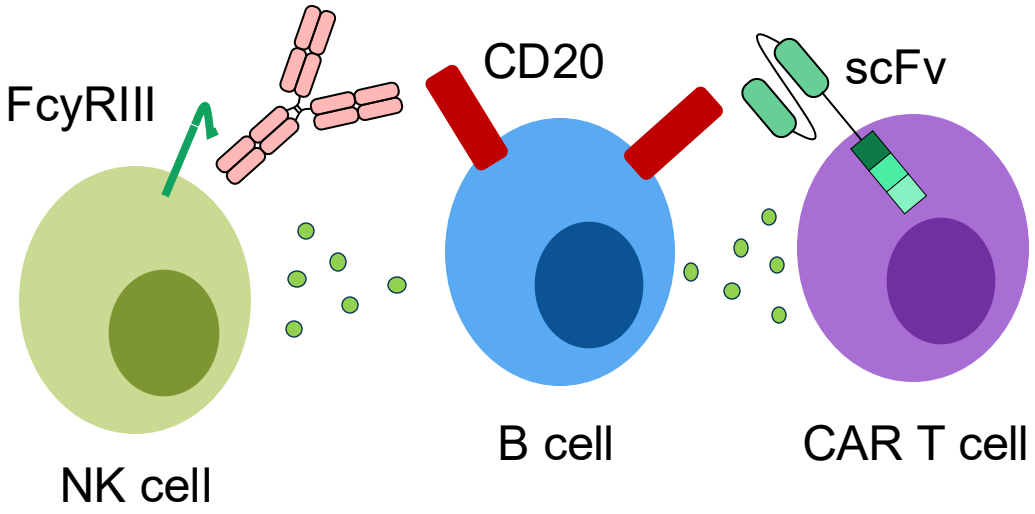
ANTIGEN-SPECIFIC B CELL TARGETING WITH A FOCUS ON MN

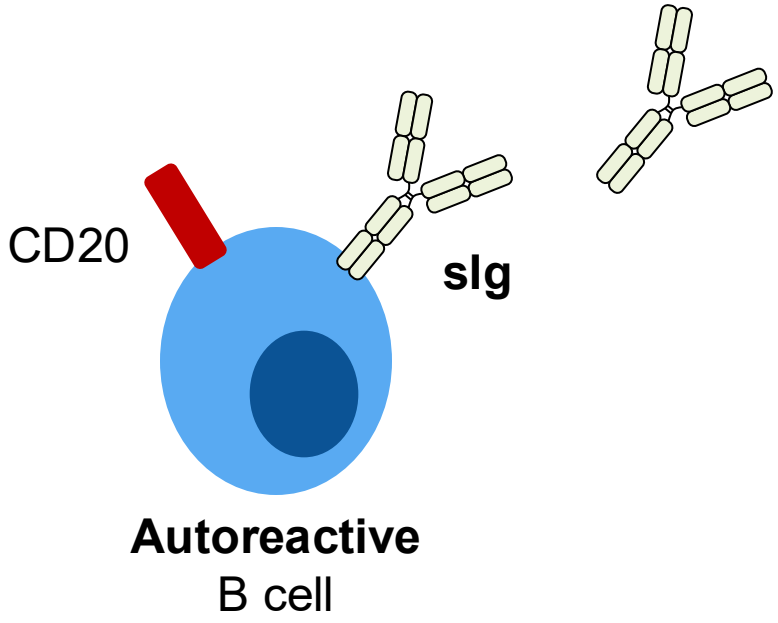
Nicola M. Tomas

DISCLOSURES

- Consultancy — Merida Bioscience
- Funding — Euroimmun, Novartis
- Honoraria — CSL Vifor, AstraZeneca
- Patents — 1878LU, EP2015/066881

ANTIGEN-SPECIFIC B CELL TARGETING – HOW AND WHY?

