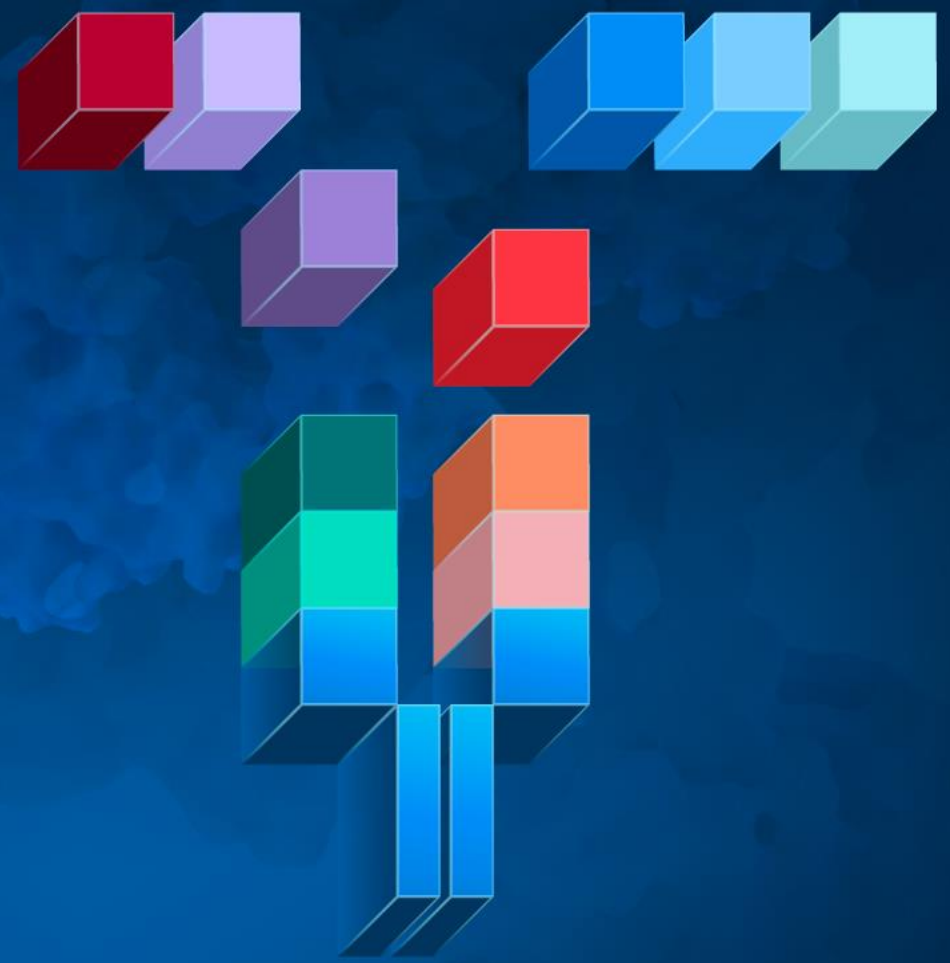
ModeX™ THERAPEUTICS
an OPKO Health Company



# Research and Development Day

MARCH 20, 2023

# Forward Looking Statements

*This presentation contains "forward-looking statements," as that term is defined under the Private Securities Litigation Reform Act of 1995 (PSLRA), which statements may be identified by words such as "expects," "plans," "projects," "will," "may," "anticipates," "believes," "should," "intends," "estimates," and other words of similar meaning, including statements regarding expected financial performance and expectations regarding the market for and sales of ModeX's products, whether the acquisition of ModeX, including the expansion of the executive management team, will positively impact OPKO Health, Inc. (OPKO), whether ModeX will receive regulatory approval for products in development and be able to successfully commercialize such products, whether the technology and benefits of ModeX's products are viable and can be realized, the risk of downturns and a changing regulatory landscape in the highly competitive healthcare industry, ModeX's product development efforts and the expected benefits of its products, whether its products in development will be commercialized, whether the relationships and collaborations with ModeX's strategic partners will be successful, whether ModeX will be able to attract additional business partners if necessary, whether its business partners will be able to commercialize its products and successfully utilize its technologies, ModeX's ability to market and sell any of its products in development, as well as other non-historical statements about ModeX's expectations, beliefs or intentions regarding its business, technologies and products, strategies or prospects. Many factors could cause its actual activities or results to differ materially from the activities and results anticipated in forward-looking statements. These factors include those described in OPKO's Annual Reports on Form 10-K filed and to be filed with the Securities and Exchange Commission and under the heading "Risk Factors" in its other filings with the Securities and Exchange Commission, as well as the continuation and success of our relationship with our commercial partners, liquidity issues and the risks inherent in funding, developing and obtaining regulatory approvals of new, commercially-viable and competitive products and treatments. In addition, forward-looking statements may also be adversely affected by general market factors, competitive product development, product availability, federal and state regulations and legislation, the regulatory process for new products and indications, manufacturing issues that may arise, patent positions and litigation, among other factors. The forward-looking statements contained herein speak only as of the date the statements were made, and we do not undertake any obligation to update forward-looking statements. We intend that all forward-looking statements be subject to the safe-harbor provisions of the PSLRA.*

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# Welcome

## Gary Nabel

Co-Founder, President/CEO ModeX Therapeutics
Chief Innovation Officer, OPKO Health

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# Agenda: ModeX Therapeutics R&D Day

| | |
|---|---|
| **Welcome** | **Gary Nabel**<br>Co-Founder, President/CEO, ModeX Therapeutics; Chief Innovation Officer, OPKO Health |
| **Opening Remarks** | **Phillip Frost**<br>CEO and Board Chair, OPKO Health |
| **R&D Day Overview** | **Elias Zerhouni**<br>Co-Founder, ModeX Therapeutics; President, OPKO Health |
| **Introduction to ModeX Therapeutics** | **Gary Nabel** |
| **EBV Vaccine Program** | **Gary Nabel** |
| **ModeX Platform Technologies**<br>• Multispecific Abs (MSTAR)<br>• Masking (STEALTH)<br>• Immune modulation | **Ronnie Wei**<br>Head, Biologics Discovery and Development, ModeX Therapeutics |
| **Multispecific Antibodies for Immuno-Oncology**<br>• Solid tumors<br>• Hematologic neoplasms | **John Mascola**<br>Chief Scientific Officer, ModeX Therapeutics |
| **Multispecific Antibodies for Infectious Diseases** | **John Mascola** |
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| **Closing Remarks** | **Gary Nabel** |
| **Question and Answer Session** | **All** |

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# Opening Remarks

## Phillip Frost

Chairman of the Board and CEO,
OPKO Health

# R&D Day Overview

## Elias Zerhouni

Co-Founder, ModeX Therapeutics
President and Vice Chairman, OPKO Heath

# Merger of ModeX Therapeutics with OPKO: a Transformational Step

- ModeX co-founded by Drs. Nabel and Zerhouni based on Breakthrough Lab led by Dr. Nabel at Sanofi
- Transformational technologies based on multispecific antibodies and nanoparticle vaccine platforms
- Focus on immuno-oncology, viral diseases and vaccines
- Track record: three multispecific antibodies in ongoing phase 1 trials
- Strong IP foundation: 28 patents applications filed to date.
- ModeX brings to OPKO a world class team and expansion into novel biotherapeutics
- Portfolio eliciting strong interest from strategic partners

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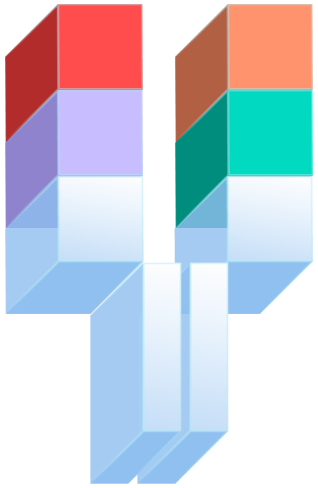
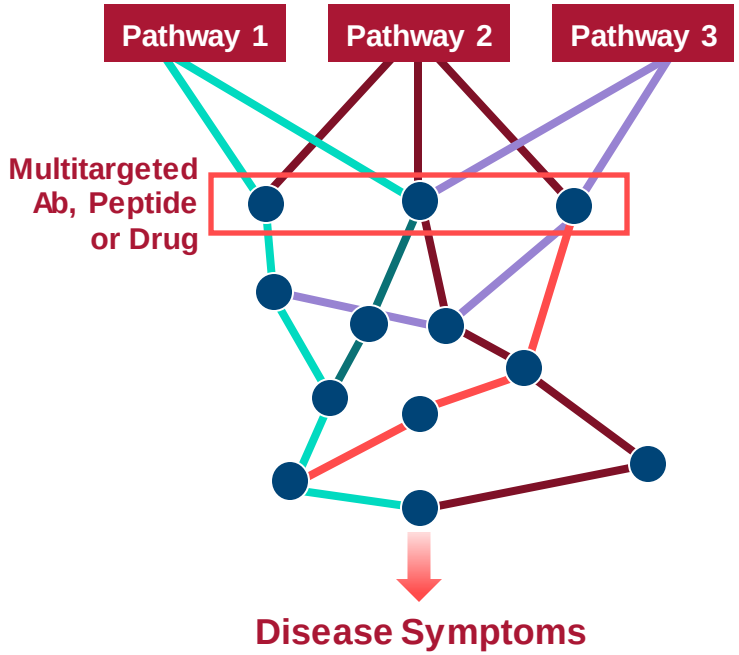
# Central Concept: Synergistic Targeting of Disease Drivers



**“Dream Molecules”**
**One Drug, Multiple Targets, Diverse Diseases**




- Deep understanding of validated molecular networks and pathways and unique combinations reduce biological risk
- Scientific evidence indicates that many diseases require a combination of therapies to achieve success
- Success in humans: chemotherapy, antibiotics, Immunotherapy (Dupixent), vaccines

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# Introduction to ModeX Therapeutics EBV Vaccine Program

## Gary Nabel

Co-Founder, President/CEO ModeX Therapeutics
Chief Innovation Officer, OPKO Health

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# ModeX Leadership Team

## Highly experienced team with deep research and technology expertise

**Elias Zerhouni**
Chair of Board/Co-Founder
President, OPKO

**Gary Nabel**
President/CEO/Co-Founder
Chief Innov. Officer, OPKO

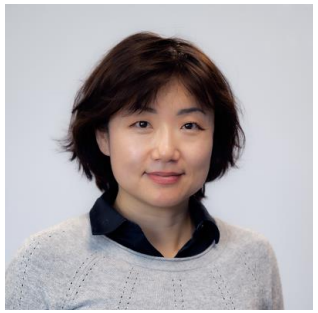
**Elizabeth Nabel**
Executive VP for Strategy
CMO, OPKO

**Ji Zhang**
Chief Operating Officer

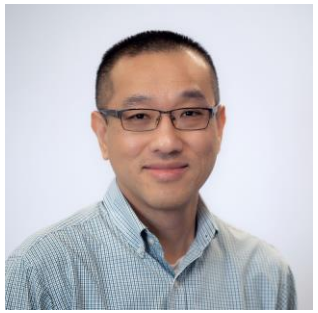
**Edward Garmey**
Consultant-Oncology

**John Mascola**
Chief Scientific Officer

**Vijay Chhajlani**
Chief Technology Officer



**Ronnie Wei**
Head, Biologics Discovery
and Development



**Chih-Jen Wei**
Head, Virology and
Infectious Diseases

**Zhi-Yong Yang**
Head, Immuno-Oncology
and Discovery Research

# The Promise of Next Generation Ab Technology

Multispecific antibody technology allows for synergistic targeting, streamlined manufacturing, rapid clinical translation and efficient protein or gene-based delivery in a single product.

# ModeX Builds on Known Pathways to Generate Effective New Medicines

- ModeX scientists utilize information about known immune mechanisms and validated targets based on clinically established biology to develop new medicines.
- Through molecular engineering, structure-based design and digital design/machine learning, ModeX candidates stimulate biologic responses with novel combinations of antibodies and immune activators to generate first-in-class candidates with best-in-class potential.

# Multiple Clinical Trials to Validate the Platform

Science — SEPT 2017

**Trispecific broadly neutralizing HIV antibodies mediate potent SHIV protection in macaques**

Ling Xu, Amarendra Pegu, Ercole Rao … Zhi-Yong Yang, John R. Mascola, Gary J. Nabel, et al.

nature cancer — NOV 2019

**Trispecific antibodies enhance the therapeutic efficacy of tumor-directed T cells through T cell receptor co-stimulation**

Lan Wu, Edward Seung, Ling Xu … Katarina Radošević, Zhi-yong Yang, Gary J. Nabel, et al.

nature — FEB 2022

**A trispecific antibody targeting HER2 and T cells inhibits breast cancer growth via CD4 cells**

Edward Seung, Zhen Xing, Lan Wu … Ronnie Wei, Zhi-yong Yang, Gary J. Nabel, et al.

YEAR TRIAL INITIATED:

**HIV Trispecific: 2019** → **CD38 Trispecific: 2020 (myeloma)** → **HER2 Trispecific: 2021 (Breast, gastric ca.)**

- Phase 1 studies in HIV treatment (HIV trispecific) with ACTG, NIAID, NIH (ModeX asset SAR441236).
- Phase 1 trial in patients with multiple myeloma (CD38-CD3/CD28 trispecific) ongoing at Sanofi.
- Phase 1 trial in patients with breast and gastric cancer (HER2-CD3/CD28 trispecific) ongoing at Sanofi.

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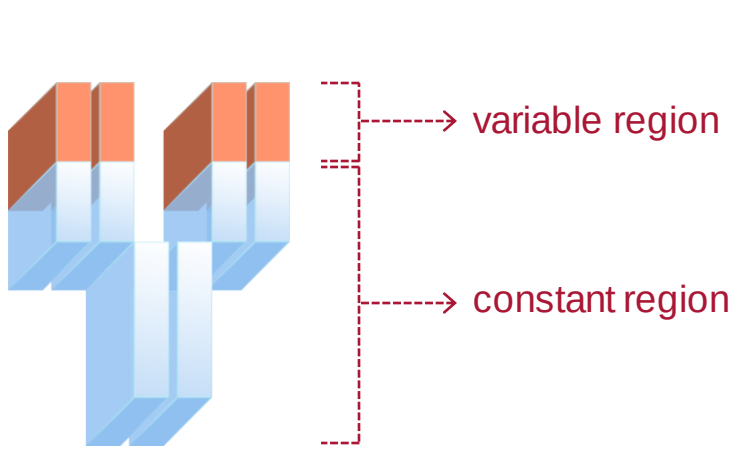
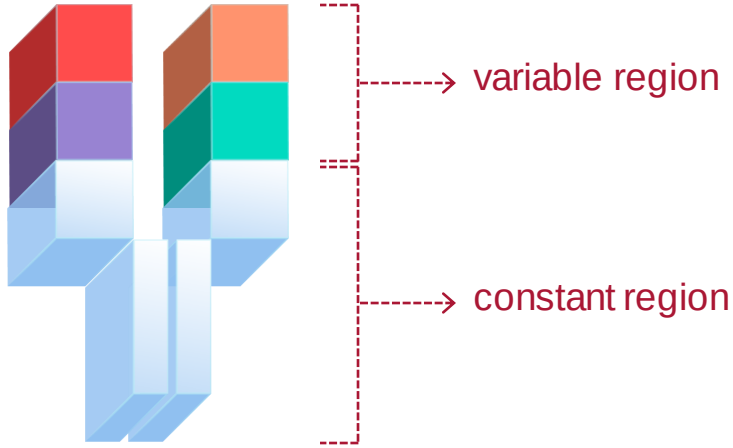
# The **MSTAR** Platform: Next Generation Wholly-Owned **M**odeX Technology
## **S**ynergistic **T**argeting of **A**ntigens and **R**eceptors

| Standard mAb (monospecific) | MSTAR Platform (modular and multispecific) |
|---|---|




- Complementary and self assembling, eliminates mispairing that reduces yield
- Simplified configuration enabling gene delivery, accelerating clinical development
- 28 pending patent applications filed to date

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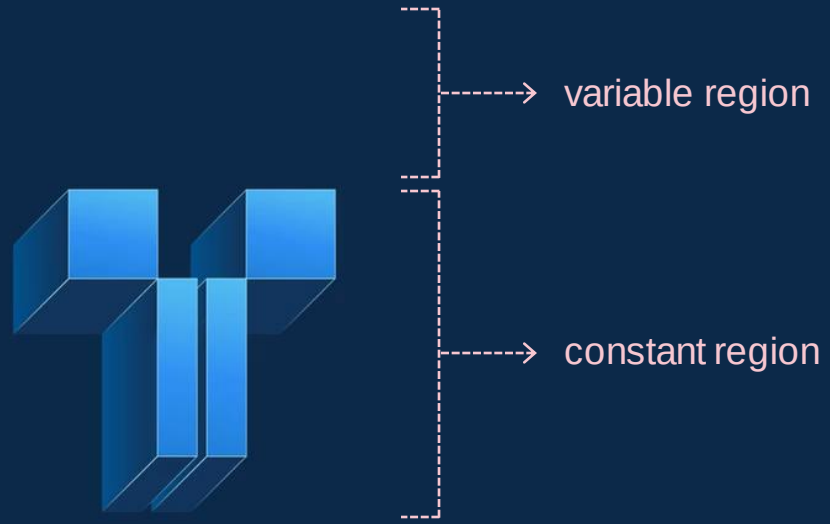
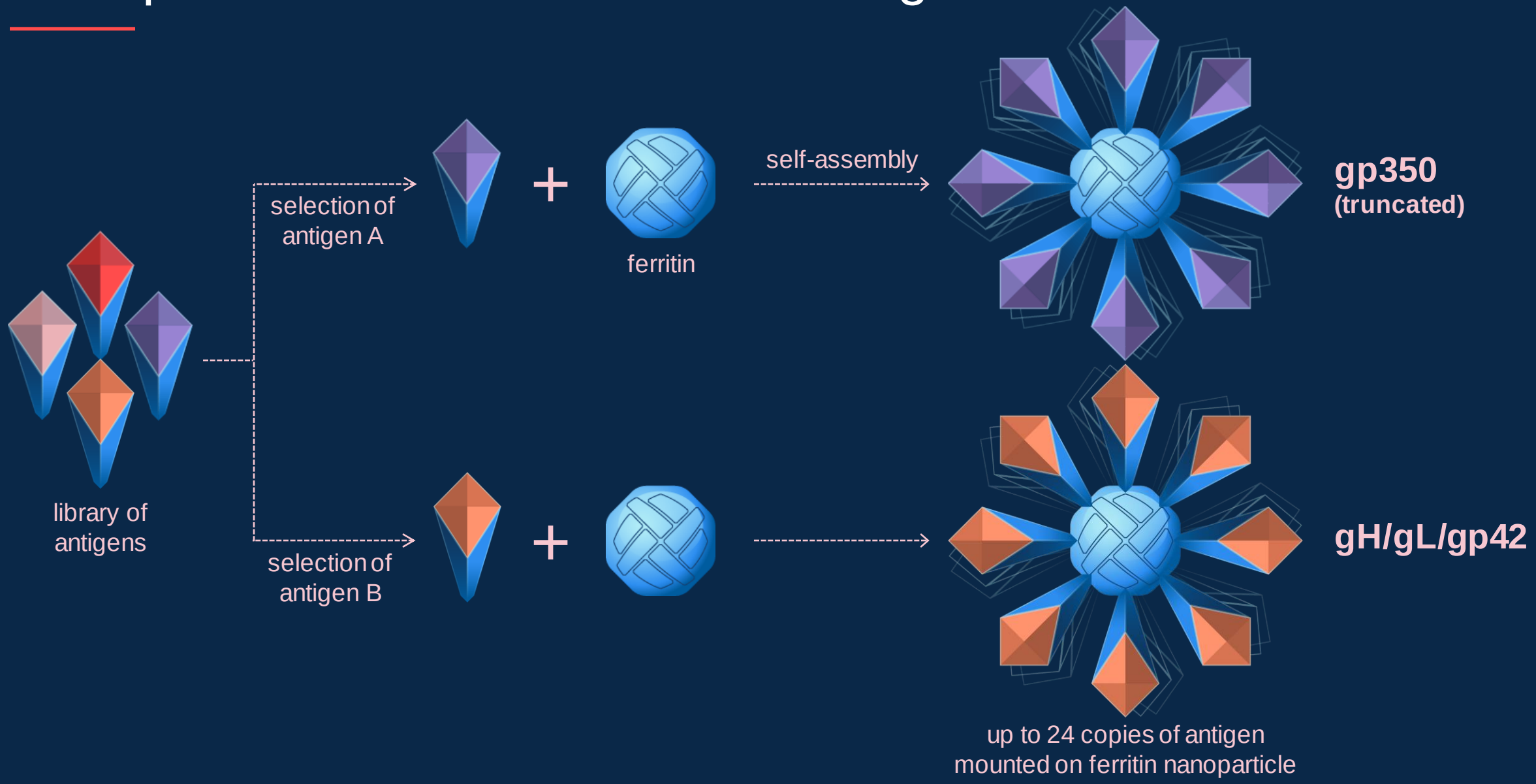
# Uniting the Power of Multiple Medicines in a Single Molecule




multispecific antibody

# Nanoparticle EBV Vaccine Technologies



# EBV Vaccine Program: ModeX Merck Collaboration

OPKO Health's ModeX Therapeutics Enters into Exclusive Worldwide License and Collaboration Agreement with Merck to Develop Epstein-Barr Virus Vaccine Candidate

MARCH 8, 2023

ENDPOINTS NEWS

REUTERS

BIOCENTURY

BIOPHARMA DIVE

FIERCE Biotech

MedCity News

- Infectious disease portfolio milestone: Exclusive worldwide licensing and collaborating agreement for MDX-2201
- Joint development to IND. Merck to assume all further milestones
- $50 million upfront payment with potential for up to $872.5 million in milestone payments, and additional tiered royalties
- Validation for ModeX platform capability to address major viral threats

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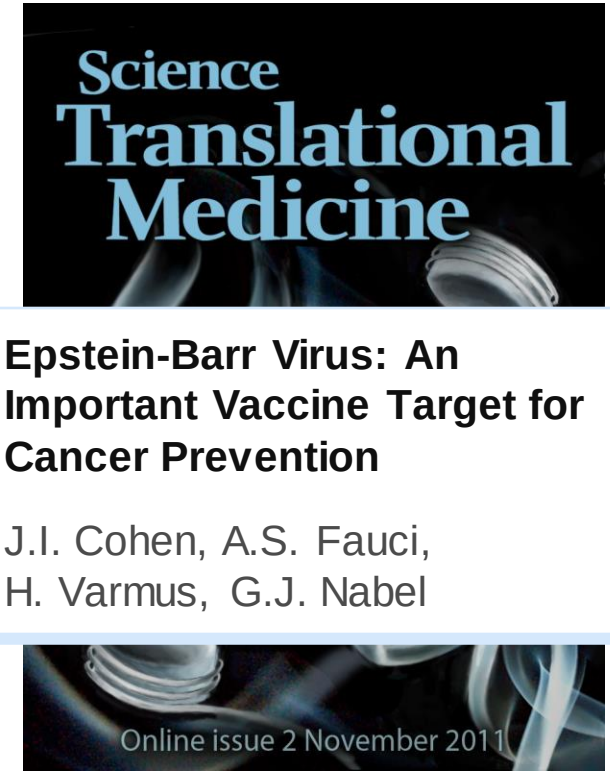
# An EBV Vaccine: A Major Unmet Medical Need Globally




**Epstein-Barr Virus: An Important Vaccine Target for Cancer Prevention**

J.I. Cohen, A.S. Fauci, H. Varmus, G.J. Nabel

- Causes infectious mononucleosis in adolescents and young adults.
- The first human cancer virus, identified over 50 years ago, linked to >200,000 cases and >150,000 deaths each year. Implicated in Hodgkins disease, Burkitt's lymphoma, gastric and nasopharyngeal cancers and post-transplant complications.
- Associated with autoimmune syndromes, including multiple sclerosis.
- No licensed vaccines or treatments.

