Healey & AMG Center

Sean M. Healey & AMG Center for ALS
at Massachusetts General Hospital

National Institute of Neurological Disorders and Stroke

EVERYTHINGALS
CARE TO CURE

RAPAtherapeutics

Webinar

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


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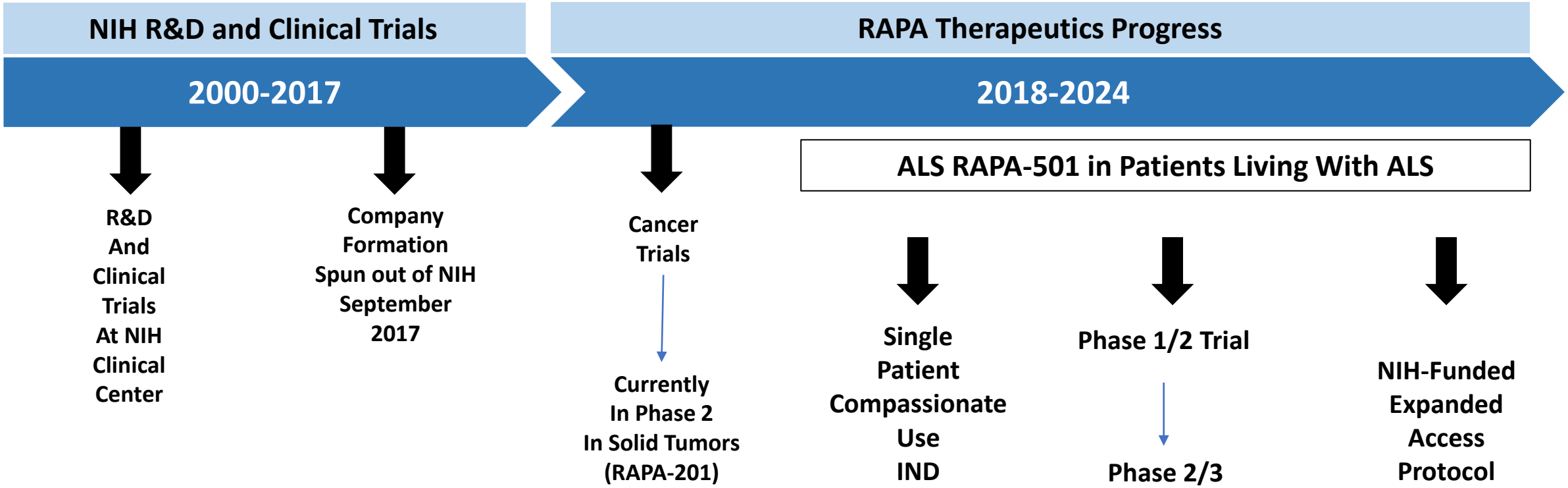
**RAPA Therapeutics – Regulatory Sponsor**
**NINDS - Funder**

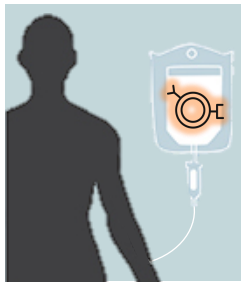
# RAPA-501 Cell Product Overview

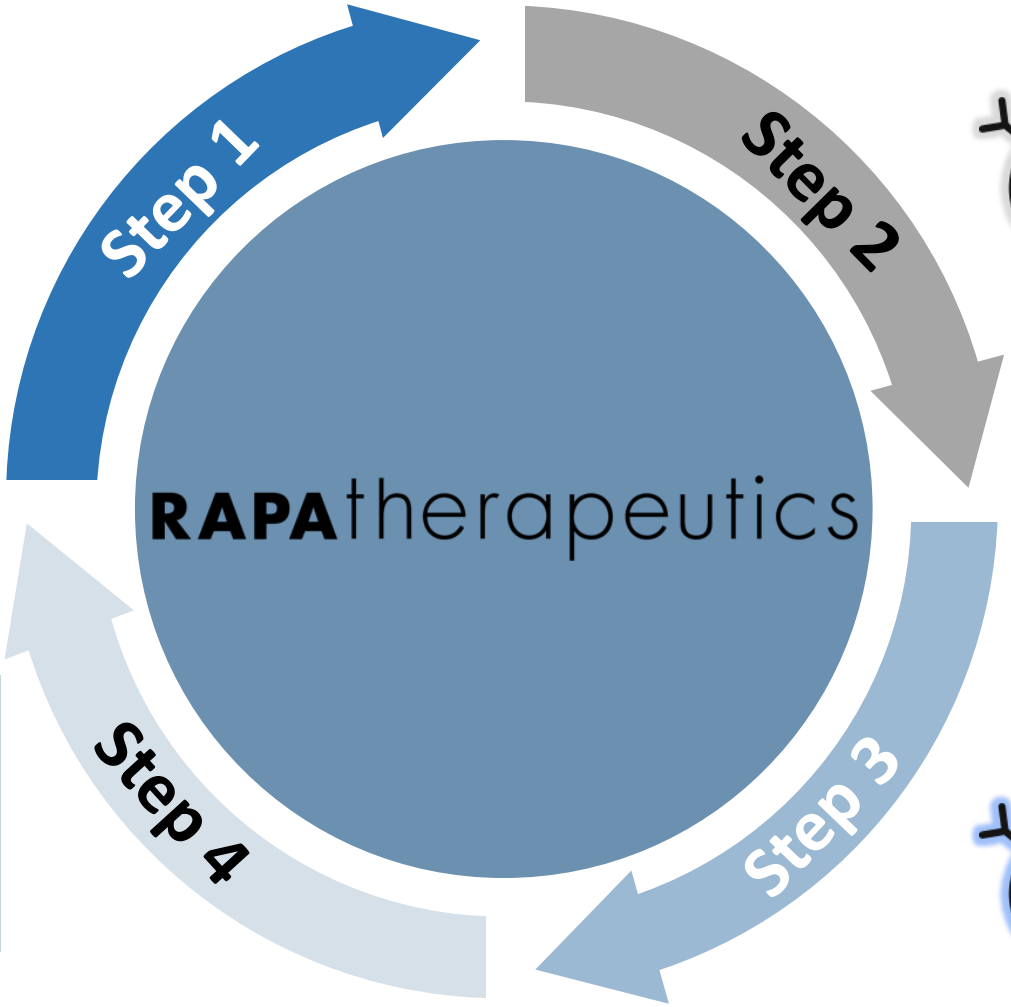
# RAPA Cell Therapy Development Timeline



