Capturing heterogeneity and the HLA-presented landscape in melanoma

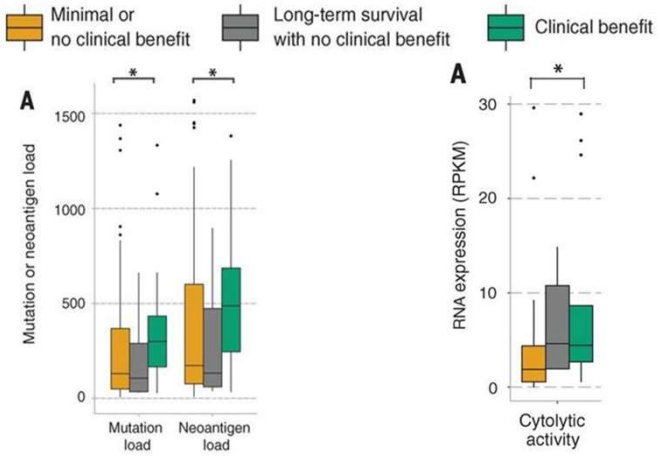
Yardena Samuels

Ph.D. Weizmann Institute of Science

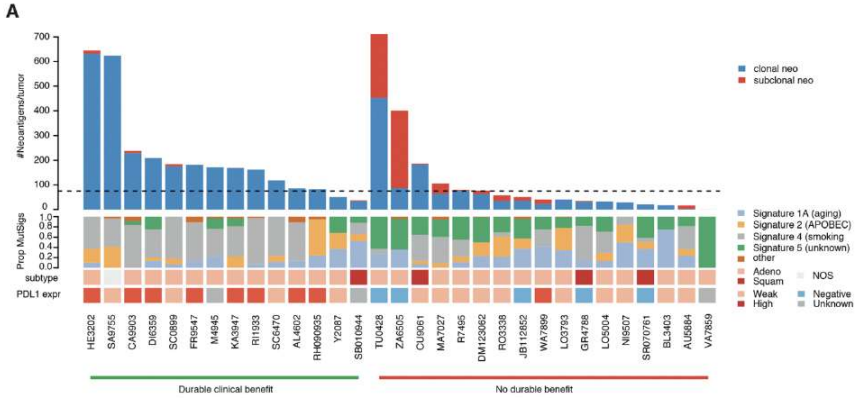
I have no conflict to disclose

Tumor heterogeneity Vs. Mutational Load: current assumptions in immunotherapy

- Tumors with increased mutational are associated with checkpoint blockade sensitivity *(Rivzi et al, Science 2015 ; Van Ellen et al, Science 2015)*
- Low heterogeneity of the tumors is also associated with better response for checkpoint blockade *(McGranahan et al, Science 2016)*



Van Allen et al, Science 2015



McGranahan et al, Science 2016

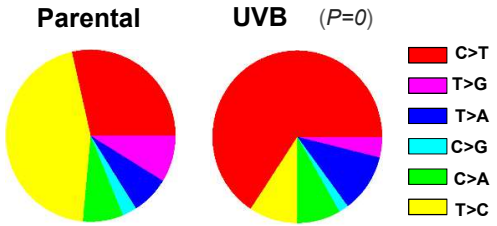
However, mutational count cannot **predict** responsiveness (Hugo et al, 2015)

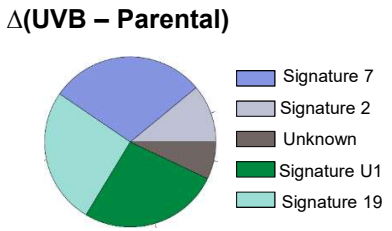
Osnat Bartok

Tumor heterogeneity Vs. Mutational Load: Experimental system

Yochai Wolf

Tumor heterogeneity Vs. Mutational Load: Experimental system

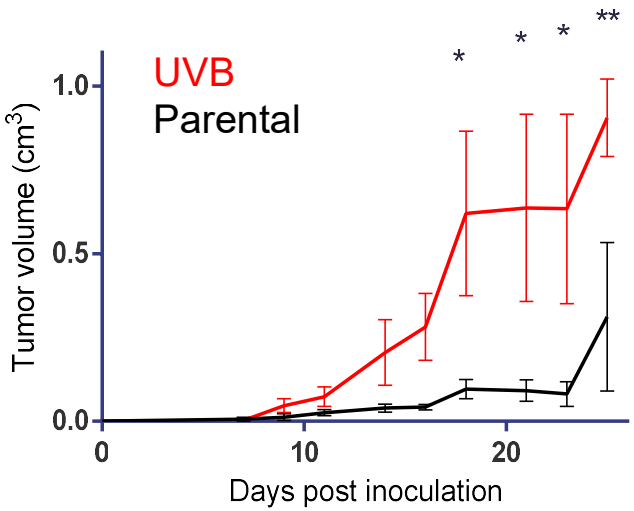




Cell lines are injected into immunocompetent/ immunocompromised mice

Wolf, Bartok, et al, *Cell* 179, 219-235, 2019

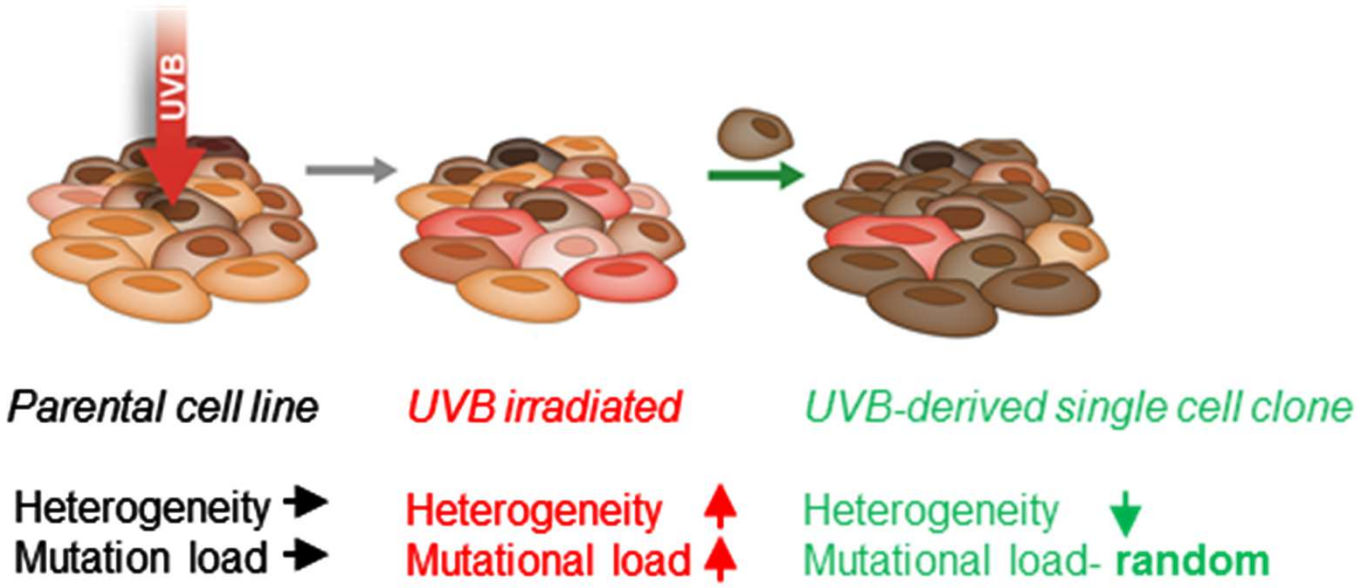
Tumor growth in UVB irradiated cell line



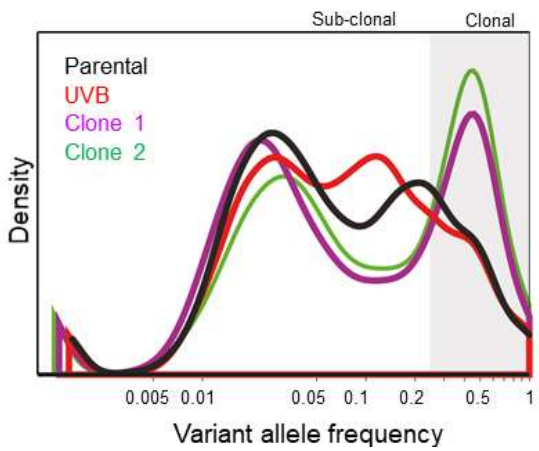
Despite higher mutational count UVB irradiated cells gave rise to highly aggressive tumors

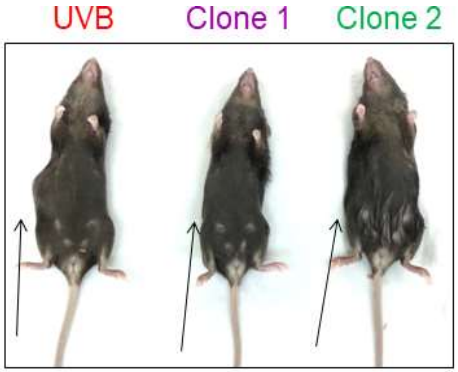
Wolf, Bartok, et al, *Cell* 179, 219-235, 2019

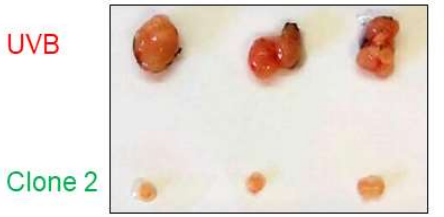
Tumor heterogeneity Vs. Mutational Load: Experimental system

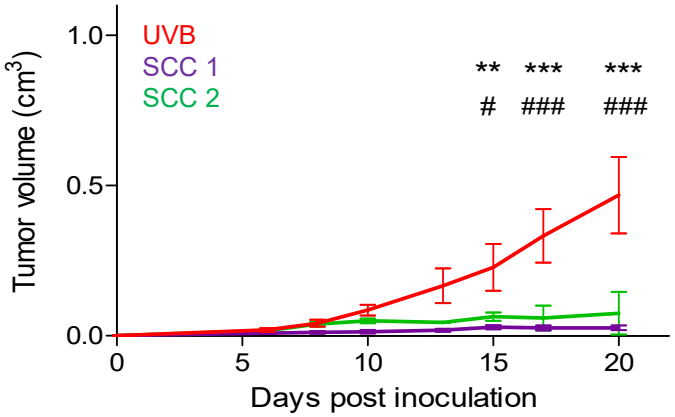


UVB irradiated single cell clones are non aggressive



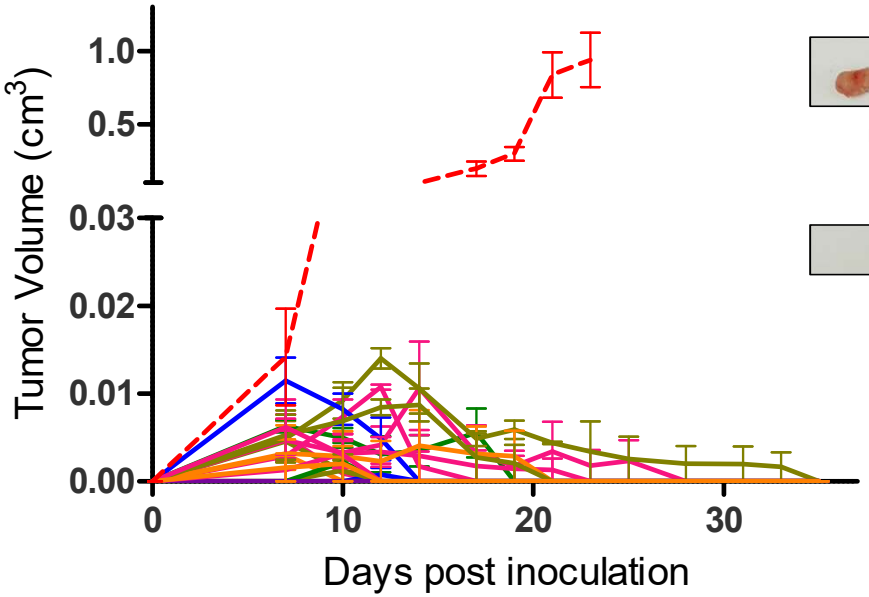


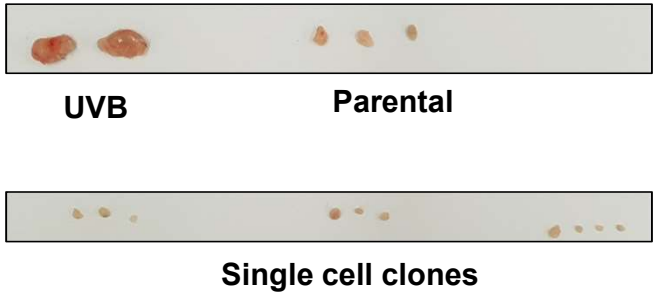




Wolf, Bartok, et al, *Cell* 179, 219-235, 2019

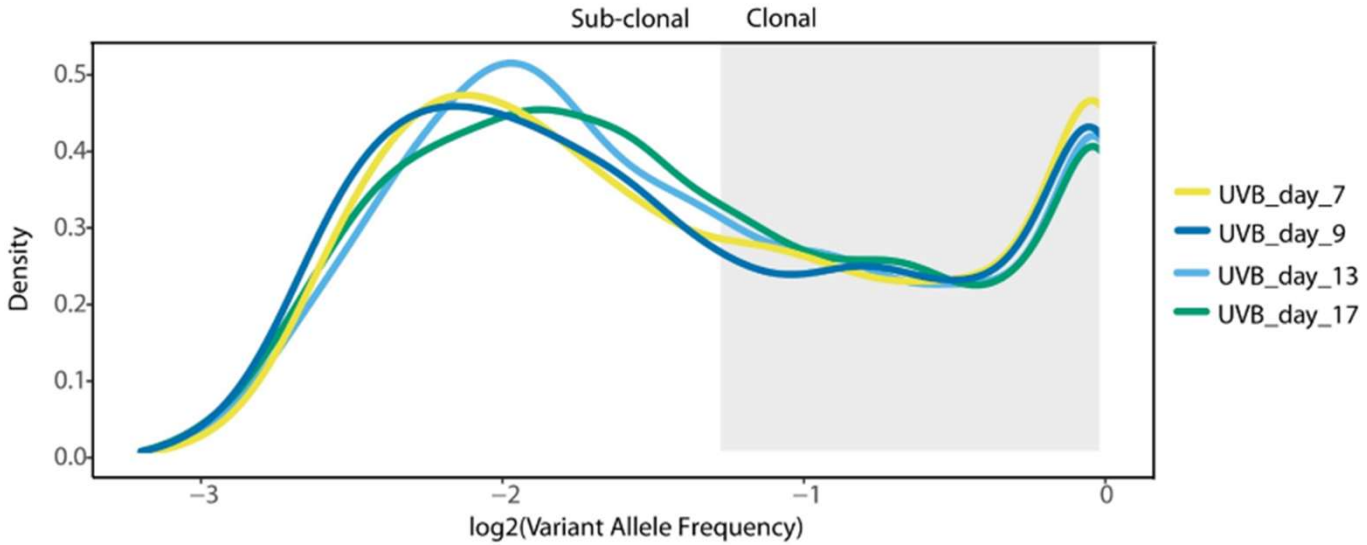
UVB irradiated single cell clones are non aggressive





Wolf, Bartok, et al, *Cell* 179, 219-235, 2019

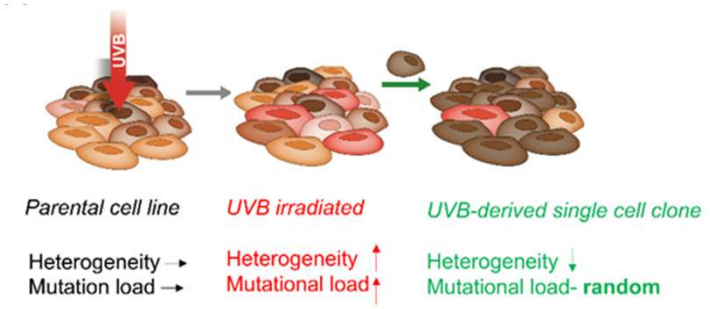
Clonal structure and heterogeneity of UVB tumors remains stable *in vivo* over time

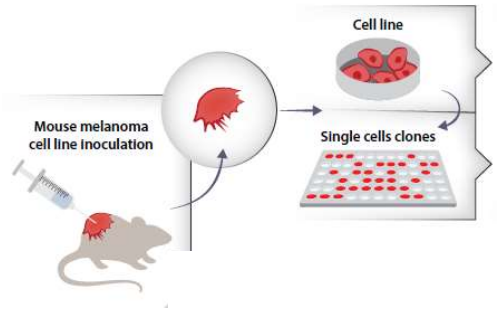


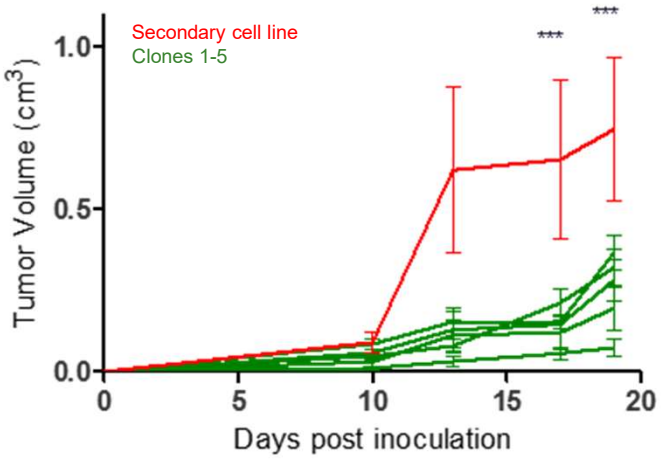
The aggressive growth of the UVB tumor is not due to an escaper clone

Wolf, Bartok, et al, *Cell* 179, 219-235, 2019

The aggressive growth of the UVB tumor Is not due to an escaper clone

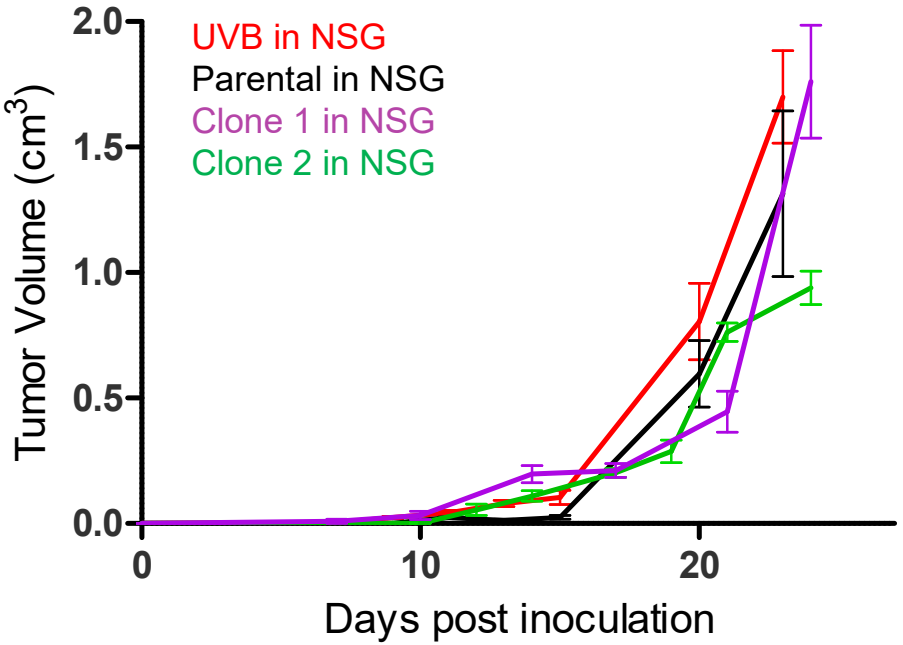






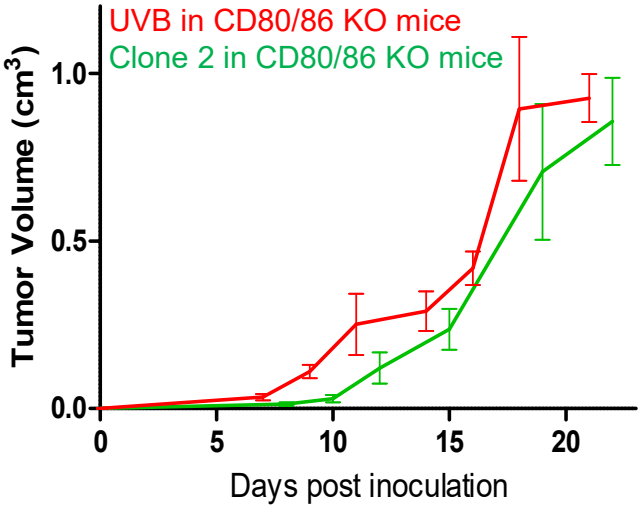
Wolf, Bartok, et al, *Cell* 179, 219-235, 2019

