Cancer Vaccines and Combination Immunotherapy

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Presenter Disclosure Information

Bernard A. Fox, PhD

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Vaccines and Combination Immunotherapy

• to provide a high-level overview of the data.

• Identification of evidence gaps and Barriers to progress.

• pragmatic opportunities for action to advance the field of immunotherapy and improve patient care.
Preclinical Models of Vaccines and combination immunotherapy

• **Prime immunity**
  – Prehn and Main – Unique antigen paradigm
    - Has stood for 50 years
  – Understanding tumor Immunogenicity
  – Application of adjuvants (Dranoff)
October 20, 1975, The Cancer Research Institute honored 15 scientists for their pioneering contributions to the field of cancer immunology

Edward J Foley, Richmond T. Prehn, and Ludwik Gross

Received awards for finding evidence that cancer cells have specific antigens that can elicit a cancer destructive response
Mouse in which tumor was originally induced

No treatment

Implantation of normal tissue

Tumor inoculation

Killed

Untreated mice fail to reject tumor inoculum

Mice immunized with normal tissues from mouse of tumor origin fail to reject tumor inoculum

Tumor-immunized mice retain skin grafts from mouse of tumor origin

Tumor-immunized mice reject second tumor inoculum

Prehn and Main, *J Natl Cancer Institute*, 1957
Tumor Vaccines are Specific for Unique MCA-Induced Sarcoma

Each independently-derived chemically induced sarcoma expresses a unique mutation whose product serves as the dominant tumor rejection antigen.

– Prehn and Main, J Natl Cancer Institute, 1957
– Basombrio, et al., Cancer Res, 1970

Schreiber, Fundamental Immunology 5th ed., Adapted from Basombrio, et al., Cancer Res, 1970
Irradiated D5 tumor cells
Or none

Challenge w/ live D5 tumor (e3, e4 or e5)

Monitor tumor growth

Vaccination with B16BL6-D5 provides no protection from live D5 tumor.

Poorly Immunogenic

J Immunol 1998; 161:3033-3041
Tumour-induced polarization of tumour vaccine-draining lymph node T cells to a type 1 cytokine profile predicts inherent strong immunogenicity of the tumour and correlates with therapeutic efficacy in adoptive transfer studies

HAUKE WINTER,∗ HONG-MING HU,∗† CHRISTIAN H. POEHLEIN,∗ ERIK HUNTZICKER,∗ JOHN J. OSTERHOLZER,∗ JAFFAR BASHY,∗¶ DAVID LASHLEY,∗¶ BRUCE LOWE,¶ JANE YAMADA,∗ GREGORY ALVORD,** WALTER J. URBA† & BERNARD A. FOX∗†§

Table 1. Cytokine profile of anti-CD3 stimulated TVDLN correlates with immunogenicity

<table>
<thead>
<tr>
<th>Tumour vaccine</th>
<th>Immunogenicity*</th>
<th>IFN-γ†</th>
<th>IL-4†</th>
<th>Ratio†</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCA 304</td>
<td>92%</td>
<td>297(111)</td>
<td>85(45)</td>
<td>3.5</td>
</tr>
<tr>
<td>MCA 309</td>
<td>69%</td>
<td>151(28)</td>
<td>142(8)</td>
<td>1.1</td>
</tr>
<tr>
<td>MCA 310</td>
<td>25%</td>
<td>28(14)</td>
<td>228(93)</td>
<td>0.1</td>
</tr>
<tr>
<td>MPR-4</td>
<td>80%</td>
<td>246(19)</td>
<td>45(21)</td>
<td>5.5</td>
</tr>
<tr>
<td>MPR-3</td>
<td>20%</td>
<td>203(82)</td>
<td>119(114)</td>
<td>1.0</td>
</tr>
<tr>
<td>MPR-5</td>
<td>0%</td>
<td>169(30)</td>
<td>175(55)</td>
<td>0.97</td>
</tr>
</tbody>
</table>
Vaccination with irradiated tumor cells engineered to secrete murine granulocyte–macrophage colony-stimulating factor stimulates potent, specific, and long-lasting anti-tumor immunity

(tumor immunology/gene transfer)

GLENN DRANOFF*†‡, ELIZABETH JAFFEE§, AUDREY LAZENBY¶, PAUL GOLUMBEK§, HYAM LEVITSKY§, KATJA BROSE*, VALERIE JACKSON*, HIROFUMI HAMADA*, DREW PARDOLL§, AND RICHARD C. MULLIGAN*∥

