Profile of Judy Lieberman

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"I am just hitting my stride," says immunologist Judy Lieberman, while discussing her multiple research projects. The former high-energy theoretical physicist is now a chairperson of cellular and molecular medicine at Boston Children's Hospital and a professor of pediatrics at Harvard Medical School. Elected to the National Academy of Sciences (NAS) in 2020, Lieberman is a pioneer in the therapeutic uses of RNA interference. She showed in an animal disease model that small RNAs can be used as a therapy and developed methods for delivering small RNAs selectively to particular cell types. Her achievements also include elucidating the molecular basis of killer lymphocyte cytotoxicity and identifying the role of microRNAs in development and cancer. Her Inaugural Article (1) reports a strategy for cancer immunotherapy that uses cancer cell-targeted gene knockdown to counteract the many ways tumor cells evade immune recognition.

Judy Lieberman. Image credit: Judy Lieberman.

Post-Sputnik Youth

Lieberman was born in Boston and raised in the New York City area. Her father was a businessman, while her mother was an elementary school teacher. She says, "I grew up in a very intellectual family, but not of scientists, although my uncle was a professor of biochemistry and member of the NAS. My parents were early feminists, who strongly believed that girls could do anything that boys could do."

The 1957 launch of Sputnik 1, the first artificial Earth satellite, heightened interest in science and led to expansion of youth educational programs. Lieberman benefited from this surge of interest while in high school, participating in a sciences and arts summer camp supported by the Ford Foundation, a Saturday science honors program at Columbia University, and a National Science Foundation (NSF) program in modern physics at Cornell University. "The NSF program turned me onto physics," she says.

High-Energy Theoretical Physicist

After earning a bachelor's degree summa cum laude from Harvard University in 1969, Lieberman attended Rockefeller University, where she worked with former Albert Einstein associate Abraham Pais and received a doctorate in theoretical physics in 1974. From 1974 to 1976 she was a postdoctoral associate under the direction of physicist Stephen Adler at the Institute for Advanced Study School of Natural Sciences. Adler, Lieberman, and colleagues investigated unified field theories of elementary particle interactions, and she attempted to reconcile general relativity with quantum field theory (2, 3). Lieberman then served as a research associate at the Fermi National Accelerator Laboratory until 1977.

Feeling isolated due to the nature of her work and the lack of women in her field, Lieberman decided to leave physics and go to medical school with the goal of becoming a practicing physician and giving up research. She earned an MD at Harvard in 1981 as part of the joint Harvard–Massachusetts Institute of Technology (MIT) Program in Health Sciences and Technology.

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There, she was mentored by the founding director of the program, hematologist Irving London.

Return to Research During AIDS Pandemic

As a medical intern at Tufts–New England Medical Center (TNEMC) in 1981, Lieberman encountered patients dying from a mysterious illness. By the time she was a resident in internal medicine at the center, the condition had been identified as HIV/AIDS. Lieberman chose to do a postdoctoral stint in the MIT Center for Cancer Research laboratory of immunologist Herman Eisen, who was then cloning the first known T cell receptors that are important in the immune response to cancer and HIV/AIDS.

The experience galvanized her interest in becoming an immunologist and setting up a laboratory. Her efforts were supported by immunologist Sheldon Wolff, who was the chair of medicine at TNEMC. Lieberman became an instructor in medicine at Tufts University in 1986 and advanced to an assistant professorship in 1987. The head of her division, hematologist Robert Schwartz, echoed Wolff's advice that Lieberman should conduct research and provided additional guidance.

Pioneer of RNA Interference-Based Therapy

In 1995 Lieberman accepted an offer from immunologist Fred Rosen to become senior investigator at the Center for Blood Research and assistant professor of pediatrics in the division of hematology/oncology at Boston Children's Hospital, where she advanced to full professor in the department of pediatrics by 2004. Since 2007, Lieberman has also served as an adjunct professor of genetics at Harvard Medical School and since 2008 as an affiliated faculty member of the Harvard Stem Cell Institute. In 2012 she additionally received the endowed chair in cellular and molecular medicine at Boston Children's Hospital and Harvard Medical School.

At Harvard, Lieberman focused on understanding the killer T lymphocyte response to HIV. She performed early-phase clinical trials of immunotherapy that involved transferring billions of antiviral T cells to HIV-infected patients. When the therapy did not work as well as she had hoped, Lieberman discovered the phenomenon of T cell exhaustion in humans (4). She and colleagues went on to show that a cytosolic nuclease, TREX1, is a key guardian against innate immune responses to cytoplasmic DNA, such as that resulting from HIV infection that enables the virus to evade immune recognition (5).

Lieberman's active research program led to a breakthrough in 2003, when she and her team reported that small-interfering RNAs (siRNAs) could be used as a therapy in an animal disease model (6). Recently, the first siRNA drugs were approved to treat genetic forms of amyloidosis, porphyria, and hyperoxaluria. More siRNA drugs are anticipated in the future.