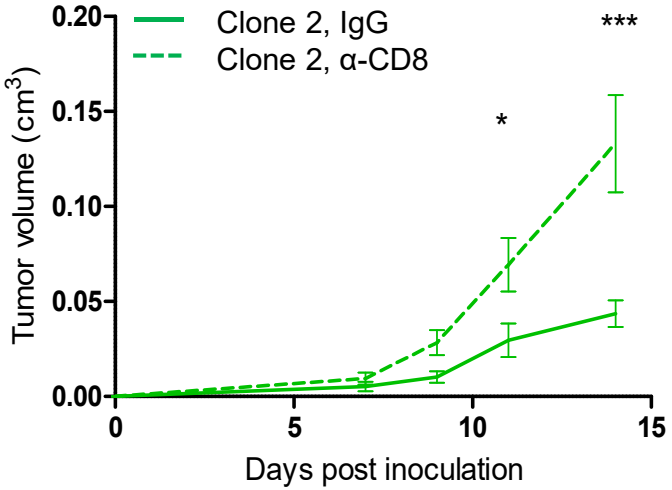
Reduced growth of low heterogeneous UVB clones is due to immune rejection



Wolf, Bartok, et al, *Cell* 179, 219-235, 2019

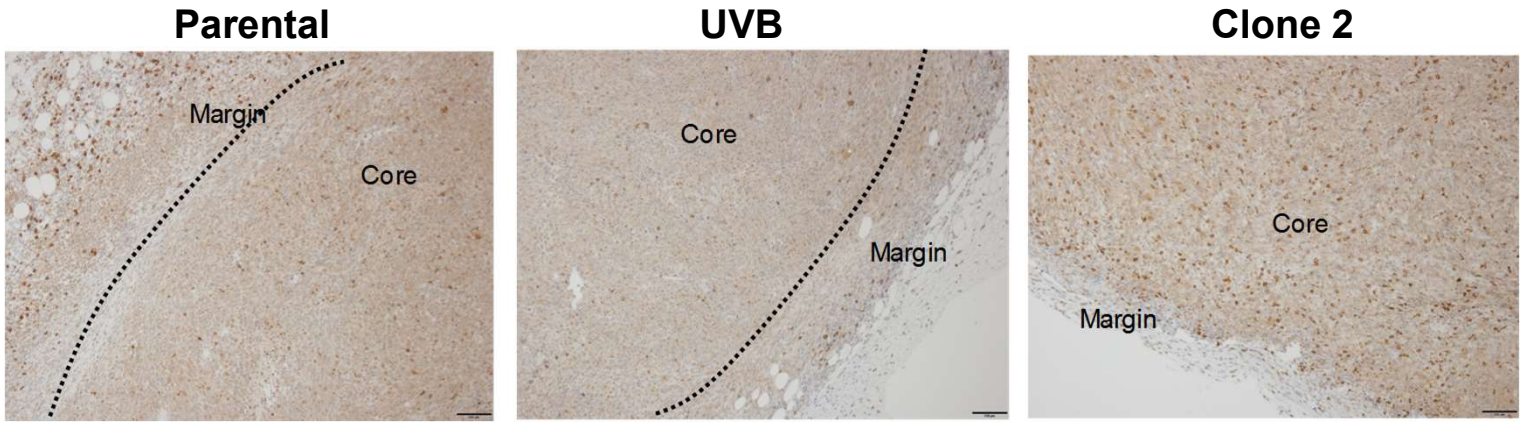
Reduced growth of low heterogeneous UVB clones is due to immune rejection

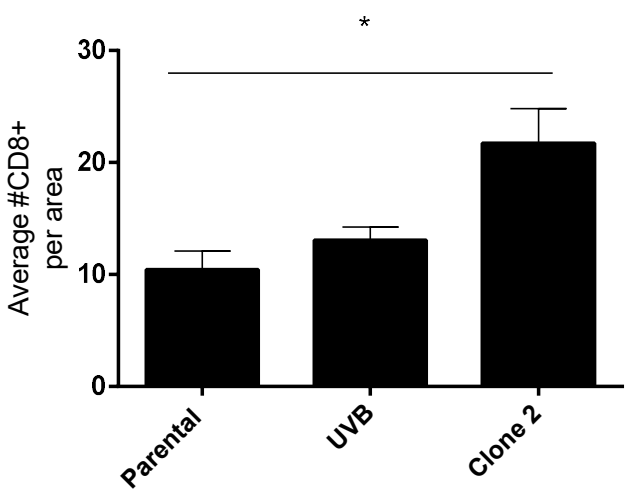


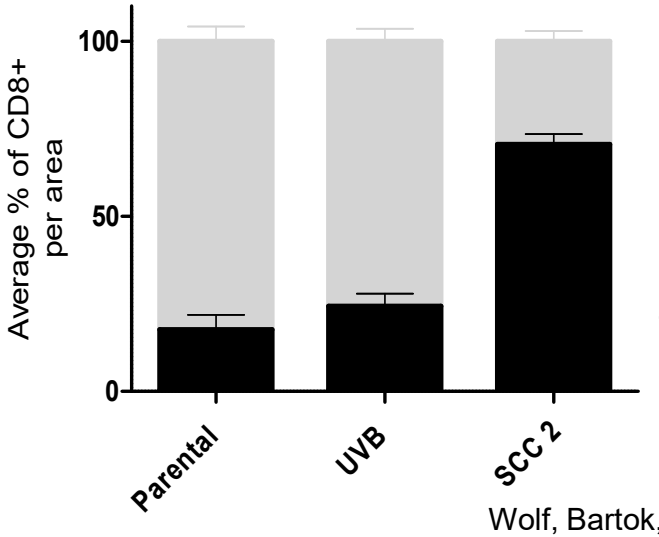


Wolf, Bartok, et al, *Cell* 179, 219-235, 2019

Efficient infiltration of T cells to tumor core in single cell derived tumors



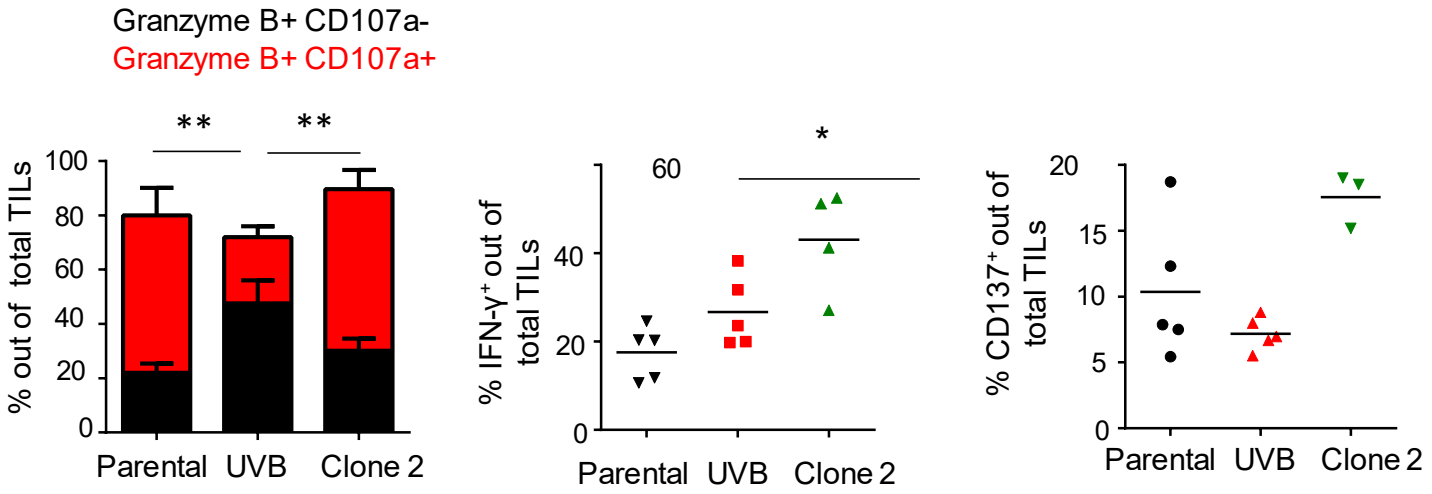




Data recapitulates in three additional clones

Wolf, Bartok, et al, *Cell* 179, 219-235, 2019

Differential immune output in tumors with varying heterogeneity



Granzyme B-Cytotoxic mediator
CD107a-degranulation marker

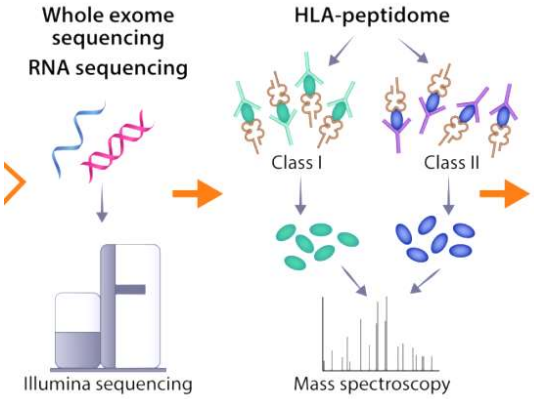
TILs with both markers significantly reduced in UVB clones

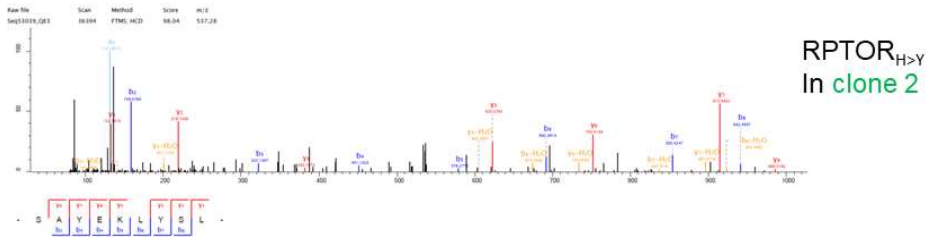
IFNγ-higher activation and cytotoxicity

CD137-activation marker

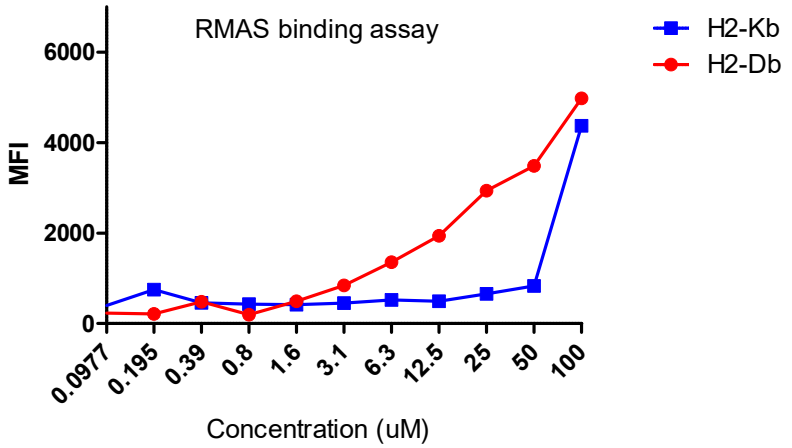
Wolf, Bartok, et al, *Cell* 179, 219-235, 2019

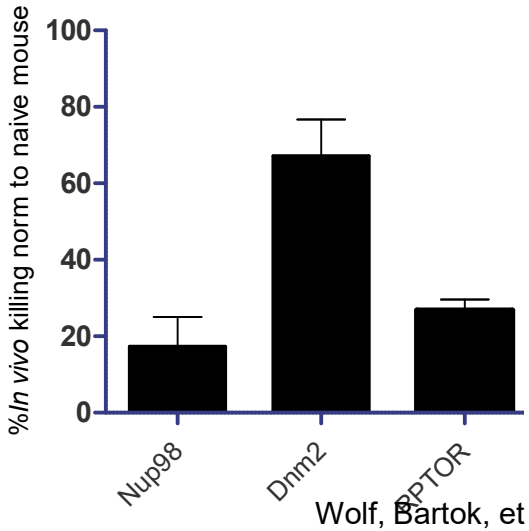
Identification of neoantigens that mediate killing *in vivo*





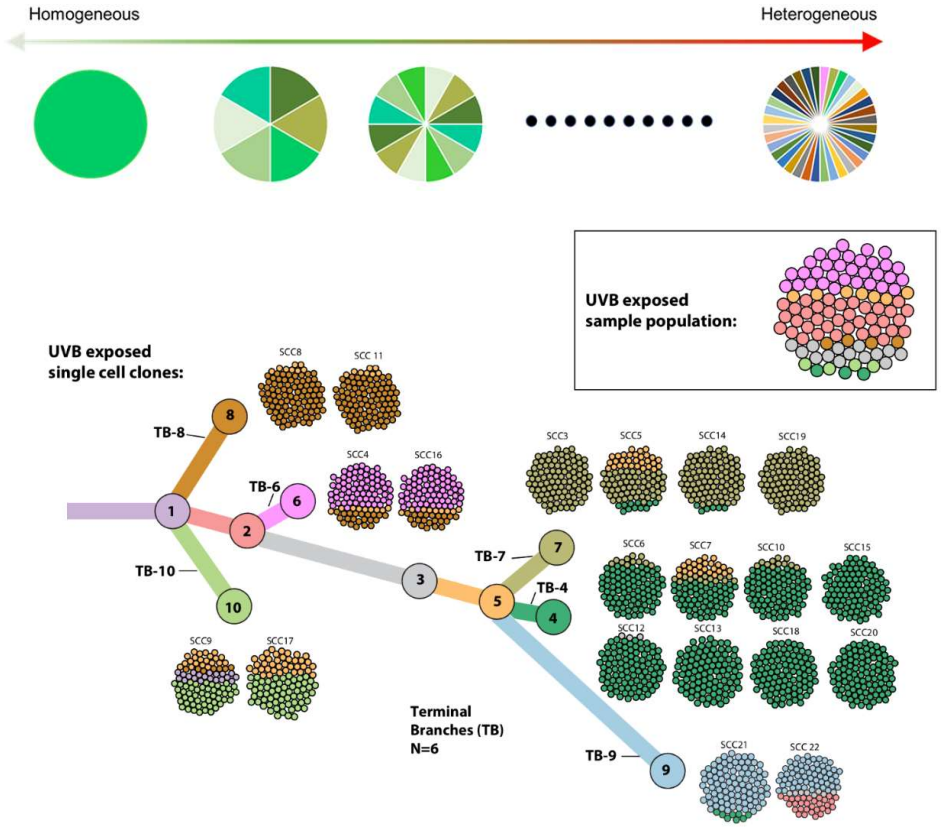
RPTOR$_{H>Y}$
In clone 2





Wolf, Bartok, et al, *Cell* 179, 219-235, 2019

Assessing the role of intra-tumor heterogeneity in tumor rejection-using phylogenetic tree reconstruction

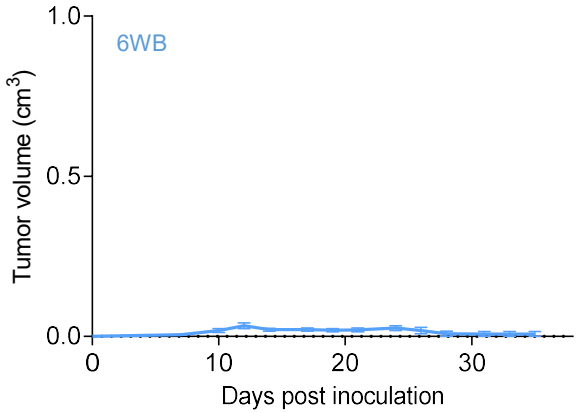


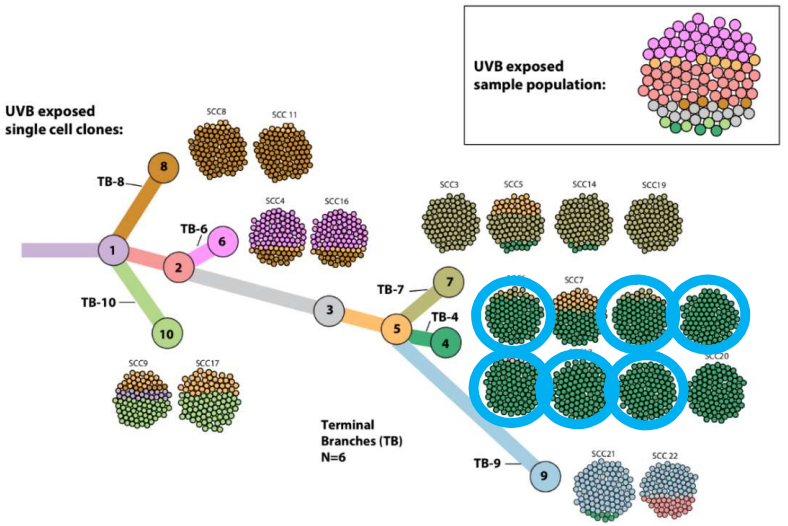
Two fundamental components of tumor heterogeneity:

- The **number of clones** comprising the tumor
- The genetic **diversity** between them

Wolf, Bartok, *et al* & Samuels, *Cell* 179, 219-235, 2019

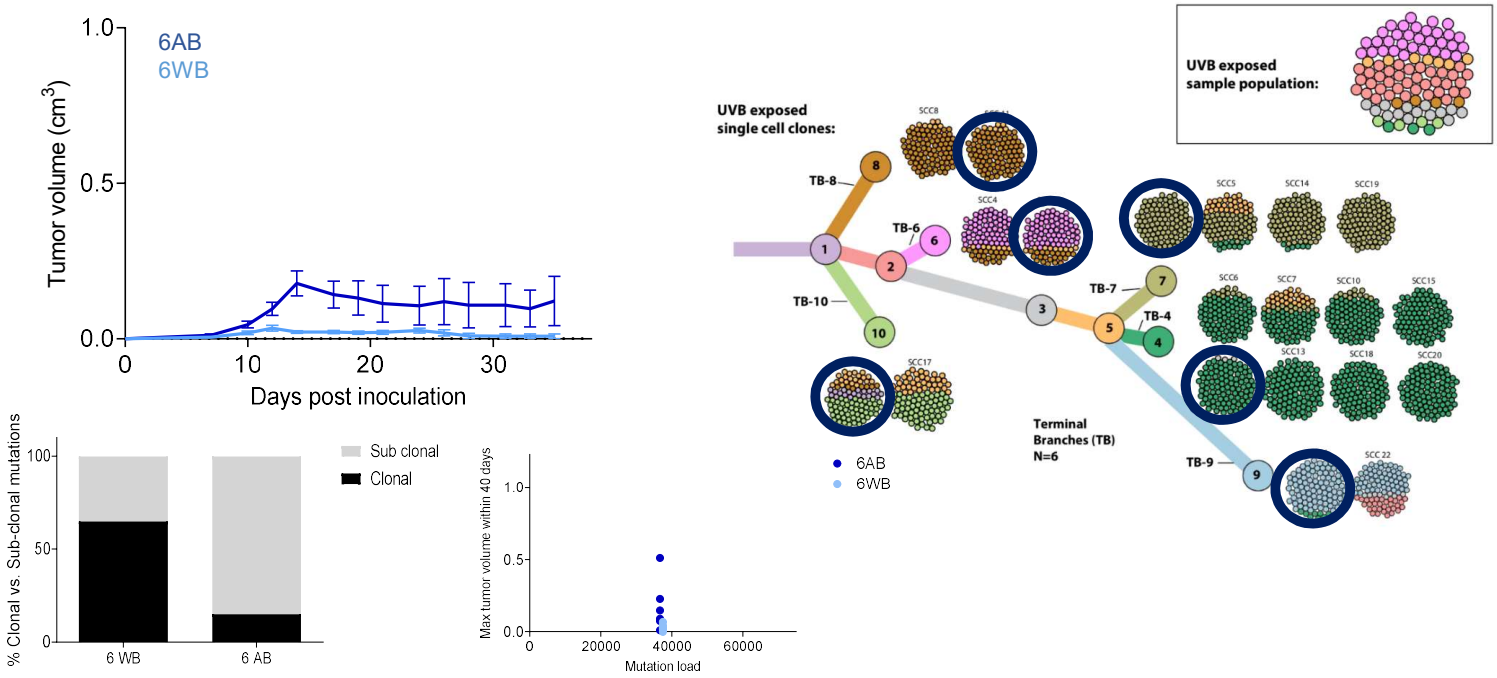
Mixture of 6 clones from the same terminal branch was swiftly rejected





