Cancer Immunology Research

The 2015 AACR Clowes Memorial Award for Outstanding Achievement in Basic Cancer Research

Left: Greg Plowman, Eli Lilly & Company; Middle, Owen Witte; Right, René Bernards

Owen Witte, a prominent physician-scientist and mentor at UCLA, is known for his significant contributions to the understanding of human leukemias, immune disorders, and epithelial cancers. Dr. Witte's research emphasizes the understanding of pathogenesis as a way to predict and develop new treatments for human disease. As the founding director of the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research at UCLA, Dr. Witte created a multidisciplinary collaborative environment including clinicians, biologists, chemists, physicists, and engineers that drives one of the most successful stem cell programs in California. His focus on stem cell research grew out of his long-term interest in understanding the cells in which cancers, such as leukemia, originate. For his outstanding accomplishments in basic cancer research, the American Association for Cancer Research (AACR) presented Dr. Witte with the 55th annual G.H.A. Clowes Memorial Award on April 20, 2015.

The Clowes Memorial Award honors George Henry Alexander Clowes (1877–1958), the biochemist responsible for the commercialization of one of the major discoveries in clinical medicine—insulin as a therapy for diabetes. A native of England, Dr. Clowes moved to New York in 1901, where he served as codirector of what was then Gratwick Cancer Research Laboratories. He left Gratwick to become the research director for Eli Lilly and Company, a global pharmaceutical company in Indiana. Following the discovery of insulin in 1921, Dr. Clowes arranged for Eli Lilly to become the manufacturer of protamine insulin, which was used for nearly a hundred years until the recombinant DNA production of insulin. At the time of his retirement in 1946, Dr. Clowes was credited not only with the commercialization of protamine insulin but also with directing research that developed liver extract, hypnotic drugs, local anesthetics, antiseptics, and sulfonamide (1). In 1961, the AACR and Eli Lilly and Company established the G.H.A. Clowes Memorial Award in recognition of Dr. Clowes, who was also a founding member of the AACR.

Dr. Witte's achievements in translating basic scientific research into treatments for disease parallel Dr. Clowes' innovative efforts to take scientific discoveries from the laboratory into the clinic. Committed to accelerating scientific exploration to make the most impact, Dr. Witte bridges academic science and industry to develop novel diagnostics and therapeutics. He cofounded biotechnology companies Onyx and Agensys and is currently associated with Sofie Biosciences (focusing on PET imaging probes critical in the new world of cell therapeutics) and Kite Pharmaceuticals (developing immunotherapy for cancer). René Bernards, cochairperson of AACR's Clowes Award selection committee, said in his introductory remarks that Dr. Witte's "work over the [past decades] serves as the most compelling case of target-validation in human cancer and illustrates the critical importance of research in fundamental disease mechanisms to guide the development of specific therapies."

At the award ceremony, which took place at the AACR 2015 Annual Meeting in Philadelphia, Dr. Witte presented his Clowes Award lecture, entitled "Finding Therapeutic Targets for Aggressive Prostate Cancer." He summarized his past discoveries related to the biology of human leukemias and immune disorders and provided a comprehensive overview of his current research, which focuses on castration-resistant prostate cancer (CRPC).

Dr. Witte was trained in the laboratories of Irving Weissman (Stanford; 1971–1976) and Nobel laureate David Baltimore (MIT; 1976–1980). The Weissman and Baltimore mentorships were invaluable to Dr. Witte's research career, and their friendship and professional collaboration have continued to this date.

As a medical student at Stanford University, Dr. Witte began his research career working in Dr. Weissman's laboratory on viruses that cause certain types of leukemia in mice. After receiving his MD, Dr. Witte decided to dedicate his career to biomedical research and pursued postdoctoral training at MIT in Dr. Baltimore's laboratory. It was there in 1980 that Dr. Witte made the first of a series of discoveries that would have a major impact on human health; while characterizing the Abelson murine leukemia (ABL1) virus protein in the genetic system of a mouse leukemia virus, Dr. Witte discovered the tyrosine kinase enzymatic activity in the ABL1 protein (2). This discovery was the impetus for Dr. Witte's future research on human leukemias, which would change the lives of patients with Philadelphia chromosome–positive leukemias, such as chronic myelogenous leukemia (CML).

CML is a cancer of the white blood cells; it is one of the few cancers known to be caused by a single specific genetic mutation. More than 90% of CML cases harbor the Philadelphia chromosome, which is created by a translocation between chromosome 22 and chromosome 9 (3). The translocation leads to the creation of the chimeric gene *BCR–ABL*. It was at UCLA in Dr. Witte's laboratory that the connection was made between the Abelson tyrosine kinase, which he identified and characterized as a

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postdoctoral fellow, and the abnormal BCR–ABL tyrosine kinase generated from chromosomal translocation. Dr. Witte's group showed that the BCR–ABL enzymatic activity was highly activated in human leukemia, and he predicted in 1984 that it would be a target for therapy (4).

