Mutational landscape and immunotherapy efficacy

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Clinical oncology development
Merck Research Laboratory
Merck & Co., Inc.

April 1st. 2016
NIH, Bethesda, Maryland

Engage . . . Collaborate . . . Learn

Conflicts of interest

A full time employee of Merck Co., Inc.

Outline

- Several unique features of cancer immunotherapy and the roles of translational Immuno-Oncology research in cancer immunotherapy
- Whole exome sequencing for neoantigen discovery and precision oncology

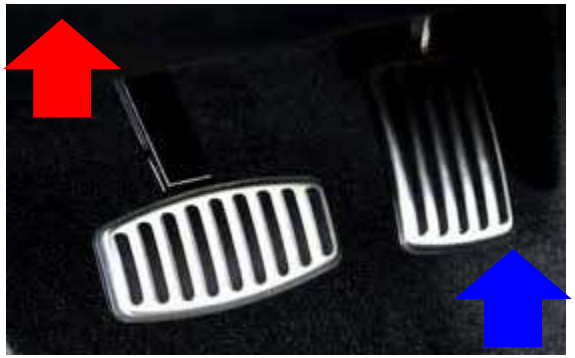
  "Mutation load as a potential biomarker"
- Strategies for translational immuno-oncology research to meet the need of personalized combination cancer immunotherapy

A paradigm shift in cancer immunotherapy

Checkpoint blockade

To “turn on” the immune response to fight cancer (i.e. vaccine)

To “release the brakes” on the immune system to unleash a pre-existing immune response against cancer. (i.e.CTLA-4, PD-1/PD-L1)

Gas  Brakes

Personalized

Modified from Dr. Jedd Wolchok

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 Tumor Responses with Lambrolizumab (Anti–PD-1) in Melanoma

Omid Hamid, M.D., Caroline Robert, M.D., Ph.D., Adil Daud, M.D., F. Stephen Hodi, M.D., Wen-Jen Hwu, M.D., Ph.D., Richard Kefford, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D., Peter Hersey, M.D., Ph.D., Richard W. Joseph, M.D., Jeffrey S. Weber, M.D., Ph.D., Roxana Dronca, M.D., Tara C. Gangadhar, M.D., Amita Patnaik, M.D., Hassane Zarour, M.D., Anthony M. Joshua, M.B., B.S., Ph.D., Kevin Gergich, M.A., Jeroen Elassaiss-Schaap, Ph.D., Alain Algazi, M.D., Christine Mateus, M.D., Peter Boasberg, M.D., Paul C. Tumeh, M.D., Bartosz Chmielowski, M.D., Ph.D., Scot W. Ebbinghaus, M.D., Xiaoyun Nicole Li, Ph.D., S. Peter Kang, M.D., and Antoni Ribas, M.D., Ph.D.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab plus Ipilimumab in Advanced Melanoma

Jedd D. Wolchok, M.D., Ph.D., Harriet Kluger, M.D., Margaret K. Callahan, M.D., Ph.D., Michael A. Postow, M.D., Naiyer A. Rizvi, M.D., Alexander M. Lesokhin, M.D., Neil H. Segal, M.D., Ph.D., Charlotte E. Ariyan, M.D., Ph.D., Ruth-Ann Gordon, B.S.N., Kathleen Reed, M.S., Matthew M. Burke, M.B.A., M.S.N., Anne Caldwell, B.S.N., Stephanie A. Kronenberg, B.A., Blessing U. Agunwamba, B.A., Xiaoling Zhang, Ph.D., Israel Lowy, M.D., Ph.D., Hector David Inzunza, M.D., William Feely, M.S., Christine E. Horak, Ph.D., Quan Hong, Ph.D., Alan J. Korman, Ph.D., Jon M. Wigginton, M.D., Ashok Gupta, M.D., Ph.D., and Mario Sznol, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 22, 2015 VOL. 372 NO. 4

PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma

Stephen M. Ansell, M.D., Ph.D., Alexander M. Lesokhin, M.D., Ivan Borrello, M.D., Ahmad Halwani, M.D., Emma C. Scott, M.D., Martin Gutierrez, M.D., Stephen J. Schuster, M.D., Michael M. Millenson, M.D., Deepika Cattry, M.S., Gordon J. Freeman, Ph.D., Scott J. Rodig, M.D., Ph.D., Bjoern Chapuy, M.D., Ph.D., Azra H. Ligon, Ph.D., Lili Zhu, M.S., Joseph F. Grosso, Ph.D., Su Young Kim, M.D., Ph.D., John M. Timmerman, M.D., Margaret A. Shipp, M.D., and Philippe Armand, M.D., Ph.D.

ABSTRACT

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.J. Grob, C.L. Cowey, C.D. Lao, D. Schadendorf, R. Dummer, M. Smylie, P. Rutkowski, P.F. Ferrucci, A. Hill, J. Wagstaff, M.S. Carlino, J.B. Haanen, M. Maio, I. Marquez-Rodas, G.A. McArthur, P.A. Ascierto, G.V. Long, M.K. Callahan, M.A. Postow, K. Grossmann, M. Sznol, B. Dreno, L. Bastholt, A. Yang, L.M. Rollin, C. Horak, F.S. Hodi, and J.D. Wolchok

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 Alaparthy, 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.

LETTER

doi:10.1038/nature13954

PD-1 blockade induces responses by inhibiting adaptive immune resistance

Paul C. Tumeh[1,2], Christina L. Harview[1], Jennifer H. Yearley[3], I. Peter Shintaku[1], Emma J. M. Taylor[1], Lidia Robert[1], Bartosz Chmielowski[1,2], Marko Spasic[1], Gina Henry[1], Voicu Ciobanu[1], Alisha N. West[1], Manuel Carmona[1], Christine Kivork[1], Elizabeth Seja[1], Grace Cherry[1], Antonio J. Gutierrez[1], Tristan R. Grogan[1], Christine Mateus[4], Gorana Tomasic[4], John A. Glaspy[1,2], Ryan O. Emerson[5], Harlan Robins[5,6], Robert H. Pierce[3], David A. Elashoff[1,2], Caroline Robert[4] & Antoni Ribas[1,2]

LETTER

doi:10.1038/nature14011

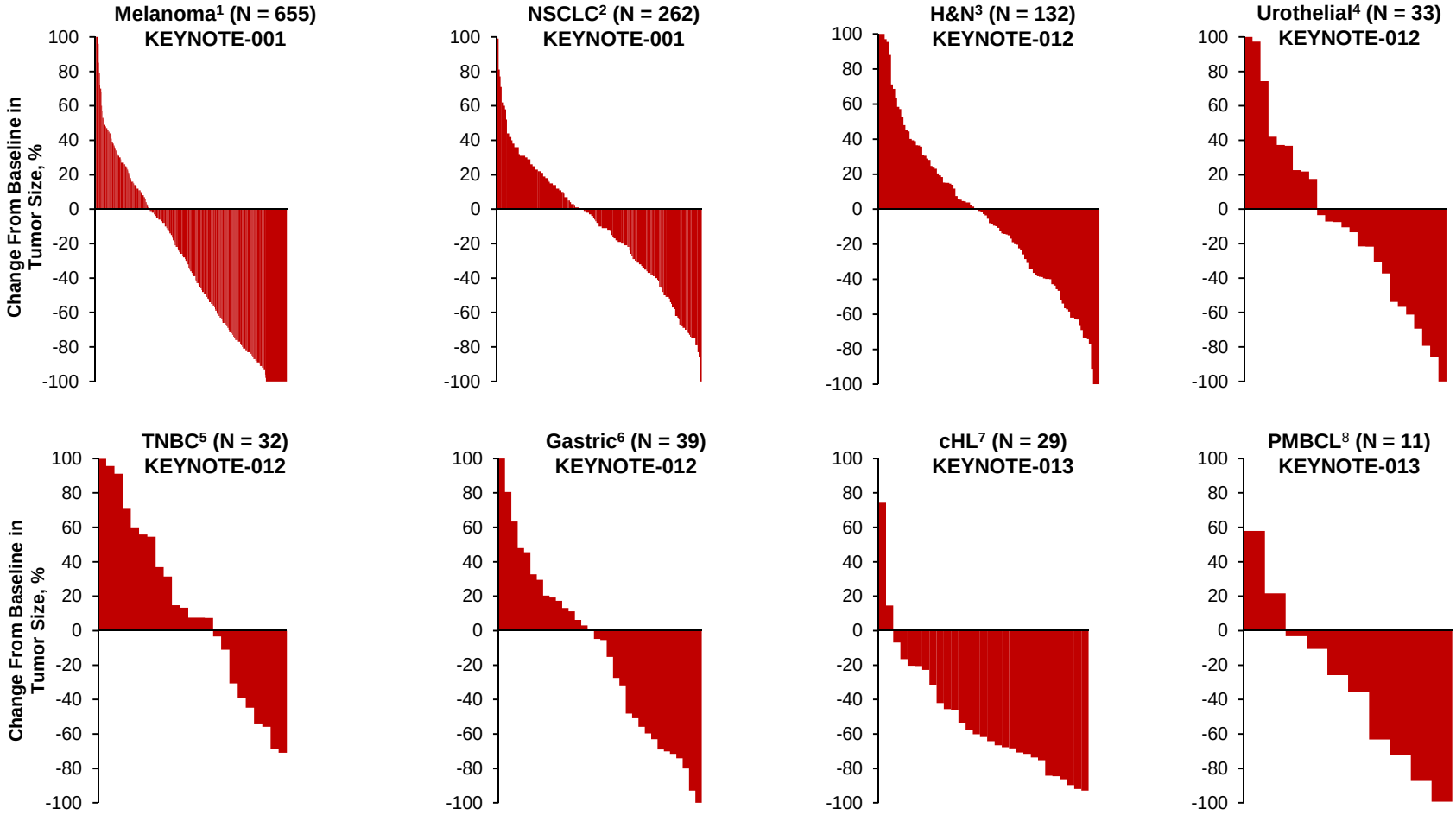
Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients

