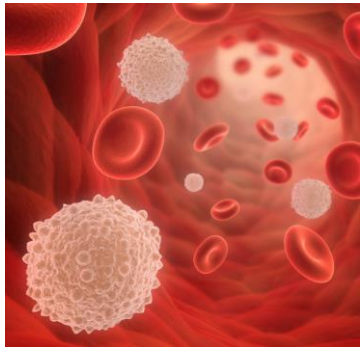
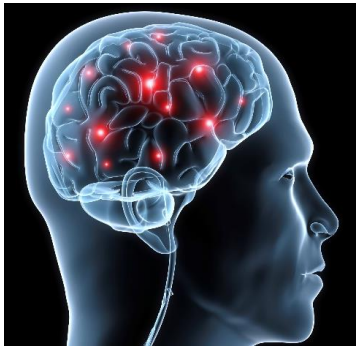
Defining T cells poised to infiltrate the brain and trigger multiple sclerosis





Marvin M. van Luijn, PhD
Assistant professor, group leader

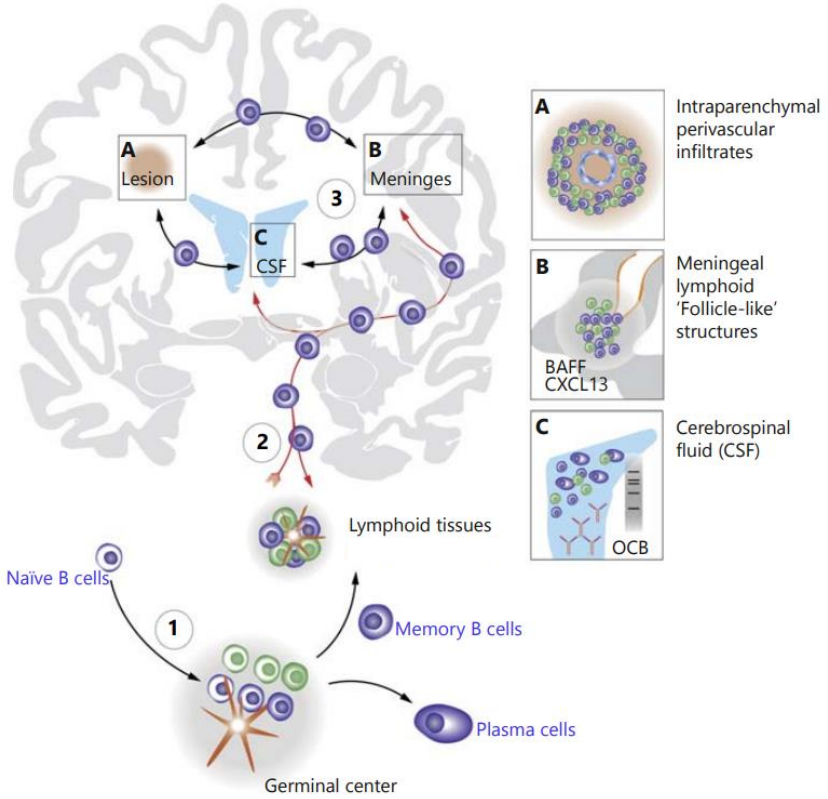
Department of Immunology
MS Center ErasMS
Erasmus MC, Rotterdam, NL

ESCCA 2023 Utrecht
Disclosure commercial conflict of interest

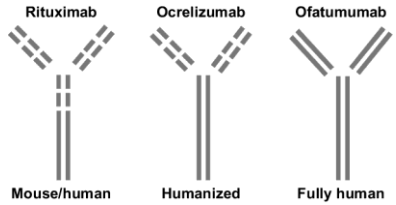
	No, nothing to disclose

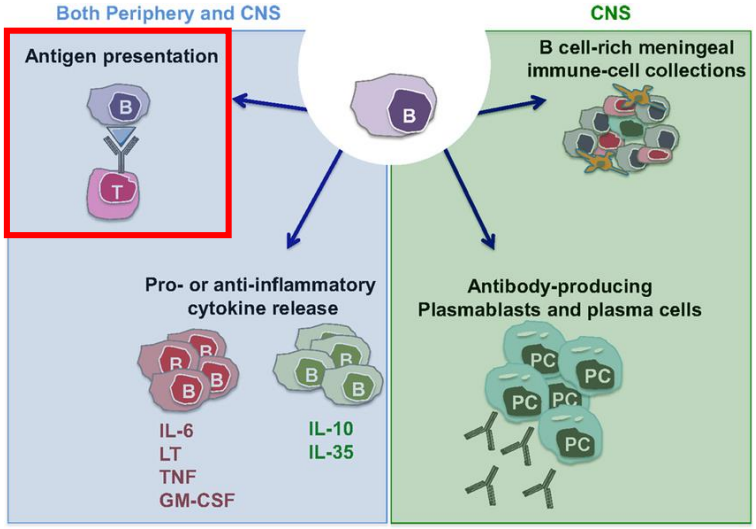
Company Name	Specification

B- and T-cell interaction as driving mechanism and therapeutic target in MS

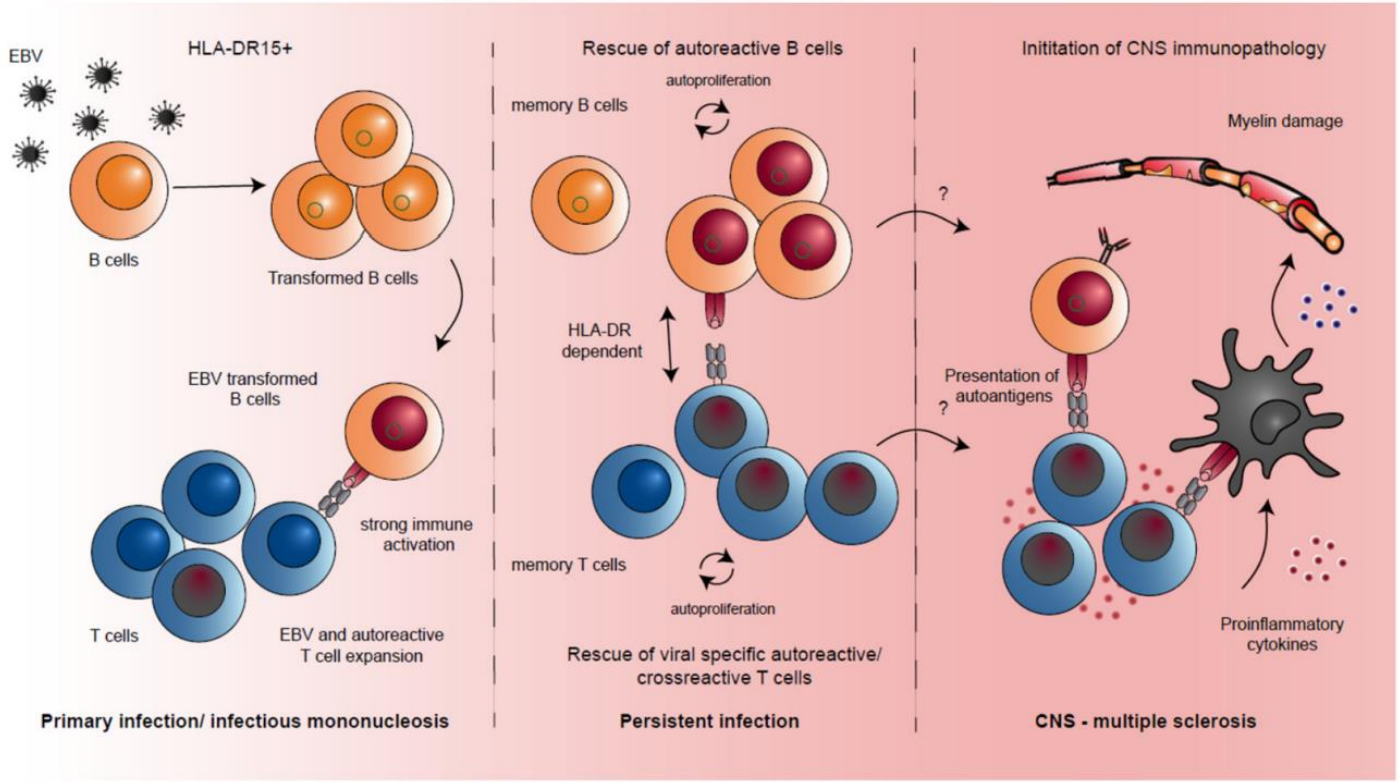


Anti-CD20 therapy





HLA-DR15: differential presentation of EBV antigens to CD4+ T cells?



Läderach & Münz, Microorganisms 2021

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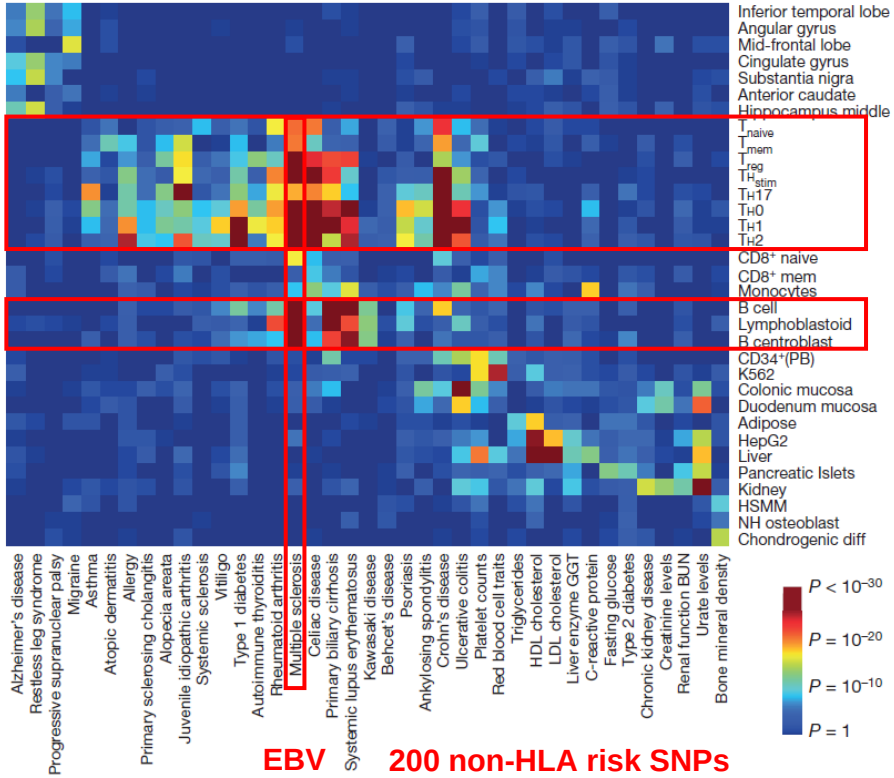
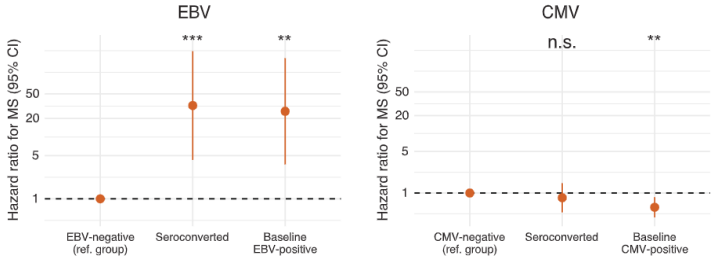
B- and T-cell interaction in MS: the influence of genetic risk variants and EBV

