Cancer Immunoediting: From Immunosurveillance to Personalized Cancer Immunotherapy

Milestones in Cancer Immunotherapy
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Disclosure Information

Financial Relationships:

Co-founder & Member BOD Igenica Biotherapeutics

Senior Advisor Jounce Therapeutics

Co-Founder Neon Therapeutics

SAB Member BioLegend and Meryx

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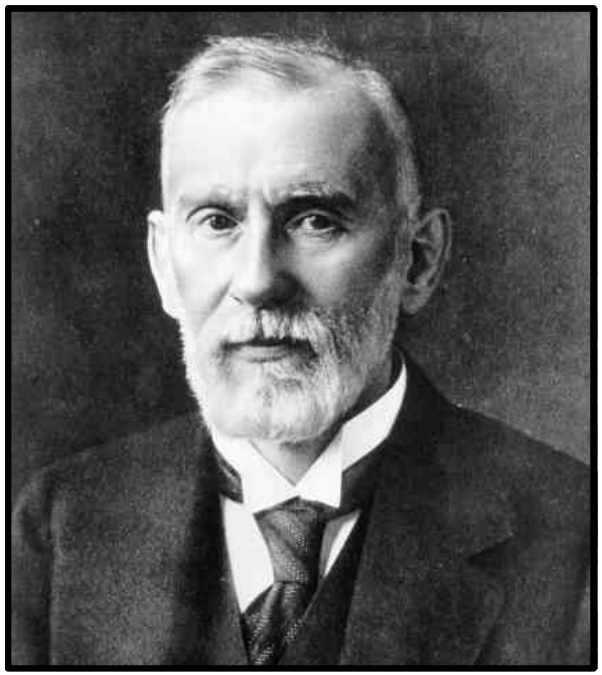
Janssen Biotech, Inc

I will not be discussing off-label- or investigational-use of any drug in my presentation

The Beginnings



Paul Ehrlich (1909): First to formally propose a host protective role of immunity against cancer.

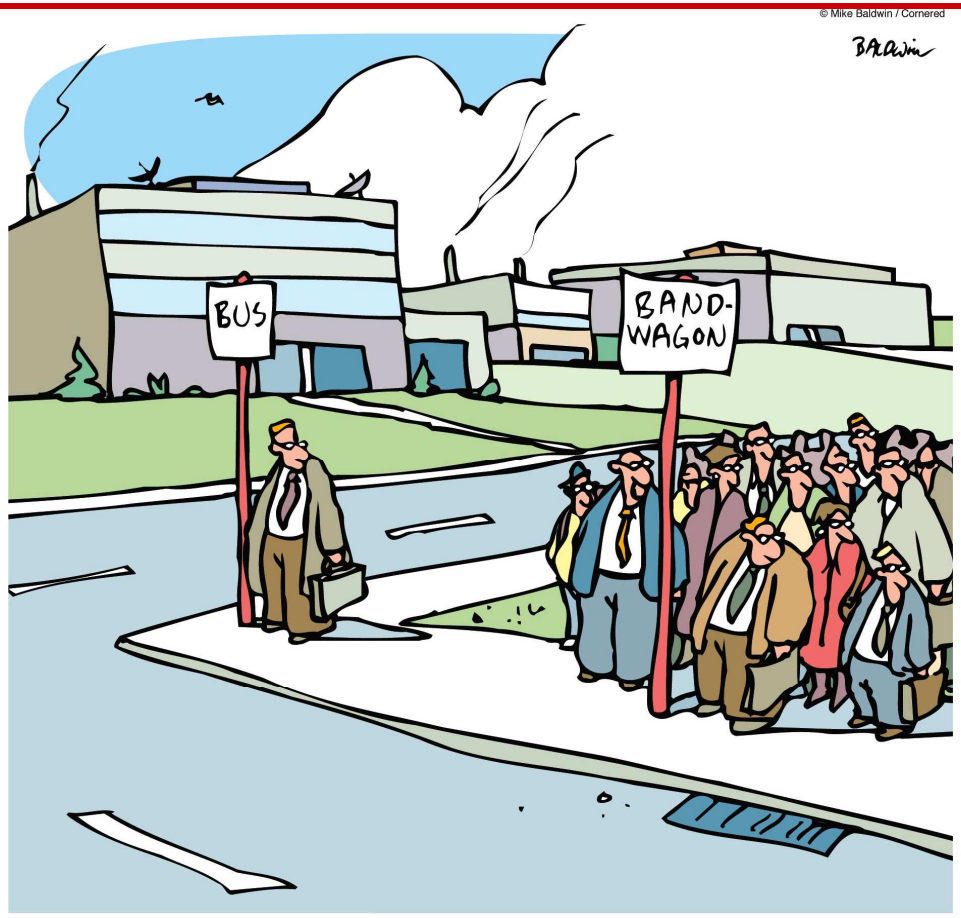
Predicted that cancer would occur at "incredible frequency" if host defenses did not prevent the outgrowth of continuously arising cancer cells.

The Cancer Immunosurveillance Hypothesis

Macfarlane Burnet *(L)* **& Lewis Thomas** *(R)* **(1960s): The "Cancer Immunosurveillance" Hypothesis.**

Proposed the term "Cancer Immunosurveillance" to describe natural immune resistance against cancer. Predicted that T lymphocytes were the major effector cells in this process.

