



APPLICATION OF NEOANTIGENS TO BLOOD MALIGNANCIES

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Disclosures

Catherine J. Wu, MD, has affiliations with Neon Therapeutics, Inc. (*Consulting Fees*); Neon Therapeutics, Inc. (*Ownership Interest*)

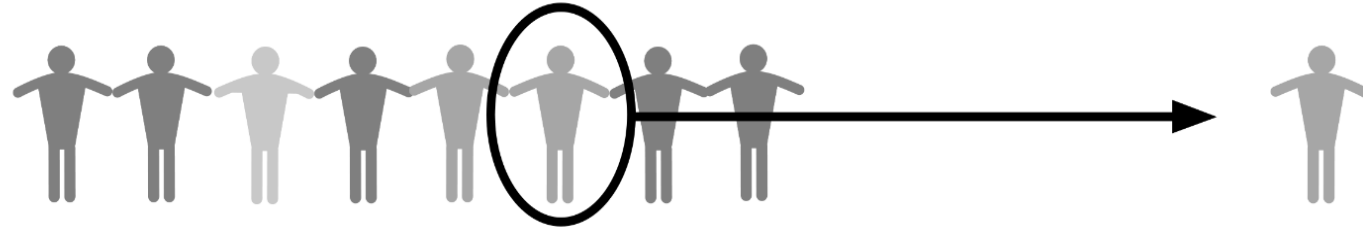


2018: Critical Questions to Address

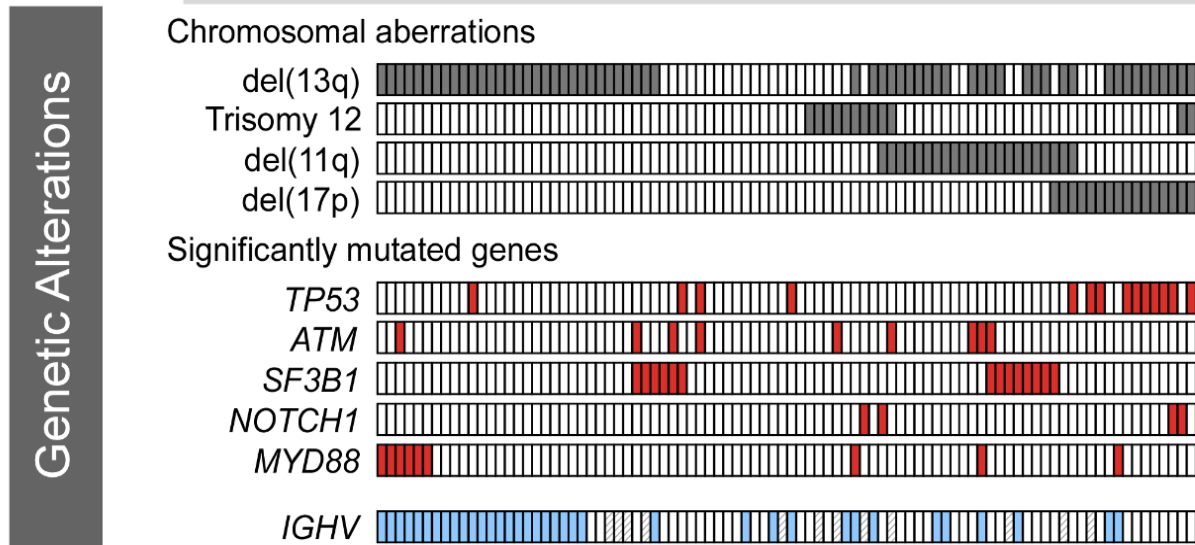
- How to increase fraction of patients with durable responses?
- How to minimize autoimmunity?



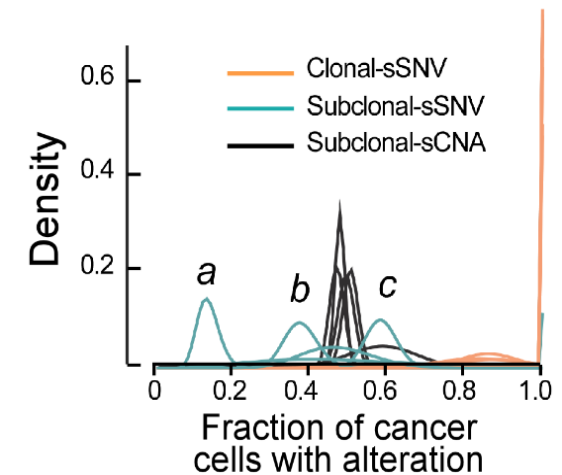
Studying Intratumoral Heterogeneity in CLL



A Inter-patient Heterogeneity

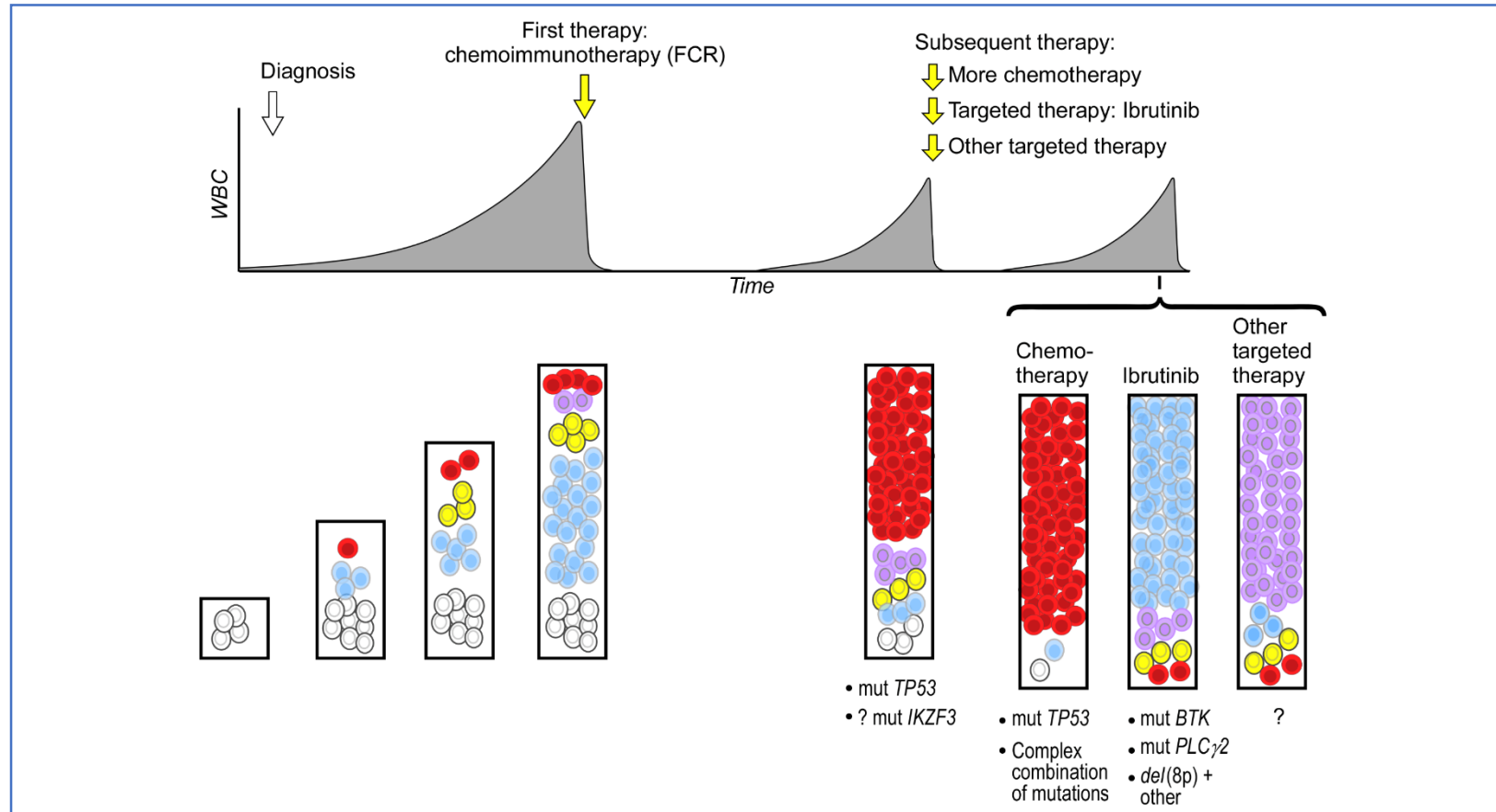


B Intra-sample Heterogeneity





Intratatumoral Heterogeneity: Fuel for the Selection of Fitter Subclones With Therapy

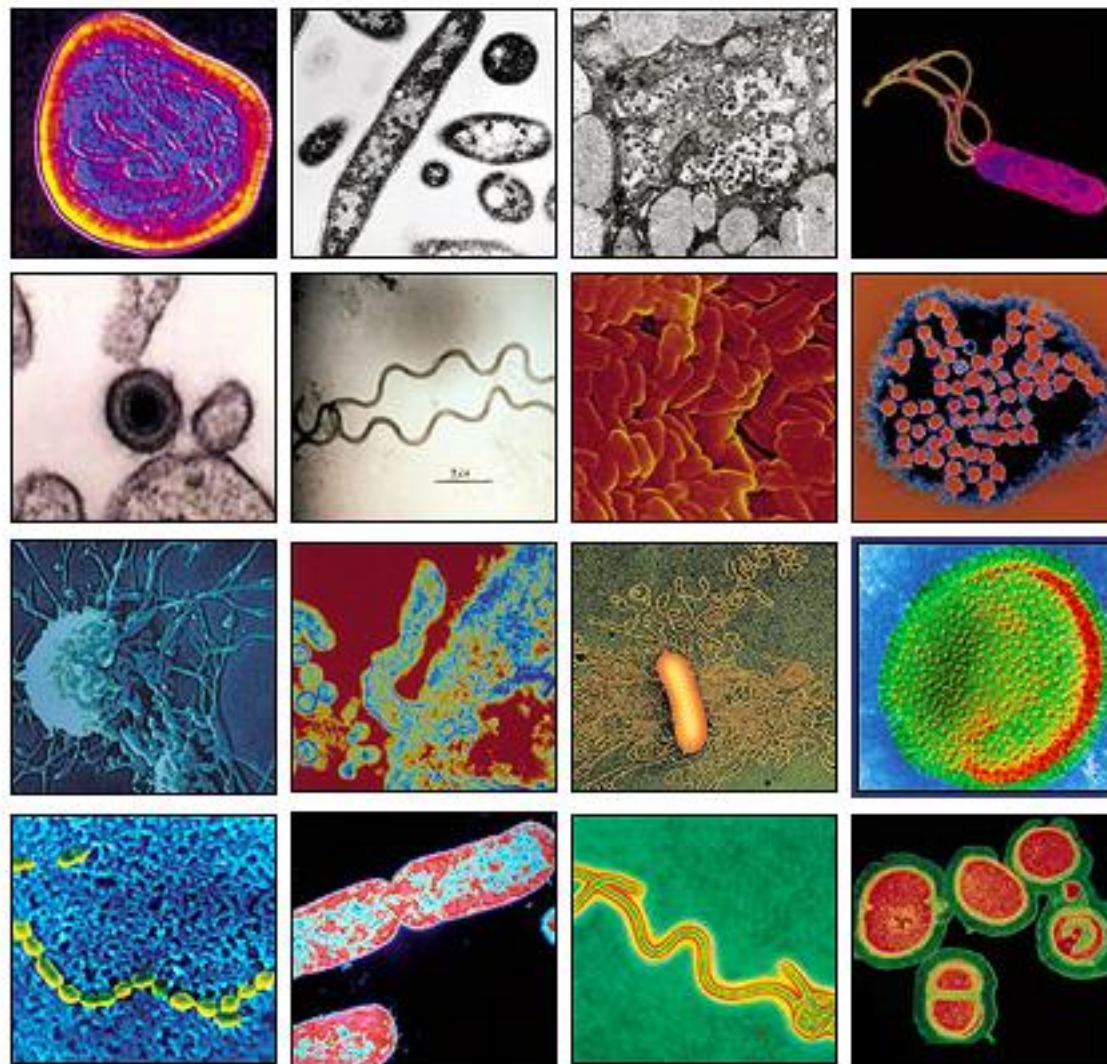


Capacity for evolution is all there already in the tumor samples at treatment initiation



