

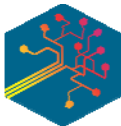
Roadmap for Bioengineering and Imaging Research 2008 BIROW 5 Preliminary Report

BIROW Preliminary Analysis by attendees:

<u>Imaging of Single Cells</u>	BIROW Consensus Score: <u>189</u>
<u>Imaging of Engineered Tissues</u>	BIROW Consensus Score: <u>160</u>
<u>Imaging of Tissues in situ</u>	BIROW Consensus Score: <u>146</u>
<u>Imaging for Targeted Rx Delivery</u>	BIROW Consensus Score: <u>154</u>

Scoring System: 100-Outstanding to 500-No Use

The **BIROW Final Report** will reflect consensus analysis of biomedical imaging research topics using the scientific input of more than 25 scientific and educational societies with more than 100 years of successful scientific and clinical collaboration that elevated the practice of biomedical imaging in medicine to the position of central importance that it occupies today. The final BIROW 5 report will be published as a white paper in one of the three collaborating journals, **Medical Physics, Radiology or Annals of Bioengineering**, with brief summaries in the other two with reference to the primary paper.



BIROW 5 Roadmap for Bioengineering and Imaging Research BIROW Consensus

Consensus Building Process

The BIROW consensus analysis of bioengineering and biomedical imaging research topics uses the scientific input of more than 25 scientific and educational societies with more than 100 years of successful scientific and clinical collaboration. **Four specific aims** of the NIH roadmap are addressed by answering four questions of how the topic:

- A1. deepens the understanding of fundamental biology,
- A2. stimulates multidisciplinary teams,
- A3. reshapes clinical research to accelerate medical discovery and
- A4. improves people's health?

The analysis also addresses **four primary challenges** by answering four additional questions of what are:

- C1. the key scientific challenges,
- C2. the primary obstacles,
- C3. the critical technologies lacking and
- C4. the impediments to translation of discovery for improved health?

Topic 1: Heterogeneous Single Cell Measurements and Their Integration into Tissue and Organism Models

BIROW Score: Mean 189 with 48 votes

Abstract: Many technologies for assessing organisms in vivo, such as conventional imaging methods, provide information that is aggregated over a volume of tissue, averaging the behavior of a very large number of cells. New technologies are providing unprecedented abilities to target and probe the detailed functions of individual cells in vivo. This presents a new type of challenge, in connecting such information to the function and health of the organism as a whole. This session focused on various approaches to this challenge.

Specific Aims:

A1. Single cell measurements deepen understanding of fundamental biology?

- To understand population need to know what individuals are doing
- Image-based screens rely on single cell measurements
- Direct building of model from images allows enhanced understanding of experiment and permits design of experiments to test model
- Deepens understanding of relationships between cells which are fundamental

A2. Single cell measurements promote collaboration of multidisciplinary teams?

- All participants in the session were part of multidisciplinary teams
- Imaging, image analysis and modeling require expertise from biology, chemistry, optics, electrical engineering, computer science, statistics, mathematics
- Probably among the fields where level of interdisciplinary collaboration is among the very highest
- Also need for interdisciplinary training

A3. Single cell measurements reshape clinical research and promote discovery?

- Progress from basic to translational to clinical
- Fluorescence-based endoscopy blocked by failure to understand basic biology behind measurements
- Cells can be used as tool to develop methods applicable to larger systems
- Look at organism in more comprehensive way – better understanding of physiology
- Measurement of single cell or small group of cells can provide better diagnostics (e.g., field effect work of Backman)
- Measurement of lymphoid subpopulations critical for understanding diseases involving immune cells (AIDS, leukemias, lymphomas)
- Single cell characterization will be critical to tissue engineering, which will have clear clinical goal

- Single cell measurements combined into models of tissue capture more complex phenotypes than can be measured by measurements at higher levels
- Rare cell detection (e.g., detection of malaria-infected cells) inherently requires single cell measurements
- Considering single cells dramatically increases sensitivity of diagnosis
- Can use single cell measurements to prune tests
- Can discover new phenotypes during screens intended for other purposes
- Precedent in analysis of breast biopsies by cellular assays to influence choice of therapy – changed clinical practice
- Multiscale modeling needs to include single cell measurements - eventual personalized models