# RAPA-501 Autologous $T_{REG}$/Th2 Therapy of ALS

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

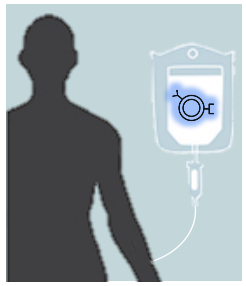




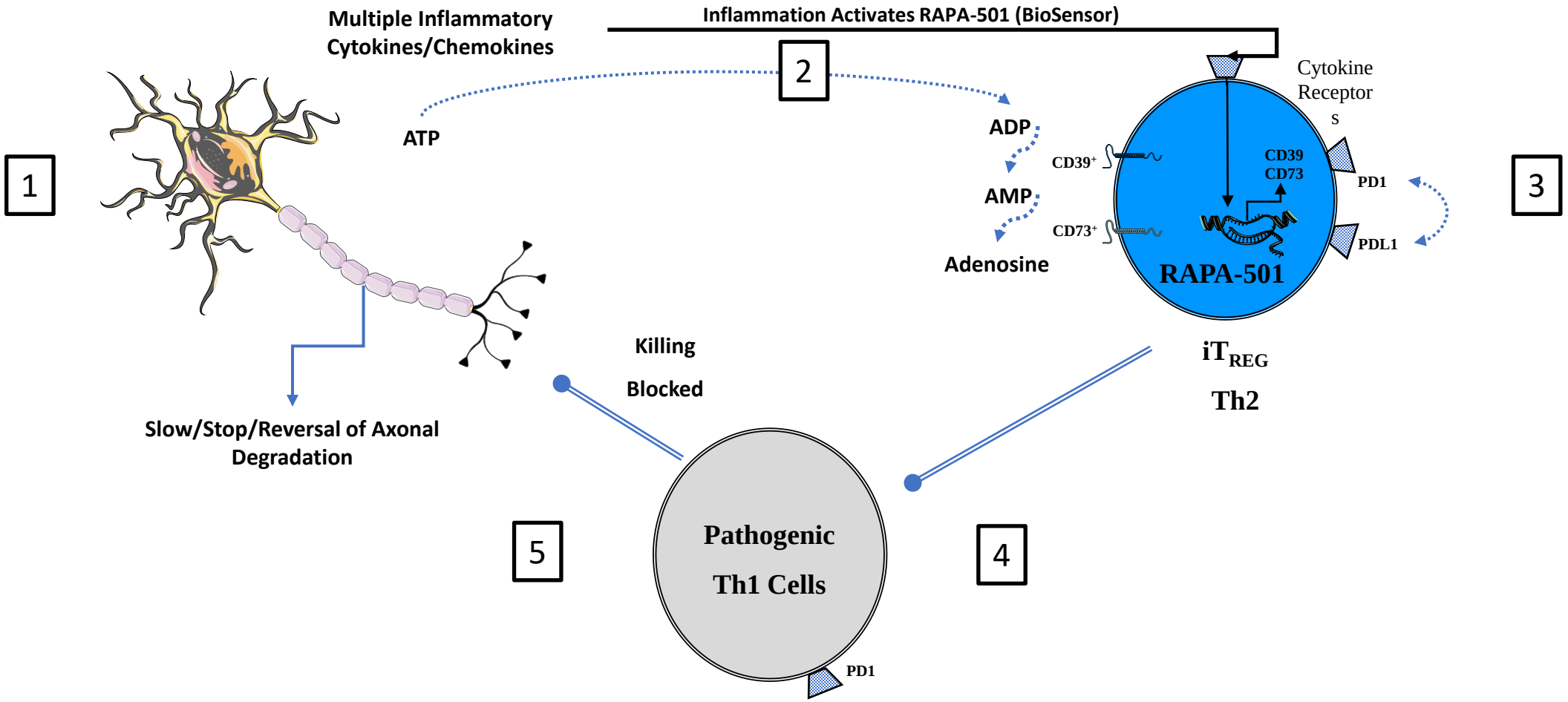

## Step 2
**T-cells undergo DE-DIFFERENTIATION through RAPA's proprietary epigenetic reprogramming**

## 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"**

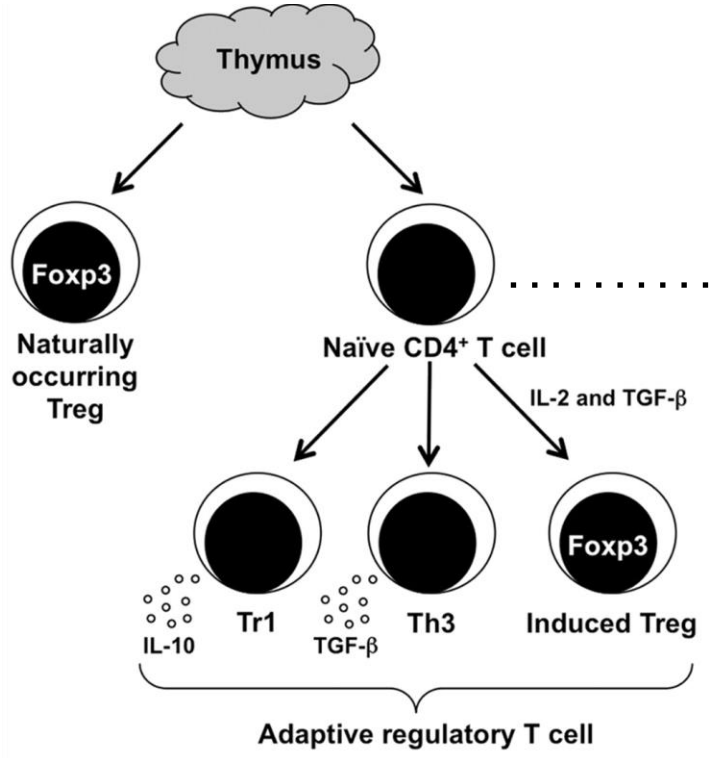


# Mechanism of Action RAPA-501 $T_{REG}$/Th2 Cell Therapy of ALS



# RAPA-501 iT$_{REG}$/Th2 Relative to Other T$_{REG}$ Populations

## Conventional Pathways of T$_{REG}$ Development




(Nishimoto and Kuwana; Seminars in Hematology, 2013)

