ALCHEMAB THERAPEUTICS

Antibodies from Resilient Individuals: A novel approach for Antibody Drug Discovery

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Our Vision: To Use The Power Of The Human Immune System To Discover New Medicines

Discovering and developing protective, patient-originated therapeutic antibodies

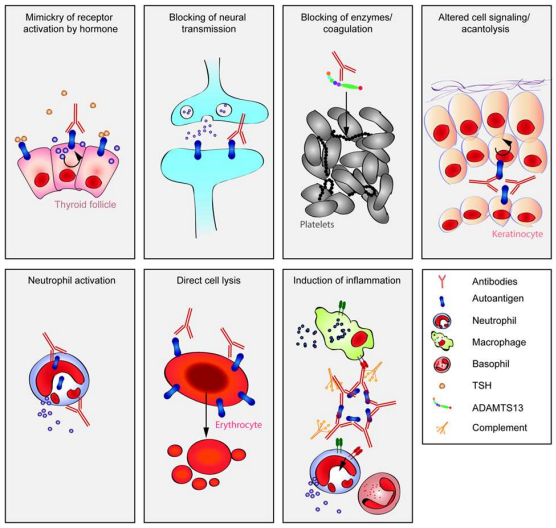
- Focus on protective antibody responses
- Convergent in resilient individuals
- Target agnostic approach
- Advanced computational approaches

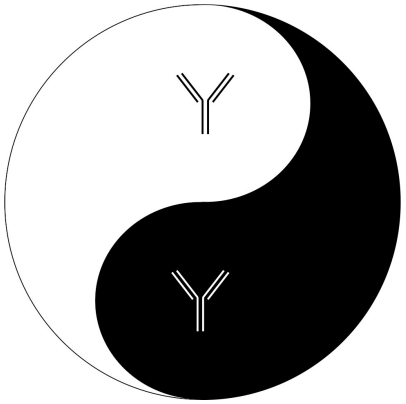
Auto-antibodies can determine disease outcomes

Pathogenic

Mechanisms of Autoantibody-Induced Pathology

Ralf J. Ludwig[1], Karen Vanhoorelbeke[2], Frank Leypoldt[3,4,5], Ziya Kaya[6], Katja Bieber[1], Sandra M. McLachlan[7], Lars Komorowski[8], Jie Luo[9], Octavio Cabral-Marques[10], Christoph M. Hammers[11], Jon M. Lindstrom[3], Peter Lamprecht[10], Andrea Fischer[6], Gabriela Riemekasten[10], Claudia Tersteeg[2], Peter Sondermann[12], Basil Rapoport[7], Klaus-Peter Wandinger[13], Christian Probst[8], Asmaa El Beidaq[14], Enno Schmidt[1], Alan Verkman[15,16], Rudolf A. Manz[14] and Falk Nimmerjahn[17]*



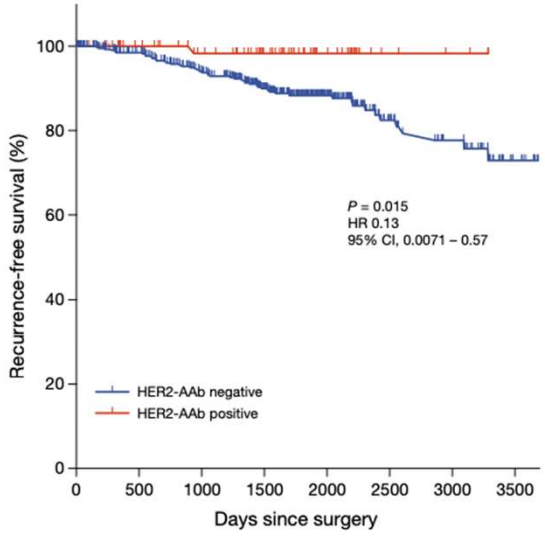


Protective

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]

