Tiziana Life Sciences KOL Event

Monday, March 14, 2022
11:00 am ET

Foralumab Clinical Update in Multiple Sclerosis: A Landmark Study with Intranasal Immunotherapy

Enabling Breakthrough Immunotherapies via Novel Routes of Drug Delivery

NASDAQ: TLSA

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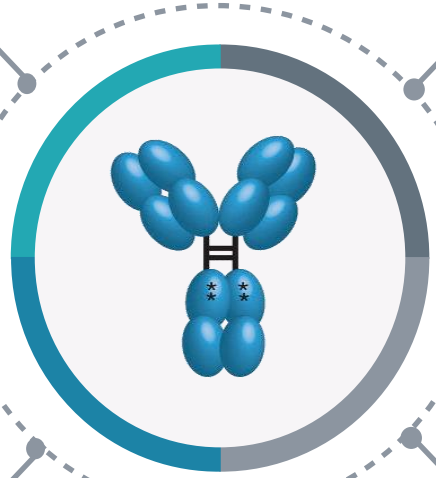
The Antibody Market is Enormous and Offers Significant Opportunities for Reformulation

Global Market was Valued at $150 Billion in 2019 and is Expected to Grow to $300 Billion by 2025[1]

Traditional administration is systemic, costly and burdensome to patients

Drug level in blood is high during the first few hours after dosing



Systemic treatment requires higher doses causing toxicity

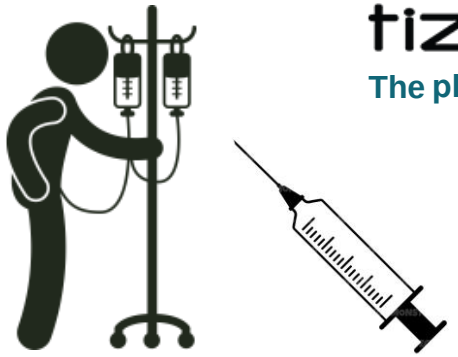
Compliance may be compromised due to the inconvenience of injecting subcutaneously or outpatient intravenous dosing visits

Source: [1] Lu et al. Journal of Biomedical Science (2020) 27:1

A Revolutionary Platform

Antibody Administration: Switching From IV and SC To Oral, Nasal And Inhaled Routes

Today's Options for Antibody Administration are Subcutaneous or Intravenous (IV)



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The platform enables…

Foralumab
Oral administration
For Crohn's Disease
IBD

Foralumab
Nasal administration
Multiple Sclerosis
Neurodegenerative diseases

TZLS- 501 Anti- IL6R
Direct delivery to lungs with a portable inhaler for pulmonary diseases

Benefits of non-systemic dosing

- Improved patient compliance
- Local activity instead of systemic distribution; may minimize side effects
- Anticipated lower cost of goods and lower price of administration

Major focus

Four Clinical Studies With Positive data completed

	Subject	PC	IND	Phase 1/IAP	Phase 2	Phase 3
FORALUMAB *Fully human anti-CD3 mAb*	Intranasal	Progressive Multiple Sclerosis (expanded program)			Ongoing IAP	
	Oral	Crohn's Disease			2Q 2022 Phase 1b	
	Subcutaneous	Type 1 Diabetes			2Q-2022 IND Submission	
MILCICLIB *Pan-CDK inhibitor*	Oral	Milciclib + Gemcitabine in NSCLC Kras+ mutants			2Q-2022 IND Submission	

Rationale for Intranasal Foralumab for the Treatment of Neurodegenerative Diseases

Howard Weiner, MD

Robert L. Kroc Professor of Neurology at the Harvard Medical School

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Today's Key Opinion Leader Speakers

Howard Weiner, MD

Robert L. Kroc Professor of Neurology at the Harvard Medical School

Director and Founder of the Partners Multiple Sclerosis Center and Co-Director of the Ann Romney Center for Neurologic Diseases at the Brigham & Women's Hospital

Also, Chairman, Tiziana Scientific Advisory Committee

Pioneered investigation of the mucosal immune system for the treatment of autoimmune and other diseases

Tanuja Chitnis, MD

Professor of Neurology at Harvard Medical School

Director of the Mass General Brigham Pediatric MS Center at the Mass General Hospital for Children

Senior Scientist at the Ann Romney Center for Neurologic Diseases at Brigham and Women's Hospital (BWH)

Also, member, Tiziana Scientific Advisory Committee

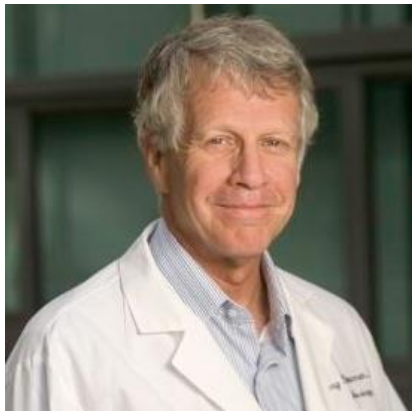
Board-certified neurologist specializing in multiple sclerosis (MS) related neuro-immunological disorders and leads several research studies and clinical trials in these areas

Tarun Singhal, MD

Assistant Professor of Neurology at Harvard Medical School

Director of PET Imaging Program in Neurologic Diseases at the Ann Romney Center for Neurologic Diseases at Brigham and Women's Hospital

Board certified in neurology and nuclear medicine and on the Harvard faculty since 2014. Dr. Singhal has led several molecular imaging projects in the neuroscience field.



Lawrence Steinman, MD

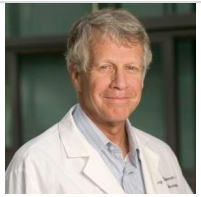
Professor of Neurology and Neurological Sciences, Pediatrics, and Genetics, Stanford Medicine

Member of the National Academy of Sciences and the National Academy of Medicine

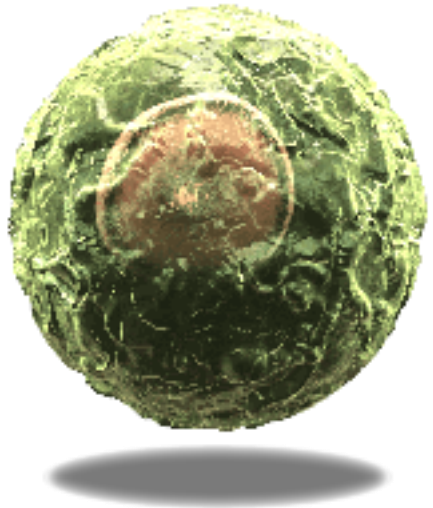
Chair of the Stanford University Interdepartmental Program in Immunology from 2003-2011.

Senior author on the seminal 1992 *Nature* article that led to the development of the drug Tysabri, which is used to treat patients with MS and Crohn's disease.

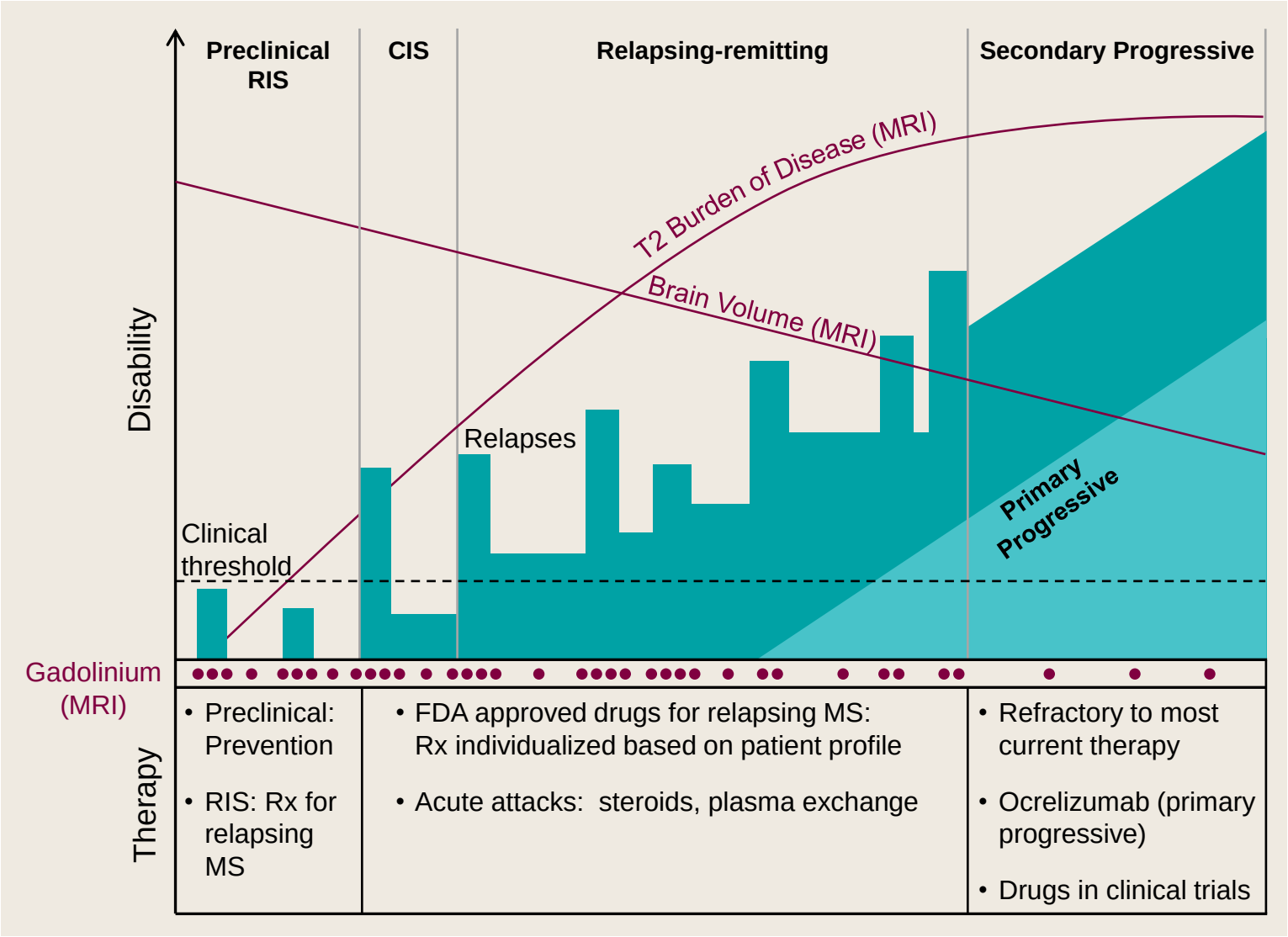
Agenda

11:00	11:05	11:15	11:25	11:35	11:45-12:00
					
Welcome and Introduction	Rationale for intranasal foralumab for the treatment of neurodegenerative diseases	Foralumab clinical data presentation	PET imaging data and interpretation	Overview of MS and conclusions	Q&A Session & Closing Remarks
Dr. Kunwar Shailubhai Chief Executive Officer and Chief Scientific Officer, Tiziana Life Sciences	**Howard Weiner, MD** Robert L. Kroc Professor of Neurology at the Harvard Medical School	**Tanuja Chitnis, MD** Professor of Neurology at Harvard Medical School	**Tarun Singhal, MD** Assistant Professor of Neurology at Harvard Medical School	**Lawrence Steinman, MD** Professor of Neurology and Neurological Sciences, Pediatrics and Genetics, Stanford Medicine	**All Speakers**

Nasal αCD3 – a novel therapeutic approach for progressive neurologic disease by modulating inflammatory microglial cells



Stages of Multiple Sclerosis



Major unmet need: Non-active progressive MS

Immune modulation to treat disease via the mucosal immune system (oral/nasal)

- Physiologic
- Safe

nature medicine

Oral CD3-specific antibody suppresses autoimmune encephalomyelitis by inducing $CD4^+CD25^-LAP^+$ T cells

Hirofumi Ochi[1,3], Michal Abraham[1,3], Hiroki Ishikawa[1], Dan Frenkel[1], Kaiyong Yang[1], Alexandre S Basso[1], Henry Wu[1], Mei-Ling Chen[1], Roopali Gandhi[1], Ariel Miller[2], Ruth Maron[1] & Howard L Weiner[1]

2006

doi:10.1093/brain/aww113 BRAIN 2016: 139; 1939–1957 | 1939

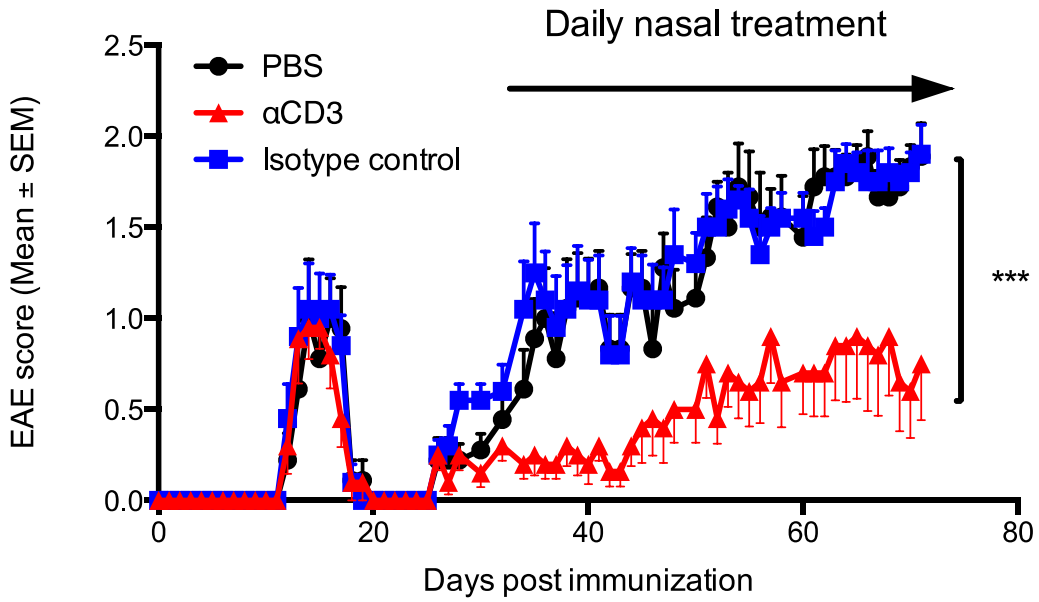
BRAIN
A JOURNAL OF NEUROLOGY

IL-10-dependent Tr1 cells attenuate astrocyte activation and ameliorate chronic central nervous system inflammation

Lior Mayo,[1,2] Andre Pires Da Cunha,[1] Asaf Madi,[3] Vanessa Beynon,[1] Zhiping Yang,[4] Jorge I. Alvarez,[5,6] Alexandre Prat,[5] Raymond A. Sobel,[7] Lester Kobzik,[4] Hans Lassmann,[8] Francisco J. Quintana[1] and Howard L. Weiner[1]

