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NEWSLETTER

SignalNeuro PARTNERS

Neurotherapeutics and Brain Health Intelligence Brief

Welcome to the inaugural issue!

SignalNeuro Partners is a boutique scientific due diligence and translational advisory firm specializing in neurotherapeutics and brain health. We bridge the translational gap between academic discovery and investment-grade insight, providing the scientific depth that investors, biopharmaceutical companies, and neurodevice developers need to evaluate assets, de-risk decisions, and identify opportunity.

This brief is a monthly publication covering emerging trends in neurotherapeutics and brain health: regulatory actions, clinical readouts, device approvals, and science at the intersection of neurology, neurotechnology, AI/ML and investment. As our readership grows, we will move to a weekly cadence to keep pace with a rapidly evolving field.

Each issue leads with a curated summary of the month's most consequential developments, followed by detailed scientific and strategic analysis through the SignalNeuro Partners lens. Our perspective is grounded in science — because in brain health, science is what matters.

Denes V. Agoston, MD PhD • Founder & CSO

MONTH IN BRIEF

A significant month for neurotherapeutics and brain health

"Rise of the Machines" (not Terminator 3)	Novel neuromodulation devices for memory restoration after traumatic brain injury (TBI) (Nia Therapeutics' Smart Neurostimulation System) and a wearable, non-invasive system for at-home treatment-resistant major depressive disorder (Neurolief Proliv™Rx, backed by BrainsWay).
Rise of Biomarkers	Growing FDA acceptance of surrogate biomarker-supported approvals in CNS therapeutics - from CSF heparan sulfate and serum Neurofilament light (NfL) in Hunter syndrom to GFAF mRNA suppression as a disease-modification endpoint in Alexander disease.
Rise of AI/ML	AI/ML emerges as a rapidly maturing tool in neuroprotective drug discovery: enabling a shift from single-target to multi-target strategies via multi-omics, creating digital twins for patient-specific treatment modeling, and predicting blood-brain barrier (BBB) penetration to replace lengthy and costly empirical screening.
"Uber" for Drug Delivery	Advancing a long-pursued field strategy, Denali's Transport Vehicle platform improves on earlier transferrin receptor (TfR)-based approaches from Genentech and Roche - to ferry enzymes and biologics across the BBB. Separately, intrathecal anti-glial acidic fibrillary protein (GFAP) mRNA offers a BBB-bypassing route for post-transcriptional knockdown of GFAP in Alexander disease.

1. "Rise of the Machines" – Neuromodulation Devices

Nia Therapeutics — FDA Breakthrough Designation for TBI Memory Restoration

Technology: Closed-loop, AI-guided brain stimulation recording neural activity from 60 channels across four brain regions. Machine-learning classifiers trained on each patient's own brain signals detect moments of impaired memory encoding in real time and deliver targeted electrical stimulation to the lateral temporal cortex.

Evidence: A randomized, sham-controlled study in neurosurgical patients with epilepsy and a history of moderate-to-severe TBI demonstrated a 19% improvement in memory recall with closed-loop stimulation; randomly timed stimulation produced no benefit, underscoring the importance of state-dependent delivery.

Unmet need: More than 4.3 million Americans live with TBI-related disability; no FDA-cleared or approved therapies exist for memory loss.

Next step: Breakthrough designation supports an IDE application in 2026 targeting a first-in-human early feasibility study, building on first in vivo validation in a large-animal model published in Brain Stimulation (January 2026).

SignalNeuro Partners' Perspective: *Nia's Breakthrough designation marks the FDA's first acknowledgment that TBI-related memory loss is a tractable target for active neurostimulation, not merely a chronic sequela to be managed. The 60-channel architecture represents an order-of-magnitude improvement over commercially available DBS devices (NeuroPace RNS: 6 channels; Medtronic Percept: 4 channels), enabling genuine state-dependent modulation.*

Neurolief Proliv™Rx — FDA PMA for At-Home Treatment-Resistant MDD

Device: First wearable, non-invasive, multi-channel brain neuromodulation system designed for at-home use, simultaneously stimulating multiple neural pathways. Indicated as adjunctive treatment for MDD in adults who have failed at least one prior antidepressant.

Commercial structure: BrainsWay completed an additional $6M milestone-based investment in Neurolief triggered by PMA approval, and retains a call option on full acquisition of Neurolief equity.

SignalNeuro Partners' Perspective: *The PMA approval and BrainsWay investment close illustrate the growing commercial appetite for at-home neuromodulation as an alternative to in-clinic TMS — a structural shift with direct implications for access, adherence, and health economics. The multi-channel simultaneous stimulation architecture distinguishes Proliv™Rx from single-pathway wearables and positions it as a platform device with potential indication expansion.*

2. Rise of Biomarkers - Regulatory Validation of Surrogate Endpoints

Denali Tividenofusp Alfa (Avlayah) — Accelerated Approval, Hunter Syndrome

Biomarker package: Accelerated approval rested on CSF heparan sulfate as surrogate endpoint — reductions of ~91% at 24 weeks, with 93% normalization. Serum NfL declined 21% by week 49 and 71% by week 104, providing longitudinal evidence of reduced neuroaxonal injury.

