Development of Recombinant Vaccines for the Therapy of Carcinomas
Monotherapy and Combination Therapy

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Laboratory of Tumor Immunology and Biology (LTIB)
Center for Cancer Research
National Cancer Institute, NIH
Disclosure

The Laboratory of Tumor Immunology and Biology, Center for Cancer Research, NCI, NIH, has Collaborative Research and Development Agreements (CRADAs) with:

- Bavarian Nordic Immunotherapeutics
- GlobeImmune

concerning the design and development of recombinant cancer vaccines

J. Schlom is an inventor on patents via NCI TTC and NIH OTT.

Drs. Schlom and Madan will discuss experimental therapeutic cancer vaccines in different states of clinical development: PROSTVAC and PANVAC.
Cancer Vaccine Development:
- Focus on human carcinoma
- Focus on development of vaccines that can be widely evaluated

Ultimate Use:
- Early in disease process/low tumor burden
- Survival as the endpoint
- Minimal toxicity

Immuno-Oncology Platform:
- Combination immune therapies
  - immune stimulation strategies
  - reduction of immune inhibitory entities
- Combination Therapies: Vaccine plus:
  - conventional therapies
  - conventional therapies in novel strategies
  - other experimental therapies
Preclinical Studies:

Laboratory of Tumor Immunology and Biology (LTIB)
- James Hodge
- Claudia Palena
- Al Tsang
- Jack Greiner
- Jianping Huang
- Ingrid Fernando
- Benedetto Farsaci
- Sofia Gameiro

CLINICAL STUDIES:

LTIB/Medical Oncology Branch
- James Gulley
- Ravi Madan
- Mary Pazdur

Medical Oncology Branch
- William Dahut
- Tito Fojo
- William Figg
- Marijo Bilusic
- Chris Heery

Radiation Oncology
- Kevin Camphausen
- Deborah Citrin

Urologic Oncology
- Marston Linehan
- Peter Pinto
- Gennady Bratslavsky

Biostatistics and Data Management Section
- Seth Steinberg

NIH Nuclear Medicine
- C.H. Paik

NIH Interventional Radiology
- Brad Wood

Vaccine Branch
- Jay Berzofsky
Translational Research Programmatic Effort

**CLINICAL STUDIES — EXTRAMURAL:**
- Georgetown – John Marshall
- Dana Farber Cancer Center – Donald Kufe, Paul Eder, Philip Kantoff
- Columbia – Howard Kaufman
- Cancer Institute of New Jersey – Edward Lattime, Robert DiPaola
- Ohio State – William Carson
- Duke – H. Kim Lyerly, Michael A. Morse

**Eastern Cooperative Oncology Group (ECOG) – Robert DiPaola**

**CANCER THERAPY EVALUATION PROGRAM (CTEP):**
- Howard Streicher
- Jan Casadei

**PRIVATE SECTOR:**
- GlobeImmune – David Apelian
- BN ImmunoTherapeutics – Wayne Godfrey, Reiner Laus

**NCI Technology Transfer Center:** Kevin Brand, Bob Wagner, Karen Maurey
**NIH Office of Technology Transfer:** Sabarni Chatterjee, Mojdeh Bahar
Recombinant Vaccine Vectors

- **Pox vectors**
  - Vaccinia (rV-) elicits a strong immune response
    - host induced immunity limits its continuous use
    - MVA (replication defective)
  - Avipox (fowlpox rF-, ALVAC)
    - derived from avian species
    - safe; does not replicate
    - can be used repeatedly with little if any host neutralizing immunity
- Can insert multiple transgenes
- Do not integrate into host DNA
- Efficiently infect antigen presenting cells including dendritic cells
T-Cell Dependence on Costimulation

Signal 1 + Signal 2

- Activation of Antigen-Specific T-cells

No Signal 1

- Clonal Anergy
- Apoptosis
- Ignorance

No Signal 2

- Clonal Anergy
- Apoptosis
- Ignorance
**Costimulatory Molecule Candidates**

- Major Costimulatory Effect must be on the T-cell
- No Overlap of T-cell Ligands
- No Redundancy of Costimulatory Mechanisms

