Studying the therapeutic effect of prospective treatment to target the relapse episode in multiple sclerosis

Rina Zilkha-Falb Ph.D

Student : Lakota Kleaver

The Multiple Sclerosis Center

Arrow project
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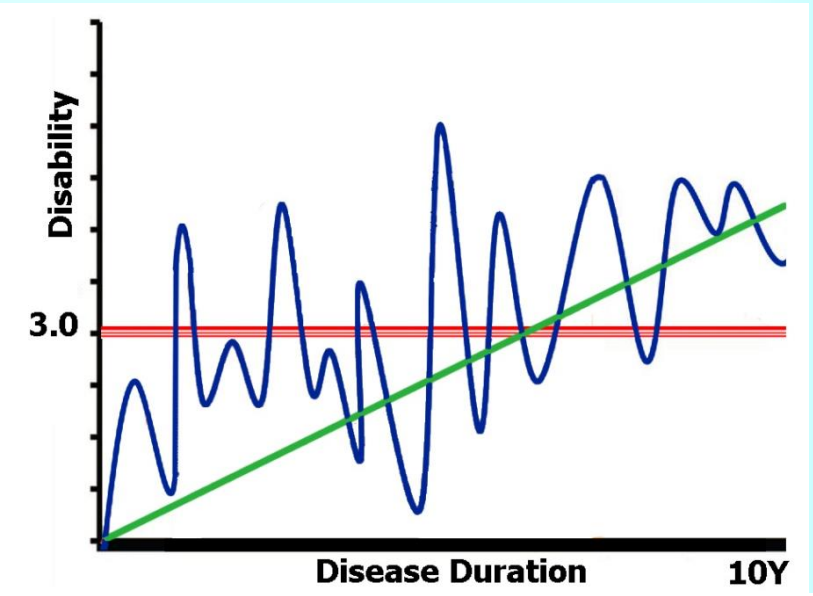
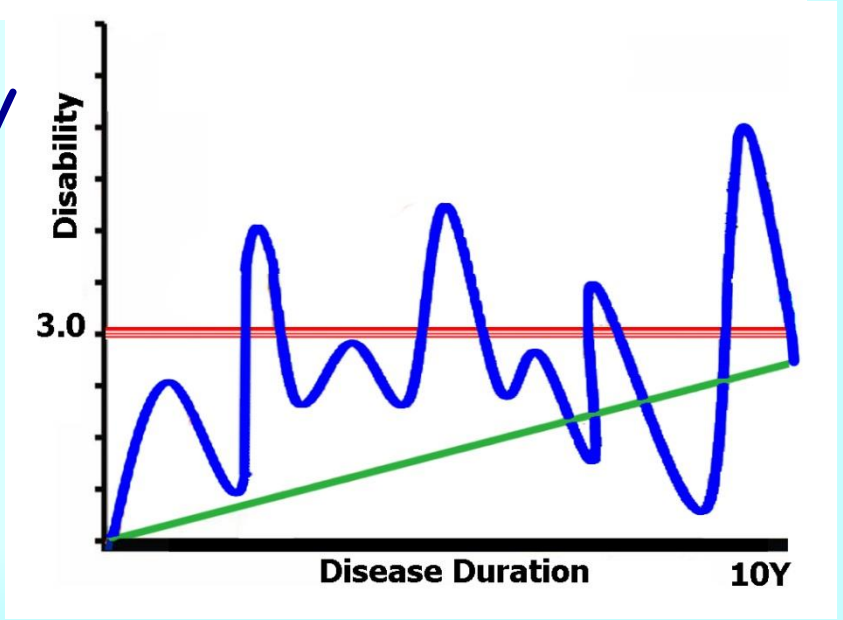
Benign Multiple Sclerosis

- Relapsing-remitting MS (RRMS) occurs in ~85% of patients.



- ~15% of patients display a non-active MS. These patients remain without significant neurological disability over-time.