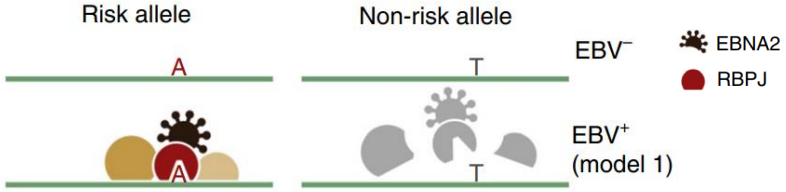


MULTIPLE SCLEROSIS

Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis

Kjetil Bjornevik[1]†, Marianna Cortese[1]†, Brian C. Healy[2,3,4], Jens Kuhle[5], Michael J. Mina[6,7,8], Yumei Leng[6], Stephen J. Elledge[6], David W. Niebuhr[9], Ann I. Scher[9], Kassandra L. Munger[1]‡, Alberto Ascherio[1,10,11]*‡





Farh *et al.*, Nature 2015; Harley *et al.*, Nat Genet 2018; IMSGC, Science 2019; Bjornevik *et al.*, Science 2022

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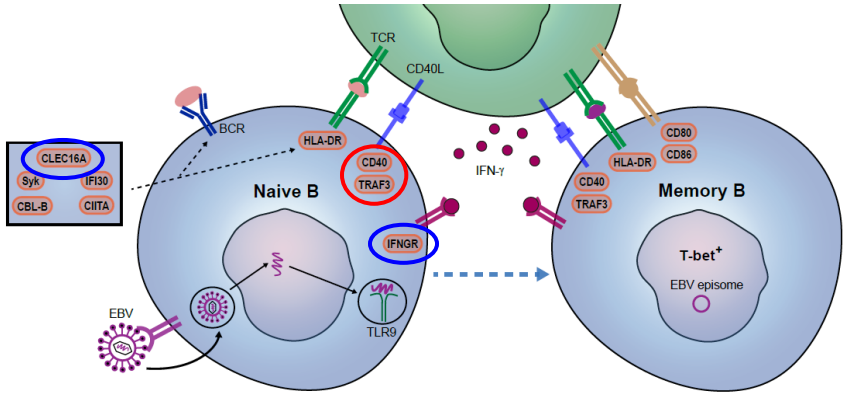
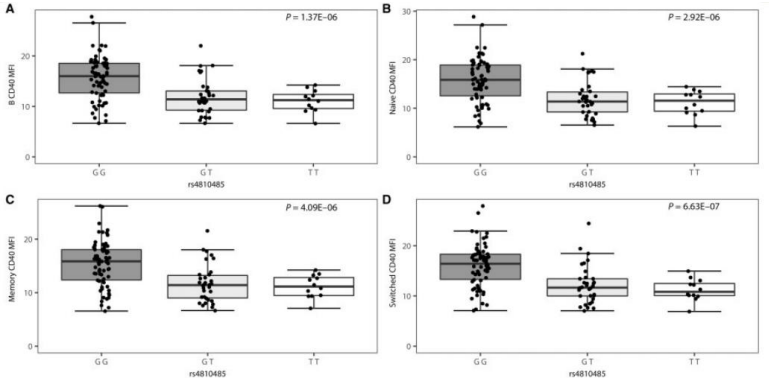
MS risk variants *CD40* and *TRAF3* are alternatively regulated by EBV in B cells



doi:10.1093/brain/awx372 BRAIN 2018: 141: 786–796 | 786
BRAIN
A JOURNAL OF NEUROLOGY

Multiple sclerosis risk variants alter expression of co-stimulatory genes in B cells

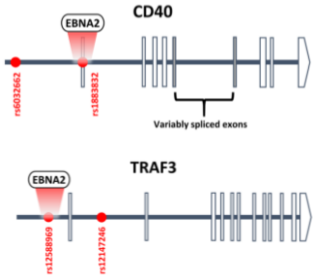
Ide Smets,[1,2,*] Barnaby Fiddes,[3,*] Josselyn E. Garcia-Perez,[4,5,*] Di He,[3,*] Klara Mallants,[1] Wenjia Liao,[3] James Dooley,[4,5] George Wang,[3] Stephanie Humblet-Baron,[4,5] Bénédicte Dubois,[1,2] Alastair Compston,[3] Joanne Jones,[3] Alasdair Coles,[3] Adrian Liston,[4,5] Maria Ban,[3] An Goris[1] and Stephen Sawcer[3]



RESEARCH

Evidence from genome wide association studies implicates reduced control of Epstein-Barr virus infection in multiple sclerosis susceptibility

Ali Afrasiabi[1†], Grant P. Parnell[1†], Nicole Fewings[1], Stephen D. Schibeci[1], Monica A. Basuki[1], Ramya Chandramohan[1], Yuan Zhou[2], Bruce Taylor[2], David A. Brown[1], Sanjay Swaminathan[1], Fi Graeme J. Stewart[1] and David R. Booth[1*]



Smets *et al.*, Brain 2018; Afrasiabi *et al.*, Genome Med 2019; van Langelaar *et al.*, Front Immunol 2020

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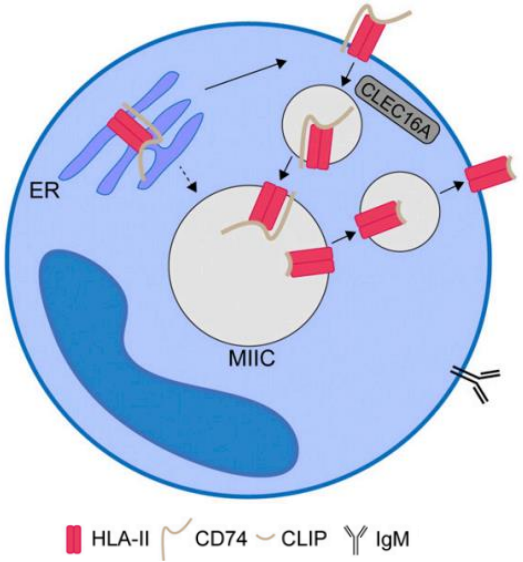
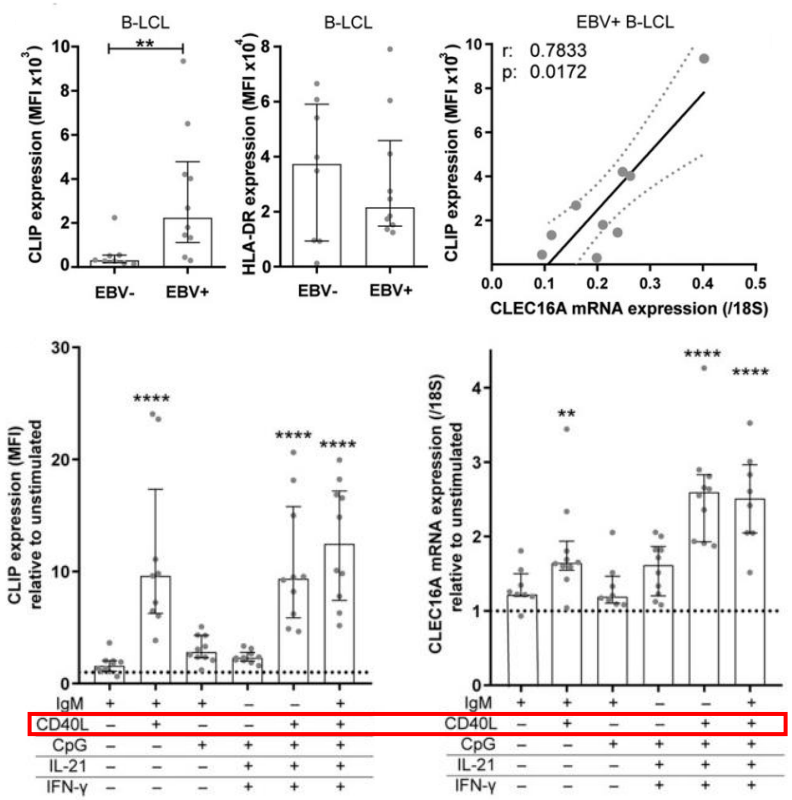
CLEC16A is induced by CD40L to control the HLA class II pathway in B cells

The Role of Autoimmunity-Related Gene *CLEC16A* in the B Cell Receptor–Mediated HLA Class II Pathway

Liza Rijvers,*,† Marie-José Melief,*,† Jamie van Langelaar,*,† Roos M. van der Vuurst de Vries,†,‡ Annet F. Wierenga-Wolf,*,† Steven C. Koetzier,*,† John J. Priatel,§,¶ Tineke Jorritsma,‖ S. Marieke van Ham,‖ Rogier Q. Hintzen,*,†,‡,1 and Marvin M. van Luijn*,†





van Luijn *et al.*, Brain 2015; Rijvers *et al.*, Eur J Immunol 2018; Rijvers *et al.*, J Immunol 2020

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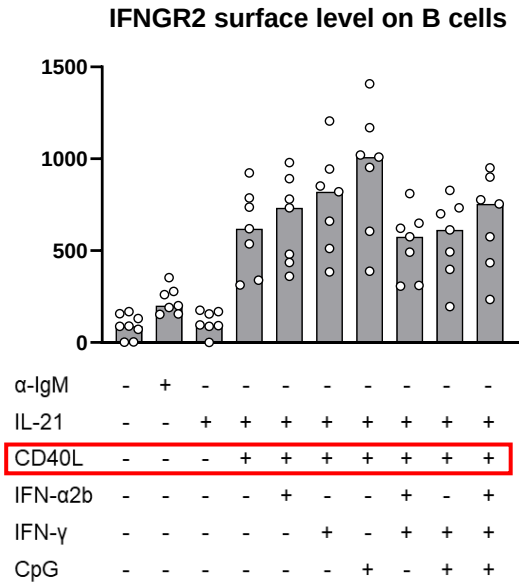
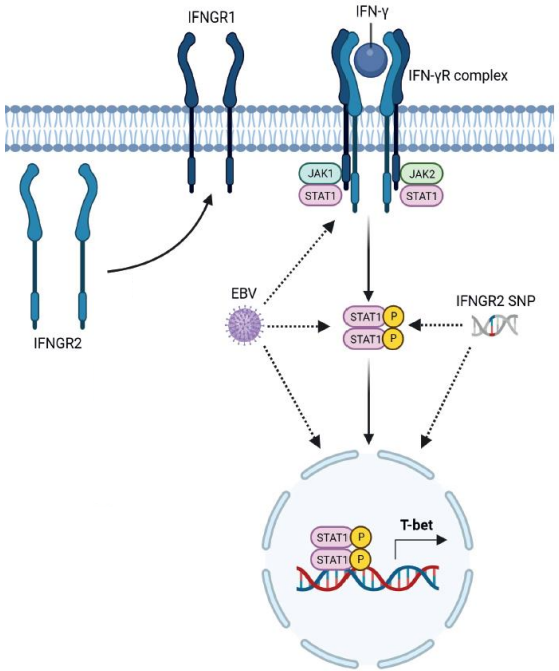
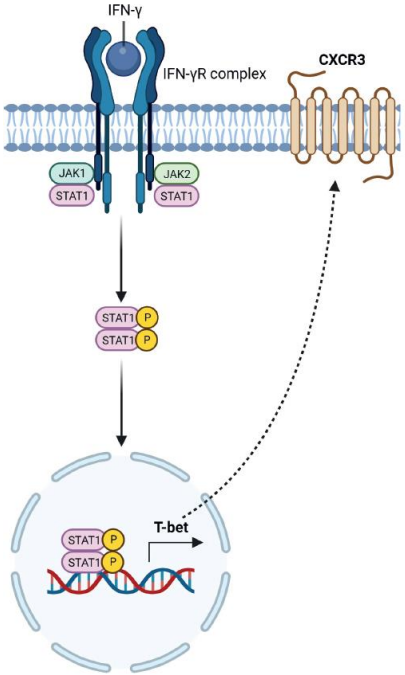
CD40L induces IFNGR2 surface expression to sensitize B cells for triggering by IFN-γ







