, SLC2A1), in which the substrate binds to the extracellular facing binding site, triggering conformational changes to an occluded state, followed by an inward-facing state where the substrate is released [22]. (ii) Transporters with the LeuT fold use a ‘rocking bundle’ or ‘gated-pore’ mechanism (e.g. SERT, SLC6A4), in which a mobile bundle domain undergoes large hinge-like rearrangements to release the substrate to the intracellular side, while the scaffold domain remains static [23, 24]. (iii) Several structural families (e.g., SLC1 and SLC13)) utilize an ‘elevator’ mechanism, in which the scaffold domain remains static as the mobile domain moves up and down like its namesake, to transport the substrate across the membrane [25–27]. Notably, knowledge of the transport mechanism, including relevant conformational changes, is important for devising a strategy for the development of small molecule modulators.

In addition, the newly determined SLC structures facilitate modeling the human SLC transporters with homology modeling, which relies on the structures of homolog proteins as templates [28], or integrative modeling, which uses restraints derived from experimental data (e.g., from cryo-EM or cross-linking data) [29]. Specifically, it is now possible to model the structures of many previously unmodelable SLC transporter targets, or SLCs with known structures in unknown conformations. For example, the crystal structure of a zebrafish homolog of the lysosomal sodium-coupled neutral amino acid transporter 9 (SLC38A9) has been recently determined [30]. SLC38A9 is associated with mTOR activation in cancer [31] and shares a sequence identity of 61.9% with the zebrafish homolog, making it useful to generate homology models suitable for rational design. The new structural information on SLCs, combined with superior computational power and the maturation of computational chemistry tools, such as ligand docking [13], next generation membrane protein Molecular Dynamics (MD) simulation approaches [32], free energy perturbation estimation [33], as well as advanced machine learning (ML) architectures (e.g., autoencoder) [34] is expected to expedite the characterization of human SLCs. Here, we outline recent studies characterizing the substrate specificities of biomedically important SLC nutrient transporters, and the discovery of small molecule modulators of these proteins using computer-aided drug design (CADD).

Structure-based ligand design for the nutrient transporter, ASCT2

The SLC1 family has seven members, including five excitatory amino acid transporters (EAATs) that transport glutamate (SLC1A1–3, SLC1A6, 7) and two neutral amino acid transporters ASCT1 (SLC1A4) and ASCT2 (SLC1A5). Over the past decade, structures of

SLC1 members from human (i.e., EAAT1 and ASCT2) and their prokaryotic homologs Glt_{Ph} (reviewed in [35]) and Glt_{Tk} [36] have been determined. Particularly, much of what is known about the structure and dynamics of the human SLC1 members has been through the characterization of Glt_{Ph} with a variety of biophysical approaches, such as Double Electron-Electron Resonance (DEER) [37], single-molecule Fluorescence Resonance Energy Transfer (smFRET) [38], and high-speed atomic force microscopy (AFM) [39]. Taken together, these studies describe a trimeric configuration and elevator transport mechanism (Figure 1A) conserved across organisms.

The SLC1 family includes several putative drug targets, such as EAAT2 for Alzheimer's disease (AD) [40] and ASCT2 for cancer [4, 41, 42], however, there are no clinically approved drugs targeting this family. Specifically, ASCT2 is frequently upregulated in various cancer types, including triple negative breast cancer [41] and NSCLC [4], where this transporter is thought to play a key role in glutamine import, thereby fueling cancer cells [42]. Thus far, efforts to inhibit ASCT2 have largely focused on substrate like-inhibitors that likely bind the substrate binding site [43–47].