Sci. Trans. Med. 3:107, p. 107fs7, DOI: 10.1126/scitranslmed.3002878

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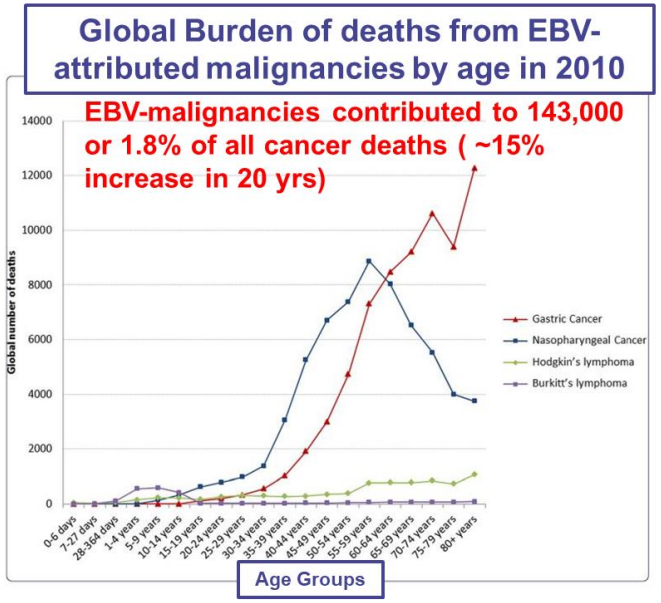
# Multispecific EBV Vaccine: Medical Value and Clinical Utility

## Medical Need

Infectious mononucleosis responsible for ~$2B in health care costs yearly.




Cohen, J., *et al.* Vaccine. 2013
Khan, G., *et al. Infectious Agent and Cancer.* 2014
Hjalgrim, H., *et al.* Human Herpesviruses. 2007

## Clinical/Commercial

1. **Infectious Mononucleosis**
   - Projected peak sales: $400M
2. **Cancer prevention**
   - Analogous to Gardasil ($5.7B in 2022 sales)
3. **Prevention of multiple sclerosis and immune disorders**
   - Market size TBD

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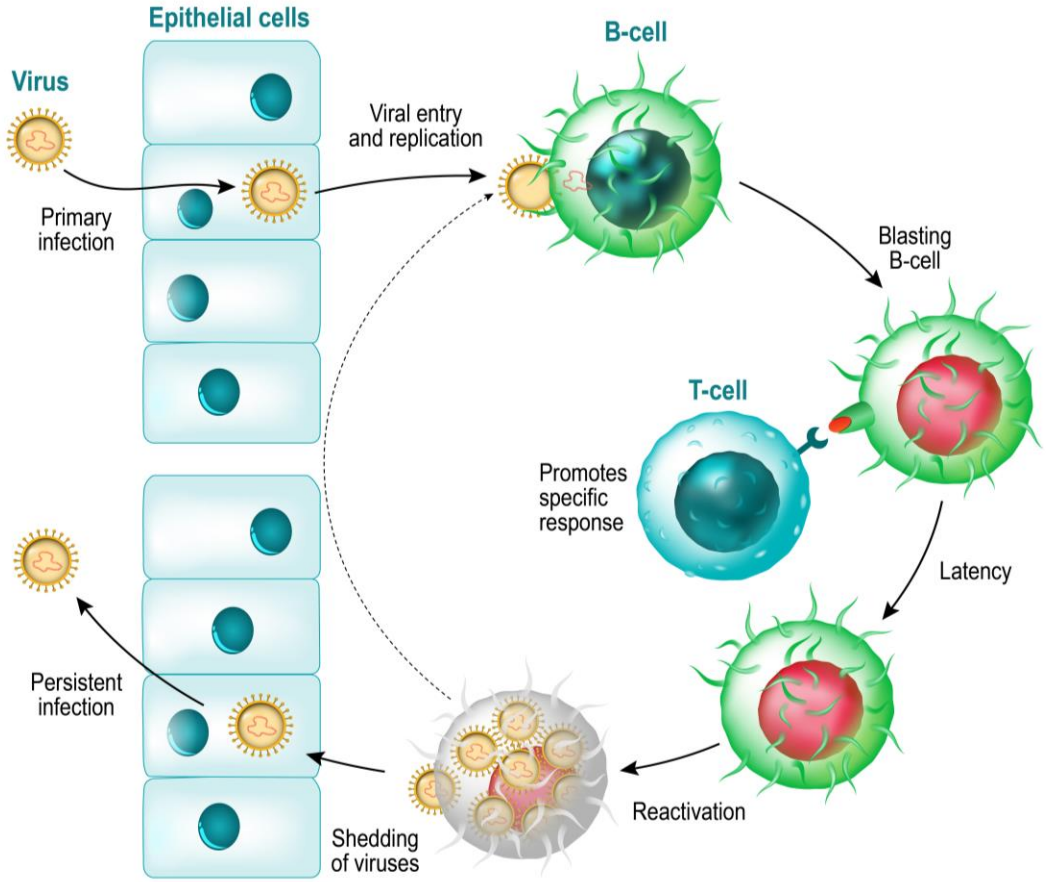
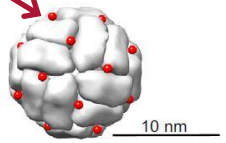
# The EBV Life Cycle: Infection of Two Cell Types

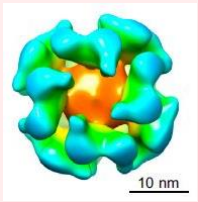


# A Vaccine for Infectious Mononucleosis and Cancer: Epstein Barr Virus

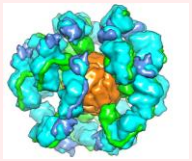
Red spheres indicates where EBV antigens are displayed on the surface of the nanoparticle




Bacterial ferritin (carrier)




gp350D$_{123}$ ferritin



gH/gL/gp42 ferritin

Two Component Vaccine

Scalable and cost-effective ferritin nanoparticle carrier derisked in phase 1 human trials by NIH.

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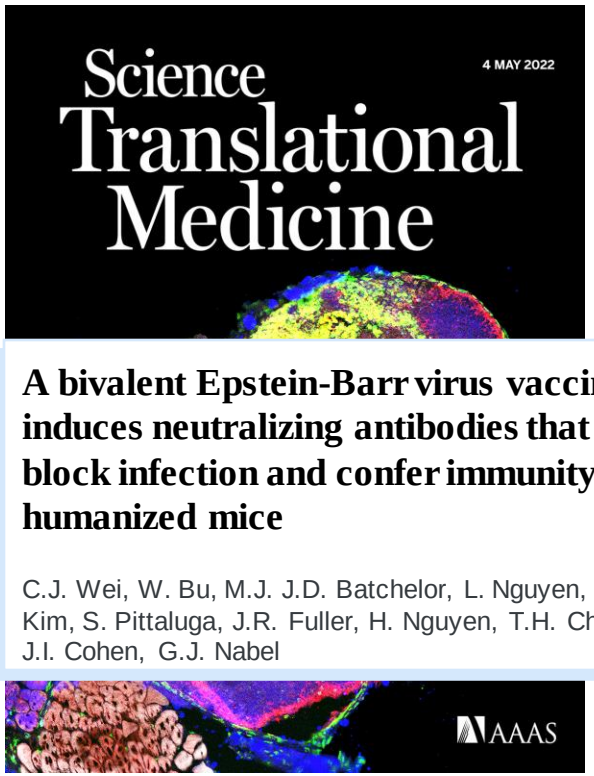
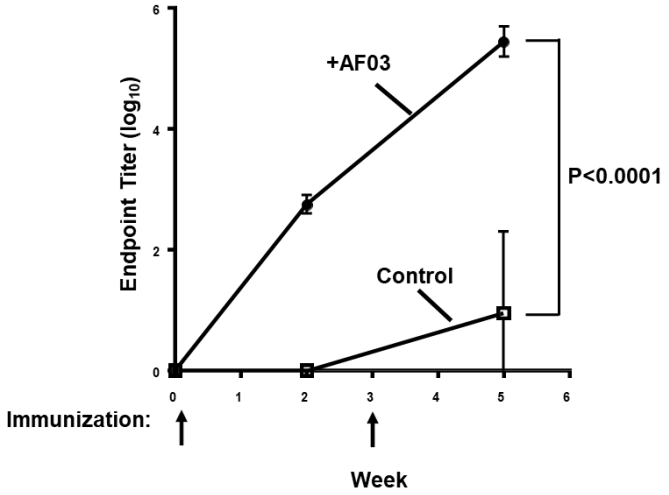
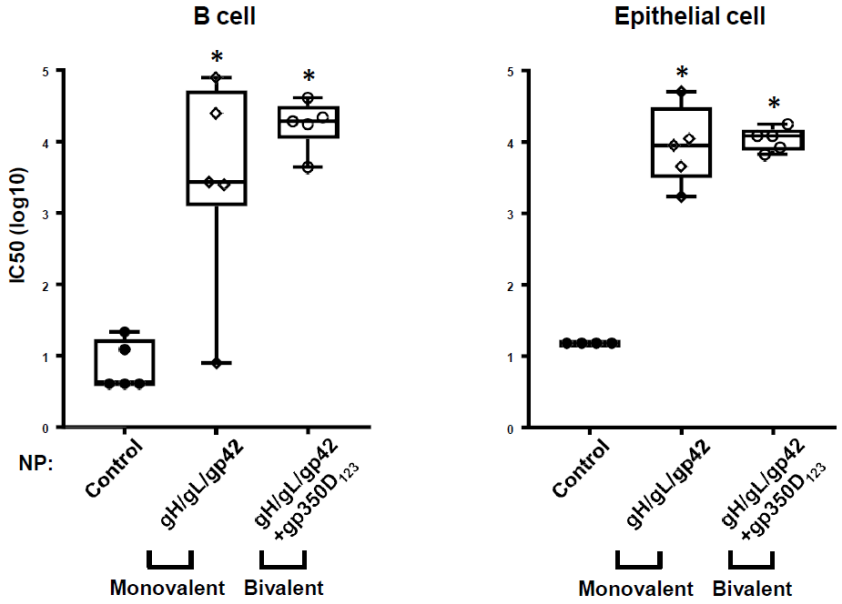
# Preclinical Immunogenicity and Efficacy of EBV Nanoparticle Vaccine




**A bivalent Epstein-Barr virus vaccine induces neutralizing antibodies that block infection and confer immunity in humanized mice**

C.J. Wei, W. Bu, M.J. J.D. Batchelor, L. Nguyen, J. Kim, S. Pittaluga, J.R. Fuller, H. Nguyen, T.H. Chou, J.I. Cohen, G.J. Nabel




- A bivalent vaccine directed to EBV gp350 and gH/gL/gp42 envelope proteins inhibits viral entry in human B cells and epithelial cells and prevent viral replication in vivo.
- The bivalent approach provides substantial differentiation from prior EBV vaccines and a straightforward development pathway..

Wei, C.-J., *et al., Sci. Transl. Med. 2022*

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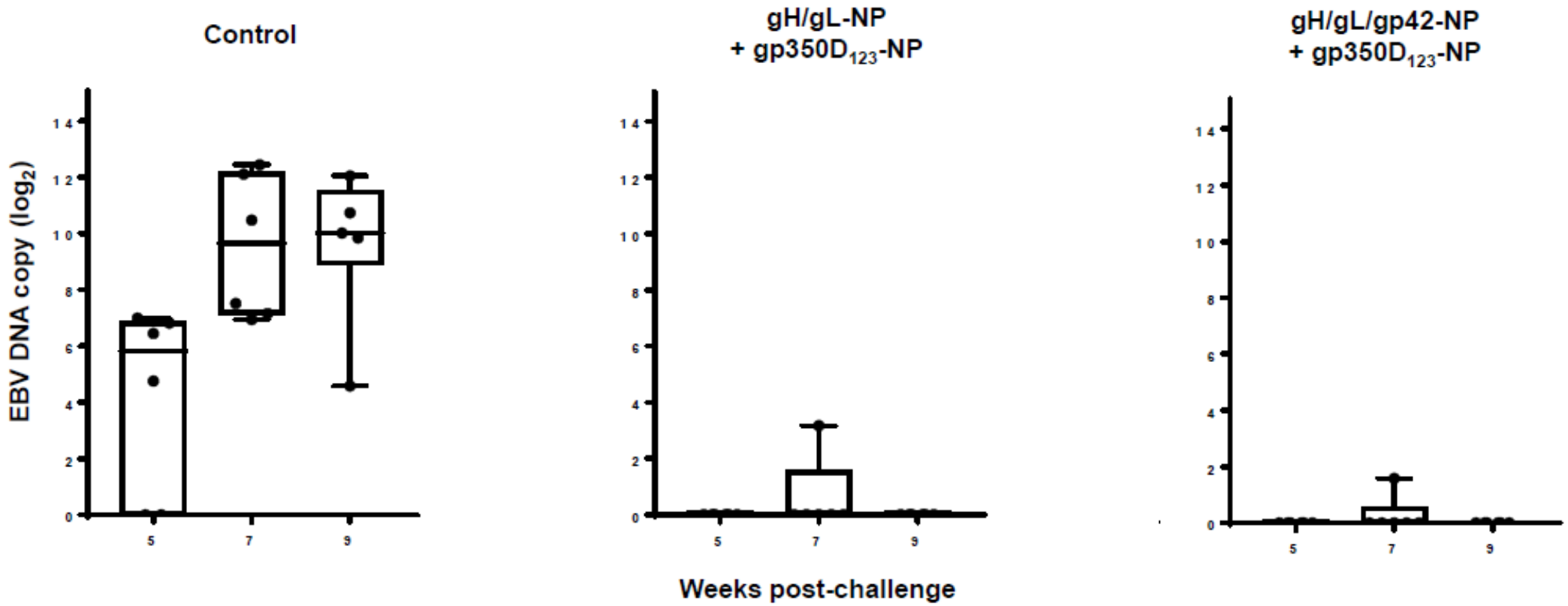
# Bivalent EBV Vaccine Confers Sterilizing Immunity in Humanized Mice




Wei, C.-J., *et al., Sci. Transl. Med. 2022*

# ModeX Product Pipeline: First-in-Class Drugs with Best-in-Class Potential

| | PRODUCT | INDICATION | DISCOVERY | IND ENABLING | PHASE 1 |
|---|---|---|---|---|---|
| Immuno-Oncology | **Tetraspecific LASER*** | Treatment of Solid Tumors | MDX2001 | | |
| | **Tetraspecific LASER*** | Treatment of Leukemia/Lymphoma | MDX2003 | | |
| | **Tetraspecific Stealth LASER*** | Treatment of Solid Tumors | MDX2002 | | |
| | **Multispecific Immune Modulation** | Hematologic Malignancies and Solid Tumors; CAR T Cells | | | |
| Antiviral | **HIV Trispecific Antibody** | Treatment and Prevention of HIV | MDX2203 | | |
| | **EBV Nanoparticle Vaccine** | Prevention of EBV-related diseases | MDX2201 | | |
| | **COVID Multispecific Antibody** | Treatment and Prevention of COVID-19 | MDX2202 | | |

**Lymphocyte Activator and Survival Extension Receptor (LASER) Antibodies*

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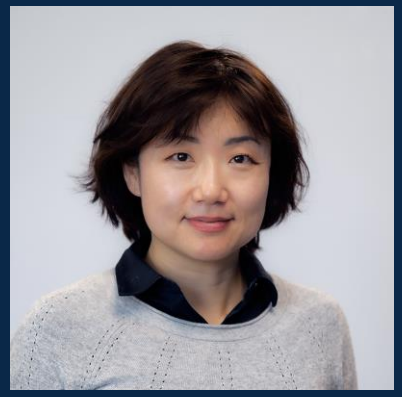
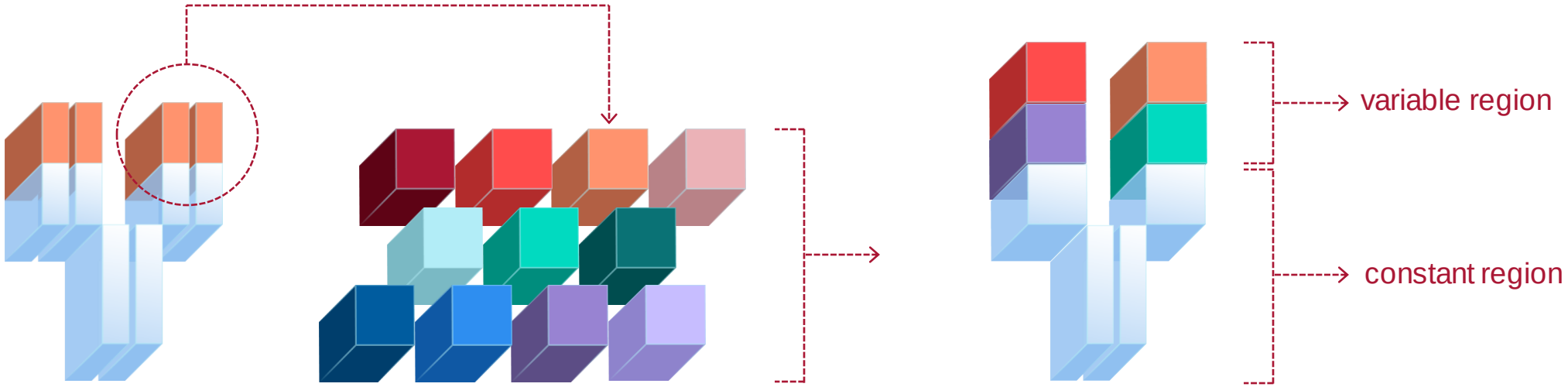
# ModeX Platform Technologies



