Artificial Intelligence and Stem Cell Therapy for Epilepsy:

Mechanisms, Clinical Evidence, and the Convergent Path to Seizure Freedom

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Abstract

Epilepsy affects approximately 50 million individuals worldwide, and nearly one-third remain refractory to all available pharmacological interventions — a population bearing enormous clinical, cognitive, and socioeconomic burdens. This paper presents a structured, evidence-based synthesis of two transformative and convergent fields: artificial intelligence (AI)-driven epilepsy diagnostics and regenerative stem cell therapy (SCT). We review the mechanistic rationale for cell-based seizure suppression, centering on the documented loss of inhibitory GABAergic interneurons in mesial temporal lobe epilepsy (MTLE) and the strategy of restoring excitatory–inhibitory (E/I) balance through transplantation of precisely differentiated neuronal subtypes. We then survey the state of AI in epilepsy care — encompassing seizure detection and prediction from multi-modal physiological signals, neuroimaging-based lesion identification, biomarker discovery, and personalized treatment stratification — before examining how AI optimizes each stage of the SCT pipeline, from cell characterization and in silico delivery modeling to post-transplant connectivity monitoring and patient outcome prediction. Clinical evidence is anchored to the first-in-human Phase 1/2 trial of NRTX-1001, a human pluripotent stem cell (hPSC)-derived GABAergic interneuron product, which demonstrated an 82% reduction in disabling seizure frequency and a favorable safety profile in drug-resistant temporal lobe epilepsy, with a Phase 3 randomized controlled trial planned for 2025. We further formalize key relationships within a mathematical framework — including a seizure-suppression dose–response model, a functional integration index, and a personalization optimization function — to enable rigorous quantitative evaluation of future trials. Remaining translational barriers are critically appraised, including dataset heterogeneity, immunosuppression burden, regulatory challenges surrounding sham-controlled trial design, and infrastructure requirements. The paper concludes that AI is not merely an ancillary tool but the essential computational backbone enabling individualized, neurorestorative epilepsy care, and that the convergence of these technologies offers a credible path toward disease modification and, ultimately, cure.

Keywords: *epilepsy · drug-resistant epilepsy · stem cell therapy · GABAergic interneurons · artificial intelligence · seizure prediction · neural integration · NRTX-1001 · personalized medicine · regenerative neurology*

1 Introduction

1.1 Clinical and Epidemiological Context

Epilepsy is among the most prevalent serious neurological disorders globally, affecting an estimated 50 million people across all demographic groups and geographies [1]. The disorder is defined by recurrent, unprovoked seizures arising from pathological hypersynchrony in neuronal networks, with aetiologies spanning structural lesions (e.g., hippocampal sclerosis, cortical dysplasia), vascular injury, neoplasia, infection, and genomic variation [3]. Beyond the immediate morbidity of seizures, patients face elevated rates of cognitive decline, psychiatric comorbidity, premature mortality, and profound socioeconomic disadvantage [1].

Current first-line management relies on anti-seizure medications (ASMs). Despite an expanding pharmacopoeial repertoire, approximately 30% of patients — those meeting criteria for drug-resistant epilepsy (DRE) — achieve neither sustained seizure freedom nor acceptable quality of life through pharmaceutical means alone [1]. Surgical interventions, including temporal lobectomy and laser interstitial thermal therapy, offer benefit to a subset of structurally eligible candidates but carry inherent risks of irreversible cognitive deficit, including memory and language impairment [7]. Neuromodulatory approaches such as deep brain stimulation (DBS) and responsive neurostimulation (RNS) represent a further tier of management, yet median seizure reduction plateaus around 70% after five years, with complete seizure freedom achieved in a minority [2].

These persistent limitations underscore a critical clinical unmet need and have motivated a paradigm shift: from symptomatic suppression to neurorestorative strategies targeting the cellular- and network-level pathology underlying epileptogenesis.

1.2 The Neurorestorative Hypothesis

Mesial temporal lobe epilepsy (MTLE), the most common form in adults and the most refractory to medication, is characterized pathologically by hippocampal sclerosis and, critically, by the selective depletion of inhibitory interneurons — neurons responsible for the release of γ-aminobutyric acid (GABA), the principal inhibitory neurotransmitter in the central nervous system [3,7]. This loss disrupts the excitatory–inhibitory (E/I) balance of hippocampal circuits, generating the sustained hyperexcitability and network hypersynchrony that drives seizure propagation.

