The Next Era in Immuno-Oncology

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### Declared Interests

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#### Advisory/Consultancy
- USG: Depts. of Defense and Homeland Security
- US Academy of Medicine Global Forum on Health

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Confronting the Clinical, Economic and Human Toll of Cancer

US Cancer Deaths (2014) 580,000
## US Cancer Prevalence Estimates 2010 and 2020

<table>
<thead>
<tr>
<th>Site</th>
<th># People (thousands)</th>
<th>% change</th>
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<td>2010</td>
<td>2020</td>
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<td>Breast</td>
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<td>Prostate</td>
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<td>Uterus</td>
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<td>Bladder</td>
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<tr>
<td>Lung</td>
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<td>Kidney</td>
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<td>Leukemia</td>
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<tr>
<td>All Sites</td>
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</table>

Cancer as a Complex Adaptive System: The Dynamic Interaction Between Host Immune Defenses and Relentless Emergence of Phenotypically Diverse Tumor Cell Clones

- Escape From Controls for Normal Tissue Architecture
- Genome Instability and Emergence of Clonal Variants
- Evasion of Clonal Detection/Destruction by Host Immune System
- Use of Host Systems to Promote Progression
- Invasion and Metastasis
- Emergence of Drug-Resistant Clones
Pembrolizumab and Therapy of Metastatic Melanoma in President J. Carter

Saturation TV Advertising
Cancer Immunotherapy Investment by Big Pharma: Big Bucks, Big Risks, Big Payoffs?
The Rationale for Cancer Immunotherapy

Overcoming the Tumor Cell Heterogeneity Problem?

Circumventing the Omnipresent Resistance Problem in Chemotherapy and Targeted Therapies?
Cancer as a Complex Adaptive System
The Relentless Emergence of Phenotypically Diverse Tumor Clones and Subclones During Progression

Rx Resistance
- intrinsic
- acquired
The Extravagant Landscape of Inter-individual Genomic Alterations in Cancer (Cell 2012: 150, 1107 and 1121)

- “malignant snowflakes”: each cancer carries multiple unique mutations and other genome perturbations
- disturbing implications for therapeutic ‘cure’ and development of new Rx
The Multi-Dimensional Matrix for Cancer Immunotherapy

- Cellular and humoral multi-component system and complex regulatory networks
- Tumor cell (epi) genetic and phenotypic heterogeneity and clonal diversification
- Dynamic tumor-host cell interactions and complex immune activation/suppression pathways

Host immune system

Tumor

Tumor micro-environments
The Multi-Dimensional Matrix for Cancer Immunotherapy

- Impact of therapy
  - Emergence of resistance
  - Immune functions

- Dynamic tumor-host cell interactions and complex immune activation/suppression pathways

- Tumor cell (epi) genetic and phenotypic heterogeneity and clonal diversification

- Cellular and humoral multi-component system and complex regulatory networks

- Host immune system

- Tumor micro-environments
Anti-Cancer Immunotherapies

- passive therapies
- active therapies
- combination therapies
Passive Immunotherapy:
Enhancement of Anti-Tumor Activities Without Direct Modification of Intrinsic Host Immune Functions

- therapeutic anti-tumor antibodies
- adoptive transfer of cytotoxic T lymphocytes (TILS, TCRs, CARs)
- oncolytic viruses
Passive Immunotherapy With Antibodies
## FDA-Approved Immunotherapy Agents

