“NCI Immunotherapy Agent Workshop” (July 12th, 2007)

iSBTc
22nd Annual Meeting

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Presenter Disclosure Information

Mac Cheever

The following relationships exist related to this presentation:

- GlaxoSmithKline: Licensed Intellectual property rights
- Merck: Cancer Vaccine Consultant
- Vaccinex: Consultant
- Vaccinoma: Consultant
- The Vaccine Company: Data Monitoring Committee
- Dendreon: Mock FDA Panel Member
Workshop Goal:

• To develop a ranked list of agents with high potential for use in cancer therapy
Problem:

- Many agents have the potential to serve as immunotherapeutic drugs
  - Few are being tested in humans.
- Cancer vaccine example:
  - Agents needed to improve cancer vaccines are not commonly available
    - Adjuvants
    - T cell growth factors
    - T cell stimulating ligands & Ab
    - Immune checkpoint inhibitors
    - Agents to neutralize suppressive cells & cytokines
Adjuvant Example

• Universal Truth
  – Adjuvants are needed to achieve highest levels of immune response
HPV Vaccine

Higher antibody levels with GSK Adjuvant (AS04)  
[AS04 = Alum + MPL (Monophosphoryl Lipid A)]

(AS04) is a novel proprietary adjuvant developed by GSK in collaboration with Corixa.  
GMT = Geometric Mean Titers

[JP Garnier, GSK CEO, Corporate Media Presentation Feb, 2005]
Adjuvant Example

- By FDA policy & custom, adjuvants are approved only as components of vaccines
  - Accordingly
    - Commonest adjuvants used by academics
      - Dendritic cells
      - GM-CSF
    - If GM-CSF had activity only as an adjuvant, it would not be available for testing in cancer vaccines
Adjuvant Example

• “Catch 22”
  – Adjuvants approved for non-adjuvant purposes are broadly available
  – Adjuvants that function only as adjuvants are not broadly available, regardless of potency
Adjuvant Example

• “Majority of cancer drug development takes place post-approval”
  – Bob Capizzi

• Adjuvants are not approved and thus not available for cancer drug development
Why aren’t adjuvants available?

• NCI
  – ~ Billion(s) for vaccines & T cell therapy
    • Little for essential vaccine components
      – Researcher hands tied behind backs

• FDA
  – No clear path forward for broad testing & approval of adjuvants that aren’t effective as monotherapy
Why aren’t adjuvants available?

• Industry
  – “Invisible hand of the market”
    • Rational decisions based on regulatory and commercial concerns
    • Don’t see a clear path forward
    • Companies with great adjuvants
      – Develop them as monotherapy
      – Leave “on the shelf” if not successful as monotherapy
Solution to agent availability?

• Small step
  – Developed an exceedingly well-vetted list with broad consensus of agents with “Highest Potential to Serve as Immunotherapeutic Drugs”
  – Purpose
    • To facilitate NCI discussions to address the availability of clinical grade immunotherapeutic drugs for human trials
BROAD INPUT & CONSENSUS
Mandatory!
BROAD INPUT: WEB Site to ask for agent suggestions

- Exceedingly well publicized
  - NCI
    - Immunotherapy grantees
    - RAID grantees
    - NCI Bulletin
  - Scientific societies
    - AAI
    - AACR
    - ASH
    - ASCO
    - iSBTc
    - CVC
**NCI WEB SITE: Submissions**

- Total Agents Suggested = 124
  - All with demonstrated immunological or physiological function

- Broad desire for:
  - Vaccine adjuvants
  - T cell growth factors
  - Agents to inhibit immune checkpoint blockade
  - Functional antibodies, cytokines, ligands & receptors
    - To activate or augment T cell responses
    - To inhibit suppressor circuits
  - Agents “left on the shelf” by drug companies.
Workshop: July 12th 2007

• Ranked top 30 agents
  – Winnowed from 124 by organizing committee

• Focused on agents with greatest potential for broad usage
  – Excluded
    • Specific antigens for vaccines
    • Antigen-specific antibodies
    • Regardless of attractiveness or potential utility
• **Criteria used for inclusion on ranked list**
  – Potential for use in cancer therapy
  – Perceived need by multiple, independent clinical investigators
  – Potential use in more than one clinical setting
    • i.e., against different tumor types or as part of multiple therapy regimens
  – Not broadly available for testing in patients
  – Not commercially available or likely to be approved for commercial use in the near future

• **Criteria *not* used**
  – Prior failed attempts to commercialize
  – Intellectual property
Organizing Committee