A4. *Single cell measurements improve people's health?*

- Already has
 - FACS revolutionized treatment of AIDS
 - Differential blood count most common test
- Single cell measurements key to personalized medicine
- Simpler, less invasive tests can change patient and screening compliance (e.g., blood oxygenation monitoring)
- Potential for drug discovery through high-content screening
- Better understanding of cellular responses enables more complex drug screens than currently used in high-content screening - can improve drug screening
- Single cell measurements and models can enable better use of off-patent drugs (important for developing countries)
- Methods for rapid, automated learning of customized models from image data will enable personalized diagnosis and monitoring

Primary Challenges:

C1. *What are the key scientific challenges to single cell measurements?*

- Improved methods for single cell segmentation methods major challenge especially in tissues
- Tools for generalizing morphologic/pattern characterization across cells and cell types
- Improving methods for imaging itself and 3D reconstruction
- Building atlas of protein localization across tissues and disease states
- Validation of measurement technologies to enable generalization to physiology of cell
- Understanding limitations of measurements

C2. *What are the primary obstacles to development of single cell measurements?*

- Insufficient resources/mechanisms for image sharing and annotating
- Limited availability of large scale annotated image collections for training machine learning systems

- Limited availability of image analysis details in publications to permit reproduction and reuse of previous work
- Limited availability of state-of-the-art imaging instrumentation
- Limited supply of interdisciplinary scientists
- Limited availability of sufficient computational power for simulations bridging scales

C3. What are the critical technologies lacking for single cell measurements?

- Better labeling and sampling methods
- Better label-free imaging methods
- Better standardization of measurements
- Methods for active learning in hierarchical systems

C4. What are the impediments to translating single cell measurements to improved health?

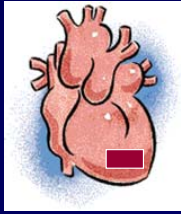
- Difficulty of linking single cell measurements to higher scale measurements
- Difficulty of tracking cells in in vivo environment
- Difficulty of predicting organ or organism-level behavior from single-cell drug screens
- Limited availability of in vivo biosensors

Topic 2. Functional Molecular and Structural Imaging of Engineered Tissue in vitro and in vivo

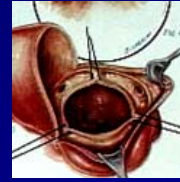
BIROW Score: Mean 160 with 47 votes

Abstract: The goal of this topic was to identify imaging needs and methods for non-invasive, fast, and accurate assessment of cell growth, differentiation, and tissue development, including matrix development, in engineered tissues. The talks covered two main topics: (1) Molecular imaging in vivo, including non-invasive tracking and assessment of the fate of implanted cells and 3-dimensional (3D) engineered constructs; and (2) Structural and functional imaging of 3D engineered tissue constructs in vitro. These topics encompass broad range of imaging modalities such as magnetic resonance imaging, micro PET, optical coherence tomography, multi-photon microscopy, as well as multi-modality imaging methods. The talks and discussion were designed to facilitate interaction between researchers in the field of tissue engineering and those in the various imaging fields that could benefit tissue engineering. The challenges and opportunities for applying advances in imaging technologies to tissue engineering to advance the field of regenerative medicine were discussed.

Clinical Application Areas for Engineered Tissues



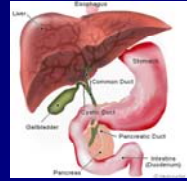
Myocardial Patch



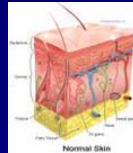
Heart Valve



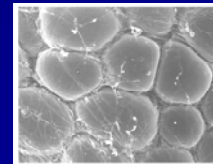
Skeletal Muscle



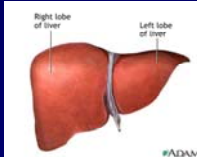
Pancreas



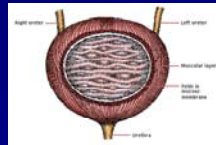
Skin



Adipose Tissue



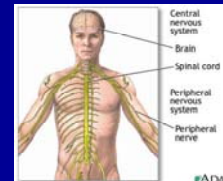
Liver



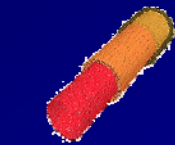
Bladder



Cartilage and Bone



Nerves



Vascular Graft

Specific Aims:

