

TRIBUTE

Paul S. Frenette (1965–2021)

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Dr. Paul S. Frenette (Figure 1), a noted stem cell researcher, physician scientist in hematology-oncology, and educator who had an extraordinary impact on several fields of research, died on July 26, 2021, at the age of 56. As a scholar, mentor, and scientific leader, Paul left a legacy of profound new insights into stem cell regeneration, the mechanisms of immunity, and the links between the nervous system and cancer. He is survived by his wife, Nadine, and their twins, Clara and Albéric, to whom he was deeply devoted.

Paul was born in Québec City, QC, Canada, and was raised in a loving family with two brothers, Julien and Jerome, and two sisters, Marie-Luce and Elise. He earned his MD degree from Université Laval (Quebec, QC, Canada). Following his internship and residency at Montreal General Hospital (Montreal, QC, Canada), McGill University (Montreal, QC, Canada), and clinical fellowship in hematology-oncology at New England Medical Center, Tufts University (Boston, MA, USA), Paul was a research fellow in the Center for Blood Research at Harvard Medical School and Massachusetts Institute of Technology (Cambridge, MA, USA) under the mentorship of Dr. D. D. Wagner and Dr. R. O. Hynes, respectively. During this training, he was promoted to Instructor in Medicine at Harvard Medical School. In 1998, he was recruited by Barry Collier as an Assistant Professor of Medicine at the Mount Sinai School of Medicine (New York, NY, USA), where he rose through the ranks to



FIGURE 1 Paul S. Frenette (1965–2021). Photo courtesy of Department of Communications and Public Affairs at Albert Einstein College of Medicine

become a tenured professor within the Departments of Medicine and of Gene and Cell Medicine in 2007. In 2010, Paul accepted the positions of Founding Director

Abbreviations: HSC, hematopoietic stem cell; SCD, sickle cell disease.

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and Chair of the Ruth L. and David S. Gottesman Institute for Stem Cell Biology and Regenerative Medicine and Professor of Medicine at the Albert Einstein College of Medicine (Bronx, NY, USA), where he continued to make seminal observations and ensure the translation of his discoveries to the clinic for the benefit of patients with intractable medical conditions.

Paul's laboratory began with a focus on the movement of hematopoietic cells throughout the body under normal and pathologic conditions. Some of his early and seminal studies elucidated mechanisms of leukocyte extravasation, the roles of P- and E-selectins in platelet and leukocyte adhesion, and the importance of both in hematopoiesis and inflammatory responses.^{1,2} Through this work, Paul posited that leukocytes could be key drivers in vessel occlusion and organ damage in patients with sickle cell disease (SCD), which is the most common congenital condition diagnosed in newborns. The discoveries from Paul and his laboratory were revolutionary, revealing that altered adhesive properties of leukocytes, not just misshapen erythrocytes, were major players in SCD pathology.³ Findings from the Frenette laboratory in this arena resulted in the development of anti-P-selectin antibodies and intravenous immunoglobulin (IVIg) as novel therapies for vaso-occlusion in SCD. More recently, Paul's group described the mechanisms by which the microbiome regulates aged neutrophils to promote vaso-occlusion and organ damage in SCD.⁴ With an eye always on the clinic, Paul was working with clinicians within the Montefiore Medical Center (Bronx, NY, USA) to test if changing the microbiome could also improve the lives of patients with SCD.

The Frenette laboratory also had a long-standing interest in the hematopoietic stem cell (HSC) niche, exploring the traffic patterns of healthy stem cells and their relevance to cancer cell migration and metastasis. These efforts yielded a total of 170 peer-reviewed articles published in high-impact journals such as *Cell*, *Nature*, *Nature Medicine*, and *Science*. One of Paul's most important contributions to the field was his demonstration that signals from the sympathetic nervous system regulate HSC egress from the bone marrow (*Cell*, 2006),⁵ and that adrenergic nerves regulate their circadian release (*Nature*, 2008; *Immunity*, 2012).^{6,7} This was the first time that neural contributions to a stem cell niche had been defined, and his studies expanded the concept of a niche to include systemic inputs. More recently, he demonstrated that somatosensory nerves collaborate with sympathetic nerves to maintain HSC populations through their demand for efficient HSC mobilization from the bone marrow (*Nature*, 2021).⁸ Paul also contributed to the identification of unique cellular constituents forming niches in the bone marrow, demonstrated that mesenchymal stem cells marked by

Nestin are a major niche candidate for HSC maintenance in both the bone marrow and fetal liver. These discoveries required Paul and his group to develop a novel imaging system to evaluate the significance of relationships between and within niche structures (*Nature*, 2010).⁹ These innovations enabled his team to identify distinct niches associated with vessel types and HSC progeny (*Nature*, 2013; *Nature Medicine*, 2014; *Science* 2016),¹⁰⁻¹² and led to the clinically relevant finding that chemotherapy-induced bone marrow nerve injury impairs hematopoietic regeneration (*Nature Medicine*, 2013).¹³ His group also delineated that age-associated neuropathy impairs hematopoietic health that could be rejuvenated by systemic administration of β -adrenoreceptor mimetics (*Nature Medicine*, 2018).¹⁴

