Building a deep immuno-oncology portfolio in less than a year

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PEGS
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Improving early development

15-20 years, >$billion for an innovative new drug

- Target discovery: 5 yrs
- Lead discovery: 3 yrs
- CMC: 2 yrs
- Phase I: 2 yrs
- Phase II: 2 yrs
- Phase III: 3 yrs
Improving early development

\[ \text{\( \uparrow \text{Speed} + \downarrow \text{Attrition rate} = \downarrow \text{Cost} + \uparrow \text{Products} \)} \]

- **Target discovery**
  - 2 yrs
- **Lead discovery**
  - 2 yrs
- **CMC**
  - 2 yrs
- **Phase I**
  - 2 yrs
- **Phase II**
  - 2 yrs
- **Phase III**
  - 3 yrs

- Massively parallel discovery
- Fully natural, fully human
- Personalized clinical studies
• Lots of groups working on a few immune checkpoint targets
• GigaGen generated antibodies against 17 known immune checkpoint targets
• We are using these resources to investigate how immune checkpoint interact
• **Eventual goal is to discover novel targets and novel combinations**
Checkpoints in the tumor microenvironment

RNA-seq from 38 cholangiocarcinoma tumors

correlation coefficient

GigaGen
Large portfolios are critical for combo screens

Owning a vast diversity of antibodies against immune checkpoint targets helps identify candidate combinations.

**PD1 associates with LAG3**

in T cells

**mAbs block PD1-LAG3 association**
GigaGen’s founders

David Johnson
Genomics
PhD Stanford
COO & Co-Founder of Natera

Everett Meyer
Immunology
MD/PhD Stanford
Stanford Professor

World-leading immune genomics technology for drug discovery

MAbs 2017 Nov/Dec; 9(8):1282-1296
MAbs 2017 Nov/Dec; 9(8):1270-1281
MAbs 2018 Apr; 10(3):431-443
Ultra-fast single cell capture

Throughput of >3 million cells per hour.
Humanized mouse immunization → Generate scFv library → scFv screening

**TRIANNI**

- Immunize humanized mouse with soluble or cell-surface expressed antigen
- Isolate millions of B cells into droplets and amplify antibody coding DNA
- Express millions-diverse scFv libraries on microbial cell surfaces
- Flow sort for binders against antigens
- Deep sequence before and after sorting to identify antibody clades of interest
Yeast display discovers high affinity binders

- Yeast display libraries cover the full diversity of each mouse (millions of antibodies)
- Native heavy-light chain pairing is retained
- Deep sequencing (Illumina) quantifies all sequences in pre- and post-sort libraries
- Three rounds of sorting captures the highest affinity antibodies
PD-1: different Abs in different tissues & mice

Enriched scFv >0.1% post-sort abundance are shown
PD-1: a diversity of antibody sequences

262 unique high affinity scFv binders to PD-1

Each color represents a different mouse
Distance = Sequence Similarity
Circle/Square = Spleen/Lymph Node
Lines indicate less than 9 amino acid difference across heavy & light chain

Enriched scFv >0.1% post-sort abundance

GigaGen
LAG-3: different Abs in different tissues & mice

467 high affinity binders

Enriched scFv >0.1% post-sort abundance are shown
LAG-3: a diversity of antibody sequences

467 unique high affinity scFv binders to LAG-3

Each color represents a different mouse
Distance = Sequence Similarity
Circle/Square = Spleen/Lymph Node
Lines indicate less than 9 amino acid difference across heavy & light chain

Enriched scFv >0.1% post-sort abundance
Prioritizing antibodies for development

- **Manufacturability**: Pilot expression as full-length mAb in CHO cells
- **Affinity kinetics**: Array surface plasmon resonance (SPR) using Carterra technology
- **Epitope binning**: Array SPR using Carterra technology
- **Cell surface binding & polyspecificity**: FACS of antibody vs. CHO cells expressing target or irrelevant target
- **In vitro efficacy**: reporter assays (Promega) and CMV recall assays

- Mouse efficacy
- CMC scale up, toxicology, PK
- IND
PD-1: a diversity of antibody kinetics

- 65% of scFv bound antigen when reformatted as mAbs
- $K_D \ 10-280\text{nM}$ (pembro benchmark was $16\text{nM}$ in our hands)
LAG-3: a diversity of antibody kinetics

- 88% of scFv bound antigen when reformatted as mAbs
- $K_D$ 0.8-185nM (benchmark was 0.5nM in our hands)
FACS cell surface binding assay

**FACS binding assay:**

- Bind antibody to cells that express target
- Bind antibody to cells that express irrelevant target
- Absolute intensity and spread between curves indicates on-target and off-target binding
PD-1: FACS cell surface binding data

- All antibodies that bound soluble antigen also bound cell surface antigen
- No antibodies bound cells expressing irrelevant target – representative plots shown
58% of antibodies that bound soluble antigen also bound cell surface antigen.

No antibodies bound cells expressing irrelevant target – representative plots shown.
PD-1: a diversity of blocking functions

- No anti-PD-1 antibodies beat pembro so far
- Poor response to immunogen means fewer antibodies, less likely to block well
LAG-3: a diversity of blocking functions

- Two antibodies beat benchmark
- Higher affinities more likely to beat benchmark
PD-1: clear delineation of functional epitopes

Blocking epitope bin

Non-blocking epitope bin
LAG-3: functional epitopes less clear
Current directions

- Immunization campaigns with DNA and cell-expressed targets
- Yeast FACS with cell lysates to capture membrane-embedded targets
- Exploring in vitro assays to identify synergistic antibody combinations
- Expression profiling of drug-exposed immune cells and terminally exhausted immune cells to discover new targets
- ...and further non-clinical and clinical development of promising candidates
Thank You

www.gigagen.com