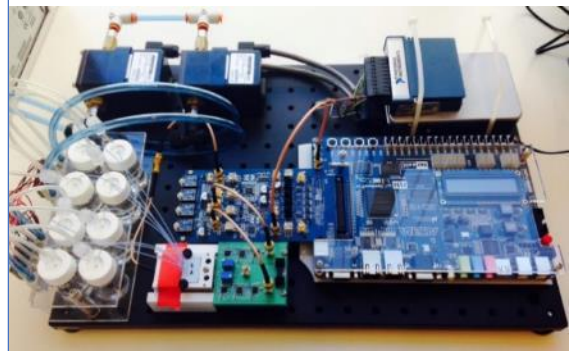
DANA-FARBER CANCER INSTITUTE

BROAD INSTITUTE

HARVARD MEDICAL SCHOOL

Defining Vulnerabilities of T-cell Lymphomas:

we are close to the finalization…of the beginning



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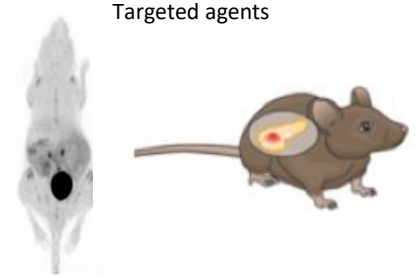
http://weinstock.dfci.harvard.edu

Disclosures

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Travera			X	X			Founder
Novartis	X		X				
Dragonfly			X				
Aileron	X						
Abbvie	X						
Astra Zeneca	X						
Surface Oncology	X						
Monsanto							Expert Witness
Genentech							Expert Witness
Verastem	X						
Daiichi	X						
DxTerity						X	

Translational Discovery in Peripheral T-Cell Lymphomas

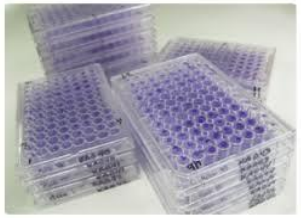
Targeted agents



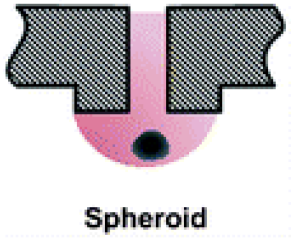
PDX clinical trials

In vitro drug response

2D

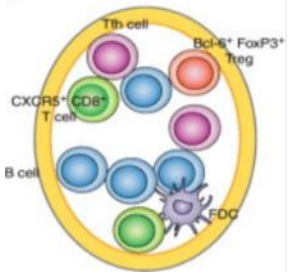


3D



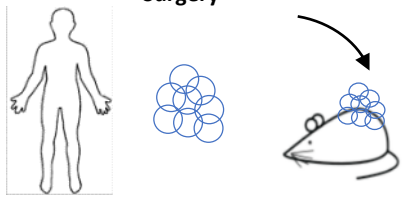
Lymphomagenesis

T-cell differentiation



Patient-Derived Xenografts (PDX) ⟷ Primary lymphomas & PDX cell lines ⟷ Transgenic models

Surgery



Model Generation Core
PDX development
Cell line generation

MSKCC

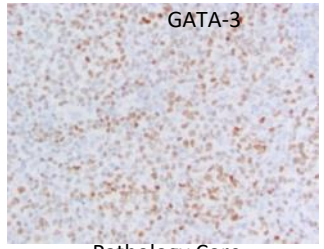
Stanford

Weill-Cornell

Nebraska

Clinical Core
Phase I and II

Dana-Farber/BWH



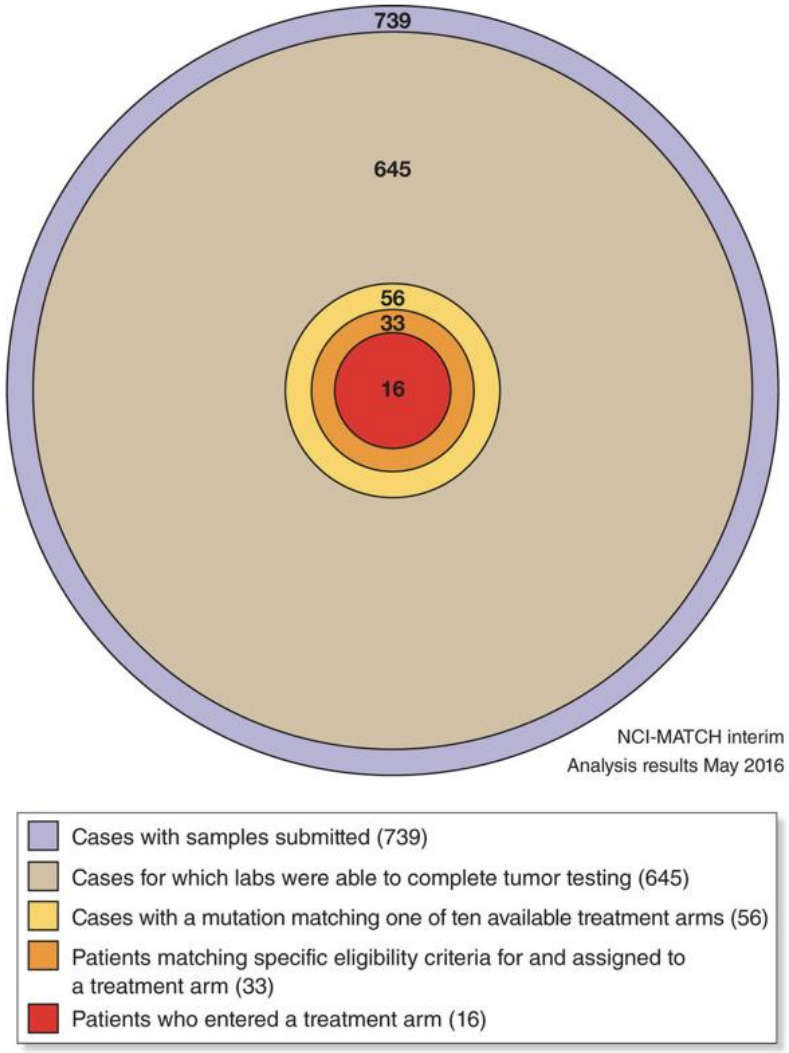
Pathology Core
Characterization, Banking,
NGS, Spectral Imaging

Industrial and Academic Partners

3 years of progress

Wu et al. Cancer Cell 2015
Crescenzo et al. Cancer Cell 2015
Townsend et al. Cancer Cell 2016
Yoda et al. Nature Medicine 2016
Dunford et al. Nature Genetics 2017
Horwitz et al. Blood 2018
Murakami and Weinstock. Nature 2018
Buchner et al. Cell 2018
Ng et al. Nature Communications 2018 (in press)
Ng et al. Blood 2018 (in press)
Intlekofer et al. Nature 2018 (in press)

Cutting edge in genomics-based drug selection



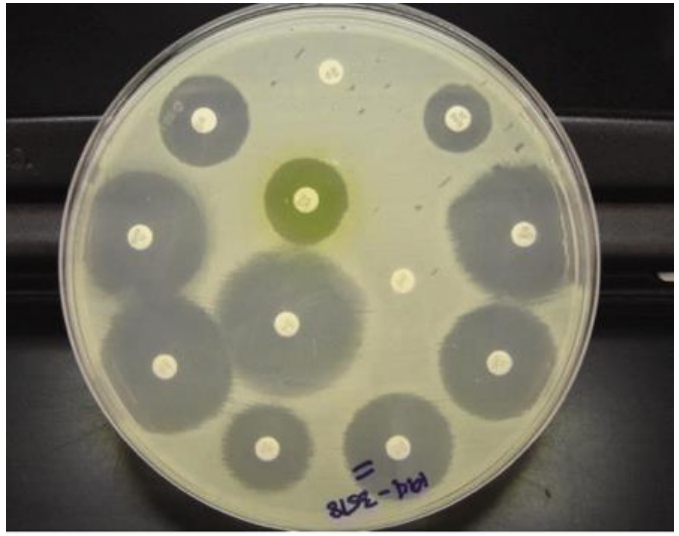
Letai. *Nature Med 2017*

Personalized Medicine for Cancer: ***Genetic Testing***

Highly successful for some cancers but unavailable for most

Letai et al. Nat. Med. (2017);
Vivek Prasad, Nature. (2016);
Friedman et al. Nat. Rev. Cancer (2015)

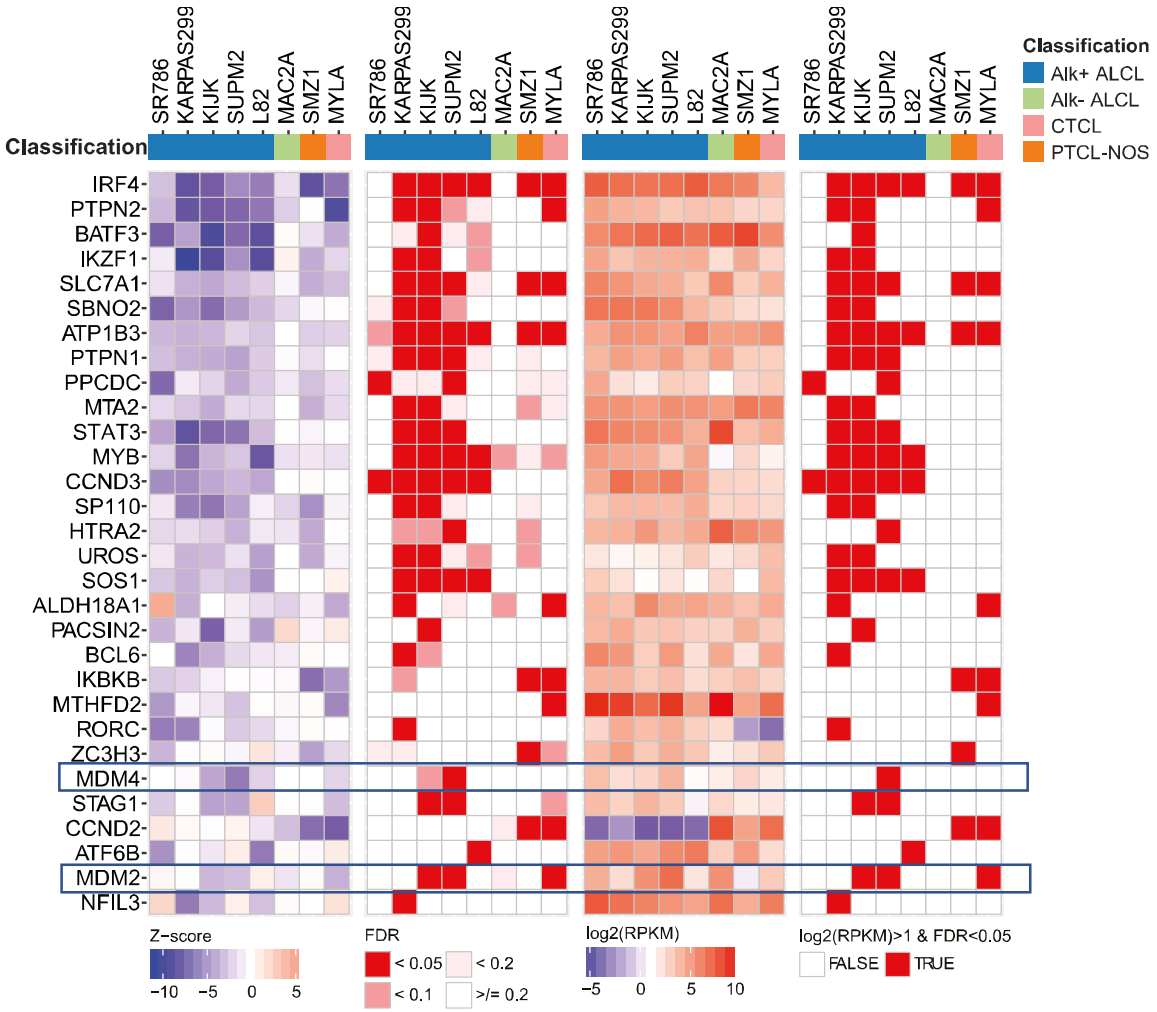
Personalized Medicine for Infectious Disease: ***Antibiotic Susceptibility Testing***

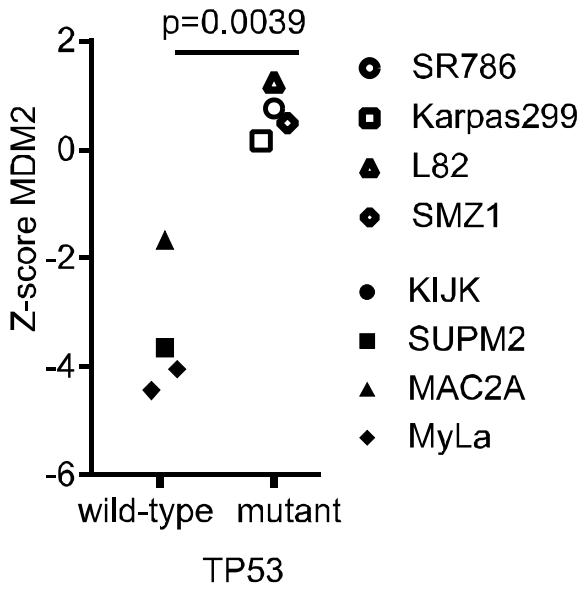


Highly successful across a wide range of organisms and drugs

Proliferation is a functional biomarker

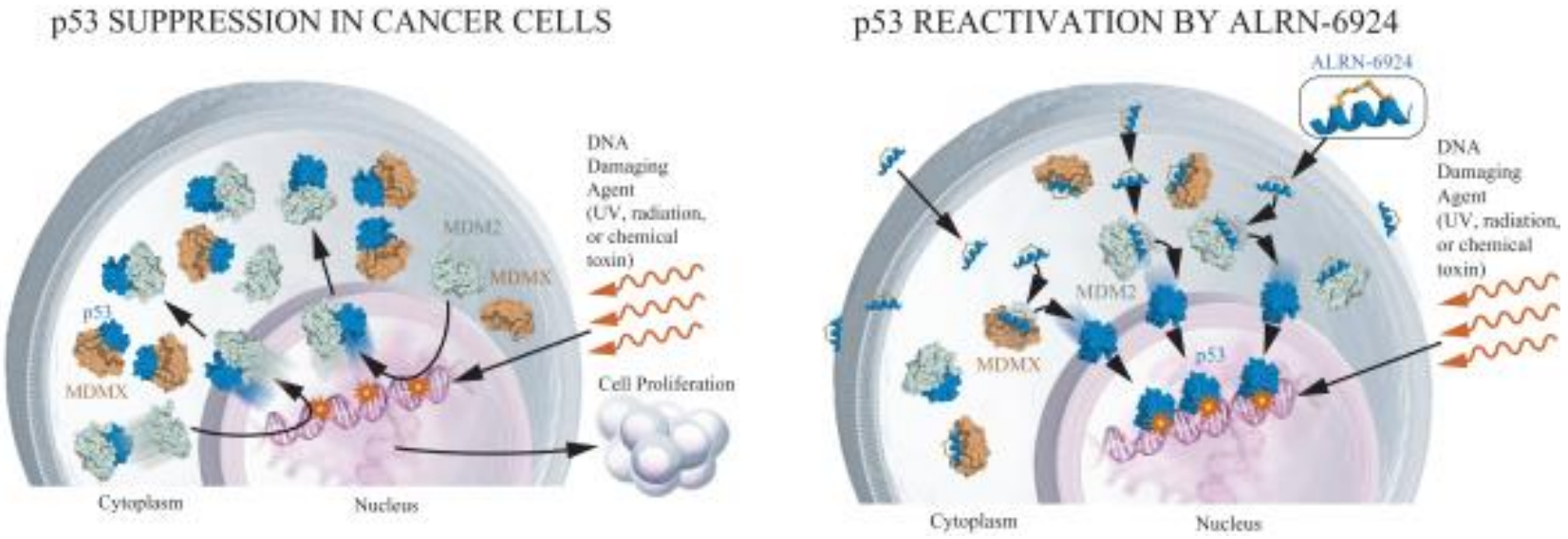
Vulnerability screening to define targets



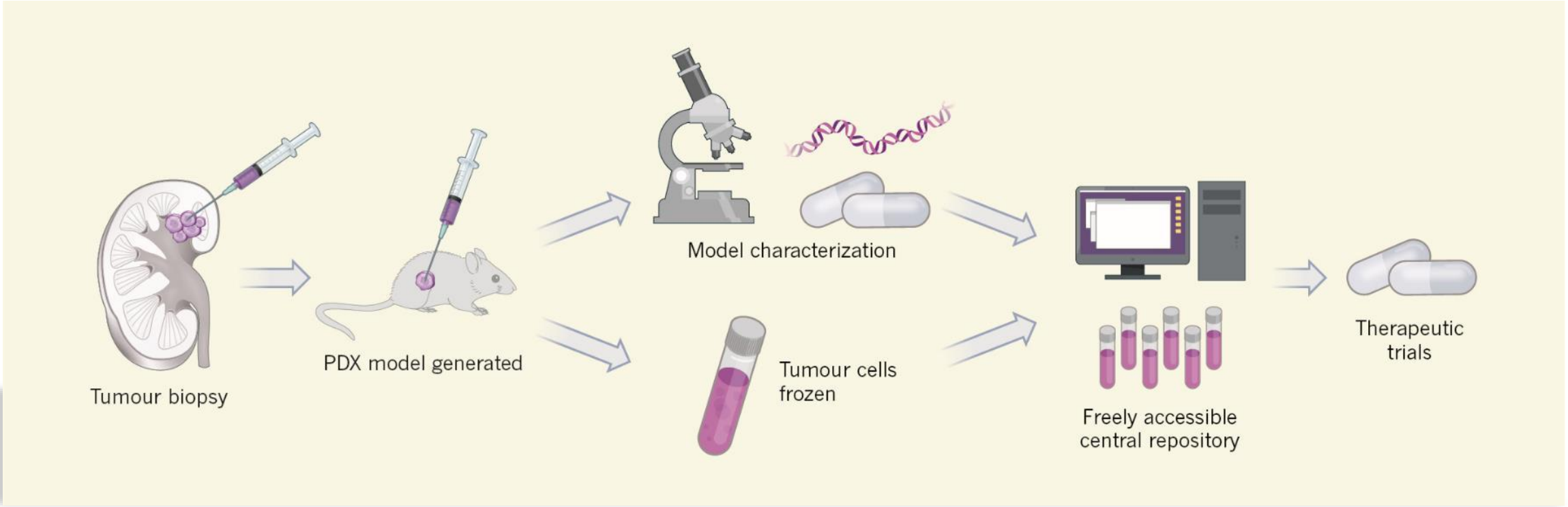


Ng et al. Nat Comm 2018 (in press)

