# Targeting the salvage pathway in ADEM and ON patients with the first clinical dCK inhibitor

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RARE NEUROIMMUNE DISORDERS SYMPOSIUM
SESSION 1: RARE NEUROIMMUNE DISORDERS RESEARCH
OCTOBER 19, 2024

# CONFLICT OF INTEREST DISCLOSURE STATEMENT

Ken Schultz, M.D., is Chairman and Chief Executive Officer of Trethera Corporation, which is actively developing TRE-515 as an orally dosed inhibitor of deoxycytidine kinase (dCK) for the treatment of cancers and autoimmune diseases.

# DEVELOPMENT HAS BEEN GRASS ROOTS DRIVEN, BUILDING AN EXPERT TEAM TO PURSUE MULTIPLE DISEASES WITH ONE DRUG

## *Current State*

- **Dosed first patient in medical history** with a dCK inhibitor, Ph1 oncology trial ongoing
- **Well tolerated, once daily, capsule** with zero limiting toxicities seen thus far
- **ADEM and ON Orphan Drug designated,** accelerating the FDA approval path
- **Awarded over $4M in NIH grants** in past 24 months for ADEM and ON preclinical work
- **Requesting preIND meeting** for ADEM Ph1 trial, cross referencing adult oncology data

## *Neuro Immune Development Team*


Peter Clark


Michael Levy

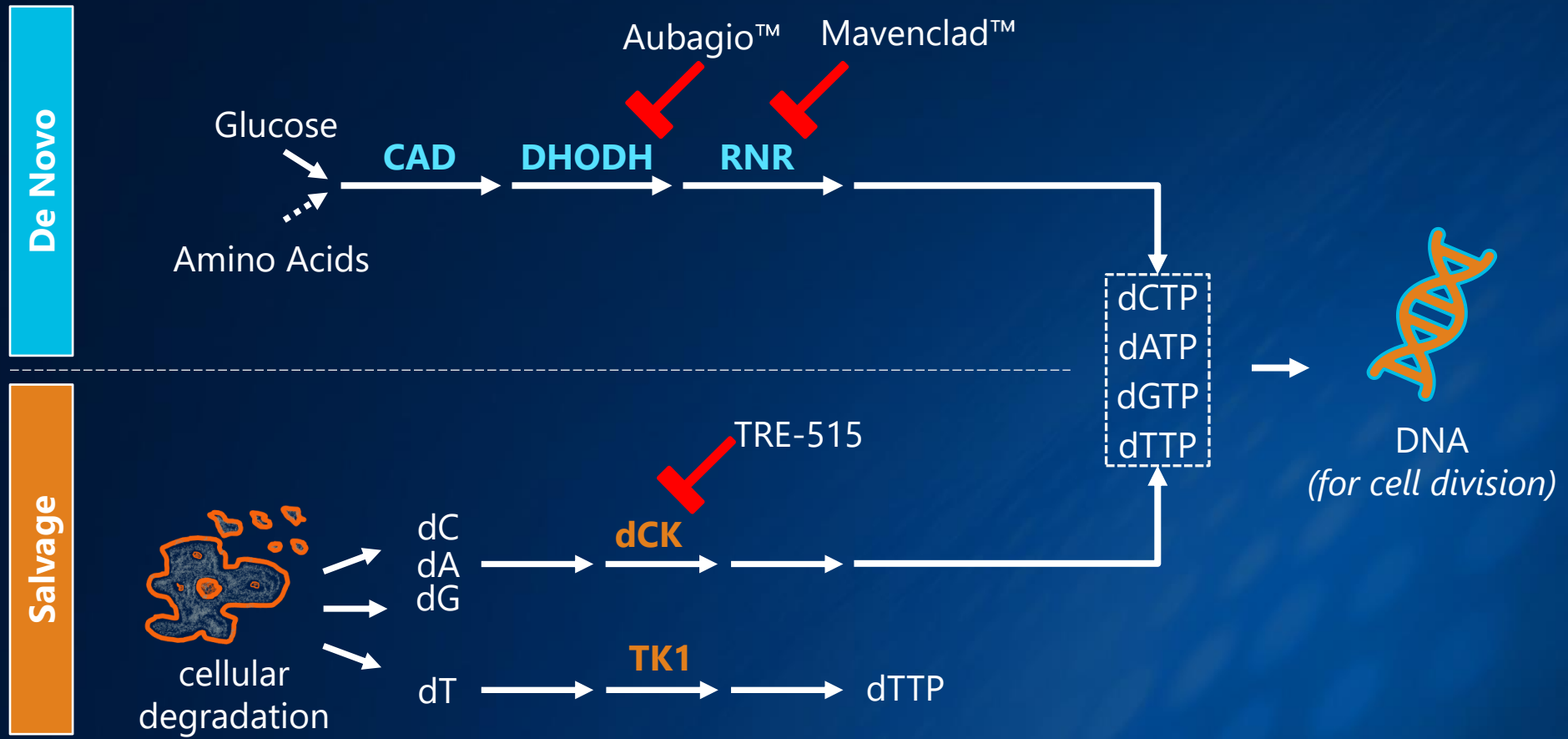

Ken Schultz


Michael Shepard


Larry Steinman


Owen Witte

# DNA REPLICATION FOR CELL DIVISION USES THE DE NOVO PATHWAY AND/OR THE SALVAGE PATHWAY




Note – deoxyadenosine (dA), deoxycytidine (dC), deoxyguanosine (dG), deoxythymidine (dT), ribonucleotide reductase (RNR), Dihydroorotate dehydrogenase (DHODH), thymidine kinase (TK1), Carbamoyl-phosphate synthetase aspartate transcarbamylase dihydroorotase (CAD); cladribine (Mavenclad), teriflunomide (Aubagio)

