# Experimental models of immune landscape

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# Question 1:

1. What are the advantages and limitations of humanized mice in immunotherapy? What is the basic immunology of immune deficient mice? –Led by Dr. Lenny Shultz

# Advantages of Humanized Mice in Immunotherapy

Supports in vivo testing of human immunotherapeutics against human targets without putting patients at risk

Can test checkpoint blockade inhibitors

Supports in vivo testing of personalized medicine

Can be used to test safety of immunotherapeutics

Cen test IPS-cell-derived therapeutics

Can genomically edit the mice for specific approaches

# Limitations of Humanized Mouse Models

**Engraftment with PBMC**

- mature T cells  cause xenogeneic GVHD

**Engraftment with HSC**

- T cell education in context of mouse MHC (H2) antigens
- Lack of human cytokines impairs HSC growth & differentiation

**Engraftment with fetal human tissues**

- Wasting disease develops after 4-5 months
- Ethical constraints

**Suboptimal lymphoid architecture and immune function**

- Poor lymph node devt, lack of FDCs  no germinal centers
- Low levels of humoral immunity, impaired Ig class switching

# Next Generation Humanized Mice

**Tg expression of human factors**

Cytokines
HLA molecules
Microenvironmental factors
Hormones

**Reduced mouse innate immunity & HSC function**

MHC class I and II
Cytokines
Macrophages
Granulocytes
Dendritic Cells
Chemokine receptors
Interferon receptors
Toll-like receptors
c-Kit receptor
Thymus

**Increased Innate Immunity**

Restore hemolytic complement

**Mouse stromal marker**

Ubiquitous GFP expression

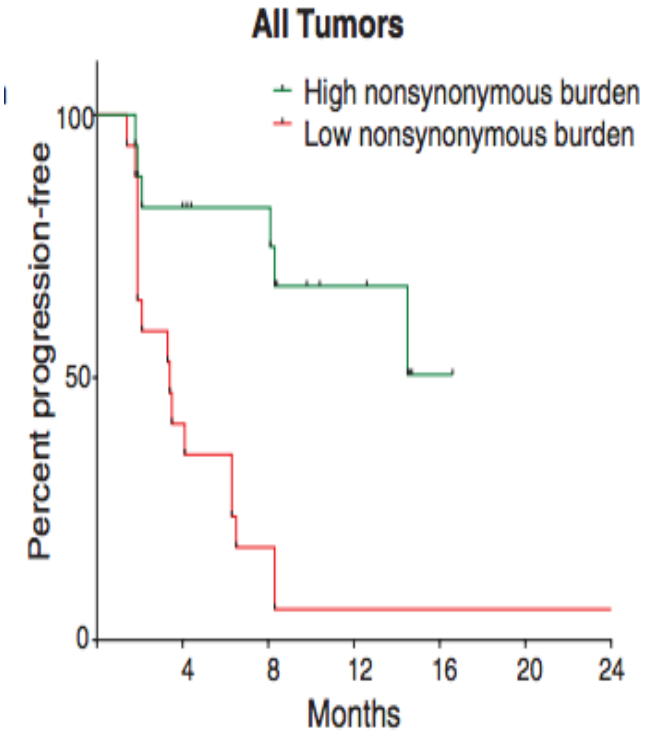
# Human Cytokines Expressed in Humanized Mice Support Human HSC Differentiation

| Human cytokine(s) | Cell populations targeted |
|---|---|
| Membrane-bound SCF | Hematopoietic stem cells (HSC), mast cells |
| SCF, IL-3, GM-CSF (SGM3) | HSC, myeloid cells, mast cells |
| BAFF | B cells |
| Thrombopoietin | HSC, platelets |
| IL2 | T cells and NK cells |
| IL-6 | Plasma cells |
| IL7 | T cells |
| IL15 | NK cells |
| FLT3L | Dendritic cells |
| CSF1 | Macrophages |

