vaccibody

Personalized Cancer Neoantigen Vaccines

Turning the Immune System Against Your own Unique Tumour-Specific Antigens

3rd Annual Advances in Immuno-Oncology Congress

London, May 24, 2018

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Vaccibody AS

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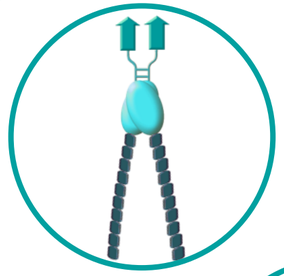
Agenda

1. Background Cancer Neoantigens

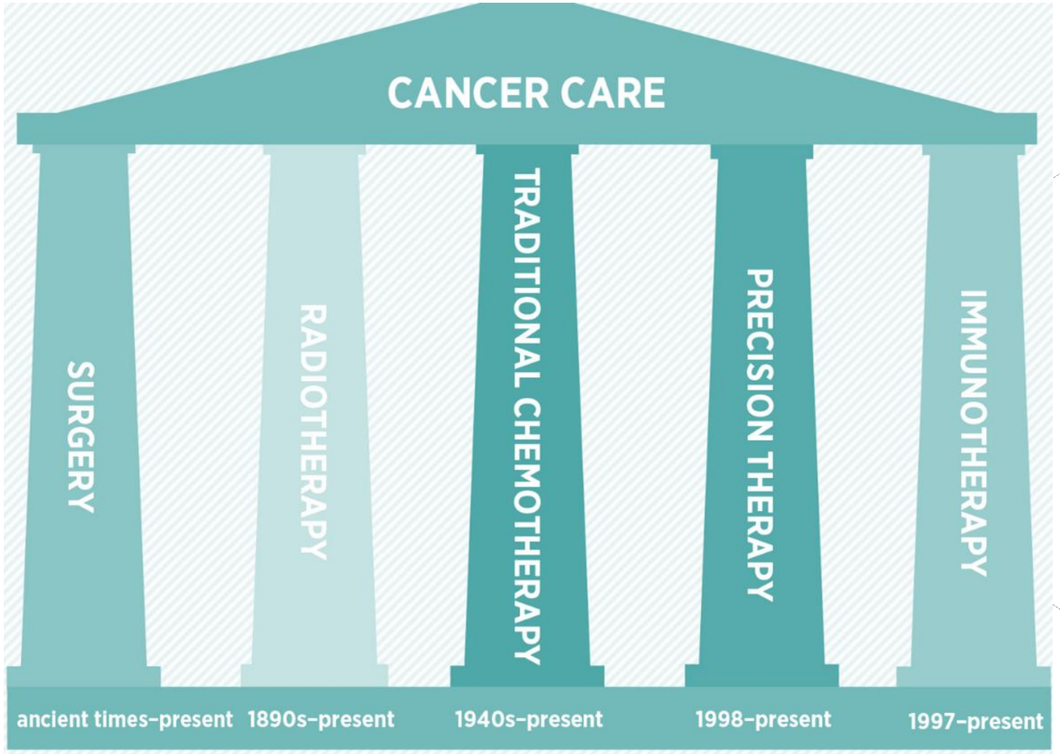
2. Vaccibody's Cancer Vaccine Strategy



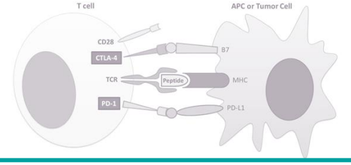
3. Neoantigen Prediction Tools
   Any general Principles?

4. Vaccibody's Clinical Trial Experience and Future Plans

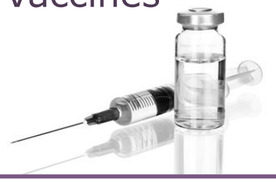
Immunotherapy: The next Wave of Cancer Therapy



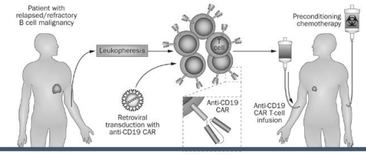
Checkpoint Inhibitors



Vaccines



Cell Therapies

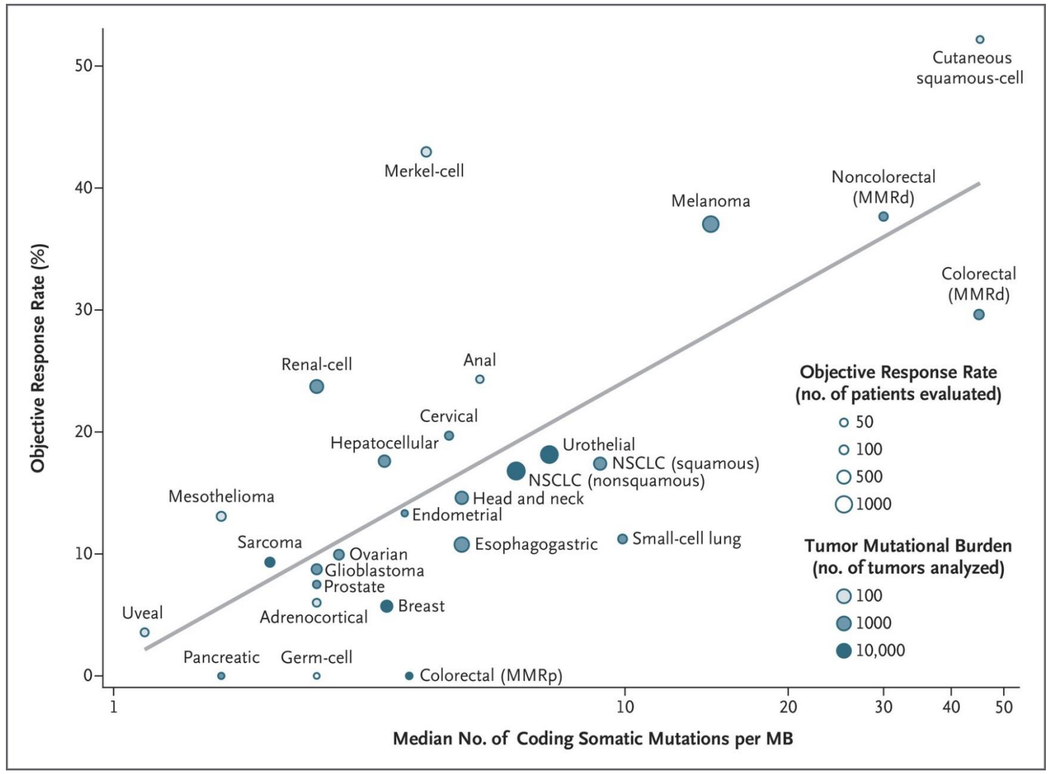


Others, e.g.

