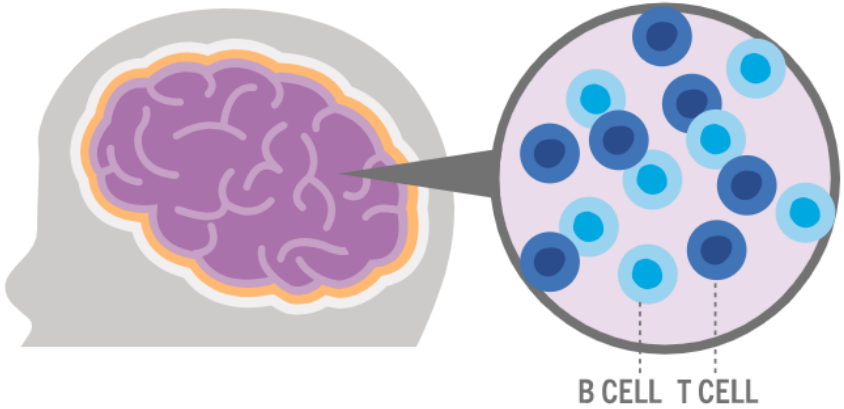
Human T-bet+ B-cell development: association with Bruton's tyrosine kinase and targeting by evobrutinib



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MS Center ErasMS, Rotterdam, NL

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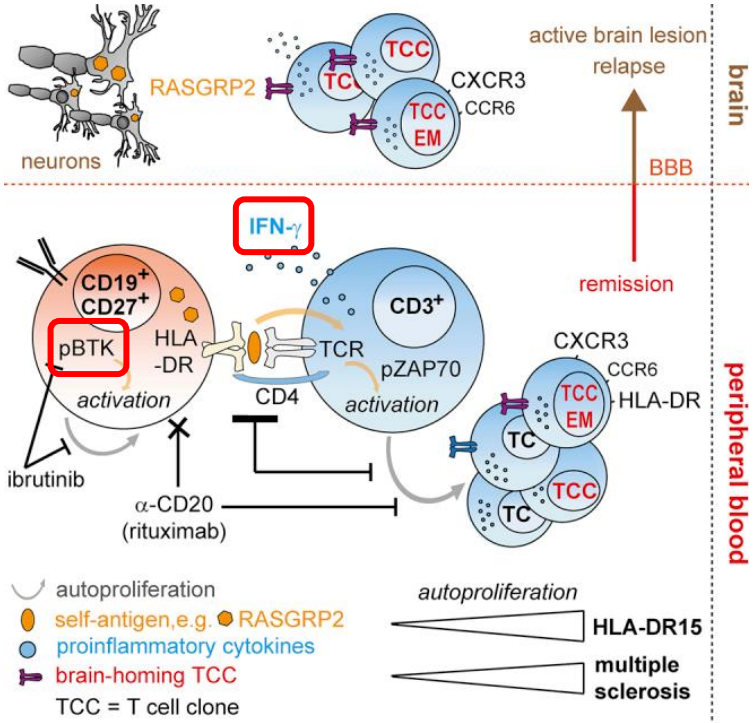
Beneficial effects of Bruton's tyrosine kinase (BTK) inhibition in MS patients