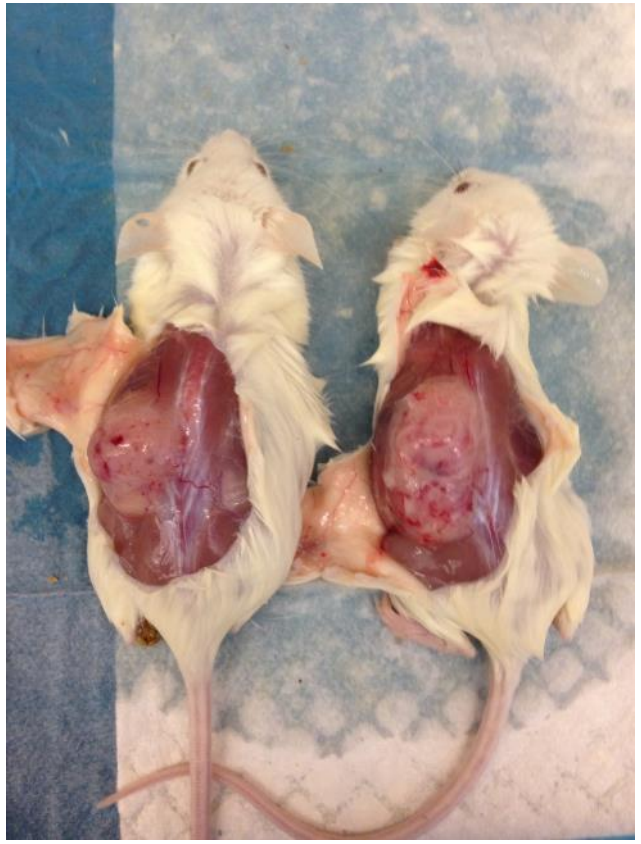
Targeting both MDM2 and MDMX



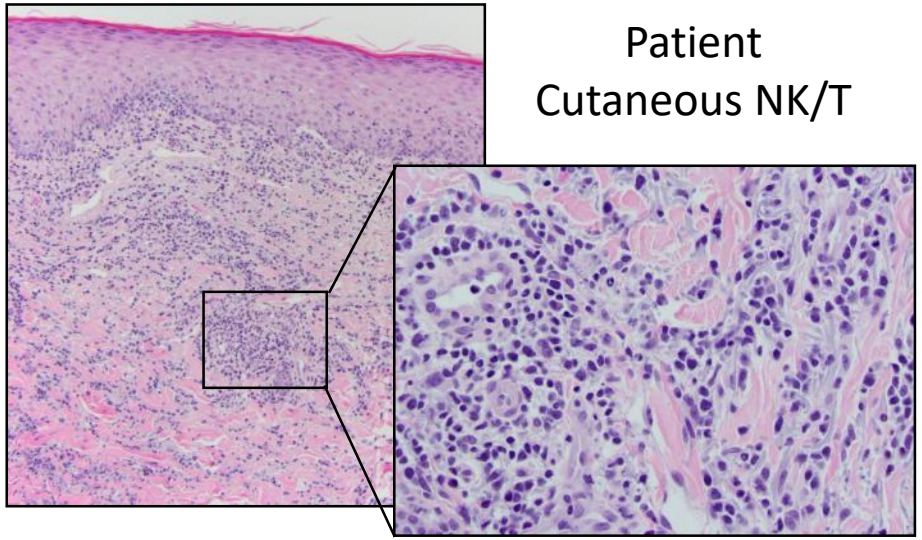
Patient-derived xenografts to model human cancer

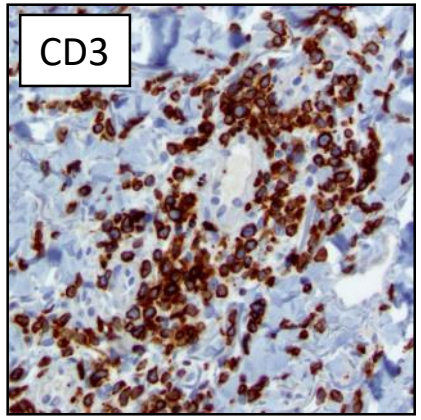


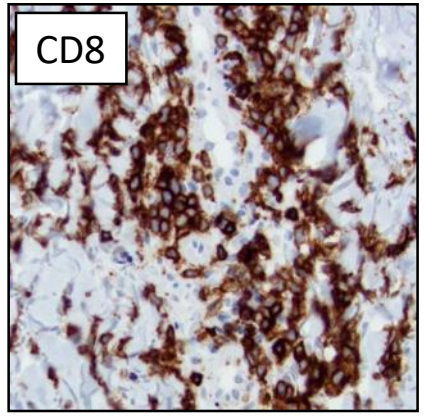
Murakami and Weinstock, *Nature* 2017

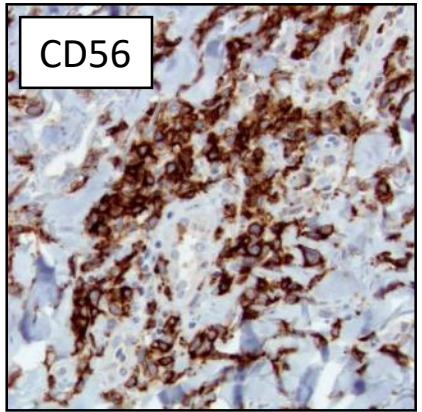


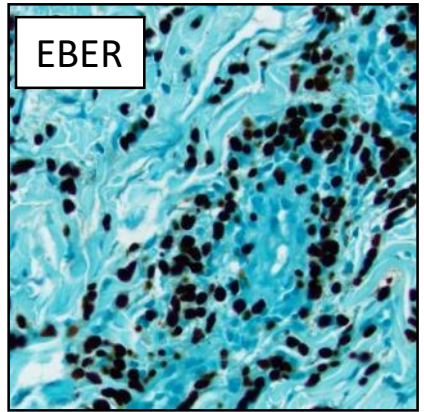
Patient
Cutaneous NK/T



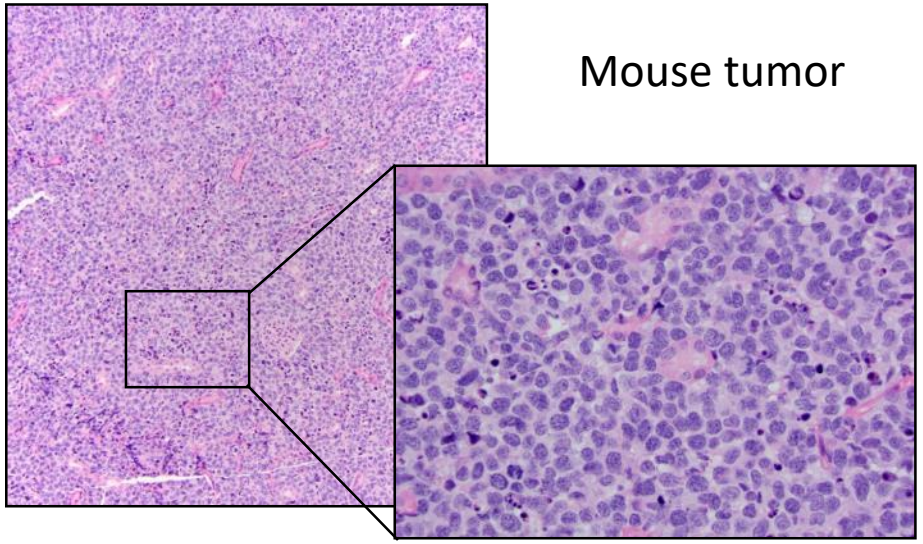


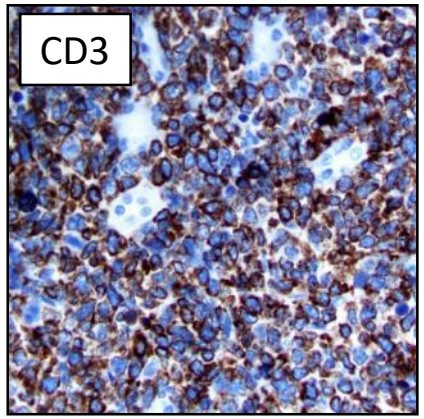


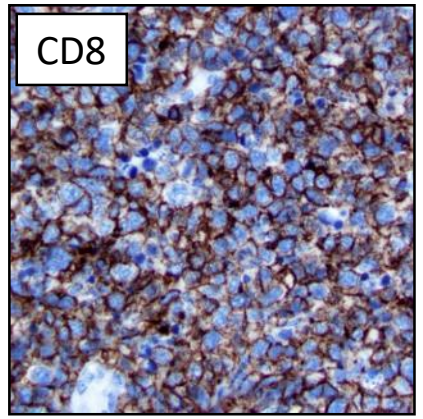


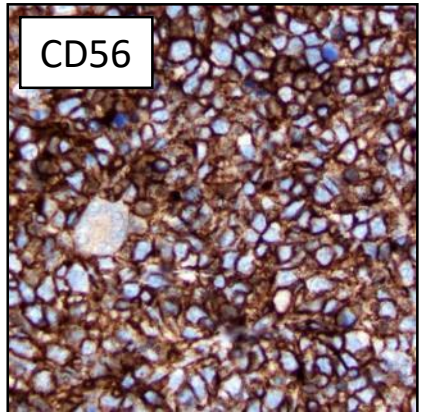


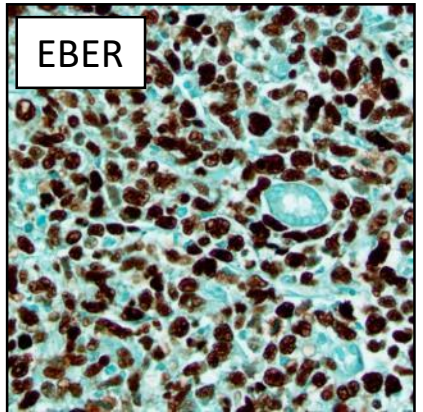
Mouse tumor



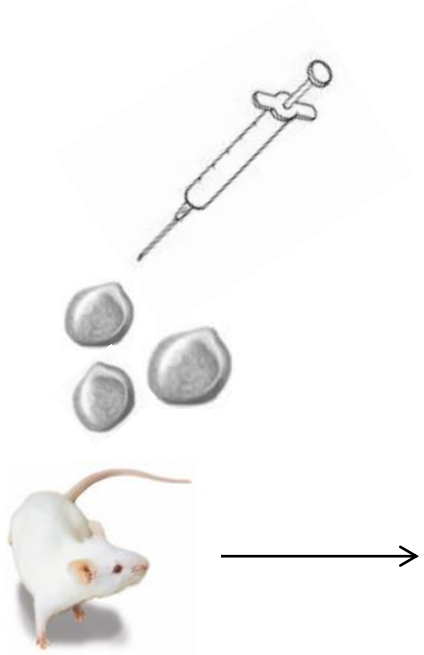






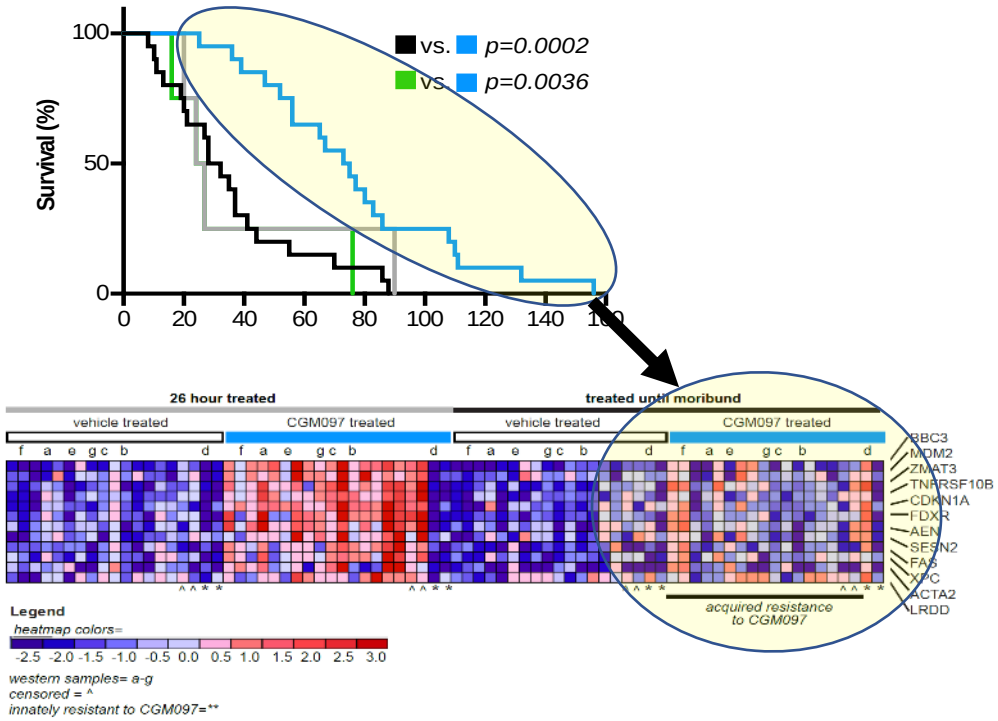


Defining biomarkers, toxicity and resistance



Randomization upon engraftment

Pharmacodynamics Biomarkers



Townsend et al. *Cancer Cell* 2016

Enabling Research on Human Cancer

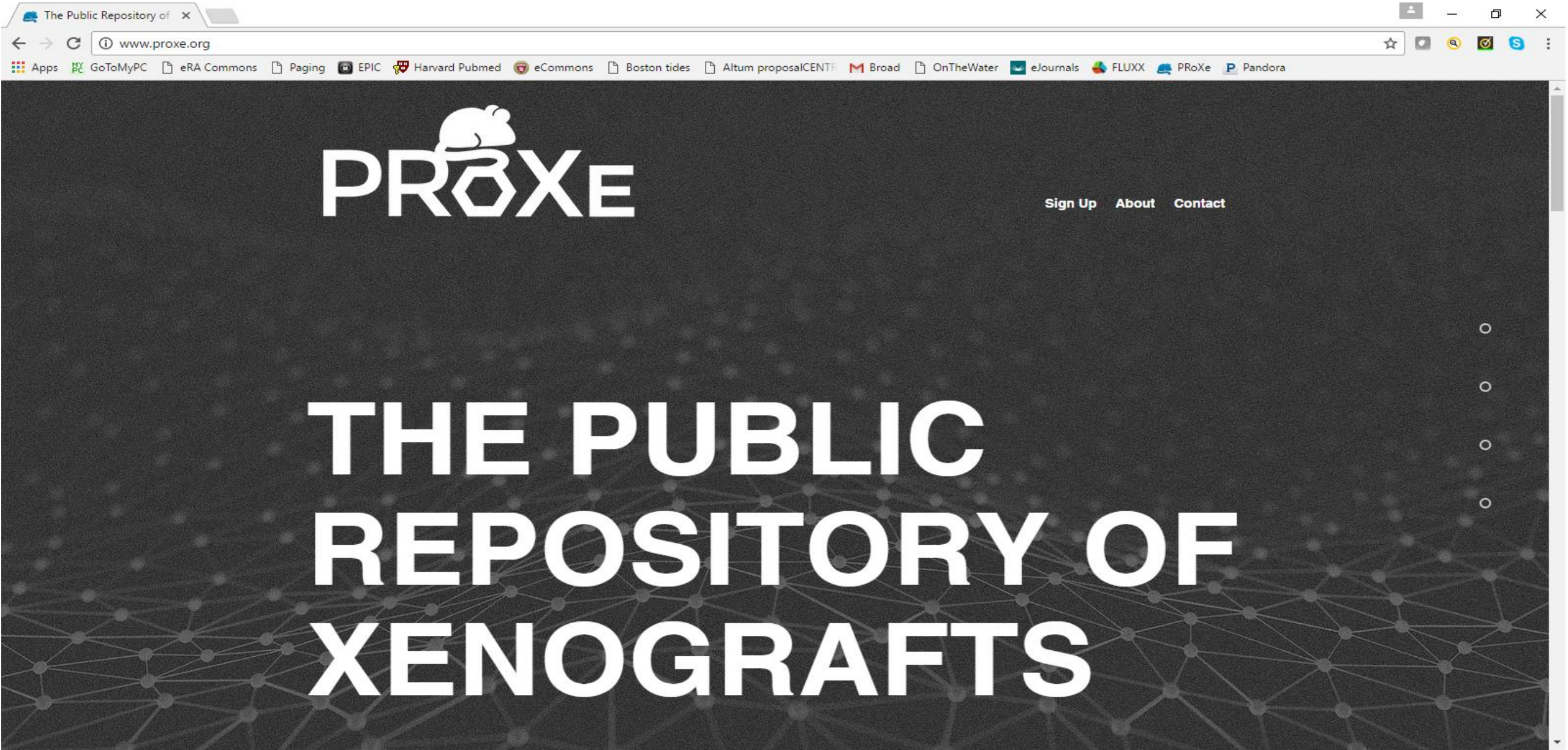
T-ALL
AML
B-ALL
AUL
BPDCN
Mantle cell lymphoma
Double-hit lymphoma
Marginal zone lymphoma
Follicular lymphoma
Transformed follicular lymphoma
Diffuse large B-cell lymphoma
High-grade with *MYC* rearr