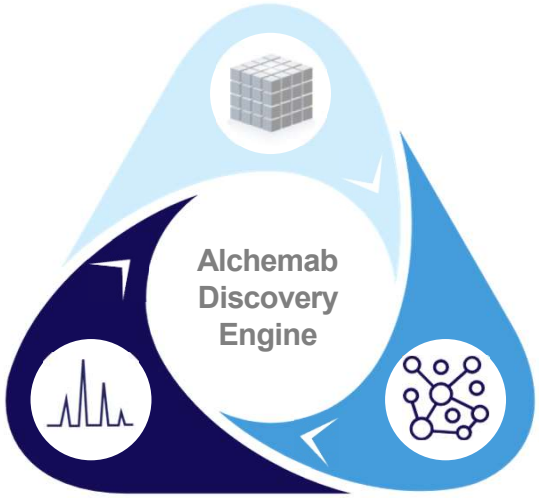


Alchemab Concept

Our approach finds naturally occurring protective antibodies, deconvolutes their targets and validates their function

Repertoire analysis to **select** antibodies

Resilient patient cohort with disease and healthy controls



Validate function *in vitro* & *in vivo*

Proteomics to **deconvolute** targets

Phenotypic assay cascade to **screen** for function

Unbiased target and drug discovery

Resilience can take many forms

Patients with years of survival with typically untreatable cancer

Pancreatic cancer survivors, alive 7+ years after diagnosis

Median survival: 10-12 months

Patients with susceptibility to neurodegenerative disease who do not progress

Confirmed Beta-amyloid in CSF, APOE4 risk allele, no or very slow disease progression

Very long-lived, healthy individuals without chronic diseases

Average >100 years, no cognitive impairment nor debilitating illness

~0.004% population

Alchemab Platform

Our Proprietary Discovery Process Combines Advanced Computational Analysis And High Throughput Phenotypic Screens

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Repertoire analysis to select antibodies

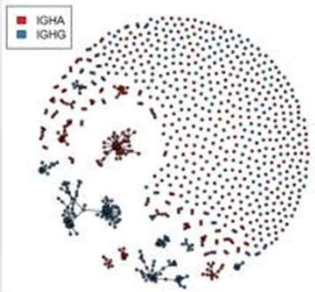
Proteomics to deconvolute targets

Phenotypic assay cascade

Resilient Patients

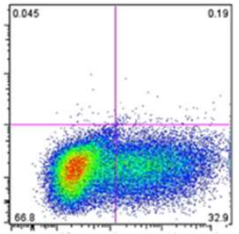
NGS from patient B cells

Antibody discovery in Data Cube



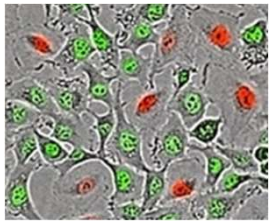
Antibody Expression

Target discovery



Proteome screen

Biological function



Live cell imaging

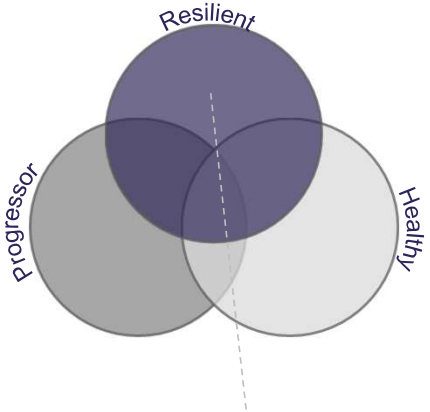
mAb Projects

We Identify BCR Sequences Of Interest Through Analysis Of Deep NGS Of Patient Samples

Core Technologies

- **Repertoire analysis**
- **Target deconvolution**
- **Phenotypic screening**

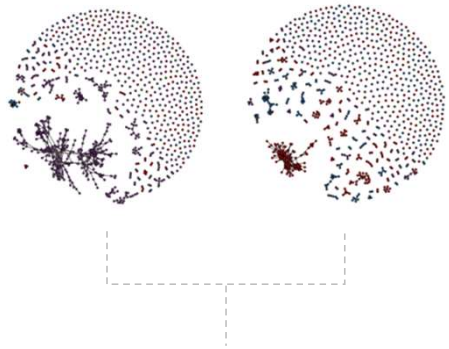
Population B Cell Repertoire Analysis



Convergence

We search for antibodies shared in the resilient group that do not occur in controls or progressors

Population B Cell Repertoire Analysis



Clonal expansions

Large expansion of highly related sequences comprising >20% of patient's entire repertoire

