

Electrical Activation of Neural Reflexes for the Treatment of Autoimmune Diseases

Can Vagal Nerve Stimulation Treat Rheumatoid Arthritis?



Eric Grigsby, MD, MBA

Founder and CEO, Neurovations
A Patient Care and Innovation Company

David Chernoff, MD

**Chief Medical Officer
Setpoint Medical**



Patient Care & Innovation Since 1992

1989-90

1991-94

1997-98

2005

2010-11

2013-14

2016

2018-19

Inaugural Napa Pain Conference

Dr Grigsby starts one of the first university pain management clinics in the US at UC Davis.

Napa Pain Institute

Dr. Grigsby is certified in first cohort of pain management by the Board of Anesthesiology.

Clinical Research

Leveraging Mayo Clinic training, Dr. Grigsby becomes Principal Investigator in early stage trials with active involvement in clinical and translational patient care

Neurovations!

Research and education combine to become Neurovations-a patient care and innovation company .

N3 Laboratories

Neuromodulation: The Science debuts focused on science and innovation of neuromodulation. Napa Pain Institute earns conference accrediting rights for continued medical education which at multiple conferences and events. N3 Laboratories is established.

Spine and Pain Center of Kaua'i

The Kauai Clinic is established in part to handle an underserved clientele. Kauai Pain Conference debuts to an international audience.

Redwood Pain Institute

Redwood Pain Institute opens in partnership with St. Joseph's Health.

Neurovations Center for Hope

The Neurovations Center for Hope begins research and development phase with 5 patients.

Clinics which do clinical research



An innovation company which owns medical
services

Rocca

FAMILY VINEYARDS

NAPA VALLEY



Certified Organic

Just the good stuff



Vegan

No fining or filtering



Native Yeast

Greater complexity



Family-run

Crafted with love



Small Production

Quality over quantity



Nothing Added

Ever

R O C C A W I N E S . C O M

The 27th Napa Pain Conference Online

August 15, 2020

Join us for Complimentary Registration and CME:

NapaPainConference.com

Speakers:

Larry F. Abbott, PhD (Columbia)

Carol A. Warfield, MD (Harvard)

Jianguo Cheng, MD, PhD (Case Western)

Penney Cowan (ACPA)

Roger B. Fillingim, PhD (U. Florida)

Yun Guan, MD, PhD (Johns Hopkins)

Sten Lindahl, MD, PhD (Nobel Committee)

Carmen R. Green, MD (U. Michigan)

David Provenzano, MD (Pain Diagnostics)

Richard W. Rosenquist, MD (Cleveland Clinic)

A long, narrow dining table is set up in a vineyard at sunset. The table is covered with a white tablecloth and is set with plates, glasses, and water bottles. A large group of people, including men and women in formal attire, are seated along the table, engaged in conversation and dining. The vineyard rows are visible on both sides of the table, and the background shows a hazy sunset sky with a mountain range in the distance. String lights are strung across the vineyard, adding a warm, ambient glow to the scene.

Welcome to
The Napa Wine College
NapaWineCollege.com

Electrical Activation of Neural Reflexes for the Treatment of Autoimmune Diseases

Can Vagal Nerve Stimulation Treat Rheumatoid Arthritis?

Vagal Nerve Stimulation - Many Possibilities

Depression

Anxiety

Seizures

Autonomic dysfunction

Tinnitus

Constipation

Atrial fibrillation

Migraine

Weight loss

Rheumatoid Arthritis

Vagus Nerve Stimulation

- VNS - Implanted electrode and pulse generator
- tVNS - transdermal vagus nerve stimulation
- taVNS - transdermal, auricular, vagus nerve stimulation

VNS and Epilepsy

The Food and Drug Administration (FDA) has approved vagus nerve stimulation for people who:

Are 4 years old and older

Have focal (partial) epilepsy

Have seizures that aren't well-controlled with medications

VNS and Depression

The FDA has also approved vagus nerve stimulation for the treatment of depression in adults who:

- Have chronic, hard-to-treat depression (treatment-resistant depression)
- Haven't improved after trying four or more medications or ECT, or both
- Continue standard depression treatments along with vagus nerve stimulation

Covid and tVNS - Airway Effects

This week the Gammacore tVNS system was approved by FDA under the EUA for:

“...adult patients with known or suspected COVID-19 who are experiencing exacerbation of asthma-related dyspnea and reduced airflow....”

David Chernoff, MD

**Chief Medical Officer
Setpoint Medical**

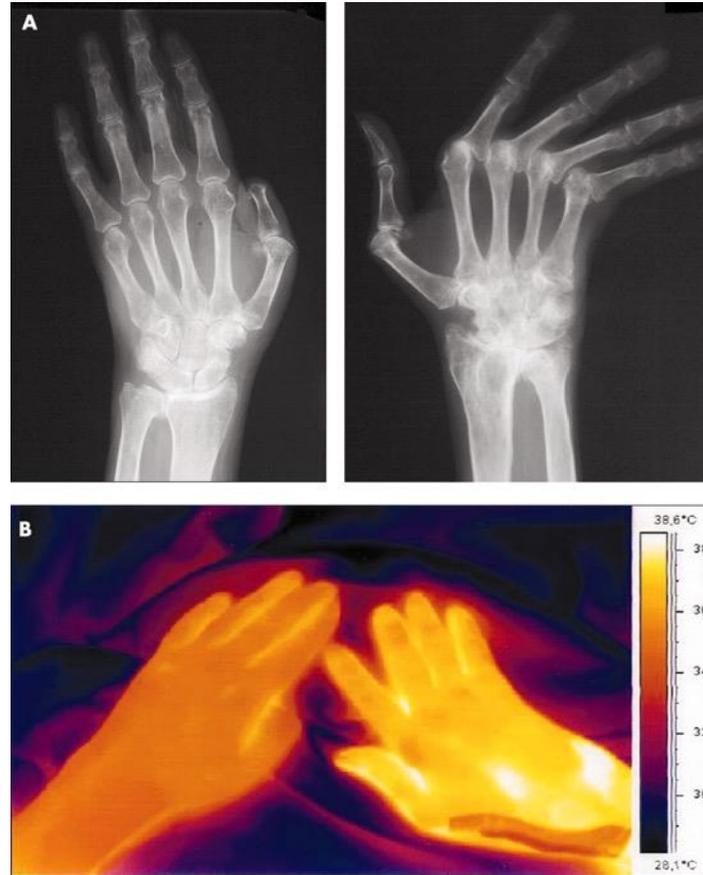




Electrical Activation of Neural Reflexes for Treatment of Autoimmune Diseases

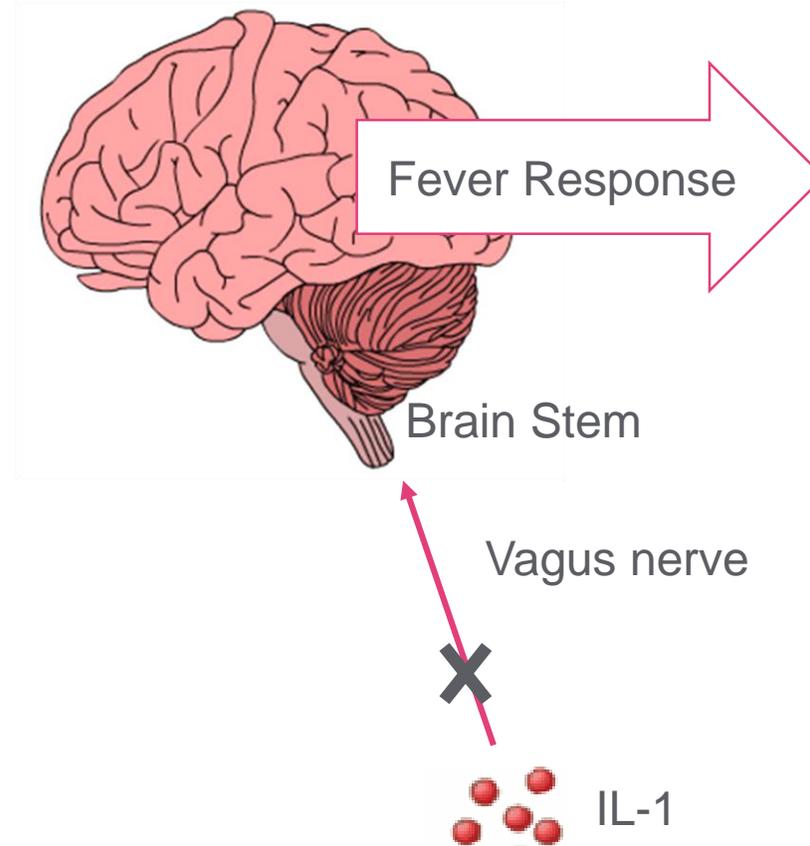
DAVID CHERNOFF, MD
Chief Medical Officer
SetPoint Medical

