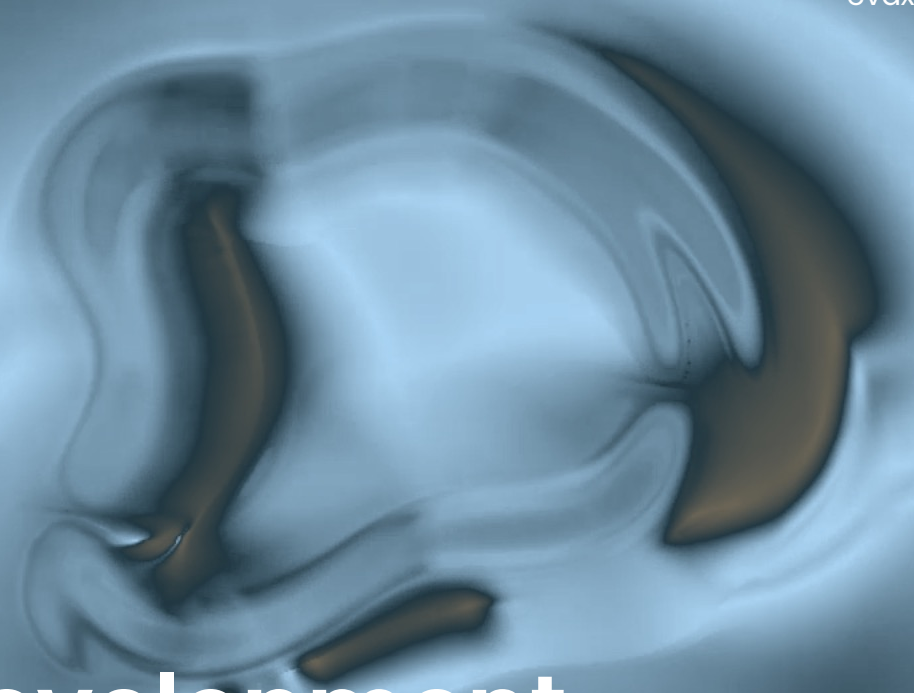
# R&D Day

*March 19, 2024*



# AI-Immunology™ – a New Era in Vaccine Development

# Agenda

## SESSION 1 - Introduction

| CET | / | EST | |
|---|---|---|---|
| 14.00 - 14.10 | / | 9.00 – 9.10 | **Welcome** |
| 14.10 - 14.20 | / | 9.10 – 9.20 | **Evaxion overview** - Setting the scene |
| 14.20 - 14.35 | / | 9.20 – 9.35 | **AI-Immunology™** - A leading AI platform |
| 14.35 - 14.55 | / | 9.35 – 9.55 | **EvaxMHC 4.0** - A cutting-edge AI building block |
| 14.55 - 15.15 | / | 9.55 – 10.15 | *BREAK* |

## SESSION 2 - Infectious Disease Vaccines

| | | |
|---|---|---|
| 15.15 - 15.35 | / | 10.15 – 10.35 | **EDEN™** - Best-in-class model assessing protectiveness of B-cell antigens |
| 15.35 - 15.55 | / | 10.35 – 10.55 | **RAVEN™** - Model for uncovering unique cross-protective T-cell antigens |
| 15.55 - 16.15 | / | 10.55 – 11.15 | *BREAK* |

## SESSION 3 - Personalized Cancer Vaccines

| | | |
|---|---|---|
| 16.15 - 16.35 | / | 11.15 – 11.35 | **PIONEER™** - Validated model for designing personalized Neoantigen vaccines |
| 16.35 - 16.55 | / | 11.35 – 11.55 | **ObsERV™** - Leading model for designing personalized ERV-antigen vaccines |
| 16.55 - 17.15 | / | 11.55 – 12.15 | BREAK |

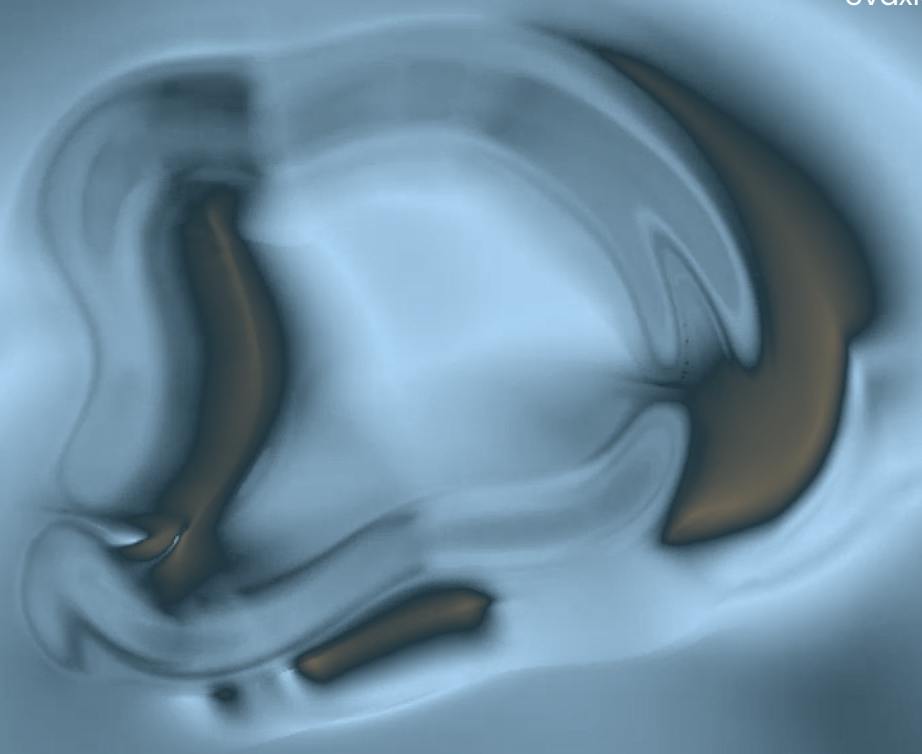
## SESSION 4 - Precision Cancer Concepts

| | | |
|---|---|---|
| 17.15 - 17.35 | / | 12.15 – 12.35 | **AI-DEEP™** - Model for predicting responses to cancer CPI immunotherapy |
| 17.35 - 17.55 | / | 12.35 – 12.55 | **Addressing difficult to treat cancers with AI-Immunology™** |
| 17.55 - 18.00 | / | 12.55 – 13.00 | *THANK YOU and concluding remarks* |
| 18.00 - 19.00 | / | 13.00 – 14.00 | *Reception with drinks and snacks* |

# Forward-Looking Statement

This presentation contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. The words "target," "believe," "expect," "hope," "aim," "intend," "may," "might," "anticipate," "contemplate," "continue," "estimate," "plan," "potential," "predict," "project," "will," "can have," "likely," "should," "would," "could," and other words and terms of similar meaning identify forward-looking statements. Actual results may differ materially from those indicated by such forward-looking statements as a result of various factors, including, but not limited to, risks related to: our financial condition and need for additional capital; our development work; cost and success of our product development activities and preclinical and clinical trials; commercializing any approved pharmaceutical product developed using our AI platform technology, including the rate and degree of market acceptance of our product candidates; our dependence on third parties including for conduct of clinical testing and product manufacture; our inability to enter into partnerships; government regulation; protection of our intellectual property rights; employee matters and managing growth; our ADSs and ordinary shares, the impact of international economic, political, legal, compliance, social and business factors, including inflation, and the effects on our business from the worldwide COVID-19 pandemic and the ongoing conflict in the region surrounding Ukraine and Russia; and other uncertainties affecting our business operations and financial condition. For a further discussion of these risks, please refer to the risk factors included in our most recent Annual Report on Form 20-F and other filings with the U.S. Securities and Exchange Commission (SEC), which are available at www.sec.gov. We do not assume any obligation to update any forward-looking statements except as required by law.

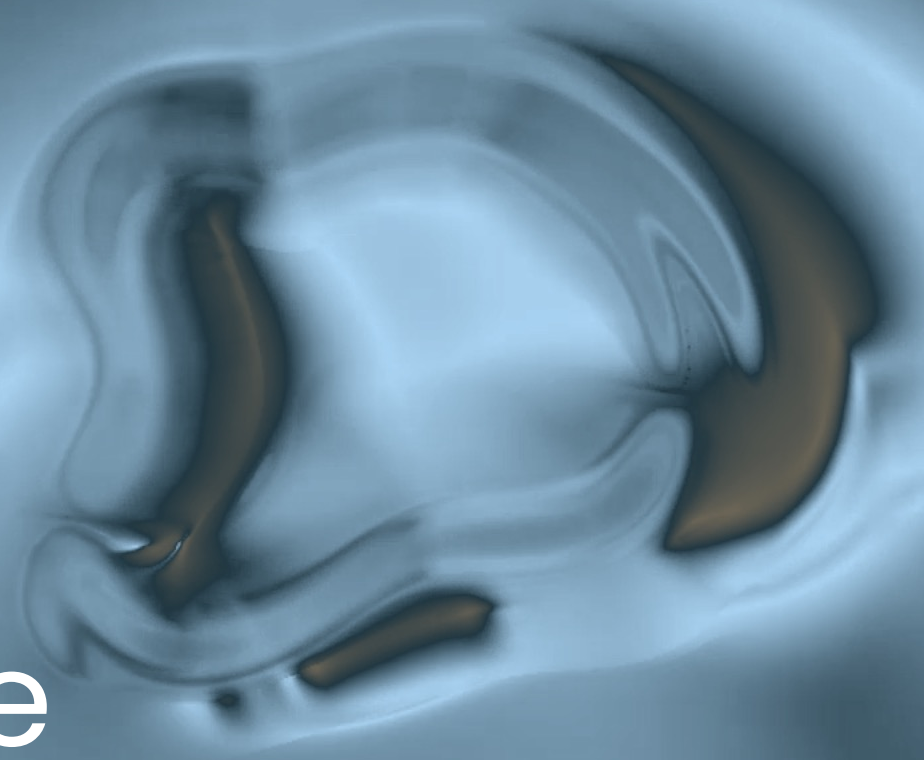
This presentation includes statistical and other industry and market data that we obtained from industry publications and research, surveys and studies conducted by third parties or us. Industry publications and third-party research, surveys and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. All of the market data used in this presentation involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. While we believe these industry publications and third-party research, surveys and studies are reliable, we have not independently verified such data. The industry in which we operate is subject to a high degree of uncertainty, change and risk due to a variety of factors, which could cause results to differ materially from those expressed in the estimates made by the independent parties and by us.



# SESSION 1
## – Introduction

# Evaxion overview

– Setting the scene



# Who We Are

Evaxion is a pioneering TechBio company with a validated and leading **AI–platform (AI-Immunology™)** for fast and effective vaccine target discovery, design and development

AI-Immunology™ allows for groundbreaking **development of novel personalized and precision vaccines** for cancer and infectious diseases

# Why Are We Here: **Saving and Improving** Lives with AI-Immunology™

10 million deaths a year due to cancer*

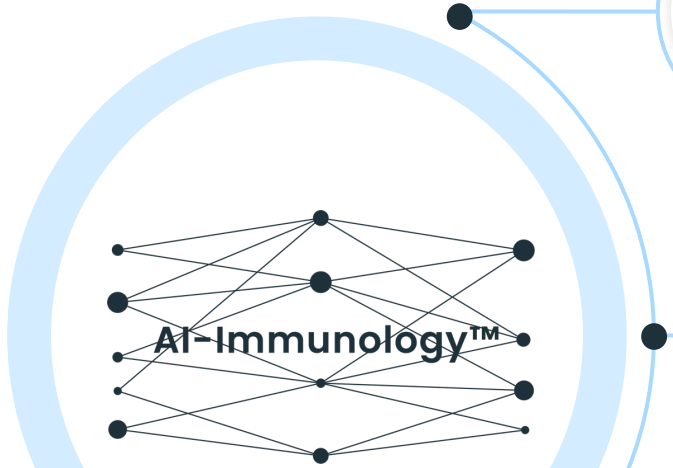
7.8 million deaths a year due to infectious diseases**



* Source: WHO, ** Source: IHME,

# Strategy: **Three-Pronged Business Model** Based upon AI-Immunology™

## Multi-partner approach to value realization




### TARGETS

Multi-partner approach focused around single or multiple vaccine target discovery, design and development agreements

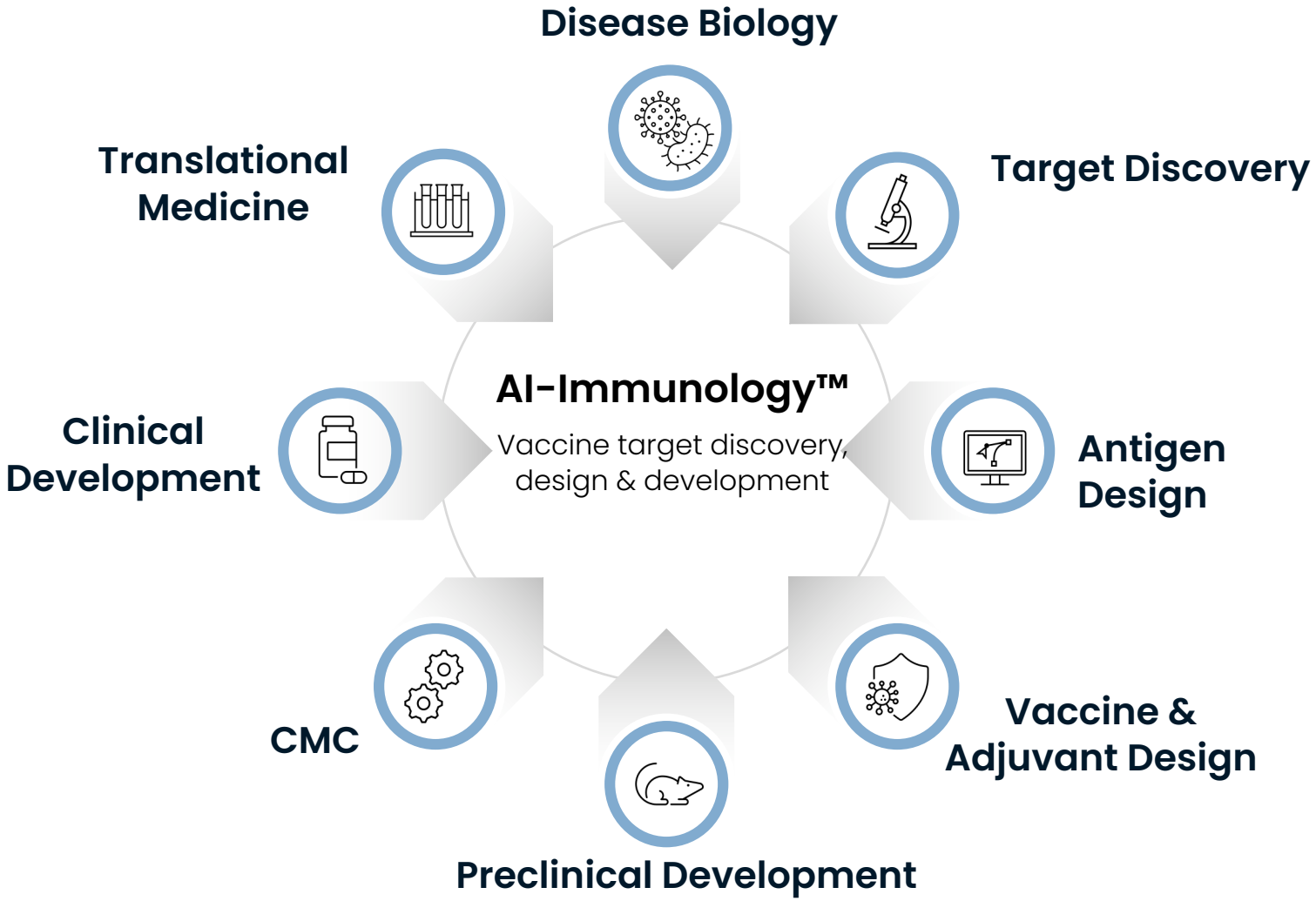
### PIPELINE

Own development programs for select high value programs; bringing programs to major value inflection point

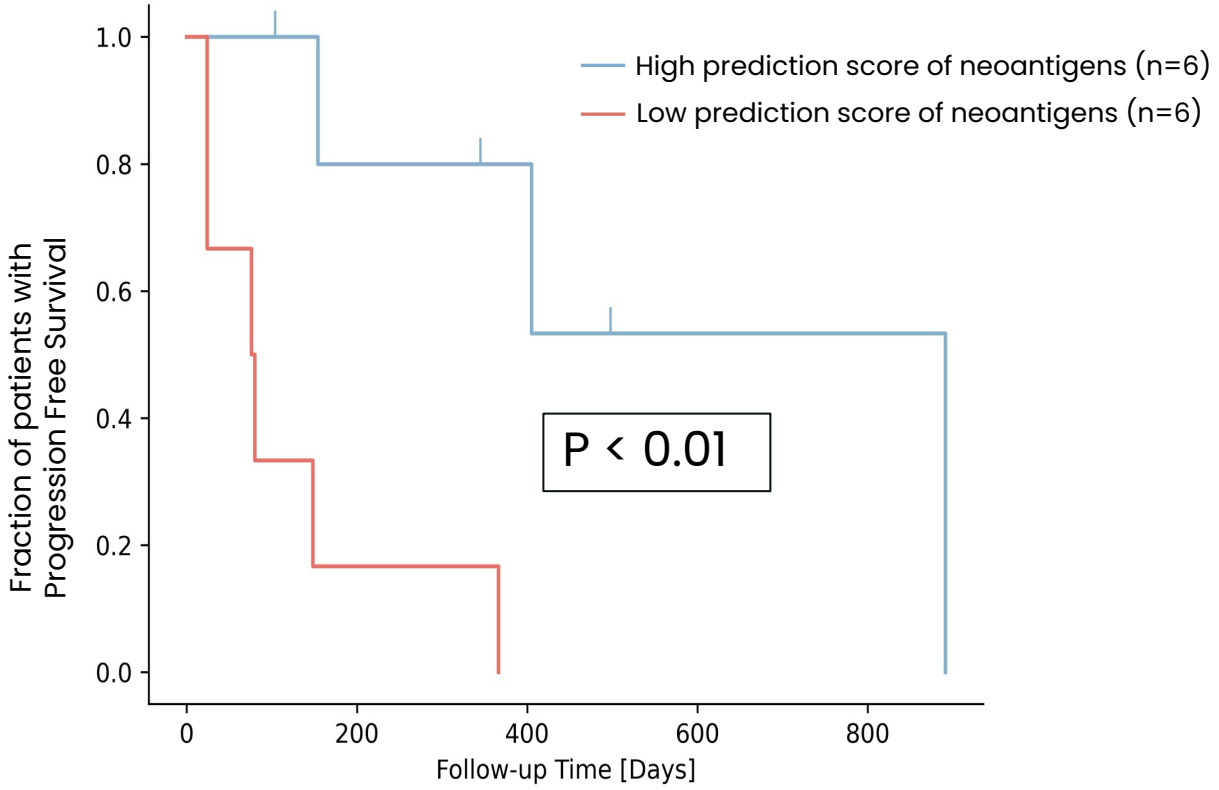
### RESPONDERS

Harnessing our data and predictive capabilities to develop responder models

# We Have Built a Strong **Multidisciplinary Capability Set** and **State of the Art Facilities**




# AI-Immunology™ - **Clinically Validated** Predictive Capabilities

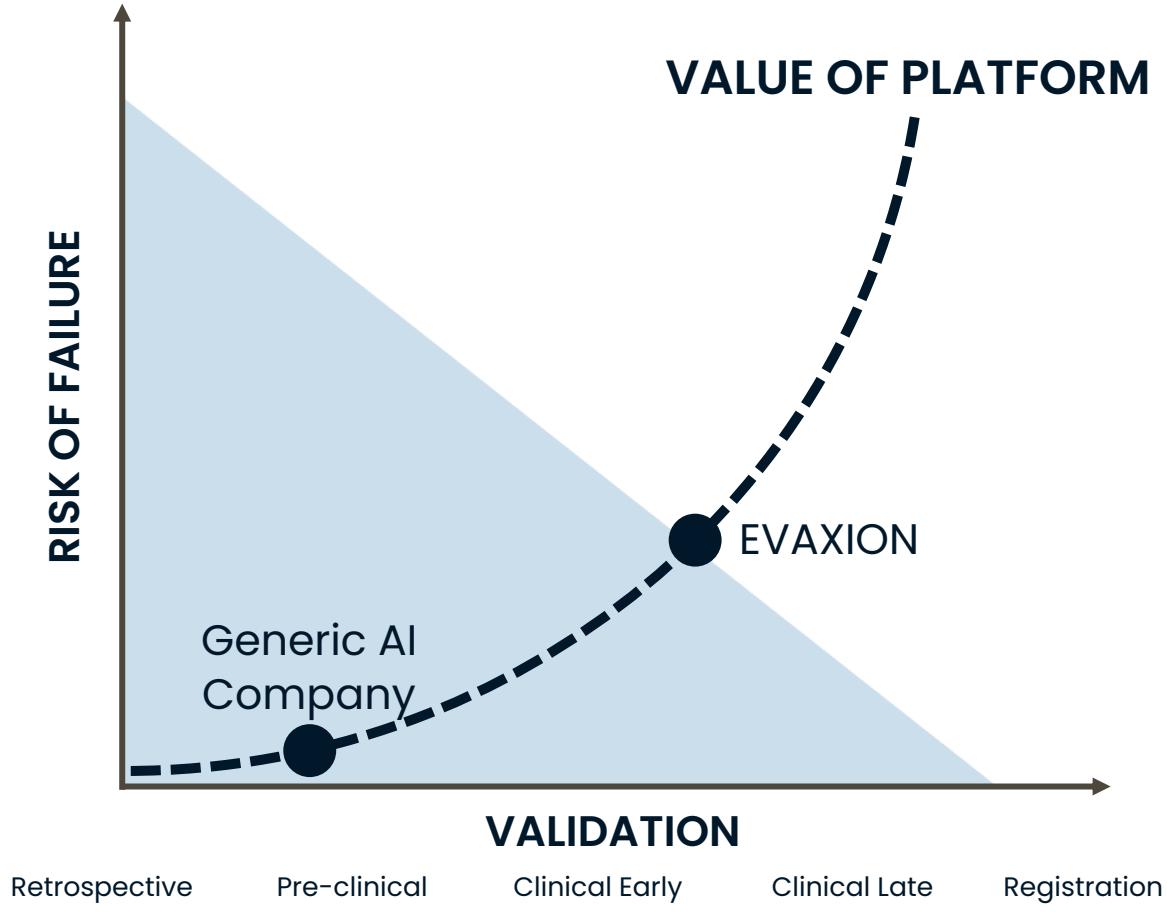



**Progression-Free Survival Based on PIONEER™ Score**
Kaplan-Meier plots displaying Progression-Free Survival (PSF) of patients based on median PIONEER™ quality score. Patients were stratified by PIONEER™ quality score into two groups corresponding to the six highest and six lowest median scores.

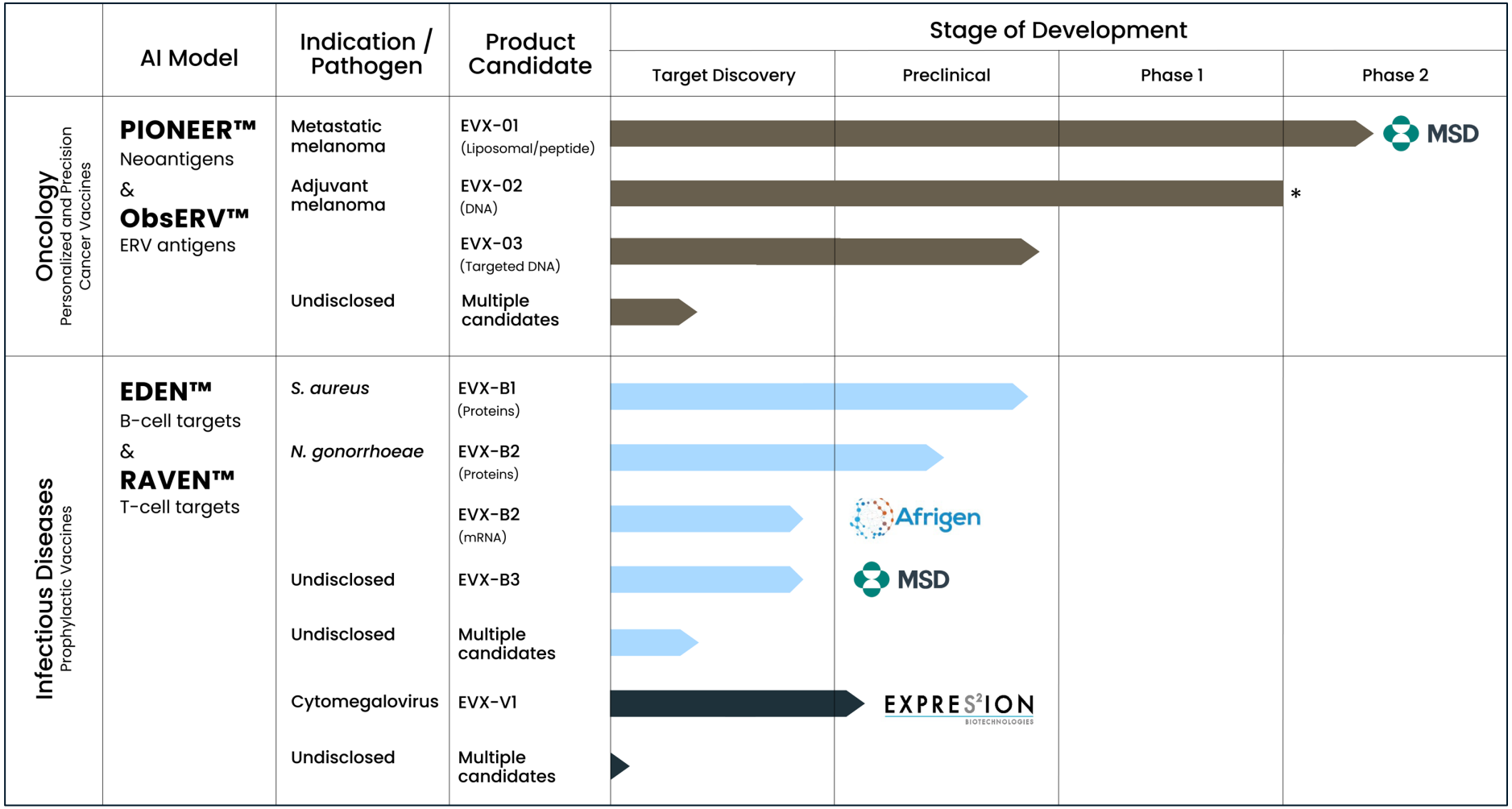
- AI response prediction (PIONEER™ score) builds on the presence of high-quality tumour neoantigens
- Patients with high PIONEER™ scores had longer progression-free survival
- A similar relationship could not be established using the conventional TMB method

# Our AI-Immunology™ Platform and Multidisciplinary Capability Set **Drive Differentiation**

- Our multidisciplinary capability set allows for:
  - Continuous iterative learning loops
  - Ongoing expansion of data sets with proprietary data
  - Rapid validation of AI predictions
  - Full control of process from idea to validation
  - Continued expansion of pipeline assets
- Significantly enhancing the value of our platform



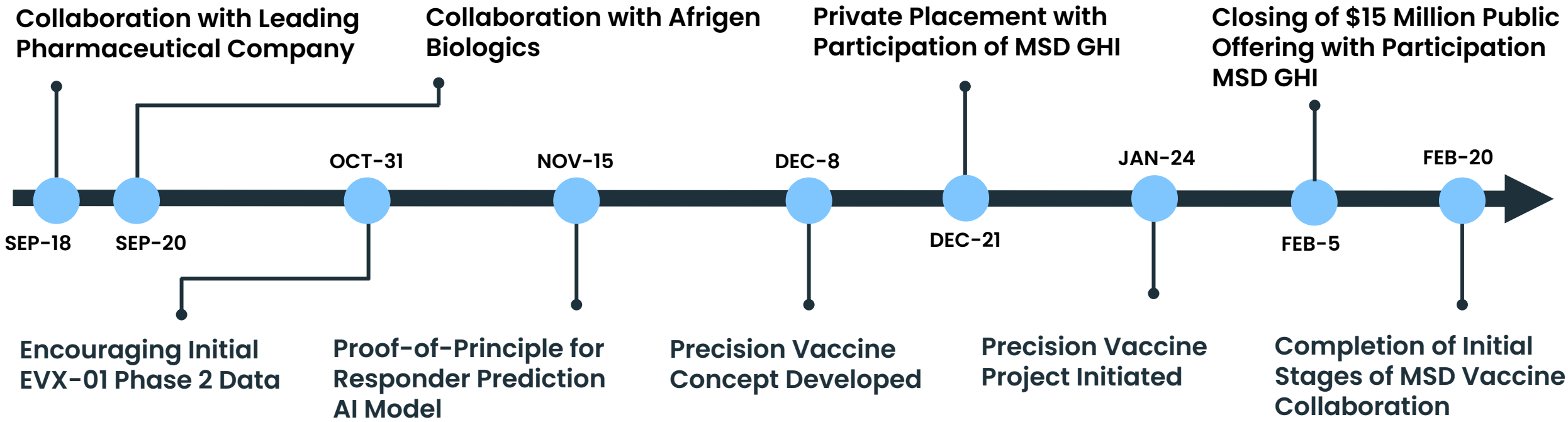
# Pipeline: Demonstrating the **Performance and Scalability of Our AI-Immunology™** Platform






*The data generated in the EVX-02 program actively informs the development of the second generation EVX-03 DNA vaccine

# Recent Highlights Confirm **Strong Strategy Execution**



# Several Important **Near-Term Milestones**

| | Milestones | Target |
|---|---|---|
| **EVX-B1** | Conclusion of final MTA study with potential partner | Q1 2024 |
| **AI-Immunology™** | Launch of EDEN™ model version 5.0 | Mid 2024 |
| **EVX-B2-mRNA** | EVX-B2-mRNA preclinical Proof-of-Concept obtained | Q3 2024 |
| **EVX-01** | Phase 2 one-year readout | Q3 2024 |
| **EVX-B3** | Conclusion of target discovery and validation work in collaboration with MSD (tradename of Merck & Co., Inc., Rahway, NJ, USA) | H2 2024 |
| **Precision ERV cancer vaccines** | Preclinical Proof-of-Concept obtained | H2 2024 |
| **Funding** | Ambition for full year 2024 is to generate business development income equal to 2024 cash burn (excluding financing activities) of 14 million USD* | |



* No assurances can be made that we will generate such business development income

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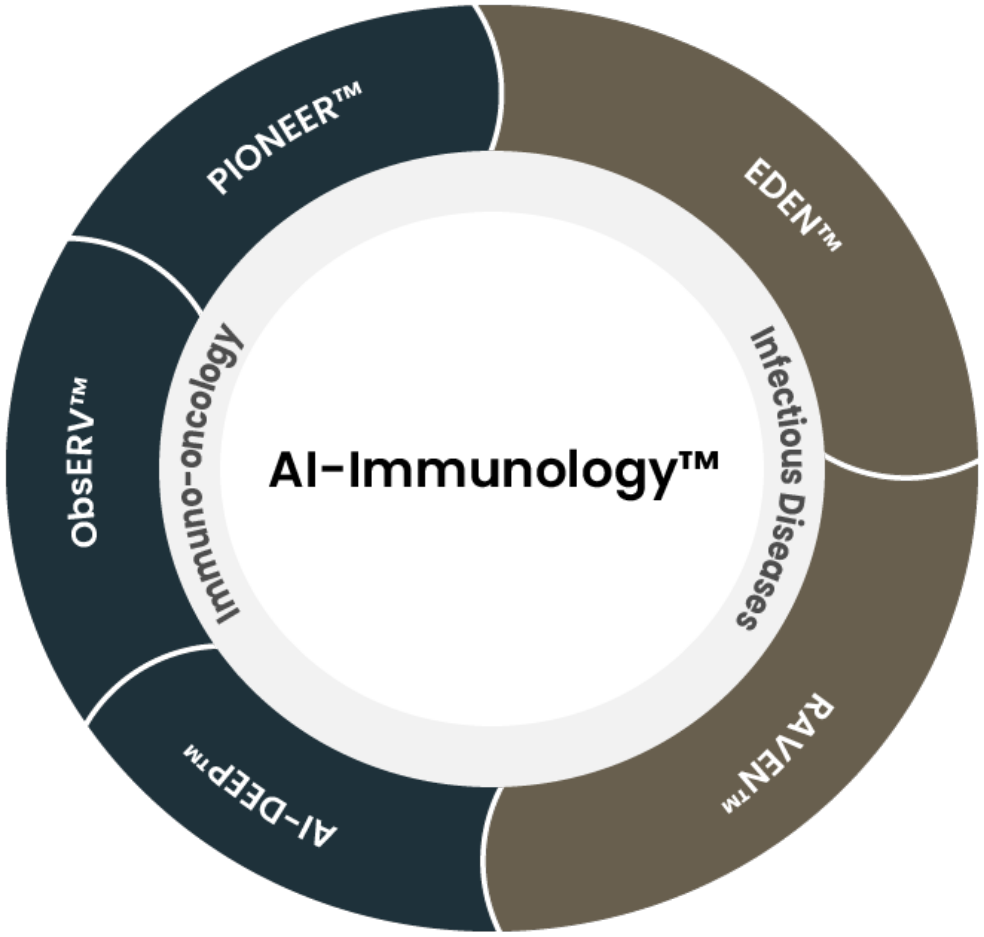
# AI-Immunology™
# – A leading AI platform

# AI-Immunology™ – A Unique Differentiator



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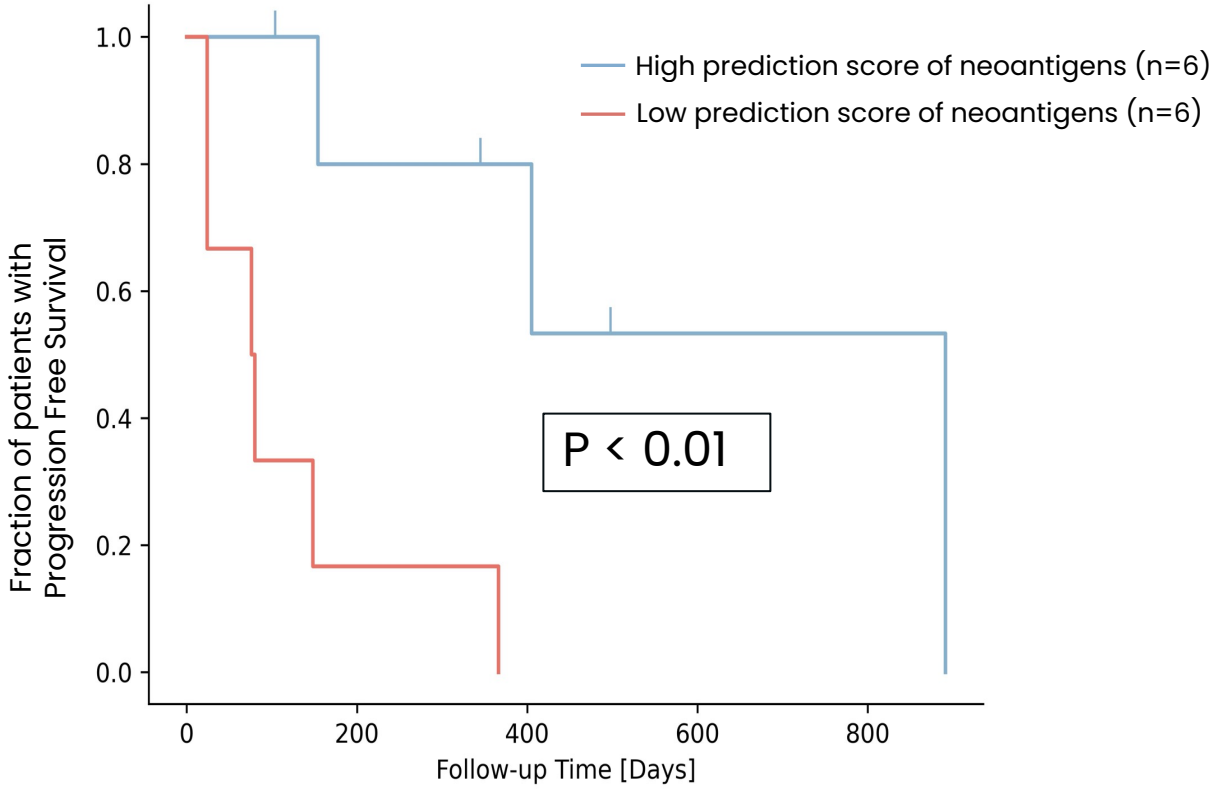


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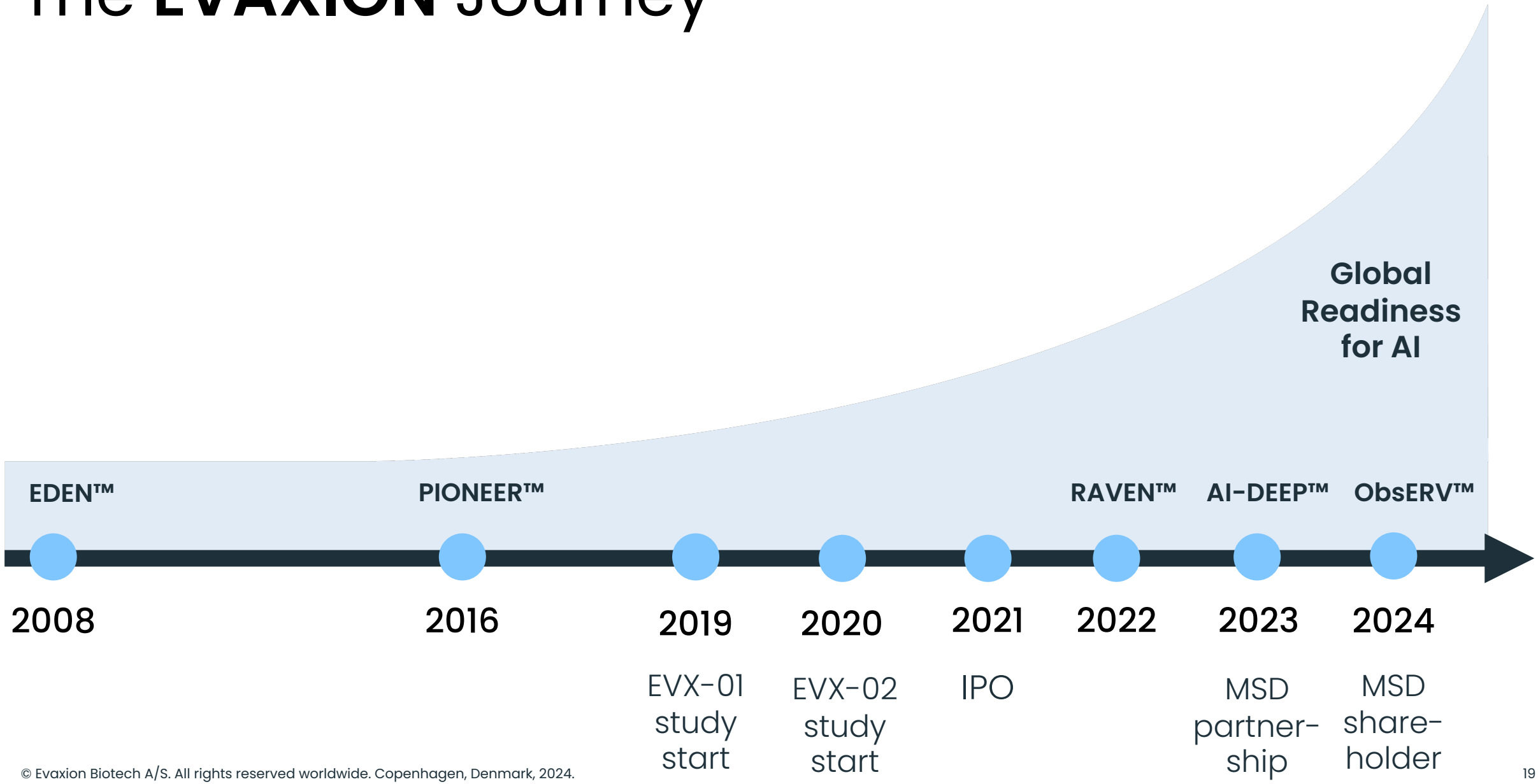
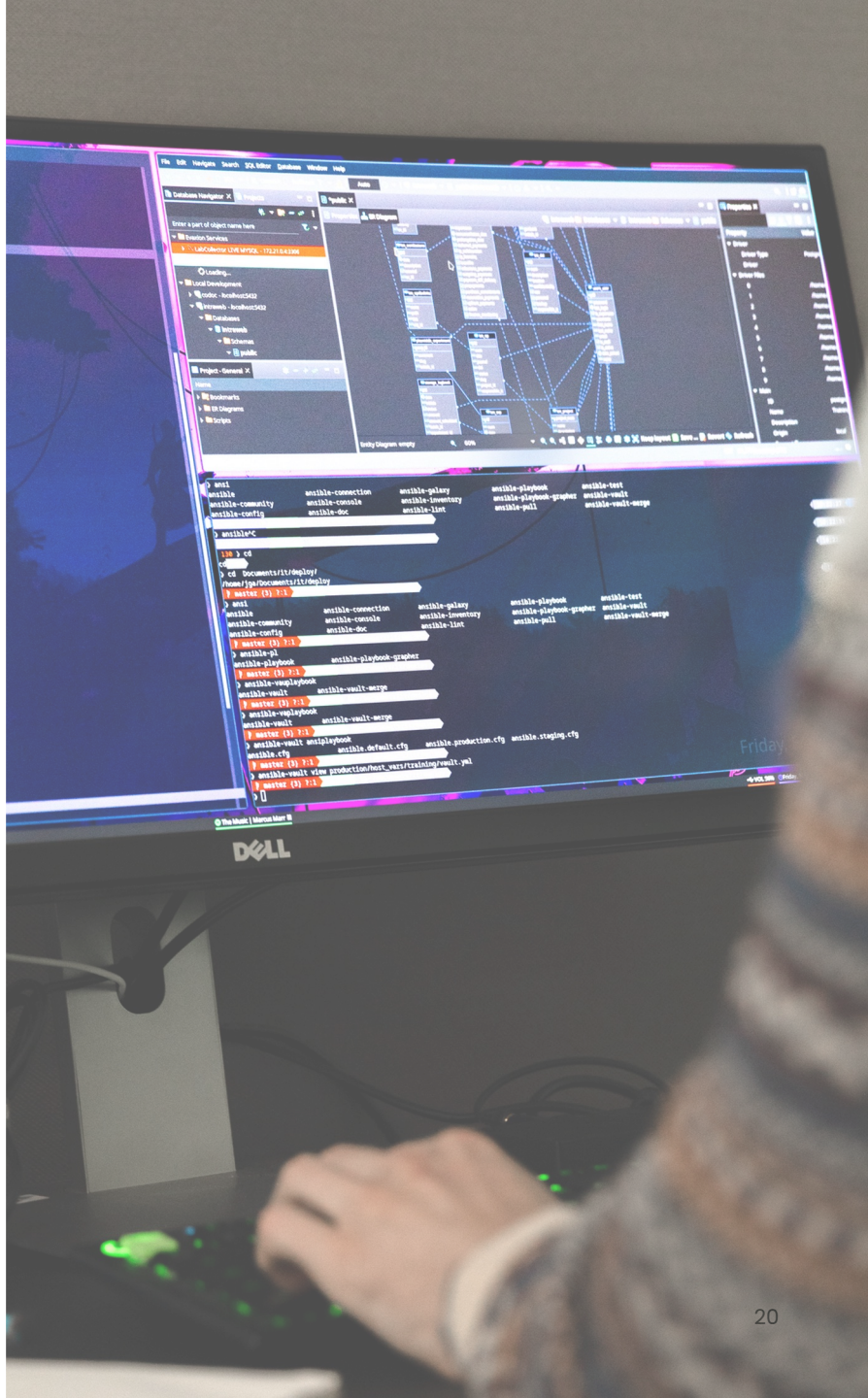
# The **EVAXION** Journey



# Why The Need for **AI-Immunology™**

- 10 million deaths a year due to cancer*
- 7.8 million deaths a year due to infectious diseases**
- We use the AI-Immunology™ platform to discover and assess the protectiveness of vaccine antigens and design candidates within hours, expediting the vaccine development process