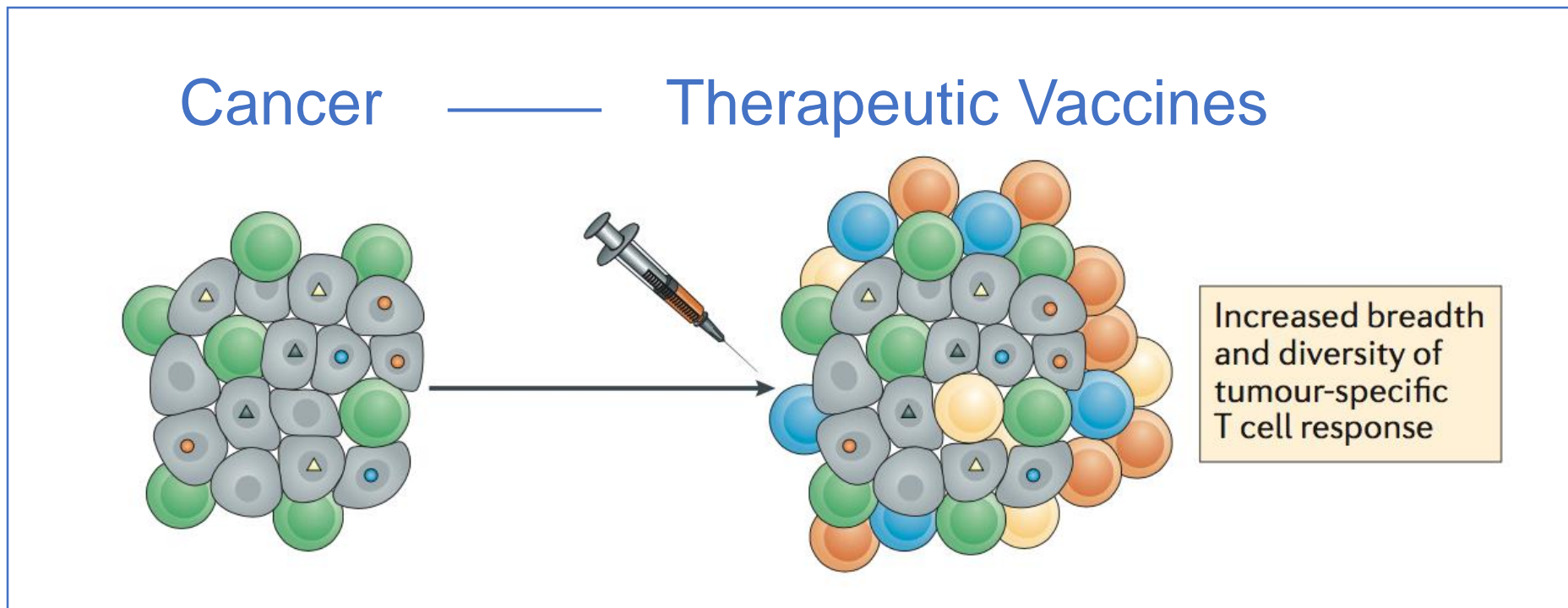


Bacteria, Fungi, Viruses, Parasites



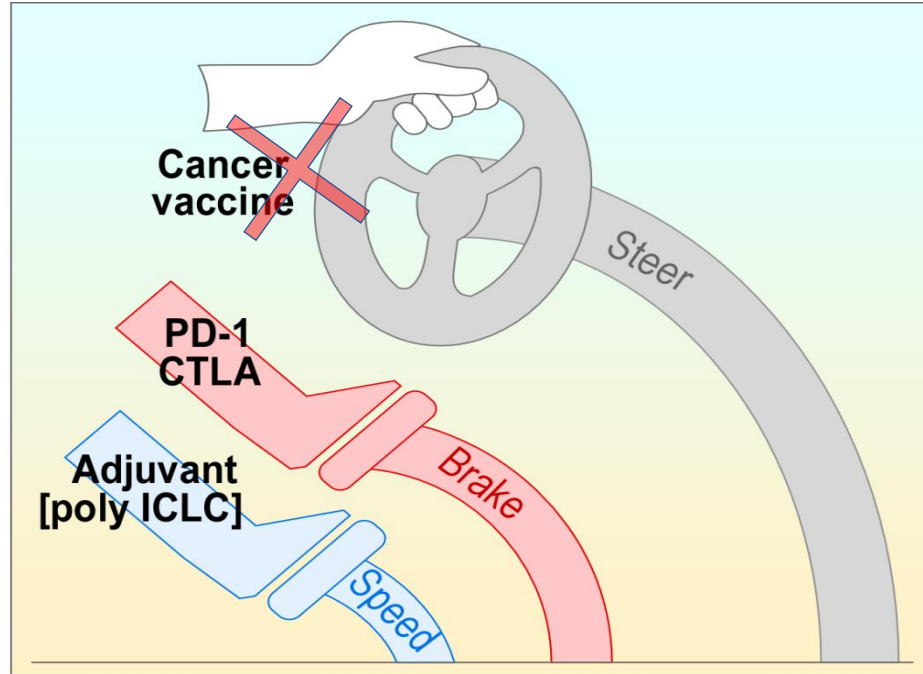


Pathogens: Prophylactic/Preventive Vaccines

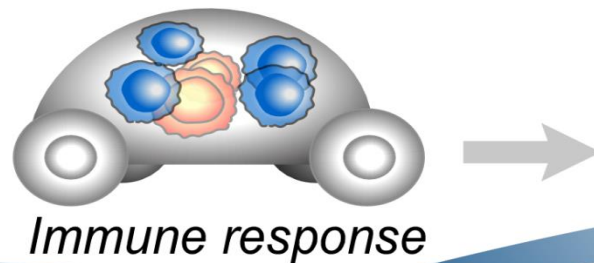




Steering the Immune Response With a Vaccine



- Expand and broaden the T cell repertoire by inducing tumor-specific T cells
- Generate highly specific anti-tumor immunity with fewer side effects on vital tissues





Cancer vaccines have been around for awhile.

What's different now?



1. 2012: Dramatic Clinical Responses After “Checkpoint Blockade Antibodies” for Solid Tumors

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety, Activity, and Immune Correlates of Anti-PD-1 Antibody in Cancer

Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D., Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D., William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D., Daniel McDonald, M.B.A., Georgia D. Kollia, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D., and Mario Sznol, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

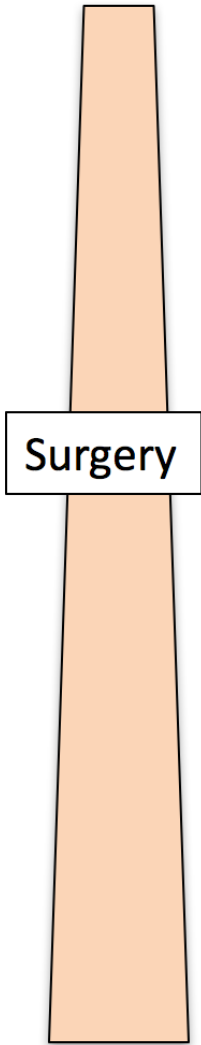
Safety and Activity of Anti-PD-L1 Antibody in Patients with Advanced Cancer

Julie R. Brahmer, M.D., Scott S. Tykodi, M.D., Ph.D., Laura Q.M. Chow, M.D., Wen-Jen Hwu, M.D., Ph.D., Suzanne L. Topalian, M.D., Patrick Hwu, M.D., Charles G. Drake, M.D., Ph.D., Luis H. Camacho, M.D., M.P.H., John Kauh, M.D., Kunle Odunsi, M.D., Ph.D., Henry C. Pitot, M.D., Omid Hamid, M.D., Shailender Bhatia, M.D., Renato Martins, M.D., M.P.H., Keith Eaton, M.D., Ph.D., Shuming Chen, Ph.D., Theresa M. Salay, M.S., Suresh Alaparthi, Ph.D., Joseph F. Grosso, Ph.D., Alan J. Korman, Ph.D., Susan M. Parker, Ph.D., Shruti Agrawal, Ph.D., Stacie M. Goldberg, M.D., Drew M. Pardoll, M.D., Ph.D., Ashok Gupta, M.D., Ph.D., and Jon M. Wigginton, M.D.

