Clinical Trials and Translational Research Advisory Committee

Translational Research Strategy Subcommittee

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March 29, 2021

January 14, 2021 TRSS Meeting

- Reviewed the Mission Statement in context of the goals for the Subcommittee as envisioned by the 2016 BSA Specialized Program of Research Excellence (SPORE) Working Group report
- Discussed translational research opportunities in gastric and esophageal cancers as requested by NCI
  - A working group is in process of formation
- Discussed need to *proactively* identify other translational research opportunities and questions

Proposed TRSS Process

- Pilot meeting quarterly
  - Members will submit suggested topics that identify a translational need or opportunity
  - Assigned member will make a brief presentation framing the topic
  - TRSS will discuss and deliberate on the importance of the topic
- Present recommendations to CTAC and NCI Director twice a year
- Reassess process after one year

Questions to Consider

- Does this topic have the potential to enhance and broaden NCI's overall translational research portfolio?
- Do members have additional information to add to this topic?
- Is additional information (e.g., portfolio analysis) needed from NCI prior to recommending this topic to CTAC?
- Is broader input or specific expertise beyond that of the TRSS subcommittee needed prior to recommending this topic to CTAC?
- Is there adequate justification to warrant recommendation of this topic to CTAC?
- Are there specific actions the group would recommend NCI take (e.g., white papers, formation of a working group, concept development)?

TRSS Meeting Schedule

- Monday, March 29, 1:00 p.m. – 2:00 p.m. ET
  - Topic: Resistance to immunotherapy
- Thursday, June 17, 11:00 a.m. – 12:00 p.m. ET
  - Topic: Assessment of the translational potential of organoid cultures and animal tumor models
- Thursday, September 9, 11:00 a.m. – 12:00 p.m. ET
  - Topic: TBD
- Thursday, December 16, 3:00 p.m. – 4:00 p.m. ET
  - Topic: TBD

Today's Topic: Resistance to Immunotherapy

- Introduction to Topic

  TRSS member facilitator: Dr. Francis Ali-Osman

- Related NCI Cancer Moonshot Programs

  Drug Resistance and Sensitivity Network (DRSN) Dr. Percy Ivy

  Immuno-oncology Translational Network (IOTN) Dr. Kevin Howcroft

  NCI Program Liaisons: Drs. Helen Chen, Jeff Hildesheim, Elad Sharon

Resistance to Immunotherapy

Dr. Francis Ali-Osman

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Cancer Immunotherapy

- **New frontier in cancer therapy. Dramatic responses in a wide variety of human tumors.**
- **Hypothesis that:**
  - **Host immune surveillance plays key role in suppression of oncogenesis by recognizing and eliminating tumor cells and that the tumor escapes immune surveillance, develops, grows, and progresses by developing an immune-evasive phenotype.** (MHC loss/dysfunction; Immune editing, Antigen identification/presentation; Immune checkpoint; Immunosuppressive TME)
- **Different immunotherapies target/exploit different components of the immune system.**
  - **Passive: Antibodies (tumor antigen-specific, growth factors, toxin/radionuclide-conjugated)**
  - **Active: Immune checkpoint inhibition, Cell-based (CAR T cells, APC/DC, CTL, T cell reactivation)**
    Vaccines (tumor cell, dendritic cell, tumor antigen, DNA,RNA)
    Viruses (herpes, polio, measles etc.)
- **With few exceptions, to date, most immunotherapies are monotherapies.**
- **Similar to other cancer treatment modalities, tumor resistance (inherent and acquired) to immunotherapy is clinically limiting.**
- **Mechanistic basis of action of and/or resistance to immunotherapy only partly understood.**

Mechanisms of Immunotherapy Resistance

A. Extrinsic (Tumor microenvironment)

- Increased immunosuppressive cells, cytokines, immune checkpoint
- Altered coinhibitory and costimulatory receptors/factors
- T cell exhaustion
- Immunosuppressive T regs:
    - Directly kill T cells and APCs
    - Inhibit MHC and costimulatory molecules (CD80 and CD86) on APCs
    - Inhibit APC and T cell proliferation/maturation and APC-T cell interaction
    - Secrete inhibitory cytokines (TGF-b, IL-10, IL-35, etc.)
- Immunosuppressive myeloid-derived suppressor cells: immune escape, angiogenesis, invasion, etc.
- Microbiome

B. Intrinsic (Tumor)

- Host genetics/epigenetics
- Immune response pathways
- Decreased antigen presentation
- Increased secretion of immune inhibitory molecules
- Mutations in critical immune response and surveillance, cell growth/death related genes, etc.
- Altered signaling

Opportunities and Recommendations

- **Molecular mechanisms, genetics, and cellular basis of response and resistance to immunotherapy**
  - Characterize neoantigens for personalized cancer immunotherapy

- **Identify and validate biomarkers of response and resistance to immunotherapy**

- **Develop rational, mechanistically-based strategies for combinations of immunotherapy with:**
  - Different immunotherapy modalities: e.g., T cell therapy or virotherapy with checkpoint inhibitors
  - Targeted therapy
  - Radiation therapy: DNA damage enhance mutational burden; release of ds DNA stimulates interferon gene expression
  - Chemotherapy: Several drugs are immune-modulatory. DNA damaging agents promote immunogenic cell death, alter inflammatory tumor microenvironment, and stimulate neoantigen production/repertoire, thereby activating an antitumor immune response

Therapeutic resistance occurs more commonly with single agents than with multi-drug/multimodal regimens, notably, with non-overlapping mechanisms and toxicities.

Opportunities and Recommendations

- **Develop immunotherapeutic agents, small molecules, delivery systems. and regimens to:**
  - reduce immune suppression
  - enhance T cell activation/reactivation
  - induce immunogenic tumor cell death

- **Understand relationship between tumor mutational burden and response/resistance to immunotherapy**

- **Precision (personalized) immunotherapy: Genomics- and biomarker-guided**
  - Directed at unique composition of genetic alterations of the tumor
  - Will require rapid mapping of the mutations, rational selection of vaccine targets, and production of a therapy customized to a patient's individual tumor
  - Emerging biological advances and technological innovations make it a feasible goal to vaccinate a patient with individual tumor mutations

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