
SITC
2017
November 8-12
NATIONAL HARBOR
MARYLAND
Gaylord National Hotel
& Convention Center
sitc
Society for Immunotherapy of Cancer

Cancer vaccines: What we need, what we have, and how we might do it better.

Ross M. Kedl

Professor

University of Colorado Denver

Goals

1. Appreciate our current understanding of the requirements for successful T cell-mediated cancer therapy
2. Become familiar with some current approaches to vaccination against cancer.
3. Appreciate and understand T cell-specific vaccine principles for designing and developing better cancer vaccines.

- Do we need T cells?

Duh

- How Many T cells do we really need to make?

More than you want to admit…

- What kind should we make?

Self renewing T_{SCM} or T_{CM}

- How should we make them?

1- antigen dose and duration… Stop starving T cells and avoid long-lasting emulsions

2- target DCs/enhance cross-presentation

3- use adjuvants that induce IL-27

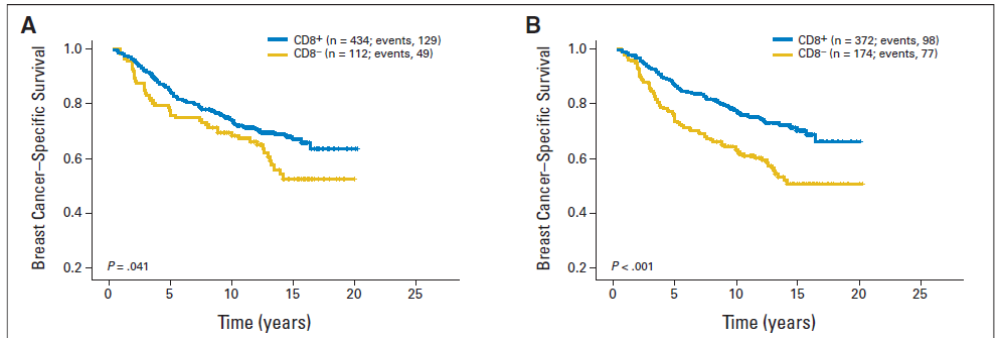
4- and CD80/86 (CD28 stimulation)

5- engage TNFR superfamily members

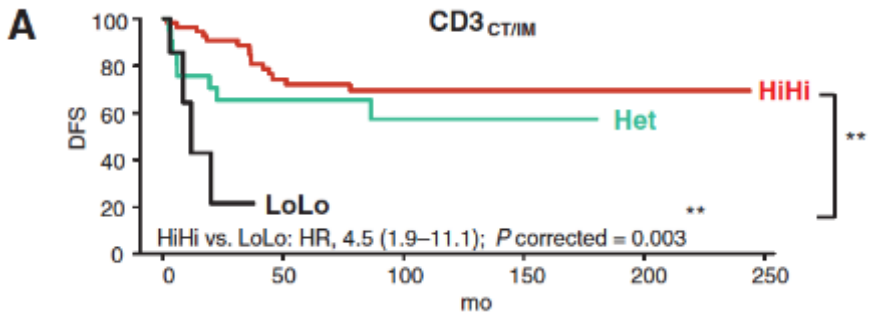
6- IL-21 for ACT

- Do we need T cells?
- How Many T cell do we really need to make?
- What kind should we make?
- Is anything working?
- How could we make them better?

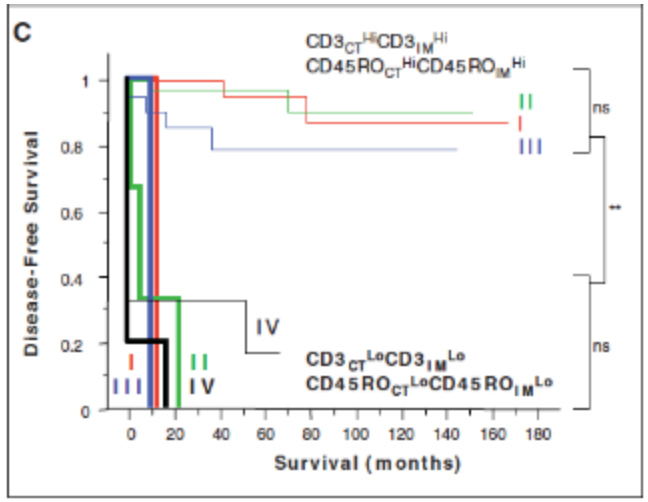
T cell activity and clinical outcomes



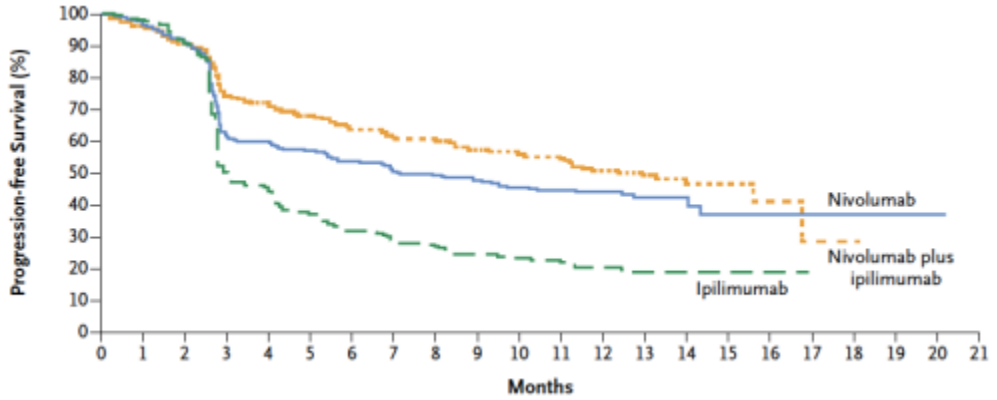
Mahmoud et al, JCO 2011



Anitei et al. CCR 2014



Galon et al. Science 2006



LETTER

doi:10.1038/nature13954

PD-1 blockade induces responses by inhibiting adaptive immune resistance

Larkin et al. NEJM 2015

Conclusion

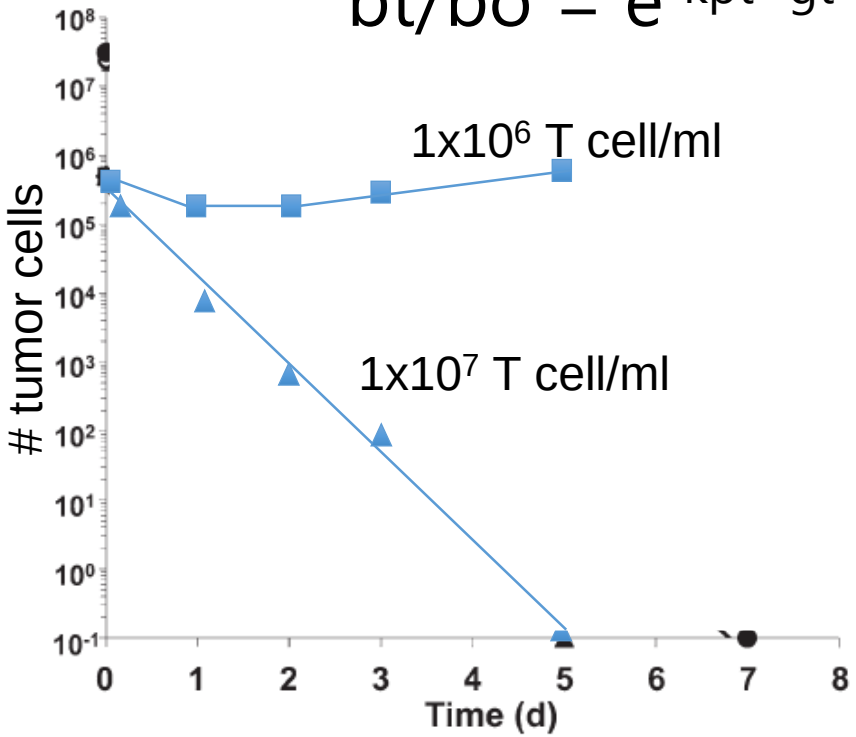
- Do we need T cells?

Therapeutic efficacy against cancer requires T cell activation and function

- Do we need T cells?
- How Many T cells do we really need to make?
- What kind should we make?
- Is anything working?
- How could we make them better?

