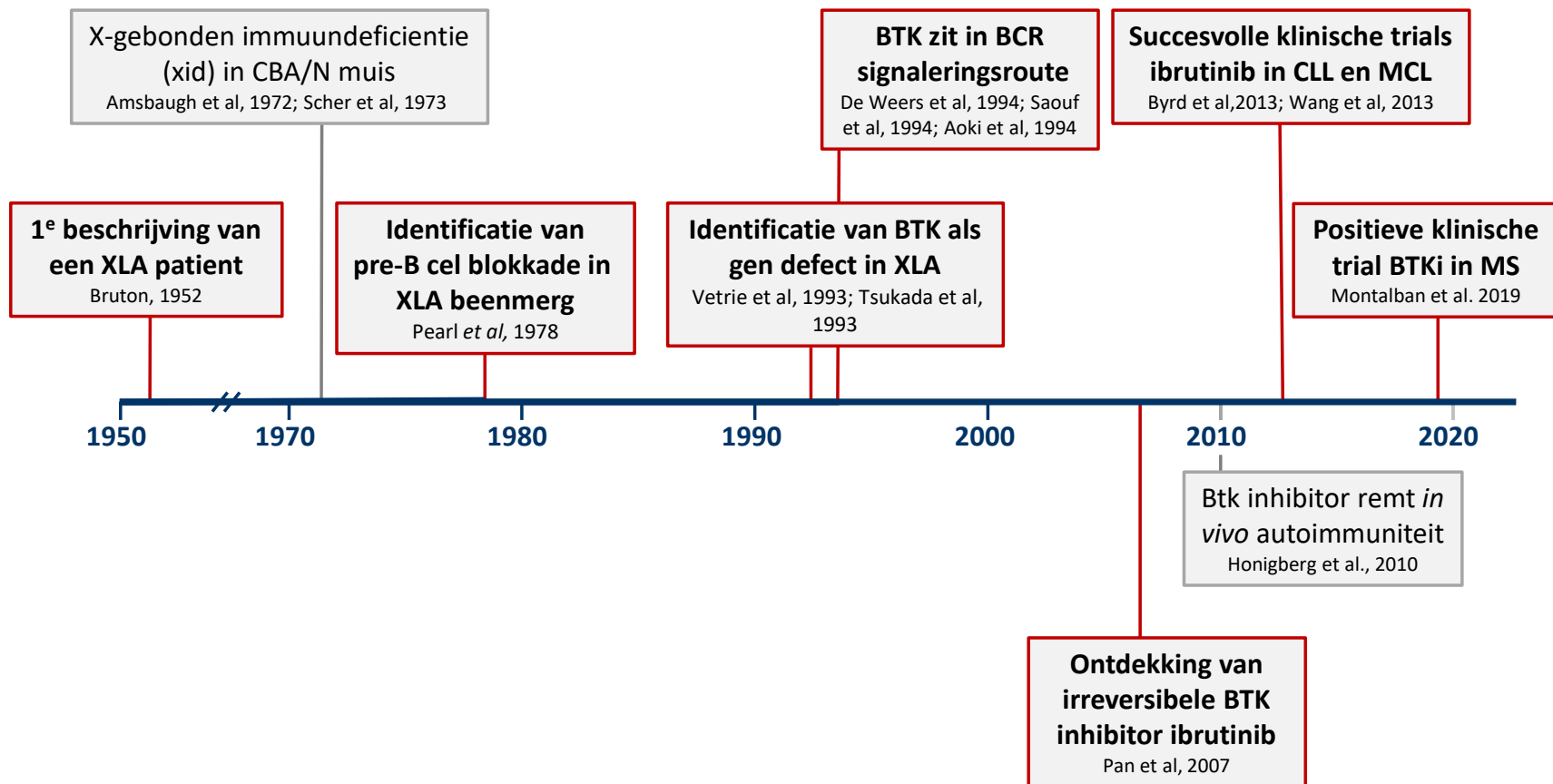


## BTK en B cel receptor signalering in systemische autoimmuun ziekten

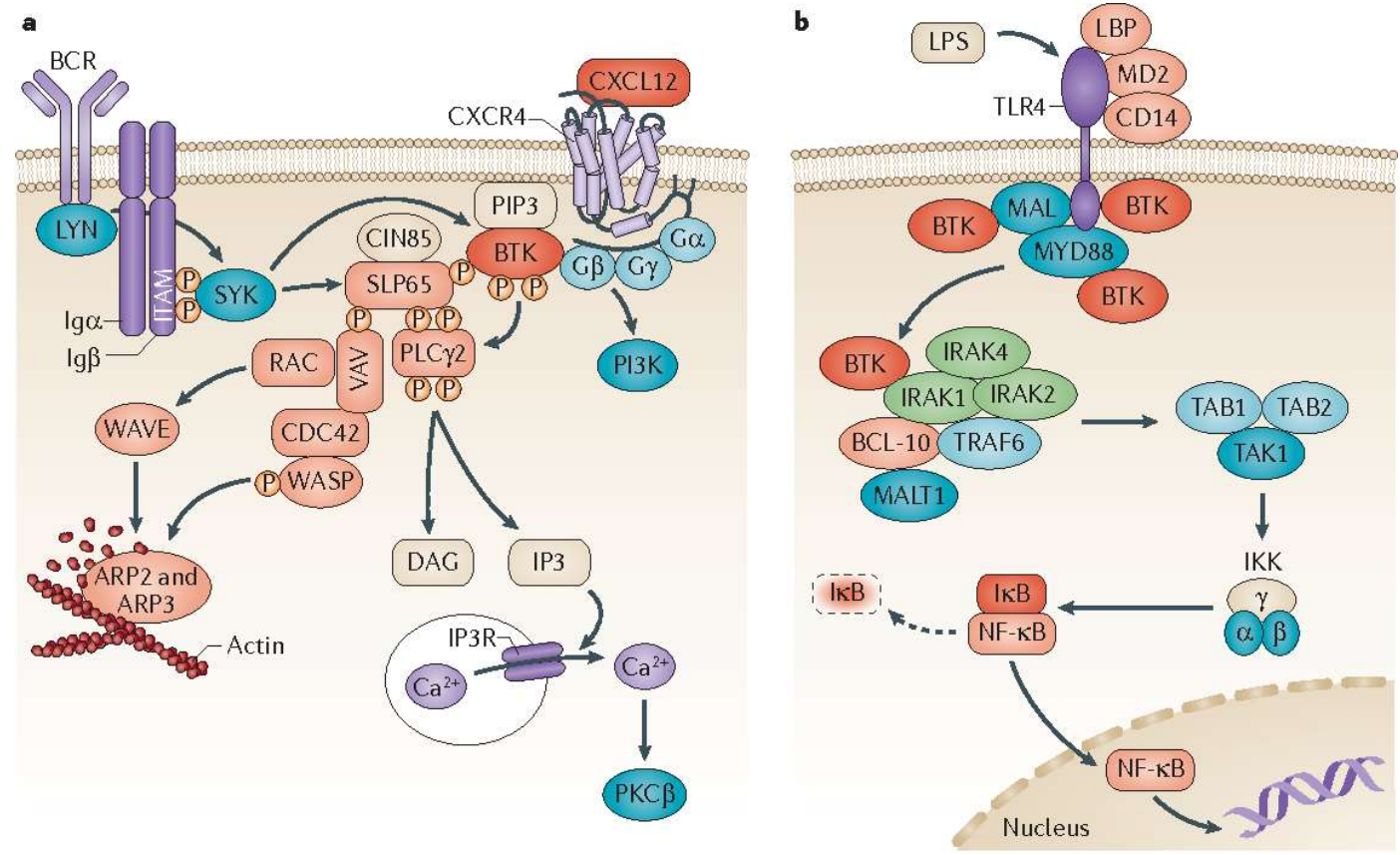
**Odilia Corneth**  
Afdeling Longziekten  
Erasmus MC Rotterdam

