

A microscopic image of a cell cluster, possibly a tumor, is visible on the left side of the slide. It shows a dense, irregular mass of cells with a textured, almost crystalline appearance, set against a dark, greenish background.

Modulating Anti-Tumor Immune Responses with B-Body™ Bispecific Antibodies

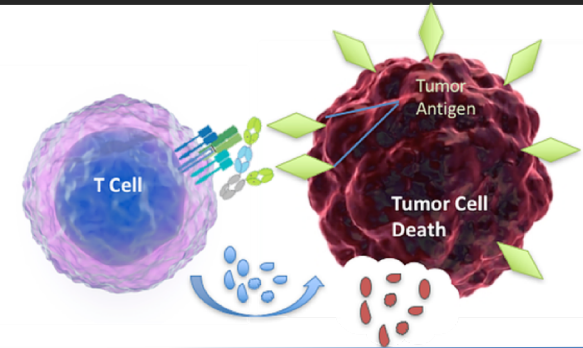
(Invenra's OX40 Agonist)

Bonnie J. Hammer, Ph.D
Cancer Immunotherapy: Executive Summit
March 12th, 2019

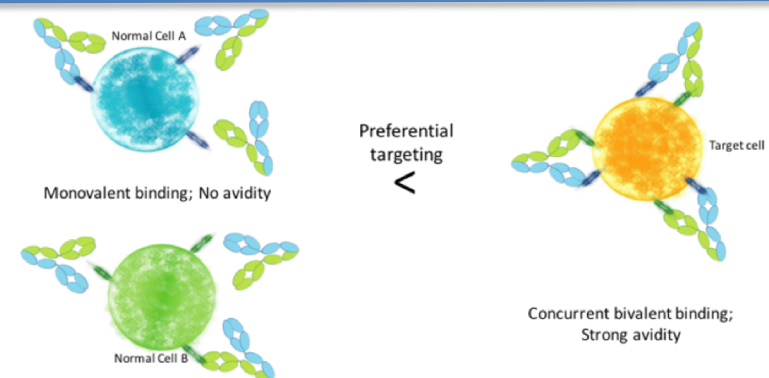
Why Multispecific Antibodies?



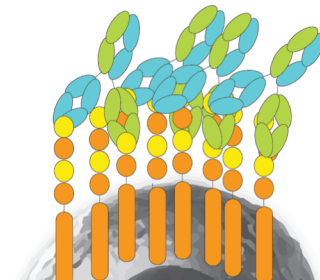
Redirecting immune cells to tumors—T cells, NK cells, Etc



Increased specificity through avidity—
SNIPERs™



Novel Mechanisms of Action—
ARCHER™ OX40 Agonists

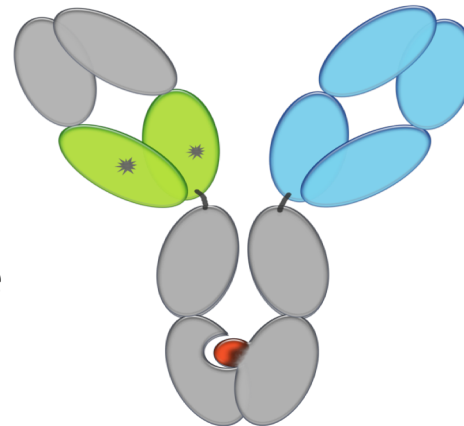


Plug-N-Play Variable Domains

- Enables direct import from all discovery sources
- Rapid in-format Discovery

CH1/CL Domain Substitution

- Derived from human antibody domain
- Multiple sets of orthogonal mutations
- Comparable thermostability to native Fab
- Proprietary 1 step separation technique for discovery