## RAPA-501 Proprietary Two-Step Process For Induced (i) T$_{REG}$/Th2 Cell Generation

IFN-α

Th1

STEP 1: De-differentiation
- mTORC1/mTORC2 Inhibition

Th0

STEP 2: Re-differentiation
- Novel T$_{REG}$/Th2 "Hybrid" Phenotype

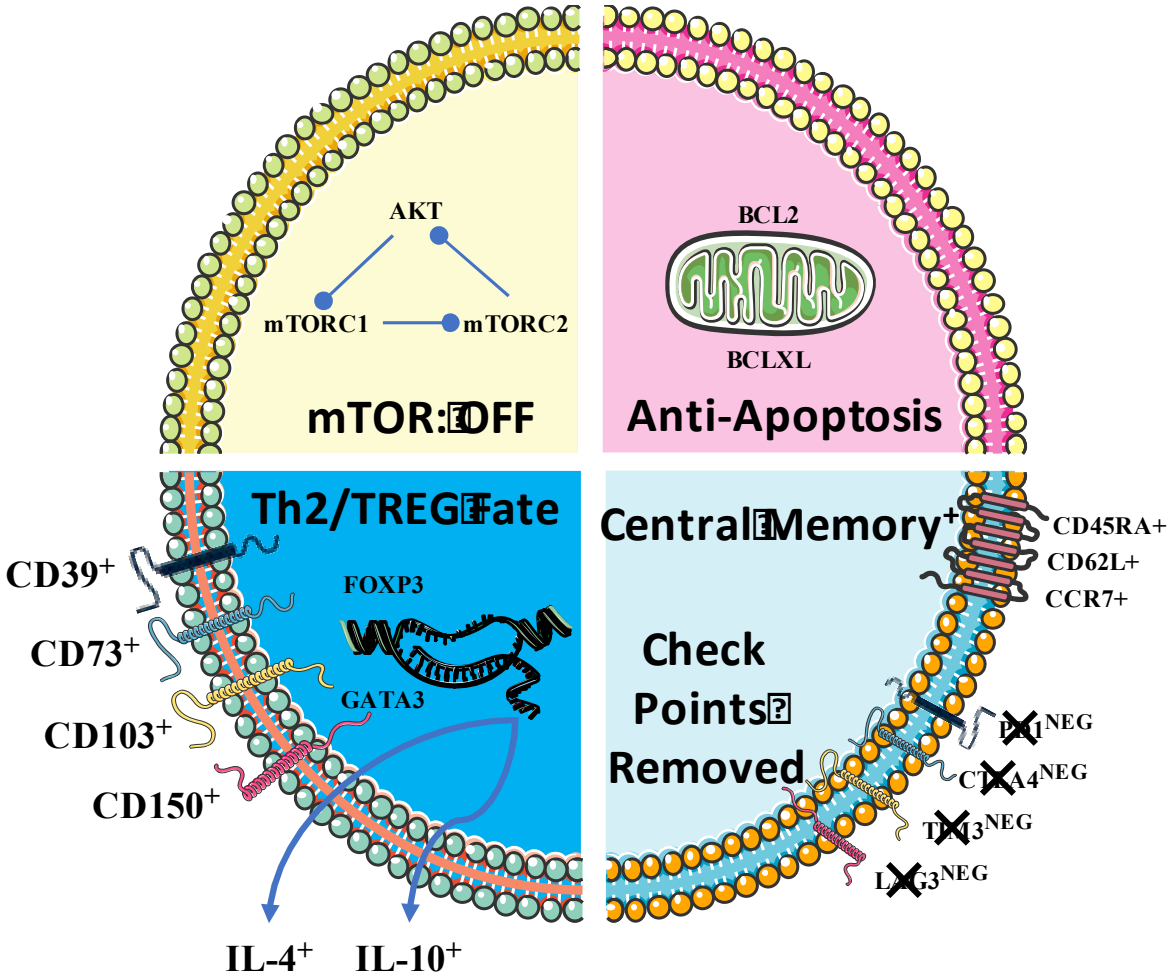
T$_{REG}$/ Th2

# RAPA-501 Therapy of ALS/Neurodegenerative Disease and Autoimmunity: Epigenetically Reprogrammed

## RAPA-501 $T_{REG}$/Th2 Cells

**mTORC1 and mTORC2 Blockade**
- Erases Inflammatory Fate