### Monoclonal Antibodies (mAbs)

<table>
<thead>
<tr>
<th>MOA</th>
<th>Agent</th>
<th>Year</th>
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<td>CD52</td>
<td>Alemtuzumab</td>
<td>2001</td>
<td>CLL</td>
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<td>CD20</td>
<td>Ofatumumab</td>
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<td>CD20</td>
<td>Rituximab</td>
<td>1997</td>
<td>NHL</td>
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<tr>
<td></td>
<td></td>
<td>2010</td>
<td>CLL</td>
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<tr>
<td>CD38</td>
<td>Daratumumab</td>
<td>2015</td>
<td>Multiple Myeloma</td>
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<tr>
<td>HER2</td>
<td>Trastuzumab</td>
<td>1998</td>
<td>Breast cancer</td>
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<td></td>
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<td>2010</td>
<td>Gastric cancer</td>
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<tr>
<td>EGF</td>
<td>Cetuximab</td>
<td>2004</td>
<td>Colorectal cancer</td>
</tr>
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<td></td>
<td></td>
<td>2011</td>
<td>Head/neck cancer</td>
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<tr>
<td>CD20 ADC</td>
<td>Y-Ibritumomab</td>
<td>2002</td>
<td>NHL</td>
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<tr>
<td></td>
<td>tiutexan</td>
<td></td>
<td></td>
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<tr>
<td>CD30 ADC</td>
<td>brentuximab</td>
<td>2011</td>
<td>Hodgkin lymphoma, ALCL</td>
</tr>
<tr>
<td></td>
<td>vedotin</td>
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</table>

**BITE antibody constructs: Bi- and Multi-Specific Antibodies**

<table>
<thead>
<tr>
<th>MOA</th>
<th>Agent</th>
<th>Year</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3/CD19</td>
<td>Blinatumomab</td>
<td>2014</td>
<td>ALL</td>
</tr>
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</table>
Intrinsic Limitations of Passive Antibody Therapies

Tumor Cell Antigenic Heterogeneity and Dynamic Emergence of New Antigenically Different Clones
Active Immunotherapies

Clone Wars

Relentless Emergence of New Tumor Cell Clones During Tumor Progression and Immune Evasion versus Activation of Host T Lymphocyte Clones to Kill (Neo)Antigen-Specific Tumor Clones
The Promise of Immunotherapy: Circumventing the Inevitable Drug Resistance Problem in Targeted Rx Therapy versus Restoration of Effective Immune Surveillance

- **Targeted drugs**
  - $Rx_1$
  - $Rx_2$
  - $Rx_3$
  - $Rx_4$
  - $Rx_5$

- **Cytotoxic T cells**
  - $NA_1$
  - $NA_2$
  - $NA_3$
  - $NA_4$
  - $NA_5$

- **Rx-resistant clones/ Rx refractory disease**
  - $NA_{n1}$
  - $NA_{n2}$

- **Immuno-therapeutic regimens**
  - Adaptive evolution of immune response and expanded cytotoxic T cell responses
Mapping the Molecular Control Pathways in Immune Responses for Rational Design of New Immunotherapeutics
Understanding Molecular Signaling (Information) Systems and Feedback Control in the Immune System
The Immunostat: The Constantly Shifting Balance Between Activation and Suppression
Active Immunotherapies

**Activation of Cytotoxic T Cells**
- Immunostimulatory cytokines
- Vaccine-induced expansion of cytotoxic T cells to cancer neoantigens
- Unanticipated immune-stimulation by targeted Rx/SOC

**Blockade/Inhibition of Immunosuppressive Pathways**
- Immune checkpoint inhibitors (CTLA-4, PD-1, PD-L1)
- Inhibition of Tregs and myeloid-derived suppression cells
- Inhibition of immunosuppressive signals from non-immune cells in the tumor microenvironment
Cancer Immunotherapy

[Diagram showing activating and inhibitory receptors in cancer immunotherapy, including Agonist and Antagonist antibodies with examples like Dacetuzumab, Chi Lob 7/4, CP-870893, Ipilimumab, Tremelimumab, αPD-1, Nivolumab, Pembrolizumab, Pidilizumab, AMP-224, αPD-L1, Avelumab, (MSB0010718C), MEDI4736, MEDL3280A, BMS-936559.]
The Immune-Checkpoint Axis

- complex networks of multiple negative checkpoint regulators to limit the scale and duration of activated immune reactions
- maintain self-tolerance
- prevent autoimmunity
- limit cytokine release storms
Immune Checkpoint Inhibitors
Timelines of FDA Approvals

