Saturday, October 1, 2022

WELCOME

1ST DEPARTMENT OF MEDICINE RESEARCH RETREAT

Andras Perl, MD/PhD
SUNY Distinguished Professor of Medicine
Vice Chair for Research

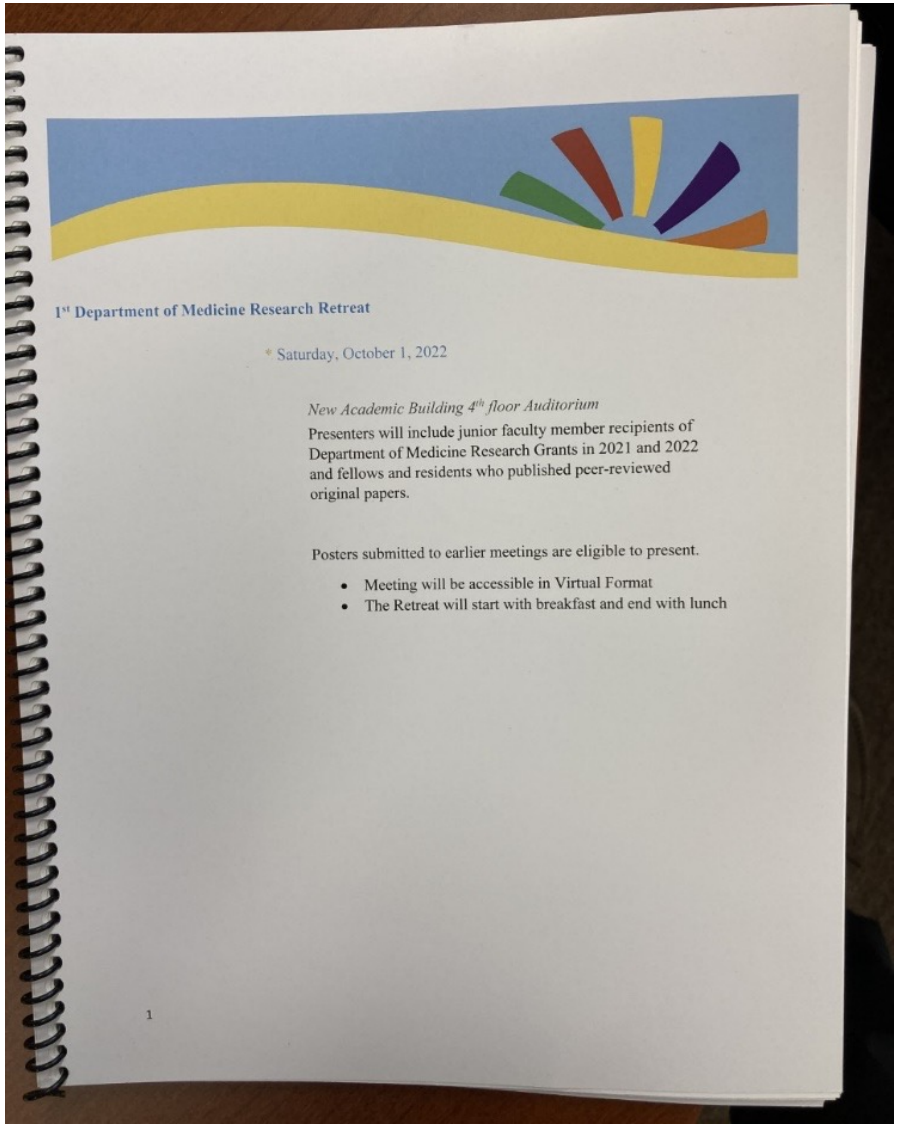
Acknowledgments:

The event is supported by the Department of Medicine

Drs. Steve Knohl and Sri Narsipur

The program was prepared by Dr. Andras Perl and Rosa Trpcevski with input from the Department of Medicine Research Council (Drs. Ruth Weinstock, Elizabeth Asiago-Reddy, Housam Hegazy, Markus Gutsche, Debanik Chaudhuri, Savio John) and Chief Residents (Drs. Christina DiCorato, Sonica Patel, and Rachael Proumen).

Program includes all participants



1st Department of Medicine Research Retreat

Saturday, October 1, 2022

New Academic Building 4th floor Auditorium

Presenters will include junior faculty member recipients of Department of Medicine Research Grants in 2021 and 2022 and fellows and residents who published peer-reviewed original papers.

Posters submitted to earlier meetings are eligible to present.

- Meeting will be accessible in Virtual Format
- The Retreat will start with breakfast and end with lunch

1

This is a 1st DOM Retreat for all of us: questions and suggestions will be sought!

Department of Medicine Research Mission Statement

The Department of Medicine conducts cutting edge research in 12 academic divisions.

Our faculty has made paradigm-shifting discoveries during the last decade which are described in the research pages of each division.

The Department is home to basic and translational research laboratories and investigator-initiated clinical trials supported by the National Institutes of Health, Research Foundations, and Pharmaceut[illegible] Organizations.

DOM VC Research Update 10 1 2022

Research Initiative

a. Monitor current funding – follow SUNY RF layout
b. Develop Plans for future growth – Research Council
c. Promote collaborative Projects
d. Develop research mentorship across the DOM including faculty and trainees
e. Designate research mentors within each division
f. Foster collaboration between divisions
g. Develop collaborations with basic science and clinical departments
h. Take advantage of Upstate and SUNY training opportunities (BERD)
i. Pilot grant started from 7/1/2021 with the notion to secure extramural funding

UPSTATE Resources

November 2021

TriNetX Month for Upstate Researchers!

TriNetX is the global health research network that optimizes clinical research and enables discoveries through real-world evidence. Use TriNetX to identify patient cohorts, participate in sponsored trials, and analyze real patient data.

To register for upcoming free training session(s) please click on one or more below dates/times.

Sessions are 1 hour long.

****

Wednesday November 3rd - 8:00 AM
Thursday November 4th - 4:00 PM
Friday November 5th - 8:00 AM
Tuesday November 9th - 4:00 PM
Wednesday November 10th - 8:00 AM
Friday November 12th - 8:00 AM

Questions: Contact Molly Dyer dyermo@upstate.edu

****

"TriNetX is a comprehensive cloud-based database of de-identified data from pooled electronic medical records (EMR), registries, and claims across many health care organizations globally. Data are integrated and mapped to clear, comprehensive and standard terminology for demographics, clinical encounter type, vitals, diagnoses, prescription drugs, lab results, procedures, and genomics. All data can be queried via the TriNetX online platform to build, explore and download custom cohorts, analyze and compare outcomes. One of the main networks is the Research Network which is composed of 55 healthcare organizations from six countries including US, and 74.4 million patients as of Sept 7th, 2021."