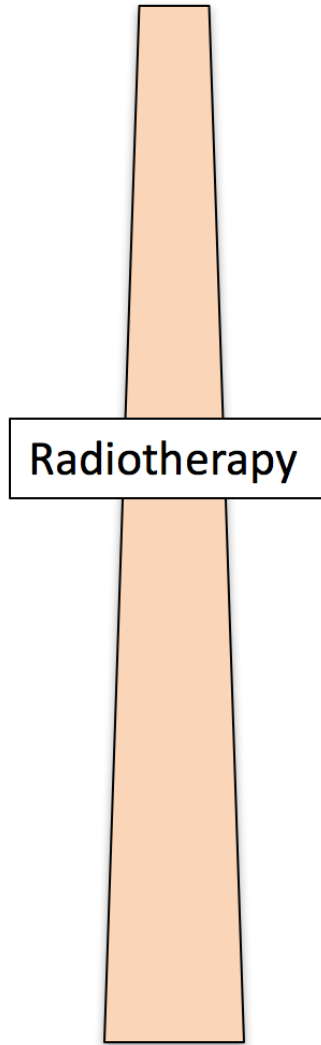




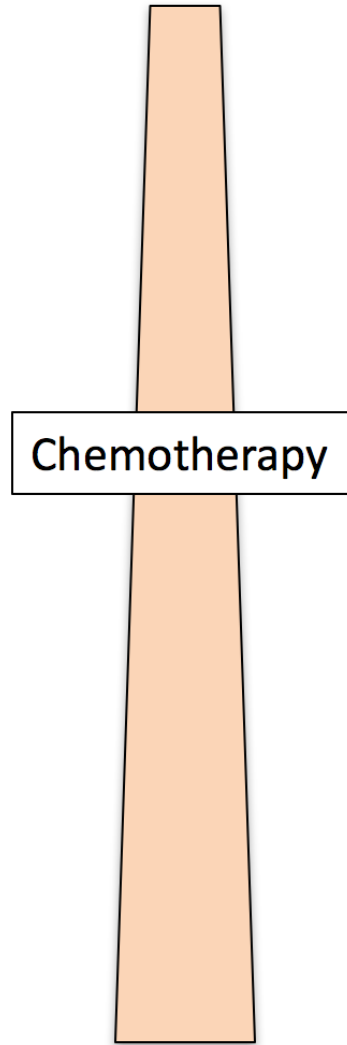
Cancer Care



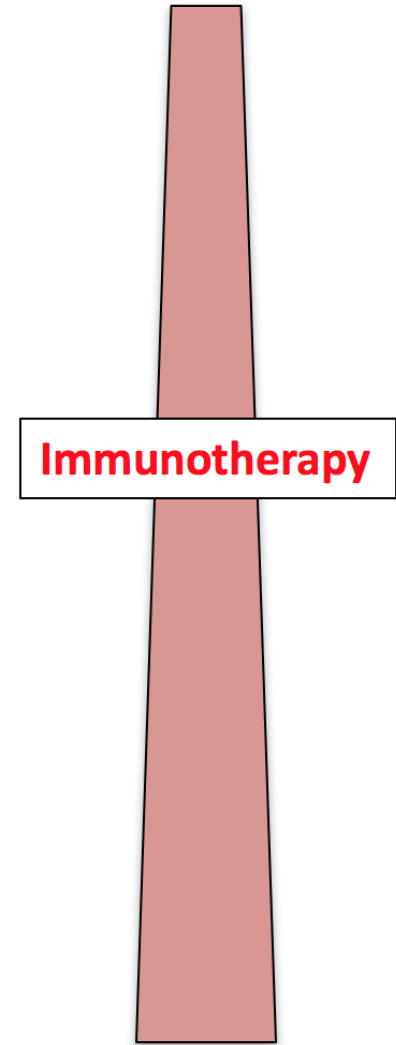
Surgery



Radiotherapy



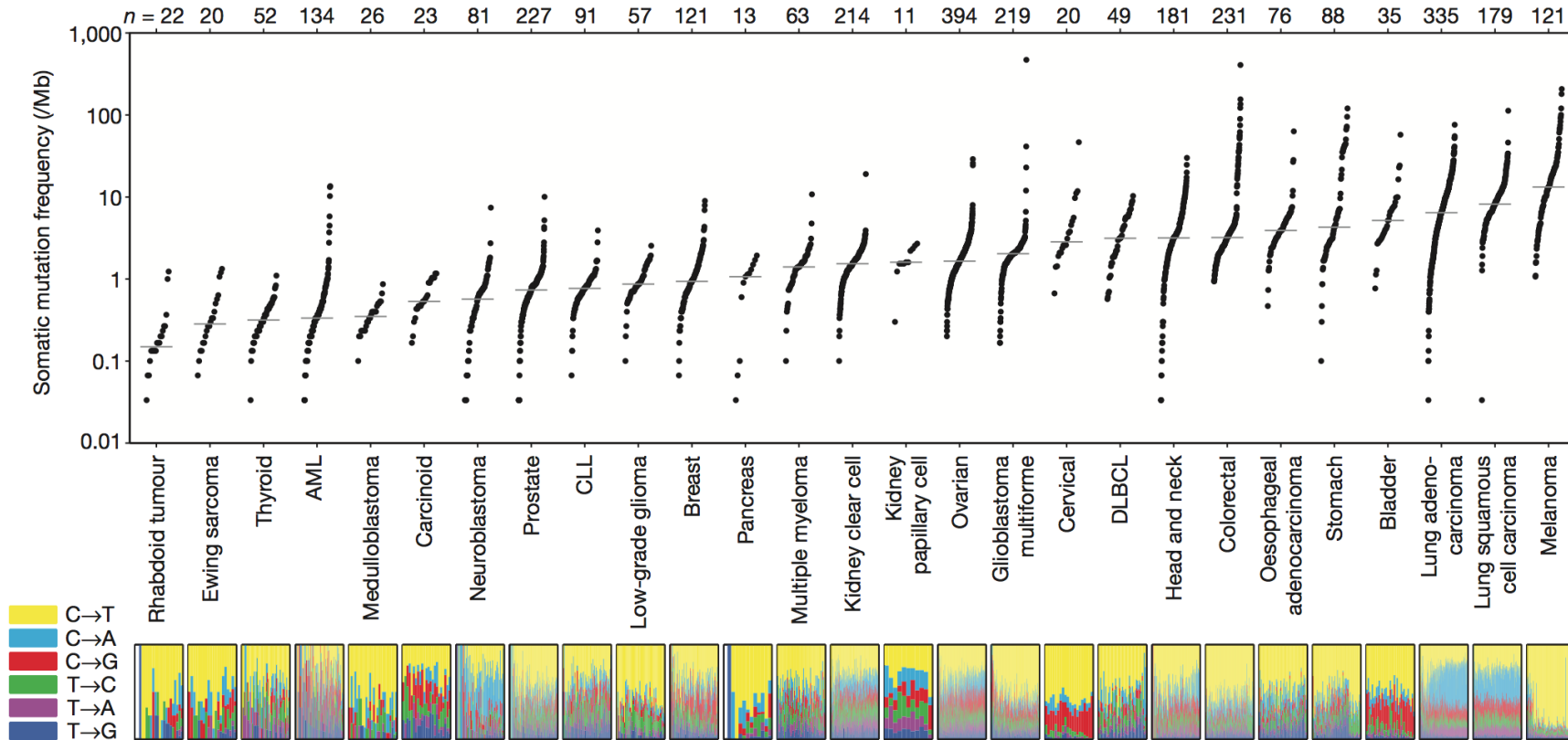
Chemotherapy



Immunotherapy

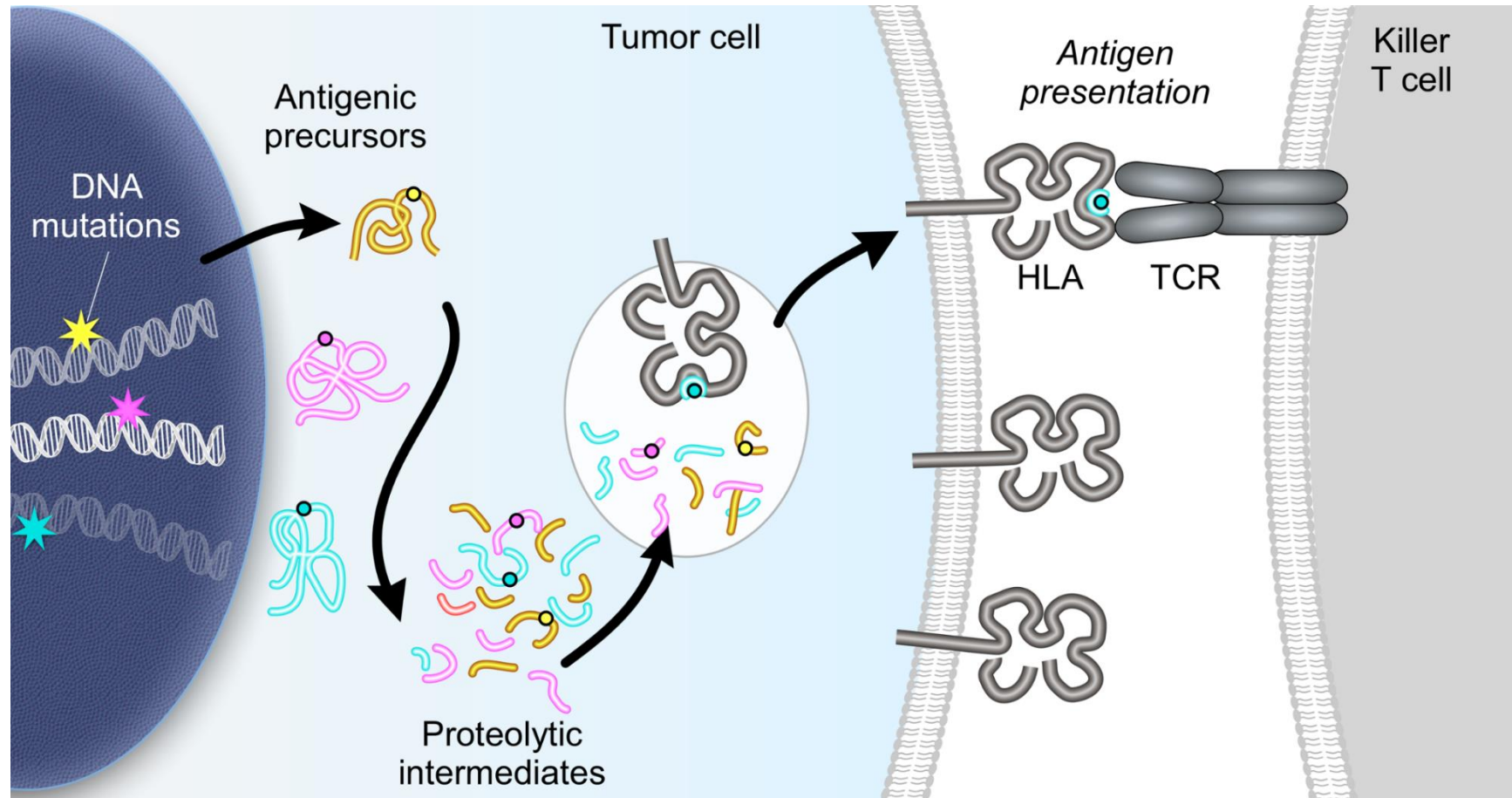


2. DNA Sequencing Across Cancers (n=>3000)





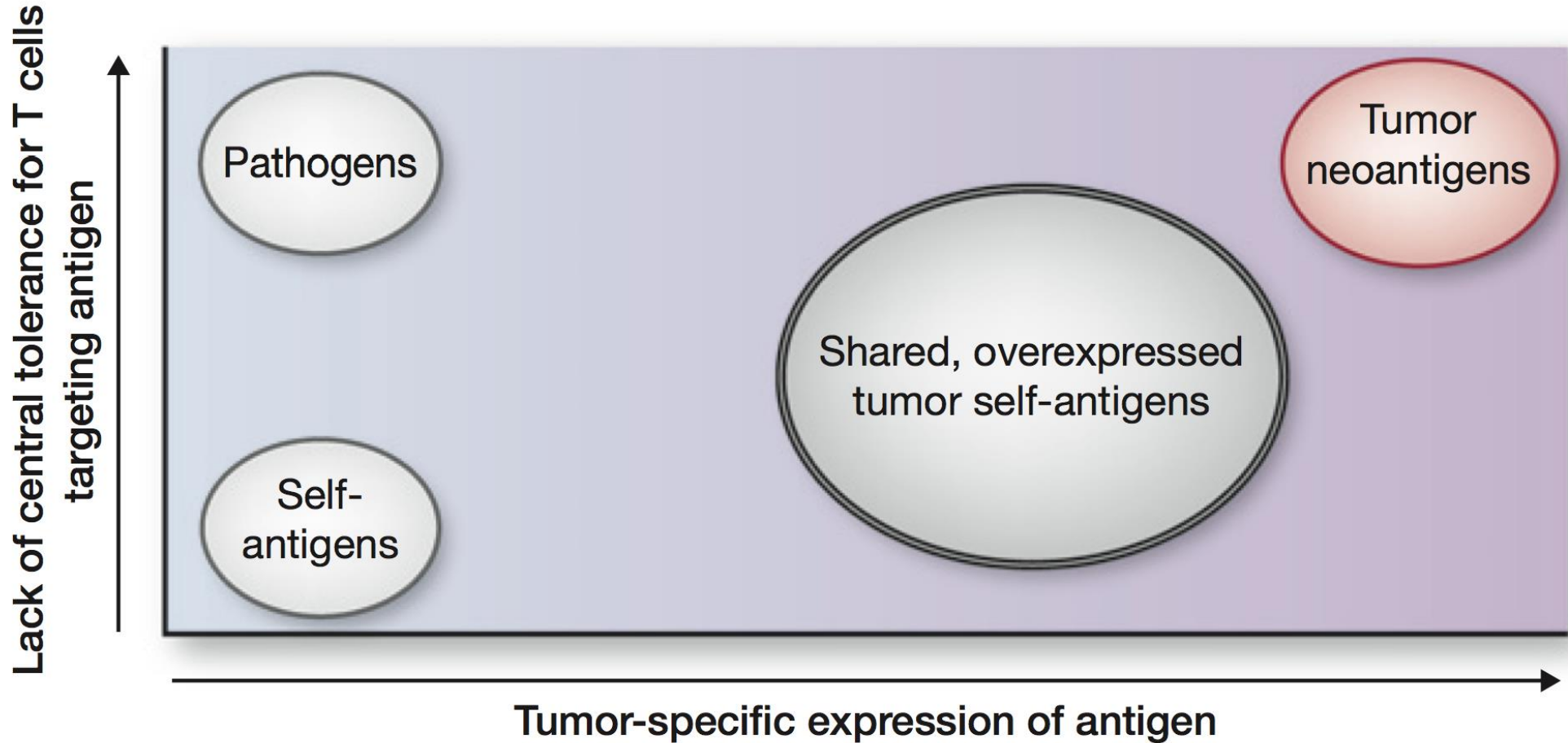
Somatic Mutations Have the Potential to Generate Neoantigens



Purroy N, et al. *Cold Spring Harb Perspect Med.* 2017;7(4):pii:a026740.

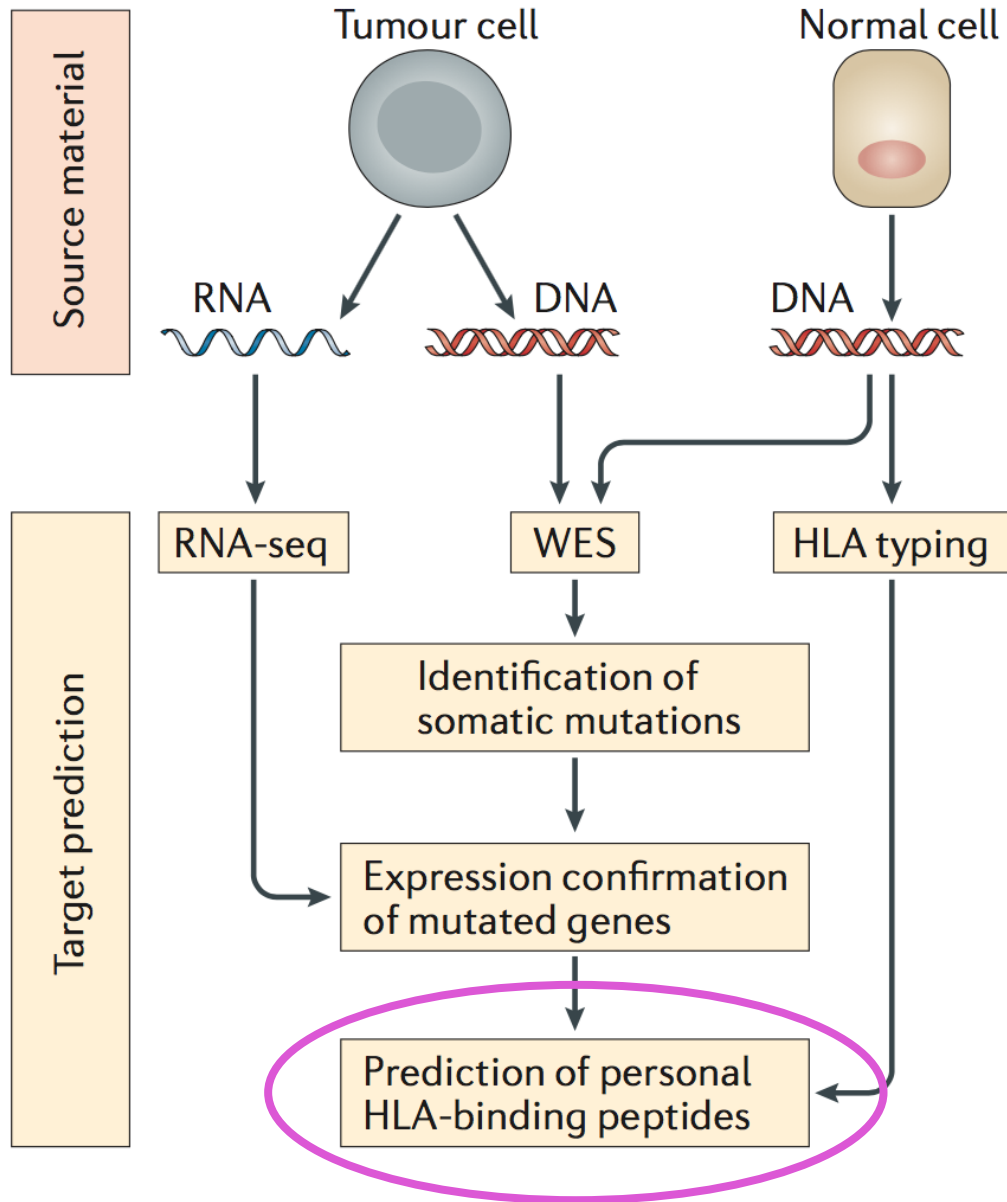


Hitting the “Sweet Spot”