- **March 2011**
  - ipilimumab: melanoma

- **September 2014**
  - pembrolizumab: melanoma

- **October 2014**
  - pembrolizumab: NSCLC

- **December 2014**
  - nivolumab: melanoma

- **March 2015**
  - nivolumab: NSCLC

- **October 2015**
  - nivolumab: renal cancer
Combination Immunotherapies
Combination Immunotherapy

- ipilimumab + nivolumab
  - melanoma 60% response versus single agent responses 44% (nivo), 19% (ipi)
  - 12% CR
  - 80% two year survival
## Combination Immunotherapies

<table>
<thead>
<tr>
<th>Combination Therapy</th>
<th>Mechanisms of Action</th>
<th>Phase</th>
<th>Indication</th>
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</thead>
<tbody>
<tr>
<td>Nivolumab + ipilimumab</td>
<td>Anti-PD1 + anti-CTLA-4</td>
<td>I/II</td>
<td>Gastric, TNBC, PA, SCLC, Bladder, Ovarian</td>
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<tr>
<td></td>
<td></td>
<td>II/III</td>
<td>Melanoma, RCC</td>
</tr>
<tr>
<td>Nivolumab + BMS-986016</td>
<td>Anti-PD1 + anti-LAG3</td>
<td>I</td>
<td>Solid tumors</td>
</tr>
<tr>
<td>Nivolumab + Viagenpumatumucel-L</td>
<td>Anti-PD1 + vaccine</td>
<td>I</td>
<td>NSCLC</td>
</tr>
<tr>
<td>Nivolumab + urelumab</td>
<td>Anti-PD1 + anti-4-1ββ</td>
<td>I/II</td>
<td>Solid Tumors, B-Cell NHL</td>
</tr>
<tr>
<td>Atezolizumab + MOXR0916</td>
<td>Anti-PDL1 + anti-OX40</td>
<td>I</td>
<td>Solid Tumors</td>
</tr>
<tr>
<td>Atezolizumab + varlilumab</td>
<td>Anti-PDL1 + anti-CD27</td>
<td>II</td>
<td>RCC</td>
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<tr>
<td>Atezolizumab + GDC-0919</td>
<td>Anti-PDL1 + IDO inhibitor</td>
<td>I</td>
<td>Solid Tumors</td>
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<tr>
<td>Epacadostat + atezolizumab, durvalumab, or pembrolizumab</td>
<td>IDO inhibitor + anti-PDL1 or anti-PD1</td>
<td>I/II</td>
<td>Solid Tumors</td>
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<tr>
<td>Pembrolizumab + T-Vec</td>
<td>Anti-PD1 + vaccine</td>
<td>III</td>
<td>Melanoma</td>
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<tr>
<td>Durvalumab + tremelimumab</td>
<td>Anti-PDL1 + anti-CTLA-4</td>
<td>I/II</td>
<td>SCCHN</td>
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<td></td>
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<td>II</td>
<td>Mesothelioma, UBC, TNBC, PA</td>
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<tr>
<td></td>
<td></td>
<td>III</td>
<td>NSCLC, Bladder</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RCC</td>
</tr>
<tr>
<td>Pidilizumab + dendritic cell/RCC fusion cell vaccine</td>
<td>Anti-PD1 + vaccine</td>
<td>II</td>
<td>RCC</td>
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# Immunotherapy Plus Chemotherapy

