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My thoughts about B cell depletion for Lupus Nephritis

Anne Davidson

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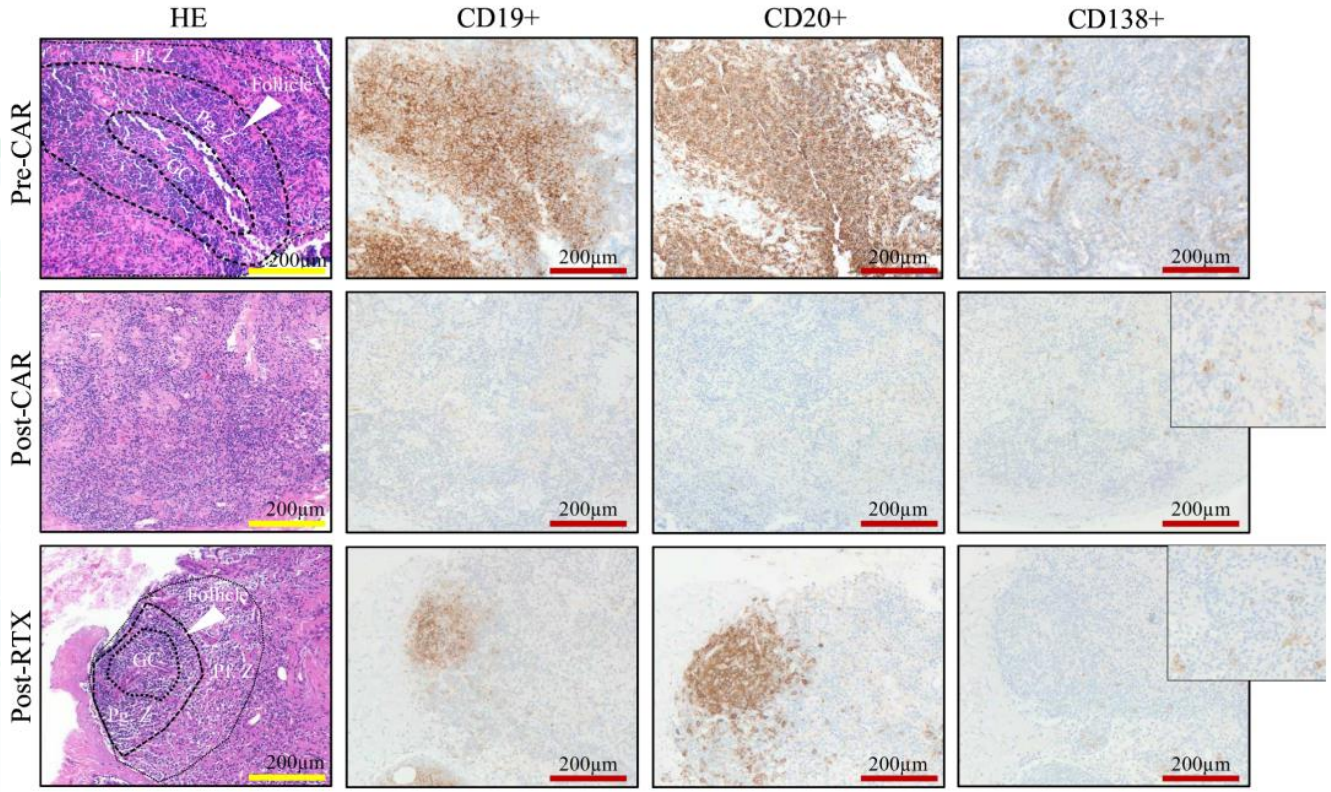
DISCLOSURES

- None

B CELL TARGETING

- Which B cells?
  - Do we need to include plasma cells?
- How best to target them?
  - Penetrating tissue with drugs
  - CD19, CD20, BAFF/APRIL, BCMA/CD38
    - BAFF inhibition targets B cell number and function
- Is there a reset and how long does it last?
- What are the consequences for other immune cells?
- Do the benefits outweigh the toxicities?
- Theoretical adverse immune consequences
  - Reconstitution of autoimmune repertoire in a high BAFF environment
  - Do we need to worry about a priming effect of cell death in affected tissues?