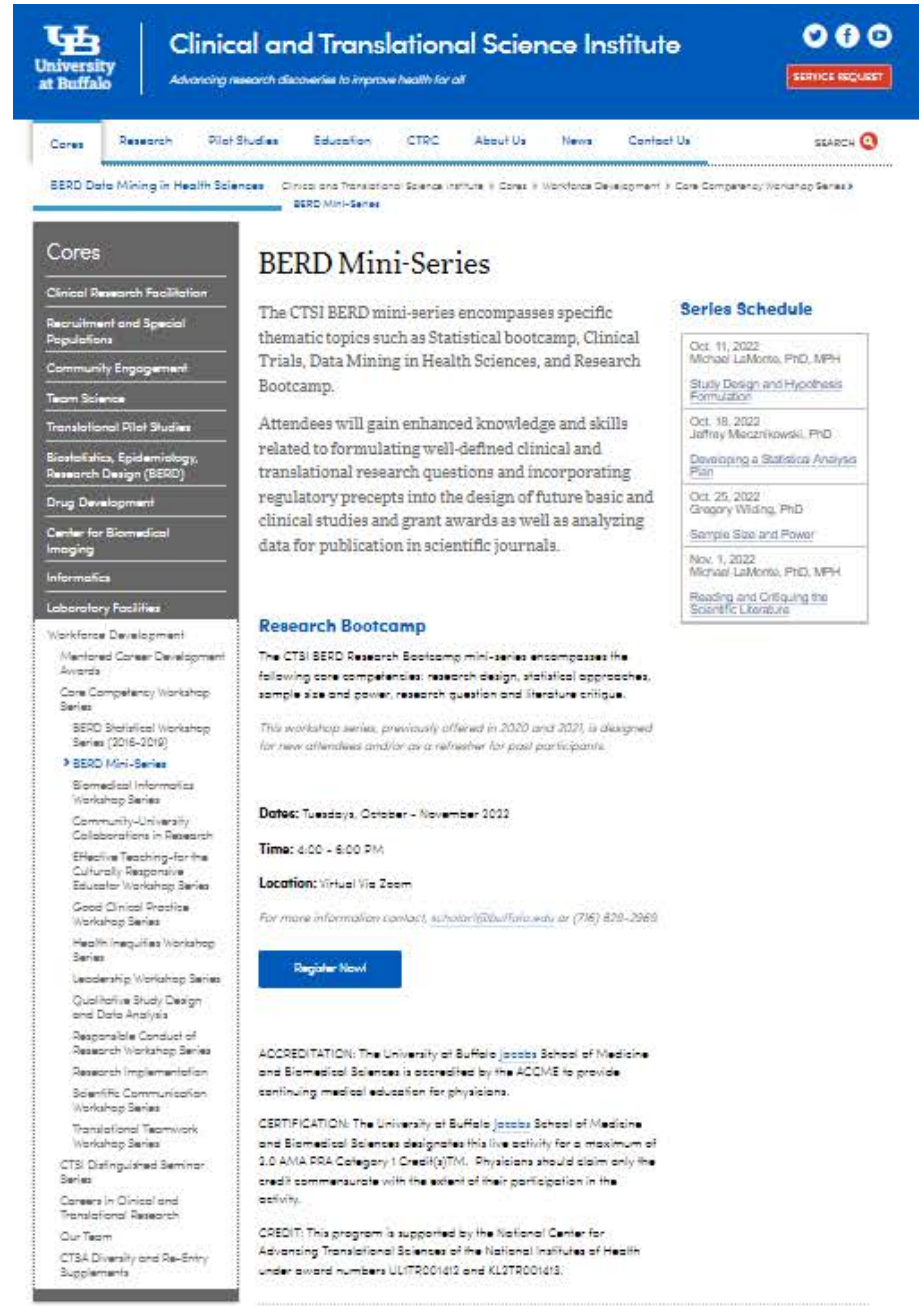
Dr. Faraone Distinguished Professor and Vice Chair for Research, Department of Psychiatry
(see attached for complete statement)

Why I Like TriNetX?:

"Intellectual and developmental disability is often underrepresented in research, due to the small number of patients and outcomes available for research at any individual institution. TriNetX allowed us to investigate the impact of SARS-CoV-2 in this vulnerable population by providing access to 'big healthcare data' in real-time, minimizing the small sample size issue that limits research for many conditions and diagnoses. While a keen understanding of quantitative research methods is needed to produce valid study results, the TriNetX platform itself is user-friendly and TriNetx staff are responsive to questions along with provide support and guidance. TriNetX is a powerful resource at Upstate that provides endless opportunities with respect to identification of clinical risk factors, health outcomes research, and health services research."

Dr. Turk Distinguished Professor and Vice Chair for Physical Medicine and Rehabilitation
(Click here to read publication)

SUNY Resources



Research Metrics in October 1, 2022

Annual Research Grant expenditures:

RF accounting: $ 21,334,685.76; This includes pharma-supported drug trials and NIH grants; detailed grants information from SUNY RF is attached and organized by division.

DOM NIH Funding 2010 as per NIH Reporter: $ 2,432,708 (total Upstate funding: $25,657,956; detailed grant information from NIH Reporter is attached; NIH total $31.2 billion)

DOM NIH Funding 2022 as per NIH Reporter: $ 2,329,441 (total Upstate funding: $29,600,529) detailed grant information from NIH Reporter is attached; NIH total $45.2 billion)

Department of Medicine Grant Program

The Department of Medicine support research projects that are based on collaboration of the Faculty and Trainees, including medical and graduate students, residents, clinical and research fellows.

Grant Application Guide and Forms for Funding period 7/1/2022-6/30/2023

The DOM grant application form provides detailed instructions on preparation and submission of the application. The application form follows the template of the Upstate Intramural Grant Program and it anticipates that all applicable regulatory policies will be satisfied.

Deadline for submission: May 1, 2023.

Important items to consider:

- The Principal Investigator is expected to be a full-time faculty member of the Department of Medicine
- Submission or active grant by a Principal Investigator is limited to one per year.
- The grant applications will be scored on the basis of significance, impact, feasibility, qualifications of the PI and collaborators, potential to secure extramural support, and inclusion of trainees.
- Trainees need to be involved and listed on the face page of the application.
- Progress report would be expected upon completion of the project.
- Applications will be reviewed by the DOM Research Council with representatives sought from each Division. Members of the council will be excluded from scoring grants of a PI from the same division.

Grant Applications Funded for the period 7/1/2021-6/30/2022

1. Alina Basnet, MD : Association of Molecular Profiles and Mutational Status with Distinct Histological Lung Adenocarcinoma Subtypes. An Analysis of the LACE Bio I and II Data.

2. Christina Geier, MD: Potential pathogenic functions and metabolic signatures of HLA-DR+CD45RA+ myeloid cells

3. Hiroshi Kato, MD: SLE Treg cells Expand Pathogenic CD8+ Memory T cells

4. Abirami Sivapiragasam, MD: Neurocognitive changes in breast cancer patients on hormonal therapy. Is there a difference between objective and perceived neurocognition?