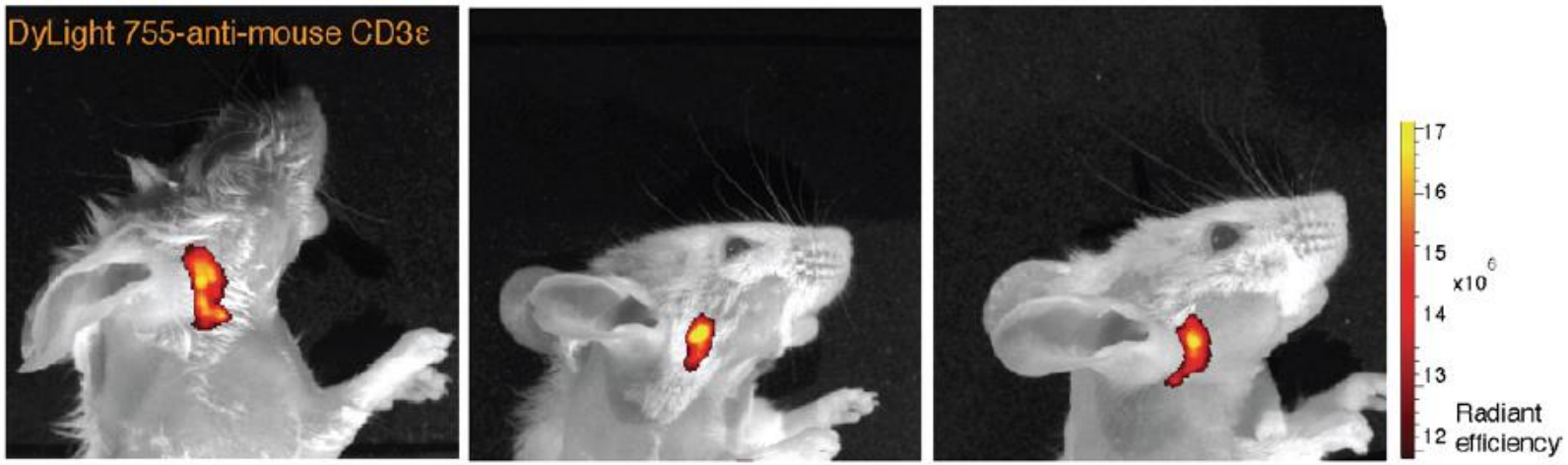
2016

Nasal αCD3 halts EAE progression in a model of progressive multiple sclerosis



* P value is < 0.0001

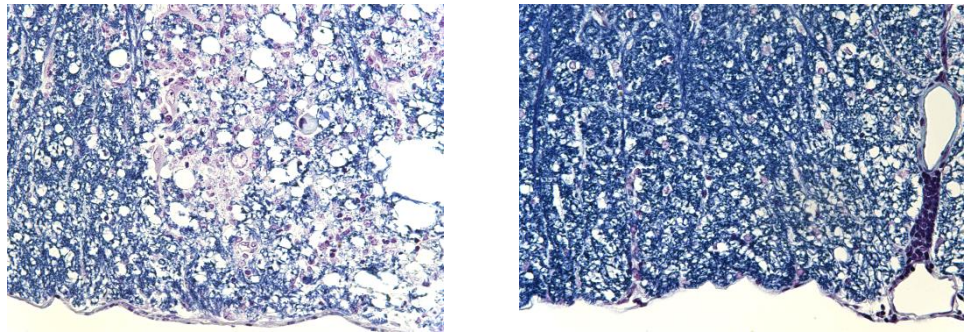
Nasal anti-CD3 localizes to cervical lymph nodes and acts peripherally

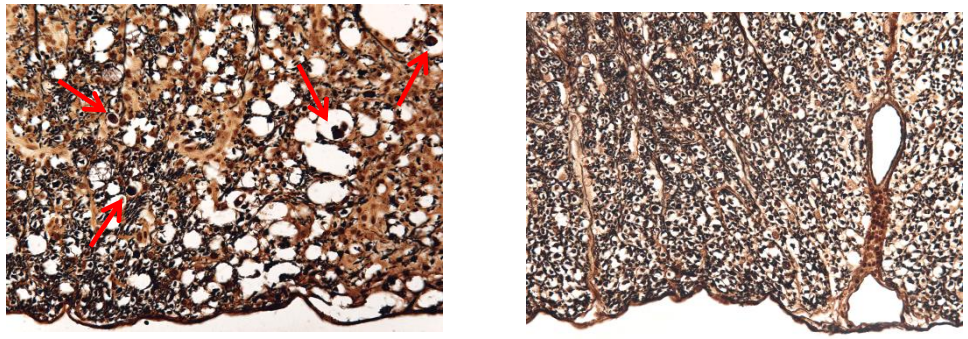


Nasal αCD3 treatment protects from myelin loss and axonal injury

Isotype control

Anti-CD3

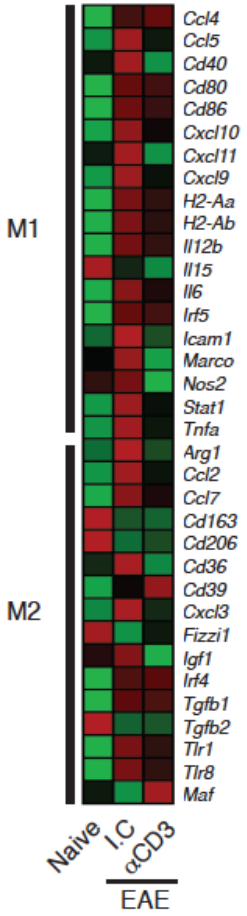


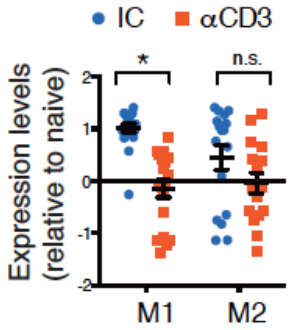


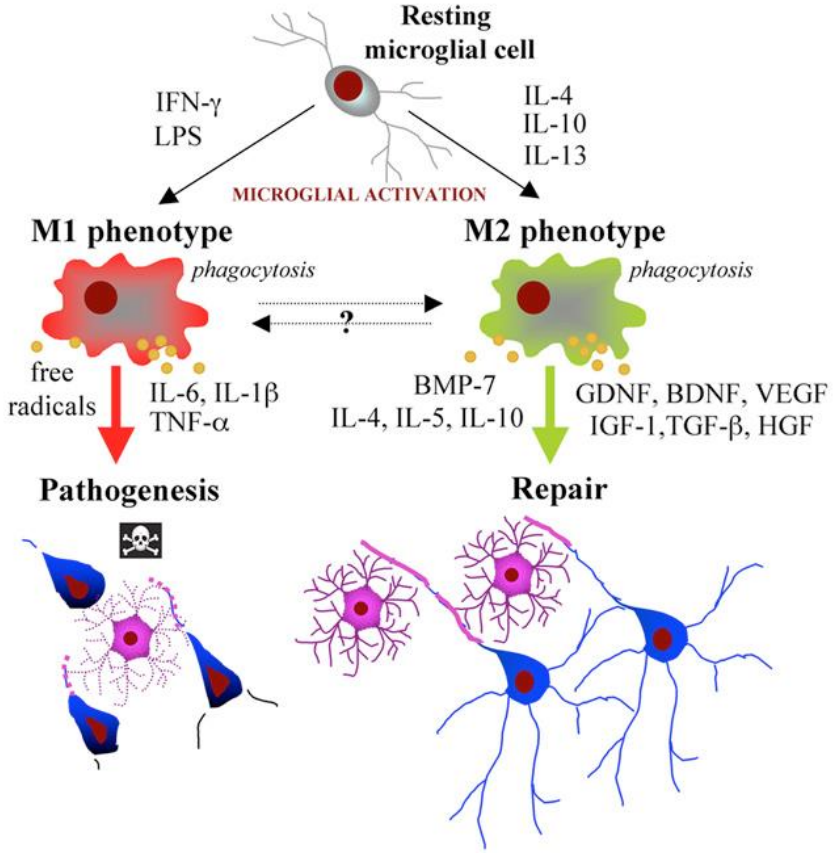
Luxol fast blue Stain
(Myelin staining)

Bielschowsky's Silver Stain
(axon staining)

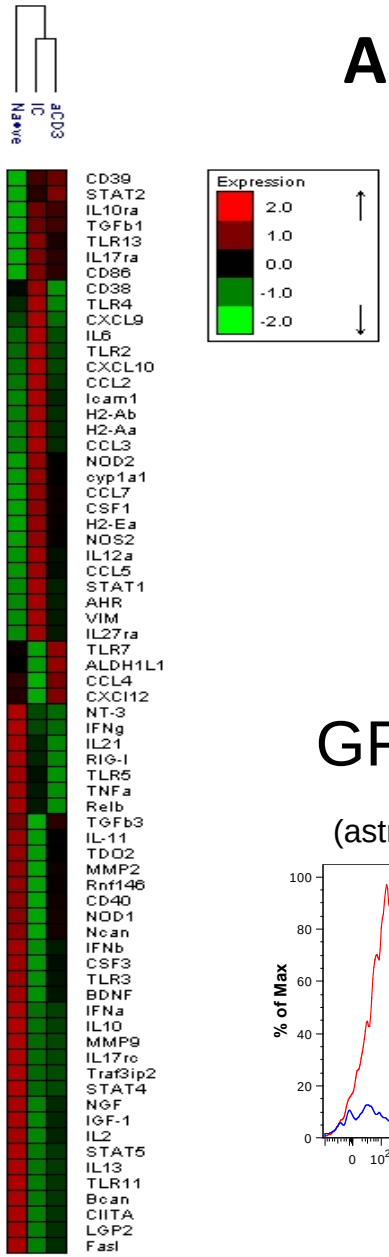
Nasal αCD3 regulates the inflammatory phenotype of the microglial cells





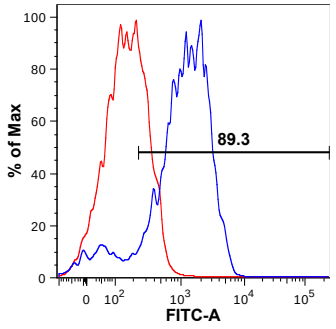


Astrocytes exhibit an altered immune phenotype *in-vivo* following nasal anti-CD3 treatment

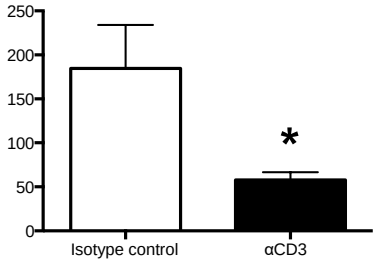


GFAP

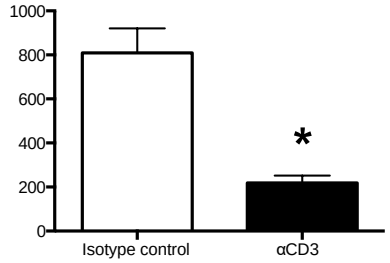
(astrocytes marker)



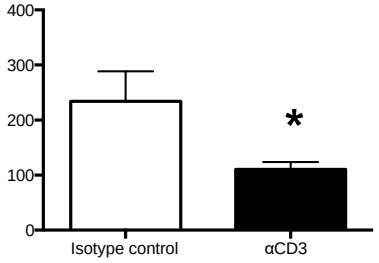
IL1b



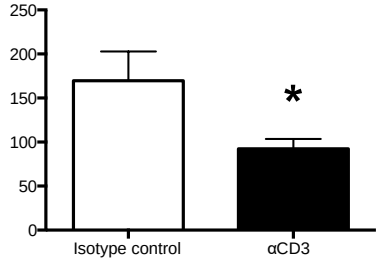
OPN



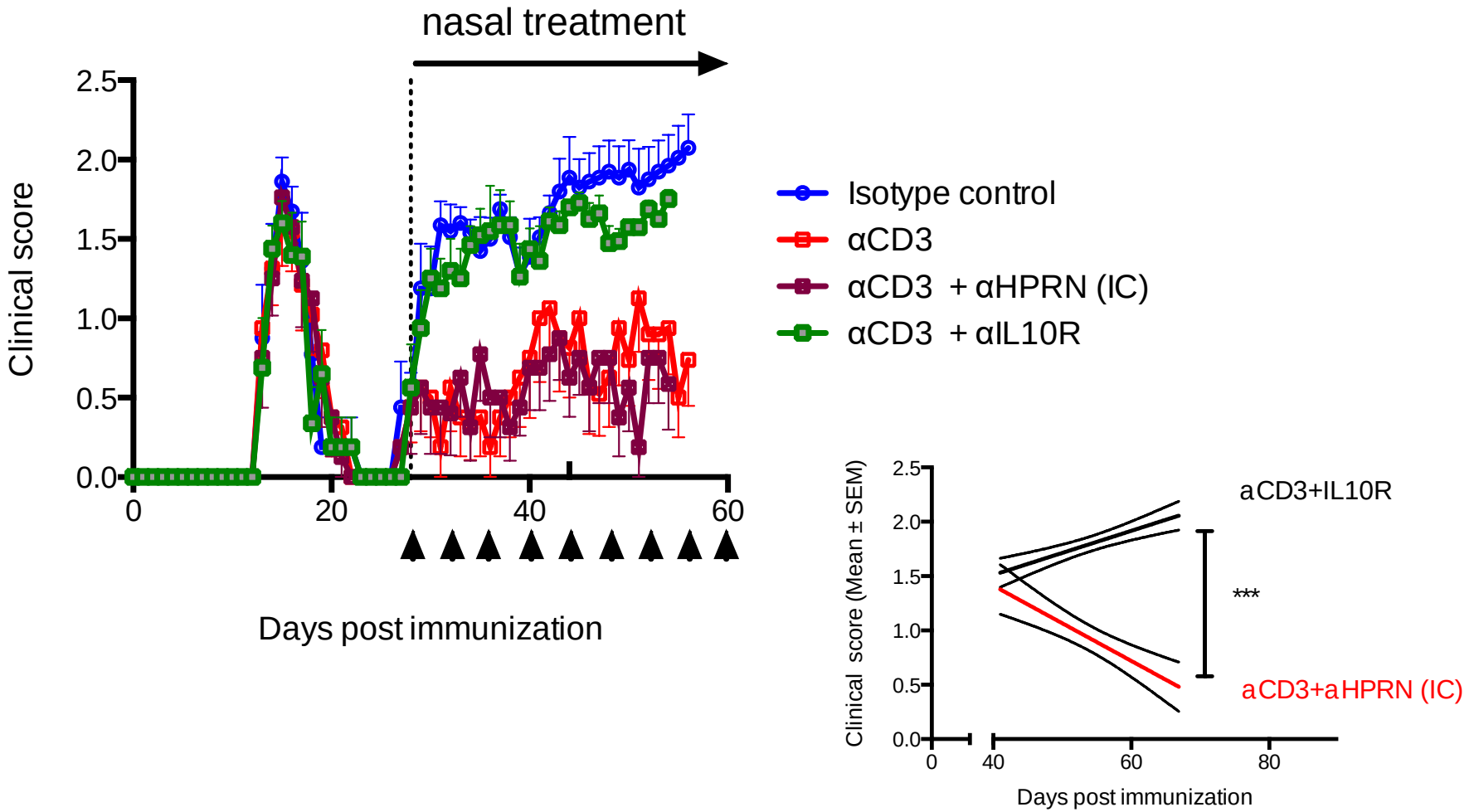
CCL2 (MCP1)



