Enabling precision immuno-oncology

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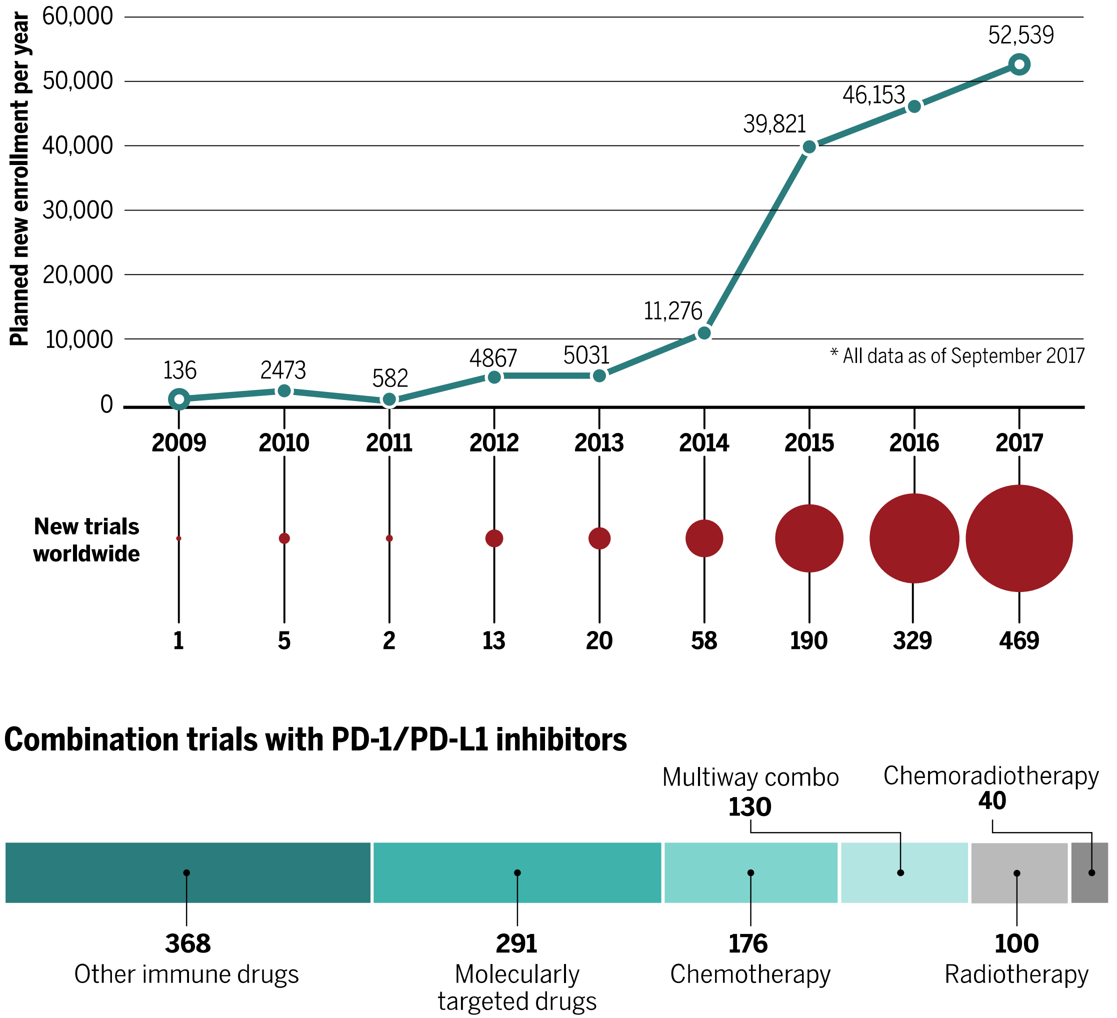
The promise of immuno-oncology



December 2017: 3042 trials

Kaiser J. *Science* 2018; 359:1346-1347

Major issues in cancer immunotherapy

- Identify mechanisms of intrinsic resistance to checkpoint blockade
  - Predictive biomarkers for response (genetic, immunological, metabolic, microbiome)

- Identify mechanisms of acquired resistance to checkpoint blockade
  - Predictive biomarkers for relapse?

- Identify combination therapies with synergistic potential
  - PD-1/PD-L1 and targeted agents (or other drugs)

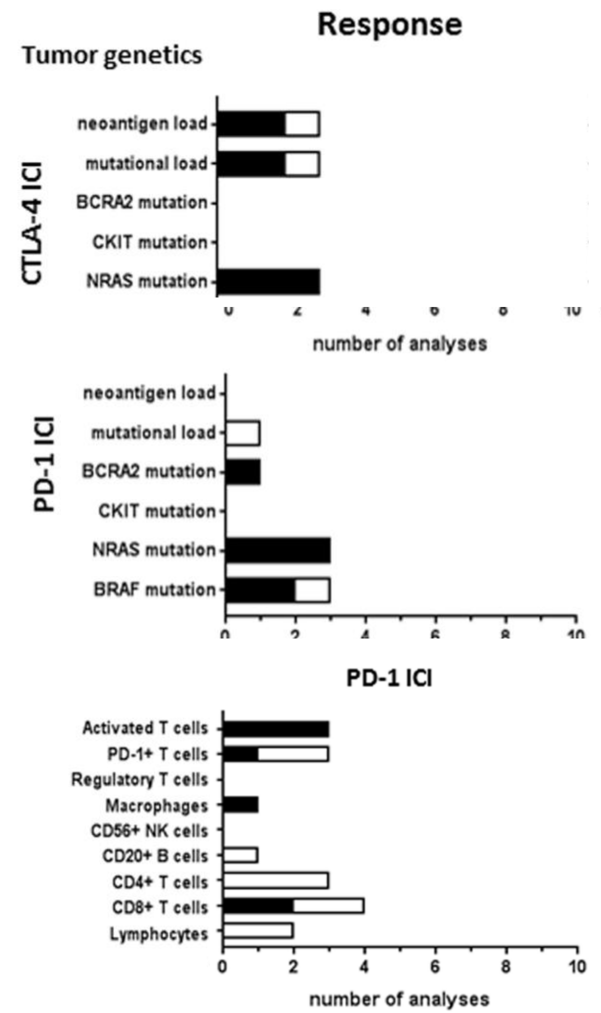
For every complex problem, there Is
an answer that is clear, simple, and wrong

H.L. Mencken

Predictive markers for immunotherapy in melanoma

Implication of potential biomarkers in response to immunotherapy.

Biomarker	Checkpoint(s)/Therapies	Effect on response
Molecular		
NRAS mutations	CTLA-4, PD-1	Positive
NF1 mutations	PD-1	Positive
CD8 + T cells at tumor margin	PD-1	Positive
DC infiltration	T cell transfer therapy	Positive
PD-1 expression	PD-1	Positive
CTLA-4 expression	CTLA-4	Positive
PD-L1 expression	CTLA-4, PD-1, PD-L1	Positive
WNT/β-catenin activation	CTLA-4, PD-L1	Negative
PTEN loss	PD-1	Negative
Mutational burden/ neoantigens	CTLA-4, PD-1, PD-L1	Positive
SERPIN family mutations	CTLA-4	Positive
IPRES transcriptional signature	PD-1	Negative
GNAQ/GNA11 mutations	CTLA-4, PD-1	Negative
MHC I/II expression	PD-1, PD-L1	Positive
JAK1/2 loss	PD-1	Negative
Clonal TCR repertoire	PD-1	Positive
Cytotoxic response	CTLA-4	Positive
IFN-γ response	CTLA-4, PD-L1	Positive
Peripheral Blood		
Elevated LDH	CTLA-4, PD-1	Negative
Low MDSCs	CTLA-4	Positive
Angiopoietin-2	CTLA-4	Negative
sPD-L1	CTLA-4, PD-1	Mixed
Circulating tumor DNA	PD-1	Negative
Clinical		
irAEs	CTLA-4, PD-1, PD-L1	Positive
Prior treatment	PD-1	Negative
Visceral involvement/tumor bulk	PD-1	Negative
Bifidobacterium in microbiome	PD-1	Positive
Uveal subtype	PD-1, PD-L1	Negative



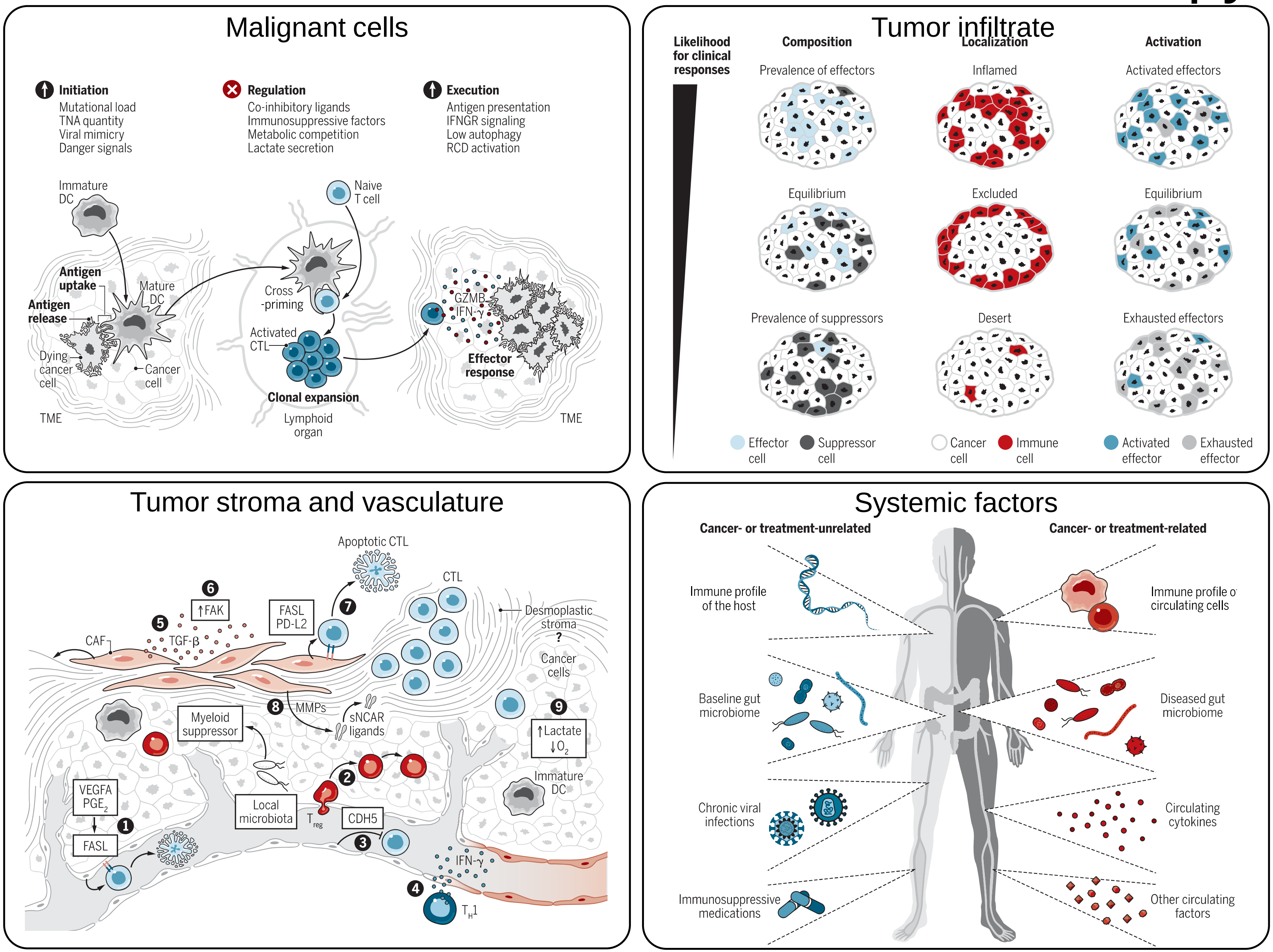
Axelrod *et al. Semin Cancer Biol*, 2017, S1044-579X(17)30121-9