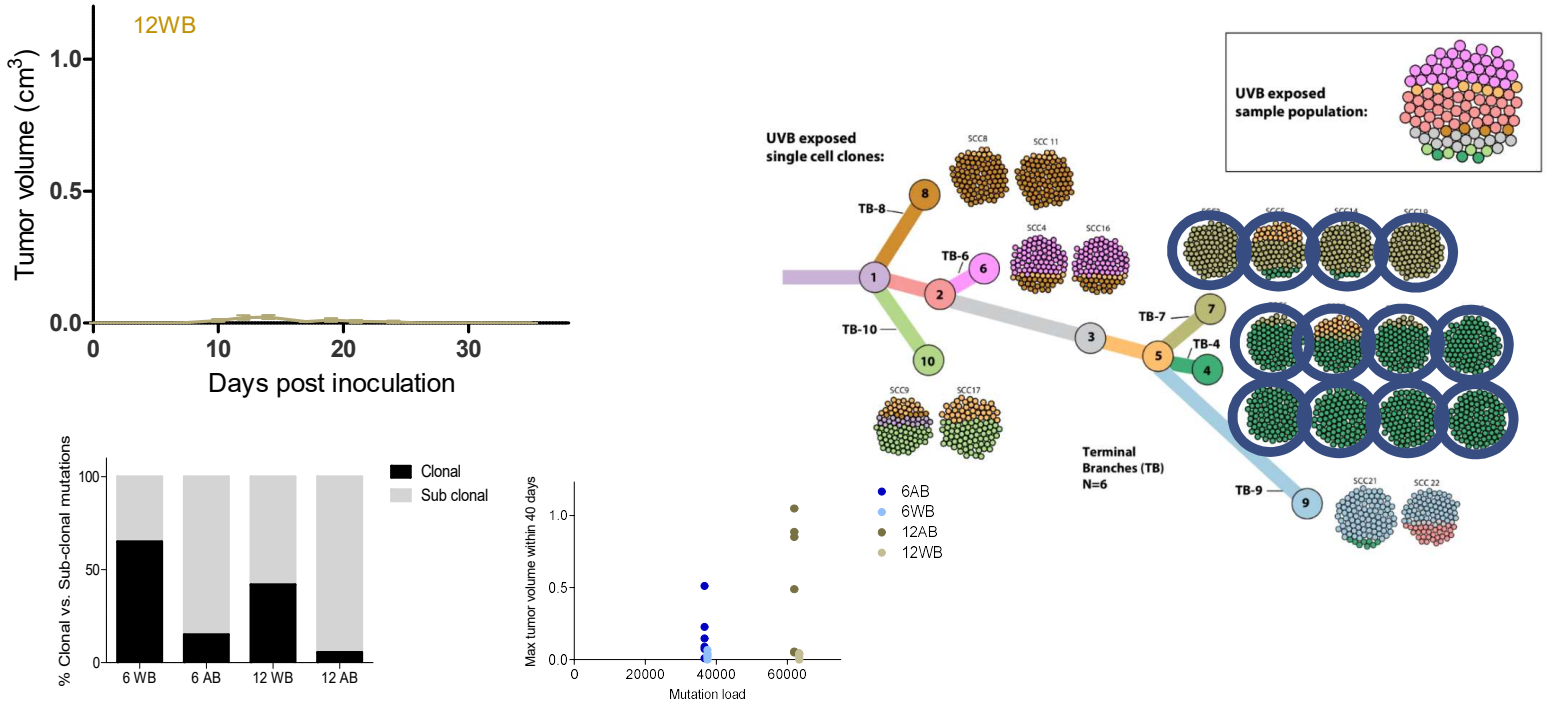
Wolf, Bartok, *et al* & Samuels, *Cell* 179, 219-235, 2019

6 clone mixes containing approximately the same number of mutations but with higher diversity, were not rejected



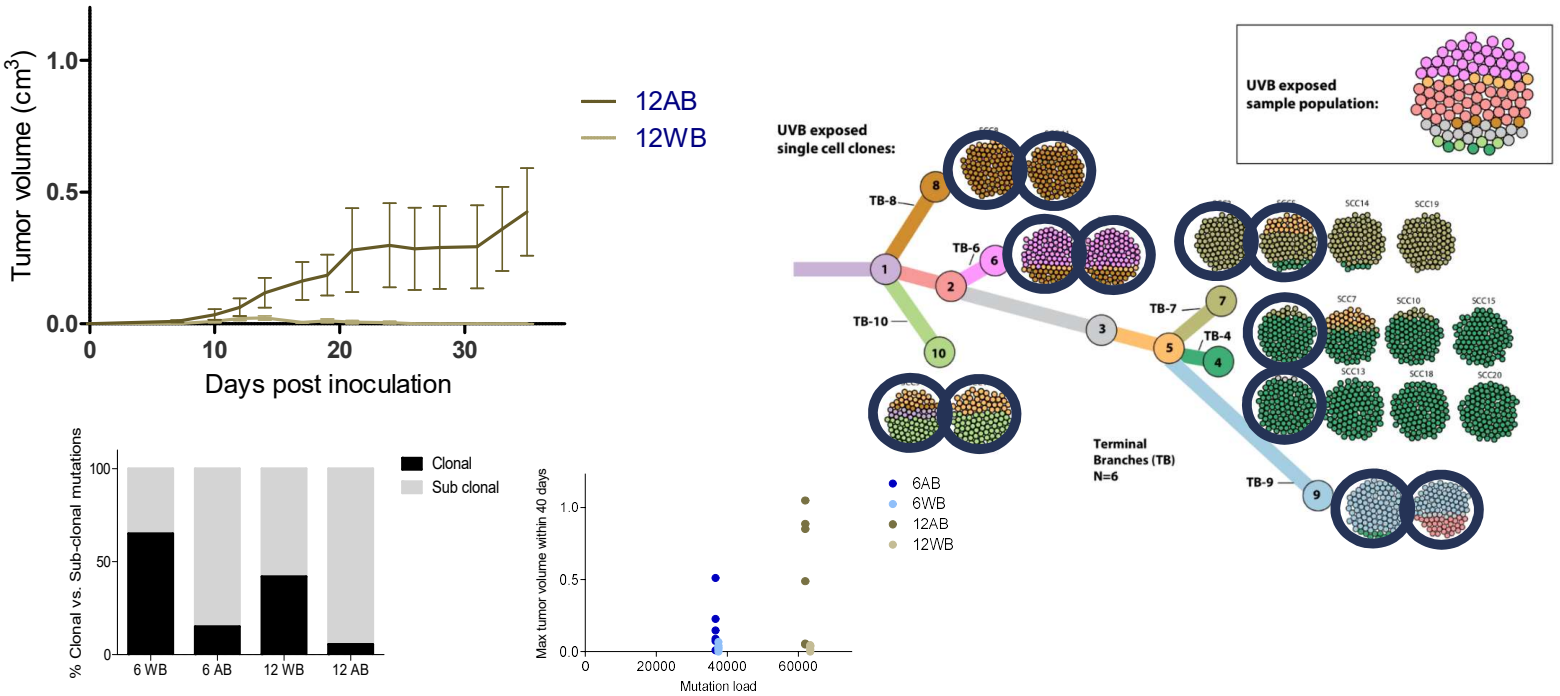
Wolf, Bartok, *et al* & Samuels, *Cell* 179, 219-235, 2019

Mixture of 12 clones from the same terminal branch was swiftly rejected



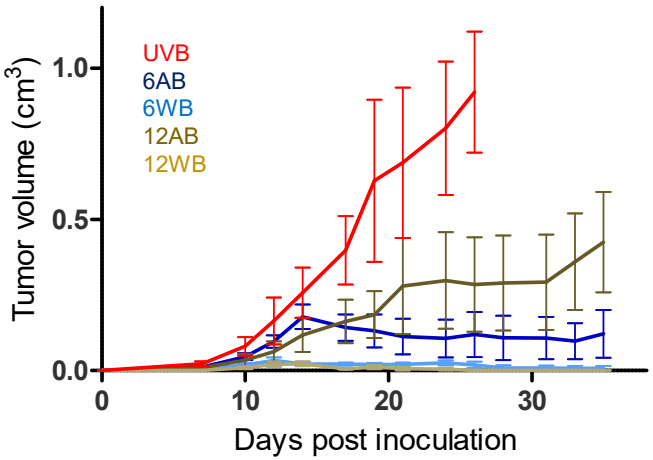
Wolf, Bartok, *et al* & Samuels, *Cell* 179, 219-235, 2019

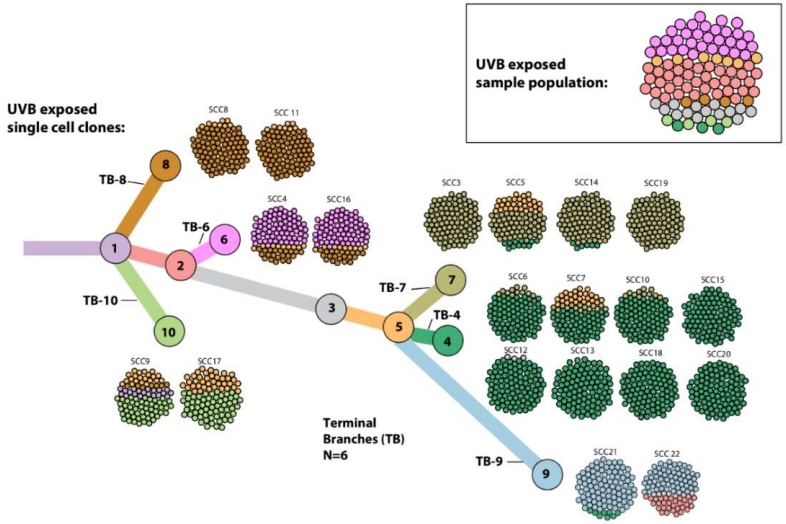
Mixes containing more clones and higher diversity were most aggressive



Wolf, Bartok, *et al* & Samuels, *Cell* 179, 219-235, 2019

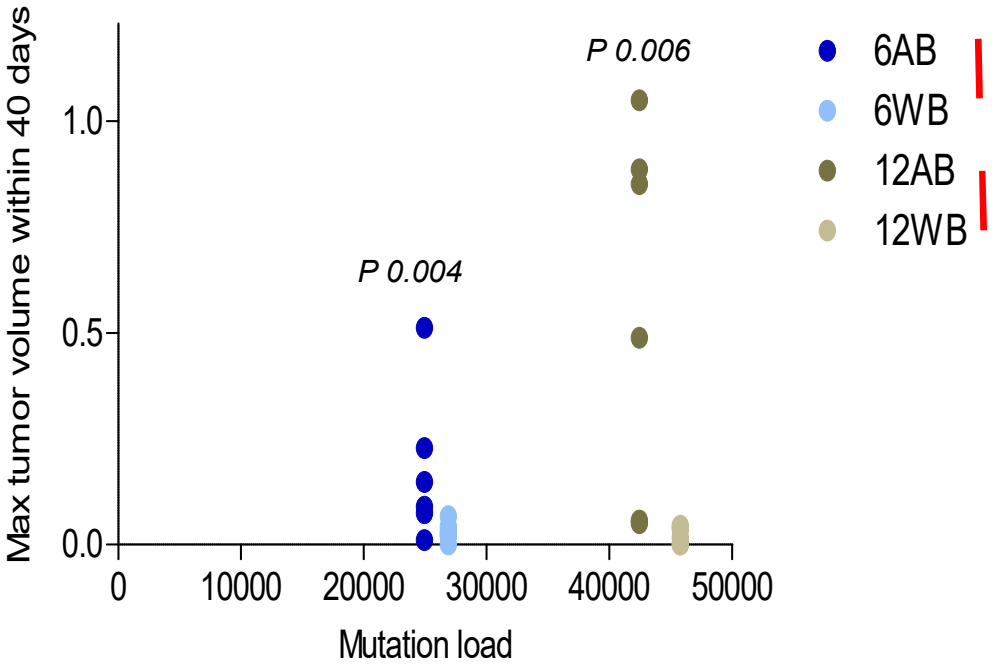
Although yielding large tumors, the 12AB tumors were still not as aggressive as the UVB-irradiated tumors





Wolf, Bartok, *et al* & Samuels, *Cell* 179, 219-235, 2019

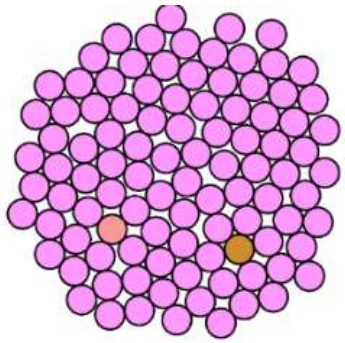
The number of clones and their genetic diversity play an important role in mediating tumor growth and rejection



Wolf, Bartok, *et al* & Samuels, *Cell* 179, 219-235, 2019

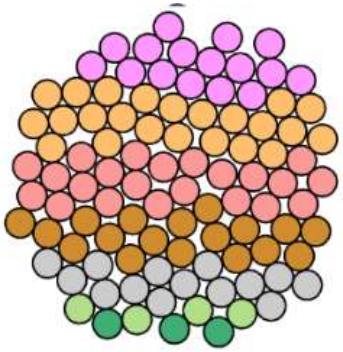
Shannon diversity index: metric to quantify both the number of clones and the diversity of the mutations across clones in one index

Shannon diversity index low:



nearly all mutations are concentrated in just one clone

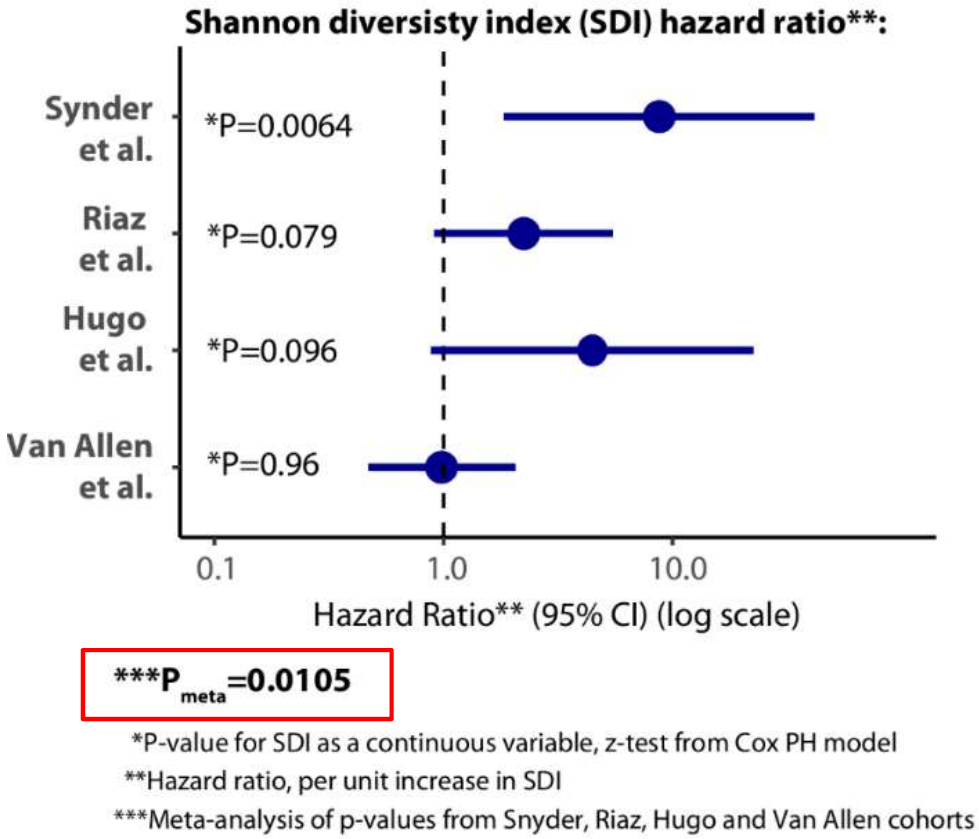
Shannon diversity index high:



high number of clones, with mutations spread evenly/diversely across each clone

Wolf, Bartok, et al, *Cell* 179, 219-235, 2019

Tumor clone number and genetic diversity are significantly associated with response to immunotherapy



Hazard ratio value corresponding to the survival risk per unit increase (i.e.each+1increment) in SDI.

Wolf, Bartok, et al, *Cell* 179, 219-235, 2019

Summary: our mouse, TCGA and ICT data are complimentary in suggesting that:

- Mutational load alone is not a sufficient predictor for immune response
- Intra-tumor heterogeneity has to be considered as an additional biomarker
- Intra-tumor heterogeneity is composed of both: **clonal diversity**
  number of clones
- Minimizing tumor heterogeneity exposes reactive neo-antigens to better immune detection

The combination of these factors will strongly dictate the extent of the overall immune response and have strong clinical implications

nature reviews immunology

Research Highlight | Published: 04 October 2019

TUMOUR IMMUNOLOGY

Tumour heterogeneity determines immune response

Alexandra F

Nature Revi

1532 Acces

nature reviews clinical oncology

Research Highlight | Published: 27 September 2019

SKIN CANCER

s a

A need to quantify intra-tumor heterogeneity to improve patient selection for checkpoint blockade therapy

CellPress

Tumor Neoantigens: When Too Much of a Good Thing Is Bad

Anne Trinh[1,2] and Kornelia Polyak[1,2,*]
[1]Department of Medical Oncology, Dana-Farber Cancer Institute Boston, MA 02215, USA
[2]Department of Medicine, Harvard Medical School, Boston, MA 02115, USA
*Correspondence: kornelia_polyak@dfci.harvard.edu
https://doi.org/10.1016/j.ccell.2019.10.009

CANCER DISCOVERY

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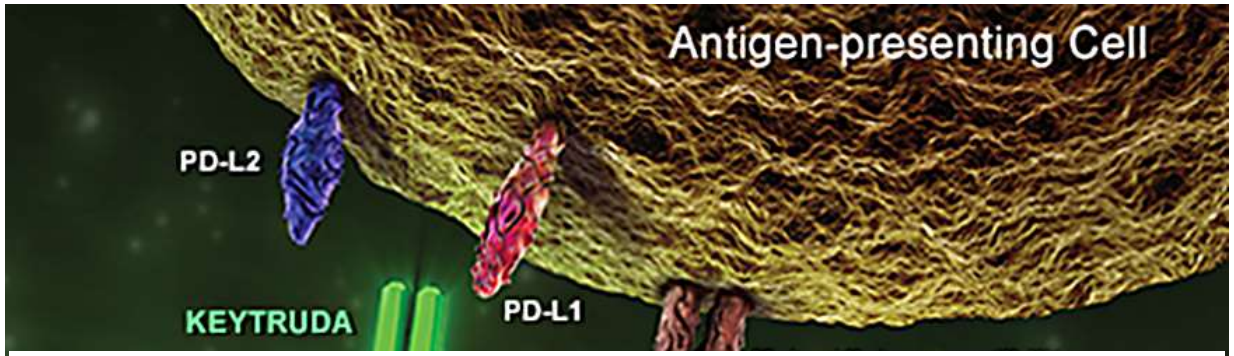
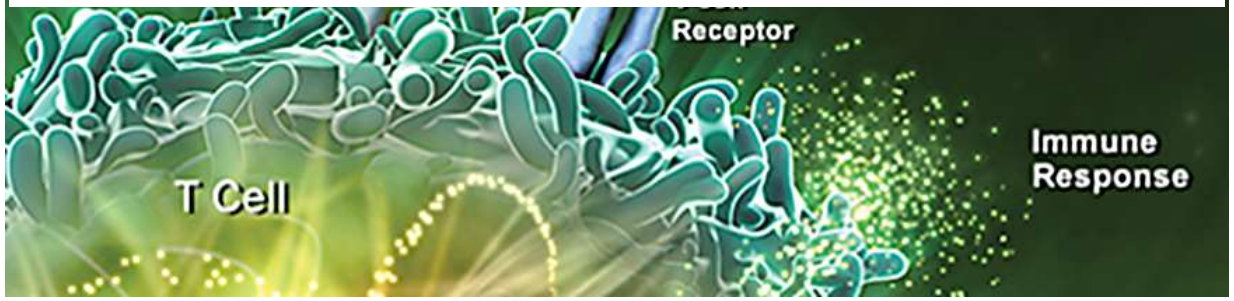
Research Watch