A1. *Imaging of engineered tissues deepens understanding of fundamental biology?*

- It is well known that 2D tissue culture systems are artificial and that the cell phenotype in these systems is altered compared to their phenotype in a 3D in vivo environment.
- In vitro 3D engineered tissue model systems capture much of the relevant complexity of tissues in vivo that traditional 2D cultures do not. As such, they represent a very important research tool for cell biologists to study cell behavior and cell/cell, cell/ matrix, and cell/medium interactions.
- 3D engineered tissue models provide new possibilities for the study of complex physiological and pathophysiological processes in a controlled environment.
- Imaging of engineered constructs aids in understanding porosity of tissues and cell growth patterns.
- Studying the both the success and failure of implanted engineered tissue aids in our understanding of fundamental biological and physiological processes.

A2. *Imaging of engineered tissues promotes collaboration of multidisciplinary teams?*

- Tissue engineering is the definition of multidisciplinary team research. Biology, engineering and medicine have self-assembled over the years to tackle tissue engineering.

- Adding imaging expertise to these teams is essential.
- Other areas of expertise missing include:
 - bioinformatics and computational biology
 - sensor technologies for analysis/sensing of microenvironment (chemical and physical). Cell itself is the best sensor. Need to engineer cell to do this.
 - Embryology, developmental biology and stem cell biology.
 - Adult biology—still a lot to learn. Development/generation of tissue vs. re-generation
 - People who know how to transfer the technology to commercialization and/or patients
 - Scalability, manufacturing expertise
- Technology developers need to be better integrated with clinical researches and clinical needs and vice versa

A3. Imaging and tissue engineering reshape clinical research and promote discovery?

- TE could provide tissues or biological fluids in short supply. Positioned to directly address the shortage of donor tissues and organs.
- Imaging is extremely important as it aids in the development of the blueprint and design principles for 3D engineered tissues.
- 3D HUMAN tissue engineered models in general could be good pre-clinical model systems.
- They are also likely to be good models for drug development because they might be more predictive of human responses to drugs than animals but not all cases. it also depends on what you are studying. So overall, may be more predictable model of what will happen pre-clinically and clinically in some cases. Also cheaper and higher throughput than animals.
- 3D engineered tissues would be a good in vitro model for developing diagnostic imaging tools.
- Extracting info that you can't get from animal models—pharmacogenomics (personalized medicine)
- In vitro systems allow for great control and could be a tool to better design animal studies.
- Allows imaging of things as they happen—DYNAMICS –
- Imaging the host response is as important as imaging engineered tissues.

A4. Imaging of engineered tissues improves people's health?

- Tissue engineering holds the promise to treat a long list of diseases.
- After implantation, imaging will allow us to monitor function in vivo and tells us if we are putting the right thing in.
- Imaging could make the process of cell, tissue or organ replacement less invasive overall.
- Imaging can monitor function and allow for early detection of failure and lead to corrective action.

- Imaging of engineered constructs could allow for monitoring of tumorigenicity vs. normal growth and differentiation
- Need for more correlations between imaging information and clinical outcomes.

Primary Challenges:

C1. *What are the key scientific challenges to imaging of engineered tissues?*

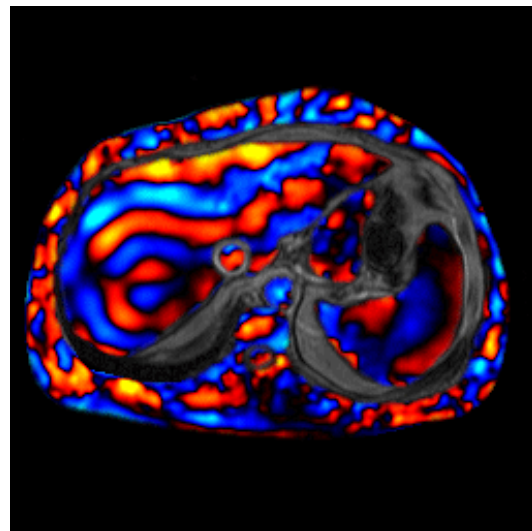
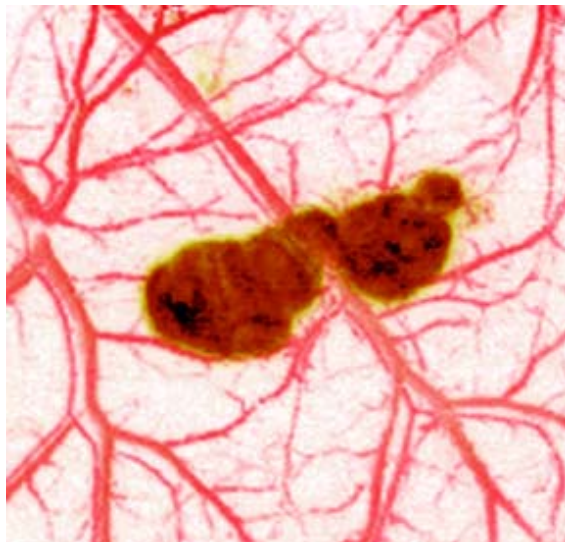
- Understanding which cell & tissue responses are linked to various molecular & physical factors
- Imaging & understanding the dynamics of the cells (non-invasive, real-time)
 - e.g. within mechanically responsive cardiac tissue (e.g. ion fluxes, signal propagation, gradients)
 - e.g. combination of proteomics & imaging as a function of time (e.g. for cell differentiation; assembly)
 - e.g. differentiation of cells (molecular imaging of gene expression)
- Imaging & understanding the integration of the engineered tissue with the host tissue
- Need ways to evaluate evolution of scaffold degradation & tissue changes over time
 - need time-dependent scaffold properties
 - need time-dependent tissue mechanical properties & mass transport properties
 - can we obtain these data for individual patients?
 - need to evaluate 3D nondestructively in vivo
 - for soft tissue: need nondestructive quantification of 3D extracellular matrix (e.g. GAG distribution, collagen I v. collagen II)
 - for nerves: need nondestructive tracking of axon growth & electrical activity in vivo
- Quantitative studies at small scales (e.g. organoids)
- Need better ways to track location of individual cells & subsets of cell populations
 - e.g. understand why stem cells don't go to the "proper" location when injected
- Need to know whether label-free imaging could be as sensitive as imaging using label
 - collagen is an example.
 - molecular level imaging for clinical applications without labels is a challenge.
 - Could labels be temporary, so that molecular environment is not changed?
 - Same comments for cellular level.
- Need ways to image deep tissue & internal organs
 - e.g. better molecular markers & identification of endogenous biomarkers
 - e.g. improved 3D image analysis & quantification [i.e. cell location within entire organ]
 - why are cells rejected after 3 months in the organ?
- For detection of viruses, need to be able to see where the virus is (after introduction)
 - possible to fluorescently label the virus? Or some other approach?

- Need level of quality, acceptable to FDA, to build enough scaffolds for clinical studies
 - are there imaging/production technologies, other than SFF & other off-the-shelf approaches, that will provide the necessary quality of fidelity and resolution?
- Need improved imaging input to develop design of engineered tissues
 - e.g. CT is good for bone structure... but what is available for function?
 - e.g. MR good for soft tissue structure; MRE, UEI for function; what other elastography methods are available?
- Need further development of elastography approaches for imaging tissues
 - need improved, automated edge detection
 - is OCT penetration sufficient?
 - can OCT be used within and/or outside a bioreactor?
 - What is needed for the many different tissue types?
 - Nonlinear elastic & viscoelastic properties

Topic 3: *New Technologies for Characterizing Cells and Tissues in situ*

BIROW Score: Mean 146 with 48 votes

Abstract: Emerging technologies offer new approaches for quantitatively assessing tissue properties that previously could not be measured in situ. Some of these opportunities involve novel imaging technologies that exploit interactions of energy with tissue and in some cases the conversion of one form of energy to another ("energy transduction") to provide new parameters for tissue characterization. Other approaches involve bringing sensors and microscopic imaging modalities into contact with tissues of interest by minimally-invasive, image guided techniques. Many of these technologies have as much relevance to the evaluation of engineered tissue constructs as they do for in vivo imaging. This session had four speakers who provided a survey of specific emerging technologies, opportunities and unsolved problems.



