Control of tumor immunity in humans: coevolution of tumor and its immune microenvironment

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Disclosures

I am co-founder of Neon Therapeutics, Inc

I will not be talking about off –label use.

Tumor Evolution is a Central Obstacle to Curative Cancer Therapy

INTRA-TUMORAL HETEROGENEITY

+

EFFECTIVE TREATMENT

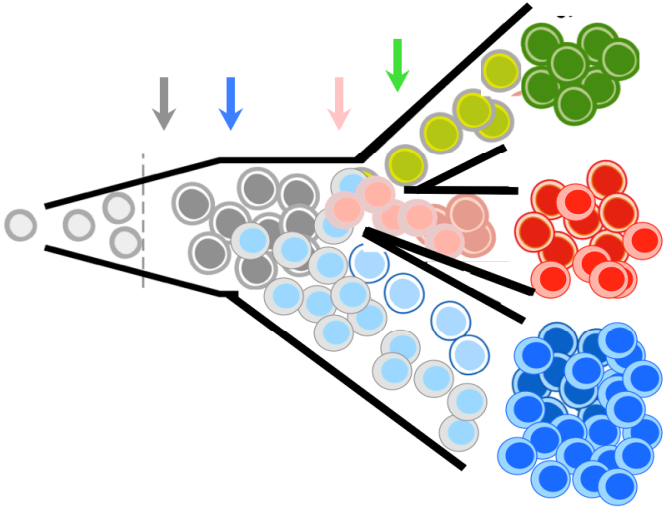
▼

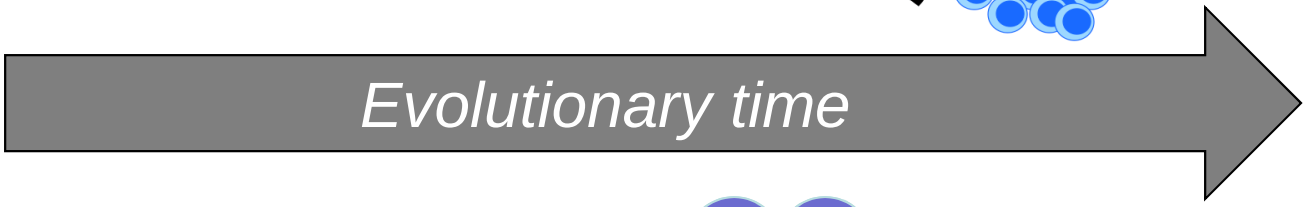
Novel targeted agents
Novel immunotherapies

TUMOR EVOLUTION = RESISTANCE

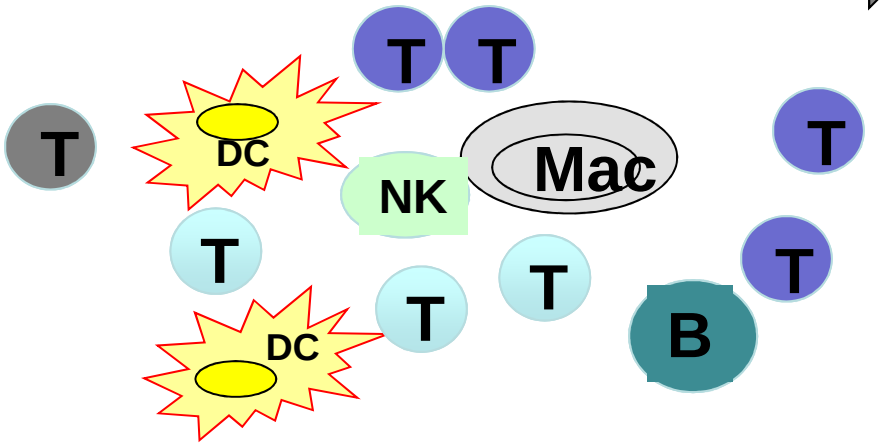
2015: What do we understand about tumor-immune co-evolution?

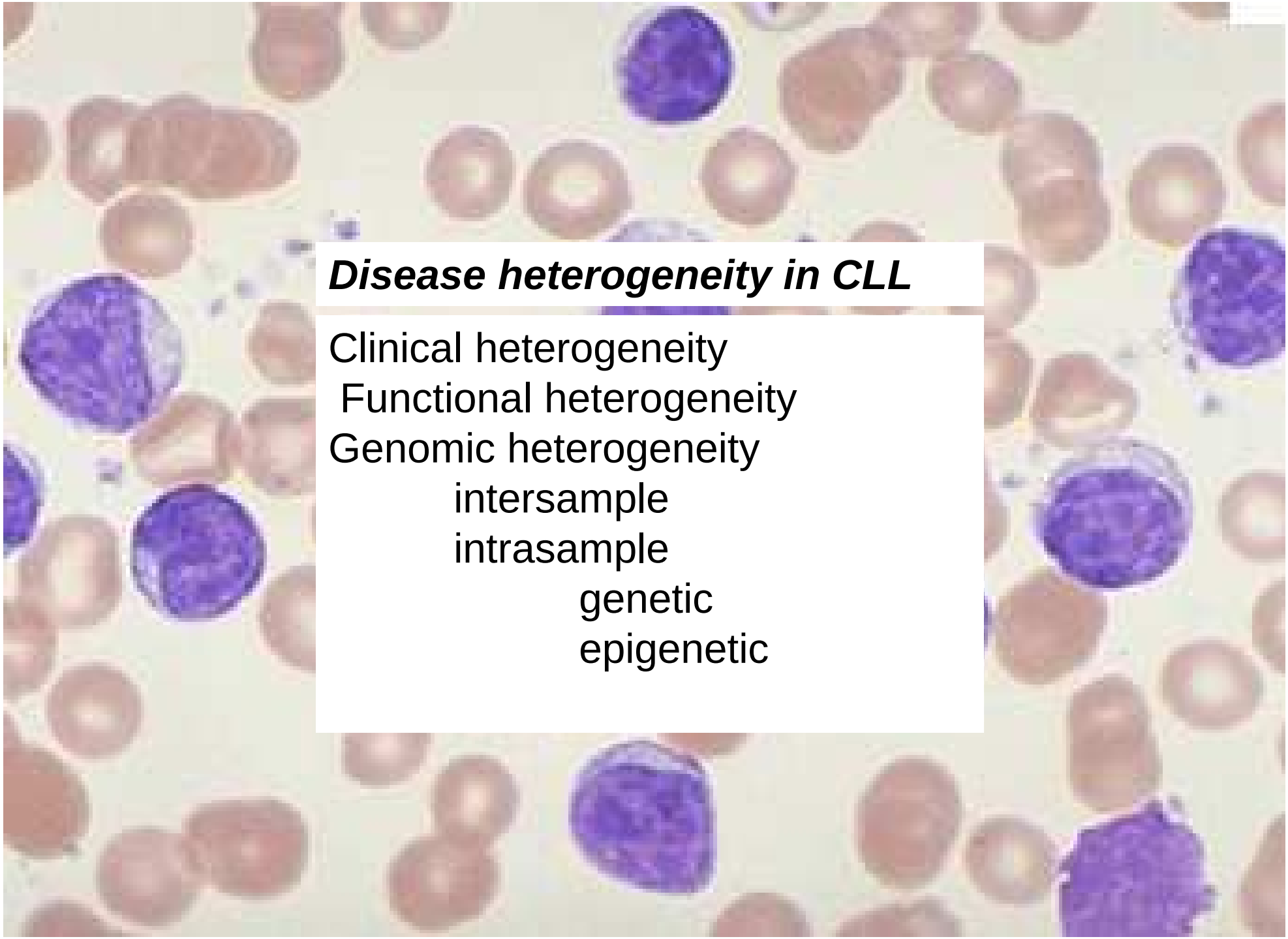
- ***How do tumors change over time and in relationship to therapy?***





- ***How does the immune system co-evolve?***

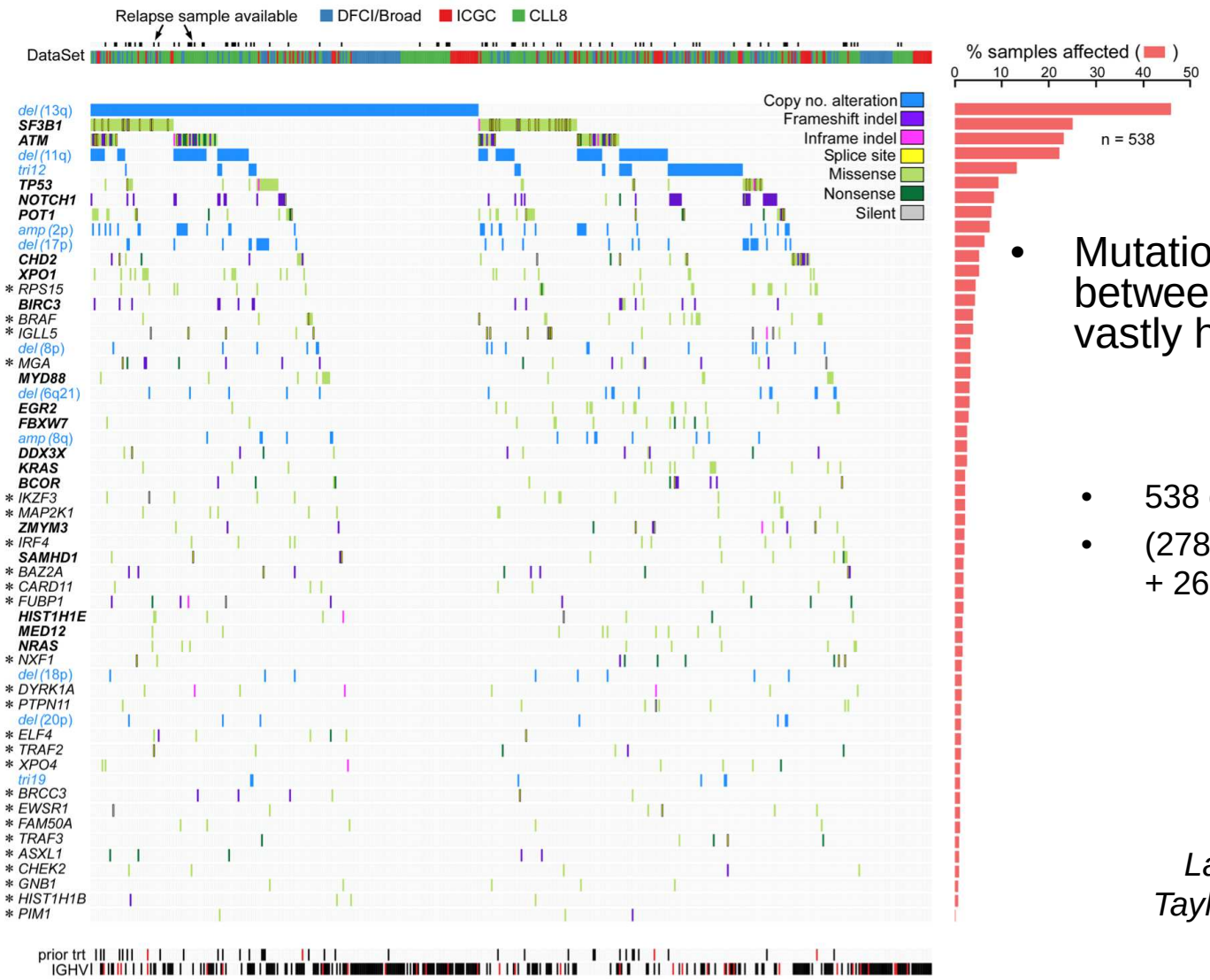




Disease heterogeneity in CLL

Clinical heterogeneity
Functional heterogeneity
Genomic heterogeneity
- intersample
- intrasample
  - genetic
  - epigenetic