https://ard.bmj.com/content/annrheumdis/early/2024/09/11/ard-2024-226142.full.pdf

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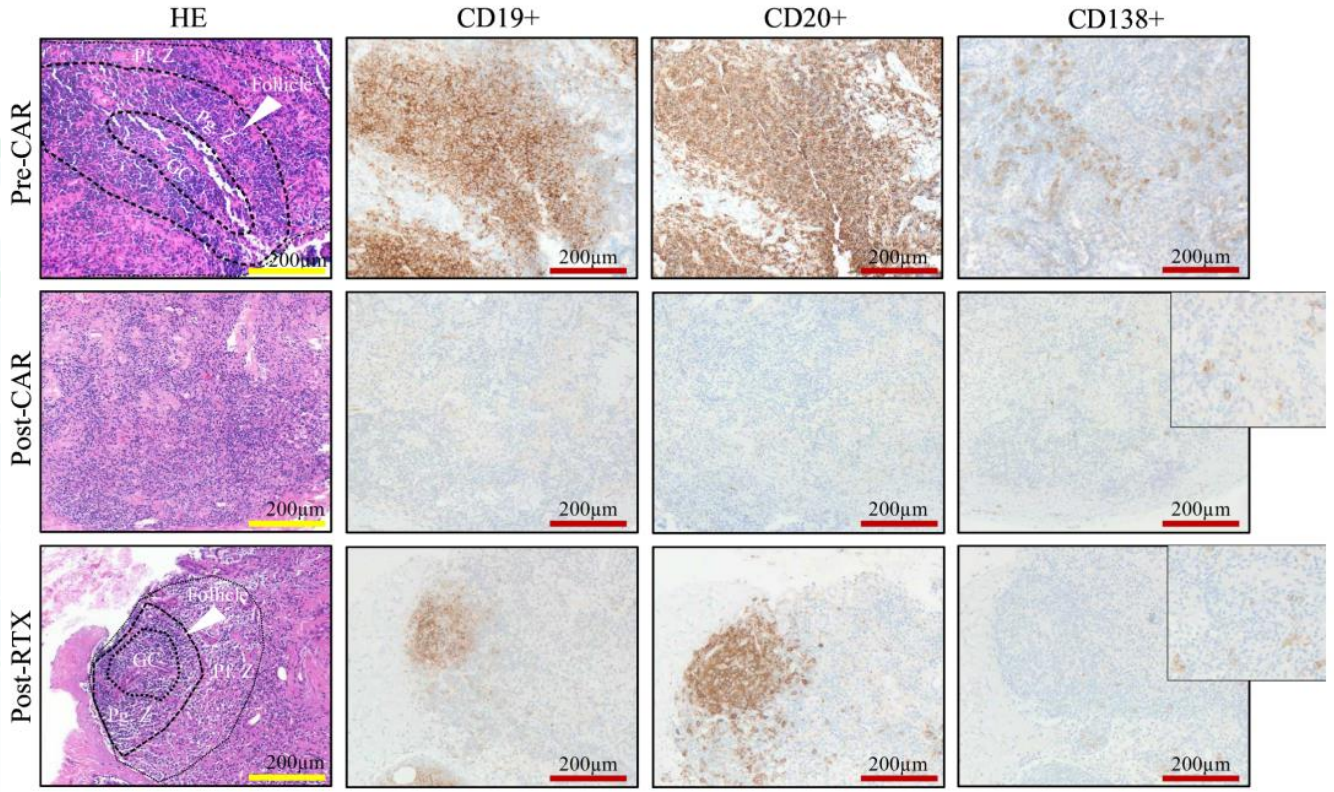

