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Discovery of a novel high affinity anti-human CD122 antagonist monoclonal antibody (ANB033) that abrogates IL-2 and IL-15 signaling for the treatment of T cell-mediated inflammatory and autoimmune diseases

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ABSTRACT

T cells play a crucial role in the development and progression of autoimmunity by regulating self-tolerance and participating in inflammation. Signaling through CD122, the beta subunit of the IL-2 and IL-15 receptors, is essential for the function of CD4, CD8 T cells and natural killer (NK) cells. CD122 signaling is also essential for tissue resident memory T cell (T_{RM}) development and survival. Blockade of CD122 leads to elimination and/or reduction of the proliferation of pathogenic T cells in autoimmune diseases. We discovered a high affinity monoclonal antibody, ANA033 (now known as ANB033), that binds CD122 and blocks IL-2 and IL-15 signaling. In vitro, using human peripheral blood, ANB033 inhibited IL-2 and IL-15-mediated primary human CD4, CD8 T cells, and NK cell proliferation. In vivo, we used a xenogeneic graft versus host disease (X-GvHD) model, in which human PBMCs were transferred into immunodeficient mice that constitutively expressed human IL-15. Over-expression of IL-15 in this GvHD model accelerated PBMC engraftment, enhanced weight loss and lethality and promoted the expansion of T cells and NK cells. Importantly, belatacept (CTLA-4 Ig), a reference standard of care (SOC) that demonstrates survival efficacy in standard GvHD models, failed to maintain survival of the mice. Administration of ANB033 improved survival and suppressed expansion of T cells and NK cells, demonstrated a profound survival benefit superior to belatacept treatment, and continued to maintain survival even after cessation of dosing. Here, we propose that blockade of CD122 may provide great therapeutic value in the treatment of T cell-mediated inflammatory autoimmune disorders.

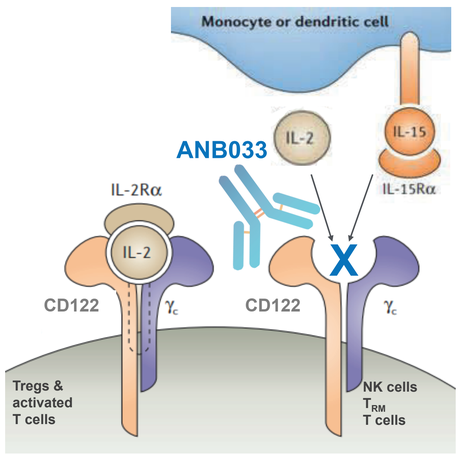
BACKGROUND & INTRODUCTION

CD122 (also referred to as IL-2Rβ) is a cytokine receptor expressed on T cells and NK cells. CD122 is a component of the multimeric receptors for type II cytokines IL-2 and IL-15. CD122 combines with CD132 (also referred to as IL-2Rγ or common γ chain) to form a dimeric “intermediate affinity” receptor that exhibits a moderate level of affinity for both IL-2 and IL-15. When CD122 and CD132 are associated with CD25 (IL-2Rα) the resulting trimeric “high affinity” receptor has strong affinity for IL-2, while when CD122 and CD132 are associated with CD215 (IL-15Rα), the resulting trimeric receptor has high affinity for IL-15.

IL-2 and IL-15 share the capacity to stimulate the proliferation of T lymphocytes and NK cells, but each possesses unique activities in the maintenance of the immune system. IL-2 also plays a role to limit T cell reactivity by priming activated T cells for apoptosis and in supporting Tregs in low IL-2 environments, while IL-15 is required for the development of NK cells, the development and maintenance of CD8+ memory T cells and may play a key role in the maintenance of pathogenic T_{RM} cells. Targeting CD122 with ANB033 may represent a promising approach to treat inflammation or autoimmune diseases with prominent T cell or T_{RM} -mediated pathology.

