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Phase 1 CD25 antibodies: Treg depleting, non-IL2 blocking

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FURTHER FASTER TOGETHER
We are beating cancer

Non-IL2 blocking anti-CD25 mAb

UCL University College London

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Phase 1; available for licensing/co-development

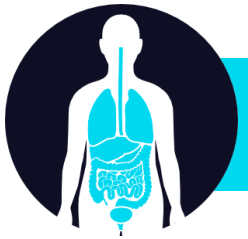
Asset: Non IL-2-blocking, ADCC/ADCP competent, fully human mAb with afucosylated Fc (low affinity, high avidity). Mechanism preserves IL-2 signalling and CTL activity, while maintaining Treg depletion. Well tolerated in 2 phase 1 trials.

Landscape: Marketed CD25 antibodies block the ligand IL-2, with immunosuppressive impact. No evidence of Teff depletion with Vopikitug/RG6292 (in contrast to Daclizumab (anti CD25) and Mogamulizumab (anti CCD4), pure Treg depleter unlike anti-CLTA4. First non-IL2 blocking CD5 antibody to enter clinical trials

Commercial: Program formerly developed by Roche (RG6292/Vopikitug). Granted composition of matter patents and broad protection of the concept of non-IL2 blocking CD25 antibodies. Opportunities in minimal residual disease/adjuvant setting, vaccine potentiation or to reformat as ADC/bispecific

Key Qualities:

- Phase 1 complete, full data package available
- Dose dependent Treg depletion demonstrated in clinic
- First movers in the non-IL2-blocking CD25 mAb space
- Broad patent protection, including mechanism and composition of matter



Two phase 1 (monotherapy and anti-PDL1 combination) trials complete in adult advanced solid tumours. Well tolerated agent with demonstrated Treg depletion.

Opportunity overview

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Asset summary

- Phase 1 anti-CD25 antibody with full phase 1 data package (Vopikitug/RG6292 formerly developed by Roche)
- ADCC/ADCP competent fully human monoclonal with afucosylated Fc region (low affinity, high avidity)
- Non-IL2 blocking to preserve IL-2 signalling and CTL activity
- Extremely well tolerated as monotherapy and in combination with atezolizumab (anti-PDL1)
- Effective dose dependent Treg depletion in periphery
- Measurable intratumoral Treg depletion in ~50% of patients

Landscape and competition

- Marketed CD25 antibodies block the ligand IL-2, with immunosuppressive impact
- No evidence of Teff depletion with Vopikitug (in contrast to Daclizumab (anti CD25) and Mogamulizumab (anti CCD4), pure Treg depleter unlike anti-CLTA4
- First non-IL2 blocking CD5 antibody to enter clinical trials

Commercial

- Granted composition of matter patents and broad protection of the concept of non-IL2 blocking CD25 antibodies
- Opportunities in MRD/adjuvant settings, vaccine immune potentiator, and reformatting as bispecific or ADC

Treg depletion landscape

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Alternative approaches:

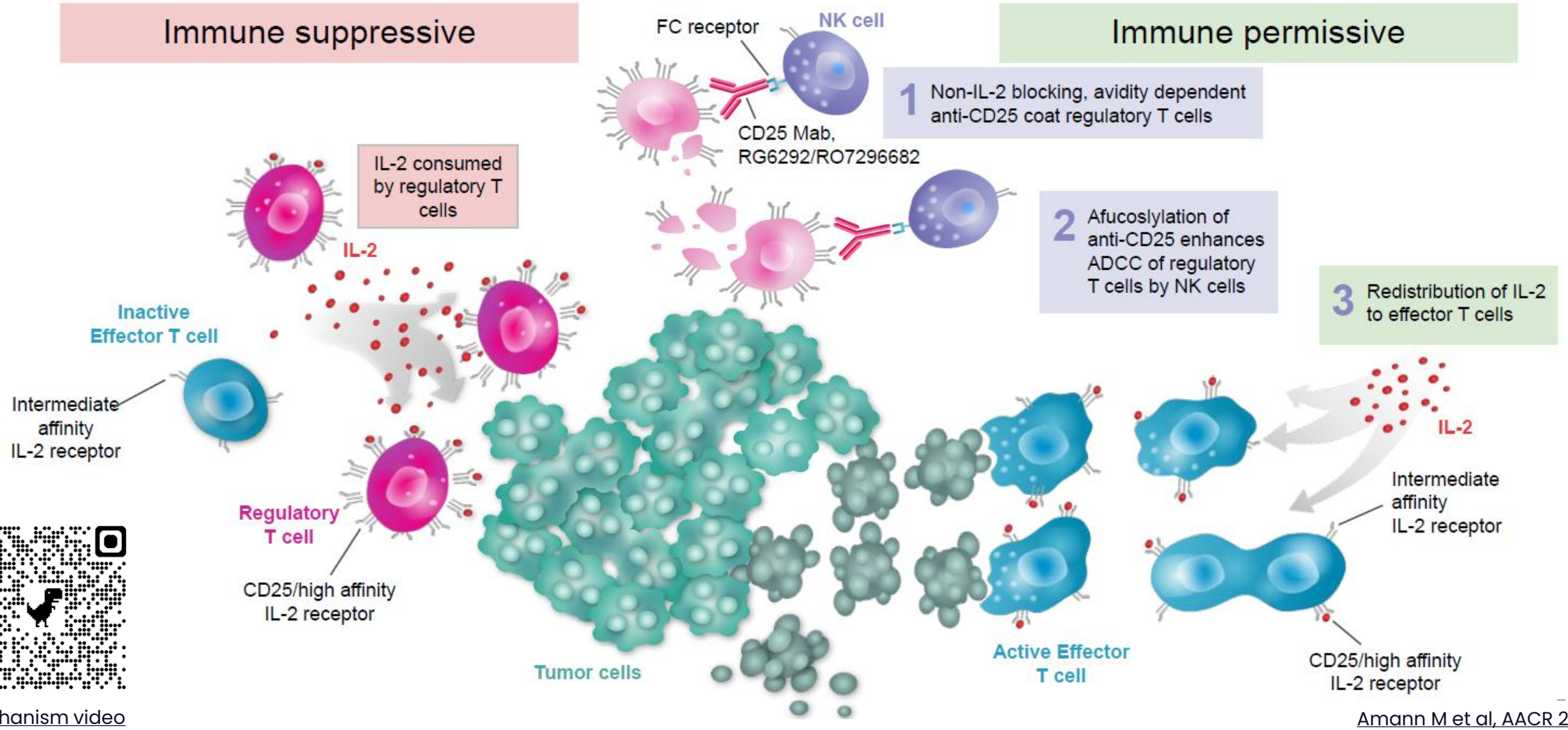
- Agents targeting costimulatory receptors (OX40, 4-1BB etc) mostly failed due to concurrent Teff depletion
- Severe immune-related adverse events (irAEs) are observed in patients given other Treg depleting mAbs such as anti-CTLA-4, potentially due to dual Treg-depletor/checkpoint inhibitor role
- Next generation Fc-optimised antibodies targeting Treg depletion (targeting CCR8, CTLA-4) demonstrate selective intratumoral Treg depletion with partially improved tolerability
- CCR8 blockade has so far demonstrated selective depletion with less frequent high-grade toxicities

Anti-CD25

- Marketed anti-CD25 antibodies are IL-2 blocking, with immunosuppressive impacts utilised for preventing transplant rejection or treatment of multiple sclerosis
- No evidence of Teff depletion with Vopikitug - in contrast to Daclizumab (anti CD25) and Mogamulizumab (anti CCD4)
- Non-IL2 blocking anti-CD25 are ‘pure’ Treg depleter (vs CTLA4 with added checkpoint inhibition),
- Vopikitug displayed a superior safety profile to other Treg depleting antibodies in clinical development

ADCC driven Treg depletion

Depletion of CD25^{high} Treg cells and allowing CD25^{low} activated T cells to thrive and expand on IL-2

