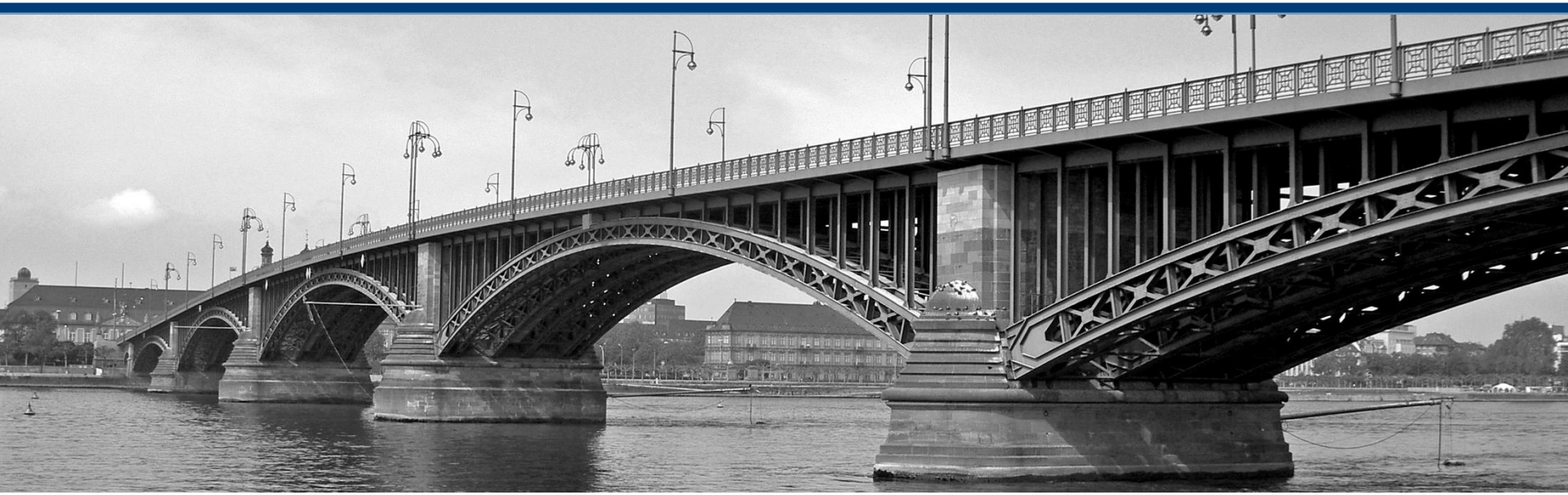
Immune recognition of tumours and mutational antigens

Opportunities for the future

Mathias Vormehr



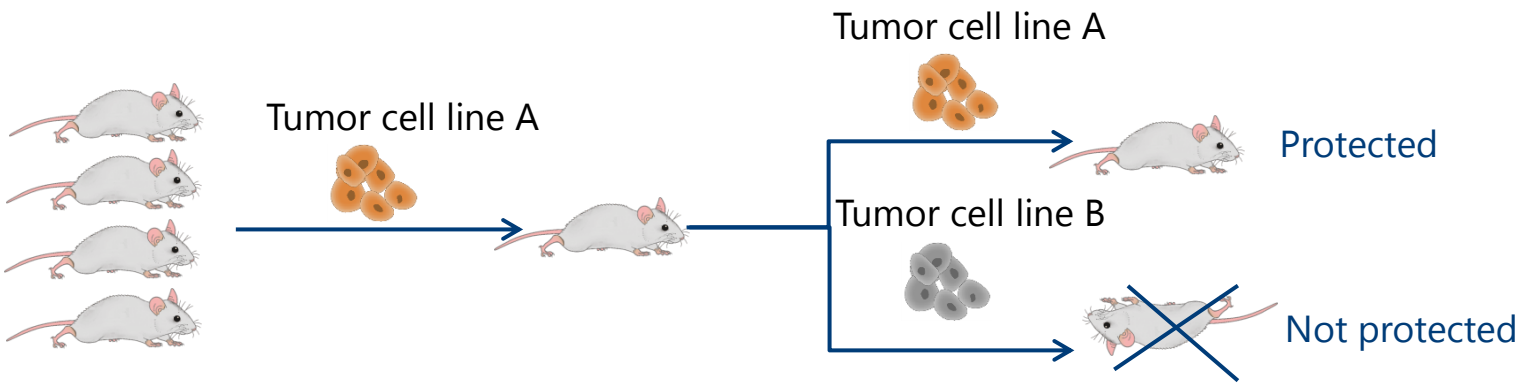
Sunday, December 20, 2015
ESMO Asia 2015, Singapore

Disclosure

- I am employed at BioNTech RNA Pharmaceuticals GmbH (Mainz, Germany), a biotechnology company investigating personalized mRNA based cancer vaccines.

- I am inventor on patents and patent applications, which cover parts of this presentation.

- GROSS, **1943**, *Cancer Res.*
- PREHN, MAIN, **1957**, *J Natl Cancer Inst.*



→ Mice challenged with a carcinogen induced tumor cell line are protected against a rechallenge with the same but not a different tumor cell line.

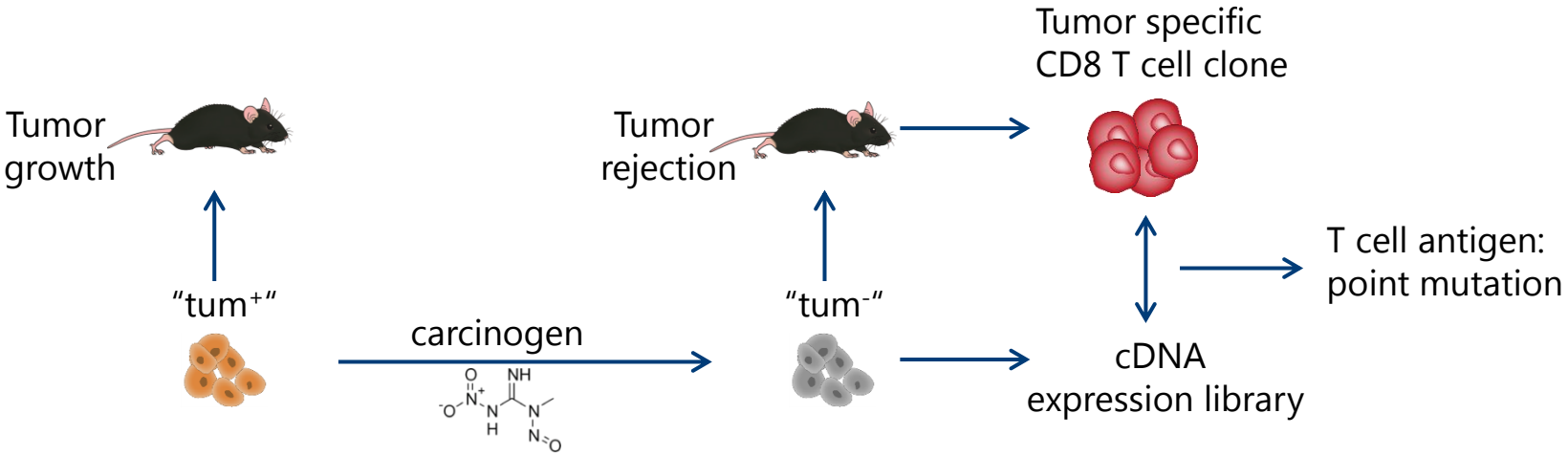
Tumor-specific T cells can recognize cancer mutations in mice

Immunogenic (tum⁻) variants of mouse tumor P815: Cloning of the gene of tum⁻ antigen P91A and identification of the tum⁻ mutation*

Proc. Natl. Acad. Sci. USA
Vol. 85, pp. 2274-2278, April 1988
Immunology

(tumor immunology/cosmid/mastocytoma P815)

ETIENNE DE PLAEN, CHRISTOPHE LURQUIN, ALINE VAN PEL, BERNARD MARIAMÉ, JEAN-PIERRE SZIKORA, THOMAS WÖLFEL, CATHERINE SIBILLE, PATRICK CHOMEZ, AND THIERRY BOON



Mutagen treatment of mouse P815 tumor cells produces tum⁻ variants that are rejected by syngeneic mice [...].

These "tum⁻ antigens" are recognized by cytolytic T lymphocytes [...].

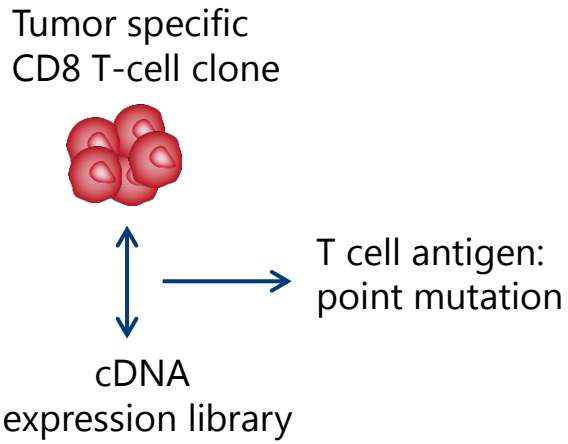
The normal and the tum⁻ of the gene differ by one nucleotide [...].