First Fab Arm

- Wild type fab architecture

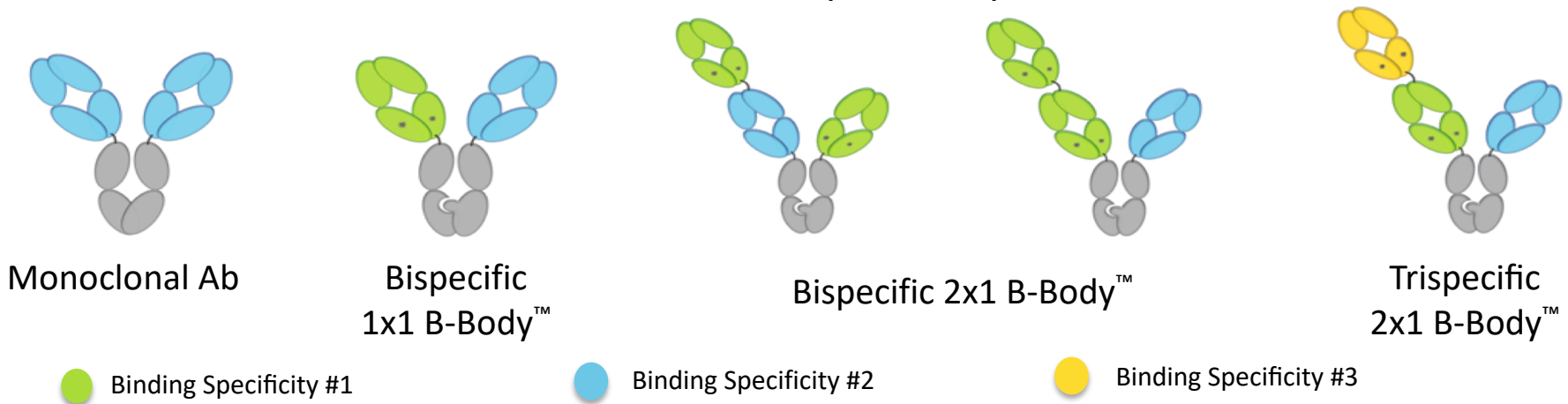
Knob-in-Hole-like Mutation

- Mutation set is clinically validated

Invenra's B-Body™ Platform

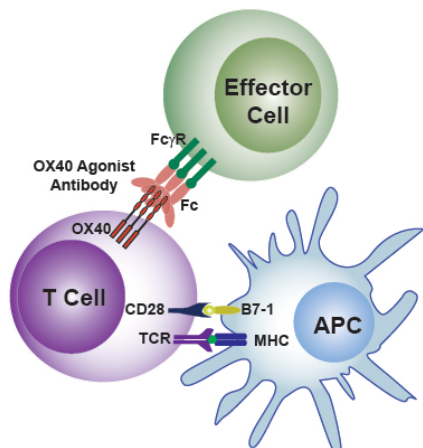


Invenra's B-Body™ Family

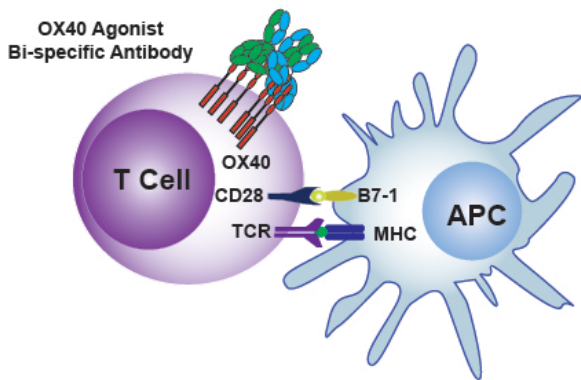


- The B-Body™ platform enables high throughput functional discovery in the final therapeutic format
 - In-format discovery avoids missing rare combinations of affinity, epitope, and architecture required for First-in-Class / Best-In-Class therapeutics
- B-Bodies™ are designed for compatibility with standard manufacturing processes required for therapeutic development

The Disconnect of Clinical OX40 Agonists

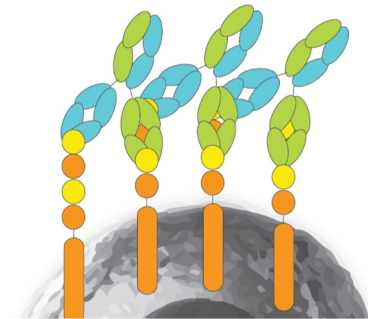
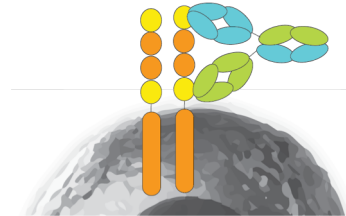
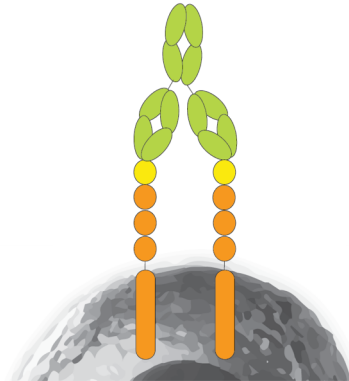


