

# Filtering out self-like neoantigens improves immune response to cancer vaccines

**Guilhem Richard**, Bethany Biron, Christine Boyle, Matthew Ardito, Leonard Moise, William Martin, Gad Berdugo, Anne S. De Groot

Prepared by:

**Guilhem Richard, Ph.D.**

[grichard@epivaxonco.com](mailto:grichard@epivaxonco.com)

*Lead Computational Immunologist*

**EpiVax Oncology, Inc.**

Prepared for:

**AACR Annual Meeting 2019**

Cancer Vaccines and Intratumoral Immunomodulation Minisymposium

Sunday Mar. 31<sup>st</sup>, 2019

Atlanta, Georgia, USA

**EpiVax**

2017

**EpiVax Oncology**

***20+ years of experience  
in vaccinology***

Ancer™

***Precision cancer  
immunotherapy***

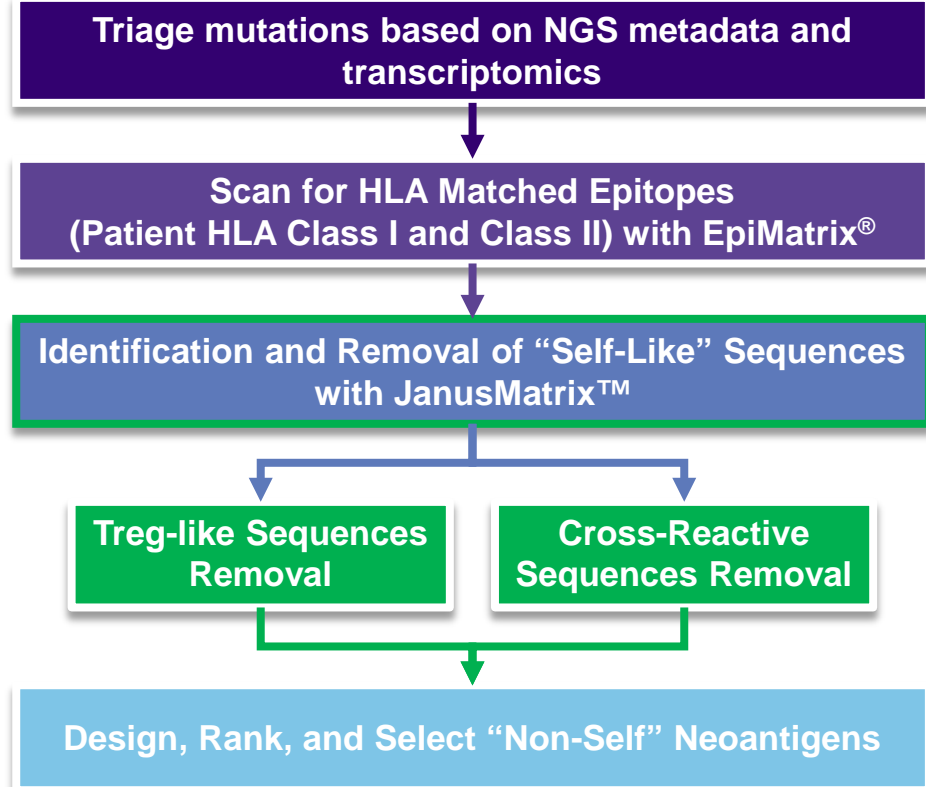
Commercial-grade *in silico*  
neo-epitope discovery platform

- EpiVax Oncology, Inc. is company created in 2017 by EpiVax, Inc.
- EpiVax, Inc. is a 20-year-old, privately held immunoinformatics biotech.

# What do we do?

## Use commercial-grade tools to design precision cancer immunotherapies

### Ancer™ platform



### Ancer™ strengths

Commercially-used CD4 and CD8 T cell prediction tools (since 1998)

Identify and remove regulatory T cells (Treg) epitopes (since 2013)