Unbiased Targets And Pathways Are Identified Using Our Suite Of Antigen Proteomics Tools

Core Technologies

- Repertoire analysis
- Target deconvolution
- Phenotypic screening

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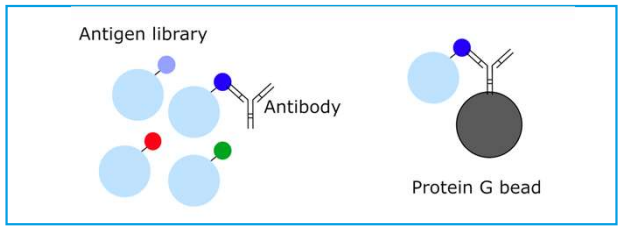
1 High throughout deconvolution using display technology



- High throughput and cost-effective
- Focuses on relevant human antigens
- Validated with 100s antibodies

2 Suite of complementary deconvolution technologies

Identify target of cell binders	→	IP / Mass spectrometry
High throughput serum screening	→	Protein microarrays
Enrich for cell and antigen binders	→	Phage libraries derived from resilient patients

A Wide Range Of Phenotypic Assays Are Used To Characterize Resilient Antibodies

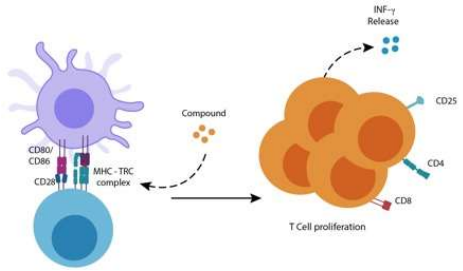
Core Technologies

- Repertoire analysis
- Target deconvolution
- **Phenotypic screening**

Example assays

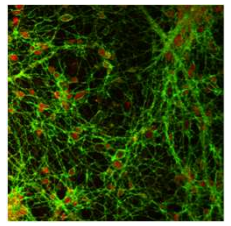
Immuno-phenotyping and activation

Mixed Lymphocyte Reaction: Measures immune activation/suppression

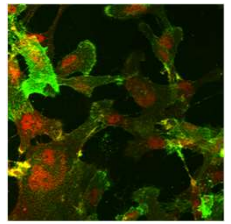


iPSC-derived CNS binding

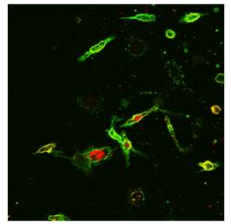
Neurons



Astrocytes



Microglia



Alchemab uses additional immuno, cell line and other phenotypic screening assays

Alchemab's Data Cube Creates Opportunities For Deep Learning

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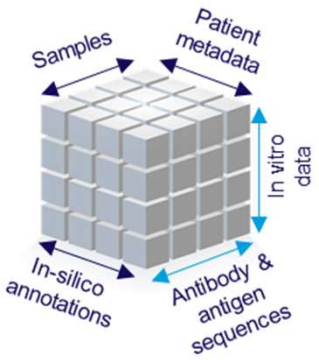
Core Technologies

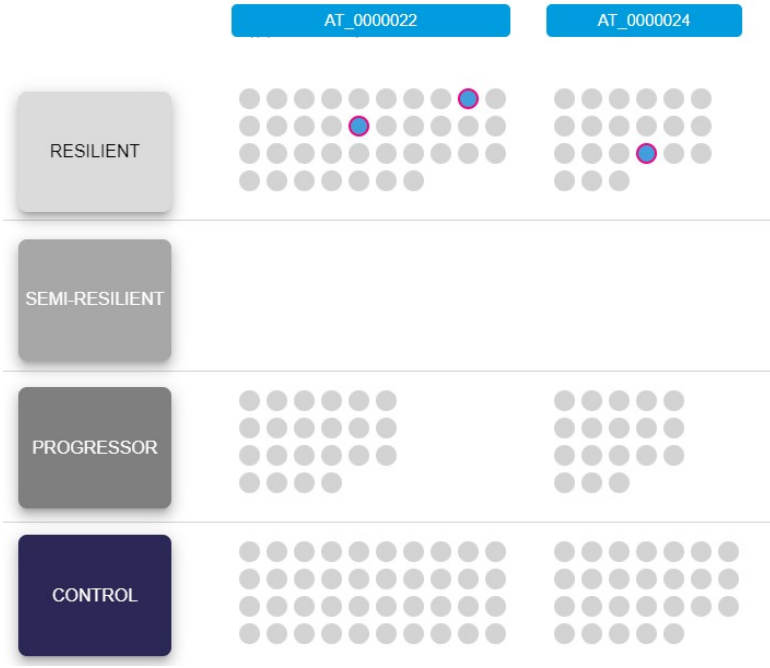
Deep learning

The largest resource of combined antibody and antigen sequence datasets, all from our unique set of resilient patient cohorts