Over the past decade, ASCT2 has been modeled in the outward-open and outward-occluded conformations based its homologs' structures [43–47]. The initial Glt_{Ph}-based models were used to guide the design of novel ASCT2 inhibitors such as 1,2,3-dithiazoles [48], serine biphenyl-4-carboxylate [43], L- γ -Glutamyl-p-nitroanilide (GPNA) analogs (*N* γ -glutamylanilides) [47] and 2-amino-4-bis(aryl-oxybenzyl)aminobutanoic acids [49]. Additionally, recent ASCT2 models based on similar structures revealed previously uncharacterized druggable pockets, pocket A (PA) and pocket B (PB) (Figure 2, left inset). PB is formed in ASCT2 by a substitution of an arginine residue in EAAT1 (R479) to a cysteine residue in ASCT2 (C467) (Figure 2, left inset). C467 was proposed by to be a key substrate specificity determinant in the SLC1 family [44, 50]. Further, virtual screening of large compound libraries from the ZINC databaseⁱⁱⁱ, combined with cellular uptake and electrophysiology assays, identified new ASCT2 ligands, including five substrate-like compounds and two ASCT2 inhibitors (e.g., γ -2-fluorobenzyl proline) [44]. This study highlighted the utility of virtual screening to capture unexplored chemical spaces of transporter ligands, which have been further optimized to obtain higher affinity inhibitors [51].

Subsequent ASCT2 models based on the human EAAT1 structure [27] (sequence identity of 46%) provided a refined conformation of TM8 and hairpin 2 (HP2), and overall a more accurate model, as measured by its ability to enrich known ligands compared to decoy molecules [52]. The EAAT1-based ASCT2 models were sufficiently accurate to guide the development of sulfonamide and sulfonic acid ester linkers that specifically target PA, providing a more quantitative structure activity relationship (SAR) [53, 54]. For example, the experimentally determined K_i correlated with estimated free energy of binding using ligand docking and molecular mechanics generalized Born and surface area (MM-GBSA) calculations [53].

The new cryo-EM structures of ASCT2 in inward-facing occluded (3.85 Å) and open (3.6 Å) conformations, provided additional mechanistic details of the structure-function of this

protein [16, 54]. For example, the inward-facing structure confirmed the role of HP2 in gating, as well as the presence of druggable pockets seen in the EAAT1-based models [16, 52]. Interestingly, the EAAT1-based outward homology models of ASCT2 showed better ligand enrichment than that obtained with the ASCT2 inward occluded cryo-EM structure [53]. This suggests that a reliable homology model in a pharmacologically relevant conformation can be as powerful a tool for rational design as a near-atomic resolution structure.

Elucidating the dynamics of SLC1 transporters

Visualization of transporter dynamics can be useful to describe the different structural states of the transport cycle, predict the effect of mutations on transport, as well as identify druggable pockets on the protein and estimate interactions between SLC and ligands, including potential drugs. A common approach to model conformational changes in SLC transporters is through MD simulations [7]. Progress in efficient simulation approaches, increased computational power and improved force fields, coupled with the growing number of SLC transporter structures have enabled researchers to address key questions in transporter biology. For example, the full transport cycle of a prokaryotic homolog of the human sugar transporter (SWEET, SLC50A1), was accurately captured with all-atom MD simulations [55]. Furthermore, MD simulations of Glp_{ph} have contributed to our knowledge of the sodium binding sites of the SLC1 transporters [56–59]. Additional studies have revealed mechanisms of uncoupled anion conductance [60], gating by HP2 [61], and ion-substrate coupling [62], as well as mechanisms of substrate binding [63] and translocation [64, 65] that occur in the SLC1 family.

While technological advancements have improved the ability to simulate longer timescales and the confidence of MD simulations, there are significant limitations that remain. Specifically, some transporters such as LeuT, have a timescale of transport ranging from milliseconds to seconds, making all-atom MD simulations extremely computationally demanding and often unfeasible [66]. Although methods such as steered MD [67] and umbrella sampling [68] can simulate at longer timescales, these approaches are often limited by the availability of suitable resolution protein structures and forcefields [32]. It should also be noted that large conformational changes are difficult to approximate with MD simulations, at a resolution sufficient for drug design.

Allosteric control of SLC1 transporters

Allosteric modulation is an attractive way to target transporters for inhibiting or enhancing their function [69]. Allosteric inhibitors can bind protein-specific subpockets and may be particularly useful to selectively target homologs or other proteins that share a similar substrate binding site.

Due in part to the highly conserved substrate binding site among SLC1 members, most currently available inhibitors are nonselective, hindering their clinical relevance. The SLC1 members, however, are amenable to allosteric modulation [70]. For example, an allosteric activator that increases the clearance of glutamate from synapses can be a potential drug for

EAAT2, a target for AD therapy [71]. Indeed, the EAAT2 specific activator parawixin1, was recently found to increase EAAT2 activity by binding an allosteric site predicted computationally [72]. Interestingly, parawixin1, sourced from spider venom, was not designed to specifically activate EAAT2. Notably, computational methods such as molecular docking and free energy perturbations are limited in their ability to distinguish between inhibitors, substrates, and activators [73].