NEURAL CONTROL OVER INFLAMMATION



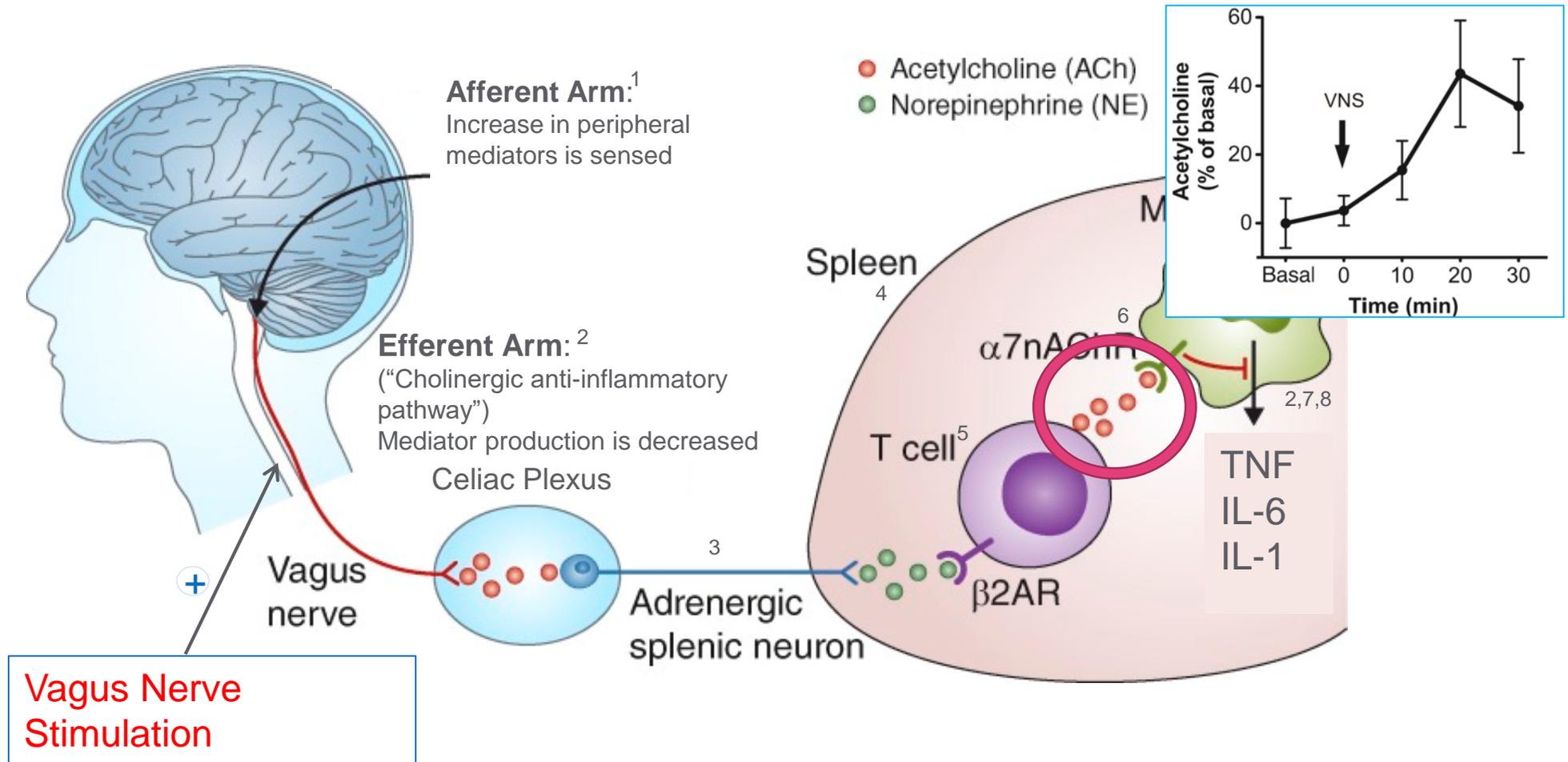
THE INFLAMMATORY REFLEX

DISCOVERY OF AFFERENT ARC



THE INFLAMMATORY REFLEX

MECHANISM OF ACTION MODULATES MULTIPLE INFLAMMATORY PATHWAYS



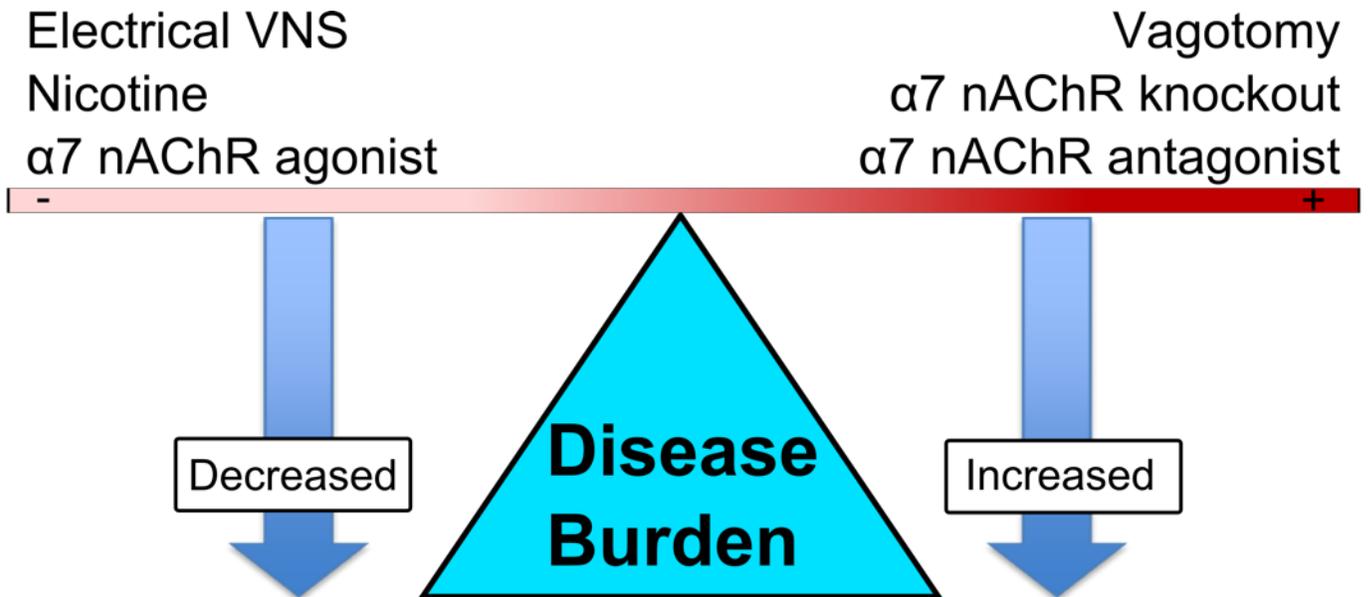
1. [Neurosci Lett 1995;183\(1\):27](#)
 2. [Nature 2000;405\(6785\):458](#)
 3. [PNAS 2008;105\(7\):11008](#)
 4. [J Exp Med 2006;203\(7\):1623](#)

5. [Science 2011;334\(6052\):98](#)
 6. [Nature 2003;421\(6921\):385](#)
 7. [Nat Immunol 2005;6\(8\):844](#)
 8. [Nat Med 2004;10\(11\):1216](#)

PRECLINICAL RESEARCH

EXPERIMENTAL INFLAMMATION MODELS USED TO CONFIRM THE MECHANISM OF ACTION FOR INFLAMMATORY REFLEX

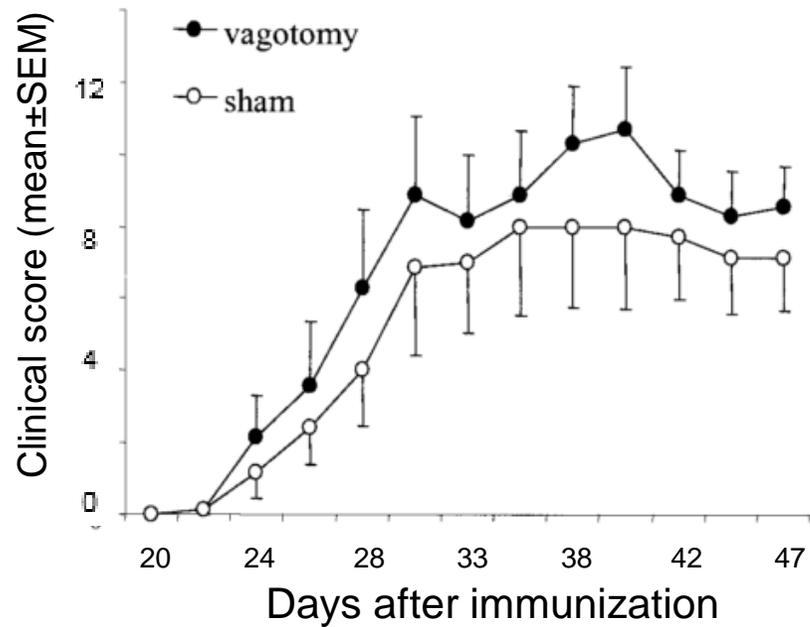
- Arthritis
- Colitis
- Multiple Sclerosis
- Endotoxemia
- Sepsis
- Pancreatitis
- Hemorrhagic shock
- Intracerebral hemorrhage
- Ischemia-reperfusion
 - Suprarenal aortic
 - Myocardial
 - Renal
 - Cerebral
- Artery occlusion shock
- Carrageenan-induced inflammation
- Burn-induced injury
- Ventilator-induced lung injury
- Post-operative ileus



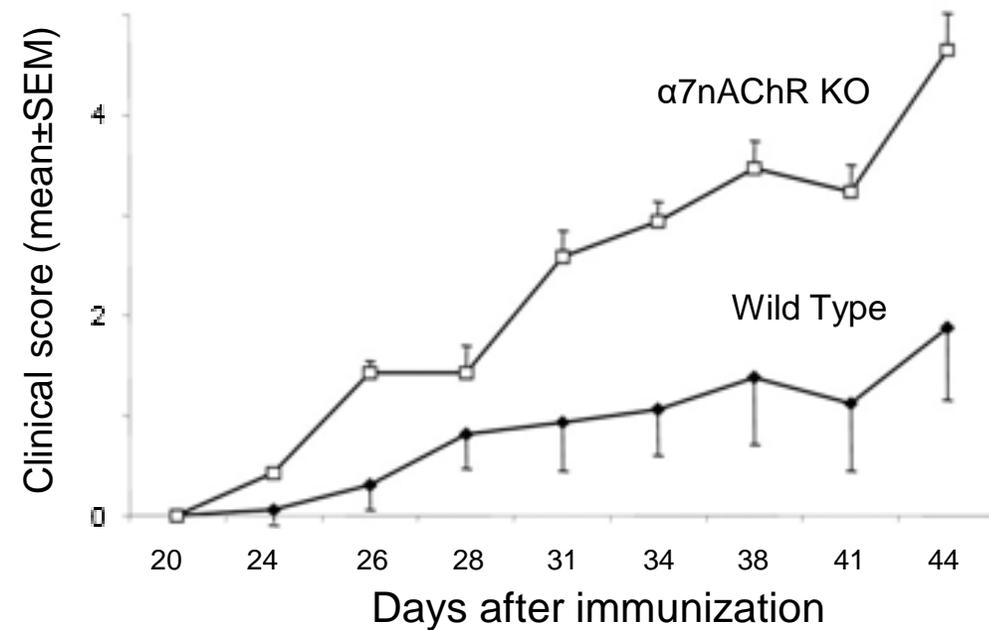
PRECLINICAL RESEARCH

MANIPULATION OF THE INFLAMMATORY REFLEX IN COLLAGEN-INDUCED ARTHRITIS (CIA) MODEL

Vagotomy worsens CIA

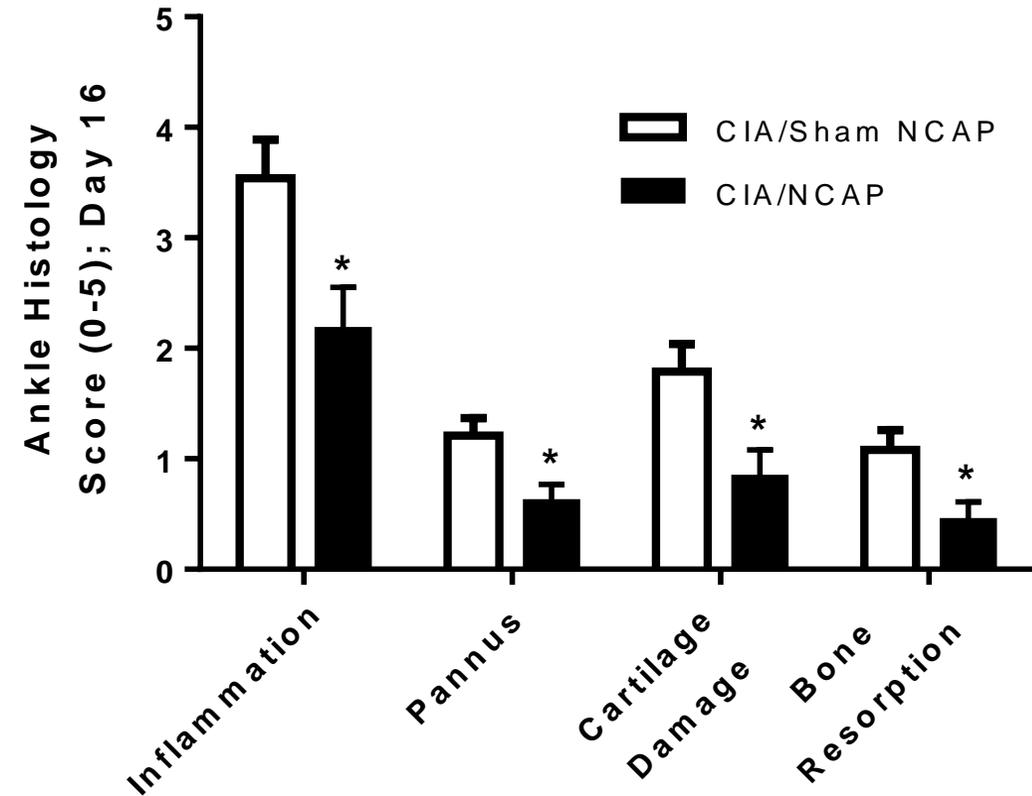
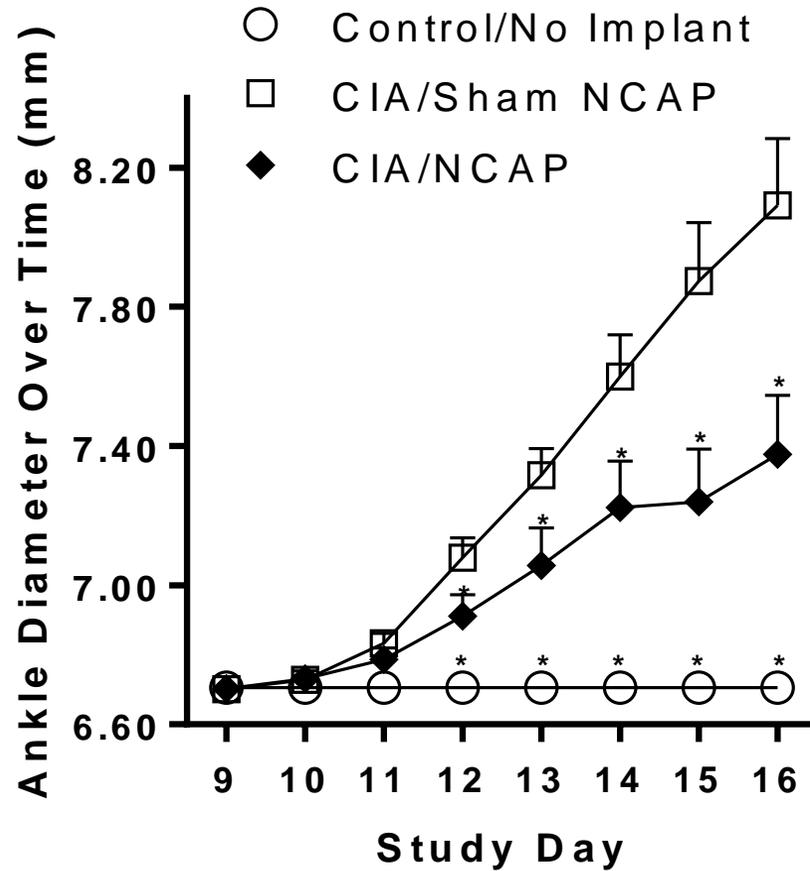


