Webinar

RAPA Therapeutics Expanded Access Program: Epigenetically Reprogrammed T Stem Cell Therapy

James D. Berry, MD – mPI
Suma Babu, MBBS – mPI
Sabrina Paganoni, MD, PhD – mPI
RAPA Therapeutics – Regulatory Sponsor
NINDS - Funder
RAPA-501 Cell Product Overview
RAPA Cell Therapy Development Timeline

NIH R&D and Clinical Trials

- 2000-2017
  - R&D And Clinical Trials At NIH Clinical Center
  - Company Formation Spun out of NIH September 2017

RAPA Therapeutics Progress

- 2018-2024
  - ALS RAPA-501 in Patients Living With ALS
  - Cancer Trials
    - Currently In Phase 2 In Solid Tumors (RAPA-201)
  - Single Patient Compassionate Use IND
  - Phase 1/2 Trial
    - Phase 2/3
  - NIH-Funded Expanded Access Protocol
RAPA-501 Autologous T\textsubscript{REG}/Th2 Therapy of ALS

**Step 1**
Patient T-Cells are harvested through apheresis and shipped to RAPA.

**Step 2**
T-cells undergo DE-DIFFERENTIATION through RAPA’s proprietary epigenetic reprogramming.

**Step 3**
RAPA’s proprietary RE-DIFFERENTIATION process is completed in 1 week; T cells are sent back to treatment facility.

**Step 4**
RAPA-501 are infused (IV) back into patient for anti-inflammatory treatment. Cells are a “living drug”.
Mechanism of Action RAPA-501 $T_{REG}/Th2$ Cell Therapy of ALS

1. Multiple Inflammatory Cytokines/Chemokines
   - ATP

2. Inflammation Activates RAPA-501 (BioSensor)
   - ADP
   - AMP
   - Adenosine

3. Cytokine Receptors
   - CD39
   - CD73
   - PD1
   - PDL1

4. Killing Blocked

5. Pathogenic Th1 Cells
   - iT$_{REG}$
   - Th2
Conventional Pathways of T_{REG} Development

RAPA-501 Proprietary Two-Step Process For Induced (i) T_{REG}/Th2 Cell Generation

STEP 1: De-differentiation
- mTORC1/mTORC2 Inhibition

STEP 2: Re-differentiation
- Novel T_{REG}/Th2 “Hybrid” Phenotype

(Nishimoto and Kuwana; Seminars in Hematology, 2013)
RAPA-501 Therapy of ALS/Neurodegenerative Disease and Autoimmunity: Epigenetically Reprogrammed

mTORC1 and mTORC2 Blockade
Erases Inflammatory Fate
Permits Reprogramming

mTOR: OFF
Anti-Apoptosis

Th2/TREG Fate
CD39+
CD73+
CD103+
CD150+
IL-4+
IL-10+

Central Memory
Check Points Removed

Metabolic Fitness
Allows T Cell Therapy Without Conditioning Chemotherapy

Multi-Faceted Immune Suppressive Function
Th2 Cytokines
Homing Molecules
Inflammasome Inhibition

T Stem Memory and Checkpoints Removed
Long-Lasting In Vivo Effects
RAPA-501 Express Both FOXP3 and GATA3 Transcription Factors

**T\_REG Factor, FOXP3**

- **Start of Culture**: 1.1%
- **Th2/T\_REG Product**: 37.3%

**Th2 Factor, GATA3**

- **Start of Culture**: 0.1%
- **Th2/T\_REG Product**: 33.5%
RAPA-501 Express a T Stem Cell Phenotype

**Graph:**
- x-axis: Day 0, RAPA-501, Control
- y-axis: Frequency (%)
- Bars: CD4+CD150+, CD8+CD150+

**Diagram:**
- Various Forms of “Stem Cell Therapy”
  - Neurologic Stem Cell
  - Hematopoietic Stem Cell Transplantation
  - Immune T Stem Cell

**Legend:**
- Various Trials In pwALS
- Standard Therapy of Blood Cancers
- RAPA-501 Trials In pwALS
RAPA-501 Up-Regulates PD1 Checkpoint on Inflammatory T Cells

PD1 Checkpoint Upregulation

- Activation of T_{REG}/Th2
- Modulation of PD-1 by T_{REG}/Th2

Inflammation Driven By Low PD1

- Th1/Tc1_{AUTO} Cells (48 hr)

RAPA-501 Increases PD1 Checkpoint

- Th1/Tc1_{AUTO} Cells (+RAPA-501) (48 hr)
RAPA-501 Suppresses Human CNS Inflammatory Microglial Cells

CNS Microglial Assay

Activation of T<sub>REG</sub>/Th2

Suppression by T<sub>REG</sub>/Th2

RAPA-501 T<sub>REG</sub>/Th2

IL-6 Secretion

IP-10 Secretion

IFN-α Secretion

HMC3

CNS Microglial

IFN-α

LPS

IL-6

IP-10

IFN-α

HMC3

HMC3 + RAPA-501

HMC3

HMC3 + RAPA-501

HMC3

HMC3 + RAPA-501
RAPA-501 Phase I Completed in Patients Living With ALS
Very Good Safety (No Product-Related Adverse Events) and Clear Biological Effect