Jumping On the Cancer Immunosurveillance Bandwagon (c. 1965)

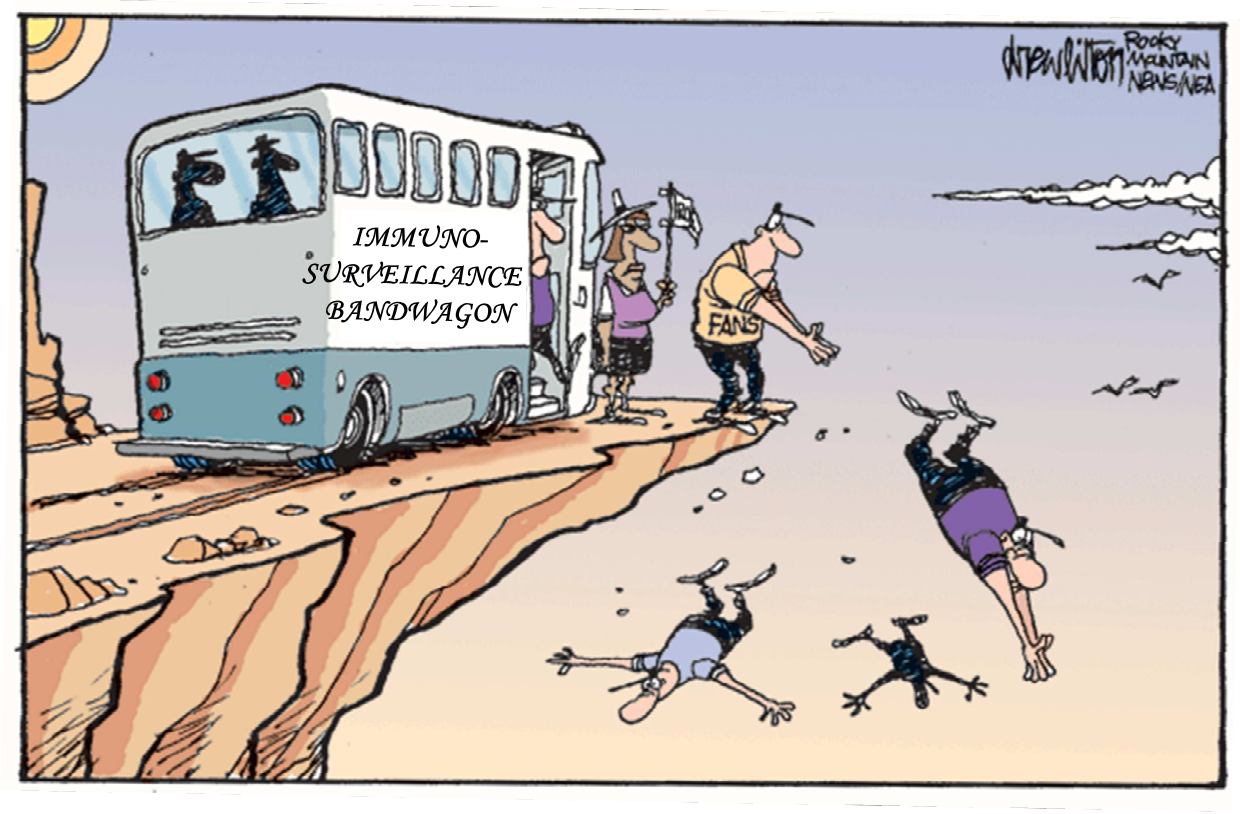


The Premature Demise of the Cancer Immunosurveillance Hypothesis (c.1973)

Osias Stutman used these observations to argue against Cancer Immunosurveillance:

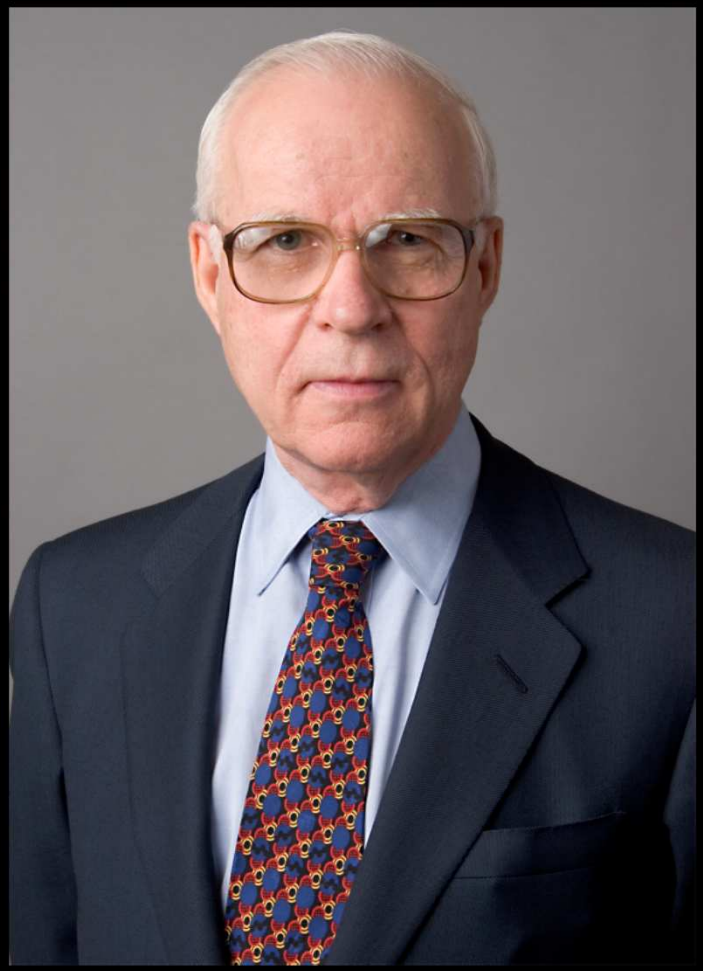
- *Nude CBA/H mice did not show higher rates of spontaneous tumors compared to wild type mice.*
- *Nude CBA/H mice did not develop more chemically-induced tumors compared to wild type mice nor did they show shortened latency periods for tumor generation.*

