Benchmarking discovery-stage antibodies from OmniChicken®
(against clinical-stage antibodies from other sources)

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Ligand Pharmaceuticals
AETC 2019
Five Platforms

Three Species

One License
Current and Upcoming Tg chicken Platforms

“HCO” V3-23

“Novel scaffold” TBD

“Novel scaffold” TBD

In development:
Heavy Chain Only scaffold
Novel scaffold HC

Conventional HxL antibodies
Choice of heavy and light chain combinations

Common LC antibodies
For bispecific applications
Design of Engineered Ig Loci

Gene conversion

For animation go to:
https://www.omniab.com/technology

Human V’s selected for:
High expression level, stability, ubiquity
High sequence diversity in CDRs
Low sequence diversity in FWs

Germline

VH 3-23 (for H locus)
VK 3-15 (for L locus)

Diversified B cells
Sequence Diversity of PGRN mAbs from OmniChicken

diversity is principally focused in the CDR regions of human VH and VL; a result of both transgene design and cellular selection

N = 98 mAbs
OmniClic™: Tg Chickens with Common Light Chain
Engineered for bispecific antibody discovery and development

Common light chain based upon human VK3-15 scaffold
- Active V gene fully germline
- Pseudogenes also germline with no CDR sequence diversity

Paired with proven VH3-23 heavy chain
- Almost all mAb diversity occurs in VH, and in CDRs
In OmniClic birds, diversity is focused on the heavy chain
Deeper screening reveals remarkable diversity in OmniChicken

High throughput recovery of sequences from single antigen-reactive B cells

- 485 unique sequences in 230 clonotypes
- Only 62% of functional repertoire

See Bob Chen’s talk:
Wednesday 10:30am
Track 1
“Ab Initio” Antigen and Antibody Generation

Cloning
- Full WT
- Mutant, tags
- N-term fusion

Expression
- Mammalian
- Insect

Purification
- Detergent optimization
- Affinity chromatography

Reconstitution
- Micelles
- Proteoliposomes

QC
- Radioligand
- Reporter assay

See John Burg’s talk:
- Wednesday Noon
- Ballroom D

Immunization
- Single-B cell cloning
- mAb panel

Purified native receptor

See John Burg’s talk:
- Wednesday Noon
- Ballroom D
Immuno-Oncology Case Studies
# Selected Targets – Clinical Activity

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<tr>
<th>Target</th>
<th>% homology with human</th>
<th>Molecule in development (Sponsor)</th>
<th>Phase</th>
<th>Indications</th>
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OmniChicken Screening Cascade

1. Immunize OmniChickens with human or human and murine antigen
2. GEM Screen
3. ELISA & FACS
4. Kinetics & Binning
5. Functional assays
GEM Screen for Species Cross-reactivity

- GEM screens contained 2 beads
  - Large bead coated with human
  - Small bead coated with murine
B7-H3
B7-H3

Inhibitor of T Cell Activation, Proliferation and Cytokine Production, Promoter of Cancer Cell Invasion

• Immune checkpoint member of B7 family, expressed on Antigen Presenting Cells
• Aberrantly expressed in wide variety of cancers (bladder, pancreatic, prostate, osteosarcoma, breast, cervical colorectal, ovarian, glioma, melanoma, gastric cancers etc.)
• Unknown receptor

Target Profile: Functional blocker

• Initial mAb panel obtained
• Murine & cyno cross-reactivity
• Advanced characterization in progress
**B7-H3 Serum Titers**

Immunized with human B7-H3 only

- **40511 (K/C)**
  - PI
  - D2
  - Final
  - Human
  - Murine

- **40579 (K/SD)**
  - PI
  - D2
  - Final
  - Human
  - Murine

- **40633 (L/SD)**
  - PI
  - D2
  - Final
  - Human
  - Murine
OmniChicken 40511

B7-H3 Elisa and cell binding

Species cross-reactivity ELISA

- OD450

Binding to huB7-H3 CHO cell line

- MFI

Species: hu B7-H3, cyno B7-H3, mu B7-H3

Confidential
B7-H3 Ab Sequence Dendrogram

Kinetics and epitope binning
OmniChicken derived mAbs cover epitopes represented by clinical grade antibodies

OmniChicken mAb cohorts contain clones with superior affinities

**B7-H3**

Epitope binning and kinetics results

![Graph showing epitope binning and kinetics results](image)
CD38
**CD38**

Inhibitor of Cytotoxic T Cell Activation and Proliferation, Inducer of Immature B Cell Differentiation

- Expressed on CD4+ and CD8+ T cells, B cells, NK cells
- Upregulated following PD1/PD-L1 blockade (resistance mechanism)
- Ectoenzyme that catalyzes the synthesis and hydrolysis of cADP-ribose from NAD+ to ADP-ribose

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**Target Profile: Antagonist**

- Initial mAb panel obtained
- Murine & cyno cross-reactivity
- Advanced characterization in progress
CD38 Serum Titers

Human only and Human / Murine immunizations

* Human/Murine Immunization
OmniChicken 40596

CD38 ELISA and cell binding

Species cross-reactivity ELISA

Cell binding to transiently transfected EXPI293

* = murine only on SPR
CD38 mAb Sequence Dendrogram

Kinetics and epitope binning

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OmniChicken derived mAbs cover epitopes represented by clinical grade antibodies

OmniChicken mAb cohorts contain clones with superior affinities
TIM3

Inhibitor of T Cell Activation and Dendritic Cell Activation and Inducer of Immune Tolerance

- Expressed on activated CD4+ T cells, NK cells and myeloid cells
- Expressed in TILs (breast, gastric, cervical, lung cancers, HCC) and in cancer stem cells (AML)
- Binds Galectin-9, Phosphatidylserine and CEACAM1

Target Profile: Antagonist

- Initial mAb panel obtained
- Cyno and rare murine cross-reactivity
- Advanced characterization in progress
TIM3 Serum Titers

Human / Murine alternating immunization

![Graphs showing TIM3 Serum Titers](image-url)
OmniChicken 43354

TIM3 ELISA and cell binding

Species cross-reactivity ELISA

- **OD450**
- **Species** cross-reactivity ELISA
- **Human**, **Cyno**, **Murine**

Cell binding to transiently transfected EXPI293

- **% PARENT**
- **Parent**, **Human**, **Murine**
TIM3 mAb Sequence Dendrogram

Kinetics and epitope binning
OmniChicken derived mAbs cover epitopes represented by clinical grade antibodies

OmniChicken mAb cohorts contain clones with superior affinities

**TIM3**

Epitope binning and kinetics results
Anti-TIM3 Blocking Activity

Phosphatidylserine Blocking Activity

Confidential

% Binding

10 ug/ml

0 ug/ml
Summary of I/O Programs POC

- OmniChicken has demonstrated the ability to generate diverse antibody panels with broad epitope coverage and multi-species cross-reactivity.
- OmniChicken derived mAbs cover epitopes covered by clinical grade antibodies for all programs.
- OmniChicken derived mAbs contained clones with superior affinity when compared to clinical grade antibodies.
- Several OmniChicken genotypes expand the OmniAb portfolio of antibody discovery platforms that are available to partners.
- Visit us at poster J20.
Acknowledgements

ANTIBODY DISCOVERY
• Kristen Chan
• Ellen Collarini
• Robyn Cotter
• Kevin Fong
• Sean Grabinski
• Darlene Pedersen
• Kevin Reynolds

GENETIC ENGINEERING
• Kathryn Ching
• Phil Leighton
• Renee Kopulos
• Marie-Cecile van de Lavoir