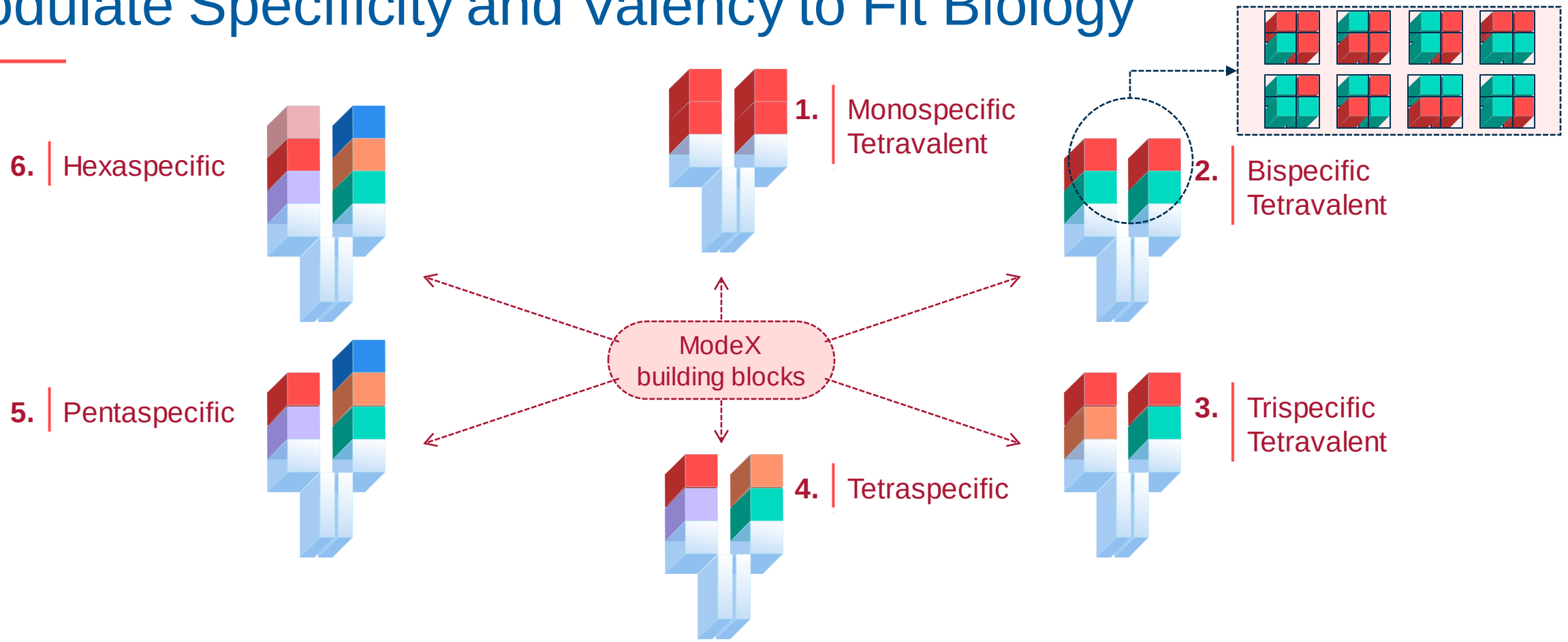
## Ronnie Wei

Head, Biologics Discovery and Development

# MSTAR Platform: Modular, Agile Multivalent and Multispecific



# ModeX STAR Technology Advantages: Modulate Specificity and Valency to Fit Biology




- Modular design enables screening large numbers of diverse candidates rapidly
- Exploit more specificities in different orientation and valency to optimize function
- Leverage both *in silico* rational design and deep learning to accelerate candidate selection

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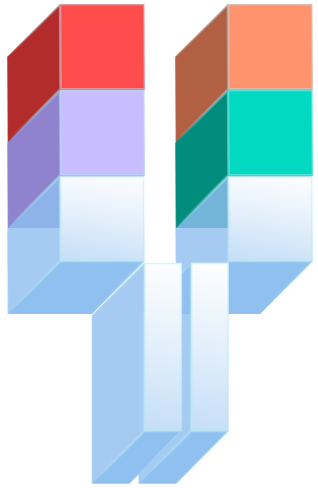
# The ModeX STAR Advantage: Functionality and Developability

## MSTAR Platform



Incorporates four or more combining sites within one molecule

- Minimize light chain mispairing and binding site interference
- All sites are functionally active
- Tunable constant (Fc) region to modulate immune functions and antibody half-life
- Favorable biophysical attributes; e.g., purity, stability, solubility
- Manufactured using standard cell lines and processes

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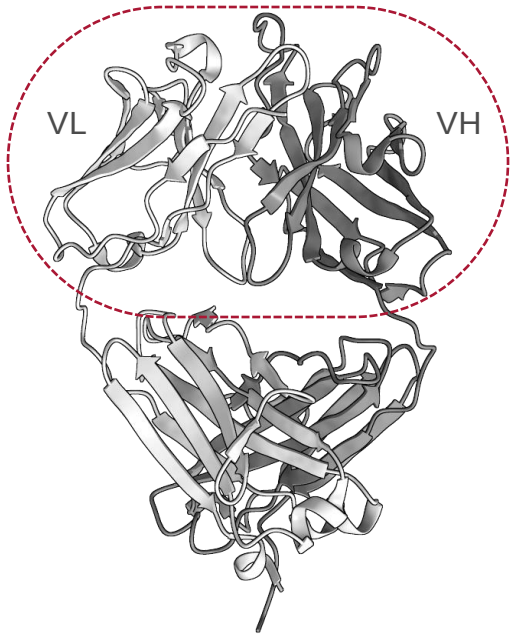
# Clinical Experience and Molecular Design Minimizes Potential Immunogenicity




Zhou *et. al* Science. 2022 Apr 22;376(6591)

- Previous studies in ~450 primary pulmonary fibrosis patients with a different bispecific format showed minimal anti-drug reactions.
- Subjects that received HIV trispecific Ab had minimal adverse effects and anti-drug responses.
- MSTAR binding domains are structurally superposable to human antibodies.
- Linkers between domains are designed to be non-immunogenic.

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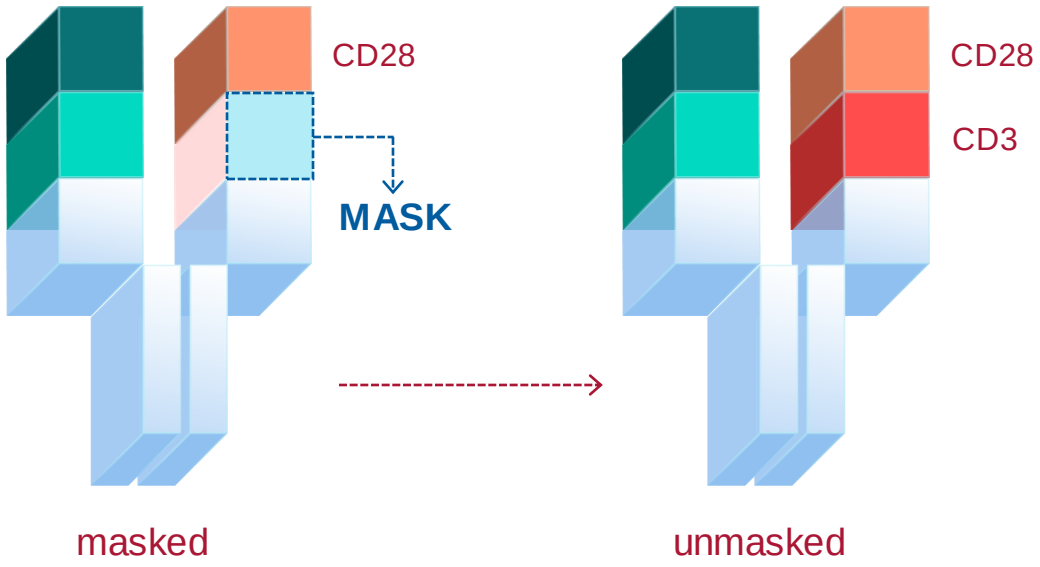
# STEALTH Platform Technology Improves Therapeutic Index

## Proprietary Masking Technology




- **Safe targeting**: Target tumor while anti-CD3 is masked. Monovalent anti-CD28 binds and recruits T cells without activation
- **Tumor-specificity**: Anti-CD3 is uncloaked by tissue-associated proteases in the tumor microenvironment.
  T cells are then activated by anti-CD3 and anti-CD28
- **Result**: Localized activation of T cells stimulates tumor killing and minimizes systemic cytokine release

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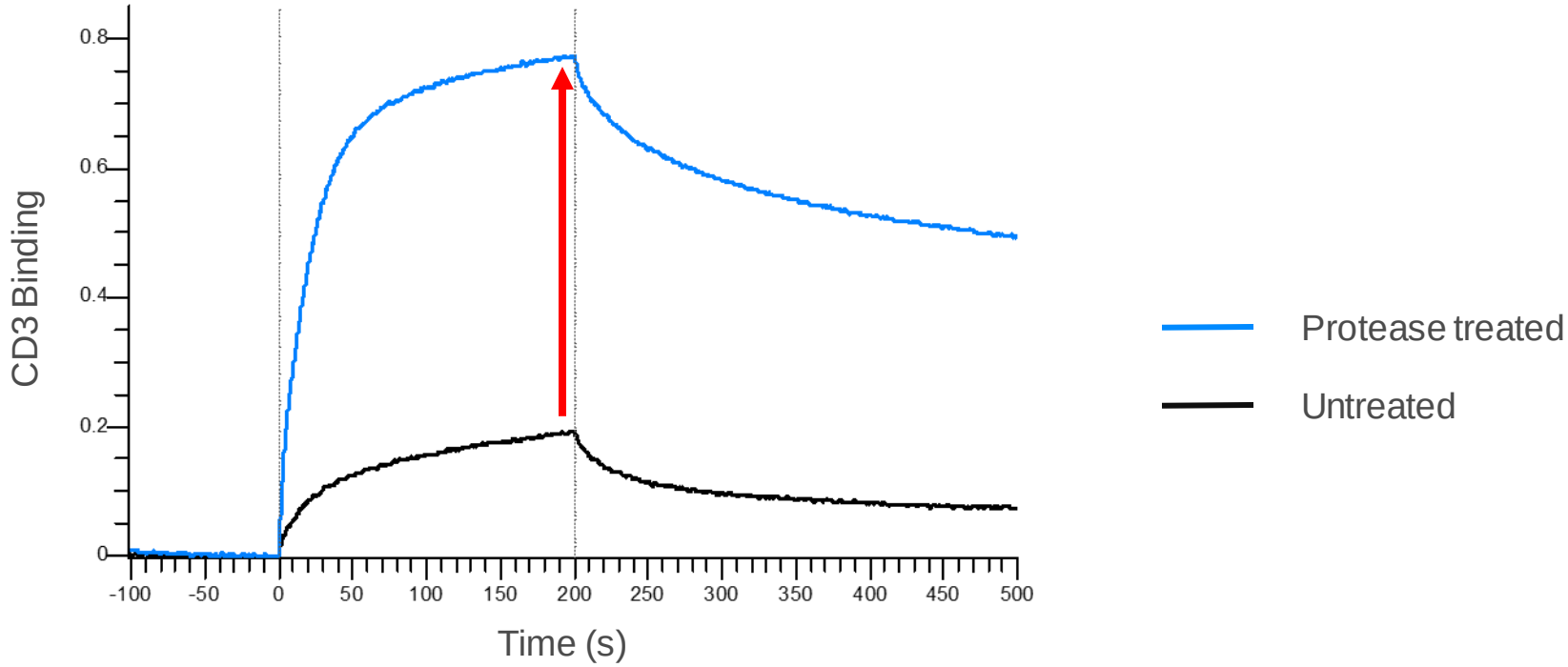
# Proof of Concept: anti-CD3 Unmasking

Protease treatment restores CD3 binding



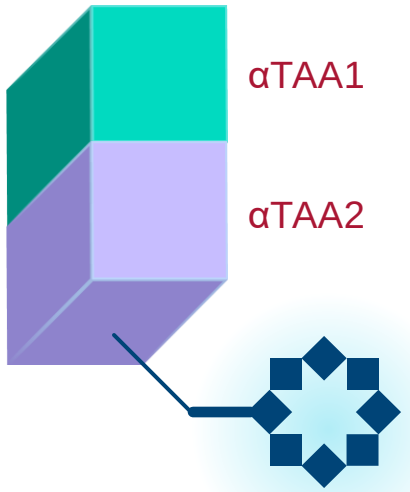
# Multispecific Antibody Immune Modulation Applications

**Broad possibilities for multi-functionality:**

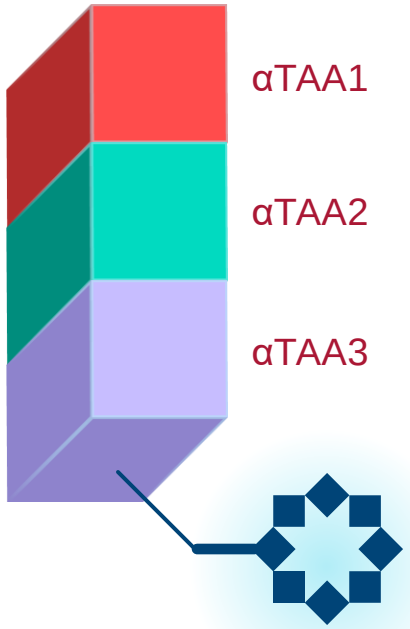
- Diverse payload conjugation
- All-in-one multispecific chimeric antigen receptors (CARs)

# Site Specific Payload Delivery with MSTAR Technology

- Single chain MSTAR Abs can deliver alternative payloads (drug or radionuclide conjugates).
- Potential to bind two or three different targets maximizes specificity and minimizes mutational escape.

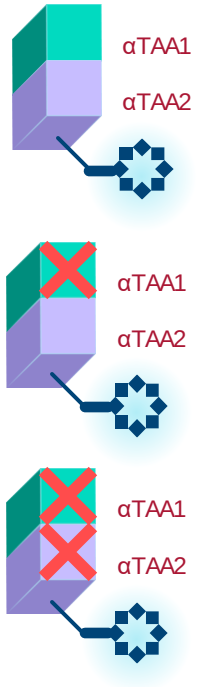


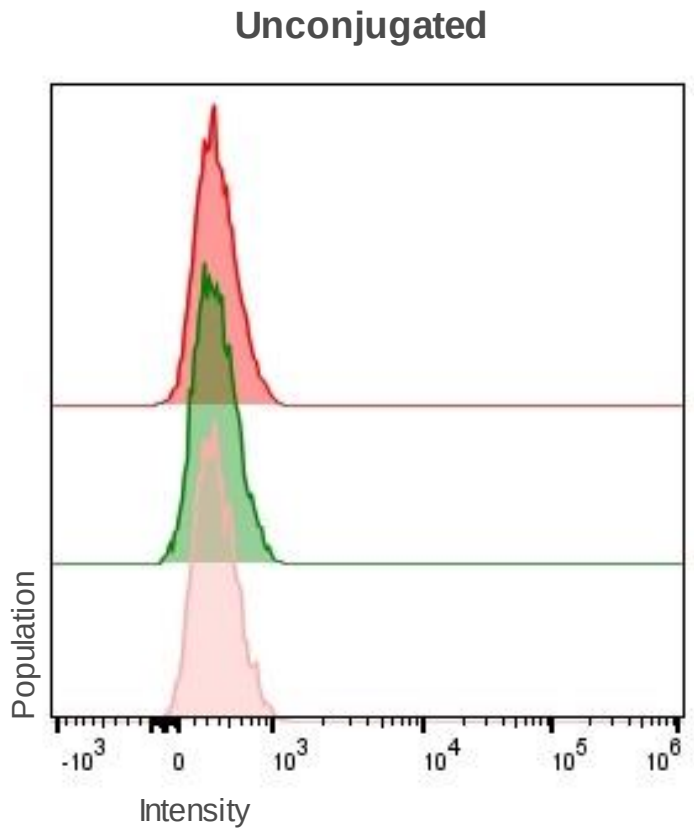

Bispecific warhead

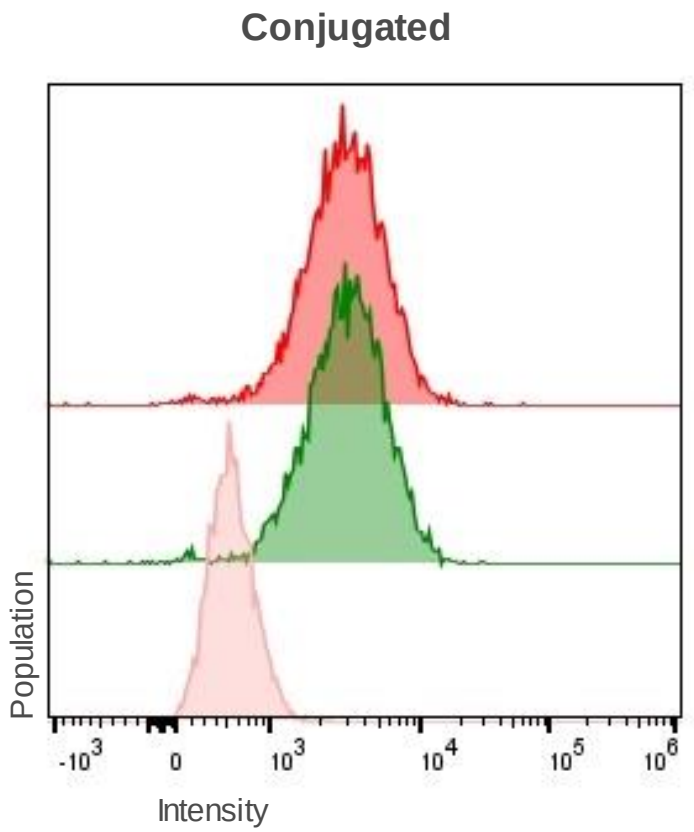



Trispecific warhead

# Binding of Bispecific MSTAR Conjugates to Prostate Cancer Cells




Two active binding sites

Single binding site knock out

Double binding site knock out

Potential to mitigate tumor resistance through antigen loss

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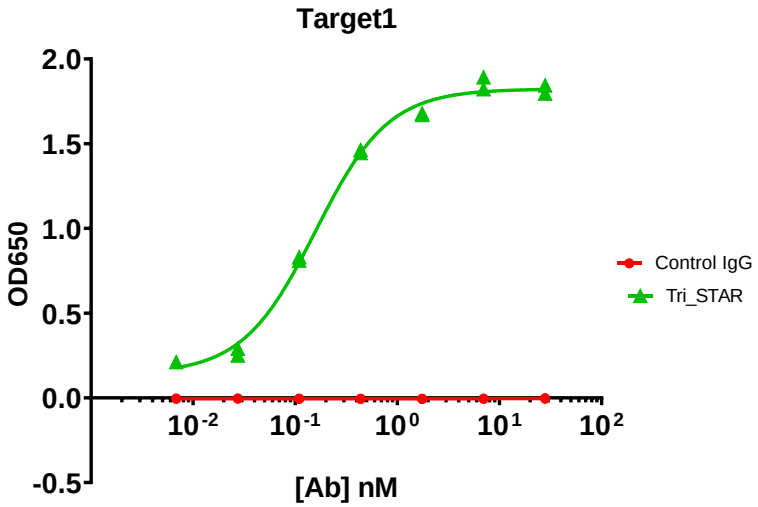
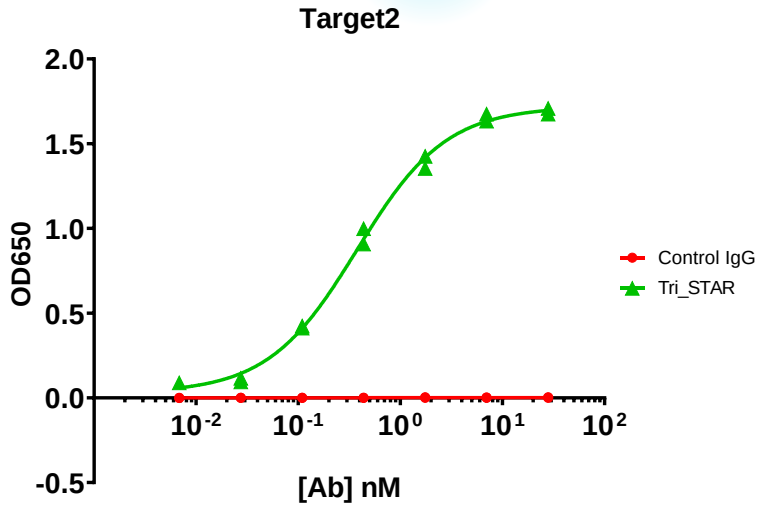
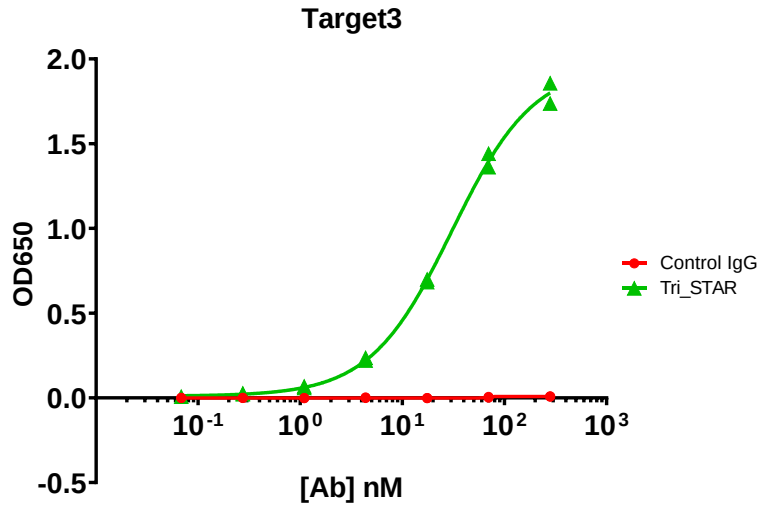
# TriSTAR Antibodies: Three Targets in One Protein