Jumping Off the Cancer Immunosurveillance Bandwagon (c. 1973)



Cancer Immunosurveillance: "Twenty" Years of Solitude

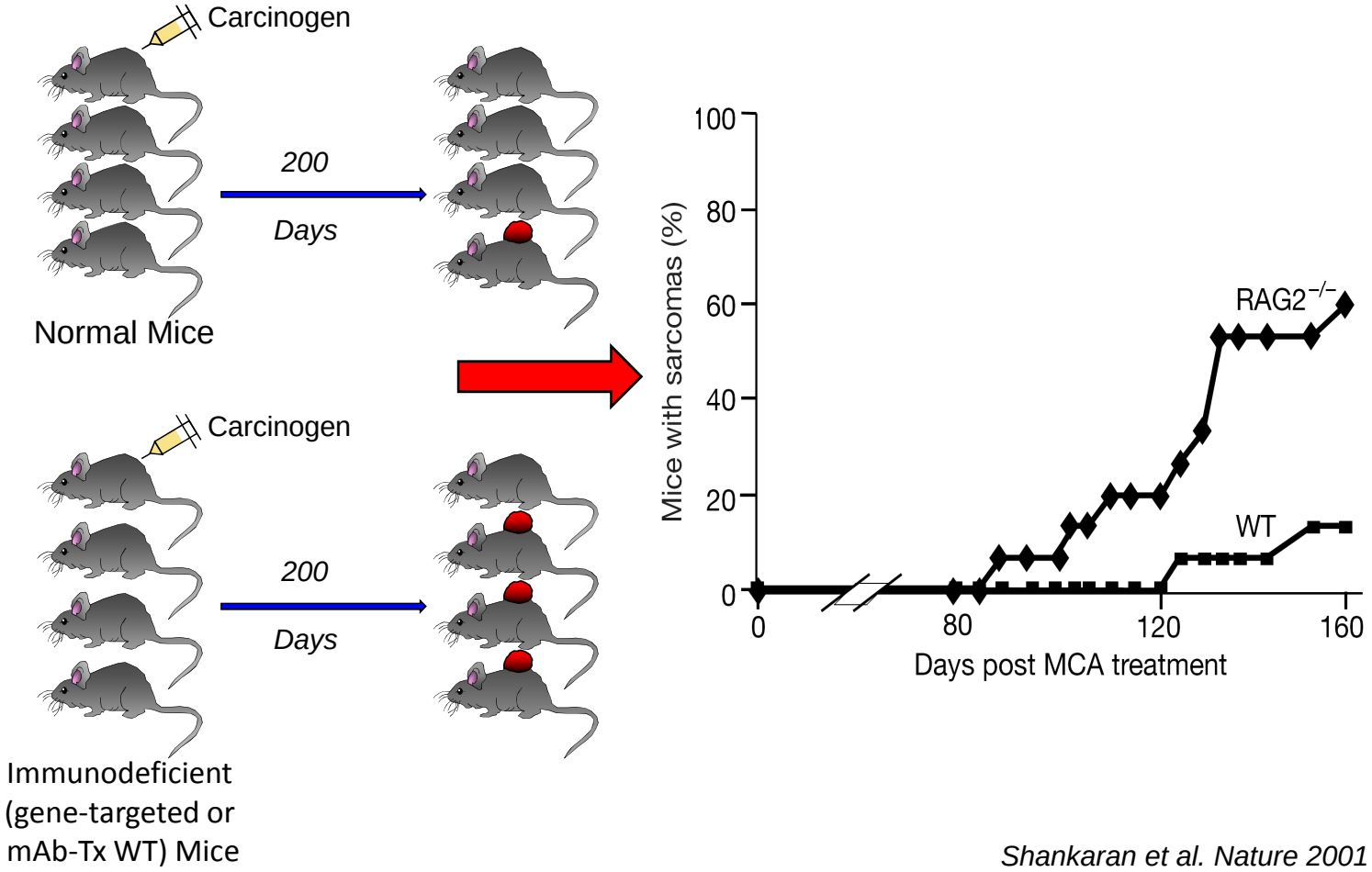
Lloyd J. Old



Why Reinvestigate the Cancer Immunosurveillance Hypothesis?

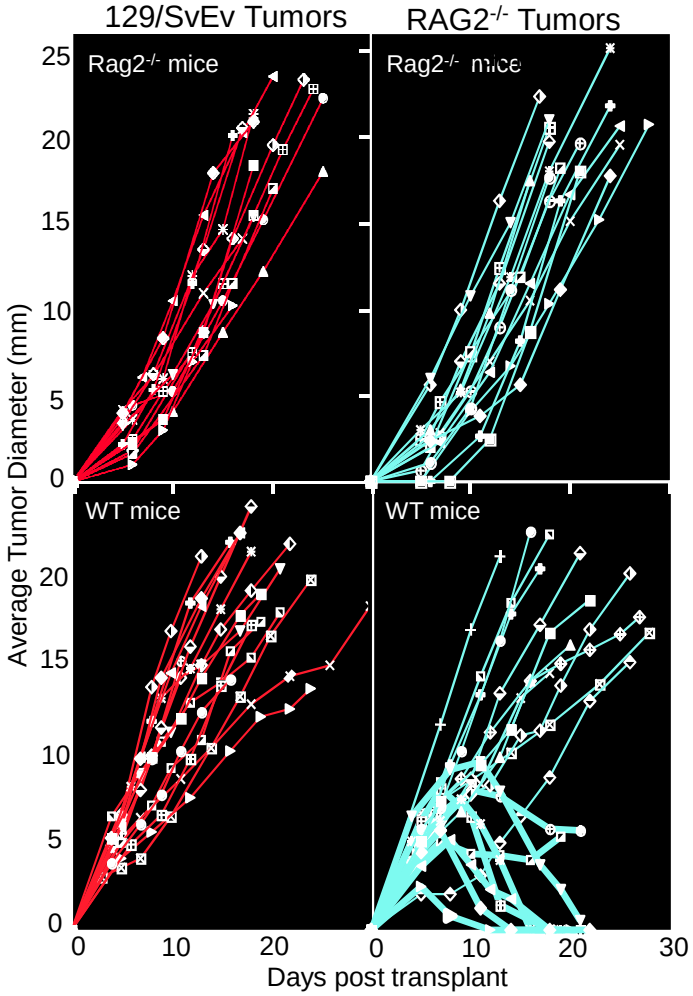
- Demonstration that IFN-γ plays a critical role in preventing outgrowth of certain tumor types
- Realization that Nude CBA/H mice used by Stutman were not ideal models of immunodeficiency
- Generation of better mouse models of immunodeficiency
- Generation of mAbs capable of blocking innate or adaptive immunity in WT mice
- Defining the chemical nature of tumor specific antigens

