Multi-specific therapeutic antibodies
Slide Presentation is Available on Teneobio’s Website
Teneobio Overview

- Proprietary transgenic rats for human antibody discovery
  - UniRat and Omniflic
- High throughput sequence-based human antibody discovery engine
  - Next-gen sequencing + custom bioinformatics
  - High throughput recombinant expression and functional screening
- Multi-valent therapeutics with superior efficacy
  - Anti-CD3 T-cell redirection platform
    - Anti-BCMAxCD3 lead program, Phase 1 complete 2021
    - Anti-PSMAxCD3, Anti-CD19xCD3 INDs 2020
  - IL2Rβ/γ agonists
  - T-cell co-stimulation platform
  - Anti-CD38 enzyme inhibitor for Autoimmunity/Inflammation
- Product development partnerships
  - UniAbs for CAR-Ts, ADC’s, nanoparticles, viral delivery, etc.
  - Multi-target discovery through IND-enabling capabilities
Human Ig Transgenic Rats for Antibody Discovery

**UniRat**
- KO of rat Ig loci
- Fully human VH, Heavy chain antibody (UniAb) or domain antibody (UniDab)

**OmniFlic**
- KO of rat Ig loci
- Fully human VH, fixed light chain IgG

Flexible and robust human multi-specific antibodies

UniAb™
- 100aa

UniDab™

FlicAb™
Our platform is a unique combination of:

- Antibody repertoire deep sequencing
- Custom bioinformatics analysis
- High-throughput vector assembly
- Recombinant expression and screening

<table>
<thead>
<tr>
<th>DEEP SEQUENCING</th>
<th>ANALYSIS</th>
<th>EXPRESSION</th>
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</thead>
<tbody>
<tr>
<td>1 Immunization</td>
<td>2 B-cell isolation and mRNA purification</td>
<td>6 High-throughput expression and screening</td>
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<tr>
<td>2 Deep sequencing of VH regions</td>
<td>3 Bioinformatic analysis</td>
<td>5 High-throughput vector assembly</td>
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Harris et al. Front. Immunol. 24 April 2018
Screening design and strategy

- **Primary screen**: diverse CDR3 sequence families, **broad epitope coverage**
- **Secondary screen**: family members of primary hits, **optimize function**
Sequence-based Antibody Discovery

We discover 100X more antibodies 3X faster than traditional approaches

| Total number of discovery projects | 100 |
| Total number of targets            | 39  |
| Total number of animals            | 1,346 |
| Total number of NGS sequence reads generated | 1,817,332,666 |
| Total number of unique antibodies screened | 39,260 |
| Total number of antigen-specific antibodies | 11,778 |

100% Success rate
High Throughput Screening Allows Early Selection for Manufacturability

<table>
<thead>
<tr>
<th>UniRat immunization, titers, repertoire sequencing, bioinformatics analysis, gene assembly</th>
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<tbody>
<tr>
<td>UniAbs</td>
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<tr>
<td>~200 UniAbs (~100 families)</td>
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<tr>
<td>10-20 UniAbs (5-10 families)</td>
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<tr>
<td>~100 UniAbs (2-4 families)</td>
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<tr>
<td>~20 UniAbs (2-4 families)</td>
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<tr>
<td>~12-16 UniAbs</td>
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<tr>
<td>6-8</td>
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<tr>
<td>4-6 UniAbs</td>
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**Early testing for developability**

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<tr>
<th>Stage</th>
<th>Goal</th>
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<tr>
<td>Primary screen (96well supernatants)</td>
<td>ID ag+ CDR3 families (poly-reactivity)</td>
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<tr>
<td>Family characterization (24well purified)</td>
<td>ID ag+ families with other desired functions (%HMW, Tm, Tagg)</td>
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<tr>
<td>Diversity screen (96well supernatant)</td>
<td>Expand range of fxn activity (screen add’l family members)</td>
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<tr>
<td>Secondary screen (24well purified)</td>
<td>In-depth comparison of family members (%HMW, Tm, Tagg)</td>
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<tr>
<td>Secondary screen (5-20mg purified)</td>
<td>Additional functional assessment, protein analytics (Thermal Stability after stress)</td>
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<td>Final lead evaluation</td>
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Corporate Strategy Drives Teneobio’s Non-Dilutive Strategy