### APC

- MHC + Peptide
- **Costimulatory Molecule**
  - B7-1 (CD80)
  - ICAM-1 (CD54)
  - LFA-3 (CD58)

### T-Cell

- TCR
- **Ligand**
  - CD2 (Region 1)
  - CD28
  - CTLA-4
- **Costimulatory Mechanism**
  - Tyrosine Kinase, Phospholipase C
  - Tyrosine Kinase, Ca²⁺ Mobilization
  - IL-2-R upregulation, IL-2 secretion

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![Bar chart showing costimulatory molecule activation](chart.png)

**T-cell Activation (CPM x 10⁵)**

- None
- LFA-3
- ICAM-1
- B7-1
- TRICOM

**Costimulatory Molecule**
TRICOM Vaccines

Tumor Antigen Gene Co-stimulatory molecule genes

- TAA
- B7-1
- LFA-3
- ICAM-1

(Triad of Co-stimulatory Molecules)

Induction of Tumor specific immune responses (T-cells)

Vaccines:
- (rV-TAA-TRICOM)
- (rF-TAA-TRICOM)
## TRICOM

TRIad of COstimulatory Molecules

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<th>Costimulatory Molecule</th>
<th>Ligand on T cell</th>
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TRICOM = B7-1/ICAM-1/LFA-3  
CEA/TRICOM = CEA/B7-1/ICAM-1/LFA-3  
CEA/MUC-1/TRICOM = CEA/MUC-1/B7-1/ICAM-1/LFA-3 (PANVAC)  
PSA/TRICOM = PSA/B7-1/ICAM-1/LFA-3 (PROSTVAC)

All vaccines contain:  
rV- as a prime vaccine  
avipox (fowlpox, rF-) as multiple booster vaccines  
CEA, MUC-1, and PSA transgenes all contain enhancer agonist epitopes
CEA-specific Lymphoproliferation of T Cells from CEA-Tg Mice Vaccinated with TRICOM Vectors

Therapy of 14-Day Established CEA\(^+\) Experimental Metastases in CEA-Tg Mice Using CEA/TRICOM Vectors

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VAAA Regimen

- CEA
- CEA/TRICOM

All groups with GM-CSF and low dose IL-2

Prostate Cancer and Vaccine Therapy

• Long interval from primary diagnosis to metastatic disease

• Serum PSA (doubling time/velocity) as a surrogate for therapeutic benefit or disease recurrence

• Nomogram (Halabi) at metastatic disease
  – can predict more indolent vs more aggressive disease
Natural History of Disease Progression in Prostate Cancer

- Asymptomatic
  - Non-Metastatic
    - Castration Sensitive
  - Metastatic
    - Castration Resistant

- Symptomatic
  - Chemotherapy

- Time

- Tumor volume & activity
### Therapies Shown to Improve Overall Survival in Metastatic Castration-Resistant Prostate Cancer

<table>
<thead>
<tr>
<th>Agent</th>
<th>Type of therapy</th>
<th>Stop treatment 2º AE</th>
<th>Improvement in median OS</th>
<th>Hazard ratio</th>
<th>Reduction in death rate</th>
<th>Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>chemotherapy</td>
<td>11%</td>
<td>2.4 months</td>
<td>0.76</td>
<td>24%</td>
<td>2004</td>
</tr>
<tr>
<td>Cabazitaxel</td>
<td>chemotherapy</td>
<td>18%</td>
<td>2.4 months</td>
<td>0.70</td>
<td>30%</td>
<td>2010</td>
</tr>
<tr>
<td>Abiraterone</td>
<td>hormone</td>
<td>19%</td>
<td>3.9 months</td>
<td>0.66</td>
<td>34%</td>
<td>2011</td>
</tr>
<tr>
<td>Sipuleucel-T</td>
<td>vaccine</td>
<td>1.5%</td>
<td>4.1 months</td>
<td>0.78</td>
<td>22%</td>
<td>2010</td>
</tr>
<tr>
<td>Prostvac*</td>
<td>vaccine</td>
<td>~2%</td>
<td>8.5 months</td>
<td>0.56</td>
<td>44%</td>
<td>—</td>
</tr>
</tbody>
</table>

