Francesco M Marincola – Distinguished Research Fellow Immuno-Oncology Discovery
ABR – AbbVie, Redwood City – CA

Session 301: Hot Topic Symposium: Advancing the Field: Can Physics and Mathematics Impact the Development of Tumor Immunotherapy?

Organized with Stand Up To Cancer

November 12th, 2017

Overview of the Immunotherapy Field

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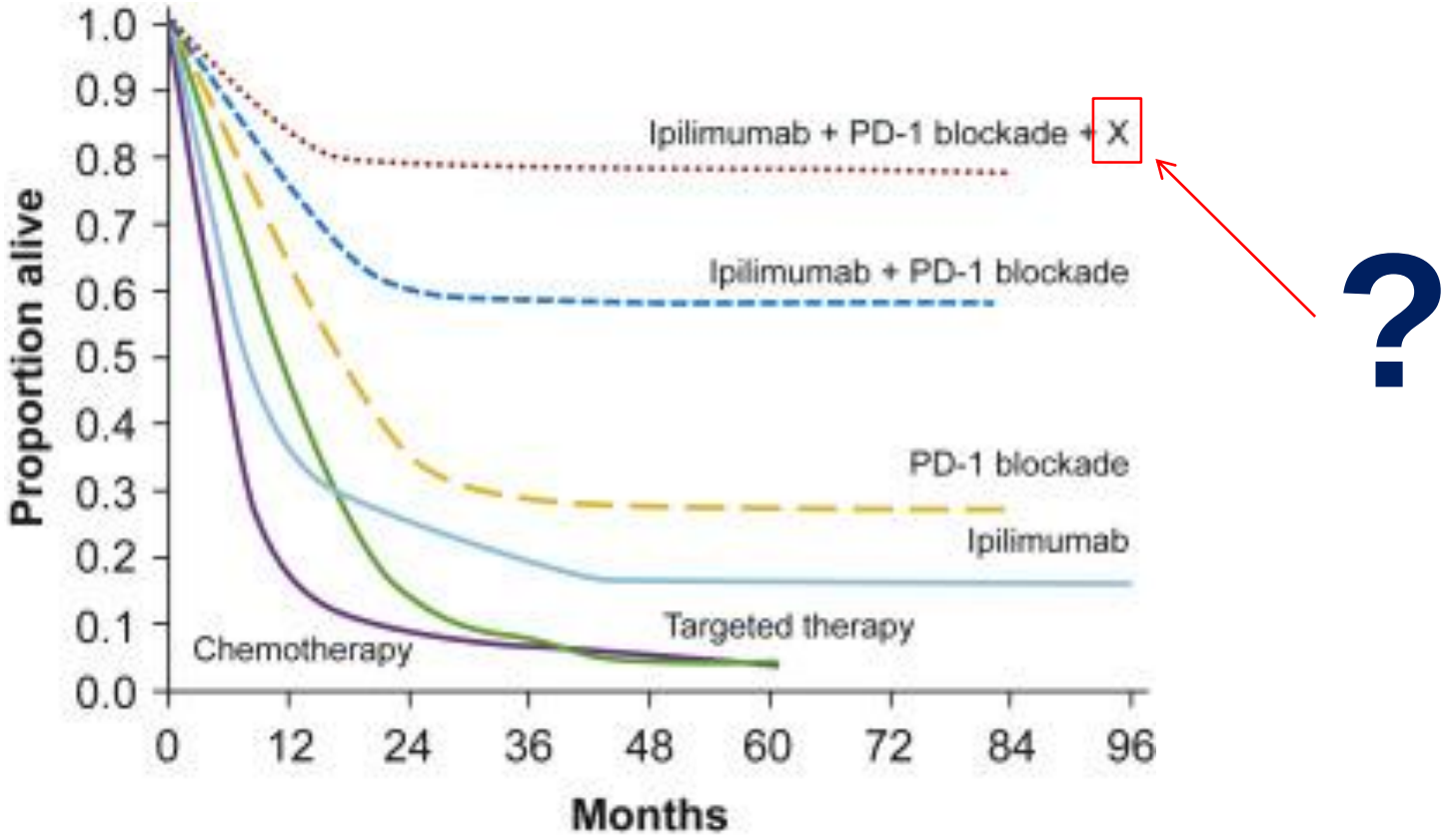
Cancer immunotherapy: Opportunities and challenges in the rapidly evolving clinical landscape

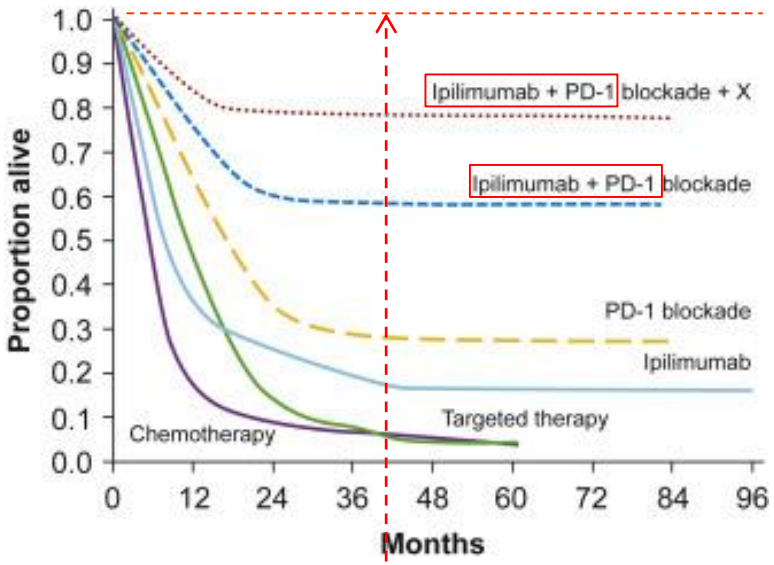
Leisha A. Emens [a], Paolo A. Ascierto [b], Phillip K. Darcy [c, d], Sandra Demaria [e], Alexander M.M. Eggermont [f], William L. Redmond [g], Barbara Seliger [h], Francesco M. Marincola [i]



FUTURE OPPORTUNITIES-NOVEL COMBINATIONS

Emens L et al. Eur J Cancer 2017

- Checkpoint inhibitors in combination (CPIc)
- Checkpoint inhibitors + pathway inhibitors
- Checkpoint inhibitors + anti-cancer vaccines
- Checkpoint inhibitors + agonist antibodies
- Checkpoint inhibitors + cytokines
- Checkpoint inhibitors + NK cell modulators
- Checkpoint inhibitors + anti-VEGF therapy
- Checkpoint inhibitors + chemotherapy
- Checkpoint inhibitors + radiotherapy
- Checkpoint inhibitors + epigenetic therapy
- Checkpoint inhibitors + adoptive cellular therapy
- Checkpoint inhibitors + DNA damage repair agents
- Checkpoint inhibitors + Oncotropic/Oncolytic viruses
- Checkpoint inhibitors + anti-metabolites (IDO, Nos etc.)



(Ipi + PD1 Blockade)$_K$ + other category$_{14}$ (n = 1 per modality) = 14 combinations

(Ipi + PD1 Blockade)$_K$ + other category$_{14}$ (n = 2 per modality) = 28 combinations

(PD1 Blockade)$_K$ + CPI (n = 10) + other modality$_{14}$ = 140 combinations

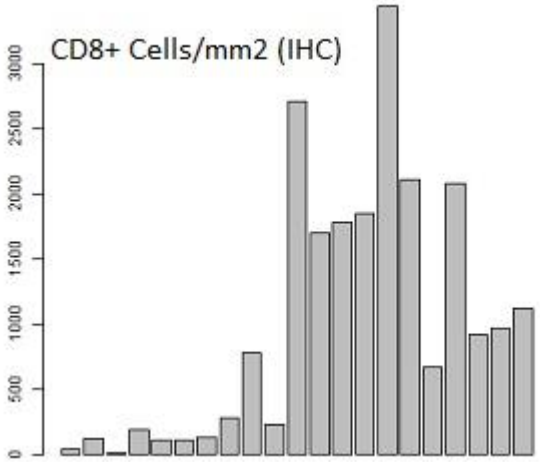
(PD1 Blockade)$_K$ + CPI (n = 10) + other modality$_{14}$ (3 candidates/ modality) = 420 comb.

(PD1 Blockade)$_K$ + CPI (3 candidates/CPI) + other modality$_{14}$ (3 candidates/modality) = 1,260 comb.

