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"Targeting Immune Checkpoints in Cancer Therapy: New Insights and Opportunities,"

By
James P. Allison, Ph.D.,
Director of Immunology
The University of Texas MD Anderson Cancer Center.

HPS President Jack Agee presented the speaker, James P. Allison, Ph.D., Director of Immunology at The University of Texas MD Anderson Cancer Center. Dr. Allison spoke on "Targeting Immune Checkpoints in Cancer Therapy: New Insights and Opportunities." James Allison is professor and chair of The University of Texas MD Anderson Cancer Center Department of Immunology in the Division of Basic Science Research. He directs MD Anderson's Immunology Platform and is deputy director of the David H. Koch Center for Applied Research in Genitourinary Cancers, Department of Genitourinary Medical Oncology – Research. He also is a Howard Hughes Medical Institute Investigator. Dr. Allison earned his doctorate at The University of Texas, Austin, and did his postdoctoral fellowship in molecular immunology at Scripps Clinic and Research Foundation, La Jolla, CA. He came to MD Anderson in 2012 from Memorial Sloan-Kettering Cancer Center in New York.

Dr. Allison is exploring combinations of immunological therapies and targeted drugs in preclinical studies to more effectively treat a variety of cancers, work which has attracted much attention in the press as well as in the medical field. He spoke on how the immune system protects us from a host of challenges but has not previously been effective in countering cancer. However, recent findings in his and M.D. Anderson's research give much promise that the immune system can be made to focus on cancer as well. He discussed these results and the complexities of how the immune system works.

Dr. Allison and his team at M.D. Anderson are working to stimulate the immune system to attack cancer cells. Immunotherapy is being pursued for a number of reasons:

Specificity. For years, Dr. Allison's laboratory has done work on how the T-cells of the immune system— the attack cells—latch onto cells infected with viruses and bacteria and ultimately kill them. That research led him to think that the immune system could be unleashed to kill cancers. You have 100,000,000 T-cells. These can recognize peptides that sweep the cell and tell the immune system what is going on in your body. Cancer is a disease of mutations into, for example, a cell that tells cells to divide only when there's a wound. Peptides in the immune system recognize these cancer cells.

Memory. Once you have the immune system working, it works for the rest of your life.

Adaptability. You have 100's of millions of cells in which the immune system can recognize tumor changes.

In the 1990's researchers began to recognize T-cells in tumors and attempted to develop vaccines to combat cancer, but it did not work because a receptor's recognition of peptides was not enough to turn on the immune system. Dr. Allison's group realized that a second signal was necessary to turn the immune system on. In the 1990s, Dr. Allison's team and another group had showed that there was a molecule on T-cells that acts like an off switch or a brake pedal for the immune system when T-cells encounter an infected cell. The receptor, called molecule CD28, , a co-inhibitory molecular expressed on T-cells, recognizes cells dying and takes them up and reproduces them. He wondered whether this switch could BE blocked off to keep the T-cells turned on. Pursuing this idea, he and his team developed an antibody to plug this off-switch. This antibody, CTLA-4, is another molecule that, after the T-cell receptor and CD 28 are turned on, blocks the switch to keep the T-cells growing. Both CD 28 and CTLA-4 are molecules localized to the T-cell-APC interface. They form a synapse when CD28 comes in and starts signaling that shuts off the CD28 receptor and makes T-cells take off. The CTLA-4 blockade enhances the tumor-specific immune response.

Therapeutic vaccines did not work because the process of blocking T-cell activity had already started. It was necessary to unleash the immune system to destroy the cancer cell rather than to attempt to destroy the cell directly with a cancer drug. Unleashing the immune system offers the possibility of being able to be used against any kind of cancer precisely because it is not a cancer drug.

The identification of CTLA-4 led to the clinical development of CTLA-4 blocking antibodies that are capable of stimulating potent anti-tumor immunity. Two of these CTLA-4 blocking antibodies are presently under clinical investigation, ipilimumab and tremelimumab.

