

Feature Article

Strategies to Overcome Blood-Brain Barrier

Complex Biology of CNS Diseases Continues to Hamper Development of Effective Drugs

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Central nervous system (CNS) diseases are a major focus of the pharmaceutical industry, with CNS drugs representing some of its most successful products. These include [Pfizer's](#) Zoloft, [Eli Lilly's](#) Cymbalta, and Abilify from [Bristol-Myers Squibb](#) and [Otsuka](#).

Drug discovery and development researchers, however, have experienced difficulty developing CNS drugs that can complete clinical trials and win regulatory approval. This is especially true for drugs that address major unmet needs in the CNS area such as Alzheimer's, Parkinson's, amyotrophic lateral sclerosis (ALS), stroke, brain cancers, and metastases to the brain.

A major bottleneck in successful development of CNS drugs is the discovery or design of drugs that can cross the blood-brain barrier (BBB).

Researchers believe that the function of the BBB is to protect the CNS from toxic molecules, including toxins that may be ingested in food, and endogenously formed toxic molecules. Unfortunately, the BBB also serves as a barrier to potentially beneficial drugs for treatment of CNS diseases. About 98% of small molecule drugs fail to cross the BBB and, no large molecule drugs cross the BBB, except for a few natural peptides and proteins such as insulin, and those specifically designed to do so.

Most current CNS drugs are small molecule drugs that cross the BBB via passive diffusion. These drugs are either old compounds that were discovered via traditional drug discovery methods (involving serendipity and animal studies), or newer drugs discovered via high-throughput screening (HTS) and medicinal chemistry.

Small molecule drugs that can cross the BBB via passive diffusion must have physicochemical properties that allow them to do so. Such drugs have a more restricted set of physicochemical properties than the universe of oral drugs. For example, the molecular weight cutoff for CNS penetrant drugs appears to be 400 daltons, as opposed to 500 daltons for all drug-like compounds. Companies such as Pfizer and [GlaxoSmithKline](#) have developed computational models, based on the physicochemical properties of compounds, which allow medicinal chemists to predict the ability of small molecule drugs to cross the BBB via passive diffusion, and to design compounds that can do so.

A particular challenge to the development of CNS-penetrant small molecule drugs is the action of efflux transporters. These are a class of ATP-dependent membrane glycoproteins that actively expel molecules that have crossed the BBB back across endothelial cell membranes and out of the brain. Researchers consider the P-glycoprotein (P-gp) to be the most important of these transporters. In addition to designing compounds that have the physicochemical properties needed to enable passive diffusion across the BBB, medicinal chemists must also ensure that these compounds are poor substrates for P-gp.

Small molecule compounds that are designed to cross the BBB via passive diffusion seem to be particularly ill-suited to address tempting new disease targets in indications with high unmet need. For example, researchers have identified the enzyme beta-secretase as being critically involved in the amyloid pathway of Alzheimer's disease. Because of the physicochemical nature of the active site of beta-secretase, it is difficult to design small molecule inhibitors that readily cross the BBB via passive diffusion.

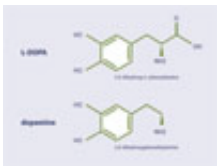


Figure 1. Dopamine cannot cross the BBB.

Researchers have been developing novel technologies that enable the design of drugs that cross the BBB via active transport. The permeation of the brain by drugs that are actively transported across the BBB is approximately an order of magnitude greater than for compounds that cross the BBB via passive diffusion. Moreover, most small molecule compounds do not cross the BBB at therapeutically significant concentrations at all. This problem might be overcome by developing versions of these compounds that can be actively transported across the BBB.

One technology for enabling active transport of small molecule drugs across the BBB involves targeting endogenous nutrient transporters. These transporters are members of the solute carrier (SLC) transporter superfamily. Transport of small molecules across the BBB by these membrane proteins is known as carrier-mediated transport (CMT).

CMT is responsible for transport of such nutrients as glucose, other sugars, lactate, nucleosides, fatty acids, and vitamins, as well as certain hormones (such as thyroid hormones) into the brain. These substances are vital for brain function. Many of the SLC transporters found in brain endothelium that are involved in CMT are also found in intestinal endothelium, where they are involved in transport of nutrients—and drugs—from the intestine into the bloodstream.