HSTL
Primary cutaneous CD30+ TCL
T-PLL
AITL
ALK+ ALCL
ALK- ALCL
Mycosis Fungoides
Sezary Syndrome
Cutaneous NK/TCL
Extranodal NK/TCL
PTCL, NOS
ATLL

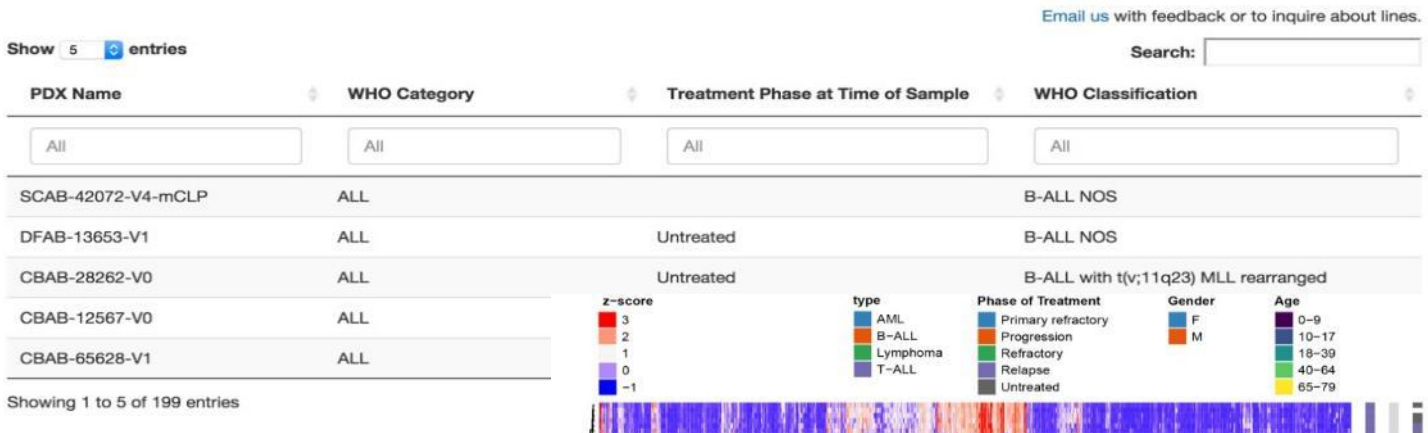
Alveolar Soft Part Sarcoma
Inflammatory myofibroblastic tumor
Neurofibroma
Osteosarcoma
Rhabdoid tumor
Solid pseudopapillary tumor
Wilms Tumor
Merkel cell carcinoma
400 Solid Tumors from Novartis

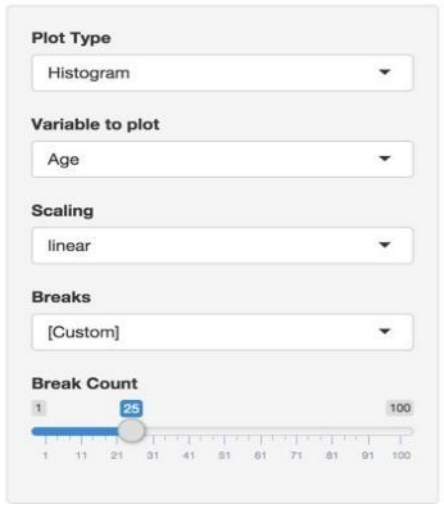
Many, many people and especially Giorgio Inghirami

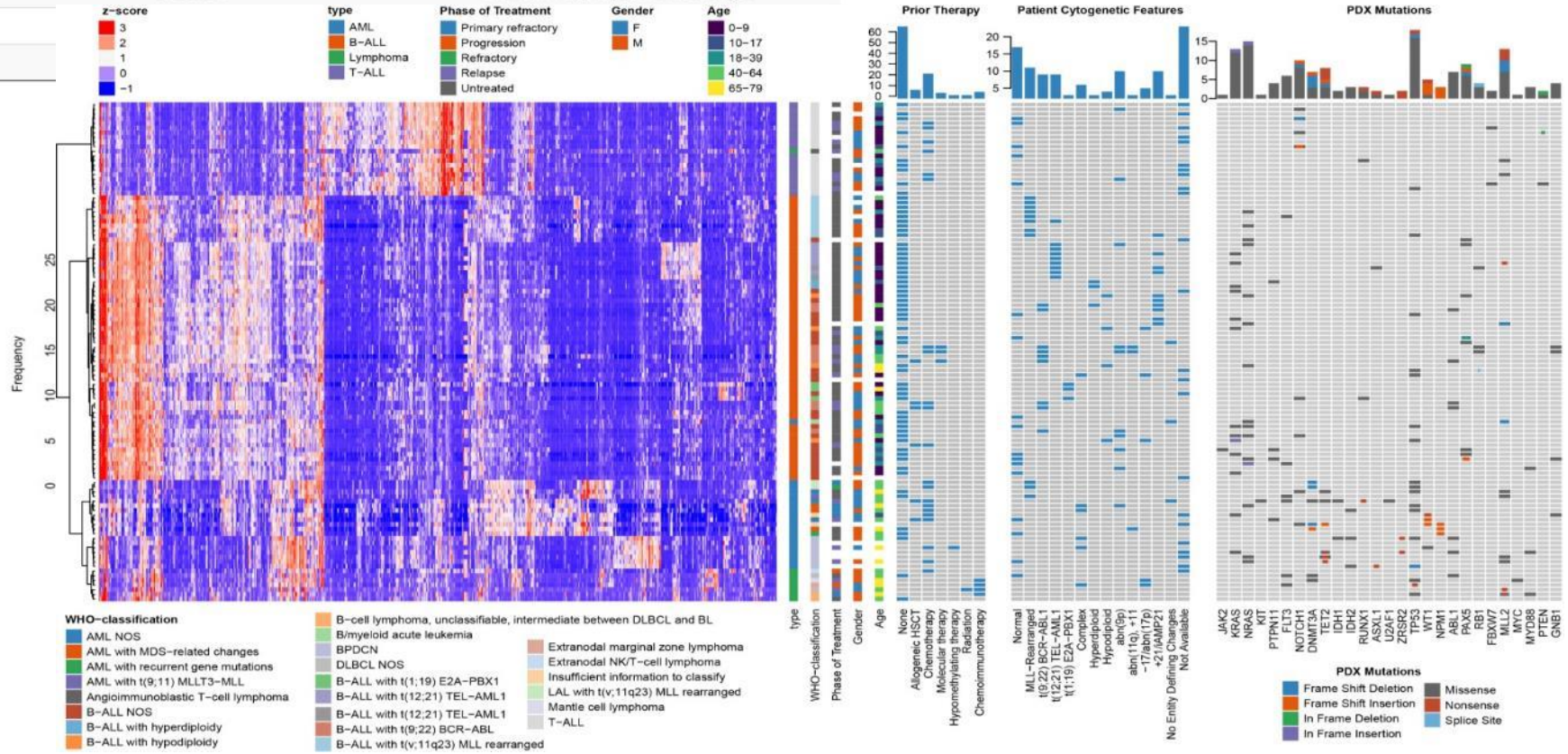
Public Repository of Xenografts (www.PRoXe.org)



Public Repository of Xenografts (www.PRoXe.org)

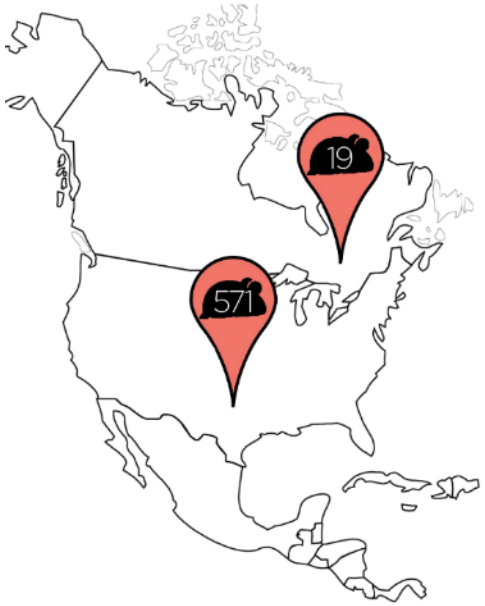






PROXE

Where Are We?



Report Card
Total Users: 824
Institutions: 334
Countries: 32

North America
USA: 571
Canada: 19

South America
Argentina: 1
Brazil: 1
Chile: 1

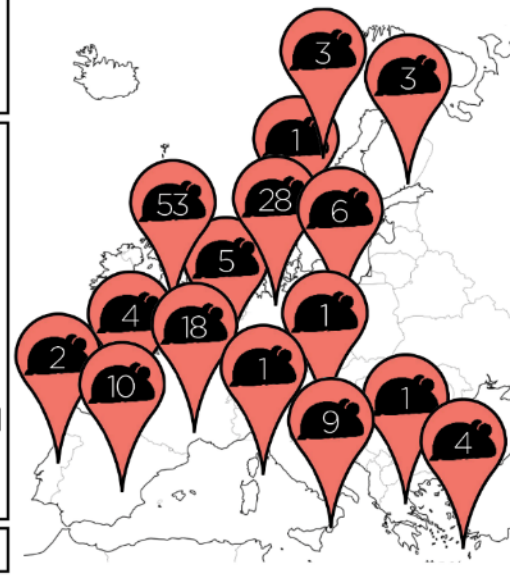
Asia

Japan: 15	India: 9
China: 4	Thailand: 1
S. Korea: 7	Taiwan: 1
Singapore: 12	

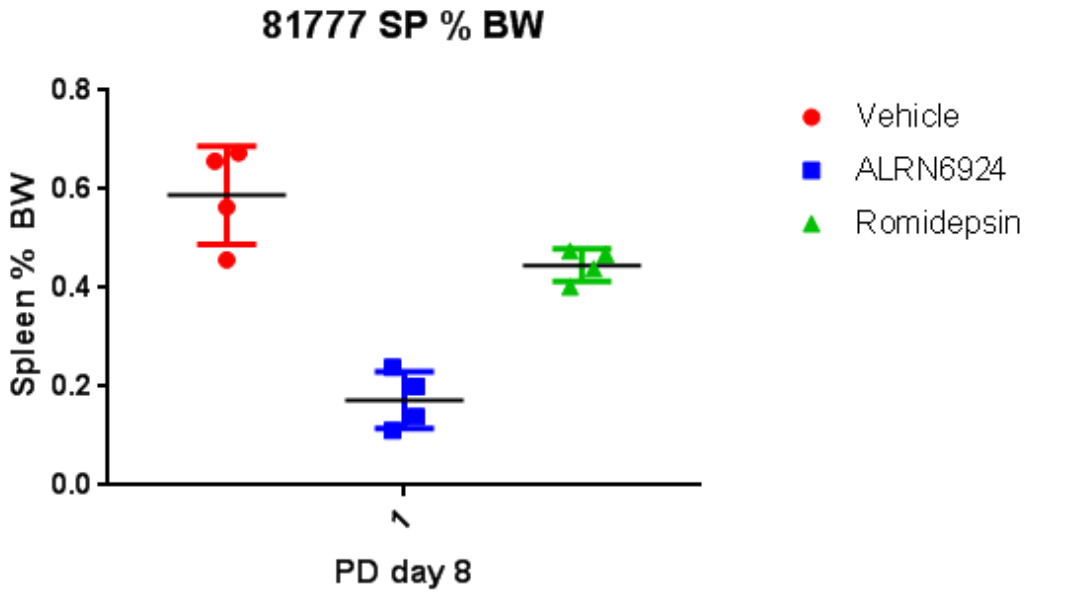
Europe

UK: 53	Israel: 4
Germany: 28	Norway: 3
France: 18	Finland: 3
Switzerland: 16	Portugal: 2
Spain: 10	Greece: 1
Italy: 9	Denmark: 1
Poland: 6	Czech Rep: 1
Netherlands: 5	Austria: 1
Belgium: 4	

Australia: 1

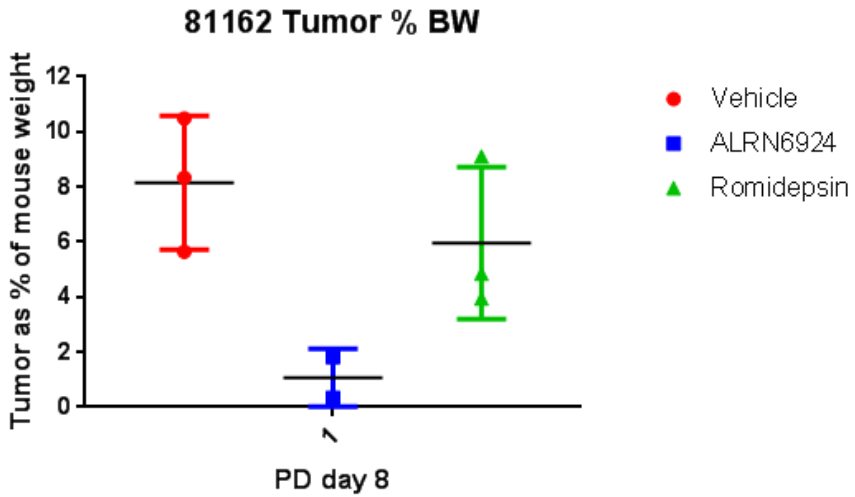


CBTL-81777; Disseminated hepatosplenic T-cell lymphoma

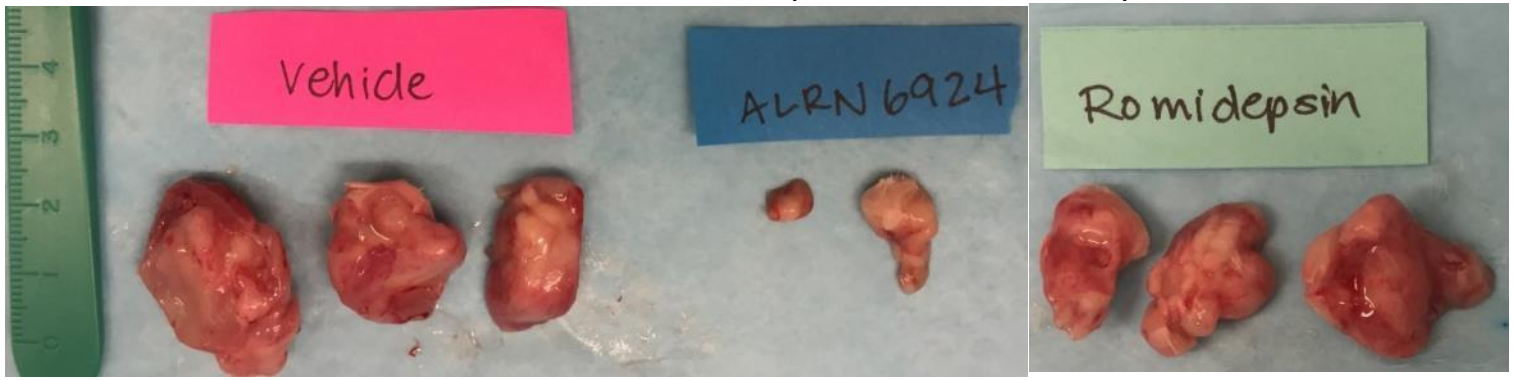


Raphael Koch, Noriaki Yoshida, Amanda Christie, Kay Shigemori

WCTL-81162; Subcutaneous Alk+ anaplastic large cell lymphoma

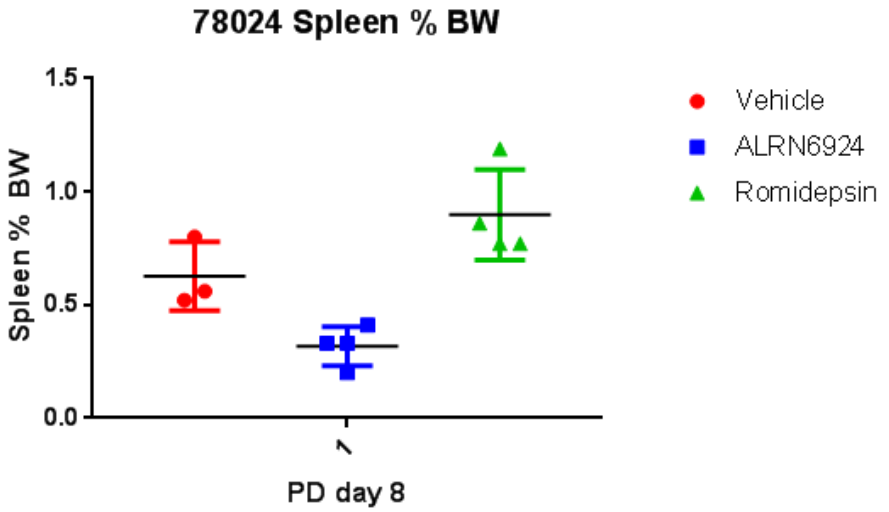


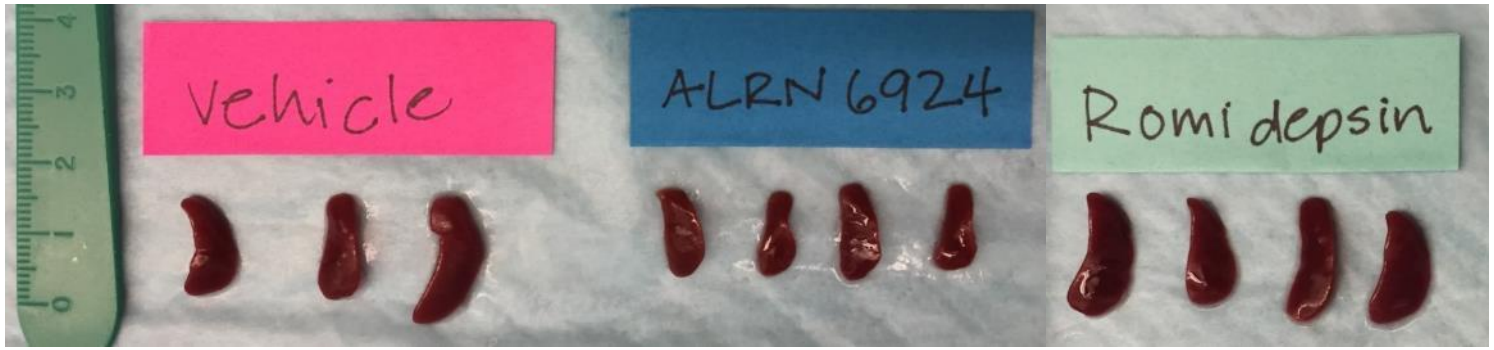
Note: 1 ALRN-treated mouse was found dead on day 3, no obvious toxicity, cause of death unknown