3 februari 2023

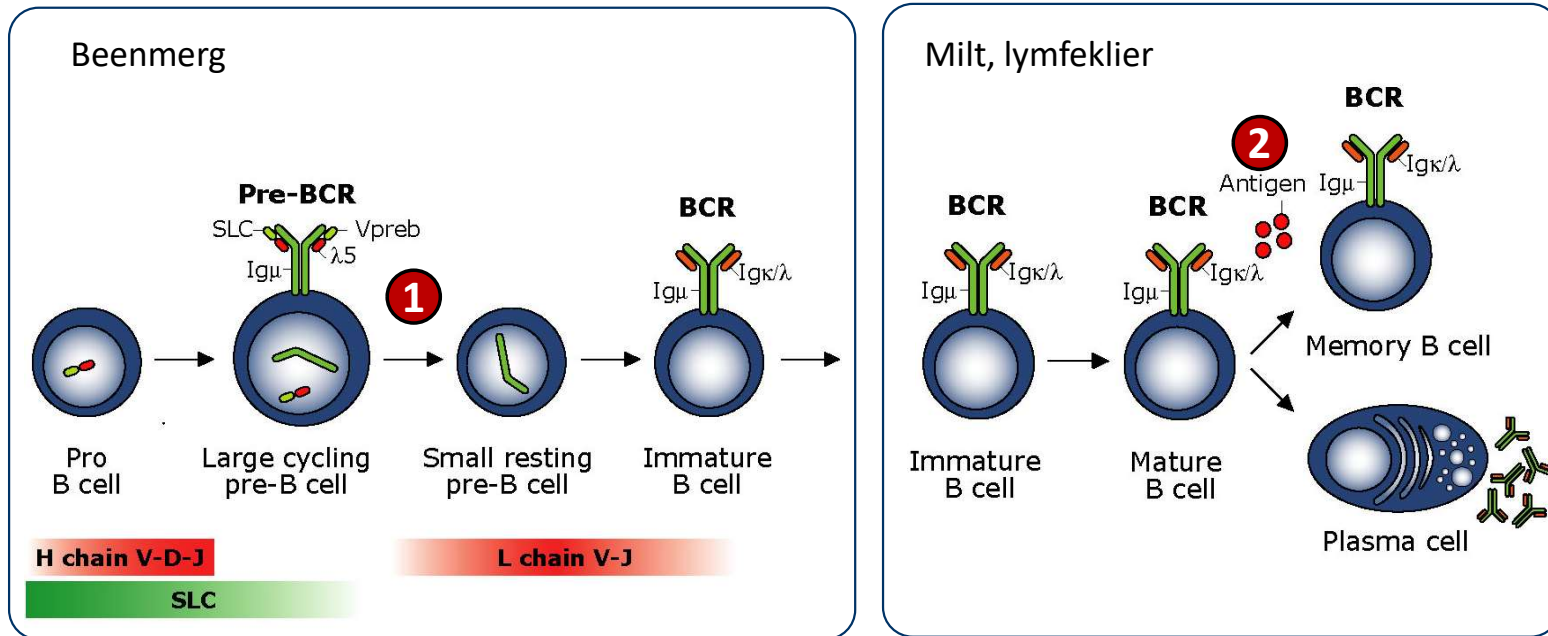
# Bruton's tyrosine kinase



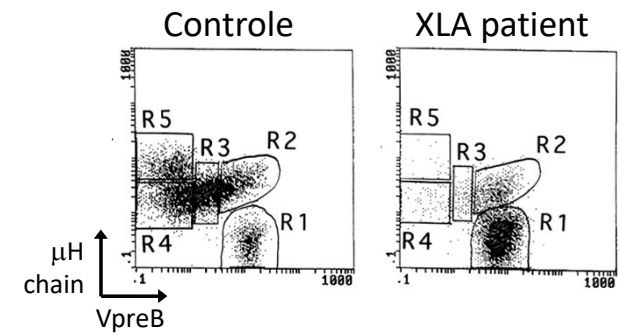
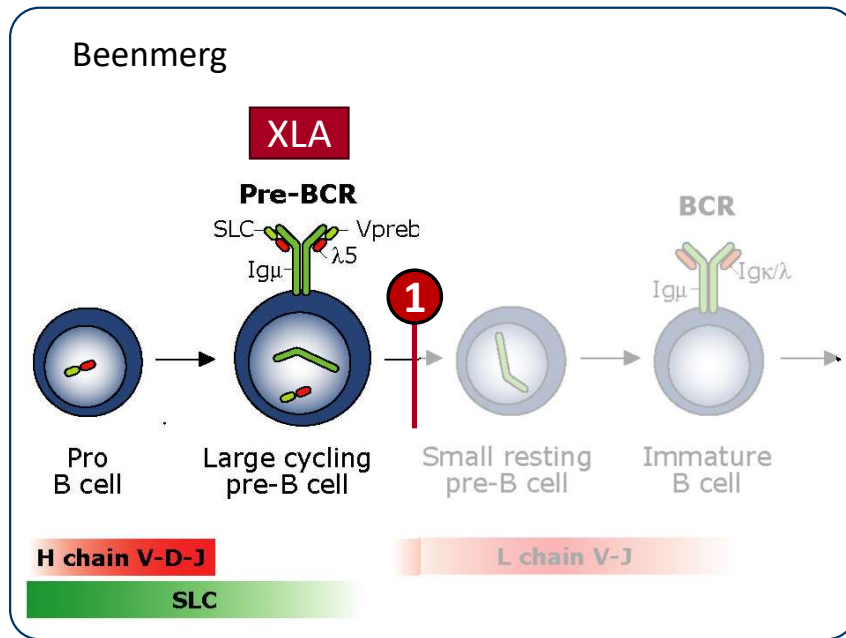
# Bruton's tyrosine kinase in B cellen



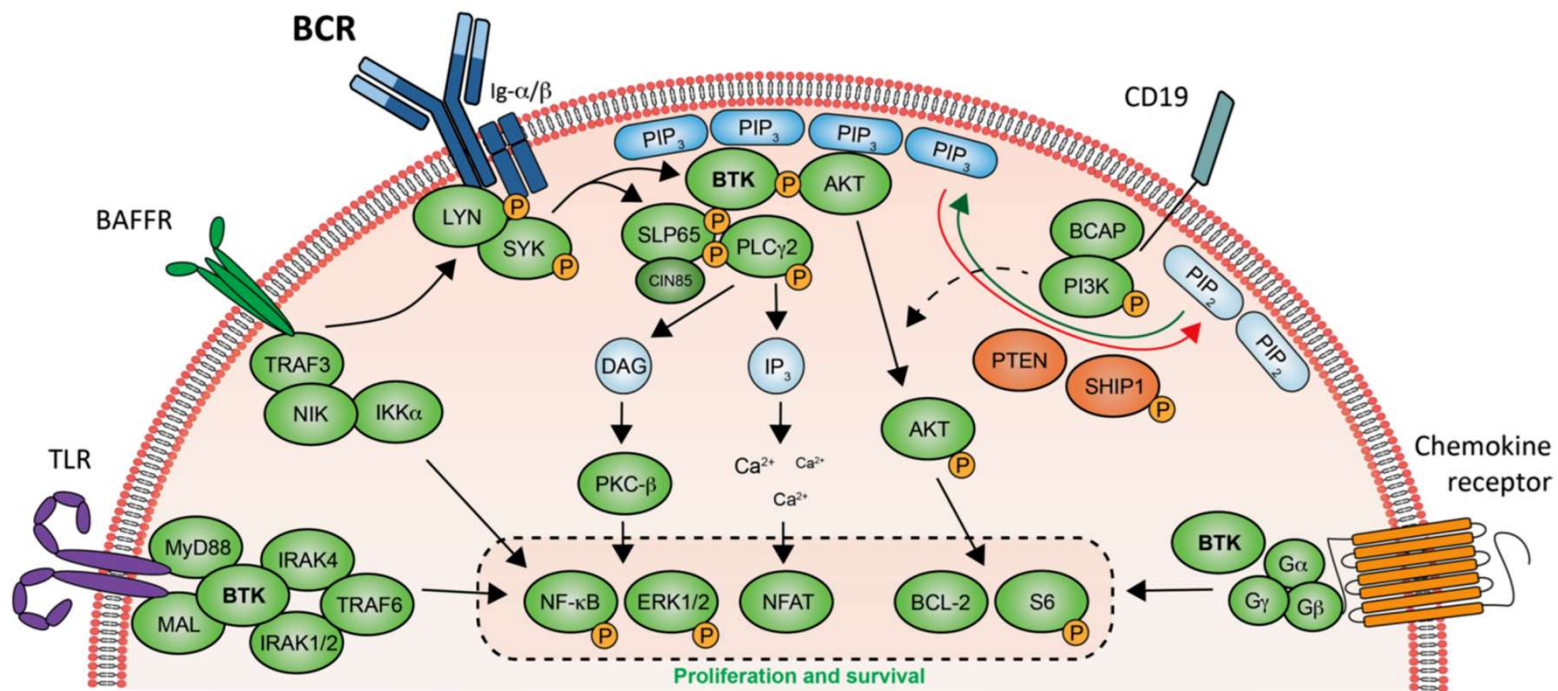
# BTK is essentieel voor normale B cel ontwikkeling en activatie