- Oncolytic viruses
- Cytokines
- Bi-specific antibodies
- Small molecules
- Adjuvants

Various Immuno-Therapy Modalities

CheckPoint Inhibitors – relationship to neoantigens

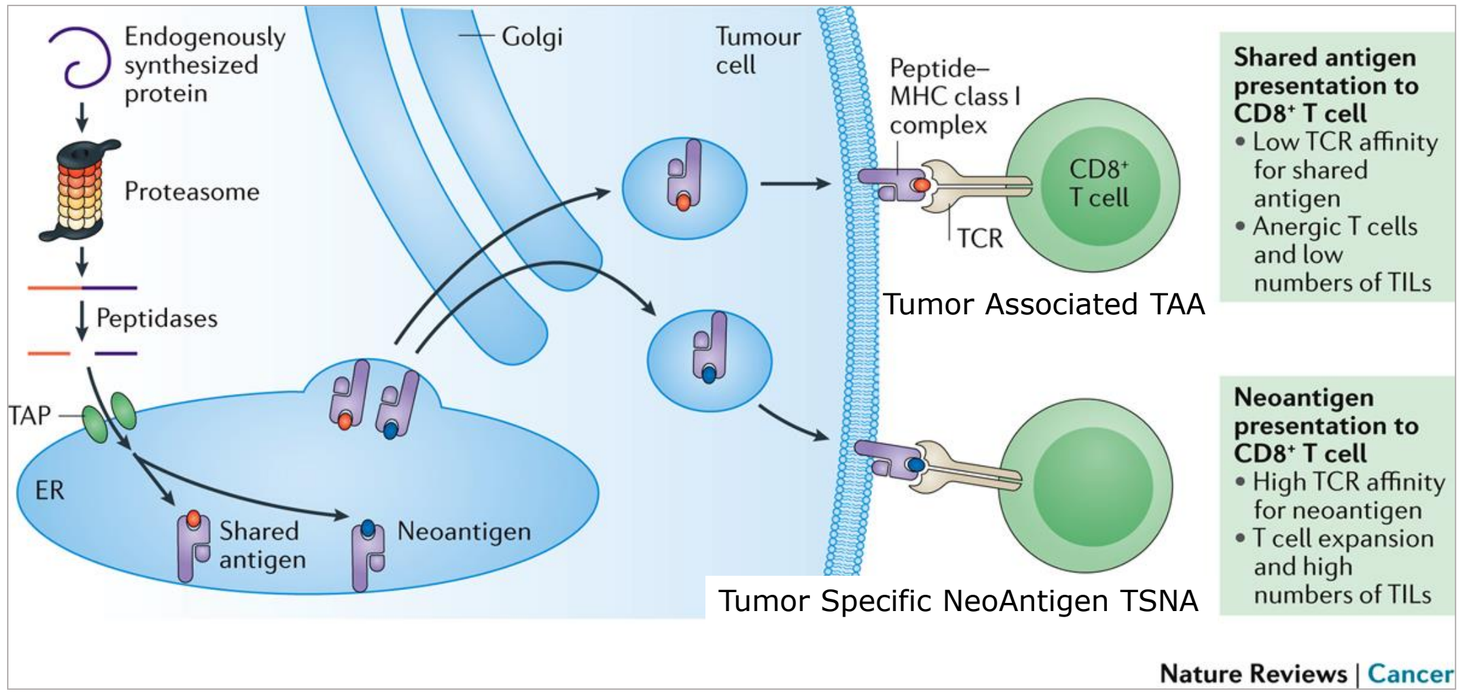


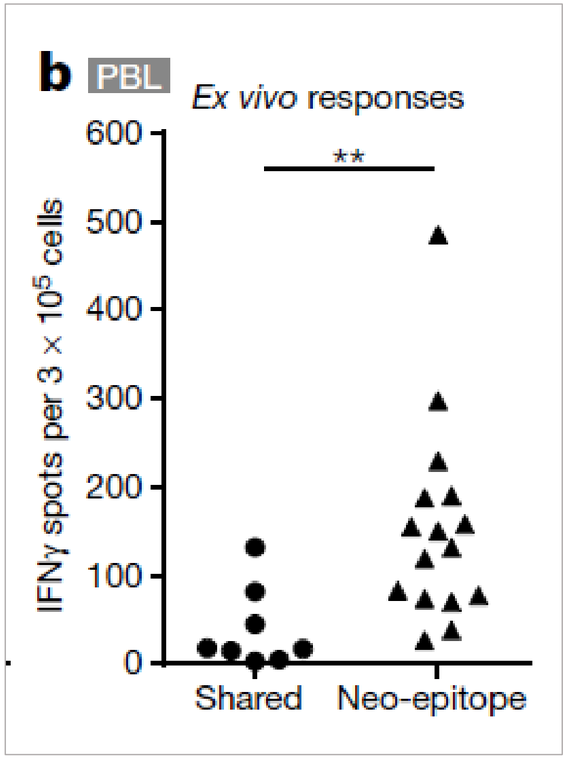
- Strong relationship between mutational burden and response to CPI
- Limits response to already existing neoantigen-specific T cell repertoire
- Reveals an important role of immune responses to neoantigens in cancer immunotherapy

Cancer neoantigen vaccines are the **optimal tool** to activate a truly specific, strong and broad neoantigen specific T cell responses

Yarchoan et al., 2017 NEJM

Neoantigens are strongly immunogenic Tumour Antigens





- Higher affinity TCR available for neoantigens than shared TAA
- IFN-γ T cell responses to neoantigens are stronger than to shared TAA

Yarchoan et al Nature Rewies 2017
Sahin et al Nature Letters 2017
McGranahan Science 2016

Proof of Concept published in Nature Letters July 2017

LETTER

NEON THERAPEUTICS

doi:10.1038/nature22991

An immunogenic personal neoantigen vaccine for patients with melanoma

Patrick A. Ott[1,2,3*], Zhuting Hu[1*], Derin B. Keskin[1,3,4], Sachet A. Shukla[1,4], Jing Sun[1], David J. Bozym[1], Wandi Zhang[1], Adrienne Luoma[5], Anita Giobbie-Hurder[6], Lauren Peter[7,8], Christina Chen[1], Oriol Olive[1], Todd A. Carter[4], Shuqiang Li[4], David J. Lieb[4], Thomas Eisenhaure[4], Evisa Gjini[9], Jonathan Stevens[10], William J. Lane[10], Indu Javeri[11], Kaliappanadar Nellaiappan[11], Andres M. Salazar[12], Heather Daley[1], Michael Seaman[7], Elizabeth I. Buchbinder[1,2,3], Charles H. Yoon[3,13], Maegan Harden[4], Niall Lennon[4], Stacey Gabriel[4], Scott J. Rodig[9,10], Dan H. Barouch[3,7,8], Jon C. Aster[3,10], Gad Getz[3,4,14], Kai Wucherpfennig[3,5], Donna Neuberg[6], Jerome Ritz[1,2,3], Eric S. Lander[3,4], Edward F. Fritsch[1,4†], Nir Hacohen[3,4,15] & Catherine J. Wu[1,2,3,4]

- 6 patients with melanoma (stage III/IV)
- 97 neoepitopes delivered as long-peptides with polyICLC (SC)
- CD4 dominated responses

LETTER

BIONTECH

doi:10.1038/nature23003

Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer

Ugur Sahin[1,2,3], Evelyna Derhovanessian[1], Matthias Miller[1], Björn-Philipp Kloke[1], Petra Simon[1], Martin Löwer[2], Valesca Bukur[1,2], Arbel D. Tadmor[2], Ulrich Luxemburger[1], Barbara Schrörs[2], Tana Omokoko[1], Mathias Vormehr[1,3], Christian Albrecht[2], Anna Paruzynski[1], Andreas N. Kuhn[1], Janina Buck[1], Sandra Heesch[1], Katharina H. Schreeb[1], Felicitas Müller[1], Inga Ortseifer[1], Isabel Vogler[1], Eva Godehardt[1], Sebastian Attig[2,3], Richard Rae[2], Andrea Breitkreuz[1], Claudia Tolliver[1], Martin Suchan[2], Goran Martic[2], Alexander Hohberger[3], Patrick Sorn[2], Jan Diekmann[1], Janko Ciesla[4], Olga Waksmann[4], Alexandra-Kemmer Brück[1], Meike Witt[1], Martina Zillgen[1], Andree Rothermel[2], Barbara Kasemann[2], David Langer[1], Stefanie Bolte[1], Mustafa Diken[1,2], Sebastian Kreiter[1,2], Romina Nemecek[5], Christoffer Gebhardt[6,7], Stephan Grabbe[3], Christoph Höller[5], Jochen Utikal[6,7], Christoph Huber[1,2,3], Carmen Loquai[3*] & Özlem Türeci[8*]

- 13 patients with melanoma (stage III/IV)
- 125 neoepitopes delivered as ivt-RNA (intranodal)
- CD4 dominated responses

- Vaccinating with neoepitopes elicits a broad and strong tumour-specific immune response
- Both peptide and RNA neoantigen based vaccines elicits predominantly CD4 T cell responses

Ott et al., Nature Letters 2017
Sahin et al., Nature Letters 2017

The Workflow of Personalised Cancer Treatment

1. Tumour biopsy and sequencing

2. Neoepitope selection (TSNA)

3. Vaccine manufacturing (n=1)

4. Vaccine administration and immunogenicity

Time, cost, efficacy?

