Identification of unique neoantigen qualities in long-term pancreatic cancer survivors

Vinod P. Balachandran, Marta Łuksza, Julia N. Zhao, Vlad Makarov, John Alec Moral, Romain Remark, Daniel K. Wells, Arnold J. Levine, Douglas T. Fearon, Miriam Merad, Sacha Gnjatic, Christine A. Iacobuzio-Donahue, Jedd D. Wolchok, Ronald P. DeMatteo, Timothy A. Chan, Benjamin D. Greenbaum, Taha Merghoub, Steven D. Leach

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Memorial Sloan Kettering

Institute for Advanced Study

Memorial Sloan Kettering Cancer Center

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Disclosures

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There **will not** be discussion about the use of products for non-FDA approved indications in this presentation.

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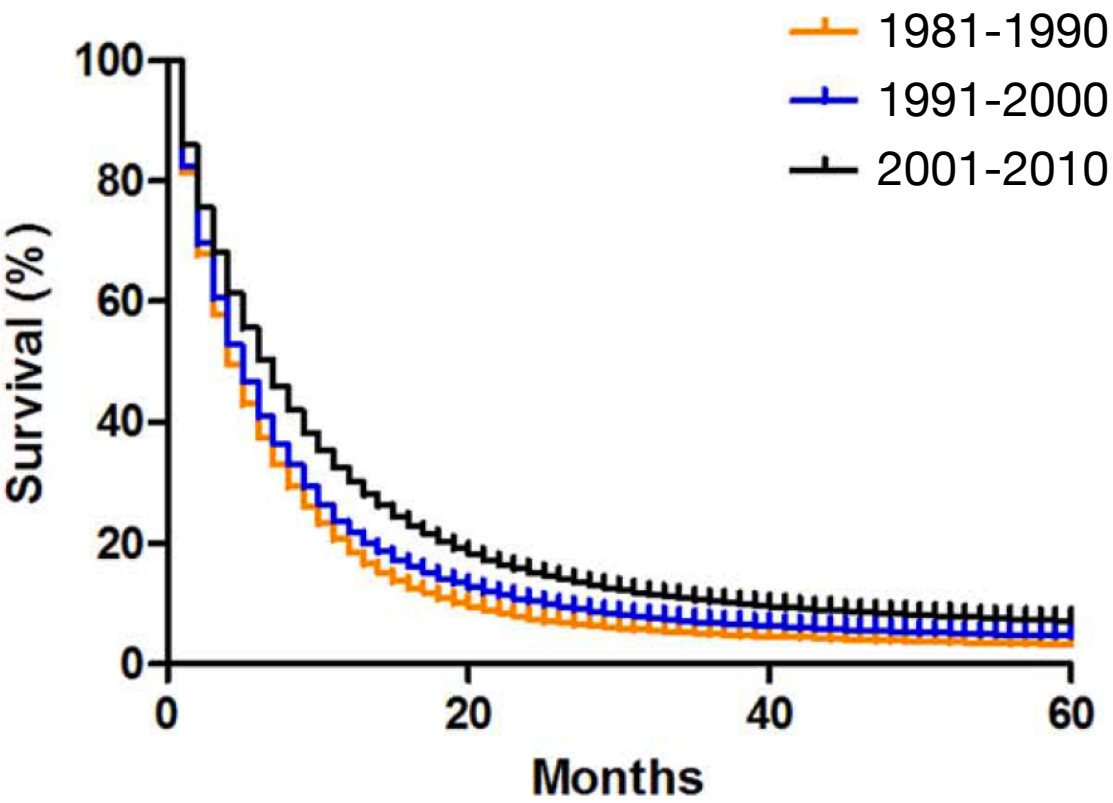
Long-Term Survivors of Pancreatic Cancer Are Rare



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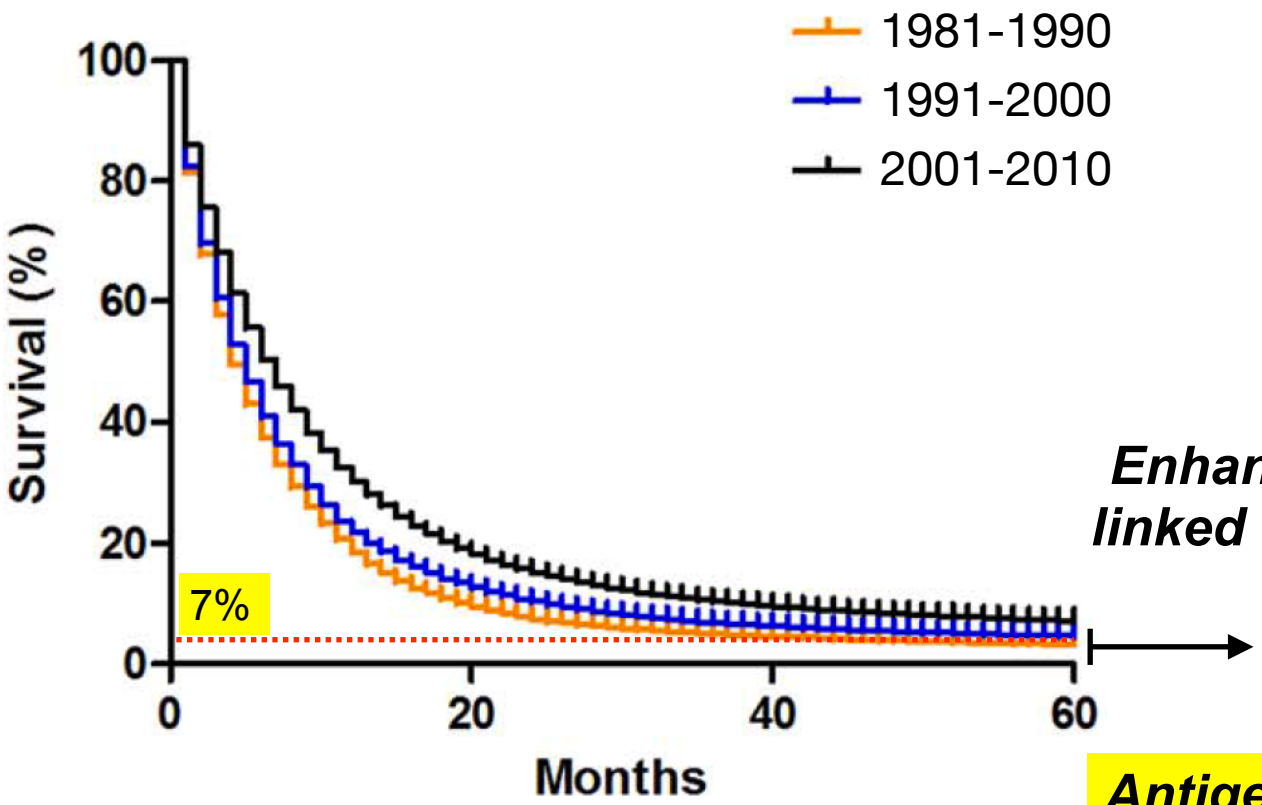
Sun Y et al. **Sci Rep**. 2014.

Long-Term Survivors of Pancreatic Cancer Are Rare



Enhanced T cell immunity linked to long-term survival

Antigens remain unknown

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Sun Y et al. **Sci Rep**. 2014.

Neoantigens in cancer immunotherapy

Ton N. Schumacher[1]* and Robert D. Schreiber[2]*

SCIENCE 3 APRIL 2015 • VOL 348 ISSUE 6230

Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade

SCIENCE 25 MARCH 2016 • VOL 351 ISSUE 6280

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

NATURE | VOL 547 | 13 JULY 2017

An immunogenic personal neoantigen vaccine for patients with melanoma

13 JULY 2017 | VOL 547 | NATURE

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Are neoantigens T cell antigens in long-term pancreatic cancer survivors?

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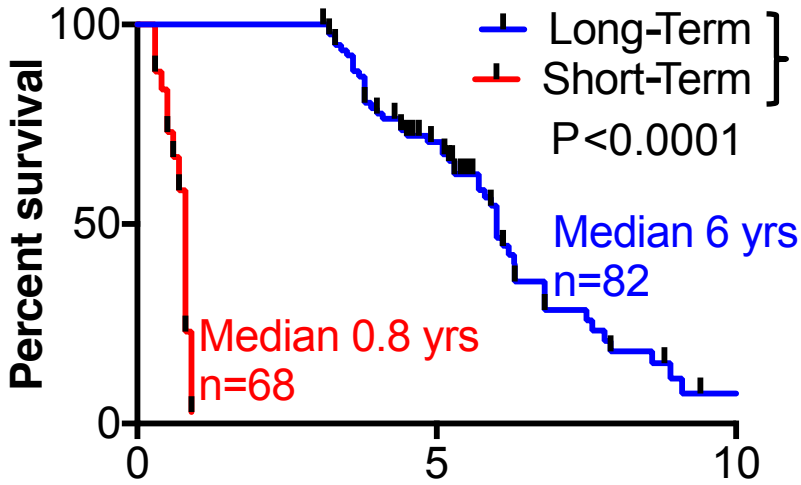
Experimental Design



Stage Matched

All patients had
- Surgically resected primary tumors
- No metastatic tumors
- No neoadjuvant chemotherapy

Whole Exome Sequencing	Multiplexed IHC	Transcriptome Profiling	TCR Vβ Sequencing
Neoantigen Discovery	Immune Phenotyping	Stromal Profiling	T cell repertoire Profiling

Computational Integration

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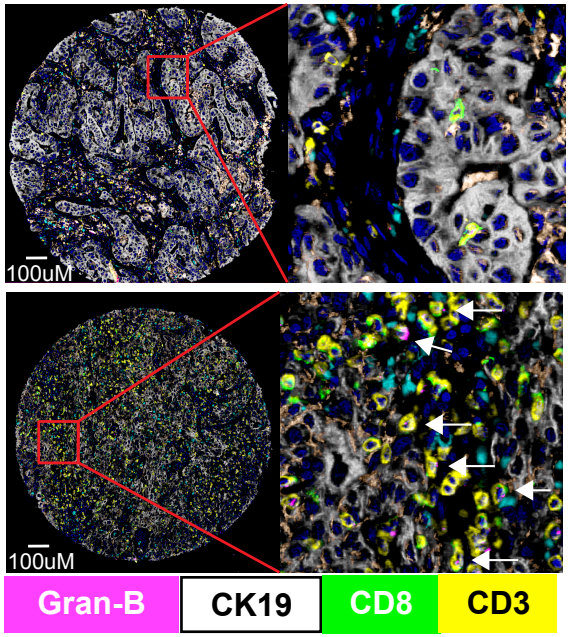
Balachandran VP et al. ***Nature 2017***
doi:10.1038/nature 24462

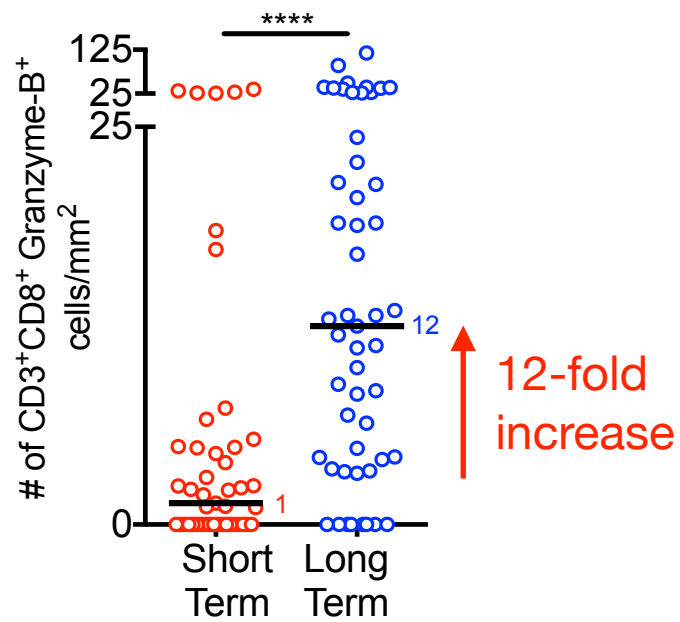
Long-Term Survivors Display Enhanced Intratumoral T cell Immunity

Short-Term

Long-Term



Cytolytic CD8+ T cells



Adaptive Immune Gene sets enriched in Long-Term Survivors

Pathway	Fold Change	P value	FDR Q value
MHC-II receptor activity	13.5	7×10^{-10}	1×10^{-6}
MHC-I receptor antigen processing	7	1×10^{-6}	0.002
Interferon-gamma signaling	6	3×10^{-10}	6×10^{-6}
T cell receptor signaling	3	2×10^{-5}	0.04

