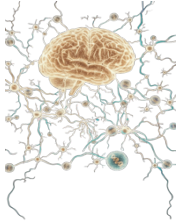

NEURON: Nano-Enabled Gene Therapies for Ultra-Rare and Orphan Neurological Disorders

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The context: a global translational bottleneck: A rare disease is defined as one affecting fewer than 1 in 2,000 people, but collectively rare diseases are common: over 7,000 conditions have been identified, with new disorders recognised every year as genomic and clinical research expands. Individually rare but collectively common, these conditions affect around 1 in 17 people – roughly 350–400 million globally and on average 3.5 million in the UK. Approximately 80% of rare diseases have a genetic origin and 75% present in childhood and are often monogenic; tragically, over 30% of affected children die before their fifth birthday and only ~12% of disease genes have an established outcome-modifying intervention. Families face a lifetime of complex and fragmented care, with profound consequences for education, financial stability, mobility, mental health, and overall quality of life. In the UK, reaching a correct rare-disease diagnosis still takes on average 5.6 years, involves consultation with eight clinicians, and includes three misdiagnoses; most families are then told that no approved treatment exists. Within paediatric neurology, the bottleneck is now translational rather than conceptual. Genomics has given us names for hundreds of ultra-rare neurogenetic disorders. We can design the right DNA- or RNA-based payload, but we cannot easily deliver it safely, repeatably, and at scale into a child's brain because of the blood–brain barrier (BBB) which is the missing layer in precision medicine: a biological fortress that excludes most large biologics and essentially all current gene therapies. Today's CNS gene therapies rely on adeno-associated viral (AAV) vectors administered via intracerebral or intrathecal surgery. These approaches have delivered isolated proof-of-concept successes – for example, eladocagene exuparvovec in AADC deficiency – but they are invasive, capacity-limited, hard to re-dose, and economically unsustainable, with per-patient costs often exceeding £1.7–2.8 million. It is estimated that rare diseases cost >$1T in annual costs in the US alone when direct and indirect costs are considered. Non-viral approaches exist but are incomplete. Antisense oligonucleotides (ASOs) and siRNAs can modulate transcripts within the CNS, and ASO drugs such as nusinersen and tofersen demonstrate that repeated intrathecal dosing can change the natural history of devastating disorders. Yet these "naked" oligos, delivered directly into the spine, demand lifelong procedures and offer no scalable route to treat hundreds of distinct, ultra-rare paediatric brain diseases. Engineered exosomes are biologically attractive but hard to industrialise, with "empty truck", "snowflake", "liver trap" and potential "Trojan horse" safety problems. Lipid nanoparticles (LNPs) have transformed liver gene therapy and enabled more than 13 billion mRNA vaccine doses, and the Baby KJ case has shown that LNP-encapsulated CRISPR base editors can rescue a fatal metabolic disease. But in the CNS, standard LNPs are filtered efficiently by the liver, lack BBB "keys", and distribute poorly even when injected into CSF. The corporate landscape reflects this imbalance. AAV-focused players such as PTC Therapeutics and Novartis provide the key precedents for CNS gene therapy, while companies like Taysha, Neurogene, Passage Bio, Lysogene, Coave and SwanBio, supported by platform capsid leaders including REGENXBIO, Voyager, uniQure, AskBio and Spark, push neurosurgical and intrathecal AAV deeper into monogenic brain diseases. In parallel, ASO and RNA specialists (Ionis, Biogen, WAVE, VICO, SynaptixBio, Dyne, Secarna and others), exosome developers (Aruna Bio, NurExone, Evox), non-viral genomic medicine platforms (Generation Bio, Beam, Sangamo) and individualised-therapy initiatives (n-Lorem, EveryONE Medicines, the UK Rare Therapies Launch Pad) are all advancing important pieces of the puzzle. Pre-clinically, non-viral Neuro-PERC which consists of monodisperse complexes of CRISPR ribonucleoproteins (RNPs) conjugated with endosome-escaping peptides, is administered using convection-enhanced delivery, and has shown efficient genome editing in multiple models and species, including mice and pigs. Neuro-PERC is being framed as a field-first demonstration of non-viral genome editing in large-animal brains. Taken together, this is a large, fast-moving field – but the same fundamental gap remains: **there is yet no safe, systemic, repeatable way to deliver gene therapies across the BBB for paediatric CNS diseases in the clinic**. That is the specific translational bottleneck NEURON is designed to unlock.