Raphael Koch, Noriaki Yoshida, Amanda Christie, Kay Shigemori

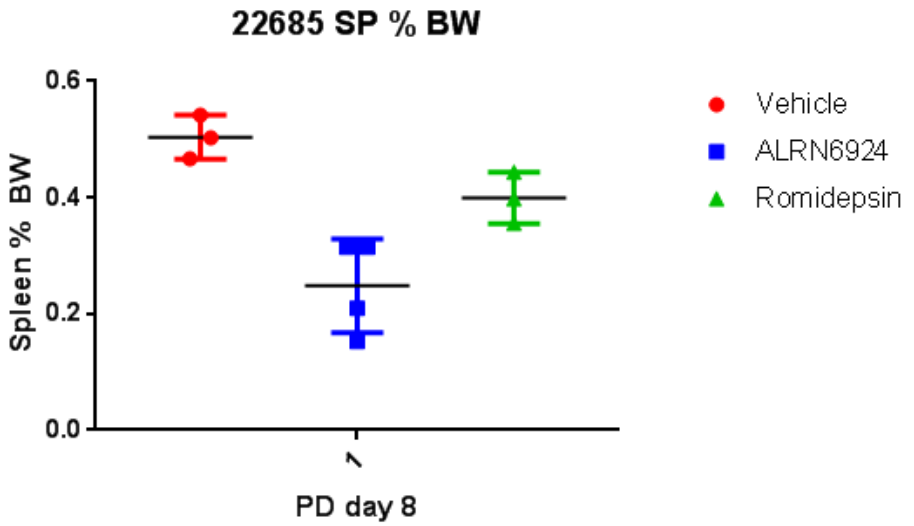
DFTL-78024; Disseminated angioimmunoblastic T-cell lymphoma

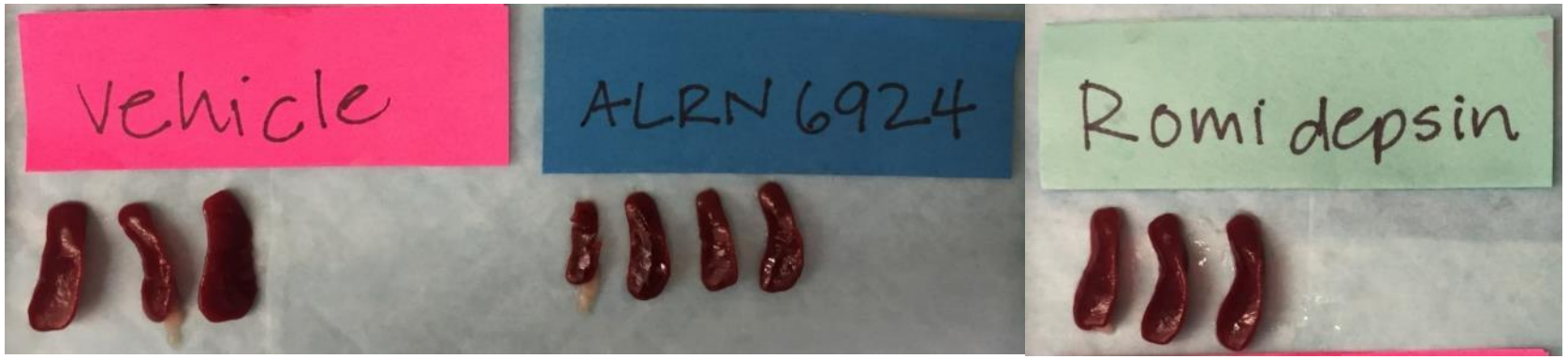




Raphael Koch, Noriaki Yoshida, Amanda Christie, Kay Shigemori

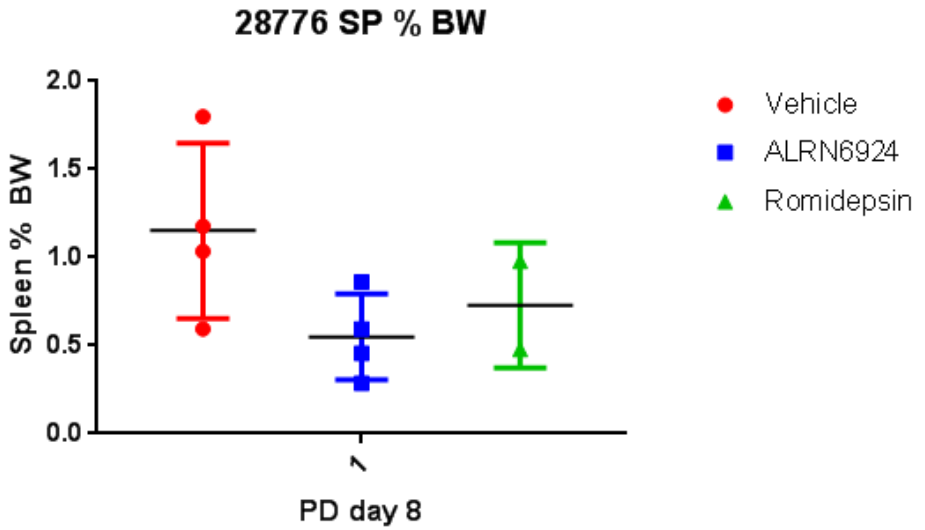
DFTL-22685; Cutaneous T-cell lymphoma/Sezary

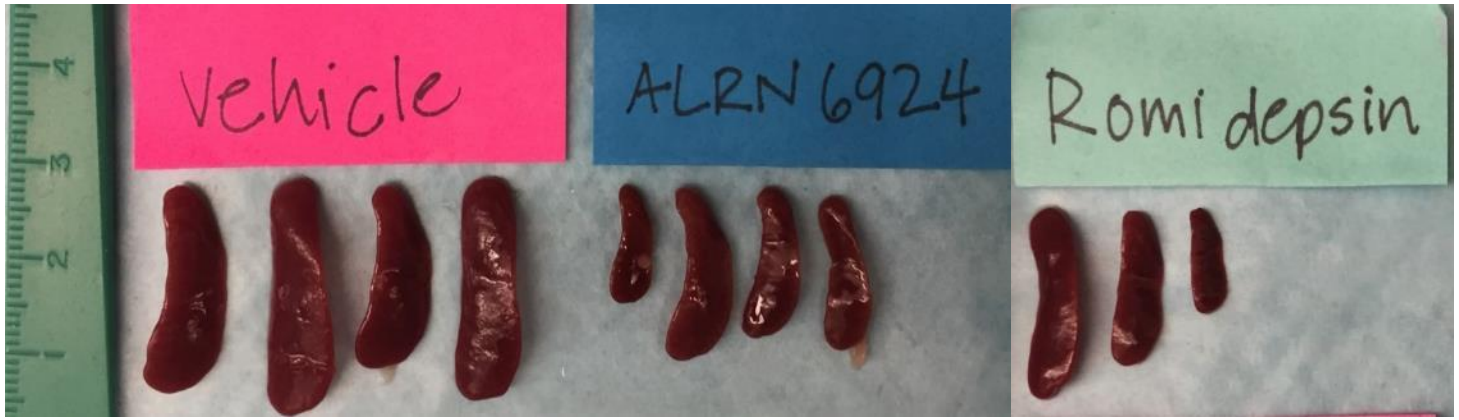




Raphael Koch, Noriaki Yoshida, Amanda Christie, Kay Shigemori

DFTL-28776; Disseminated T-cell prolymphocytic leukemia



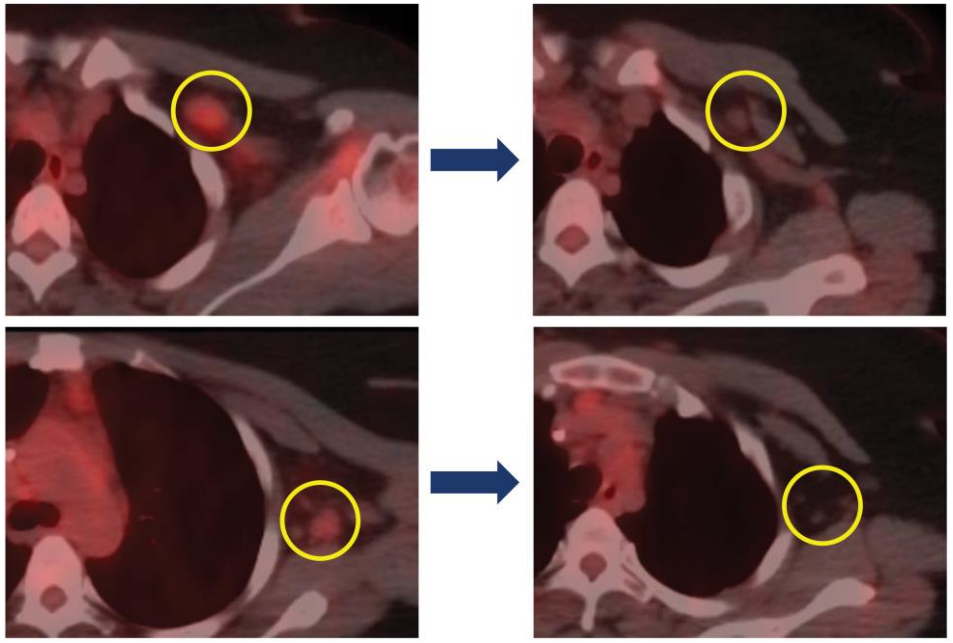


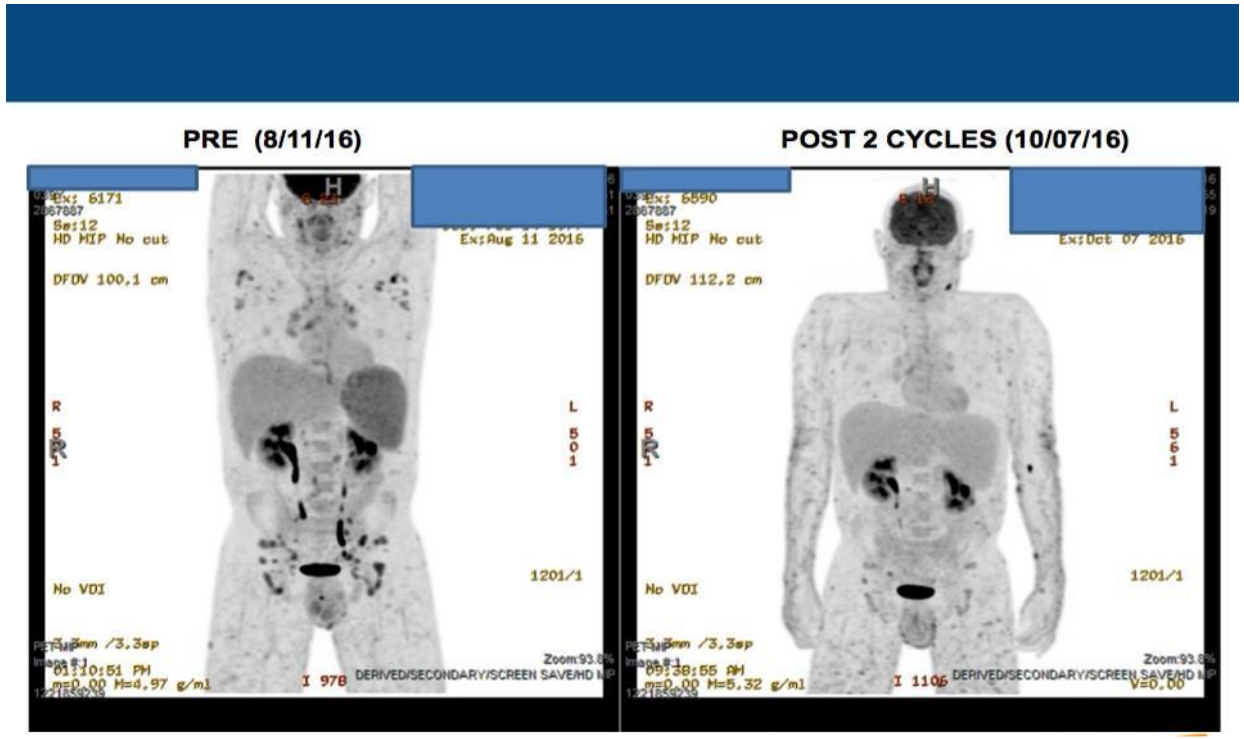
Raphael Koch, Noriaki Yoshida, Amanda Christie, Kay Shigemori