Evobrutinib

ORIGINAL ARTICLE

Placebo-Controlled Trial of an Oral BTK Inhibitor in Multiple Sclerosis

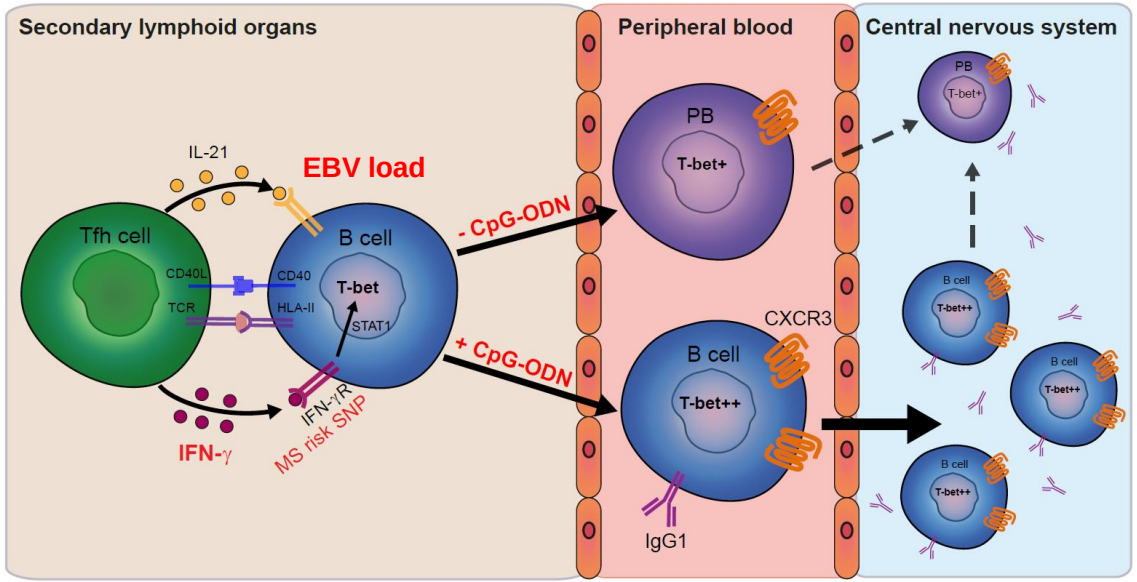
Xavier Montalban, M.D., Ph.D., Douglas L. Arnold, M.D., Martin S. Weber, M.D., Ivan Staikov, M.D., Ph.D., Karolina Piasecka-Stryczynska, M.D., Ph.D., Jonathan Willmer, M.D., Emily C. Martin, Ph.D., Fernando Dangond, M.D., Sana Syed, M.D., M.P.H., and Jerry S. Wolinsky, M.D., for the Evobrutinib Phase 2 Study Group*

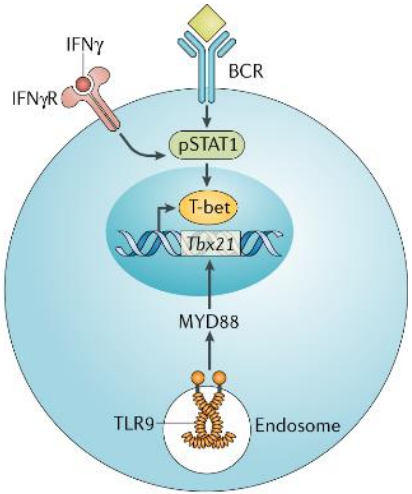
B => T

B <= T

Jelcic, Cell 2018; van Langelaar, Brain 2018; Montalban, N Engl J Med 2019; Koetzier, N2 2020; Wang, Cell 2020

T-bet+ B cells are preferentially induced to infiltrate the CNS of MS patients





- **Potent** antigen-presenting and antibody-producing cells
- Increased responsiveness during chronic viral infections

BTK?

Pritchard, Nat Rev Immunol 2019; van Langelaar, Ann Neurol 2019; Front Immunol 2020; Eur J Immunol 2020

Main objective and study design

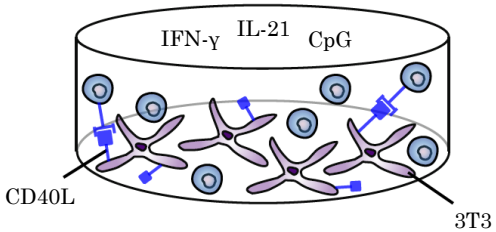
To explore the impact of BTK activity on T-bet+ B-cell development in MS