Intertumoral heterogeneity in CLL: independent evolutionary events

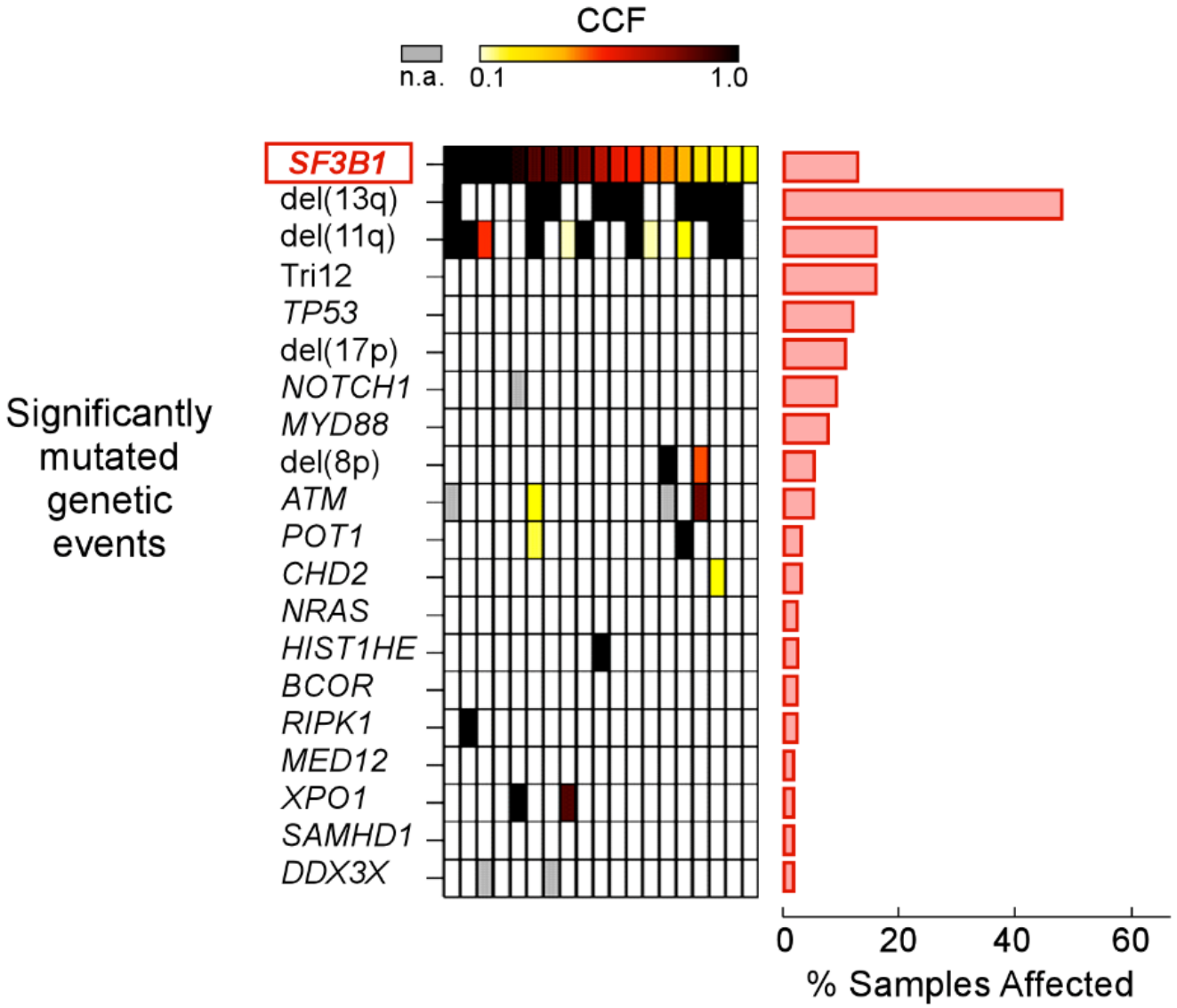


- Mutation profiles between individuals are vastly heterogeneous

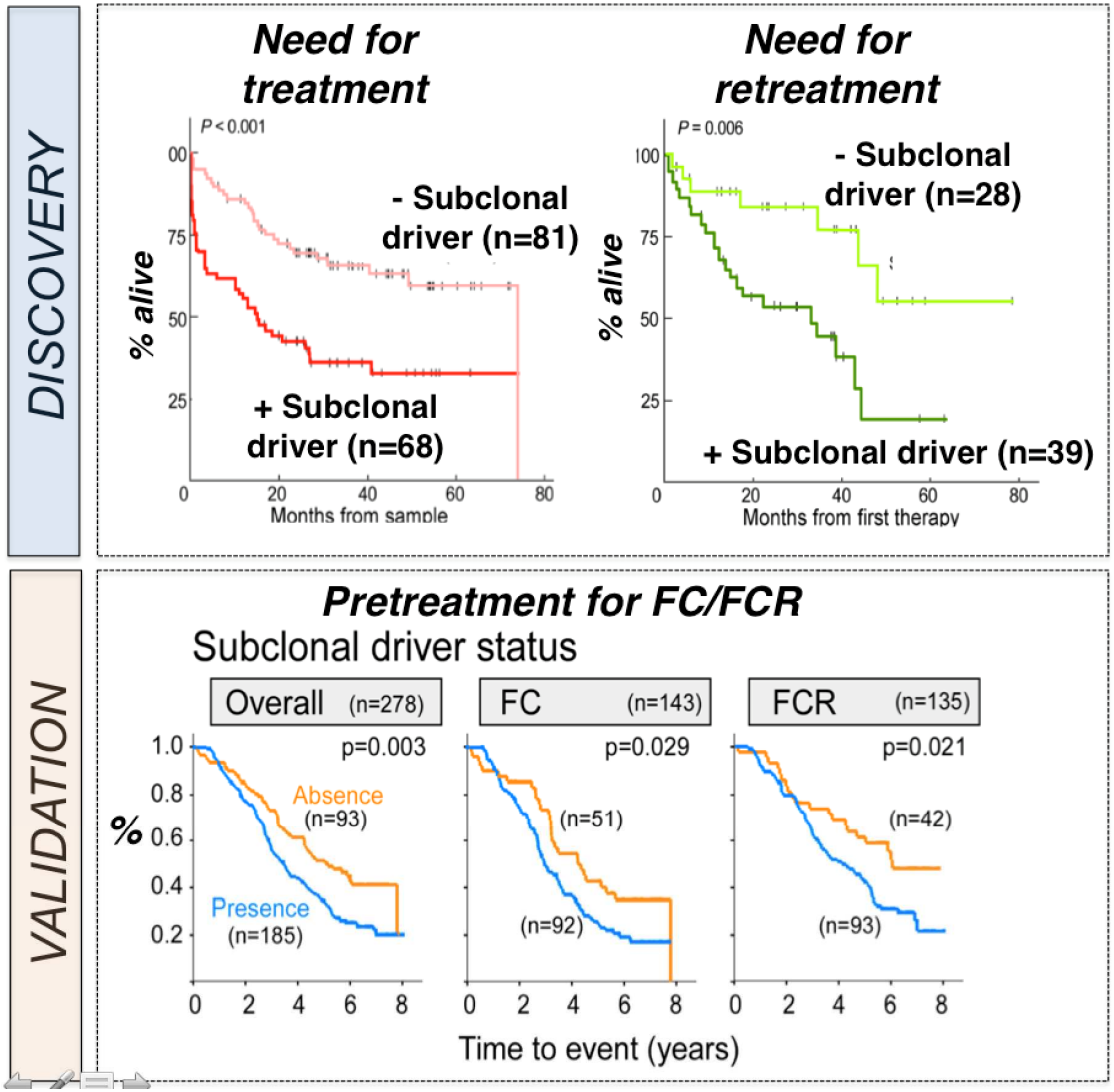
- 538 cases, WES
- (278 GCLLSG-CLL8 + 260 DFCI-ICGC)

Landau Tausch & Taylor Weiner, Nature 2015

Mutated *SF3B1* is a predominantly subclonal event



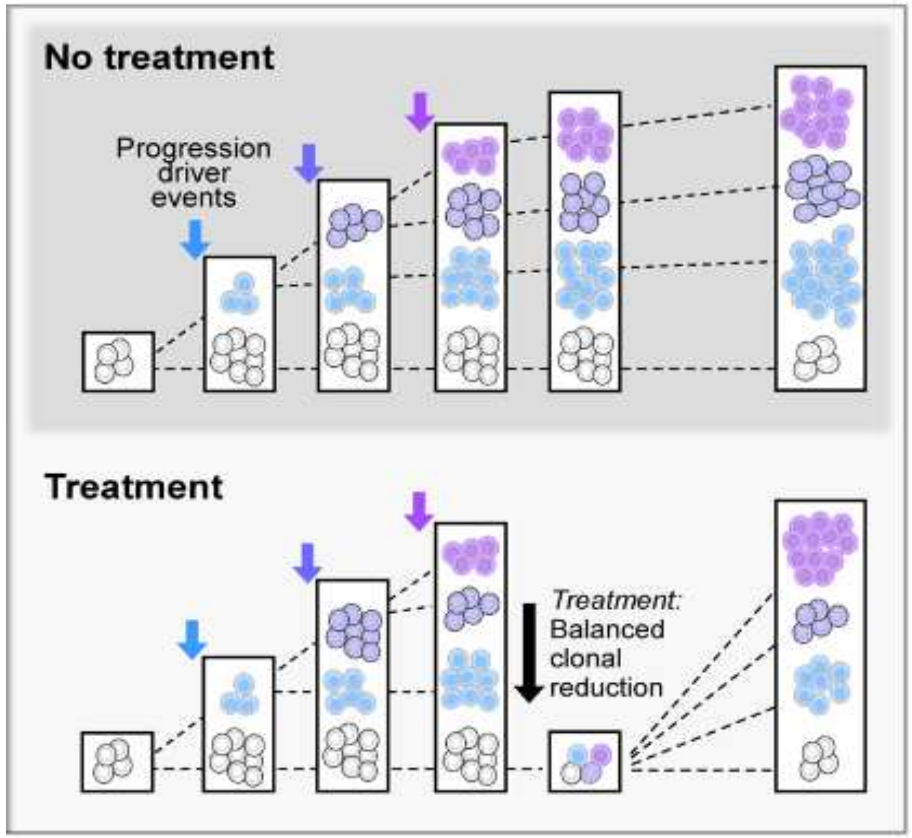
Subclonal driver status as a marker of active evolution – associated with poorer outcome



