CRA Insights

Life Sciences

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Part I: A new era in CNS drug delivery: Crossing the blood brain barrier

The challenge

The blood–brain barrier (BBB) is a highly selective interface that shields the central nervous system (CNS) from pathogens and toxins, reducing the need for local immune responses and maintaining brain homeostasis.[1] However, this protective function severely limits therapeutic access: less than 0.1–0.2% of circulating monoclonal antibodies (mAbs) naturally cross the BBB, making it extremely difficult to achieve pharmacologically relevant concentrations in the brain without very high systemic doses.[2]

A breakthrough solution

Receptor-mediated transport (RMT) offers a breakthrough in CNS drug delivery. By engineering biologics to engage natural transport receptors on brain endothelial cells, this approach actively transfers therapies across the BBB.[3,4] A growing body of preclinical evidence and an increasing number of first-in-human studies demonstrate that receptor-mediated transport can significantly increase drug concentrations in the CNS, enabling improved efficacy and potentially reducing systemic exposure.[5,6,7]

Receptor options & design challenges

Several receptors can be targeted for brain delivery, such as TfR1, insulin receptor, CD98hc, GLUT1, and others with TfR1 being the most widely studied and used in clinical-stage programs. Despite the availability of various receptor options, making these tools safe and effective is anything but simple. Building a viable receptor-mediated transport technology requires years of engineering to:

- *Avoid interfering with the receptor's normal function*
- *Prevent the construct from getting trapped inside endothelial cells*
- *Ensure the therapeutic payload remains active after crossing the BBB*

Benefits of receptor mediated transport

- **Significantly higher brain exposure**

  RMT-based brain shuttles are shown to deliver up to 20-fold more mAb to the brain in preclinical models, enabling lower systemic doses

- **Broader CNS distribution**

  Improves penetration beyond perivascular spaces, potentially enhancing efficacy for diffuse targets

- **Platform versatility**

  Applicable to mAbs, enzymes, anti-sense oligonucleotides (ASOs), and small interfering RNA (siRNA), expanding therapeutic options for neurodegenerative and rare CNS diseases

Risks of receptor mediated transport

- **Peripheral receptor engagement & systemic risks**

  High-affinity or bivalent designs can disrupt normal receptor function and cause off-target effects, including hematologic or metabolic issues

- **Payload-specific risks persist**

  Higher brain exposure amplifies both desired and undesired pharmacology; inherent target biology risks (e.g., neuroinflammation) remain

- **Manufacturing complexity**

  Bispecific or engineered formats may increase CMC (Chemistry, Manufacturing, and Controls) challenges, scale-up costs, and regulatory scrutiny

Industry trends: Recent investments / developments for receptor-mediated transport technologies

Over the past two to three years, there has been significant industry investment and strategic collaboration in receptor-mediated drug delivery platforms aimed at overcoming the blood-brain barrier. These technologies are increasingly viewed as critical enablers for next-generation CNS therapies. Below is a summary of key recent developments and investments:

Date	Company	Therapeutic area	Investment	Details
Jan 2026	Novartis & SciNeuro	Alzheimer's disease	$165M upfront, up to $1.5B milestones	Novartis gains exclusive worldwide license to advance SciNeuro's antibody program, leveraging proprietary shuttle technology and developing therapeutic agents to treat Alzheimer's Disease.[8]
Nov 2025	Roche & Manifold Bio	Neurological and neurodegenerative diseases	$55M upfront, up to $2B milestones	Collaboration to utilize Manifold's mDesign direct-to-vivo AI-guided drug discovery engine and tissue-targeting shuttle portfolio to create "multiple next-generation BBB shuttles."[9]
Aug 2025	Novartis & BioArctic	Undisclosed target in neurodegeneration	$30M upfront; up to $772M milestones	Collaboration to develop a new candidate combining BioArctic's BrainTransporter™ (TfR-targeting) with a Novartis antibody.[10]
Jul 2025	Secarna Pharma & Vect-Horus	CNS indications	Undisclosed	Combining Secarna's OligoCreator® technology with Vect-Horus' VECTrans® platform to enable systemic delivery of oligonucleotide therapies across the blood-brain barrier.[11]
Jul 2025	Novartis & Sironax	Undisclosed	Up to $175M upfront and near-term	Novartis gains exclusive option to acquire Sironax's Brain Delivery Module (BDM) platform; receptor mechanism undisclosed.[12]
Jul 2025	Roche	Alzheimer's disease	N/A	At AAIC 2025, Roche announced plans for Ph3 trials of trontinemab, an amyloid-beta mAb engineered with Brainshuttle™ (TfR1-directed).[13,14]
Jul 2025	Acumen & JCR Pharmaceuticals	Alzheimer's disease	Not disclosed upfront; up to $555M milestones	Collaboration combines JCR's J-Brain Cargo® (TfR-targeting) with Acumen's amyloid beta oligomer (AβO)-selective antibodies.[15,16]