Roy S. Herbst[1], Jean-Charles Soria[2], Marcin Kowanetz[3], Gregg D. Fine[3], Omid Hamid[4], Michael S. Gordon[5], Jeffery A. Sosman[6], David F. McDermott[7], John D. Powderly[8], Scott N. Gettinger[1], Holbrook E. K. Kohrt[9], Leora Horn[10], Donald P. Lawrence[11], Sandra Rost[3], Maya Leabman[3], Yuanyuan Xiao[3], Ahmad Mokatrin[3], Hartmut Koeppen[3], Priti S. Hegde[3], Ira Mellman[3], Daniel S. Chen[3] & F. Stephen Hodi[1,2]

Durable clinical response, new clinical response pattern, irRC.

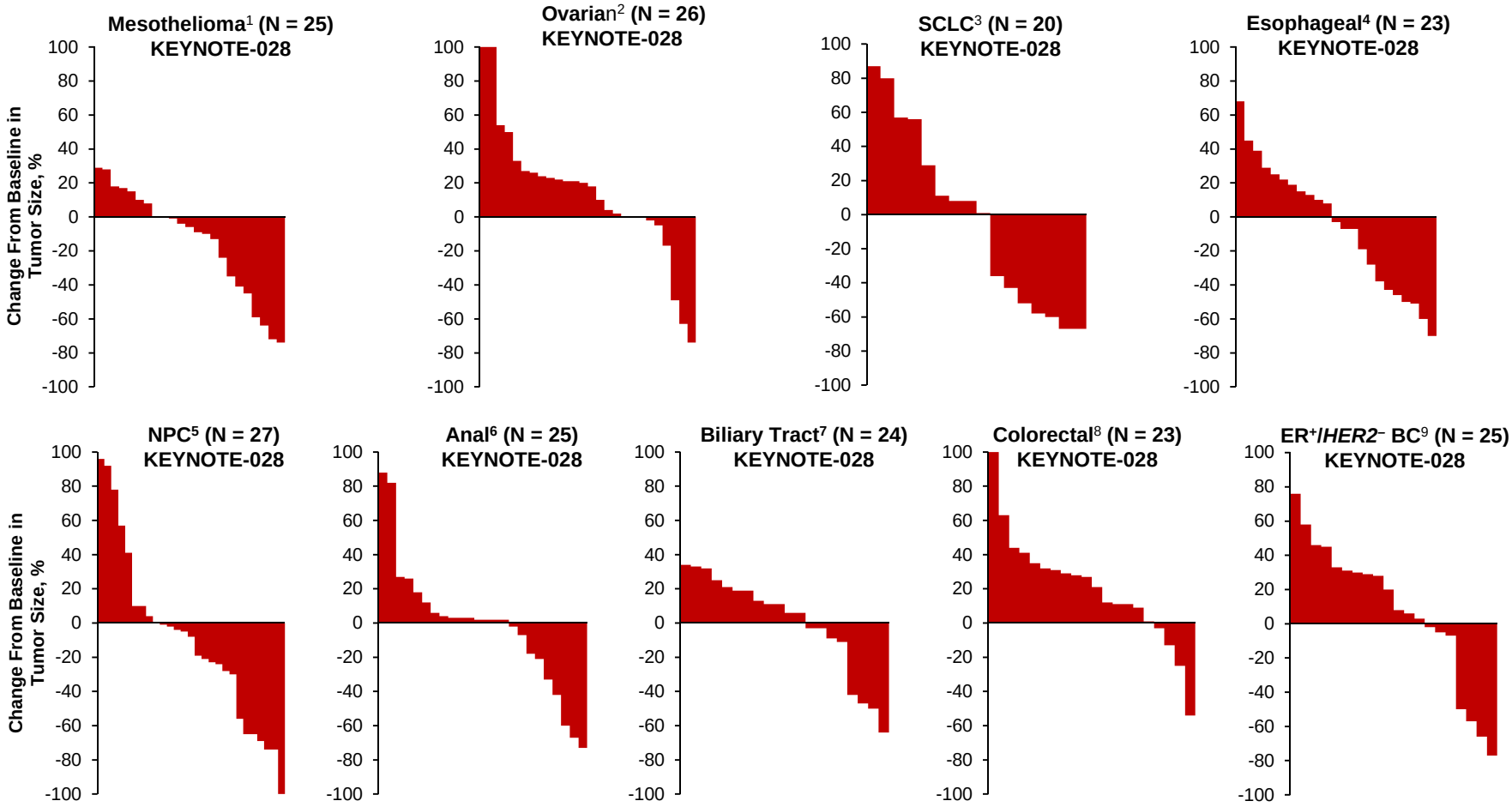
2011 → *2016*

PD-1 blockade monotherapy shows activity in most tumors selected for screening



1. Daud A et al. ASCO 2015; 2. Garon EB et al. ESMO 2014; 3. Seiwert T et al. ASCO 2015 ; 4. Plimack E et al. ASCO 2015; 5. Nanda R et al. SABCS 2014; 6. Bang YJ et al. ASCO 2015 ; 7. Moskowitz C et al. ASH 2014; 8. Zinzani PL et al. ASH 2015.

PD-1 blockade monotherapy shows activity in most tumors selected for screening



Data have also been presented for MSI-high cancers,[10] Merkel cell carcinoma,[11] and endometrial cancer[12]

1. Alley EA et al. AACR 2015; 2. Varga A et al. ASCO 2015; 3. Ott PA et al. 2015 ASCO; 4. Doi T et al. ASCO 2015; 5.. Mehnert JM et al. AACR-NCI-EORTC 2015. Hsu C et al. ECC 2015; 6. Ott PA et al. ECC 2015; 7. Bang Y-J et al. ECC 2015; 8. O'Neil B et al. ECC 2015; 9. Rugo HS et al. SABCS 2015; 10. Le D et al. ASCO 2015; 11. Nghiem P et al. ECC 2015; 12