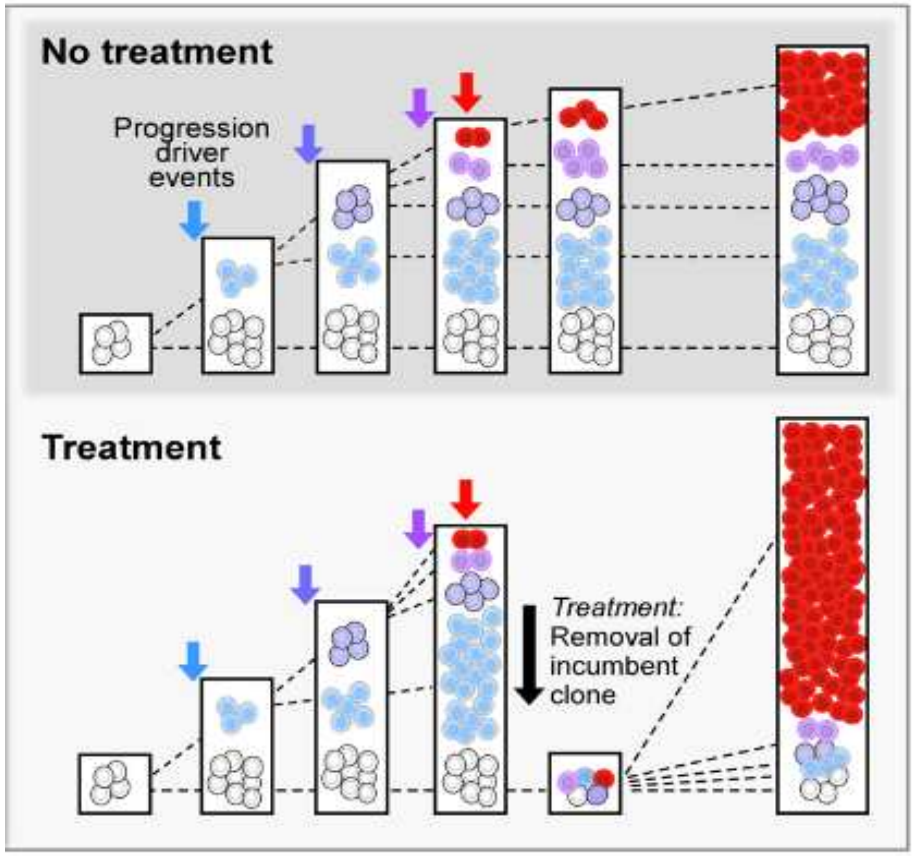
Landau Cell 2013

Landau Nature 2015

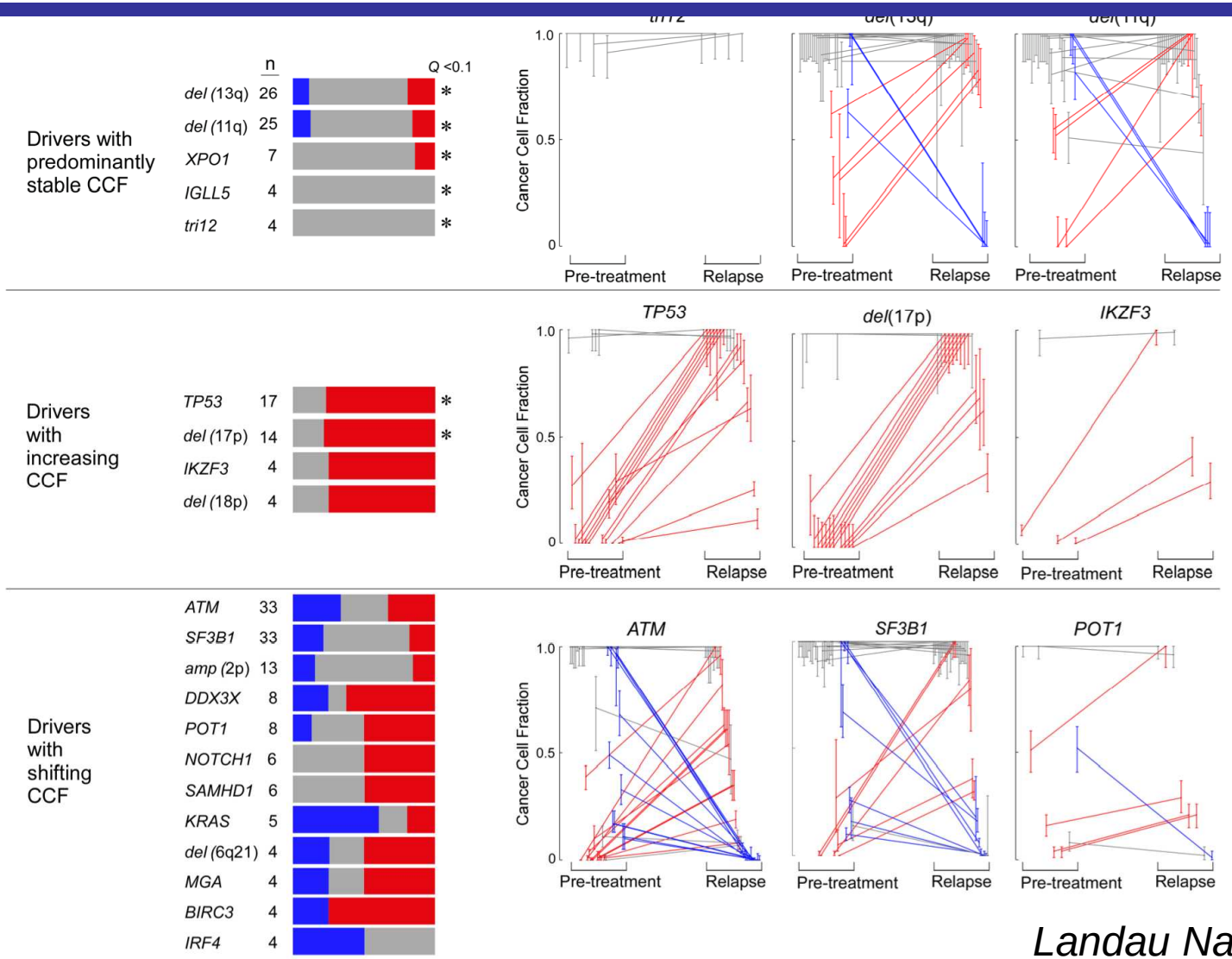
Stable:
clonal equilibrium



Evolving:
fitter subclones emerge with therapy

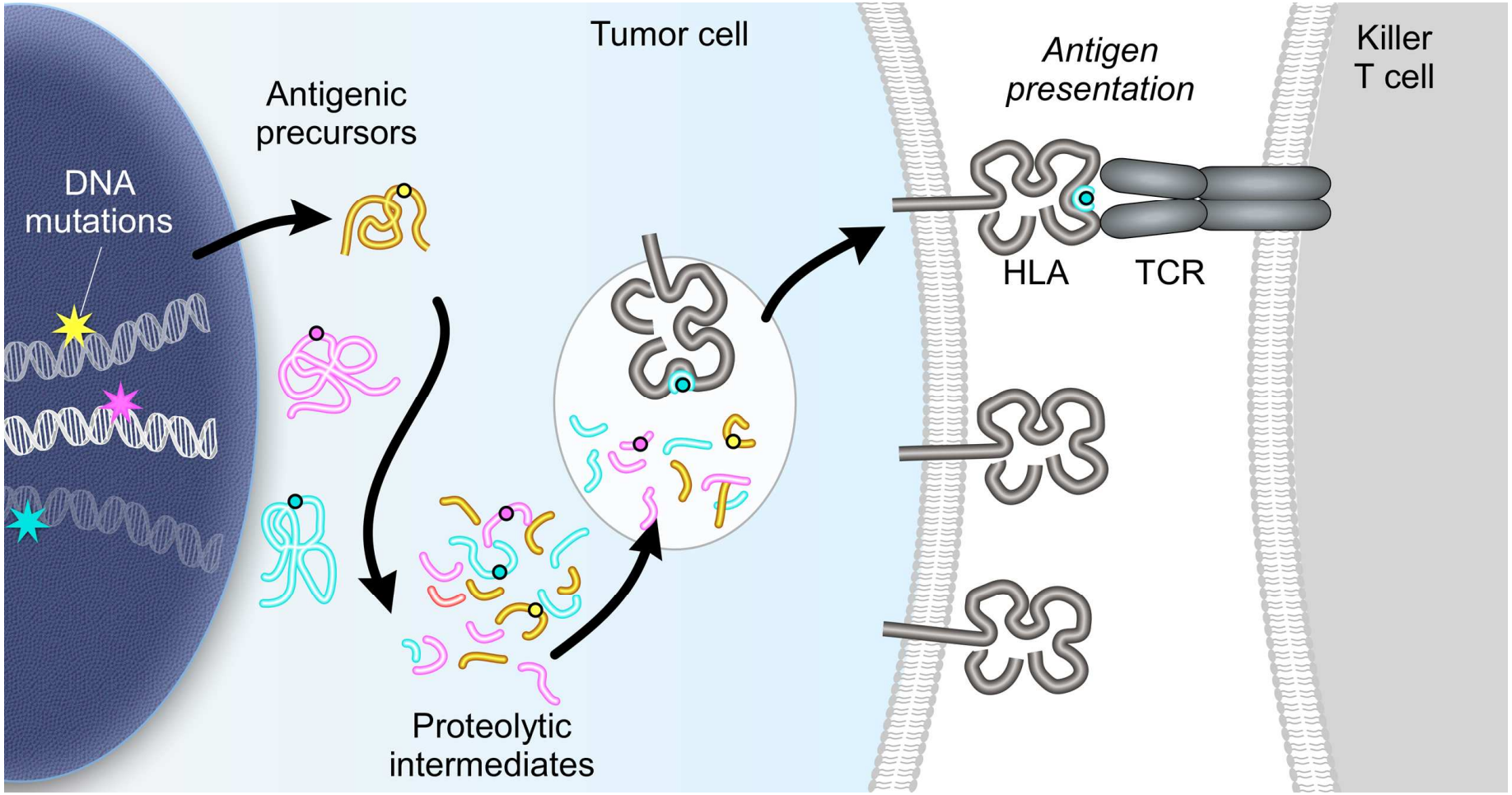


Diverse genetic escape trajectories and clonal evolution with relapse after *chemotherapy*

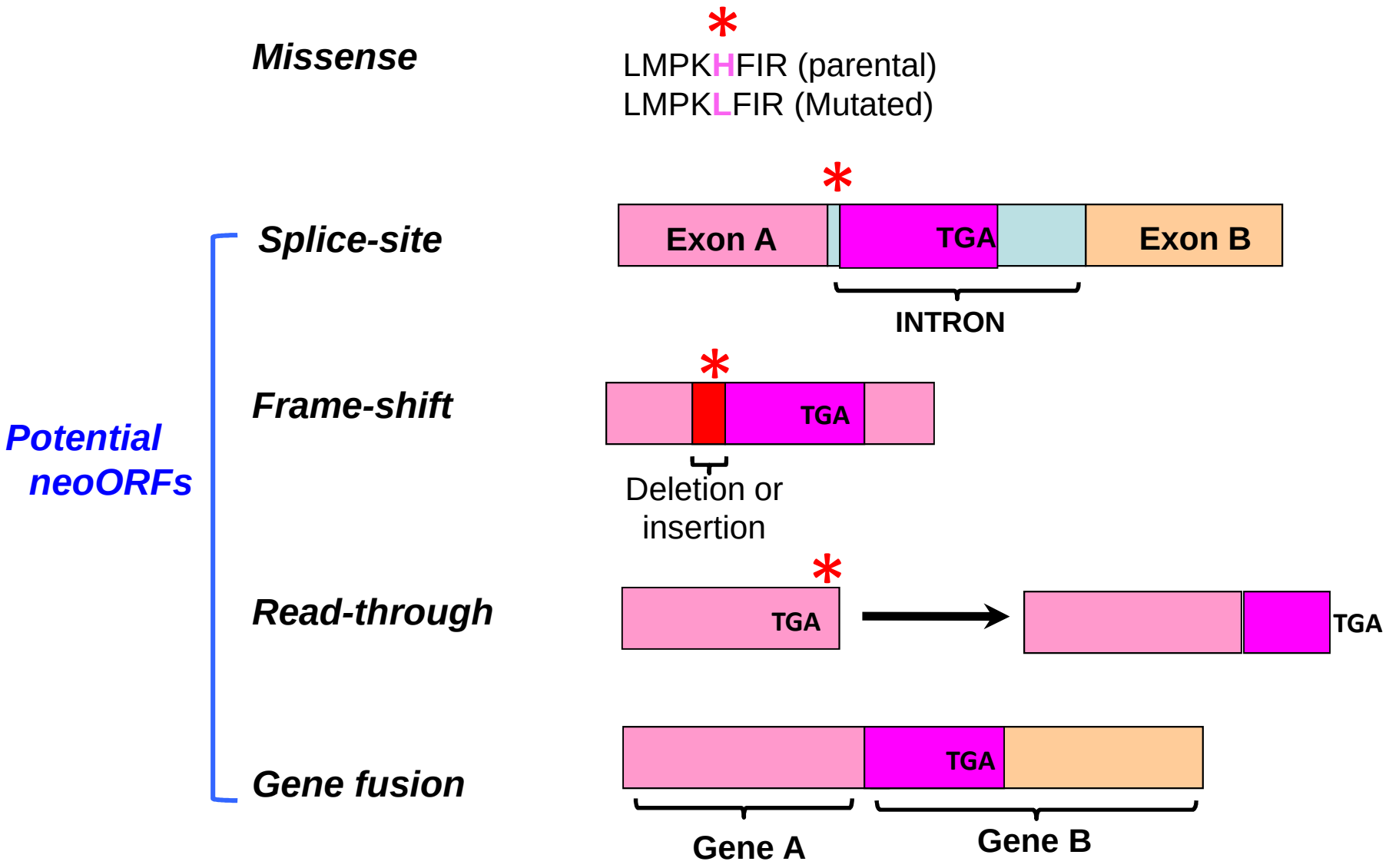


Landau Nature 2015

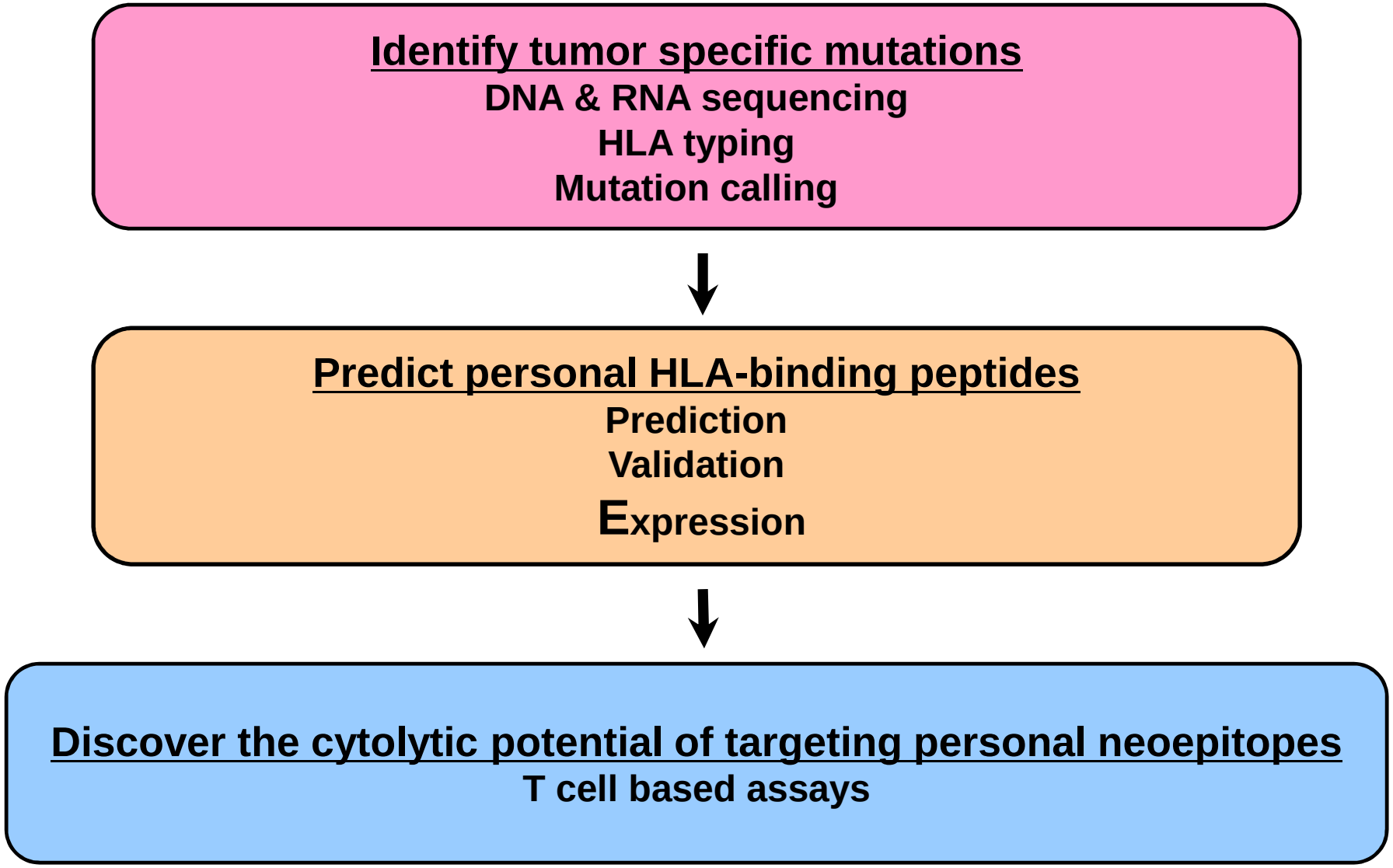
Somatic mutations have the potential to generate neoantigens