<table>
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<th>Combination Therapy</th>
<th>Mechanisms of Action</th>
<th>Phase</th>
<th>Indication</th>
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</thead>
<tbody>
<tr>
<td>Nivolumab + platinum doublet chemo</td>
<td>Anti-PD1 + chemotherapy</td>
<td>III</td>
<td>NSCLC</td>
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<tr>
<td>Pembrolizumab + cisplatin</td>
<td>Anti-PD1 + chemotherapy</td>
<td>III</td>
<td>Gastric</td>
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<tr>
<td>Pidilizumab + lenalidomide</td>
<td>Anti-PD1 + chemotherapy</td>
<td>I/II</td>
<td>Multiple Myeloma</td>
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<tr>
<td>Pidilizumab +sipuleucel-T + cyclophosphamide</td>
<td>Anti-PD1 + vaccine + chemotherapy</td>
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<td>Prostate</td>
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<td>Atezolizumab + carboplatin/paclitaxel +/- bevacizumab</td>
<td>anti-PDL1 + chemotherapy +/- anti-VEGF</td>
<td>III</td>
<td>NSCLC</td>
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# Immunotherapy Plus Targeted Therapy

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<th>Mechanisms of Action</th>
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<tr>
<td>Atezolizumab + bevacizumab</td>
<td>Anti-PDL1 + anti-VEGF</td>
<td>II/III</td>
<td>RCC</td>
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<tr>
<td>Atezolizumab + cobimetinib</td>
<td>Anti-PDL1 + MEK inhibitor</td>
<td>I</td>
<td>Solid Tumors</td>
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<tr>
<td>Atezolizumab + vemurafenib</td>
<td>Anti-PDL1 + BRAF inhibitor</td>
<td>I</td>
<td>Melanoma</td>
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<tr>
<td>Atezolizumab + erlotinib or alectinib</td>
<td>Anti-PDL1 =EGFR or ALK inhibitor</td>
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<td>NSCLC</td>
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<tr>
<td>Nivolumab + bevacizumab</td>
<td>Anti-PD1 + anti-VEGF</td>
<td>II</td>
<td>RCC</td>
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<td>Pembrolizumab + pazopanib</td>
<td>Anti-PD1 + tyrosine kinase inhibitor</td>
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<td>Pembrolizumab + dabrafenib + trametinib</td>
<td>Anti-PD1 + BRAF inhibitor + MEK inhibitor</td>
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<td>Melanoma</td>
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<td>Durvalumab + dabrafenib + trametinib</td>
<td>Anti-PDL1 + BRAF inhibitor + MEK inhibitor</td>
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<td>Melanoma</td>
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<td>Nivolumab + sunitinib, pazopanib or ipilimumab</td>
<td>Anti-PD1 + RTK inhibitor, RTK inhibitor</td>
<td>I</td>
<td>RCC</td>
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Combination of PD-1, PDL-1 and CTLA-4 Blockade

- higher clinical response rates than single agent
  - melanoma, NSCLC, head and neck
- lower tolerability and higher discontinuation rates
- management of toxicity in broad patient populations in community settings
- cost
- dosing and sequence
- competition and cutting corners in dose optimization
Cell-Based Therapies
Immunotherapeutic Strategies to Enhance Immune Responses to Patient-Specific Tumor Neoantigens

**Immune Checkpoint Modulation**
- Induce tumor cell destruction
- Provide checkpoint blockade

**Cancer Neoantigen Vaccines**
- Identify potential neoantigens
- Create synthetic vaccine (RNA, DNA, peptide)
- Provide in combination with adjuvant and checkpoint blockade

**Adoptive Cell Therapy TILs, TCRs, CARs**
- Identify potential neoantigens
- Induce or expand neoantigen specific T cells
- Provide in combination checkpoint blockade

Adoptive T Cell Transfer in Cancer Immunotherapy

- collect patient’s T cells
- expand T cells ex vivo
- +/- lymphodepletion/conditioning prior to reinfusion of expanded cells

<table>
<thead>
<tr>
<th>TILs</th>
<th>TCRs and CARs</th>
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<tr>
<td>• no modification only expansion</td>
<td>• transfection with genes for T cell receptors (TCRs) or chimeric antigen receptors (CARs) against specific tumor neoantigens</td>
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</table>
Design of Chimeric Antigen Receptors for Cancer Immunotherapy: Engineered Combination of Elements of Antibody Structure and T Cell Receptors