Unpublished data

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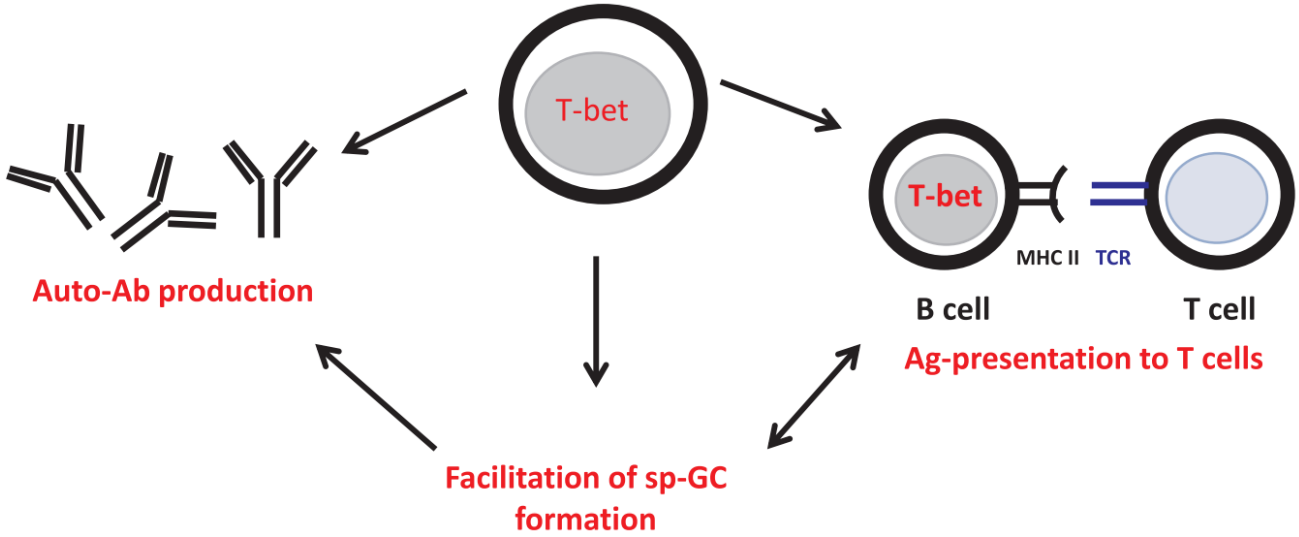
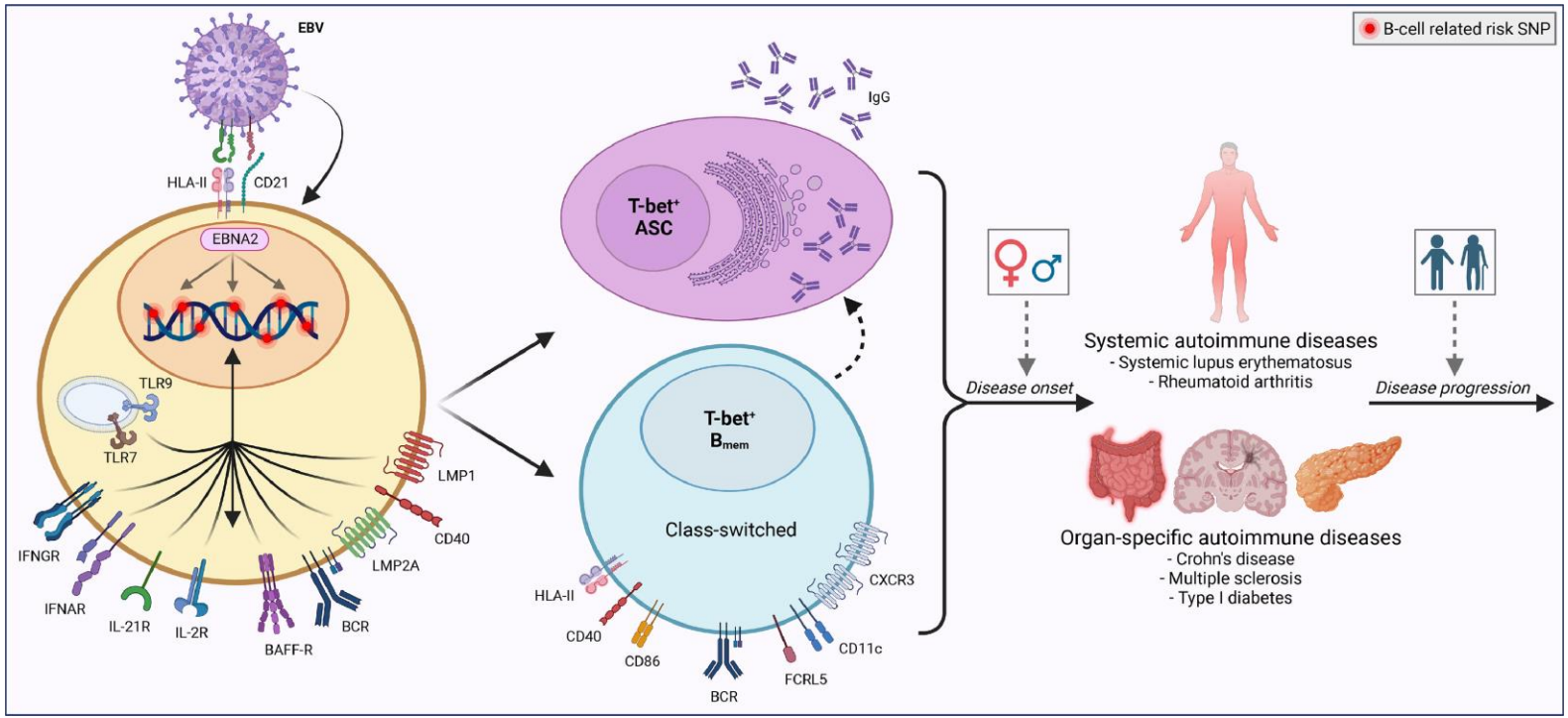
T-bet+ B cells are potent APCs and triggers of autoimmunity in mice



Rubtsov *et al.*, J Immunol 2015; Rubtsova *et al.*, J Clin Invest 2017

Genetic predisposition as determinant of T-bet+ B cells serving as APCs?



Bogers *et al.*, Immunol Lett 2023

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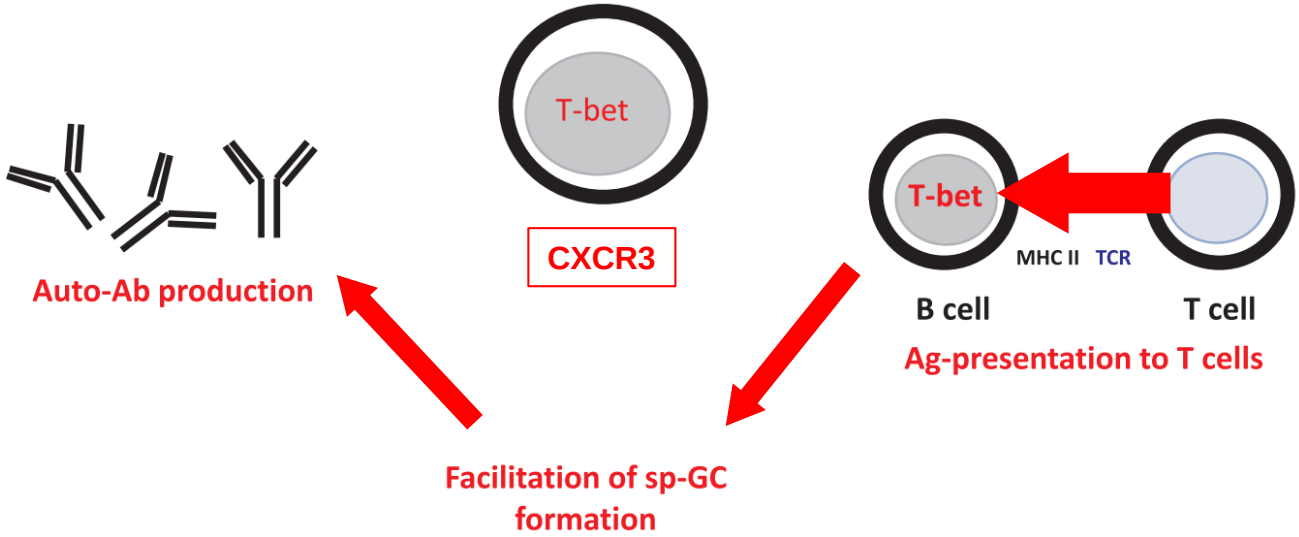
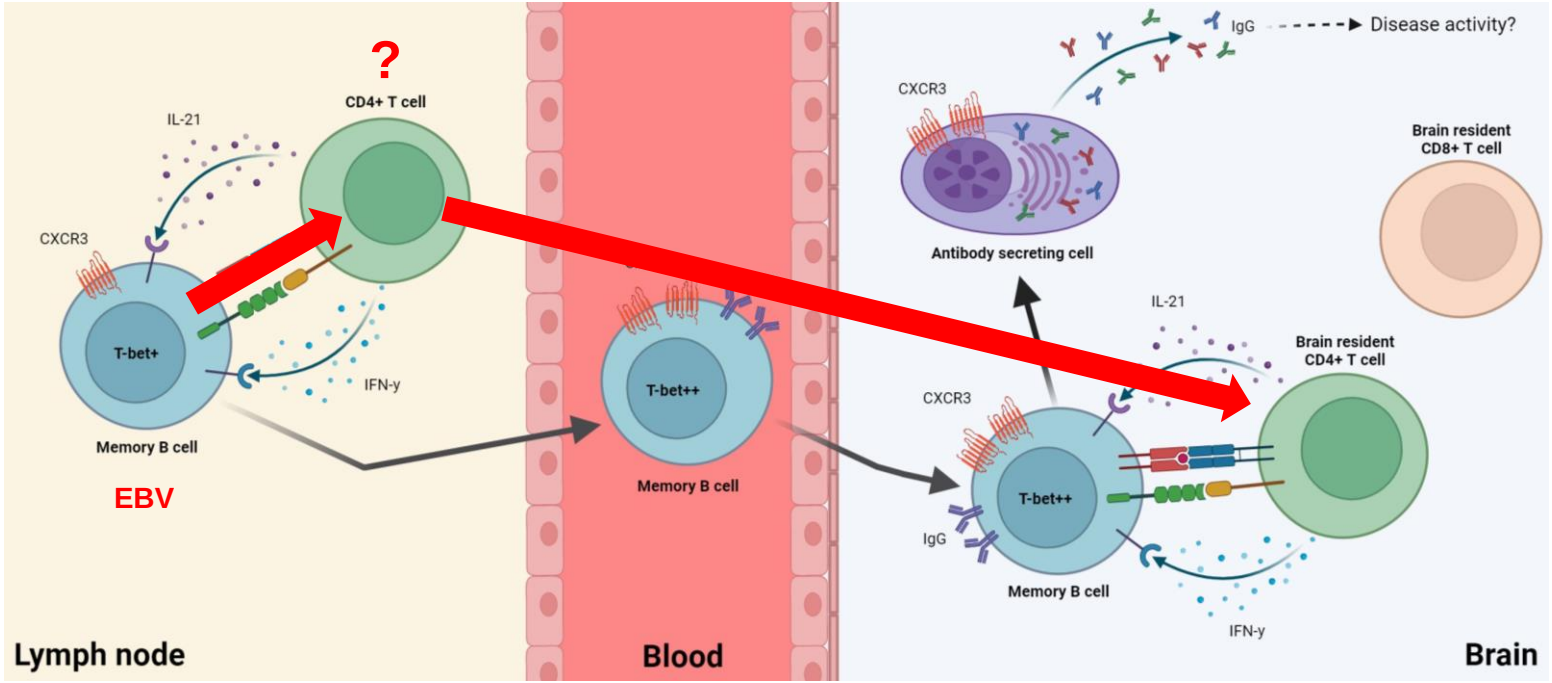
T-bet+ B cells further mature into effectors through T cell-derived signals