Low-Heterogeneity Melanomas Are More Immunogenic and Less Aggressive

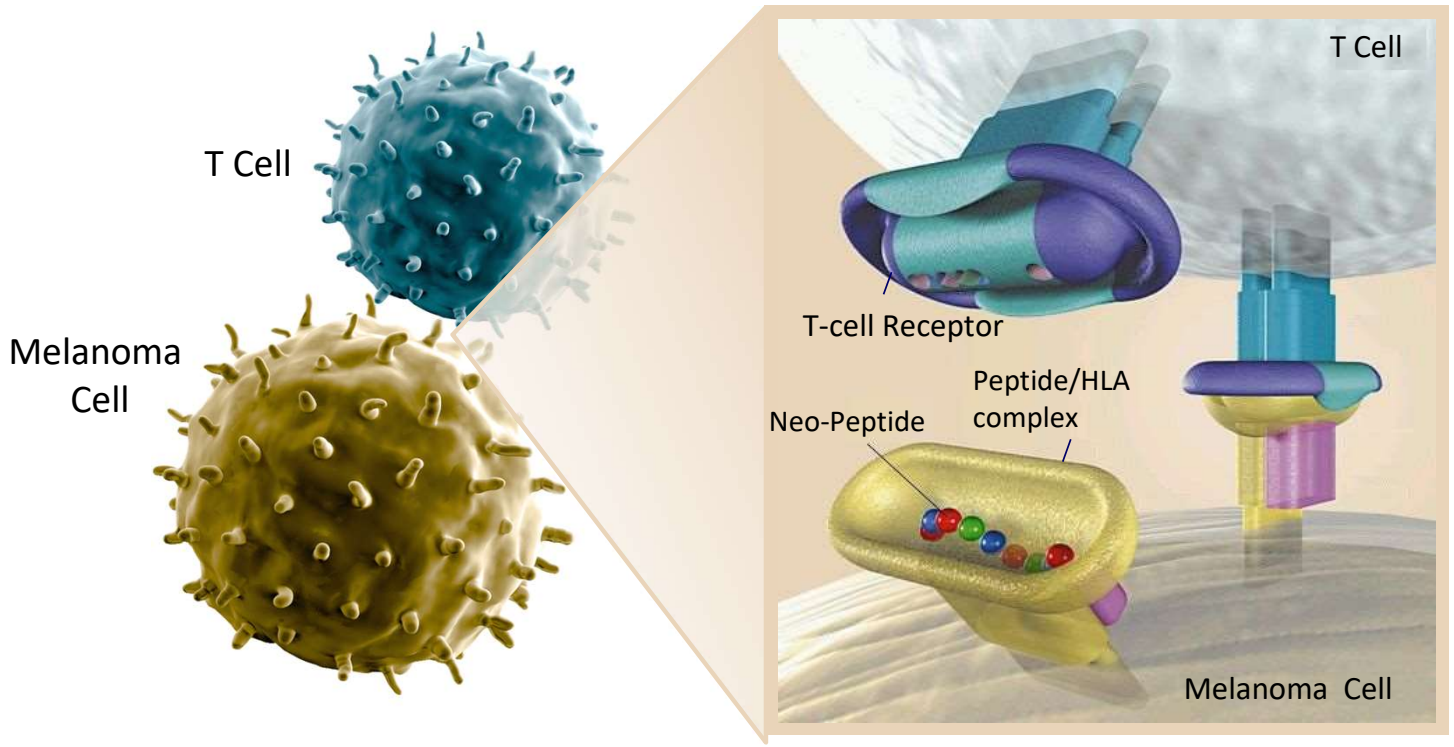
Costimulatory and coinhibitory interactions determine the amplitude of T-cell activation



The success of checkpoint inhibitors relies on T cell recognition of the neo-antigen



How do T cells recognize and kill tumor cells?

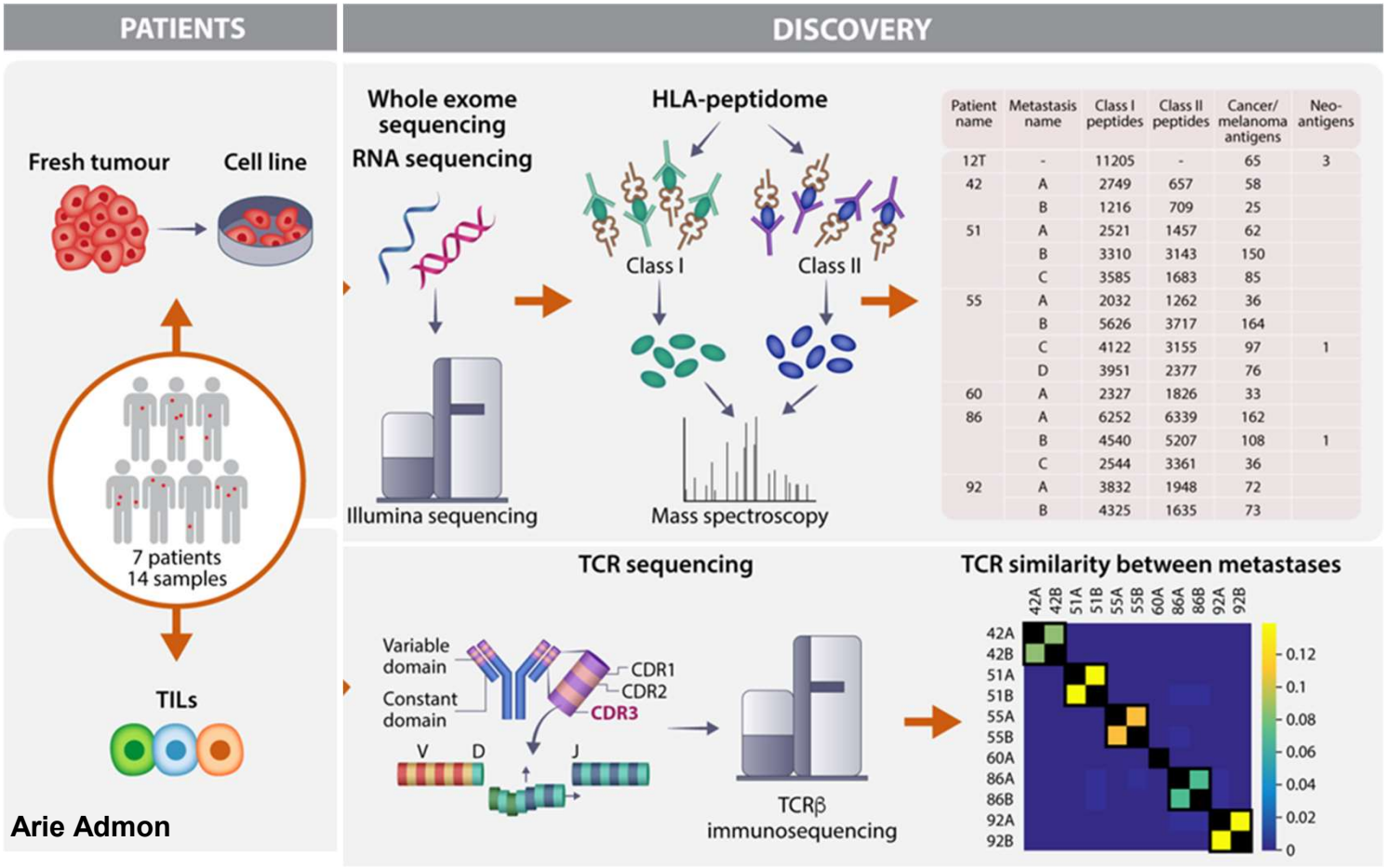


Kalaora *et al* & Samuels, *Oncotarget* 2015

Scheme kindly provided by Paul Robbins and Cyrille Cohen

HLA Peptidomics to Identify Human Immunogenic Neo-antigens

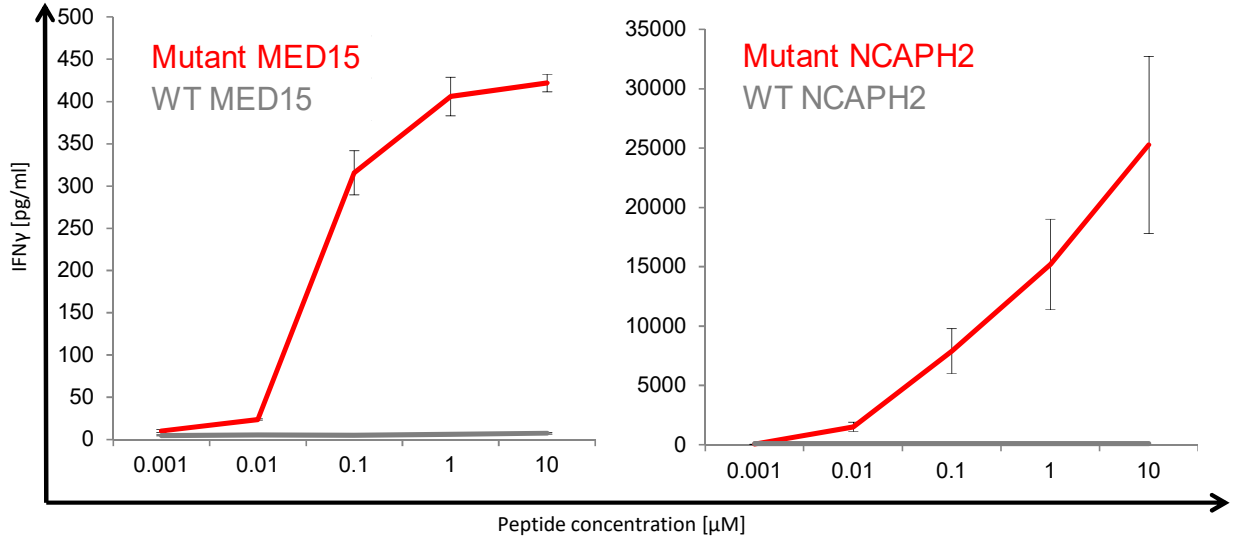
Shelly Kalaora



Patient name	Metastasis name	Class I peptides	Class II peptides	Cancer/ melanoma antigens	Neo-antigens
12T	-	11205	-	65	3
42	A	2749	657	58	
	B	1216	709	25	
51	A	2521	1457	62	
	B	3310	3143	150	
	C	3585	1683	85	
55	A	2032	1262	36	
	B	5626	3717	164	
	C	4122	3155	97	1
	D	3951	2377	76	
60	A	2327	1826	33	
86	A	6252	6339	162	
	B	4540	5207	108	1
	C	2544	3361	36	
92	A	3832	1948	72	
	B	4325	1635	73	

Proof of Concept: Neoantigen characterization in melanoma line 12T

Sequence	Protein name	Mutation	HLA allele
DANSFLQSV	MED15	P677S	B*51
KLFEDRVGTIK	TPD52L2	S123L	A*03
GVYPMPGTQK	NCAPH2	S174Y	A*03



Kalaora et al, *Cancer Discovery* 8, 1366-1375, 2018

Identification of bacteria-derived HLA-presented peptides

Identification of intra-tumor bacteria

Research — Genome Research 2012

Genomic analysis identifies association of *Fusobacterium* with colorectal carcinoma

Aleksandar D. Kostic.[1,2] Dirk Gevers.[1] Chandra Sekhar Pedamallu.[1,3] Monia Michaud.[4]
Fujiko Du

OPEN ACCESS Freely available online — PLOS ONE 2014

However

It has never been shown whether **tumor** HLA class I and HLA class II molecules can present microbial antigens

Noam Shental,[6] Deborah Nejman,[1]
Zachary A. Cooper,[7,8‡] Kevin Shee,[2]
Jonathan Livny,[2] Roi Avraham,[10] D
Kelly Chatman,[13] Stephen E. Johnst
Garold Fuks,[15] Candice Gurbatri,[16]
Mark W. Hurd,[17] Matthew Katz,[8] J
Matt Skalak,[3] Jeffrey Bu,[8] Monia M
Talia Golan,[21,22] Judith Sandbank,[2]
Wendy S. Garrett,[2,19,24] Sarah P. Th
Curtis Huttenhower,[2,27] Sangeeta N
Jennifer A. Wargo,[7,8] Todd R. Golul

CANCER

The human tumor microbiome is composed of tumor type–specific intracellular bacteria

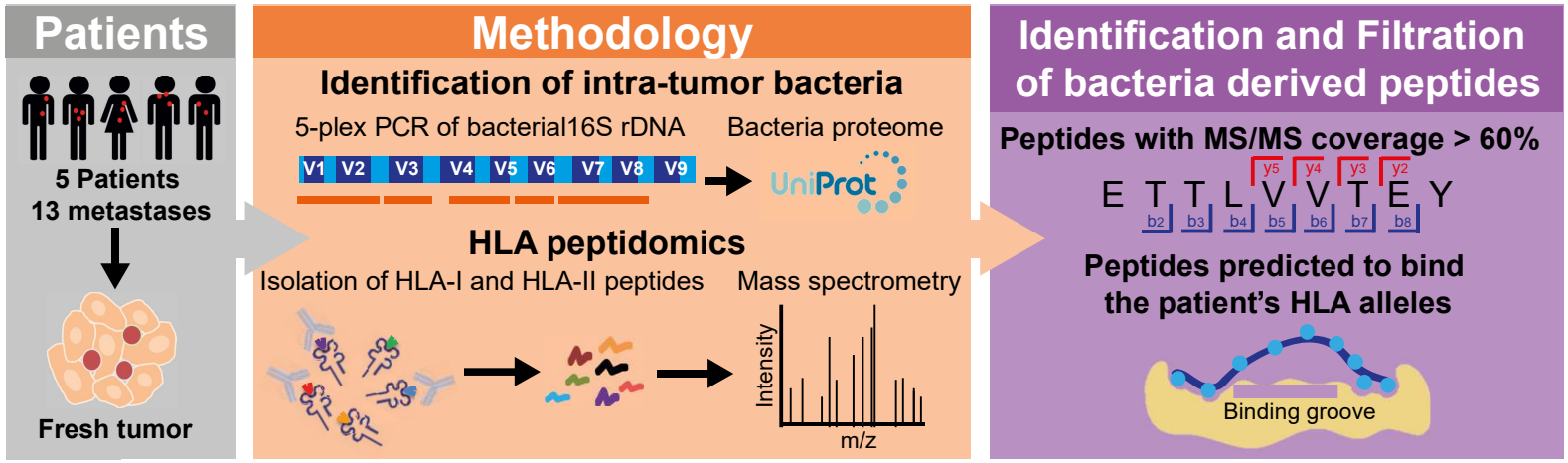
Deborah Nejman[1]*, Ilana Livyatan[1,2]*, Garold Fuks[3]*, Nancy Gavert[1], Yaara Zwang[1], Leore T. Geller[1], Aviva Rotter-Maskowitz[1], Roi Weiser[4,5], Giuseppe Mallel[1], Elinor Gigi[1], Arnon Meltser[1], Gavin M. Douglas[6], Iris Kamer[7], Vancheswaran Gopalakrishnan[8]†, Tali Dadosh[9], Smadar Levin-Zaidman[9], Sofia Avnet[10], Tehila Atlan[11], Zachary A. Cooper[12], Reetakshi Arora[8], Alexandria P. Cogdill[13], Md Abdul Wadud Khan[8], Gabriel Ologun[8], Yuval Bussi[1,2,14], Adina Weinberger[1,2], Maya Lotan-Pompan[1,2], Ofra Golani[15], Gili Perry[16], Merav Rokah[17], Keren Bahar-Shany[16], Elisa A. Rozeman[18], Christian U. Blank[18], Anat Ronai[19], Ron Shaoul[19], Amnon Amit[20,21], Tatiana Dorfman[22,23], Ran Kremer[24], Zvi R. Cohen[5,25], Sagi Harnof[5,26], Tali Siegal[27], Einav Yehuda-Shnaidman[28], Einav Nili Gal-Yam[29], Hagit Shapira[28], Nicola Baldini[10,30], Morgan G. I. Langille[6,31], Alon Ben-Nun[5,17], Bella Kaufman[5,7], Aviram Nissan[32], Talia Golan[5,7], Maya Dadiani[16], Keren Levanon[5,16], Jair Bar[5,7], Shlomit Yust-Katz[5,27], Iris Barshack[5,33], Daniel S. Peeper[34], Dan J. Raz[35], Eran Segal[1,2], Jennifer A. Wargo[8,13], Judith Sandbank[28], Noam Shental[36]‡, Ravid Straussman[1]‡§

Science 2020

Shelly Kalaora

Pipeline for the identification of intra-tumor Bacterial antigens

Adi Nagler

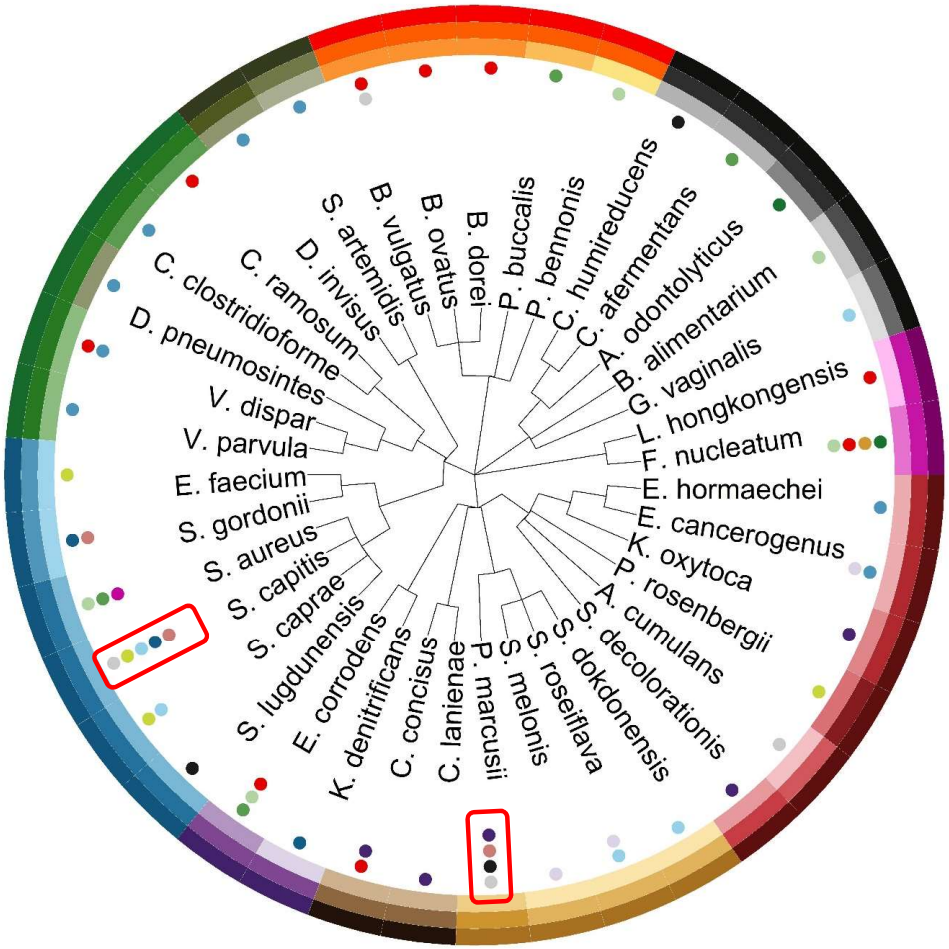


Short talk to be given by Adi Nagler
Concurrent Session 108: Diet and Microbiome
11/11/2020, 3:45 pm