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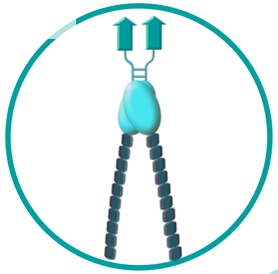

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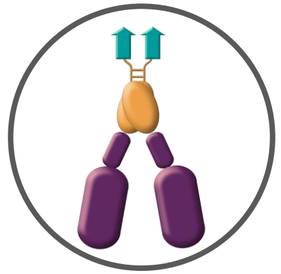
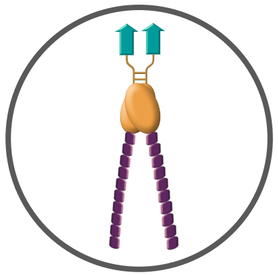
Vaccibody Product Pipeline

PROGRAM	DISCOVERY	PRE-CLINICAL	PHASE I	PHASE II	PHASE III
Precancerous cervical lesions	VB C-01 (VB10.16)				
MELANOMA LUNG (NSCLC) BLADDER RENAL HEAD AND NECK	VB N-01 (VB10.NEO)				





Vaccibody – Proprietary Vaccine Technology Platform

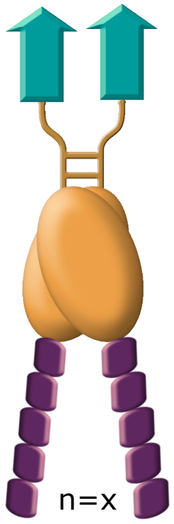
The Vaccibody Technology Platform was developed based on the concept of **targeting antigen to APC** in order to create more efficacious vaccines.

Exchangeable DNA Cassette

Vaccibody DNA Vaccine Plasmid

VB10.NEO

In vivo expression



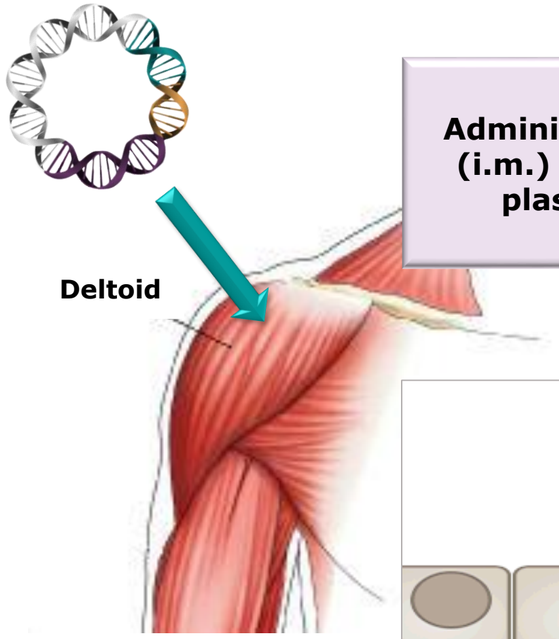
Vaccibody in Protein Format

Target to Antigen Presenting Cell

Dimerization for crosslinking target receptor

Antigen moiety

Mechanism of Action – Intrinsic Adjuvant

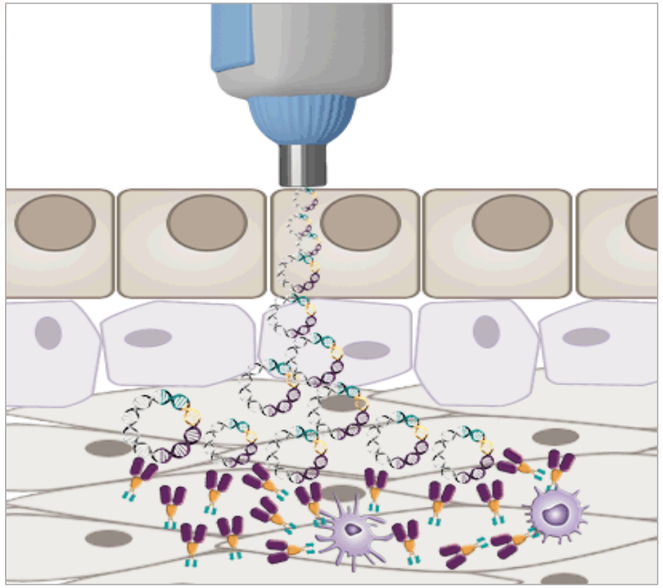


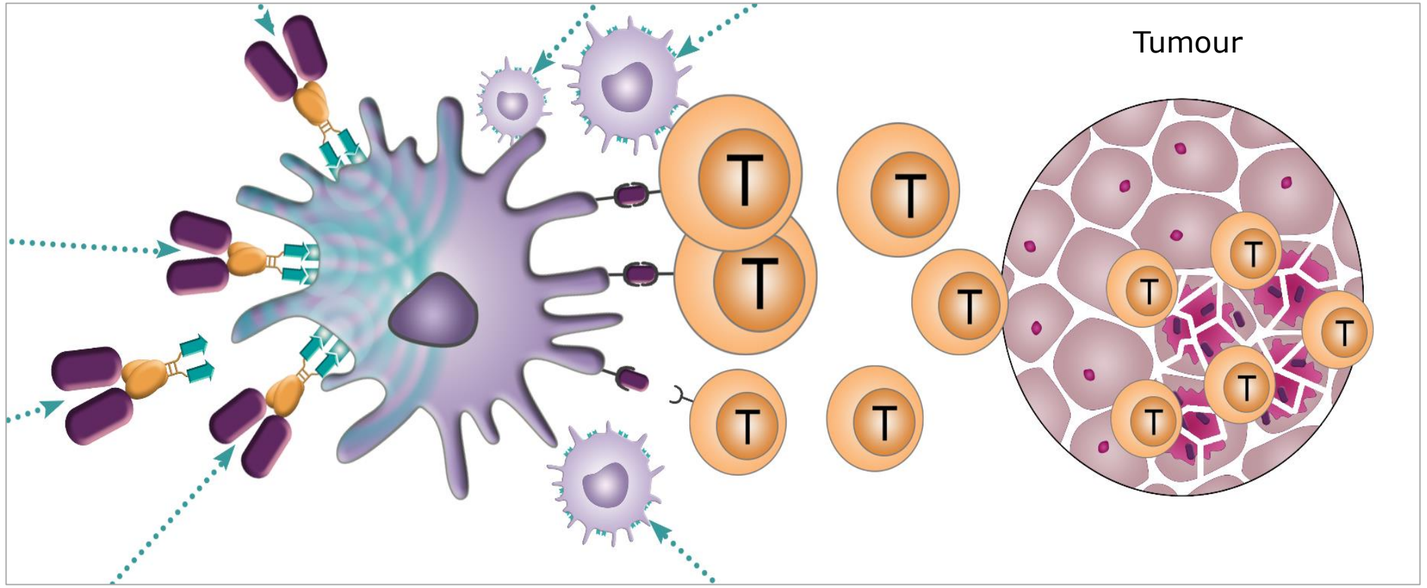
Administration (i.m.) of DNA plasmid

***In vivo* protein expression and secretion**

Chemokine MIP-1α

Target – Attract –Mature –Deliver-Cross-present





Patient Friendly, simple Vaccine Delivery

PharmaJet®

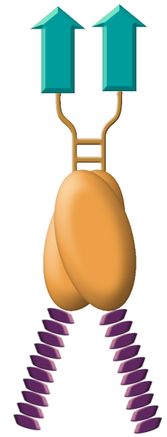
- ✓ Needle free injection
- ✓ Small, handy, easy to use
- ✓ Minimal pain compared to electroporation
- ✓ Cost effective
- ✓ Applicable for multiple immunizations
- ✓ High patient compliance

