First-in-Human Study of NRTX-1001 GABAergic Interneuron Cell Therapy for Treatment of Focal Epilepsy - Emerging Clinical Trial Results.

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NEURONA THERAPEUTICS

NO – PHOTO / RECORD

CIRM CALIFORNIA'S STEM CELL AGENCY (TRAN1-11611; CLIN2-13355)

Rationale

This clinical study is investigating whether one-time transplantation of human GABAergic interneurons derived from allogeneic human stem cells (NRTX-1001) can lead to seizure control in drug-resistant mesial temporal lobe epilepsy (MTLE). Transplantation of human cortical-type GABAergic interneurons in the hippocampus of mice with kainate-induced mesiotemporal sclerosis can control focal seizures (Priest et al., 2021 AES poster 1.091; Bershteyn et al., 2023 CellStemCell v30:1331–50), with over two-thirds of the cell-treated animals becoming seizure-free, without producing lethargy, memory deficits, or other dose-limiting toxicities. The interneuron cell therapy also reduced hippocampal damage and increased animal survival. Interneuron cell therapy offers a novel approach to the potential treatment of human focal epilepsy that is regenerative and not tissue destructive.

Methods

This is a first-in-human Phase I/II clinical trial (NCT05135091). Subjects have unilateral MTLE with hippocampal sclerosis and focal seizures refractory to drug treatment. Testing includes EEG, imaging, tests of memory, mood, and assessment of visual fields. There is a 6-month retrospective baseline. Subjects receive immunosuppression beginning 1 week prior to surgery, tapering to discontinuation after 1 year. Cells are transplanted via stereotactic injection along the long axis of the hippocampus with intra-operative MRI imaging. The primary endpoint is safety, and the key secondary endpoint is seizure frequency from month 7 to month 12 post-transplant.

Data are reported as of 20 October 2023

Clinical Trial Design

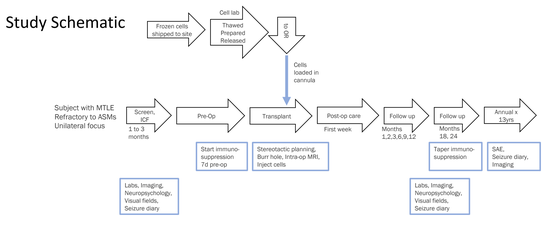
Key Inclusion Criteria

- Male or Female, age ≥18 to 65
- Focal seizures, clinically defined as TLE
- Has failed to achieve seizure control despite adequate trials of at least 2 ASMs at appropriate doses
- Currently on stable doses (at least 1 month) of approved ASMs
- Single seizure focus confirmed as within one temporal lobe; MRI shows MTS and EEG telemetry recording of seizures confirms focus
- Seizure frequency averages ≥2 per 28-day period over the 6 months prior to screening.
- If Dominant side focus, Verbal Learning <1.5 SD below mean

Key Exclusion Criteria

- Epilepsy due to other and/or progressive neurologic disease
- Significant other medical condition which would impair safe participation
- Primary or secondary immunodeficiency
- Suicide attempt in the past year
- Severe psychiatric disorders
- Chronic indwelling intracranial device
- MRI indicating potential malignant lesion
- Pregnancy, or currently breastfeeding

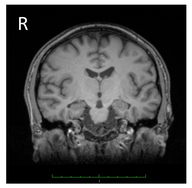
Study Schematic



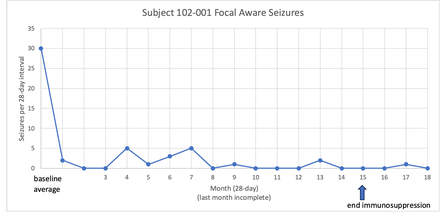
Abbreviations: ASM=Anti-Seizure Medication; BVMT=Brief Visuo-Spatial Memory Test; EEG=electroencephalogram; HLA=Human Leukocyte Antigen; MRI=Magnetic Resonance Imaging; MTLE=Mesial Temporal Lobe Epilepsy; MTS=mesial temporal sclerosis; OR=Operating Room; RAVLT=Rey Auditory Verbal Learning Test; SD=standard deviation; TLE=Temporal Lobe epilepsy

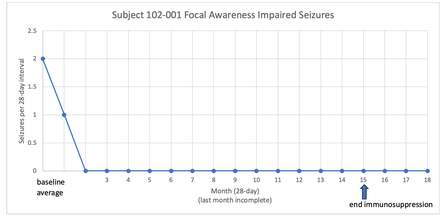
Subject 1: SUNY Upstate Medical University
Neurologist: Robert Beach; Neurosurgeon: Harish Babu

- Subject: 26-year-old male, seizure onset age 19
- Seizures: 30 focal aware/month; 2 focal awareness-impaired/month; no tonic-clonic
- Neurological exam: normal except nystagmus
- Neuropsych studies (past): mild visuospatial deficits
- MRI brain: right Mesial Temporal Sclerosis
- Video EEG study (depth): right hippocampal onset
- ASM: levetiracetam, lacosamide, clobazam, oxcarbazepine, as needed lorazepam



This subject underwent cell transplantation in June 2022, and tapered immunosuppressants beginning in June 2023, with discontinuation of immunosuppression by August 2023