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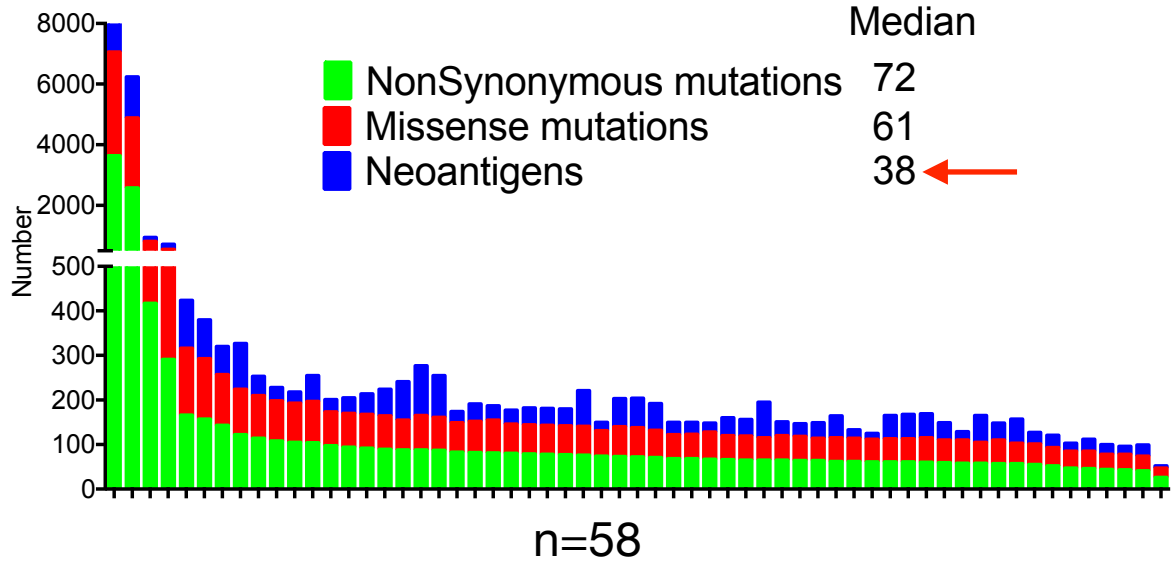
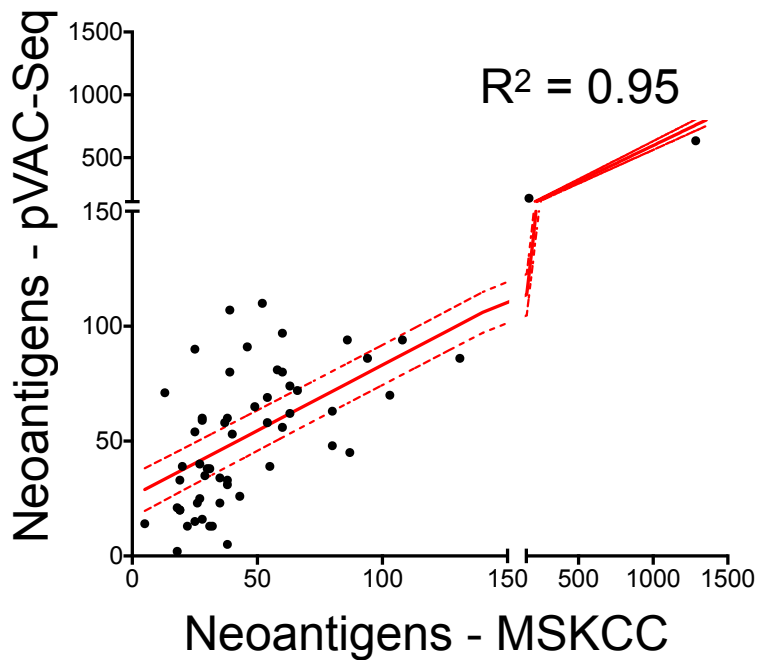
Balachandran VP et al. ***Nature 2017***
doi:10.1038/nature 24462

Putative neoantigens are present in human pancreatic cancer



MSKCC vs. pVAC-Seq Neoantigen Pipelines



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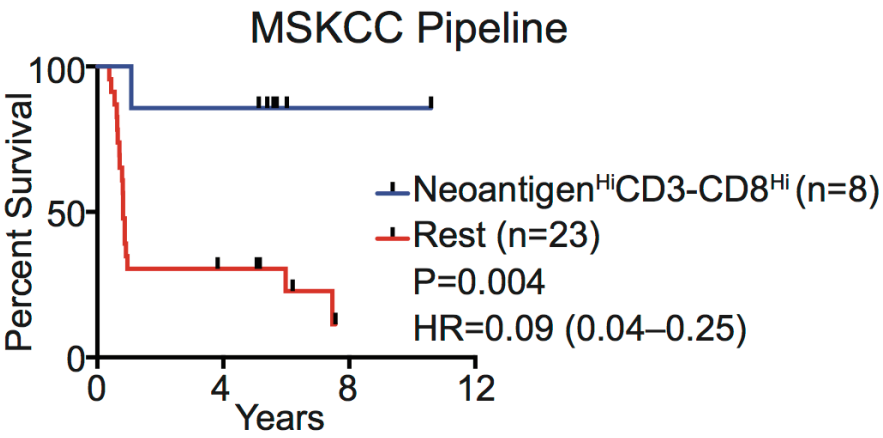
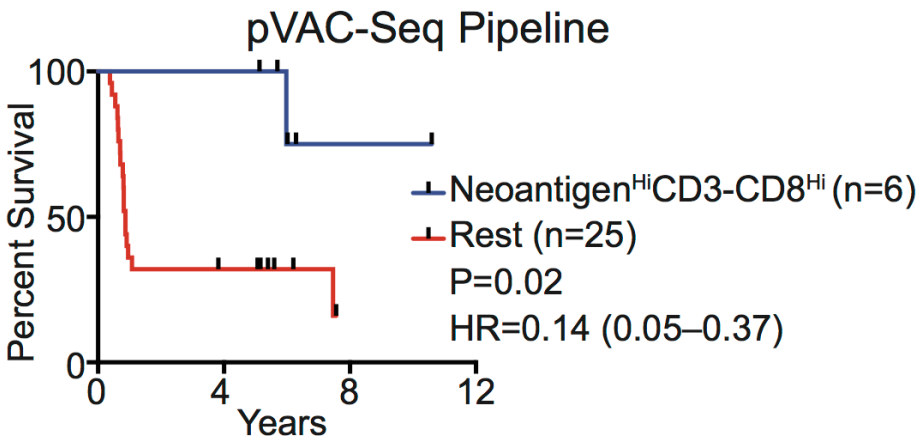
doi:10.1038/nature 24462

CD8+ T cells and neoantigens identify longest survivors





Variable	Univariate			Multivariate		
	Hazard Ratio	95% CI	P-value	Hazard Ratio	95% CI	P-value
Adjuvant Chemotherapy	0.5	0.2-1.4	0.2	0.6	0.2-1.7	0.4
Pathologic Stage	1.3	0.3-4.6	0.6	-	-	-
Margin	2.2	0.7-6.3	0.1	-	-	-
Neoantigen CD3-CD8 density	0.09	0.01-0.7	0.02	0.09	0.01-0.7	0.02

Confirmed with MSKCC and pVAC-Seq neoantigen pipelines

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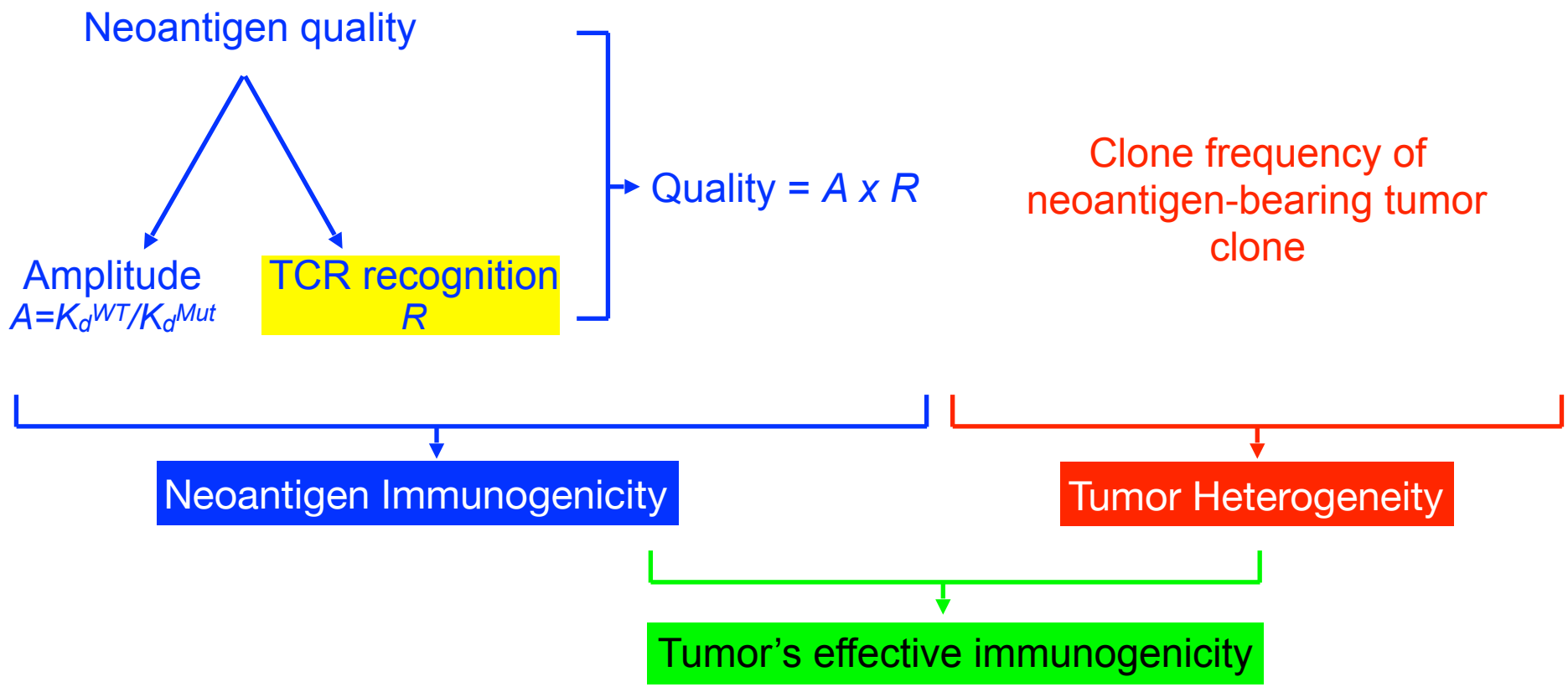
doi:10.1038/nature 24462

A computational model of neoantigen quality based immunogenicity

Which neoantigen(s) are the most immunogenic?



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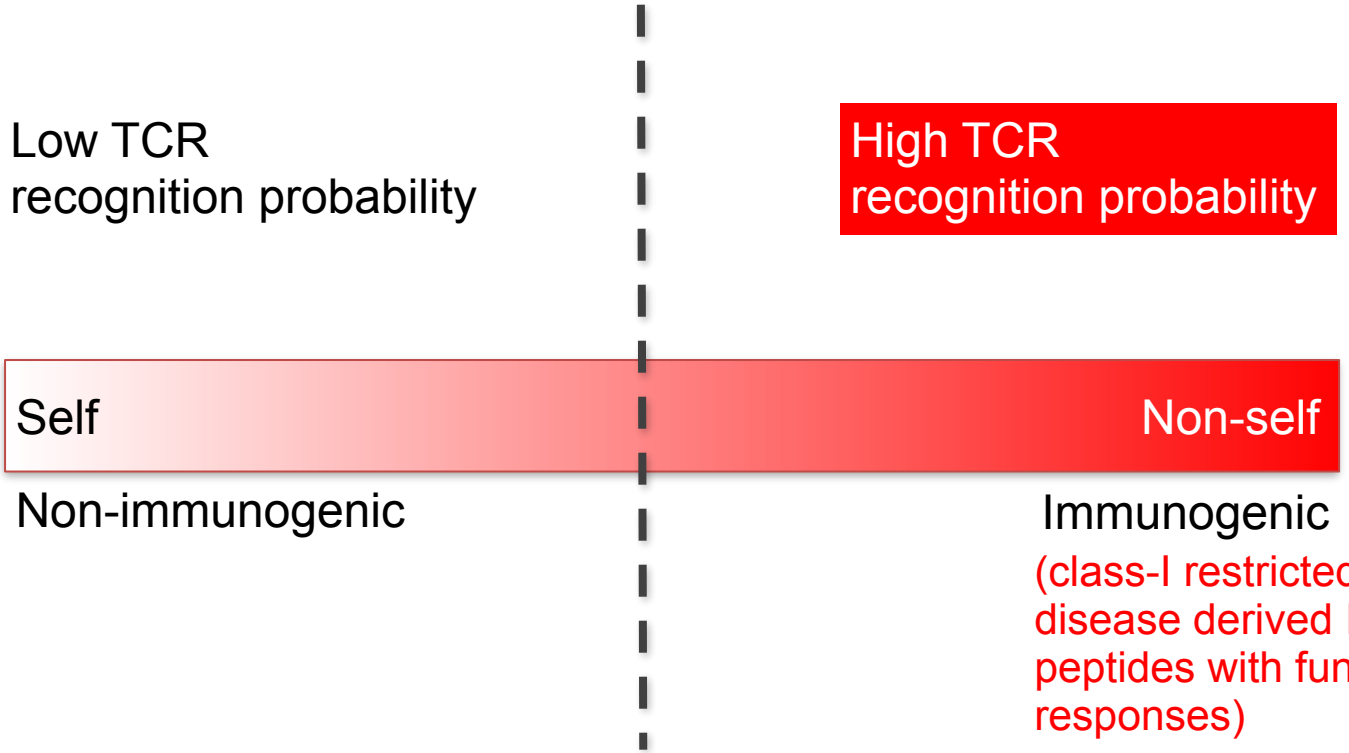
Balachandran VP et al. ***Nature 2017***
doi:10.1038/nature 24462

