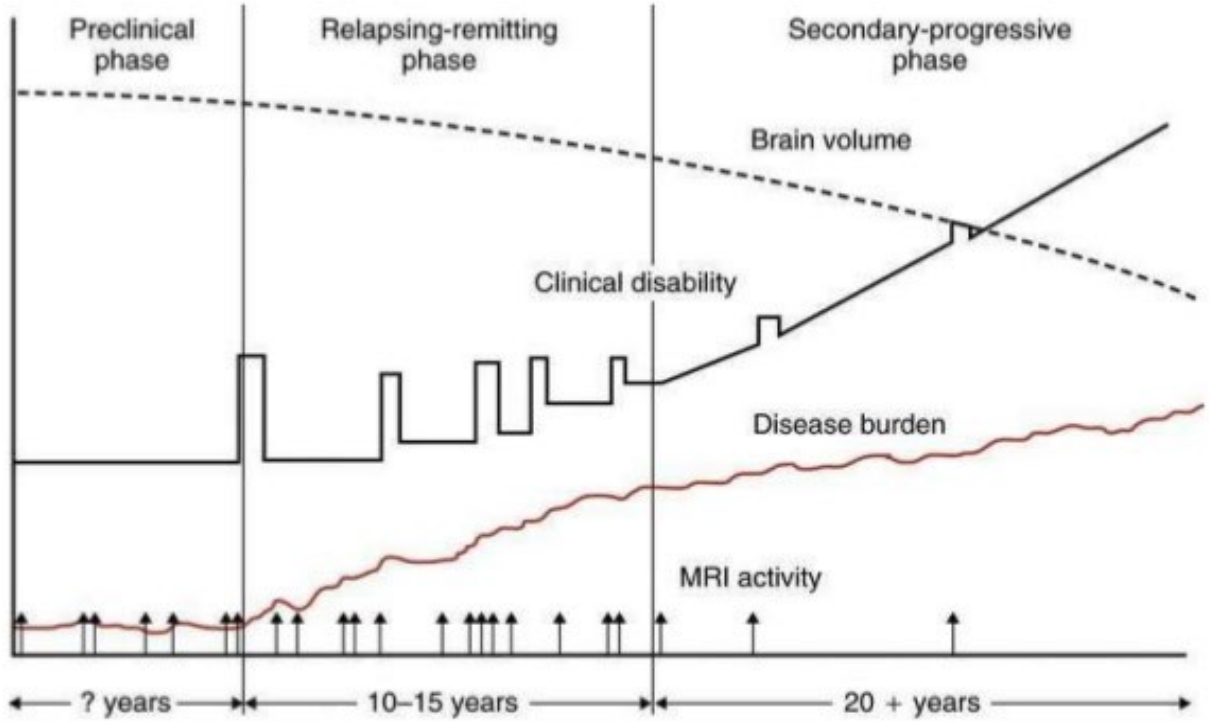
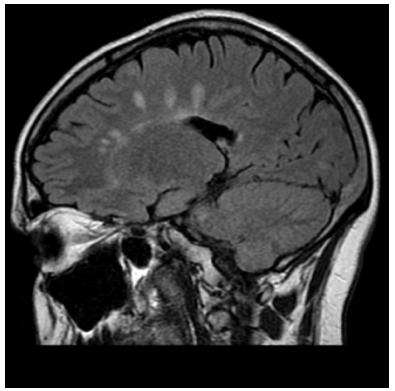
MS research at OSU

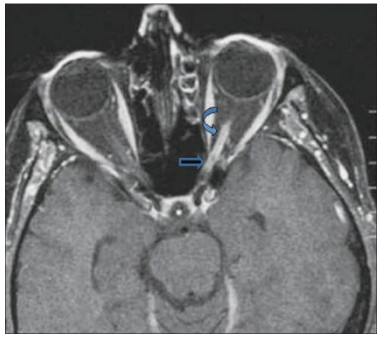
Benjamin M. Segal, M.D.
Chair of Neurology
Director, Neuroscience Research Institute
Co-Director, Neurological Institute