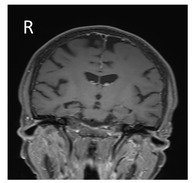
TERM (as reported)	SERIOUS	SEVERITY
bilateral hand tremors	No	Mild
GI upset	No	Mild
fatigue	No	Mild
constipation	No	Mild
weight loss	No	Moderate
tremor	No	Mild

Cognition tests	Baseline	6-month	9-month	12-month
Boston Naming Test	50	57	55	57
RAVLT sum # correct Immediate recall (5 trials)	27	34	34	39
RAVLT delayed free recall	2	6	4	7
RAVLT delayed recognition	8	9	10	12
BVMT delayed recall score	6	10	10	10
BVMT % retained	67%	91%	100%	100%

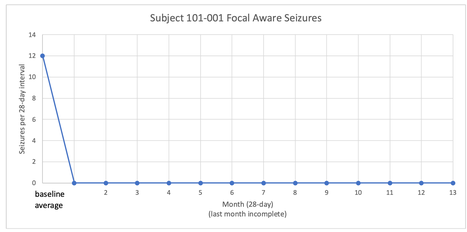
No antibodies to donor HLA type have been detected

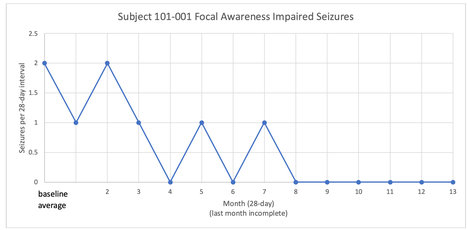
Subject 2: Oregon Health Sciences University
Neurologist: David Spencer; Neurosurgeon: Kim Burchiel

- Subject: 59-year-old female, seizure onset age 50
- Seizures: 12 Focal aware seizures/month; 2 focal awareness impaired/month
- MRI brain: right Mesial Temporal Sclerosis
- Video EEG study: right hippocampal onset
- ASM: Levetiracetam, lacosamide, clobazam and rescue benzodiazepines



This subject underwent cell transplantation in October 2022, and will taper immunosuppressants beginning in October 2023





TERM (as reported)	SERIOUS	SEVERITY
Delirium	No	Mild
Night Sweats without Fever	No	Mild
Resting Bilateral Hand Tremor	No	Mild
Intermittent Diarrhea	No	Moderate
Bladder Infection	No	Moderate
Hyponatremia	No	Mild
Anemia	No	Mild
Bladder Infection	No	Moderate
Syncope	No	Moderate

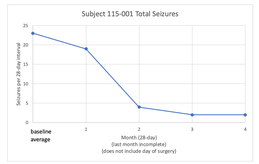
	Baseline	6-month	9-month	12-month
Boston Naming Test	58	54	53	Not yet avail.
RAVLT sum # correct Immediate recall (5 trials)	36	34	33	Not yet avail.
RAVLT delayed free recall	4	3	6	Not yet avail.
RAVLT delayed recognition	9	5	8	Not yet avail.
BVMT delayed recall score	6	6	6	Not yet avail.
BVMT % retained	67%	75%	86%	Not yet avail.

No antibodies to donor HLA type have been detected

Subject 3: University of California, San Diego
Neurologist: Jerry Shih; Neurosurgeon: Sharona Ben-Heim

- Subject: 38-year-old male, seizure onset age 22
- History of head injury
- MRI brain: left Mesial Temporal Sclerosis
- Video EEG: left temporal onset

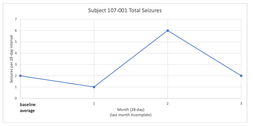
- Cell transplantation surgery in July 2023
- No serious adverse events



Subject 4: Rush University Medical Center
Neurologist: Rebecca O'Dwyer; Neurosurgeon: Sepher Sani

- Subject: 25-year-old male, seizure onset age 19
- MRI brain: left Mesial Temporal Sclerosis
- Video EEG: left temporal lobe onset

- Cell transplantation surgery in August 2023
- No serious adverse events

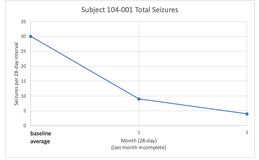


does not include seizure on day of surgery

Subject 5: Duke University Medical Center
Neurologist: Matthew Leudke, Neurosurgeon: Derek Southwell

- Subject: 27-year-old male, seizure onset age 24
- MRI shows right Mesial Temporal Sclerosis
- Video EEG: right temporal lobe onset

- Cell transplantation surgery in August 2023



Addenda 03-November: Subject hospitalized for focal to bilateral tonic-clonic seizure cluster; deemed not related to cell treatment, surgery, or immunosuppression

SUMMARY

- NRTX-1001 cells are differentiated to post-mitotic inhibitory interneurons

- Effective in mouse intra-hippocampal kainate model
- No detectible deficit on mouse behavior assays
- Safe in animal toxicology studies
- No migration outside graft site, no tumor growth

- Cells transplanted into hippocampal focus with Mesial Temporal Sclerosis

- First human trial underway with encouraging results
- NRTX-1001 has been well tolerated
- No significant surgical complications
- Favorable effects on seizure control
- No deterioration in modality-specific cognitive tests

- An additional 5 subjects to be recruited following DSMB review

- For additional information:
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