* Source: WHO, ** Source: IHME

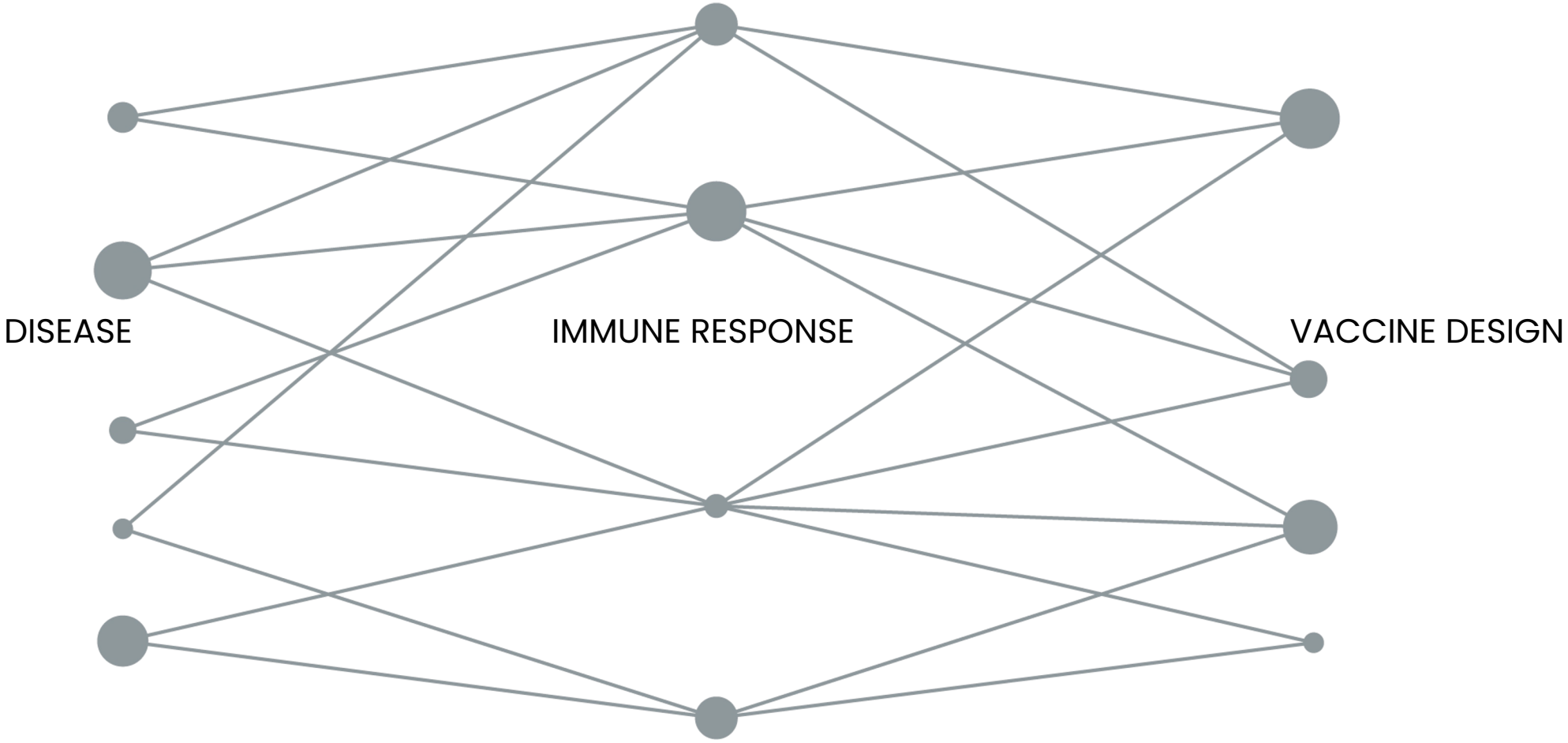
# A Vaccine **‘Teaches’** the Body to Fight an Infectious Agent or Disease

- A vaccine is a drug that is introduced into the body to trigger an immune response to prevent infection or to control a disease like cancer

- A vaccine contain parts of the infectious agent or cancer that can trigger a successful immune response – these are known as ‘antigens’

* Source: WHO, ** Source: IHME, *** Source: Precedence Research

# **Key Areas** for Building a Successful Vaccine



# The **Key Areas** of AI-Immunology™

DISEASE DECODING

IMMUNE RESPONSE DECODING

VACCINE DESIGN

# AI-Immunology™ is an **Ensemble of Smaller Building Blocks** Utilized Across the AI-Immunology™ Models

| | | |
|---|---|---|
| SNVs | EvaxMHC | Precision design |
| Frameshifts | HLA typing | BIFROST |
| HLA loss | Epitope hotspots | Personalized design |

# The **Building Blocks** of AI-Immunology™

## 1 DISEASE DECODING

Our disease decoding building blocks scan the disease of interest and pinpoint the weak spots for recognition by the immune system

**VIRUS** **BACTERIA** **CANCER**

# The **Building Blocks** of AI-Immunology™

## 1 DISEASE DECODING

| | | | |
|---|---|---|---|
| SNVs | Frameshifts | Gene fusions | HLA loss |
| ERV antigens | TME impact | Clonality | Expression |
| Bacterial antigens | Viral antigens | Antigen conservation | Treatment effect |
| Neoantigens | | | |

# The **Building Blocks** of AI-Immunology™

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## 2 IMMUNE RESPONSE DECODING

Our immune response decoding building blocks rank the weak spots from the disease - from best to worst - by their ability to induce an immune response toward the disease

**B CELLS** **T CELLS** **ANTIGEN PRESENTING CELLS**

# The **Building Blocks** of AI-Immunology™

## 1 DISEASE DECODING

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## 2 IMMUNE RESPONSE DECODING

| | | | |
|---|---|---|---|
| EvaxMHC | HLA typing | HLA frequencies | Distance to self |
| Protective antigens | Epitope hotspots | | |

# The **Building Blocks** of AI-Immunology™

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## 3 VACCINE DESIGN

Our vaccine design building blocks are designed to select optimal sets of antigens for a given patient/population and ensure that the antigens included in the vaccine can be manufactured and delivered optimally

**SAFETY** **SEQUENCE OPTIMIZATION** **ANTIGEN DESIGN**

# The **Building Blocks** of AI-Immunology™

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## 3 VACCINE DESIGN

| | | | |
|---|---|---|---|
| Antigen quality | Antigen safety | B-cell antigen modelling | B-cell antigen design |
| Precision design | Personalized design | BIFROST | |

# How We Built **ObsERV™**

## 1 DISEASE DECODING

| | | | |
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# How We Built **ObsERV™**

## ObsERV™

1st layer is decoding the disease

HLA loss | Expression | ERV antigens

2nd layer is decoding the immune response

EvaxMHC | HLA typing

3rd layer is designing the best vaccine

Antigen quality | Antigen safety | Personalized design

## 1 DISEASE DECODING

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## 2 IMMUNE RESPONSE DECODING

| | | | |
|---|---|---|---|
| EvaxMHC | HLA typing | HLA frequencies | Distance to self |
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## 3 VACCINE DESIGN

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# AI-Immunology™ **Models**

## PIONEER™

| | | | |
|---|---|---|---|
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| Expression | Clonality | Neoantigens | |
| EvaxMHC | HLA typing | Distance to self | |
| Antigen quality | Antigen safety | Personalized design | |

## RAVEN™

| | | |
|---|---|---|
| Expression | Viral antigens | Antigen conservation |
| EvaxMHC | HLA frequencies | Epitope hotspots |
| Precision design | BIFROST | |

## AI-DEEP™

| | | | |
|---|---|---|---|
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| Treatment effect | | | |
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## ObsERV™

| | | |
|---|---|---|
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## EDEN™

| | | |
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| Bacterial antigens | Viral antigens | Antigen conservation |
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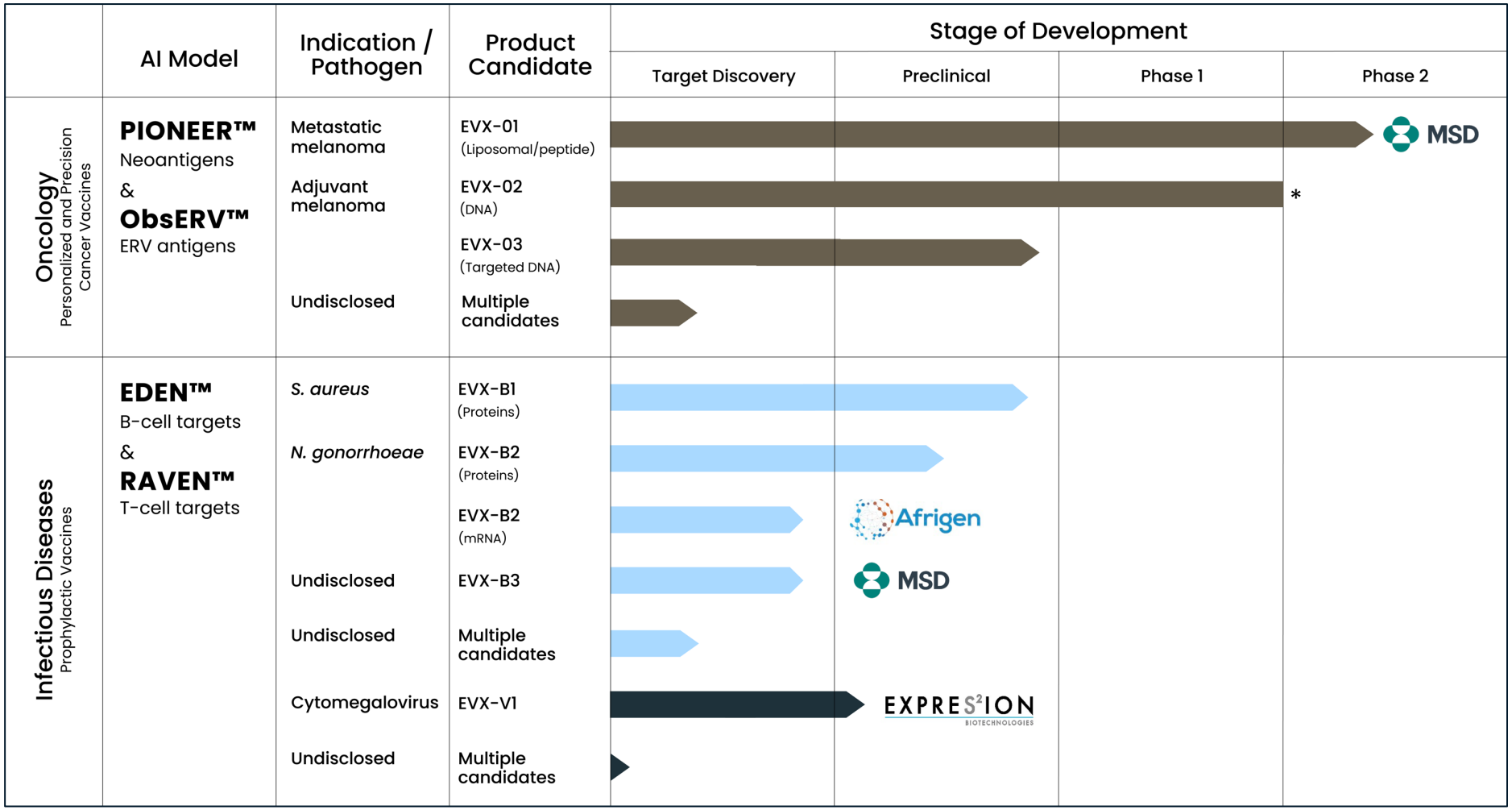
# Pipeline: Demonstrating the **Performance & Scalability of Our AI-Immunology™** Platform






*The data generated in the EVX-02 program actively informs the development of the second generation EVX-03 DNA vaccine

# Building **Future** Models

*EvaxNext™*


## 1 DISEASE DECODING

| | | | |
|---|---|---|---|
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## 3 VACCINE DESIGN

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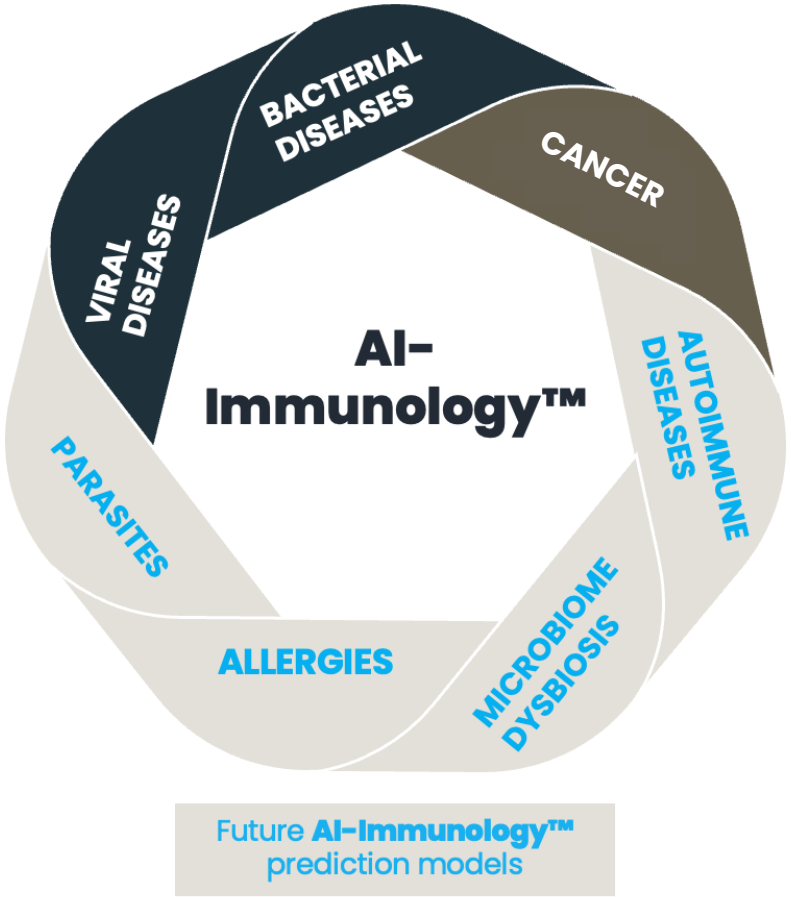
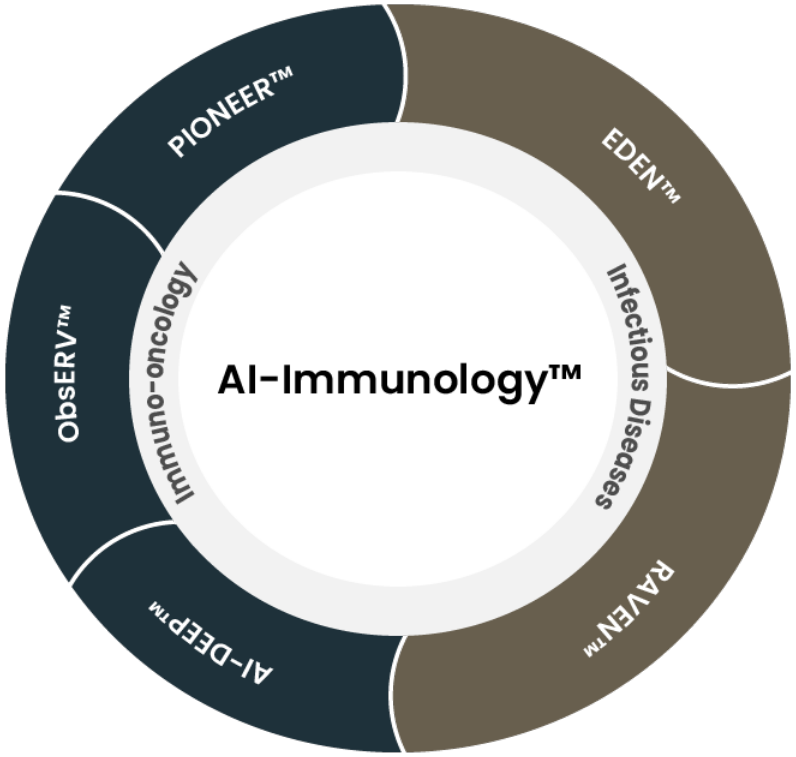
# **Building Block Architecture** Enables Scaling to Other Therapeutic Areas



# Summary

- Evaxion is first mover in using AI for vaccine target discovery, design & development and clearly differentiated
- AI-Immunology™ platform is trained in cancer and infectious diseases
- AI-Immunology™ has been clinically validated
- AI-Immunology™ is an ensemble of smaller building blocks utilized across the AI-Immunology™ models
- The AI-Immunology™ building block architecture enables scaling to therapeutic areas beyond cancer and infectious diseases



# EvaxMHC our **Central Building Block**

## PIONEER™

| | | | |
|---|---|---|---|
| SNVs | Frameshifts | Gene fusions | HLA loss |
| Expression | Clonality | Neoantigens | |
| EvaxMHC | HLA typing | Distance to self | |
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## ObsERV™

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| CET / EST | |
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| 14.00 - 14.10 / 9.00 – 9.10 | **Welcome** |
| 14.10 - 14.20 / 9.10 – 9.20 | **Evaxion overview** - Setting the scene |
| 14.20 - 14.35 / 9.20 – 9.35 | **AI-Immunology™** - A leading AI platform |
| 14.35 - 14.55 / 9.35 – 9.55 | **EvaxMHC 4.0** - A cutting-edge AI building block |
| 14.55 - 15.15 / 9.55 – 10.15 | *BREAK* |

## SESSION 2 - Infectious Disease Vaccines

| | |
|---|---|
| 15.15 - 15.35 / 10.15 – 10.35 | **EDEN™** - Best-in-class model assessing protectiveness of B-cell antigens |
| 15.35 - 15.55 / 10.35 – 10.55 | **RAVEN™** - Model for uncovering unique cross-protective T-cell antigens |
| 15.55 - 16.15 / 10.55 – 11.15 | *BREAK* |

## SESSION 3 - Personalized Cancer Vaccines

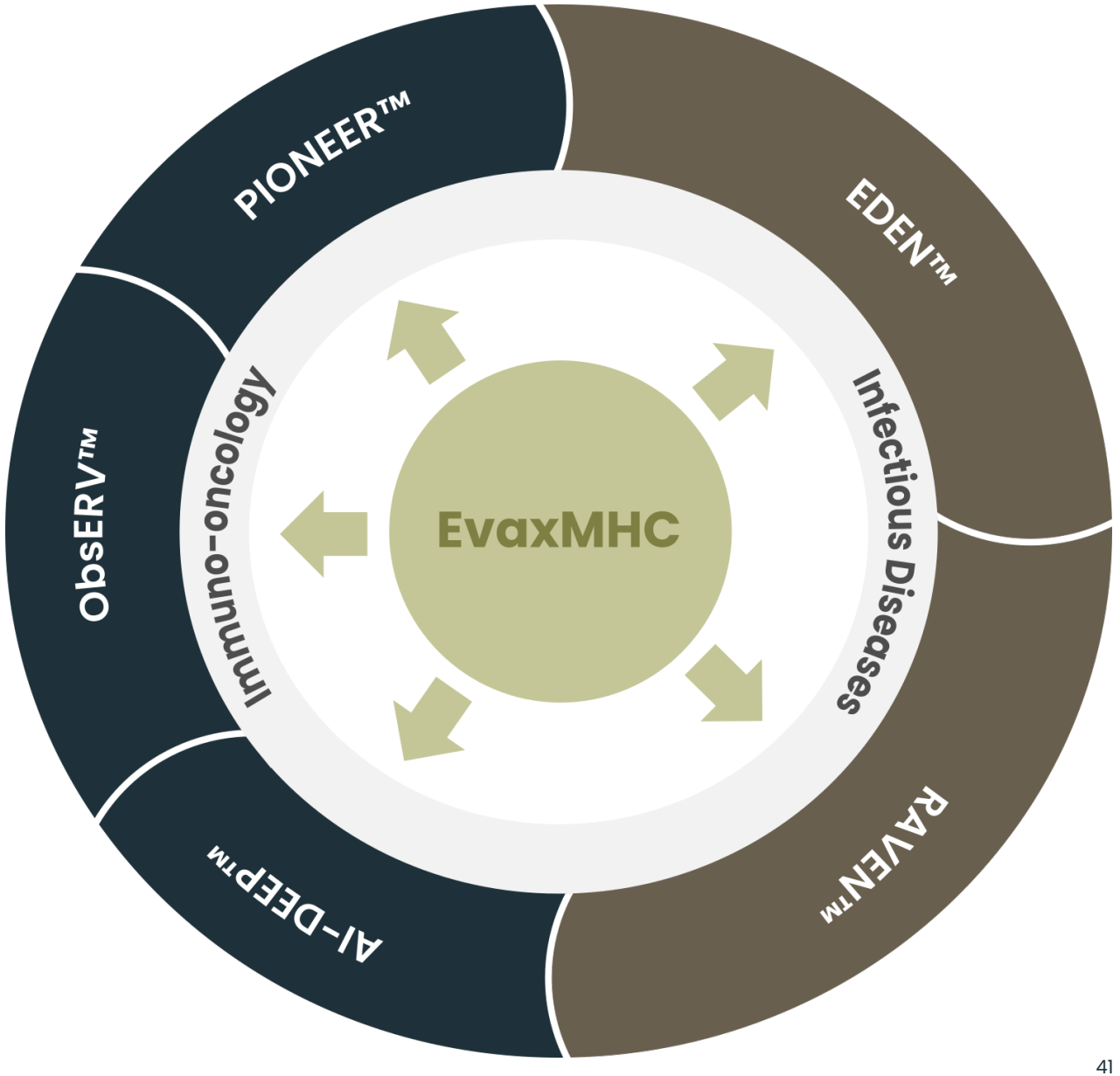
| | |
|---|---|
| 16.15 - 16.35 / 11.15 – 11.35 | **PIONEER™** - Validated model for designing personalized Neoantigen vaccines |
| 16.35 - 16.55 / 11.35 – 11.55 | **ObsERV™** - Leading model for designing personalized ERV-antigen vaccines |
| 16.55 - 17.15 / 11.55 – 12.15 | BREAK |

## SESSION 4 - Precision Cancer Concepts

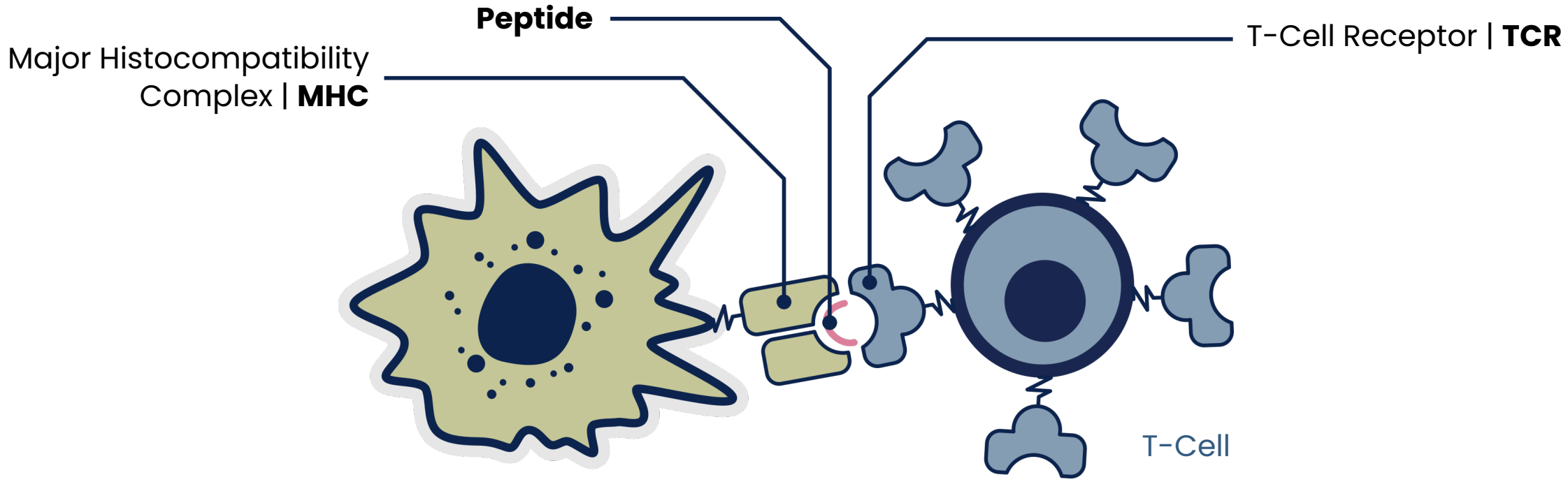
| | |
|---|---|
| 17.15 - 17.35 / 12.15 – 12.35 | **AI-DEEP™** - Model for predicting responses to cancer CPI immunotherapy |
| 17.35 - 17.55 / 12.35 – 12.55 | **Addressing difficult to treat cancers with AI-Immunology™** |
| 17.55 - 18.00 / 12.55 – 13.00 | *THANK YOU and concluding remarks* |
| 18.00 - 19.00 / 13.00 – 14.00 | *Reception with drinks and snacks* |

# EvaxMHC 4.0
## – A cutting-edge AI building block

# **EvaxMHC** is a **Central Building Block** Across All AI-Immunology™ Models



# The **Adaptive Immune System** Revolves Around the **MHC•Peptide•TCR** Interaction

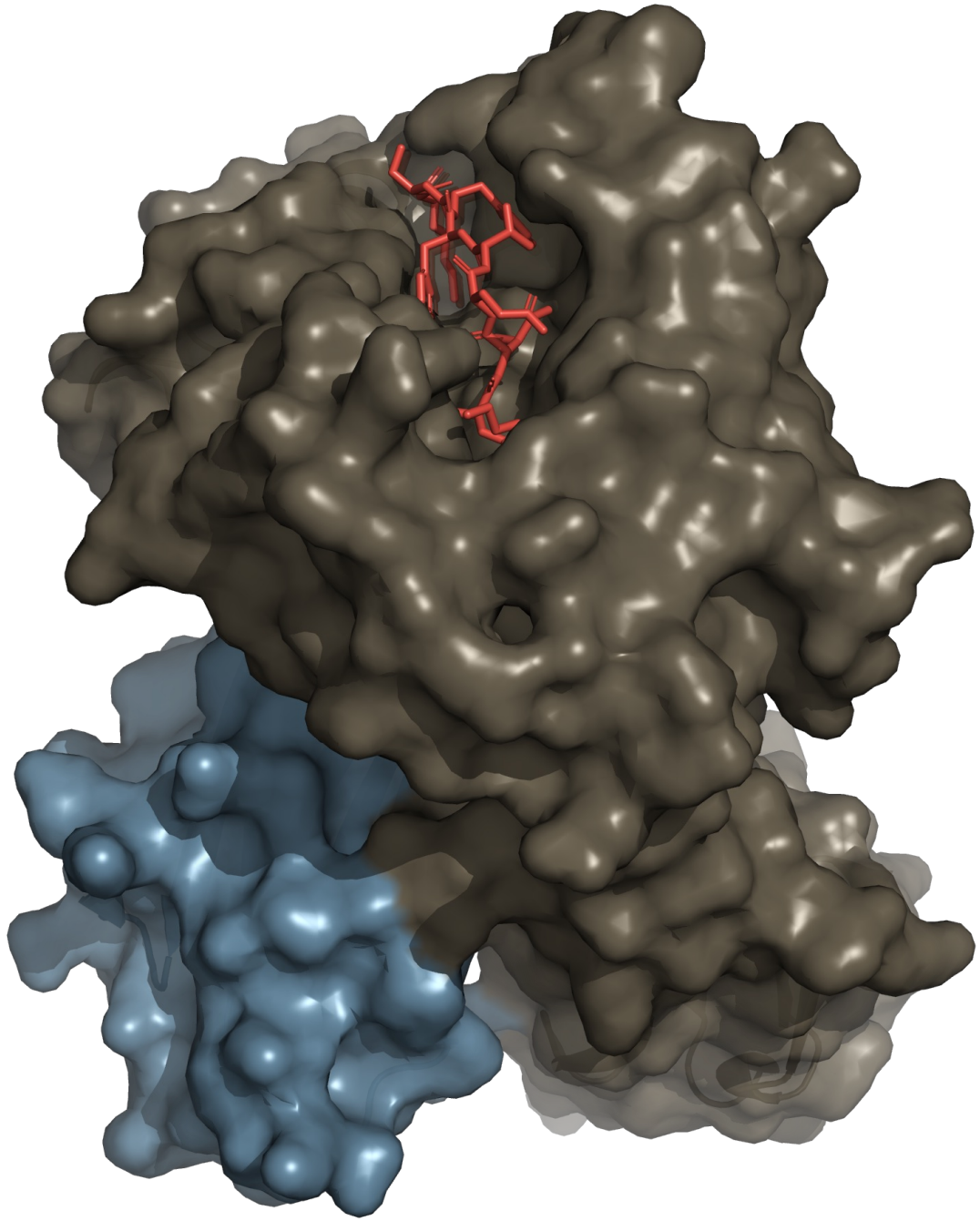


# **MHC Genes** are the **Most Diverse Genes** Across All Individuals

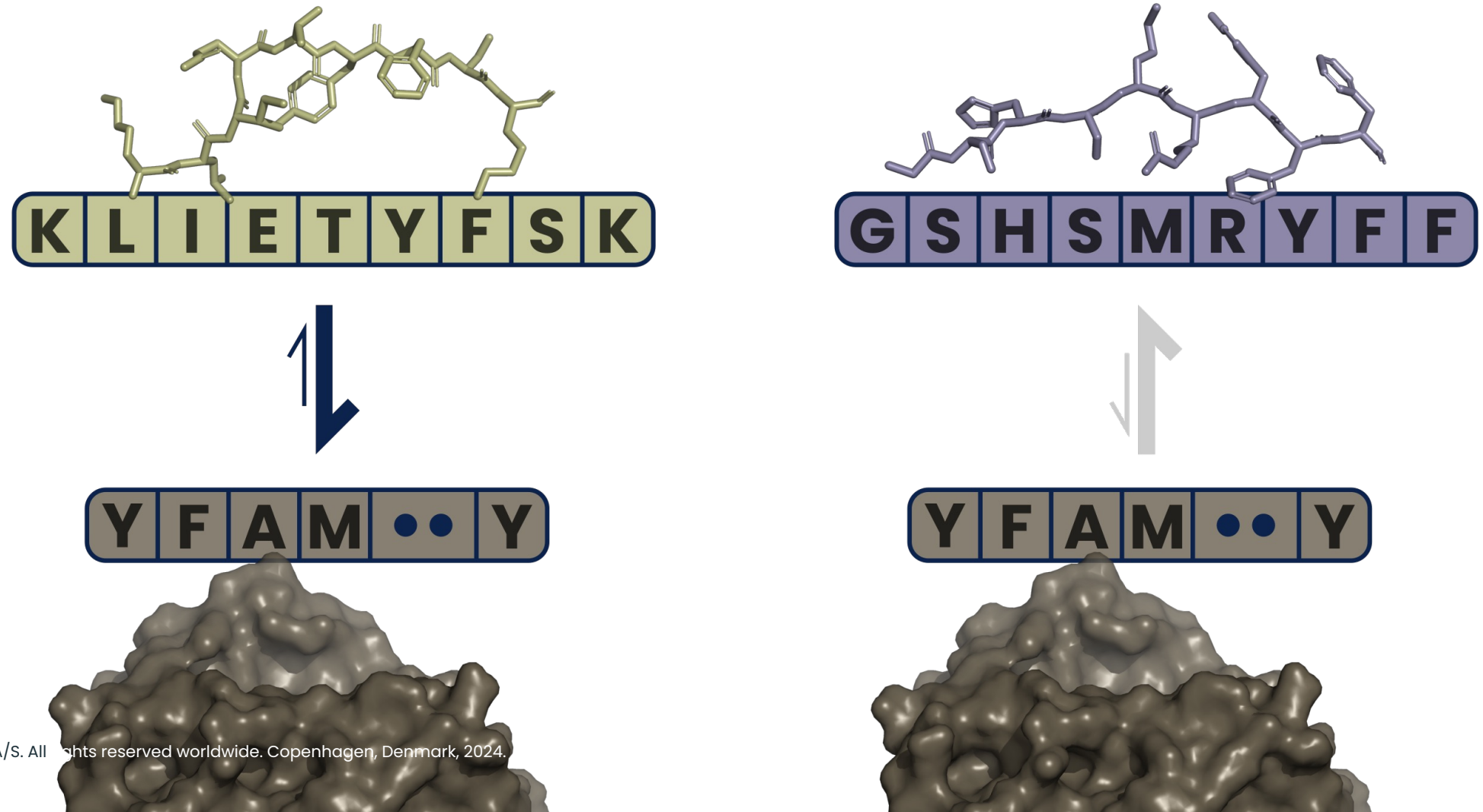
**MHC:** Major Histocompatibility Complex
**HLA:** Human Leukocyte Antigen

Human Class I MHCs: **HLA-A**, **B**, and **C**
Class II: **HLA-DR**, **DQ**, and **DP**

Currently **26,610 HLA class I alleles** and **11,398 HLA class II alleles** are known.

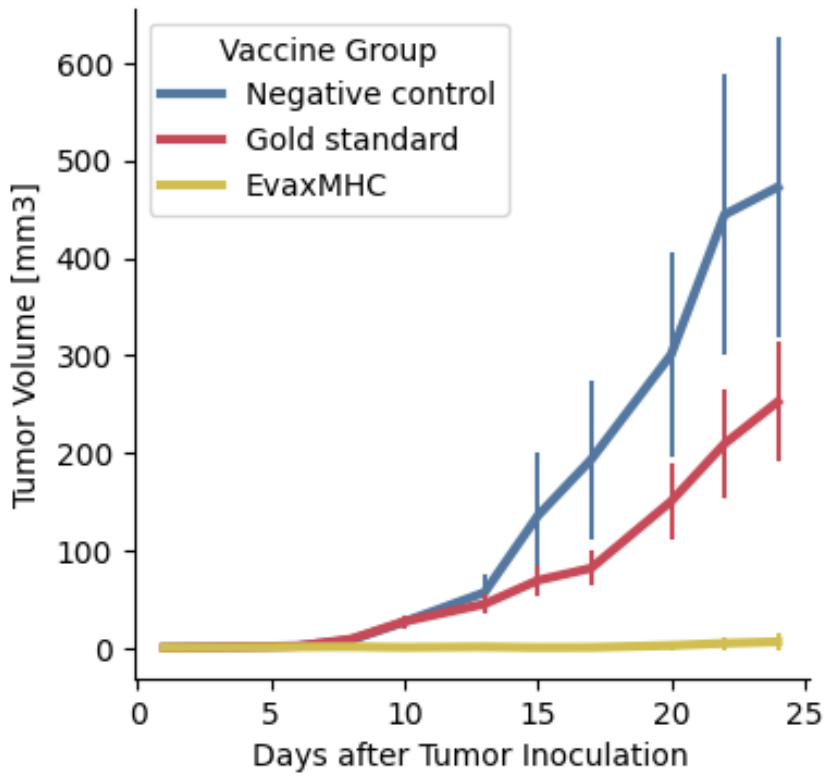


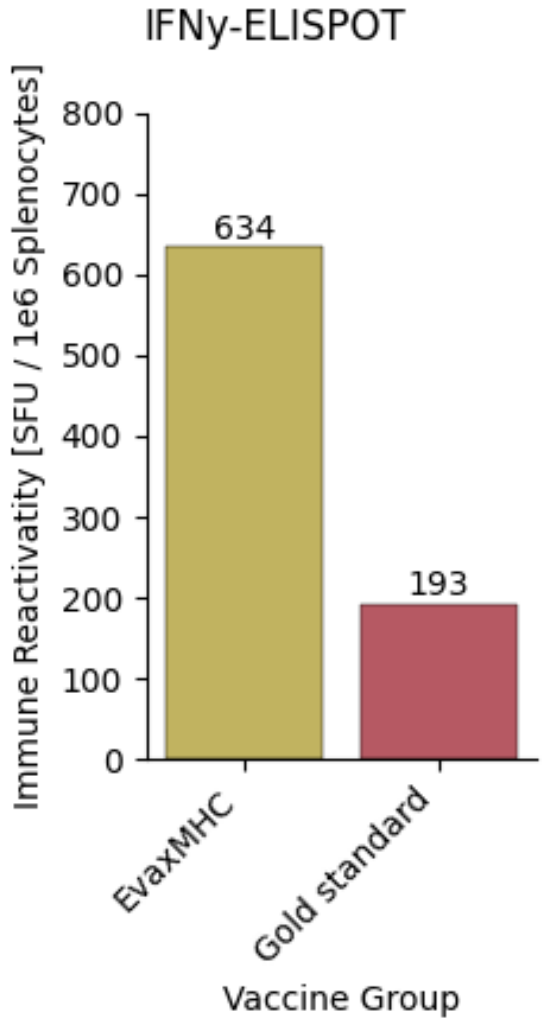
# MHC•Peptide Predictors Classify Presentation for **Millions of Peptides** on **Thousands of MHC Alleles**



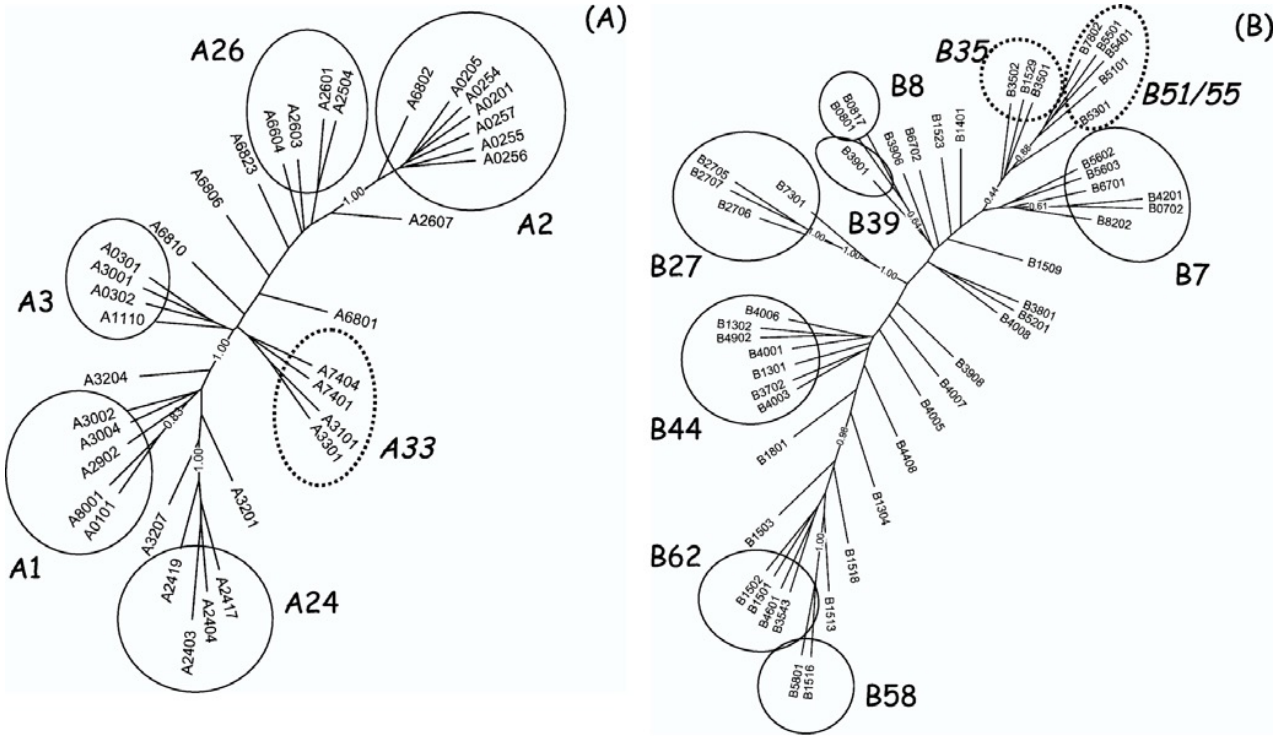
# **EvaxMHC** Empowers **ObsERV™** to Design **Efficacious** ERV-Based Cancer **Vaccines**

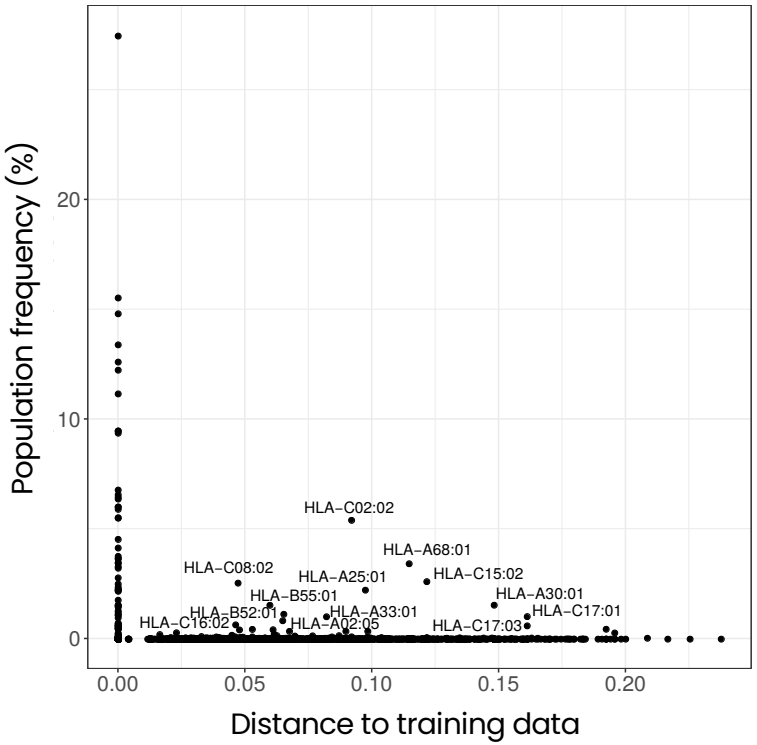
- Peptide-MHC prediction is a core element in ObsERV™
- Vaccine group designed after swapping out EvaxMHC with Gold standard tool
- EvaxMHC  vaccine group mounts stronger and sustained immune response and tumor protection



# Evaxion has Generated **Proprietary Datasets** for MHC Alleles that are **Underrepresented in Public Datasets**



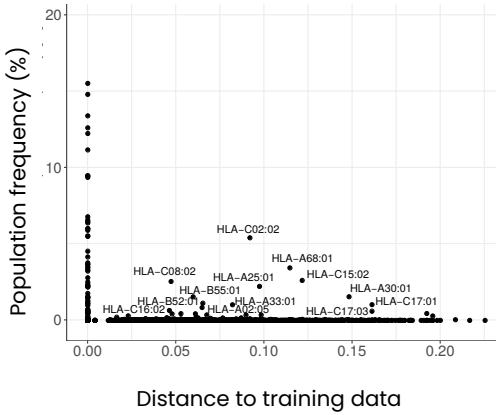



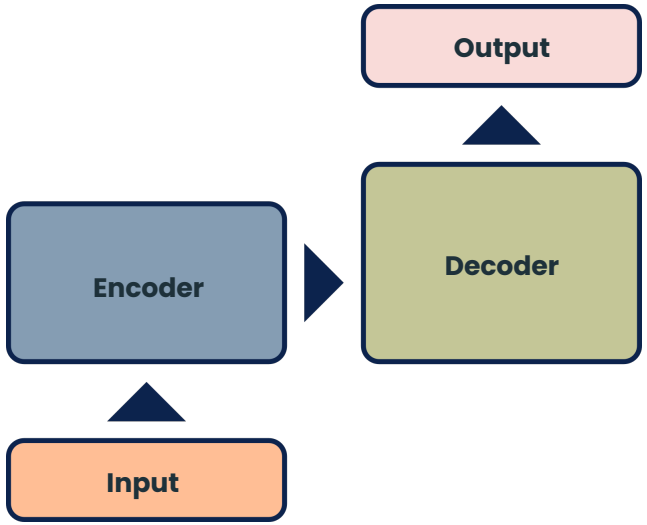
# EvaxMHC4 Improvements are Driven by **Proprietary Datasets**, Novel **Architectures** and **Training Strategy**

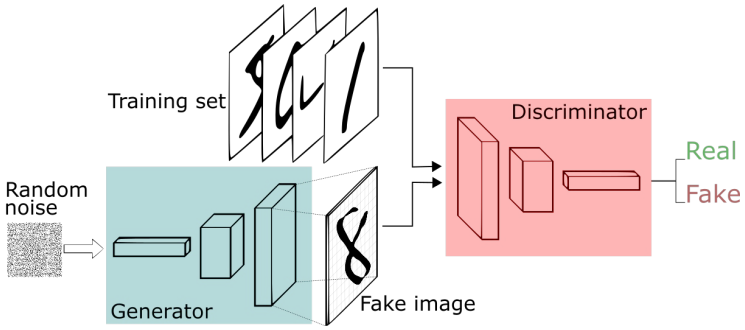
1. Integrating deep neural networks with Peptide-MHC data have proven a significant challenge

2. EvaxMHC uses an AI model architecture inspired by machine translation

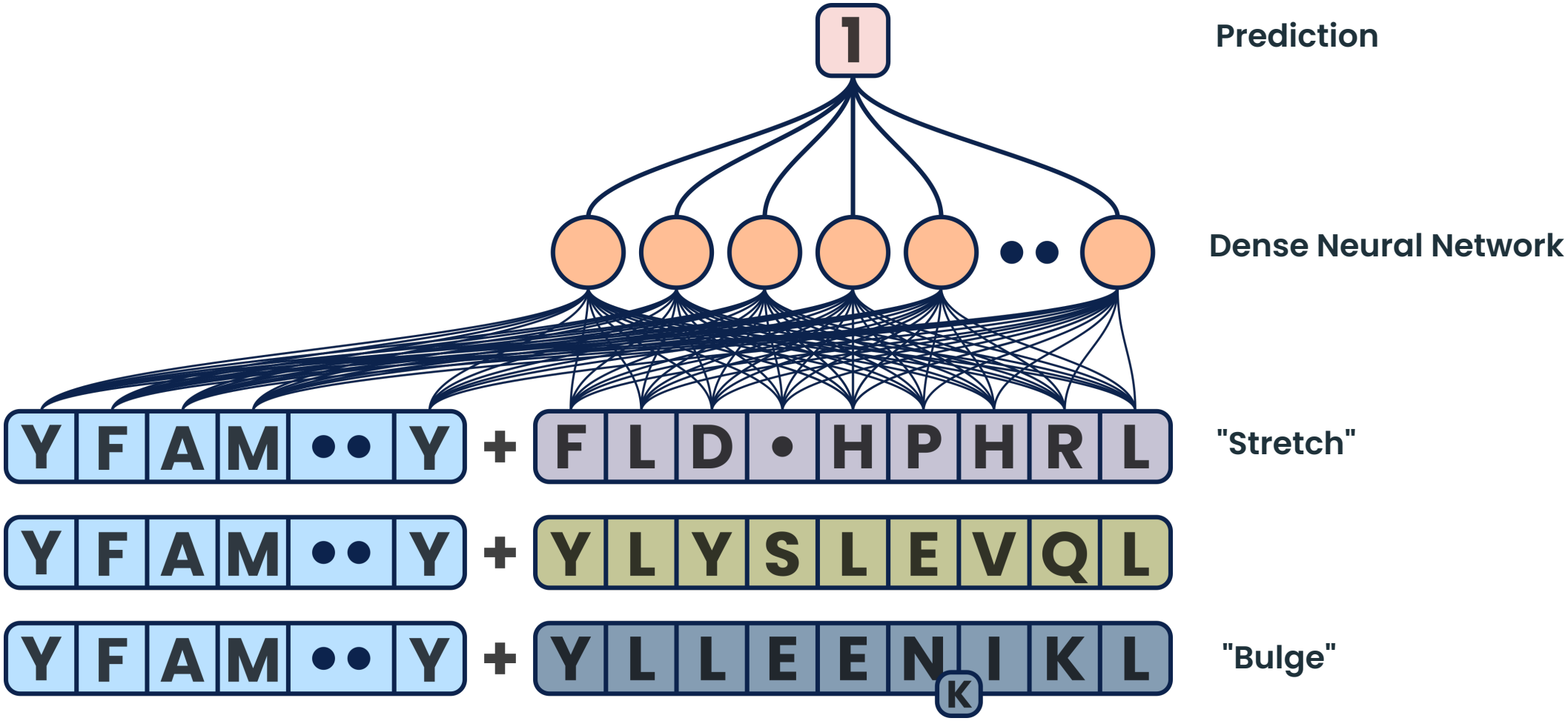
3. EvaxMHC has been trained as a generative adversarial network