Jessurun *et al. Front Oncol*, 2017, 7:233

Predictive markers for immunotherapy with anti-PD-1 antibodies in melanoma

Publication	Marker(s)	Cohort size /p Value
Johnson DB *et al*., *Cancer Immunol Res* 2016, 4:959-967	Mutational load	n=32/33; p=0.003/0.002
Hugo *et al*., *Cell* 2016, 165:35-44	IPRES signature	n=28; p=0.04
Johnson DB *et al*., *Nat Commun* 2016, 7:10582	HLA-DR	n=30/23; p=0.055/0.046
Diem *et al*. *Br J Cancer* 2016, 114:256-261	LDH	n=29; p<0.001 (ANOVA)
Charoentong *et al*., *Cell Rep* 2017, 18:248-262	162 immune genes	n=28; p=0.025
Ayers *et al*., *J Clin Invest* 2017, 127:2930-2939	28 immune genes	n=62; p=0.027

The hallmarks of successful immunotherapy

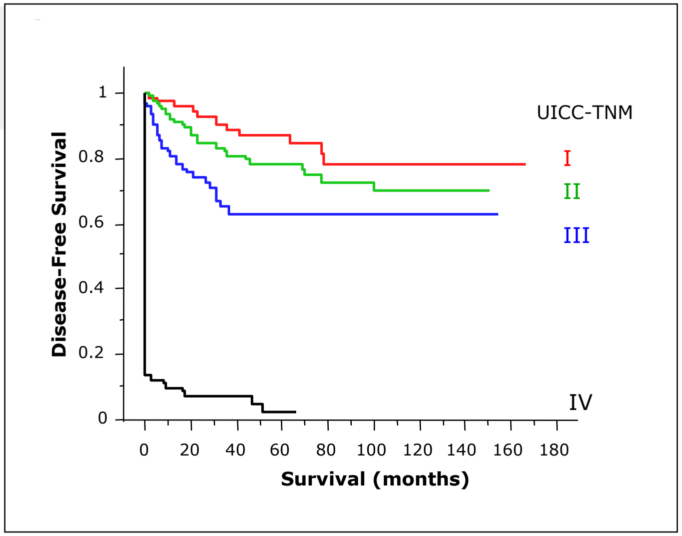


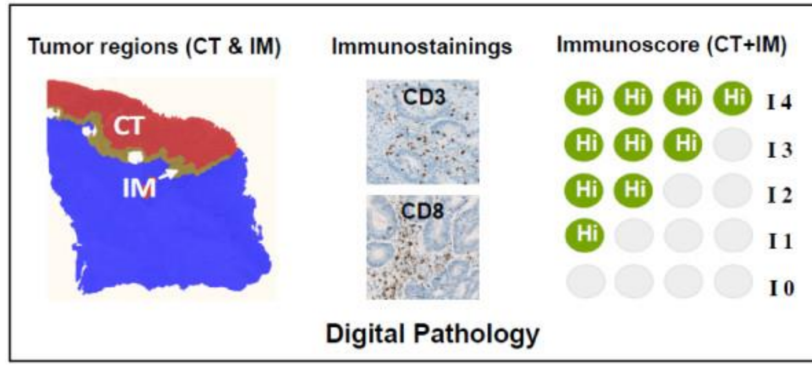
Galluzzi *et al. Sci Transl Med*, 2018, 10:eaat7807

Immunoscore: prognostic biomarker for tumor recurrence in colorectal cancer

Tumor histopathology

UICC-TNM
Staging system



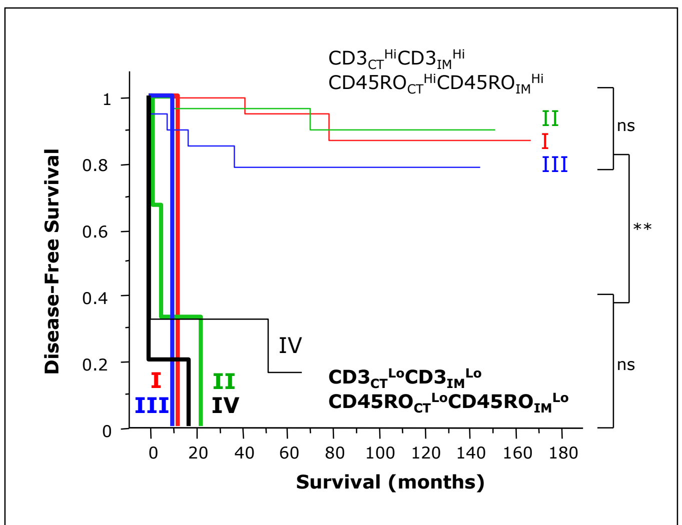


Mlecnik *et al. J Clin Oncol* 2011, 29:610-618

$CD3_{CT}$ $CD3_{IM}$
evaluation

plus

$CD45RO_{CT}$ $CD45RO_{IM}$
evaluation



International validation of the consensus Immunoscore for the classification of colon cancer: a prognostic and accuracy study

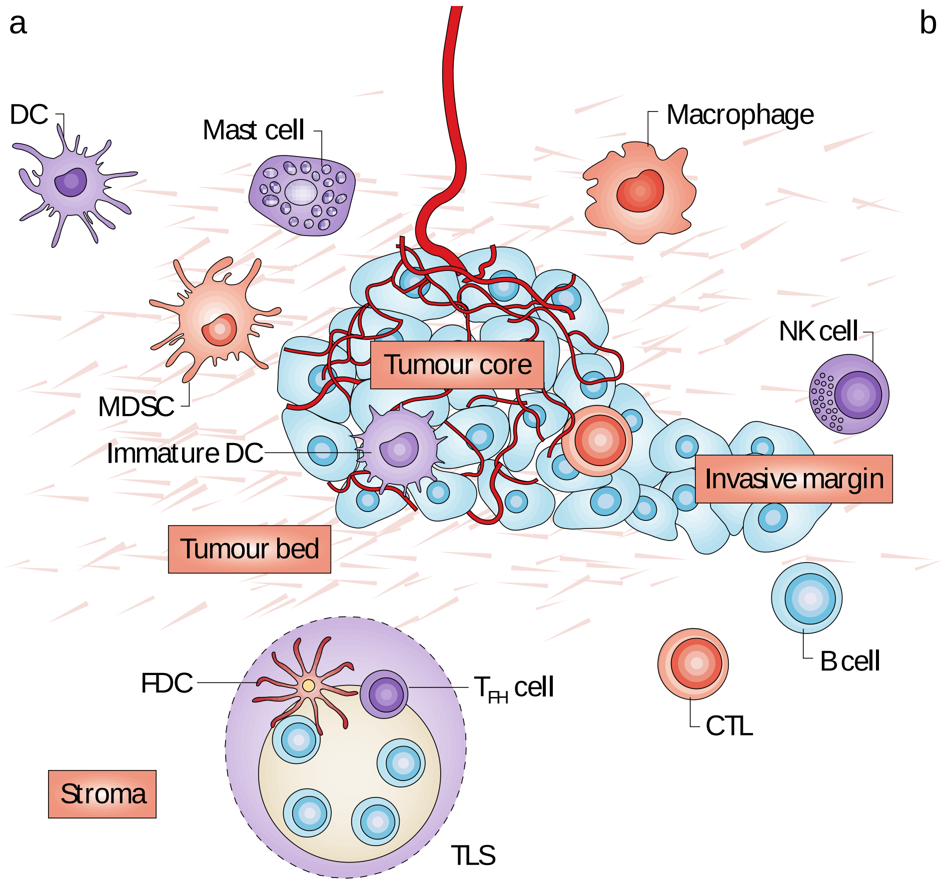
Franck Pagès, Bernhard Mlecnik, Florence Marliot, Gabriela Bindea, Fang-Shu Ou, Carlo Bifulco, Alessandro Lugli, Inti Zlobec, Tilman T Rau, Martin D Berger, Iris D Nagtegaal, Elisa Vink-Börger, Arndt Hartmann, Carol Geppert, Julie Kolwelter, Susanne Merkel, Robert Grützmann, Marc Van den Eynde, Anne Jouret-Mourin, Alex Kartheuser, Daniel Léonard, Christophe Remue, Julia Y Wang, Prashant Bavi, Michael H A Roehrl, Pamela S Ohashi, Linh T Nguyen, SeongJun Han, Heather L MacGregor, Sara Hafezi-Bakhtiari, Bradly G Wouters, Giuseppe V Masucci, Emilia K Andersson, Eva Zavadova, Michal Vocka, Jan Spacek, Lubos Petruzelka, Bohuslav Konopasek, Pavel Dundr, Helena Skalova, Kristyna Nemejcova, Gerardo Botti, Fabiana Tatangelo, Paolo Delrio, Gennaro Ciliberto, Michele Maio, Luigi Laghi, Fabio Grizzi, Tessa Fredriksen, Bénédicte Buttard, Mihaela Angelova, Angela Vasaturo, Pauline Maby, Sarah E Church, Helen K Angell, Lucie Lafontaine, Daniela Bruni, Carine El Sissy, Nacilla Haicheur, Amos Kirilovsky, Anne Berger, Christine Lagorce, Jeffrey P Meyers, Christopher Paustian, Zipei Feng, Carmen Ballesteros-Merino, Jeroen Dijkstra, Carlijn van de Water, Shannon van Lent-van Vliet, Nikki Knijn, Ana-Maria Mușină, Dragos-Viorel Scripcariu, Boryana Popivanova, Mingli Xu, Tomonobu Fujita, Shoichi Hazama, Nobuaki Suzuki, Hiroaki Nagano, Kiyotaka Okuno, Toshihiko Torigoe, Noriyuki Sato, Tomohisa Furuhata, Ichiro Takemasa, Kyogo Itoh, Prabhu S Patel, Hemangini H Vora, Birva Shah, Jayendrakumar B Patel, Kruti N Rajvik, Shashank J Pandya, Shilin N Shukla, Yili Wang, Guanjun Zhang, Yutaka Kawakami, Francesco M Marincola, Paolo A Ascierto, Daniel J Sargent, Bernard A Fox, Jérôme Galon*

