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Summary for the DCTD Cancer Immunotherapy Workshop

NCI Shady Grove, January 14-15, 2016

Helen Chen, M.D. CTEP, on Behalf of DCTD

A 1.5-day meeting with thought leaders in the field to discuss …

- Opportunities and gaps in cancer immunology/immunotherapy
- What NCI should do to facilitate further development

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The context

- **NCI has a long history of supporting cancer immunology and immunotherapy research**
- **Recent breakthroughs revealed the tremendous therapeutic potential of immunotherapy, and call for expedited progress to extend the benefit to more patients**
- **There is a rapid emergence of interest and investment in immunotherapy from**
  - Academia, scientific organizations, philanthropy, industry
- **What priorities and new initiatives should NCI consider in this collective effort?**

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Goals and Agenda of the Workshop

Essential Questions to participants:

- **What is limiting further success of cancer immunotherapy in the clinic?**
  - Biology? Models? Biomarkers/Assays?

- **What is needed in the research community that is critical to scientific progress?**
  - Which of these needs are not being addressed or supported sufficiently by industry or NCI?

- **What specific initiatives should NCI support or create to accelerate further success?**

Agenda:

- Presentations of perspectives by basic, translational and clinical scientists
- ~ 6 hours of Panel Discussions (Scientific questions/gaps and Biomarkers)

Speakers and invited guests

Extramural scientists

- **Jim Allison,** MD Anderson Cancer Center
- **Ira Mellman,** Genentech
- **Karolina Palucka,** Jackson Lab
- **Liz Jaffee,** Johns Hopkins University
- **Mario Sznol,** Yale University
- **Padnanee Sharma,** MD Anderson
- **Mac Cheever,** Fed Hutchinson

Biomarker/informatics experts:

- **Kurt Schalper,** Yale University
- **Elaine Mardis,** Wash University
- **Lisa Butterfield,** University of Pittsburgh
- **Anna Wu,** UCLA
- **Atul Butte,** UCSF
- **Stan Hamilton,** MD Anderson Caner Center
- **Diagnostic:** Adaptive, NanoString, Nodality, Immudex

Industry:

- **Merck, Incyte, AstraZeneca/MedImmun, Genentech**

NCI Intramural Scientists

- **Steve Rosenberg**
- **Nick Restifo**
- **Jay Berzofsky**
- **Remy Bosselut**
- **Stephen Hewitt**

DCTD:

- J Doroshow, J Abrams, T Hecht
- **CTEP**: H Chen, H Streicher, E Sharon, J Zwiebel
- **Cancer Diagnostic Program**: M Thurin
- **Biologics Resource Branch**: S Creekmore, A Welch
- **Radiotherapy Program**: M Ahmed, N Coleman
- **BRP**: R Simon

Division of Cancer Biology:

- C Marks, S McCarthy, K Howcroft

CaBIIT: Warren Kibbe

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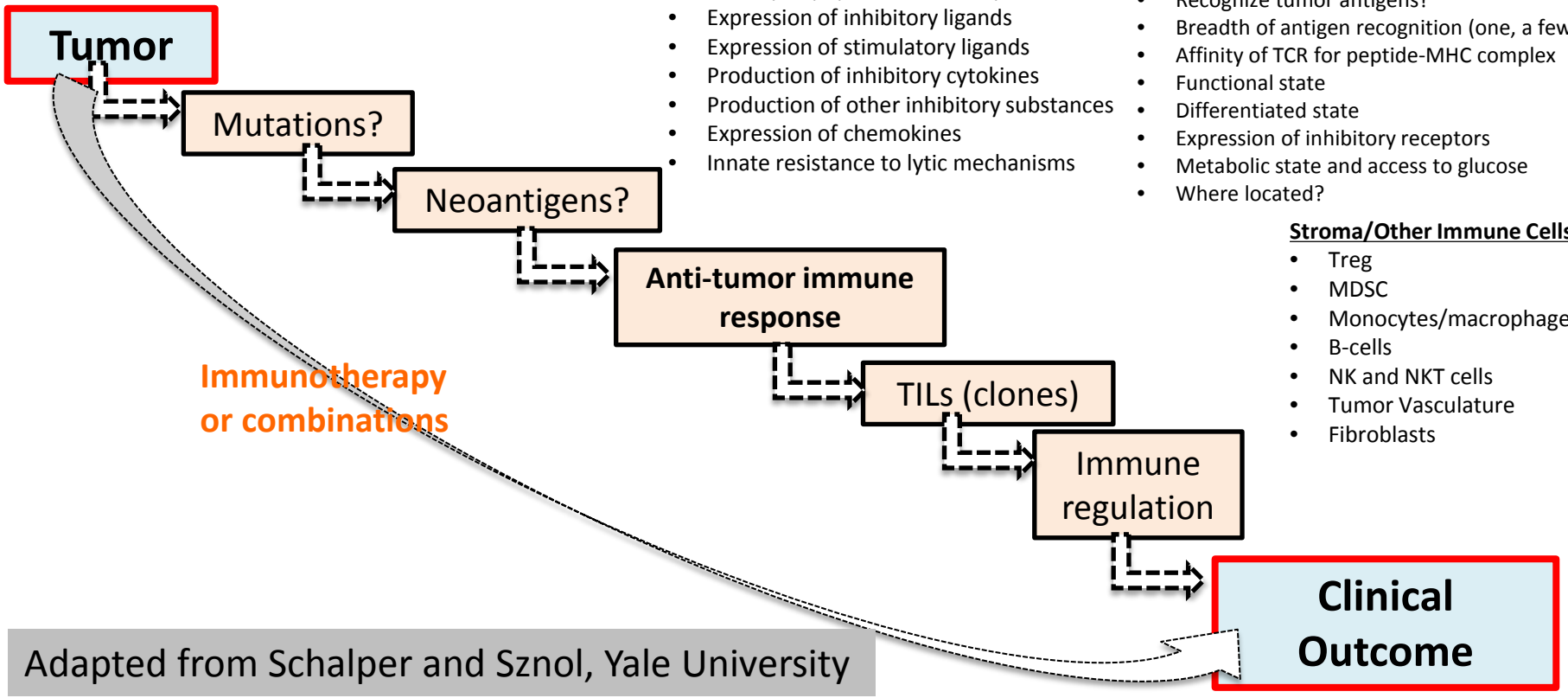
General Perspectives – Scientific Challenges