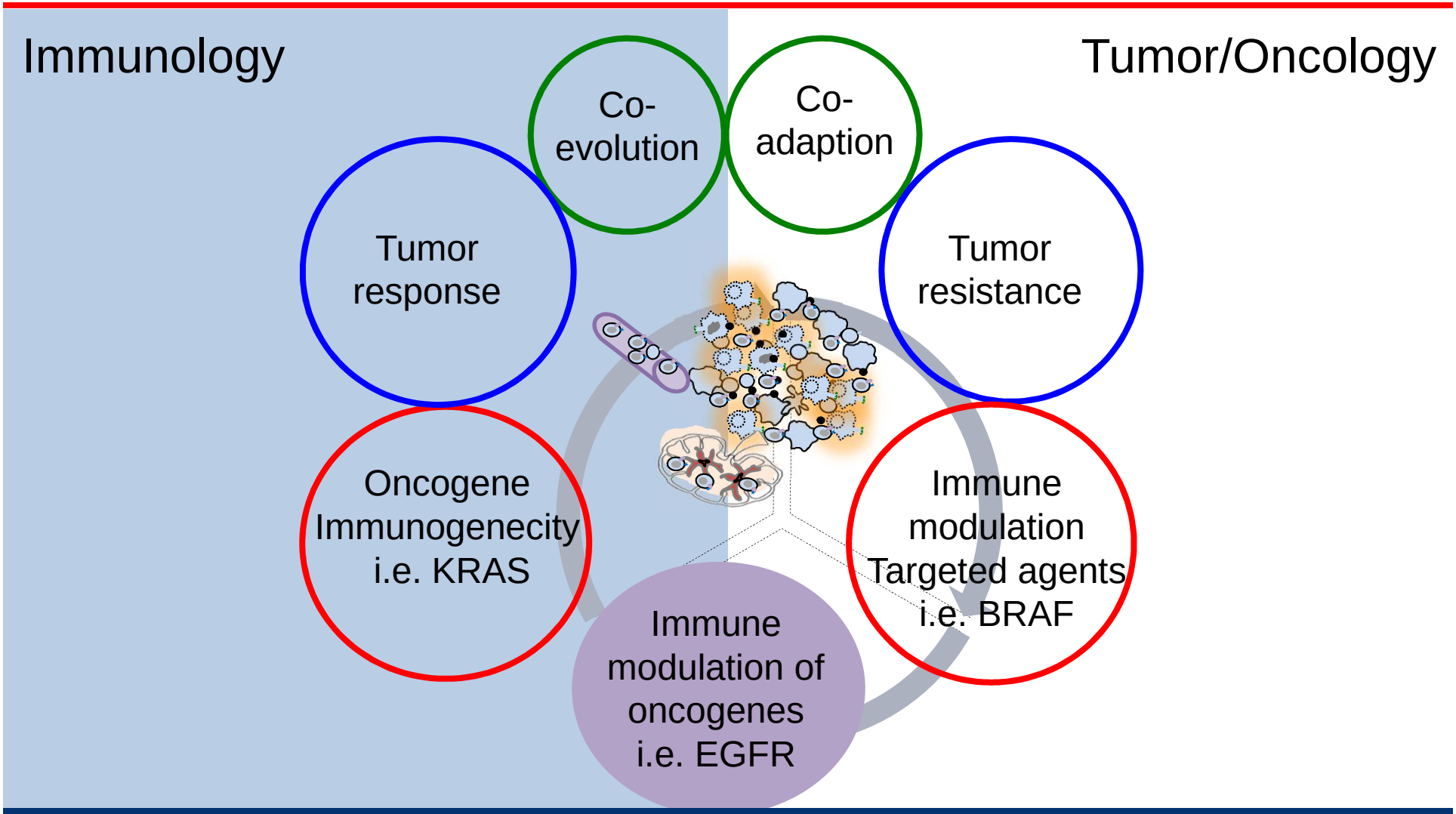
Drugs in clinical development that block PD-1/PD-L1

Target	Drug Name	Other Names	Source	Isotype and Characteristics	Clinical Testing Phase
PD-1	MEDI0680	AMP-514	MedImmune/ AstraZeneca	information not available	phase I
	nivolumab	Opdivo, BMS-936558, MDX-1106, ONO-4538	Bristol-Myers Squibb, Ono Pharmaceuticals	fully human IgG4a	approved treatment-refractory unresectable melanoma (Japan, United States) and squamous NSCLC (United States)
	pembrolizumab	Keytruda, MK-3475, lambrolizumab	Merck	humanized IgG4	approved treatment-refractory unresectable melanoma (United States)
	pidilizumab	CT-011	CureTech	humanized IgG1	phase I-II
PD-L1	BMS-936559	MDX-1105	Bristol-Myers Squibb	fully human IgG4[a]	phase I
	MEDI4736	none	MedImmune/ AstraZeneca	Fc-modified human IgG1[b]	phase I-III
	MPDL3280A	RG7446	Genentech/ Roche	Fc-modified human IgG1[b]	phase I-III
	MSB0010718C	none	EMD Serono	fully human IgG1[a]	phase I-II

a Fully human mAbs were produced in genetically engineered mice.
b Fc-modified mAbs were engineered to abrogate ADCC and complement-dependent cytotoxicity (CDC).

Modified from Topalian S et al 2015 Cancer Cell 27(4) 450–461

Future cancer immunotherapy: Tumor immunology meets oncology.



Novel technologies, new knowledge and clinical success

The roles of translational Immuno-Oncology research in cancer immunotherapy

- To elucidate pharmacokinetics/pharmacodynamics changes
- To understand the potential mechanisms of action
- To find new correlates associated with clinical benefits and/or toxicity
- To identify new targets and patients potentially responding to therapy
- To guide us toward providing appropriate therapies based upon our better understanding of the mechanism-based modulation impact of cancer immunotherapies

Outline

- Several unique features of cancer immunotherapy and the roles of translational Immuno-Oncology research in cancer immunotherapy

- Whole exome sequencing for neoantigen discovery and precision oncology

  "Mutation load as a potential biomarker"

- Strategies for translational immuno-oncology research to meet the need of personalized combination cancer immunotherapy

A long standing interest in mutated antigens

Proc. Natl. Acad. Sci. USA
Vol. 92, pp. 7976–7980, August 1995
Immunology

A mutated intron sequence codes for an antigenic peptide recognized by cytolytic T lymphocytes on a human melanoma

PIERRE G. COULIE*, FRÉDÉRIC LEHMANN, BERNARD LETHÉ, JEAN HERMAN, CHRISTOPHE LURQUIN, MARIAM ANDRAWISS, AND THIERRY BOON

Ludwig Institute for Cancer Research, 74 Avenue Hippocrate, UCL 7459, B-1200 Brussels, Belgium; and Cellular Genetics Unit, Université Catholique de Louvain, B-1200 Brussels, Belgium

Communicated by Christian de Duve, ICP, International Institute of Cellular and Molecular Pathology, Brussels, Belgium, May 24, 1995

Biochemical Identification of a Mutated Human Melanoma Antigen Recognized by CD4$^+$ T Cells

By Rembert Pieper,* Robert E. Christian,‡ Monica I. Gonzales,* Michael I. Nishimura,* Gaorav Gupta,* Robert E. Settlage,‡ Jeffrey Shabanowitz,‡ Steven A. Rosenberg,* Donald F. Hunt,‡ and Suzanne L. Topalian*

Immunity, Vol. 11, 263–270, September, 1999, Copyright ©1999 by Cell Press

The Makings of a Tumor Rejection Antigen Review

Eli Gilboa*
Center for Genetic and Cellular Therapies
Department of Surgery
Duke University Medical Center
Durham, North Carolina 27710

strong tumor rejection antigens, describing quantitatively the impact of the immune response on tumor growth. The extent to which an antigen is a tumor rejection antigen is also a function of the immunization protocol. A weak tumor rejection antigen can record as a

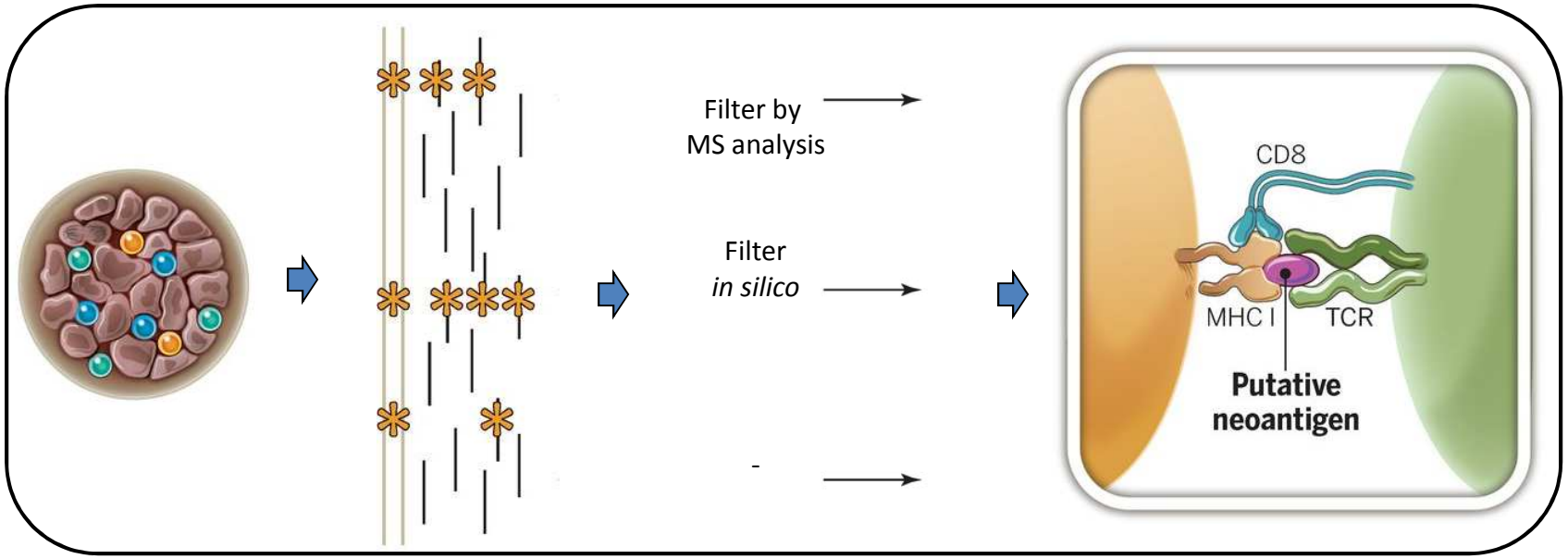
Cancer exome–based identification of neoantigens