# SALVAGE PATHWAY CLINICAL ADVANCEMENT BUILDS ON OVER A DECADE OF NUCLEOTIDE METABOLISM DISCOVERIES

**2009**

dCK inactivation alters T & B cell development

**2012**

dCK inactivation induces replication stress; knockout

**2014**

Targeting dCK effective in T cell cancer models

**2014-2015**

Potential dCK inhibitors screened

**2016**

PET and plasma biomarkers measure dCK activity

**2017-2020**

TRE-515 selected for development, company formed, neuro pilot study

**2021-2024**

Orphan Status: Optic Neuritis & ADEM

First-in-Human: Dosed Phase 1 Oncology

*Mediated by dCK, the salvage pathway plays a pivotal role in rapid and abnormal cell division, suggesting a therapeutic target for inflammatory disorders and cancers*

TRETHERA

Source: Chen et al. *Immunology,* 2023; Kim et al., PNAS, 2016; Toy et al. PNAS, 2010; Austin, et al. J Exp Med. 2012; Nathanson, et al. J Exp Med. 2014; Bunimovich et al., PLoS One. 2014; Company website

# TRE-515 EARNED ORPHAN DRUG STATUS FOR DRAMATICALLY IMPROVING PHYSICAL ACTIVITY IN SEVERAL DEMYELINATING DISEASE MOUSE MODELS

No Drug

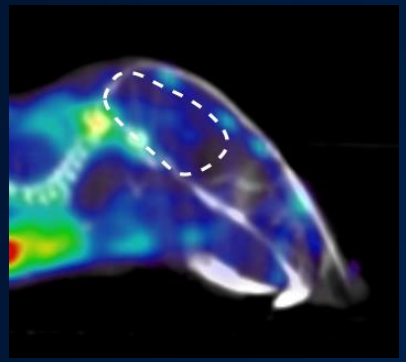
With Drug

Note – Experimental autoimmune encephalomyelitis (EAE); Myelin Oligodendrocyte Glycoprotein (MOG 35-55)
Source: Internal and MTA research, 2020; FDA Orphan Drug website