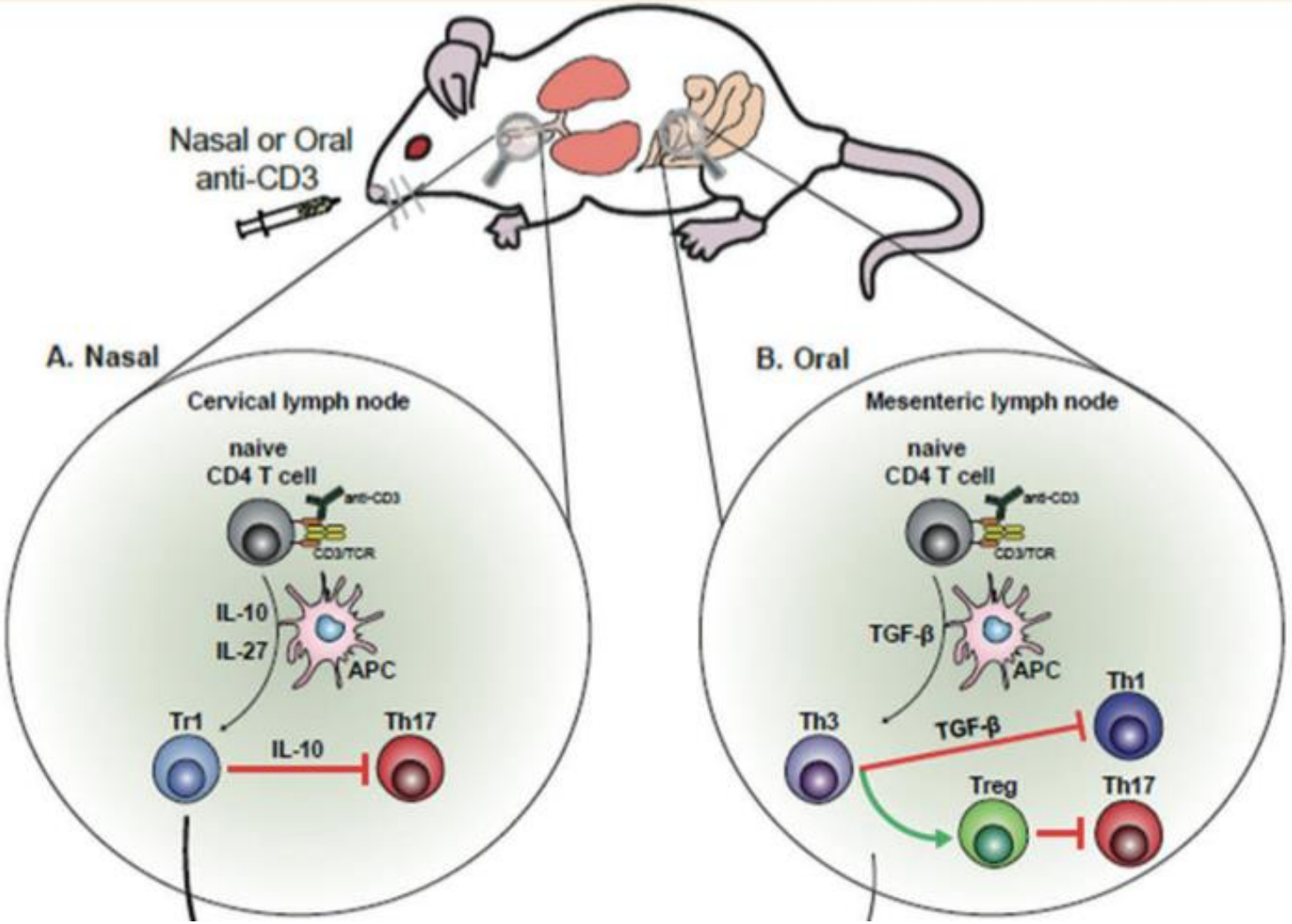
Cxcl10 (IP10)



The therapeutic effects of nasal aCD3 treatment are dependent upon IL-10 signaling



Mechanism of oral and nasal anti-CD3



IL-10 Treg

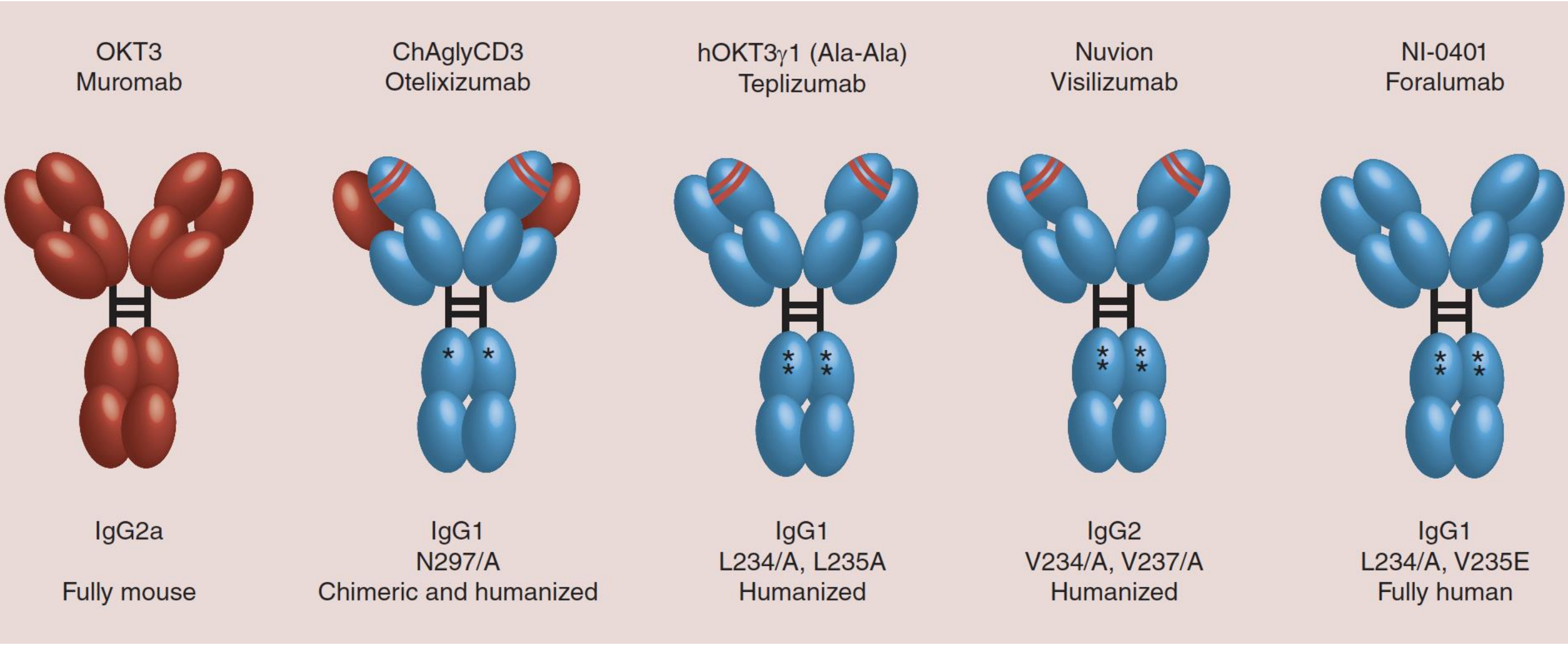
TGF-β Treg

Nasal anti-CD3 treats animal models of neurologic disease

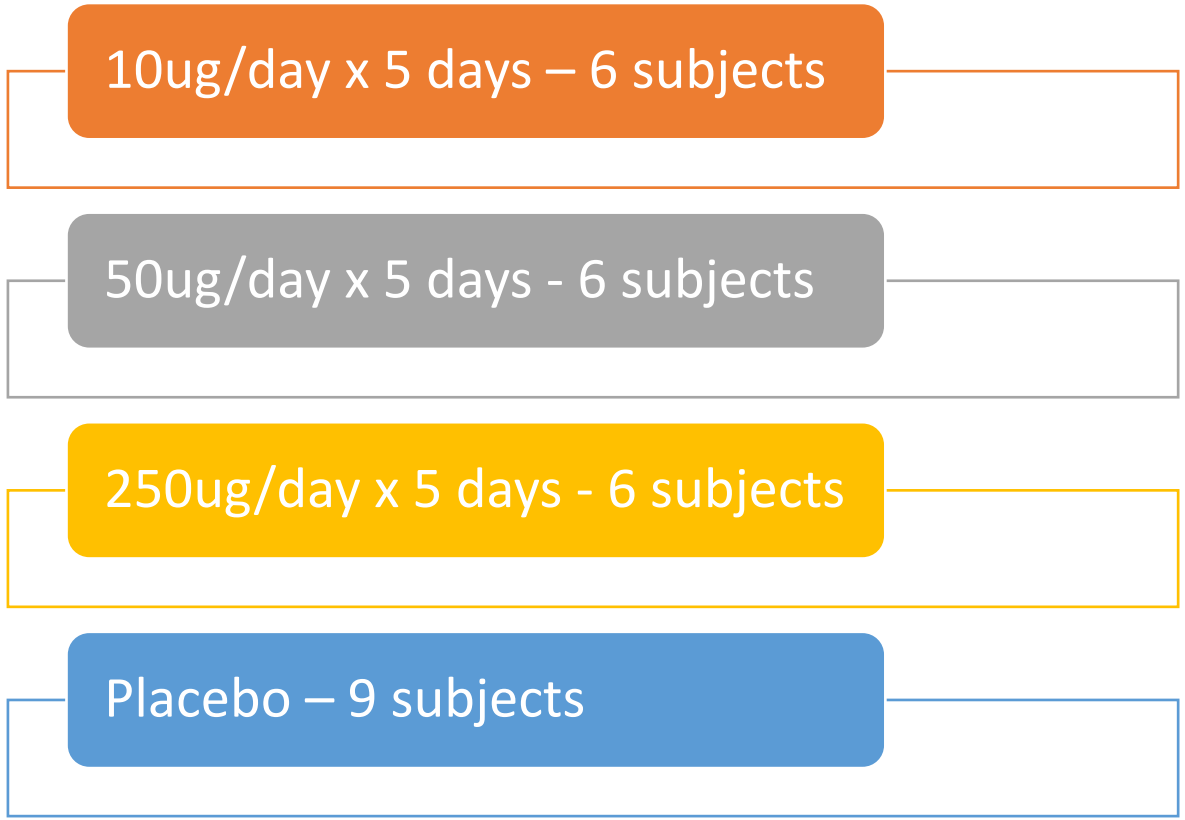
- Progressive MS (published)
- Alzheimer’s disease
- ALS
- Traumatic Brain Injury

Translation of nasal anti-CD3 to humans with foralumab, a fully human mAb

(Tiziana Life Sciences)


OKT3
Muromab
ChAglyCD3
Otelixizumab
hOKT3γ1 (Ala-Ala)
Teplizumab
Nuvion
Visilizumab
NI-0401
Foralumab
IgG2a
Fully mouse
IgG1
N297/A
Chimeric and humanized
IgG1
L234/A, L235A
Humanized
IgG2
V234/A, V237/A
Humanized
IgG1
L234/A, V235E
Fully human

Phase 1 Safety and Dose Ranging Study of Nasal Foralumab in Healthy Volunteers



Results

Safe with no side effects at any dose

Immune effects observed: 50ug dose is optimal

Treating human disease with nasal foralumab

frontiers in Immunology

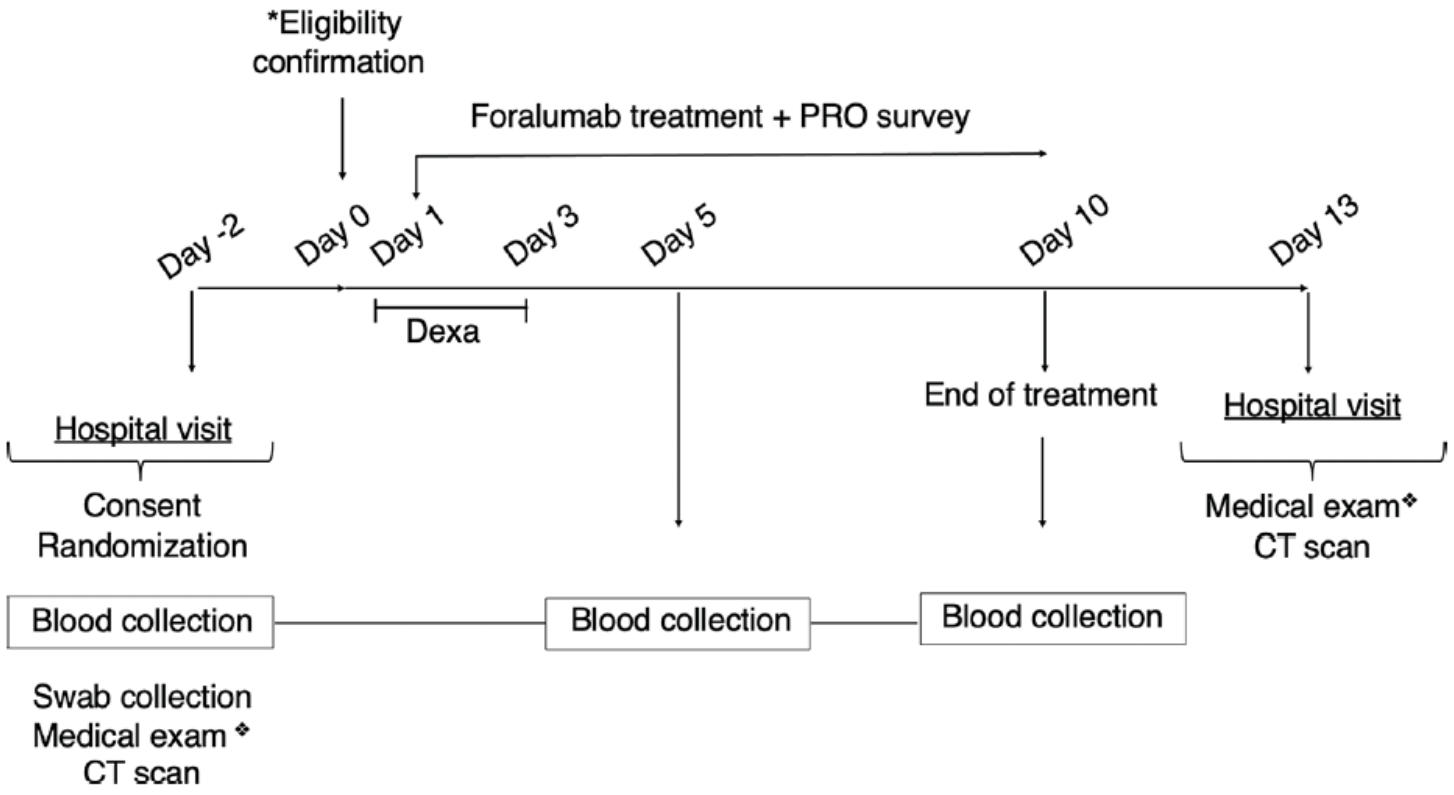
ORIGINAL RESEARCH
published: 12 August 2021
doi: 10.3389/fimmu.2021.709861

Nasal Administration of Anti-CD3 Monoclonal Antibody (Foralumab) Reduces Lung Inflammation and Blood Inflammatory Biomarkers in Mild to Moderate COVID-19 Patients: A Pilot Study

Thais G. Moreira[1], Kimble T. F. Matos[2], Giovana S. De Paula[3], Thais M. M. Santana[3], Raquel G. Da Mata[3], Fernando C. Pansera[3], Andre S. Cortina[3], Marcelle G. Spinola[2], Gerson D. Keppeke[2], Jules Jacob[4], Vaseem Palejwala[4], Karen Chen[5], Saef Izzy[1], Brian C. Healey[1], Rafael M. Rezende[1], Rogerio A. Dedivitis[3], Kunwar Shailubhai[4] and Howard L. Weiner[1*]*