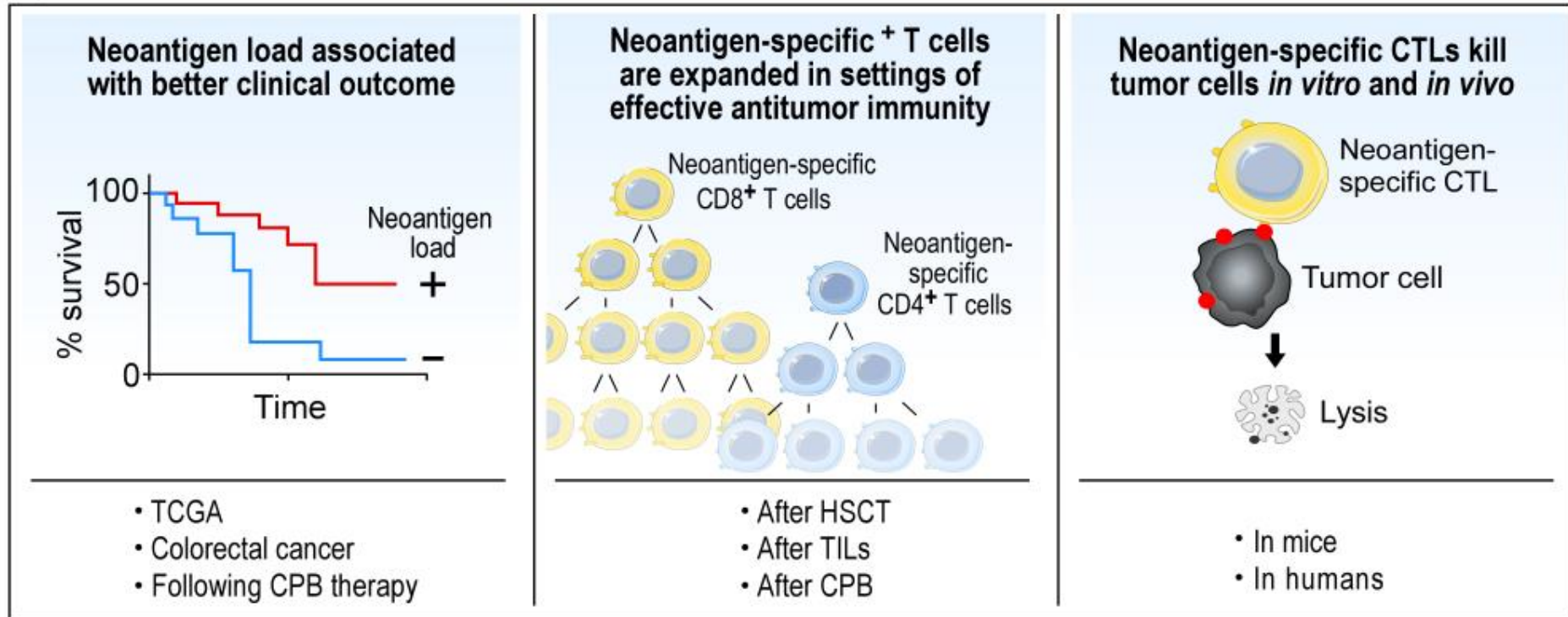
3.



Rajasagi M, et al. *Blood*. 2014;124(3):453-462; Rooney MS, et al. *Cell*. 2015;160(1-2):48-61; Shukla SA, et al. *Nat Biotechnol*. 2015;33(11):1152-1158; Van Allen EM, et al. *Science*. 2015;350(6257):207-211; Giannakis M, et al. *Cell Rep*. 2016;17(4):1206.



Growing Compelling Evidence for Neoantigens as Effective Tumor Rejection Antigens



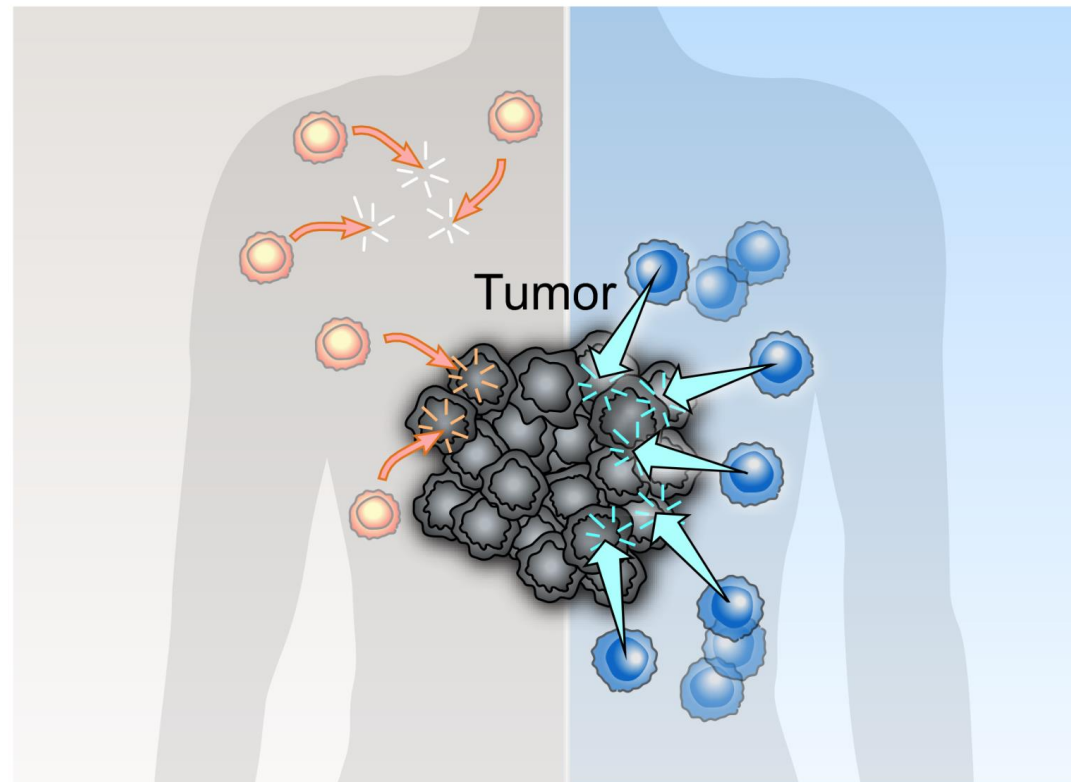
Castle JC, et al. *Cancer Res.* 2012;72(5):1081-1091; Brown SD, et al. *Genome Res.* 2014;24(5):743-750; Snyder A, et al. *N Engl J Med.* 2014;371(23):2189-2199; Rivzi NA, et al. *Science.* 2015;348(6230):124-128; Cai A, et al. *Clin Cancer Res.* 2012;18(20):5761-5772; Rajasagi M, et al. *Blood.* 2014;124(3):453-462; Robbins PF, et al. *Nat Med.* 2013;19(6):747-752; van Rooij N, et al. *J Clin Oncol.* 2013;31(32):e439-e442; Rooney MS, et al. *Cell.* 2015;160(1-2):48-61; Rivzi NA, et al. *Science.* 2015;348(6230):124-128; Tran E, et al. *Science.* 2014;344(6184):641-645; Gubin MM, et al. *Nature.* 2014;515(7528):577-581; Yadav 2014.



Paradigm Shift

Native antigens

Neoantigens



Central tolerance
Auto-immunity



Immunogenicity
Tumor-specificity



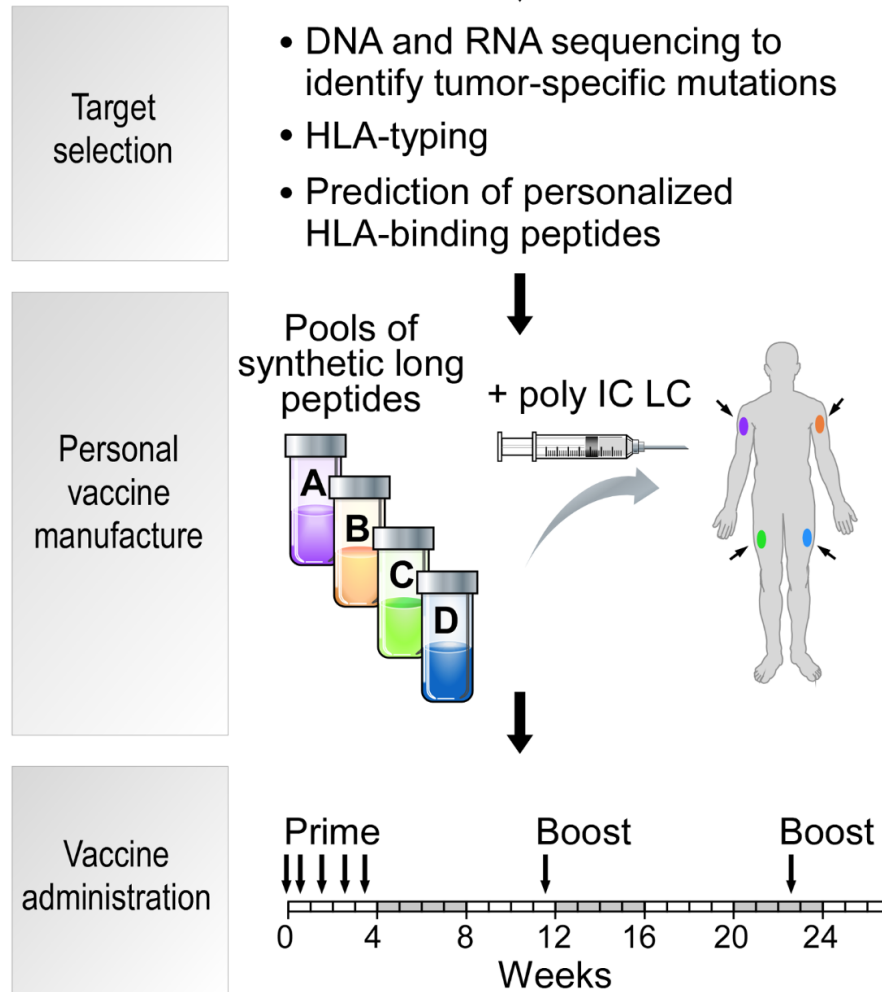
Can a Personalized Cancer Vaccine Stimulate Anti-tumor Immunity in Humans?

Disease: Melanoma

- Stage III/resectable
- Stage IV



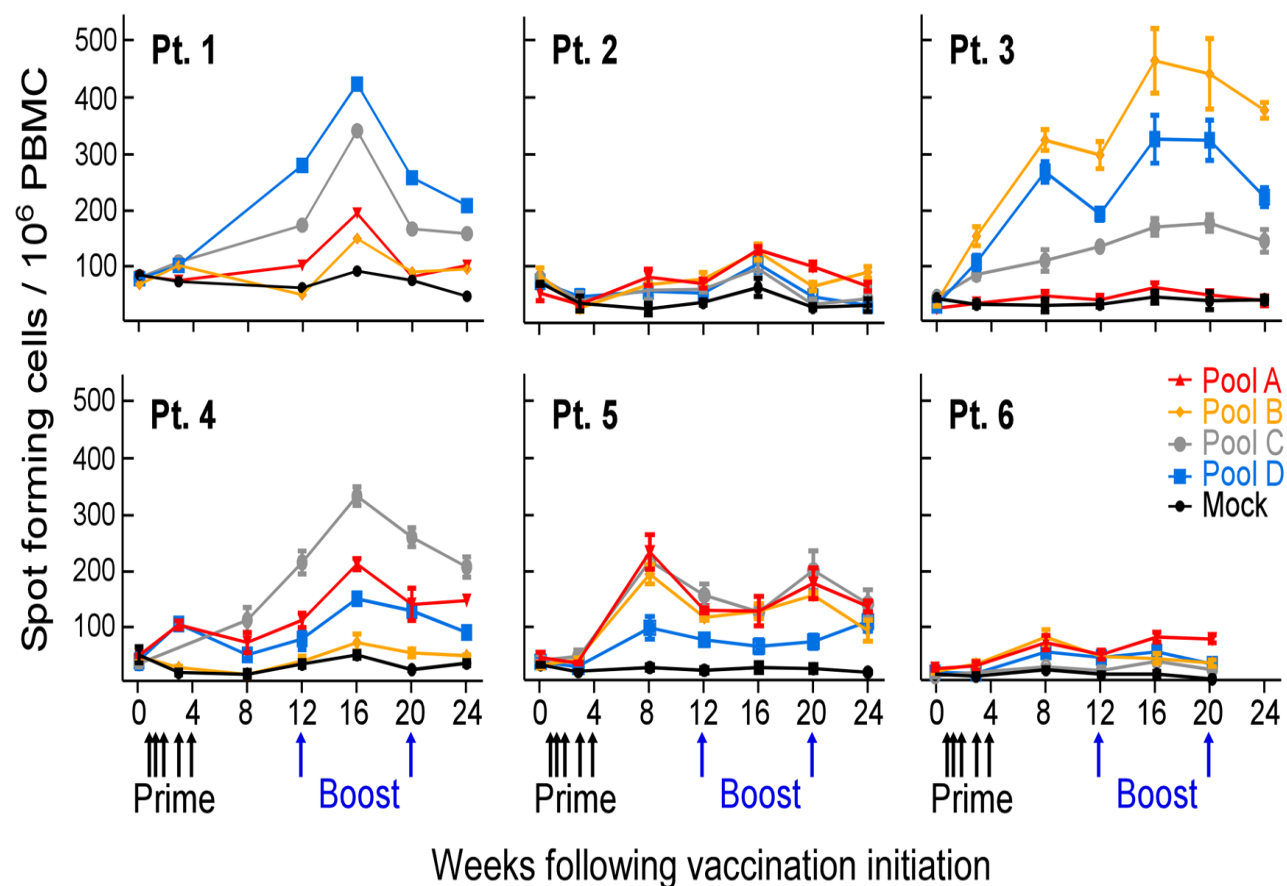
Vaccine: Up to 20 Personalized Neoantigens as SLPs with Adjuvant (Poly-ICLC)