The discovery of the BCR–ABL tyrosine kinase led to the identification of a compound that paralyzes the enzymatic activity of BCR–ABL. The compound was tested in clinical trials by several physician-scientists, including one of Dr. Witte's trainees, Charles Sawyers, resulting in dramatic remissions for patients with CML. The compound, now called Gleevec (imatinib; Novartis), was approved by the FDA in 2002 as the first targeted treatment for CML and certain types of rare gastrointestinal tumors, with minimal side effects.

In 1993, Dr. Witte's laboratory codiscovered the gene for Bruton's tyrosine kinase (BTK), a protein essential for normal B-lymphocyte development (5). When mutated, the *BTK* gene is responsible for a genetic defect in the immune system called Bruton's X-linked agammaglobulinemia (XLA) in humans, resulting in a lack of production of B cells and immunoglobulins (6). People with XLA are prone to serious infections and sometimes die from them.

The work of Dr. Witte and his colleagues also showed that, in addition to being implicated for the treatment of XLA, BTK could be an important drug target for treating immune disorders and certain lymphomas and leukemias. Inhibiting BTK causes lymphoid cells of a certain subclass to fail to thrive and grow. Drugs that block BTK enzymatic activity, such as ibrutinib, result in a loss of growth of lymphoid cells and a decrease in leukemias and lymphomas in which BTK plays a critical role.

In the mid-1990s, Dr. Witte turned his attention to pursuing research projects with the greatest potential to improve survival and reduce side effects for men with advanced prostate cancer, with a focus on the deadly CRPC. Prostate cancer, which is the most common cancer among men in the United States—with an estimated 230,000 new cases each year (7)—is typically treated with surgery or localized radiotherapy. Medical or surgical castration, in the form of androgen deprivation therapy (ADT), can be used to reduce the production of androgen and the function of the androgen receptor in the tumor. However, the tumor can become resistant to castration therapies and grows back in a very aggressive form, resulting in CRPC. When ADT is not effective, few options remain for patients with prostate cancer.

Dr. Witte is taking several independent approaches with the intent to pinpoint specific biologic functions of CRPC that can be targeted with therapies or drugs. His laboratory is currently using phosphoproteomic analysis by mass spectrometry and other technologies to understand signaling inside advanced prostate cancer cells. They are searching for the most active pathways in the cells that utilize specific tyrosine or other kinases, such as serine or threonine kinases. Furthermore, the Witte laboratory is working to define the kinases expressed in prostate cancer cells that have the greatest impact on their growth.

Recognizing that CRPC is often associated with increased neuroendocrine features, the Witte group is collaborating with researchers at UCLA to study how different types of aggressive cancers are affected by neuroendocrine differentiation. To that end, the Witte laboratory has created a tumor model by transforming naïve prostate epithelial cells with the introduction of specific oncogenes, including *MYCN*, and an activated form of AKT1 (a serine kinase). This produces a very aggressive tumor model, which Dr. Witte and his team are using to test for a new therapeutic intervention. Dr. Witte is collaborating with Dr. Baltimore on another approach to treatment of prostate cancer; they are working on a T-cell gene therapy approach that has the potential to eliminate prostate tumors.

Dr. Witte's prostate cancer research has been enhanced by his association with a Stand Up To Cancer Dream Team grant from the AACR–Prostate Cancer Foundation consortium. The West Coast Prostate Cancer Dream Team, comprising prominent prostate cancer researchers on the West Coast, will collect biopsies and blood samples from late-stage prostate cancer patients and subject the tissue and blood to a comprehensive molecular assessment and pathway-based analysis to determine the activity level of known and novel pathways, with the goal of developing patient-specific treatment approaches based on these findings (8).

Dr. Witte joined the UCLA faculty in 1980 and is a distinguished professor of microbiology, immunology, and molecular genetics. He is an investigator for the Howard Hughes Medical Institute, and he receives funding support from the NIH, the Prostate Cancer Foundation, and the California Institute of Regenerative Medicine. Dr. Witte currently holds the UCLA David Saxon Presidential Chair in Developmental Immunology. He is a distinguished professor of molecular and medical pharmacology at the UCLA David Geffen School of Medicine, and he is a member of the UCLA Jonsson Comprehensive Cancer Center.

Dr. Witte is a member of President Obama's Cancer Panel, which monitors the development and execution of the National Cancer Program. He is an elected member of the U.S. National Academy of Science, the Institute of Medicine, and the American Academy of Arts and Sciences. He has received numerous recognitions for his research, including the Milken Foundation Award, the AACR Rosenthal Award, the Dameshek Prize of the American Society of Hematology, the Alpert Foundation Prize, and The Leukemia and Lymphoma Society's de Villiers International Achievement Award.

– *Mirabai Vogt-James*
Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research
University of California, Los Angeles, CA

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