Development of Multi-Parameter Assays to Predict Therapeutic Response in Cancer Immunotherapy

Dr. George Poste
Chief Scientist, Complex Adaptive Systems Initiative and Regents Professor of Health Innovation
Arizona State University
george.poste@asu.edu
www.casi.asu.edu

26th International Molecular Med TRI-CON
March 12, 2019 San Francisco, CA
Moscone South Convention Center
Confronting the Clinical, Economic and Human Toll of Cancer

Cancer (2019): New Diagnoses 1.68 million; Deaths: 600,920

Projected Increase in Incidence of 20% by 2020 and 30% by 2030
Realizing the Promise of Cancer Immunotherapy

- wide variation in Rx response rates
  - only 20 - 40% positive responses even in most responsive malignancies
  - even lower percentage of clinically durable responses (KM long tail)
- improve response rates across all malignancies
- management of serious AEs (CRS, autoimmune)
- will I/O combination regimens increase response rates?
- rationale for selection of combination regimens
- unsustainable long term cost of treating non-responder patients

Urgent clinical and economic need for multi-parameter immunophenotyping to reliably predict responder vs non-responder patients and toxicity risk
The Clinical Trial Landscape for PD-1/PDL-1 Immune Checkpoint Inhibitors (2018)
2250 trials; 1716 combination Rx; 240 Rx targets

380K pts needed for current listed trials

Cancer as a Complex Adaptive System

- Innate and adaptive immune phenotype(s)
- Tumor (sub)clonal diversity
- Germline genetics
- HLA genetics
- Predisposition alleles
- Inter-patient/ intra-patient
- Mutagen burden and neoantigen profile
- Immuno-editing
- Intrinsic and acquired Rx resistance
- Rx
- Local and systemic
- Microbiome
Cancer as a Complex Adaptive System

- germline genetics
- HLA genetics
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- tumor (sub)clonal diversity
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- mutagen burden and neoantigen profile
- immuno-editing
- intrinsic and acquired Rx resistance
- local and systemic
- innate and adaptive immune phenotype(s)
- microbiome
- ill-defined systemic factors affecting disease risk, progression and Rx responses
- age
- gender
- ethnicity
- environmental risk factors/lifestyle
- adiposity
- comorbidities
- microbiome
- chronic subclinical inflammation
- selection pressure of prior Rx regimen(s)
- variations in clinical practice: AMCs vs community practices
Cancer: The Interplay Between Multiple Complex Adaptive Systems

- **Host**
  - predisposition (germline)
  - cumulative combinatorial risk exposure (somatic)
  - immune response repertoire (germline & somatic)
  - microbiome

- **Tumor**
  - lineage and subtype-dependent dysregulation
  - clonal/subclonal heterogeneity

- **Tumor-Host Interactions**
  - elimination
  - equilibrium
  - evasion

**Spatial and Temporal Dynamic Range**
- molecular networks to the whole organism
- preclinical events and clinical phase events
The Discovery, Development and Validation of Predictive and Prognostic Biomarkers in Immunotherapy: A Complex Multi-step, Multi-dimensional Process

- specimen(s) and sampling frequency
- analytes and analytical platforms
- standards for pre-analytical and analytical validation
- clinical validation and utility
- regulation
- reimbursement, pricing and value-based contracting
The Discovery, Development and Validation of Predictive and Prognostic Biomarkers in Immunotherapy: A Complex Multi-step, Multi-dimensional Process

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- pre-treatment baseline and longitudinal Rx response profiling, AE and HP risk
- concordance of liquid biopsies with intratumoral microenvironment
- standards for clinical staging: ORR, PFS, RFS, OS, AEs, HP
- effect of disease co-morbidities and prior Rx regimen(s)
- cost-effectiveness and value-based pricing
Identification and Validation of Predictive and Prognostic Biomarkers in Immunotherapy

- tissue, body fluids
- bulk versus single cell analysis
- static single biopsy sample versus serial sampling
- germline and somatic variants
- continuous versus discrete biomarker expression dynamic ranges
- laser dissection capture
- frozen/FFPE