$\alpha 7$ nAChR KO Mice get more severe disease



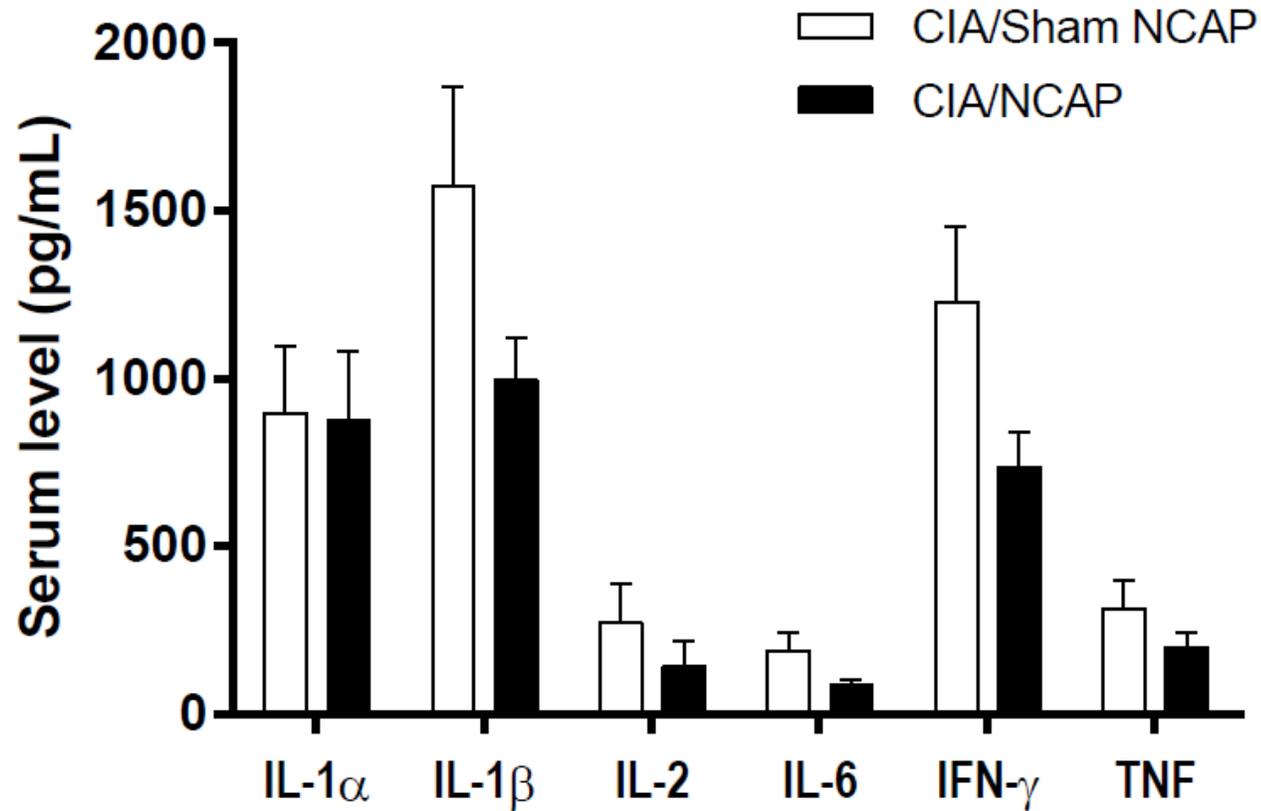
PRECLINICAL RESEARCH

NEUROSTIMULATION OF CHOLINERGIC ANTI-INFLAMMATORY PATHWAY IN RAT COLLAGEN-INDUCED ARTHRITIS (CIA) MODEL



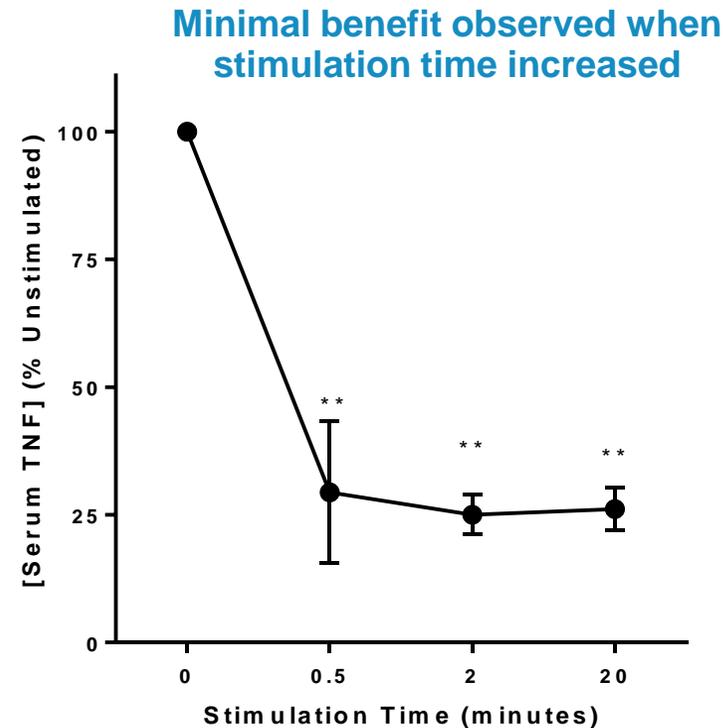
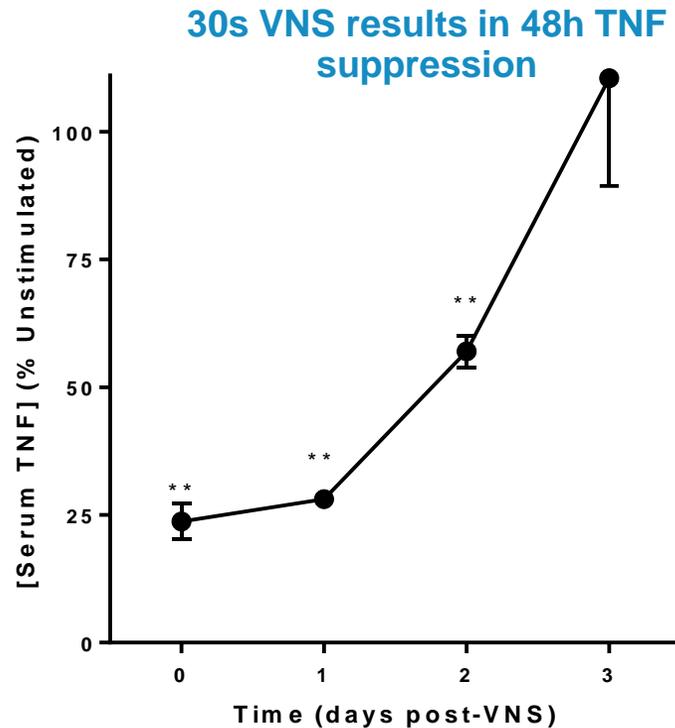
PRECLINICAL RESEARCH

VAGUS NERVE STIMULATION IN RAT COLLAGEN-INDUCED ARTHRITIS (CIA) MODEL REDUCES KEY CIRCULATING PROINFLAMMATORY CYTOKINES



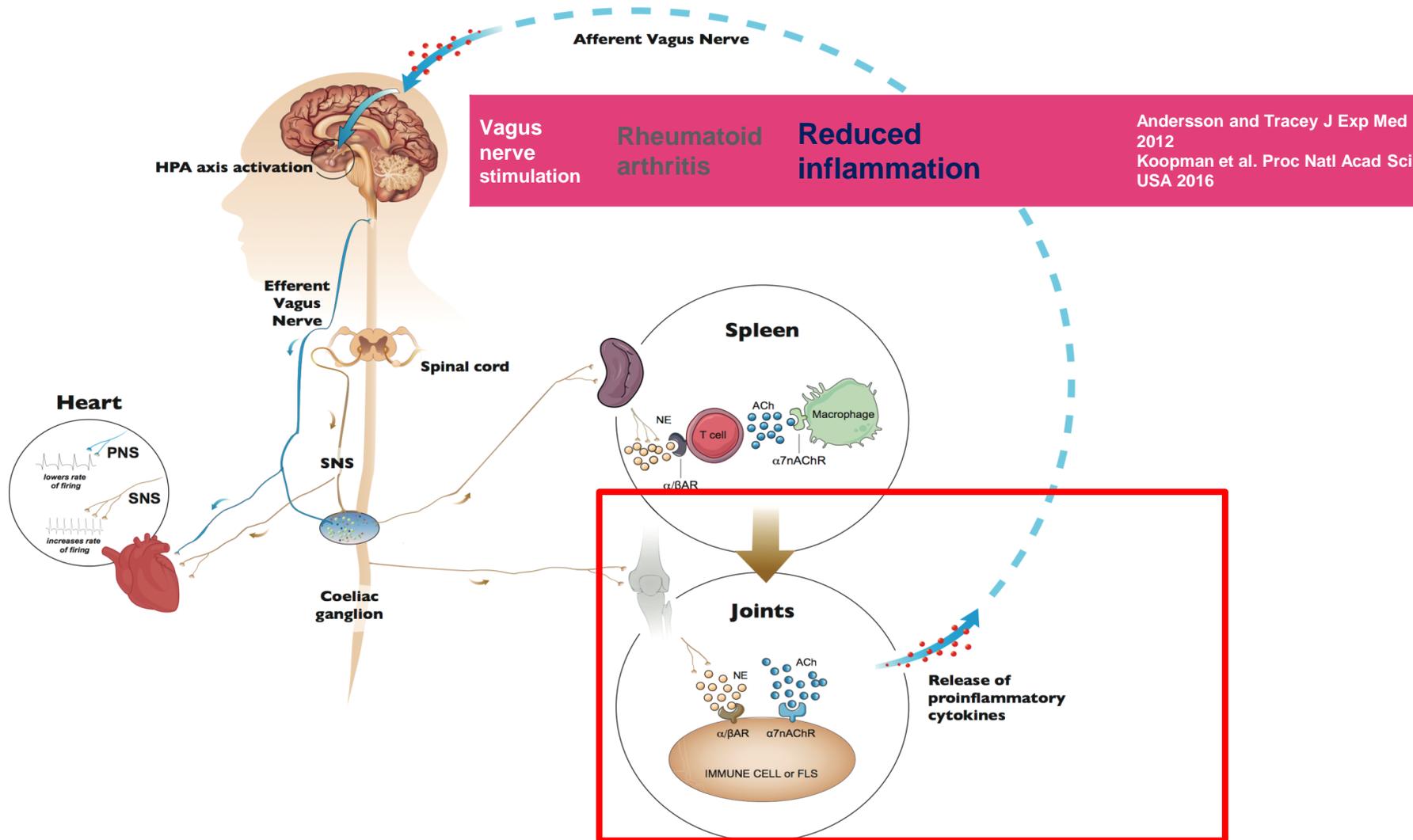
TRANSLATIONAL RESEARCH

BRIEF PERIODS OF ELECTRICAL VAGUS STIMULATION IN MICE INDUCED PROLONGED REDUCTION IN LPS-INDUCED TNF PRODUCTION



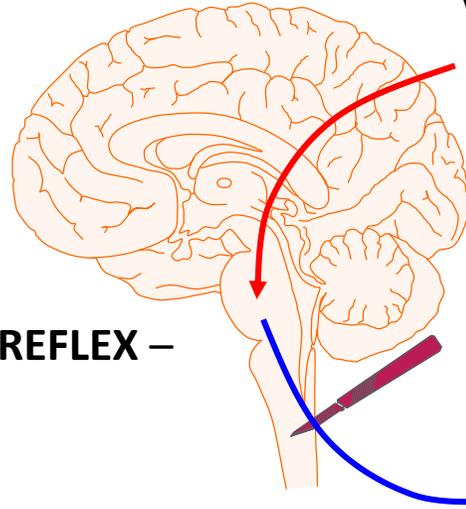
Implication: Therapeutic effect can likely be achieved chronically in humans with low duty cycle stimulation

Could the cholinergic anti-inflammatory pathway control *chronic* inflammation?



