PROPOSED NCRC IMAGING INSTITUTE

EXECUTIVE SUMMARY

Rationale & Impact (Why NCRC)

Molecular, functional and structural imaging span all clinical areas. They are key technologies that enable health sciences research and advance clinical care. Currently basic and translational research involving the imaging sciences occurs across the University of Michigan campuses. These diverse research programs could significantly benefit from a centralized Imaging Institute which would provide an opportunity to co-locate investigators to NCRC and serve as a centralized administrative entity for assisting the larger imaging community. The Imaging Institute will stimulate new interdisciplinary collaborations within the Institute, throughout the University, and beyond with other international institutions thus having a global impact. The Imaging Institute will provide a Phase I clinical translational facility to support externally-sponsored drug trials, as well as provide the infrastructure for rapid development and clinical testing of new technologies conceived within the NCRC. The Institute will leverage NCRC resources in technology transfer and business incubation to commercialize the next-generation technologies developed within the Institute. The Imaging Institute will also provide seminars, symposia and education/training of students, postdoctoral fellows and visiting scientists. In addition, the Imaging Institute will provide a Service Center of imaging equipment and expertise which will span all programs located at the NCRC. The net impact of the Imaging Institute will provide a centralized structure and resources to optimize the interactions of basic and clinical scientists to make new discoveries and solve significant problems in biology and medicine. Overall, this Institute will be unparalleled in scope and integration and provide the framework and vision for other institutions to follow.

Faculty and P.I.'s

Based on a survey of faculty involved in imaging research, the Imaging Committee have identified approximately 50 Principal Investigators who would be interested in co-locating at the NCRC. The breakdown of these individuals is as follows:

(1) Center for Molecular Imaging (School of Medicine): 20 PI's
(2) Neuro fMRI lab (College of Engineering): 10 PI's
(3) Other independent key investigators wherein imaging is a focus of their research: 20 PI's

It is envisioned that the institute, upon establishment, would double in size over a period of five years through the development of research projects as well as additional funding obtained due to synergistic interactions. As an example, a key shortcoming identified by the committee was the lack of a radioisotope production facility dedicated to imaging research. A need for a dedicated cyclotron and radio-chemistry laboratories has been echoed by clinical and basic research faculty. This capability is critical for the long term success of the Imaging Institute and we believe would entail recruitment of approximately 5 PI's and 10 staff with expertise in developing radiotracers for imaging of molecular events specific for disease processes.

In summary, the five-year projection of the Imaging Institute will constitute 100 PIs each with a staff of 5, thus totaling 600 individuals.

Equipment & Space

Small Animal Imaging Resource Facility:

Based on the current small animal facility, this resource is anticipated to require **8,000 sq. ft**.

(1) Two Small Bore MRI systems
(2) PET/CT
(3) SPECT/CT
(4) Bioluminescence Imaging (3 systems)
(5) Intravital microscopy
(6) Fluorescence Imaging/endoscopic imaging
(7) High Frequency Ultrasound

Clinical Imaging and Interventional Suites:

This resource is anticipated to require **13,000 sq. ft**.

(1) Clinical PET/MRI and PET/CT
(2) Clinical 3T interventional MRI and High Intensity Focused Ultrasound (HIFU)
(3) High Field 7T MRI
(4) Digital Image Processing Facility
(5) PACS systems
(6) Optical Imaging
(7) Ultrasound
(8) Two 3T systems for neuro-fMRI studies
(9) EEG and MEG labs
(10) SPECT/CT
(11) Biplane fluoroscopy

Radiochemistry Facility:

This resource is anticipated to require **7,000 sq. ft**.

(1) Cyclotron
(2) Hot chemistry lab (GLP certified)
(3) Cold chemistry lab

Lab Space for PI's:

As outlined above, the institute is currently 50 PI's with 50 more to be recruited over five years. Estimating 1,000 sq.ft/PI, this would require **100,000 sq. ft**.

Total Space Requirements:

Equipment space (28,000 sq ft) + Lab Space (100,000 sq. ft.) = **128,000 sq. ft**.