All binding sites are functional with respect to their targets

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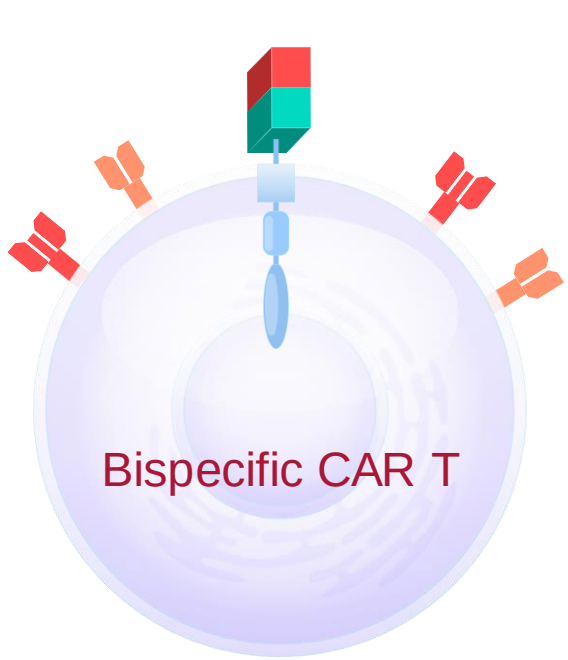
# MSTAR Multispecific CAR T Cells: All-in-One Single Chain Design for Adoptive Cell Therapies

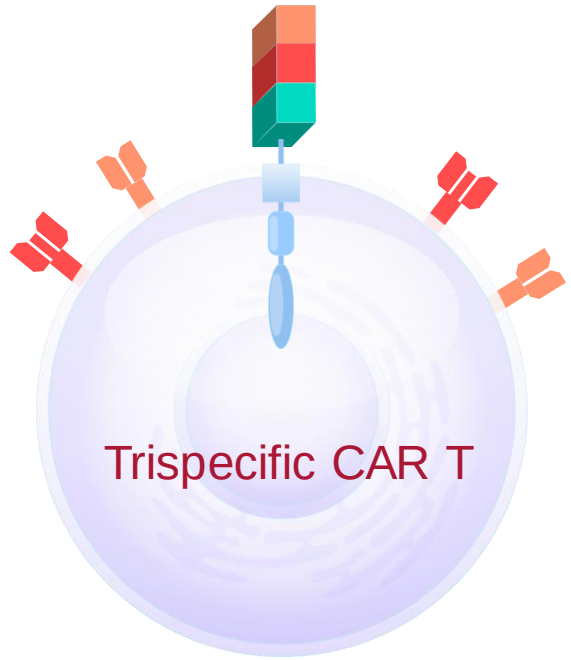
CD3/TCR

CD28

Bispecific MSTAR cassette

Trispecific MSTAR cassette




- MSTAR format with CAR T receptors
- Expands specific recognition of up to 3 different targets in one receptor
- Single gene construct

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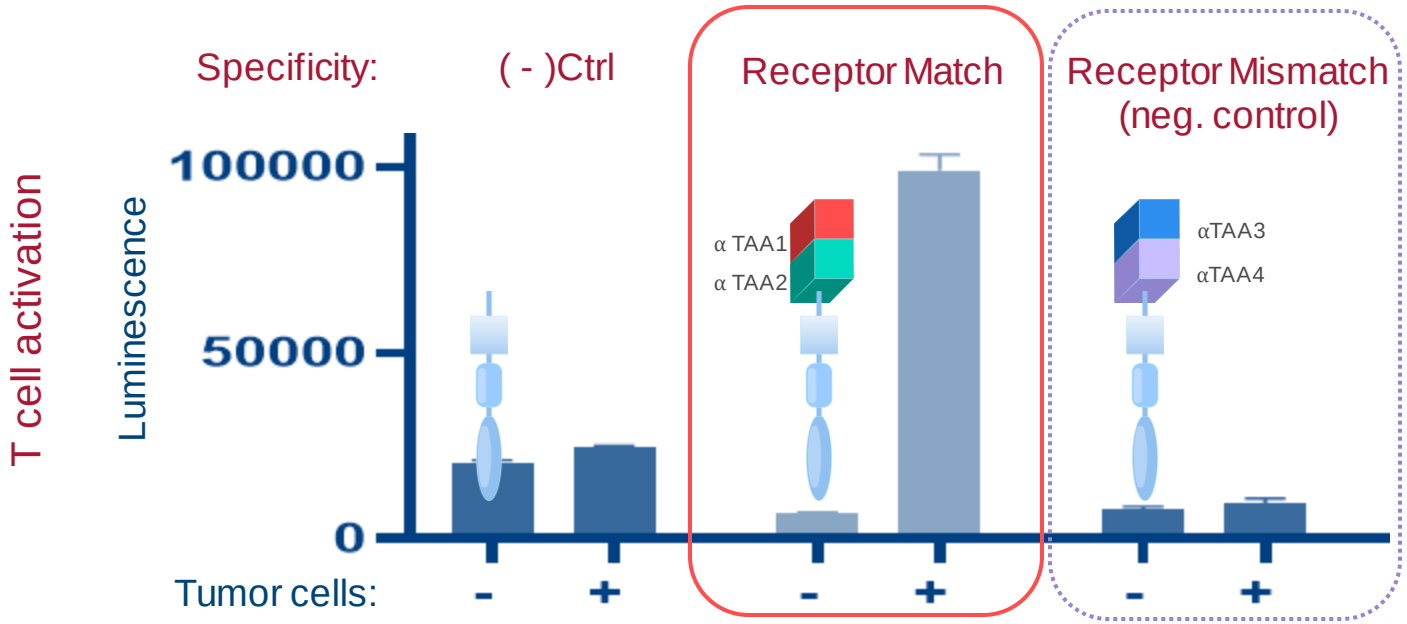
# Proof of Concept: MSTAR CAR T Cells Respond to Specific Antigens

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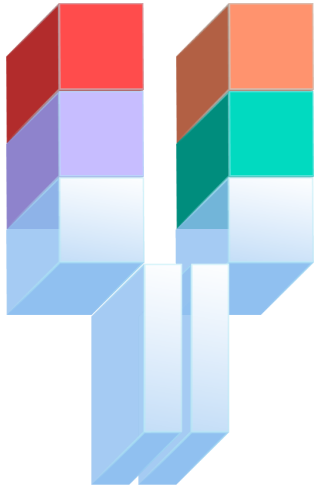
# MSTAR Platform: Summary



- Modular plug and play
- Functional flexibility and adaptability
- Diverse potential applications
- Enable gene delivery
- 28 pending patent applications filed in the past two years

# Agenda: ModeX Therapeutics R&D Day

| | |
|---|---|
| **Welcome** | **Gary Nabel**<br>Co-Founder, President/CEO, ModeX Therapeutics; Chief Innovation Officer, OPKO Health |
| **Opening Remarks** | **Phillip Frost**<br>CEO and Board Chair, OPKO Health |
| **R&D Day Overview** | **Elias Zerhouni**<br>Co-Founder, ModeX Therapeutics; President, OPKO Health |
| **Introduction to ModeX Therapeutics** | **Gary Nabel** |
| **EBV Vaccine Program** | **Gary Nabel** |
| **ModeX Platform Technologies**<br>• Multispecific Abs (MSTAR)<br>• Masking (STEALTH)<br>• Immune modulation | **Ronnie Wei**<br>Head, Biologics Discovery and Development, ModeX Therapeutics |
| **Multispecific Antibodies for Immuno-Oncology**<br>• Solid tumors<br>• Hematologic neoplasms | **John Mascola**<br>Chief Scientific Officer, ModeX Therapeutics |
| **Multispecific Antibodies for Infectious Diseases** | **John Mascola** |
| **Manufacturing for Clinical Development** | **Vijay Chhajlani**<br>Chief Technical Officer, ModeX Therapeutics |
| **Closing Remarks** | **Gary Nabel** |
| **Question and Answer Session** | **All** |

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# Multispecific Antibodies for Immuno-Oncology


John Mascola

Chief Scientific Officer


OPKO

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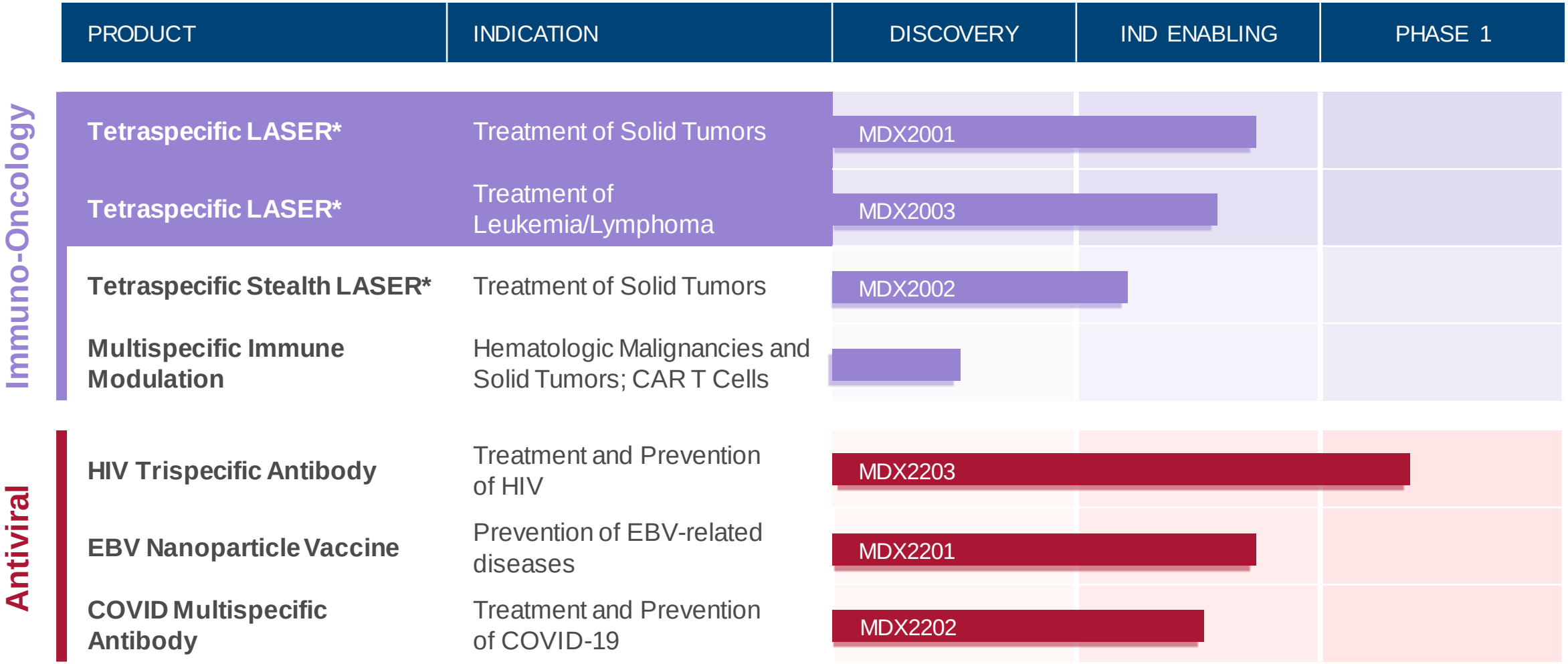
# ModeX Product Pipeline: First-in-Class Drugs with Best-in-Class Potential




**Lymphocyte Activator and Survival Extension Receptor (LASER) Antibodies*

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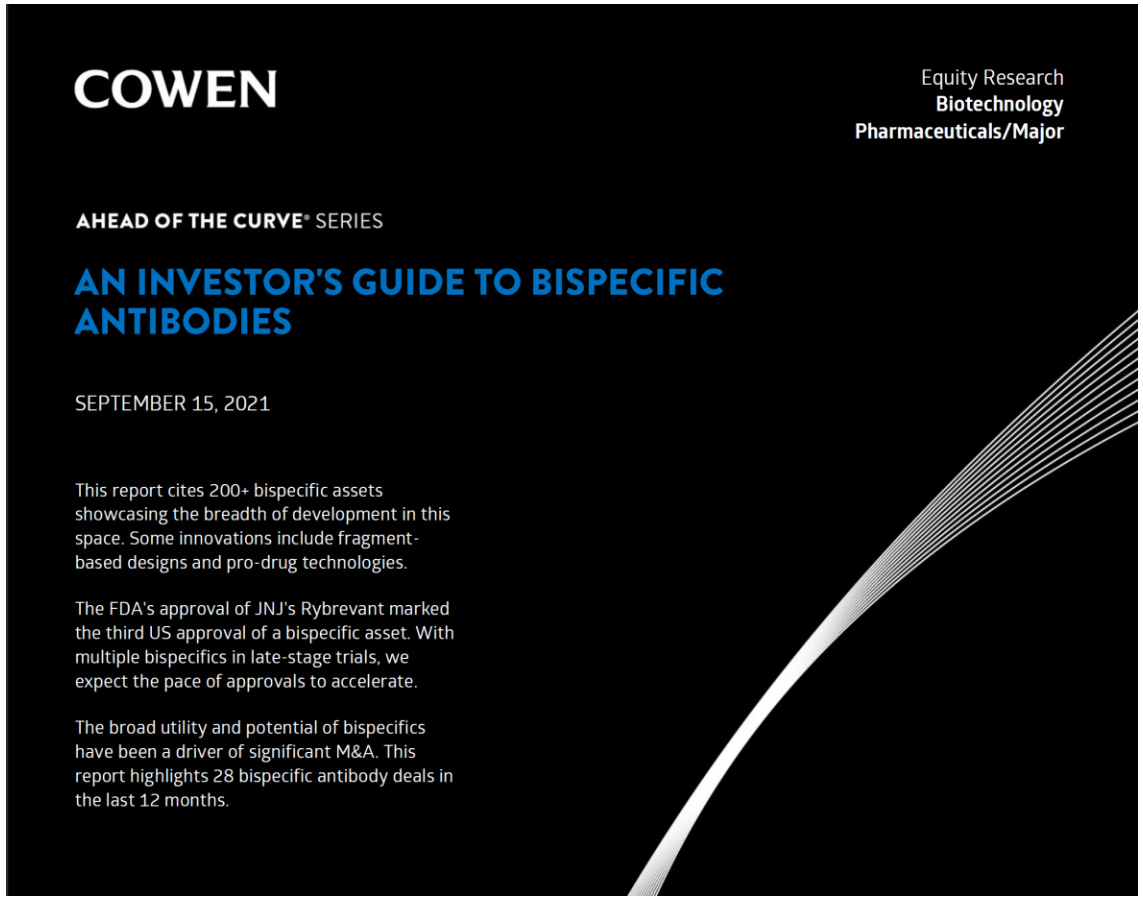
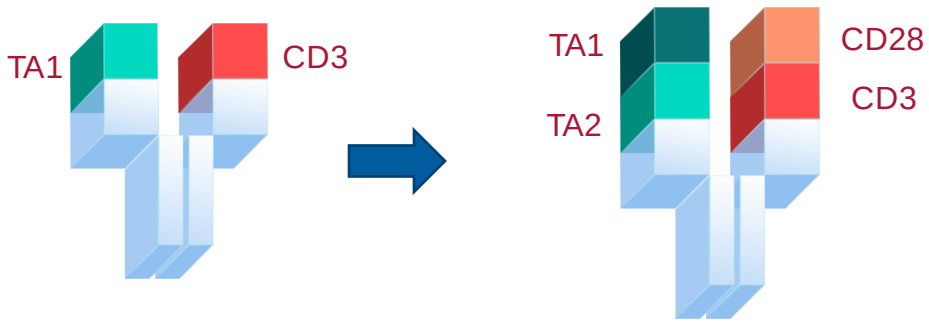
# Growing Value Proposition and Success of Bispecific Abs

## Validation of Commercial Opportunity




- Bispecfic T cell engager (BITE) antibodies show clinical efficacy for B cell malignancies.
- BITEs are being developed for solid tumors with encouraging clinical data.
- However, BITEs are limited to two targets total, one tumor antigen and one T cell antigen.
- Tetraspecific antibodies can engage two T cell antigens and two tumor antigens, providing the potential for expanded mechanisms of action and clinical indications.

# Beyond Bispecifics: Modex Tetraspecific Antibodies




- Existing bispecific T cell engager antibodies harness the immune system by directing T cells to kill cancer cells.
- ModeX is developing the next generation of multispecific antibodies with greater power to recognize tumors antigens (TA) and enhance T cell killing.

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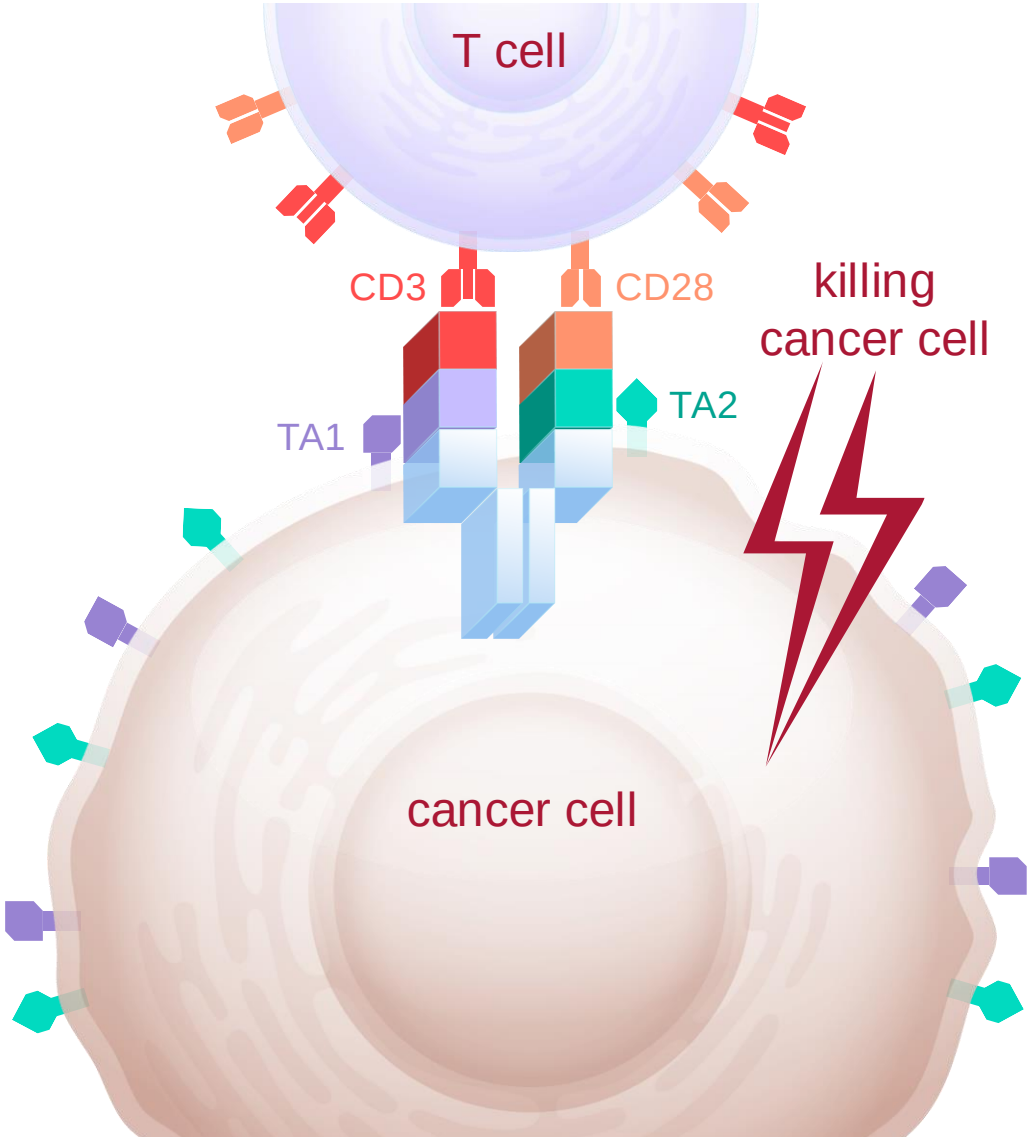
# From T Cell Engagers to T Cell LASERS




## Lymphocyte Activation and Survival Enhancement Receptor Antibodies (LASER)

- A next generation multispecific antibody activating T cells using signal 1 (CD3) and enhancing survival via signal 2 (CD28) to optimize sustained tumor killing.
- Dual tumor targeting increases specificity of tumor recognition and mitigates escape resistance that can occur through loss of a single tumor antigen.