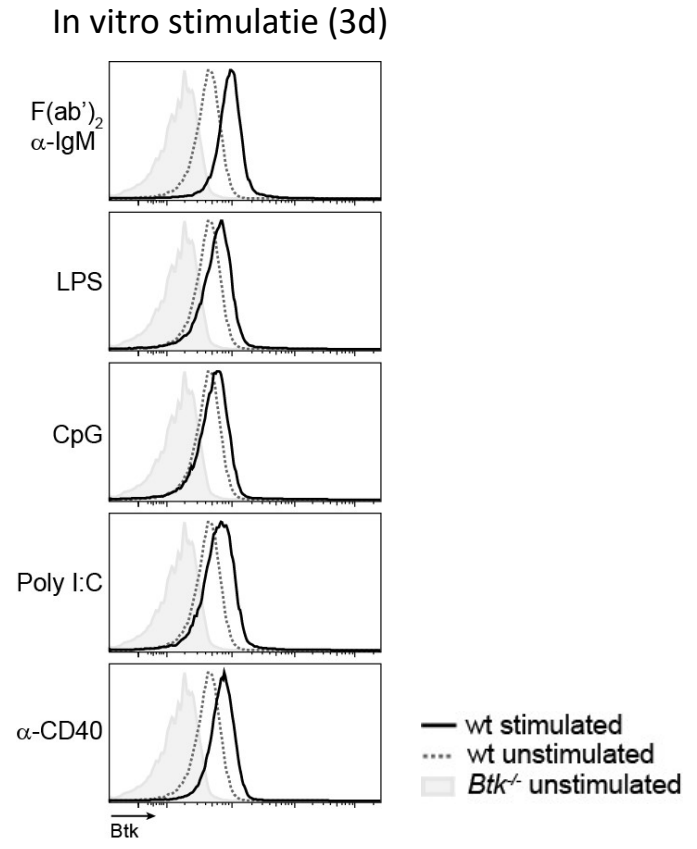
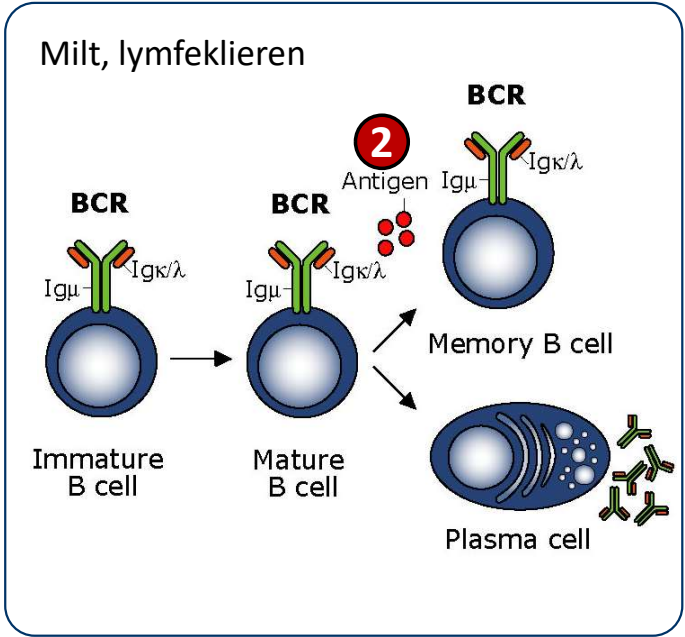
# XLA: geen functioneel BTK eiwit



# BTK is betrokken bij meerdere signalerings routes in B cellen



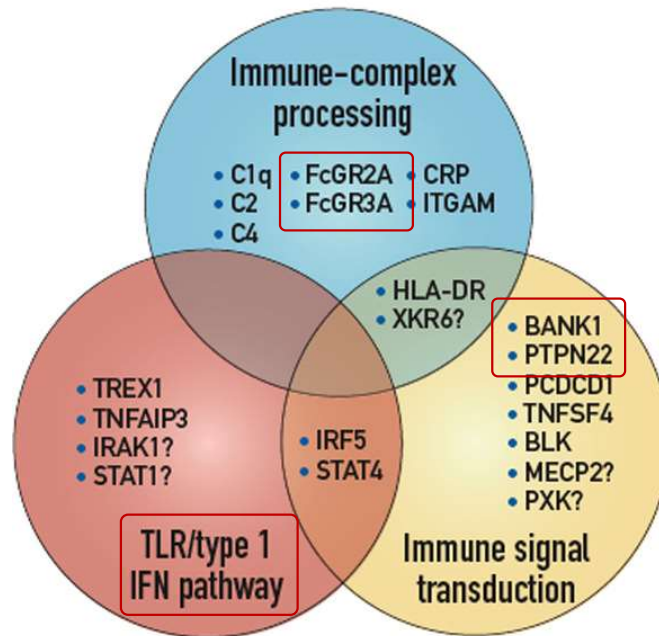
# BTK eiwit wordt opgereguleerd na stimulatie



Kil et al., Blood, 2012



# BTK in autoimmunititeit

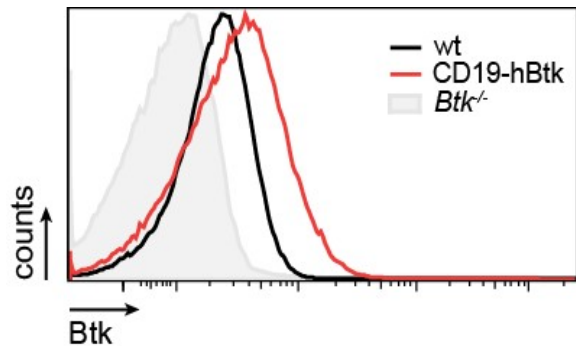


## Genetische analyses (GWAS):

- Het *BTK* locus is **geen** risico locus
- Maar: veel genen in de drie belangrijkste signalerings pathways waarin BTK een rol speelt zijn wel risico loci