# Questions:

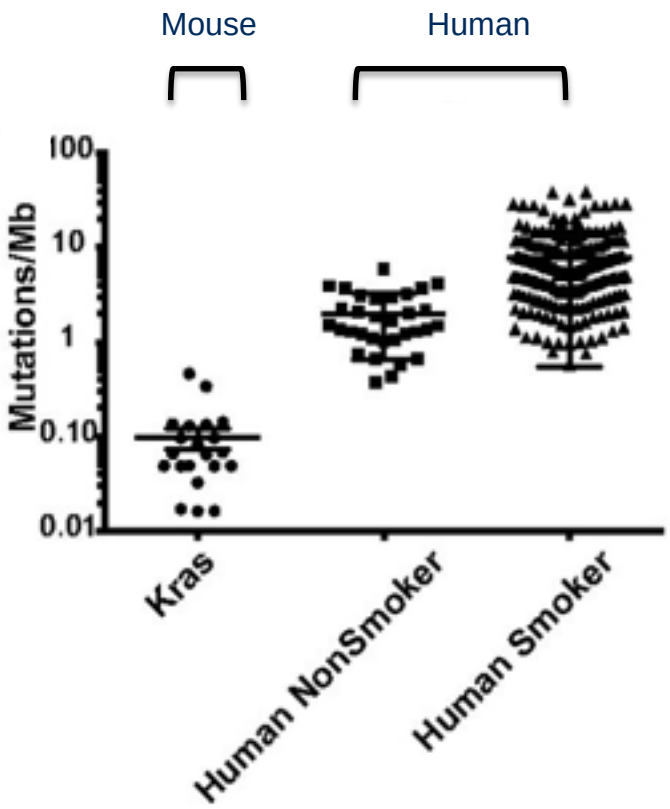
2. What are the available GEMM and carcinogen induced mouse models in immunotherapy space? What are the advantages and limitations of those models?  ---Led by Dr. Kate Politi

# Mutation Burden Correlates to Higher Response to PD-1 Inhibitors



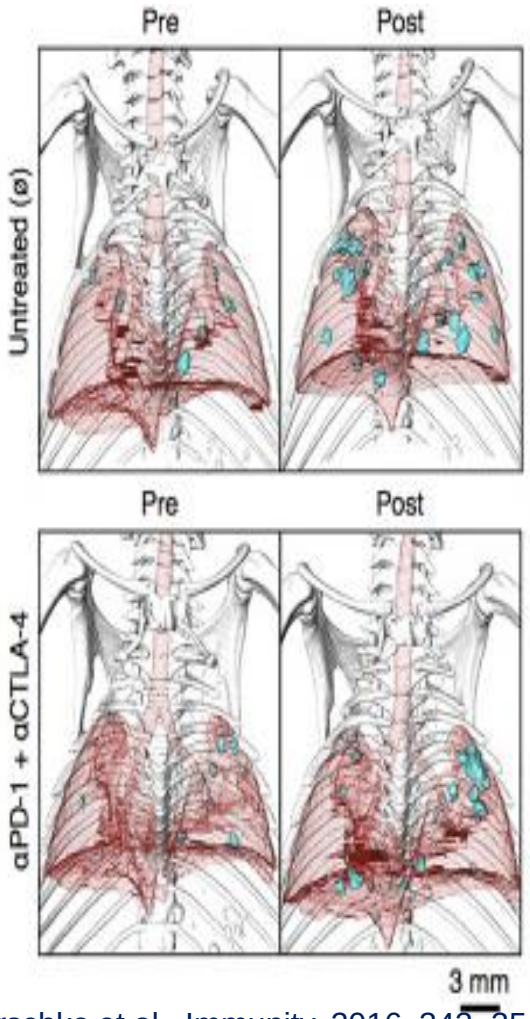

Rizvi et al., Science 2015

**Mouse model vs. Human tumor mutation load**




McFadden et al, PNAS 2016

***Kras, p53***




Pfirschke et al., Immunity, 2016, 343–354

# Initiatives to Increase the Tumor Mutation Burden in Cancer Models

Generating murine lung tumors models that better **model sensitivity and resistance to immune checkpoint inhibitors**