Jennifer Wargo
Ravid Straussman
Deborah Rosenberg

Kalaora, Nagler et al & Samuels, *Nature*, *In Revision*

Phylogenetic tree of all bacteria that were identified in the tumors using 16s rDNA

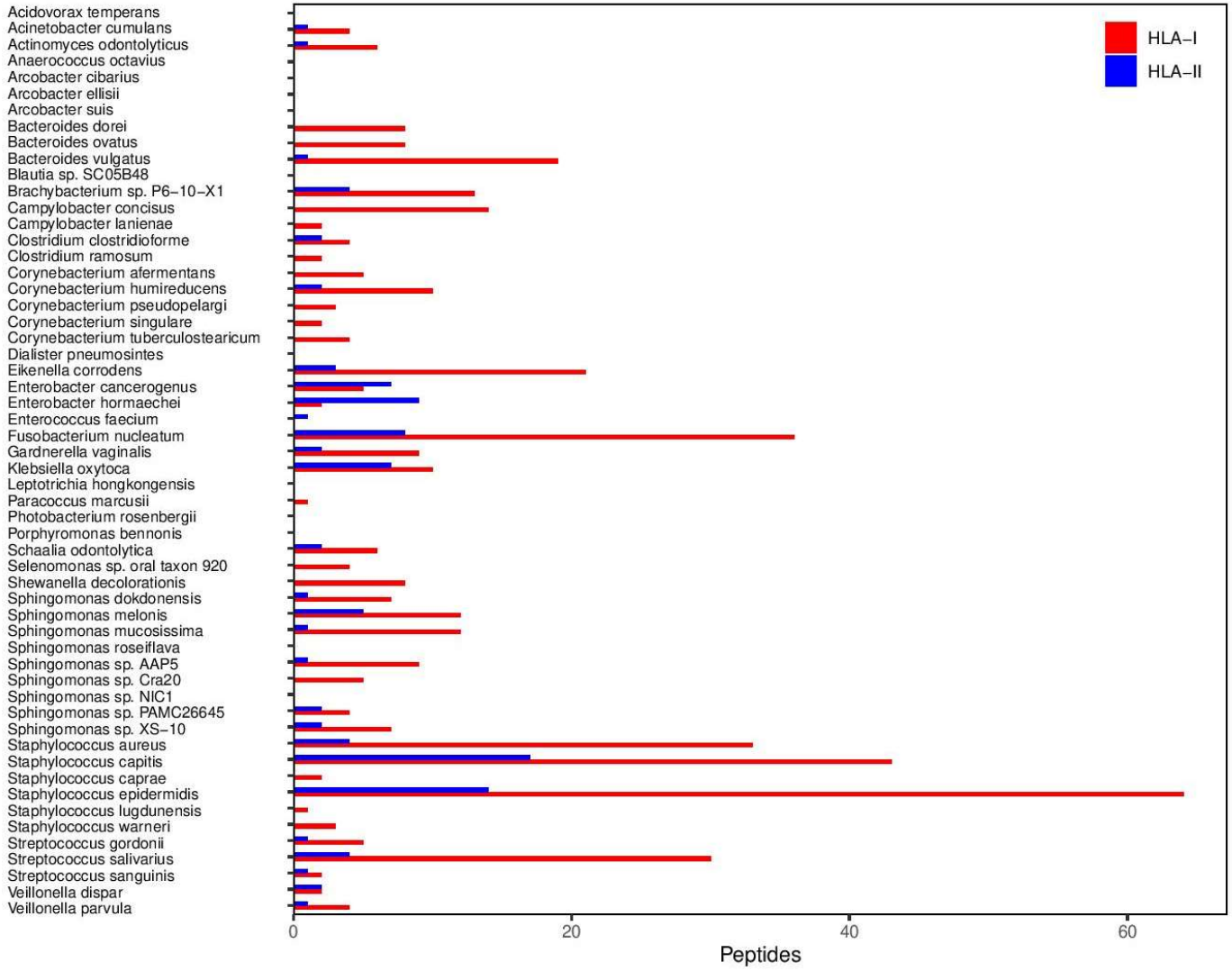


Class	Order	Genus
Bacilli	Bacillales Lactobacillales	Staphylococcus Streptococcus
Bacteroidia	Bacteroidales	Bacteroides Prevotella Porphyromonas
Epsilonproteobacteria	Campylobacterales	Campylobacter
Clostridia	Clostridiales	Clostridium Veillonella Dialister
Betaproteobacteria	Neisseriales	Eikenella Kingella
Fusobacteriia	Fusobacteriales	Fusobacterium Leptotrichia
Gammaproteobacteria	Vibrionales Enterobacteriales Alteromonadales Pseudomonadales	Photobacterium Klebsiella Shewanella Enterobacter Acinetobacter
Actinobacteria	Actinomycetales Micrococcales Bifidobacteriales	Actinomyces Schaalia Corynebacterium Brachybacterium Gardnerella
Alphaproteobacteria	Rhodobacterales Sphingomonadales	Paracoccus Sphingomonas
Negativicutes	Veillonellales Selenomonadales	Dialister Selenomonas

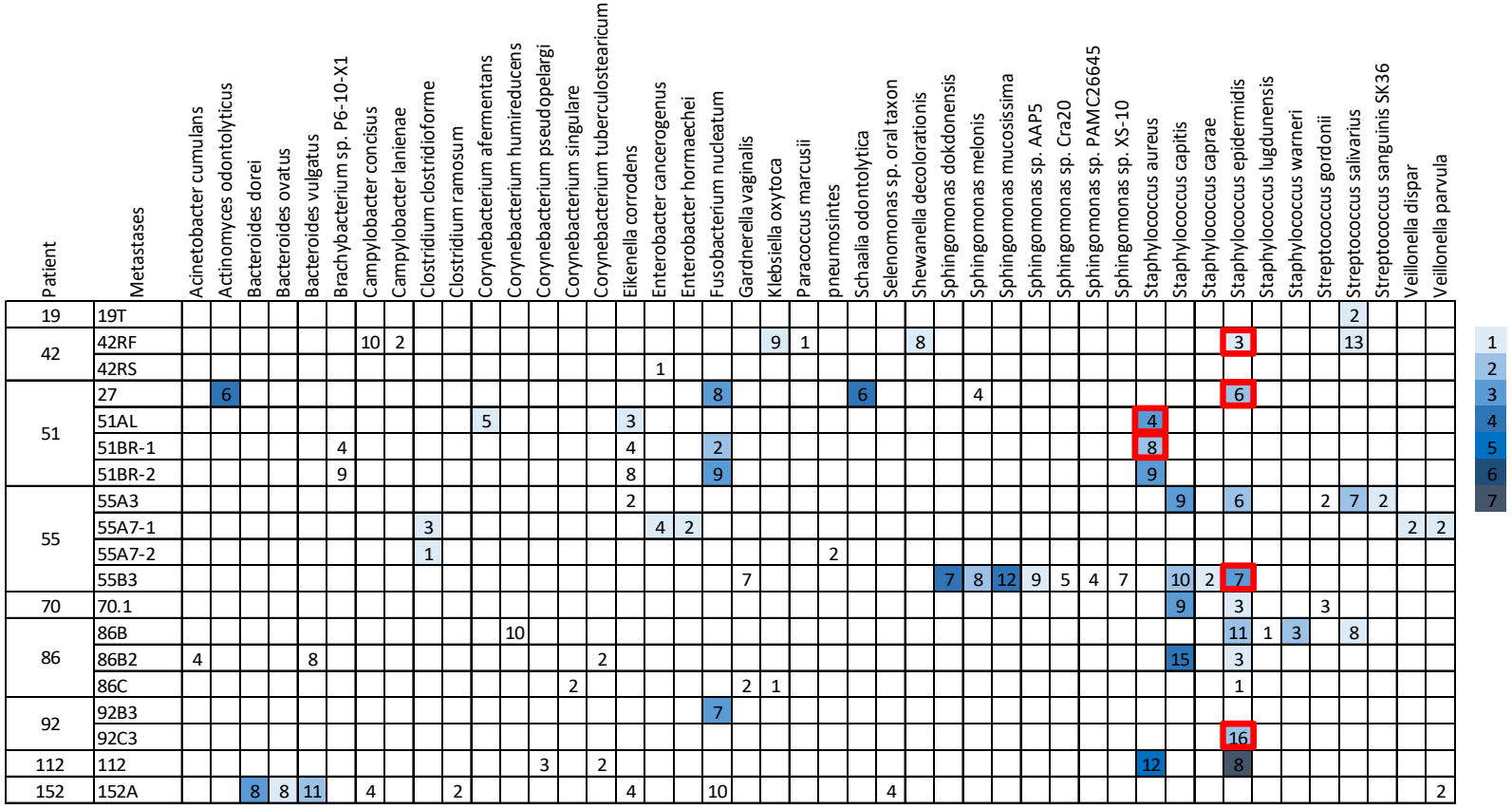
Patients and metastases

19	42	51	55	70	86	92	112	152
19T	42RF 42RS	27 51AL 51BR	55A3 55A7 55B3	70.1	86B 86B2	92B3	112	152A2

Bacterial peptides presented on HLA-I and HLA-II in each patient



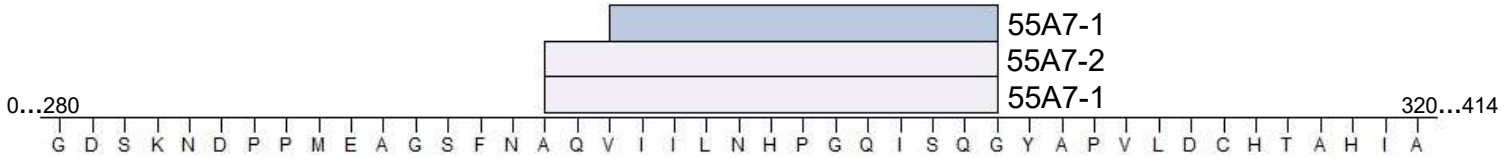
Recurrent HLA class-I presented bacterial peptides



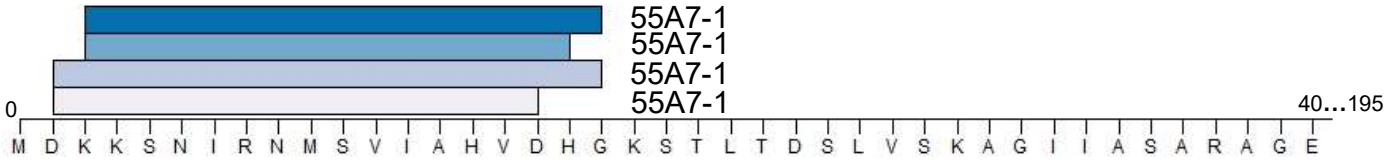
Patient	Metastases	Acinetobacter cumulans	Actinomyces odontolyticus	Bacteroides dorei	Bacteroides ovatus	Bacteroides vulgatus	Brachybacterium sp. P6-10-X1	Campylobacter concisus	Campylobacter lanienae	Clostridium clostridioforme	Clostridium ramosum	Corynebacterium afermentans	Corynebacterium humireducens	Corynebacterium pseudopelargi	Corynebacterium singulare	Corynebacterium tuberculostearicum	Eikenella corrodens	Enterobacter cancerogenus	Enterobacter hormaechei	Fusobacterium nucleatum	Gardnerella vaginalis	Klebsiella oxytoca	Paracoccus marcusii	pneumosintes	Schaalia odontolytica	Selenomonas sp. oral taxon	Shewanella decolorationis	Sphingomonas dokdonensis	Sphingomonas melonis	Sphingomonas mucosissima	Sphingomonas sp. AAP5	Sphingomonas sp. Cra20	Sphingomonas sp. PAMC26645	Sphingomonas sp. XS-10	Staphylococcus aureus	Staphylococcus capitis	Staphylococcus caprae	Staphylococcus epidermidis	Staphylococcus lugdunensis	Staphylococcus warneri	Streptococcus gordonii	Streptococcus salivarius	Streptococcus sanguinis SK36	Veillonella dispar	Veillonella parvula
19	19T																																								2			
42	42RF							10	2													9	1				8										3				13			
	42RS																	1																										
51	27		6																	8					6			4							6								
	51AL											5					3																	4									
	51BR-1						4										4			2														8									
	51BR-2						9										8			9														9									
55	55A3																2																		9		6			2	7	2		
	55A7-1									3								4	2																								2	2
	55A7-2									1														2																				
	55B3																				7							7	8	12	9	5	4	7		10	2	7						
70	70.1																																		9		3			3			
86	86B												10																								11	1	3		8			
	86B2	4				8										2																			15		3							
	86C														2						2	1															1							
92	92B3																			7																								
	92C3																																				16							
112	112													3		2																			12			8						
152	152A			8	8	11		4			2						4			10						4																	2

“Hot spot” HLA - presented bacterial peptides

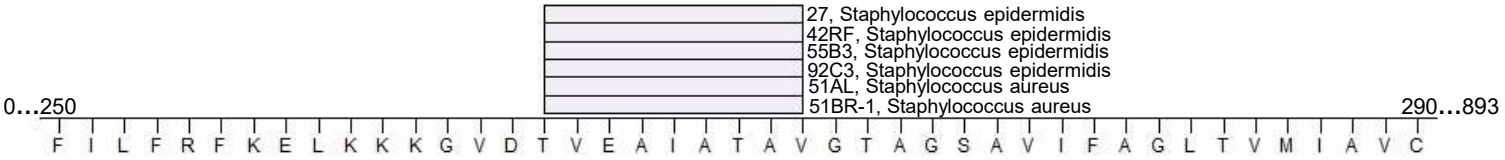
Translation elongation factor EF-1 subunit alpha, Enterobacter hormaechei, HLA-II



Tr-type G domain-containing protein, Enterobacter hormaechei, HLA-II

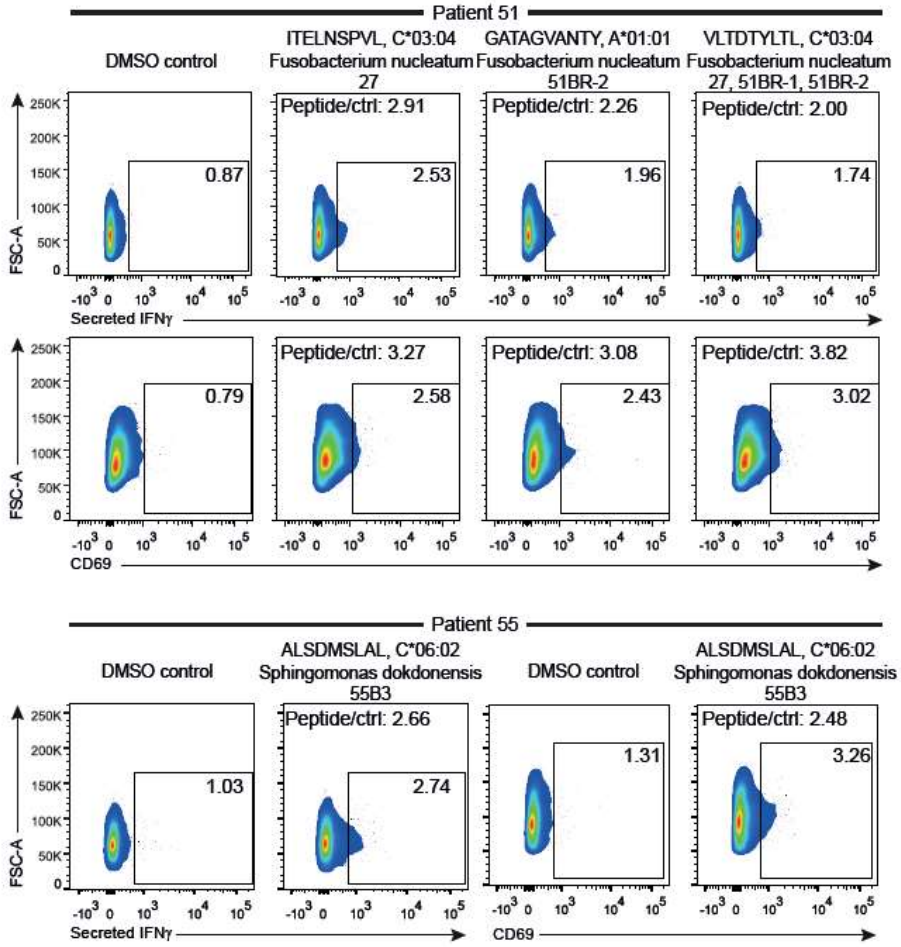


MMPL family transporter , HLA-I



Kalaora, Nagler et al & Samuels, *Nature*, *In Revision*- **please do not post**

Immunogenicity of bacterial peptides



Kalaora, Nagler et al & Samuels, *Nature*, *In Revision*- **please do not post**

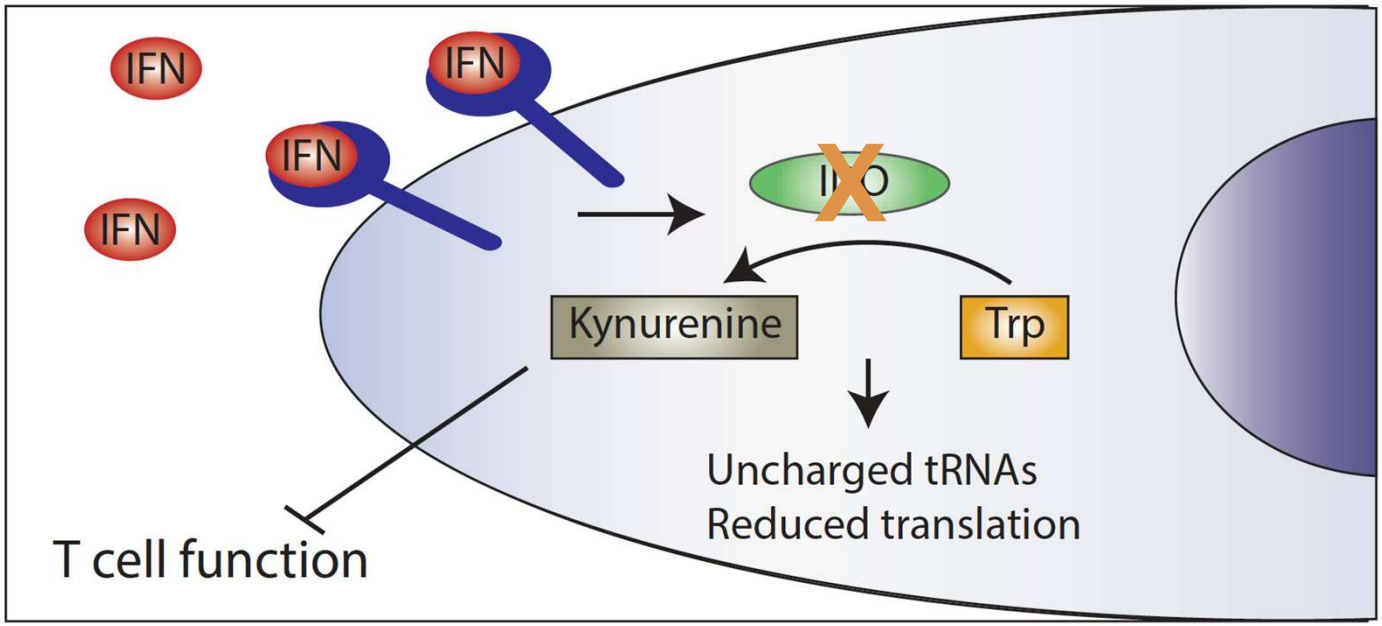
Summary

- HLA peptidomics revealed bacterial antigens bound to HLA class I and class II in melanoma tumors

- The identified antigens are derived from bacteria that enter the melanoma cells, some are recurrent and some are immuno-reactive

Identification of IFNγ-Induced ribosomal frame-shifting and HLA-presentation of aberrant peptides