Experimental Support for Cancer Immunosurveillance



Shankaran et al. Nature 2001

Evidence That Editing of Tumor Cell Immunogenicity Promotes Tumor Outgrowth

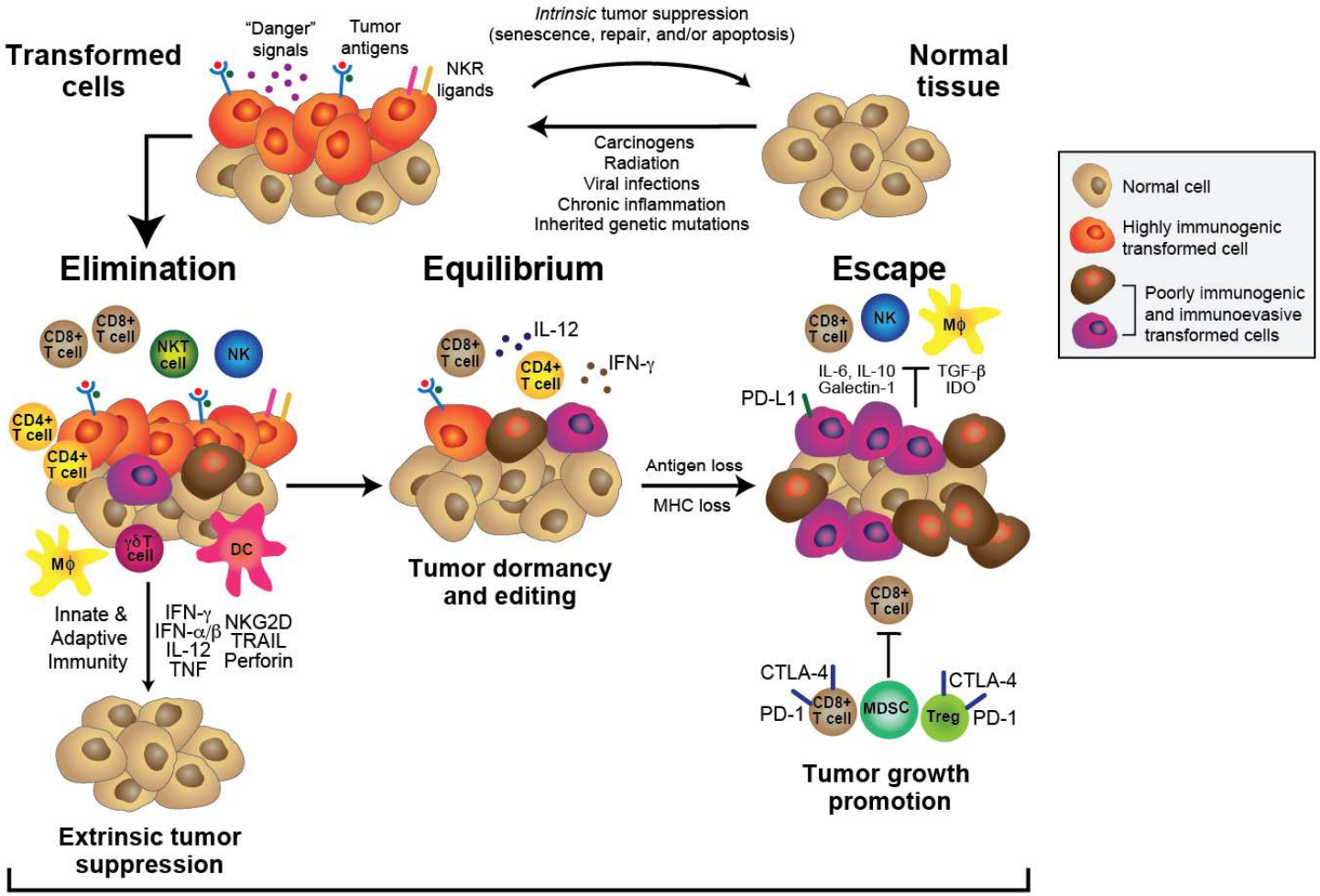


Tumors from RAG2$^{-/-}$mice are "unedited" (display high immunogenicity) and thus are good models of nascent tumors.

Tumors from WT mice are "edited" (display reduced immunogenicity) and thus are models of clinically apparent, mature tumors.

