Judith Hellman, M.D., Recipient of the 2019 Excellence in Research Award

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The American Society of Anesthesiologists chooses a recipient for the Excellence in Research Award annually. The award is to honor an individual investigator for research work that substantially advances science in the service of saving lives. This year's recipient, Judith Hellman, M.D., has engaged in research that is the perfect example of this mission.

Physician-scientist Judith Hellman, M.D., the William L. Young Endowed Professor and Vice Chair for Research in the University of California, San Francisco Department of Anesthesia and Perioperative Care, has spent her career tracking how the interactions between microorganisms and the body's innate immune system lead to shock and organ dysfunction in sepsis and inflammatory critical illness. Given the role of sepsis in so many intensive care unit (ICU) deaths and our ongoing struggles to diagnose the condition and help our patients recover from its effects, it is hard to imagine more important work.

Dr. Hellman's path to this work was not a straight line, but had a unifying theme. She grew up in New York City, before her family's San Francisco roots eventually drew her to University of California Berkeley where she majored in microbiology. She then attended medical school at Columbia University, where she decided to become an ICU physician—and then completed residencies in internal medicine at Oregon Health Sciences University and in anesthesia at Massachusetts General Hospital. At the latter, her department chair discovered her microbiology background and referred her to the lab of H. Shaw Warren, M.D., an infectious disease physician and sepsis researcher.

That's where Dr. Hellman connected the dots between her interests in microbiology, intensive care, and sepsis. After completing an intensive care fellowship, also at Massachusetts General Hospital, she moved on to do postdoctoral work in Dr. Warren's lab on a T-32 training grant and began making her own mark on our understanding of sepsis.

Her initial research path was unusually fruitful. She demonstrated that bacteria shed commonly expressed bacterial lipoproteins into the circulation of septic animals and into human serum[1–5]; that bacterial lipoproteins induce inflammation and lethality in mice; that *Escherichia coli* lacking the bacterial lipopeptide peptidoglycan-associated lipoprotein have reduced lethality in sepsis; and that Toll-like receptor 2 agonists synergistically induce inflammation with other Toll-like receptor agonists.[4–6] In addition, she found that bacterial lipopeptide causes respiratory dysfunction and contributed to the understanding of the effects of Toll-like receptor 2 activation on cardiomyocyte function.[7–9]

Fig. 1. Judith Hellman, M.D., recipient of the American Society of Anesthesiologists 2019 Excellence in Research Award.

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In these same years, while continuing to provide clinical care in ICUs, Dr. Hellman observed the complex bleeding and clotting derangements that occur in patients with sepsis. Motivated by that observation, she began to explore whether the processes that occur in the endothelium, which is important in coagulation homeostasis and is activated in sepsis, might be at the heart of sepsis-induced organ failure—a condition that occurs in roughly half of patients who succumb to septic shock. Ultimately, Dr. Hellman became the first to define the broad spectrum of effects of Toll-like receptor 2 activation on endothelial cells, including showing that Toll-like receptor 2 activation upregulates inflammatory mediators, increases endothelial-neutrophil adhesion, and modulates endothelial permeability and the expression of coagulation pathway intermediaries.[10–12]

Next, Dr. Hellman turned her attention to defining the role of the extracellular signal regulated kinase 1 and 2 and extracellular signal regulated kinase 5 in acute inflammation and sepsis. That research path has led her to identify novel roles for extracellular signal regulated kinases 1, 2, and 5, in activation of leukocytes and endothelial cells by microbial and endogenous inflammatory agonists. Moreover, while mapping out endothelial Toll-like receptor 2 signaling pathways, she and her team uncovered a previously unrecognized role for extracellular signal regulated kinases 5 in mediating Toll-like receptor 2-dependent activation of endothelial cells and leukocytes.[13] She then identified a role for extracellular signal regulated kinases 5 in inflammatory activation of cells by agonists of other Toll-like receptors, and by endogenous inflammatory agonists including interleukin 1β and tumor necrosis factor α[14]—and found that extracellular signal regulated kinase 5 mediates inflammation in mice with sepsis or with lung ischemia-reperfusion injury.[14] Finally, her work suggests that extracellular signal regulated kinase 1 and 2 activation plays divergent roles in the inflammatory activation of human endothelial cells *versus* leukocytes.[13]