The interferon gamma (IFN) response

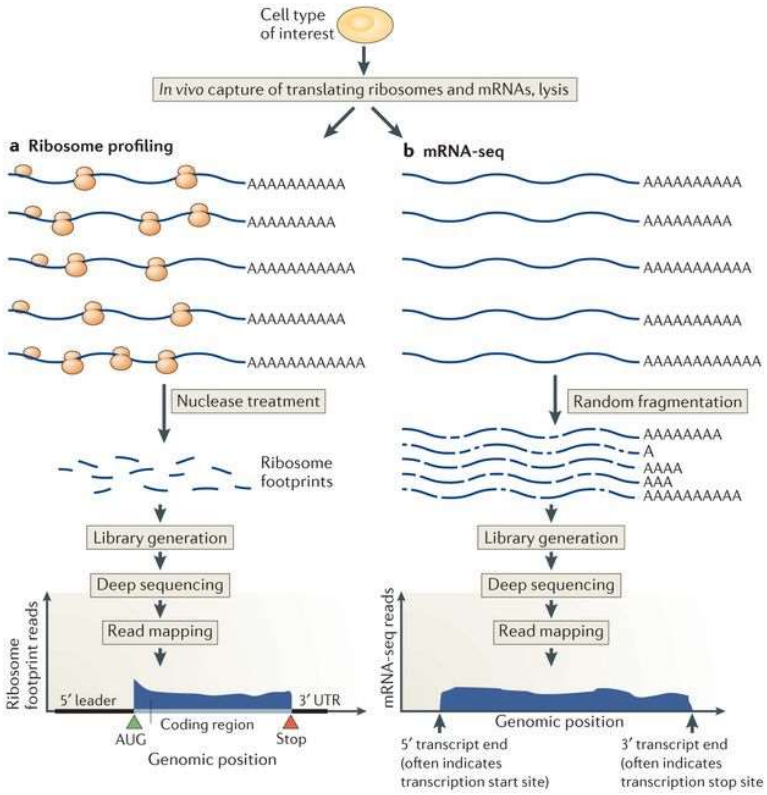


We still don't completely understanding of the role of IDO1 and the consequences of Tryptophan degradation on cancer progression

Riboseq and mRNAseq from three melanoma cell lines exposed to IFNγ

Osnat Bartok

108T
12T → -/+ 48h IFNγ
MD55A3

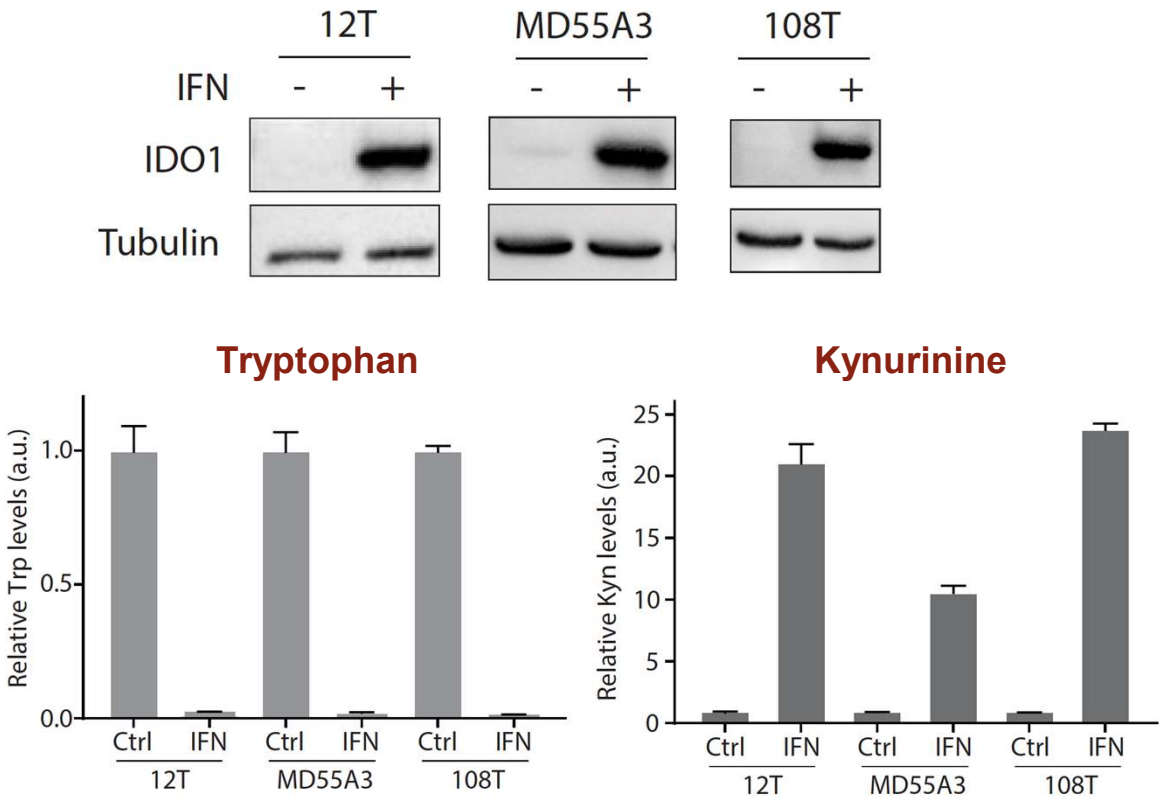


Tranlatome **Transcriptome**

Noam Stern-Ginossar

Brar GA and Weissman JS, *Nat. Rev. Mol. Cell Biol.*, 2015.

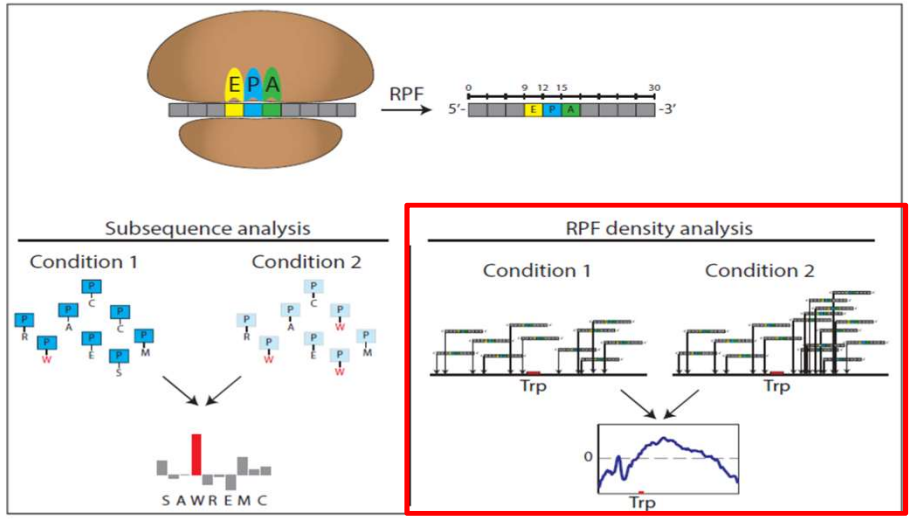
IDO1 induction results in Trp to Kyn conversion

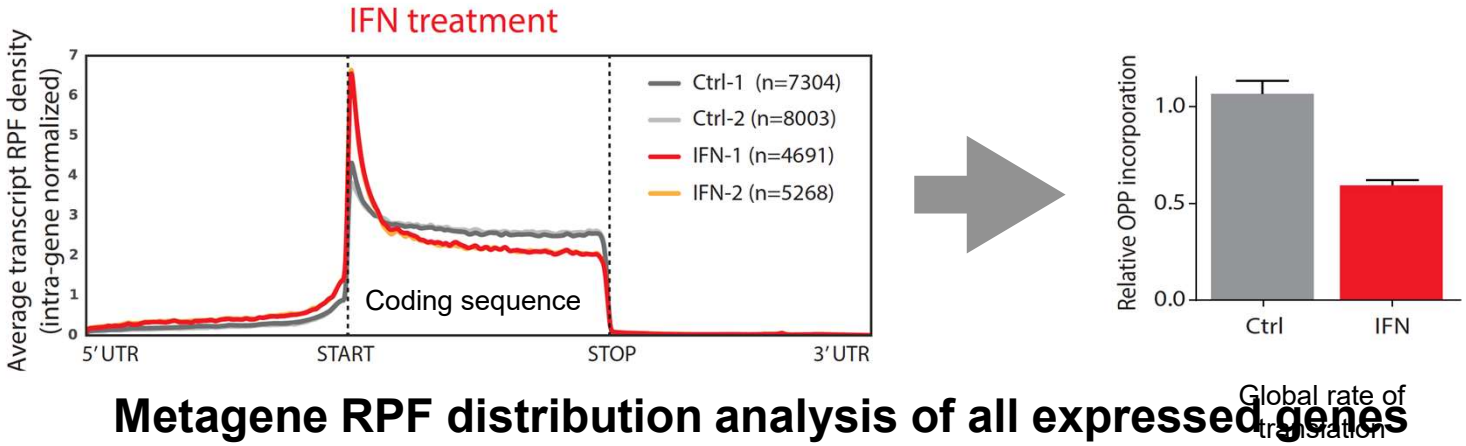


Bartok et al & Samuels*, Agami* , *Nature, In Revision*- **please do not post**

Effects on mRNA translation (initiation)

Analysis of Ribosome Protected Fragments (RPF) by DIRICORE (DIfferential Ribosome COdon REading)





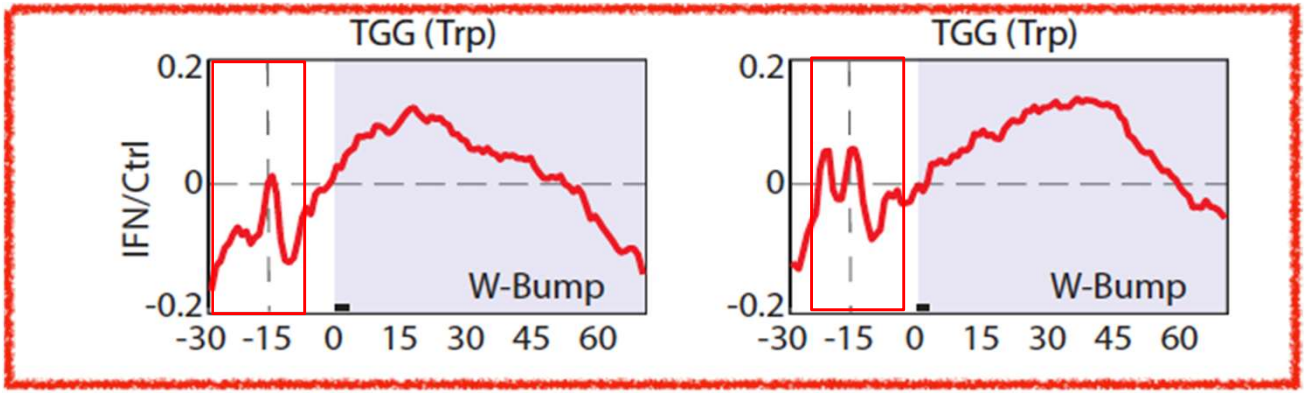
Metagene RPF distribution analysis of all expressed genes

Reuven Agami

Analysis of RPFs at position 15 demonstrates ribosome pausing on Tryptophan codons

Analysis of Ribosome Protected Fragments (RPF) by DIRICORE (DIfferential Ribosome COdon REading)

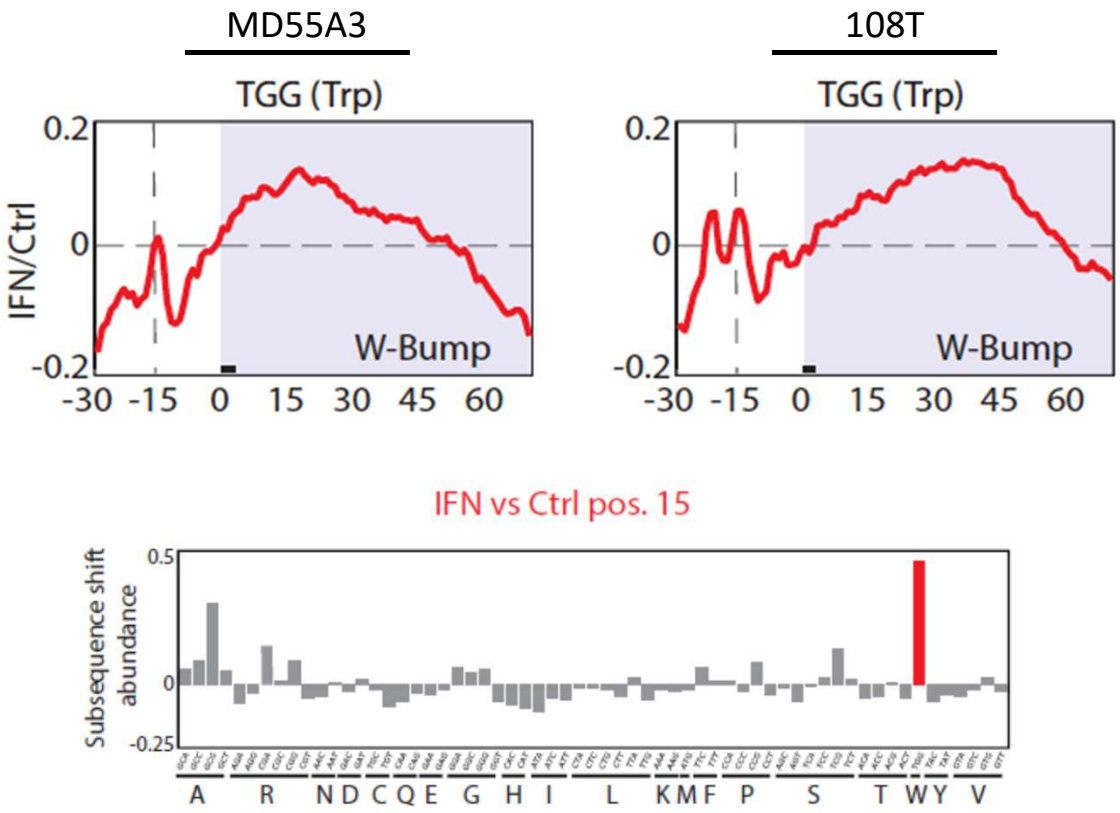
Analysis of RPFs by DIRICORE (DIfferential Ribosome COdon REading)



Bartok et al & Samuels*, Agami* , *Nature, In Revision*- **please do not post**

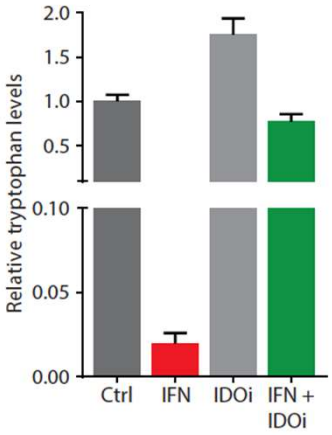
Effects on mRNA translation (elongation)

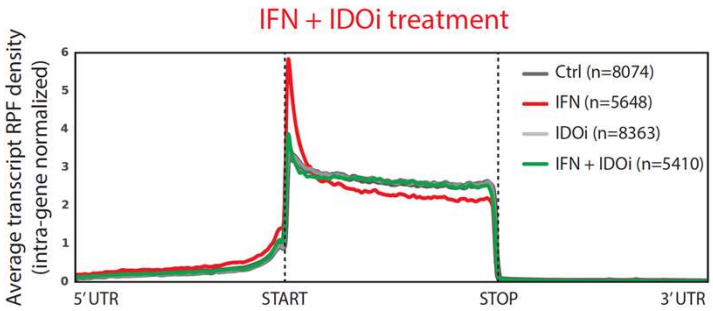
Analysis of RPFs by DIRICORE (DIfferential Ribosome COdon REading)



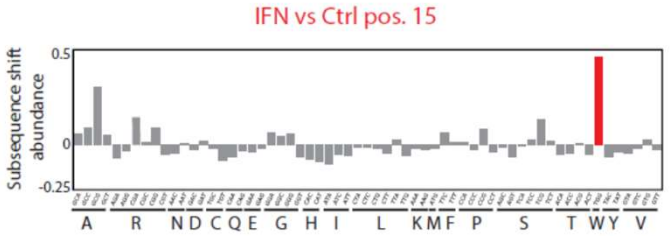
A strong accumulation of RPFs *downstream* of Trp- 'W Bumps'

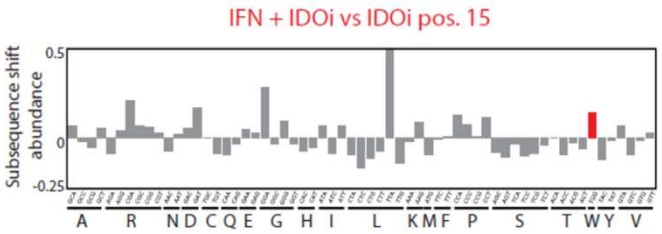
Effects of IDO1 inhibition (IDOi)