Shankaran et al, Nature 2001

The 3 Es of Cancer Immunoediting



Schreiber, Old and Smyth, Science 2011

Defining Cancer Immunoediting
Targets and Mechanisms

What are the targets of cancer immunoediting and by what mechanism does editing occur?

LETTER

doi:10.1038/nature10755

Cancer exome analysis reveals a T-cell-dependent mechanism of cancer immunoediting

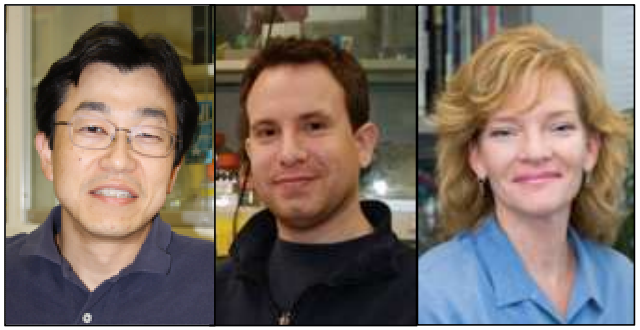
Hirokazu Matsushita[1]†*, Matthew D. Vesely[1]*, Daniel C. Koboldt[2], Charles G. Rickert[1], Ravindra Uppaluri[3], Vincent J. Magrini[2,4], Cora D. Arthur[1], J. Michael White[1], Yee-Shiuan Chen[1], Lauren K. Shea[1], Jasreet Hundal[2], Michael C. Wendl[2,4], Ryan Demeter[2], Todd Wylie[2], James P. Allison[5,6], Mark J. Smyth[7,8], Lloyd J. Old[9], Elaine R. Mardis[2,4] & Robert D. Schreiber[1]

Nature 482:400-404 (2012)

- Used exome and transciptome sequencing and epitope prediction to show that a R913L point mutation in Spectrin-β2 formed a highly antigenic tumor specific mutant antigen (TSMA) responsible for spontaneous rejection of the d42m1 unedited MCA sarcoma

- d42m1 tumor cell variants that escape in vivo elimination lack mutant Spectrin–β2 expression

- Cancer immunoediting occurs via T cell mediated immunoselection



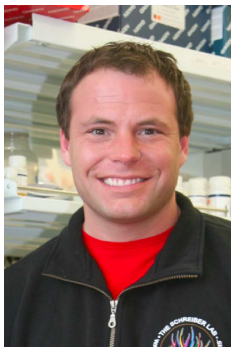
Hirokazu Matsushita **Matthew Vesely** **Elaine Mardis**

Moving from Natural Resistance to Cancer to Therapeutically Induced Cancer Control

Can edited tumors be controlled by checkpoint blockade immunotherapy?

If so what are the antigenic targets of T cells that are reinvigorated by this therapy?

Can we improve upon checkpoint blockade therapy?



Matthew Gubin

LETTER

doi:10.1038/nature13988

Checkpoint blockade cancer immunotherapy targets tumour-specific mutant antigens

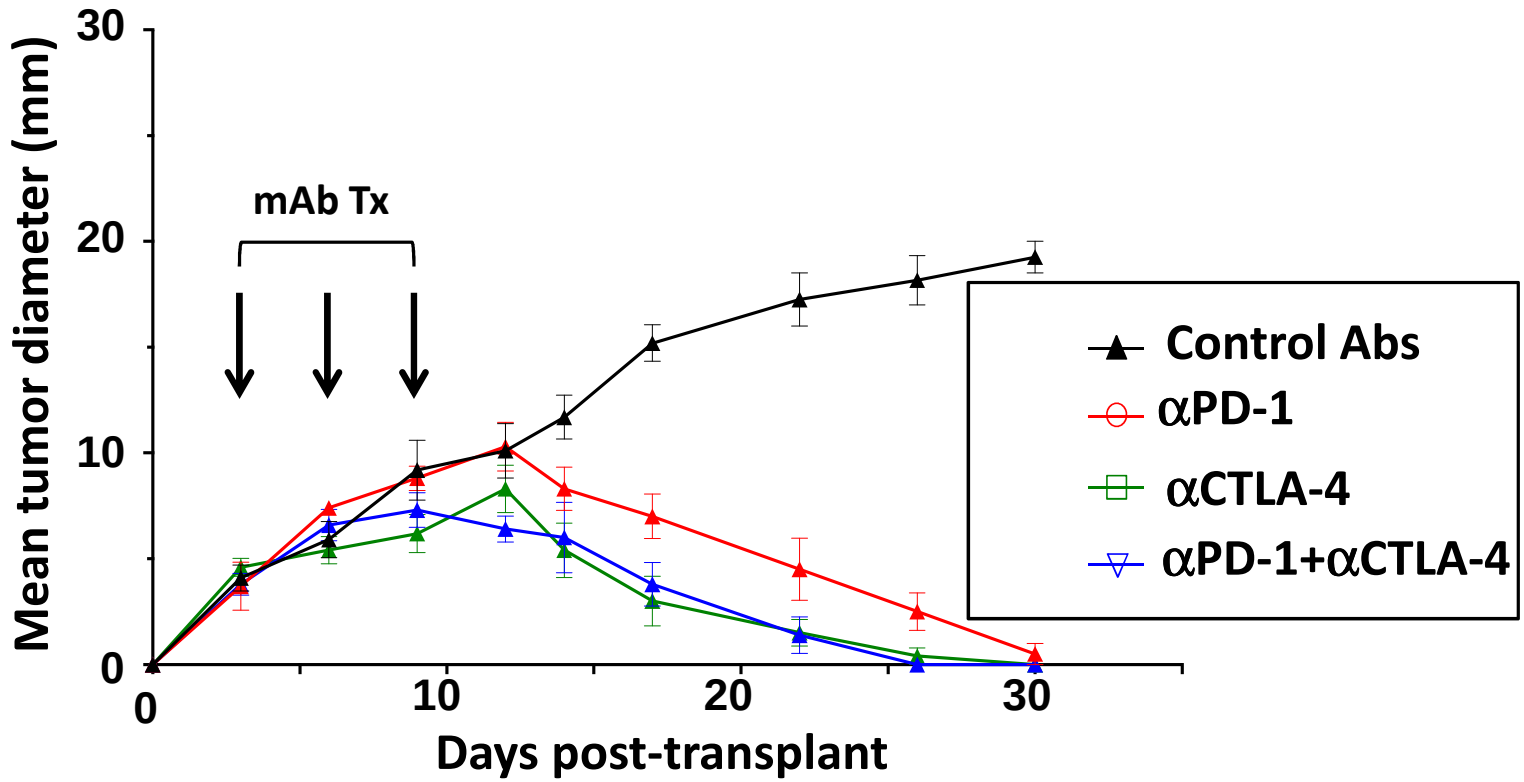
Matthew M. Gubin[1], Xiuli Zhang[2], Heiko Schuster[3], Etienne Caron[4], Jeffrey P. Ward[1,5], Takuro Noguchi[1], Yulia Ivanova[1], Jasreet Hundal[6], Cora D. Arthur[1], Willem-Jan Krebber[7], Gwenn E. Mulder[7], Mireille Toebes[8], Matthew D. Vesely[1], Samuel S. K. Lam[1], Alan J. Korman[9], James P. Allison[10], Gordon J. Freeman[11], Arlene H. Sharpe[12], Erika L. Pearce[1], Ton N. Schumacher[8], Ruedi Aebersold[4,13], Hans-Georg Rammensee[3], Cornelis J. M. Melief[7,14], Elaine R. Mardis[6,15], William E. Gillanders[2], Maxim N. Artyomov[1] & Robert D. Schreiber[1]

