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SLC Transporters as Therapeutic Targets: Emerging Opportunities

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Abstract

Solute carrier (SLC) transporters — a family of more than 300 membrane-bound proteins that facilitate the transport of a wide array of substrates across biological membranes — have important roles in physiological processes ranging from the cellular uptake of nutrients to the absorption of drugs and other xenobiotics. Several classes of marketed drugs target well-known SLC transporters, such as neurotransmitter transporters, and human genetic studies have provided powerful insight into the roles of more-recently characterized SLC transporters in both rare and common diseases, indicating a wealth of new therapeutic opportunities. This Review summarizes knowledge on the roles of SLC transporters in human disease, describes strategies to target such transporters, and highlights current and investigational drugs that modulate SLC transporters, as well as promising drug targets.

Introduction

Transporters are membrane-bound proteins that mediate the translocation of substrates across biological membranes. Membrane transporters are widely expressed throughout the body, most notably in the epithelia of major organs, such as the liver, intestine, kidney, and organs with barrier functions, such as the brain, testes and placenta. Different transporters are localized to the plasma membrane, as well as to membranes that compose various subcellular organelles, thus ensuring the regulated delivery of required substrates and thereby cellular homeostasis. Many transporters are also expressed in an organ-specific manner, and facilitate the entry and elimination of endogenous and xenobiotic compounds.

The two main transporter superfamilies are the ATP-binding cassette (ABC) superfamily and the solute carrier (SLC) superfamily. ABC transporters harness energy from ATP hydrolysis and function as efflux transporters, whereas SLC transporters are primarily involved in the uptake of small molecules into cells. In drug development, there is considerable interest in transporters from both families, particularly those with broad

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substrate specificities — such as multidrug resistance protein 1 (MDR1; also known as P-glycoprotein or ABCB1) and organic anion transporter 1 (OAT1; also known as SLC22A6) — and those that serve in the absorption, distribution and elimination of structurally and pharmacologically diverse drugs[1]. Such transporters may be the site of drug–drug interactions that underlie drug toxicities.

By contrast, much less attention has been given by drug developers to transporters with narrow substrate specificities that function principally in the disposition of endogenous compounds. However, defects in functionally specific transporters with narrow substrate specificities have been linked to many Mendelian diseases (also known as monogenic disorders). Monogenic disorders constitute a substantial source of novel drug targets[2] (given that the mutated-gene product is causal for the disease), and moreover may provide important insight into therapeutic opportunities for common diseases (Box 1). Indeed, more than 80 SLC transporters have been implicated in monogenic disorders, indicating that this transporter superfamily could have substantial untapped therapeutic potential.

Box 1

Monogenic diseases as a source of drug targets

More than 7,000 monogenic diseases are described in the Online Mendelian Inheritance in Man (OMIM) database (see Databases). Of these, the genes and the primary mutations that underlie approximately 3,600 monogenic diseases have been identified through candidate gene studies and linkage mapping within families[155]. Monogenic disorders of known causes constitute a valuable source for the discovery of novel drug targets in several ways[2].

First, they provide the cause of the disease, which may provide a rationale for the development of a new therapy. In particular, the mechanism of several drugs that are approved to treat common diseases could have been rationalized through understanding the causes of a Mendelian disease. For example, the mechanism responsible for the beneficial effects of oestrogen-replacement therapy in osteoporosis can be rationalized by knowing that mutations in the gene encoding the oestrogen receptor are associated with osteoporosis in Mendelian disease[156, 157]. Mutations in the gene encoding the low-density lipoprotein (LDL) receptor that are associated with familial hypercholesterolaemia provide a rationale for the pharmacological effects of statins, which, through interactions with their target, 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, result in upregulation of the LDL receptor and lower lipid levels[158, 159].

Second, monogenic disorders directly provide targets to treat disease; that is, a mutated (loss-of-function) transporter that is causal for human disease is in itself a drug target for that disease. In this case, high-throughput screening strategies can be used to identify compounds that may enhance transport activity (such as potentiators) or that enhance trafficking to the plasma membrane (such as correctors).

Furthermore, methods to bypass the transporter can be developed. Clinical findings in patients with Amish lethal microcephaly (OMIM #607196) suggested a defect in 2-ketoglutarate metabolism[160] and *SLC25A19* (which encodes the mitochondrial

deoxynucleotide carrier (DNC)) was identified as the gene responsible for this disorder[161]. Studies in *Slc25a19*-knockout mice revealed that DNC transports thiamine pyrophosphate (TPP), which is a cofactor for enzymes involved in the citric acid cycle, into the mitochondria[162]. The lack of TPP therefore explains the biochemical characteristics of Amish lethal microcephaly. For treatment, the transporter can be targeted with drugs to enhance its activity, or a method to bypass the transporter can be developed — for example, delivery of TPP to the mitochondria.

Finally, a monogenic disorder may also suggest a target to treat a common disease. For example, mutations in *SLC5A2* that lead to hypoglycaemia in patients with familial renal glucosuria (OMIM #233100), informed the development of sodium–glucose cotransporter 2 (SGLT2) inhibitors for the treatment of hyperglycaemia associated with type 2 diabetes.

Developing drugs to treat a rare disorder (known as orphan drugs) may pose greater logistical and economical challenges than developing drugs to treat common diseases, but the European Union and the United States incentivize the development of orphan drugs by providing tax credits, waived user fees and enhanced patent protection to the sponsor, resulting in considerable fiscal savings. In addition, there may be opportunities to expand the use (and thus the market) of a drug developed for a rare indication to other indications after its initial approval. For example, imatinib, which was initially approved to treat chronic myelogenous leukaemia, was then rapidly approved for five other indications, and now ranks in the top 25 pharmaceutical products globally, making ~US$4.75 billion in worldwide sales in 2014 (see PMLive Top Pharma List in Further information). Increasingly, there are pharmaceutical companies whose main focus is to develop drugs for rare diseases, such as Alexion Pharmaceuticals, Ultragenyx Pharmaceutical and Rare Disease Therapeutics, and many larger companies also have units dedicated to rare diseases.

In this article, we review the role of SLC transporters in human health and discuss how defects in SLC transporters cause rare, monogenic disorders. We provide a brief description of results from genome-wide association studies (GWASs) that implicate SLC transporters in common disease, followed by a discussion of methodologies that may be used to develop drugs to treat diseases associated with genetic variants of SLC transporters. Finally, we highlight examples of marketed drugs and candidates in clinical development that target SLC transporters and discuss future opportunities to target additional SLC transporters.

SLC transporters in health

Hydrophilic compounds, including charged molecules, cannot readily diffuse across membranes and thus rely on channels, pumps or transporters to move in and out of cells and subcellular organelles. In humans, there are 395 membrane-spanning SLC transporters that are organized into 52 families. SLC transporters interact with a diverse array of substrates, including inorganic and organic ions[3, 4], and range in specificity — from highly selective transporters that interact with a narrow group of substrates, such as amino acid transporters in the SLC7 family[5, 6], to transporters that accept a broad range of chemically diverse

substrates such as do the OATs in the SLCO family[7, 8]. Even within a family, various transporters may differ in their degree of specificity. For example, in the SLC22 family, urate anion exchanger 1 (URAT1; also known as SLC22A12) is selective for uric acid, whereas OAT1 accepts a wide range of organic anions, including various antibiotics, antiviral drugs and endogenous molecules[9].

SLC transporters are predominantly facilitative or secondary-active; that is, they rely either on an electrochemical gradient to facilitate the movement of substrates across membranes, or on ion gradients generated by ATP-dependent pumps to transport substrates against the concentration gradient. Tertiary-active transporters, such as OAT1, rely on gradients generated by secondary-active transporters and can also transport their substrates against a concentration gradient.

Much remains unknown about SLC transporters — partly because many cell lines that have undergone multiple passages lose transporter expression and activity — although the field is advancing rapidly. Within the past 10 years, 9 new SLC families have been identified and nearly 100 human SLC genes have been recognized. Crystal structures and molecular models of SLC transporters are increasingly available[10, 11]. *Slc*-knockout mice have also enabled the study of the contributions of specific transporters, although often deciphering these contributions is complex (Box 2). The SLC families of transporters have recently been reviewed[4].

Box 2

Study of transporter–transporter interplay using knockout mice

Although *in vitro* studies provide a wealth of information on individual transporters, *in vivo*, transporters often work together. Therefore, the use of knockout mice has been particularly helpful in deciphering the relative contribution of a specific transporter when multiple transporters with overlapping substrate specificities are expressed in the same tissue. Overall, knockout mice studies are useful to determine the relationship between transporters with similar transport functions. However, knockout of a transporter may be compensated by the availability or upregulation of other transporters that can transport the same substrate.

For example, creatinine is a substrate of the kidney transporters organic anion transporter 1 (OAT1; encoded by *SLC22A6*) and OAT3 (encoded by *SLC22A8*). Both *Slc22a6*$^{-/-}$ mice and *Slc22a8*$^{-/-}$ mice showed lower net renal creatinine secretion compared with wild-type mice, but plasma creatinine levels were significantly higher in *Slc22a8*$^{-/-}$ compared with wild-type mice, whereas this effect was not as pronounced in *Slc22a6*$^{-/-}$ mice[163]. This result suggests that OAT3 may be more important than OAT1 in the renal secretion of creatinine in mice.