• AAI/AACR Extramural Immunology Expert Steering Committee

• Martin A. “Mac” Cheever, M.D. Fred Hutchinson Cancer Research Center

• Jim Allison PhD Memorial Sloan-Kettering

• Olivera Finn PhD University of Pittsburgh

• Ira Melman MD PhD Yale/Genentech

• Drew Pardoll MD PhD Johns Hopkins

• Ralph Steinman PhD Rockefeller Institute

• Louis Weiner MD Fox Chase

• NCI DCB & DCTD

• Steve Creekmore, M.D., Ph.D. Biological Resources Branch

• Richard Camalier, RAID, DTP, DCTD, NCI

• Jerry Collins, Ph.D. Developmental Therapeutics Program

• Jill Johnson, DTP, DCTD, NCI

• Toby Hecht, Ph.D. Biological Resources Branch

• Kevin Howcroft, Ph.D. Division of Computational Bioscience

• Susan McCarthy, Ph.D. Division of Cancer Biology

• Robert Mufson, Ph.D. Division of Cancer Biology

• Howard Streicher, M.D. CTEP

• James Zwiebel, M.D. CTEP
Workshop Participants

• Selected from suggestions by
  – AACR, AAI, ASCO, ASH, CVC & iSBT
  – NCI intramural & extramural

• Broad representation
  – Academia
  – Industry
  – NCI

• Observers invited & asked to comment
  – Industry
  – NCI
  – FDA

• Workshop was open to the public
Workshop Participants

• Chairpersons
  • Martin A. "Mac" Cheever, M.D. Fred Hutchinson Cancer Research
  • Steve Creekmore, M.D., Ph.D. Biological Resources Branch, NCI

• Participants
  • Jay Berzofsky, M.D., Ph.D. Vaccine Branch, CRC, NCI
  • Frank Calzone, Ph.D. Amgen, Inc
  • Mary Lenora Disis, M.D. University of Washington
  • William Ho, M.D., Ph.D. Genentech, Inc.
  • Alan Houghton, M.D. Memorial Sloan Kettering Cancer Center
  • Elizabeth Jaffee, M.D. Johns Hopkins University School of Medicine
  • Crystal Mackall, M.D. Pediatric Oncology Branch, NCI
  • Kim Margolin, M.D. City of Hope
  • Michael Morin, Ph.D. Pfizer
  • Anna Karolina Palucka, M.D., Ph.D. Baylor Research Institute
Workshop Participants

- **Drew Pardoll, M.D., Ph.D.** Johns Hopkins University
- **George Prendergast, Ph.D.** Lankenau Institute for Medical Research
- **Ellis Reinherz, M.D.** Harvard Medical School
- **Steven Rosenberg, M.D., Ph.D.** Surgery Branch, CCR, NCI
- **Jeffrey Schlom, Ph.D.** Laboratory of Tumor Immunology and Biology, NCI
- **Paul Sondel, M.D., Ph.D.** University of Wisconsin
- **Walter Urba, M.D., Ph.D.** Robert W. Franz Cancer Research Center
- **Thomas A. Waldmann, MD** CCR, NCI
- **Jeffrey Weber, M.D., Ph.D.** H. Lee Moffitt Cancer Center
- **Louis Weiner, M.D.** Fox Chase Cancer Center
- **Theresa Whiteside, Ph.D.** University of Pittsburgh Cancer Institute
- **Jon Wigginton, M.D.** Merck and Co., Inc
Invited Observers

- **FDA**
  - Kimberly Benton, Ph.D. CBER, FDA
  - Raj Puri, M.D., Ph.D. CBER, FDA
  - Amy Rosenberg, M.D. DTP, FDA
  - Daniel Takefman, Ph.D. CBER, FDA

- **Industry**
  - Lothar Finke, M.D. Argos Therapeutics, Inc.
  - Jesus Gomez-Navarro, M.D. Pfizer Global
  - Steve Herrman, Ph.D. Wyeth Research
  - David Urdal, Ph.D. Dendreon Corporation

- **NCI**
  - Robert Wiltrout, Ph.D. CCR, NCI
Process

- Agents presented by a Workshop Participant
  - PowerPoint slides based on a standard template
  - Comments by secondary and tertiary reviewer
- Agents ranked at end of each presentation by consensus
- Final Ranking by e-mail ballots
  - After e-mail comments/discussion
- Slides and Workshop report are available online

http://web.ncifcrf.gov/research/brb/site/home.asp
Ranked List
1. IL-15
T Cell Growth Factor

• Made by DCs, macrophages, & stromal cells
  – Not by T cells
• Acts on CD8+ & CD4+ T cells, NK & mast cells.
  – Inhibits antigen-induced cell death T cells (in contrast to IL-2)
  – Promotes induction of longer-lived and higher-avidity CD8+ T cells
2. Anti-PD1 and/or anti–B7-H1 (PD1L) T-Cell Checkpoint Blockade Inhibitor

- PD1 (Programmed Death 1)
  - Structurally related to **CTLA-4 and CD28
    - Member of the immunoglobulin super family
  - Up-regulated on activated T and B cells and monocytes.
- Abrogation of PD-1 increases the numbers of functional cytokine-secreting CTLs

**Anti-CTLA4 not ranked
  - Considered close to approval and thus soon to be “broadly available”
3. IL-12
Vaccine Adjuvant