Tumor-specific T cells can recognize cancer mutations in humans

A p16^{INK4a}-Insensitive CDK4 Mutant Targeted by Cytolytic T Lymphocytes in a Human Melanoma

Thomas Wölfel,* Martina Hauer, Jörg Schneider,
Manuel Serrano, Catherine Wölfel, Eva Klehmann-Hieb,
Etienne De Plaen, Thomas Hankeln,
Karl-Hermann Meyer zum Büschenfelde, David Beach

SCIENCE • VOL. 269 • 1 SEPTEMBER 1995

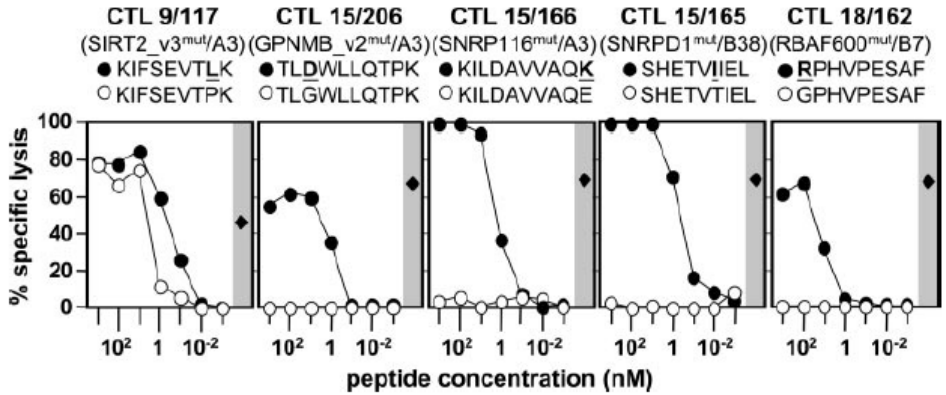


The response of autologous T cells to a human melanoma is dominated by mutated neoantigens

Volker Lennerz[†], Martina Fatho[†], Chiara Gentilini[‡], Roy A. Frye[§], Alexander Lifke[†], Dorothea Ferel[†], Catherine Wölfel[†], Christoph Huber[†], and Thomas Wölfel[†¶]

[†]Department of Medicine, Hematology/Oncology, Johannes Gutenberg University, Langenbeckstrasse 1, D-55101 Mainz, Germany; [‡]Department of Medicine, Hematology/Oncology, University of Leipzig, Liebigstrasse 22, D-04103 Leipzig, Germany; and [§]Department of Pathology, Veterans Affairs Medical Center, University Drive C, Pittsburgh, PA 15240

PNAS | **November 1, 2005** | vol. 102 | no. 44 | **16013–16018**



Next-generation sequencing revolutionized mutation detection

- Sequencing of the first human genome *(Human Genome Project)*

13 years, $2.7 billion*

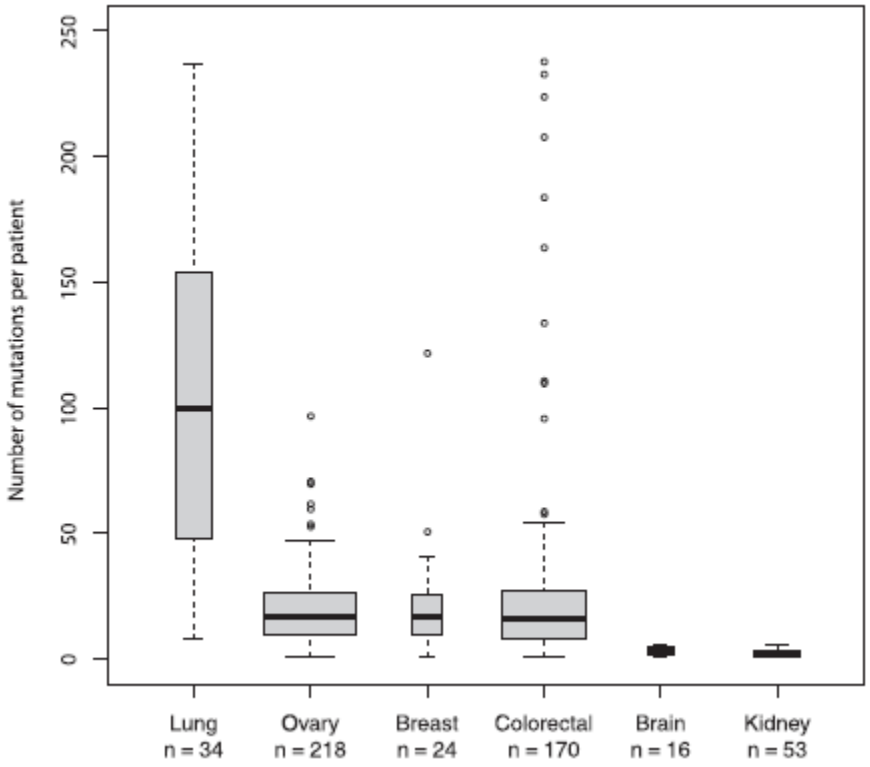
- Next-generation sequencing: exome and transcriptome

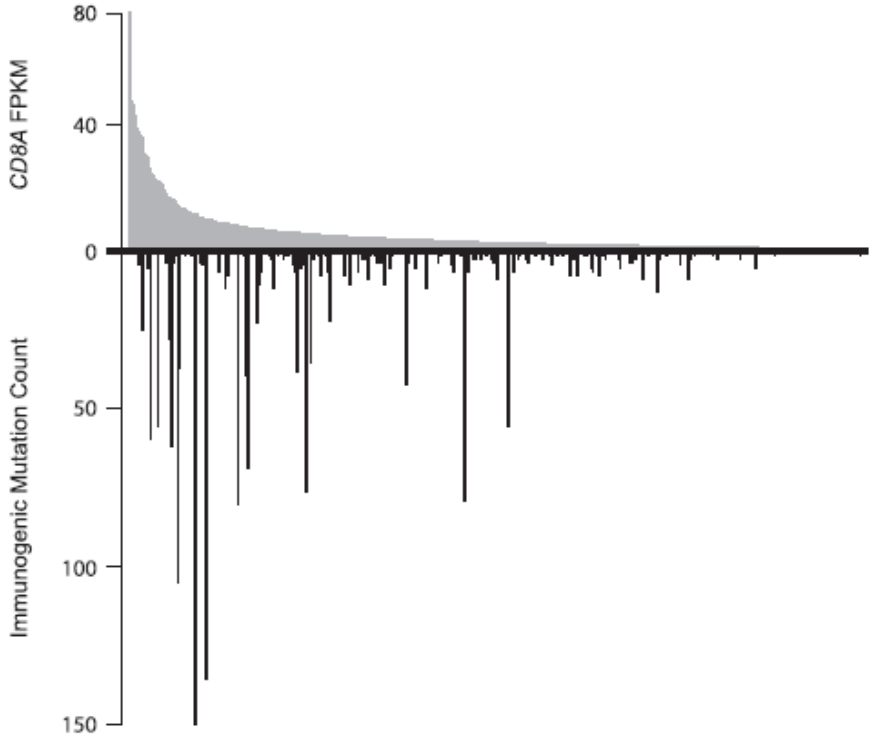
1 week, <$5000

*http://www.genome.gov

Predicted CD8 neo-epitopes correlates with patient survival

Meta-analysis of next-generation sequencing data:



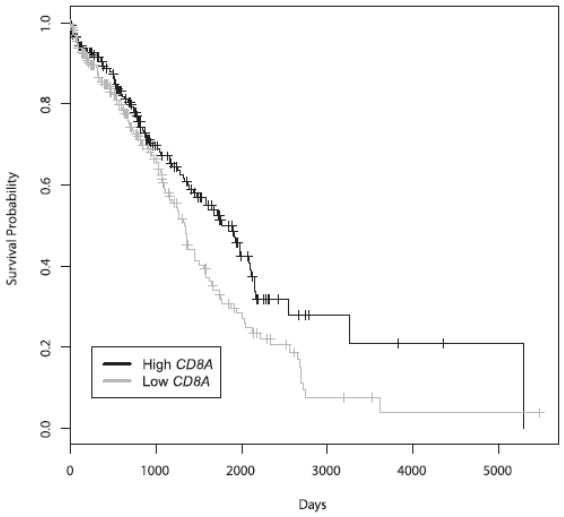


Brown SD et al.: **Neo-antigens predicted by tumor genome meta-analysis correlate with increased patient survival.** *Genome Res.* 2014, **24**:743–750.