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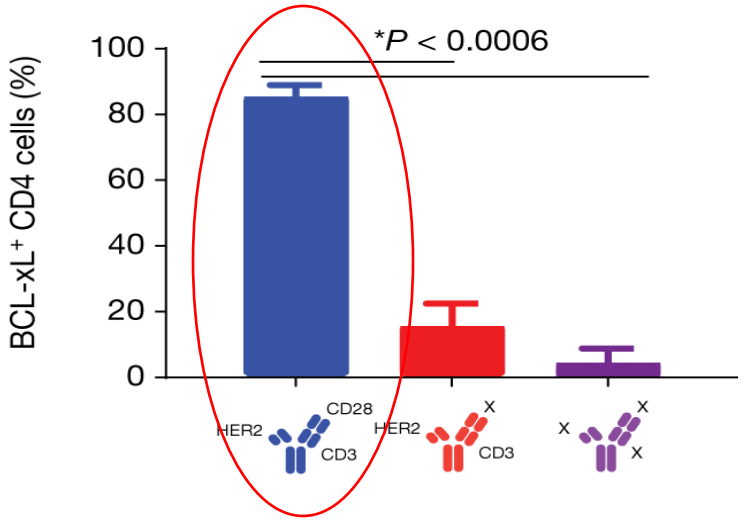
# Enhanced T cell survival and proliferation by engaging CD28 in the presence of CD3 activation

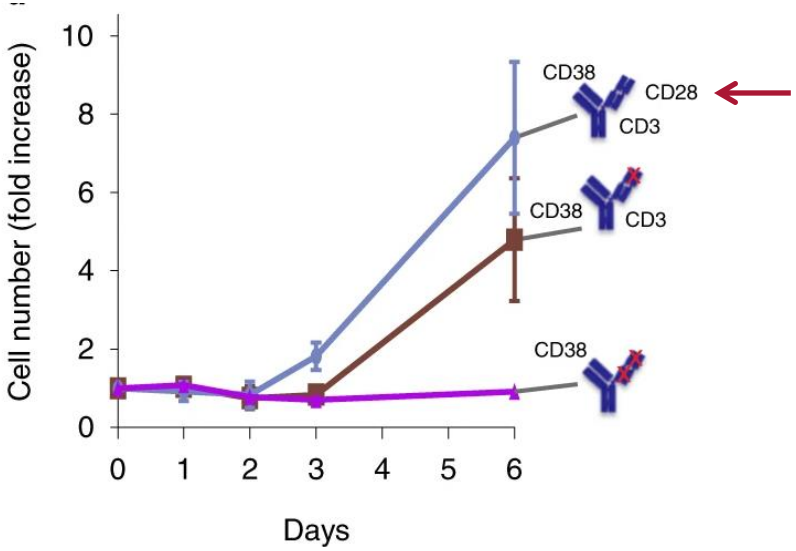

**A trispecific antibody targeting HER2 and T cells inhibits breast cancer growth via CD4 cells**

Edward Seung, Zhen Xing, Lan Wu … Ronnie Wei, Zhi-yong Yang, Gary J. Nabel, et al.


**Upregulation of a CD4 cell survival signal**




**T cell proliferation**




**CD3/CD28 co-signaling activates Bcl-xL, a protein that promotes T cell survival, providing the potential for long-lasting activity against cancer cells**

www.nature.com/articles/s41586-022-04439-0

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# Medical Need and Clinical Potential of Solid Tumor Multispecific Antibodies

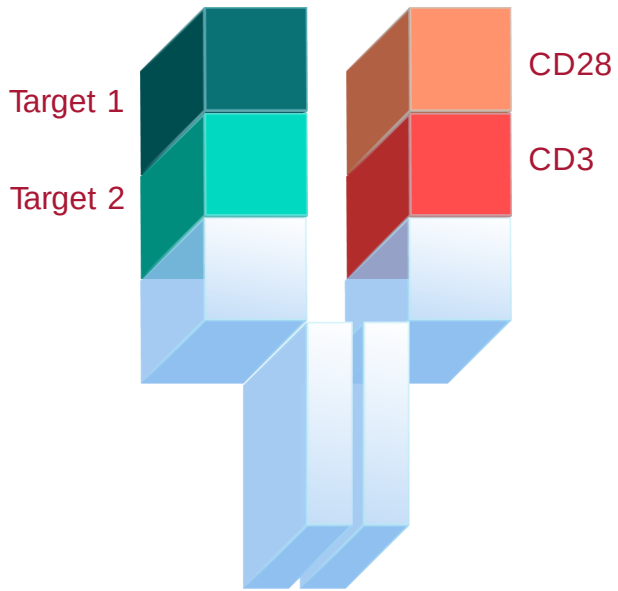
- Limitations of standard of care treatments: For many solid tumors, existing treatments do not induce complete and sustained remission. For example, the long-term survival rate for lung cancer is < 30%, even with immune modulator therapy.
- Immunotherapy with antibodies: Has shown promise for some solid tumors, but relapse and development of resistance remains common, often due to loss of expression of tumor antigens.
- Modex tetraspecific antibodies: Have activity against the most common and deadly solid tumors with potential to be active against relapsed disease after chemotherapy and immuno-oncology therapies, including CAR T treatment.

# Tetraspecific LASER Antibody for Solid Tumors: MDX2001


**MDX2001**

- Lead candidate selected and in IND enabling phase
- Dual T cell signaling activates T cells via CD3 and enhances survival via CD28, optimizing potent and sustained T cell killing of cancer cells
- Binds to two tumor antigens (undisclosed) that are highly expressed on diverse solid tumors
- Minimizes potential for resistance through loss of a single antigen

# MDX2001 Targets Tumor Driver Antigens on the Four Most Common Solid Tumor Cancers




**MDX2001**

**Estimated U.S. Cancers Cases for 2023**

| Cancer | Estimated New Cases/ Year | Estimated Deaths/Year |
|---|---|---|
| | | |
| Breast | 300,000 | 43,700 |
| Prostate | 288,000 | 34,700 |
| Lung | 238,000 | 127,000 |
| Colon and Rectal | 153,000 | 52,500 |
| | | |
| Total | 977,000 | 257,700 |

https://www.cancer.gov/types/common-cancers

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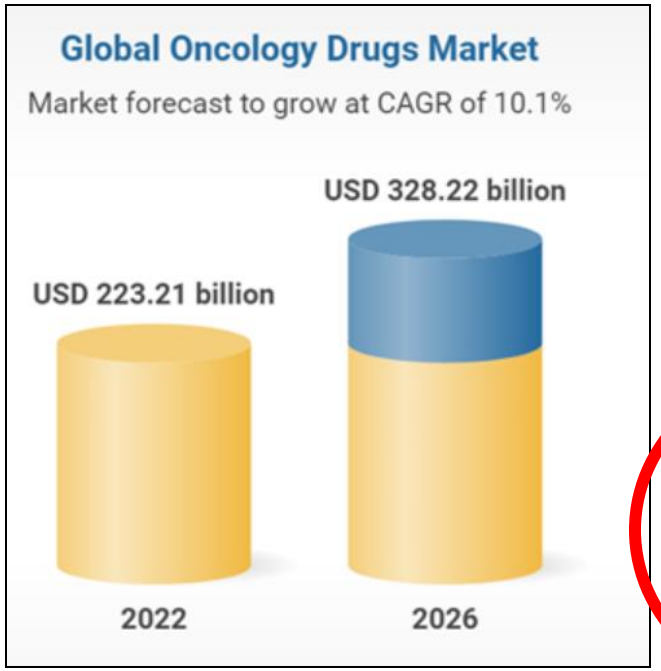
# Four Most Common Solid Tumor Malignancies: Medical Value




| | | | | |
|---|---|---|---|---|
| Global Oncology Drug Market Forecast for 2026* | | | | $328.2 B |
| | | | North America (est. 57%) | $187.1 B |
| | | | N.A. Solid Tumors (est. 60%) | $112.3 B |
| Projected New U.S. Cancer Cases 2023** | 1,958,310 | | | |
| | Cases | % Total | Proj. Deaths | |
| Breast | 300,590 | 15 | 43,700 | ~$50 B |
| Prostate | 288,300 | 15 | 34,700 | ~$50 B |
| Lung | 238,340 | 12 | 127,070 | ~$39 B |
| Colorectal (CRC) | 153,020 | 8 | 52,550 | ~$26 B |

**Total Addressable Global Market for Top 4 Solid Tumors**

* https://www.businesswire.com/news/home/20220620005396/en/Oncology-Drugs-Global-Market-Research-Report-2022---ResearchAndMarkets.com

** https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2023/2023-cancer-facts-and-figures.pdf

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# MDX2001: Functional Criteria for Lead Selection

- **Tumor-specific T cell activation:**

  Low T cell activation in the absence of tumor cells.

- **Potent tumor cell killing *in vitro*:** ⟸

  Potently kills diverse tumor cell lines.

- **Anti-tumor efficacy *in vivo*:** ⟸

  Anti-tumor growth activity in humanized mice challenged with cancer cells.

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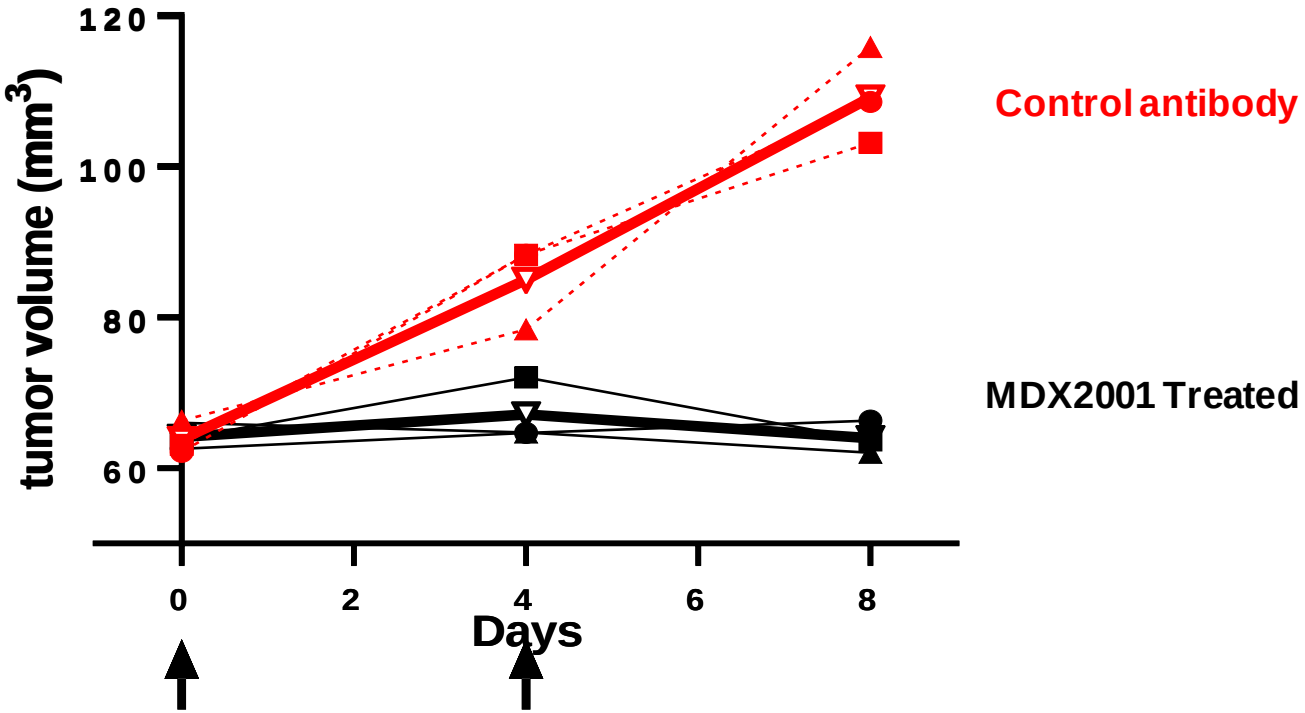
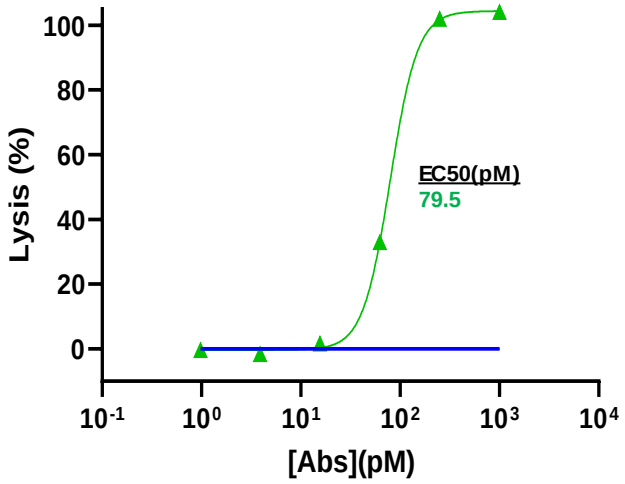
# MDX2001 LASER: Anti-Tumor Efficacy *In Vivo*

**Tumor Regression in a Xenograft Breast Cancer Mouse Model**

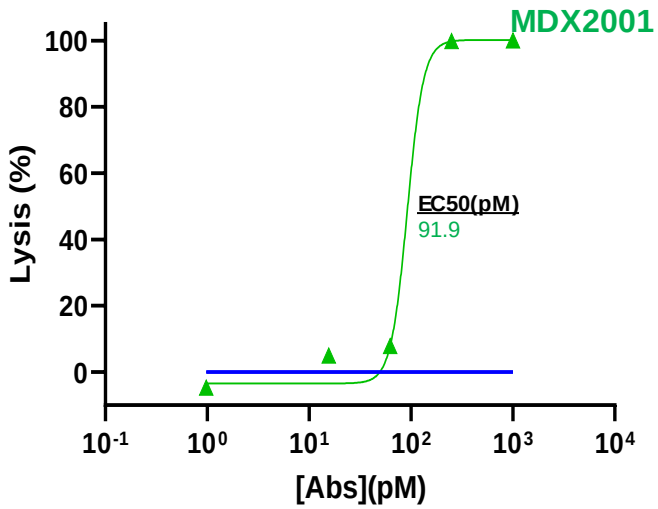


# MDX2001 Tetraspecific LASER Advantage: Killing of Diverse Solid Tumors *In Vitro*

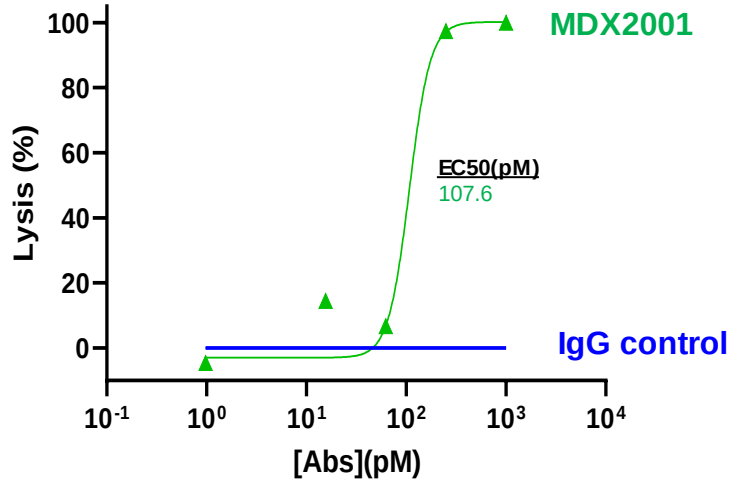
Prostate Cancer




Gastric Cancer




Breast Cancer




*In vitro* data from human T cell mediated killing of tumor cell lines

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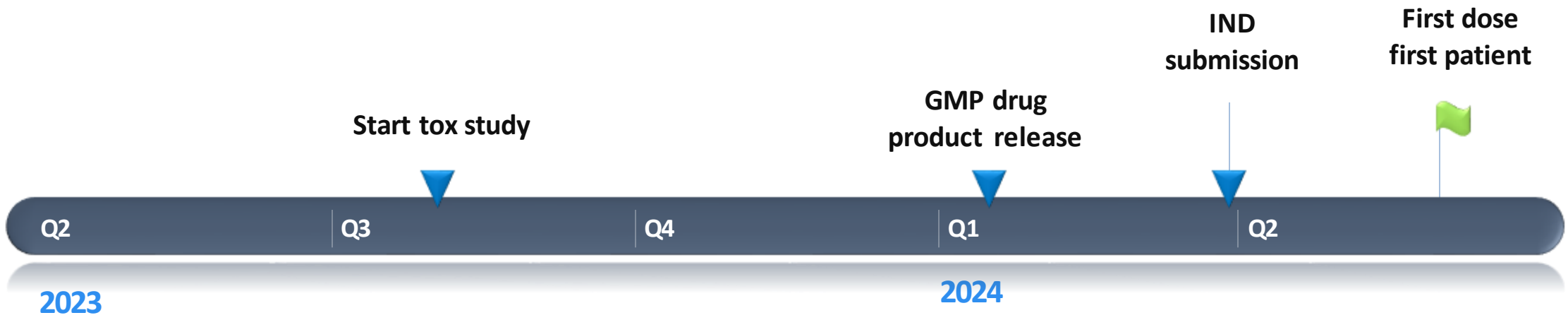
# MDX2001 Projected Timeline and Pathway to Clinic




Have met with key opinion leaders

Evaluating optimal clinical study designs based on major unmet medical need and market potential

# ModeX Product Pipeline: First-in-Class Drugs with Best-in-Class Potential

| | PRODUCT | INDICATION | DISCOVERY | IND ENABLING | PHASE 1 |
|---|---|---|---|---|---|
| Immuno-Oncology | **Tetraspecific LASER*** | Treatment of Solid Tumors | MDX2001 | | |
| | **Tetraspecific LASER*** | Treatment of Leukemia/Lymphoma | MDX2003 | | |
| | **Tetraspecific Stealth LASER*** | Treatment of Solid Tumors | MDX2002 | | |
| | **Multispecific Immune Modulation** | Hematologic Malignancies and Solid Tumors; CAR T Cells | | | |
| Antiviral | **HIV Trispecific Antibody** | Treatment and Prevention of HIV | MDX2203 | | |
| | **EBV Nanoparticle Vaccine** | Prevention of EBV-related diseases | MDX2201 | | |
| | **COVID Multispecific Antibody** | Treatment and Prevention of COVID-19 | MDX2202 | | |

**Lymphocyte Activator and Survival Extension Receptor (LASER) Antibodies*

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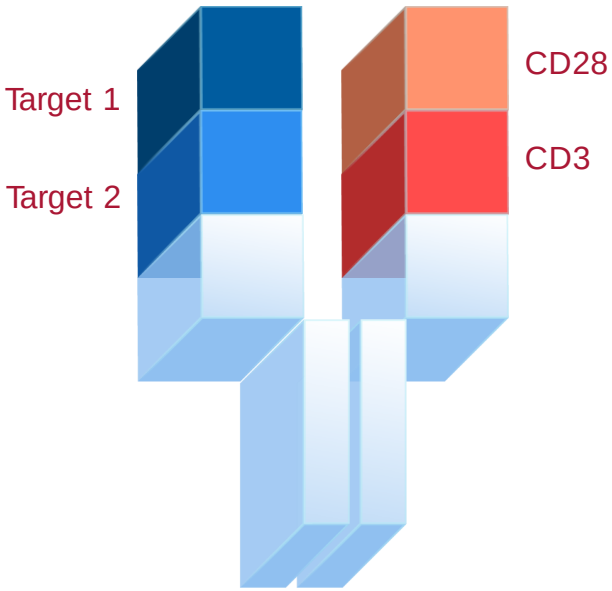
# B Cell Cancer Multispecifics: Medical Need and Market Value

- B cell leukemias and non-Hodgkin lymphomas account for > 140,000 new cases and 43,000 deaths per year in the U.S.
- The overall 5-year survival for B cell malignancies varies widely by disease type. Unfortunately, relapse is common for more aggressive types and complete remission rates for relapsed disease is often < 50%.
- Antibody immunotherapies, including bispecific T cell engagers can be effective, but are often limited by incomplete responses and loss of expression of key tumor antigens.
- Total global addressable drug market for leukemias and NHLs ~ $22B

# Tetraspecific LASER Antibody for B Cell Malignancies: MDX 2003

## B cell Malignancies: Lymphoma/leukemia




**MDX2003**

- Lead candidate selected and in IND enabling phase
- Dual T-cell signaling stimulates T cells via CD3 and enhances survival via CD28, optimizing potent and sustained T cell killing of cancer cells
- Binds to two tumor antigens (undisclosed) that are highly expressed on diverse B cell cancers
- Minimizes potential for resistance through loss of a single antigen.