1. What NEURON is trying to do: NEURON aims to develop the first systemic, non-viral, biodegradable and totally bioeliminable nanoparticle platforms capable of reliably crossing the BBB after intravenous injection and delivering curative genetic payloads with cell-type precision. The programme will identify, validate and translate nano-enabled gene therapies for rare paediatric neurological disorders, running a full pipeline from automated molecular design through mice and pigs to IND/CTA readiness. The overarching objective is to address a long-standing global bottleneck: more than 700 genetic neurological disorders are diagnosable but remain untreatable in practice because existing delivery systems cannot cross the BBB at scale. Unlike a traditional biotech company (focused on a narrow set of commercial assets) or an academic grant (focused on early discovery), NEURON is structured as a **Focused Research Alliance (FRA)**, adopting the mission-led, public-goods ethos of a Focused Research Organisation. This structure allows us to build scientific, translational and regulatory assets that are inherently non-exclusive – predictive BBB datasets, standardised assays, regulatory standards and manufacturing templates – which commercial entities are disincentivised to create given the fragmented nature of the rare-disease market. **NEURON's concrete goals are to:**

- Achieve safe, systemic BBB transport with brain-wide biodistribution and cell-specific CNS targeting, reaching ≥0.5% injected dose per gram in capillary-depleted mouse brain and ≥1% in defined pig brain regions—i.e. several-fold higher brain uptake than typical values (~0.1% ID) reported for current targeted nanoparticles.
- Develop biodegradable, bioeliminable "molecular-lego" nanocarriers using an AI-driven **BioNanoAIChemi** automated discovery platform that integrates *in silico* design with *in biochemico* and *in vivo* testing.
- Apply these breakthroughs to advance at least one lead candidates – to IND/CTA readiness within five years.
- Define and publish a **Neuro-Nano-Safe** regulatory standard for nano-enabled CNS gene therapies.
- Train the next generation of CNS-focused scientists and innovators, embedding translational thinking, regulatory literacy and patient-centred design.

- Establish an evergreen 'Focused Research Alliance" (FRA) model to sustain NEURON beyond the initial five-year horizon and share scientific, manufacturing and regulatory knowledge through an open platform involving patient organisations, regulators, clinicians, academic partners, industry and initiatives such as the Rare Therapies Launch Pad.

2. How it is done today, and the limitations: A substantial fraction of rare diseases are neurological or neurodevelopmental, frequently progressive and life-limiting. Yet no systemic therapeutic modality currently exists that can safely and efficiently cross the BBB to deliver curative genetic payloads to the CNS. Viral vectors – predominately AAV – have shown that gene replacement or augmentation can rescue catastrophic paediatric disorders, but only under very constrained conditions. AAV vectors require neurosurgical or intrathecal administration, are immunogenic, cannot be reliably re-dosed, carry limited cargo, and often struggle to provide durable benefit in developing brains. Intracranial and intrathecal procedures demand highly specialised teams, expose children to significant procedural risk and achieve inconsistent tissue penetration, limiting therapeutic impact. Non-viral RNA-targeted therapies, especially intrathecal ASOs, have become the most clinically advanced CNS genetic medicines. They are powerful, but they remain bespoke, invasive and chronic. Exosome platforms offer biological elegance but face substantial challenges in loading, standardisation, biodistribution and safety. LNPs and related synthetic nanoparticles have transformed liver gene therapies and vaccines, as illustrated by Baby KJ, yet they remain trapped in a liver-first biodistribution profile and have not crossed the translational gap from rodent to human BBB delivery. Meta-analyses indicate that <1% of systemically administered nanoparticles accumulate in the brain using standard formulations, and substantially less (<0.1%) reaches the parenchyma where neurons reside. Meanwhile, the cost and complexity of AAV manufacturing and neurosurgical delivery are unsustainable for health systems and ill-suited to personalised or repeat dosing. Regulatory frameworks for nano-enabled CNS therapies are still nascent, creating uncertainty, delay and financial risk. NEURON will break this bottleneck by developing next-generation synthetic nanocarriers that enable systemic BBB crossing and cell-specific targeting after intravenous administration, and by working closely with partners such as the UK Rare Disease Consortium. **The goal is not incremental change but a paradigm shift:** to build the scientific, translational and regulatory foundations required to transform rare paediatric brain diseases from largely untreatable conditions into tractable, repeatable, precision-targeted therapeutic opportunities.