T cell numbers and Immune protection

$$bt/bo = e^{-kpt+gt}$$

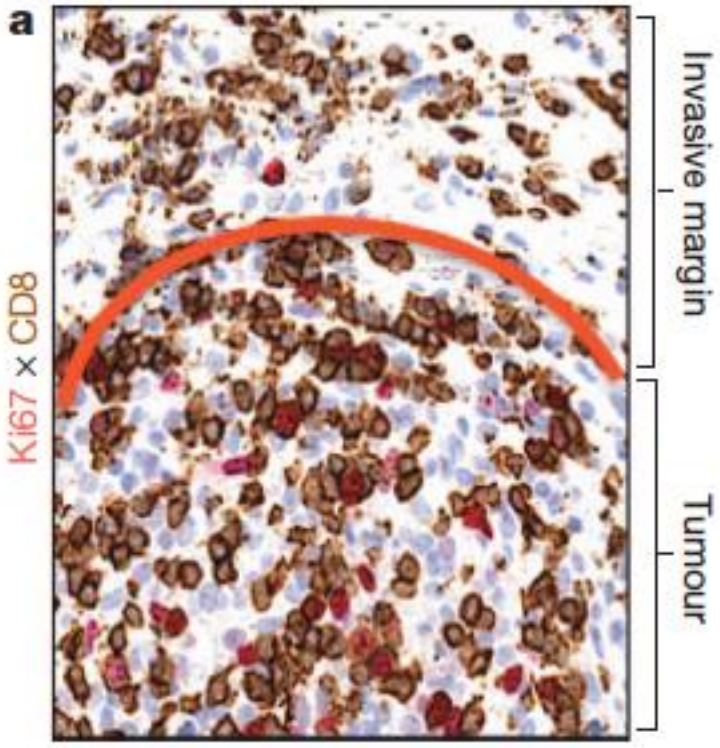


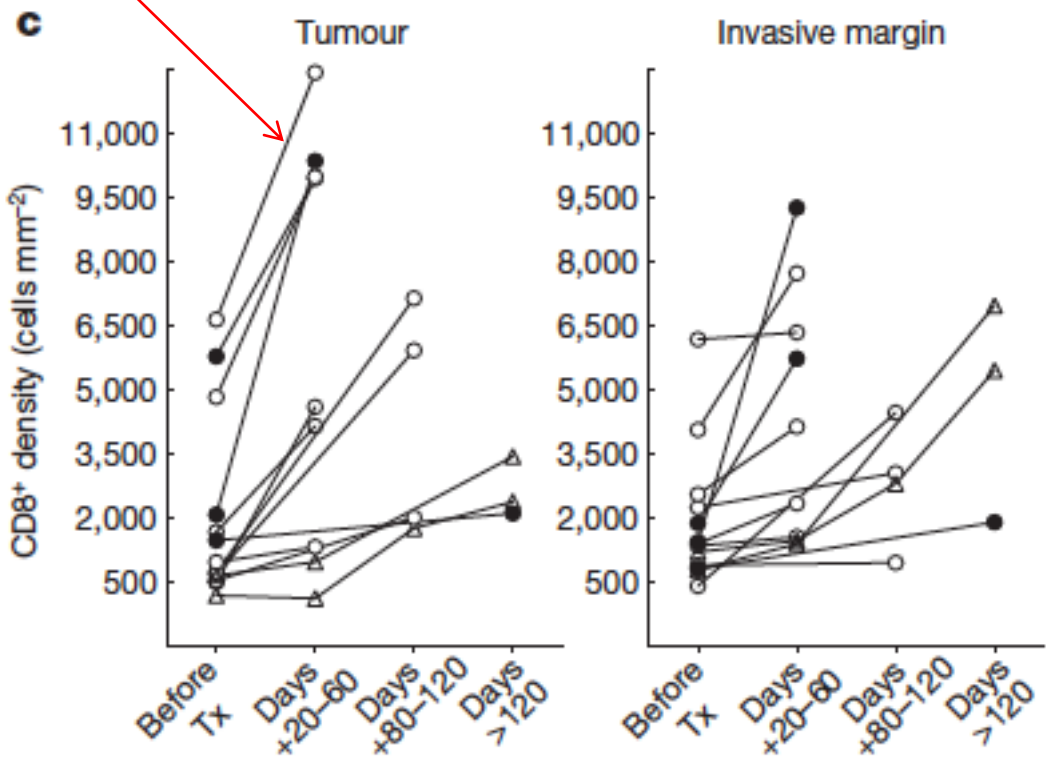
Budhu et al.
J Exp Med.
2010

"…a concentration of ≥10^7 [T] cells/ml … is required to produce sterilizing immunity…"

T cell numbers and Immune protection

~1x10^6/ml

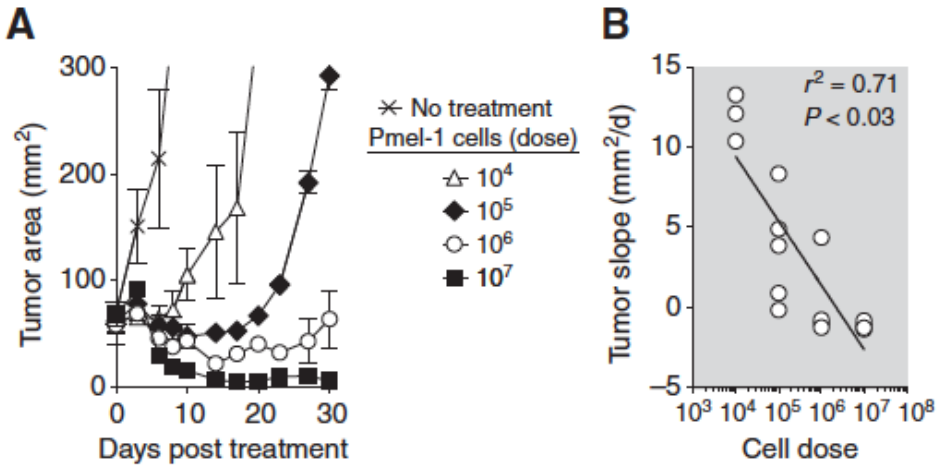




Tumeh et al. Nature 2014

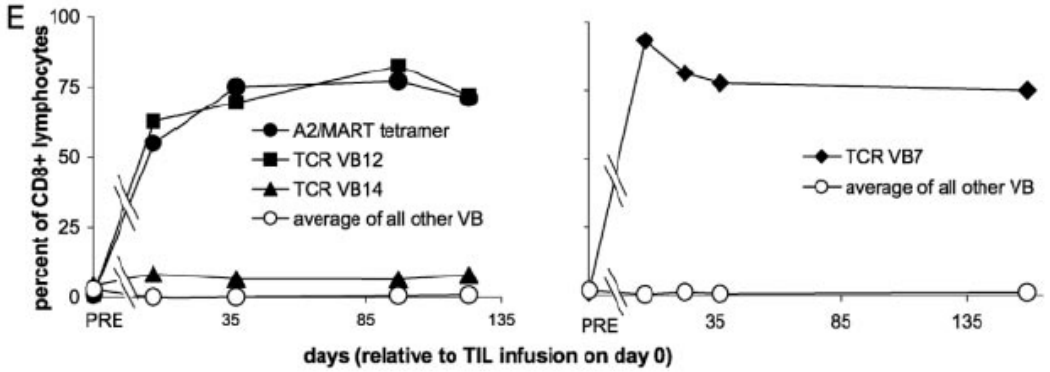
T cell numbers and Immune protection

Mouse ACT



Klebanoff et al. Clin. Can. Res. 2011

Human ACT



M. E. Dudley et al., Science 298, 850–854 (2002).

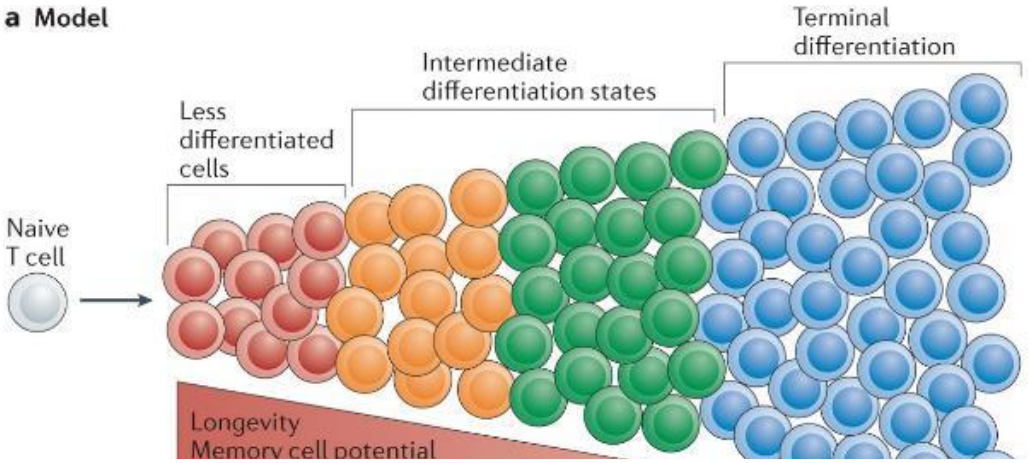
Conclusion

- How Many T cells do we really need to make?