2021

Study Design



100ug nasal Foralumab for 10 consecutive days

Decrease in inflammatory blood markers

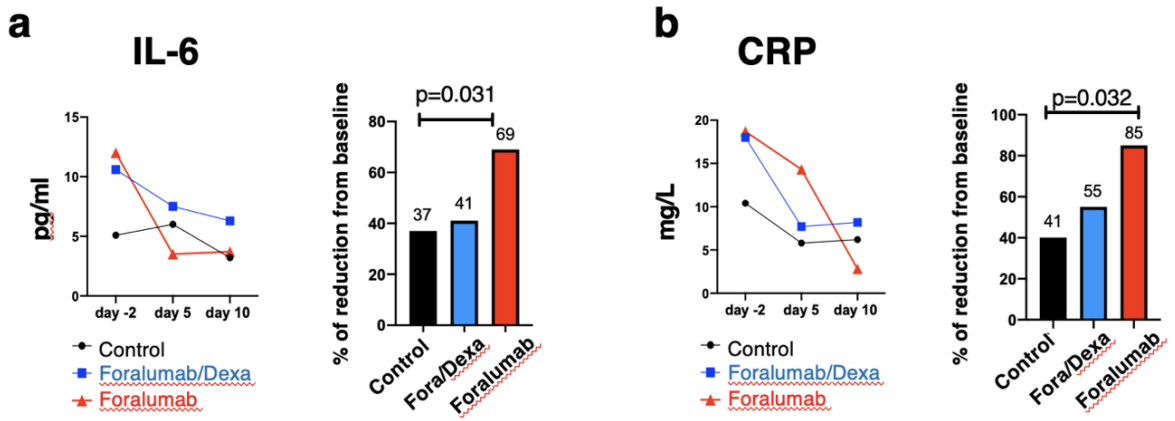
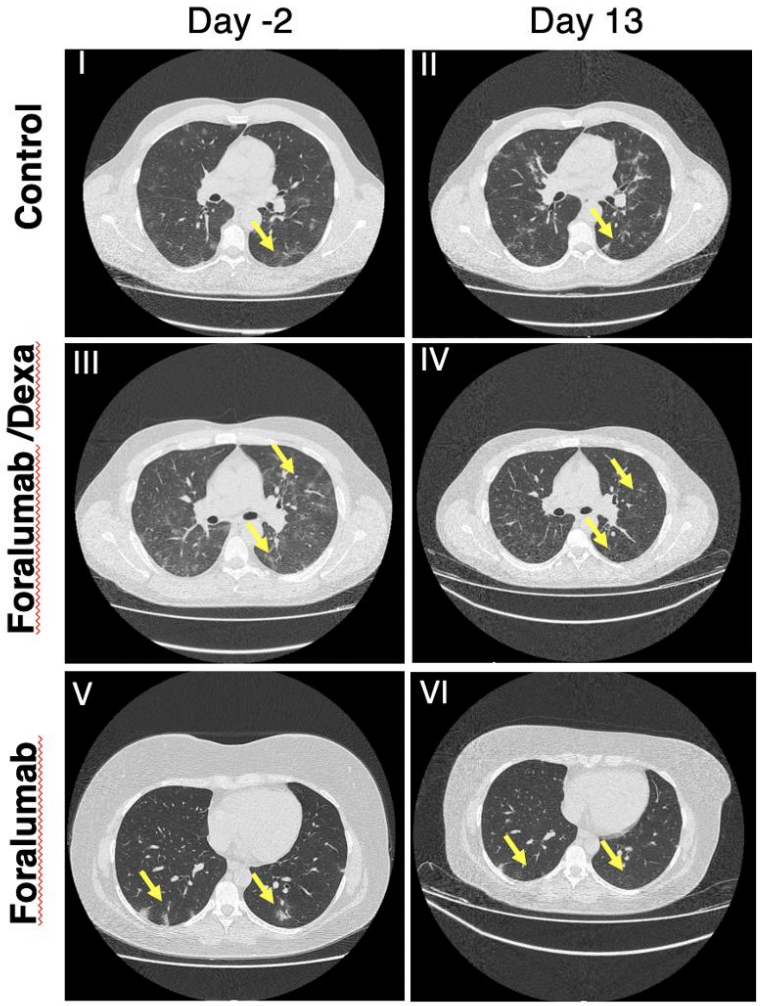


Figure 2: Blood inflammatory markers IL-6 and C-reactive protein.
Serum quantification and percentage of reduction of (a)IL-6 and (b) C-reactive protein
Linear regression was used to compare three-group comparison of each time point. A linear mixed model with a random intercept was used to baseline comparison. Percent of baseline was compared using Wilcoxon rank sum test. p= <0.05. IL= Interleukin, CRP= c-reactive protein, Dexa= dexamethasone.

More rapid clearing of lung inflammation



Treating progressive MS with nasal foralumab

The cutting-edge science behind treatments for Alzheimer's, MS, Parkinson's, ALS, and more

The Brain Under Siege

Solving the Mystery of Brain Disease, and How Scientists Are Following the Clues to a Cure

HOWARD L. WEINER, MD

PROFESSOR OF NEUROLOGY, HARVARD MEDICAL SCHOOL

Results of nasal foralumab in a patient with progressive MS

Tanuja Chitnis, MD: Clinical and Immunology

Tarun Singhal, MD: Microglial PET Imaging

Foralumab

Clinical and Immunological data

Tanuja Chitnis, MD

Professor of Neurology at Harvard Medical School

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Disclosures

- Consulting: Dr. Chitnis has served as a consultant for Biogen, Novartis and Genentech-Roche
- Clinical trial advisory boards and/or clinical trial participation: Novartis, Sanofi and Genentech-Roche
- Research support from: Bristol Myers Squibb, Octave Bioscience, Novartis, Sanofi.
- Member SAB: Tiziana Life Sciences

Patient: 61-year-old man – non-active secondary progressive MS

- At baseline, he walks with a walker and has significant bilateral leg weakness
- Experienced worsening disease progression over the past 2 years
- Previously treated with rituximab, glatiramer acetate, teriflunomide, ocrelizumab
- No interim relapses in the prior 2 years
- No new lesions on brain or spine MRI in the prior 2 years

FDA-approved expanded access treatment with nasal foralumab

Nasal Foralumab Treatment Cycle:

Nasal Foralumab 50ug/day three times per week x 2 weeks, then one week rest

Treatment schedule:

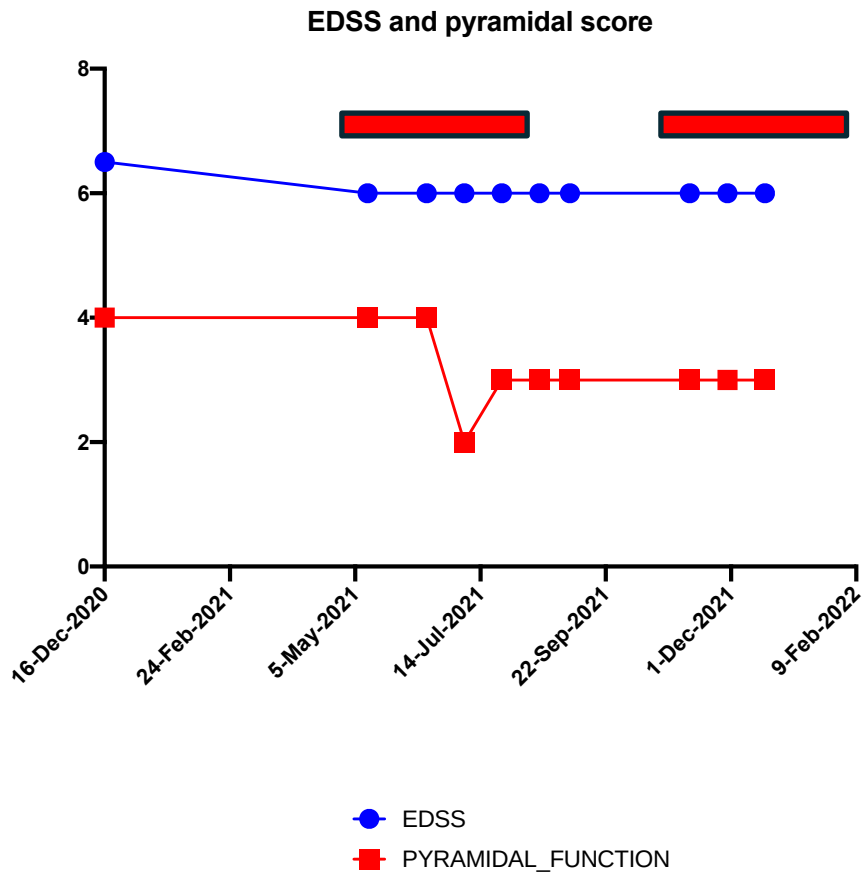
- First dose - May 2021
- Stopped – August end 2021 (completed 5 cycles)
- 6 week away vacation
- Restarted – November 2021
- February 2022 - Completed a total of 10 treatment cycles – 6 months of dosing
- FDA approved to continue for a total of 12 months
- Will restart treatment in 2 weeks

Schedule of events

Activity / Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15 - 21	1
	M	T	W	Th	F	S	Su	M	T	W	Th	F	S	Su	M-Su	M
Cycle	**Cycle 1**															**Start Cycle 2**
Dosing Week	Week 1							Week 2							Week 3	
Dosing Day																
Physical Exam	X															X
Nasal Exam by ENT	X															X
Neurologic Exam - Detailed																X
Laboratory Studies: Hematology	X															X
Chemistry	X															X
Total Nasal Symptom Score (TNSS)	X		X		X			X		X		X				X
Dosing by HCP in Clinic	X		X		X			X		X		X				X
In-Clinic Monitoring Post-dose	2h		2h		2h			1h		1h		1h				2h

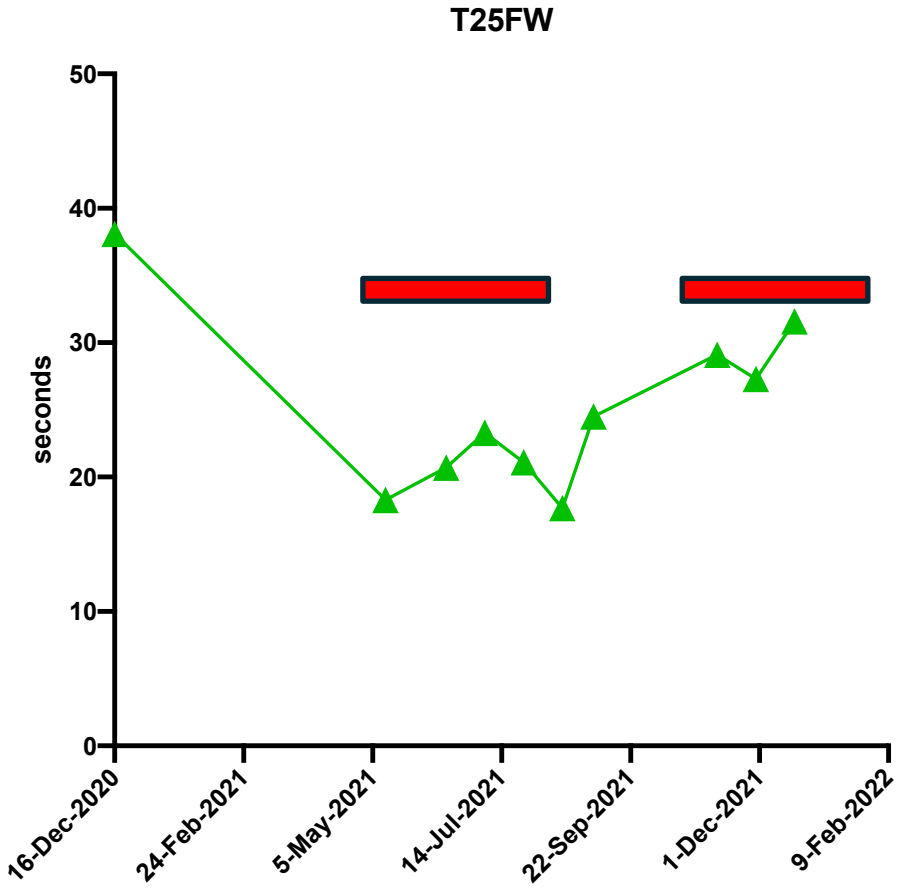
Safety monitoring

- ✓ Bloodwork stable – blood count, liver function tests, renal tests, EBV labs
- ✓ Nasal questionnaire at each dosing visit – stable
- ✓ ENT exams – every 3 weeks – stable



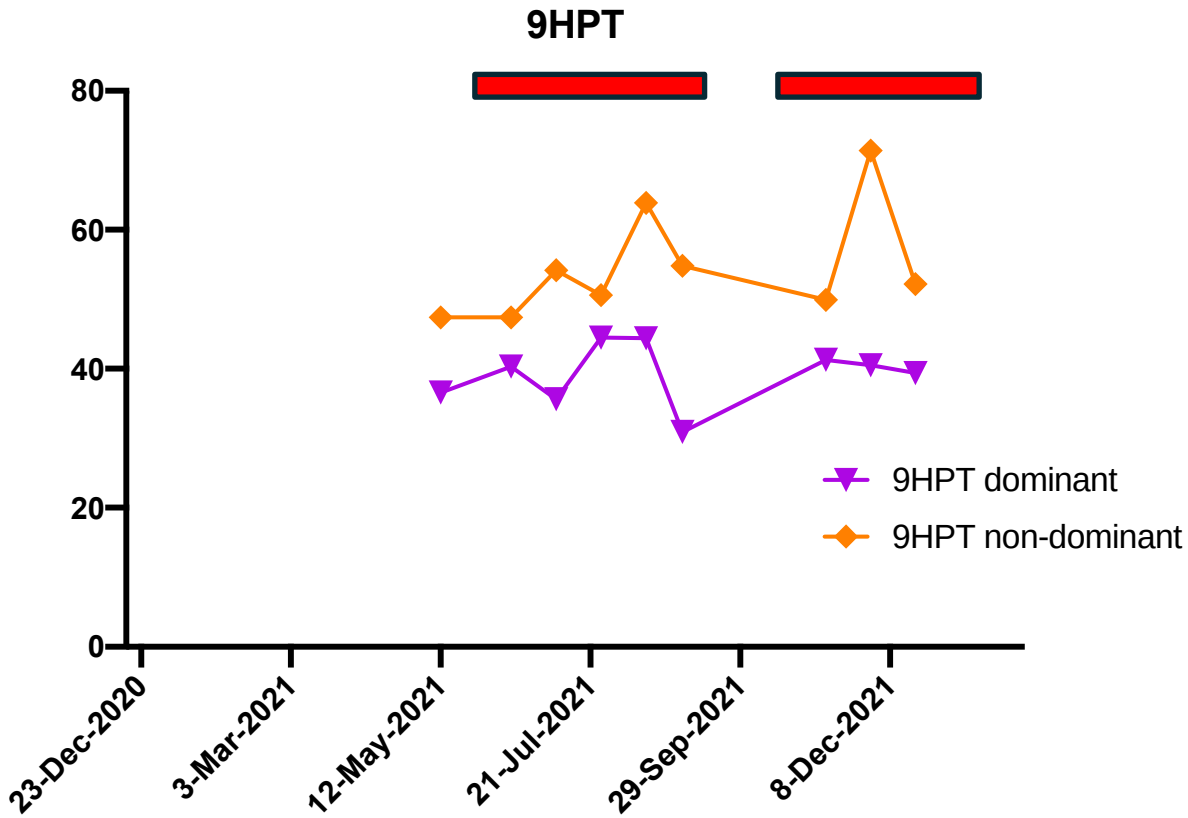
- **Expanded Disability Status Scale (EDSS)**
- **Pyramidal function**

