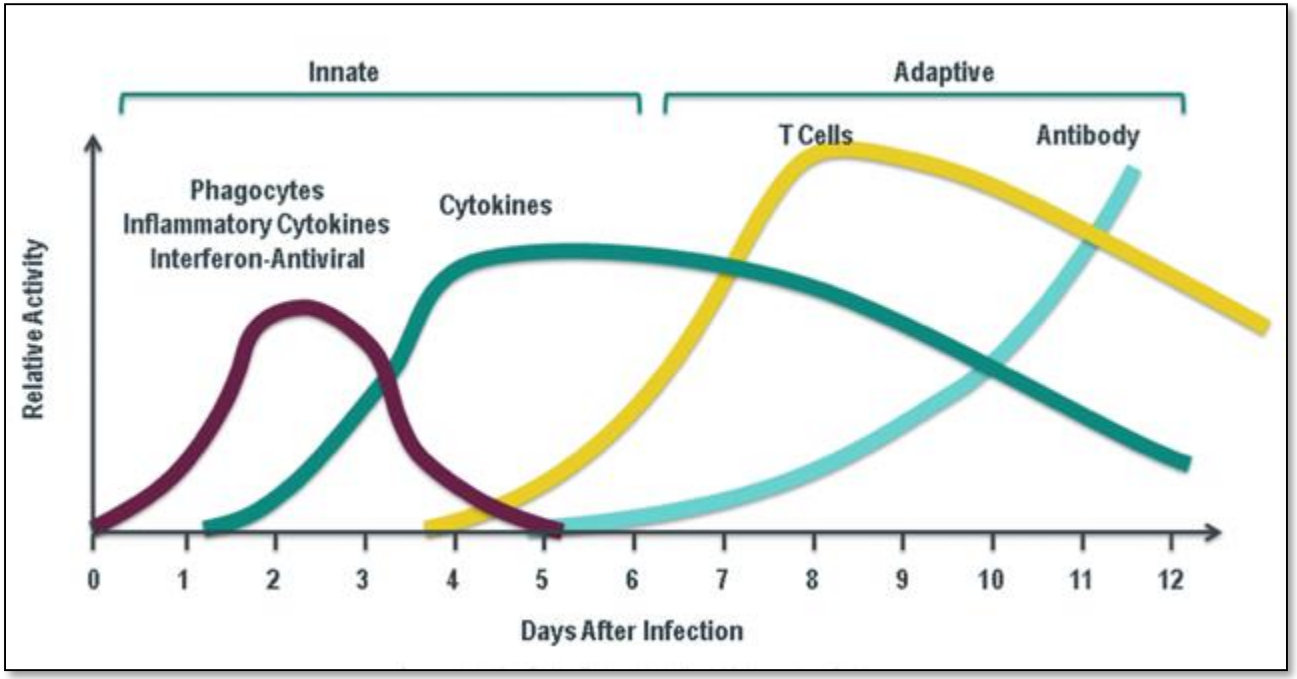
Cancer Immunology 101

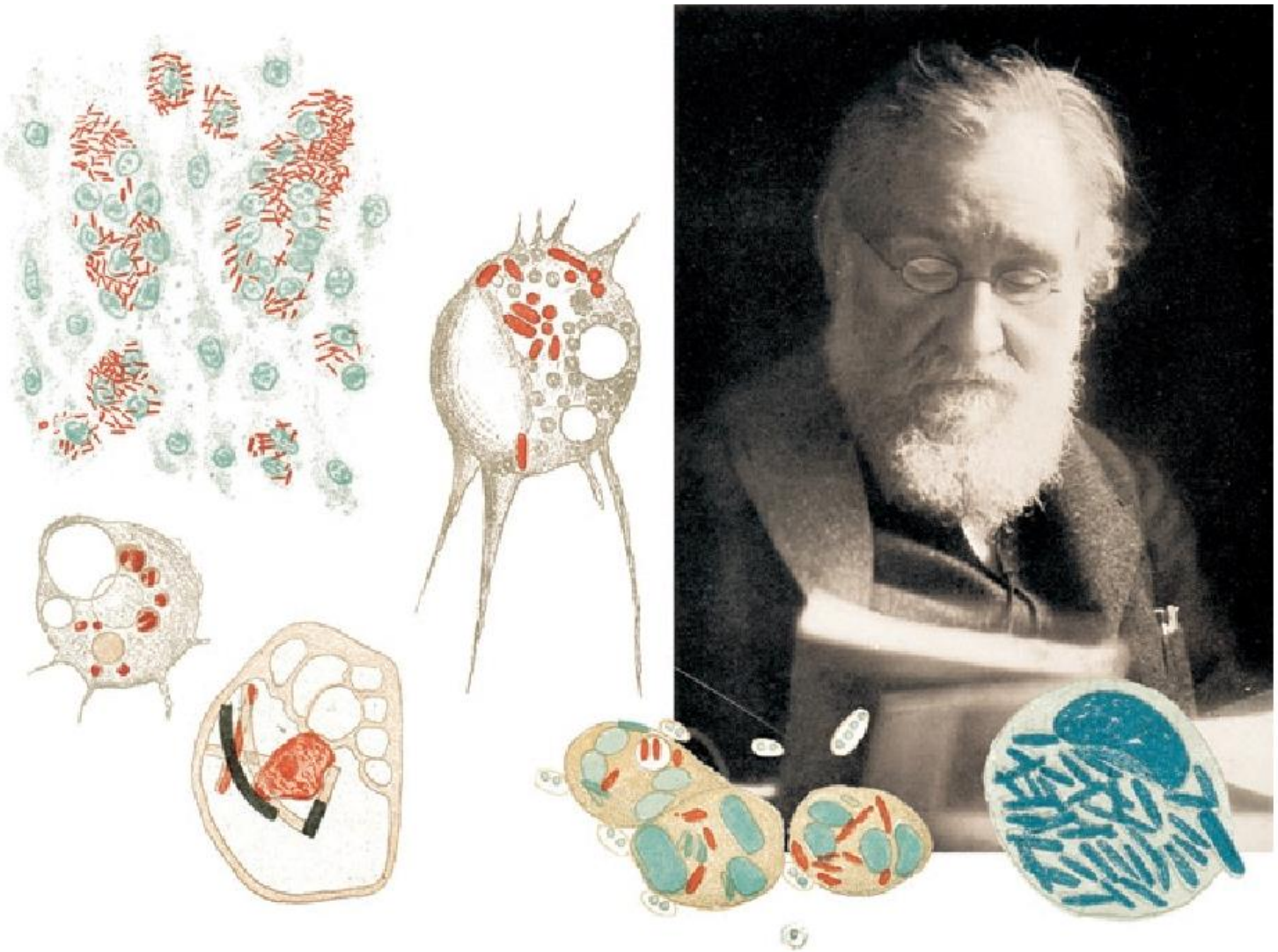
Max N.Artyomov, Sep 24, 2019

Part I:
Recap.
progression of events during “normal” immune response

Immune response consists of two phases

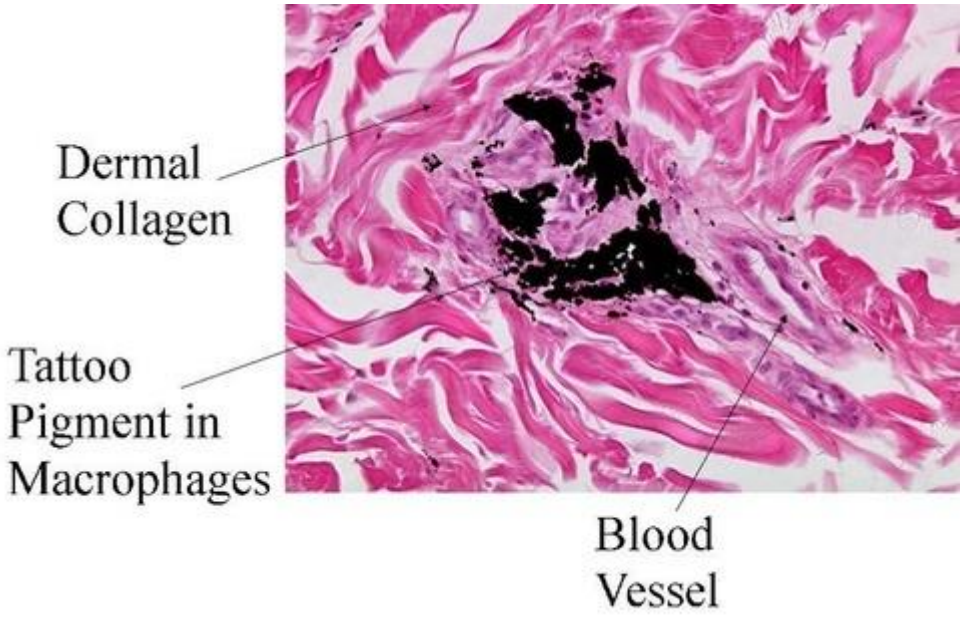


Innate immune actors: macrophages, DCs..



Ilya Mechnikov

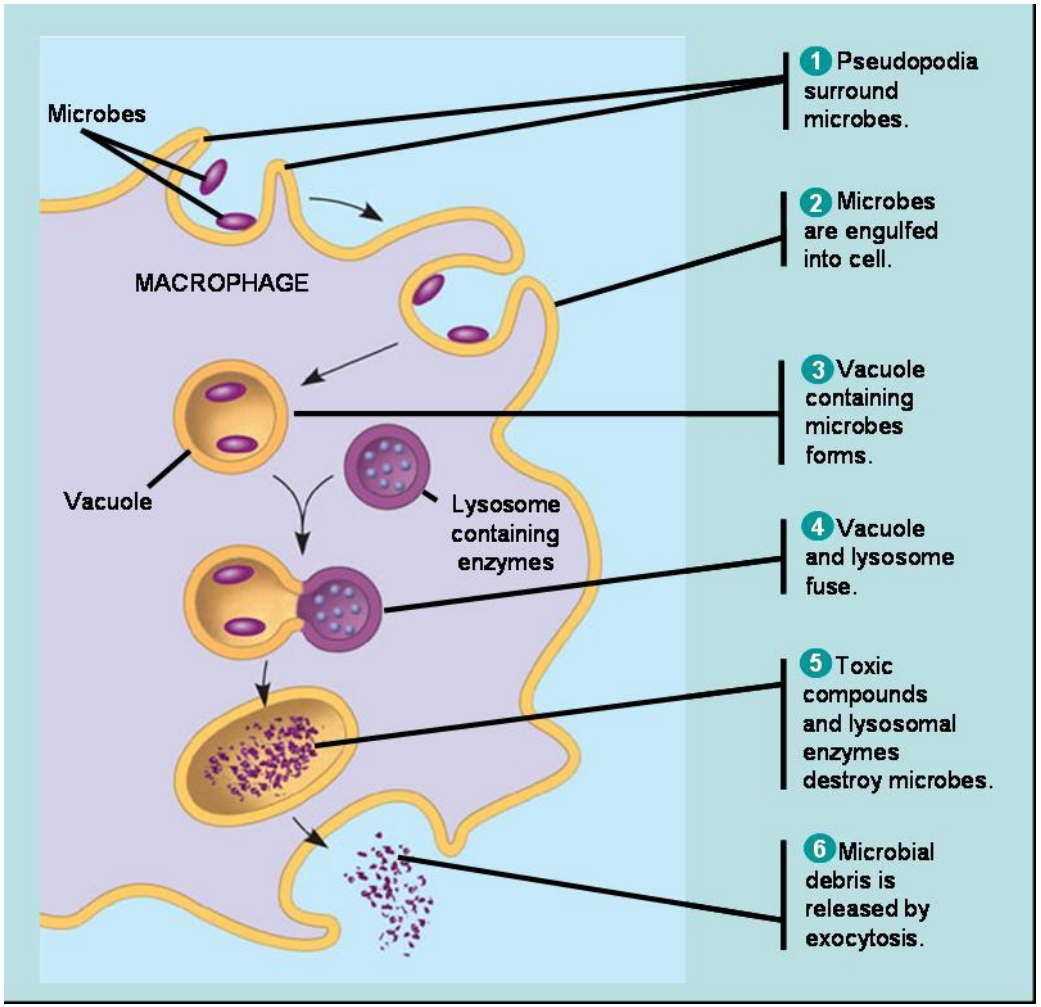
Macrophages surveillance – no danger



Fun fact – macrophages are your “tattoo cells”!