The logical therapeutic inference from this pathophysiology is direct: if lost interneurons can be replaced with functional, precisely differentiated GABAergic inhibitory cells that integrate into host circuitry and restore inhibitory tone, seizure activity should diminish or cease. Stem cell therapy (SCT) represents the primary experimental vehicle for this hypothesis, with preclinical and emerging clinical evidence lending it substantial credibility.

1.3 Artificial Intelligence as an Enabling Technology

In parallel, artificial intelligence (AI) and machine learning (ML) are transforming the epilepsy care landscape across multiple dimensions: enhancing the sensitivity and specificity of seizure detection and prediction from complex multi-modal physiological data; enabling the identification of subtle epileptogenic lesions that elude conventional neuroimaging; facilitating data-driven patient stratification; and, critically, supporting the optimization of SCT development and deployment from cell manufacturing through post-transplant monitoring [14,16]. The convergence of AI and SCT is therefore not incidental — AI provides the computational architecture needed to realize the full potential of regenerative interventions in the heterogeneous, high-dimensional domain of human epilepsy.

1.4 Scope and Contributions

This paper makes the following structured contributions:

- A critical synthesis of the mechanistic basis, preclinical evidence, and current clinical status of stem cell therapies for epilepsy, with particular focus on the NRTX-1001 program.
- A comprehensive review of AI applications in epilepsy diagnostics, prognosis, and patient stratification.
- An analysis of how AI optimizes the SCT pipeline — from cell characterization through neural integration monitoring and outcome prediction.
- A formal mathematical framework for quantitative evaluation of seizure suppression, functional integration, and personalization in the context of AI-guided cell therapy.
- A candid appraisal of translational barriers and a forward-looking research agenda.

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2 Background and Related Work

2.1 Stem Cell Biology Relevant to Epilepsy

Several stem cell classes have been investigated as therapeutic substrates for epilepsy, each with distinct biological properties and translational profiles:

Human Pluripotent Stem Cells (hPSCs): Encompassing both human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs), hPSCs can be directed through defined differentiation protocols toward virtually any neural subtype, including the medial ganglionic eminence (MGE)-derived GABAergic interneurons critically implicated in MTLE pathology [6]. Patient-specific iPSCs further enable autologous therapeutic strategies that may obviate the need for immunosuppression and provide personalized in vitro disease models ('epilepsy in a dish') [4,33].

Mesenchymal Stem Cells (MSCs): Multipotent adult progenitor cells, frequently harvested from adipose tissue, MSCs exert primarily paracrine immunomodulatory and trophic effects within the CNS microenvironment. Their utility in epilepsy is hypothesized to derive from anti-inflammatory signaling and potential induction of endogenous neuroplasticity rather than direct neuronal replacement [8].

Neural Stem Cells (NSCs): Endogenous, self-renewing progenitors found in the subventricular zone and hippocampal dentate gyrus, NSCs offer intrinsic neurogenic capacity. Their utility in epilepsy research is

primarily investigational, with a focus on understanding activity-dependent neurogenesis and on whether exogenously administered NSCs can recapitulate or augment this process [36].

2.2 Prior AI Applications in Neurology

The application of AI in clinical neurology has grown rapidly over the preceding decade. Convolutional and recurrent neural network architectures have achieved expert-level performance on tasks ranging from fundoscopic diabetic retinopathy grading to MRI-based glioma classification. Within epilepsy specifically, foundational contributions include automated spike and seizure detection from EEG [17], computational models of epileptic network dynamics [42], and ML-based surgical outcome prediction [1]. The present paper extends this literature by examining AI's specific role within the SCT development and delivery pipeline — a domain that has received comparatively limited systematic treatment in prior reviews.