Łuksza M, Balachandran VP, Greenbaum BG et al. ***Nature 2017***
doi:10.1038/nature 24473

“Non-self” is a surrogate for TCR neoantigen recognition



Threshold for immune activation

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Łuksza M, Balachandran VP, Greenbaum BG et al. ***Nature 2017***
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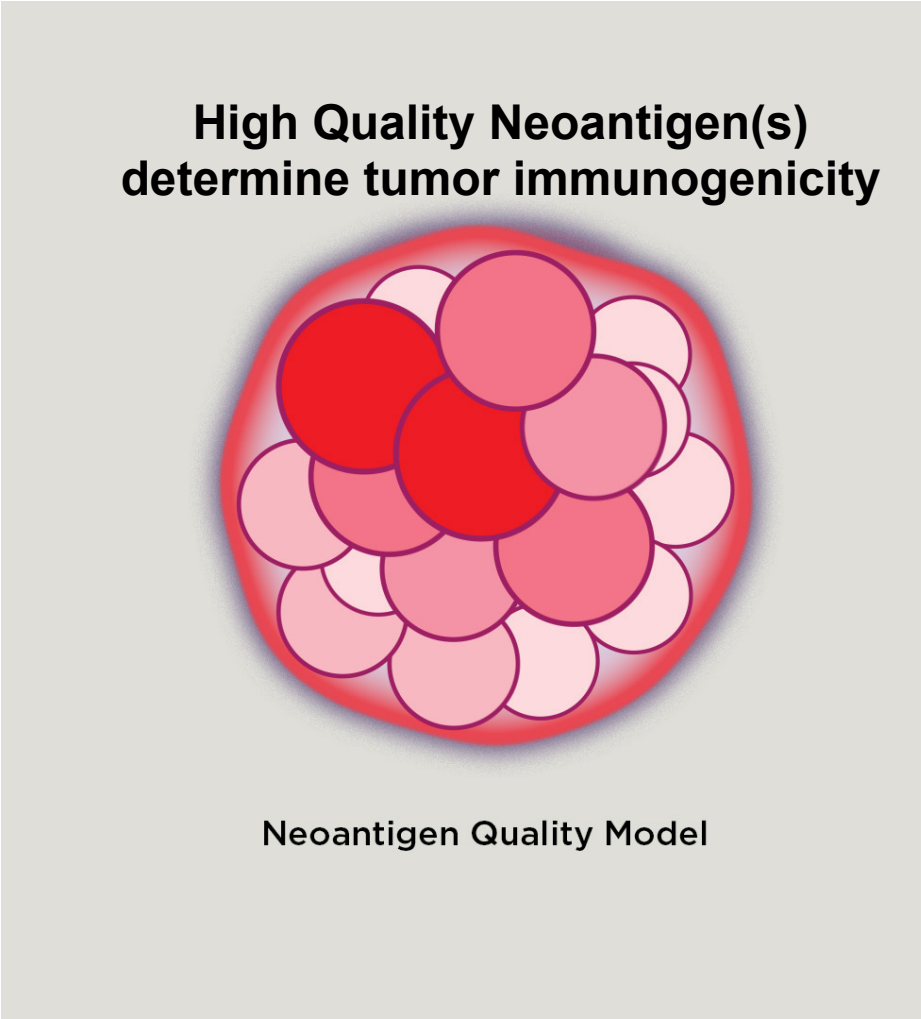
Neoantigen Models of tumor immunogenicity



Increasing
Immunogenicity

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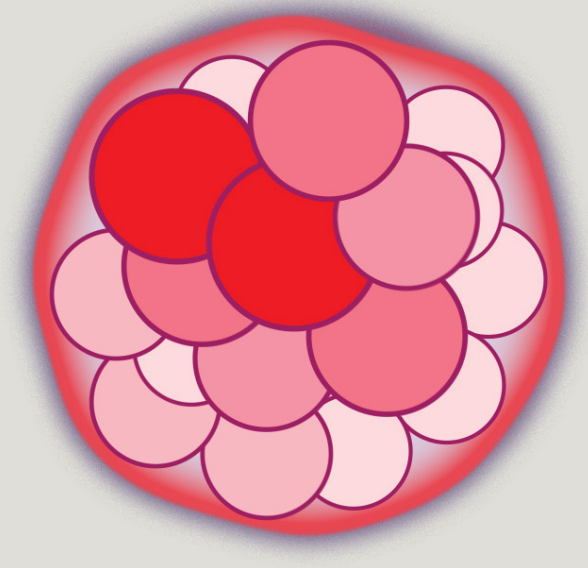
Neoantigen Models of tumor immunogenicity

High Quality Neoantigen(s) determine tumor immunogenicity



Neoantigen Quality Model

Neoantigen number determines tumor immunogenicity

Neoantigen Quantity Model

Increasing Immunogenicity

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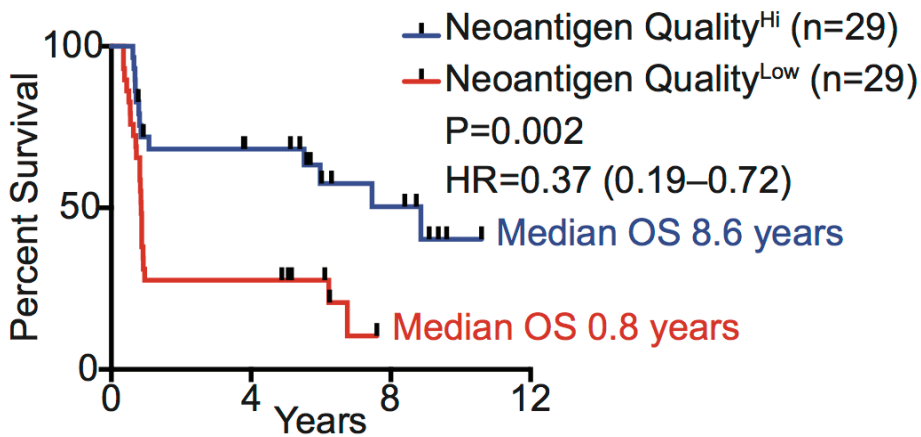
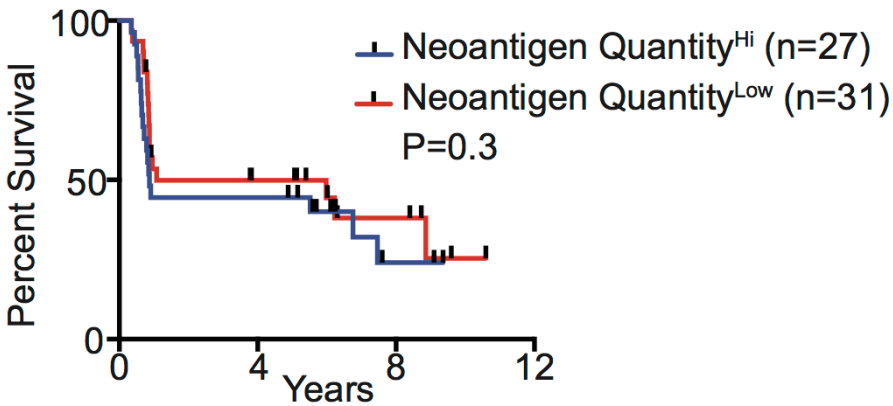
Neoantigen quality but not quantity stratifies long term survivors





Variable	Univariate			Multivariate		
	Hazard Ratio	95% CI	P-value	Hazard Ratio	95% CI	P-value
Adjuvant Chemotherapy	0.4	0.1-0.9	0.02	0.5	0.2-1.2	0.1
Pathologic Stage	1.4	0.5-4.1	0.4	-	-	-
Margin	1.5	0.7-3.4	0.2	-	-	-
Neoantigen Quality	0.3	0.1-0.7	0.003	0.3	0.1-0.7	0.008

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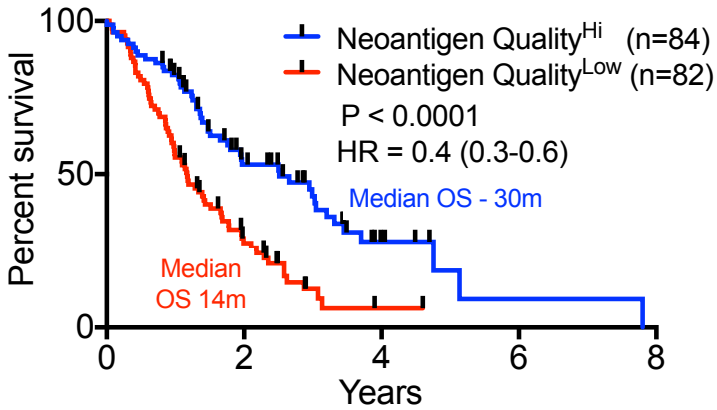
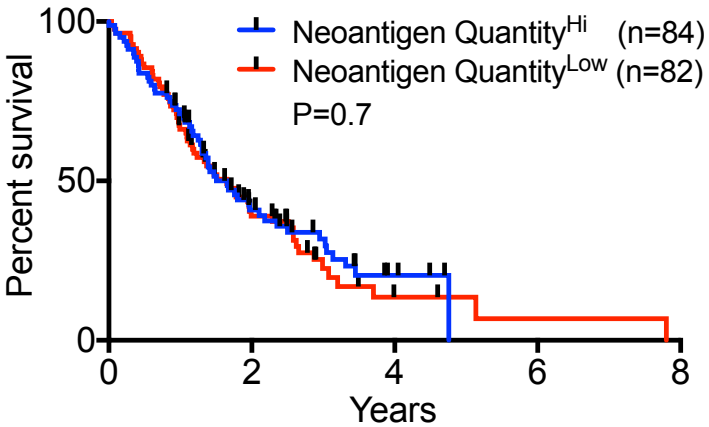
doi:10.1038/nature 24462

Neoantigen quality is prognostic of survival in pancreatic cancer

International Cancer Genome Consortium





Variable	Univariate			Multivariate		
	Hazard Ratio	95% CI	P-value	Hazard Ratio	95% CI	P-value
Adjuvant Treatment	0.4	0.2-0.5	0.0001	0.4	0.2-0.7	0.001
Pathologic Stage						
- Stage I	-	-	-	-	-	-
- Stage II	2.5	0.9-7	0.07	3.7	0.9-15.9	0.07
- Stage III/IV	6.8	1.9-24.8	0.004	12.7	1.1-146	0.04
Margin						
- R0	-	-	-	-	-	-
- R1	2.3	1.4-3.7	0.0001	2.7	1.6-4.5	0.001
- R2	3.6	1.6-8	0.001	0.9	0.09-9.5	0.9
Neoantigen Quality	0.4	0.3-0.64	0.0001	0.5	0.3-0.9	0.01

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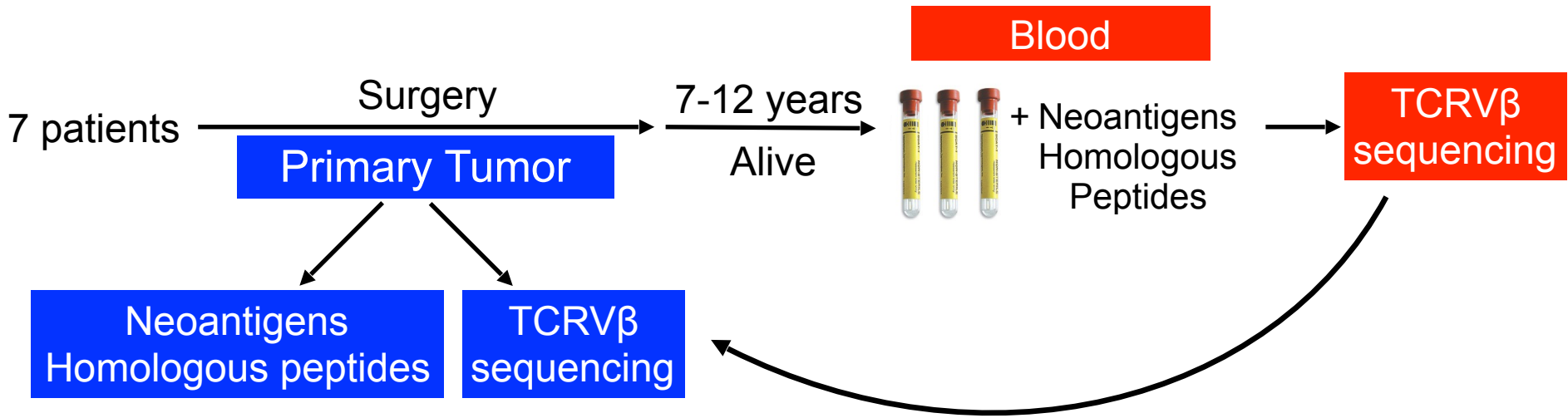
Are high quality neoantigens T cell targets in long term survivors?