### Btk overexpressie in B cellen

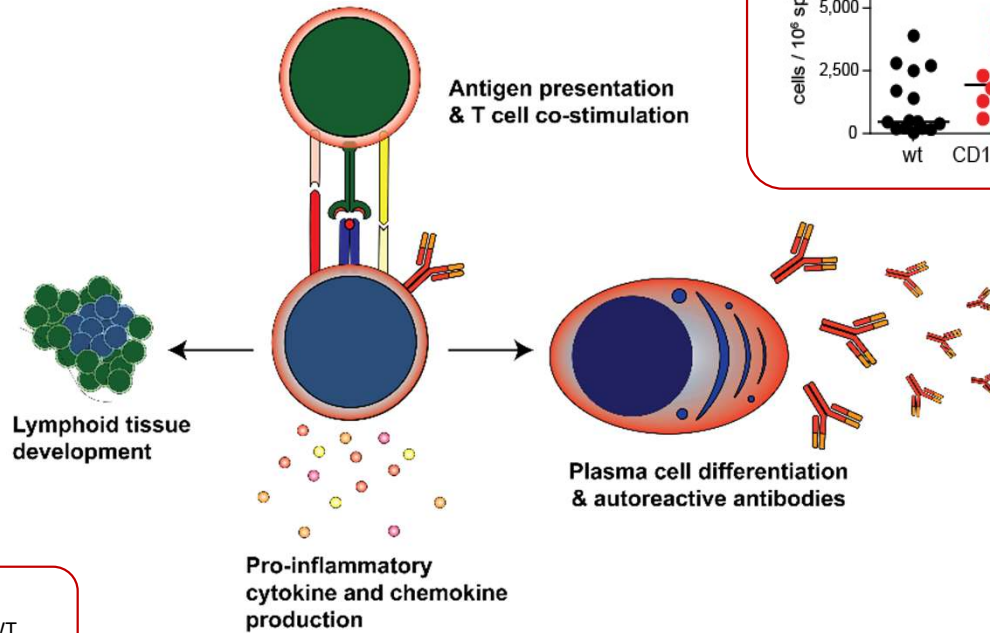
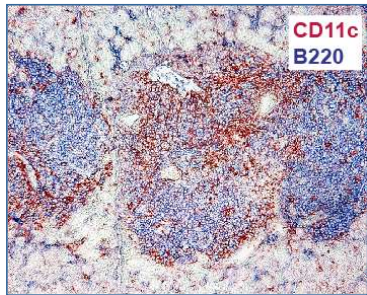


**Btk wordt opgereguleerd na BCR  
stimulatie:**

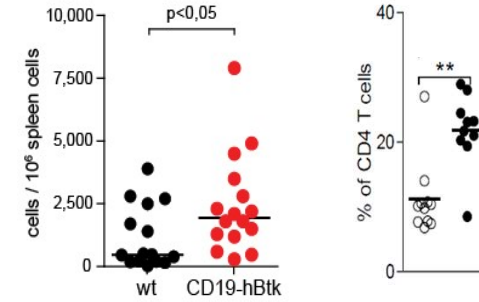
**Zijn BTK eiwit levels cruciaal voor  
normale B cel functie?**

# Spontaan autoimmuun fenotype in BTK transgene muizen

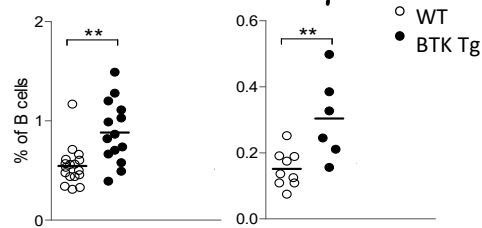
## immuun infiltratie



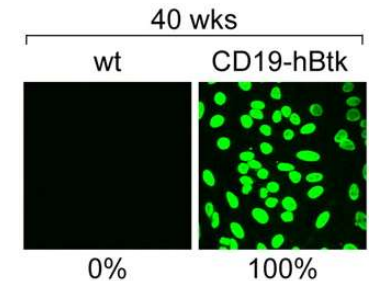
## GC B cellen and Tfh cellen



## IL-6 en IFN $\gamma$

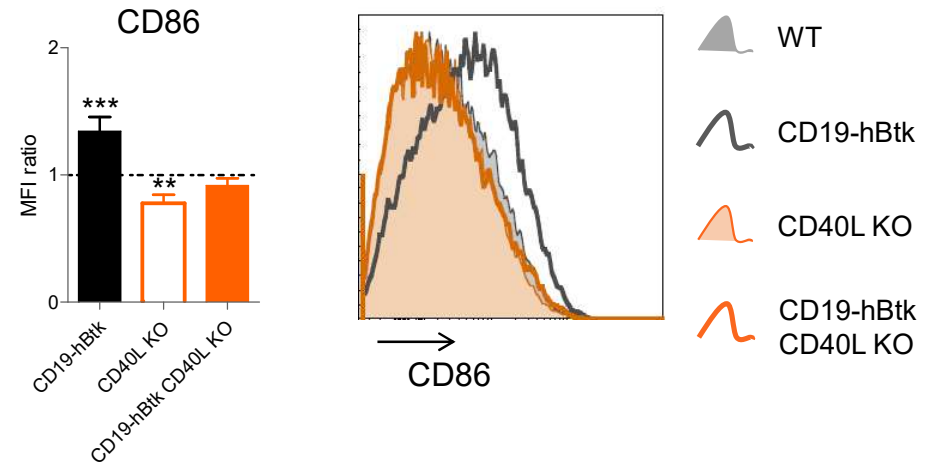
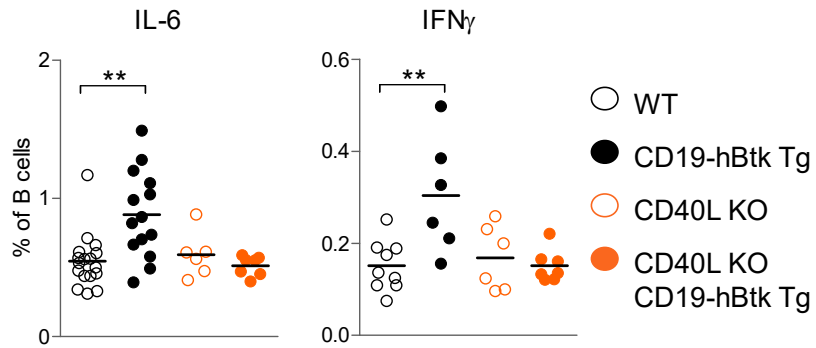


## autoantistoffen



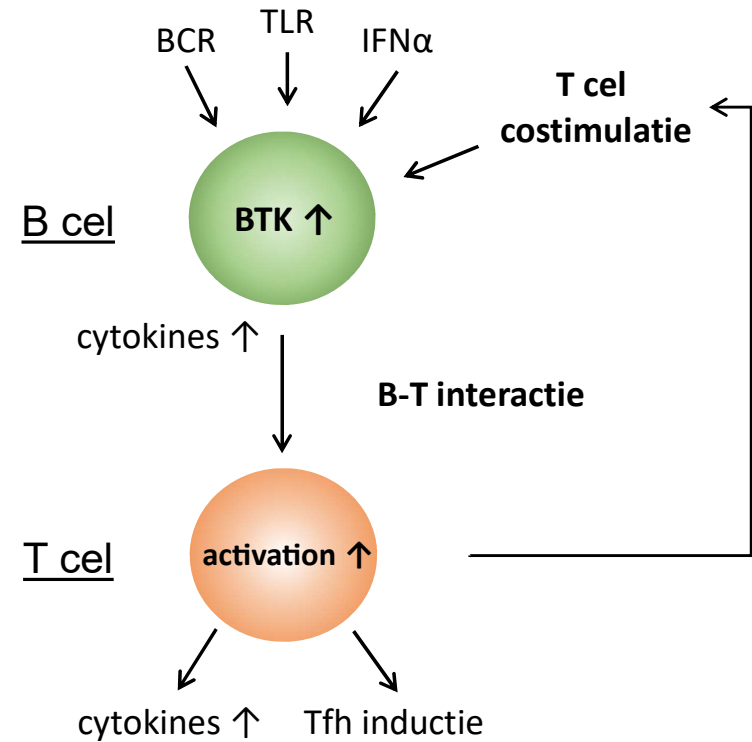
# B-T cel interactie is essentieel voor het autoimmuun fenotype