However, in some cases, certain transporters may be upregulated in knockout mice, sometimes obscuring the relative contribution of a transporter to a particular phenotype. For example, organic cation transporter 3 (OCT3; encoded by *SLC22A3*) and serotonin transporter (SERT; encoded by *SLC6A4*) transport serotonin with low and high affinity, respectively[164]. In SERT-knockout mice (*Slc6a4*$^{-/-}$), *Slc22a3* transcript levels increase

in the hippocampus but not in other regions of the brain[165]. This upregulation of *Slc22a3* in the absence of *Slc6a4* plays an important part in the uptake of serotonin, and may obscure the full effect of SERT *in vivo*.

Not surprisingly, if the substrate of a transporter is an important endogenous compound, rare loss-of-function mutations in the gene encoding the transporter will often lead to a disease phenotype (see Supplementary information S2 (table)). In mice, thiamine is absorbed in the intestine through the thiamine transporters THTR1 (encoded by *SLC19A2*) and THTR2 (encoded by *SLC19A3*). In *Slc19a2*$^{-/-}$ mice, *Slc19a3* transcript levels increase in the intestine, although there is no upregulation of *Slc19a2* in *Slc19a3*$^{-/-}$ mice[166]. Interestingly, these knockout mouse studies reflect characteristics of human disease in patients with thiamine-responsive megaloblastic anaemia. These patients are homozygous for mutations in *SLC19A2* and show normal thiamine plasma levels due to sufficient thiamine absorption in the intestine by THTR2. However, patients with a mutation in *SLC19A3* suffer from thiamine metabolism dysfunction syndrome 2 (Online Mendelian Inheritance in Man (OMIM) database #607483; see Databases), and exhibit thiamine deficiency and related CNS symptoms[167, 168]. Although it is not known whether the expression levels of the thiamine transporter paralogues are altered in these diseases, this is an illustrative example of how loss of function of one of two transporters that are thought to have the same function can have very different effects.

Members of the SLC transporter families are important in human physiology

For example, amino acids, which are needed for protein synthesis, are absorbed and reabsorbed by transporters of the SLC1, SLC3, SLC6, SLC7, SLC25 and SLC36 families, many members of which are expressed in the intestine and kidney. In the intestine, amino acids are absorbed from the lumen into the body; in the kidney, amino acids that are filtered out of the bloodstream by the glomerulus are reabsorbed in the proximal tubule by many of the same transporters that are involved in intestinal absorption[12]. Members of the SLC2, SLC5 and SLC50 families are required for intestinal absorption and renal reabsorption of glucose and for glucose uptake into neurons, erythrocytes, hepatocytes and other cell types[13, 14]. Metals often serve as essential cofactors for important enzymes, but toxicities may occur when they are present at excess concentrations. Zinc transporters of the SLC30 and SLC39 families and iron transporters of the SLC11 and SLC40 families regulate zinc and iron levels in the body, respectively. Similarly, water-soluble vitamins are essential for various processes but require transporters for cellular uptake; for instance, SLC19 family members transport folate and thiamine, SLC46 family members transport folate and the SLC52 family transports riboflavin. In the brain, neurotransmitters released into the synapse are taken back into presynaptic neurons through SLC1 and SLC6 transporters. Interestingly, the roles of many transporters in human physiology have been discovered through studies of Mendelian disease (Table 1; see Supplementary information S1 (table)).

SLC transporters in disease

Mendelian diseases associated with SLC transporters

Given the key physiological roles of SLC transporters, it is not surprising that defects in a single transporter can result in a serious disease. Mutations in 20% of the genes encoding known SLC transporters in humans have been associated with Mendelian disease (see the Online Mendelian Inheritance in Man (OMIM) database in Databases), and it is likely that mutations in more SLC transporter genes will be found to be causal for some of the remaining half of Mendelian diseases with no known cause. The defective transporters or transporter deficiencies that cause these diseases result in a wide range of symptoms that affect almost all organ systems; although some of these diseases are considered to be benign, others cause serious illness and death. Table 1 and Supplementary information S1, S2 (tables) summarize the information that is known about each transporter and the Mendelian disease associated with its dysfunction or lack of expression. Figure 1 illustrates the potential mechanisms through which mutations in genes encoding SLC transporters can result in reduced function. Figure 2 shows the transporters that are implicated in Mendelian diseases, organized by the general class of substrates they transport.

Common diseases associated with SLC transporters

SLC transporter gene polymorphisms that are associated with common disease have generally been identified through the genotyping of candidate genes, or from GWASs (see Catalog of Published Genome-wide Association Studies in Further information). Examples of transporter genes for which polymorphisms have been associated with human traits or disease include the following: *SLC22A4* and *SLC22A5*, which are associated with inflammatory bowel disease[15, 16, 17]; *SLC2A9*, *SLC22A11* and *SLC22A12*, which are associated with gout and uric acid levels[18, 19, 20]; *SLCO1B1* and *SLCO1B3*, which are associated with high bilirubin levels[21, 22, 23, 24]; and *SLC24A5* and *SLC45A2*, which are associated with skin colour[25, 26]. Many of the polymorphisms implicated in human disease are non-synonymous — that is, they cause amino acid substitutions in the encoded transporter that reduce transporter function or expression levels. For example, non-synonymous variants of the uric acid transporters encoded by *SLC2A9*, *SLC22A11* and *SLC22A12* show reduced uric acid transport *in vitro*. A reduced-function variant will reabsorb less uric acid from the urine. As a result, hypouricaemia can occur, thus reducing the risk of gout.

Polymorphisms in the genes encoding the hepatic transporters OATP1B1 (*SLCO1B1*) and OATP1B3 (*SLCO1B3*) provide a second example. These transporters are responsible for the uptake of conjugated bilirubin — the product of haem metabolic catabolism — into hepatocytes. From there, it is excreted into the bile. Common polymorphisms in the genes of transporters that are involved in the hepatic bilirubin elimination pathway may lead to hyperbilirubinaemia and jaundice. Moreover, the complete loss of *SLCO1B1* and *SLCO1B3* results in a rare disease known as Rotor syndrome[27] (Box 3). This example, wherein a common reduced-function gene polymorphism is associated with a less serious phenotype, whereas a rare, more severe defect in the same gene causes a Mendelian disease, is not uncommon in human genetic studies.

Box 3

Rotor syndrome: a loss of function in two SLC transporters

Mutant solute carrier (SLC) transporters are frequently linked to rare but clinically significant (inherited) disease phenotypes. For certain inherited diseases associated with bilirubin metabolism or transport, the molecular basis of such defects has been elucidated for more than a decade. For example, the efflux multidrug resistance-associated protein 2 (MRP2; encoded by *ABCC2*) secretes conjugated bilirubin in the bile duct, and complete-loss-of-function mutations in *ABCC2* are the basis of Dubin–Johnson syndrome[169].

Interestingly, the genetic basis for another similar condition, known as Rotor syndrome, which is also known to result in conjugated hyperbilirubinaemia, had remained unresolved. Recently, two hepatic SLC transporters, organic anion transporter family member 1B1 (OATP1B1; encoded by *SLCO1B1*) and OATP1B3 (encoded by *SLCO1B3*), have been implicated in Rotor syndrome[170]. Notably, mutations or deletions that affect both *SLCO1B1* and *SLCO1B3* are required to result in this phenotype. Moreover, the pathway of hepatic conjugated-bilirubin secretion and reuptake was further clarified through the linkage of mutations in the genes encoding these OATP transporters.

It is now clear that the conjugated hyperbilirubinaemia observed in Rotor syndrome is not due to an inability to secrete conjugated bilirubin into bile through transporters such as MRP2 that are expressed on the canalicular domain. Rather, a considerable proportion of conjugated bilirubin seems to be actively extruded into the sinusoidal blood through the hepatocytic MRP3 (encoded by *ABCC3*), another ATP-binding cassette (ABC) transporter, whereas OATP1B1 and OATP1B3 take up conjugated bilirubin back into hepatocytes. Interestingly, a complete absence of both OATP1B1 and OATP1B3 does not appear to result in substantial liver pathology, as Rotor syndrome is considered a benign condition[27]. The fact that an absence of both these transporters alters the clearance of conjugated bilirubin suggests that there may be another as yet undetermined transporter (or transporters) for unconjugated bilirubin. It should be noted that commonly occurring single nucleotide polymorphisms in *SLCO1B1* have been associated with adverse responses to substrate drugs, including the statin class of lipid-lowering drugs[171].

The genetic basis of Rotor syndrome suggests that profound loss-of-function mutations in the genes encoding these transporters may be more common than currently appreciated, and that a more worrisome phenotype among those who carry such mutations may be severe toxicity to substrate drugs.

There have been several transporters discovered through GWASs that were not previously known to be important in human disease, including the following examples: *SLC30A8*, which encodes a pancreatic β-cell-specific zinc transporter, a genetic polymorphism of which has been associated with diabetes[28, 29]; *SLC14A1*, which encodes a urea transporter, variants of which have been associated with bladder cancer[30]; *SLC4A7*, which encodes a bicarbonate transporter, for which certain polymorphisms have been associated with abnormal blood pressure[31, 32] or with breast cancer[33]; and the gene encoding a nucleoside-

sugar transporter that also transports thiamine, *SLC35F3*, some polymorphisms of which have been associated with increased blood pressure and predicted to cause disturbances in cardiac and autonomic function[34].

