ALCHEMAB THERAPEUTICS

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

ALCHEMAB THERAPEUTICS

Discovering and developing protective, patient-originated therapeutic antibodies

- Focus on protective antibody responses
- Convergent in resilient individuals
- Target agnostic approach
- Advanced computational approaches

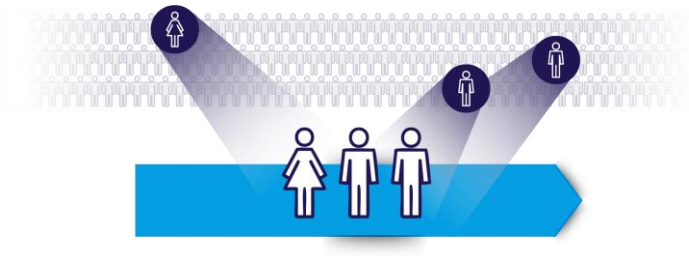
Alchemab concept

ALCHEMAB
THERAPEUTICS

Alchemab concept

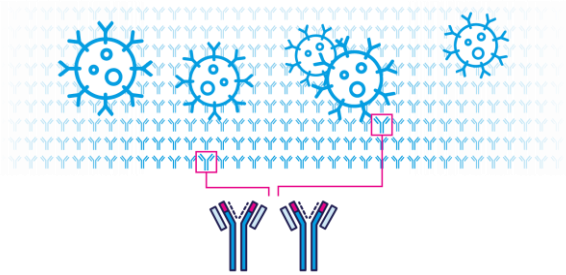
WE IDENTIFY

We identify especially resilient individuals – and learn how they overcome or resist disease



WE SEQUENCE

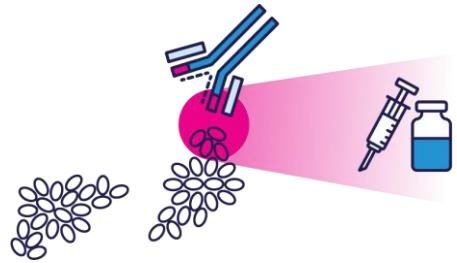
We sequence B cells from the resilient individuals and identify antibodies with similar properties



Antibodies

WE DISCOVER

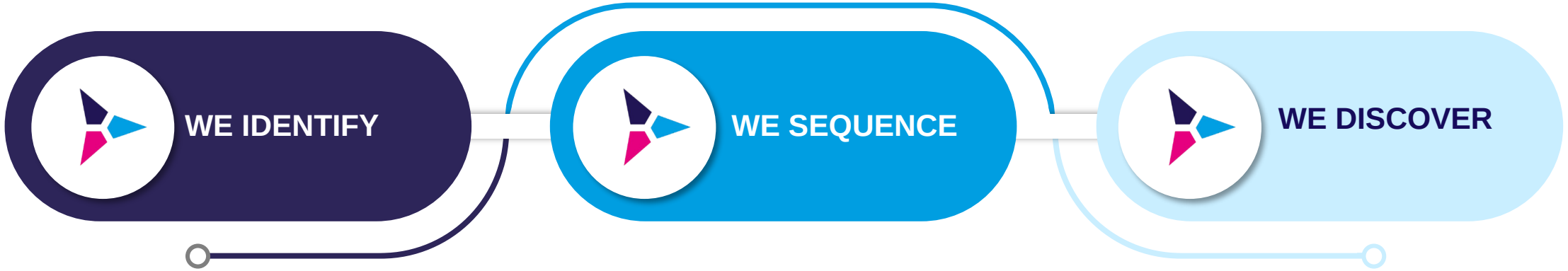
We discover the binding targets of the antibodies, understand their protective properties and develop candidates that replicate the protective effect



Novel Antibody Therapeutic

Unbiased platform to identify novel therapeutics

Patient-originated, physiologically validated therapeutics

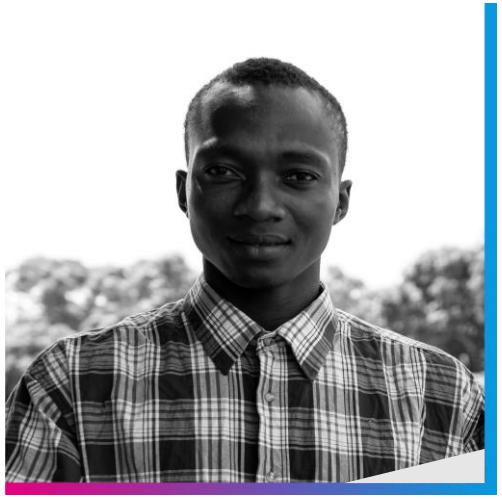


Our therapeutic antibodies are physiologically validated, increasing the likelihood that the targets are critical disease modifiers

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

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

A human-derived antibody targets misfolded SOD1 and ameliorates motor symptoms in mouse models of amyotrophic lateral sclerosis

Marcel Maier[1]*, Tobias Welt[2]*, Fabian Wirth[1], Fabio Montrasio[1], Daniel Preisig[2], Jordan McAfoose[2], Fernando G. Vieira[3], Luka Kulic[2], Claudia Späni[2], Thilo Stehle[4], Steve Perrin[3], Markus Weber[5], Christoph Hock[1,2], Roger M. Nitsch[1,2], Jan Grimm[1†]

Article

Cancer Cell

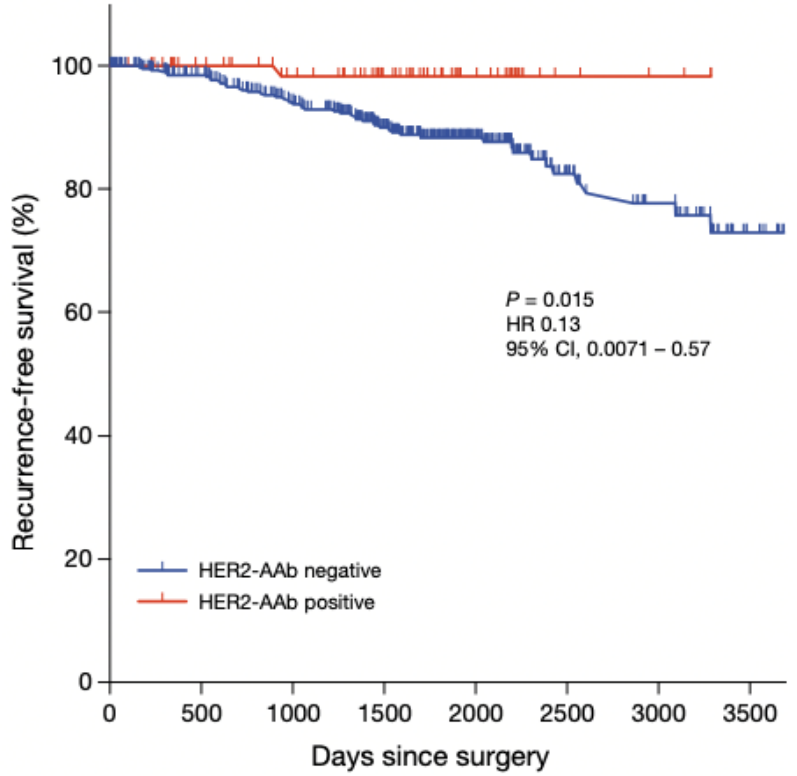
Intratumoral plasma cells predict outcomes to PD-L1 blockade in non-small cell lung cancer