Proc. Natl. Acad. Sci. USA
Vol. 90, pp. 3539–3543, April 1993

vaccinated with 5 × 10^5 irradiated (3500 rads) transduced cells as indicated. Animals were challenged 7 days later with 1 × 10^6 live nontransduced B16 cells. o, Animal succumbed to tumor challenge; ⋄, animal protected from tumor challenge.
Preclinical Models of Vaccines and combination immunotherapy

• What it takes to protect or “cure” mice in poorly immunogenic models
  - At minimum: Role for CD4 and CD8 W/o CD4
  - Potential role for B cell / Ab MOA? Role in preventing metastases?
Divergent Roles for CD4\textsuperscript{+} T Cells in the Priming and Effector/Memory Phases of Adoptive Immunotherapy\textsuperscript{1}

Hong-Ming Hu,\textsuperscript{*\,*} Hauke Winter,\textsuperscript{2\,*} Walter J. Urba,\textsuperscript{*\,**} and Bernard A. Fox\textsuperscript{3\,*\,**\,**\,**}

FIGURE 5. Adoptive immunotherapy fails to cure tumor-bearing MHC II KO mice. Adoptive immunotherapy was performed as described in Table I, except that mice were observed for survival. Twenty wt and 11 MHC II KO mice were injected i.v. with D5 tumor cells. Ten wt and six MHC II KO tumor-bearing mice were treated with \(70 \times 10^6\) effector T cells and IL-2. The remaining mice received IL-2 alone.
Cytomegalovirus-based cancer vaccines expressing TRP2 induce rejection of melanoma in mice

Guangwu Xu, Tameka Smith, Finn Grey, and Ann B. Hill


Role for Antibodies

- Vaccination protects from challenge
- Depletion of T cells does not affect protection
- Protection can be transferred by sera
  - Ab against TRP2

A

Days after tumor challenge

% Tumor free mice

- MCMV
- MCMV-mTRP2

Days after tumor challenge

% Tumor free mice

- MCMV
- MCMV-mTRP2 + Iso Ab
- MCMV-mTRP2 + AntiCD4
- MCMV-mTRP2 + AntiCD8
- MCMV-mTRP2 + AntiCD4 + AntiCD8

Days after tumor challenge

- No-sera
- Sera
Potential vaccine: vaccine combinations

Strategies that induce both T and B cell responses.
Preclinical Models of Vaccines and combination immunotherapy

• Strategies to induce broad sterilizing immunity
  – Why it’s important (tumor burden)
    • Heterogeneity – Vogelstein
    • “Triple E” Hypothesis - Schreiber
  – Cancer Antigens
    • NCI Prioritized - Cheever
    • Her2/neu (mesothelin) – ML Disis / E Jaffee
    • SLiPs and DRiPs – J Yewdell
Hypothesis:
Effective treatment of metastatic cancer will require an immune response to many antigens.
Dealing with Immunoediting

In addition to heterogeneity add immunoediting. Induce a strong immune response against an antigen and you put incredible pressure on tumor cells to escape.

R D Schreiber et al. Science 2011
The Prioritization of Cancer Antigens: A National Cancer Institute Pilot Project for the Acceleration of Translational Research

Martin A. Cheever,¹ James P. Allison,² Andrea S. Ferris,³ Olivera J. Finn,⁴ Benjamin M. Hastings,³ Toby T. Hecht,⁵ Ira Mellman,⁷ Sheila A. Prindiville,⁶ Jaye L. Viner,⁶ Louis M. Weiner,⁸ and Lynn M. Matrisian⁶

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**Therapeutic Function**

0.32

**Immunogenicity**

0.17

**Specificity**

0.15

**Oncogenicity**

0.15

**Expression Level & % Positive Cells**

0.07

**Stem Cell Expression**

0.05

**Number of Patients with Antigen Positive Cancers**

0.04

**Number of Epitopes**

0.04

**Cellular Location of Expression**

0.02

*Clin Cancer Res 2009;15:5323-5337*
Beware the streetlight effect
Novel technologies and emerging biomarkers for personalized cancer immunotherapy

Diversity of Antigen-Specific Responses Induced In Vivo with CTLA-4 Blockade in Prostate Cancer Patients

Serena S. Kwek,* Vinh Dao,* Ritu Roy,† Yafei Hou,* David Alajajian,* Jeffrey P. Simko,‡ Eric J. Small,* and Lawrence Fong*

September 5, 2012, doi:10.4049/jimmunol.1201529

Prostate CR: Strong Antibody Response to HIBCH
And HIBCH is Expressed in Patient’s Tumor