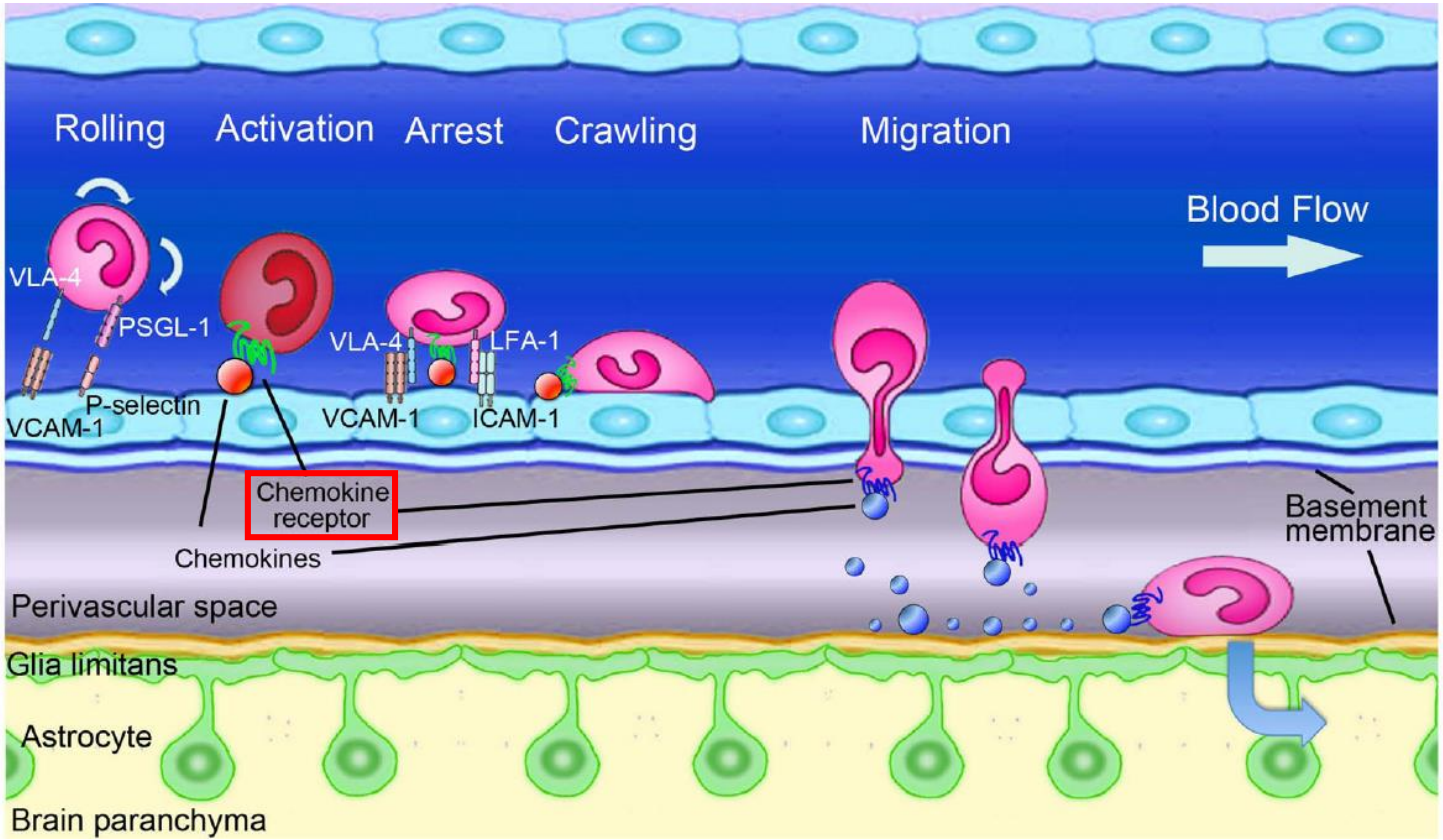


Rubtsov *et al.*, Cell Immunol 2017

Which exact CD4+ T cells are triggered by B cells to enter the MS brain?

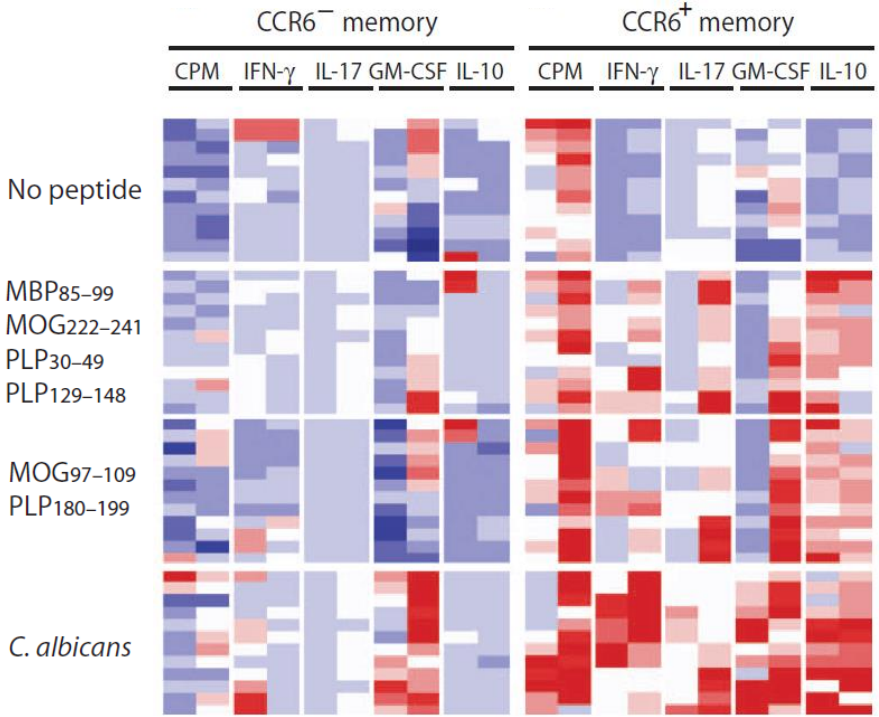


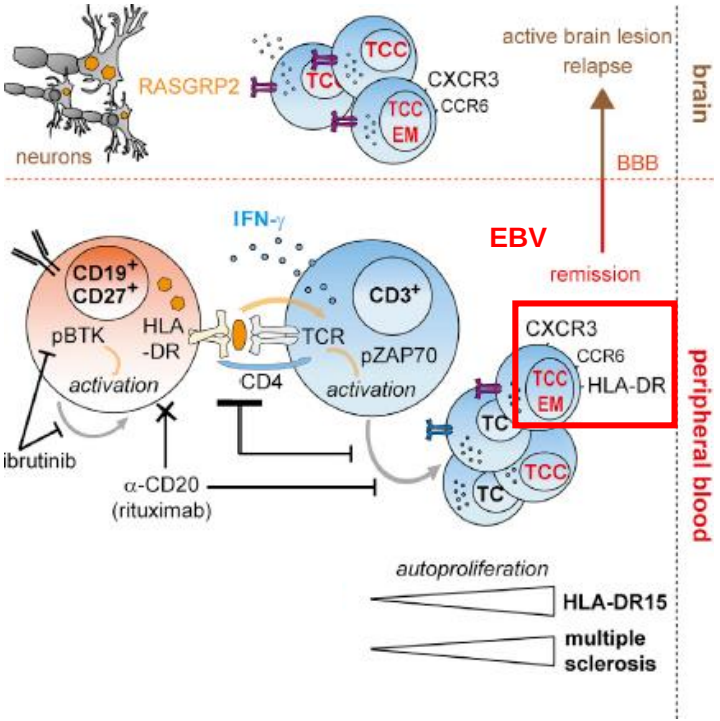
Differentiation, transmigration, inflammation: chemokine receptors



Takeshita & Ransohoff, Immunol Rev 2012

Memory B cells induce CCR6-expressing CD4+ T cells to enter the MS brain





Cao *et al.*, Sci Transl Med 2015; Jelcic *et al.*, Cell 2018; Wang *et al.*, Cell 2020

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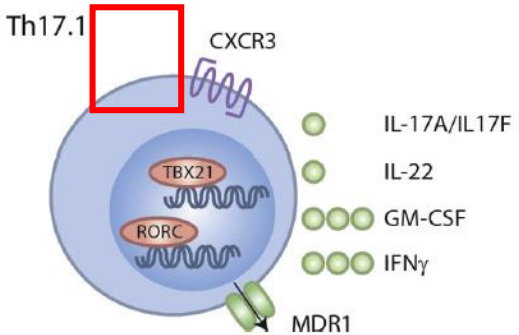
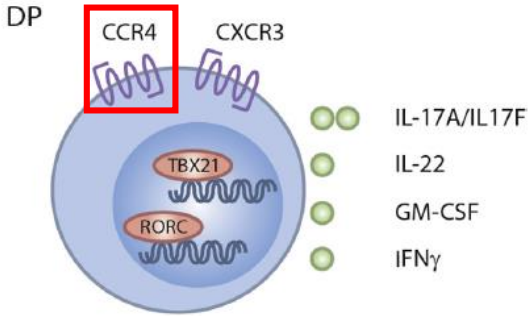
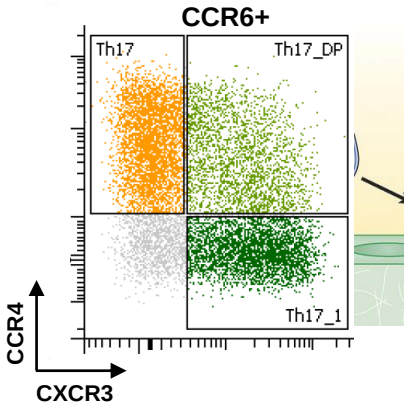
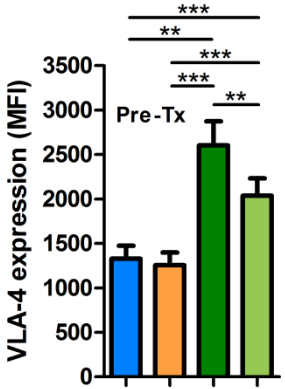
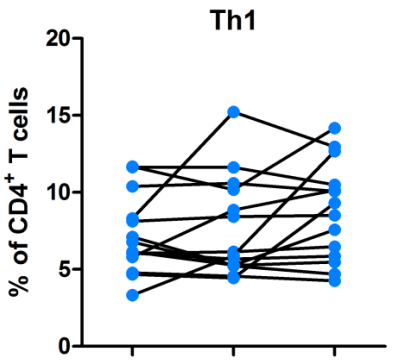
Th17.1 cells accumulate in the blood of clinical MS responders to natalizumab