Lancet **2018; 391: 2128–39**

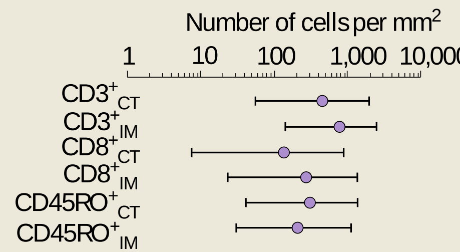
Galon *et al. Science*, 2006, 313:1960-1964

Immune contexture

a



b

Immune contexture	Parameters: positive association with survival
Type	CTLs ($CD3^+CD8^+$)
	Memory T cells ($CD45RO^+$)
Location	Core of the tumour
	Invasive margin
Density	
Functional orientation	T_H1 cell-associated factors (IFNγ, IL-12, T-bet and IRF1)
	Cytotoxic factors (granzymes, perforin and granulysin)
	Chemokines (CX3CL1, CXCL9, CXCL10, CCL5 and CCL2)
	T_H17 cells, T_{Reg} cells and T_H2 cells have a variable [illegible]
TLS	Presence and quality

Fridman et al. *Nat Rev Cancer* 2012, 15:298-306

Additional obstacles

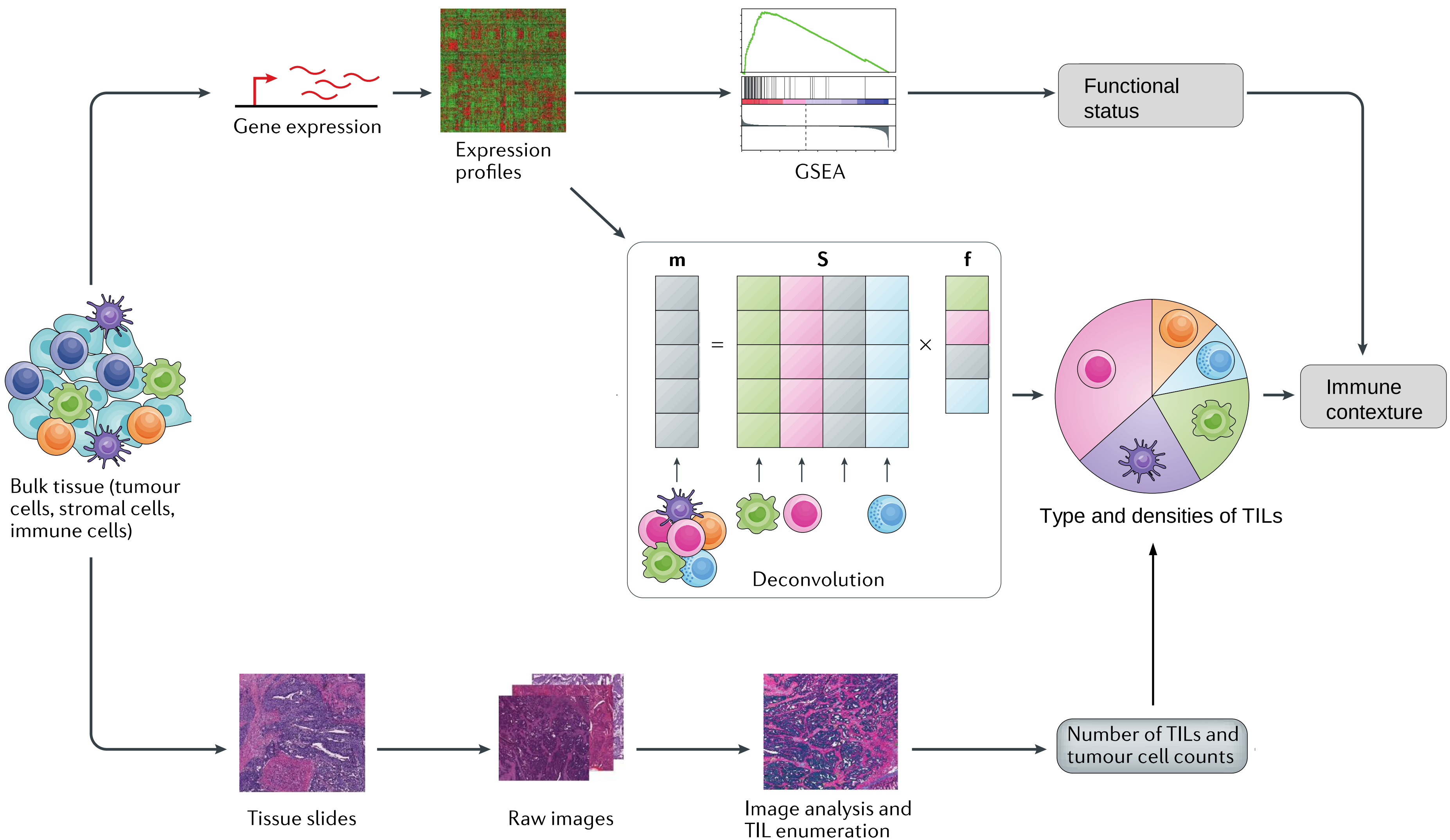
1. Epigenetic, genetic and immunologic heterogeneity; tumor evolution
   - Multi-region sampling
   - Multiple time points sampling

2. Cancer-cell extrinsic factors
   - Metabolism
   - Cellular senescence

3. Interactions between other treatment forms and immunotherapy
   - Chemotherapy, radiotherapy
   - Targeted therapy

4. Missing techniques to assay the entire complexity of TME
   - RNA-seq
   - Immunohistochemistry

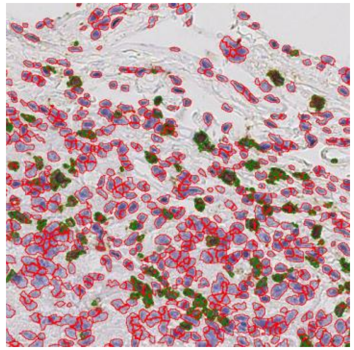
Quantifying immune contexture using NGS and imaging data

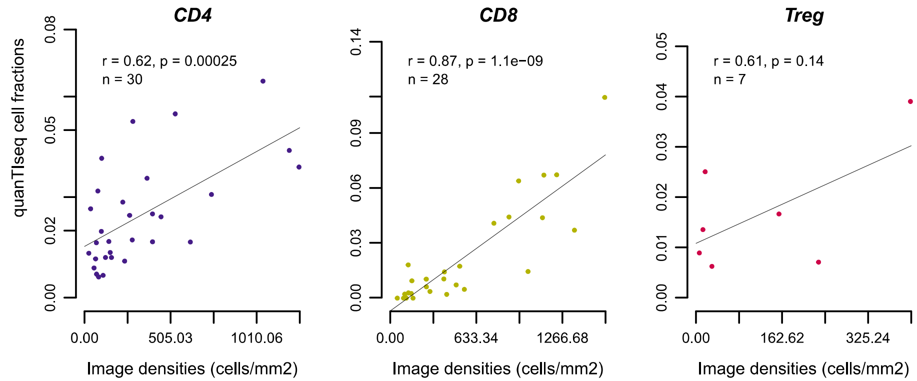


Hackl H *et al*. *Nature Rev Genetics* 2016; 17: 441-458

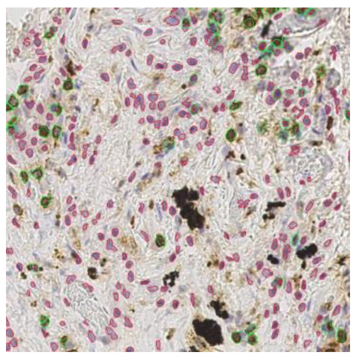
quanTIseq validation

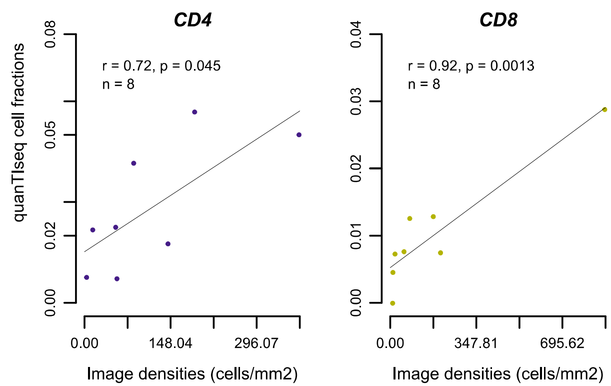
Melanoma
n=30
J. Balko
Vanderbilt University