1. Obtain tumor material and normal cells

2. Identify tumor-specific mutations within expressed genes

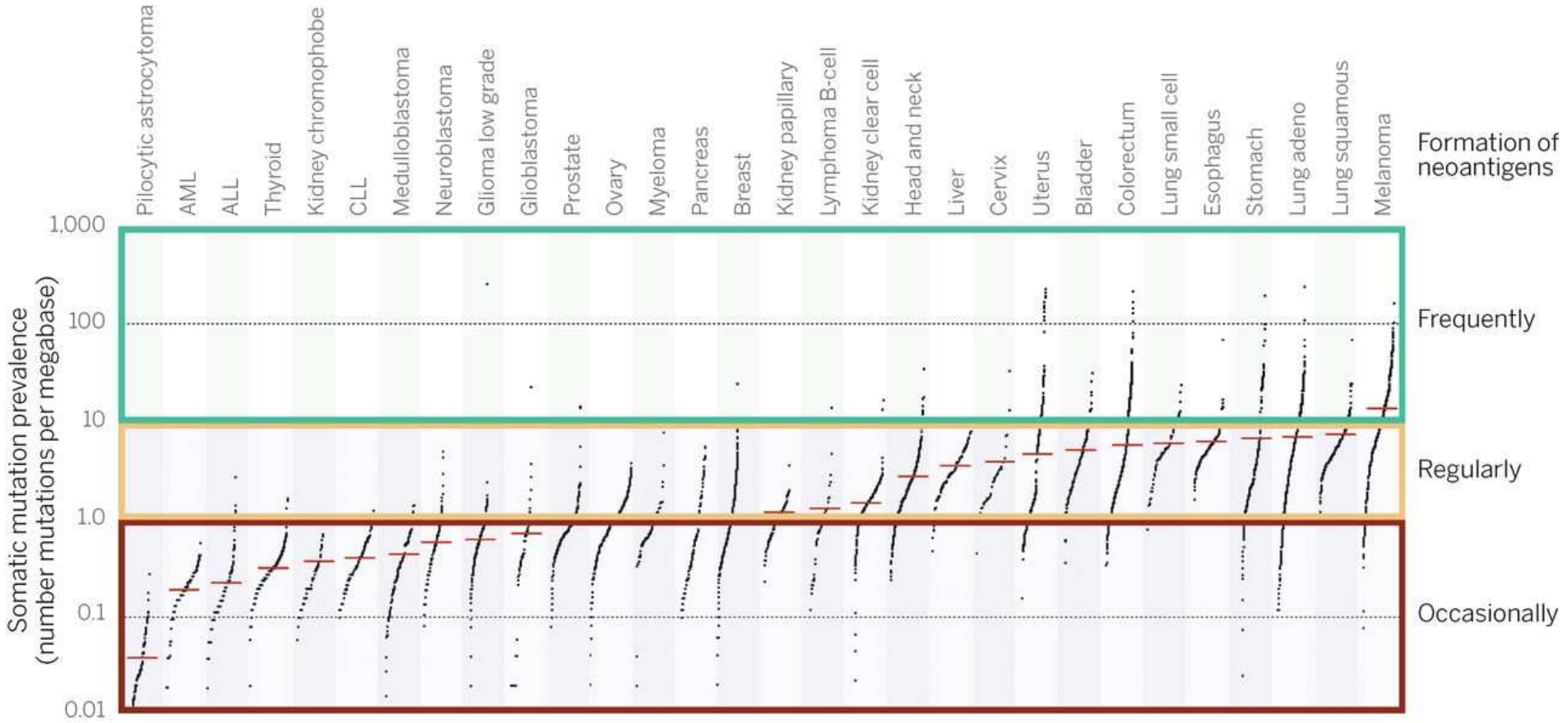
3. Filter

4.Assess T cell recognition /binding



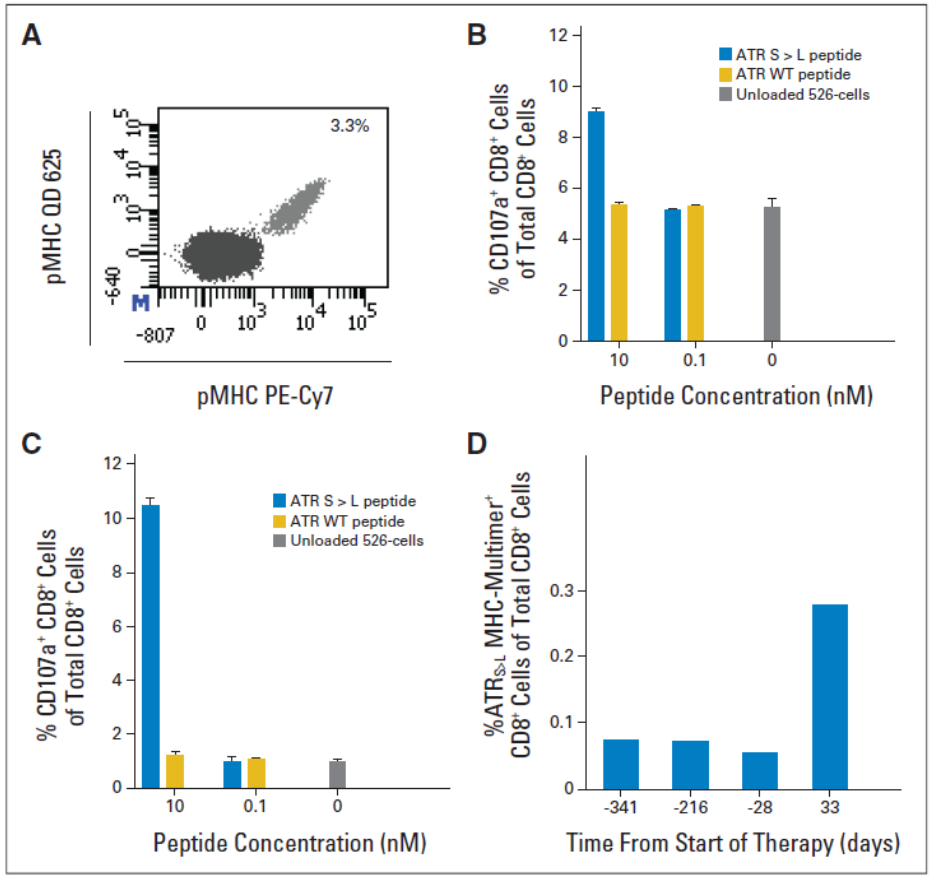
Modified from Schumacher TN, and Schreiber RD Science 2015;348:69-74

Estimate of the neoantigen repertoire in human cancer.



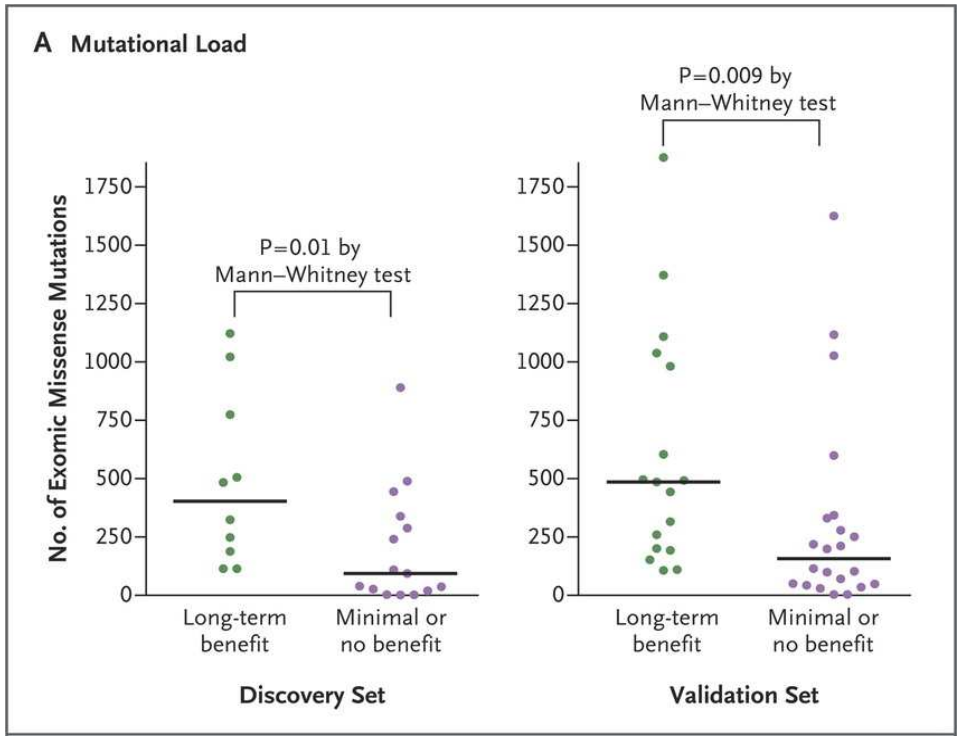
Modified from Schumacher TN, and Schreiber RD Science 2015;348:69-74