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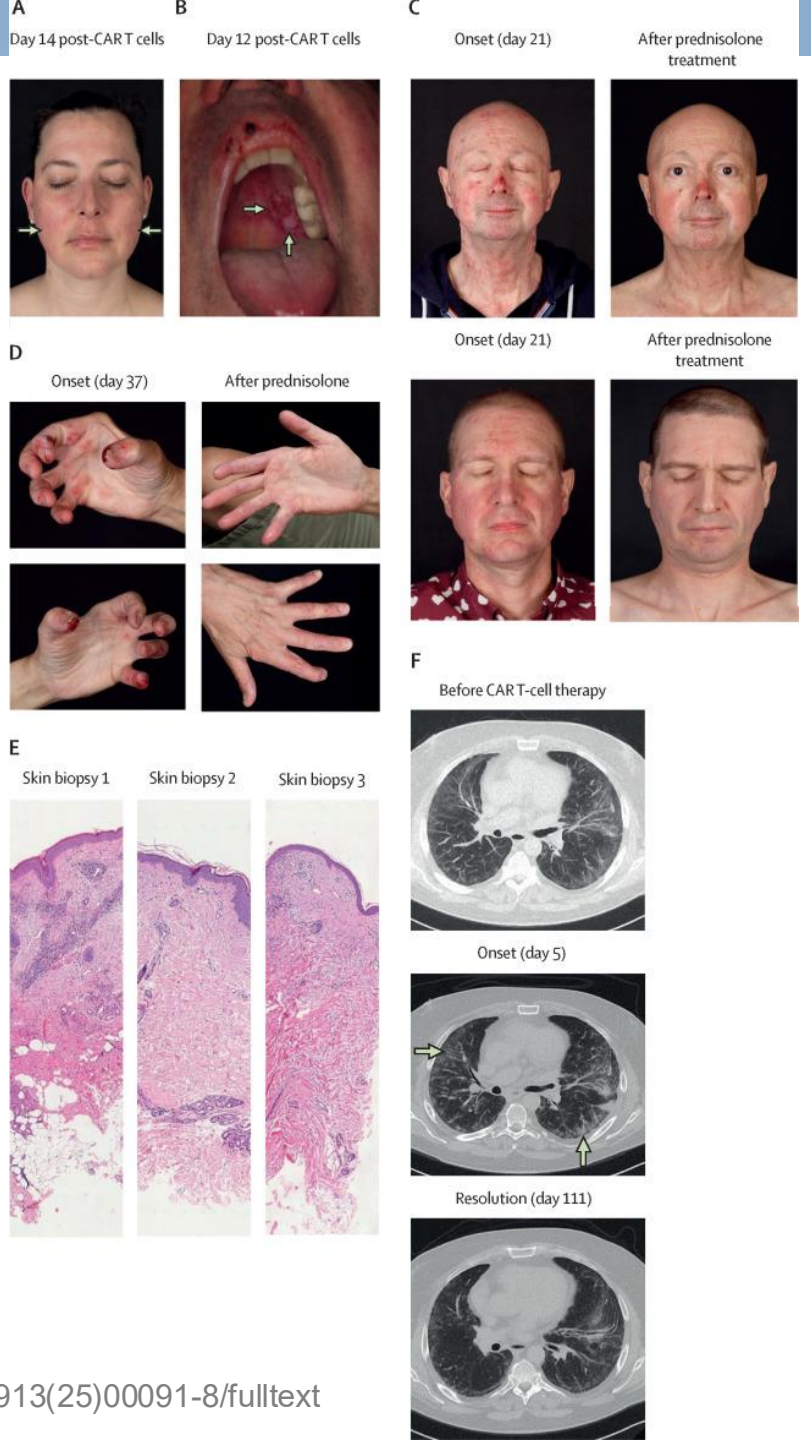
Clinical Questions

- Is conditioning needed?
- Why are some autoantibodies susceptible and others resistant?
  - Where are the plasma cell niches and how do we look for them?
- Can the CAR-T dose be repeated?
  - Are they more immunogenic in SLE?
- What causes LICATS and do we need to worry about priming effector cells?
- What is the advantage of BCMA-CAR? –
  - Do we need to specifically target plasma cells?
- How much damage is reversible?
- Is replacement Ig needed to prevent viral reactivation?
- What are the revaccination needs?