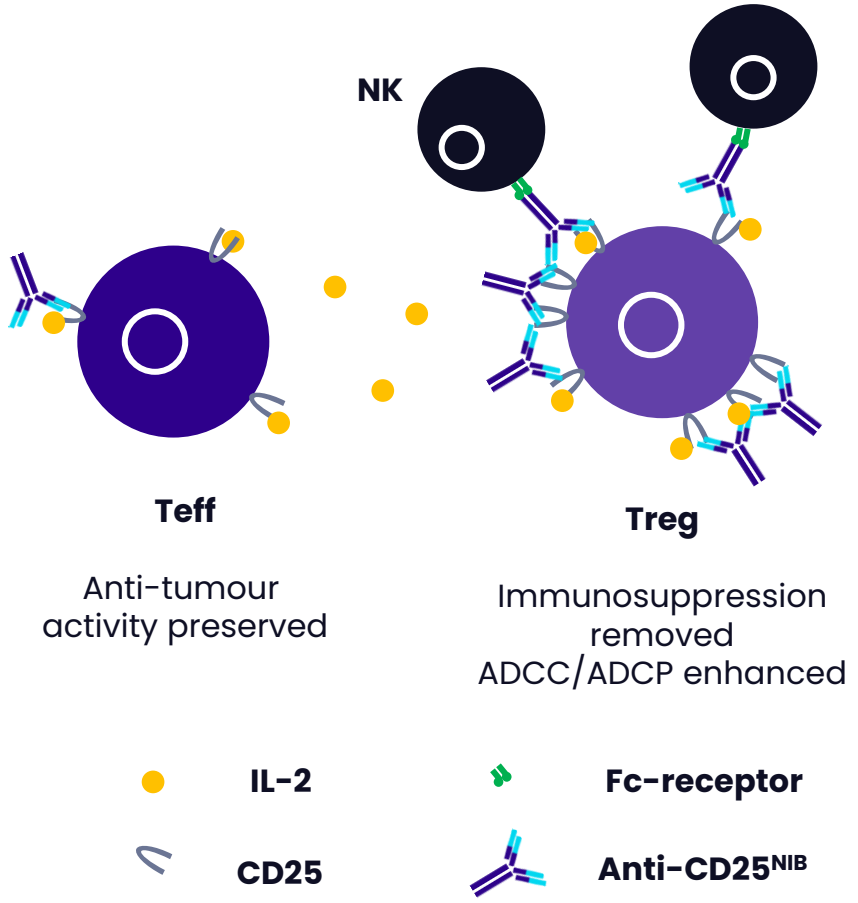


Mechanism video

Amann M et al, AACR 2020

Antibody characteristics

- Human afucosylated IgG1 mAb targeting human CD25 (IL-2Rα)
- Non-IL2 blocking ($CD25^{NIB}$)
  - Binds opposite to IL-2-CD25 interaction site
  - Preserving IL-2R pSTAT5 signalling and Teff activity
- Afucosylation – glycoengineered by afucosylation to mediate FcγR-dependent, CD25-targeted cell cytotoxicity (for enhanced ADCC/ADCP)
- Low affinity, high avidity – preferential binding of high surface density of CD25 (e.g. Treg>>>Teff)
  - Monovalent affinity ~250 nM, but avidity increases ~100-fold at high CD25 density (KD ~ 2–3 nM)
- Cmax reached ~4-6 hours post infusion
- Half-life 8-13 days (mean elimination half-life)