Grant Applications Funded for the period 7/1/2022-6/30/2023

Auyon Ghosh, MD, MPH: Optimizing the Lung Gene Expression and Network Imputation Engine

Christian Geier, MD: Transcriptomic characterization of HLA-DR+ myeloid cells for potential pro-inflammatory pathways

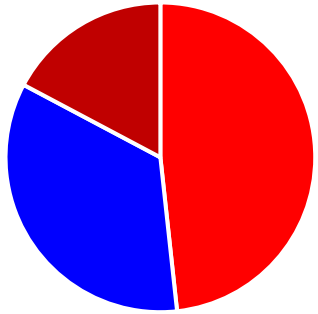
DOM VC Research Strategic Plan

1. Training – Research Residency
    a. Scholarship model for 3rd IM year, seek UH allocation for years 1-2
    b. Grant writing – integrate with MD/PhD Program
    c. Statistics: open to all residents, fellows, and faculty; needed for QI projects
        a. Take advantage of BERD
        b. Use DOM grant support to fund statistical analysis
2. Mentoring – Promotion incentive
    a. Resident
    b. Fellow
    c. Junior Faculty
3. Career Development – Academic track/tenure track
    a. Salary protection for 3 years for new recruits
    b. Salary protection with continued extramural support
4. Research Council – Representatives from each division: response in from Endocrine (Dr. Weinstock), Hem-Onc (Seah Lim), ID (Drs. Asiago-Reddy and Thomas), Hospitalists (Dr. Hegazy) and Pulmonary (Dr. Gutsche), Dr. Shady, Dr. Knohl.
    a. Mentoring
    b. Review and help adjudicate pilot projects
    c. Bioinformatics
    d. Centers (indirect cost incentive)
    e. Formulate Research Incentive Plan

Unmet Need in Rheumatology
Infections are the Leading Cause of Mortality in SLE

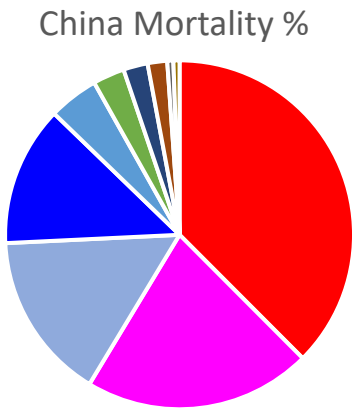
Overall Mortality 10% in 5 years

Curr. Opin. Rheumatol. 13:345-351, 2001



1	Infections	47.8
2	Cardiovascular	27
3	Cancer	13.5

382 death in UK, Rheumatology, Volume 54, Pages 836–843, May 2015



1	Infections	33.2
2	Renal	18.7
3	Encephalopathy	13.8
4	Cardiovascular	11.5
5	Multiple organ failure	4.1
6	Cerebrovascular disease	2.6
7	Lung failure	2
8	GI bleed	1.6
9	Liver failure	0.5
10	Cancer	0.5

2179 death in > 20,000 Chinese patients. Wang et al; *Medicine* Volume 94, May 2015

THE LANCET

Volume 391 · Number 10126 · Pages 1121-1236 · March 24-30 2018 www.thelancet.com

"When will the UK Government wake up to the timebomb that Brexit is for the NHS and the nation's health?"

See Editorial page 1122

Editorial
Diagnosis of heavy menstrual bleeding
See page 1122

Articles
Lenvatinib versus sorafenib for hepatocellular carcinoma
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Articles
Sirolimus in systemic lupus erythematosus
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Atraumatic versus conventional lumbar puncture needles
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Review
Health systems development in Thailand
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Founded 1823 · Published weekly

Sirolimus in patients with clinically active systemic lupus erythematosus resistant to, or intolerant of, conventional medications: a single-arm, open-label, phase 1/2 trial

Zhi-Wei Lai, Ryan Kelly, Thomas Winans, Ivan Marchena, Ashwini Shadakshari, Julie Yu, Maha Dawood, Ricardo Garcia, Hajra Tily, Lisa Francis, Stephen V Faraone, Paul E Phillips, Andras Perl

Seven Rheumatology Fellows

Lancet 2018; 391: 1186–96
Published Online March 15, 2018 http://dx.doi.org/10.1016/S0140-6736(18)30485-9

See Comment page 1126

Division of Rheumatology (Prof A Perl MD, Z-W Lai MD, R Kelly PhD, T Winans BSc, I Marchena MD, A Shadakshari MD, J Yu MD, M Dawood MD, R Garcia MD, H Tily MD, L Francis MD, Prof P E Phillips MD), **Department of Psychiatry** (Prof S V Faraone PhD), **Department of Medicine** (Prof A Perl, Z-W Lai, R Kelly, T Winans, I Marchena, A Shadakshari, J Yu, M Dawood, R Garcia, H Tily, L Francis, Prof P E Phillips), **Department of Microbiology and Immunology** (Prof A Perl), **and Department of Biochemistry and Molecular Biology** (Prof A Perl), **State University of New York Upstate Medical University, Syracuse, NY, USA**

Correspondence to: Prof Andras Perl, Department of Medicine, State University of Upstate Medical University New York, Syracuse, NY 13210, USA
perla@upstate.edu

Summary

Background Patients with systemic lupus erythematosus have T-cell dysfunction that has been attributed to the activation of the mammalian target of rapamycin (mTOR). Rapamycin inhibits antigen-induced T-cell proliferation and has been developed as a medication under the generic designation of sirolimus. We assessed safety, tolerance, and efficacy of sirolimus in a prospective, biomarker-driven, open-label clinical trial.

Methods We did a single-arm, open-label, phase 1/2 trial of sirolimus in patients with active systemic lupus erythematosus disease unresponsive to, or intolerant of, conventional medications at the State University of New York Upstate Medical University (Syracuse, NY, USA). Eligible participants (aged ≥18 years) had active systemic lupus erythematosus fulfilling four or more of 11 diagnostic criteria defined by the American College of Rheumatology. We excluded patients with allergy or intolerance to sirolimus, patients with life-threatening manifestations of systemic lupus erythematosus, proteinuria, a urine protein to creatinine ratio higher than 0·5, anaemia, leucopenia, or thrombocytopenia. Patients received oral sirolimus at a starting dose of 2 mg per day, with dose adjusted according to tolerance and to maintain a therapeutic range of 6–15 ng/mL. Patients were treated with sirolimus for 12 months. Safety outcomes included tolerance as assessed by the occurrence of common side-effects. The primary efficacy endpoint was decrease in disease activity, assessed using the British Isles Lupus Assessment Group (BILAG) index and the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). Blood samples of 56 matched healthy individuals were obtained as controls for immunobiological outcomes monitored at each visit. The primary efficacy endpoint was assessed in all patients who completed 12 months of treatment, and all patients who received at least one dose of treatment were included in the safety analyses. This trial is registered with ClinicalTrials.gov, number NCT00779194.