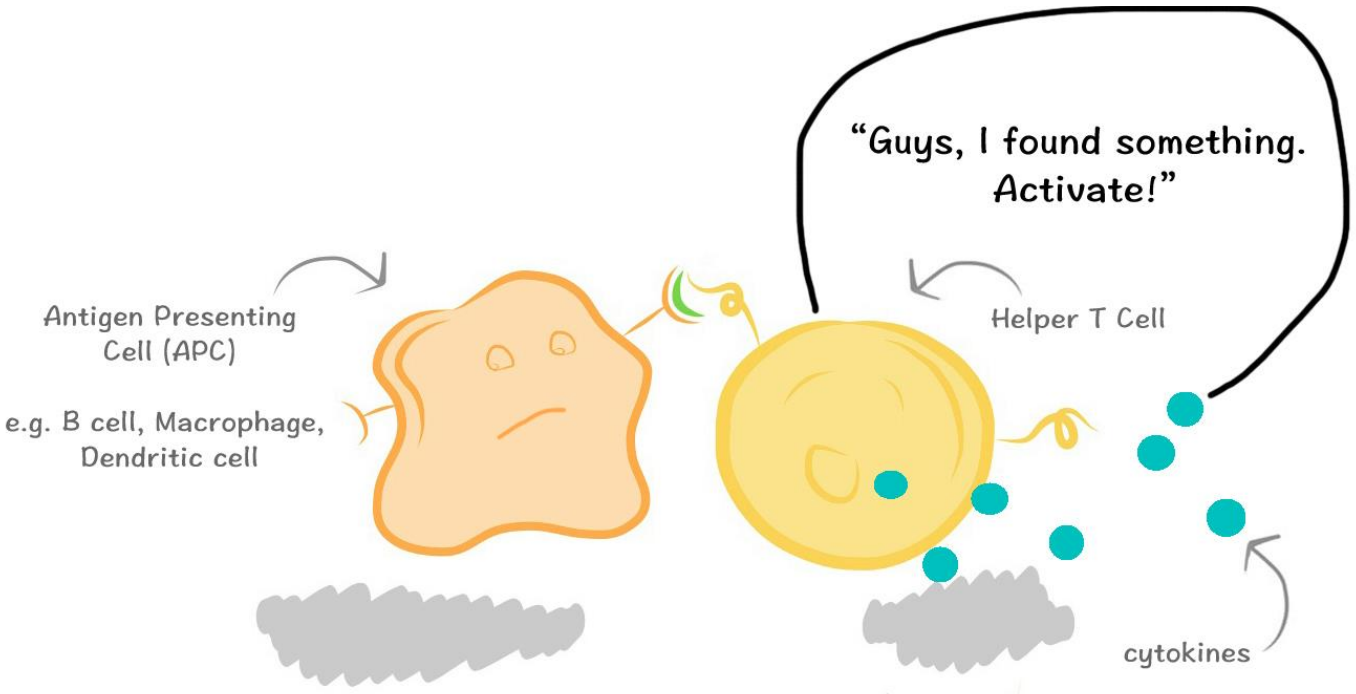
Roles of activated innate immune cells

1. Immediate destruction of pathogens



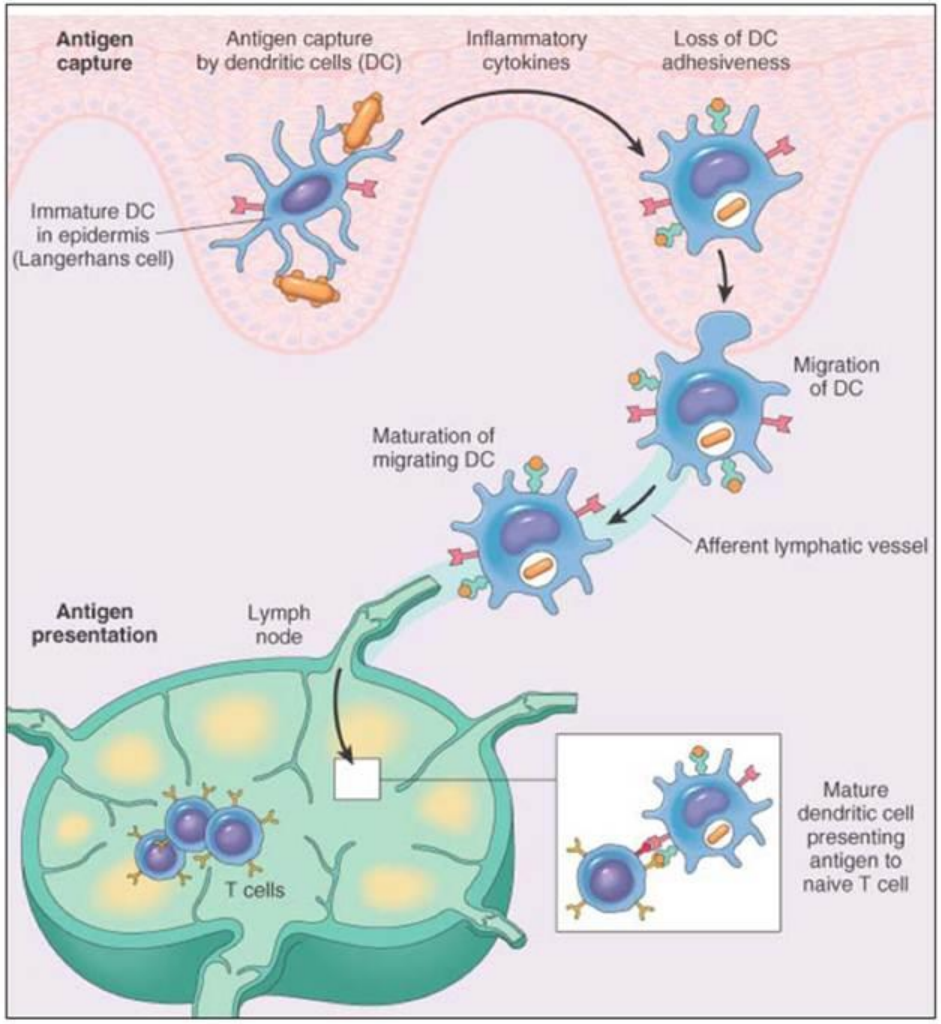
Roles of activated innate immune cells

2. Priming of adaptive immune system

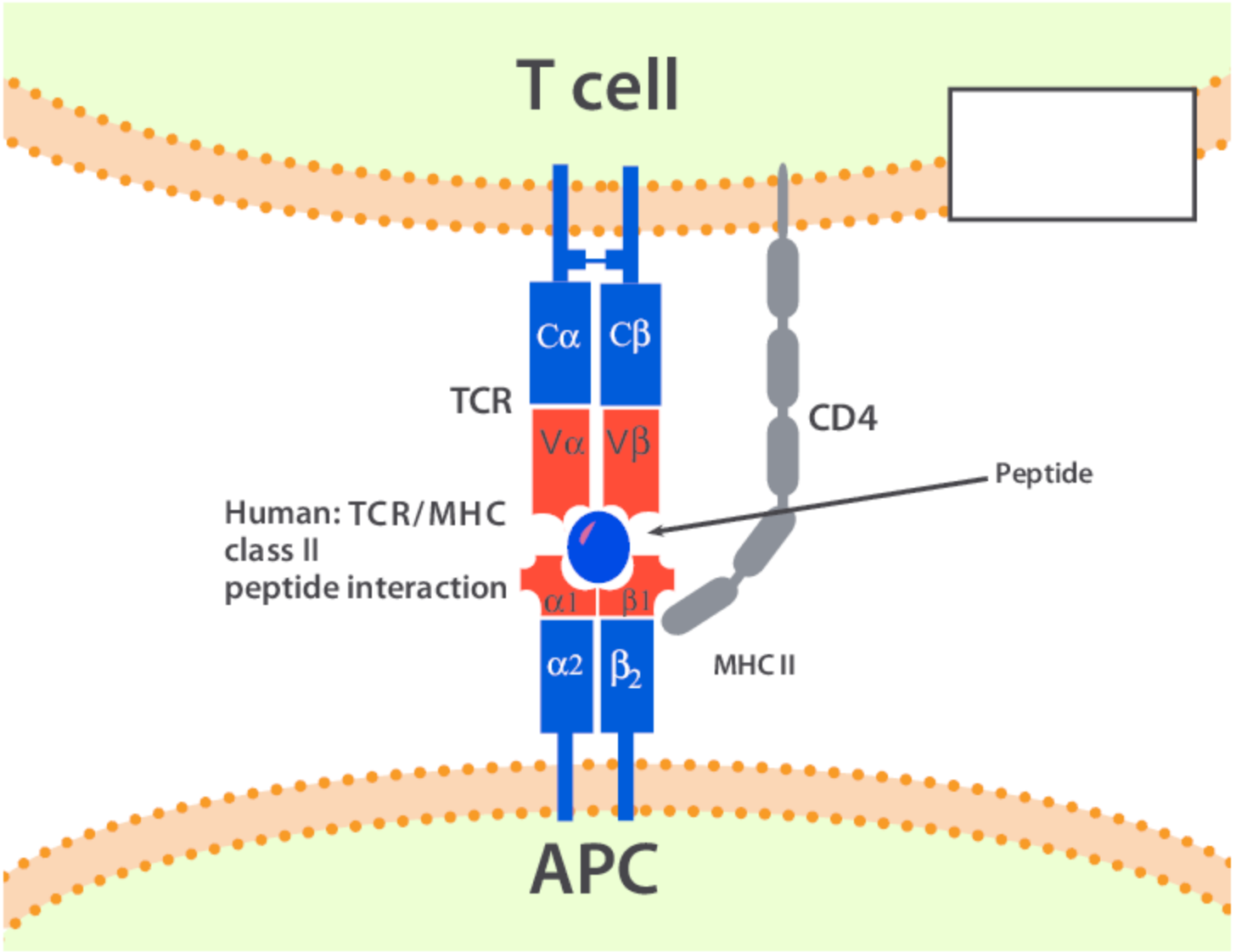


T-cells can recognize pathogen only with the help of macrophages from the same genetic background

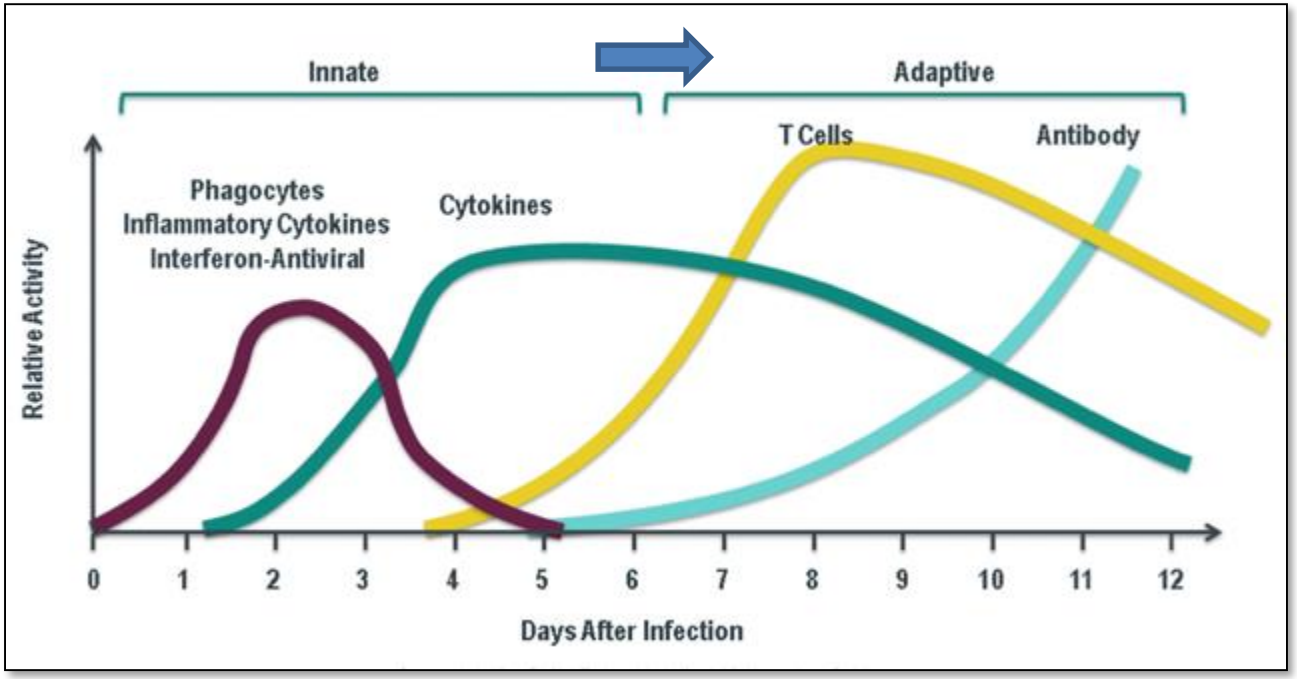
Priming occurs in lymph node



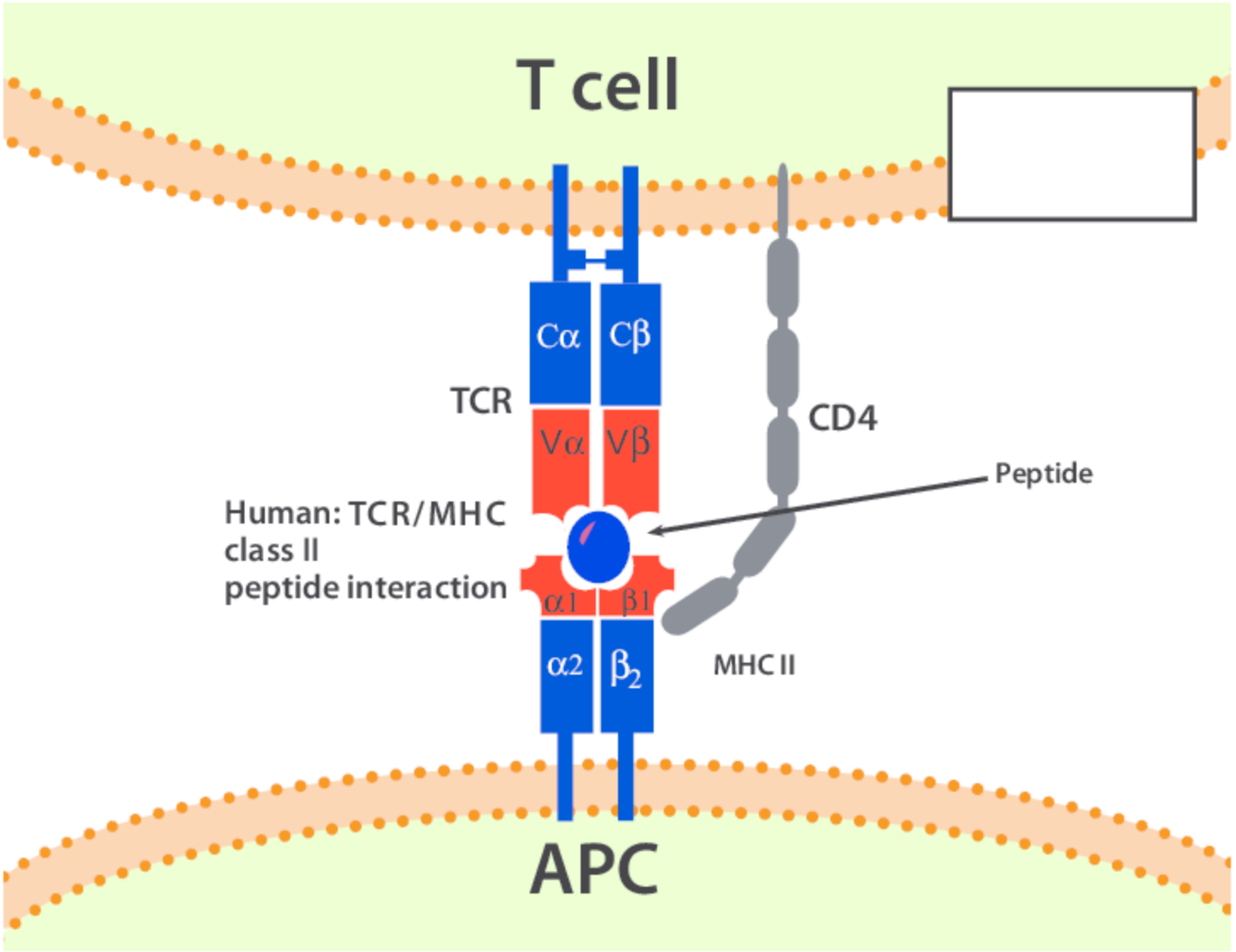
TCR-pepMHC interactions



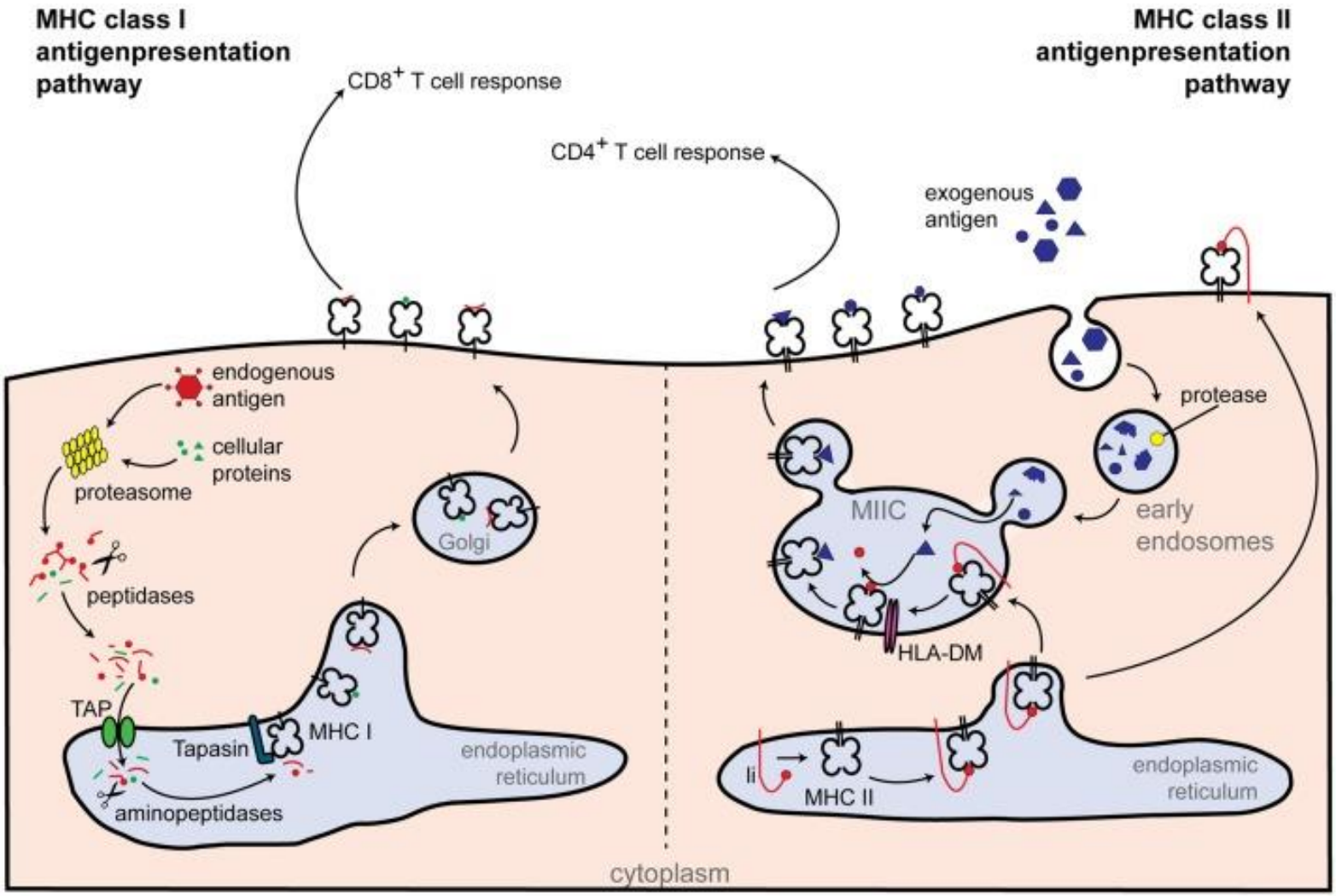
TCR-pepMHC interactions: kickstarts of adaptive immune response



TCR-pepMHC interactions



Where peptide-MHC is coming from



Innate immune cells prime adaptive immunity

Emil R. Unanue

Emil Raphael Unanue is an immunologist and the current Paul & Ellen Lacy Professor at Washington University School of Medicine. He is a member of the National Academy of Sciences, the American Academy of Arts and Sciences and the Institute of Medicine. Wikipedia

Born: September 13, 1934 (age 85 years), Havana, Cuba

Residence: St. Louis, Missouri, United States

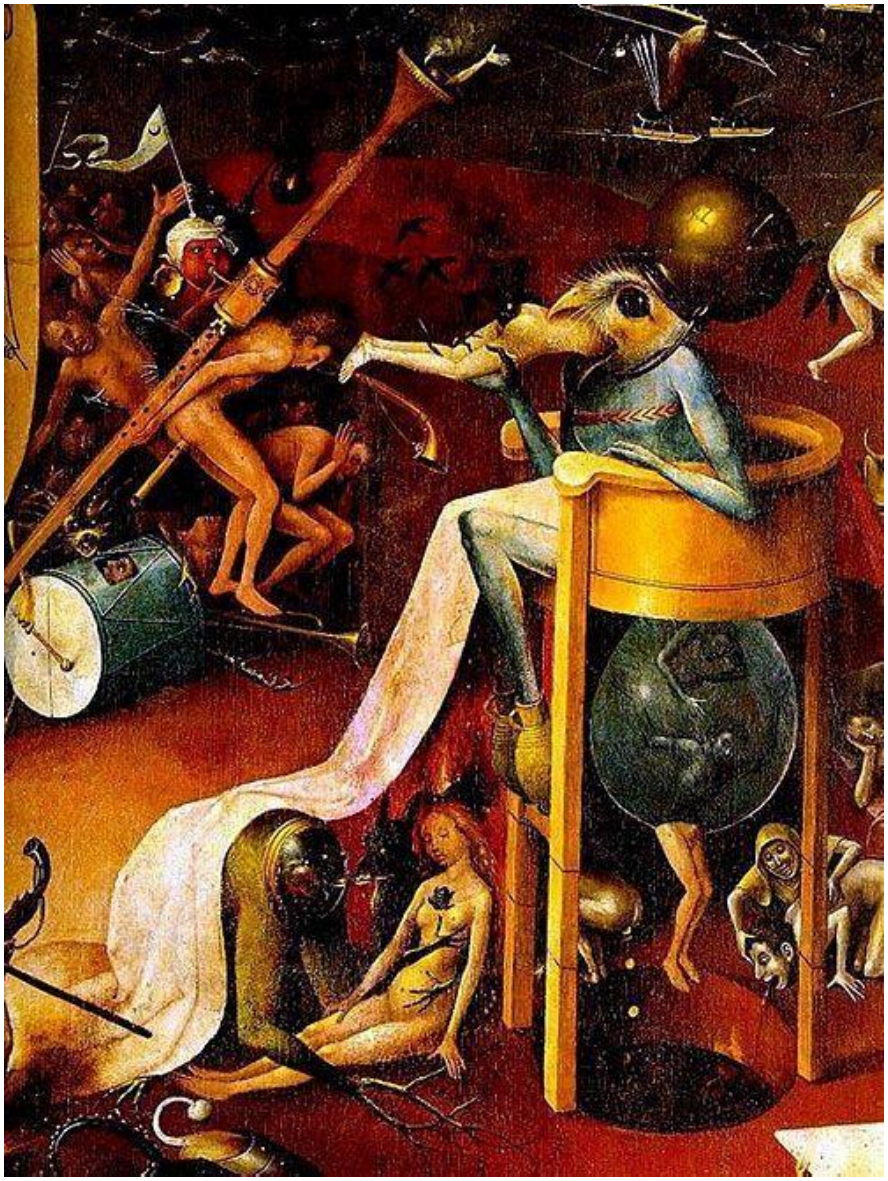
Books: Macmillan Dictionary of Immunology, Textbook of Immunology

Education: Universidad de la Habana (1960), University of Pittsburgh

Awards: Albert Lasker Award for Basic Medical Research, MORE

Notable student: Herbert W. Virgin

One way to think about it…



Emil Unanue
For seminal discoveries in antigen processing and MHC-peptide binding which deciphered the biochemical basis of T-cell recognition.