- **Diversification is Important**
  - Oncology: T-Cell Engagement, T-Cell Co-Stimulation
  - Autoimmunity: CD38 Enzyme Inhibition
  - Infectious Disease: Polyomavirus, Hepatitis B Virus

- **Focus on problems that demand a multi-specific or HCA approach**: Teneo’s T-Cell Engagers

- **Be Collaborative**: CD38 Enzyme Inhibition
  - Academic Researchers
  - Service Providers
  - Biotech
  - Physicians

- **Pursue High-Risk, High-Reward Programs**: Anti-Polyoma Domain Antibody Strings

- **Grant Writing/Execution as a Crucible**
# Teneobio’s Pipeline: Diversification through Non-Dilutive Funding

<table>
<thead>
<tr>
<th>Program</th>
<th>Discovery</th>
<th>Pre-clinical</th>
<th>IND</th>
<th>Phase I</th>
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<tbody>
<tr>
<td>TNB-383B (BCMA x CD3)</td>
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<td>TNB-486 (CD19 x CD3)</td>
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<td>2020</td>
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<td>TNB-585 (PSMA x CD3)</td>
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<td>FRa x CD3</td>
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<td>ST4 x CD3</td>
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<td>CD79b x CD3</td>
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<td>CD38 enzyme inh</td>
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<td>2021</td>
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<tr>
<td>IL2/15R agonist</td>
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<td>2022</td>
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<tr>
<td>Polyomavirus</td>
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<td>Hepatitis B Virus</td>
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<td>CAR-T</td>
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(ND = Not disclosed)
Teneobio’s T-Cell Engagement Platform

Better Bispecific T-Cell Engagers Using UniAbs
~75% of BsAbs in development use an anti-CD3 derived from SP34, OKT3, or UCHT1 (Wu et al. Pharm. and Ther. 2017)

Our goal: discover new anti-CD3 antibodies that in bispecific format are well tolerated and efficacious
  ▪ Efficient tumor cell lysis
  ▪ Minimal CRS, T-cell exhaustion and AICD
  ▪ Low immunogenicity
  ▪ Long Half-Life
T cell activation occurs in discrete stages based on TCR-pMHC complex formation

- Faroudi et al. PNAS 2003
- Purbhoo et al. Nature Imm. 2004

- Mature immune synapse is not necessary for cytolytic activity
- 2 TCR-pMHC complexes sufficient for inducing cytotoxicity = threshold 1
- >10 necessary for full synapse formation and cytokine release = threshold 2
- Can new CD3 antibodies be developed that stimulate threshold 1 but not threshold 2?

Window of engagement to stimulate tumor cell lysis without cytokine release
TNB-486 (anti-CD19/CD3) is Efficacious With Low Cytokine Release
TNB-496 Is Efficacious In Vivo

In Vivo Efficacy of TNB-486 in Disseminated Murine Model of Burkitt Lymphoma

TNB-486 results in tumor regression in Burkitt Lymphoma disseminated model.
Modular Bispecific Antibody Development

Anti-CD3 T-cell activator

High affinity anti-Tumor antigen

TAA+ Tumor cells + T-cells

BsAb-mediated
  • T-cell activation,
  • Cytokine release
  • Tumor cell lysis

Trinklein et al. mAbs 20 Feb 2019
Teneobio’s Platform has been Validated Both Solid and Liquid Tumors

- BsAb-mediated tumor lysis for multiple different tumor associated antigens
TNB-Bispecific Molecules on Track for IND Throught 2021

TNB-383B Phase 1 initiated Q2 2019, Multiple Myeloma
Stable Cell Line Yield: 4.7 g/L