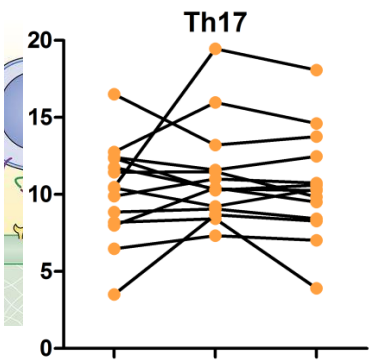


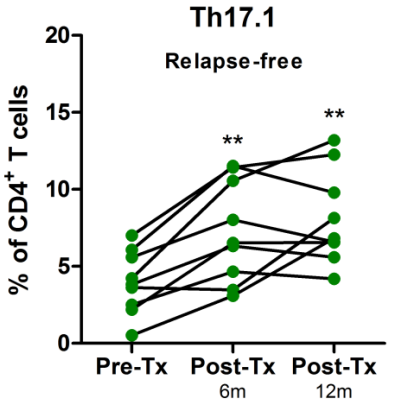


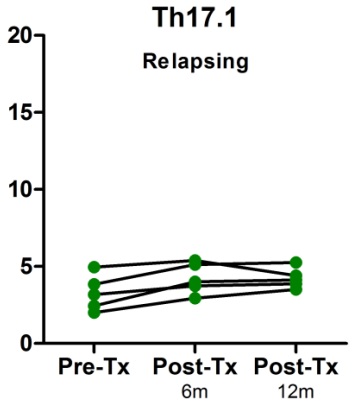












Paulissen *et al.*, Cytokine 2015; van Langelaar *et al.*, Brain 2018

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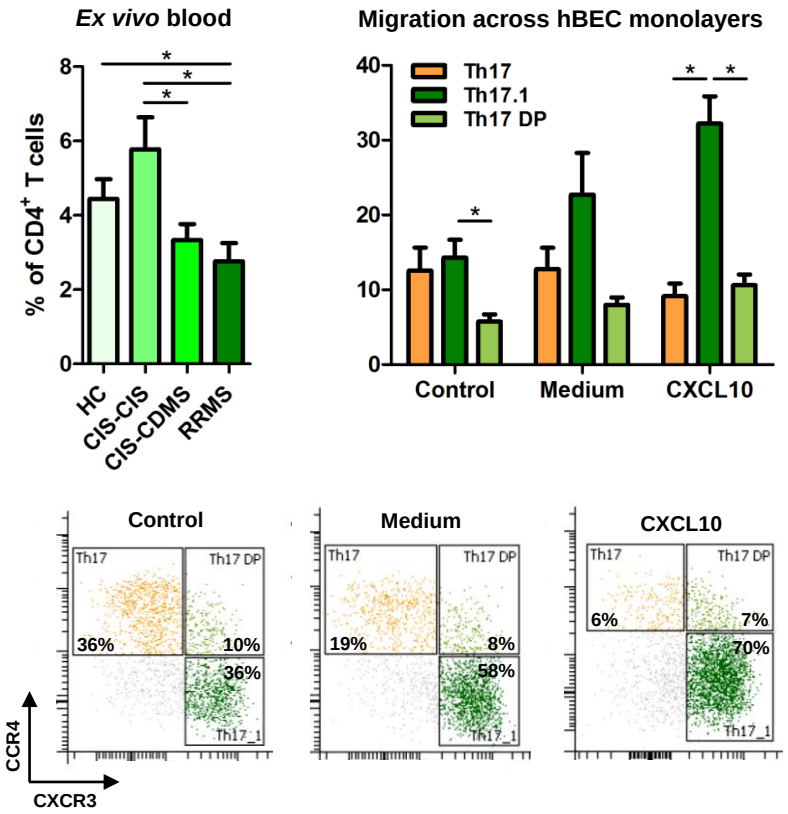
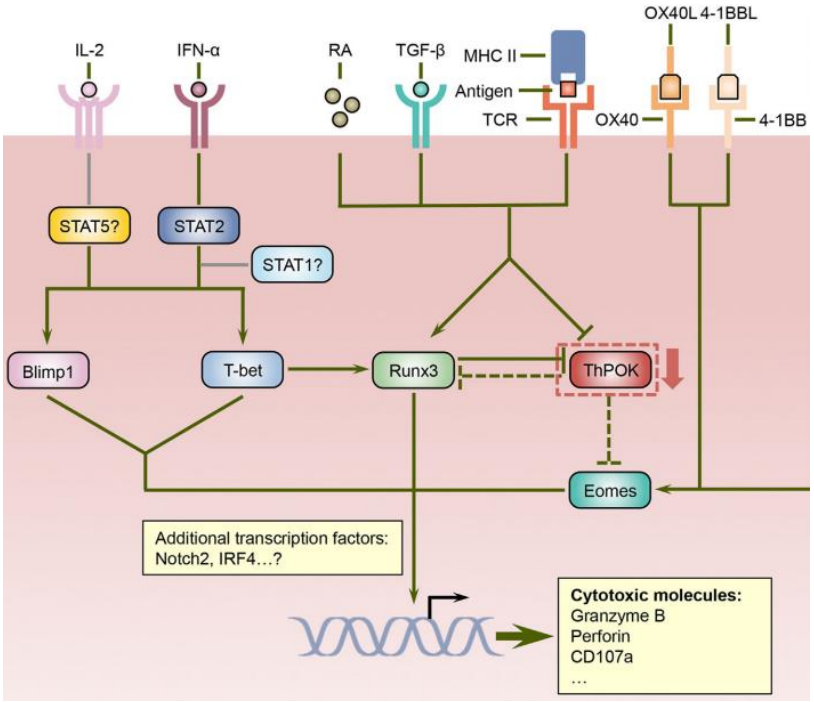
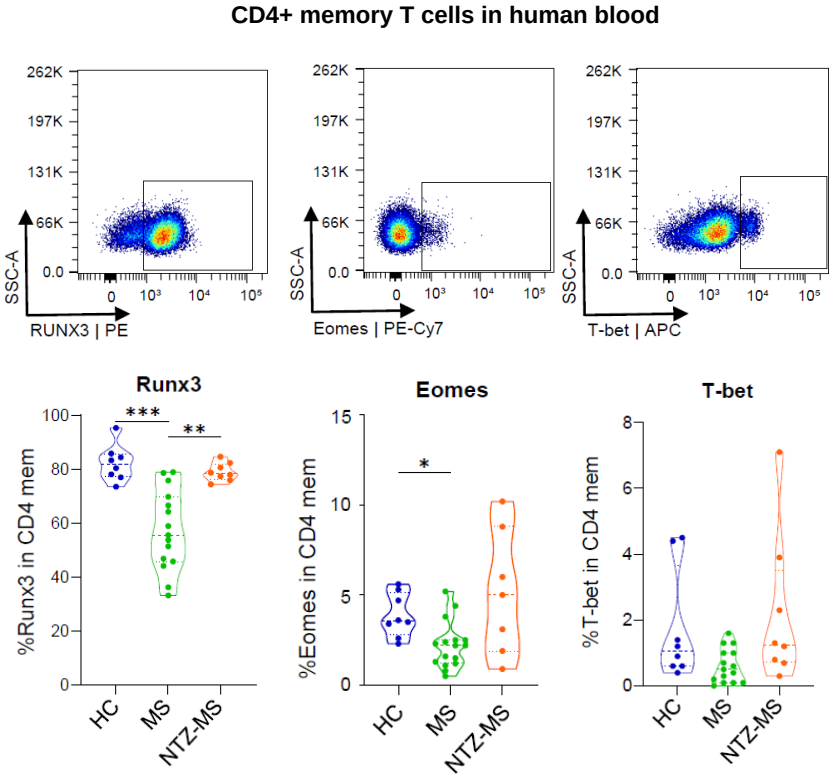
Th17.1 cells are selectively recruited to the CSF of early MS patients



Cytotoxic-like CD4+ T cells: close interaction between Runx3, Eomes and T-bet





Tian *et al.*, Front Immunol 2016; Hoeks, van Puijfelik & Koetzier *et al.*, under consideration

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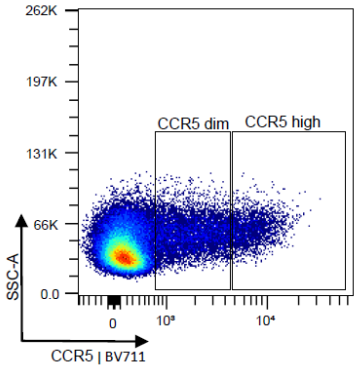
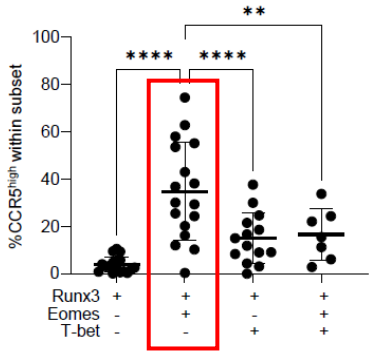
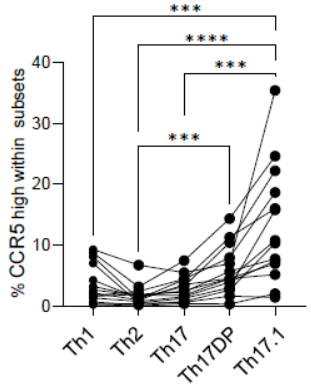
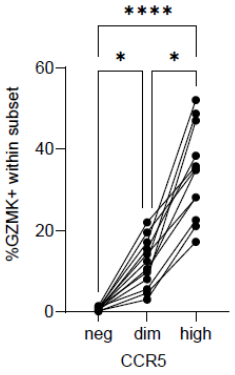
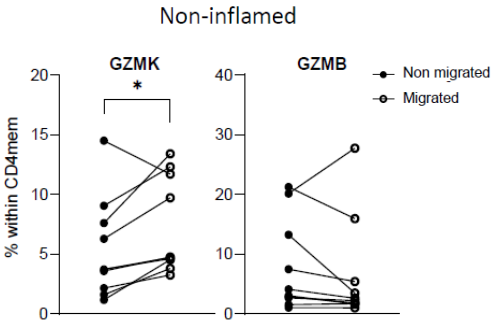
Runx3 and Eomes define brain-homing GZMK^{high}CCR5^{high} Th17.1 cells