Classes of mutations that can generate potential tumor neoepitopes



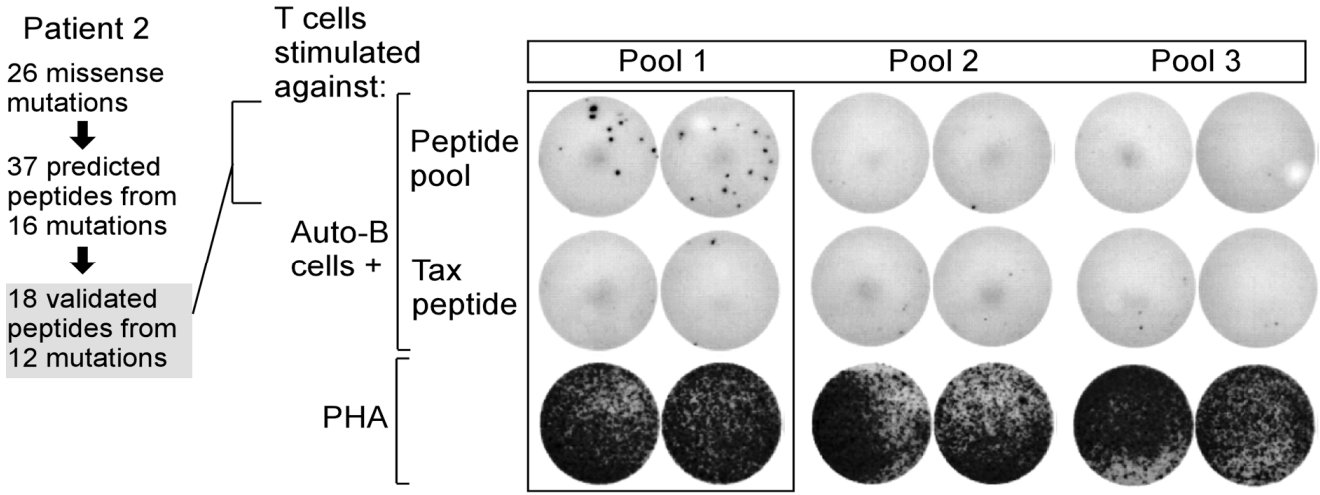
Neoantigen discovery workflow



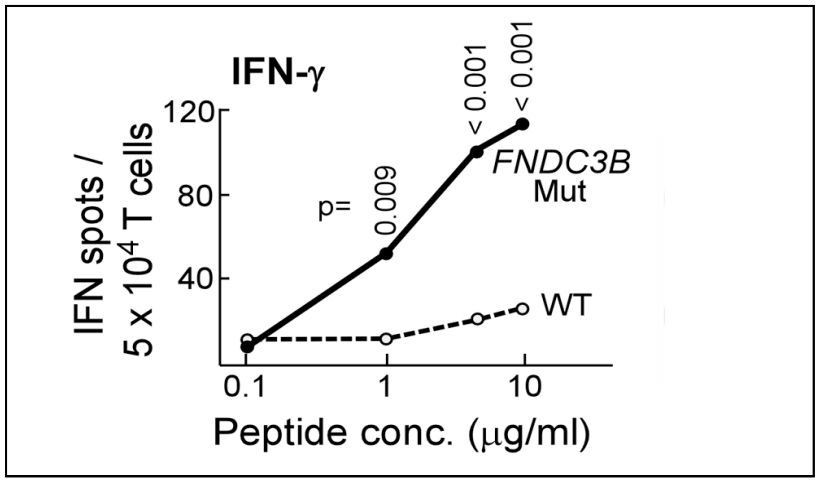
Systematic eval of neoantigen responses after autologous whole CLL vaccines/HSCT

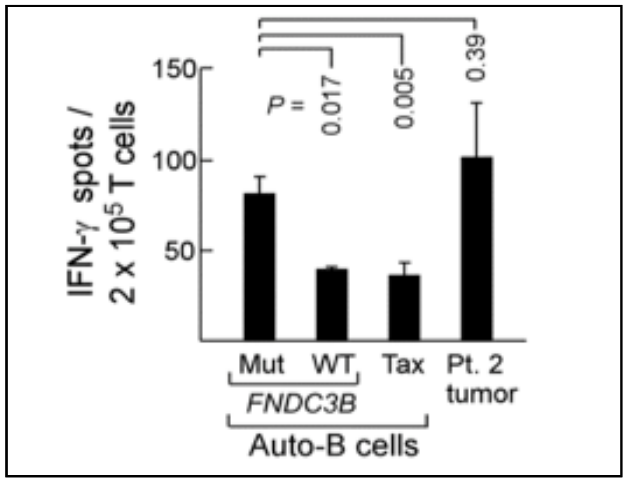
CLL patients in continuous remission from immune-based therapy

- Ex vivo stimulation of T cells with mutated peptides
- CD8+ T cell responses detected by IFN-γ ELISPOT assay

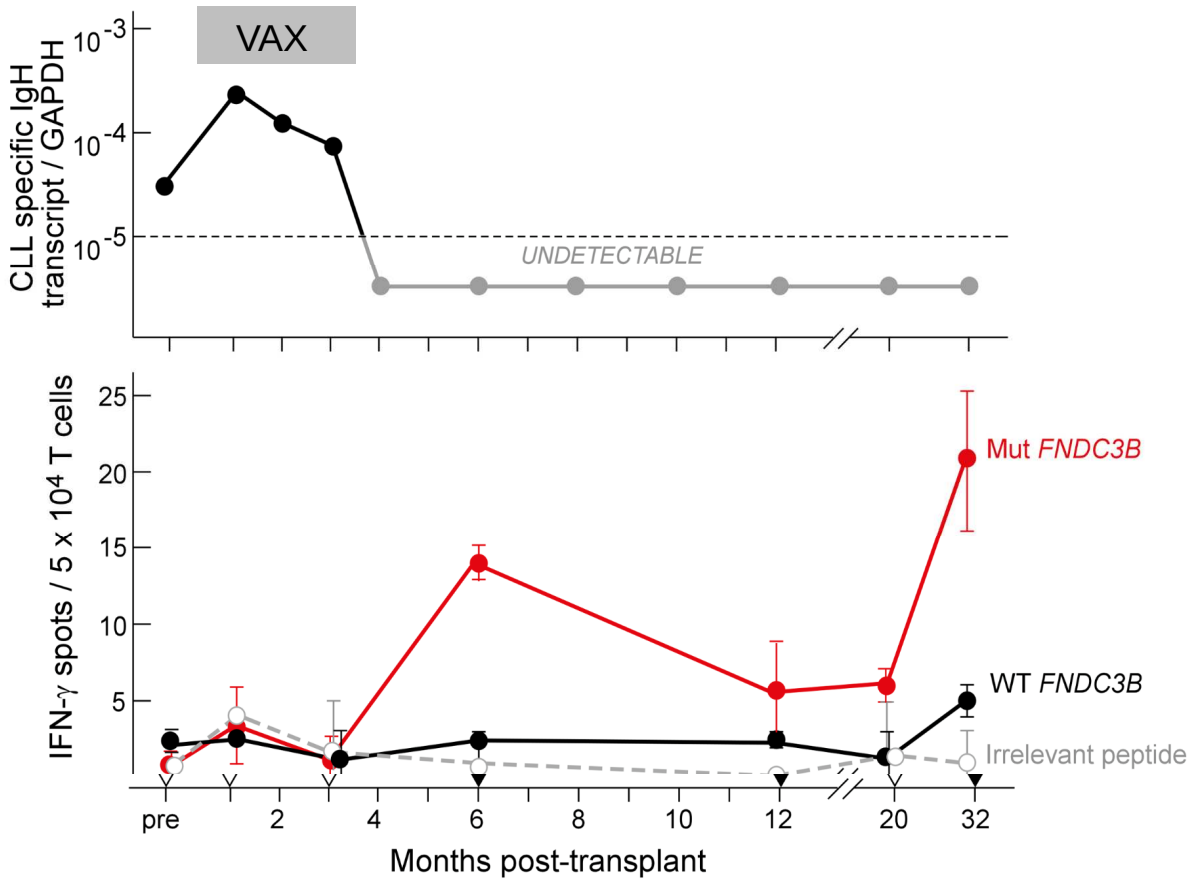


Rajasagi et al Blood 2014

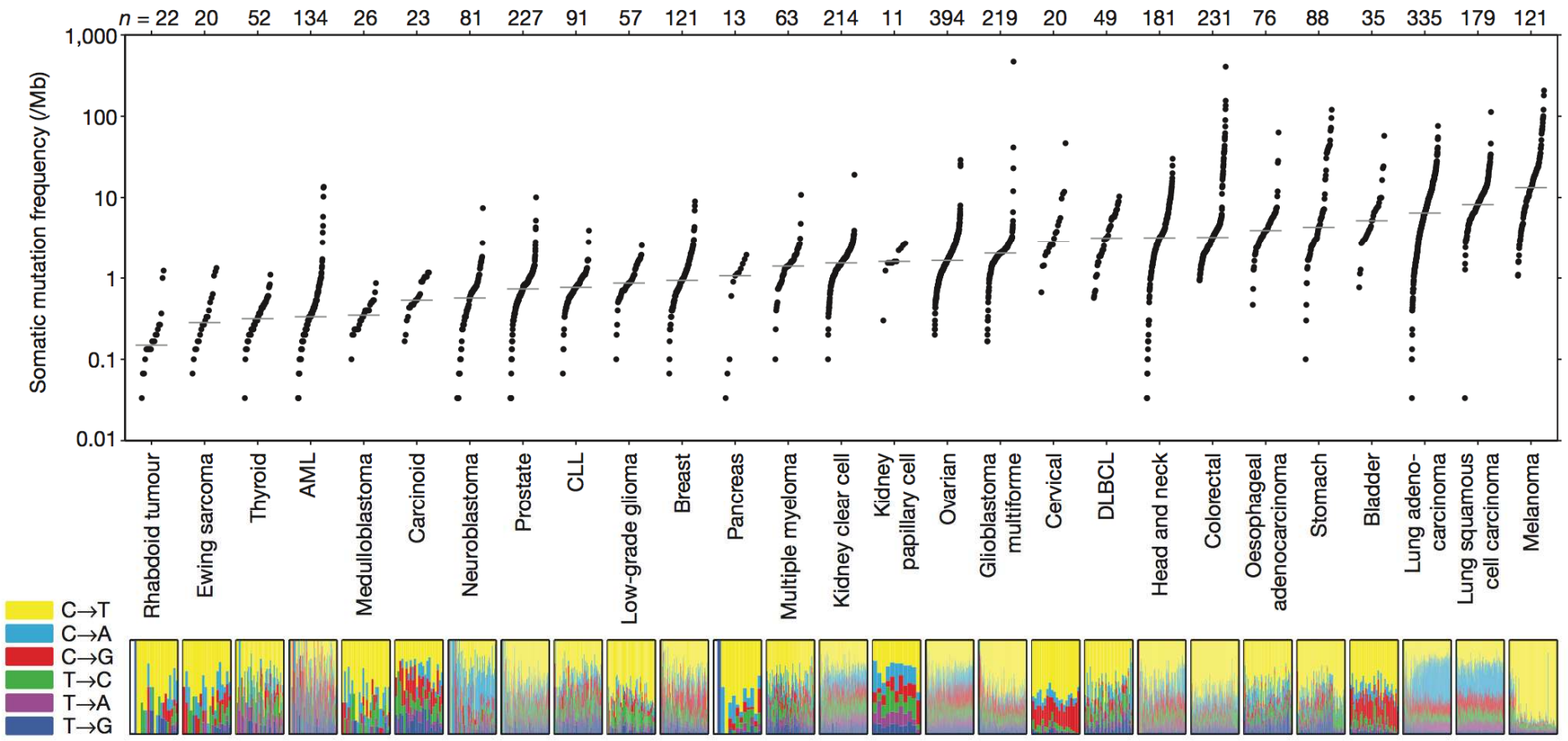




Long lived mut-*FNDC3B* memory T cells



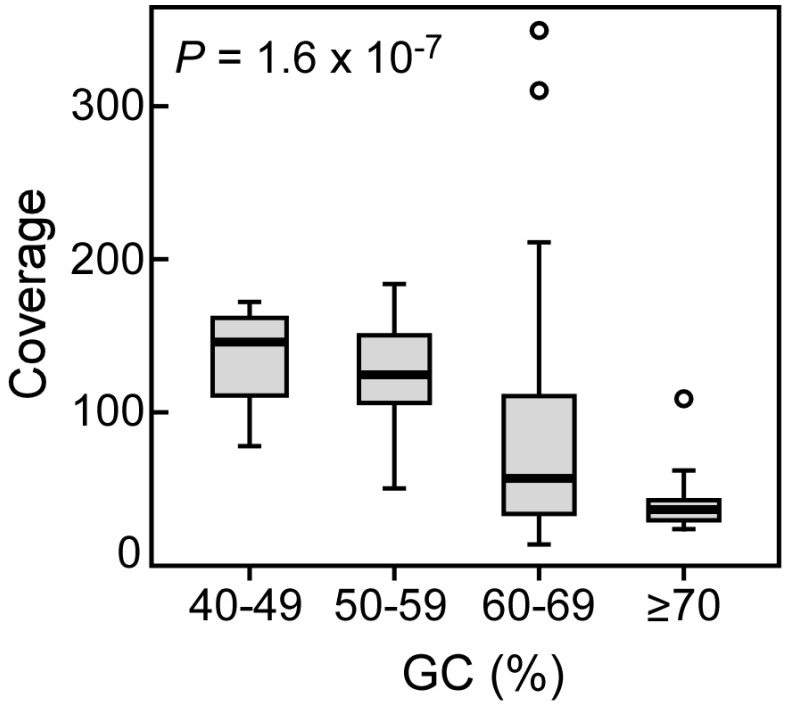
DNA sequencing across cancers (n= >3000)

