Focal Drug Delivery Program

Workshop 1

Workshop Syllabus
21–23 March 2011

Boar’s Head Inn and Conference Center
Charlottesville, VA, USA
Welcome Letter  
Workshop I, 2011

Dear Colleagues,

Welcome to the Foundation’s first workshop on focused ultrasound-mediated drug delivery. This invitational event is being held at the request of researchers in the FUS community who believe the Foundation can add unique value by serving as a nexus of collaboration through workshops and working groups.

The objectives of this workshop are to:
- Provide a forum for collaboration
- Establish and/or validate the priority indications defined at the Core Stakeholder meeting
- Develop a clear path to clinical implementation in 2-3 indications through research roadmap development

The workshop will begin with a welcome reception from 6:30-8:30 PM on Monday night. On Tuesday, the program will run from 7:45 AM to 6:00 PM with three short breaks during the day in addition to lunch. There will be classroom style presentations throughout the day, yet the emphasis will be on lively discussions around the presented material. The day is structured to allow 15-20 minutes of discussion following nearly all presentations. We will convene for dinner at 7:00 PM.

On Wednesday, we will begin at 8:00 AM in parallel breakout sessions in three different rooms. Each breakout group will address one of the three most pressing indications identified during Tuesday’s discussions. It is possible that the list of indications selected during this workshop may differ from the priorities identified at last year’s Core Stakeholders meeting. That list emphasized pancreatic cancer, brain tumors and liver cancer due to need, potential impact and incidence.

Because they will be selected by consensus, breakout topics may not match the key interests of some workshop attendees. In those instances, attendees will be asked to join the breakout conversation most closely aligned with their interests. Given that all drug delivery indications share many common challenges; our intention is that everyone gains valuable insights from participating in breakout discussions.

Before bringing the workshop to a close at 4:00 PM on Wednesday, we will have presentations of breakout session outcomes followed by several brief presentations on experimental models and funding opportunities.

We are delighted and honored that almost every major academic and industrial thought leader in drug delivery applications of focused ultrasound will be participating in this workshop. We anticipate intense, passionate discussion and debate leading to actionable solutions. Our goal is to advance the development of FUS-mediated drug delivery therapies to provide new hope and a better life for patients seeking new, more effective treatment options.

Sincerely,

JOY M. POLEFRONE, PhD
Program Director, Focal Drug Delivery
Focused Ultrasound Surgery Foundation

NEAL F. KASSELL, MD
Chairman
Focused Ultrasound Surgery Foundation
Professor of Neurosurgery
University of Virginia
Today, researchers and manufacturers around the world are developing focused ultrasound therapies for many deadly and debilitating medical conditions. Since its founding in 2006, the Focused Ultrasound Surgery Foundation has been dedicated to accelerating the development and adoption of these new, noninvasive treatments so that they become a standard of care worldwide. Motivating the Foundation’s work is the belief that every day without access to focused ultrasound treatments is a day of needless death, disability and suffering for countless patients.

Thanks to the support of philanthropic and corporate donors, the Foundation funds a variety of research and educational initiatives. We also promote collaboration, coordination and communication among researchers, clinicians and others who are pioneering this exciting and rapidly emerging area of medicine.

Our key initiatives include:

- Organizing, coordinating and funding research leading to new applications
- Establishing global collaboration between the research and development initiatives in academia and industry
- Funding training fellowships for clinicians and scientists
- Establishing new Centers of Excellence—luminary sites for research, training and patient care
- Supporting meetings, symposia and workshops
- Facilitating regulatory approval and third-party reimbursement
- Increasing awareness of what has been termed “medicine’s best kept secret”

To learn more about focused ultrasound and the Focused Ultrasound Surgery Foundation, visit the Foundation’s website: [www.fusfoundation.org](http://www.fusfoundation.org)
General Information

Registration

Monday 4:00-8:30 PM
Tuesday 7:00-8:00 AM

Contact Information

The Boar’s Head Inn 434.296.2181

FUSF Staff
Joy Polefrone 434.825.0240 (m)
Jade Faulkner 434.882.1442 (m)
Chris Faulkner 434.760.1170 (m)

Daily Events
*Please see Overview for detailed schedule

Monday, March 21

6:30 - 8:30 PM Welcome Reception, Hearth Room
Includes drinks and hors d’oeuvres

Tuesday, March 22

7:45 AM - 6:00 PM General Session - Ballroom
7:00 - 8:30 PM Dinner - Meeting Pavilion

Wednesday, March 23

8:00 AM - 4:00 PM General Session - Ballroom

Meals

Tuesday, March 22

7:00 – 7:45 AM Breakfast - Old Mill Room
12:15 – 1:15 PM Lunch - Meeting Pavilion
7:00 – 8:30 PM Dinner - Meeting Pavilion

Wednesday, March 23

7:00 – 7:45 AM Breakfast - Old Mill Room
12:30 – 1:30 PM Lunch - Hearth Room
Workshop Overview

Description of Events

Monday, March 21

Registration followed by the Welcome Reception will take place in the Hearth Room. Drinks and hors d’oeuvres will be provided.

Tuesday, March 22

Presentations will take place throughout the day in the Ballroom. After each clinical indication presentation, thirty minutes has been allotted for lively discussion.

Wednesday, March 23

Please note that we will begin just after breakfast in three different rooms in parallel breakout sessions, with a thirty minute break midway through this time to allow for checkout. During the breakout sessions we will be discussing the top three indications. We will report out to the whole group via presentations of our breakout session outcomes followed by several brief presentations on experimental models and funding opportunities before bringing the meeting to a close.

<table>
<thead>
<tr>
<th>Monday, March 21</th>
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<tbody>
<tr>
<td><strong>Registration Open - 4:00 PM</strong></td>
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<tr>
<td><strong>Free time</strong></td>
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<tr>
<td>4:00-6:30 PM</td>
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<tr>
<td><strong>Registration</strong></td>
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<tr>
<td><em>Entrance to Hearth Room</em></td>
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<td>4:00-8:30 PM</td>
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<tr>
<td><strong>Welcome Reception</strong></td>
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<td><em>Hearth Room</em></td>
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<td>6:30-8:30 PM</td>
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4:00 PM
4:00-6:30 PM
5:00 PM
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<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>7:00 AM</td>
<td>Breakfast Old Mill Room 7:00-7:45</td>
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<tr>
<td>8:00 AM</td>
<td>Meeting Orientation, Ballroom 7:45-8:00</td>
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<tr>
<td>8:00 AM</td>
<td>Program Background &amp; Meeting Priorities Ballroom 8:00-8:45</td>
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<tr>
<td>9:00 AM</td>
<td>Scientific Background Ballroom 8:45 - 10:30</td>
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<tr>
<td>10:00 AM</td>
<td>BREAK</td>
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<tr>
<td>11:00 AM</td>
<td>REPORT: NCI Workshops on IGDD Ballroom 10:45-11:15</td>
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<tr>
<td>12:00 PM</td>
<td>Regulatory Overview &amp; Discussion Ballroom 11:15-12:15</td>
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<td>1:00 PM</td>
<td>Lunch Meeting Pavilion 12:15-1:15</td>
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<td>2:00 PM</td>
<td>Clinical Indication 1: Pancreatic Cancer Ballroom 1:15-2:00</td>
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<tr>
<td>2:00 PM</td>
<td>Clinical Indication 2: Head &amp; Neck Cancer Ballroom 2:00-2:45</td>
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<tr>
<td>3:00 PM</td>
<td>BREAK</td>
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<tr>
<td>3:00 PM</td>
<td>Clinical Indication 3: Liver Cancer Ballroom 3:05-3:50</td>
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<tr>
<td>4:00 PM</td>
<td>Clinical Indication 4: Prostate Cancer Ballroom 3:50-4:35</td>
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<tr>
<td>5:00 PM</td>
<td>BREAK</td>
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<tr>
<td>5:00 PM</td>
<td>Clinical Indication 5: Brain Cancer Ballroom 4:55-5:40</td>
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<tr>
<td>6:00 PM</td>
<td>Review &amp; Wednesday Agenda Ballroom 5:40-6:00</td>
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<tr>
<td>6:00 PM</td>
<td>Adjourn</td>
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<tr>
<td>7:00 PM</td>
<td>Dinner Meeting Pavilion 7:00 - 8:30</td>
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# Workshop Overview

## Wednesday, March 23

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<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>7:00 AM</td>
<td>Breakfast</td>
<td>Old Mill Room</td>
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<tr>
<td>7:00-7:45</td>
<td>Meeting to convene at 8 AM in Breakout Sessions</td>
<td>Commonwealth Room</td>
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<tr>
<td>8:00 AM</td>
<td>Breakout Session: Indication A</td>
<td>Commonwealth Room</td>
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<tr>
<td>8:00-11:30*</td>
<td>*A 30 min. break will be held midway through this session</td>
<td>Commonwealth Room</td>
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<tr>
<td>9:00 AM</td>
<td>Breakout Session: Indication B</td>
<td>Albemarle Room</td>
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<tr>
<td>8:00-11:30*</td>
<td>*A 30 min. break will be held midway through this session</td>
<td>Albemarle Room</td>
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<tr>
<td>10:00 AM</td>
<td>Breakout Session: Indication C</td>
<td>Blue Ridge Room</td>
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<tr>
<td>8:00-11:30*</td>
<td>*A 30 min. break will be held midway through this session</td>
<td>Blue Ridge Room</td>
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<tr>
<td>11:45 AM</td>
<td>Lunch</td>
<td>Hearth Room</td>
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<tr>
<td>12:00 PM</td>
<td>Group Discussion - Presentation of Conclusions of Breakout to Group</td>
<td>Ballroom</td>
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<tr>
<td>11:45 - 12:30</td>
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<td>Ballroom</td>
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<td>1:00 PM</td>
<td>Lunch</td>
<td>Hearth Room</td>
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<td>12:30-1:30</td>
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<td>Commonwealth Room</td>
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<tr>
<td>2:00 PM</td>
<td>Animal Models and Assays</td>
<td>Ballroom</td>
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<td>2:15-3:00</td>
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<td>Ballroom</td>
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<tr>
<td>3:00 PM</td>
<td>Long term funding Strategies - NCI funding Opportunities</td>
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<td>3:00-3:30</td>
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<td>Ballroom</td>
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<tr>
<td>3:30-4:00 PM</td>
<td>Outcomes and Next Action Items, Adjourn</td>
<td>Ballroom</td>
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<td>3:30-4:00 PM</td>
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<td>Ballroom</td>
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<tr>
<td>4:00 PM</td>
<td>Adjourn</td>
<td>Commonwealth Room</td>
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Program Rationale

Program Overview

Introduction

The American Cancer Society estimated that in 2009 nearly 1.5 million new cases of cancer would be diagnosed and just over half a million individuals would die from cancer. Of those 1.5 million patients diagnosed with cancer in 2009, most will be treated with what is still the standard combination of surgery, radiation therapy and chemotherapy, all of which have well documented deleterious side effects and low success rates. Imagine a treatment option by which all three could be performed with minimal invasiveness and side effects—we at the FUS Foundation believe MR-guided focused ultrasound-mediated drug delivery has the potential to be that solution.

The FUS Foundation is dedicated to accelerating research and development of patient treatments using one of today’s most revolutionary and promising medical technologies: non-invasive Magnetic Resonance-Guided Focused Ultrasound (FUS). The Foundation’s work is motivated by the belief that FUS treatments could become the ultimate in minimally invasive surgery, serve as a viable alternative to radiation therapy and offer a new platform for precise drug delivery—applications with the potential to alleviate suffering, save lives and quicken recovery times for millions of patients worldwide.

Rationale

FUS-mediated drug delivery has the potential to impact the largest number of patients numerically in an epidemiological sense, yet has considerable challenges to surmount as it sits at the intersection of multiple industries (both device and medical therapies) and stakeholders. The FUS Foundation has an established track-record of engaging various stakeholder groups through its Brain Program Initiative and has a unique capacity to aid in the direction and collaboration within FUS-mediated drug delivery. For this reason the FUS Foundation has initiated a Program in focal drug delivery.

Strategy

The FUS Foundation will assume facilitative and leadership roles in the development of an internally driven research program in focal drug delivery (Mission Statement below). This is consistent with the foundations vision and mission and role in bringing together industry, academia, and funding to accelerate the development and adoption of MR-guided Focused Ultrasound. Modeled after the Foundation’s Brain Program, the goal of the Foundation’s Focal Drug Delivery Program is to work with the key stakeholders, including academic researchers, clinicians, pharmaceutical companies, focused ultrasound manufacturers, governmental agencies and disease-specific foundations to accelerate clinical applications of FUS-mediated drug delivery. The approach will combine advanced imaging techniques, activation of the immunological response, tumor ablation and the targeted delivery of drugs, thus reducing the system-wide effects of current drug therapies. Success will hinge on collaboration among the best and the brightest in the field.