Clinical signals: Gains on Vineland Adaptive Behavior Scales (+33.8) and Bayley Scales of Infant and Toddler Development (+5.9), plus liver volume normalization and improved hearing thresholds.

Confirmatory path: Continued approval contingent on the ongoing Phase 2/3 COMPASS trial versus idursulfase.

SignalNeuro Partners Perspective: *The NfL arc (21% → 71% decline over two years) is among the most compelling demonstrations of longitudinal biomarker utility published in a rare CNS approval package. CSF heparan sulfate established target engagement behind the BBB; decreased serum NfL translated mechanism to neuroprotection. Together, they set a precedent for biomarker-driven neurotherapeutics approvals in CNS disease that extends well beyond Hunter syndrome.*

Ionis Zilganersen — Priority Review Accepted for Alexander Disease

Mechanism: Antisense oligonucleotide targeting GFAP mRNA via intrathecal delivery, suppressing the pathological astrocyte protein driving Alexander disease (AxD) — a rare, fatal neurological disorder caused by GFAP gene mutation resulting in astrocyte damage, Rosenthal fiber formation, and progressive neurological decline.

Regulatory status: Priority review accepted; PDUFA target date September 22, 2026. If approved, first disease-modifying therapy for AxD and Ionis's first wholly owned neurological commercial asset.

SignalNeuro Partners Perspective: *Zilganersen closes a striking translational loop: GFAP, long established as a circulating biomarker of astrocyte injury, is now the therapeutic target itself. Plasma GFAP dynamics under treatment could establish both a pharmacodynamic and surrogate endpoint template applicable across astrocytopathies more broadly — a biomarker-to-target inversion with significant pipeline read-across implications. Commercially, this marks a deliberate strategic inflection for Ionis: its first wholly owned CNS asset demonstrates that intrathecally delivered ASOs can reach regulatory maturity without a large pharma partner.*

3. Rise of AI/ML – Maturing Tool in Neuroprotective Drug Discovery

A new market analysis from BCC Research released this week characterizes AI/ML as a rapidly maturing tool in neuroprotective drug discovery, with several structural trends now evident:

Multi-target strategies: AI enables a shift from single target to multi-target approaches supported by multi-omics data integration, addressing the mechanistic complexity of CNS disease better than traditional reductionist models.

Digital twins: Patient-specific treatment modeling via digital twins allows in silico prediction of individual therapeutic responses, potentially transforming clinical trial design and patient stratification.

BBB penetration prediction: AI-powered tools are beginning to replace lengthy and costly empirical BBB screening, accelerating the identification of CNS-penetrant candidates earlier in discovery.

Market context: The neuroprotective agents market in North America is estimated to grow at ~4.5% CAGR through 2030, with AI-driven development timelines potentially accelerating this trajectory.

SignalNeuro Partners Perspective: *For CNS investors, the signal is not the market size estimate — it's the convergence of biomarker-informed patient stratification with AI-driven target identification as a de-risking strategy. This is precisely the translational gap that historically accounts for Phase 2–3 attrition in CNS, and where platforms with validated biomarker anchors carry premium value.*

4. "Uber" for Drug Delivery – Novel CNS Delivery Mechanisms

Denali Transport Vehicle Platform — BBB Transcytosis

Mechanism: Fusion protein combining iduronate-2-sulfatase (IDS) with Denali's proprietary Transport Vehicle (TV) — an engineered Fc domain targeting the transferrin receptor for receptor-mediated BBB transcytosis. Under FDA Priority Review (PDUFA date: April 5, 2026), tividenofusp alfa would be the first approved therapeutic to use an Fc-engineered TfR transport vehicle for CNS delivery.

Platform implications: The TV technology is designed to be modular across biologics, meaning the same delivery scaffold can be coupled to different therapeutic payloads targeting distinct CNS diseases.

SignalNeuro Partners Perspective: *Denali's TV platform approval is a landmark delivery validation: transferrin receptor–mediated transcytosis has now crossed the regulatory finish line, materially de-risking the broader CNS pipeline built on this mechanism. For investors, the question shifts from 'will it work?' to 'which payload is next?' — a modular delivery platform with FDA precedent is a structurally differentiated asset in the CNS space.*

Cont:

4. "Uber" for Drug Delivery – Novel CNS Delivery Mechanisms

Ionis Zilganersen — Intrathecal ASO Delivery

Delivery approach: Intrathecal administration delivers the antisense oligonucleotide directly into the CSF, bypassing systemic exposure and maximizing CNS parenchymal penetration to reach astrocytes throughout the neuraxis.

Disease context: Alexander disease is caused by dominant gain-of-function mutations in the GFAP gene, leading to toxic GFAP protein accumulation, Rosenthal fiber formation in astrocytes, and progressive neurological deterioration including developmental delays, seizures, and premature death.

SignalNeuro Perspective: *Intrathecal delivery validates a scalable paradigm for CNS-targeted ASOs in rare neurological disease. The route avoids hepatic first-pass metabolism and systemic immunogenicity risks while achieving high CNS drug levels — a delivery strategy now demonstrating regulatory maturity across multiple programs. Combined with the GFAP-as-target narrative, this approval would establish a new class of astrocyte-directed therapeutics.*