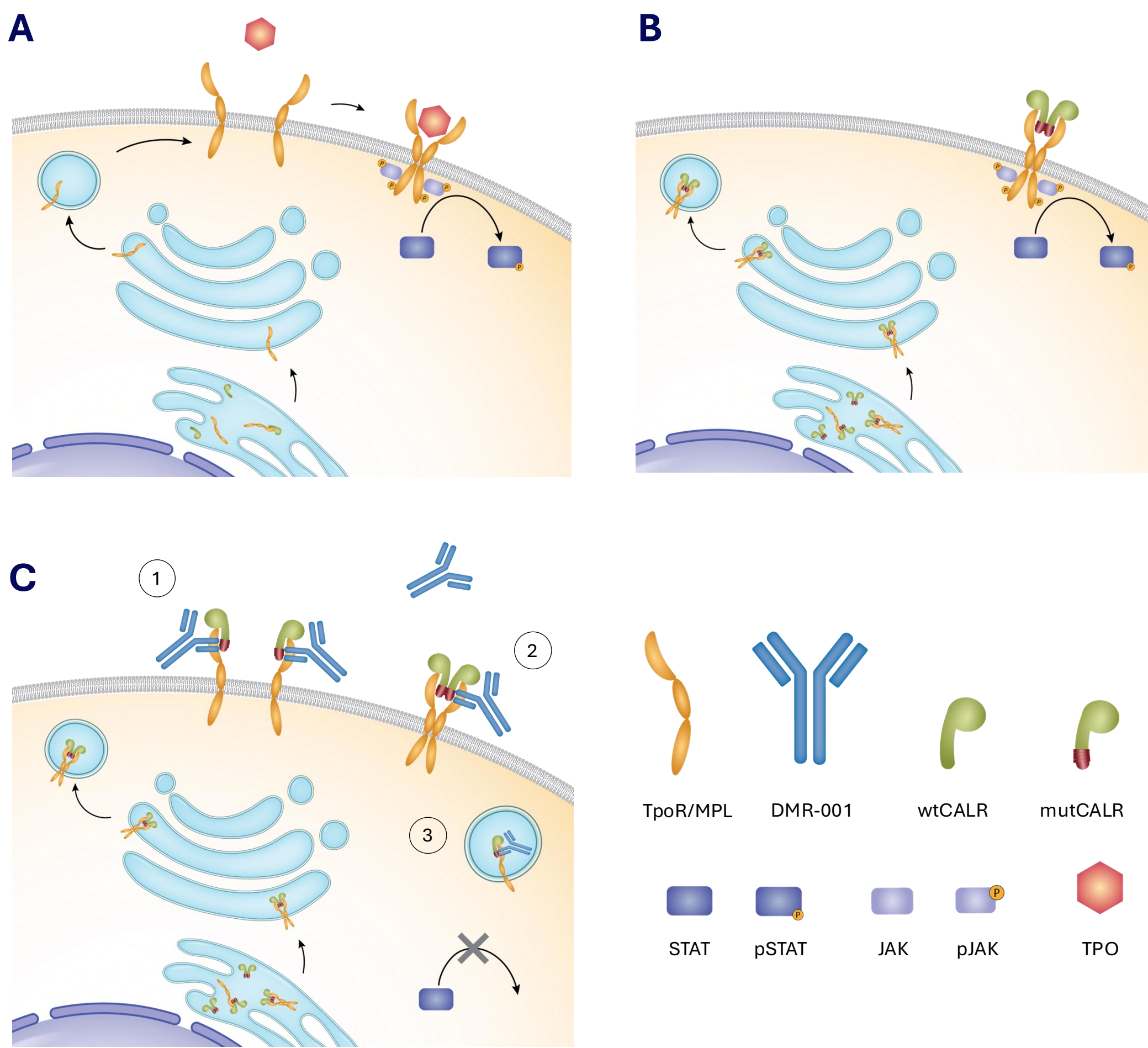


Introduction

- Essential thrombocythemia (ET) and myelofibrosis (MF) are myeloproliferative neoplasms (MPNs) often driven by frameshift mutations in calreticulin (CALR).
- CALR mutations are found in ~25% of ET cases and ~35% of MF cases.
- CALR mutations produce a neomorphic mutant C-terminus that permits binding to and constitutive activation of the thrombopoietin receptor (TpoR), which drive a range of disease symptoms from increased risk of thrombosis to severe, life-threatening bone marrow fibrosis. The most common mutations in CALR are Type 1 (del52) and Type 2 (ins5).
- Disease modifying treatments selectively targeting mutant CALR (mutCALR) are needed to improve patient outcomes.
- Here we describe the discovery and preclinical activity of DMR-001, a novel, selective, anti-mutCALR mAb with high affinity and anti-proliferative potency against both Type 1 and Type 2 mutations and optimized PK properties.