- First-generation of OX40 antibodies are monoclonal
 - Higher order cross-linking dependent upon local tumor environment, F_c engagement
 - Very good activity in preclinical animal studies
 - Have had limited activity in clinical studies



- Second-generation agonists exploit alternative strategies for higher order clustering
 - OX40 x Tumor Antigen
 - F_c Oligomerization variants
 - Bispecific Antibodies

ARCHER™ Soluble Agonist Design



Format	Monoclonal Antibody	Biparatopic Antibody	Biparatopic Antibody
Binding	Single Epitope	Two Non-overlapping Epitopes	Two Non-overlapping, constrained Epitopes
Clustering Potential	Binds 2 Receptors	Weak clustering of Receptors	High Density clustering of Receptors

High Throughput B-Body™ Discovery

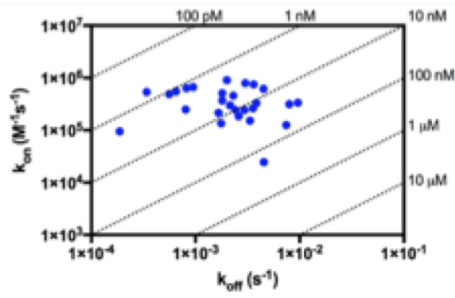
Antibody
Discovery

mAB Characterization

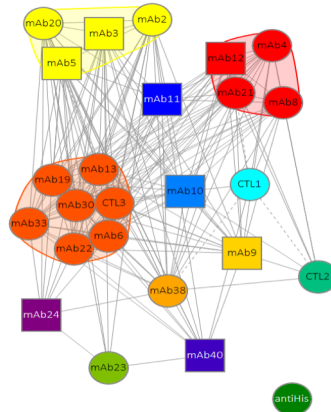
Clone into B-Body™
in 4 Individual Chains