C.L. Batlevi et al. (2016) Nature Reviews Clinical Oncology 13,25
Design of Chimeric Antigen Receptors for Cancer Immunotherapy

C.L. Batlevi et al. (2016) Nature Reviews Clinical Oncology 13,25
Design of Chimeric Antigen Receptors

‘armored CARs’
- incorporation of additional T cell activation mechanisms into CAR-T cells to counter immunosuppression in the tumor microenvironment

‘switchable CARs’
- integration of ‘kill switches’ (reversible/irreversible) to shut down CAR-T cells for better control of toxicities
Future Needs in the Evolution CAR Therapy

- need to establish efficacy in solid tumors
- lymphodepletion by preconditioning appears necessary for successful treatment and CAR-cell persistence
- reduction of AEs and CRS
  - CRS is observed more frequently in patients with high tumor burden
  - merits of prior Rx tumor-debulking in improving safety profile?
- dose selection is difficult since transferred cell expansion in vivo appears highly variable
- reduce cost and complexity of ex vivo scale up of cells for reinfusion
- ‘off-the-shelf’ use of allogeneic cells HLA matched to recipients
NK Cells: The Next Target for Selective Activation of Anti-Tumor Cell Responses?
The Next Generation of Immuno-Oncology Therapeutics

Beyond CTLA-4 and PD-1/PD-L1 as Targets for Cancer Immunotherapeutics
Next Generation Immunotherapies

- better response rates
- extended durable clinical benefits
- better tolerability
- improved knowledge of how to best use I/O combinations or I/O plus SOC
- predictive biomarkers for reliable stratification of responder and non-responder patients and monitoring treatment efficacy
The Complex Dynamics of the Host Immune System-Tumor Ecosystem

- corrupted tumor microenvironment
  - protumor inflammatory responses and immunosuppressive signals
- intrinsic immune checkpoint regulators (suppression)
  - CD28-CTLA-4, PD1-PD-L1, TIM-3, LAG
- blockade of T cell infiltration
- extrinsic checkpoint regulators (suppression)
  - regulatory T cells (Tregs), myeloid suppressor cells (MDSC)
- T cell anergy and exhaustion (suppression)
- immune evasion (escape)
  - antigen-deletion clones, neoantigens with low affinity
Negative Immune Checkpoint Regulators (NCRs) as New Targets for Next-Generation Immunotherapeutics

- TIM-3
  - T-cell immunoglobulin and mucin-containing protein 3
- LAG-3
  - Lymphocyte-activated gene-3 (CD223)
- TIGIT
  - T-cell immunoreceptor with Ig and ITIM domains
- BTLA
  - B- and T-lymphocyte attenuator
- VISTA
  - V-domain Ig suppressor or T cell activatin
The Immunosuppressive Tumor Microenvironment  
The New Frontier, A Wealth Of Targets  

From: K.M. Mahoney et al. (2015) Clinical Therapeutics 34, 764
The Tumor Microenvironment and the “Stromagenic Switch”
The Stromagenic Switch

- role of stroma surveillance mechanisms in preventing tumorigenesis or imposition of dormant states

- transition of cancer-associated stromal cells (CASC) to protumorigenic drivers
  - inflammation
  - ECM remodeling
  - immunosuppressive signaling
  - M1 to M2 macrophage conversion
  - angiogenesis
  - invasion, EMT and metastasis

- altered stromal elements as new Rx Targets
Predictive Identification of Responder and Non-Responder Patients
Why Are Some Cancer Types More Responsive to Immunotherapy?

More Responsive

- melanoma
- NSCLC
- bladder
- renal
- head and neck

Less Responsive

- pancreatic
- colorectal
- ovarian
Immunogenic Versus Non-Immunogenic Tumor Microenvironments?