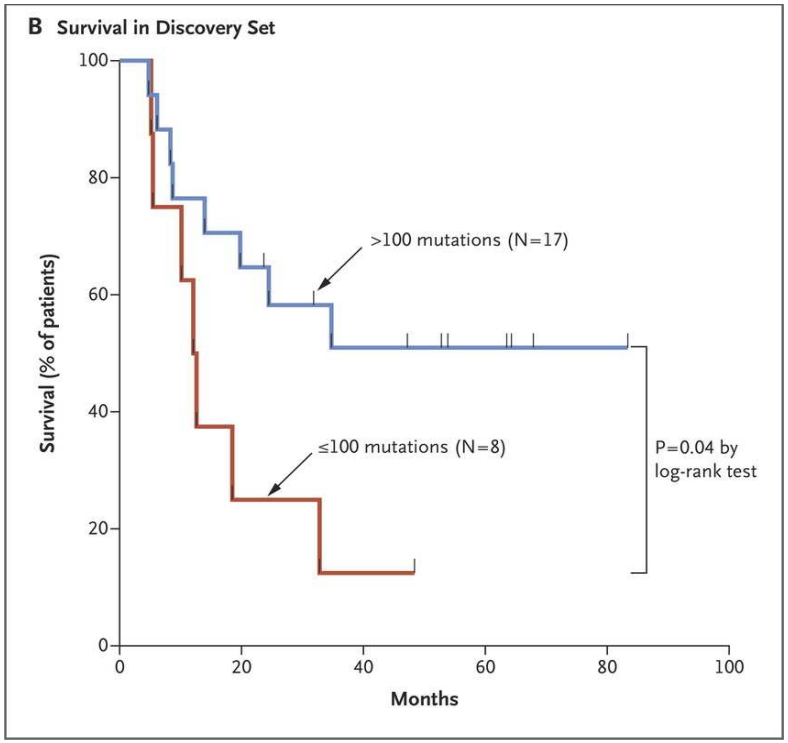
Tumor exome analysis reveals neoantigen-specific T-cell reactivity in an ipilimumab responsive melanoma



Van Rooij N, et al JCO 2013 31(32):439-42

Mutational landscape of tumors according to clinical benefit from ipilimumab treatment (Melanoma)

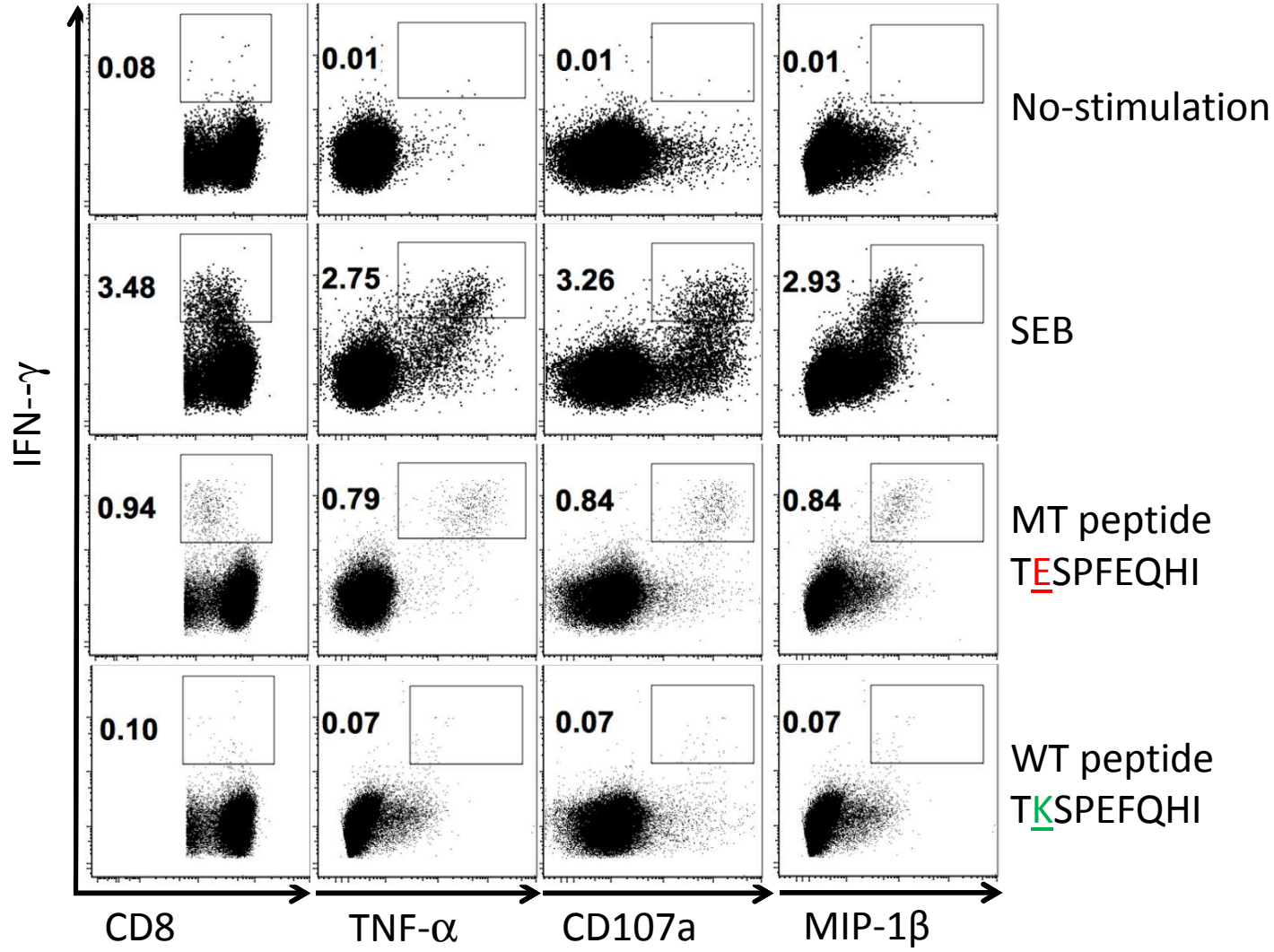




Whole exome sequencing

Snyder A et al. N Engl J Med 2014;371:2189-2199.

Polyfunctional T cell response to TESPFEQHI versus wild type peptide TKSPFEQHI.