Do high quality neoantigen-specific T cell clones found in primary tumors persist in the peripheral blood?

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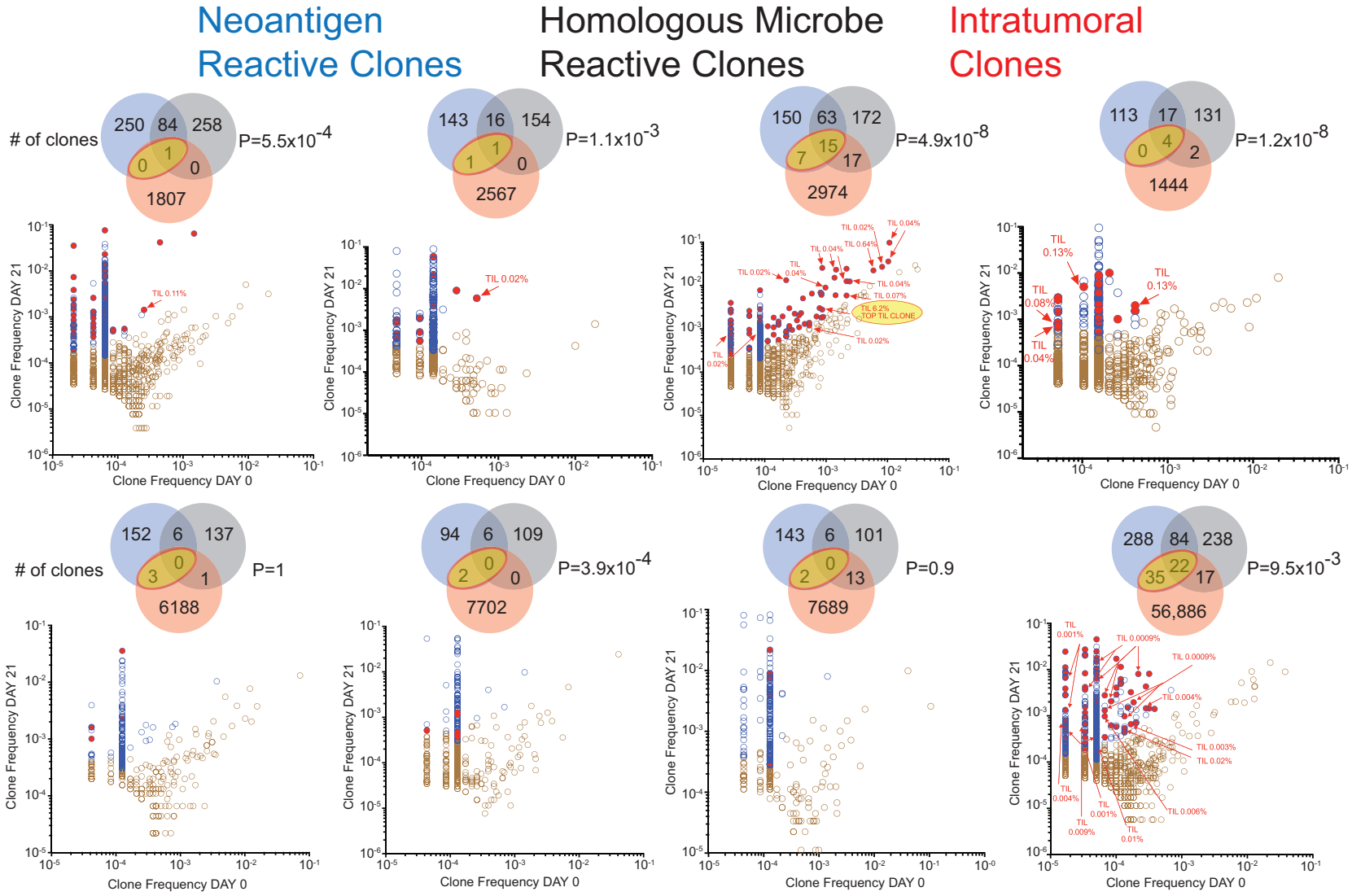
doi:10.1038/nature 24462

Neoantigen-specific T cells persist in the blood of Pancreatic Cancer Survivors

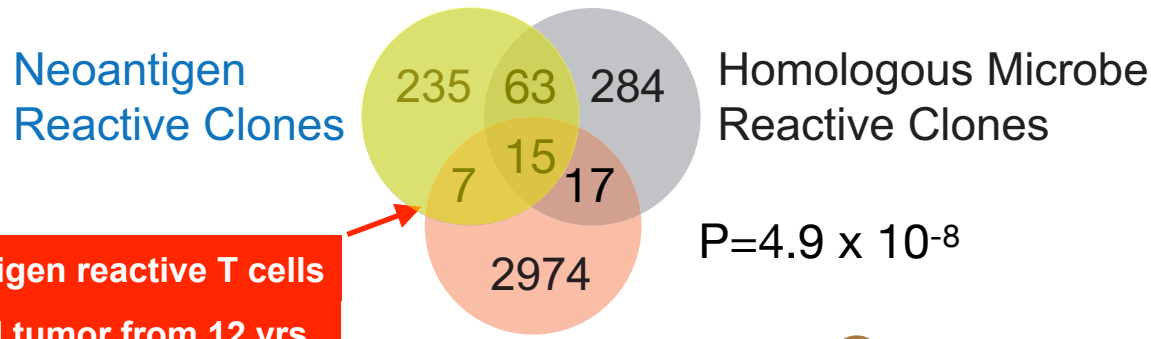


High Quality Neoantigen Reactive Intratumoral T cells persist in the blood in 7/7 patients tested

Balachandran VP et al. ***Nature 2017***
doi:10.1038/nature 24462

Neoantigen-specific T cells persist in the blood of Pancreatic Cancer Survivors

Patient 3 - NED, Alive 11.5y

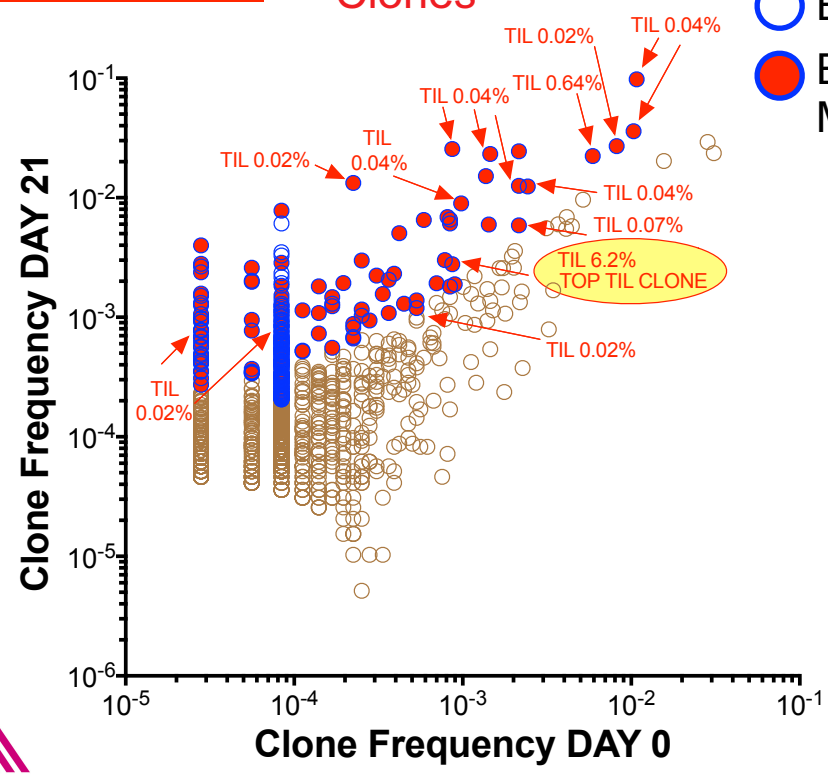


$P=4.9 \times 10^{-8}$

229 high quality neoantigen reactive T cells

79/229 found in archival tumor from 12 yrs

Includes highest frequency TIL (6.2%)



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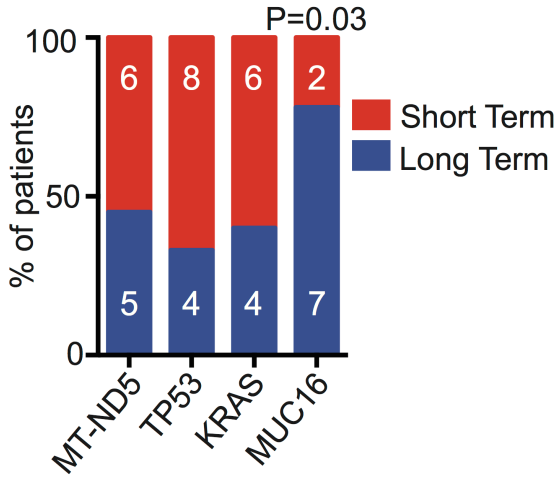
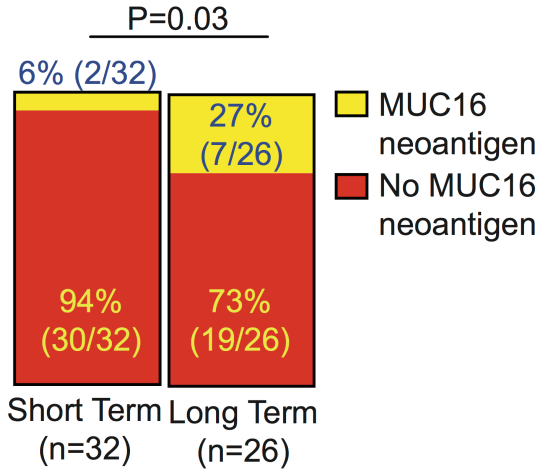
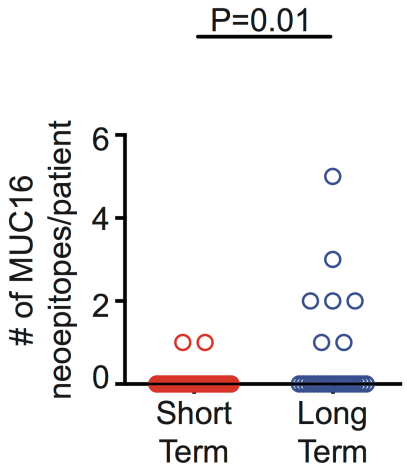
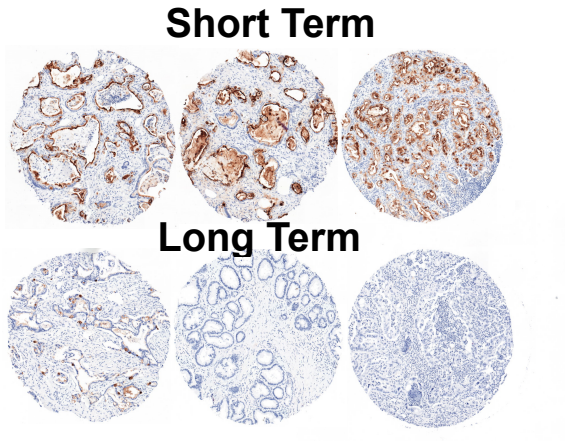
doi:10.1038/nature 24462