Findings Between March 9, 2009, and Dec 8, 2014, 43 patients were enrolled, three of whom did not meet eligibility criteria. 11 of the 40 eligible patients discontinued study treatment because of intolerance (n=2) or non-compliance (n=9). SLEDAI and BILAG disease activity scores were reduced during 12 months of treatment in 16 (55%) of 29 patients who completed treatment. Mean SLEDAI score decreased from 10·2 (SD 5·6) at enrolment to 4·8 (4·5) after 12 months of treatment ($p<0·001$) and the mean total BILAG index score decreased from 28·4 (12·4) at enrolment to 17·4 (10·7) after 12 months of treatment ($p<0·001$). The mean daily dose of prednisone required to control disease activity decreased from 23·7 mg (SD 9·6) to 7·2 mg (2·3; $p<0·001$) after 12 months of treatment. Sirolimus expanded $CD4^+CD25^+FoxP3^+$ regulatory T cells and $CD8^+$ memory T-cell populations and inhibited interleukin-4 and interleukin-17 production by $CD4^+$ and $CD4^-CD8^-$ double-negative T cells after 12 months. $CD8^+$ memory T cells were selectively expanded in SRI-responders. Patient liver function and lymphocyte counts were unchanged. Although HDL-cholesterol ($Z=-2·50$, $p=0·012$), neutrophil counts ($Z=-1·92$, $p=0·054$), and haemoglobin ($Z=-2·83$, $p=0·005$) were moderately reduced during treatment, all changes occurred within a range that was considered safe. Platelet counts were slightly elevated during treatment ($Z=2·06$, $p=0·0400$).

Interpretation These data show that a progressive improvement in disease activity is associated with correction of pro-inflammatory T-cell lineage specification in patients with active systemic lupus erythematosus during 12 months of sirolimus treatment. Follow-up placebo-controlled clinical trials in diverse patient populations are warranted to further define the role of mTOR blockade in treatment of systemic lupus erythematosus.

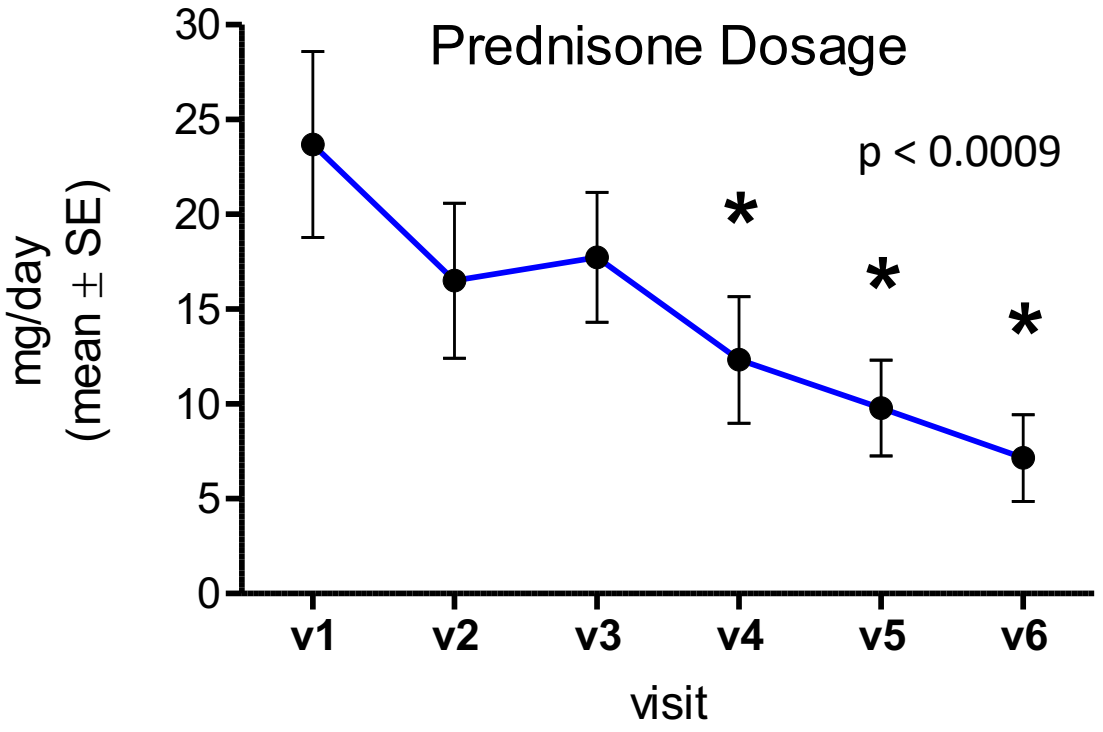
Funding Pfizer, the National Institutes of Health, and the Central New York Community Foundation.

Introduction

Systemic lupus erythematosus is a chronic inflammatory disease that primarily affects women of child-bearing age, with debilitating and potentially life-threatening consequences.[1] The disease represents an unmet medical need because the drugs that are available are only partly effective and have considerable side-effects.[2] Consequently, 10% of patients with systemic lupus erythematosus die within 5 years of diagnosis.[3] Although the cause of systemic lupus erythematosus is incompletely understood, it is thought to involve cellular dysfunction of the immune system

Rapamycin Reduced Daily Prednisone Dosage

Visit 1: Baseline
Visit 2: Month 1
Visit 3: Month 3
Visit 4: Month 6
Visit 5: Month 9
Visit 6: Month 12



*** *p* < 0.05 compared to visit 1**

Daily prednisone use was reduced from 23.7±4.9 mg to 7.2±2.3 mg after 12 months (p=0.02).

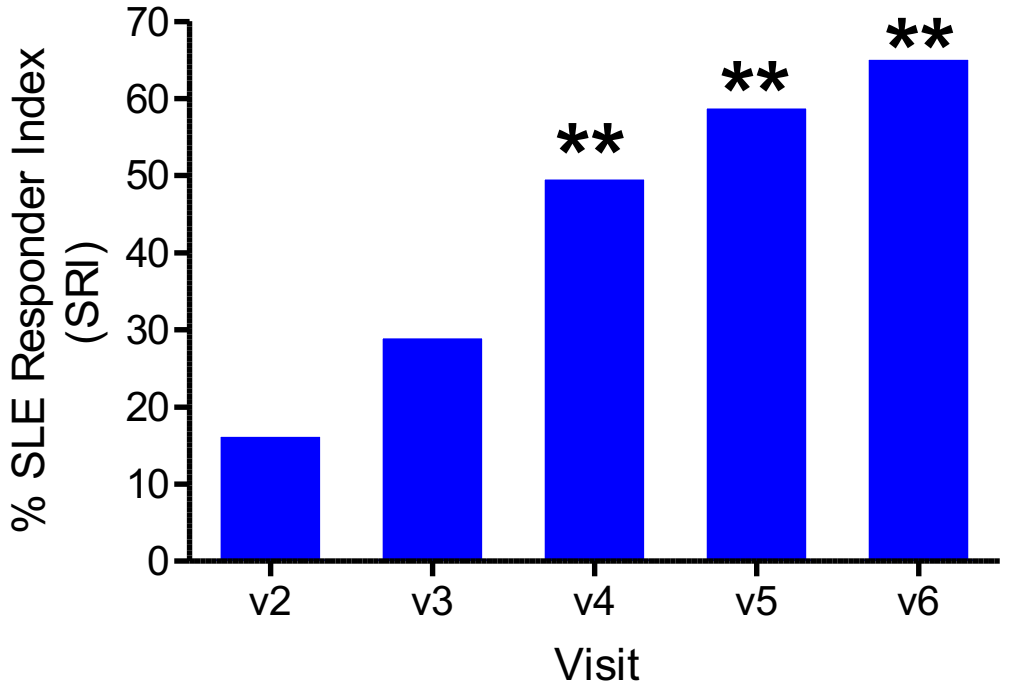
Prospective Study of Rapamycin for the Treatment of SLE;
ClinicalTrials.gov Identifier: NCT00779194