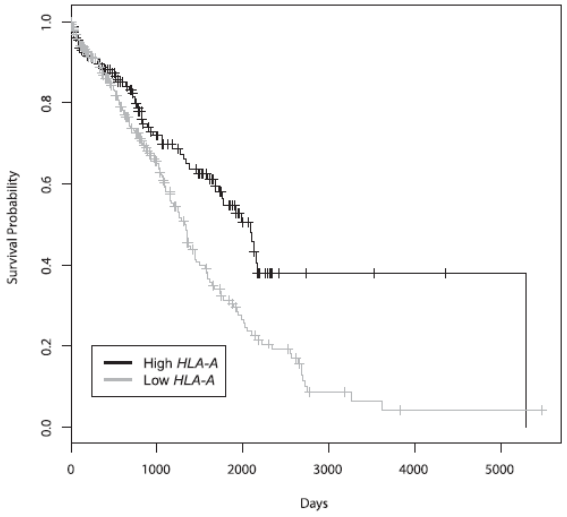
Predicted CD8 neo-epitopes correlates with patient survival

Patient survival correlates with:

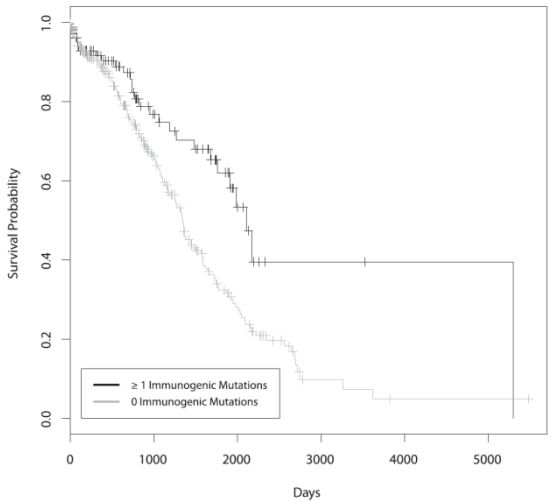
Intratumoral CD8 expression



Intratumoral HLA expression



Predicted neo-epitopes

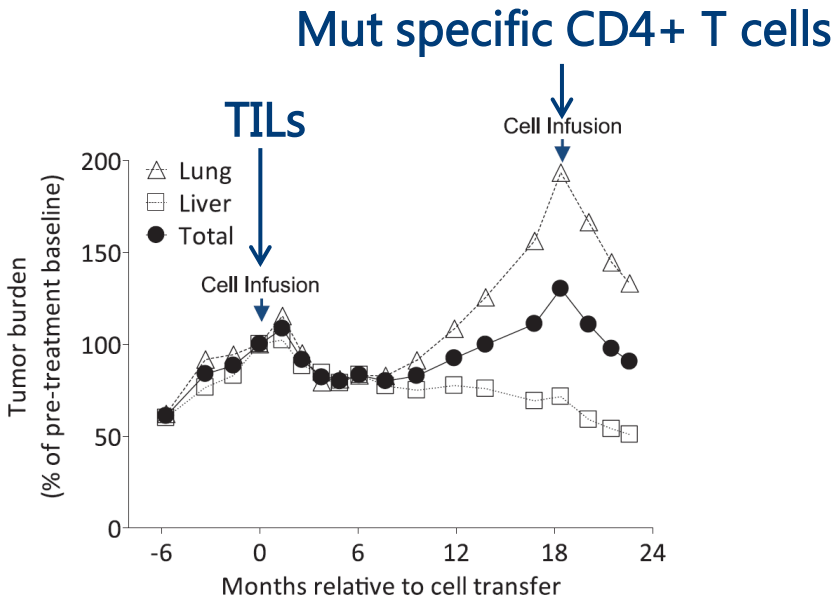


Brown SD et al.: **Neo-antigens predicted by tumor genome meta-analysis correlate with increased patient survival.** *Genome Res.* 2014, **24**:743–750.

Melanoma TILs contain neo-antigen specific T cells

- Robbins et al., 2013, Nat Med.
- Tran et al., 2014, Science
- Cohen et al., 2015, JCI
- Tran et al., 2015, Science

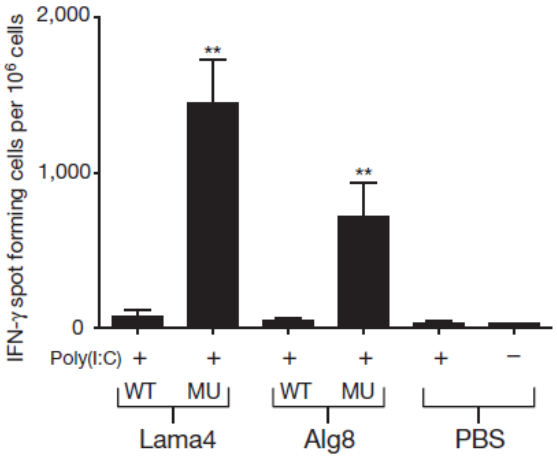
→ Identificantion of neo-epitope specific CD8+ and CD4+ T cells within TILs of melanoma and epethelial cancer patients

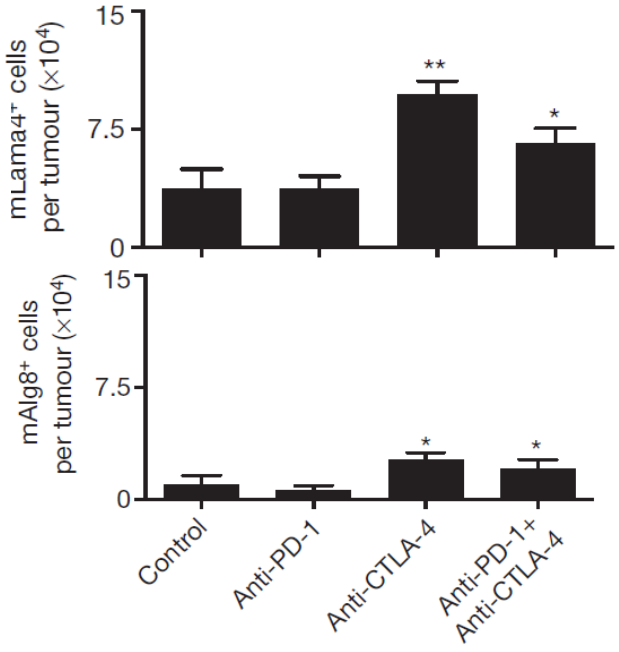


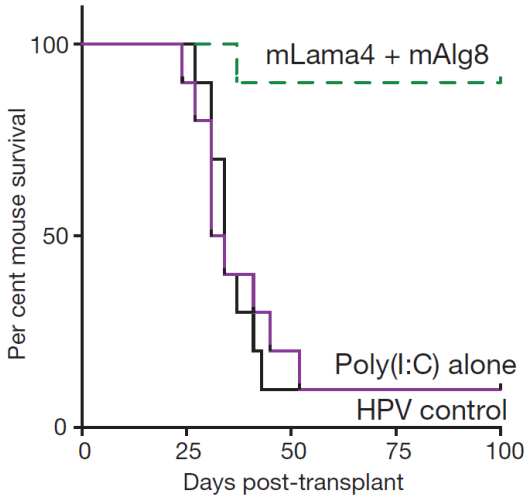
Tran et al.: **Cancer immunotherapy based on mutation-specific CD4+ T cells in a patient with epithelial cancer.** *Science* 2014, **344**:641–645.

Checkpoint blockade unleashes neo-antigen specific T cells

D42m1-T3 tumor model
(carcinogen induced)

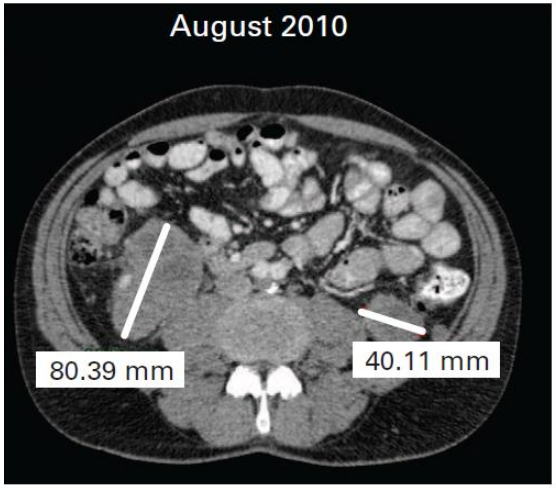


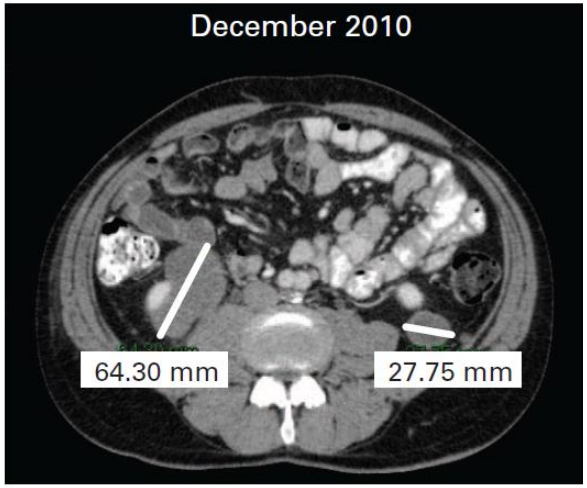


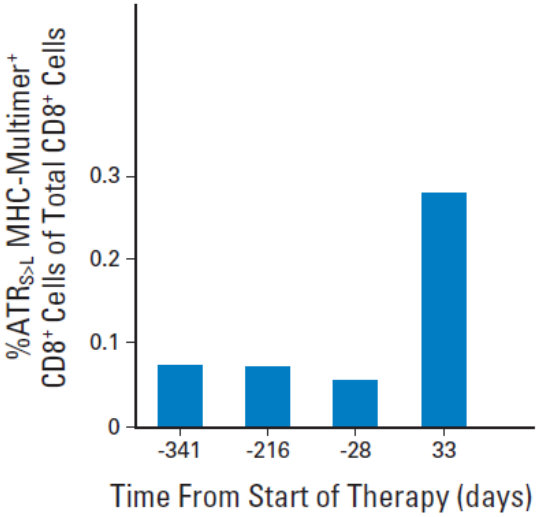


Gubin et al.: **Checkpoint blockade cancer immunotherapy targets tumour-specific mutant antigens.** *Nature* 2014, **515**:577–581.