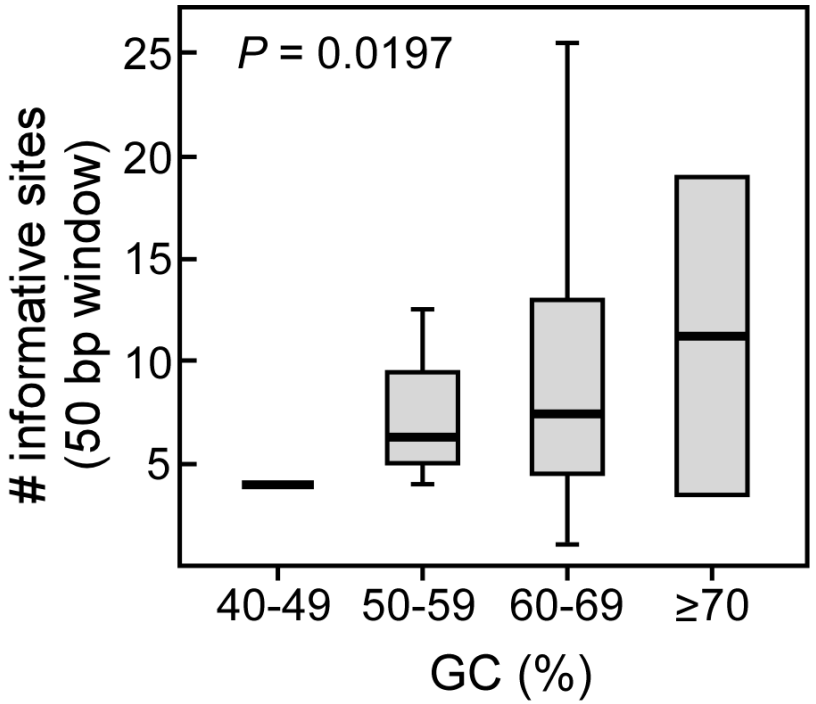


Lawrence MS Nature 2013

Challenges in HLA typing using WES data

- Polymorphic with many highly similar alleles
- GC rich
  - Capture efficiency
  - Sequencing

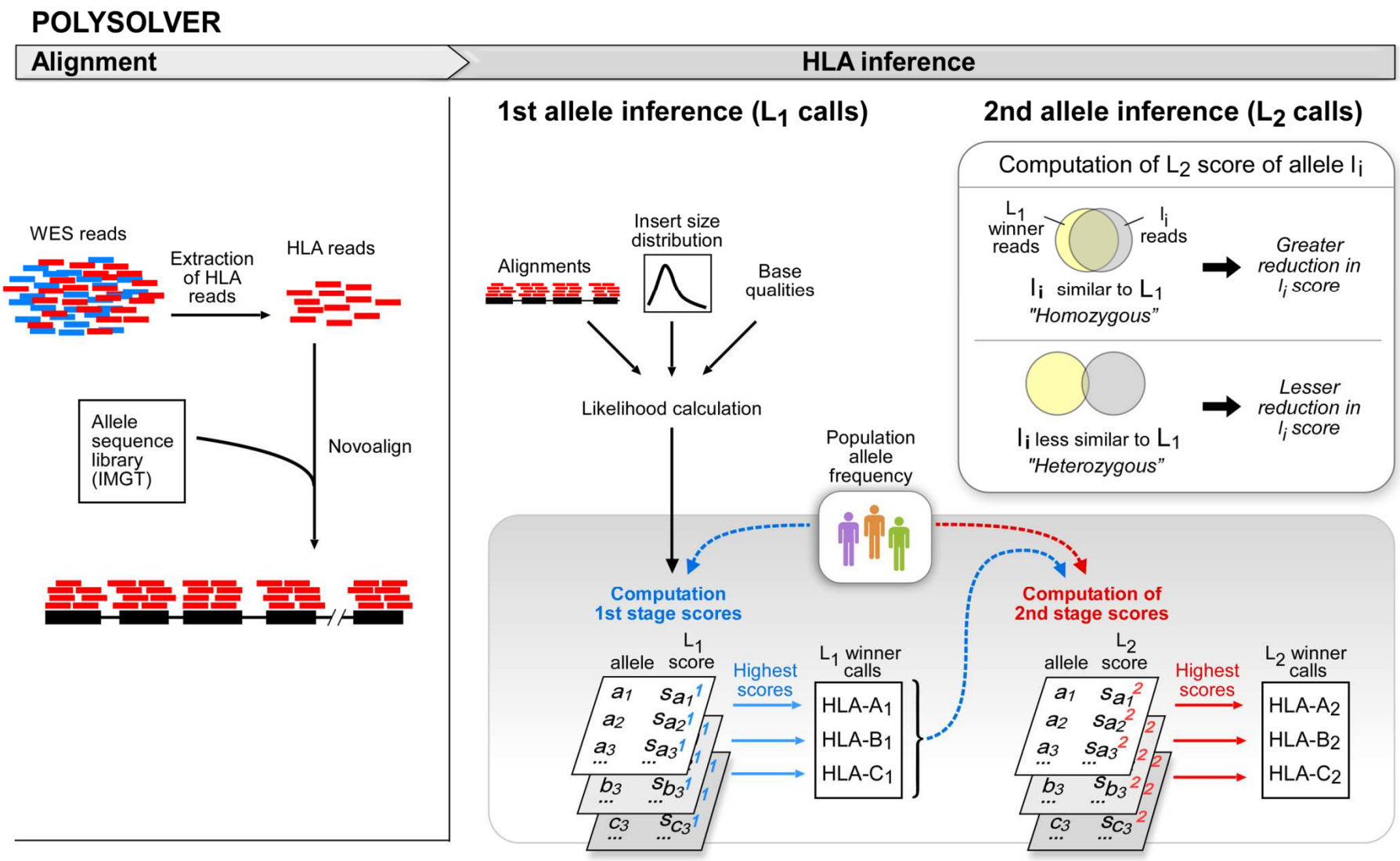




- Coverage is inversely correlated with GC content

- Informative site density is directly correlated with GC content

POLYSOLVER (POLYmorphic loci reSOLVER)

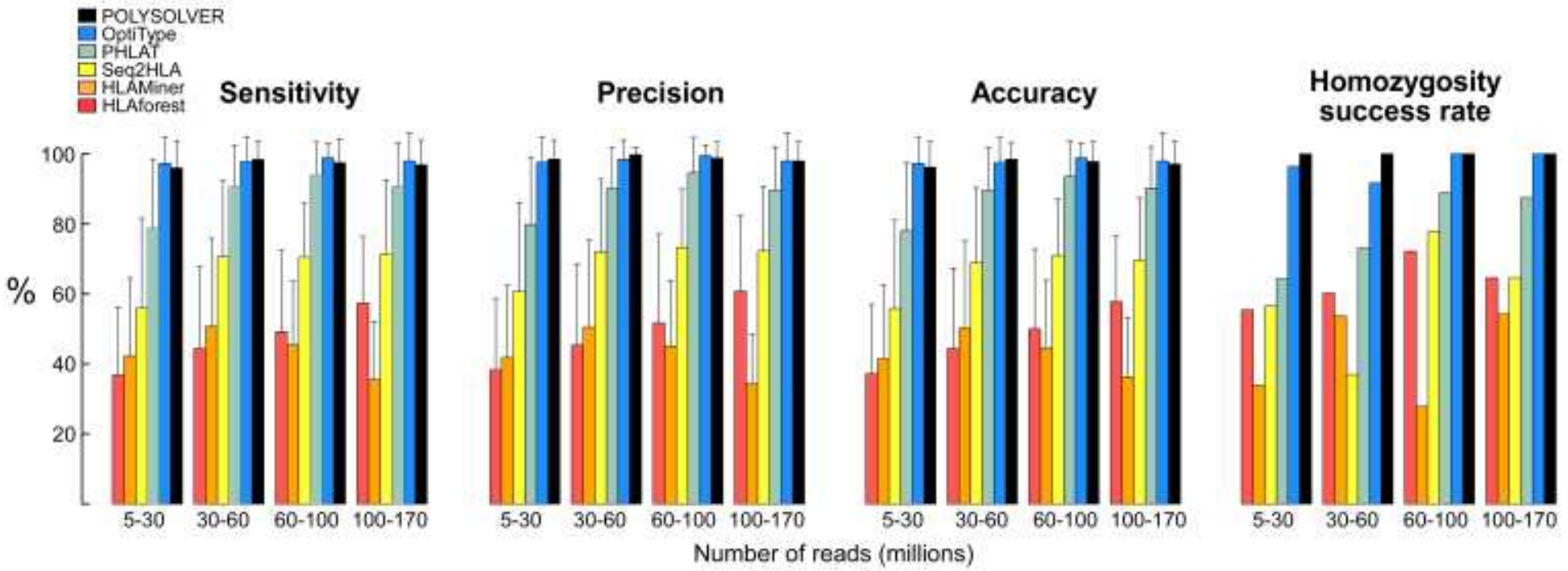


97% accuracy at protein-level resolution

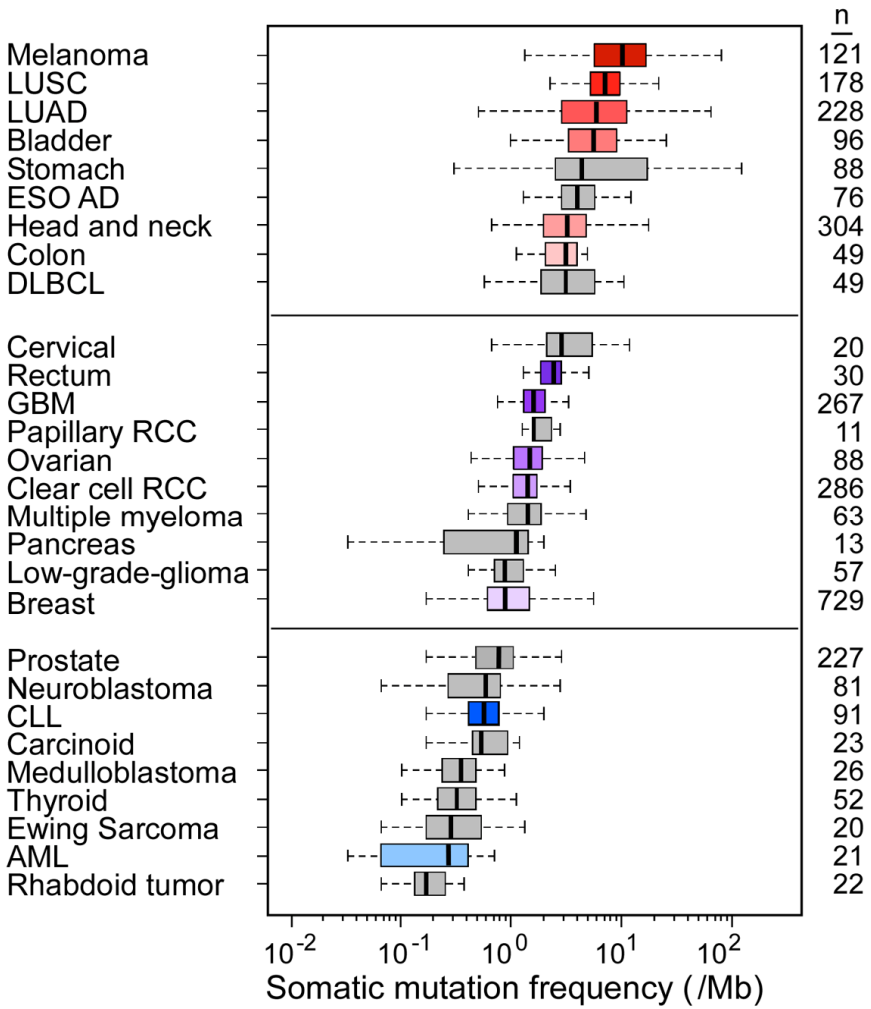
Shukla Nat Biotech 2015

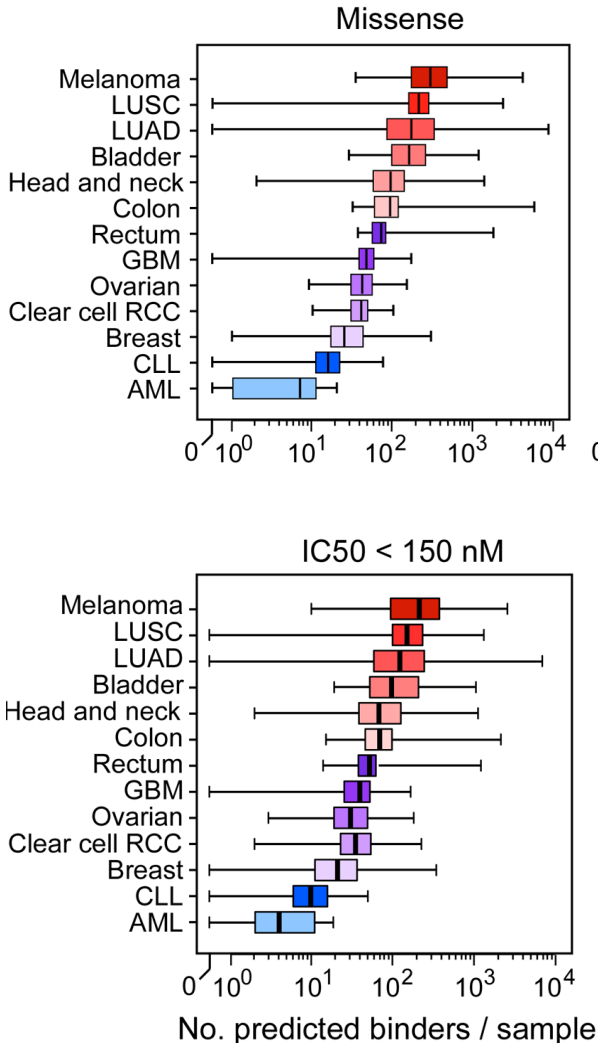
Performance characteristics of POLYSOLVER

- 253 Hapmap samples
  - exome sequencing data (HapMap)
  - experimental HLA type data (Hapmap)
  - 47 Caucasians, 50 Blacks, 86 Asian individuals



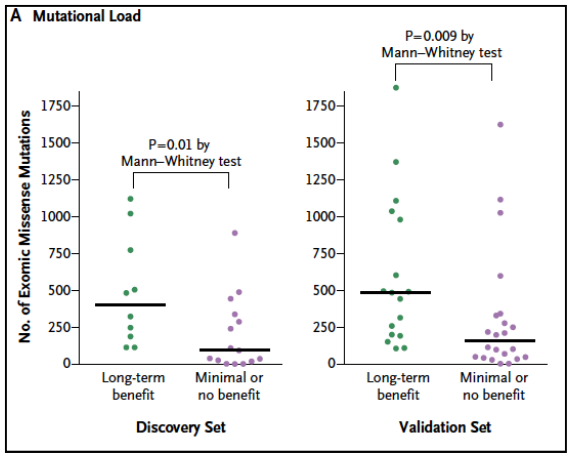
Estimates of tumor neoantigen load across cancers