Conversely, the EAAT1-specific inhibitor (UCPH₁₀₁), was crystallized in an allosteric site located in the interface between the mobile and static domains of this protein, highlighting residues such as F369 and Y127 which provide critical interactions with the transporter (Figure 2, right inset). The UCPH₁₀₁ binding site is thought to be distinct from the EAAT2 parawixin1 binding site [72]. The structural and biochemical data indicated that the compound can access the allosteric site from the intracellular side and its binding does not preclude substrate binding. Since the EAAT1 structure was solved as a trimer, the compound UCPH₁₀₁ also added further support of independent transport by each subunit [27]. Notably, the structure with bound ligand also provided a framework for developing allosteric inhibitors specific to individual family members.

Design of ligands for ADME transporters

Membrane transporters, including several SLC families, can play an important role in drug absorption, distribution, metabolism and excretion (ADME) (i.e., ‘ADME transporters’) [74]. Examples include, members of the SLC22 family of organic cation, anion, and zwitterion transporters, which are expressed in the kidney, liver, and blood-brain-barrier, to regulate drug pharmacokinetics (PK) [75]. The SLC22 family members transport a broad range of drugs and prodrugs, such as metformin [76] for the treatment of type II diabetes, and gemcitabine, a first-line chemotherapy for NSCLC [77]. Additionally, drug-drug interactions are often mediated by ADME transporters similarly to those occurring in metabolic enzymes, and genetic variation in ADME transporters can lead to differential drug response among patients (i.e., pharmacogenomics) [74]. Key questions in drug discovery of ADME transporters include: (i) Can we develop predictive models for distinguishing between SLC variants leading to differential drug absorption and dynamics among patients? (ii) Can we identify SLC small molecule ligands, including inhibitors, substrates, or activators that may cause drug-drug interactions? and (iii) Can we rationally design efficient transporter substrates with optimal PK properties or bioavailability, including drugs that can be handled by transporter variants? Multiple recent studies have combined a range of ligand-based and structure-based computational and experimental methods to discover ligands for various ADME SLC targets, such as the organic cation transporter (OCT1, SLC22A1) [78] and the human intestinal transporter, the organic anion transporting polypeptides (OATP2B1, SLC21A9) [79], with varying levels of success, as well as explain the effects of mutations on drug uptake and dynamics (reviewed in [7, 12]).

An important group of ADME transporters include members of the SLC15 transporters that mediate the uptake of a broad range of peptides and peptide-like drugs. Particularly, the proton-dependent di/tri-peptide transporter 1 (PepT1, SLC15A1) is primarily responsible for intestinal absorption of luminal di- and tri-peptides from dietary protein digestion and

peptide-like drugs, such as the β -lactam antibiotics cefadroxil and antiviral prodrug valacyclovir [80]. The three-dimensional structures of mammalian SLC15 members are unknown. Our current understanding of PepT1 structure and drug-transporter interactions has primarily relied on structures of various prokaryotic homologs [81]. Recently determined crystal structures of PepT_{Sh} from the bacterium *Staphylococcus hominis*, bound to two drugs (i.e., valacyclovir and 5-aminolevulinic acid) propose a pharmacophore model for PepT1-drug recognition [82]. For example, the amino acid scaffold and ester linker of valacyclovir makes critical contacts with the binding site of PepT_{Sh}, providing guidance for future optimization for drugs with better absorption [82] (Figure 3).

Samsudin *et al.* have recently used state-of-the-art computational techniques to describe the substrate specificity of PepT1 and its bacterial homologs [83]. Estimates of free energy of binding suggested that the properties of the N-terminus of the transported peptide ligands were more critical for transport than those of the C-terminus [83]. In parallel, Colas *et al.* have identified new substrates and inhibitors of PepT1 using a combined approach of homology modeling, virtual screening, and experimental testing with cellular uptake and electrophysiology assays, providing novel scaffolds for future tool compound development [84]. While both of these computer-guided studies attempted to estimate the free energy of binding of small molecules to PepT1, it is important to note that: (i) even if successful, computational prediction of affinity can usually determine only whether a small molecule likely to bind or not; and (ii) a compound's affinity or potency (e.g., as measured with IC₅₀) does not necessarily correlate with its ability as a substrate to get transported across the membrane [85].

