Title: Beyond Immune Checkpoint Blockade: Manipulation of T Cell Regulatory Circuits in Cancer Therapy

Speaker

James P. Allison, Ph.D.
David H. Koch Chair in Immunologic Studies, Memorial Sloan-Kettering Cancer Center, New York, NY
Attending Immunologist, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY
Co-Chair, Graduate Program in Immunology and Microbial Pathogenesis, Weill Graduate School of Medical Sciences of Cornell University, New York, NY
Professor, Weill Medical College of Cornell University, New York, NY
Director, Ludwig Center for Cancer Immunotherapy, Memorial Sloan-Kettering Cancer Center, New York, NY

Chairman

Ryuzo Ueda, M.D., Ph.D.
Professor Emeritus, Senior Adviser, Nagoya City University
Professor, Dept. of Tumor Immunology, Aichi Medical University, Japan

James P. Allison, Ph.D.

EDUCATION:

1969	B.S. Microbiology, The University of Texas, Austin, Texas
1973	Ph.D. Biological Sciences, The University of Texas, Austin, Texas

POSTDOCTORAL TRAINING:

1974-1977.1.1.1	Postdoctoral Fellow, Department of Molecular Immunology, Scripps Clinic and Research Foundation, La Jolla, California

POSITIONS AND APPOINTMENTS:

2004-Present	David H. Koch Chair in Immunologic Studies, Memorial Sloan-Kettering Cancer Center, New York, NY
2004-Present	Attending Immunologist, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY
2004- Present	Co-Chair, Graduate Program in Immunology and Microbial Pathogenesis, Weill Graduate School of Medical Sciences of Cornell University, New York, NY
2004- Present	Professor, Weill Medical College of Cornell University, New York, NY
2006- Present	Director, Ludwig Center for Cancer Immunotherapy, Memorial Sloan-Kettering Cancer Center, New York, NY

RECENT HONORS AND AWARDS:

2010	2010 Richard V. Smalley, MD, Memorial Lectureship Award, International Society for Biological Therapy of Cancer
2011	Lifetime Achievement Award, American Association of Immunologists
2011	Roche Award for Cancer Immunology and Immunotherapy
2011	Breakthrough Achievement in Translational Cancer Research, American Skin Association
2011	Jacob Heskel Gabbay Award in Biotechnology and Medicine, Brandeis University
2011	Advancement of Cancer Research Award, Gilda's Club
2012	Lifetime Achievement Award, Molecular Targeted Therapy Group

LATEST PUBLICATIONS:

1. Corse E., Gottschalk R.A., Krogsgaard M., Allison J.P. Attenuated T cell responses to a high-potency ligand in vivo. PLoS Biol 8(9): e1000481. Doi:10.1371/journal.pbio.1000481; 2010.
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3. Pedicord, V.A., Montalvo W., Leiner I.M., Allison J.P. Single dose of anti-CTLA-4 enhances CD8+ T-cell memory formation, function and maintenance. Proc Natl Acad Sci USA. 108:266-71; 2011.
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5. Donkor D.K., Sarkar A., Savage P.A., Franklin R.A., Johnson L.K., Jungbluth A.A., Allison J.P., Li M.O. T cell surveillance of oncogene-induced prostate cancer is impeded by T cell-derived TGF-β1 cytokine. Immunity 35:123-134; 2011.
6. Curran M.A., Kim M., Montalvo W., Al-Shamkhani A., Allison J.P. Combination CTLA-4 blockade and 4-1BB activation enhances tumor rejection by increasing T-cell infiltration, proliferation, and cytokine production. PLoS One. 29;6(4); 2011.
7. Wei J., Zang X., Loke P., Allison J.P. Tissue specific expression of B7x protects from T cell mediated autoimmunity. J Exp Med. 208(8):1683-94; 2011.
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9. Krummel M.F., Allison J.P. Pillars article: CD28 and ctla-4 have opposing effects on the response of T cells to stimulation. The journal of experimental medicine. 1995. 182: 459-465. J Immunol. 1;187(7):3459-65; 2011.
10. Yuan J., Adamow M., Ginsberg B.A., Rasalan T.S., Ritter E., Gallardo H.F., Xu Y., Pogoriler E., Terzulli S.L., Kuk D., Panageas K.S., Ritter G., Sznol M., Halaban R., Jungbluth A.A., Allison J.P., Old L.J., Wolchok J.D., Gnjatic S. Integrated NY-ESO-1 antibody and CD8+ T-cell responses correlate with clinical benefit in advanced melanoma patients treated with ipilimumab. Proc Natl Acad Sci USA. 108(40):16723-8; 2011.
11. Curran M.A., Callahan M.K., Subudhi S.K., Allison J.P. Response to "Ipilimumab (Yervoy) and the TGN1412 catastrophe". Immunobiology; 2011.
12. Waitz R., Solomon S.B., Petre E.N., Trumble A.E., Fasso M., Norton L., Allison J.P. Induction of tumor immunity through cryoablation and cytotoxic T lymphocyte-associated antigen 4 blockade combination therapy. Cancer Res. Jan 15;72(2):430-9; 2012.
13. Gottschalk R.A., Hawthorn H.M., Beuneu H., Corse E., Dustin M.L., Altan-Bonnet G. Allison J.P. Distinct influences of peptide-MHC quality and quantity on in vivo T cell responses. Proc Natl Acad Sci. USA. Jan 17;109(3):881-6; 2012.