Focal Drug Delivery Program Mission Statement

The aims of this program are to define and engage the research community in FUS-mediated drug delivery in order to:

1. Clarify the clinical applications that will benefit most from MR guidance
2. Develop a research roadmap for clinical applications for MR-guided FUS-mediated drug delivery
3. Accelerate research by fostering collaboration among the academic researchers, pharmaceutical companies, focused ultrasound companies and clinical community

Organization

Core Stakeholder group

- Academicians already working with ultrasound and drug delivery systems
- Will serve as the foundation for the program’s Steering Committee

Broader Stakeholder group

- Researchers and Clinicians with experience in drug delivery systems and/or focus ultrasound in clinical applications relevant to FUS-mediated drug delivery
- Existing Public-Private Partnerships
  - Government Funded Projects
    - SonoDrugs
      - Funded by the NMP program of the European Commission’s
      - 7th Framework
Program Rationale

- MRgFUS and Drug Nano-capsule Project
  - European Union funded
- United Kingdom Collaborative Research Initiative
  - Funded by UK’s Engineering and Physical Sciences Research
    - Public-Private Partnerships
      - ThermoDox® Collaboration
        - Aim is to explore MRI-guided focused ultrasound combined with ThermoDox® to treat a broad range of cancers.
- Industry
  - Device Industry
    - MR-guided focused ultrasound manufacturers
    - InSightec
    - Philips
  - Pharmaceutical Industry
    - Open invite
  - Ultrasound Contrast Agents
  - Nanotechnology Industry
    - Bracco
    - Targeson
    - Others
- Foundations
  - Disease-based Foundations as clinical indications are defined.
- Working Groups: Research groups for specific indications or applications
  - These groups will implement the roadmaps defined at the workshop
- Steering Committees for Clinical Trials
- Academic Research Sites
- Focal Drug Delivery Foundation Team
- Related Foundations
- NIH and equivalent foreign funding Agencies
- FUS Foundation

Deliverables

Stakeholder group definition
- Core Stakeholders and Steering Committee
- Broader Stakeholder Group (includes Industry and Foundations)

Bibliographies
- Researchers and Clinicians with experience in drug delivery systems and/or focus ultrasound in clinical applications relevant to FUS-mediated drug delivery
- Existing Public-Private Partnerships

FUS-mediated drug delivery specific news
FUS-mediated drug delivery capabilities on the Foundation’s Collaborative Research Network
Research Roadmaps
- FUS-mediated drug delivery roadmaps for 2-4 clinical indications
- Technical questions (gating factors and burning questions)

Program Framework

Phases of the Drug Delivery Program

Phase I: Start-Up
The Start-Up Phase of the project is critical to gaining understanding of the research, researchers and projects that currently exist in focused ultrasound-mediated drug delivery. A thorough literature review of publications and exploratory discussions with researchers will supply the framework for the role the Foundation may play in the field. In addition, Start-Up will include discussions with industry, academia, governmental organizations,
Program Rationale

regulatory experts, and other relevant groups to define where the Foundation may add value in FUS-mediated drug delivery.

Project Objectives:
- Literature Review
- Identify Core Researchers/Stakeholders
- Perform exploratory conversations with Core Stakeholders
- Create Program Rationale Document and Charter
- Conference Call with Core group

Phase II: Core Stakeholder Planning Meeting
The principle goal of the Core Stakeholder Meeting Phase of the Focal Drug Delivery Program is to preliminarily define the key research questions that serve as gating factors to clinical applications of FUS-mediated drug delivery as well as the top 2-4 clinical applications. The Core Stakeholder Meeting will begin with pre-meeting work including the solicitation of research questions from the identified Core Stakeholders and the larger Stakeholder group. This will be followed by a survey of the Core group which aims to define the key research questions and the top 2-4 clinical applications of FUS-mediated drug delivery. The meeting itself will bring together the Core group to refine and clarify the research questions as defined by the Survey Results. During this meeting the ranking of the questions will be reviewed and questions may be distilled down, combined and/or restructured. Technical feasibility will be discussed and preliminary framework for experimental flow will be defined. Lead researchers in clinical areas will be discussed in regard to the top clinical applications defined by the Core Group.
- Research Questions solicited form Core Stakeholder group
- Identify larger Stakeholder Group
- Research Questions presented to larger stakeholder group for comments and input.
- Survey created and administered to Rank Questions among Core Stakeholders
- Work with Core group to write White paper/Supplement to NIH White Paper due out in Late April
- Core Stakeholder meeting to refine and clarify Questions (face-to-face)
- Identify Lead Researchers in Clinical Application areas defined by Core Group

Phase III: Workshop
The Workshop is the forum that brings representatives from all stakeholders together to review the key research questions that serve as gating factors to clinical applications of focused ultrasound-mediated drug delivery. The Core Stakeholder group will have leadership roles within individual areas of expertise during this Workshop. Emphasis of the workshop will be on technical feasibility of research questions as well as development and refinement of research road maps in the top 2-3 clinical applications of this approach. A white paper will be produced from this workshop that chronicles the process for developing research questions and outcomes of the Workshop.

Phase IV: Research Roadmaps
Research roadmaps (2-3 clinical indications) will define pathways to clinical applications of focused ultrasound-mediated drug delivery. The framework for the roadmaps will come out of the workshop, yet they will need refined with input from the Core Stakeholder group. The Core Stakeholder group will have leadership roles for the research roadmap development and implementation within individual areas of expertise.
Core Stakeholder Meeting
Summary

Purpose
The principle goal of the Core Stakeholder Meeting Phase of the Focal Drug Delivery Program is to provide an answer to the question:

Is there a compelling role for the Foundation in focused ultrasound-mediated drug delivery whereby it can add unique value while contributing to its mission of accelerating the adoption of MR-guided focused ultrasound (FUS) clinical applications?

Initial interest of this Core Stakeholder group indicated the approach may be similar to that of the FUSF Brain Program, thus through the survey and the Core Stakeholder meeting we aimed to preliminarily define the top 2-4 clinical applications of FUS-mediated drug delivery, as well as the key research questions that serve as gating factors to clinical applications of this approach.

Process
The Core Stakeholder Meeting began with pre-meeting work which included the solicitation of clinical indications and research questions from the identified Core Stakeholders and the larger Stakeholder group. This information was then compiled into an online survey – completed by all Core Stakeholders. The aim of the survey was to facilitate our definition of clinical indications and research questions via a priority setting process.

The meeting itself brought together the Core group, as well as several ad hoc members, to define clinical indications and research questions as defined by the survey results. Importantly, we hoped to build a framework for collaboration and community among this group, with a clearly defined path forward together.

Outcome
Five clinical indications were identified as top priority:

- Pancreatic Cancer (adenocarcinoma) - Unresectable, stage 3 (locally advanced) or 4 (metastatic)
- Blood Brain Barrier Opening in Brain – GBM (Unresectable & after resection – adjuvant therapy) and metastasis
- Liver Cancer - For central lesions/risky lesions near critical structures
- Head and Neck Cancer - Unresectable, stage 3 or 4 (locally advanced)
- Prostate Cancer - Recurrent

The initial treatment approach will emphasize focused ultrasound mild hyperthermia using existing chemotherapeutics in conjunction with HIFU.

Indication-specific research questions were identified as well as a set of pre-clinical, mechanistic and/or technical questions common to all five indications.

While the initial emphasis is on focused ultrasound mild hyperthermia in combination with chemotherapy, animal experiments will be designed with multiple arms to include microbubbles, as literature suggests significant drug delivery enhancement with the addition of microbubbles.

FUSF Take-away recommendation for the Foundation’s role in FUS-mediated drug delivery

- Serve as a nexus for collaboration
  - Working groups, Workshops, etc.
- Supply seed funding

Next Steps
Minutes
- Distributed to Core Stakeholder group
- Reviewed and comments integrated

Assignments
- Individual indications
  - Team leaders confirmed, identify clinical experts for each indication, refine indication-specific research questions – FUSF site visits
- Literature and/or references to be shared
- Sign-up for on-line Collaborative Research Network (CRN)
- Identify industry experts
  - FUS & micro-FUS vendors
  - Pharmaceutical companies (specifically for drugs currently used for each indication)
Program Update

We are currently in Phases III & IV of the Focal Drug Delivery Program Plan (please see below).

PHASE I: START-UP: COMPLETED
The Start-Up Phase of the project was critical to gaining an understanding of the research, researchers and projects that currently exist in focused ultrasound-mediated drug delivery (FUS-mediated drug delivery). A thorough literature review of publications and exploratory discussions with researchers helped to supply the framework for the role the Foundation may play in the field. In addition, Start-Up included discussions with industry, academia, governmental organizations, regulatory experts, and other relevant groups to define where the Foundation may add value in FUS-mediated drug delivery.

Project Objectives:
- Literature review
- Identify Core Researchers/Stakeholders
- Perform exploratory conversations with Core Stakeholders
- Create program rationale document and charter
- Conference call with Core group

PHASE II: CORE STAKEHOLDER PLANNING MEETING: COMPLETED
The principle goal of the Core Stakeholder Meeting phase of the Focal Drug Delivery Program was to define the key research questions that serve as gating factors to clinical applications of FUS-mediated drug delivery as well as the top 2-4 clinical applications of this approach.

The Core Stakeholder Meeting began with pre-meeting work including solicitation of research questions from the identified Core Stakeholders and the larger Stakeholder group. This was followed by a survey of the Core group which aimed to define the key research questions and the top 2-4 clinical applications of FUS-mediated drug delivery.

The meeting itself brought together the Core group to refine and clarify the research questions as defined by the survey’s results. During this meeting ranking of questions were reviewed and questions were distilled down, combined and/or restructured – in fact, at the meeting we substantially restructured the approach and subsequent path forward.

At this time, the following Program work has been completed:
- Research questions solicited form Core Stakeholder group
- Identify larger Stakeholder group
- Research questions presented to larger stakeholder group for comments and input.
- Survey created and administered to rank questions among Core Stakeholders
- Core Stakeholder meeting to refine and clarify questions (face-to-face)

In addition, we refined a key objective of the Core Stakeholder Phase of the Focal Drug Delivery Program is to provide an answer to the question:

Is there a compelling role for the Foundation in FUS-mediated drug delivery whereby it can add unique value while contributing to its mission of accelerating the adoption of MR-guided focused ultrasound clinical applications?

Core Stakeholder Face-to-Face Meeting Outcomes:
Five clinical indications were identified as top priority (listed in rank order):
- Pancreatic Cancer (adenocarcinoma) – unresectable, stage 3 (locally advanced) or 4 (metastatic)
- Blood Brain Barrier Opening in Brain – GBM (Unresectable & after resection – adjuvant therapy) and metastasis to the brain
- Liver Cancer - For central lesions/risky lesions near critical structures
- Head and Neck Cancer - Unresectable, stage 3 or 4 (locally advanced)
- Prostate Cancer - Recurrent
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While the initial emphasis is on focused ultrasound mild hyperthermia in combination with chemotherapy, animal experiments will be designed with multiple arms to include microbubbles, as literature suggests significant drug delivery enhancement with the addition of microbubbles.

Indication-specific research questions were identified as well as a set of pre-clinical, mechanistic and/or technical questions common to all five indications.

FUSF Take-away recommendation for the Foundation’s role in FUS-mediated drug delivery
- Serve as a nexus for collaboration
  o Working groups, Workshops, etc.
- Supply seed funding

PHASE III: INDICATION-SPECIFIC RESEARCH & ROADMAP DEVELOPMENT
Research:
- Define:
  o Prevalence, patient demographics, current standard of care, outcomes
- Update bibliographies to include:
  o Indication-specific mechanisms, acoustic path and targeting organ/region, experimental models, status of current chemotherapeutic
- Identify Indication-specific Individuals and Companies
  o Pharmaceutical Companies
    ▪ Is the current drug still under patent? If yes, there may/may not be an ally in the pharma company
    ▪ Relationship building for:
      • Future research protocols, donation of resources (drug), potential funding/co-funding source
  o Working Groups
    ▪ Core Group lead investigators and collaborators, to include:
      • Treating physician, Radiology, Radiation oncology, Surgical oncology, Medical oncology, Patient coordinator, Clinical Trials coordinator, animal researchers
    ▪ Identify and confirm available resources (both time and financial)
      • MR-guided FUS
      • Animal systems
  o Patient Groups
    ▪ Future advocates, two-way educational opportunities, access to experts identified by patient community, potential for co-funding opportunities
  o Donors

Roadmap Development – the first Workshop will aim to cover 2-3 Indications based on the input of the focal drug delivery Steering Committee
- Pancreatic Cancer Roadmap Draft
  o Based on Core F2F Meeting outcomes, request key next steps/experiments from Core group
  o Core group lead send draft to FUSF – late 2010
  o FUSF/lead refine draft prior to Workshop
- BBB Opening (GBM & metastasis) Roadmap Draft
  o Align with Brain Program
  o Based on Core F2F Meeting outcomes, request key next steps/experiments from Core group
  o Core group lead send draft to FUSF – late 2010
  o FUSF/lead refine draft prior to Workshop
Program Update

- Liver Cancer Roadmap Draft
  o Based on Core F2F Meeting outcomes, request key next steps/experiments from Core group
  o Core group lead send draft to FUSF – late 2010
  o FUSF/lead refine draft prior to Workshop
- Head and Neck Cancer Roadmap Draft
  o Based on Core F2F Meeting outcomes, request key next steps/experiments from Core group
  o Core group lead send draft to FUSF – late 2010
  o FUSF/lead refine draft prior to Workshop
- Prostate Cancer Roadmap Draft
  o Based on Core F2F Meeting outcomes, request key next steps/experiments from Core group
  o Core group lead send draft to FUSF – late 2010
  o FUSF/lead refine draft prior to Workshop

PHASE IV: WORKSHOP – MARCH 21-23, 2011
The workshop is the forum that will bring representatives from stakeholder groups together to review state of the art and the FUS-mediated drug delivery working groups drafted path forward (Roadmap) for each indication. The first workshop, March 2011, will cover 2-3 Indication-specific Roadmaps based on the input of the focal drug delivery Steering Committee. In addition, standards and protocols for experimental models will be explored. The Core Stakeholder group will have leadership roles within individual areas of expertise during this Workshop. Emphasis of the workshop will be on technical feasibility of research questions as well as development and refinement of research road maps in the top 3 clinical applications of FUS-mediated drug delivery.

Proposed Workshop Structure
Day 1: FUS-mediated drug delivery research presentations
  • Open Session
  • Classroom-style presentations of the state of the art for FUS-mediated drug delivery in each of the clinical indications based on the draft roadmaps
  • Open discussions of research challenges and solutions – facilitated panels
Day 2: Working Groups
  • Closed Session
  • Roadmap review and revision

PHASE V: EXECUTE RESEARCH ROADMAPS
Research roadmaps (pursuit of first set of roadmaps will be based on progress from clinical leads in roadmap development for particular indications) will define pathways to clinical applications of focused ultrasound-mediated drug delivery.
The framework for the roadmaps will come out of the Workshop. The Core Stakeholder group will have leadership roles for the research roadmap development and implementation within individual areas of expertise.
Core Stakeholder Charter

Purpose
The Foundation will bring together investigators and other key individuals from the device industry, pharmaceutical industry, and academic environment in a collaborative setting that crosses clinical and biomedical disciplines in order to provide oversight of and direction to FUS-mediated drug delivery research and clinical applications. The FUS Foundation will assume facilitative and leadership roles in the development of an internally driven research program in drug delivery. The Core Stakeholder group will supply their expertise and academic leadership in developing the list of gating factors to clinical adoption of FUS-mediated drug delivery and assisting in the definition of pathways to gaining FDA approval for clinical applications for FUS-mediated drug delivery in an accelerated fashion.