## Geen B cel activatie zonder B-T cel interactie



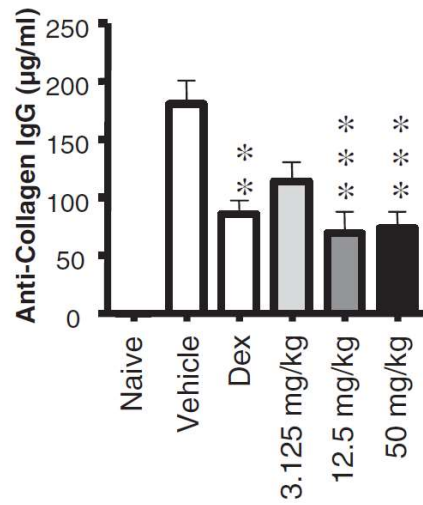
# Model B-T cel interactie in autoimmuniteit

- Verhoogd BTK leidt tot:
  - verhoogde activatie van B cellen
  - spontane GCs en plasma cellen
  - spontaan autoimmuun fenotype
- B-T cel interactie is essentieel voor het fenotype

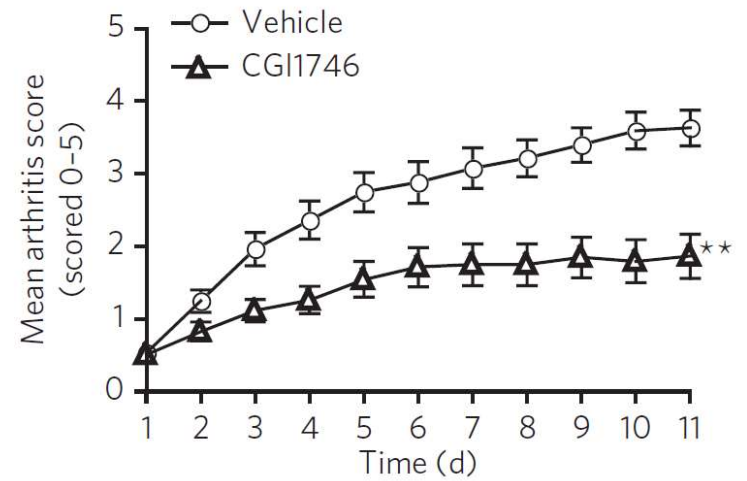
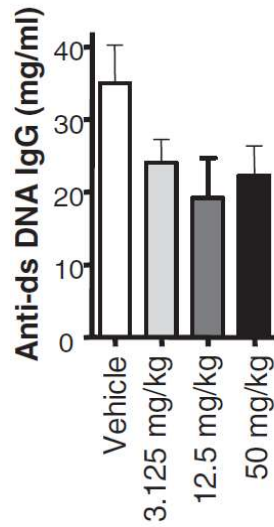