Checkpoint blockade unleashes neo-antigen specific T cells





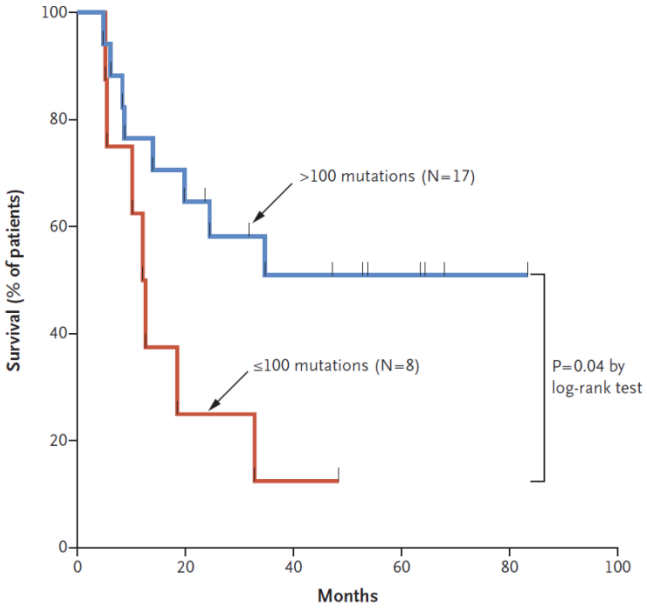


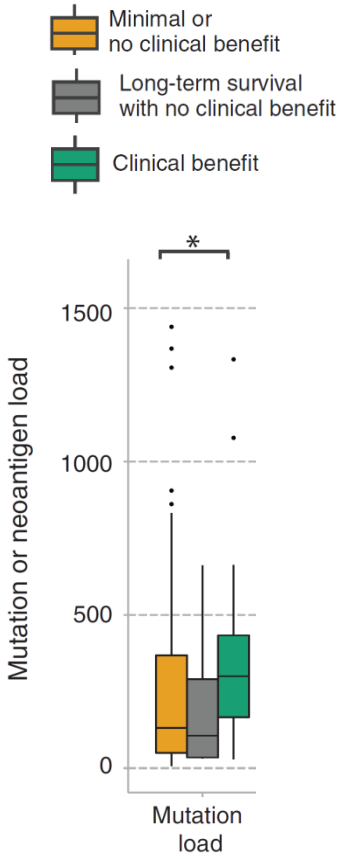
Patient with clinical response after Ipilimumab treatment demonstrates a mutation specific T-cell response

Van Rooij N et al.: **Tumor exome analysis reveals neoantigen-specific T-cell reactivity in an ipilimumab-responsive melanoma**. *J. Clin. Oncol.* 2013, **31**:e439–442.

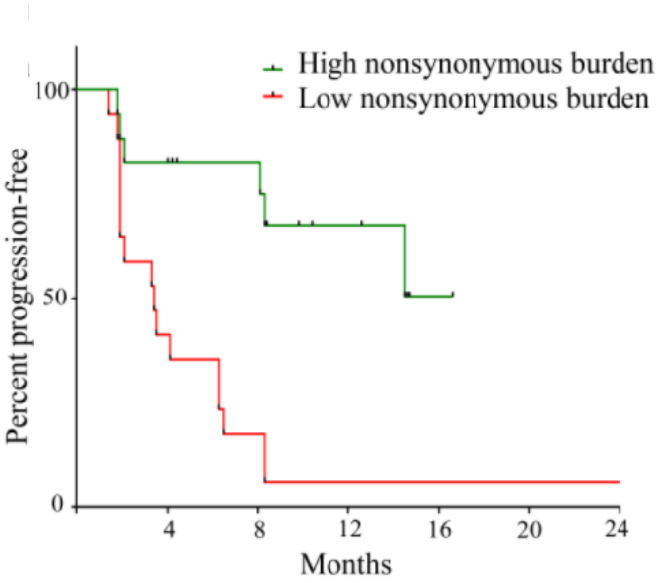
Mutational load correlates with clinical outcome of checkpoint blockade

Ipilimumab (anti-CTLA-4) Melanoma



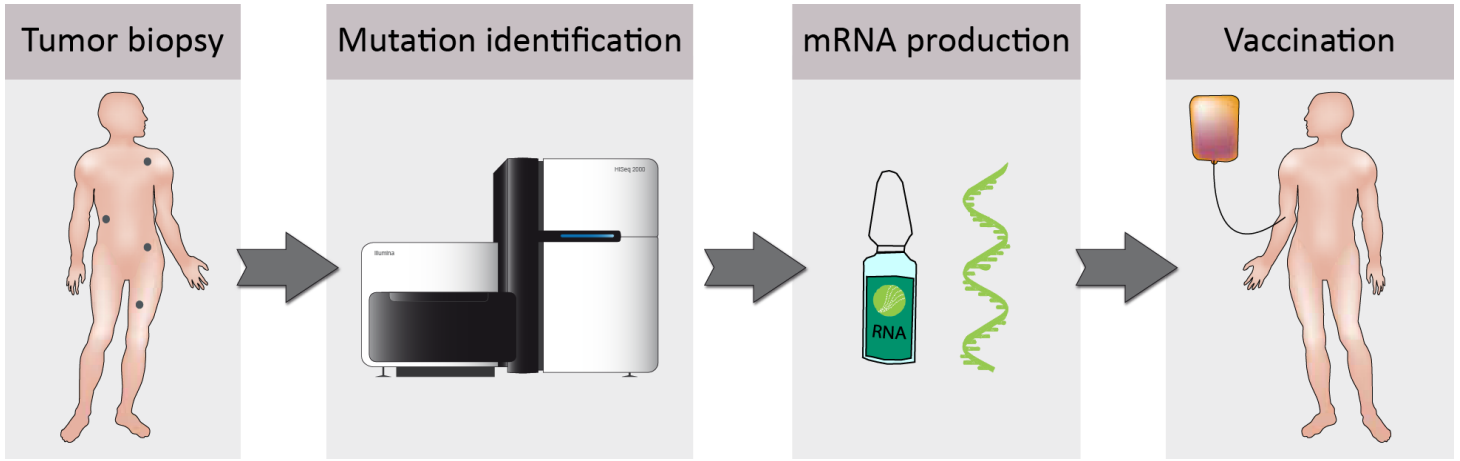


Pembrolizumab (anti-PD-1) NSCLC



- Snyder et al., 2014, NEJM
- Van Allen et al., 2015, Science
- Rizvi et al., 2014, Science

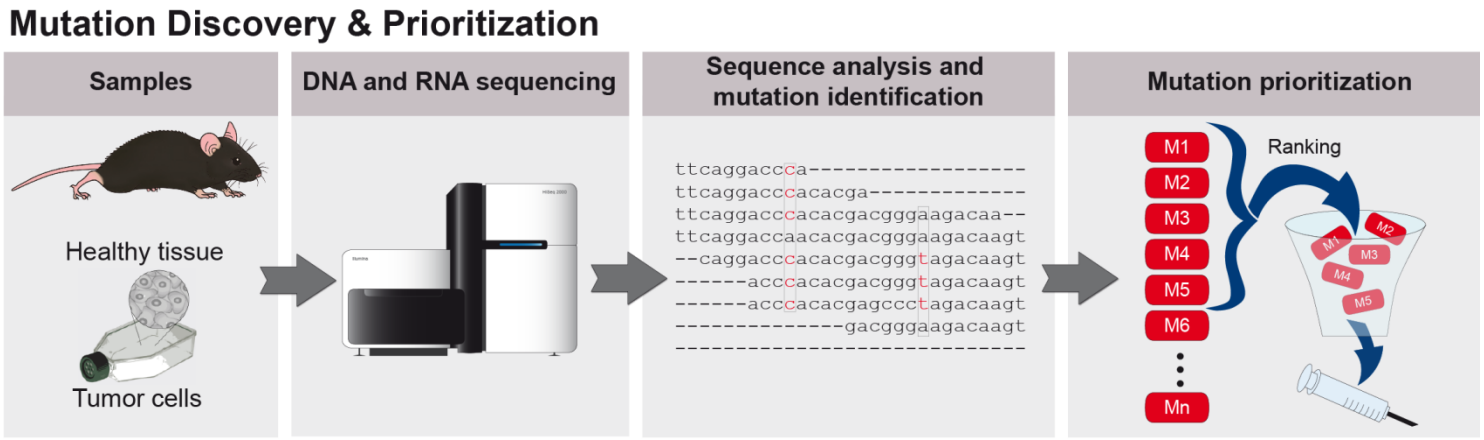
Mutanome Engineered RNA Immunotherapy (MERIT)



Castle JC et al.: **Exploiting the mutanome for tumor vaccination.**
Cancer Res. 2012, **72**:1081–1091.

Kreiter S et al.: **Mutant MHC class II epitopes drive therapeutic immune responses to cancer**.
Nature 2015, **520**:692–696.