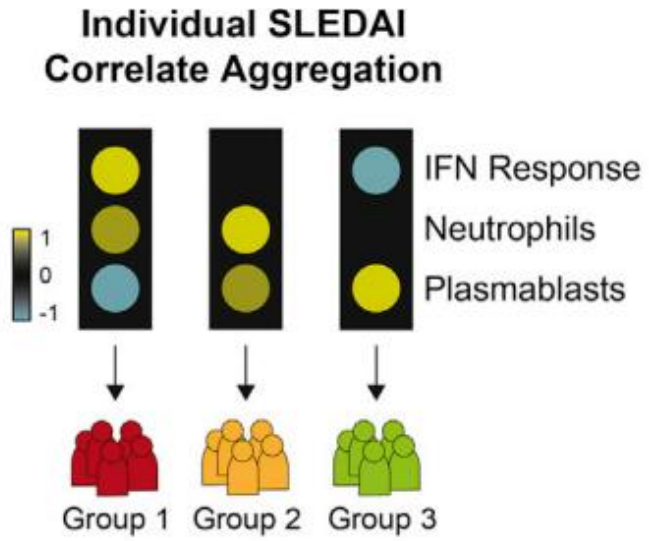
https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(25)00091-8/fulltext

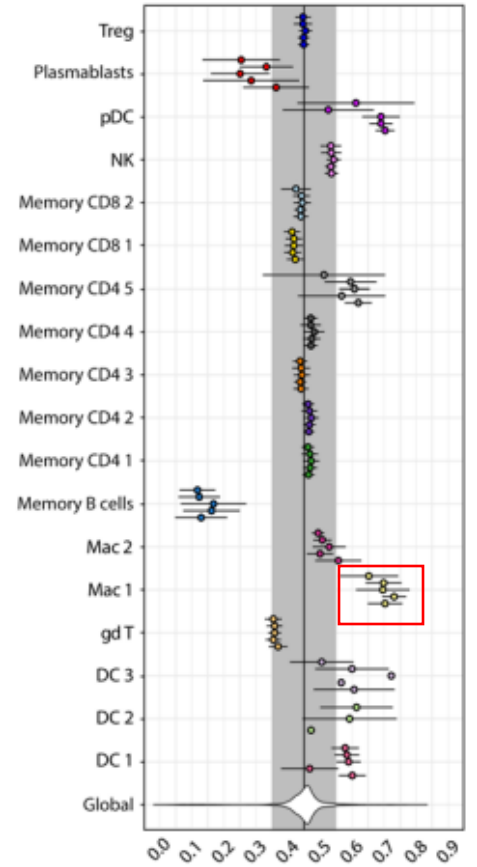
Biologic Questions

- Is every case of SLE B cell driven?

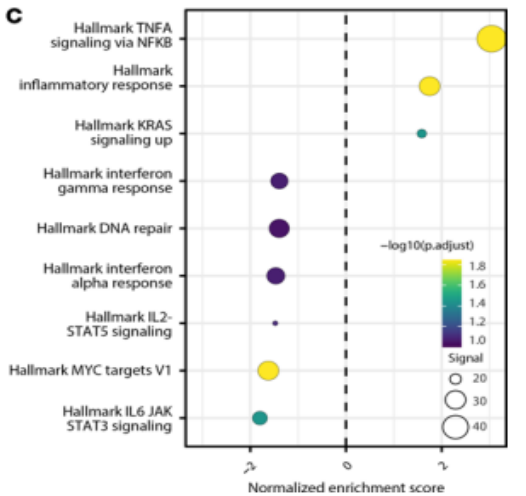
- Is there actually a reset?
  - Type 1 IFN signature
  - Reversal of epigenetic changes
  - Memory
  - Repertoire/autoreactivity of reconstituted cells
  - Genetic load unchanged
  - Microbiome