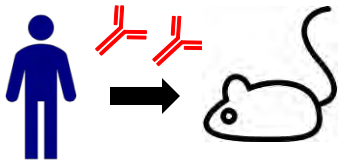


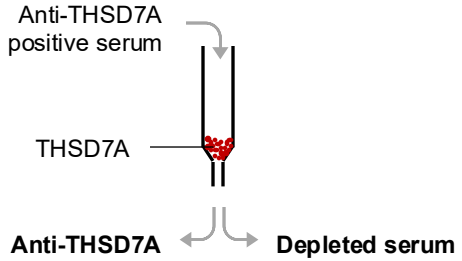


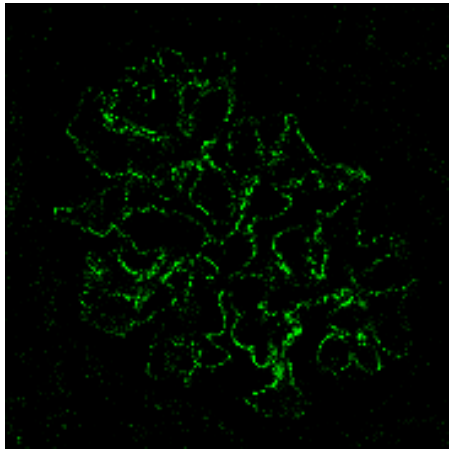
→ Exclusive depletion of autoantibody-producing cells

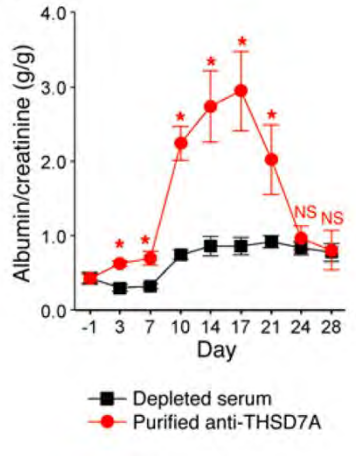
WHY MN?

