The New Frontier: Immunotherapy of Cancer

Combination Immunotherapies: Engage, Expand, Enable

Demystifying Medicine
February 6th, 2018

James W. Hodge, Ph.D., MBA
Senior Investigator
Deputy Chief
Laboratory of Tumor Immunology and Biology
Head, Recombinant Vaccine Group
Center for Cancer Research
National Cancer Institute, NIH, USA.
Laboratory of Tumor Immunology and Biology
Dr. Jeffrey Schlom

Recombinant Vaccine Group
Dr. Dr. Rika Fujii
Dr. Kelsye Fabian
Michelle Padget
Marion Taylor

Immunomodulation Group
Dr. Sofia Gameiro

Cellular Immunology Group
Dr. Caroline Jochems

Clinical Trials Group
Dr. Gulley
Dr. Madan
Dr. Julius Strauss
Why is Combination Therapy Needed?

Timeline: The history of chemotherapy

- Louis Goodman and Alfred Gilman use nitrogen mustards to treat a patient with non-Hodgkin’s lymphoma and demonstrate for the first time that chemotherapy can induce tumour regression.
- The National Chemotherapy Program begins at the National Cancer Institute (NCI): a systematic programme for drug screening commences.
- The Food and Drug Administration (FDA) approves the alkylating agent cyclophosphamide.
- A combination of cyclophosphamide, methotrexate and fluorouracil (CMF) was shown to be effective as adjuvant treatment for node-positive breast cancer.
- The NCI introduces “disease oriented” screening using 60 cell lines derived from different types of human tumour.
- Studies by Brian Drucker lead to FDA approval of imatinib mesylate (Gleevec) for chronic myelogenous leukaemia, a new paradigm for targeted therapy in oncology.
- The FDA approves bevacizumab (Avastin), the first clinically proven anti-angiogenic agent, for the treatment of colon cancer.

<table>
<thead>
<tr>
<th>FOLFIRINOX</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FOL</td>
<td>folinic acid</td>
</tr>
<tr>
<td>F</td>
<td>Fluorouracil (5-FU)</td>
</tr>
<tr>
<td>IRIN</td>
<td>Irinotecan</td>
</tr>
<tr>
<td>OX</td>
<td>oxaliplatin</td>
</tr>
</tbody>
</table>


Sydney Farber uses antileukemic to successfully induce remissions in children with acute lymphoblastic leukemia (ALL).

- Roy Hertz and Min Chiu Li demonstrate that methotrexate as a single agent can cure choriocarcinoma, the first solid tumour to be cured by chemotherapy.
- Combination chemotherapy (POMP regimen) is able to induce long-term remissions in children with ALL.
- Emil Frei and colleagues demonstrate that chemotherapy given after surgical removal of osteosarcoma can improve cure rates (adjunct chemotherapy).
- The FDA approves paclitaxel (Taxol), which becomes the first “blockbuster” oncology drug.
- Researchers at Harvard University define mutations in the epidermal growth factor receptor that confer selective responsiveness to the targeted agent gefitinib, indicating that molecular testing might be able to prospectively identify subsets of patients that will respond to targeted agents.

Modified from Nature Reviews Cancer 2005

- Monotherapy: Some activity in select tumor types
- Combination Therapy: Improved ORR, DUR, and OS

Are we already seeing the same trend with immunotherapy?

- Monotherapy: Some activity in select tumor types
- Limited Data with Combination IO Therapy: (Improved ORR, DUR, and OS)
  - How to rationally choose IO Agents?

Next Generation Therapy: SOC Agents Plus IO Combinations
Standard-of-Care Therapy (Radiation/Chemotherapy, others): Combination with Immunotherapy

Hypotheses:

• Cancer Patients Harbor Tumor Antigen Specific T-cells
  • These T-cells can have activity increased by manipulation of the peripheral and tumor environment*

• Standard-of-Care Therapy** Can Induce and/or Enable Additional Antigen Specific T-cells
  • These T-cells can have activity increased by manipulation of the peripheral and tumor environment*

*anti-CTLA-4, anti-PD1/PD-L1, Cytokines (IL-12, IL-15), anti-Vegf, anti-TGF-beta, JAK/STAT inhibitors, Inflammatory Agonists (CD137, TLR3/7/8), Vaccines
Can Radiation or Chemotherapy Alone Induce Immune Responses?