Introduce defects in DNA repair genes

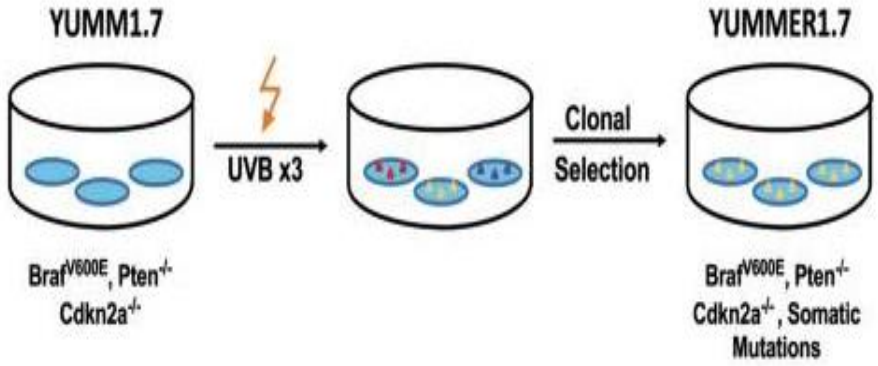
e.g. Germano et al., Nature. 2017 Dec 7;552(7683):116-120.

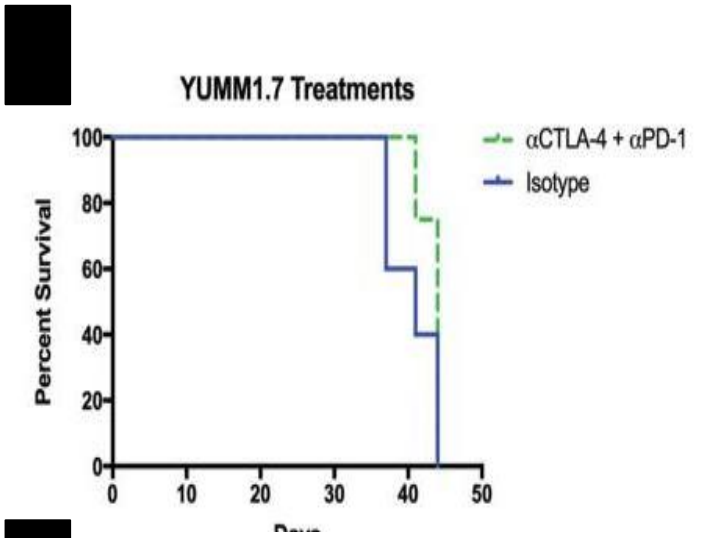
Carcinogen treatment

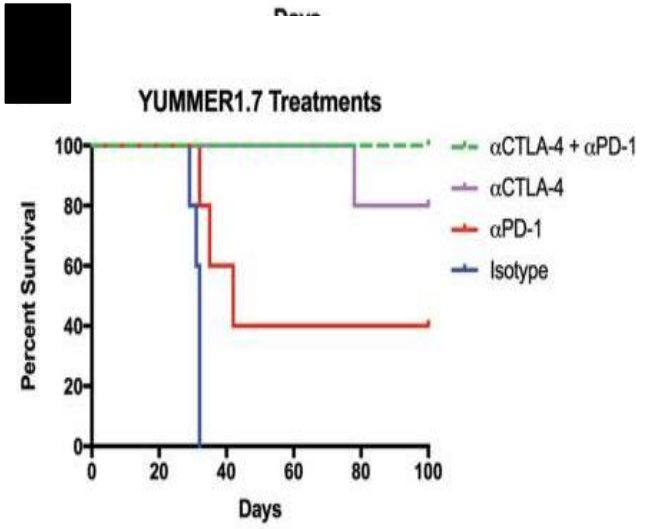
UV Irradiation

e.g. Wang et al., Pigment Cell Melanoma Res. 2017 Jul;30(4):428-435.

# UV-induced Mutations Elicit a Functional T cell Response in a Mouse Melanoma Model

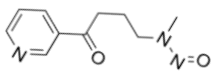



Wang et al., Pigment Cell Melanoma Res. 2017 Jul;30(4):428-435.

