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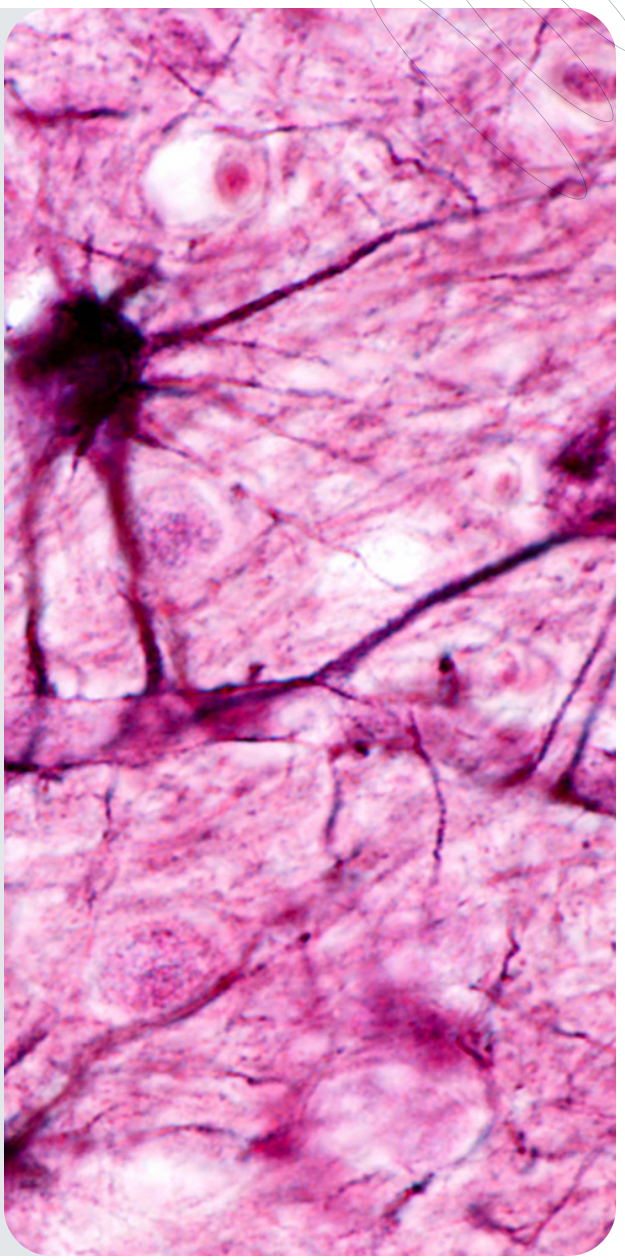
BIOPHARMA STRATEGY



Transporting Macromolecules Across the Blood-Brain-Barrier: **The Next Frontier in CNS Disease Treatment**

Our understanding of the pathobiology and molecular mechanisms underlying central nervous system (CNS) diseases has advanced significantly in recent years, and researchers continue to identify and characterize novel pharmacotherapy targets. However, the blood-brain barrier (BBB) remains a significant challenge, particularly for the increasingly complex modalities needed to address novel targets within relevant tissues. One prominent example is the delivery of oligonucleotides targeting the huntingtin transcript through the BBB to the striatum[1].

Methods to transport large molecules into the brain are likely to cause a paradigm shift in disease treatment and offer lasting solutions to patients for whom only symptom management has so far been available. Here, by analyzing the entire pipeline of biologics and oligonucleotides in development for CNS indications, we identified emerging approaches and platform technologies designed to address the issue of BBB penetration, a few of which are already in clinical trials and may provide first proof-of-concept of a new frontier in CNS disease treatment.

Biologics and oligonucleotides for the treatment of CNS diseases: A large and growing pipeline

Using Scitaris' integrated database, which combines commercial asset information and clinical trial registry data, we identified approximately 2,000 preclinical and clinical biologics or oligonucleotides (excluding gene and cell therapies) in development for CNS indications **(Figure 1)**, with an additional 170 assets intended for genetic diseases with prominent CNS manifestations. Of this combined pool, approximately 4% (88 in total) of the pipeline assets have been described as having moieties to enable BBB penetration, and these are being developed by 51 of the more than 730 unique companies and institutions represented in the pipeline.

The 51 companies we identified in our pipeline as having BBB penetration technology platforms are scattered across key geographies in the pharmaceutical market **(Figure 2)**. While North America accounts for roughly half, notable advances have emerged from East Asia, JCR Pharmaceuticals in Japan and ABL Bio in South Korea, and from Europe, where BioArctic's BrainTransporter program illustrates the continent's innovative potential.