Naked DNA plasmid as IMP

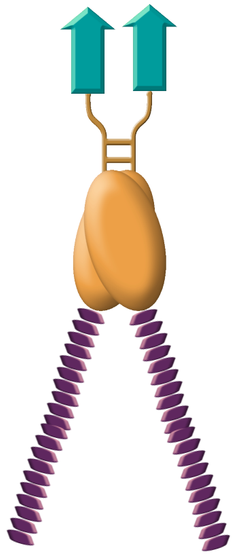
- ✓ Proven Safety
- ✓ Simple, Rapid and Generalized process
- ✓ Simple Formulation
- ✓ Versatile
- ✓ Easy i.m. Delivery
- ✓ Effective Homologous Boost
- ✓ CD8 prone

DNA plasmid is an ideal platfrom for bringing individualized neoantigen vaccines to the market as a viable product

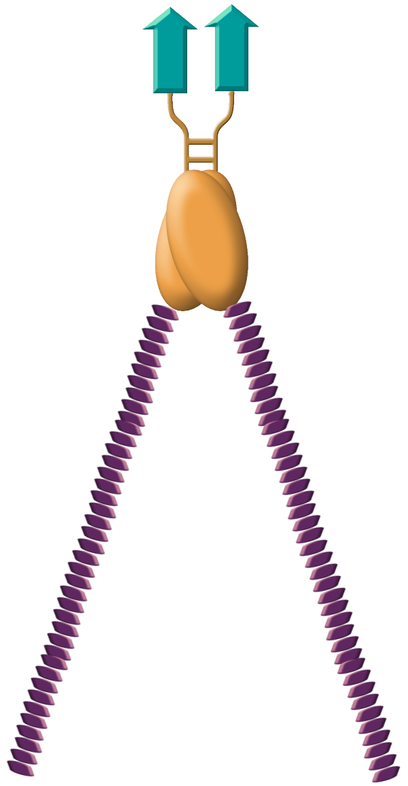
VB10.NEO – A Robust Vaccine Format



VB10.NEO-X



VB10.NEO-XX

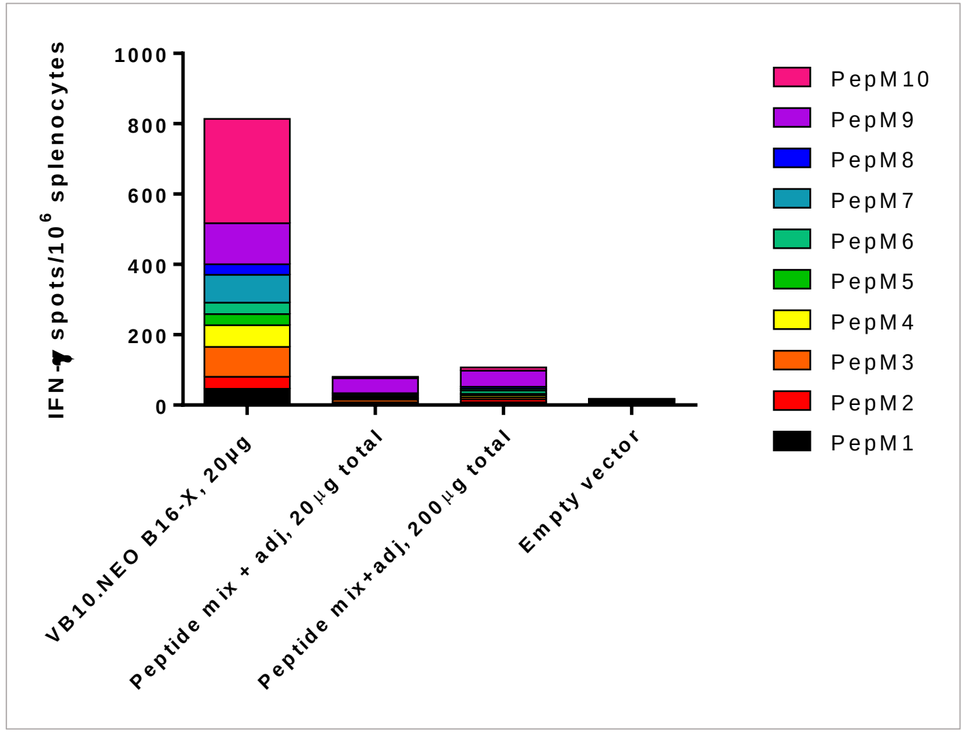


VB10.NEO-XD

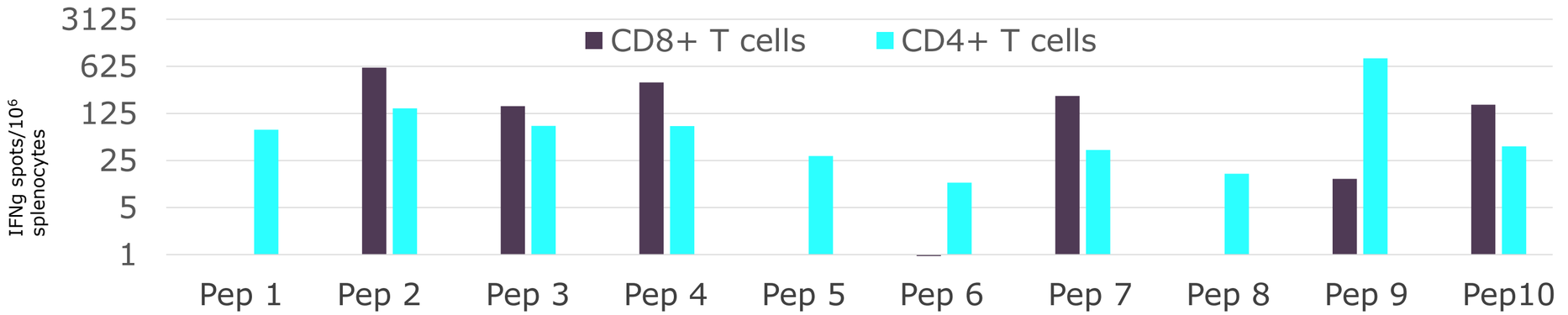
>80 different VB10.NEO constructs with >250 neoepitopes constructed to date with up to 40 neoepitopes

VB10.NEO induces Rapid, Broad and Strong responses to multiple Neoepitopes by single Vaccination

- VB10.NEO induces a broader and stronger response than Peptide + Poly (I:C) Adjuvant vaccines after a single immunization.
- VB10.NEO vaccinated animals respond to all 10 neoepitopes after a single immunization.
- Immunodominant neoepitopes differ between delivery vehicles



VB10.NEO generates a broader immune response profile dominated by CD8+ T cells than competing technologies



Peptide*	CD4										
	CD8										
RNA*	CD4										
	CD8										
VB10.NEO	CD4										
	CD8										