Anti-THSD7A



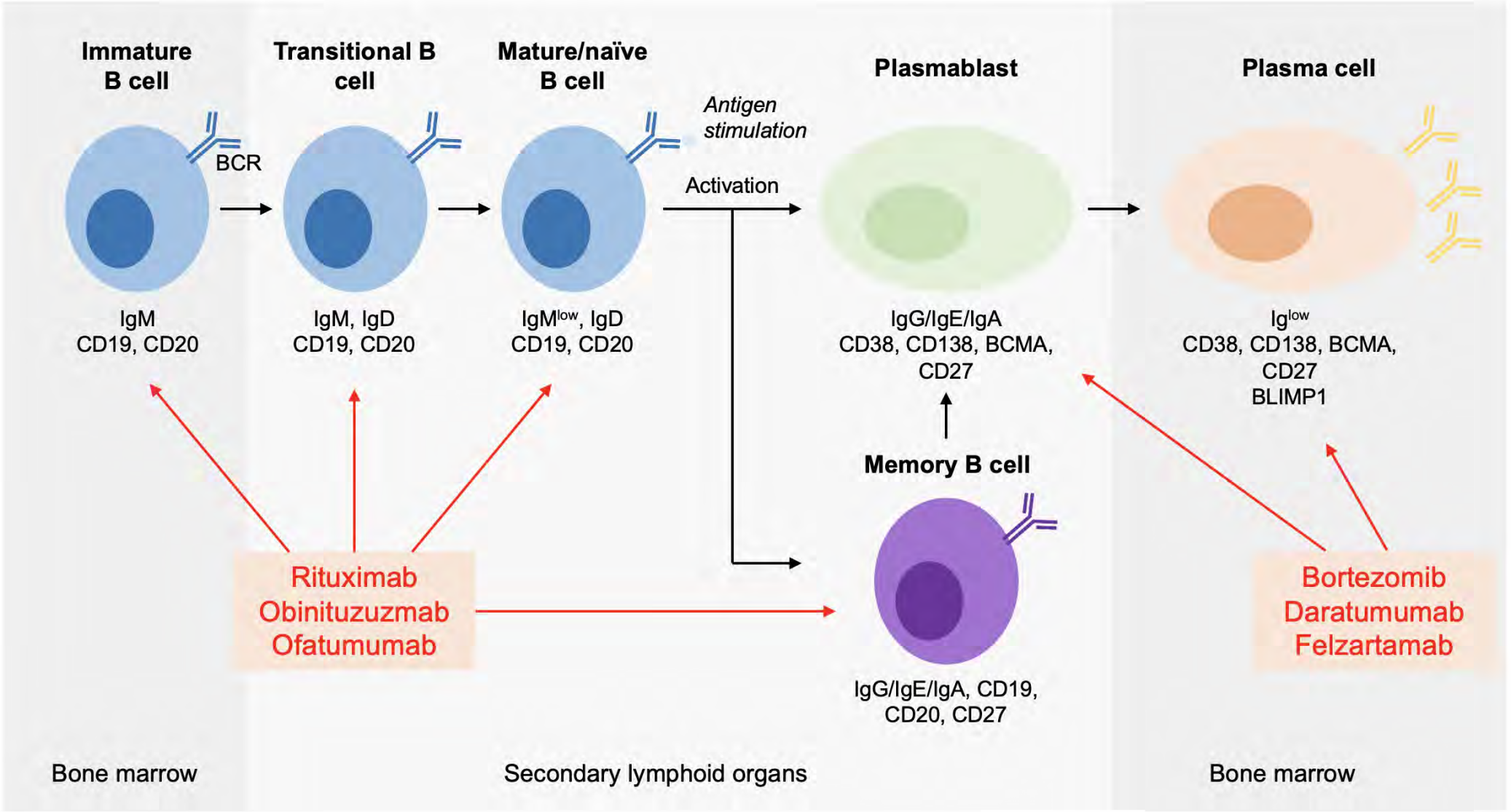






Tomas NM et al., **J Clin Invest (2016)**

ROLE OF BROAD B CELL DEPLETION IN MN



ROLE OF BROAD B CELL DEPLETION IN MN - RITUXIMAB

Table 1: Comparison of complete and partial responses for MN patients from RCTs.

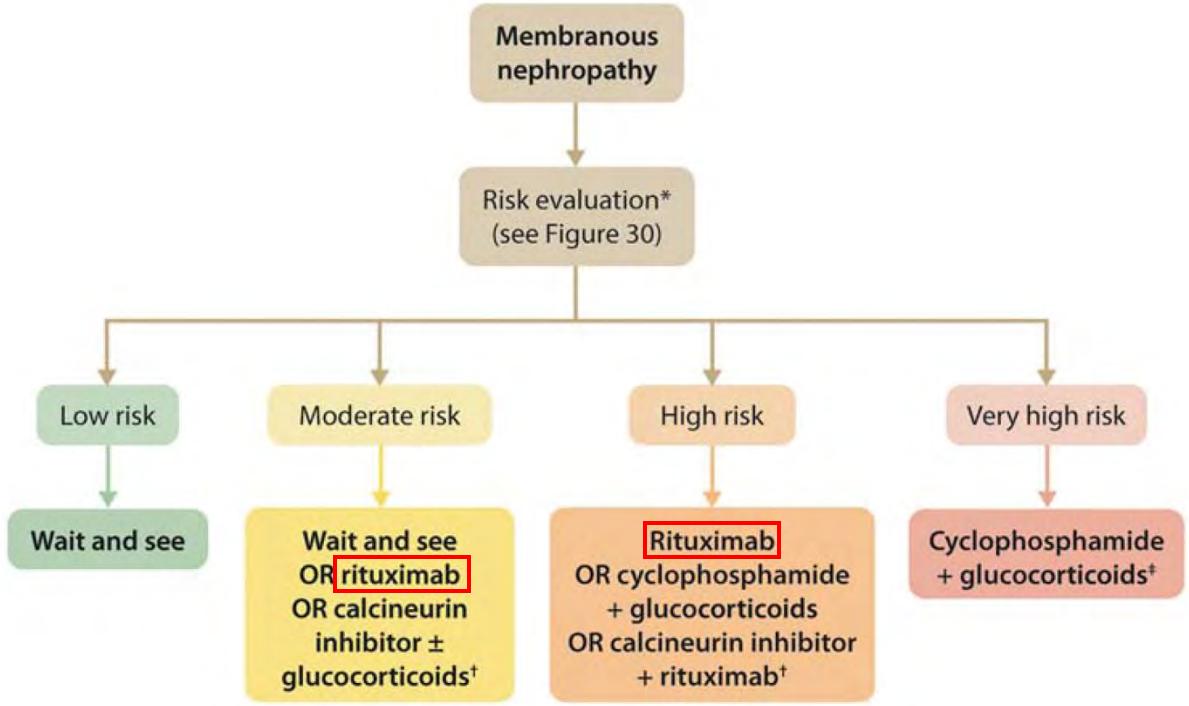
RCT comparison	Year	eGFR (ml/min/1.73 m^2) (SD)	Proteinuria (g/24 h) (SD/IQR)	Anti-PLA2R antibody (RU/ml) (IQR)	CR 12 months	CR/PR 12 months	CR 24 months	CR/PR 24 months	Serious adverse events—no. of patients
RI-CYCLO [6] RTX (2 g) vs. CTX	2021	84 (24)	6.0 (4–10)	58 (43–86)	RTX: 6/37 (16%) CTX: 12/37 (32%)	RTX: 23/32(62%) CTX: 27/37 (73%)	RTX: 11/26 (42%) CTX: 11/31 (35%)	RTX: 22/26 (85%) CTX: 25/31 (81%)	RTX: 7 (19%) CTX: 5 (14%)
STARMEN [7] CNI + RTX (1 g) vs. CTX	2021	80 (24)	7.4 (5.2–11.5)	80 (44–149)	CNI + RTX: 4/43$^+$ (9%) CTX:14/43 (33%)	CNI + RTX: 22/43 (51%) CTX: 34/43 (79%)	CNI + RTX: 11/43 (26%) CTX: 26/43 (60%)	CNI + RTX: 25/43 (58%) CTX: 36/43 (84%)	CNI + RTX: 6 (14%) CTX: 8 (19%)
MENTOR [8] RTX (4 g) vs. cyclosporin	2019	85 (30)	8.9 (6.8–12.3)	409^{++} (163–834)	RTX: 9/65 (13.8%) CNI: 3/64 (4.6%)	RTX: 39/65 (60%) CNI: 34/65 (52%)	RTX: 23/65 (35.4%) CNI: 0/65 (0%)	RTX: 39/65 (60%) CNI: 13/65 (20%)	RTX: 11 (17%) CNI: 20 (31%)
GEMRITUX [5] RTX (1.5 g) vs. supportive	2017	67 (55–83)*	7.6 (4.5–10.3)	40.5 (0–275)	NA	NA	NA	NA	RTX: 6 (16%)$^\Phi$ Supp: 5 (15%)