Two decades of extraordinary studies by **Emil Unanue** have fundamentally advanced the field of molecular immunology. The experiments in which Dr. Unanue demonstrated that molecules of the major histocompatibility complex (MHC) bind to antigenic peptides blazed a trail out of a thicket of theories toward a lucid understanding of how cell-surface antigens are recognized by T lymphocytes.

Dr. Unanue's highly original discoveries began in the late 1960s. By the combination of *in vivo* cell transfers in mice with cell-culture experiments, he first found direct evidence that the immunogenicity of proteins increased greatly after phagocytosis and catabolism by macrophages. This seminal finding flew in the face of immunological dogma, which held that the macrophage destroyed antigens, and that the immune response targeted folded portions of intact protein molecules.

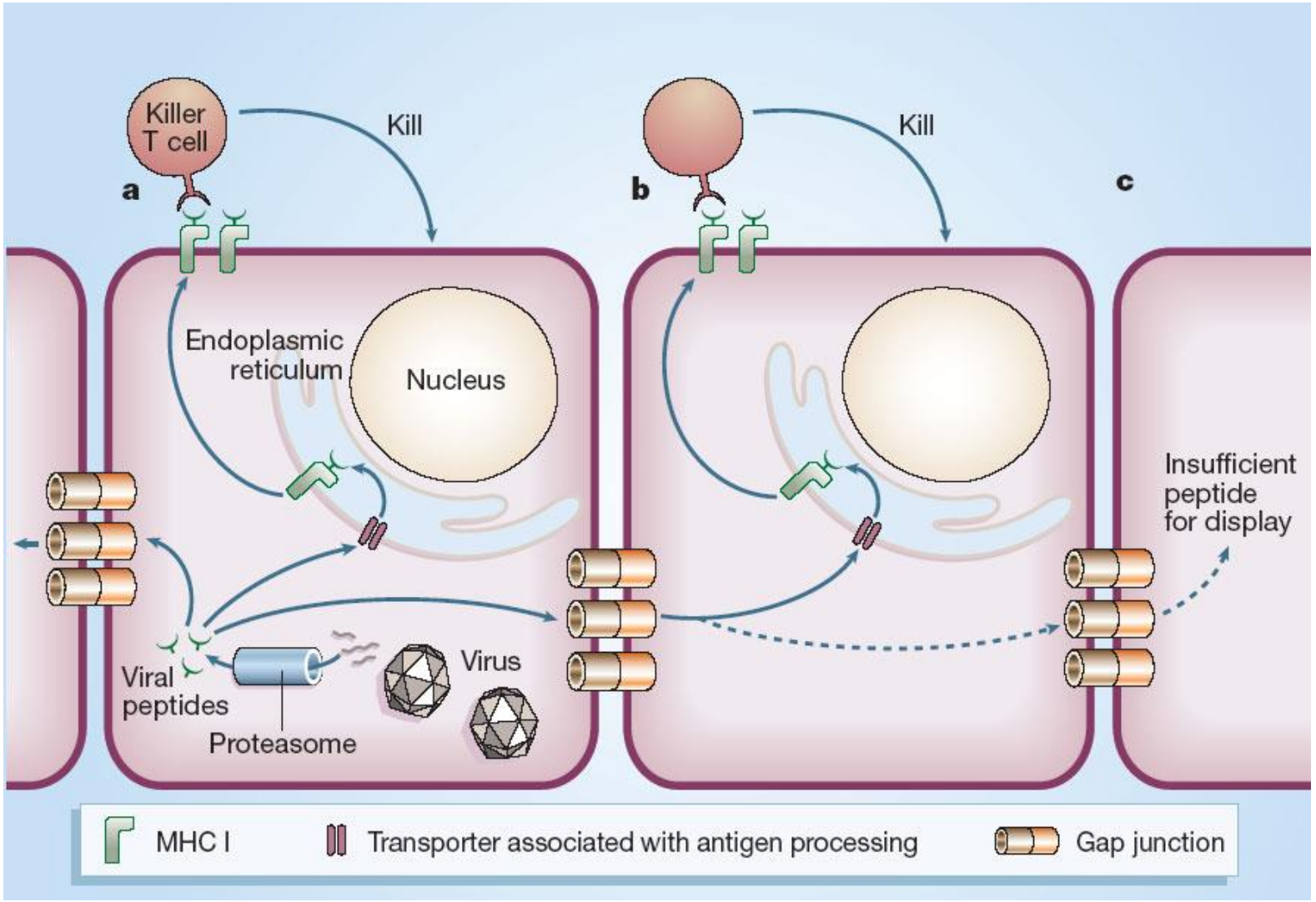
!!! Despite collegial skepticism, Dr. Unanue proceeded to trace the enhanced response to a fraction of the antigenic protein embedded in the macrophage cell wall. His pivotal observations were quickly confirmed and the macrophage was acknowledged to have a previously unrecognized function—presenting antigen to helper T cells.

Dr. Unanue broke new ground again in the 1980s, following the description of MHC restriction of T-cell recognition by Peter Doherty and Rolf Zinkernagel. He showed that proteins needed to be processed intracellularly prior to their recognition by T cells. In a crucial collaboration with Paul Allen, Dr. Unanue then proved that after internalization and catabolism by macrophages, the immunogenic fragments which appeared on the cell membrane were peptides. The puzzle of immune recognition remained to be solved, however, as Dr. Unanue turned his attention to MHC antigens and the T-cell receptor.

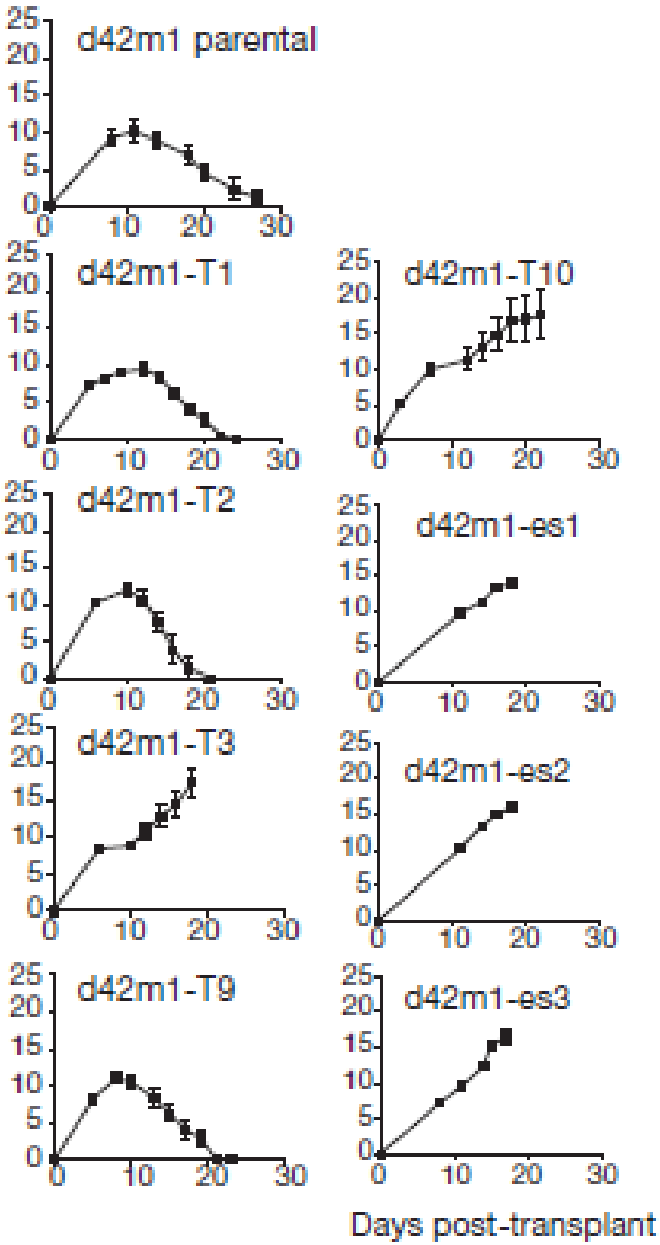
In a landmark paper which has become one of the most widely cited studies in immunology, Dr. Unanue, collaborating with Allen and Babbitt, demonstrated that class II MHC molecules would

http://www.laskerfoundation.org/awards/show/t-cells-and-immune-defense/

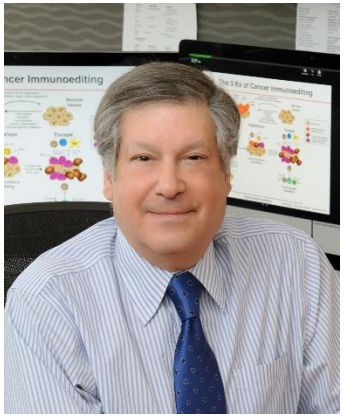
Peptide presentation allows killing infected cells



Mouse model of tumor rejection – panel of sarcomas



Some mouse sarcomas are naturally rejected while others grow out



Robert Schreiber
Pathology&Immunology Dept
Washington Univesity in St.Louis

Matsushita et al, Nature 2012

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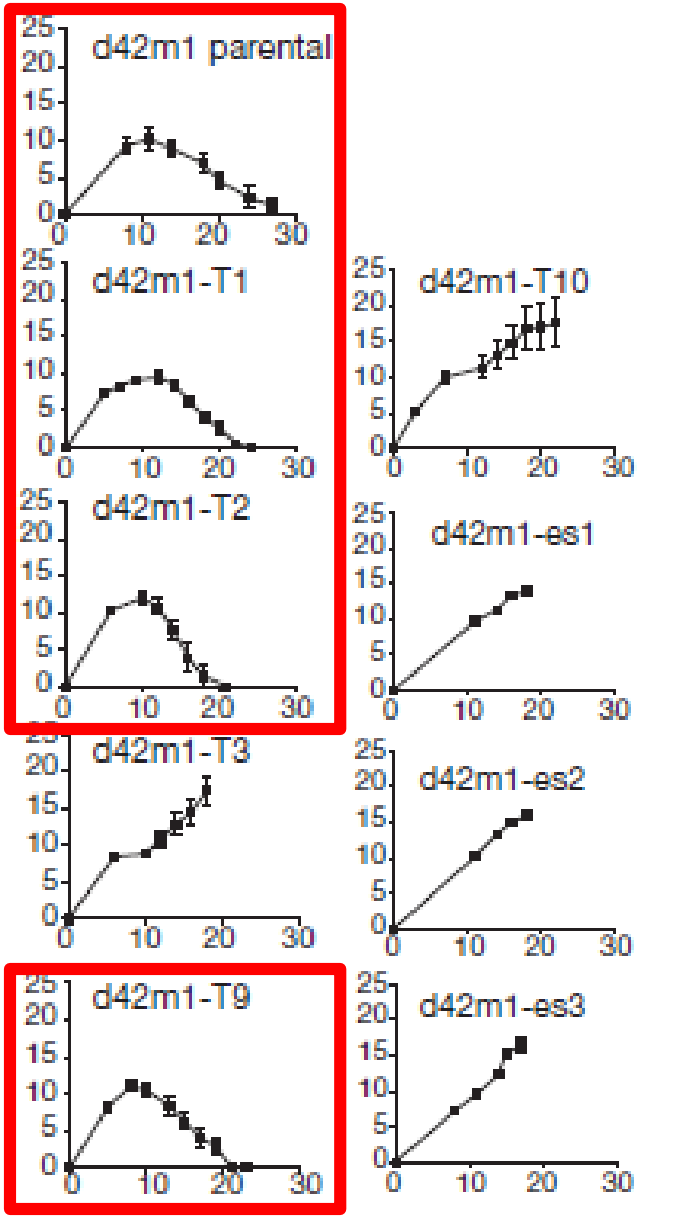
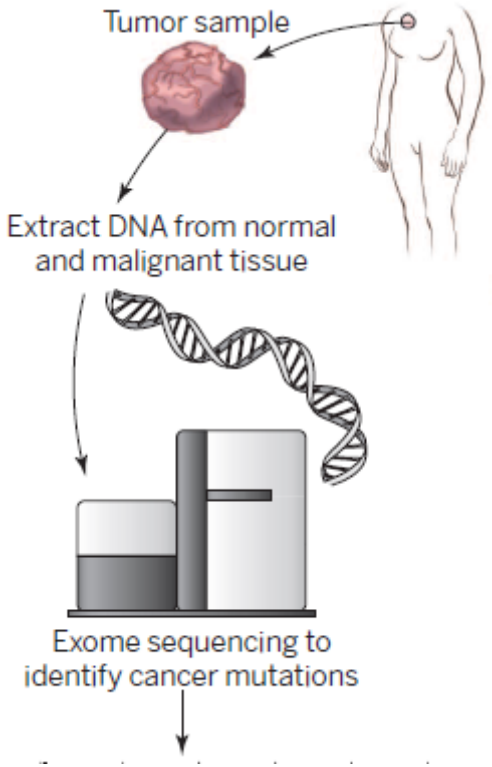


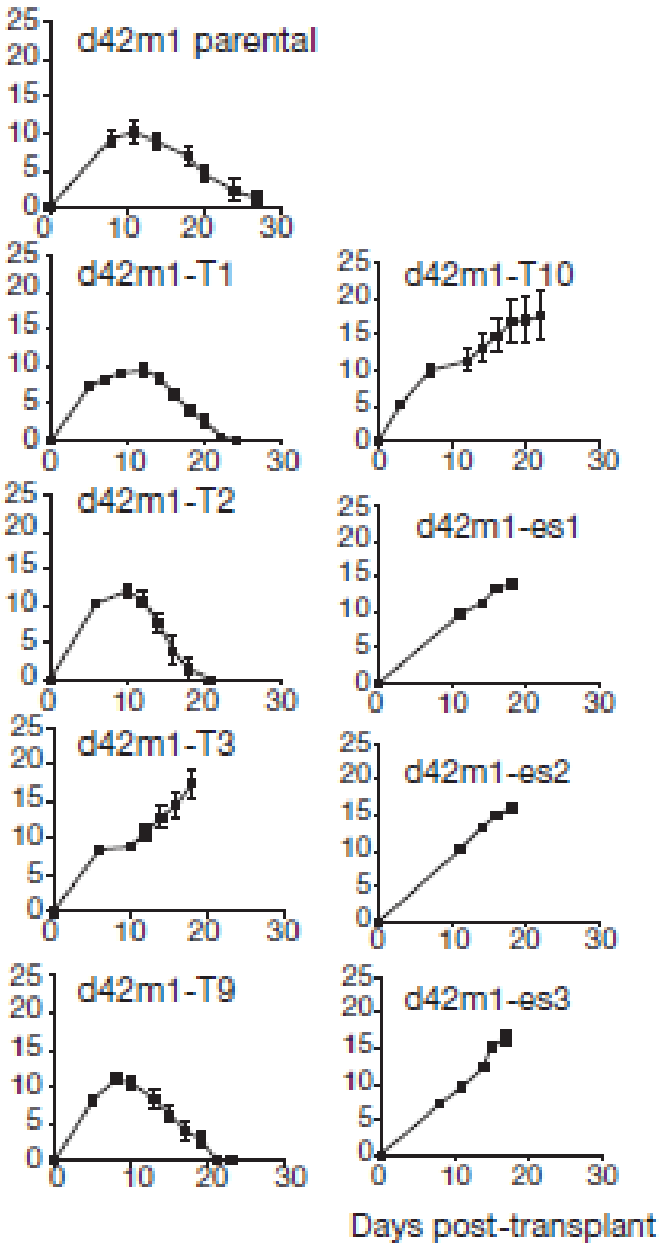
Hypothesis:
Tumor neoantigen is responsible for rejecion