TNB-486, IND in July 2020, Lymphoma
Stable Cell Line Yield: 4.5 g/L

TNB-585, IND in November 2020, Prostate cancer
Stable Cell Line Yield: 7.6 g/L

TNB-###, IND in Q3 2021, Ovarian cancer

Grant Supported
Teneobio T-cell Engager Platform

- Novel proprietary fully human anti-CD3 antibodies
  - Novel epitope, large range of affinities
- One-of-a-Kind, Plug-and-Play, Stable Protein Chemistry
- Unique MOA
  - Retained Anti-Tumor Efficacy
  - Improved Safety: Dramatically Reduced Cytokine Secretion
  - Reduced Treg stimulation, Reduced Exhaustion
- Low immunogenicity
- Long half-life
- High affinity/avidity TAA binding

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Teneobio’s CD38 Enzyme Inhibitor

Cutting Edge Autoimmunity Therapy via Metabolic Regulation

Potent Inhibition of hCD38 by Biepitopic UniAbs

CD38_A
Competition group 3

CD38_B
Competition group 1

Synergy

Tetravalent CD38_A_B

Human CD38 Hydrolase Activity

% of max activity

Antibody [nM]

UniAb A
UniAb B
UniAb A + B

Human CD38 Hydrolase Activity

% of max activity

Antibody [nM]

UniAb A + B
TetrAb A_B
CD38 Regulates NMN/NAD+ in Young and Old Mice

Day one
- A68 injection
- Ip, 5 mg/kg

Day three
- 0h - NMN Injection
- 500 mg/kg
- 6h – Euthanasia and tissue collection

Groups
- Young and Old Control, A68, NMN, NMN+A68

Measure
- NAD, NMN, NA

Tissues:
- Spleen
- Liver
- Mesenteric Fat
- Muscle (Gast)
- Inguinal Fat
- Jejuno
- Blood/Plasma
Teneobio’s CD38 Inhibitor: Collaboration to Solve Complex Biology

NAD+ METABOLISM

- HIV
- AUTOIMMUNITY
- COLITIS
- NAD+
- METABOLISM
- INFLAMMATION
- AUTOIMMUNITY
- PREMATURITY AGING
- APLASTIC ANAEMIA
- INFLAMMAGING
- AGING
- CELL EXHAUSTION
- CAR T CELLS
- PULMONARY
- FIBROSIS
- SCLERODERMA
- ENDOTHELIAL DYSFUNCTION
- ISCHEMIC REPERFUSION
- HEART FAILURE

- MAYO CLINIC
- INBELM, FRANCE
- TRANSPANTATION
- INFLAMMATION
- METABOLIC DISORDERS
- MEDICAL UNIVERSITY SOUTH CAROLINA
- BLUE – CD38 BLOCKADE EFFECTIVE IN MOUSE MODELS
- GREEN – SCIENTIFIC LITERATURE, ANIMAL MODELS
- ORANGE – DISEASE AREAS

NATIONAL INSTITUTE ON AGING

NORTHWESTERN MEDICAL SCHOOL
Teneobio’s CD38 Inhibitor: A Unique Modulator of NAD+

- **TNB-738 Solves Critical Problems with Existing CD38i Therapies**
  - Existing Inhibitory Antibodies are Cytotoxic
  - Small Molecule Inhibitors Enter the CNS
  - NMN Supplementation Does Not Increase Tissue NAD+, and Increases NAD Degradation Products

- **TNB-738 is a Potent CD38 Inhibitor with Long Half-Life and Good Manufacturability**
  - Sustained Increases in Tissue NAD+
  - Stable Protein Chemistry
  - Robust Process for Manufacturing/Purification

- **Broad Collaboration with Metabolic Experts Enables Bench-to-Bedside Transition**
  - CD38 Inhibition Improves Diverse Disease States
  - Independent Validation of MOA
  - Provides Foundation for Clinical Development with IND in 2021.
Teneobio’s Anti-Polyoma Virus Therapy

Novel Domain Antibody Strings to Reach Immune-Priviledged Sites
Antibodies to Treat BK/JC Viral Diseases