3. Why this is new, and why it will succeed. An AI-first, multi-scale view of the BBB: AI-based prediction of BBB permeability for small molecules is already highly advanced, exemplified by Lantern Pharma's predictBBB.ai™ platform, which reports around 89–92% accuracy. At the same time, major pharma is committing substantial capital to BBB delivery technologies, as illustrated by Roche's $2B deal to pilot Manifold Bio's protein shuttles to the brain. Recently an AI model designed to predict the BBB permeability of small-molecule ligands showed strong alignment with experimental results for BBB targeted LNPs conjugated with small molecule ligands, providing *in vivo* validation of its predictive capacity. Taken together, these developments show that AI-driven BBB solutions are technically mature and commercially validated for small molecules - creating a clear rationale for NEURON to bring comparable AI capability to complex modalities and nanomedicines**.** Qiu et al. present a large-scale, AI-driven framework to rationally design brain-targeting drug delivery systems by coupling machine-learning models with experimental validation in a "lab-in-the-loop" pipeline. Using a literature-derived dataset from ~9,500 nanomedicine papers and ~17,600 features, they show that ML models can accurately predict intracranial biodistribution, with particle size and zeta potential emerging as key determinants of brain delivery. Bayesian optimisation in this learned design space yields novel DDS formulations with experimentally confirmed improvements in brain targeting, and the data and framework are released as an open resource to support community-wide, rational design of brain-targeted nanomedicines. Building on this AI-centric paradigm, NEURON treats BBB transcytosis as a multi-scale modelling problem rather than a classical formulation exercise.

The **BioNanoAIChemi** platform integrates:

- graph-based molecular models of polymeric and hybrid nanoparticle chemistries.
- neurosymbolic neurovascular knowledge graphs capturing endothelial receptors, transporters, pericytes, astrocytes and neural cell types; and
- high-content experimental readouts from human BBB organoids, CNS co-cultures, mice and pigs generated within NEURON.

All data feed into a **digital twin of the BBB**, grounded in UK Biobank imaging, genomic and clinical data and aligned with the emerging PULSAR-style multi-scale foundation model work on brain vasculature and microstructure and cellular biochemistry. This provides a rigorous, state-of-the-art foundation for predicting transport, distribution and clearance in human-relevant neurovascular systems. **Extending AI beyond small molecules to nano- and gene-therapy carriers:** BioNanoAIChemi extends AI into a design space order of magnitude larger than traditional medicinal chemistry. It uses a modular, fully biodegradable mix and match "molecular-lego" architecture in which AI simultaneously optimises: the biophysicochemical properties of the nanoparticles including their molecular building blocks, linkers, charge, polydispersity, size, shape, loading efficiency, degradative routes via innate pathways, hydrophilic/hydrophobic balance, inherent pka and the ligand type and density, receptor features, multivalency, dosing regimens, nucleic acid type and delivery strategies, protein corona, PK, BD, ADME/Tox, repeat dosability. High-throughput robotic synthesis and nanoengineering enable rapid preparation of thousands of distinct nanoparticles. These are assayed in BBB organoids, CNS cell co-cultures and animal models for transcytosis efficiency, biodistribution, clearance, cell-type specificity (endothelial, pericytes, neurons, astrocytes), immunogenicity and acute toxicity. Active-learning algorithms continuously update the model, prune weak designs and focus the search on candidates most likely to cross the BBB safely after intravenous injection. AI has already transformed LNP stability and manufacturability for mRNA vaccines, for example by identifying formulations that remain potent after freeze-drying and room-temperature storage, eliminating the need for ultra-cold chains. NEURON generalises this paradigm to the brain: AI and digital twins become the primary engines for safe systemic CNS delivery, not an add-on.

Human–AI collaboration and ecosystem integration: NEURON plugs into the emerging "AI-scientist" ecosystem, using orchestrated AI agents to run continuous hypothesis → design → experiment → analysis loops dedicated to BBB delivery. In parallel, it exploits human–

AI collaboration through gamified or crowd-powered tools for BBB design and microvascular annotation, in the spirit of Foldit, with modern predictors underneath. This expands curated training data and engages the wider scientific and patient community. Feasibility is high because NEURON is grounded in validated materials: the proposed "molecular-lego" scaffolds already degrade via natural metabolic pathways, addressing key safety concerns. Current targeted nanoparticles achieve around 0.1–0.2% injected dose in pre-clinical brain parenchyma; NEURON's proposed 0.5–1% targets are ambitious yet plausible through optimised receptor-mediated transcytosis (for example via transferrin receptor or LRP1) and multi-ligand surface functionalisation strategies, refined through BioNanoAIChemi. From day one, NEURON is embedded in structured partnerships with MHRA and EMA under the Neuro-Nano-Safe framework, and with NHS delivery partners, Genomics England, Great Ormond Street Hospital, the Rare Therapies Launch Pad, the UK Rare Disease Consortium and the Cell and Gene Therapy Catapult. This alignment on analytical methods, comparability, safety endpoints and trial design reduces late-stage regulatory risk and shortens the path from discovery to first-in-child studies.