Membership
Members of the Core Stakeholder Group will include the following representatives:

- Christian J. Diederich, PhD, University of California, San Francisco, San Francisco, CA
- Matthew R. Dreher, PhD, National Institutes of Health, Bethesda, MD
- Keyvan F. Farahani, PhD, National Cancer Institute, Bethesda, MD
- Katherine W. Ferrara, PhD, University of California, Davis, Davis, CA
- Wladyslaw M. Gedroyc, MD, St. Mary’s Hospital, London, England
- Holger Grill, PhD, Eindhoven University of Technology, Eindhoven, The Netherlands
- Joo Ha Hwang, MD, PhD, University of Washington, Seattle, WA
- Kullervo Hynynen, PhD, Sunnybrook Health Sciences Centre, Toronto, Canada
- Alexander L. Klibanov, PhD, University of Virginia, Charlottesville, VA
- Joseph Kost, PhD, MBA, Ben-Gurion University of the Negev, Beer-Sheva, Israel
- King C. Li, MD, MBA, Methodist Hospital, Houston, TX
- Nathan J. McDannold, PhD, Brigham & Women’s Hospital, Harvard Medical School, Boston, MA
- Andreas Melzer, MD, DDS, University of Dundee, Dundee, Scotland
- Chrit Moonen, PhD, University of Bordeaux, Bordeaux, France
- Joy M. Polefrone, PhD, Focused Ultrasound Surgery Foundation, Charlottesville, VA
- Richard J. Price, PhD, University of Virginia, Charlottesville, VA
- Bradford J. Wood, MD, National Institutes of Health, Bethesda, MD

Ad hoc attendees may be invited for special purposes. Sponsor representatives may attend, but will not be considered members of the Core Stakeholder group.

Primary Responsibilities

- Submit FUS-mediated drug delivery research questions and the Top 2-4 clinical indications that could rapidly benefit from drug delivery
- Complete Survey on the compiled research questions and clinical indications, weighing in on the most significant gating factors to accelerating clinical adoption of FUS-mediated drug delivery
- Participate in one Face-to-Face Meeting of focal drug delivery Core Stakeholder group to refine Research Questions and preliminary Research Road maps.
- Contribute to Supplemental White Paper – FUS-mediated drug delivery focal piece based on NCI IGDD White Paper
- Participate in Broader focal drug delivery Workshop
Core Stakeholder Charter

Meetings

The Focal Drug Delivery Program Director will be responsible for coordinating and facilitating the meetings, preparing the agenda, and documenting the meeting minutes. Most meetings will be via teleconference with the option for an occasional in-person meeting, as needed. While scheduling conflicts arise periodically for members, each member should strive to attend all meetings.
Steering Committee Charter

Purpose
The Steering Committee members of the Focal Drug Delivery Program provide advice and counsel to the Focused Ultrasound Surgery Foundation (FUSF) team on both research and development (R&D) and program activities.

Membership
Members of the Steering Committee:

Christian J. Diederich, PhD, University of California, San Francisco, San Francisco, CA
Keyvan F. Farahani, PhD, National Cancer Institute, Bethesda, MD
Wladyslaw M. Gedroyc, MD, St. Mary’s Hospital, London, England
Nathan J. McDannold, PhD, Brigham & Women’s Hospital, Harvard Medical School, Boston, MA
Chrit Moonen, PhD, University of Bordeaux, Bordeaux, France
Joy M. Polefrone, PhD, (Chair), Focused Ultrasound Surgery Foundation, Charlottesville, VA
Bradford J. Wood, MD, National Institutes of Health, Bethesda, MD

Advice and/or input may be solicited from ad hoc attendees who may be invited for special purposes.

Primary Responsibilities

- Prioritize clinical indications based on roadmaps submitted by Core group.
- Recommend sites and investigators most capable of carrying out the research roadmap.
- Participate in Drug Delivery Workshop
- Review Drug Delivery roadmap proposals for feasibility, scientific merit, investigator/site competency to do the proposed work, etc.

Meetings
The Chair of the Committee will be responsible for coordinating and facilitating an annual meeting, preparing the agenda and meeting minutes. Most meetings will be via teleconference with the option for an occasional in-person meeting, as needed.
Suggested Background Reading for Workshop I

**Review Articles**

- Microbubbles: (Hernot and Klibanov 2008)
- Ultrasound triggered image-guided drug delivery: (Deckers and Moonen 2010)
- Ultrasound for drug and gene delivery to the brain: (Hynynen 2008)
- Ultrasound mediated drug and gene delivery to solid tumors: (Frenkel 2008)

Deckers, R. and C. T. Moonen (2010). "Ultrasound triggered, image guided, local drug delivery." *J Control Release.* Ultrasound allows the deposition of thermal and mechanical energies deep inside the human body in a non-invasive way. Ultrasound can be focused within a region with a diameter of about 1mm. The bio-effects of ultrasound can lead to local tissue heating, cavitation, and radiation force, which can be used for 1) local drug release from nanocarriers circulating in the blood, 2) increased extravasation of drugs and/or carriers, and 3) enhanced diffusivity of drugs. When using nanocarriers sensitive to mechanical forces (the oscillating ultrasound pressure waves) and/or sensitive to temperature, the content of the nanocarriers can be released locally. Thermo-sensitive liposomes have been suggested for local drug release in combination with local hyperthermia more than 25 years ago. Microbubbles may be designed specifically to enhance cavitation effects. Real-time imaging methods, such as magnetic resonance, optical and ultrasound imaging have led to novel insights and methods for ultrasound triggered drug delivery. Image guidance of ultrasound can be used for: 1) target identification and characterization; 2) spatio-temporal guidance of actions to release or activate the drugs and/or permeabilize membranes; 3) evaluation of bio-distribution, pharmacokinetics and pharmacodynamics; and 4) physiological read-outs to evaluate the therapeutic efficacy.


It has long been shown that therapeutic ultrasound can be used effectively to ablate solid tumors, and a variety of cancers are presently being treated in the clinic using these types of ultrasound exposures. There is, however, an ever-increasing body of preclinical literature that demonstrates how ultrasound energy can also be used non-destructively for increasing the efficacy of drugs and genes for improving cancer treatment. In this review, a summary of the most important ultrasound mechanisms will be given with a detailed description of how each one can be employed for a variety of applications. This includes the manner by which acoustic energy deposition can be used to create changes in tissue permeability for enhancing the delivery of conventional agents, as well as for deploying and activating drugs and genes via specially tailored vehicles and formulations.


Ultrasound contrast agents, in the form of gas-filled microbubbles, are becoming popular in perfusion monitoring; they are employed as molecular imaging agents. Microbubbles are manufactured from biocompatible materials, they can be injected intravenously, and some are approved for clinical use. Microbubbles can be destroyed by ultrasound irradiation. This destruction phenomenon can be applied to targeted drug delivery and enhancement of drug action. The ultrasound field can be focused at the target tissues and organs; thus, selectivity of the treatment can be improved, reducing undesirable side effects. Microbubbles enhance ultrasound energy deposition in the tissues and serve as cavitation nuclei, increasing intracellular drug delivery. DNA delivery and successful tissue transfection are observed in the areas of the body where ultrasound is applied after intravascular administration of microbubbles and plasmid DNA. Accelerated blood clot dissolution in the areas of insonation by cooperative action of thrombolytic agents and microbubbles is demonstrated in several clinical trials.


Noninvasive, transient, and local image-guided blood-brain barrier disruption (BBBD) has been demonstrated with focused ultrasound exposure in animal models. Most studies have combined low pressure amplitude and low time average acoustic power burst sonifications with intravascular injection of pre-formed micro-bubbles to produce BBBD without damage to the neurons. The BBB has been shown to be healed within a few hours after the exposure. The combination of focused ultrasound beams with MR image guidance allows precise anatomical targeting as demonstrated by the delivery of several marker molecules in different animal models. This method may in the future have a significant impact on the diagnosis and treatment of central nervous system (CNS) disorders. Most notably, the delivery of the chemotherapy agents (liposomal Doxorubicin and Herceptin) has been shown in a rat model.
Drug Delivery Generic Roadmap
Suggested considerations for all applications
Submitted by Chrit Moonen, Matt Dreher and Brad Wood

General questions:
1. What drug?
2. What carrier?
3. What method for FUS activation (pressure, temperature, mechanical, biological)?
4. What FUS platform? What imaging method?
5. Is targeting beneficial?
7. Should cavitation be used or avoided?
8. Why deliver drugs if we can ablate with MR-HIFU?
9. How to communicate potential to Pharma for broadening therapeutic window?

Track 1: Animal models
- What tumor cell lines?
- What small animal tumor model?
- What large animals (pig/sheep/companion animal)?

Track 2: Nanocarrier development and characterization
- Choice of drugs
- Choice of carrier
- Choice of contrast agents
- Choice of targeting
- Chemical, biophysical characterization, release rates, PK

Track 3: Technology Development track for temp sensitive nanocarriers
- MRI temperature mapping
- MR-FUS heating of organ: gated FUS
- Feedback coupled MR-FUS of moving organ – if needed
- Interference of bone
- Monitoring drug release from nanocarriers
- Interleaved temperature and contrast imaging
- Monitoring drug extravasation, cellular internalization
- Regulatory drug + device

Track 4: Technology Development track for pressure sensitive nanocarriers
Track 4a: Technology for cavitation induced extravasation and permeabilization
- Detection of cavitation
- Monitoring of extravasation
- Monitoring of permeabilization

Track 4b: Technology for cavitation induced drug release
- Detection of cavitation
- Monitoring release
- Monitoring drug extravasation, internalization
Drug Delivery Generic Roadmap
Suggested considerations for all applications
Submitted by Chrit Moonen, Matt Dreher and Brad Wood

Track 5: Applications in animal models
- Measuring carrier and drug biodistribution with MRI and/or other modalities
- Measuring PK parameters
- Measuring PD parameters
- Modeling of PKPD
- Develop optimized FUS protocols for TDD
- Develop safety model
- Heterogeneity of delivery
- Is the drug bioavailable?

Track 6: Clinical application
- Determine what application and what therapeutic standard to compare with?
- Easy standard control (ie- pancreas CA good bec no effective conventional therapies)
- What tumor location? nearby non-target anatomy?
- Patient population-pre-treatment with other agents? patient selection biases
- Previous treatments – cross over
- Inclusion / exclusion criteria
- Possible study design : randomization with cross-over : HIFU + drug vs best standard therapy – where when standard therapy fails, one can cross over to HIFU + drug
Pancreatic Cancer Overview

Disease Background

Epidemiology
- 13th most common cancer worldwide.
- In the US, only lung, colon and breast cancers cause more cancer deaths.
- WW incidence rate of about 232,000/year.
- Overall 5-year survival rate of 3-5%
- 37,000 deaths/year in US (Jemal et al., 2010; Boyle & Levin, 2008).

Etiology
- With few exceptions, occurs with advancing age of 65 years or greater.
- 20-30% attributed to smoking (Lodice et al., 2008) or diet.
- Diabetes is associated with a 2-fold increased risk of pancreatic cancer.
- Chronic inflammatory pancreatitis is associated with >10-fold risk (Key, 2007).
- Familial basis in 5-10% of cases (Brune & Klein, 2008).

Diagnosis
- No diagnostic tests or screening procedures at this time.
- Presenting symptoms (>75%), jaundice, weight loss, and nausea (Key, 2007).
- <4% of patients diagnosed at an early disease stage (Key, 2007).

Pathology
- 85% of pancreatic tumors are invasive ductal adenocarcinoma derived from exocrine tissue (Adsay et al., 2008).
- 34% of the tumors in the body and tail of the pancreas, 66% in the head region.
- Advanced ductal adenocarcinoma tumors surrounded by dense fibrous tissue (desmoplastic stroma) (Volkan et al., 2008) and also display a reduced microvascular density and perfusion (D-Onofrio et al., 2009).
- Cancer pain is primarily caused by the mass of the tumor compressing the vasculature, lymphatics or other adjacent organs (Pruemer & Rockey, 2008).
- It is considered a “silent killer” because the tumor can grow for years prior to any notable signs or symptoms (Key, 2007).

Staging
- Frequently, based on likelihood of successful resection.
- Resectable: cancer is limited to the pancreas without involvement of celiac axis or major vessels.
- Locally advanced: cancer has metastasized, however cannot be completely removed, likely due to portal or mesenteric vein involvement or extension to the celiac axis and presence of metastases (Katz et al., 2008).

Current Standard of Care & Alternative Treatments

Surgery

Pancreaticoduodenectomy/Whipple Procedure (Whipple et al., 1935)
- Only curative treatment, however (80-85%) of patients too advanced for procedure at diagnosis.
- Typically pancreas head, duodenum, gallbladder, part of the bile duct, part of the stomach and local lymph nodes removed (Shirley and Yeo, 2008).
- High volume centers have post-operative mortality as low as 1% (Lillemoe and Rikkers 2006).
- For the ideal Whipple candidate the 5-year survival rate 41%; over-all Whipple yields an 18% 5-year survival rate (Cameron et al., 2006).

Distal Pancreatectomy (Resnick & Drebin, 2008).
- Resection of the body and tail of the pancreas.
- Uncommon procedure (preformed 3-4x less frequently than the Whipple).
- Procedure rate is in decline.
Pancreatic Cancer Overview

- Local recurrence is seen in up to 85% of pancreatic cancer patients treated by surgery alone. There is no adjuvant treatment that is the standard of care for pancreatic cancer.