Specific Aims:

A1. *Characterizing tissues in situ deepens understanding of fundamental biology?*

- Improving tissue characterization
 - Direct path
 - Indirect path
- There are levels of biology
 - Measuring hemoglobin is a higher level process
 - New modalities can measure at cellular level
- Help characterize interplay between target tissue and surrounding tissue cells
 - Relationship between biology and disease
- Can lead to creation of multi-label probes
 - Large scale collaborative effort to determine what the normal range of tissue is

A2. *Characterizing tissues in situ promotes collaboration of multidisciplinary teams?*

- Work is multidisciplinary by nature
- Many disciplines represented in breakout session
- Potential team members
 - Biology, physics, chemistry, computer science, engineering, mathematician, clinician
- Image analysis can cross scales and encourage collaboration
- Need to train people to bridge disciplines and be multi-lingual
 - Biomedical engineering / bioengineering is one good discipline for this

A3. *Characterizing tissues in situ reshapes clinical research and promotes discovery?*

- In-situ characterization of tissues could fundamentally change the way clinical trials are done
 - New means to monitor changes as they occur
- Need to develop models to link imaging and biology
 - Imaging observes underlying biological processes
- Examples
 - Elastography suggests tumors might be stiffer
 - Biologist could investigate why this occurs
- Confocal microscopy could enable in-vivo histology

A4. *Characterizing tissues in situ improves people's health?*

- Can enable personalized medicine through individual specific imaging
- With image-guided biopsy tissue characterization can be more specific
- May lead to new screening methodologies that could be low cost for underserved populations
 - Elastography for liver fibrosis
 - Imaging for cancer monitoring

Primary Challenges:

C1. *What are the key scientific challenges to characterizing tissues in situ?*

- In vivo sensing of dynamics- transient vs chronic phenomena
- Multi-scale imaging
- Response of cell or tissue to stress or perturbation
- Response of tissues to successive stimuli (unique advantage of in vivo imaging)
- Characterize interactions between focal lesions and surrounding tissues
- Precancer states in cells / tissues
- Gene modulation by cell environment
- Characterizing psychiatric disease
- Can we image memory?
- 100's of currently inaccessible parameters – for example: hydrostatic pressure
- What parameter(s) would be the equivalent of a moonshot?

C2. *What are the primary obstacles to development of characterizing tissues in situ?*

- Validation
 - If we now can measure what we could not measure previously...
 - ... how can we validate?
 - what is normal?
- Prioritization and Resources
 - are we investing resources in a way that will promote the next technology that would have the impact of CT or other similar breakthrough of last 50 years?
 - need to prioritize
 - innovation should be a key criterion, emphasized by study sections
 - need sustained funding - developing breakthrough technologies requires time
- Approach
 - we measure the things that we know
 - sometimes we define the problem with the tool that is available
 - we don't always know what is normal – should we start with disease or with what is normal?
 - a key challenge is to put aside preconceptions
- Sensitivity vs Specificity
 - sometimes, the main obstacle is specificity – false positives
 - must differentiate sensitivity in an engineer's sense versus biological point of view
 - downstream detection - high sensitivity – leads to upstream challenges
- Significance
 - Drive to find cancer earlier and earlier – leads to basic problems re unknown tumor-host interaction – natural history
 - Example is thyroid cancer -elevated PSA; prostate cancer

C3. *What are the critical technologies lacking for characterizing tissues in situ?*

- Better sensors of all types: chemical sensors, x-ray detectors, coils, etc.
- More sensitivity, speed, spatial resolution
- Multiparametric sensing and dual/multimodal probes
- More funding needs to be devoted to development of new instrumentation

C4. What are the impediments to translating characterizing tissues in situ to improved health?

