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Chemical and Biomolecular Engineering
and
the Golden LEAF Biomanufacturing Training and Education Center

announce the 2nd annual

D. F. Ollis Lecture in Biochemical Engineering

Challenges in Blood Cell and Platelet Production in Culture

presented by

Prof. William M. Miller
Department of Chemical and Biological Engineering
Northwestern University
Evanston, IL

Monday, March 23, 2009
10:45-11:40 am
1011 Engineering Building I
NCSU Centennial Campus

Abstract

Stem cells in the bone marrow differentiate into blood cells via several rounds of lineage-restricted commitment and expansion, followed by lineage-specific proliferation and maturation. Production of platelets from cultured blood stem and progenitor ($CD34^+$) cells would increase the supply of rare blood types and decrease the risk from blood-borne pathogens. However, producing one transfusion dose of 500 billion platelets using current technology would require 250 million $CD34^+$ cells, which is equivalent to more than 50 cord blood harvests or several $CD34^+$ cell harvests from the peripheral blood of donors pretreated with cytokines. Thus, the *ex vivo* platelet yield must be increased by several orders of magnitude. Because there are profound changes in cell physiology, regulation, and gene expression during Mk commitment and maturation, optimal conditions will differ greatly for the processes of Mk progenitor (CFU-Mk) expansion, Mk cell production, and terminal maturation (polyploidization and proplatelet formation). Inspired by gradients of increasing pH and pO_2 with increasing Mk maturation in the bone marrow, we showed that low pH and pO_2 enhance CFU-Mk production, while supervascular pH and pO_2 increase Mk ploidy (platelet-producing potential). We also showed that the vitamin nicotinamide (NIC) greatly increases maximal Mk ploidy and proplatelet formation in culture. We are developing a 3-step process with conditions tailored for each step. We have identified cytokines that produce at least 3 Mk progenitors per input $CD34^+$ cell, while enriching for Mk progenitors. Shifting from low to high pO_2 and pH after 5-7 days and adding NIC produced 35% high-ploidy ($\geq$ 8N) Mk cells. We have shown that NIC increases Mk ploidy by inhibiting the SIRT1/2 histone/ protein deacetylases. Understanding the mechanisms will facilitate regulatory approval for using NIC to produce platelets for transfusions and may lead to the discovery of even more effective conditions for Mk polyploidization.

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This seminar series celebrates the pioneering contributions of David F. Ollis Distinguished Professor of Chemical and Biomolecular Engineering at North Carolina State University to the field of biochemical engineering. Prof. Ollis' academic career spans biochemical engineering, catalysis and photocatalysis, and engineering education. His corresponding books in these areas are *Biochemical Engineering Fundamentals* (1977, 1986, with James E. Bailey), *Photocatalytic Purification of Air and Water* (1993, co-edited with Hussain Al-Ekabi), and *Liberal Education for 21st Century Engineering* (2004, co-edited with Kathryn Neeley and Heinz Luegenbiehl). His books and research papers have been cited approximately 7,000 times. Prof. Ollis joined the NC State faculty in 1985.

Prof. Miller received a B.S. in Chemical Engineering from Lehigh and an M.S. from MIT. After 8 years with Rohm & Haas and Air Products, he received a Ph.D. from the University of California, Berkeley. Bill has been at Northwestern since 1987; he served as department chair and is Director of the Master of Biotechnology Program. Prof. Miller received a PYI Award from NSF and chaired the AIChE Food, Pharmaceutical and Bio-engineering Division. He chaired the Cell Culture Engineering VII conference and served on the Scientific Advisory Board of the Stem Cell Network of Canada and the NRC Task Group to evaluate NASA's Biotechnology Facility for the Space Station. He is a Fellow of the American Association for the Advancement of Science and the American Institute of Medical and Biological Engineers. Prof. Miller has authored more than 90 peer-reviewed publications and serves on the editorial boards for *Biotechnology Progress* and *Biotechnology & Bioengineering*. He is Editor of the *Biochemical Engineering Journal*.

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