Treatment

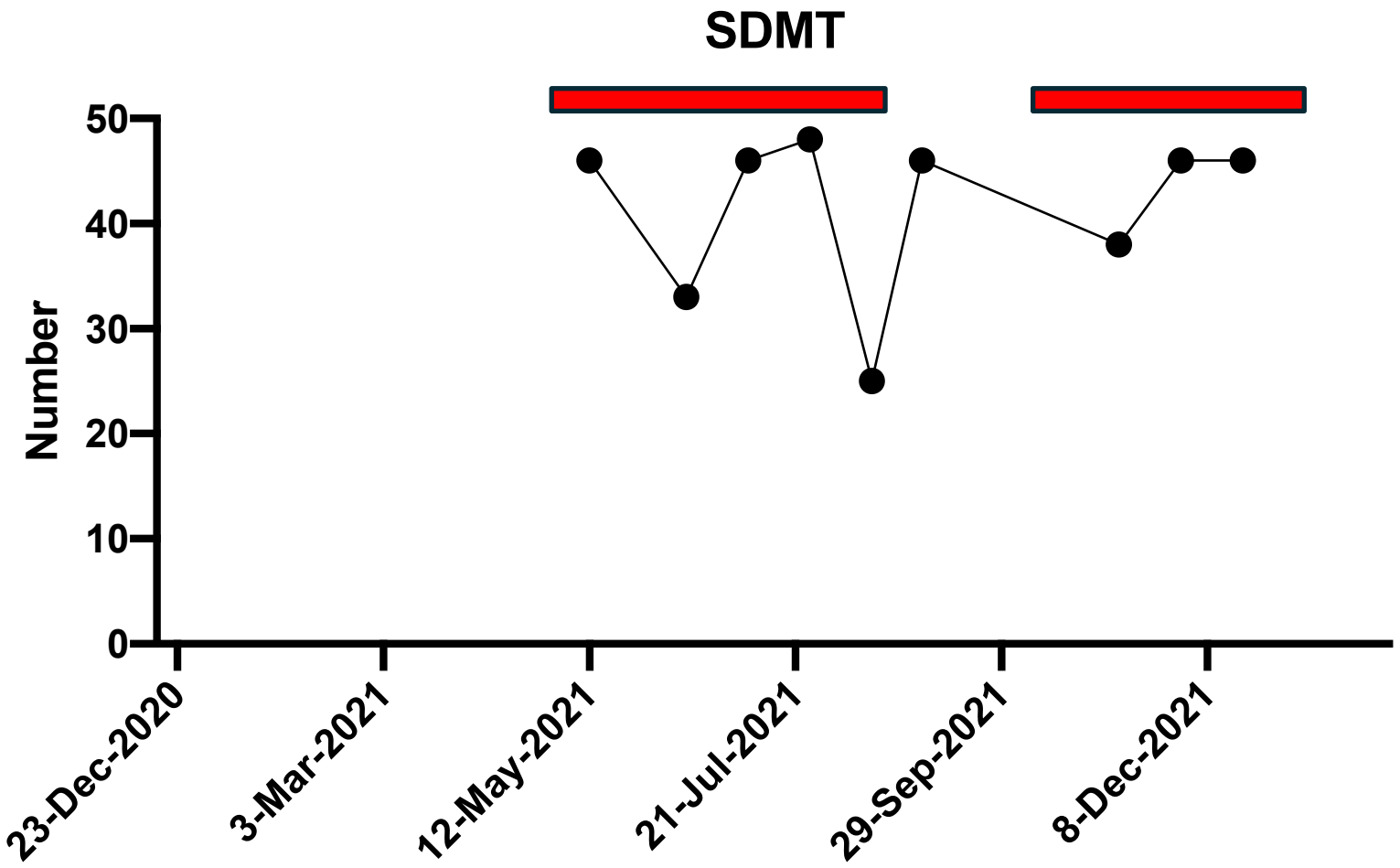


Timed 25-foot walk

9-Hole Peg Test



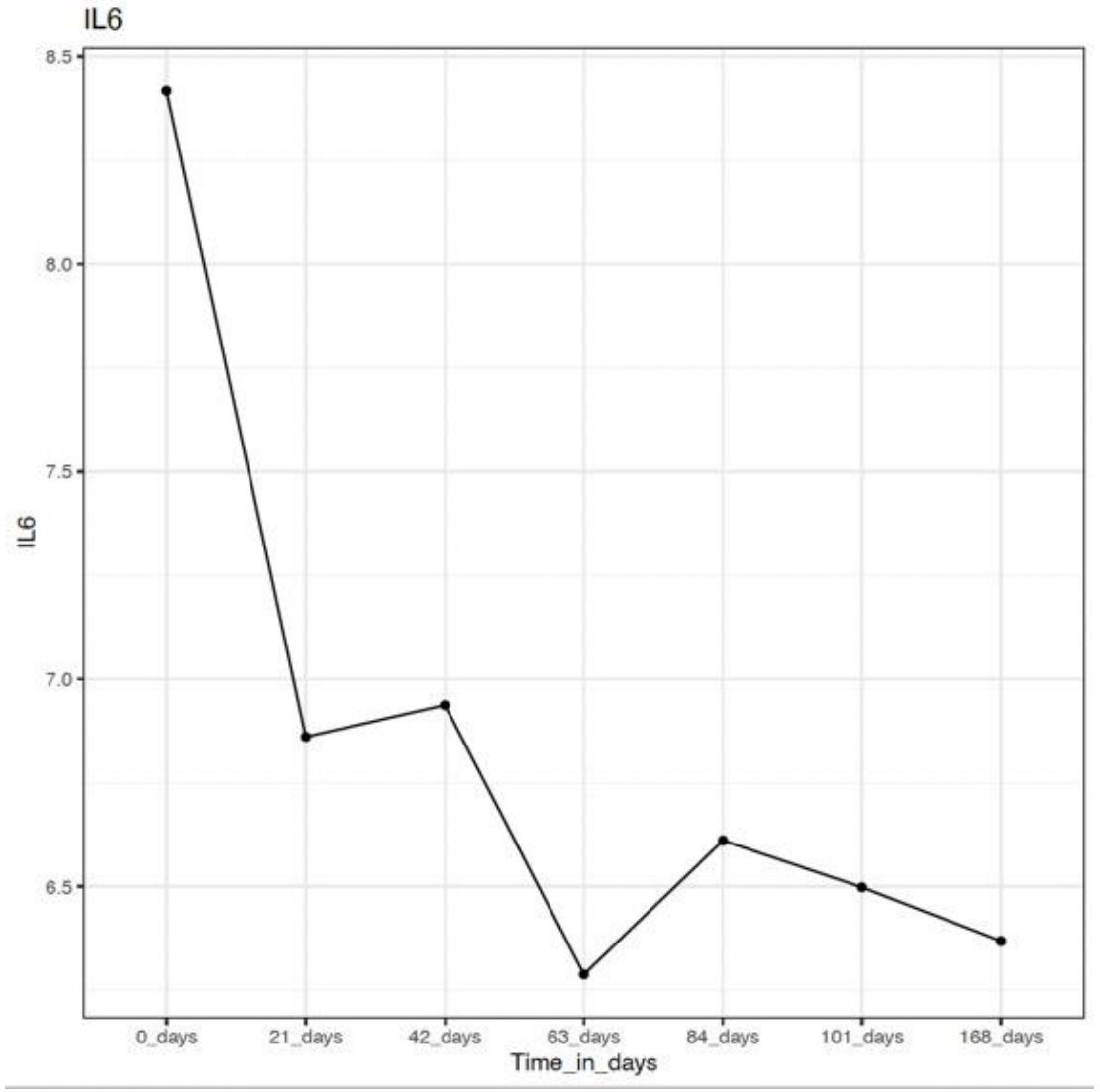
Symbol Digit Modality Test



Serum cytokines:

IL-6

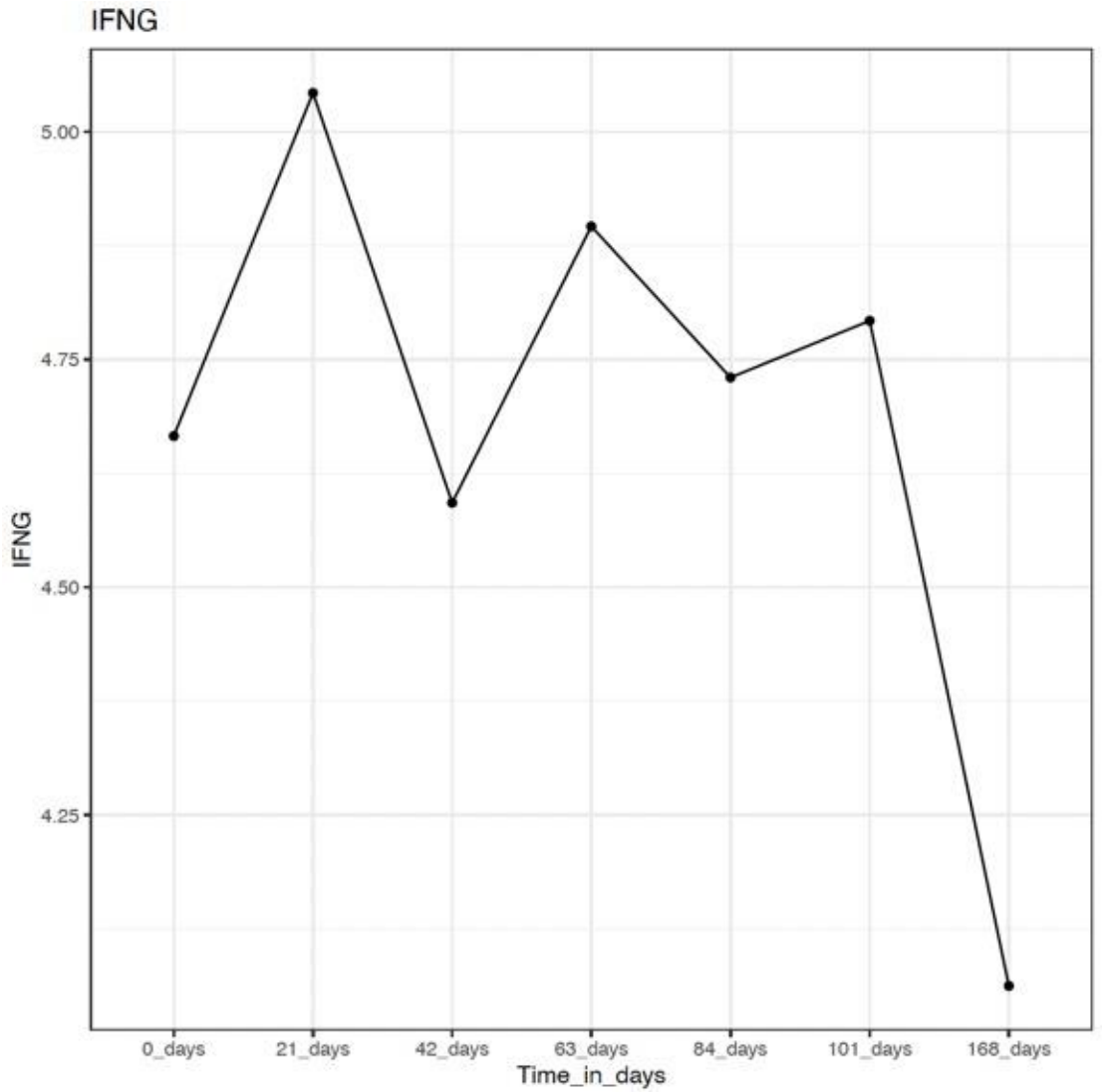
(Olink assay)



Serum cytokines:

IFN-gamma

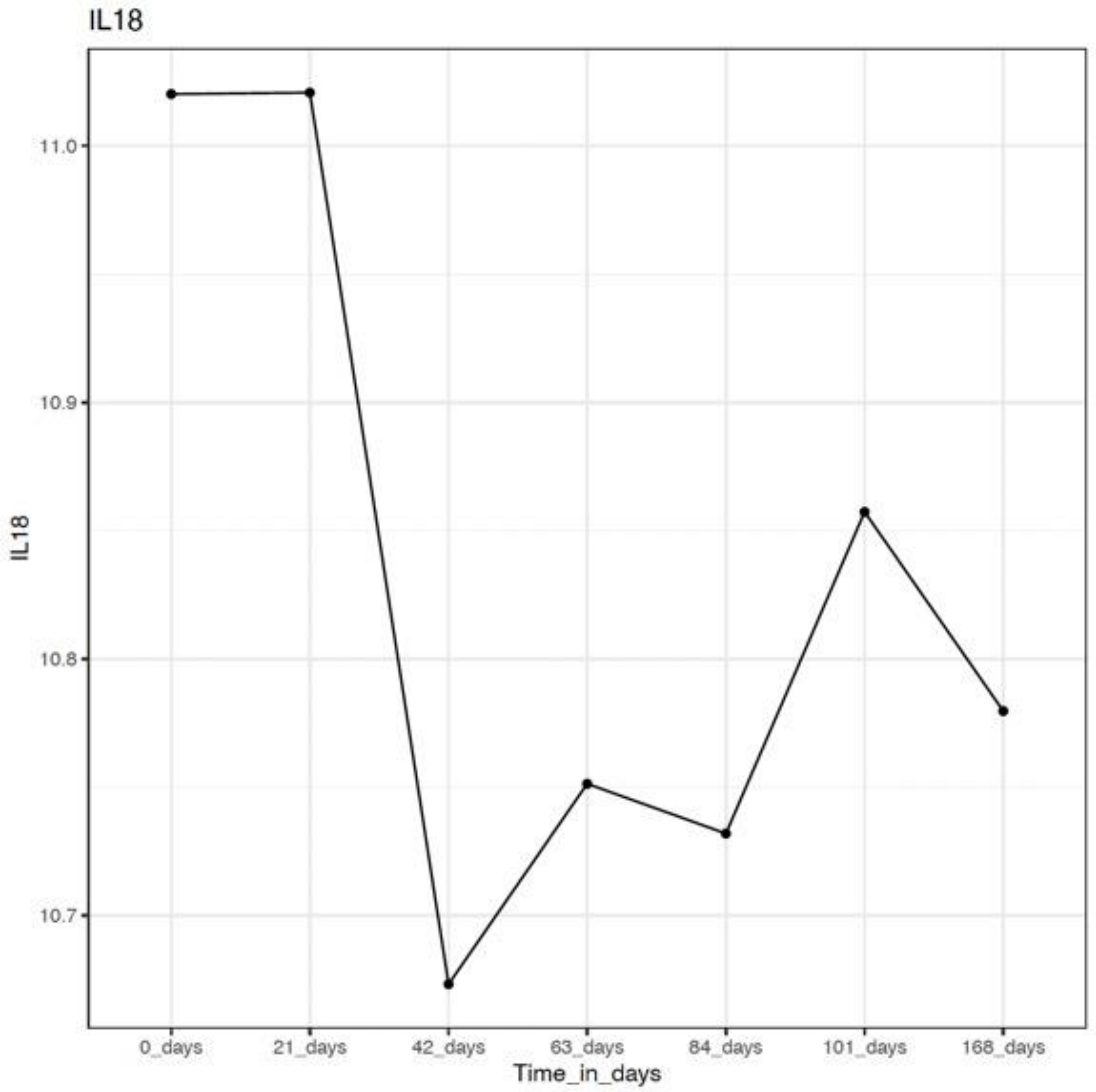
(Olink assay)



Serum cytokines:

IL-18

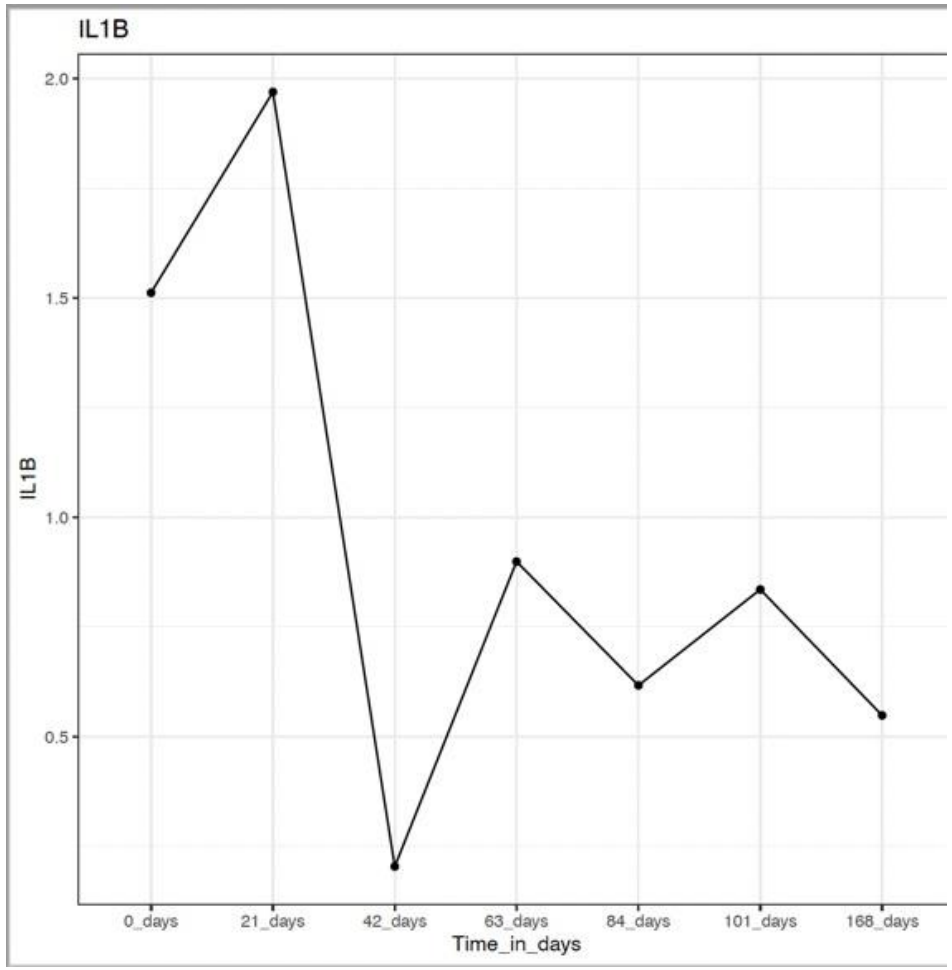
(Olink assay)



Serum cytokines:

IL-1beta

(Olink assay)



Summary

- A 61-year-old non-active secondary progressive multiple sclerosis patient was treated with nasal foralumab for a total of 6 months (10 x 3-week cycles)
- No significant adverse events observed; well tolerated
- Stabilization of neurological measures: EDSS, pyramidal scale, timed 25-foot walk
- Reduction in serum cytokines: IL-6, IL-1B, IFN-gamma, IL-18 over treatment period
- Microglial PET imaging: next presentation

PET Imaging Data and Interpretation

Tarun Singhal, MD

Assistant Professor of Neurology at
Harvard Medical School

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Ann Romney Center for Neurologic Diseases

LONGITUDINAL MICROGLIAL ACTIVATION PET IMAGING IN FIRST SPMS PATIENT AFTER FORALUMAB TREATMENT

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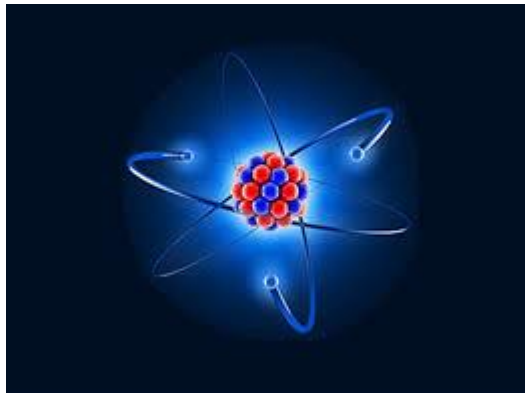
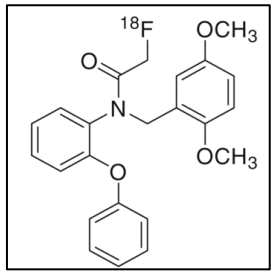
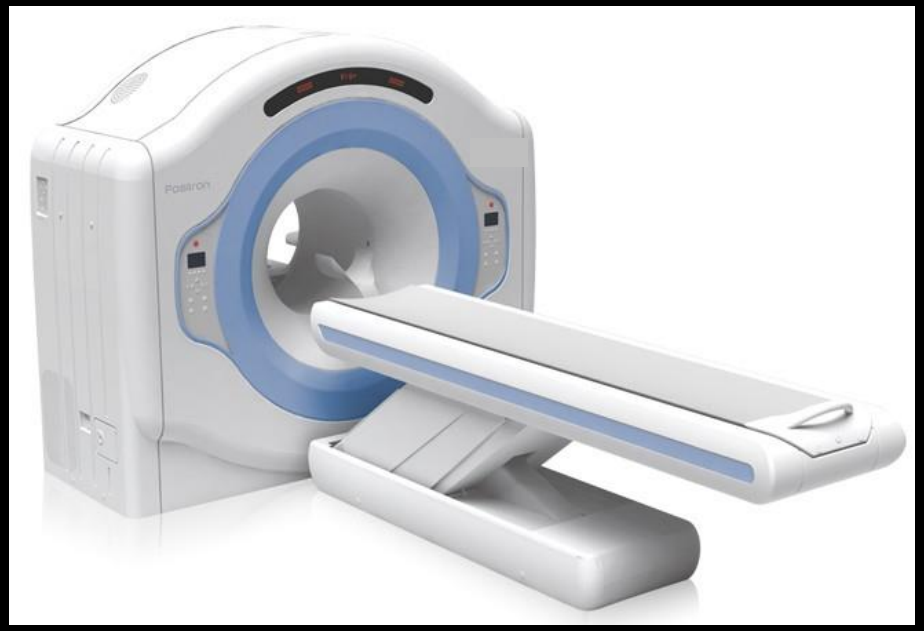
Director, PET Imaging Program in Neurologic Diseases
Ann Romney Center for Neurologic Diseases
Assistant Professor of Neurology
Brigham Multiple Sclerosis Center
Brigham and Women's Hospital
Harvard Medical School, Boston, MA

- Neurology and Nuclear Medicine
- Clinical Investigation



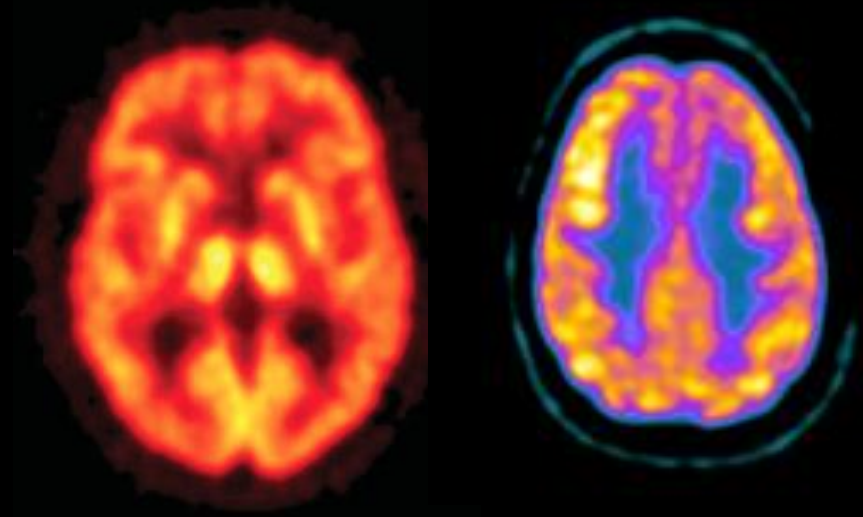


Understand and Treat Brain diseases better

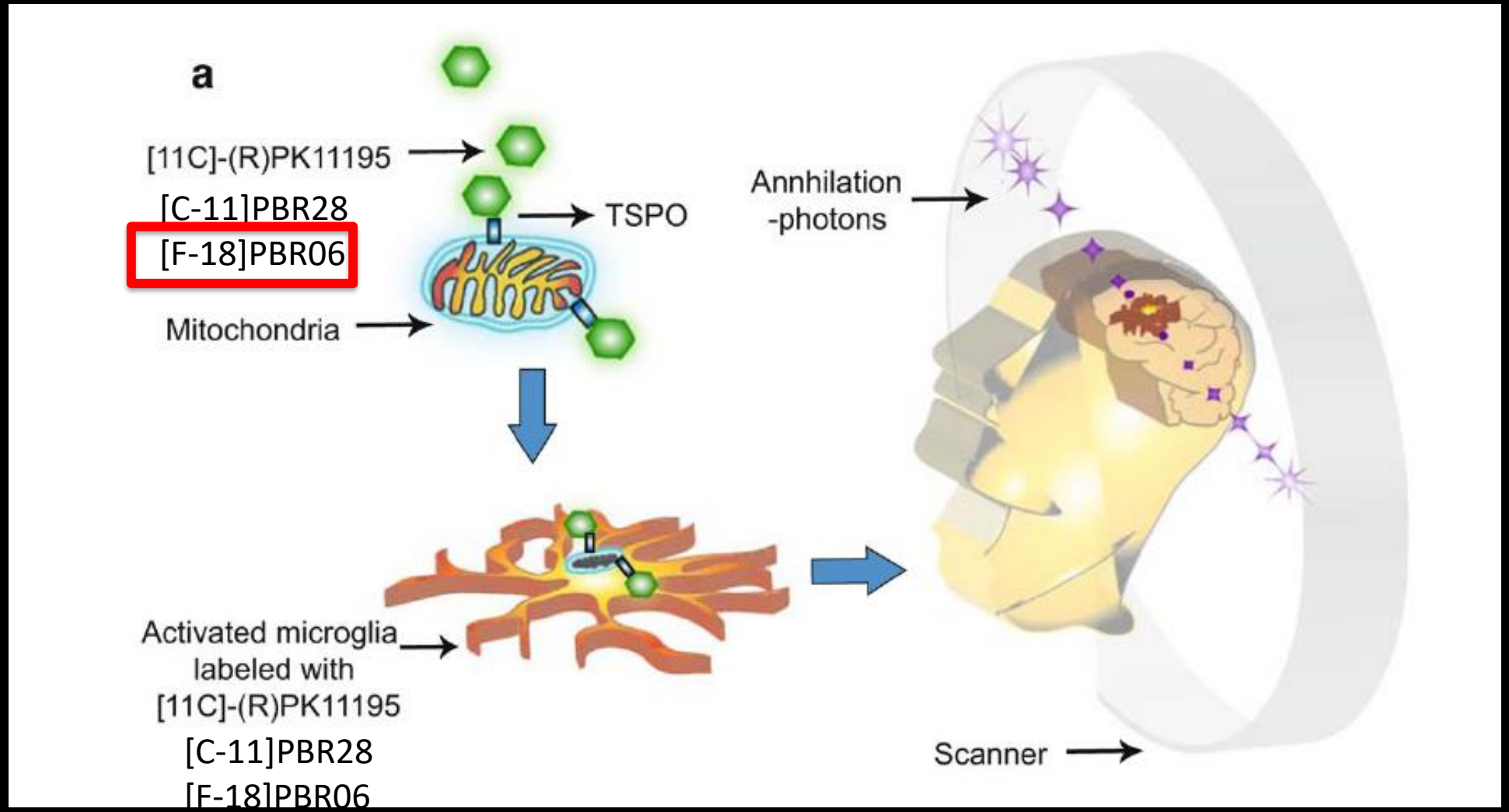


PET SCANNING
MOLECULAR
AND
FUNCTIONAL
IMAGING

CELLULAR IMAGING
THROUGH
MOLECULAR
TARGETTING

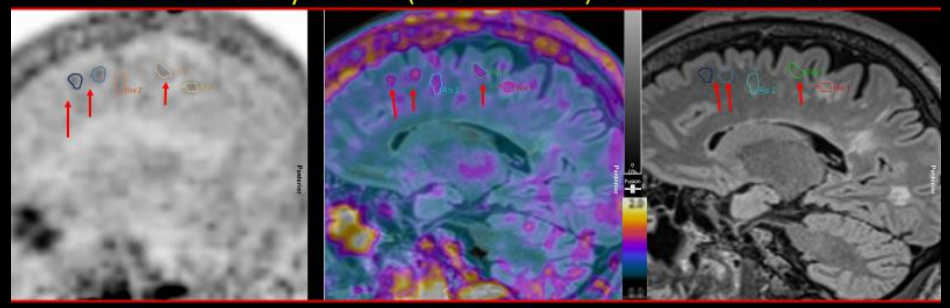


Principle of TSPO PET Imaging



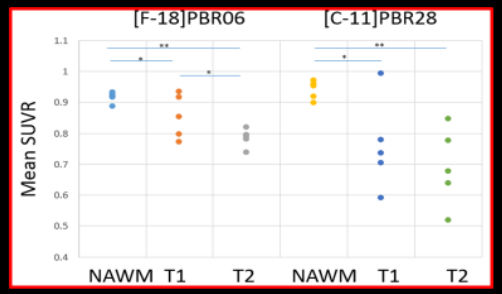
J Neuroimmune Pharmacol. 2009 June ; 4(2): 227–243.

"Normal" appearing white matter in MS shows inflammatory areas (red arrows): It's not normal