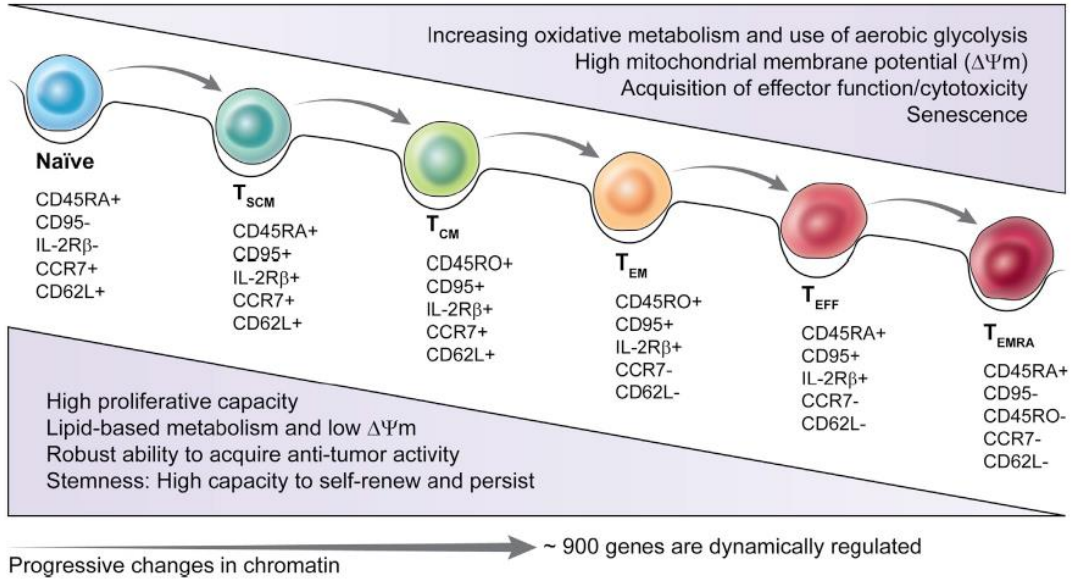
Lots… ~10^6-10^7 T cells/cm^3

- Do we need T cells?
- How Many T cell do we really need to make?
- What kind should we make?
- Is anything working?
- How could we make them better?

Lineages and inter-relationships among memory subsets

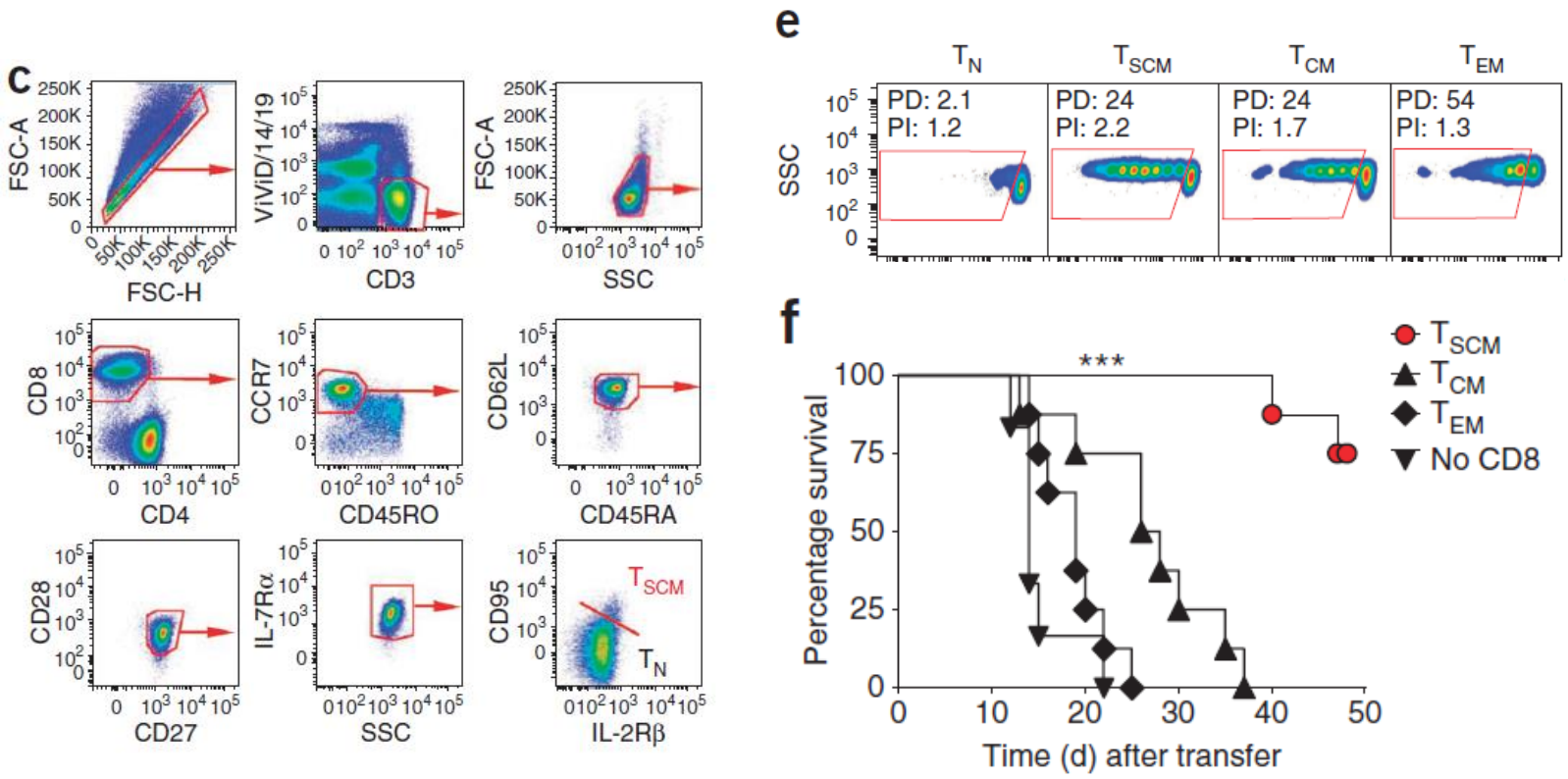


Kaech & Cui
Nat Rev Imm 2012



Kishton et al.
Cell Metab. Rev. 2017

Stem cell memory- superior self renewal and persistence



Gattinoni et al. 2011

nature medicine

Conclusion

- What kind should we make?

Self renewing memory cells- T_{SCM} or T_{CM}

- Do we need T cells?
- How Many T cell do we really need to make?
- What kind should we make?
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Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer

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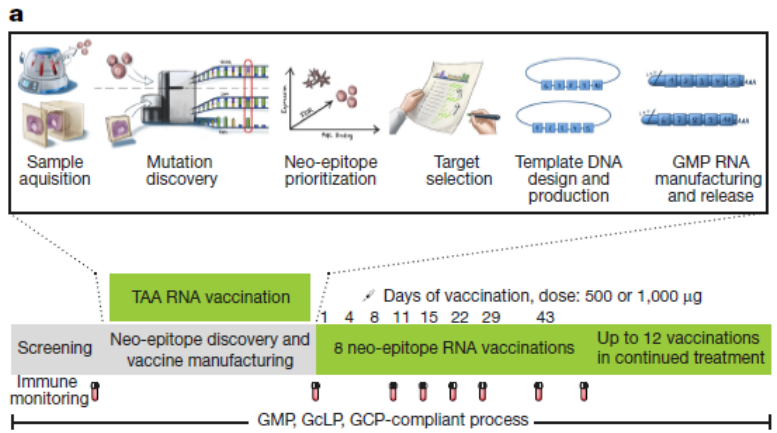

doi:10.1038/nature23003

An immunogenic personal neoantigen vaccine for patients with melanoma

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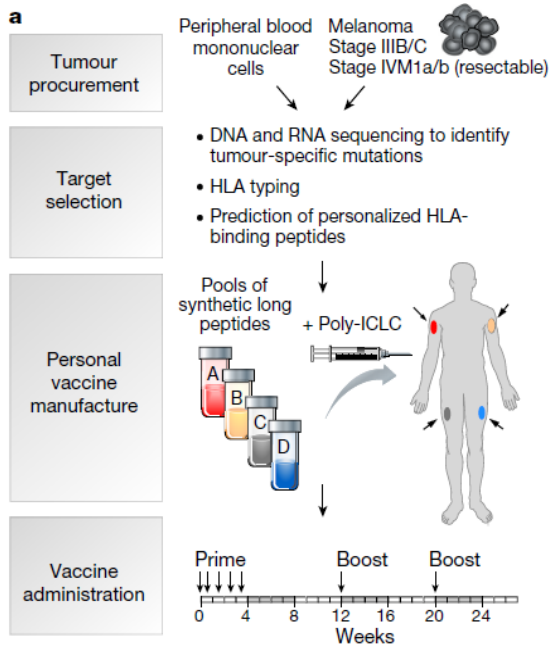

doi:10.1038/nature22991

CANCER IMMUNOTHERAPY

A dendritic cell vaccine increases the breadth and diversity of melanoma neoantigen-specific T cells