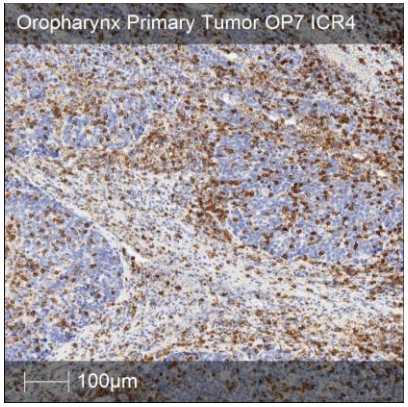
Does this apply to all cancers?

Three basic cancer-immune phenotypes

A

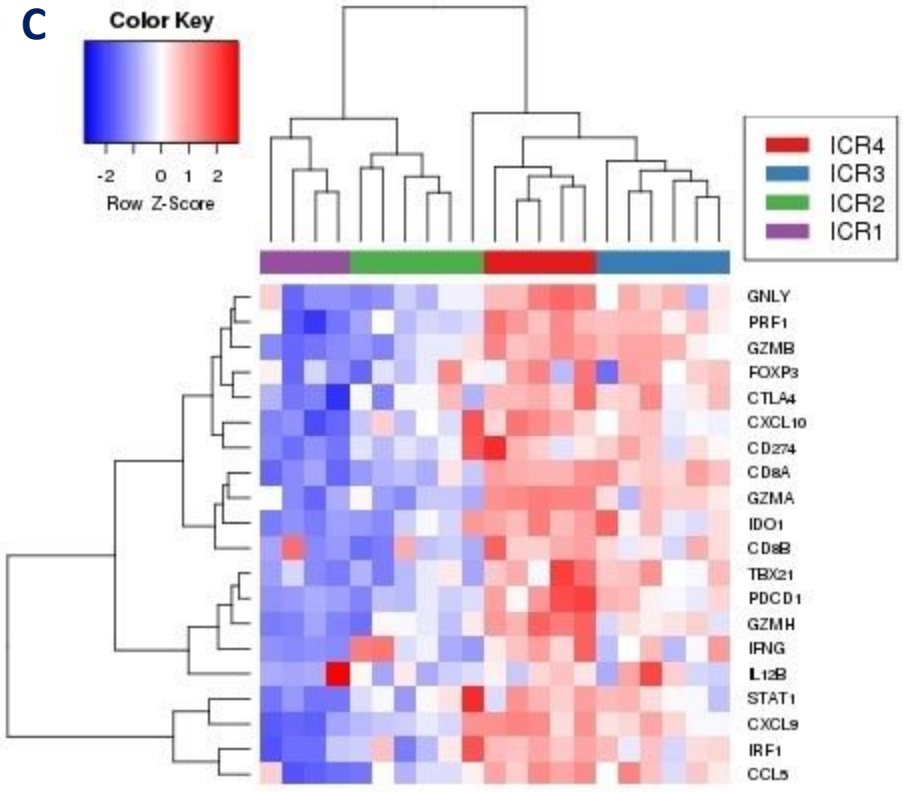


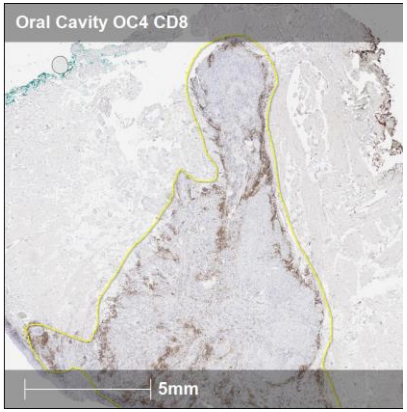
B



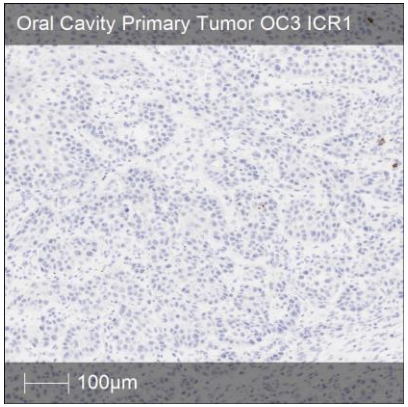
Inflamed

C



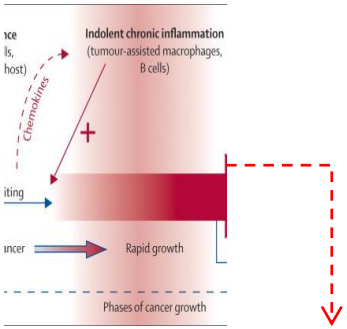


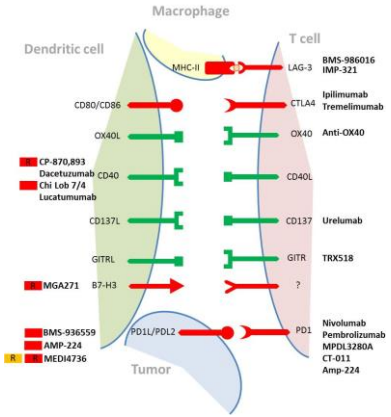
Stromal Excluded



Immune Desert

The immune landscape of cancer





Immunogenicity: metagenome
Adjuvancy: Immunogenic cell death

"Sloppy" Tumors

Immune Active

- Growth Factors
- Pro-inflammatory Factors (CytDNA*/STING/pTNK1/IRF3/IFN)
- Chemokines (i.e. Batf3+IRF8/CD103,CD141 DCs)

Excluded Tumors

Immune Exclusion:
Interference Hypothesis

↑ β-catenin/↓batf3 DCs ⊣ CCL4/IFN-β

Epithelial Barriers and Stromal Components:
Dystonin → Immune depletion (x)
Tight Junction, Desmosomal Proteins } Mixed Expression Immune genes (w)
Cancer-associated Fibroblasts, Secretome, Matrix deposition and remodeling

Fibrotic Mechanical Barries
TGF-β driven fibro-genesis

Vascular Fidelity
VEGF ⊣ VCAM, ICAM

- Growth Factors

Pro-inflammatory Factors

"Clean/Silent" Tumors

No Inflammation
Immune Ignorance
Epigenetic Silencing

Distinct hypotheses/mechanisms:

Immune stimulatory
SCFN11
RxTx (suppressed by Trex1)
Chemotx and Necroptosis
HMGB1/TLR4/MyD88
CALR/LRP1
Extracellular ATP ⟷ P2RY2/P2RX7
Microbiota

Immune suppressive/proliferative
PI3Kγ
TIM-3
MAP Kinase Activation
AIM2, IL1β/IL18-driven Pyroptosis
CD73-driven ATP degradation
IL-23/IL-17 axis/pSTAT3
iNOS
Mesenchymal transition
Efferocytosis (MERTK)
Hypoxia/Adenosine

Immune Oncology, Immune Responsiveness and the Theory of Everything

Tolga Turan, Deepti Kannan, Maulik Patel, Matt J. Barnes, Sonia G. Tanlimco, RongZe Lu, Kyle Halliwill, Douglas E. Kline, Wouter Hendrickx, Alessandra Cesano, Lisa H. Butterfield, Howard L. Kaufman, Thomas J Hudson, Davide Bedognetti, Francesco Marincola, Josue Samayoa

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Barrier Molecules	
Type 1 (Group W)	Associated with poor survival
Type 2 (Groups x and y)	(Not associated with prognosis)
Type 3 - Endotelin Receptor B)	(association with prognosis controversial)
Mesenchymal Transition	IPRES (Innate α-PD1 immune resistance) signature
TAM receptor tyrosine kinases (TAMs)	
Tolerogenic DCs (TolDCs)	
Hypoxia/Adenosine Immune Cell Suppressic	Signature including CD73 associated with poor prognosis
Stromal cell suppressive mechanisms	
TREX1 (clearance of Cytosolic DNA/indirect inhibitor of STING	
Checkpoint Cluster	

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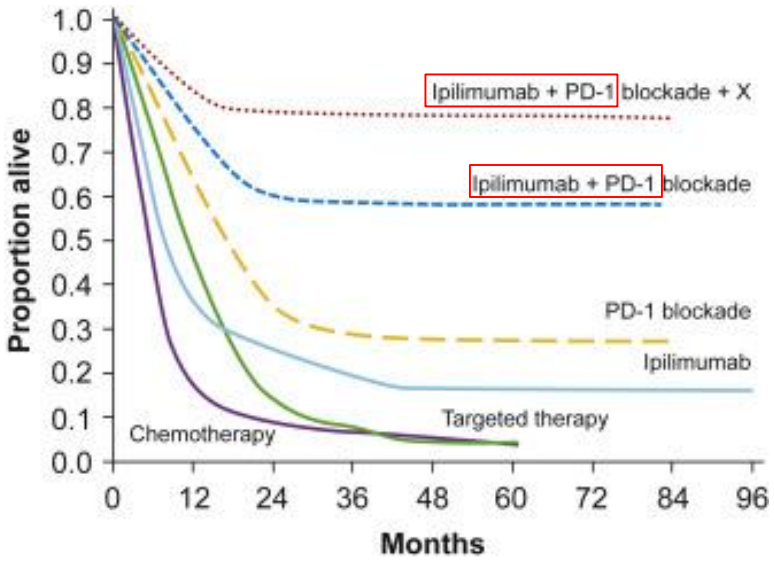