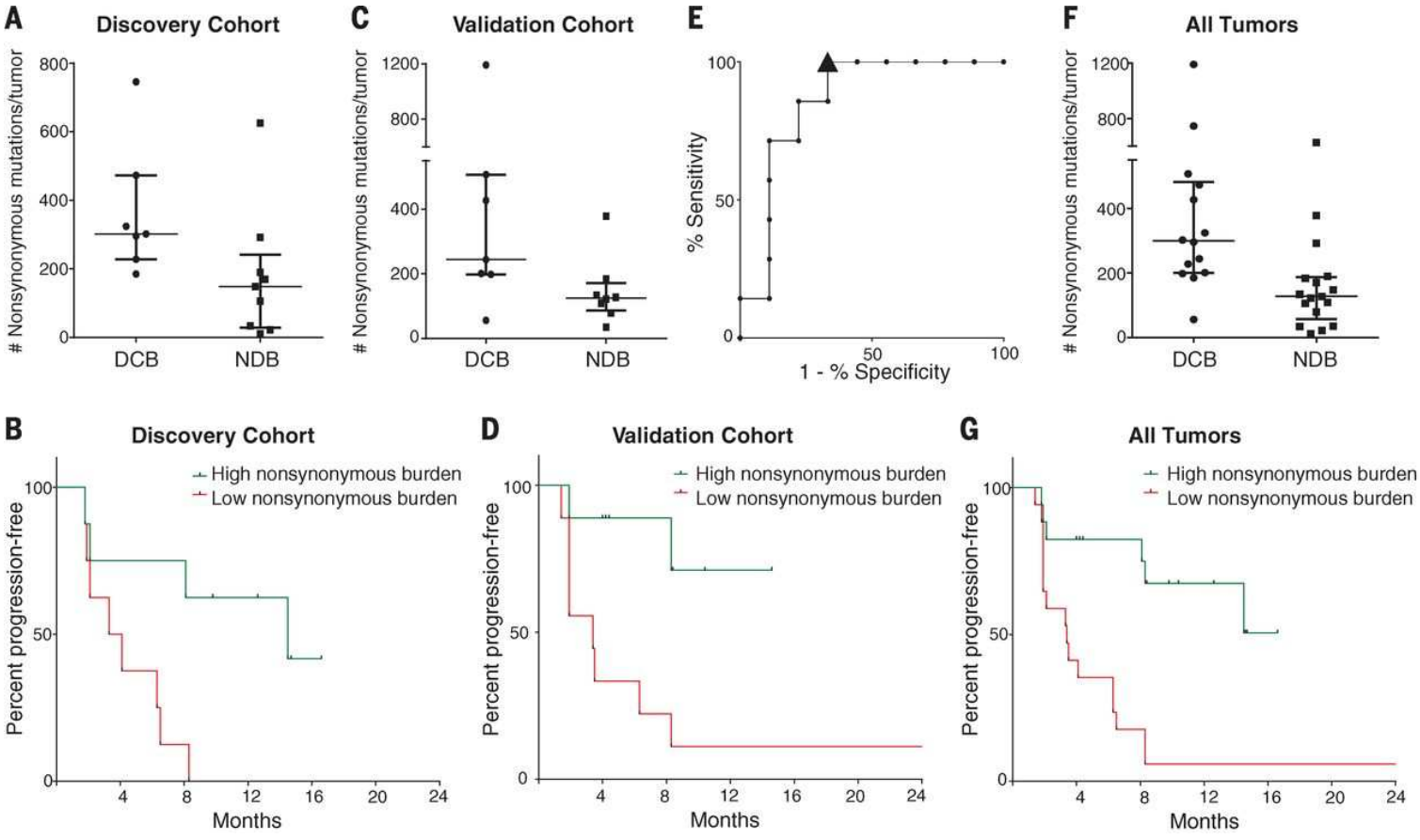


Whole exome sequencing

Flow ICS

Snyder A et al. N Engl J Med 2014;371:2189-2199.

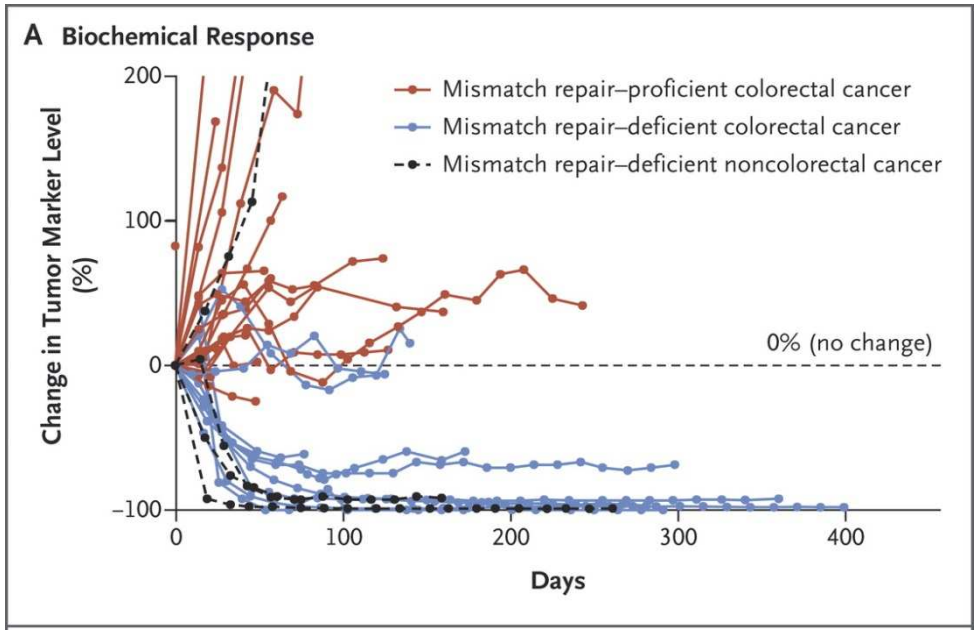
Nonsynonymous mutation burden associated with clinical benefit of anti–PD-1 therapy (NSCLC).

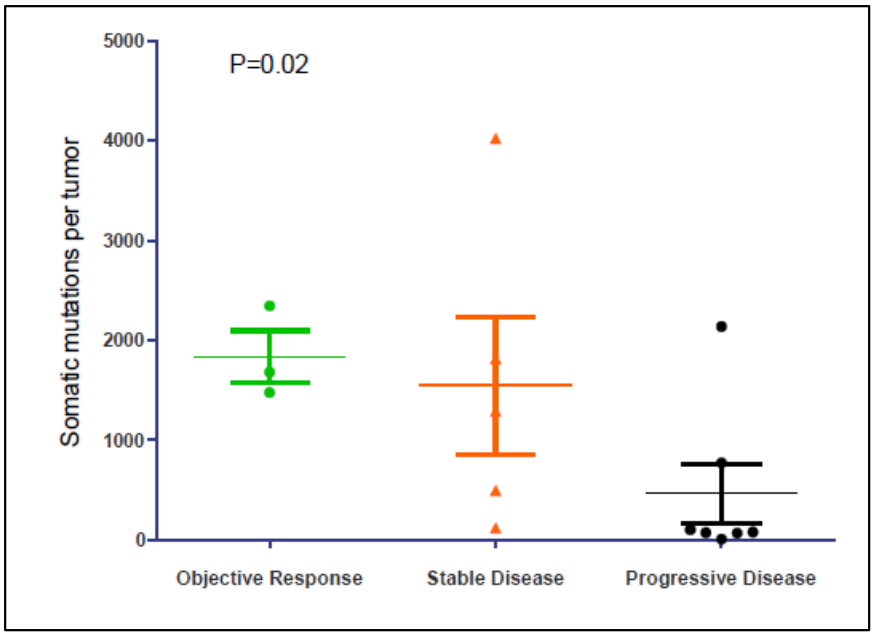


Whole exome sequencing

Rizvi NA et al. Science 2015;348:124-128

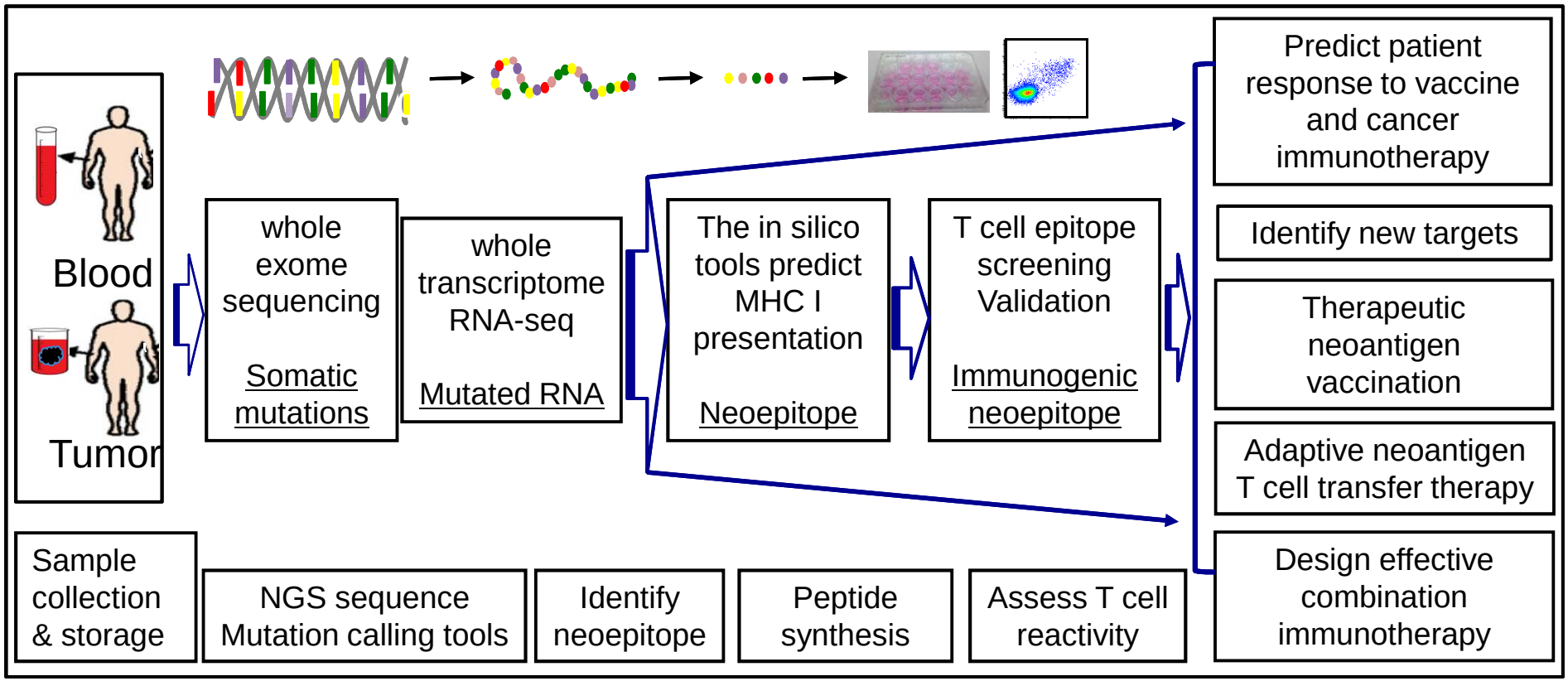
PD-1 blockade in tumors with mismatch-repair deficiency