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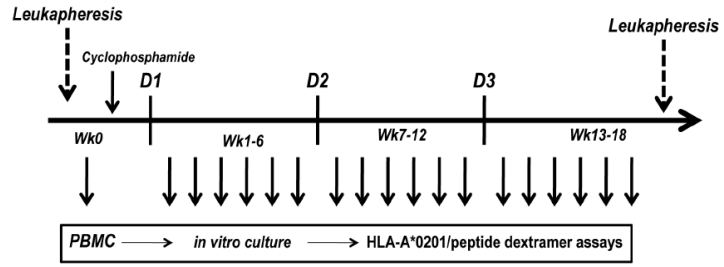

SCIENCE sciencemag.org
15 MAY 2015 • VOL 348 ISSUE 6236 803

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Lancet 2015; 386: 2078–88
Published Online
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http://dx.doi.org/10.1016/
S0140-6736(15)00239-1

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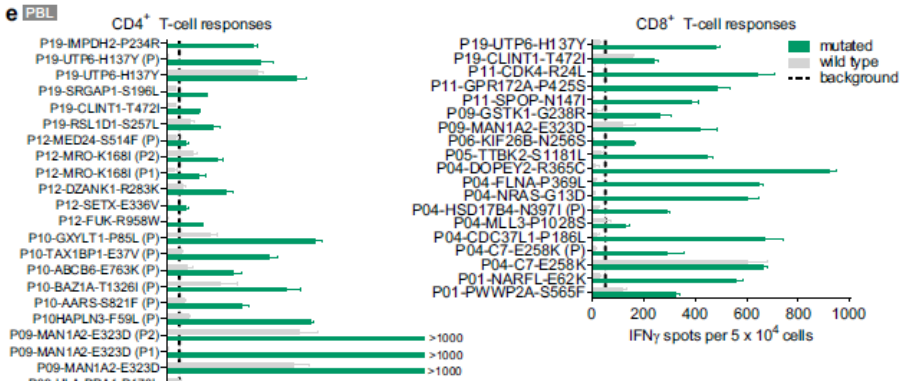

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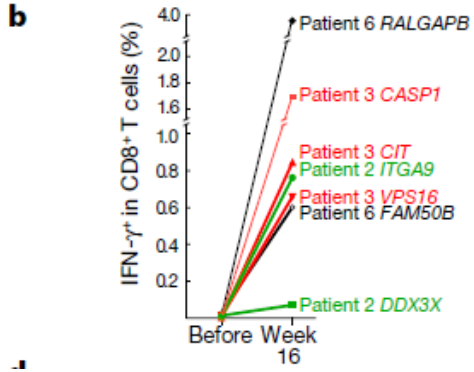

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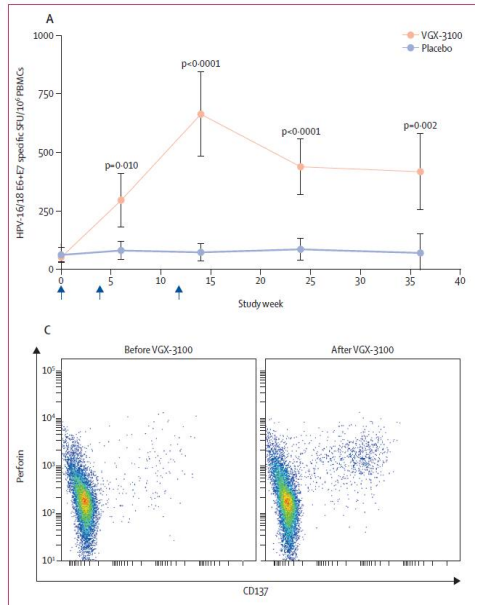

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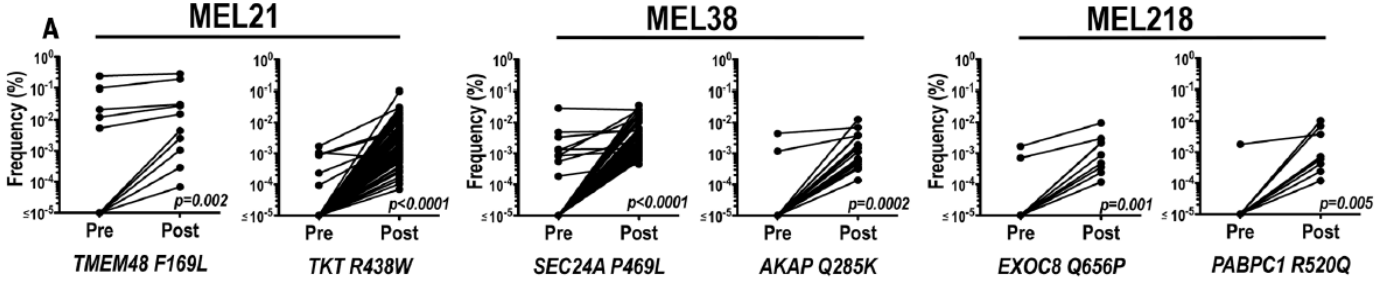


Conclusion

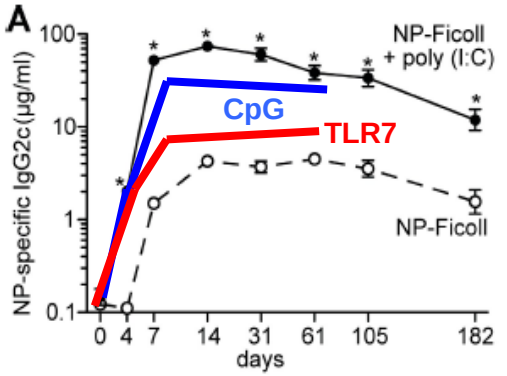
- Is anything working?

Surprisingly… yes.

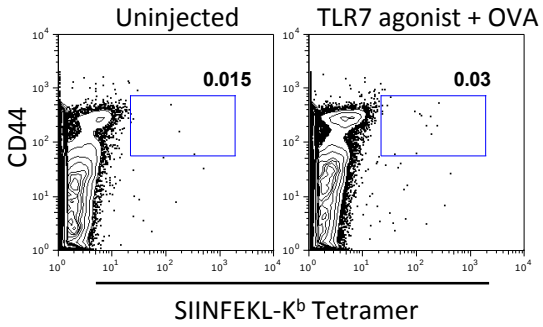
But could we do better?

Making better T cell responses

- **Making 10-20,000 lymphocytes is easy.**
- **10-20,000 B cells work great for providing antibody protection.**
- **10-20,000 CD8+ T cells rarely did anyone any good**



Swanson et al
JEM 2012
207:1485



Oh and Kedl, *JI* 2010
Oh et al. *Blood* 2012

6 easy steps to better cancer vaccines

1. antigen dose and duration… Stop starving T cells and avoid long-lasting emulsions
2. target DCs/enhance cross-presentation
3. use adjuvants that induce IL-27
4. and CD80/86 (CD28 stimulation)
5. engage TNFR superfamily members
6. IL-21 for ACT

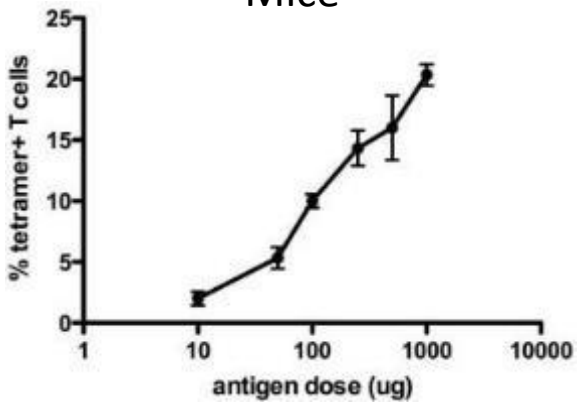
Step 1: Appropriate antigen dose and duration

- Doses that successfully raise CD8+ T cell responses in mice are usually 10-200ug of antigen
- These are the same amounts of antigen used in humans (ie. HBsAg is 10-20ug/dose), derived as a result of analyzing antibody responses
- Antigen processing and presentation for non-infectious antigen is notoriously inefficient
- Humans are ~3000X increase in mass and 200X in surface area.
- Mouse=1-10mg/kg (30mg/m^2)… Human=0.0001mg/kg!!!