- Unique database with billions of data points
- Deep learning toolkit
  - Clustering
  - Cross disease analysis
  - Patient stratification

Data Cube





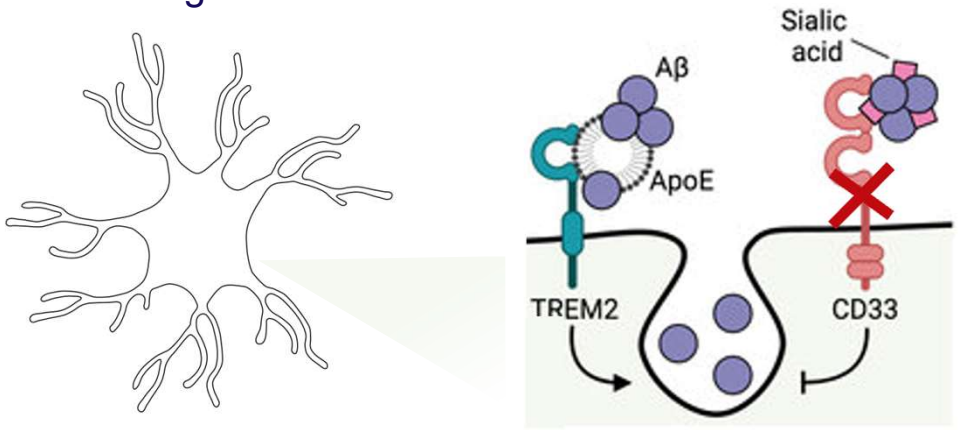
Neurodegeneration case study: CD33 Antibody Program

We have identified a novel, differentiated CD33 antibody to restore microglial function in Alzheimer's Disease

- CD33 (Siglec-3) is a transmembrane sialic acid-binding receptor on the surface of microglial cells.
- Target has strong resilience association and genetic validation in AD
- Different MoA from reported CD33 therapeutic antibodies, with potential for improved PK and PD

CD33 inhibits microglial activation and suppresses phagocytosis and degradation of harmful proteins

Microglial cell



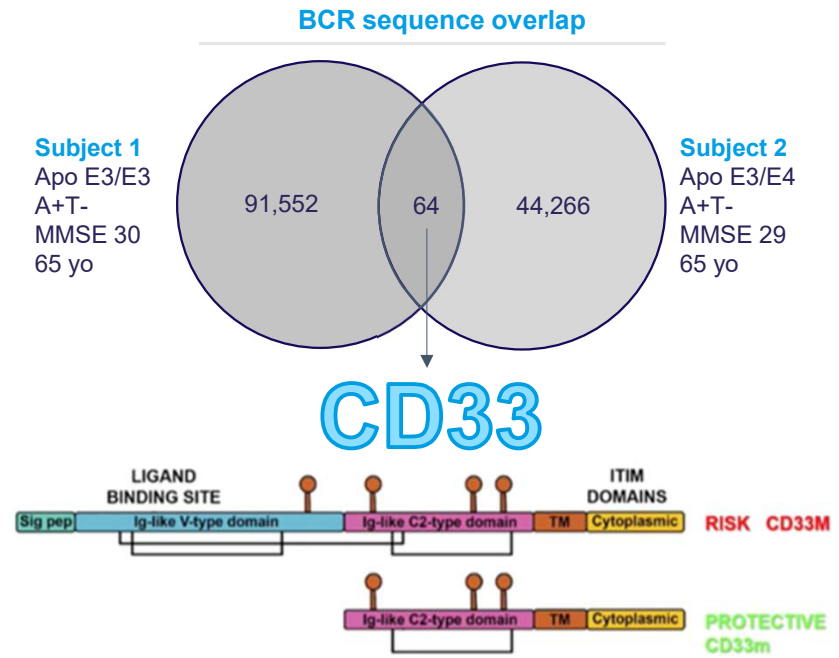
Microglial dysfunction:

- Slow migration to sites of damage
- Sustained inflammation
- Defective phagocytosis

- Microglia are brain-resident immune cells which maintain neural networks and repair damage
- Microglial dysfunction is one of the hallmarks of Alzheimer's Disease
- CD33 signalling inhibits normal homeostatic function of microglia, including phagocytosis
- It is a member of the immunoglobulin supergene family and is activated by sialoglycan (sialic acid) binding
- CD33 is expressed in microglia and found in other myeloid cells, mast cells and NK cells

Image from Microglia in Alzheimer's Disease in the Context of Tau Pathology Biomolecules 2020 10(10):1439

Our anti-CD33 antibody was discovered from individuals with Alzheimer's Disease risk factors

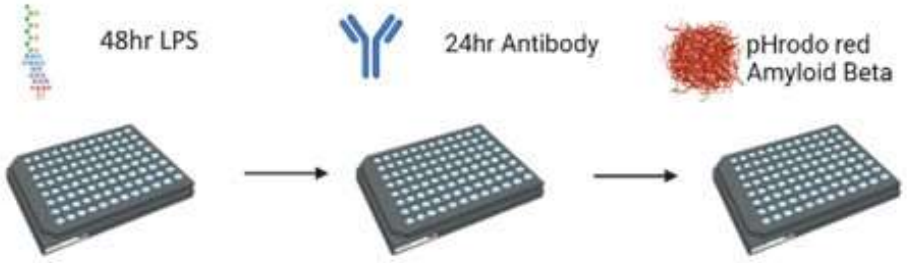


Longer Means Riskier. *Alternative splicing produces two isoforms of CD33; the long isoform, aka CD33M, contains a ligand binding site. The short version, aka CD33m, lacks that site and is favored by the protective variant. [Courtesy of Peter St. George-Hyslop.]*

- CD33 identified by convergence in two individuals who were positive for amyloid, but negative for tau and cognitively normal
- CD33m (protective allele for AD) lacks ligand binding site so non-inhibitory
- CD33M (risk allele; full length) is elevated in microglia of AD patients
- Multiple antibodies identified from resilient patients; all bind near ligand binding site

ATLX-1088 causes a significant increase in phagocytosis in human iPSC microglia

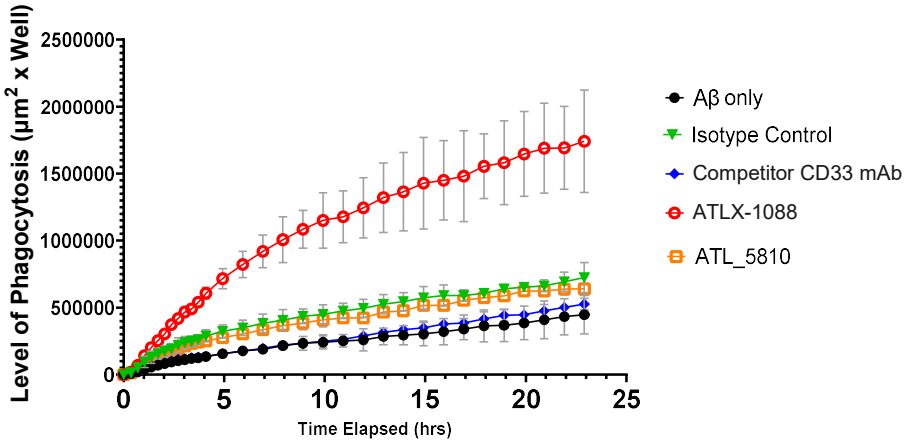
- Phagocytosis of toxic proteins by microglia is an important function suppressed by CD33 signalling
- An assay was devised to measure phagocytosis of amyloid beta following incubation with CD33 mAbs



- ATLX-1088 results in a significant increase in amyloid beta phagocytosis
- Other antibodies show minimal effect