→ 30-40% of complete, and 60-85% of complete or partial remission rates at 24 months using rituximab

Zand and Fervenza, **Clin Kidney J** (2023)

ROLE OF BROAD B CELL DEPLETION IN MN - RITUXIMAB

Low risk	Moderate risk	High risk	Very high risk
• Normal eGFR, proteinuria <3.5 g/d and serum albumin >30 g/l OR • Normal eGFR, proteinuria <3.5 g/d or a decrease >50% after 6 months of conservative therapy with ACEi/ARB	• Normal eGFR, proteinuria >3.5 g/d and no decrease >50% after 6 months of conservative therapy with ACEi/ARB AND • Not fulfilling high-risk criteria	• eGFR <60 ml/min/1.73 m²* and/or proteinuria >8 g/d for >6 months OR • Normal eGFR, proteinuria >3.5 g/d and no decrease >50% after 6 months of conservative therapy with ACEi/ARB AND at least one of the following: • Serum albumin <25 g/l† • PLA2Rab >50 RU/ml‡ • Urinary α_1-microglobulin >40 µg/min • Urinary IgG >1 µg/min • Urinary β_2-microglobulin >250 mg/d • Selectivity index >0.20§	• Life-threatening nephrotic syndrome OR • Rapid deterioration of kidney function not otherwise explained