Clinical course (*ex vivo*)

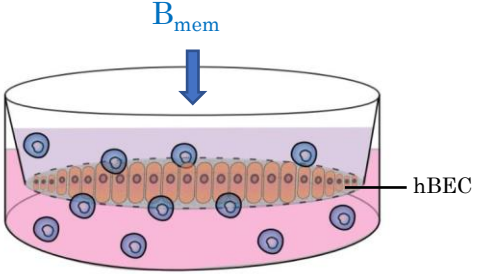
HC RRMS --► SPMS

Induction and outgrowth

B_{naive} --► B_{mem} --► ASC



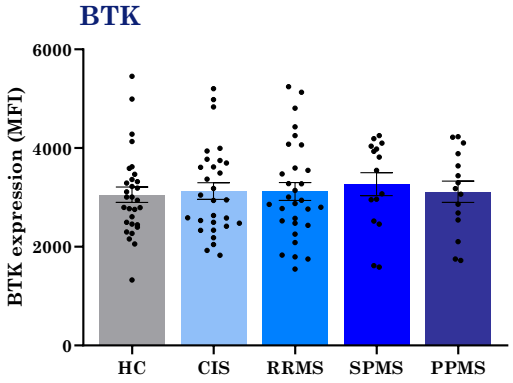
Brain-homing capacity

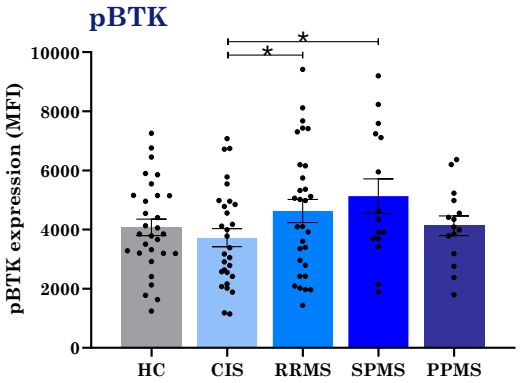


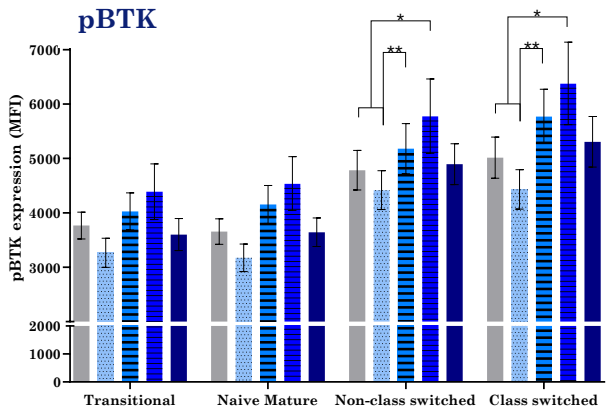
+/- Evobrutinib

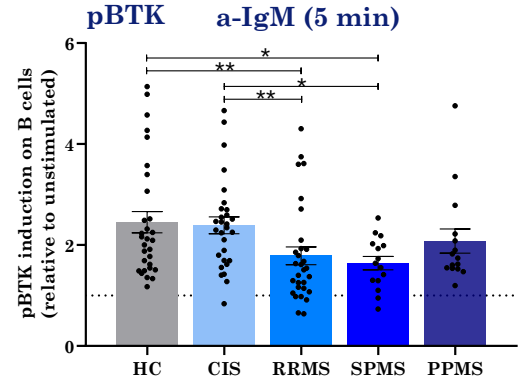
ASC = antibody-secreting cell; hBEC = human brain endothelial cell

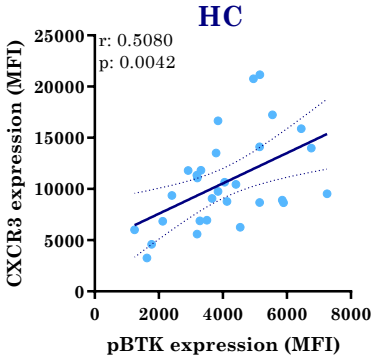
pBTK is upregulated and correlates with CXCR3 levels in B cells of MS patients