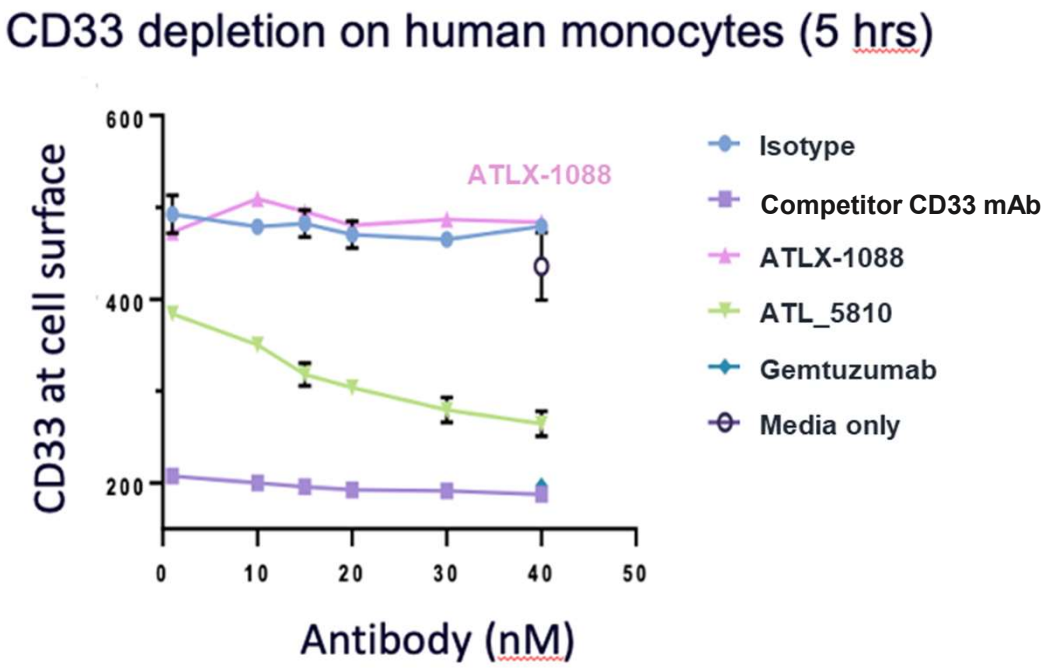
Phagocytosis

Phagocytosis of fluorescent beta amyloid* in human iPSC microglia



* Now testing other baits eg Tau, neuronal debris in same assay

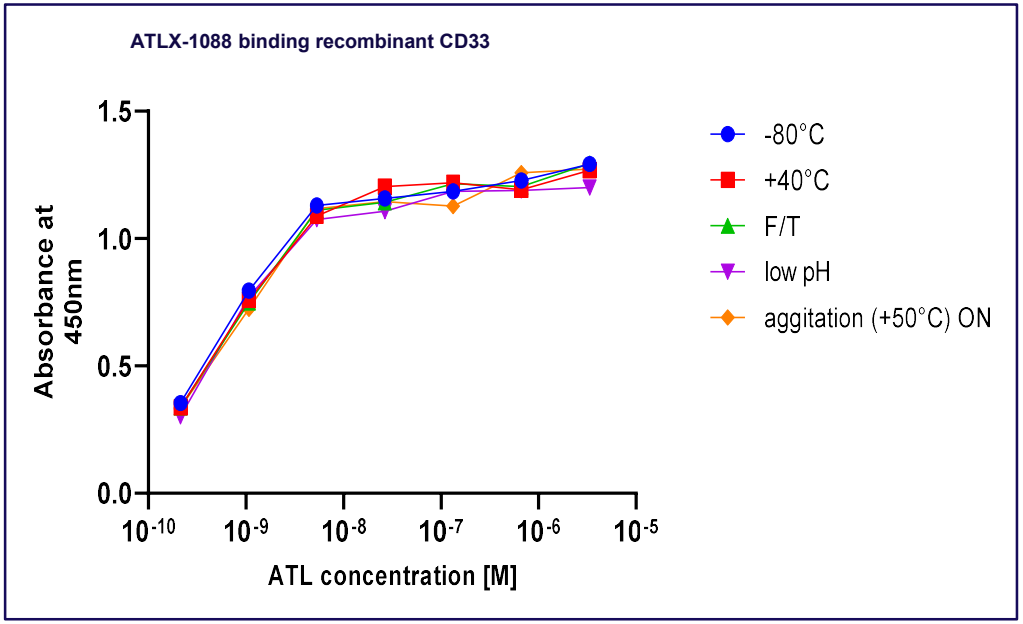
ATLX-1088 demonstrates reduced internalization of CD33, suggesting potential for improved PK