Stapled peptide against MDM2/MDM4 – patients #1 and #2

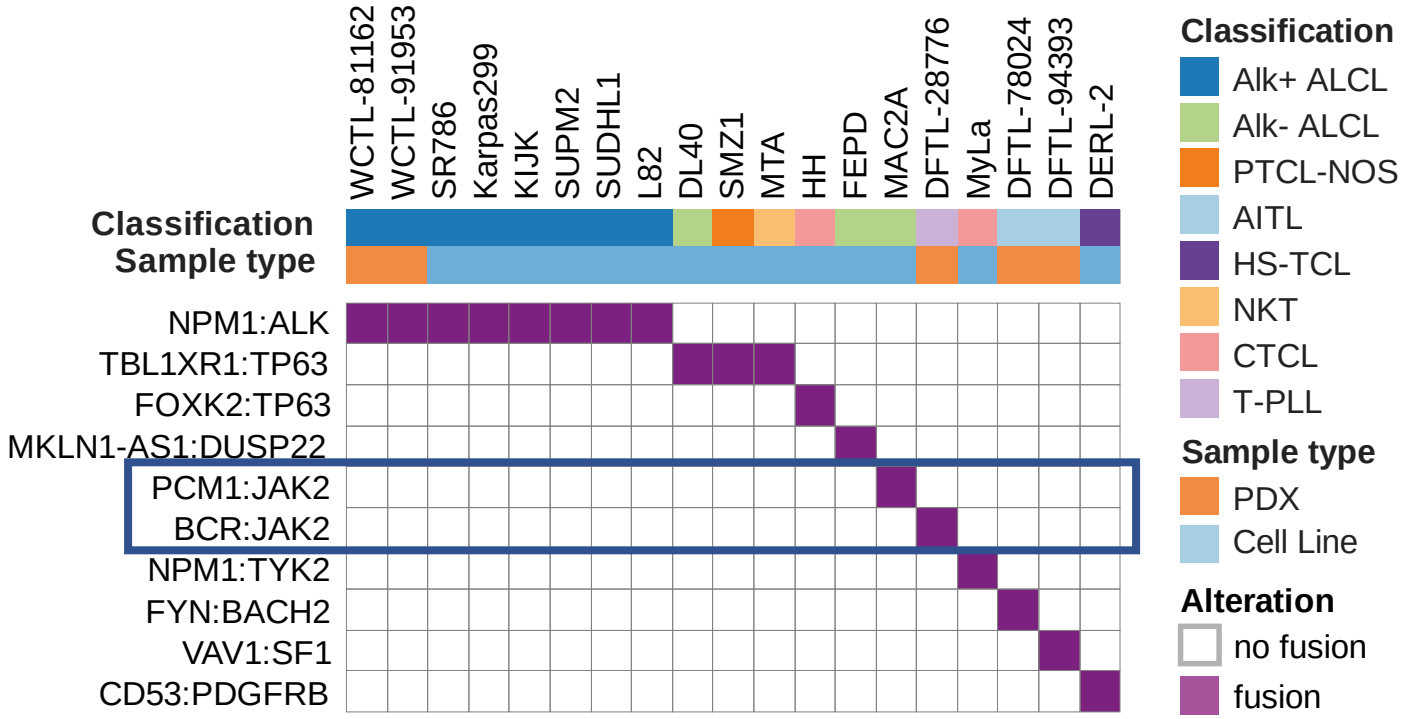
Oct 22, 2015: Pre-Dose, 2.1 mg/kg

May 2, 2016: Cycle 6



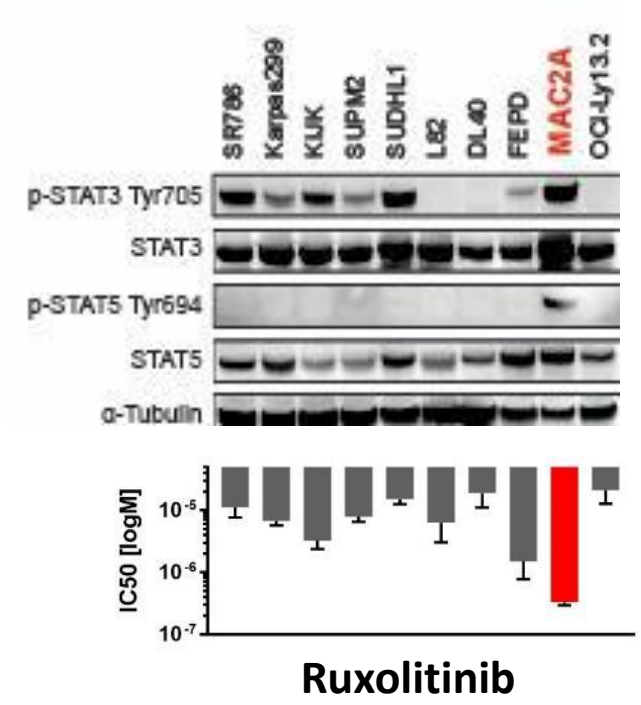


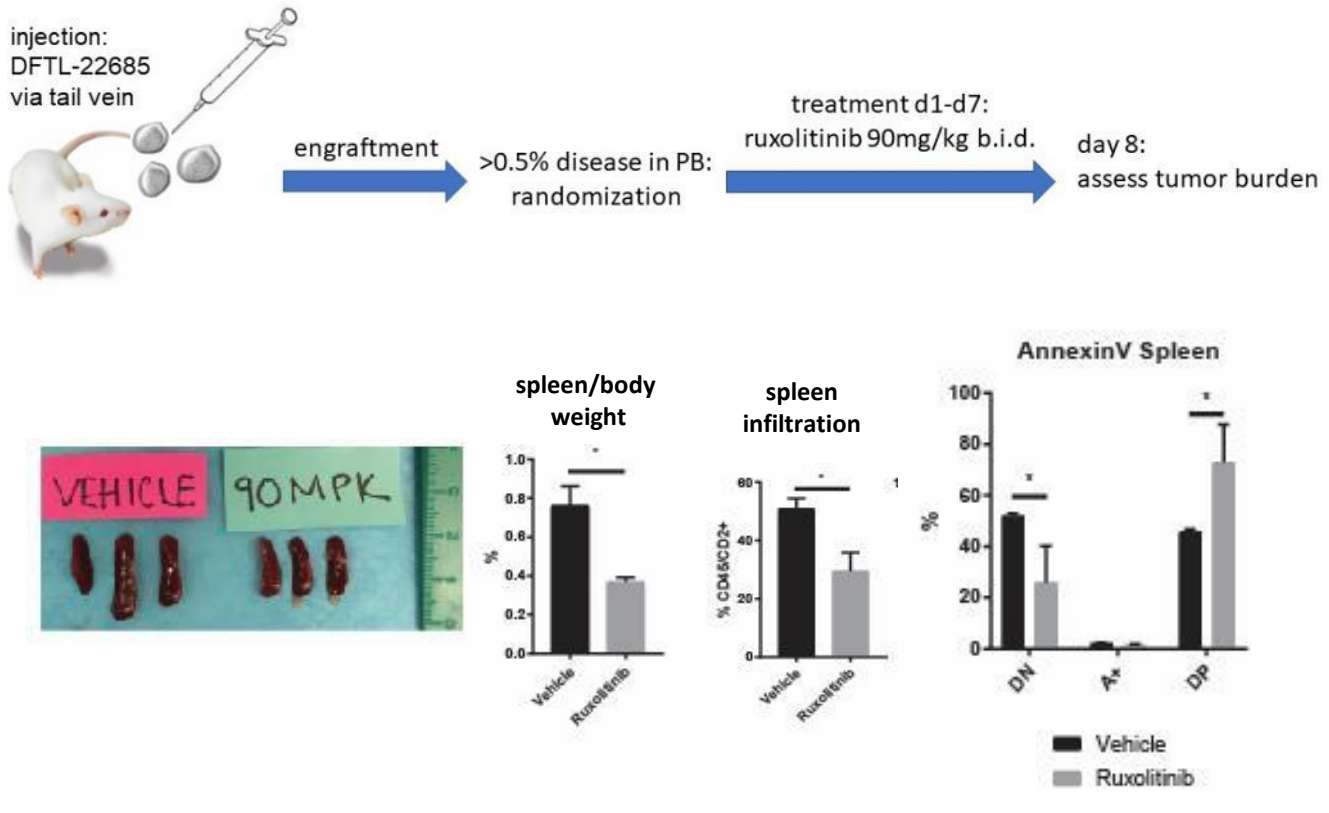
Start with low-hanging fruit: highly targetable



Ng et al. Nature Commun 2018 (in press)

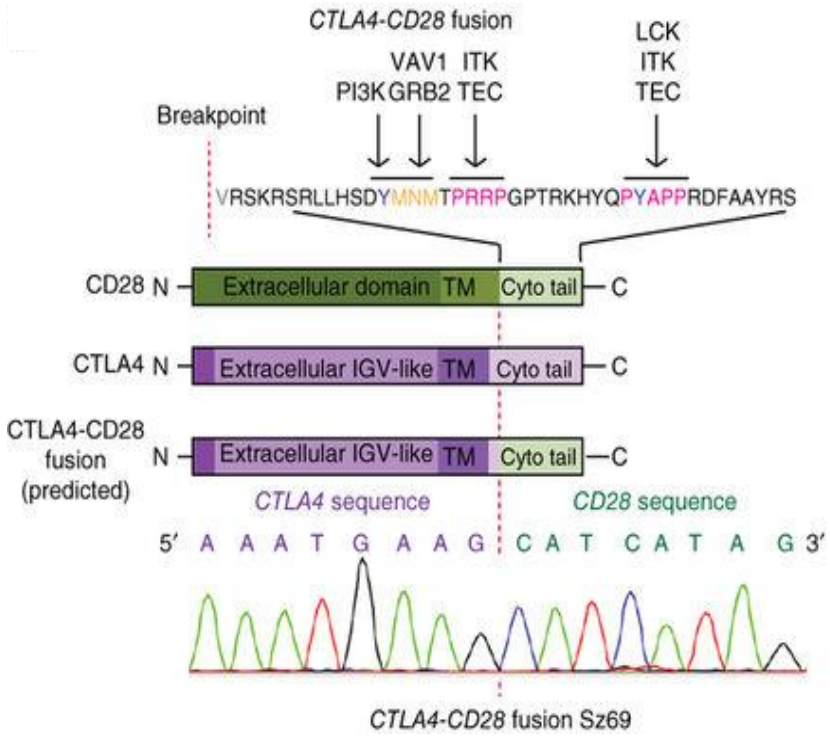
Start with low-hanging fruit: JAK2 fusions

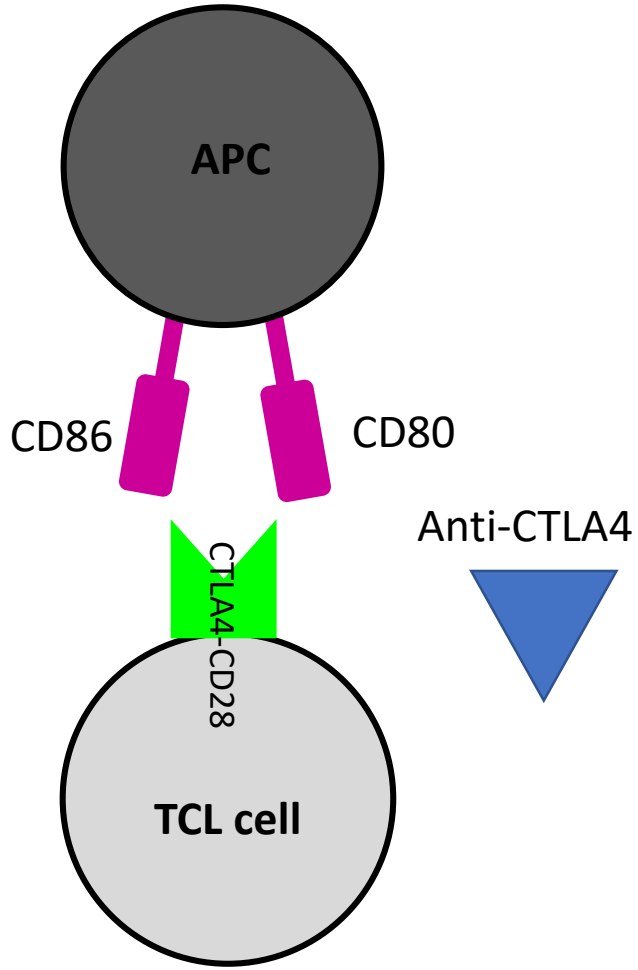




Wu et al. Cancer Cell 2015; Ng et al. Nature Commun 2018 (in press)

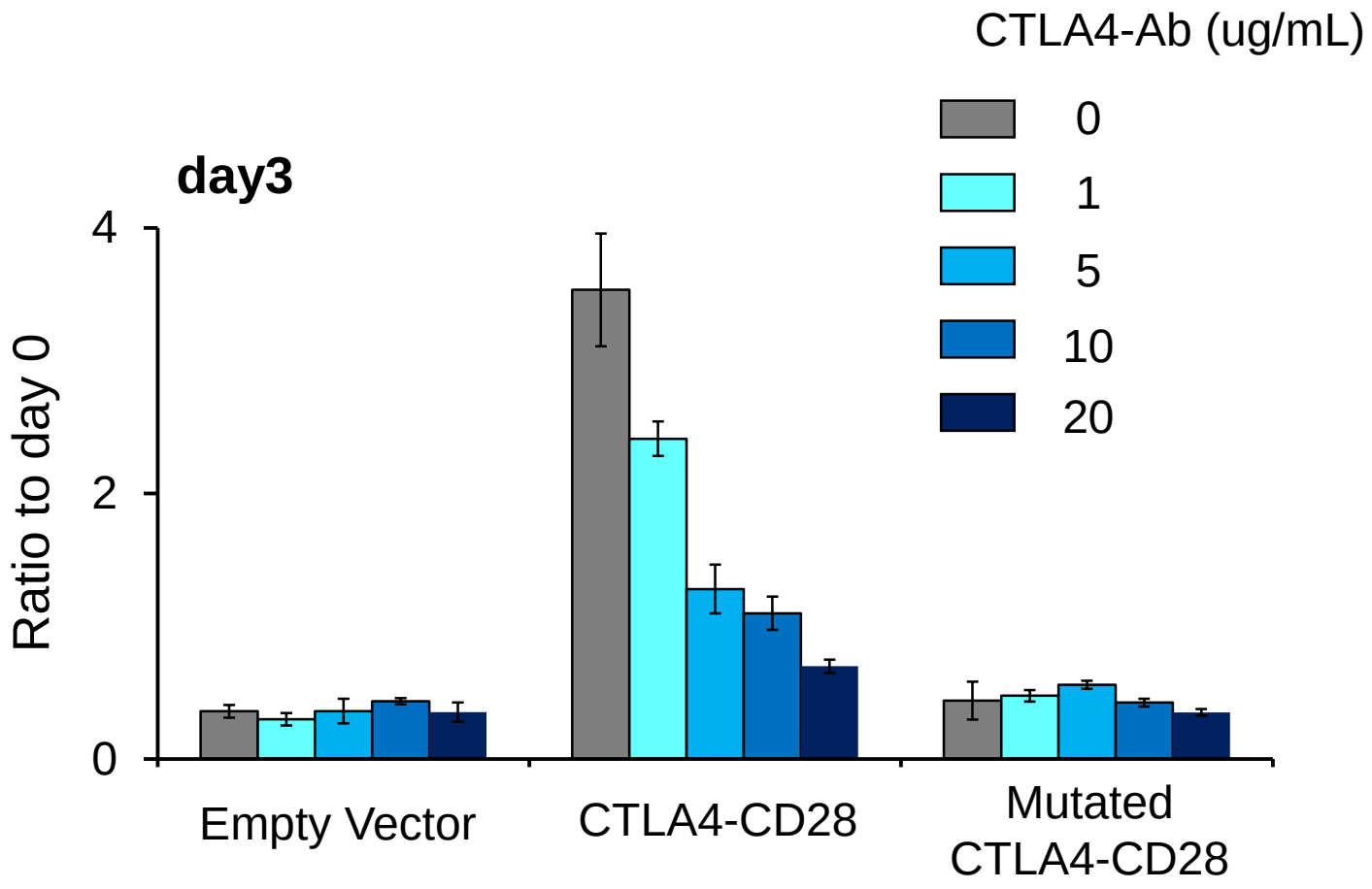
CTLA4-CD28 and ICOS-CD28 fusions co-opt checkpoint signaling





Nat Genet. 2015 47(9):1056-60

Ipilimumab blocks CTLA4-CD28-mediated transformation



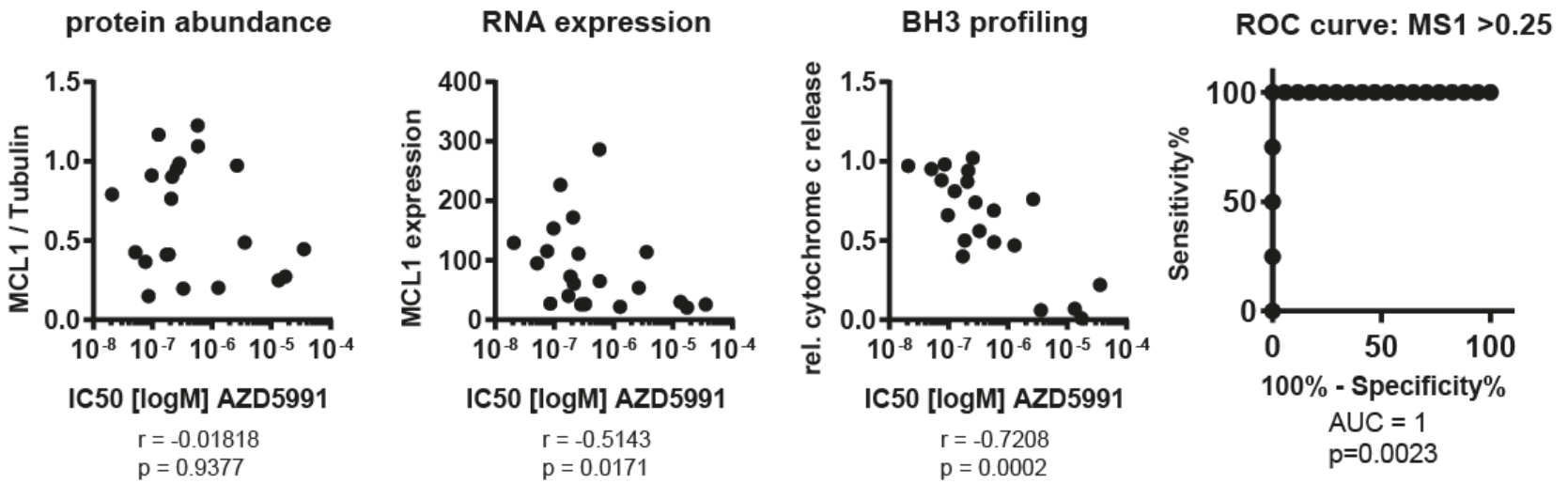
PERSPECTIVE

VOLUME 23 | NUMBER 9 | SEPTEMBER 2017

nature medicine

Functional precision cancer medicine—moving beyond pure genomics

Anthony Letai



Raphael Koch, Liz Brem, Tony Letai

PERSPECTIVE

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nature medicine

Functional precision cancer medicine—moving beyond pure genomics

Anthony Letai

NATURE REVIEWS | CANCER

OPINION

Targeting minimal residual disease: a path to cure?