- multiOmics
- cyTOF
- multiplex IHC digital imaging and spatial interaction patterns
- exosomes/EVs
- patient derived organoids and xenografts
- radiomics
- statistically-powered ‘N’
The Discovery, Development and Validation of Predictive and Prognostic Biomarkers in Immunotherapy

- retrospective vs prospective studies
- RCTs vs platform trials
- real-world evidence observational trials and synthetic control arms
- clinical staging standards
- ORR, PFS, RFS, OS, HP, AEs

regulation of multiplex multiparameter assays

- research use only (RUO)
- 510 (K) vs PMA
- tumor class specific or agnostic pan-tumor efficacy
- Dx for combination Rx
- ML/AI algorithms for multiparameter integration
Cancer-Immune Phenotypes

From: D. S. Chen and I. Mellman (2017) Nature 541,34
System-Level Characterization of Tumor-Immune Interaction Networks

Intractable to Reductionist Methods
Classification of 47 Modules Defined by Weighted Gene Cluster Network Analysis in 28 Human Immune Cell Subsets

From: J. C. Rieckmann et al. (2017) Nature Immunol. 18, 583
Cell-Type and Context-Dependent Expression of Secreted Proteins in Activated Myeloid Dendritic Cells

From: J. C. Rieckmann et al. (2017) Nature Immunol. 18, 583
The Discovery, Development and Validation of Predictive and Prognostic Biomarkers in Immunotherapy

- high dimensional phenotyping on an unprecedented scale
  - from multiOmics profiling to stringent clinical annotation
- daunting level of theoretical ‘large N’ combinatorial interactions
  - tumor (sub)clonal heterogeneity, diversity of immune cell subsets, signaling molecules and intracellular pathways
- different dynamic ranges for different analytes/feature sets
- continuous versus discrete signals
- linear and non-linear effects in input:output interactions and biological outcomes
- inter-dependent and independent variables affecting the same phenotype
- need for very large analytical cohorts for multiparameter analysis
The Discovery, Development and Validation of Predictive and Prognostic Biomarkers in Immunotherapy

- massive data
  - design of experimental protocols to integrate diverse datasets
  - data standards and format for data exchange and meta-analysis
- new computational ML/AI algorithms for multiparameter feature extraction and building classifiers
- new regulatory paradigms for Dx-Algo validation and constant refinement (V1, 2...n)
The Discovery, Development and Validation of Predictive and Prognostic Biomarkers in Immunotherapy: A Complex Multi-step, Multi-dimensional Process

- specimen(s) and sampling frequency
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The Curse of Dimensionality ($n < p$)

- number of independent observation ($n$) is vastly smaller than number of potential features in the raw data sets ($p$) and omnipresent risk of overfitting
# A Broad Classification of Tumor-Immune Microenvironment (TME)

<table>
<thead>
<tr>
<th>High TMB</th>
<th>Low TMB</th>
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<tbody>
<tr>
<td>High T cell-inflamed signature</td>
<td>Low T cell-inflamed signature</td>
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</table>

<table>
<thead>
<tr>
<th>High TMB</th>
<th>Low TMB</th>
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</thead>
<tbody>
<tr>
<td>Low T cell-inflamed signature</td>
<td>Low T cell-inflamed signature</td>
</tr>
</tbody>
</table>
Tumor Immunophenotypes Associated With Responsiveness to Immune Checkpoint Blockade

“Hot”, “Inflamed”, “Immunogenic”

- high tumor mutation burden
- high tumor-infiltrating CD8+ cytotoxic cells
- activation of tissue-resident T cells (Tres)
- long lived memory T cells (Tem)
- high Th1 and T17 helper cells
- CD21+DCs
- high expression of Th1 stimulating cytokines
  - CCL2,3,4,5, CSC29, CXCd10
- higher expression of TIL checkpoint receptors
  - PD-1, PD-L1, CTLA-4, LAG3
- M1 phenotype tumor-associated macrophages (TAM)
- low Tregs, MDSCs
- low TGF-β
Shifts of Intratumoral Immune Cell Populations to Immunosuppressive Phenotypes with Tumor Progression