- 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

Breast Cancer Res Treat (2016) 157:55–63
DOI 10.1007/s10549-016-3801-4

Protective effect of naturally occurring anti-HER2 autoantibodies on breast cancer

Yukiko Tabuchi[1] · Masafumi Shimoda[1] · Naofumi Kagara[1] · Yasuto Naoi[1] · Tomonori Tanei[1] · Atsushi Shimomura[1] · Kenzo Shimazu[1] · Seung Jin Kim[1] · Shinzaburo Noguchi[1]



We collaborate with a broad and growing network of institutions

Neurodegeneration

CHDI FOUNDATION
Accelerating therapeutic development for Huntington's disease

Queen Mary University of London

EPAD
European Prevention of Alzheimer's Dementia Consortium

Lumind IDSC DOWN SYNDROME FOUNDATION

UCL

Oncology

CY-Biobank Research and Innovation Center of Excellence

UNIVERSITY OF OXFORD

AstraZeneca

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

CANCER RESEARCH UK

ST MARK'S THE NATIONAL BOWEL HOSPITAL

HCL HOSPICES CIVILS DE LYON

Infectious Disease and other areas

Amsterdam UMC Universitair Medische Centra

NHS Barts Health NHS Trust

JOHNS HOPKINS UNIVERSITY

UNIVERSITY OF OXFORD

NVIDIA

illumina

Platform enabling collaborations

Our platform has generated numerous program opportunities across a variety of diseases

Sourcing → BCR-seq → *In silico* Ab triage → Antibody discovery → Cell function → Optimisation & Lead candidate selection → *In vivo* pharmacology

Oncology
- Solid tumour
- Solid tumour: pancreatic
- Solid tumour: breast
- Solid tumour: prostate
- Solid tumour: mesothelioma
- Solid tumour: glioblastoma
- Solid tumour: colorectal

Neurodegeneration
- Alzheimer's Disease
- Huntington's Disease
- Parkinson's Disease
- Amyotrophic lateral sclerosis
- Fronto-Temporal Dementia

ID & Other
- Healthy aging
- Covid-19

How do we do what we do?

ALCHEMAB THERAPEUTICS

Discovery process powered by advanced sequencing, big data, and deep learning

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Core Technologies

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

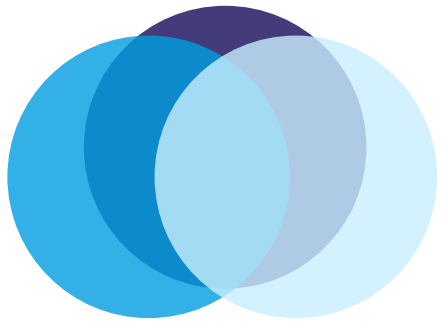
Process

Convergent autoantibody sequences provide the starting point for discovery

Population B Cell Repertoire Analysis

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

Convergence
Shared antibodies that do not occur in controls or progressors



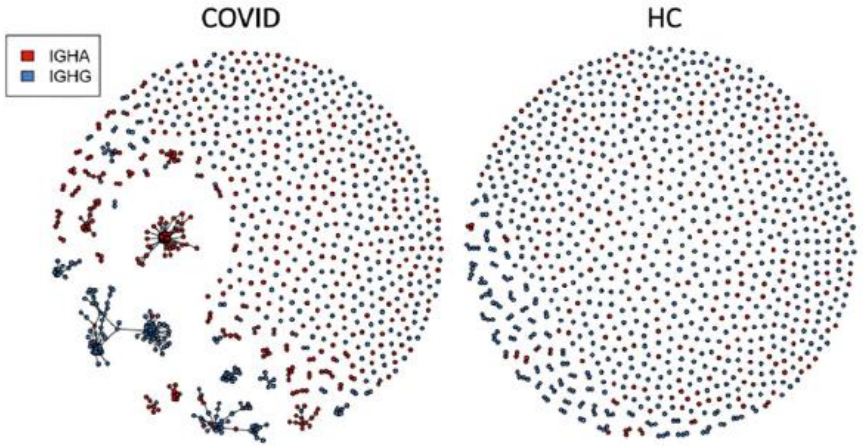
- Convergence reflects similar antibodies that are shared among members of a cohort and directed against a common antigen
- Convergence is rare, and therefore meaningful
- The result is target and pathway agnostic therapeutics
- We have a unique deep learning enabled process to express functional antibodies