Immunogenic Cell Death

Not Sufficient

20 trials
2 radiation types
7 chemotherapy types

• Weak efficiency
• Potential to be augmented with active immunotherapy

Nesslinger et al, Clin Ca Res 2007
Galluzzi et al., Cancer Cell, Dec 14, 2015
## Vaccines: Initiating an Antitumor Immune Response

<table>
<thead>
<tr>
<th>Vector</th>
<th>Target</th>
<th>Phase I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pox</td>
<td>PSA</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>CEA/MUC-1</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Brachyury</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Yeast</td>
<td>CEA</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Brachyury</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Adeno</td>
<td>CEA</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CEA-Triad</td>
<td>In review</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PSA-Triad</td>
<td>In Review</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TSNA</td>
<td>Planned</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*TSNA: Tumor-specific neo-antigen*

*rec Pox viruses: Bavarian Nordic (BN)*  
*rec Saccharomyces: NantCell*  
*rec Adeno: Etubics*
Combination of Standard-of-Care or Emerging Therapies with Immune Oncology Reagents

Immunogenic Modulation

Modulation of Tumor Phenotype to Render Cells More Sensitive to Immune Mediated Killing

Immune Conditioning

Modulation of Immune Cell Subsets to Enable Productive Immune Interactions
Why Study Immunogenic Modulation and Immune Conditioning in the Context of Immunotherapy?

- The optimal use of immunotherapy may be in combination with standard of care or emerging experimental therapies.
- Allows immunotherapy use earlier in the disease process.
- Certain modalities may act synergistically with immunotherapy by:
  - enhancing immune responses
  - inhibiting immune suppressive functions
  - altering the phenotype of tumor cells to render them more susceptible to immune-mediated killing.
- Radiation, chemotherapy, small-molecule inhibitors, or biologic therapy could serve as a boost to immunotherapy (vaccine).
- Can combination therapy convert increased overall survival to PFS or CR?
Attacking Tumor Cells That Survive Therapy: Exploiting Immunogenic Modulation

T-cell induction/expansion

- Vaccine
- Anti-CTLA-4
- Anti-PDL-1

Immune Checkpoints

- Anti-CTLA-4
- Anti-PDL-1

Tumor Targets

- Anti-Her2
- Anti-EGFR
- Anti-CD20

Immunotherapy

Death

Autophagy

Surviving cell fraction

Autophagy

Tolerogenic Cell Death

- Rapid plasma membrane rupture
- Loss of intracellular contents such as TAA
- Inefficient activation of innate immune response

Immunogenic Cell Death

- Calreticulin/ERp57 translocation
- HMGB1 secretion
- ATP secretion

Immunogenic Modulation

- Phenotype changes: Upregulation of MHC I, adhesion molecules, tumor antigen(s) and mAb Targets
- Downregulation of anti-apoptotic/pro-survival genes
- Antigen processing machinery modulation
- Calreticulin translocation
- Modulation of immune-responsive genes

Mediated by Stress Response and Unfolded Protein Response

-Dose

-Memory T-cell Protection
Immune Conditioning

- Immunogenic Modulation
  - External-Beam Radiation
  - Multiple IO Combinations
  - Taxanes
Radiation Therapy: Immunogenic Modulation

Treatment of tumor cells with sublethal therapy modulates tumor phenotype to render them more sensitive to immune mediated destruction.