- **Immunogenic**
  - ‘hot’
  - ‘inflamed’
  - ‘stimulatory’

- **Non-Immunogenic**
  - ‘cold’
  - ‘non-inflamed’
  - ‘silent’
Immunogenic Versus Non-Immunogenic Tumor Microenvironments

**Immunogenic**
- ‘hot’
- ‘inflamed’
- ‘stimulatory’
- high mutagenic burden
- high tumor neoantigen expression

**Non-Immunogenic**
- ‘cold’
- ‘non-inflamed’
- ‘silent’
- low mutagenic burden
- low tumor neoantigen expression
Cancer Immunotherapy

- in situ infiltration of activated T cells is critical for therapeutic response and tumor regression
- not all immune infiltrates are equal
- therapeutic success depends on the dynamics balance of immune activation/suppression factors in the tumor microenvironment
T-Cell Tumor Infiltration

From: K. Wkatsuki et al. (2013) Spandidos Publications (DOI: 10.3892/or.2013.2302)
Profiling Intratumoral Immune Cell Populations

**positive prognosis: immune activation dominant**
- cytotoxic T cells and memory-T cells
- antigen-presenting cells

**negative prognosis: immune suppression dominant**
- T regulatory cells (Treg)
- Th2 helper T cells
- myeloid-derived suppressor cells
- M2 phenotype macrophages
The Immunophenotype

Biomarker Development for Immuno-Oncology

Developing An Immunoscore for Individual Patients
The Paucity of Biomarkers to Identify Responder and Non-Responder Patients

- Major problem in patient selection and cost of futile Rx
- Conflicting data on relationship of PD-L1 expression and responsiveness to anti-PD1 therapy
  - KEYNOTE – 001: 45.2% of patients below predetermined PD-L1 cutoff still responded to pembrolizumab
- Use of different antibody assay platforms and PD-L1 cutoff levels in different clinical trials
## PD-L1 Expression and Response Rate (RR) for Immune Checkpoint Modulation in Melanoma

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<tr>
<th>Agent</th>
<th>Response Rate</th>
<th>Median PFS Months</th>
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<tr>
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<td>PD-L1 none/low</td>
<td>PD-L1 high</td>
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<tr>
<td>iplimumab</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>nivolumab</td>
<td>41</td>
<td>57</td>
</tr>
<tr>
<td>iplimumab plus nivolumab</td>
<td>54</td>
<td>72</td>
</tr>
</tbody>
</table>

characterization of immune functions in three anatomic compartments
- lymphoid organs/nodes, systemic circulation and neoplastic lesions

formation of international consortium to establish a classification metric designated TNM-I (TNM-Immune)
Profiling of Intratumoral Core (GZMB) Cytotoxic T Cells and Lymphatic Vessel Density at the Invasive Margin (PDPN) in 838 CRC Patients and Relationship to Overall Survival

From: B. Mlecnik et al. (2016) Science Translational Medicine 8, 327ra26
The Tumor Mutational Landscape and Responses to Immunotherapy Agents

- hypothesis that high(er) non-synonymous mutation burden generates neoantigens recognized by the immune system
- patients with higher neoantigen burden exhibit higher durable clinical benefit (DCB)
- ‘mutanome’ profiling
  - ID mutant nonamer peptides with <500nM binding affinity for patient-specific class I HLA alleles
- combination with targeted anti-cancer agents
  - increase neoantigen release?
Estimates of Likelihood of Neoantigen Expression Based on Somatic Mutation Prevalence in Different Tumor Types

The Tumor Mutational Landscape and Response to Immunotherapy Agents

- higher non-synonymous mutation burden correlates with improved objective response, PFS and durable clinical benefit
- highest response rates in melanoma and NSCLC
  - chronic mutagen burden (UV, tobacco carcinogens)
- high inter-patient variation in NSCLC
  - smokers vs non-smokers
  - paradoxical greater DCB in smokers to PD-1 blockade
Molecular ‘Smoking Signature’ in NSCLC and PFS in Patients Treated with Pembrolizumab