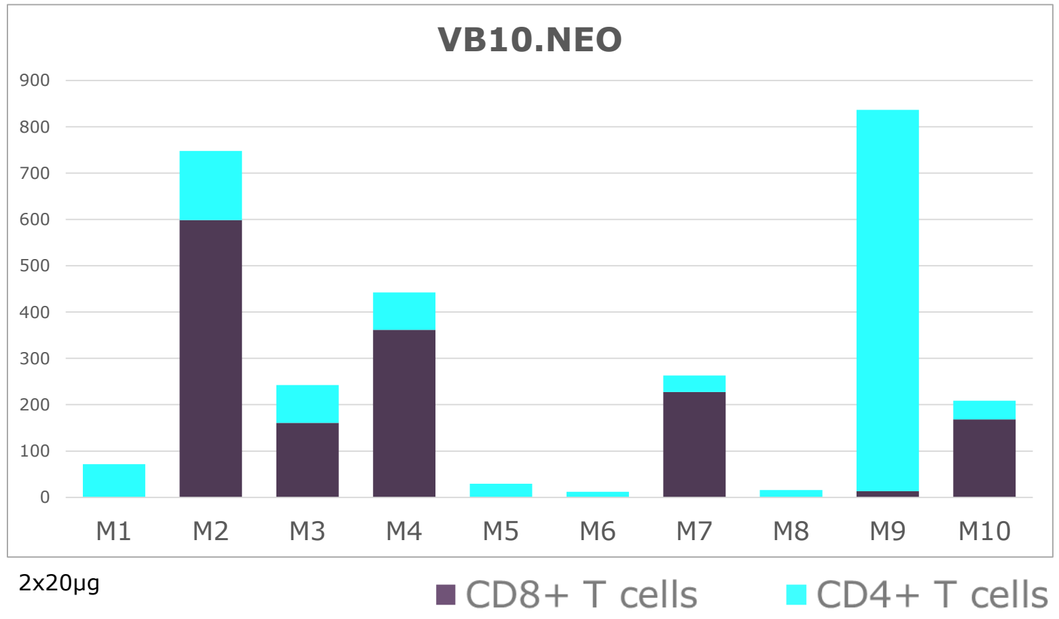
* Tested IFN-γ CD4 and CD8 T cell response against 10 identical neoepitopes from B16 melanoma

Peptide and RNA vaccines induces primarily CD4 T cell responses, while VB10.NEO induces strong, dominating CD8 responses to the identical neoepitope sequences

* Castle et al., 2012 and Kreiter et al., 2015

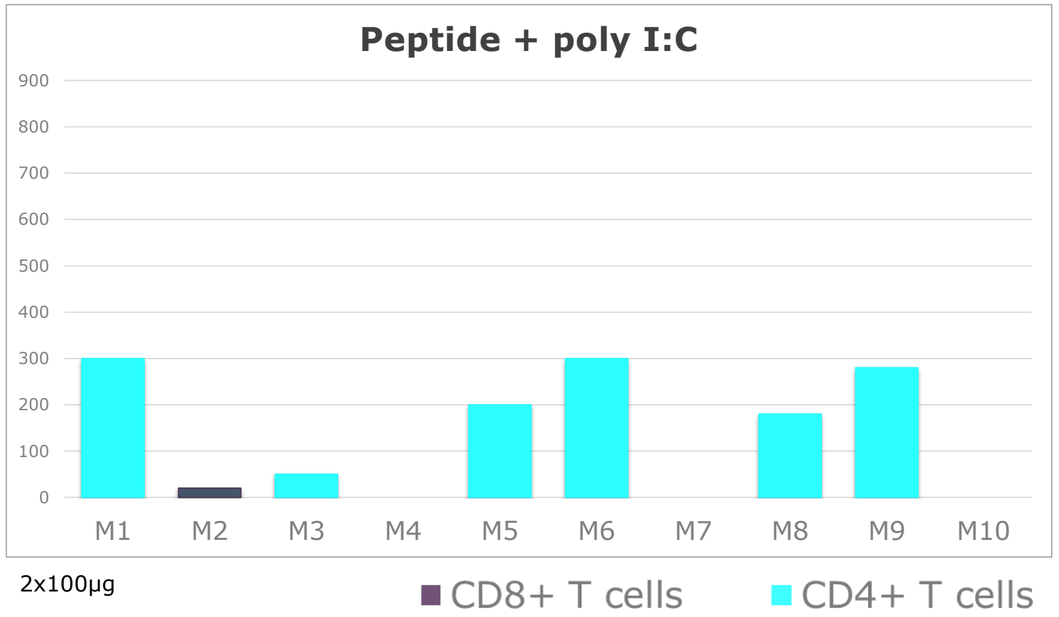
VB10.NEO leads to a unique CD8 dominated neoepitope response

VB10.NEO induces a **strong, broad** immune response **dominated by CD8+** T cells



2x20µg

Peptide + poly I:C vaccination has been reported to induce **dominantly CD4 T cell responses**



2x100µg

VB10.NEO induces strong, dominantly CD8+ T cell response to identical neoepitopes that induces **no or weak** immune response if delivered as peptide vaccine

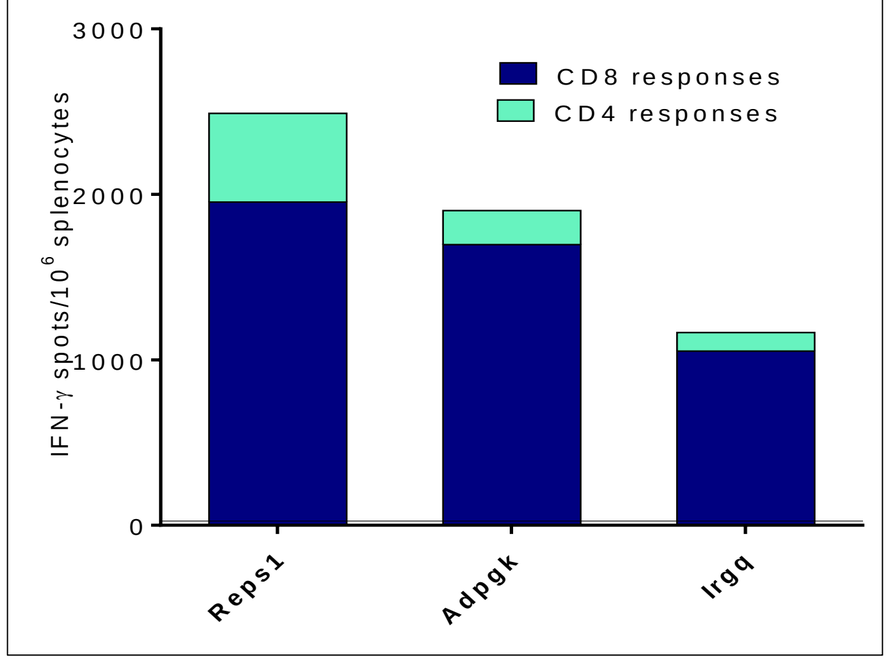
* Castle et al., 2012 and Kreiter et al., 2015-adapted figure based on B16 melanoma results

Confirmation of VB10.NEO's unique ability to induce strong neoepitope-specific CD8 responses