# Creating Genetically Diverse Tumors Through Carcinogen Administration

NNK 

(4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone):

**Naturally occurring tobacco product**

**Pros**: single injection; tumors harvested @ 20-40 weeks :*Kras*$^{G12}$ mutation induction

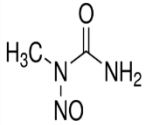
**Cons:** uncharacterized WES

MNU (*N*-Nitroso-*N*-methylurea)

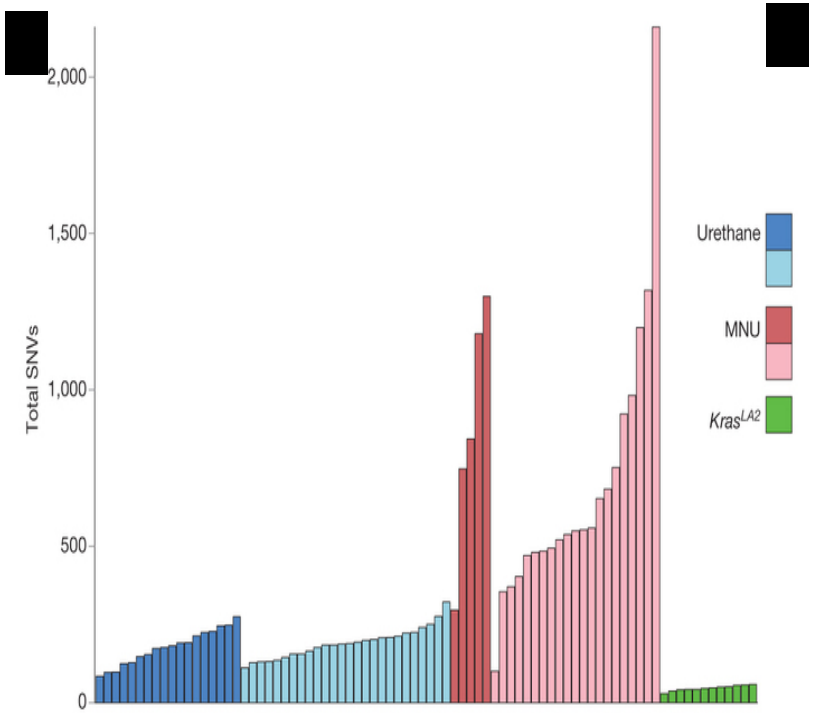
**~400-800 mutations**

**Pros**: single injection; *Kras*$^{G12}$ mutation induction; tumors harvested at 20 weeks

**Cons**: weight loss

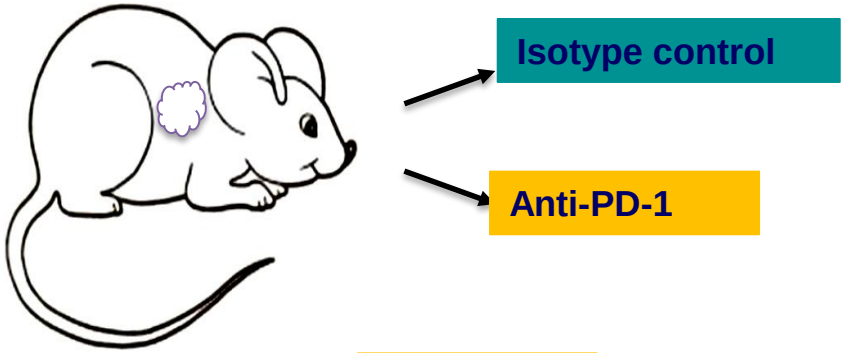


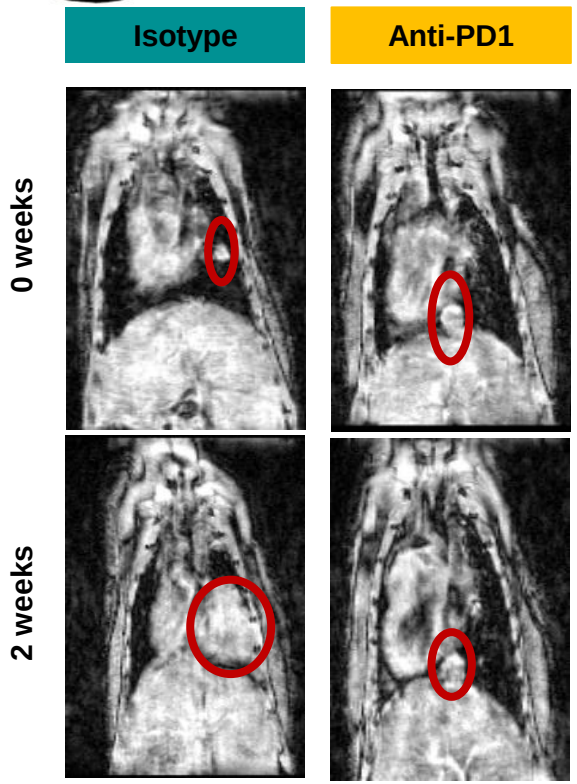

**Elevated mutation load in carcinogen-induced lung adenocarcinomas**

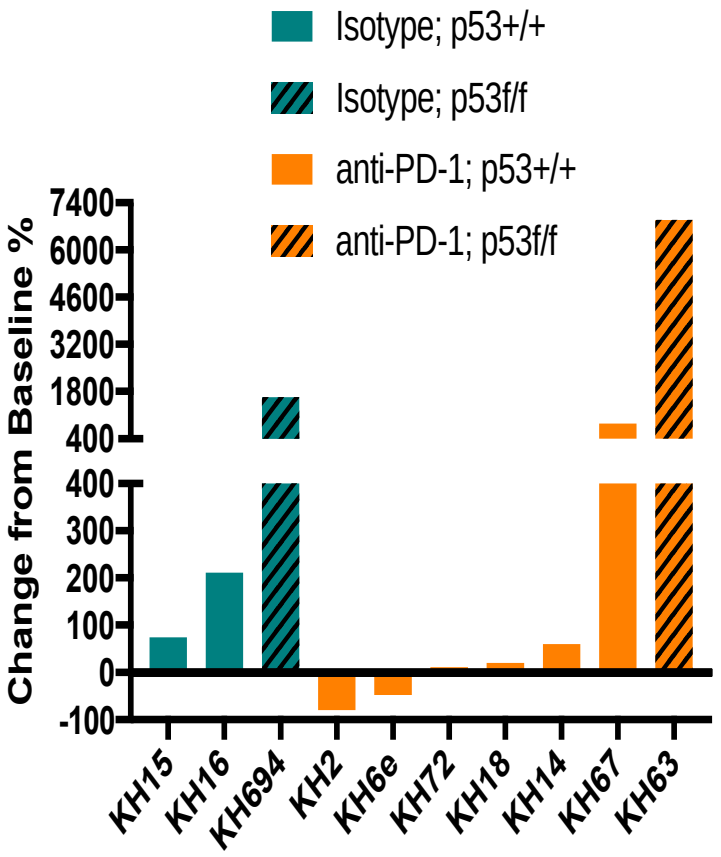



Westcott et al., Nature (2015)

# Tumor Control in Carcinogen-Induced Lung Tumors Following Immune Checkpoint Blockade




Katherine Hastings, unpublished

Do Not Post

# Question 3:

3. What are better mouse models to enhance correlation to clinical efficacy? – Vaccine as example – Led by Dr. Karolina Palucka

# Vaccine adjuvants:
# Activation of innate immunity

- **How the differences between mouse and human innate sensing impact development of adjuvants?**
- **What are the right models?**
- **Why vaccines that work in the mouse are failing in phase III?**

INFORMAL- DO NOT POST

Some conclusions from NCI workshop October 2017 (Bult, Marks, Liu et al)

- Current state of models in immuno-oncology: the good and bad
  - Models have helped us with important insights
  - Existing models have significant limitations
  - No consensus on a single model or approach (match model to the question)
- Challenges for adoption of model systems and data integration
  - How we move forward is as important as what questions we pursue
  - **Phenotyping standards (how to measure) and data standards (how to report measurements).**
- Challenges (opportunities) for model improvement
  - Many possibilities for research into basic biology with clinical relevance

Conclusion

# Embrace the Complexity!