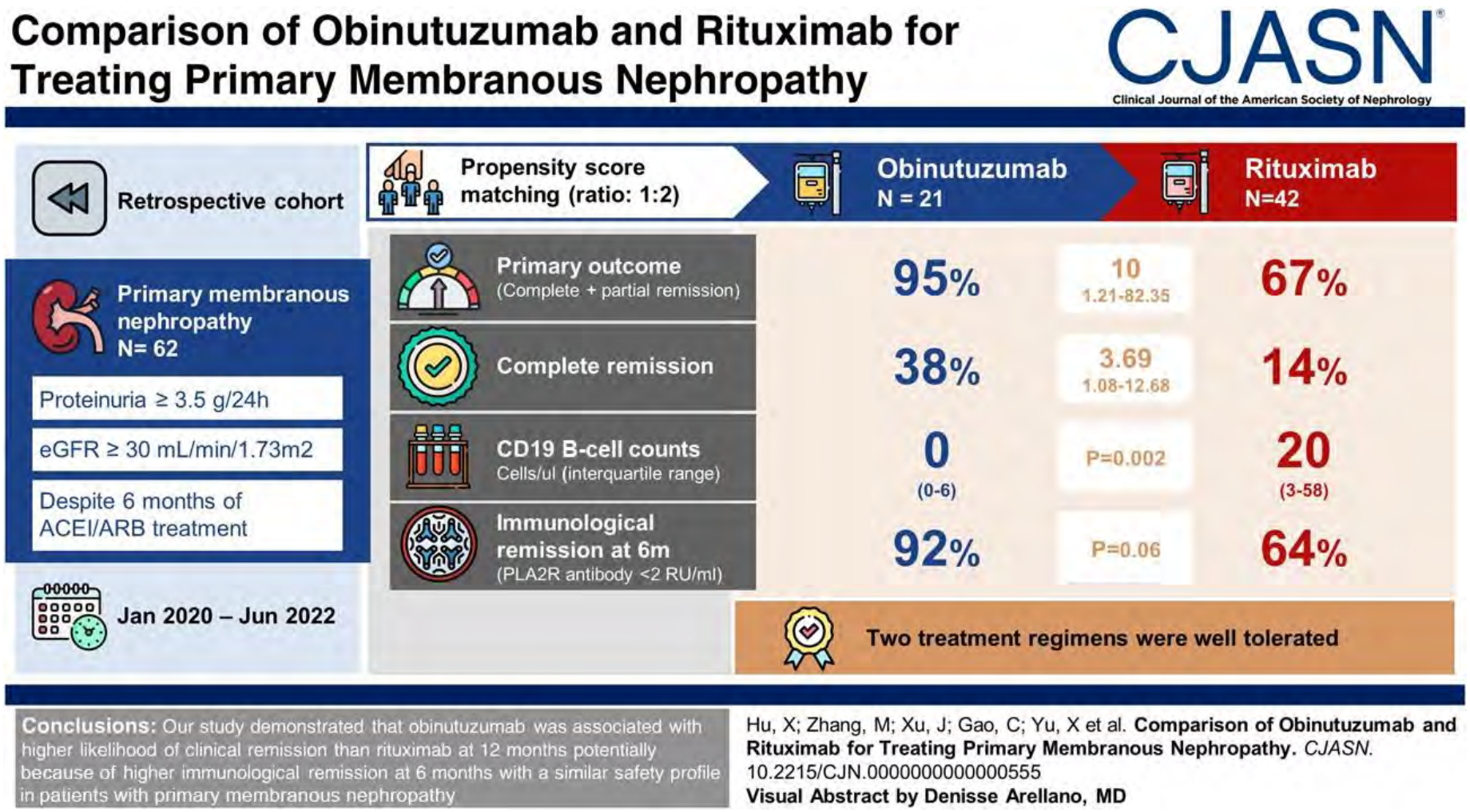


KDIGO Practice Guidelines 2021 for the Management of Glomerular Diseases

Role of broad B cell depletion in MN – Obi/Ofa

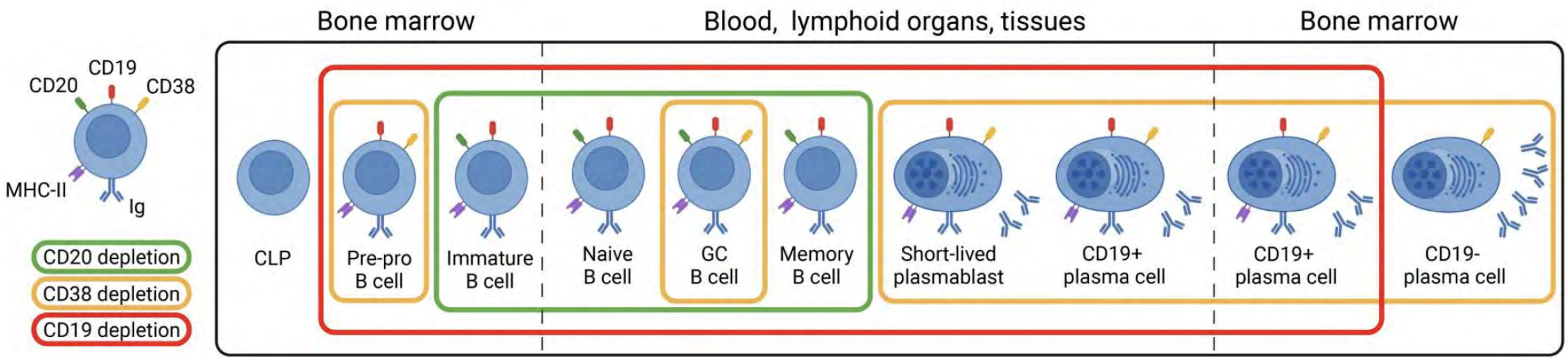
	Rituximab	Obinutuzumab	Ofatumumab
Type	Chimeric m/h IgG1	Humanized IgG1	Fully human IgG1
CD20 binding site	Large extrac. loop	Large loop (other than Rtx)	Small and large extrac. loops
CDC	Strong	Moderate	Very strong
ADCC	Moderate	Very strong (glycoengineered)	Moderate
ADCP	Moderate	High	Low