De-risk vaccines for Treg induction or immune adverse events

Precise design of neoantigen-based vaccines

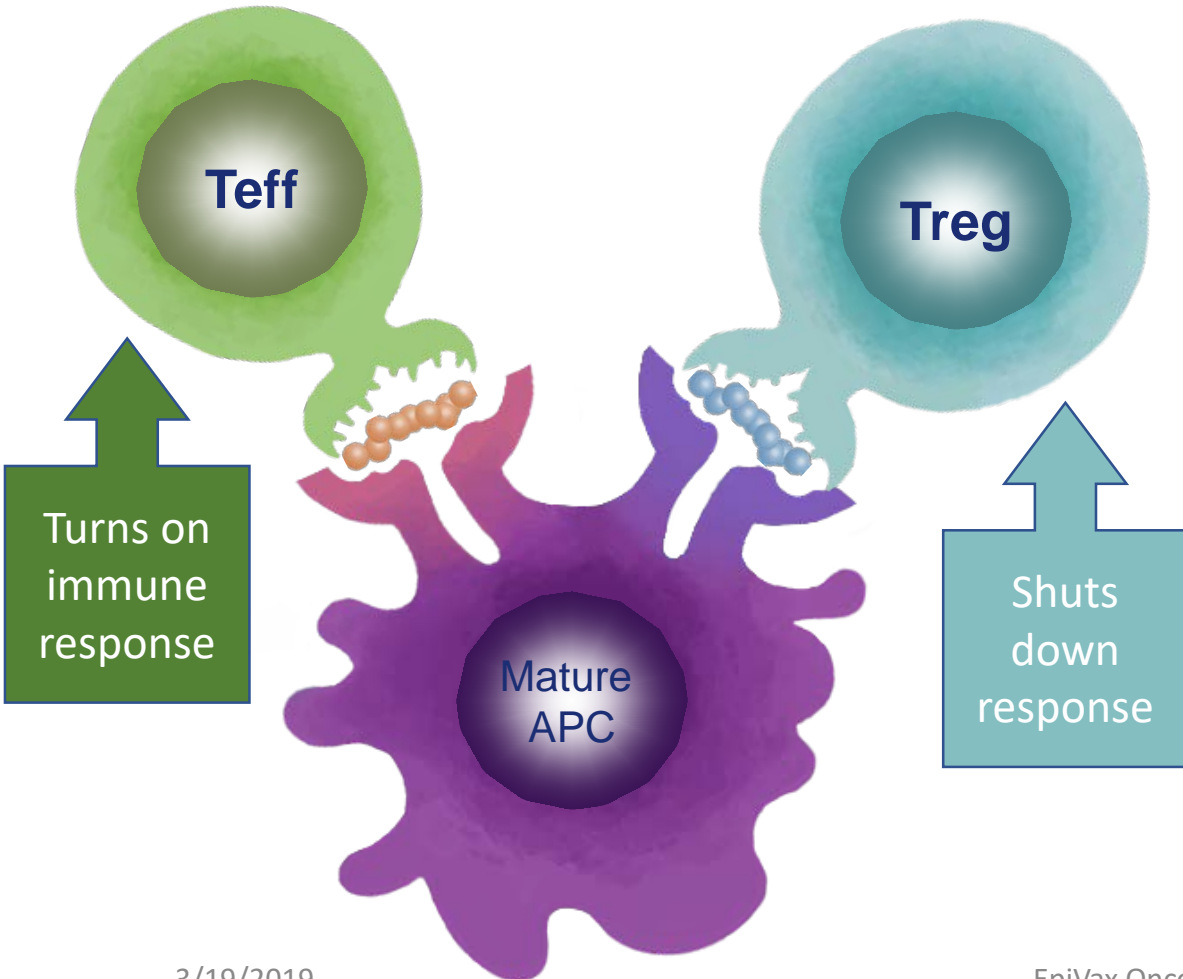
## Talk Overview?

It's all about finding and removing Treg neo-epitopes.

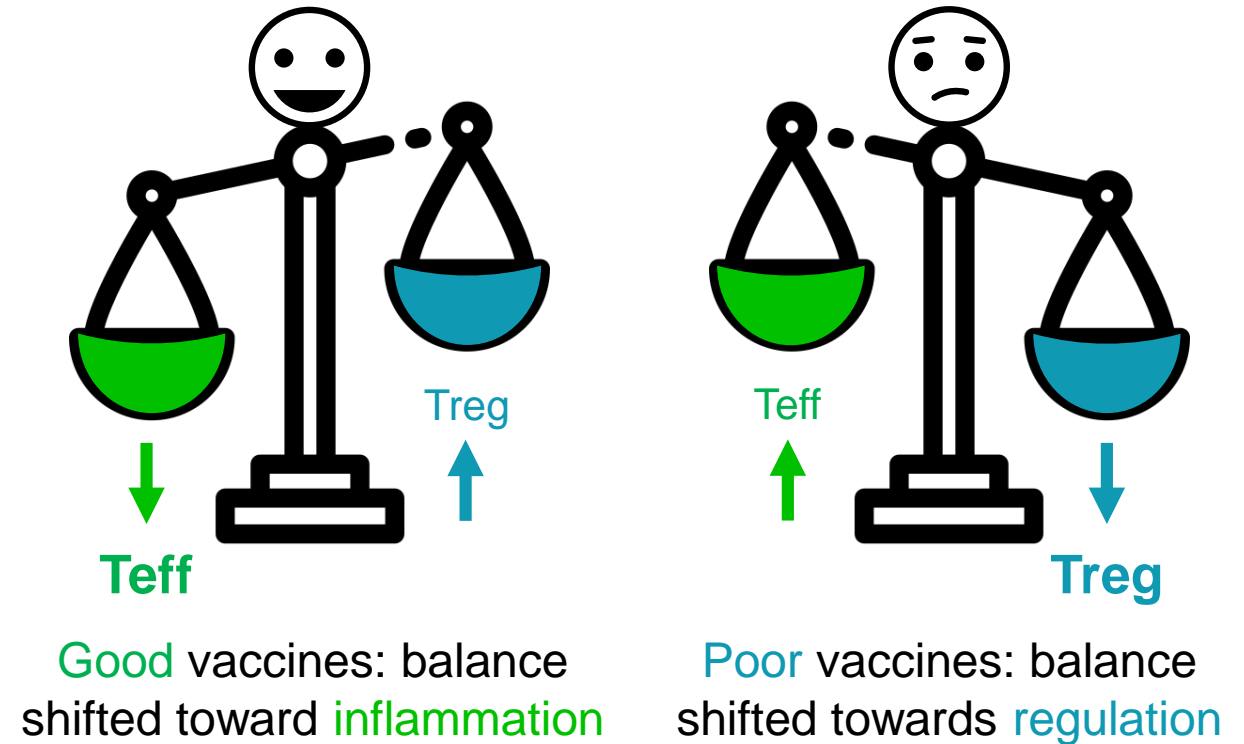
- Some MHC II T cell epitopes are recognized by Tregs and reduce vaccine efficacy.
- In this presentation I will show you that:
  1. We find self-like (i.e. putative Treg) neo-epitopes in cancer mutanomes and remove them from vaccines.
  2. We design highly immunogenic vaccines by precisely selecting MHC I and MHC II effector neo-epitopes.
  3. Some self-like MHC II neo-epitopes reduce vaccine immunogenicity by 5-fold.
- Inclusion of Treg neo-epitopes in cancer immunotherapies may be a cause for lack of efficacy.