Radiation Mono-therapy
- Disease control failure rates in excess of 70% (Roldan et al., 1988).
- Radiation dose limited due to radiosensitivity of the adjacent uninvolved organs.
- Primarily used for pain palliation, 50% success rate. (Spalding & Ben-Josef, 2008).

Radiation and Chemotherapy (Blackstock & Wentworth 2008)
- Commonly used as surgical adjuvants for locally advanced unresectable pancreatic cancer.
- 5-Fluorouracil (PVI-5-FU) + radiation reflect the current standard of care.
- Current clinical trials with bevacizumab, capecitabine, gemcitabine or cisplatin.
- No preferred treatment has emerged for advanced pancreatic cancer.

Radiofrequency Ablation (RFA)
- Radiofrequency ablation is being investigated for the palliative treatment of locally advanced, non-resectable, localized tumors (D’Onofrio et al., 2010). The immediate goal is reduction in tumor mass. Pain relief and improved quality of life have been reported (Girelli et al., 2010; Wu et al.; 2006 Hadjicostas et al., 2006), but the single report of improved survival (Spiliotis et al., 2007) has not been validated.

Chemotherapy (Desai & Zalupski, 2008)
- Gemcitabine monotherapy is the standard chemotherapy for locally advanced, recurrent, and metastatic disease and has shown a small but statistically significant increase in overall survival.
- Key advantage is reduction in pain level and/or analgesic consumption.
- Common combination therapies with response rates from 13 to 43%.
  - Fluorouracil + Doxorubicin + Mitomycin (FAM).
  - Streptozocin + Mitomycin + Fluorouracil (SMF).
- Investigational combinations of gemcitabine with docetaxel, capecetabine, oxaliplatin and cisplatin are ongoing.

Pain Management (Pruemer & Rockey, 2008)
- Opioids (morphine) are primarily used for pain relief.
- Common side effects are constipation, nausea and sleepiness.

There is an urgent need for new treatments for pancreatic cancer patients. The ideal treatment would shrink tumors enough to render them amenable to curative resection. In the next best case, they should provide local tumor control, thus increasing survival. Minimally, a new therapy should better palliate pain and/or other symptoms.

High intensity focused ultrasound

High intensity focused ultrasound (HIFU or simply “focused ultrasound” or FUS) is an emergent noninvasive therapeutic technique being developed for the treatment of solid tumors. The focal point of the ultrasound beam can be directed to treat any site within the body, as long as there is a clear ultrasound beam path that does not pass through either bone or air. The focused ultrasound beam can be guided by several imaging techniques, the most common of which are ultrasound imaging (USgFUS) or magnetic resonance imaging (MRgFUS). Depending on the applied ultrasound parameters, the deposition of ultrasound energy can lead to heating and/or mechanical energy at the focal spot, leading to a multitude of anti-neoplastic, therapeutic affects (Emami et al., 1980; Kampinga et al., 2006; Issels, 2008).

- Hyperthermia
  - Mild heating or hyperthermia may be used to heat or ablate tissues, yet it is unclear which approach is best for pancreatic tumors.
Pancreatic Cancer Overview

- **Mechanical**
  - Mechanical energy may be useful in facilitating drug penetration through the unique dense stroma surrounding pancreatic tumors by opening cell membranes for improved drug delivery.

**Targeted Drug Delivery**

**Antibody Targeting of Chemotherapy**

Antibodies are currently being studied for their ability to target gemcitabine and other chemotherapeutic agents to pancreatic tumors.

- Erlotinib (Tarceva®) in combination with the chemotherapy drug gemcitabine (Gemzar®), is currently the only FDA approved targeted therapy for pancreatic cancer (Moore et al., 2007).
- >50 targeted chemotherapeutics are currently in clinical trials for pancreatic cancer (Philip et al., 2009). Below is a sample list of target types:
  - tumor cell signaling
  - stem cell signaling
  - tumor microenvironment
  - microvasculature
  - K-ras pathway (over 90% of resected pancreatic cancers are found to have an activating point mutation in K-ras)

Several phase II and phase III trials have been completed with the following pairs of (targeting agent linked to gemcitabine & targets): (Marimastat & MMPI), (bevacizumab & VEGF), (Bortezomib & proteasome), (cetuximab & EGFR), (Tipifarnib & FTT), (ISIS-2503 & Ras). Overall, the results have been disappointing, showing either no significant difference between test and control arms, or a median survival improvement of 2.5-8.8 months (El-Rayes, 2008).

**Heat Sensitive Therapy for Local Treatment**

Temperature sensitive liposomes (TSLs) were first reported by Yatvin and colleagues (Yatvin et al., 1978) and further developed for the treatment of solid tumors as a temperature sensitive drug delivery system (Anyarambhatla et al., 1999, Needham et al., 2000, Matteucci et al., 2000, Kong et al., 2000). A low temperature sensitive liposomal formulation is now being commercialized by Celsion Corporation for the treatment of HCC. When used in combination with mild hyperthermia (delivered by RFA or HIFU in HCC), the temperature sensitive liposome release the enclosed chemotherapeutic.

**Current and Proposed Clinical Trials of LTSLs in Pancreas**

- No clinical trials are currently underway in the use of LTSLs for treatment of pancreatic cancer.
- Celsion has announced its intention to pursue the combination of HIFU and ThermoDox® for the treatment of pancreatic cancer.

**Clinical Trials Utilizing HIFU Monotherapy**

There are no completed or active clinical trials utilizing HIFU for the treatment of pancreatic cancer listed in clinicaltrials.gov. However, there are multiple study reports of Chinese origin demonstrating ultrasound-guided HIFU monotherapy for safe ablation of pancreatic adenocarcinoma. In the largest study, Xiong et al. (2009) treated 4 stage II patients, 39 stage III patients, and 46 stage IV patients. There were no device-related serious adverse events. Complications included superficial skin burns (3%), subcutaneous fat sclerosis (7%), and an asymptomatic pancreatic pseudocyst (1%). Ultrasound guided HIFU monotherapy has shown promising rates of complete pain response in pancreatic adenocarcinoma. In the table below, pain response is summarized from a number of recent studies.
# Pancreatic Cancer Overview

## Uncertainties/Risks Related to HIFU, and Drug Delivery

- **Scientific:** It is unknown if HIFU energy will adversely react with chosen drug.
- **Medical:** Potential for thermal damage to organs adjacent to the therapeutic target. An adequate acoustic window must be available to avoid air pockets of the gut. *In vivo* positioning of pancreas must be feasible for alignment of tumor with beam path.
- **Device:** Transducer and MRI table require optimization for pancreatic therapy. Algorithm must be developed correct for motion during therapy due to the patient’s breathing. However, recent studies demonstrate that this hurdle can be overcome (Pauly, 2010).
- **Regulatory:** Safety may be the largest issue due to the possibility of releasing pancreatic digestive enzymes upon ablation.

## Author Year | # of pts | Treatment                  | Pain Relief Outcome | Adverse Effects |
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<tbody>
<tr>
<td>Xiong et al.</td>
<td>2001</td>
<td>21 HIFU monotherapy</td>
<td>15/17 (88%)</td>
<td>none</td>
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<tr>
<td>Wang et al.</td>
<td>2002</td>
<td>13 HIFU monotherapy</td>
<td>8/10 (80%)</td>
<td>mild pancreatitis</td>
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<tr>
<td>Xie et al.*</td>
<td>2003</td>
<td>41 HIFU mono vs. HIFU + gemcitabine</td>
<td>HIFU mono (66.7%)</td>
<td>BM suppression</td>
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<td>Xu et al.*</td>
<td>2003</td>
<td>37 HIFU of tumor + celiac plexus</td>
<td>24/30 (80%)</td>
<td>none</td>
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<tr>
<td>Yuan et al.*</td>
<td>2003</td>
<td>40 HIFU monotherapy</td>
<td>32/40 (80%)</td>
<td>none</td>
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<tr>
<td>Wu et al.</td>
<td>2005</td>
<td>8 HIFU monotherapy</td>
<td>8/8 (100%)</td>
<td>none</td>
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<tr>
<td>Xiong et al.</td>
<td>2009</td>
<td>99 HIFU monotherapy</td>
<td>54/67 (80.6%)</td>
<td>3 superficial skin burns, 6 subcutaneous sclerosis, 1</td>
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<tr>
<td>Orsi et al.</td>
<td>2010</td>
<td>6 HIFU monotherapy</td>
<td>6/7 (86%)</td>
<td>portal vein thrombosis</td>
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<tr>
<td>Zhao et al.</td>
<td>2010</td>
<td>39 HIFU + gemcitabine</td>
<td>22/28 (78.6%)</td>
<td>Neutropenia, thrombocytopaenia, nausea, diarrhea, fever</td>
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<tr>
<td>Wang et al.</td>
<td>2011</td>
<td>40 HIFU monotherapy</td>
<td>35/40 (87.5%)</td>
<td>none</td>
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(*Modified from Jang et al., 2010)

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## Author Year | # of pts | Treatment                  | Pain Relief Outcome | Adverse Effects |
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# Pancreatic Cancer Overview

## References

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<th>Author(s)</th>
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http://www.celsion.com/releasedetail.cfm?releaseid=410968
Pancreatic Cancer Overview


## Pancreatic Cancer Overview

|---|
Pancreatic Cancer Draft Roadmap
Submitted by Joo Ha Hwang et al.

Parameters
- Identify the appropriate small animal model of pancreas cancer for studying MRgFUS-drug delivery
- Identify candidate chemotherapeutic agent(s)*
- Complete characterization of the HIFU transducer (metrology)
- Determine ultrasound parameters to perform initial in vivo studies*
- Does MRgFUS enhance drug delivery? – Acute studies
- Optimize ultrasound parameters – Acute studies
- Assess toxicity and efficacy of MRgFUS-drug delivery in a genetically engineered mouse model – survival studies

Assumptions
- Pancreas adenocarcinoma tumors exhibit a dense desmoplastic (fibrotic) stroma that inhibits penetration of systemically administered drug into the tumor.
- Ideally, drug delivery approach should utilize thermal mechanisms of drug release to capitalize on the benefit of MR to monitor temperature in response to FUS therapy.
- Mechanical mechanisms of drug delivery can also be exploited using MRgFUS due to the ability of MR to guide therapy (identify the focus).

Broad Research Questions
- Can focused ultrasound enhance the penetration of systemically administered chemotherapeutic agents into pancreas tumors?
- What are the optimal in situ ultrasound parameters that will enhance penetration of systemically administered chemotherapeutic agents?
- What are the mechanisms involved in FUS-enhanced drug delivery of chemotherapeutic agents into pancreatic tumors (thermal, mechanical, both)?
- Can the pancreas be safely and effectively targeted by MR guided focused ultrasound? What are the potential risks? How can these risks be minimized?
- What is the best method for addressing respiratory movement of the pancreas during MRgFUS treatment?
- Will MRgFUS-enhanced drug delivery for treatment of pancreas cancer result in improved patient outcomes (palliation/survival)?

Safety
- Determine the optimal large animal model to assess safety*
- Develop a method to address movement of the target (pancreas) due to respiration
- Determine safety of MRgFUS-drug delivery in normal pancreas tissue in a large animal model

Clinical Research
- What are the goals of therapy for MRgFUS-drug delivery in the treatment of pancreas cancer?*
- Feasibility Clinical Trial*
- Pilot Clinical Trial
- Pivotal Clinical Trial

*Denotes items that can be performed in parallel
Head and Neck Cancer Overview

Disease Background
Head and Neck cancers are relatively rare and in the United States accounting for about 3-5% of all cancers. This cancer typically originates in the squamous cells lining the mucosal surfaces of the oral cavity (55%), larynx (25%), oro and hypo pharynx (15%), sinuses (4%), and nasopharynx 1% (Skeel, 2007). Excluded from this summary are melanomas, lymphomas, sarcomas, salivary gland cancers and thyroid cancer.

Epidemiology
- US incidence rate ≈ 40,000/year (NCI fact sheet).
- Worldwide (WW) Incidence rate ≈ 460,000/year (Boyle & Levin)
  - 400,000 oral cavity and pharynx
  - 160,000 larynx
- Overall 5-year survival rate of 40% in US and EU (Boyle & Levin)
- Stage III disease, 3-5 year survival rate is 25-60% (Skeel, 2007)
- Stage IV disease, survival ranges from 10-30% (Skeel, 2007)
- 300,000 deaths/year WW (Boyle & Levin)
- Male incidence rate 3x female (Skeel 2007)

Etiology
- Greater than 70% of head & neck cancers can be attributed to tobacco or alcohol use worldwide
  - Tobacco use increases risk 3.4% to 7.0% (Gandini et al., 2008)
  - Heavy alcohol use increases risk by 10x (Boyle & Levin)
- Human papilloma virus (HPV) is a cause for some H&N cancers.
- In the United States, 85% of head and neck cancers can be directly linked to tobacco use (NCI fact sheet) (Boyle & Levin).

Pathology
- Majority of H&N cancers are derived from squamous cells carcinomas (SCC). Malignancies are most likely to spread to adjacent structures and regional lymphatics mandible or skull
- Spread below the clavicle is unusual, but pulmonary most likely site (Skeel 2007)

Current Standard of Care & Alternative Treatments

Surgery
Surgery is the gold standard for head and neck cancers. Eligible candidates for surgical resection will have a small lesion without regional extension. Surgical deformity may result.

Radiotherapy
Radiotherapy is routinely utilized for non-surgical candidates or in combination with surgery and chemotherapy. Indicated for tonsils, base of tongue, floor of mouth and locally advanced cancers. Compliance (treatments 1-2x/day, 5 days/week for 5-7 weeks) can be an issue for patients without necessary social support, such as the elderly or chronic alcohol abusers.

Chemotherapy
Occasionally, chemotherapy is used in addition to radiotherapy. This is challenging due to narrow therapeutic index, high rates of moderate to severe side effects and modest benefits for most patients (Skeel 2007), with tumor response only anticipated in 20-50% of patients. However, median survival is 6-9 months. A wide variety of chemotherapy agents are available for use in the treatment of recurrent head and neck cancer. Higher response rates include: methotrexate (10-50%), Cisplatin (9-40%), Paclitaxel (40%), Docetaxel (34%), and Doxorubicin for nasopharynx only (39%) (Skeel, 2007).