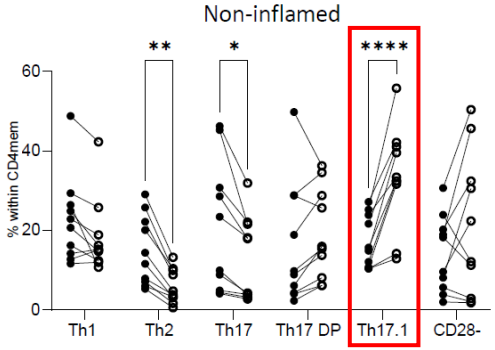


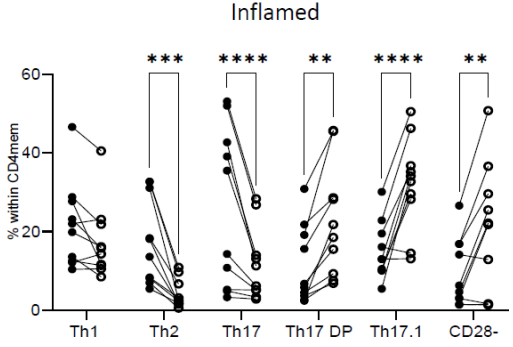












Hoeks, van Puijfelik & Koetzier *et al.*, under consideration

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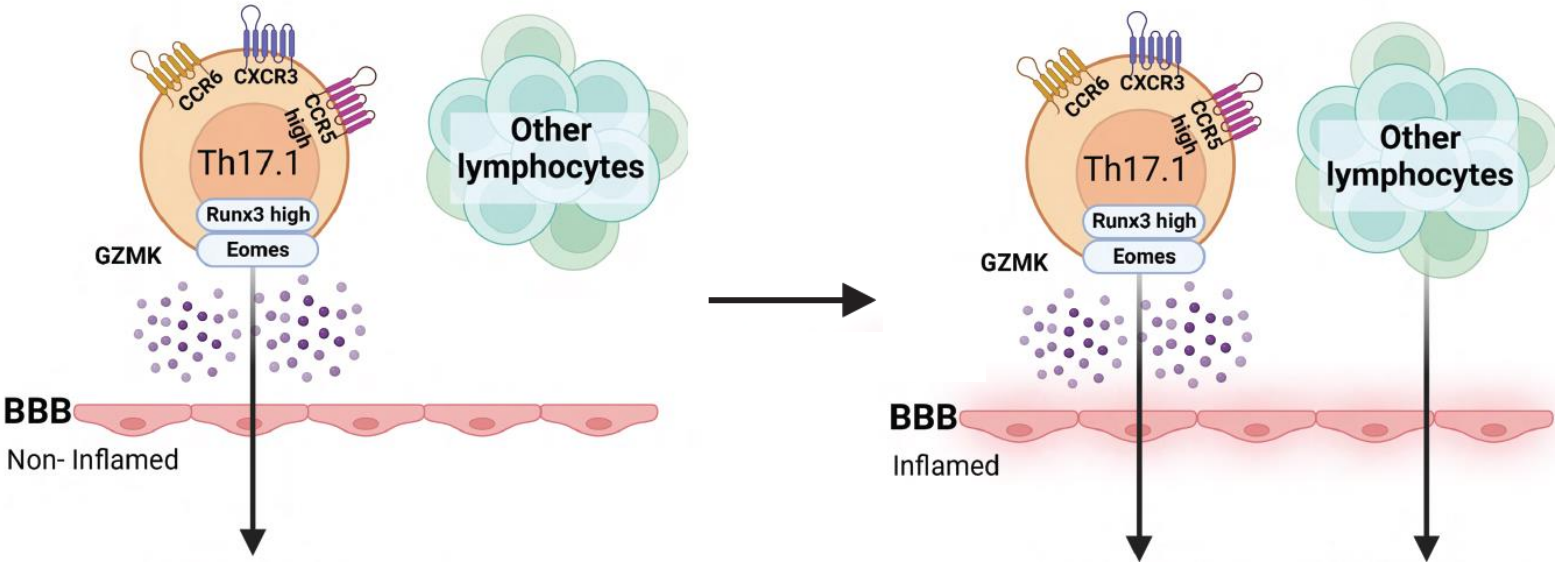
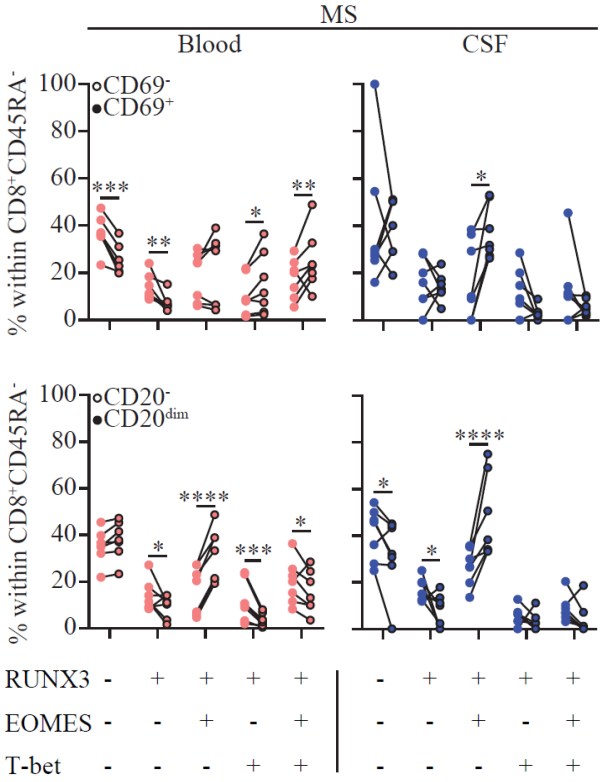
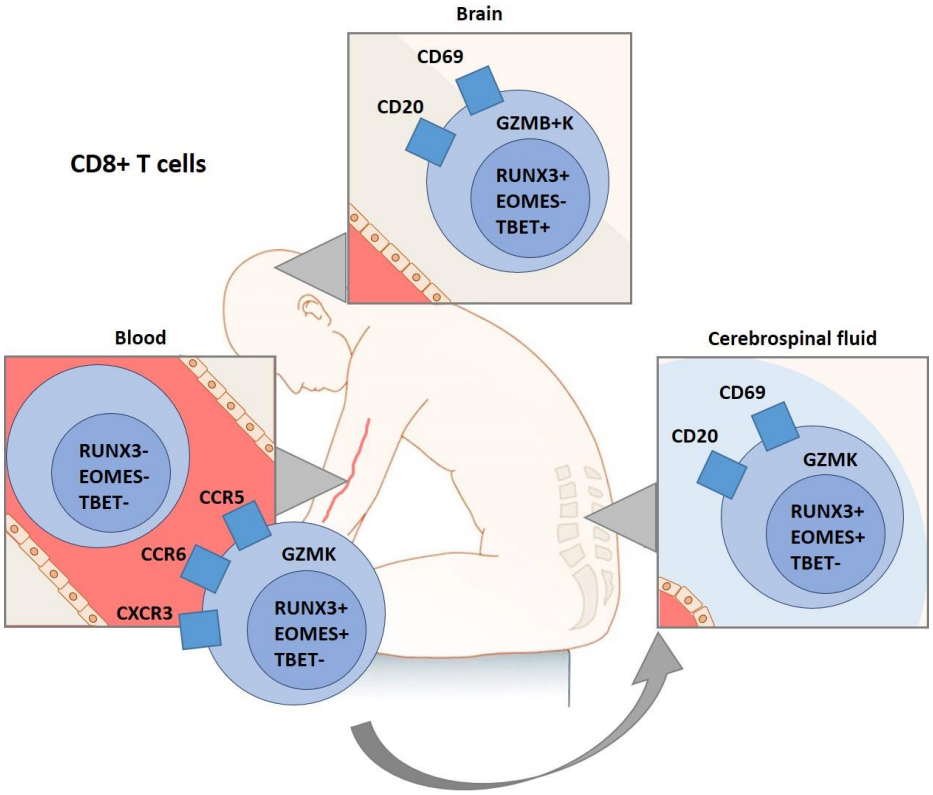
Th17.1 may be the first to activate and cross the blood-brain barrier in MS



Hoeks, van Puijfelik & Koetzier *et al.*, under consideration

Runx3 and Eomes define CD8+ T cells with a brain residency-like phenotype





Koetzier *et al.*, Cells 2021; Hsiao *et al.*, Eur J Immunol 2021

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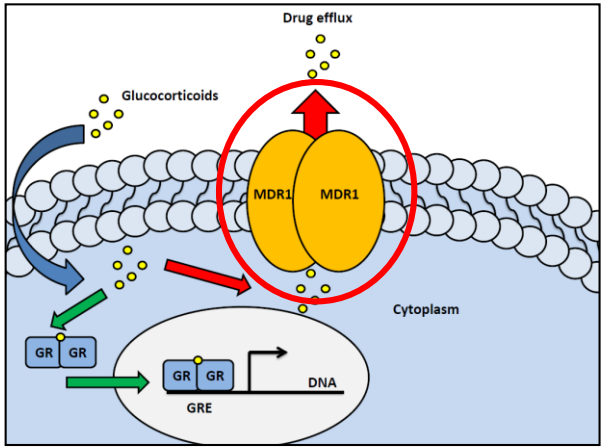
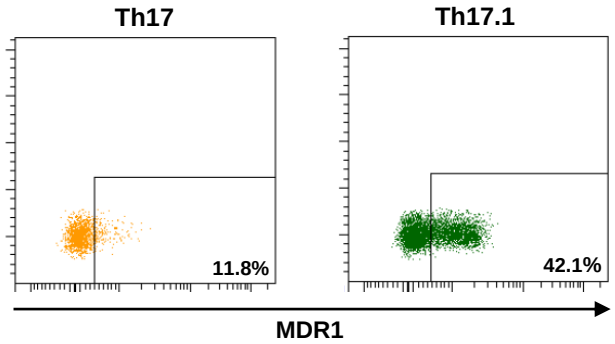
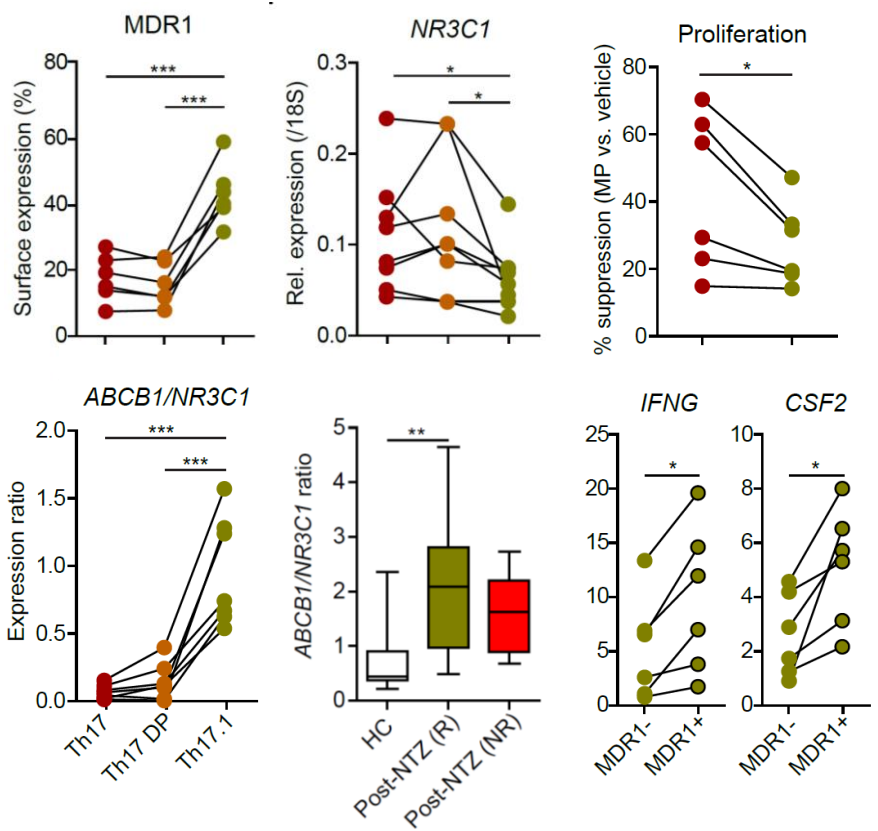
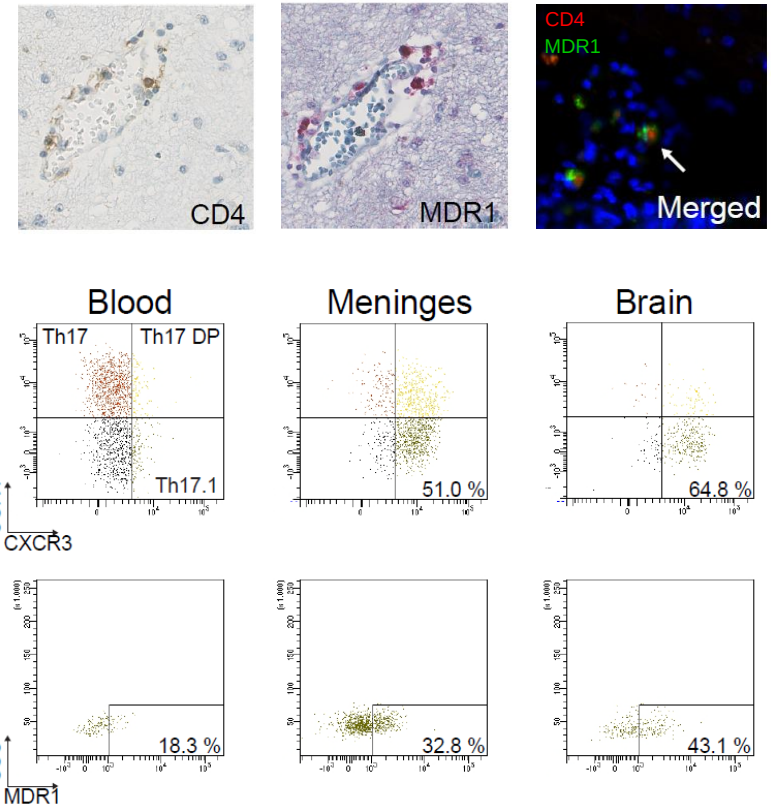
Th17.1 cells have a distinct glucocorticoid resistance profile (MDR1^{high}GR^{low})