# Some T cell epitopes may engage Tregs. Achieving the right balance between Teff and Treg epitopes is important.

Epitopes can be either effector or regulatory



Inclusion of Treg epitopes may hinder vaccine efficacy



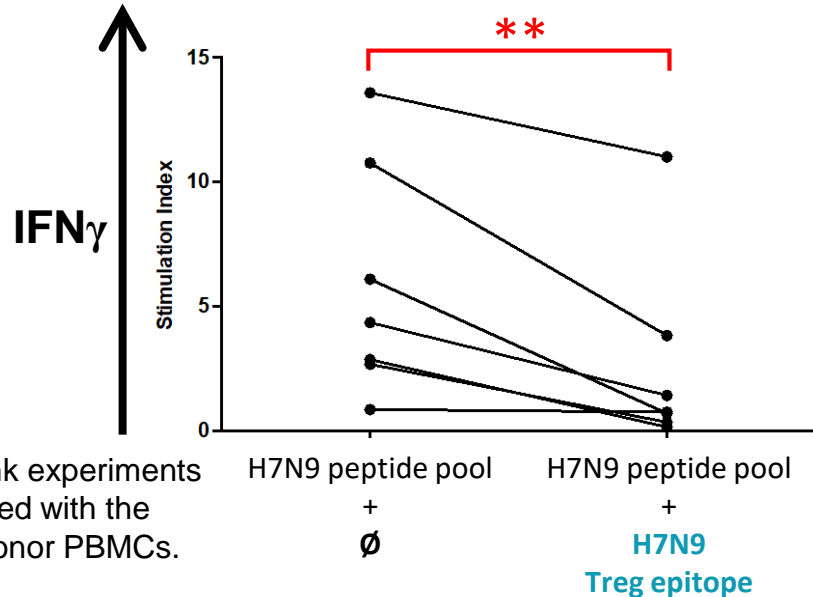
How to eliminate Treg responses?

# We identified Treg epitopes in pathogens. Can lessons learned from infectious disease be translated to oncology?

*In silico* tools help us identify immunosuppressive T cell epitopes.

Moise, Hum Vaccin Immunother 2013

Flu case study:



***In silico***-derived influenza (H7N9) Treg epitope reduces IFN $\gamma$  responses to effector peptides.

Liu, Hum Vaccin Immunother 2015

He et al. BMC Bioinformatics 2014, 15(Suppl 4):S1  
http://www.biomedcentral.com/1471-2105/15/S4/S1

BMC Bioinformatics

RESEARCH Open Access

**Integrated assessment of predicted MHC binding and cross-conservation with self reveals patterns of viral camouflage**

Lu He<sup>1</sup>, Anne S De Groot<sup>2,3</sup>, Andres H Gutierrez<sup>2</sup>, William D Martin<sup>3</sup>, Lenny Moise<sup>2,3</sup>, Chris Bailey-Kellogg<sup>1\*</sup>

From The 3rd ISV Pre-conference Computational Vaccinology Workshop (ICoVax 2013) Barcelona, Spain. 26 October 2013

Human Vaccines & Immunotherapeutics 11:9, 2241–2252; September 2015; Published with license by Taylor & Francis Group, LLC

RESEARCH PAPER

**H7N9 T-cell epitopes that mimic human sequences are less immunogenic and may induce Treg-mediated tolerance**

Rui Liu<sup>1</sup>, Leonard Moise<sup>1,2</sup>, Ryan Tassone<sup>1</sup>, Andres H Gutierrez<sup>1</sup>, Frances E Terry<sup>2</sup>, Kotou Sangare<sup>3</sup>, Matthew T Ardito<sup>2</sup>, William D Martin<sup>2</sup>, and Anne S De Groot<sup>1,2,4\*</sup>

<sup>1</sup>Institute for Immunology and Informatics; University of Rhode Island; Providence, RI USA; <sup>2</sup>EpiVax Inc.; Providence, RI USA; <sup>3</sup>Laboratory of Applied Molecular Biology (LBMA); University of Bamako; Bamako, Mali

www.nature.com/scientificreports

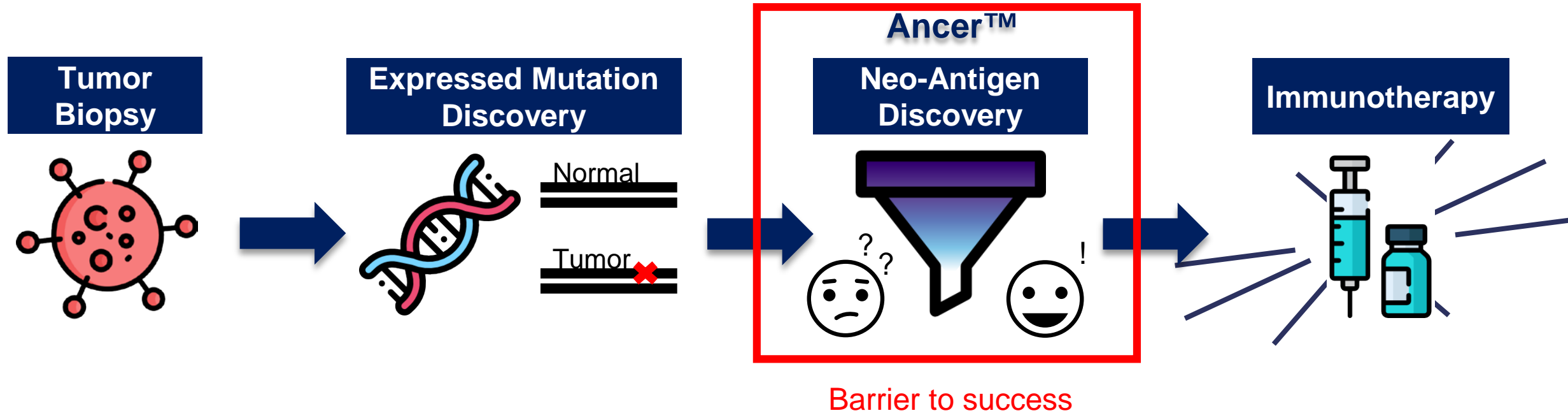
SCIENTIFIC REPORTS

OPEN A humanized mouse model identifies key amino acids for low immunogenicity of H7N9 vaccines