Variants in *SLC30A8* have been associated with type 2 diabetes in several GWASs and across different ethnic groups. A non-synonymous variant in *SLC30A8*, with a high allele frequency (>25% in Caucasians and Asians), p.Arg325Trp (rs13266634), was identified through a GWAS[28]. This risk allele, p.Arg325Trp, is associated with reduced susceptibility to type 2 diabetes and higher zinc transport activity. It was subsequently demonstrated in *Slc30a8*-knockout mice that the transporter plays a part in transporting zinc ions from the cytoplasm into insulin granules[35], and further studies suggested that zinc may have an important role as an endogenous regulator of insulin homeostasis[36, 37]. Furthermore, although *Slc30a8*-deficient mice exhibit phenotypic variability, they generally show lower blood insulin levels and increased insulin clearance[38]. Interestingly, a recent paper by Flannick *et al*.[39] demonstrated that carriers of loss-of-function and rare missense variants in *SLC30A8* were at reduced risk for type 2 diabetes. The researchers performed sequencing or genotyping on more than 150,000 individuals and demonstrated that loss-of-function missense *SLC30A8* variants that led to truncation of the transporter protein actually protected individuals from type 2 diabetes. Overall, these human genetic studies suggest that SLC30A8 could be a potential target for the treatment and/or prevention of type 2 diabetes.

Strategies for targeting SLC transporters

Inhibition of transporter function

Most current drugs — as well as novel drugs in clinical trials — that modulate SLC transporters do so by inhibiting transporter activity, and examples of these are described in more detail in the subsequent sections. For diseases in which decreased transporter activity leads to a potentially beneficial effect, high-throughput screening (HTS) of large compound libraries using cell lines that overexpress the transporter of interest can be used to discover lead inhibitor molecules[40, 41].

Many SLC transporters may function in both influx and efflux of their substrates, and the net direction of flux across a cellular membrane is dependent on the substrate gradient (or, in the case of secondary or tertiary transporters, the gradient of the co- or counter-transported ions). Because of their simplicity, influx assays are frequently used in screening studies. In particular, cells that are grown on solid support are typically used to screen for inhibitors that prevent the uptake or influx of a fluorescent substrate probe[42, 43, 44]. Even for transporters that require a co- or counter-transported ion, the assays may be set up in the influx mode for convenience. For example, a high concentration of extracellular sodium may be used to drive the influx of a fluorescent probe, or the cells may be pre-loaded with a counterion to drive fluorescent probe influx. For transporters that are primarily efflux transporters, such as the ABC transporters bile salt export pump (BSEP; also known as ABCB11), canalicular multidrug resistance protein (cMRP; also known as ABCC2) and breast cancer resistance protein (BCRP; also known as ABCG2), a vesicular-transport assay is frequently used. Instead of adherent cells, membrane fractions that contain inside-out vesicles are prepared from cells that overexpress the efflux transporter[45, 46, 47, 48].

A fluorescent or radiolabelled substrate probe that can be quantitatively measured is added to each well in the presence and absence of each test compound to determine the transporter-inhibiting activity of the compounds. The concentration of the substrate probe and uptake time that produce the best Z′ assay sensitivity factor is selected; a $Z' > 0.8$ is ideal for HTS, although $Z' > 0.5$ is also acceptable[49]. Such methods have been used to screen thousands of compounds in HTS campaigns. However, HTS also suffers from limitations. One commonly observed issue relates to assay interference, whereby aggregation of a test compound that causes protein sequestration or nonspecific inhibition results in a false-positive hit; this problem affects 1.7–1.9% of total compounds in compound libraries[50, 51, 52]. Another problem arises from the interference of fluorescent test compounds or contaminating particulate matter with the measurement of the fluorescent substrate probe. A ‘pre-read’ control measurement after the addition of the test compound but before substrate addition can prevent this problem. Use of an orange or red fluorophore as the substrate also helps to avoid this interference, as fluorescence and spurious light emissions from test compounds have been found to be more likely to occur at shorter wavelengths[50].

The structure of identified potential inhibitors can be modified to produce more-potent or more-selective molecules. Pharmacophore modelling and quantitative structure–activity relationship (QSAR) modelling may be used to engineer improved compounds with more-desirable properties[53, 54]. Novel inhibitors for many transporters have been identified through these methods, including inhibitors of apical sodium-dependent bile acid transporter (ASBT; also known as SLC10A2)[55, 56], excitatory amino acid transporter 3 (EAAT3; also known as SLC1A1)[57], dopamine transporter (DAT; also known as SLC6A3), serotonin transporter (SERT; also known as SLC6A4), noradrenaline transporter (NET; also known as SLC6A2)[58, 59, 60] and vesicular glutamate transporter 2 (VGLUT2; also known as SLC17A6)[61]. For example, the *O*-spiroketal C-arylglucoside scaffold — which forms the basis of tofogliflozin (Apleway/Deberza; Chugai Pharmaceutical/Sanofi/Kowa, a selective sodium–glucose cotransporter 2 (SGLT2; also known as SLC5A2) inhibitor recently approved in Japan for the treatment of diabetes — was found by pharmacophore modelling of SGLT2 inhibitors and a search of the Cambridge Structural Database[62] (see Databases).

Homology modelling and docking have been widely used to identify and optimize lead compounds. As the crystal structures of SLC transporters from various species become increasingly available[3, 63], homology models of human orthologues are being constructed that can be used in molecular docking studies to design more-selective transporter inhibitors. These methods have been successfully used to identify binding sites, to accurately predict the inhibitory actions of already-prescribed drugs on SLC transporters and to identify potent transporter inhibitors for treating diseases[5, 11, 64]. For example, high-throughput docking of the glutamate-binding site on the *Pyrococcus horikoshii* glutamate transporter homologue was used to identify a potent inhibitor of EAAT2 (also known as SLC1A2)[65], and the crystal structure of the same concentrative nucleoside transporter from *Vibrio cholerae* was used to identify a selective anticancer drug[66, 67]. The crystal structures of bacterial homologues of neurotransmitter transporters bound to antidepressant drugs were recently elucidated, enabling researchers to identify the amino acid residues that comprise the binding sites of

these transporters[68, 69, 70]. Such information may be implemented to design and synthesize more-potent serotonin- and/or noradrenaline-reuptake inhibitors[71].

Enhancement of transporter function

For most Mendelian diseases in which causal variants of the genes encoding SLCs result in loss of transporter function, compounds that enhance the function of the affected transporter are needed; these compounds are also of interest in the treatment of common diseases. To our knowledge, no current drugs were originally developed specifically to activate SLC transporters. Riluzole, a drug used to treat amyotrophic lateral sclerosis, inhibits glutamate release, thereby preventing glutamate-induced activation of sodium channels on postsynaptic neurons[72], reducing excitotoxicity. However, riluzole was subsequently found to enhance the transport activity of EAAT1 (also known as SLC1A3), which takes up extracellular glutamate from the synapse and thus reduces glutamate levels in the synaptic cleft[73, 74]. Another study showed that riluzole stimulates glutamate uptake by increasing excitatory amino acid carrier 1 (EAAC1; also known as SLC1A1) levels in astroglial cells[75], although the exact mechanism for this effect is not completely understood.

There is interest in identifying additional targets to increase glutamate clearance. Similar to EAAT1, EAAT2 (the principal glutamate transporter in astrocytes) reduces glutamate levels in the synaptic cleft, thereby attenuating excitotoxicity. Some examples of neurodegenerative diseases that could benefit from upregulated EAAT2 function include Alzheimer disease, amyotrophic lateral sclerosis and Parkinson disease — all of which have been associated with decreased EAAT2 protein expression levels[76, 77] — as well as epilepsy, stroke and neurotrauma[78]. Therefore, developing a drug that enhances EAAT2 activity represents a promising approach in central nervous system (CNS) drug development[79]. Two approaches are currently being used to identify enhancers of EAAT2. First, an HTS assay that used a reporter gene containing the *SLC1A2* promoter upstream of the luciferase gene found that several currently prescribed drugs, such as ceftriaxone, increased luciferase transcript levels[80]. Second, an astrocyte-based enzyme-linked immunosorbent assay has been developed to screen large compound libraries for molecules that can induce translation of silenced *SLC1A2* transcripts, as the expression of EAAT2 protein is highly regulated at the translational level by extracellular factors[81].

These and other screening technologies — for example, high-throughput fluorescence assays — could be used to identify compounds that enhance SLC transporter activity. The development of drugs that enhance the activity of cystic fibrosis transmembrane conductance regulator (CFTR; also known as ABCC7), the ABC transporter that is defective in cystic fibrosis, could provide a model for the identification of small molecules that may rescue mutated SLC transporters. Small-molecule therapies for modulating CFTR fall into two categories: potentiators and correctors. Various assays have been developed to identify potentiators and correctors, such as ivacaftor, the first US-regulator-approved drug to target a specific CFTR mutant, CFTR-G551D. Ivacaftor acts as a potentiator; it increases the activity of CFTR-G551D that is already present on the plasma membrane, by increasing the probability of the open state of the CFTR channel[82]. By contrast, correctors enhance the trafficking of mutant proteins such as the most common cystic-fibrosis-causing mutant

protein, CFTR-F508del, to the plasma membrane. Early clinical results suggest that the combination of a corrector and a potentiator results in enhanced efficacy in the treatment of individuals with cystic fibrosis who harbour the *CFTR*-F508del mutation[83].