PROPOSED IMAGING INSTITUTE

AT THE NORTH CAMPUS RESEARCH COMPLEX (NCRC)

Vision Statement

Imaging crosses all boundaries of medical and biological sciences, and imaging techniques are vital to medical research. New imaging technologies will undoubtedly impact future medical advances. In particular, molecular and functional imaging are technologies which are key enabling technologies essential for nearly all clinical areas of health sciences research and for advancing clinical care. The UM Imaging Institute will be unparalleled by peer institutions as it will provide the unification of multidisciplinary teams to allow translation and improvement of human health on an unprecedented scale.

Overview

It is vital for the University of Michigan to form an Imaging Institute in order to become the top translational research institution in the world. The Imaging Institute will be a "game changer" without peer. It will integrate basic and applied imaging research and provide cutting-edge services to other researchers.

A key differentiating factor for the NCRC Imaging Institute will be its interwoven nature within all aspects of life sciences research activities at Michigan, from basic biology and engineering through clinical translation and subsequent commercialization. Imaging will be integrated with basic cellular and molecular biology research activities at an unprecedented level. This approach will allow the study of complex interacting biological processes within the intact milieu of cells, whole animals and ultimately patients which will reveal unexplored and exciting new discoveries that will directly impact our understanding and treatment of human diseases. Interweaving imaging within biological research has not been attempted by our peer institutions to this degree. This strategic advance will provide investigators at the University of Michigan with a unique perspective from which to interrogate a wide variety of biological processes in numerous human diseases through an integrated systems approach.

Another key component of the Imaging Institute will be to integrate instrumentation and software development with pre-clinical and clinical translational activities of the institution. An additional game-changing feature of the Institute will be the establishment of a Phase 0/1 clinical trials research imaging facility within Michigan Institute of Clinical Health Research (MICHR). Integration of instrumentation and software development with pre-clinical and clinical imaging will provide key opportunities to seamlessly and rapidly move new discoveries from the bench to the bedside and back again.

The following summarizes our vision of a highly integrated Imaging Institute with a special focus on translational research.

Background

Molecular Imaging has been identified by the National Institutes of Health as a key component of its overall roadmap. Funding through the NCI has provided the initial push which has lead to

the establishment of small animal imaging resources as well as Molecular Imaging Centers of Excellence, both of which are funded at Michigan.

The Imaging Institute will provide the centralized infrastructure needed to integrate imaging within clinical research ranging from drug discovery to translation into clinical applications. In concept, the Institute will include and broaden the NIH mandate in the following ways:

- Identification, characterization and validation of new molecular targets in cell based assays using molecular imaging reporters.
- Development of new drugs and imaging probes that hit these targets.
- Development of new imaging modalities and image-guided intervention methodologies
- Evaluate these new drugs, imaging agents and technologies in clinical trials. These range from the development of imaging biomarkers in cancer to the use of functional imaging in the neurosciences and interventional procedures in cardiovascular biology.

The University of Michigan is already one of the leading institutions in the world in many of the above areas. The development of the Imaging Institute affords us an unparalleled opportunity to leverage our existing strengths for the development of a pre-eminent translational program to significantly impact clinical care.

Imaging Research at the University of Michigan

The University of Michigan is a top-tier institution with respect to imaging. The Michigan Small Animal Imaging Resource (MSAIR) was formally established in 1998 through an R24 NIH funded grant. The MSAIR facilitates imaging research throughout the University with over 60 investigators and 200 users resulting in the contribution of infrastructure for Federal funding in the range of $10MM's annually. The Center for Molecular Imaging was established by funding received from the NIH in 1999. The Center is a matrix organization with members representing different department and schools across campus. In addition, there are several other Center grants using the MSAIR along with funded PO1 grants. Furthermore, the Engineering Campus based neuro fMRI facility has been operational for over 5 years and supports investigators from over 20 funded NIH grants. There also multiple distinct training grants related to imaging.

U-M imaging investigators have made numerous basic discoveries over the past decade and have initiated many clinical trials investigating the utility of imaging to diagnose or monitor treatment of diseases. The creation of an Imaging Institute at the NCRC represents a unique opportunity to more fully develop and integrate imaging across campus and with other proposed NCRC habitants.

The Imaging Institute at the NCRC

A mission of the Imaging Institute at the NCRC will be to enable, through the development of imaging probes and technological advances, the early detection of molecular events that precede symptomatic expression of a disease process. In addition, imaging probes and technological advances will also be developed to enable early biomarkers of therapeutic intervention.