Le DT et al. N Engl J Med 2015;372:2509-2520.

Current potential pipelines of whole exome sequencing for neoantigen discovery and precision oncology



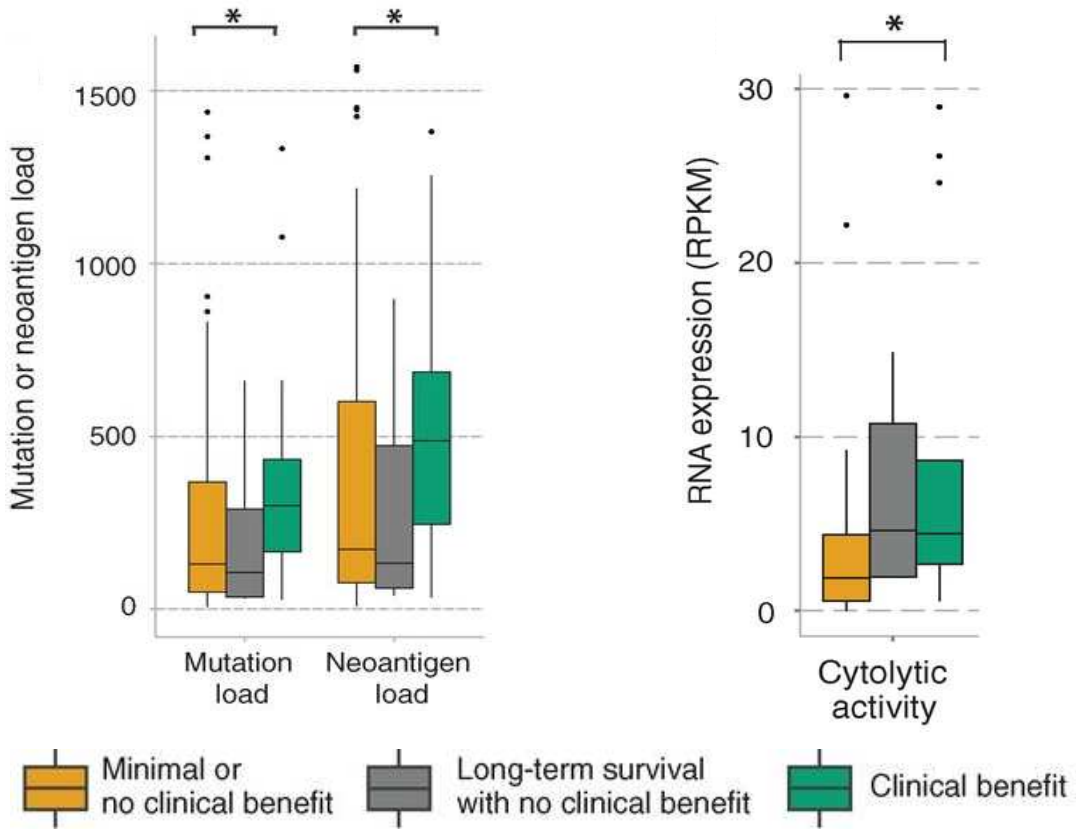
Kvistborg P et al JITC 2016 in press

Outline

- Several unique features of cancer immunotherapy and the roles of translational Immuno-Oncology research in cancer immunotherapy
- Whole exome sequencing for neoantigen discovery and precision oncology

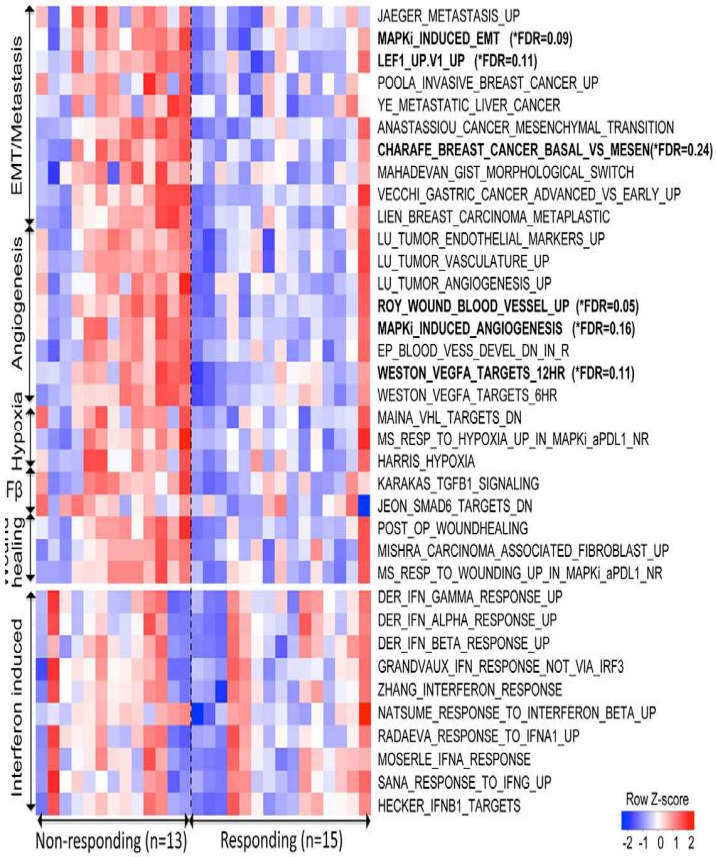
  "Mutation load as a potential biomarker"
- Strategies for translational immuno-oncology research to meet the need of personalized combination cancer immunotherapy

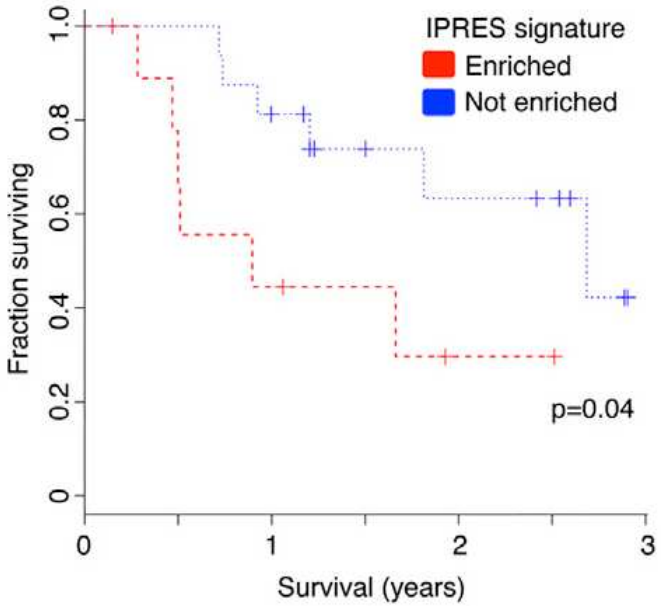
Overall mutational load and cytolytic immune microenvironment correlate response to ipilimumab.



