

**PROGRAM UPDATE: 2007 WORKSHOP ON COMBINATION
BIOLOGICAL THERAPY OF CANCER**

**ISBTC ANNUAL SCIENTIFIC PROGRAM
NOVEMBER 1, 2008
SAN DIEGO, CA**

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**INTERNATIONAL SOCIETY
FOR THE
BIOLOGICAL THERAPY OF CANCER**



WORKSHOP ON FUTURE OPPORTUNITIES FOR THE COMBINATION BIOLOGICAL THERAPY OF CANCER

**NOVEMBER 1, 2007
BOSTON, MASSACHUSETTS**

Organizing Committee:

- **Bernie Fox, PhD-Earl Chiles Cancer Research Institute**
- **Thomas Gajewski, MD, PhD-University of Chicago**
- **Rachel Humphrey, MD-Bristol-Myers Squibb**
- **Hy Levitsky, MD-Johns Hopkins University**
- **Jon Wigginton, MD-Merck Research Laboratories**

WORKSHOP PROGRAM

Program Structure:

- Overview of 2006 Think-Tank
- State-of-the-Science Sessions
- Abstract Program
- Perspectives Presentations
- Breakout Sessions

Objectives:

- Review and define key scientific opportunities.
- Define central obstacles to progress.
- Articulate specific solutions.
- Promote dialogue between academicians, industry and regulatory agencies and enhance shared capabilities.
- Facilitate communication regarding these issues between US, European and Asia-Pacific scientific communities.

CHALLENGE:

Creation of “ideal” scientific, regulatory and commercial environment for the clinical development of biologic combinations.

OPPORTUNITIES AND OBSTACLES

THE GOOD NEWS!

- **Exciting range of new options for combination therapy**
 - Immunotherapy-Immunotherapy
 - Immunotherapy-Angiogenesis Inhibitors
 - Immunotherapy-Apoptosis Inducers
 - Immunotherapy-Chemotherapy