P. Charoentong et al. (2017) Cell Reports 18, 248

Blue = enrichment
Yellow = depletion
Understanding the (Pre) Exhaustion T Cell Phenotypes Induced by Upregulation of Immune Checkpoint Molecules and Chronic TCR Stimulation

Identification of T Cell ‘State Spaces’ and Responsiveness to Reinvigoration by ICB (and other I/O Rx)
t-SNE Clusters (7) of Single Cell Analysis and Clustering of T Cell Subsets in Cancer

Single Cell Analysis of CD8+ Cell State Transitions

Adapted from X. Guo et al. (2018) Nat. Med. 24, 479
CD8+ T Cell State Heterogeneity and Association with Clinical Response in Melanoma

Adapted from: M. Sade-Feldman et al. (2018) Cell 175, 998-1013
Mechanisms of T Cell Exclusion from Tumor Infiltration

The Vascular: Immune Checkpoint as a Therapeutic Target?
The T Cell-Vascular Interface: Vessel Architecture and T Cell Extravasation

The Vascular: Immune Checkpoint: A New Therapeutic Target?

- tumor-mediated exclusion of T cell extravasation and intratumoral infiltration
- inhibition of T cell adhesion and rolling on activated HEV
- PAK4 upregulation and β-catenin (SITC 2018 Abstract 039)
- GDF-15 upregulation (growth and differentiation factor 15)
  - impaired activation of IFA-1 on T cells and reduced endothelial binding (SITC 2018 Abstract 041)
- melanoma CDK4 upregulation signature associated with exclusion but role in T cell egress unknown

Tumor Immunophenotypes Associated With Non-Responsiveness to Immune Checkpoint Blockade

“Cold”: “Non-Inflamed”, “Non-Immunogenic”, “Immune Desert”

- low mutational and neoantigen burdens
- low CD8+ effector cells
- high Tregs and MDSCs, low Th1
- immunoediting and loss/down-regulation of neoantigens
- impaired antigen presentation
  - loss/downregulation of MHC
  - JAK 1/2 and β2 microglobin mutations in MHC1
- increased levels of immunosuppressive cytokines
  - PTEN loss and increased CCL2, VEGF and reduced T cell infiltration
  - catenin/Wnt mutations and reduced CCL4 chemokine production and dendritic cell recruitment
- CCR2/CCL2 and M2 phenotype TAMs
- IPRES (innate PD-1 resistance) gene signature
  - immunosuppressive cytokines, EMT-TFs and pro-angiogenic factors
PDL-1 Expression as a Predictive Biomarker for Anti-PD-1 and Anti-PDL-1 Therapy
PDL-1 Expression as a Predictor of ICB Response

- imperfect as stand alone response predictor
- multiple studies correlating PDL-1 expression on tumor cells with response to ICB but others detect no association
- patients with low to no detectable PDL-1 can experience durable clinical benefit
- heterogeneity in cell type expression
  - TILs versus tumor cells
- non-standardized detection assays and cut-off points for IHC positivity and staining intensity
Tumor Mutation Burden (TMB), DNA Mismatch Repair Deficiency (MMRd), Microsatellite Instability (MSI-H), Neoantigen Burden and Response to ICB
Mismatch repair deficiency in 12,019 samples across 24 tumor types

From: D. T. Lee et al. (2017) Science 357, 409
Cancer Phenotype Agnostic Profiling for Microsatellite Instability (MSI) and DNA Mismatch Repair Deficiency (MMRd)

- MSI-high (MSI-H) as lineage agnostic predictive marker for anti-PD-1 immunotherapy
  - FDA approval
- Lynch Syndrome (LS): germline MMRd due to mutations in MLH1, MSH2, MSH6, PMS3, EPCAM
- Historical recognition of LS germline MMRd for predisposition to CRC and endometrial cancer
- LS phenotype higher prevalence in other malignancies than previously recognized
Distribution of MSI and Germline MMRd Mutation Across Cancer Types (N=15,045)