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3 Methodology

3.1 Literature Review Protocol

A systematic narrative review was conducted using PubMed, Scopus, IEEE Xplore, and bioRxiv/arXiv preprint servers with searches executed through May 2025. Search terms combined MeSH headings and free-text variants of: (epilepsy OR seizure) AND ("stem cell" OR "cell therapy" OR "interneuron transplant") AND ("artificial intelligence" OR "machine learning" OR "deep learning" OR "neural network"). Additional targeted searches were performed for specific named programs (NRTX-1001, PERSIST), clinical trial registries (ClinicalTrials.gov), and FDA designation records. Studies were included if they reported primary empirical data or provided authoritative methodological frameworks relevant to AI-enhanced epilepsy diagnostics or SCT. Commentaries and reviews were included selectively for contextual framing.

3.2 Data Synthesis and Analytical Framework

Extracted evidence was organized across four thematic domains: (i) AI in epilepsy diagnosis and prediction; (ii) stem cell mechanisms and preclinical evidence; (iii) clinical trial outcomes; and (iv) AI–SCT integration. Where quantitative performance metrics were reported (accuracy, AUC, seizure reduction rates), these are presented verbatim with original confidence intervals where available. Qualitative synthesis followed thematic coding to identify convergent findings, key limitations, and research gaps. Mathematical formulations (Section 4) were developed de novo by the authors to provide a unifying quantitative language for the AI–SCT interface.

3.3 Scope Limitations

This paper does not conduct a primary meta-analysis or pooled statistical inference across trials, given the heterogeneity in outcome measures and patient populations among the included studies. Clinical recommendations are not made; the paper is intended as a research synthesis and conceptual framework document. Readers seeking clinical guidance should consult current consensus guidelines from the International League Against Epilepsy (ILAE).

4 Mathematical Formulations

To support rigorous quantitative evaluation of AI-guided stem cell therapy, we introduce a set of formal constructs that can serve as analytical scaffolding for future trial design and computational modeling.

4.1 Seizure Suppression as a Function of Graft Dose

Let S(t) denote the normalized seizure frequency at time t post-transplantation, relative to pre-treatment baseline (S(0) = 1). We model the dose-dependent suppression effect of a GABAergic interneuron graft as a modified Hill equation:

$$S(t, D) = S_{min} + (1 - S_{min}) \cdot \exp(-k \cdot D^{n} \cdot t) \quad \text{(Eq. 1)}$$

where D is the transplanted cell dose (cells × 10^6), k is a patient-specific rate constant reflecting engraftment efficiency and host circuit receptivity, n is the Hill coefficient capturing dose–response cooperativity, and S_min is the theoretical seizure frequency floor (minimum achievable suppression). The term exp(-k · D^n · t) models the time-dependent accrual of inhibitory tone as grafted interneurons mature and form synaptic connections. This formulation predicts a monotonically decreasing seizure trajectory as dose increases at fixed t, consistent with preclinical observations for NRTX-1001 [9,12,13].

4.2 Functional Integration Index

We define a Functional Integration Index (FII) as a composite measure of the degree to which transplanted cells have successfully incorporated into host neural circuitry:

$$FII = \alpha \cdot C_{syn} + \beta \cdot C_{conn} + \gamma \cdot C_{inhib} \quad \text{(Eq. 2)}$$

where $C_{syn} \in [0,1]$ represents normalized synaptic density formed by grafted cells (assessable via immunohistochemistry or ultrastructural analysis), $C_{conn} \in [0,1]$ is a functional connectivity measure derived from resting-state fMRI or cortico-cortical evoked potentials comparing pre- and post-transplant network topology, and $C_{inhib} \in [0,1]$ reflects inhibitory efficacy indexed by EEG-derived reduction in interictal epileptiform discharge (IED) rate. The coefficients α, β, γ (with $\alpha + \beta + \gamma = 1$) are empirical weighting parameters determined from clinical trial data, representing the relative contribution of each connectivity domain to overall therapeutic integration. A composite FII approaching 1 corresponds to full functional integration; FII < 0.3 may serve as a threshold warranting dose escalation or adjunctive intervention.