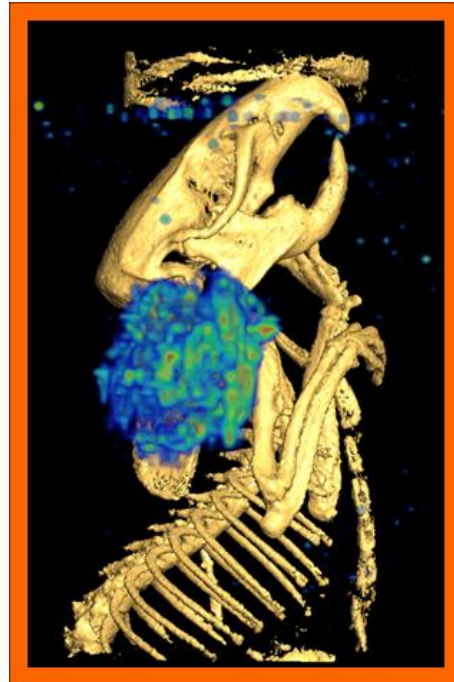
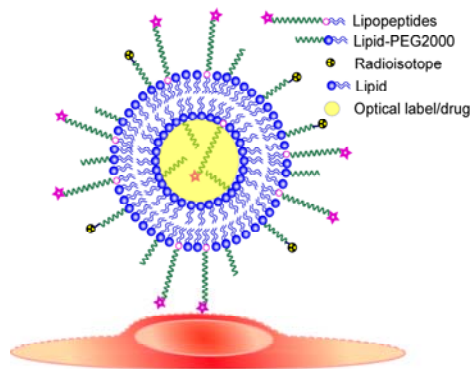
- “Multi-lingual study” sections are needed.
- Need appropriate level of expertise to review a proposals
- Optical imaging – an example slow translation, given level of investment, surprising how little is applied
- Are we putting enough money behind grants that require a major effort to translation?
- Use of academic research model rather than applied research model
- Regulatory issues – a huge impediment
- Need more small grants so more ideas can be tried
- Cost / Medical Economics
 - Imaging is underfunded compared with impact
 - How to emphasize development of cost-effective technologies, care for underserved
 - Why is after 30 years is CT still expensive?
 - Our perceptions of medical technology “cost” are based on charge, which involves cost shifting in our system and introduces distortions

Topic 4: *Imaging for Targeted Cell, Gene and Drug Delivery*

BIROW Score: Mean 154 with 46 votes

Abstract: The main goal of this session was to present the data regarding the cutting edge research on the border between drug delivery and imaging. We concentrated on very recent and new topics, which currently attract a lot of attention, such as cell-penetrating peptides, siRNA and gene silencing, image-guided drug delivery, acoustic delivery and imaging, etc. Speakers were asked to concentrate more on critical areas to make the whole program remain consistent.

Multi-modal particles



Specific Aims:

A1. *Imaging therapeutic delivery deepens understanding of fundamental biology?*

- Drug delivery imaging involves basic understanding of cell functions, receptor kinetics, cell membrane structure, biochemical pathways, signal pathways, transporters, endocytosis, etc.
- Imaging for drug delivery can non-invasively increase our understanding of disease biology.
- Imaging can show specific biomarkers involved in a disease process.
- Imaging also can show the release therapeutic agents from a carrier in a specifically targeted tissue.
- Imaging for drug delivery can also explain cancer therapy failures if the drug does not reach the cancer. The drug may be effective for the cancer, but the problem may be the lack of drug delivery into the solid tumor.

A2. *Imaging therapeutic delivery promotes collaboration of multidisciplinary teams?*

- Imaging for drug delivery will require a team science approach from radiologists, nuclear medicine physicians, imaging scientists, engineers, pharmacologists, biologists, and chemists as well as equipment manufacturers, image analysis experts and software specialists.
- It is a clear example of projects that will link physical and life scientists with engineers and clinicians

A3. *Imaging therapeutic delivery reshapes clinical research and promote discovery?*

- Drug delivery imaging is very important for conducting clinical research.

- Drug delivery imaging studies can be conducted for discovery and development of new drug delivery technologies as well as understanding of why many drugs fail to be effective in humans in spite of promising results in smaller animals.
- Imaging for drug delivery will help us understand why certain drugs do not reach the intended target and why they are not effective even they do reach the target.
- It can also involve new groups of clinicians dedicated to development and research of drug delivery systems.

A4. Imaging therapeutic delivery improves people's health?

