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Boosting the Immune System to Fight Cancer - James Allison at the IMP in Vienna

Professor James Allison of the MD Anderson Cancer Center in Houston, Texas, is a giant in the field of immunology and a pioneer of modern cancer therapy. Upon invitation of the Research Institute of Molecular Pathology in Vienna, he presented his latest successful approaches in immunotherapy as a "Max Birnstiel Lecturer" on January 14.

Although the concept of using the immune system to fight cancer has been around for decades, translating this vision into an effective therapy is a very recent success. We owe these advances largely to James Allison and his tireless research efforts. His discoveries have led to an important paradigm shift in cancer therapy: While former therapies have focused on the cancer cell itself, the so-called immune checkpoint therapy alerts T-cells of the immune system to eliminate cancer cells and can thus be used to eradicate cells of different tumor types.

From the very beginning of his research career, James Allison was interested in unravelling the basic principles of immunology. His ground-breaking discoveries greatly influenced the development of this field. He was the first person to biochemically identify and isolate the different components of the T-cell receptor-complex, a protein-complex on the surface of T-cells that enables them to recognize and fight antigens. Allison subsequently demonstrated that active T-cell receptor-signalling requires a second co-stimulatory signal from the CD28 receptor. Next, he discovered that a protein named CTLA-4, which is closely related to the CD28 molecule, is an inhibitory receptor that blocks T-cell signalling by antagonizing the function of CD28.

When a cancer is analysed, numerous immune cells are found in the tissue, among them many T-cells. Their activity, however, is blocked by the presence of CTLA-4. Based on this finding, James Allison developed the immune checkpoint therapy for cancer treatment by realizing that blocking the inhibitory CTLA-4 receptor with a neutralizing antibody activates T-cells that can then attack tumor cells. His research led to the clinical development of an anti-CTLA-4 antibody known as Ipilimumab. In 2011, it was approved by the FDA for the treatment of metastatic melanoma and already saved the lives of many cancer patients.

In his talk at the IMP, James Allison presented impressive clinical data from studies as recent as 2014. The results show that a previously fatal condition like metastatic melanoma can be turned into a treatable disease by activating the body's own arsenal – the immune system.

In principle, the immune checkpoint therapy should work for any kind of cancer. However, clinical results show big differences in the efficacy of the treatment. Paradoxically, it seems to work best in the most aggressive types of tumours. In these cancers, the tumour cells are severely mutated and differ considerably from healthy cells. As a result, they show stronger antigenicity and offer more targets for T-cells.

The future of immunotherapy clearly lies in the strategic combination of several checkpoint therapies. Current studies are looking, for example, into the combination of Ipilimumab with antibodies that target the "Programmed Cell Death Protein" PD1. First results suggest that this regime may be beneficial to patients. Studies like these are powerful demonstrations of basic research driving advances in modern medicine.

Professor James P. Allison studied microbiology and obtained his PhD at the University of Texas in Austin. After postdoctoral years at the Scripps Clinic in La Jolla, he took up a faculty position at the MD Anderson's Science Park in Smithville, Texas. In 1985, he was appointed professor of immunology and director of the Cancer Research Laboratories at UC Berkeley and in 2004, he moved to the Memorial Sloan-Kettering Cancer Center, New York. Since 2012, he is back at the MD Anderson Cancer Center in Houston, where he is Professor and Chair of Immunology and Executive Director of the Immunotherapy Platform.

The Research Institute of Molecular Pathology (IMP) in Vienna is a basic biomedical research institute largely sponsored by Boehringer Ingelheim. With over 200 scientists from 35 nations, the IMP is committed to scientific discovery of fundamental molecular and cellular mechanisms underlying complex biological phenomena. Research areas include cell and molecular biology, neurobiology, disease mechanisms and computational biology. The IMP is located at the Vienna Biocenter.

The Max Birnstiel Lectures are a public lecture series of the Research Institute of Molecular Pathology (IMP) in Vienna. Leading scientists are invited to talk about their current research and future projects. The series is named after the IMP's founding director, Professor Max L. Birnstiel, who passed away in December of 2014.

Link: *www.imp.ac.at/seminars/max-birnstiel-lecture-series*