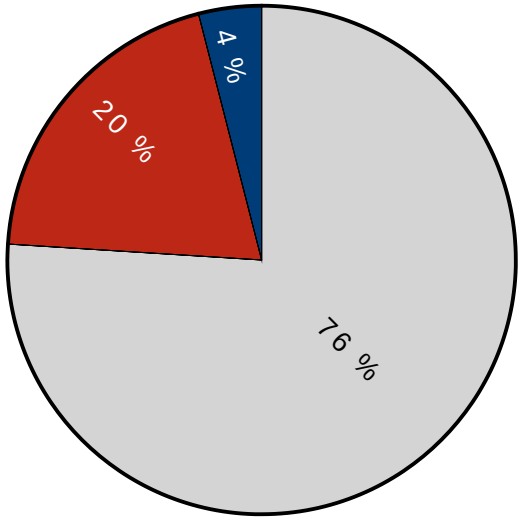
Preclinical proof of concept



The majority of mutations are recognized by CD4+ T cells

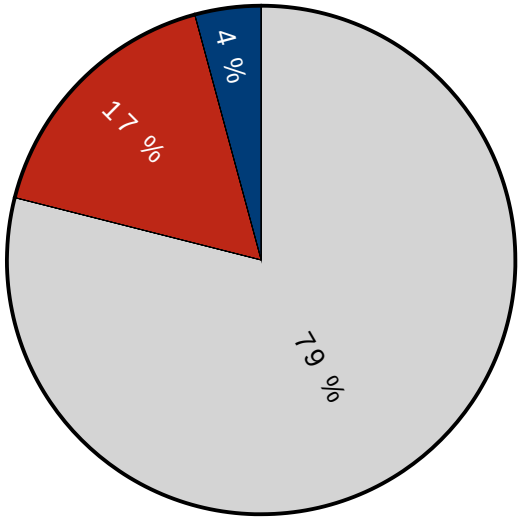
RNA vacination

B16F10 melanoma



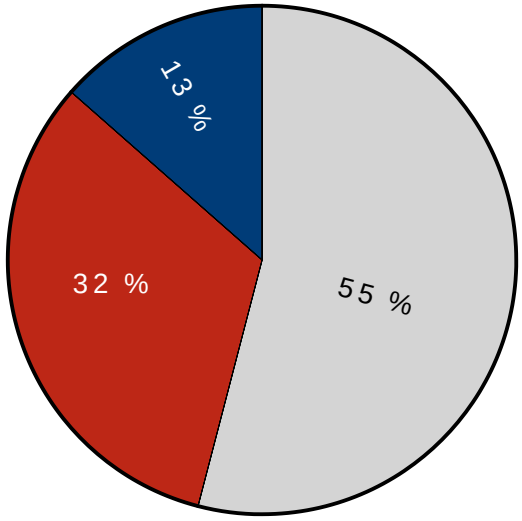
Total=50

CT26 colon carcinoma



Total=96

4T1 mammary carcinoma



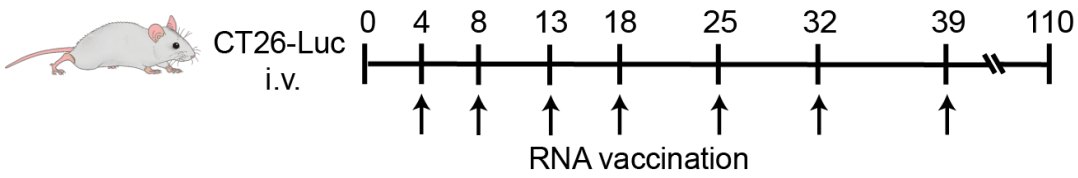
Total=38

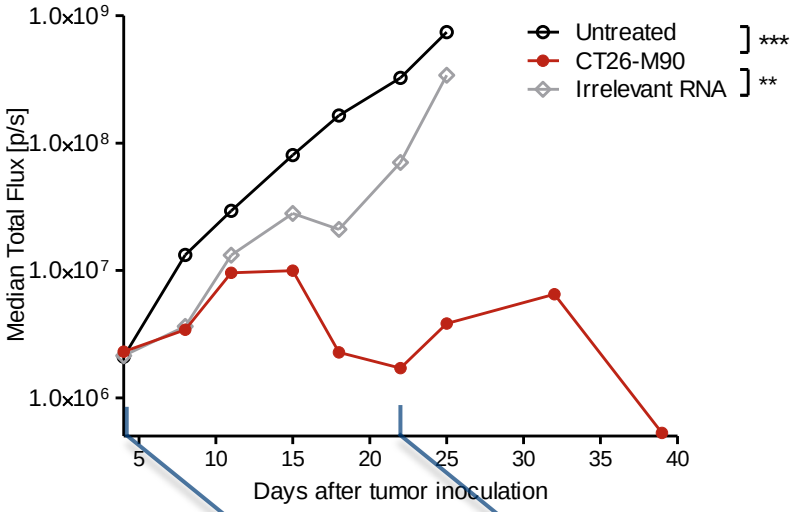
Non-immunogenic

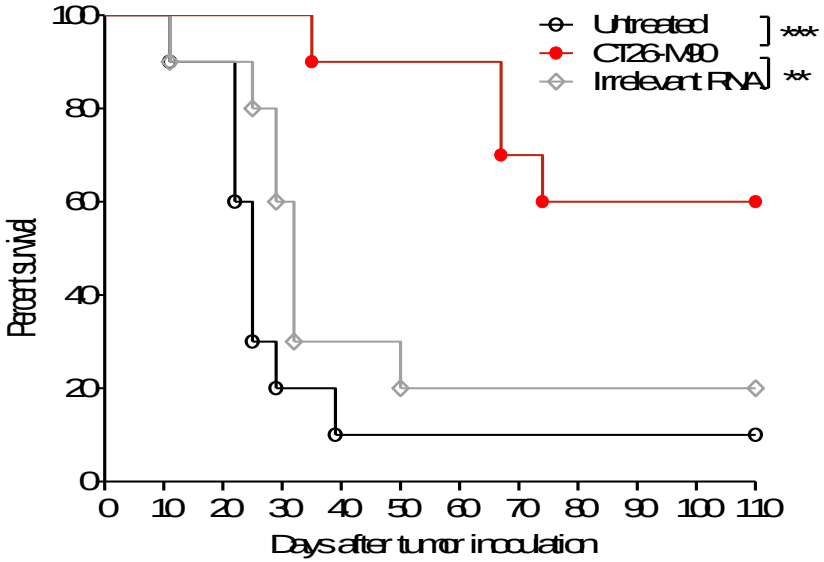
MHC II restricted

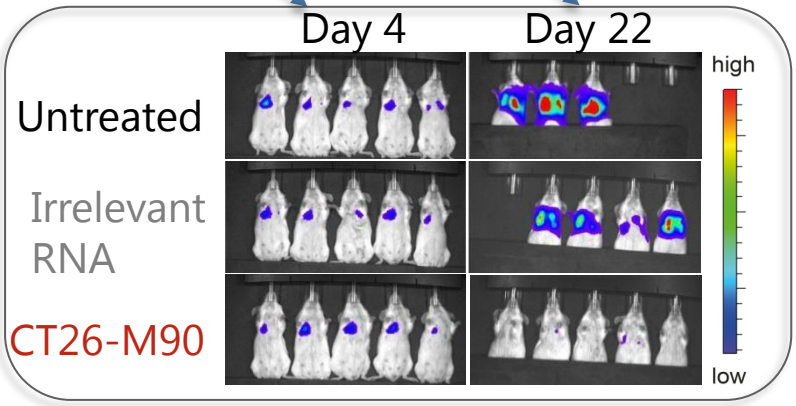
MHC I restricted

Therapeutic effect of Aldh18a1$_{P145S}$ (CT26-M90) vaccination

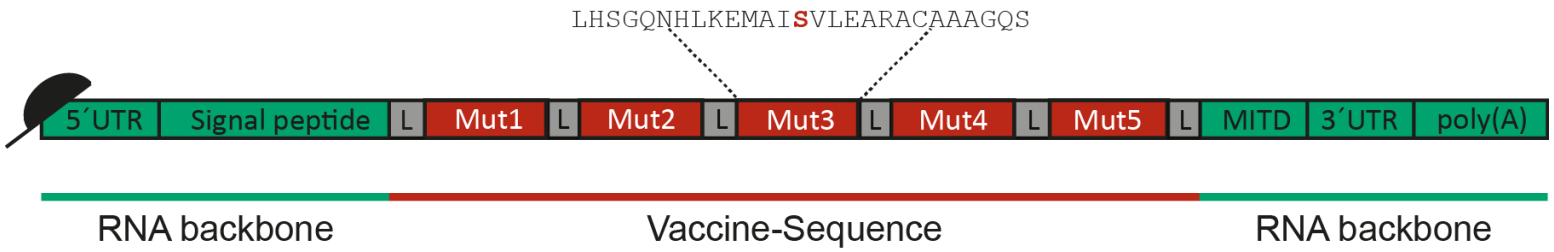


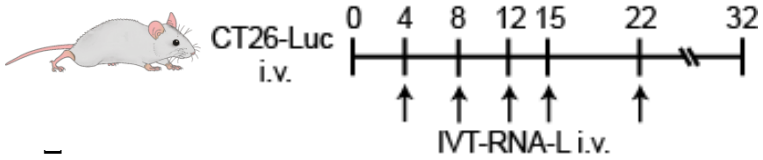




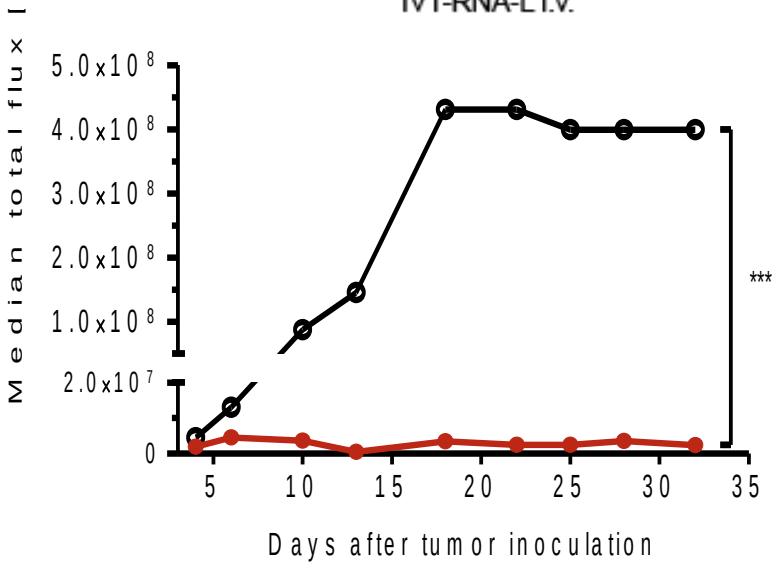


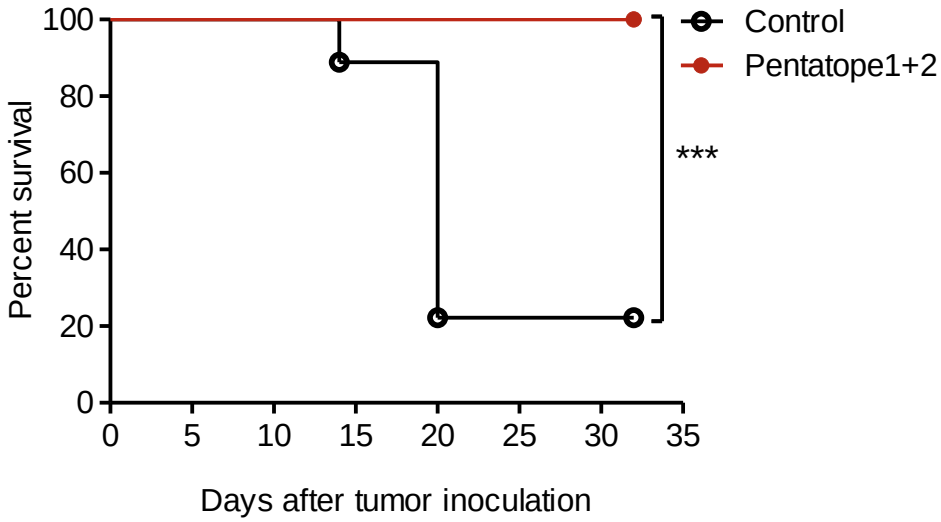
Pentatope RNA induces therapeutic tumor rejection (1)





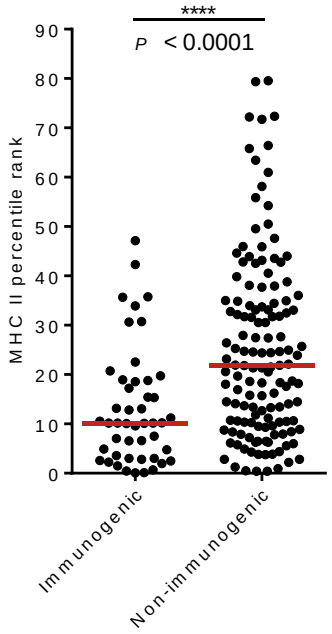