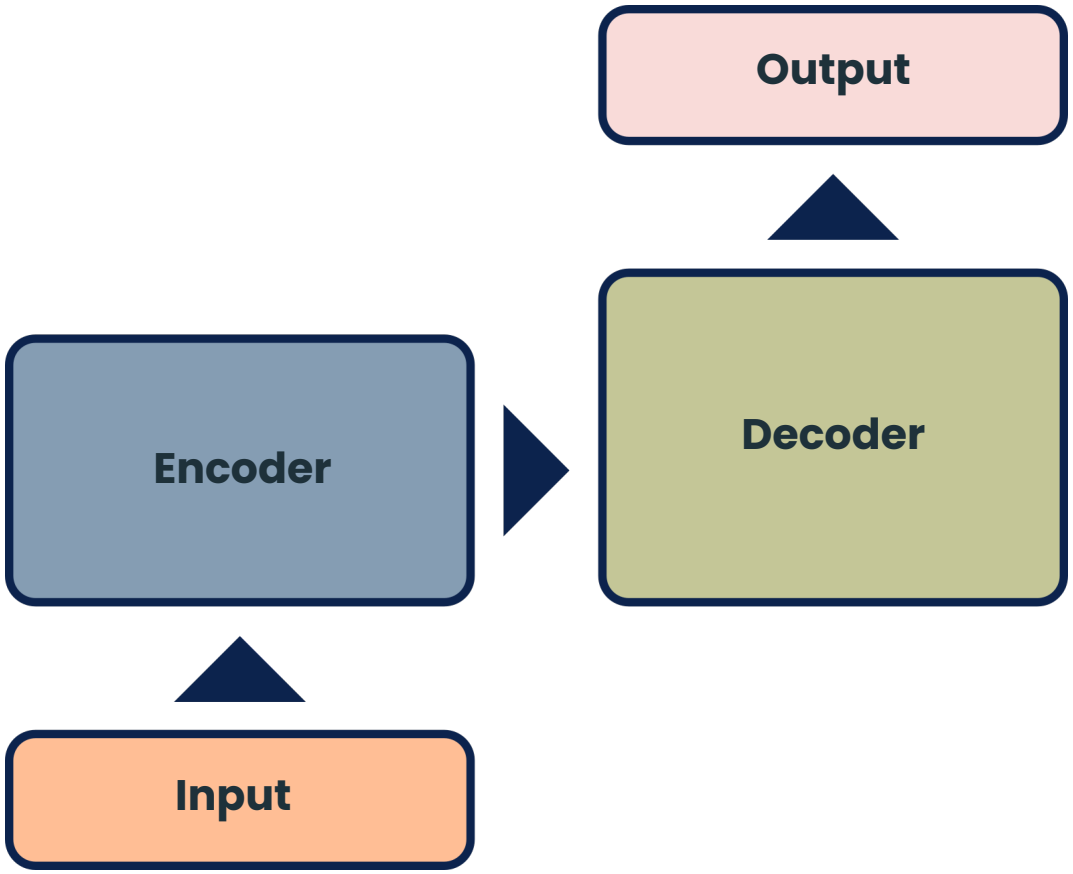
# Conventionally, Peptide•MHC Predictions are Driven by **Deep Knowledge** and **Feature Engineering**



# Deep Learning Techniques are Used to Leverage **Increasing Amounts of Data**

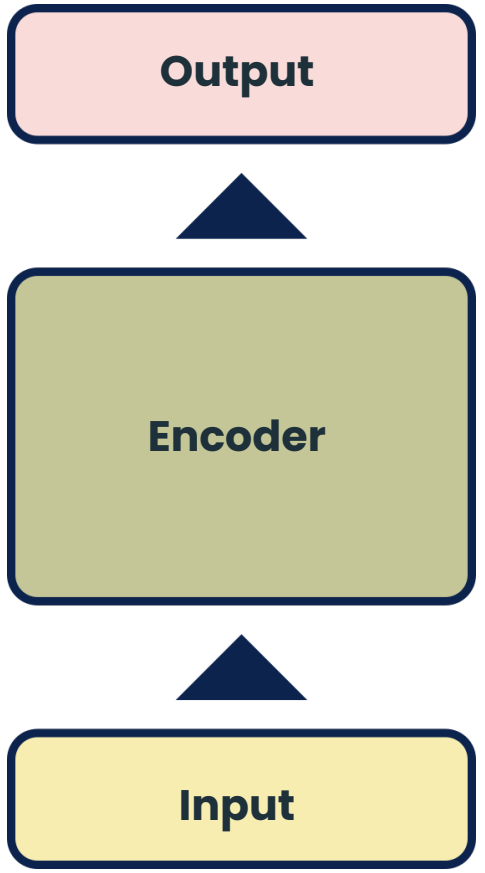
**Encoder-Decoder**

E.g. machine translation




**Encoder-only**

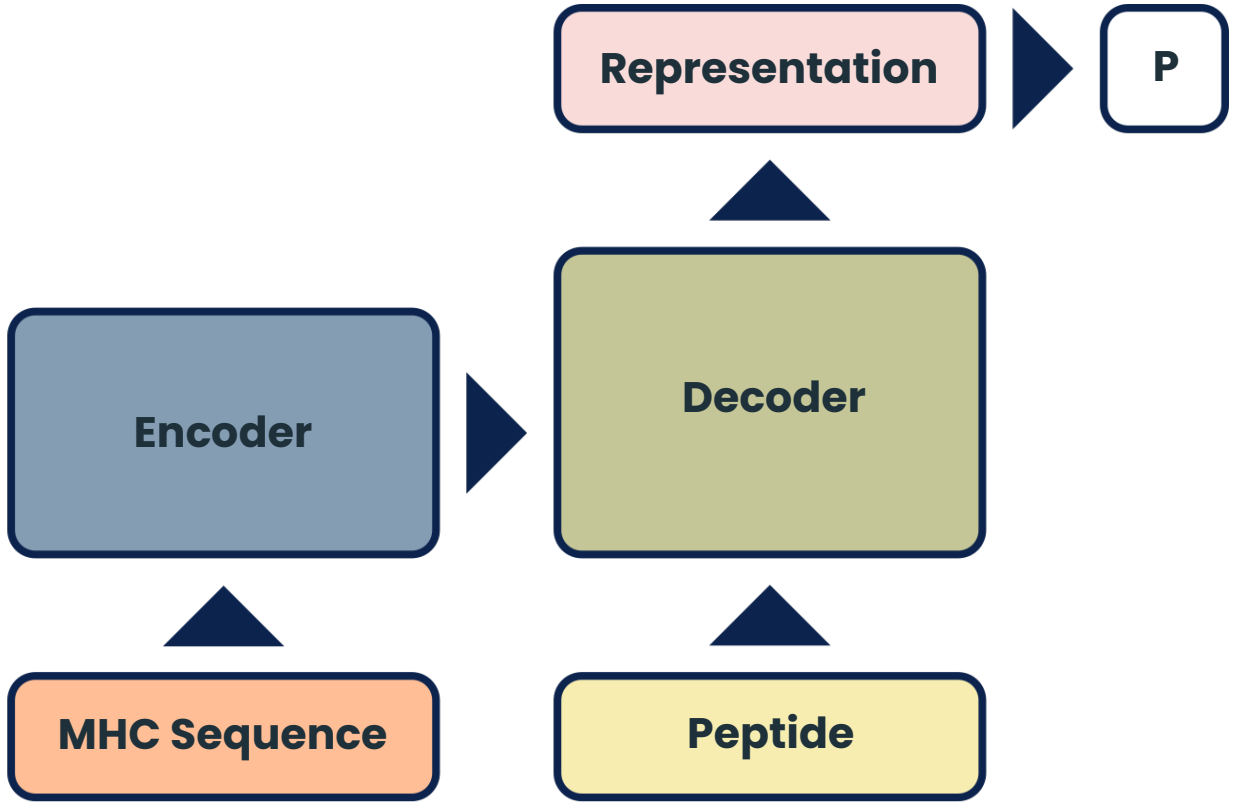
E.g. autocomplete, ChatGPT



# **Deep Learning** Techniques are Used to **Leverage Increased Amounts** of **Data**

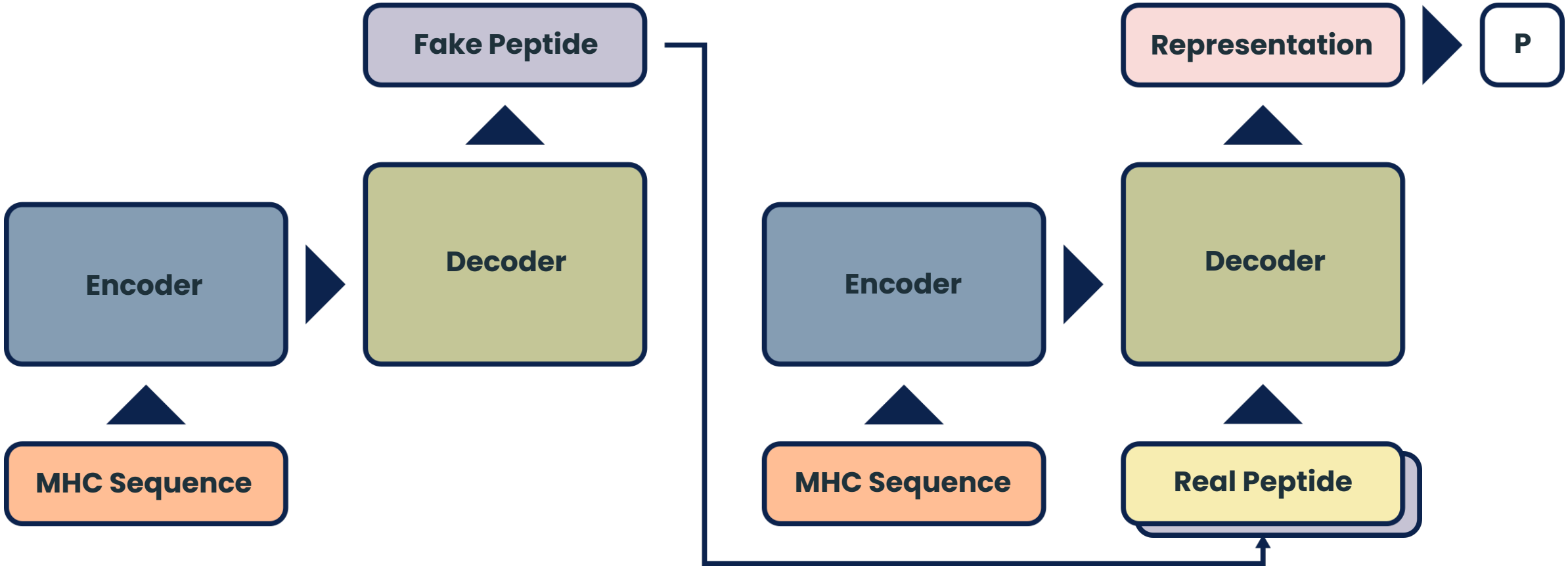
**Encoder-Decoder**
For Peptide•MHC modelling

- Logical fit to model Peptide•MHC interaction
- MHC Sequence as the **"Input language"**
- **Peptide + Encoded MHC** is decoded to a binding yes/no answer



# **Deep Learning** Techniques are Used to **Leverage Increased Amounts** of **Data**

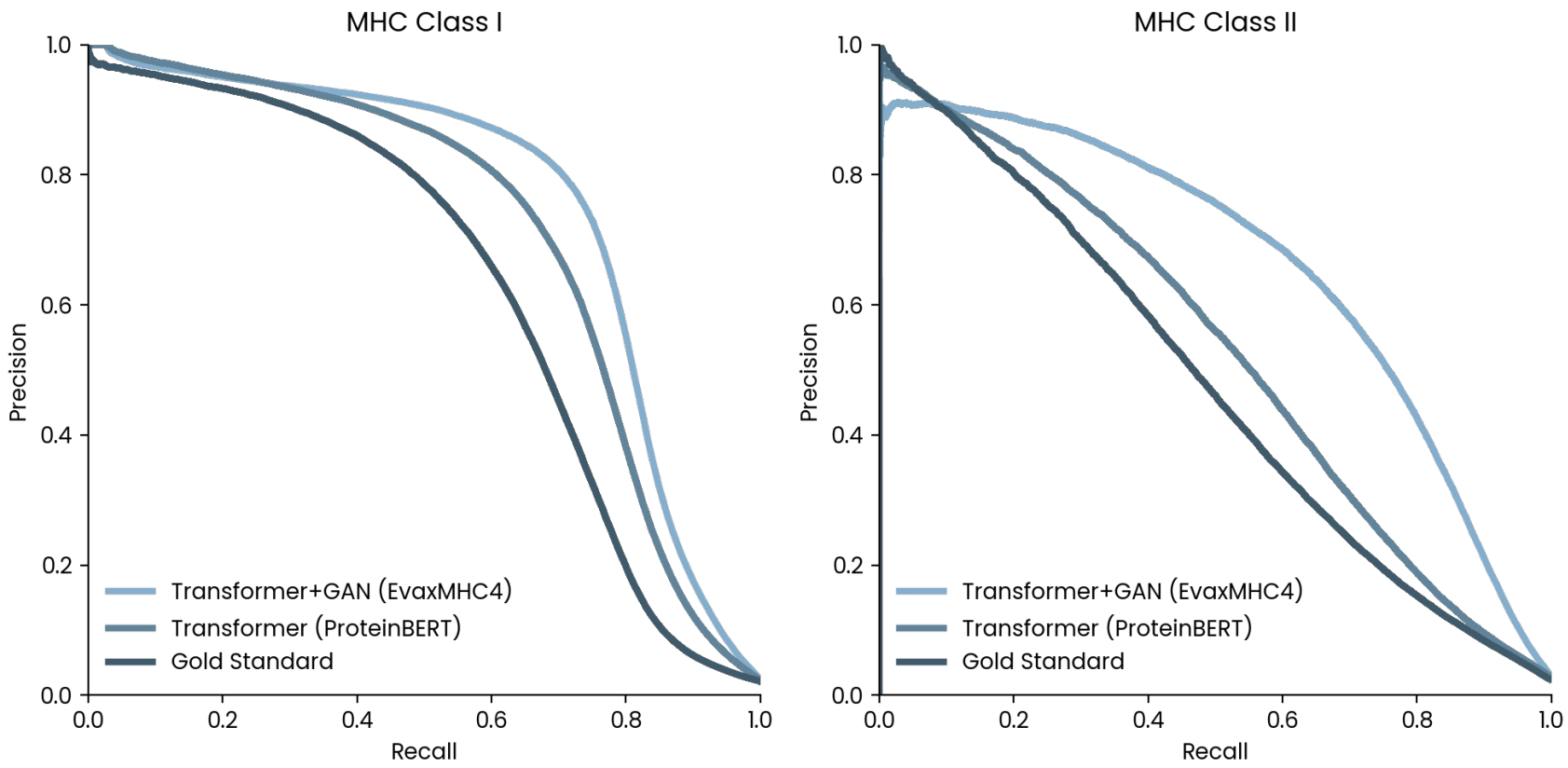
**Encoder-Decoder + Generative Adversarial Network**
For Peptide•MHC modelling



# **Deep Learning** Techniques are Used to **Learn Connections Between MHC Class I and Class II Binding**

Transformer Architecture allow a combination of MHC class I and class II data

# **EvaxMHC** is a **State-of-the-Art Peptide•MHC Interaction** Predictor



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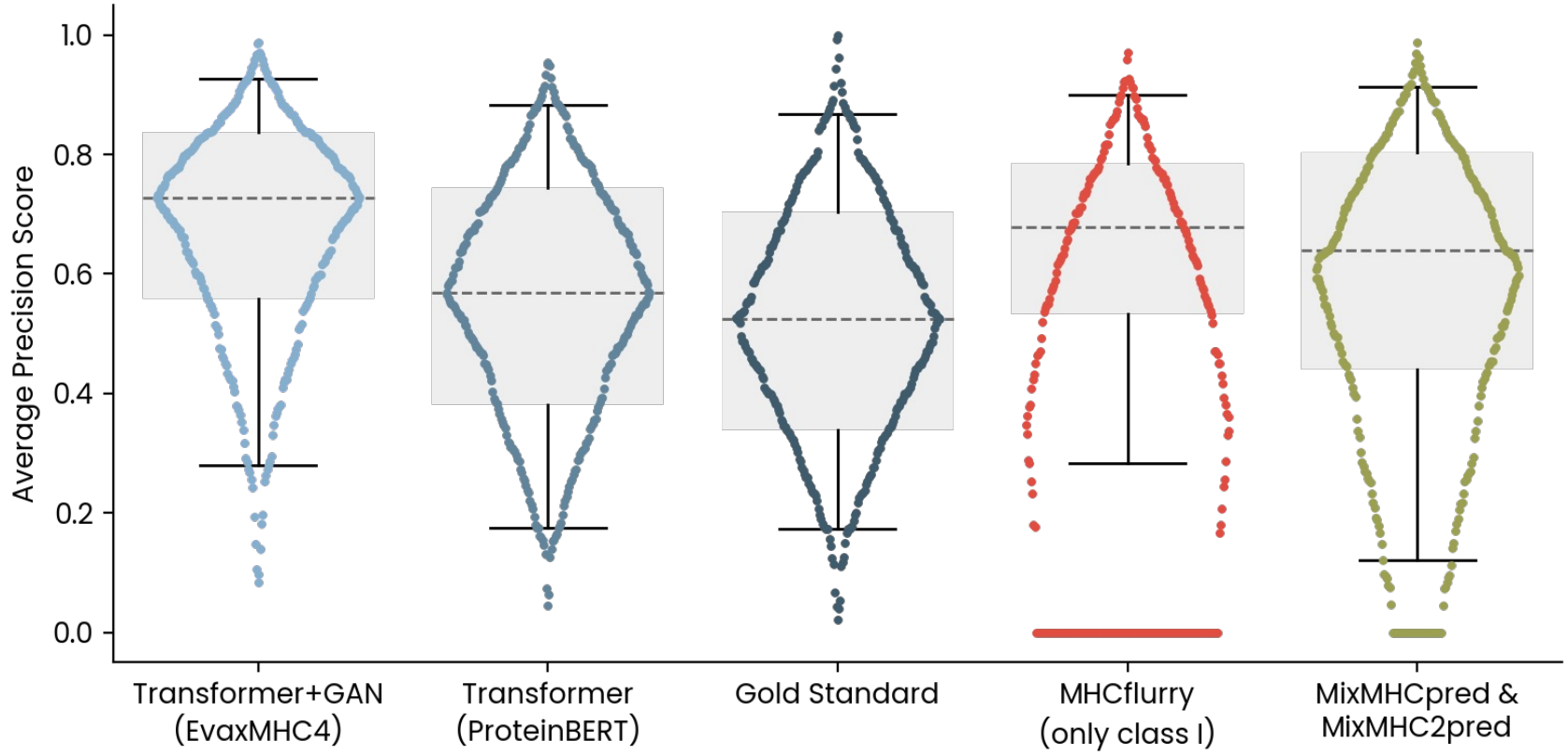
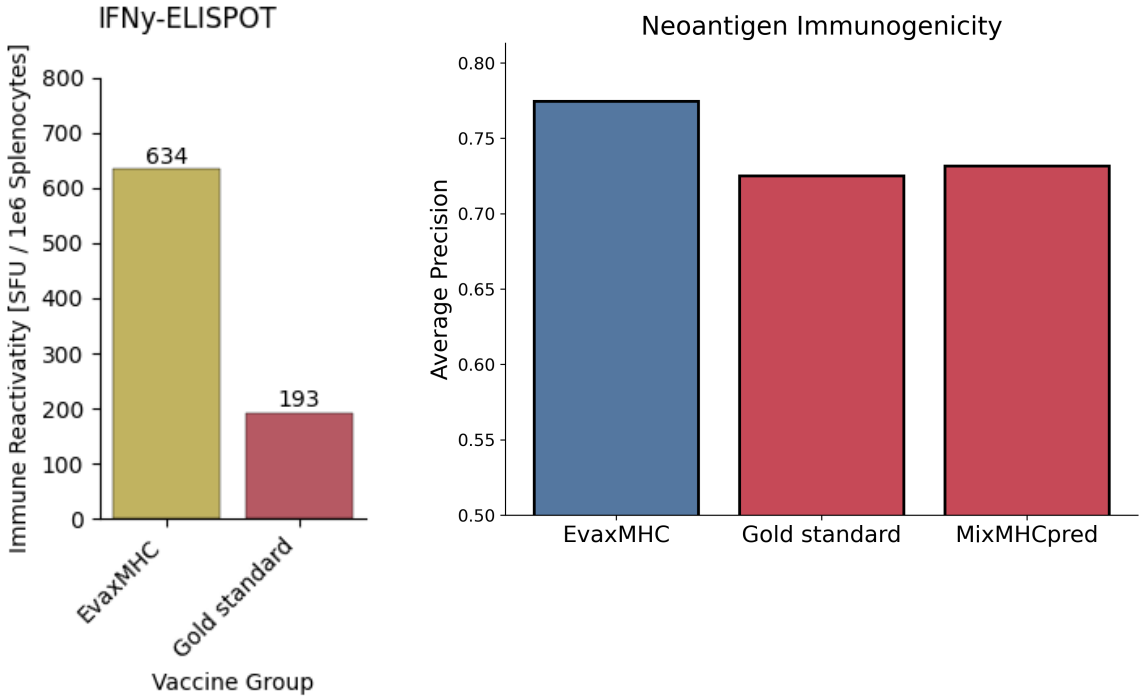
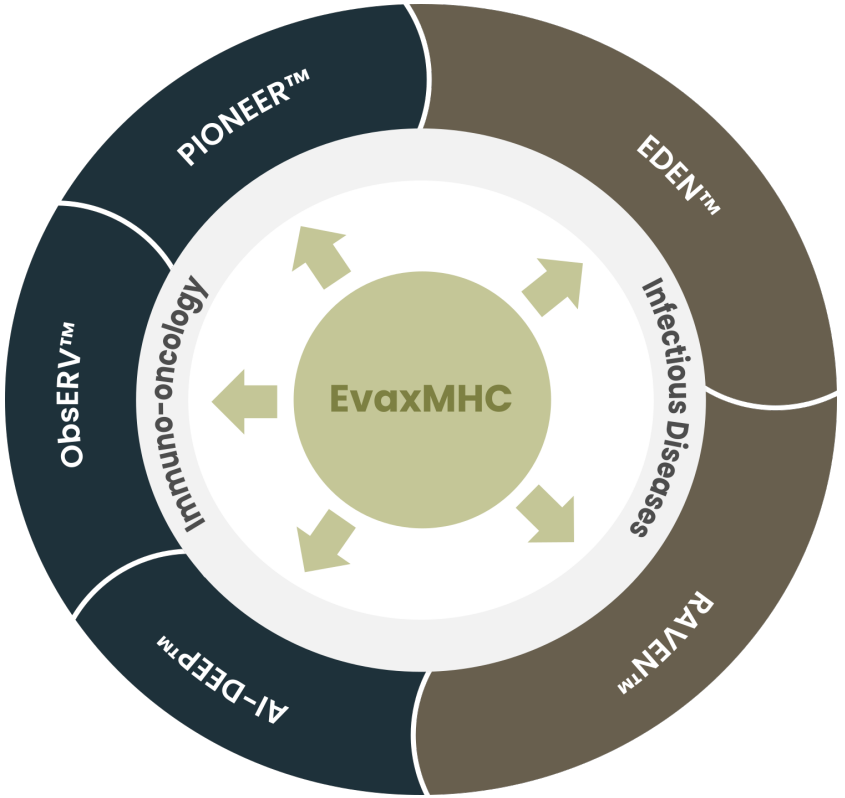


# State-of-the-Art Peptide•MHC Predictions **Impacts Across Our AI-Immunology™ Models**



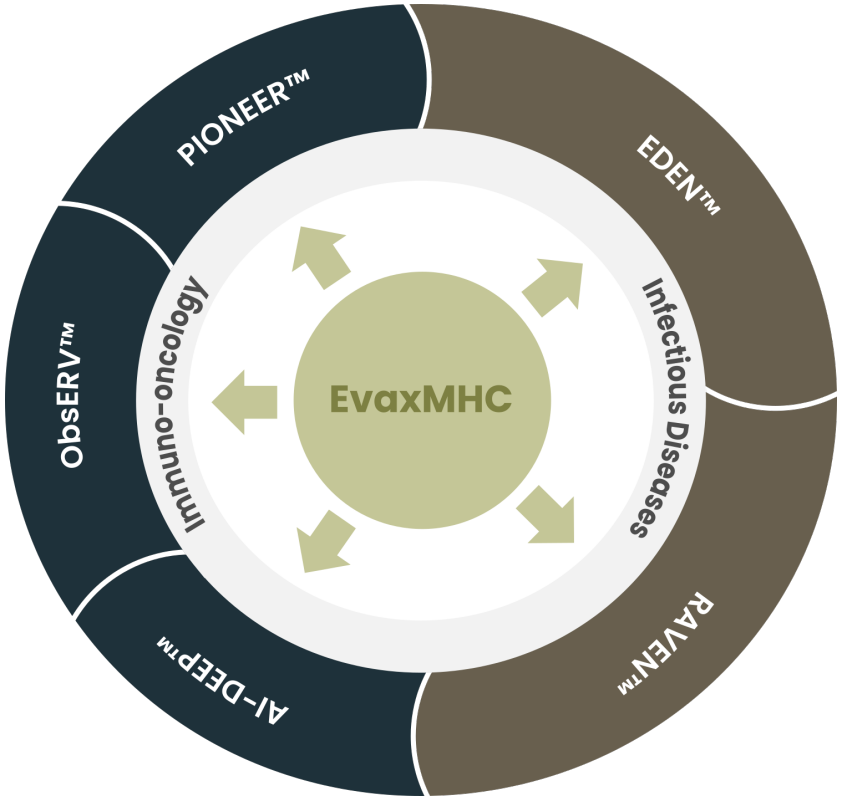






# Summary

- Peptide•MHC interactions communicate self/non-self across cell boundaries
- Peptide•MHC predictions are crucial for modern design of vaccines
- EvaxMHC 4.0 is a major leap forward in Peptide•MHC prediction performance
- Advances in Peptide•MHC prediction precision improves vaccine performance



# Q&A SESSION

# **BREAK** – Be Back at 15.15 CET / 10.15 EST

# Agenda

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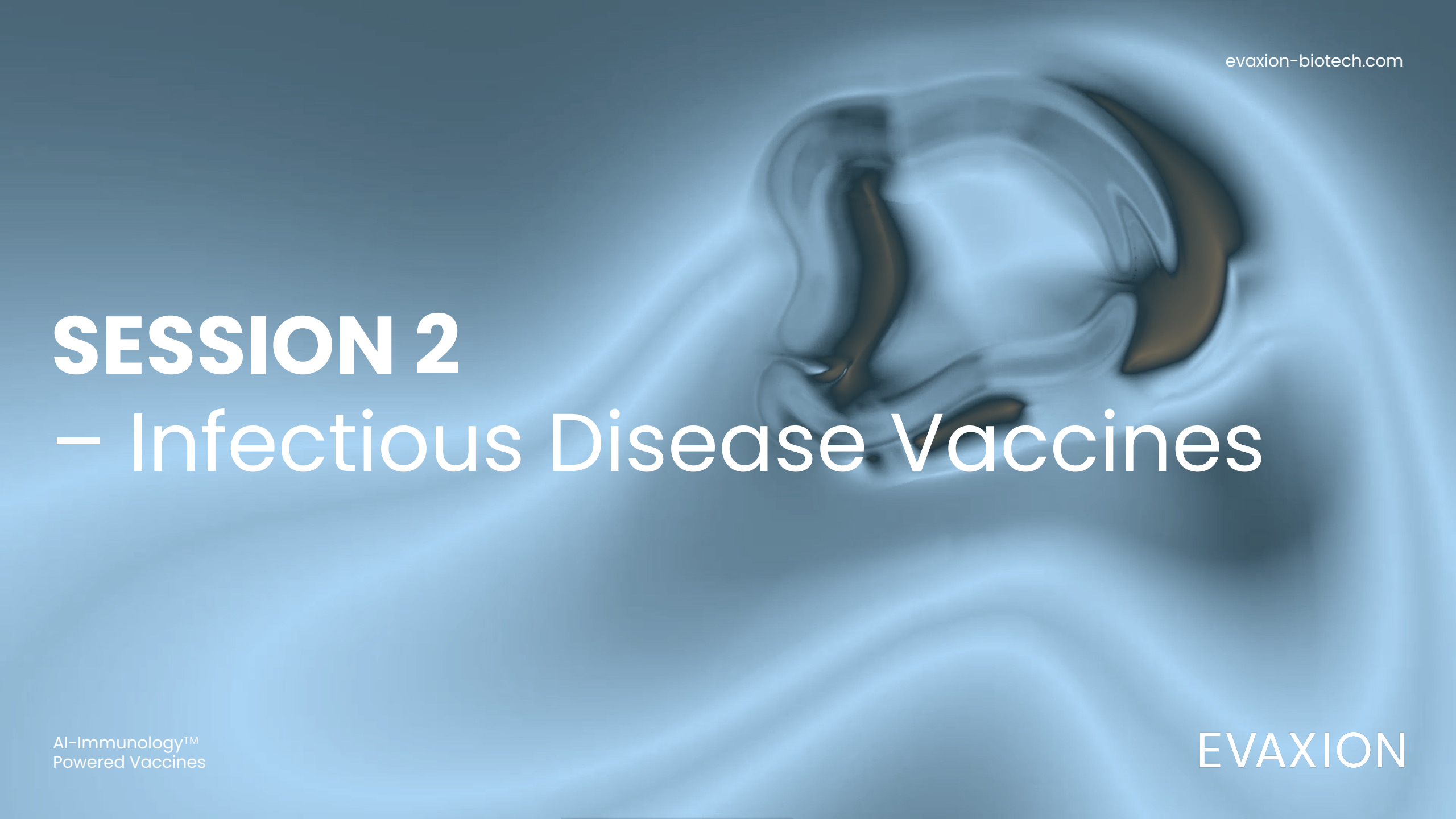
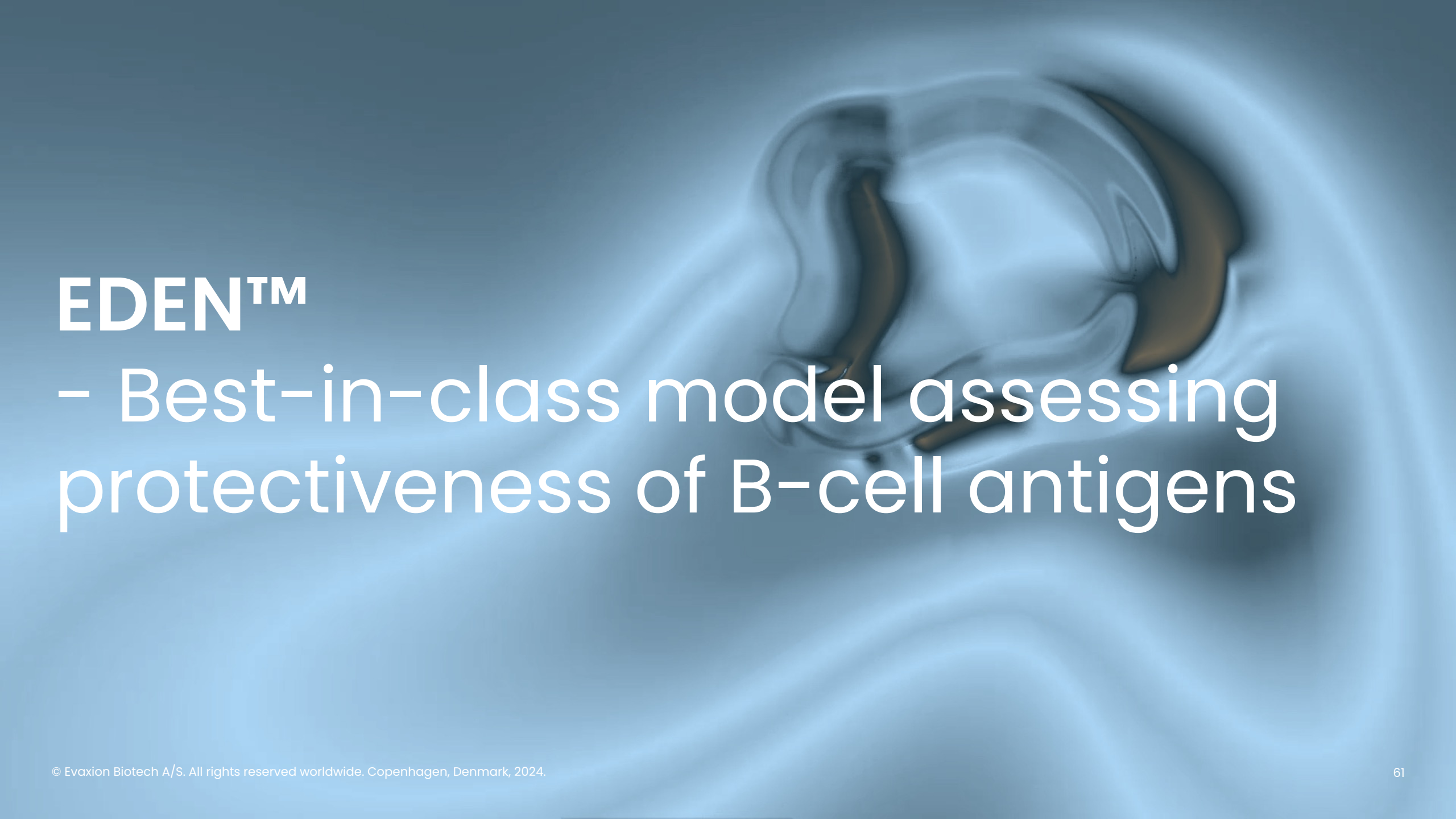


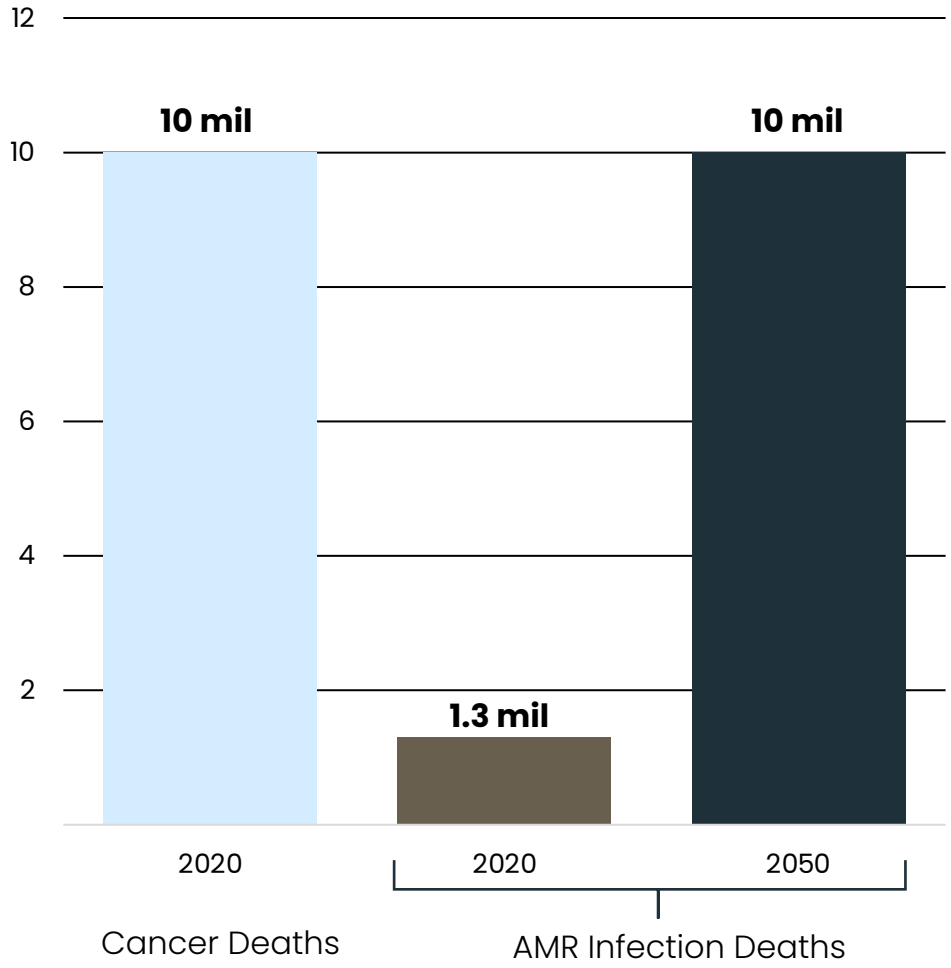
# SESSION 2
## – Infectious Disease Vaccines

# EDEN™

- Best-in-class model assessing protectiveness of B-cell antigens



# **Global Deaths from Antimicrobial Resistant** (AMR) Infections Sets to Skyrocket




- **2020** - 10 million deaths a year due to cancer*
- **2020** - 1,3 million death of AMR infections**
- **2050** - 10 million death of AMR infections**



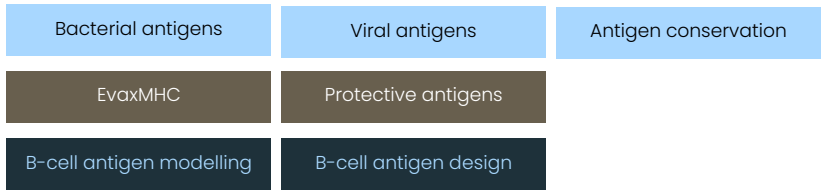
* Source: WHO, ** Source: Statista

# We Need **AI for Accelerated Vaccines Development** against AMR Infections

- Vaccines have a proven track-record of tackling AMR infections
- Traditional vaccine development 'Reverse Vaccinology' is both costly and time-consuming, relying on luck to find protective antigen targets
- We use our EDEN™ AI model to rapidly and precisely discover these highly and broadly protective vaccine antigens which are needed for AMR vaccine development

# How We Built **EDEN™**

**EDEN™**

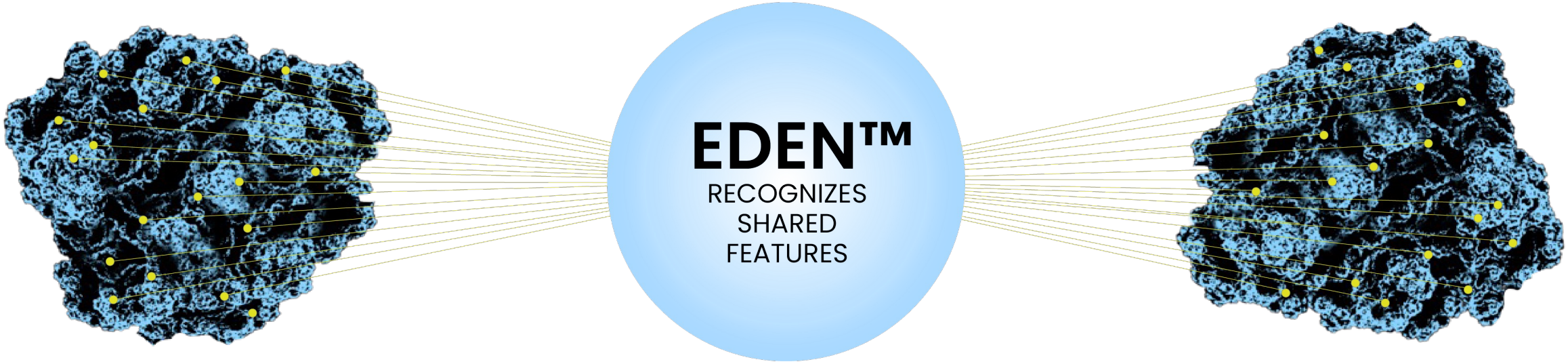



## 1 DISEASE DECODING


## 2 IMMUNE RESPONSE DECODING


## 3 VACCINE DESIGN

# EDEN™ Identifies **Novel Protective Antigen** Targets by Feature Recognition



# EDEN™ **Predict Antigen Protectiveness** and **Ranks Proteome**

## Proteome

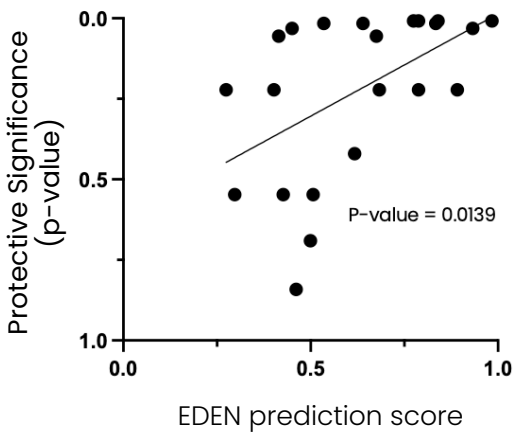
| Protein ID | AA Sequence |
|---|---|
| prot_0001 | MNRKKTVIIS... |
| prot_0002 | MKVKNKILTM... |
| prot_0003 | MFDAKDIKKD... |
| prot_0004 | MKKRILSAVL... |
| prot_0005 | MKMNKKVLLT... |
| prot_0006 | MSKKRLHEIA... |
| prot_0007 | MTKKHLKTLA... |
| prot_0008 | MSKQKVMATL... |
| prot_0009 | MSKRQNLGIS... |
| prot_0010 | MSEDQKHPFF... |
| ... | |
| prot_2617 | MNKRRKLSKL... |


## Ranked by predicted protectiveness

| EDEN rank | EDEN score | Protein ID |
|---|---|---|
| # 1 | 0.9912 | prot_0124 |
| # 2 | 0.9825 | prot_0057 |
| # 3 | 0.9804 | prot_0325 |
| # 4 | 0.9783 | prot_0012 |
| # 5 | 0.9266 | prot_1524 |
| # 6 | 0.8888 | prot_0524 |
| # 7 | 0.8546 | prot_0658 |
| # 8 | 0.8485 | prot_0998 |
| # 9 | 0.8389 | prot_1654 |
| # 10 | 0.808 | prot_0004 |
| ... | | |
| # 2617 | 0.00002 | prot_0054 |

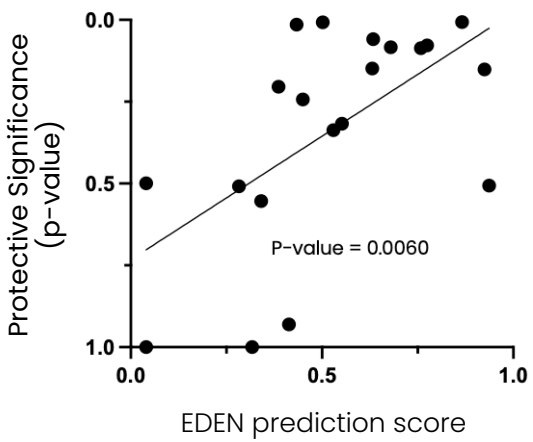
# EDEN™ **AI-Score Correlates with Protection** Identifying Most Protective Antigens