Rapid and Durable Anti-Inflammatory Effect
(MDC Levels; UPN 01-003)

Consistent Anti-Inflammatory Effect on Phase 1
(MDC Levels; Phase 1 Patients)
RAPA-501 EAP Study Overview
NIH Funded RAPA-501 Expanded Access Protocol

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Sean M. Healey & AMG Center for ALS awarded NIH U01 Grant to support Rapa Therapeutics’ Expanded Access Protocol of Epigenetically Reprogrammed RAPA-501

The Sean M. Healey & AMG Center for ALS at Massachusetts General Hospital has been awarded a three-year grant to support Rapa Therapeutics’ intermediate size Expanded Access Protocol (EAP) in Amyotrophic Lateral Sclerosis (ALS) from the National Institute of Neurological Disorders and Stroke (NINDS) at the National Institutes of Health (NIH). The grant is supported by the ACT for ALS (Accelerating Access to Critical Therapies for ALS Act). This EAP will evaluate the benefits of Rapa Therapeutics’ (Rapa) investigational product RAPA-501, an Epigenetically Reprogrammed Autologous Hybrid T\textsubscript{REG}/Th2 T-Stem Cell Therapy, in people living with ALS (pwALS). The project will be led by Healey & AMG Center faculty, Drs. Suma Babu, MBBS, MPH James Berry, MD, MPH and Sabrina Paganoni, MD, PhD in conjunction with Rapa.

(ClinicalTrials.gov, Protocol Identification Number, NCT06169176)
NIH NINDS Expanded Access Program in ALS
- Grant program for research using data from expanded access to investigational drugs
- Specifically designed for individuals not otherwise eligible for ALS-related clinical trials
- Funded by ACT for ALS
- Must not interfere with ongoing clinical development

Defining the EAP Population
- Slow Vital Capacity (SVC): must be < 50% of predicted normal value
- Otherwise relatively open inclusion criteria
  - sporadic or familial
  - El Escorial Criteria ➔ possible or greater category
  - OK to continue other medications
  - No restriction on time from diagnosis
- NOTE: must have sufficient immune T cells for RAPA-501 manufacturing
  - CD3+ T cell count >/= 500 cells per microliter
AIM #1: Accrual/Involvement
- 40 participants
- Offer access to RAPA-501 to participants unable to access it in trials
- Help ensure prompt accrual of a diverse population of people living with ALS

AIM #2: Data Collection
- Safety/Tolerability
- Effects on Immune Function and NfL (blood collection)
- ALSFRS-R, ROADS, and Vital Capacity
- Remote Monitoring (Everything ALS):
  - Proctored Sessions approximately every 2 weeks
  - Home Data Collection (Everything ALS):
    - Surveys (ALSFRS-R and ROADS)
    - Respiratory Pulmonary Function Testing (SVC, Zephyrx Spirometer)
    - Speech Analysis (Aural Analytics)
    - Accelerometry Activity Monitoring
Scope of Study
- 40 participants
- 10 ALS trial centers

Primary Objective
- Provide PALS with Access to RAPA-501
- Evaluate the Feasibility and Safety of RAPA-501 in plwALS and VC<50%

Secondary Objectives
- Characterize Immune System Pre- and Post-RAPA-501
- Assess NfL changes
- Monitor Clinical Measures (ALSFRS-R, ROADS, VC)
- Use the Origent Prediction Algorithm to create “synthetic” controls and determine potential effect on ALSFRS-R, VC, and Survival

Exploratory Objective
- Collect data from participants in their homes using simple to use tools provided by the study
- Collaboration with Everything ALS
RAPA-501 EAP: Potential Clinical Trial Sites

- Providence Portland
- UCSF
- UC-Irvine
- Barrow Neurological Institute
- Mayo Phoenix
- University of Iowa
- University of MINN
- MGH
- Hackensack
- Emory
Interested PALS

Screening Visit

40 Participants

Apheresis

Infusion Visit #1

Infusion Visit #2

Infusion Visit #3

Infusion Visit #4

2 Monthly Remote Follow-up Visits

Everything ALS Remote Monitoring: Surveys, Speech, VC, and Accelerometry
# RAPA-501 EAP: Schedule of Activities

<table>
<thead>
<tr>
<th>Procedure</th>
<th>SCREEN</th>
<th>APHERESIS</th>
<th>Cycle 1 Day 1 (d 35)</th>
<th>Cycle 2 Day 1 (d 77)</th>
<th>Cycle 3 Day 1 (d 119)</th>
<th>Cycle 4 Day 1 (d 161)</th>
<th>Follow-up Visit (d 190)</th>
<th>Virtual Follow-Up (d 220 and 250)</th>
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Clinical Trial Participants and Families
NIH NINDS Expanded Access Program
Dr. Berry and Entire Team at Mass General
   - Megan Okoro, Clinical Research Coordinator
Entire Team at RAPA Therapeutics
   - Jenny Sunga and Sylvia Yip
Clinical Research Organization, Ozmosis

Clinical Trial Sites
Origent Data Sciences
Everything ALS
The ALS Association
ALS Northwest
RAPA Therapeutics Expanded Access Program:
Epigenetically Reprogrammed T Stem Cell Therapy

Questions and Answers

Questions about Participation:
Megan Okoro – mokoro@mgh.harvard.edu