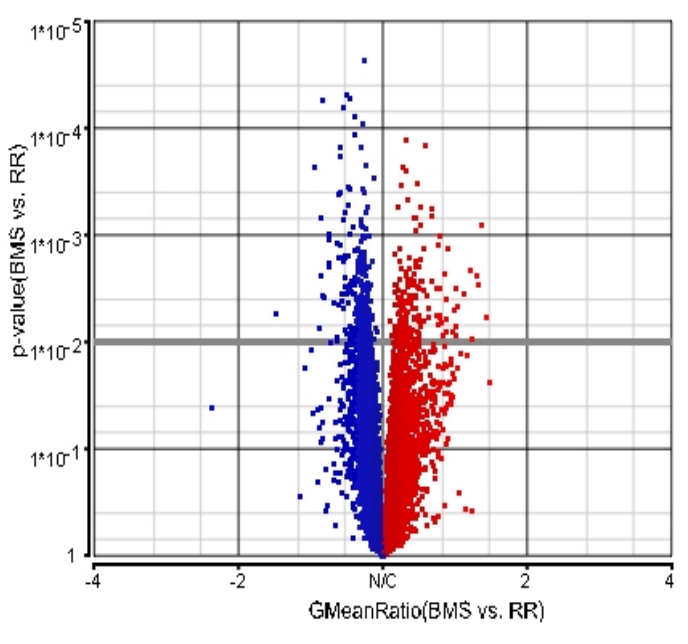


How it all begun ?

- Whether the RR and benign courses of MS result from distinct molecular pathways

- What are the molecular mechanisms that maintain the benign course ?

B9MS vs RRMS



Red dots demonstrate over-expressed genes, blue dots down-expressed genes.

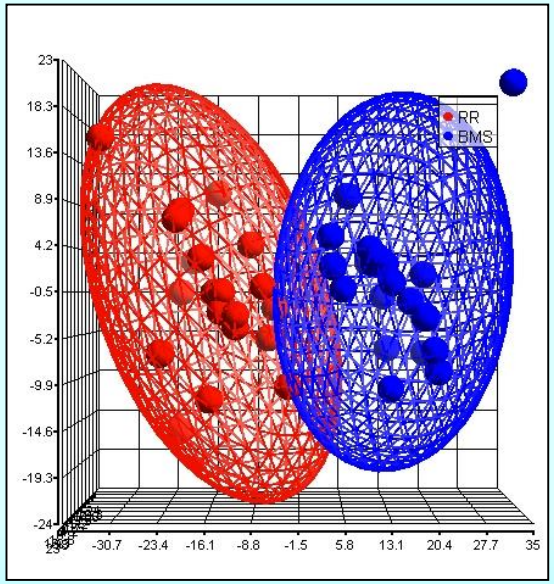
B9MS differed from RRMS by:

406 genes with p<0.01

171 over-expressed

235 down-expressed

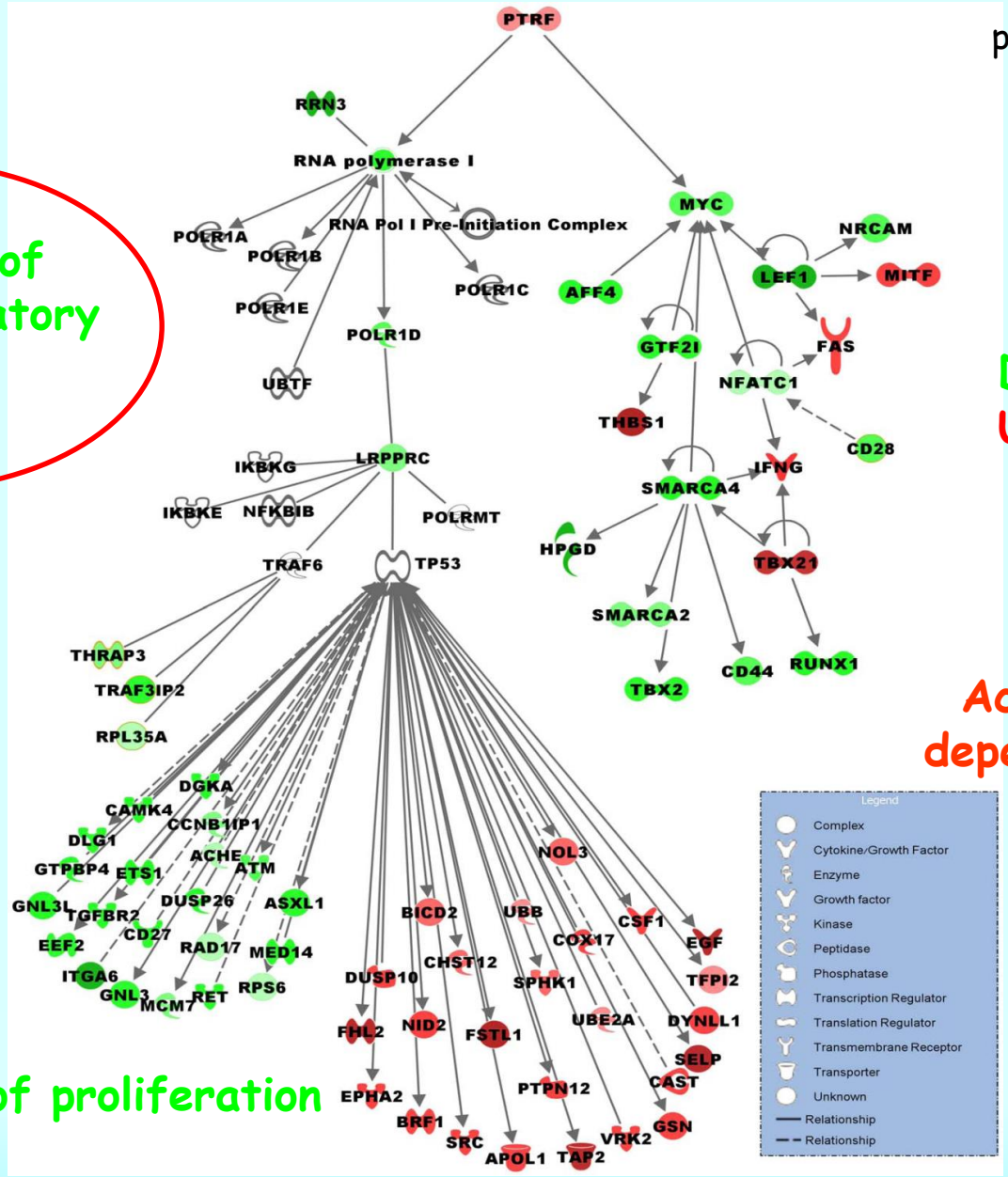
log fold change range -3.1 to 3.3



Regulatory network in BMS

Achiron A, et al. Suppressed RNA-polymerase 1 pathway is associated with benign multiple sclerosis. PLoS One. 7(10):e46871, 2012.

Suppression of POL1 regulatory pathway



Down-regulated

Up-regulated

Activation of P53 dependent apoptosis

Suppression of proliferation

RNA Pol 1 pathway

- Pol I is responsible for transcription of rRNA gene to generate pre-rRNA that is processed to mature rRNAs.

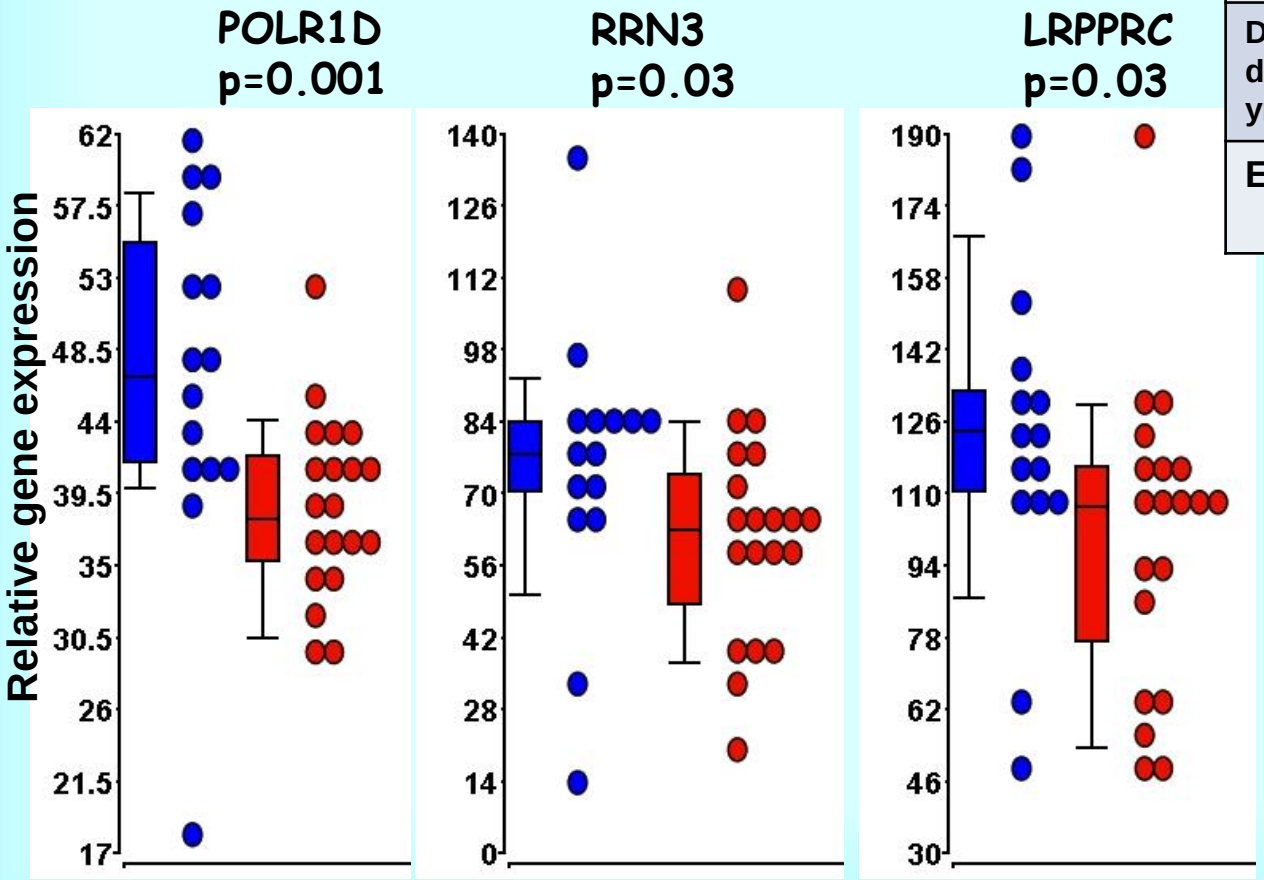
- Because rRNA synthesis is the rate-limiting step of ribosome biogenesis, Pol I is highly regulated, and many of its regulators play critical roles in autoimmune diseases.