Eliezer M. Van Allen et al. Science 2015;350:207-211

Transcriptomic signatures of innate resistance to anti-PD-1 therapy

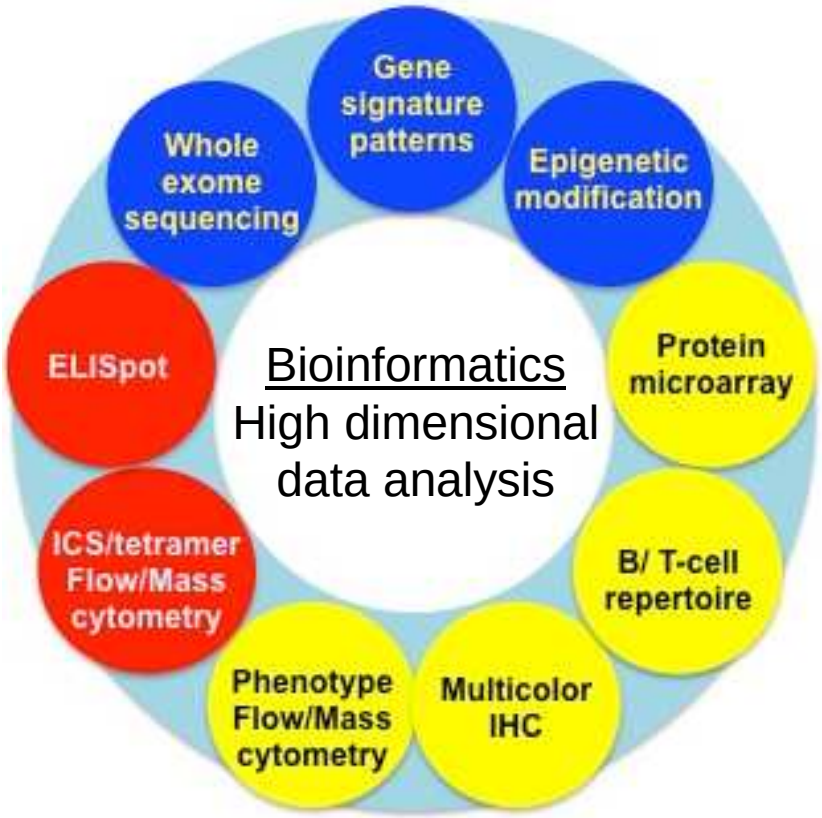


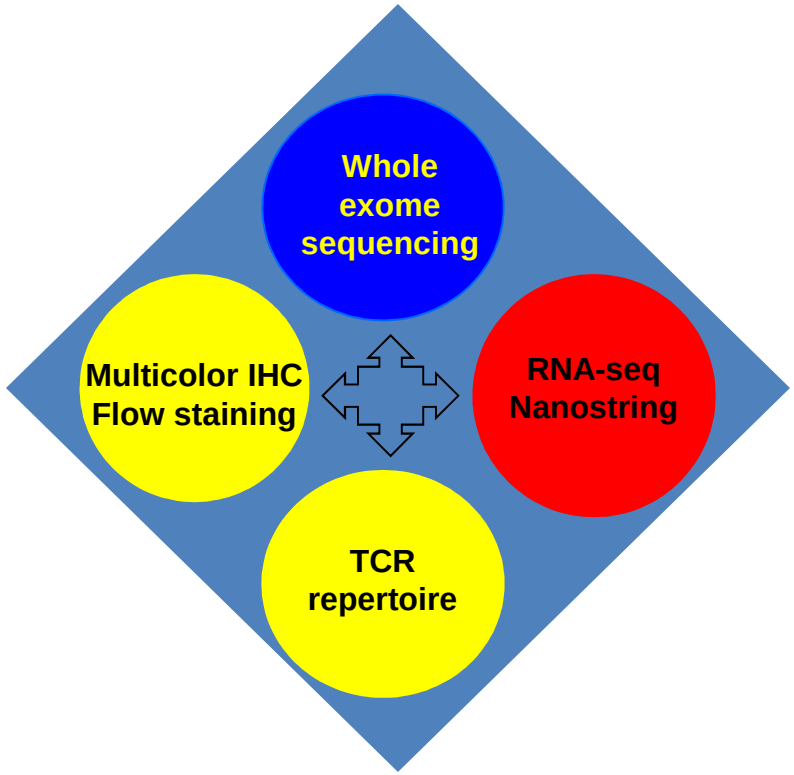


IPRES Innate anti-PD-1 resistance
A transcriptional signature

Hugo W et al. Cell 2016;165:35-44

Recommendations and strategies for translational Immuno-Oncology research

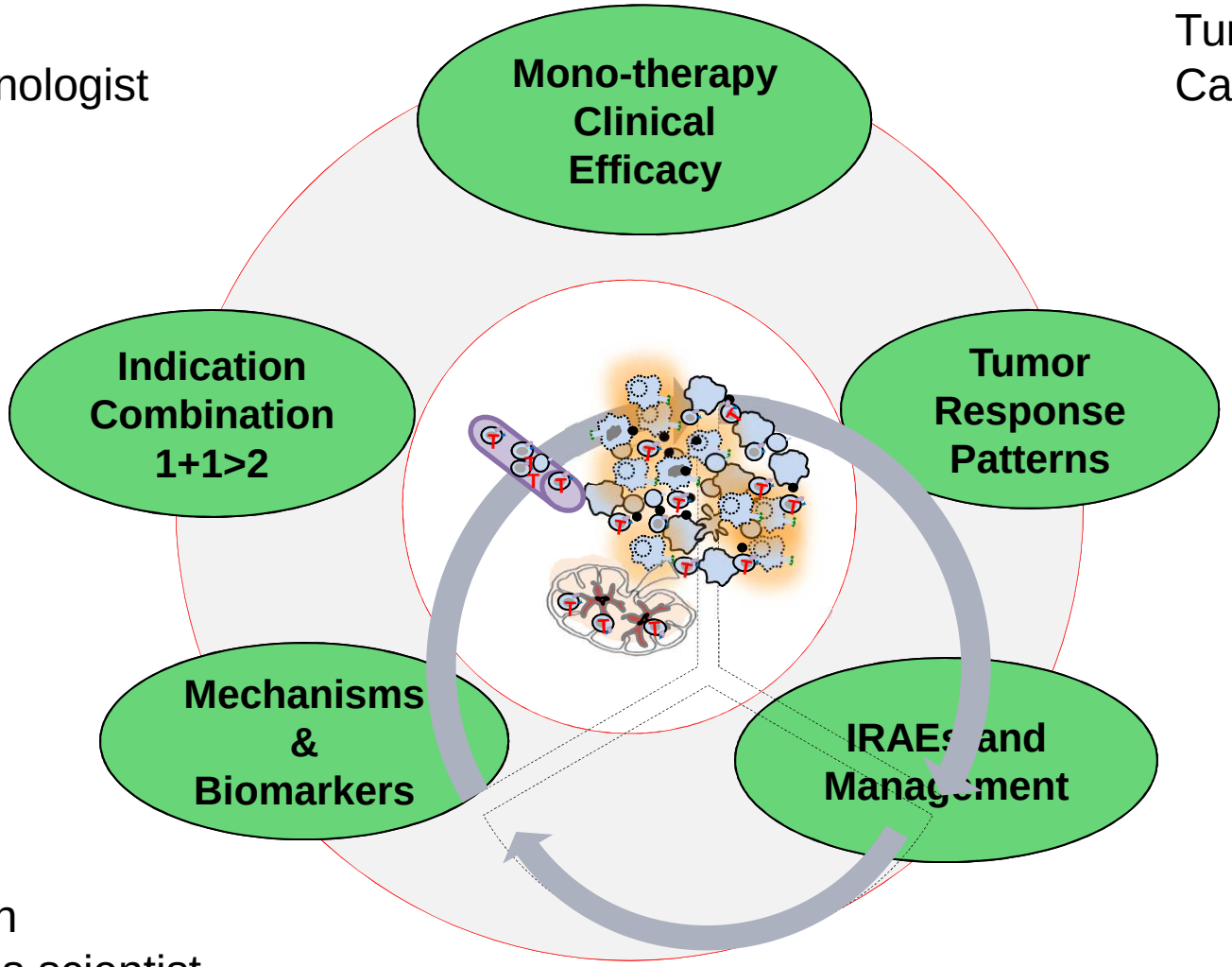




Conclusions: From immune checkpoint blockade monotherapy to combination therapy

Immunology
Tumor immunologist

Tumor/Oncology
Cancer biologist



Biostatistician
Bioinformatics scientist

Physician

"Drug" → "Personalized" → "Tumoralized"

Acknowledgment

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Jedd D Wolchok
Alan N Houghton
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Valdimir Makarov
Taha Merghoub
Jonathan Havel
David Page
Teresa S Ho
Phillip Wong

Our patients

SITC Biomarker Task WG2

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Engage . . . Collaborate . . . Learn

sitc
Society for Immunotherapy of Cancer