In the area of development for early detection of markers in the areas of cancer, neuroscience, cardiovascular, inflammatory and metabolic diseases, the existing leadership of investigators at the University of Michigan is well recognized. Despite this, translation of these novel

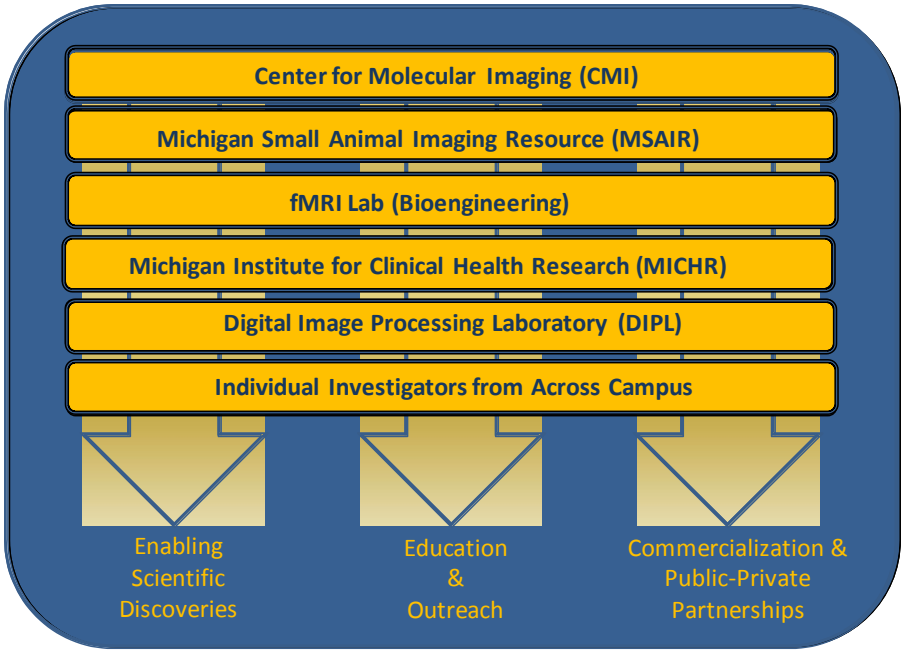
discoveries into clinical impact has been substantially slower than should be possible. For example, the discovery of gene fusions in prostate cancer at Michigan was paradigm shifting, yet an imaging probe for the detection of these fusions non-invasively does not exist. Through the formation of the Imaging Institute, a concerted effort of biologists, clinical scientists, radio and medicinal chemists and imaging scientists, it is clear that a diagnostic test could be developed that would revolutionize the diagnosis and treatment of prostate cancer. While this is just one example, the Imaging Institute is anticipated to provide the infrastructure enabling many other significant advances.

To be able to undertake these endeavors, the Imaging Institute will include researchers whose expertise involves the development of imaging probes targeted to a specific molecule or molecular event. These probes include existing and synthesis of new small molecules, immunological reagents (antibodies). U-M strengths in instrumentation and computation will be leveraged within the Imaging Institute to provide a unique synergy with the biological imaging applications.

In addition, these basic scientists will need to closely interact with clinical research colleagues. Such close links will give U-M a competitive advantage vis-à-vis peer universities. These links will be forged by the existence of a properly scaled Phase 0/1 clinical facility on the NCRC campus.

Components of the Imaging Institute

The organizations depicted in the graphic below are enthusiastic about participating in the Imaging Institute, as are many individual investigators across campus. This diagram represents both the significant primary and support functions imaging will play in the NCRC. The Imaging Institute interacts with all areas at all levels of development. Over 50 Imaging Investigators have been identified within the schools of Engineering, LS&A, Pharmacy, Public Health and the Medical School. Co-location of many of these scientists and clinicians with common interests would significantly impact basic and clinical advances in medicine.



1. Cell and Molecular Biology

An area of focus will involve the development of an Imaging Agent Discovery Program for identification of novel small molecules that target specific cellular signaling pathways using high throughput screening in an effort to develop new diagnostic imaging agents. This will involve the use of cell-based molecular imaging platforms developed over the last decade in the Center for Molecular Imaging (CMI) to identify novel chemical entities using natural and synthetic libraries. Large libraries of chemicals will be tested using molecular imaging reporter assays for their ability to modify the target. The identified "hits" will be investigated as potential diagnostic imaging agents by evaluating their selectivity using additional screening runs to identify if the "hits" against the chosen target will interfere with other related targets is a process termed cross-screening. Cross-screening is important, because the more unrelated targets a compound hits, the more likely that off-target toxicity will occur with that compound once it reaches the clinic.