Illustration 1:



(A) Normal function of wild-type calreticulin (wtCALR), with TPO-dependent activation of TpoR. (B) Ligand-independent signaling in the context of mutCALR binding to TpoR. (C) Inhibition of mutCALR signaling by DMR-001 via three possible mechanisms: 1) disruption of TpoR dimer, 2) inhibition of surface tetramer signaling, or 3) internalization of complex

Aims

To engineer and characterize an Fc-null, half-life extended mutCALR-targeted mAb with activity against both Type 1 and Type 2 mutCALR variants and drug-like properties enabling convenient clinical dosing.

Methods

Antibody discovery campaigns utilized engineered phage and yeast display libraries to identify clones specific to the mutCALR epitope of the C-terminus. Target specificity was increased through affinity maturation and iterative rounds of negative selection against wtCALR and positive selection against Type 1 and Type 2 mutCALR antigens. Antibodies were evaluated for inhibition of proliferation in Type 1 and Type 2 Ba/F3 cell lines to further refine potency.

Results

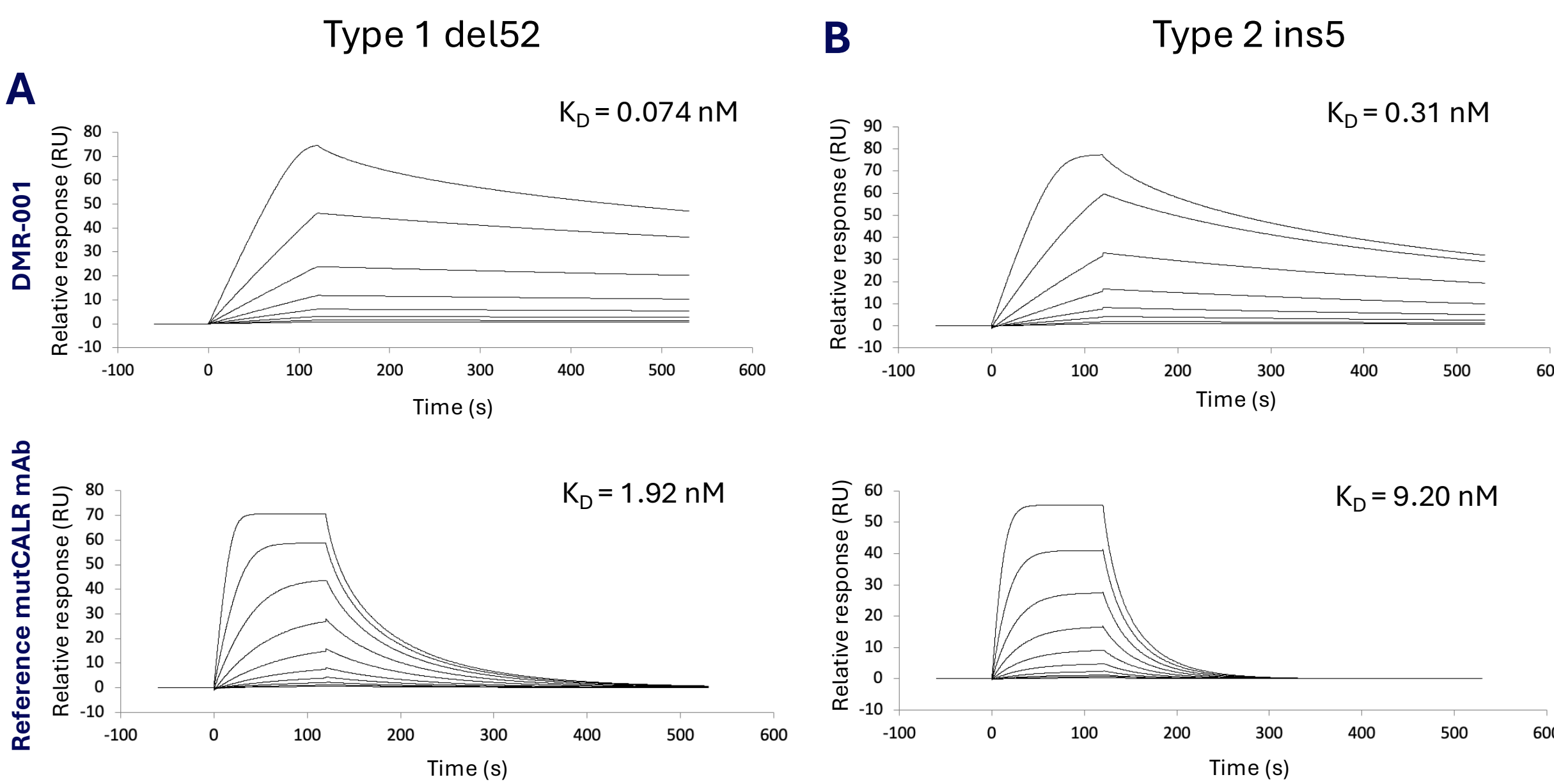
DMR-001 shows significantly improved Type 1 and Type 2 mutCALR affinity and PK properties predicted to enable less frequent SC dosing