Finally, PepT1 variants have been associated with reduced transport activity in specific populations [86]. For example, F28Y variation in PepT1 (Figure 3, inset) is a rare mutation in African Americans which reduces substrate uptake. Structures of PepT1 homologs and the homology model of PepT1 indicate that the mutation occurs near the substrate binding site (Figure 3, inset) which may have an effect on helix packing and binding site conformation, thereby hindering transport.

Concluding remarks and future outlook

The SLC transporters provide a wealth of underexplored therapeutic targets. Here, we first outlined the structure, function, and pharmacology of the human SLCs (Table 1, Figure 1). We then presented examples of how rational design was used to develop small molecule ligands targeting the substrate and allosteric sites of SLC1 transporters (Figure 2) and summarized key limitations of current computational approaches. Finally, we show how structures of SLC15 homologs can help explain intestinal drug absorption by the human PepT1 and the deleterious functional effect of a mutation in patients (Figure 3).

Many challenges remain in understanding SLC biology, as well as in pharmacological targeting of these proteins (see Outstanding Questions). Chemical tools for human SLCs are needed to characterize the structure and function of these biomedically important transporters, and to deorphanize SLCs with unknown function. Currently, rational design of SLC modulators is hampered by the limited understanding of transporter structure and

dynamics. While CADD has proven useful for the development of tool compounds for SLCs, limitations remain. For example, at present, computational methods provide useful information about binding but not kinetics (e.g., residence time on target) [87]. Thus, they cannot distinguish between inhibitors that may bind tightly to the target, substrates that bind and unbind the target triggering transport, and activators that make the transporter more efficient [13].

In the near future, methods can be improved by using ML algorithms (reviewed in [88]). For example, recently, deep learning algorithms were used to aid in image processing and secondary structure assignment of cryo-EM maps [89], as well as to explore conformational space with MD simulations [90]. In addition, while ML approaches have been used for many years for drug prediction in QSAR, including for membrane transporters [7], the new deep learning architectures such as autoencoder can also be used to design drug-like chemicals de novo [34]. Notably, these emerging ML methodologies usually require large sets of active and inactive compounds in order to be optimally trained. However, for SLCs, often times this is simply not yet the case [6]. We expect that the advancements discussed in this review and renewed interest in SLCs in both academia and industry will lead to an expansion in tool compounds available for the further characterization of SLCs and the development of eventual SLC drugs.

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GLOSSARY

Activator

A molecule that enhances or increases the activity of an SLC by binding to the transporter in a substrate or allosteric site.

Allosteric inhibitor

A molecule that binds at a different site than the substrate binding site and inhibits SLC transport.

Alternating access

Conformational changes that cause the transporter to alternately expose its substrate-binding site to either side of the membrane.

Druggable

Disease-related target that is amenable to small molecule binding and modulation.

Molecular dynamics (MD) simulation

Application of Newton's equations of motion to predict the positions of atoms in a biomolecular system as a function of time using a force field to specify the parameters in the system.

Molecular mechanics generalized Born and surface area (MM-GBSA)

Molecular mechanics generalized Born and surface area, a popular method to estimate the free energy of the binding of small molecules to SLC transporters.

Pharmacophore modeling.

Ligand or structure-based methods that use the spatial arrangement of physicochemical features from the ligand and structure, respectively, to develop quantitative models that are predictive of bioactivity.

Quantitative structure-activity relationship (QSAR).

Structural descriptors of ligands, such as number of hydrogen bond acceptors and donors, size, charge, are used to develop a statistical model predicting biological activity.

Substrate

A molecule that gets transported across the membrane by membrane transporter.