Nature 515:577-581 (2014)

Max Artyomov

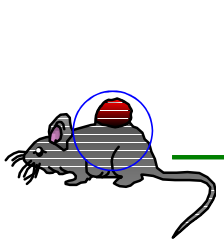
- Edited tumors are susceptible to cancer immunotherapy
- Whole exome sequencing/RNA-Seq + epitope prediction can identify tumor specific mutant antigens (TSMA) in edited tumors
- TSMA are favored targets for T cells activated by checkpoint blockade
- Personalized cancer vaccines targeting TSMA are specific and safe and can be as effective as checkpoint blockade therapy

Edited T3 MCA Sarcoma Cells Are Rejected in Mice Following Checkpoint Blockade Immunotherapy



Gubin et al. Nature 2014

Current Method for Predicting and Validating Mutational Class I Epitopes



Tumor

Whole Exome Sequencing + RNA-Seq

Tumor vs Normal

ID Expressed mutations

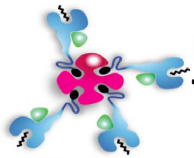
Epitope Prediction:

Use multiple (3) algorithms, median binding affinity to MHC I

Apply Filters

- *Processing*
- *Neo-epitopes*
- *Hypothetical proteins*

Synthesize Peptides



p-MHC-I Tetramers

or

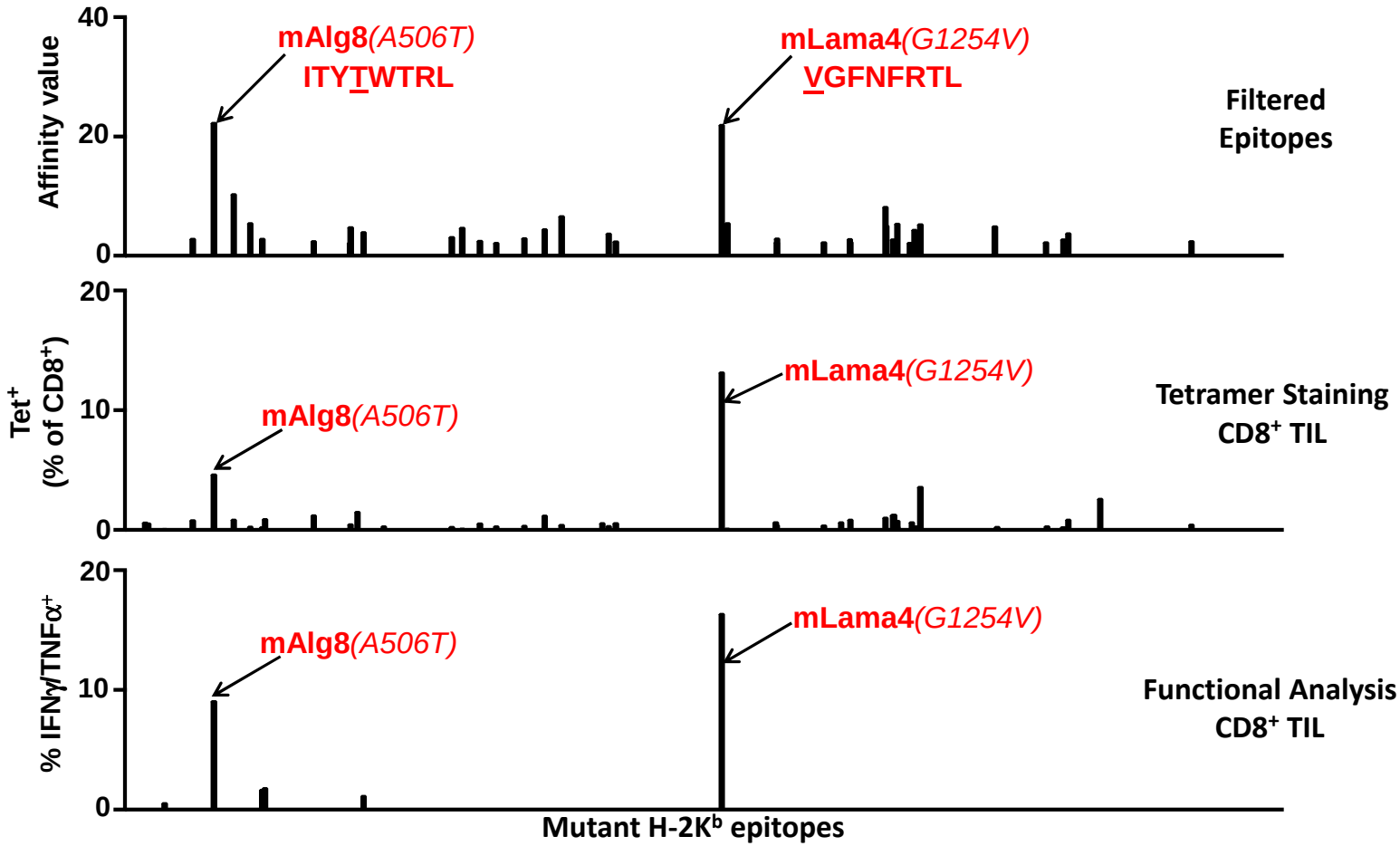
CD8⁺ TILs Ex Vivo

Analyze

Peptide-pulsed irrad splenocytes

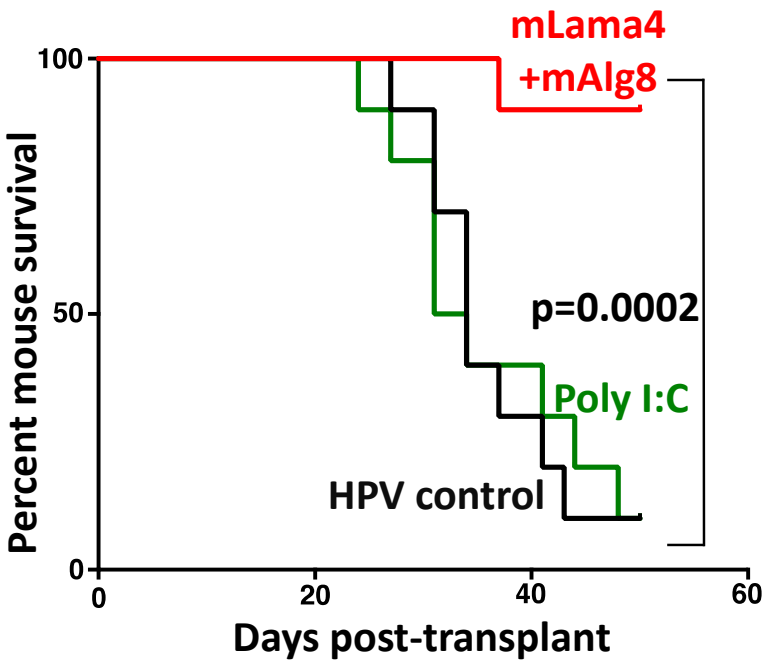
Gubin et al. Nature 2014

Rapid Identification and Validation of Dominant Tumor Specific Mutant Antigens in T3 MCA Sarcomas



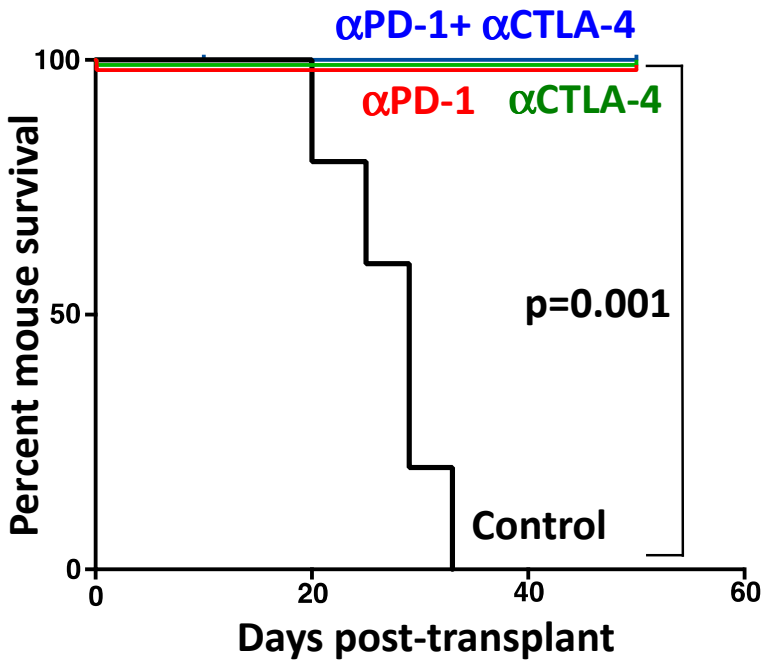
Comparable Efficacies Between Checkpoint Blockade and Personalized Cancer Vaccines