14. Gottschalk R.A., Corse E., Allison J.P. Expression of Helios in Peripherally Induced Foxp3+ Regulatory T cells. J Immunol. Feb 1;188(3):976-80; 2012.
15. Matsushita H., Vesely M.D., Koboldt D.C., Rickert C.G., Uppaluri R., Magrini V.J., Arthur C.D., White J.M., Chen Y., Shea L.K., Hundal J., Wendl M.C., Demeter R., Wylie T. Allison J.P., Smyth M.J., Old L.J., Mardis E.R., Scheiber R.D. Cancer exome analysis reveals a T-cell-dependent mechanism of cancer immunoediting. Nature. Feb 8; 482(7385):400-4; 2012.
16. Postow M.A., Callahan M.K., Barker C.A., Yamada Y., Yuan J., Kitano S., Mu Z., Rasalan T., Adamow M., Ritter E., Sedrak C., Jungbluth A.A., Chua R., Yang A., Roman R.A., Rosner, S., Benson B., Allison J.P., Lesokhin A.M., Gnjatic S., Wolchok J.D. Immunologic Correlates of an Abscopal Effect in a Patient with Melanoma. N Engl J Med. Mar 8;366(1):923-31; 2012.
17. Yu P., Steel J.C., Zhang M., Morris J.C., Waitz R. Fasso M., Allison J.P., Waldermann T.A. Simultaneous inhibition of two regulatory T-cell subsets enhanced Interleukin-15 efficacy in a prostate tumor model. Proc Natl Acad Sci. USA. Apr 17;109(16):6187-6192; 2012.
18. Jenq R.R., Curran M.A., Goldberg G.L., Liu C., Allison J.P., van den Brink M.R. Repertoire enhancement with adoptively transferred female lyphocytes controls the growth of pre-implanted murine prostate cancer. PLoS One. Apr 6;7(4):e35222; 2012.
19. Zhang M., Ju W., Yao Z., Yu P., Wei B.R., Simpson R.M., Waitz R., Fasso M., Allison J.P., Waldmann T.A. Augmented IL-15Rα Expression by CD40 Actiation Is Critical in Synergistic CD8 T Cell-Mediated Antitumor Activity of Anti-CD40 Antibody with IL-15 in TRAMP-C2 Tumors in Mice. May 16: J Immunol; 2012.
20. Waitz R., Fasso M., Allison J.P. CTLA-4 blockade synergizes with cryoablation to mediate tumor rejection. Oncoimmunology. Jul 1;1(4):544-546; 2012

CURRENT INTEREST:

One of our major areas of current interest is in the mechanisms that regulate T cell responses and the development of strategies for manipulating the process in clinical situations, such as autoimmunity, allergy, vaccination, and tumor therapy. It is now well accepted that recognition of specific antigen by the TCR is not sufficient for activation but that a second antigen nonspecific “co-stimulatory” signal is required. We have demonstrated that this second signal is provided the co-stimulatory receptor CD28 upon recognition of its counter-receptors, members of the B7 family, on the antigen-presenting cell. CD28 engagement is required under most situations for IL-2 production and proliferation. The lack of a CD28-mediated co-stimulatory signal upon TCR engagement can result in the induction of a long-lived state of nonresponsiveness. We are studying the intracellular mechanisms of co-stimulatory signal transduction. We are also examining the relevance of this costimulatory model of T cell activation to immune responses in vivo with the goal of understanding the basis of self-tolerance and to develop means for regulating immune responses.

We have recently found that co-stimulation is more complex than previously thought. CTLA-4, a homolog of CD28, also binds members of the B7 family, and binds them with affinities much higher than CD28. A wealth of data accumulated in the past few years show that CTLA-4 is an important downregulator of T cell responses. We have proposed that CTLA-4 plays a critical role in both the initiation and termination of T cell responses. According to this view, T cell activation is a dynamic process that is determined by the strength of the TCR signal; the strength of co-stimulation provided by CD28; and the magnitude of inhibitory signals generated by CTLA-4. We have begun to analyze the mechanisms by which the signals generated by these different pathways are integrated in T cell activation. We have found that CTLA-4 and CD28 have distinct sites of localization in the T cell, and that both transit to the site of T cell receptor engagement upon the encounter of the T cell with an antigen presenting cell. We are currently studying this relocalization in the context of formation of the immunological synapse between the T cell and the APC.

IAAO2012 Title of the Talk:

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ABSTRACT:

We conducted extensive pre-clinical studies in mouse models which showed that blockade of the inhibitory signals mediated by CTLA-4 in T cells, either alone or in combination with a variety of immunologic and conventional therapies, led to tumor rejection and long-lived immunity. Ipilimumab, an antibody to human CTLA-4 developed (Bristol Meyers-Squibb) has been given to over 10,000 patients in clinical trials. Objective responses have been observed in melanoma, prostate, kidney, ovarian, and lung cancer. A randomized, placebo controlled trial of ipilimumab documented an increase in survival of patients with advanced melanoma, the first drug of any type to do so, with more than 20% of patients alive for over 4 years after treatment. In 2011 ipilimumab was approved for the treatment of patients with late stage melanoma and it is now a standard of care for this diseases. While CTLA-4 blockade can lead to durable responses in patients, there is clearly a need to increase the response rate. Recent trials have shown that blockade of another immune checkpoint mediated by the molecule PD-1 can also produce objective responses in several tumor types.

We have shown that administration of anti-CTLA-4 results in an increase of the frequency of CD4 T cells that express ICOS in both tumor tissue and blood of bladder cancer patients. The ICOS+ population contained tumor-specific effector CD4 T cells. We also showed that sustained elevation of ICOS+ CD4 T cells correlated with increase survival of advanced melanoma patients treated with Ipilimumab. Together, these data suggested to us that ICOS might play an important role in the therapeutic effects of CTLA-4 blockade. To test this we used a mouse model of melanoma. We found that the efficacy of anti-CTLA-4 was markedly diminished in mice that were deficient in either ICOS or ICOS ligand (ICOSL), confirming that the pathway plays a critical role in anti-CTLA-4 therapy.

These observations led us to test the possibility that engagement of ICOS could enhance the efficacy of anti-CTLA-4 therapy. We transduced mouse B16F10 melanoma cells with a cDNA encoding ICOSL or a control construct. B16ICOSL+ cells (IVAX) and control B16 cells were irradiated and used alone or in combination with anti-CTLA-4 to treat mice bearing established B16F10 tumors. We found that the combination of IVAX with anti-CTLA-4 was markedly more effective than the other combined or single treatments. The increase in therapeutic efficacy was accompanied by a marked in increase in the density and functionality of CD4 and CD8 T cells within the tumor.

These results suggest a novel strategy for manipulating the immune system to enhance anti-tumor responses: checkpoint blockade coupled with provision of agonist signals mediated by ICOS to enhance costimulation.