In 2005, using antibody-mediated delivery of siRNAs, Lieberman and her team described a method to selectively suppress gene expression in specific cell types (7). The following year, Lieberman and colleagues showed that RNA interference could be harnessed to prevent the spread of sexually transmitted infections by using topical microbicides containing siRNAs as the active ingredient (8). RNA drugs are now being explored by pharmaceutical companies to treat hepatitis B and SARS-CoV-2 infections.

Molecular Basis of Cytotoxicity

Another focus of Lieberman's laboratory is studying cytotoxic T lymphocytes and natural killer (NK) cells of the adaptive and innate immune system, respectively. In 2008 she led research that identified a novel mitochondrial programmed cell death pathway activated in target cells by the killer lymphocyte granzyme A (9). The article demonstrated that generation of superoxide anion is required for killer lymphocyte induction of caspase-dependent and caspase-independent programmed cell death.

Lieberman also showed that killer lymphocyte granzymes surprisingly cause programmed cell death in bacteria. Using differential proteomics, Lieberman and colleagues identified proteolytic targets of the other abundant killer lymphocyte protease, granzyme B, in three unrelated bacteria: *Escherichia coli*, *Listeria monocytogenes*, and *Mycobacteria tuberculosis* (10). While granzyme B cleaves a set of proteins in bacteria, antibiotics typically attack a single target. The findings hold potential for informing the development of new approaches to combat antibiotic resistance.

Pore-Forming Proteins in Innate and Adaptive Immunity

Cytotoxic granules contain two pore-forming proteins that disrupt either mammalian (perforin) or microbial (granulysin) membranes. Lieberman and colleagues showed that killer lymphocytes use granulysin to deliver granzymes to intracellular bacteria and kill bacteria in infected target cells by disrupting electron transfer and causing oxidative stress, while simultaneously inactivating bacterial oxidative defense enzymes (11). She and her team determined that killer lymphocytes have a similar response to intracellular parasites (12). Lieberman and her team termed the process "microptosis" (microbe-programmed cell death), which is being explored for its potential in antimicrobial and antiparasitic drug development.

Recently, Lieberman and colleagues found that decidual NK cells in pregnancy transfer granulysin to destroy intracellular bacteria without killing the host cell (13). The findings help explain how maternal decidual NK cells protect against placental infection while maintaining fetal tolerance. The identified mechanism is not restricted to pregnancy, since they demonstrated peripheral NK cells also transfer granulysin to kill bacteria within macrophages and dendritic cells without killing the host cell.

Strategy for Cancer Immunotherapy

Lieberman's laboratory has identified microRNAs that regulate stemness, proliferation, DNA repair, EMT (epithelial-mesenchymal transition), anoikis (a form of

programmed cell death), growth factor signaling, and metastasis (14–17). For decades she has explored how RNA interference using microRNA, siRNA, and related methods may treat cancer.

Lieberman's Inaugural Article (1) reports an application for a strategy originated by molecular biologist Paloma Giangrande. It involves linking an siRNA to an aptamer that binds with high affinity to a cell surface receptor. For the study, an aptamer-siRNA chimera, or AsiC, was delivered to cancer cells, where the aptamer activated the knockdown of six genes involved in different pathways and stages of the interaction of cancer cells with the immune system.

Four of the AsiCs significantly improved immune responses and suppressed tumor growth, while the other two AsiCs were less active but trended toward reduced tumor growth. Lieberman says, "In two cases, where compounds are in clinical use or in development to inhibit a knocked-down gene product, AsiC performed better than the inhibitors." The study offers preliminary proof that AsiCs may be effective agents of immune modulation that could help expand the range of cancers successfully treated by immune therapies.

SARS-CoV-2 Research, Other Projects

Lieberman's laboratory recently determined how signs of danger and invasive infections trigger a form of inflammatory death called pyroptosis, which recruits and activates immune cells to sites under threat (18). Lieberman's laboratory is presently focused on understanding how pyroptosis is regulated in cells and developing methods to increase it for cancer immunotherapy and other applications, understanding how cytotoxic T lymphocytes and innate-like immune killer cells recognize their targets and defend against infection, developing RNA-based therapies against cancer, understanding immune defense against infection in the placenta, and understanding the mechanism responsible for the development of severe COVID-19 disease.

Lieberman's work on SARS-CoV-2 builds on her team's prior work identifying the mechanism behind pyroptosis. In collaboration with structural immunologist Hao Wu and colleagues, she demonstrated that the Food and Drug Administration-approved drug disulfiram inhibits inflammatory death (19). The drug is now in clinical trials as a potential therapeutic for COVID-19.

Lieberman's work ethic and drive extend to her loyal team. "They make me look good," she says, adding that she is also grateful for the support of her husband. An elected member of the American Academy of Arts and Sciences (2008) and the National Academy of Medicine (2020), Lieberman has inspired a new generation of scientists: Her son Eric is an assistant professor in pediatrics at Harvard Medical School, and her son Paul is an assistant professor at the University of Massachusetts Medical School.

After following an unconventional path to become an immunologist, Lieberman says she has grown to love her chosen field. "It took me a long time to really get the hang of how to be successful in biology," she says. "Now that I understand it, I feel more and more excited. I am having fun. I don't want to retire for a while."

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