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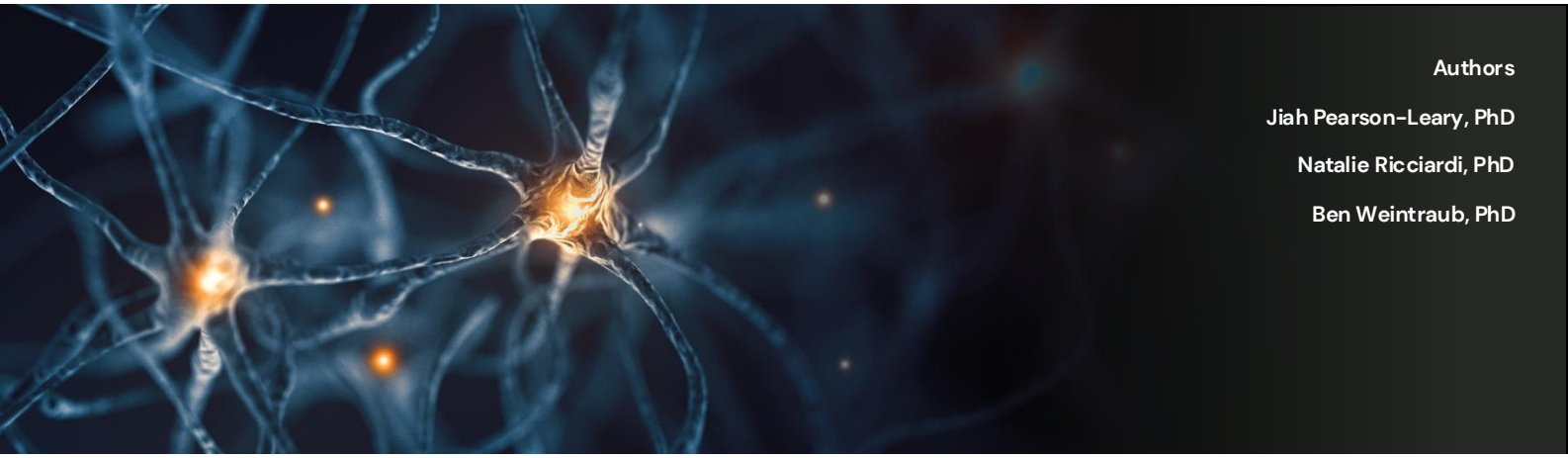

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Crossing the Blood-Brain Barrier

LOOKING BEYOND TFR1 SHUTTLES TO USHER A NEW ERA OF PROGRAMMABLE BRAIN-PENETRANT BIOLOGICS

The blood–brain barrier (BBB) has long constrained drug development for central nervous system (CNS) disorders, excluding nearly all biologics and nucleic acids. Yet recent scientific and clinical progress suggests this bottleneck can now be engineered. For investors and developers, three priorities emerge:

1 Receptor and scaffold diversification

The field's consolidation around transferrin receptor 1 (TfR1) antibody shuttles creates white space for alternative receptor targets (e.g., ALPL, LDLR, IGF1R) and smaller scaffolds (e.g., peptides and nanobodies) with differentiated pharmacokinetic and pharmacodynamic properties, and potentially-improved safety profiles (e.g., no anemia).

2 Oligonucleotide transport optimization

The largest opportunity lies in nucleic acid therapeutic delivery. TfR1 shuttles have been shown to limit oligonucleotide activity vs uptake with no carrier. New linkers and carrier formats will be required to move antisense oligonucleotides (ASOs) and siRNAs into the right cellular compartments.

3 Realistic development planning.

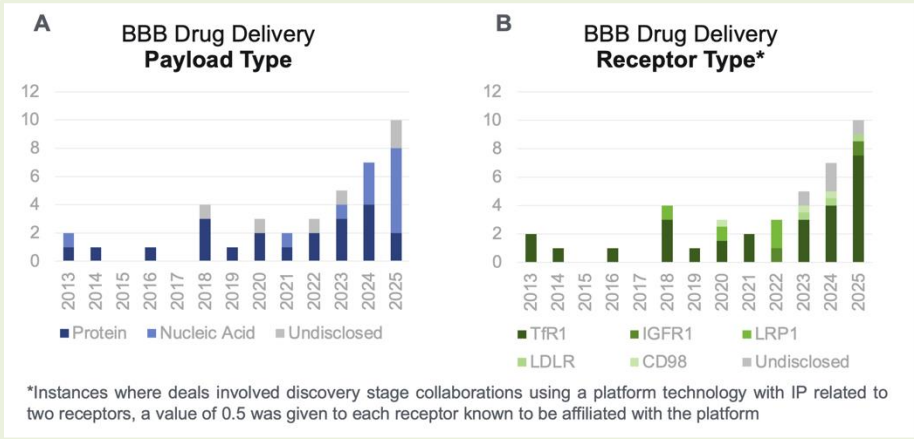
Brain shuttles are not fully modular leading to many stalled deals. Each payload–shuttle combination requires bespoke optimization, extending timelines and costs. Hybrid strategies that blend internal flagship assets with partnered programs may be best positioned to succeed, especially as pharma saturates its pipeline with partnered-shuttles.