Received: 17 November 2016  
Accepted: 29 March 2017

Yamato Wada<sup>1,2</sup>, Arnone Nithichanon<sup>1,3</sup>, Eri Nobusawa<sup>4</sup>, Leonard Moise<sup>5,6</sup>, William D. Martin<sup>6</sup>, Norio Yamamoto<sup>4,7</sup>, Kazutaka Terahara<sup>1</sup>, Haruhisa Hagiwara<sup>1</sup>, Takato Odagiri<sup>1</sup>, Masato Tashiro<sup>8</sup>, Ganjana Lertmemongkolkhai<sup>9</sup>, Haruko Takeyama<sup>2</sup>, Anne S. De Groot<sup>1,6</sup>, Manabu Ato<sup>2</sup> & Yoshimasa Takahashi<sup>1</sup>

# Finding the right neo-epitopes to include in personalized immunotherapies remains a challenge.



Which neo-epitopes should be included in personalized immunotherapies?

## Traditional considerations:

- Variant Expression
- Variant Clonality
- Class I MHC binding (CD8 T cells)

## Additional novel considerations:

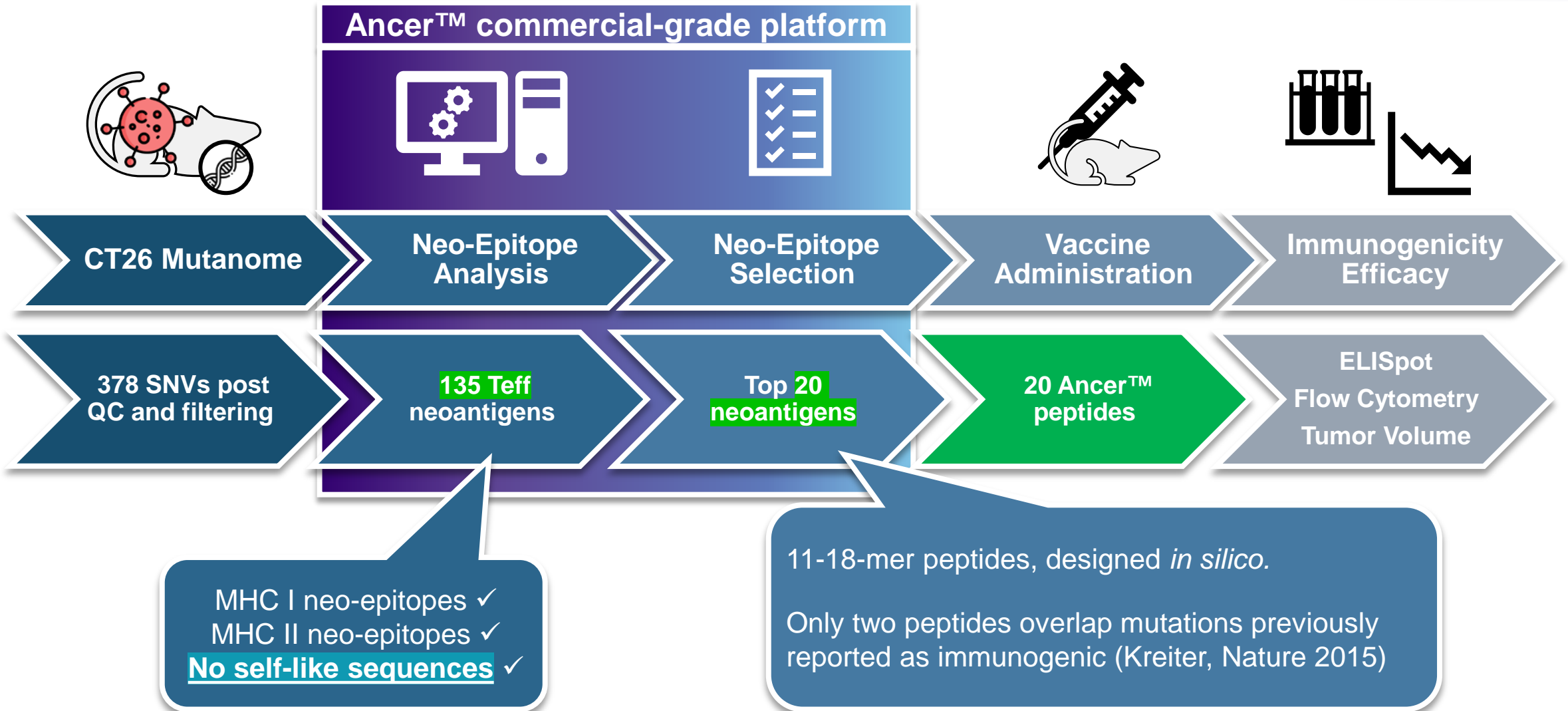
- **Class II MHC binding (CD4 T cells)**
- **Type of T cell response (Teff or Treg)**

# Outline

- Background
- Can our *in silico* platform generate immunogenic neo-epitope-based vaccines?
- Can certain neo-epitopes negatively affect the outcome of immunotherapies?
- Summary and next steps