- 11 Enrolled
- 8 Vaccines generated
- **6 Dosed**



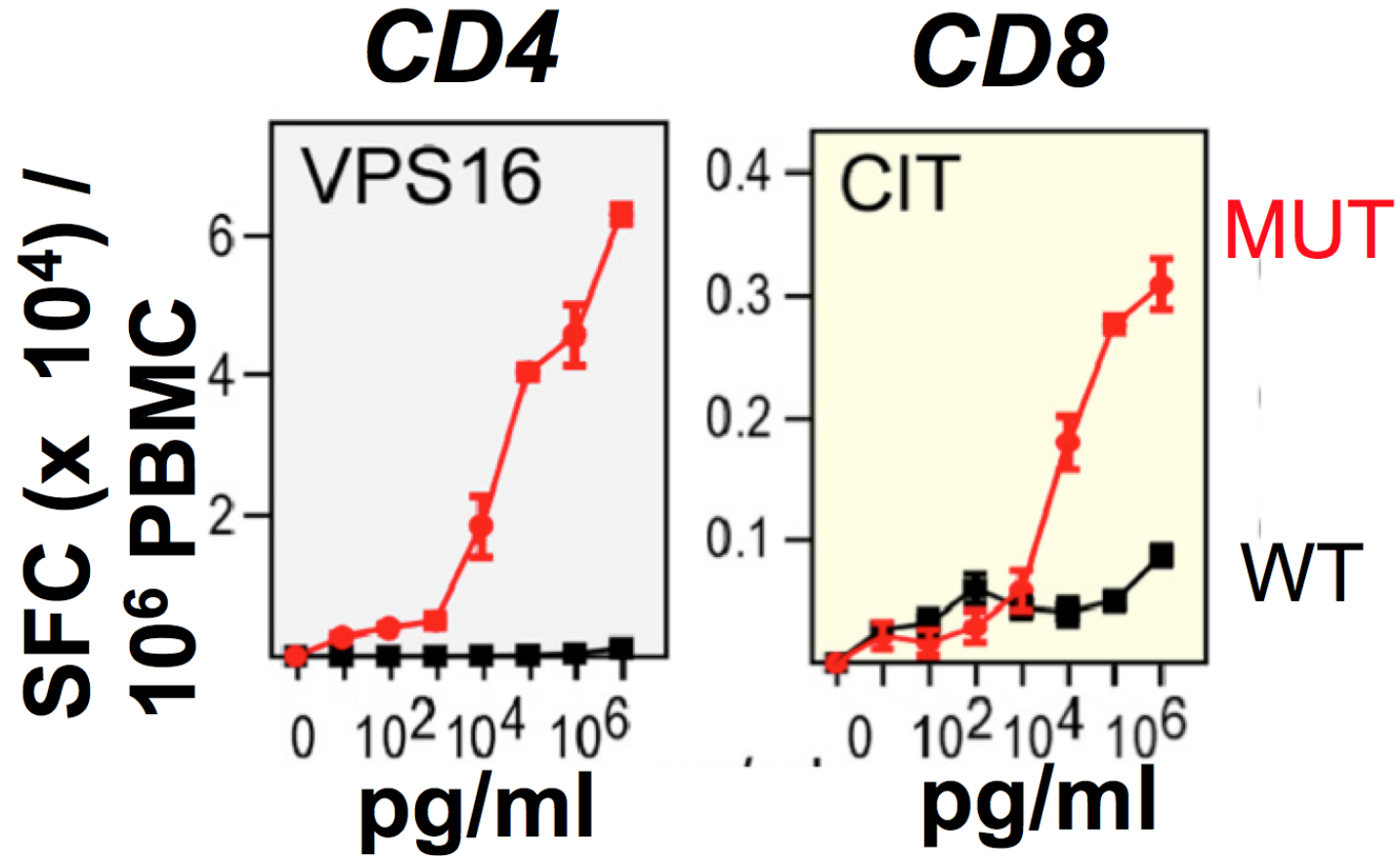
Vaccine Induces T Cells Against Almost All Pools



20% of selected neoantigens induced CD8 T cell responses
>30% of selected neoantigens induced CD4 T cell responses

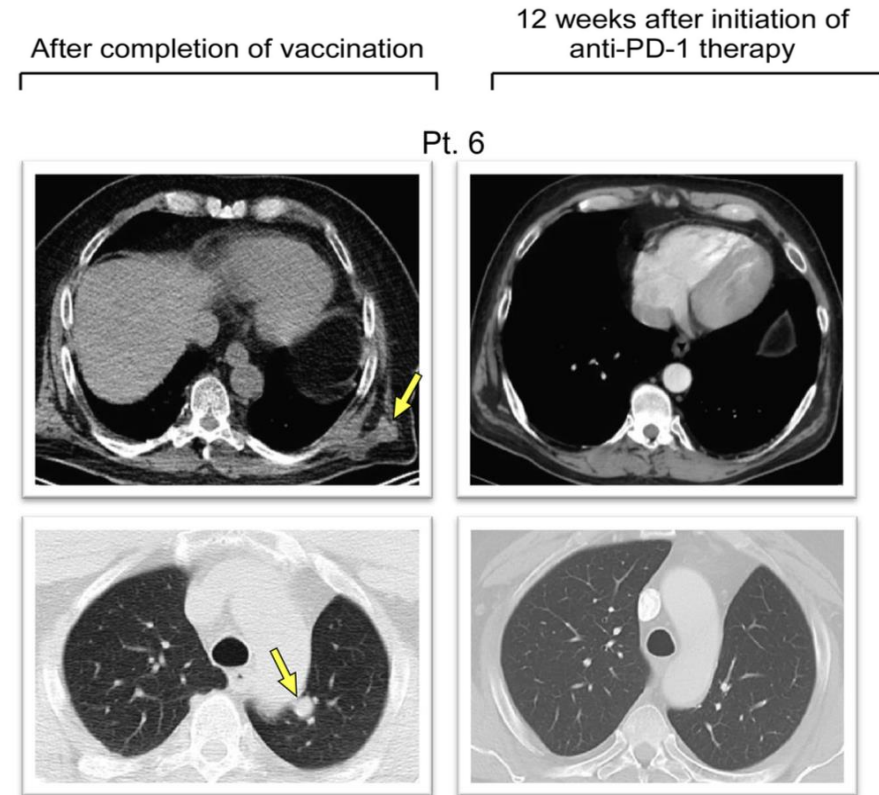
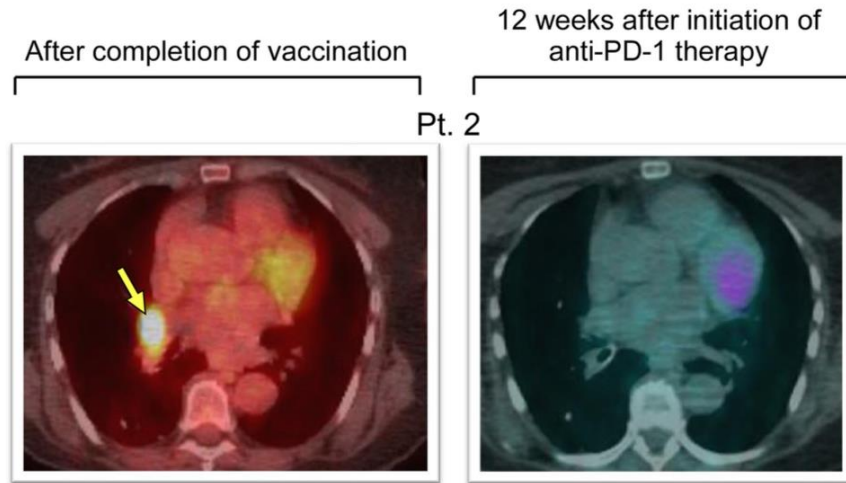


T Cells Recognize Mutated but Not Wild Type Epitopes





Enduring Complete Radiographic Responses After Neovax + α -PD-1 Treatment





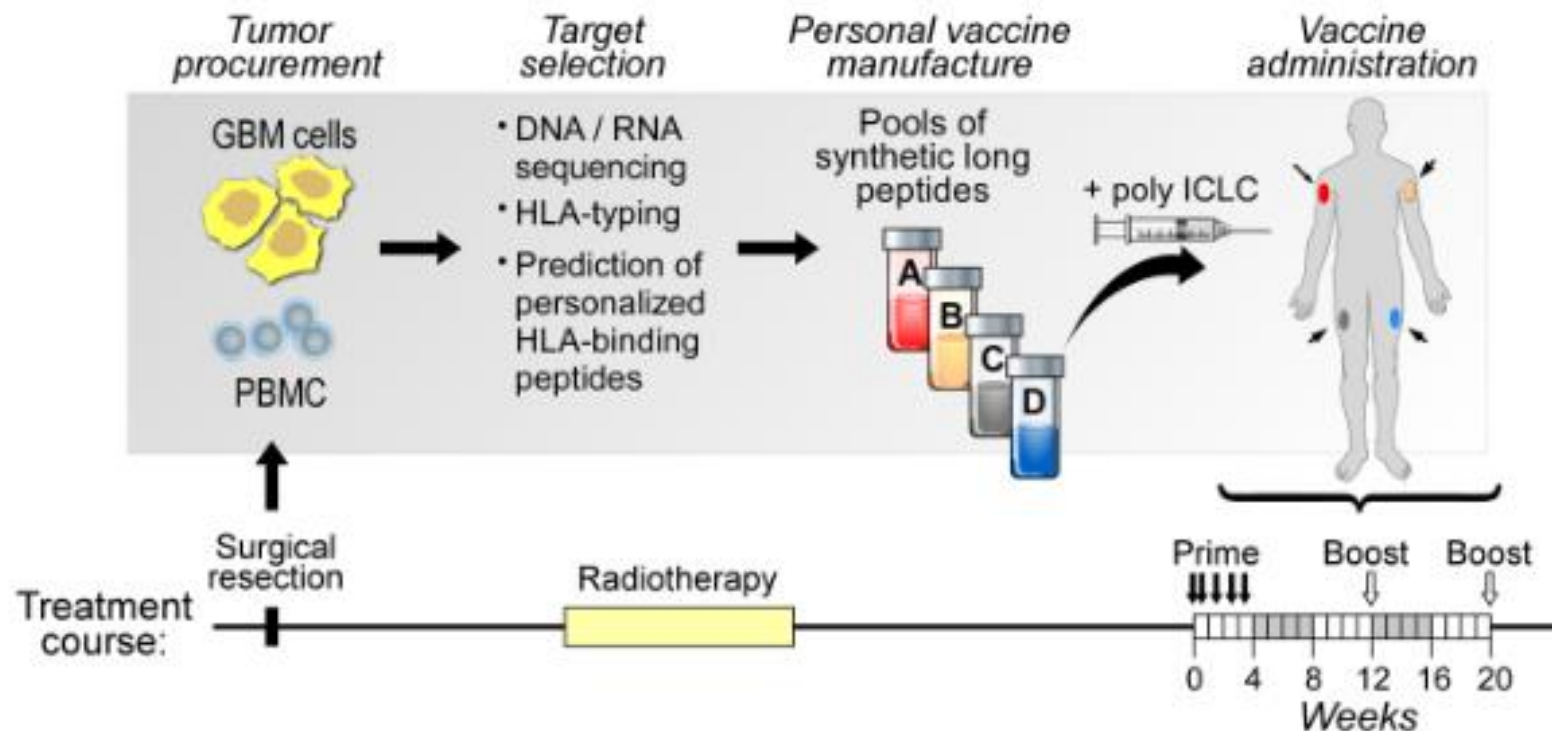
Can Such a Vaccination Approach be Tested in Lower Mutation Rate Tumors?

Disease: GBM

- Rapidly fatal
- Cold tumor
- Blood-brain barrier?
- Impact of steroids?