IMMUNOTHERAPY COMBINATIONS

Thomas F. Gajewski-U. Chicago

Jon Wigginton-Merck

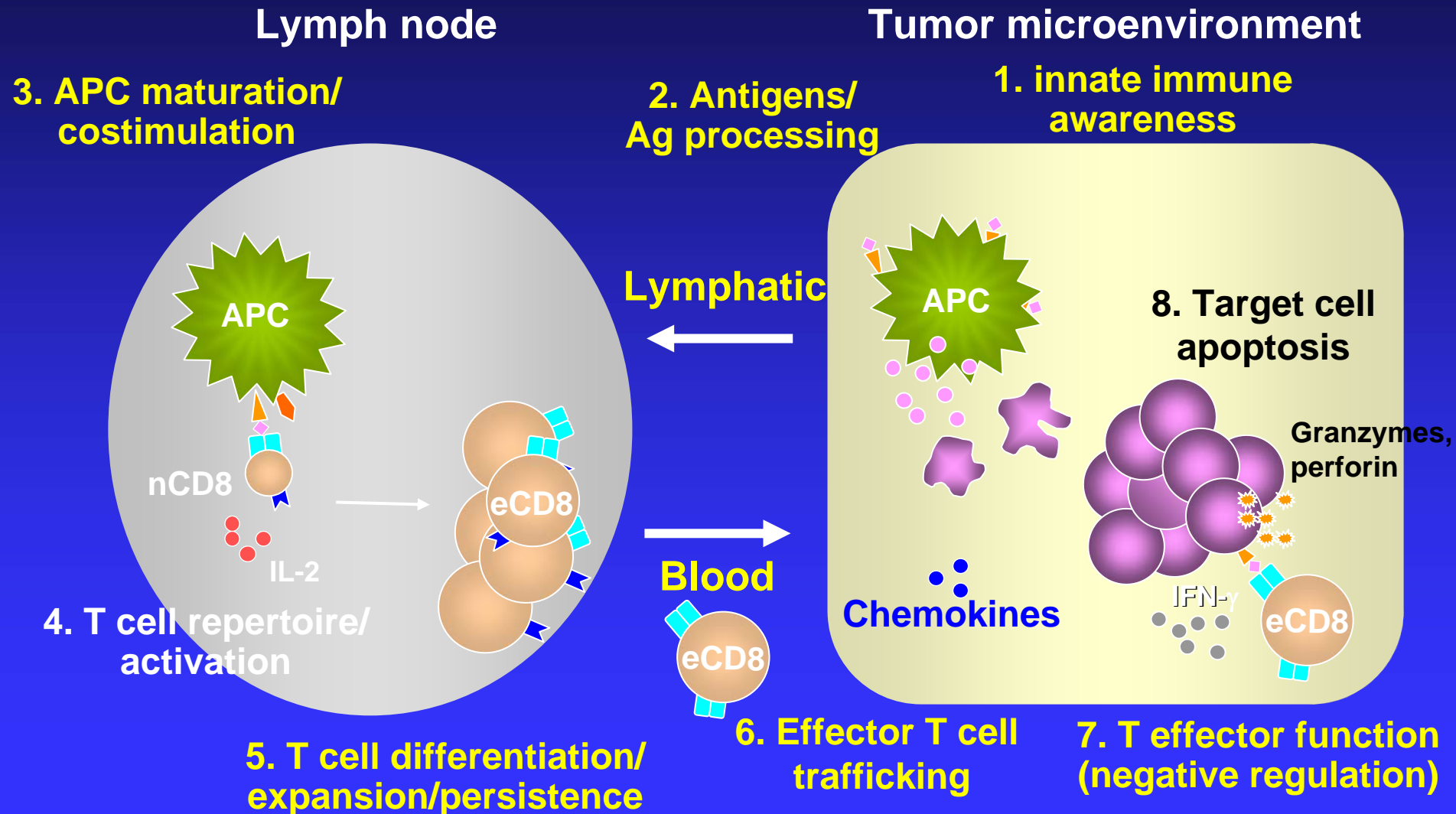
Lieping Chen-John Hopkins

Glenn Dranoff-Dana Farber

BACKGROUND

- **Anti-tumor immune response is a complex and multi-stage process that can become dysregulated at several levels in the context of a growing tumor.**
- **Overcoming each of these defects may require a distinct intervention, and therefore combination therapies may be important in order to translate immune responses into tumor regression.**
- **Another way to look at it: with T cell-based immunotherapy, the “drug” is not necessarily the product administered (e.g. vaccine)—rather, the therapeutic entity is the properly generated tumor antigen-specific effector T cell population that has penetrated the tumor microenvironment and maintained effector function there**

At what levels can a spontaneous anti-tumor T cell response fail?



CANDIDATE TREATMENT STRATEGIES

- 1. Innate immune awareness/Ag presentation/APC maturation**
 - Innate immune cells and cytokines, TLR agonists, CD40 ligands, vaccination—novel Ag sources
- 2. T cell repertoire/initial activation**
 - B7 and other costimulatory ligands
 - Interference with lymph node-based or systemic negative regulators (CTLA4, IDO, arginase, anergy, Tregs)
- 3. T cell differentiation/expansion/persistence**
 - Differentiation cytokines (IL-12, IL-18)
 - Expansion, survival factors (IL-2, IL-7, IL-15, anti-41BB; homeostatic proliferation)
- 4. T cell trafficking into tumor sites**
 - Intratumoral chemokines, LIGHT
 - Pro-inflammatory treatments (XRT, TLR agonists, innate cytokines)
- 5. Executing effector function in tumor microenvironment**
 - Blockade of tumor microenvironment-based negative regulators (IDO, PD-1/PD-L1, Tregs, anergy, TGF- β , IL-10, iNOS)
 - Promote effector cell proliferation (regenerate cytotoxic granules)
- 6. Tumor cell susceptibility to recognition and killing**
 - Blockade of key anti-apoptotic molecules (Bcl2 and Spi inhibitors)
 - Inhibit oncogenic pathways that create resistant phenotype and/or resistant microenvironment (Stat3; MEK? Notch? Wnt?)