Circumventing transporters

Another potential therapeutic strategy for treating rare diseases caused by mutant SLC transporters is to develop substrates that circumvent transporters. SLC transporter gene mutations that lead to Mendelian disease often also lead to subnormal levels of an essential nutrient, such as thiamine or carnitine, in specific tissues. Therapies that circumvent the use of the mutant transporter could be developed. For example, creation of a hydrolysable hydrophobic derivative of an essential nutrient that is normally hydrophilic may result in enhanced permeability of the nutrient. Thus, the hydrophobic derivative would enter the cell (without the aid of a transporter) where it would undergo hydrolysis and release the nutrient, thus enhancing the availability of the nutrient in the cell to treat, for instance, thiamine deficiency[84].

However, a potential problem in the development of diffusible analogues that circumvent transporters may be the low cellular availability of the analogue. For example, many transporters are secondary-active and therefore concentrate their substrates intracellularly, whereas diffusible analogues may not accumulate to the same extent. Furthermore, hydrophobic diffusible analogues may be substrates for efflux pumps of the ABC transporter families, such as MDR1, that preferentially handle hydrophobic substrates, and may therefore exhibit poor cellular availability. Finally, diffusible analogues may distribute widely into body tissues rather than selectively targeting the tissues of greatest need (for example, in the case of carnitine deficiency, the liver).

Gene therapy

Gene therapy, in principle, may be a strategy for the treatment of diseases caused by mutant transporter proteins. Several animal studies have provided proof of concept for this strategy. For example, Yiu *et al*.[85] infused an adenoviral vector containing the gene encoding human glucose-6-phosphate transporter (*SLC37A4*) into *Slc37a4*-deficient mice (which recapitulate the human glycogen-storage disease type Ib that is attributable to mutations in *SLC37A4*). The gene therapy restored *SLC37A4* expression in various tissues (including the liver), normalized serum glucose and serum lipid profiles, and reduced glycogen deposition in the liver. Although historically fraught with issues, gene therapy may become a viable strategy for the treatment of Mendelian disorders that involve defective membrane transporters as more-advanced methods are applied.

SLC transporters as targets of drugs

Many SLC transporters have been identified as druggable — that is, they contribute to a disease phenotype and can be modulated by drugs[86]. More information can be found in Table 1 and Table 2. Databases[87, 88, 89, 90, 91] such as the Sophic Integrated Druggable Genome Database, the DrugBank database (see Databases) and recent review articles[88, 92] provide useful and detailed information about already-approved drugs that target SLC

transporters for various diseases. In this section, we provide four examples of approved drug classes for which the primary mechanisms of action involve inhibition of SLC transporters: diuretics, neurotransmitter-reuptake inhibitors for neuropsychiatric indications, glucose transporter inhibitors for diabetes and uric acid transporter inhibitors for gout. We also highlight several other examples of transporters that are being targeted by drugs in development.

SLC12 transporters as targets of diuretic drugs

Diuretics are important drugs used to treat hypertension and heart failure. The discovery of the first diuretic, chlorothiazide (which belongs to the thiazide class), in 1957, was followed by the discoveries of the loop diuretics bumetanide and furosemide. Subsequently, Wiley and Cooper[93] observed that furosemide inhibits the influx and efflux of sodium and potassium in human red blood cells and concluded that the drug inhibits the cotransport of sodium and potassium. In addition, using isolated perfused rabbit kidney tubules, Burg *et al*.[94] described the inhibitory effect of furosemide on active chloride transport in the thick ascending limbs of the loop of Henle, which results in a decreased net absorption of sodium chloride and a decreased electrical potential (that is, a more positive electrical potential) in tubule cells. Sodium–chloride cotransport was recognized in the 1970s and has since been studied in a wide variety of animal cells and tissues.

The role of a sodium–chloride cotransporter is to maintain and regulate cell volumes and ion gradients; thus, diuretics that inhibit such cotransporters in the renal tubules decrease extracellular fluid volume and regulate electrolyte levels in the body[95]. The functional expression of the sodium–potassium–chloride cotransporter in HEK293 kidney cells was first revealed by Xu *et al*.[96], who used radiolabelled rubidium as a tracer for potassium movement and showed that cells transfected with the sodium–potassium–chloride cotransporter had a greater influx of ^{86}Rb, which was inhibited by bumetanide, a loop diuretic. Subsequently, it was established that diuretics inhibit the sodium–potassium–chloride cotransporter NKCC2 (also known as SLC12A1) to reduce sodium reabsorption in the thick ascending limb of the loop of Henle. The reduction in sodium reabsorption results in increased sodium levels in the tubule fluid and a corresponding loss of body water, thus increasing urine production and decreasing blood volume.

Interestingly, mutations in the gene encoding NKCC2 (*SLC12A1*), which is expressed in the kidney, were found to cause Bartter syndrome, an inherited hypokalaemic alkalosis featuring hypercalciuria and severe blood volume depletion[97]. Moreover, mutations in *SLC12A3*, which encodes the sodium–chloride cotransporter TSC (normally expressed in the renal distal tubule) were found to cause Gitelman syndrome, in which patients present with hypokalaemic alkalosis and abnormalities in electrolyte homeostasis[98]. In contrast to NKCC2, which is sensitive to loop diuretics such as bumetanide but insensitive to thiazides, TSC is sensitive to the thiazides chlorothiazide and hydrochlorothiazide but is insensitive to loop diuretics.

At high doses, thiazides are used to relieve systemic and pulmonary oedema due to chronic heart failure, and at lower doses to reduce blood pressure. One of the major adverse effects of thiazides and loop diuretics is hypokalaemia, which is especially dangerous in patients

with severe cardiovascular disease. Furthermore, high doses of thiazides can also cause hyperuricaemia. One possible explanation for this effect is that diuretics may inhibit renal transporters such as OAT1 (SLC22A6), OAT3 (also known as SLC22A8), sodium–phosphate cotransporter 1 (NPT1; also known as SLC17A1) and NPT4 (SLC17A3), which are all involved in uric acid secretion, and thus increase serum uric acid levels[99, 100].

Urea transporters of the SLC14 family also play an important role in the recycling of urea and in concentrating urine. As a result, several research groups are screening for small-molecule inhibitors to target urea transporters, particularly UTB (also known as SLC14A1) and UTA (also known as SLC14A2). Such inhibitors cause an increase in urine output due to decreased urea concentrations in the urine. Perhaps in the near future, a new class of diuretics that inhibit UTB and UTA transporters will be developed.

SLC6 transporters as neuropsychiatric drug targets

Drugs for treating depression can be classified according to their presumed targets, which may be transporters. For example, the monoamine-reuptake inhibitors — which include the serotonin-selective reuptake inhibitors (SSRIs) and noradrenaline-reuptake inhibitors (NRIs) — inhibit neurotransmitter transporters. Over the past several decades, the development of novel antidepressants has moved from ‘discovery by chance’ to single-target strategies, and then to multiple-target strategies.

Several transporters in the SLC6 family have important roles in the uptake of monoamines in the synapses of the CNS. These include NET (SLC6A2), DAT (SLC6A3) and SERT (SLC6A4), which are transporters for noradrenaline, dopamine and serotonin (also known as 5-hydroxytryptamine), respectively, although they all exhibit overlapping substrate specificity. Inhibition of these transporters by drugs reduces the clearance of monoamine neurotransmitters from the synapse, thus increasing their dwell time in the synaptic cleft. The resulting increased concentrations of monoamines in the synaptic cleft enhance receptor occupancy, leading to increased activation of ligand-gated ion channels and modulation of G-protein-coupled receptor signalling[101]. However, the downstream mechanisms by which such drugs ultimately exert antidepressant effects (which can take weeks to become apparent) are not yet clear[102].

The first-generation tricyclic antidepressants (TCAs) inhibit serotonin and noradrenaline reuptake, but also interact with other targets in the CNS. In the 1960s, several investigators showed that TCAs such as imipramine competitively inhibit serotonin and noradrenaline uptake in several tissue types, including platelet-rich plasma, brain slices and synaptosomes. TCAs were used as the primary treatment for depression until the US approval of the first SSRI, fluoxetine, in 1987. Fluoxetine was found to inhibit serotonin uptake into rat brain synaptosomes, without inhibiting noradrenaline uptake into rat hearts[103, 104].

Since the discovery of fluoxetine and other SSRIs, other classes of compounds that affect neurotransmitter reuptake have been developed. For example, serotonin–noradrenaline reuptake inhibitors (SNRIs), such as venlafaxine, are a newer class of antidepressants that selectively target two transporters, NET and SERT. The use of SSRIs and SNRIs has also expanded to other neuropsychiatric disorders, including anorexia nervosa, bulimia nervosa,

obsessive-compulsive disorder, panic disorders and anxiety disorders, as well as for relief of menopausal symptoms.

Another therapeutic target for the treatment of neuropsychiatric disorders is vesicular monoamine transporter 2 (VMAT2; also known as SLC18A2), which transports monoamines from the cellular cytosol into synaptic vesicles. An inhibitor of VMAT2, tetrabenazine, is currently US-approved for the treatment of hyperkinetic disorders associated with Huntington disorder[105]. Other VMAT2 inhibitors are in clinical development, including NBI-98854 (developed by Neurocrine Biosciences), which is in Phase III trials for dyskinesia (ClinicalTrials.gov identifier: NCT02274558; note that all trials cited in this article are from this database (see Databases)) and a natural product, lobeline (developed by Yaupon Therapeutics), which is in Phase II trials for the treatment of attention-deficit hyperactivity disorder in adults (NCT00664703). VMAT2 inhibitors may also be developed for the treatment of psychostimulant abuse and addiction[106].