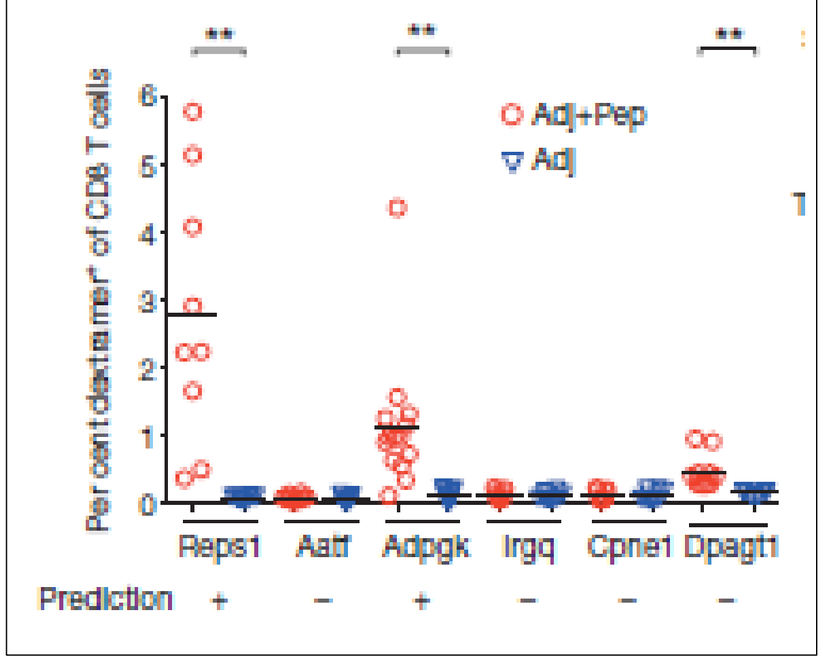
MC38 colon carcinoma

Yadav et al., 2014

VB10.NEO



Peptide + poly I:C + anti-CD40 mAb



-VB10.NEO induces a strong CD8 T cell response, combined with a CD4 T cell response **to all** peptides tested for MC38 colon carcinoma.

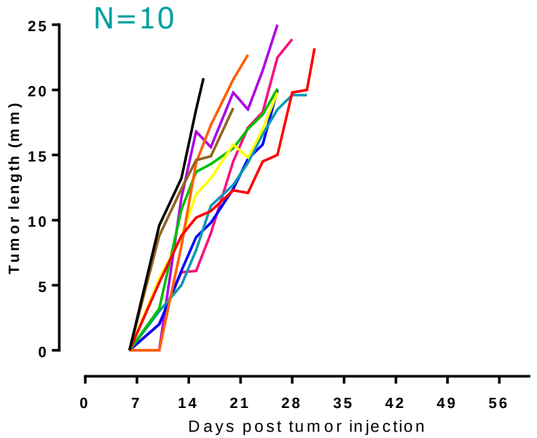
-1/3 of these neoepitopes have been shown to be **non-immunogenic delivered as peptide + adjuvant**

-Confirmation of VB10.NEO's ability to induce stronger CD8 responses to neoantigens

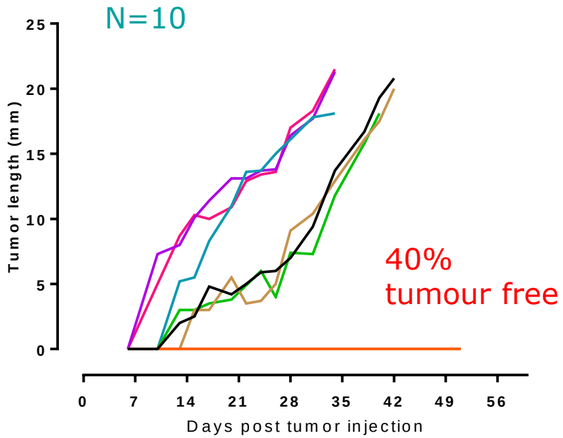
Vaccibody Induces Tumor Protection as Monotherapy

CT26 colon carcinoma model

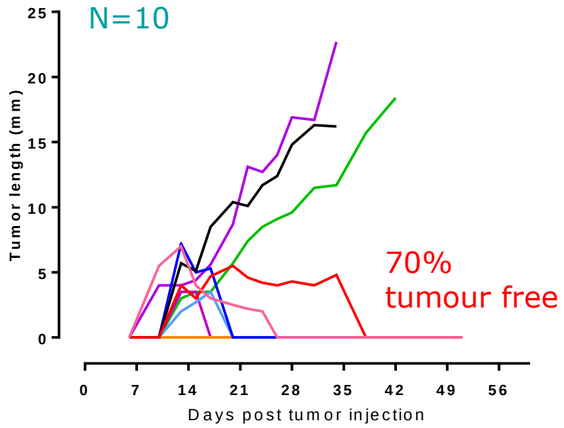
Control



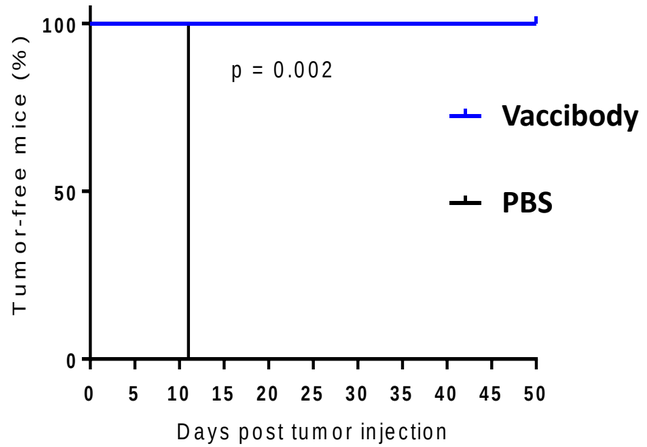
Vaccibody Monotherapy



Vaccibody Combination Therapy



Re-challenged mice are protected



- Vaccibody vaccination induces strong CD8+ T cell responses and **tumor protection as Monotherapy**
- Combination with anti-PD-1 immunotherapy induced enhanced anti-tumour responses in mice involving **complete tumour regression** of large, established tumours
- **Long-term memory responses** ensure effective anti-tumour responses after a 2nd tumour challenge in surviving mice with no sign of tumour growth

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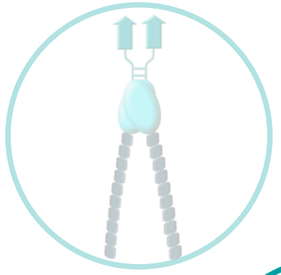
   Why the perfect fit for individualised Vaccines?