Immunotherapy is used together with vaccines, radiation, and chemotherapy and anything that causes "cross-priming" to enhance tumor-specific immune responses. For example, anti-CTLA-4 induces repression of transplantable colon carcinomas. If we block the reception, the tumor grows faster. Anti-CTLA-4and the GM-CSF tumor-cell vaccine synergize to eradicate established B16 melanomas. If GM-vaccine is put into the tumor cell it causes the cell to die and the immune system to come in, but it does not work therapeutically. Anti-CTA-4/GVAX therapy activates the tumor vasculature and increases infiltration of tumors by CD4 and CD8 effector cells, which causes an increase in the Teff/Treg ratio in the tumor. This is teamed up with the addition of a fully human antibody to CTLA-4.

More than 50,000 patients have been treated with immunotherapy to date, causing objective responses in many tumors, including, for example, melanomas, and prostate, bladder, ovarian, and lung cancer. Adverse events include colitis, hepatitis, hypophysitis (pancreatic inflammation), and others, but these are manageable. The longest survivor on Ipilimumab—a cancer medication that interferes with the growth and spread of cancer cells in the body and is used to treat melanoma that cannot be surgically removed—is now 15 years out with a single treatment and no relapse.

Anti-CTLA-4 immunotherapy is also being used to treat metastatic brain cancer and prostate cancer. Phase three trials are ongoing. There has been an evolution of the response of these cancers to immunotherapy from an initial increase in the total tumor burden to a decrease, as shown by a standard Kaplan-Meier Analysis of Survival rates approved by an 2011 FDA analysis showing the fraction of patients

who survived for a certain amount of time after treatment. Since 2011 nobody who has received treatment has died. Many have shadows on their cat scans, but in almost 5000 patients, 22% were living 10 years after one treatment of the immune system.

The discovery of CTLA-4 opened a new field of Anti-CTLA-4 antibody therapy or, more generally, immune chemokine therapy. For example, for patients with melanoma receiving CTLA-4 and PD-1 cancer antibodies, which promotes rejection of B16 melanomas, the overall survival rate is 88% in two years, versus 10% 10 years ago. Currently, if you make it for two years, you are good for twenty.

Yet critical issues remain for further development, including targeting; the determination of the cellular and molecular mechanisms involved in the anti-tumor effect; the identification of predictive, prognostic, or pharmacodynamics biomarkers which indicate the severity or presence of a disease state; improving the standard of care; and crafting new molecules.

Projects include integrating laboratory and clinical research. For example, mice are inbred and disease-homogenous while humans are polymorphic and heterogeneous. Hence, rethinking clinical trial design to obtain appropriate samples for lab studies. Including setting up phases to deal with safety issues, boundaries analysis, mechanization, efficacy insights, and comparison to the standard of care.; conducting tissue analysis and finding out what kind of T-cells are involved; identifying cancer pathways; and investigating immunological signatures for ipilimumab therapy.

Current developments include using combination treatments, which include engaging the CD278 or ICOS (Inducible T-cell costimulatory) molecules—CD28-superfamily costimulatory molecules expressed on activated T-cells—to increase efficacy, multiple checkpoints, inhibiting factors, and the blocking of other immunosuppressive factors.

We are studying the origins of tumors and associated antigens. Different cancers have different events and initiations. We can identify them by genomic sequencing and using an analytic device and can improve survival with combination therapy--now within our grasp for the first time.

You cannot predict prior to therapy who *will* respond, but if they do not respond to ICOS, you *can* tell who will *not* respond to therapy. Immunotherapy is not used in people with immune-deficiency or those who have auto-immune diseases. We started with melanoma because it is a particularly deadly cancer, and you get a quick response, and nobody had looked at it. We are exploring its use for kidney and prostate cancers. We do not know why a vast number of tumors still do not respond to this therapy, but we are exploring and we are making progress.