Lancet, 391:1186-1196 (2018)

Effect of Rapamycin on SRI-4

- SLE Responder Index (SRI)
- Prospective Study of Rapamycin for the Treatment of SLE; ClinicalTrials.gov Identifier: NCT00779194
- Preliminary analysis of SRI at Month 12 (visit 6): 19/29: 65.5%

Visit 1: Baseline
Visit 2: Month 1
Visit 3: Month 3
Visit 4: Month 6
Visit 5: Month 9
Visit 6: Month 12

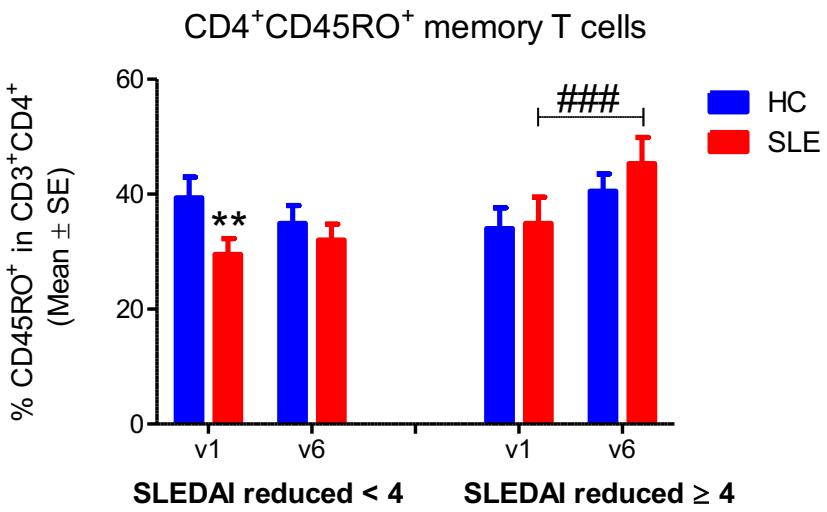


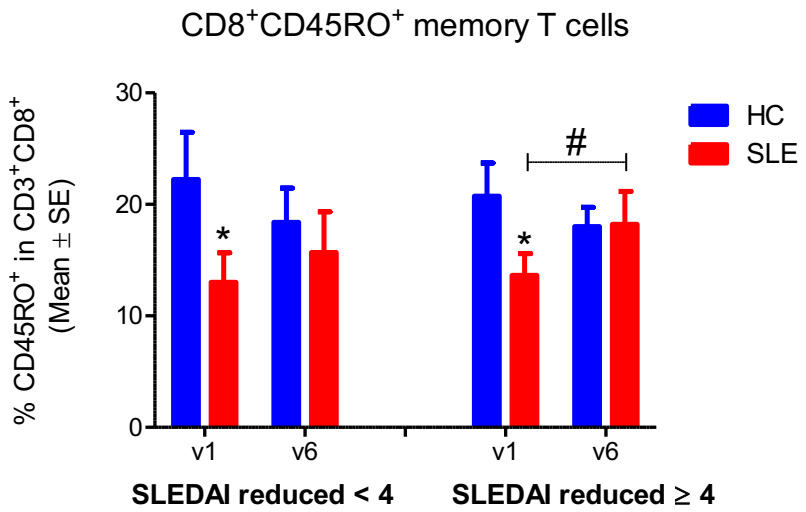
$\chi^2 = 12.76$
$p = 0.0004$

** $p < 0.01$ compared to visit 2

Lancet, 391:1186-1196 (2018)

Rapamycin expanded CD4 and CD8 T cells memory T cells *only* among SRI-responders

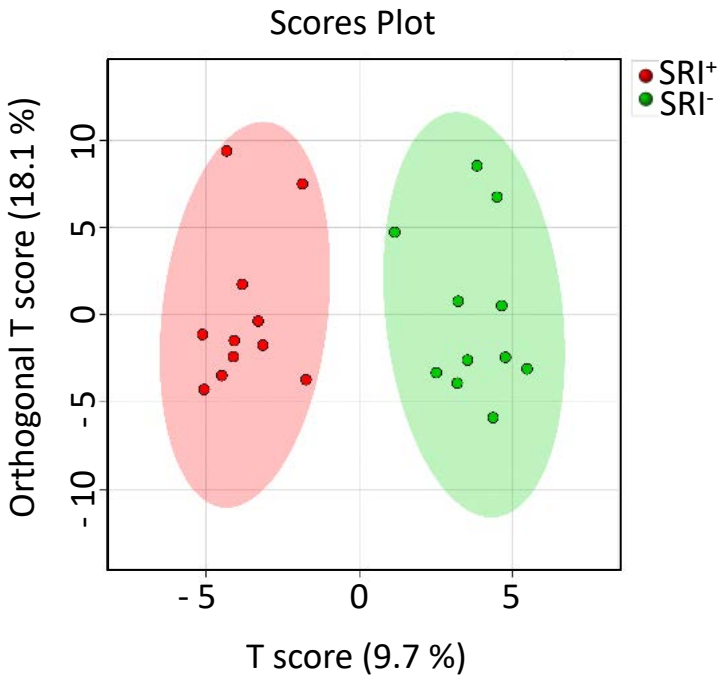


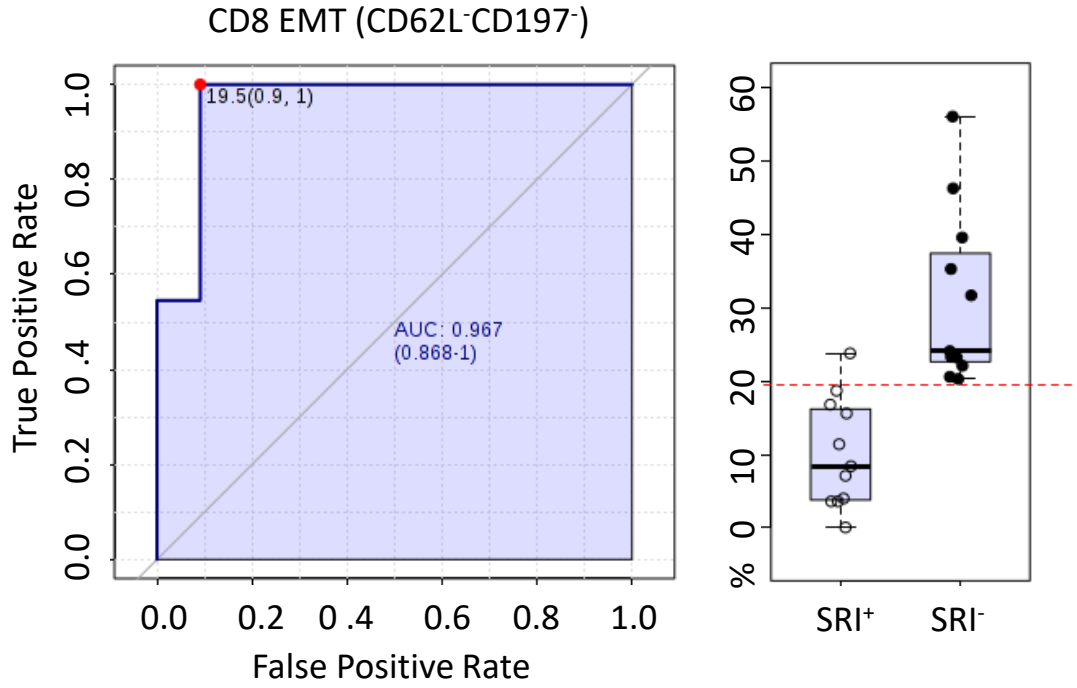


Lancet, 391:1186-1196 (2018)