From: N.A. Rizvi et al. (2016) Science 348, 124
Wagner Parsimony Profiling of Intratumoral Clonal Heterogeneity in 11 Lung Adenocarcinomas and Different Trunk (Blue), Branch (Green) and Private (Red) Branches

From: J. Zhang et al. (2014) Science 346, 256
Neoantigen Clonal Architecture and Clinical Benefit of Immune Checkpoint Blockade (anti-PD1 pembrolizumab)

From: N. McGranahan et al. (2016) Science DOI.10.1126/aaf490
Use of Combination Therapies to Increase Neoantigen Expression and Release
Lessons from Breast Cancer Trials of HER-2 Kinase Inhibitors

- trastuzumab as a singular success story for HER-2 positive breast cancer
- exploration of value of small molecular TKIs
  - lapatinib (EGFR + HER2) afatinib (EGFR, HER2, HER4) neratinib (HER1, HER2, HER4)
  - inferior outcomes and higher toxicity
- is consistent superiority of trastuzumab over other TKIs due to additional effects on immune responses?
  - tumors enriched for immune signatures benefit from trastuzumab
  - level of tumor-infiltrating lymphocytes predicts trastuzumab benefit
  - not all studies concordant
Potential Previously Unrecognized Immunostimulatory Effects of Conventional Chemotherapeutics?

- low dose, metronomic administration schedule with immune checkpoint agents and enhanced responses?
- off-target effects in activation of immune system directly?
  - 5-fluorouracil killing of tumor-associated myeloid suppressor cells
- value in increasing mutagen burden and neoantigen expression as activation trigger for immune response?
# Oncolytic Pipeline

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<th>COMPANY</th>
<th>PRODUCT</th>
<th>PH I</th>
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<td>Cold Genesys</td>
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<td>SillaJen / Green Cross / Lee's Pharma / Transgene</td>
<td>Pexa-Vect pexastimogene devacirepvec</td>
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<td>ONCOS-102</td>
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</table>

Biocentury 02/29/16
Intersection of population variation and autoimmunity genetics in human T cell activation

Chun Jimmie Ye, Ting Feng, Ho-Keun Kwon, Towfique Raj, Michael Wilson, Natasha Asinovski, Cristin McCabe, Michelle H. Lee, Irene Frohlich, Hyun-il Paik, Noah Zaitlen, Nir Hacohen, Barbara Stranger, Philip De Jager, Diane Mathis, Aviv Regev,* Christophe Benoist*
Immunogenetics: Individual Genetic Variation in Immune Responses

- how does individual genetic variation affect the nature and intensity of T cell responses?
- identification of single nucleotide polymorphisms that influence susceptibility/relative resistance to autoimmune diseases and responses to pathogens
- wide individual variation and eQTLs polymorphisms for activation-induced cytokine levels
- no information on how these parameters may link to individual variation in immunotherapy-induced anti-tumor responses
Imaging Endpoints for Immunotherapy Response Evaluation

- Limitations of traditional RECIST criteria due to ‘pseudo-progression’ caused by T cell infiltration/inflammation edema
  - tumor size and density

- Nivolumab CheckMate 057 trial
  - Reported short PFS but significant prolongation of OS
    - Superiority versus docetaxal at 9 months

- Development of irRECIST criteria
Need for New Minimally-Invasive Assays for Monitoring Patient Responses to Immunotherapy

- ‘static’ snapshot of immune profile in resected lesions/biopsies versus longitudinal monitoring of dynamic changes with tumor progression /Rx responses

- how far does the immune profile assayed in blood (liquid biopsy) mirror intratumoral events in anatomically dispersed metastases?
  - immune cell subsets?
  - cytokines?
  - ctDNA?
  - exosomes?
Does the Gastrointestinal Microbiome Affect Immunotherapy Efficacy?
A Role for the Microbiome in Regulating Systemic Cancer Risk, Immune Responses and Responses to Therapy?