* rV-, rF-PSA-TRICOM – Results of a Phase II randomized, placebo (vector)–controlled, 43-center trial.
PROSTVAC Significantly Extended Overall Survival

Δ 8.5 months

Hazard ratio:
0.56 (95% CI 0.37–0.85)

$p=0.0061$

Kantoff (Schlom, Gulley) et al. J Clin Oncol 2010
Randomized Multicenter Placebo-controlled Vaccine Therapy Trial in Castrate-resistant Metastatic Prostate Cancer Patients

Observations:

A. Time to Progression: no difference in arms

B. Median survival (at 4 years median follow-up)
   Placebo: 16.6 months
   Vaccine: 25.1 months (p=0.006)

C. 44% reduction in death rate in vaccine arm
Phase II Study of PSA-TRICOM

- 32 patients with metastatic castration-resistant prostate cancer (CRPC)
- Chemotherapy naive
- Primary endpoint: immune response by ELISPOT
- Secondary / exploratory endpoints: Response, Survival

Gulley, (Madan, Schlom) et al., Clin Immunol Immunother, 2010
Conclusion: Can predict survival probabilities.
## Predicted Survival by Halabi Score vs Actual Survival

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Patients with Halabi predicted survival &lt; 18 mos</th>
<th>Patients with Halabi predicted survival ≥ 18 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vaccine: PROSTVAC (n=32)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predicted survival by Halabi score (mos)</td>
<td>17.4</td>
<td>12.3</td>
<td>20.9</td>
</tr>
<tr>
<td>Actual median overall Survival (mos)</td>
<td>26.6</td>
<td>14.6</td>
<td>Not reached (8 of 15 pts alive at 37.3 mos)</td>
</tr>
<tr>
<td>Difference (mos)</td>
<td>9.2</td>
<td>2.3</td>
<td>≥16.4</td>
</tr>
<tr>
<td>Patients survival longer than predicted by Halabi nomogram</td>
<td>22 of 32 (69%)</td>
<td>10 of 17 (59%)</td>
<td>12 of 15 (80%) p = 0.035</td>
</tr>
<tr>
<td><strong>Docetaxel therapy (n=22)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predicted survival by Halabi score (mos)</td>
<td>16.5</td>
<td>13.0</td>
<td>21.0</td>
</tr>
<tr>
<td>Actual median overall survival (mos)</td>
<td>15.5</td>
<td>15.4</td>
<td>16.9</td>
</tr>
<tr>
<td>Difference (mos)</td>
<td>(-1.0)</td>
<td>2.4</td>
<td>(-4.1)</td>
</tr>
<tr>
<td>Patients survival longer than predicted by Halabi nomogram</td>
<td>11 of 22 (50%)</td>
<td>8 of 13 (62%)</td>
<td>3 of 9 (33%)</td>
</tr>
</tbody>
</table>
Planned Phase III

Patient Population: Metastatic CRPC (Asymptomatic or minimally symptomatic)

- Arm A: PSA TRICOM vaccine with GM-CSF (n=400)
- Arm B: PSA TRICOM vaccine + placebo GM (n=400)
- Arm C: Empty Vector + placebo GM-CSF (n=400)

Primary endpoint: OS
Power = 90%  \( \alpha = 0.005 \)
Critical HR 0.8

PI: Gulley

Expected to open 2011
Tumor Growth Rate

Tumor Growth Rate

Tumor Burden vs. Time

**PROSTVAC – Interesting Case History**

- **Gleason grade:** 4 + 3 = 7

  - Trend before radical prostatectomy: 5.8 months, 65 years
  - Trend after radical prostatectomy, External beam radiation: 9.6 months, 75 years
  - Trend after first vaccine trial: 28.6 months, 93 years
  - Trend after second vaccine trial: 27 years

