Parallel Discovery of Therapeutic Antibodies and Novel Targets Using the Antibody Repertoires of Resilient Individuals

PEGS Boston – May 4th 2022
Our vision: To use the power of the human immune system to discover new medicines and diagnostics

Discovering and developing protective, patient-originated therapeutic antibodies

Focus on protective antibody responses

Convergent in resilient individuals

Target agnostic approach

Advanced computational approaches
Alchemab concept
We identify especially resilient individuals – and learn how they overcome or resist disease.

We sequence B cells from the resilient individuals and identify antibodies with similar properties.

We discover the binding targets of the antibodies, understand their protective properties and develop candidates that replicate the protective effect.
Patient-originated, physiologically validated therapeutics

Our therapeutic antibodies are physiologically validated, increasing the likelihood that the targets are critical disease modifiers.
How do we think about resilience?

Patients who survive advanced cancer

Patients progressing unusually slowly with neuro-degenerative disorders

People who survive grievous, deadly infectious disease

Long-lived, healthy individuals
Humans benefit from naturally-occurring protective autoantibodies in many diseases

**Cancer Cell**

**Intratumoral plasma cells predict outcomes to PD-L1 blockade in non-small cell lung cancer**

- Three populations of intratumoral B and plasma cells identified by scRNA-seq in NSCLC
- Plasma cells show the strongest predictive association with overall survival to PD-L1 blockade
- Plasma cell benefits are independent of intratumoral CD8 T cells and PD-L1 expression
- B and plasma cells are present in tertiary lymphoid structures in NSCLC tumors
We collaborate with a broad and growing network of institutions

Neurodegeneration

Oncology

Infectious Disease and other areas

Platform enabling collaborations
Our platform has generated numerous program opportunities across a variety of diseases.
How do we do what we do?
Discovery process powered by advanced sequencing, big data, and deep learning

Core Technologies

- Repertoire analysis: Leading expertise & capabilities in BCR repertoire analysis
- Antigen proteomics: Comprehensive set of target deconvolution tools
- Deep learning: Proprietary technologies

Process

Samples

Data driven phenotypic and functional biology cascade
Convergent autoantibody sequences provide the starting point for discovery

**Population B Cell Repertoire Analysis**

- Sequences of disease-free population
- Sequences of resilient patients
- Sequences of disease progressors

10's-100's of Individuals; Millions of BCR sequences

**Convergence**

Shared antibodies that do not occur in controls or progressors

- Convergence reflects similar antibodies that are shared among members of a cohort and directed against a common antigen
- Convergence is rare, and therefore meaningful
- The result is target and pathway agnostic therapeutics
- We have a unique deep learning enabled process to express functional antibodies
Covid-19 study provides proof-of-concept

Deep Sequencing of B Cell Receptor Repertoires From COVID-19 Patients Reveals Strong Convergent Immune Signatures

Jacob D. Galson 1, Sebastian Schaetzle 1, Rachael J. M. Bashford-Rogers 1,2, Matthew I. J. Raybould 3, Aleksandr Kovaltsuk 3, Gavin J. Kilpatrick 1, Ralph Minter 1, Donna K. Finch 1, Jorge Dias 1, Louisa K. James 4, Gavin Thomas 4, Wing-Yiu Jason Lee 4, Jason Betley 5, Olivia Cavlari 1, Alex Leech 1, Charlotte M. Deane 5, Joan Seoane 6, Carlos Caldas 1, Daniel J. Pennington 1, Paul Pfeffer 1 and Jane Osbourn 1

Potent multi-strain covid neutralizing antibodies identified

Galson et al., https://doi.org/10.3389/fimmu.2020.605170
Alchemab’s growing Data Cube can stratify patients into diseases and disease-subtypes

Disease stratification example

Alchemab data demonstrates that antibody convergence is specific to disease cohorts, suggesting that separation between diseases is possible**

*Breast cancer; **Heatmap of 1,337 COVID-19 clonotypes, 1,180 Influenza clonotypes and 351 breast cancer clonotypes, demonstrating that the convergent signatures are unique to each disease cohort. Healthy controls subtracted.
Representation learning could uncover unique patient signatures

- Discovers hidden patterns in the data
- Alchemab’s AntiBERTa – ‘learns the language of antibodies’
- It also learns additional information we cannot yet interpret with our current state of biological knowledge

We apply this to our resilient patient antibody data sets and believe that it could be a transformative patient stratification tool.
Oncology – Case study
Convergence: Breadth of opportunities

Convergence between patients:

- Shared antibodies may indicate protection at the population level.

Convergence within patient:

- Related antibodies suggest active selection against important targets.