Figure 1. ANB033 Mechanism of Action (MoA)

CD122 (IL-2Rβ) is a shared subunit of the receptors for IL-2 and IL-15

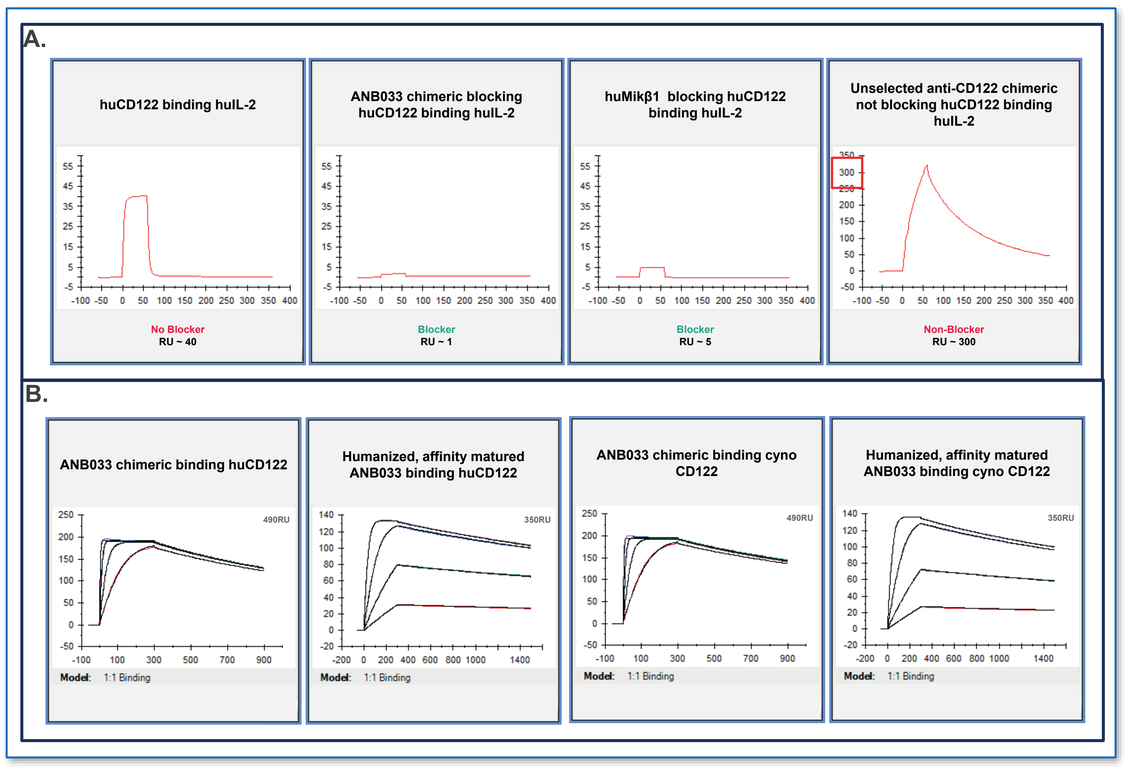


A CD122 antagonist monoclonal antibody (mAb) will potently inhibit IL-2 and IL-15 signaling

- CD122 is expressed on NK cells and subset of T cells, most notably on tissue-resident memory T cells (T_{RM}). T_{RM} require IL-15 for development and survival maintenance[1]
- IL-2 and IL-15 mediate
  - Proliferation of T cell subsets and NK cells
  - Survival of T cell subsets and NK cells (CD122 high cells)
  - Augments inflammatory cytokine secretion (IFNγ) during T cell activation
- ANB033 is designed to bind to CD122 and inhibit signaling via the low affinity IL-2/IL-15 receptor complex on T cells and NK cells, while sparing the high affinity IL-2 receptor on Tregs