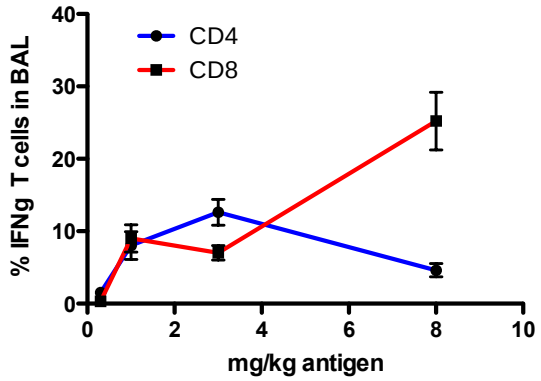
T cell responses to clinical vaccines are starving for antigen.

Step 1: Appropriate antigen dose and duration

Mice

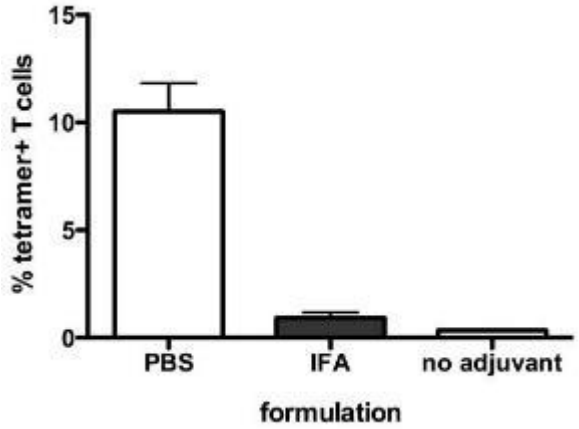


Primates

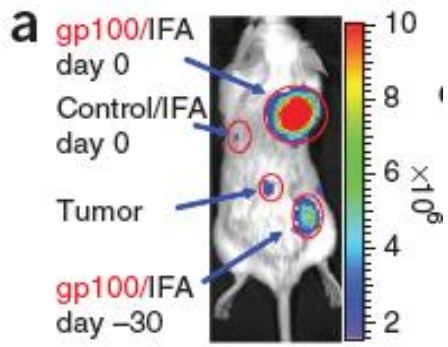


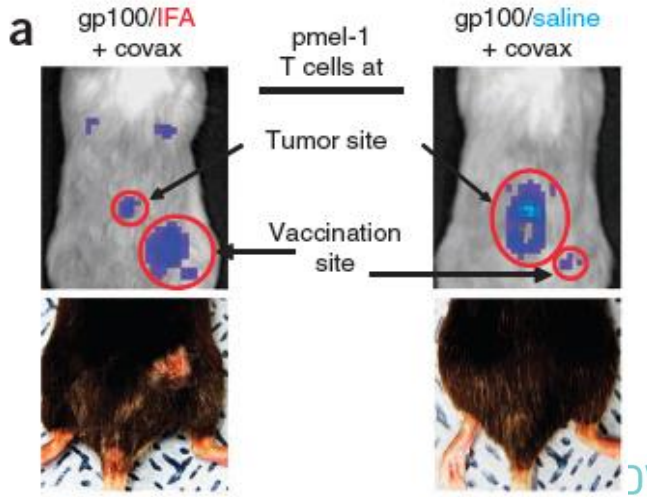
Step 1: Appropriate antigen dose and duration

Emulsions neutralize the T cell response to vaccination



Burchill et al. *Vaccine* 2013 31:297-305





Hailemichael et al. *Nat. Med*. 2013

Cho & Celis Cancer Res. 2009

Reinhardt et al. JEM 2003

Conclusion

- Can we make them better?

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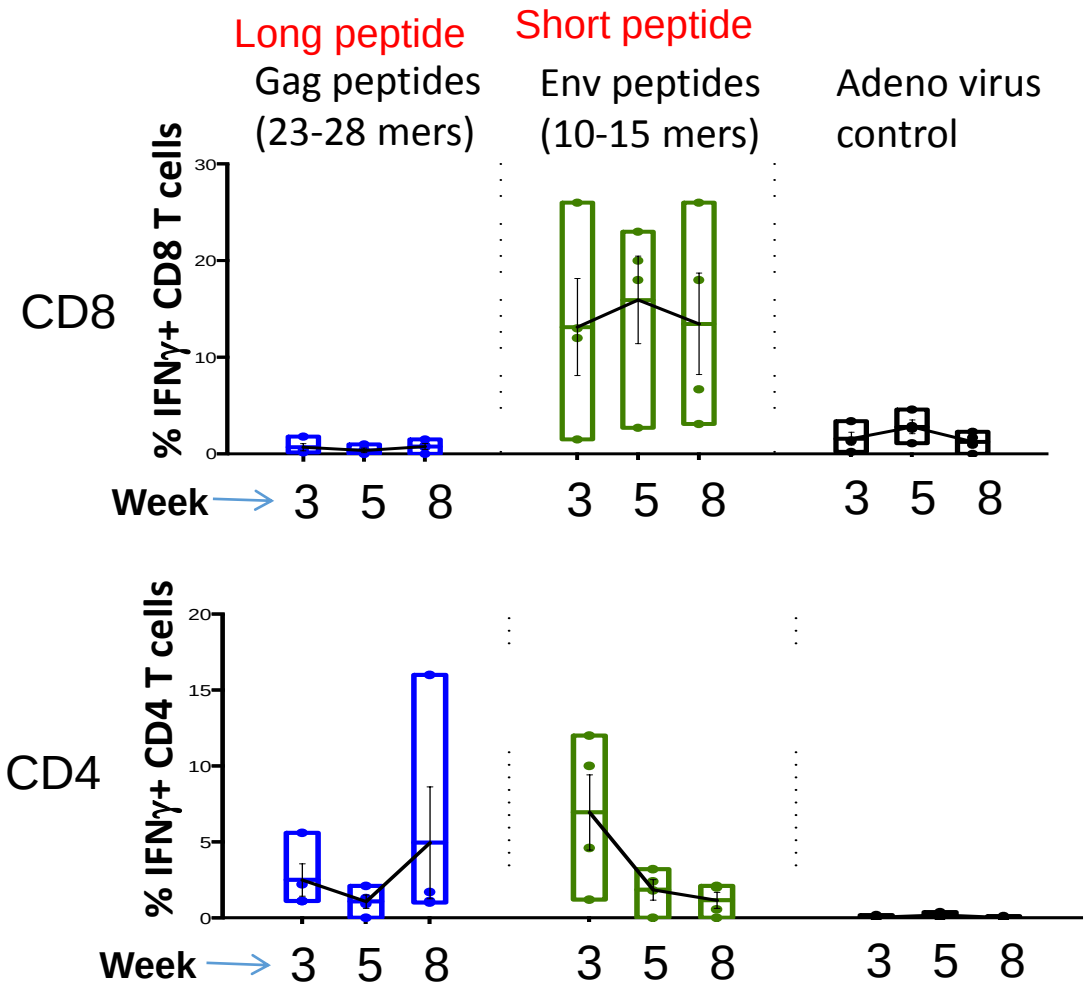
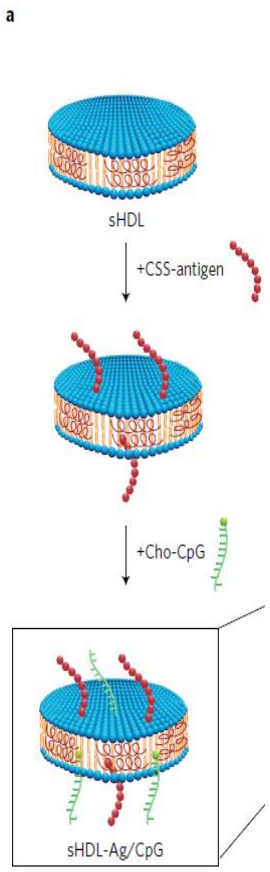
Step 2: Target DCs to augment cross presentation