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$(\underline{\text{PD1 Blockade}})_K$ + CPI$_{10}$ (3 cand/CPI) or IOs$_{15}$ (3 cand/IO) + other category$_{14}$ (3 cand/mod) = 6,786 comb

$(\underline{\text{PD1 Blockade}})_K$ + CPI$_{10}$ (3 cand/CPI) + IOs$_{15}$ (3 cand/IO) + other category$_{14}$ (3 cand/mod) = 260,130 comb

"The answer to biological problems pre-exists, it is the question that needs to be discovered"

Jonas Salk – Ann NY Acad Sci 164: 365, 1969

"Our goal should be to define a human evidence-based, systematic strategy for the identification and/or the selection of candidate targets in Immune Oncology"

- **How does tumor rejection occur**

- **Why does rejection occur**

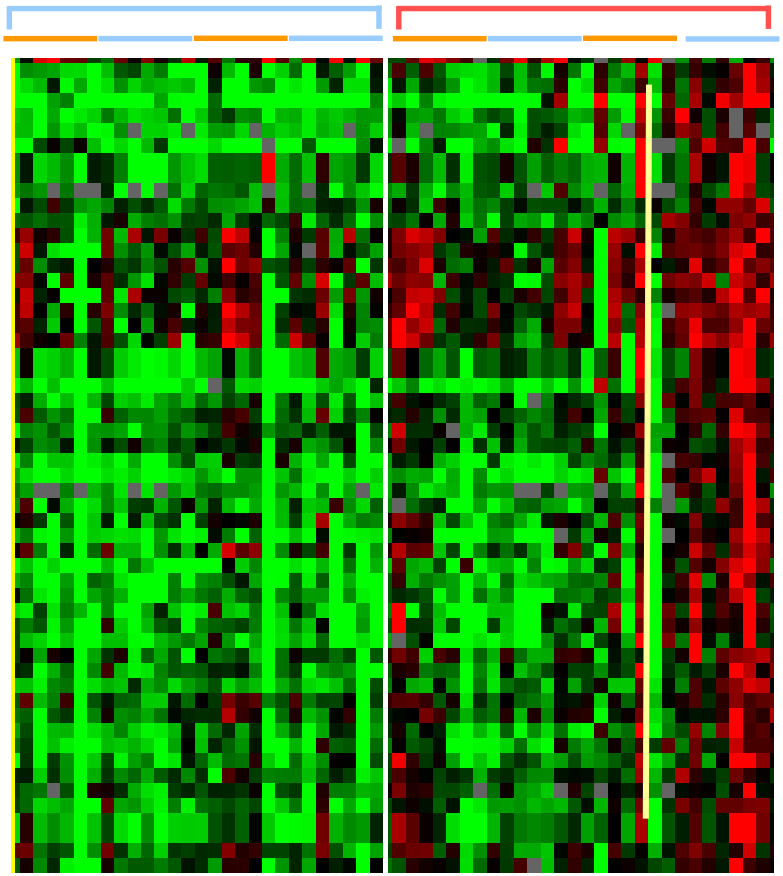
- **How does tumor rejection occur**

- **Why does rejection occur**

Imiquimod (TLR-7a)-Basal cell Carcinoma

Pre-treat TLR-7a Treat

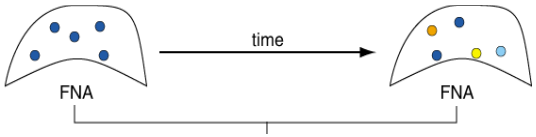
Placebo X 4 days
Placebo X 8 days
Treat X 4 days
Treat X 8 days



Interferon Stimulated Genes
STAT1 1/IRF1
Allograft inflammatory factor 1
IL-15/IL-2/IL15 R b
IL-15 R a/IL-2/IL-4/IL-7/IL-9/IL-15 R g
IL6

CCR5 Ligands
(CCL4/CCL5)
CXCR3 Ligands
(CXCL9
CXCL10)

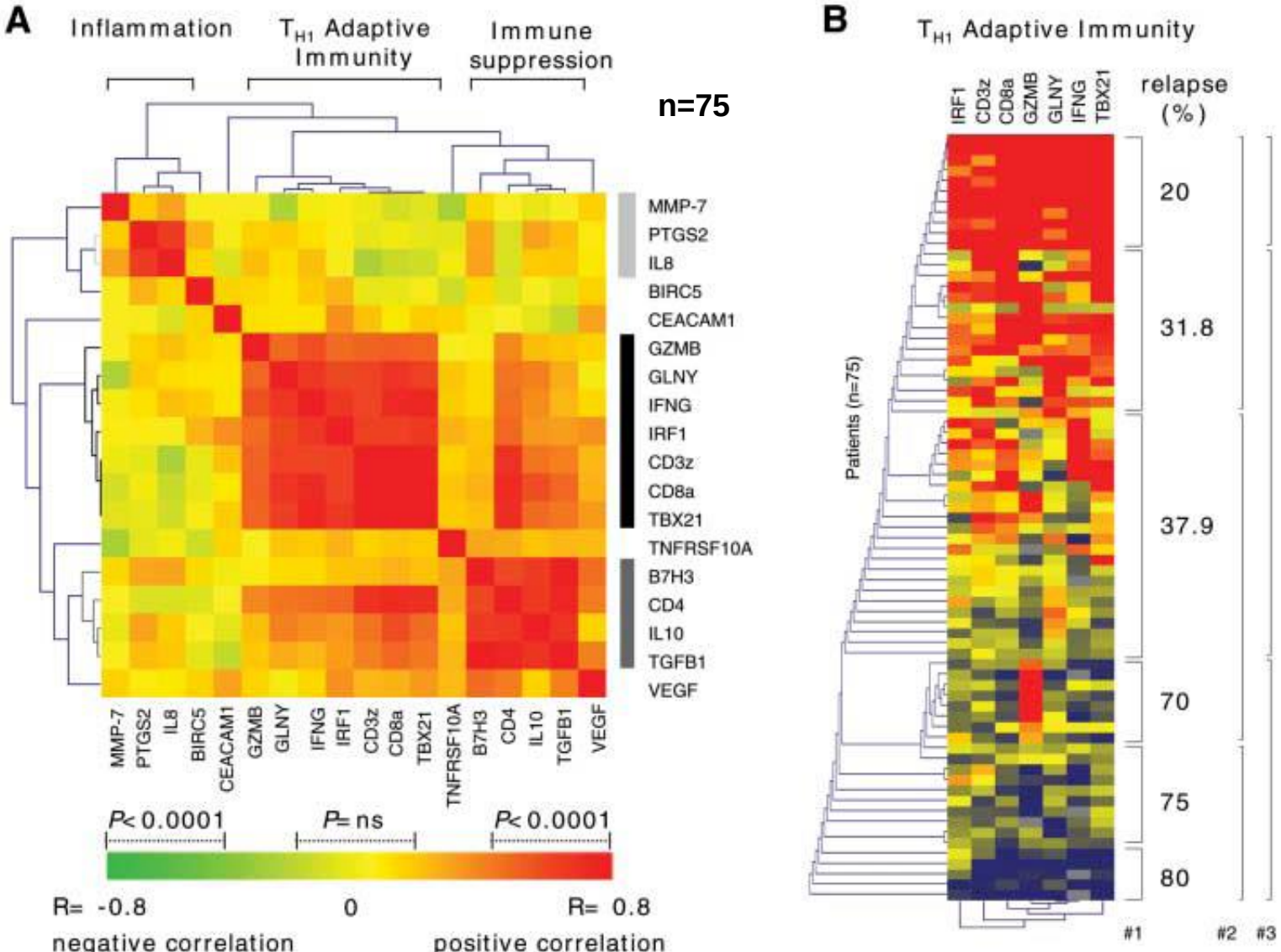
Immune Effector Genes (IEG)
Granzyme A, B, K
Perforin



Panelli et al. Genome Biol 2007

Type, Density, and Location of Immune Cells Within Human Colorectal Tumors Predict Clinical Outcome