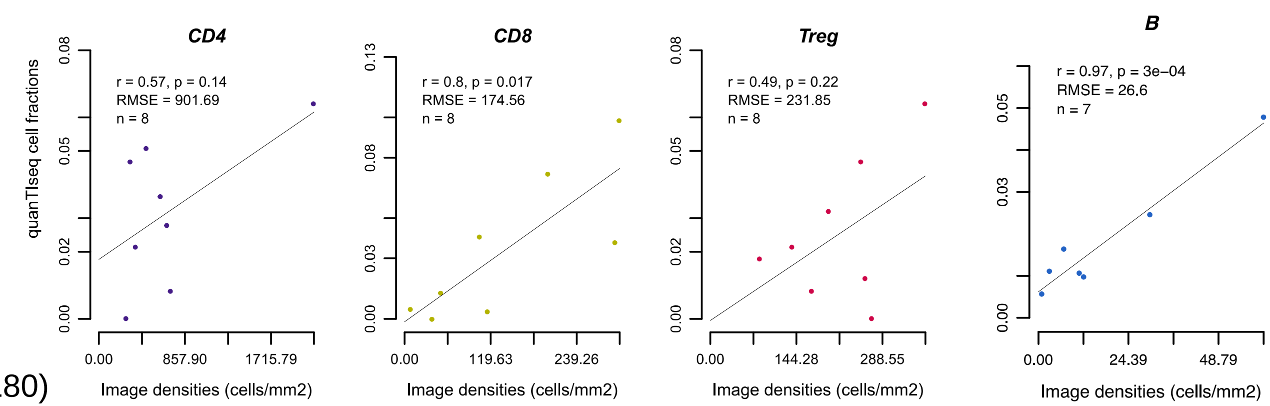


Lung cancer
n=8
J. Balko
Vanderbilt University



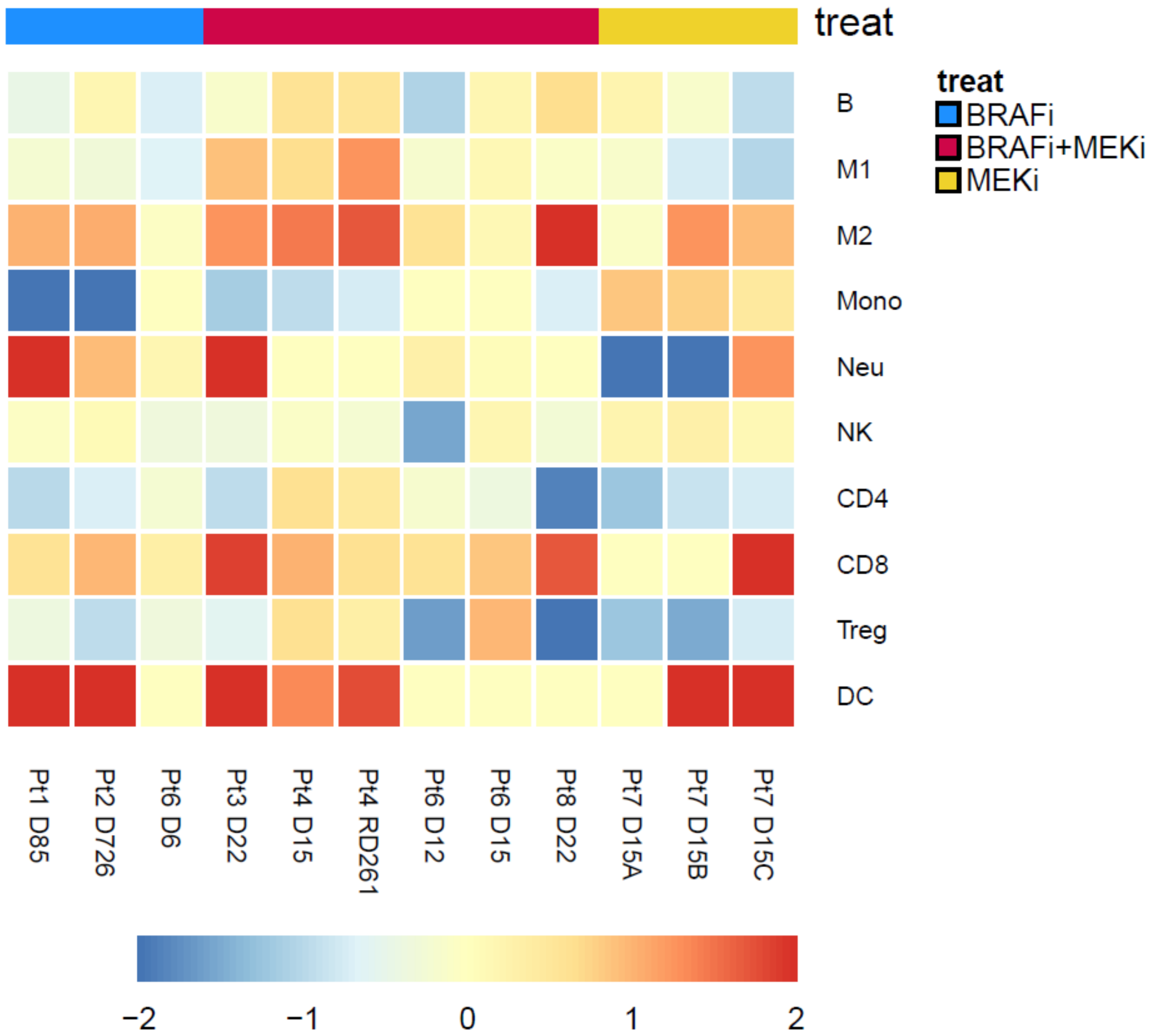


CRC
n=8
N. de Miranda
Leiden University



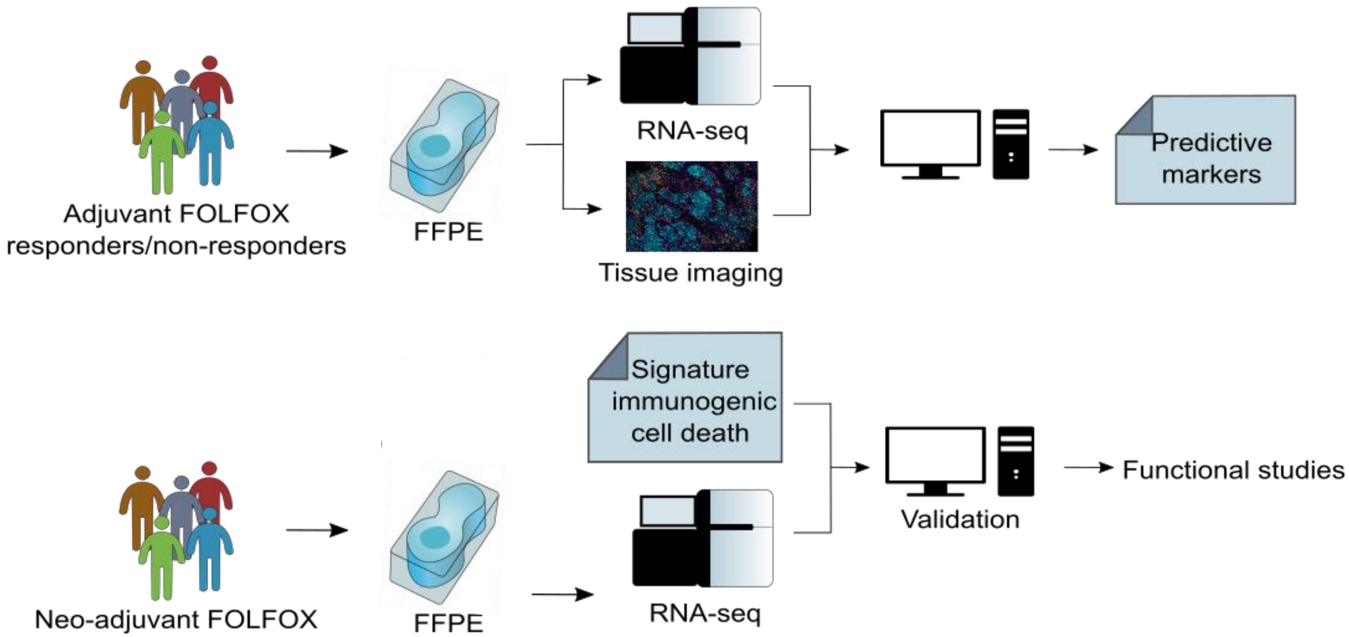
Finotello *et al*., (bioRxiv 223180)

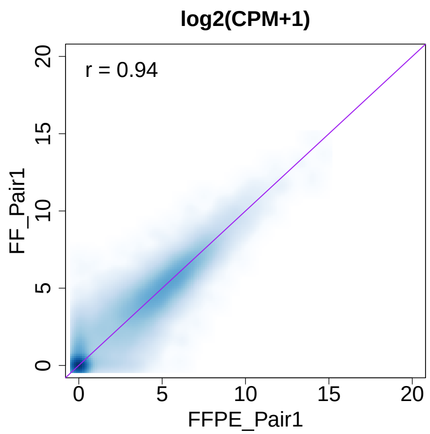
Immunogenic effects of BRAFi/MEKi in melanoma



Finotello *et al*., (bioRxiv 223180); Data from Song *et al*., *Cancer Discovery* 2017, 7:1248-1265

Immunogenic effects of chemotherapy





Collaboration with H. Fiegl, C. Marth
Medical University Innsbruck

A. Krogsdam, F. Finotello (unpublished)

Major issues in cancer immunotherapy

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  - Predictive biomarkers for response (genetic, immunological, metabolic, microbiome)

- Identify mechanisms of acquired resistance to checkpoint blockade
  - Predictive biomarkers for relapse?