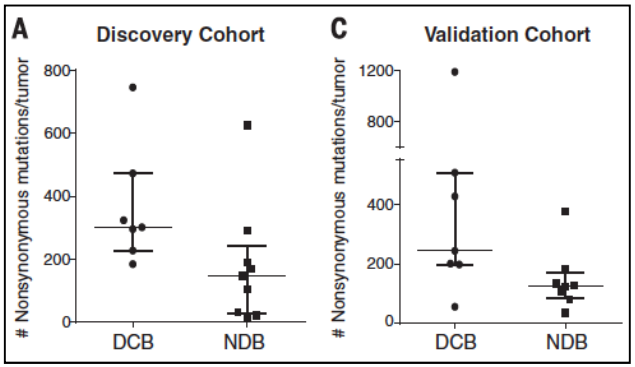


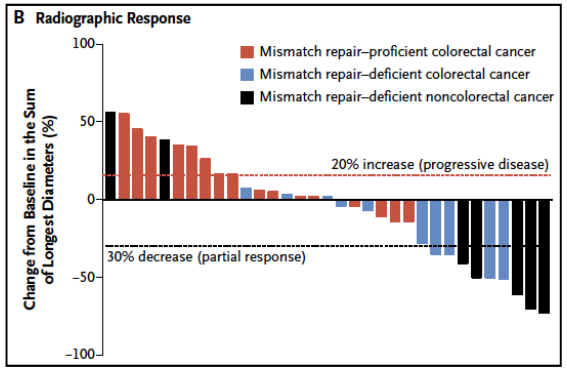


Rajasagi et al Blood 2014

Mutational load and immunotherapy response







CTLA4 Ab and advanced melanoma

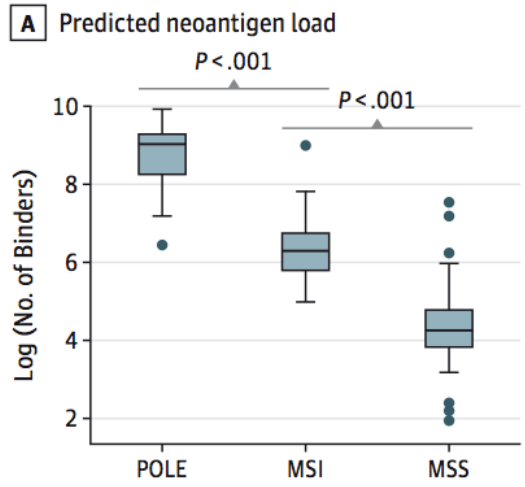
PD-1 Ab and NSCLC

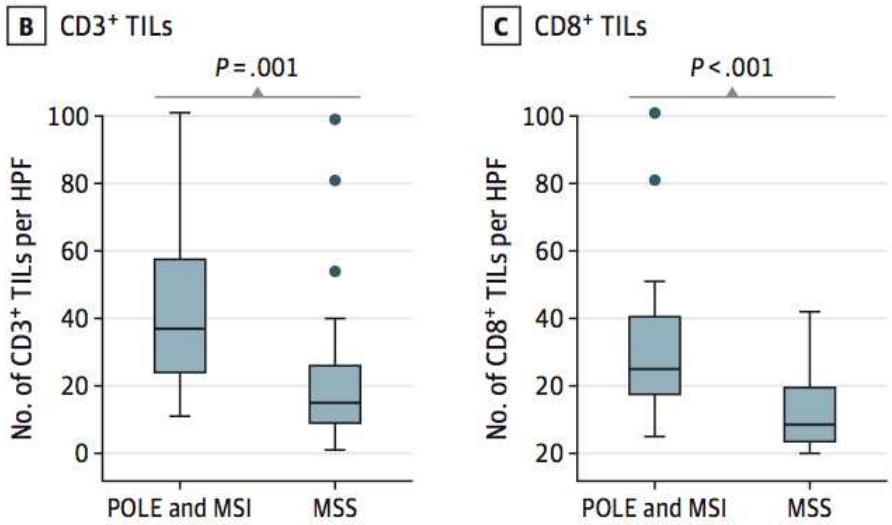
PD-1 Ab and colorectal cancer

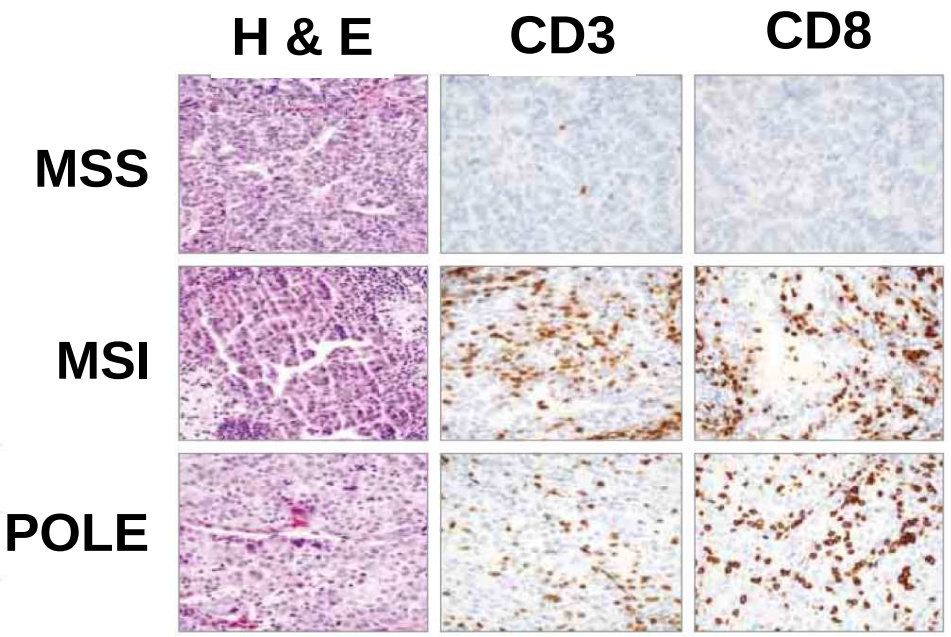
Snyder et al NEJM 2014
Rizvi et al Science 2015
Le et al NEJM 2015

High mutational load related to neoantigen load and presence of T cell infiltrates

Endometrial adenocarcinoma







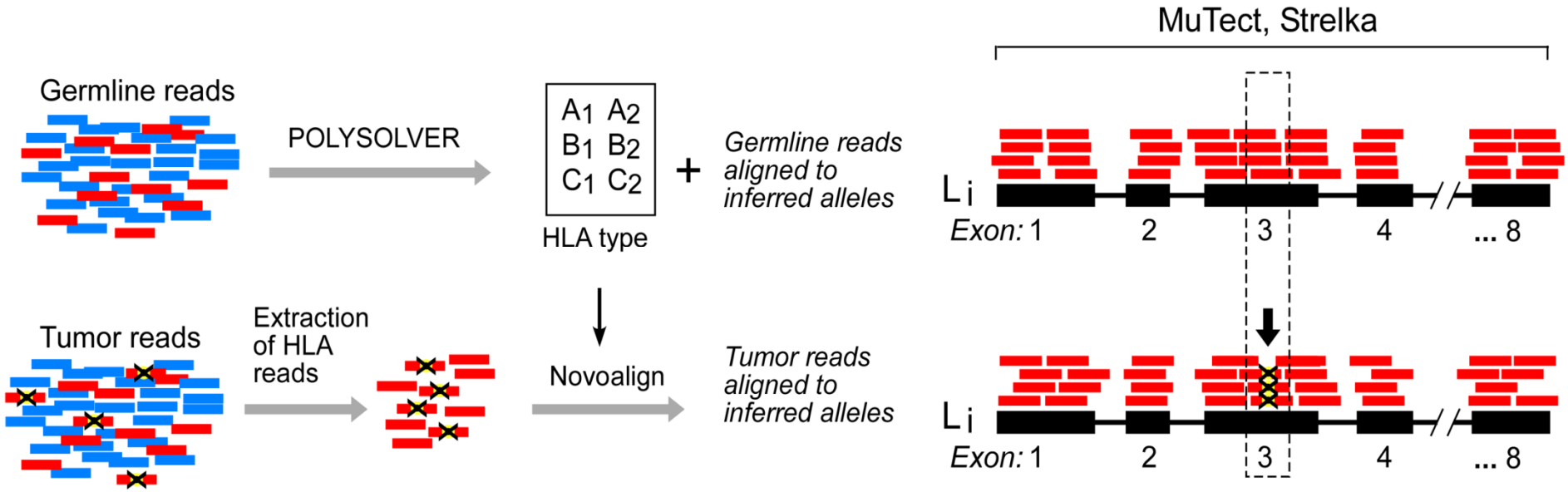
Howitt JAMA Onc 2015

A more direct look….

- WES of 619 tumor/normal pairs of patients with CRC on FFPE specimens collected on 2 prospectively collected cohorts (NHS and HPFS)
- More than 20 year follow up
- Integration of genomic information, pathology (immune infiltration data) and clinical data Nosho et al. J Pathol 2010; 222:350-366
- Immune cell subtype and infiltrate pattern previously examined

Giannakis, Mu & Shukla
L Garraway
C Fuchs
S Ogino

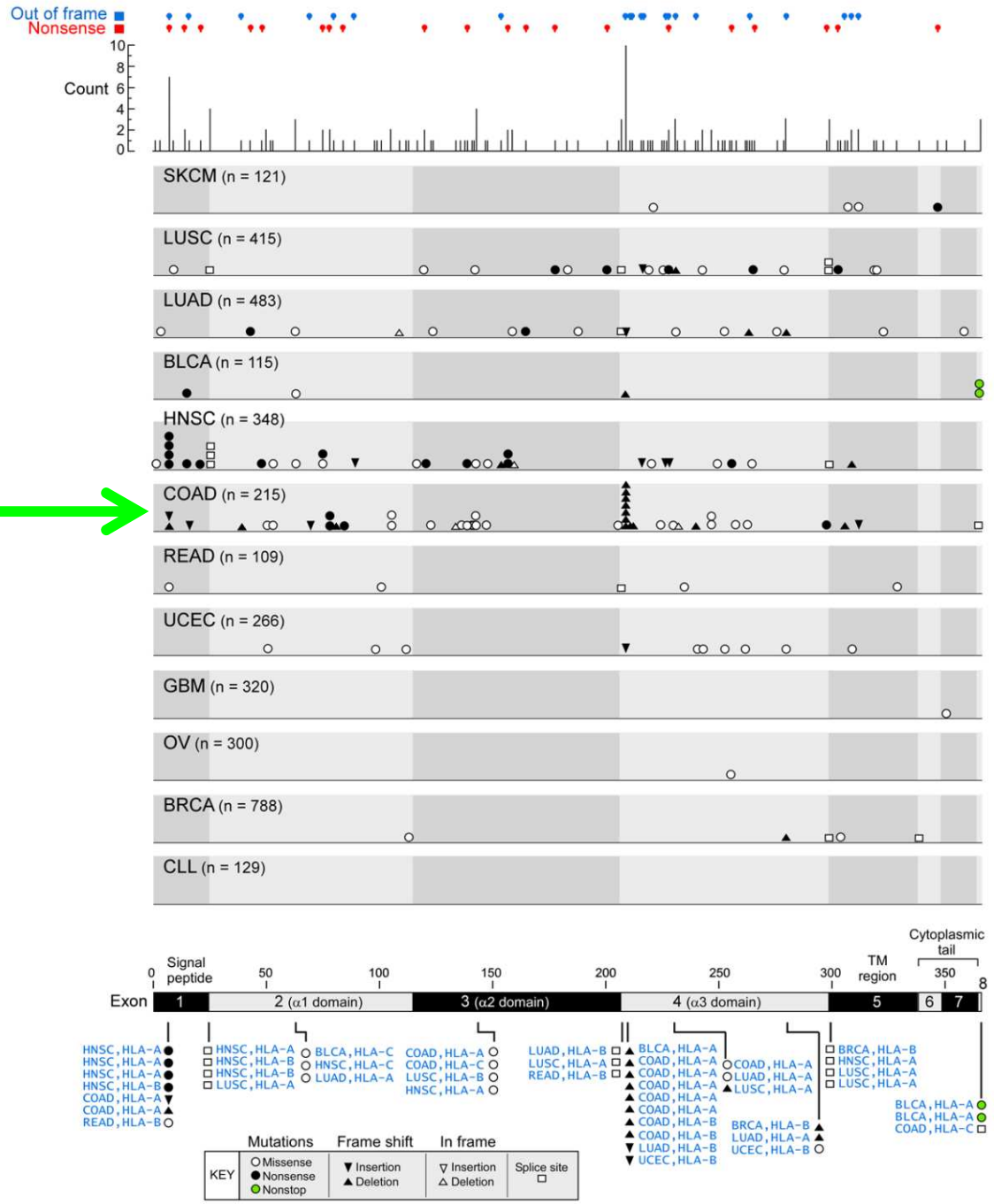
HLA mutation detection pipeline for somatic mutations in HLA –A and -B



Shukla Nat Biotech 2015

•Applied POLYSOLVER and HLA mutation detection pipeline to 3,708 samples across 12 tumor types

Colon cancer identified as significant by MutSig



Shukla Nat Biotech 2015

Are HLA mutations associated with immune infiltration?