677 biomarkers effectively distinguished responders (SRI^+) from non-responders (SRI^-)

Area under the receiver operating characteristic (ROC) curve (AUC) logistic regression approach identified $CD8^+$ EMT cells (AUC = 0.967) to have the greatest specificity and sensitivity to distinguish SRI^+ and SRI^- patients

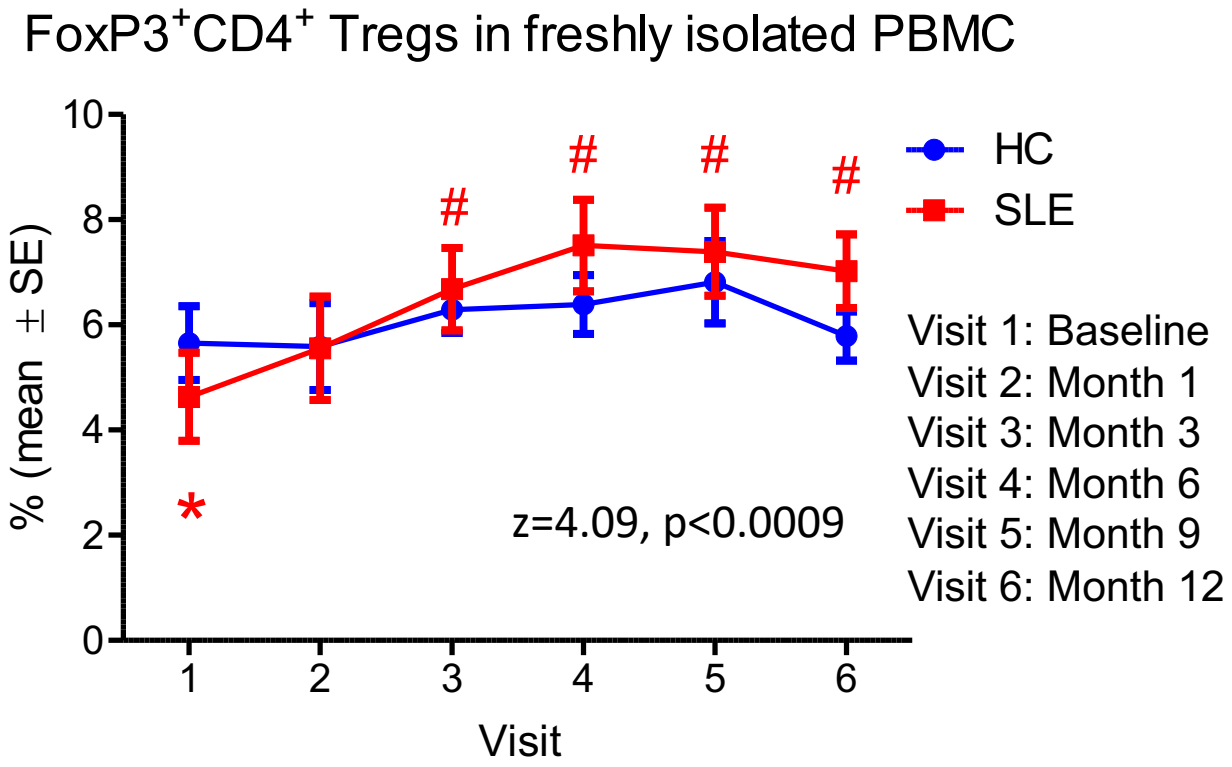




Depletion of $CD8^+$ EMT cells predicts responsiveness to rapamycin

Lancet, 391:1186-1196 (2018)

Rapamycin expands Tregs in SLE patients in Vivo



* $p < 0.05$, ** $p < 0.01$ compared to control (HC); # $p < 0.05$, ## $p < 0.01$ compared to baseline (visit 1)

Lancet, 391:1186-1196 (2018)