Pentatope1	CT26-M19	CT26-M39	CT26-M13	CT26-M55	CT26-M68
T cell subtype	CD8	CD8	CD4	CD4	CD4
Pentatope2	CT26-M20	CT26-M26	CT26-M03	CT26-M37	CT26-M27
T cell subtype	CD4	CD8	CD4	CD4	CD4

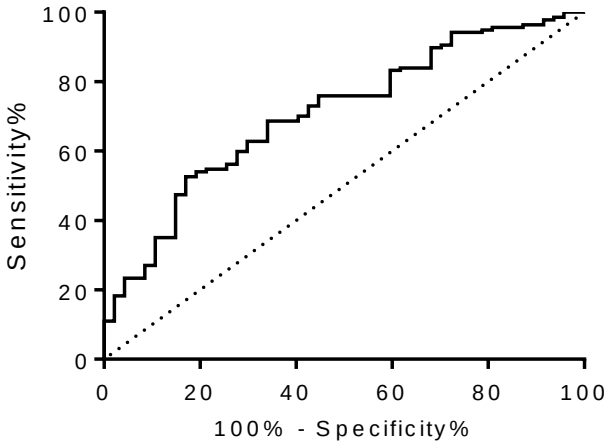




Influence of MHC class II binding prediction

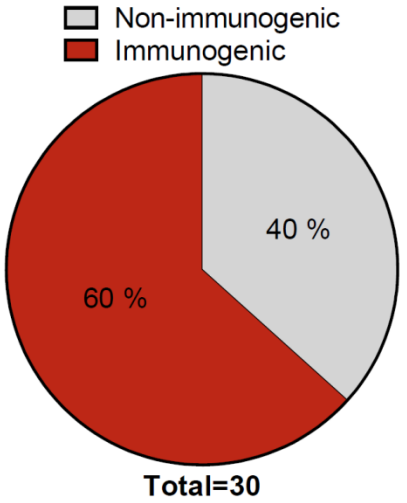
Meta-analysis reveals strong impact of MHC class II binding prediction on immunogenicity



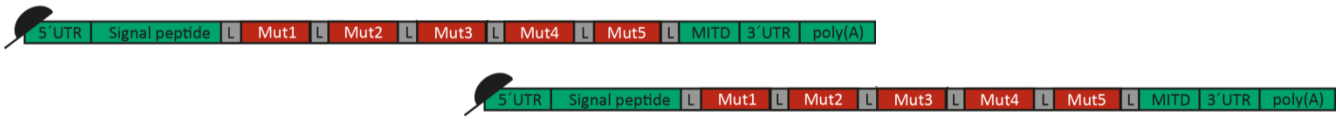


Area	0.7079
Std. Error	0.04238
95% confidence interval	0.6248 to 0.7910
P value	< 0.0001

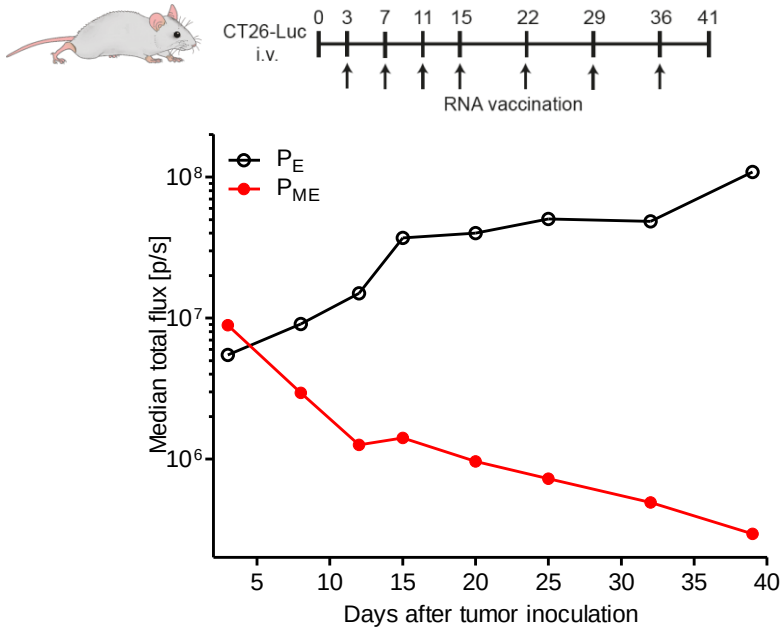
Mutations selected with an MHC II score < 10

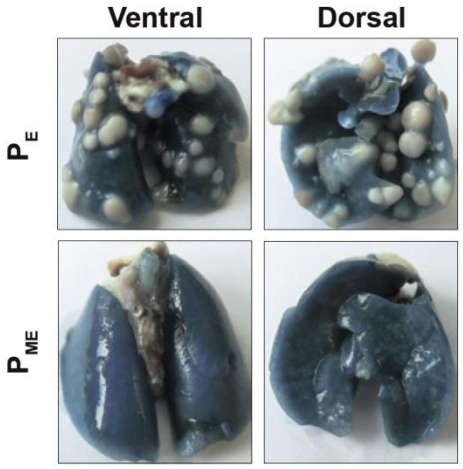


From *in silico* to *in vivo*



P_E: 10 mutations with abundant expression, bad MHC II binding prediction
P_{ME}: 10 mutations with abundant expression , good MHC II binding prediction