MAJOR QUESTIONS

- **What are the most promising combination opportunities irrespective of logistical issues?**
- **What are the most appropriate clinical endpoints for immunotherapy trials? Biomarkers/Immune monitoring?**
- **Should we focus on metastatic disease setting? MRD/adjuvant setting?**
- **Should we thinking about integrating non-immunologic agents that possess immunomodulatory properties?**
- **Will there be an immunologic cocktail for each patient? Each tumor type? Common themes?**
- **What non-scientific barriers are limiting progress (legal/IP, reagent availability, regulatory)?**

CONCLUSIONS

- **Spontaneous anti-tumor T cell responses may fail at one of several levels.**
- **Specific mechanisms of failure have identified new targets and strategies for intervention.**
- **Strong scientific basis for combination therapies to increase the therapeutic efficacy of T cell-based immunotherapy of cancer.**
- **Some agents are becoming available for clinical translation, but others need broad-based community support to be made available for clinical studies based on a sound rationale and preclinical data.**

Antiangiogenesis - Immune Therapy Combinations

George Coukos-U Pennsylvania

Heinz Zwiertzina-Innsbruck Medical Univ.

Michael Atkins-Beth Israel

Steve Libutti-NCI

OPPORTUNITIES

- **Angiogenesis-targeting immunotherapy**
- **Thalidomide and analogs (antiangiogenic/anti-inflammatory and Th1 costimulatory)**
- **ETBR inhibitors**
- **STAT3 inhibitors ?**
- **COX-2 inhibitors ?**
- **Sorafenib ?**
- **Sunitimib ?**

MAJOR THEMES

- **Strong mechanistic interaction between angiogenesis and regulation of immune responsiveness.**
 - VEGF and dendritic cell maturation/function
 - Concept of vascular dendritic cells
 - COX-2 inhibition and enhancement of vaccination
 - VEGF neutralization and enhancement of vaccination
 - Activated DC can produce VEGF and promote angiogenesis
 - VEGFR blockade and reduction in regulatory T cells
 - Endothelin receptor antagonism can enhance T cell response.
 - Successful immunotherapy can lead to inhibition of angiogenesis
- **Above observations directly suggest specific therapeutic combinations based on immunotherapeutic and antiangiogenic agents.**

MAJOR QUESTIONS/ISSUES

Basic scientific questions / potential obstacles:

- Preclinical assays are limited in their potential to predict toxicity and effects in patients.
- Companion animals with spontaneous tumors may represent a better model.
- How to discriminate relative role of antiangiogenic versus immunoregulatory effects of combinations to inform dosing/schedule.

MAJOR QUESTIONS/ISSUES

Clinical questions / potential obstacles:

- How to optimize dose and schedule for clinical testing
- Significant limitations in the ability to quantitate angiogenesis
- Biomarkers, biomarkers, biomarkers!
- Patient selection
- Role for testing in adjuvant versus advanced populations

APOPTOSIS INDUCTION AND IMMUNOTHERAPY-HOW TO IMPROVE RESULTS OF IMMUNOTHERAPY

Peter Hersey-U. Newcastle

James Finke-Cleveland Clinic

Douglas Green-St. Judes

James Mier-Beth Israel-Deaconess

CELL KILLING MECHANISMS USED BY LYMPHOCYTES DEPEND ON THE INDUCTION OF APOPTOSIS IN TARGET CELLS

Granzyme – Perforin Mediated Killing

CD8 CTL (CD4 CTL)

NK Cells and ADCC

Death Ligand Mediated Killing

TRAIL, FasL, TNF

CD4 T Cells

Monocytes, Dendritic Cells

BASIC PREMISE:

- **Tumors have elaborated a variety of molecular mechanisms that can confer intrinsic resistance to apoptosis.**
 - Overexpression/activity of antiapoptotic factors**
 - Downregulation/defective proapoptotic proteins.**
- **Improved understanding of these mechanisms will highlight pathways that may be therapeutically targeted to enhance the sensitivity of tumor cells to immunotherapeutic regimens.**

THERAPEUTIC TARGETING OF ANTIAPOPTOTIC PROTEINS

- **BCL-2**
- **IAP/survivin**
- **AKT**
- **ERK-1/2**

DOES THE WAY A CELL DIES INFLUENCE THE IMMUNE RESPONSE?