Banchereau et al., 2016, Cell 165, 551–565



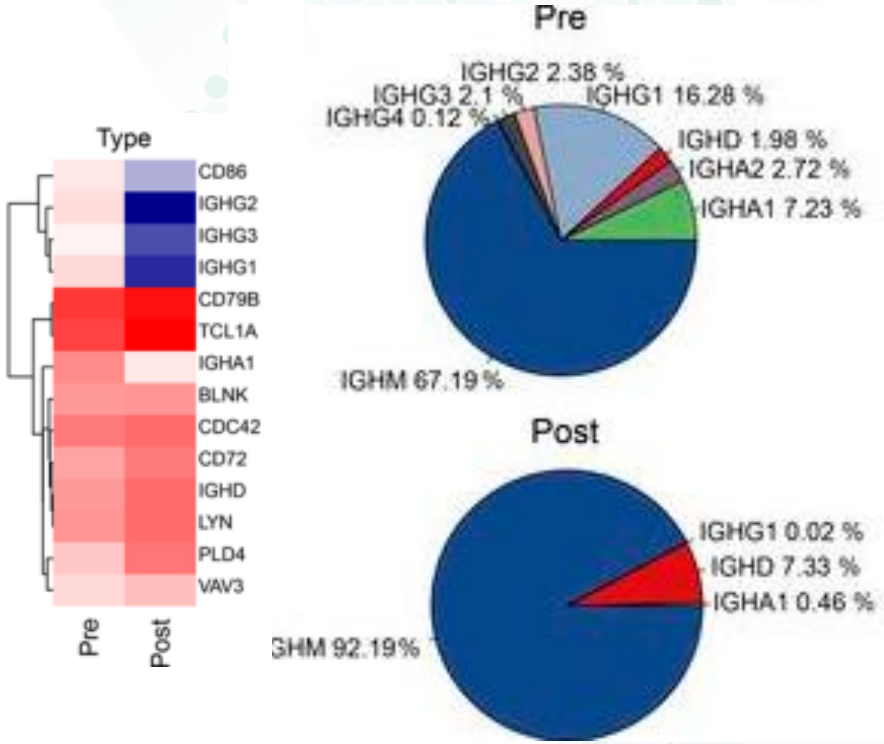


- What is the effect of B cell depletion on other cell types?
  - Increased (anti-inflammatory) CD16+ Macs
  - Decreased Tcm-Tfh, and Tem-Tph
  - Increased effector Tregs ?via TNF
  - Decreased memory CD8+CD20+ and central memory CD8+ T cells (but increased CD8 response to SARS-CoV2 vaccine)



J Clin Invest. 2025;135(9):e182790 https://doi.org/10.1172/JCI182790

B CELL REPERTOIRE



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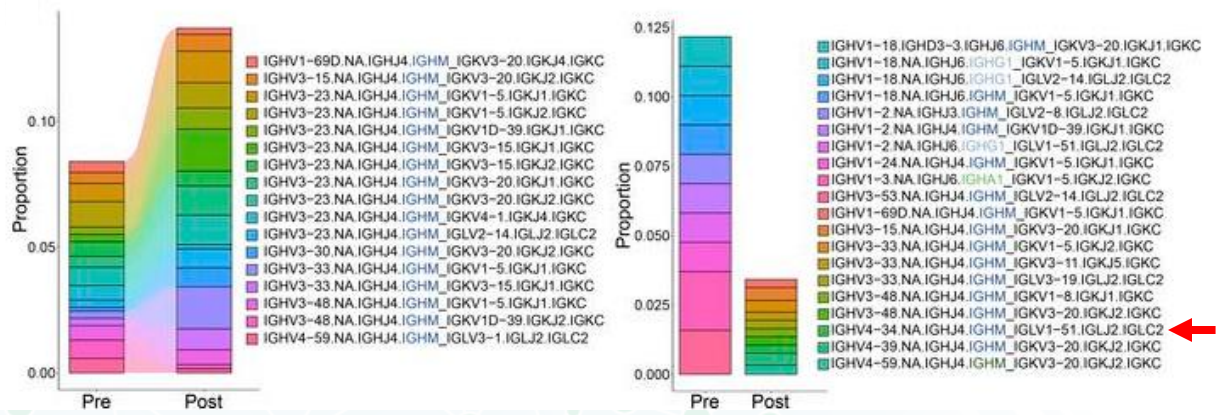
IgM Expanded

