

April 21, 2009

Massachusetts General Hospital, Richard B. Simches Research Center, Room 3110

185 Cambridge Street, Boston

4:00 – 6:00PM

Lester Wolfe Workshop in Laser Biomedicine Stem Cells See the Light

Stem cell research has become a hot topic in biomedical research for several reasons, including: a change in federal funding policy, their enormous potential in regenerative medicine, fundamental discoveries in developmental biology, and their role in cancer progression and metastasis. This workshop will highlight the role that biomedical optics can play in imaging, tracking, measuring and destroying various classes of stem cell.

4:00PM Welcome: John A. Parrish, MD, CIMIT Executive Director, japarrish@partners.org

Moderator: Michael Hamblin, PhD, Associate Professor, Harvard Medical School; Associate Chemist, Wellman Center for Photomedicine, Massachusetts General Hospital, mhamblin@partners.org

4:10PM Program Overview: Charles Lin, PhD, Associate Professor, Wellman Center for Photomedicine, MGH, clin0@partners.org

4:20PM Bone Marrow Hematopoietic Stem and Progenitor Cells Go Live: Tracking HSPC/niche Interactions at Single Cell Resolution

Cristina Lo Celso, PhD, Instructor in Medicine, Massachusetts General Hospital (MGH) Center for Regenerative Medicine, clocelso@partners.org

Among adult stem cells, the hematopoietic lineage has been the most extensively studied in terms of both functional assays and phenotypic characterization, yet direct analysis of HSC niche in the bone marrow has so far been elusive.

Using two-photon/confocal hybrid microscopy Cristina Lo Celso's lab has assessed the micro-anatomic events accompanying stem cell transplantation. First, they documented that transplanted hematopoietic cells localize according to their differentiation state. More immature cells such as long term repopulating hematopoietic stem cells (LT-HSC) localize in close proximity to osteoblasts than more mature cells. Second, they showed that among LT-HSC, those closer to osteoblasts divided at lower frequency than those more distant. Third, we showed that under a setting where the stem cell pool is known to expand (col2.3kb PPR transgenic mice), cells were in closer proximity to the endosteum. The lab did not find all LT-HSC in direct contact with osteoblasts, but rather in their proximity (0-30um). In a setting where genetically modified LT-HSC are known not to engraft (Gs alpha conditional knock out mice), they documented that the cells do not engage the niche due to reduced ability to exit the circulation.

Micro-anatomic assessment of stem cell interactions with their niche can discriminate and quantitate the process of stem cell egress from the circulation, their position in relation to multiple microenvironment constituents and relative rate of cell division. This approach will add a refined means of evaluating the impact of genetic and pharmacologic interventions on stem cell function.

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4:50PM Therapeutic and Diagnostic Stem Cells for Cancer Therapy

Khalid Shah, PhD, Assistant Professor, Department of Radiology and Neurology, Massachusetts General Hospital, Harvard Medical School, kshah@partners.org

The recognition that neural stem cells (NSCs) can integrate appropriately throughout the mammalian brain following transplantation has unveiled new possibilities for their use in neural transplantation. Khalid Shah's lab's research is based on simultaneously targeting cell death, proliferation and angiogenic pathways in an effort to treat glioblastomas. The lab engineers NSCs (i) to secrete therapeutic protein, S-TRAIL (secreted Tumor necrosis factor receptor-apoptosis inducing ligand) to specifically induce apoptosis in tumor cells and anti-angiogenic TSP-1 (thrombospondin-1) to inhibit tumor angiogenesis. These NSCs are then used to populate primary tumors and their microsatellite deposits in the brain in an effort to eradicate established tumors in mouse models of glioblastoma. Inherently linked to the brain tumor therapy paradigm, the team employs fluorescent/bioluminescent imaging markers and optical imaging techniques to track NSC, image apoptosis and changes in tumor volumes in real time in vivo.