Marlise R. Luskin, Mark A. Murakami, Scott R. Manalis and David M. Weinstock

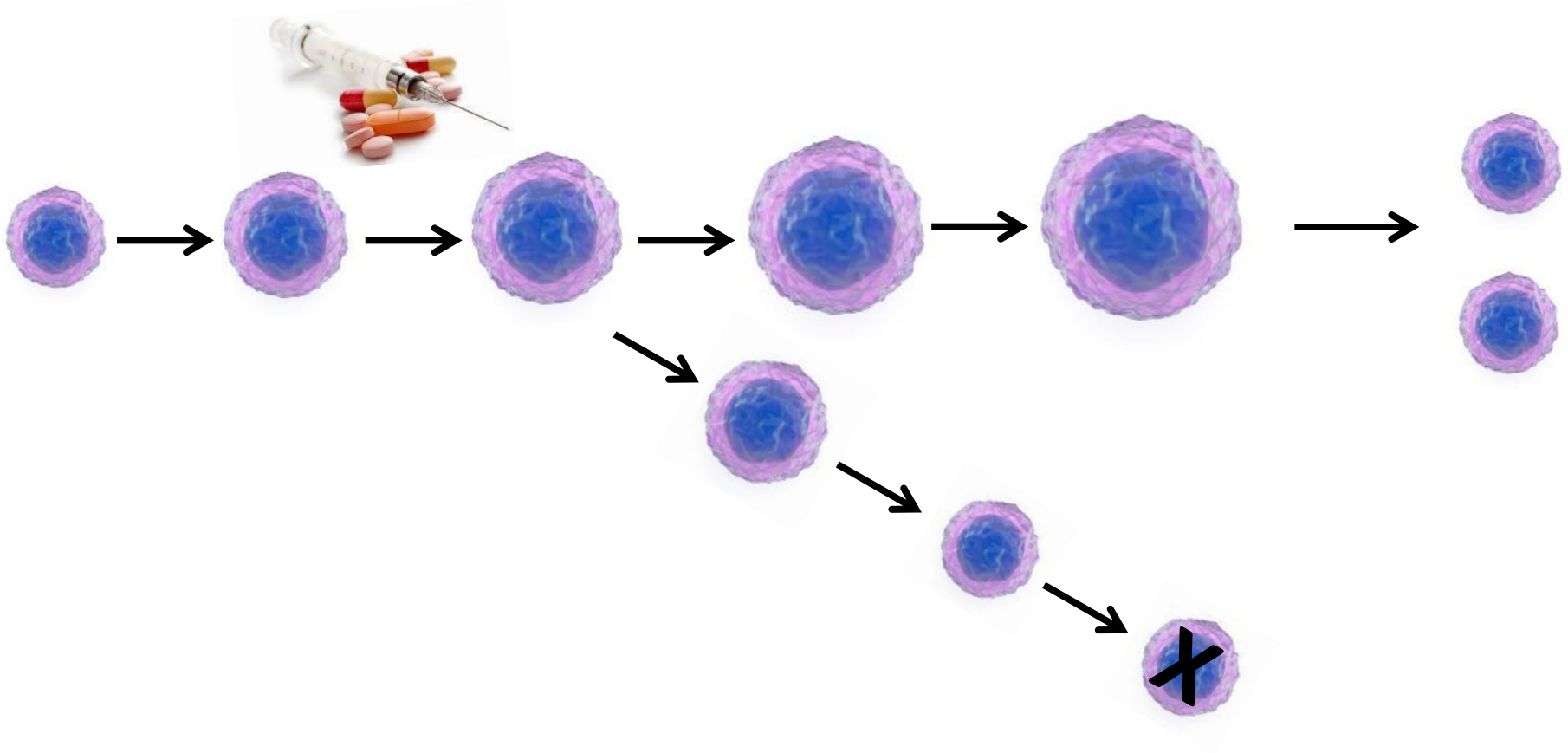
Defining therapeutic vulnerabilities using functional approaches

Requirements

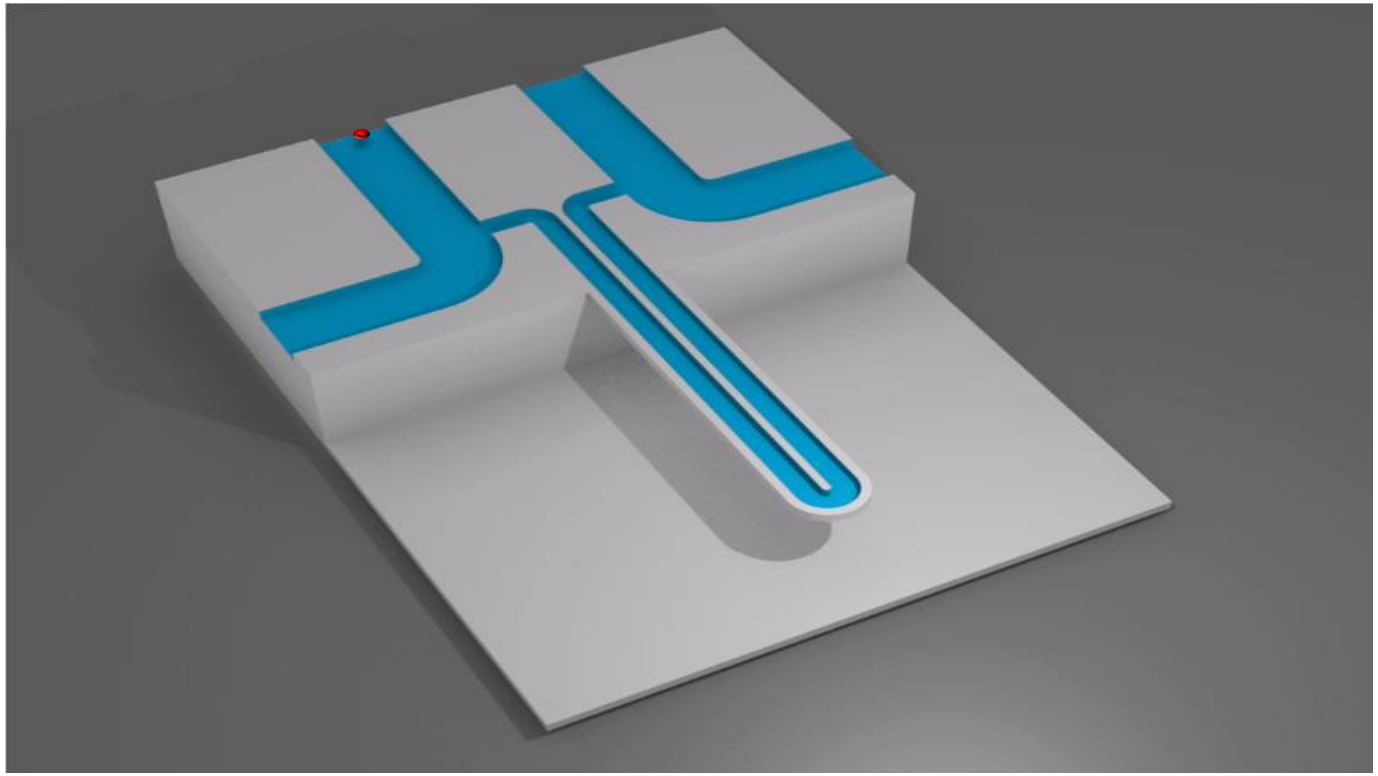
1. Rapid and precise
2. Small sample size from blood or fine needle aspirate
3. Single cell resolution

Scott Manalis, PhD
Koch Institute/MIT

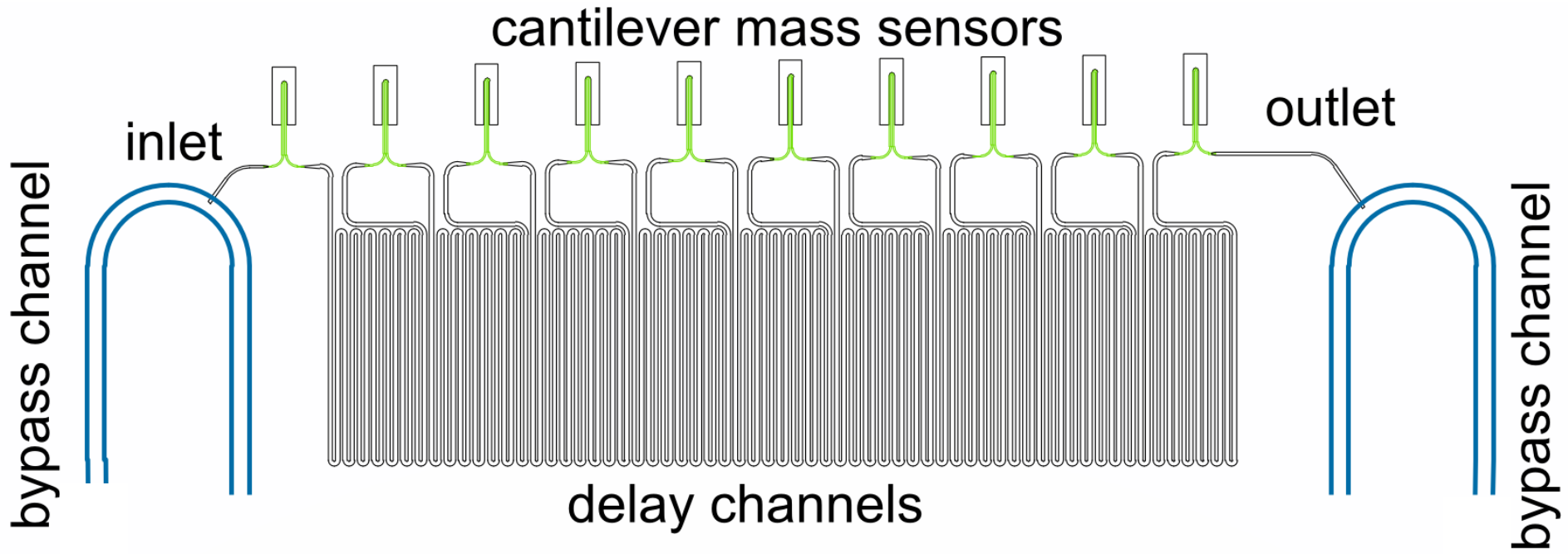
Change in mass indicates drug effect



Suspended microchannel resonator (SMR)