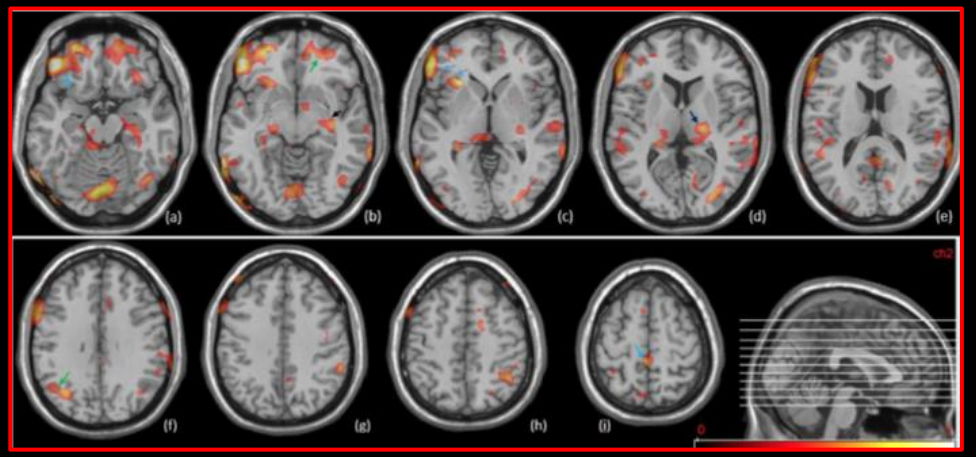


Singhal et al. Clinical Nuclear Medicine 2018 Sep;43(9):e289-e295

"Normal" appearing white matter has more tracer binding than lesions

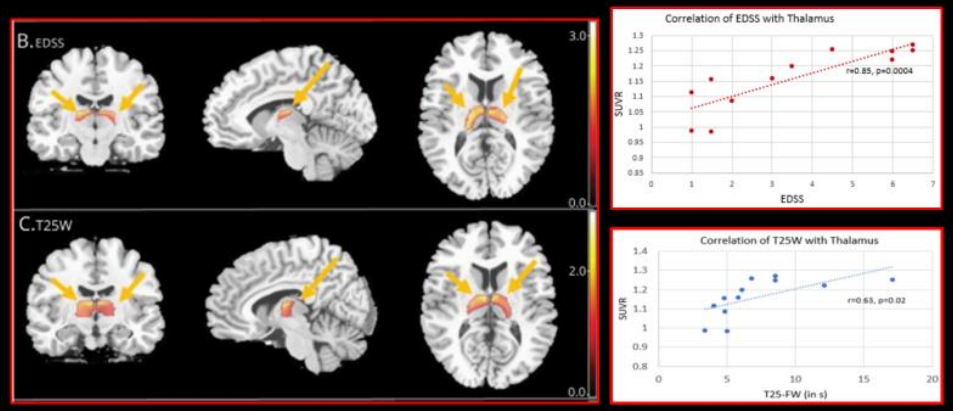


Grey matter microglial activation in SP versus RRMS

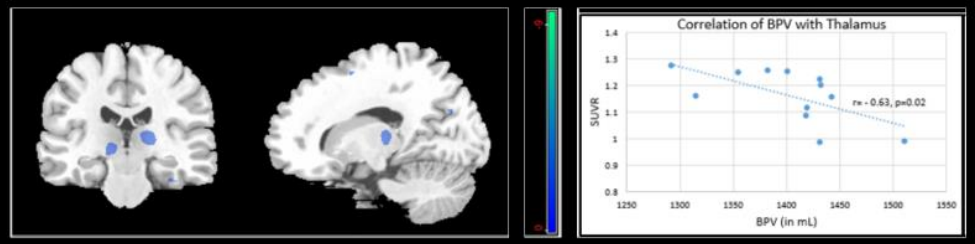


Singhal et al. Neurol Neuroimm Neuroinflamm 2019,6:e587

Thalamic SUVR correlates with EDSS and T25-FW



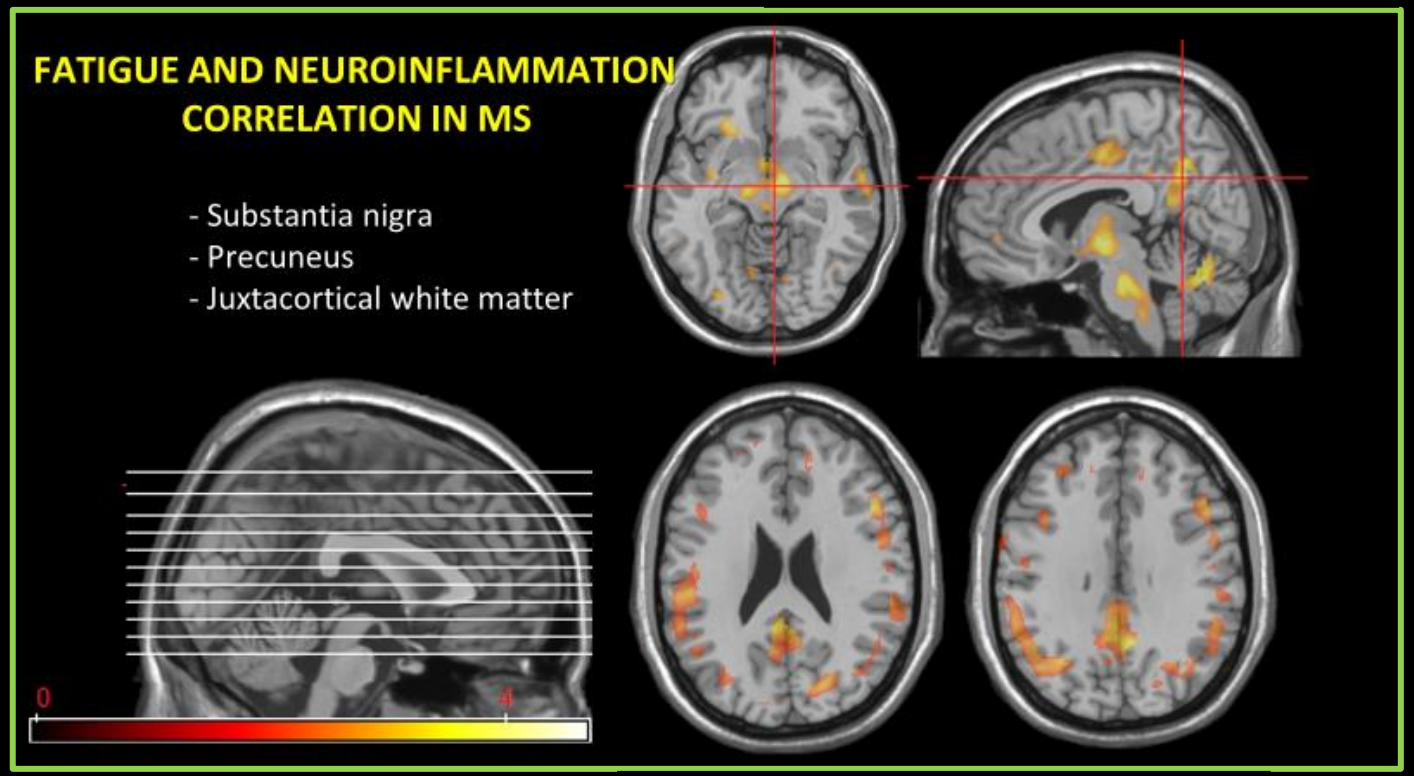
Thalamic SUVR correlates with whole brain atrophy



Singhal et al. Neurol Neuroimm Neuroinflamm 2019,6:e587

FATIGUE AND NEUROINFLAMMATION CORRELATION IN MS

- Substantia nigra
- Precuneus
- Juxtacortical white matter



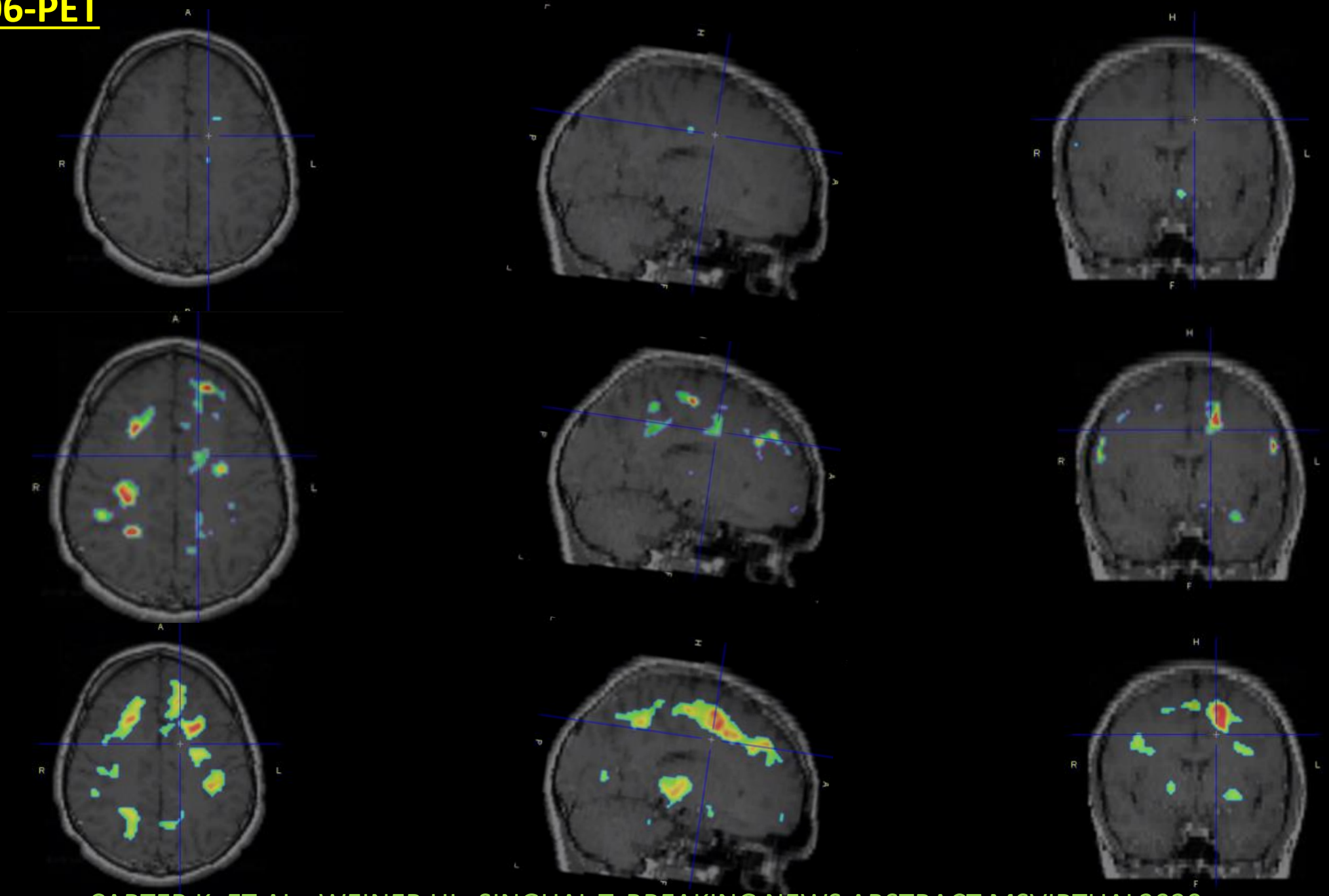
Singhal et al. Neurol Neuroimm Neuroinflamm 2020,7:e854

[F-18]PBR06-PET

HC

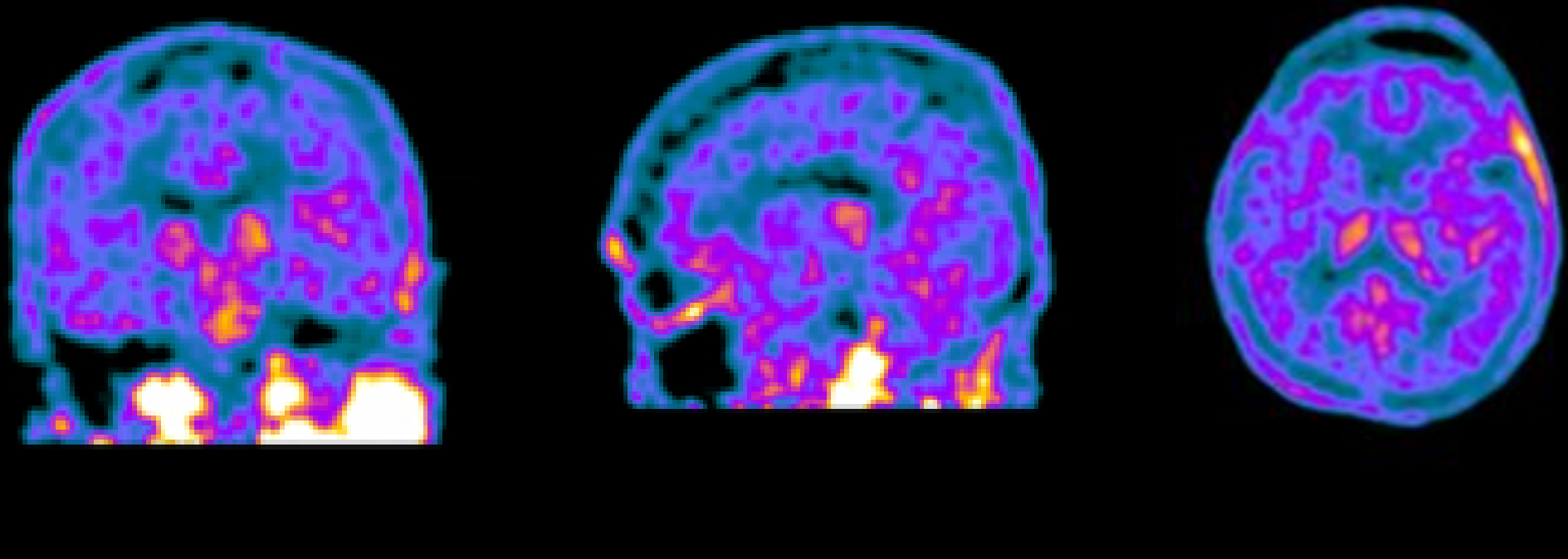
RRMS

SPMS



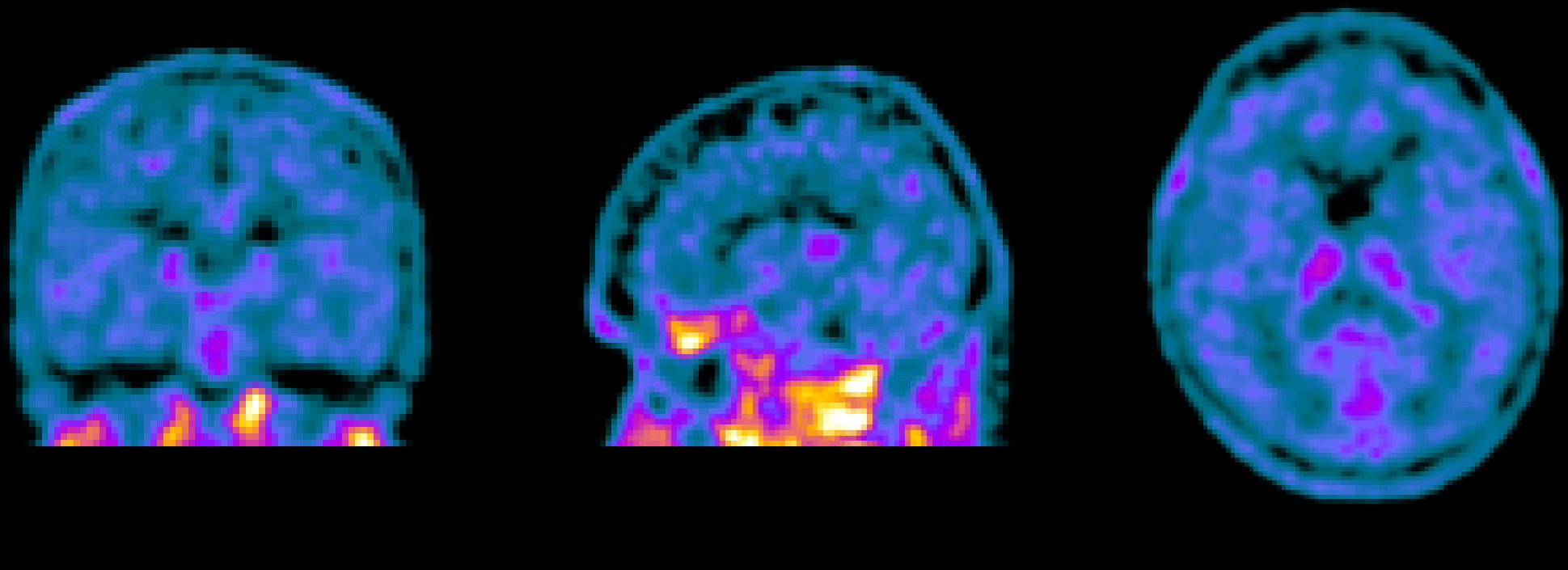
CARTER K, ET AL., WEINER HL, SINGHAL T. BREAKING NEWS ABSTRACT MSVIRTUAL2020

Pre- Nasal Foralumab in Progressive MS



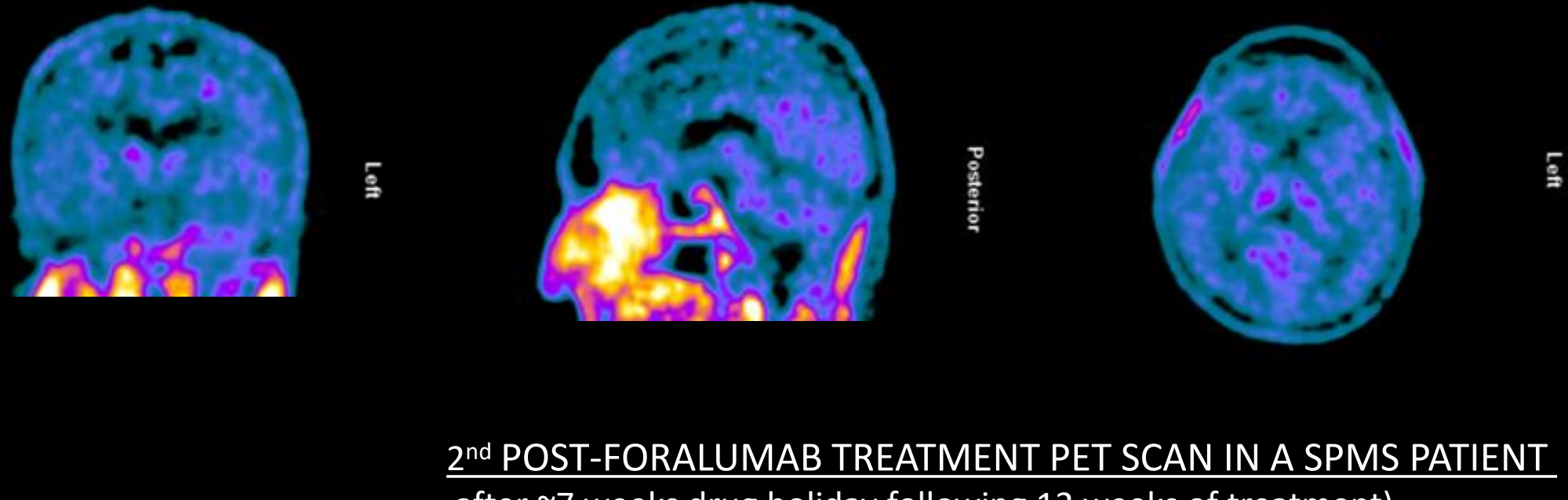
PRE-FORALUMAB TREATMENT PET SCAN IN A SPMS PATIENT