HT B-Body™
Production

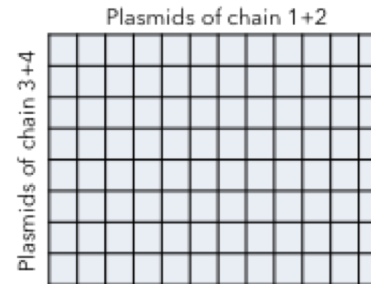
Affinity



Epitope Binning



Plasmid Mixing
Transient Transfection
Protein Expression and Purification

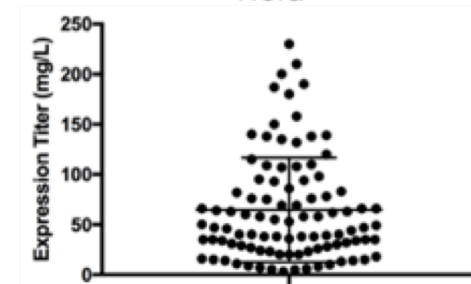


Representative B-Body™ Purity



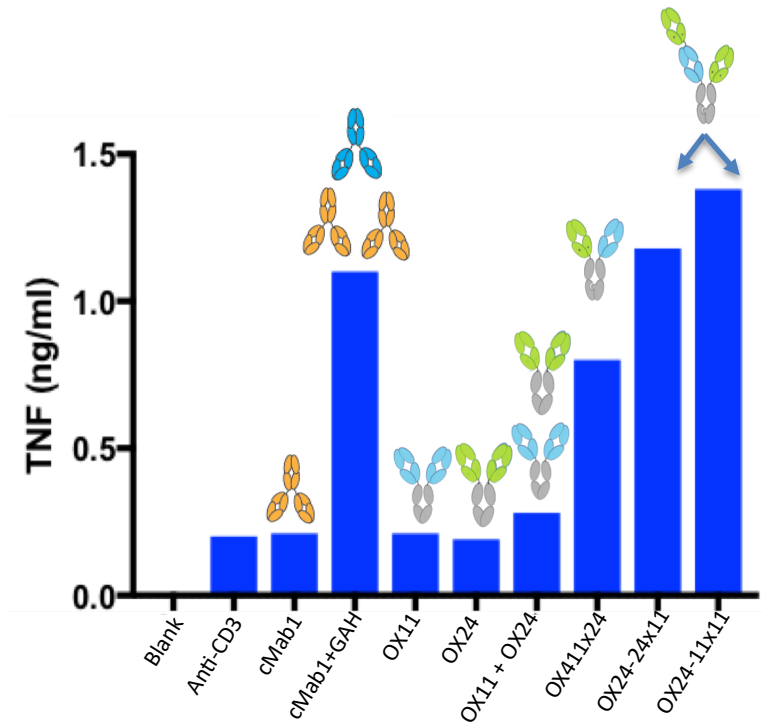
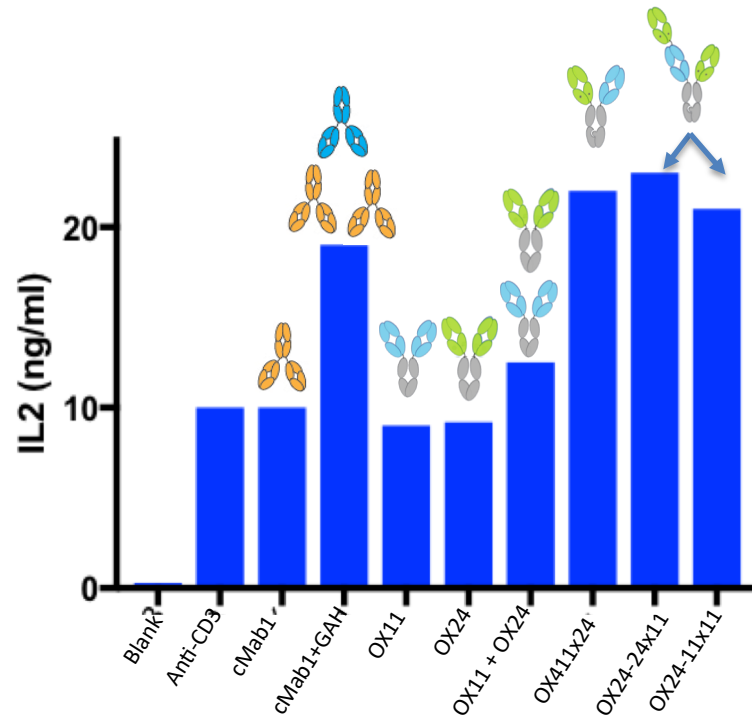
Small-scale (1.5 mL) expression and one-step affinity purification

Yield



B-Body™ Platform Enables High Throughput Functional Discovery

Lead Agonist Selection

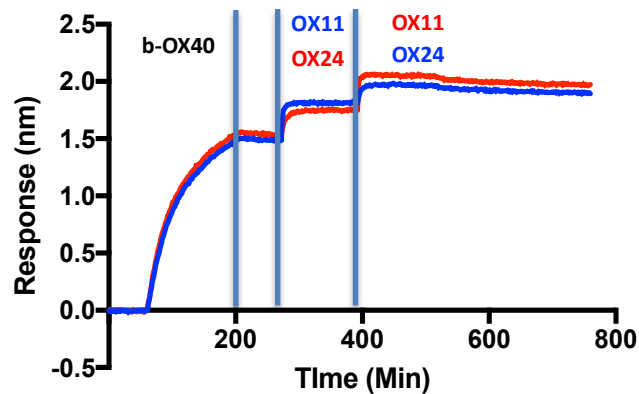


- ARCHER™ bispecifics outperform cross-linked clinical candidates and combinations of parent IgG in primary T-cell activation assays
- Soluble IgGs have no activity without secondary cross-linking