	DMR-001	mutCALR reference mAb
Specificity	CALR mutant specific	CALR mutant specific
Affinity to Type 1 del52 mutCALR (K _D)	0.074nM	1.92nM
Affinity to Type 2 ins5 mutCALR (K _D)	0.31nM	9.20nM
Fc status	Effector null	Effector null
Non-Human Primate PK half life (days)	15	3.1
Expected Ph1 Dosing	SC Q4W	IV Q2W

Desired profile Insufficient

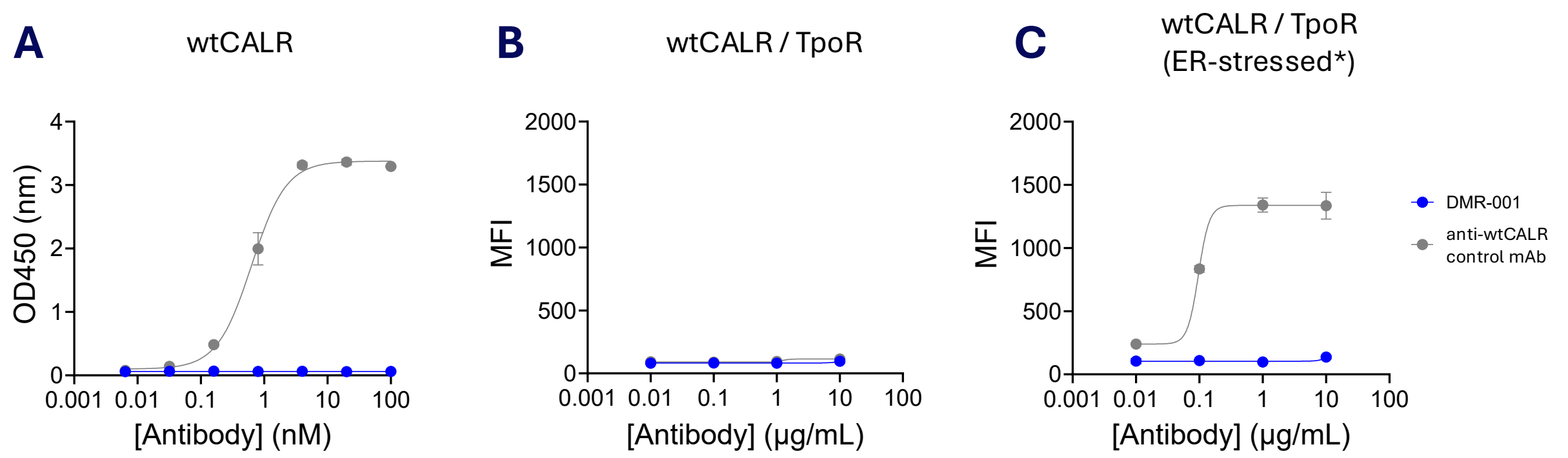
Reference mutCALR mAb produced recombinantly based on U.S. patent application US20230272055A1. All comparative studies of DMR-001 and mutCALR reference mAb were conducted in parallel under the same conditions.