Verification of Pol-1 pathway key genes by qRT-PCR

Active RRMS N=15

Benign MS N=20

	Benign MS (N=20)	Active RRMS (N=15)
Age, yrs	46.9 ±2.1	41.5± 2.8
F/M	15/5	11/4
Disease duration, yrs	18.1 ± 1.6	7.9 ± 1.2
EDSS	1.9 ± 0.3	4.4 ± 0.3

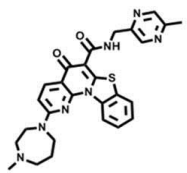


Achiron A, et al. PLoS One, 2012.

Achiron A, et al. Autoimmune reviews, 2018.

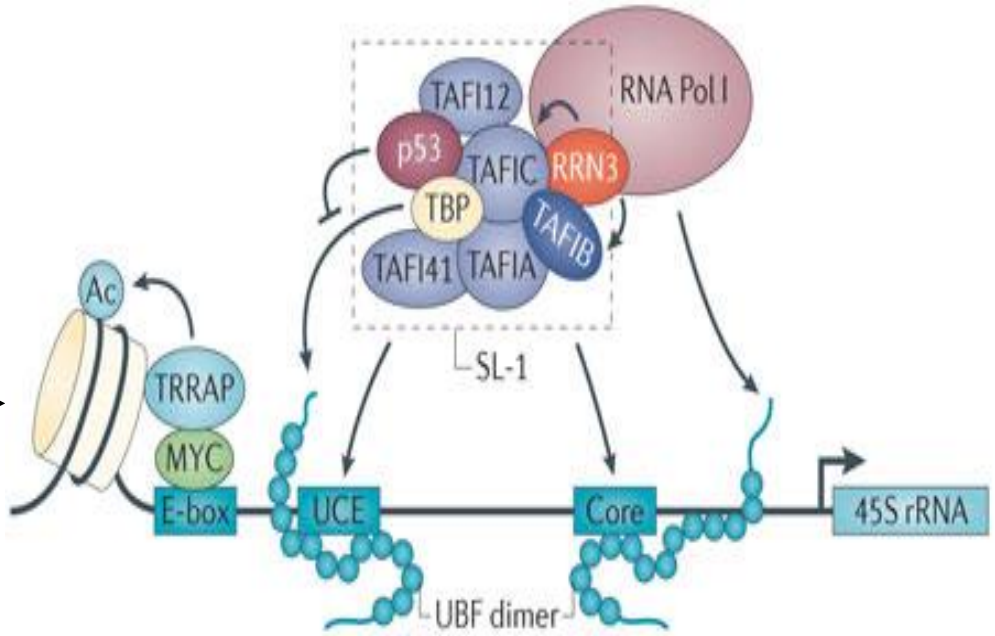
POL1 inhibitors to treat multiple sclerosis