- Polyomaviruses Threaten Immune Compromised Patients
  - **BK Nephropathy**: 5-10% of Kidney Transplants, incl. graft loss
    Peak Sales Projection = ~$200M/Year
  - **Progressive Multifocal Leukoencephalopathy (PML)**: up to 5% of HIV pts, 30-50% mortality
    Peak Sales Projection = $550M/Year
  - **Hemorrhagic Cystitis**: Rare complication of marrow transplant, 2-4% mortality
  - **Interstitial Cystitis**: Correlative association with BK. US prevalence ~1,000,000. significant morbidity.
    Peak Sales Projection = $250M+/Year

- No effective treatment for any BK/JC viral disease!

- Antibodies are a Promising Therapeutic Approach
  - **Novartis**: huMAb (MAU 868) against BK virus to treat BK nephropathy; entered Phase 1.
  - **Neurimmune**: huMAb against JC virus to treat PML
  - High dose IVIg has shown limited efficacy
  - *Conventional antibodies cannot enter the urinary space where polyomaviruses replicate.*
Antibodies to Treat BK/JC Viral Diseases

- **Slowly Mutating Viruses**
  - Limited Escape from Antibody Therapy

- **Replicate in the Urinary Space**
  - Inaccessible to Conventional Antibodies
  - Domain Antibodies (UniDAbs) and 2-4 UniDAb ‘strings’ are freely filtered into the Urine

- **Multiple Serotypes Necessitate a Broadly Neutralizing Approach**
  - Teneoseek Enables Identification of Broadly Neutralizing Antibodies
  - *UniDAb Strings can Combine Multiple Specificities in a Single Molecule*
Teneobio’s Anti-Polyoma UniAbs

- 2 Broadly Neutralizing UniAb families
  - <100 pM IC50 against ALL tested PYV strains
    - BK I
    - BK IV
    - JCV WT
    - JCV S293F (PML-inducing mutant)
  - Good Developability
    - Well expressed
    - Tm/Tagg
    - Stable at 37°C for 1 mo.
  - Domain UniAb strings in development

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Anti-BK/JC UniAbs and Domain UniAb Strings: Summary

- **Validated Scientific Rationale**
  - Multiple huMAbs in development to treat Polyomaviral diseases

- **UniAbs are Uniquely Suited to Combat BK/JC-Mediated Diseases**
  - **Broad Neutralization**: <100 pM IC50 for all tested BK/JC strains
  - **Multivalency**: Expect tetravalent IC50 ~10-100X stronger than bivalent (~5pM-500fM IC50)
  - **Small Size**: UniDAb strings can enter the urine
  - **Excellent Manufacturability**: Grams/L yields anticipated
  - **Customizable Half-Life**: HSA- or Ig-binding
  - **Absence of framework regions**: No STRATIFY cross-reactivity
The Crucible: Grant Writing as a Means towards Better Science

- **Grant Proposal ≈ Detailed TCP**
  - Feasibility
  - Timelines
  - Cost/FTE
  - Gap Analysis: Where do You Need Help?

- **Grants as a Catalyst for Collaboration**
  - Funding to Support Collaborators
  - Scientific Credibility

- **Review Process Validates Approach**
Lessons From Teneobio’s Non-Dilutive Funding Strategy

- **Diversification is Important → Use Grants to Expand Your Pipeline (Especially Early Pipeline)**
  - Oncology: T-Cell Engagement, T-Cell Co-Stimulation
  - Autoimmunity: CD38 Enzyme Inhibition
  - Infectious Disease: Polyomavirus, Hepatitis B Virus

- **Teneo’s T-Cell Engagers → Play to Your Strengths, Find Problems Suited to Your Innovations**

- **CD38 Enzyme Inhibition → Grants Enable, and Thrive on, Collaboration**
  - Academic Researchers
  - Service Providers
  - Biotech
  - Physicians

- **Anti-Polyoma Domain Antibody Strings → Use Grants to Try the Crazy Stuff You’ve Always Wanted to Try!**
  - Grant Writing/Execution as a Crucible