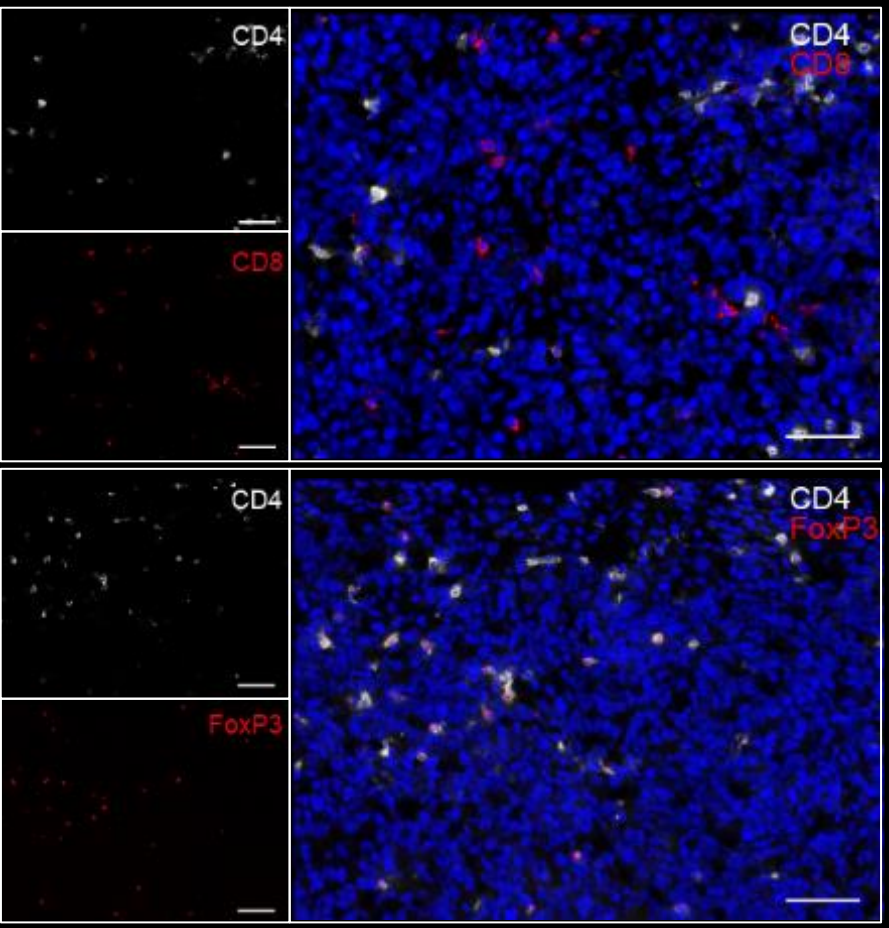


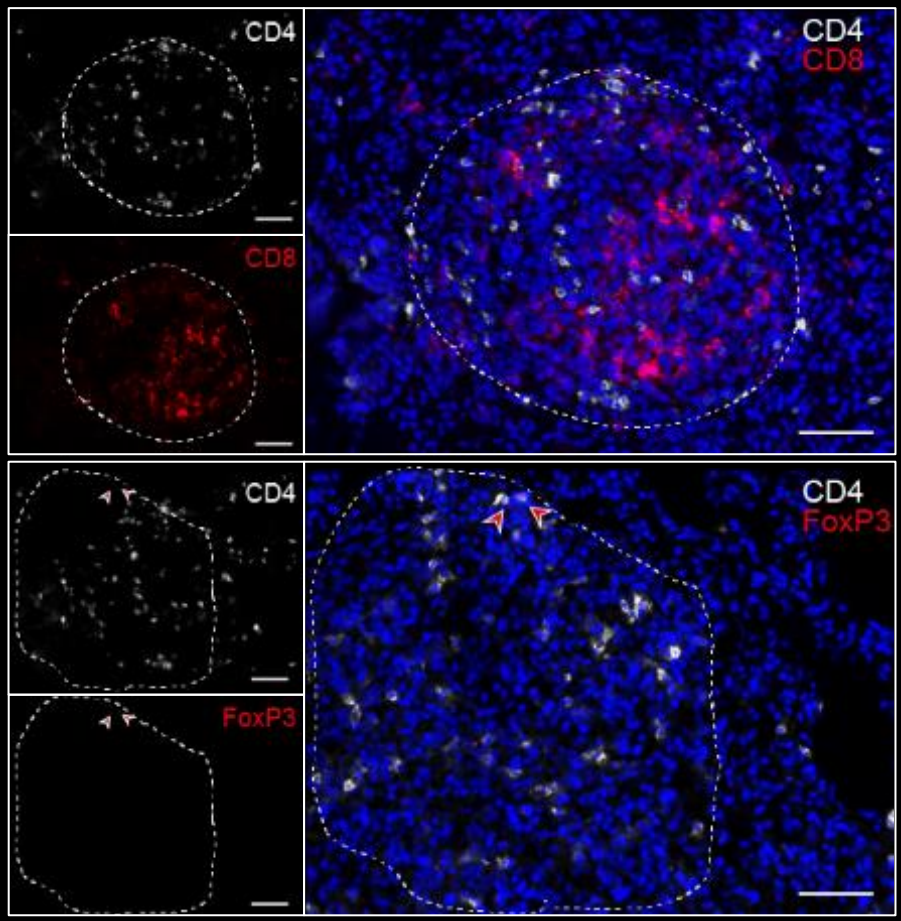


RNA vaccination induces profound changes in the tumor

Irrelevant RNA

Pentatope2



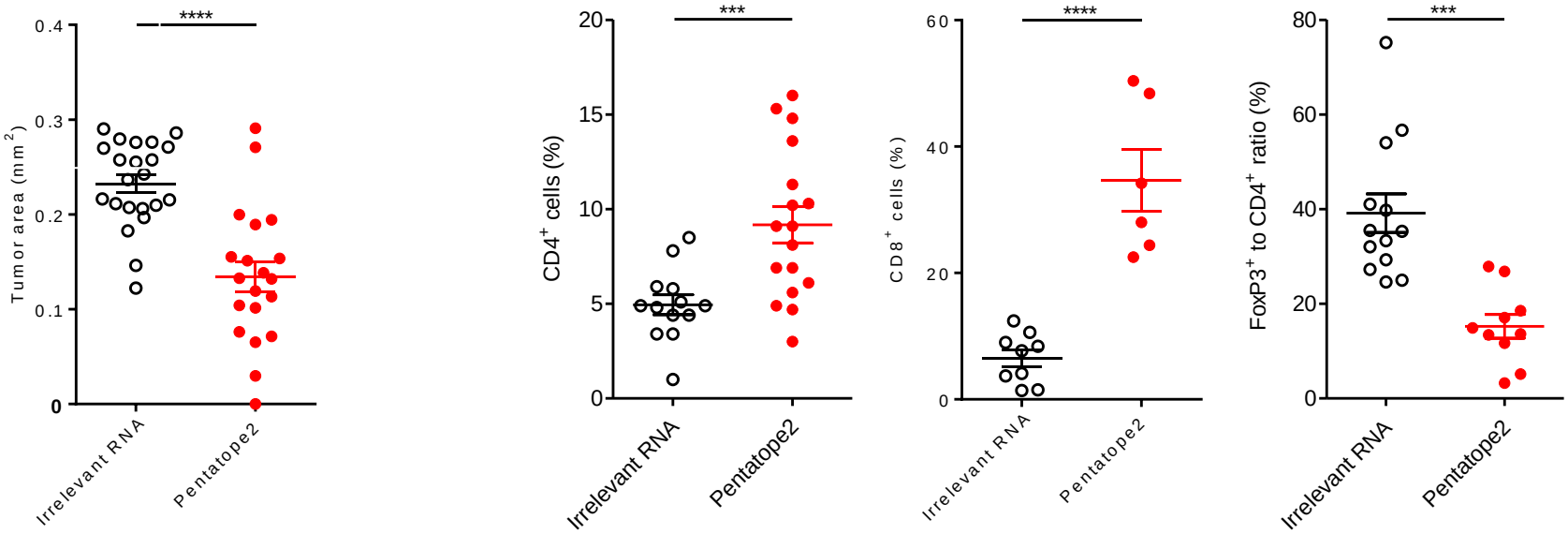


50µm

RNA vaccination induces profound changes in the tumor

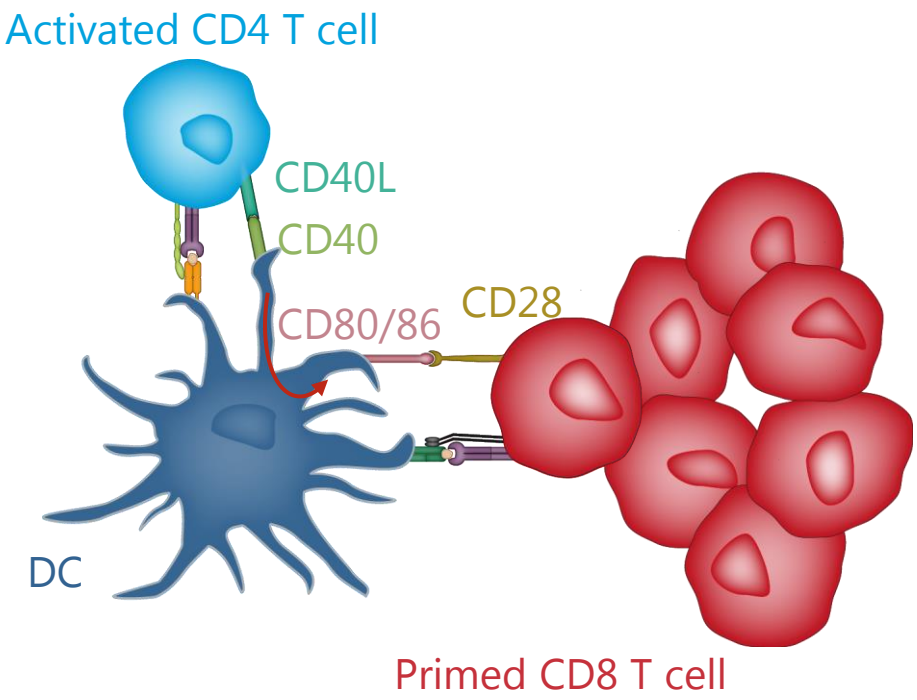
Mutanome vaccination induces significant