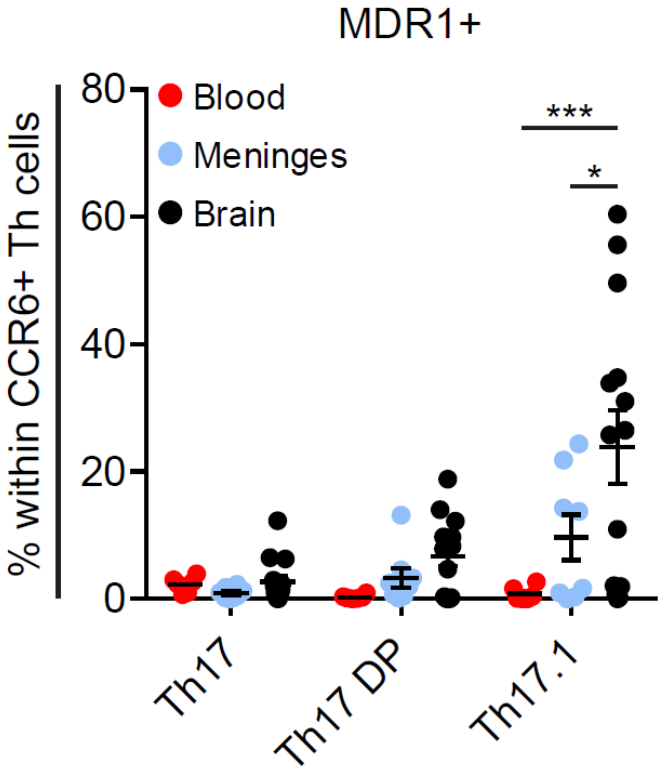




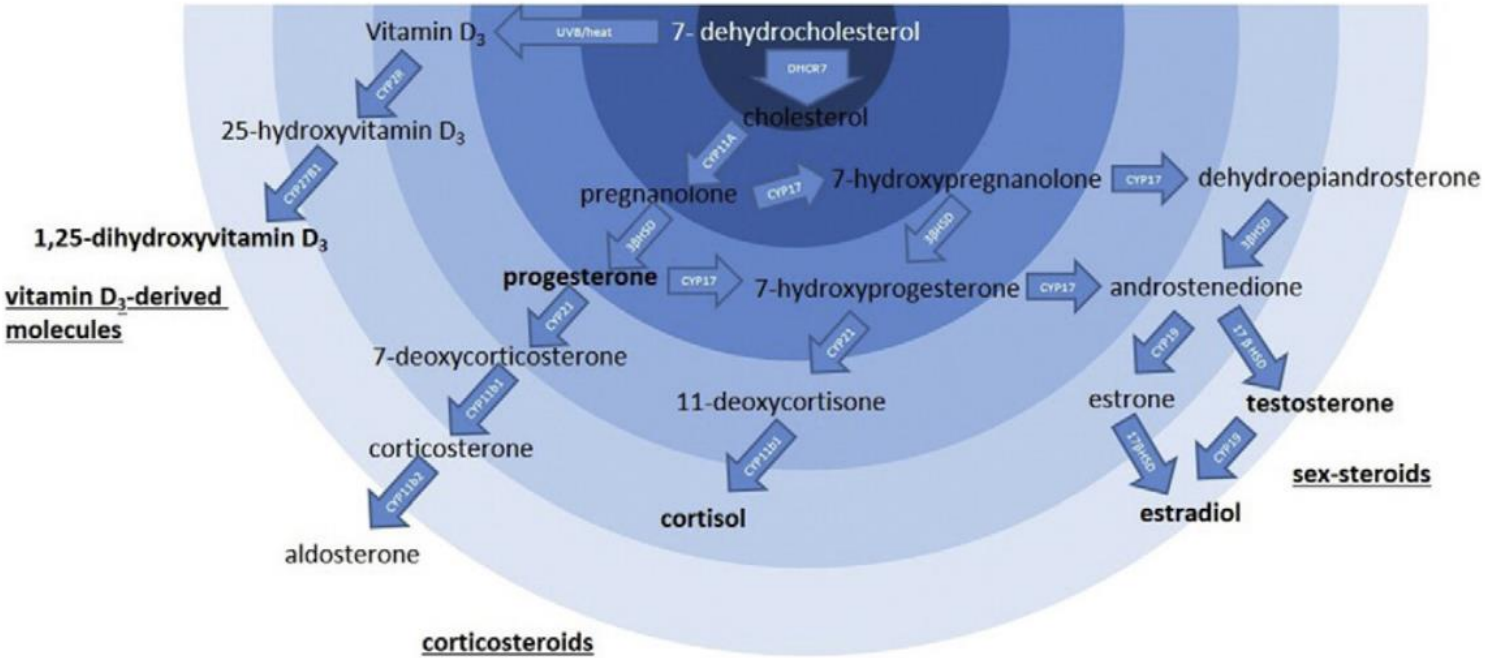


MDR1^{high} Th17.1 cells are localized in MS white matter lesions





Glucocorticoids: functional interaction with vitamin D and sex steroids



Rolf *et al.*, Autoimmun Rev 2016

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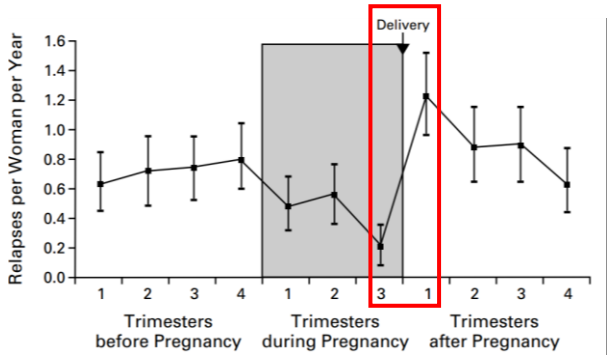
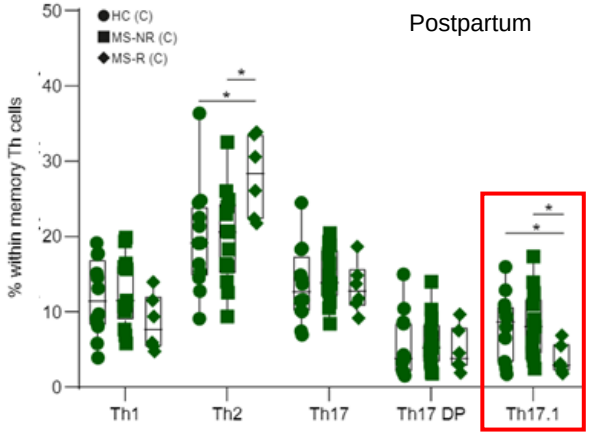
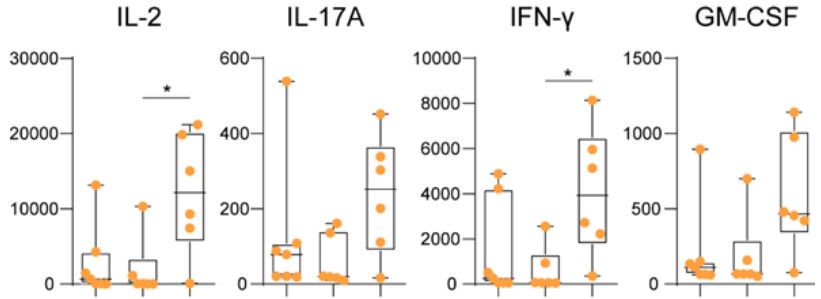
Pregnancy as natural disease modifier: association of Th17.1 with a relapse



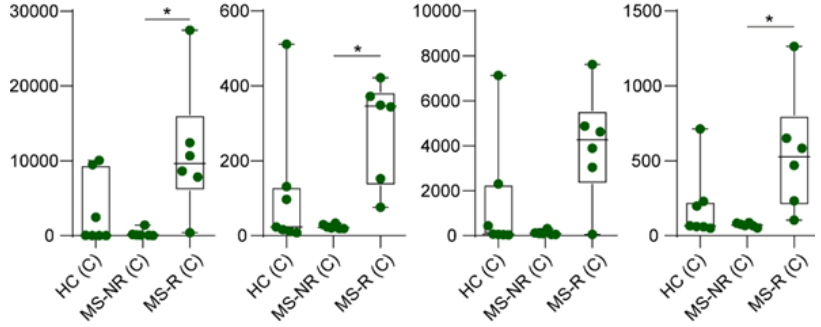


Postpartum

3rd trimester



Postpartum



Confavreux *et al.*, N Engl J Med 1998; Koetzier *et al.*, Front Immunol 2021

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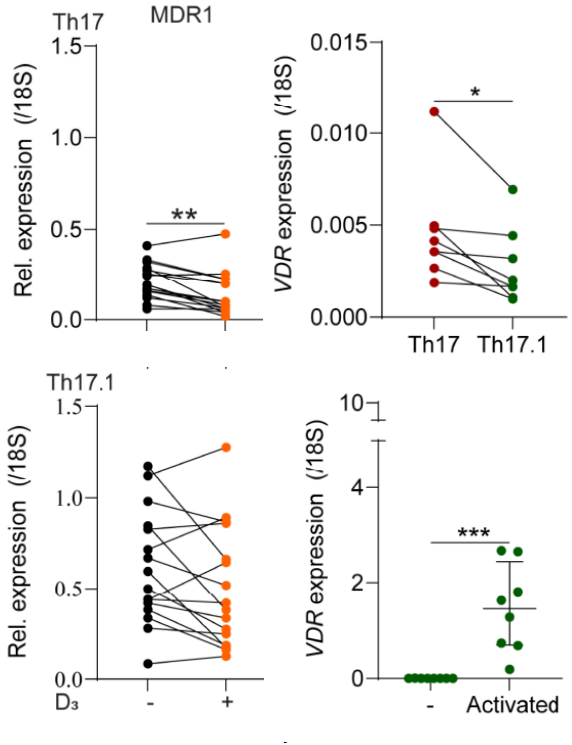
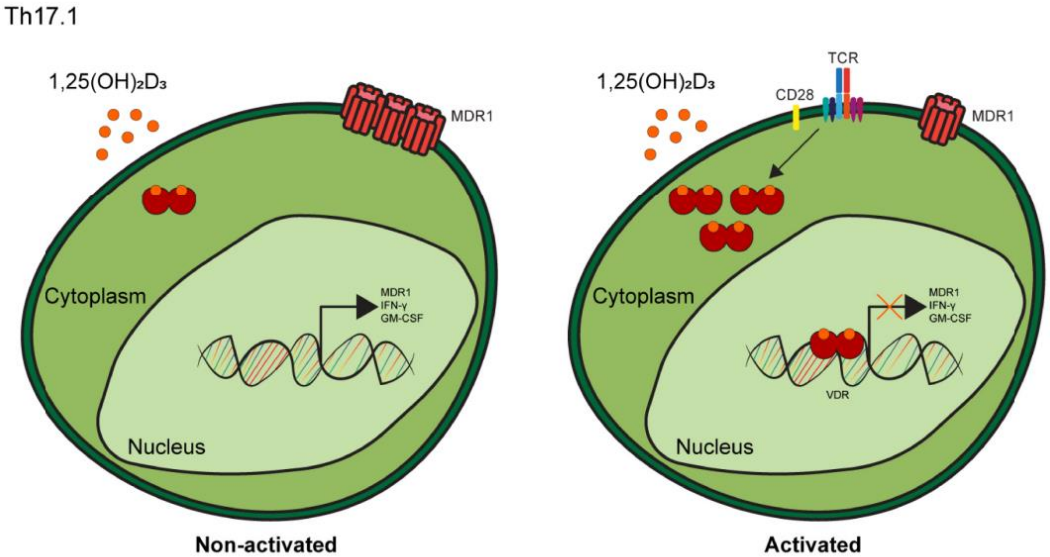
Th17.1 cells are less sensitive to vitamin D, which is increased after activation