  - Age at which PSA would equal 1000:
    - 65 years
    - 75 years
    - 93 years

[Graph showing PSA levels and treatment effects]
Vaccine Combination Therapies

The use of cancer vaccines with other immune-mediating therapies:

- enhancers of immune stimulation
  (e.g., GM-CSF, IL-12, IL-15)
- immune checkpoint inhibitors
  (e.g., anti-CTLA-4, MAb, inhibitors of TGF-β)
- T-cell adoptive transfer therapy
- other cancer vaccines
  TRICOM + yeast
Effect of Multiple Costimulatory Modalities to Enhance CTL Avidity

Vaccine Modality | Precursor Frequency/10^5 CD8 T Cells | Δ Precursor | Peptide Concentration for CTL (nM) | Δ Avidity
--- | --- | --- | --- | ---
rV-CEA | 321 | 1.0x | 510 | 1.0x
rV-CEA/TRICOM | 769 | 2.4x | 5 | 102.0x
rV-CEA/TRICOM+ anti-CTLA-4 | 1,303 | 4.0x | 0.4 | 1,275x

* Avidity defined as the natural log of the peptide concentration that results in 50% maximal target lysis. Derby, Berzofsky. J Immunol. 166:1690–7.
Combination Therapy: Vaccine and α–CTLA-4

Mouse: CEA/Tg
Tumor: MC32a
Vaccine: Prime on Day 4 and Boost on Day 11, 18 and 25
CTLA-4 antibody on Day 4, 7 and Day 10

Hodge et al.
Vaccine + anti-CTLA-4

- Patient population: metastatic CRPC

- Design
  - Phase I
    - fixed dose vaccine
    - dose escalation of ipilimumab (1, 3, 5 and 10 mg/kg)

- Endpoints
  - 1º Safety
  - 2º Clinical responses, PSA kinetics, OS, Immune responses

NCI# 05-C-0167 Gulley PI
Preclinical Data from Hodge et al.
Comparing OS of Prostvac Alone to Prostvac + Ipilimumab

This compares two studies done at the NCI with Prostvac in metastatic CRPC (Updated 9/21/2010)

<table>
<thead>
<tr>
<th>Prostate Cancer Treatment</th>
<th>Median Overall Survival</th>
<th>Halabi Predicted Survival</th>
<th>Δ OS</th>
<th>Alive at 24 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostvac alone</td>
<td>26.3 months</td>
<td>17.2 months</td>
<td>9.1 months</td>
<td>53%</td>
</tr>
<tr>
<td>Prostvac and Ipilimumab</td>
<td>34.4 months</td>
<td>18.5 months</td>
<td>15.9 months</td>
<td>73.3%</td>
</tr>
</tbody>
</table>
Overall Survival for All Patients (updated 9/21/2010)

Median Overall Survival

- PSA-TRICOM alone: 26.3 months
- PSA-TRICOM and Ipilimumab: 34.4 months

Halabi Predicted Survival

- PSA-TRICOM alone: 17.2 months
- PSA-TRICOM and Ipilimumab: 18.5 months

Δ OS

- PSA-TRICOM alone: 9.1 months
- PSA-TRICOM and Ipilimumab: 15.9 months

Alive at 24 mos

- PSA-TRICOM alone: 53%
- PSA-TRICOM and Ipilimumab: 73%

10 mg/kg
Median OS not reached

P = 0.061

1, 3, & 5 mg/kg
Median OS = 31.7 months
The use of cancer vaccines in combination with conventional therapies

- Chemotherapy
- Hormone therapy
- Local radiotherapy of tumor
- Small molecule targeted therapeutics
Vaccine Combination Therapies

1. Vaccines Induce Minimal Toxicity
   – can act independently of concomitant therapy

2. Do NOT confuse
   multiple therapies used prior to vaccine
   vs.
   therapies used with vaccine or following vaccine
Certain chemotherapeutics when given post-vaccine therapy will lyse populations of tumor cells acting as a boost for the initial vaccine therapy.