Another area of focus will be the creation of an Imaging Agent Development Program using lead candidates identified in the Discovery Program for potential imaging and therapeutic agents. The use of structure-activity relationships (SAR) for improving certain features of the lead compound will be employed to increase activity against the chosen target, reduce activity against unrelated targets and to improve the "drug-like" or ADME (an acronym in pharmacokinetics and pharmacology for absorption, distribution, metabolism, and excretion, and describes the disposition of a pharmaceutical compound within an organism) properties of the molecule. This process requires iterative screening runs in an effort to improve the properties of the new molecular entities to select favored compounds for further advancement into *in vitro* and *in vivo* testing for activity in the disease model of choice. This process will involve the use of medicinal chemistry to develop clinically viable derivatives (minimal toxicity, maximal efficacy and optimal pharmacodynamics) of the compound hits identified in the Discovery Program. Molecular imaging technologies will significantly streamline this process of "lead optimization".

2. Pre-clinical and Clinical Imaging Infrastructure

The infrastructure of the Imaging Institute will include two key areas of activities. The first will be the creation and development of new imaging techniques and their application to biomedical problems. Interaction between imaging scientists (instrumentation /computation/application) and the broad scientific community working at the NCRC will be an ideal environment to spawn such developments. The most promising of these ideas will be supported through internal funding and will require tech transfer support for intellectual property protection. The Institute will provide a diverse, blue ribbon review panel to identify the most promising of these applications, and will aid investigators in "getting the work off the ground".

A second role for this infrastructure will be to function as a core service. The Imaging Core will function very similarly to MSAIR, but will also have human imaging capabilities. The Imaging Core will be equipped with a broad range of state-of-the-art commercially developed imaging equipment that can be applied toward investigator initiated projects in the NCRC. The MICHR clinical research Imaging Core will include at a minimum a CT scanner, a PET/CT and PET/MR systems, a 3T MRI, ultrasound scanners, cyclotron for radioisotope production, biplane fluoroscopy, and optical imaging capabilities for hollow organ imaging. A dedicated high-field (7T or higher) human imaging magnet should also be considered. Animal Imaging Core capabilities will include high-frequency animal ultrasound scanners, a PET/CT scanner, optical

imaging (fluorescent and bioluminescent), x-ray and fluoroscopic units, high-field MRI systems, animal operating suites with x-ray and ultrasound imaging, and contrast agent infusion equipment. Certain identified members of the Imaging Institute will have their primary assignment to the core and will provide operating support for these devices and consultation on their optimal usage.

The vision for this infrastructure will be that it will be the hub of the NCRC as these are enabling technologies that will facilitate cross-fertilization of ideas and the application of imaging technologies to solve problems in the fields of neuroscience, cardiovascular, metabolic, inflammation and cancer diseases.

3. Engineering and Imaging Sciences

New device/detector engineering, modeling of image data acquisition, reconstruction, and manipulation, and their implementation are the foundations of the Imaging Sciences. Strong and continued effort and investment in these fundamental aspects of imaging is the key to ensuring future advancement and innovation. The Imaging Institute will provide members an integrated environment that facilitates closer collaborations between basic scientists and clinical researchers. Such closer interaction will serve as the core force to stimulate new opportunities beyond the conventional mode of technology development. This is a unique opportunity for us to establish a world-class biomedical imaging center and to greatly enhance the pace of basic research, interdisciplinary endeavors, and clinical translation of emerging technologies.

4. Clinical Trials (Diagnostic, Therapeutic and Interventional)

Treatment of patients is currently based primarily upon results obtained from large clinical trials. The vision for the clinical trials program within the Imaging Institute will be to make personalized medicine a reality. Imaging will allow for early detection of disease as well as the early response of a patient to a therapeutic intervention, thus transforming the practice of medicine by capitalizing on the ability to individualize patient care. This will significantly impact the effectiveness and cost of treatments. The proposed Clinical Trials Program will have a tremendous impact on the University of Michigan as it will be used in support of large-scale clinical and research grants as well as recruitment of top-tier scientific talent. It is also anticipated that the program within the Imaging Institute will play an integral role in attracting industry and pharmaceutical-sponsored clinical trials to Michigan.