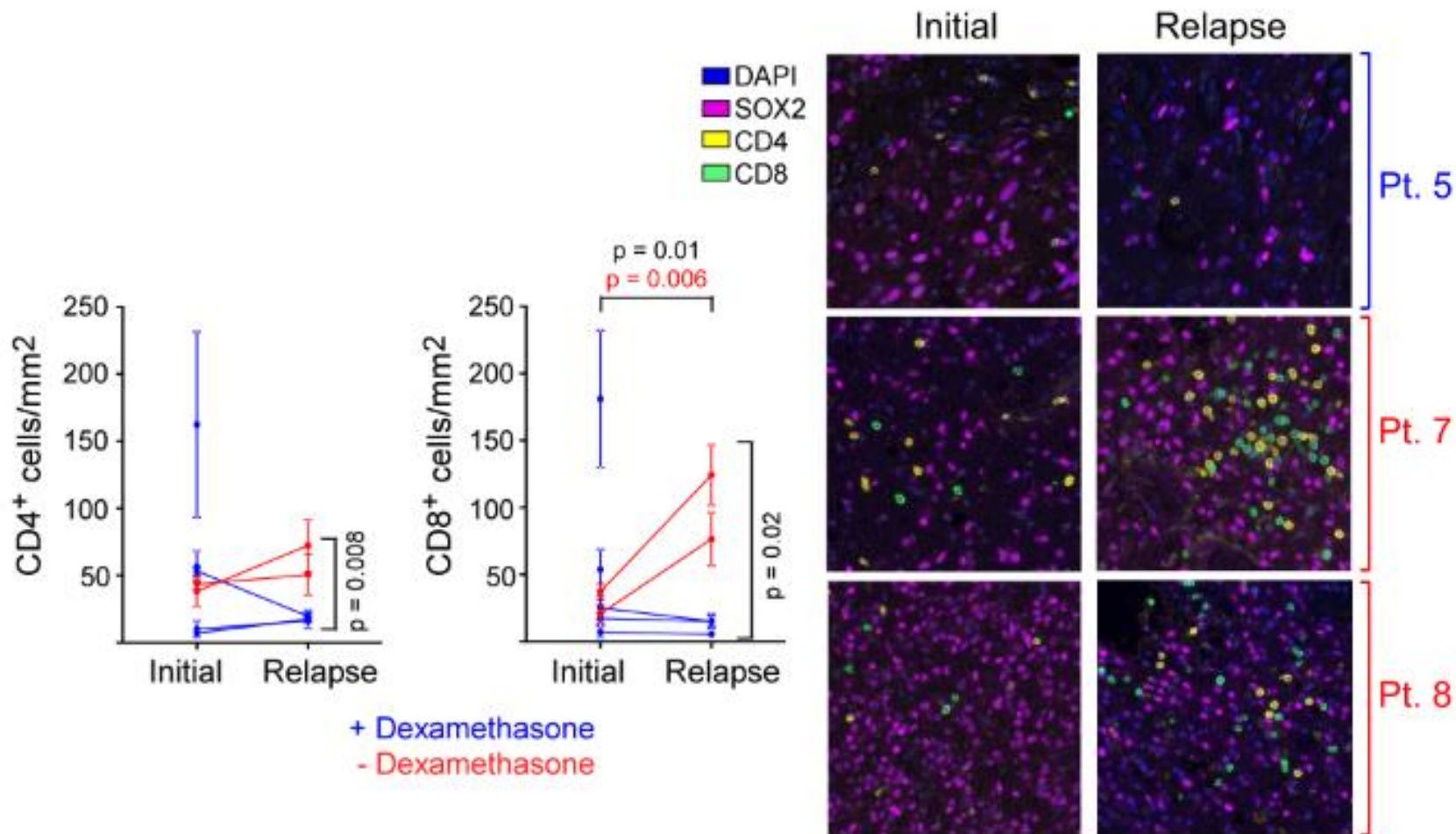
Testing Neovax in a Lower Mutation Rate Tumor and Within Context of SOC Therapy: GBM



- 10 Enrolled
- 8 Vaccines dosed

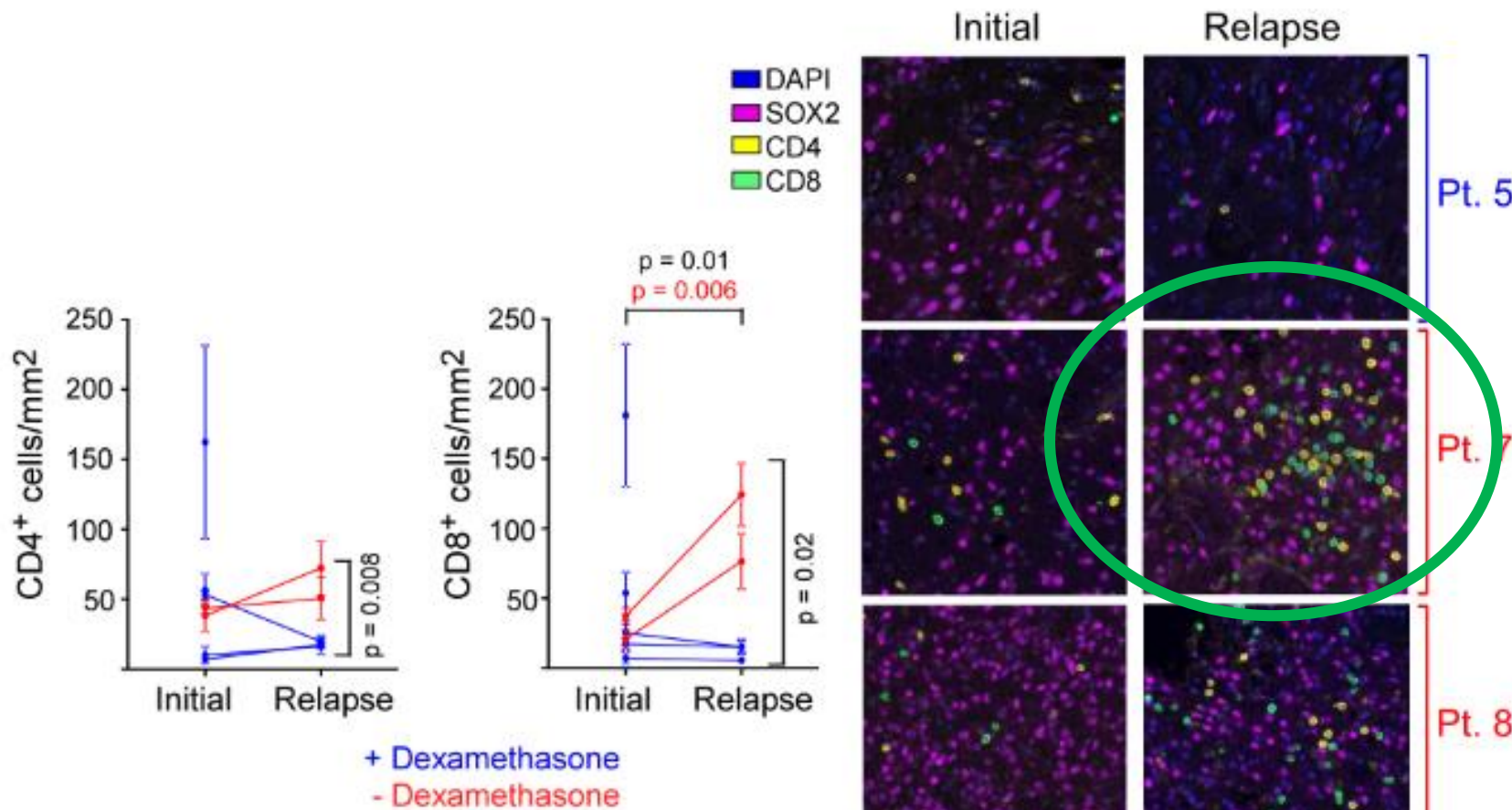


Neovax: 'Warming' a Cold Tumor





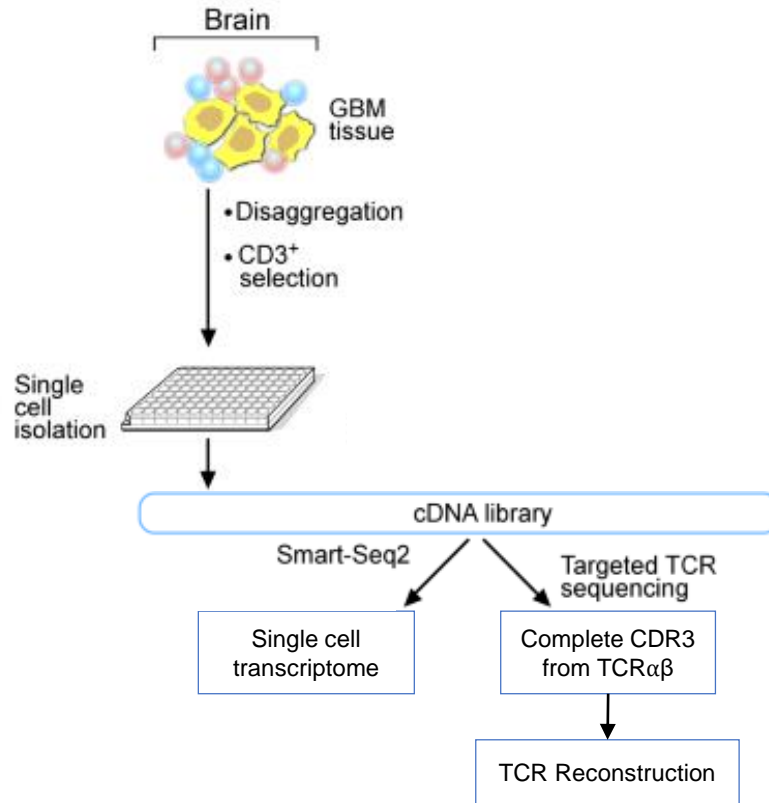
Neovax: 'Warming' a Cold Tumor



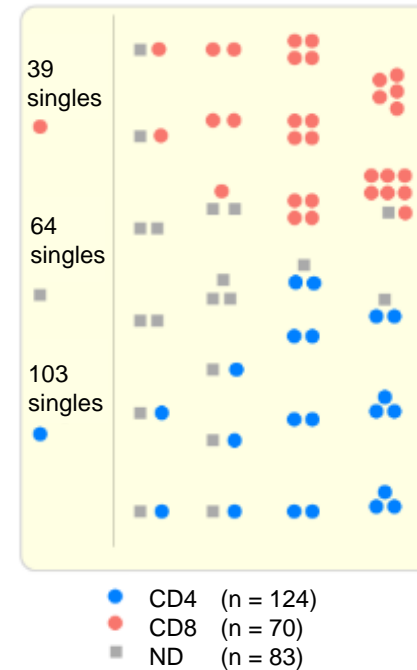
CD3+ CD45+ Selection
SMART-Seq2



Pt 7: Strategy to Identify Intratumoral Neoantigen-specific T Cells

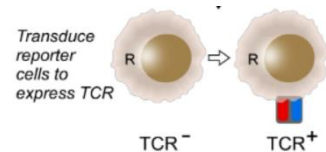
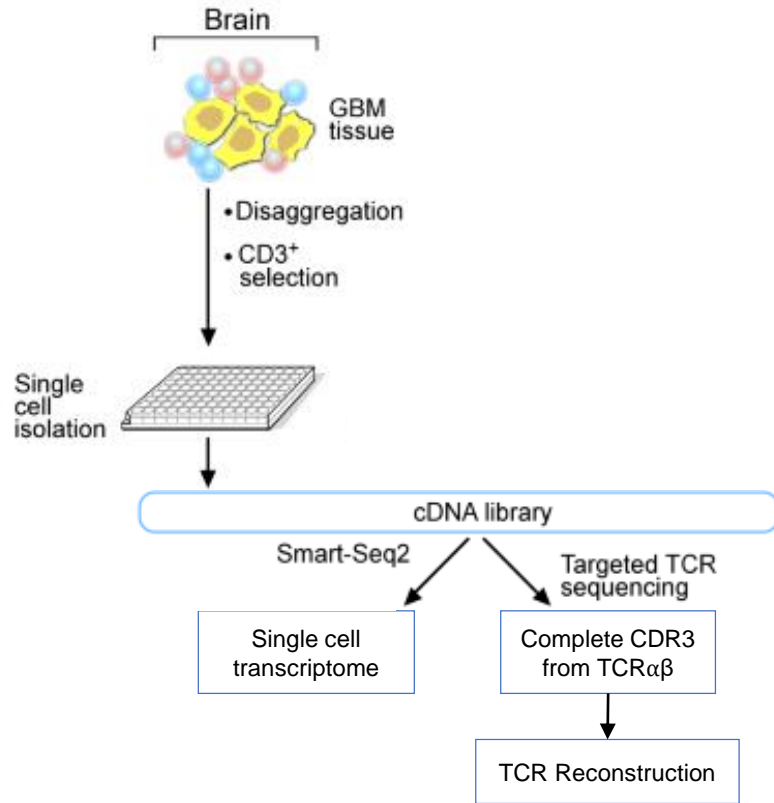