+ 5 Review Articles
+ 3 Clinical Trials

Hodge, Guha, Oncology 2008
Combination Therapy: Vaccine + External Beam Radiation

Days Post Tumor Transplant

Tumor Volume (mm³)

No Treatment

Vaccine

Irradiation

Vaccine + Irradiation

Days Post Tumor Transplant

Vaccine + Radiation: Tumor Infiltrating Cells and Antigen Cascade

No Treatment  Vaccine Alone  Radiation Alone  Vaccine + Radiation

CD4+ T-cells (IHC)

Gp70 specific CD8 T-cells

**Vaccine + Radiation: Induction of Antigen Cascade**

### CD4⁺ T-cell Responses (stimulation index)

<table>
<thead>
<tr>
<th></th>
<th>CEA</th>
<th>p53</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine + Radiation</td>
<td>3.9</td>
<td>3.8</td>
</tr>
<tr>
<td>Control</td>
<td>1.1</td>
<td>0.8</td>
</tr>
</tbody>
</table>

### CD8⁺ T-cell Responses (IFN-γ, pg/ml)

<table>
<thead>
<tr>
<th></th>
<th>CEA</th>
<th>p53</th>
<th>GP70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine + Radiation</td>
<td>2,000</td>
<td>320</td>
<td>28,940</td>
</tr>
<tr>
<td>Control</td>
<td>&lt; 2.5</td>
<td>&lt; 2.5</td>
<td>&lt; 2.5</td>
</tr>
</tbody>
</table>

Antigen Cascade Observed in a Phase II clinical trial of Metastatic Prostate Cancer Patients Treated with PSA/TRICOM Vaccine and Standard of Care Fractionated Radiation (PSA, PSMA, PAP, MUC-1)


Antigen Cascade

- Cryptic determinants, epitope spreading, determinant spreading, cryptic epitopes, antigen spreading.

- Defined as an immunological response demonstrating epitopes distinct from and non-cross-reactive with the inducing epitope *(Including Neoepitopes)*

- Antigen cascade could be a possible mechanism for the regression of:
  - antigen variant tumors
  - tumors at distal sites
  - micrometastatic deposits
Randomized Phase II Trial: Radiotherapy ± Vaccine

Background: ~1/3 have PD after radiation therapy, often 2º to occult metastasis. Perhaps this could be improved with a well tolerated systemic therapy (vaccine). The addition of vaccines to radiation → minimal risk of toxicity, potential synergy.

Hypothesis: Immune responses can be raised to TAA despite local RT.

30 patients with localized / locally advanced prostate cancer (most were high risk)