Combined Modality
The combination of chemotherapy, radiation and surgery has been the focus of clinical research for decades. The addition of chemotherapy concurrently with radiation therapy results in up to a 4-8% improvement in survival. Many regimens and approaches yield similar results, which enables individualization to match patient’s needs. Chemotherapy is also used a radiation sensitizer and as neoadjuvant (Skeel, 2007).
High Intensity Focused Ultrasound

High intensity focused ultrasound (HIFU or simply “focused ultrasound” or FUS) is an emergent noninvasive therapeutic technique being developed for the treatment of solid tumors, although it has not been used clinically for treatment of head and neck cancer. In the case of early-stage cancer, the goal can be curative, and the targeted region should include the tumor and a normal tissue margin of 1.5-2 cm. In advanced cancers, the course of focused ultrasound is palliative, to inhibit tumor growth and increase the quality of life. The focal point of the ultrasound beam can be directed to treat any site within the body, as long as there is a clear ultrasound beam path that does not pass through either bone or air. The focused ultrasound beam can be guided by several imaging techniques, the most common of which are ultrasound imaging (USgFUS) or magnetic resonance imaging (MRgFUS). Depending on the applied ultrasound parameters, the deposition of ultrasound energy can lead to heating and/or mechanical energy at the focal spot, leading to a multitude of anti-neoplastic, therapeutic affects (Emami et al., 1980; Kampinga et al., 2006; Issels, 2008).

- Hyperthermia
  - Mild heating or hyperthermia can be used to heat tissues or ablate tumors. Heat deposition can be precisely controlled.
  - Xenografts of SCC7 cells in a mouse flank undergo necrosis or apoptosis when exposed to HIFU, suggesting that HIFU may be a viable alternative treatment for head and neck patients in the future (Hundt, et al., 2007 & 2009).

- Mechanical/Cavitation
  - May force drug through tumor stroma
  - May open cell membranes for improved drug delivery
  - May lyse microbubbles for delivery of therapeutic to tumor
  - Interaction of ultrasound waves with the tissue may also enhance extravasation

Local Drug Delivery

HIFU enhanced delivery of therapeutic agents (mechanical)
- Poff et al., (2008) have reported that pulsed HIFU enhances the delivery of the antibody bortezomib to SCC7 xenografts in mice. The treatment resulted in apoptosis and growth inhibition of SCC7 xenografts.
- Pulsed HIFU has been shown to enhance the delivery and expression of systemically injected naked DNA to SCC7 tumors in mice (Dittmar et al., 2005).
- Reports also show enhanced delivery of systemic therapeutic agents with the use of pulsed HIFU (Frenkel, 2006, Stone et al., 2007).
- Microbubbles may be used to deliver drugs or gene therapy to tumors with targeting ligands on their surface. (Stride & Coussios 2010)

HIFU enhanced delivery of therapeutic agents (heat)
- Temperature sensitive liposomes (TSLs) were first reported by Yatvin and colleagues (Yatvin et al., 1978) and further developed for the treatment of solid tumors as a temperature sensitive drug delivery system (Anyarambhatla et al., 1999, Needham et al., 2000, Matteucci et al., 2000, Kong et al., 2000). A low temperature sensitive liposomal formulation is now being commercialized by Celsion Corporation for the treatment of HCC. When used in combination with mild hyperthermia (delivered by RFA or HIFU), the temperature sensitive liposome release the enclosed chemotherapeutic. This has potential for the treatment of nasopharynx carcinomas.

Clinical Trials Utilizing HIFU Monotherapy

There are no reports on the use of focused ultrasound for the clinical treatment of head and neck cancers at this time. Although HIFU has been used extensively in China to treat thousands of patients (Fu et al., 2004), the devices used were ultrasound-guided which lack real-time temperature monitoring. Given the dense packing of critical nerves, arteries and vessels in the neck region, it is imperative the focused ultrasound device has fine control of: 1) the spatial positioning of the beam; 2) the temperature at the site of heat deposition; and 3) temperature monitoring of the surrounding tissues. Unlike ultrasound-guided systems, the MRI-guided
Head and Neck Cancer Overview

focused ultrasound systems can meet these requirements. However, at this time the primary manufacturers of MRI-guided focused ultrasound systems (Philips and InSightec) have not announced an intention to investigate head and neck cancers. Since head and neck will require engineering and manufacture of dedicated hardware and ultrasound transducer, it doesn’t appear that this indication will be addressed by focused ultrasound in the immediate future.

Potential Benefits Related to HIFU, and Drug Delivery
- Repeated treatments possible
  - Ideal for those with maximum radiation exposure
- Focal point can be as small as 5 mm³
- It may provide a treatment option with reduced trauma and improved quality of life
- May eliminate multiple clinic visits required for irradiation
- Non-invasive
- Real-time imaging allows evaluation of area during treatment
- No risk of increased metastasis due to seeding along incision
- Potentially curative
- HIFU+ heat sensitive drug likely to destroy micromets in tumor margin

Uncertainties/Risks Related to HIFU, and Drug Delivery
- Scientific: It is unknown if HIFU energy will adversely react with drug.
- Medical: Potential for thermal damage to nerves and vessels adjacent to the therapeutic target.
- Device: Transducer requires optimization for head and neck therapy.
# Head and Neck Cancer Overview

## References

<table>
<thead>
<tr>
<th>Author</th>
<th>Title</th>
<th>Journal</th>
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</thead>
</table>
# Head and Neck Cancer Overview

<table>
<thead>
<tr>
<th>Reference</th>
<th>Details</th>
</tr>
</thead>
</table>
Head and Neck Cancer Draft Roadmap
Submitted by Kathy Ferrara et al.

Parameters and safety

Assumptions:
- Squamous head and neck tumors limit diffusion of drug and particles
- FUS-mediated drug delivery should utilize thermal mechanisms to enhance accumulation and drug release.
- Lipoplatin will be efficacious and safe

Research Questions:
- Can focused ultrasound enhance the penetration of systemically administered chemotherapeutic agents into head and neck tumors?
- What are the optimal in situ ultrasound parameters that will enhance penetration of systemically administered chemotherapeutic agents?
- Will MRgFUS-enhanced drug delivery result in improved patient survival?

Clinical Research

What are the goals of therapy for MRgFUS-drug delivery in the treatment of head and neck cancer?

Evaluate the efficiency of US-enhanced drug delivery in the hamster cheekpouch

Create a transducer for treating head and neck cancer and melanoma in canines/humans

Create infrastructure for treatment of canines within Veterinary MRI

Evaluate the efficiency of US-enhanced drug delivery in the canine

Evaluate the efficacy and safety of US-enhanced drug delivery in the canine

Evaluate the efficacy and safety of US-enhanced drug delivery in the hamster cheekpouch.

Optimize US and delivery vehicle

Pilot/Feasibility Clinical Trial

Pivotal Clinical Trial
Notes
Liver Cancer Overview

Disease Background
Primary and secondary malignancies in the liver present one of the most challenging problems in clinical oncology. At the time of diagnosis, only 20% of patients are surgical candidates. Radiofrequency ablation of liver tumors is a common minimally invasive treatment for those not eligible for surgery; however, recurrence rates are unacceptably high. Part of the reason for the high recurrence rate is that micrometastases seed the tumor margin and frequently are not destroyed or removed by surgery or ablation methods.

Primary Hepatocellular Carcinoma (HCC)

Epidemiology
- HCC accounts for 80% of all primary liver cancers
- 5th most common malignancy worldwide (WW); incidence >550,000
- 54% of cases are in China, another 29% in developing countries
- USA, Japan, UK have trending increase in HCC incidence
- Overall 5-year survival rate: 5-9%
- Most patients survive less than 6 months from diagnosis
- Men 3X higher incidence than women (Boyle & Levin, 2008)

Etiology
- Hepatitis B infection causal for >50% of HCC
- Hepatitis C infection causal for >31% of HCC
- Alcohol/tobacco
- Obesity/diabetes/fatty liver
- Aflatoxin exposure (Boyle & Levin 2008)

Diagnosis
- 70% of HCC patients have elevated α-fetoprotein (Skeel, 2007); however, this marker is not specific to liver cancer
- Genetic screening for point mutations is on the horizon for HCC

Pathology
- Symptoms include abdominal pain, weight loss, fatigue, abdominal swelling and eventually jaundice

Prevention
- Since the early 1980's, HBV vaccines have been available to reduce chance of HCC
- No HCV vaccines are available

Secondary Liver Cancer
- Est. nearly 2,000,000 WW annual incidence of mets to liver (Boyle and Leven, 2008; Pickren, 1982)
- Primary tumors that metastasize to liver:
  - breast, stomach, colorectal, pancreas, gallbladder and eye (Pickren, 1982)
- In 90% of cases, liver metastases are multiple (Khan, 2009)
- Metastatic colorectal cancer to liver has a 5-year survival rate 38% (Fong, 1997)

Current Standard of Care & Alternative Treatments

Surgical Resection
This is the gold standard and can be curative. Surgical resection is only viable if a single or a few tumors are found in the liver. The vast majority patients (80%) are not surgical candidates because of tumor size, location near major intrahepatic blood vessels precluding a margin-negative resection, or inadequate hepatic function related to coexistent cirrhosis (Curley, 2001). In any resection or ablation of a hepatic tumor it is critical to remove a 1-2 cm margin around the tumor in order to remove any micrometastases that would result in a recurrence. (Wakai et al., 2008; Shi et al., 2007).
Liver Cancer Overview

Chemotherapy
Chemotherapy regimens are dependent on the type of primary tumor, so therapies and outcomes are quite different between HCC and secondary mets to liver patients (Skeel, 2007). Chemotherapeutics may be used to temporarily shrink the tumor, making it eligible for resection but they are not curative. Unfortunately, 40% of patients have advanced HCC disease at diagnosis and are not eligible for either surgery or ablation (Giglia, 2010), leaving chemotherapy as the only viable treatment option.

- Chemotherapy for HCC includes doxorubicin, fluoropyrimidines, and gemcitabene/oxaliplatin combinations (Giglia, 2010). However, response rates are extremely low, with a representative 2% response rate to doxorubicin therapy (Skeel, 2007).
- Chemotherapy for liver metastases may lead to a response in 20% of patients (Khan, 2009), yet metastases from the various primary tumors have different recommended treatments - and consequently, outcomes. Treatments for colorectal metastasis to liver have the most promise.

Radiation Therapy
Typically radiation therapy is utilized for palliation of pain, yet it has found to have minimal benefit beyond pain reduction.

Percutaneous Ablation
- Radiofrequency ablation (RFA) utilizes radiofrequency energy to cause cellular death by coagulation necrosis. This technique is widely used as an adjuvant to resection or in cases where resection is not advisable. It can be an effective treatment option in both primary and metastatic liver tumors. Candidates for RFA typically have four or fewer tumors, each of ≤5cm in diameter with no extrahepatic disease. The ideal tumor for RFA therapy is distant from major hepatic vessels/bile ducts, yet these tumors are difficult to completely ablate due to the cooling effect from flowing blood (Khan, 2009). Success rates reported for RFA vary widely with 5-year survival rates ranging from 14-55% and local tumor recurrence rates ranging from 3.6-60% (Tsoufas, 2011). In general, RFA is considered to be a safe, well-tolerated, effective treatment for unresectable hepatic malignancies (Curley, 2001).
- Other Ablation Methods (Khan, 2009)
  - Transcatheter arterial chemoembolization (TACE)
  - Cryoablation
  - Microwave ablation
  - Ethanol ablation, or percutaneous ethanol injection (PEI)
  - Laser ablation

Targeted Therapies
Recently, considerable efforts have been made toward drugs that target the molecular pathways known to lead to HCC. Antibodies capable of targeting chemotherapeutics to known HCC pathways are being actively explored (Giglia, 2010). Sorafenib, bevacizumab, erlotinib, cetuximab, sunitinib and sirolimus have all been evaluated in clinical trials. Sorafenib, a kinase inhibitor is recommended as a first-line therapy in patients ineligible for resection or loco-regional ablation therapy. Patients who do not respond to sorafenib may be put on combination therapy regimens that include doxorubicin, capecetabine, or gemcitabine/platinum combinations.

Heat Sensitive Therapy for Local Treatment
Temperature sensitive liposomes (TSLs) were first reported by Yatvin and colleagues (Yatvin et al., 1978) and further developed for the treatment of solid tumors as a temperature sensitive drug delivery system (Anyarambhata et al., 1999, Needham et al., 2000, Matteucci et al., 2000, Kong et al., 2000). A low temperature sensitive liposomal formulation is now being commercialized by Celsion Corporation for the treatment of HCC. When used in combination with mild hyperthermia (delivered by RFA or HIFU in HCC), the temperature sensitive liposome release the enclosed chemotherapeutic.

Current and Proposed Clinical Trials of LTSLs in HCC
LTSls and RFA
Lyso-thermosensitive liposomal doxorubicin (ThermoDox® Celsion Corporation, Columbia MD) in combination with RFA is in a phase III worldwide clinical trial for the treatment of HCC.

Focused Ultrasound Surgery Foundation | Drug Delivery Workshop I, 2011
Liver Cancer Overview

LTSLs and HIFU
Celsion and Philips have been awarded a Center for Translational Molecular Medicine (CTMM) grant in collaboration with several Dutch academic institutions for the HIFU-CHEM program. One project is to study the combination of HIFU and ThermoDox® for the treatment of liver cancer.