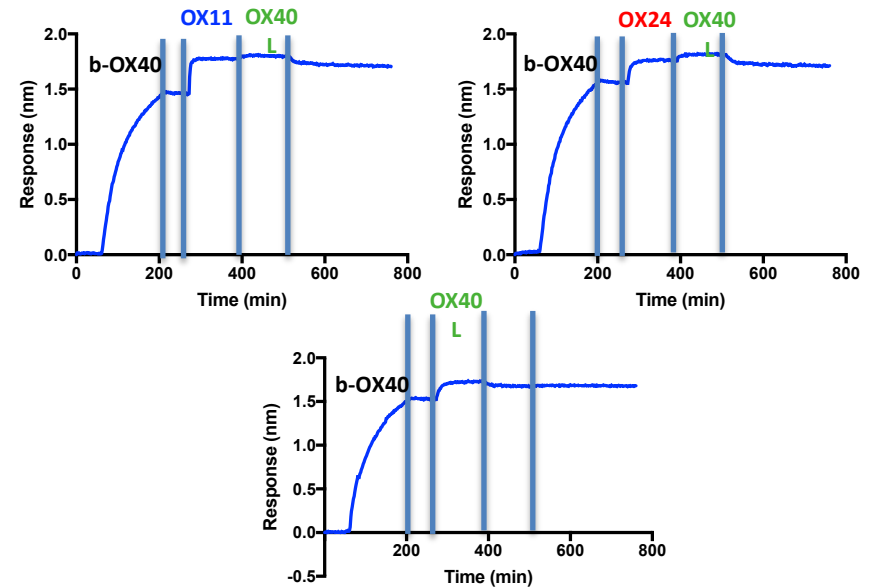
Lead Binding Characterization



Epitope Binning



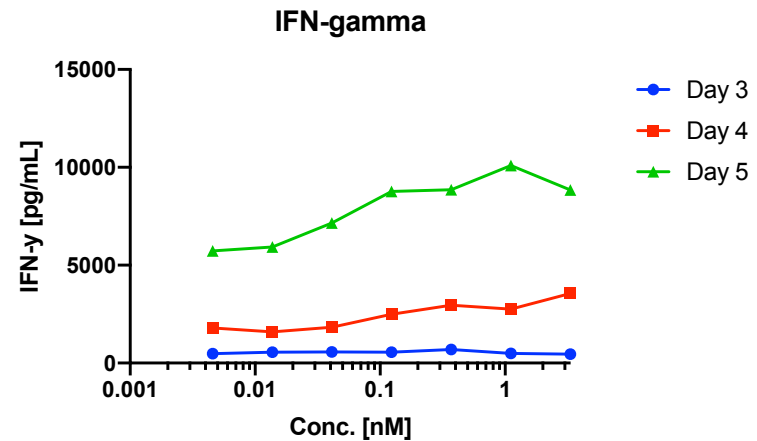
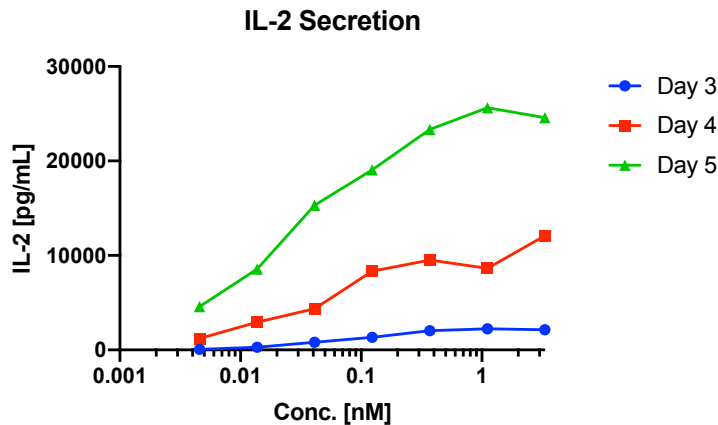
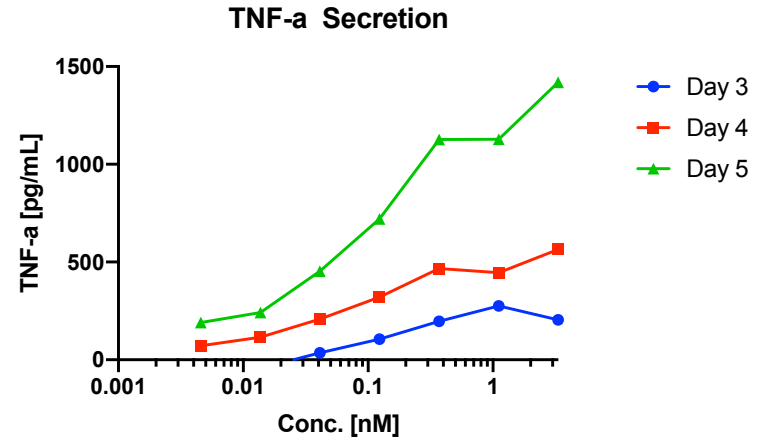
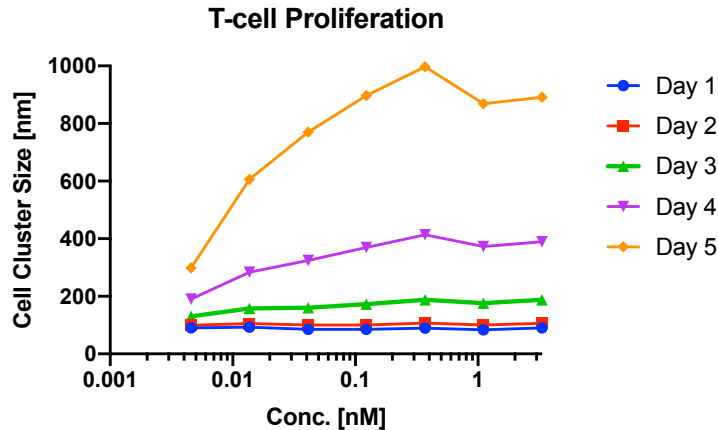
OX40-L Competition Binding