Of the 88 BBB-penetrating assets identified, only 11 have been studied in clinical trials, with the remaining 77 in various stages of discovery and preclinical development **(Figure 3)**. Antibodies and recombinant proteins (including enzymes) are highly represented at over 68% (60/88), followed by oligonucleotides at over 29% (26/88). Approximately 69% (61/88) of assets make use of receptor-mediated transcytosis (RMT) to cross the BBB.

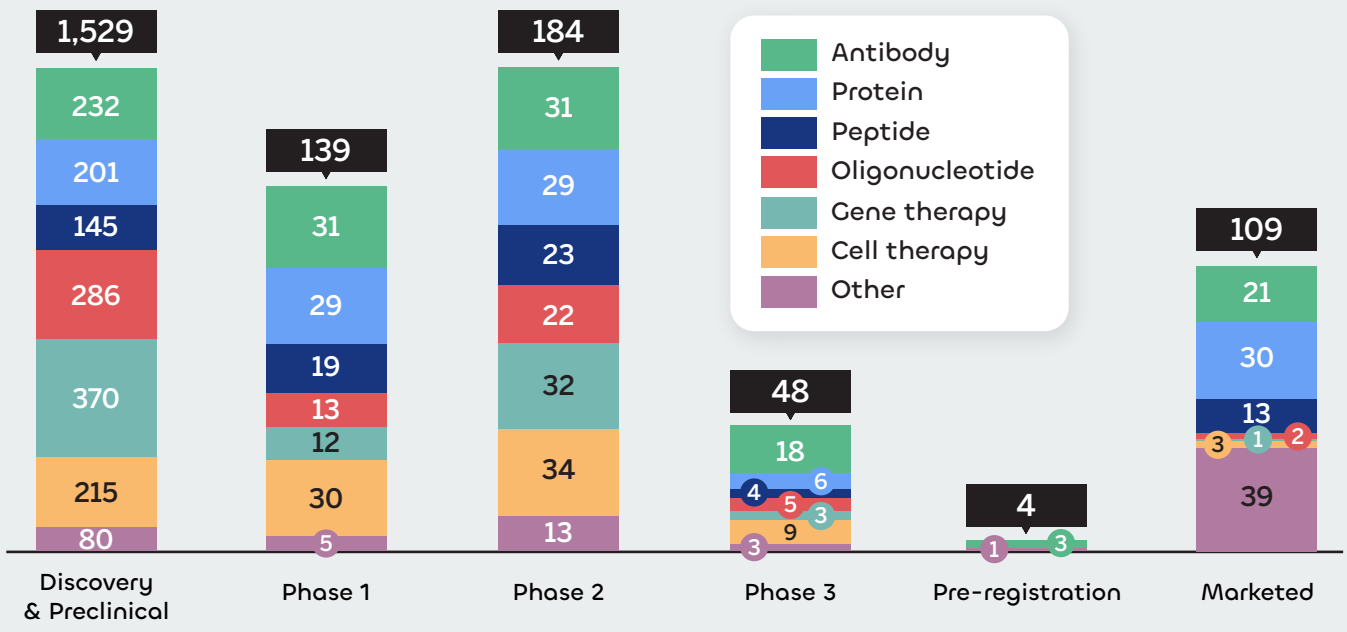


Figure 1. Pipeline of biologics and oligonucleotides in development for central nervous system indications across 8 major markets (US, Japan, 5 EU countries, and China). Data from publicly available clinical trial registries and commercial asset databases integrated in-house by Scitaris. Antibodies, proteins, peptides, and oligonucleotides were evaluated for whether blood-brain-barrier penetration technologies are used; gene therapies and cell therapies were not included in this analysis.