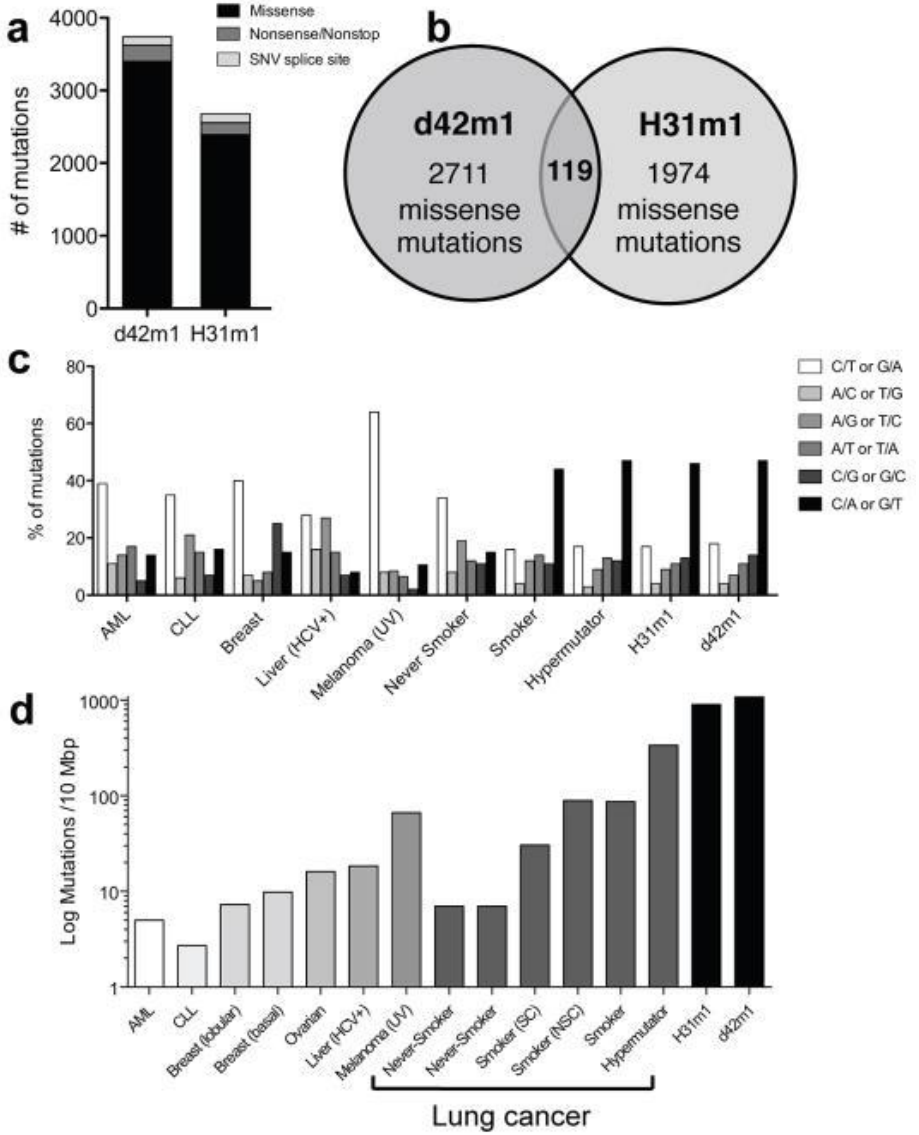


compare mutational landscape of regressor vs progressor tumors

Matsushita et al, Nature 2012

Overall sequencing statistics





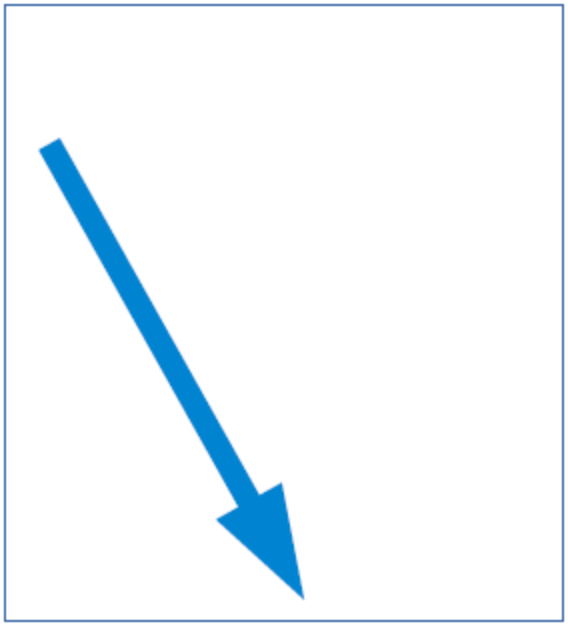
Matsushita et al, Nature 2012

Computational filtering allows to go identify neoantigens

cDNA Cap-Seq
Tumor vs Normal

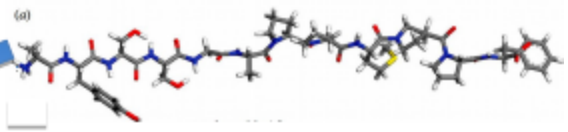
ID Expressed mutations

~40,000 peptides



~40,000 peptides

Synthesize Peptides



In Vitro/Ex Vivo Analyses

- *Mass Spec of eluted peptides*
- *Peptide binding to RMA-S*
- *Tetramer staining of TILs*

In Vivo Analyses

- *Vaccine induced T cell response*
- *Prevention of tumor outgrowth*

By Jeffrey Ward

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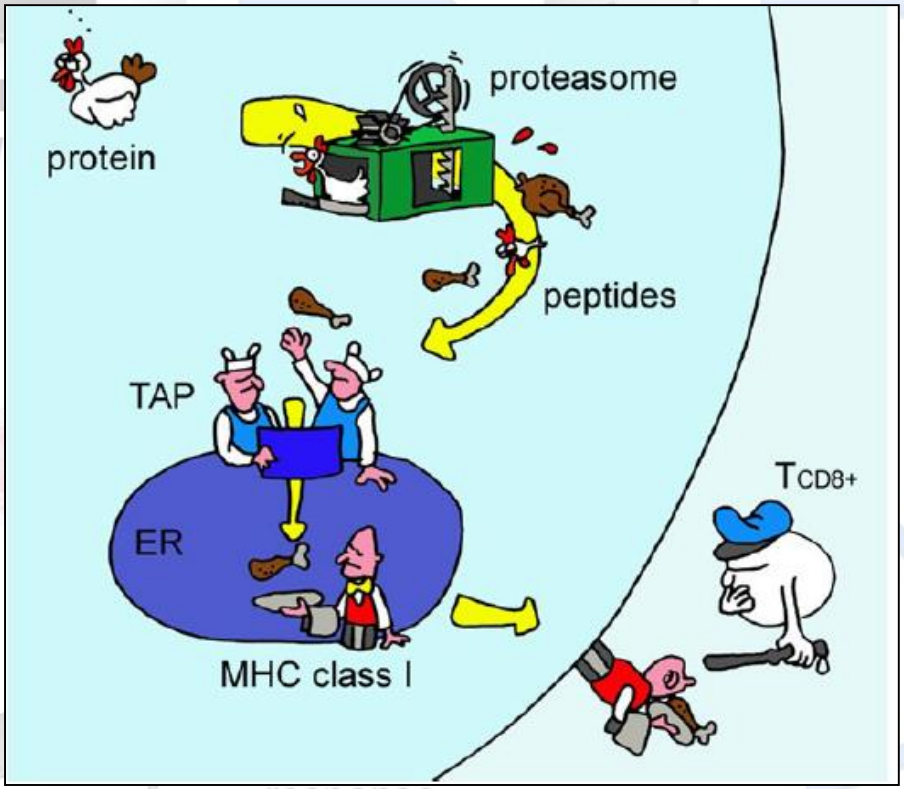
By Jeffrey Ward

Pep-MHC interaction is “rate-determining” step



Computational filtering allows to go identify neoantigens

YTRGFQHTGIY**S**VMIQKVILRDL
~~YTRGFQHTGIY~~
TRGFQHTGIY**S**
RGFQHTGIY**S**V
GFQHTGIY**S**VM
FQHTGIY**S**VMI
QHTGIY**S**VMIQ
HTGIY**S**VMIQK
TGIY**S**VMIQKV
GIY**S**VMIQKVI
IY**S**VMIQKVIL
Y**S**VMIQKVILR
SVMIQKVILRD
~~VMIQKVILRDL~~

~40,000 peptides

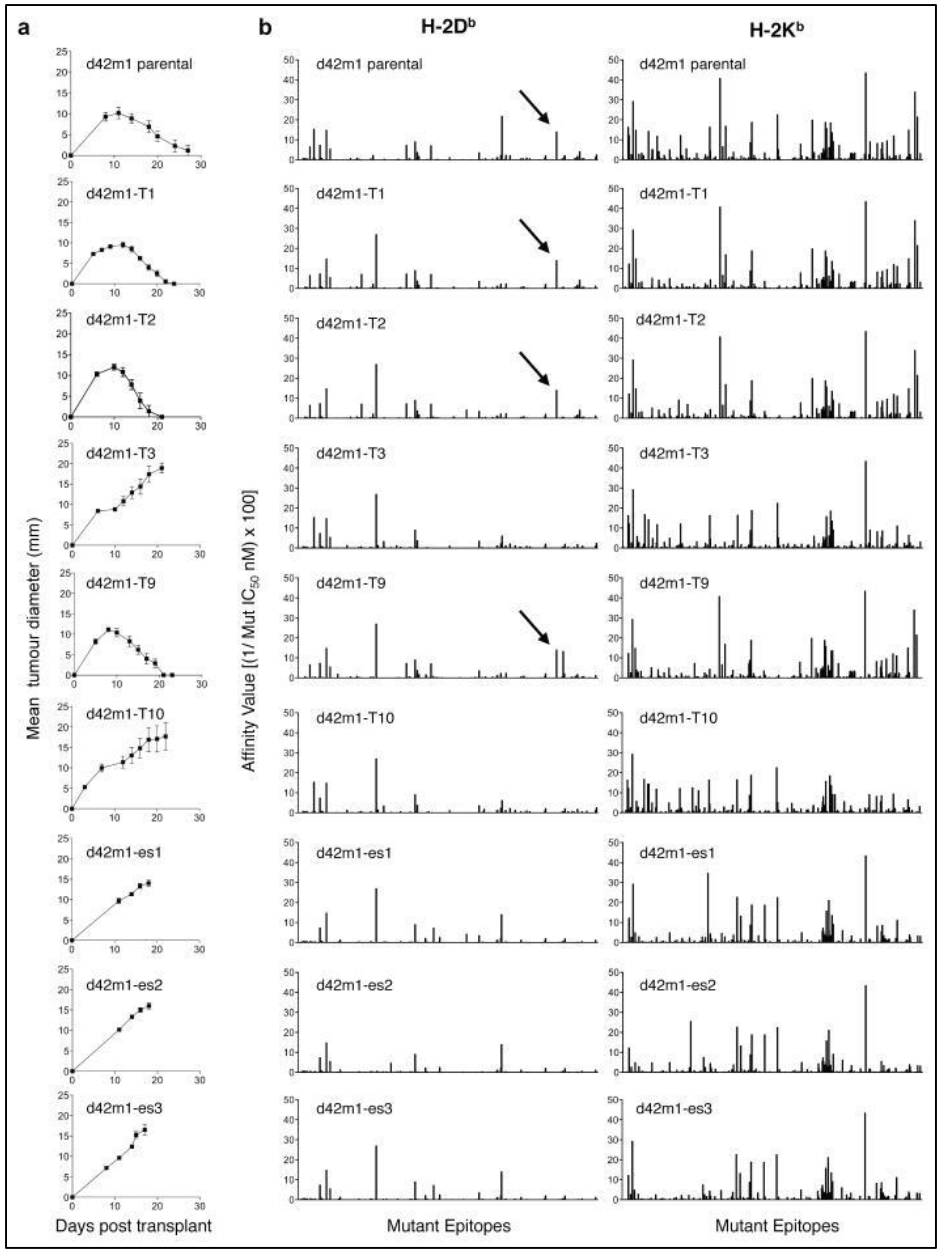
~40 peptides

Synthesize Peptides

response
- Prevention of tumor outgrowth

By Jeffrey Ward

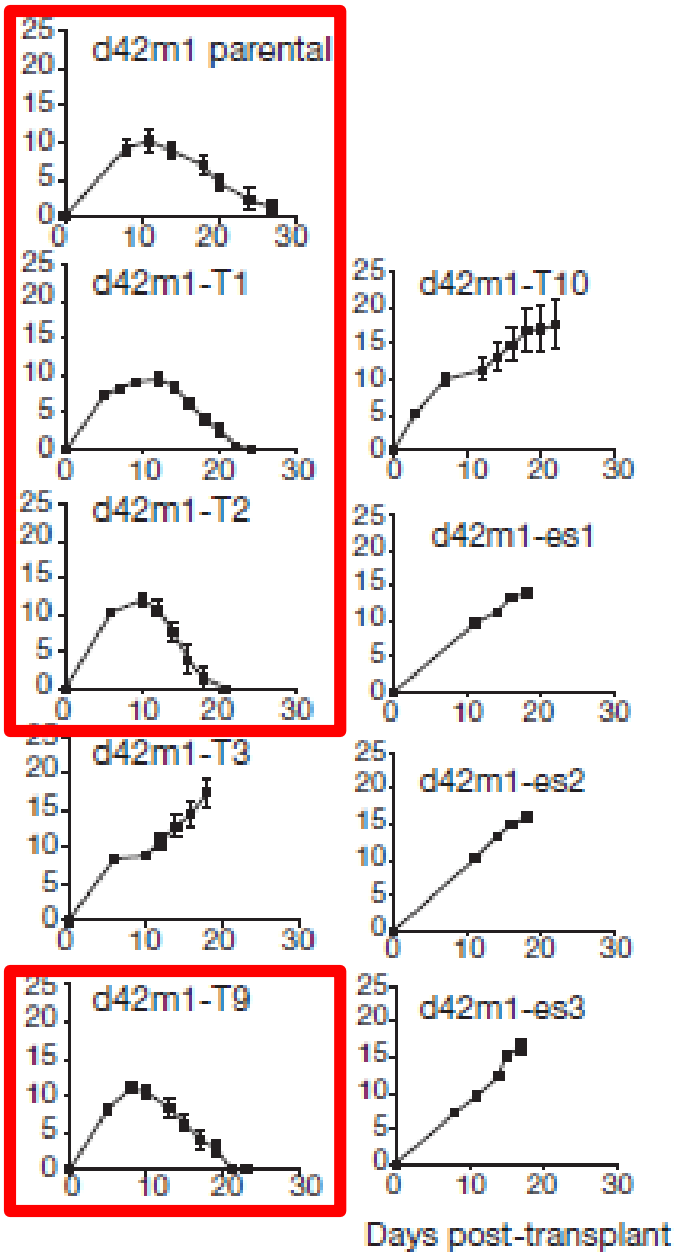
Computational filtering allows to identify neoantigens

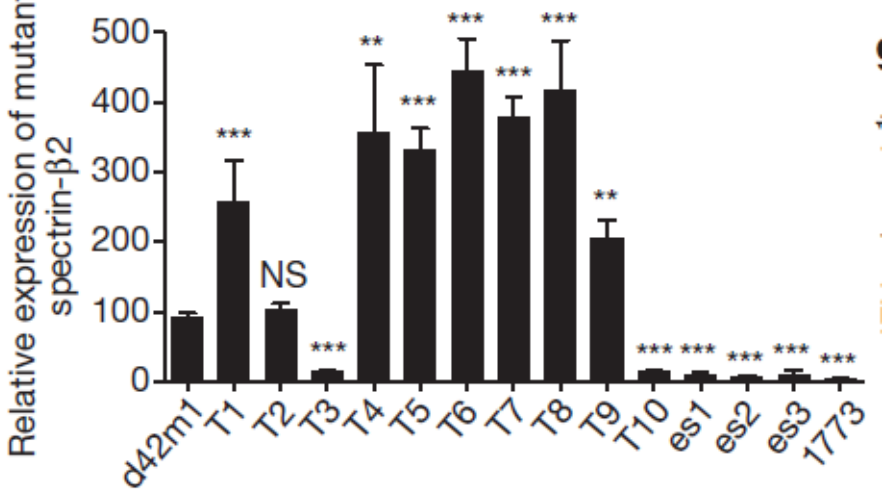


peptide-MHC predictions
for each mutation

Matsushita et al, Nature 2012

Only regressor tumors express spnb2 mutant!





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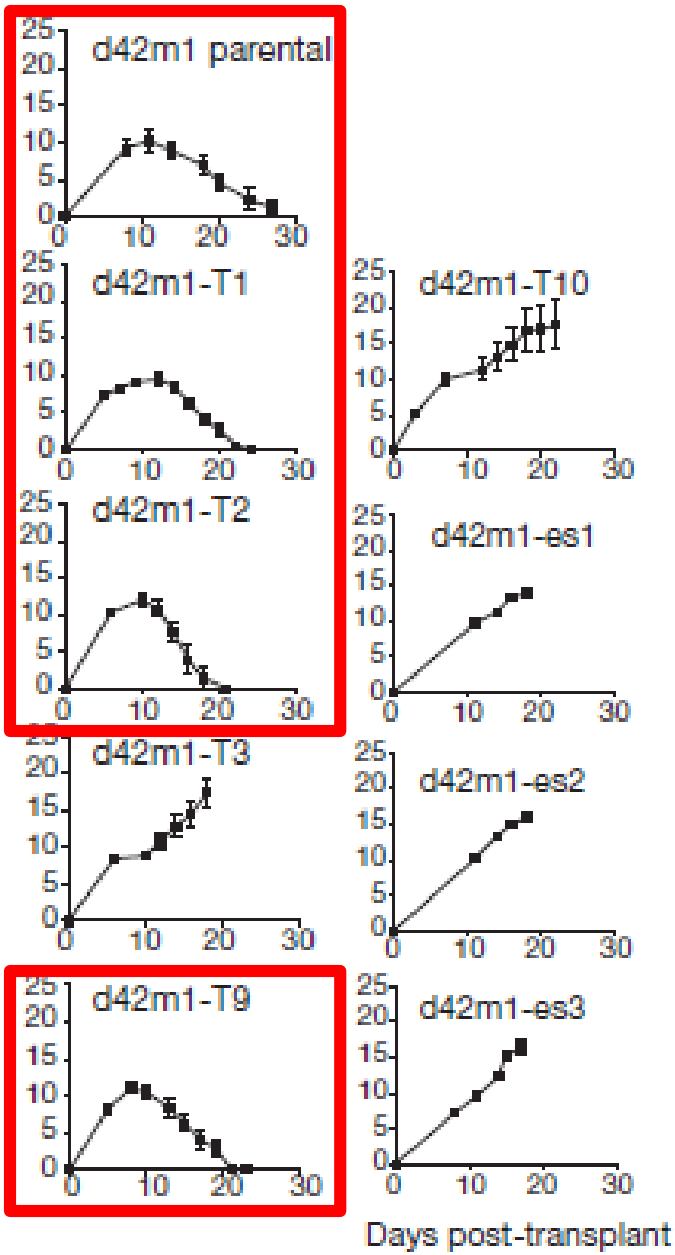
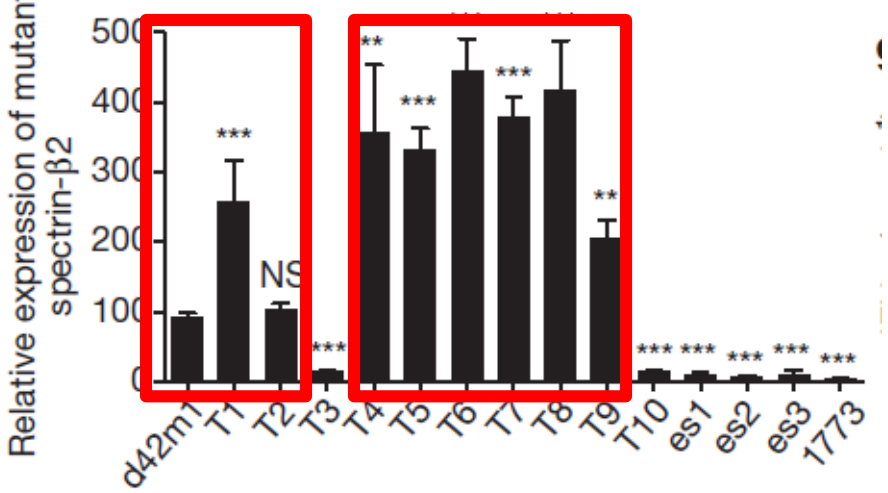
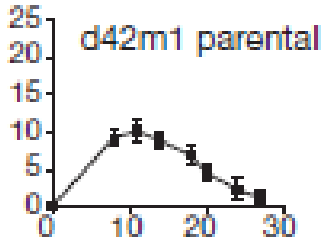
Only regressor tumors express spnb2 mutant!