Jérôme Galon,[1*†] Anne Costes,[1] Fatima Sanchez-Cabo,[2] Amos Kirilovsky,[1] Bernhard Mlecnik,[2] Christine Lagorce-Pagès,[3] Marie Tosolini,[1] Matthieu Camus,[1] Anne Berger,[4] Philippe Wind,[4] Franck Zinzindohoué,[5] Patrick Bruneval,[6] Paul-Henri Cugnenc,[5] Zlatko Trajanoski,[2] Wolf-Herman Fridman,[1,7] Franck Pagès[1,7†]

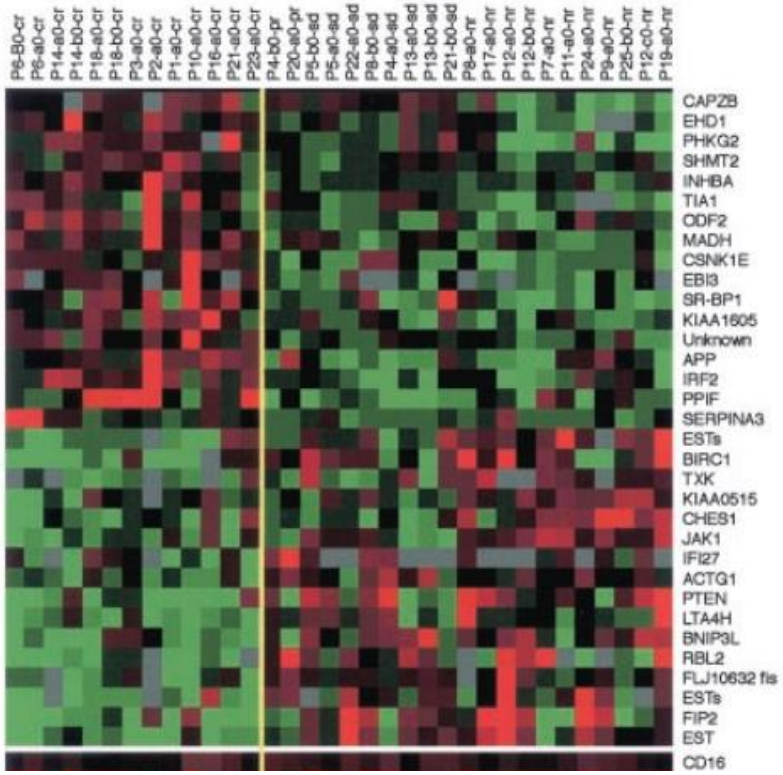


- How does tumor rejection occur
- **Why does rejection occur**

CANCER RESEARCH 62, 3581-3586, 2002

Prospective Molecular Profiling of Melanoma Metastases Suggests Classifiers of Immune Responsiveness

Ena Wang, Lance D. Miller, Galen A. Ohnmacht, Simone Mocellin, Ainhoa Perez-Diez, David Petersen, Yingdong Zhao, Richard Simon, John I. Powell, Esther Asaki, H. Richard Alexander, Paul H. Duray, Meenhard Herlyn, Nicholas P. Restifo, Edison T. Liu, Steven A. Rosenberg, and Francesco M. Marincola[1]



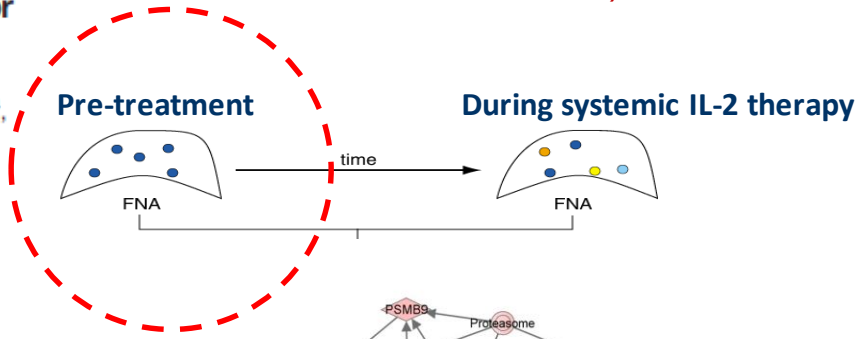
come. Ranking of gene expression data from pretreatment samples identified ~30 genes predictive of clinical response ($P < 0.001$). Analysis of their annotations denoted that approximately half of them were related to T-cell regulation, suggesting that immune responsiveness might be predetermined by a tumor microenvironment conducive to immune recognition.

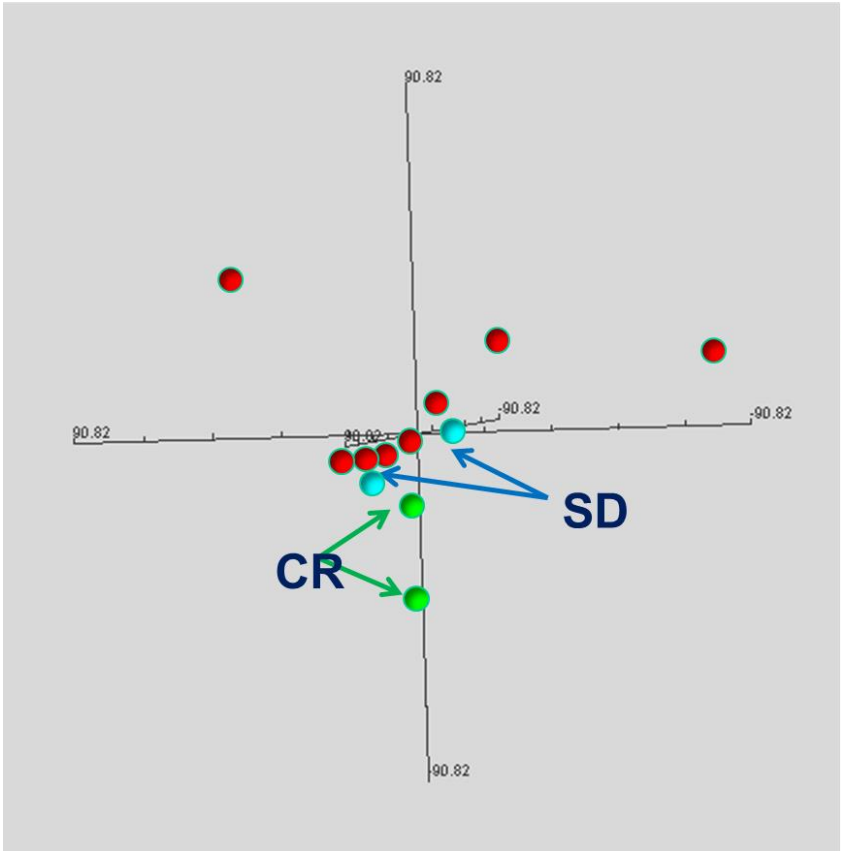
Clinical Cancer Research

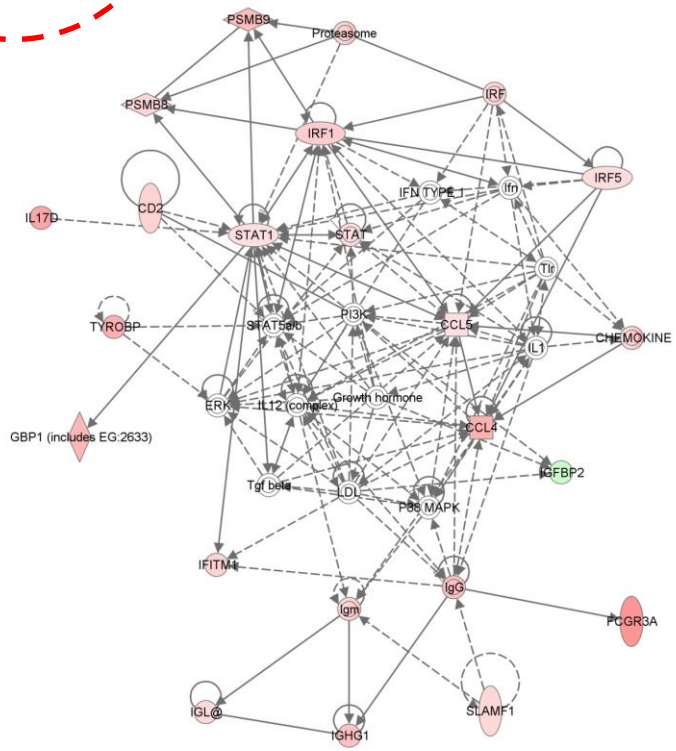
Molecular Insights on the Peripheral and Intratumoral Effects of Systemic High-Dose rIL-2 (Aldesleukin) Administration for the Treatment of Metastatic Melanoma