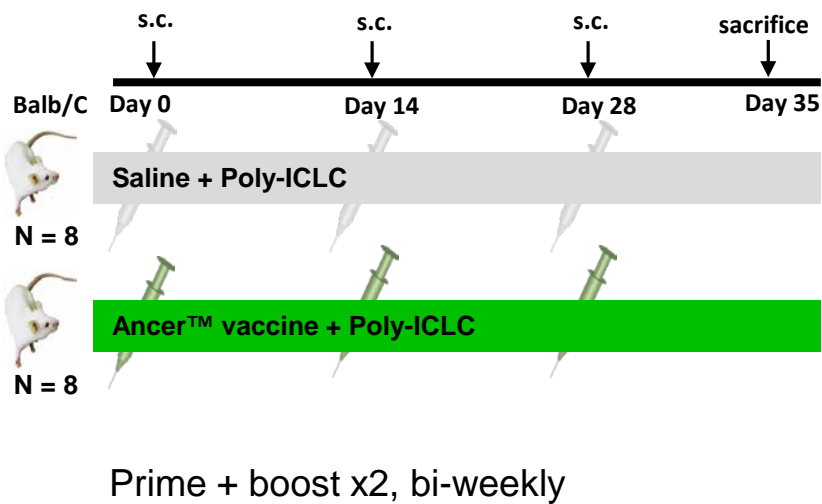


# We precisely designed a new CT26 vaccine enriched for Teff content and with reduced risk of engaging Tregs

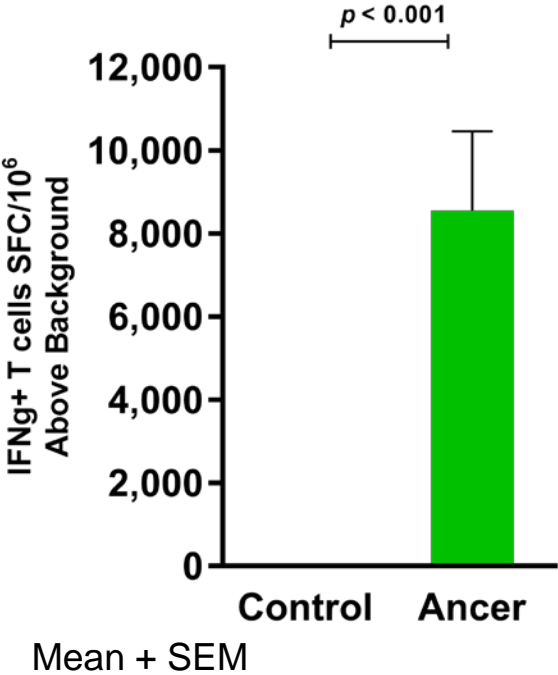


# Immunization of naïve Balb/c mice with our CT26 vaccine induced strong IFN $\gamma$ ELISpot responses

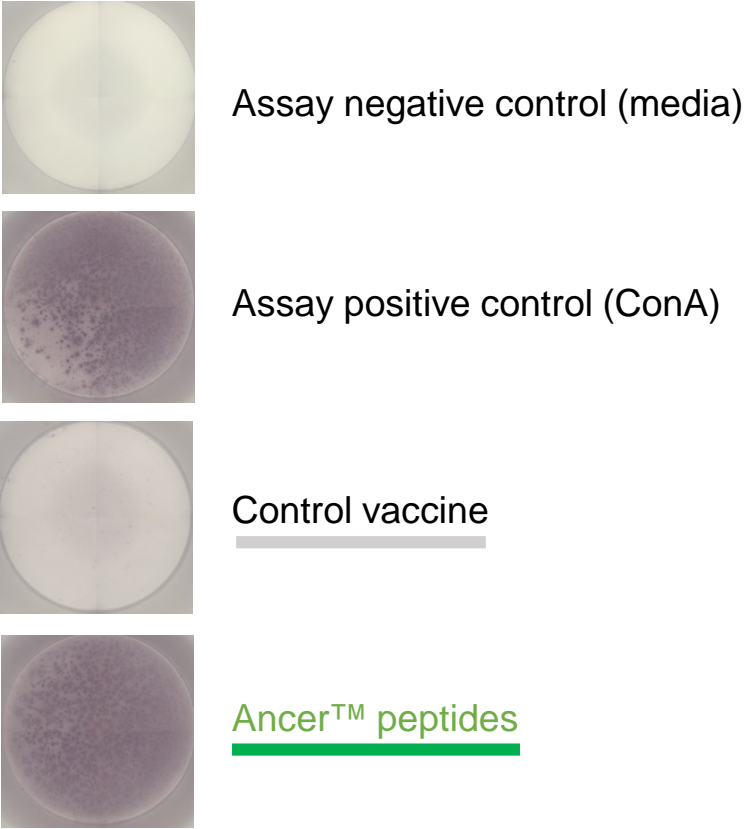