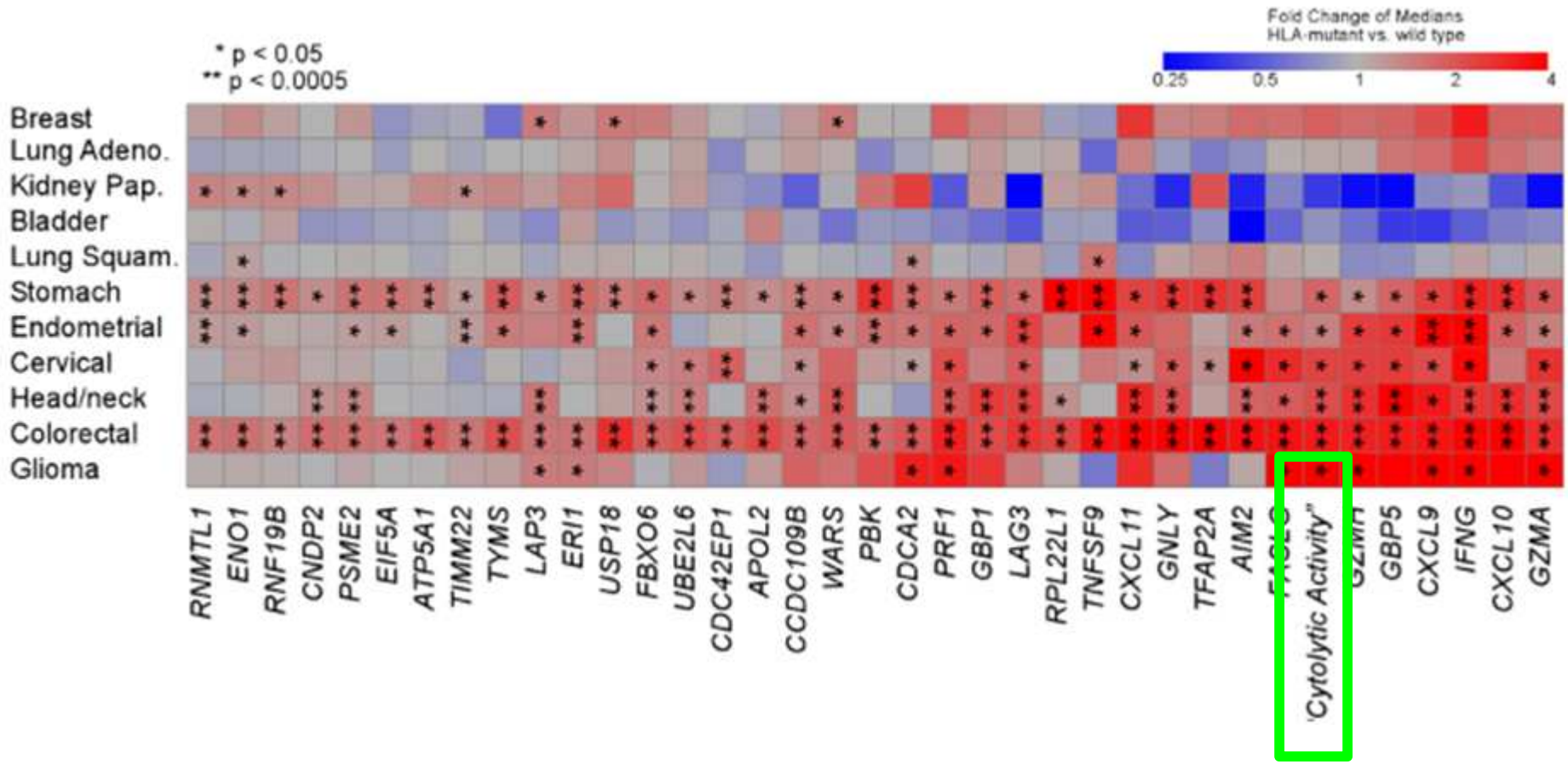
- Hypothesis: HLA mutations are more likely to arise in tumors infiltrated with cytotoxic T cells (CTLs) and natural killers cells (NKs) and would provide a strong selective advantage to emergent subclones

- We examined the expression of 18,000 genes in matched RNA-seq data from 4512 samples across 11 tumor types

- Most significantly enriched genes
  - IFNG
  - T cell attractive chemokines (CXCL9, CXCL10, CXCL11)
  - lytic molecules (GZMA, GZMH, PRF1, GNLY)
  - "Cytolytic Activity“: metagene analyzed previously as a measure of anti-tumor T/NK cell activity (Rooney *et al*, Cell, 2015)

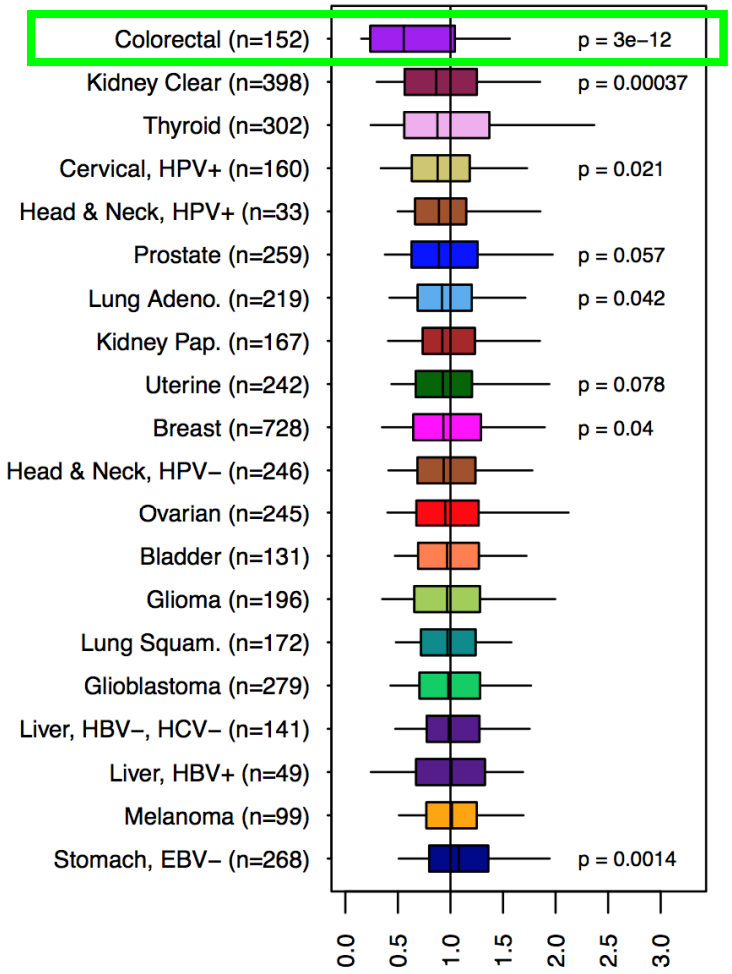
Shukla, Rooney

HLA mutations in TCGA samples are associated with immune infiltration and may serve as an immune escape mechanism

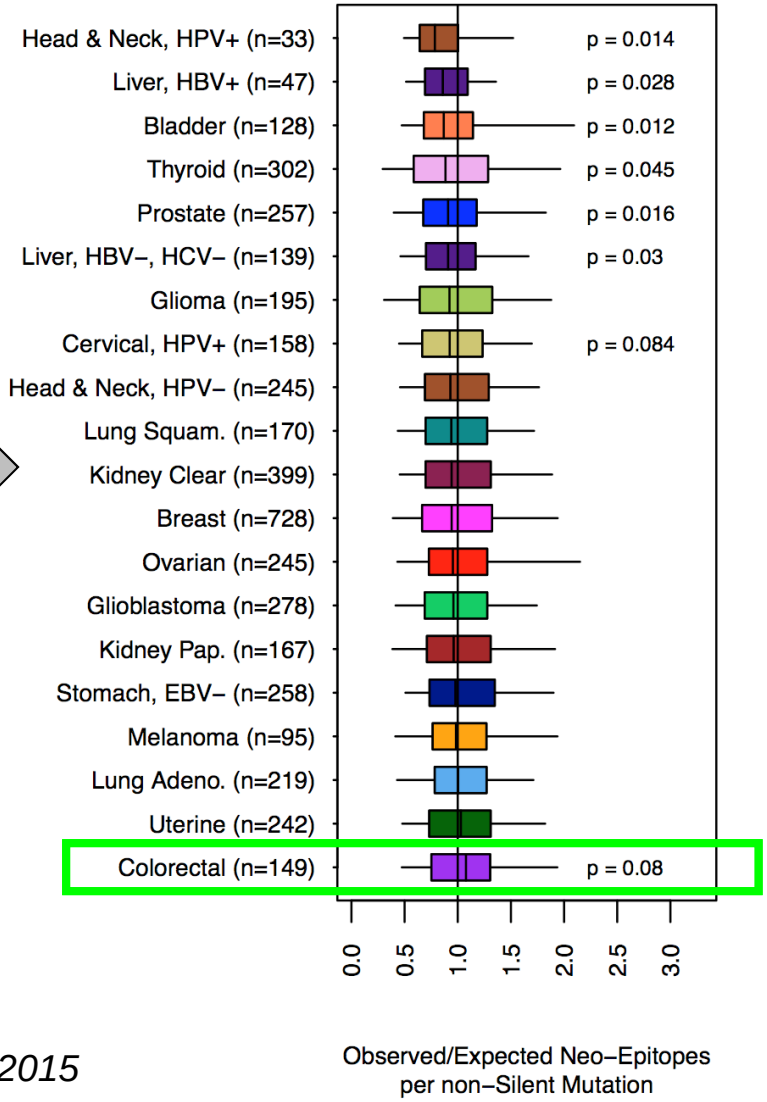


Shukla Nat Biotech 2015

Multiple tumor types show reduced rates of predicted HLA-binding mutations *vs.* expected