- Permits Reprogramming

**Metabolic Fitness**
- Allows T Cell Therapy
- Without Conditioning
- Chemotherapy

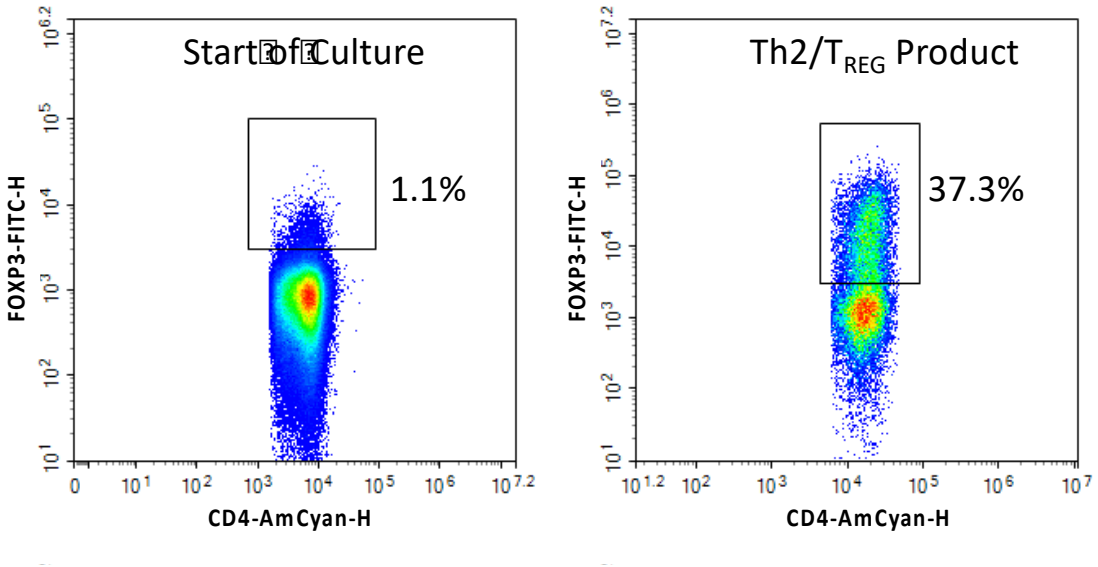



**Multi-Faceted Immune Suppressive Function**
- Th2 Cytokines
- Homing Molecules
- Inflammasome Inhibition

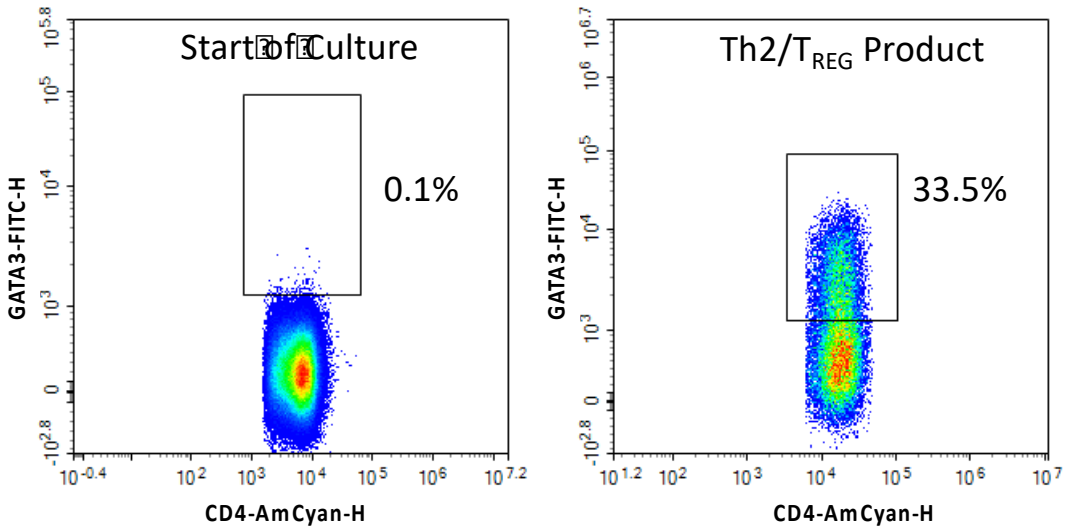
**T Stem Memory and Checkpoints Removed**
- Long-Lasting
- In Vivo Effects