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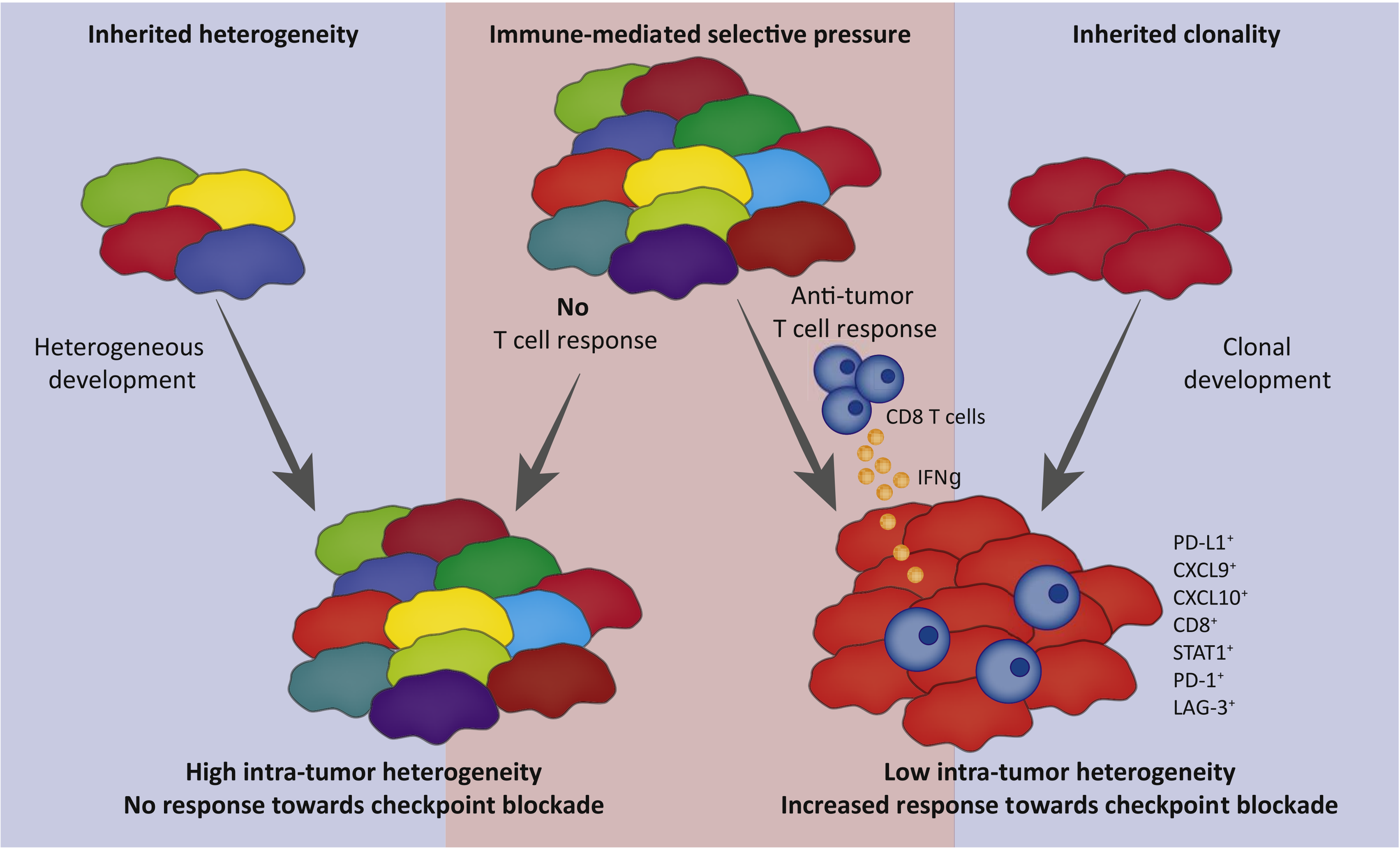
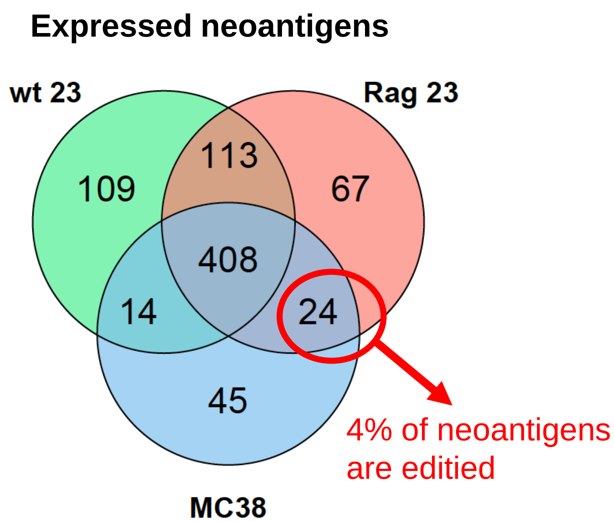
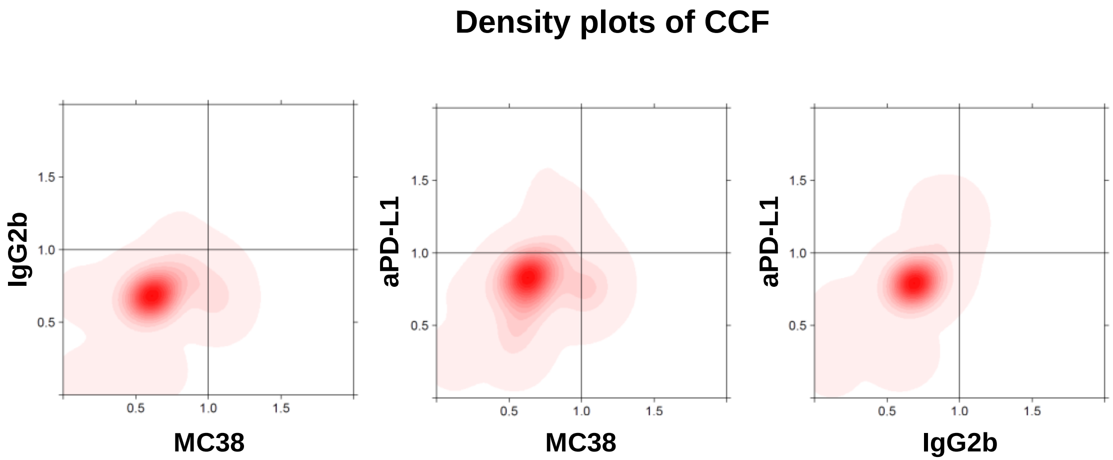
Immunoediting and tumor heterogeneity

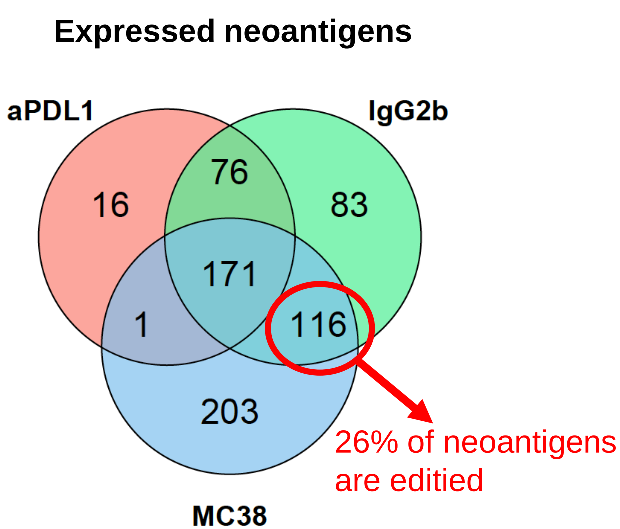


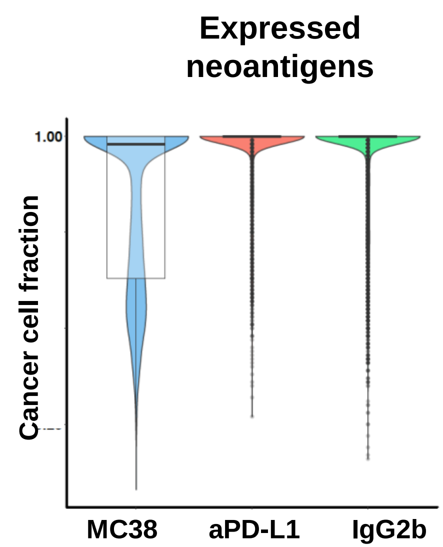
Spranger S *et al.*, *Trends in Immunology* 2016, 37: 349-351

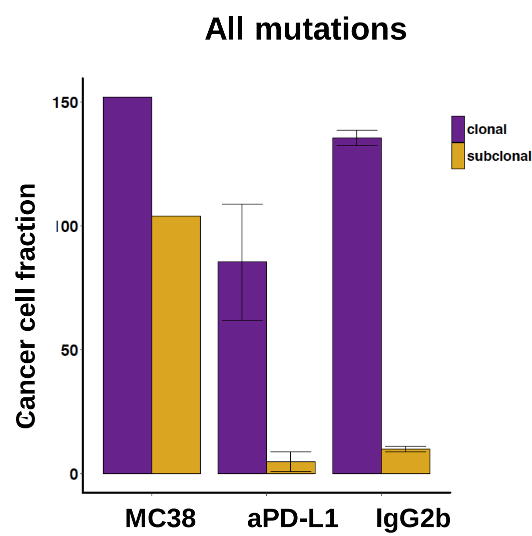
Targeting the PD-1/PD-L1 pathway broadens the T cell repertoire and renders the tumors more homogeneous