# BTK inhibitie bij autoimmuniteit in muizen

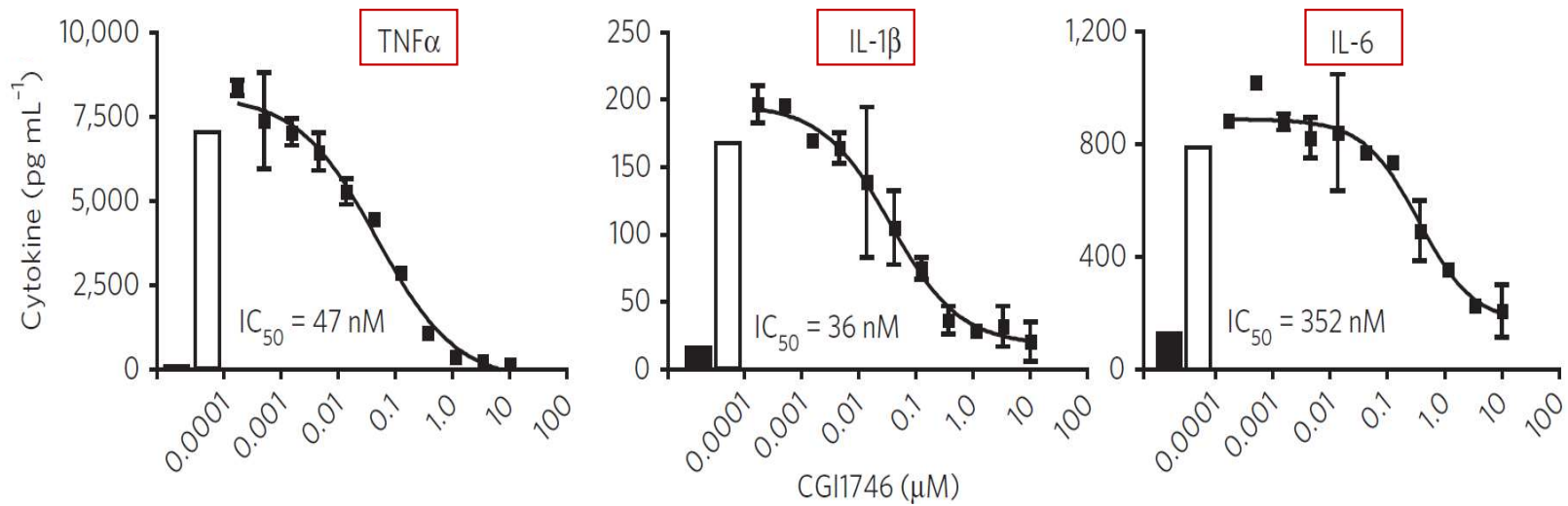
## Collageen-geïnduceerde artritis



## MRL-Fas(lpr) lupus muizen



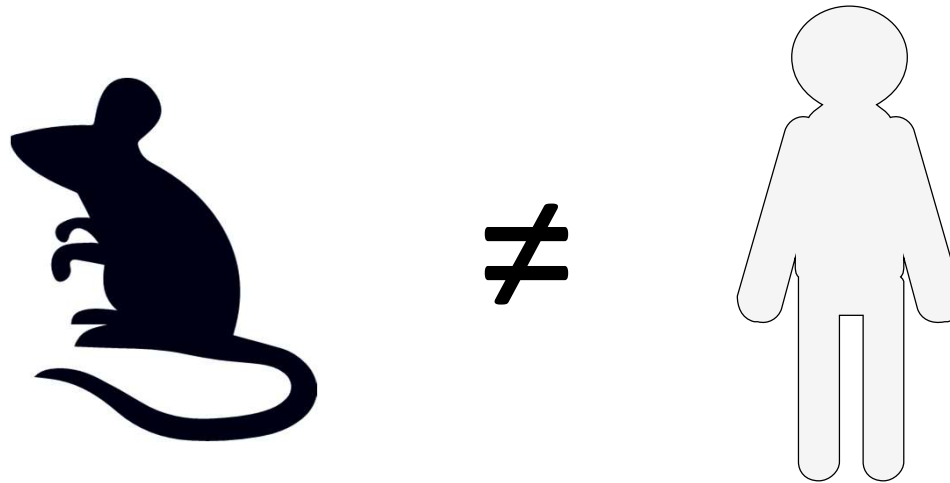
## BTK inhibitie in monocyten



**CGI-1746 verlaagt cytokine productie in Ig complex-geactiveerde humane monocyten**

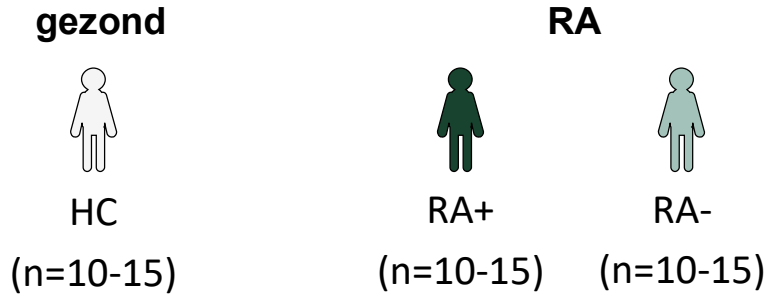
# Relevantie voor de mens

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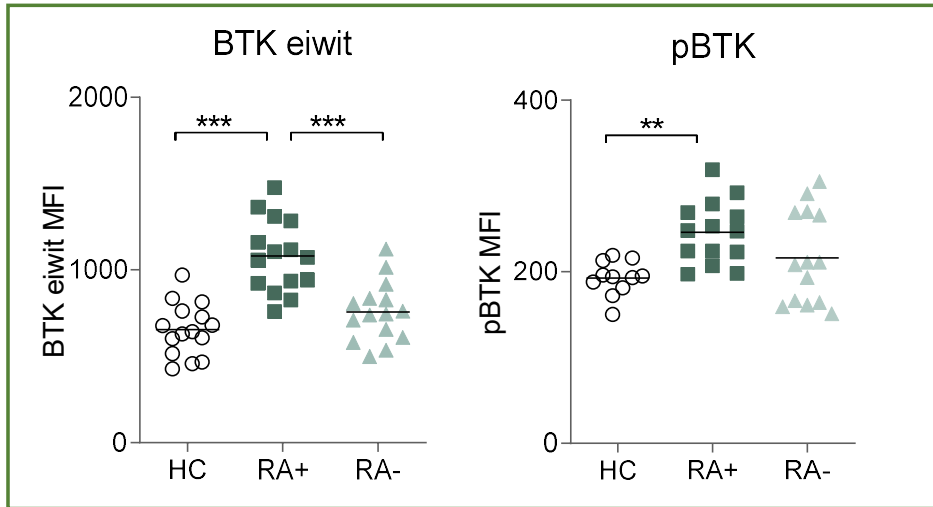




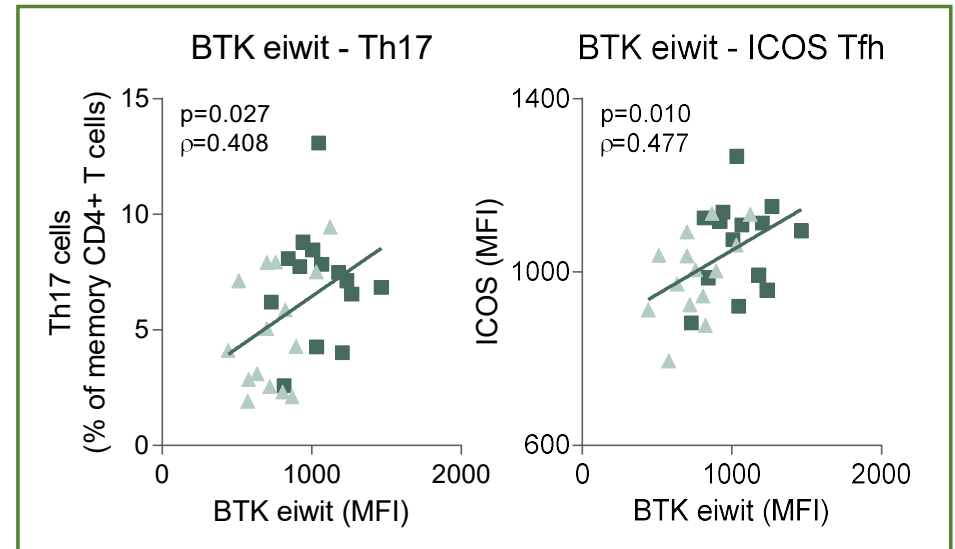
# Verhoogde BTK eiwit expressie in ACPA+ reumatoïde artritis patiënten



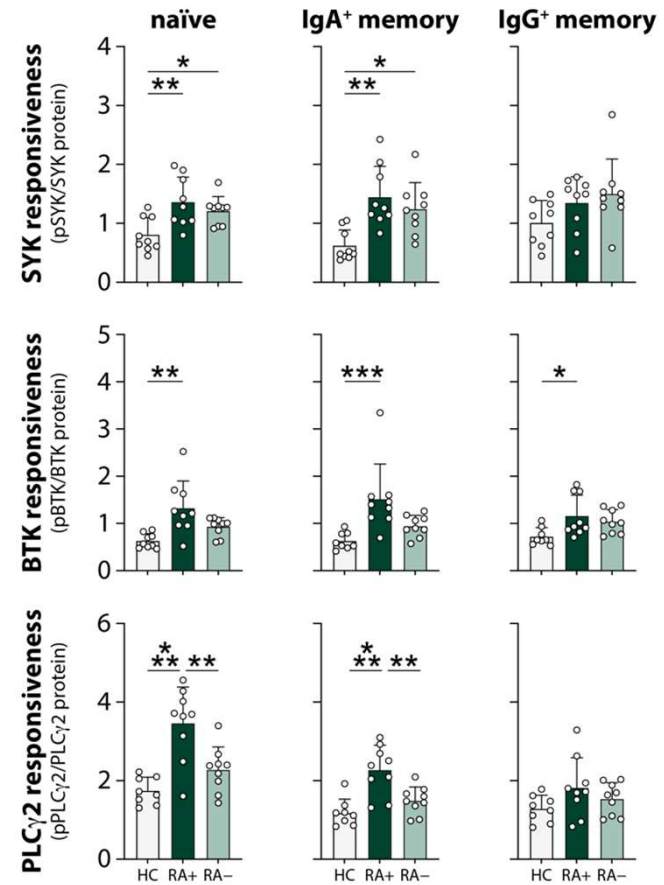
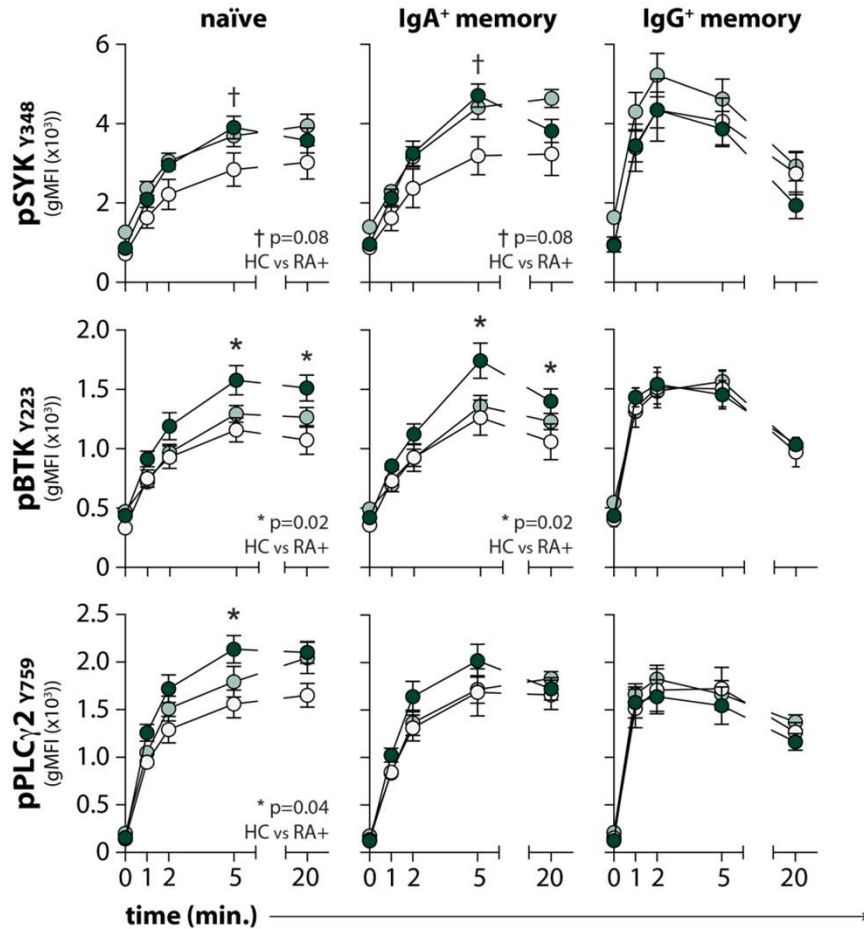
## Verhoogd BTK in B cellen in ACPA+ RA