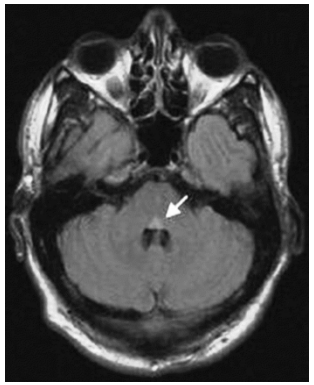
THE OHIO STATE UNIVERSITY

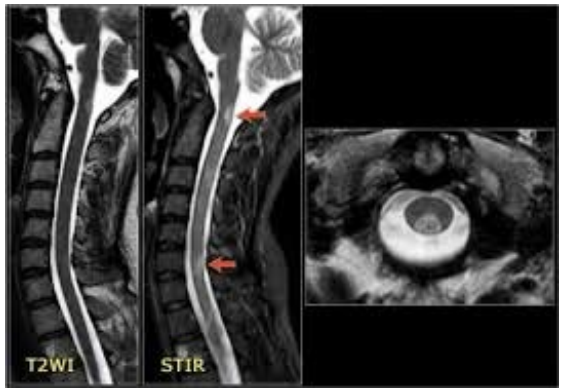
Natural History Of Multiple Sclerosis











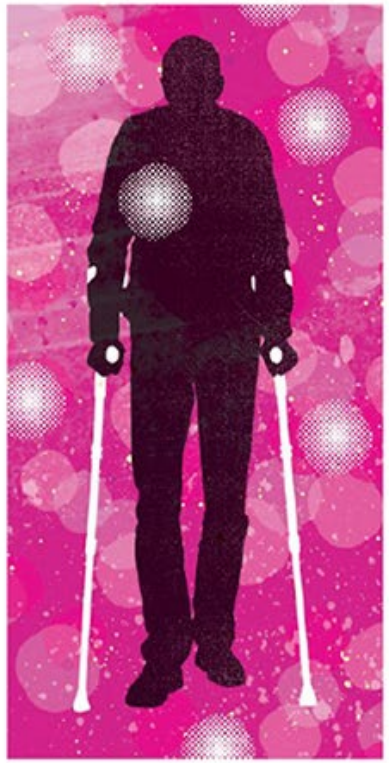
Research Priorities

- Discover treatments that reverse damage in MS
- Discover safer, more effective drugs for relapsing remitting MS
- Discover treatments that slow or halt MS progression
- Design new tests that allow doctors to diagnose progressive MS earlier
- Assess the effectiveness of the COVID19 vaccine in MS

Research Question

How can we reverse neurological damage in MS and other diseases?

Harnessing humans' mighty immune systems



DISCOVERY OF A NEW TYPE OF IMMUNE CELL offers hope for recovery from degenerative neurological diseases such as ALS and multiple sclerosis as well as from damage caused by traumatic brain and spine injuries and stroke.

Researchers at Ohio State and the University of Michigan, using a mouse model, discovered the new type of cell, which rescues damaged nerve cells from death and partially reverses nerve fiber damage. The team also identified a human immune cell line that promotes nervous system repair.

The findings were published in October in the journal *Nature Immunology*.

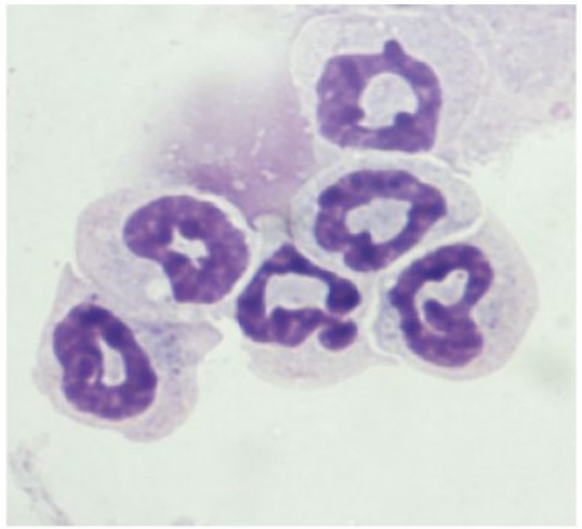
"This immune cell subset secretes growth factors that enhance the survival of nerve cells following traumatic injury to the central nervous system," says Dr. Benjamin Segal, co-director of The Ohio State University Wexner Medical Center's Neurological Institute and professor and chair of the Department of Neurology in the College of Medicine. "It stimulates severed nerve fibers to regrow in the central nervous system, which is really unprecedented."