TMB, Neoantigen Expression and I/O Rx Efficacy

From: C-H Lee et al. (2018) Trends in Immunol. 39, 536
https://doi.org/10.1016/j.it.2018.04.005
Tumor Mutation Burden (TMB) and ICB Response

- positive pan-cancer correlation with PFS across 27 tumors
- outliers
  - Merkel cell carcinoma and RCC higher response than predicted by TMB
  - mismatch repair proficient CRC less responsive than predicted by TMB
- TIL immune infiltration correlates with TMB and/or neoantigen burden
  - correlation for cancers driven by recurrent mutations but not those driven by copy number alterations (breast, pancreas)
  - RCC outlier as highest immune infiltration score despite low TMB
- case by case patient variation within every lineage
# Tumor Mutational Burden (TMB)

## Analytical Validation

<table>
<thead>
<tr>
<th>Workflow</th>
<th>Step 1: In silico analysis</th>
<th>Step 2: Empirical analysis</th>
<th>Step 3: Clinical analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samples</td>
<td>Publicly available TCGA data</td>
<td>Cells derived from human tumors</td>
<td>Clinical Samples</td>
</tr>
<tr>
<td>Goals</td>
<td>Identify sources of variability between TMB calculated using whole exome sequencing (WES) &amp; various targeted panels used in the clinic</td>
<td>Agree upon creation of a universal reference standard using WES Identify sources of variability after alignment of TMB scores from targeted panels to the reference standard</td>
<td>Conduct a retrospective analysis using patient outcome data to assess the variability around clinically meaningful cut-off values and inform clinical use.</td>
</tr>
<tr>
<td>Timeframe</td>
<td>May 2018</td>
<td>Fall 2018</td>
<td>Winter 2018/Spring 2019</td>
</tr>
</tbody>
</table>
Cutpoint for Top 20% TMB Associated with Longer OS with ICB Therapy Varies Across Different Tumor Types

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>No. of patients</th>
<th>Cutoff</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All samples in cohort</td>
<td>1,662</td>
<td>-</td>
<td>$1.59 \times 10^{-6}$</td>
</tr>
<tr>
<td>Bladder</td>
<td>214</td>
<td>17.6</td>
<td>0.040</td>
</tr>
<tr>
<td>Breast</td>
<td>45</td>
<td>5.9</td>
<td>0.605</td>
</tr>
<tr>
<td>ER+</td>
<td>24</td>
<td>6.8</td>
<td>0.287</td>
</tr>
<tr>
<td>ER-</td>
<td>21</td>
<td>4.4</td>
<td>0.731</td>
</tr>
<tr>
<td>Unknown primary</td>
<td>90</td>
<td>14.2</td>
<td>0.155</td>
</tr>
<tr>
<td>Colorectal</td>
<td>110</td>
<td>52.2</td>
<td>0.031</td>
</tr>
<tr>
<td>Esophagogastric</td>
<td>126</td>
<td>8.8</td>
<td>0.221</td>
</tr>
<tr>
<td>Glioma</td>
<td>117</td>
<td>5.9</td>
<td>0.465</td>
</tr>
<tr>
<td>Head and neck</td>
<td>138</td>
<td>10.3</td>
<td>$7.42 \times 10^{-3}$</td>
</tr>
<tr>
<td>Melanoma</td>
<td>321</td>
<td>30.7</td>
<td>0.067</td>
</tr>
<tr>
<td>Non-small cell lung</td>
<td>350</td>
<td>13.8</td>
<td>$2.30 \times 10^{-4}$</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>151</td>
<td>5.9</td>
<td>0.569</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Drug class</th>
<th>No. of patients</th>
<th>Cutoff</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combo</td>
<td>260</td>
<td>-</td>
<td>0.018</td>
</tr>
<tr>
<td>CTLA4</td>
<td>146</td>
<td>-</td>
<td>$1.89 \times 10^{-3}$</td>
</tr>
<tr>
<td>PD-1/PDL-1</td>
<td>1,256</td>
<td>-</td>
<td>$6.95 \times 10^{-4}$</td>
</tr>
</tbody>
</table>