Glucose transporter inhibitors

The SGLT2 (SLC5A2) transporter, which has a low affinity and high capacity for glucose, plays a major part in renal glucose reabsorption, whereas the high-affinity, low-capacity SGLT1 (also known as SLC5A1) transporter has a major role in glucose absorption in the small intestine[107]. By mimicking the effects of a loss-of-function mutation in *SGLT2* (Table 1), SGLT2 inhibitors enhance renal glucose excretion and consequently lower plasma glucose levels.

Many companies have been developing drugs that target SGLT1 and SGLT2 for type 2 diabetes, in which patients exhibit hyperglycaemia owing to insulin resistance. In such programmes, compound libraries were screened for lead compounds that inhibit glucose uptake in cell lines that stably expressed human SGLT1 or SGLT2 (Refs 108,109). Once the lead compounds were identified, their *in vivo* effects were determined in murine and other animal models to confirm that the compound could increase urinary glucose excretion by inhibiting renal glucose reabsorption. Importantly, oral glucose tolerance tests in diabetic rats revealed that these animals were responsive to treatment with SGLT2 inhibitors[110]. Moreover, patients with type 2 diabetes who were treated with the SGLT2 inhibitor empagliflozin showed improved β-cell function and insulin sensitivity. Chronic dosing with empagliflozin for 4 weeks in these patients led to a significant decline in both glycated haemoglobin and fasting glucose levels[111].

Canagliflozin (Invokana; Mitsubishi Tanabe Pharma/Johnson & Johnson) was the first SGLT2 inhibitor to be approved by the US Food and Drug Administration (FDA) in 2013, and was followed by dapagliflozin (Farxiga/Forxiga; Bristol-Myers Squibb/AstraZeneca) and empagliflozin (Jardiance; Boehringer Ingelheim/Eli Lilly and Company) in 2014. All three drugs are being prescribed as second-line therapy for patients whose diabetes is inadequately controlled by a single antidiabetic agent[112]. Tofogliflozin and ipragliflozin (Suglat; Astellas/Kotobuki) have both been approved for the treatment of type 2 diabetes in Japan, and both have active Phase IV trials ongoing (tofogliflozin: NCT02201004 and NCT02284269; ipragliflozin: NCT02291874 and NCT02175784). Other SGLT1 and/or SGLT2 inhibitors are being studied in early- and late-phase clinical studies either alone or in

combination with metformin (which suppresses glucose production by the liver)[113, 114, 115]. These SGLT inhibitors include the following: remogliflozin (also known as GSK189075; developed by GlaxoSmithKline), which is in Phase II trials (NCT00495469); GSK1614235 (GlaxoSmithKline), in Phase I trials (NCT01607385); sotaglifozin (Lexicon Pharmaceuticals), in Phase III trials (NCT02384941); and ertugliflozin (Merck &Co./ Pfizer), in Phase III trials (NCT01986881, NCT01999218, NCT01958671, NCT01986855, NCT02036515 and NCT02226003). In addition to having notable effects on reducing plasma glucose levels and increasing urinary glucose excretion, SGLT2 inhibitors have also been associated with weight loss and lowering of blood pressure owing to their osmotic diuretic effects[116].

Uric acid transporter inhibitors

Gout is the most common inflammatory arthritic disease, and has been increasing in prevalence in the United States and in other countries, partly as a consequence of the obesity epidemic[117]. Gout is caused by the accumulation of monosodium urate monohydrate crystals in the joints and soft tissue, as a result of hyperuricaemia. Most current treatments for gout generally target the inflammation that occurs during an acute gout attack or reduce uric acid production by inhibiting the enzymes involved (for example, allopurinol, which inhibits xanthine oxidase). However, many patients fail to respond to these treatments or suffer from serious side effects (for instance, allopurinol can cause drug hypersensitivity reactions)[118].

Recent advances in the understanding of uric acid transporters, through GWASs and other studies, have opened the door for the development of novel compounds that target these transporters in the kidney as a way to block reuptake of uric acid and thereby promote elimination of uric acid in the urine. The primary uric acid reabsorption transporters include URAT1 (SLC22A12) and glucose transporter type 9 (GLUT9; also known as SLC2A9), which are expressed in the proximal tubule, although other transporters have also been identified that transport urate or are associated with gout[118, 119]. Although probenecid, which has been used for decades to treat gout, blocks uric acid reabsorption through organic anion transporters, several novel compounds are currently in development for this indication that are more selective, and most target URAT1. Lesinurad, a URAT1 inhibitor developed by Ardea Biosciences/AstraZeneca was recently approved by the European Medicines Agency on the basis of results from two trials testing the drug for the treatment of hyperuricaemia in combination with xanthine oxidase inhibitors in patients with gout (NCT01510158 and NCT01493531). Another URAT1 inhibitor, RDEA3170, is also being developed by Ardea Biosciences/AstraZeneca and has completed Phase II trials (NCT01927198)[120]. Meanwhile, Pfizer recently licensed KUX-1151 from Kissei Pharmaceutical; this dual inhibitor of xanthine oxidase and of URAT1 is currently in a Phase II trial in Japan (NCT02190786). As URAT1 inhibitors selectively inhibit URAT1 and reduce uric acid reabsorption in the kidney, their effects mimic those observed in patients with *URAT1* mutations that lead to renal hypouricaemia type 1.

Glycine transporter inhibitors

In the CNS, glycine has important roles in neuronal inhibition and excitation. It functions as an inhibitory neurotransmitter by activating ionotropic glycine receptors, enabling an influx of chloride ions and hyperpolarization of the postsynaptic membrane. Glycine also binds to excitatory *N*-methyl-D-aspartate (NMDA) receptors to enable receptor activation by glutamate[121]. The glycine transporters GLYT1 (also known as SLC6A9) and GLYT2 (also known as SLC6A5) on neurons, astrocytes and glial cells regulate levels of extracellular glycine in the brain, and thereby regulate NMDA receptor activity. According to the glutamate hypothesis of schizophrenia, symptoms of the disease are caused by deficient glutamatergic (NMDA) signalling, and therefore GLYT1 inhibitors have been developed to inhibit glycine reuptake and increase levels of glycine at NMDA receptors to enhance NMDA signalling in this disorder.

Bitopertin (also known as RO4917838), a highly selective and potent GLYT1 inhibitor developed by Roche, is furthest along in development[122]. However, several Phase III studies of bitopertin in schizophrenia (NCT01235559, NCT01235585, NCT01192906 and NCT01192880) failed to reach their primary end point, leaving bitopertin with an uncertain future. Nevertheless, there is a Phase II trial currently ongoing using bitopertin with SSRIs in patients with obsessive-compulsive disorder (NCT01674361). The GLYT1 inhibitor PF-04958242 is still listed in Pfizer's Phase I pipeline and has completed multiple Phase I studies (NCT01159483, NCT02228395, NCT02332798, NCT01511510 and NCT01518894), but the development of several other investigational GLYT1 inhibitors for the treatment of schizophrenia, including compounds from Pfizer, GlaxoSmithKline, Amgen, Merck, Johnson & Johnson and Sanofi, appears to have stopped (see Evaluate Pharma article 21 Jan 2014 in Further information). However, there is evidence to suggest that GLYT2 inhibitors reduce pain in animal models of chronic pain, and thus there is probably work ongoing in the development of partial GLYT2 inhibitors that can be used for pain relief without serious side effects[123]. One such compound, VVZ-149, a dual inhibitor of GLYT2 and 5-hydroxytryptamine receptor 2A, is under development by Vivozon and completed a Phase I study in 2014 (NCT01905410).

Bile acid transporter inhibitors

Bile acids are the principal components of bile and their primary function is to solubilize fat and other dietary nutrients, although they can also function as signalling molecules[124]. Bile acids are synthesized in the liver from cholesterol through the action of the rate-limiting enzyme cytochrome P450 7A1. Bile acid uptake and efflux transporters in the intestine and liver play key roles in the highly efficient enterohepatic recycling pathway, through which more than 90% of the total pool of bile acids are reabsorbed from the intestine and transported back to the liver via the portal circulation[125]. ASBT (SLC10A2) mediates the reabsorption of bile acids from the lumen of the intestine[126]. Inhibition of bile acid reabsorption in the intestine would result in a loss of bile acids and increased conversion of cholesterol to bile acid in the liver, thereby lowering circulating cholesterol levels and potentially ameliorating or preventing the progression of cardiovascular disease. Thus, not surprisingly, inhibiting ASBT has received a substantial amount of attention as a potential therapeutic strategy for lowering cholesterol[127], and several pharmaceutical companies are

developing potent and specific inhibitors of ASBT as therapeutic agents with this aim[126]. Interestingly, the rare genetic disorder primary bile acid malabsorption syndrome is caused by loss-of-function mutations in *ASBT*[128]. Individuals with this disorder suffer from chronic diarrhoea and fat-soluble vitamin deficiency, and importantly, exhibit lower plasma cholesterol levels[128].