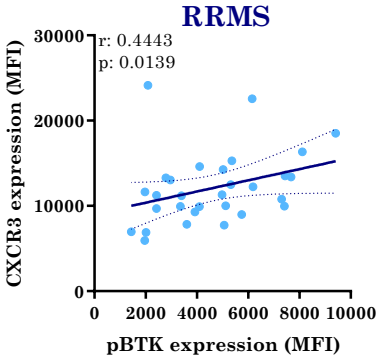


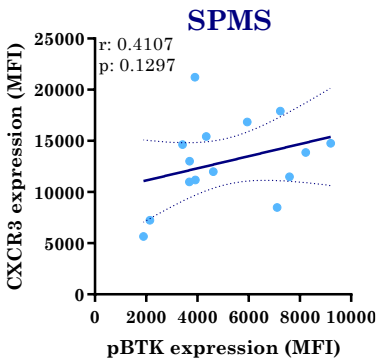












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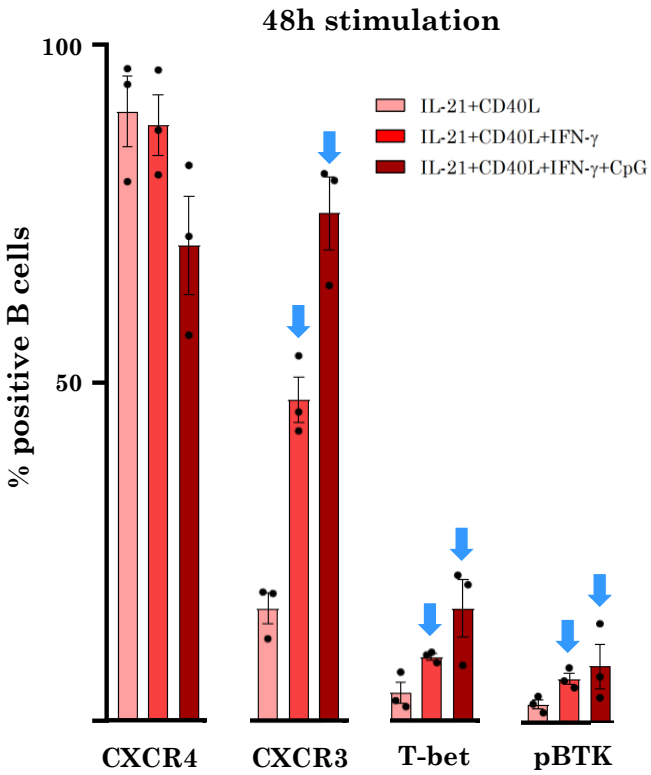
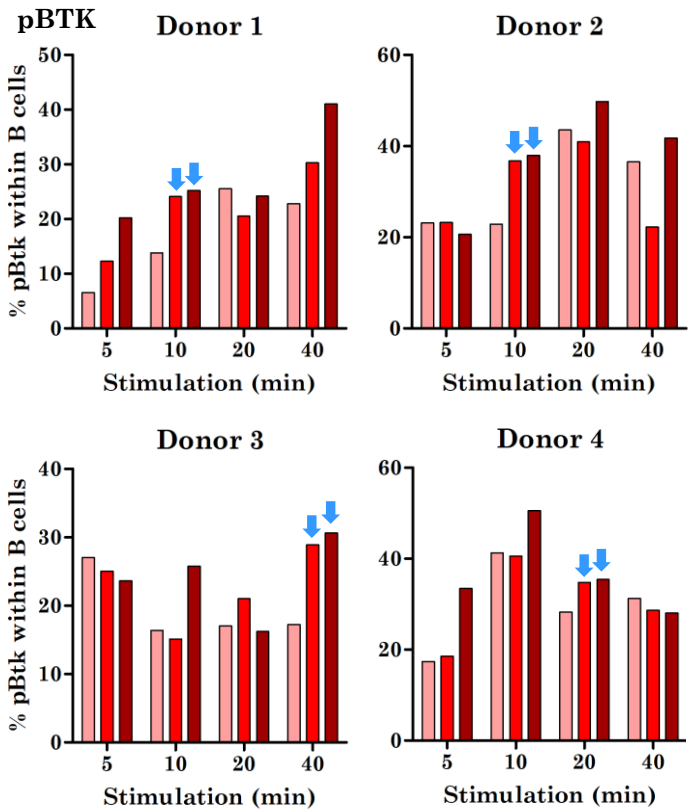
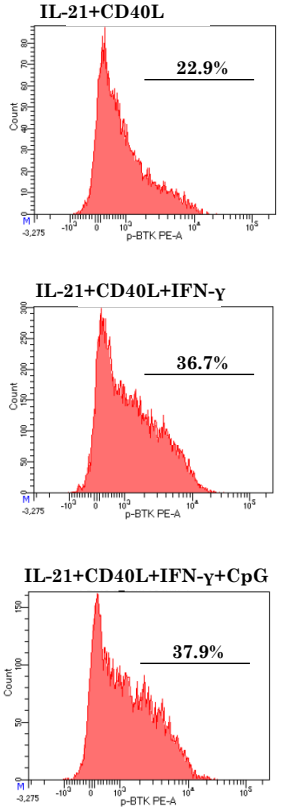
IFN-γ and CpG do not only induce CXCR3 and T-bet, but also pBTK in B cells







