

April 22, 2008

Massachusetts General Hospital, Richard B. Simches Research Center, Room 3110
185 Cambridge Street, Boston
4:00 – 6:00PM, Refreshments 3:30PM

Lester Wolfe Workshop in Laser Biomedicine Shining Light on Melanoma

The rapid increase in the incidence of malignant melanoma and its high associated mortality necessitates improvements in diagnosis and therapy. This workshop will feature the contributions that can be made in managing this disease by biomedical optics. Although melanoma is highly visible macroscopically, non-invasive optical imaging techniques can improve microscopic detection. Laser-induced thermotherapy can give effective local control and at the same time stimulate the host immune response.

Workshop Moderator: Michael R. Hamblin, PhD, Associate Professor of Dermatology, Harvard Medical School, Wellman Center for Photomedicine, Massachusetts General Hospital, mhamblin@partners.org

Introduction: Framing the Problem of Melanoma Diagnosis

Arthur J. Sober, MD, Associate Chief of Dermatology, Massachusetts General Hospital, sober@partners.org

Photoacoustic Tomography and Melanoma Imaging

Lihong Wang, PhD, Gene K. Beare Distinguished Professor, Department of Biomedical Engineering, Washington University in St. Louis, lhwang@biomed.wustl.edu

Professor Lihong Wang's lab develops photoacoustic imaging technologies for early-cancer detection and functional imaging by physically combining non-ionizing electromagnetic and ultrasonic waves. Unlike ionizing x-ray radiation, non-ionizing electromagnetic waves, such as optical and radio waves, pose no health hazard and, at the same time, reveal new contrast mechanisms. Unfortunately, electromagnetic waves in the non-ionizing spectral region do not penetrate biological tissue in straight paths as x-rays do. Consequently, high-resolution tomography based on non-ionizing electromagnetic waves alone, as demonstrated by confocal microscopy and two-photon microscopy as well as optical coherence tomography, is limited to superficial imaging within about one optical transport mean free path (~1-2 mm) of the surface of biological tissue. Ultrasonic imaging, on the contrary, provides good image resolution but has strong speckle artifacts as well as poor contrast in early-stage tumors. The lab has developed ultrasound-mediated imaging modalities by combining electromagnetic and ultrasonic waves synergistically to overcome the above limitations. The hybrid modalities provide relatively deep penetration at high ultrasonic resolution and yield speckle-free images with high electromagnetic contrast.

In photoacoustic computed tomography, a pulsed broad laser beam illuminates the biological tissue to generate a small but rapid temperature rise, which leads to emission of ultrasonic waves due to thermoelastic expansion. The short-wavelength pulsed ultrasonic waves are then detected by unfocused ultrasonic transducers. High-resolution tomographic images of optical contrast are then formed through image reconstruction. Endogenous optical contrast can be used to quantify the concentration of total hemoglobin, the oxygen saturation of hemoglobin, and the concentration of melanin. Melanoma and other tumors have been imaged in vivo in small animals. Exogenous optical contrast can be used to provide molecular imaging and reporter gene imaging.

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In photoacoustic microscopy, a pulsed laser beam is focused into the biological tissue to generate ultrasonic waves. The ultrasonic waves are then detected with a focused ultrasonic transducer to form a depth resolved 1D image directly. Raster scanning yields 3D high-resolution tomographic images.

Thermoacoustic tomography is similar to photoacoustic tomography except that low-energy microwave pulses, instead of laser pulses, are used. Although long-wavelength microwaves diffract rapidly, the short-wavelength microwave-induced ultrasonic waves provide high spatial resolution. Microwave contrast measures the concentrations of water and ions.

Clinical Imaging of Melanoma

Zeina Tannous, MD, *Attending Dermatologist, Massachusetts General Hospital; Chief of Mohs/Dermatologic Surgery, Boston VA hospitals; Associate Program Director, Dermatopathology, Harvard Dermatology Residency Program, ztannous@partners.org*

Laser Immunotherapy for Melanoma

Mark F. Naylor, MD, *Associate Professor, Department of Dermatology, University of Oklahoma Health Sciences Center, Tulsa Campus; Clinical Associate Professor, Department of Surgery, University of Oklahoma Health Sciences Center; Associate Clinical Member, Arthritis & Immunology, Oklahoma Medical Research Foundation*