Given the potency and efficacy of statins, as well as newer agents such as ezetimibe (Zetia; Merck & Co.) that target cholesterol absorption in the intestine, the extent of clinical benefit of ASBT inhibition (relative to the potential side effects) remains to be clarified. However, there now appears to be more-compelling evidence for targeting ASBT for cholestatic liver diseases such as primary biliary cirrhosis, for which treatment options have been limited. LUM001, an ASBT inhibitor developed by Lumena Pharmaceuticals (now Shire), is currently in Phase II clinical trials for the treatment of cholestatic liver diseases, including primary biliary cirrhosis[129] (NCT02057718, NCT01904058, NCT02057692, NCT02117713 and NCT02061540). Another ASBT inhibitor developed by Shire, SHP626, is currently recruiting participants for Phase I trials for the treatment of nonalcoholic steatohepatitis in overweight adults (NCT02287779). Albiero Pharma is also currently developing ASBT inhibitors of its own — elobixibat has just completed a Phase III trial for chronic idiopathic constipation (NCT01895543). A4250 (Albireo) received orphan drug designation from the FDA in 2012 for the treatment of progressive familial intrahepatic cholestasis and primary biliary cirrhosis, and is currently in Phase II trials in patients with primary biliary cirrhosis (NCT02360852). It is likely that there are other pharmaceutical companies pursuing ASBT as a therapeutic target for cholestatic liver disease, as many have done so for reducing cholesterol.

Because bile acids promote the secretion of intestinal incretin peptides (such as glucagon-like peptide 1) that in turn stimulate pancreatic insulin secretion, inhibition of ASBT may also be a viable strategy for the treatment of type 2 diabetes[130]. GlaxoSmithKline recently completed two Phase II studies using a combination of GSK2330672 plus metformin to treat diabetes (NCT02202161 and NCT01929863). Furthermore, targeting ASBT has also been proposed as a prodrug strategy for compounds that have poor oral bioavailability, as coupling an active drug molecule with a bile acid moiety would increase the absorption of the drug in the intestine[131].

Nutrient transporter inhibitors

Tumour cells have an increased demand for nutrients owing to their rapid proliferation and growth. However, many amino acids and carbohydrates are too polar to diffuse across cell membranes, and thus require transporter proteins for cellular uptake. In theory, tumour growth can be controlled by starving the cells of the metabolic precursors needed for sustained growth. Such an approach can be used to selectively kill tumour cells, which are generally locked into a state of rapid growth by oncogenes and are therefore more sensitive to starvation than are normal cells. Moreover, nutrient transporters have been found to be overexpressed in a wide variety of cancers[132]. To date, no anticancer drug has been developed to specifically inhibit a nutrient transporter with the explicit goal of controlling cell growth. However, inhibition of key nutrient transporters, such as the glucose

transporters of the SLC2 and SLC5 families, amino acid transporters of the SLC7 family and lactate transporters of the SLC16 family, may be a reasonable approach for discovering new anticancer drugs[133].

As glucose is the primary energy source in most cells, it is unsurprising that glucose transporters such as GLUT1 (SLC2A1) are often overexpressed in tumour cells in a variety of tissues[134, 135]. Indeed, [^{18}F]-fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission tomography (PET) imaging, which is used to detect and stage tumours, is dependent on the rate of cellular glucose uptake. However, increased glycolysis is associated with an increase in the generation of lactate, which cells need to remove to maintain cellular pH levels. There is often also an upregulation of lactate transporters (such as monocarboxylate transporter 1 (MCT1; also known as SLC16A1))[136, 137], or transporters important in pH regulation (such as sodium–hydrogen exchanger 1 (NHE1; also known as SLC9A1))[138, 139] in cancer cells.

Various research groups have identified MCT1 inhibitors. For example, the MCT1 inhibitor AZD3965, developed by Cancer Research UK, is currently in Phase I clinical trials for patients with advanced solid tumours or lymphoma (NCT01791595). Similarly, amino acid transporters (such as L-type amino acid transporter 1 (LAT1; also known as SLC7A5)[140, 141], ASC amino acid transporter 2 (ASCT2; also known as SLC1A5)[142] and cystine–glutamate exchange transporter (XCT; also known as SLC7A11)[143]) are also overexpressed in a variety of tumours and may be potential anticancer targets. Sulfasalazine, which was initially developed as an anti-inflammatory drug to treat rheumatoid arthritis, was subsequently found to inhibit XCT[144] and has anticancer effects in various cancer xenograft models[143]. As our understanding of the importance of transporters in tumour cell metabolism increases, it is highly likely that the development of anticancer drugs that target different nutrient transporters will continue.

SLC-targeting imaging agents

PET imaging probes, some of which exploit SLC transporters for uptake into cells, are widely used in the clinic, particularly in diagnosing disease[145. ^{18}F-FDG, a widely used PET imaging probe, is transported into cells via GLUT1, which is upregulated in many cancers. GLUT1 upregulation, which enables higher ^{18}F-FDG uptake in tumour cells, is frequently associated with poor cancer prognosis[146, 147].

In addition to cancer diagnosis, several PET imaging probes that inhibit SLC transporters are in clinical development for guiding drug treatment in other disorders. For example, PET radioligands that inhibit SERT, DAT or NET can provide information on the occupancy of these neurotransmitter transporters by various drugs in patients with depression, to understand the mechanisms of nonresponses to drug therapies[148, 149, 150]. Another interesting use of PET imaging probes is the detection of monoaminergic degeneration in Parkinson disease. ^{18}F-9-fluoroprolyl-(+)-dihydrotetrabenzazine (^{18}F-DTBZ) is a radioligand that targets VMAT2, which transports monoamine neurotransmitters from the neuronal cytosol into synaptic vesicles. As VMAT2 density is correlated with the integrity of dopaminergic neurons in the brain, measuring VMAT2 occupancy using ^{18}F-DTBZ may enable early diagnosis and monitoring of monoaminergic degeneration in Parkinson

disease[151]. This imaging agent is under investigation as an *in vivo* biomarker for Parkinson disease; it has completed one Phase II trial (NCT01283347) and is currently in two more (NCT02059733 and NCT02039024). As VMAT2 can be a marker of islet β-cells, observational studies using the same agent are ongoing to measure β-cell mass in healthy individuals and in patients with diabetes (NCT02236754 and NCT00771576). Similarly, an imaging probe for the vesicular acetylcholine transporter VACHT is currently under investigation to assist in the detection of early Alzheimer disease[152], which typically leads to deficits in acetylcholine transmission.

Drug–drug interactions can also be studied using PET imaging by administering a radiolabelled drug that is known to be a transporter substrate in conjunction with an unlabelled drug[153]. In this way, an interaction between a substrate and an inhibitor of a transporter may be observed in multiple organs simultaneously. For example, [^{11}C]-metformin could be useful as PET probe to study drug–drug interactions that are mediated by multidrug and toxin extrusion protein 1 (MATE1; also known as SLC47A1) in the liver and kidney[154].

Conclusions and future directions

SLC transporters represent a plethora of new therapeutic targets for rare diseases, and may be particularly amenable to targeting with small molecules. Importantly, many SLC transporters are expressed on the cell surface and are therefore targetable by both small molecules and therapeutic antibodies. Furthermore, there are many examples of SLC transporters that are targets of already approved drugs, as well as of drugs in development.

However, several challenges remain for targeting SLC transporters. Although 92% of known drug-target structures have been deposited in the Protein Data Bank (see Databases), most SLC transporters have not been crystallized, thus limiting computer-aided drug discovery efforts[3]. Moreover, many SLC transporters remain orphans, with unknown function and unknown substrates. Finally, SLC transporters located in intracellular compartments may not be as amenable to drug targeting. For example, to our knowledge, the SLC25 family of mitochondrial transporters, some of which are associated with Mendelian disease, have not yet been targeted.

Despite these obstacles, the potential for discovering inhibitors of transporters or modulators of transporter activity is enormous. The development of small molecules that can target specific variants of the ABC transporter CFTR suggests that efforts to target mutant SLC transporters may be possible. In some rare diseases, hydrophobic nutrient derivatives that can circumvent dysfunctional membrane transporters could be used to deliver necessary nutrients to cells. A comprehensive understanding of the mechanisms responsible for rare and common diseases — including the function of the transporters and the pathways in which they act — will be crucial for recognizing other proteins that may be therapeutically targeted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

- Membrane transport proteins mediate the transport of molecules across cell membranes and have key roles in human health. More than 100 Mendelian diseases are caused by a defect in a single solute carrier (SLC) transporter.
- Genetic studies have provided a wealth of information on the roles that SLC transporters play in human health, and in common and rare diseases, enhancing our understanding of the biology of these membrane transporters.
- High-throughput screening technologies and computational methods may be used to discover novel inhibitors and activators of SLC transporters for therapeutic purposes.
- Utilizing transporters as drug targets may require indirect methods, such as developing molecules that function as potentiators or correctors, or developing substrates that bypass the transporter.
- Some currently marketed drugs, including diuretics, neuropsychiatric drugs and antidiabetic drugs, target SLC transporters.
- Uric acid-, glycine- and bile acid-transport inhibitors are currently in various stages of clinical development for the treatment of various human diseases. First-in-class compounds that target SLC transporters are anticipated to be approved in the near future.
- Positron emission tomography (PET)-imaging probes may utilize transporters for uptake into cells, enabling transporter function to be visualized *in vivo*.

