THE Flexner DISCOVERY LECTURE SERIES

Upcoming Discovery Lecture:

DANE WITTRUP, Ph.D.

C.P. Dubbs Professor of Chemical Engineering and Biological Engineering

Associate Director, Koch Institute for Integrative Cancer Research

Investigator, HHMI

March 22, 2018

208 Light Hall / 4:00 P.M.

THE Flexner DISCOVERY LECTURE SERIES

JAMES P. ALLISON, Ph.D.

IMMUNE CHECKPOINT BLOCKADE IN CANCER THERAPY:
NEW INSIGHTS AND OPPORTUNITIES, AND PROSPECTS FOR CURES

MARCH 8, 2018

4:00 P.M.

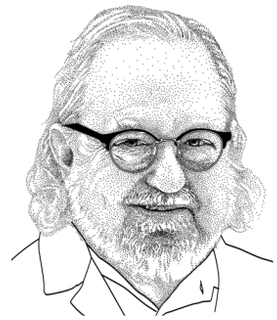
208 LIGHT HALL

SPONSORED BY:
THE VANDERBILT-INGRAM CANCER CENTER

VANDERBILT UNIVERSITY
MEDICAL CENTER

IMMUNE CHECKPOINT BLOCKADE IN CANCER THERAPY: NEW INSIGHTS AND OPPORTUNITIES, AND PROSPECTS FOR CURES

The non-redundant mechanisms that limit T cell responses offer strategies for mobilizing the cancer immune response. CTLA-4, the best characterized immune checkpoint, inhibits T cell proliferation by blocking the interaction of the costimulatory molecule CD28 with its ligands on dendritic cells. Ipilimumab, an anti-CTLA-4 antibody, has been effective against multiple tumor types in pre-clinical and clinical studies, and provides long term survival to ~20% of late stage melanoma patients. PD-1, another checkpoint, seems to inhibit T cell antigen receptor mediated signaling. Many tumor cells express PD-L1, the PD-1 ligand. Antibodies to PD-1or PD-L1 provided objective responses against several tumor types in clinical trials in about 25% of patients. Combined anti-PD-1 and anti-CTLA-4 provided objective responses in ~50% of late stage melanoma patients. We used high parameter flow cytometry to identify the mostly non-overlapping cellular mechanisms of CTLA-4 and PD-1 blockade, which may partially explain the enhanced effect of their combination. T cell responses to tumor cells appear directed toward neoantigens arising from carcinogenesis-related mutational events. While all tumors with antigens recognizable by the immune system should be targets for checkpoint blockade, tumors with lower mutational burdens (prostate, breast, and kidney cancer) present challenges. Strategies for their treatment will be discussed.



JAMES P. ALLISON, Ph.D.

VIVIAN L. SMITH DISTINGUISHED CHAIR IN IMMUNOLOGY

PROFESSOR AND CHAIR, DEPARTMENT OF IMMUNOLOGY

EXECUTIVE DIRECTOR, IMMUNOTHERAPY PLATFORM

DIRECTOR, PARKER INSTITUTE FOR CANCER IMMUNOTHERAPY; THE UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER

Jim Allison has spent a distinguished career studying the regulation of T cell responses and developing strategies for cancer immunotherapy. Among his most notable discoveries are the determination of the T cell receptor structure and that CD28 is the major costimulatory molecule that allows full activation of naïve T cells and prevents anergy in T cell clones. His lab resolved a major controversy by demonstrating that CTLA-4 inhibits T-cell activation by opposing CD28-mediated costimulation and that blockade of CTLA-4 could enhance T cell responses, leading to tumor rejection in animal models. He proposed that blockade of immune checkpoints such as CTLA-4 might be a powerful strategy for therapy of many cancer types, and conducted preclinical experiments showing its potential. These seminal findings established the field of immune checkpoint blockade therapy for cancer. Work in his lab led to the development of ipilimumab, an antibody to human CTLA-4 and the first immune checkpoint blockade therapy approved by the FDA. Since that time ipilimumab has been approved as part of the therapeutic regimen for metastatic melanoma, renal cell carcinoma, and lung cancer. His current work seeks to improve immune checkpoint blockade therapies currently used by our clinicians and identify new targets to unleash the immune system in order to eradicate cancer. Among many honors, he is a member of the National Academies of Science and Medicine. He received the Lasker-Debakey Clinical Medical Research award in 2015, the Balzan Prize in 2017, and the Kovalenko Medal from the National Academy of Sciences in 2018.