Cross-presentation is harder to induce in primates

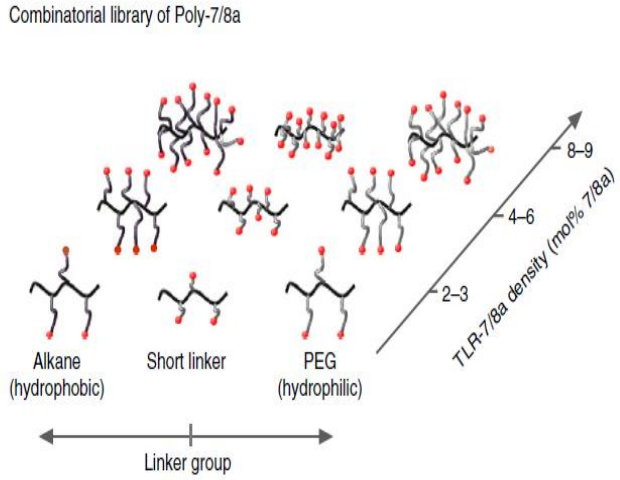
Step 2: Target DCs to augment cross presentation



Kai et al.
Nature Materials 2016

Strategies for targeting APCs:

- TLR agonist-antigen conjugates
- Antibody-linked antigens (dec-205, CD40, etc)
- Nanoparticle technology (liposomes, ISCOMS, etc)



Lynn et al.
Nature Biotech 2015

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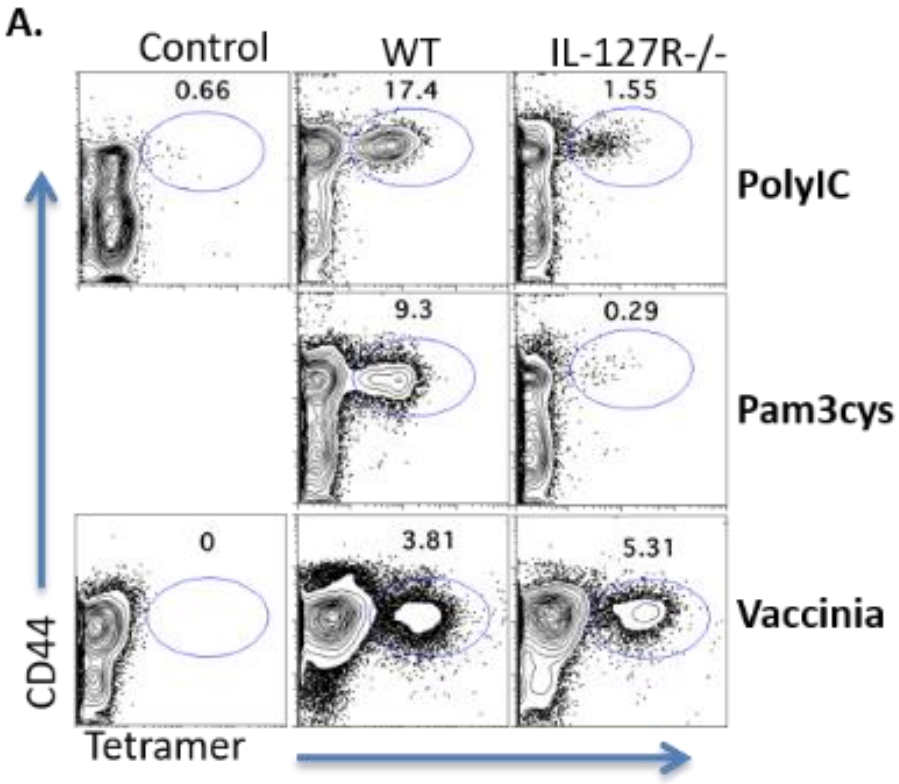
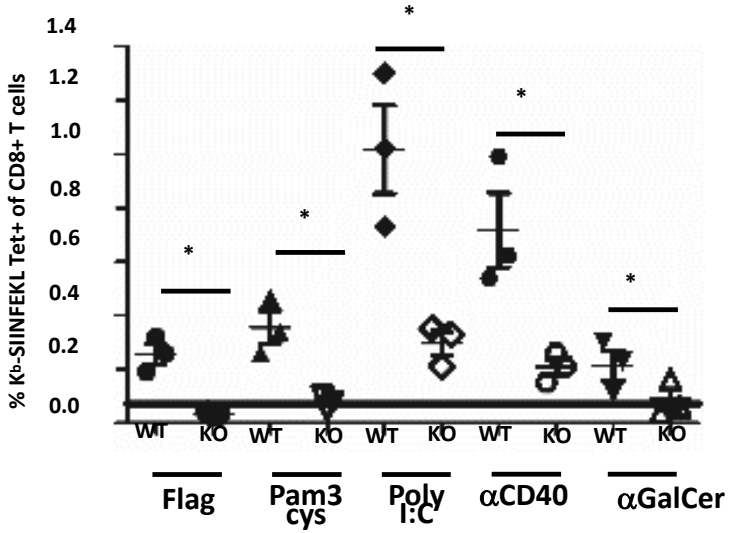
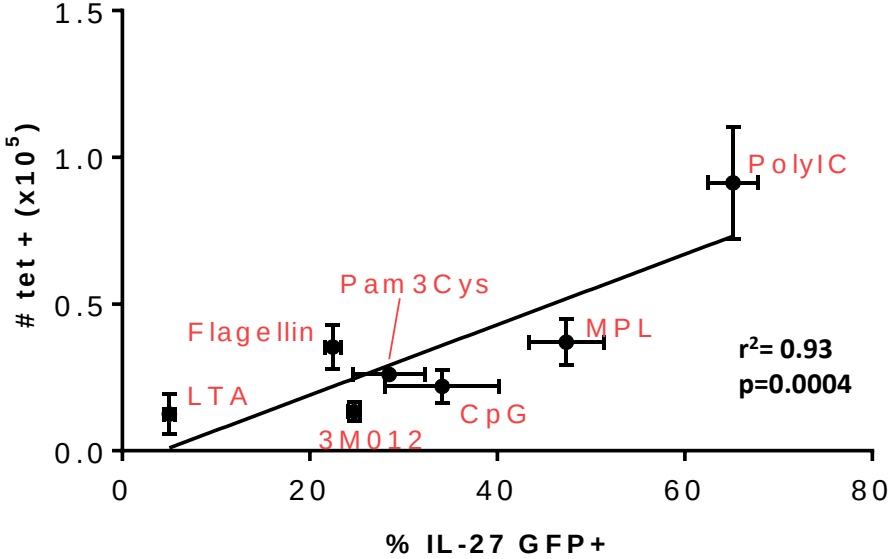
Step 3: IL-27 as signal 3