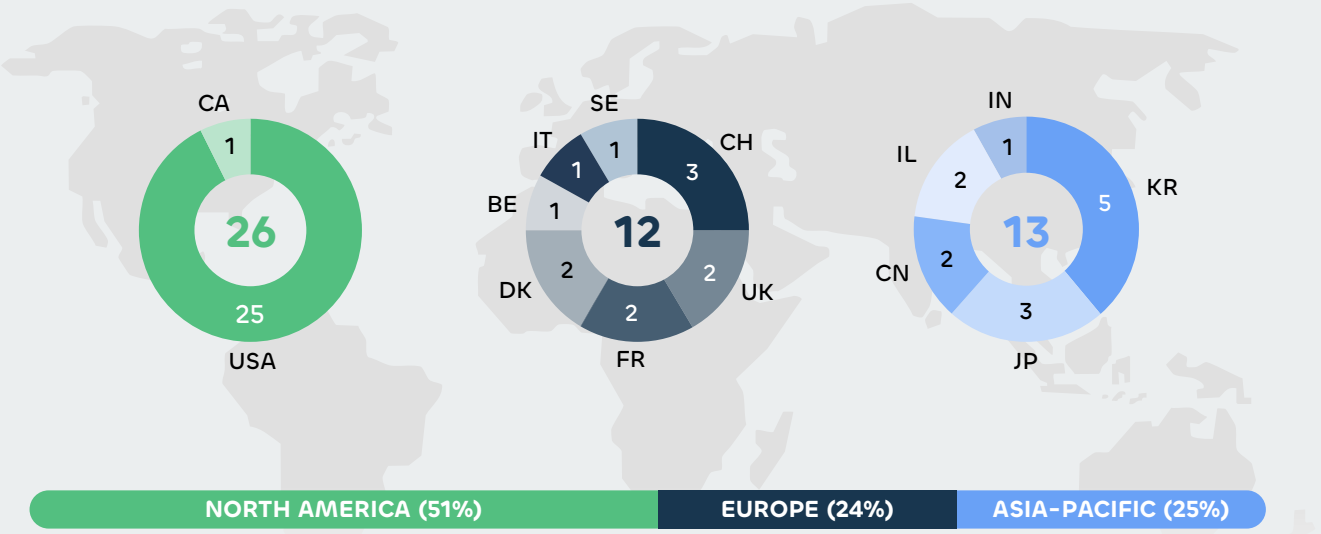


Figure 2. Geographical breakdown of companies with brain-targeting assets in development. 51 individual companies with brain-targeting assets were identified in pipeline review of biologics and oligonucleotides in development for central nervous system indications and genetic diseases with prominent CNS manifestations across 8 major markets (US, Japan, 5 EU countries, and China). Geographical distribution of companies are shown. Abbreviations: BE = Belgium; CA = Canada, CH = Switzerland, CN = China, DK = Denmark, FR = France, IL = Israel, IN = India, IT = Italy, JP = Japan, KR = South Korea, SE = Sweden, UK = United Kingdom, USA = United States of America.

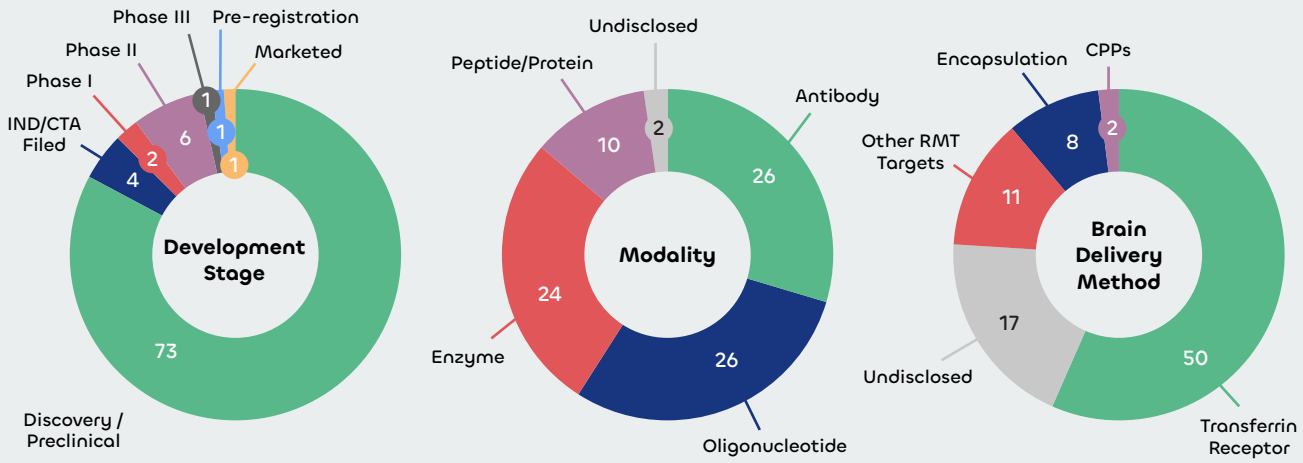


Figure 3. Distribution of brain-targeted drugs by development stage, modality and method of brain delivery. 88 individual assets were identified in pipeline review of biologics and oligonucleotides in development for central nervous system indications and genetic diseases with prominent CNS manifestations across 8 major markets (US, Japan, 5 EU countries, and China). Distribution of these assets by current development stage (left), their modality (middle) and the method for brain delivery (right) are depicted. Abbreviations: CPP = cell-penetrating peptide