- **Necrosis said to release inflammatory mediators which stimulate NF-Kb, ERK and STAT 1/3, release of TNF, IL-1, IL-6, IL-8, IL-23 cytokines which can stimulate tumor growth and or induce Th17 helper T cells.**
- **HMGB1(High Mobility group B1) and Heat shock proteins may be key stimulators of DC maturation and immune responses ?**
- **Apoptosis said to be a more silent death which delivers antigens to APC without the marked release of inflammatory mediators and no generation of CD4+ T cells.**
- **Resulting “help-less” CD8+ T cells said to be tolerant.**

CYTOTOXIC CHEMOTHERAPY AND IMMUNOTHERAPY

Ron Gress, NCI

Bernie Fox-Earl Chiles

Bruce Blazar-U. Minnesota

Leisha Emens-Johns Hopkins

GENERAL ISSUES

MAJOR THEMES: LEADERSHIP PERSPECTIVES

- **FDA extremely motivated to facilitate communication with scientific community.**
- **Regulatory pathways may differ substantially based on nature of combination and may be important differences between US, Europe, Asia and Latin America.**
- **FDA and investigator definitions of what constitutes a combination therapy may differ.**
- **Strong interest by the NCI in facilitating both investigation and rapid clinical translation of combination approaches for the treatment of cancer.**

MAJOR THEMES: INVESTIGATOR PERSPECTIVES

- **Major specific challenges for development of combinations:**
 - Access to Reagents
 - Patient Population
 - Regulatory Issues
 - Funding

ACCESS TO REAGENTS

- **Combining agents difficult even in preclinical setting.**
 - Intellectual Property
 - Liability
 - Contracting, MTA, CTA
 - Impact of toxicity from combination studies on registration
- **Many single agents moth-balled prematurely due to “inactivity”.**
- **Need for additional funding to support DTP-RAID mechanism for synthesis of novel agents.**
- **Solutions**
 - Enhance coordination of efforts between NCI, FDA and industry
 - IP template language shared by NCI, academia, industry
 - Incentives to industry for early access to drugs for combo studies
 - Increase role for CTEP in negotiating contracts for combinations

PATIENT POPULATION

- **Treatments may be less effective in immunosuppressed patients with advanced disease and/or extensive pretreatment.**
- **Adjuvant treatments require surrogate markers or large randomized studies for assessment of clinical activity.**
- **Complex adjuvant treatments in patients who may be cured may be more difficult to justify in some settings.**
- **Solutions:**
 - **Improved animal models for preclinical studies**
 - **More informed correlative biomarker studies**
 - **More translational research funds from NCI, industry**

REGULATORY ISSUES

- **Evolving standards for regulation of biologic combinations.**
- **Costly to comply with standards for manufacturing and safety testing.**
- **Investigator often ends up holding the IND for IISPs**
 - Inadequate training, funding and staff
- **Solutions:**
 - Tailor regulatory burden to disease severity
 - Increased support for RAID or alternative mechanism for production of reagents.
 - Consider unique study populations and designs
 - Focus on combinations with “targeted” biologic agents

FUNDING ISSUES

- **Costs of holding/managing IND**
- **Need funding for correlative biomarker studies-costly**
- **Increasing funding pressure based on contracting federal funding sources.**

THE ROAD FORWARD

- **Strong rationale for combination biological therapy of cancer.**
- **Convergence of interests seeking to enable the development of novel combinations.**
- **Coordination of resources and strategy will be essential to maximize impact on this issue by stakeholders in the field.**
- **Field may need to consider ways to provide incentives to industry that will address issues relating to mitigation of risk to the interpretation of safety profiles for individual agents in the setting of combination therapy, mitigation of risk for IP protection in light of necessities for data sharing, etc.**



Academia

Industry

THANK YOU!



BARRIERS/STRATEGIES FOR INTERVENTION

1. Innate immune awareness/Ag presentation/APC maturation

- Are there “danger” signals to ensure productive antigen display?