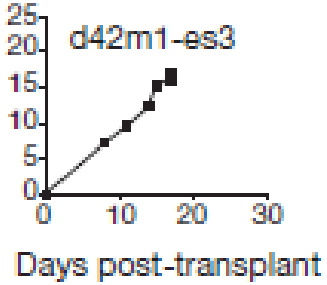


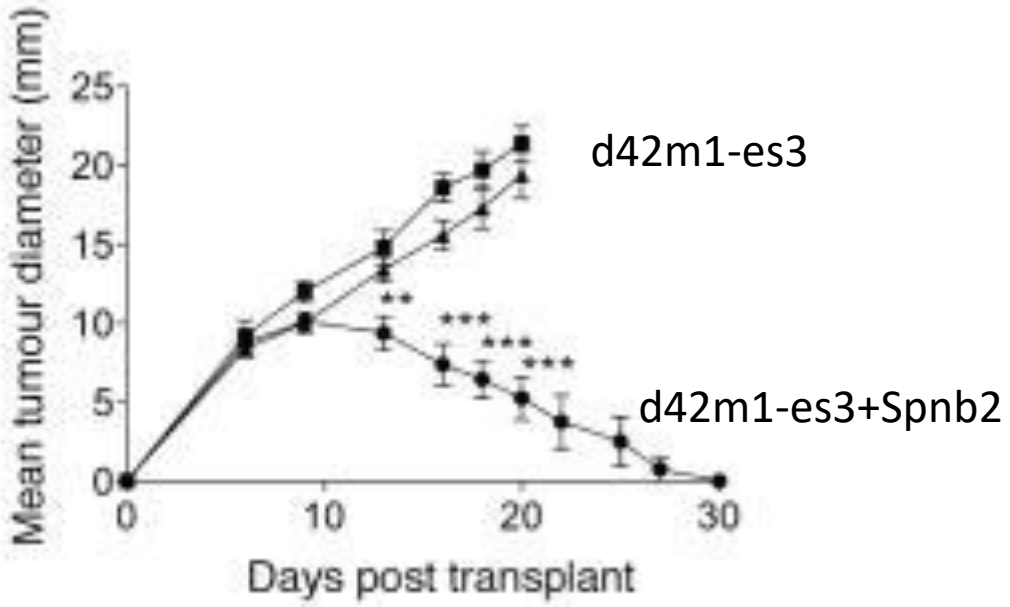


Matsushita et al, Nature 2012

Mutated Spnb2 is sufficient for tumor rejection



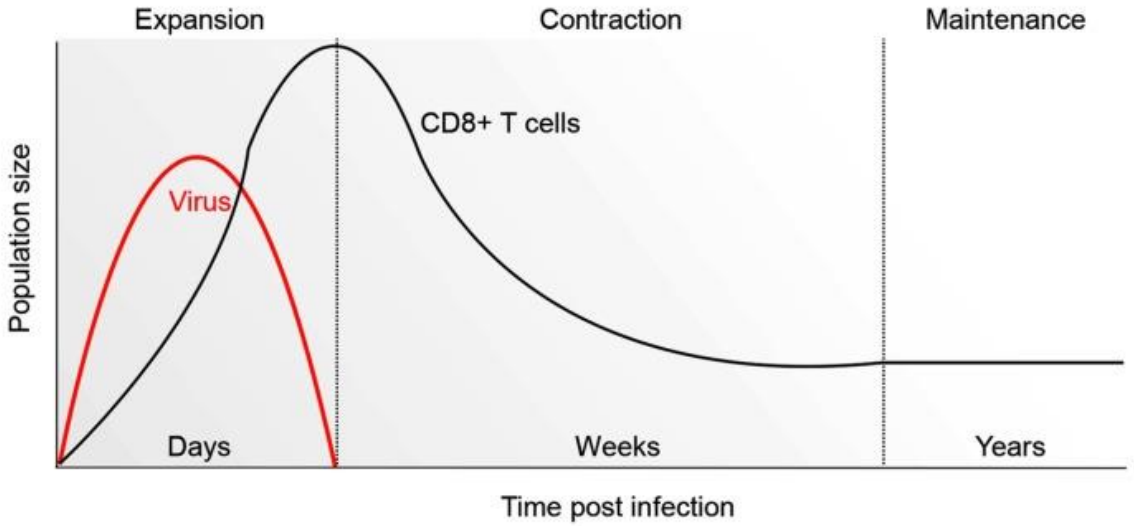


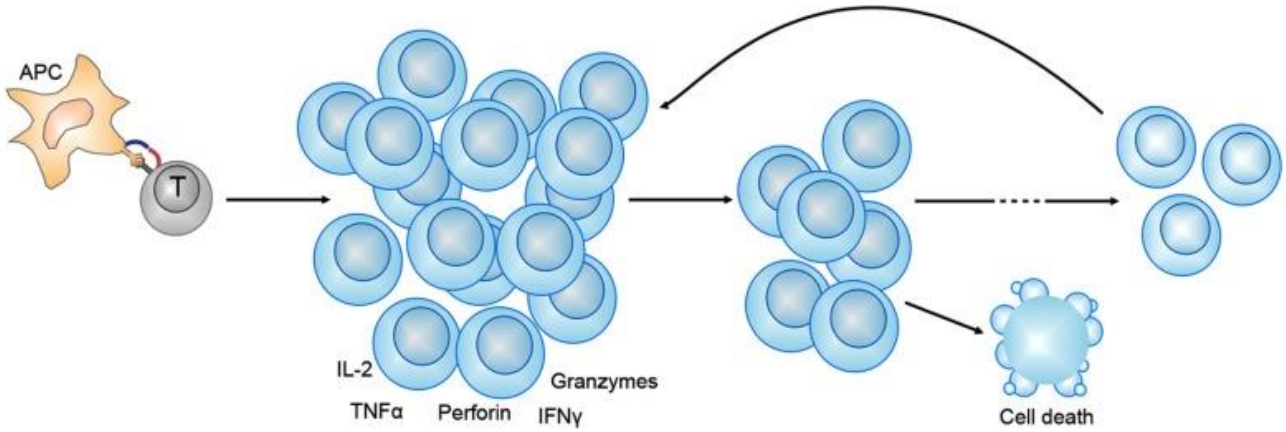


Matsushita et al, Nature 2012

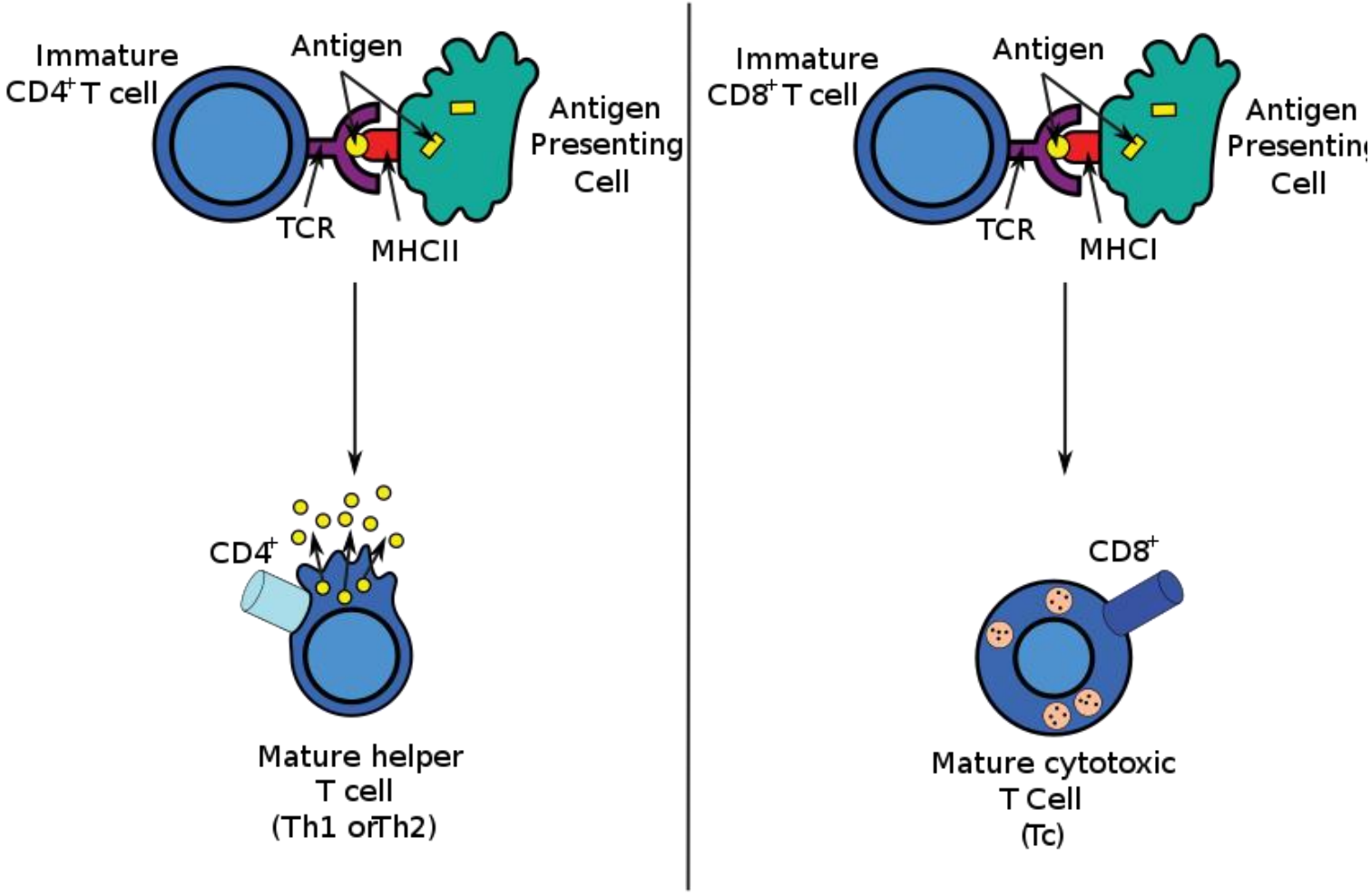
Part II:
T-cell 007.
License to Kill

T-cell clonal expansion

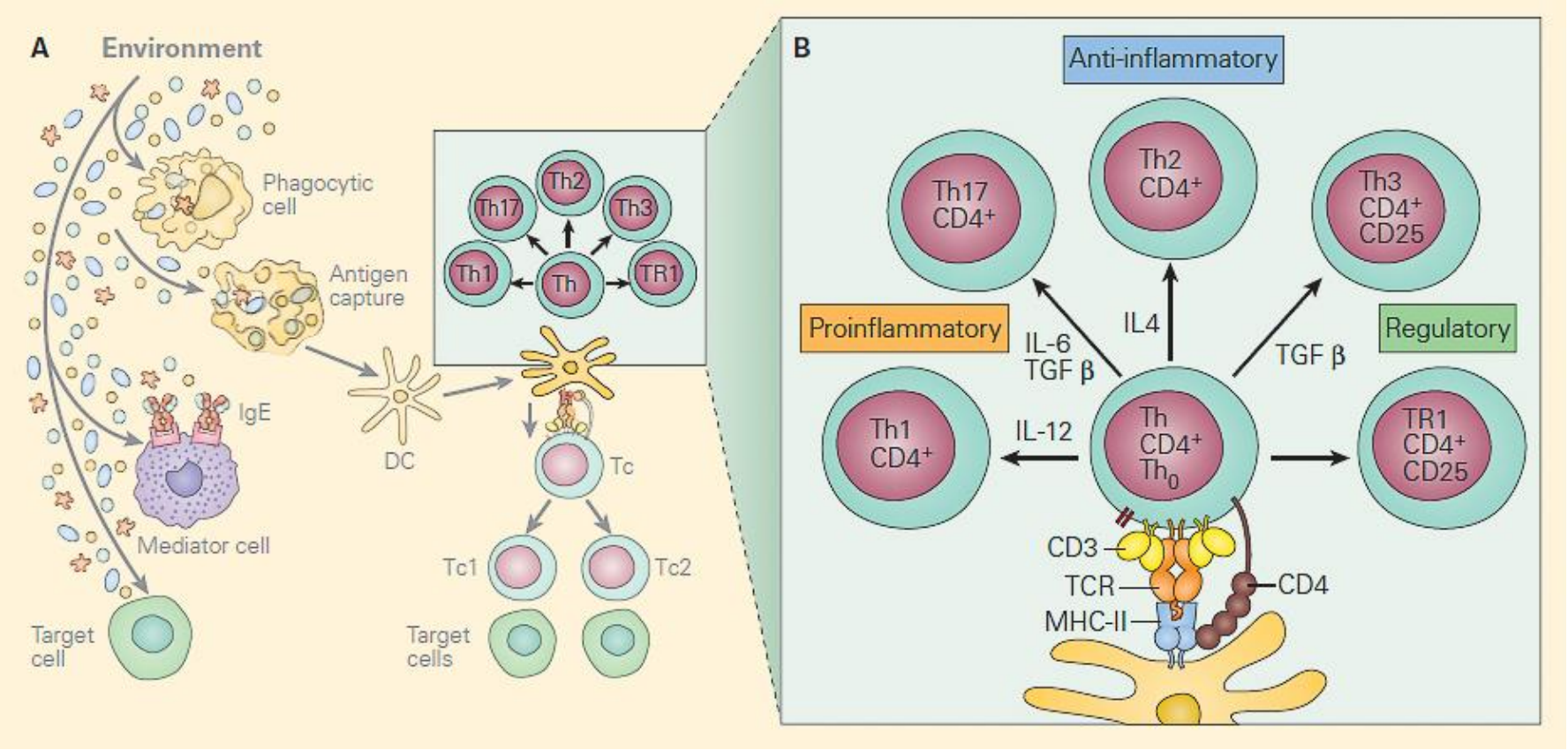




Two kind of T-cells: helper and killers



Inflammatory process one-cell-at-a-time



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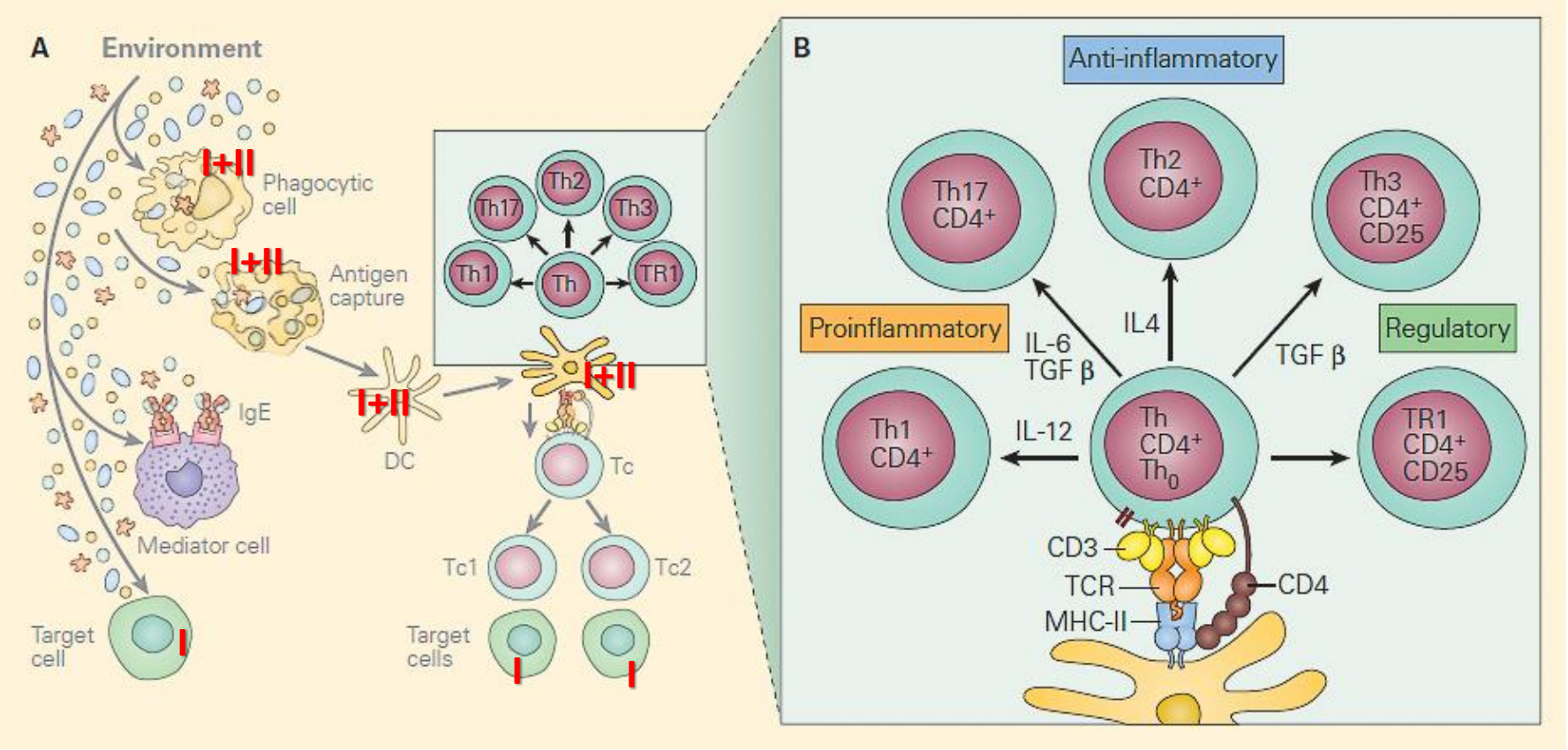
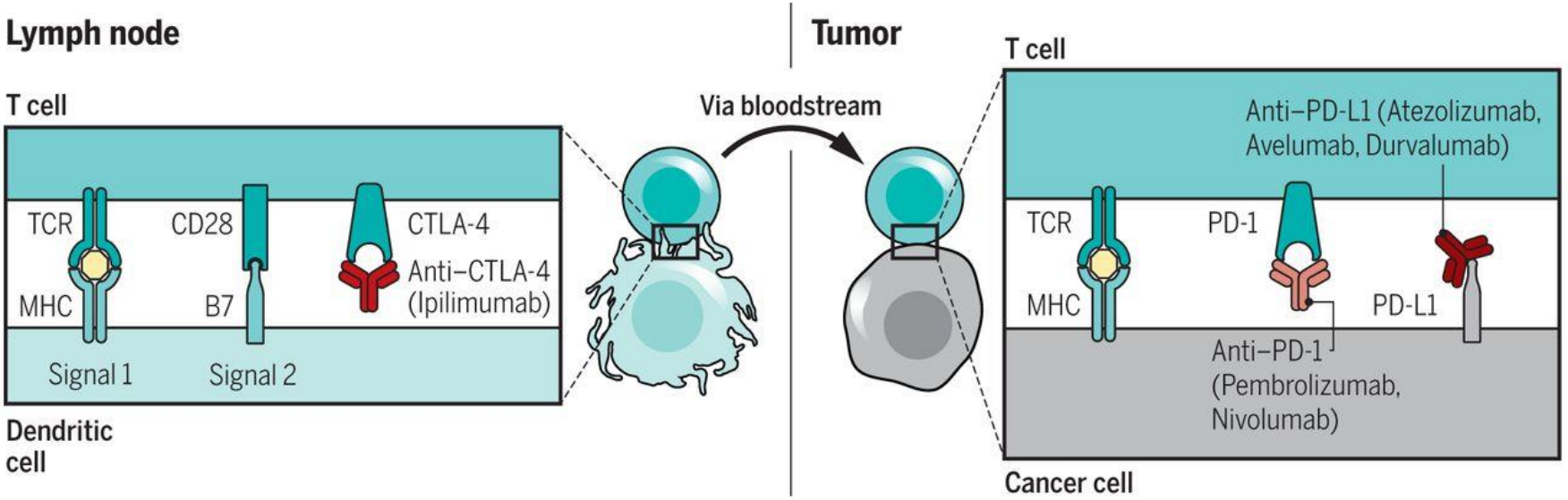


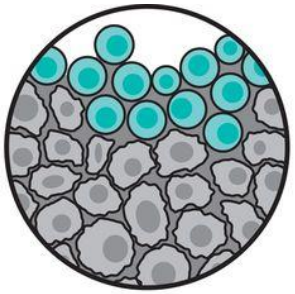
I - MHC class I – expressed by all cells

II - MHC class II – expressed only by professional APCs

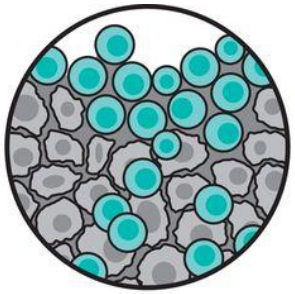
How is the contraction phase controlled?