In order to design drugs that utilize CMT to cross the BBB, researchers modify their chemical structures so that they resemble nutrients that are transported across the BBB by specific SLCs. The prototypical drug that uses this strategy (which was developed long before mechanisms of CMT were known) is L-DOPA, the major current drug for Parkinson's disease. L-DOPA is used to replace dopamine that is lost due to degeneration of dopaminergic neurons in the substantia nigra of the brain.

Dopamine itself cannot cross the BBB. It can, however, be modified to produce L-DOPA, an amino acid that is recognized by the large neutral amino acid transporter. This SLC family member transports L-DOPA into the brain, where it is converted to dopamine by the enzyme aromatic amino acid decarboxylase. L-DOPA thus serves as a prodrug that crosses the BBB and is converted into the active agent in the brain. The structures of L-DOPA and dopamine are shown in *Figure 1*.

[XenoPort](#) has been designing small molecule drugs that exploit CMT to enable improved absorption from the gut or transport across the BBB. The company refers to its products as Transported Prodrugs. These are prodrugs that target SLC nutrient transporters, either in the BBB or in the intestine. XenoPort's main therapeutic focus is on CNS drugs, but it is also developing a drug for gastroesophageal reflux disease.

All of XenoPort's clinical-stage drugs target SLCs in the intestine. They are Transported Prodrugs that are derivatives of FDA-approved drugs and are modified to target an SLC. Once they are transported from the intestine into the bloodstream, they are converted into the active drug, analogous to the conversion of L-DOPA to dopamine.

XenoPort's research aimed at development of drugs that cross the BBB similarly involves the design of Transported Prodrugs that target SLCs in brain capillaries. Once they are transported through the BBB, they are converted into active drugs.

Receptor-Mediated Transport

The other major system that is used in normal mammalian physiology to enable needed molecules to cross the BBB is receptor-mediated transport (RMT). The brain uses RMT to transport proteins, peptides, and lipoproteins that are needed for brain function across the BBB. Examples of biomolecules that are transported into the brain via RMT include insulin, insulin-like growth factor (IGF), leptin, transferrin, and low-density lipoprotein (LDL).

In RMT, molecules in the circulation may bind to specific receptors on the luminal surface of brain capillaries (i.e., the surface that interfaces with the bloodstream). Upon binding, the receptor-ligand complex is internalized into the endothelial cell by a process called receptor-mediated endocytosis. The ligand may then be transported across the abluminal membrane of the endothelial cell (i.e., the membrane that interfaces with brain tissue) into the brain. This whole process is called receptor-mediated transcytosis.

William Pardridge, M.D., professor of medicine at UCLA, has been exploiting RMT to develop large molecule CNS drugs that can cross the BBB. Such large molecule drugs may include peptides, recombinant proteins, monoclonal antibodies (mAbs), and small interfering RNAs (siRNAs).

In designing such large molecule drugs, researchers use what are called molecular Trojan horses (MTHs). MTHs are either peptide or protein ligands that target RMT systems (e.g., receptor-binding sequences of insulin) or MAbs that are specific for target receptors. In designing protein drugs that can transit the BBB, researchers typically construct fusion proteins between the desired therapeutic protein and the MTH. BBB receptors that are typically targeted with MTHs include the receptors for insulin, transferrin, IGF, leptin, and LDL.

[ArmaGen](#) has an MTH technology that utilizes RMT to cross the BBB. The company is a spin-off of Dr. Pardridge's laboratory. ArmaGen and the Pardridge laboratory have developed fusion proteins between mAbs to the transferrin and insulin receptors with various therapeutic proteins that cannot themselves cross the BBB. They have demonstrated that these MTH-based agents cross the BBB in animal models, including nonhuman primates.

ArmaGen's lead product, AGT-120, is a fusion protein between a human transferrin receptor mAb and brain-derived neurotrophic factor. It is in the pre-IND stage and is intended for treatment of stroke and neurodegenerative diseases.

AGT-181, a fusion protein between a human insulin receptor (HIR) mAb and the enzyme alpha-L-iduronidase (IDUA), is an enzyme-replacement therapeutic for treatment of the lysosomal storage disease Hurler's syndrome (Mucopolysaccharidosis Type 1).