Daily Radiotherapy

- **Gr. A**
  - No vaccine
  - Blue: rV-PSA + rV-B7.1
  - n = 19

- **Gr. B**
  - No vaccine
  - Light blue: rF-PSA
  - n = 11

= Blood for ELISPOT

# Prostate Cancer Patients Receiving a PSA-based Poxviral Vaccine Generate Immune Responses to Multiple Tumor Antigens Not in the Vaccine (Antigen Cascade)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sample</th>
<th>FMP</th>
<th>PSA3</th>
<th>PSMA</th>
<th>PAP</th>
<th>PSCA</th>
<th>MUC-1</th>
<th>HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>pre</td>
<td>1/75,000</td>
<td>&lt;1/200,000</td>
<td>&lt;1/200,000</td>
<td>&lt;1/200,000</td>
<td>&lt;1/200,000</td>
<td>&lt;1/200,000</td>
<td>&lt;1/200,000</td>
</tr>
<tr>
<td></td>
<td>post 3</td>
<td>1/100,000</td>
<td>1/85,714</td>
<td>&lt;1/200,000</td>
<td>1/85,714</td>
<td>1/85,714</td>
<td>1/23,077</td>
<td>&lt;1/200,000</td>
</tr>
<tr>
<td>6</td>
<td>pre</td>
<td>1/20,690</td>
<td>&lt;1/200,000</td>
<td>&lt;1/200,000</td>
<td>&lt;1/200,000</td>
<td>&lt;1/200,000</td>
<td>&lt;1/200,000</td>
<td>&lt;1/200,000</td>
</tr>
<tr>
<td></td>
<td>post 3</td>
<td>1/22,222</td>
<td>1/66,667</td>
<td>1/85,714</td>
<td>&lt;1/200,000</td>
<td>&lt;1/200,000</td>
<td>1/60,000</td>
<td>&lt;1/200,000</td>
</tr>
<tr>
<td>7</td>
<td>pre</td>
<td>1/21,429</td>
<td>&lt;1/200,000</td>
<td>&lt;1/200,000</td>
<td>&lt;1/200,000</td>
<td>&lt;1/200,000</td>
<td>&lt;1/200,000</td>
<td>&lt;1/200,000</td>
</tr>
<tr>
<td></td>
<td>post 3</td>
<td>1/21,429</td>
<td>1/60,000</td>
<td>1/200,000</td>
<td>1/85,714</td>
<td>&lt;1/200,000</td>
<td>&lt;1/200,000</td>
<td>1/200,000</td>
</tr>
<tr>
<td>8</td>
<td>pre</td>
<td>1/50,000</td>
<td>1/200,000</td>
<td>&lt;1/200,000</td>
<td>&lt;1/200,000</td>
<td>1/200,000</td>
<td>1/200,000</td>
<td>&lt;1/200,000</td>
</tr>
<tr>
<td></td>
<td>post 3</td>
<td>1/37,500</td>
<td>1/42,857</td>
<td>1/62,500</td>
<td>&lt;1/200,000</td>
<td>&lt;1/200,000</td>
<td>1/46,154</td>
<td>&lt;1/200,000</td>
</tr>
<tr>
<td>11</td>
<td>pre</td>
<td>1/85,714</td>
<td>&lt;1/200,000</td>
<td>&lt;1/200,000</td>
<td>&lt;1/200,000</td>
<td>&lt;1/200,000</td>
<td>&lt;1/200,000</td>
<td>&lt;1/200,000</td>
</tr>
<tr>
<td></td>
<td>post 3</td>
<td>1/54,545</td>
<td>1/75,000</td>
<td>&lt;1/200,000</td>
<td>&lt;1/200,000</td>
<td>&lt;1/200,000</td>
<td>1/40,000</td>
<td>&lt;1/200,000</td>
</tr>
<tr>
<td>12</td>
<td>pre</td>
<td>1/66,667</td>
<td>1/120,000</td>
<td>&lt;1/200,000</td>
<td>1/200,000</td>
<td>1/200,000</td>
<td>&lt;1/200,000</td>
<td>&lt;1/200,000</td>
</tr>
<tr>
<td></td>
<td>post 3</td>
<td>1/42,857</td>
<td>1/120,000</td>
<td>&lt;1/200,000</td>
<td>&lt;1/200,000</td>
<td>&lt;1/200,000</td>
<td>1/35,294</td>
<td>&lt;1/200,000</td>
</tr>
</tbody>
</table>

Results are expressed in precursor frequencies of specific T cells. ELISPOT assay for IFN-γ.

**Effect of Radiation on Sensitivity to CTL Killing: Human Tumor Cells**

**Mechanism:**
- Modulation of Antigen Processing Machinery (APM)
- Upregulation/Translocation of Calreticulin

**Results:**
- Lung H522
- Breast MDA-MB-231
- Prostate LnCaP

**CEA (TV8)**
- Lung H522
- Breast MDA-MB-231
- Prostate LnCaP

**MUC-1 (P93L)**
- Lung H522
- Breast MDA-MB-231
- Prostate LnCaP

**Translation:**

*Use of Radionuclide Sm-153 with Vaccine*

*QUADRAME* is a therapeutic agent consisting of radioactive samarium and a tetraphosphonate chelator, ethylenediaminetetramethylenephosphonic acid (EDTMP). It preferentially binds to osteoblastic metastatic tumor deposits in bone.

$^{153}\text{Sm}$ is currently FDA approved and clinically utilized for palliation of bone metastasis in multiple tumor histologies.

<table>
<thead>
<tr>
<th></th>
<th>Gamma</th>
<th>$^{90}\text{Y}$</th>
<th>$^{153}\text{Sm}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-Life</td>
<td>0</td>
<td>64.1 hr</td>
<td>46.3 hr</td>
</tr>
<tr>
<td>Radiation Type</td>
<td>Pure $\gamma$</td>
<td>Pure $\beta$</td>
<td>Mixed $\beta$, $\gamma$</td>
</tr>
<tr>
<td>Dose to Tumor</td>
<td>10-20 Gy</td>
<td>18-25 Gy</td>
<td>17.5-80 Gy</td>
</tr>
</tbody>
</table>

*In-vitro Studies (human)*

Do palliative levels of Sm-153 modulate metastatic human tumor phenotype? (0-50 Gy)?