Tumor infiltrating lymphocytes

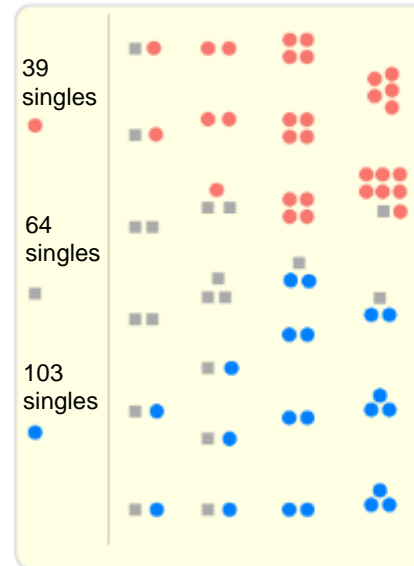




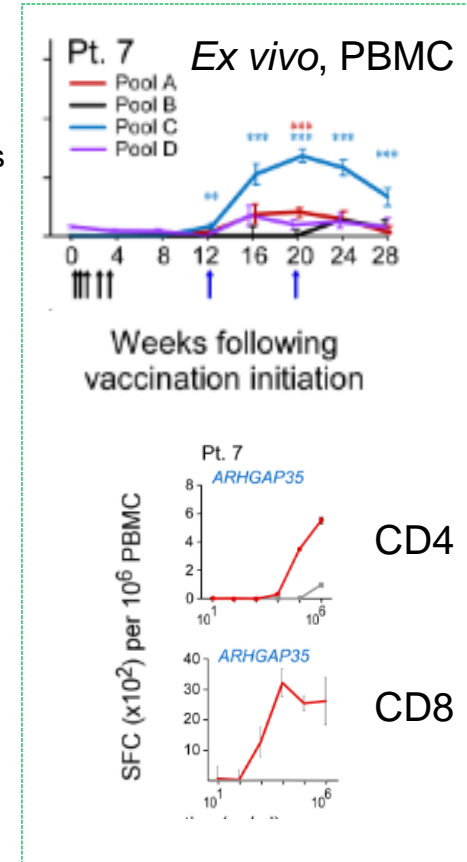
Strategy to Identify Intratumoral Neoantigen-specific T Cells



Tumor infiltrating lymphocytes



● CD4 (n = 124)
● CD8 (n = 70)
■ ND (n = 83)

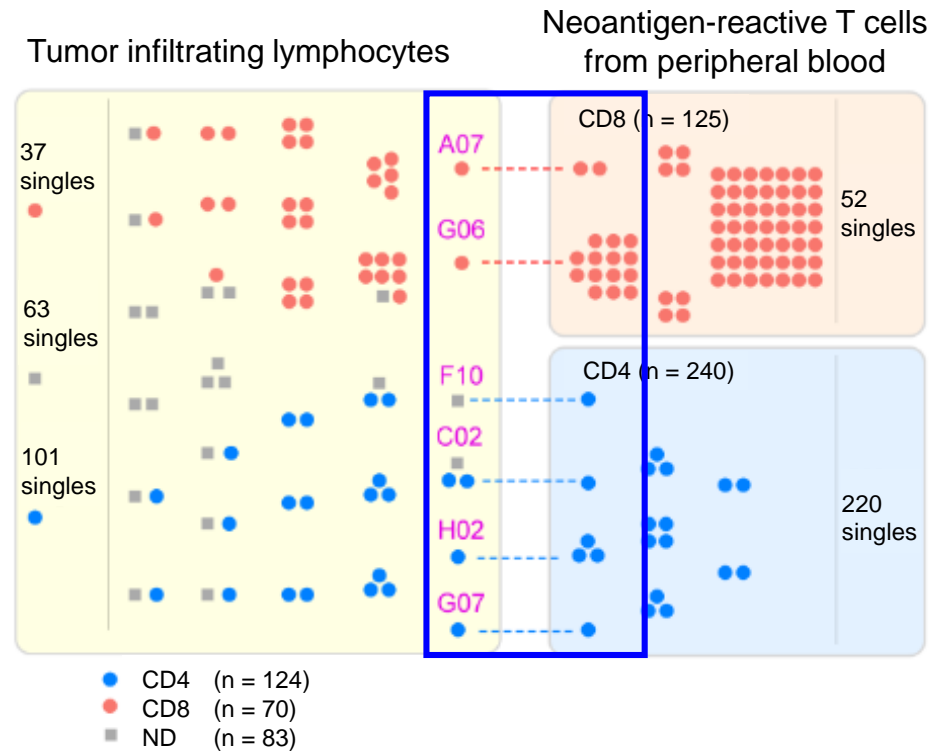
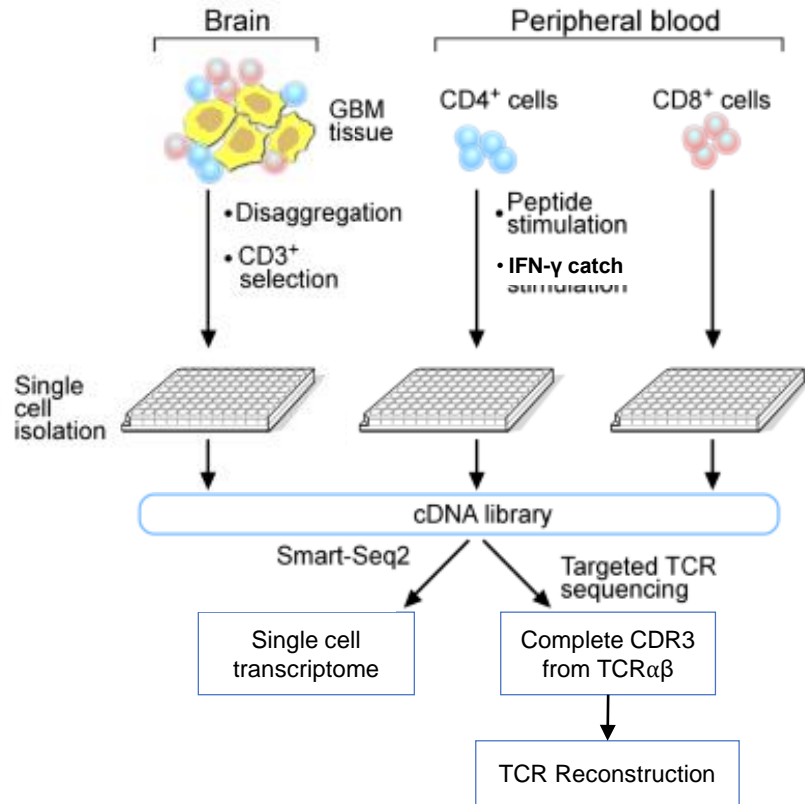


Hu Z, et al. *Blood*. 2018.

<http://www.bloodjournal.org/content/early/2018/08/27/blood-2018-04-843763?sso-checked=true>. Accessed October 30, 2018.



Strategy to Identify Intratumoral Neoantigen-specific T Cells





mutARHGAP35 Epitopes

ARHGAP35

WT

T

IMP12 HNLDLAEKDF **M** VNTVAGAMK

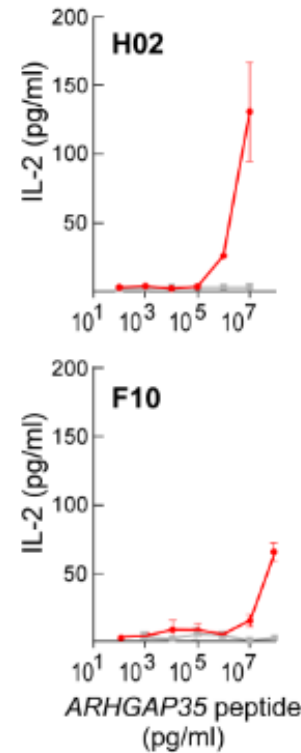
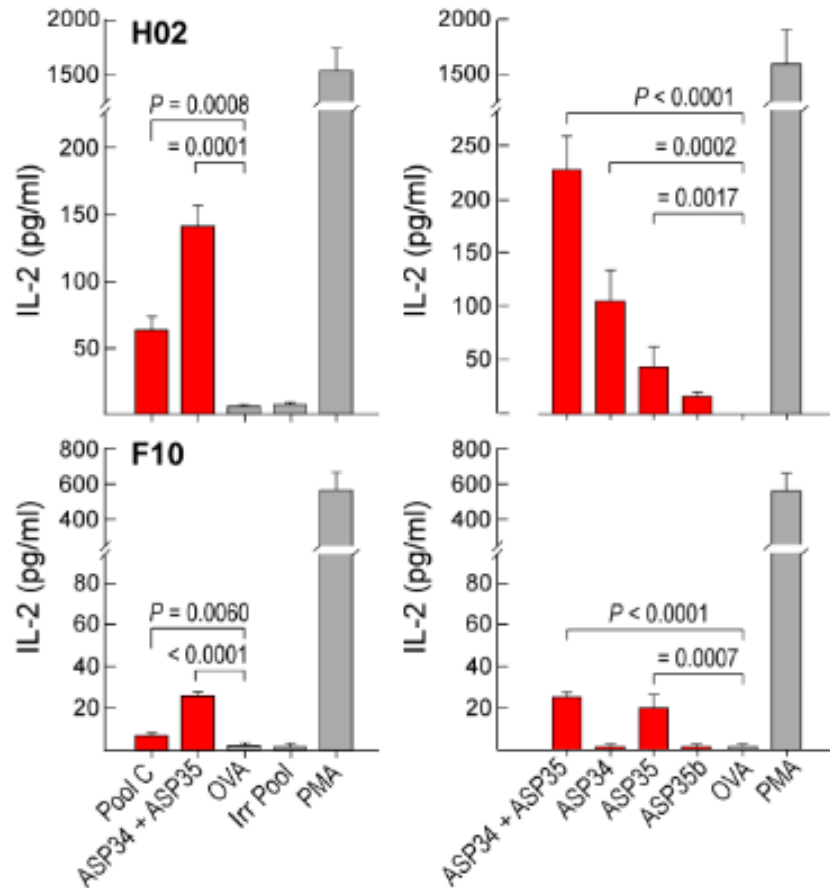
ASP34 HNLDLAEKDF **M** VNTV

ASP35 LAEKDF **M** VNTVAGAMK

ASP35b LAEKDF **M** VNTV



ARHGAP35-Specific T Cell Identified at Site of Disease

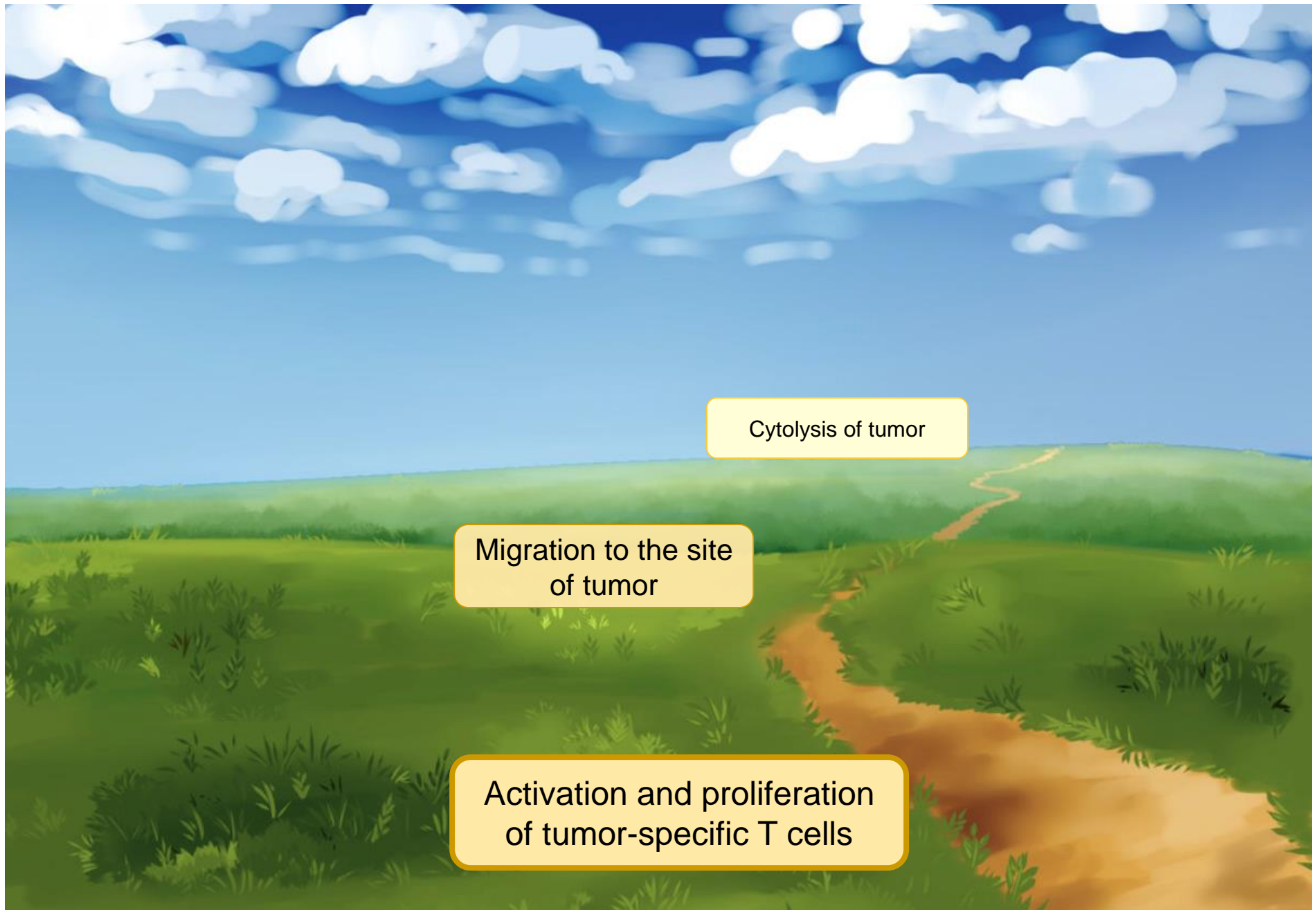


- Mutant
- Wildtype
- ▲ OVA



Summary

- Adverse impact of steroids with T cell priming
- Neoantigen-specific T cells can (variably) track to the site of tumor
- Neoantigen-specific T cells at the tumor site have variable transcriptional profiles
- On the horizon: combination with checkpoint therapy