New Era of Programmable Brain-Penetrant Biologics

Number of Partnership Agreements and Acquisitions for Neuro-targeted Delivery Platforms and Assets.

Figure 1: Deal Activity

After modest deal activity from 2013-21, deal activity has been increasing significantly each year
(A) Post-2021, nucleic acid payloads are taking center stage while protein-based payloads (including antibodies and enzyme replacement therapies [ERTs]) fade into second place.



(B) Investment is still aggregated around TfR1-based delivery systems although diversification in this second wave of deals is becoming more apparent.

Pharma's Race to Cross the BBB

The human brain's 400 miles of capillaries form one of biology's most selective barriers. Nearly 98% of large molecules fail to penetrate it, leaving biologics largely absent from neurology. Approved biologics for Alzheimer's disease (AD) highlight both the promise and limitations of current approaches. Lecanemab and donanemab effectively clear amyloid plaques, yet only about 0.1% or less of circulating antibody reaches the brain, and ARIA remains a significant safety concern.

The prospect of delivering these drugs more efficiently has ignited intense industry investment. Over the past five years, Roche, Denali, AbbVie, GSK, Novartis, and Takeda have all established brain-shuttle partnerships or acquisitions **(Fig. 1).** Roche's **trontinemab** and Denali's **DNL310** have become reference points for what may emerge as a new therapeutic class—systemically administered biologics that actively cross the BBB.

Field Focus: The Transferrin Receptor

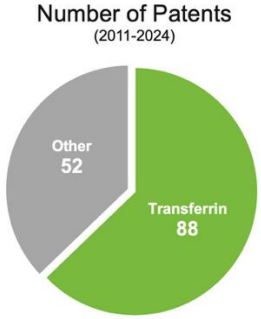
The modern brain-shuttle field has coalesced around the transferrin receptor (TfR1) pathway, first described by William Pardridge in the 1980s. Figure 2 shows the dominance of TfR1 among U.S. patents in the recent decade. TfR1 is highly expressed on brain endothelial cells and mediates receptor-mediated transcytosis (RMT) of iron-bound transferrin. Engineering antibodies to bind TfR1 with moderate affinity enables therapeutic cargo to "hitchhike" across this system. After decades of refinement, such shuttles now achieve brain uptake of 0.5–2% of the injected dose. While this increase is still modest, it's significantly higher than unmodified antibodies; whether this is clinically meaningful remains to be seen.

Roche's trontinemab provides the clearest clinical demonstration. By fusing an anti-amyloid antibody to a TfR1 shuttle, Roche achieved rapid amyloid clearance and <5% ARIA incidence, compared with 13–24% ARIA in lecanemab and donanemab trials. Another example, Denali's DNL310, a TfR1-based ERT for Hunter syndrome, reduced cerebrospinal heparan sulfate by 90% and improved cognition in pediatric patients, supporting the receptor's functional validity in humans for delivering ERTs.

These successes have established TfR1 as the default receptor in nearly all current brain-shuttle programs and partnerships. Out of 140 patents filed since 2011, 64% cite TfR1 constructs in core claims.

Figure 2: Number of Issued US Brain Shuttle Patents

IP landscape around non-viral BBB-receptor targeted drug delivery is TfR1 focused.



Overcoming TfR1's Limitations

Despite strong momentum, TfR1 shuttles are imperfect, imposing several liabilities:

- **Peripheral effects.** TfR1 is abundant on reticulocytes, and repeated dosing can reduce red-blood-cell production, leading to anemia. Although many constructs have been conducted to engineer out anemia, these efforts are mostly preclinical, and anemia remains a concern in human clinical trials.
- **Immunogenicity and receptor down-regulation.** Several shuttle platforms have shown anti-drug antibodies or reduced surface TfR1 after repeated exposure. Long-term impact in humans is unknown.
- **Endosomal entrapment.** Cargo often accumulates in endosomes or lysosomes rather than entering the cytosol or nucleus, which restricts the use of TfR1 for intracellular or genetic targets.

The perception that TfR1 is "clinically validated" is overstated. While clinical data confirm transcytosis and improved pharmacodynamics for some antibodies and ERTs, true proof of disease modification independent of the payload remains unproven. Even so, the receptor's familiarity, safety data, and entrenched IP ensure it will remain central to partnering strategies through the decade and continued efforts to optimize.

The Next Frontier: Nucleic Acid Therapeutics

The opportunity for brain shuttles is perhaps greatest for **nucleic acid medicines;** antisense oligonucleotides (ASOs), siRNAs, and gene-editing payloads. These constructs can modulate intracellular targets unreachable by antibodies. Hundreds of oligo-based CNS programs are in development, yet almost all rely on **intrathecal injection**, a burdensome route that delivers uneven distribution and carries infection risk, or other risks related to oligonucleotide toxicities, such as hydrocephalus.