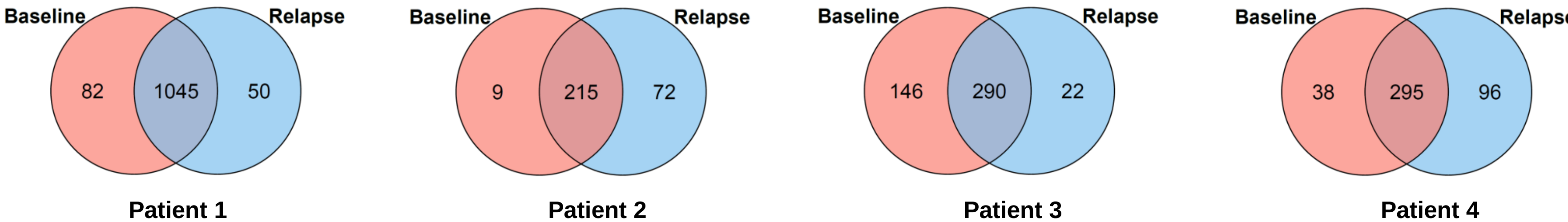


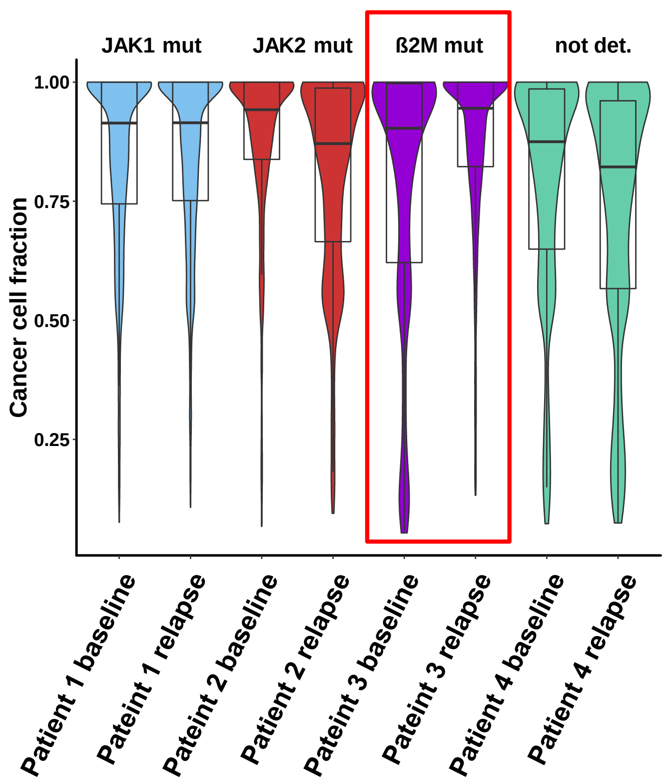


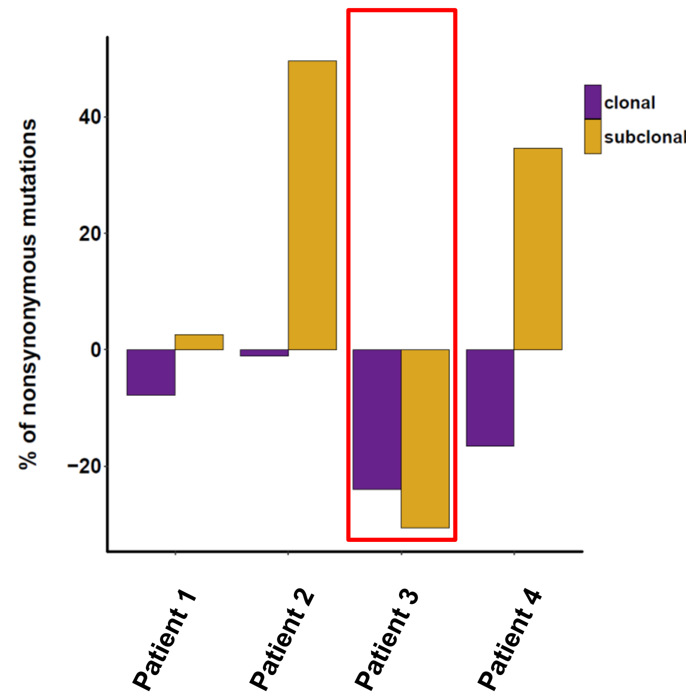


Efremova *et al*., *Nat Commun*, 9:32, 2018

Acquired resistance to PD-1 blockade in melanoma

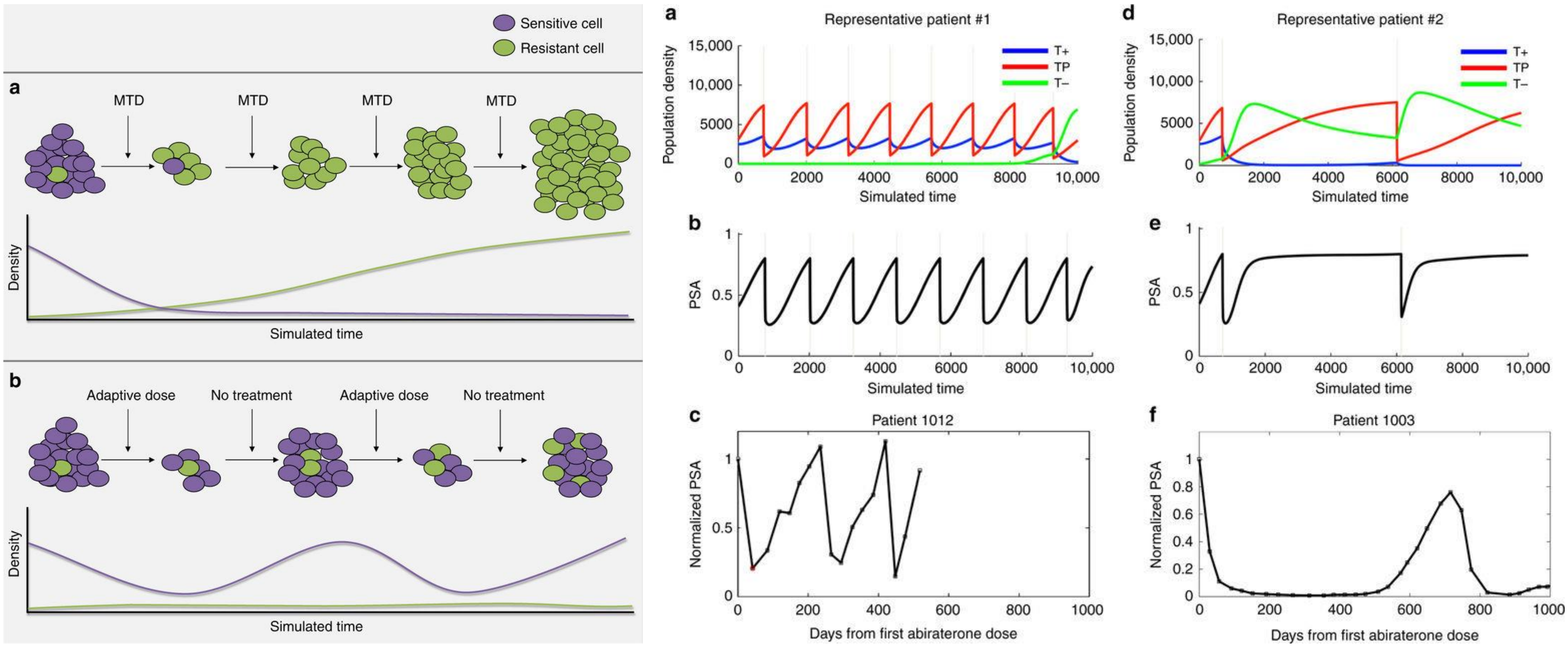






Efremova *et al*., *Nat Commun*, 9:32, 2018, Data from Zaretsky et al., *New Engl J Med* 2016; 375:819-829

Adaptive therapy in metastatic prostate cancer using patient-specific evolutionary dynamics



Development of treatment algorithms for cancer immunotherapy:

- Monitoring tumor evolution (liquid biopsies, radiomics, TCR repertoire)
- Evolutionary dynamic models of immunoediting

Zhang *et al*., *Nat Commun* 2017, 8:1816

Major issues in cancer immunotherapy

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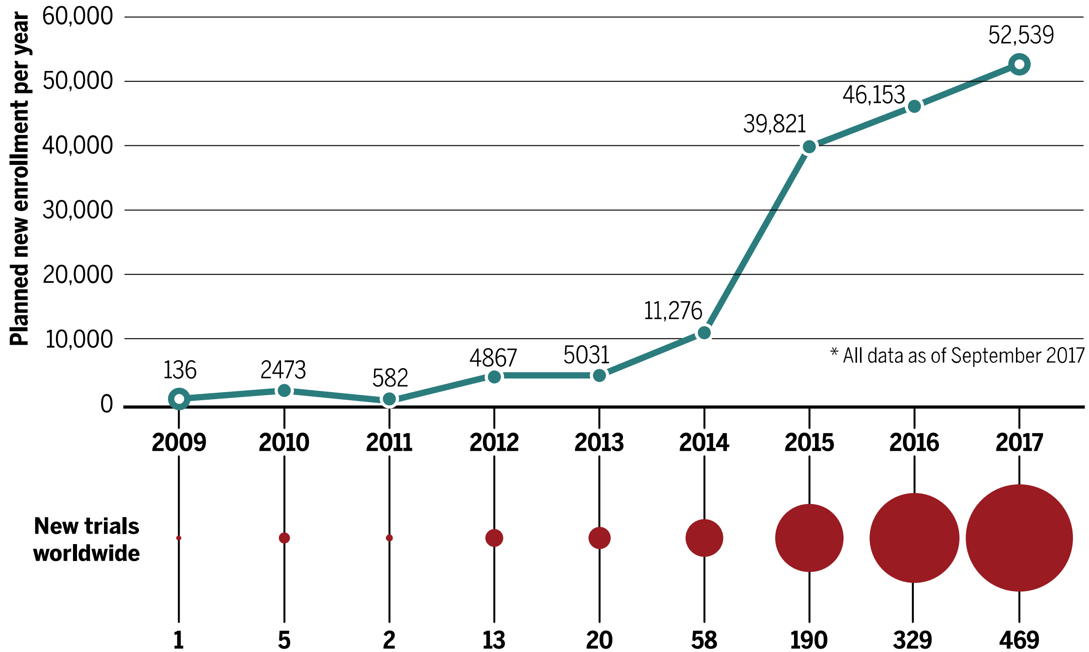
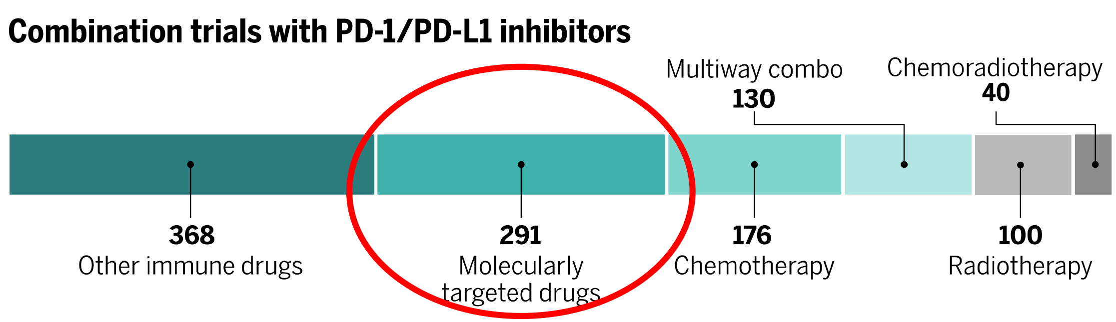
Cancer immunotherapy





December 2017: 3042 trials

Kaiser J. *Science* 2018; 359:1346-1347

Enabling precision immuno-oncology?