Tumor-Specific Antigen Vaccine



SLP Vaccine on d+3, +9, +15, +21

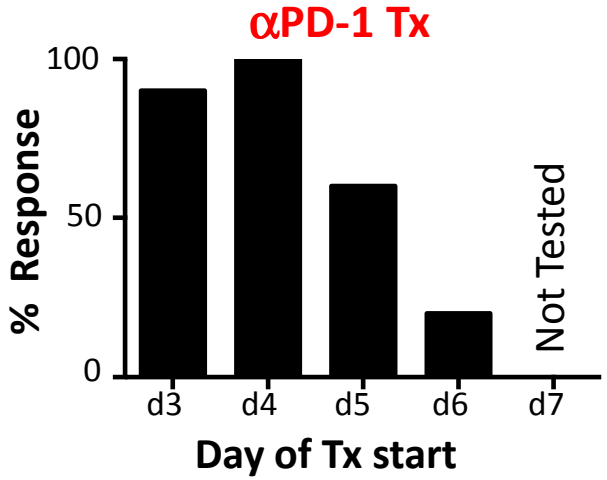
Checkpoint Blockade Therapy

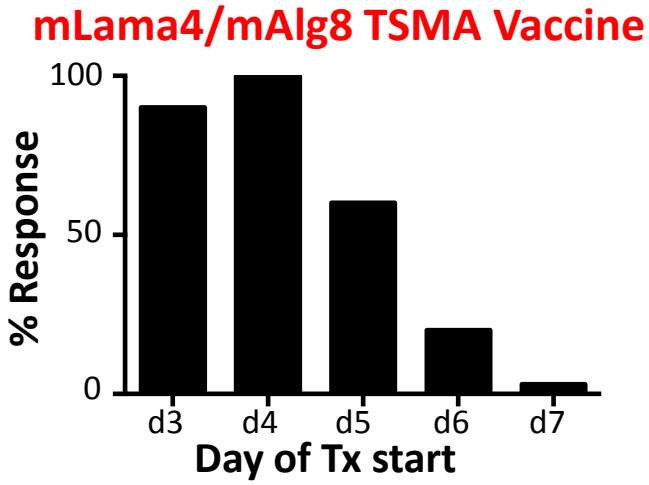


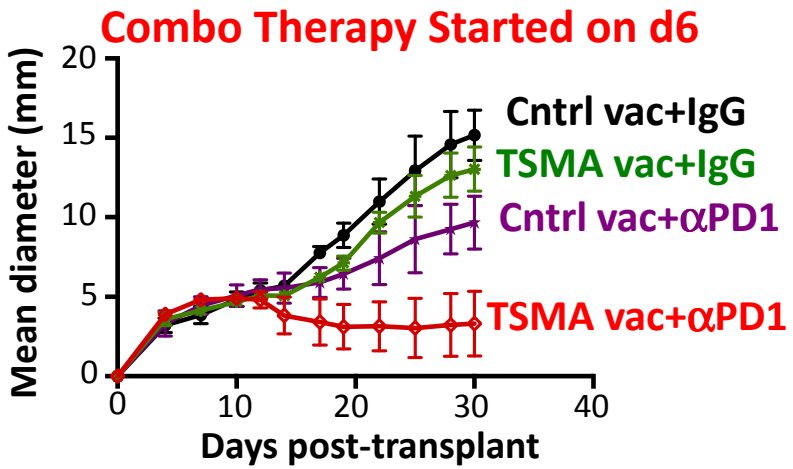
Checkpoint mAbs on d+3, +6, +9

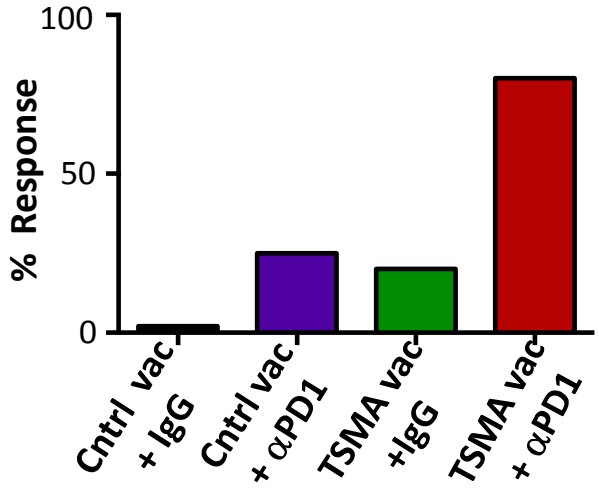
Gubin et al. Nature 2014

Tumor Specific Mutant Neoantigen Vaccine Extends the Anti-PD-1 Therapeutic Window for T3







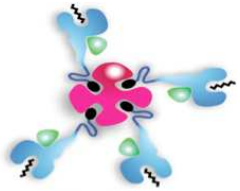


Eight Week Time Frame from Biopsy to Personalized Cancer Vaccine

Exome sequence
+ RNA-Seq
tumor vs normal
2 weeks

Data analysis
Select candidate epitopes
2 days

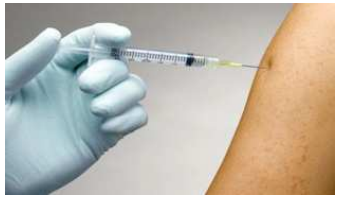
Short peptide
synthesis
2 weeks



Tetramer
Generation
2 days

Analyze PBL for
neoantigen specific T cells
4 days

Long peptide
vaccine synthesis
3 weeks



Initiate vaccine
treatment

Take Home Messages

- The immune system protects against cancer development and shapes cancer immunogenicity via Cancer Immunoediting
- Highly antigenic, tumor specific antigens are favored targets of cancer immunoediting (some are mutant neoantigens)
- After cancer immunoediting, cancers display reduced (but not absent) immunogenicities but often can be controlled by immunotherapy
- Mutant neoantigens remaining in tumors after editing are favored targets of T cells reinvigorated by checkpoint blockade therapy
- Personalized cancer immunotherapies (vaccines/ACT) targeting tumor specific mutant neoantigens are now possible *and are currently being explored in the clinic*

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