Vagotomy Delays Resolution and Reduces SPM

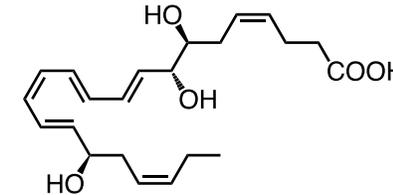
Kevin Tracey
INFLAMMATORY REFLEX –
 ANTI-INFLAMMATION



Vagal nerve stimulation

Cytokines
 Pro-inflammatory eicosanoids
 DAMPs
 PAMPs

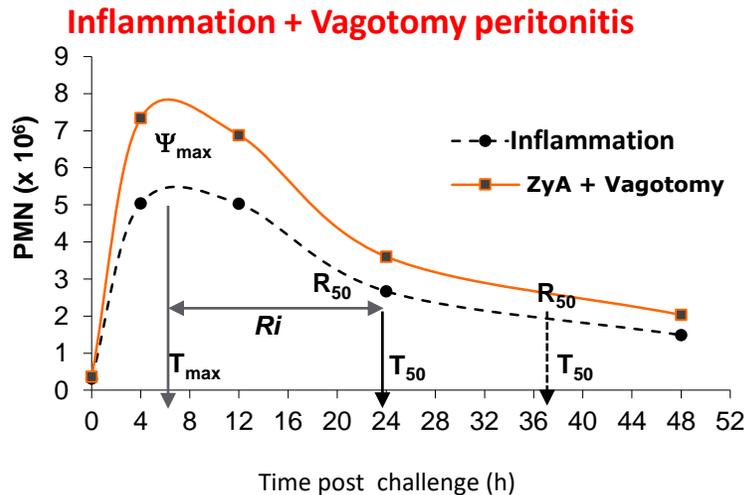
Resolvin D1



Resolution

↑ Pro-Resolving Mediators

↓ Pro-inflammatory Mediators



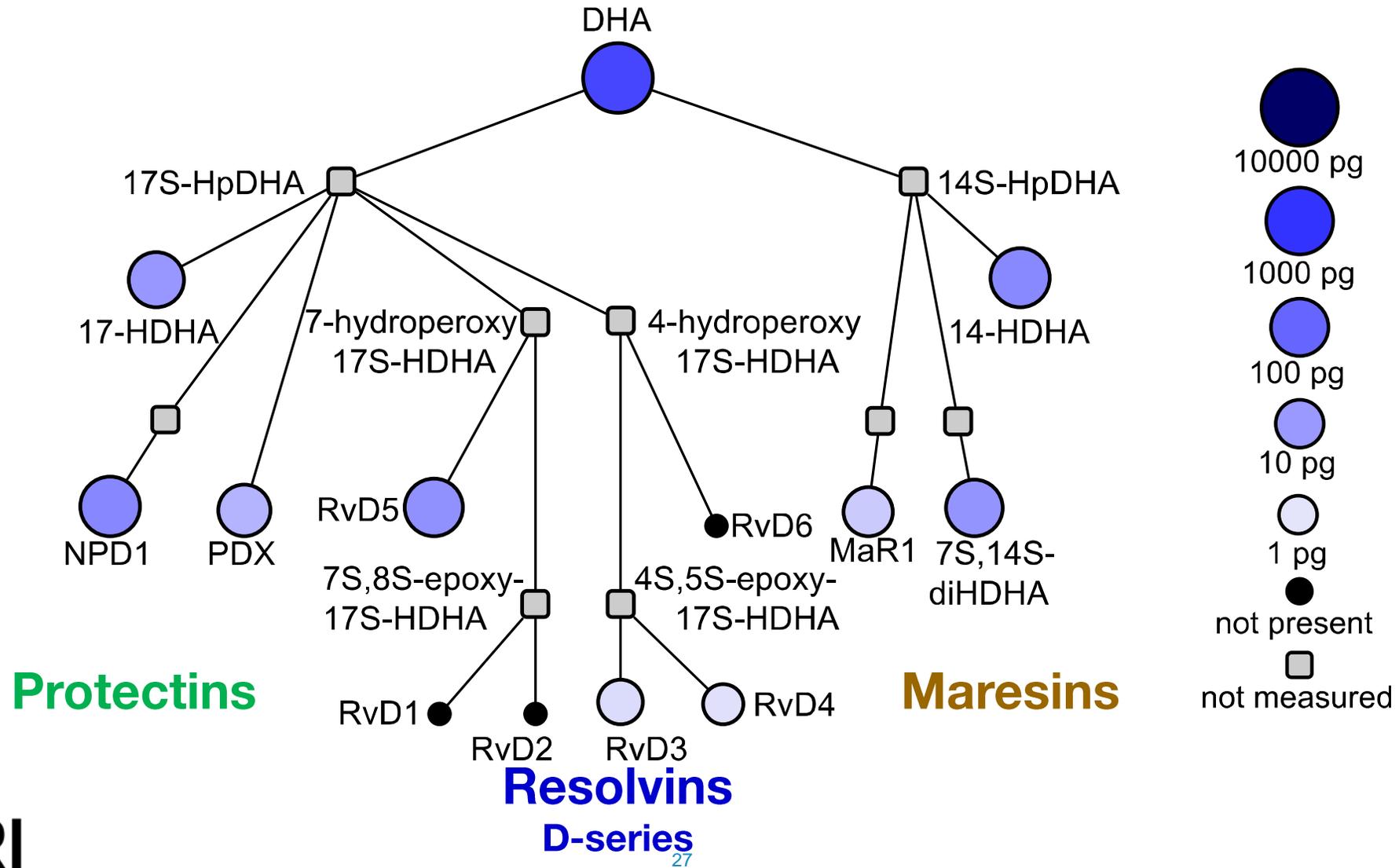
JEM

Vagus nerve controls resolution and pro-resolving mediators of inflammation

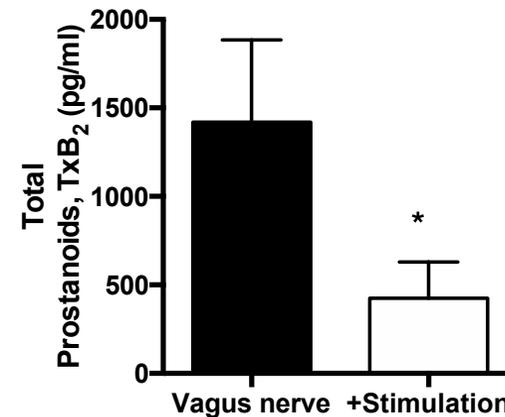
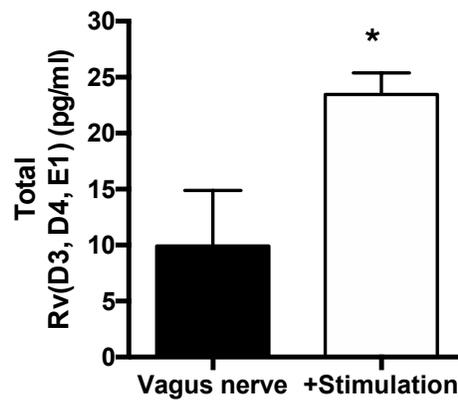
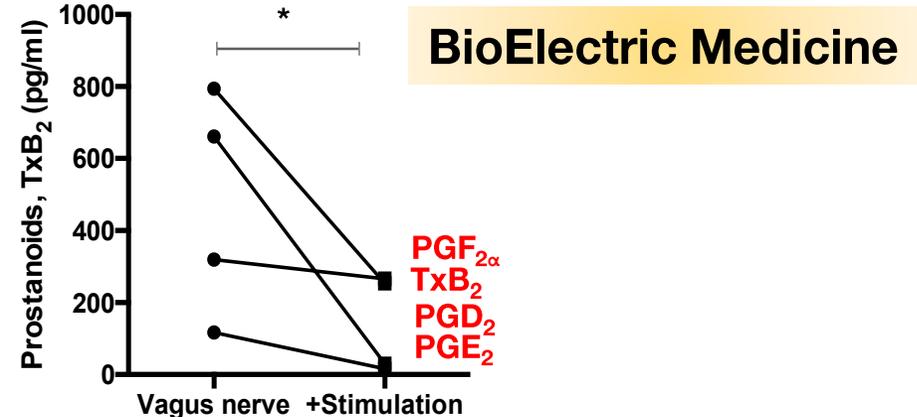
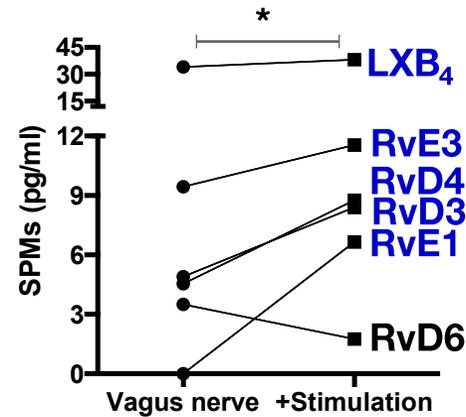
Valbona Mirakaj,^{1,2} Jesmond Dalli,¹ Tiago Granja,² Peter Rosenberger,² and Charles N. Serhan¹

¹Center for Experimental Therapeutics and Reperfusion Injury, Harvard Institutes of Medicine, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02115

