

Optical molecular imaging for early detection of cancer

Abstract: We describe a comprehensive strategy to develop inexpensive, rugged and portable optical imaging systems for molecular imaging of cancer, which couples the development of optically active contrast agents with advances in functional genomics of cancer.

Progress toward a molecular characterization of cancer would have important clinical benefits, including (1) detecting cancer earlier based on molecular characterization, (2) predicting the risk of precancerous lesion progression, (3) detecting margins in the operating room in real time, (4) selecting molecular therapy rationally and (5) monitoring response to therapy in real time at a molecular level. While molecular markers can be visualized in vitro using complex immunohistochemical staining protocols, there is an important need to image the molecular features of cancer in vivo. Imaging the molecular features of cancer requires molecular-specific contrast agents which can safely be used in vivo as well as cost-effective imaging systems to rapidly and non-invasively image the uptake, distribution and binding of these agents in vivo.

Here we describe the general approach our group has taken to solve this problem and describe initial results obtained using optically active contrast agents to image the expression of three well known molecular signatures of neoplasia: including over expression of the epidermal growth factor receptor (EGFR), matrix metallo-proteases (MMPs), and oncoproteins associated with human papillomavirus (HPV) infection. This same approach can be used to develop contrast agents to image the expression of promising new biomarkers. For example, SAGE libraries can be used to identify novel targets for contrast agent development from the pool of genes differentially expressed in early neoplasia. Alternatively, in vivo phage display can be used to identify peptides that specifically bind to the surface of neoplastic cells and tumor vascular endothelium in target organ sites. Discovering new biomarkers and developing techniques to image their expression in vivo could be particularly useful for monitoring response to therapy.

At the same time, we are developing inexpensive, portable optical systems to image the morphologic and molecular signatures of neoplasia noninvasively in real time. We are developing systems to image both reflected light and fluorescent light at two spatial scales: (1) confocal microscopy, with micron resolution to image cell morphology from a small field of view and (2) multi-spectral digital imaging with mm resolution to image tissue morphology from large fields of view. These systems can assess both native optical contrast as well as that afforded by optically active contrast agents. These real-time, portable, inexpensive systems can provide tools to characterize the molecular features of cancer in vivo.

Our contrast agents consist of three parts: (1) a probe molecule which provides molecular specific recognition of cancer biomarkers conjugated to (2) an optically interrogatable label in (3) a mucoadhesive, permeation enhancing formulation. In our work, we are testing three different types of optically active labels, including metal nanoparticles, quantum dots and organic fluorescent dyes. We are pursuing two types of molecular probes: monoclonal antibodies against cancer specific biomarkers and peptides which bind selectively to cancer specific biomarkers. With this approach, we can significantly expand the number of molecular changes that can be probed using optical imaging. In this paper, we describe contrast agents based on metal nanoparticles, organic fluorescent dyes and quantum dots coupled to monoclonal antibodies against cancer related biomarkers.

BIOGRAPHY:

Rebecca Richards-Kortum holds the Cockrell Family Chair in Engineering #10 and is a Professor of Biomedical Engineering at the University of Texas at Austin. She is the Associate Chair for Research of the Biomedical Engineering Department at The University of Texas at Austin where she is also a Distinguished Teaching Professor. After receiving a B.S. in Physics and Mathematics from the University of Nebraska-Lincoln in 1985, she continued her graduate work at the Massachusetts Institute of Technology, where she received an MS in Physics in 1987 and a PhD in Medical Physics in 1990. That same year, she began her academic career at The University of Texas in the Electrical and Computer Engineering Department as an Assistant Professor, (1990), Associate Professor (1995) and Professor (1999). She joined the Department of Biomedical Engineering at UT Austin when it formed in 2001.

In addition to being named a Howard Hughes Medical Institute Professor in 2002, her awards include, Presidential Young Investigator, National Science Foundation (1991), Presidential Faculty Fellow, National Science Foundation (1992); Becton Dickinson Career Achievement Award, Association for the Advancement of Medical Instrumentation (1992); Outstanding Engineering Teaching by an Assistant Professor Award, College of Engineering, The University of Texas at Austin (1994); Y.C. Fung Young Investigator Award, Bioengineering Division, American Society of Mechanical Engineers (1999). In 2001, she was elected to the Academy of Distinguished Teachers at The University of Texas at Austin and received the Chancellor's Council Outstanding Teaching Award for 2002. She also currently serves on the National Advisory Council for Biomedical Imaging and Bioengineering for the National Institutes of Health and directs an Integrative Graduate Education and Research Training Grant in Optical Biomolecular Engineer, funded by the National Science Foundation.

Dr. Richards-Kortum's research group is developing miniature microscopes and spectrometers to enable early detection of precancerous changes in living tissue. Her research group is currently developing fluorescence-based techniques for the diagnosis of cervical pre-cancer *in vivo*, and in collaboration with Dr. Michele Follen has carried out clinical trials of this technique involving over 1,500 patients at the University of Texas MD Anderson Cancer Center. In collaboration with Dr. Michael Descour at the University of Arizona, her group is developing miniature confocal microscopes to visualize the microscopic changes which accompany precancer. In collaboration with Dr. Konstantin Sokolov at the University of Texas MD Anderson Cancer Center, her group is developing contrast agents for *in vivo* molecular imaging of changes associated with precancer including expression of epidermal growth factor receptors. Also under study are spectroscopic techniques for improving and automating screening for precancer of the oral cavity in collaboration with Dr. Ann Gillenwater.

Rebecca is married and has three sons, Alexander, Maxwell and Zachary and one daughter, Katie.