Cancer Immunology Miniatures

Sustained Complete Response to CTLA-4 Blockade in a Patient with Metastatic, Castration-Resistant Prostate Cancer

Julie N. Graff¹,², Sachin Puri⁴, Carlo B. Bifulco⁴,⁵, Bernard A. Fox²,³,⁴, and Tomasz M. Beer²
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Julie N. Graff,1,2 Sachin Puri,4 Carlo B. Bifulco,4,5 Bernard A. Fox,2,3,4, and Tomasz M. Beer2
Two Protein Degradation Pathways

- mRNA
- Ribosomes
- ER and cytoplasm
- SLiPs
- DRiPs
- Proteasome
- TAP
- ER
- Autophagosome
- Endosome
- Autolyosome
- Long-lived Proteins
Proteosome Blockade shunts DRiPS and SLiPS to Autophagy Pathway

Use as a Vaccine
Proposed Model for Autophagosome Vaccine Cross-Presentation

- APC-Targeted vesicle
- >100 antigens, 12 NCI prioritized cancer antigens
- 15 DAMPs and agonists for TLR 2, 3, 4, 7 and 9.
Autophagosome Vaccine more Therapeutic than “Gold Standard” Vaccine in 3 Day-established 3LL

Tumor Vaccines are Specific for Unique MCA-Induced Sarcoma

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Schreiber, *Fundamental Immunology 5th ed.*, Adapted from Basombrio, et al., Cancer Res, 1970
Autophagosomes from one unique sarcoma can prime an immune responses against other independently-derived syngeneic sarcomas

Whole Cell Vaccine

Autophagosome Vaccine

Combination Immunotherapy
Vaccination + anti-OX40: Three breast tumor models to contrast allogeneic whole cell and DRibble vaccines

4T1 Model:
- Day 0: 25,000 viable 4T1 tumor cells
- Day 5: 10ug DRibble (i.n.) or 10x10^6 tumors (s.c.) + 100ug OX86 (i.p.)
- Day 7+9: 100ug OX86 (i.p.)

C57MG Model:
- Day 0: 25,000 viable C57MG tumor cells
- Day 7: 10ug DRibble (i.n.) or 10x10^6 tumors (s.c.) + 100ug OX86 (i.p.)
- Day 9+11: 100ug OX86 (i.p.)

FAT Model:
- Day 0: 25,000 viable FAT tumor cells
- Day 9: 10ug DRibble (i.n.) or 10x10^6 tumors (s.c.) + 100ug OX86 (i.p.)
- Day 11+13: 100ug OX86 (i.p.)
Therapeutic immunity in three allogeneic tumor models using DRibbles but not whole cell vaccines

### Whole Cell Vaccine

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Tumor Inoculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>4T1</td>
<td>4T1 C57mg FAT</td>
</tr>
<tr>
<td>C57MG</td>
<td></td>
</tr>
<tr>
<td>FAT</td>
<td></td>
</tr>
</tbody>
</table>

Mouse Strain: BALB/c C57BL/6 FVB
Tumor Est.: 5d 7d 9d

### DRibble Vaccine

<table>
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<tr>
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Mouse Strain: BALB/c C57BL/6 FVB
Tumor Est.: 5d 7d 9d
Identification of gaps and barriers to progress.

- Limitations
  - No high density ProtoArrays (Ab detection)
  - A mouse with cancer is not a human with cancer
    - Time (tumor growth and age)
    - Tumor burden
    - Immune selection
    - Microbiome / SPF
  - Different models can give very different results.
    - Combination immunotherapy
Anti-OX40/PDL1 Combo in MCA205 Tumor Model
(Treating Larger Tumors)

.5e^6 MCA205 tumor cells

B6

10-12d
(tumor ~50mm^2)

\( \alpha \)-OX40 \( \alpha \)-OX40

4d

\( \alpha \)-PDL1 \( \alpha \)-PDL1 \( \alpha \)-PDL1 \( \alpha \)-PDL1

C57Bl6:MCA205

Monitor tumor growth; sacrifice mice when tumors reach 150mm^2

Survival proportions:

Days (post tumor inoculation)

Percent survival

0 20 40 60 80

0

50

100

Rat IgG

OX86

aPDL1

OX86 + aPDL1

p<0.0001

Days (post tumor inoculation)
Concurrent addition of anti-PD-1 and anti-OX40 reduces antitumor effect of anti-OX40 alone.
Identification of gaps and barriers to progress.

• Pilot human studies: Combination Immunotherapy
  – Small numbers of patients
  – Well Studied for MOA
  – Intratumoral?