RMT: the most advanced BBB penetration platform in development

RMT is a mechanism by which proteins, lipids, and other large molecules enter the brain. The cargo binds to a receptor on the luminal side of the BBB, which triggers endocytosis of the cargo-bound receptor. This complex is then processed within the BBB cell through endosome sorting, after which the receptor is recycled back to the luminal side while the cargo is transferred to the abluminal side of the BBB via exocytosis[2]. By fusing an RMT receptor-binding moiety to a therapeutic molecule, this mechanism can be co-opted to transfer macromolecules into the brain. Due to this potential application, RMT receptors are colloquially termed "brain shuttles".

The transferrin receptor leads the "brain shuttle" field

The most commonly used receptor in the CNS pipeline is the transferrin receptor (TfR), which represents approximately 57% (50/88) of all brain-penetrating assets. TfR is an iron transporter that is broadly expressed in various tissues and also detected at the luminal side of the BBB[3]. Assets using TfR to enter the brain include bispecific antibodies targeting both TfR and the CNS drug target, enzymes modified to bind to TfR, and antibodies fused with a Fab domain, in which the Fc region is engineered to bind to TfR[3].

Clinical proof-of-concept has so far been demonstrated by two programs:

- **JCR Pharmaceutical's pabinafusp alfa:** A BBB-penetrating iduronate-2-sulfatase (IDS) for mucopolysaccharidosis II, and the first of the "brain shuttles" to be approved in a major market.
- **Roche's trontinemab:** TfR-based anti-amyloid-beta antibody for Alzheimer's disease, which demonstrated a significantly stronger pharmacodynamic effect than its first-generation predecessor, gantenerumab, which lacked a TfR-binding moiety. At 28 weeks, trontinemab achieved nearly 10-fold greater reduction in amyloid PET burden compared to gantenerumab[4,5] **(Figure 4)**.

Despite these advances, questions remain for the transferrin receptor approach. Off-target delivery of the therapeutic cargo is a concern given the ubiquitous expression of TfR[6], as are potential long-term safety issues associated with iron homeostasis, given the endogenous function of TfR[7]. Due to the relatively low degree of TfR extracellular domain sequence conservation between humans and common model organisms, clinical studies of different TfR-targeting moieties will be highly informative on the merits and pitfalls of this RMT mechanism[6].

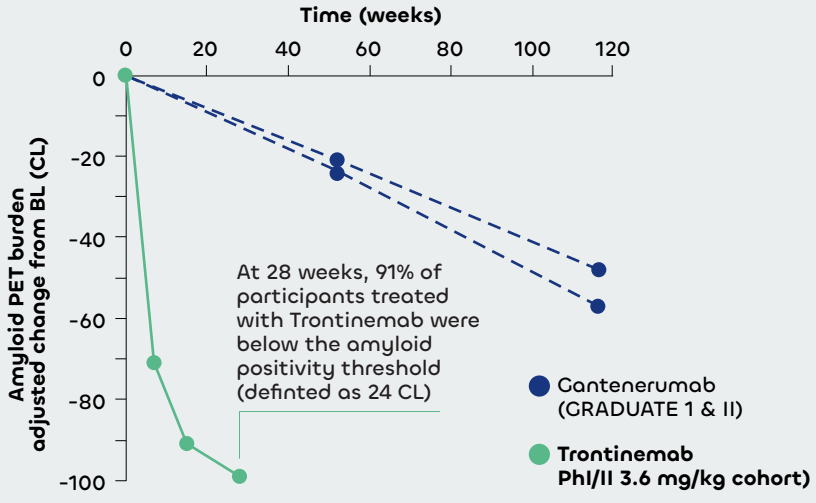


Figure 4. Brain shuttle enhances antibody-mediated brain amyloid beta clearance compared to the unconjugated antibody. Results for the change from baseline in brain amyloid burden on PET as measured in centiloids for anti-Aβ antibody Gentenerumab in GRADUATE I (NCT03444870) & GRADUATE II (NCT03443973) Phase III trials, and TfR-based anti-Aβ brain-shuttle antibody Trontinemab for 3.5 mg/kg dose cohort in ongoing PhI/II trial (NCT04639050). Trontinemab is based on Gantenerumab antibody. Data graphed based on published clinical trial data[3,4].