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Resources

- i). <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation>
- ii). <https://www.centerwatch.com/drug-information/fda-approved-drugs>
- iii). <http://zinc.docking.org/>
- iv). <https://www.centerwatch.com/drug-information/fda-approved-drugs/drug/100244/steglatro-ertugliflozin>
- v). <https://www.centerwatch.com/drug-information/fda-approved-drugs/drug/100198/ingrezza-valbenazine>
- vi). <https://www.centerwatch.com/drug-information/fda-approved-drugs/drug/100197/austedo-deutetrabenazine->
- vii). <https://www.centerwatch.com/drug-information/fda-approved-drugs/drug/100127/zurampic-lesinurad>

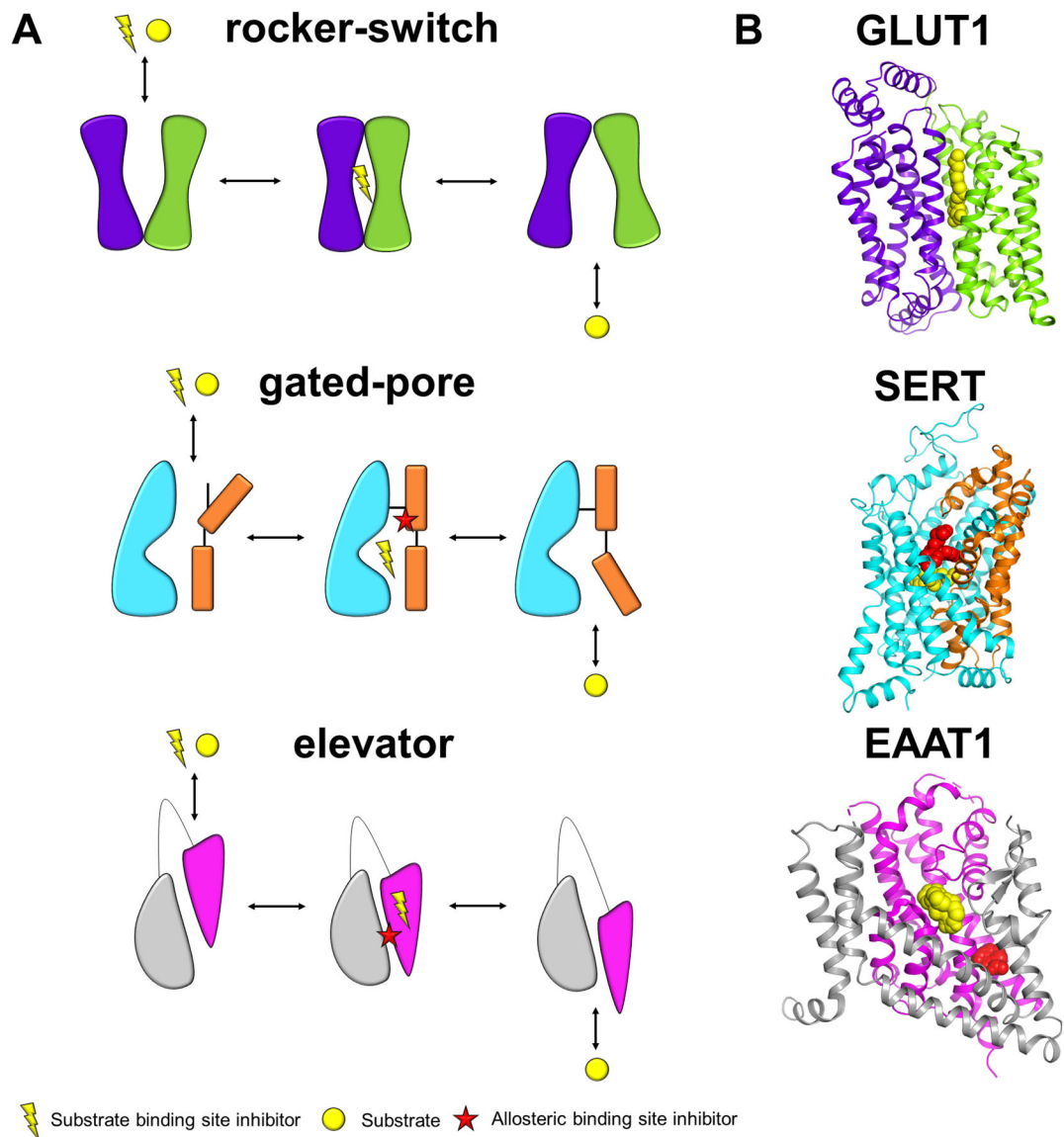


Figure 1. Different SLC alternating access transport mechanisms.