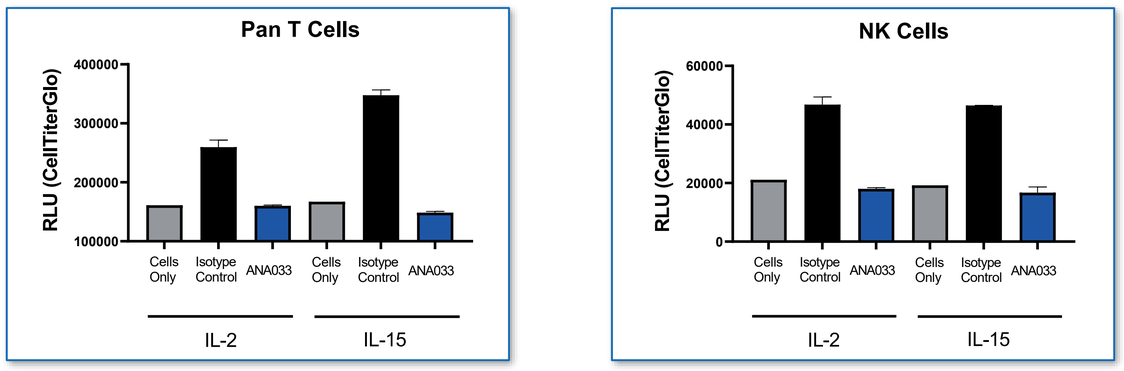
- Our anti-CD122 antagonist antibody, ANB033, targets the common beta subunit shared by the IL-2 and IL-15 receptors
- Presence of long-lived and persistent T_{RM} have been shown to drive tissue-specific immune-mediated inflammation[2]

Figure 2. ANB033 binds with high affinity to CD122 and blocks IL-2



Optimization phase included evaluation of chimeric and humanized mAbs binding to huCD122 and cyCD122 and blocking of huIL-2 binding to huCD122. This is shown above: A) Pre-incubation of ANB033 chimeric with huCD122 blocks binding to huIL-2. B) Humanized, matured ANB033 binds huCD122 and cyCD122 with higher affinity than the chimeric

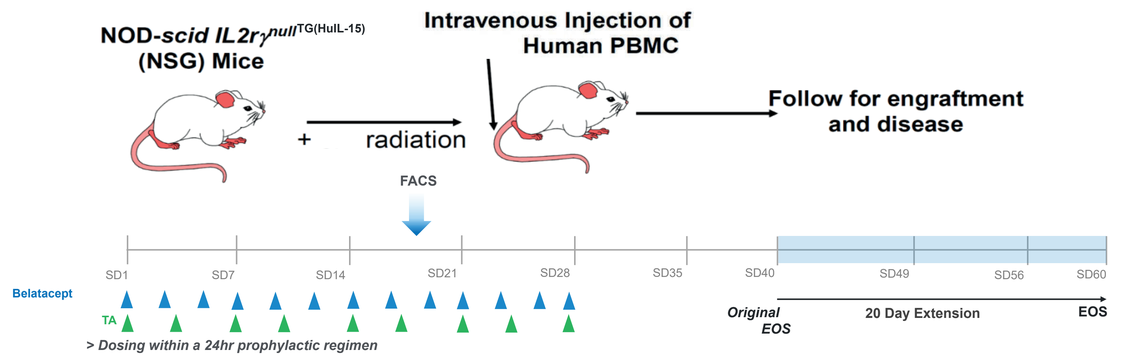
Figure 3. ANB033 inhibits proliferation of primary human Pan T and NK cells in-vitro



Pan-T cells (CD3+ T cells containing both CD4+ and CD8+ T cells) or NK cells were purified from human PBMCs, then incubated with medium only, 100nM Isotype Control, or 100nM ANB033; and each with recombinant human IL-2 or IL-15 for up to 1 week. Cells were assayed using Cell Titer Glo as a measure of proliferation. Representative of N=3 donors. This demonstrates that ANB033 inhibits IL-2- or IL-15-mediated proliferation of purified human Pan-T or NK cells.

Figure 4. In vivo proof of concept: ANB033 is effective in a humanized murine GvHD model

Human IL-15 transgenic mouse GvHD (severe disease) model supports T cell and NK cell proliferation