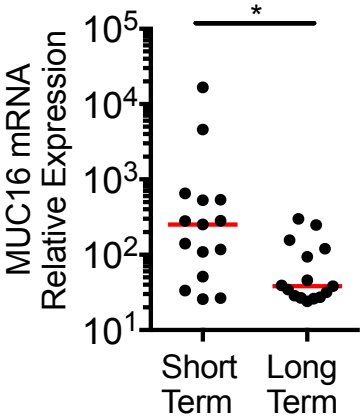
MUC16 is an immunogenic hotspot in long term survivors

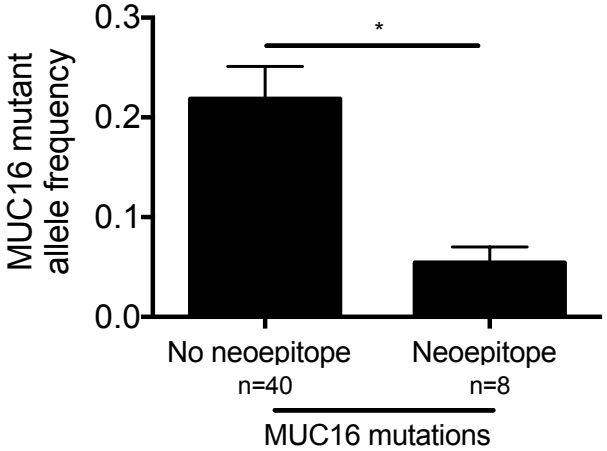












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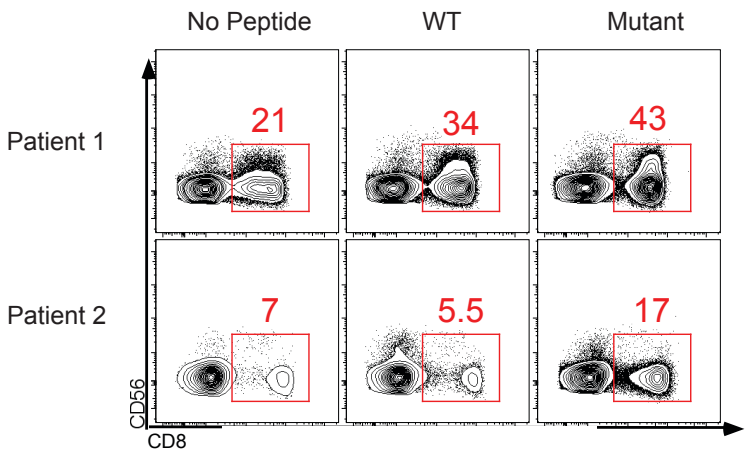
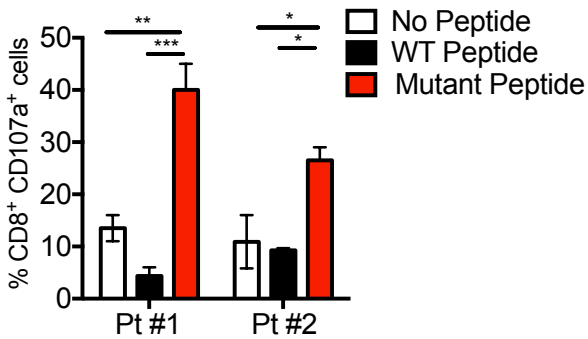
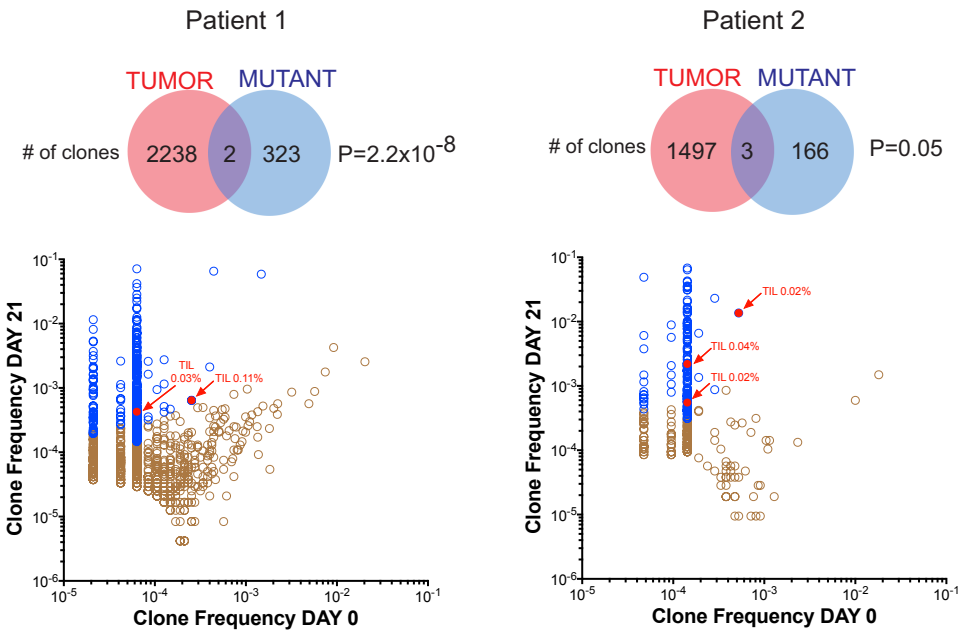
T cells in long term survivors recognize mutated *MUC16* neopeptides







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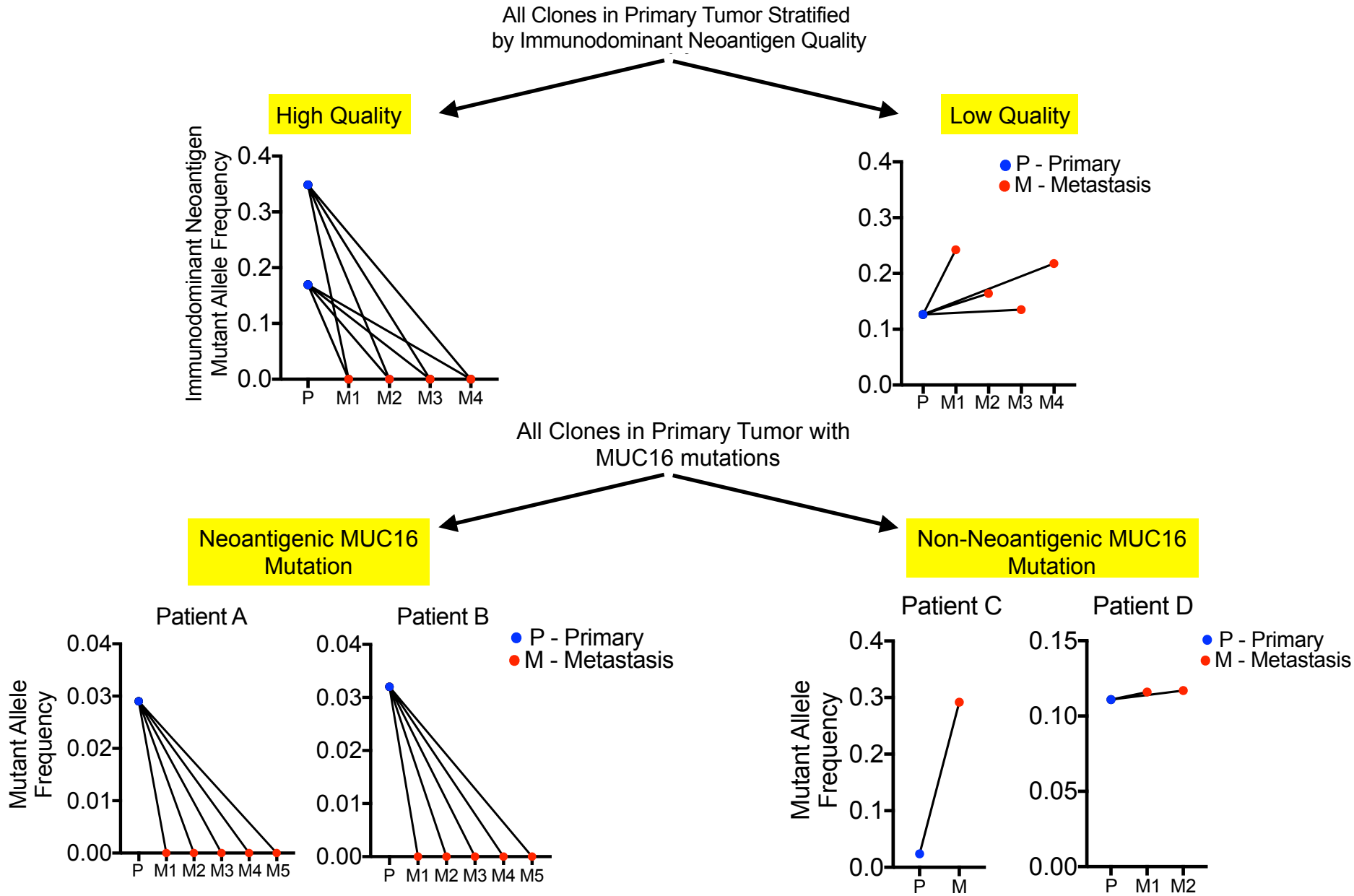
doi:10.1038/nature 24462

Immunoediting of high quality neoantigens



LETTER

doi:10.1038/nature24462

Identification of unique neoantigen qualities in long-term survivors of pancreatic cancer

Vinod P. Balachandran[1,2,3], Marta Łuksza[4], Julia N. Zhao[1,2,3], Vladimir Makarov[5,6], John Alec Moral[1,2,3], Romain Remark[7], Brian Herbst[2], Gokce Askan[2,8], Umesh Bhanot[8], Yasin Senbabaoglu[9], Daniel K. Wells[10], Charles Ian Ormsby Cary[10], Olivera Grbovic-Huezo[2], Marc Attiyeh[1,2], Benjamin Medina[1], Jennifer Zhang[1], Jennifer Loo[1], Joseph Saglimbeni[2], Mohsen Abu-Akeel[9], Roberta Zappasodi[9], Nadeem Riaz[6,11], Martin Smoragiewicz[12], Z. Larkin Kelley[13,14], Olca Basturk[8], Australian Pancreatic Cancer Genome Initiative*, Mithat Gönen[15], Arnold J. Levine[4], Peter J. Allen[1,2], Douglas T. Fearon[13,14], Miriam Merad[7], Sacha Gnjatic[7], Christine A. Iacobuzio-Donahue[2,5,8], Jedd D. Wolchok[3,9,16,17,18], Ronald P. DeMatteo[1,2], Timothy A. Chan[3,5,6,11], Benjamin D. Greenbaum[19], Taha Merghoub[3,9,18]§, Steven D. Leach[1,2,5]§

LETTER

doi:10.1038/nature24473

A neoantigen fitness model predicts tumour response to checkpoint blockade immunotherapy

Marta Łuksza[1], Nadeem Riaz[2,3], Vladimir Makarov[3,4], Vinod P. Balachandran[5,6,7], Matthew D. Hellmann[7,8,9], Alexander Solovyov[10,11,12,13], Naiyer A. Rizvi[14], Taha Merghoub[7,15,16], Arnold J. Levine[1], Timothy A. Chan[2,3,4,7], Jedd D. Wolchok[7,8,15,16] & Benjamin D. Greenbaum[10,11,12,13]

Summary

Neoantigens with unique qualities are T cell targets in long-term survivors

Neoantigen quality but not quantity is prognostic of survival

Neoantigen quality is a biomarker of immunogenic tumors

Neoantigen quality assessment may facilitate rational application of neoantigen-based therapies

Center for Pancreatic Research

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AACR American Association for Cancer Research

PARKER INSTITUTE for CANCER IMMUNOTHERAPY

DAMON RUNYON CANCER RESEARCH FOUNDATION

PANCREATIC CANCER ACTION NETWORK

David M. Rubenstein Center for Pancreatic Research
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S↑2C STAND UP TO CANCER

NIH NATIONAL CANCER INSTITUTE

AACR American Association for Cancer Research

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A computational model of neoantigen quality based immunogenicity

Which neoantigen(s) are the most immunogenic?