Geoffrey R. Weiss[1], William W. Grosh[1], Kimberly A. Chianese-Bullock[2], Yingdong Zhao[3], Hui Liu[4], Craig L. Slingluff Jr[2], Francesco M. Marincola[4], and Ena Wang[4]

Weiss G R et al. Clin Cancer Res 2011;17:7440-7450



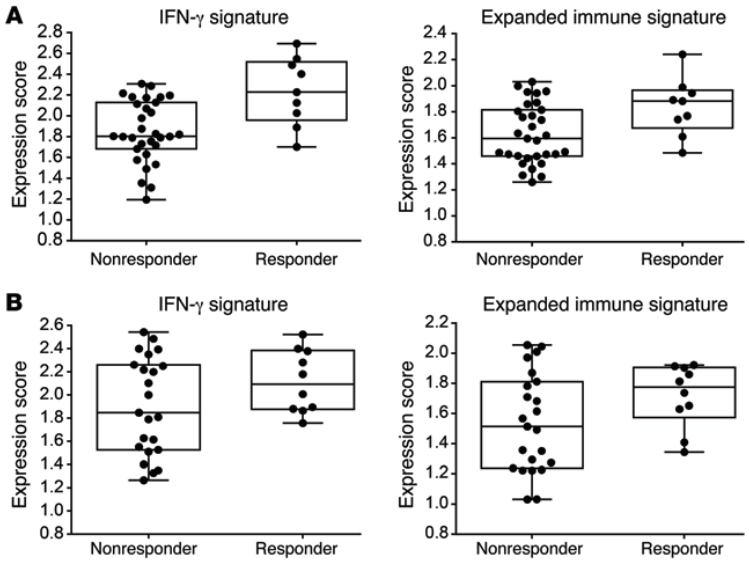


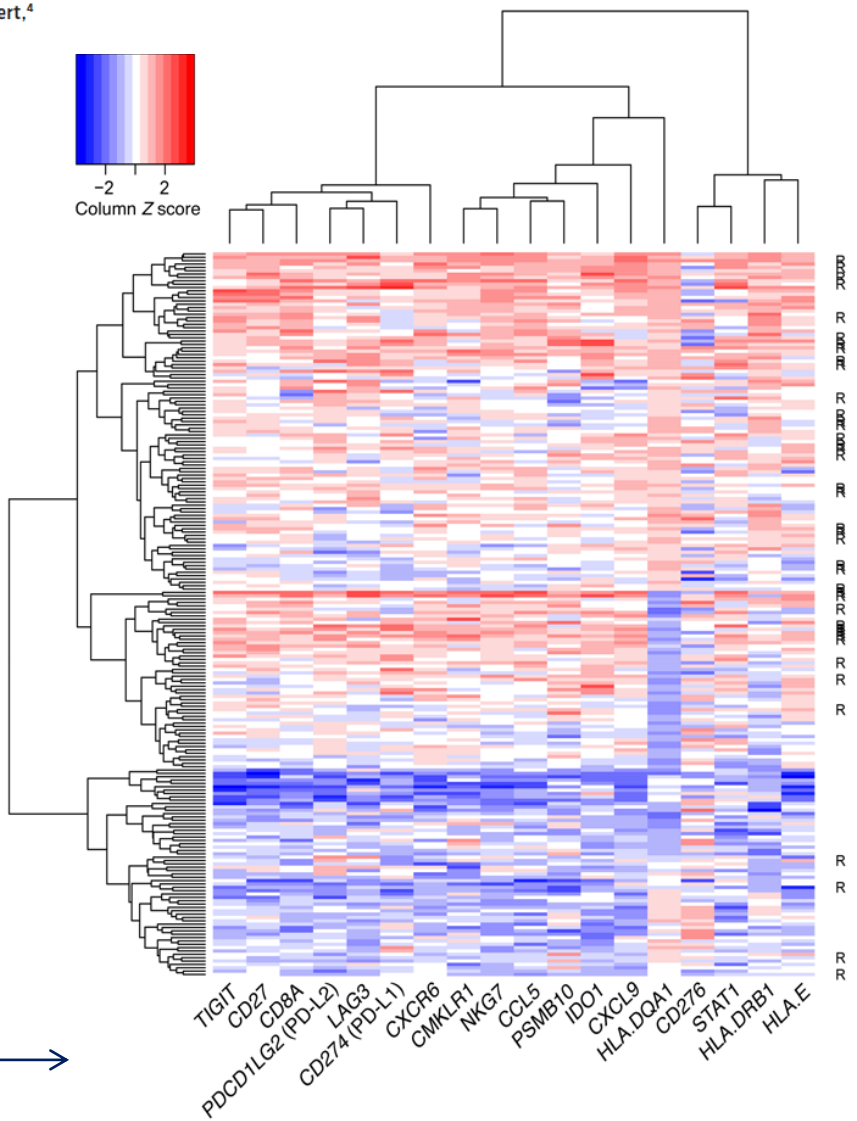


The Journal of Clinical Investigation RESEARCH ARTICLE J Clin Invest. 2017 Aug 1;127(8):2930-2940..

IFN-γ–related mRNA profile predicts clinical response to PD-1 blockade

Mark Ayers,[1] Jared Lunceford,[1] Michael Nebozhyn,[1] Erin Murphy,[1] Andrey Loboda,[1] David R. Kaufman,[1] Andrew Albright,[1] Jonathan D. Cheng,[1] S. Peter Kang,[1] Veena Shankaran,[2] Sarina A. Piha-Paul,[3] Jennifer Yearley,[1] Tanguy Y. Seiwert,[4] Antoni Ribas,[5] and Terrill K. McClanahan[1]



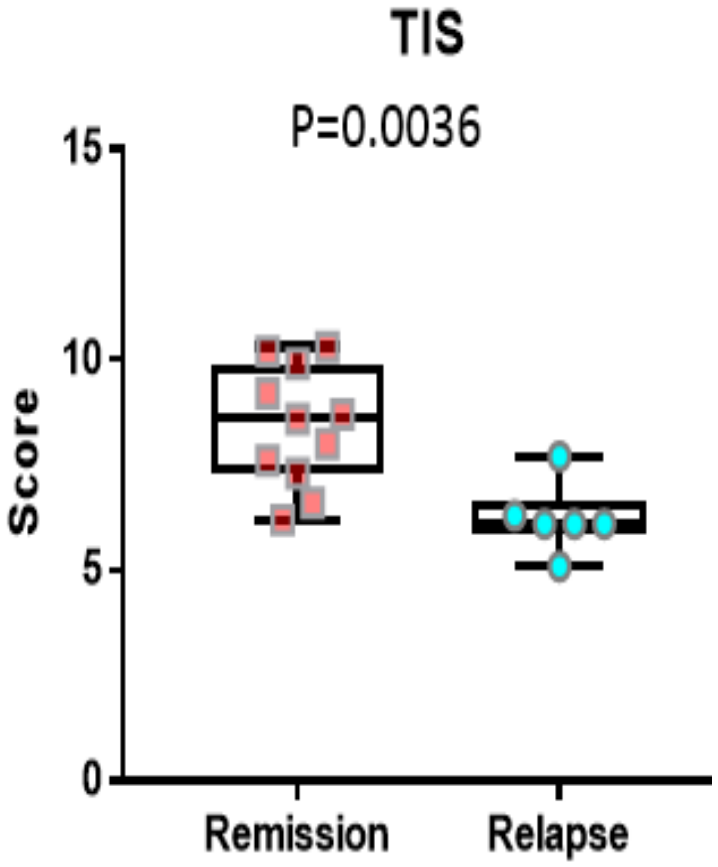


Tumor Inflammation Signature is Predictive in Combination Immune Checkpoint Blockade

Tumor Inflammation Signature - 18 gene biomarker classifier of peripherally suppressed adaptive immune responses in tumor (Ayers 2017 JCI)

OpACIN Trial – neo-/adjuvant ipilimumab + nivolumab in stage III melanoma

Gene expression profiling shows elevated TIS score correlates with durable remission



EA Rozeman…CU Blank
SITC 2017 #P99

ONCOIMMUNOLOGY
2017, VOL. 6, NO. 2, e1253654 (19 pages)
http://dx.doi.org/10.1080/2162402X.2016.1253654