- Gut microbiota dramatically impacted by many anti-neoplastic drugs
- Translocation of gut microbiota across intestinal epithelium and activation of DCs in lymphodepleting irradiation and improved responses to ACT
- *Bifidobacterium* prevalence influences efficacy of anti-PD-1 and anti-CTLA-4 mAb therapy and efficacy reduced by antibiotic therapy
Immune-Medicated Colitis in Melanoma Patients Treated with CTLA-4 Blockade Correlates with Lower Levels of Bacteroides Phylum Families in the Gut Microbiome

Adapted from: K. Dubin et al. (2016) Nature Communications 10391
Could Selective Manipulation of Gut Microbiota Impact Cancer Risks and/or Improve Efficacy of Some Anti-Cancer Therapies?

- adverse impact of antibodies in eliminating ‘beneficial’ species?
- use of antibiotics to reduce untoward bacterial species?
- use of probiotics to optimize ‘beneficial’ species?
- postbiotics: metabolic products from ‘beneficial’ species that exert therapeutically valuable effects?

Cancer and the gut microbiota. an unexpected link
Price and Affordability!!!
The Cost of Complex Cancer Care

Evan Johnson sits on a terrace at the Mayo Clinic Hospital, Methodist Campus in Rochester, Minn. during the summer of 2014.

From: Winslow, R. (2016) Cancer Treatment's New Direction. WSJ

- AML
- An 18 month journey to remission
- 3 approved drugs, 2 investigational drugs
- 2 stem cell transplants
- $4 million dollars
Is Widespread Adoption of Immunotherapy Economically Feasible?

- direct Rx cost
- indirect care cost
- escalating cost of combination regimens (> $200K)
- extravagant cost of cell-based therapies ($500K - $1.5 million)
- complex clinical management challenges and compatibility with community oncology services
What Are We Willing to Pay for Added Months of Survival in Cancer?

<table>
<thead>
<tr>
<th>Lifetime cost above standard care</th>
<th>If cancer is on par with other diseases ($150,000 per life year gained), months of added overall survival benefit needed</th>
<th>Treating cancer as worthy of much higher reimbursement ($250,000 per life year gained), months of added overall survival benefit needed</th>
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<tbody>
<tr>
<td>$50,000</td>
<td>4 months</td>
<td>2.4 months</td>
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<td>$100,000</td>
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<td>$200,000</td>
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<td>$500,000</td>
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Source: Pink Sheet 13 Sept. 2010. Adapted from S. Ramsey FHCRC, ASCO 2010
Performance Comparison for New Anti-Cancer Drugs Approved 2002-2014 for Top Ten Pharmaceutical Companies

Gains in Progression-Free Survival (PFS) and Overall Survival (OS) for 71 Drugs Approved by the FDA From 2002 to 2014 for Metastatic and/or Advanced and/or Refractory Solid Tumors

From: T. Fojo et al. (2014) JAMA Otolaryngology–Head & Neck Surgery 140, 1225
Value-Based Rx Pricing of Oncology Therapeutics

- outcomes-based payments
- indication-specific pricing
- reference pricing (maximum price for all drugs in a therapeutic class)
Deconvolution of the Multi-Dimensional Matrix of Immuno-Oncology Therapeutics

- clonal
- heterogeneity
- mutagen burden
- neoantigen profile

- complex non-immune cell contributions to suppressive environment
- localization of immune cells/soluble mediators and impact of Rx

- balance of stimulatory and suppressive factors

- tumor
- host immune response
- tumor microenvironment
The Evolution of Cancer Immunotherapeutics

- likely to become SOC in increasing number of indications
- need for better informed rationale for combination regimens
- identification of new I/O intervention points
  - Tregs, MDSC, NK cells, TME resistance mechanisms
- risk of MDR and recurrence in long DOR patients?
- improved immunophenotyping (immunoscore) of individual patients for predictive ID of responders and non-responders
- intense competitive corporate landscape and massive financial investments
- price and new pharmaco-economic-realities for approval and reimbursement
KEEP CALM AND boost your immune system