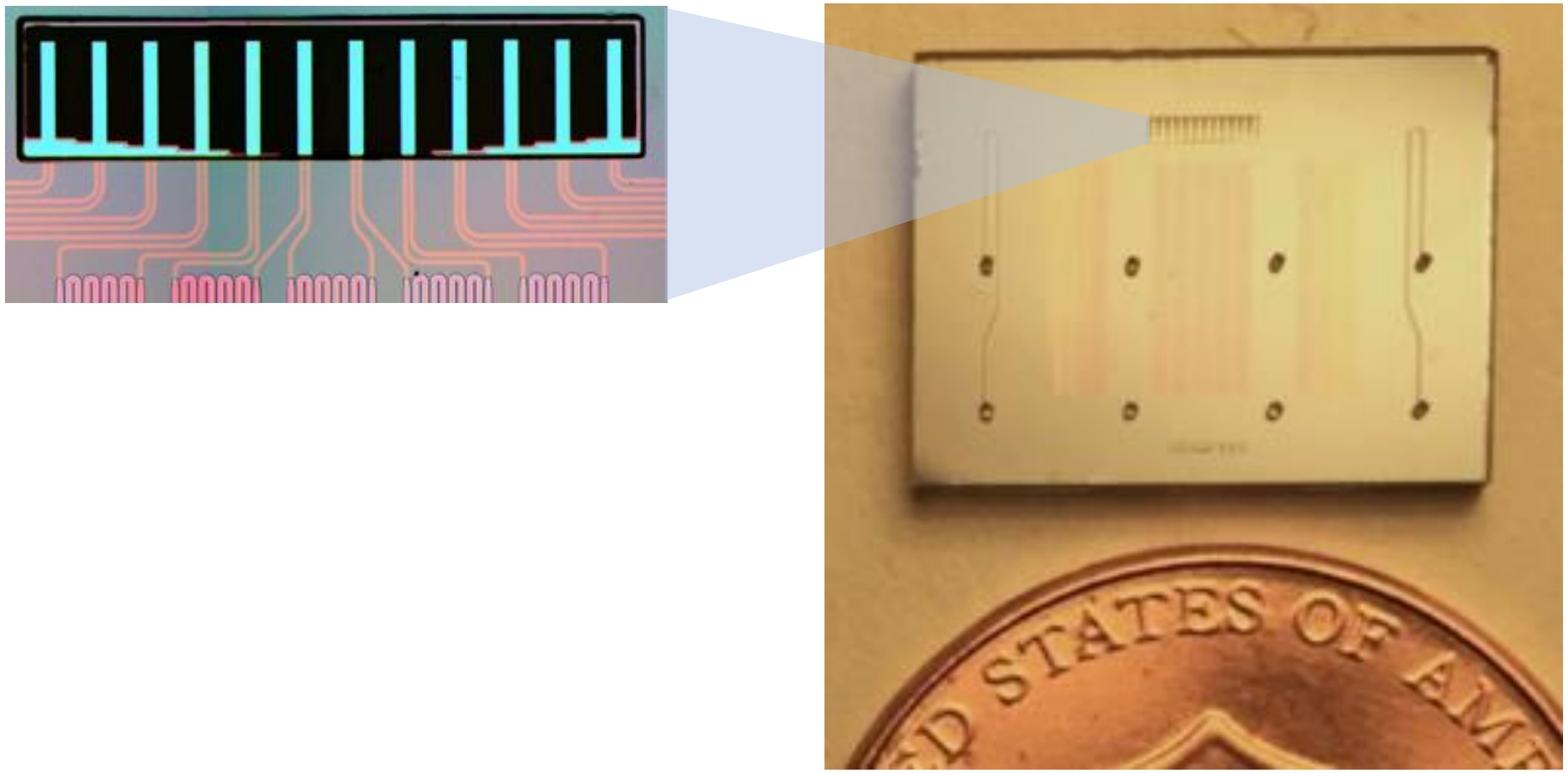


Suspended microchannel resonator (SMR) in array

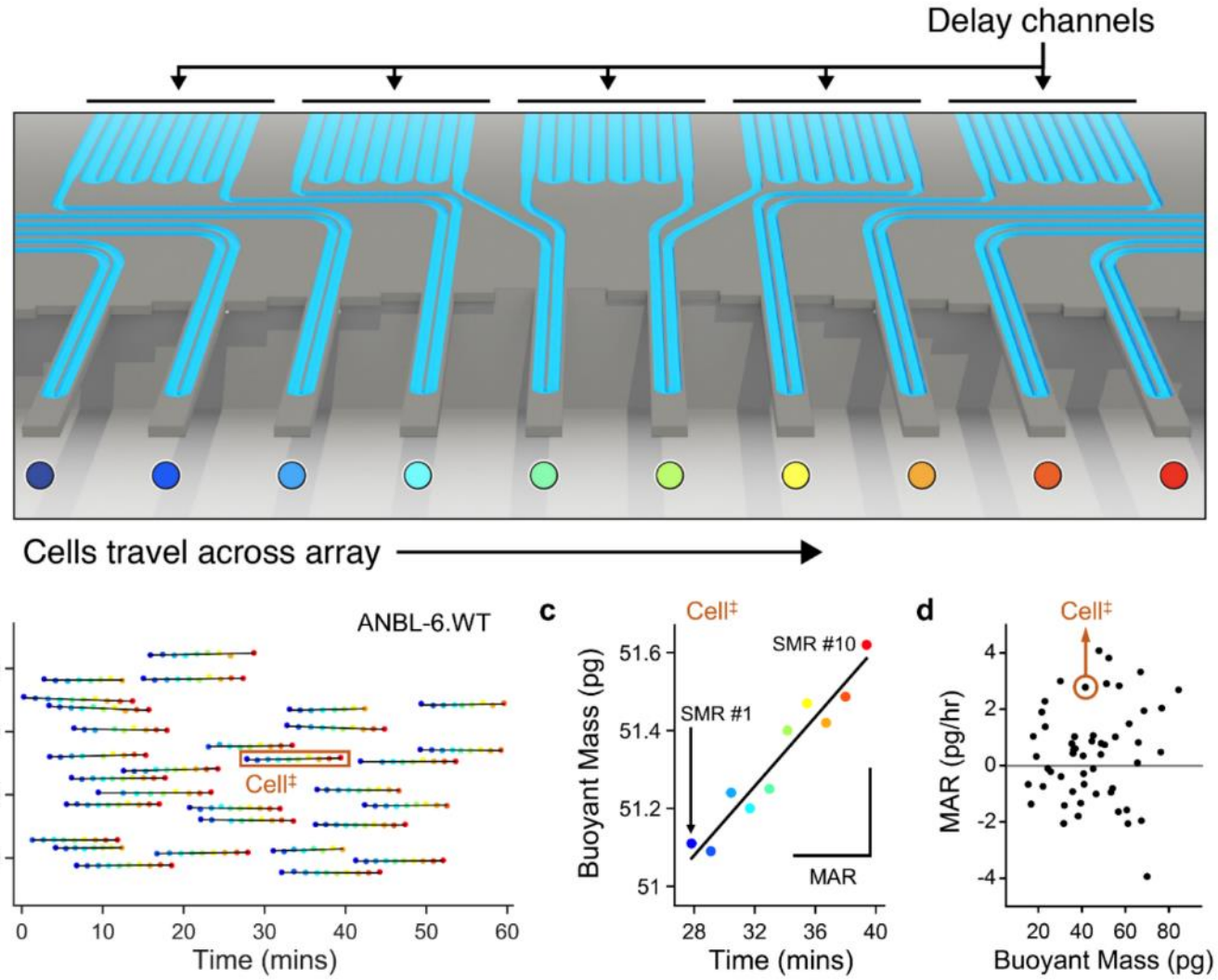


Cermak et al. *Nat Biotech* 2016

Serial SMR



Testing multiple drugs in leukemia samples

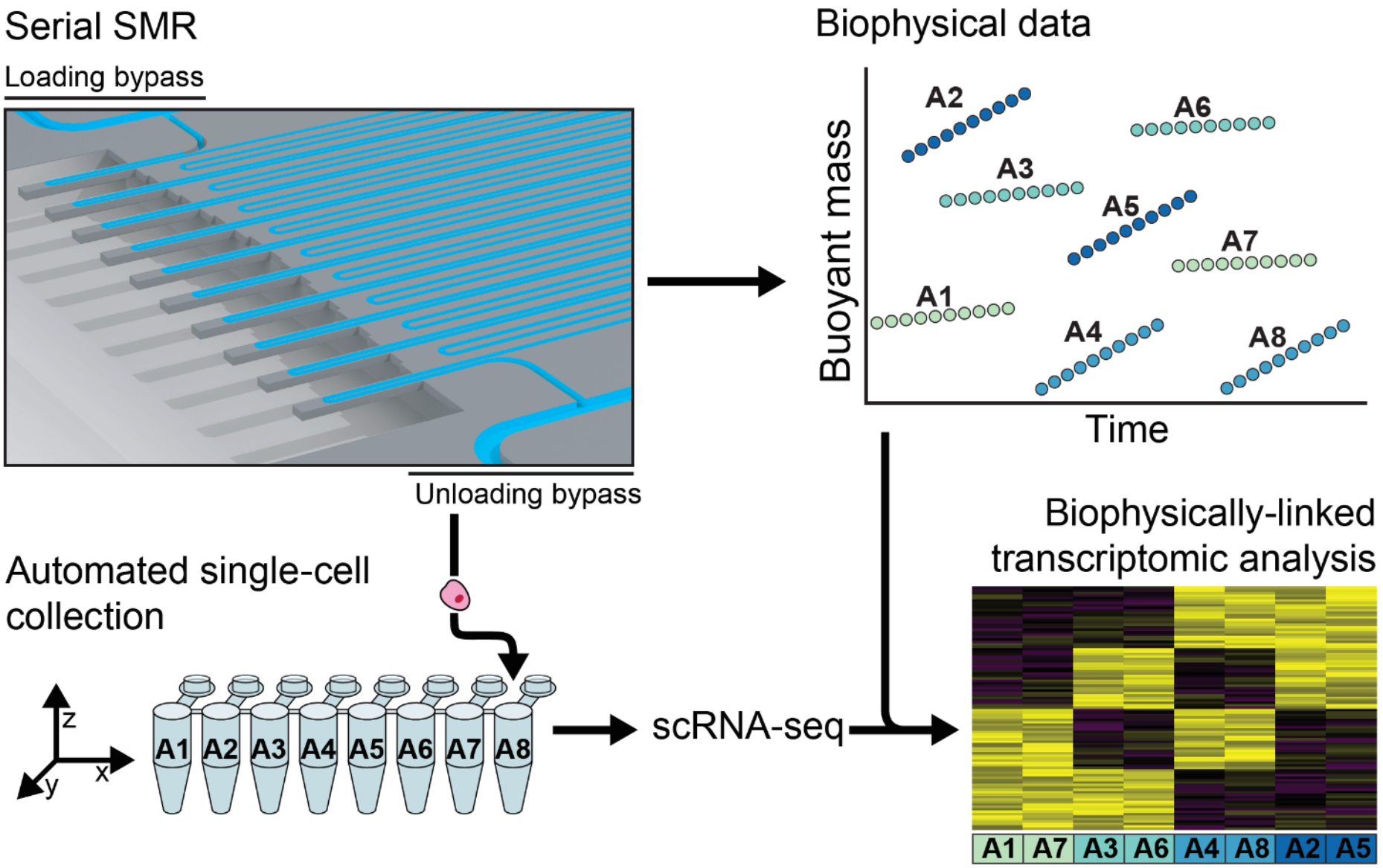


Mark Murakami, MD

Mark Stevens, PhD

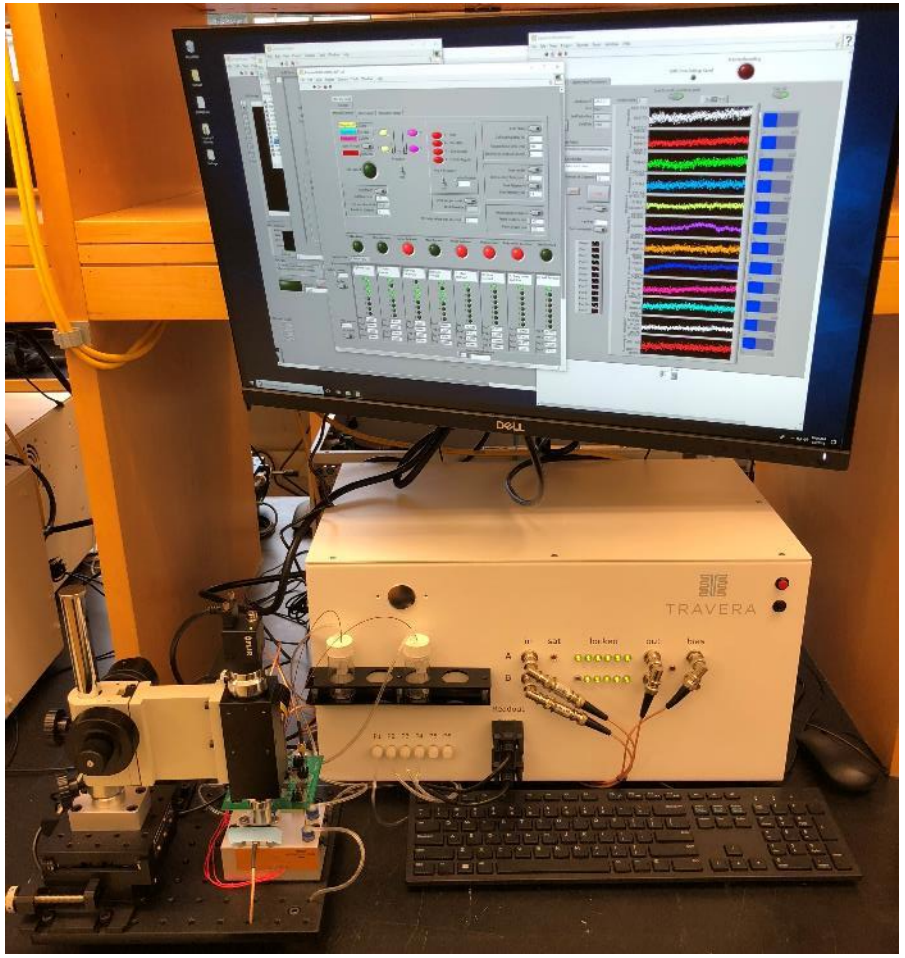
Cermak et al. *Nat Biotech* 2016, Stevens et al. *Nat Biotech* 2016

Linking Mass and MAR to scRNA-Seq for each cell



Alex Shalek, Doug Lauffenberger, MIT

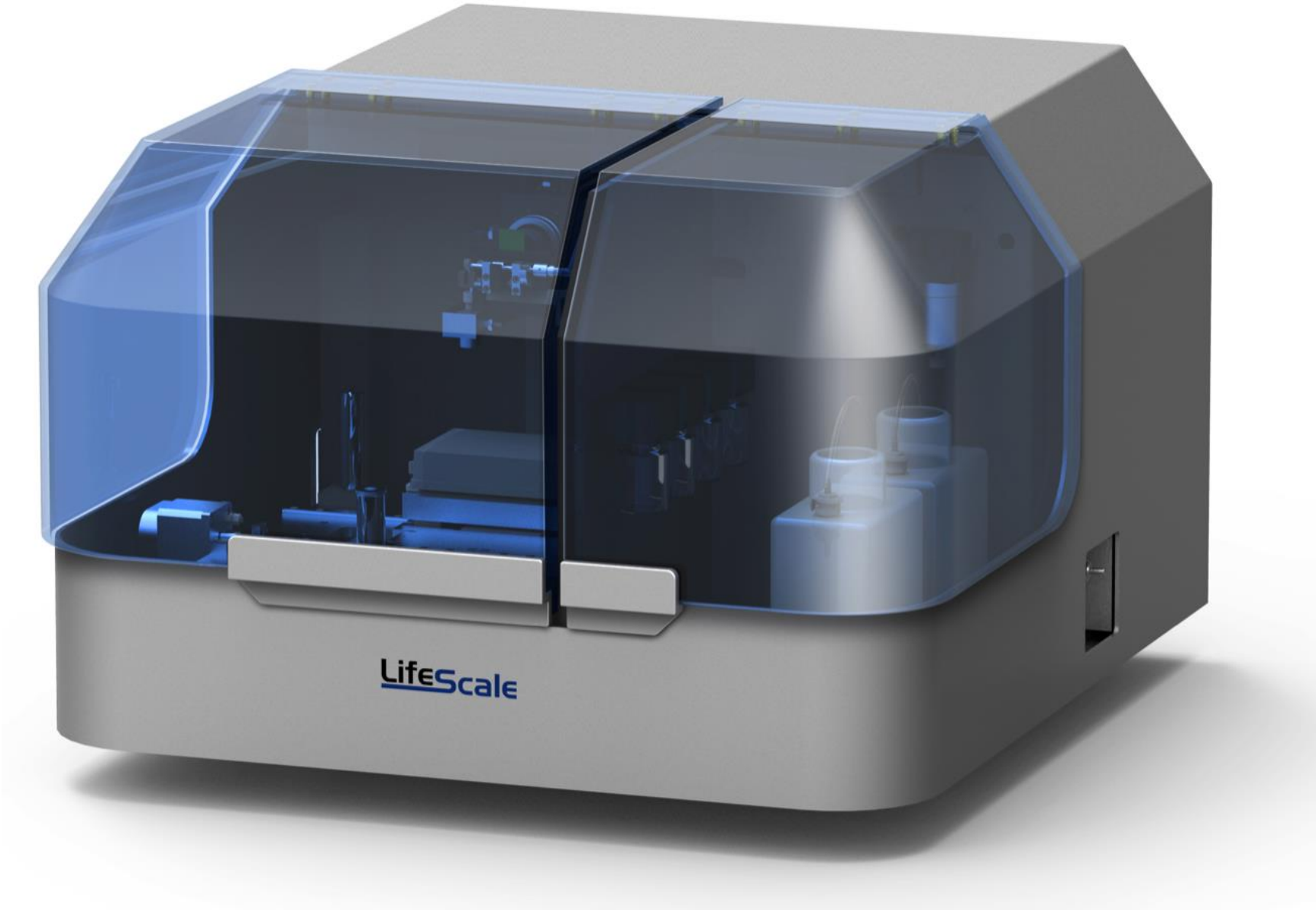
TRAVERA



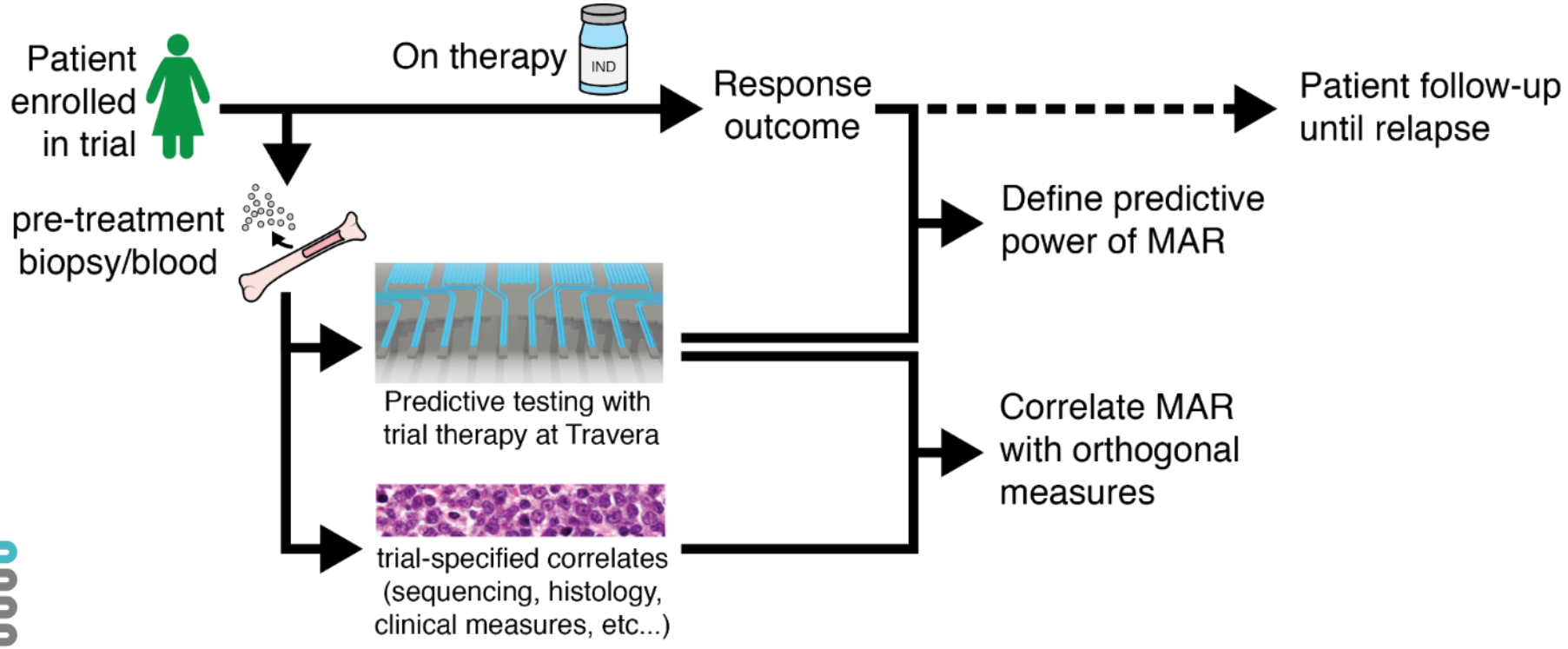
Single-box design

Ten systems are up and running

Stage II: LifeScaleAST for Rapid Antibiotic Susceptibility Testing

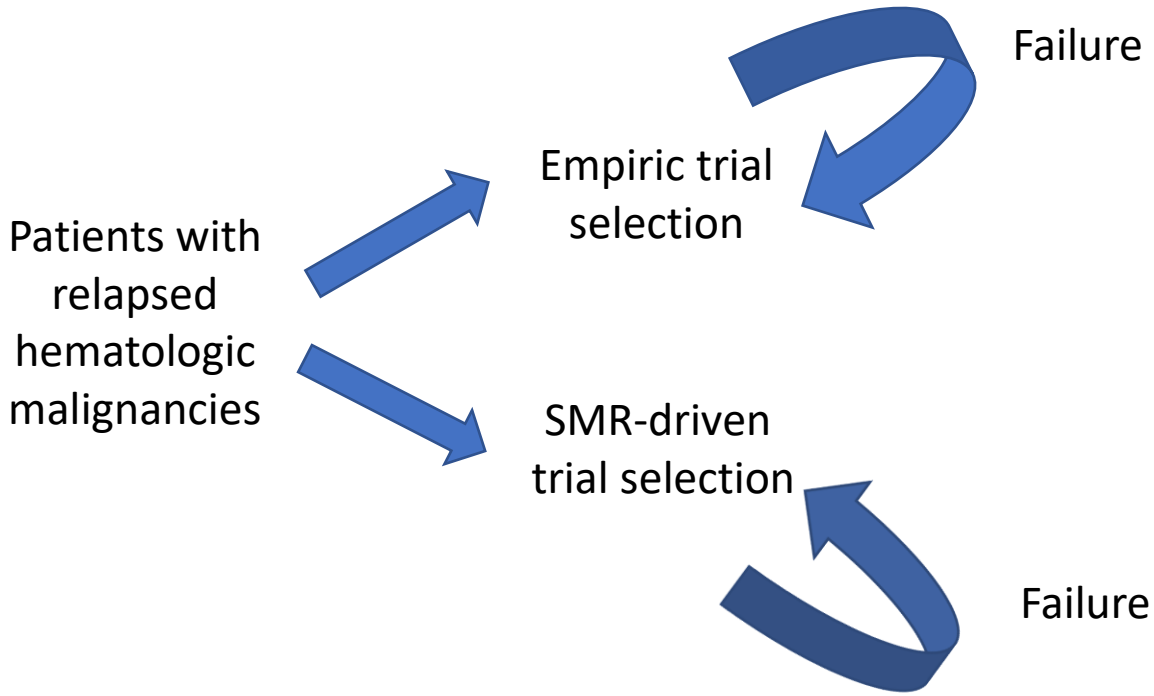


fNIH funded testing in humans – 2018



TRAVERA

Testing in humans – projected 2019



<u>Examples of available agents</u>

IDH2 inhibitors
BCL2 inhibitors
PI3K inhibitors
MCL1 inhibitors
CDK9 inhibitors
XPO1 inhibitors
Bromodomain inhibitors
SYK inhibitors
JAK inhibitors
MDM2 inhibitors
HSP90 inhibitors
Spliceosome inhibitors
Demethylating agents
Anti-metabolites
Antibody-drug conjugates
Novel chemotherapies

Weinstock laboratory

- Nicolas Cordero
- Tovah Day, Ph.D.
- Hailey Fuchs
- **Saliva Jain, M.D.**
- **Kristen Jones**
- Jacob Layer, M.S.
- Catharine Leahy
- Loretta Li, M.D.
- **Huiyun Liu**
- Chen Lossos, M.S.
- Abner Louissaint, M.D., Ph.D.
- Sara Morrow
- **Mark Murakami, M.D.**
- **Sam Ng, M.D., Ph.D.**
- Foster Powers
- **Kay Shigemori**
- Tony Tran
- **Alex van Scoyk**
- **Amanda Christie (former)**
- **Mark Stevens, Ph.D. (former)**
- **Noriaki Yoshida, M.D. (former)**

DFCI Hematologic Oncology

- Andrew Lane, M.D., Ph.D.
- Dan DeAngelo, M.D., Ph.D.
- Arnie Freedman, M.D.
- Ilene Galinsky, N.P.
- **Jim Griffin, M.D.**
- **Margaret Shipp, M.D.**
- Philippe Armand, M.D., Ph.D.
- Richard Stone, M.D.
- Martha Wadleigh, M.D.
- **David Fisher, M.D.**
- **Eric Jacobsen, M.D.**
- Caron Jacobson, M.D.
- Ann LaCasce, M.D.
- Marlise Luskin, M.D.
- Ore Odejide, M.D.

DF/HCC

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- David Dorfman, M.D., Ph.D.
- Alejandra Gutierrez, M.D., Ph.D.
- Tim Graubert, M.D.
- Marian Harris, M.D.
- Tom Kupper, M.D., Ph.D.
- Tom Look, M.D.
- Marcela Maus, M.D., Ph.D.
- **Elizabeth Morgan, M.D.**
- Stu Orkin, M.D.
- Hidde Plough, Ph.D.
- Jerry Ritz, M.D.
- Scott Rodig, M.D., Ph.D.
- Scott Armstrong, M.D., Ph.D.
- David Williams, M.D., Ph.D.
- Henry Long, Ph.D.
- Myles Brown, M.D., Ph.D.