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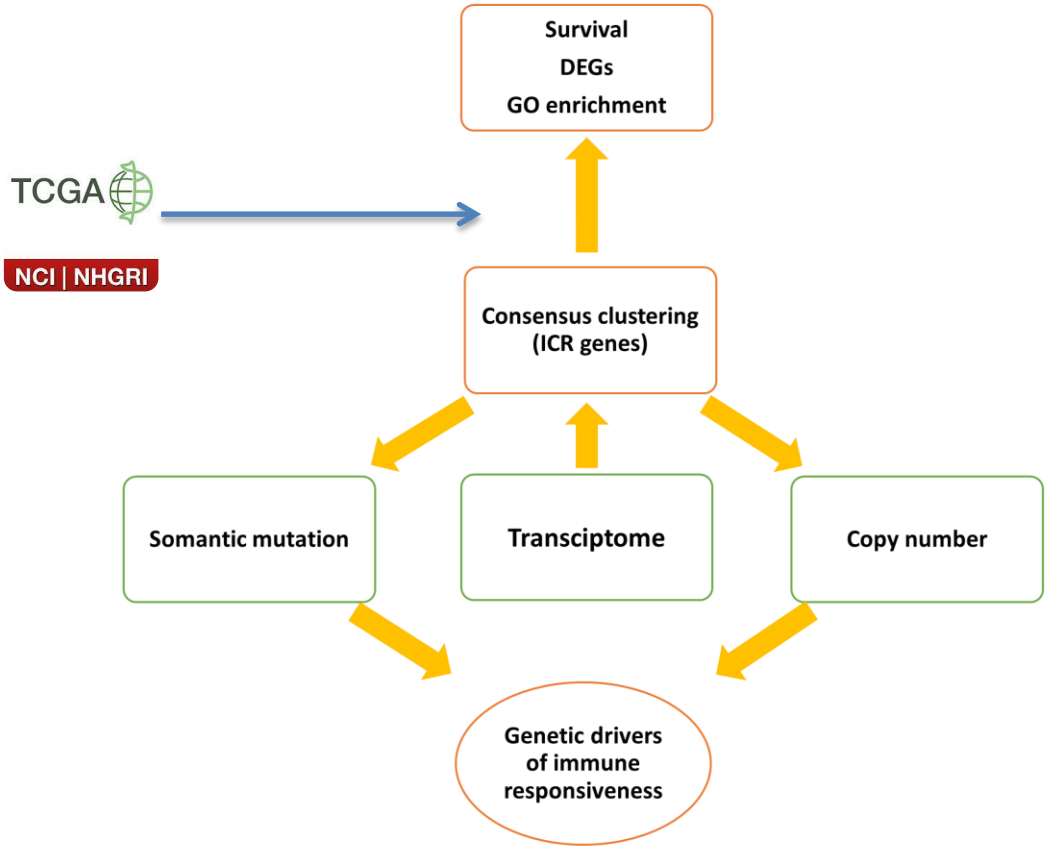
ORIGINAL RESEARCH

OPEN ACCESS

Identification of genetic determinants of breast cancer immune phenotypes by integrative genome-scale analysis

Wouter Hendrickx[a,*], Ines Simeone[b,c,*], Samreen Anjum[b], Younes Mokrab[d], François Bertucci[e,f,g], Pascal Finetti[e], Giuseppe Curigliano[h], Barbara Seliger[i], Luigi Cerulo[c,j], Sara Tomei[k], Lucia Gemma Delogu[l], Cristina Maccalli[a], Ena Wang[k], Lance D. Miller[m], Francesco M. Marincola[n], Michele Ceccarelli[b,#], and Davide Bedognetti[a,#]