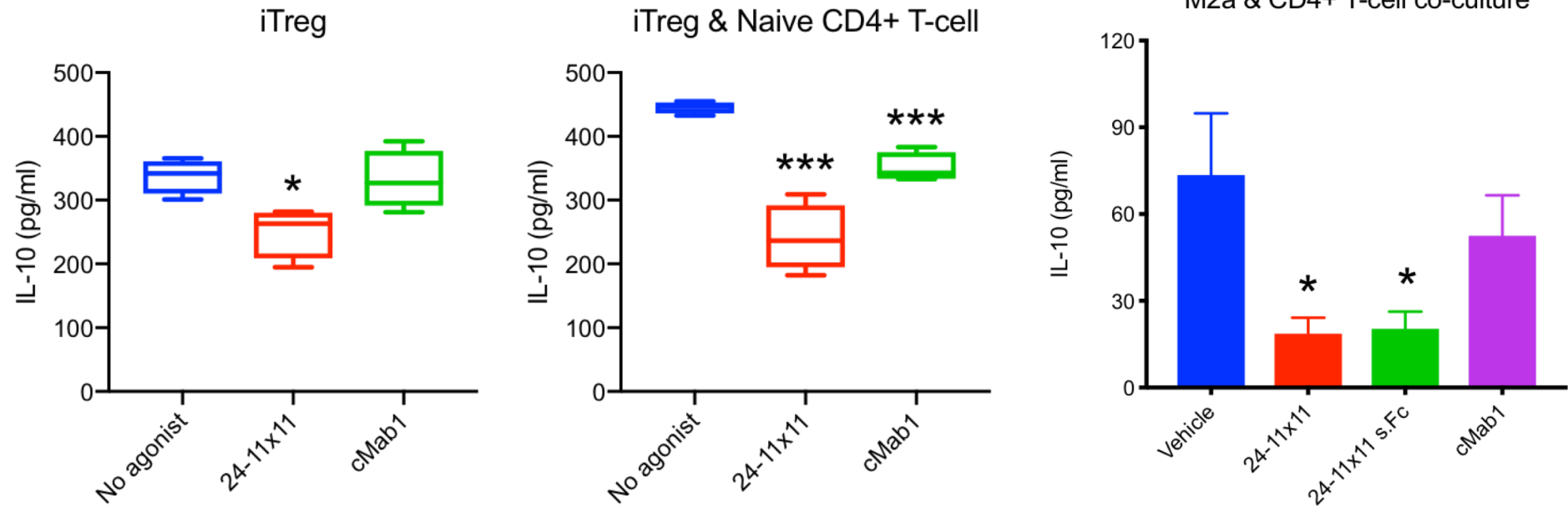
- OX24 and OX11 IgG can simultaneously bind OX40
- Both OX24 and OX11 prevent OX40L binding to OX40