Lineage-Specific TMB Cutoff Scoring

- rank individual patient TMB score as a percentile within overall dynamic range for their tumor class
Neoantigen Expression and Detection in Prediction of Responsiveness to Immune Checkpoint Blockade (ICB)

- antigen loss/reduced expression
- impaired immune recognition and antigen processing

- loss of mutations encoding neoantigens
  - clonal immuno-editing
  - chromosomal deletion(s)

- HLA genotype and loss of HLA heterozygosity

- pathway mutations in antigen processing
  - JAK, 1, 2
  - β2M, TAP1
  - IFN-γ

intrinsic and acquired resistance to ICB
HLA Loss of Heterozygosity in Lung Adenocarcinoma and Lung Squamous Cell Carcinoma

- HLA loss of heterozygosity and failure to recognize antigenic peptides no longer presented on the lost allele
- enrichment of neoantigens predicted to bind with high affinity to lost vs retained HLA alleles
- higher frequency of LOH in subclones at metastatic sites
  - role of immune microenvironment(s) as a selective force in shaping branched clonal evolution?

Epigenetic Marker of anti-PD-1 Response in Stage IV NSCLC*

- unmethylated status of the regulatory T-cell transcriptome factor forkhead box IP (EPIMMUNE positive)
- no correlation with clinical benefit in patients not treated with immunotherapy
- EPIMMUNE-negative signature in unresponsive tumors enriched in TAMS, neutrophils, CAFs and endothelial cells with senescence phenotype

*M. Duruisseaux et al. (2018) Lancet Resp. Med. 6, 771
Demethylation Agents for Combination Immunotherapy

- Demethylation agents enhance chemokine production by Th cells and T cell trafficking to tumor in preclinical models
  - N. Nagarsheth et al. (2016) Cancer Res. 76, 225
Deep Phenotyping and ID of Genetic Contributions to Individual Variation in Cytokine Responses

O.B. Bakker et al. (2018) Nature Immunology 19, 776

- 91 cytokine-stimulus pairs in 534 individuals elicited by 20 pathogens
- 70% heritability

Do germ line variants in lumphokine/cytokine affect responsiveness to I/O therapy and AE risk (cytokine release syndrome)?
Integration of scRNA Seq and Spatial Transcriptomic in the Analysis of Immune Cell Subsets in Pancreatic Ductal Carcinoma

Adapted from: R. Moncada et al. (2018) bioRxiv254375
• use of Google inception v3 algorithm for analysis of histopathology
  - 10,000 to > 100,000 pixels for 20x to 40x stained images
• robust identification of LUAD and LUSC (AUC of 0.97) comparable to pathologist histopathology classification
• prediction of presence or absence of genes from image data alone
  - EGR, STKII, FAT1, SETBP1, KRA5, TP53
New Digital Pathology Imaging Systems for In Situ Multi-, Super- and Hyperplex Molecular Profiling

- fluorophore-, hapten- or metal-coupled antibodies
- oligonucleotide barcoding
- IF Immunohistochemistry (IF-IHC)
- In Situ Hybridization (ISH)
- Laser Capture Microdissection (LCM)
- Matrix-Assisted Laser Desorption Ionization Imaging Mass Spectrometry (MALDI-IMS)
- Vibrational Spectroscopy
  - two photon absorption fluorescence (TPAF)
  - coherent Raman scattering microscopy (CRS)
  - Fourier Transform Infrared Spectroscopy (FTIR)
Circulating Biomarkers to Monitor ICB Response Patterns
Circulating Biomarkers Associated With ICB Response*