TfR1 shuttles have had challenges delivering oligonucleotide; but this might be a class-effect for antibodies leveraging receptor-mediated transport for delivery. siRNAs require delivery to the cytosol while many ASOs must reach the nucleus. Studies from Denali showed that most oligos entering through TfR1 are degraded in late endosomes. Without optimized linkers or endosomal-escape chemistry, functional utilization remains low. Antibody carriers may also hinder oligo activity due to steric interference or insufficient release. Other tau-targeting ASO conjugates demonstrated reduced gene-knockdown efficacy compared with free ASOs, illustrating this challenge.

As a result, we expect a diversification of investment toward smaller, modular carriers such as peptides or VHH nanobodies optimized for the needs of oligonucleotides. In fact, many of the TfR1-oligo deals struck in the "first wave" of BBB partnerships have stalled or already been discontinued. Differentiated receptor and scaffold platforms may achieve better release kinetics and intracellular routing while avoiding anemia and immunogenicity. In the meantime, the field will likely pivot towards siRNA delivery as there are fewer barriers to cross (i.e. needs cytosolic delivery to RISC complex vs ASOs, which often require nuclear delivery). This will leave large unmet need for haploinsufficiency and loss-of-function diseases but may be sufficient for some diseases that require gene knockdown, such as Alzheimer's disease (e.g., MAPT) or Parkinson's diseases (e.g., SNCA). This clinical direction has already been observed, with Arrowhead and Lilly both conducting clinical trials for TfR1-shuttles delivering MAPT siRNA.

Even in these cases, knockdown has been limited in deep brain regions and it's not clear if this effect is enough for meaningful efficacy. The field needs to expand its efforts to move beyond TfR1-based antibodies in order to fully-unlock the potential of brain shuttles in genetic-driven neurological disorders.

Scale of the Unmet Need

The rationale for solving BBB delivery of oligonucleotides is overwhelming. Over **1,700 monogenic neurological disorders** have been identified, representing tens of thousands of potential genetic targets in the CNS. Even a fraction of these could support high-value rare-disease programs. The current reliance on intrathecal dosing restricts market reach to specialized centers and small populations. Systemically delivered, brain-penetrant oligo therapies could expand the addressable CNS market by tens of billions of dollars annually and enable treatment of common diseases such as Alzheimer's and Parkinson's through direct knockdown of **MAPT** and **SNCA, respectively**.

Partnerships, Patents, and Industry Traction

Partnership data reinforce how rapidly pharma is mobilizing, mostly still in the discovery and preclinical stage. **Novartis** recently completed the 2nd largest acquisition of 2025, buying **Avidity's** three, phase 3 TfR1-based antibody-oligo conjugate (AOC) assets in rare neuromuscular disorders for $12 billion. This is the latest and largest of a string of shuttle deals in CNS and neuromuscular therapeutic areas since 2023 for Novartis. **AbbVie's** 2024 acquisition of **Aliada Therapeutics** secured a proprietary TfR1/CD98 platform. **GSK–ABL Bio** ($2.5 billion) and **Novartis–Sironax** ($175 million) agreements followed, centered on IGFR1 and TfR1 antibodies, respectively. Meanwhile, **Ionis and Vect-Horus** are co-developing nanobody-based TfR1/LDLR shuttles for ASO delivery, signaling at least some diversification toward smaller scaffolds and differentiated receptors. **Roche's** $55 million upfront-partnership with **Manifold Bio** is expected to explore novel receptor targets while exemplifying the back-loaded, multi-billion-dollar ("biobucks"; in this case $2B) deal structures increasingly favored as pharma companies saturate their brain-shuttle portfolios.

Patent filings reflect this evolution. First-generation TfR1 constructs (priority 2014–2018) expire around 2034–2038, while newer filings extend into the 2040s. Most claim broad receptor-mediated transcytosis methods rather than single assets, raising barriers to entry and incentivizing collaboration with incumbents. Companies with differentiated receptors (e.g., LRP1 or IGF1R) or superior linker technologies will have strategic leverage as the field inevitably shifts beyond TfR1.

Outlook: From Antibody Transport to Genetic Medicine

The first FDA approval of a brain-shuttle therapy expected with Denali's DNL310 (ERT in Hunter syndrome) in 2026 will mark a turning point. By 2030, multiple BBB-enabled biologics should be in late-stage trials for Alzheimer's and lysosomal storage disorders, followed by systemically delivered oligonucleotide programs, predominantly delivering siRNA to knockdown genes.

We expect the field to evolve in three stages:

- **Validation Phase (2024–2026):** Proof of concept from DNL310 and trontinemab while pharma companies explore both partnered and internal R&D programs on shuttles, looking for unique ways to differentiate.
- **Optimization Phase (2026–2029):** Engineering improvements addressing TfR1 challenges and endosomal escape; proliferation of alternative carriers, and novel receptor targets as interest in oligonucleotide delivery expands.
- **Expansion Phase (2029–2032):** Entry of shuttled oligonucleotides for prevalent neurodegenerative and genetic diseases.

By 2030, the central question in neurology will shift from "Can we get this drug into the brain?" to "Which shuttle system delivers it most effectively?"

LEARN MORE ABOUT THE AUTHORS

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