Convergence between tumor and periphery:

- Tumor-surveilling antibodies may identify targets active in the TME.
## Pancreatic cancer collaborations to date

<table>
<thead>
<tr>
<th>Collaborator</th>
<th>Type</th>
<th>Donors (#)</th>
<th>Resiliency definition</th>
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</thead>
<tbody>
<tr>
<td>UNIVERSITY OF OXFORD</td>
<td>RNA</td>
<td>28</td>
<td>Significant B cell infiltration</td>
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<td>CENTER LEON BERARD</td>
<td>RNA</td>
<td>31</td>
<td>LTS (5+ years)</td>
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<td>Case study</td>
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<td>Vall d'Hebron</td>
<td>RNA</td>
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Pancreatic cancer cohort

All PDAC patients have undergone resection

- **11 Healthy control**
- **12 Resilient**
- **10 Progressors**

**Sex**:
- Male
- Female

**Age**: 7 – 10 years

**Days between diagnosis and sample**: IIB

**Metastatic Origin**: All primary

**Histologic Grade**: IIB

**Cancer Stage (Pathological)**: IIB
Early analysis shows high convergence in resilient group

Convergent clonotypes
Total: 135,554

There are many more Resilient-convergent than Progressor-convergent clonotypes

Class-switch isotype distribution

IGHG1: Increased levels in resilient, & associated with antigen response & improved survival

Mean CDR3 length

Longer loop lengths in class-switched antibodies
Two large clonal expansions found in resilient subjects

SU859-Resilient

29% repertoire

SU857-Resilient

16% repertoire
Highly convergent resilient clonotypes found in multiple individuals

10 clonotypes found with exceptional convergence among resilient individuals *which were not found in progressors*, and evidence for disease relevance:

- Length-independent super-convergence
- Low probability of generation & rare in healthy controls
- Predominantly IgG1

<table>
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<th>CLUSTER SIZE</th>
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<th>CDR3 LENGTH</th>
<th>MUTATIONS</th>
<th>GENERATION PROBABILITY</th>
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*Similar sequences despite length differences*
Mining the Alchemab Data Cube

Convergent Clonotypes
(Total: 150133)

Resilient

Control

Progressor

18,443
56,071
17,711
15,203
11,219
15,197
1,710

Antibodies of interest
from current Tissue
Solutions PDAC study

Other Alchemab PDAC studies

External datasets of interest

Alchemab curated antibody database

~10,000 Abs from the literature with known binding properties

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Mining PDAC datasets for convergence

Other Alchemab PDAC studies

• Alchemab pilot PDAC study comparing high and low B cell infiltrate groups
• Single-cell sequencing from blood and tumor
• Two matches to PDAC case study demonstrating convergence from pilot

External datasets of interest

• Triple Negative breast cancer study from Harris et al. investigating prognostic B cell profiles
• Single-cell sequencing from tumor samples
• Two matches to PDAC case study demonstrating high levels of convergence between different solid tumor studies
Homology to approved KDR mAb translates to target binding

Ramucirumab is a VEGFR2 (KDR) antibody, approved for treatment of solid tumors

One of Alchemab’s convergent clusters is highly homologous to ramucirumab

- Assay shows binding for multiple antibodies from one clonotype to KDR

Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial

Dr Prof Charles S Fuchs, MD, Jiri Tomasek, MD, Prof Cho Jae Young, MD, Filip Dumitru, MD, Rodolfo Passalacqua, MD, Prof Chanchal Goswami, MD, et al. Show all authors + Show footnotes

Published: October 03, 2013 - DOI: https://doi.org/10.1016/S0140-6736(13)61719-5
Summary
Convergence analysis could be the next wave of antibody generation

(A) Mouse hybridoma
- Harvest Splenocytes
- Generate hybridomas
- Immunization With targets
- Screening
- Chimerization
- CDR graft
- Chimeric mAb
- Mouse mAb

(B) Phage display
- scFv or Fab
- Phage-displayed Ab libraries
- Biopanning With targets (3-5 cycles)
- Screening
- Chimeric mAb
- Humanized mAb

(C) Transgenic mouse
- Harvest splenocytes
- Generate hybridomas
- Immunization with targets
- Screening
- Construction of Human IgG
- Human mAb

(D) Single B cell
- PBMC
- Sort B cells with labeled antigens
- PCR, construct \( V_H \) and \( V_L \)
- Screening
- Chimerization
- CDR graft
- Chimeric mAb
- Humanized mAb

(E) B cell convergence
- Computation
- Convergence & triage
- Screening

Source: Journal of Biomedical Science, 21:1 (2020) - Adapted
We have proven the concept and we are expanding our capabilities

**Antibody Therapeutics**

Unique resilient-convergent antibodies identified from PDAC cohort

Antibodies with sequences highly similar to known, efficacious antibodies identified

**Target Identification**

Antibodies undergoing target deconvolution

**Patient Stratification**

Early evidence of ability to stratify patients into disease sub-groups

**Alchemab Discovery**

World’s most advanced machine learning model evaluating B cell repertoires demonstrating potential to identify new biology
Thank you!