ArmaGen is also developing a product for treatment of Alzheimer's disease. This is a trifunctional fusion antibody, which consists of moieties that bind to HIR, Abeta peptide (which makes up amyloid plaques that researchers believe causes Alzheimer's disease), and the neonatal Fc receptor. The anti-HIR moiety serves as an MTH to enable the agent to cross the BBB, the anti-Abeta peptide moiety binds to amyloid plaque and disaggregates it, and the anti-neonatal Fc receptor moiety enables the Abeta-bound agent to exit the brain via the BBB.

The Pardridge laboratory and ArmaGen have also developed a delivery system to enable siRNAs to cross the BBB. This agent consists of an mAb to the transferrin receptor, linked to streptavidin. This carrier is designed to bind biotinylated siRNAs (via streptavidin-biotin binding), and transfer them across the BBB.

Another company that has been developing MTH technology is [to-BBB](#), a spin-off of the Blood-Brain Barrier Research group of [Leiden University](#). to-BBB's technology platform, 2B-Trans, is based on the use of the nontoxic diphtheria toxin mimetic CRM197. CRM197 binds to a receptor on capillaries of the BBB, which is a membrane-bound precursor of heparin-binding epidermal growth factor. This receptor is also known as the diphtheria toxin receptor (DTR). DTR is constitutively expressed on brain capillaries and in neurons and glial cells of the brain.

to-BBB's lead product, 2B3-101, is a liposome-encapsulated ribavirin conjugated to CRM197. It is intended as a therapeutic against Japanese encephalitis virus (JEV).

[The Immune Disease Institute at Harvard Medical School](#) has been developing a MTH for delivery of siRNAs to the brain. This MTH, called the CORVUS peptide, is a fusion peptide between a 29-amino acid peptide from the rabies virus glycoprotein (RVG) and a 9-amino acid peptide made up entirely of D-arginine units.

The CORVUS peptide is designed to bind the negatively charged si-RNAs via its nona-D-arginine moiety, and to bind the receptor for the virus, the nicotinic acetylcholine receptor (nAChR). nAChR is expressed on capillaries of the BBB and on neurons of the brain. CORVUS thus serves to transport the siRNAs across the BBB and into neurons. The CORVUS MTH is in the research stage. The researchers showed that intravenously injected CORVUS complexed with an siRNA specific for the JEV envelope gene gave mice 80% protection from JEV infection.

Outlook

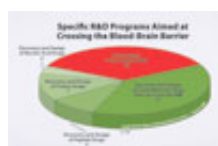


Figure 2

CNS drug researchers generally agree that design and discovery of drugs that can readily cross the BBB is a major bottleneck for the development of new CNS drugs, especially those that address major unmet needs. Academic and corporate researchers have been developing technologies that enable the design of small and large molecule drugs that are actively transported across the BBB, and have demonstrated the feasibility of these technologies in animal studies.

Nevertheless, the majority of companies developing CNS drugs continue to rely on traditional medicinal chemistry-based methods for design of small molecule drugs that cross the BBB via passive diffusion (and which are poor substrates for P-gp), or they have no specific programs on crossing the BBB at all.

This is seen in the results of a survey carried out by Cambridge Healthtech Institute in

conjunction with our recent BBB report. Despite the traditional orientation of most companies' BBB research programs, many of them are focusing on CNS indications such as neurodegenerative diseases that are underserved by current CNS drugs, and for which drugs that cross the BBB via passive diffusion have so far been poorly applicable.

However, the survey indicates that a substantial minority of companies are working on development of large-molecule (protein, peptide, or nucleic acid) drugs that can cross the BBB via use of MTH technology. Others are using another early-stage technology, nanoparticle carriers, to enable their large molecule drugs to cross the BBB (*Figure 2*).

Thus, although most companies developing CNS drugs are not applying novel technologies that enable active transport of drugs across the BBB, these technologies have begun to penetrate the industry. As these early-stage technologies prove themselves in the clinic, we expect that there will be a great interest in utilizing them, including partnering between large pharmaceutical and biotechnology companies and BBB specialty companies, and commercialization of academic research in this area. We expect that, as this occurs, those companies that are already utilizing these technologies will have an advantage over others.

Researchers cite the BBB as a major challenge to developing novel CNS drugs, and some see the BBB as the major bottleneck in this area. However, understanding the complex biology of CNS diseases is an equally important challenge. Thus, although development of clinically proven BBB transport technologies will represent a major breakthrough, the biology of CNS diseases will still challenge CNS drug developers.

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