***N. gonorrhoeae***



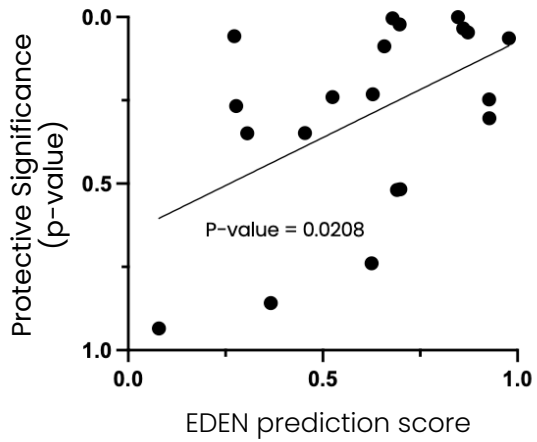

P = 0.01

***A. baumannii***



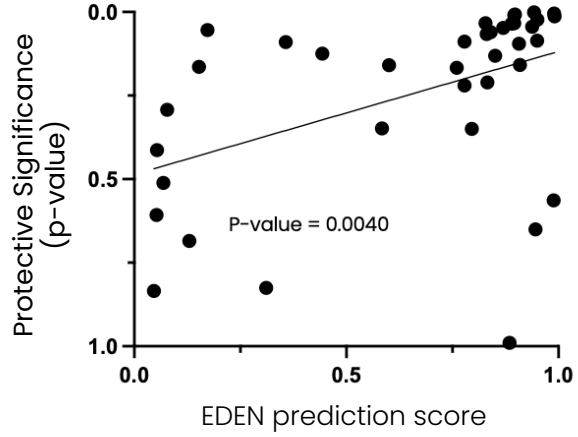

P < 0.01

***K. pneumoniae***



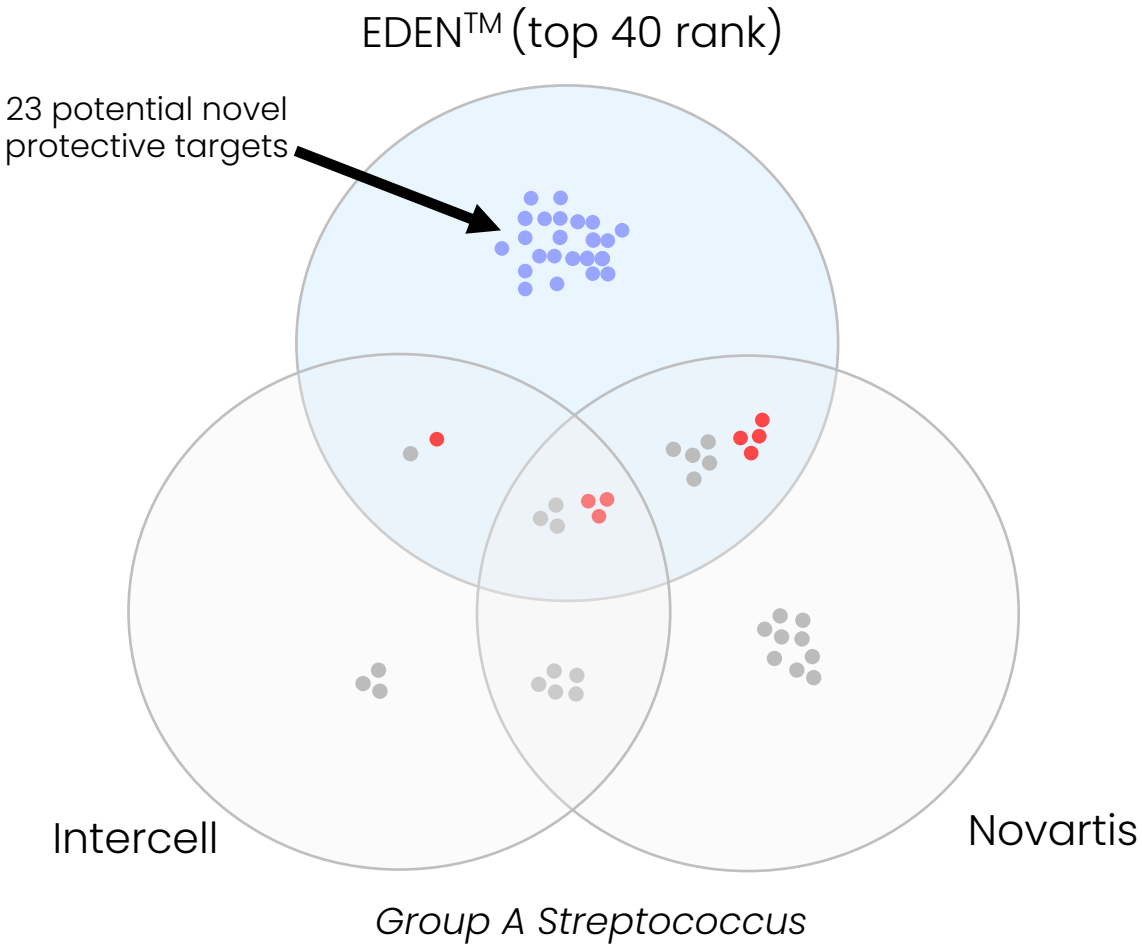

P = 0.02

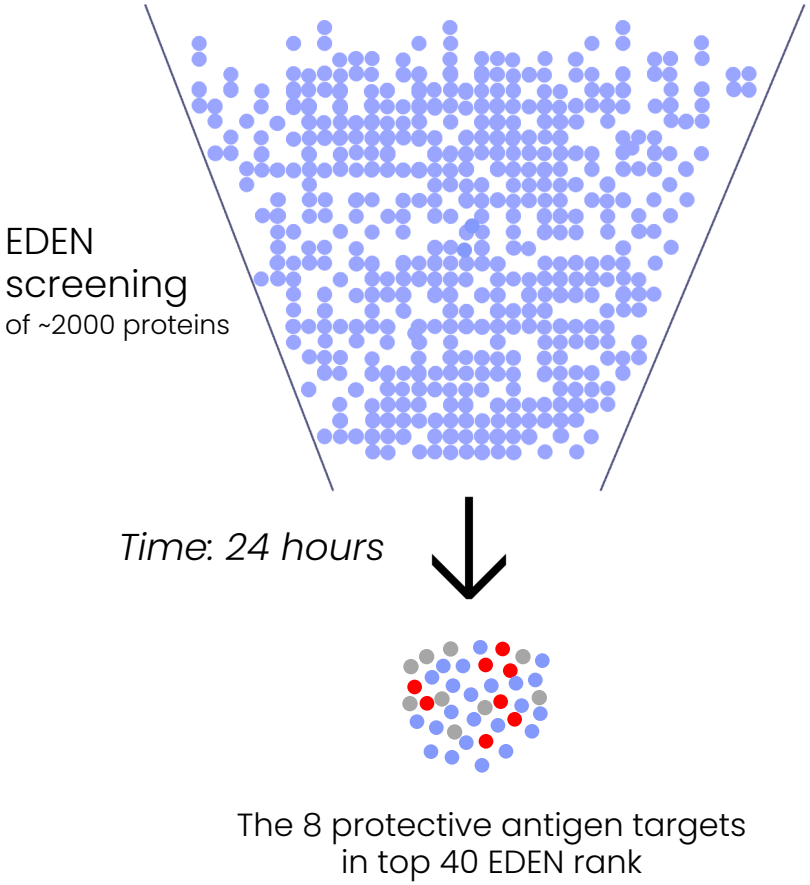
***S. aureus***




P < 0.01

# EDEN™ **Outperforms Reverse Vaccinology**



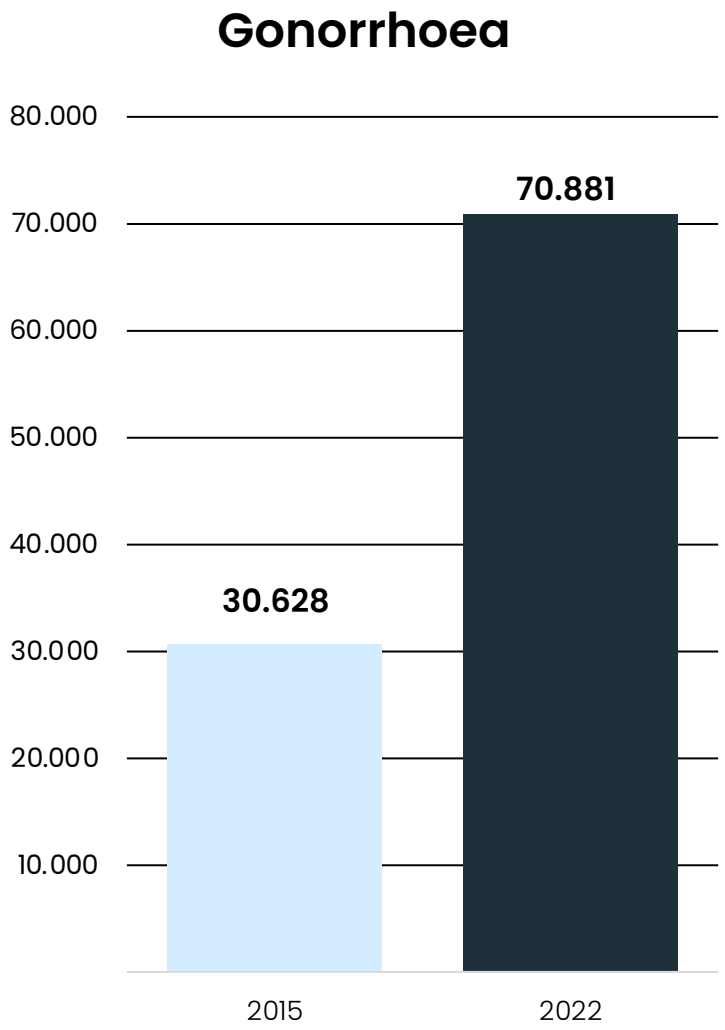








Source: Bensi G, et al. Mol Cell Proteomics. 2012 Jun; DOI: 10.1074. PMID: 2228675
Source: Fritzer A. et al. Infection and Immunity. 2010;78(9); DOI: 10.1128. PMID: 20624906

# **Gonorrhea** Skyrockets Today



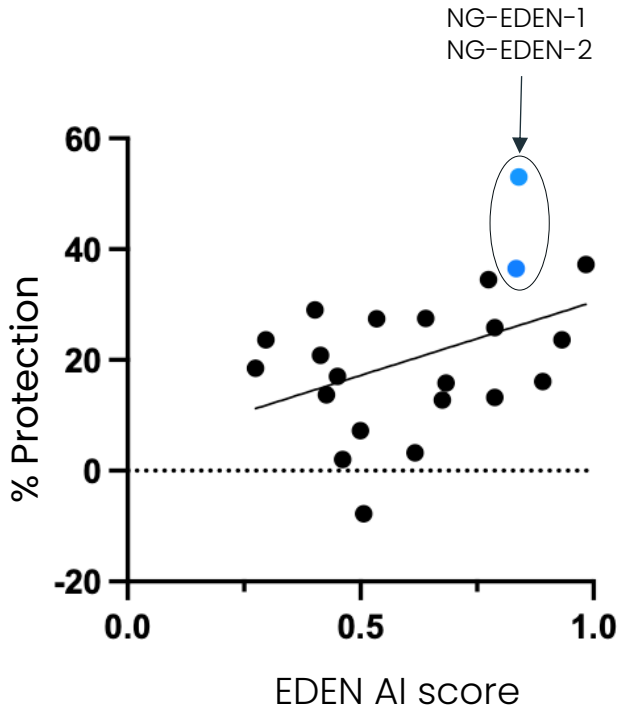

- Gonorrhea is a sexually transmitted disease caused by infection with the ***Neisseria gonorrhoeae*** **bacterium**
- *N. gonorrhoeae* infections are often **without symptoms and untreated**
- CDC classifies gonorrhea as an **urgent threat due to increasing antibiotic resistance**
- **Untreated gonorrhea can cause**
  - Lethal sepsis
  - Blindness of newborns
  - Infertility
  - Pregnancy complications
  - Permanent damage to nervous system
  - Permanent damage to cardiovascular system
  - Chronic pain

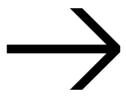


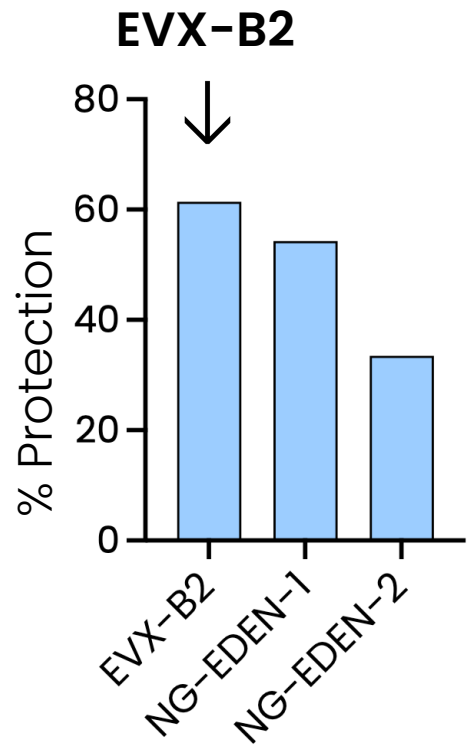
Source: ECDC Surveillance Atlas of Infectious Diseases

# EVX-B2: Two **Superior Top Ranked EDEN™** Antigens

Multiple
*N. gonorrhoeae*
strain proteomes
processed by
EDEN™ AI model

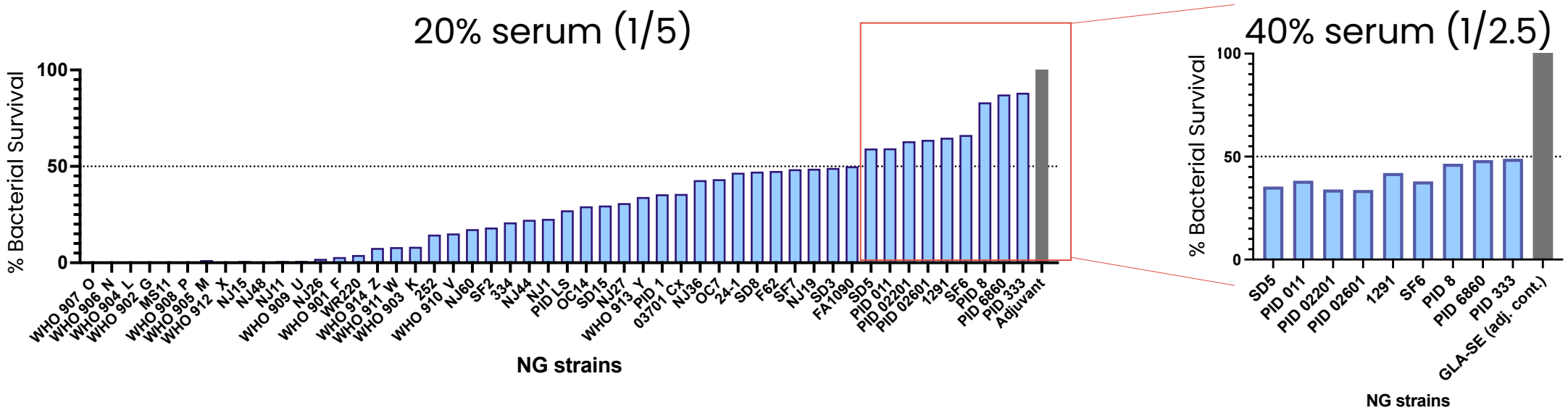





Source: Gulati S et al. mBIO 2023 Oct 31; DOI: 10.1128/mbio.02500-23. PMID: 37905891

# EVX-B2 Shows Unprecedented **Broad Bacteria Killing**

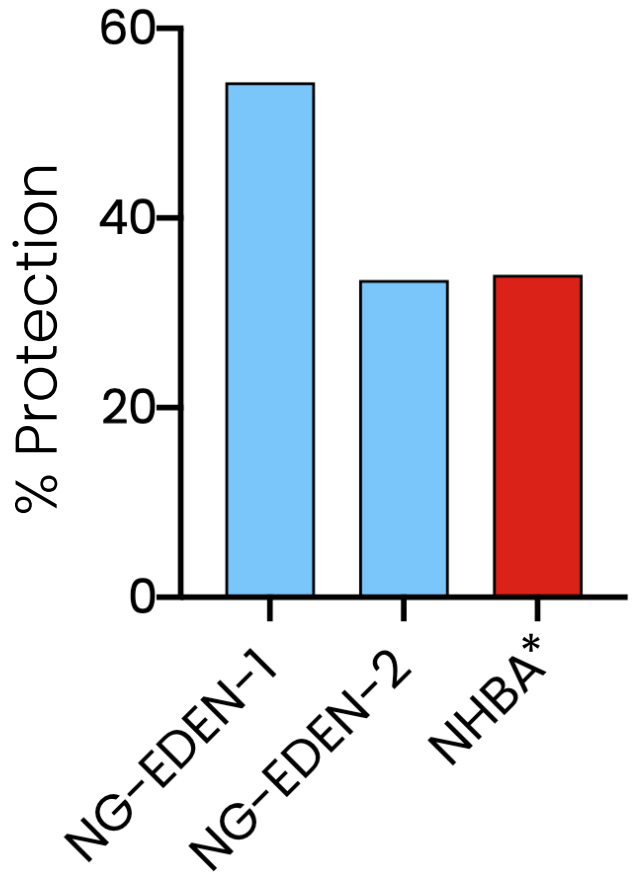
Bactericidal efficacy against a panel of 50 clinically relevant strains






Source: Gulati S et al. mBIO 2023 Oct 31; DOI: 10.1128/mbio.02500-23. PMID: 37905891

# EVX-B2 Antigen Shows **Stronger Protection** than Clinical Lead Antigen (NHBA)

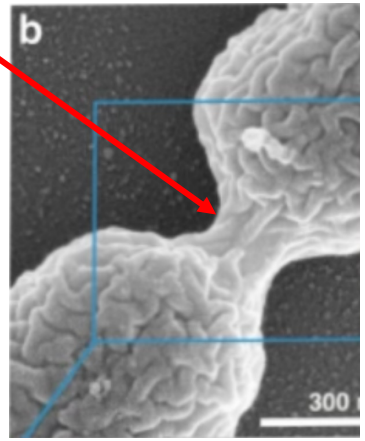





* N.B: GSK, LimmaTech and Griffith University collaborate on developing a Ng vaccine including the NHBA antigen

# EDEN™ Identifies **New Class of Antigens** with Potential **Broad Applicability**

EVX-B2 antibodies attack the weak spot of the bacteria!




Targeting bacteria during cell division

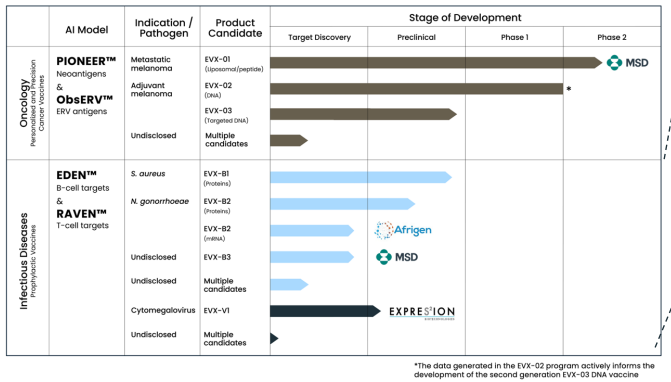


Source: Gulati S et al. mBIO 2023Oct 31; DOI: 10.1128/mbio.02500-23. PMID: 37905891

# EDEN™ is **Behind Several** of Evaxion's Infectious Disease **Product Candidates**

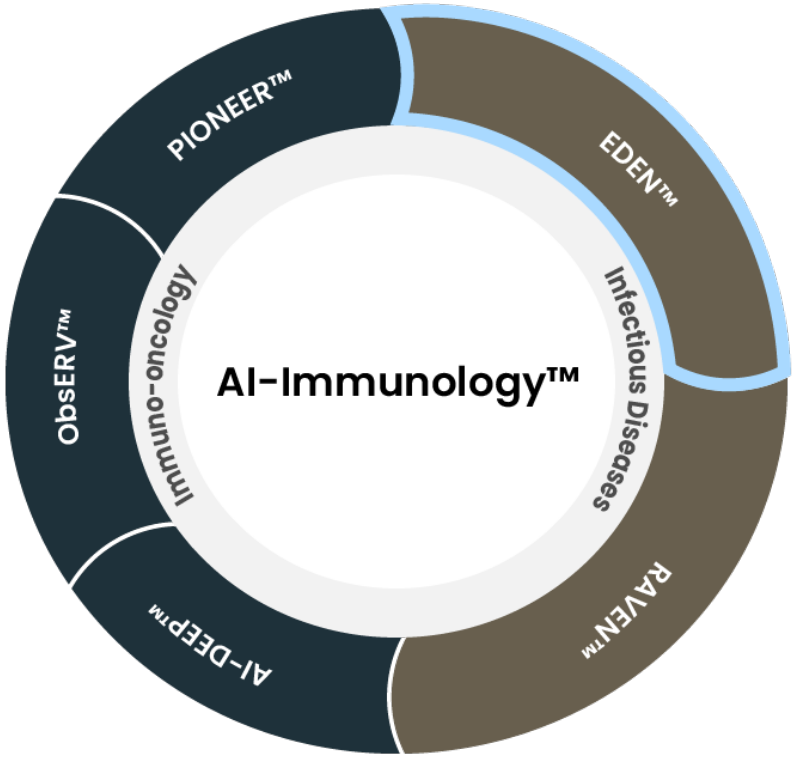
| | AI Model | Indication / Pathogen | Product Candidate | Stage of Development: Target Discovery | Preclinical | Phase 1 | Phase 2 |
|---|---|---|---|---|---|---|---|
| Infectious Diseases – Prophylactic Vaccines | **EDEN™** B-cell targets & **RAVEN™** T-cell targets | *S. aureus* | EVX-B1 (Proteins) | | | | |
| | | *N. gonorrhoeae* | EVX-B2 (Proteins) | | | | |
| | | | EVX-B2 (mRNA) | | Afrigen | | |
| | | Undisclosed | EVX-B3 | | MSD | | |
| | | Undisclosed | Multiple candidates | | | | |
| | | Cytomegalovirus | EVX-V1 | | EXPRES²ION BIOTECHNOLOGIES | | |
| | | Undisclosed | Multiple candidates | | | | |

*The data generated in the EVX-02 program actively informs the development of the second generation EVX-03 DNA vaccine



# Summary

- EDEN™ AI-score correlates with protection identifying most protective antigens potentially enabling lower clinical risk
- EDEN™ outperforms reverse vaccinology for faster and cheaper vaccine discovery
- Our EVX-B2 vaccine is the solution against Gonorrhea
- EVX-B2 shows unprecedented broad bacteria killing
- EVX-B2 antigen shows stronger protection than clinical lead antigen (NHBA)
- EDEN™ identifies new class of antigens with potential broad applicability



# Q&A SESSION

# Agenda

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|---|---|
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| | |
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| 15.15 - 15.35 / 10.15 – 10.35 | **EDEN™** - Best-in-class model assessing protectiveness of B-cell antigens |
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| | |
|---|---|
| 16.15 - 16.35 / 11.15 – 11.35 | **PIONEER™** - Validated model for designing personalized Neoantigen vaccines |
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## SESSION 4 - Precision Cancer Concepts

| | |
|---|---|
| 17.15 - 17.35 / 12.15 – 12.35 | **AI-DEEP™** - Model for predicting responses to cancer CPI immunotherapy |
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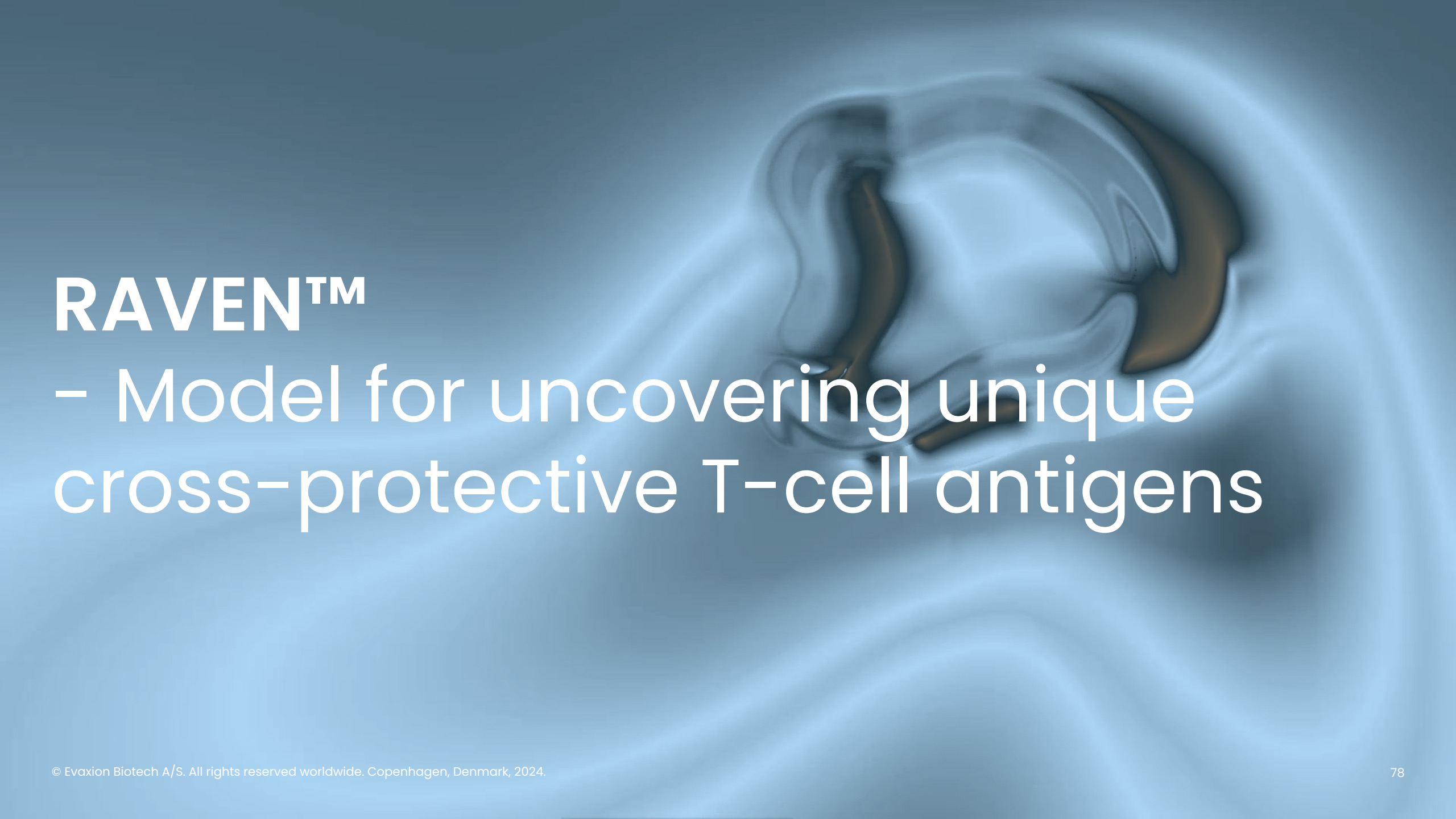
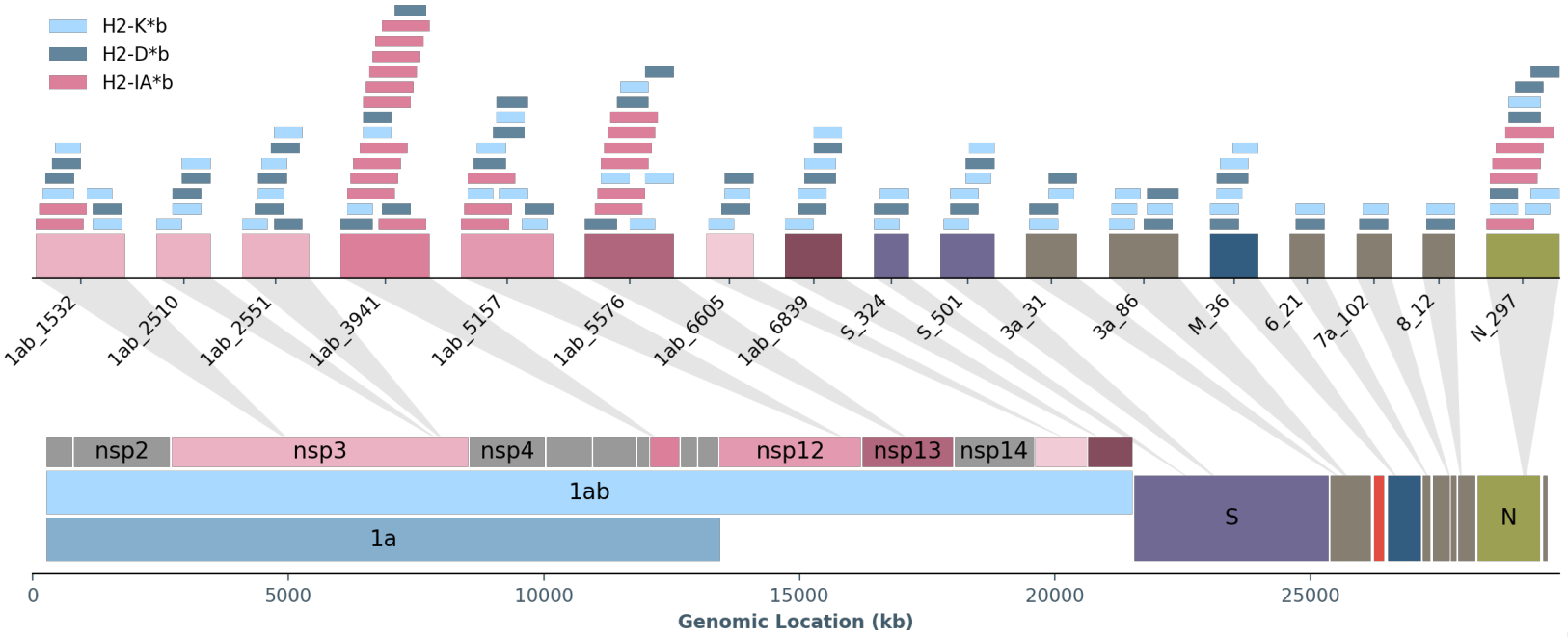
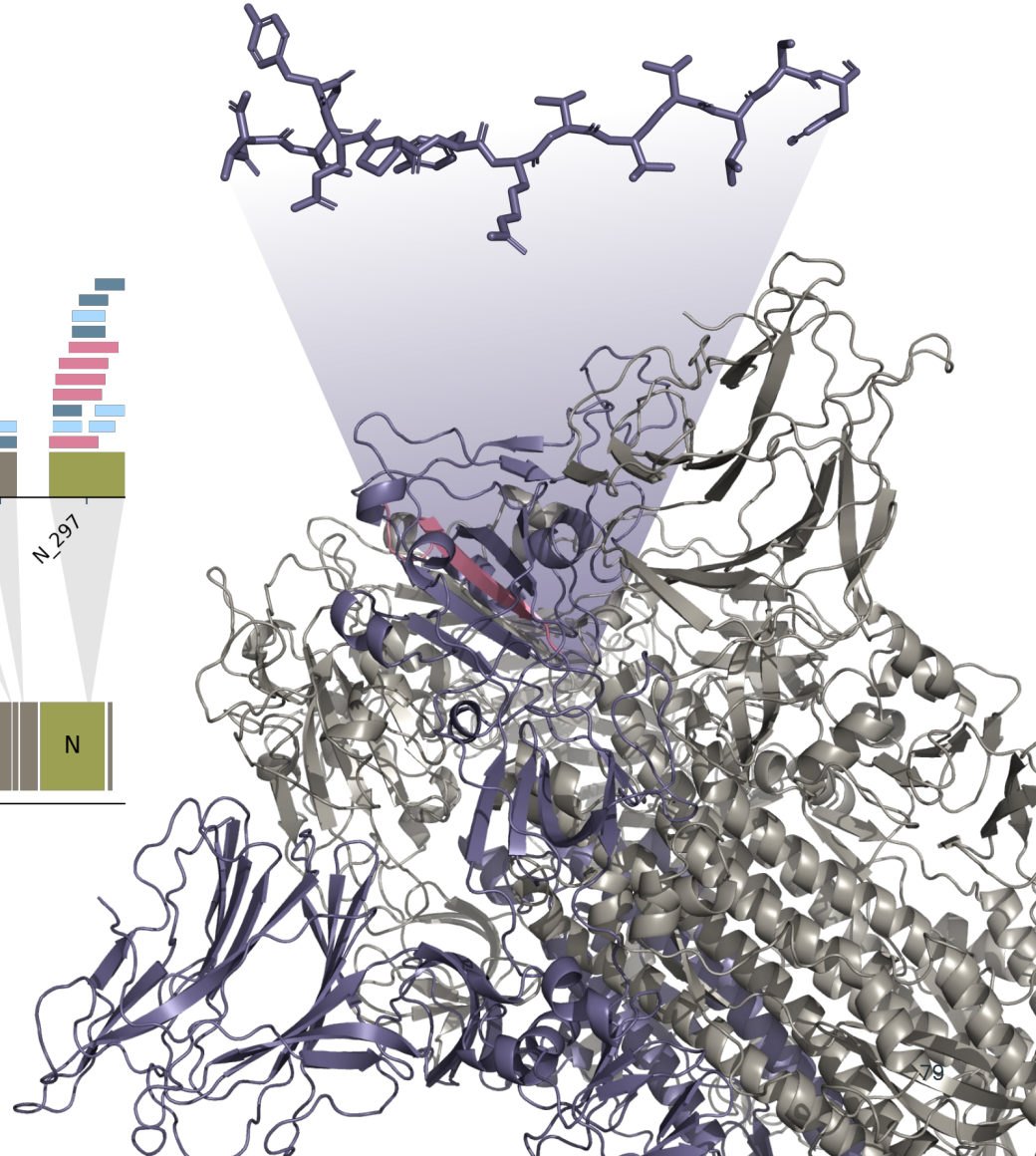
| 17.55 - 18.00 / 12.55 – 13.00 | *THANK YOU and concluding remarks* |
| 18.00 - 19.00 / 13.00 – 14.00 | *Reception with drinks and snacks* |

# RAVEN™
## – Model for uncovering unique cross-protective T-cell antigens

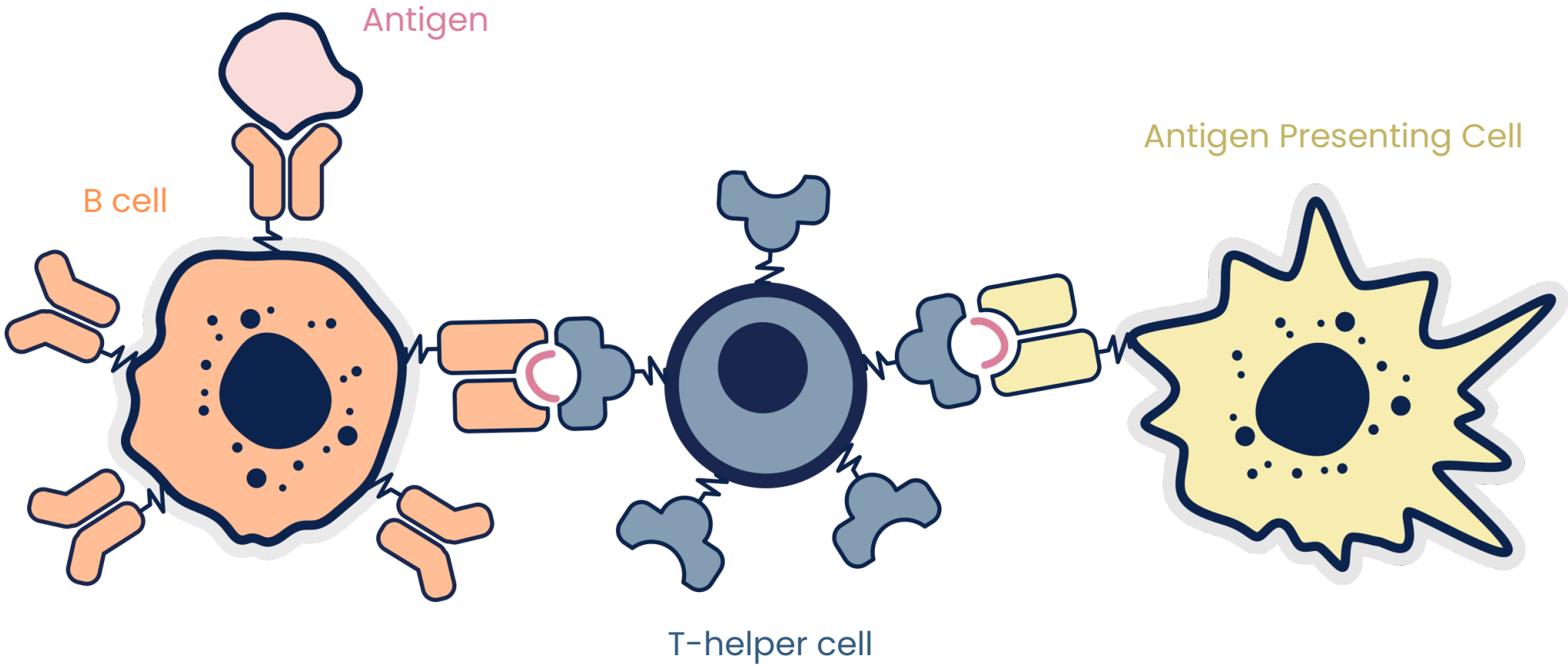


# RAVEN™ **Distills the Immunogenic Components** of a Pathogen down to an **Enhanced Subunit Vaccine**

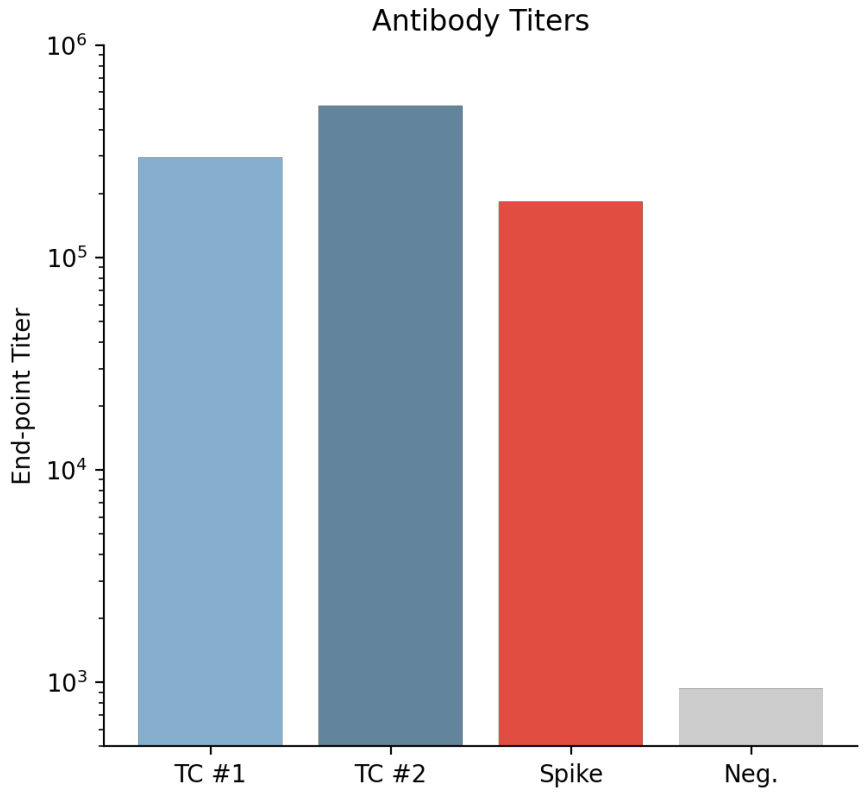


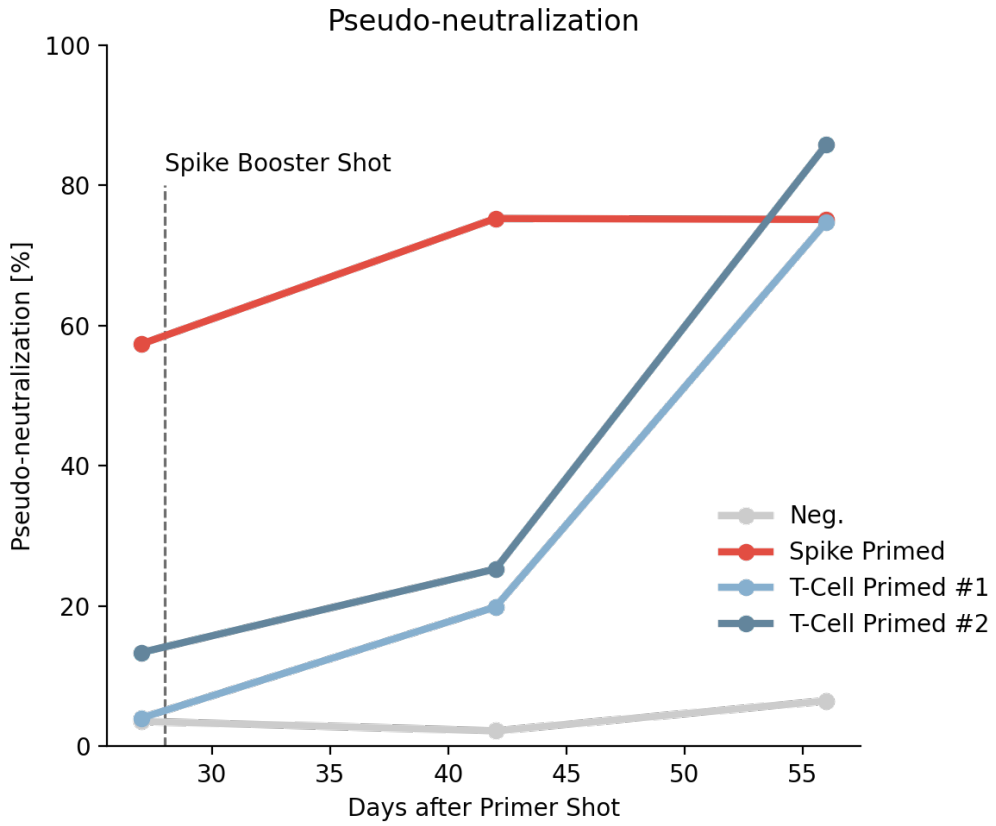



# T-Cell Epitopes Can **Boost** Subunit Vaccine **Efficacy** and **Response Time**

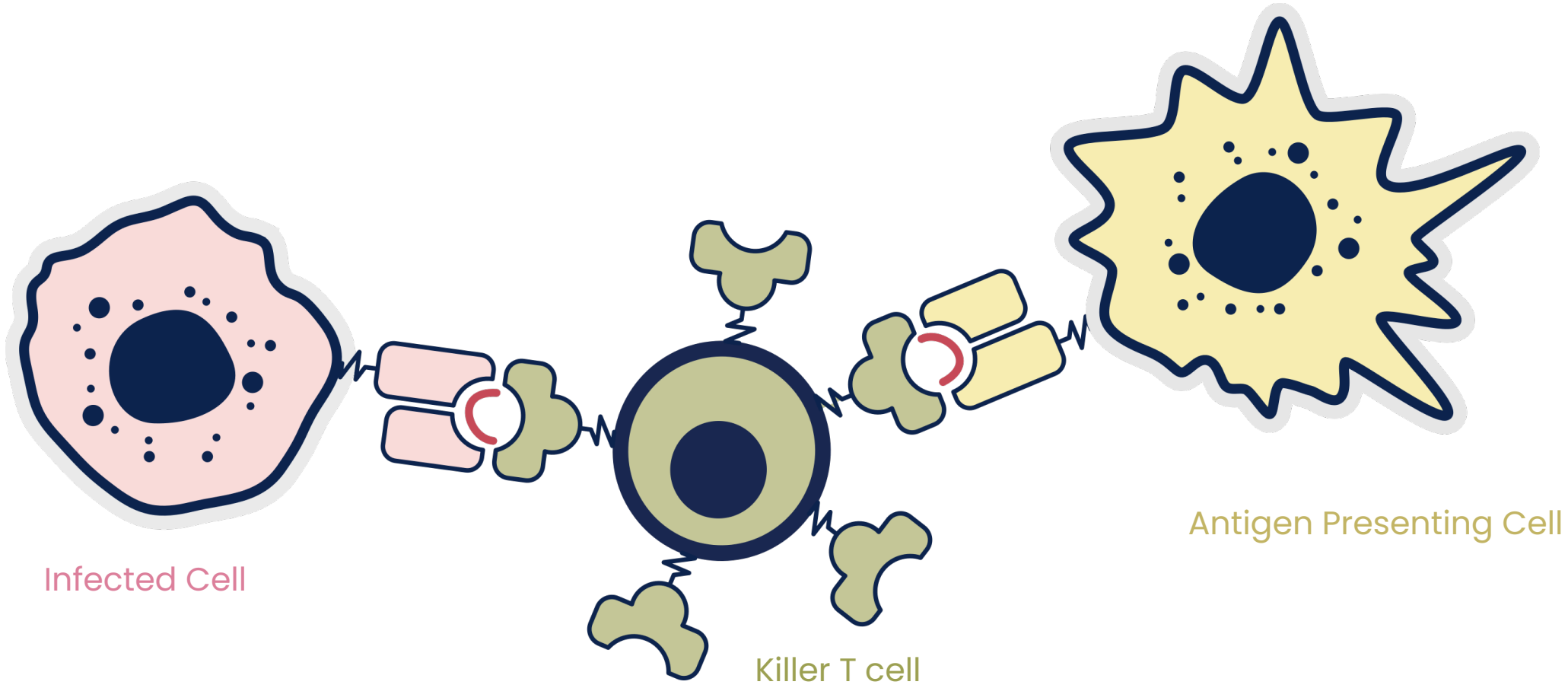


# RAVEN™ Designed **T-Cell Hotspot Primer** Enables **One-Shot Antibody Titers**



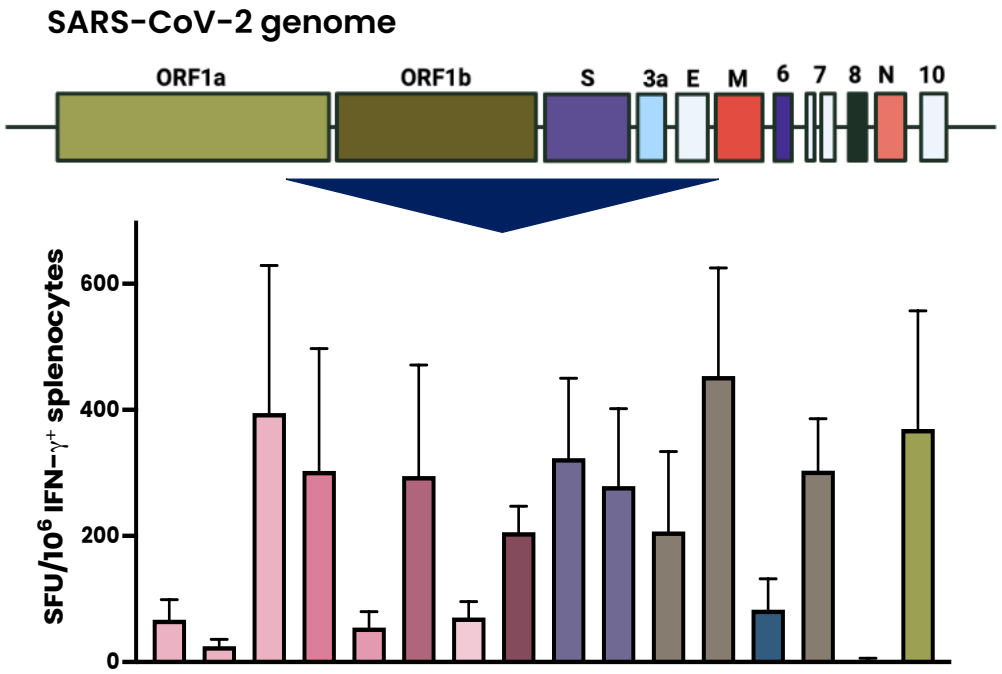



# T-Cell Epitopes Can Provide **Protection** Against Infectious Pathogens

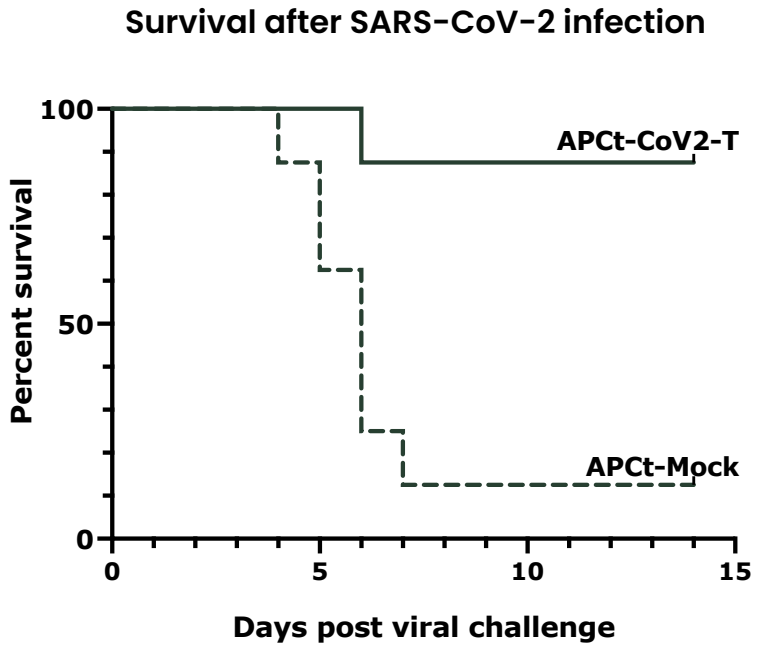


# RAVEN™ Designed T-Cell Hotspot Vaccine Provides **Significant Protection** Against Lethal Challenge

Verified **IFN-$\gamma$ response** towards 88% (15/17) of the included hotspots




Vaccination with T-cell epitopes alone is sufficient for **protection against lethal infection** in K18-hACE2/BL6 mice