IgG Contracted



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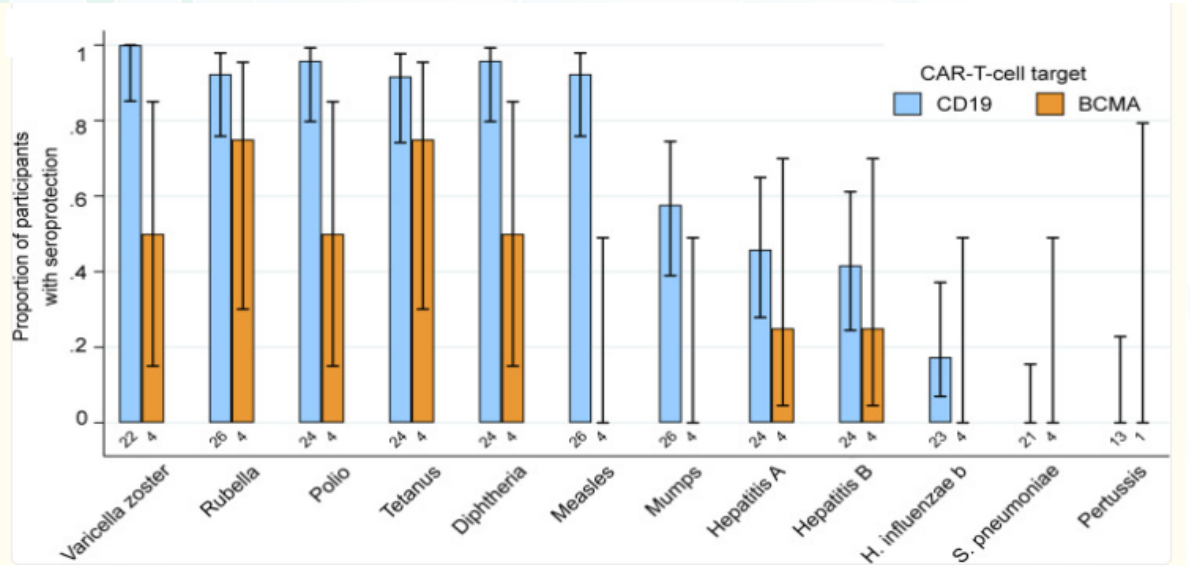


https://pmc.ncbi.nlm.nih.gov/articles/PMC8262349/

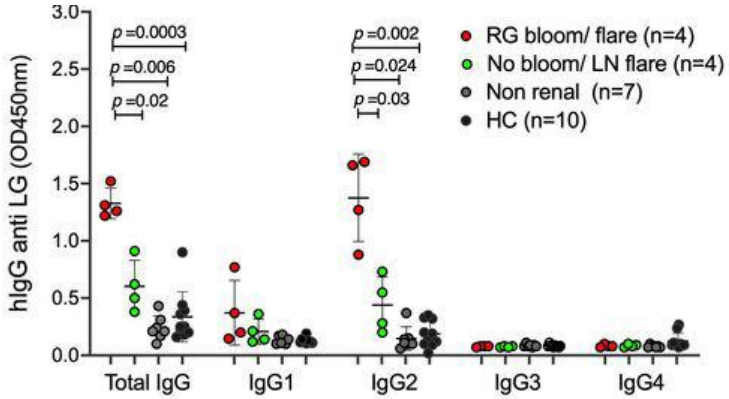
Biomarkers

Current markers of B cell depletion

- B cell numbers and subsets during recovery
- Antibody and autoantibody titers
- Organ B cell depletion (lymph node, tonsil)
  - Can this be done non-invasively? eg CD19 PET

Experimental validation of "reset"

- IFN signature
- ANA flow cytometry
- Altered T cell and macrophage function
- Reversal of B cell epigenetic changes
- Normalization of B cell repertoire
- Reversal of microbiome abnormalities
  - Ruminococcus species and antibodies
- Genetic correlates of good response
- Testing for immunogenicity



https://www.sciencedirect.com/journal/annals-of-the-rheumatic-diseases/vol/82/issue/10