Beyond the transferrin receptor

Notably, a majority of the assets not making use of the TfR mechanism are targeting undisclosed receptors, indicating that the search for new RMT pathways is a highly competitive field of active research. Among disclosed targets, ABL Bio's insulin-like growth factor 1 receptor (IGF1R) platform has attracted significant industry interest with several high-profile licensing deals in recent years[8,9], though clinical proof-of-concept is still some time away with the recent deprioritization of Sanofi's α-synuclein-targeting SAR446159[10].

To improve on TfR, a new "brain shuttle" would ideally be specifically expressed in the CNS to reduce off-target delivery and have a sufficiently exposed extracellular domain for antibody binding that does not interfere with the endogenous function of the receptor. An obstacle inherent to identifying such receptors is the lack of sequence conservation between putative human receptors and their counterparts in relevant model organisms.

Cell-penetrating peptides (CPPs) and vesicular approaches take a different route, making use of the biophysical properties of the BBB. These approaches are less constrained by sequence conservation issues, but are still in early preclinical stages **(Figure 3)** and face the difficulty of limited CNS specificity.

The shared challenge: distribution within the brain

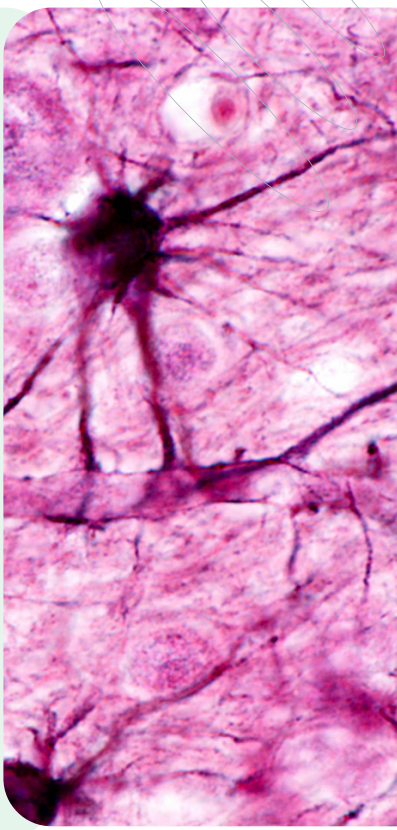
For both brain shuttles and other cell-penetrating technologies, the shared issue is drug distribution within the brain. Inside the CNS, different regions have varying degrees of relevance in disease pathology, for example, the substantia nigra in Parkinson's disease[11] and the amygdala and hippocampus in early Alzheimer's disease[12]. Not only does a therapeutic molecule need to enter the brain, but it needs to reach the target region at a pharmacologically relevant concentration; more imaging and quantitative data on the distribution of brain-penetrating biologics and oligonucleotides will be key in the ongoing development of these molecules.

Outlook: An innovation-driven field

Considering the high unmet medical needs and large patient populations in CNS diseases, it is unsurprising that there is significant industry interest in technologies to transport large molecules across the BBB.

What is striking, however, is *how* large multinational pharmaceutical companies have entered the field. With the exception of Roche, which developed trontinemab in-house, other multinational pharmaceutical companies have relied on in-licensing technologies from small- to mid-size biotechnology companies to gain a foothold in the field. This pattern suggests an area where innovation at the academic level can very rapidly translate into industry investment, and where drug discovery platforms with the potential of rapidly identifying novel RMT receptors could become key value generators in CNS drug discovery.

It's clear that, in the transport of therapeutic macromolecules across the BBB, there is a vibrant field of research and development that can be expected to yield exciting drug candidates in the years to come.



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Kai-Hsin trained at National Taiwan University before completing her PhD at the Max Planck Institute for Biophysical Chemistry in Göttingen, focusing on ribosome function and dynamics. During her PhD, she constructed a full kinetic mechanism of alternative ribosome-rescue in bacteria, gaining expertise in biochemistry, biophysics, and enzyme kinetics.

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Michael's scientific training spans Chemistry and Biochemistry at the Max Planck Institute of Biochemistry and LMU Munich, with research experience across leading institutions, including Harvard University, the German Center for Neurodegenerative Diseases, and the German Cancer Research Center. His doctoral work centered on developing molecular tools to investigate the biochemical principles of protein aggregation, with a focus on neurodegenerative disorders.

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