Figure 1: DMR-001 shows higher affinity and slower off rate to Type 1 and Type 2 mutCALR compared to reference mutCALR mAb



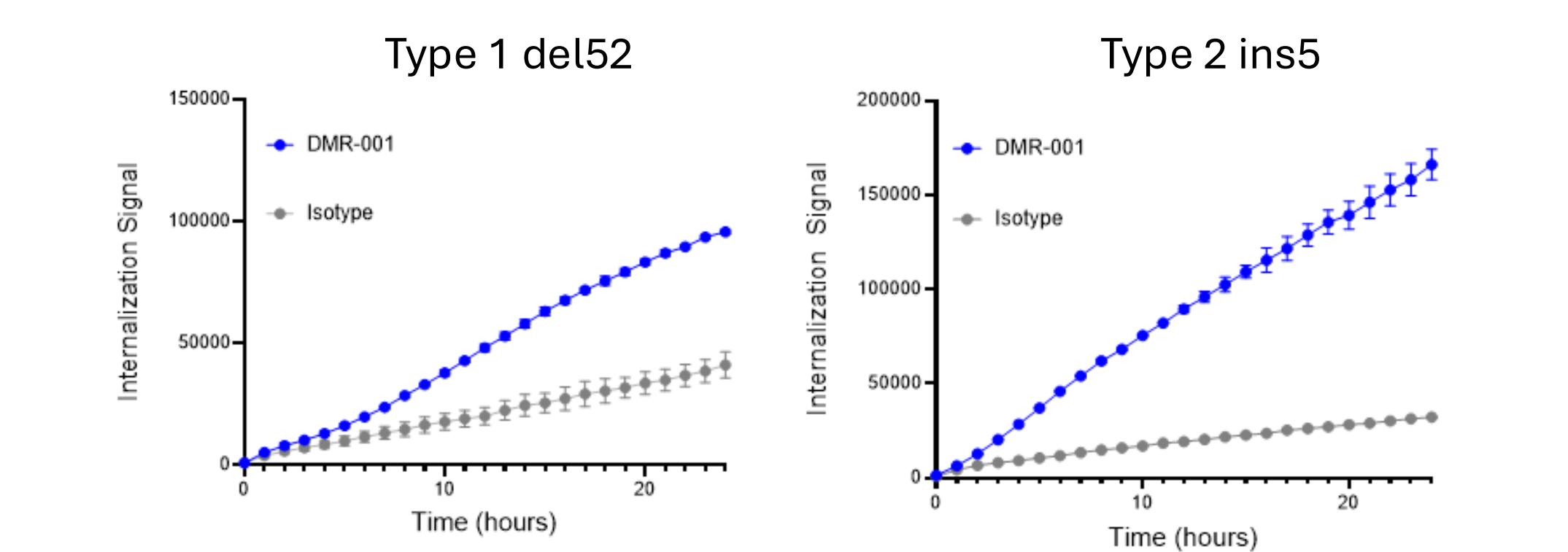
Binding affinity (K_D) of antibodies to mutCALR Type 1 del52 (A) & Type 2 ins5 (B) mutCALR proteins was determined by surface plasmon resonance (SPR) using a Biacore 8K SPR system (Cytiva). A 1:1 kinetic binding model was utilized to determine the dissociation rate constant (K_D). Exposure ranges tested in Type 1 del52 were DMR-001 0.02–2.5 nM and mutCALR reference mAb 0.02–10 nM (A), and in Type 2 ins5 were DMR-001 0.04–5 nM and mutCALR reference mAb 0.04–20 nM (B). Data shown are fits of the raw sensorgrams.