Jul 2025	Denali Therapeutics	Hunter Syndrome	N/A	Denali submitted BLA for Tividenofusp alfa, an enzyme replacement therapy leveraging TransportVehicle™ for enhanced brain penetration.[17]
Apr 2025	GSK & ABL Bio	Multiple - neurodegenerative diseases	£77.1M upfront; up to £2.075B milestones	Multi-program deal using ABL Bio's Grabody-B platform (IGF1R-targeting) for BBB penetration.[18]
Dec 2024	BMS & Bioarctic	Alzheimer's disease	$100M upfront; up to $1.25B milestones	Exclusive license for BioArctic's PyroGlu-Aβ antibody program leveraging BrainTransporter™.[19]
Oct 2024	Eli Lilly & Qinotto	Undisclosed	Undisclosed	Research collaboration and license agreement to discover next-generation antibody-based vehicles for brain transport using QinoTrans platform.[20]
Oct 2024	AbbVie & Aliada	Alzheimer's disease and other CNS diseases	$1.4B acquisition	AbbVie acquired Aliada and its MODEL™ platform targeting TfR and CD98 receptors for CNS delivery.[21]
Aug 2024	Denali & Biogen	Alzheimer's disease	N/A	Biogen returned rights to Denali's antibody transport vesicle (ATV):Aβ program; Denali advancing TfR- and CD98hc-targeting ATV molecules.[22]
Apr 2024	Eisai & Bioarctic	Alzheimer's disease	Not disclosed	Agreement to combine BioArctic's BrainTransporter™ with an Eisai Alzheimer's candidate.[23]
Jan 2024	Ionis & Vect-Horus	RNA therapeutics	Upfront payment in the double-digit million-dollar range	Exclusive license for a specified set of targets to utilize Vect-Horus' platform VECTrans for RNA-targeted therapeutics.[24]

Why Alzheimer's disease could showcase RMT's potential

Alzheimer's disease is emerging as the flagship indication for receptor-mediated transport (RMT) technologies. Current anti-amyloid antibodies face a critical limitation: the risk of amyloid-related imaging abnormalities (ARIA), which significantly constrain dosing and impact the benefit-risk profile. ARIA is strongly associated with vascular amyloid deposition and neuroinflammation resulting from antibody engagement in large cerebral vessels.

RMT offers a fundamentally different delivery paradigm. By enabling antibodies to cross the BBB through brain microvessels and capillaries, these technologies achieve a more uniform distribution across the brain parenchyma. This means antibodies can engage plaques directly rather than being trapped in larger vessels, reducing vascular stress and inflammation.

Preclinical studies and early human data suggest that RMT-enabled delivery may significantly reduce ARIA risk with anti-beta amyloid (Aβ) mAbs. While these early findings are promising, both safety and potential benefits, such as improved efficacy and optimized dosing regimens, remain under active investigation.

Implications & how CRA can help

Receptor-mediated brain delivery is not just an incremental innovation, it represents a paradigm shift in CNS drug development. By helping to overcome the blood-brain barrier related limitations, this technology may unlock new therapeutic potential, revive previously failed assets, and enable best-in-class profiles across efficacy, safety, and convenience. It opens doors to multiple CNS indications, from rare genetic disorders to highly prevalent neurodegenerative diseases.

This breakthrough will have significant implications for CNS portfolio strategy, including:

- **Portfolio reprioritization:** Identifying which existing or pipeline assets could benefit most from BBB-crossing technologies
- **Unlocking latent value:** Reassessing compounds that previously failed due to insufficient brain penetration
- **Therapeutic area expansion:** Assessing where enhanced brain delivery creates the strongest commercial upside
- **Competitive positioning:** Understanding how early adoption can shape leadership in next-generation CNS markets
- **Lifecycle management:** Exploring opportunities to extend product IP lifespans
- **Investment focus:** Redirecting R&D resources toward receptor-mediated delivery platforms to capture long-term value

How CRA Life Sciences can help

CRA combines deep CNS expertise with commercial and strategic assessment capabilities to help you:

Internally focused efforts

- Evaluate the impact of BBB-crossing technologies on existing and pipeline assets to prioritize high-value candidates
- Identify opportunities to unlock latent value in molecules previously constrained by brain penetration challenges
- Build robust business cases for investment in brain delivery platforms to ensure long-term value creation

Externally focused efforts

- Map unmet CNS needs and assess where innovation could create breakthrough opportunities
- Explore new therapeutic areas and indications for portfolio expansion leveraging receptor-mediated transport
- Track competitor activities, partnerships, and technology adoption to inform proactive positioning

Reach out to CRA Life Sciences team to uncover the true potential of your CNS portfolio and explore how brain delivery technologies can transform your long-term strategy.

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