Human Vagus Nerve Produces Endogenous SPMs



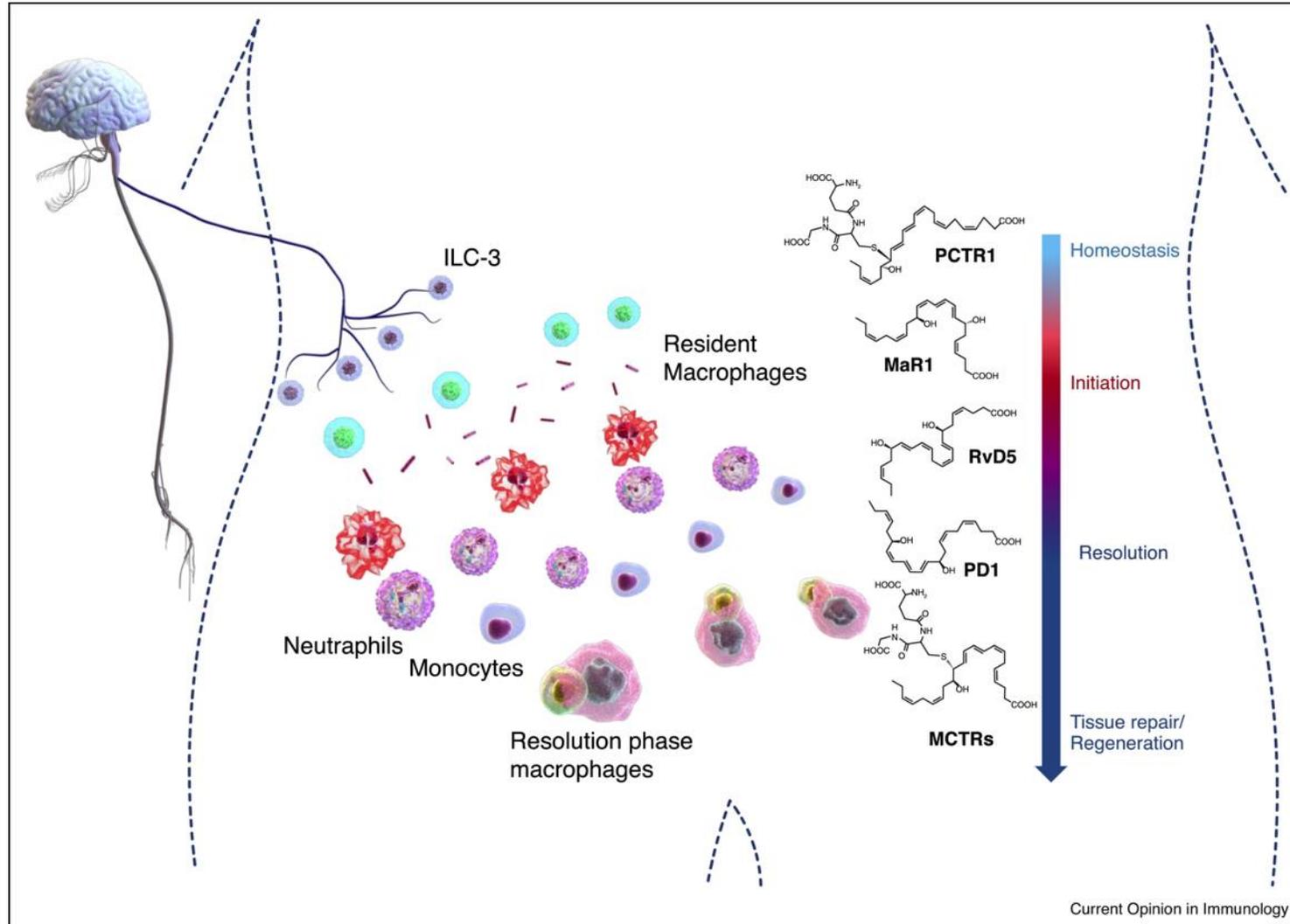
Electrical Stimulation of Vagus Nerve Increases Endogenous Production of SPMs and Reduces Prostaglandins



Results are express as mean ± SEM from three independent animals. **p*<0.05.

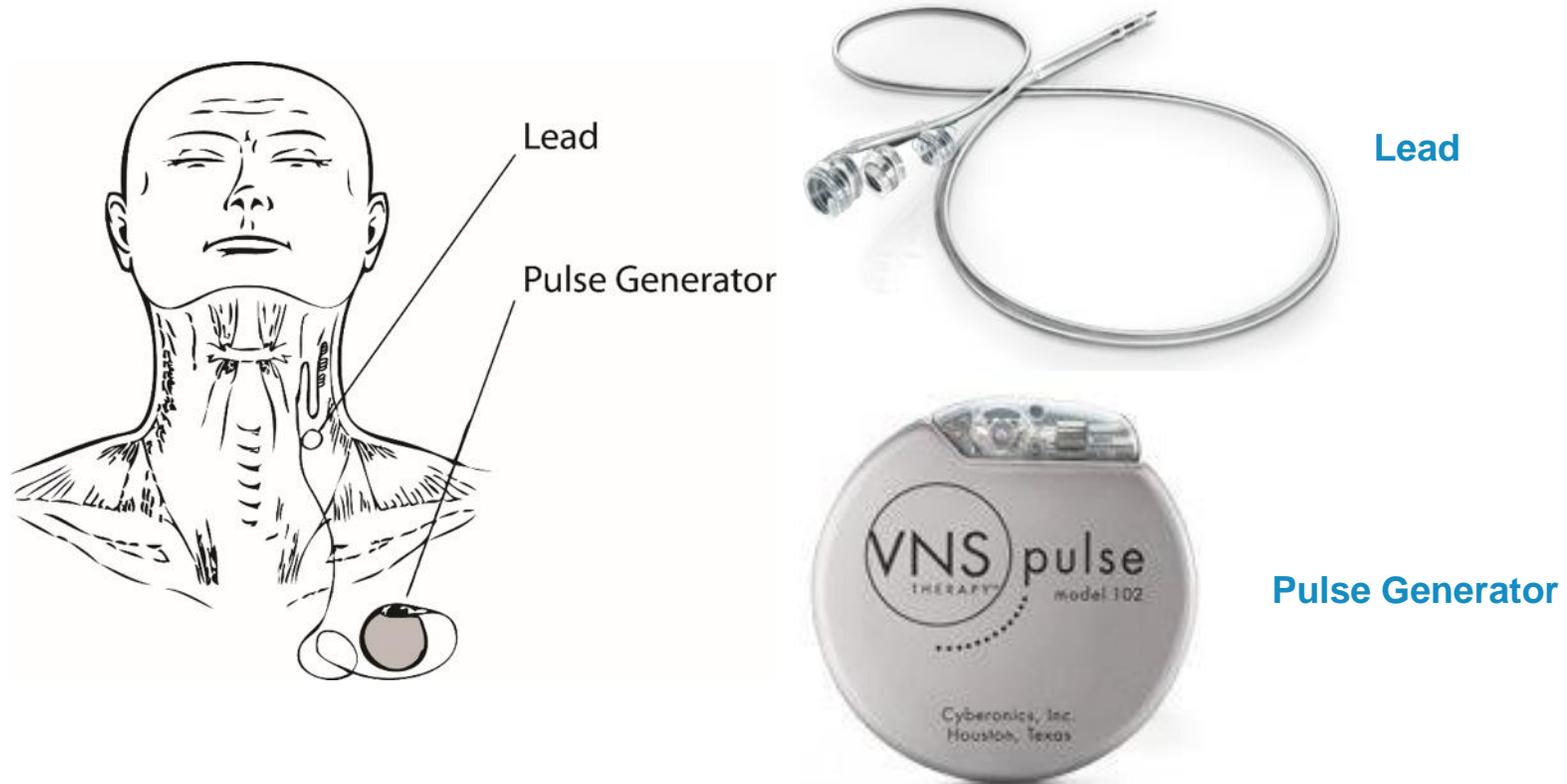
PRECLINICAL RESEARCH

VAGUS NERVE STIMULATION AND IMMUNO-RESOLUTION



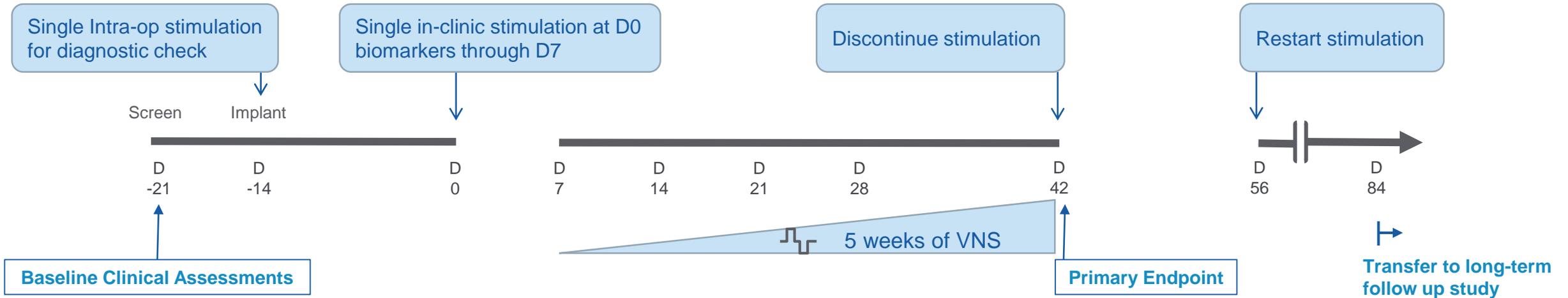
CLINICAL RESEARCH – RA PROOF OF CONCEPT

COMMERCIALLY AVAILABLE VAGUS NERVE STIMULATOR (CYBERONICS) WAS EVALUATED WITH REPROGRAMMED PULSE PARAMETERS



CLINICAL RESEARCH – RA PROOF OF CONCEPT

17 PATIENT, OPEN LABEL STUDY CONDUCTED IN EUROPE



4 centers; 12/17 patients from Academic Medical Center in Amsterdam

Cohort I: MTX-IR (7),

Cohort II Multiple Biologic-IR (10)

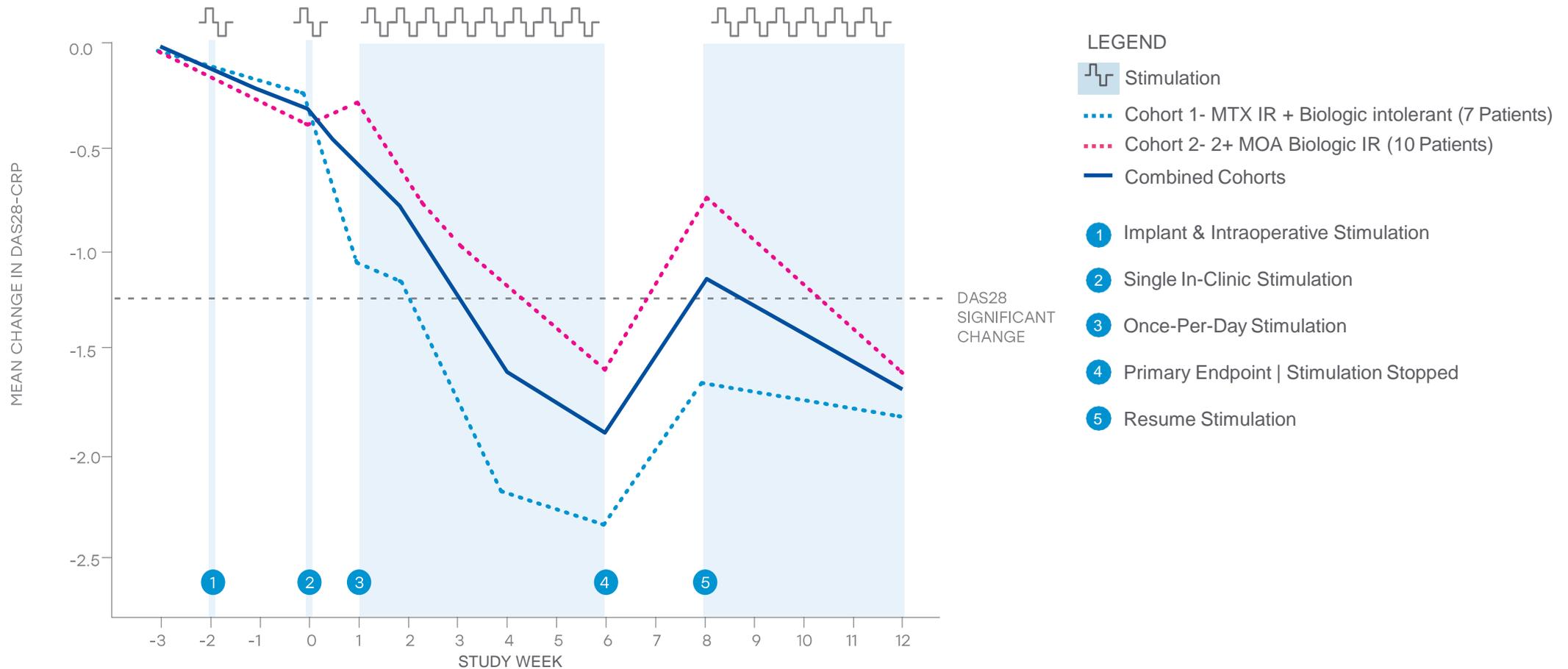
Stimulation Parameters:

60s QD to QID

Average tolerated current was 1.22 and 1.60 mA in cohorts I and II, respectively

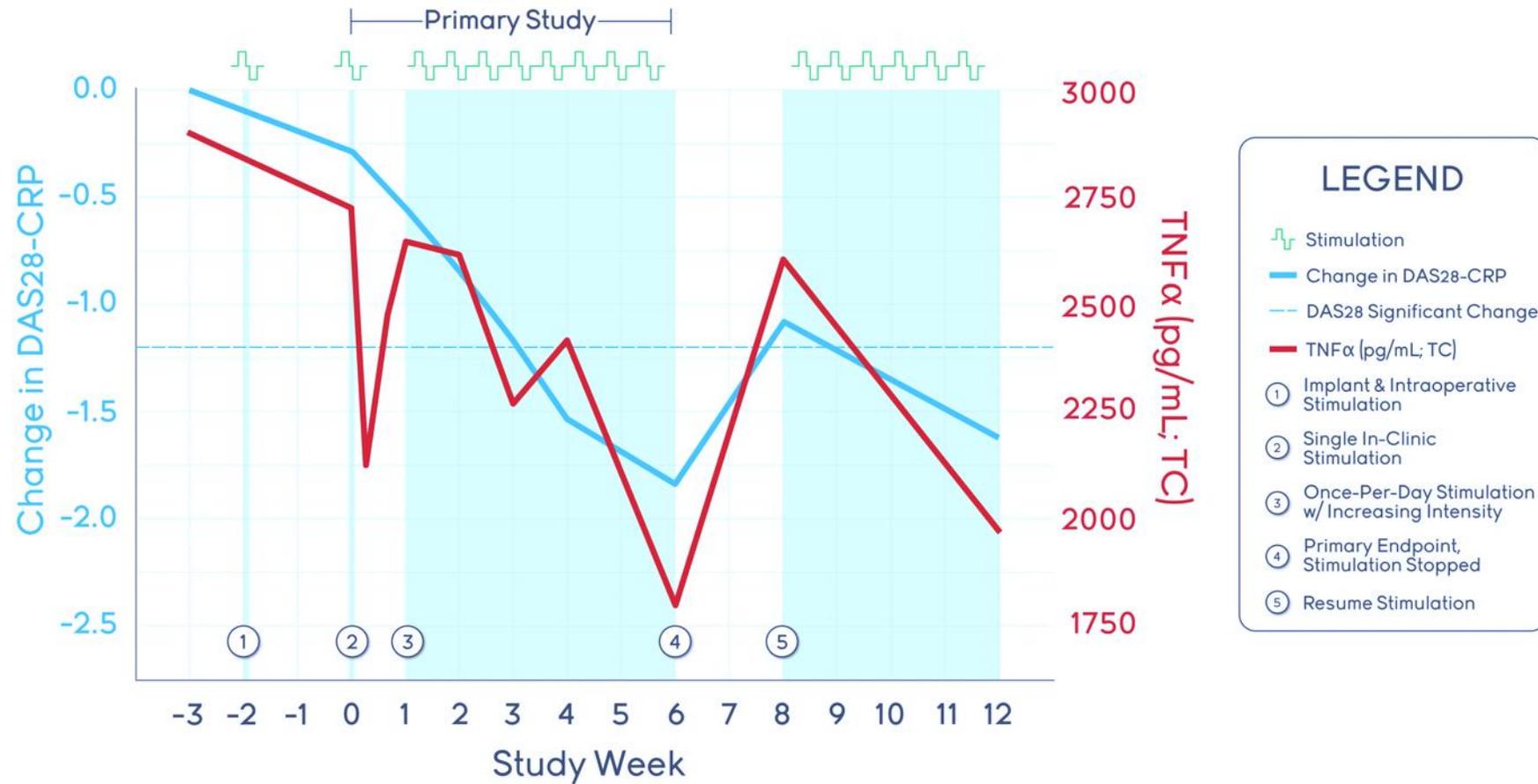
CLINICAL RESEARCH – RA PROOF OF CONCEPT

17-PATIENT EUROPEAN STUDY RESULTS DEMONSTRATE EARLY EFFICACY SIGNAL



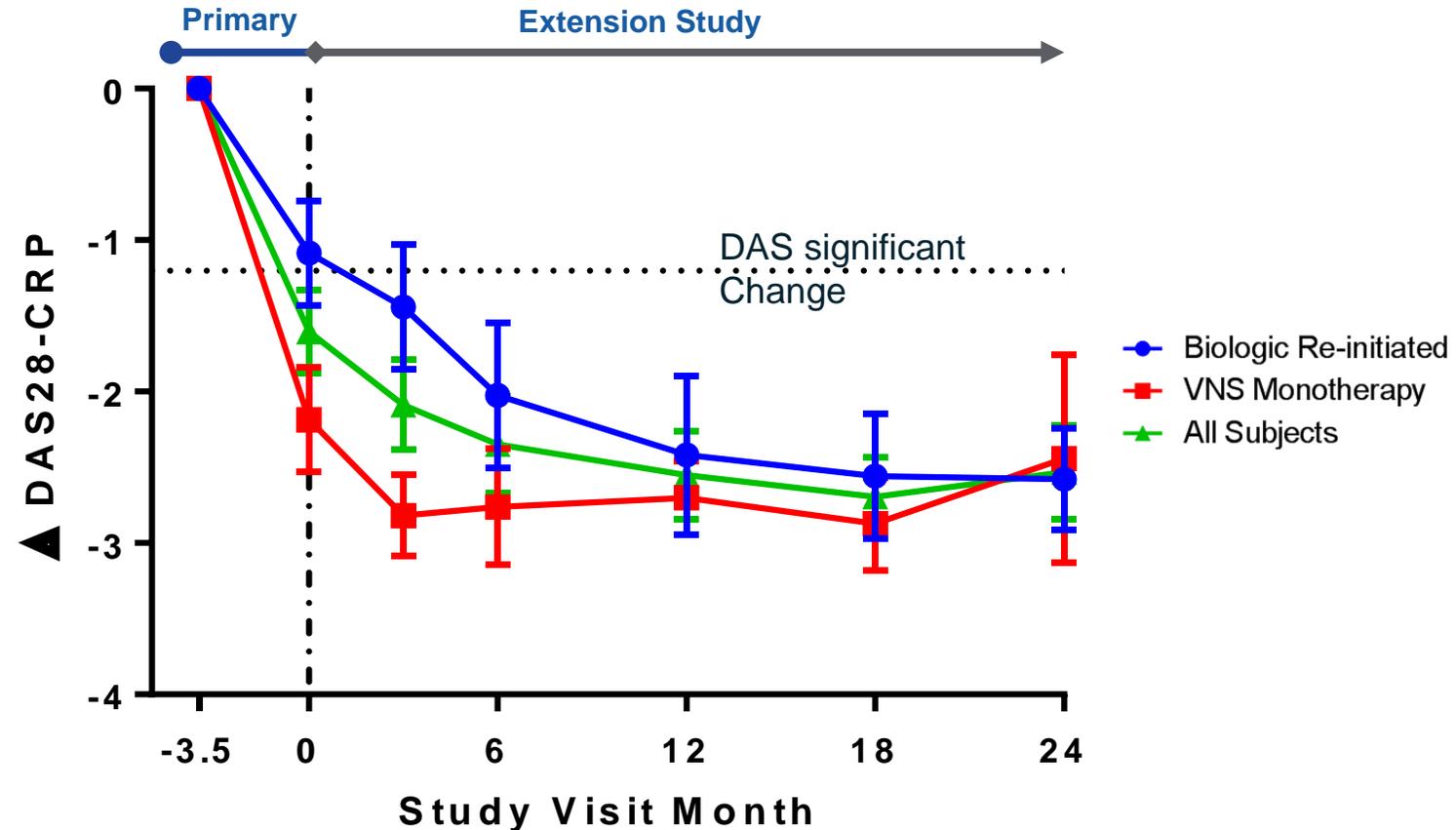
CLINICAL RESEARCH – RA PROOF OF CONCEPT

TNF KINETICS IN *EX VIVO* BIOASSAY PARALLELS CLINICAL ACTIVITY MEASURED BY DAS28-CRP



CLINICAL RESEARCH – RA PROOF OF CONCEPT

IMPROVEMENT IN DISEASE ACTIVITY MAINTAINED OVER 24 MONTHS



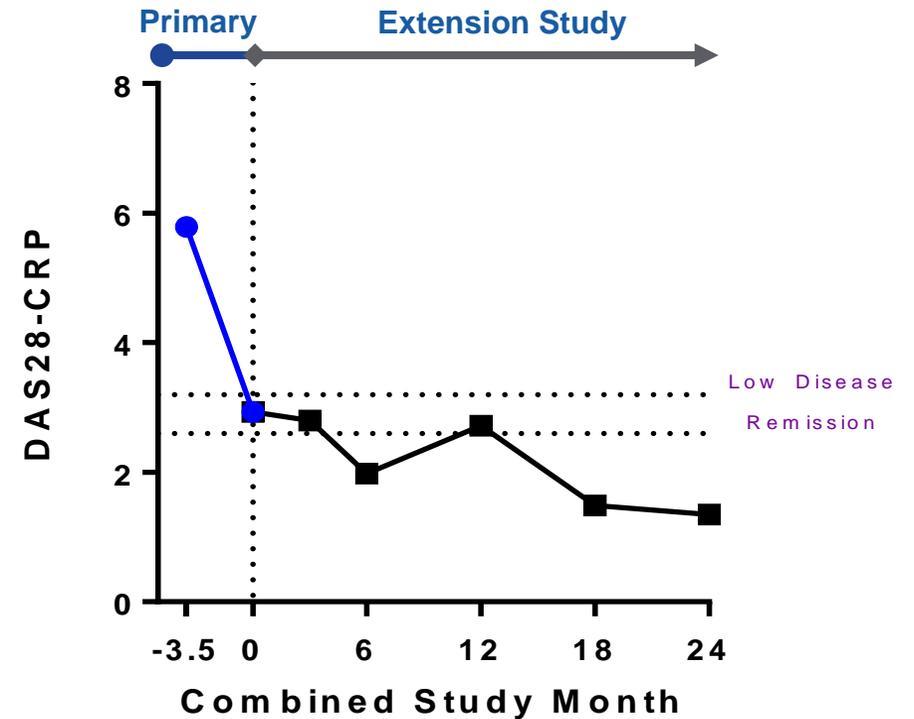
- All 17 subjects continued on active VNS treatment to 24 months of the long term follow-up study

CLINICAL RESEARCH – RA PROOF OF CONCEPT

PATIENT IN LONG-TERM "BOOLEAN" REMISSION

Patient Medical History and Outcomes

Nationality	Dutch	
Gender	Female	
Years since diagnosis	18	
Previous non-biologic DMARDs	methotrexate, sulfasalazine, leflunomide, prednisone	
Previous biologic DMARDs	Etanercept, Adalimumab, Tocilizumab	
RF factor, ACPA	Seronegative	
<u>Measurement</u>	<u>Baseline</u>	<u>Month 24</u>
hsCRP (mg/dL)	0.637	0.15
Baseline DAS28-CRP	5.79	1.35
Baseline CDAI	38.3	0.8
Tender/Swollen Joint Count	17 (T) / 6 (S)	0 (T) / 0 (S)
Patient Global Assessment	8/10	0.4/10