- TMB high
- ctDNA initial increase with decline to undetectable levels
- loss of PD-L1 positive CTCs (CD45+ CK+ but need to exclude CD11b+ CD4510 CK+ myeloid cells as potential false positive)
- initial increase in Tregs followed by decline
- sustained high and expanded TCR clonality
- rising exosomal PD-1 and CD28 expression
- high baseline PD-L1 levels (>1.5 ng/ml) in anti-PD-1 but not anti-CTLA4

Increased Frequency of Circulating of CD14+CD16−HLA-Drhi Monocytes and Association with Positive Response to Anti-PD-1 Immunotherapy in Stage IV Melanoma

Systemic Predictive Markers for ICB Therapy

- Peripheral blood neutrophil to lymphocyte ratio greater than five associated with decreased PFS and OS across multiple cancer types
- High circulating T cell BIM levels (BCL-2 interacting mediator of cell death) association with poor prognosis and low likelihood of ICB response
Immune Suppression by Cancer-Derived Exosomes

- exosomal PD-LI suppression of CD8+ T cells
- decreased production of immunostimulatory molecules
  - IL-2, IL-17 and IFN-γ
- increased levels of immune inhibitory proteins
  - TGF-β, IL-10, COX-2
- miR212 induction of reduced MCH II expression
- miR222, miR494 and M1 to M2 shift in tumor associated macrophages
- immunosuppression of B cells by exosome membrane-associated CD39 and CD73 via production of extracellular adenosine
- impaired differentiation of DCs from bone marrow precursors
- enhanced survival of MDSC via activation of STAT3
- inhibition of NK cells by exosome surface MICA/MICB liquids, TGF-LAG and induction of inhibitory TGF-β
Peripheral T Cell Dynamics in Neoadjuvant anti-PD-1 Blockade in NSCLC *

- opportunity for neoadjuvant Rx to assess major pathological responses (MPRs)
- dynamic remodeling of peripheral TIL clonotypes post-Rx
- TIL clonotypes detected in peripheral blood at significantly higher frequency than intratumoral clonotypes

*J. Zhang et al. (2018) SITC Abstract 047
Commensal Microbiota and ICB Responses

- diversity and composition of gut but not oral microbiota influence response in mice and humans
  - NSCLC, RCC, melanoma and urothelial cancer
- decreased response in patients treated with antibiotics but not PPIs during ICB therapy
- adoptive transfer of response-associated bacteria to germ-free or antibiotic-treated mice conferred ICB sensitivity
  - different microbial species identified in different publications
  - different sequencing and metagenomic analysis methods
- major geographic variation in predominant gut microbiota phyla
Hyperprogressive Disease (HD) in Anti-PD-1/PDL-1 Immunotherapy

- reported variable incidence across different solid tumors (6% to 29%)
- discrimination of HD from naturally aggressive disease and pseudoprogression
- requires integration of dynamic estimates of tumor growth rates (TGR)
  - TGR = estimate of increase in tumor volume over time between two CT scans assuming exponential growth
- TGR algorithms publically available on line but not integrated into majority of imaging software packages in routine use

Combination Immunotherapies
Combination Immunotherapy in Cancer

- new neoadjuvant protocols
- amplification of neoantigen exposure by cytotoxic agents, oncolytic viruses
- stimulation of innate immune system and type 1 IFN signaling to enhance priming/activation of adaptive immune responses
- co-stimulation of CD8⁺ and CD4⁺ cells by agonist OX40, GITR or 4-1BB antibodies
- STING stimulation of dendritic cells to produce IFNβ
- use of drug delivery scaffolds for extended release of agonists
The Design of I/O Combination Clinical Trials

- combine agent with non-redundant MOAs and different targets
- need for evidence of efficacy as single agent as rationale for anticipated additive/synergistic efficacy?
  - cf. IDO1 inhibitor implosion
- dose, duration and sequence of administration
- approved dose for each agent or dose escalation titration?
- validation of preclinical models for new I/O agent discovery and evaluation of combination options (efficacy/safety)
  - allometry extrapolation for dose, duration, PK
  - shared human: murine immune determinants versus human-specific targets with need for humanized immune system mouse models
Chronobiology and Chronopharmacodynamics: Neglected Variables in Immunotherapy?
Framework for Temporally-Programmed $R_x$ Combinations in Cancer Immunotherapy