- Imaging for drug delivery has the potential to very specifically improve drug therapy and improve patient selection for specific drug therapies.
- Imaging can quantify the amount of drug that is delivered to a disease and it also has the potential to determine the specific local distribution of the drug in the targeted region.
- Imaging can also be used to determine patient selection and monitoring of the therapeutic response of targeted therapies. For instance, imaging could be used to screen for specific targeted receptors such as growth factor receptors.
- Therapy often requires a combination of drugs to which each patient reacts differently. Imaging for drug delivery will make possible the goal of personalized medicine. It may be possible to determine individual treatment protocols and their efficacy, accounting for patient to patient variability.

Primary Challenges:

C1. What are the key scientific challenges to imaging therapeutic delivery?

- One of the key scientific challenges is that we have little knowledge of where and how a drug localizes after injection. Many drugs may fail because they fail to reach their target in adequate levels, although the drug itself may be quite effective against the particular disease if the delivery were adequate.
 - Even drugs that do work effectively currently, could work even better, if the delivery of the specific drug was improved. It is also important to know where drugs that do not hit the target go, so that these unwanted localizations can be closely examined for toxicity.
 - This problem of drug delivery is particularly crucial for local drug administration, such as gene delivery, in which there have been very few imaging studies of both delivery and outcome components.
 - At a minimum, imaging studies are required to know the immediate distribution of the injected drug following administration and to be able to quantitatively determine distribution.
 - Distribution of the drug is important not only in terms of relative organ biodistribution, but also in terms of biodistribution over the local region of the injected agent throughout the locally targeted disease process. For instance, if a tumor is targeted by local injection, the distribution should be homogeneously spread throughout the tumor and not just localized on the periphery of the tumor or in a small local portion of the tumor.

- A particular challenge is how to track viruses in the body. It is important to track the initial distribution of the virus in the body. Another very challenging goal would be to track virus that replicates and changes distribution following injection *in vivo*. This tracking of viral particles is thought to be particularly important for human clinical trials.
- Another challenge, which may be beyond current imaging technology, is to know whether or not the drug is in the right intracellular compartment. It is also a challenge to develop tools (labeling kits, imaging analysis software) that can be easily transferred to many labs. To assure that the drug will be delivered to the intended target in a sufficient quantity for detection and without losing the label in the process.
- One has to notice, that the absolute majority of drug delivery imaging studies have been done for cases of cancer therapy, leaving many other pathologies without proper attention.

C2. *What are the primary obstacles to imaging therapeutic delivery?*

- For local drug delivery, a specific obstacle is the regulatory hurdles involved in receiving approval for labeling a specific therapy to permit imaging during the initial clinical evaluation. Some of this may be related to the fact that it is very hard to get initial approval to test a drug and then the drug is considered changed if an imaging tracer is attached to it, so that the approval process has to be redone.
 - A possible approach might be to have the therapeutic agent be labeled with a radiotracer from the start. Imaging could be an integral part of the therapeutic agent because proper deposition and coverage of the agent throughout the therapeutic target may require labeling with a tracer for image-guidance as well as for verification of proper localization of the drug delivery within the target.
- Another obstacle is the high cost of some commercially available markers. Are these costs significantly affected by volume? One potential way to address the roadblocks to translating imaging is to have the NIH inexpensively disseminate some imaging tools such as imaging agents that are widely desired by a large number of researchers such as a specific tracer chelator, or NIR dye.
- Another obstacle may be that clinicians may not understand what they are looking at when we see an image of a new developed agent? How can the image be accurately interpreted?
- If imaging is needed for every treatment, (e.g., for infusing into large solid tumors), this is a very different challenge than if imaging is only needed for use in development and clinical trials.
- There is a need to come up with image-guided standards in animal studies that can be transferred into the clinic.
- There is a lack of quantifiable imaging for stem cells. Stem cell tracking is considered a very important requirement for the successful development of stem cell therapies.

- More attention needs to be paid to "pre-clinical imaging" standardization; standardization of small animal imaging is even worse than the clinical arena. But yet, drug development starts in pre-clinical imaging.

C3. What are the critical technologies lacking for imaging therapeutic delivery?