Pennock et al. *PNAS* 2015



Kilgore et al. *submitted*

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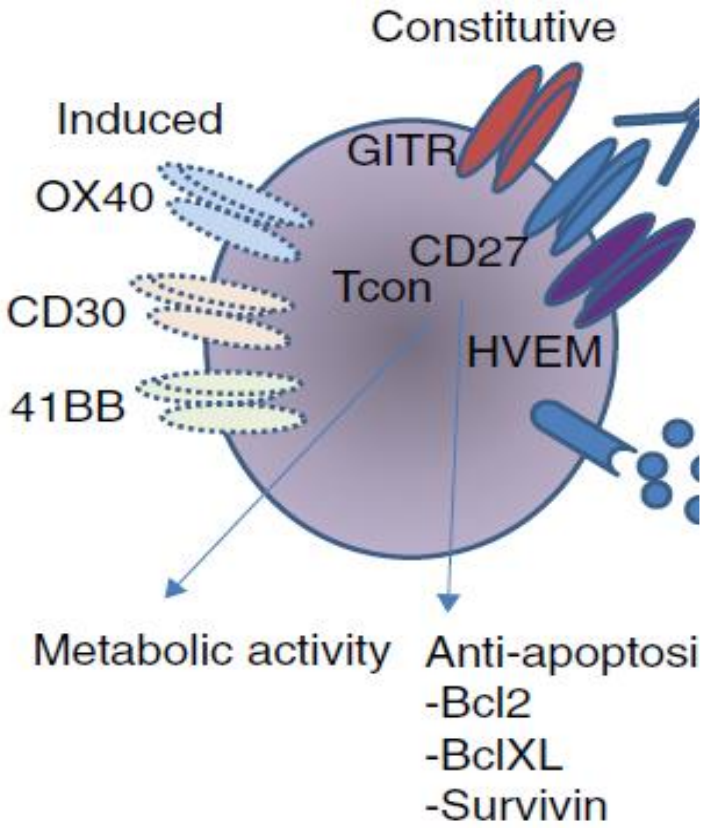
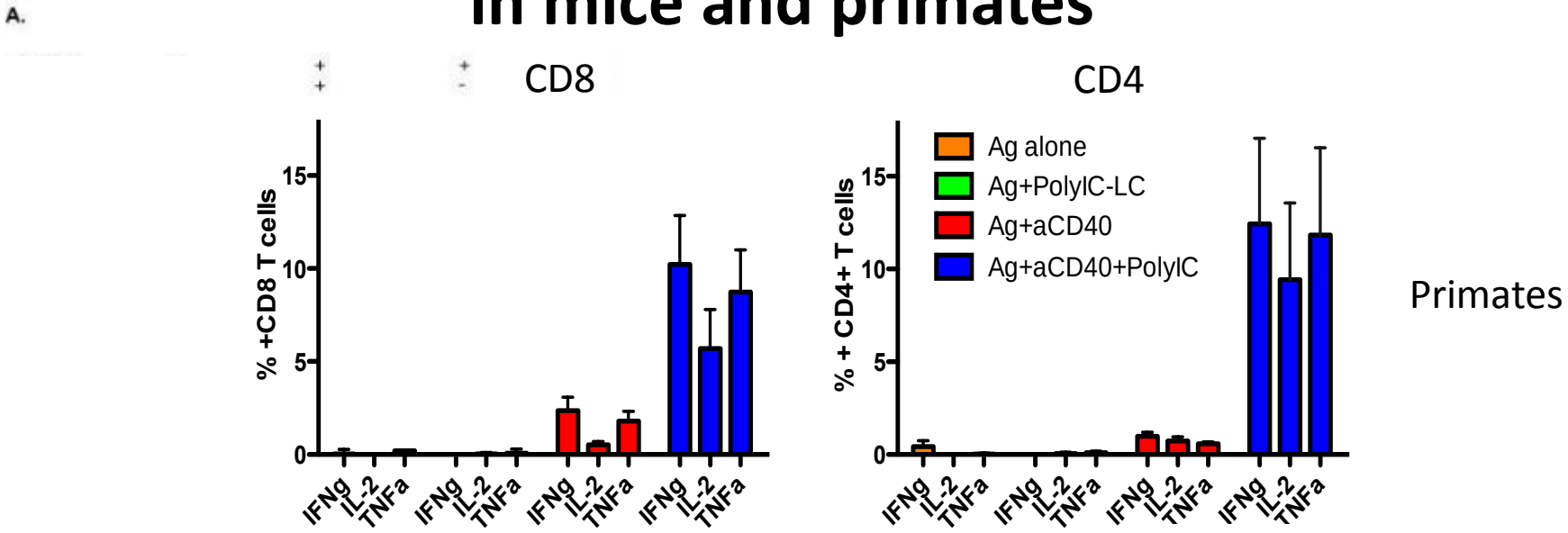
Step 5: TNF Receptor/Ligand engagement