Drug identification



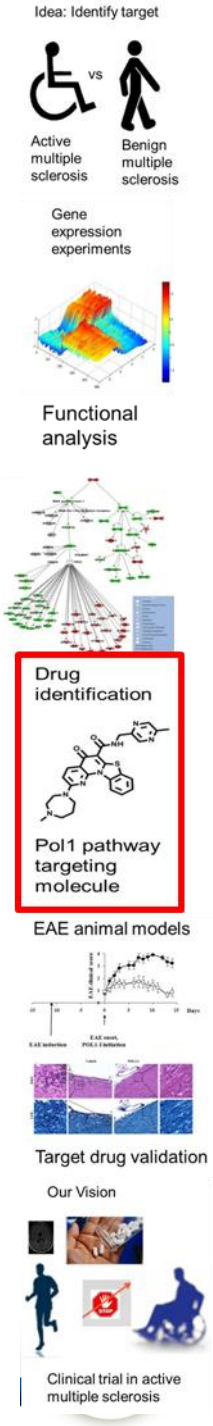
Pol1 pathway targeting molecule

POL1 inhibitors

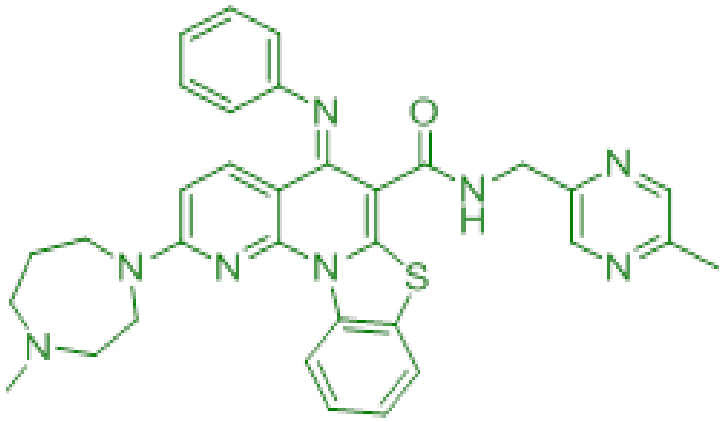


Suppression of inflammation
Activation of apoptosis

Non-active MS



RAM 589.555



Characteristics: MW: 589.555

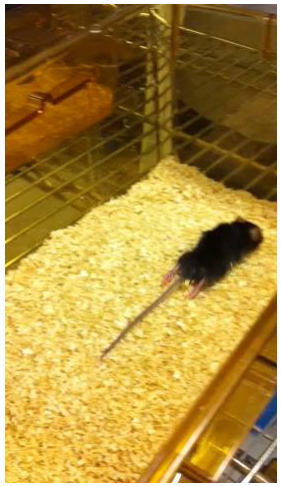
Long term stability in RT, +4^{0}C and -20^{0}C by LCMS