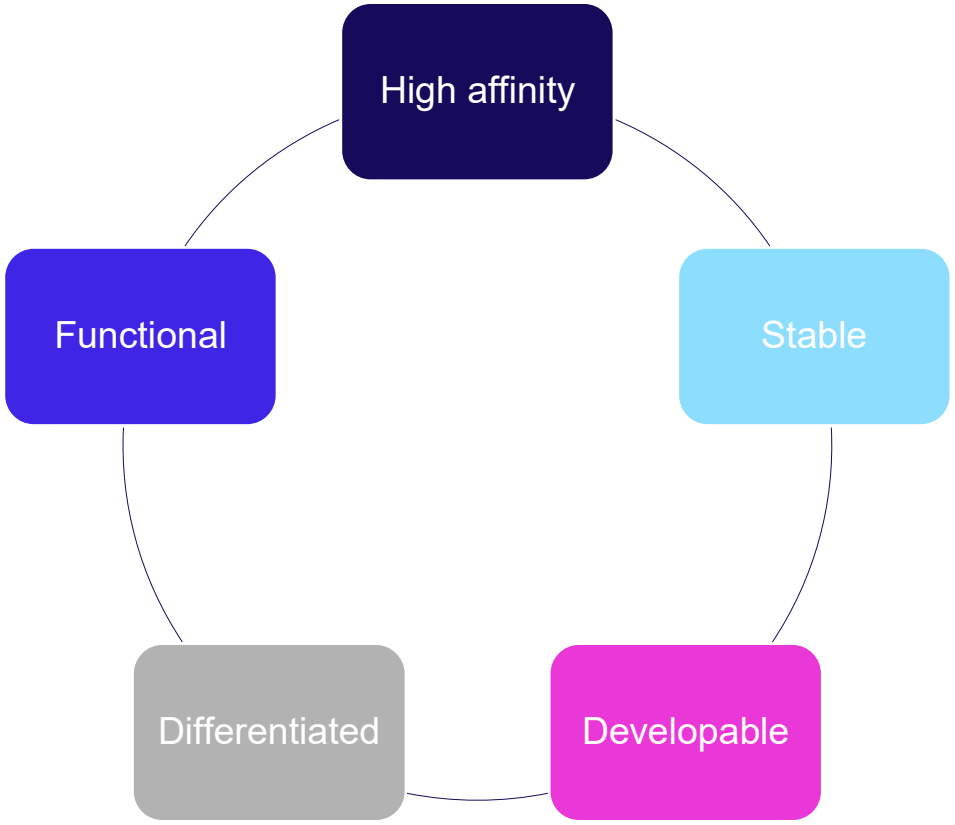
- CD33 is expressed at high levels in peripheral monocytes
- ATLX-1088 does not reduce CD33 expression at the cell surface
  - This suggests ATLX-1088 is not causing internalisation of CD33
  - Hence, reducing the antigen sink in the periphery
- Gemtuzumab and alternative therapeutic CD33 antibodies have been shown to internalise and reduce CD33 expression on monocytes.
  - This may negatively impact the pharmacokinetic profile of these antibodies.

ATLX-1088 performs well in stability studies

- CD33 binding by ATLX-1088 remains unchanged following:
  - 2 weeks at -80°C
  - 2 weeks at +40 °C
  - 3x Freeze/thaw cycles (-80°C to room temperature)
  - Low pH
  - Agitation and elevated temperature overnight



Characteristics of Alchemab's resilience-associated antibodies



Alchemab's discovery platform: advantages for discovery

- Novel targets and therapeutic candidates through an un-biased, efficient approach
- Cross-disease analysis using the Data Cube to inform mAb development and clinical direction
- Wide variety of target classes, resilience situations and cell types of interest
- 'Physiologically validated' targets and candidates

Acknowledgements

- The Alchemab Team
- Our Investors
- Our Collaborators
- The Patients