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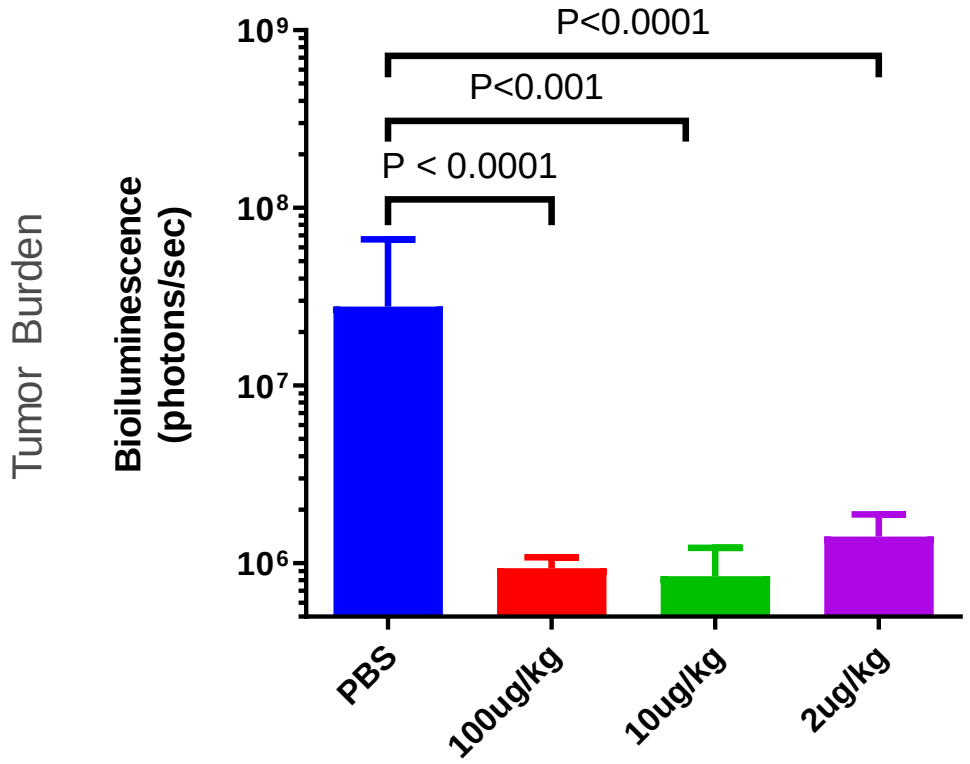
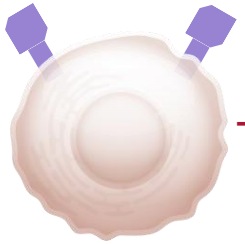
# MDX2003 Tetraspecific LASER: Anti-tumor Efficacy *In Vivo*

**Tumor Regression in Disseminated B cell Lymphoma Xenograft Mouse Model**



# MDX2003 Tetraspecific LASER Advantage: Dual Targeting Overcomes Antigen Loss that Confers Tumor Resistance

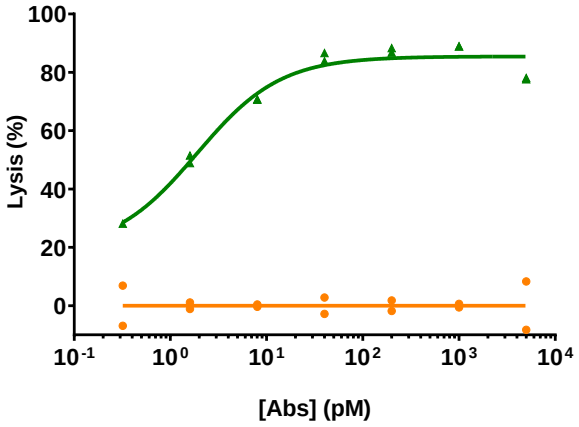
TA1 + TA2

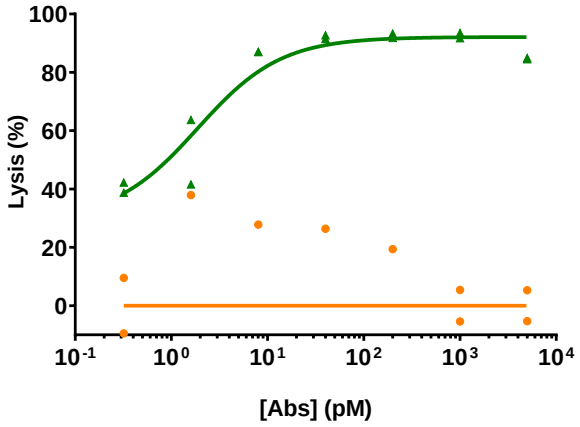


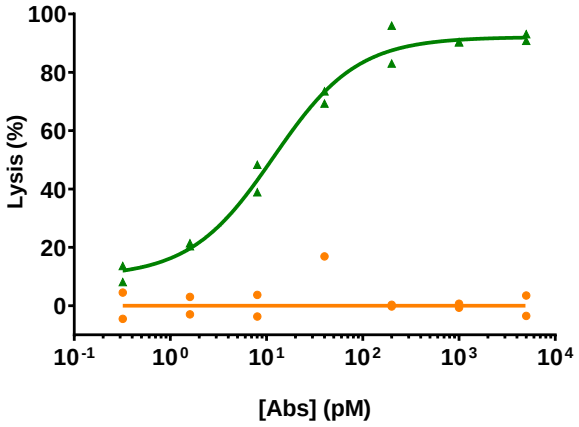
TA1 only

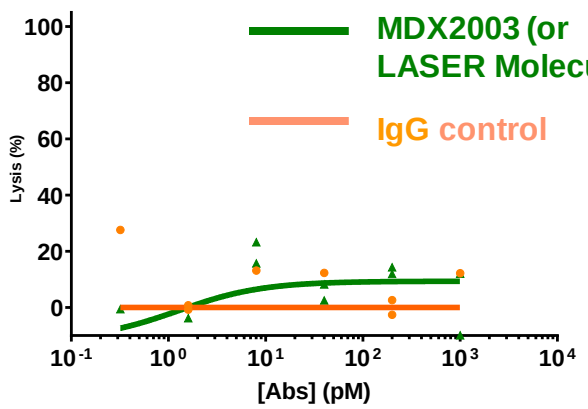
TA2 only

Null





In vitro tumor cell killing mediated by human T cells

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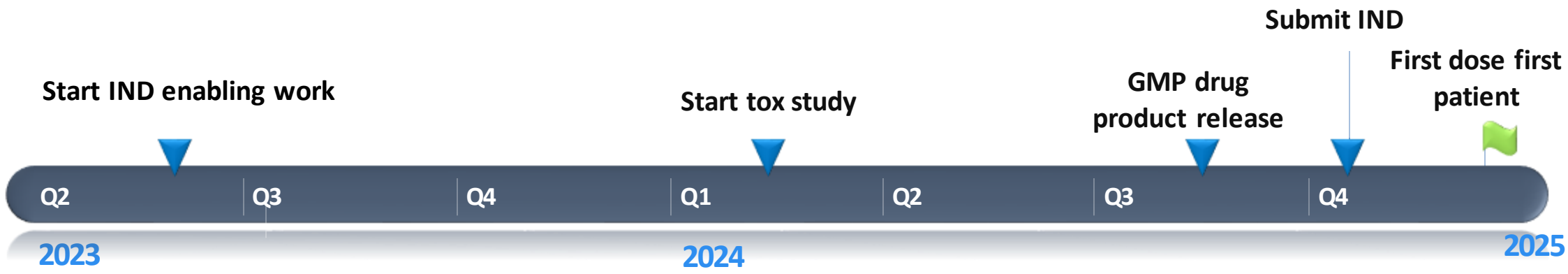
# MDX2003: Projected Timeline and Pathway to Clinic



# Summary MDX2003: For Leukemia/Lymphoma

- Modex tetraspecific antibodies are potential therapies against B cell leukemias and non-Hodgkins lymphomas, including relapsed disease after bispecific T cell engager and CAR T cell treatments.
- Multispecifics address immune escape from down-modulation of single target antigens (e.g., C19 resistance after CAR T cell treatment)
- Offer a potential “off-the-shelf” alternative to individualized CAR T cells treatment
- IND planned for late 2024

# Agenda: ModeX Therapeutics R&D Day

| | |
|---|---|
| **Welcome** | **Gary Nabel**<br>Co-Founder, President/CEO, ModeX Therapeutics; Chief Innovation Officer, OPKO Health |
| **Opening Remarks** | **Phillip Frost**<br>CEO and Board Chair, OPKO Health |
| **R&D Day Overview** | **Elias Zerhouni**<br>Co-Founder, ModeX Therapeutics; President, OPKO Health |
| **Introduction to ModeX Therapeutics** | **Gary Nabel** |
| **EBV Vaccine Program** | **Gary Nabel** |
| **ModeX Platform Technologies**<br>• Multispecific Abs (MSTAR)<br>• Masking (STEALTH)<br>• Immune modulation | **Ronnie Wei**<br>Head, Biologics Discovery and Development, ModeX Therapeutics |
| **Multispecific Antibodies for Immuno-Oncology**<br>• Solid tumors<br>• Hematologic neoplasms | **John Mascola**<br>Chief Scientific Officer, ModeX Therapeutics |
| **Multispecific Antibodies for Infectious Diseases** | **John Mascola** |
| **Manufacturing for Clinical Development** | **Vijay Chhajlani**<br>Chief Technical Officer, ModeX Therapeutics |
| **Closing Remarks** | **Gary Nabel** |
| **Question and Answer Session** | **All** |

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# ModeX Product Pipeline: First-in-Class Drugs with Best-in-Class Potential

| | PRODUCT | INDICATION | DISCOVERY | IND ENABLING | PHASE 1 |
|---|---|---|---|---|---|
| Immuno-Oncology | **Tetraspecific LASER*** | Treatment of Solid Tumors | MDX2001 | | |
| | **Tetraspecific LASER*** | Treatment of Leukemia/Lymphoma | MDX2003 | | |
| | **Tetraspecific Stealth LASER*** | Treatment of Solid Tumors | MDX2002 | | |
| | **Multispecific Immune Modulation** | Hematologic Malignancies and Solid Tumors; CAR T Cells | | | |
| Antiviral | **HIV Trispecific Antibody** | Treatment and Prevention of HIV | MDX2203 | | |
| | **EBV Nanoparticle Vaccine** | Prevention of EBV-related diseases | MDX2201 | | |
| | **COVID Multispecific Antibody** | Treatment and Prevention of COVID-19 | MDX2202 | | |

**Lymphocyte Activator and Survival Extension Receptor (LASER) Antibodies*

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# Medical Need: Global and U.S. impact of HIV infection

**Globally:**

**~38 million are HIV-infected**

**~1.5 million new infections/year**

**650,000 deaths/year**

**Global HIV drug Sales > $28B annually**

**United States:**

**1.2 million are HIV infected and require lifelong antiviral therapy**

**37,800 new HIV infections/year**

https://www.who.int/data/gho/data/themes/hiv-aids

https://www.hiv.gov/hiv-basics/overview/data-and-trends/statistics/

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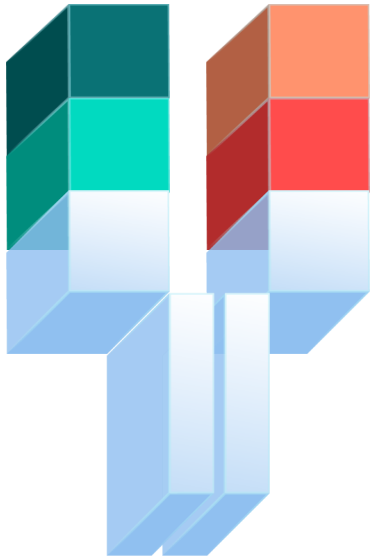
# Medical Need: Limitations of Current HIV Therapy



**MDX2203**

- **Drug Toxicity due to lifelong treatment: Renal, metabolic, neurologic and others**
- **Drug Resistance impacting efficacy of viral suppression**
- **Need for daily drug therapy**
- **Need for lifelong therapy**
- **No vaccine or antibodies to prevent infection**

# Medical Need: Potential of Multispecific Antibody for HIV Treatment and Prevention

+HIV

**Salvage Therapy**

*In pts with drug resistant strains of HIV*

HIV multispecific "add-on"

Failing optimal antiretroviral drugs

+HIV

**Maintenance Therapy**

*In pts who need better long-term therapy*

HIV multispecific (long acting)

Antiviral drugs (daily)

Antiviral drugs (long acting)

-HIV

**Prevention**

*Those at high risk of acquiring HIV who need a safe long-acting option*

HIV multispecific antibody (long acting)

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# HIV Multispecific Development: Guided by Detailed Structural Knowledge of Vulnerable Regions HIV

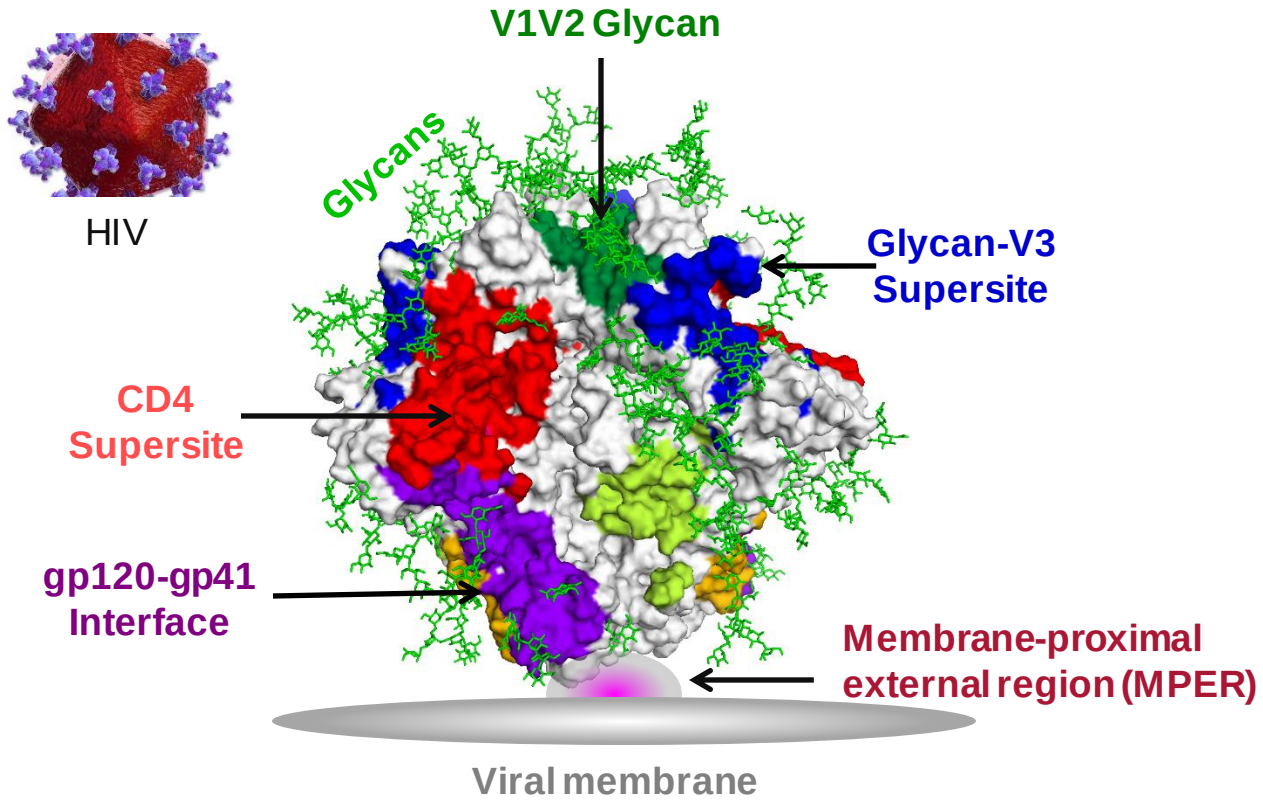


Image by Stewart-Jones, Doria-Rose, Stuckey
Adapted from Stewart-Jones et al.
Cell 2016 and Pancera et al. Nature 2014

## Goal: develop a potent HIV multispecific that can:

- Attack and neutralize diverse strains of HIV worldwide by targeting independent sites on the virus.
- Be dosed simply and efficiently.
- Be used for both treatment and prevention of HIV infection.

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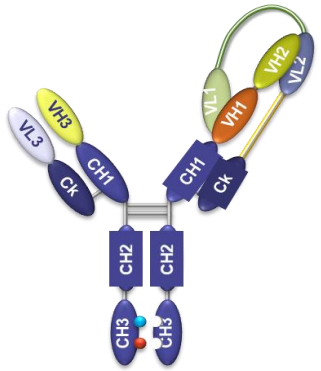
# Trispecific Antibody to Target Diversity of HIV

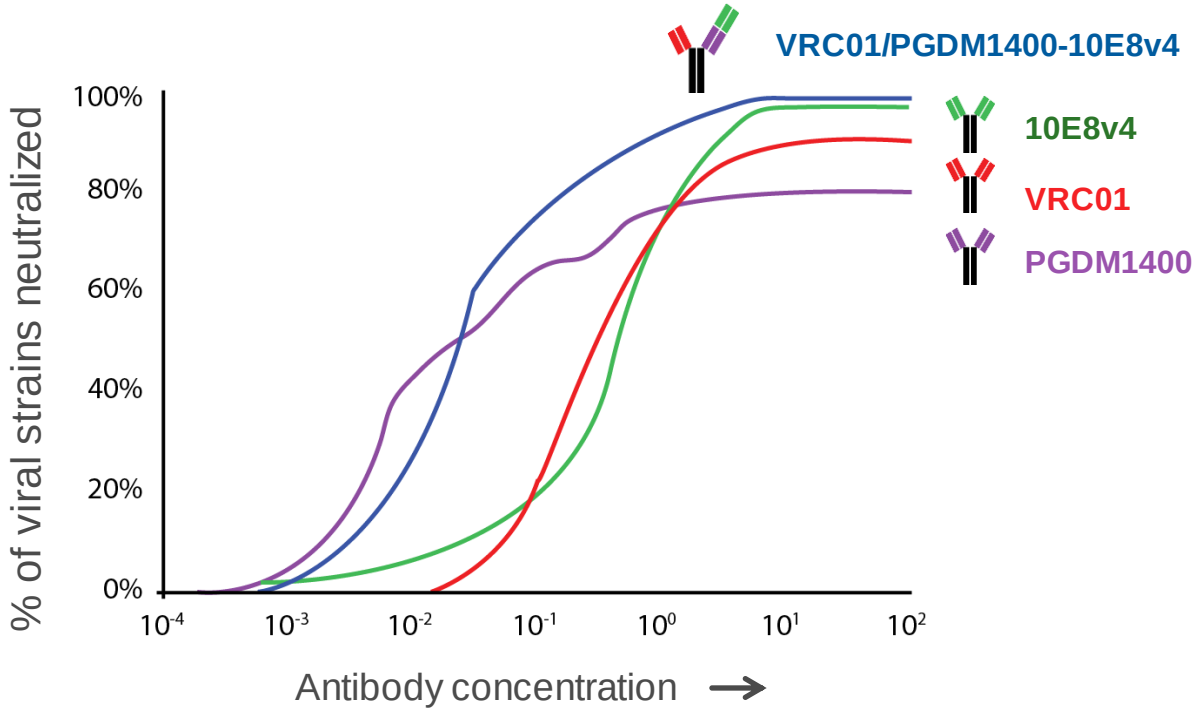

**Trispecific broadly neutralizing HIV antibodies mediate potent SHIV protection in macaques**

Ling Xu, Amarendra Pegu, Ercole Rao, Nicole Doria-Rose, . .. Richard Koup, Peter Kwong, Zhi-yong Yang, John Mascola, Gary Nabel et al.

Xu et al. *Science* 358: 85-90 (2017)
Collaboration with VRC, NIAID




CODV
Trispecific




A trispecific antibody has greater potency and coverage of HIV diversity than any single parental antibody

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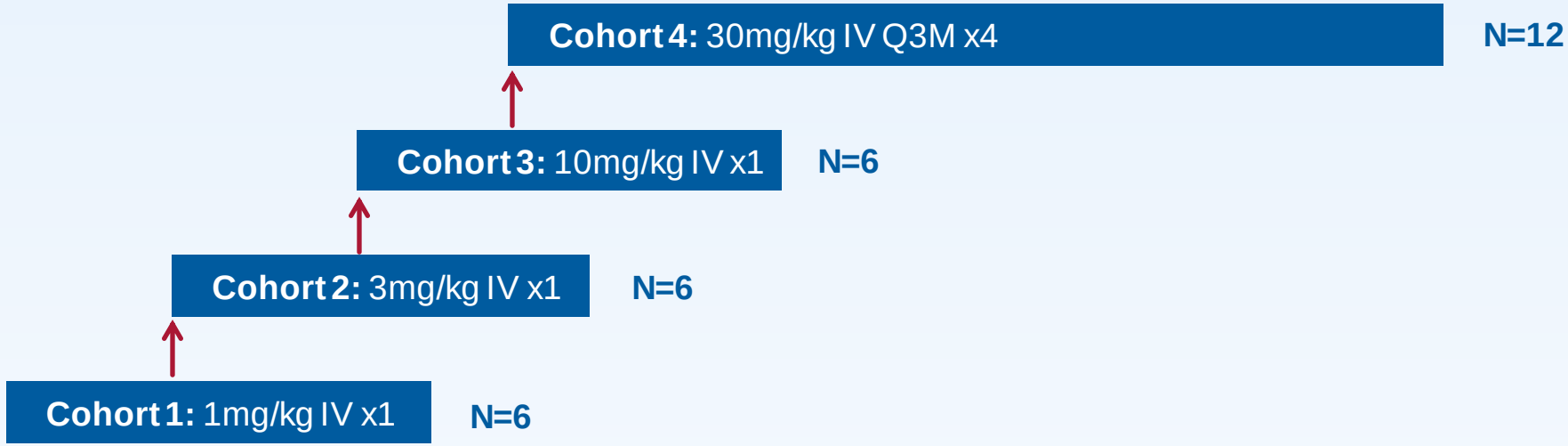
# A Phase I First-in-Human Study of SAR441236, a Trispecific Broadly Neutralizing Antibody, in Participants with HIV




Dose escalation based on 2-wk safety review

ACTG AIDS CLINICAL TRIALS GROUP

NIH National Institute of Allergy and Infectious Diseases

Safe and well tolerated: single and multiple doses.
Additional data expected in Q2/3 2023

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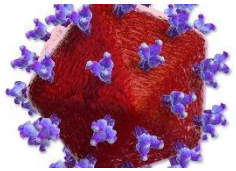
# Next Generation Multispecifics for HIV: >10-fold Improved Potency and Breadth

