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

iSBTc
22nd Annual Meeting

Martin A. “Mac” Cheever, MD
Fred Hutchinson Cancer Research Center
University of Washington

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:

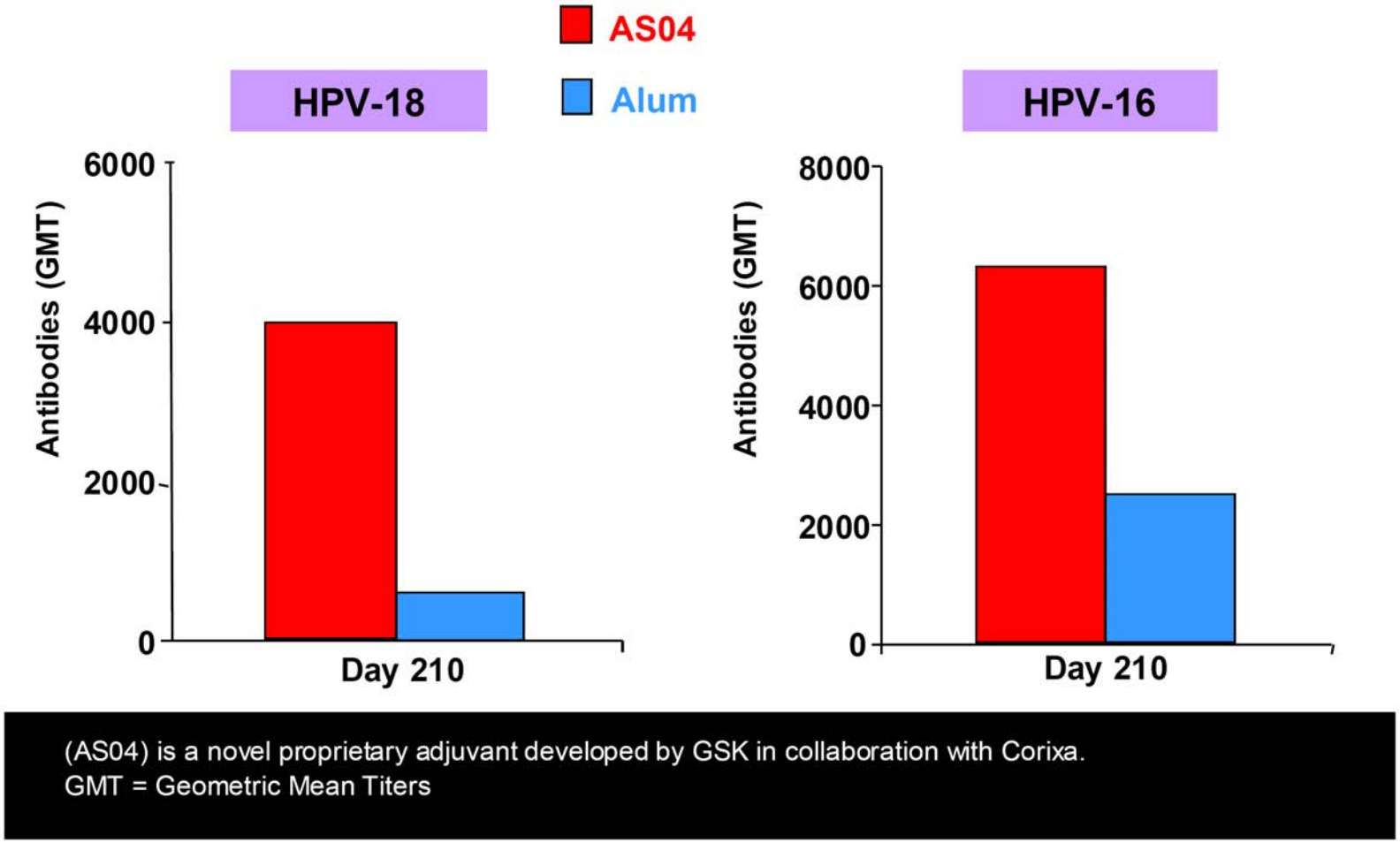
- Many agents have the potential to serve as immunotherapeutic drugs
  - Few are being tested in humans.
- Cancer vaccine example:
  - Agents needed to improve cancer vaccines are not commonly available
    - Adjuvants
    - T cell growth factors
    - T cell stimulating ligands & Ab
    - Immune checkpoint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



[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 immunosurveilance

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 ICLC 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

1. IL-15	T Cell Growth Factor
2. Anti-PD1 and/or anti–B7-H1 (PD1L)	T-Cell Checkpoint Inhibitor
3. IL-12	Vaccine Adjuvant
4. Anti-CD40 and/or CD40L	APC Stimulator
5. IL-7	T Cell Growth Factor
6. CpG	Vaccine Adjuvant
7. 1-methyl tryptophan	Enzyme Inhibitor
8. Anti-CD137 (anti–4-1BB)	T-Cell Stimulator
9. Anti–TGF-beta	Signaling Inhibitor
10. Anti–IL-10 receptor or anti–IL-10	Suppression Inhibitor
11. Flt3L	DC Growth Factor/Adjuvant
12. Anti-GITR	T-Cell Stimulator
13. CCL21 Adv	T-Cell Attracting Chemokine
14. MPL	Vaccine Adjuvant
15. Poly I:C and/or poly ICLC	Vaccine Adjuvant
16. Anti-OX40	T-Cell Stimulator
17. Anti–B7-H4	T-Cell Checkpoint Inhibitor
18. Resiquimod and/or 852A	Vaccine Adjuvant
19. LIGHT and/or LIGHT vector	T-Cell Stimulator
20. Anti–LAG-3	T-Cell Checkpoint Inhibitor

We have a well vetted list with broad in put.

- 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