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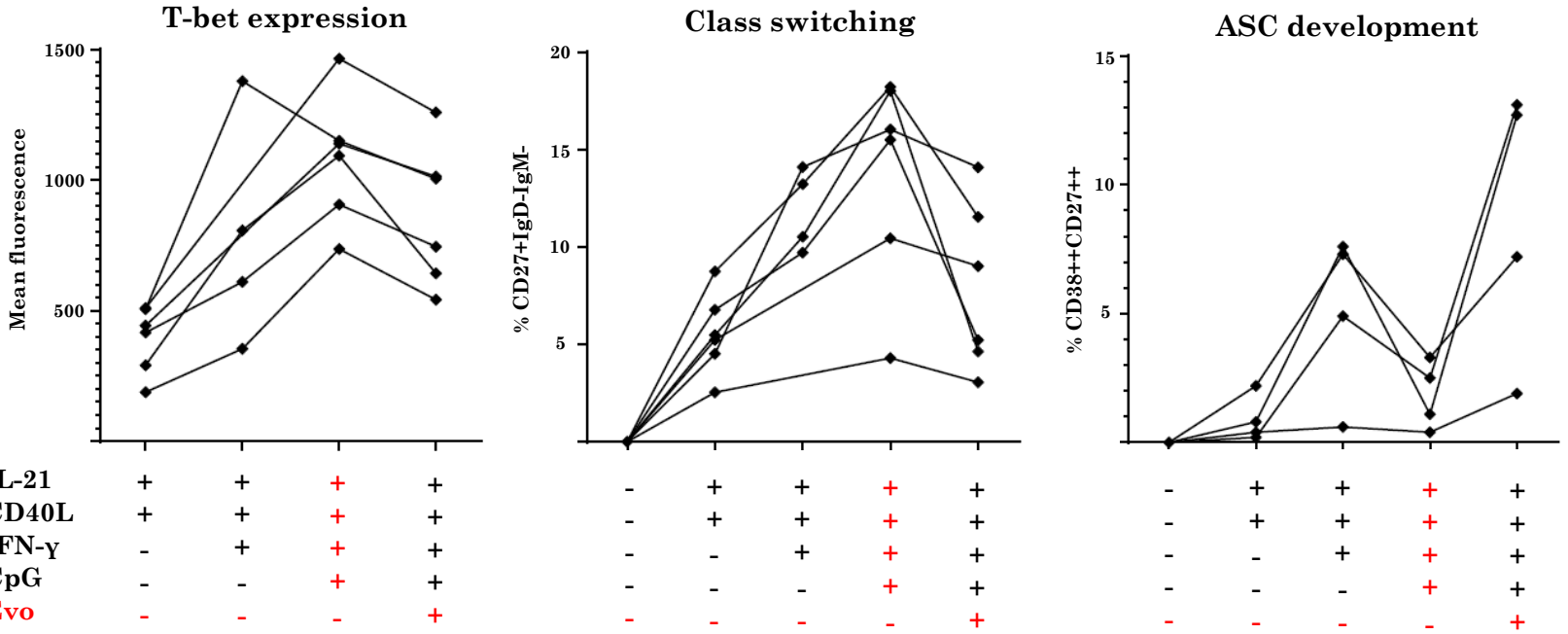
GC-like naive B-cell cultures: reduced T-bet induction, impaired class-switching and more ASC development in the presence of evobrutinib

