Summary for the DCTD Cancer Immunotherapy Workshop

NCI Shady Grove, January 14-15, 2016

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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
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?
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 Cancer 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
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

Adapted from Schalper and Sznol, Yale University
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
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”
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”
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)
What Should NCI Do?

- Strategic considerations
- Specific recommendations:
  - Basic science
  - Clinical Research
  - Biomarkers and Database
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**
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
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... example: “Immunotherapy Platform” at MD Anderson
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
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
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
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)
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