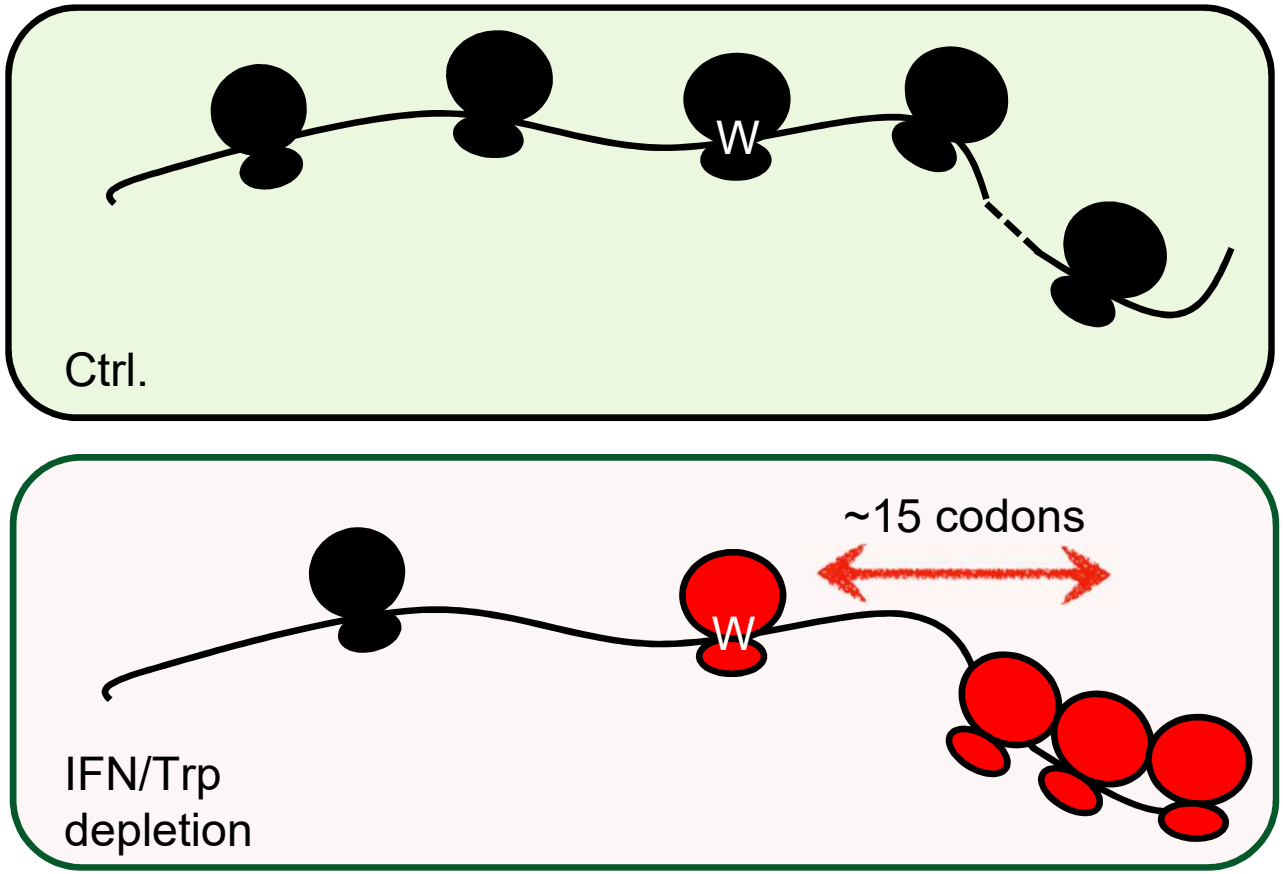


Position-specific codon enrichment analysis



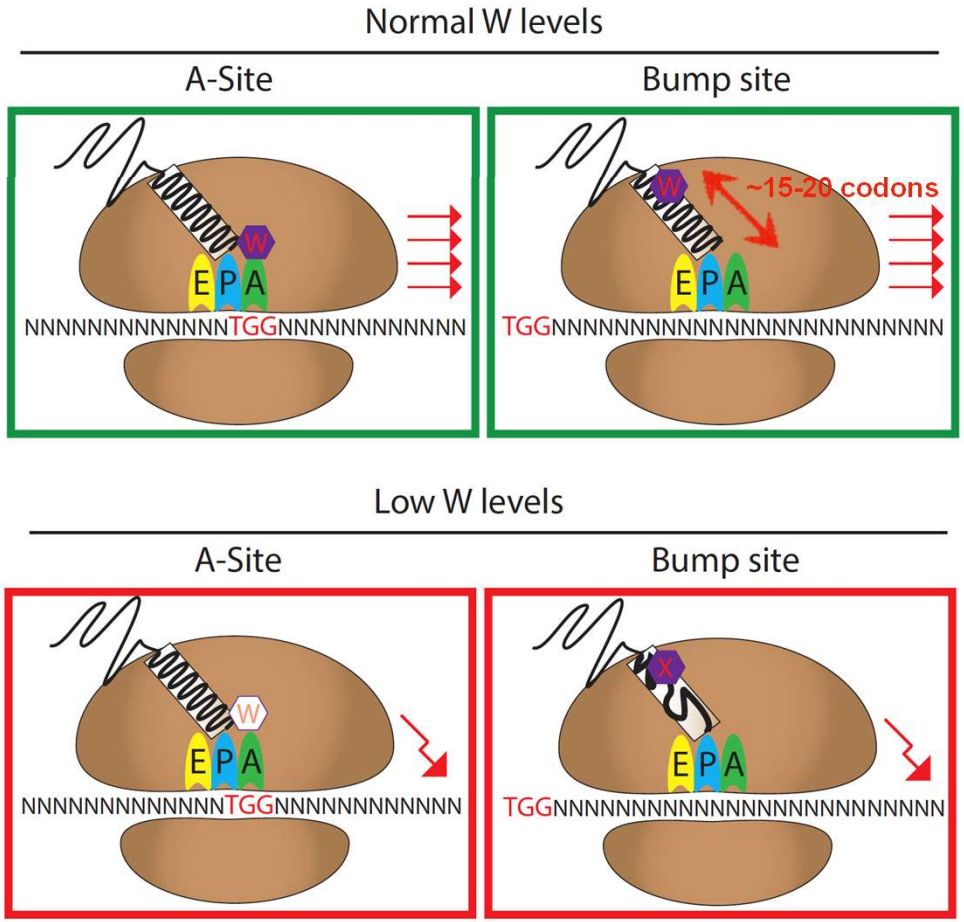


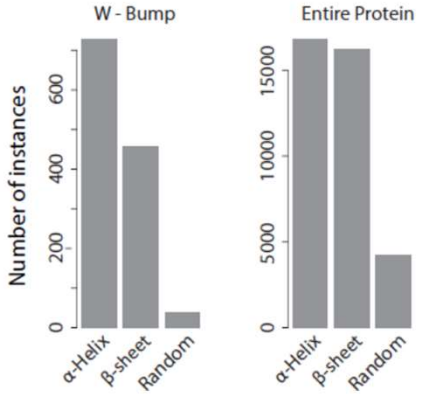
Summary so far . . .



Why bumps at ~15 amino acids after Trp codons?

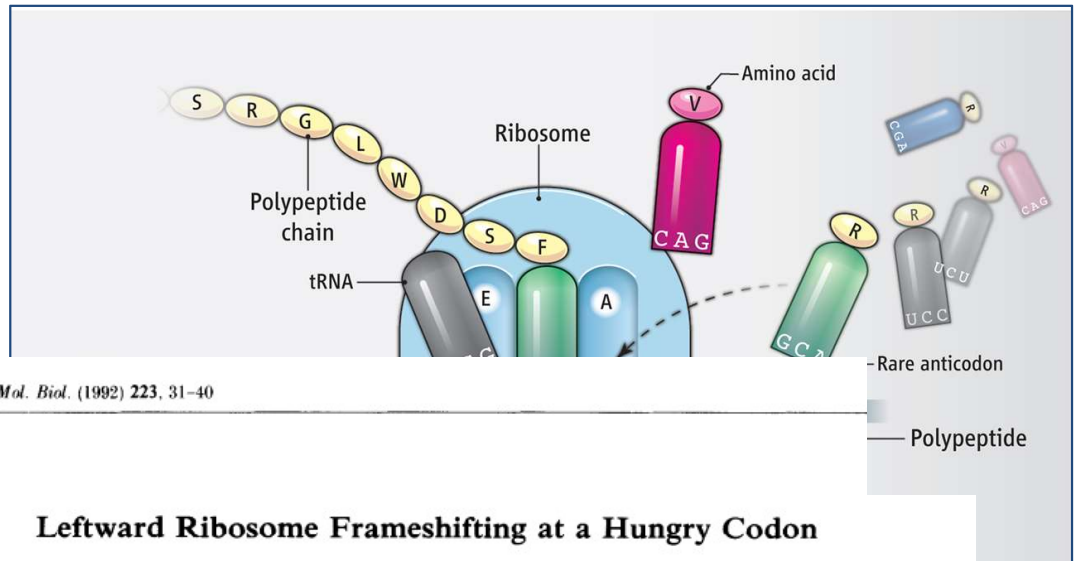
W-Bumps and protein disorderedness





Peptide sequences corresponding to the W-Bumps region form an α-helix structure more frequently than other regions in the proteome

Disorderedness created by frameshifting



J. Mol. Biol. (1992) 223, 31–40

Leftward Ribosome Frameshifting at a Hungry Codon

Jonathan A. Gallant and Dale Lindsley

Department of Genetics SK-50
University of Washington, Seattle, WA 98195, U.S.A.

(Received 22 May 1991; accepted 3 September 1991)

Vol. 187, No. 12

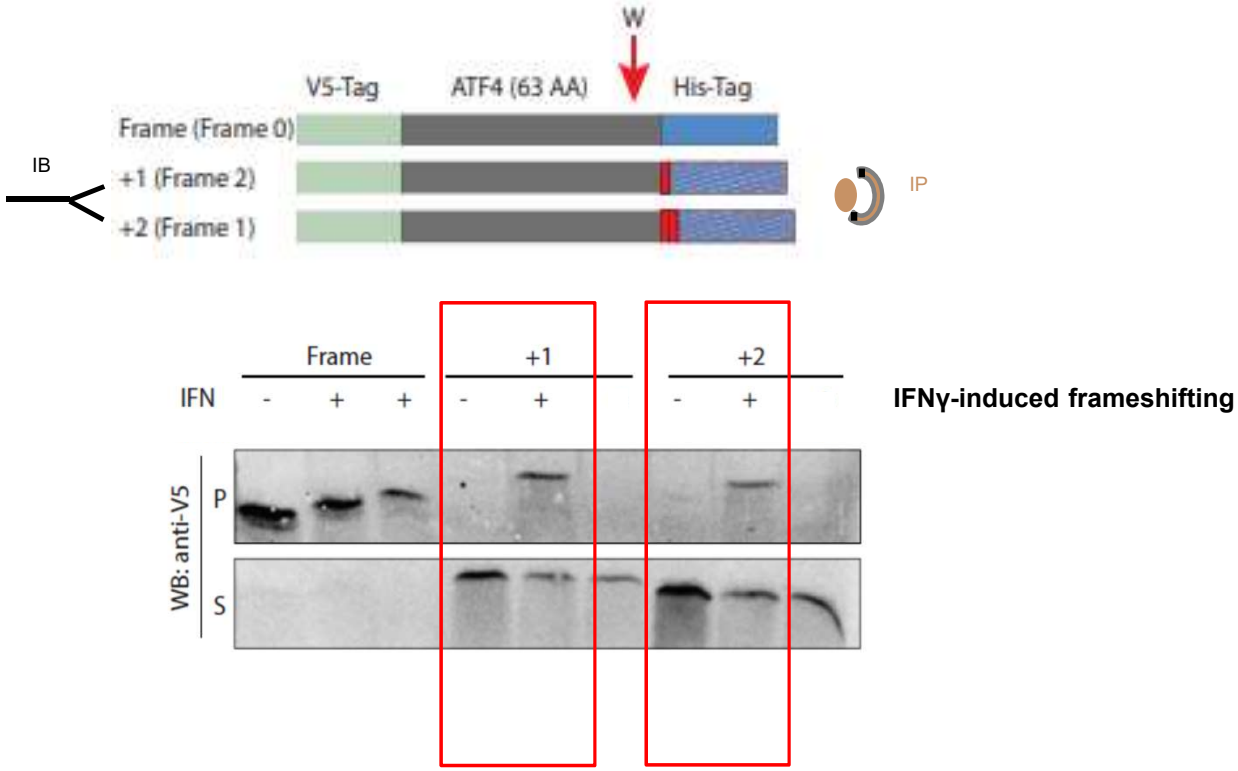
ting at the Tandem
GA_AGA

Olga L. Gurvich,[1] Pavel V. Baranov,[1,2] Raymond F. Gesteland,[1] and John F. Atkins[1,2]*

Department of Human Genetics, University of Utah, 15N 2030E, Rm. 7410, Salt Lake City, Utah 84112-5330,[1] and Bioscience Institute, University College Cork, Cork, Ireland[2]

Received 2 December 2004/Accepted 4 March 2005

Lentiviral Reporter System For The Identification of IFNγ-Induced Ribosomal Frame-Shifting



Bartok et al & Samuels*, Agami* , *Nature, In Revision*- **please do not post**

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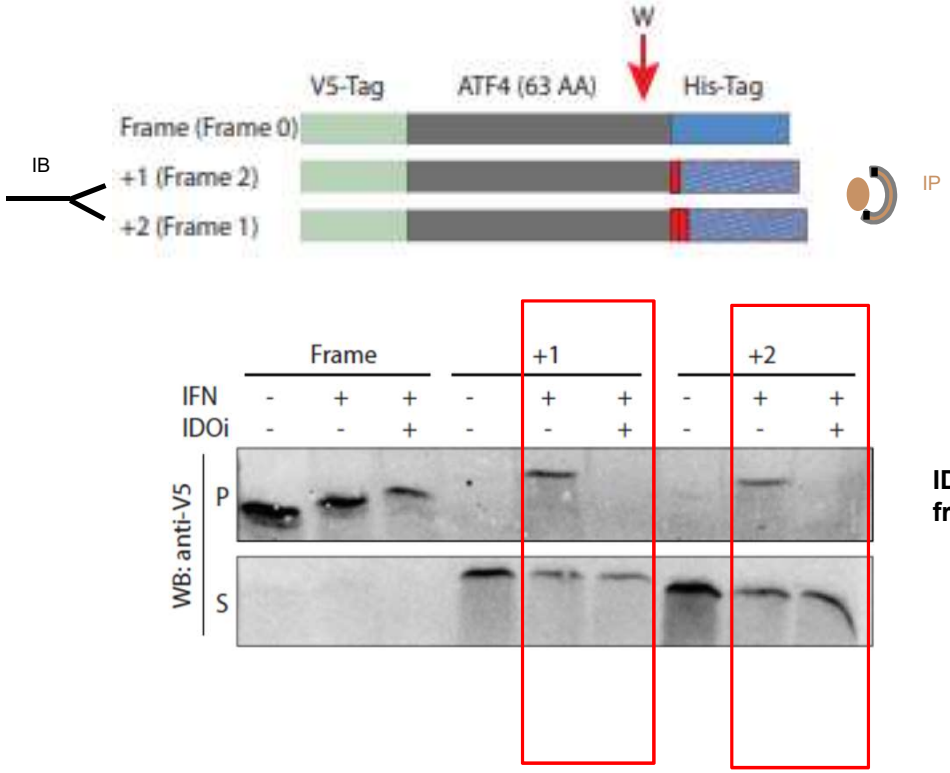
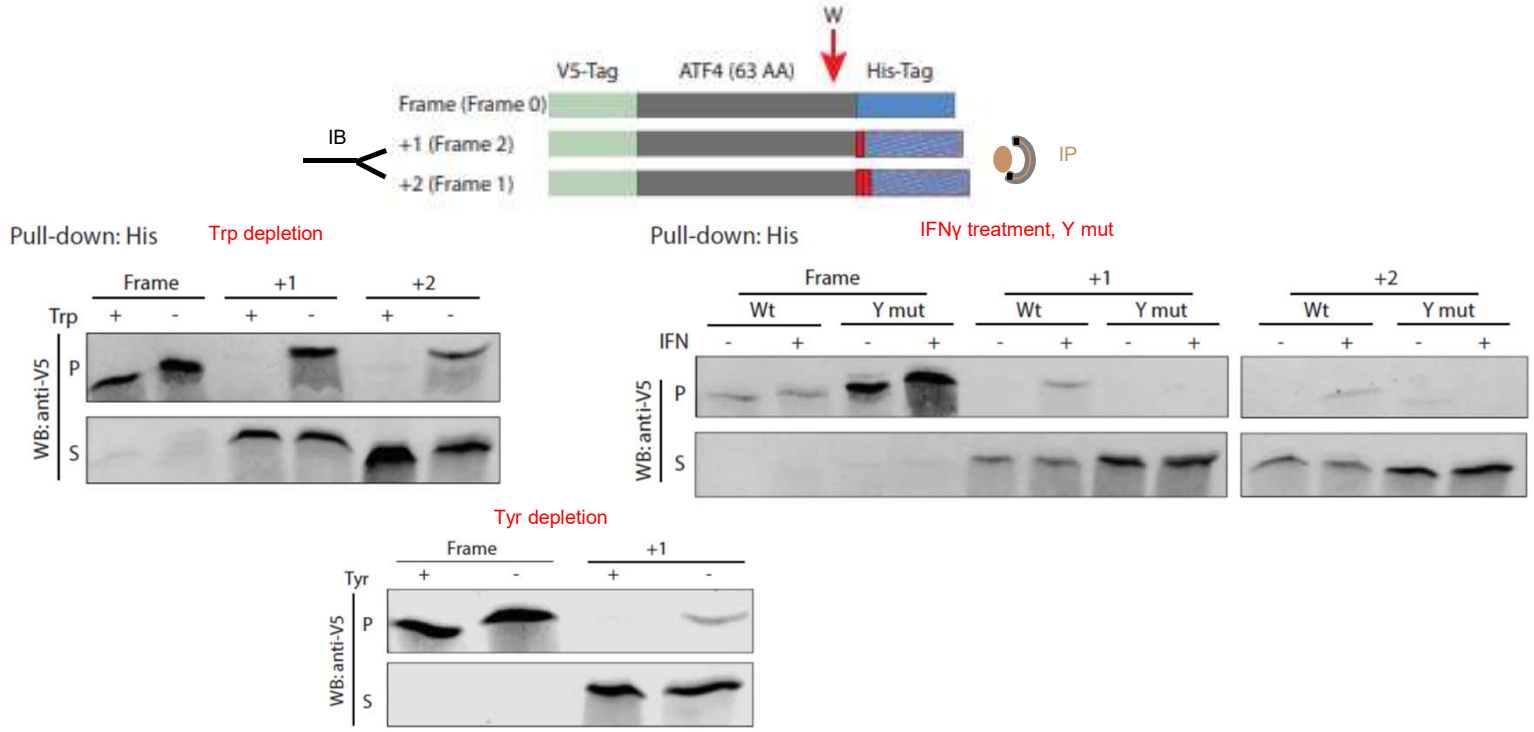


IDOi abolishes IFNγ-induced frameshifting

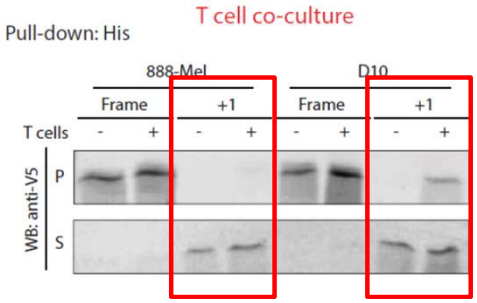
Lentiviral Reporter System For The Identification of IFNγ-Induced Ribosomal Frame-Shifting



Lentiviral Reporter System For The Identification of IFNγ-Induced Ribosomal Frame-Shifting

888-Mel-
IFNγ **resistant**,
MART1⁺ melanoma cells

D10 -
IFNγ**-sensitive**,
MART1⁺ melanoma cells



Frameshifting events are detected also in this native context

Bartok et al & Samuels*, Agami* , *Nature, In Revision*- **please do not post**

Lentiviral Reporter System For The Identification of IFNγ-Induced Ribosomal Frame-Shifting

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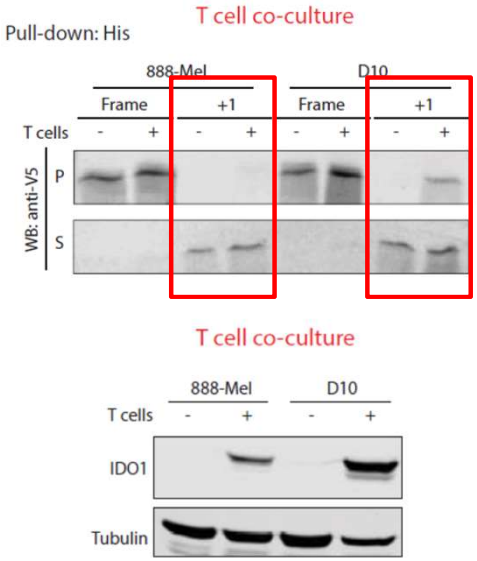
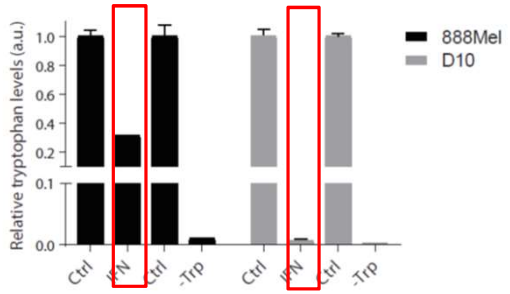


The weaker IDO1 induction in 888-Mel by IFNγ signaling is the likely cause of the lower frameshifting rate.