Collaboration with NIH Nuclear Medicine
Treatment of LnCaP Prostate Cells with Palliative Levels of $^{153}$Sm Modulates Phenotype, Upregulates TAA, and Increases Sensitivity to Antigen Specific CTL Killing

**Tumor antigen genes**

<table>
<thead>
<tr>
<th></th>
<th>0 Gy</th>
<th>25 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA</td>
<td>1</td>
<td>2.79</td>
</tr>
<tr>
<td>PSMA</td>
<td>1</td>
<td>4.14</td>
</tr>
<tr>
<td>PAP</td>
<td>1</td>
<td>29.0</td>
</tr>
<tr>
<td>CEA</td>
<td>1</td>
<td>10.3</td>
</tr>
<tr>
<td>MUC-1</td>
<td>1</td>
<td>3.67</td>
</tr>
</tbody>
</table>

Phase II Clinical Trial

$^{153}$Sm +/- PSA-TRICOM

Patient Population: CRPC Metastatic to bone

**Arm A:** PSA-TRICOM + $^{153}$Sm (n=34)

**Arm B:** $^{153}$Sm (n=34)

Vaccine:  
- rV-PSA/TRICOM s.c. d 1  
- rF-PSA/TRICOM s.c. d 15, 29, q 4 wks

$^{153}$Sm:  
- 1 mCi/kg **d8**, may be repeated  
- q 12 wks upon hematologic recovery.

NCI# 7678  PI Gulley  
CINJ (DiPaola) and UC (Stadler)
**\(^{153}\text{Sm} +/- \text{PSA-TRICOM}**

- Final data of n = 44 patients with mCRPC
- 1º endpoint: PFS
- Progression defined by utilizing PCWG, but not PSA criteria

**Graph:**
- **\(^{153}\text{Sm} + \text{PSA-TRICOM}**
  - TTP = 3.7 months
  - \(P_2 = 0.03\)

- **\(^{153}\text{Sm Alone}**
  - TTP = 1.7 months

**Legend:**
- \(n = 44\)

---

Heery…Gulley ASCO GU 2013
PCWG = Prostate Cancer Working Group response criteria

Foundation for Planned Phase II Trial (PROSTVAC + \(^{223}\text{Ra}\) (Xofigo)
<table>
<thead>
<tr>
<th></th>
<th>Local Therapy</th>
<th>Clinical Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>External-Beam Radiation</strong></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td><strong>Radiofrequency Ablation</strong></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td><strong>Brachytherapy</strong></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td><strong>Radionuclide Chelate for bone metastases</strong></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td><strong>Radiolabeled anti-tumor antigen monoclonal antibody</strong></td>
<td></td>
</tr>
</tbody>
</table>
Immune Conditioning

Immunogenic Modulation

- External-Beam Radiation
- Multiple IO Combinations
- Taxanes
Can We Define Mechanism of Immunogenic Modulation With Chemotherapy (Docetaxel)?

Increased CTL Sensitivity

<table>
<thead>
<tr>
<th>Docetaxel (ng/ml)</th>
<th>LNCaP</th>
<th>PSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>25</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>250</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

APM Modulation and Calreticulin Translocation

Chemotherapy Resistant Cells Treated with Docetaxel Still Undergo Immunogenic Modulation

Do Cells Resistant to Docetaxel Increase Sensitivity to CTL Following Docetaxel Treatment?