## Potent antiviral activity against the vast majority of global HIV strains



HIV

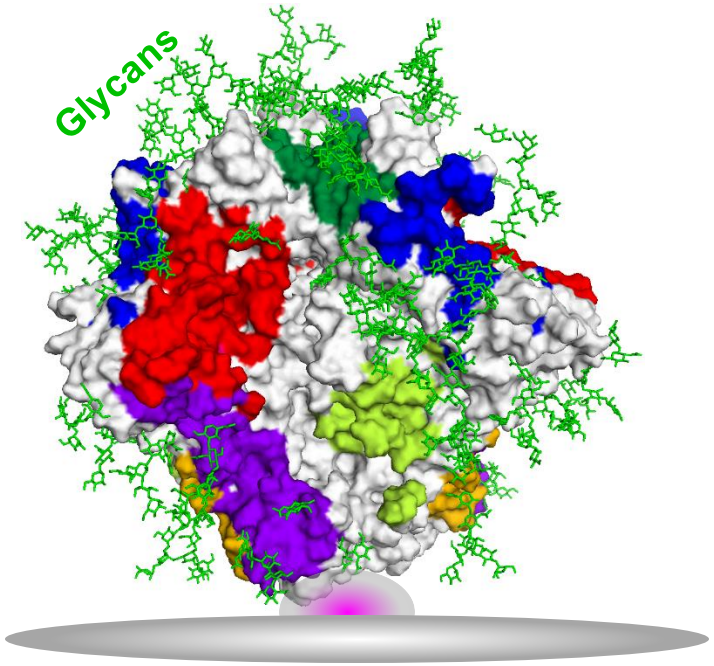



Image by Stewart-Jones, Doria-Rose, Stuckey
Adapted from Stewart-Jones et al.
Cell 2016 and Pancera et al. Nature 2014

- Collaboration between ModeX, Vaccine Research Center (VRC), NIH, the Scripps Research Institute & International AIDS Vaccine Initiative (IAVI)
- Several preclinical pre-IND candidates under development including 2nd generation CODV trispecific
- 3rd generation multispecific using MSTAR format

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**Lymphocyte Activator and Survival Extension Receptor (LASER) Antibodies*

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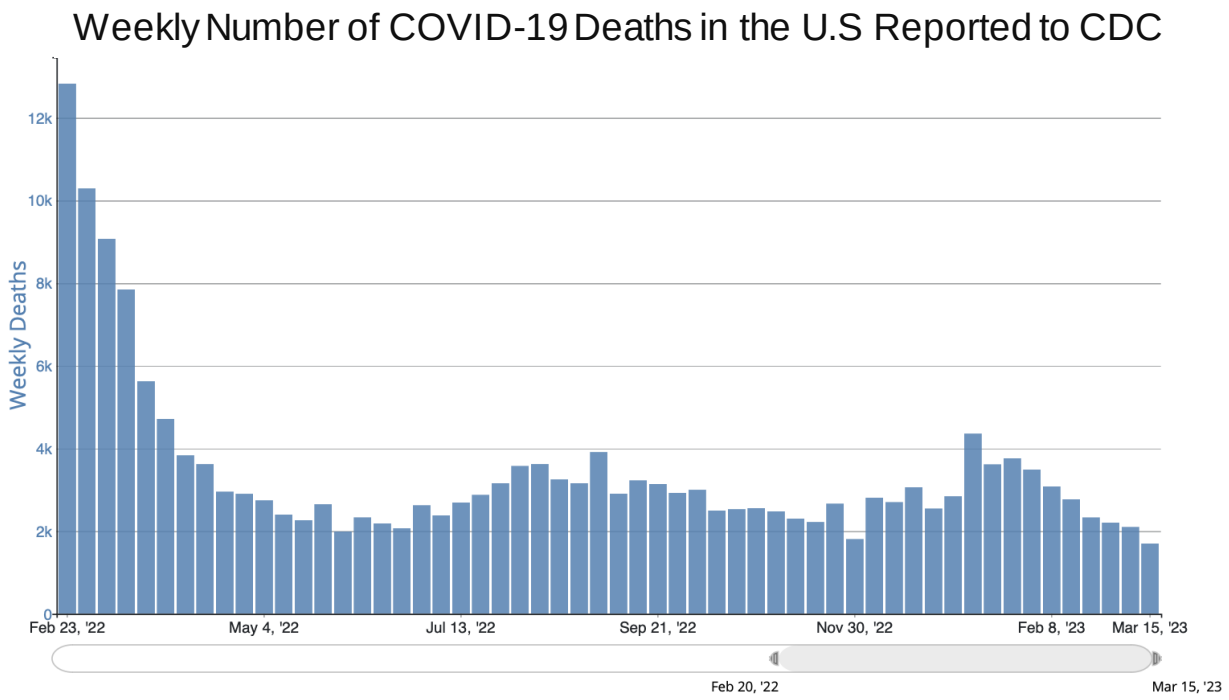
# COVID19: Ongoing Medical Need in the Post-pandemic Era




https://covid.cdc.gov/covid-data-tracker/#trends_weeklydeaths_select_00

## COVID-19 Ongoing Health Impact

- Over 1500 deaths per week (2023); > 78,000 lives lost per year.
- > 100,00 cases per week and 5 million cases annually.
- Medically vulnerable (immune suppressed, pre-existing conditions, cancer patients) remain at risk for severe disease and death.

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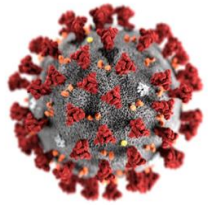
# The Problem of Viral Diversity: The Global Emergence of Resistant COVID Variants



SARS CoV2 virus
(CDC image)




- Antibodies have proven effective for the treatment of acute COVID with > 80% efficacy in preventing progression to severe COVID
- Antibodies are also highly effective for passive immunization – to protect medically vulnerable patients from acquiring COVID
- However, new Omicron variants have rendered prior antibodies ineffective, highlighting the need for new antibodies that are broadly active against all circulating variants.

Annual 2022 sales of COVID mAbs > $7 billion.

No antibody treatments currently effective.

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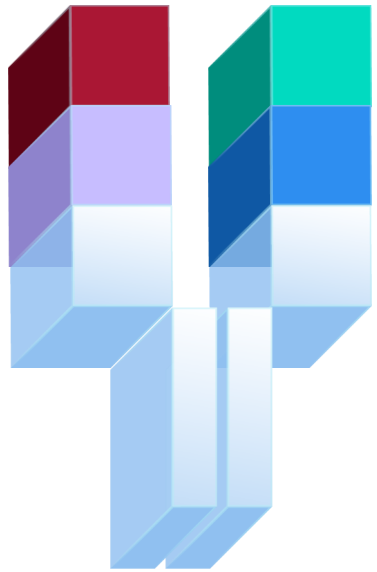
# Clinical Indications for Multispecific Antibodies in COVID



- Treatment of acute COVID in high-risk patients to prevent progression to severe disease
- Passive immunization with long-acting antibody to prevent infection in those with compromised immunity
- Potentially as a treatment for long COVID.

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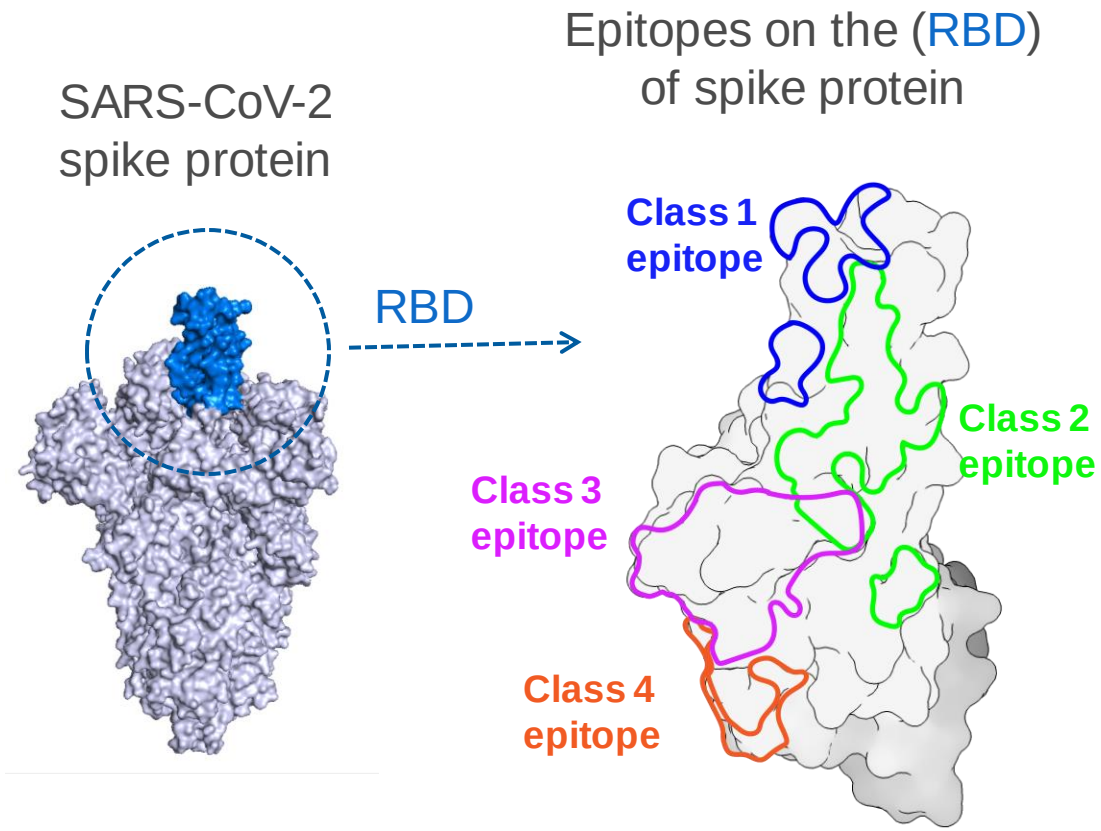
# The MSTAR Advantage: Addressing SARS-CoV-2 Diversity




## MSTAR Multispecifics:

- Modular platform allows rational selection of antibodies to optimize potency against current and future variants
- Potential for synergistic neutralization leading to improved potency and lower therapeutic dose
- Provide simultaneous immune pressure to prevent viral escape mutations
- Potently neutralize all current variants of concern including the predominant XBB.1.5 strain

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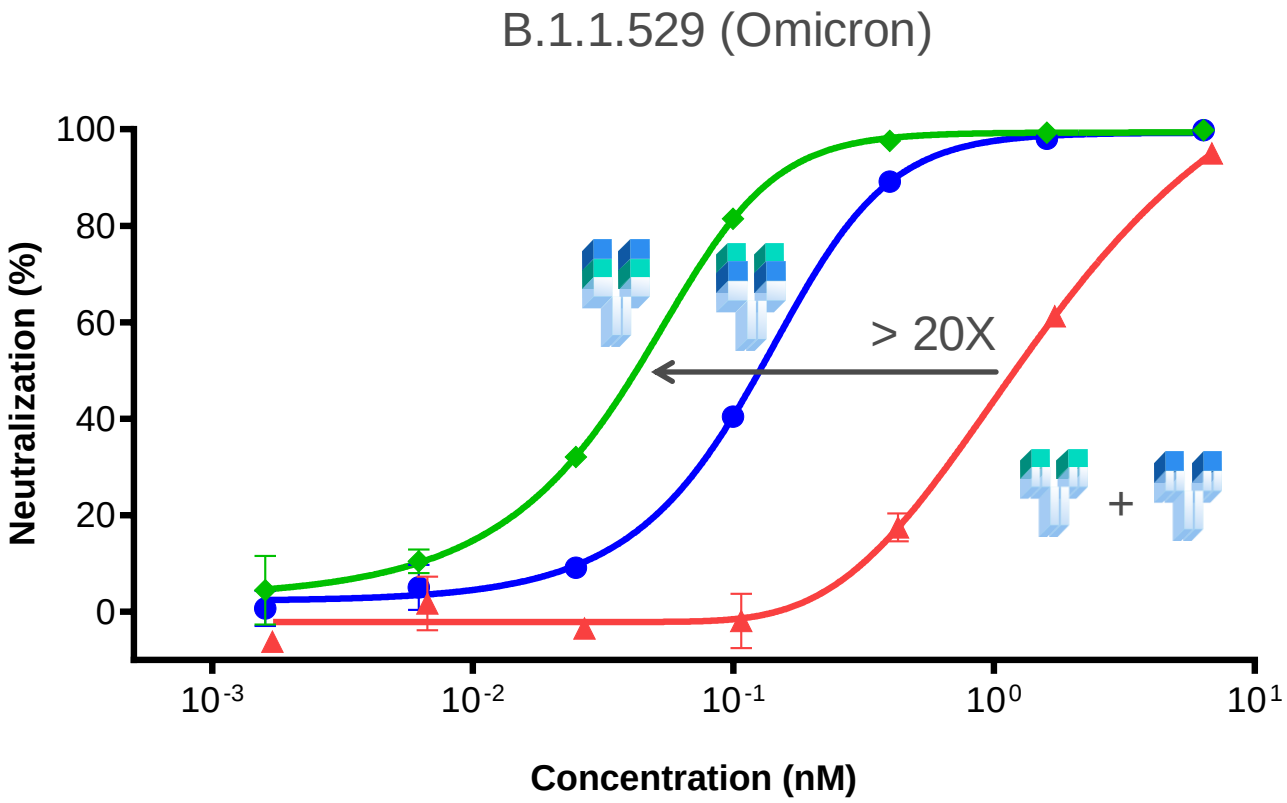
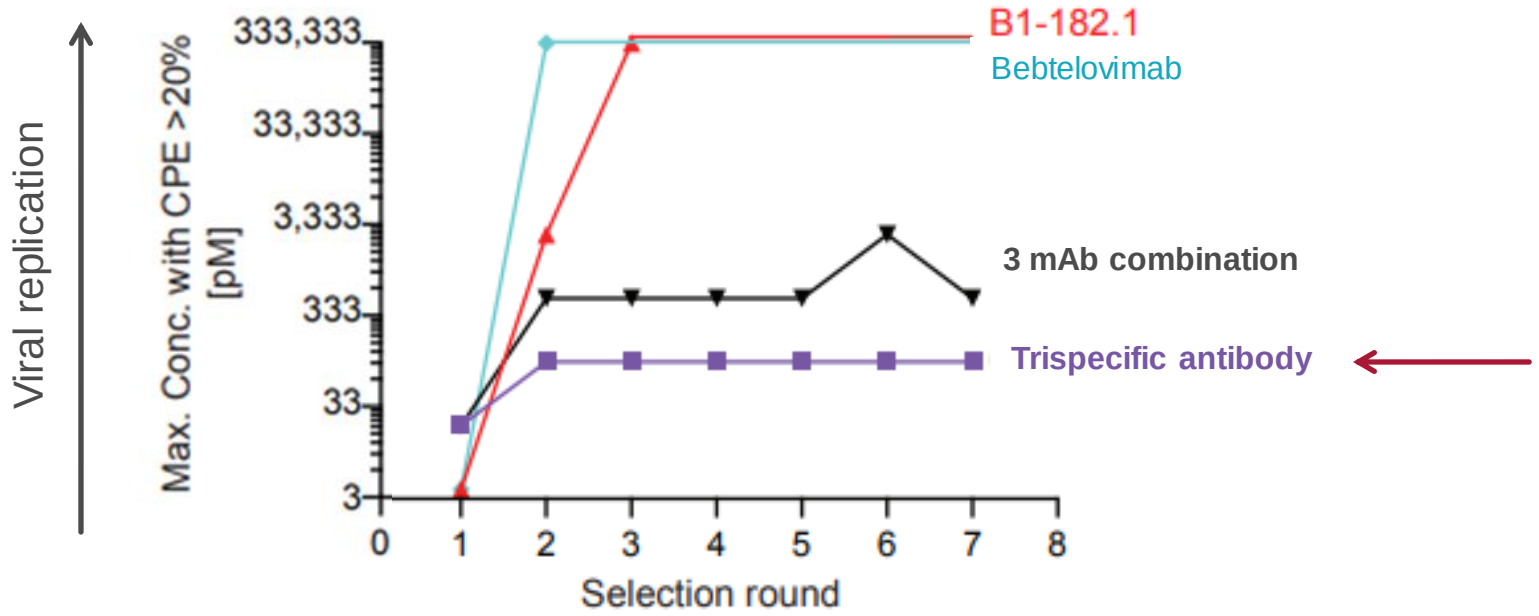
# Synergistic Neutralization: MSTAR Bispecific Abs are More Potent than 2 mAb Cocktail




Tetravalent bispecific Ab is ≥ 20-fold more potent than combination of 2 parental mAbs at equimolar concentrations

# Pre-empting Viral Escape with Multispecific Antibodies Not Seen with Potent Single mAbs




Trispecific antibody, but not single mAbs prevents viral escape during serial passage *in vitro*

- Trispecific exerts simultaneous immune pressure to protect against viral escape
- Trispecific is better than single antibody
- Trispecific is better than combination of 3 individual antibodies

**Collaboration and CRADA with VRC/NIAID, NIH**

biorxiv.org/content/10.1101/2022.07.29.502029v3

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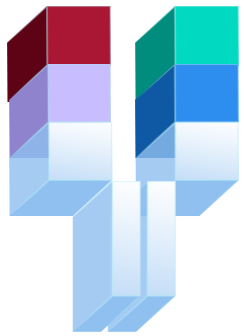
# Tetravalent Trispecific Antibody for COVID: MDX2202 Potent Neutralization of All Circulating Variants



| Tetravalent Trispecific ($IC_{50}$) | |
|---|---|
| **BA.4/5** | <0.01 |
| **BQ.1** | <0.01 |
| **BQ.1.1** | 0.01 |
| **BA.2.75.2** | 0.01 |
| **XBB** | 0.01 |
| **XBB.1.5** | 0.2 |
| **BF.7** | 0.07 |

Values are antibody inhibitory concentration ($IC_{50}$; nM)

- Lead candidate selected
- Developability assessments successfully concluded with lead candidate meeting manufacturability criteria.

Collaboration and CRADA with VRC/NIAID, NIH

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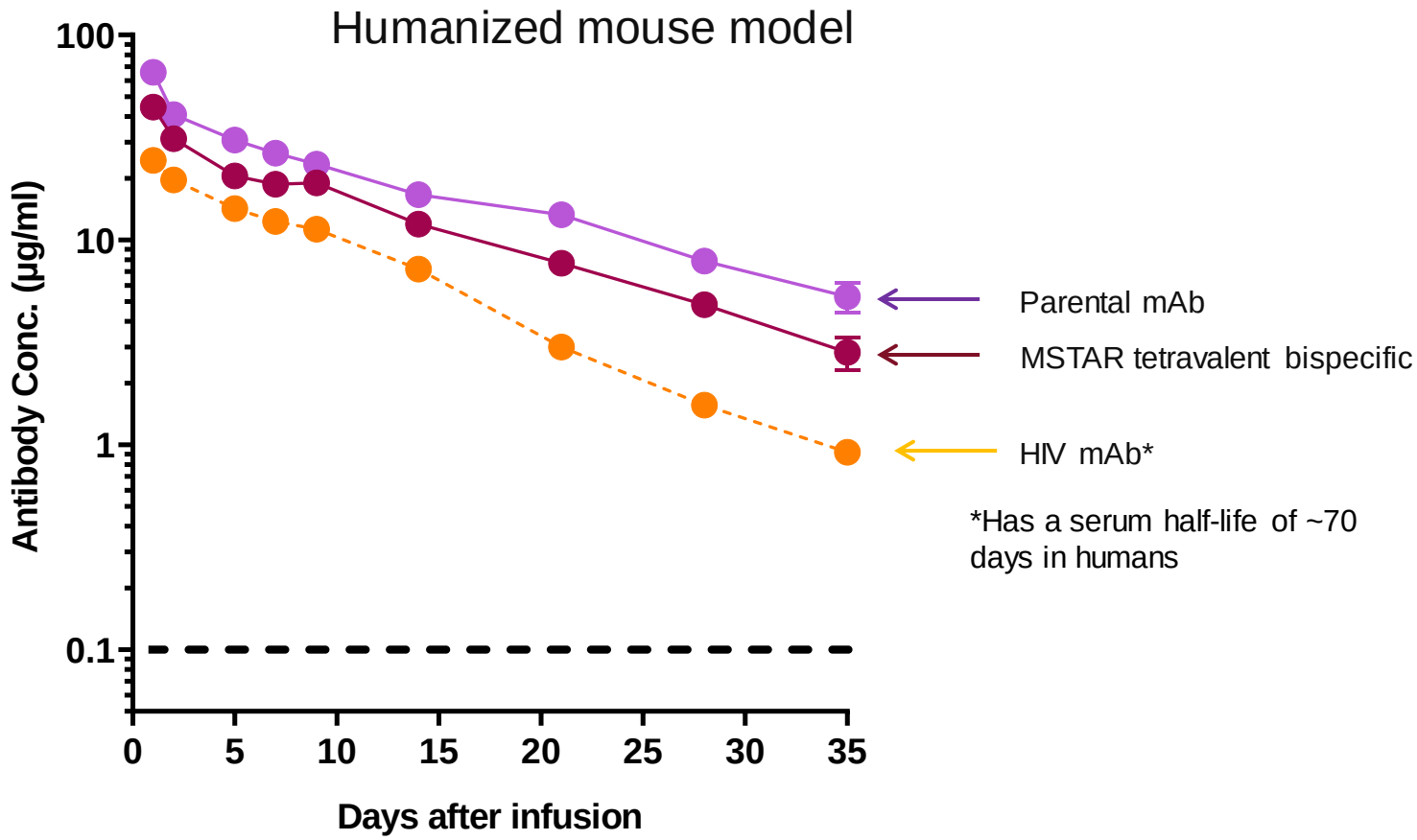
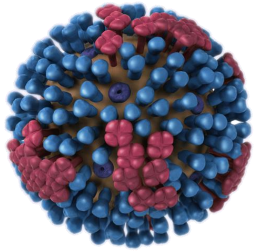
# MSTAR Antibodies: Circulating Half-Life Similar to Monoclonals in Animal Models