EAE model

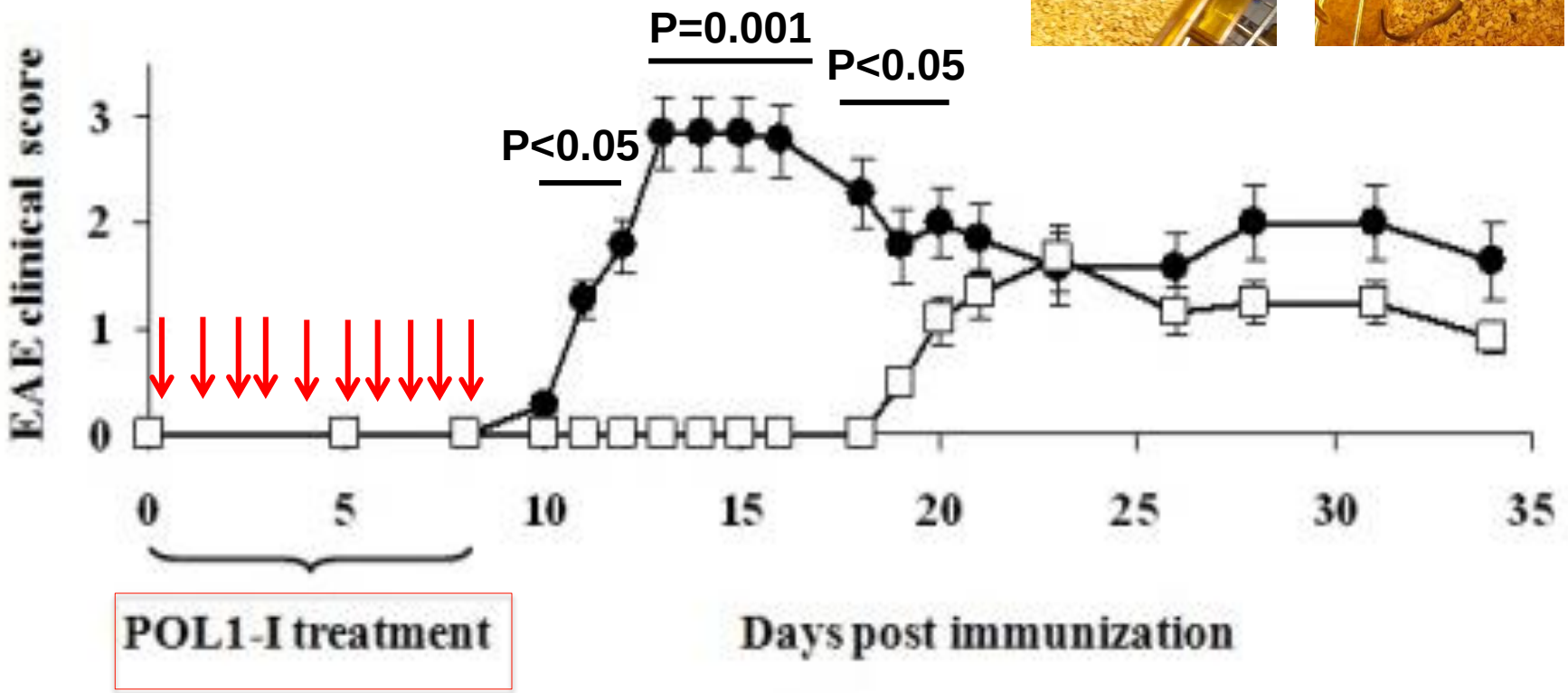
- Targeting POL1 transcription machinery as a strategy for suppressing Experimental Autoimmune Encephalomyelitis (EAE), an animal model of MS.

- Assessing the molecular and cellular mechanisms associated with POL1 inhibitor (POL1-I) induced amelioration in EAE

MOG35-55 induced EAE prevention model



- vehicle
- 12.5mg/Kg POL1-I



Polymerase I pathway inhibitor ameliorates experimental autoimmune encephalomyelitis

Journal of Neuroimmunology 263 (2013) 91–97

Anat Achiron [a,b,*], Roi Mashiach [c,d], Rina Zilkha-Falb [a], Michael M. Meijler [c,d], Michael Gurevich [a]

- POL1-I suppresses and delays the development of EAE.

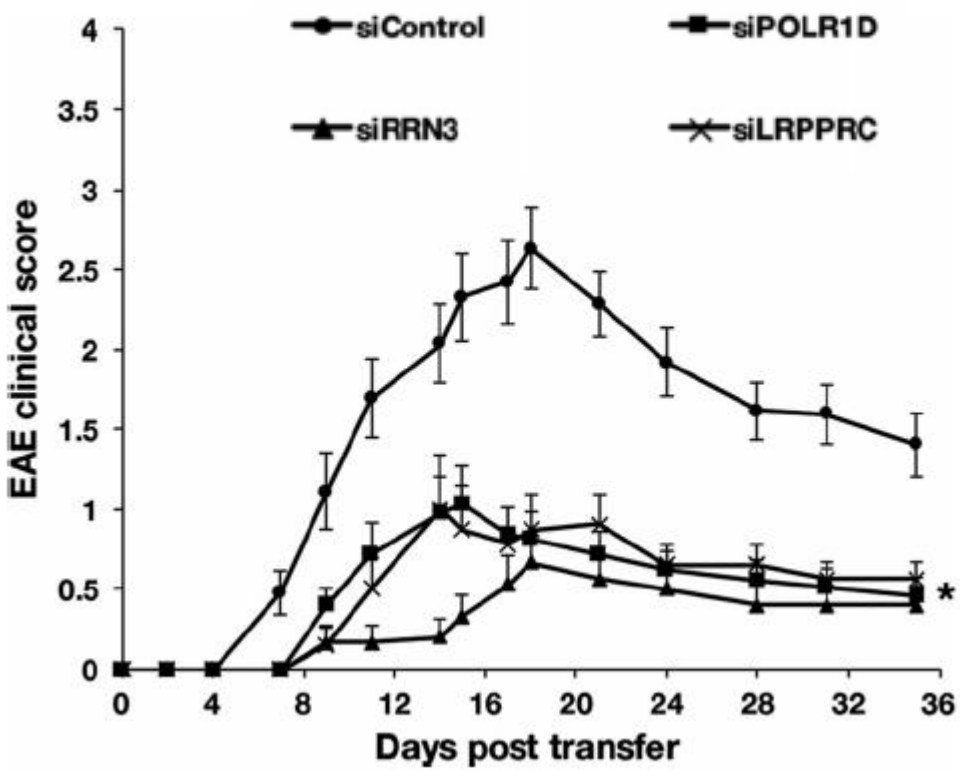
- EAE suppression occurs by :
  - Inhibition of SPCs proliferation and activation of apoptosis in CD4+ lymphocytes.
  - down-regulation of pre-rRNA and POL1 pathway associated genes.