4.3 AI-Driven Personalization Objective

The selection of optimal transplant parameters for an individual patient i can be framed as a constrained optimization problem over the space of therapy parameters θ = {D, L, T} (dose, anatomical placement, timing):

$$\theta^*_i = \text{argmax}_{\theta} \left[E[FII_i(\theta)] - \lambda \cdot Risk_i(\theta) \right] \quad \text{(Eq. 3)}$$

where $E[FII_i(\theta)]$ is the AI model's expected functional integration index for patient i under parameter set θ, $Risk_i(\theta)$ is a composite risk score (encompassing surgical morbidity, immunological rejection probability, and off-target graft effects) also predicted by the AI model, and λ is a risk-aversion hyperparameter tuned to patient preference and clinical context. This objective function operationalizes the clinical intuition that optimal therapy maximizes benefit while minimizing harm and renders the optimization problem tractable when sufficiently rich patient feature vectors (neuroimaging, genomics, EEG phenotype, clinical history) are provided as inputs to the predictive model.

4.4 Seizure Prediction Confidence Threshold

For closed-loop or preemptive clinical systems, an AI-based seizure prediction model generates a real-time probability $P(t) \in [0, 1]$ of imminent seizure onset. A decision function D(t) is defined as:

$$D(t) = 1 \quad \text{if } P(t) \geq \tau, \quad \text{else } D(t) = 0 \quad \text{(Eq. 4)}$$

where τ is a threshold selected to balance sensitivity and false positive rate for a given clinical application. In pre-ictal prediction windows of 30 minutes [20], empirically optimized τ values using CNN-BiLSTM architectures yield sensitivities approaching 97% in patient-specific models [22]. The formal specification of this threshold is critical for regulatory submissions and enables objective cross-study performance comparisons.

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5 AI in Epilepsy Diagnosis and Prediction

5.1 Electrophysiological Signal Analysis

Recurrent neural network (RNN) architectures — and their gated variants, LSTM and GRU — have demonstrated particular aptitude for time-series EEG data given their capacity to model long-range temporal dependencies [16]. Deep neural networks trained on large scalp EEG corpora have achieved detection of interictal epileptiform discharges (IEDs) that surpass the performance of expert neurophysiologists, a finding with direct clinical implications for presurgical evaluation of epilepsy [4]. The 1D CNN-GRU architecture, augmented with attention mechanisms, achieved 96.06% accuracy, 95.48% sensitivity, and an AUC of 0.9637 in epilepsy detection tasks using EEG [21].

Pre-ictal seizure prediction represents a more demanding task, requiring the model to identify subtle network perturbations preceding clinical seizure onset. Personalized CNN-BiLSTM models trained on individual patient physiological data from wearable sensors (blood volume pulse, electrodermal activity, heart rate, accelerometry, and skin temperature) demonstrated substantial performance improvement over generalized models, achieving prediction accuracies up to 97% for individual patients within a 30-minute pre-ictal window [22]. This personalization finding is mechanistically consistent with the high inter-patient variability in epileptic network signatures.

5.2 Neuroimaging and Lesion Detection

AI-powered convolutional neural networks applied to structural MRI enable detection of subtle epileptogenic lesions — including focal cortical dysplasia subtypes and hippocampal sclerosis — that remain invisible to standard radiological reporting [1,25]. At Mayo Clinic, machine learning applied to high-field 7T MRI with doubled spatial resolution has improved hippocampal segmentation and morphometric analysis, enhancing surgical candidacy assessment [25]. Multimodal approaches integrating diffusion tensor imaging (DTI) with ML — specifically, Random Forest analysis of white matter tract integrity — have enabled the lateralization of temporal lobe epilepsy and the longitudinal tracking of progressive structural changes [24].

AI has further been applied to develop unsupervised epilepsy taxonomies from structural MRI using subtype-and-stage inference, identifying distinct spatiotemporal atrophy trajectories that correlate with clinical phenotype and may predict therapeutic responsiveness [26]. This data-driven nosology represents a significant advance over purely symptom-based classification systems.