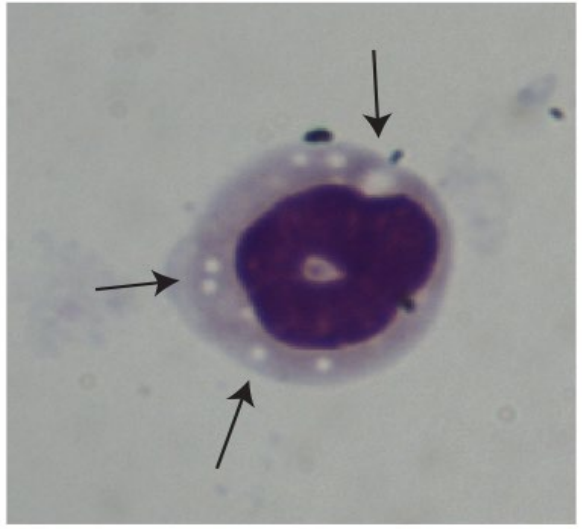
The next step is to harness this cell and expand it in a lab to enhance its healing effects. Researchers hope these cells can then be injected into patients to improve function and mobility and slow or stop progressive neurological decline.

Dr. Andrew Sas, an assistant professor and physician scientist in the Department of Neurology, was first author on the study. "Our findings could ultimately lead to the development of novel immunotherapies that reverse central nervous damage and restore lost neurological function across a spectrum of diseases," he says. — EILEEN SCAHILL *

Ohio State research led to the discovery of a new immune cell that offers hope for those living with ALS, multiple sclerosis and other neurodegenerative disorders.

A new inflammatory cell that stimulates nerve fiber regeneration





No cells

Plus cells

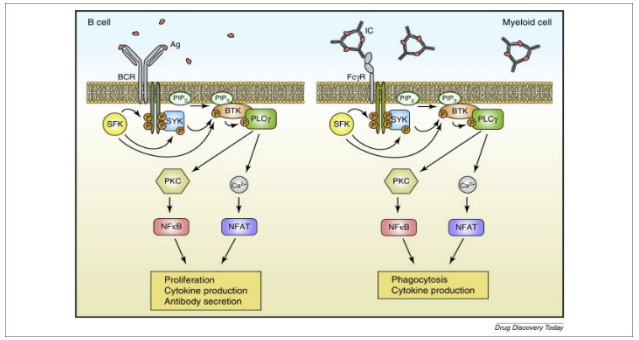
Research Questions

Are there new alternative drugs that decrease the risk of relapses in people with relapsing MS?

Are there new drugs that slow progressive clinical decline in people with MS?

Bruton's Tyrosine Kinase (BTK): A novel therapeutic target in MS

- BTK is an enzyme expressed in immune cells (including B cells and myeloid cells) and is necessary for their activation.
- B cells are the antibody producing cells.
- Myeloid cells are early responders to infections and other threats. When inappropriately activated they can also cause destructive inflammation. Myeloid cells include monocytes in the blood and microglia in the brain and spine.
- B cells and myeloid cells are believed to play important roles in both relapsing and progressive forms of MS.
- Ibrutinib, a small molecule BTK inhibitor (BTKi) is FDA approved for the treatment of B cell malignancies as well as GVHD.



Whang JA and Chang BY. Drug Discovery Today. 2014; 19:1200

A Placebo Controlled Trial of Evobrutinib in Relapsing MS

- Double blind, randomized Phase 2 trial
- Placebo controlled phase: 24 weeks; blinded extension phase: 24 weeks
- Subjects: relapsing MS
  (87% RRMS, 13% active SPMS; 69% women; all white)
- 5 arms: placebo, evobrutinib x 3 doses, open label dimethyl fumarate
  (52-54 subjects/ arm)
- Primary outcome: total # of gad^{+} lesions on MRI at weeks 12, 16, 20 and 24
- Results: **The total number of gad^{+} lesions, measured at weeks 12-24, was significantly lower among patients in the evobrutinib 75 mg once-daily group than in the placebo group**
- Side effects: elevated LFTs; nasopharyngitis

