The 2015 AACR Joseph H. Burchenal Memorial Award for Outstanding Achievement in Clinical Cancer Research

Joseph H. Burchenal (1912–2006) was among the true pioneers and preeminent cancer researchers to change the treatment of cancers from surgery and radiotherapy to new chemotherapy regimens (1). Sparked by a fascination with antibiotics that succeeded in treating infections, Dr. Burchenal sought opportunities to expand this therapy to drugs that could combat cancer cells. Dr. Burchenal, along with drug-developer colleagues George Hitchings and Gertrude Elion (who were awarded the 1988 Nobel Prize along with Sir James Black for their discoveries of important principles for drug treatment), were among the first to develop studies of chemotherapies to treat childhood leukemia using the chemical compound 6-mercaptopurine. Although small successes were seen with this chemotherapy regimen, these researchers were encouraged to experiment with other combinatorial chemotherapies for the treatment of solid tumors. Dr. Burchenal and Herbert Oettengen, along with 14 other scientists, received the 1972 Albert Lasker Award for Medical Research for their contributions to the treatment of Burkitt lymphoma (2, 3).

Dr. Burchenal was Vice President of the Sloan Kettering Institute, Memorial Sloan Kettering’s Chief of Clinical Chemotherapy, a past president and board member of the American Association for Cancer Research (AACR), and one of the scientific coauthors whose report led to the National Cancer Act, signed into law in 1971. Through his many years of leadership, service, and mentorship, a promising era of scientific discovery advanced.

In 1996, the AACR Joseph H. Burchenal Memorial Award for Outstanding Achievement in Clinical Cancer Research was established. Elizabeth Jaffee was presented with this prestigious award at the 2015 AACR Annual Meeting in Philadelphia for her pioneering efforts toward developing immunotherapies for the treatment of breast and pancreatic cancers. Dr. Jaffee is Deputy Director of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University.

The award was presented by Susan Bates from the National Cancer Institute, who said of Dr. Jaffee, “Her pioneering work in immunotherapy for breast cancer and pancreatic cancer has been tremendously influential to our understanding of the basic mechanisms and role for immunotherapy in cancer. Dr. Jaffee’s work gave impetus to the field in developing immunotherapy, now an accepted cancer treatment and providing new hope for all patients with cancer. Dr. Jaffee is credited with opening the door to immunotherapy as a potential treatment strategy for patients with pancreatic cancer. Dr. Jaffee recently led a phase II trial that showed that a GVAX prime [a cell-based vaccine secreting granulocyte-macrophage colony-stimulating factor (GM-CSF)] and Listeria vaccine boost [regimen] improved overall survival for patients with pancreatic cancer. This approach was recently granted breakthrough status by the FDA.”

Dr. Jaffee’s award lecture began with her description of the dismal survival rates for patients with pancreatic cancer, making this still one of the most deadly of cancers. Unlike some cancers, pancreatic cancer does not respond well to most treatment modalities, including radiotherapy and chemotherapy. Unfortunately, patients with pancreatic cancer have not benefited from the successes of single-agent immune modulators such as anti–PD-1 and anti–CTLA-4 blocking antibodies. Although combinatorial chemotherapy regimens have increased the average survival from about 6 to 12 months for many patients, most patients with pancreatic cancer will die within a few years of diagnosis.

Dr. Jaffee’s Burchenal Award lecture focused on recent advances in our understanding of the immunobiology of pancreatic cancer. Genetically engineered mouse models of pancreatic cancer are providing new insight into the multiple inflammatory cell types that infiltrate the pancreatic cancer tumor microenvironment. We are just now learning that nonneoplastic cells, including cancer-associated myofibroblasts, regulatory T cells, dendritic cells, myeloid-derived suppressor cells, and tumor-associated macrophages, are hijacked by preinvasive and invasive cancer cells to create a tolerogenic tumor microenvironment (4). Current research is focused on elucidating the mechanisms of this cancer-supporting polarization within the tumor microenvironment with the goal of tipping the balance in favor of an anticancer immunity. With the recent advances in molecular technologies and the development of relevant pancreatic cancer mouse models, it is now within our reach to dissect the inhibitory pathways within the pancreatic tumor microenvironment. This work will, in turn, lead to new therapeutic opportunities that will eliminate these barriers and convert this deadly cancer into a treatable and, one hopes, preventable disease.