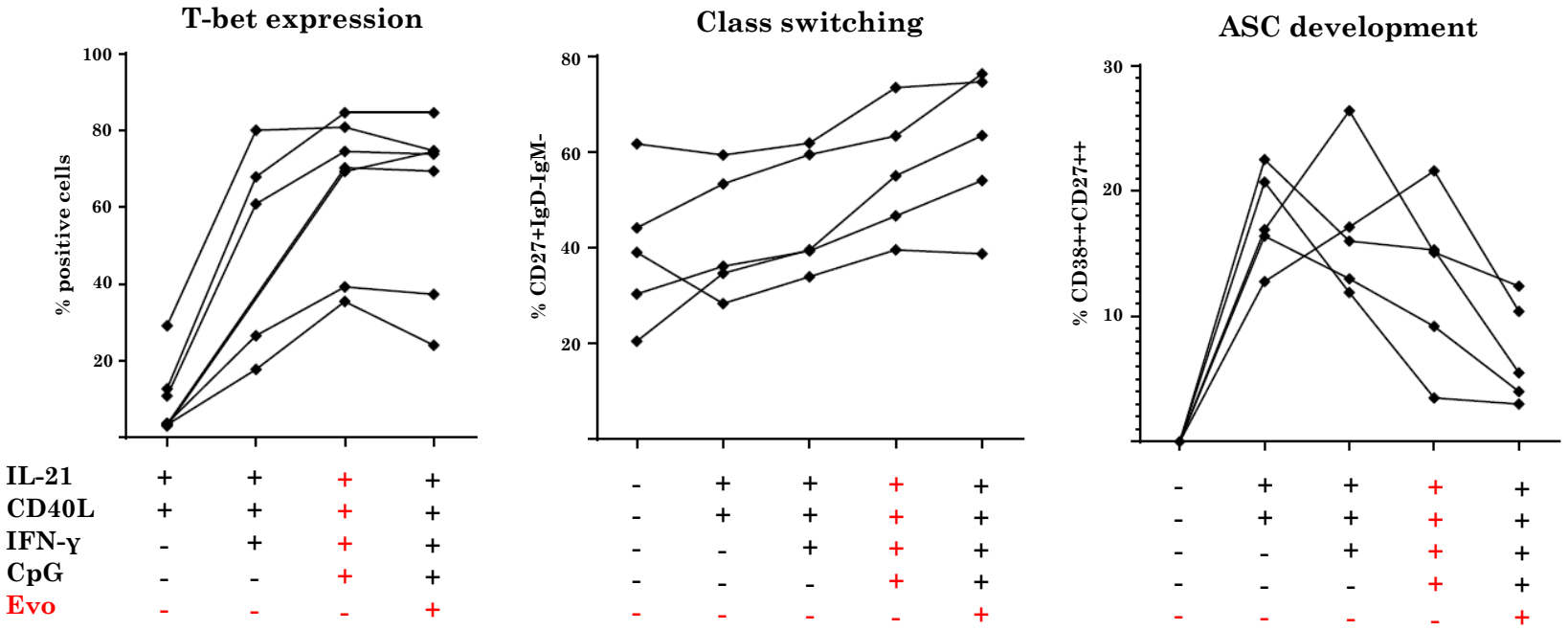
Day 11



GC = germinal center; ASC = antibody-secreting cell; Evo = Evobrutinib

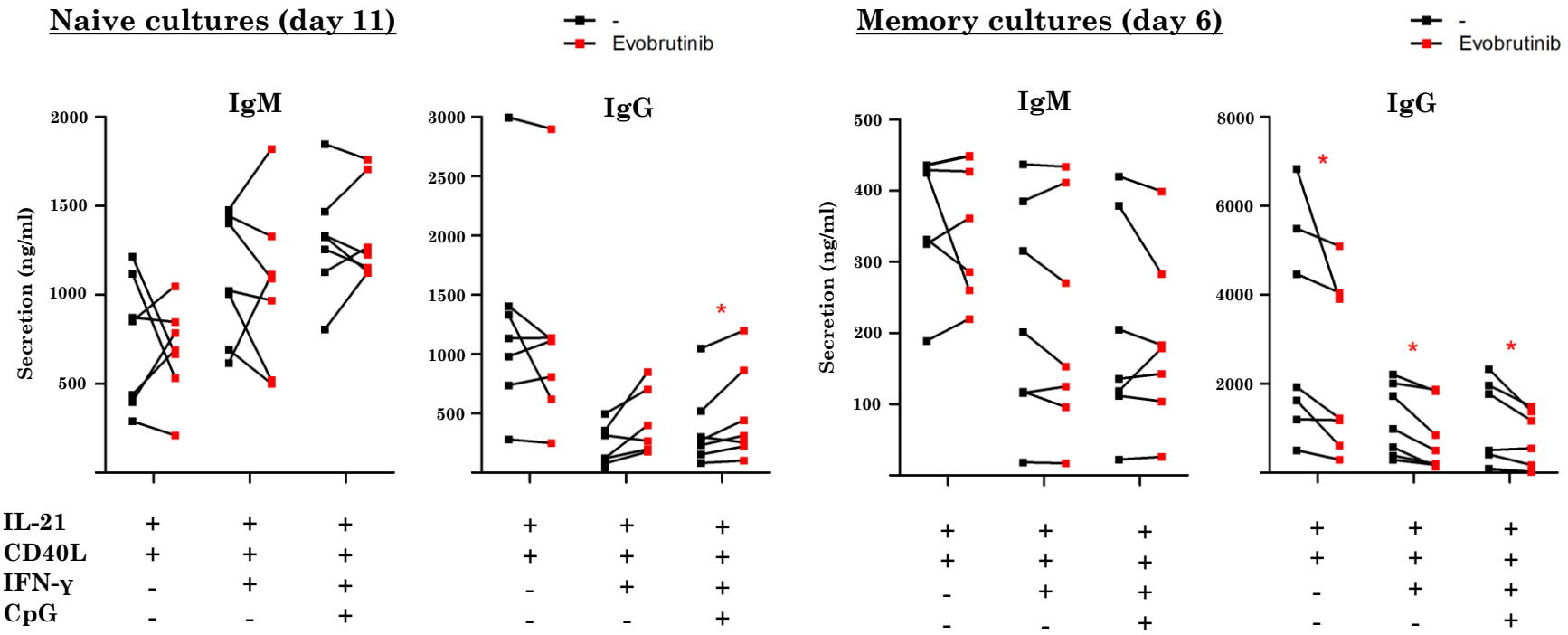
GC-like memory B-cell cultures: no impact on T-bet levels and class-switching, but less ASC development in the presence of evobrutinib