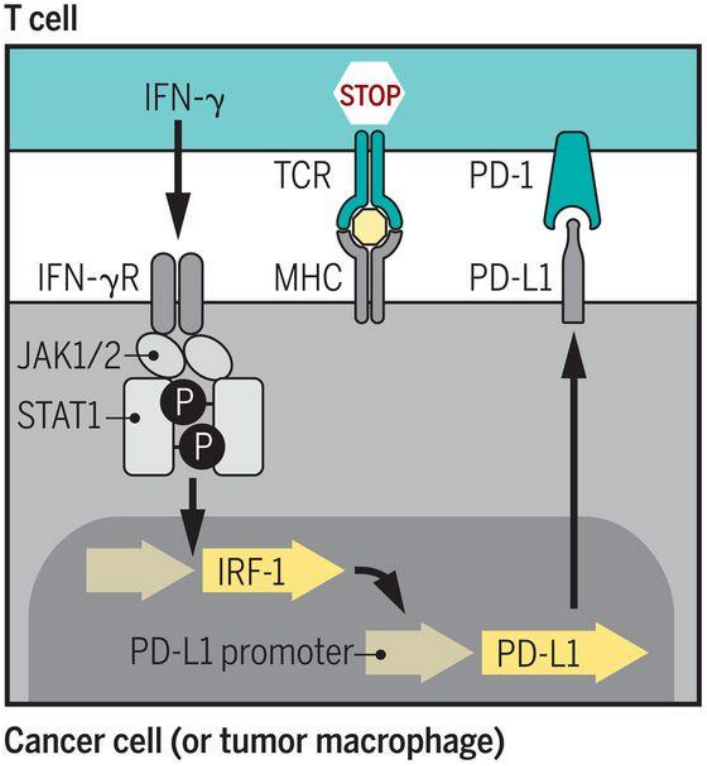
T-cell exhaustion!

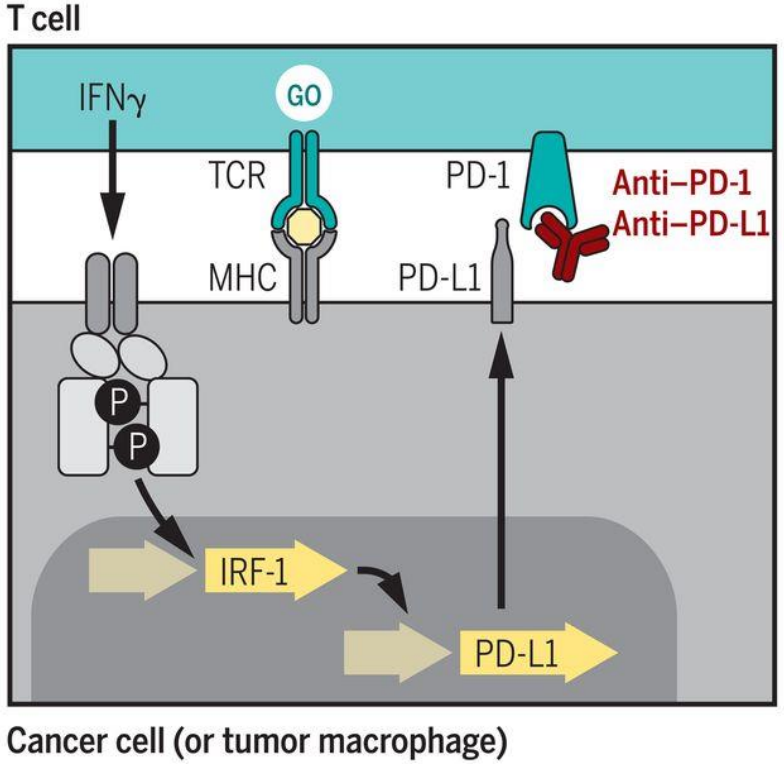


Cancer cells sense they are under attack from T cells by recognizing IFN-γ, which leads to the reactive expression of PD-L1.



Blocking the PD-1–PD-L1 interaction takes away the signal that prevented T cells from attaching to cancer cells and leads to tumor infiltration.

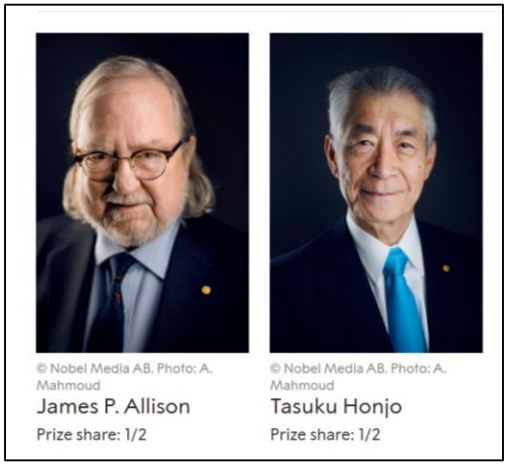




Huge success both in clinics and in academia

2011 -
ipilimumab approved by FDA
for melanoma

2013 -
breakthrough of the year



2018 -
Nobel Prize

Paradigm shift – long survival tail

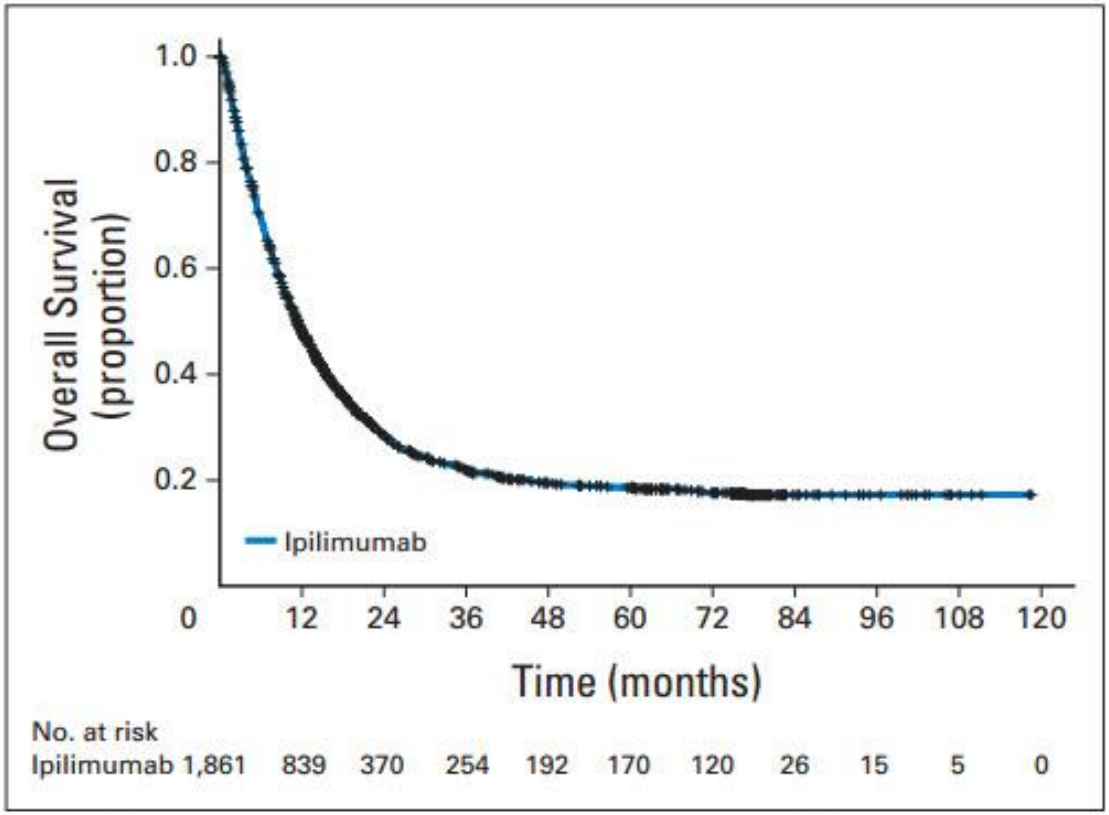
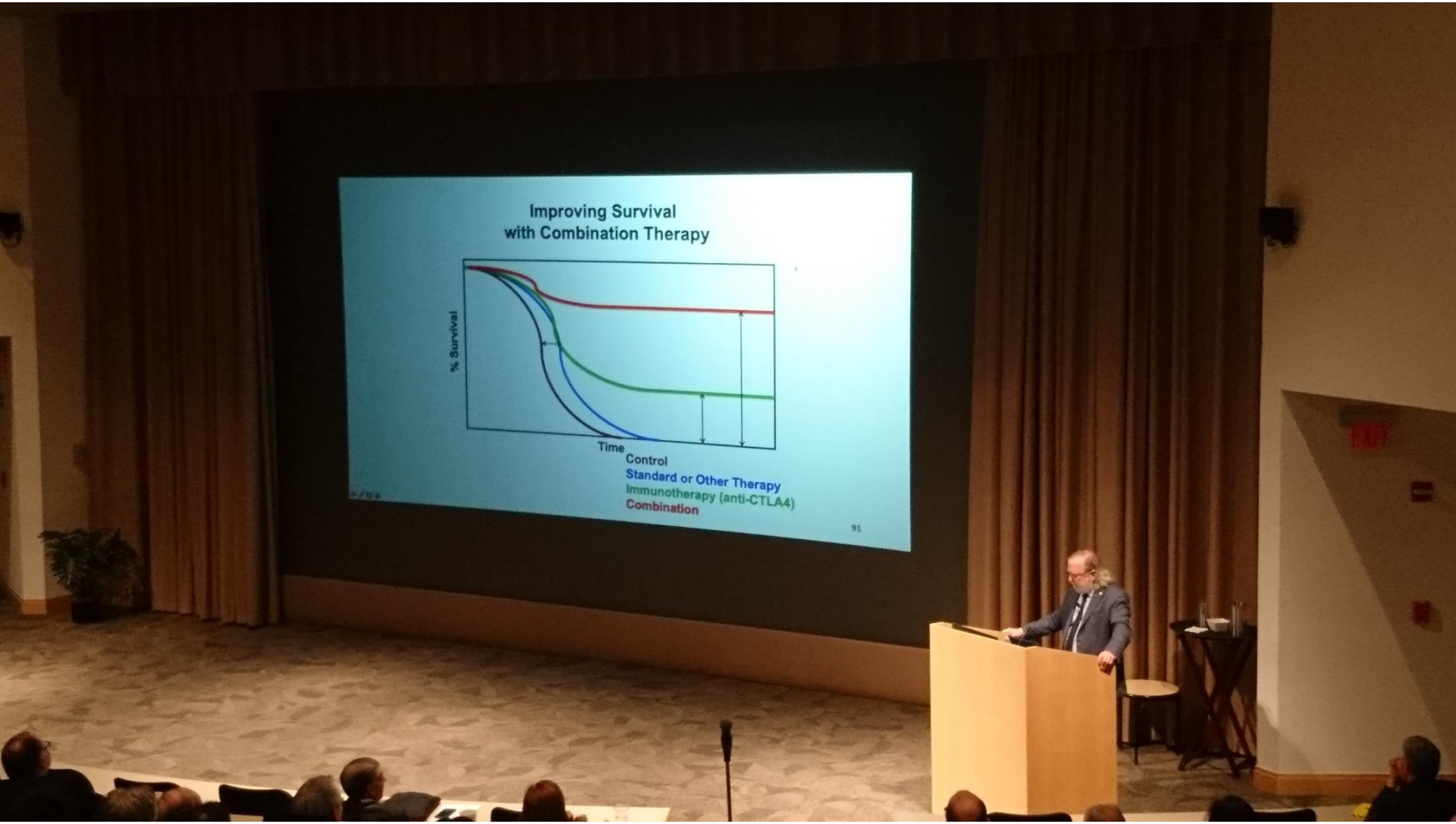
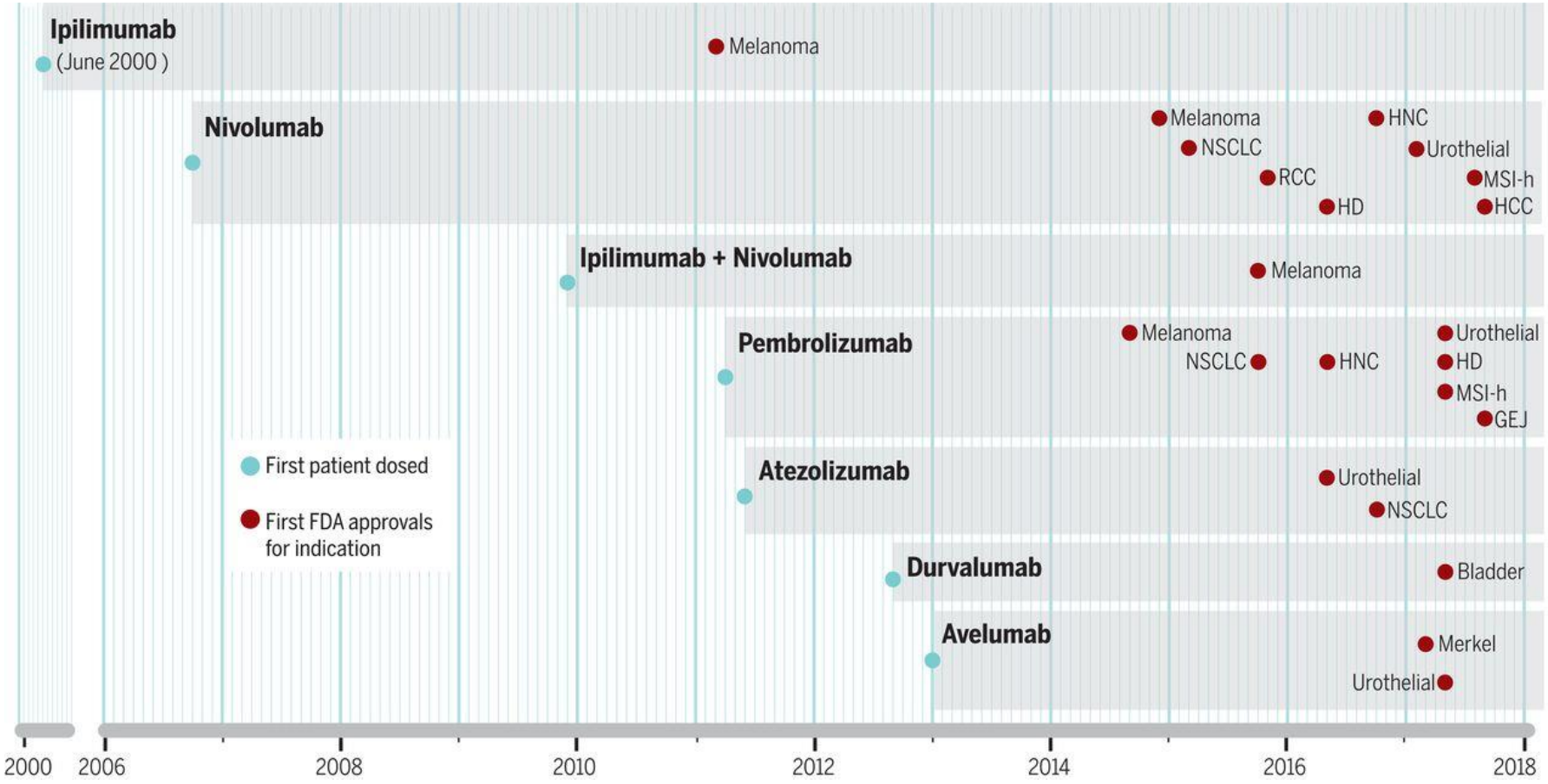


Fig 1. Primary analysis of pooled overall survival (OS) data. Individual patient data were pooled from 10 prospective trials and two retrospective, observational studies of ipilimumab in metastatic melanoma (n = 1,861). Median OS was 11.4 months (95% CI, 10.7 to 12.1 months) with a 3-year survival rate of 22% (95% CI, 20% to 24%). Crosses indicate censored patients.