Persson et al. Front Immunol. 2023 Apr 11;14:1166546. doi: 10.3389/fimmu.2023.1166546. PMID: 37114047

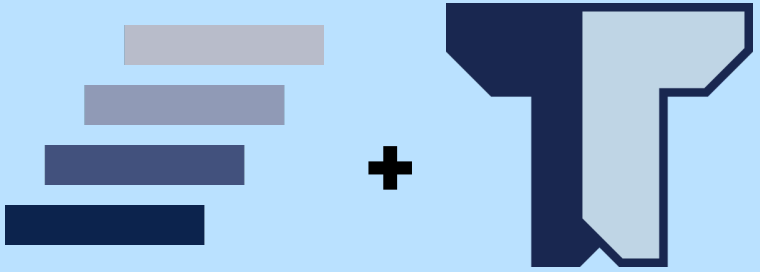
# RAVEN™ Enables **Multiple Strategies** for T-Cell Vaccine Integration

### Stand-Alone T-Cell Vaccine

- Extremely fast to produce
- Can elicit broad but limited protection

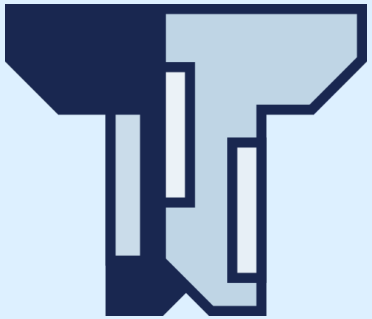
### T-Cell Primer Vaccine

- Extremely fast to produce
- Improves onset and quality of antibody eliciting vaccines



### T-Cell Grafted Vaccine

- Simpler distribution and delivery
- Broadest possible antibody response

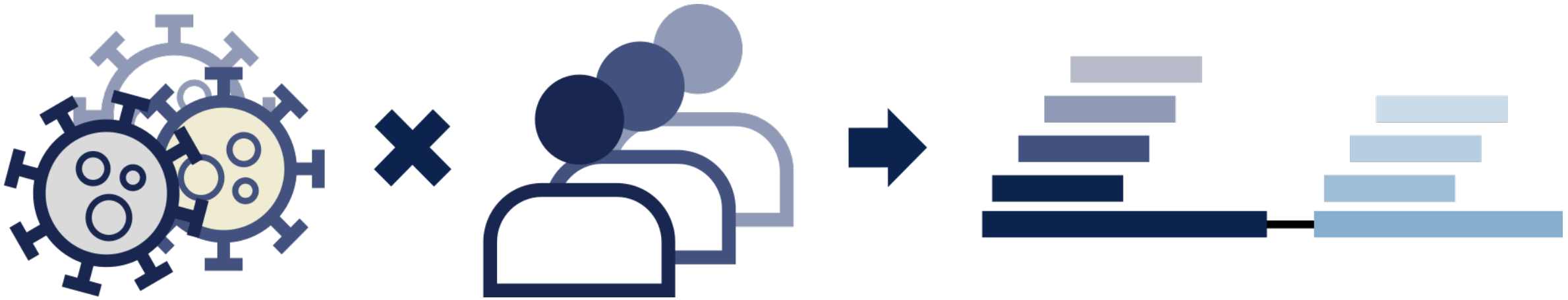


# RAVEN™ Models the **Crucial Components** for a **Cytotoxic** and **Helper T-Cell Response**

1. Viral Genomes

2. Target Population

3. Optimal T-Cell Hotspots



Expression

Viral antigens

Antigen conservation

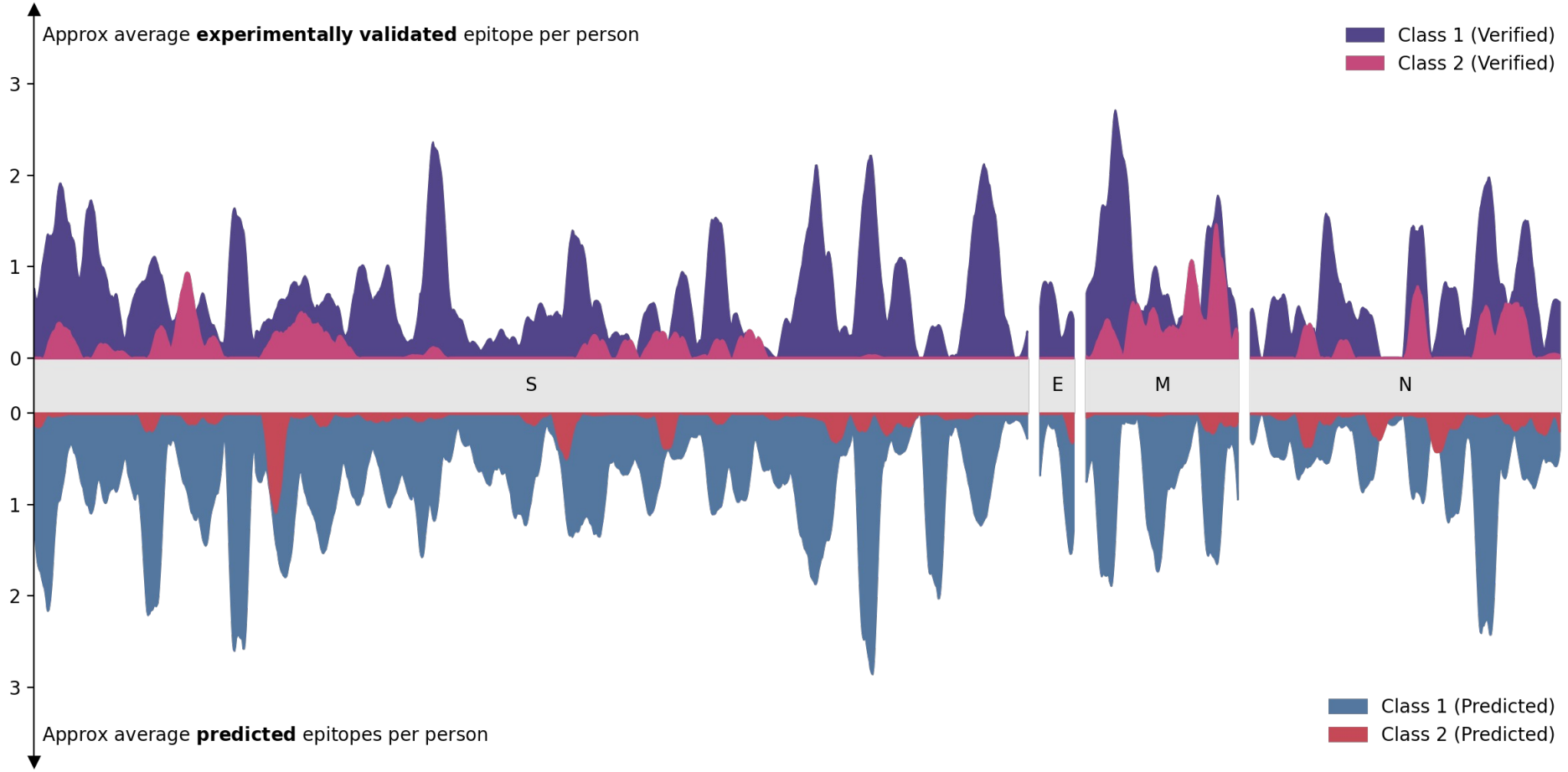
Epitope hotspots

HLA frequencies

EvaxMHC

Precision design

# Using EvaxMHC, RAVEN™ Can Find **Key Immunogenic Hotspots** in Days



# RAVEN™ Includes Modules for **Structural Modelling**

4. B-Cell Antigen
- EDEN™ Selected
- Viral Glycoprotein

5. Enhanced B-Cell Antigen
- Epitope Grafting
- Structure Stabilization

Precision design

Antigen conservation

Bacterial antigens

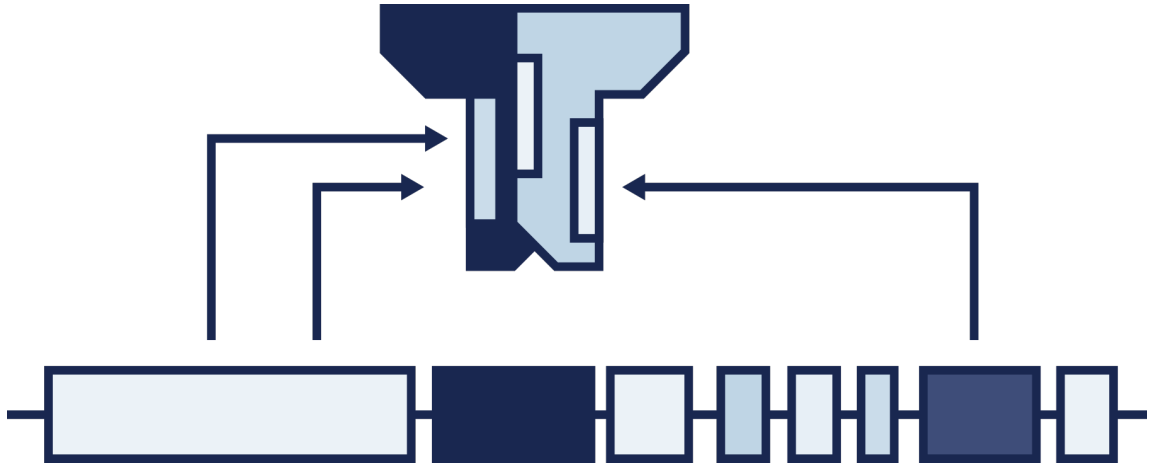
B-cell antigen modelling

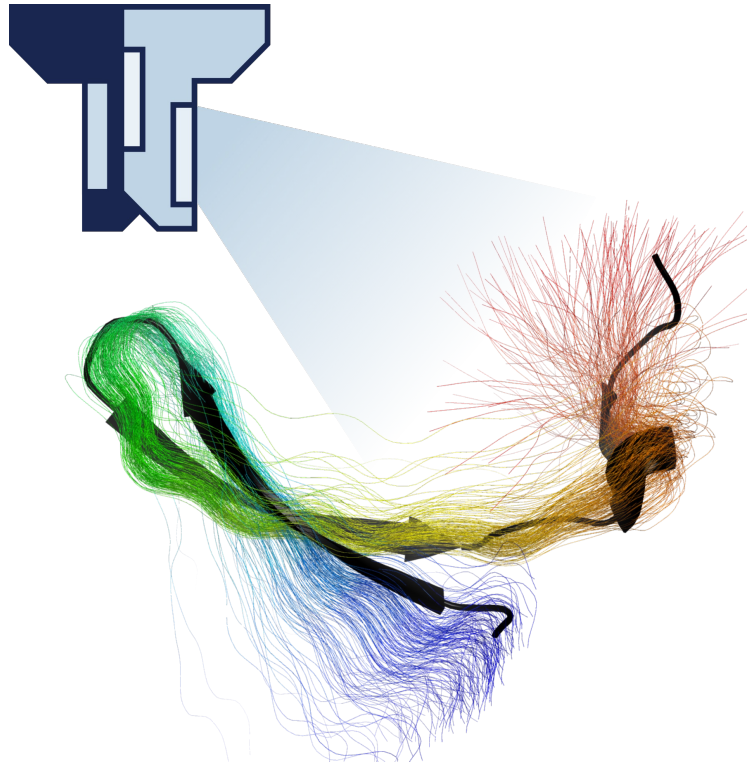
B-cell antigen design

BIFROST

# **Intelligent Grafting** of T-Cell Epitopes **Into B-Cell Antigens** is under development

RAVEN identified T-cell epitopes can be grafted into B-cell antigens using AI autoencoders





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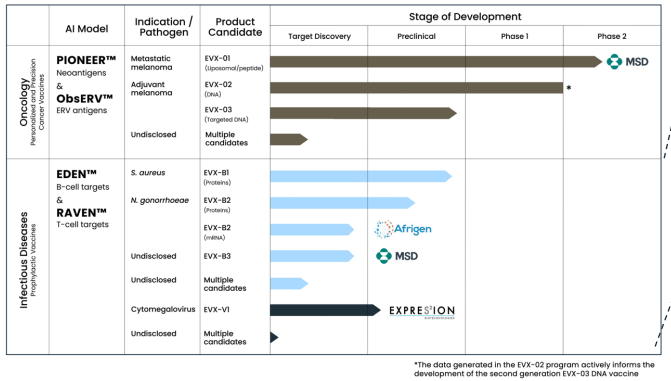
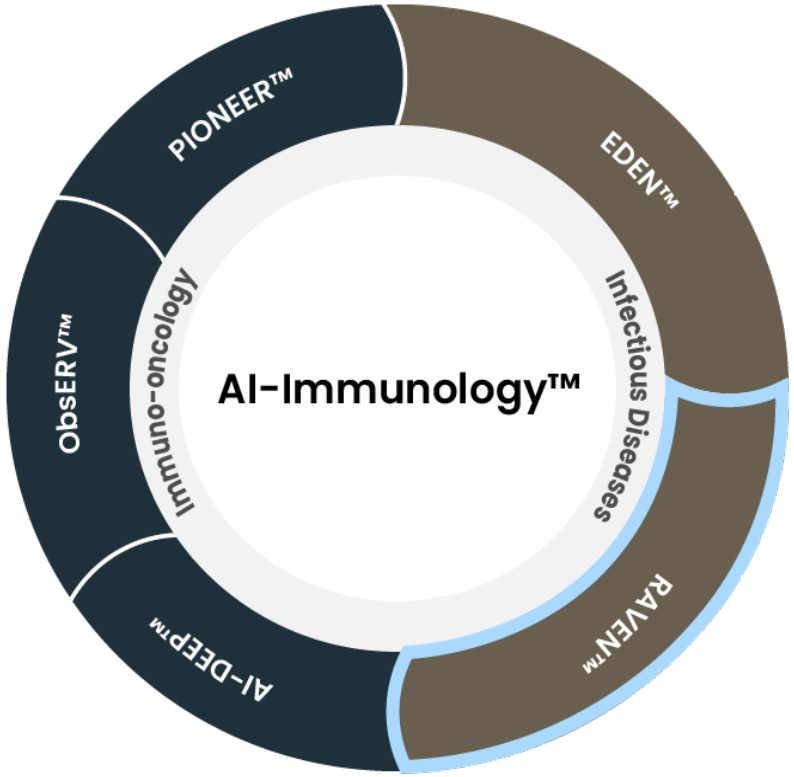



| | AI Model | Indication / Pathogen | Product Candidate | Stage of Development | | | |
|---|---|---|---|---|---|---|---|
| | | | | Target Discovery | Preclinical | Phase 1 | Phase 2 |
| Infectious Diseases<br>Prophylactic Vaccines | **EDEN™**<br>B-cell targets<br>&<br>**RAVEN™**<br>T-cell targets | Undisclosed | EVX-B3 | | MSD | | |
| | | Undisclosed | Multiple candidates | | | | |
| | | Cytomegalovirus | EVX-V1 | | EXPRES²ION BIOTECHNOLOGIES | | |
| | | Undisclosed | Multiple candidates | | | | |

# Summary

- RAVEN is designed to find efficacious T-cell hotspots
- RAVEN can design protective T-cell vaccines using technology from our personalized rapid production
- RAVEN can choose T-cells to boost efficacy of B-cell vaccine candidates



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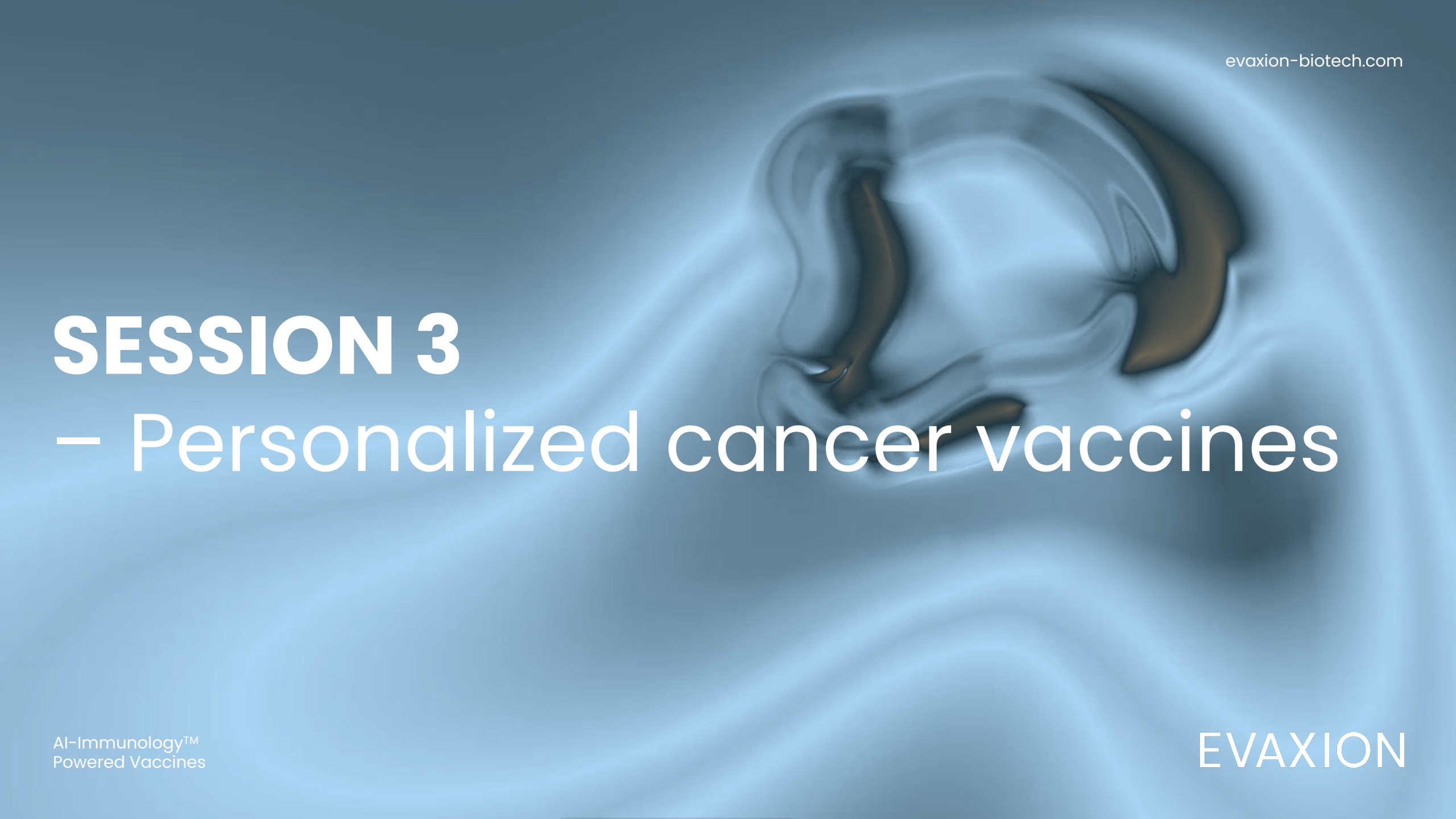
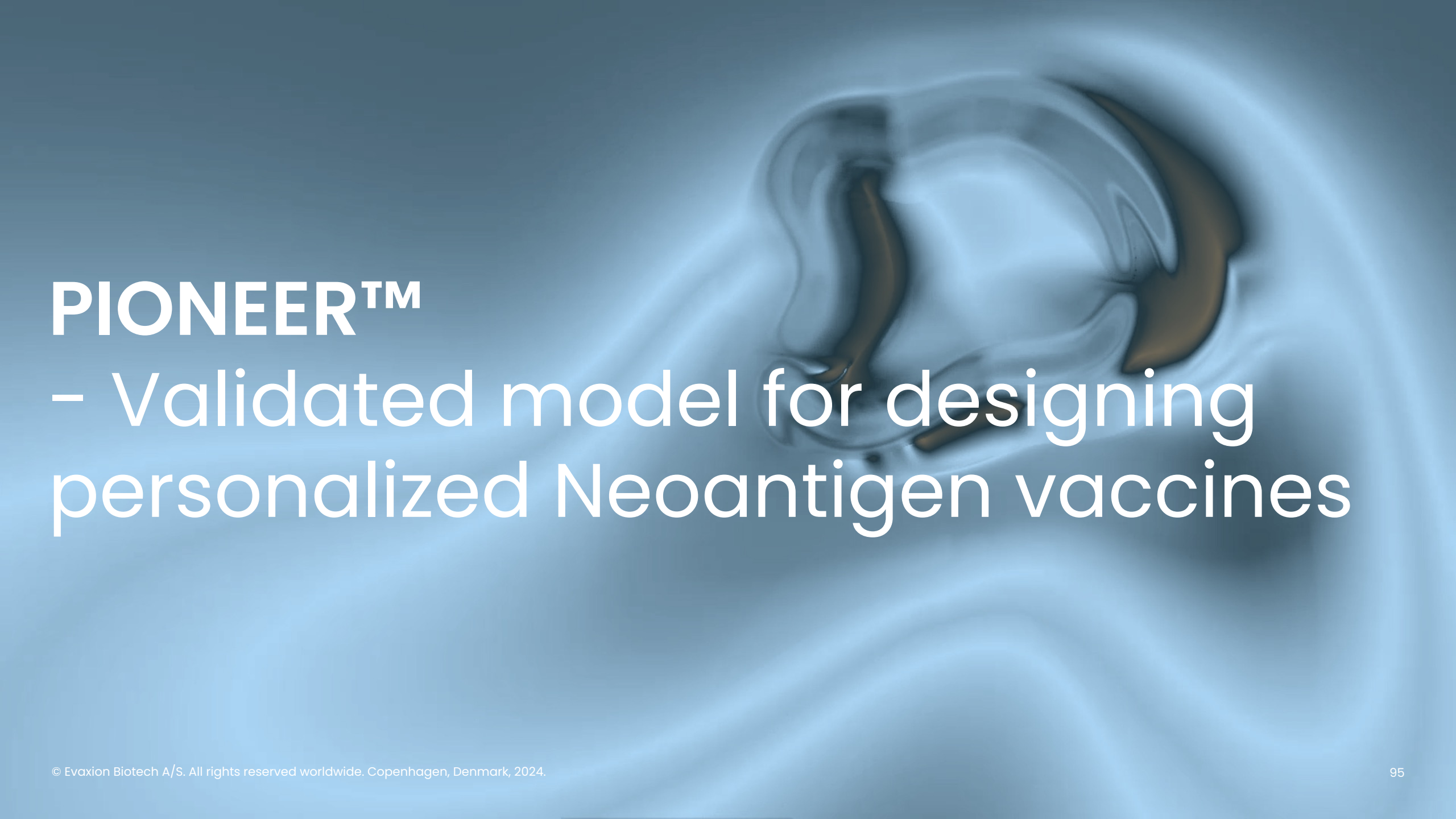


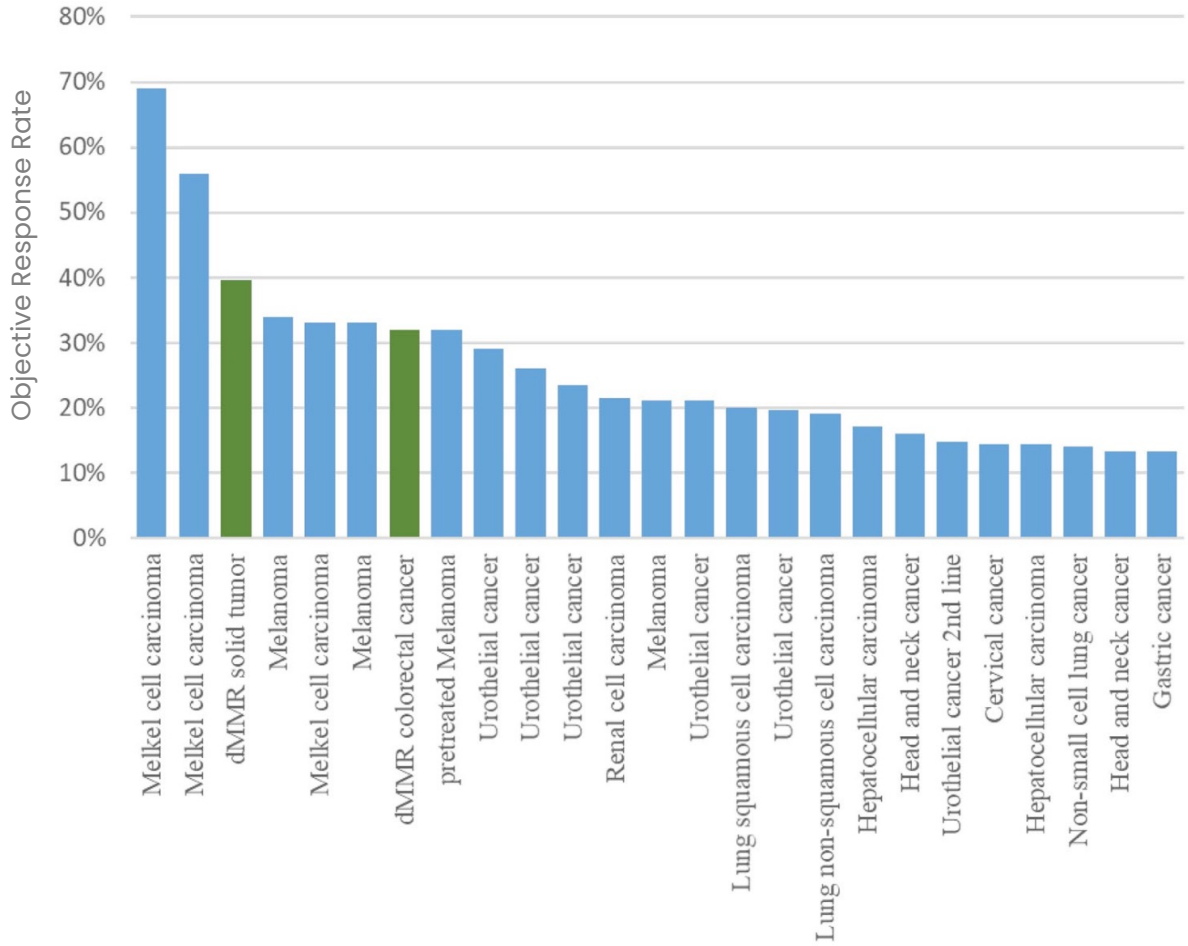
# SESSION 3
## – Personalized cancer vaccines

# PIONEER™
- Validated model for designing personalized Neoantigen vaccines



# Despite the Advent of Cancer Immunotherapy there is Still a **Need for Better Cancer Treatments**

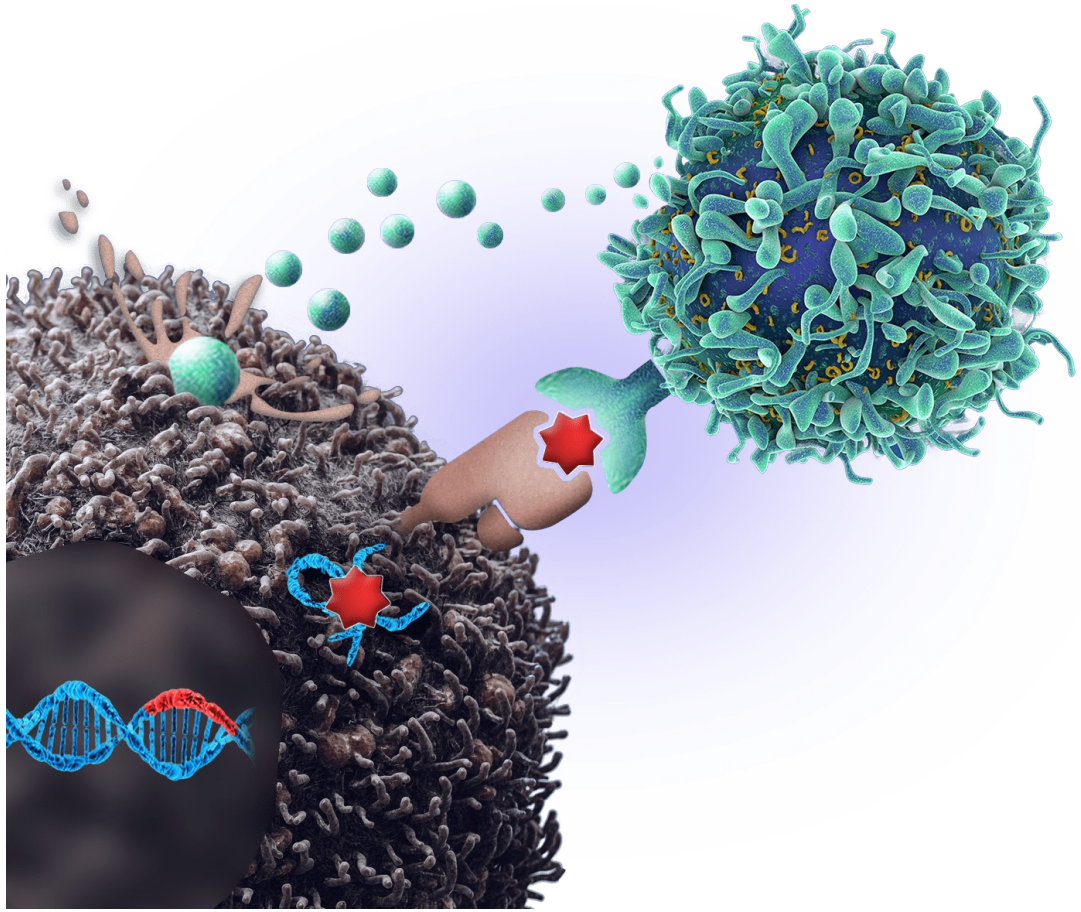
- Cancer immunotherapy based on checkpoint inhibitors (CPI) has revolutionized the treatment of previously untreatable cancers such as melanoma
- Only 20-30% of cancer patients respond to CPI treatment, highlighting the need for improved treatment options






Mishima *et al.* (2020). Int J Clin Oncol *25*, 217–239. 10.1007/s10147-019-01498-8

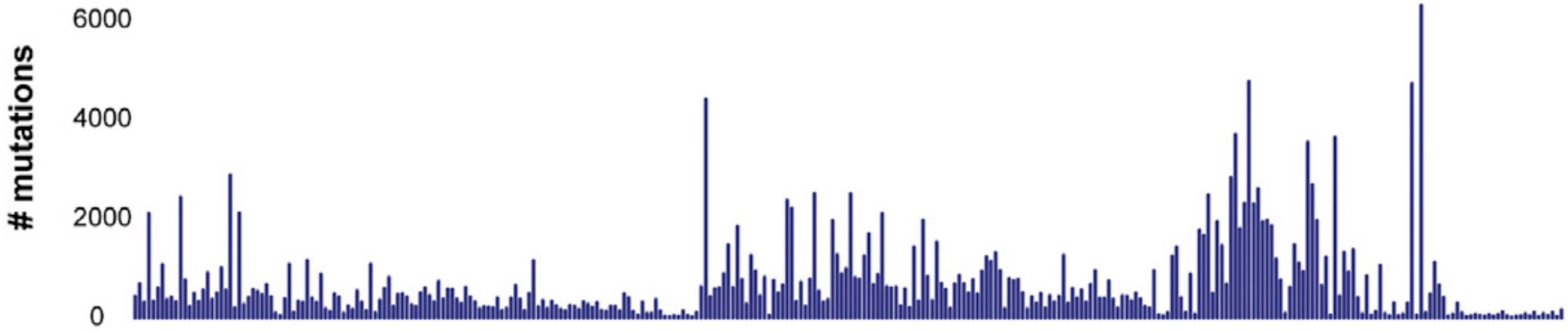
# Neoantigen-Based Cancer Vaccines are the **Next Evolution of Cancer Immunotherapies**



Neoantigens are ideal cancer vaccine targets that:

- arise from cancer-specific DNA mutations
- are found specifically in tumors and absent from normal tissues
- elicit potent, highly specific immune responses
- synergize with current cancer immunotherapies

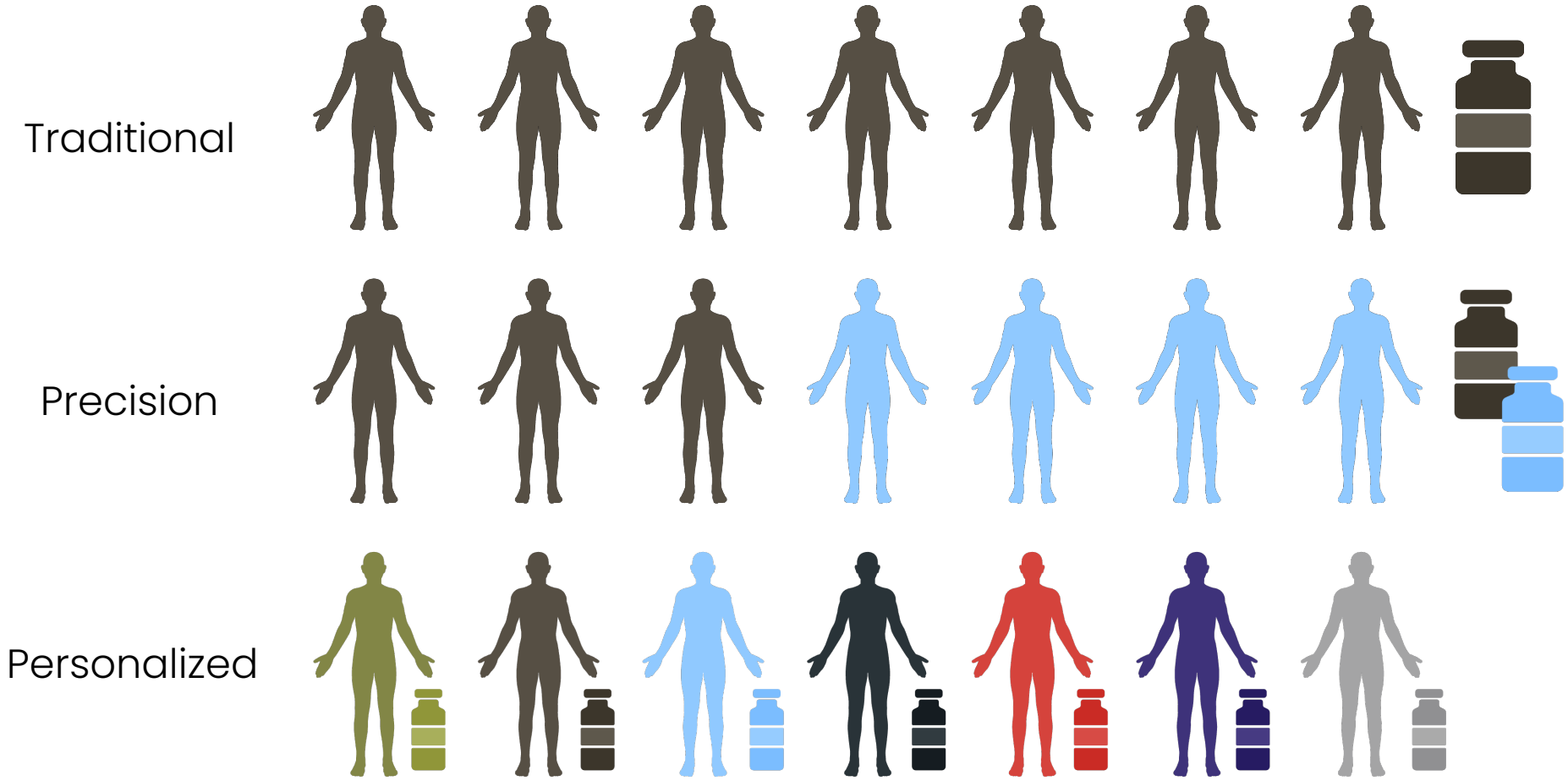
# Cancer Patients Have **Distinct Neoantigens Hindering** the Development of a **Universal Neoantigen Vaccine**






Cancer Genome Atlas Network (2015). Cell *161*, 1681–1696. 10.1016/j.cell.2015.05.044.

# Future Cancer Treatments Will Be **Tailored** More Specifically to **Each Patient**



# How We Built **PIONEER™**

## PIONEER™

| | | | |
|---|---|---|---|
| SNVs | Frameshifts | Gene fusions | HLA loss |
| Clonality | Expression | Neoantigens | |
| EvaxMHC | HLA typing | Distance to self | |
| Antigen quality | Antigen safety | Personalized design | |

## 1 DISEASE DECODING

| | | | |
|---|---|---|---|
| SNVs | Frameshifts | Gene fusions | HLA loss |
| ERV antigens | TME impact | Clonality | Expression |
| Bacterial antigens | Viral antigens | Antigen conservation | Treatment effect |
| Neoantigens | | | |

## 2 IMMUNE RESPONSE DECODING

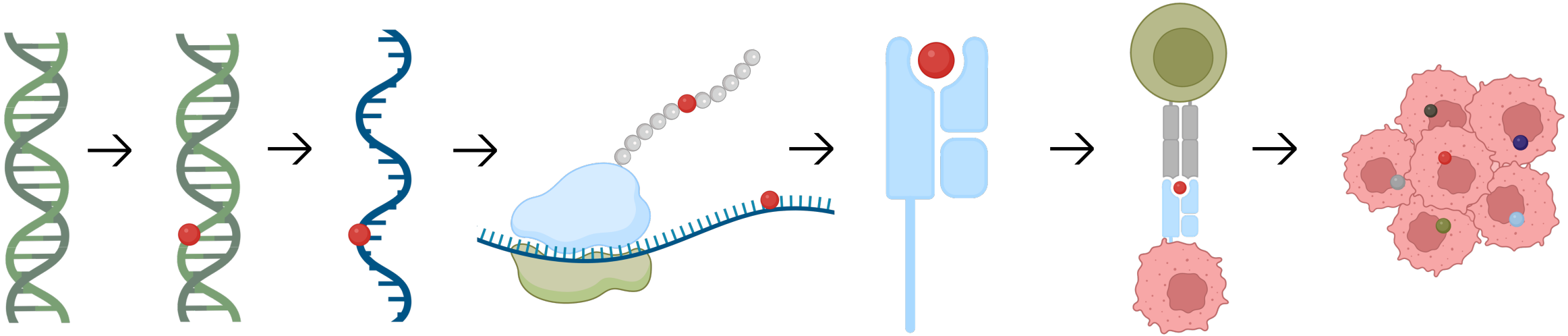
| | | | |
|---|---|---|---|
| EvaxMHC | HLA typing | HLA frequencies | Distance to self |
| Protective antigens | Epitope hotspots | | |

## 3 VACCINE DESIGN

| | | | |
|---|---|---|---|
| Antigen quality | Antigen safety | B-cell antigen modelling | B-cell antigen design |
| Precision design | Personalized design | BIFROST | Neoantigens |

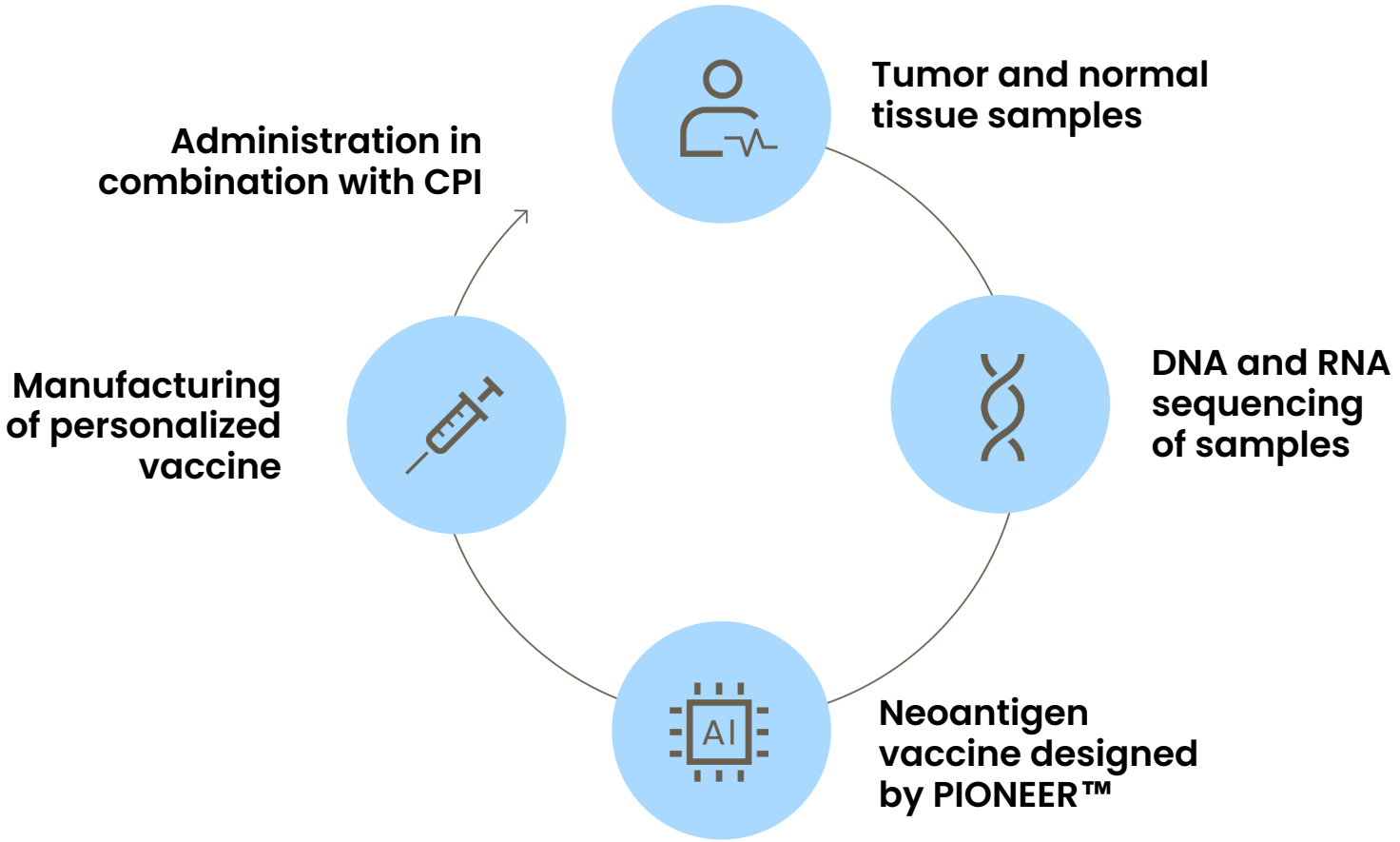
# **PIONEER™ Models the Mechanisms** Inside Cancer Cells that Generate Effective Neoantigens for Cancer Vaccines

1. Cancer-specific mutation
2. Expression
3. Translation
4. Presentation on MHC
5. T-cell response
6. Clonal neoantigens

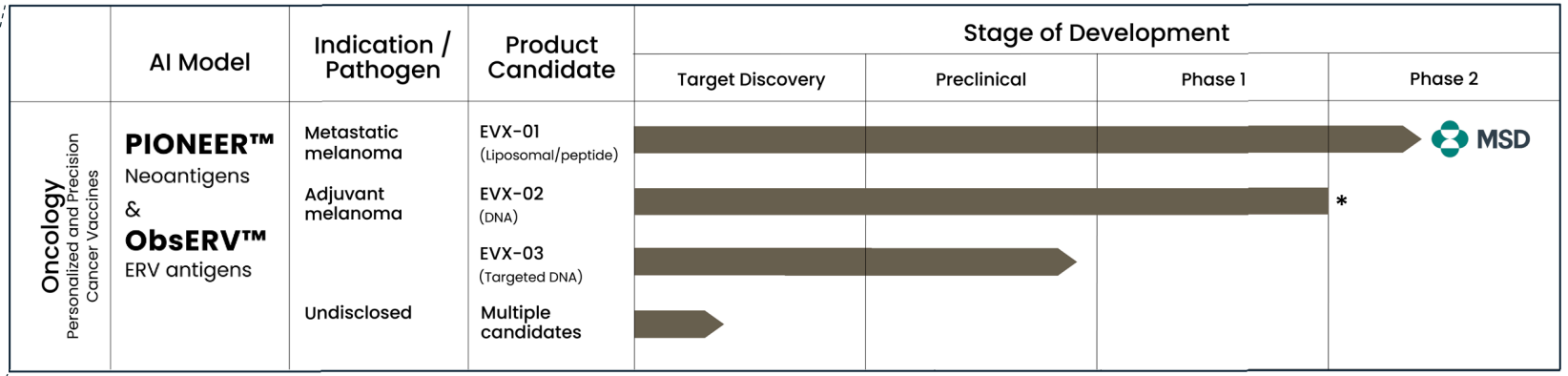


- SNVs
- Frameshifts
- Gene fusions
- Expression
- Neoantigens
- EvaxMHC
- HLA typing
- HLA loss
- Distance to self
- Antigen quality
- Antigen safety
- Personalized design
- Clonality