- Binds to IL-12 receptor on NK, T cells, DCs, & macrophages
  - Promotes IFN & induces Th1 polarization
- Exceedingly potent adjuvant
4. Anti-CD40 and/or CD40L
Antigen Presenting Cell Stimulator

• Antigen Presenting Cells (APC) activation & induction of T cell immunity
• Direct tumor inhibition (especially in CD40-bearing B-cell lymphomas)
5. IL-7
T Cell Growth Factor / Adjuvant

• Required for T cell development & naive T cell survival in the periphery
• Phase I trials
  – Dramatic increases in total body CD4+ and CD8+ T cells
  – Modest increases in NK cells
6. CpG
Vaccine Adjuvant

• TLR-9 agonist
• Leads to B-cell proliferation and differentiation, maturation of plasmacytoid DCs, and activation NK cells
7. 1-methyl tryptophan
Enzyme Inhibitor

- Small molecule
- Inhibits immunosuppressive enzyme
  IDO (indoleamine 2,3-dioxygenase)
  – IDO suppresses T cell activation via
    tryptophan catabolism
8. Anti-CD137 (anti–4-1BB) T-Cell Stimulator

- CD137 is a member of the TNF super family of receptors
  - On activated T cells, NK cells & NK T cells
- Co-stimulatory, anti-apoptotic & proliferative
9. Anti–TGF-beta Signaling Inhibitor

- Complex biology
- Inhibits CTL-mediated tumor immunosurveillance
10. Anti–IL-10 receptor or anti–IL-10 Suppression Inhibitor

- Neutralization of IL-10
  - Complex biology
    - Both immunosuppressive & immunostimulatory activities
  - Blockade diminishes Treg effect
11. Flt3 Ligand
DC Growth Factor/Vaccine Adjuvant

- Hematopoietic growth factor
- Binds to the Flk2/Flt3 receptor tyrosine kinase in the c-kit/fms family
- Induces expansion and differentiation of DC progenitors in human clinical trials
12. Anti-GITR
T-Cell Stimulator

- Glucocorticoid-induced TNF receptor
  - Constitutively expressed at high levels by Tregs
    - Minimally by naïve CD4+ and CD8+ T cells
  - Signaling abrogates Treg suppressive activity in vitro
  - Co-stimulatory for effector CD4+ and CD8+ T cells.
13. CCL21 Adenovirus T-Cell Attracting Chemokine

- Secondary lymphoid tissue chemokine
- Strong attractant of naïve T cells and mature DCs via CCR7
14. MPL
Vaccine Adjuvant

• Monophosphoryl lipid A
  – Component of lipopolysaccharide (LPS), or endotoxin

• TLR4 agonist
  – Used in >100,000 patients
15. Poly I:C and/or poly IICLC Vaccine Adjuvant

- Double-stranded polyinosinic:polycytidylic acid
- TLR-3 agonist
  - Strong activators of Th1 responses, CD8 T cells, and natural killer cells
16. Anti-OX40
T-Cell Stimulator

• OX40 (CD134)
  – Co-stimulatory receptor for CD4+ and CD8+ T cells
  – Involved in signaling for T cell survival, generation of memory T cells, and reactivation of memory T cell responses
  – Seems to inhibit Tregs in vitro
17. Anti–B7-H4
T-Cell Checkpoint Blockade Inhibitor

- B7-H4
  - Structure similar to B7-1,2
    - But lacks binding sequences for CTLA-4 or CD28
  - Expressed on activated T cells, B cells, DCs, monocytes, and tumor-associated macrophages
  - Increase expression on Tregs enable antigen-presenting cell-suppressive activity
    - A process that is IL-10 dependent.
- Blockade increases T cell proliferation & reduced tumor volumes in vivo
18. Resiquimod and/or 852A
Vaccine Adjuvant

- TLR7/8 agonists
  - Biology is similar to imiquimod (TLR7 agonist)
- Induces production of IFN-alpha, IL-6, IL-8, IL-12; TNF-alpha
  - Stimulates the innate immunity
  - Leads Th1 responses
19. LIGHT and/or LIGHT vector
T-Cell Stimulator

- TNF superfamily member
- Co-stimulatory activity on T cells through expression of herpes virus entry mediator (HVEM)
  - LIGHT-HVEM interactions mediate GVHD
20. Anti–LAG-3
T-Cell Checkpoint Blockade Inhibitor

• Lymphocyte Activation Gene 3/ CD223
  – Negative regulator of activated T cells
    • Expressed on activated NK & T cells
    • Not on resting lymphocytes
  – Selectively up-regulated on Tregs
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<tr>
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<th>Description</th>
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<tr>
<td>1.</td>
<td>IL-15</td>
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<td>1-methyl tryptophan</td>
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<td>Anti–TGF-beta</td>
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We have a well vetted list with broad input.

• What next?
Possible positive outcomes

• Encouragement of RAID applications for manufacture
• NCI distribution of company-manufactured agents
• Reinvigoration of pharma/biotech efforts to develop agents
• Provide a benchmark for the strength & resolve of the national cancer therapy development enterprise