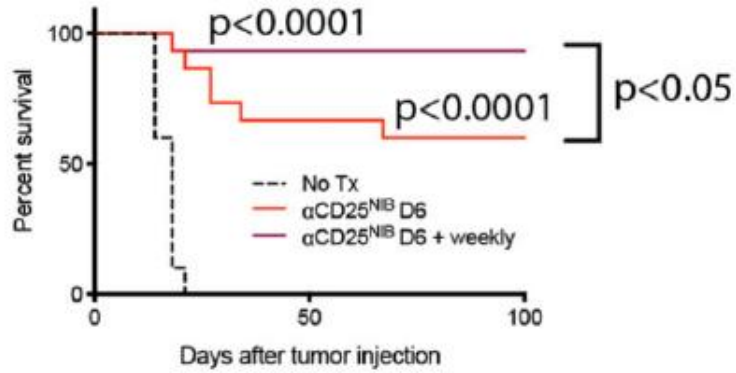
Preclinical data summary

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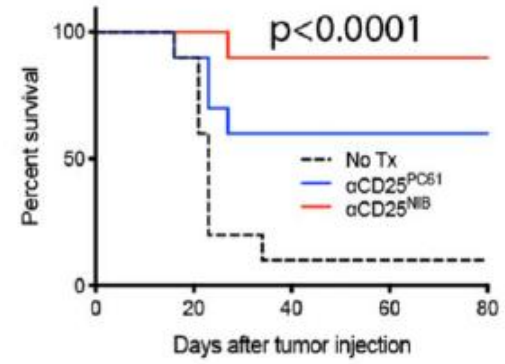
Superior efficacy of non-IL-2 blocking vs 'IL-2 blocking' αCD25

- Non-IL2 blocking CD25 antibodies ($CD25^{NIB}$) did not effect pSTAT5 signalling (downstream of IL-2)
- In a range of syngeneic tumour models, $CD25^{NIB}$ displays superior activity than 'IL-2 blocking' CD25 antibody PC61
- $CD25^{NIB}$ induces Treg depletion in vivo but unlike PC61 does not impact Teff populations
- Effective Treg depletion in patient-derived tumour samples and cynomolgous monkeys
- Synergy with anti-PDL-1 in vivo tumour models

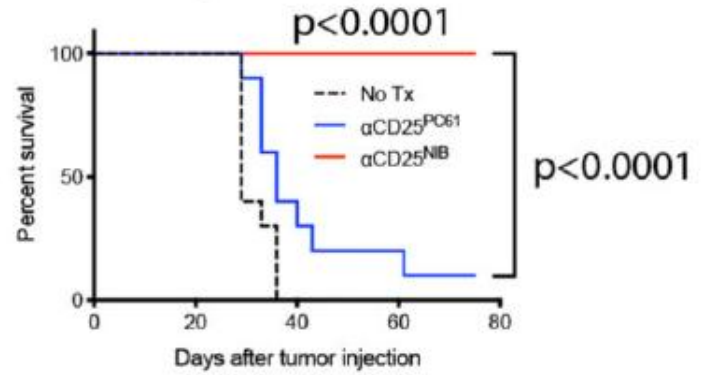
MCA205 (sarcoma)

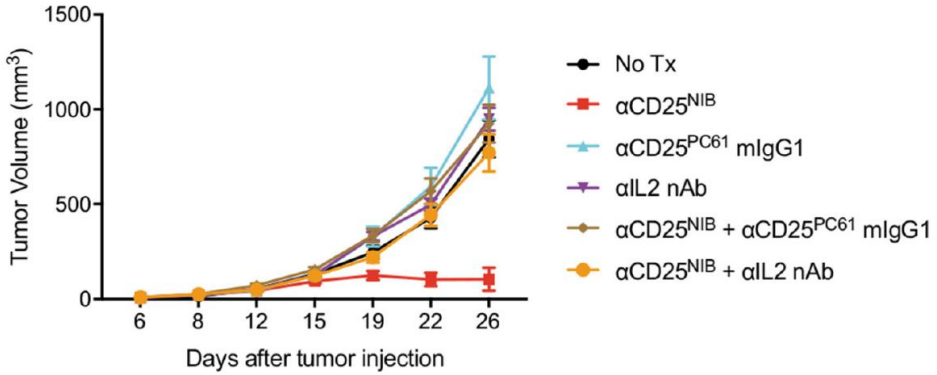


MC38 (colon adenocarcinoma)



CT26 (colorectal)