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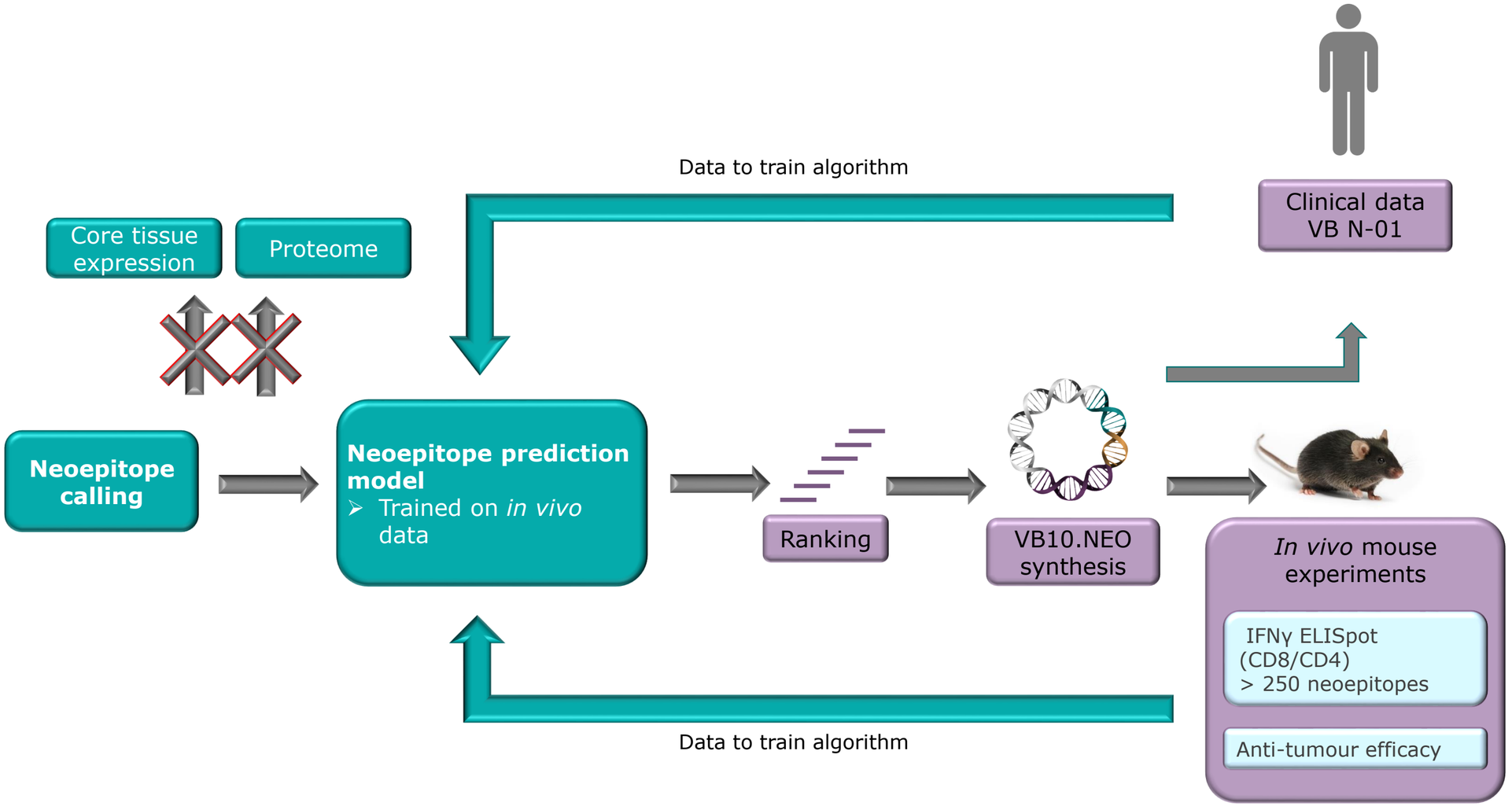
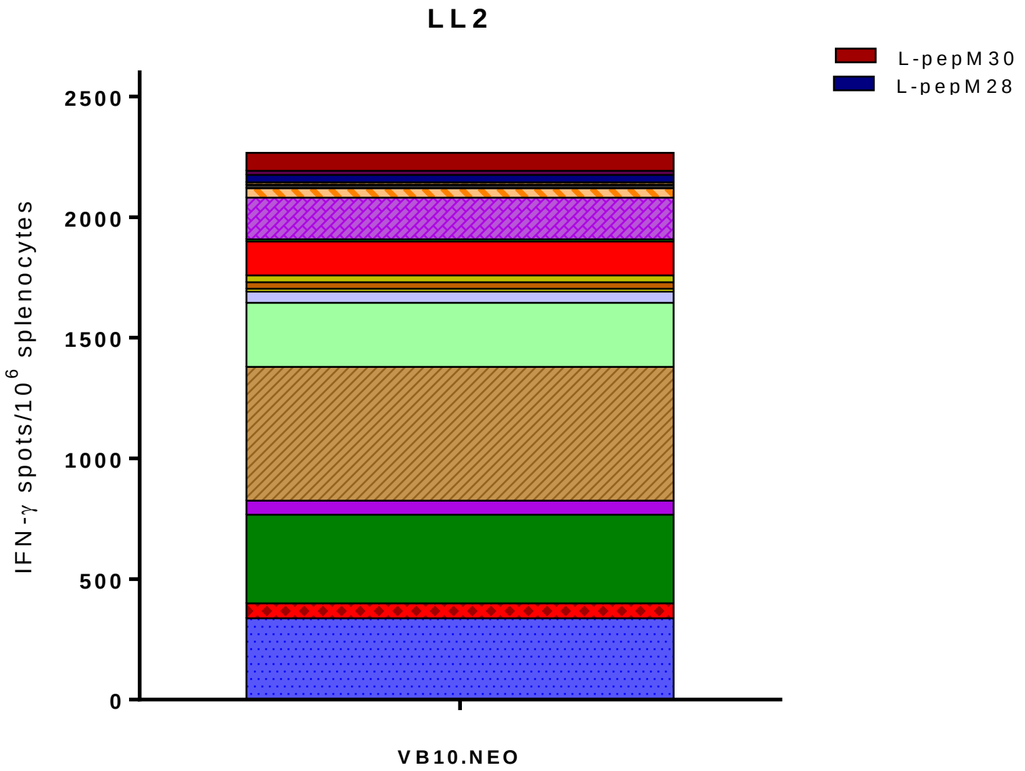
Developing VB10.NEO specific Neoepitope Selection



Verification of VB10.NEO neoepitope prediction tool-NeoSELECT™



VB10.NEO specific Neo-epitope Selection Tool employed in uncharacterized LL2 lung cancer tumour model

NeoSELECT™ has a strong ability to select immunogenic neoepitopes

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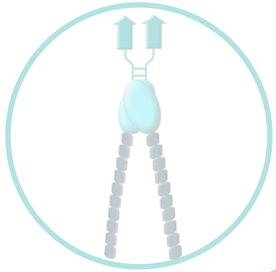

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Vaccibody Vaccine Product Pipeline

PROGRAM	DISCOVERY	PRE-CLINICAL	PHASE I	PHASE II	PHASE III
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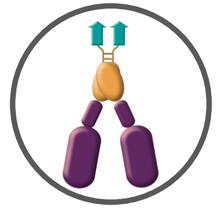
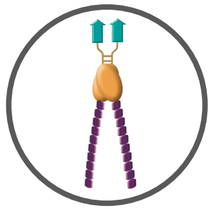
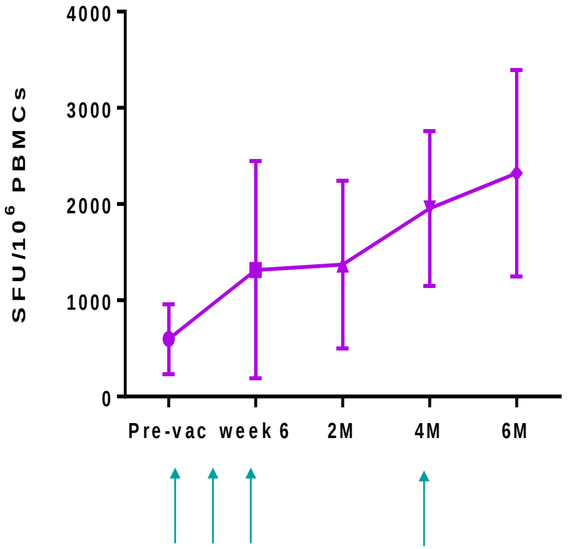
MELANOMA LUNG (NSCLC) BLADDER RENAL HEAD AND NECK	VB N-01 (VB10.NEO)				