Imaging for Clinical Trials is currently a relatively small component intertwined within the large volume of imaging procedures performed throughout the UMHS system. Despite the economy of shared resources within UMHS facilities, imaging of clinical trial subjects demands unique considerations that are not conducive to a hospital environment geared for high diagnostic throughput of a large number of patients fed through an assortment of scanners and imaging modalities. Often “diagnosis” is not even the objective of imaging in clinical trials since the disease and its staging have already been determined prior to trial enrollment. The clear trajectory for imaging in clinical trials transcends subjective interpretation of anatomical/lesion size and shape features. Clinical trial imaging of the future must provide objective assessment of physiologic and functional status of tissue/lesions derived from image-based observables. Beyond this, there is compelling need for imaging to become an active element in trials by way of patient-specific image-guided customization of minimally-invasive interventions. These capabilities are not deliverable as simple options even on state-of-the-art imaging systems since

most of the technology resides in the skill of imaging scientists to create and exploit the linkage from biology to image. Outside of a few isolated labs, this level of expertise does not exist at UM or peer institutions in a centralized form.

Creation of the Imaging Institute at the NCRC with the specific charge to develop and provide MICHR integrated Phase 0/1 clinical trial imaging and image-guided intervention facilities would be a highly innovative, tangible component along the continuum of translational science. Physical design of the Imaging Institute within the NCRC must facilitate exposure and interaction of NCRC members with the full imaging spectrum from cell-based imaging assays, through in vivo pre-clinical and human imaging, to finally the conceptualization and engineering of entirely new imaging systems. A key function of "clinical imaging" component of the Imaging Institute would be to provide access to specialists with expertise in both biological and technological imaging spheres for their input through all phases of study design, protocol development and integration into clinical studies, and finally implementation on high-end clinical-grade imaging systems maintained for high scientific standards of quality control. The clinical facility must have a large enough capacity and be appropriately located to enable successful translational efforts.

5. Pipeline for Commercialization

An enhanced pipeline for commercialization is critical to the University becoming the top translational research institution in the world. A goal of the proposed Commercialization Program within the Imaging Institute will be to provide continuity from scientific concept through commercial development. In addition, enabling communication among clinicians, basic researchers, and technology developers by virtue of co-location and interactive events will provide for a culture of innovation. Commercialization activities will help to draw-in resources that span the development gap to take advantage of and contribute to the growing entrepreneurial culture in the NCRC, the University Research Corridor, and Michigan. To assist with technology development and spin-off creation, we propose the creation of a "Start-up Factory" at the NCRC. Assistance to academic entrepreneurs will be provided and include development of standard operating procedures (SOPs), processes, and a culture cognizant of regulatory (e.g. FDA) issues. Moreover, these procedures and processes are often similar among companies. Prepackaged SOPs and training could be licensed to the spin-off along with the technology. In turn, the University may command a larger equity stake in a spin-off company as it would provide the spin-off a significant competitive advantage over those formed in less organized environments. The Institute will leverage these resources when they are available at NCRC or the greater University environment, and will develop them when they are not available.

The Imaging Institute will also provide criteria for investigators involved in technology development to advance academically in the university system. Different criteria will be used to assess advancement from the standard instructional track promotions. Investigators will advance through a system that recognizes teaching, non-first author publications, funded extramural grants for which an individual is recognized as a resource, patents received, and start-up companies founded could all contribute to evidence of achievement in this track. Academic ranks would be commensurate to other tracks with all of the rights and privileges assigned therein.

6. Public-Private Partnerships

Imaging naturally lends itself to public-private partnerships. Complexities such as large ticket instrumentation, need for large patient volumes and the needed regulatory and specialized clinical expertise make the Imaging Institute an ideal environment for public-private partnerships. These partnerships may be focused on the development and testing of new instrumentation (e.g. current relationship with Philips Medical for the development of a clinical PET/MRI instrument), software (e.g. current relationship with Varian Medical Systems), probe development (e.g. current relationship with Olympus Optical), and clinical trials of novel imaging techniques and agents (e.g. current relationship with GE Medical).

These partnerships not only provide our faculty access to state of the art imaging methods and instruments, they also positively impact the funding of investigator initiated grants.