Treatment with topical TLR-agonists stimulates immune responses against cutaneous tumors and can be useful as monotherapy for treating skin cancers including melanoma. Phototherapy with either PDT or laser also has significant immunostimulatory properties. Dr. Mark Naylor's lab combined these two techniques to treat cutaneous metastases from melanoma, a therapy termed in situ photoimmunotherapy or ISPI. The lab is currently conducting a phase I trial of ISPI in stage III and IV melanoma with cutaneous metastases. Initial results of this therapy demonstrate an impressive response rate, exceeding 60% complete initial clearance in regional (stage III). Complete clearance has been seen in early stage IV and it is possible that we may see prolonged survival in subjects with complete initial clearance. Further study is needed to replicate and confirm these preliminary results. ISPI therapy has the potential to become the treatment of choice for stage IIIC melanoma (in transit metastases).

Summary:

Photoacoustic Tomography and Melanoma Imaging

Lihong Wang, PhD, Washington University

In diagnosing the stage and severity of melanoma, an important criterion is the depth of tumor penetration. Unfortunately, this information is difficult to glean from most non-invasive imaging data. Optical coherence tomography (OCT) allows clinicians to achieve some depth but struggles to provide resolution beyond 1mm. A new method, called photoacoustic computed tomography (PCT), is being developed to provide resolution deeper than 1mm. PCT involves turning optical energy into sound. When a tissue sample is bombarded with laser pulses, absorption and heating occur, and ultrasonic waves are released in a manner that is dependent on the composition of the tissue. Lihong Wang, of Washington University of St. Louis, has shown that dark-field confocal photoacoustic microscopy can be used to image to a depth of 3 mm.

PCT has several potential applications beyond imaging melanoma tumors. It could be used in patients with other types of cancer, such as breast cancer, to image sentinel lymph nodes, the first lymph nodes to be infiltrated by cancerous cells metastasizing through the lymphatic system. Finally, PCT could be used to image wounds in the process of healing.

PCT is a fundamentally fast imaging technology that uses non-ionizing radiation and involves relatively low costs. It is limited by the number of ultrasonic transducers and by the pulse repetition rate

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of the laser. It may become a valuable diagnostic tool for evaluating melanoma and other types of cancer.

Laser Immunotherapy for Melanoma

Mark F. Naylor, MD, University of Oklahoma

Melanoma is the deadliest form skin cancer. The prognosis of Stage III melanoma (pathologically documented involvement of regional lymph nodes or the presence of in-transit or satellite metastases) and Stage IV melanoma (distant metastases, extension to distant organs) is poor. The FDA-approved therapies for treating unresectable Stage III or Stage IV melanoma are high-dose interleukin therapy (IL-2), which offers an 18 % response rate (defined as tumor shrinkage greater than or equal to 50%) and a 6% cure rate; and dacarbazine (DTIC), which offers a 25-30% response rate and a cure rate of less than one percent. DTIC is essentially a palliative therapy that shrinks the tumor temporarily. *In situ* photoimmunotherapy (ISPI) for advanced melanoma combines an immunostimulating drug (imiquimod) with laser therapy based on the concept that intense, local immunostimulation will create a local response, then a regional response, followed by a systemic immune response capable of killing tumors throughout the body. ISPI involves a 6-week treatment cycle beginning with 2 weeks of topical immunostimulation with imiquimod followed by infrared laser killing of cutaneous metastases at week 2 and week 4 while continuing topical imiquimod for the entire 6 weeks.

Mark Naylor's group at the University of Oklahoma used ISPI to treat eleven patients with advanced melanoma, and they obtained the following results:

- Complete response
 - 3 Stage III
 - 1 Stage IV patient
- Useful palliative response (50% reduction in cutaneous tumor load)
 - 2 Stage III
 - 2 Stage IV patients
- No useful response
 - 3 Stage IV patients.

Local pain beyond that relieved by as-needed oral codeine occurred in approximately 20% of patients, and nausea occurred in approximately one third of patients.

In summary, ISPI demonstrates a high complete local response rate making it an excellent palliative treatment; the cure rate is currently unknown, but could exceed the cure rate of high-dose interleukin therapy. Dr. Naylor predicts that over the next five or ten years, ISPI will become the treatment of choice for surgically unresectable cutaneous Stage III melanomas.