Covid-19 study provides proof-of-concept

frontiers in Immunology

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

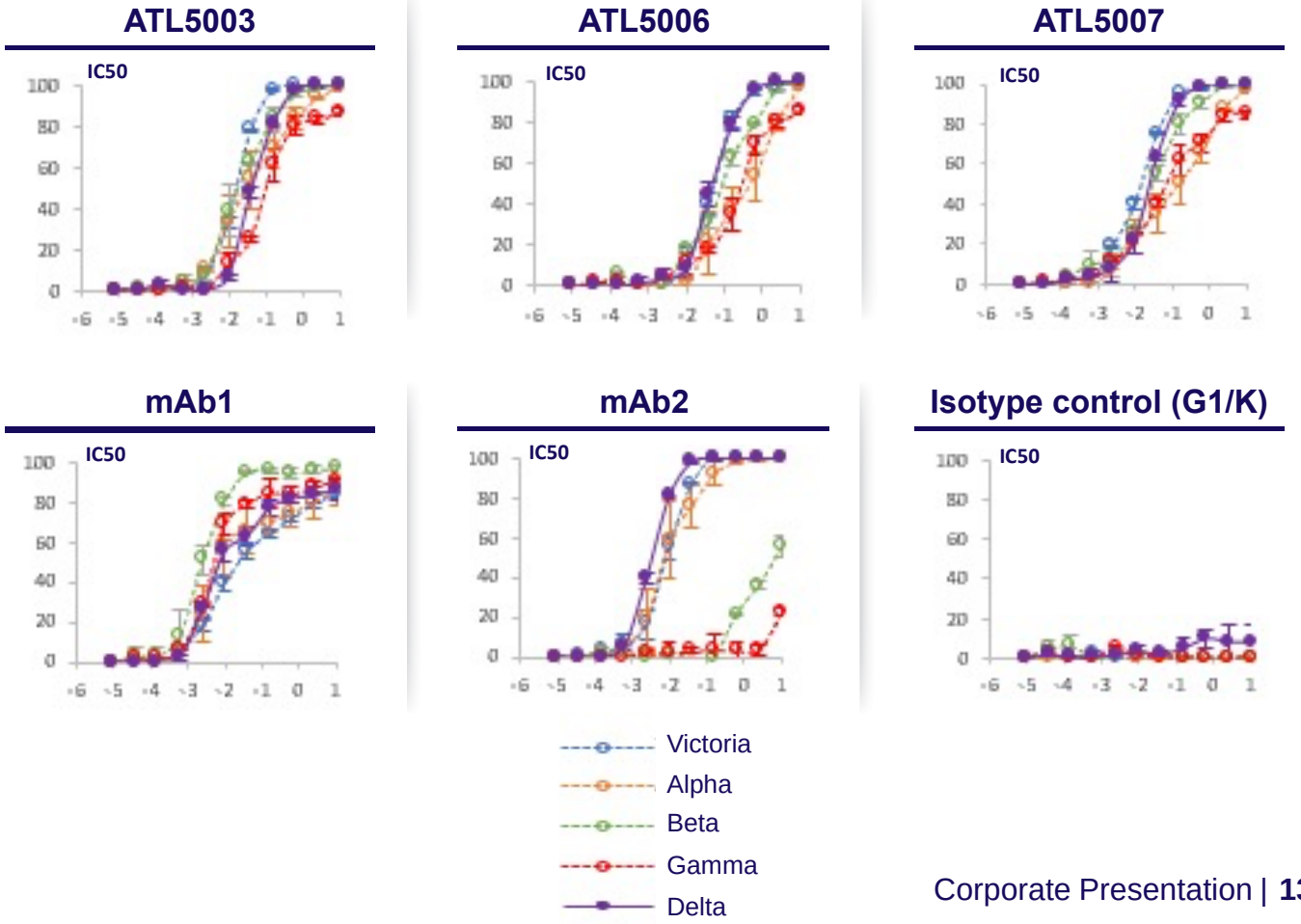
Jacob D. Galson[1], Sebastian Schaetzle[1], Rachael J. M. Bashford-Rogers[1,2], Matthew I. J. Raybould[3], Aleksandr Kovaltsuk[3], Gavin J. Kilpatrick[1], Ralph Minter[1], Donna K. Finch[1], Jorge Dias[1], Louisa K. James[4], Gavin Thomas[4], Wing-Yiu Jason Lee[4], Jason Betley[5], Olivia Cavlan[1], Alex Leech[1], Charlotte M. Deane[3], Joan Seoane[6], Carlos Caldas[7], Daniel J. Pennington[4], Paul Pfeffer[4] and Jane Osbourn[1]*



Potent multi-strain covid neutralizing antibodies identified

Alchemab

Commercial cocktail & control

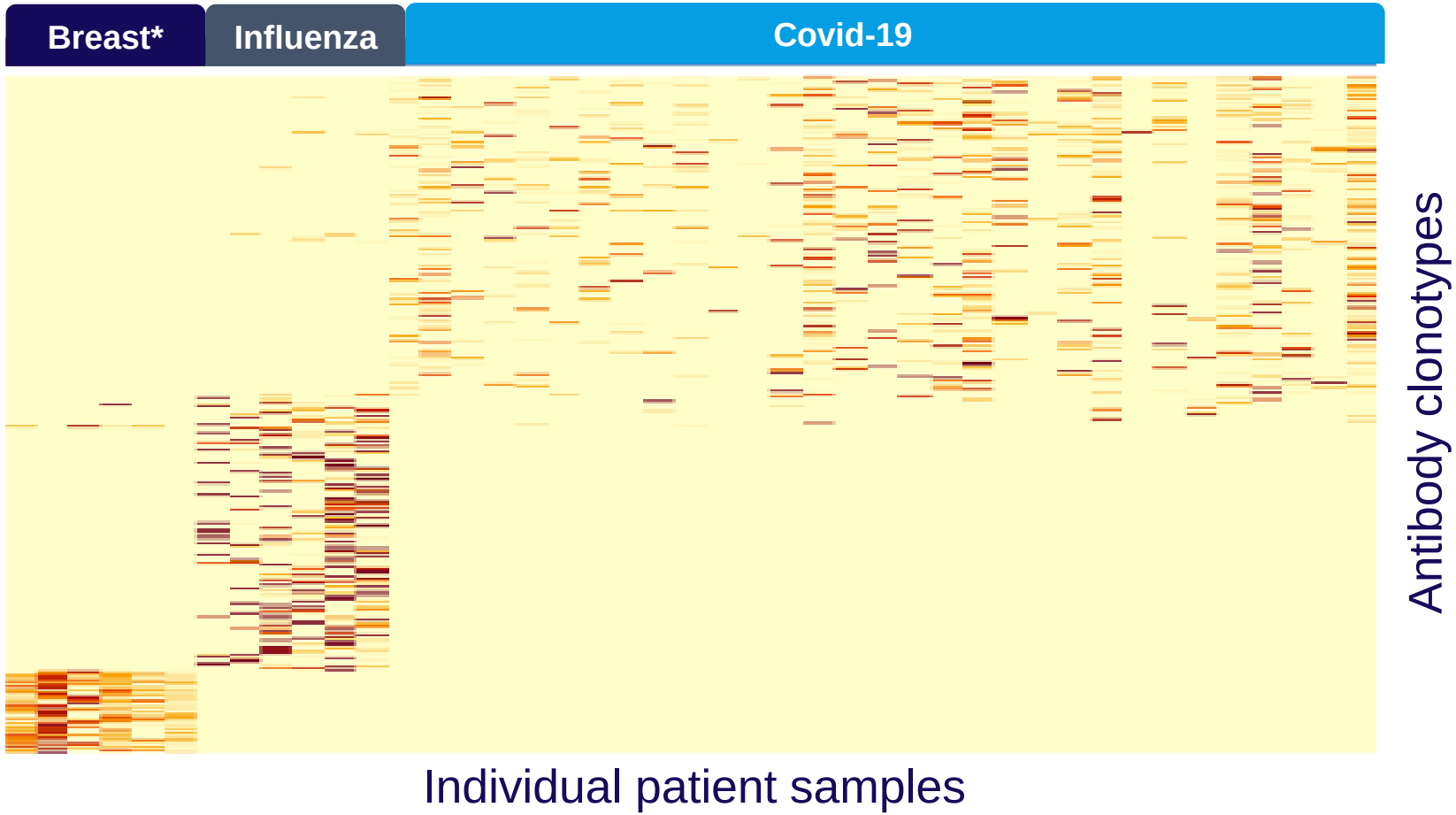


Galson *et al*., https://doi.org/10.3389/fimmu.2020.605170

Alchemab's growing Data Cube can stratify patients into diseases and disease-subtypes