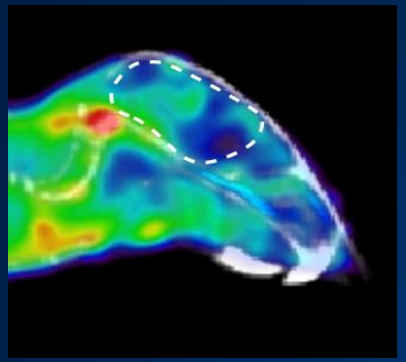
# THE SALVAGE PATHWAY ENZYME, DCK, IS SIGNIFICANTLY ELEVATED IN DEMYELINATING DISEASES AND EFFECTIVELY BLOCKED BY TRE-515

**High dCK levels found in MS/ON/ADEM…** **… TRE-515 significantly blocks dCK activity**

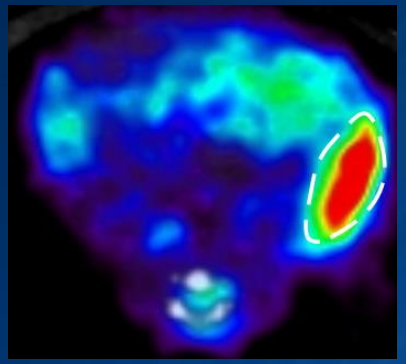
Normal



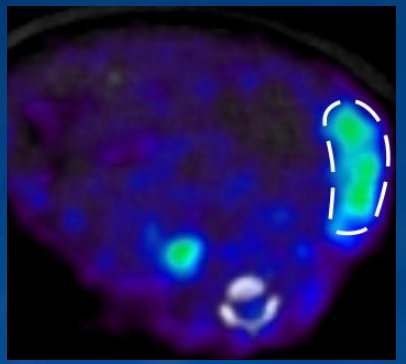
Diseased



No Drug



With Drug



dCK activity, %ID/g

18% %ID/cc 1%

Blocking dCK selectively impacts abnormally rapidly dividing cells found in many autoimmune diseases, including ON and ADEM

Source: *Immunology*, 2023 Jan;168(1):152-169 (PMID 35986643); AACR, Abstract #2635, New Orleans, Louisiana, 2022

# TRE-515 REDUCES ABNORMAL T-CELL AND B-CELL PROLIFERATION BUT DOES NOT IMPACT NORMAL CELL POPULATIONS

## *Nonclinical (Neurology)*

- Decreased populations of activated $CD4^+$ T and B cells
- No measurable effect on other immune cell populations