High Intensity Focused Ultrasound
High intensity focused ultrasound (HIFU or simply “focused ultrasound” or FUS) is an emergent noninvasive therapeutic technique being developed for the treatment of solid tumors, among other non-cancerous applications. The focal point of the ultrasound beam can be directed to treat any site within the body, as long as there is a clear ultrasound beam path that does not pass through either bone or air. The focused ultrasound beam can be guided by several imaging techniques, the most common of which are ultrasound imaging (USgFUS) or magnetic resonance imaging (MRgFUS). Depending on the applied ultrasound parameters, the deposition of ultrasound energy can lead to heating and/or mechanical energy at the focal spot, leading to a multitude of anti-neoplastic, therapeutic affects (Emami et al., 1980; Kampinga et al., 2006; Issels, 2008). While both US and MRI guidance are currently being utilized to guide focused ultrasound therapy, MRI provides anatomical information for planning of the therapeutic intervention and real-time temperature mapping for local hyperthermia control. If the delivered drug has been developed to include an MR-imaging agent, MRgFUS can allow for monitoring of the drug release (de Smet M et al., 2010). Additionally, FUS has been shown to stimulate an increase in the patient’s host immune response (den Brok et al, 2004).

One of the biggest issues to overcome in the treatment of liver tumors with focused ultrasound is motion correction during therapy due to the patient’s breathing. However, recent studies demonstrate that this hurdle can be overcome (Pauly, 2010).

Hyperthermia
- Can be used to mildly heat or ablate tissues. Heat deposition can be precisely controlled.

Mechanical (cavitation)
- May be useful in enhancing drug penetration for improved drug delivery.
- Interaction of ultrasound waves with the tissue may also enhance extravasation and membrane permeability leading to a further increase of drug uptake.

Clinical Trials Utilizing HIFU Monotherapy
At February 2011, one clinical trial for HIFU in liver cancer is listed on USFDA’s web site www.ClinicalTrials.gov. This is a safety trial entitled Hepatic and Renal Thermography Using Magnetic Resonance Imaging (Ther-IRM) sponsored by the University Hospital of Bordeaux. In the near future, the HIFU-CHEM project supported by CTMM will initiate a study assessing the potential for MRgFUS technology to mediate drug release from ThermoDox® and increase the doxorubicin concentration within the tumors of patients with liver cancer.

Sites in Asia have advanced at a faster rate in the utilization of focused ultrasound for treatment of liver cancer. The Model-JC HIFU System (Chongqing HAIFUt Company) is the most widely used clinical device, having been used in China and throughout Asia since 1997. Over 1000 treatments in various solid tumors and other applications were reported with the Model-JC HIFU System during the four-year period of 1997-2001 (Wu et al., 2004).

Zhang et al. (2010) recently reviewed a number of studies treating liver cancer with ultrasound-guided focused ultrasound (USgHIFU or USgFUS). The authors concluded that USgHIFU ablation is emerging as a safe, effective, and feasible modality for the ablation of both malignant and benign liver tumors. Importantly, ultrasound-guided focused ultrasound does not have the safety benefit of real-time thermometry available in the MRI-guided focused ultrasound systems.
Liver Cancer Overview

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th># Pts.</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu, F</td>
<td>2001</td>
<td>56</td>
<td>USgHIFU for HCC</td>
<td>6/6 resections, irreversible damage to treated tumor</td>
<td>None reported</td>
</tr>
<tr>
<td>Wu, F</td>
<td>2005</td>
<td>50</td>
<td>TACE or TACE +USgHIFU for HCC</td>
<td>Median survival: 4.0 mo TACE 11.3 mo TACE + USgHIFU</td>
<td>One low-grade fever (temperature up to 38.5°C). Two ultrasound-induced skin burns. Four patients mild local pain 5 days after ablation,</td>
</tr>
<tr>
<td>Illing, RO</td>
<td>2005</td>
<td>22</td>
<td>USgHIFU for liver mets</td>
<td>100% Ablation</td>
<td>CTC grade 3: n=1 Discomfort at treatment site; n=2 oedema. CTC grade 1 or 2: Skin toxicity and fever.</td>
</tr>
<tr>
<td>Li, YY</td>
<td>2007</td>
<td>151</td>
<td>USgHIFU for HCC vs. no treatment control</td>
<td>Overall response rate 88.9% 1 yr survival 50% 2 year survival 31%</td>
<td>No severe complications</td>
</tr>
<tr>
<td>Zhang, L</td>
<td>2009</td>
<td>39</td>
<td>HIFU of HCC tumors adjacent to veins</td>
<td>21/42 tumors completely ablated, 21/42 tumors &gt;50% ablated.</td>
<td>None reported. Specifically no blood vessel injury observed</td>
</tr>
<tr>
<td>Orsi, F</td>
<td>2010</td>
<td>17</td>
<td>HIFU of liver mets</td>
<td>Complete response 22/24 tumors treated</td>
<td>None reported</td>
</tr>
</tbody>
</table>

Benefits Related to FUS and/or Drug Delivery

- It may provide a treatment option with reduced trauma and improved quality of life
- Reduced hospitalization time
- Noninvasive, safe – morbidity much less than surgery
- Real-time imaging allows evaluation of area during treatment
- No risk of increased metastasis due to seeding along incision
- Potentially curative
- Repeatable procedure
- FUS + heat sensitive drug likely to destroy micromets in tumor margin

Uncertainties/Risks Related to FUS and/or Drug Delivery

- Algorithm must be developed to overcome/correct for repetitive organ movement due to patient breathing and any other motion artifacts
- An adequate acoustic window must be available to avoid ribs in the beam path
- Tumors must be positioned such that they are in the beam path
- Potential for thermal damage to organs adjacent to the therapeutic target
- The higher flow and perfusion rates in the liver require modifications of the system and software platforms to allow for enhanced monitoring and parameter control
- Long time taken (2 hours avg.) to ablate liver tumors
- Common adverse events include local pain, oedema and skin toxicity
- It is unknown if FUS energy will adversely react with drug
# Liver Cancer Overview

## References


Liver Cancer Overview


Liver Cancer Draft Roadmap
Submitted by Chrit Moonen, Matt Dreher and Brad Wood

Approach/objective:
1. Use MRI-HIFU to heat liver tumors to mild hyperthermia temperatures (40-42°C) in order to deliver drug from temperature sensitive carriers in a distribution or location that would otherwise not be attainable
2. Use MRI-HIFU to increase liver tumor drug uptake by using cavitation based approaches in combination with pressure sensitive carriers and/or cavitation induced extravasation/permeabilisation
3. Establish methodology & validity of combining MRI-HIFU for ablation with MRI-HIFU for drug delivery or sensitization

Parameters:
MR-HIFU technology development
1. Temperature monitoring and heating in the moving liver – provides accuracy and safety
2. Intercostal firing – to be able to heat more regions within the liver
3. Conformal heating – to cover an entire tumor
4. Interleaved imaging – to monitor heat and contrast delivery, more rapidly optimize HIFU
5. Minimize skin heating – to limit drug release in skin and provide safety
6. Monitor cavitation with and without microbubbles

Drug system development
1. Clinically relevant DDS – translatable
2. Image-able DDS – To improve the speed of experiments & optimize use of imaging

Important liver specific questions:
1. Can temperature monitoring be performed in a moving liver?
2. What regions in the liver are accessible (+/- intercostal firing)?
3. How large of a tumor volume can be heated?
4. Can liver be heated without heating other structures such as skin?
5. What is the optimum HIFU exposure for drug accumulation using temperature sensitive or pressure sensitive carriers?
6. What Pharmacokinetic information can be obtained by co-releasing contrast agents?
7. What imaging methods should be used for early Pharmacodynamic assessment?
8. What is the gold standard, TACE-DEB, RFA, Y90?
9. What liver tumor (histology & patients) can be targeted with such methods, and what drugs (drug combinations) should be used?
10. What patient population to study?

Key experiments (MR-HIFU):
1. Demonstrate ability to heat liver without heating skin
2. Demonstrate ability to conformally heat a tumor
3. Demonstrate ability to target a tumor using cavitation
4. Demonstrate ability to heat large volumes

Key experiments (drug delivery):
1. Demonstrate improved drug delivery to an entire tumor
2. Optimize HIFU exposures (time and temperature) for sufficient drug delivery
3. Comparison with reference methods like TACE-DEB
4. Randomized clinical trial to compare to standard local – regional therapies?
Prostate Cancer Overview

Disease Background
Carcinoma of the prostate primarily affects the elderly. It is the most common cancer in the United States with the highest rate found among African-Americans. However, this does not reflect the world status. In the EU prostate cancer is the fourth most common cancer in men while in Asia, India and northern Africa, the incidence rates are extremely low. The situation is confounded as the environmental and/or genetic factors causing the disease remain unclear. In recent years, aggressive diagnostic testing for prostate specific antigen (PSA) has led to an upward (paper) trend in incidence, while an increase in early detection rates have contributed to a decline in mortality in many countries (Boyle & Levin, 2008).

Epidemiology
- 900,000 annual WW incidence in 2008
  - Western/Developed countries have highest incidence (Boyle & Levin, 2008)
- 5 year relative survival is country dependent, near 100% in the US but 40% in less developed countries (ACS, 2011)
- 6th leading cause of cancer death in men WW (ACS, 2011)

Etiology
- Underlying causes unknown, not related to tobacco or alcohol use
- No major contributing genetic causes have been identified (Boyle & Levin, 2008)

Diagnosis
- Prostate-specific antigen (PSA) levels are not reliable, as elevated PSA levels have multiple causes.
- Digital rectal examination only detects palpable physical changes in the prostate gland.
- Biopsy only dependable confirmatory test

Staging
- Usually accomplished with consideration of both clinical and pathological indicators
- TNM staging system most commonly used

Current Standard of Care & Alternative Treatments
Selection of appropriate therapy for prostate cancer is complex and is based on the extent of disease, age, and general medical condition of the patient and tumor features (Gleason score, TNM stage and PSA level). No good randomized trials have been performed that compare the treatment modalities for early stage disease (Skeel, 2007). Surgery and/or radiation therapy can be curative for patients that present with early stage disease. In the US this equates to about 75% (Cooperberg et al., 2004).

Early Stage Standard of Care: T1, T2 (organ confined) Disease (Skeel, 2007).
- Radical prostatectomy (surgical resection) (open, laparoscopic, robotic-assisted)
- Radical Radiotherapy
  - External Beam Radiation Therapy (EBRT)
  - Brachytherapy
- Cryoablation (Lidner, 2010)

Late Stage Standard of Care: T3: Tumor extends through prostatic capsule T4: Invasion of local structures (Skeel, 2007).
- Hormonal therapy. 75% of patients have subjective response lasting 18 mo., until the tumor becomes androgen-independent
  - Orchiectomy or luteinizing hormone-releasing hormone (LHRH) analogs are first line.
  - If effective against cancer, will also result in sexual dysfunction
- Chemotherapy, for hormone-refractory prostate cancer. (Harrison, 2009)
  - Docetaxel & prednisone on a 3 week cycle are standard
  - Mitoxantrone, Estramustine, 5-fluorouracil, and doxorubicin achieve up to 50% reduction in PSA.
- Radiation
- Combinations of above
Prostate Cancer Overview

Targeted Therapies
Much effort has been put toward blocking targets in the molecular pathways leading to metastatic prostate cancer. Key targets under investigation include tumor vasculature, signaling pathways for androgen resistance and cell stress/survival signals. Also being investigated are immunotherapies against antigenic targets on cancer cells and host immune modulation. Many (+20) clinical trials are ongoing (Stavridi, 2010). Another route is to leverage localized heating capability of focused ultrasound to activate heat inducible promotors on heat-responsive gene therapy systems (Walther & Stein, 2009).

Heat Sensitive Therapy for Local Treatment
Temperature sensitive liposomes (TSLs) were first reported by Yatvin and colleagues (Yatvin et al., 1978) and further developed for the treatment of solid tumors as a temperature sensitive drug delivery system (Anyarambhata et al., 1999, Needham et al., 2000, Matteucci et al., 2000, Kong et al., 2000). A low temperature sensitive liposomal formulation is now being commercialized by Celsion Corporation for the treatment of HCC. When used in combination with mild hyperthermia (delivered by RFA or HIFU in HCC), the temperature sensitive liposome release the enclosed chemotherapeutic.

Current and Proposed Clinical Trials of LTSLs
- Lyso-thermosensitive liposomal doxorubicin (ThermoDox® Celsion Corporation, Columbia MD) in combination with RFA is in a phase III worldwide clinical trial for the treatment of HCC.
- Celsion has completed a Phase I Dose Escalation, Pharmacokinetics, and Safety Study of Doxorubicin Encapsulated in Temperature Sensitive Liposomes Released Through Microwave Therapy in the Treatment of Prostate Cancer. The company does not appear to be pursing this indication (www.clinicaltrials.gov).

High Intensity Focused Ultrasound
High intensity focused ultrasound (HIFU or simply “focused ultrasound” or FUS) is utilized as a transrectal therapeutic technique for ablation in the treatment of prostate cancer. Ablatherm®(EDAP-TMS Lyon, France) is CE marked and has an IDE in phase II/III for T1, T2 (localized) prostate cancer. Sonablate® 500 (Focus Surgery, IN, USA) is also CE marked (benign prostatic hyperplasia (BPH )+ prostate cancer) and approved in Japan for BPH. Neither device is FDA approved, but both are approved in Canada, EU, South Korea and Russia. Worldwide, tens of thousands of patients have been treated with Sonablate® 500 or Ablatherm®. A recent systematic literature review was conducted by the Genitourinary Cancer Disease Site Group of Ontario Canada (Lukka et al., 2011). After a review of Ablatherm and Sonoblate treatment data from nearly 7000 patients they concluded that the “use of HIFU should be restricted to clinical trials and to patients for whom other local curative treatment options are not suitable.”

The Ablatherm and Sonoblate HIFU devices do not have temperature control or monitoring features and are only used for ablation. They are both guided by ultrasound imaging (USgHIFU). HIFU energy is converted to heat and/or mechanical energy when it interacts with tissues leading to a multitude of anti-neoplastic, therapeutic affects (Emami et al., 1980; Kampinga et al., 2006; Issels, 2008).

Ablative Hyperthermia
- Coagulative necrosis of targeted neoplastic tissue.
- Ablation and disruption of cellular membranes has the potential for up-regulation of the patient’s host immune response against the cancer (den Brok et al, 2004).