nature aging

ARTICLES

https://doi.org/10.1038/s43587-022-00278-w

Check for updates

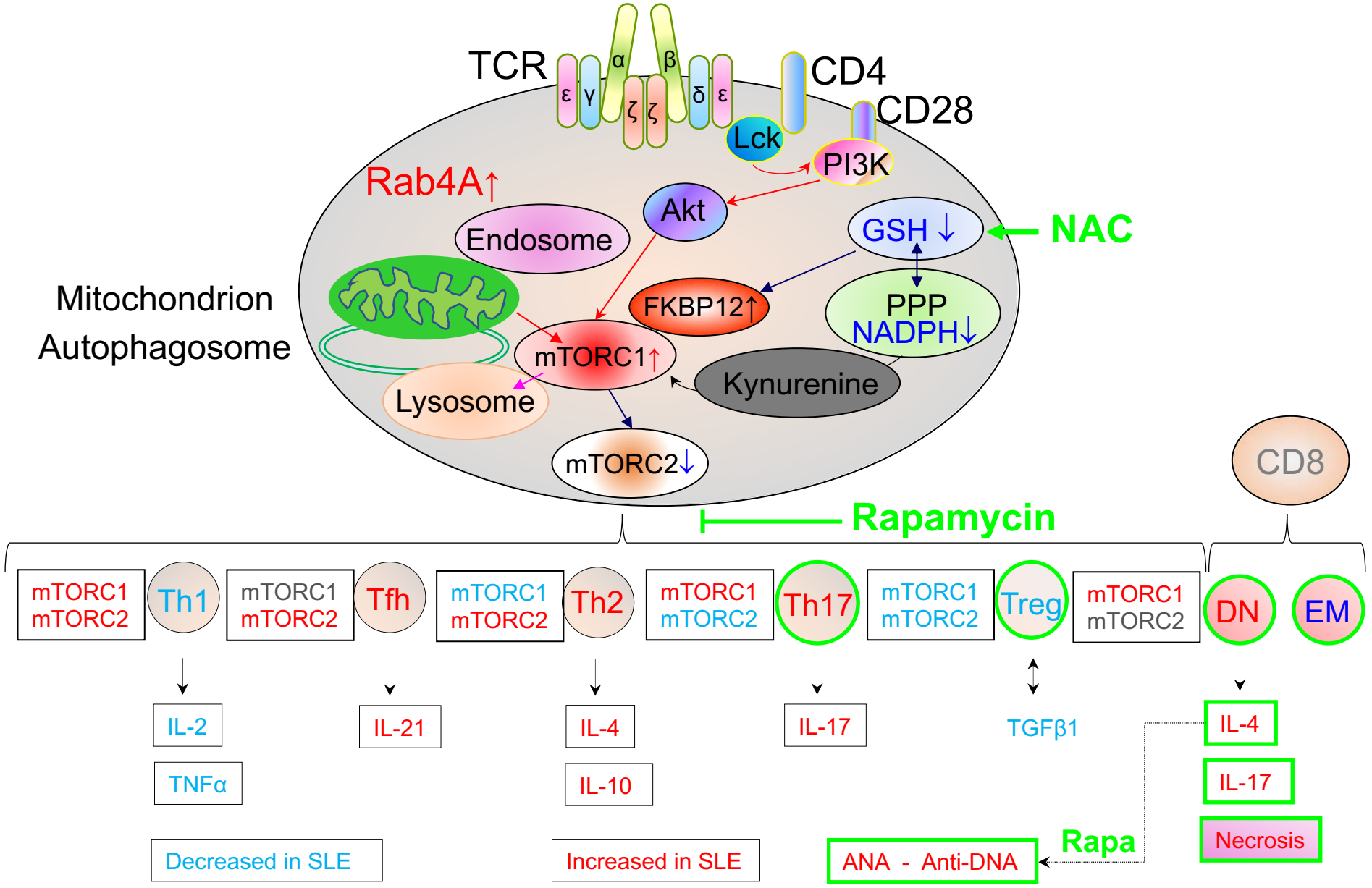
OPEN

Long-lasting geroprotection from brief rapamycin treatment in early adulthood by persistently increased intestinal autophagy

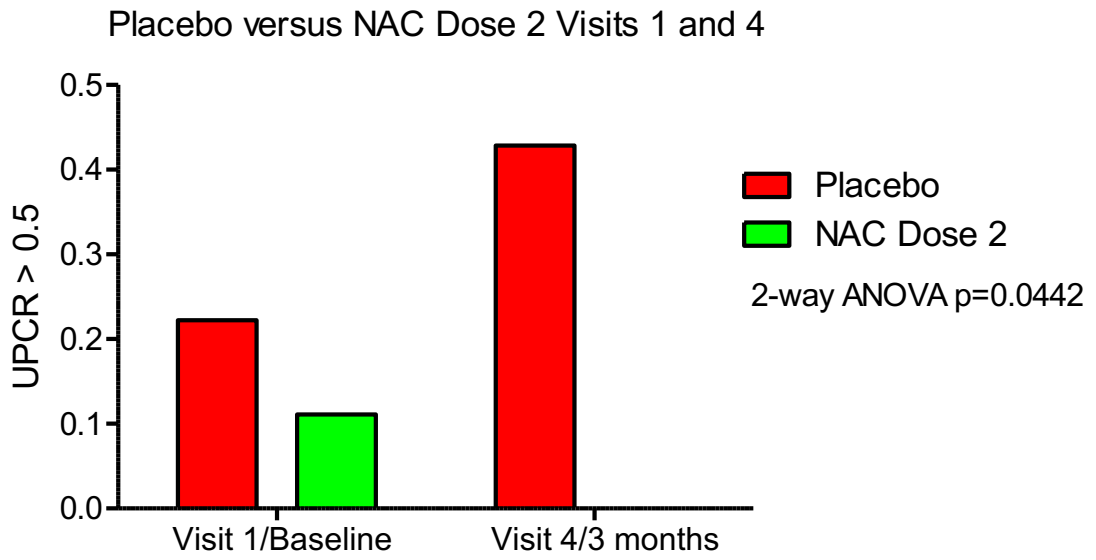
Paula Juricic[1,3,5], Yu-Xuan Lu[1,5], Thomas Leech[1,5], Lisa F. Drews[1], Jonathan Paulitz[1], Jiongming Lu[1], Tobias Nespital[1], Sina Azami[1], Jennifer C. Regan[2,4], Emilie Funk[1], Jenny Fröhlich[1], Sebastian Grönke[1] and Linda Partridge[1,2] ✉

Mice were treated with oral rapamycin was added at concentration of 14 ppm (mg of drug per kg of food) using Eudragit S100 (Evonik) between ages of 3-6 months. Published: 29 August 2022

mTOR is a sensor of metabolic and oxidative stress and effector of T-cell lineage specification



NAC (1.2 g bid) reduced proteinuria



	Placebo		NAC Dose 2	
Visits	Proteinuria +	Proteinuria -	Proteinuria +	Proteinuria -
Baseline/Visit 1	2	7	1	8
3-month/Visit 3	3	4	0	8
	Two patients' urine samples were missing, one had proteinuria on visit 1		One urine sample missing, which did not show proteinuria on visit 1	

Arthritis & Rheumatology

AN OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF RHEUMATOLOGY

AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

Systemic Lupus Erythematosus | Free to Read

Brief Report: Attention Deficit and Hyperactivity Disorder Scores Are Elevated and Respond to *N*-Acetylcysteine Treatment in Patients With Systemic Lupus Erythematosus†‡

Three Rheumatology Fellows

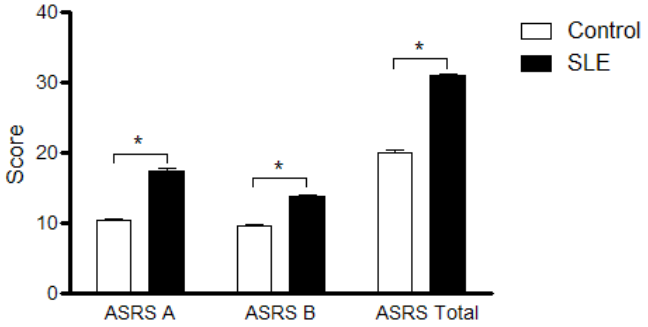
Ricardo J. Garcia, Lisa Francis, Maha Dawood, Zhi-Wei Lai, Stephen V. Faraone, Andras Perl

First published: 11 February 2013 | https://doi.org/10.1002/art.37893 | Citations: 67

† ClinicalTrials.gov identifier: NCT00775476.

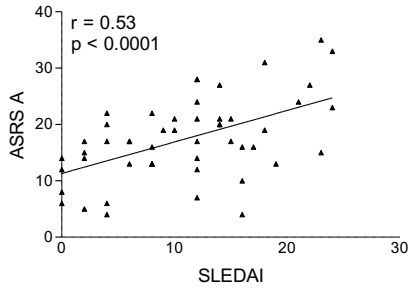
‡ Presented in part at the 74th Annual Scientific Meeting of the American College of Rheumatology, Atlanta, GA, 2010.