## *Clinical (Oncology)*

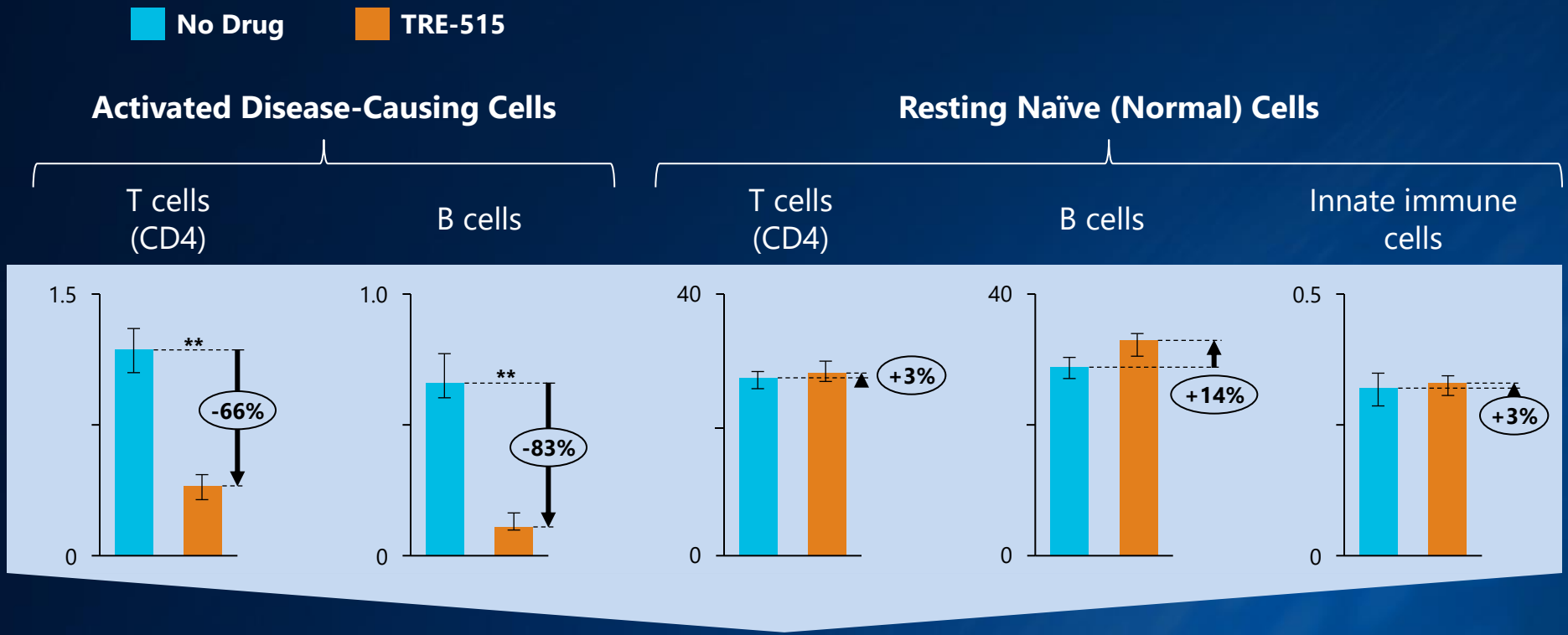
- No change in normal cell populations
- Absolute neutrophil and lymphocyte counts also remained normal

Complete Blood Count Changes C1D1 to C2D1

| Cohort | WBC | RBC | Platelets |
|---|---|---|---|
| 40 mg | 6% | 4% | 4% |
| 480 mg | -4% | 2% | -1% |

Note - Positive numbers denote increased cell counts; White blood cells (WBC), Red blood cells (RBC)
Sources: ANA Annual Meeting , Abstract #S215, Chicago, Illinois, 2022; TRE-515 Phase 1 solid tumors trial database

# TRE-515 REDUCED DISEASE-CAUSING T AND B CELLS WHILE SPARING THE NORMAL HEALTHY IMMUNE CELLS




TRE-515 reduced the number of abnormal T cells and B cells, which cause diseases ADEM and ON, but had no effect on the healthy T cells, B cells, and other immune cells our body uses to fight diseases

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Note – Y-axis is percent of CD45+ cells (e.g., general immune cells) represented by each population CyTOF analyzed in the EAE mouse model ; ** p < 0.01 Source: ACTRIMS Conference, 2023, Abstract #P138, San Diego, California, 2023

# ONGOING PHASE 1 CANCER TRIAL SHOWING FAVORABLE SAFETY, COMPELLING BIOMARKERS, AND SIGNS OF CLINICAL BENEFIT

"there are even days that I forget I have cancer"
– Stephanie (Phase 1 Solid Tumors Patient)

## Phase 1 Dose Escalation Oncology Trial

- **Safety:** Well tolerated, **no dose limiting toxicities** in any cohort (40mg to 480mg)
- **Dose:** Rapid oral absorption, 6 hour plasma half-life supporting a **once daily capsule**
- **Benefit:** One in four patients had antitumor activity, despite aggressive late-stage disease
- **Biomarkers:** Increased plasma dC levels provide compelling on-target evidence ($p < 0.0001$)

"TRE-515 is a one-of-a-kind molecule with potential to durably treat devastating diseases."
**- Mike Shepard, PhD** (Invented Herceptin, awarded Lasker-DeBakey Prize, Trethera Adviser)

Note – Trethera treated 22 patients in the first 6 cohorts and is currently enrolling
Source: Trethera solid tumors trial (NCT 05055609)

# DEVELOPMENT STRATEGY LEVERAGES EXISTING SAFETY AND PK PATIENT DATA TO ENABLE RAPID ADEM AND OPTIC NEURITIS CLINIC ENTRY