Koetzier *et al.*, Front Immunol 2022

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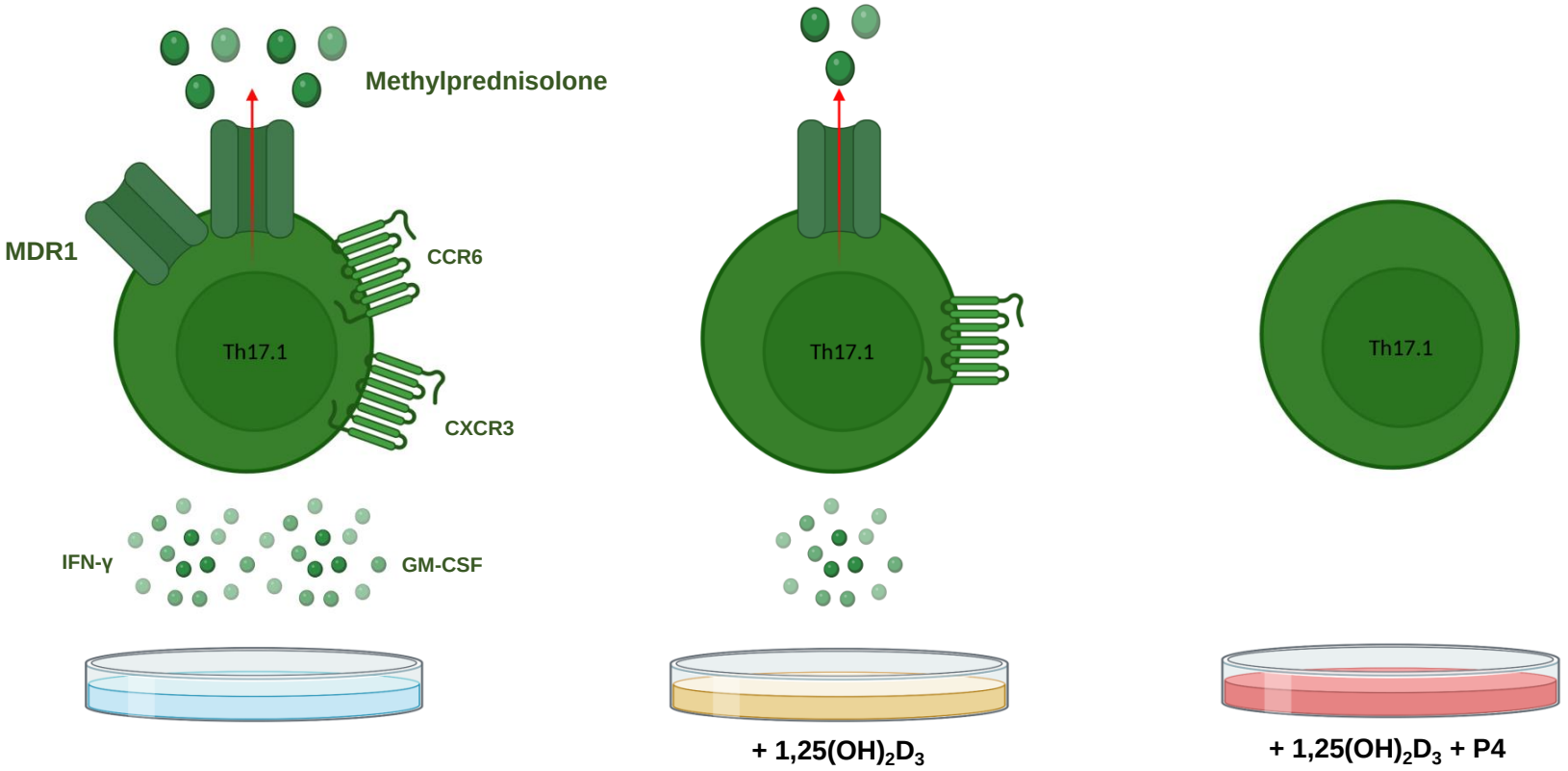
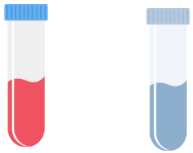
Vitamin D synergizes with glucocorticoids and sex steroids to inhibit Th17.1



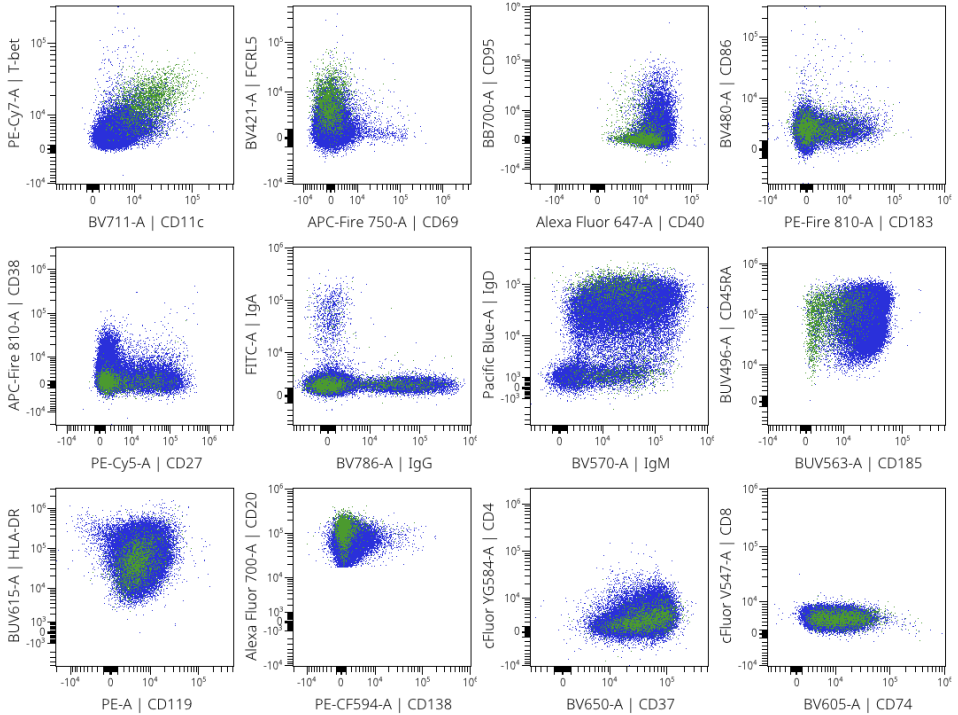
Integration of functional assays with single-cell technologies (Aurora, 10X)

Spectral cytometry

scRNA-seq



33 color-based, B cell-focused spectral cytometric panel



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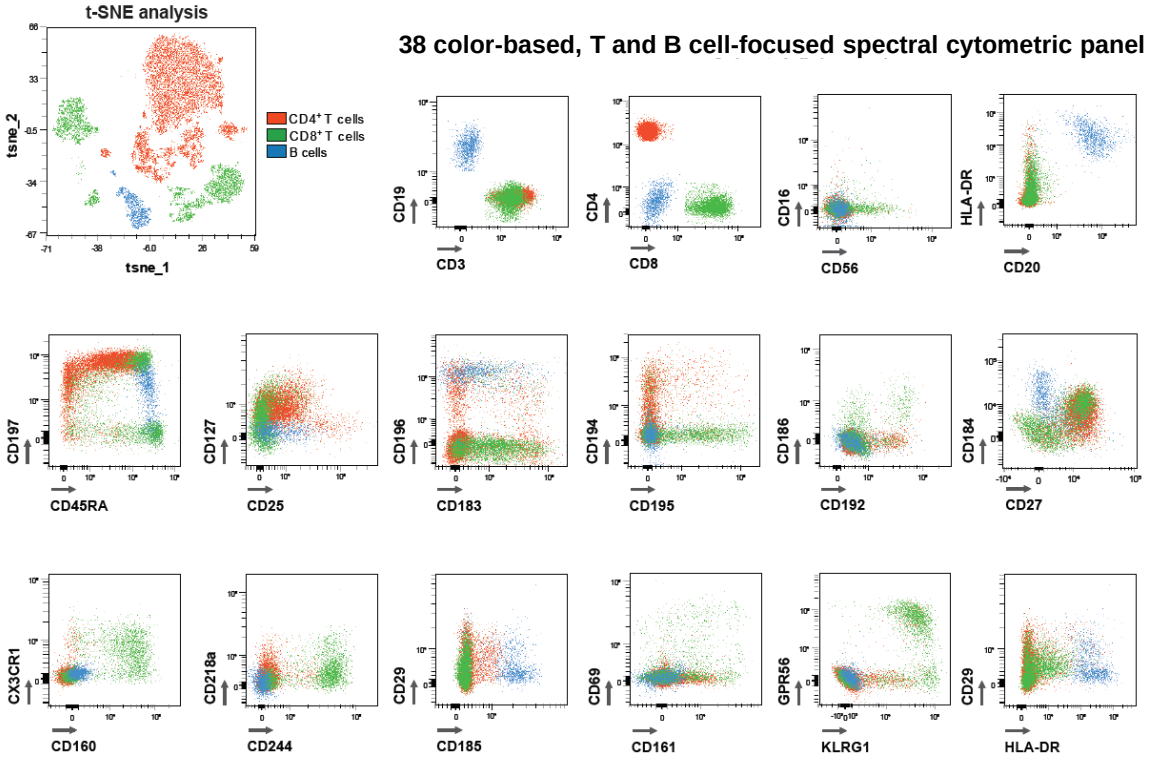
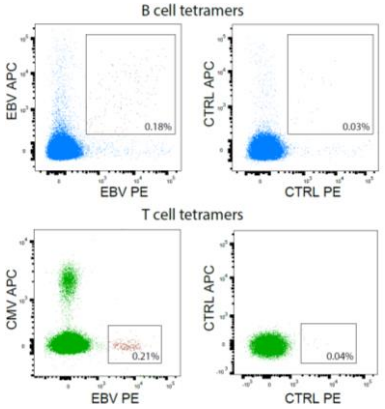
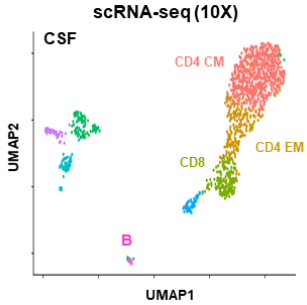
Integration of functional assays with single-cell technologies (Aurora, 10X)







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Erasmus MC

MS Center ErasMS

Erase MS

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Elga de Vries

Inge Huitinga

UMCG, Groningen

Iris Jonkers

LACDR / LUMC

Amanda Foks

Monash / Erasmus

Menno van Zelm

Birmingham University

Andrew Bell

Contact: m.vanluijn@erasmusmc.nl