“We are in an incredibly exciting time, but we have an enormous number of challenges in order to move forward effectively” - *Sznol*

We don't know everything at the level needed to properly treat a patient or to effectively develop the therapy



Tumor?

- Antigens/neo-antigens
- Density of peptide/MHC complexes
- Expression of inhibitory ligands
- Expression of stimulatory ligands
- Production of inhibitory cytokines
- Production of other inhibitory substances
- Expression of chemokines
- Innate resistance to lytic mechanisms

T-cells?

- How many?
- What type?
- Recognize tumor antigens?
- Breadth of antigen recognition (one, a few, many)
- Affinity of TCR for peptide-MHC complex
- Functional state
- Differentiated state
- Expression of inhibitory receptors
- Metabolic state and access to glucose
- Where located?

Stroma/Other Immune Cells?

- Treg
- MDSC
- Monocytes/macrophages/APC
- B-cells
- NK and NKT cells
- Tumor Vasculature
- Fibroblasts

Adapted from Schalper and Sznol, Yale University

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What is limiting further success of immunotherapy? Everything

- **Superficial understanding of the underlying biology**
  - *"We do not know how anti-PD-1 regulator T-cells" (Allison)*
  - *"The field has an insufficient scientific base to support the growth justified by its promise for patients" (Mellman)*
- **Lack of biomarkers, biomarker assays, and instrumentation that can be used in human cancer patients**
- **Lack of large, accessible datasets (archival, trial results) and computational methods for immune parameters**

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What is needed in the field to promote progress?

- **Basic investigation to backfill the science**
  - Including “bed-bench” (reverse) translation and bench-bed translation
- **Biomarker strategies suitable for the complexity of biology**
  - Innovation around sample collection, biomarker discovery and biomarker assays
  - Bioinformatics, computational methodologies for multidimensional, multi-metric data analysis
- **Large, public database**
  - For host genomics, host microbiome, ”immunomics” … in addition to tumor genomic

“Unless we do something about it, we’re not really going to be able to have this field progress in anything except a haphazard fashion”

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What Should NCI Do?

"NCI must do for cancer immunotherapy what it did for cancer genomics and oncogene science"

"NCI is a unique resource in cancer research and therapy … and should address the scientific and strategic barriers through leadership and strong support"

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Strategic Recommendations

What NCI can do better than industry (or what industry will not do)

- **Basic science research**
- **Training for a new-generation cancer immunology scientists** (basic and translational research, bioinformatics …)
- **Infrastructure for centers of excellence (or a virtual network of expertise) to enable bed-bench-bed translation** (clinical sites, biobanks, core labs, data center, basic science labs…)
- **Database, common platforms for data integration or data mining across studies** (Industry data sharing is often restricted and delayed…)
- **Large public data base for cancer immunology** (clinical trial or non-trial patients)
  - **"TCGA" for immunology –The Cancer Immunology Atlas (TCIA)**

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What Should NCI Do?

- Strategic considerations
- **Specific recommendations:**
  - **Basic science**
  - **Clinical Research**
  - **Biomarkers and Database**

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Recommendations – Basic Science

- **Solicit ideas of key questions for basic research** (RFA, provocative questions ..)