5:20PM Spotlight on Cancer Stem Cells

Janet Morgan, PhD, Department of Dermatology, Roswell Park Cancer Institute, Buffalo, NY, janet.morgan@roswellpark.org

Many photosensitizing molecules used in clinical and preclinical photodynamic therapy (PDT) are substrates of the ATP-dependent transporter and multiple drug resistance (MDR) pump ABCG2. ABCG2 when present in the plasma membrane and under favorable conditions can pump out substrate photosensitizers (PS) such as the pyropheophorbide analogue 2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a (HPPH, or Photochlor) leaving intracellular concentrations which may be insufficient for a phototoxic effect. For cancer cells expressing high levels of ABCG2, it is obvious that resistance to PDT can occur with substrate PS. However, many cancer cells appear to be negative for ABCG2 in the bulk of the tumor, but a small proportion of cells, often < 1% of the tumor, express ABCG2 and efflux fluorescent dyes such as Hoechst, producing a (blue/red fluorescence) double negative side population (SP) in flow cytometry. The SP compared to the NON-SP phenotype is enriched for stem cell-like properties and in many tumor models can recapitulate the original tumor if serially transplanted, a characteristic of cancer stem cells (CSC). If the SP by effluxing photosensitizer can evade phototoxicity, then the tumor is likely to regrow from the survivors, a possible explanation for recurrences observed both pre-clinically and clinically. Janet Morgan's lab examined the role of PDT on the SP. SP cells from tumor models treated in vitro and in vivo with the ABCG2 substrate HPPH were relatively resistant to PDT compared to the non-substrate HPPH-Gal (a galactose conjugate of HPPH). Thus, putting the spotlight on the CSC was less effective at targeting the cells for PDT induced death if the activating PS was an ABCG2 substrate. Sensitivity of the CSC to the spotlight could be restored by ABCG2 inhibitors preventing efflux of substrate PS, or by designing effective non-substrate photosensitizers.

5:50PM Refreshments and Networking

The Lester Wolfe Workshop in Laser Biomedicine is sponsored by the G. R. Harrison Spectroscopy Laboratory, MIT; MGH Wellman Center for Photomedicine; Harvard-MIT Division of Health Sciences and Technology; and CIMIT (Center for Integration of Medicine and Innovative Technology).

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Lester Wolfe Biography

Lester Wolfe was an inventor with a special interest in optics and photography. He died in 1983 at the age of 86. He was a benefactor of MIT, and his will provided funds "for fellowships for studies in molecular biology and for research using optical methods in the investigation of the structure and properties of matter." Lester was born in Boston in 1897 to a family of modest means. He enrolled at MIT as physics undergraduate and graduated in the class of 1919 -- well before the advent of quantum mechanics, the atomic bomb or lasers! During World War I he served in the armed forces as an inventor, and received a commendation for design of the "fuel quantity gauge", which used a radioactive source to measure the supply of fuel stored in the wings of an airplane. After the war he became active in industry, and he made his fortune in the field of containerized shipping between the United States and Japan. He became an expert in pre-Colombian art and technology, and a collector in this field and several others. Toward the end of his life Lester became interested in furthering research in biology and medicine as well as in the area that he loved most, optics. That is how he developed an interest in the research projects of the Spectroscopy Laboratory.

The Lester Wolfe Workshop in Laser Biomedicine is a series of talks dedicated to a particular aspect in biomedical optics. The panel of speakers of the Workshop is chosen from expert researchers in academia, medical profession and industry. Held twice a year, the Lester Wolfe Workshop is sponsored by the George R. Harrison Spectroscopy Laboratory, MGH Wellman Center for Photomedicine, Harvard-MIT Division of Health Sciences and Technology, and CIMIT (Center for Integration of Medicine and Innovative Technology). Information obtained from the MIT Spectroscopy Website: <http://web.mit.edu/spectroscopy/events/wolfe.html>.