Figure 2: DMR-001 shows no off-target binding to wtCALR



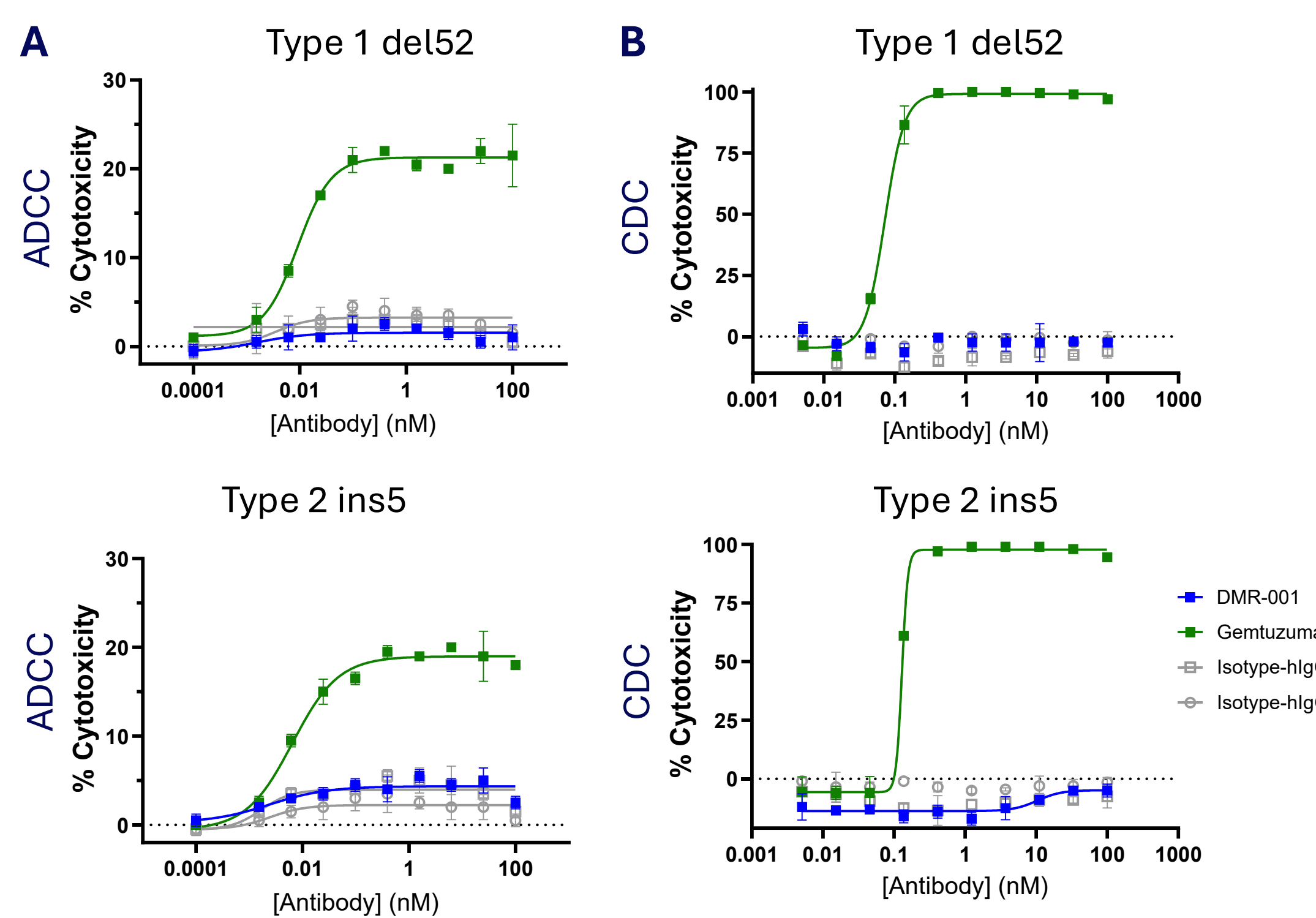
A) An ELISA assay demonstrates no binding of DMR-001 to wtCALR. B, C) DMR-001 binding was assessed against wtCALR expressed in Ba/F3-TpoR cells. Thapsigargin treatment induces ER stress (C), which translocates wtCALR to the cell surface. DMR-001 did not bind to cell-associated wtCALR. Control wtCALR antibody was included in (A-C).