(A) For each transport mechanism, there is a representative schematic of an unbound outward-open conformation that is accessible to both inhibitor and substrate, an occluded inhibitor bound state, representative of when inhibitor binding blocks substrate transport and an inward open conformation, which is accessible to substrate from the intracellular side of the membrane. The colors denote the two different domains involved in the mechanism. The figure only shows one protomer even if more than one subunit is involved. *The rocker-switch* mechanism, the substrate binds to the extracellular facing binding site, triggering conformational changes to an occluded state, followed by an inward-facing state where the substrate is released. *Rocking bundle* or *gated-pore* mechanism has a mobile bundle domain (in orange) that undergoes large hinge-like rearrangements to release the substrate to the intracellular side, while the scaffold domain (in cyan) remains static. The *elevator* mechanism has a mobile domain (pink) that moves up and down, relative to a scaffold

domain (gray), to transport the substrate across the membrane. **(B)** Representative structures of transporters using the transport mechanisms in (A) where the colors correspond to the respective domains as shown in (A), substrate binding site and allosteric site inhibitors are shown in yellow and red spheres, respectively. PDB IDs: GLUT1: 4PYP, SERT: 5I73, EAAT1: 5LLM.

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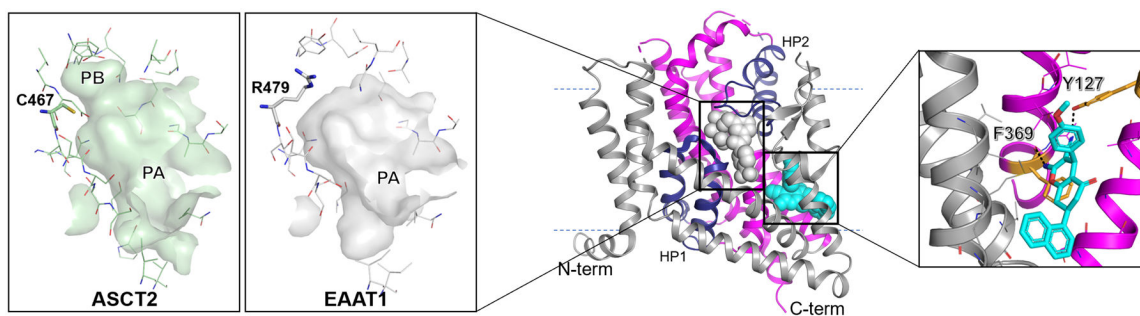


Figure 2. Substrate and allosteric binding sites of EAAT1 and ASCT2.

Here, gray represents the scaffold domain and; dark blue hairpins 1 and 2 (HP1 and 2) and pink comprise the transport domain. The substrate and allosteric binding sites of EAAT1 (PDB ID: 5MJU) are shown in gray and cyan spheres respectively. Here, dotted lines show the approximate location of the membrane. **Inset left:** Surface representations of the substrate binding site of the outward-open conformation for ASCT2 and EAAT1. Pockets A and B (PA and PB) are highlighted and residues impacting substrate specificity and binding site shape are shown as sticks with oxygen, nitrogen, and sulfur atoms shown in red, blue, and yellow. **Inset right:** The allosteric inhibitor UCPH₁₀₁ bound to EAAT1. Key residues making polar contacts with UCPH₁₀₁ are highlighted as orange sticks. Images were generated with PyMOL (<https://pymol.org/2/>).