Disease stratification example

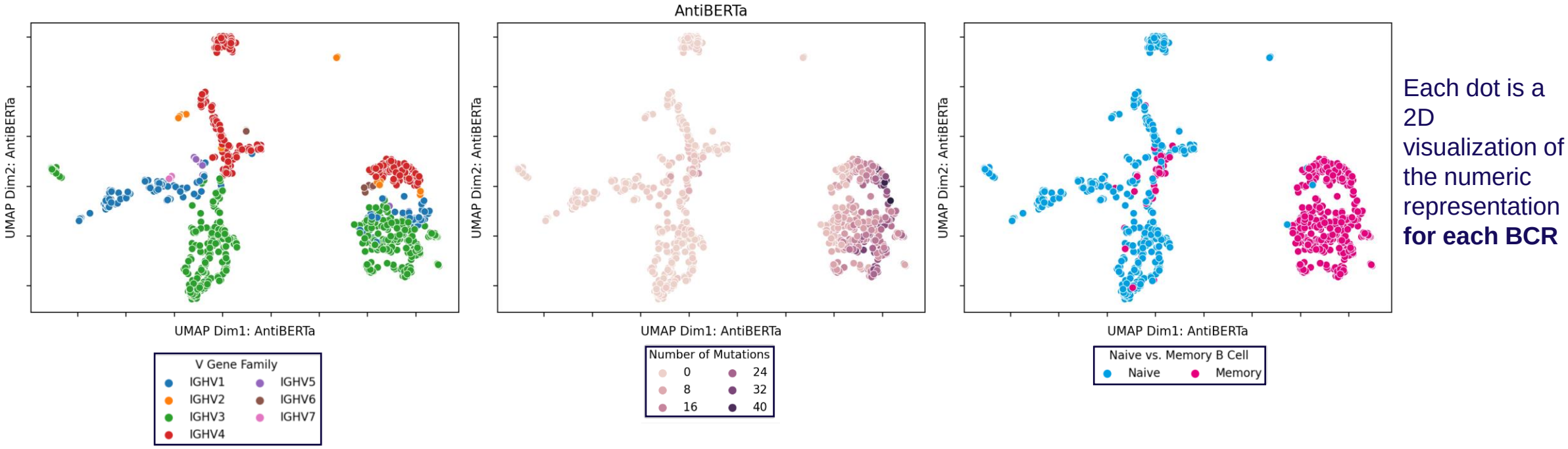
Alchemab data demonstrates that antibody convergence is specific to disease cohorts, suggesting that separation between diseases is possible**



*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



Each dot is a 2D visualization of the numeric representation **for each BCR**

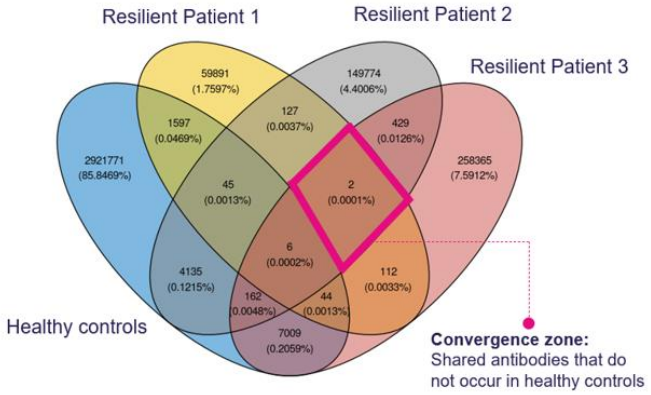
We apply this to our resilient patient antibody data sets and believe that it could be a transformative patient stratification tool

Oncology – Case study

ALCHEMAB THERAPEUTICS

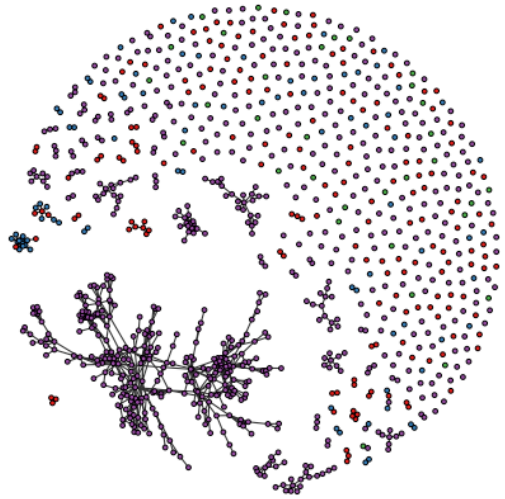
Convergence: Breadth of opportunities

Convergence between patients



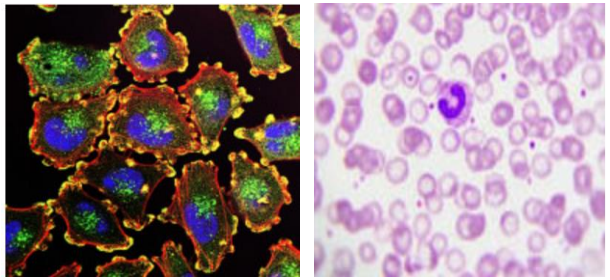
Shared antibodies may indicate protection at the population level

Convergence within patient



Related antibodies suggest active selection against important targets

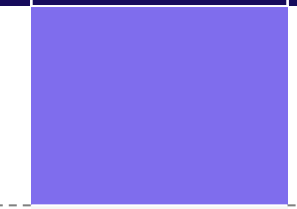
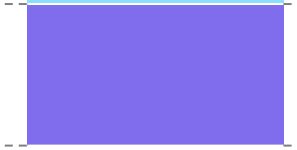
Convergence between tumor and periphery