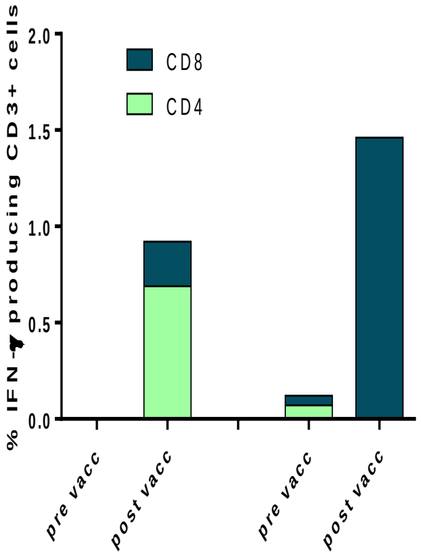


VB10.16 induces strong CD8 dominated T cell responses

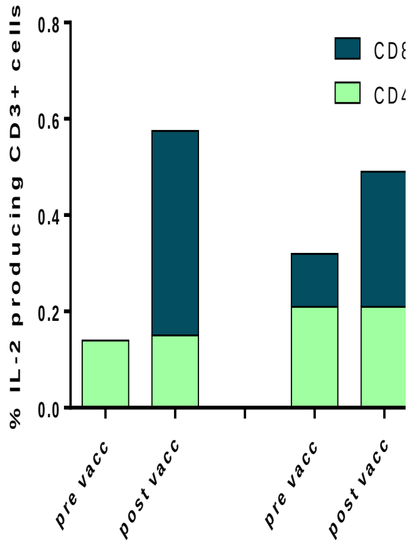
Interim Phase I/IIa results



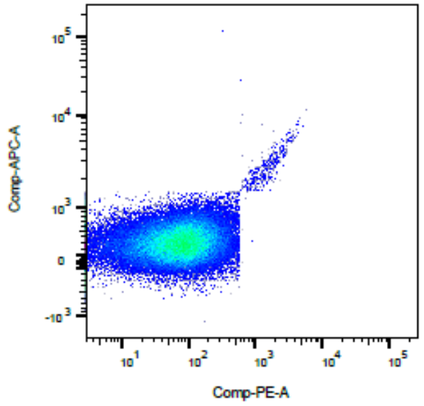
IFN-γ Ex vivo



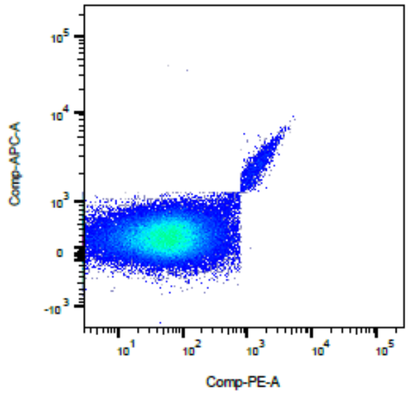
IL-2 Ex vivo



Pre vacc



Post vacc

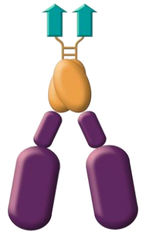


- No SAEs observed
- 96% of patients tested so far (n=24) elicit increased HPV16-specific T cell responses after vaccination with VB10.16
- A strong induction of CD8 T cells in patients is confirmed in a clinical setting

Clinical learnings –Vaccibody platform VB C-01 study

- HPV16-specific T cell response correlates with clinical responses
  - All patients with a **strong** (>650SFU/mill) T cell response experienced lesion size reduction

- VB10.16 induces high degree of CIN regression to CIN1 or less during the trial
  - Co-infection with other high-risk HPV and/or PD-L1 upregulation may inhibit CIN regression



VB10.16 induces a strong HPV16-specific T cell response and kills HPV16-infected precancerous cells if not inhibited by PD-1/PD-L1 checkpoint blockade

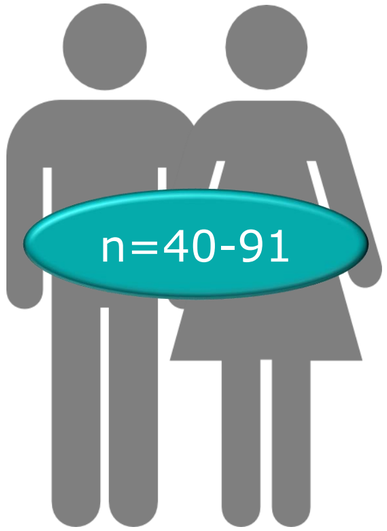
Clinical Trial VB N-01

VB N-01: An open labelled first human dose phase 1/2a study to evaluate safety, feasibility and efficacy of multiple dosing with individualised VB10.NEO immunotherapy in patients with locally advanced or metastatic melanoma, NSCLC, clear renal cell carcinoma, urothelial cancer or squamous cell carcinoma of head and neck, who did not reach complete responses with current standard of care immune checkpoint blockade

FPI April 2018

VB10.NEO

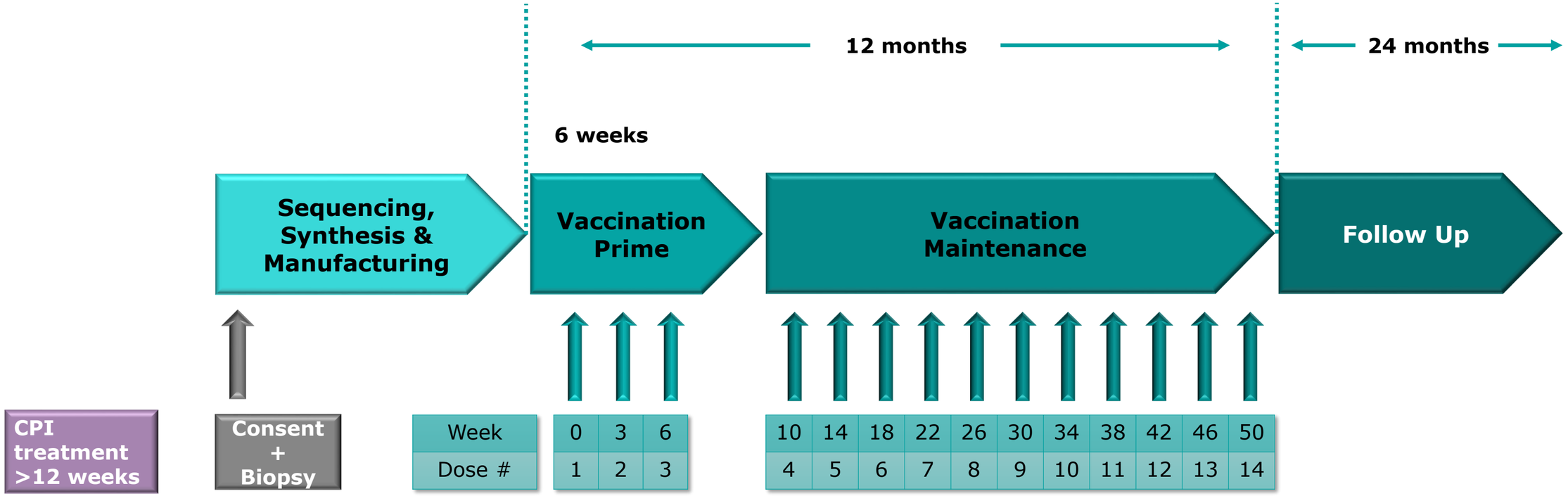
VB N-01



- Melanoma
- NSCLC
- Clear Renal Cell Carcinoma
- Urothelial Cancer
- Squamous Cell Carcinoma of the Head and Neck

- Approved CPI as SOC
- Moderate to high mutational load

Study Design and Treatment Schedule VB N-01



Vaccibody's Solution to Personalised Cancer Treatment

1. Tumour biopsy and sequencing

2. Neoepitope selection (TSNA)

NeoSELECT™

3. Vaccine manufacturing (n=1)

-DNA vaccine:

-Robust, rapid, cost-effective, stable, safe

-up to 20 neoepitopes

4. Vaccine administration and immunogenicity

-Needle-free

-Target, Attract, Mature, Deliver, Cross-present

-Rapid, strong, long-lasting

-CD8 dominated

Rapid, cost-effective, efficacious

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