4. Who cares? For patients and families, NEURON's approach transforms rare paediatric neurological disorders from "incurable" labels into treatable – and in some cases curable – diseases. Early genetic diagnosis, combined with safe intravenous delivery, enables life-saving intervention while the brain is still plastic. Non-viral, systemic therapies remove the need for repeated neurosurgical procedures and anaesthetics, dramatically improving safety, accessibility and equity of access, particularly for children far from major neurosurgical centres. For healthcare systems, NEURON shifts the paradigm away from bespoke, seven-figure neurosurgical gene therapies toward repeatable, affordable intravenous formulations. By replacing biological vectors with chemically synthesised, biodegradable nanoparticles and building in continuous-flow, micro-batch-capable manufacturing, NEURON aims to reduce cost of goods to <£80,000 per treated patient and shorten time-to-dose from months to weeks. These features are compatible with newborn genomic screening and rare-disease diagnostic pathways, making precision CNS medicine realistic in public systems such as the NHS. For industry and investors, NEURON unlocks a new therapeutic class: systemic, non-viral CNS gene therapies supported by orphan-disease incentives, potential priority-review vouchers and a platform that can be applied across hundreds of indications. Instead of investing heavily in one or two bespoke assets, a £33 million investment in NEURON builds shared infrastructure and a delivery operating system that can power an entire generation of brain-targeted genetic medicines. For the broader scientific ecosystem, breakthroughs in BBB biology, AI-driven material design and regulatory standard-setting will have wide-ranging impact across oncology (brain metastases and primary gliomas), neurodegeneration (Alzheimer's, Parkinson's), psychiatric disease, neuroinflammation and systemic immune and metabolic disorders with CNS involvement. Publicly shared Neuro-Nano-Safe standards, datasets and manufacturing workflows will strengthen global translational capacity well beyond NEURON's initial portfolio.

5. Risks and how they are mitigated. To address the risk of insufficient BBB delivery, NEURON co-optimises payload potency, switching to self-amplifying RNA if necessary to ensure biological rescue rather than just exposure. Safety is managed using biodegradable, low-immunogenic materials and rigorous animal toxicity studies with strict "no-go" thresholds. Manufacturing and analytical consistency are ensured through standardised pipelines and GMP-ready continuous-flow production. Operational and talent risks are mitigated by co-designing NHS pathways and leveraging Imperial's ecosystem. Complexity and regulatory uncertainty are handled via strict KPIs, early MHRA/EMA engagement, and embedded ethical oversight. Commercially, the FRA will operate as a holding entity spinning out asset-specific companies to fund trials, while partnering with impact investors to ensure viability for ultra-rare indications.

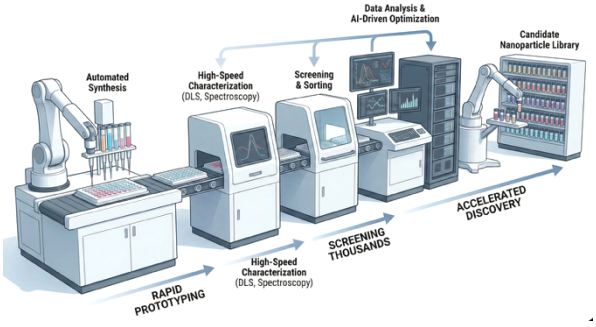
6. How much will it cost? We propose the creation of **NEURON Focused Research Alliance (FRA),** a £33M, 5-year initiative to build the world's first "BioNanoAIChemi" loop. NEURON will build a reusable platform and shared infrastructure rather than a single-asset programme.

The Roadmap:

- **Phase 1 (The Engine):** We will build an automated platform to synthesize and screen nanoparticle libraries at a scale previously impossible, using *in silico* to *in biochemico* translation identifying carriers that achieve ≥0.5% Injected Dose (ID) in the brain without relying on viral vectors.
- **Phase 2 (The Translation):** We will bridge the "rodent-to-human" valley of death using quantitative PET/qPCR in pigs, validating re-dosing durability and ≥1% ID in large, gyrencephalic brains.
- **Phase 3 (The Standard):** We will operationalize the platform for global utility. We will finalize IND/CTA packages for 4 indications affecting key BBB components: endothelial cells, neurons, pericytes, and astrocytes, reduce manufacturing costs to ≤£80k/patient, and release "**Neuro-Nano-Safe**" open standards for public use.

The Exit: By Year 5, NEURON will dissolve, leaving behind:

1. A Spin-out Company - ready to commercialize the lead assets.
2. An Evergreen Platform - a validated discovery engine available to the wider ecosystem.
3. A Regulatory Precedent - cleared path for non-viral CNS delivery.



7. Timeline and "exams" for success: NEURON is structured around clear mid-term and final "exams" that make progress legible and investable. By combining frontier AI-driven nanoengineering with a collaborative, philanthropic-venture model and a platform-first mindset, NEURON aims to redefine how rare paediatric brain disorders are addressed – making systemic, non-viral CNS gene therapy scalable, equitable and sustainable.