Tumor-surveilling antibodies may identify targets active in the TME

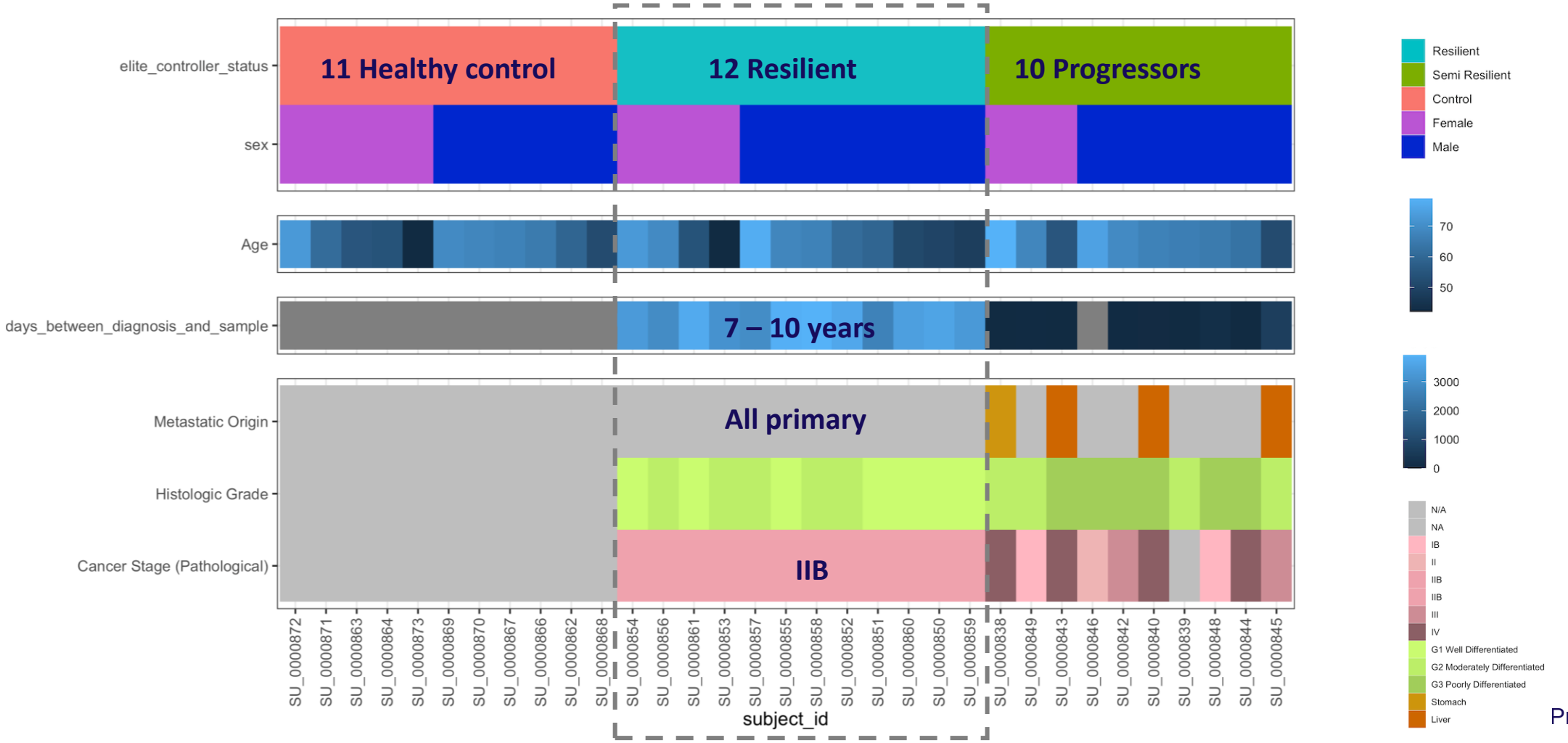
Pancreatic cancer collaborations to date

RNA Plasma/Serum Tumour Tissue / B cells

Collaborator	Type	Donors (#)	Resiliency definition
UNIVERSITY OF OXFORD		28	Significant B cell infiltration
CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD		31	LTS (5+ years)
Case study		36	LTS (7+ years)
Barts Cancer Institute Queen Mary University of London		30	LTS (5+ years)
Vall d'Hebron Institut de Recerca VHIR		40	LTS (5+ years)

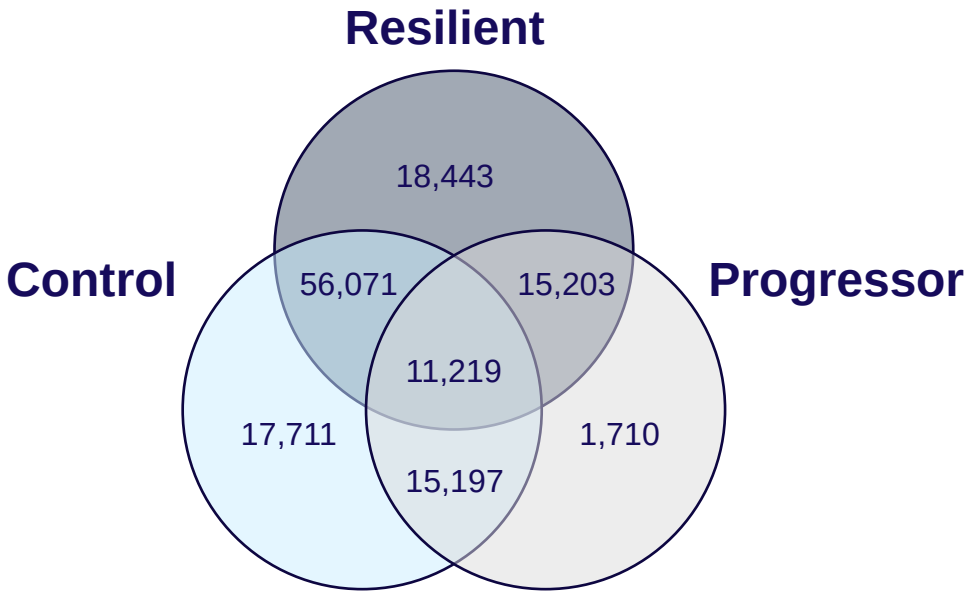
Pancreatic cancer cohort

All PDAC patients have undergone resection



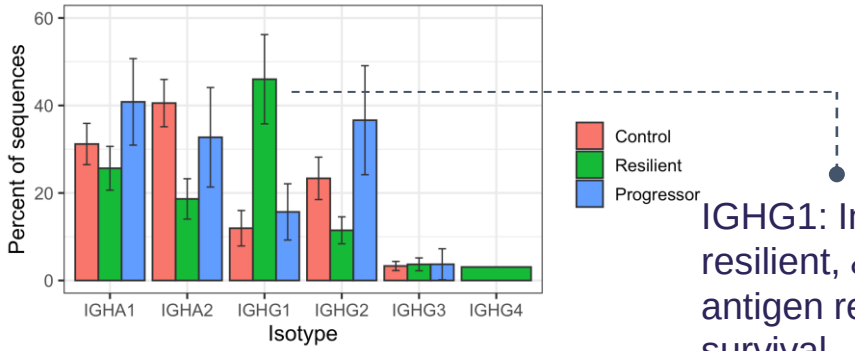
Early analysis shows high convergence in resilient group