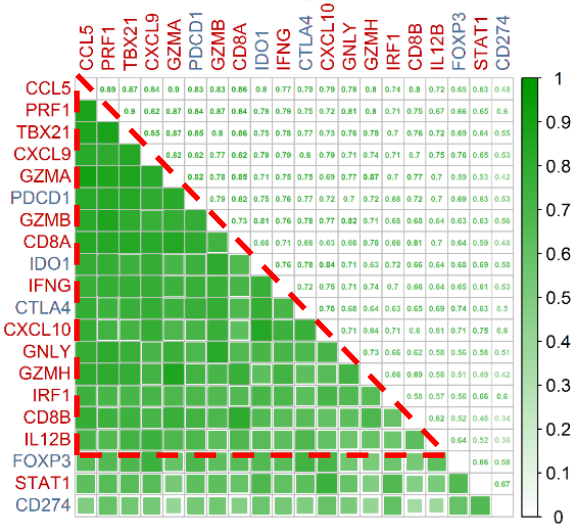


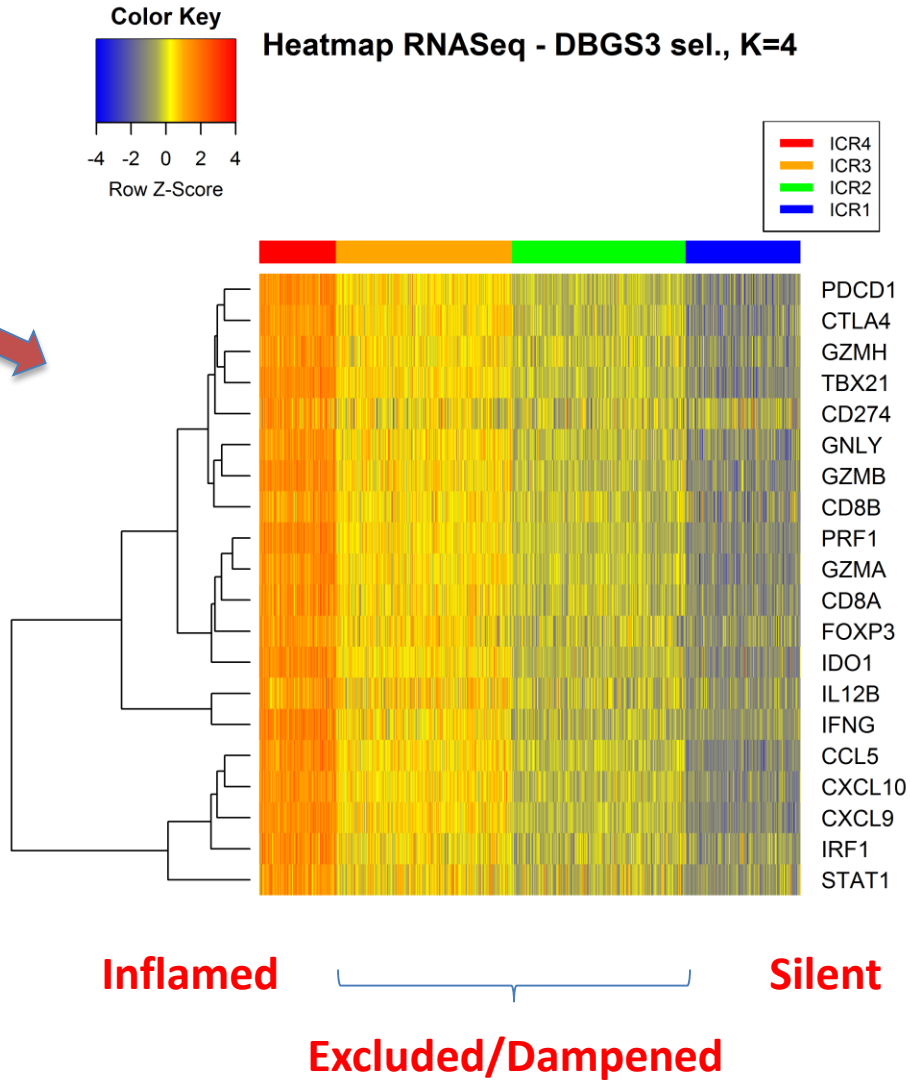
Functional pipeline

ICR based Consensus Clustering

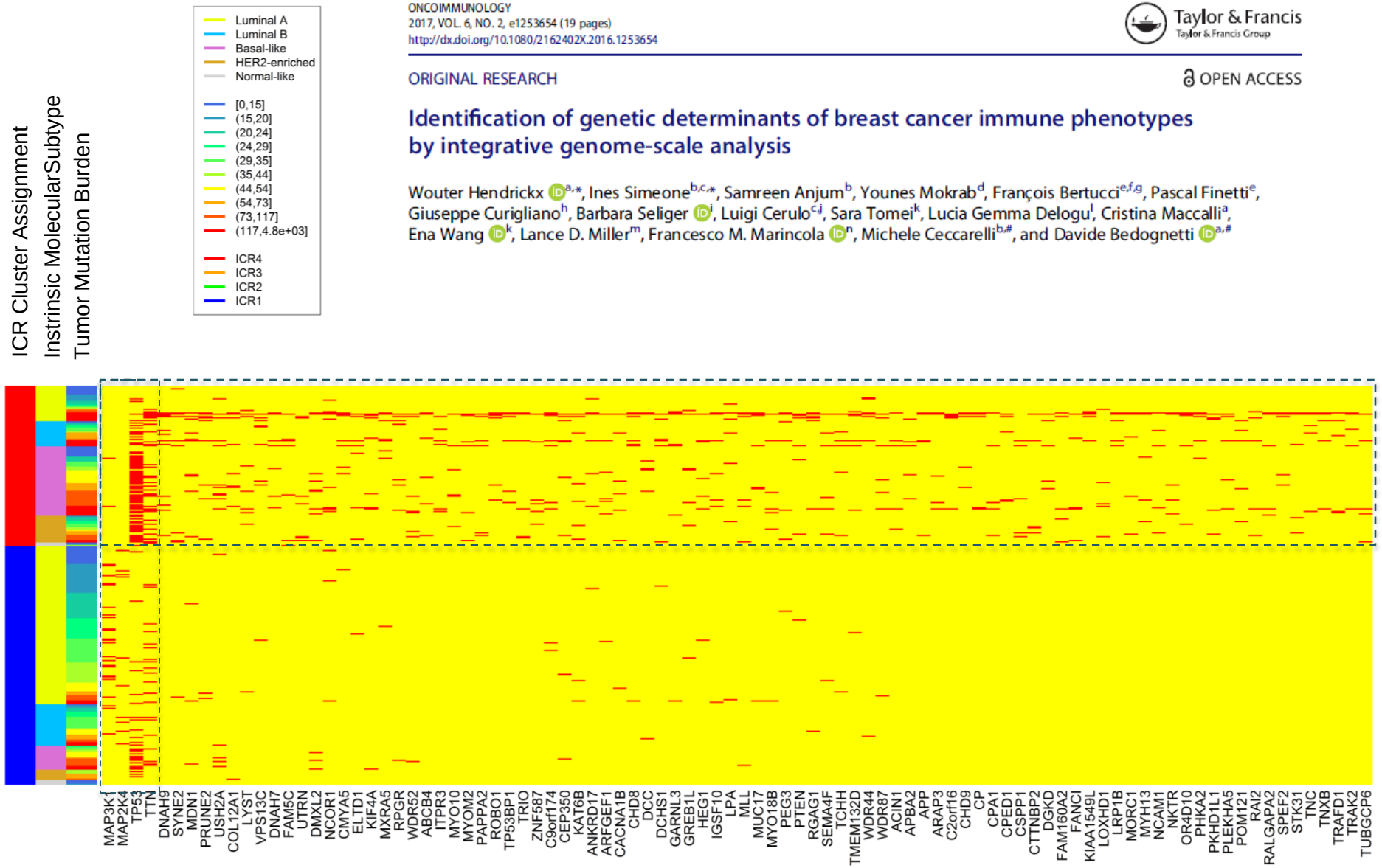
Immunologic Constant of Rejection

CXCR3/CCR5 Chemokines	Th1 signaling	Effector functions	Immune regulatory
CXCL9	IFNG	GNLY	CD274
CXCL10	TBX21	PRF1	CTLA4
CCL5	CD8A	GZMA	FOXP3
	IL12B	GZMB	IDO1
	CD8B	GZMH	PDCD1
	STAT1		
	IRF1		





Driver genes (Chisqr < 0.05)



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WNT/beta Catenin Hypothesis	Not associated with prognosis
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Th17 AxiS (Psoriatic Signature/pSTAT3 Activ	Associated with poor survival
Th2 Signatures	No association with survival
PI3Kγ Signature	Associated with poor response to checkpoint inhibitors
NOS1 Signature	Low likelihood to respond to TIL therapy
SGK1 Signature	
Barrier Molecules	
Type 1 (Group W)	Associated with poor survival
Type 2 (Groups x and y)	(Not associated with prognosis)
Type 3 - Endotelin Receptor B)	(association with prognosis controversial)
Mesenchymal Transition	IPRES (Innate α-PD1 immune resistance) signature
TAM receptor tyrosine kinases (TAMs)	
Tolerogenic DCs (TolDCs)	
Hypoxia/Adenosine Immune Cell Suppressic	Signature including CD73 associated with poor prognosis
Stromal cell suppressive mechanisms	
TREX1 (clearance of Cytosolic DNA/indirect inhibitor of STING	
Checkpoint Cluster	

TOE – Distribution of signatures among 999 Breast Cancers

Major hypotheses explaining immune resistance	
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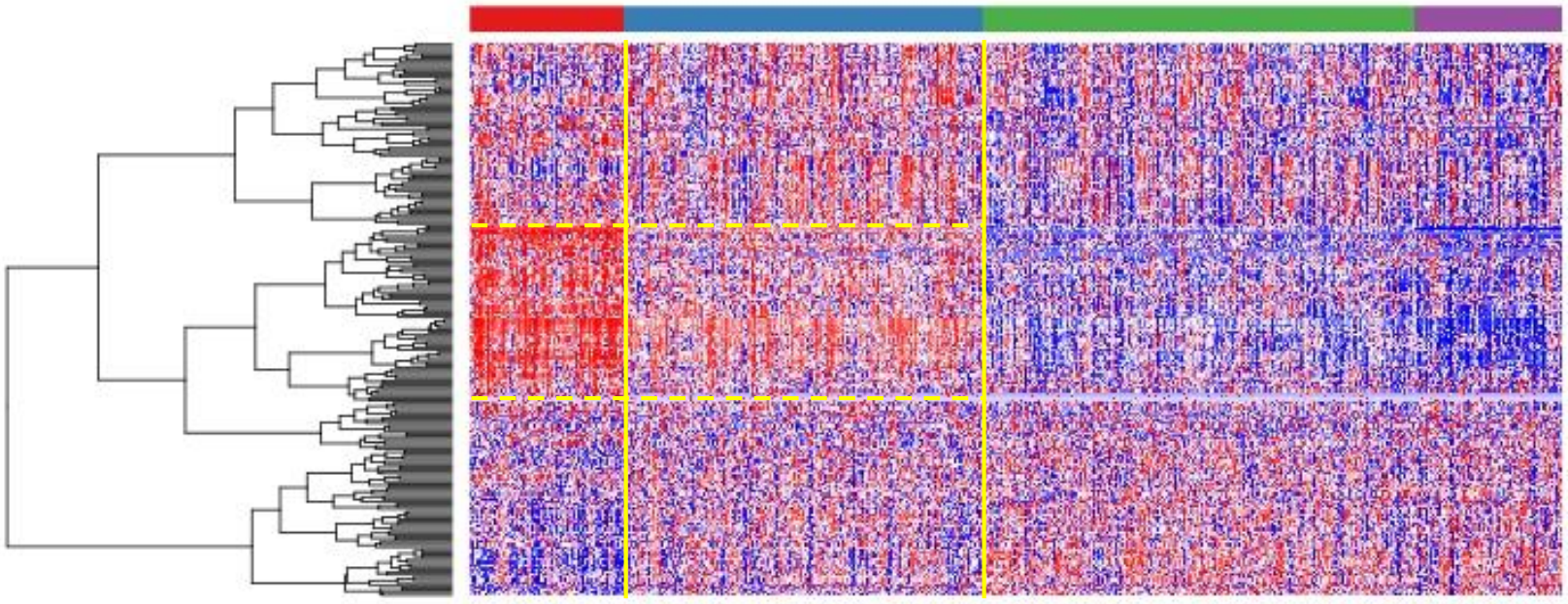
Immune-active
Compensatory Resistance