Montalban X, et al. N Engl J Med. 2019; 380:2406

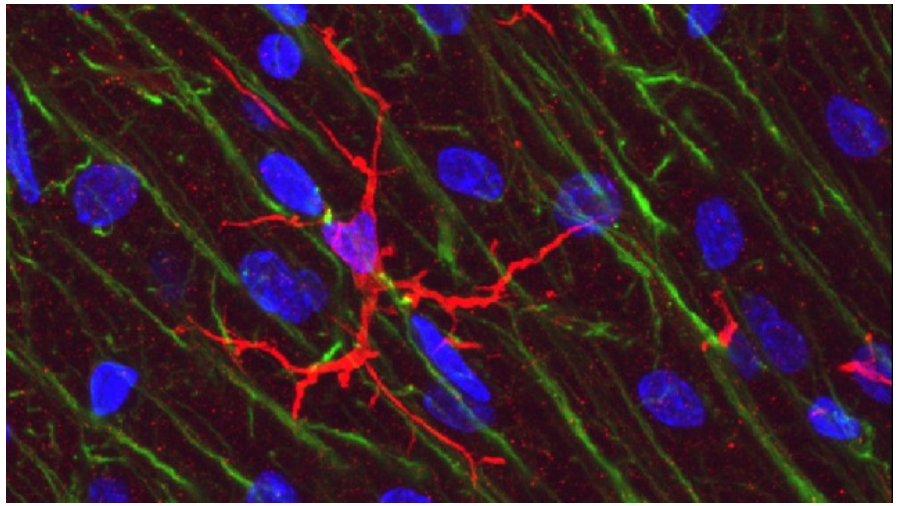
A Placebo Controlled Trial of SAR442168 (tolebrutinab) in Relapsing MS

- Double blind, randomized Phase 2b trial
- 12 week crossover
- Subjects: RRMS
- 5 arms: placebo, SAR442168 x 4 doses
  (52-54 subjects/ arm)
- Primary outcome: new gad+ lesions
- Results: **85% relative reduction in new gad^{+} lesions in the highest dose group**
  89% relative reduction in new or enlarging T2 lesions (secondary outcome)

Reich DS, et al. Eur J Neurol. 2020; 27:1-102

Potential Target of Action of BTKi in Progressive MS

- Activated microglia in the rim of smoldering white matter lesions and in cortical lesions
- Activated microglia scattered through out the perilesional and NAWM



Ongoing Clinical Trials of BTKi's in MS

Compound	Clinical Trials.gov Identifier	Study Type	Subjects	Control Group
SAR442168 (Tolebrutinib)	NCT03889639	Phase 2b	Relapsing MS	Placebo
SAR442168	NCT04410991	Phase 3	Relapsing MS	Placebo, Teriflunomide
SAR442168	NCT04410978 (GEMINI 1)	Phase 3	Relapsing MS	Placebo, Teriflunomide
SAR442168	NCT04458051 (PERSEUS)	Phase 3	PPMS	Placebo
SAR442168	NCT04411641	Phase 3	Non-relapsing SPMS	Placebo
M2951	NCT02975349	Phase 2	RRMS	Placebo, DMF
BIIB091	NCT03943056	Phase 1	Healthy volunteers	Placebo

Impact of BTKi on COVID-19

- 5/6 Waldenstrom's macroglobulinemia patients treated with ibrutinib (420 mg/ day) had a relatively mild course of COVID-19 infection. 1 of the 6 patients, treated with a reduced dose of 140 mg, developed respiratory insufficiency, which improved upon re-initiating ibrutinib, and subsequently quickly resolved upon increasing the dose to 420 mg/day.