Bullock. *Curr. Opin. Imm*. 2017

Augmenting T cell responses by Targeting TNF receptors… in mice and primates

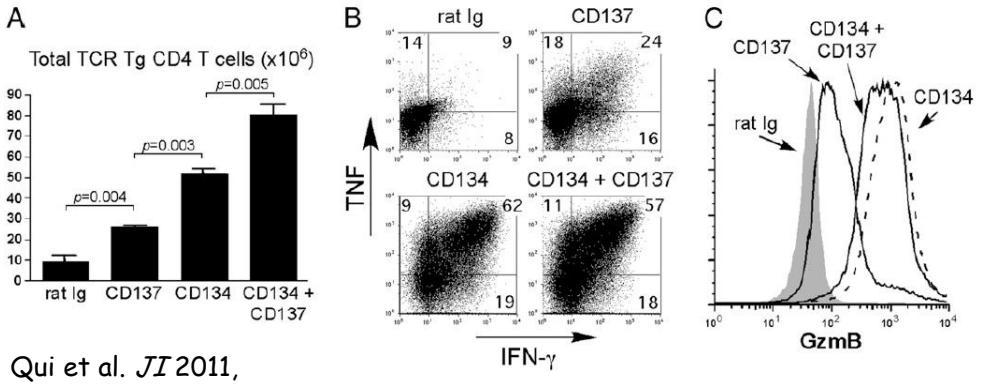
CD27



Primates

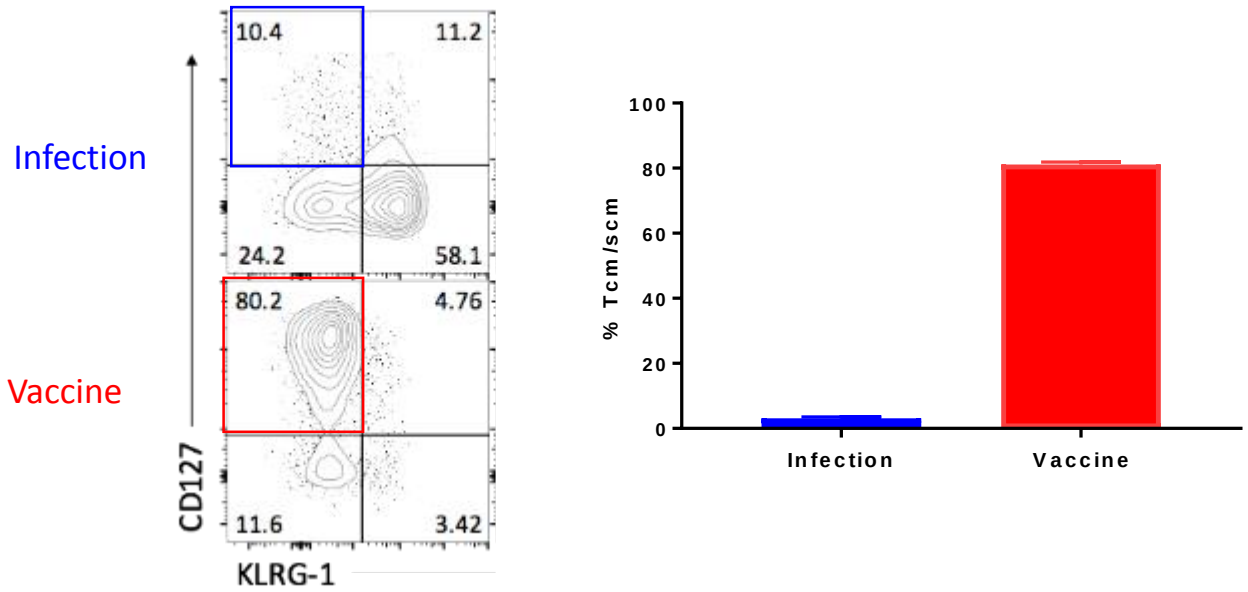
Thompson et al. JI, *2015*

OX40 and 41BB



Qui et al. *JI* 2011,

Targeting TNF receptors augments Tcm/Tscm



Edwards et al. Immunol. Res. 2013

Conclusion

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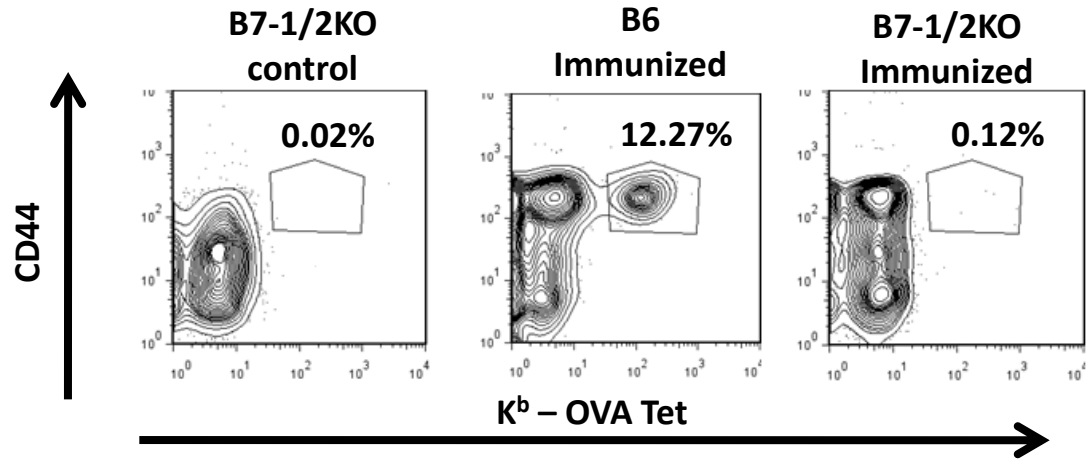
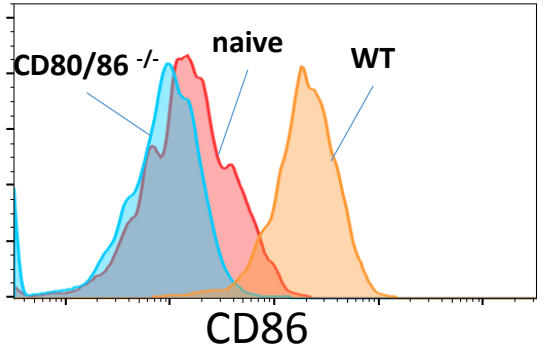
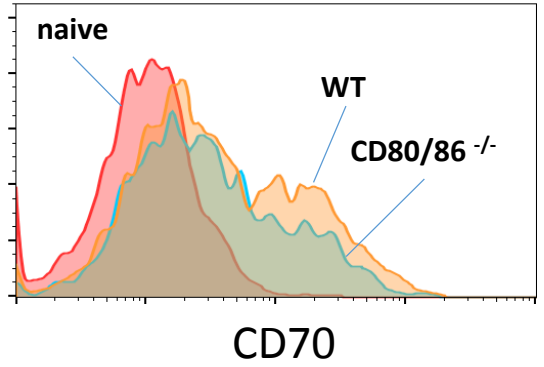
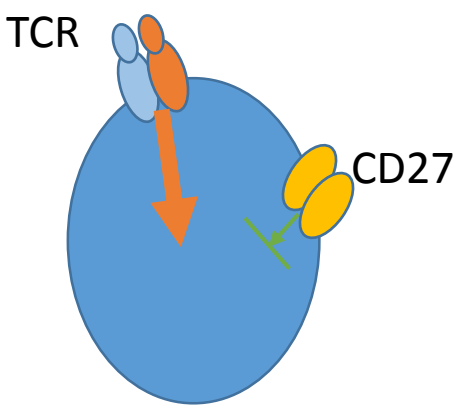
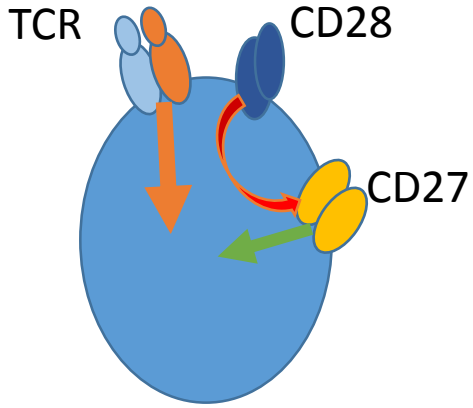
Step 4: strong CD28 costimulation











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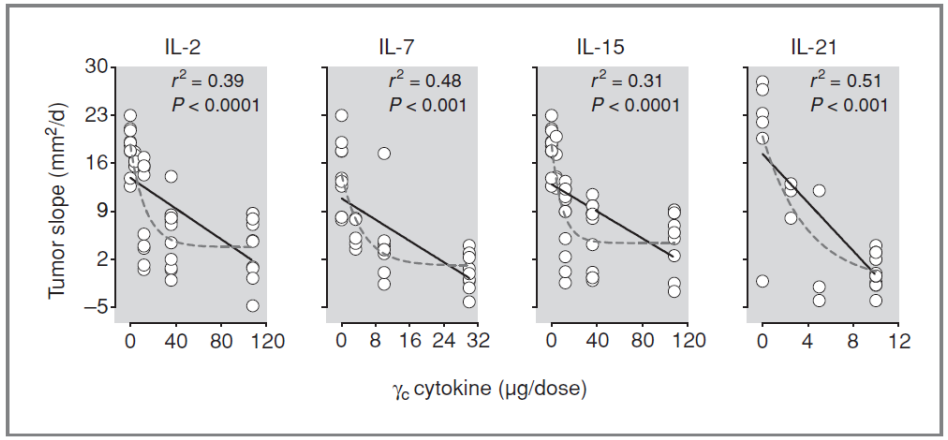
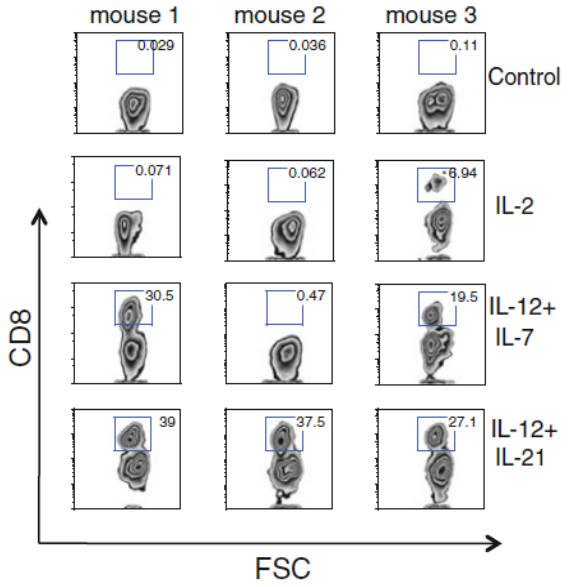
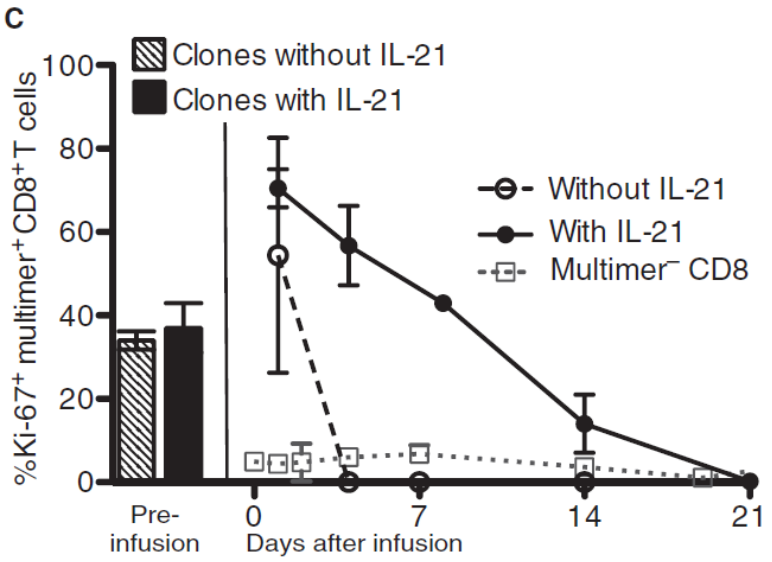
Step 6 (For adoptive cell therapy): Use IL-21



Klebanoff et al. Clin. Can. Res. 2011



Yang et al. Can. Immunol. Immunother. 2013



Chapuis et al. Sci. Trans. Med. 2013

6 easy steps to better cancer vaccines

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Clinical approaches engaging these vaccine principles

- TNFR-targeting antibodies;
  - Varilimumab (CD27)
  - Utomilumab (CD137/41BB)
  - CD134/OX40 (Medimmune/PF/Genetech)
  - TRX5-18 (GITR)
  - APX005M/RO7009789/CP-870,893 (CD40)
- CMB305- lentiviral vector + TLR4 agonist
- NC-6300- pH-sensitive lipid particles

- Do we need T cells?

Duh

- How Many T cells do we really need to make?

More than you want to admit…

- What kind should we make?

Self renewing T_{SCM} or T_{CM}

- How should we make them?

1- antigen dose and duration… Stop starving T cells and avoid long-lasting emulsions

2- target DCs/enhance cross-presentation

3- use adjuvants that induce IL-27

4- and CD80/86 (CD28 stimulation)

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Goals

1. Appreciate our current understanding of the requirements for successful T cell-mediated cancer therapy
2. Become familiar with some current approaches to vaccination against cancer.
3. Appreciate and understand T cell-specific vaccine principles for designing and developing better cancer vaccines.