- immunogenic modulation was distinct from immunogenic cell death
- chemotherapy induced modulation of antigen-processing machinery and calreticulin
- chemotherapy resistant cells increased CTL sensitivity after chemotherapy exposure

**Also seen with Paclitaxel**

Foundation for Phase II Clinical Trial:
Docetaxel + PANVAC in Breast Carcinoma

Combination Therapy Vaccine Plus Chemotherapy

Docetaxel Alone or in Combination With a Therapeutic Cancer Vaccine (PANVAC) in Patients With Metastatic Breast Cancer
A Randomized Clinical Trial

Christopher R. Heery, MD; Nuhad K. Ibrahim, MD; Philip M. Arlen, MD; Mahsa Mohebtash, MD; James L. Murray, MD; Kimberly Koenig, MD; Ravi A. Madan, MD; Sheri McMahon, RN; Jennifer L. Marté, I; Seth M. Steinberg, PhD; Renee N. Donahue, PhD; Italia Grenga, MD; Caroline Jochems, MD, PhD; Benedetto Farsaci, MD; Les Folio, MD; Jeffrey Schlom, PhD; James L. Gulley, MD, PhD

Figure 2. Progression-Free Survival in the 2 Treatment Arms

JAMA Onc, Aug 20, 2015

Patients also received steroid prior to docetaxel

3.9 vs. 7.9 months

The combination treatment group underwent a median of 5 treatment cycles over 7.9 months; the docetaxel group, 3 cycles over 3.9 months (1-sided \( P = .09 \), which met the predefined statistical definition of \( P \leq .10 \)); hazard ratio, 0.65 (95% CI, 0.34-1.14). Median potential follow-up was 42.8 months.
Immunotherapy Combinations: Chemotherapy, Radiation, Targeted Small Molecules

- Immunogenic Modulation Can be Exploited for Combination of Standard-of-Care and Emerging Experimental Therapeutics with Immunotherapy
  - **Taxanes** (Docetaxel, Paclitaxel, nab-Paclitaxel)
  - **Cisplatin/5-FU, Cisplatin/Vinorelbine**
  - **Radiation** (EBRT, Proton, Brachy, RAIT, Chelate, RFA)
  - **PARPi** (Olaparib)
  - **TKIs** (Sunitinib/Sorafenib/Cabozantinib)
  - **HDAC Inhibition** (Vorinostat, Entinostat)
  - **Endocrine Deprivation**
    (Enzalutamide, Abiraterone, Tamoxifen, Aromatase inhibitors); independent of ER or AR Expression (**TNBC**)
Immune Conditioning

Immunogenic Modulation

External-Beam Radiation

Multiple IO Combinations

Taxanes
Hypothesis: Effective Therapy of Established Tumors Requires Multiple Agents Targeting Diverse Immune-Tumor Interactions

Effective anti-tumor response

- Induction of Ag-specific immune cells
- Enhanced immune cell infiltration in the TME
- Prolonged and persistent effector functions in the TME
Hypothesis: Effective Therapy of Established Tumors Requires Multiple Agents Targeting Diverse Immune-Tumor Interactions

- Chemokines
- Cytokines
- Checkpoint blockade
- Depletion of suppressive cells

- Cancer vaccines
- CAR T cells
- Chemo

- Chemokines
- Cytokines
- Co-stimulatory signals
- TLR ligands
Multifactoral Approach to Cancer Immunotherapy

I. **Engage:** Generation of an Effective Immune Response
   - Vaccine: TAA, neoantigens
   - Immunocytokine: IL-15 superagonist (ALT-803)
   - IDOi: enhance DC function

II. **Expand:** Maintenance of an Effective Immune Response at the Tumor Site/ Reduction of Immunosuppressive Entities
   - anti-PD-L1 (avelumab)
   - anti-PD-L1/TGFβR2 (M7824)
   - Immunocytokine: NHS-IL12
   - Agonist MAbs to GITR, OX40, 41BB
   - IDOi
   - anti-PD-L1/IL15-FP (FP-809)

III. **Enable:** Modification of the Tumor/Tumor Microenvironment to Enhance Immune-mediated Effectiveness
   - Immunogenic tumor cell death
   - Immunogenic modulation of tumor phenotype
   - anti-PD-L1/TGFβR2 (M7824)
   - IL-8R antagonist

IV. Adaptive Clinical Trial Designs Encompassing I, II, and III
Questions?

James W. Hodge, Ph.D., MBA
Senior Investigator
Deputy Chief
Laboratory of Tumor Immunology and Biology
Head, Recombinant Vaccine Group
Center for Cancer Research
National Cancer Institute, NIH, USA.

National Institutes of Health