5.3 AI Models Summary

AI Model	Primary Application	Data Modality	Key Performance / Notes
RNNs	Seizure prediction; EEG signal interpretation	EEG time-series	Substantial gains over prior rule-based methods
Deep Neural Networks (DNNs)	IED detection; seizure prediction	Scalp EEG; wearable physiological signals (BVP, EDA, HR)	Outperformed human experts on IED detection [4]; up to 97% personalized accuracy [22]
CNNs	Neuroimaging lesion detection; epilepsy classification	MRI, PET, EEG	96.06% accuracy; AUC 0.9637 [21]
CNN-BiLSTM	Pre-ictal seizure prediction	Wearable physiological data	91.94% general; 97% patient-specific [22]
1D CNN-GRU + Attention	Epilepsy detection from EEG	EEG	Accuracy 96.06%, Sensitivity 95.48% [21]
Random Forest / XGBoost	Post-stroke epilepsy risk stratification	Clinical records (NIHSS, D-dimer, WBC)	AUC 0.99 [30]
Extended Graphical Models	Drug-response prediction; clinical phenotyping	Multi-modal clinical + genomic data	Superior modeling of dynamic, graph-structured data [4]
Subtype & Stage Inference	Epilepsy taxonomy; atrophy trajectory mapping	Structural MRI	Identifies subtypes by spatiotemporal atrophy pattern [26]
Explainable AI (XAI)	Clinical decision support for seizure prediction	EEG	Improves interpretability and clinician trust [31]

Table 1. Summary of AI model architectures and their applications in epilepsy diagnosis, prediction, and phenotyping.

5.4 Personalized Medicine and Biomarker Discovery

A critical theme across AI applications in epilepsy is the superiority of patient-specific models over population-level models, particularly for prediction tasks [22]. This motivates a precision medicine framework in which AI models are continuously refined on individual patient longitudinal data — an architecture directly applicable to post-transplant monitoring in SCT. Extended graphical models that encode multimodal clinical, genetic, physiological, and environmental data outperform conventional statistical approaches for modeling dynamic disease trajectories and predicting treatment response [4].

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6 Stem Cell Therapies: Mechanisms and Evidence

6.1 Mechanistic Rationale: Restoring E/I Balance

The excitatory–inhibitory imbalance hypothesis of MTLE provides a direct and falsifiable mechanistic target for SCT. Loss of MGE-derived, somatostatin- and parvalbumin-expressing interneurons from hippocampal subfields — documented consistently in human and rodent MTLE pathology — disrupts the lateral inhibition and feedback inhibition circuits that normally constrain pyramidal cell firing and prevent hypersynchronous discharge [3,7]. Transplantation of exogenous GABAergic interneurons, if they engraft, mature appropriately, and form functional inhibitory synapses on host excitatory neurons, should restore this restraint and reduce seizure propensity.

Critically, the precision of this approach — targeting a defined cell type to correct a defined neurochemical deficit — distinguishes it mechanistically from both nonspecific ASMs (which broadly modulate ion channels and neurotransmitter systems across the entire CNS) and current neurostimulation approaches (which electrically disrupt pathological activity without addressing underlying tissue pathology). This specificity also implies that therapeutic efficacy is directly contingent on the purity and functional identity of the transplanted cell population, with implications for AI-assisted manufacturing quality control.

6.2 NRTX-1001: From Preclinical to Phase 1/2

NRTX-1001 is the most advanced clinical-stage SCT product for epilepsy, consisting of highly purified hPSC-derived GABAergic inhibitory interneurons developed by Neurona Therapeutics. In murine kainic acid MTLE models, hippocampal transplantation of NRTX-1001 significantly reduced seizure frequency, decreased hippocampal dentate granule cell dispersion (a neuropathological hallmark of MTLE), improved survival rates in chronic models, and produced cells that dispersed locally, integrated into host circuitry, and generated inhibitory postsynaptic potentials that reversed electrographic hyperactivity [9,12,13].

The first-in-human Phase 1/2 open-label study (NCT05135091) enrolled adults with unilateral drug-resistant temporal lobe epilepsy with mesial temporal sclerosis. NRTX-1001 was administered as a single stereotactic intracerebral injection. As of July 2024, ten patients had received the investigational therapy, with no treatment-related serious adverse events reported. In the low-dose cohort, a median 82% reduction in disabling seizure frequency was observed over the 4–6 month post-treatment window, with 80% of participants achieving the predefined responder threshold of ≥50% seizure reduction. Additionally, preliminary evidence of cognitive improvement on select memory assessments was observed in a subset of patients [12].

Building on these findings, Neurona Therapeutics announced initiation of the Phase 3 EPIC trial for the second half of 2025 — a randomized, double-blind, sham-controlled multicenter study representing the first Phase 3 investigation of any human cell therapy for epilepsy. This milestone is supported by the FDA Regenerative Medicine Advanced Therapy (RMAT) designation [34]. Immunosuppression is currently required for approximately one year post-procedure to prevent allograft rejection, as NRTX-1001 is an allogeneic product.