ROLE OF BROAD B CELL DEPLETION IN MN – OBI/OFA



Hu X et al., **CJASN** (2024)

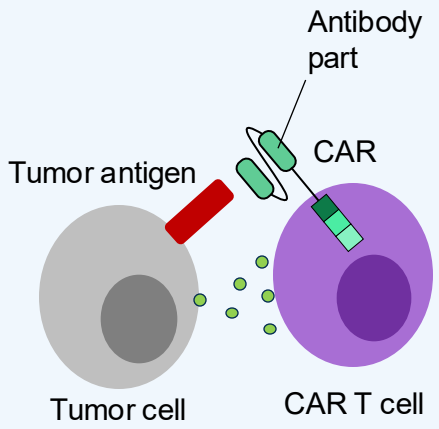
ANTIGEN-SPECIFIC B CELL DEPLETION



Suan D et al., **J Immunol** (2025)

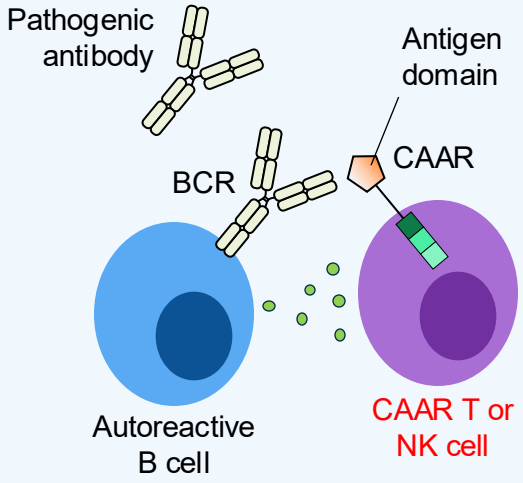
PRINCIPLES OF ANTIGEN-SPECIFIC TARGETING

Chimeric antigen receptor (CAR) principle



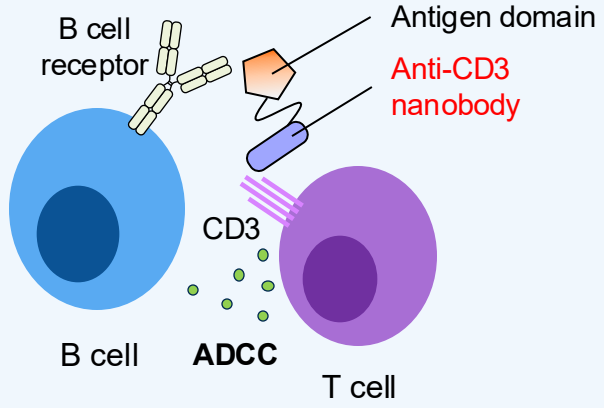
Elimination of tumor cell

Chimeric autoantibody receptor (CAAR) principle



Elimination of pathogenic cells

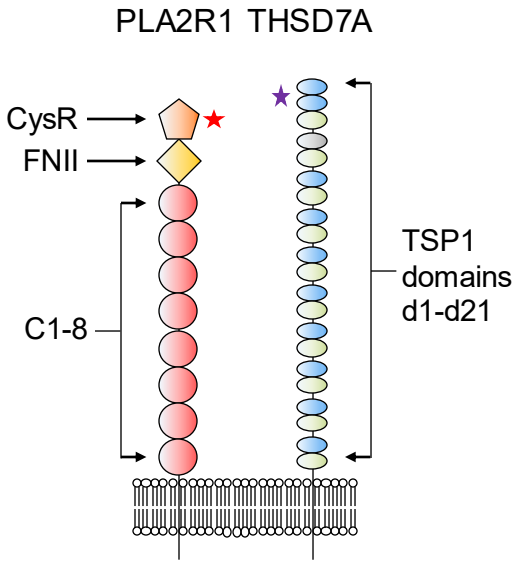
Bispecific T cell engager (BiTE) principle