  Examples …

  - *"Provocative Questions"* for immunology – "How does anti-PD-1 regulator T cells?" - *Allison*
  - Stroma/microenvironment of pancreatic cancer
  - Impact of non-immunotherapies on immune cells (chemo, targeted agents, RT)

- **Animal models** – Critical to reverse translation, MOA, combination strategies
  - Create and share "open-source" mouse models
  - Efforts in "credentialing" mouse models; developing model database
  - Support development of models that better recapitulate tumor-immune interplay in human cancers
- 3-D models for studies of immune cells and immune microenvironment

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What should NCI do?

- **Strategic considerations**
- **Specific recommendations:**
  - **Basic science**
  - **Clinical Research**
    - **Clinical trials rich in “translation”**
    - **Clinical trials for Adoptive Cell Therapy**
  - **Biomarkers and Database**

Recommendations – Clinical Research (1)

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Prioritize translational studies

- Align with industry efforts
  - Industry has huge investment in clinical trials, esp. common tumors and registration trials (at least large companies)
  - Novel combinations studies are also feasible within companies, although limitations still exist

- Prioritize studies that will enhance scientific understanding … not just for clinical proof of principle:
  - Combinations, focusing on challenges - mechanisms, optimal doses, predictive markers
  - Novel designs or novel endpoints (for predictive markers, early indicator of outcome, pharmacodynamics)
  - Support "reverse translation" for proven agents – generate hypothesis of MOA from patient studies to back feed preclinical studies for in-depth exploration

- *Establish and provide stable support for a consortia of "centers of excellence" to enable translation... e*xample: "Immunotherapy Platform" at MD Anderson

Recommendations – Clinical Research (2)

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Call for NCI to expand cancer center capacities for Adoptive T cell Therapies (ACT)

- **Antigen-specific T cell are the final effectors**
- **Clinical success is not limited to melanoma and ALL**

Examples
* NY-ESO1-specific TCR engineered T –cells - *response in sarcoma
* RAS G12D mutation-specific TIL (in unique HLA subset) – *response in colon cancer
* Neoantigen-specific TIL (patient-specific) - *response in cholangiocarcinoma

- **However, more basic and clinical studies are required to improve the extent of benefit**
- **ACT modalities in early exploratory stage or personalized ACT, are not often prioritized by industry**

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Recommendations – Adoptive Cell Therapy

NCI is ideally positioned to promote further development of ACT

- Potential to work with cell therapy companies, without conflict of interest
- Potential to collaborate with CCR with expertise in cell therapy techniques
- Facility (at NCI or contractors) for GMP production of vectors and cell expansion

- Centers with ACT capabilities already exist and can be expanded in the established NCI clinical trial network
- NCI may support or sponsor ACT sites for coordinated clinical trials …
  - For novel /personalized constructs; conditioning regimens; combinations; or comparison to SOC

➢ Bring the benefit of ACT to unique patient populations who do not have other effective treatment options

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What should NCI do?

- Strategic considerations
- Specific recommendations:
  - Basic science
  - Clinical Research
    - Clinical trials rich in “translation”
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Biomarker Perspectives

Biomarkers are critical to effective clinical development

… *reveal MOA, guide combinations and patient selection, improve efficiency*

- **We are still in the early exploratory stage of immunotherapy biomarkers**
  - Biomarker studies should be unbiased, multiplexed … hypothesis-generating
  - Not all assays have to be “perfect”
  - … *However there should be minimal QC requirements appropriate for the intended use*
  - … *Tissue banking in clinical trials is important for future testing of new hypotheses and new markers*

- **Infrastructures for high quality innovative biomarker studies are inadequate (funding, personnel, database, informatics)**

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Recommendations - Biomarkers

Call for Biomarker Initiatives …

- **Support biomarker development, from marker discovery to assay development to clinical validation**
- **Develop guidelines and SOPs for biospecimen banking, tissue collection**
- **Establish or support core/reference labs to provide service for key immune assays/panels**
- **Generate reference samples or reagents for assay standardization** (e.g. for PD-L1 IHC; multiplex flow)
- **Establish database or common platform for integration and analysis of clinical/biomarker data across trials**

Summary of Recommended Tasks for NCI

Basic science

- Funding for basic research
- Support for animal models
- Support reverse translation
- Train cancer immunologists

Clinical research

- Strengthen Infrastructure for "translation-rich" clinical trials
- Support combination studies for MOA, biomarkers
- Support clinical studies of adoptive cell therapy

Biomarkers and tools

- Strengthen biospecimen infrastructure
- Establish core labs
- Support marker discovery and development
- Establish database for biomarkers correlates from clinical trials

- Provide common platforms and computational tools for clinical/biomarker data across trials, to enhance the power of analysis and engage collective expertise
- Develop "TCGA" for Cancer Immunology Atlas
- Foster collaboration across fields of investigation in cancer biology, immunology, molecular characterization, biomarker development, system biology, informatics, … and all funding resources with common interest in cancer immunotherapy