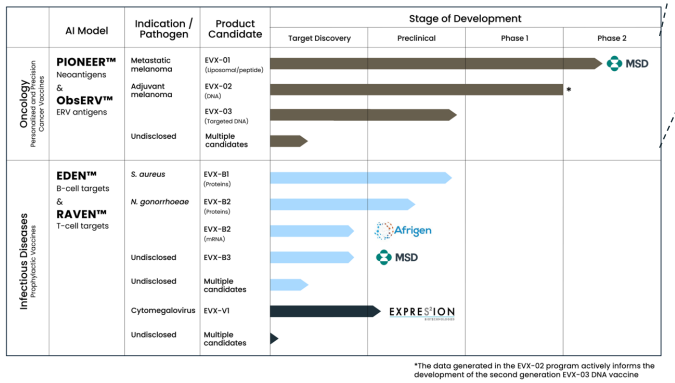
# PIONEER™ is Part of a Larger **Process from Patient Tumor to Treatment**



# PIONEER™ is **Behind Several** of Evaxion's Oncology **Product Candidates**

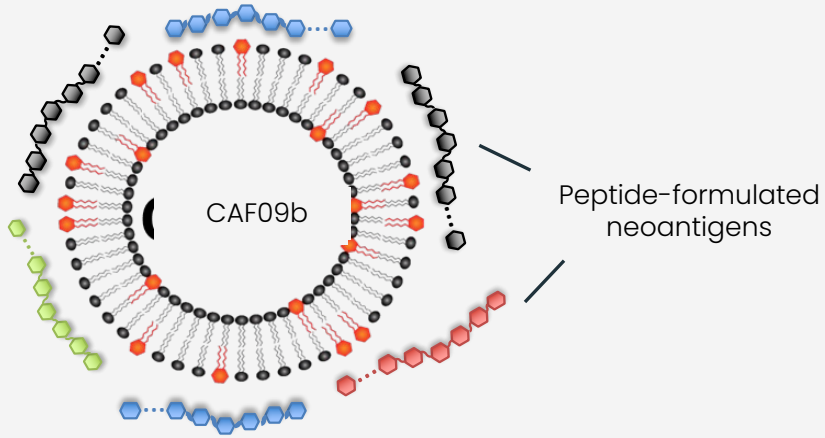



*The data generated in the EVX-02 program actively informs the development of the second generation EVX-03 DNA vaccine



# **EVX-01** - Personalized Neoantigen Vaccine in Metastatic Melanoma

**EVX-01**



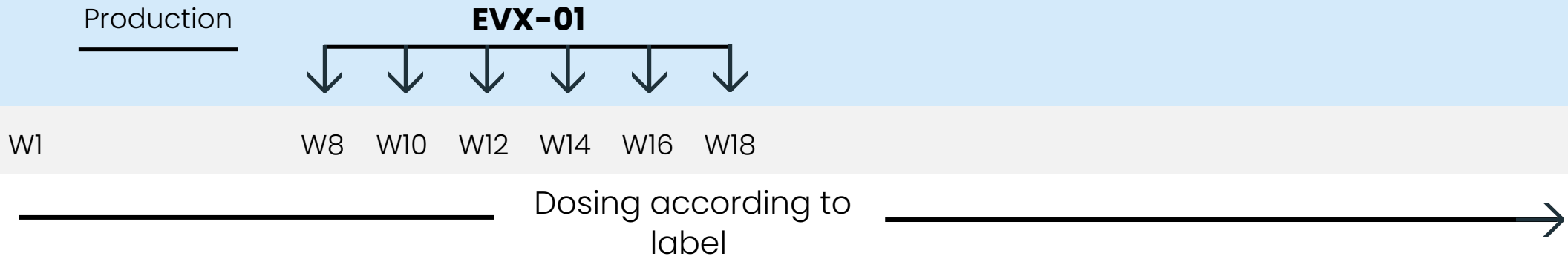

Phase 1 clinical trial (NCT03715985)

Stage IV Metastatic melanoma (N=12)

Primary endpoint: Safety and tolerability

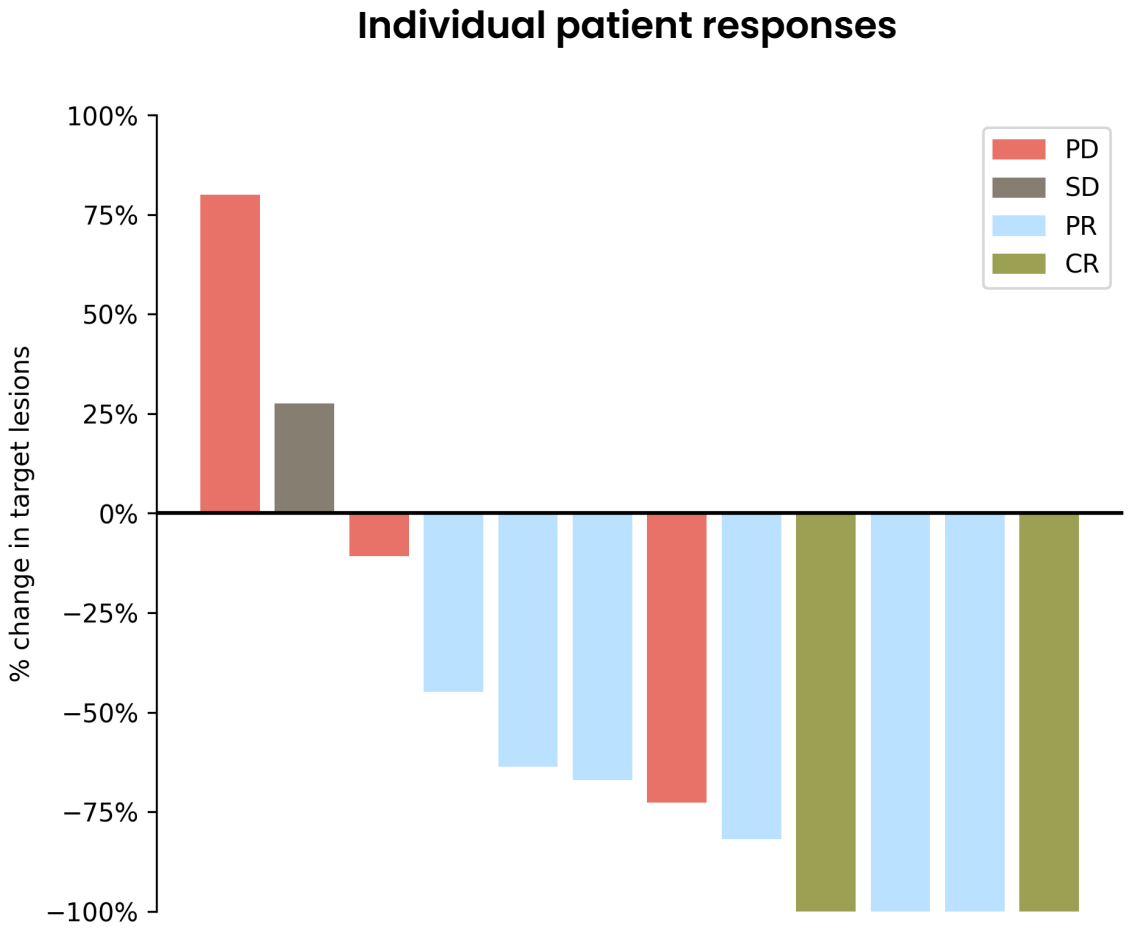
Selected secondary endpoint:
- Immune response induced by **EVX-01**

CAF09b liposomal adjuvant



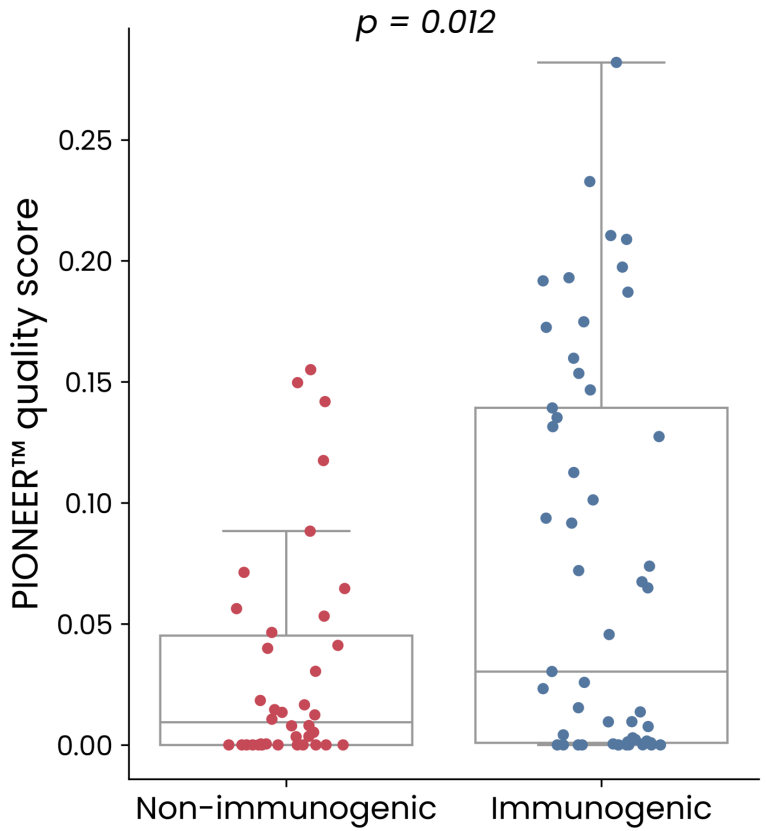
# **EVX-01** - Strong Phase 1 Clinical Data

- Trial met the primary endpoint
- Neoantigen-specific immune response in all patients
- Clinical response in 8 out of 12 patients with 2 complete responders

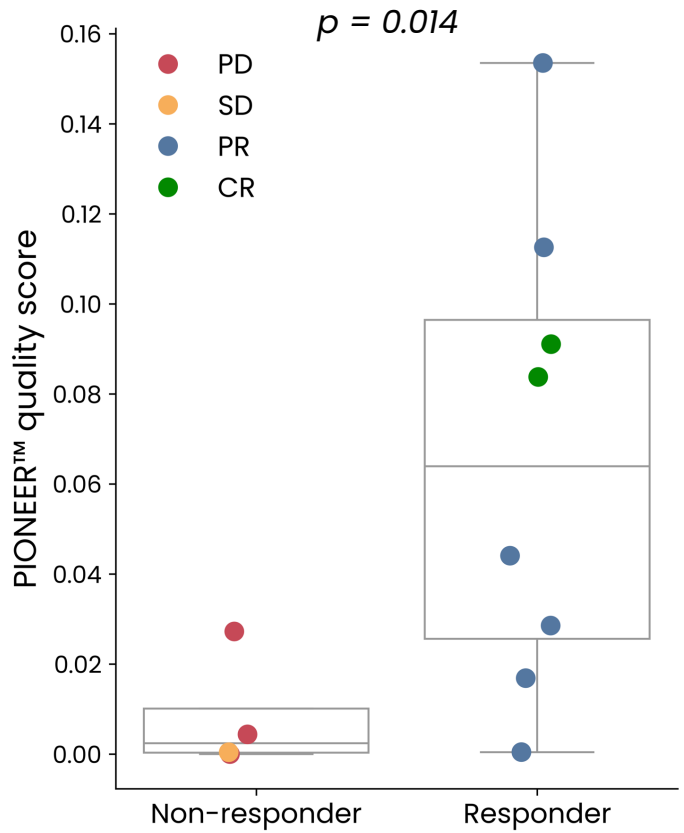


# PIONEER™ Scores **Predict Immunogenicity & Clinical Response**

Neoantigens with higher PIONEER™ scores are more likely to be immunogenic

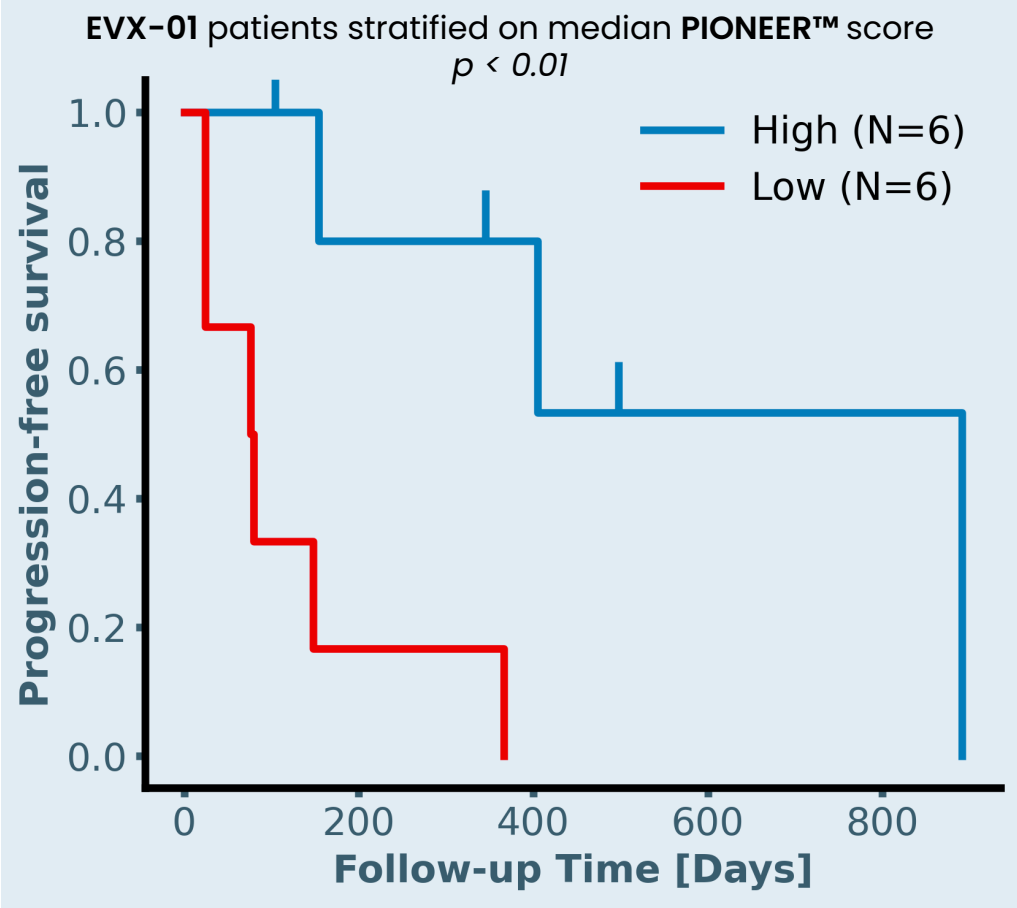


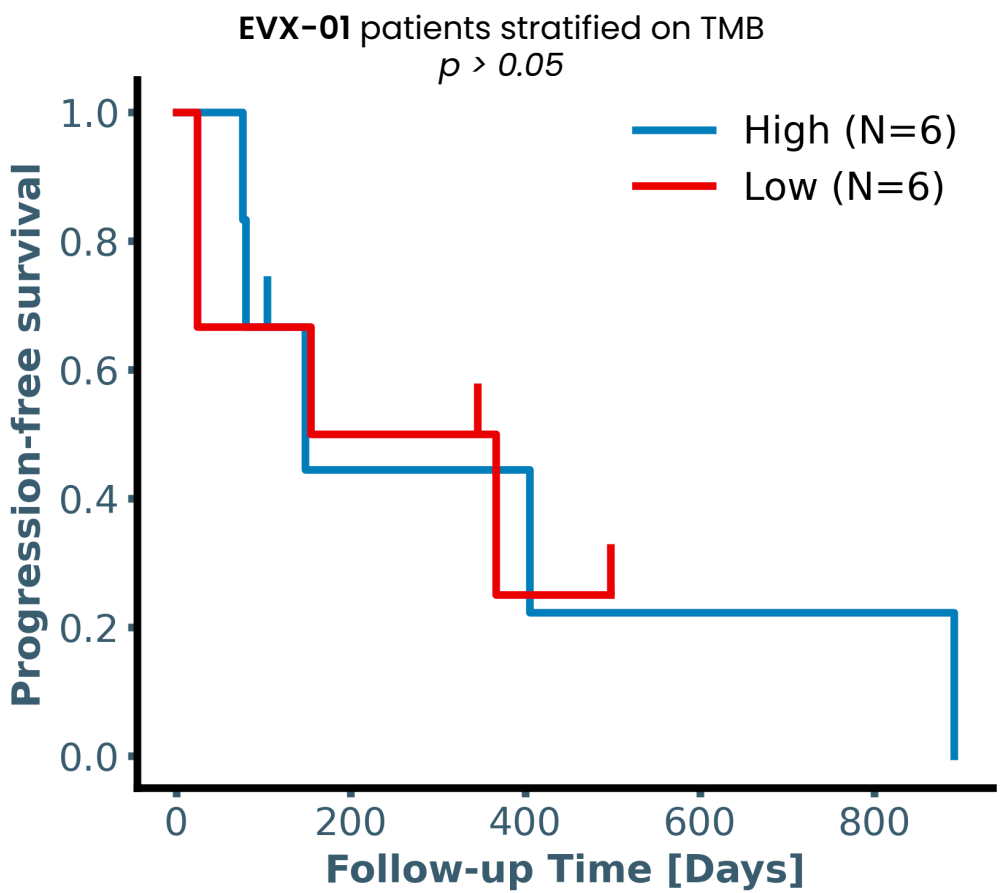

PIONEER™ scores are predictive of clinical response




*Median TMB:* *176.6 M/Mb* *126.8 M/Mb*

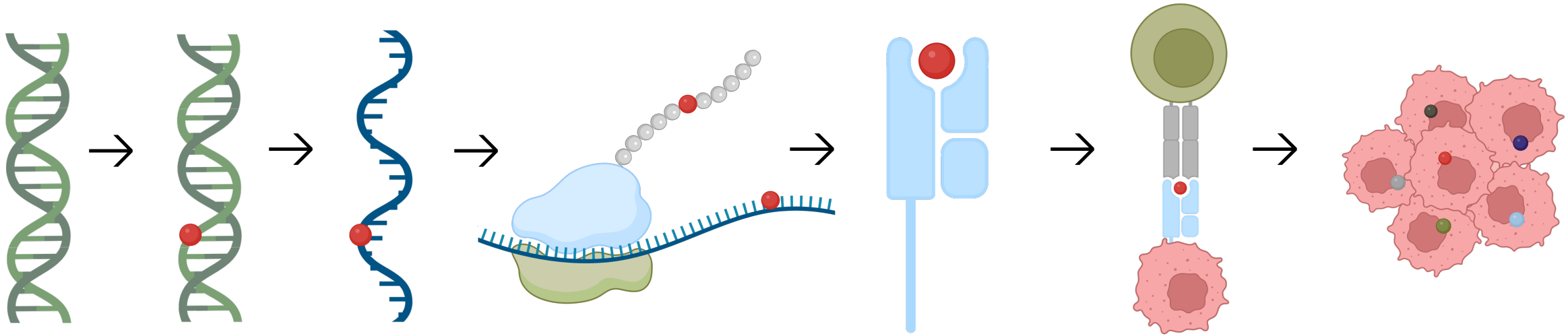
# Superior **Neoantigen Quality** Leads to **Prolonged Progression-Free Survival** Independent of TMB



# **EvaxMHC** is Required for **Optimal Prediction** of Immunogenic Neoantigens

1. Cancer-specific mutation
2. Expression
3. Translation
4. Presentation on MHC
5. T-cell response
6. Clonal neoantigens

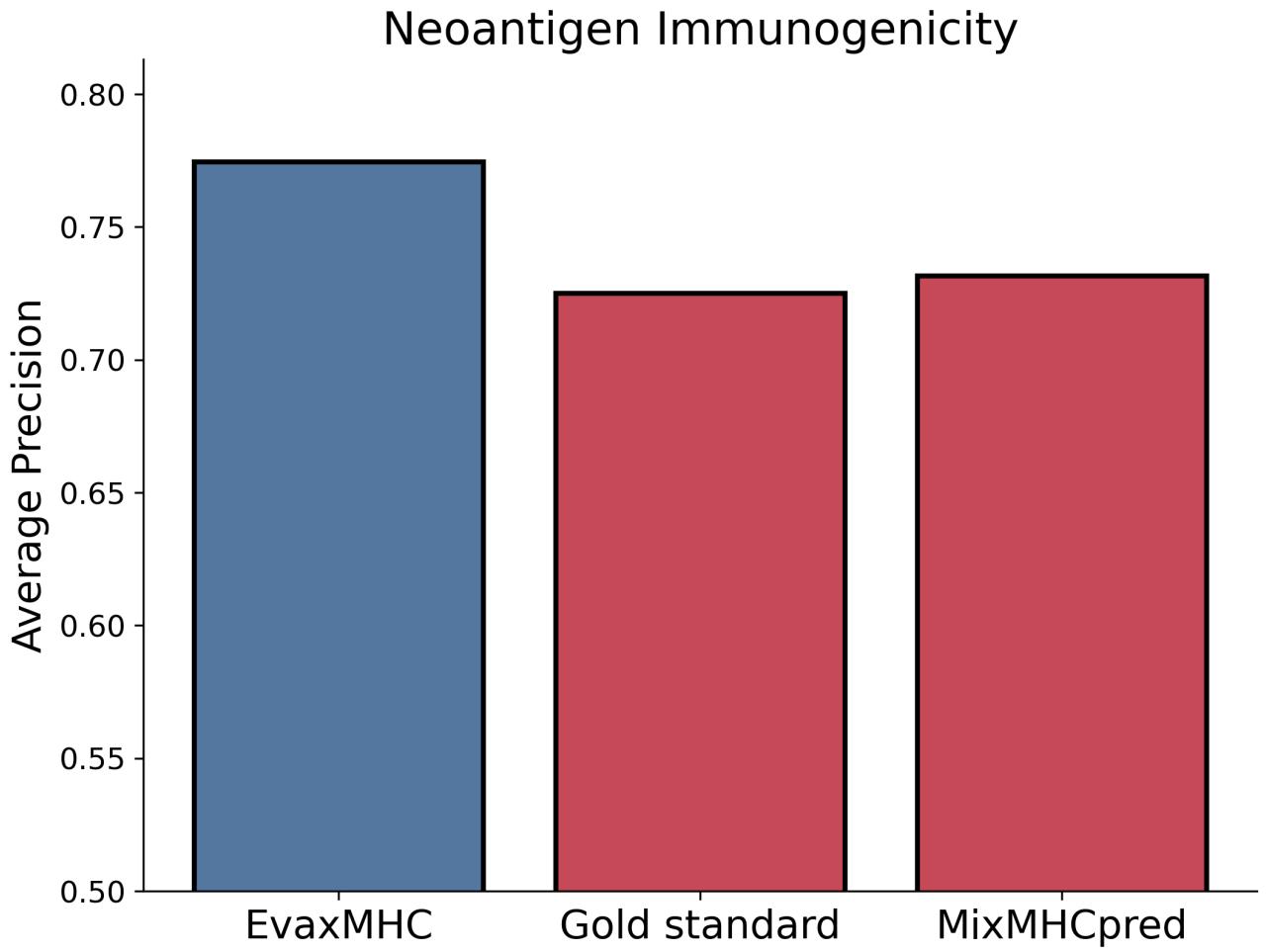


EvaxMHC → 
- Gold standard
- MixMHCpred



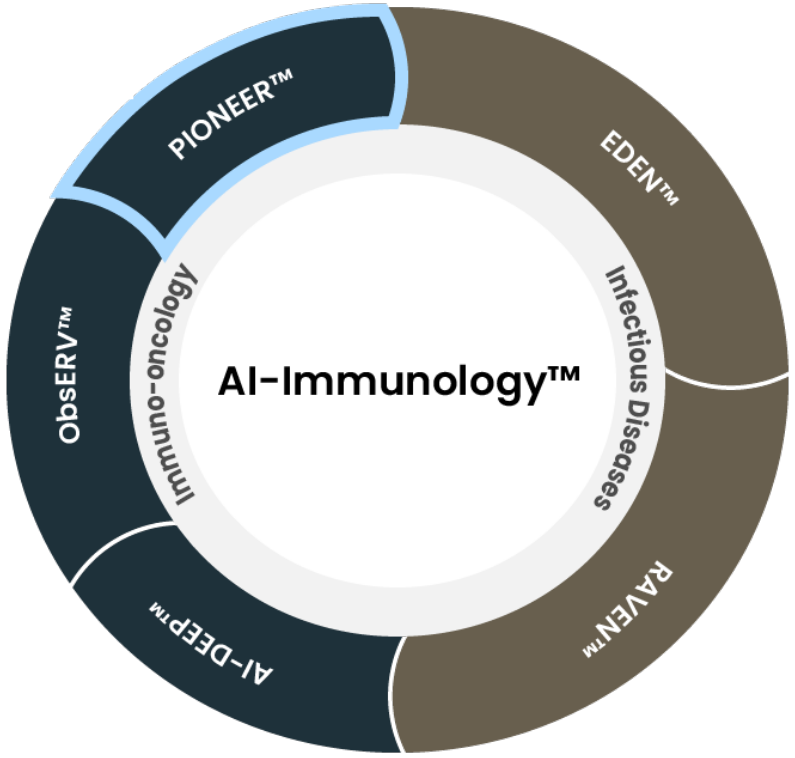
Garde et al. (2019). Immunogenetics 71, 445–454. 10.1007/s00251-019-01122-z
Gfeller et al. (2023). Cell Syst *14*, 72-83.e5. 10.1016/j.cels.2022.12.002
Racle et al. (2023). Immunity *56*, 1359-1375.e13. 10.1016/j.immuni.2023.03.009

# **EvaxMHC** is Required for **Optimal Prediction** of Immunogenic Neoantigens



# Summary

- The PIONEER™ model selects relevant neoantigens for personalized cancer vaccines
- PIONEER™ has been tested in two Phase 1 clinical trials and is being tested in an ongoing Phase 2 trial
- PIONEER™ scores are predictive of neoantigen immunogenicity and clinical response to the neoantigen treatment
- EvaxMHC is critical for optimal PIONEER™ performance



# Q&A SESSION

# Agenda

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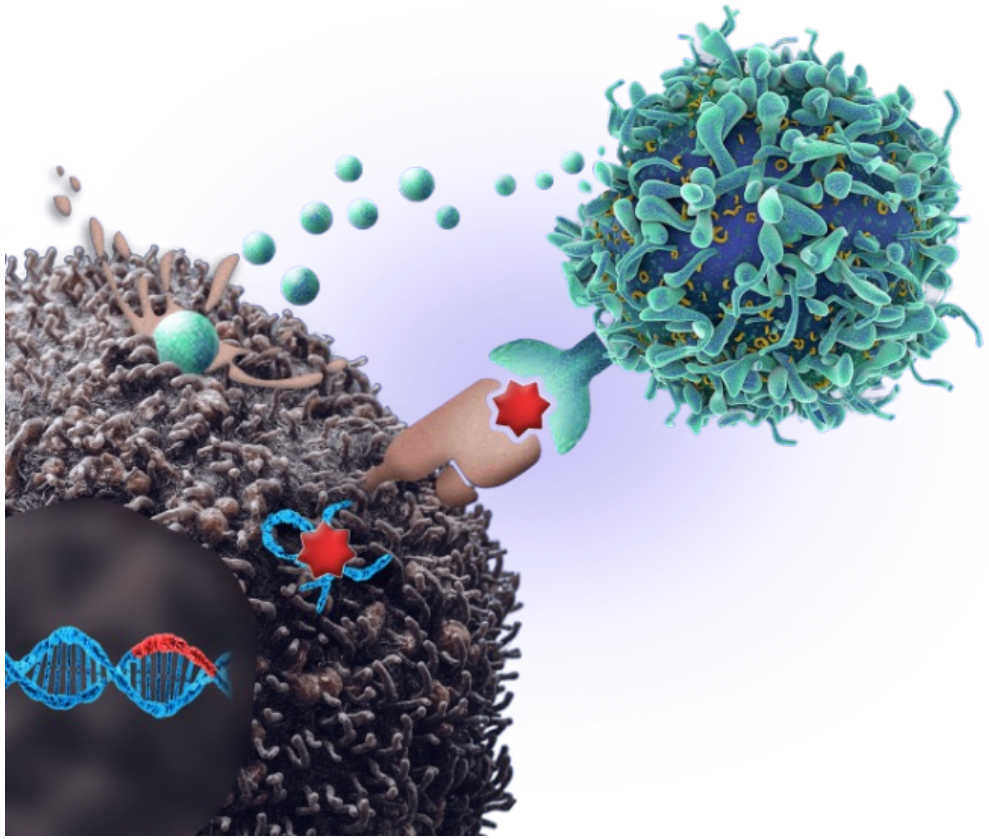
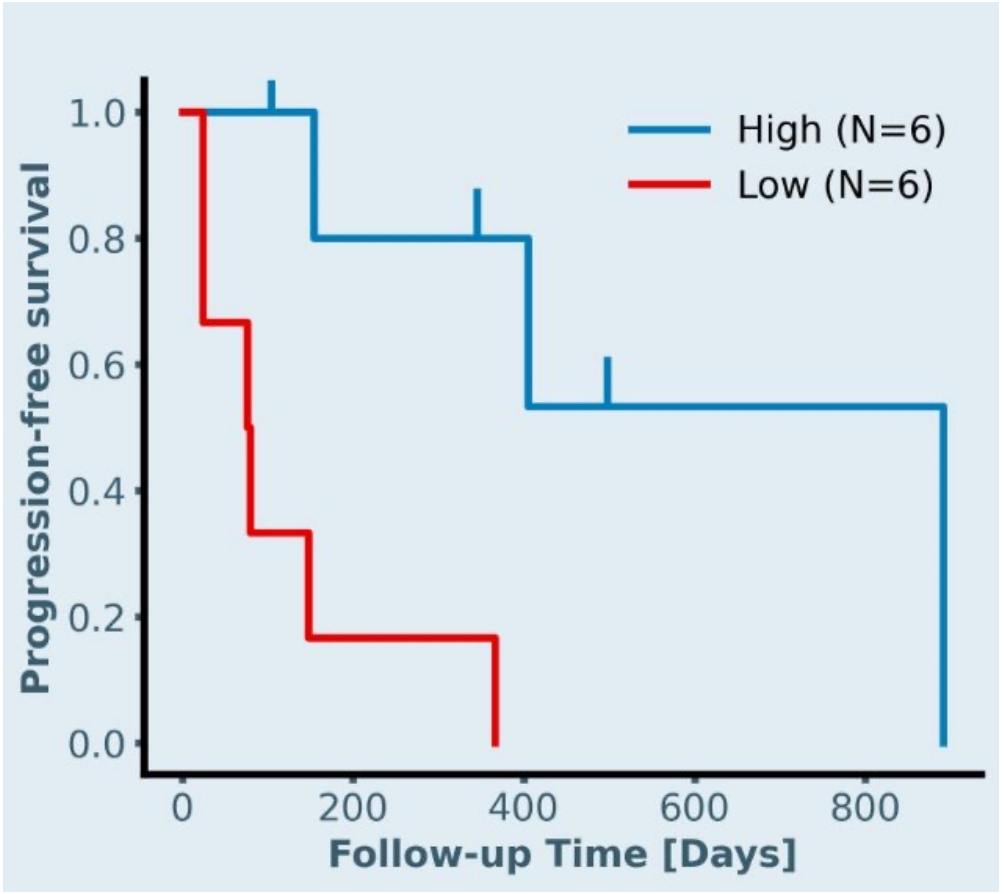
# ObsERV™
# – Leading model for designing personalized ERV-antigen vaccines

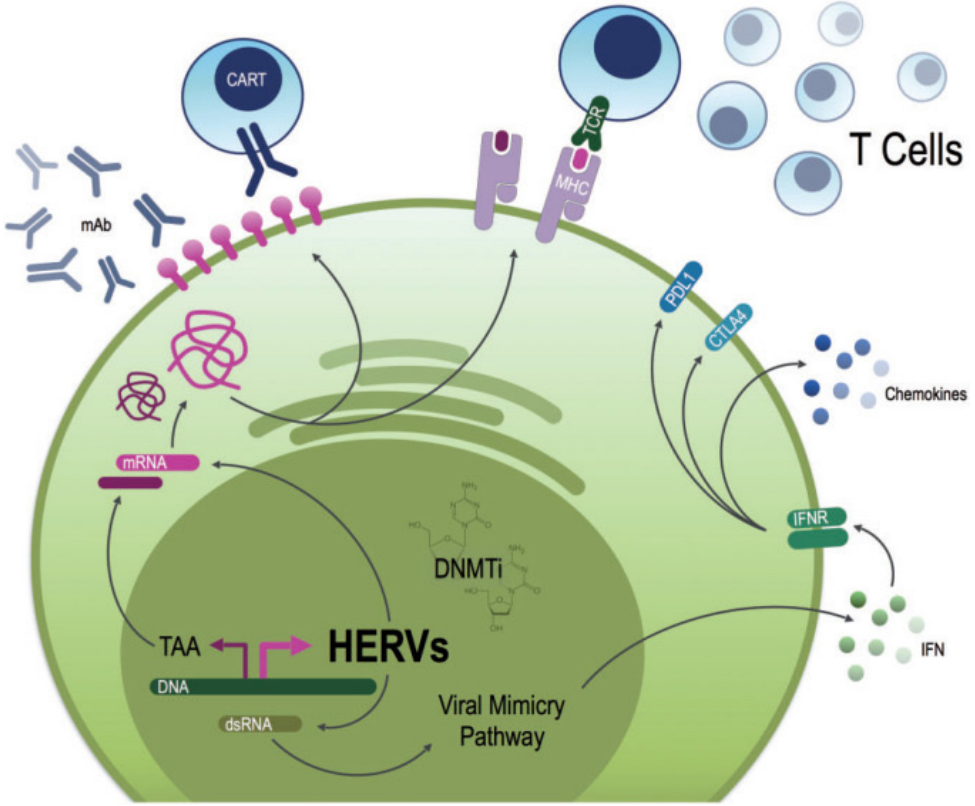
# Some Cancer Patients Have Few Quality Neoantigens Underscoring the **Need for Additional Antigen Source**





# **Endogenous Retroviruses (ERVs)** May be Promising Antigens for Cancer Therapies

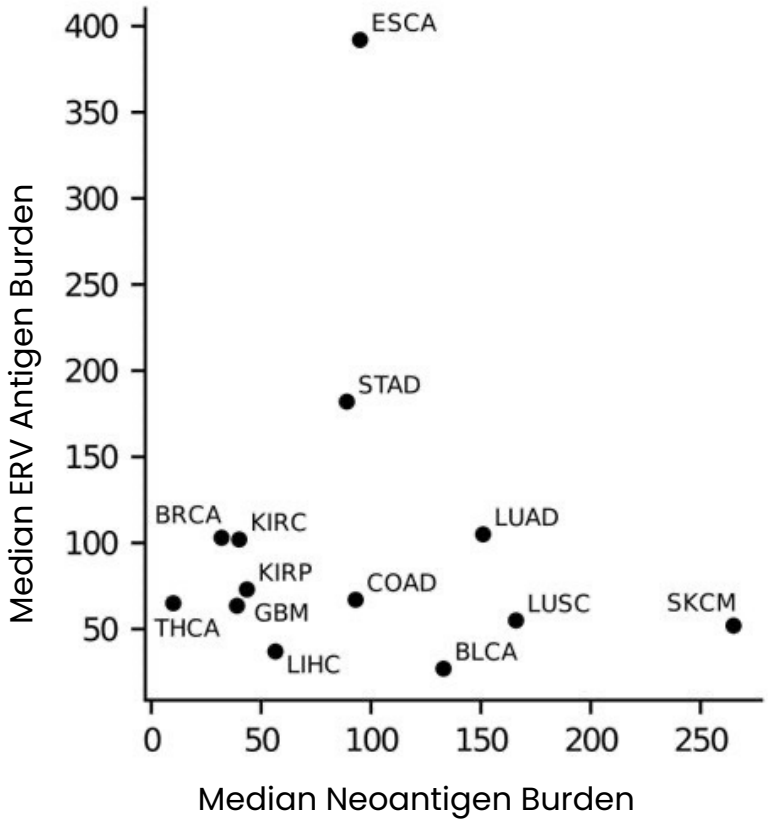
- Ancient viruses that have integrated into the genome and are passed down through generations.
- Constitute up to 8% of the human genome
- Epigenetically suppressed in healthy tissue, but expressed in cancers
- Examples of ERVs are found to elicit specific T-cell responses and confer tumor protection in mice
- ERV specific T-cell responses have been measured in cancer patients
- In vitro killing of human tumor cell lines by ERV-specific T-cells




Atterman et al. (2018), Annals of Oncology 29: 2183–2191,

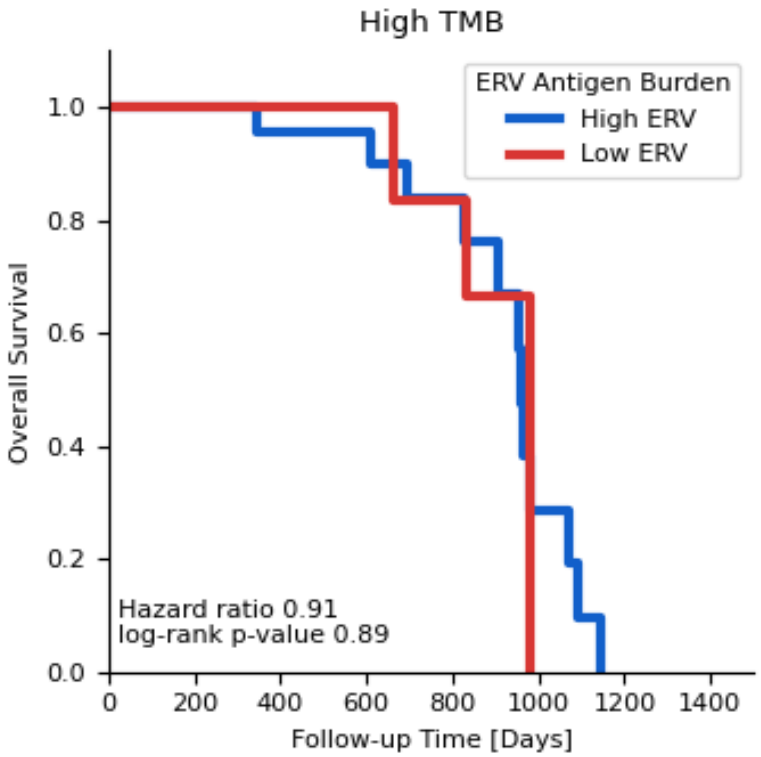
# **ERVs** May Facilitate Personalized Cancer Vaccine Development for Patients with Few Neoantigens

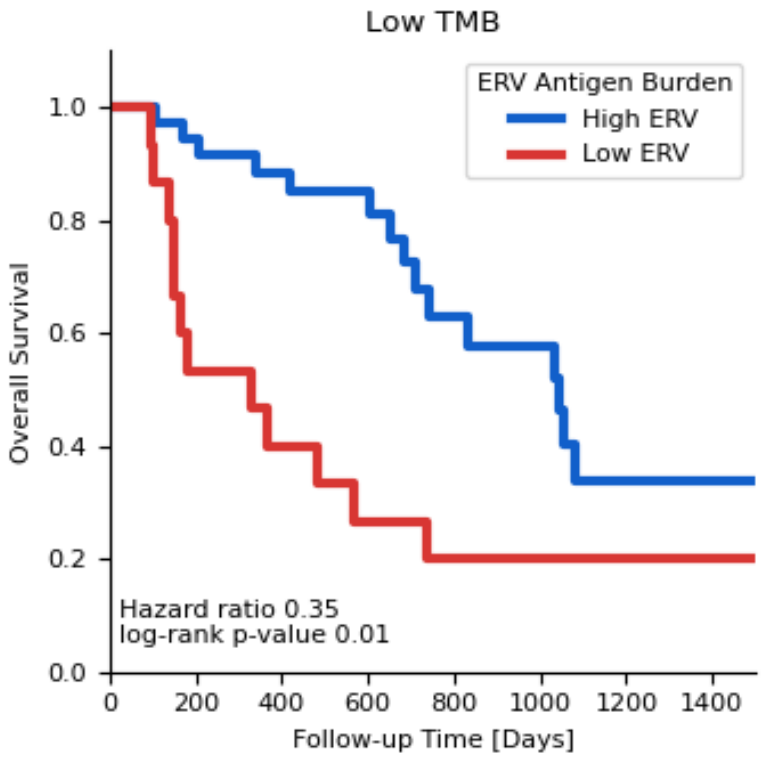
- Pan solid cancer investigation of neoantigens and ERV antigens
- The number of neoantigens and ERV antigens is not correlated
- Patients with few neoantigens could leverage ERVs as alternative source of antigens for vaccine design
- May enable personalized cancer vaccines to a new segment of cancer patients



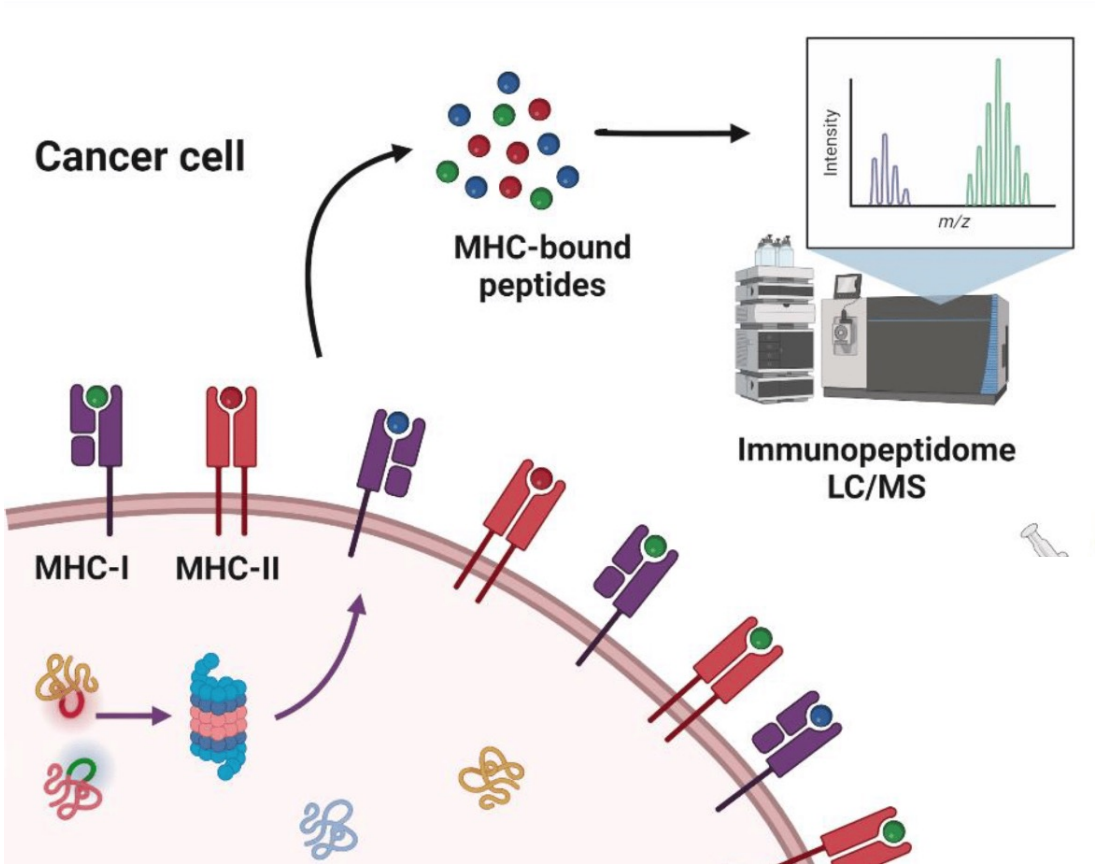
# Patient Stratification with the ERV Antigen Burden Supports Their **Potential as Effective Cancer Antigens**

- CPI treated malignant melanoma patients
- Genomic analysis of baseline tumor biopsies for neoantigens and ERV antigens
- Low-TMB patients are stratified by ERV antigen burden
- ERVs may facilitate clinical response to CPI for patients with few neoantigens

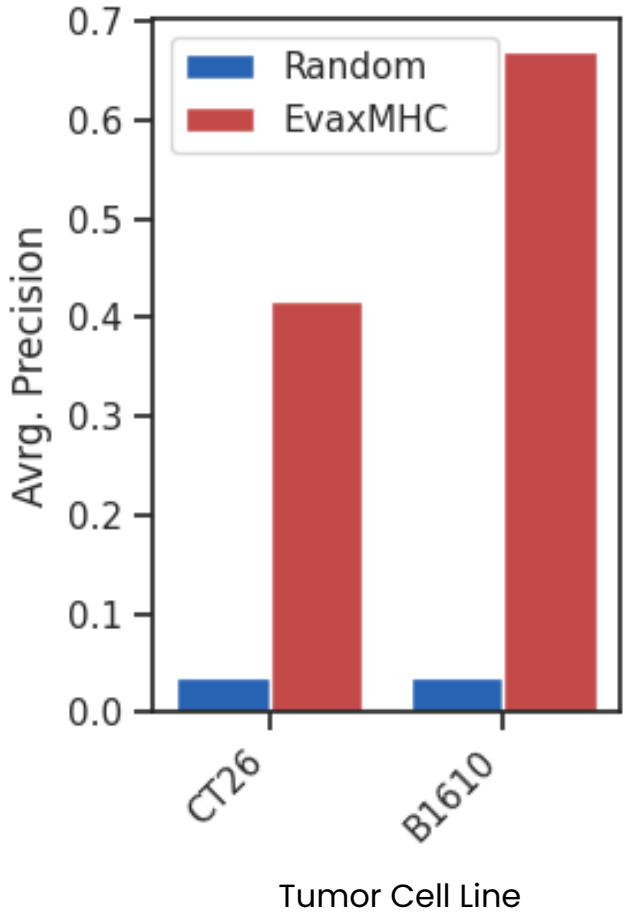


# **ERVs** Are Presented as **MHC Ligands** on Tumors and Can be Predicted by **EvaxMHC**




Pak et al. (2021), Mol Cell Proteomics



# Leveraging our Modular **AI-Immunology™** Platform to Build **ObsERV™**

**ObsERV™**

| | | |
|---|---|---|
| HLA loss | Expression | ERV antigens |
| EvaxMHC | HLA typing | |
| Antigen quality | Antigen safety | Personalized design |

## 1 DISEASE DECODING

| | | | |
|---|---|---|---|
| SNVs | Frameshifts | Gene fusions | HLA loss |
| ERV antigens | TME impact | Clonality | Expression |
| Bacterial antigens | Viral antigens | Antigen conservation | Treatment effect |
| Neoantigens | | | |