2. T cell repertoire/initial activation

- Repertoire may be restricted or of low avidity
- Immune suppression may carry over to DLN compartment

3. T cell differentiation/expansion/persistence

- Proper T cell phenotype might not be induced (Th1/CTL/memory)
- Magnitude or duration of T cell response may be inadequate

4. T cell trafficking into tumor sites

- Lack of proper chemokine receptors on T cells, or chemokines at tumor site
- Signals for penetrating extracellular matrix?

5. Executing effector function in tumor microenvironment

- Dominant negative regulatory pathways
- Poor maintenance of effector function (e.g. regeneration of cytotoxic granules)

6. Tumor cell susceptibility to recognition and killing

- Loss of antigens, processing machinery, MHC
- Anti-apoptotic mechanisms: tumor cells can be resistant
- Interface with tumor cell-intrinsic biology: oncogenic pathways orchestrating resistance

CLINICAL CONSIDERATIONS

- **Metastatic versus minimal residual disease setting**
 - Metastatic
 - Pros: biopsiable tumor, tumor biology effects (Ag loading, necrosis/inflammation), better risk/benefit, measurable clinical response, faster time to clinical endpoint, smaller sample size
 - Cons: tumor bulk, poor PS, global immunosuppression
 - MRD
 - Pros: less immunosuppression, less tumor bulk
 - Cons: hard to study tumor microenvironment, difficult to assess response, longer clinical endpoints, larger sample size, less favorable risk/benefit
 - Possible compromise? Low volume metastatic disease
- **Clinical endpoints for immunotherapy trials**
 - Are standard response criteria adequate?
 - Time to response
 - Progression then regression
 - Prolonged stable disease
 - Risk of attributing response to downstream therapy
 - Is objective response the best endpoint?
 - TTP, OS
 - Is there need for a new response assessment tool?
- **Biomarkers**
 - Gather data early
 - Need favorable and unfavorable clinical outcome patients in order to validate biomarkers as surrogate or predictor
 - This requires resources, effort, patient cooperation—but the scientific need is great
 - Biomarker alone unlikely to gain approval—clinical activity trumps

MAJOR THEMES: LEADERSHIP PERSPECTIVES

- **The NCI noted mechanisms to facilitate translational research**
 - Translational Research Working Group (TRWG)**
 - NCI-FDA Interagency Oncology Task Force (IOTF)**
 - Developmental Therapeutics Program (DTP)**
 - Cancer Therapeutics Evaluation Program (CTEP)**
 - CCR-DCTD Early Therapeutics Program**
- **Both organizations (NCI and FDA) recognize the unique complexities that can impede the development of combinations and the importance of addressing these issues in a timely manner.**

Multiple combinations:

Another layer of complexity and excitement through combined manipulation of regulatory checkpoints

- **Anergy reversal + Treg-depletion**
- **Anti-4-1BB + anti-CTLA-4**
- **Anti-4-1BB + anti-PD-L1**
- **Anti-CTLA-4 + Treg depletion**
- **TLR agonist + Treg-depletion**

NCI IMMUNOTHERAPY AGENT WORKSHOP-MAC CHEEVER

Table 1. Final Rankings of Agents with High Potential for Use in Treating Cancer

Rank*	Agent	Agent Category
1	IL-15	T-Cell Growth Factor
2	Anti-Programmed Death-1 (PD1)and/or anti-B7-H1 (PD1 Ligand)	**T-Cell Checkpoint Blockade Inhibitor
3	IL-12	Vaccine Adjuvant
4	Anti-CD40 and/or CD40L	Antigen Presenting Cell 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	Dendritic Cell Growth Factor/ Vaccine Adjuvant
12	Anti-Glucocorticoid-Induced TNF Receptor (GITR)	T-cell Stimulator
13	CCL21 Adenovirus	T-Cell Attracting Chemokine
14	Monophosphoryl Lipid A (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 Blockade Inhibitor
18	Resiquimod and/or 852A	Vaccine Adjuvant
19	LIGHT and/or LIGHT vector	T-Cell Stimulator
20	Anti-Lymphocyte Activation Gene-3 (LAG-3)	T-Cell Checkpoint Blockade Inhibitor