## Development Timeline

**2024**

**PreIND Meeting for ADEM Clinic Entry**

- Pediatric & adult ICU focus
- Cross-linked to oncology IND

**2025**

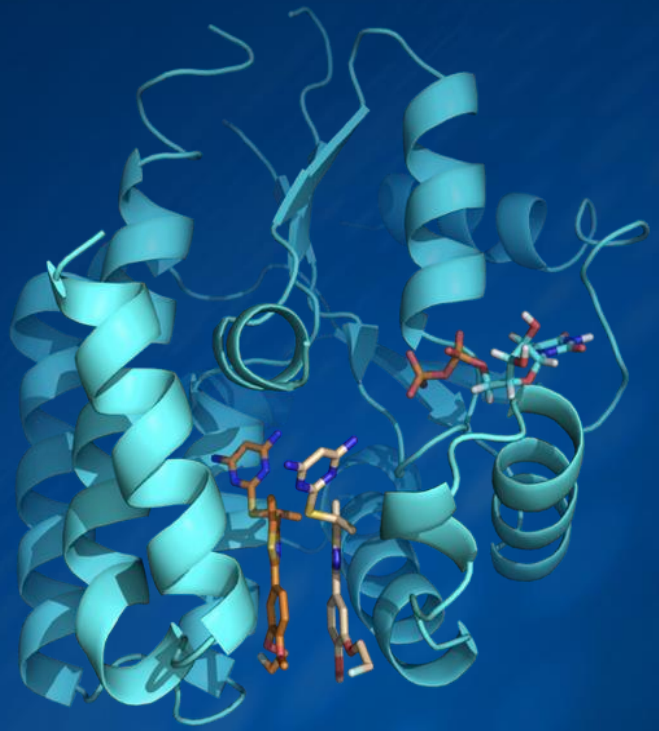
**ADEM Study May Proceed FDA Letter**

- Capital raise for clinical operations
- US based Phase 1 trial activated

**2026+**

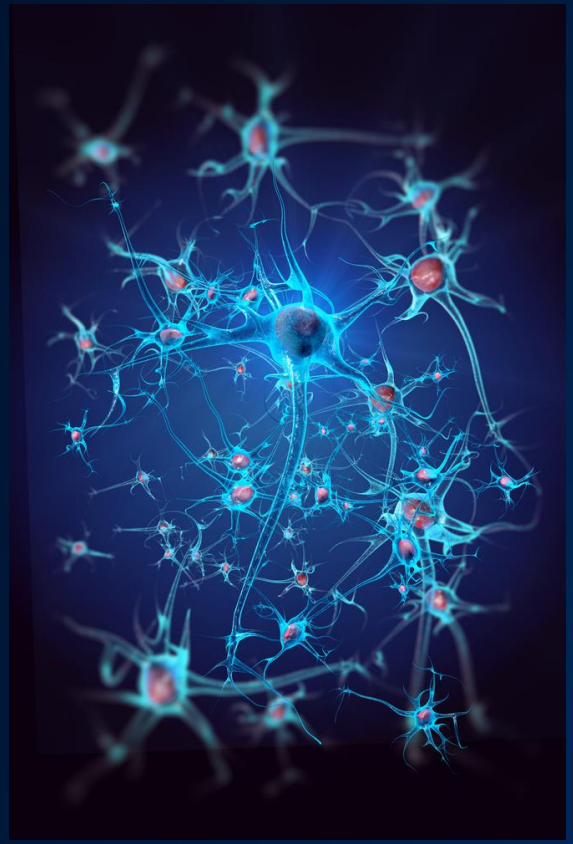
**Neuroimmune Clinical Trial Expansion**

- Optic neuritis adult Phase 1 trial
- ADEM Phase 2 registrational



3D Co-Crystal Structure

# QUESTIONS AND DISCUSSION



SRNA
connect. care. cure.

## Thank You For Hearing Our Story!

*Immunology*, 2023