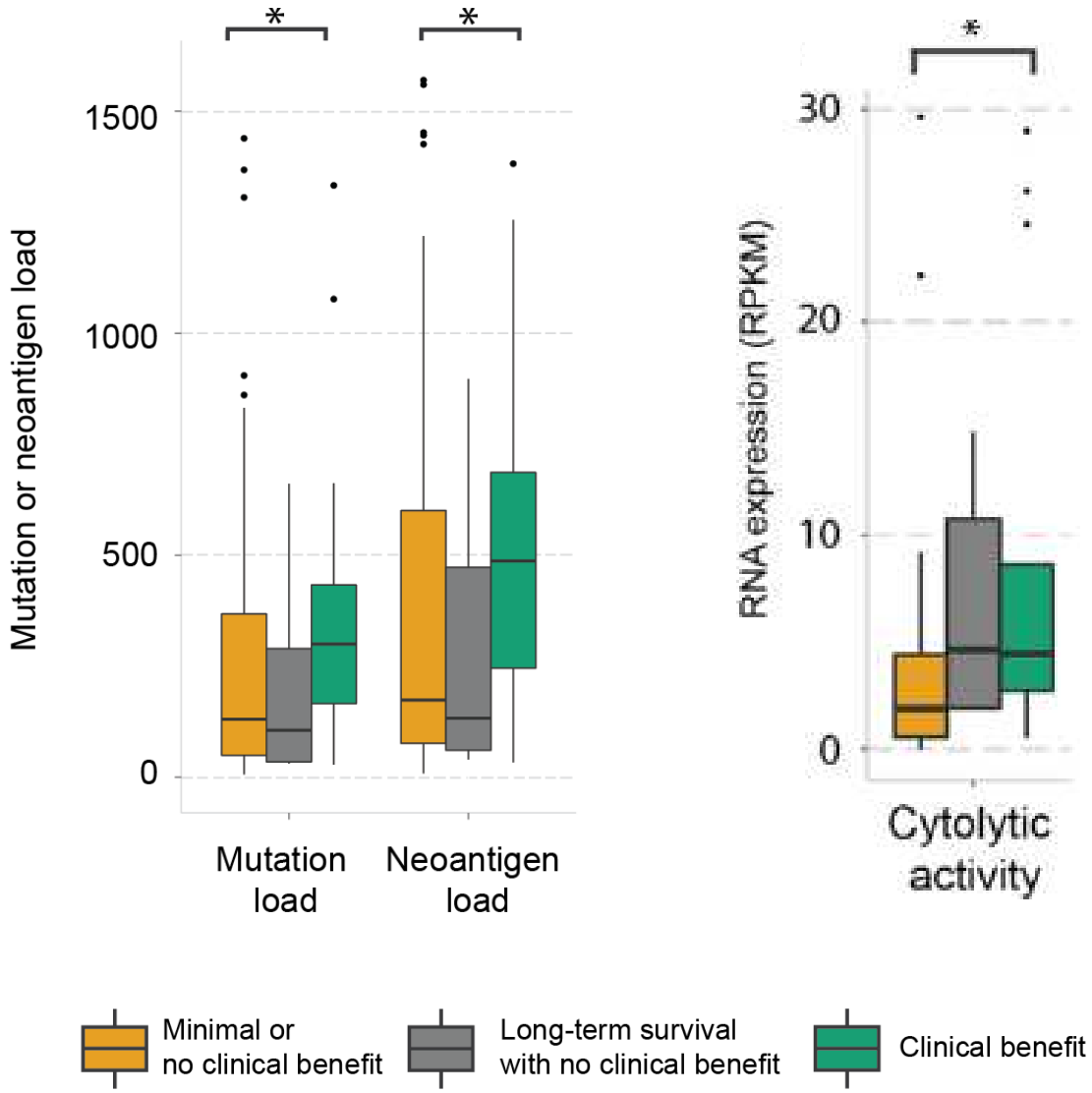
Random shuffling of HLAs



Rooney Cell 2015

Ipilimumab and melanoma cohort study: clinical correlates

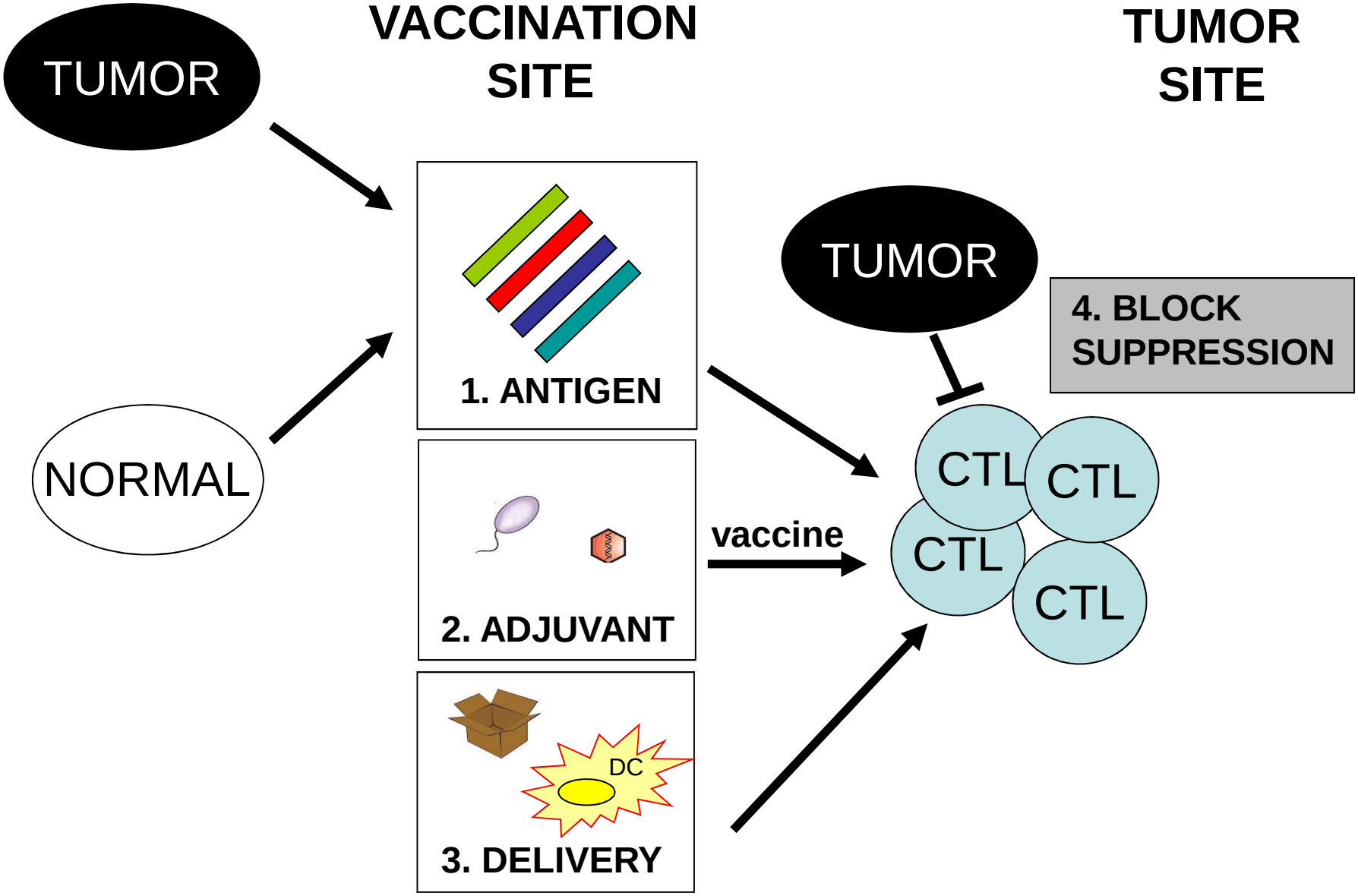
- WES on FFPE pretreatment samples from 110 pts with metastatic melanoma
- Matched RNA seq on 40

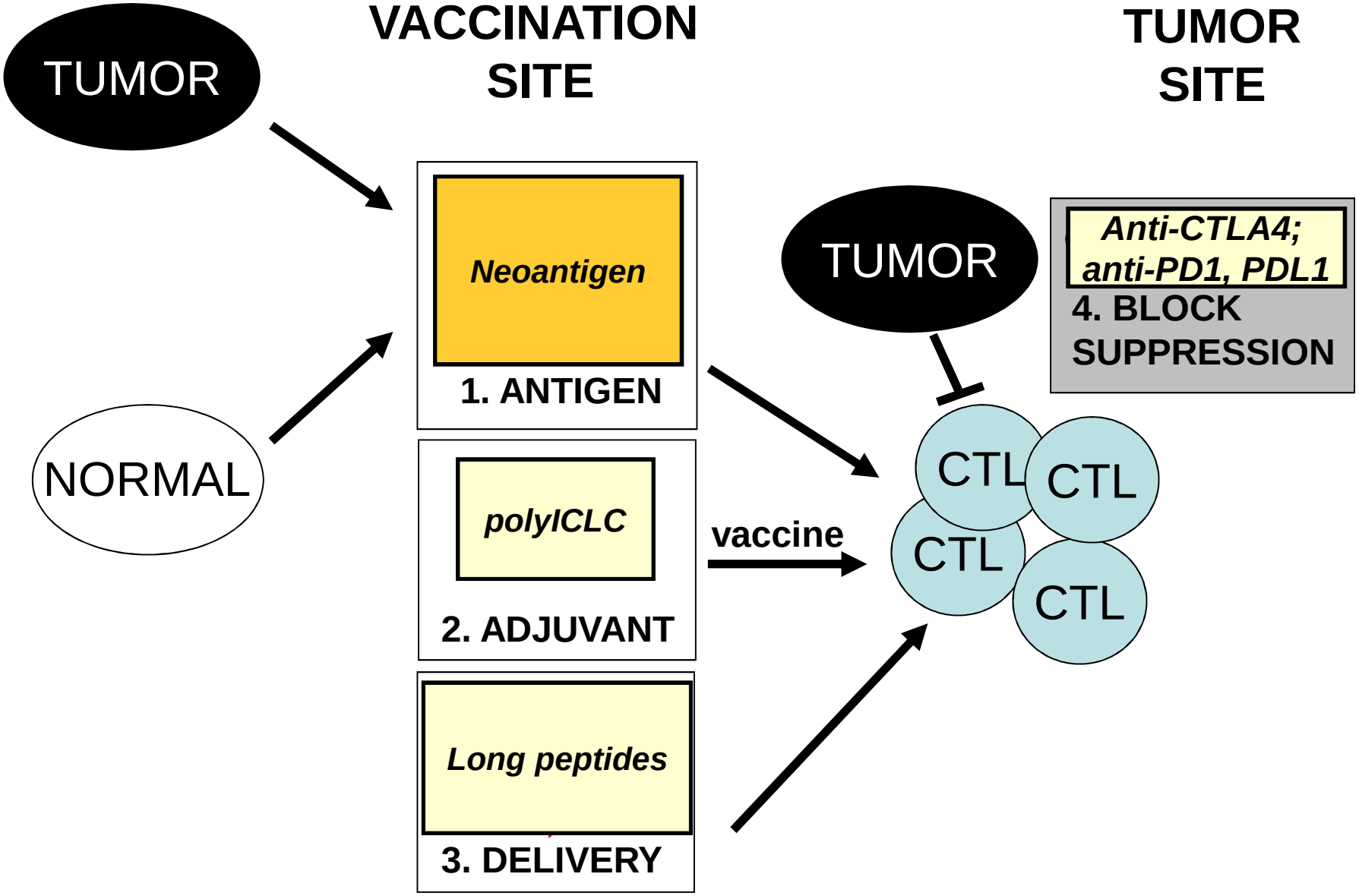


Van Allen, Miao, Schilling et al, *Science* 2015

“Fighting fire with fire”

Immune-based therapy is uniquely suited to addressing the challenge of cancer heterogeneity


TUMOR
VACCINATION SITE
TUMOR SITE
NORMAL
1. ANTIGEN
2. ADJUVANT
3. DELIVERY
DC
vaccine
TUMOR
4. BLOCK SUPPRESSION
CTL
CTL
CTL
CTL

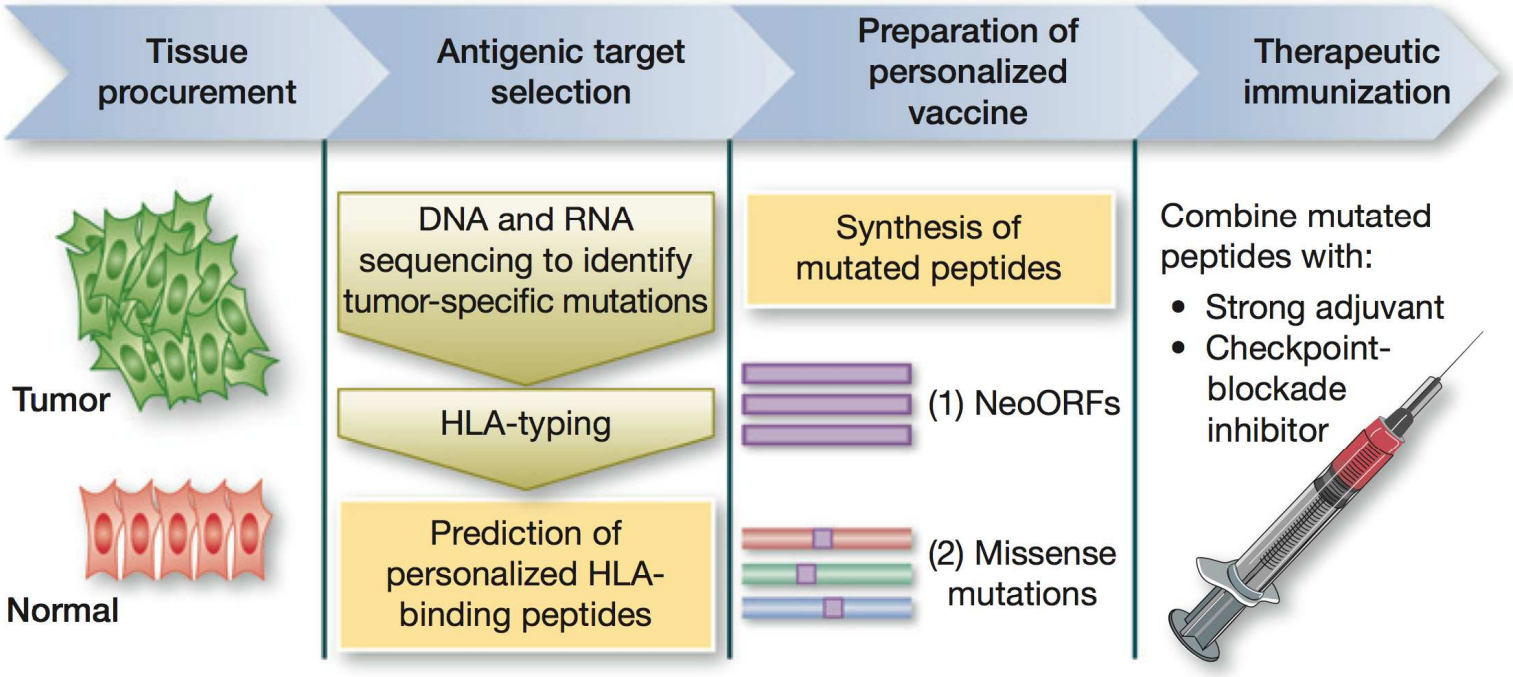

TUMOR
NORMAL
VACCINATION SITE
Neoantigen
1. ANTIGEN
polyICLC
2. ADJUVANT
Long peptides
3. DELIVERY
vaccine
TUMOR
TUMOR SITE
Anti-CTLA4; anti-PD1, PDL1
4. BLOCK SUPPRESSION
CTL
CTL
CTL
CTL

What could a personalized cancer vaccine do?

- Increase T cell infiltration
  - Recruit new T cells
  - Increase the repertoire of tumor-specific T cells
- Alter the immune milieu

Increase efficacy, minimize toxicity

Developing NeoVax: based on multiple coding mutations unique to each pt tumor



Hacohen et al, CIR 2013

Summary

- Next-generation sequencing capabilities now enable systematic mining of the genome for potential neoantigens as well as characterization of the immune context
- Tumor neoantigens appear to be an important class of immunologic targets against which tumor-specific responses can be generated
- Phase I clinical trials to test a personalized cancer neoantigen vaccine have started

Acknowledgements

Wu lab
Lili Wang
Wandi Zhang
Youzhong Wan
Mohini Rajasagi
Ann Cai
Sachet Shukla
Ed Fritsch
Jintaek Kim
Masayasu Naito
Michaela Gruber
Dan-Avi Landau
Ute Burkhardt
Melinda Biernacki
Ursula Hainz
Ana Brusic
Jing Sun

DFCI
Marios Giannakis
Levi Garraway
Eli Van Allen
Glenn Dranoff
Patrick Ott
David Reardon
F. Stephen Hodi

CMCF and Pasquarello Tissue Bank
Heather Daley
Jerome Ritz
Doreen Hearsey

Clinical Team
Patrick Ott
Edwin Alyea
Jennifer Brown
Rob Soiffer
John Koreth
Philippe Armand
Joe Antin
Corey Cutler

DFCI Biostatistics
Kristen Stevenson
Donna Neuberg

Broad Institute
Eric Lander
Nir Hacohen
Stacey Gabriel
Carrie Sougnez
Gaddy Getz
Mike Lawrence
Petar Stojanov
Andrey Sivachenko
Gordon Saksena
Scott Carter
David Deluca
Angela Brooks

S2C

National Heart Lung and Blood Institute
People Science Health

National Cancer Institute

The Leukemia & Lymphoma Society
Fighting Blood Cancers

Blavatnik Family Foundation