Figure 3: DMR-001 induces internalization of surface Type 1 and Type 2 mutCALR



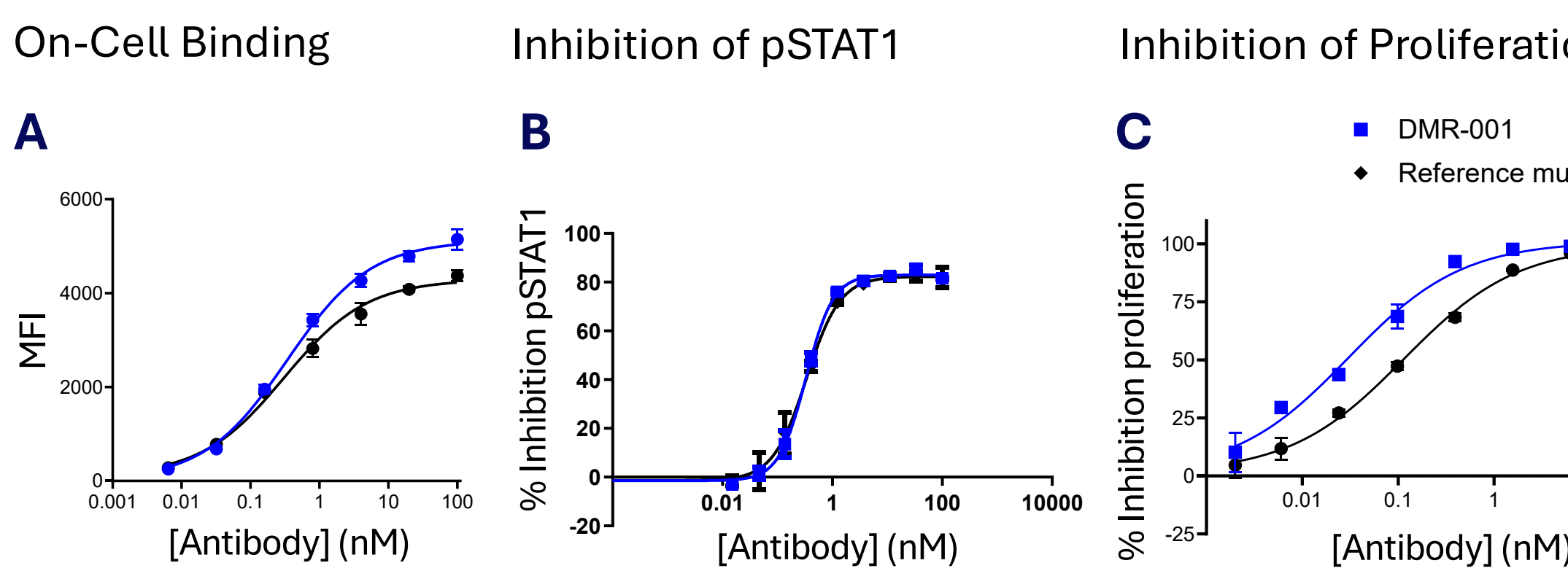
Ba/F3-TpoR cells expressing either Type 1 del52 mutCALR or Type 2 ins5 mutCALR were used to assess antibody internalization. Test antibodies were mixed with a pH-sensitive dye that is highly fluorescent in the low pH environment of lysosomes, which is a readout of internalization. Images were acquired every hour for 24 hours in an Incucyte. Internalization signal was measured as the integrated fluorescent intensity per well normalized to cell confluence.

Figure 4: DMR-001 does not cause ADCC or CDC



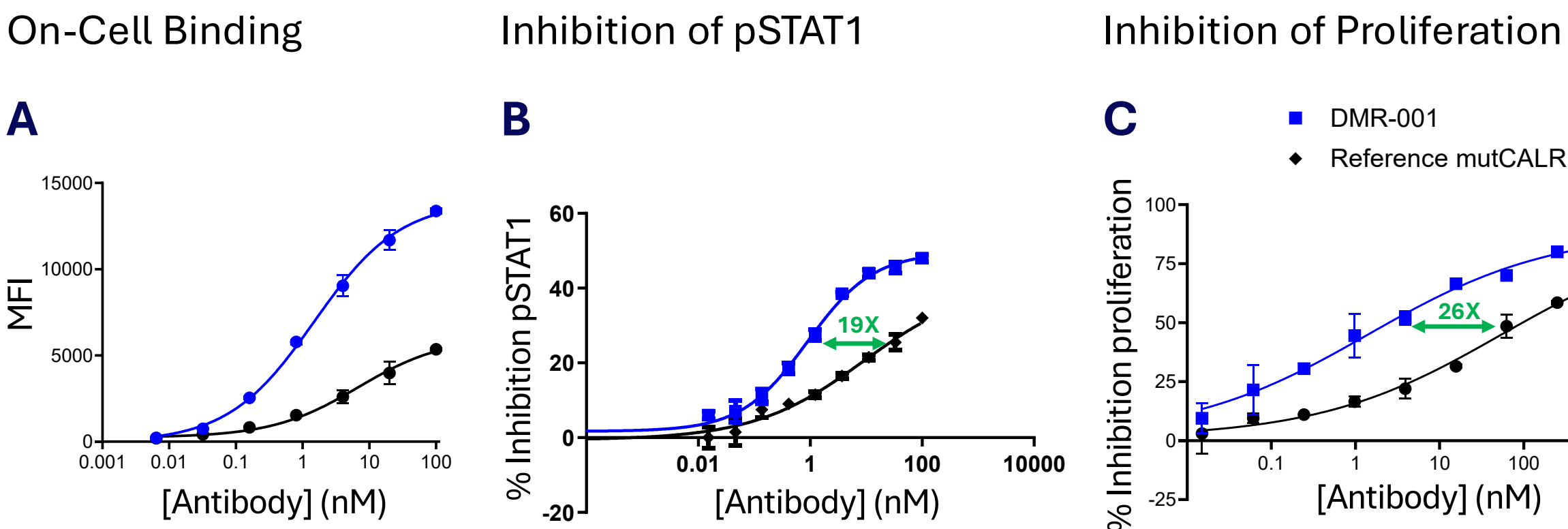
A) DMR-001 did not elicit antibody-dependent cellular cytotoxicity (ADCC) in a primary human NK cell assay to assess Fc-mediated effector function. ADCC activity was evaluated against ELF153-TpoR target cells expressing either Type 1 del52 mutCALR or Type 2 ins5 mutCALR using NK cells at an effector to target ratio of 5:1. B) DMR-001 did not elicit complement-dependent cytotoxicity (CDC) against ELF153-TpoR target cells expressing either Type 1 del52 mutCALR or Type 2 ins5 mutCALR. ELF153 cells express CD33, therefore gemtuzumab (anti-CD33) was used as a positive control for ADCC and CDC activity.