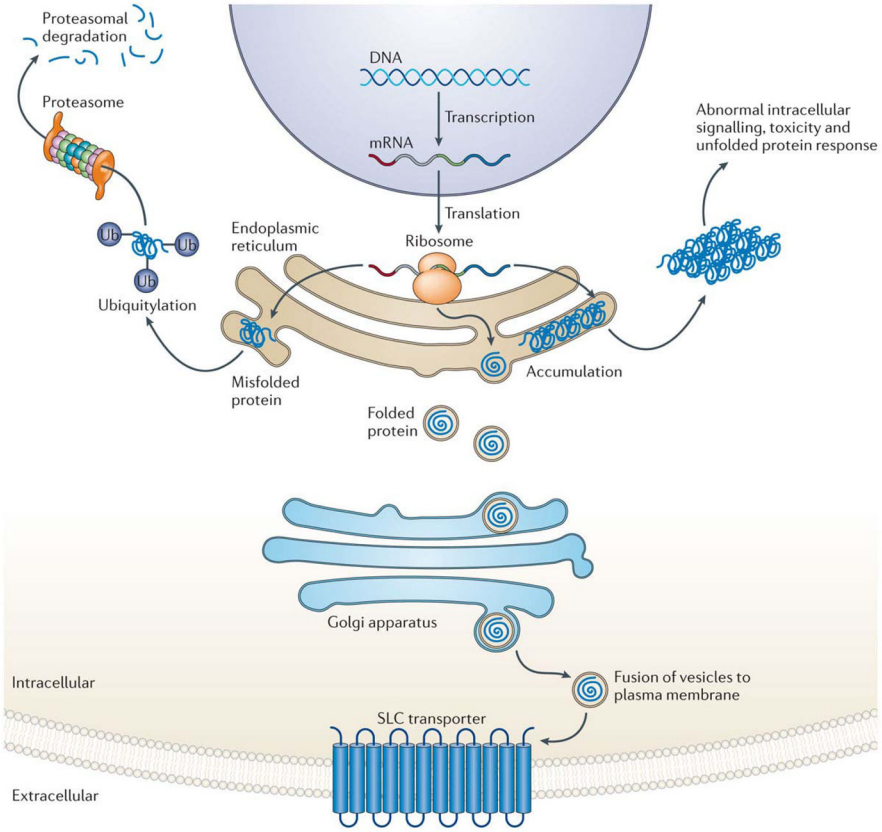

Figure 1. Overview of the different types of mutations in SLC transporter genes, and their effects

Transcription occurs in the nucleus and translation in the ribosomes. Normal, folded proteins translocate in vesicles across the endoplasmic reticulum and to the Golgi apparatus. Once through the Golgi, proteins are trafficked to the cell surface membrane, where they fuse to the plasma membrane to form the functional solute carrier (SLC) transporter. Mutations in the gene encoding the transporter may result in poor transporter function owing to several different factors. First, improper translation could result in a misfolded protein. In this case, the misfolded protein may be ubiquitylated and degraded in the proteasome. Second, the SLC transporter protein may not be trafficked to the cell surface membrane. Finally, mutations in the gene could cause an intracellular accumulation of the misfolded protein, resulting in abnormal intracellular signalling and initiation of the unfolded protein response to degrade the protein. Drugs can affect any of the various steps to alter transport function. For example, riluzole increases the RNA transcript levels of excitatory amino acid carrier 1 (EAAC1), ultimately resulting in an enhanced uptake of glutamate from the neuronal synapse.

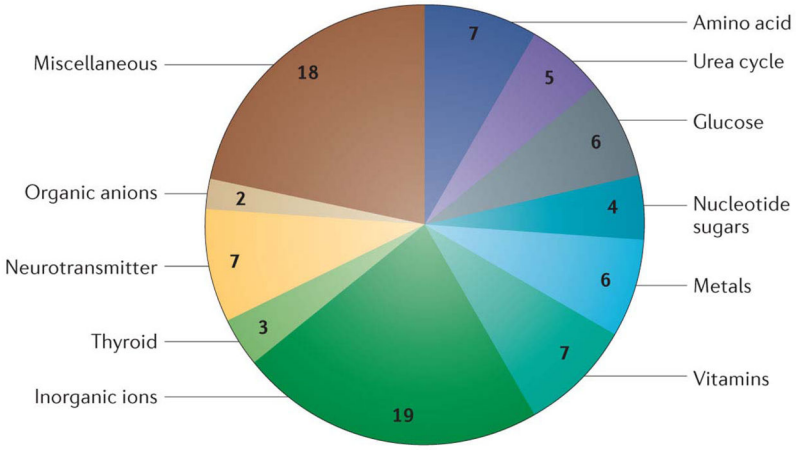

Figure 2. SLC transporters implicated in Mendelian diseases, grouped by substrate type

A total of 84 solute carrier (SLC) transporters have been implicated in Mendelian diseases. The number in each segment indicates the number of transporters. See Supplementary information S1 (table) for more information.

Table 1

SLC transporters that are implicated in Mendelian diseases and other disorders

Substrate category	No. of transporters implicated in Mendelian disease (total 84)	No. of Mendelian diseases (total 100)	SLC transporters with mutations leading to Mendelian disease (total 84)	Examples of substrates	Comments
Amino acids	7	6	SLC3A1, SLC6A19, SLC6A20, SLC7A9, SLC25A12, SLC25A38, SLC36A2	Glutamate, glycine, proline, cysteine, tryptophan, aspartate	• SLC7A5 (Refs 140,141) and SLC7A11 are potential new targets for cancer • Sulfasalazine, originally developed for arthritis, inhibits SLC7A11 (Ref. 172)
Urea cycle	5	6	SLC2A9, SLC7A7, SLC22A12, SLC25A13, SLC25A15	Lysine, ornithine, citrulline, aspartate, uric acid, glutamate	
Glucose	6	9	SLC2A1, SLC2A2, SLC2A10, SLC5A1, SLC5A2, SLC37A4	Glucose, galactose, mannose, fructose, glucose-6- phosphate	
Nucleotide sugars	4	4	SLC35A1, SLC35A2, SLC35C1, SLC35D1	UDP-glucuronic acid, GDP-fucose, UDP-galactose, UDP-*N*-acetylgalactosamine	
Metals	6	6	SLC11A2, SLC30A2, SLC30A10, SLC39A4, SLC39A13, SLC40A1	Zinc, iron, ferrous ion, manganese	
Vitamins	7	9	SLC19A2, SLC19A3, SLC25A19, SLC46A1, SLC52A1, SLC52A2, SLC52A3	Folate, thiamine, thiamine pyrophosphate, riboflavin	
Neuro- transmitter	7	7	SLC1A3, SLC5A7, SLC6A2, SLC6A3, SLC6A5, SLC17A8, SLC25A22	Noradrenaline, serotonin, dopamine, glutamate, glycine, aspartate, choline	• Tiagabine, a drug used for the treatment of epilepsy, inhibits SLC6A1 (Ref. 174) • SLC18A2 inhibitors such as amphetamine, reserpine and tetrabenazine are used for the treatment of movement disorders and hypertension • Novel SLC18A2 inhibitors in clinical development include NBI-98854, which is in Phase III trials for dyskinesia (NCT02274558), and lobeline, which is in Phase II trials for ADHD (NCT00664703) • An SLC6A9 inhibitor, bitopertin, was in Phase III clinical trials for the treatment of schizophrenia but failed to meet the primary end point (NCT01235559, NCT01235585, NCT01192906 and NCT01192880) • Clinical trials are ongoing for bitopertin for the treatment of OCD (NCT01674361)[175]

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Substrate category	No. of transporters implicated in Mendelian disease (total 84)	No. of Mendelian diseases (total 100)	SLC transporters with mutations leading to Mendelian disease (total 84)	Examples of substrates	Comments
					• Another SLC6A9 inhibitor, PF-04958242, is in Phase I trials (NCT02341482) • Inhibition of SLC17As after nervous system injury may mitigate further damage[176] • SLC18A2 imaging agent 18F-DTBZ is in Phase II trials as a biomarker for Parkinson disease (NCT01283347); it is also in observational studies to measure β-cell mass (NCT02236754 and NCT00771576) • An imaging probe targeting SLC18A3 is under investigation to detect early Alzheimer disease152 • Glutamate transporters may be drug targets for various neuropsychiatric and neurodegenerative diseases[177]
Inorganic ions	19	27	SLC4A1, SLC4A4, SLC4A11, SLC9A3R1, SLC9A6, SLC12A1, SLC12A3, SLC12A6, SLC20A2, SLC24A1, SLC24A5, SLC25A3, SLC26A3, SLC26A2, SLC26A5, SLC26A8, SLC34A1, SLC34A2, SLC34A3	Chloride, bicarbonate, hydroxide, sodium, calcium, potassium, phosphate, sulfate, oxalate, rubidium	• Diuretic drugs such as bumetanide and furosemide inhibit various SLC12 transporters, including SLC12A1, SLC12A2, SLC12A3, SLC12A4 and SLC12A5 • Transporters in the SLC9A family have been studied as drug targets in cancer[139, 173] • SLC9A1 is activated during oncogene-dependent transformation and may represent a potential new target for the treatment of cancer[139, 173]
Thyroid	3	4	SLC5A5, SLC16A2, SLC26A4	Iodide, iodothyronines	
Organic anions	2	1	SLCO1B1, SLCO1B3	Oestradiol glucuronide, oestrone sulfate, bilirubin	• Probenecid, an SLC22A6 inhibitor, can be co-administered to prevent nephrotoxicity associated with drug (for example, cidofovir) overdose
Miscellaneous	18	21	SLC6A8, SLC10A2, SLC13A5, SLC16A1, SLC16A12, SLC17A5, SLC22A5, SLC25A1, SLC25A4, SLC25A20, SLC27A4, SLC29A3, SLC33A1, SLC42A1, SLC45A2, SLC49A1, SLC49A2, SLCO2A1	Carnitine, creatinine, taurocholic, ADP–ATP, acetyl-CoA, melanin, prostaglandin, sialic acid, pyruvate, lactate, long-chain fatty acids, adenosine, citrate, haem, ammonia	• Clodronate, an inhibitor of SLC25A4, SLC25A5 and SLC25A6, is used for the treatment of osteoporosis[178]

^{18}F-DTBZ, ^{18}F-9-fluoroprolyl-(+)-dihydrotetrabenazine; ADHD, attention-deficit hyperactivity disorder; GDP, guanidine diphosphate; OCD, obsessive-compulsive disorder; SLC, solute carrier; UDP, uridine diphosphate.