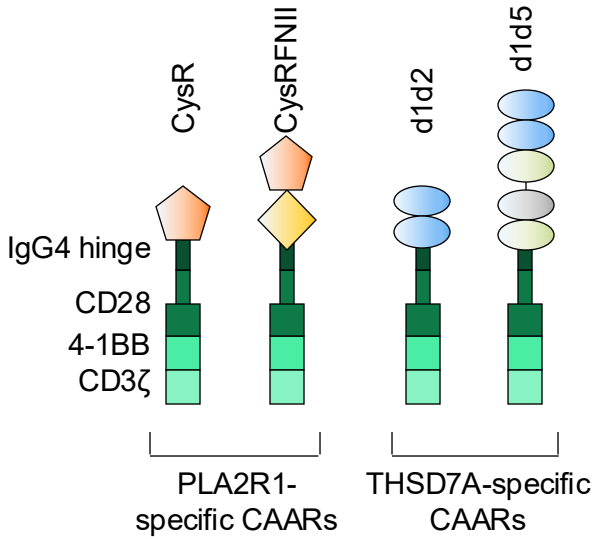
Elimination of pathogenic cells

CAAR T AND NK CELLS

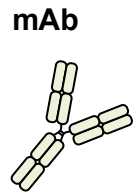
MN antigens

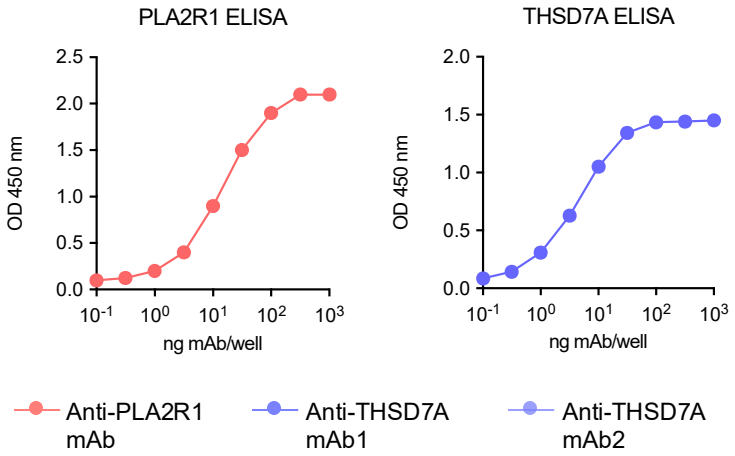


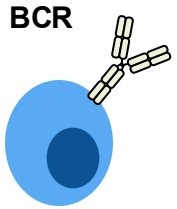
Set of CAARs

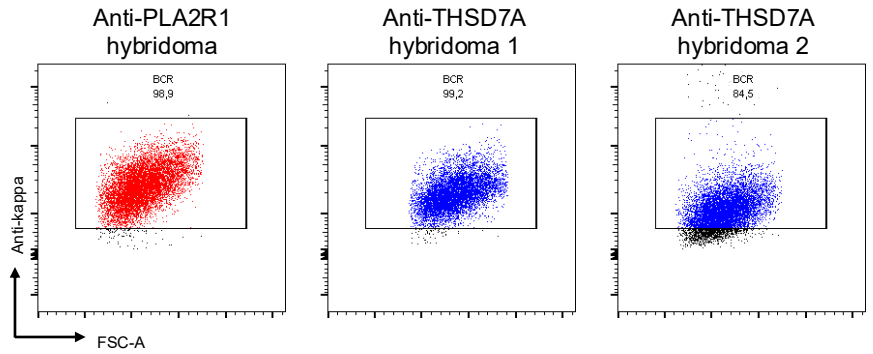


Hybridoma generation





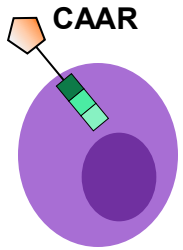