- Mutational and neoantigen landscapes are highly individual
  - Colorectal cancer (Angelova *et al*., *Genome Biology*, 2015, 16:64)
  - Solid cancers (Charoentong *et al*., *Cell Rep,* 2017, 18:248-262)

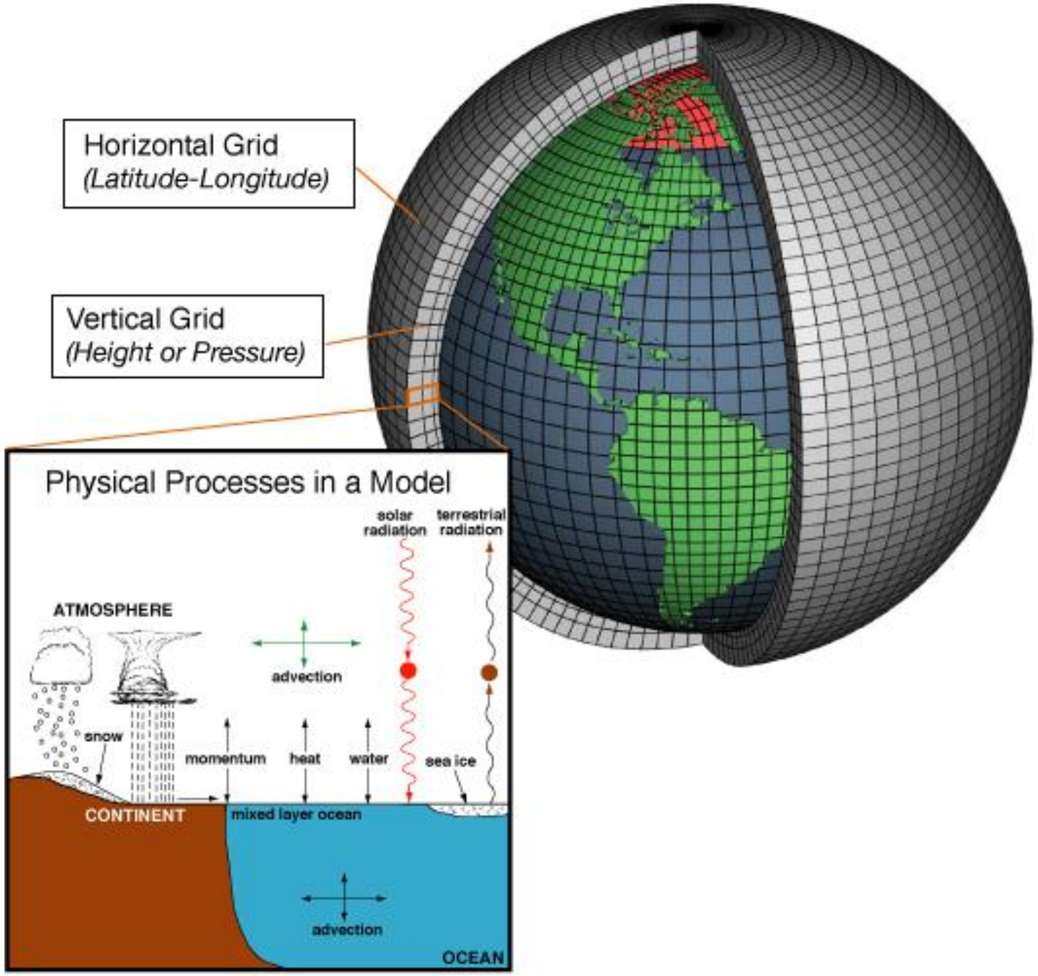
- Oncogenic signaling is cell context-specific
  - BRAF mutant CRC is resistant to BRAF inhibitors (Prahalad *et al*., *Nature* 2012, 483:100-103)

- Tumor evolution and immune responses are dynamic and interwoven systems
  - In general molecular data only from single time points is available

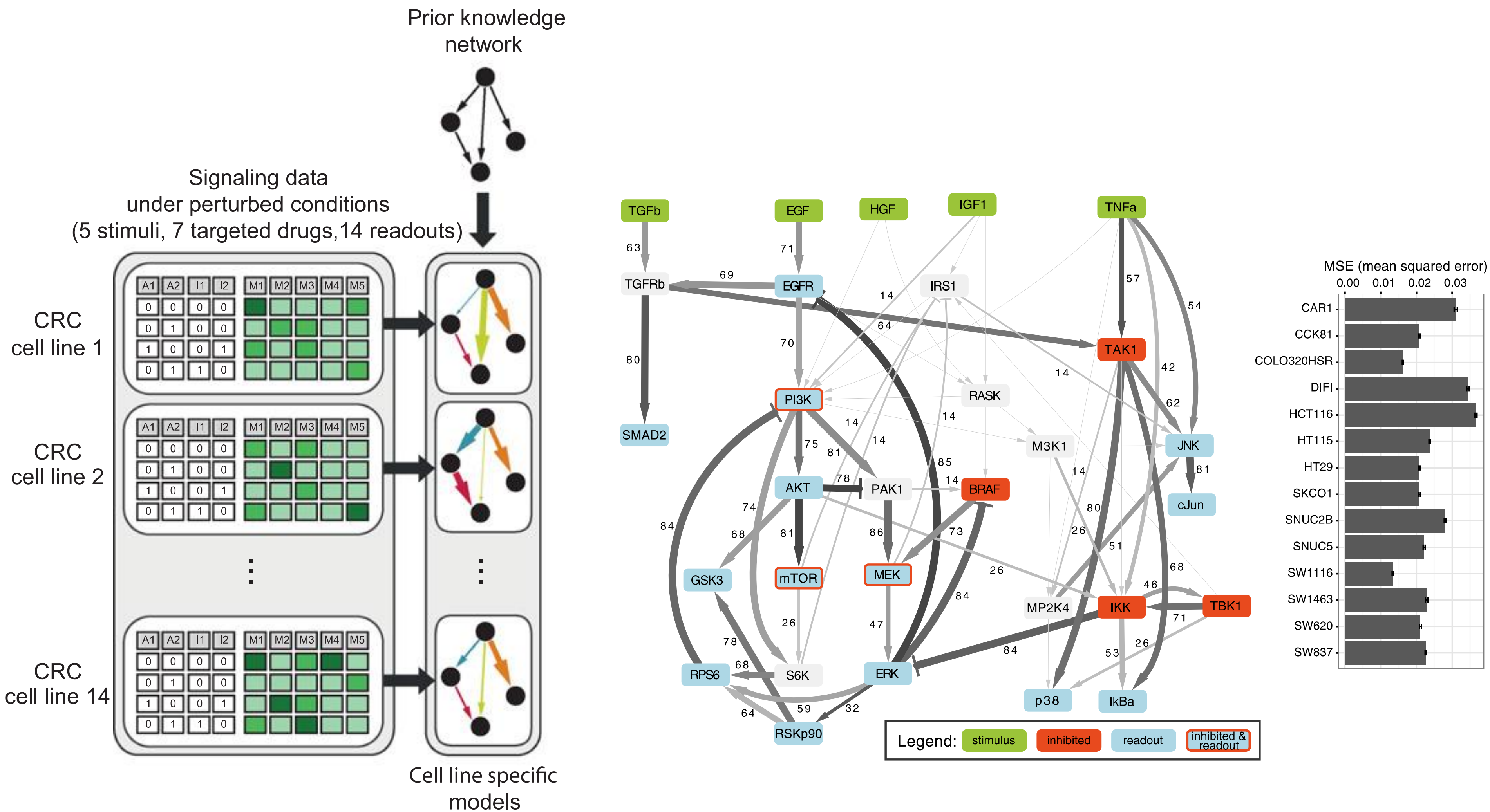
- Mouse models are not suitable for testing precision immuno-oncology
  - Patient-derived xenografts (PDX) mouse models are immunocompromised
  - Current humanized mouse models cannot mimic the entiry complexity of the tumor microenvironment