- The results support the GE findings in MS patients and suggest that POL1 inhibition can serve as a new-targeted therapeutic approach in MS.

Experimental Autoimmune Encephalomyelitis Ameliorated by Passive Transfer of Polymerase 1-Silenced MOG35-55 Lymphatic Node Cells: Verification of a Novel Therapeutic Approach in Multiple Sclerosis

Neuromol Med
DOI 10.1007/s12017-017-8456-8

R. Zilkha-Falb[1] · M. Gurevich[1] · A. Achiron[1,2]

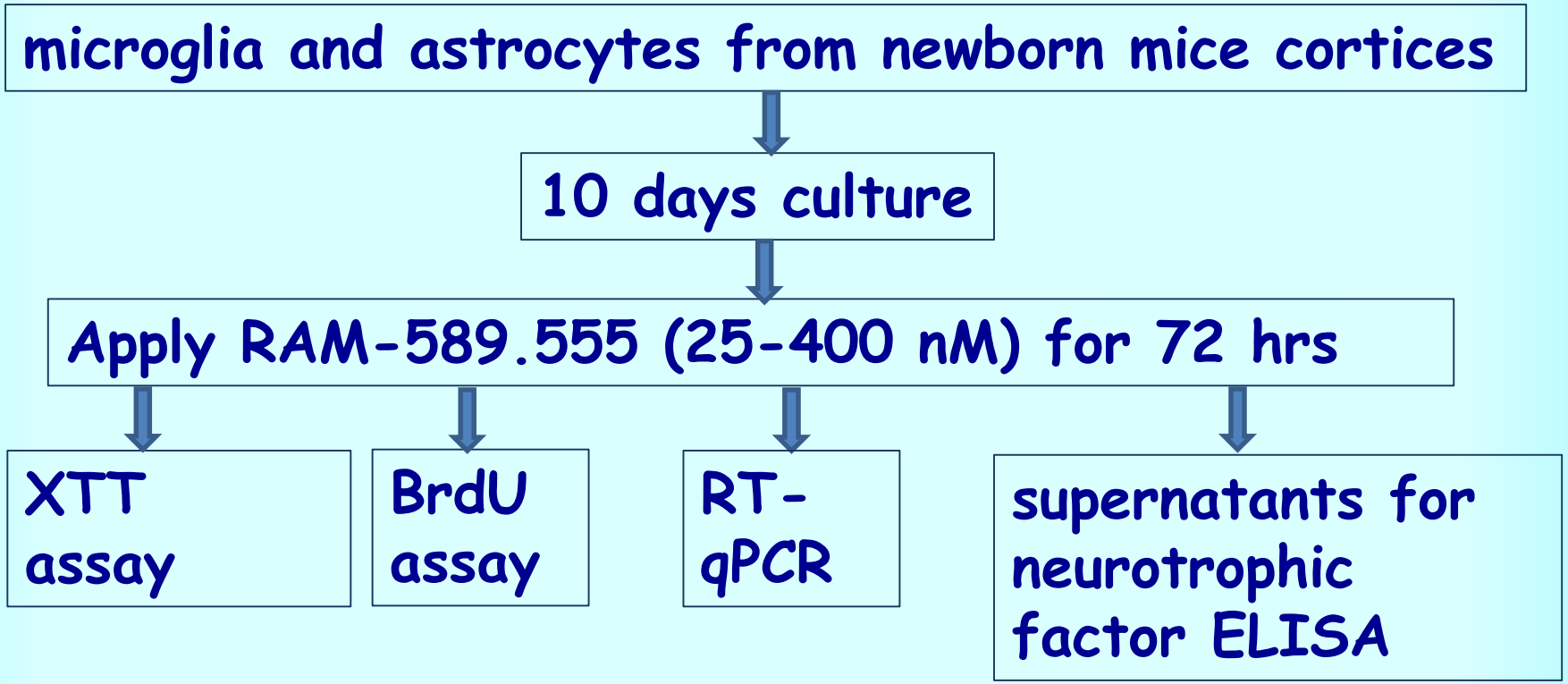


Does RAM-589.555 affects central nervous system resident cells ?