7. Education

An educational component is essential for the Imaging Institute to have maximum impact. Medical imaging is an inherently multi-disciplinary research field with growing emphasis on multi-modality technique (PET-CT, PET-MRI, photo-acoustic imaging, etc.). To best prepare trainees (graduate students and postdoctoral scholars) for their future, they should be exposed to a range of modalities and should be made aware of the entire imaging chain from the molecular contrast agents through the imaging systems and the clinical applications. Although there are numerous examples of graduate students working jointly with researchers in different divisions, e.g., with one mentor in Engineering and another in Radiology, there is considerable "silo-ization" of research and training today. An Imaging Institute would provide the umbrella for seminar series, focused workshops, informal information exchange, etc. The publicity and web presence associated with a vibrant Imaging Institute would also help attract first-rate trainees. The ability to obtain training grants (NIH T32 etc.) would be significantly enhanced by the synergies of an Imaging Institute.

U-M has numerous experts in imaging who would be first-class resources for an imaging science curriculum. However, many of these are in research positions with funding models that discourage educational efforts. The Biomedical Engineering graduate program offers a concentration in biomedical imaging, and the Electrical Engineering Systems graduate program offers a minor in biosystems, and the Nuclear Engineering and Radiological Sciences graduate program also offers a radiological sciences option. These programs are all heavily engineering based and the broader context of imaging at the molecular level and of the clinical aspects are not emphasized. Forming connections with an Imaging Institute potentially could strengthen these programs.

Education is a life-long process and in addition to the benefits to trainees, the investigators associated with the Imaging Institute will benefit from interactions with a broad spectrum of experts in other aspects of imaging. Although there are many successful examples of clinical scientists collaborating with engineers and basic scientists, many of these interactions have occurred by chance. An Imaging Institute would provide forums for spawning such collaborations.

8. International Activities and Relationships

The formation of an Imaging Institute will provide Michigan with an excellent opportunity to establish new international collaborations and to better capitalize on existing international relationships. As an example, the committees proposal that the Imaging Institute consider

acquisition of a high-field MRI system, could be enhanced by extending an existing close collaboration with Neurospin (a world leader in high field MRI technologies based in France). Collaborations of this nature would dramatically decrease the time required for adaptation of new technologies. These relationships will also enable cross-fertilization of ideas, recruitment of trainees and resources.

NCRC and Cross-Campus Collaborations and Synergies

Imaging will be an enabling technology for most of the activities that have been proposed for NCRC. For example, imaging and drug development studies are being conducted across the campuses including the Medical School, School of Pharmacy, School of Public Health, LS&A (i.e. Departments of Chemistry, Psychology and Biology). Establishment of an Imaging Institute will facilitate these efforts by providing a unique infrastructure for facilitating the needs of individual investigators and programs requiring the use of imaging in small animal evaluation but also in translational Phase 0/1 clinical trials. The broad impact of this effort will include for example neurosciences, metabolic diseases, cancer, cardiovascular and inflammatory diseases.

Metrics for Success

The co-location of these accomplished investigators and their programs at the NCRC will enable complementary research and tremendous synergies with the potential to dramatically hasten the pace of discovery. The primary objectives of the Imaging Program at the NCRC are to develop new diagnostic and therapeutic agents and methods to improve outcomes for patients. A clear focus on this translational research goal leads to the following specific metrics that will define our success:

- Development of therapeutics and diagnostics proven to improve patient outcomes.
- Funding of large multi-investigator grants such as program project grants and center grants.
- Successful performance of high-quality, high-impact clinical trials in the Phase I unit and throughout the statewide Phase I Network.
- Technological innovations that lead to intellectual property and economic development in Michigan.

APPENDIX: Imaging Committee

CO-CHAIRS	
Jeffrey Fessler	College of Engineering, Electrical Engineering and Computer Science
Brian Ross	Medical School, Radiology
Jonathan Rubin	Medical School, Radiology
MEMBERS	
Maria Ceo	Medical School, Radiology CDA
Thomas Chenevert	Medical School, Radiology
Neal Clinthorne	Medical School, Radiology
Cheri Deng	College of Engineering, Biomedical Engineering
Mark Kaminski	Medical School, Medical Oncology
MaryAnn Mycek	College of Engineering, Biomedical Engineering
Alnawaz Rehemtulla	Medical School, Radiation Oncology
Thomas Wang	Medical School, Internal Medicine
Rick Weitzel	Medical School, Internal Medicine