Lead Candidate Achieved Original Binding Design Specs

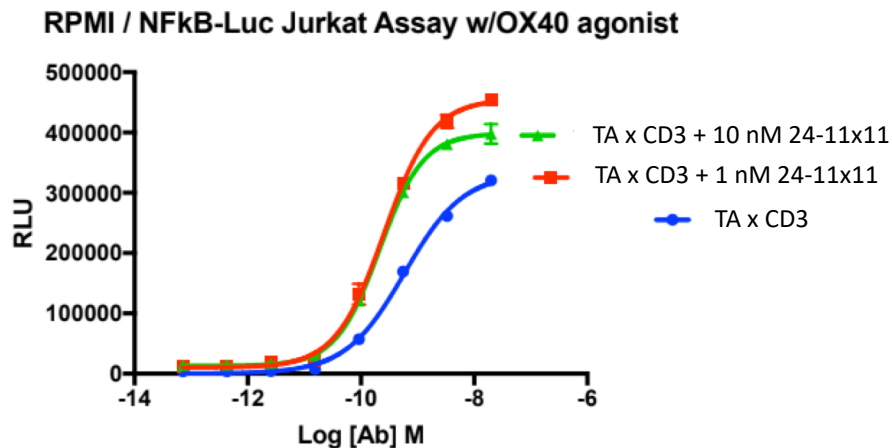
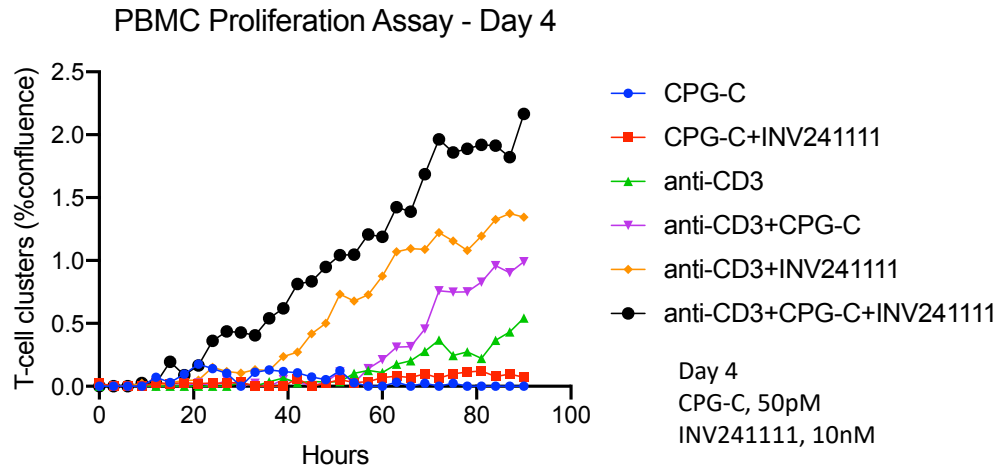
Kinetics of Activation



Suppression of iT_{regs} and M2 Macrophages



INV24-11x11 Combination Studies



- OX40 Agonists have potential to benefit many T-cell based MOAs
- Confirmed activity in combination with:
 - TLR9 Agonists
 - T-cell Redirecting Bispecifics
- Additional Uses:
 - Combination with Checkpoint Inhibitors
 - Combination with CAR-Ts

Broad Potential for Use in Combinations

Summary and Next Steps



- Lead candidate identified
- *In vivo* models
 - Exploratory Cyno PK model (Underway)
 - Efficacy Model Crown Bio OX40 HuGEMM model (Underway)
- Preclinical Development
 - Cell line development (Underway)

Acknowledgements



The Invenra Team