Figure 5: DMR-001 shows strong on-cell binding, inhibition of pSTAT1 signaling, and inhibition of proliferation in Type 1 mutCALR



Ba/F3-TpoR cells expressing Type 1 del52 mutCALR were used for (A), (B) and (C). A) DMR-001 on-cell binding was assessed by flow cytometry. B) Cells were incubated with antibodies for 2 hours. A FACS assay was used to measure phospho-STAT1 signal. The plot shown is a representative run from 4 independent experiments. C) Cells were incubated with antibodies for 3 days. A CellTiter-Glo assay was used to assess cellular proliferation. The graph shown is a representative run from at minimum 12 independent experiments.

Figure 6: DMR-001 shows greatly improved on-cell binding, inhibition of pSTAT1 signaling, and inhibition of proliferation in Type 2 mutCALR versus reference mutCALR mAb



Ba/F3-TpoR cells expressing Type 2 ins5 mutCALR were used for (A), (B) and (C). A) DMR-001 on-cell binding was assessed by flow cytometry. B) Cells were incubated with antibodies for 2 hours. A FACS assay was used to measure phospho-STAT1 signal. The plot shown is a representative run, and the fold decrease in IC50 relative to mutCALR reference antibody is an average of 4 independent experiments. C) Cells were incubated with antibodies for 3 days. A CellTiter-Glo assay was used to assay cellular proliferation. The graph shown is a representative run, and the fold decrease in IC50 relative to mutCALR reference antibody is an average of at minimum 12 independent experiments.

Figure 7: A single dose of DMR-001 results in near normalization of spleen weight in an in vivo model of Type 1 del52 mutCALR