## Protocol



## IFN $\gamma$ ELISpot Results

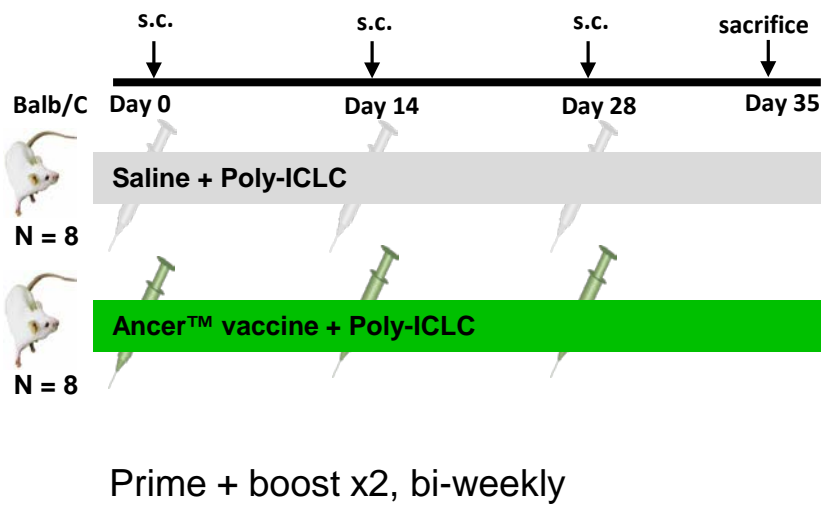


Strong neo-epitope responses

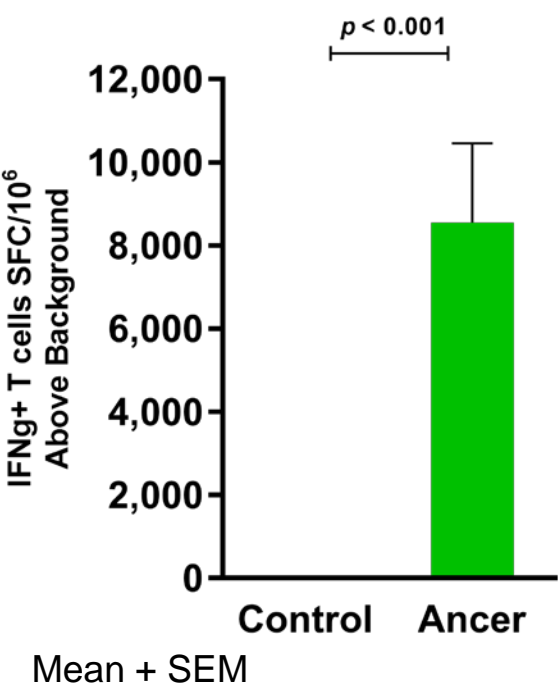


# Flow cytometry confirmed that our CT26 vaccine stimulated multifunctional CD4+ and CD8+ T cells

## Protocol

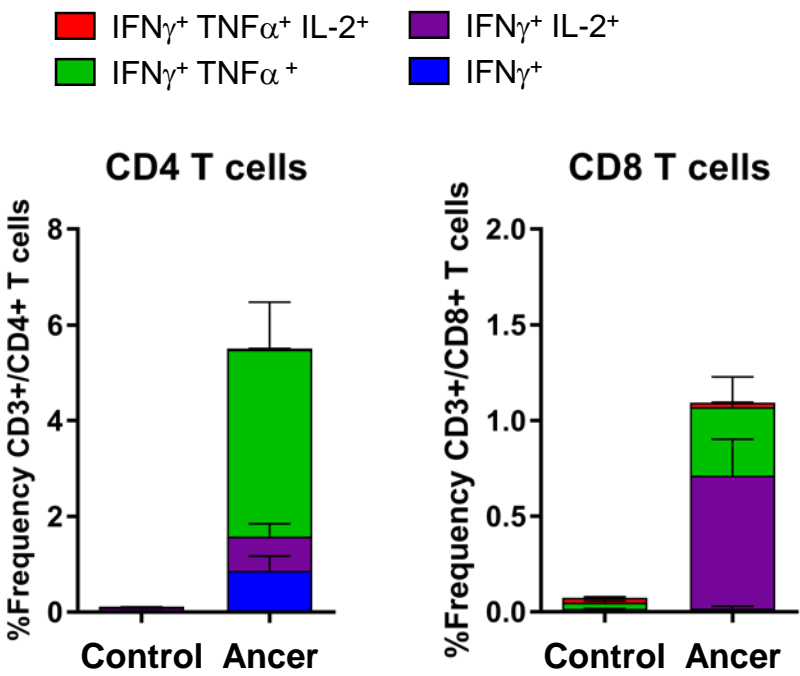


## IFN $\gamma$ ELISpot Results



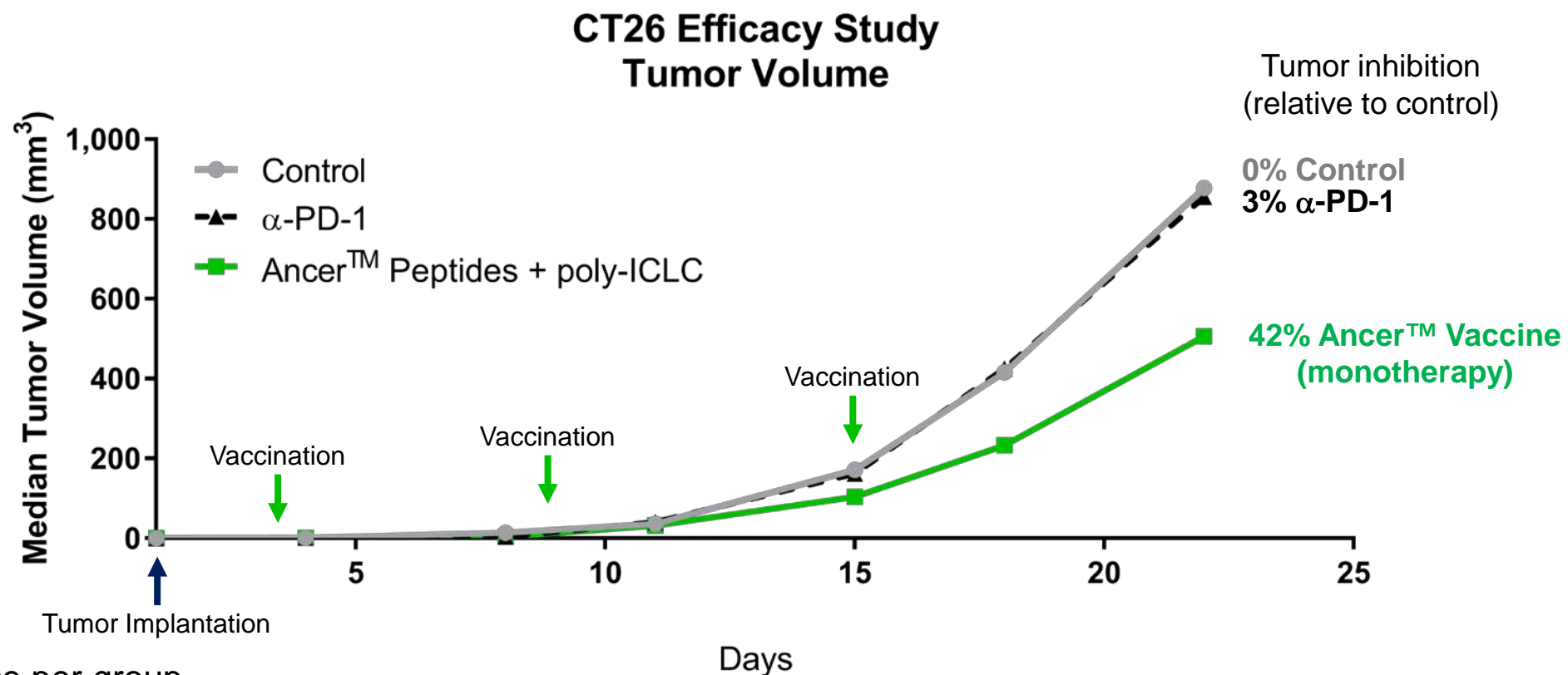
Strong neo-epitope responses