  Treon S, et al. *Blood*. 2020; 135:1912

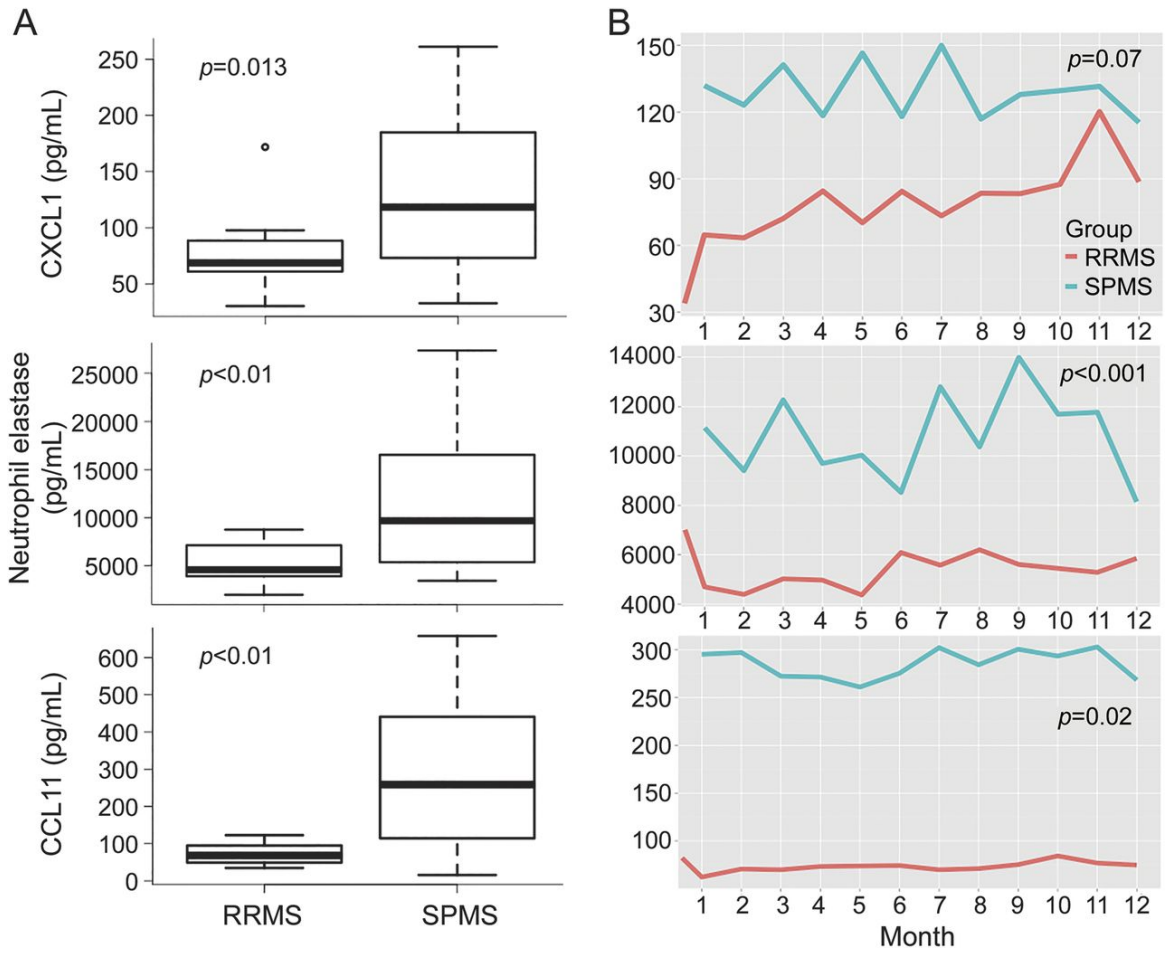
- 2/2 patients treated with ibrutinib for mantle cell lymphoma (560 mg daily) contracted COVID19 and developed respiratory insufficiency. Both discontinued ibrutinib and fully recovered.

  Alusiam T, et al. *Curr Res Transl Med*. 2020; 69:103273.