Dr. Jaffee reviewed a number of the specific inflammatory signals found in the tumor as it progresses that prevent activation and trafficking of effector T cells into the tumor during this ongoing process. At the time of diagnosis, pancreatic cancers appear to be immunologically quiescent without effector T cells.

Left: Susan Bates, NCI; Middle: Elizabeth Jaffee; Right: Jonathan Yingling, Bristol-Myers Squibb.

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In contrast, other cancers, such as melanomas, naturally attract these effector T cells and therefore respond to single immunotherapy agents that are designed to activate these tumor-infiltrating effector T cells [5].

Work from Dr. Jaffee’s laboratory demonstrated that pancreatic cancer can be converted from an immunologically quiescent tumor to one that has infiltrating effector T cells. One recently published study in which patients were given a pancreatic tumor vaccine 2 weeks prior to surgical resection resulted in the infiltration and establishment of tertiary lymphoid structures that attract potential effector T cells and educate these T cells to become antigen experienced. However, as Dr. Jaffee pointed out in her lecture, these lymphoid aggregates are merely the first step in converting a pancreatic cancer from an immunologically quiescent cancer into one that is effector T-cell permissive. These novel areas of immune infiltration serve a regulatory function and can either induce additional inhibitory signals, such as PD-1/PD-L1, or go on to fully activate effector T cells that prevent pancreatic cancer recurrence for years. Gene array analysis of microdissected aggregates demonstrated that a particular gene signature (upregulation of T-helper 17 and downregulation of regulatory T-cell signals) is associated with improved disease-free survival over the long term (6).

Dr. Jaffee presented the recent results of a number of groundbreaking “proof-of-principle” clinical trials. The first study was designed to demonstrate the induction of effector T cells following vaccination with a new and more potent vaccine approach. This randomized phase II study demonstrated the ability of a priming vaccine (cyclophosphamide plus a GVAX derived from an allogeneic pancreatic cancer cell line) followed by a second boosting vaccine (L. monocytogenes genetically modified to express the pancreatic tumor antigen, mesothelin) to induce improved survival in patients with advanced pancreatic cancer who were previously treated with chemotherapy (7). The second study compared the single immune-modulating agent ipilimumab alone with ipilimumab given with GVAX. This second study was designed to demonstrate that a vaccine for inducing effector T cells given together with an effector T-cell–activating agent will be more effective than an effector T-cell–activating agent alone. In fact, this study showed for the first time that it is possible to induce objective responses in patients with advanced metastatic pancreatic cancer that are associated with prolonged survival (27% 1-year survival rate with GVAX + ipilimumab versus 7% for ipilimumab alone). Only patients receiving the combination showed objective responses (8). Taken together, these findings indicate that immunotherapies are active in many cancers, but understanding each cancer’s tumor microenvironment is critical for developing the optimal immunotherapeutic approaches. Dr. Jaffee’s work opens up new avenues for developing immunotherapies for pancreatic cancer.

Dr. Jaffee received her BS in biochemistry from Brandeis University, and her MD from New York Medical College. She completed a residency in internal medicine at the University of Pittsburgh Medical Center and a fellowship in medical oncology at the Johns Hopkins University. She worked in the laboratory of Drew Pardoll on developing the first human genetically altered tumor vaccine approach. In 1992, Dr. Jaffee established her independent laboratory and translational research program as an assistant professor of oncology at Johns Hopkins. She has remained at Johns Hopkins, where she is currently the Dana and Albert “Cubby” Broccoli Professor of Oncology and the Deputy Director of the Sidney Kimmel Cancer Center.

References
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