After 3 months of Nasal Foralumab treatment in Progressive MS



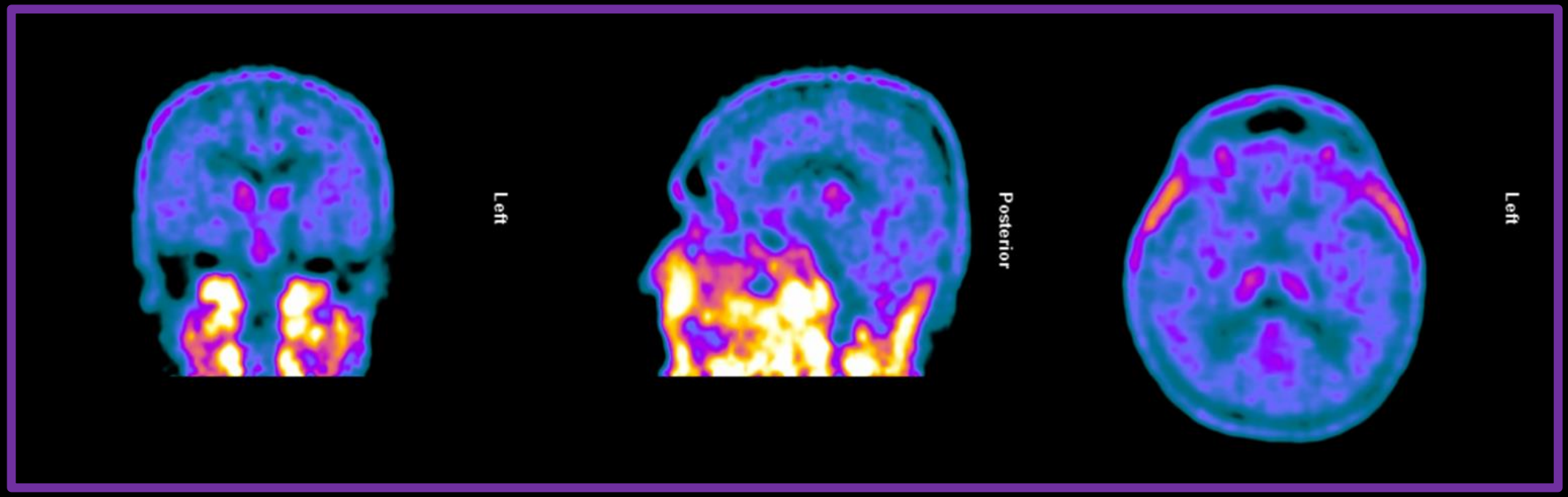
POST-FORALUMAB TREATMENT PET SCAN IN A SPMS PATIENT

2nd Post-Nasal Foralumab PET scan in Index patient with Progressive MS (7 weeks washout)

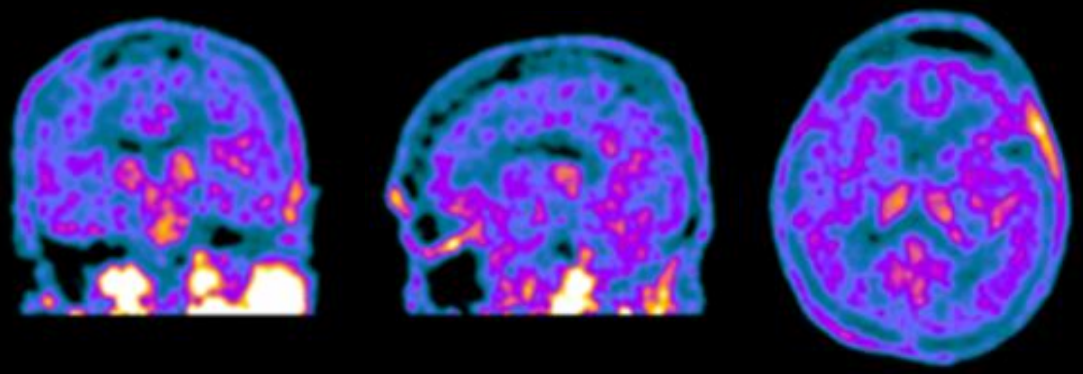


2nd POST-FORALUMAB TREATMENT PET SCAN IN A SPMS PATIENT
after ~7 weeks drug holiday following 12 weeks of treatment)

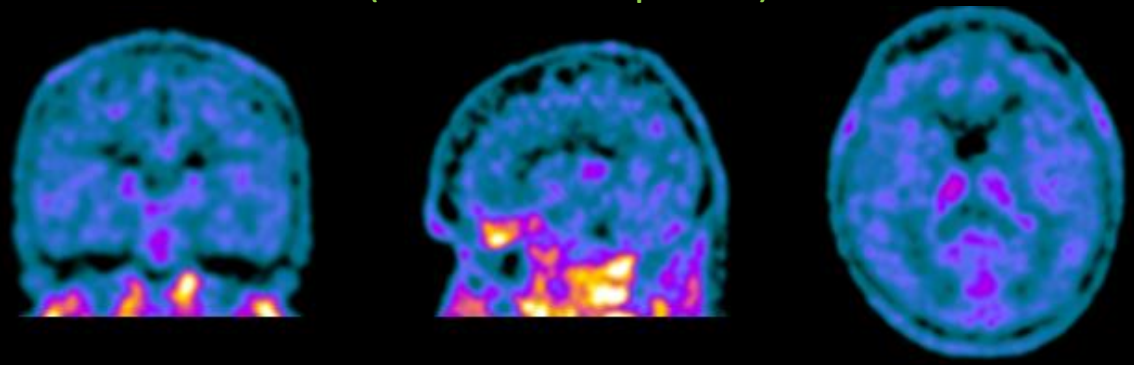
6 months Post-Nasal Foralumab PET scan in Index patient with Progressive MS



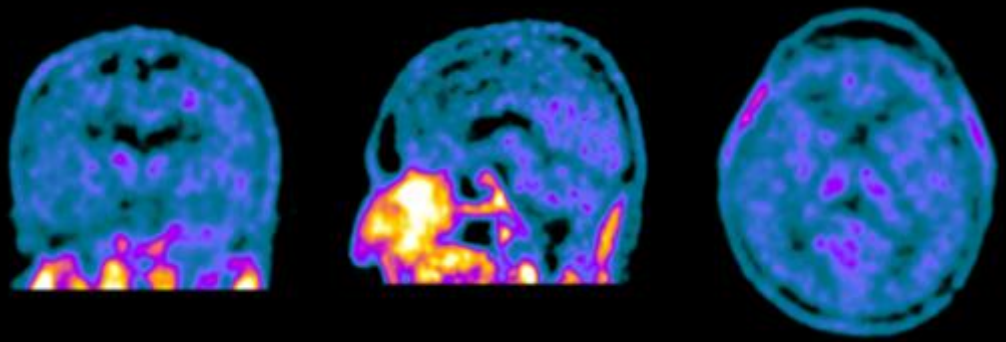
Pre-Nasal Foralumab treatment
(Baseline)



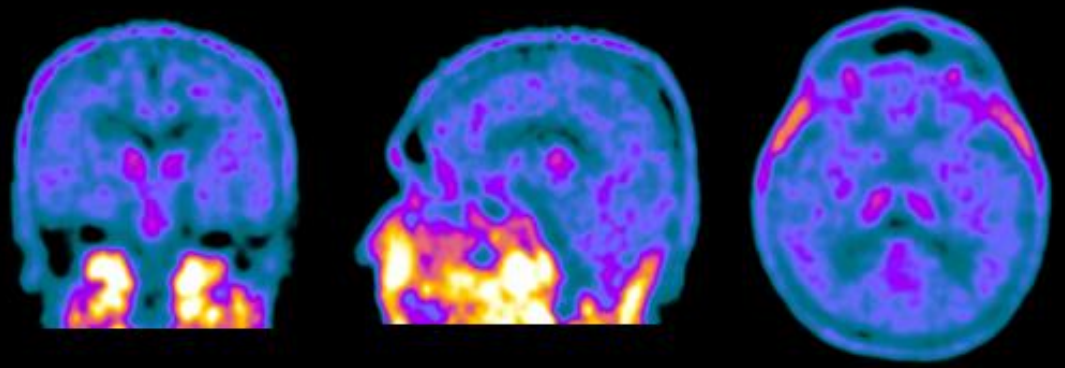
After 3 months of Foralumab treatment
(First follow-up scan)



7-weeks washout after 3 months of Foralumab treatment
(Second follow-up scan)



After total 6 months of Foralumab treatment
(Third follow-up scan)

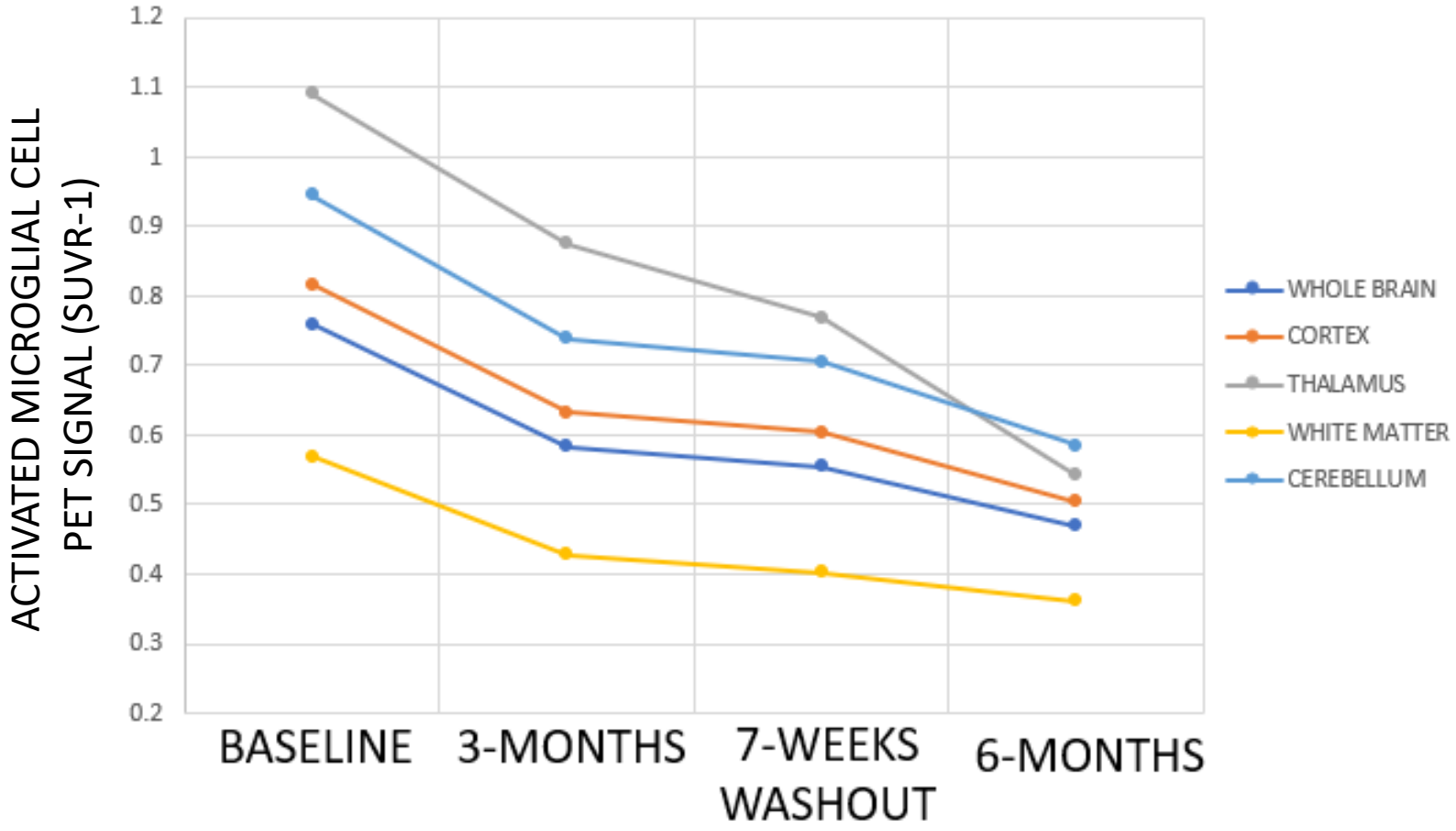


Percent Reduction in Microglial PET Signal as Compared to Baseline in Various Brain Regions After Starting Nasal Foralumab

SUVR-1 (% change)	Whole Brain	Cortex	Thalamus	White Matter	Cerebellum
3 Months	-23.1209	-22.53	-19.7841	-24.8364	-21.8116
4.7 Months	-26.8157	-26.0158	-29.5988	-29.1464	-25.2992
6 Months	-38.1203	-38.2784	-50.3726	-36.4418	-38.1906

*Percent reduction is based on changes in “SUVR-1” as compared to baseline, which is considered a surrogate index for PET binding potential. SUVR=Standardized Uptake Value Ratio, calculated with reference to a pseudoreference region in cerebral white matter that showed minimal change in PET SUV, across time points.

Graph Depicting Microglial Activation PET signal in Different Regions of the Brain at Various Time Points



PET Imaging results are unique

- No prior studies in an exclusive sample of SPMS patients
- No previous studies have shown PET signal reduction extensively in multiple regions of the brain after other treatments, even in RRMS patients
- Prior studies show only a 12-25% reduction after a year of treatment with older drugs in RRMS or mixed populations of RR and SPMS (as compared to 35-50% reduction after 6 months of treatment with Foralumab, which is unprecedented) , although hard to fully compare across studies and methodologies

Neurol Neuroimmunol Neuroinflamm. 2019 Jun 7;6(4):e574.
J Nucl Med. 2017 Oct;58(10):1646-1651

Next Steps

- Pursue microglial activation PET imaging in a larger population of SPMS patients

- Longitudinal study design using [F-18]PBR06-PET tracer and other quantitative approaches

Overview of MS and Conclusions

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Q&A

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