## Correlatie BTK eiwit met pathogene T cellen

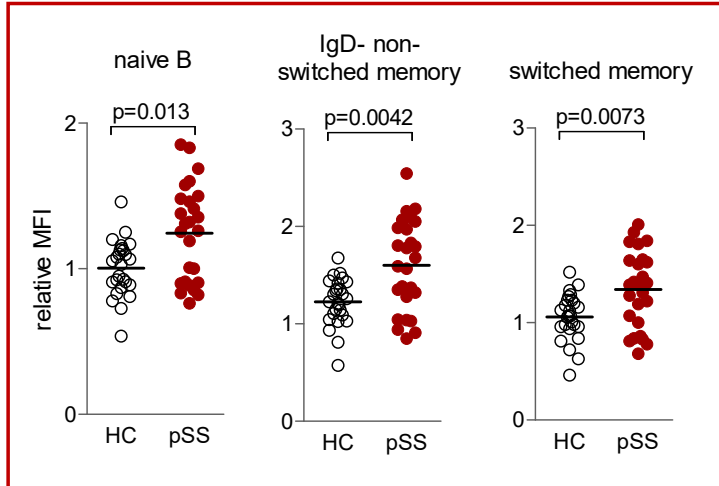


# Verstoorde BCR signalering in ACPA+ RA patiënten

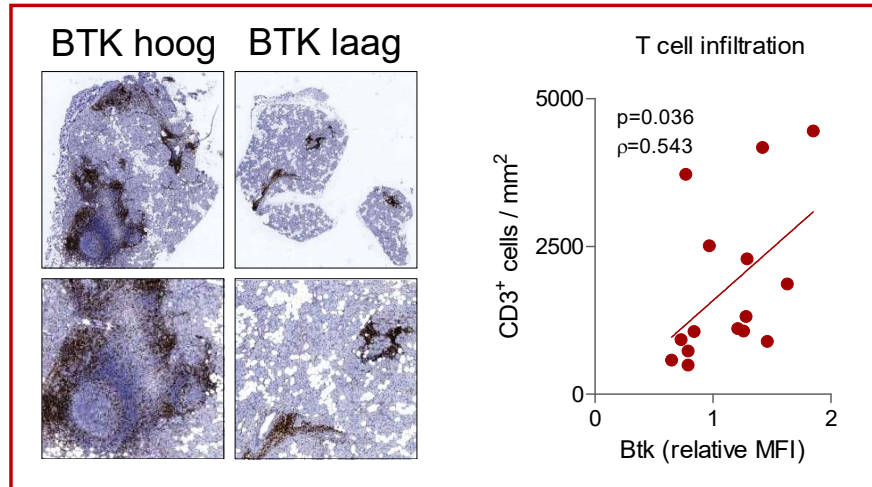
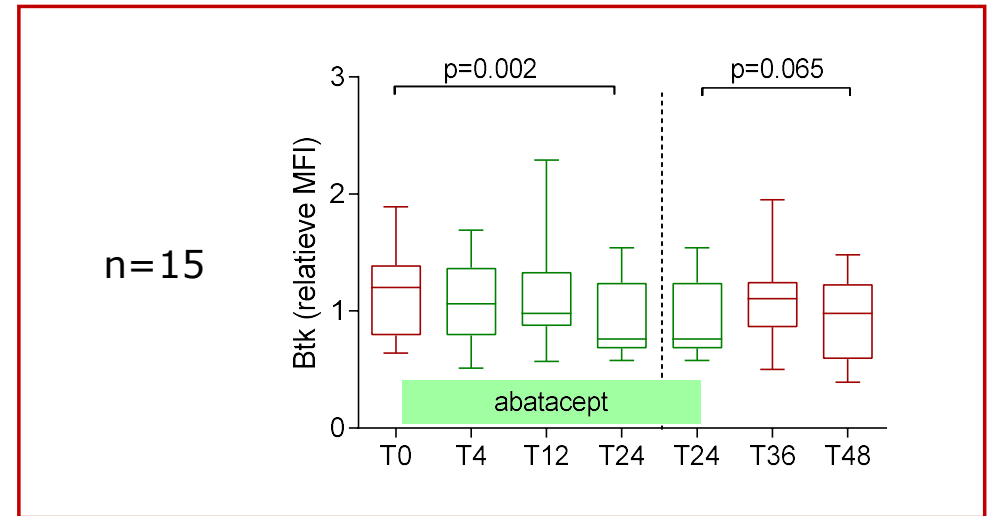


# Verhoogd BTK eiwit in Sjögren patiënten is afhankelijk van B-T cel interactie

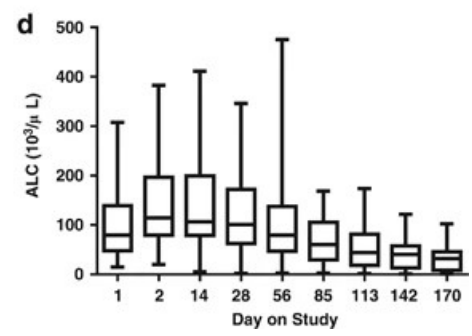
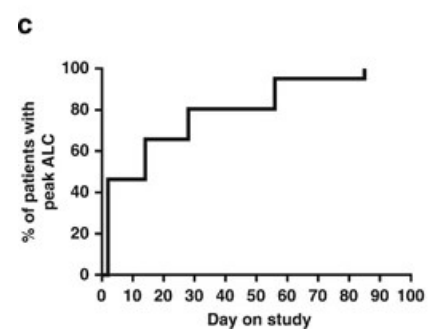
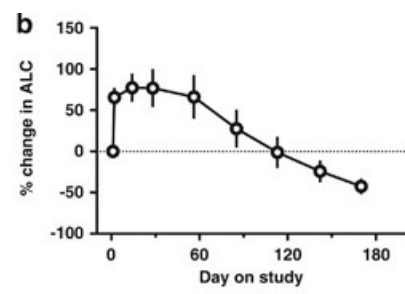
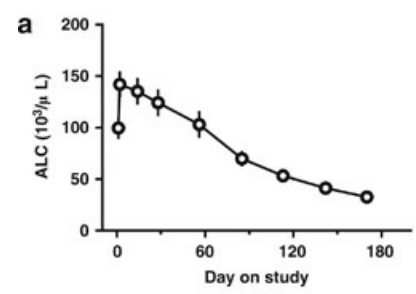
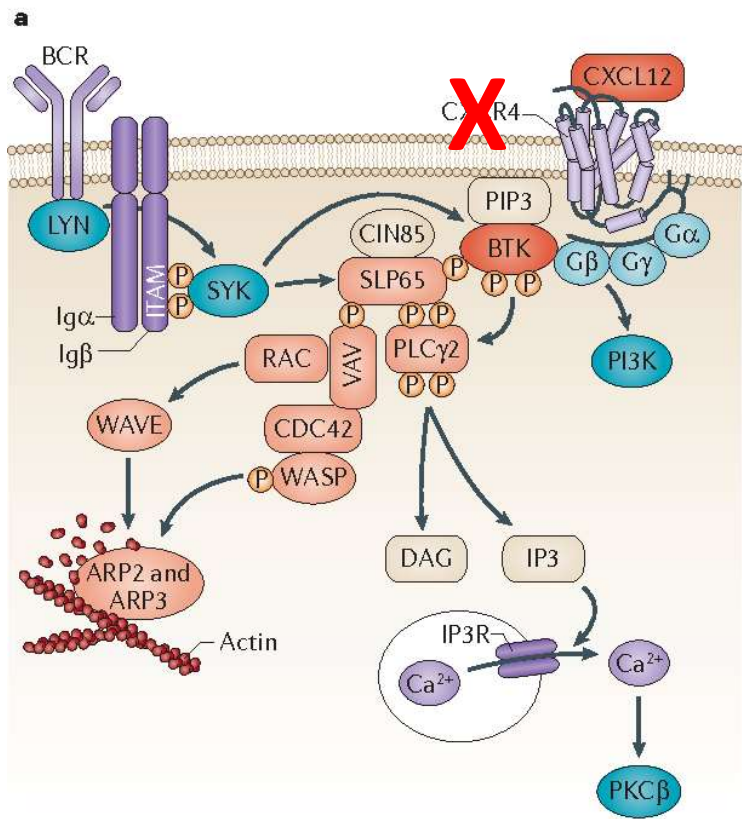
## Verhoogd BTK eiwit in Sjögren