# RAPA-501 Express Both FOXP3 and GATA3 Transcription Factors

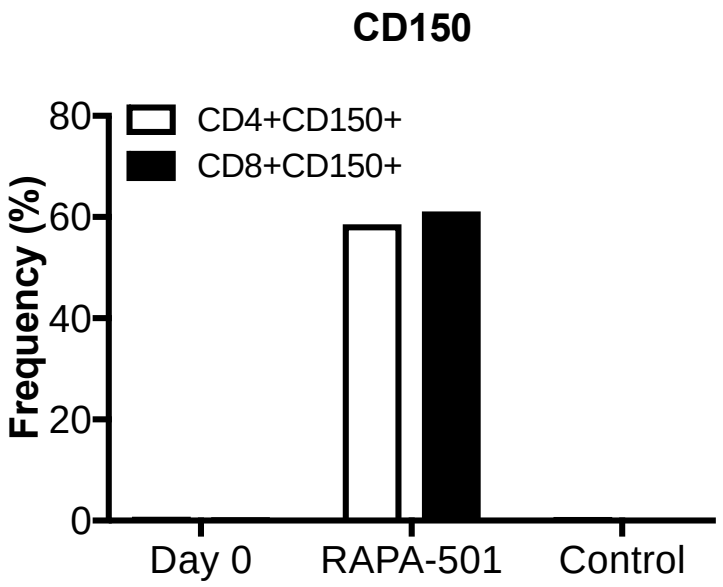
## $T_{REG}$ Factor, FOXP3




## Th2 Factor, GATA3



# RAPA-501 Express a T Stem Cell Phenotype

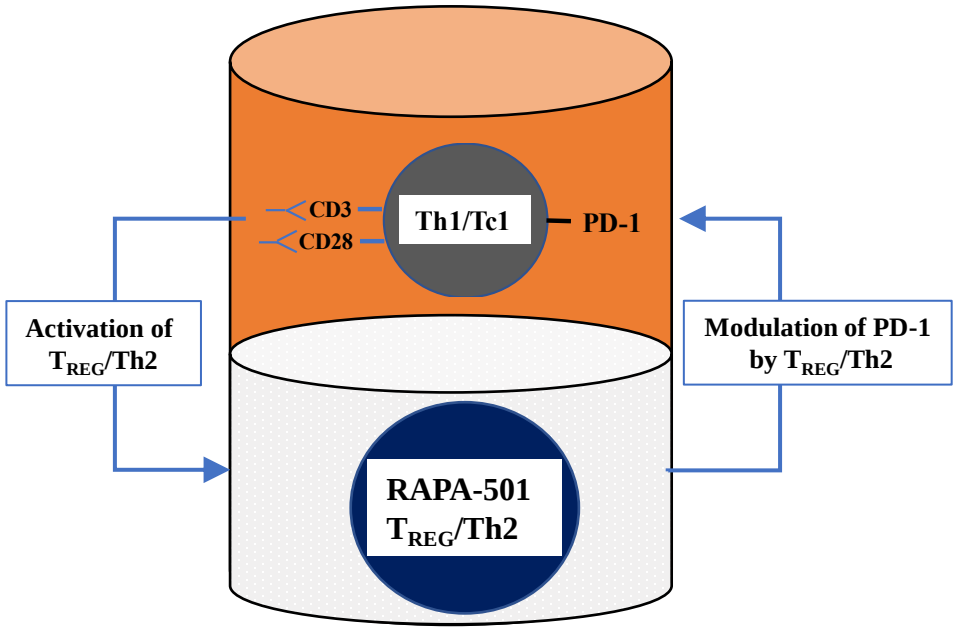



**Various Forms of "Stem Cell Therapy"**

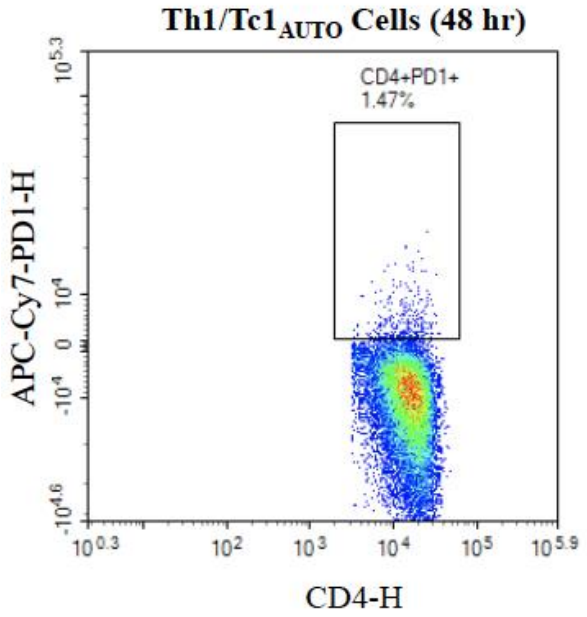
| Neurologic Stem Cell | Hematopoietic Stem Cell Transplantation | Immune T Stem Cell |
|---|---|---|
| Various Trials In pwALS | Standard Therapy of Blood Cancers | RAPA-501 Trials In pwALS |