Highest Amplitude
Least central tolerance

TCR recognition
Most non-self

Most highly represented

Neoantigen Immunogenicity

Tumor Heterogeneity

Tumor's effective immunogenicity

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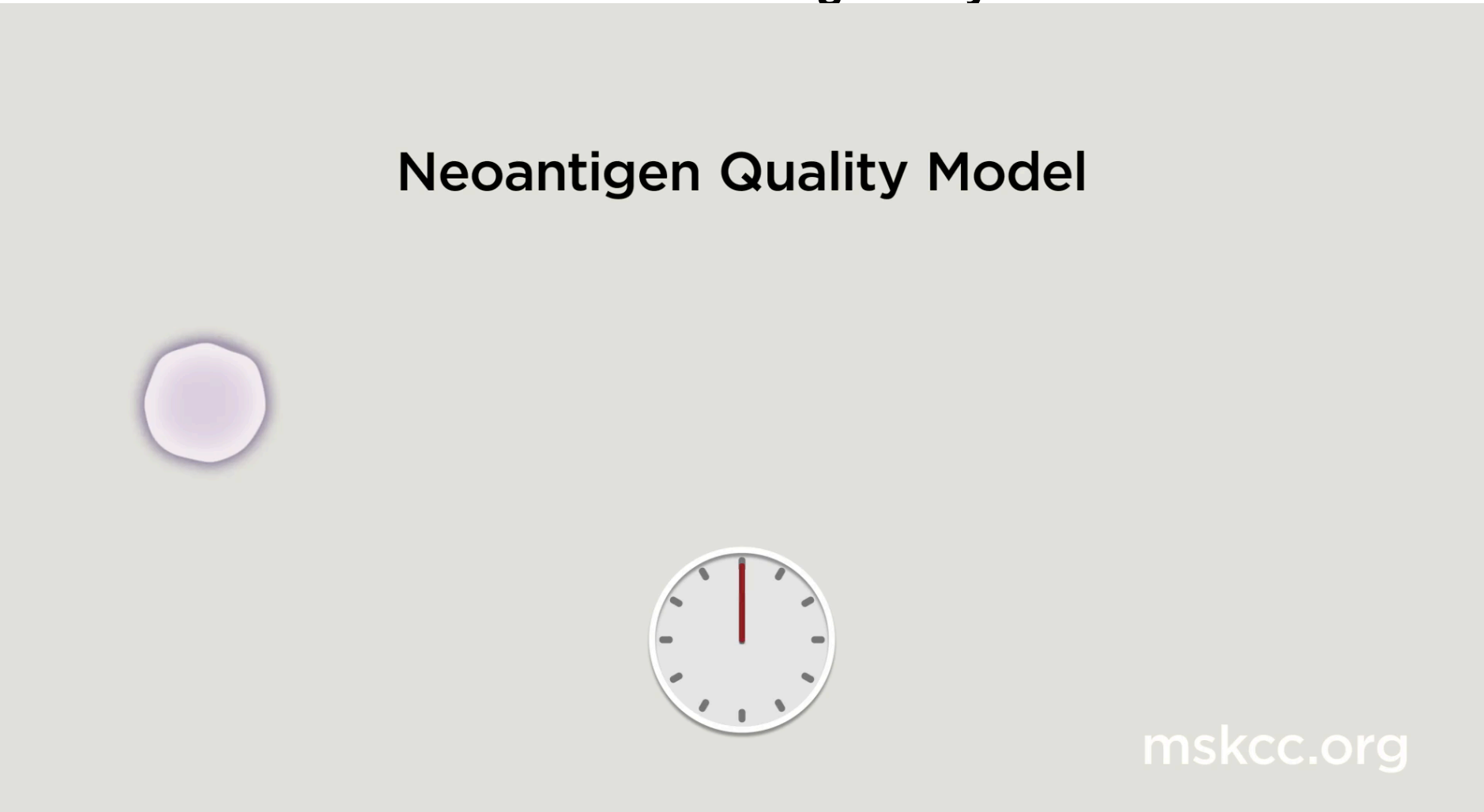
Balachandran VP et al. ***Nature 2017***
doi:10.1038/nature 24462

Łuksza M, Balachandran VP, Greenbaum BG et al. ***Nature 2017***
doi:10.1038/nature 24473

Quality Model - Dominant High Quality Neoantigen(s) determine tumor immunogenicity



Increasing Immunogenicity

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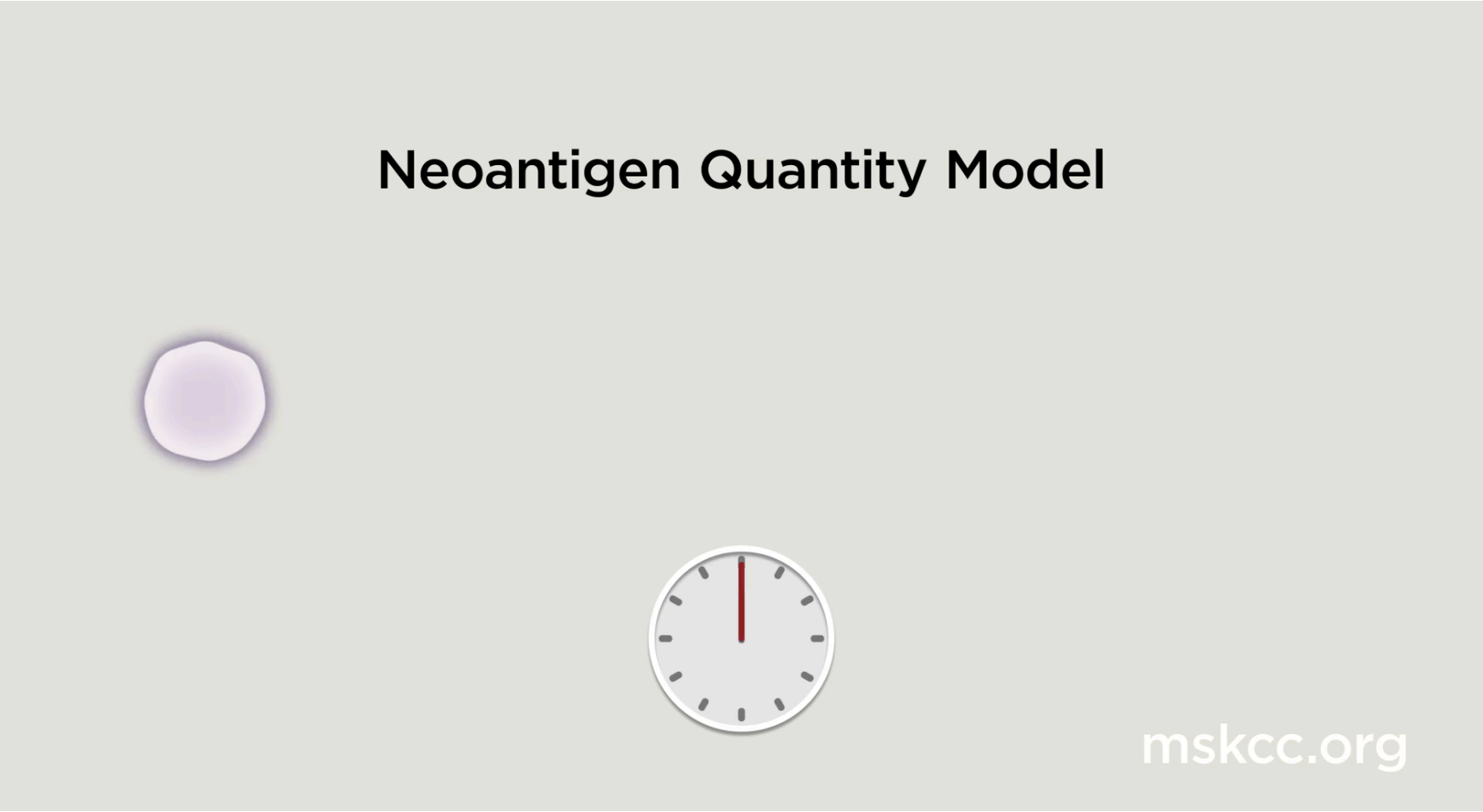
Quantity Model - Total Neoantigen number determines tumor immunogenicity



Increasing Immunogenicity

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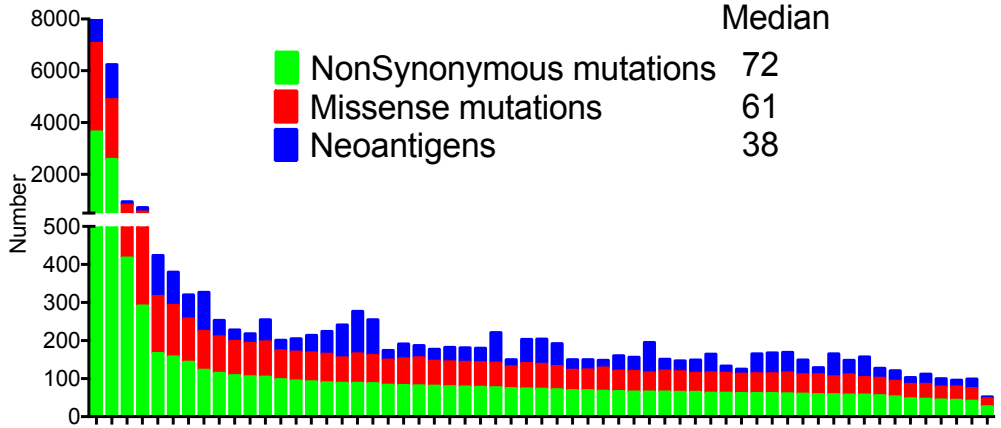
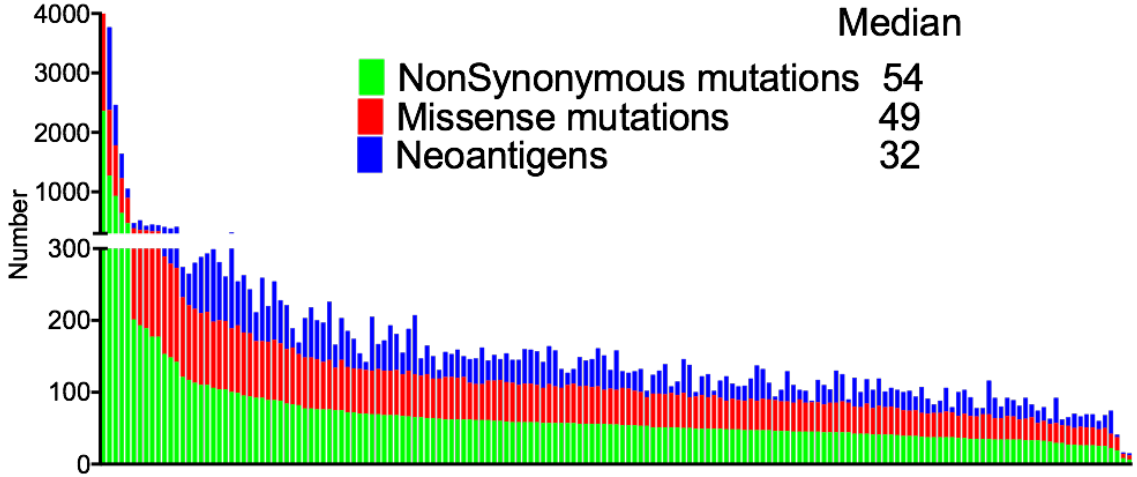
Neoantigens are present in human pancreatic cancer