Moreover, Dr. Hellman's novel discoveries on immune modulation by the endocannabinoid and endovanilloid systems could eventually lead to important therapeutic targets for sepsis and acute inflammation. She has published two papers on the antiinflammatory effects of the endogenous lipid, *N*-arachidonoyl dopamine, which activates cannabinoid receptors as well as the pain receptor, transient receptor potential vanilloid 1. She and her team discovered that *N*-arachidonoyl dopamine has potent antiinflammatory effects *in vitro* on leukocytes and endothelial cells, and *in vivo* in endotoxemic and septic mice.[15,16] She also found that *N*-arachidonoyl dopamine downregulates acute inflammation in mice transient receptor potential vanilloid 1 expressed by nonhematopoietic cells.[16] In as yet unpublished work, she found that another acyl-dopamine transient receptor potential vanilloid 1 agonist, N-oleoyl dopamine, as well as the phytocannabinoid, THC, also have potent antiinflammatory effects *in vitro* and *in vivo*.

In connected research, Dr. Hellman has made important contributions to understanding lung ischemia-reperfusion injury. She collaborated with Dr. Arun Prakash (University of California San Francisco Anesthesia Department, San Francisco, California), a K08-funded anesthesiologist for whom she is the primary mentor, to find that alveolar macrophages, Toll-like receptor 4, and the NLRP3 inflammasome mediate inflammation in lung ischemia-reperfusion; that manipulation of the intestinal microbiome affects ischemia-reperfusion–induced lung inflammation; and that lung ischemia-reperfusion affects bacterial containment in mice with *E. coli* pneumonia.[17–19] Her group has also made important contributions to understanding other aspects of immune modulation. They have shown that rats with metabolic syndrome have impaired bacterial clearance and exaggerated lung inflammation during *Staphylococcus aureus* infection,[20] and Dr. Hellman has contributed to studies that show how the intestinal microbiome regulates lung injury and systemic infection.[18,21]

This is extraordinarily important work, yet Dr. Hellman's influence goes far beyond her own research program. She has served as a reviewer for multiple publications, as well as an editor, associate editor, or section editor for journals that include the *Journal of Immunology* and *SHOCK*. And for more than two decades, she has contributed substantially to research training and mentoring in anesthesia and critical care at the institutional and national levels.

As the University of California San Francisco department's vice chair for research since 2013, she is responsible for everything from the education of research trainees through the recruitment of faculty, fellows, and residents. As director of the department's research training program, she trains and mentors students, residents, postdoctoral fellows, and junior faculty. In addition, she is the program director for the Anesthesia National Institutes of Health T32 training grant and helped establish and now runs the department's Pathway to Scientific Independence program, which facilitates the research training of anesthesiologist physician-scientists.

Similarly, in her own research lab, Dr. Hellman trains medical students, graduate students, postdoctoral fellows, and junior faculty. In clinical settings, she has taught medical students and house officers at the bedside and in lectures. She has served as the primary research advisor and mentor for many, served on multiple Research Advisory Committees, and been a short-term mentor for a number of undergraduate and medical students doing summer research projects. In 2018, she received the Fellows' Leadership and Advocacy Group Mentorship Award by the University of California San Francisco Pediatrics Department (San Francisco, California).

All of this is in addition to serving in numerous leadership roles and on important committees for the Society of Critical Care Medicine (Mt. Prospect, Illinois), the American Association of Immunologists (Rockville, Maryland), the

Shock Society (Bethesda, Maryland)—*and* the American Society of Anesthesiologists (Schaumburg, Illinois).

Dr. Hellman's cumulative impact on our specialty and on an essential area for medical research is hard to quantify, but it is considerable and rare. We are honored to have her as a colleague and thrilled to see her receive an honor that is so richly deserved.

Competing Interests

The author declares no competing interests.

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