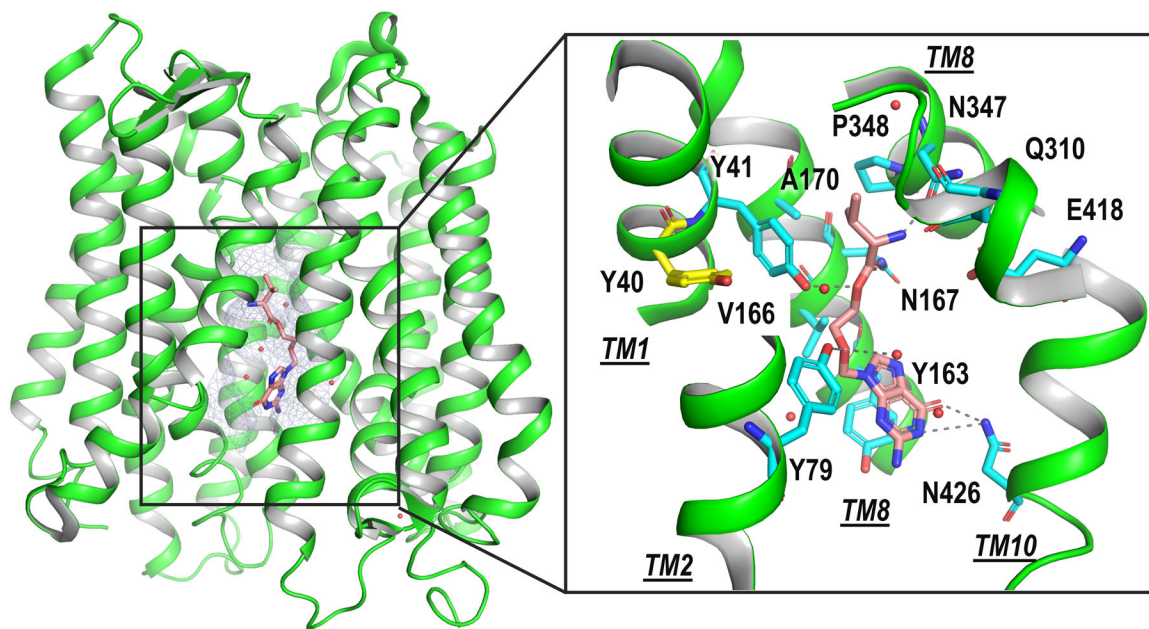


Fig. 3. Structure of an ADME transporter homolog, PepT_{Sh}.

The crystal structure of PepT_{Sh} (green cartoon) in complex with the antiviral drug valacyclovir (peach sticks) is shown. The substrate binding site is shown in light blue mesh. Inset shows the magnified view of the interaction of valacyclovir with the binding site of PepT_{Sh}. The sidechain atoms of key residues in PepT_{Sh} are illustrated with cyan sticks, with Y40, in yellow. Y40 is equivalent to F28 in the human PepT1. Rare mutation in this position in African Americans (F28Y) reduces substrate uptake by PepT1. Hydrogen bonds between binding site residues and valacyclovir are displayed as dashed gray lines. Images were generated with PyMOL (<https://pymol.org/2/>).

Table 1.

FDA and PMDA approval of SLC drugs from 2015 to 2018.

^a SLC	^b Other name	^c Drug	^d Year	Indication	Mechanism of action	References / Resources
SLC10A2	ASBT	Elobixibat ^e (A3309)	2018	Chronic idiopathic constipation	Increases bile acid delivery to colon to accelerate and increase colonic secretion.	[8]
SLC5A2	SGLT2	Steglatro™ (ertugliflozin)	2017	Type II diabetes mellitus	Increases urinary glucose excretion via SGLT2 inhibition to reduce blood glucose levels.	iv
SLC18A2	VMAT2	Ingrezza™ (valbenazine)	2017	Tardive dyskinesia	Reversible inhibition of VMAT2 activity.	v
SLC18A2	VMAT2	Austedo™ (deutetrabenazine)	2017	Chorea associated with Huntington's disease; Tardive dyskinesia	Mechanism of action for anti-chorea effects is currently unknown.	vi
SLC22A12	URAT1	Zurampic™ (lesinurad)	2015	Hyperuricemia associated with gout	Inhibition of URAT1 and organic anion transporter 4 (OAT4) (to a lesser extent), to increase uric acid excretion and reduce serum uric acid levels.	vii

^a SLC marks the primary SLC target of the newly approved drug

^b Other name corresponds to alternative name of the SLC gene or protein

^c Drug is the brand name of the drug with the generic name in parenthesis

^d Year marks the approval year of the drug by the FDA

^e Elobixibat is a PMDA-approved drug. All others are FDA-approved.