Building on his demonstration that sympathetic nerves regulate HSC migration, Paul questioned if nerve input affected cancer pathophysiology, with a focus on leukemia and prostate cancer. His group examined autonomic nervous system regulation of prostate cancer progression, and showed that sympathetic nerves were critical for tumor initiation, whereas parasympathetic nerves regulated tumor invasion and metastasis (*Science*, 2013).¹⁵ He further demonstrated that endothelial β 2-adrenergic receptor signaling via adrenergic nerve-derived noradrenaline is required for activation of an angiogenic switch in the prostate stroma that stimulates cancer growth by maintaining endothelial aerobic glycolysis and preventing oxidative phosphorylation (*Science*, 2017).¹⁶ In leukemia, they found that neuropathy of the sympathetic nervous system promotes bone marrow infiltration of acute myeloid leukemia cells, and subsequent reprogramming of the bone marrow microenvironment to a protumorigenic milieu at the expense of healthy HSCs (*Cell Stem Cell*, 2014).¹⁷

The esteem of the scientific community for Paul is evident by his receipt of numerous awards and accolades throughout the years. Here are a few highlights that exemplify the breadth and extent Paul was respected by his peers. Paul was an elected member of the American Society for Clinical Investigation and the Association of American Physicians. He received the Gloire de l'Escolle Medal (Prix Grands Diplômés) from Université Laval and the Saul Korey Prize for Translational Medicine and Science. Additionally, he gave countless prestigious lectureships and keynote addresses, such as the Nobel Lecture series, Danny Thomas Lecture, and Alexander S. Wiener Lecture, as well as numerous invited seminars, such as his talks at several Federation of American Societies for Experimental Biology (FASEB) meetings over the years. In addition, Paul was highly engaged in the scientific community via his service to many societies and journals. For example, Paul

served on the editorial boards of *Blood*, the *Journal of Clinical Investigation*, *Stem Cell Reports*, *Oncogene*, and *Developmental Cell*, as well as the Medical Advisory Board of the New York Stem Cell Foundation, the American Society of Hematology (ASH) Committee on Government Affairs, and the Sickle Cell Advisory Council of the U.S. National Institutes of Health (NIH)/National Heart, Lung, and Blood Institute (NHLBI). He also served as a standing member of the NIH Molecular and Cellular Hematology (MCH) and Hemostasis, Thrombosis, Blood Cells and Transfusion (HTBT) study sections along with numerous stem-cell-related panels, NIH boards, and other institutions and groups. Paul's work as President of the International Society of Experimental Hematology (ISEH) in 2015 was particularly noteworthy, as his leadership in promoting hematology research received very high marks from the membership. Paul was an esteemed colleague in the fields of stem cell and cancer biology, neuroscience, and immunology whose loss will be felt for years to come.

While Paul was respected worldwide for his science and service, he was loved and revered by his laboratory for being a dedicated and passionate mentor. Eighteen of his former postdoctoral fellows now occupy independent positions in academic research at prominent institutions across the globe, including within the United States at University of Pennsylvania (Philadelphia, PA, USA), New York Blood Center (New York, NY, USA), Cincinnati Children's Hospital Medical Center (Cincinnati, OH, USA), University of Illinois in Chicago (Chicago, IL, USA), and abroad at University of Cambridge (Cambridge, UK), Centro Nacional de Investigaciones Cardiovasculares (CNIC; Madrid, Spain), Université de Genève (Geneva, Switzerland), Institut National de la Santé et de la Recherche Médicale (INSERM; France), Federal University of Minas Gerais (Belo Horizonte, Brazil), and Kobe University (Kobe, Japan). He was a director of the NYSTEM Einstein Training Program, and as Director of the Einstein Stem Cell Institute, hired and guided a cadre of successful junior faculty members. His commitment to education and mentorship was further evidenced by receipt of the Julius Marmur Mentorship Award from the Einstein Graduate Programs in Biomedical Sciences, as well as the notable growth of the junior faculty at the Stem Cell Institute, a trend largely due to Paul's support and guidance.

Beyond his scientific pursuits, Paul had many other passions; he loved skiing, classical music, good food, and great wine. Above all, he adored his family and friends, and loved life in an open and ardent way. Those lucky enough to work closely with Paul were always impressed by his generosity, wit, and buoyant heart, and cherished the opportunity to chat with him whenever their paths

might cross. Paul just as often stopped by his colleagues' offices to enjoy a cup of coffee, and was glad to share his thoughts with ease, clarity, and joy no matter the setting or topic, from his thoughts on the challenges of team leadership to the latest news from his favorite sport, ice hockey. He will be fondly remembered and greatly missed by his many colleagues and friends. A visionary scientist, inspiring leader, and devoted educator, Paul's legacy will live on at the Einstein Stem Cell Institute he founded, as well as through the myriad of students, trainees, and faculty he guided and mentored.

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