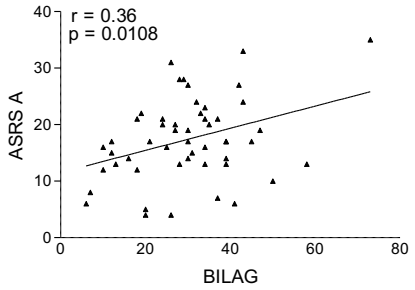
ADHD Self-Report Scale (ASRS) scores are increased in SLE

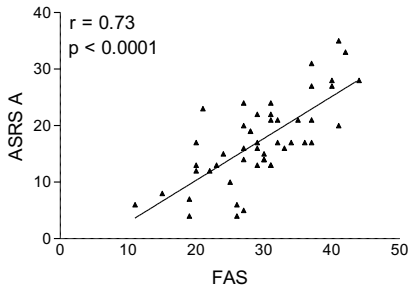


The cognitive/inattentive (ASRS part A), hyperactivity/impulsive (ASRS part B), and combined (total) ASRS scores are increased in patients with SLE

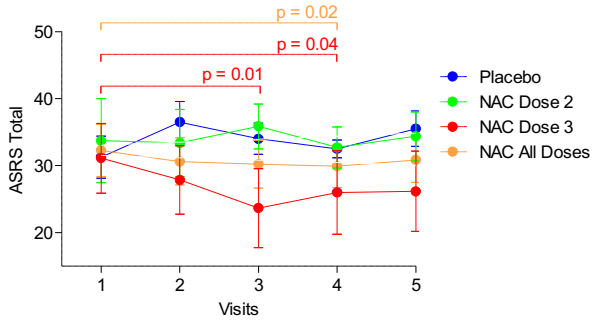
…correlate with disease activity…

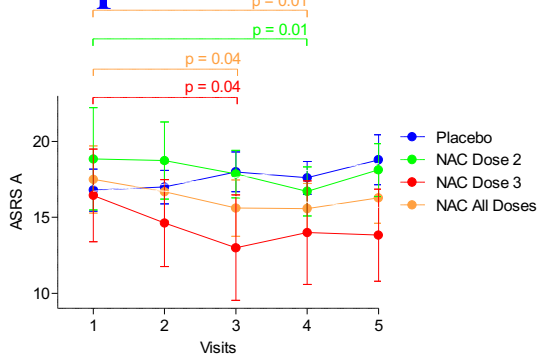






… and ASRS A scores respond to NAC in SLE





Arthritis Rheum. 65: 1313-1318 (2013). PMID: 23400548.

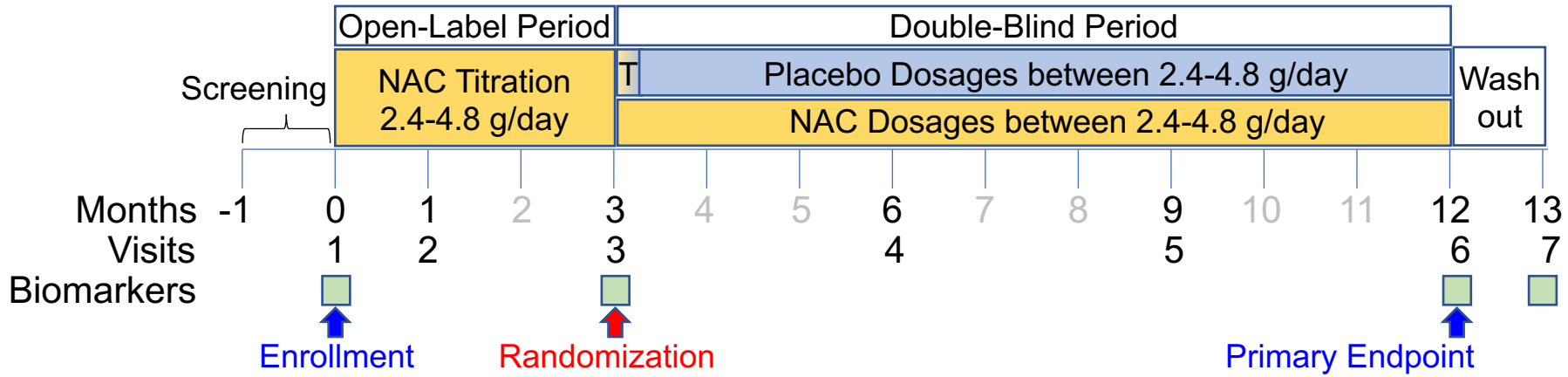


Figure 1. Schematic overview of the SNAC study. All participants will receive NAC for a 3-month open-label period, titrated up to the individual's maximally tolerated dosage between 2.4-4.8 g/day. Subjects who tolerate at least 2.4 g/day NAC will be randomized 1:1 to receive either NAC (at the subject's tolerated dosage) or matching placebo for the remaining 9 months (double-blind period). To minimize the risk of unblinding, NAC will be tapered down in the placebo arm over 1 week (T, taper) (2).The primary endpoint will be the achievement of SRI-4 (yes/no) at Month 12 relative to enrollment at Month 0.

It is an antidote for acetaminophen-induced liver failure, the leading cause of death due to acute liver failure
This safe intervention may also work in ILD
This safe intervention may also work in mTOR-dependent proteinuria
mTOR blockade extends lifespan via reducing inflammation, cardiovascular disease, and cancer rates

DISCLOSURE OF RESEARCH SUPPORT

NIH RO1 AI48079:
Genetic and immunological impact of the HRES-1 human endogenous retrovirus locus in SLE (1992-2015)

NIH RO1 AI72648:
Metabolic control of systemic autoimmunity (2008-2025)

NIH RO1 AI122176:
Endocytic Control of Autophagosome Formation in Lupus T cells (2016-2021)

NIH U01 AR076092 (2020-2026) **SLE Treatment with N-acetylcysteine (SNAC)**
FDA: IND # 101,320; RO1 AT004332 (2008-2012); R34AR068052 (2016-2019)

Wyeth/Pfizer Investigator-Initiated Research Grant:
Prospective Study of Rapamycin for the Treatment of Systemic Lupus Erythematosus (2009-2015; FDA: IND # 101,566)

NIH R34 AI141304: Treatment of SLE with sirolimus (2018-2020); U01 is pending

Thank you…

Rosa Trpcevski
Joanne Chilton
Paul Phillips
Zhi-Wei (Tony) Lai
Julie Yu
Hiroshi Kato
Christian Geier
Thomas Winans
Akshay Patel
Joy Park
Joshua Lewis
Xianjing Wang
Gyorgy Nagy
Agnes Koncz
David Fernandez
Tiffany Caza
Edward Doherty
Zachary Oaks
Bartos Adam
Miklossy Gabi
Hanczko Robi

October 1,2022
NAB-4th floor Auditorium
Hybrid meeting: also available via Webex

8 am - 1 pm

Starts with breakfast – Ends with lunch

8 am - 12 pm (15 min Coffee Break at 10 am)

Oral presentations:

Presentations should last 8 (eight) minutes allowing for 2 (two) minutes for discussion.

Junior Faculty Grantees and Trainees Present

Further discussions can take place during the poster session.

Attendees via Webex can post questions

Boxed meals and drinks from Panera

Poster Session during Lunch

Separate desks by division for faculty – for trainees

1 pm Dr. Knohl – Closing Remarks

Generate New Knowledge through Collaboration

Thank you….

Shouldn’t you control your mTOR

Discussions can follow during Lunch Poster Session and Beyond