Certain chemotherapeutic agents and/or radiation can alter the phenotype of tumor cells rendering them more susceptible to T-cell–mediated lysis.
Potential Multiple Effects of Chemotherapy, Small Molecule Targeted Therapeutics, or Local Irradiation of Tumors

- **Direct Tumor Killing**
- **Indirect Tumor Killing**
  - Architecture Changes
  - Vasculature Damage
- **No Direct Tumor Killing**
  - Phenotypic Changes

Dose
Potential Multiple Effects of Local Irradiation of Tumors

Hodge et al., Oncology 22:1064-70.
Combination Therapy: Vaccine + External Beam Radiation

Tumor (MC38-CEA+ SQ)

Day 0 8 14 15 22 29

rV-CEA/TRICOM rF-GM-CSF

8 Gy (2 Gy x 4)

rV-CEA/TRICOM rF-GM-CSF

QUADRAME is a radioactive samarium ($^{153}\text{Sm}$)-chelate:

It preferentially binds to osteoblastic metastatic tumor deposits in bone.

$^{153}\text{Sm}$ is FDA approved and clinically utilized for palliation of bone metastasis in multiple tumor histologies.
Treatment of LnCaP prostate cancer cells with palliative doses of $^{153}$Sm results in the upregulation of MHC class I and Fas.

Chakraborty, Wansley…Schlom, Hodge, NCI. Clin Cancer Res. 2008
Collaboration with Nuclear Medicine Branch
153Sm +/- PSA-TRICOM

Patient Population: CRPC Metastatic to bone

Randomize

Arm A: PSA-TRICOM + 153Sm (n=34)

Arm B: 153Sm (n=34)

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

153Sm:
- 1 mCi/kg d 8, may be repeated
- q 12 wks upon hematologic recovery.

PI Gulley  NCI# 7678
in collaboration with Nuc Med

Preclinical Data from Hodge et al.
Mode of Action of Vaccine Combination Therapies

- Evidence of non-coordinate lytic susceptibility of tumor cells
  - tumor cells have shown differential susceptibilities to killing by chemotherapy/radiation vs. T cells

- Exploitation of the phenomenon of homeostatic proliferation of T cells post-chemotherapy
  - certain effector immune cell subsets can be expanded more rapidly vs. regulatory cells
Human Carcinoma Cells Resistant to Chemotherapy Are Sensitive to CTL Killing After Treatment
TRICOM
TRIad of COstimulatory Molecules

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All vaccines contain: rV- as a prime vaccine
avipox (fowlpox, rF-) as multiple booster vaccines
CEA, MUC-1, and PSA transgenes all contain enhancer agonist epitopes
**Docetaxel +/- PANVAC**

**Patient Population:** Metastatic Breast Cancer (Docetaxel Naïve) n=48

- **Arm A:** Weekly Docetaxel + PANVAC
- **Arm B:** Weekly Docetaxel alone

**Primary endpoint:** TTP

**NCI 6977:** PI, Gulley

*Preclinical Data from Hodge et al.*
Tumor Growth Rate

Unique Properties of Therapeutic Cancer Vaccines

- Minimal toxicity

- Effect on the host immune system
  - indirect effect on the tumor
  - anti-tumor effects may be delayed

- Overall survival vs RECIST or time to progression as the appropriate primary endpoint

- Induction of host immunity is a dynamic process that can persist post-vaccination

- Potential for an enhanced effect on concomitant or subsequent therapies
Chemotherapy vs. Vaccine Followed by Chemotherapy (ECOG Multicenter Trial)

**Patient Population:** Metastatic CRPC (Halabi Predicted Survival ≥ 18 months)

Arm A: PSA-TRICOM vaccine $\rightarrow$ Docetaxel + Prednisone (n=90)

Arm B: Docetaxel + Prednisone (n=45)

Phase II (n=135)
Primary endpoint: OS

Protocol Chair: Doug McNeel
Co-Chair: Gulley