MSKCC



International Cancer Genome Consortium



IAS

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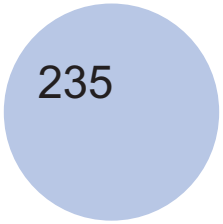
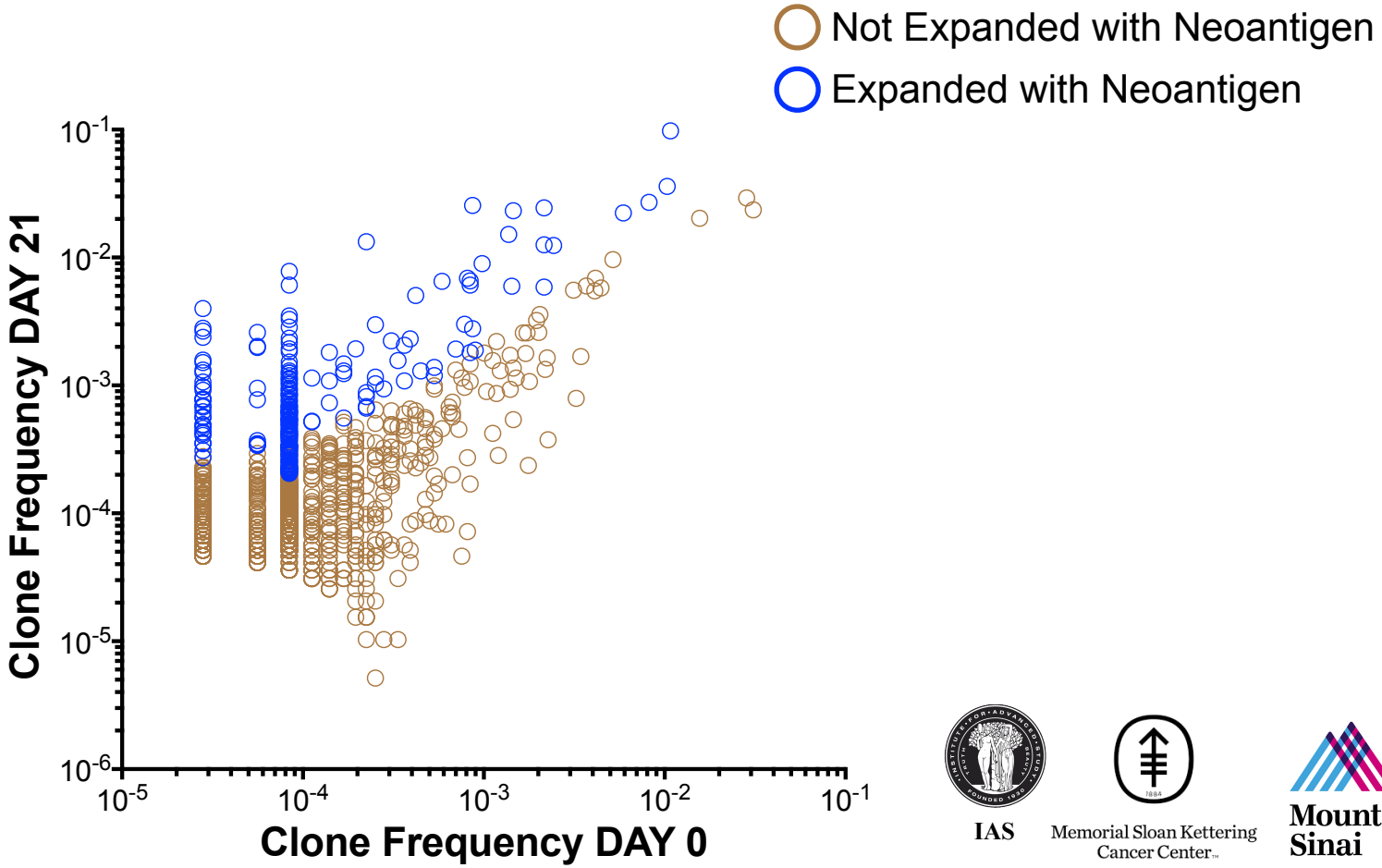
High Quality Neoantigen Reactivity in Long Term Pancreatic Cancer Survivors

Patient 3 - NED, Alive 11.5y

Neoantigen Reactive Clones





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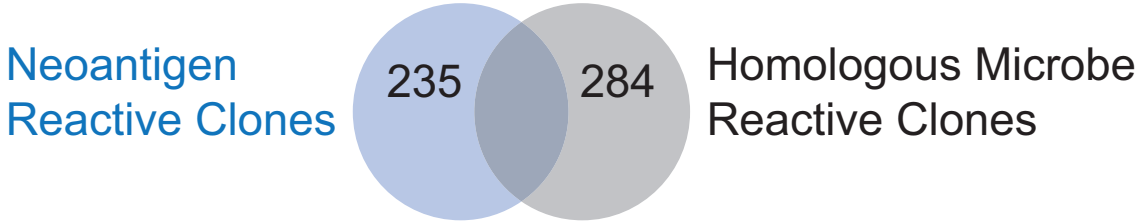

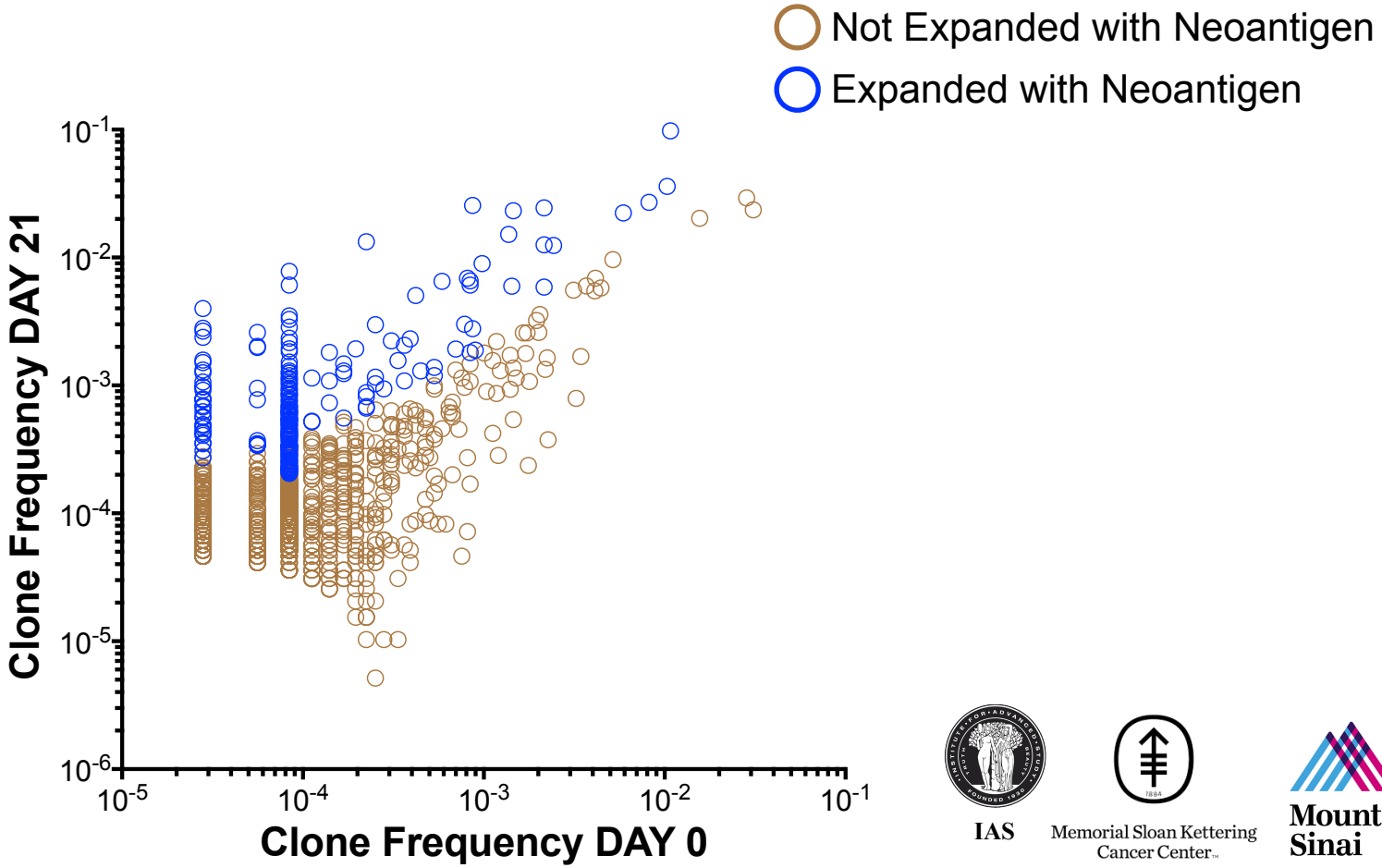

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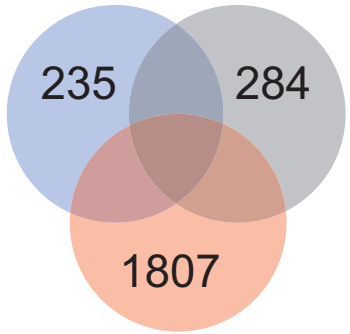

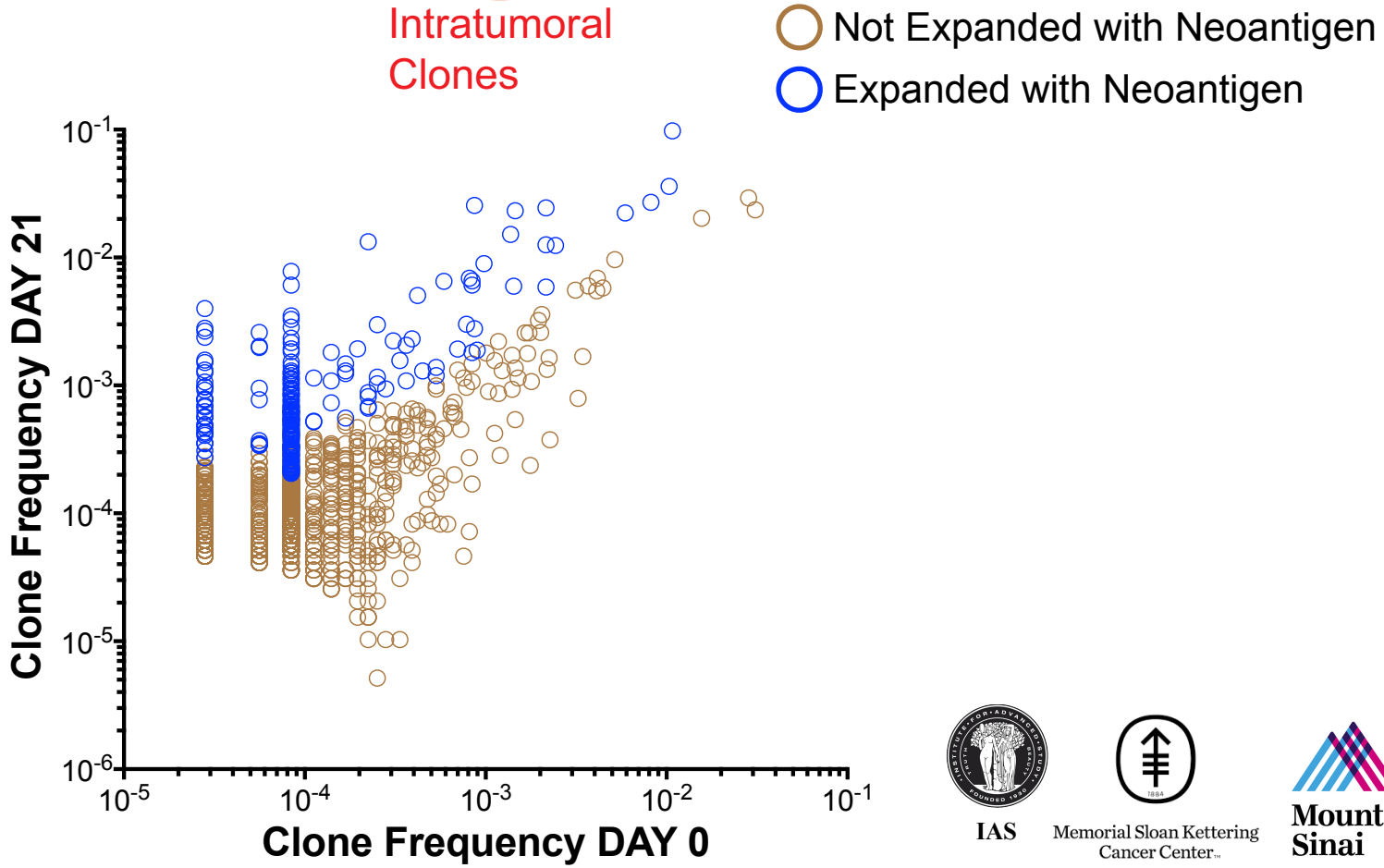

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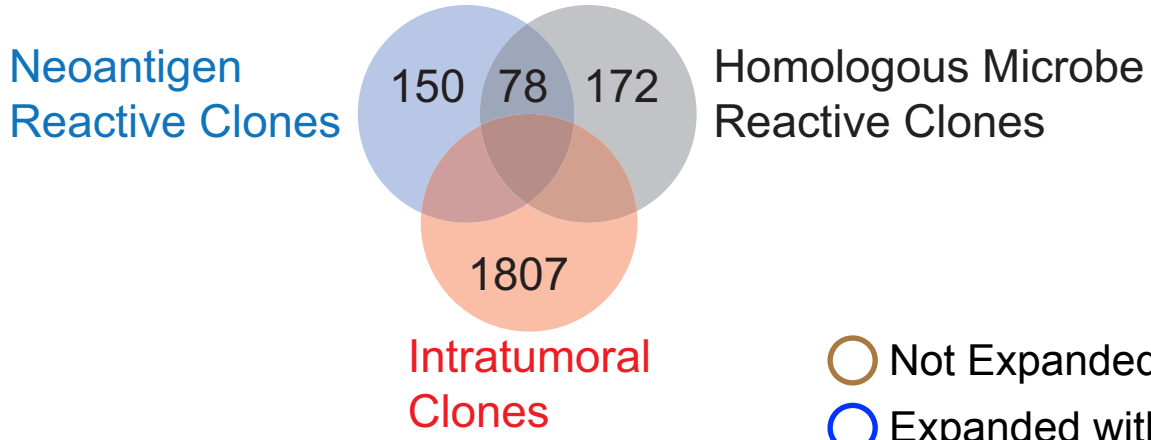