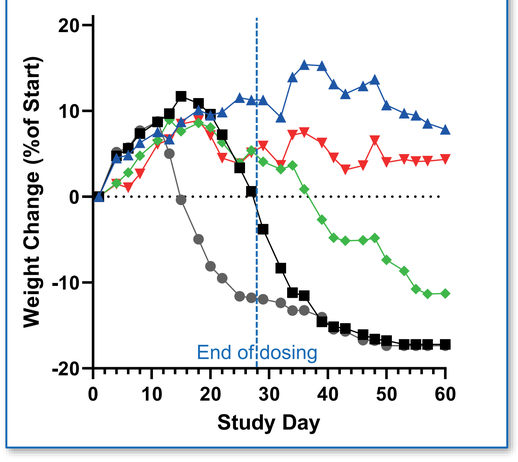


Group	N	Test Agent	Dose
1	10	Isotype Control	10 mg/kg
2	10	Belatacept	75 µg
3	10	ANB033	10 mg/kg
4	10	ANB033	3 mg/kg
5	10	ANB033	1 mg/kg

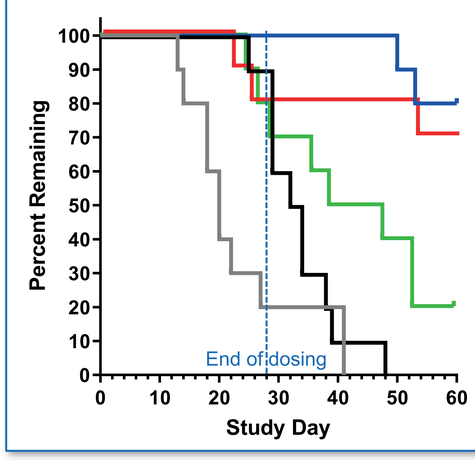
Endpoints:
- Weight loss
- Death
- GvHD disease activity index (DAI) scores (Fur, posture, activity)

	Median Survival (Days)
Isotype Control	20
Belatacept	33
ANB033 10mg/kg	>60
ANB033 3mg/kg	>60
ANB033 1mg/kg	44

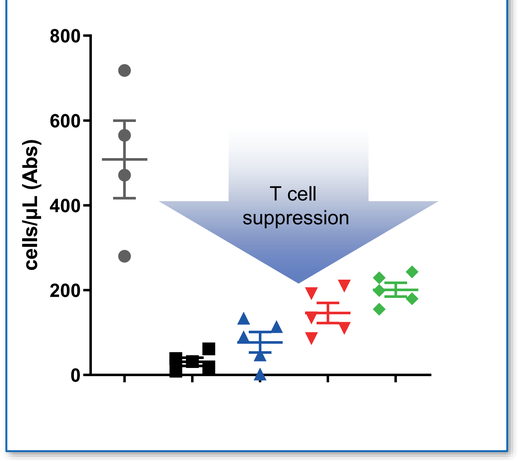
Average Body Weights (carried)



Survival



T cells Absolute Counts (SD18)



- ANB033 treatment shows a clear survival benefit
- ANB033 treated animals maintain body weights during dosing, and post dosing at 10mg/kg and 3mg/kg
- ANB033 suppresses CD3 T cell proliferation in a dose dependent manner
- Belatacept (GvHD SOC which only impedes T cell activation) shows minimal benefit over control
- ANB033 preclinical data suggest targeted elimination of pathogenic T cells drives more potent and durable response than belatacept
- GvHD model is biologically relevant to CD122 antagonist MoA with translation to inflammatory diseases driven by pathogenic T cell and Treg imbalance including rheumatology, dermatology, gastroenterology, and respiratory

CONCLUSIONS

ANB033:

- **High affinity anti-CD122 mAb**
- **Inhibits in vitro IL-2- or IL-15-mediated proliferation of human Pan-T or NK cells**
- **A clear dose-dependent survival benefit in murine GvHD huIL-15 model over belatacept SOC**
- **Maintained body weights in murine GvHD huIL-15 model**
- **Suppressed T cell proliferation in murine GvHD huIL-15 model**
- **We propose that blockade of CD122 may provide great therapeutic value in the treatment of T cell-mediated inflammatory autoimmune disorders.**

ACKNOWLEDGEMENTS

*All authors are current or past employees of AnaptysBio
Royce Moleno and Jennifer Michaels made significant contributions to the studies presented
Joe Valvo and Rosemary Cesario provided project management support

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Presented at Federation of Clinical Immunology Societies (FOCIS) Meeting June 20-23, 2023