MSKCC

- **Andy Intlekoffer, M.D., Ph.D.**
- **Steve Horwitz, M.D.**
- **Allison Moskowitz, M.D.**
- **Natasha Galasso**
- Craig Thompson, M.D.
- **Ahmet Dogan, M.D., Ph.D.**
- Ross Levine, M.D.

Koch Institute-MIT

- **Scott Manalis, Ph.D.**
- **Alex Shalek, Ph.D.**

Cornell

- **Giorgio Inghirami, M.D., Ph.D**
- **Danilo Fiore, Ph.D.**
- **Jia Ruan, M.D.**

Stanford University

- Youn Kim, M.D.
- Michael Khodadoust, M.D.

University of Gottingen

- **Raphael Koch, M.D.**

Aileron Therapeutics

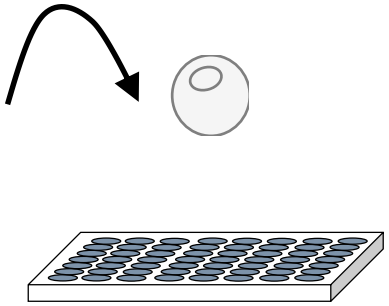
- **Manuel Aivado, M.D.**

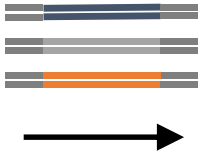
Travera, inc.

- **Mark Stevens, Ph.D.**
- Rob Kimmerling, Ph.D.

Linked scRNA-seq: Workflow

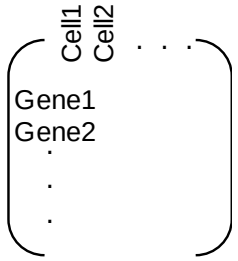
From SMR





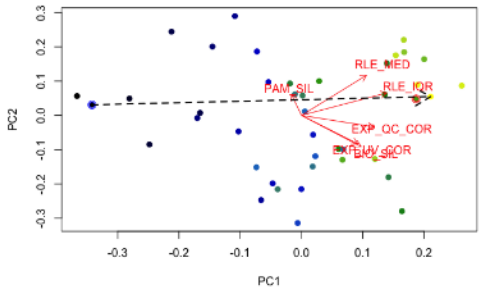
scRNA-seq library prep (smart-seq2) and sequencing

Genes x cells matrix

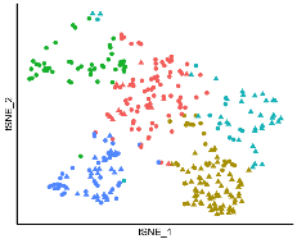


Trimming for quality cells (*scone**)

Prioritize normalization schemes (*scone**)



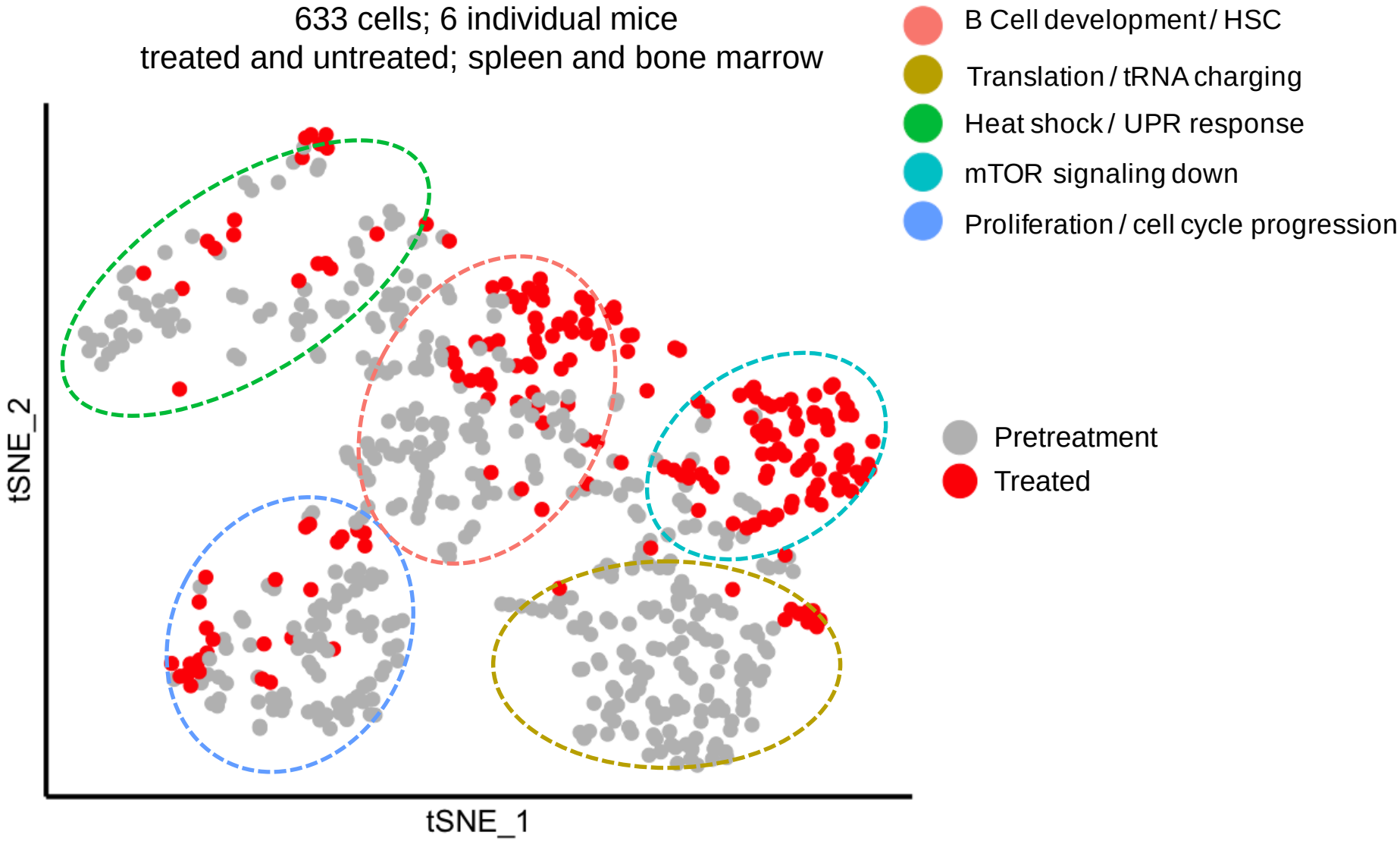
Analyze complete dataset



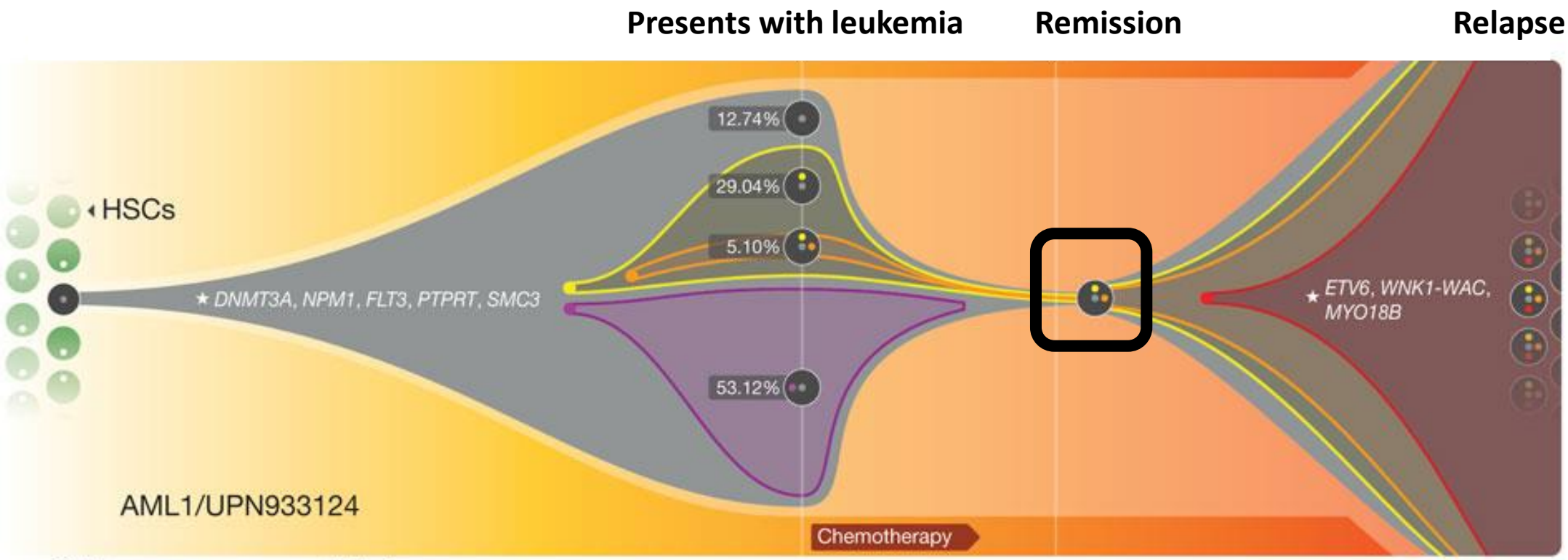
*SMR step is a “viability filter” so we enrich for at least somewhat healthy cells

*Cole, M. *et al.* Performance Assessment and Selection of Normalization Procedures for Single-Cell RNA-Seq (bioRxiv, 2017)

scRNA-seq: Treatment

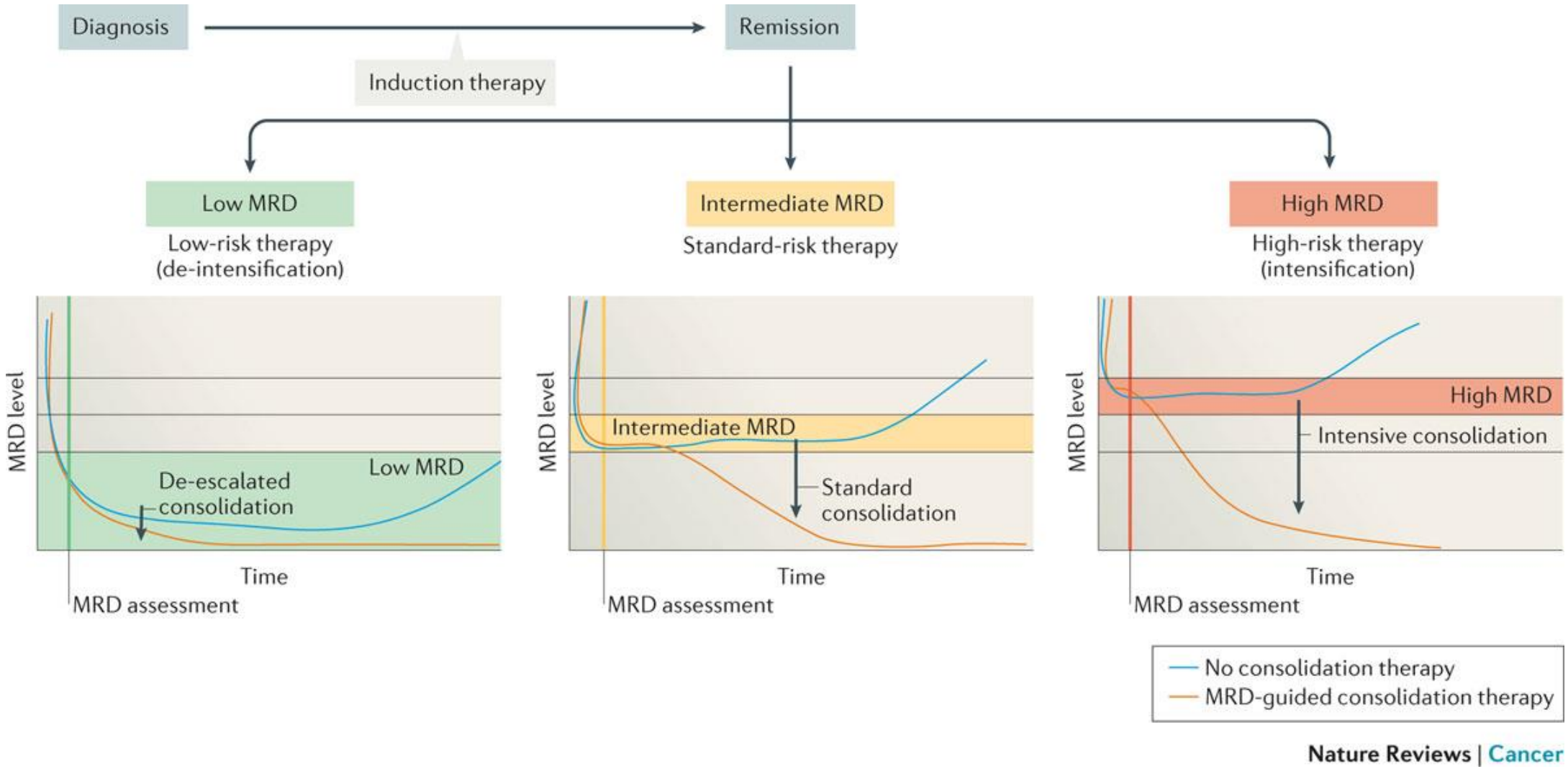


Minimal residual disease is the roadblock to cure



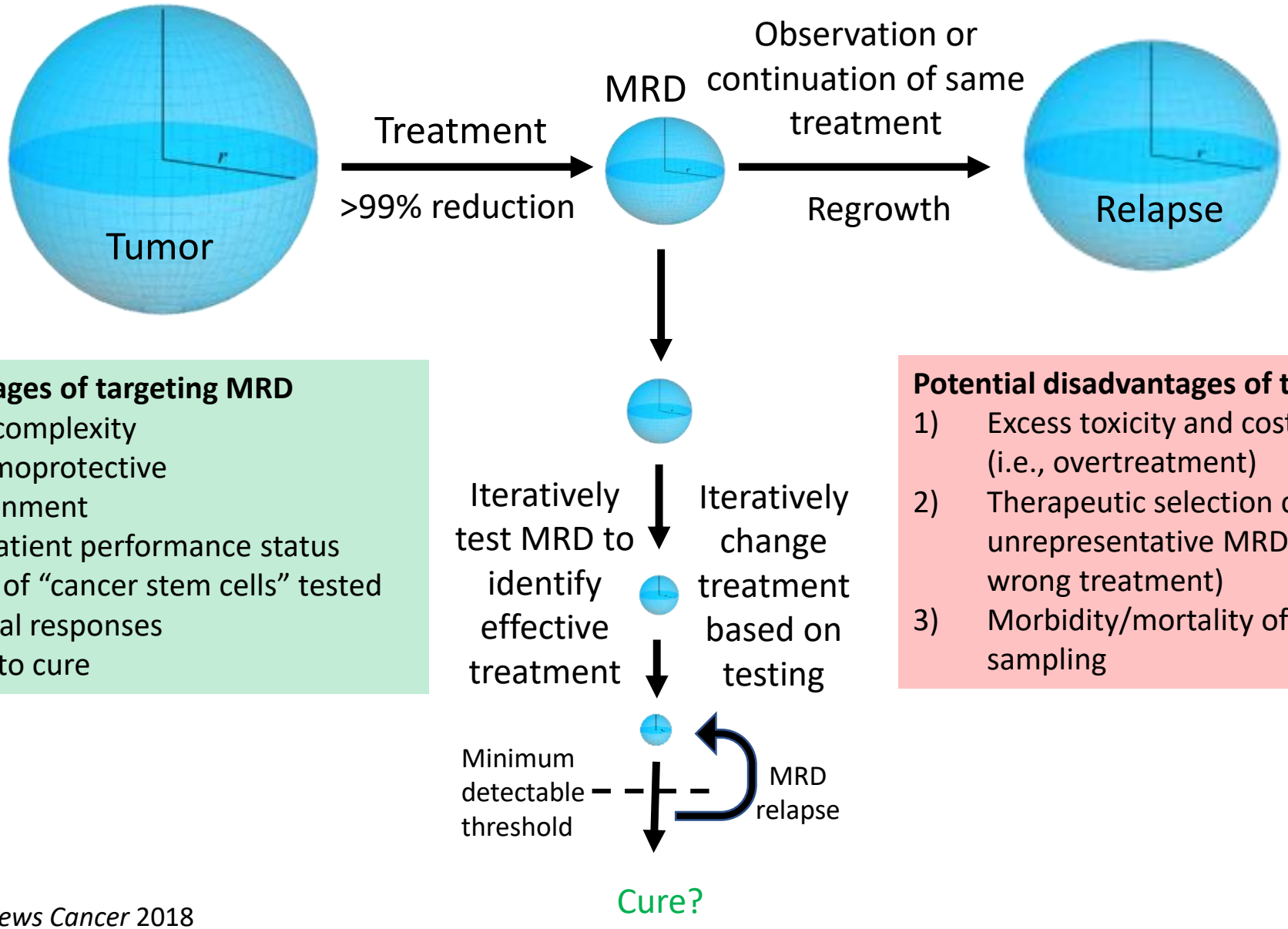
Ding et al. *Nature 2013*

Current approach to minimal residual disease (MRD)



Luskin et al. *Nature Reviews Cancer* 2018

Paradigm of precision targeting for MRD



Potential advantages of targeting MRD

1) Less clonal complexity
2) Loss of chemoprotective microenvironment
3) Improved patient performance status
4) Enrichment of "cancer stem cells" tested for functional responses
5) Fewer cells to cure

Potential disadvantages of targeting MRD

1) Excess toxicity and cost from treatments (i.e., overtreatment)
2) Therapeutic selection confounded by unrepresentative MRD sampling (i.e., wrong treatment)
3) Morbidity/mortality of repeated MRD sampling

Luskin et al. *Nature Reviews Cancer* 2018