Immune-silent
Primary Ignorance

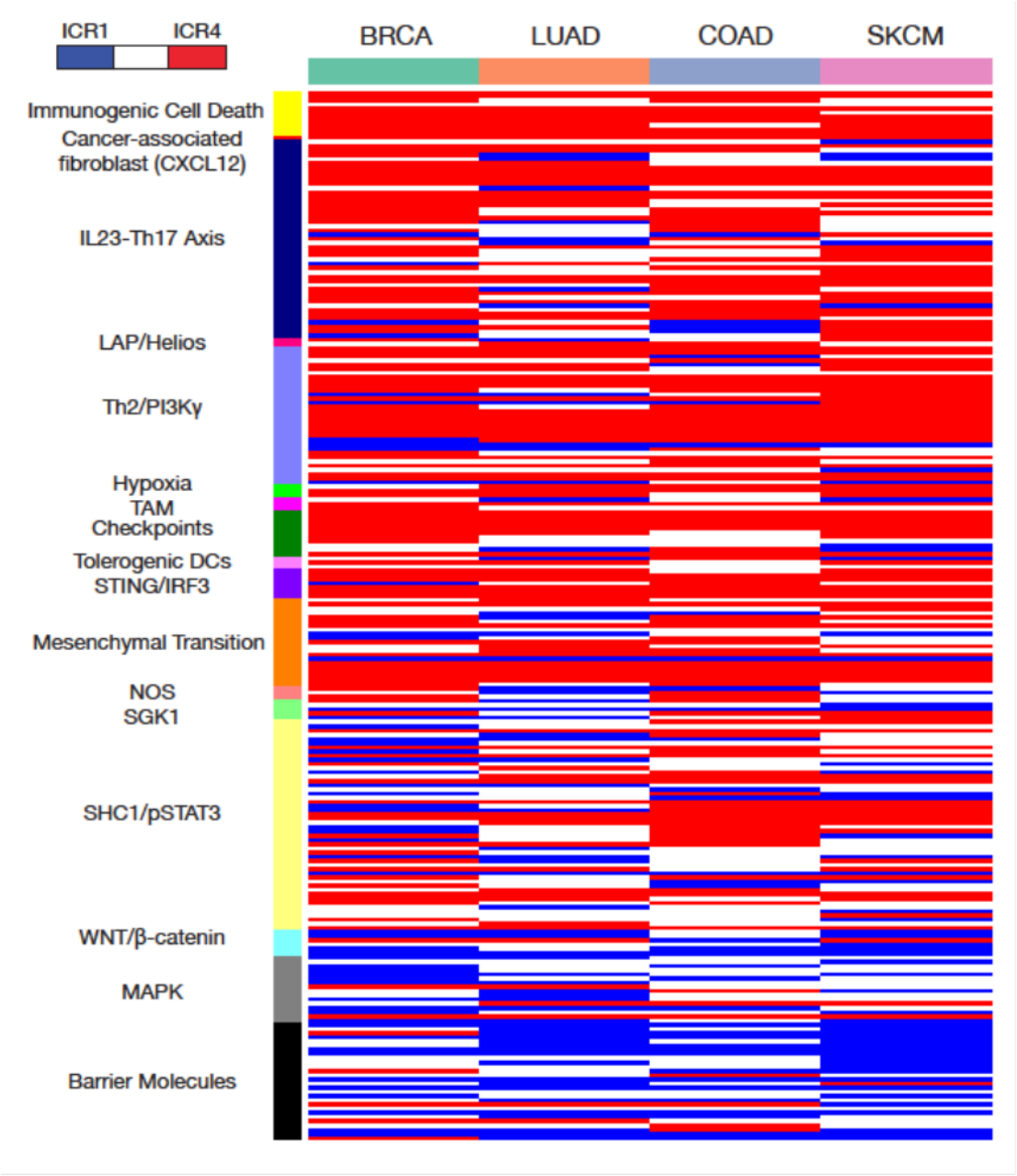


Ubiquitous:
- NOS
- Mesenchymal Transition
- SHC1/STAT3
- Barrier Molecules
- Checkpoints: B7-H3, B7-H4

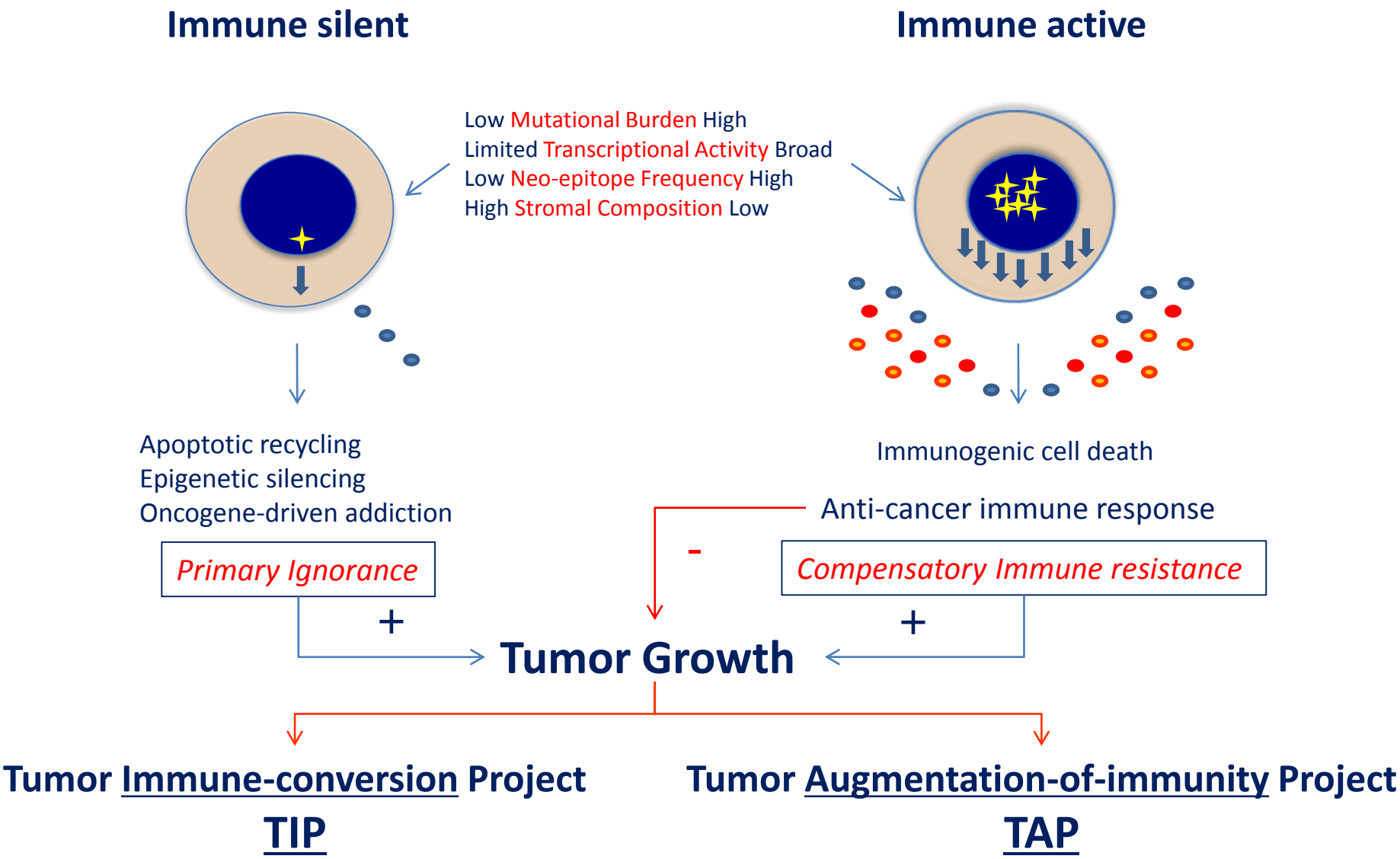
Immune enriched:
- Sting/Immunogenic Cell Death
- IL23/Th17 axis
- Th2 Signatures
- Most Checkpoints
- TAM receptors
- Hypoxia

Immune depleted:
- β-catenin
- MAPK
- PI3Kγ
- SGK1
- SHC1/STAT3
- Barrier Molecules
- Mesenchymal Transition

Mapping Big TOE genes to ICR landscapes in all 4 tumor types



The "Two-Option Choice" (TOC) determinism in the natural history of cancer: A conserved evolutionary crossroad for cancer survival



SITC Task Force on Immune Responsiveness

- A workshop associated with the Biomarker Task Force (with AbbVie, Nanostring and Celgene)

- "*To educate the scientific community on the status of immunotherapy research by bringing together leaders in the field of immunology, cell biology, genetics and computational biology*"

- Fundamental questions to be addressed:
  - ✓ Do cancers of different histology display different immune landscapes?
  - ✓ Are the ICR, TIS or other equivalent signatures accurate predictors of immune responsiveness?
  - ✓ Do immune silent tumors follow a distinct evolutionary process?
  - ✓ Is the transcriptional enrichment observed in immunogenic tumors due to immune infiltrates?
  - ✓ Are there oncogenic pathways broadly shared among immune silent cancers?
  - ✓ Can therapeutic disruption of oncogenesis in silent tumors activated immunogenic cell death?
  - ✓ How can experimental observation be validated in relevant pre-clinical settings using human tissues or rodent models?
  - ✓ How can the information gained be utilized to inform drug development in the discovery and development phase?

- Five working groups:
  - **Somatic Genetics/Epigenetics of Immune landscapes** (Organizer, Josue Samayoa)
  - **Transcriptional Patterns of Immune Landscapes** (Organizer, Stefanie Spranger)
  - **Role of Immunogenic Cell Death** (Organizer, Sara Warren)
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