6.3 MSCs and Combinatorial Approaches

Mayo Clinic investigators are pursuing a complementary strategy combining adipose-derived MSC transplantation with DBS for DRE patients unresponsive to single-modality interventions [8]. The rationale for MSC addition to DBS rests on their anti-inflammatory and trophic paracrine activity: MSCs may attenuate the neuroinflammatory milieu that perpetuates epileptogenicity, while DBS provides concurrent electrophysiological normalization. Early signals from this ongoing trial suggest safety and tolerability; long-term efficacy data are pending.

6.4 iPSC-Based Disease Modeling and the PERSIST Initiative

Patient-derived iPSC neuronal models — including both 2D cultures on microelectrode arrays (MEAs) and three-dimensional cerebral organoids — provide experimentally tractable, genetically authentic platforms for mechanistic studies and drug screening at scale [4]. The PERSIST project (Personalizing Epilepsy Regimes using Stem cells and artificial Intelligence models for Superior Treatment outcomes), a collaboration between the University of Queensland and Monash University, aims to integrate in vitro iPSC-derived organoid electrophysiology with patient genomics and clinical data through AI models to generate personalized drug efficacy predictions — a framework directly extensible to cell therapy candidate selection [5].

6.5 Clinical Trial Comparison

Therapy	Cell Type	Mechanism	Clinical Stage & Key Outcomes	Challenges
NRTX-1001	hPSC-derived GABAergic interneurons	Restore E/I balance; durable silencing via graft integration	Phase 1/2 (ongoing); Phase 3 planned H2 2025: 82% seizure reduction (low-dose); 80% ≥50% responder rate; no treatment-related SAEs [12]	Immunosuppression ~1 year; optimal dosing/placement TBD [7]
MSCs + DBS (Mayo Clinic)	Adipose-derived MSCs adjunct to DBS	Anti-inflammatory paracrine signaling; potential neural differentiation	Phase 1 (ongoing): early improvement in seizure management [8]	Long-term safety unclear; mechanistic interaction with DBS requires elucidation [8]
iPSC Brain Organoids (PERSIST)	Patient-derived iPSCs	In vitro drug screening; personalized efficacy profiling with AI	Preclinical/translational: identifies abnormal neuronal activity; drives AI predictive models [4,5]	Limited in vitro seizure-like fidelity; bridging gap to in vivo EEG validation [4]

Table 2. Comparison of major stem cell therapeutic strategies for epilepsy across preclinical and clinical development stages.

7 AI Optimization of the Stem Cell Therapy Pipeline

7.1 Cell Characterization and Manufacturing Quality Control

The therapeutic precision of NRTX-1001 — and the general principle that cell type specificity drives efficacy — creates a direct requirement for high-fidelity quality control in cell manufacturing. Deep neural networks trained on phase-contrast microscopy and transcriptomic data can track human pluripotent stem cell morphogenesis, predict differentiation efficiency, and identify aberrant cell populations prior to clinical release [41]. This application of AI directly addresses a fundamental bottleneck in scalable SCT manufacturing: ensuring that the final cell product contains the intended proportion of functionally appropriate interneurons with minimal contaminating populations that could generate unintended activity or neoplastic risk [40].

7.2 Computational Delivery Modeling

The stereotactic delivery of cell suspensions into a complex, heterogeneous biological medium introduces significant uncertainty regarding final cell distribution and engraftment zone. AI-augmented computational fluid dynamics models, informed by patient-specific structural MRI geometry, can simulate intraparenchymal infusion spread and predict optimal cannula placement, infusion rate, and volume to maximize target coverage while minimizing off-target deposition [43]. Cedars-Sinai investigators have developed ultrarealistic computational models of human epileptic brain circuits derived from patient biopsy tissue data, enabling in silico testing of therapeutic scenarios — including gene delivery and cell transplantation — before in vivo experiments [43].

Generative Adversarial Networks (GANs) extend this capability by enabling virtual experiments on synthetic brain organoid models, predicting how specific mutations or pharmacological perturbations alter organoid electrophysiology and thereby accelerating hypothesis generation for biological validation [20].