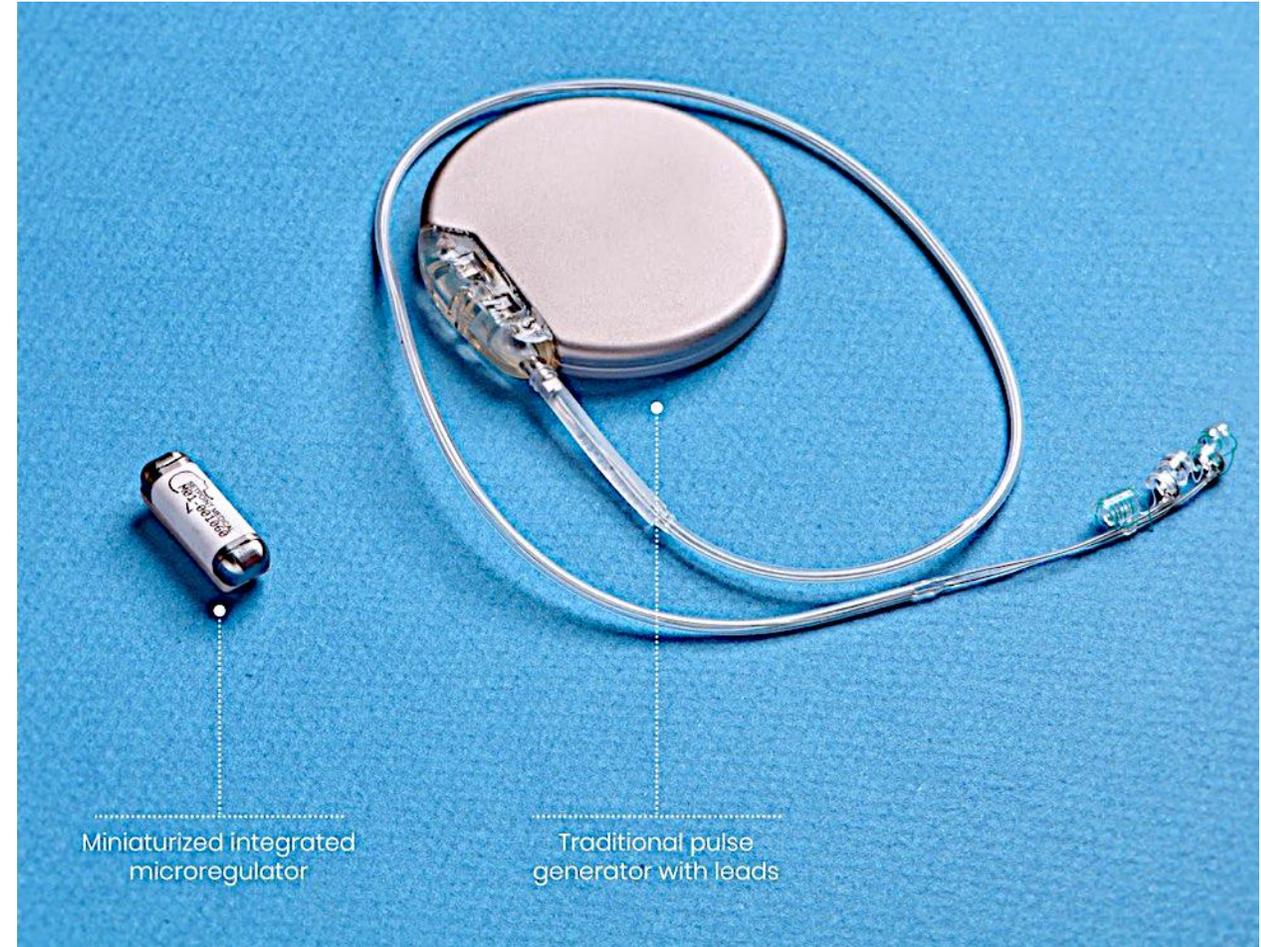


Boolean Remission: $\leq 1TJ/1SJ/1PGA/1CRP$

SETPOINT MEDICAL SYSTEM

INTEGRATED MICROREGULATOR

- Integrated leadless system implanted via a single incision
- Miniaturized, about an inch long; less than 2cc volume
- Rechargeable battery is inductively charged and expected to last over 10 years
- MRI Conditional at 1.5T and 3.0T*
- Device is programmed to dose automatically at patient's therapeutic level, removing need for patient compliance



*The SetPoint System, specifically the MicroRegulator and POD, is MR Conditional. Scanning can be safely performed under the following conditions:

- Static magnetic field of 3 Tesla/128 MHz or less in a cylindrical-bore, horizontal field orientation, whole body coil (no transmitting local coils allowed, receiving local coils can be used),
- Maximum spatial gradient magnetic field of 720 Gauss/cm or less,
- MR system reported whole-body averaged specific absorption rate (SAR) of 2.9 W/kg for 15 minutes of scanning.

SETPOINT MEDICAL SYSTEM

INTEGRATED SYSTEM DESIGNED TO MODULATE INFLAMMATORY REFLEX

Microregulator
or
Pulse Generator



IMPLANT
Along the
vagus nerve

Wireless Charger



CHARGE
A few minutes
each week

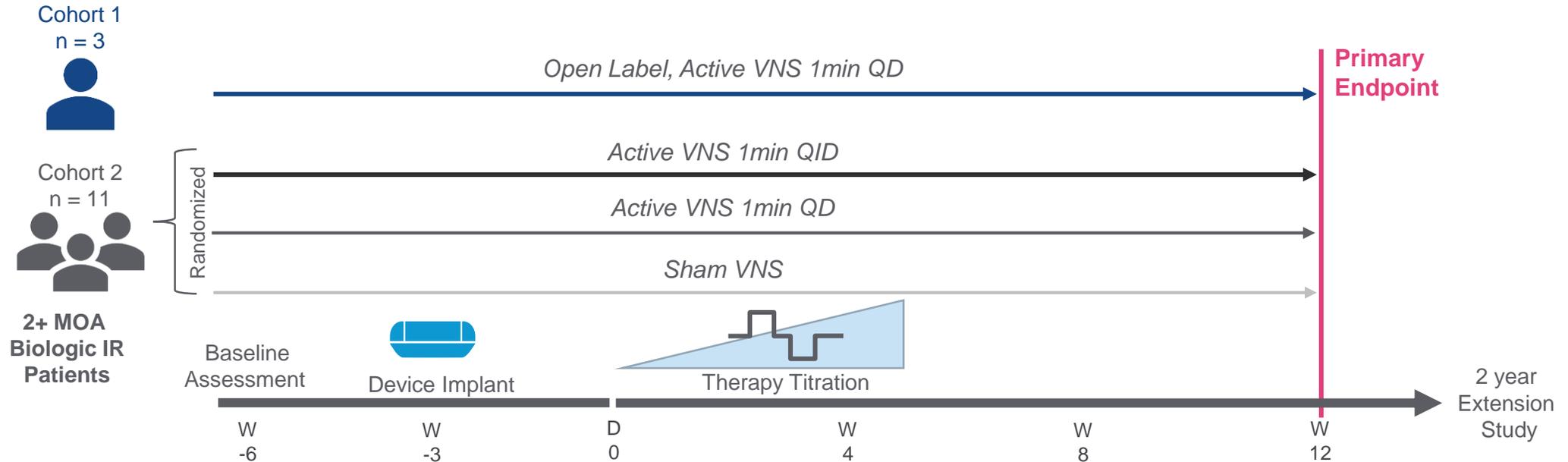
iPad App



PRESCRIBE
HCP prescribes
therapy delivery
through iPad app

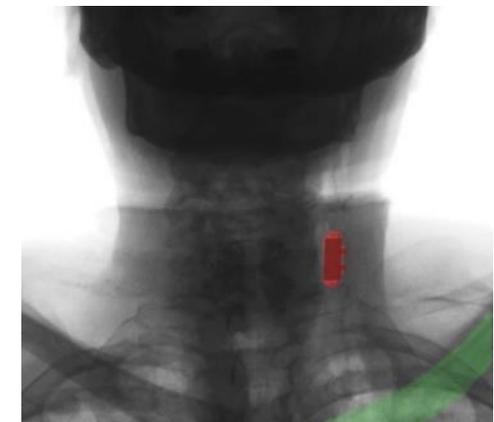
CLINICAL RESEARCH - RA PILOT STUDY

14 PATIENT U.S. STUDY TO EVALUATE SAFETY, PERFORMANCE AND SHAM EFFECT IN MULTI-BIOLOGIC REFRACTORY RHEUMATOID ARTHRITIS



KEY OBJECTIVES

- Safety and feasibility of SetPoint platform (Primary Endpoint)
- Confirmation of mechanism-of-action using cytokine analysis
- Assessment of clinical improvement and sham effect



RA PILOT STUDY - BASELINE DEMOGRAPHICS

MULTIBIOLOGIC AND JAKi REFRACTORY PATIENTS WITH SEVERE DISEASE ACTIVITY

SUBJECT	TREATMENT GROUP	YEARS WITH RA	PRIOR bDMARD/TARGETED SYNTHETICS	GENDER	AGE (YRS)	CDAI (W -6)	DAS28-CRP (W -6)	RF/ACPA
005-01	Ph1 QD	49	4	F	66	45.5	5.55	+/+
005-03	Ph1 QD	13	4	F	47	22	4.20	-/-
006-01	Ph1 QD	24	5	F	46	58	7.06	+/+
002-01	Ph2 QD	6	4	F	26	41.5	7.04	+/+
005-06	Ph2 QD	3	2	M	73	29.5	4.47	-/+
005-07	Ph2 QD	17	10	F	45	43.5	6.79	+/+
Average	QD	18.6	4.8		50.5	40	5.85	
006-03	Ph2 QID	11	8	F	58	45.5	6.55	+/+
008-01	Ph2 QID	11	3	F	50	58	6.93	+/+
008-03	Ph2 QID	10	6	F	32	62	7.27	+/+
008-04	Ph2 QID	13	6	F	50	20	3.97	+/+
Average	QID	11.2	5.8		47.5	46.4	6.18	
005-05	Sham	10	4	F	66	53.5	6.75	+/+
006-02	Sham	15	4	M	44	29	4.42	+/+
006-04	Sham	16	3	F	53	24.5	4.45	+/+
008-02	Sham	4	3	M	57	64.5	7.64	+/+
Average	Sham	10.8	3.8		55	42.6	5.82	
Overall Study		14.25	4.8		50.9	42.6	5.94	

- All subjects on background DMARDS (Methotrexate or Hydroxychloroquine)
- 9/14 patients had failed JAK inhibitors in addition to multiple biologics



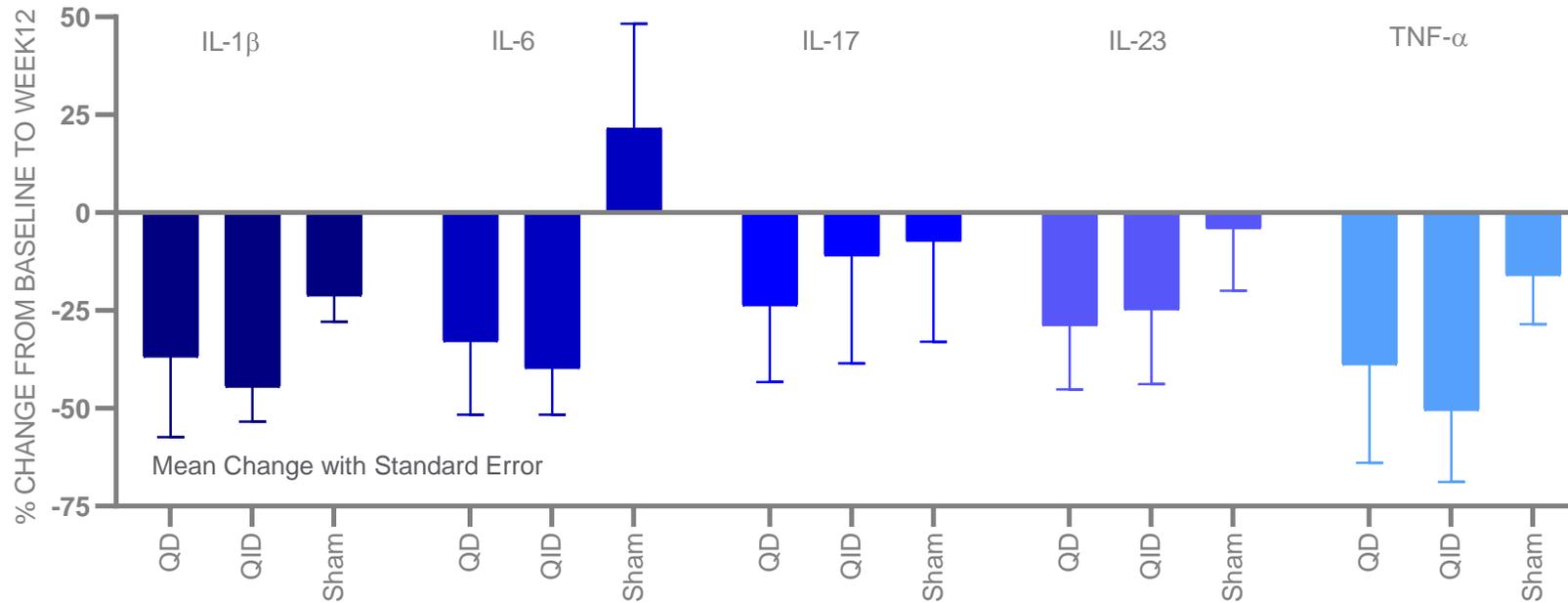
RA PILOT STUDY: SUMMARY OF OUTCOMES

STUDY MET PRIMARY ENDPOINTS WITH MEANINGFUL CLINICAL RESPONSE IN ACTIVE ARMS

- **Successfully implanted the device in 14 multi-biologic refractory RA patients**
 - Device is safe and well tolerated; no device related adverse events
- **SetPoint system performed as designed**
 - Device placement, communication between components, programmability, and delivery of stimulation occurred as specified
- **Pharmacodynamic response confirmed mechanism-of-action**
 - Reduction of proinflammatory cytokines was observed for QD and QID groups using validated biomarker assay
- **Meaningful clinical response in treatment groups, with no apparent sham effect**
 - 5 out of 10 patients in treatment groups met or exceeded meaningful clinically important difference (MCID) in DAS28-CRP at 12 weeks;
 - 2 patients achieved DAS28-CRP remission
 - Overall lack of DAS response in sham group
- **Trends of joint structure preservation emerged in the MRI analysis**
 - Improvement in RAMRIS erosion scores correlated with DAS response; synovitis and osteitis scores were inconclusive

