Paul S. Frenette (1965–2021)

On 26 July 2021, the scientific community suffered a major loss with the untimely death of Dr Paul S. Frenette at the age of 56. Over the past three decades, Paul's work on stem-cell microenvironments in health, cancer and vascular biology translated into the development of drugs and changed clinical practice. His scientific accomplishments have been recognized by a long list of national and international awards, but Paul was foremost a great mentor, having trained numerous scientists who have gone on to establish successful programs in academia and industry. Paul will be remembered as a brilliant and creative hematologist, an inspirational mentor and a cherished friend.

Paul was born in Quebec City, Canada, where he grew up with his four siblings. During adolescence, Paul battled Hodgkin's lymphoma. According to him, this experience fueled his passion for hematology and research. He received his medical degree from Laval University in Quebec City and completed his residency and internship at Montreal General Hospital, McGill University. In 1991, Paul moved to Boston for a fellowship in Hematology/Oncology at Tufts-New England Medical Center (now Tufts Medical Center) and research training at Harvard Medical School and Massachusetts Institute of Technology (MIT). During this time, he met his wife, Nadine. This period was crucial in shaping Paul's career. Under the mentorship of Drs Denisa Wagner and Richard Hynes, he generated and characterized the first double-knockout for the endothelial adhesion molecules P- and E-selectin. This uncovered the crucial roles of both selectins in leukocyte trafficking. This study, published in *Cell* in 1996, became a landmark paper and the spark for his two major scientific interests — inflammatory leukocytes and hematopoietic stem cells (HSCs). As it turns out, he would devote his scientific career to understand the where, when and how of these two fundamental blood cell types.

In 1998, Dr Barry S. Coller recruited Paul to join the faculty of Mount Sinai School of Medicine (now Icahn School of Medicine at Mount Sinai) in New York City. There, Paul's initial focus was to investigate why the vessels of patients with sickle cell disease (SCD) tended to occlude and cause organ damage and pain crises. Using animal models of SCD and intravital microscopy, Paul's team

Paul Frenette — Photo courtesy of Ali Zahalka.

demonstrated that leukocyte adhesion, activation and capture of circulating erythrocytes was driving vascular occlusion — a finding that reshaped the field by correcting the prevailing dogma that occlusion was primarily caused by erythrocytes directly sticking to the vessel wall. More importantly, this seminal discovery provided a link between inflammation and sickle cell crises, and spurred the development of anti-adhesive drugs, such as crizanlizumab, which was approved in 2019 for the treatment of vaso-occlusion in patients. Over the years, Paul maintained a very successful program in vascular inflammation. His group discovered that the activation of neutrophils, the key leukocytes that drive vascular occlusion, was influenced by a broad spectrum of systemic cues, from the gut microbiota and molecules present in inflamed vessels to circadian rhythms and neural cues associated with psychological stress.

Paul quickly rose through the ranks to tenured professor at Mount Sinai School of Medicine. His interest in understanding the mechanisms that control hematopoietic cell trafficking, a fundamental process during bone marrow transplantation, led to another ground-breaking discovery in 2006, when the team realized that signals from the peripheral nervous system regulated the release of HSCs from the bone marrow into blood. The group further uncovered that adrenergic nerves regulate this release in a circadian manner. This revolutionary series of studies led to two key paradigms in the field: the nervous system is a key regulator of hematopoiesis, and systemic signals regulate stem-cell niches and HSCs. Subsequently, Paul discovered that this nerve–marrow axis regulates stem-cell engraftment and physiological aging of the hematopoietic system and, surprisingly, that it controlled the progression of tumors.

As a leading stem-cell and vascular biology researcher, Paul was appointed the founding director of the new Ruth L. and David S. Gottesman Institute for Stem Cell and Regenerative Medicine Research at Albert Einstein College of Medicine in 2010. There, he spearheaded various studies that led to the identification of key components of HSC niches in the bone marrow. Using state-of-the-art bone marrow imaging techniques and refined genetic mouse models, Paul's group identified a population of Nestin-expressing mesenchymal stem cells that was innervated by sympathetic nerves and supported HSC maintenance in the bone marrow. This seminal study revealed that the bone marrow niche is composed of at least two types of stem cell (hematopoietic and mesenchymal), and influenced the scientific community by redirecting the interest to mesenchymal cells as true protagonists in hematopoietic organs. This finding also led to the discovery that distinct niches exist for different populations of hematopoietic stem and progenitor cells in the marrow. Paul continually redefined the field, as he and others went on to demonstrate that macrophages influence the very niche in which their hematopoietic precursors resided. His team also showed that megakaryocytes are key components of the niche for a specific HSC subset. The originality of Paul's discoveries over the years made him a respected leader in the stem-cell niche field and prompted many productive collaborative studies with other researchers.

Paul was widely recognized and served as president of the International Society of Hematology in 2015. He was also an elected member of the American Society for Clinical Investigation and the Association of American Physicians. At the American

Society of Hematology, he served as member and chair of the Scientific Committee on Thrombosis and Vascular Biology; member of the Scientific Committee on Hematopoiesis; and co-chair of the Scientific Program. He also served on the advisory board of the New York Stem Cell Foundation and on multiple panels at the National Heart, Lung, and Blood Institute of the National Institutes of Health and on the editorial boards of several journals.

Paul cared deeply about his family, friends, colleagues and the members of his laboratory (the 'Frenettocytes'). Over the course of his career, he created a flourishing research environment in which ideas and discussions were highly encouraged, and scientific rigor was a priority. As a mentor, Paul was honest and candid. These qualities ensured that his trainees learned how to think critically and focus on the important scientific questions before performing the best possible in vivo experiments to test those hypotheses, always with an eye towards the physiological value of the question. Hence the lab motto "in vivo veritas". Working with Paul was also fun, as he possessed a unique sense of humor and loved to bet a beer against his students or postdocs about some scientific result, and he was almost always right! With the invaluable help and organizational support of Joan Pitcan and Colette Prophete, Paul mentored dozens of trainees over the years, many of whom have gone on to successful biomedical careers. As the Founding Director of the Stem Cell Institute, he also hired several successful junior stem-cell faculty members who contributed to the growth of the Institute into the major research establishment it is today.

In addition to Paul's professional accomplishments, he had a rich family and personal life, shared with his wife Nadine and their twins, Clara and Albéric. The hematology and biomedical research communities have lost a brilliant mind, and we, his trainees, have lost a mentor, a guide and a friend whom we will miss tremendously. ❐

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