## Flow Cytometry Results



Multifunctional CD4+/CD8+ response

# Preliminary results show a 42% reduction in tumor burden with our CT26 vaccine (unoptimized dosing schedule)



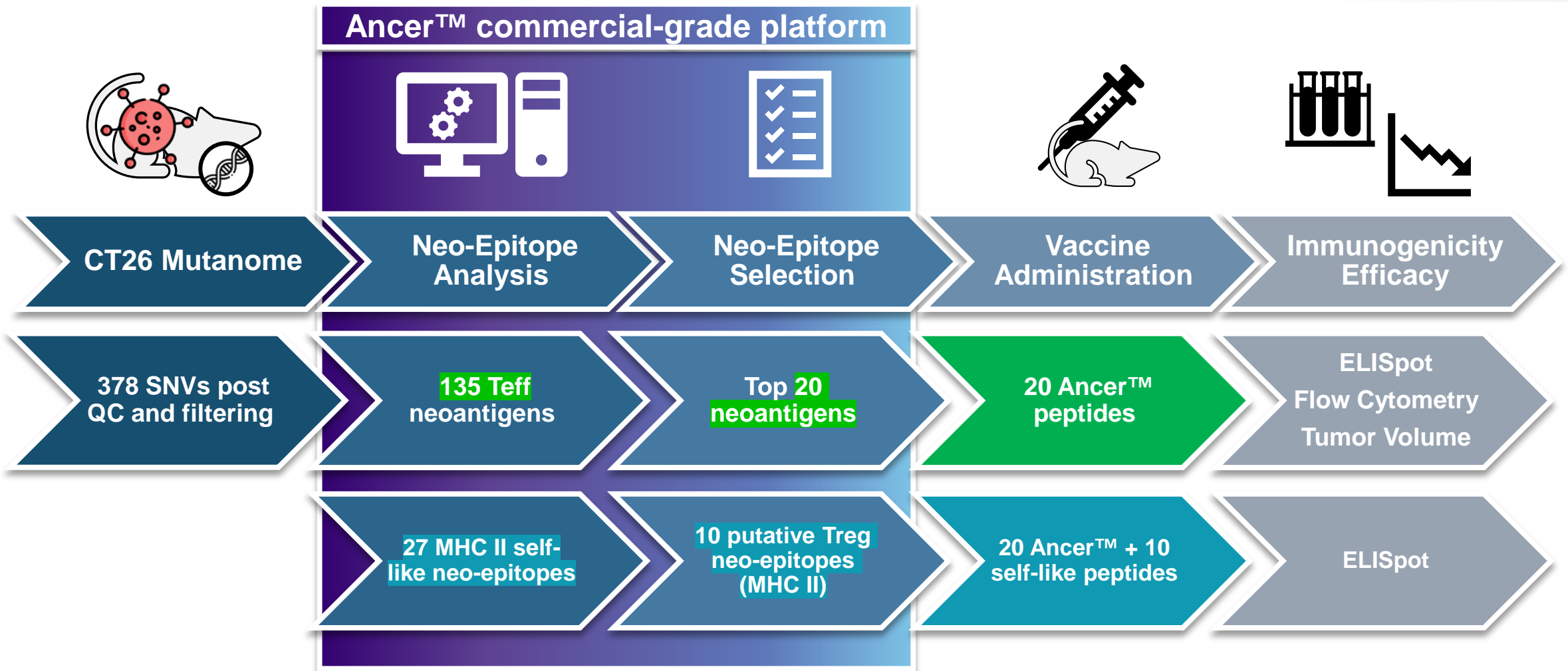
N = 12 mice per group

**Ancer<sup>™</sup> vaccine alone reduces median CT26 tumor burden by 42% at day 22.** Additional efficacy studies are ongoing.