Lentiviral Reporter System For The Identification of IFNγ-Induced Ribosomal Frame-Shifting

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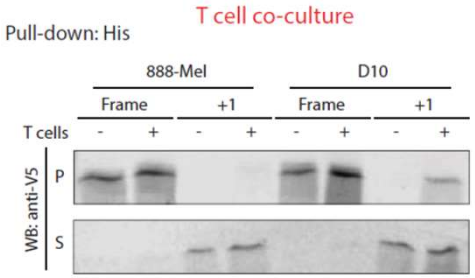
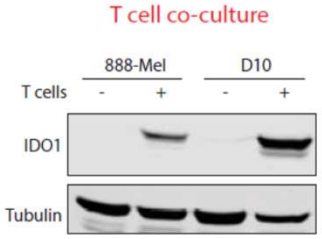
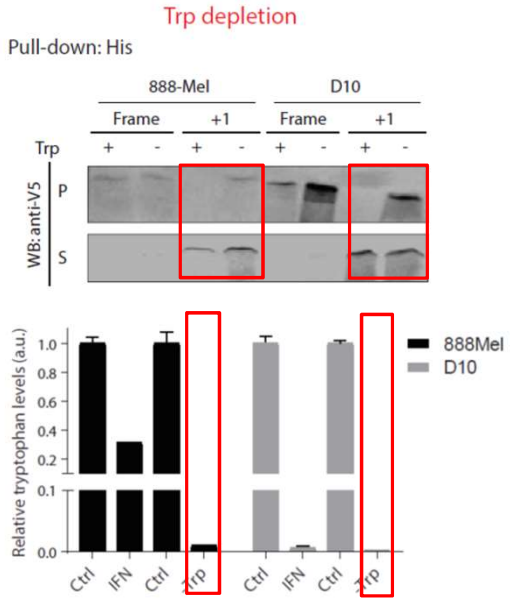
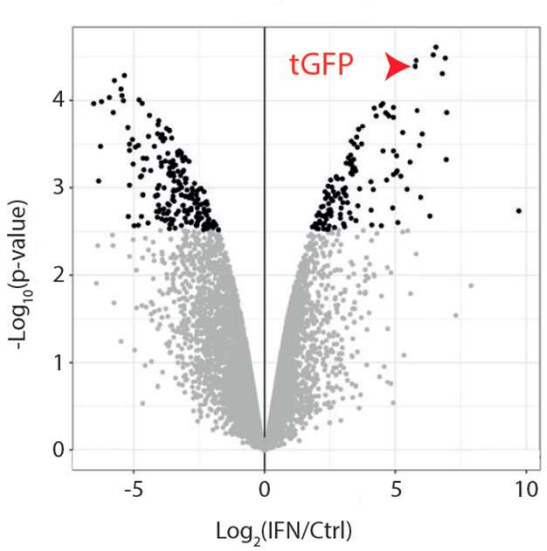




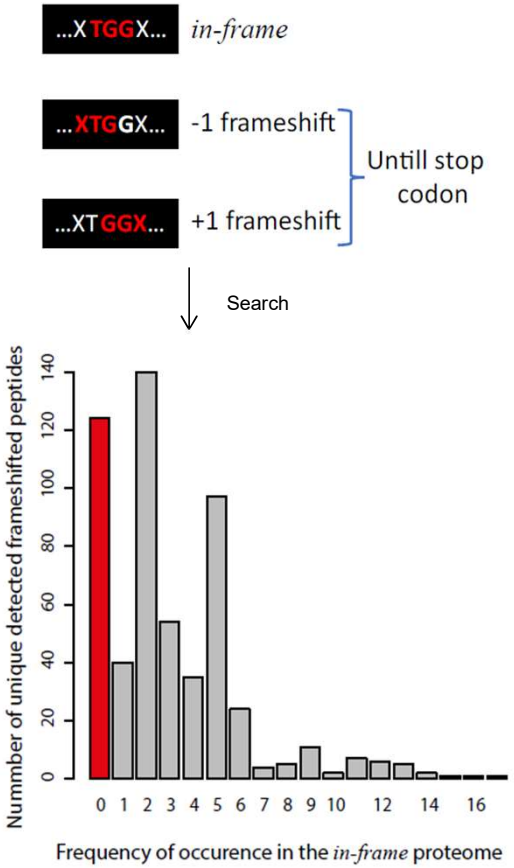


Frame-shifted polypeptides observed using deep proteomics



IFNγ treatment induced a strong expression
Allowing the detection of frameshifted peptides

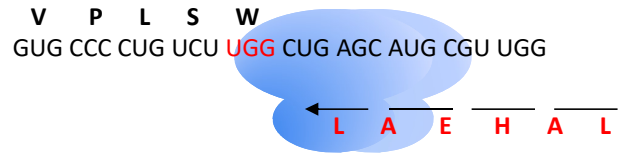
Frame-shifted data base: predicted out-of-frame -1 and +1 polypeptides created by frameshifting at endogenous tryptophans of proteins expressed in MD55A3 cells, as determined by ribosome profiling



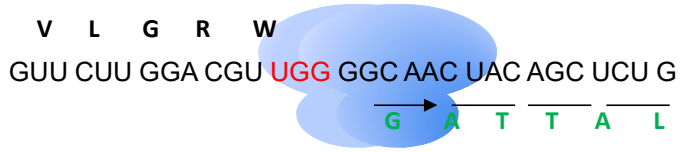
Endogenous production of *trans-frame* proteins and their presentation at on the cell surface

Gene	Sequence	Found in sample
KCNK6	VPLSLAEHAL	IFNγ
DBNDD2	SPLSSLSTL	IFNγ
DIP2B	QFLAEILQV	IFNγ
AC129492.1	SPTLSQCSL	IFNγ
HSP90AB1	MVSPLAGVPK	mTRP
ZNF513	VGQEGLVSL	mTRP
STK25	SPALRTLTL	IFNγ,mTRP
FCGBP	APSGVAAGL	IFNγ,mets
ESPNL	LFLSHLEEI	IFNγ,mets
RPL7A	VAAAESHPL	IFNγ,mets
TRAM1L1	TSLVNLSTL	mTRP,mets
GEMIN5	SPRGPPSSL	IFNγ,mTRP,mets

-1
+1



Aberrant: VPLSLAEHAL Canonical: VPLSWLSMRW

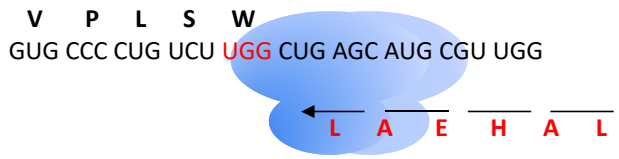


Aberrant: VLGRGATTAL Canonical: VLGRWGNYSS

Endogenous production of *trans-frame* proteins and their presentation at on the cell surface

Gene	Sequence	Found in sample
KCNK6	VPLSLAEHAL	IFNγ
DBNDD2	SPLSSLSTL	IFNγ
DIP2B	QFLAEILQV	IFNγ
AC129492.1	SPTLSQCSL	IFNγ
HSP90AB1	MVSPLAGVPK	mTRP
ZNF513	VGQEGLVSL	mTRP
STK25	SPALRTLTL	IFNγ,mTRP
FCGBP	APSGVAAGL	IFNγ,mets
ESPNL	LFLSHLEEI	IFNγ,mets
RPL7A	VAAAESHPL	IFNγ,mets
TRAM1L1	TSLVNLSTL	mTRP,mets
GEMIN5	SPRGPPSSL	IFNγ,mTRP,mets

-1
+1

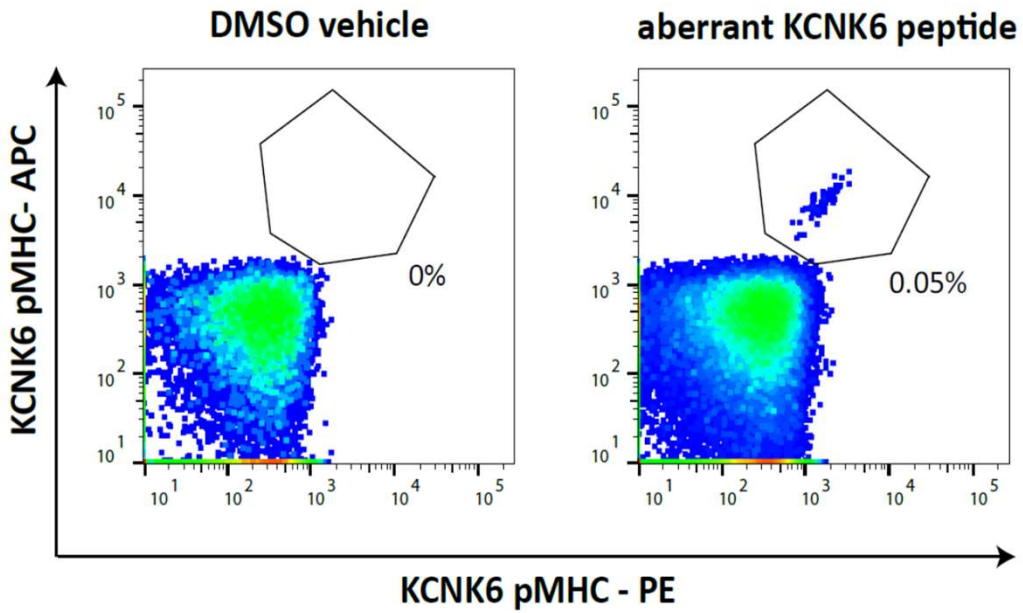


Aberrant: VPLSLAEHAL Canonical: VPLSWLSMRW

Aberrant: VLGRGATTAL Canonical: VLGRWGNYSS

Identification of reactive T cells to tryptophan-derived aberrant peptides

Tetramer screening of B07:02/C07:02 co-culture at Day 10 (D#18)

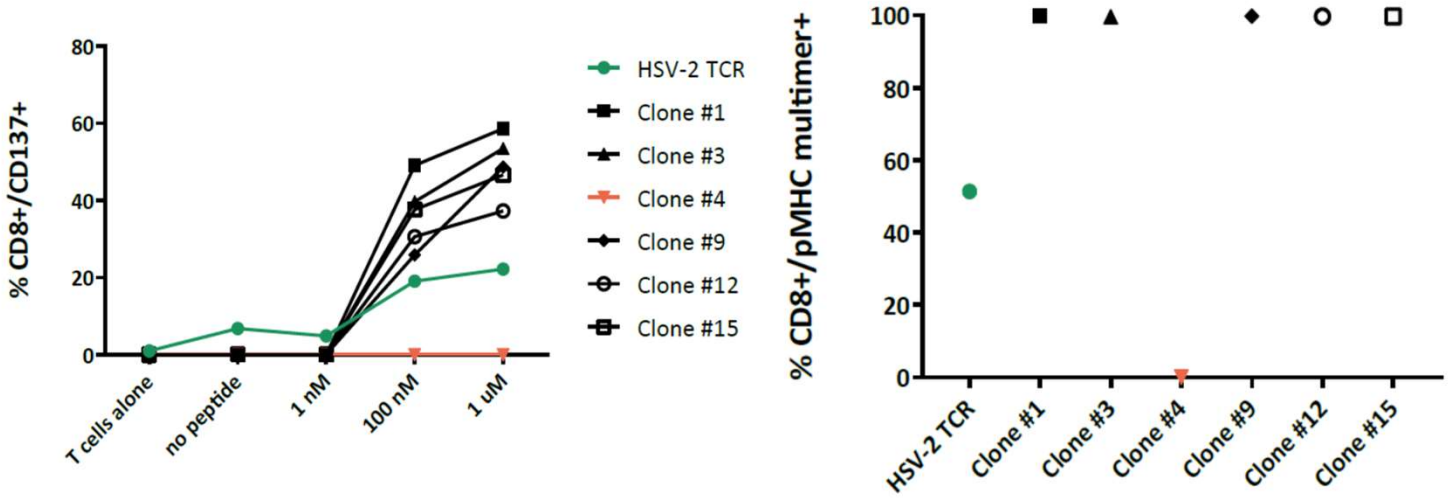


KCNK6 peptide specific T cell population (0.05%) was detected in one well of D#18 T cells.
This population was single cell sorted onto feeders for T cell cloning and further validation

Maarja Laos
Johanna Olweus

Identification of reactive T cells to tryptophan-derived aberrant peptides

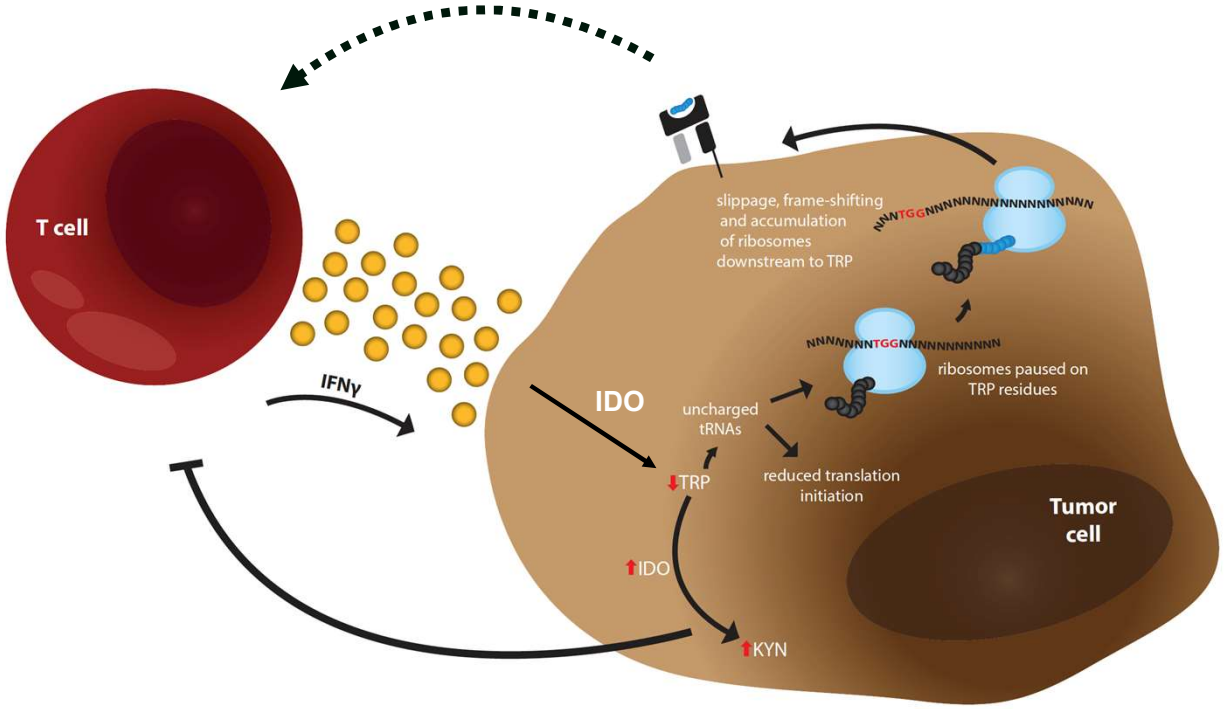
16 out of 180 single cell sorted T cells from KCNK6 tetramer positive population grew out on feeders.



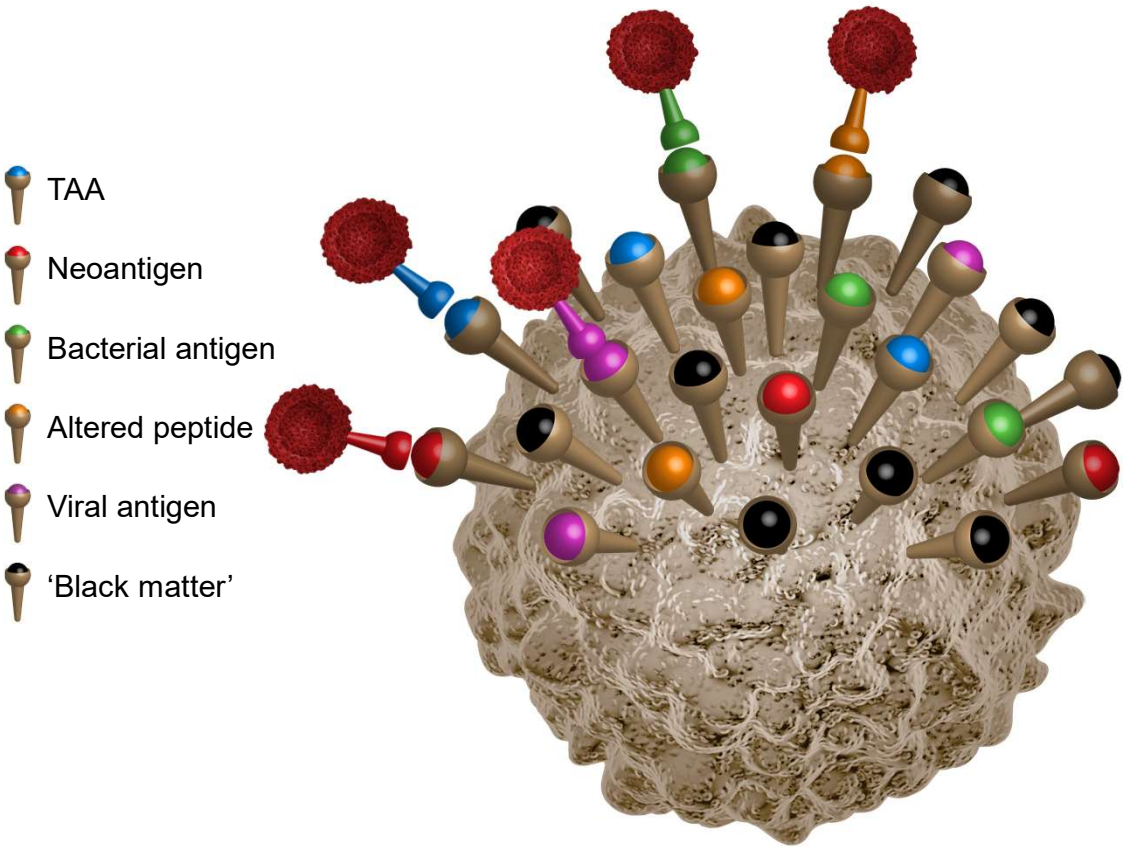
All 13 tetramer positive KCNK6 T cell clones reacted positively with KCNK6 peptide loaded K562-B07:02 cells.
Clone #4 that was tetramer negative did not react.

Maarja Laos
Johanna Olweus

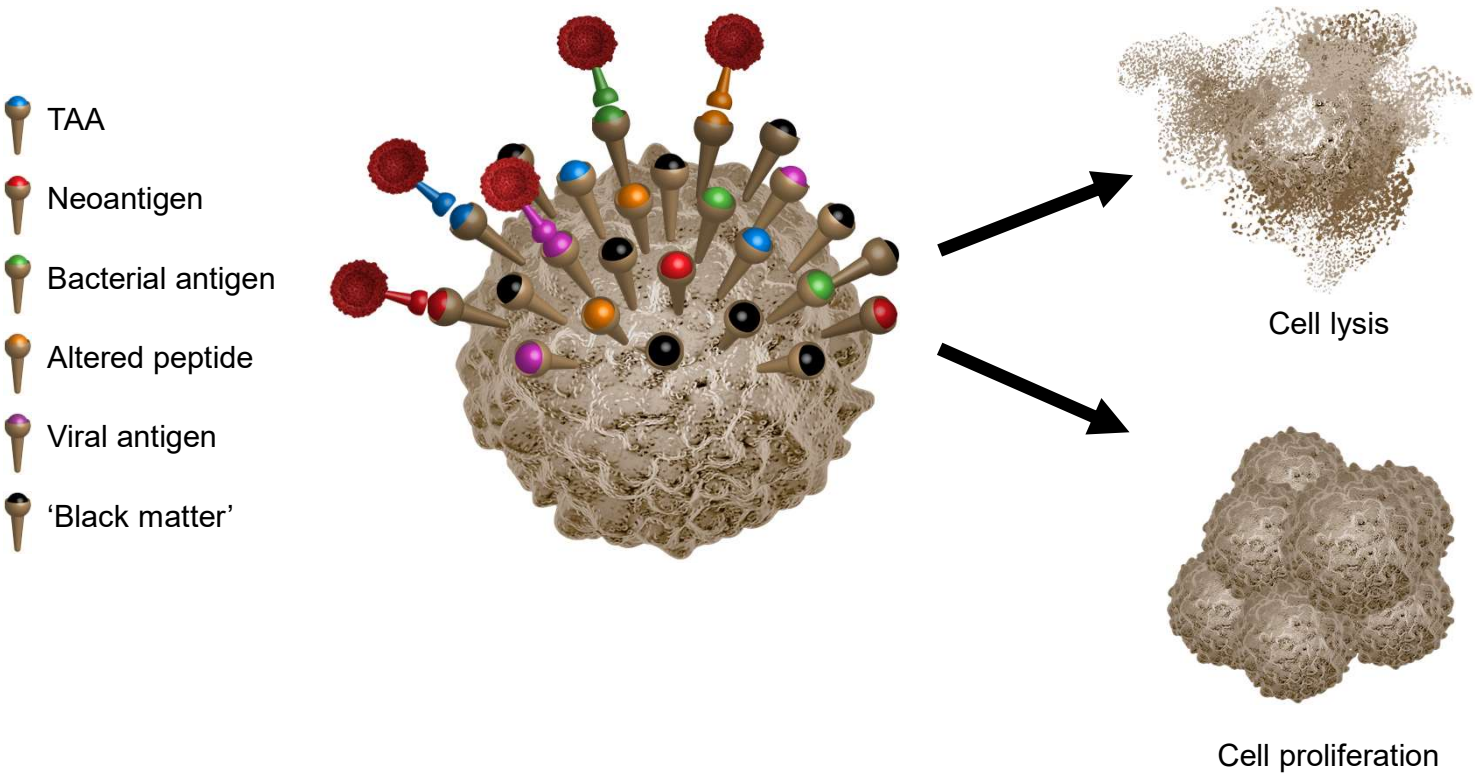
Summary


T cell
IFNγ
IDO
uncharged
tRNAs
↓TRP
↑IDO
↑KYN
reduced translation
initiation
slippage, frame-shifting
and accumulation
of ribosomes
downstream to TRP
NNNTGGNNNNNNNNNNNNNNN
NNNNNNNTGGNNNNNNNNNN
ribosomes paused on
TRP residues
Tumor
cell

New layer of intra-tumor heterogeneity: on the HLA-presentation level



New layer of intra-tumor heterogeneity: on the HLA-presentation level



The Samuels Lab

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Samuels Lab
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cnio stop cancer

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