All the clinical trials mentioned in this table are registered on ClinicalTrials.gov (see Databases). For detailed information about each of these SLC transporters and the Mendelian diseases, see Supplementary information S1, S2 (tables).

Table 2

SLC transporters implicated in Mendelian diseases that may potentially be targets of new drugs

Substrate class	Protein (gene)	Disease (disease prevalence if known)	Current or potential drug target
Neurotransmitter	EAAT1 (*SLC1A3*)	Episodic ataxia type 6	• Riluzole, which facilitates EAAT1, is used for ALS[73] • Loss of EAAT1 has been found in patients with ALS[179] • EAAT1 is upregulated in chronic brain ischaemia[180] • EAAT1 inhibitors have been developed as pharmacological tools[181, 182, 183]
Glucose	GLUT1 (*SLC2A1*)	GLUT1 deficiency syndrome; also known as dystonia 9 or dystonia 18 (1 in 90,000 in Australia)	• Triheptanoin has reached Phase II trials to treat GLUT1 deficiency syndrome (NCT02036853) • GLUT1 expression levels are correlated to ^{18}F-FDG uptake values[184, 185] • A small-molecule inhibitor of GLUT1 was able to inhibit cancer cell growth in vitro and in vivo[186]
Glucose	SGLT1 (*SLC5A1*)	Glucose–galactose malabsorption (300 cases to date)	• Several inhibitors of SGLT1 and/or SGLT2 have been approved to treat type 2 diabetes, including canagliflozin, dapagliflozin and empagliflozin[187, 188]; tofogliflozin and ipragliflozin are approved for use in Japan • Clinical trials are ongoing or have completed for other SGLT1 and/or SGLT2 inhibitors including: GSK1614235, which is in Phase I trials (NCT01607385); remogliflozin, in Phase II trials (NCT00495469 and NCT00376038); sotagliflozin, in Phase III trials (NCT02384941); and ertugliflozin, in Phase III trials (NCT01986881, NCT01999218, NCT01958671, NCT01986855, NCT02036515 and NCT02226003)
Glucose	SGLT2 (*SLC5A2*)	Familial renal glucosuria (0.16–6.3% in the United States[189])	• See entry for SGLT1
Thyroid	NIS (*SLC5A5*)	Thyroid dyshormonogenesis (1 in 100,000 newborns)	• A PET imaging probe, [^{99m}Tc]-pertechnetate, is being studied for imaging and radioiodine therapy by targeting NIS[190, 191]
Neurotransmitter	NET (*SLC6A2*)	Orthostatic intolerance	• Many antidepressants, including fluoxetine, citalopram, sertraline, venlafaxine and duloxetine target neurotransmitter-reuptake transporters including NET, DAT and SERT
Neurotransmitter	DAT (*SLC6A3*)	Infantile parkinsonism- dystonia (8 cases to date)	• See entry for NET • A radioligand for DAT, (1*R*)-2β-carbomethoxy-3β-(4-[^{123}I]iodophenyl)tropane ([^{123}I]β-CIT), could be used clinically as a nuclear imaging marker for Parkinson disease[192, 193]
Neurotransmitter	GLYT2 (*SLC6A5*)	Hyperekplexia 3 (<1 in 1,000,000)	• Inhibitors of GLYT2 may be used for the glycinergic control of pain[194] or overactive bladder[195]

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Substrate class	Protein (gene)	Disease (disease prevalence if known)	Current or potential drug target
			• An SLC6A5 inhibitor, VVZ-149, is in Phase I trials for pain (NCT01905410)
Miscellaneous	CRTR (*SLC6A8*)	Cerebral creatine deficiency syndrome (0.3–3.5% in males)	• Creatine analogues may be used to enhance creatine levels in the brain[196, 197, 198]
Inorganic ions	NHE6 (*SLC9A6*)	Christianson syndrome (<30 cases to date)	• NHE6 is upregulated in tumour cells under hypoxic conditions[139, 173]
Miscellaneous	ASBT (*SLC10A2*)	Primary bile acid malabsorption	• ASBT is a potential drug target in diabetes and in individuals with hypertriglyceridaemia[127, 199] • Drugs can be conjugated to bile acids to target ASBT to enhance drug uptake into intestine[131, 200] • Several inhibitors of ASBT are in development: LUM001 is in Phase II trials for cholestatic liver diseases (NCT02057718, NCT01904058, NCT02057692, NCT02117713 and NCT02061540); SHP626 is in a Phase I trial for the treatment of NASH (NCT02287779); elobixibat is in Phase II trials for chronic idiopathic constipation (NCT01895543); and A4250 is in Phase II trials for PBC (NCT02360852)
Inorganic ions	NKCC2 (*SLC12A1*)	Bartter syndrome type I (1 in 1,000,000)	• Diuretic drugs such as bumetanide and furosemide inhibit NKCC2
Miscellaneous	MCT1 (*SLC16A1*)	Erythrocyte lactate transporter defect	• MCT1 is upregulated in cancer[201, 202] • Inhibitors of MCT1 may be used as a target for immunosuppression or cancer[201, 203, 204] • An MCT1 inhibitor, AZD3965, is in Phase I trials for patients with cancer (NCT01791595)
Neurotransmitter	VGLUT3 (*SLC17A8*)	Autosomal dominant deafness type 25	• VGLUT inhibitors block the uptake of glutamate into vesicles and reduce excitotoxic events to prevent acute CNS injury and chronic neurodegenerative disease[61, 176, 205, 206]
Vitamins	THTR2 (*SLC19A3*)	Thiamine metabolism dysfunction syndrome 2	• A Janus kinase 2 inhibitor, fedratinib, led to thiamine deficiency and Wernicke encephalopathy, resulting in the withdrawal of the drug during Phase III trials; it was later found to inhibit THTR2[207]
Urea cycle	URAT1 (*SLC22A12*)	Renal hypouricaemia 1 (2.37% in Japan[208])	• Lesinurad, a URAT1 inhibitor, is US-approved for the treatment of gout • Clinical trials are ongoing for other URAT1 inhibitors, including RDEA3170 in Phase II trials (NCT01927198) and KUX-1151 in Phase II trials (NCT02190786)[120]
Miscellaneous	CACT (*SLC25A20*)	Carnitine-acylcarnitine translocase deficiency	• Statins, fibrates and retinoic acid upregulate SLC25A20 expression[209]

Substrate class	Protein (gene)	Disease (disease prevalence if known)	Current or potential drug target
Thyroid	PDS (*SLC26A4*)	Pendred syndrome (7.5% of congenital deafness[210])	• PDS has an important role in the distal tubule salt reabsorption and may represent a novel target for a new diuretic[211]
Glucose	G6PT1, (*SLC37A4*)	Glycogen-storage disease type Ib or Ic (1 in 100,000 (Ref. 212))	• Mice with glycogen-storage disease type Ia show increased *Slc37a4* mRNA levels after a 24-hour fast; gene therapy to restore G6PT1 function has been shown in these mice[213, 214]
Miscellaneous	FLVCR1 (*SLC49A1*)	Posterior column ataxia with retinitis pigmentosa (20 cases to date)	• Inhibition of FLVCR1 results in decreased haem export in an erythroid cell line; however, Slc49a1-knockout mice develop iron overload in microphages[215]

^{18}F-FDG, ^{18}F-fluoro-2-deoxy-d-glucose; ALS, amyotrophic lateral sclerosis; ASBT, apical sodium-dependent bile acid transporter; CACT, carnitine-acylcarnitine translocase; CNS, central nervous system; CRTR, creatine transporter; DAT, dopamine transporter; EAAT1, excitatory amino acid transporter 1; FLVCR1, feline leukaemia virus subgroup C receptor-related protein 1; G6PT1, glucose-6-phosphate translocase 1; GLUT1, glucose transporter type 1; GLYT2, glycine transporter 2; MCT1, monocarboxylate transporter 1; NASH, non-alcoholic steatohepatitis; NET, noradrenaline transporter; NHE6, sodium–hydrogen exchanger 6; NKCC2, sodium–potassium–chloride cotransporter 2; NIS, sodium–iodide symporter; PBC, primary biliary cirrhosis; PDS, pendrin; PET, positron emission tomography; SERT, serotonin transporter; SGLT, sodium–glucose cotransporter; SLC, solute carrier; THTR2, thiamine transporter 2; URAT1, urate anion exchanger 1; VGLUT3, vesicular glutamate transporter 3.

Additional information on diseases mentioned in this table can be found via the Online Mendelian Inheritance in Man (OMIM) database (see Databases) or the US National Library of Medicine's Genetics Home Reference or Orphanet (see Further information). All of the clinical trials mentioned in this table are registered on ClinicalTrials.gov (see Databases).