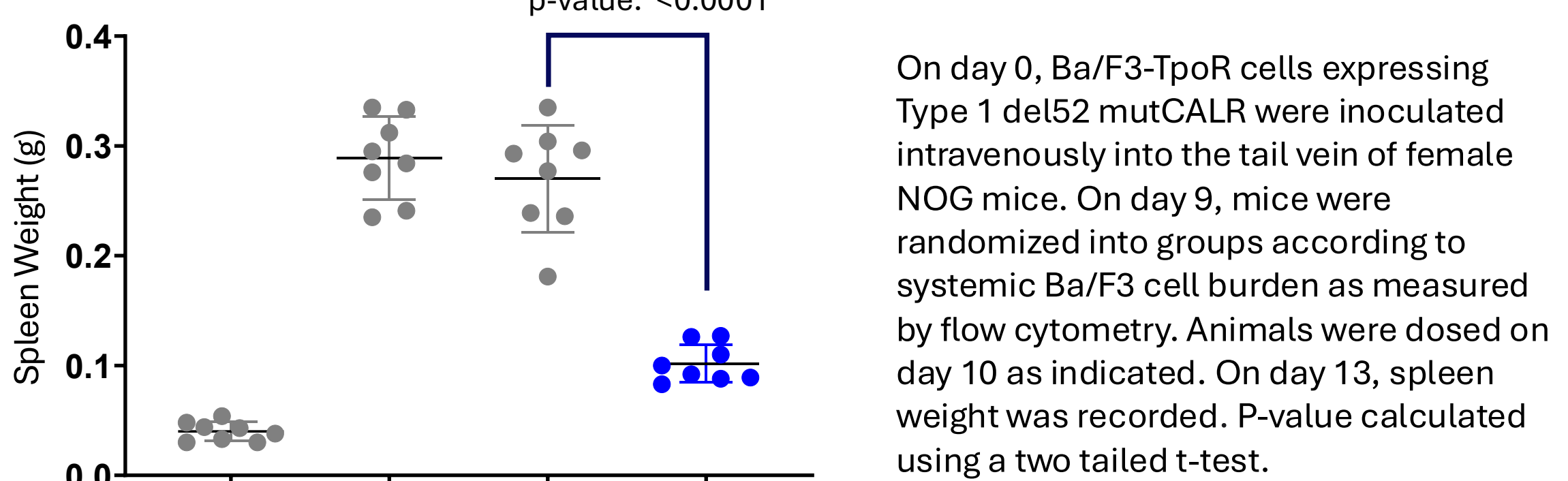
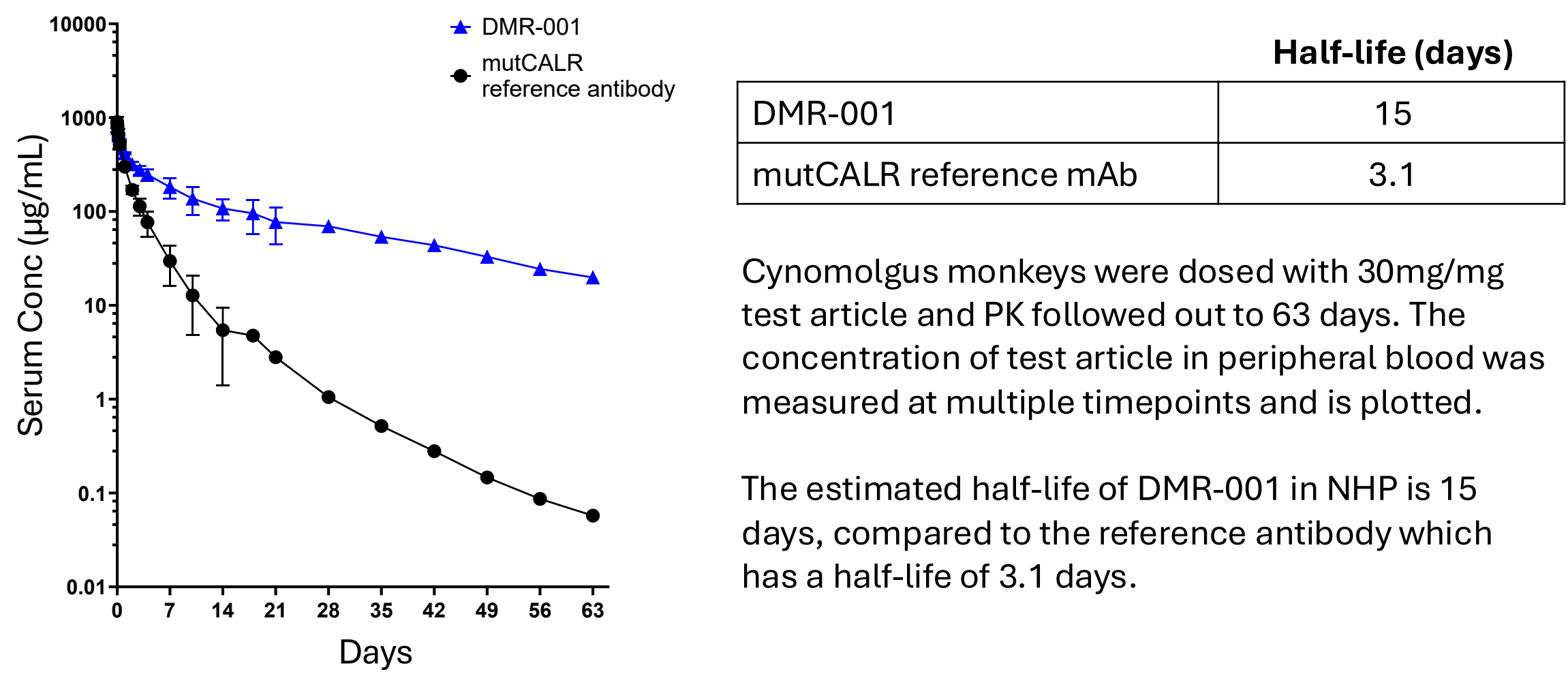


Figure 8: DMR-001 shows ~5x longer half-life in Non-Human Primates versus reference mutCALR mAb



Conclusions

- DMR-001 has best-in-class potential based on superior preclinical anti-mutCALR activity and extended half-life, which is expected to enable both improved efficacy and dosing convenience.
- DMR-001 is a highly potent and selective inhibitor of both Type 1 and Type 2 mutCALR.
- DMR-001 demonstrates extended half-life predicted to enable prolonged target engagement and at least Q4W SC dosing.
- The global Phase 1/1b CLARITY-101 study of DMR-001 in mutCALR-driven MPN (ET and MF) patients was initiated in mid-2026 following health authority approval in Australia; the Phase 1 program is expected to initiate in other geographies in the second half of 2026.