# RAPA-501 Up-Regulates PD1 Checkpoint on Inflammatory T Cells

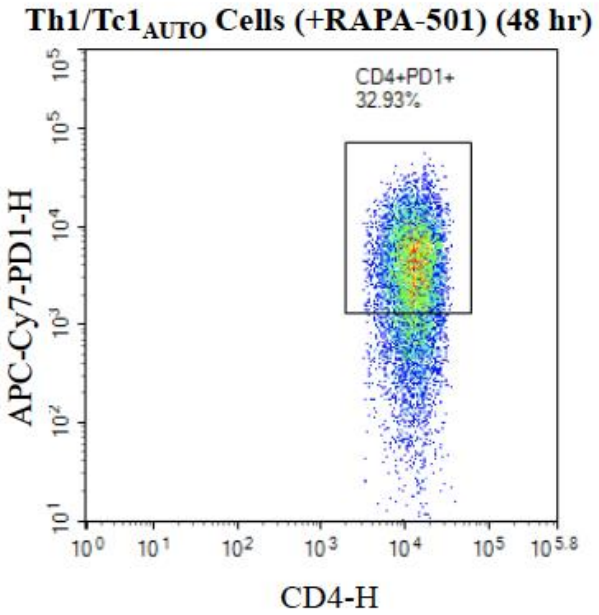
## PD1 Checkpoint Upregulation



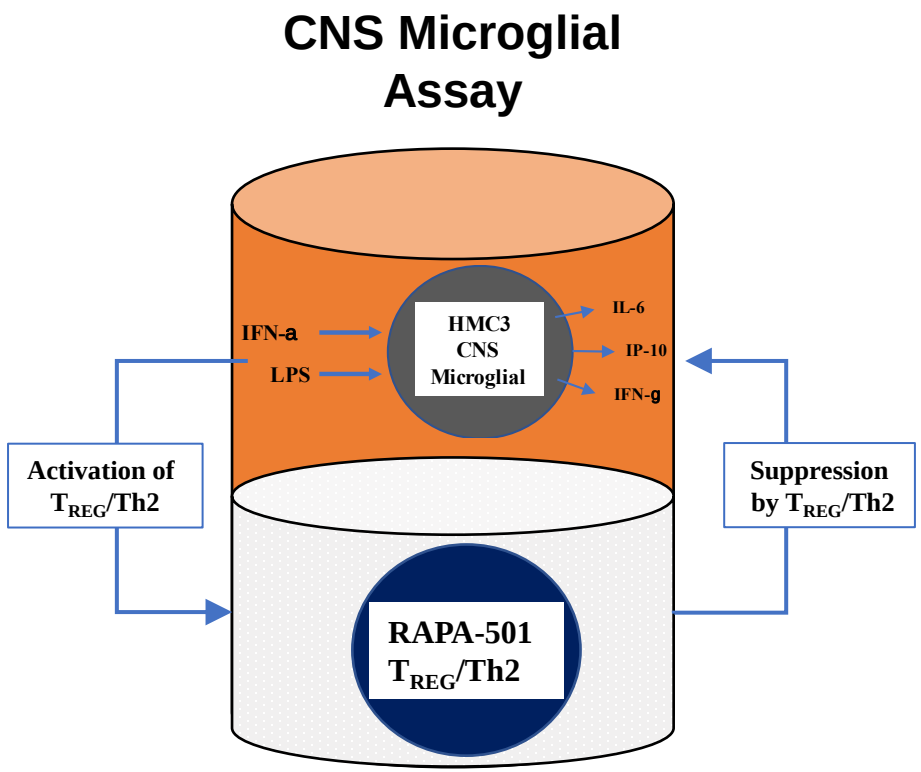

## Inflammation Driven By Low PD1

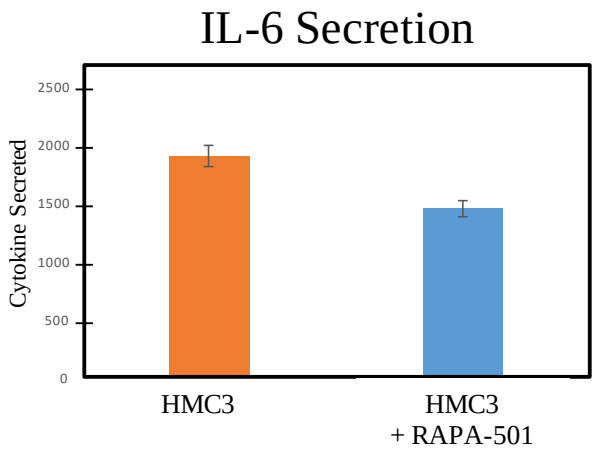


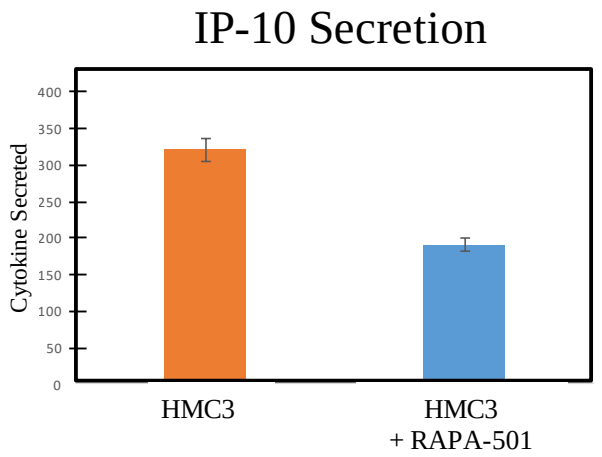

## RAPA-501 Increases PD1 Checkpoint

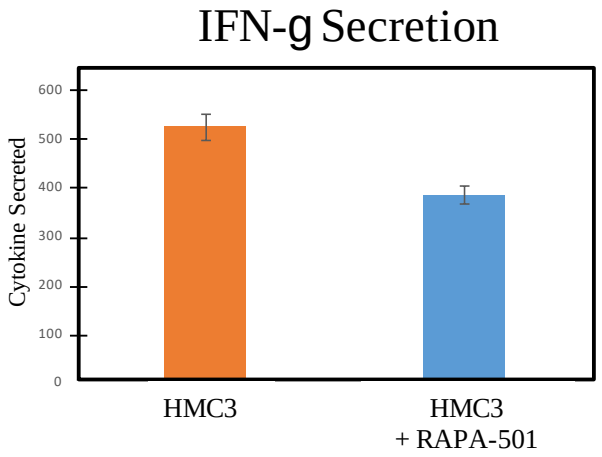