Convergent clonotypes
Total: 135,554



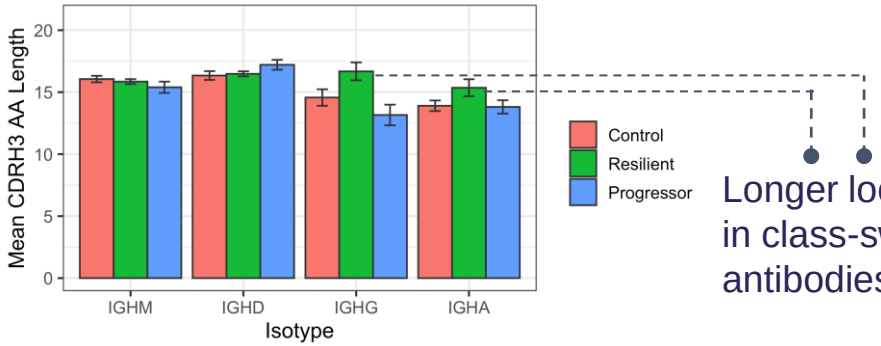
There are many more Resilient-convergent than Progressor-convergent clonotypes

Class-switch isotype distribution



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

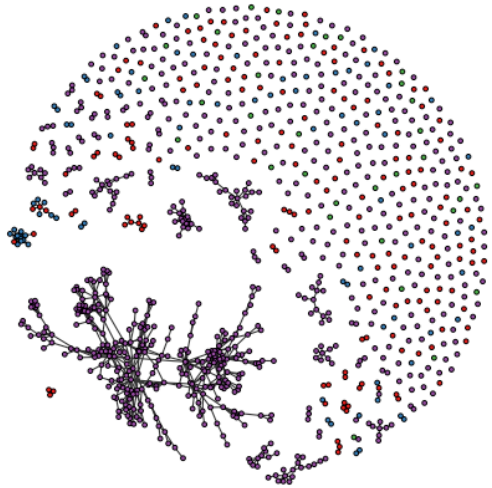
Mean CDR3 length

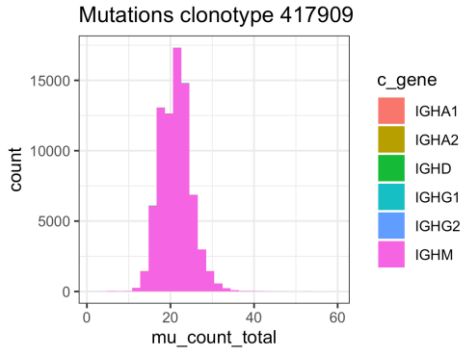


Longer loop lengths in class-switched antibodies

Two large clonal expansions found in resilient subjects

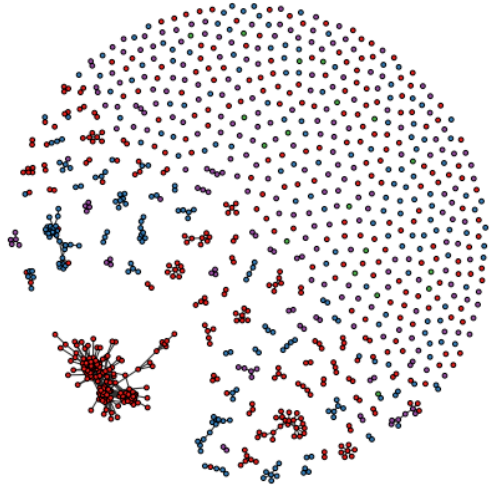
SU859-Resilient

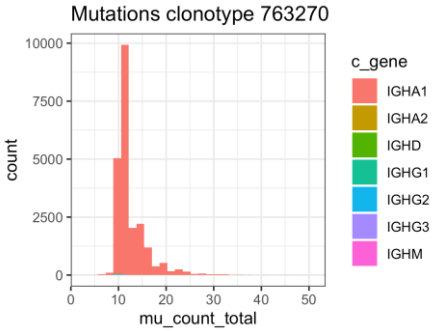




29% repertoire

SU857-Resilient





16% repertoire

Highly convergent resilient clonotypes found in multiple individuals

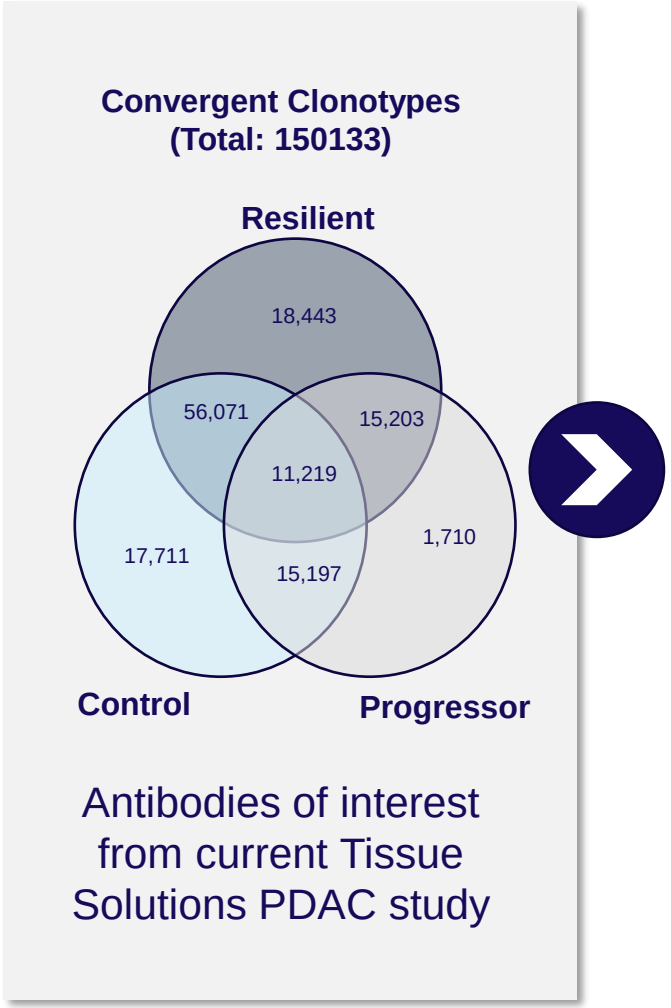
10 clonotypes found with exceptional convergence among resilient individuals **which were not found in progressors**, and evidence for disease relevance:

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

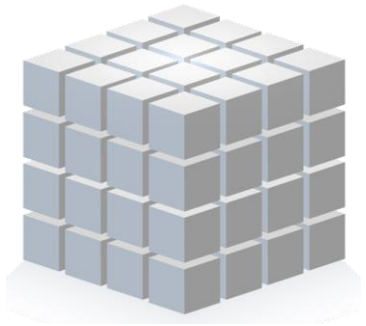
CLUSTER SIZE	CONVERGENCE LEVEL (OUT OF 12)	CDR3 LENGTH	MUTATIONS	GENERATION PROBABILITY	PROP. IN HEALTHY CONTROL	PREVALENT ISOTYPE
151	8	20	1.58	4.35E-12	0.060	IGHG1
40	8	20*	1.65	9.34E-12	0.050	IGHG1
43	8	19*	1.35	4.63E-20	0.186	IGHG1
73	7	16	1.51	2.13E-13	0.055	IGHG1
42	5	16	2.07	1.29E-12	0	IGHG1
73	5	15*	1.41	7.42E-11	0.082	IGHG1
33	5	14*	1.52	7.69E-11	0	IGHG1
17	5	13	1.18	1.14E-11	0.059	IGHG1
16	6	13	17.63	1.01E-11	0	IGHM
22	5	11	25.59	5.20E-10	0.091	IGHA1

*Similar sequences despite length differences

Mining the Alchemab Data Cube



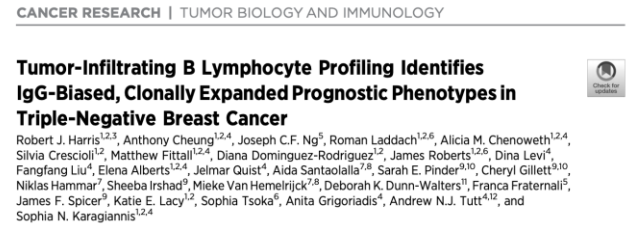
Antibodies of interest from current Tissue Solutions PDAC study



Other Alchemab PDAC studies

Collaborator	Type	Donors (#)	Resiliency definition
UNIVERSITY OF OXFORD		28	Significant B cell infiltration
CENTRE LEON BERARD		31	LTS (5+ years)
Case study		36	LTS (7+ years)
Barts Cancer Institute		30	LTS (5+ years)
		40	LTS (5+ years)

External datasets of interest



CANCER RESEARCH | TUMOR BIOLOGY AND IMMUNOLOGY

Tumor-Infiltrating B Lymphocyte Profiling Identifies IgG-Biased, Clonally Expanded Prognostic Phenotypes in Triple-Negative Breast Cancer

Robert J. Harris[1,2,3], Anthony Cheung[1,2,4], Joseph C.F. Ng[5], Roman Laddach[1,2,6], Alicia M. Chenoweth[1,2,4], Silvia Crescioli[1,2], Matthew Fittall[1,2,4], Diana Dominguez-Rodriguez[1,2], James Roberts[1,2,6], Dina Levi[4], Fangfang Liu[4], Elena Alberts[1,2,4], Jelmar Quist[4], Aida Santaolalla[7,8], Sarah E. Pinder[9,10], Cheryl Gillett[9,10], Niklas Hammar[7], Sheeba Irshad[9], Mieke Van Hemelrijck[7,8], Deborah K. Dunn-Walters[11], Franca Fraternali[5], James F. Spicer[9], Katie E. Lacy[1,2], Sophia Tsoka[6], Anita Grigoriadis[4], Andrew N.J. Tutt[4,12], and Sophia N. Karagiannis[1,2,4]

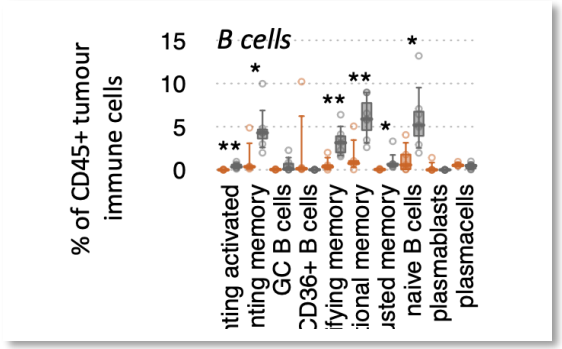
Alchemab curated antibody database

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

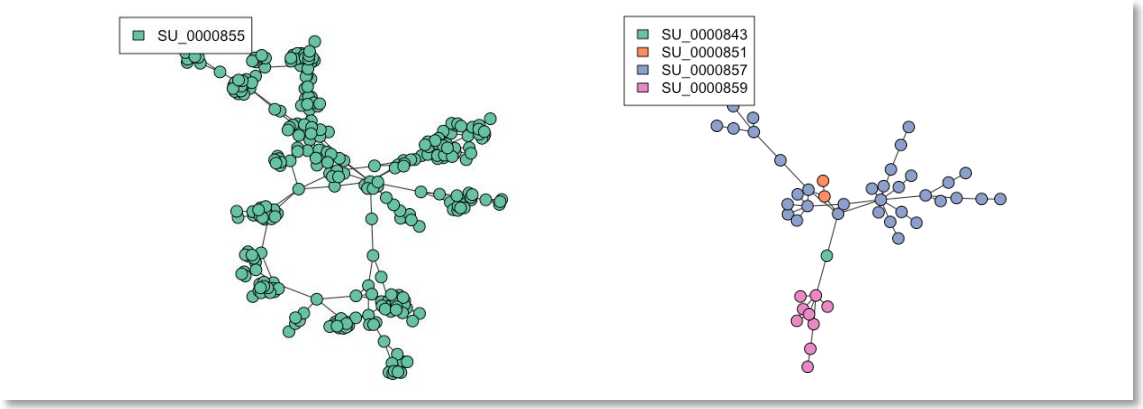
Mining PDAC datasets for convergence

Other Alchemab PDAC studies

- Alchemab pilot PDAC study comparing high and low B cell infiltrate groups
- Single-cell sequencing from blood and tumor