Chronobiology of Immune Response Timescales and Rational Design of Combination Therapies Using Animal Models

- CD4+ T cells exposed to IL-1 prior to priming/co-stimulation impairs activation, proliferation and memory formation
- expression of high affinity IL-2R on CD8+ T cells after activation is transient (versus Treg in which expression is constitutive) - implications for pulsatile versus continuous infusion
- brief IFN signaling induces activation of CD8+ cells but persistent signaling confers ICB resistance
- dosing of IFNα two days after IL-2 and cytotoxic Rx enhances tumor eradication versus simultaneous co-administration
- concurrent anti-PD-1 blockade negates effect of agonist OX40 antibody
Chronobiology of Immune Cell Trafficking Patterns:* Potential Implications for Immuno-Pharmacodynamics?

- circadian oscillations in number of circulating immune cells and trafficking to lymph nodes (LN) and tissues
- T and B cells express classic circadian core clock genes
- circulating lymphocyte numbers peak around Zeitgeber Time 5 (ZT) (5 hrs after light onset)
- CD4$^+$ and CD8$^+$ cells exhibit peak LN levels at ZT13
- expression of CCR7 on HEV in LN exhibits parallel rhythmicity
- lymphocyte egress from LN to efferent lymph regulated by circadian expression of sphingosine-1-phosphate receptor 1 (S1P1R)
- engineered deletion of core clock gene Bmal1 in T cells ablates circadian rhythmicity

D. Druzd et al. (2017) Immunity 46, 120
Is the Unrestricted Use of Immunotherapy With Current High Non-Responder/Failure Rates Economically Sustainable?

The Looming Expansion of the ‘Baby Boomers’ Cancer Burden
Expensive Industry DTC Advertising Campaigns

Hype Versus Hope: A Delicate Ethical Balance
Come and Be Cured by Us: (Go Elsewhere at Your Peril)!
Immunotherapy: Hype and Hope

- Deserved recognition of ICB as a major therapeutic advance
- Media hype, scale of corporate DTC and AMC advertising campaigns
  - Biased emphasis on responder/super-responders distorts public awareness of NR>R and potential for serious toxicities
  - Unrealistic patient expectations of successful outcome
- Patient demands for immunotherapy despite no evidence of efficacy in their specific malignancy
Is the Bar in the ASCO Value Frameworks Too High in Assessing Long-Term Benefits in I/O Therapy?

- JAMA Oncology (2018) 4,326
  - analysis of approved I/O agents (2011 to 8/17)
- 23 indications for 6 I/O agents for metastatic solid tumors
- only 3 gained durable survival bonus points under ASCO framework
Performance-Based Contracts and Pricing: The Inevitable Future Landscape for Immunotherapy?

- robust identification of responders and non-responders
- companion diagnostics and labeling requirements
- performance-based outcomes and premium pricing

Integration of R:NR immunophenotypes into clinical trials and registration dossier

Risk sharing
The Urgent Clinical and Economic Imperatives for Predictive Markers to Differentiate Responder and Non-Responder Patients in Different I/O Regimens

- single most important opportunity for the (bio)pharmaceutical industry?
- increased payer pressure for performance-based outcomes?
- premium pricing for proactive industry engagement or reactive response to payer imposition of outcomes-based reimbursement?
Biomarkers for Prediction and Prognosis in Cancer Immunotherapy

- single biomarkers versus composite biomarker score
- static versus dynamic immuno-profiling
- standardized immuno-profiling methods (e.g., TMB cutoffs)
- large N cohorts for clinical validation and utility
- validation of cross-study cohort comparisons based on standardized profiling methods and similarity of (pre)treatment regimen/duration
- extended longitudinal monitoring for OS
- machine learning algorithms for multiparameter composite scores and deconvolution of independent and inter-dependent indicators
- regulatory standards for complex multiparameter Dx-software platforms for prediction and prognosis (monotherapy and combination therapy)