- Combined systems are needed for image-guided drug delivery. These systems could be composed of high resolution combined SPECT and PET systems for accurate determination of drug delivery and localization and monitoring combined with CT or MRI for accurate imaging guidance. Ultrasound systems could also be included that fuse with the CT and or MRI for image-guided therapy.
- A lack of standardization and ability reproducible quantify images was also cited as a deficiency of current imaging equipment. Emphasis should be placed on developing more standardization procedures so that images obtained in one location can be quantified in a similar manner to images obtained from imaging equipment at different locations. Standardization could be approached with appropriate standards; improvements in equipment dedicated to better standardization are also needed.
- Small animal imaging has a major role to play in the development of better imaging agents and protocols. All protocols for planned translation to human studies should be proven feasible in small animal imaging. More funding should be dedicated for support of small animal imaging. Emphasis should be placed on small animal imaging having quantified data which should support.
- Use of optical imaging of many wavelengths can be developed to define an image-guided drug delivery methodology in animals which can then be converted to SPECT imaging of different photon energies in humans.
- There needs to be automation technologies in labeling and image analysis. Quantization methodologies for estimating drug concentration need to be developed. Technologies that are easily transferable from pre-clinical imaging to clinical imaging; e.g. the Bruker ClinScan 7T MRI scanner using the same software platform as the clinical MRI scanners. Image fusion technologies (hardware and software) are important for multi-modality imaging.

C4. What are the impediments to translating imaging therapeutic delivery to improved health?

- The challenges and obstacles are very diverse. One significant problem is the lack of funding that is being dedicated to clinical translation. More funding is needed for specifically guiding researchers with promising preclinical drug into phase I studies of these drugs so that they will have a drug delivery imaging component.
- More emphasis needs to be made of development of quantitative imaging in animals that can be translated into humans. New dedicated human imaging systems need to be developed that are specifically dedicated to drug delivery imaging.
- Training of scientists to have a basic understanding of all the multidisciplinary knowledge is important so that they will be able to integrate scientists from various disciplines.

- Research funding needs to be set aside for qualifying imaging biomarkers. For example, funding should be available not only for synthesizing novel compounds, but also for validating labeled drugs. More financial help should be available to help academic institutions set up pre-clinical imaging core labs and special attention should be paid to states with disadvantages in competing for shared instrumentation grants.
- More standard tools should be made available to imaging core labs, such as labeling kits that are shake and bake. Need to educate physicians to embrace imaging as "standard of care" in their practice.

Appendix – General Discussion

Applied Research and Development – An Opportunity

Traditionally, much medical research conducted in medical institutions and funded by the NIH has been conducted under a classic American academic model. This model prizes intellectual freedom, pursuit of innovative areas of research, publication in the peer-review literature, and *external* recognition of the value of scientific contributions. Scholarly clinicians and researchers are encouraged to freely choose the focus of their research programs and to pursue these activities to the full extent permitted by the intramural and extramural funding to that they are able to obtain. Academic appointment and promotion at most institutions is based on these classic criteria. Research finance policies and allocation of intramural research funding generally reflects and supports this model. Many of the most important advances in medicine of the last decades have been accomplished through this model.

Yet, for over a century, a distinctly different approach has been used by the commercial sector and government agencies. Investigational talent and assets are employed in a more directed fashion. This approach is most often called “Applied Research and Development” (AR&D). Other designations are “Applied Research”, or the application of “Applied Science”. In this model, investigators and research teams are presented with goals or challenges that have been determined by the organization to represent strategic opportunities or critical responses to competition or threats. Programs are sized and resourced according to the near term importance of the goal, ongoing progress, and the financial and competitive consequences of attaining the goal. Some of the most important advances in medicine of the last decades have been accomplished through this model, as well.

It is appropriate to ask whether it is now time for academic institutions and the NIH to more systematically engage the scientific talents of investigators - and to advance discovery and translation - by applying the Applied Research model as a *complement* (not a replacement) to an ongoing traditional academic research model.

Approaches for Increasing Applied Research Activity at Academic Institutions

In order to more explicitly pursue the benefits that a strategy of Applied Research and Development could provide, institutional policies and practices should be reviewed and modified to reflect this goal. Some of areas that should be reviewed include hiring, promotion, incentives, recognition, and research finance policies.

Most important of all is to develop a system to provide leadership challenges, expectations, and sponsorship of AR&D in targeted areas that offer greatest opportunity.