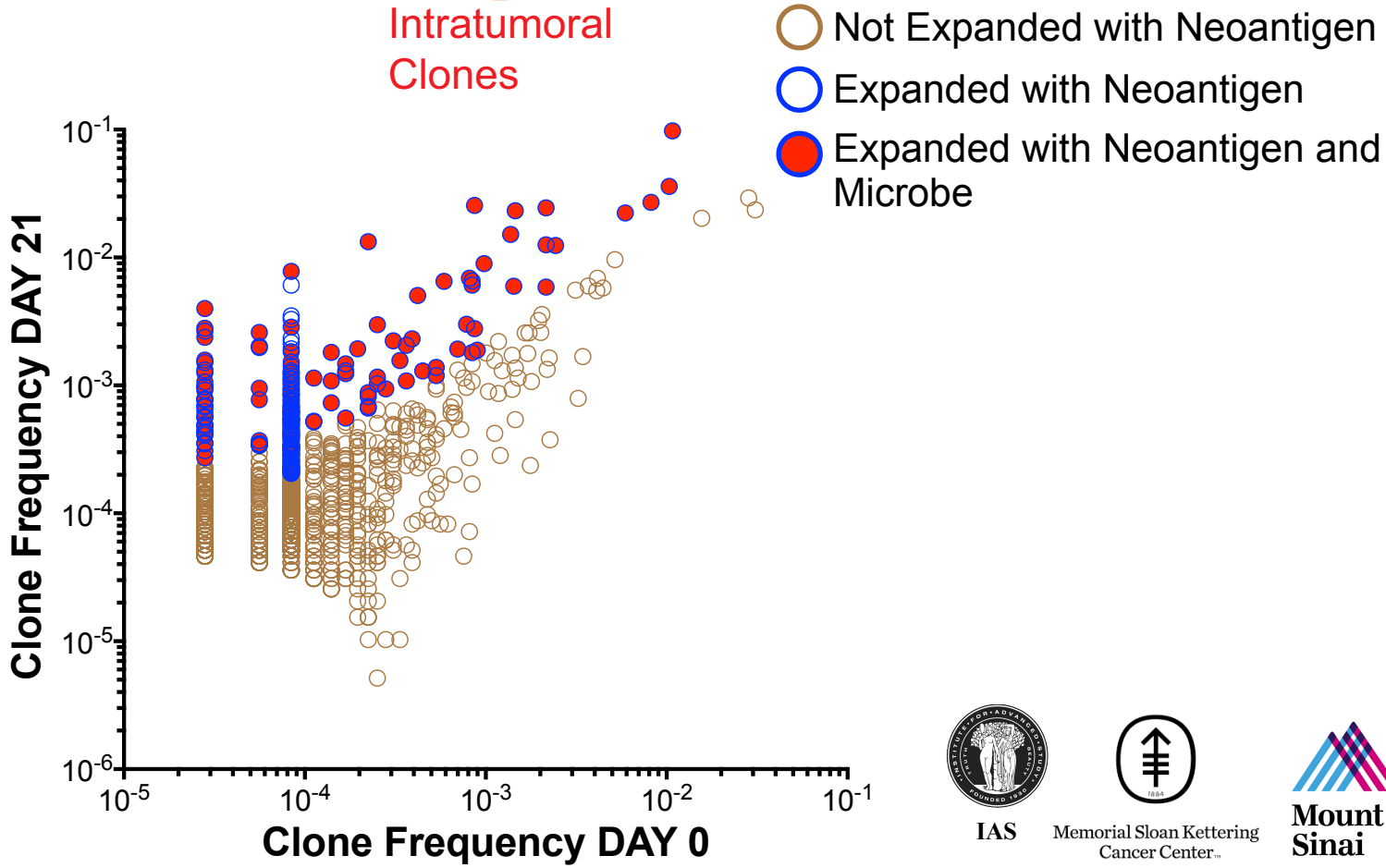

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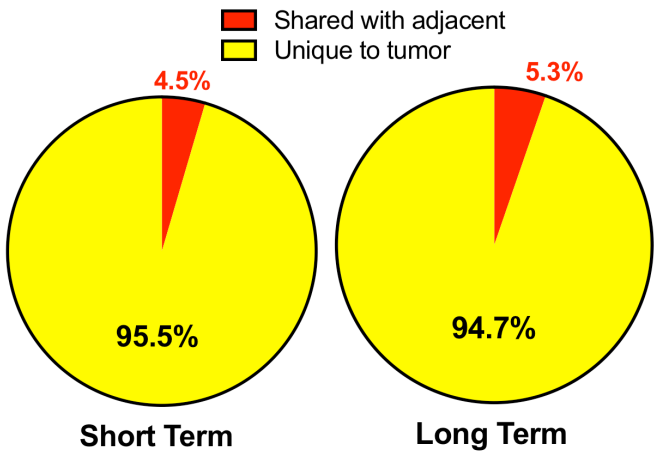
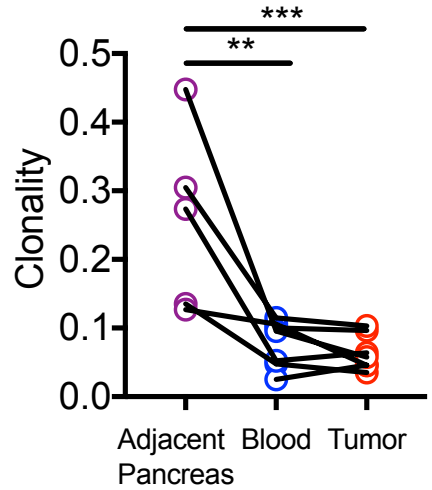
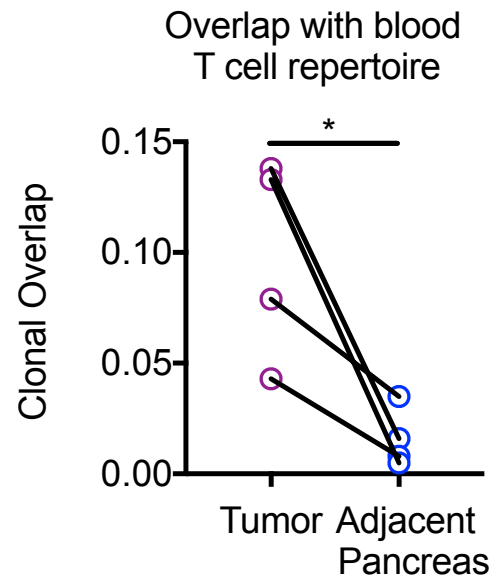
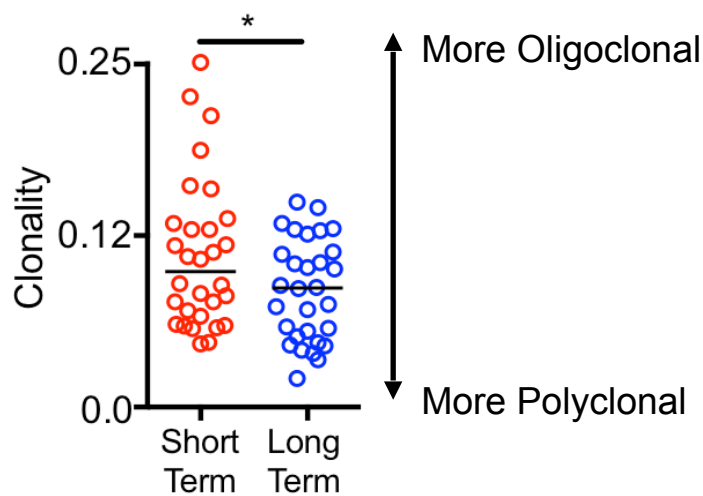
Tumor T cell clones are tumor-unique and blood derived







Long Term Survivor intratumoral T cell repertoire is polyclonal



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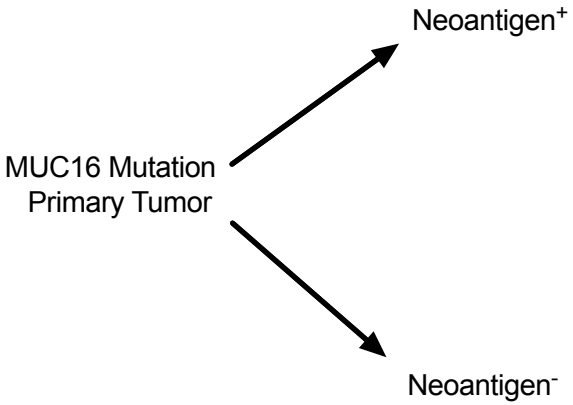
Long Term survivors display possible MUC16 immunoediting



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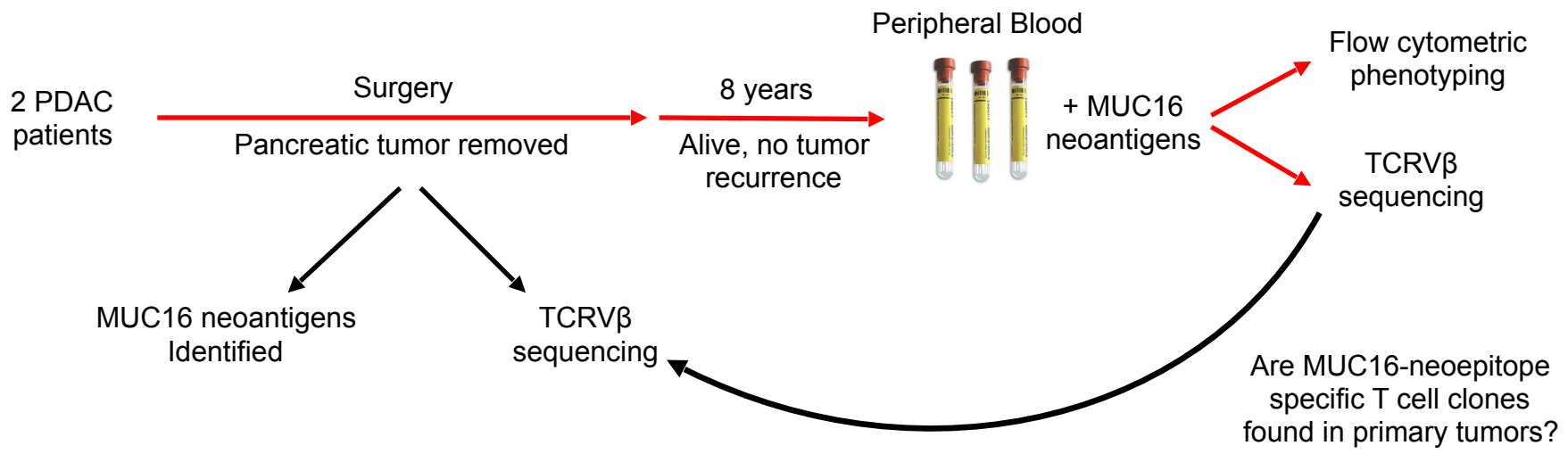
Attiyeh M, Iacobuzio-Donahue C

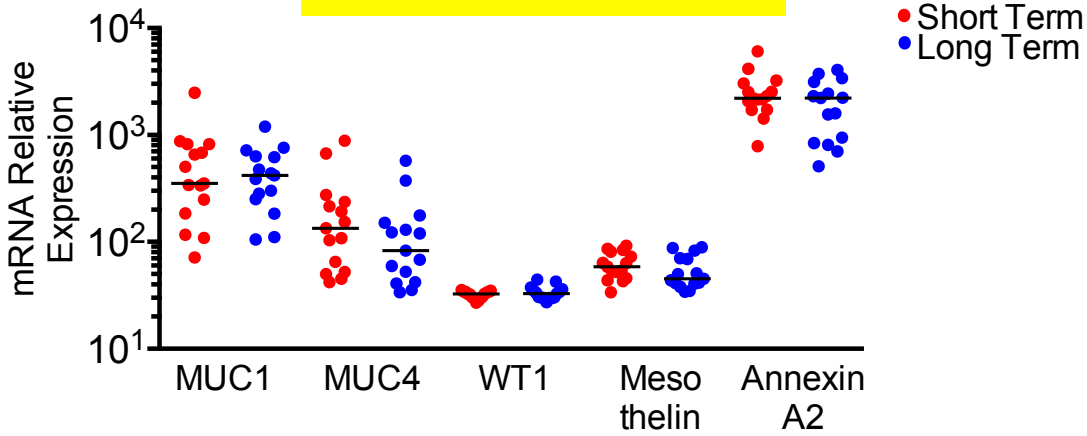
Can we detect MUC16 neoantigen reactive intratumoral T cells in long term survivors?



MUC16 is an immunogenic hotspot in long term survivors

MUC16 mRNA

Non-MUC16 mRNA



MUC16 Protein

MUC16 Mutant Allele Frequency