Solomon *et al* 2020

Clinical trials summary

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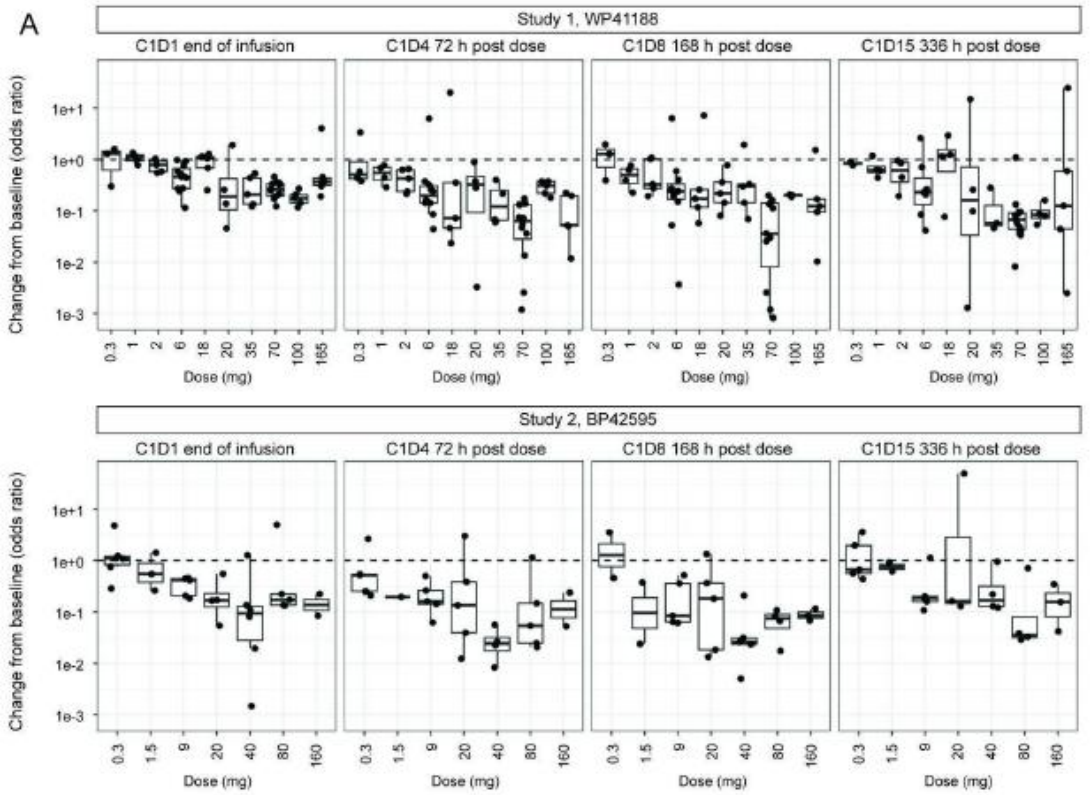
Single agent (n=76)

- MTD @165mg, manageable safety (skin)
- Dose dependent PK/PD with intratumoral Treg depletion (POM)
- SD as BOR (ORR=0%)
- RP2D 70mg

Atezo combi. (n=49)

- MTD not reached, max dose 160mg
- No enhanced safety concerns
- 3PRs (ORR=6%)
- No biopsy

- Cohort – adult patients with advanced solid tumours
- RG6292 was well tolerated (manageable pruritus and rash most frequent AEs)
- Serum levels of RG6292 increased with dose proportionally
- RG6292 induced a sustained dose-dependent depletion of peripheral Tregs with no effect on other immune cells
- Measureable depletion of intratumoral Tregs



Commercial opportunities

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Patent estate:

- Family 1 (Priority 2018): Lead antibody composition of matter – broad territories granted/pending
- Family 2 (Priority 2017): Claims protecting the space for the use of 'non-IL2 blocking CD25 antibodies' in the treatment of solid tumours.
- Family 3 (Priority 2016): Claims protecting the use of CD25 antibodies in the treatment of solid tumours, via depletion of Tregs, also in combination with PD-1 antagonist

Competitive landscape

- Most advanced and well characterised anti-CD25^{NIB} in development
- First movers in the 'non-IL2 blocking CD25 space' – first conceived by Prof. Sergio Quezada, and has led to a huge opportunity for Treg depletion in cancer

Opportunities

- Co-development and/or licensing opportunities for parties interested in:
    - Utilisation of RG6292 in Treg high cancers, minimal residual disease and adjuvant therapy
    - Vaccine – immune potentiator to improve vaccine responses (cancer and infectious disease)
    - Reformat candidate antibody CDRs into ADC / bispecific products

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Thank you

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