# RAPA-501 Suppresses Human CNS Inflammatory Microglial Cells



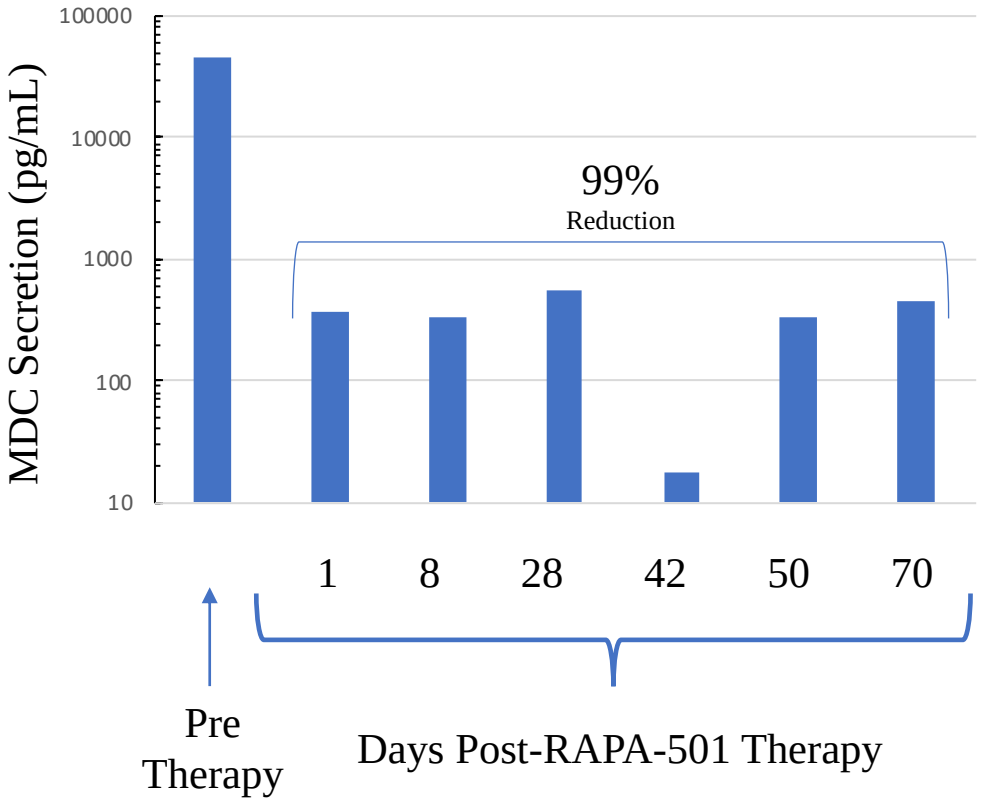



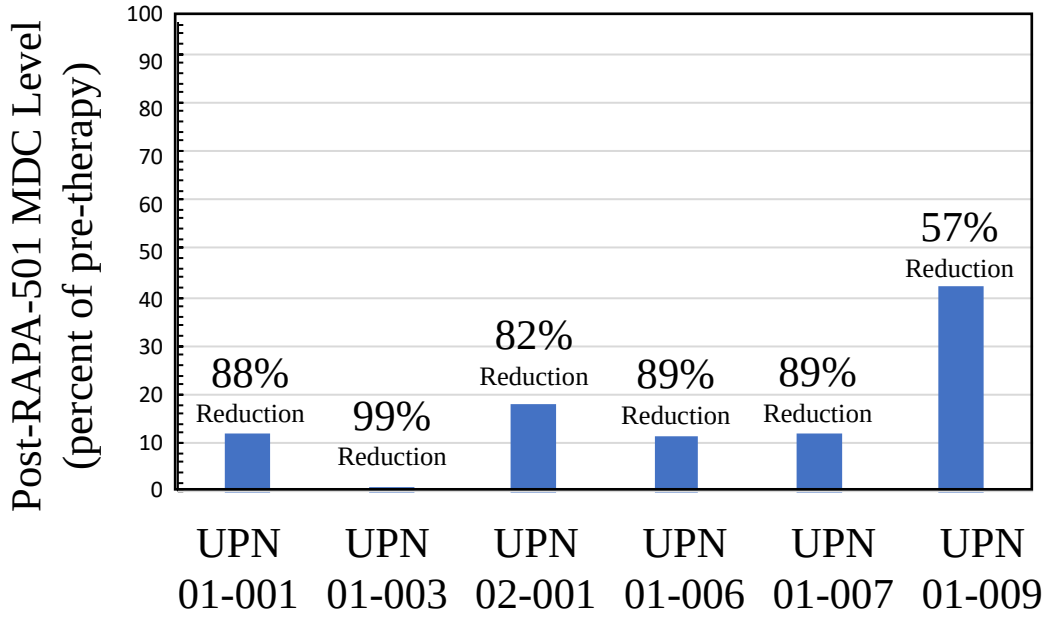
# RAPA-501 Phase I Completed in Patients Living With ALS

## 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

**PRESS RELEASE · OCT | 5 | 2023**

## Sean M. Healey & AMG Center for ALS awarded NIH UO1 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 $T_{REG}$/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)**