7.3 Post-Transplant Connectivity Monitoring

The ultimate biological goal of interneuron transplantation — functional integration and durable inhibitory innervation of the epileptic focus — requires sensitive monitoring tools to verify achievement in vivo. AI-driven dynamic connectivity mapping applied to resting-state fMRI time-series can quantify changes in network topology before and after transplantation, providing non-invasive evidence of graft-induced network normalization [20,44]. Cortico-cortical evoked potentials (CCEPs) offer complementary electrophysiological evidence of new effective connectivity.

At single-cell resolution, single-nucleus RNA sequencing (snRNA-seq) combined with AI clustering algorithms enables molecular characterization of transplanted cell identity, maturation state, and interaction with host cell populations — including potentially pro-epileptic microglial activation states [49]. Deep learning multitask networks trained to classify cell identity and predict electrophysiological perturbations from transcriptomic features provide a direct bridge from molecular phenotype to functional prediction [50].

Looking further ahead, neuromorphic computing platforms and 'biological computer' systems such as Cortical Labs' CL1 — which fuses cultured human neurons with silicon hardware — may offer real-time, high-resolution windows into graft–host circuit dynamics that surpass the temporal resolution of current neuroimaging and electrophysiology [48].

7.4 Patient Selection and Outcome Prediction

AI models integrating multi-modal preoperative data — including MRI volumetrics, EEG network features, iPSC-derived in vitro drug response profiles, and genomic risk scores — can be trained to predict individual patient likelihood of responding to SCT (as formalized in Eq. 3). The PERSIST framework exemplifies this approach, constructing patient-specific predictive models that combine in vitro organoid electrophysiology with clinical and genomics data [5]. Analogous ML models have already demonstrated an AUC of 0.99 for post-stroke epilepsy risk prediction using clinical variables [30], establishing proof of concept for AI-driven patient stratification in epilepsy.

Intraoperative AI-assisted stereotactic navigation offers additional precision, reducing targeting errors in cell delivery to subcortical structures and providing real-time feedback on cannula positioning relative to patient-specific anatomy [23].

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8 Discussion

8.1 Synthesis: A Convergent Paradigm

The evidence reviewed herein supports a coherent and compelling convergent paradigm: AI and SCT are not parallel technologies on independent trajectories but deeply interdependent components of a next-generation epilepsy care system. AI provides the data-analytical infrastructure to make SCT precise, personalized, and monitorable, and to scale it; SCT provides the biological intervention that AI's diagnostic and predictive capabilities are designed to optimize. Neither technology is sufficient on its own: the most sophisticated AI seizure prediction system cannot restore lost interneurons, and the most biologically potent cell graft cannot select itself, place itself, or verify its integration without computational support.

The 82% seizure reduction observed in the NRTX-1001 Phase 1/2 low-dose cohort [12] is a landmark result — not because it establishes definitive efficacy (Phase 1/2 samples are small, follow-up is limited, and placebo effects cannot be excluded without a sham-controlled comparator), but because it demonstrates that the biological hypothesis of E/I restoration via interneuron transplantation is viable in the human CNS. Phase 3 RCT data will be essential for determining whether this signal is replicated, durable, and causally attributable to the graft.

8.2 Translational Barriers

Several substantial barriers must be addressed before AI-guided SCT becomes a standard therapeutic option for DRE:

- **Published AI models for epilepsy are trained on datasets that differ markedly in EEG recording hardware, clinical phenotype, patient demographics, and outcome definitions. This heterogeneity compromises cross-study comparability and limits the generalizability of models to real-world**

clinical populations [15]. Multi-center data harmonization initiatives and federated learning architectures — which enable model training across distributed datasets without centralizing sensitive patient data — are essential priorities. Dataset Heterogeneity and AI Generalizability:

- **The current requirement for ~12 months of immunosuppression following allogeneic NRTX-1001 administration represents both a safety consideration (infection risk, metabolic side effects) and a patient burden that may limit uptake. Autologous iPSC-derived approaches could eliminate this requirement but would introduce substantial manufacturing costs and lead times. Immune-evasive cell engineering strategies, including HLA knockdown or PD-L1 overexpression, represent a potential intermediate solution [33].** Immunosuppression Burden:
- **The design of sham-controlled trials for invasive cell therapies in patients with refractory epilepsy presents genuine ethical complexity: sham stereotactic procedures carry procedural risk without therapeutic benefit, and equipoise may be difficult to maintain as open-label signal data accumulates. Innovative adaptive trial designs, Bayesian stopping rules, and external control arms constructed from historical data or real-world evidence may help reconcile scientific rigor with patient welfare [7].** Regulatory and Trial Design Challenges:
- **Specialized manufacturing of hPSC-derived cell products, cryopreservation logistics, stereotactic neurosurgical expertise, and AI-enabled monitoring infrastructure will initially concentrate this therapy at high-volume academic epilepsy centers. Ensuring equitable access across geographies and healthcare systems — including in low- and middle-income countries where the majority of the untreated epilepsy burden resides — will require deliberate health systems planning and international collaboration [19].** Infrastructure and Access Equity:

8.3 Future Research Priorities

The field would benefit from focused investment in the following research areas:

1. Long-term (> 5-year) follow-up from SCT trials to characterize the durability of seizure suppression and cognitive outcomes.
2. Development and validation of the Functional Integration Index (FII) formalized in Section 4.2 as a quantitative biomarker endpoint in clinical trials.
3. Multicenter, standardized iPSC biobanking and organoid electrophysiology protocols to enable robust AI training datasets for personalized therapy prediction.
4. Investigation of combinatorial approaches pairing interneuron transplantation with complementary neuromodulation, pharmacological adjuncts, or gene therapy to address residual seizure burden.
5. Explainable AI (XAI) frameworks applied to SCT patient selection models to ensure transparency, clinician trust, and regulatory approvability [31].
6. Prospective evaluation of AI-driven intraoperative navigation and real-time delivery optimization in stereotactic cell transplantation.

8.4 Limitations of This Review

This paper is a narrative synthesis and does not apply formal meta-analytic methodology; quantitative pooling of effect estimates across trials was not attempted, given the heterogeneity of outcome measures. Clinical trial evidence for SCT in epilepsy remains early-stage, with the largest human dataset comprising ten patients from a single Phase 1/2 study; conclusions regarding efficacy are therefore preliminary. The mathematical frameworks presented in Section 4 are theoretical constructs proposed to structure future research, not

validated clinical tools. The review focuses predominantly on MTLE and may not generalize to other epilepsy syndromes.

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9 Conclusions

This white paper has argued for and substantiated the proposition that AI and stem cell therapy are converging into a transformative paradigm for epilepsy care — one that moves decisively beyond symptom management toward the biological restoration of the diseased neural network. The case rests on three pillars:

First, the mechanistic precision of the GABAergic interneuron transplantation strategy, grounded in well-characterized MTLE pathophysiology, provides a biologically coherent and empirically supported rationale for regenerative intervention. The NRTX-1001 Phase 1/2 results demonstrate that this strategy can be implemented safely in humans and produces a substantial signal of seizure reduction.

Second, AI has achieved capabilities — in seizure prediction, lesion detection, phenotyping, and outcome modeling — that are qualitatively distinct from prior computational tools, enabling a shift from population-level to individually optimized epilepsy management. The consistent finding that personalized AI models outperform general ones reinforces the alignment between AI's core strength (individualization from high-dimensional data) and SCT's core requirement (patient-specific selection and delivery optimization).

Third, at every stage of the SCT pipeline — from cell manufacturing quality control through computational delivery modeling, post-transplant connectivity monitoring, and long-term outcome prediction — AI provides an indispensable layer of precision and intelligence that conventional clinical tools cannot replicate.

For the ~15 million people worldwide living with drug-resistant epilepsy, the convergence of these technologies represents more than scientific progress: it represents a credible, advancing path toward the historically elusive goal of seizure freedom through genuine neurobiological repair. Realizing this potential will require sustained interdisciplinary collaboration, harmonized data infrastructures, ethically rigorous trial design, and proactive attention to equitable access. The scientific foundation, however, is firmly established.

Conflict of Interest Statement

The authors declare no conflicts of interest with respect to the research, authorship, or publication of this article.

Data Availability

This article is a narrative synthesis. No original datasets were generated. All referenced data are available in the cited primary sources.

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