Day 6

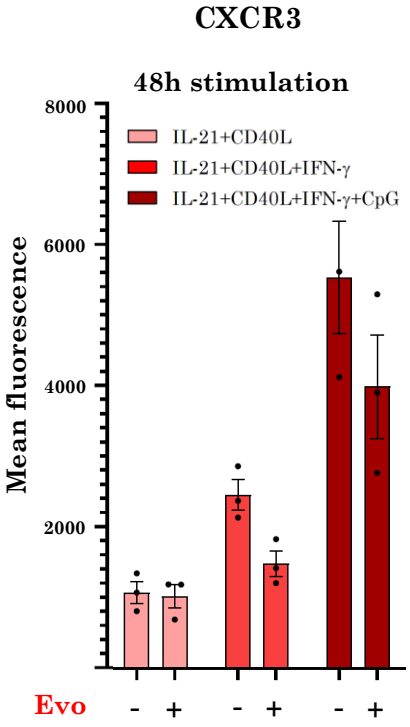


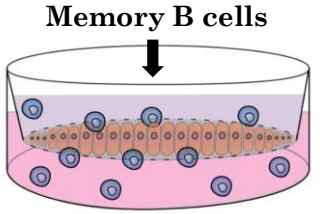
GC = germinal center; ASC = antibody-secreting cell; Evo = Evobrutinib

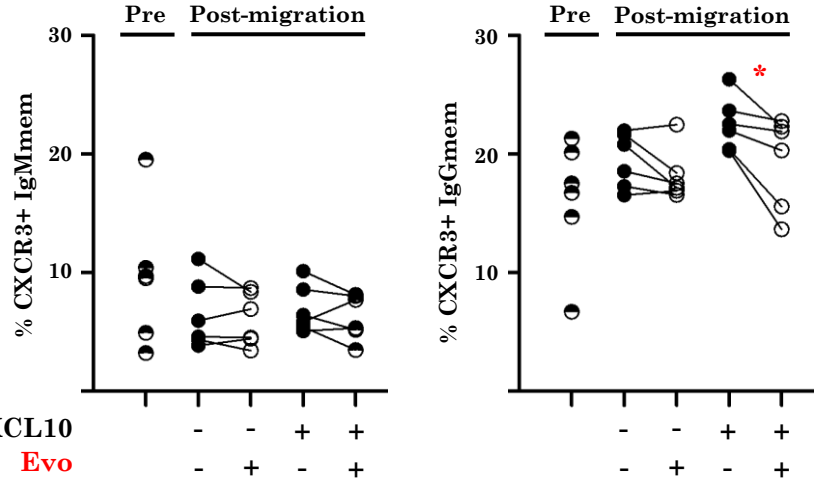
The *in vitro* effect of evobrutinib on naive and memory B-cell differentiation is associated with differences in IgG secretion



Evobrutinib attenuates CXCL10-mediated transmigration of CXCR3+ memory B cells across confluent hBEC monolayers *in vitro*







Evo = Evobrutinib

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Conclusions

Ex vivo

- pBTK and not BTK is upregulated in memory B cells of RRMS and SPMS patients
- pBTK is less induced by anti-IgM triggering of B cells of RRMS and SPMS patients
- pBTK correlates with CXCR3 surface levels in B cells of both patients and controls

In vitro

- Both IFN-γ- and CpG-induced T-bet and CXCR3 corresponds to pBTK expression
- Evobrutinib: suppresses IFN-γ- and CpG-induced T-bet levels and class-switching
  interferes with memory B cell to IgG+ ASC formation (T-bet-unrelated)
  attenuates CXCL10-mediated memory B-cell migration across hBEC

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