## 2 IMMUNE RESPONSE DECODING

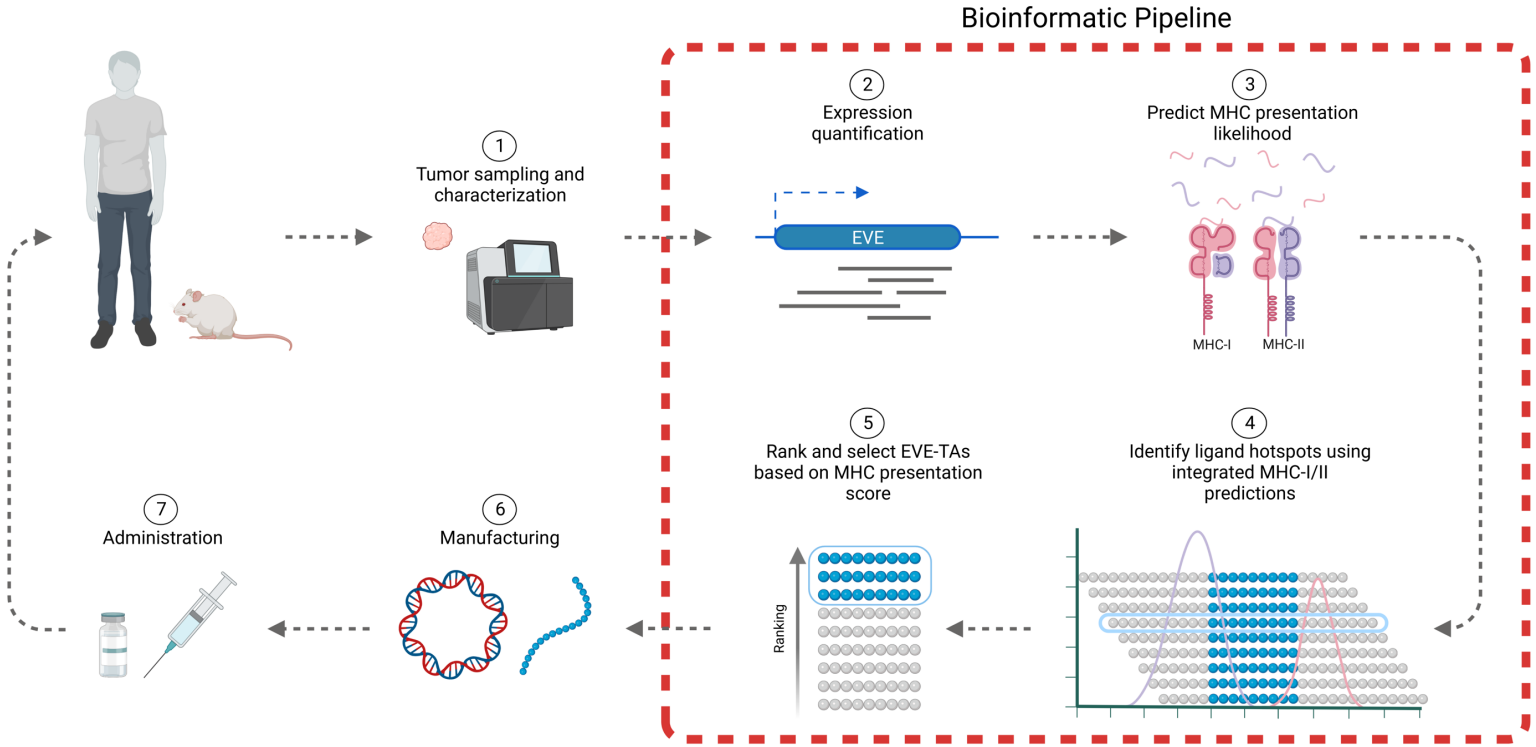
| | | | |
|---|---|---|---|
| EvaxMHC | HLA typing | HLA frequencies | Distance to self |
| Protective antigens | Epitope hotspots | | |

## 3 VACCINE DESIGN

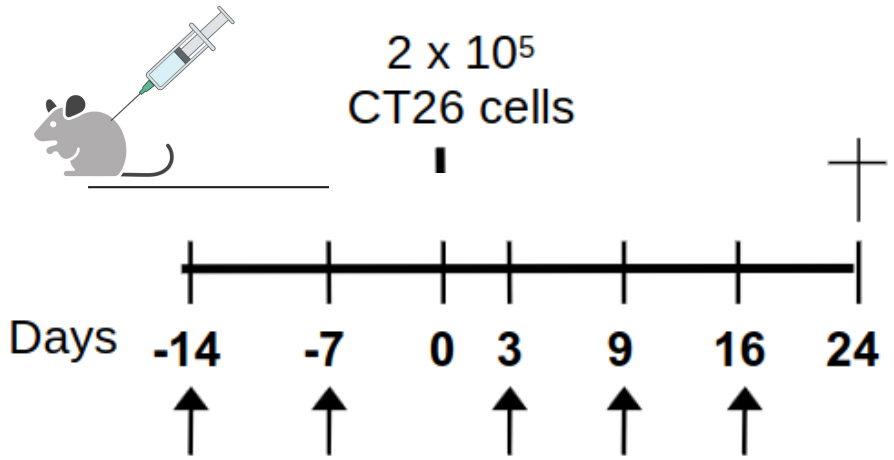
| | | | |
|---|---|---|---|
| Antigen quality | Antigen safety | B-cell antigen modelling | B-cell antigen design |
| Precison design | Personalized design | BIFROST | |

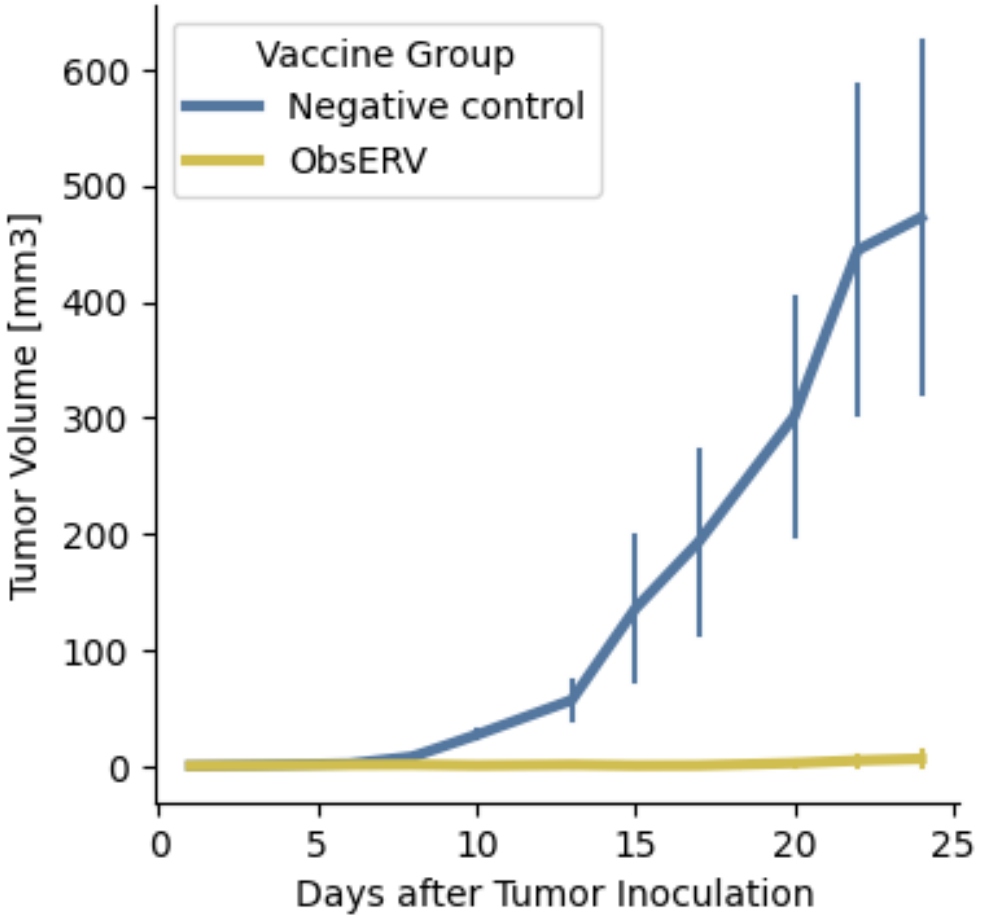
# **ObsERV™:** A New AI-model for **Development of Personalized Cancer Vaccines** Based on ERV Antigens

- Fits into established clinical workflows
- Requires standard RNA-seq of tumor biopsy and patient's HLA-type
- Designed to identify potent ERV antigens that activate $CD4^+$ and $CD8^+$ T cells
- Aiming to provide sustained effective T-cell responses and clinical response



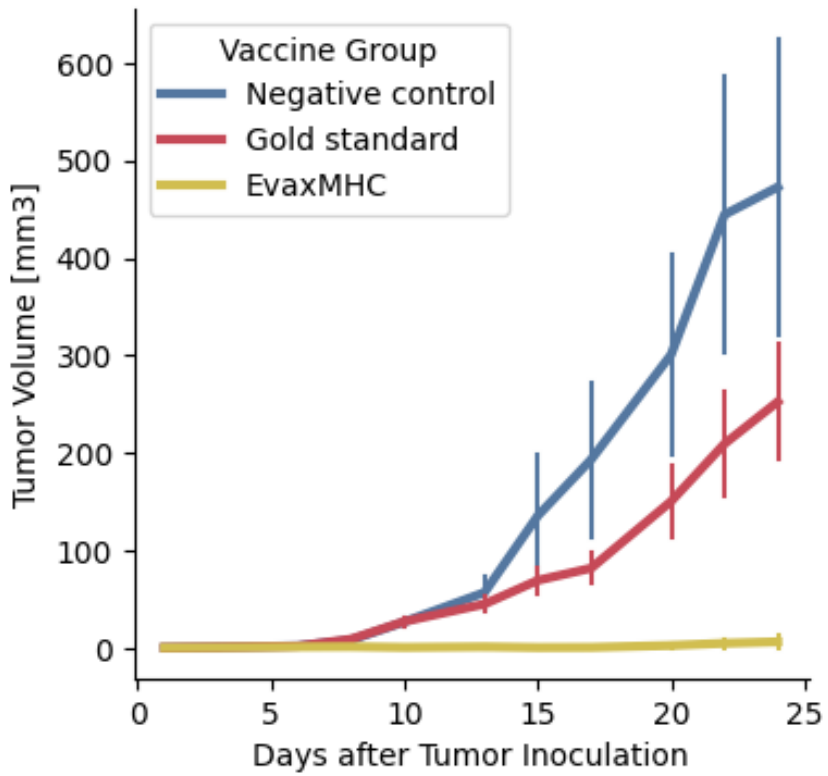
# **ObsERV™** Designs **Efficacious** ERV-Based Cancer **Vaccines**

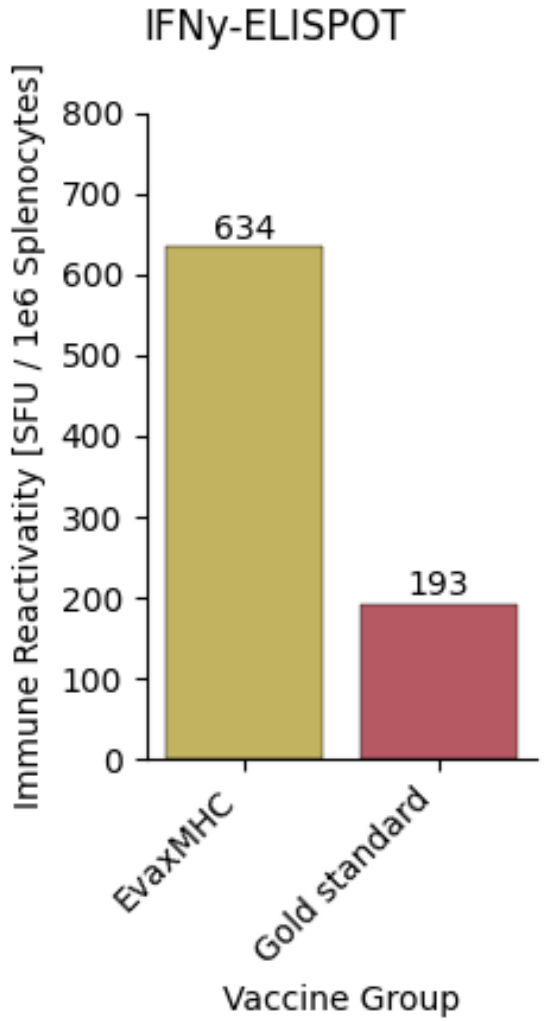


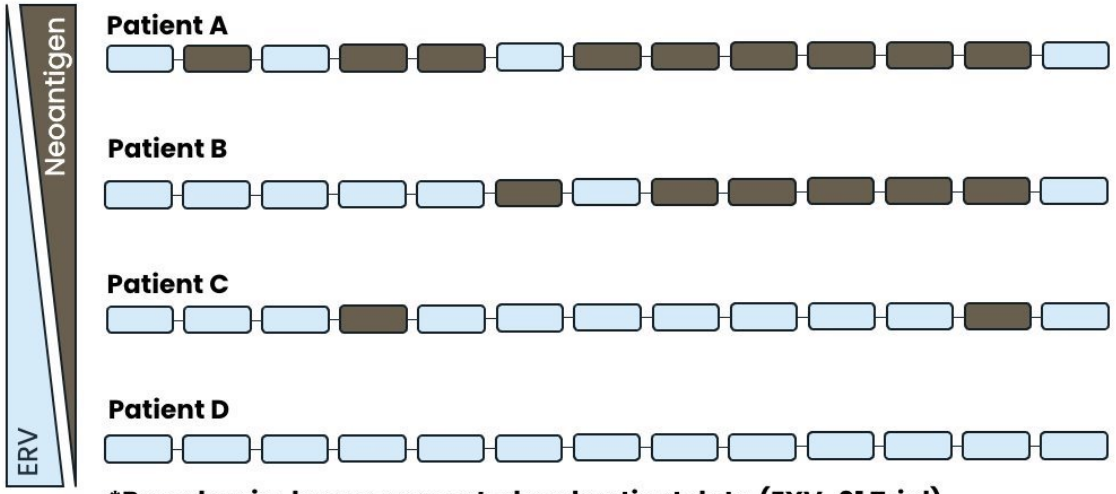
# **EvaxMHC** Empowers **ObsERV™** to Design **Efficacious** ERV-Based Cancer **Vaccines**

- Peptide-MHC prediction is a core element in ObsERV™
- Vaccine group designed after swapping out EvaxMHC with Gold standard tool
- EvaxMHC vaccine group mounts stronger and sustained immune response and tumor protection

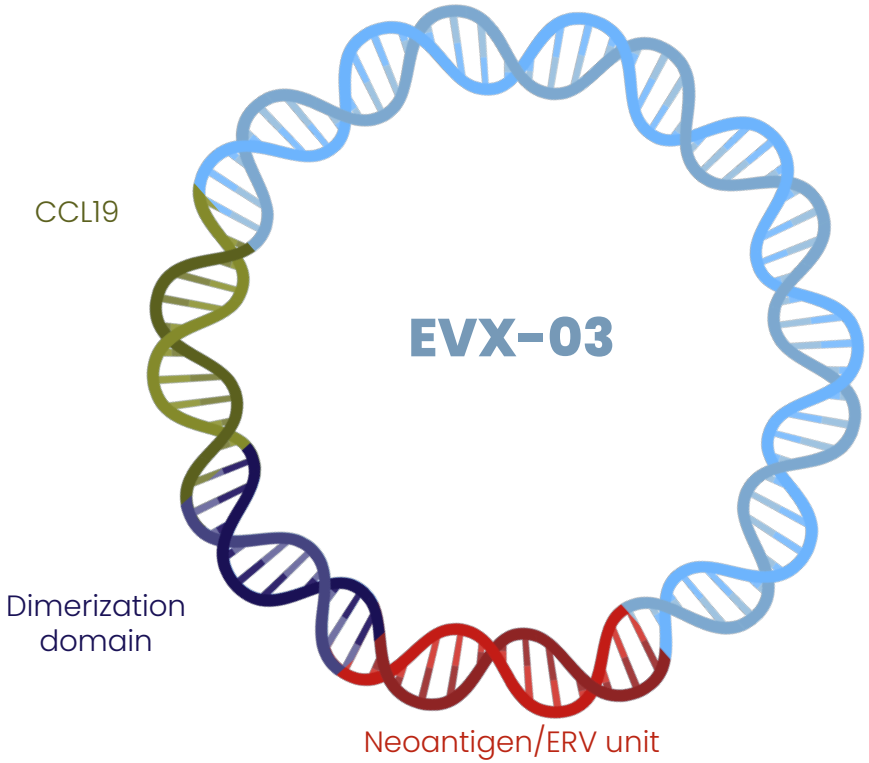


# **EVX-03** Will Evaluate **Personalized** Cancer Vaccines Leveraging **Neoantigens** and **ERVs**

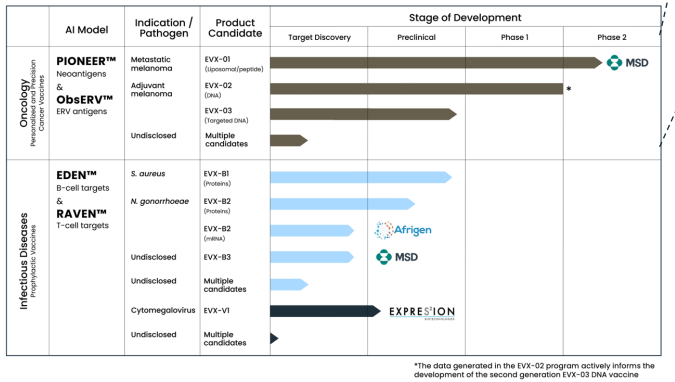



***Based on in-house generated real patient data (EXV-01 Trial).**
*Patients were selected based on resulting designs to display the variance in final vaccine design if neoantigens and ERVs are scored equally.*



# **Pipeline:** Demonstrating the Performance and Scalability of Our AI-Immunology™ Platform

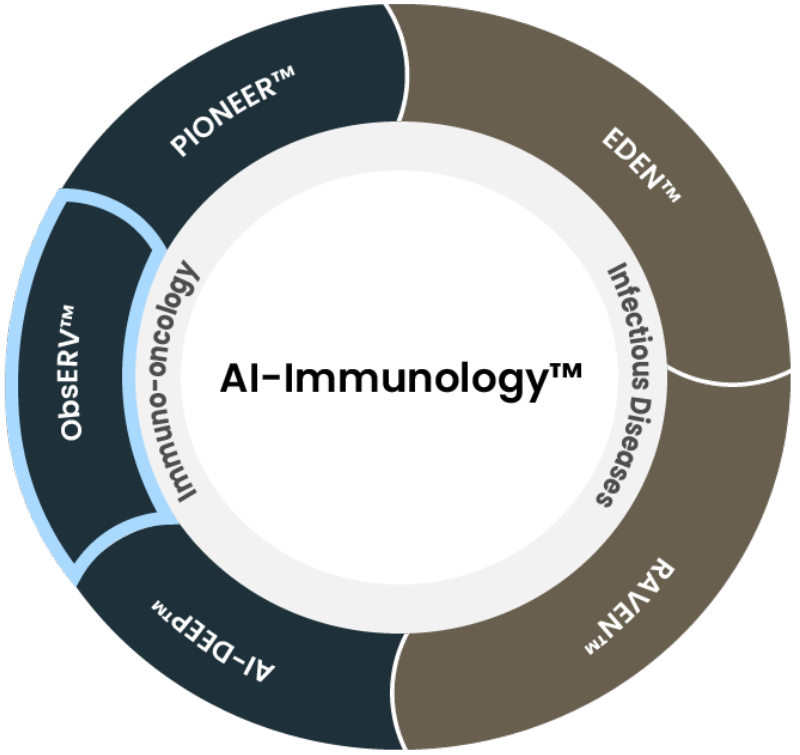
| | AI Model | Indication / Pathogen | Product Candidate | Stage of Development | | | |
|---|---|---|---|---|---|---|---|
| | | | | Target Discovery | Preclinical | Phase 1 | Phase 2 |
| **Oncology** Personalized and Precision Cancer Vaccines | **PIONEER™** Neoantigens & **ObsERV™** ERV antigens | Undisclosed | EVX-03 (Targeted DNA)<br>Multiple candidates | | | | |




*The data generated in the EVX-02 program actively informs the development of the second generation EVX-03 DNA vaccine

# Summary

- ERVs constitute a complementary source of cancer antigens
- ObsERV™ enables development of ERV based personalized cancer vaccines
- Preclinical proof-of-concept
- IND ready for clinical testing (EVX-03)






Garde, C. et al. (2023). Endogenous viral elements constitute a complementary source of antigens for personalized cancer immunotherapy. bioRxiv. https://doi.org/10.1101/2023.03.23.533908

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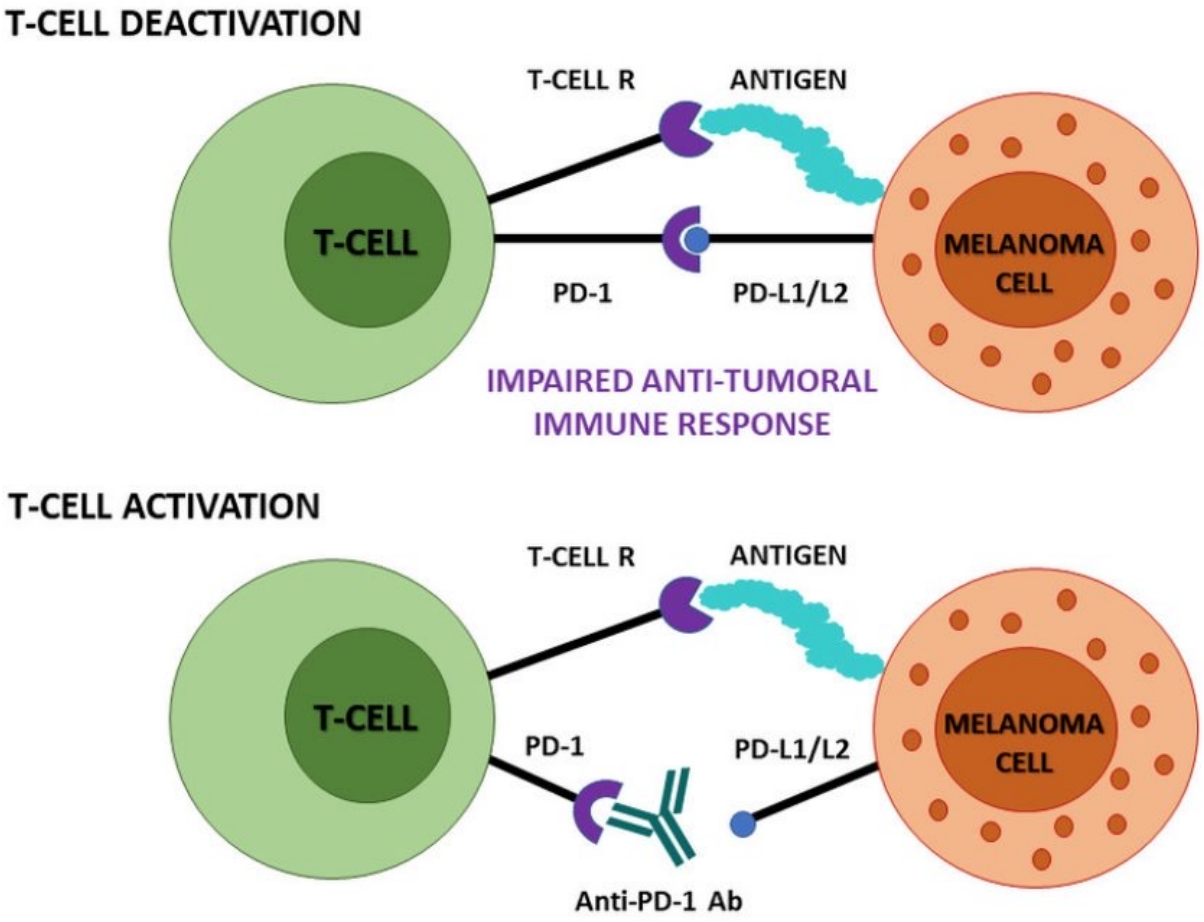
# SESSION 4
## – Precision cancer concepts

# AI-DEEP™

- Model for predicting responses to cancer CPI immunotherapy

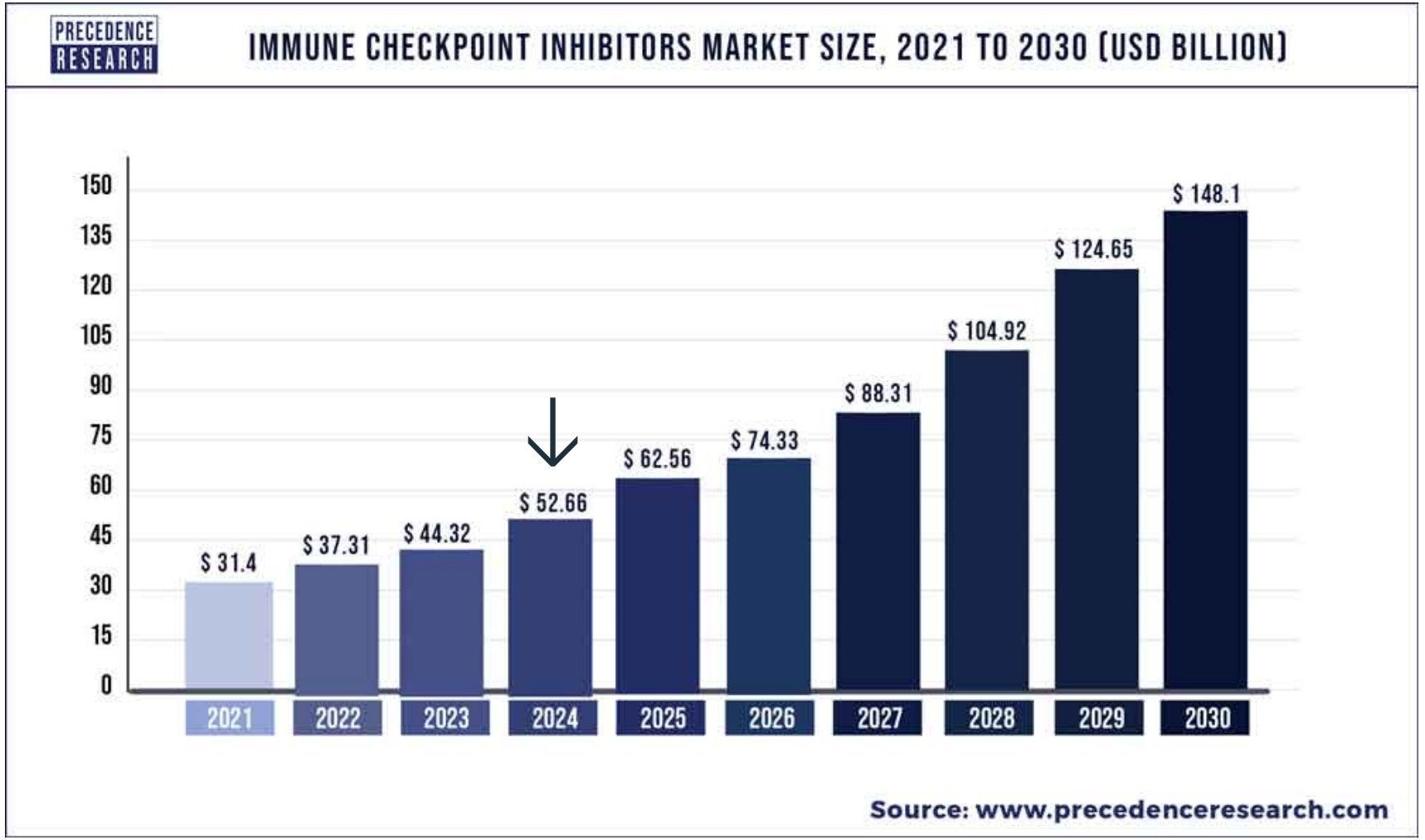
# **Checkpoint Inhibitors** Are Widely Used as First Line Therapy

- Cancers exploit immune checkpoints to impair the immune system
- Checkpoint inhibitors remove the impairment and reinvigorate the immune system
- Improved treatment of several solid cancers
- Approved for an increasing number of cancer types



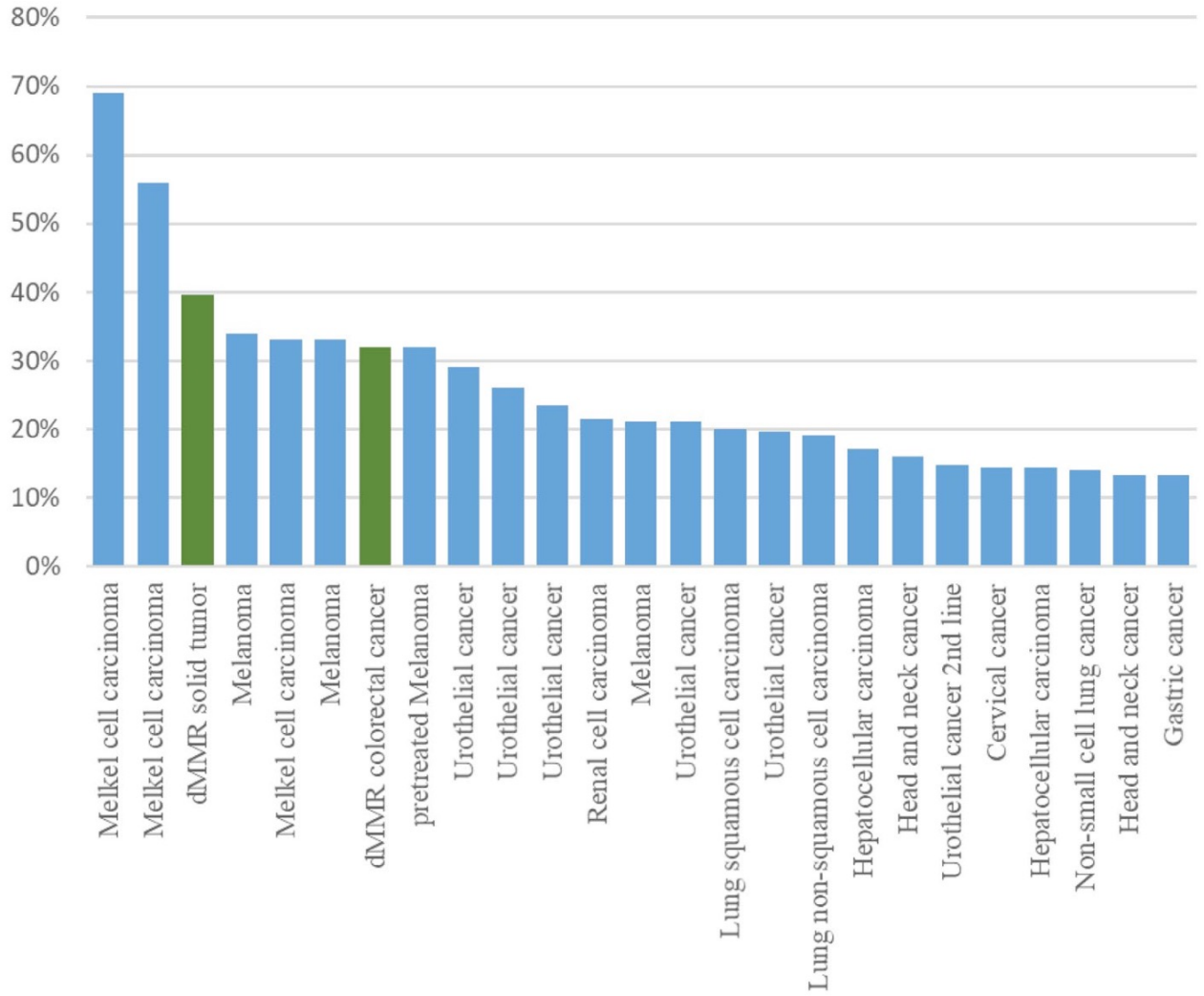

Kaminiska et al. (2021)

# The **Market** for Checkpoint Inhibitor Therapy Is Projected to Reach almost **$150 BN by 2030**

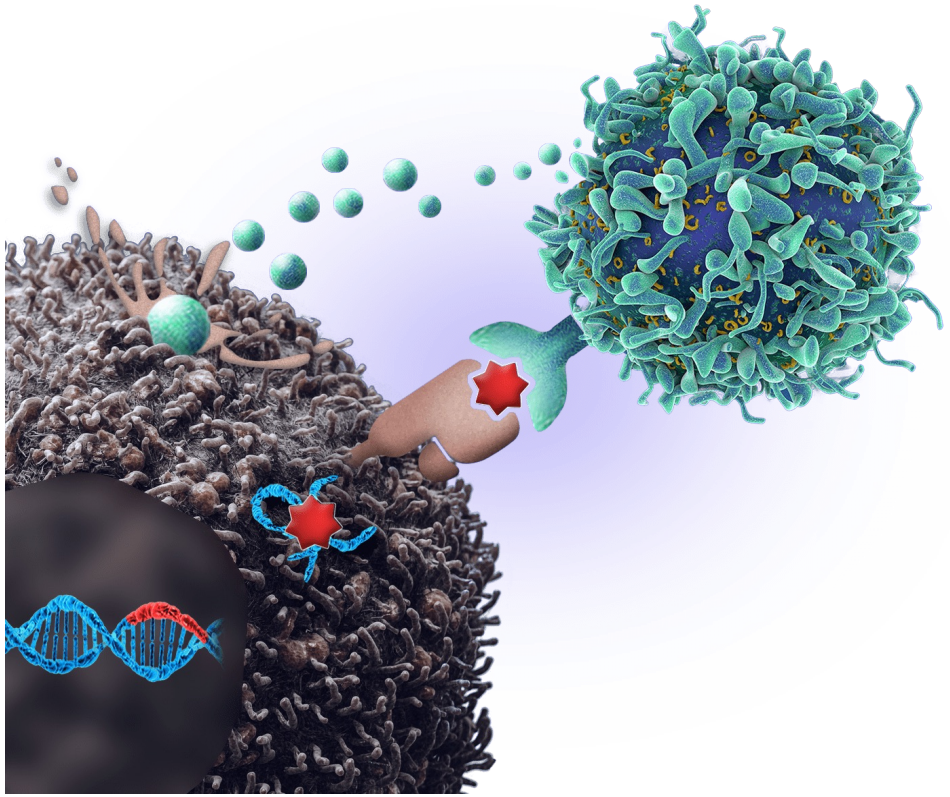


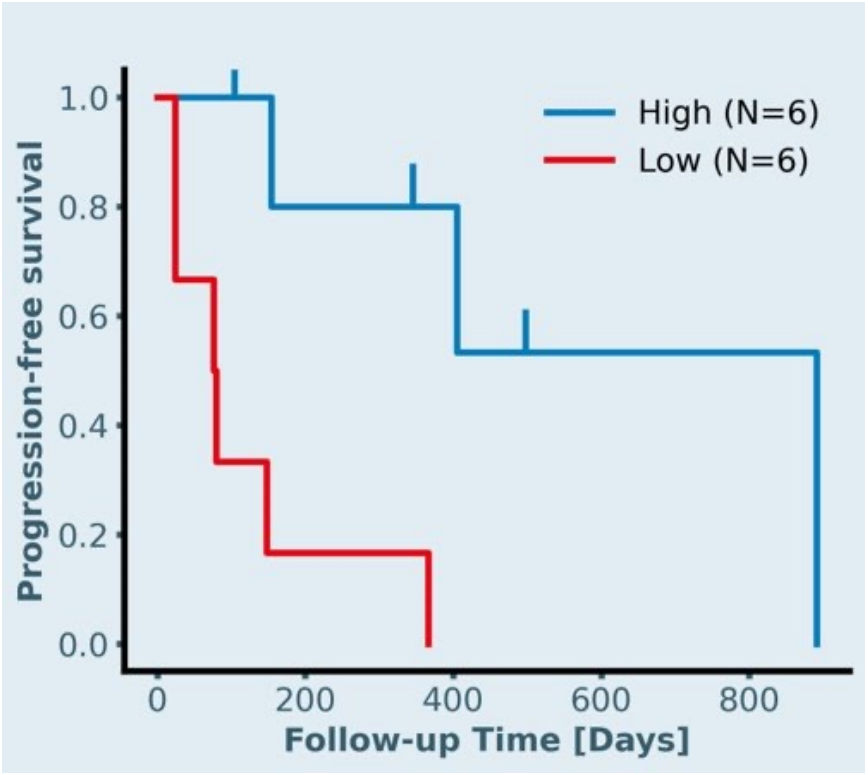
# A **Large Fraction** of Cancer Patients **Do Not Benefit** from Checkpoint Inhibitor Therapy

- Demand for continued development of immunotherapies
- Demand for Identifying non-responders
- Some patients get severe side effect
- No established highly predictive  biomarkers

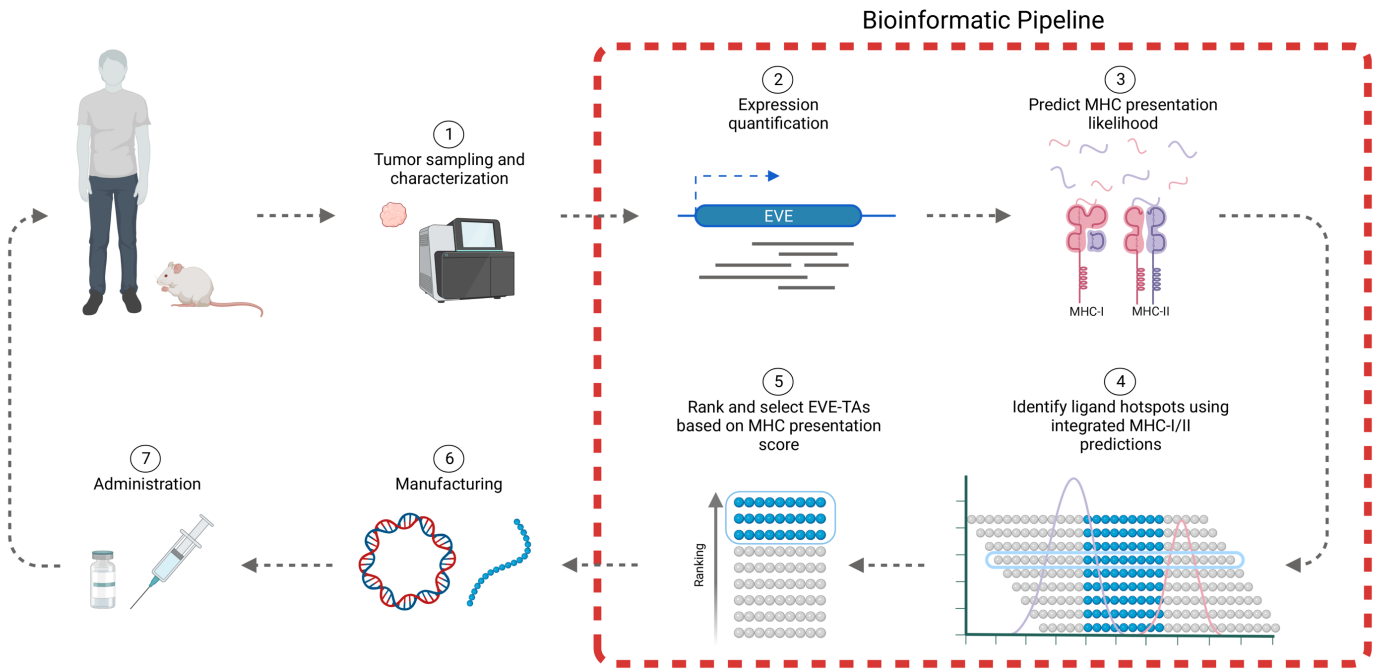


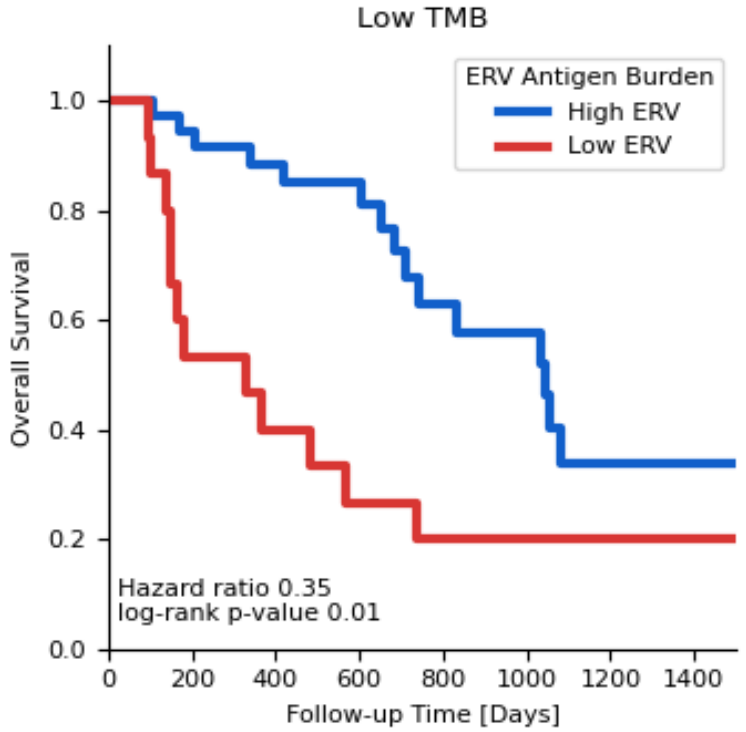
# **PIONEER™** Derived **Biomarker** Predicts Clinical Response to the EVX-01 & anti-PD1 Combination Immunotherapy





# **ObsERV™** Derived **Biomarker** Stratifies Low-TMB Cancer Patients Treated with Checkpoint Inhibitor

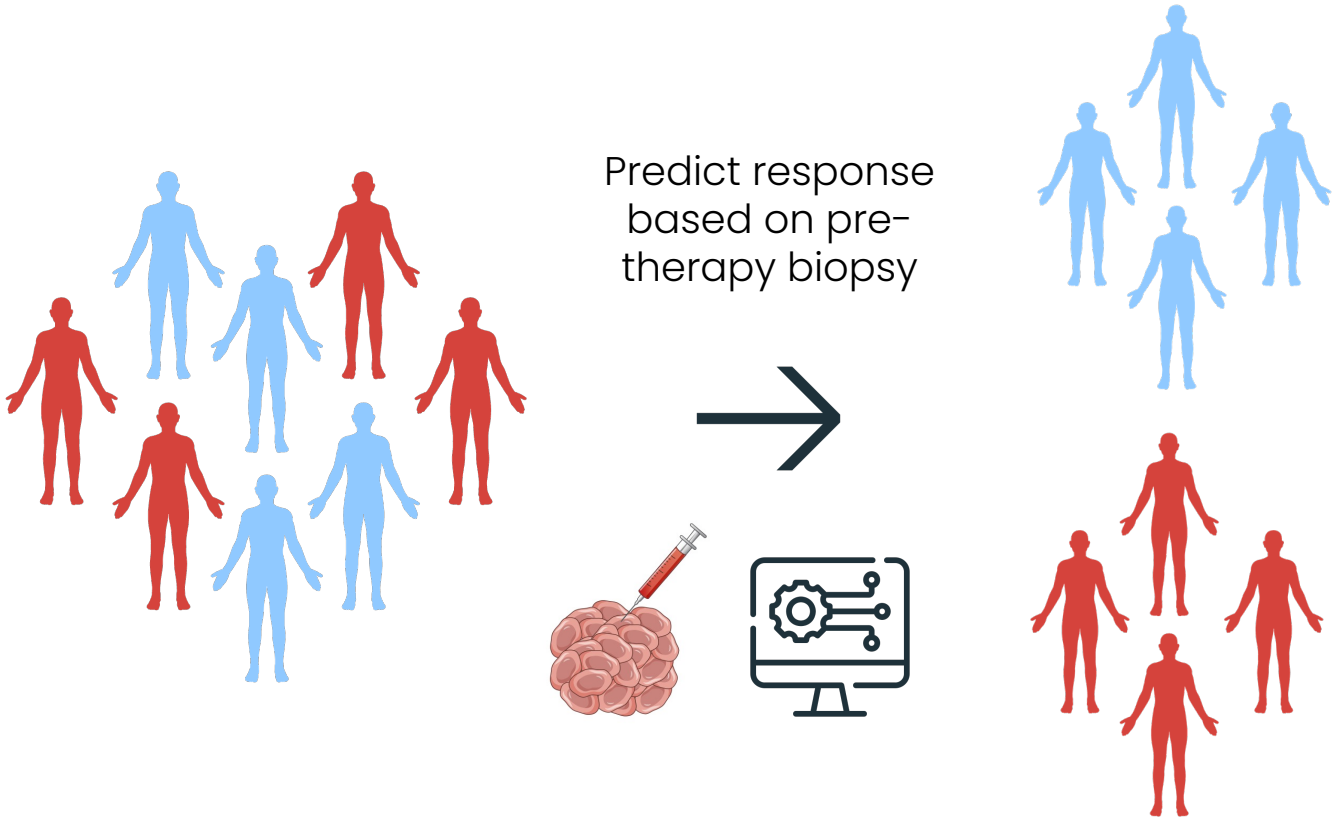





Garde, C. et al. (2023). Endogenous viral elements constitute a complementary source of antigens for personalized concer immunotherapy. bioRxiv. https://doi.org/10.1101/2023.03.23.533908