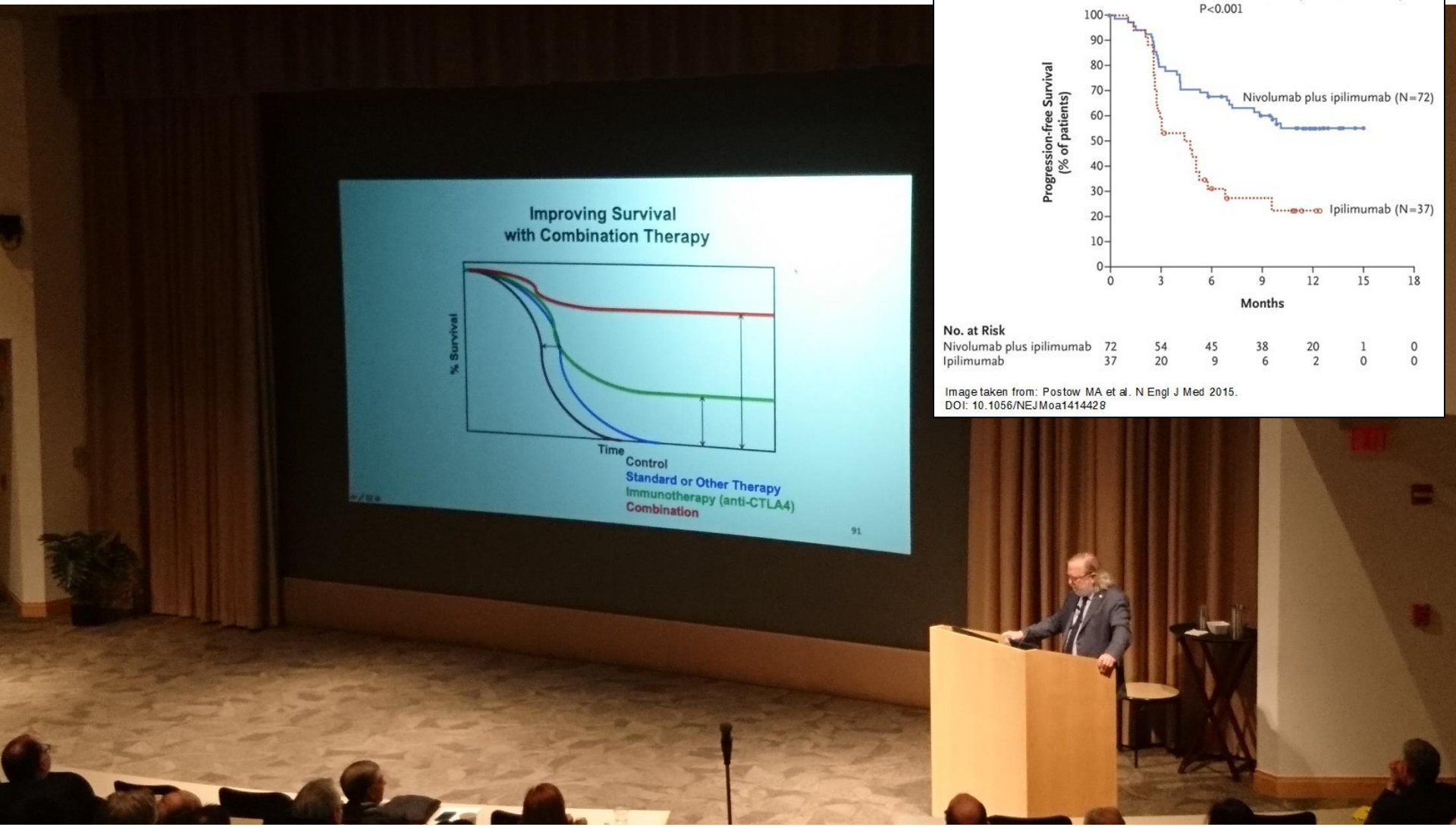
Combinations?



More checkpoints!



Paradigm shift



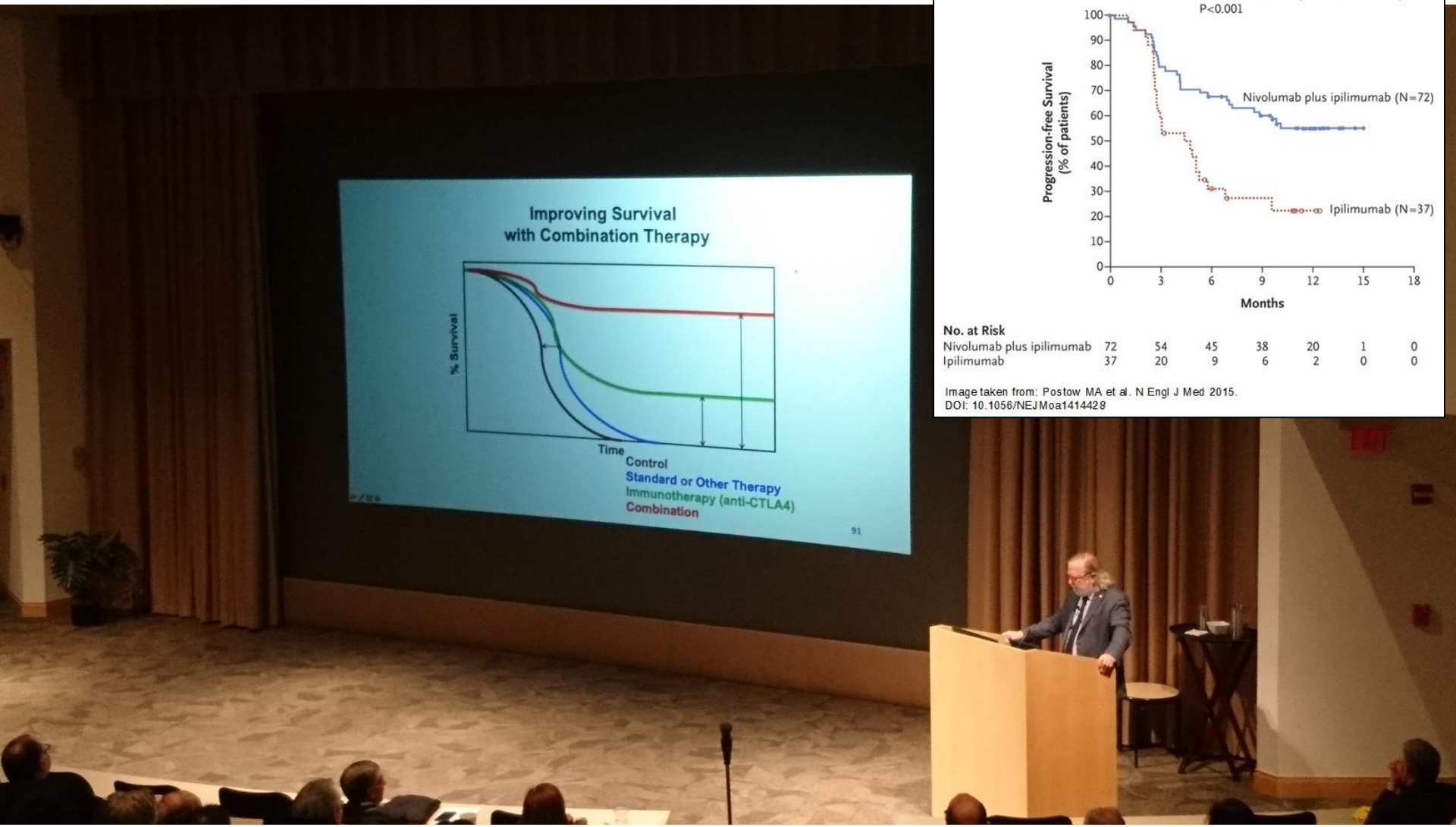
	Death or Disease Progression	Median Progression-free Survival
	no. of patients/total no.	*mo (95% CI)*
Nivolumab plus Ipilimumab	30/72	NR
Ipilimumab	25/37	4.4 (2.8–5.7)

Hazard ratio, 0.40 (95% CI, 0.23–0.68)
P<0.001

No. at Risk							
Nivolumab plus ipilimumab	72	54	45	38	20	1	0
Ipilimumab	37	20	9	6	2	0	0

Image taken from: Postow MA et al. N Engl J Med 2015.
DOI: 10.1056/NEJMoa1414428

Paradigm shift



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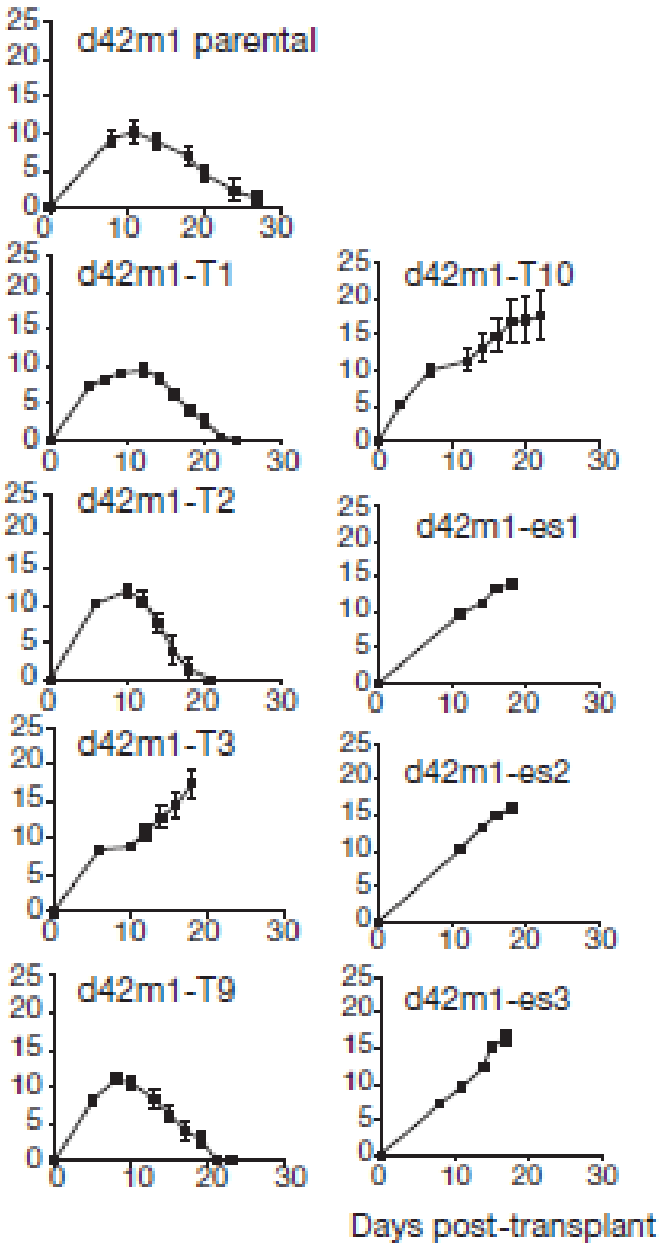
Hazard ratio, 0.40 (95% CI, 0.23–0.68)
P<0.001

No. at Risk							
Nivolumab plus ipilimumab	72	54	45	38	20	1	0
Ipilimumab	37	20	9	6	2	0	0

Image taken from: Postow MA et al. N Engl J Med 2015.
DOI: 10.1056/NEJMoa1414428

But why not 100%?

Back to sarcoma cell panel of Schreiber lab



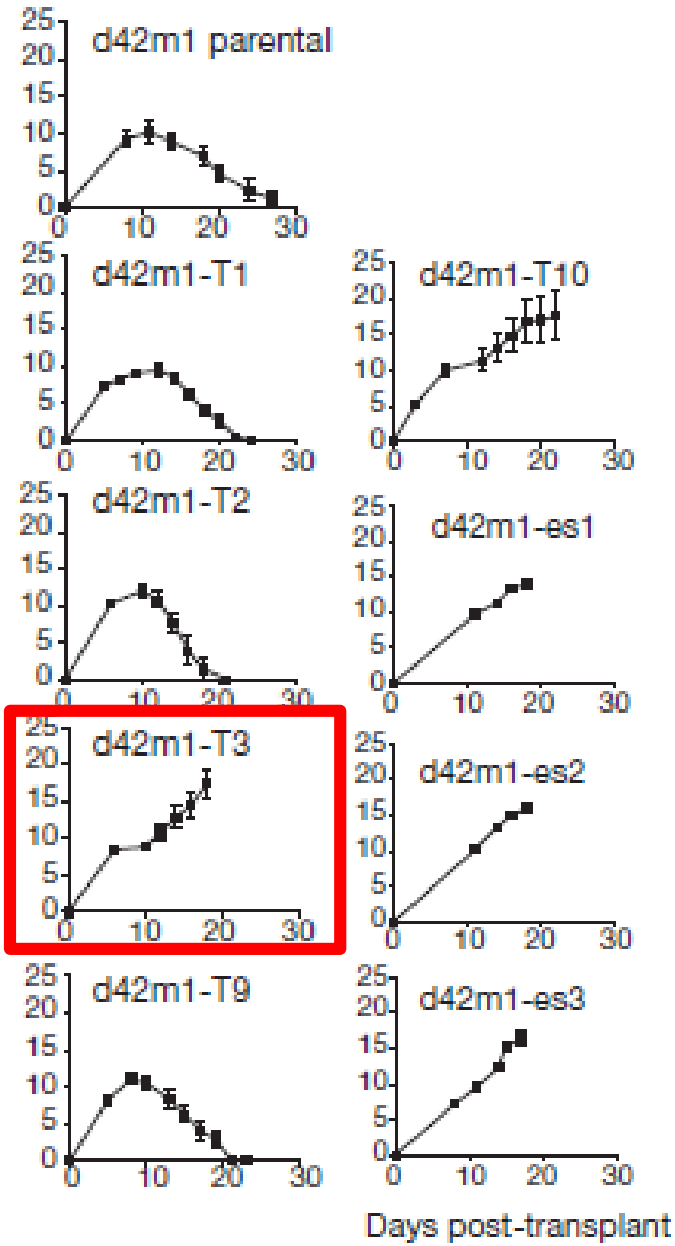
Some mouse sarcomas are naturally rejected while others grow out

Are growing sarcomas “immunologically dead”?

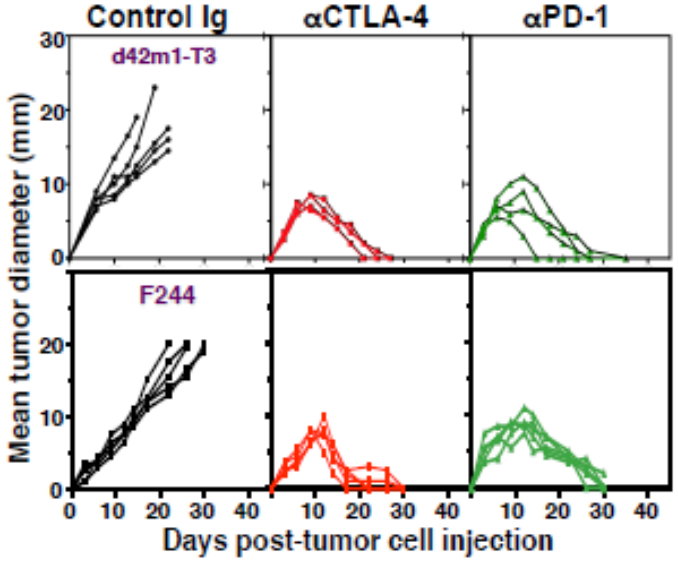
Could growing sarcomas be responsive to checkpoint blockade?