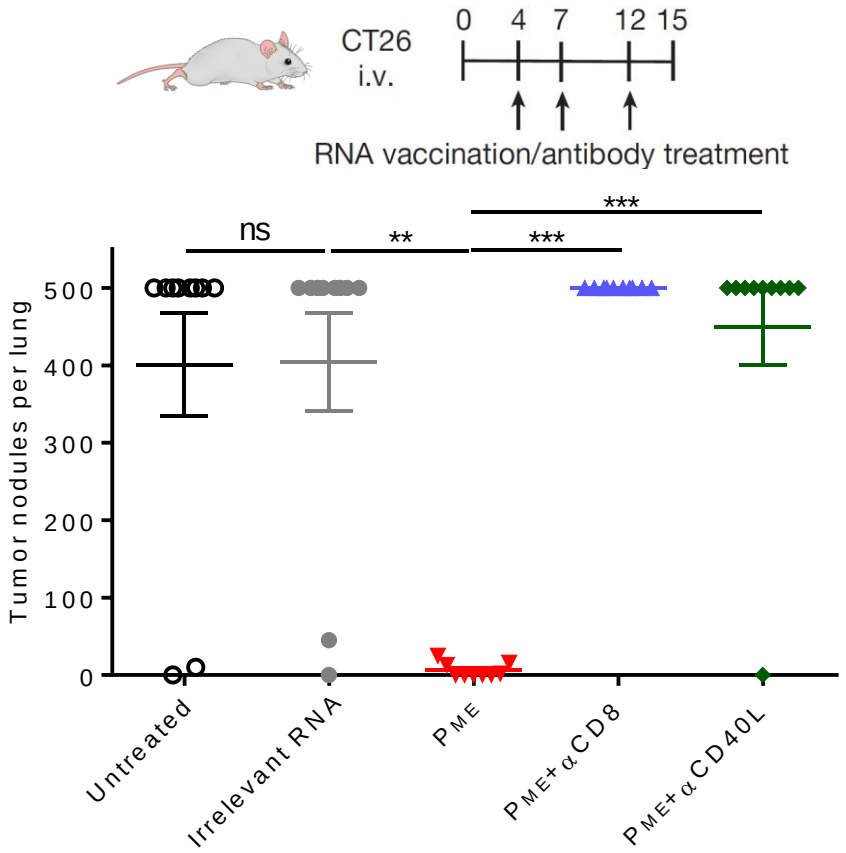
- Infiltration of $CD4^+$ and $CD8^+$ T cells
- Decrease of tumor burden and the FoxP3 to CD4 ratio



Tumor control depends on CD8 T cells and CD40L signaling

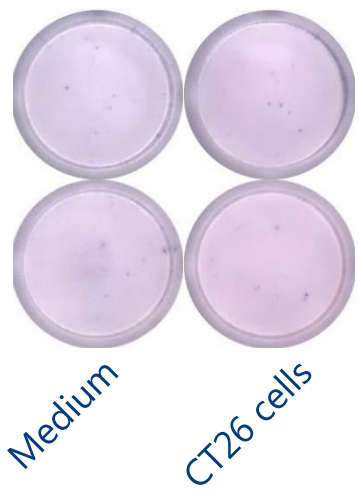
DC licensing



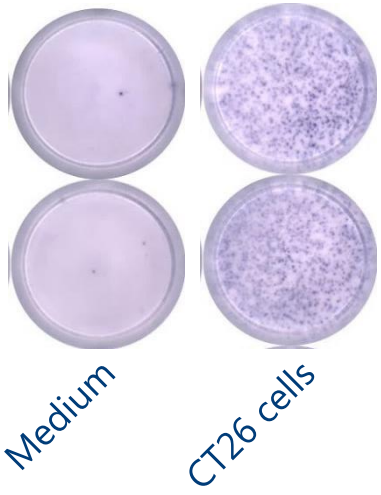


CD4 epitope vcaccination induces CD8 responses

Irrelevant RNA vaccinated

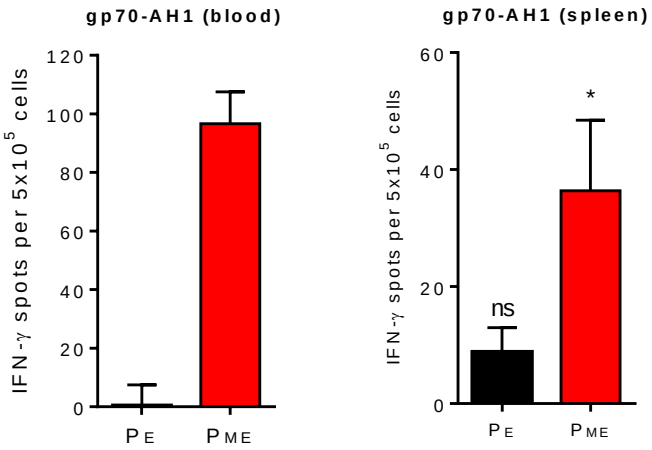


CD4 epitope vaccinated

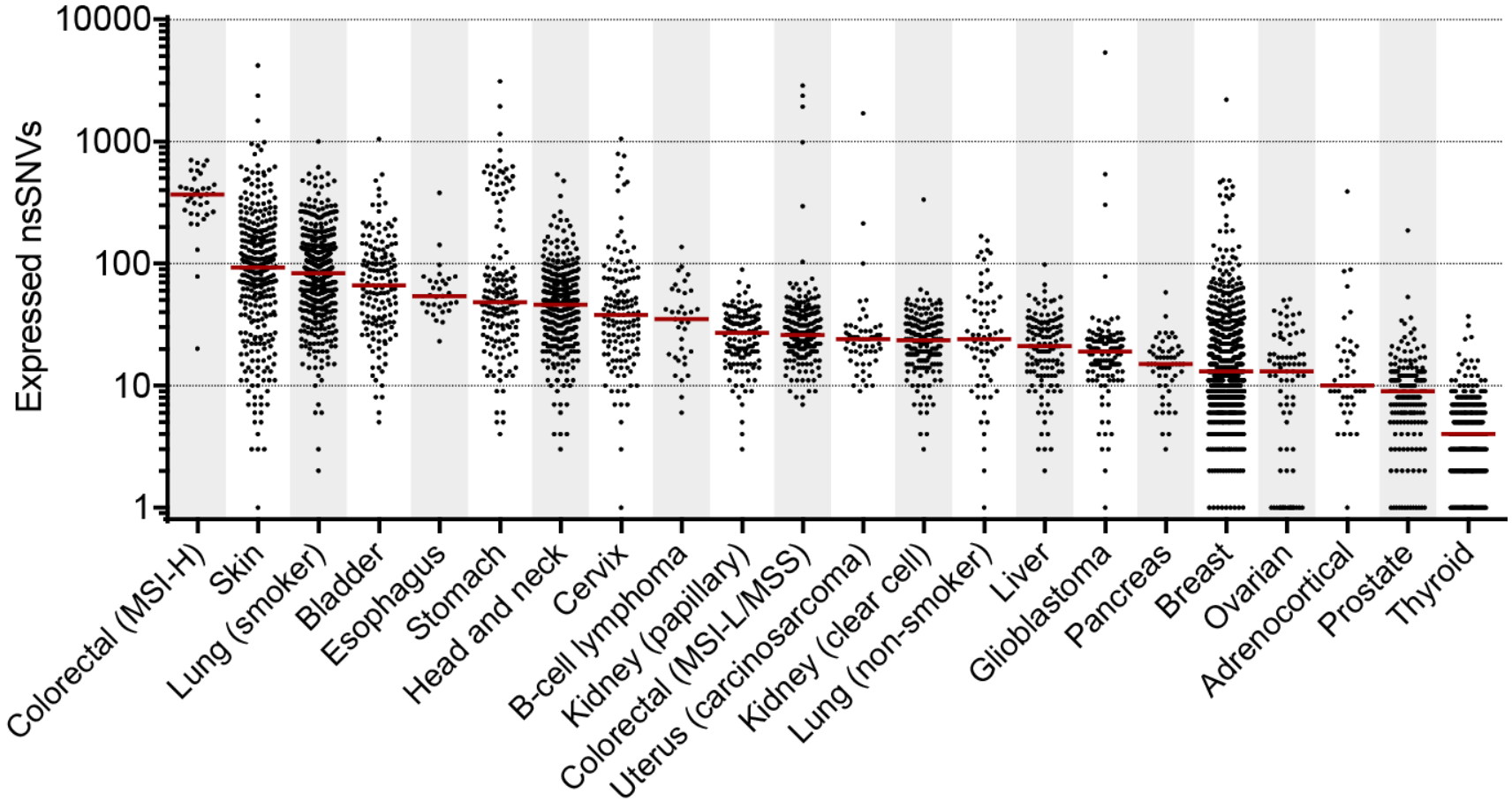


CD8 T cells
(CD4 T cell depleted splenocytes)

P_{ME} vaccinated



Human tumors express a plentitude of SNVs



Vormehr M et al.: **Mutanome directed cancer immunotherapy**. *Curr. Opin. Immunol.* 2016, in press

IVAC Mutanome Trial (NCT02035956) - Phase I

- Indication: Malignant Melanoma, stage IIIA-C or tumor free stage IV patients
- Patient No.: 15
- Treatment: 1. RBL001/RBL002 RNA i.n.
  2. IVAC mutanome RNA i.n. (10 mutations on 2 pentatopes)
- Design: Multicenter (Mainz, Mannheim, Vienna), Open-label, Interventional
- Endpoints: Primary: Safety, adverse reactions, tolerability
  Secondary: Immunogenicity

TRON

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