Cytolysis of tumor

Migration to the site
of tumor

Activation and proliferation
of tumor-specific T cells



Active Disease: Targeting Indolent Lymphomas

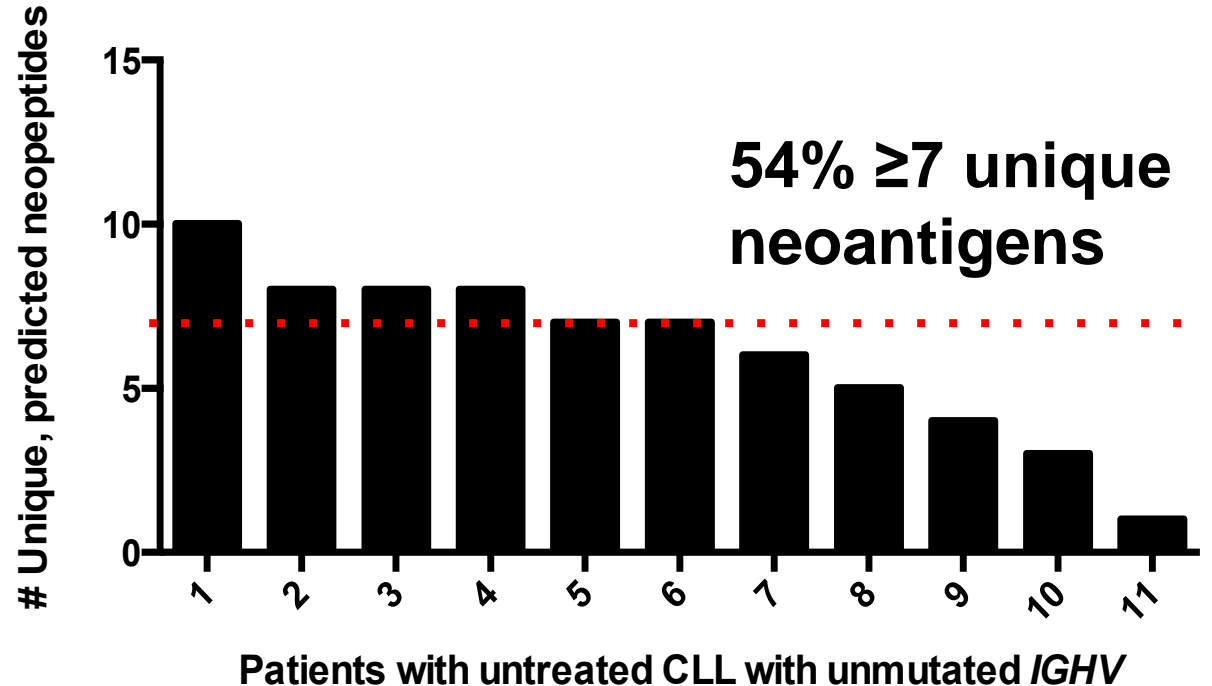
- **Advanced stage follicular lymphoma and chronic lymphocytic leukemia are incurable malignancies**
 - CLL: Unmutated Ig heavy chain variable gene (IGHV) = aggressive biology and poor therapeutic response
 - No curative option exists for either disease
 - “Watch and wait” for asymptomatic disease
- **Immune escape is central to lymphoma biology**
 - T cell dysfunction widely reported
 - Immunotherapies are effective but low therapeutic index

Neoantigen vaccination *early in the disease course* can exploit 1) tumor specificity, 2) setting conducive to immune stimulation, and 3) **active disease setting allowing for study of evolving tumor-immune responses**



Neoantigen Load in CLL

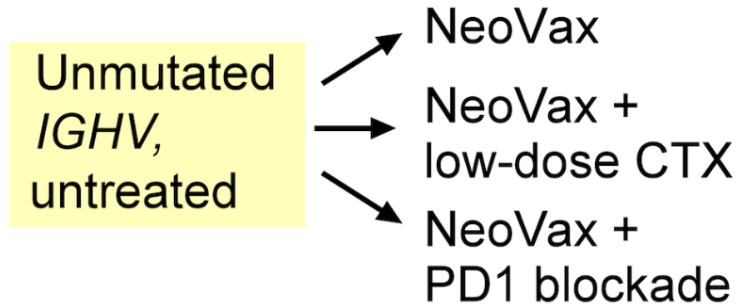
- Nonselected, population-based patient cohort with WES, n=54
- 11 patients met criteria:
 - Unmutated IGHV
 - Untreated at time of sample and no treatment for at least 100 days
 - RNA seq
- 160 untreated CLL patients/yr; ~80 unmutated IGHV



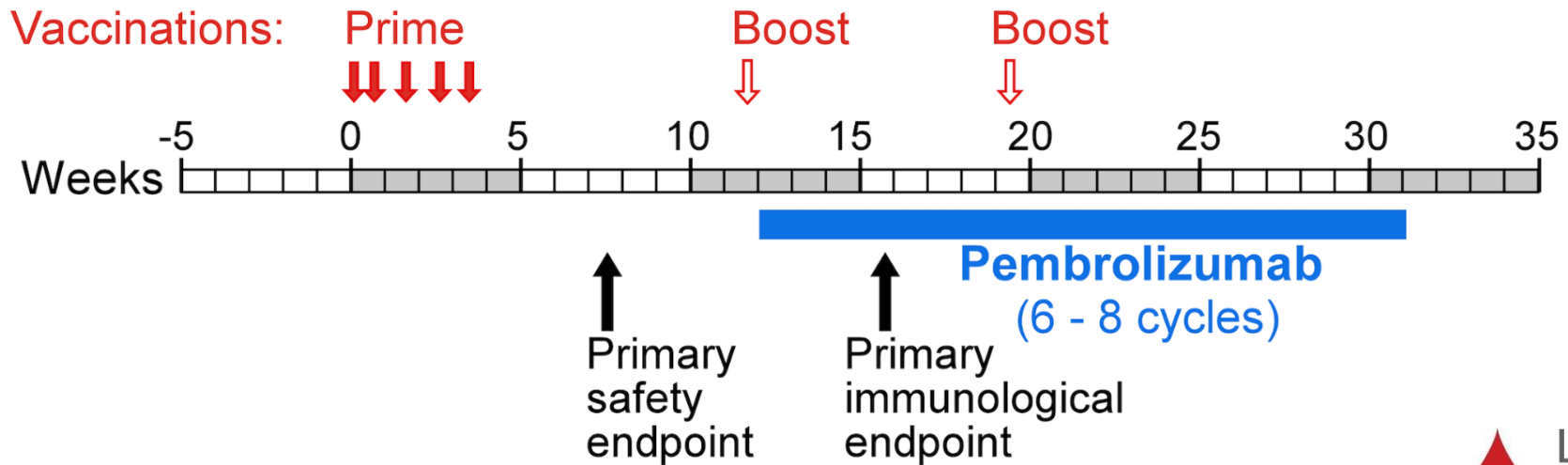
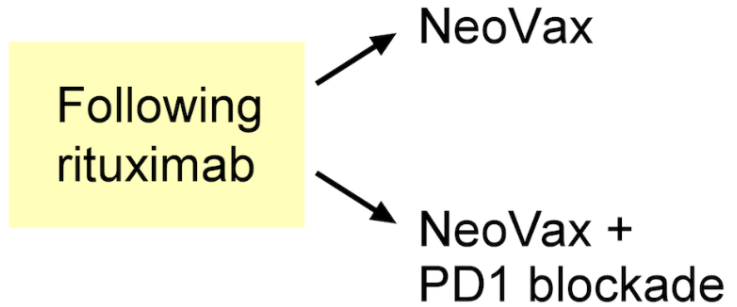


Going Earlier in Disease.....

Chronic lymphocytic leukemia



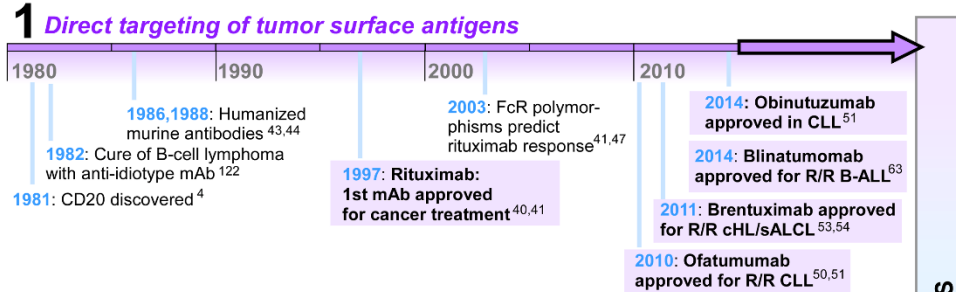
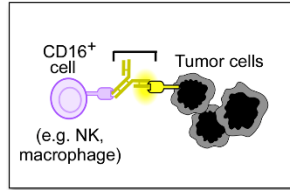
Follicular lymphoma



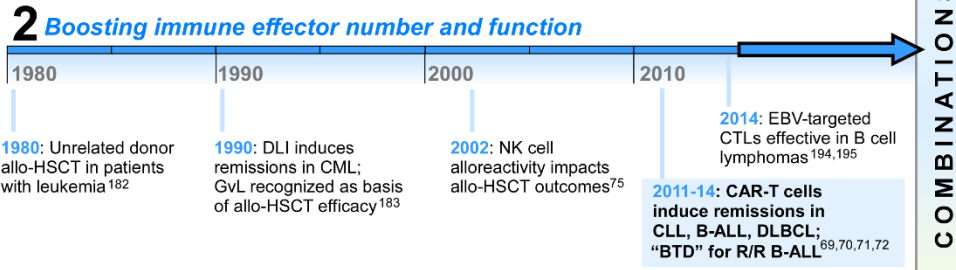
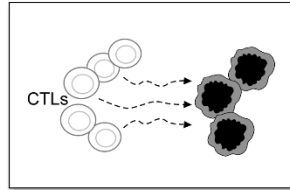


Future Directions: Combinations

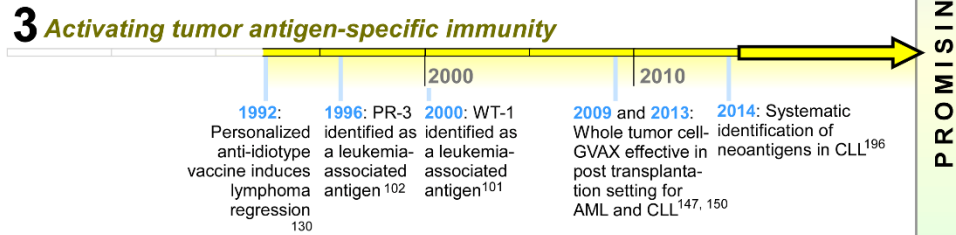
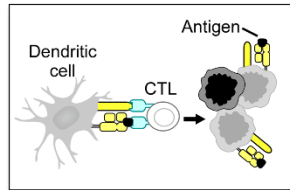
Obinutuzumab



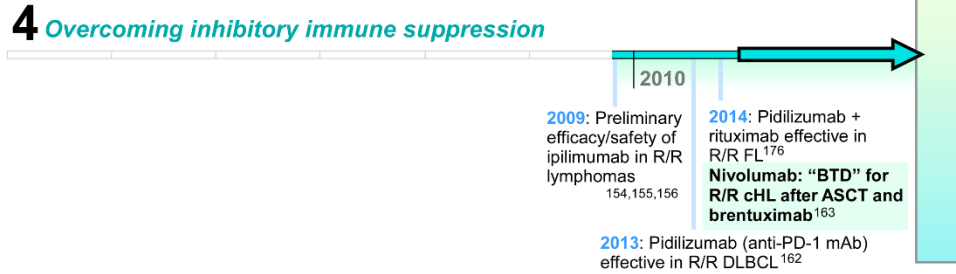
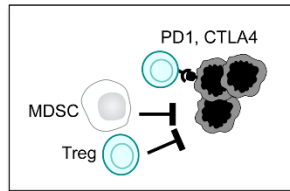
CAR-T Ibrutinib



NeoVax



Anti-PD1/CTLA4



PROMISING COMBINATIONS



Summary

- Cancer-specific mutations can generate neoantigens that may drive immunotherapeutic responses
- Neoantigen vaccines offer a personalized approach to cancer immunotherapy and can induce cancer-specific immune responses
- Hematologic malignancies offer a unique platform for immunotherapeutic evaluation



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