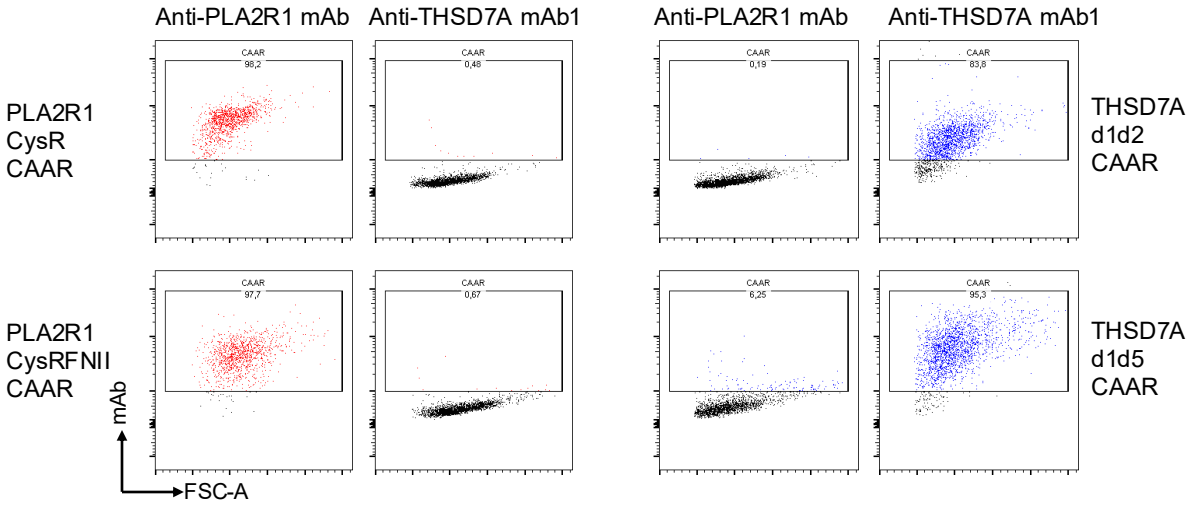


Seifert L et al., **Kidney Int** (2024)

CAAR T AND NK CELLS

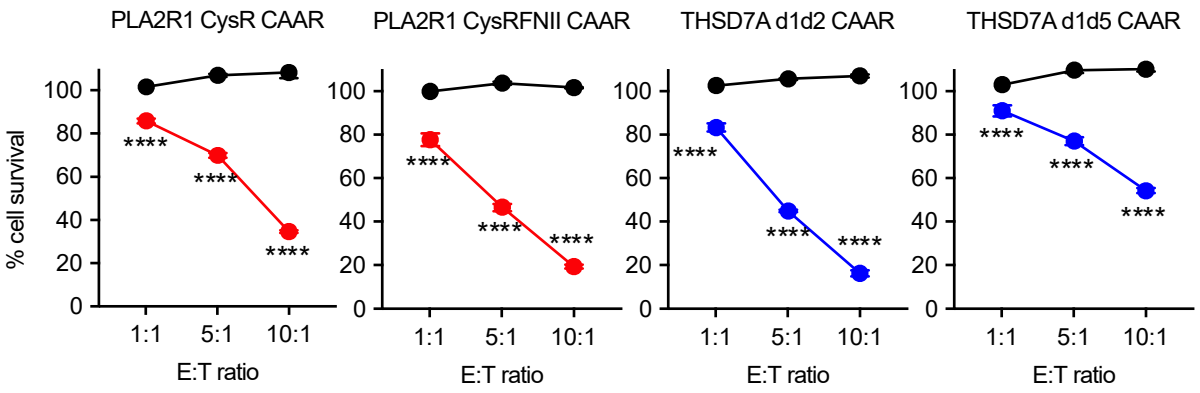
CAAR surface staining



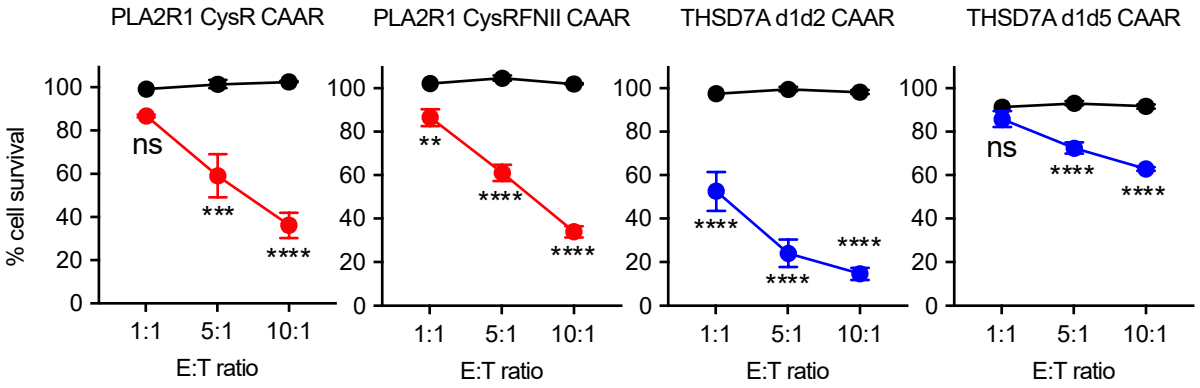


Seifert L et al., **Kidney Int** (2024)

Primary human CAAR T cells



CAAR NK-92 cells



Control hybridoma | Anti-PLA2R1 hybridoma | Control hybridoma | Anti-THSD7A hybridoma