# RAPA-501 Expanded Access Protocol: Definitions

## 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

# RAPA-501 EAP: EVERYTHING ALS COLLABORATION

## 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

# RAPA-501 EAP: Study Objectives

## 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%

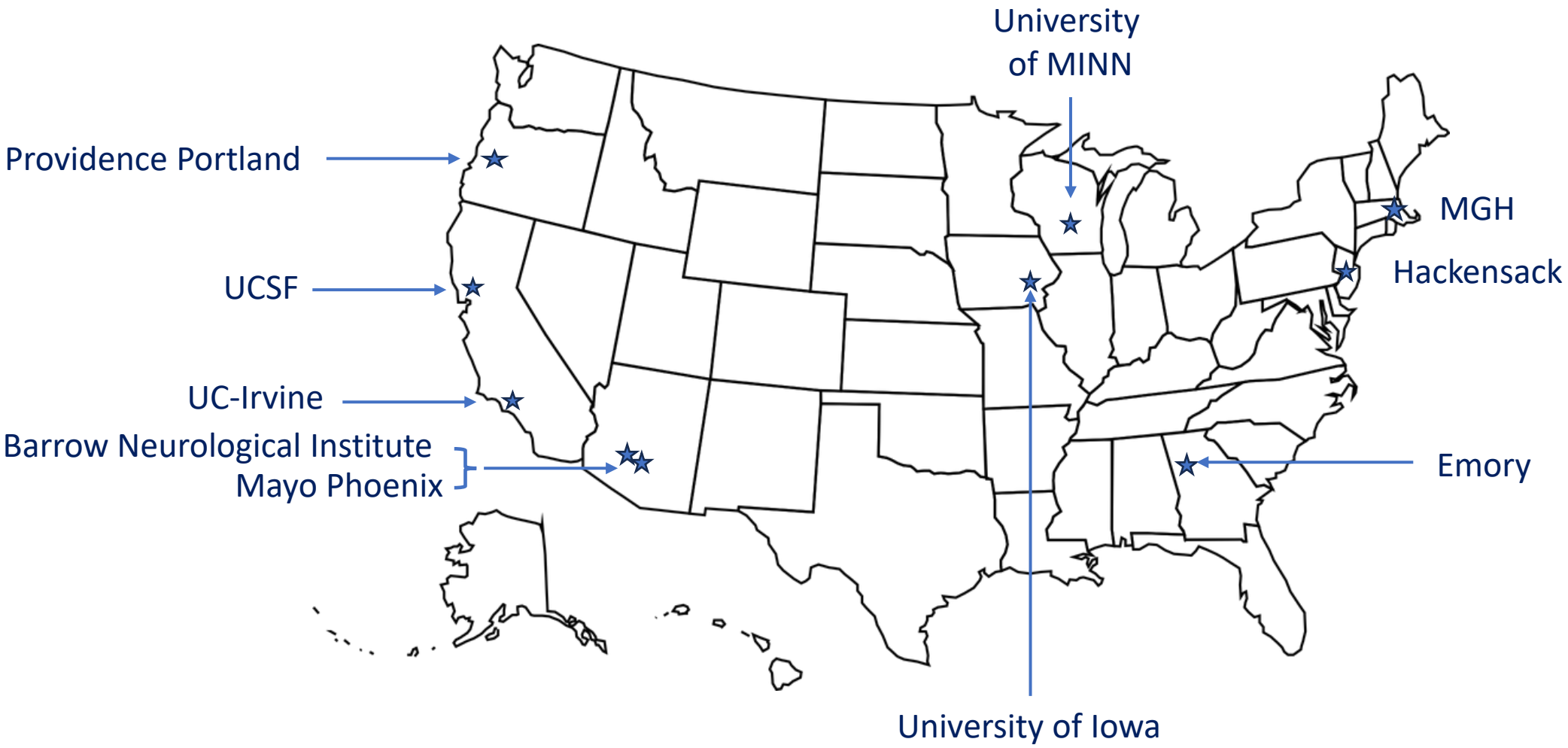
## Secondary Objectives

- 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

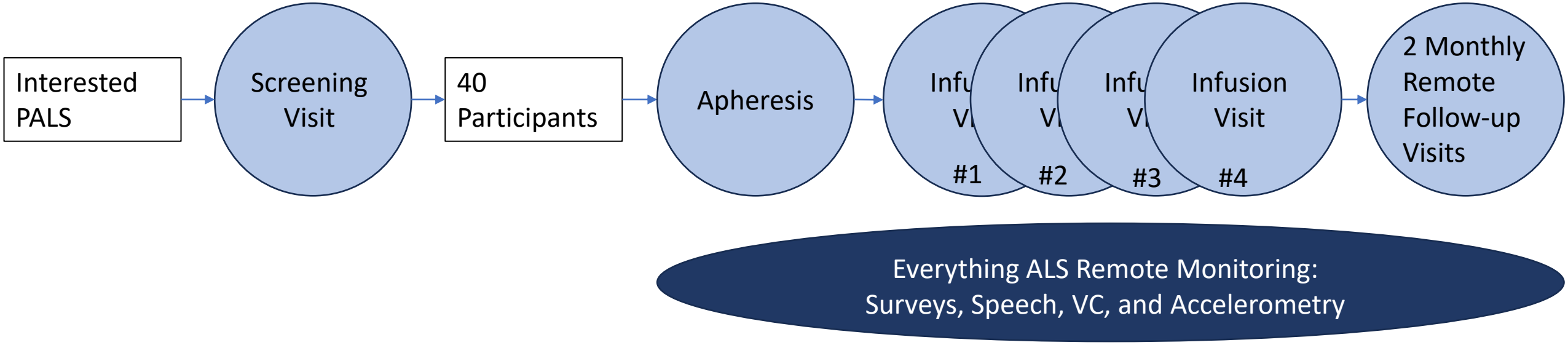
## Exploratory Objective

- 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



# RAPA-501 EAP: Study Flow



# RAPA-501 EAP: Schedule of Activities

| Procedure | SCREEN[g] | APHERESIS | Cycle 1 Day 1 (d 35) | Cycle 2 Day 1 (d 77)[e] | Cycle 3 Day 1 (d 119)[e] | Cycle 4 Day 1 (d 161)[e] | Follow-up Visit (d 190)[e] | Virtual Follow-Up (d 220 and 250) |
|---|---|---|---|---|---|---|---|---|
| Visit Window (calendar days) | | Day 0 | ± 14 | ± 14 | ± 14 | ± 14 | ± 14 | |
| Informed Consent | X | | | | | | | |
| Medical History/Demographics | X | | | | | | | |
| Con Med Review | X | (Con Meds will be reviewed throughout) | | | | | | |
| Physical Exam | X | | X | X | X | X | X | |
| Vital Signs | X | | X | X | X | X | X | |
| Height | X | | | | | | | |
| Weight | X | | X | X | X | X | X | |
| Blood Tests[a] | X | X | X | X | X | X | X | |
| TBNK Immune Testing[b] | X | | X | X | X | X | X | |
| Pregnancy Test | X | | X | X | X | X | | |
| AE Review/Evaluation | X | (AEs will be reviewed throughout) | | | | | | |
| Viral Testing | X | | | | | | | |
| Lung Testing, Hand-Strength Testing[c] | X | | X | X | X | X | X | |
| Apheresis | | X | | | | | | |
| RAPA-501 Cell Administration[f] | | | X | X | X | X | | |
| Research Labs Sent to Sponsor | X | X | X | X | X | X | X | |
| Surveys[d] | X | | X | X | X | X | X | X |
| Remote Monitoring[f] | (Remote monitoring performed throughout) | | | | | | | |

# RAPA-501 EAP: Thank You

**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**

Healey & AMG Center

Sean M. Healey & AMG Center for ALS
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National Institute of Neurological Disorders and Stroke

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RAPAtherapeutics

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

# Questions and Answers

**Questions about Participation:**

**Megan Okoro – mokoro@mgh.harvard.edu**