Prediction of dynamic systems

Weather forecasting

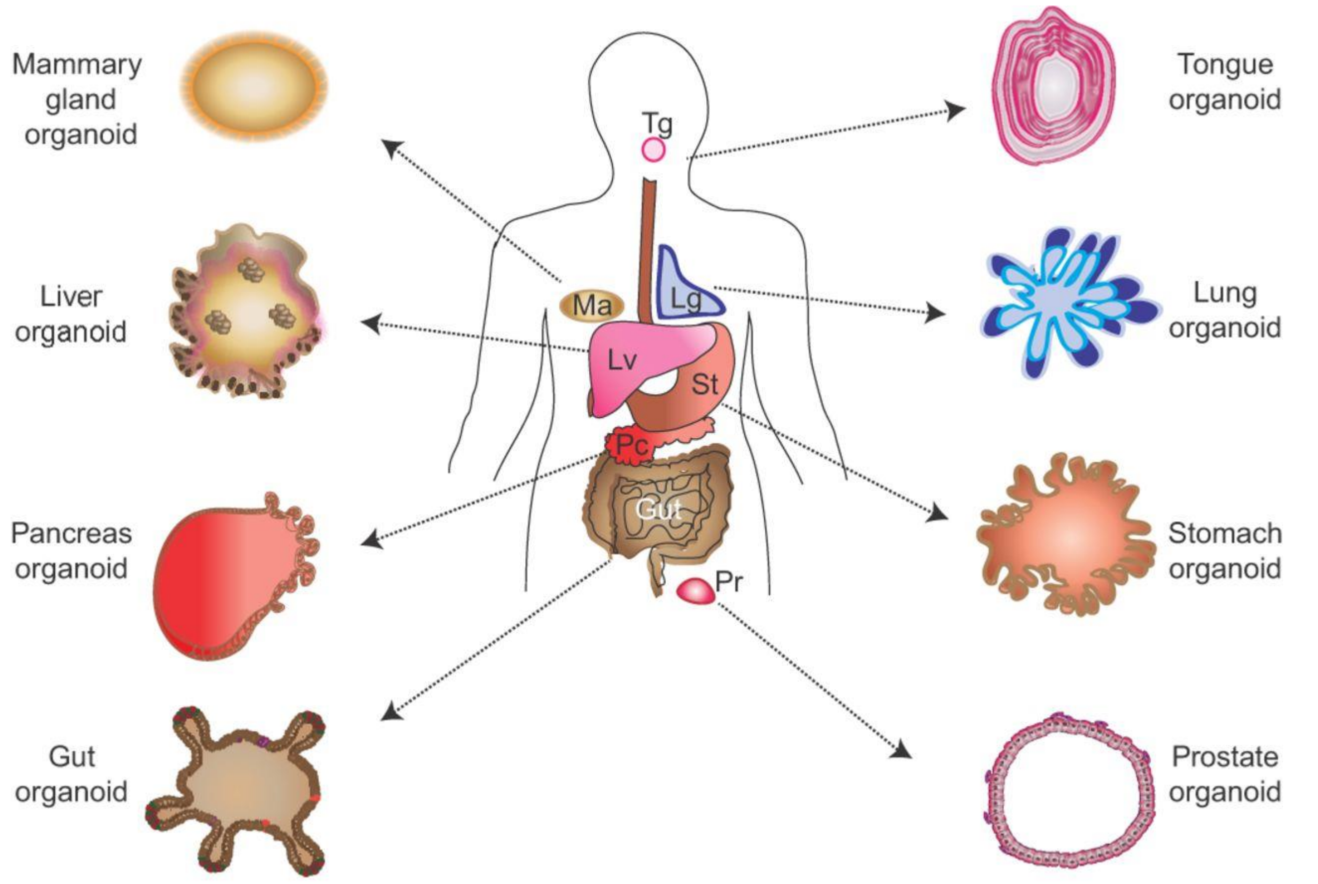


Perturbation biology



Eduati *et al*. *Cancer Res* 2017, 77:3364-3375

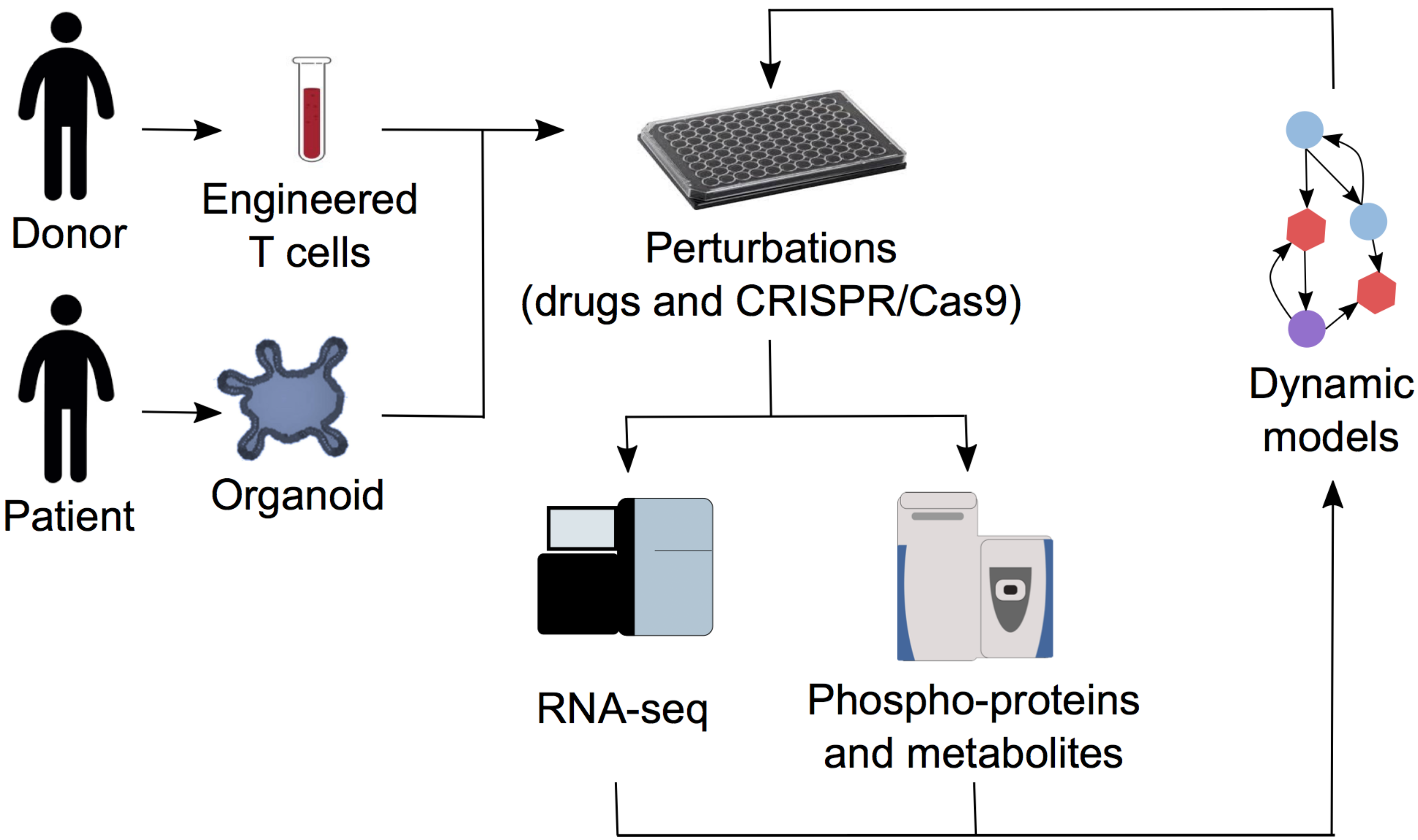
In vitro models: Organoids



Huch M, Koo B-K, *Development* 2015; 142:3113-3125
Clevers H. *Cell*, 2016; 165:1586-1597

Hybrid avatars using *in vitro* and *in silico* models

Perturbation biology to derive mechanistic rationale



Hybrid avatars using *in vitro* and *in silico* models

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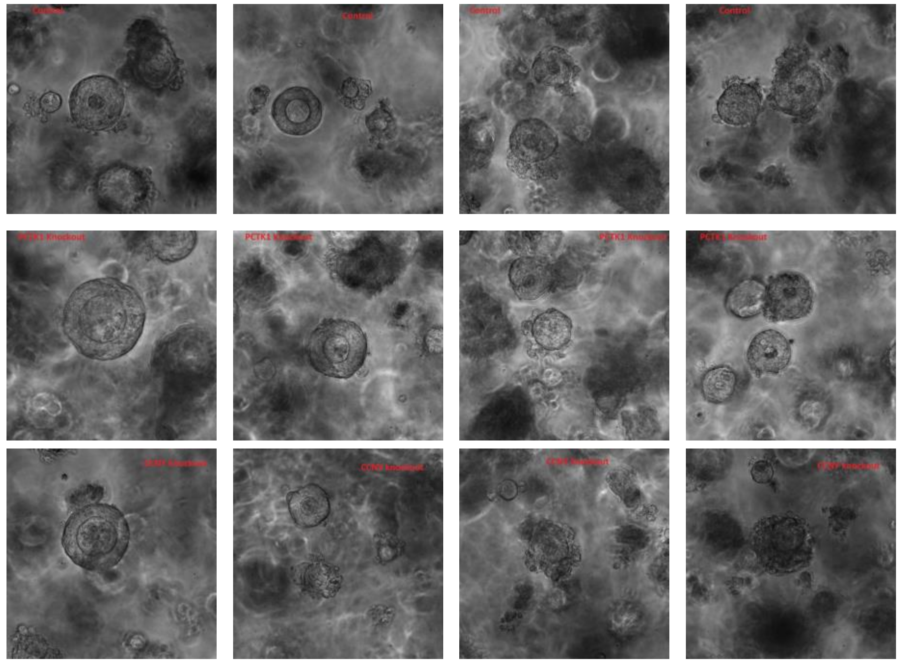

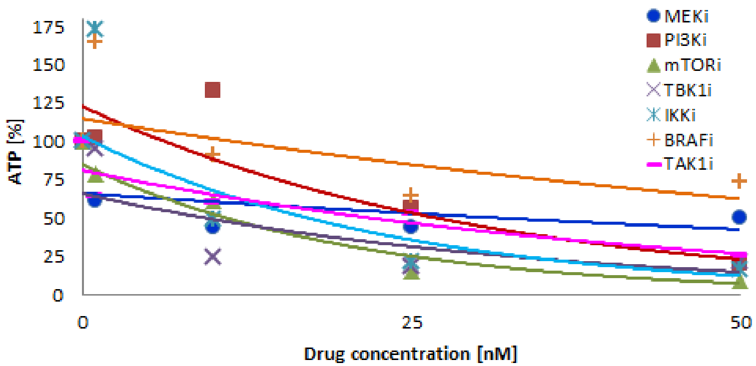

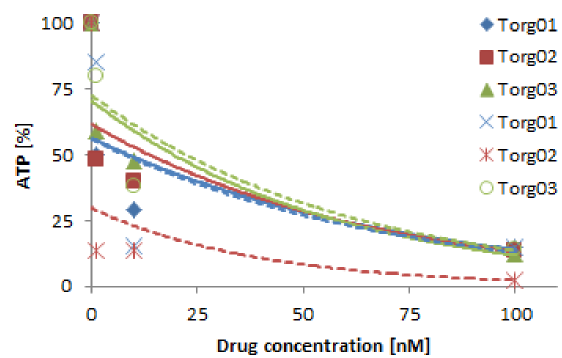

Collaboration with H. Farin, F. Greten, University of Fankfurt;
S. Scheidl, D. Öfner-Velano, G. Gastl, H. Zwierzina, L. Huber, S. Gelley, Medical University Innsbruck

Experiments: G. Lamberti, A. Noureen

Summary

- Identification of predictive biomarkers for response to immune checkpoint blockade:
  - Novel comprehensive assays/assay combinations are required

- Identification of predictive biomarkers for relapse:
  - Non-invasive assays for tumor monitoring are required

- Enabling precision immuno-oncology:
  - Need for avatars and perturbation data

Enabling precision immuno-oncology

Grossvenediger 3666 m

Stilfser Joch

Zlatko Trajanoski
Division for Bioinformatics, Medical University of Innsbruck, Austria
Email: zlatko.trajanoski@i-med.ac.at http://icbi.at

FWF Der Wissenschaftsfonds.
W|W|T|F
APERIM Advanced Bioinformatics Platform for Personalised Cancer Immunotherapy
THE EU FRAMEWORK PROGRAMME FOR RESEARCH AND INNOVATION HORIZON 2020 EXCELLENT SCIENCE COMPETITIVE INDUSTRIES BETTER SOCIETY
erc European Research Council Established by the European Commission