Mechanical (cavitation)
- May be useful in forcing drug through cell membranes for improved drug delivery.
- Interaction of ultrasound waves with the tissue may also enhance extravasation and membrane permeability leading to a further increase of drug uptake.

Clinical TrialsUtilizing HIFU Monotherapy
HIFU as Primary Treatment
There is very little information regarding the comparability of HIFU treatments with other established primary treatment options for prostate cancer. There are no published randomized controlled trials in the literature.
Prostate Cancer Overview

(Williams, 2010). However, at least 29 studies treating a total of 6912 patients have been published on the efficacy of HIFU in the primary treatment of prostate cancer (reviewed by Lukka et al., 2011). In a very large recent study, Crouzet et al., (2010) treated 803 localized prostate cancer patients with HIFU. The disease free survival rate at 8 years was 97%.

- Extensive publications on thousands of patients treated
- 5-yr disease free survival of 70-80% (no comparative studies available)
- Common complications (n= >500) (Lukka et al., 2011)
  - Urethral stricture 12.3%
  - Urinary incontinence 8.1%
  - Stenosis (urethra, bladder, neck) 7.8%
  - Urinary retention 5.3%
  - Chronic perineal pain 3.4%
  - Impotence 44%
- Randomized and comparative trials are necessary prior to HIFU becoming a standard treatment option

HIFU as Salvage Treatment following EBRT

- Morbidity similar to other salvage treatments following EBRT
- Data from 5 studies is slim (Lukka et al., 2011), but treatment is easier to ethically justify given lack of less invasive alternatives
- Common complications (n= ≥50) (Lukka et al., 2011)
  - Urethral stricture 10%
  - Urinary incontinence 28%
  - Stenosis (urethra, bladder, neck) 17%
  - Urinary retention 16%
  - Chronic perineal pain 18%
  - Impotence 47%

Selected Studies: Efficacy of HIFU as a salvage treatment for prostate cancer following EBRT

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>Negative Biopsy Rate (%)</th>
<th>Nadir PSA ≤.5 ng/ml</th>
<th>Disease-free survival (%)</th>
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<tr>
<td>Berge</td>
<td>2010</td>
<td>46</td>
<td>N/A</td>
<td>91.3</td>
<td>NR</td>
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<td>Murat</td>
<td>2009</td>
<td>167</td>
<td>73</td>
<td>N/A</td>
<td>17 (5 yr)</td>
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<tr>
<td>Mallick</td>
<td>2006</td>
<td>50</td>
<td>NR</td>
<td>66</td>
<td>54 (1 yr)</td>
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<tr>
<td>Gelet</td>
<td>2006</td>
<td>106</td>
<td>84</td>
<td>57</td>
<td>40 (40 mo)</td>
</tr>
</tbody>
</table>

Table modified from Williams et al., (2010). NR, not reported; PSA, prostate-specific antigen

In a pilot study (n=9), of HIFU as salvage first-line treatment for locally recurrent prostate cancer after radical prostatectomy the authors concluded HIFU is a feasible therapy with acceptable morbidity profile (Asimakopoulos, 2011).

Development of Magnetic Resonance Guided HIFU (MRgHIFU) for treatment of prostate.

ExAblate® OR prostate module (InSightec, Tirat Carmel, Israel) is being investigated for the treatment of early stage, low risk prostate cancer. Thus far, a total of 7 patients have been treated in feasibility studies, which InSightec announced, “show initial promising results”. The device utilizes MR guidance. The potential advantages of MR guidance over US guidance include 1) improved imaging and 2) real-time measurement of thermal energy deposition for safety (www.insightec.com). InSightec is also sponsoring A Multi-Center Prospective Single Arm Intervention Trial Evaluating Focal Therapy Using High Intensity Focused Ultrasound (Sonablate 500) for Localized Prostate Cancer (ClinicalTrials.gov Identifier: NCT01194648). This study began in November 2010 and has an enrollment target of 272 patients.
Prostate Cancer Overview

Philips Health Care has also demonstrated interest in this area (Anand et al., 2009). Philips is optimizing transrectal array configurations for prostate focused ultrasound ablation with the goal of faster ablations and ablation volumes up to 70cc.

Benefits Related to HIFU
- It may provide a treatment option with reduced trauma and improved quality of life
- No ionizing radiation
- Single treatment session
- Reduced hospitalization time
- Noninvasive
- Real-time imaging allows evaluation of area during treatment.
- No risk of increased metastasis due to seeding along incision
- Potentially curative
- Repeatable procedure

Uncertainties/Risks Related to HIFU
- Potential thermal damage to neurovascular bundles critical for erectile function
- 11% of patients require urinary sphincter implantation (Boukaram & Hannoun-Levi, 2010)
- Long time (2-2.5 hours avg.) to ablate with Ablatherm
- Neither Ablatherm nor Sonablate 500 can reliably treat prostate volumes greater than 40 cc. (Williams et al., 2010)
- HIFU ablation scars the prostate bed, making salvage RP potentially difficult (Williams, 2010)
- US and EU regulatory authorities likely to require MR imaging guidance to monitor the effects of the high heat deposition prior to approval
- No long term clinical follow up data is yet available. Because prostate cancer is slow to develop, a minimum of 7-10 yrs data (on current optimized devices) required (Lukka et al., 2011).
Prostate Cancer Overview

References


# Prostate Cancer Overview


Notes
Prostate Cancer Draft Roadmap
Submitted by Brad Wood, Peter Pinto, Andreas Melzer, Ghulam Nabi and Christopher Cheng

Approach/objective:
MRI-HIFU focal hyperthermia enabled targeted drug delivery for prostate tumor:
Use MRI-HIFU to heat prostate tumors to mild hyperthermia temperatures (40-42°C) in order to deliver drug from temperature sensitive carriers in a distribution or location that would otherwise not be attainable, and in a nerve sparing and organ sparing fashion. This is to avoid the side-effects of traditional ablative prostate tumor treatments such as surgery or radiation.

MRI-HIFU targeted drug delivery in combination with MRI-HIFU ablation:
Use MRI-HIFU to increase prostate tumor drug uptake used in combination with ablative therapies.

Standards for effective delivery and measurements:
Establish methodology & validity of combining MRI-HIFU for ablation with MRI-HIFU for drug delivery or sensitization. To establish verifiable intermediate endpoints in targeted drug delivery or combination MRI-HIFU ablation and targeted drug delivery endpoints.

Parameters:
MR-HIFU technology development
1. Transurethral vs transrectal
2. Temperature monitoring and heating – accuracy & safety
3. Nerve sparing/organ sparing with MRI accuracy?
4. Multiparametric MRI prostate imaging improving tumour localization
5. Gleason 6 and lower: Active surveillance
6. Monitor rectal heating/tissue drug concentration
7. Monitor nerve/sphincter heating/tissue drug concentration

Drug system development
1. Clinically relevant DDS – translatable
2. Image-able DDS – To improve the speed of experiments & optimize use of imaging

Important prostate specific questions:

Imaging questions
1. Can MRI temperature monitoring protect the neurovascular bundle?
2. Compare vs US guided HIFU? Contrast enhanced ultrasound (CEUS)

Pathology questions
3. HIFU followed by prostatectomy? No pathologic tissue?
4. Always biopsy? Non extirpative experiments, HIFU alone without surgery
5. Can the prostate be heated without heating other structures such as urethra / nerve / rectum?

Pharmacokinetics questions
6. What is the optimum HIFU exposure for drug accumulation using temperature sensitive or pressure sensitive carriers?
7. What Pharmacokinetic information can be obtained by co-releasing contrast agents?
8. What imaging methods should be used for early Pharmacodynamic assessment?

Drug development
9. Compare to other ablative therapies: laser, cryo, US HIFU
10. What drugs (drug combinations) should be used? Microbubbles

HIFU ablation
11. Only prostate cancer or include BPH?
12. What patient population to study?
Prostate Cancer Draft Roadmap
Submitted by Brad Wood, Peter Pinto, Andreas Melzer, Ghulam Nabi and Christopher Cheng

Key experiments (MR-HIFU):
1. Demonstrate ability to heat prostate without heating rectal mucosa
2. Demonstrate ability to conformally heat a tumor
3. Demonstrate ability to target residual/recurrent disease
4. Demonstrate ability to heat large volumes/whole organ

Key experiments (drug delivery):
1. Demonstrate improved drug delivery to an entire tumor.
2. Optimize HIFU exposures (time and temperature) for sufficient drug delivery.
3. Randomized clinical trial to compare to standard local – regional therapies?
4. Any needs for further animal experimentation on HIFU alone, TDD alone or combination

Key clinical pitfalls
1. Not all agree that focal therapy is ever indicated
2. Not all agree about watchful waiting
3. MRI imaging in prostate is young and improving but not uniform or widespread
4. Not all agree that local TDD help

Clinical Trials Background:
Prostate cancer is either treated by radical prostatectomy, radiation or systemic chemotherapy. Focal treatment such as cryo, laser, US guided HIFU and recently MRgFUS are under clinical evaluation.

In recent clinical trials, chemotherapy for hormone refractory carcinoma of prostate has been shown to improve progression free survival, pain control and quality of life (J Clin Oncol. 2008 Jan 10;26(2):242-5.). Trials clearly have shown that Docetaxel (Taxotere®) has been clinically effective in hormone refractory disease. High risk prostate cancer disease (Gleason score of 8 and more) has increased risk of biochemical recurrence and poor survival, and could be an initial patient population to consider for MRgFUS mediated increased drug delivery to treat clandestine local / regional cancer spread. Likewise, patients with high risk clinically localised visible disease may also benefit from chemotherapy.

In past, there have been small trials investigating the role of Docetaxel in neoadjuvant and adjuvant setting for high risk localised prostate cancer (Oncologist. 2005 Oct;10 Suppl 2:18-22), a large multi-site phase III randomized study of radical prostatectomy with versus without neoadjuvant chemohormonal therapy comprising Docetaxel and androgen-deprivation therapy with leuprolide acetate or goserelin in patients with high-risk, clinically localized prostate cancer is underway [http://www.cancer.gov/clinicaltrials/CALGB-90203#StudyIdInfo_CDR0000526353].

Although Docetaxel has been proven to be clinically effective in patients with hormone refractory disease and safe in patients with localised disease, more than ~10% patients discontinued medications due to side effects (ref) and drug is not indicated in several high risk group (abnormal liver function, neutropenia, risk of fluid retention). These side effects can potentially be avoided by MR guided ultrasound mediated local delivery of drug into the prostate (at a very high local but low systemic concentration).

Possible clinical trials
1. High risk Gleason 8+ and / or localized prostate cancer
2. Clinically localized disease after failed primary therapy; e.g. biochemical failure after radiation therapy; post-prostatectomy recurrence or residual; HIFU, cryotherapy and primary ADT. Endpoints could be biochemical regression.
3. Soft tissue or bone metastases which are traditionally poor candidates for ADT.
Notes
Brain Diseases Overview

Diseases of the Brain

Diseases of the brain can be divided into two groups degenerative/debilitating or fatal. In either instance, diseases of the brain are a substantial societal burden worldwide both in terms of economic costs and impact on quality of life. Furthermore, for the vast majority of patients, there are no effective treatments available, positioning the treatment of brain diseases as one of the largest unmet medical needs in the world today.

The Blood-Brain Barrier (BBB)

A critical consideration in treatment of any brain disease is targeting the treatment to the diseased areas alone while minimizing undesired side effects. In order to achieve more localized treatments, some have pursued approaches where the therapy is delivered directly. Direct delivery of drug almost always requires a craniotomy, subjecting the patient to risk of hemorrhage and infection. Alternatively, therapeutics can be systemically administered via intravenous infusion. If this route is taken, systemic toxicity must be avoided, a therapeutic dose must reach the target and the blood-brain barrier (BBB) must be traversed.

The BBB acts as a 400 Dalton micro filter for the brain, protecting it from blood born pathogens. High resistance tight junctions make up the closely connected endothelial cells lining the brain capillaries and are critical to the BBB’s functionality (Brightman and Reese, 1969). When the BBB is functioning normally, it prevents the patient’s own immune system cells, as well as most drugs, from reaching the brain. Few drugs that pass the BBB are <400Da, have high lipid solubility, and pass across the BBB by passive diffusion. Drugs may also enter the brain via receptor-mediated transport across cellular membranes (Pardridge, 2007). Overcoming the BBB is a crucial step to successfully treating brain diseases.

*For a comprehensive review of the BBB and disruption/targeting strategies please refer to Vytkovtseva et al., 2008.

BBB Disruption

Available methods to open the BBB include systemic infusion of mannitol for transient osmotic disruption or other biochemical means, as well as photodynamic therapy. However, the general failing of current approaches to BBB opening is that they are not localized. Given the large surface area of the BBB, opening all the endothelial cell’s tight junctions would expose an extensive amount of normal tissue to therapeutic drug. For example, doxorubicin, cisplatin, and taxanes can all cause neurotoxicity, even though the drug is systemically tolerated (Bidros & Vogelbaum 2009). Another approach to BBB opening, photodynamic therapy utilizes a tumor-localizing photosensitizer that is activated by light. The photochemical and photobiological events cause irreversible damage to tissues. (Hirschberg, 2008). In addition, photochemical internalization (Hirschberg, 2009) is another light based therapy being investigated for site-specific disruption of the BBB to enhance drug delivery.