RA PILOT STUDY - PHARMACODYNAMICS

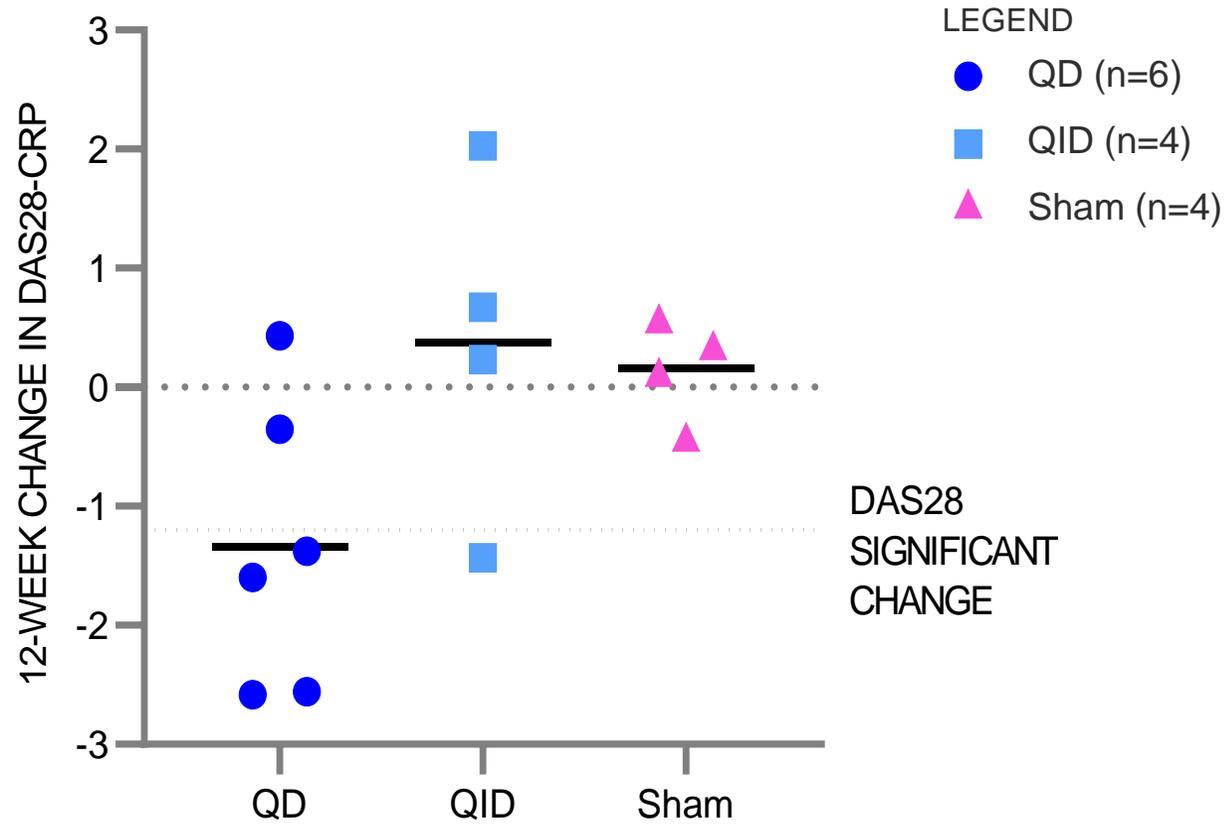
CYTOKINE ANALYSIS CONFIRM ACTIVATION OF INFLAMMATORY REFLEX IN STIMULATED COHORTS



- Validated immunoassay confirms reduction in proinflammatory cytokines for both treatment groups
- Biomarker analysis reaffirms mechanism-of-action observed in preclinical and European clinical studies

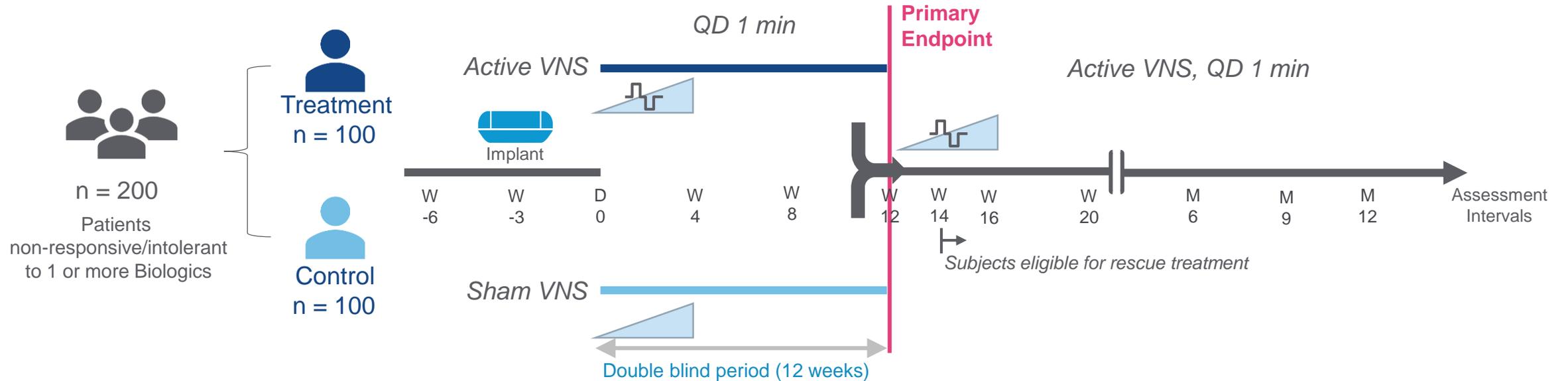
RA PILOT STUDY – CLINICAL RESPONSE

MEANINGFUL CLINICAL IMPROVEMENT NOTED IN 50% OF ACTIVE GROUP
NO OBSERVED SHAM EFFECT



PROPOSED PIVOTAL STUDY DESIGN

RANDOMIZED, SHAM CONTROLLED, DOUBLE BLIND STUDY DESIGN



- **Primary Endpoints:**

- Improvement in clinical disease activity compared to sham at 12 weeks

- **Safety, Secondary and Descriptive Endpoints:**

- Safety of device via a description of all reported adverse events.
- Joint structure improvement, responder and remission rates, quality of life measures



CONCLUSION AND DISCUSSION

- The inflammatory reflex is a prototypical cholinergic neuro-immune reflex that contributes to immunological homeostasis.
- Electrically stimulating the vagus nerve can activate this reflex therapeutically in many rodent models of disease, including rheumatoid arthritis
- Electrical stimulation of the vagus activates a proresolution of inflammation reflex
- Brief period of VNS was sufficient to induce a therapeutic response in half of patients with rheumatoid arthritis, many who had insufficient response to multiple biological drugs/JAKi
- Reduction of disease activity was sustained for at least two years in a substantial fraction of patients treated in EU study
- Upcoming clinical study designed to evaluate this therapy in a larger patient population with inadequate responses to biologics/JAKi

Questions?

Thank you for attending!

The 27th Napa Pain Conference Online

August 15, 2020

Join us for Complimentary Registration and CME:

NapaPainConference.com

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Sten Lindahl, MD, PhD (Nobel Committee)

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David Provenzano, MD (Pain Diagnostics)

Richard W. Rosenquist, MD (Cleveland Clinic)

The 2020 NPC Legacy Lecture

Navigating Career Crossroads

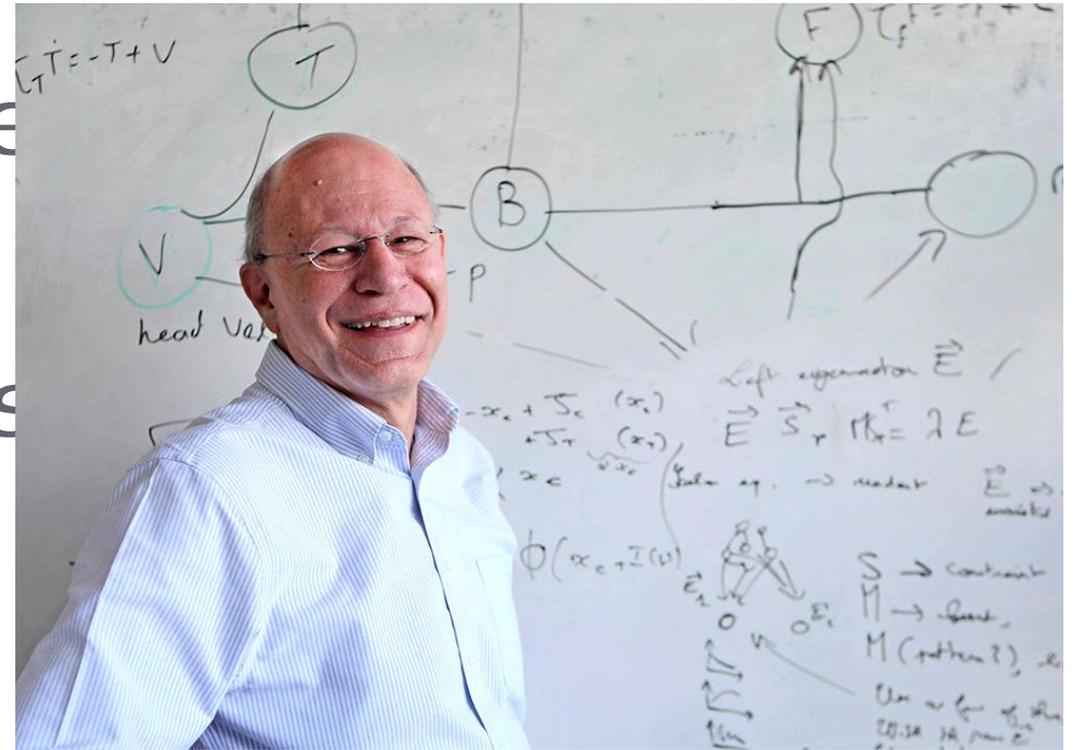
Carol A. Warfield, MD

Edward Lowenstein Distinguished
Professor of Anaesthesia,
Harvard Medical School



The 2020 Lindahl Lecture

Homeostasis Mechanisms *Göteborg Berzerk*



Larry Abbott, PhD

William Bloor Professor of Theoretical Neuroscience
Professor of Physiology and Cellular Biophysics
Principal Investigator at Columbia's Zuckerman Institute

Welcome to
The Napa Wine College
NapaWineCollege.com



Roccawines.com



What are our next steps?
Email us at
education@Neurovations.com

Thank you for attending!