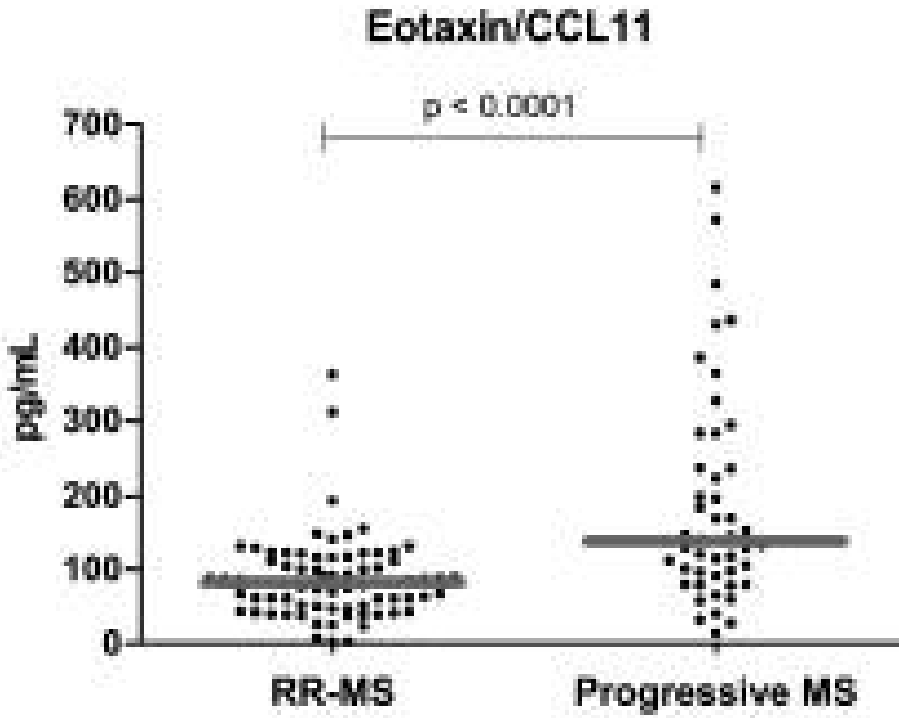
Research Question

How can we improve doctors' ability to make a diagnosis of progressive MS more accurately and sooner in a patient's disease course?

Elevated plasma levels of myeloid factors in SPMS



Huber A K et al. Neurology 2014; 83:1500.



Tejera-Alhambra, et al. PLoS One. 2015; 10(6): e0128952

AMERICAN ACADEMY OF NEUROLOGY

Research Questions

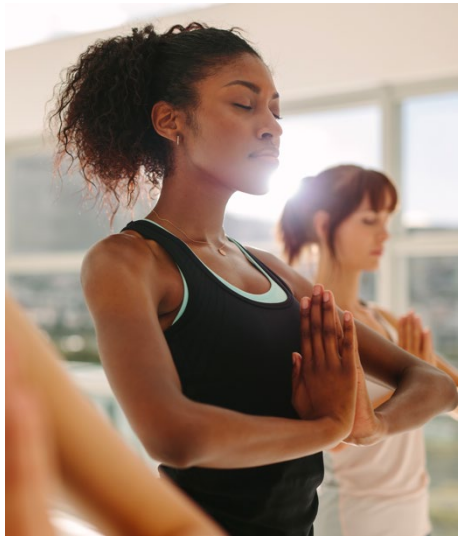
- How do people with MS respond to the COVID19 vaccine compared to the general population?

- Do MS drugs reduce the effectiveness of the COVID19 vaccine?

Effects of MS disease-modifying therapies on effectiveness of vaccines

- Several studies demonstrated preserved immune responses to multiple vaccine types in people treated with beta-interferons to multiple vaccine types.
- Limited data suggest vaccine responses to be preserved with dimethyl fumarate treatment.
- Vaccine responses were reduced to varying degrees in those treated with glatiramer acetate, teriflunomide, sphingosine-1-phosphate receptor modulators, and natalizumab.
- Antibody vaccine responses were significantly impaired by B cell depleting anti-CD20 monoclonal antibody therapies.

Mult Scler Relat Disord. 2020 Oct;45:102439



Multiple Sclerosis and the COVID19 vaccine

- Do you have multiple sclerosis (MS) or a similar disorder like neuromyelitis optica (NMO) or MOG-antibody related disorder?
- You may qualify for an interesting study with the OSU MS center.

The Ohio State Department of Neurology is currently enrolling for a research study to determine the effectiveness of the COVID19 vaccine in patients with MS and similar diseases.

YOU MAY QUALIFY IF:

- You are age 18 years and above
- You have a diagnosis of MS, NMO or MOG-antibody related disorder
- You plan on taking the COVID19 vaccine when it becomes available

Participants will have blood samples taken before and after they receive the COVID19 vaccine.

For more information, please call 614-293-6486 or email misty.green@osumc.edu