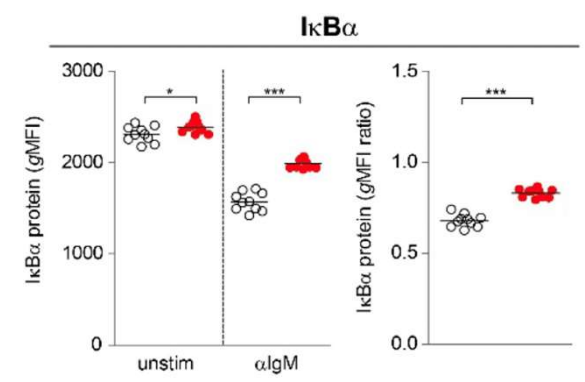
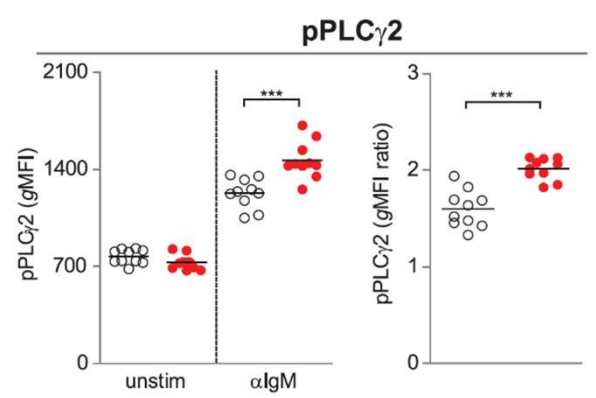
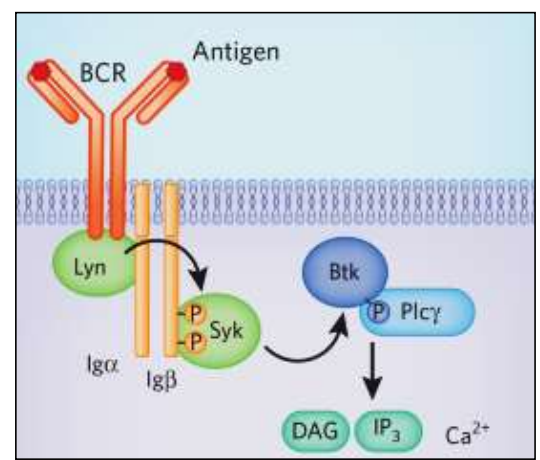
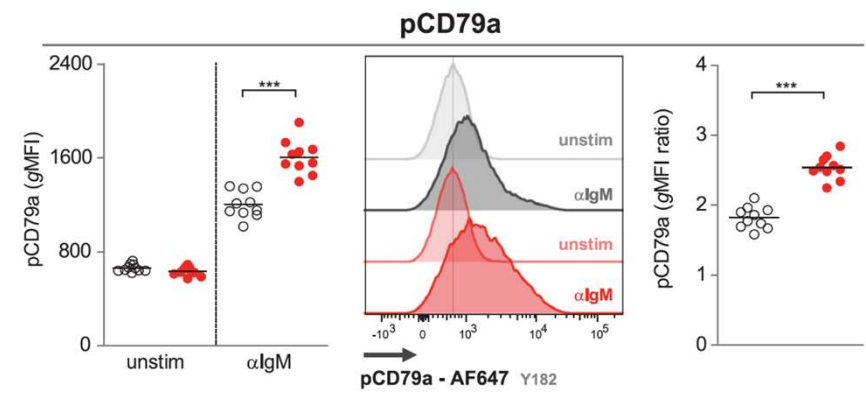
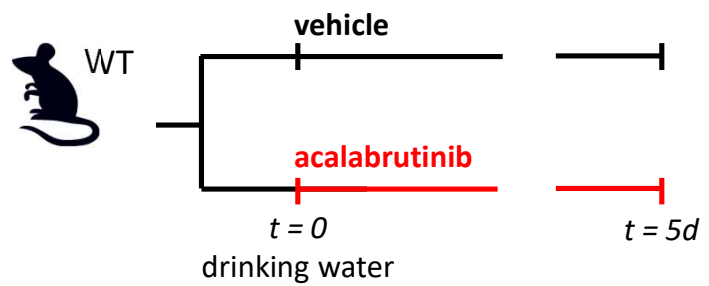
## Abatacept behandeling verlaagt BTK eiwit



# BTK inhibitie is heel effectief in CLL



# 'Rewiring' van BCR signalering na BTK inhibitie *in vivo*



# BTK inhibition in MS

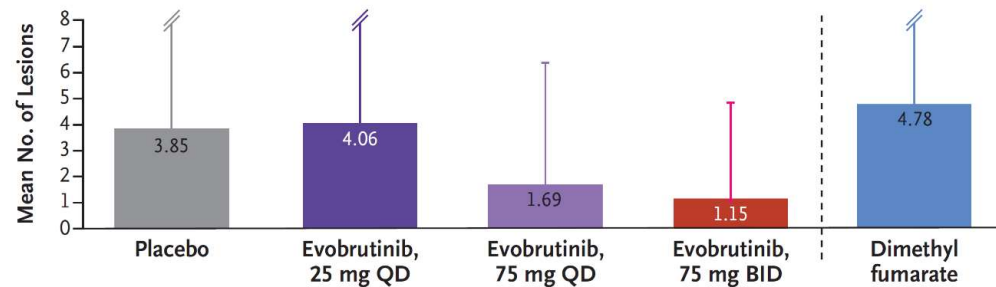
The NEW ENGLAND JOURNAL of MEDICINE

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\*

**A** Total No. of Lesions at Wk 12 through 24



|                                |                  |                  |                  |
|--------------------------------|------------------|------------------|------------------|
| Lesion rate ratio (95% CI)     | 1.45 (0.72–2.91) | 0.30 (0.14–0.63) | 0.44 (0.21–0.93) |
| Adjusted P value vs. placebo   | 0.32             | 0.005            | 0.06             |
| Unadjusted P value vs. placebo | 0.29             | 0.002            | 0.03             |



Cynthia Fehres  
Jeska de Vries-Bouwstra  
Rene Toes

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Rheumatology

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