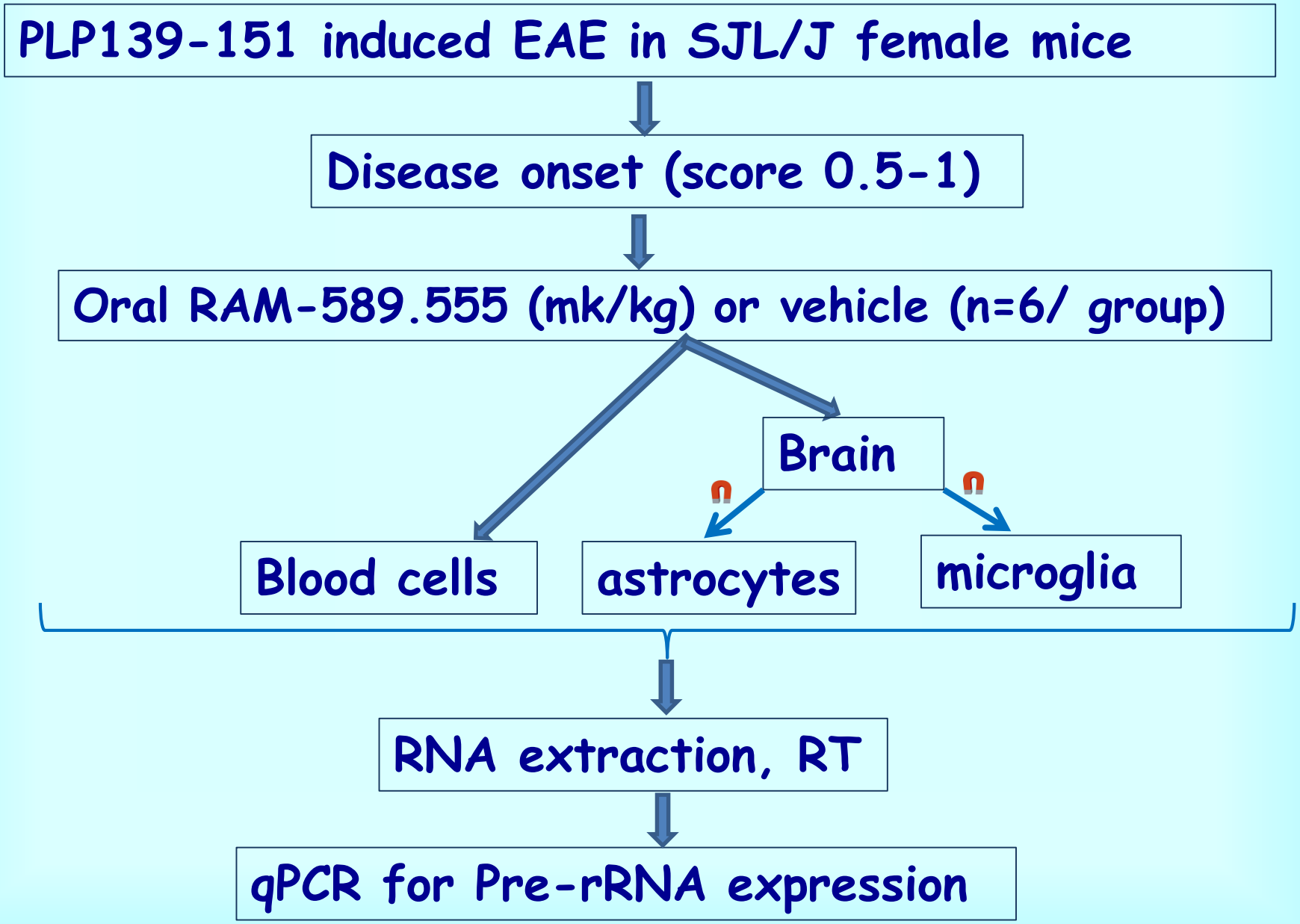
Objectives

1. To assess in-vitro effect of RAM-589.555 on microglia and astrocytes
   - Viability and proliferation
   - levels of pre-rRNA as RNA POL1 pathway product
   - Neuroprotective capacity
2. To assess in-vivo effect of RAM-589.555 on pre-rRNA expression in microglia and astrocytes

Methodology



Methodology (cont.)



Thanks for attention