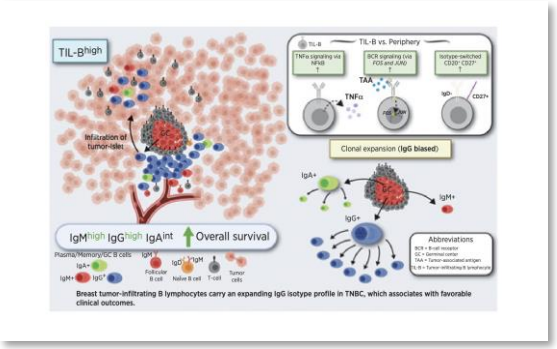


- Two matches to PDAC case study demonstrating convergence from pilot

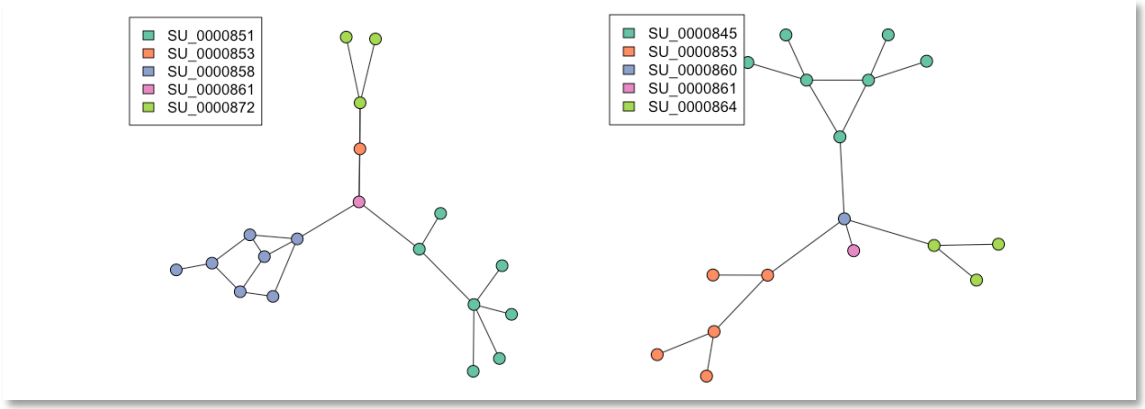


External datasets of interest

- 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

ARTICLES | VOLUME 383, ISSUE 9911, P31-39, JANUARY 04, 2014

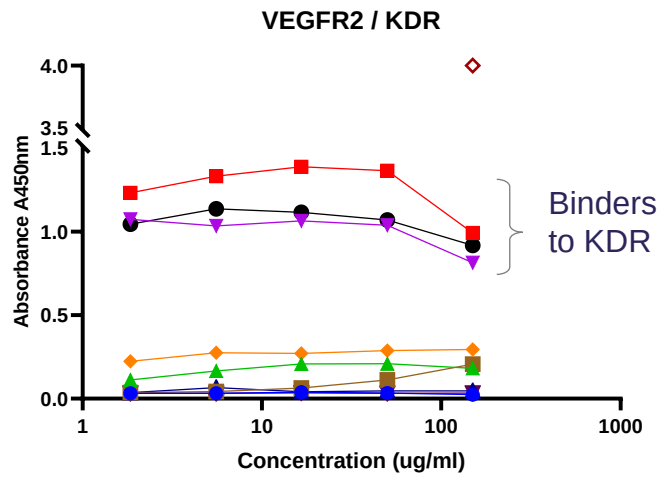
Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial

Dr Prof Charles S Fuchs, MD • Jiri Tomasek, MD • Prof Cho Jae Yong, 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 • Check for updates

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

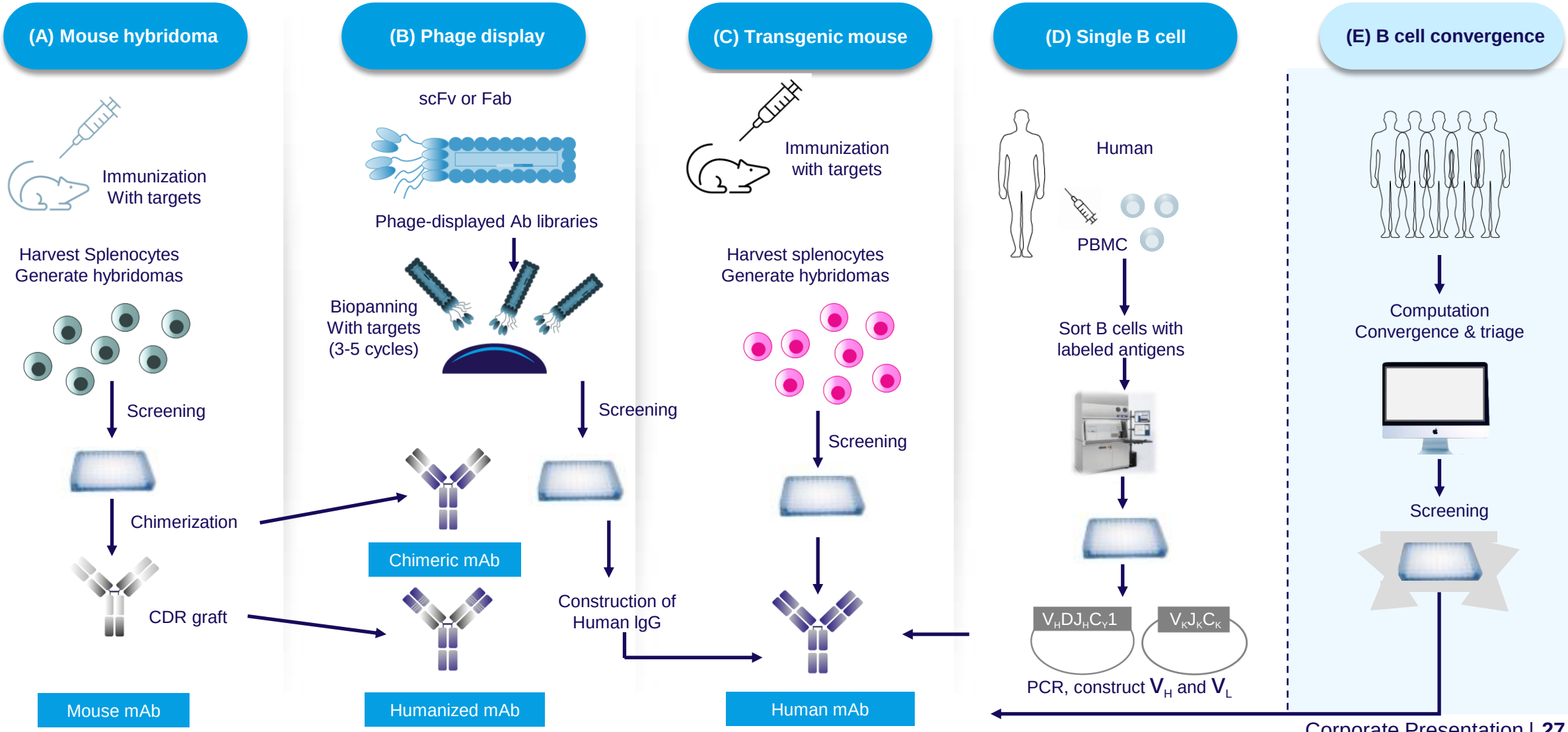
- Assay shows binding for multiple antibodies from one clonotype to KDR



Summary

ALCHEMAB THERAPEUTICS

Convergence analysis could be the next wave of antibody generation



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!

ALCHEMAB THERAPEUTICS