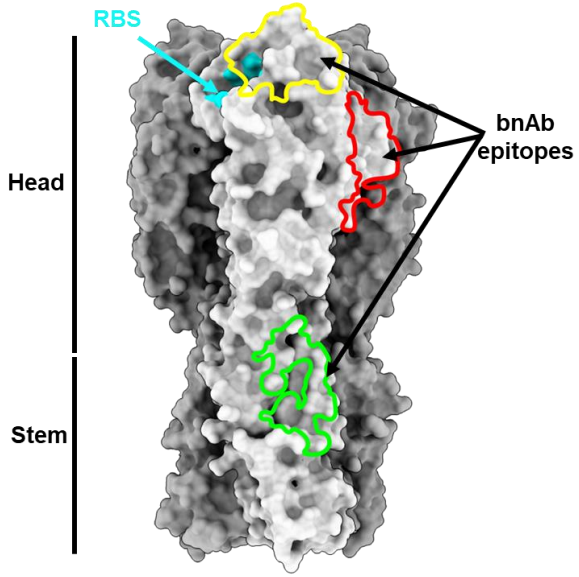


# Multispecific Abs For Seasonal and Pandemic Influenza

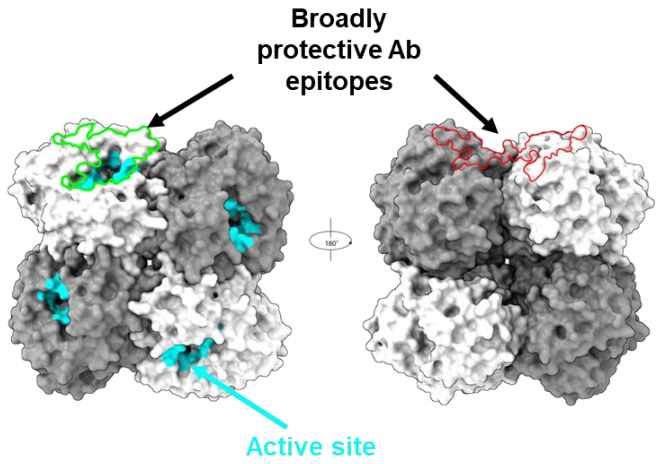


Influenza virus
(CDC image)

**Hemagglutinin**




**Neuraminadase**




- Multispecific antibodies target highly conserved and functionally constrained regions of influenza HA and NA glycoproteins to improve potency and breadth
- Pre-exposure prophylaxis and treatment of seasonal influenza and pandemic outbreaks.
- Early-stage candidate evaluation

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# Advantages of MSTAR over Monoclonals for Viral Infections

| Attributes |  MSTAR Multispecific Ab |  mAb |
|---|---|---|
| Targets different sites on a viral protein | ✓ | ✗ |
| Synergistic neutralization | ✓ | ✗ |
| Cross coverage of antigenic variants | ✓ | ✗ |
| Minimize viral escape | ✓ | ✗ |
| Likely to remain active despite viral evolution | ✓ | ✗ |
| Fc mediated effector functions (e.g., cell killing) | ✓ | ✓ |
| Extended serum half-life | ✓ | ✓ |
| Standard manufacturing technology | ✓ | ✓ |

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# Agenda: ModeX Therapeutics R&D Day

| | |
|---|---|
| **Welcome** | **Gary Nabel**<br>Co-Founder, President/CEO, ModeX Therapeutics; Chief Innovation Officer, OPKO Health |
| **Opening Remarks** | **Phillip Frost**<br>CEO and Board Chair, OPKO Health |
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| **Introduction to ModeX Therapeutics** | **Gary Nabel** |
| **EBV Vaccine Program** | **Gary Nabel** |
| **ModeX Platform Technologies**<br>• Multispecific Abs (MSTAR)<br>• Masking (STEALTH)<br>• Immune modulation | **Ronnie Wei**<br>Head, Biologics Discovery and Development, ModeX Therapeutics |
| **Multispecific Antibodies for Immuno-Oncology**<br>• Solid tumors<br>• Hematologic neoplasms | **John Mascola**<br>Chief Scientific Officer, ModeX Therapeutics |
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| **Closing Remarks** | **Gary Nabel** |
| **Question and Answer Session** | **All** |

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# Manufacturing for Clinical Development

## Vijay Chhajlani

Chief Technology Officer

OPKO

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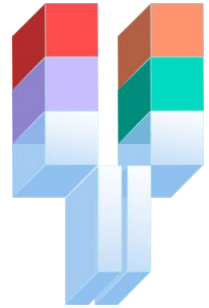
# Biophysical and Developability Attributes of MSTAR Multispecific Antibodies



**Summary Information Based on Multiple Molecules for Virology and Immuno-oncology**

- **Binding affinity:** Each combining site is fully functional with retained binding affinity to target
- **Expression, Yield, Purity:** Robust expression, yield and purity; Laboratory scale productivity >0.5g/L
- **Solubility:** Achieved solubility up to 100 mg/ml
- **pH Stability:** Demonstrated stability at pH3.5 and 8.0 stress conditions
- **Stability:** Stable under thermal, pH and oxidative stress
- **Off-Target binding**: None observed to neutrophils, platelets, RBCs
- **Human Serum Stability:** Stable up to 14 days
- **Half-life:** Comparable to IgG monoclonals

**MSTAR Multispecifics possess attributes favorable to process development & manufacturing**

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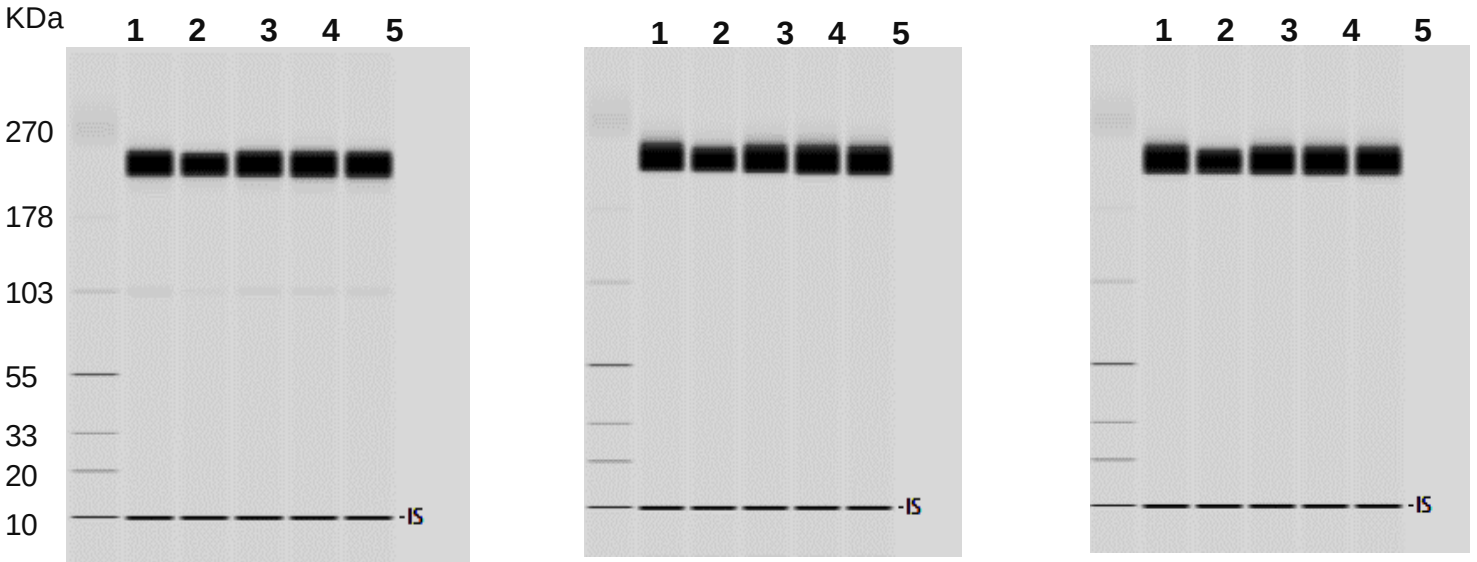
# Tetravalent MSTAR Prototypes Are Stable Under Stress

## Example data for thermal and pH stress

Tetravalent Bispecific

Tetravalent Trispecific-1

Tetravalent Trispecific-2




CE-SDS electropherograms showing molecules in lane format

**Antibodies were subjected to stress conditions and analyzed by non-reducing CE-SDS:**

1. Unstressed control
2. pH 3.5 room temp for 4 hours
3. pH 8.0 room temp for 24 hours
4. pH 6, 40 ℃ for 1 week
5. pH 6, 40 ℃ for 2 weeks

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# Early Assessment Demonstrate Manufacturability

| Assessment | MDX2001 | MDX2003 |
|---|---|---|
| Productivity 0.5g/L | ✓ | ✓ |
| Purification to >98% Correct Heterodimer | ✓ | ✓ |
| Thermal Stress | ✓ | ✓ |
| Low & High pH Stress | ✓ | ✓ |
| Oxidation Stress | ✓ | ✓ |
| Light Sensitivity | ✓ | ✓ |
| Agitation | ✓ | ✓ |
| Freeze Thaw Stress | ✓ | ✓ |
| Serum Stability 14 Days | ✓ | ✓ |
| No Nonspecific binding to predominant blood cells | ✓ | ✓ |

**MSTAR Tetraspecific IO Lead candidates perform like monoclonal IgG under stress conditions.**

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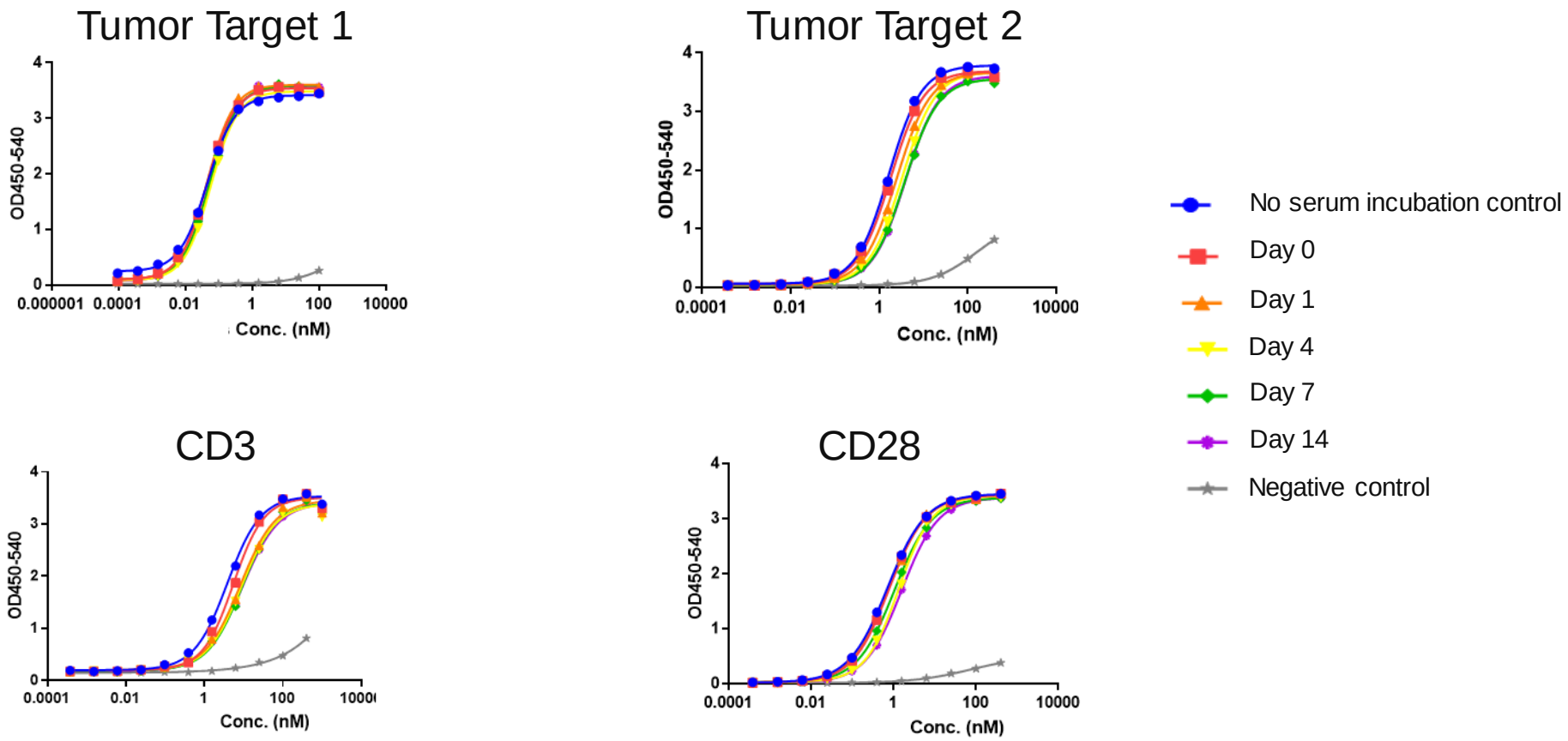
# Immuno-oncology Clinical Candidate MDX2001: Potency and Stability in Human Serum




**MSTAR molecule maintains potency in serum on all four targets for at least 14 days**

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# GMP Manufacturing: Immuno-oncology Clinical Candidate MDX2001

- Cell-line development nearing completion: top three clones identified
- Early clonal lines productivity >1 g/L
  - High content of correctly assembled heterodimer, >95%
  - Minimal product related impurities (homodimer, half antibody)
- Demonstration of fit with typical mAb purification process
  - Three-column downstream purification process
  - Conditions optimized to maximize product stability during manufacturing
  - 50L Bioreactor run successfully completed
- Short-listed two formulations for enhanced stability of drug product.
  - Compatible with liquid and lyophilized formulations
- GMP manufacture is scheduled to start mid-July 2023

**MSTAR molecule demonstrates compatibility with platform monoclonal antibody manufacturing processes**

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ModeX THERAPEUTICS an OPKO Health Company

# Delivering the ModeX Pipeline

## First-in-Class Drugs with Best-in-Class Potential

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| | **EBV Nanoparticle Vaccine** | Prevention of EBV-related diseases | **TBD** |
| | **COVID Multispecific Antibody** | Treatment and Prevention of COVID-19 | **2024/2025** |

**Lymphocyte Activator and Survival Extension Receptor (LASER) Antibodies*

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# Key Takeaways: Promise of People, Platforms, and Pipeline

- World class scientific team with novel platforms and 7 products advancing into the clinic with a proven track record for manufacturing.
- Mastery of the multispecific and nanoparticle platforms using structure-based design and digital/machine learning. Ability to deliver products as protein or by gene delivery (mRNA and/or DNA) and rapid path to clinic.
- Strong foundational IP with 28 patent applications filed
- Platforms allow the company to generate its own products and pursue partnerships to maximize the value of ModeX technology.
- Existing relationships with external partners: NIH, Duke, DARPA, recent license and collaboration agreement with Merck.

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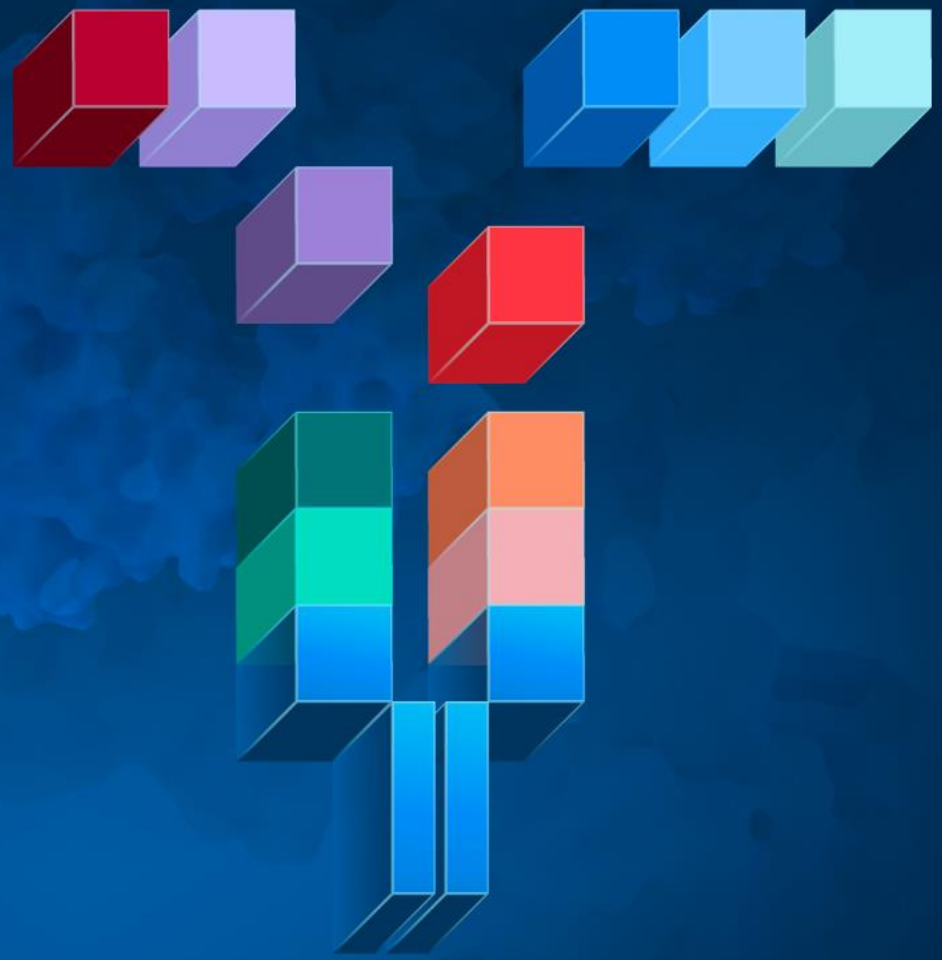
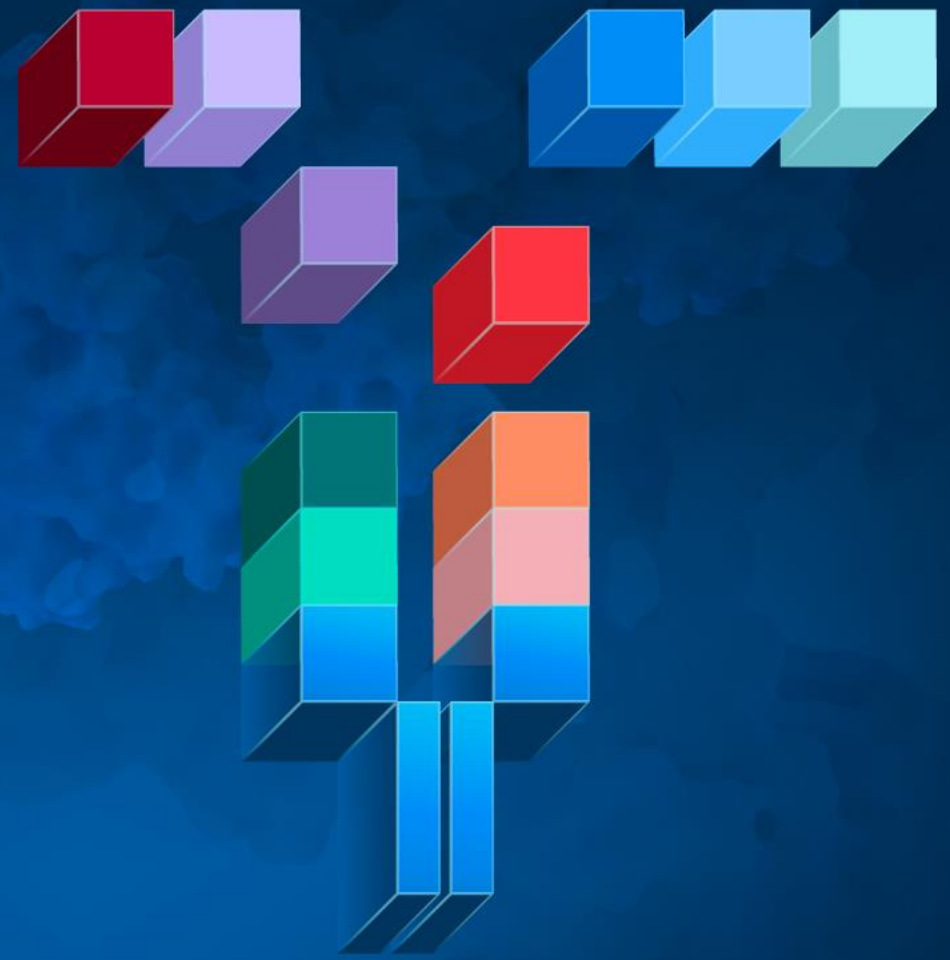
# Q&A Session

## Uniting the power of multiple medicines in a single molecule



# Thank you



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