# Predict Non-Responding Cancer Patients with **High Precision**



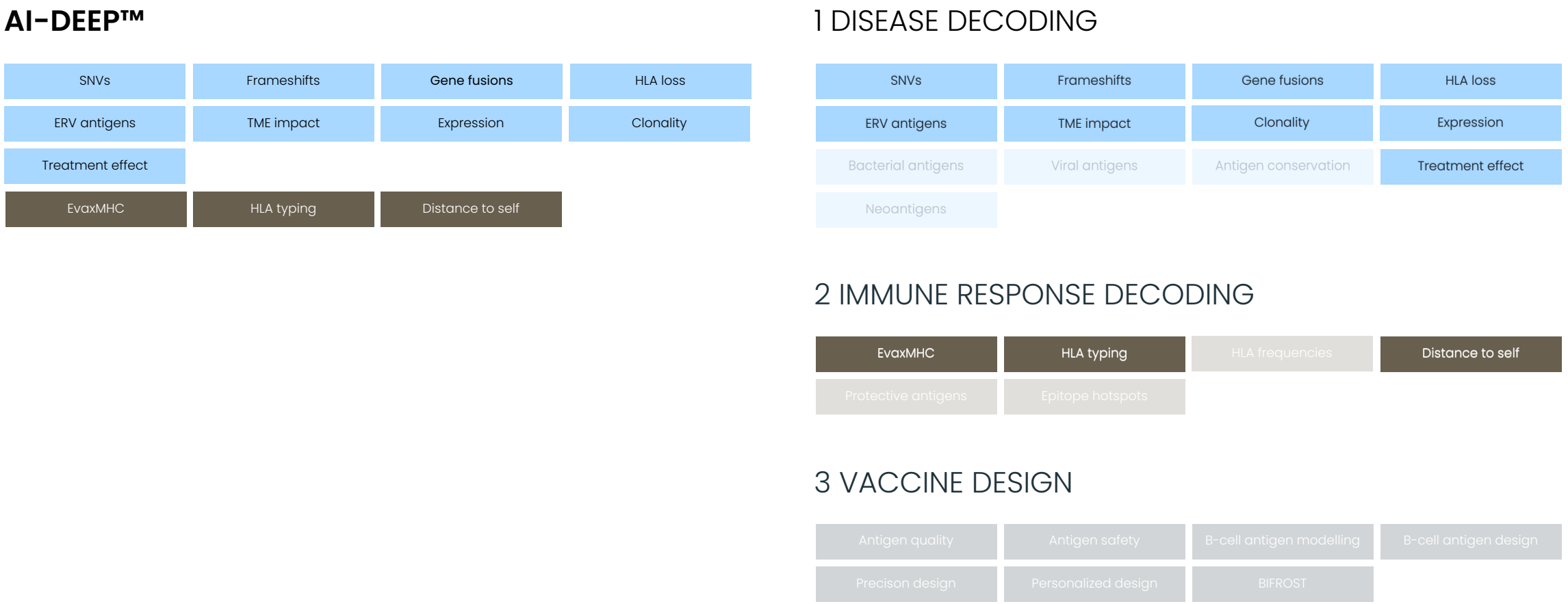

**Benefits for patients and society**

- Redirection to better suited treatments
- Avoid side effects from CPI treatment
- Health care budget

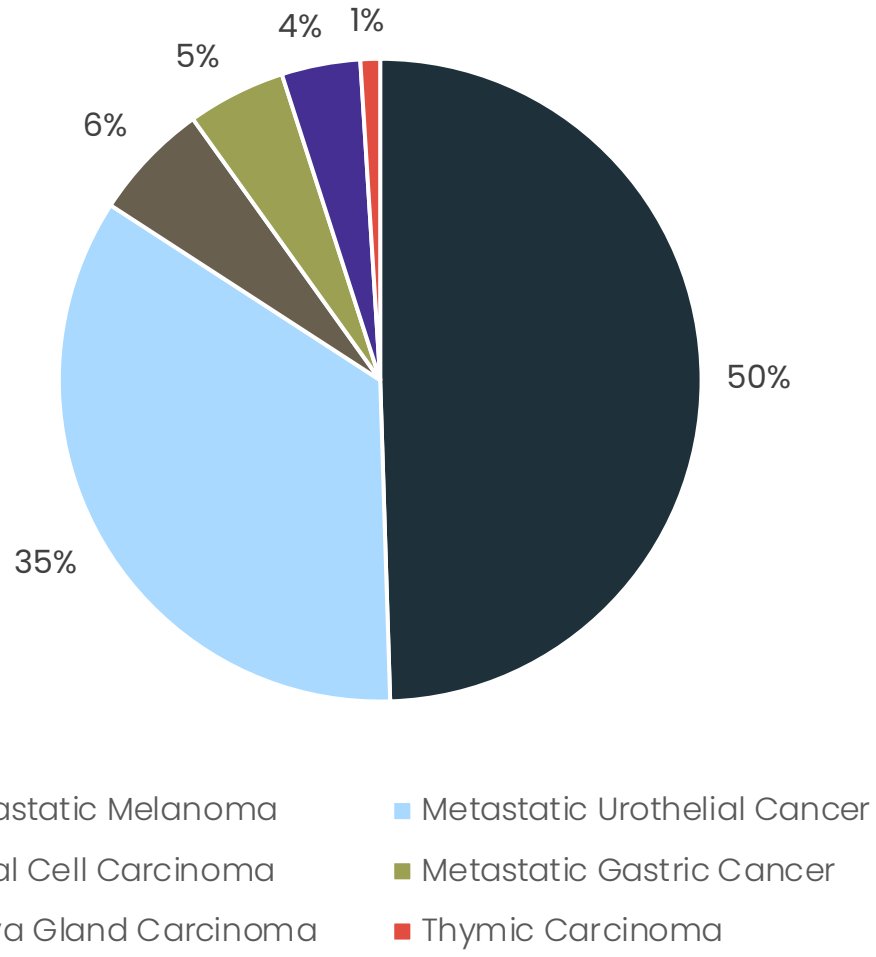
**Genomic biomarkers**

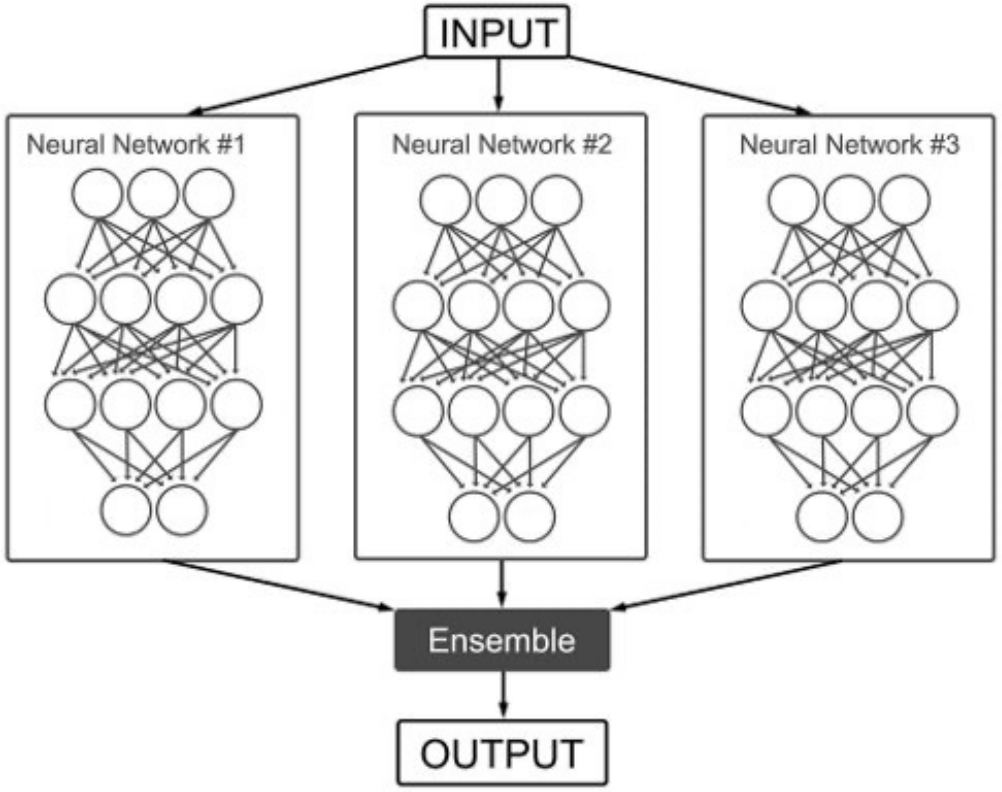
- Driver mutations
- Tumor microenvironment signatures
- Immune evasion signatures
- Antigen burdens, MSI and structural variants
- ObsERV™ and PIONEER™

# Leveraging our Modular **AI-Immunology™** Platform to Build **AI-DEEP™**



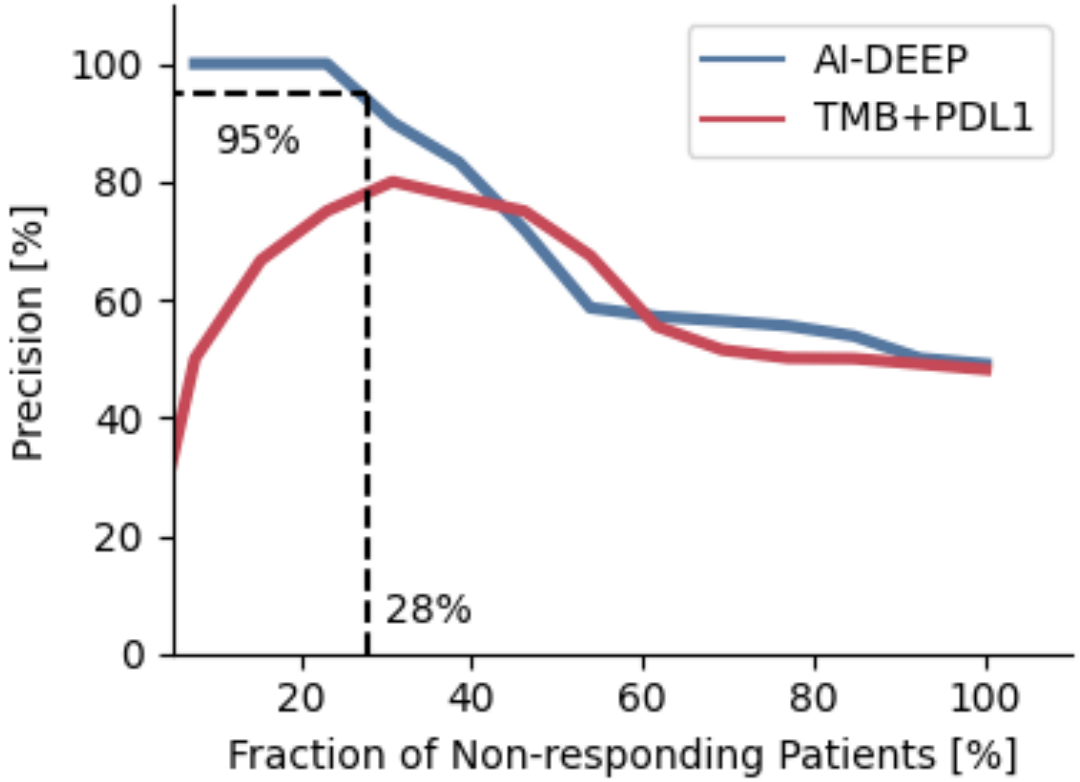
# **Pre-Therapy Biopsies Data** from 937 CPI Treated Cancer Patients Were Collected for Model Development



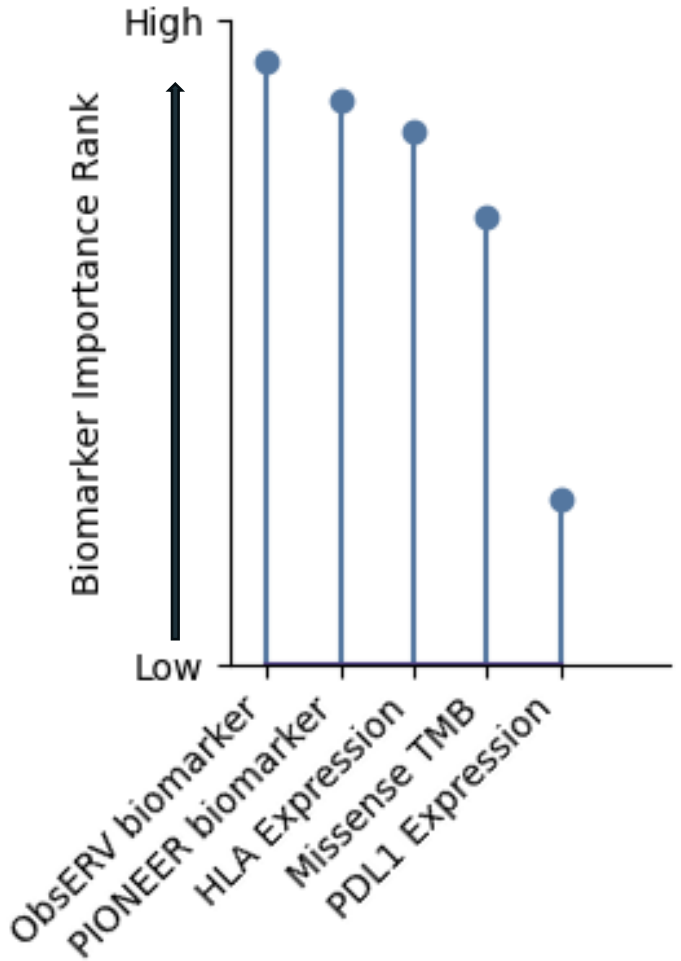
# AI-DEEP™ **Predicts 28% of Non-Responders** to Checkpoint Inhibitor Therapy with **High Precision**

- Gold standard biomarkers (TMB and PDL1) fail to identify non-responding patients with high precision
- AI-DEEP™ predicts 28% of non-responding patients with high precision
- AI-DEEP™ could guide treatment decisions to improve patient care and health care budgets



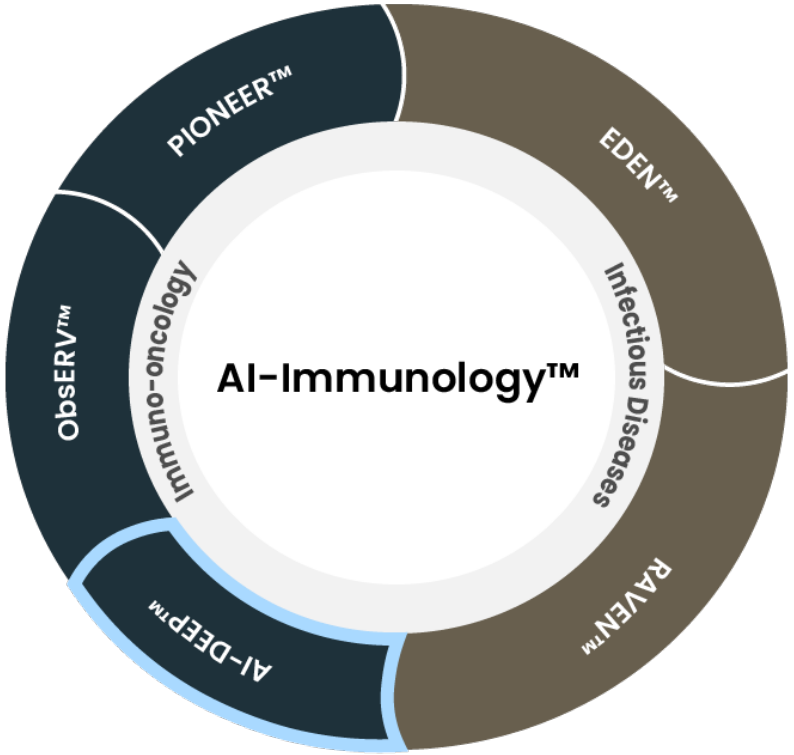
# **ObsERV™ & PIONEER™** Derived **Biomarkers** Are **Important** for Prediction of Non-Responding Patients

- Feature ablation study ranks biomarkers according to their importance for the predictive performance
- In-house models ranked among the most informative biomarkers out of an initial set of >2000 biomarkers
- Gold standard biomarkers (TMB and PDL1) are ranked as less important



# Summary

- AI-DEEP™ leverages PIONEER™ and ObsERV™ to predict clinical response to checkpoint inhibitor therapy
- AI-DEEP™ can accurately identify a subset of non-responding cancer patients and may inform treatment decisions
- We are currently exploring options for a commercial offering and further clinical validation as a companion diagnostic



# Q&A SESSION

# Agenda

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| CET / EST | |
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| 15.15 - 15.35 / 10.15 – 10.35 | **EDEN™** - Best-in-class model assessing protectiveness of B-cell antigens |
| 15.35 - 15.55 / 10.35 – 10.55 | **RAVEN™** - Model for uncovering unique cross-protective T-cell antigens |
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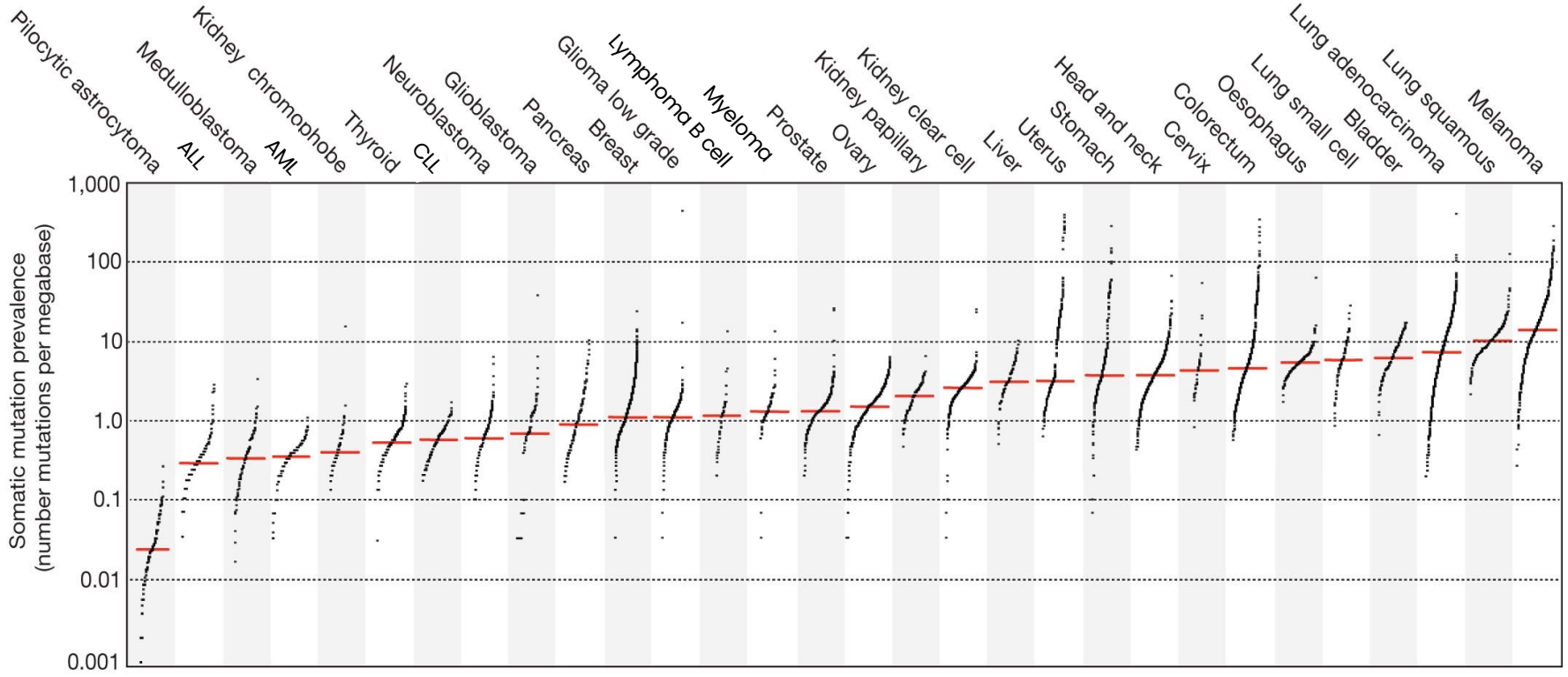
|---|---|
| 16.15 - 16.35 / 11.15 – 11.35 | **PIONEER™** - Validated model for designing personalized Neoantigen vaccines |
| 16.35 - 16.55 / 11.35 – 11.55 | **ObsERV™** - Leading model for designing personalized ERV-antigen vaccines |
| 16.55 - 17.15 / 11.55 – 12.15 | BREAK |

## SESSION 4 - Precision Cancer Concepts

| | |
|---|---|
| 17.15 - 17.35 / 12.15 – 12.35 | **AI-DEEP™** - Model for predicting responses to cancer CPI immunotherapy |
| 17.35 - 17.55 / 12.35 – 12.55 | **Addressing difficult to treat cancers with AI-Immunology™** |
| 17.55 - 18.00 / 12.55 – 13.00 | *THANK YOU and concluding remarks* |
| 18.00 - 19.00 / 13.00 – 14.00 | *Reception with drinks and snacks* |

# Addressing difficult to treat cancers with AI-Immunology™

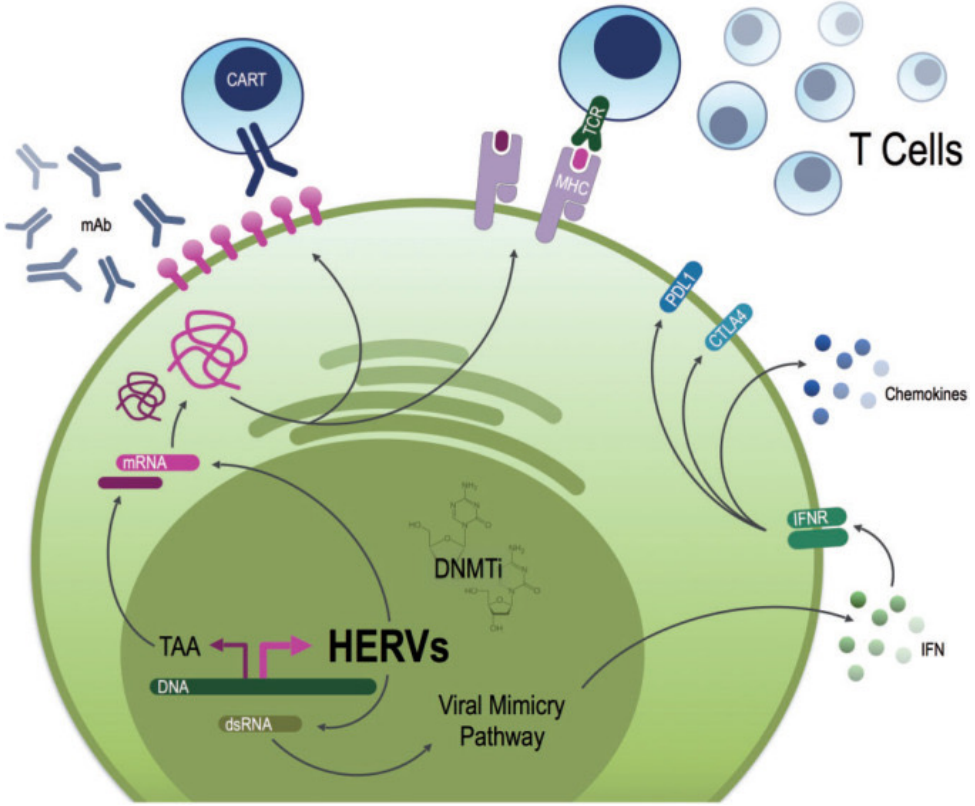
# Some Cancers Have **Few Targets** for Modern Cancer Vaccines




Alexandrov et al (2013) Nature 50, p415–421
Hilf et al (2018) Nature 565 p240-245

# **Endogenous Retroviruses (ERVs)** May be Promising Antigens for Cancer Therapies

- Ancient viruses that have integrated into the genome and are passed down through generations.
- Constitute up to 8% of the human genome
- Epigenetically suppressed in healthy tissue, but expressed in cancers
- Examples of ERVs are found to elicit specific T-cell responses and confer tumor protection in mice
- ERV specific T-cell responses have been measured in cancer patients
- In vitro killing of human tumor cell lines by ERV-specific T cells

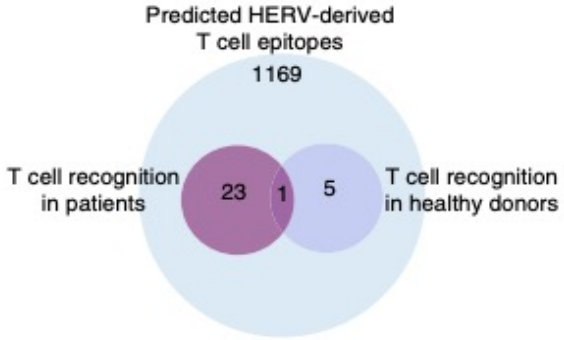



Atterman et al. (2018), Annals of Oncology 29: 2183–2191,

# The **Immune System Targets ERVs** in Blood Cancer Patients

## Saini et al 2020 – Nat. Com.

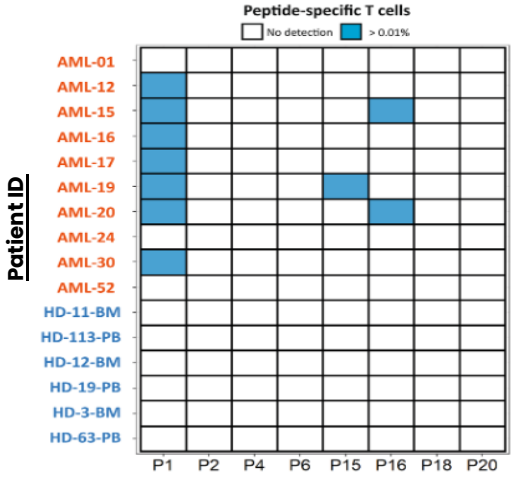
23 unique ERV T-cell targets in AML/MDS patients




Nat. Com. (2020) 11:5660

## Alcazer et al 2022 – Am J Hematol.

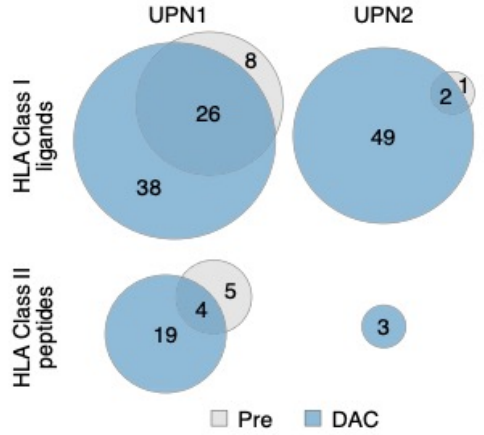
8 different HLA-A*02 epitopes identified in AML patients




Am J Hematol. (2022) 97:1200–1214

## Goyallet al 2023 – Nat. Com.

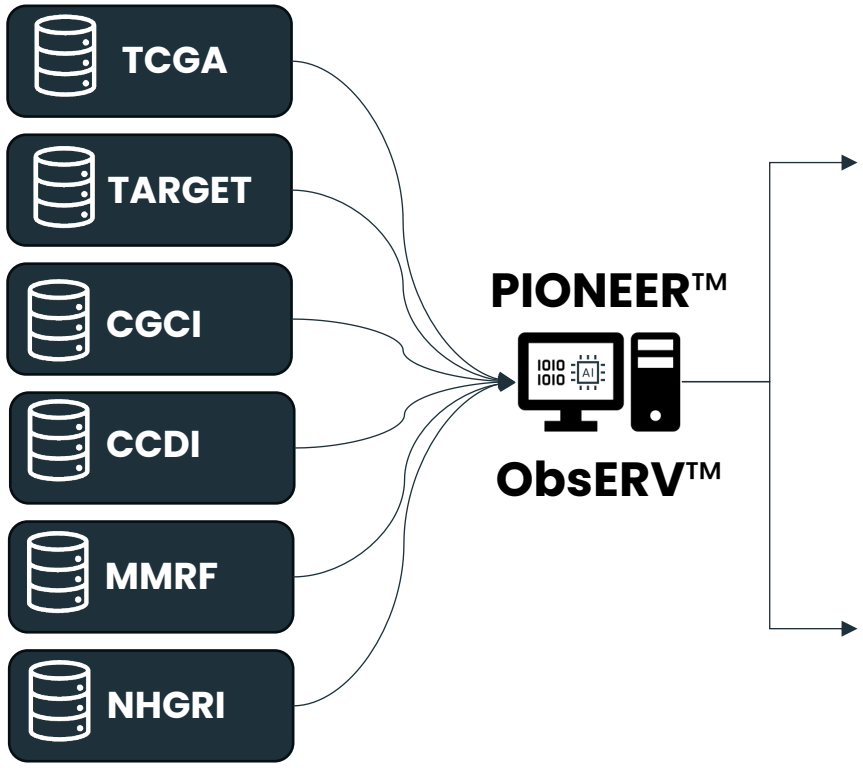
Proof that ERVs are displayed on the surface of blood cancer cells



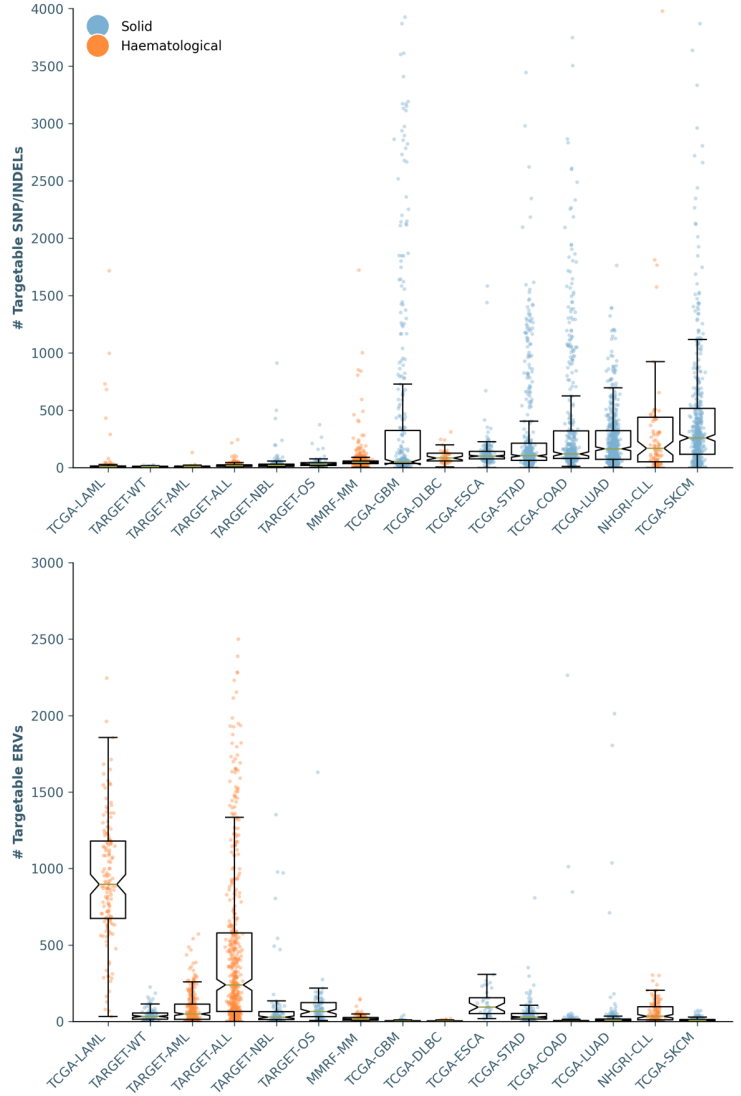

Nat. Com. (2023) 14:6731

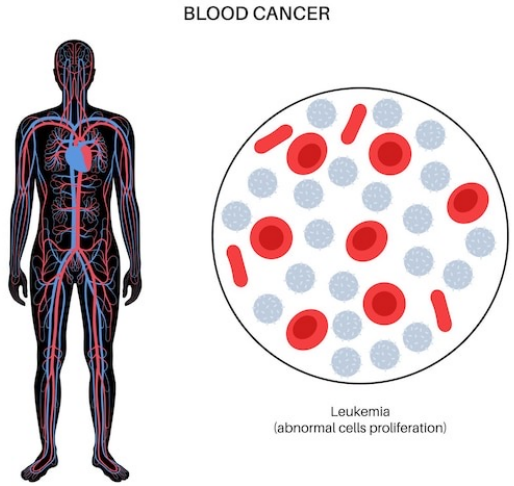
# Inclusion of ERV Targets Allows Design of **Personalized Cancer Vaccine in Difficult to Treat Cancers**

**Patient data sources (n= >15.000)**




The Cancer Genome Atlas Program (TCGA) - Therapeutically Applicable Research to Generate Effective Treatments (TARGET)- The Cancer Genome Characterization Initiative (CGCI) - Childhood Cancer Data Initiative (CCDI) - The Multiple Myeloma Research Foundation (MMRF) .-National Human Genome Research Institute (NHGRI)



# ERVs Conservation Allows for the **Design of Shared Vaccines**

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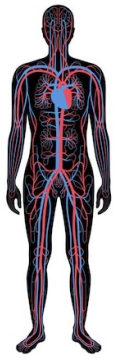
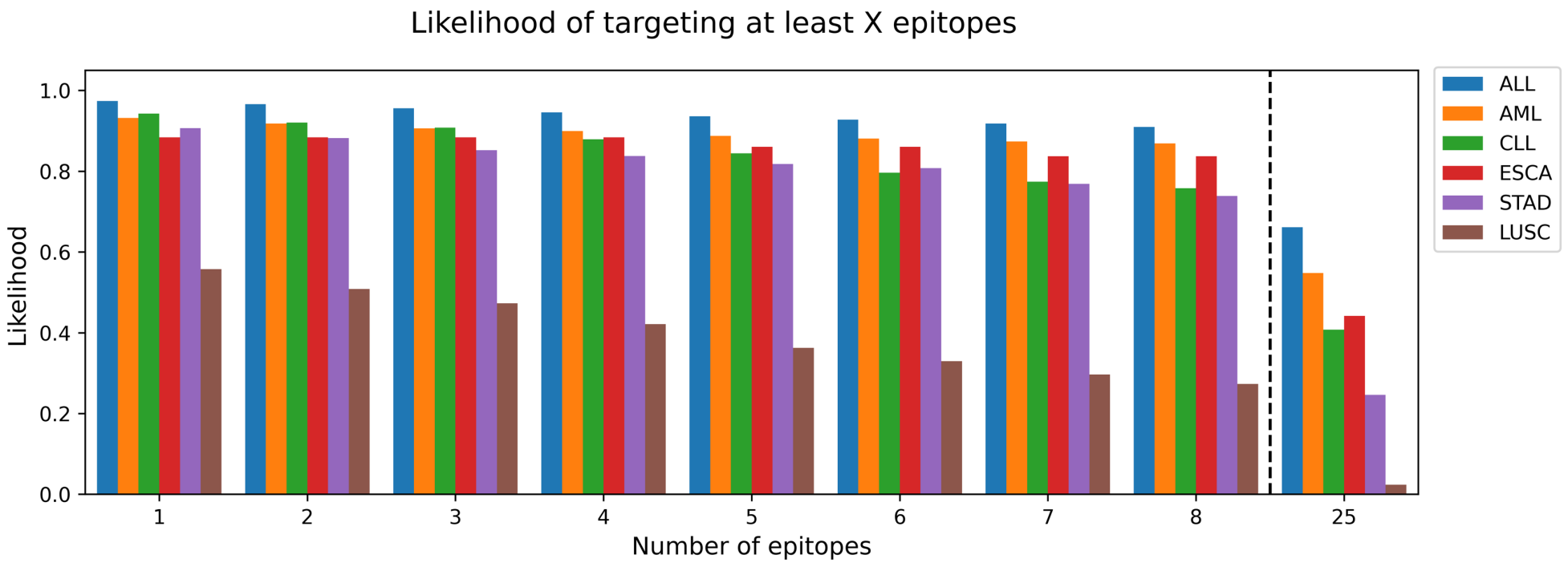
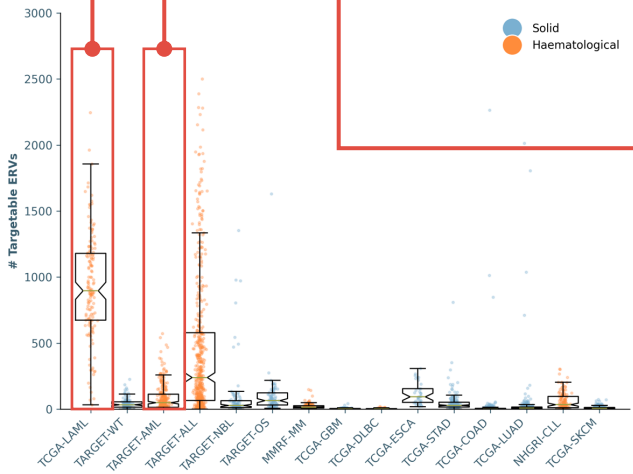
**ObsERV™ 2.0** → Shared Vaccine

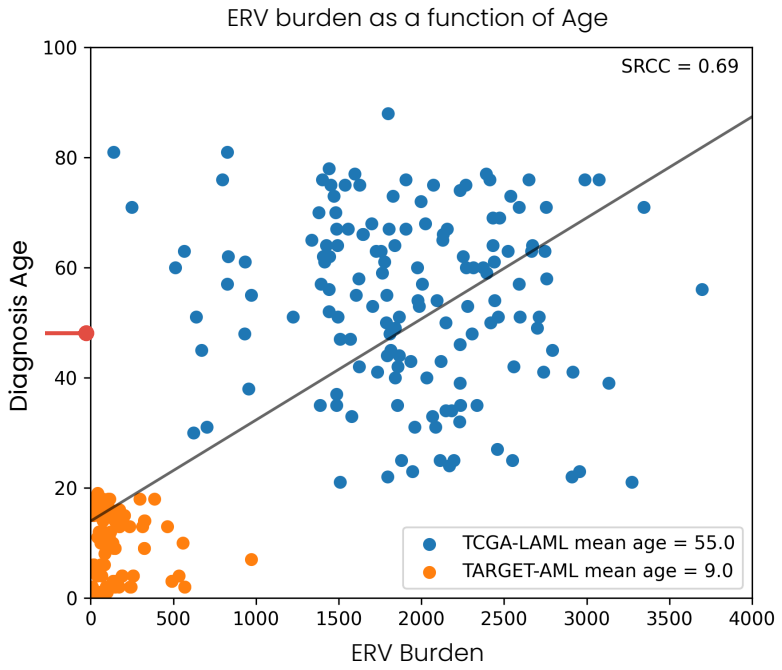


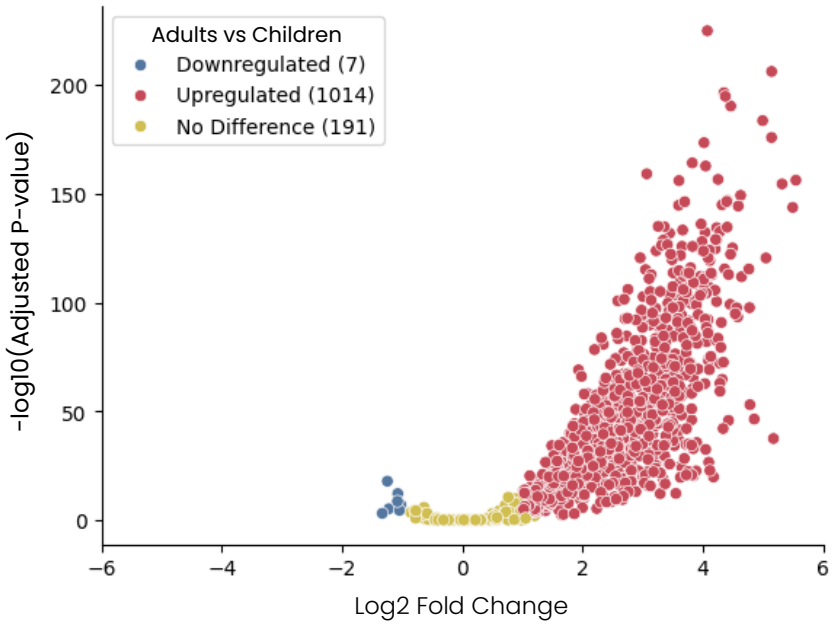


# **AML ERV Targets** are Different Depending on Age

Significant difference between ERV expression in young and old AML patients



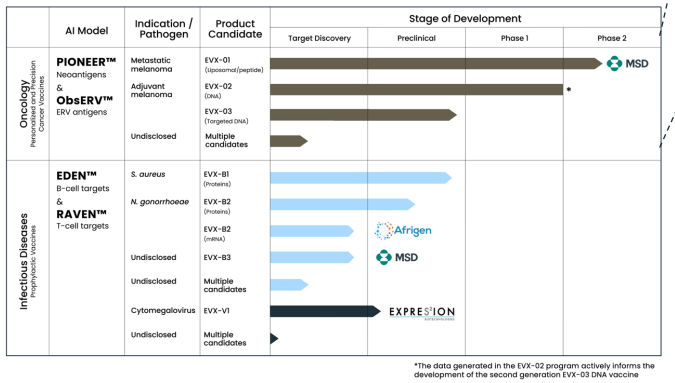



# Precision-Based Vaccines Potentially **Improves Effect** in **Childhood AML**

# **Pipeline:** Demonstrating the Performance and Scalability of Our AI-Immunology™ Platform

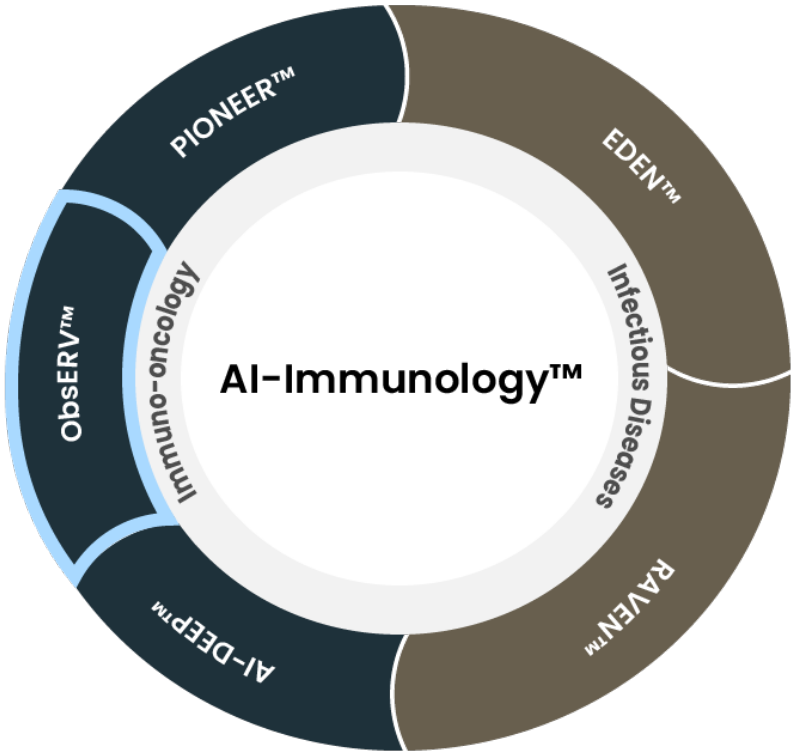
| | AI Model | Indication / Pathogen | Product Candidate | Stage of Development | | | |
|---|---|---|---|---|---|---|---|
| | | | | Target Discovery | Preclinical | Phase 1 | Phase 2 |
| Oncology<br>Personalized and Precision Cancer Vaccines | **PIONEER™**<br>Neoantigens<br>&<br>**ObsERV™**<br>ERV antigens | Undisclosed | Multiple candidates | | | | |




*The data generated in the EVX-02 program actively informs the development of the second generation EVX-03 DNA vaccine

# Summary

- Targeting ERVs allows Evaxion to design vaccines for cancers that are difficult to treat with current vaccine approaches
- With development of ObsERV™ 2.0, using building blocks from RAVEN™, shared vaccines can be designed for multiple different cancer types
- Shared vaccines have a low manufacturing cost and no lag time from diagnose to treatment
- ObsERV™ 2.0 also allows for the design of precision vaccines based on ERV expression and patient HLA profiles
- Precision vaccines allow for cost effective vaccines in cancer types where shared vaccines cannot be designed



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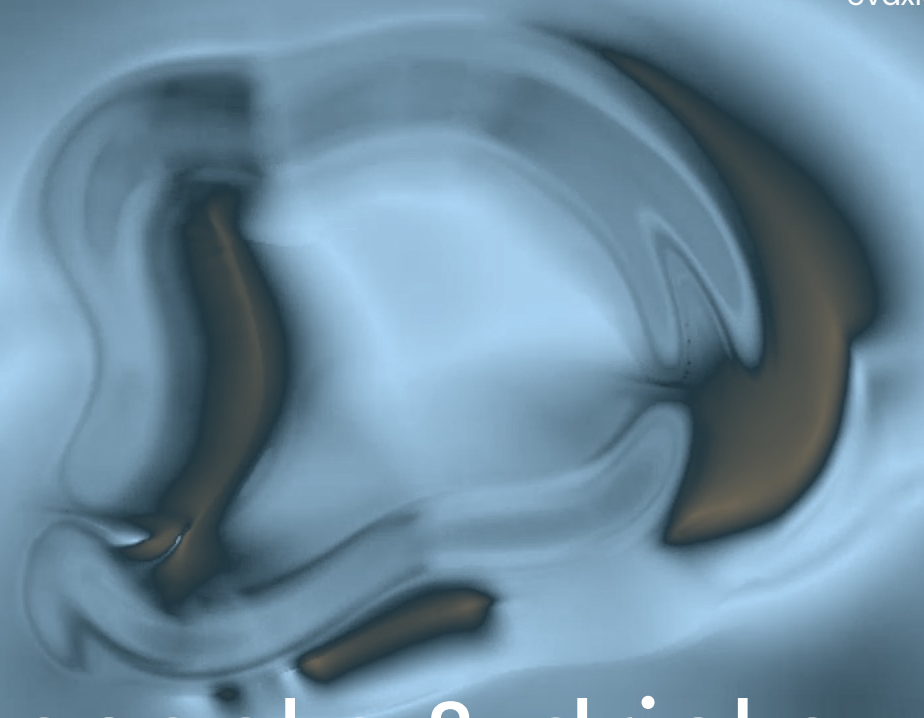
# Concluding Remarks - AI-Immunology™

- Holds the promise for a new era in vaccine discovery, design and development
- Uses advanced AI and machine learning technologies
- Outcompetes standard vaccine target discovery approaches
- Identified targets hold the promise for addressing serious unmet needs
- A unique modular architecture creates a scalable and adaptable platform
- Is validated by already established partnerships

LinkedIn:
Evaxion Biotech A/S

evaxion-biotech.com



# Thank you!

## Please stick around for snacks & drinks

AI-Immunology™
Powered Vaccines

EVAXION