Matsushita et al, Nature 2012

Checkpoint blockade works in progressor tumors



aCTLA4/aPD1 treatments “cure” the mice

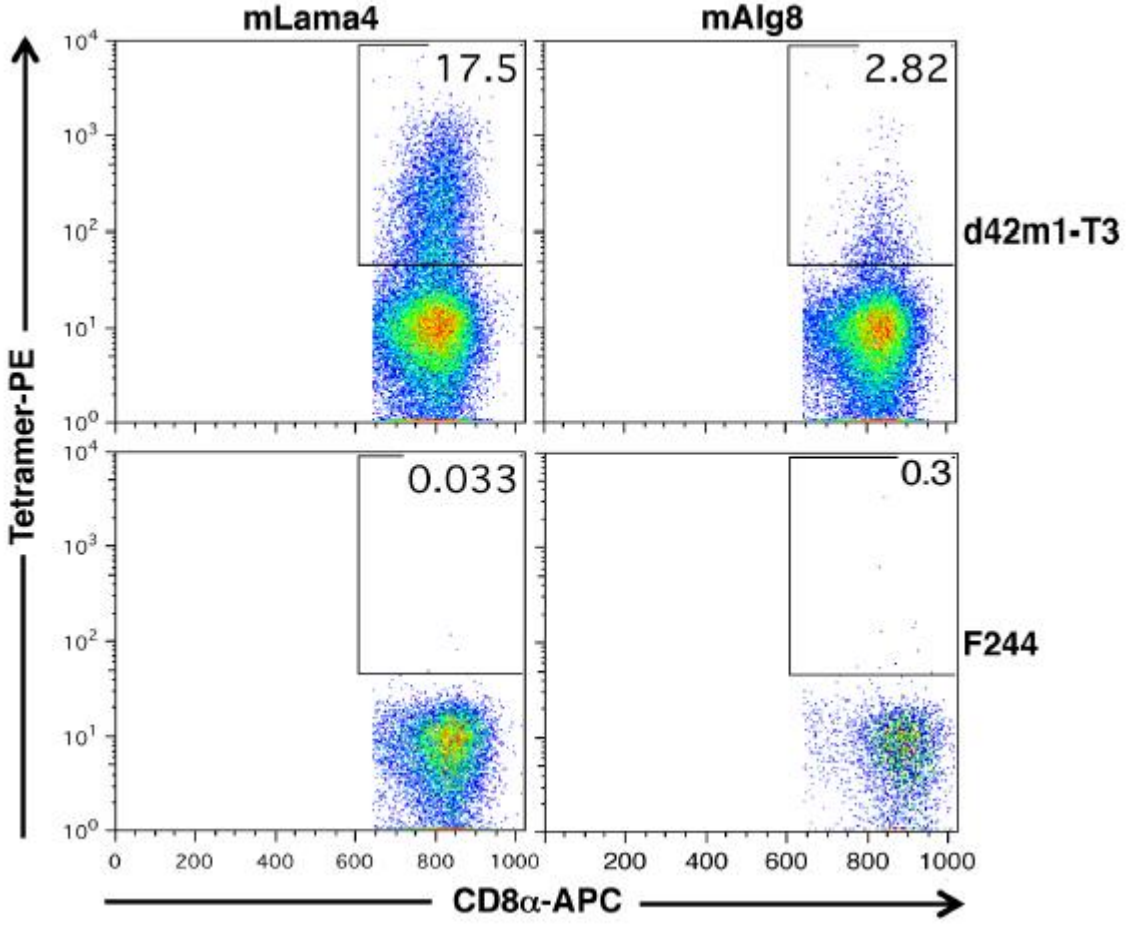


Gubin et al, Nature 2014

Potential Antigens identified for T3 tumor

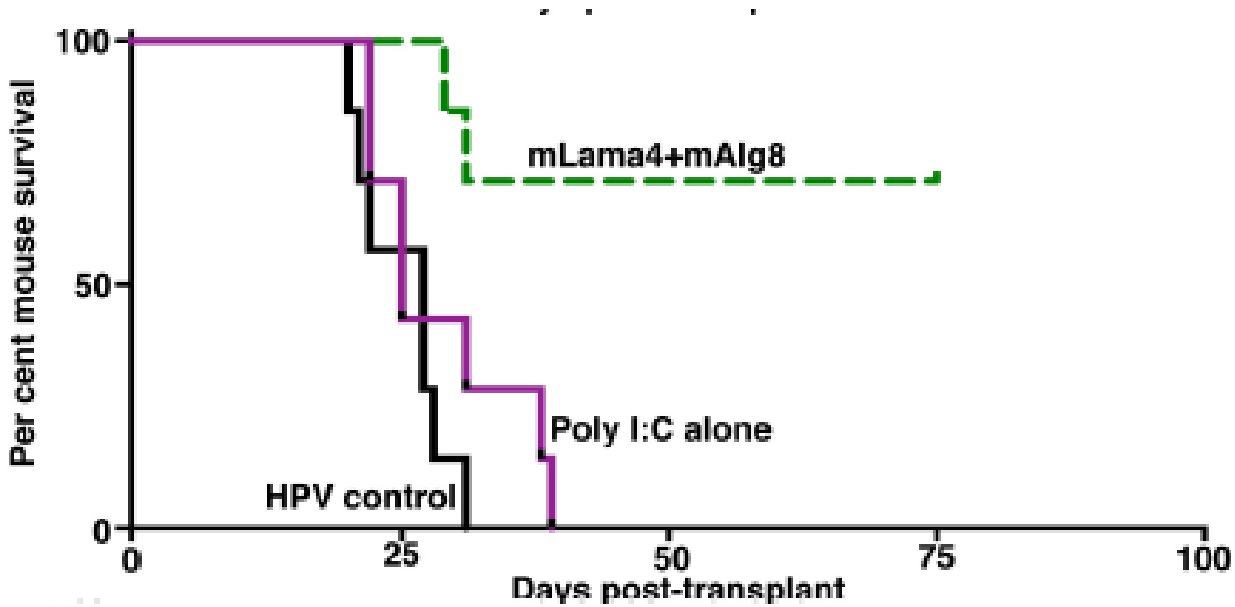
Rank	Id	WT peptide	Mut peptide	Median mutant affnity (nm^{-1})	Cutting score	Neoepitope ratio
1	Sbf2_V511L	FNYLYSPV	FNYLYSPL	0.3998714058	0.542809	3.5952400634
2	Alg8_A506T	ITYAWTRL	ITYTWTRL	0.2223404132	0.954498	1.0616164751
3	Lama4_G1254V	GGFNFRTL	VGFNFRTL	0.2188577796	0.967372	12.8123805304
4	6430548M08Rik_H290R	KVYLYTHL	KVYLYTRL	0.1841609862	0.847512	1.2786360207
5	Apob_T1328S	STNVYSNL	SSNVYSNL	0.1027451056	0.870279	1.6649288887
6	Olfr168_P253H	VTFYYAPF	VTFYYAHF	0.0916300653	0.823354	0.667371074
7	Olfr1121_D127Y	MSYDRYVAI	MSYYRYVAI	0.0883059591	0.478287	1.4165113789
8	Olfr12_I133M	MAYDRFMAI	MAYDRFMAM	0.0818398718	0.975672	1.7597270663
9	Tpm2_I266T	ITLLFSFL	TTLLFSFL	0.0712708996	0.923923	0.3596749785
10	Olfr849_G208R	VSVLFFGV	VSVLFFRV	0.0698917259	0.368878	1.7065708369

Antigen-specific T-cells are present in tumor even before treatment!



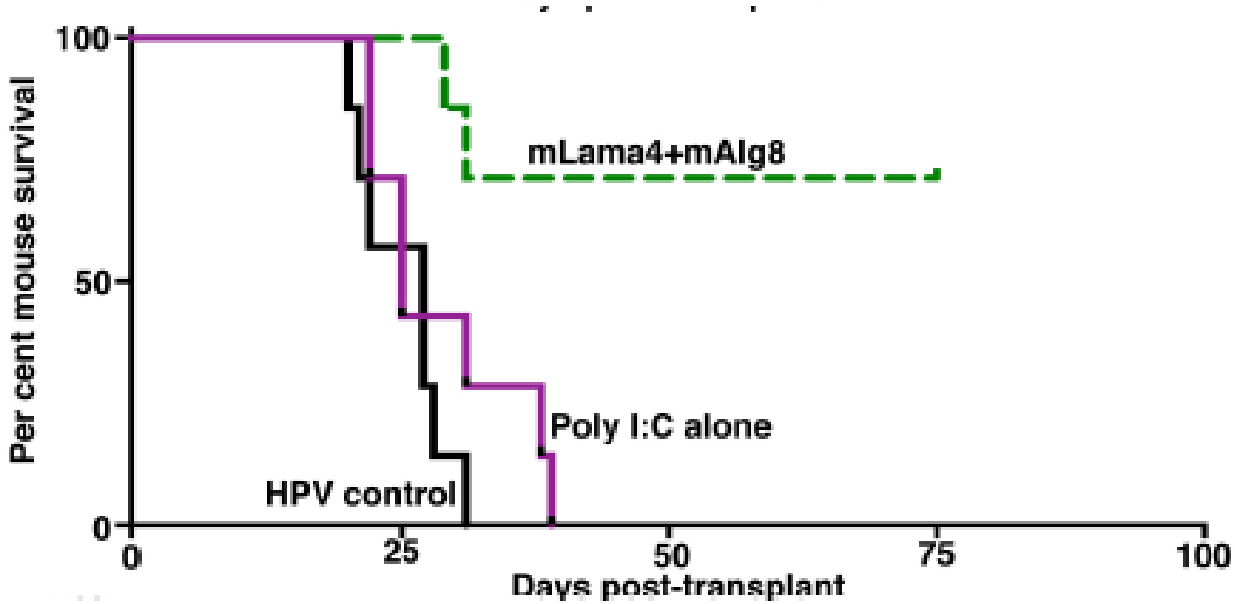
Gubin et al, Nature 2014

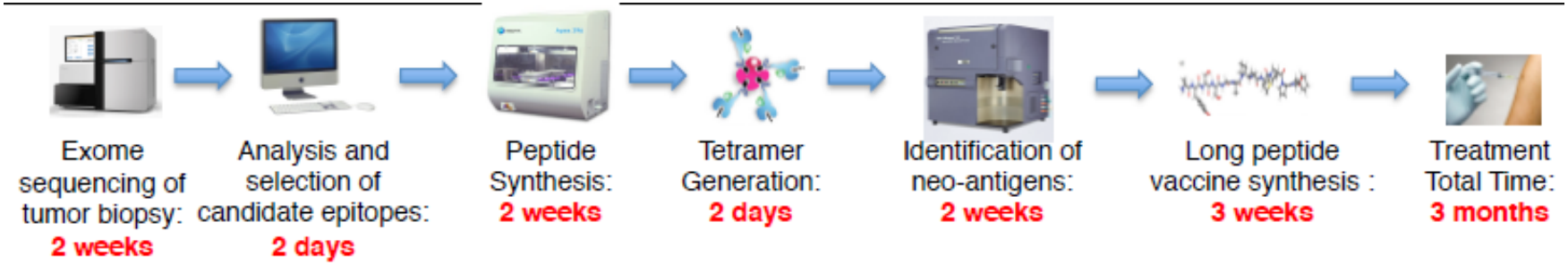
Theraputic vaccination saves the mouse!



Gubin et al, Nature 2014

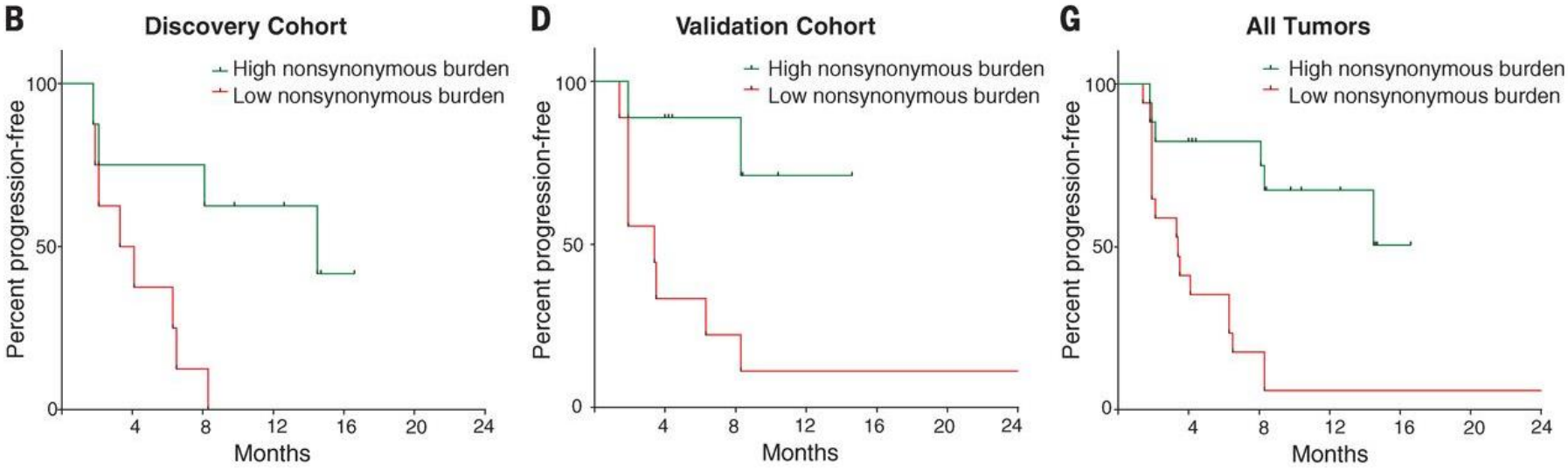
Theraputic vaccination saves the mouse!





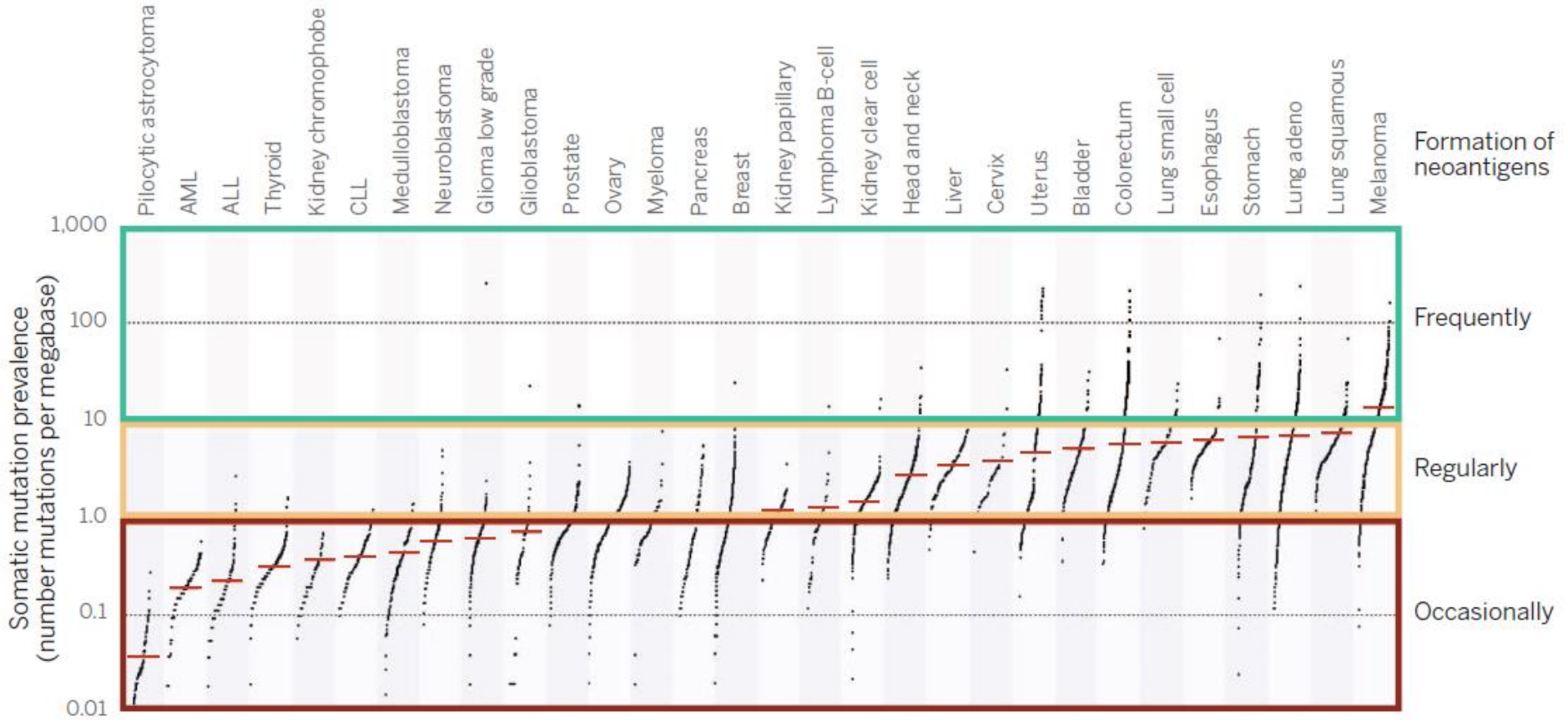
Gubin et al, Nature 2014

Mutational load is predictive of immunotherapy response



Rizvi et al, Science 2015

This is why first successes of checkpoint blockade are in melanoma!!



It all started in 19th century

Fig. 1. Dr William B. Coley (active career 1891–1936).

Worked in New York Cancer Hospital
(later became a part of Memorial Sloan Kettering Cancer Center)

- Noticed that infection with erysipelas often leads to spontaneous regression of sarcomas

- Started therapeutically infection patients with inoperable sarcomas

"There can be no doubt that the influence of erysipelas upon malignant tumors is much more powerful than any other febrile disease." (Coley, 1931.)

It all started in 19th century

Fig. 1. Dr William B. Coley (active career 1891–1936).

Fig. 3. First patient Coley treated by deliberate induction of erysipelas (Coley, 1896a). Large lesion on neck broke down and disappeared under treatment; see text for description. Patient remained well for 8 years, then died of recurrence (Coley, 1909).

"There can be no doubt that the influence of erysipelas upon malignant tumors is much more powerful than any other febrile disease." (Coley, 1931.)

It turns out that *Streptococci* alone is not enough!

What we refer to as **Coley's toxins** is combination of two components:

- Streptococci – gram-positive bacterial infection (no endotoxins)
- Serratia – gram-negative bacteria (endotoxins)

"I wish at the outset to state what is known to every one who has read my previous papers, that the mixed toxins, prepared in the way described in these papers, have been shown to have a curative effect sufficient for practical purposes only in cases of sarcoma and not in cases of carcinoma." (Coley, 1908.)

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Note resemblance to classical vaccine formulation:

Adjuvant + Adaptive Immunity Target

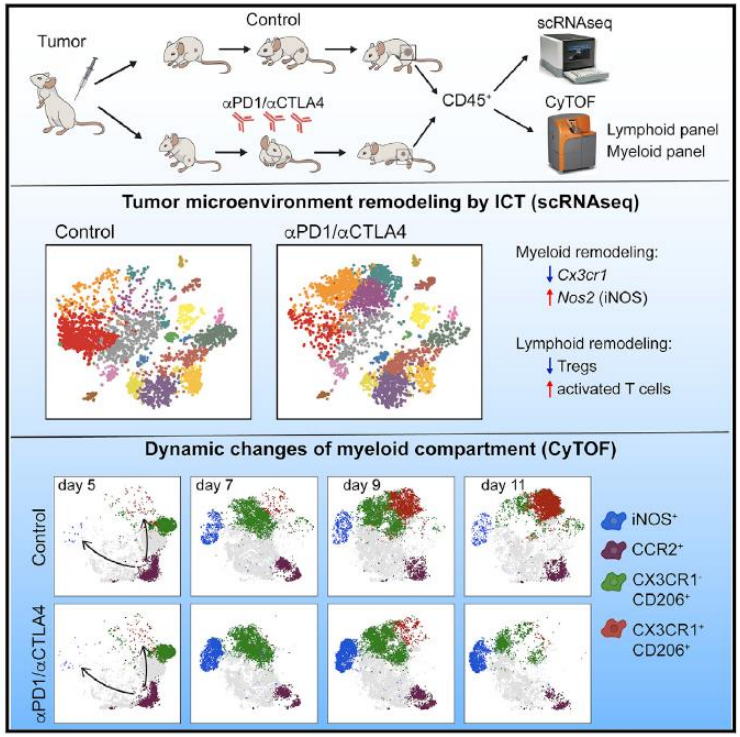
Next – understanding of checkpoint therapy at the single-cell resolution

Article

Cell

High-Dimensional Analysis Delineates Myeloid and Lymphoid Compartment Remodeling during Successful Immune-Checkpoint Cancer Therapy

Graphical Abstract



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In Brief

Comprehensive changes in the tumor microenvironment during successful immune-checkpoint therapy are profiled, implicating a key role for polarization of infiltrating macrophages in the anti-tumor immune milieu.

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