# Outline and preliminary conclusions

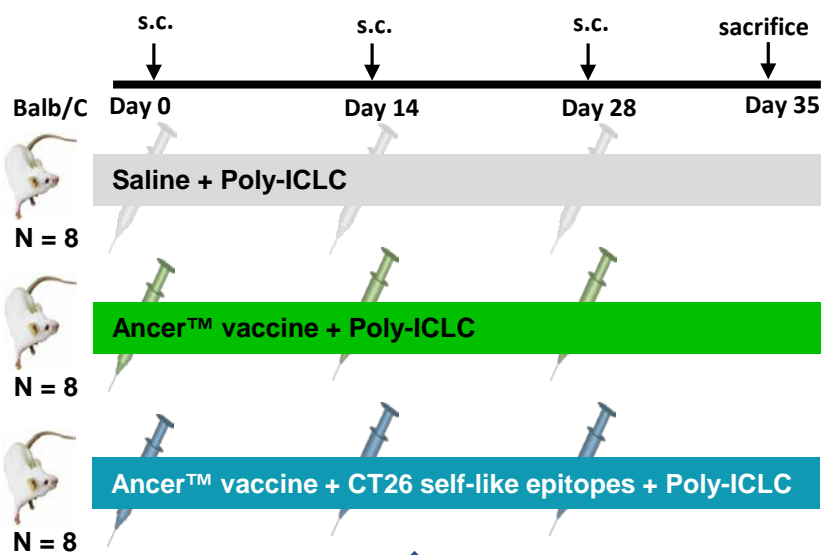
- Background
- Can our *in silico* platform generate immunogenic neo-epitope-based vaccines?  
YES
- Can certain neo-epitopes negatively affect the outcome of immunotherapies?
- Summary and next steps

We selected 10 MHC II “self-like” CT26 neo-epitopes.  
We hypothesize these may be Treg epitopes.



# Co-administration of CT26 self-like neo-epitopes with our immunogenic vaccine diminished IFN $\gamma$ ELISpot responses by 5-fold

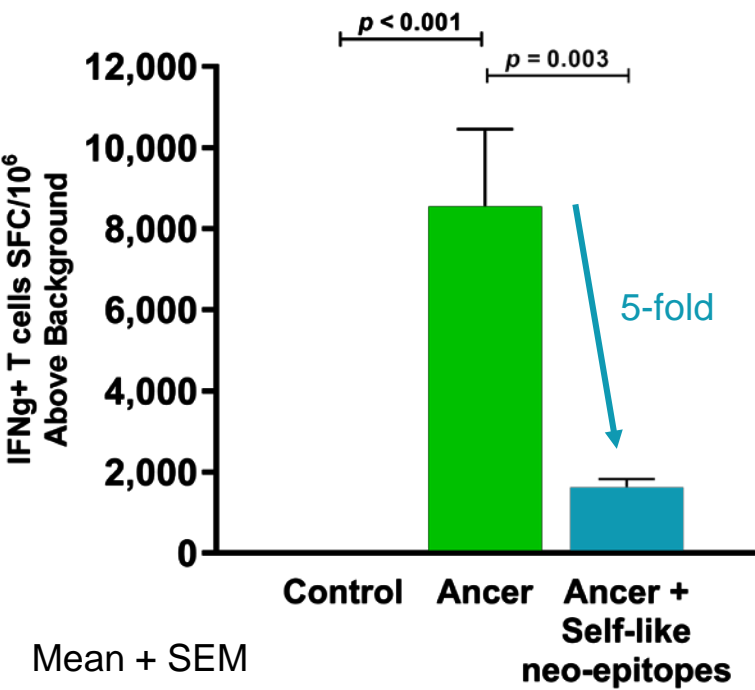
## Protocol



Does adding back “Treg” neo-epitopes suppress the immune response?

Prime + boost x2, bi-weekly

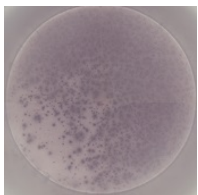
## IFN $\gamma$ ELISpot Results



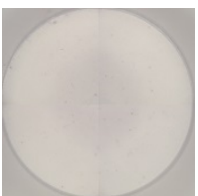
Immunogenicity reduced 5-fold when including MHC II self-like neo-epitopes



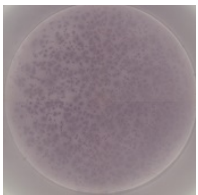
Assay negative control (media)



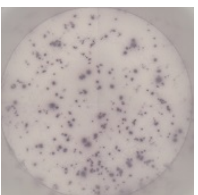
Assay positive control (ConA)



Control vaccine



Ancer™ peptides



Ancer™ + self-like peptides

# Outline

- Background
- Can our *in silico* platform we generate immunogenic neo-epitope-based vaccines? YES
- Can certain neo-epitopes negatively affect the outcome of immunotherapies? YES
- Summary and next steps



# Summary

- ***Not all neo-epitopes are created equal!***
- **Some neo-epitopes may suppress immune responses due to their homology with self-sequences.**
- **We designed a new highly immunogenic CT26 neoantigen-based vaccine enhanced for both CD4 and CD8 T effector content and devoid of self-like epitopes.**
- **Our vaccine induced strong IFN $\gamma$  ELISpot responses and multifunctional CD4+ and CD8+ T cell responses.**
- **Co-administration of self-like MHC II neo-epitopes with our vaccine reduced its immunogenicity by 5-fold.**

## Next Steps

- Perform bystander suppression (Treg) assays to confirm the suppressive effect of the CT26 self-like neo-epitopes.
- Determine if CT26 self-like neo-epitopes affect both CD4 and CD8 T cell responses.
- Efficacy studies are ongoing and will clarify the role of self-like neo-epitopes on survival.

Collaborations are welcomed!

# Acknowledgments to the EpiVax and EpiVax Oncology family

## EpiVax Oncology



Gad Berdugo  
CEO  
[gberdugo@epivaxonco.com](mailto:gberdugo@epivaxonco.com)



Dominique Bridon  
CTO  
[dbridon@epivaxonco.com](mailto:dbridon@epivaxonco.com)



Guilhem Richard  
Lead Computational Immunologist  
[grichard@epivaxonco.com](mailto:grichard@epivaxonco.com)

## EpiVax

Annie De Groot  
William Martin

Vaccine Research  
Lenny Moise  
Christine Boyle  
Bethany Biron

Immunoinformatics  
Matthew Ardito

Laboratory  
Bethany McGonnigal  
Danielle Medeiros  
Drasti Kanakia