<table>
<thead>
<tr>
<th>Common Brain Diseases (World Wide Est.)</th>
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<tbody>
<tr>
<td>Tumors, Primary Brain (Incidence)</td>
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<tr>
<td>Glioma, Glioblastoma</td>
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<td>Glioma, Other</td>
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<tr>
<td>NonGlioma</td>
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<td></td>
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<tr>
<td>Tumors, Metastatic to Brain (Incidence)</td>
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<tr>
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</tr>
<tr>
<td>Stroke (Mortality)</td>
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<tr>
<td>Parkinson's (Prevalence)</td>
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<tr>
<td>Alzheimer's (Prevalence)</td>
</tr>
</tbody>
</table>

(a) (Boyle & Levin, 2008)  
(b) (Barnholtz-Sloan, 2004)  
(c) (Truelsen, 2007)  
(d) (Dorsey, 2007)  
(e) (Brookmeyer, 2007)
Brain Diseases Overview

MR-guided focused ultrasound has the potential to be an ideal modality for BBB disruption. Focused ultrasound can open the BBB transiently, reversibly and in a localized area, with minimal damage to normal structures. Studies have shown that FUS can cause vascular leakage without tissue damage and localized cavitation (generated mechanical stress by intravenous injection of preformed gas bubbles just prior to pulsed ultrasound treatment). These experiments showed complete closure of the BBB within 24 hours (Hynynen et al., 2001).

Focused ultrasound for BBB opening has been used in an animal model of glioblastoma to demonstrate increased localized chemotherapeutic drug delivery across the BBB by over 200% (Liu et al., 2010). This technique may be utilized in a non-heating cavitation mode to transiently open the BBB and allow penetration of systemically administered drugs, especially in conjunction with microbubbles (Mears & Alonso, 2009). Choi et al. (2010) have recently demonstrated that focused ultrasound can open the BBB and allow for delivery of dextran molecules of at least 70Kda in weight and about 10 nm in diameter. In a separate study FUS opening of the BBB allowed from hereceptin (148Kda) to pass (Kinoshita, 2006). As mentioned above, the BBB prohibits large biomolecules such as recombinant proteins, monoclonal antibodies, RNA interference (RNAi) drugs, and gene therapy from reaching the brain (Madsen and Hirschberg 2010). Thus, eliminating many modern drug advancements from potentially treating brain diseases. HIFU’s ability to transiently open the BBB has a huge potential to fundamentally change treatment of brain diseases as this will enable therapeutic targeted drug delivery in the brain.

Brain Tumors

In the United States, the 5-year survival rate for all types of brain tumors is 20%, which has not improved since the early 1970’s (Wrensch, 2002). Glioblastoma (grade IV glioma) is the most common primary malignant brain tumor in adults. Known causes of primary brain tumors are limited to rare hereditary syndromes, therapeutic ionizing radiation, and immune suppression giving rise to brain lymphomas (Barnholtz-Sloan et al., 2007). However, this only accounts for a small fraction of cases. Metastatic brain tumors are the most common brain neoplasms in adults and are a significant cause of morbidity and mortality (Barnholtz-Sloan, 2004). Interestingly, while the brain is separated from the immune system by the BBB, it is a common site of metastasis.

Current Standard of Care Brain Tumors

The standard of care for brain tumors is the maximal safe surgical resection, followed by a combination of radiation and chemotherapy with temozolomide (TMZ), and referred to as the Stupp regimen. (Nishikawa, 2010). Glioblastomas are particularly insidious and infiltrative in nature. In approximately 80% of all cases, recurrent tumor growth occurs within a 2–3 cm margin of the surgical resection cavity (Wallner, 1989). Bevacizumab is the first of the second line chemotherapies following recurrence. Bevacizumab is a molecular targeted therapy against vascular endothelial growth factor (VEGF). Other second line therapies include nitrosourea or PCV, cyclophosphamide and the platinum-based chemotherapeutics (Nishikawa, 2010).

MR-guided Focused Ultrasound Brain Tumor Ablation

Image guided focused ultrasound holds great promise for the treatment of brain tumors (For review please see Colen & Jolesz, 2010). Focused ultrasound can be applied in an ablative mode to non-invasively destroy solid tumors in the brain and treat surrounding neoplastic tissues at mild hyperthermic temperatures (Baronzio et al., 2006). While the first attempt at transcranial focused ultrasound failed due to distortion of the focused ultrasound beam foci and high heat deposition in the skull (Fry & Gross, 1980), recent advances in the development of hemi-spherical phased array transducers and skull correction algorithms (Clement & Hynynen, 2000), as well as chilled water circulation surrounding the patient’s head (Colen & Jolesz, 2010) have addressed these issues. Now, with the benefits of MR thermometry and guidance, focused ultrasound is being used to ablate discrete areas of brain tissues, without the necessity of a craniotomy. Unlike surgery and radiation therapy, the non-invasive, non-ionizing radiation applied with focused ultrasound can be used repeatedly to debulk recurring tumors. In the cases of metastasis, which frequently have well-defined borders, total ablation may be possible.
Brain Diseases Overview

MR-guided Focused Ultrasound for Sonothrombolysis

Ischemic stroke and intracranial hemorrhage have a very high worldwide incidence and mortality rate. A recent extensive literature review concludes that the use of transcranial high-intensity focused ultrasound is efficacious for thrombolysis (Medel et al., 2009) and is an attractive modality for the noninvasive or minimally invasive management of stroke.

Transcranial MR-guided Focused Ultrasound Devices

ExAblate 3000 Neuro, InSightec (Haifa, Israel)

ExAblate 3000 Neuro is a transcranial MR-guided focused ultrasound prototype. Preclinical work is underway studying transcranial sonothrombolysis in ischemic stroke (Hoelscher et al., 2010), intracerebral hemorrhage (Monteith et al., 2010) opening of the BBB for target drug delivery (Arvanitis et al., 2010) and brain tumor ablation. In a Phase I clinical trial, InSightec has used MRgFUS to successfully treat two of three patients with recurrent glioblastoma at Brigham and Women’s Hospital in Boston (Ram et al., 2006). Currently a new phase I clinical trial is recruiting 10 patients with inoperable glioblastoma, (McDonnold et al., 2010). Preliminary results on three patients are promising.

SuperSonic Imagine (Aix en Provence, France)

A clinical prototype ultrasound phased array dedicated to transcranial brain treatment is currently under development (Gâteau, 2010, Marsac, 2010).

Benefits of Transcranial MRgFUS

- Non-invasive (no craniotomy)
- Low risk of:
  - Non-target tissue damage
  - Infection
  - Hemorrhage
- Non-Toxic
  - No ionizion radiation.
  - Multiple focused ultrasound treatments are feasible
- Real-time MRI of target tissue and surrounding area allows for:
  - Beam targeting accuracy
  - Temperature monitoring
  - Over-all higher safety

Uncertainties/Risks Related to Transcranial MRgFUS

- Variability in intracranial calcification
- Long treatment session times
- Effect of microbubbles and focused ultrasound at the molecular level of the BBB unknown
- Possible thermal damage to nearby normal tissue
- Unforeseen interaction between drug and focused ultrasound energy
References


http://works.bepress.com/cgi/viewcontent.cgi?article=1022&amp;amp;context=rbrookmeyer


Brain Diseases Overview


Brain Diseases Overview


# Brain Cancer Draft Roadmap
Submitted by Kullervo Hynynen and Nathan McDannold

## Parameters

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Identify the appropriate preclinical animal model of brain cancer for studying BBB opening &amp; drug delivery</td>
</tr>
<tr>
<td>2.</td>
<td>Identify candidate chemotherapeutic agent(s) and microbubble(s)</td>
</tr>
<tr>
<td>3.</td>
<td>Determine ultrasound parameters to perform initial in vivo studies</td>
</tr>
<tr>
<td>4.</td>
<td>Optimize ultrasound parameters in small animal model</td>
</tr>
<tr>
<td>5.</td>
<td>Determine FUS targeting and monitoring parameters without thermometry</td>
</tr>
<tr>
<td>6.</td>
<td>Determine drug delivery and monitoring parameters</td>
</tr>
</tbody>
</table>

## Completed Experiments and Supporting Citations

- Rabbit model and delivery
- Rat model and Glioma

*note: there are additional experiments that are complete — should be added, along with citations

## Research Questions

- What is the cavitation threshold in FUS system with chosen microbubbles?
- What is the behavior of bubble mediated cavitation below safety threshold?
- How large a volume can be practically treated? In what time?
- How will dose delivery be monitored? Quantitatively? In preclinical models as well as in clinical applications (ex. drug and contrast within same drug delivery system?)

## Additional questions

- Does treatment planning go in here – seems critical part of the roadmap if our goal is patient treatment?
- Would survival studies be necessary?

## Safety

<table>
<thead>
<tr>
<th>Step</th>
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<tbody>
<tr>
<td>1.</td>
<td>Develop preclinical safety model(s)</td>
</tr>
<tr>
<td>2.</td>
<td>Determine safety of BBB opening parameters in large animal model in normal brain</td>
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<tr>
<td>3.</td>
<td>Determine safety of BBB opening parameters combined with dose escalation in normal brain</td>
</tr>
<tr>
<td>4.</td>
<td>Determine safety of BBB opening parameters combined with dose escalation in neoplastic brain</td>
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</tbody>
</table>

## Clinical Research

<table>
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<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Pilot clinical trial – BBB opening with MRgFUS in GBM</td>
</tr>
</tbody>
</table>
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Dr. Itzhak Avital is currently a Senior Investigator and the Head of the GI and Hepatobiliary Malignancies Section in the Surgery Branch at the National Cancer Institute (NCI). He graduated from the New York University School of Medicine and completed his general surgery residency at Cedars-Sinai Medical Center/UCLA, as well as a 3-year research fellowship in liver regeneration, bioartificial liver, and liver stem cells in the Bioartificial Liver Support Laboratory. Dr. Avital then completed two clinical fellowships in surgical oncology and hepatobiliary surgery at Memorial Sloan-Kettering Cancer Center in New York. Subsequently he was appointed to the Surgery Branch at the National Cancer Institute, NIH. He received NIH tenure track in 2006 and was appointed assistant professor of surgery with the Uniformed Services University of the Health Sciences in 2009. His clinical interests include surgical management of complex metastatic malignancies; in particular, colorectal, liver, pancreatic, gastric, and breast metastatic cancers. His translational research efforts are focused on generating novel cancer treatments based on targeting solid organ cancer stem cells.

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Dr. Lili Chen received her PhD in medical physics and biophysics from the Institute of Cancer Research and Royal Marsden Hospital, University of London in 1994. She was a postdoctoral fellow at Toronto University and a postdoctoral fellow and staff member at Stanford University School of Medicine specializing in MR-guided focused ultrasound (MRgFUS). She joined Fox Chase Cancer Center (FCCC) in 2001, where she has been the project leader on MRgFUS. Her duties include radiotherapy physics services, clinical research support, and medical physics education. Her research interests include IMRT, IGRT and MRgFUS for cancer therapy. She has published over 40 peer-reviewed papers and book chapters. She is a member of the AAPM Task Group 180 on validation of software tools for quantification of DCE MRI data and a member of the AAPM Task Group 193 on Image-Guided FUS. She has been the principal investigator on several research grants from federal agencies and nonprofit foundations. She also served as a member of several scientific review panels and reviewed papers for several scientific journals.

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Dr. Christopher Cheng graduated from Singapore University in 1982 and obtained his postgraduate degree in Surgery FRCS in 1986, and FAMS (Urology) from the Academy of Medicine, Singapore in 1993. He obtained his Uro- oncology Fellowship after spending two years at the Mayo Clinic from 1990 to 1992. He is the Chairman, Transplant Workgroup Committee, Singapore General Hospital and a member of the Transplant Advisory Committee at the Ministry of Health, Singapore. He is also the Chairman of the Robotic Minimally Invasive Surgery Steering Committee at SGH. Dr. Cheng's clinical and research fields of interest include uro-oncology, renal transplantation (living-related and cadaveric) and minimally invasive surgery. He has over 90 publications in local and international journals on Prostate Cancers, Bladder Cancers and Stone Diseases. He has contributed to several book chapters on urology in local and international publications. He is on the editorial board of several well-known journals, namely Journal of Robotic Surgery and Oncology & Haematology News. He was the Editor of the MOH Clinical Practice Guidelines on Prostate Cancer, published by Ministry of Health in May 2000.
Workshop Attendees

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Dr. Rajiv Chopra is an Assistant Professor in the Department of Medical Biophysics at the University of Toronto. He has been a Scientist in the Discipline of Imaging Research at Sunnybrook Health Sciences Centre since 2006. He obtained his undergraduate degree in the Department of Physics at McMaster University (1996), and completed his graduate training in the Department of Medical Biophysics at the University of Toronto (2002). Dr. Chopra's research focuses on integrating ultrasound and magnetic resonance imaging technology for novel diagnostic and therapeutic applications. Current areas of interest include the development of minimally invasive, image-controlled thermal treatments in medicine, MR elastography, and targeted delivery of agents within the body using ultrasound energy. Dr. Chopra is a member of the International Society of Magnetic Resonance in Medicine, IEEE, and International Society of Therapeutic Ultrasound in Medicine. Dr. Chopra is also the co-founder of Profound Medical Inc., a private company focused on commercializing prostate therapy technology developed in his laboratory, and FUS Instruments, a company developing preclinical focused ultrasound systems for research.

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Dr. Gregory Czarnota is an Assistant Professor in the Departments of Radiation Oncology and of Medical Biophysics at the University of Toronto. He is also a Clinician Scientist in the Department of Radiation Oncology and Imaging Research at Sunnybrook Health Sciences Centre. He received his BSc from McMaster University, and his MD and PhD from the University of Toronto. Now Dr. Czarnota is conducting research focused on using ultrasound imaging and spectroscopy at conventional- and high-frequencies to detect apoptosis and other forms of cell death in response to chemotherapy and radiation therapy. In addition to being a Scientist in the Imaging Division he is an MD in the Department of Radiation Oncology with applied research in breast cancer patients. His basic-science research interests include studies in biochemistry, chromatin biology, biophysics, medicine and oncology.

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Dr. Cynthia Davis is currently the platform leader for therapy programs at GE Global Research. She leads programs in interventional MR, x-ray and ultrasound imaging as well as focused ultrasound therapy, drug delivery, stem cell therapy and wellness. Previously, she was the laboratory manager for x-ray systems which developed new radiography, mammography and cardio-vascular systems and technologies. Prior roles have included program manager for the digital x-ray detector development for cardiovascular (Innova) and mammography (Senographe 2000D) products. Dr. Davis holds a PhD in Nuclear and Particle Physics from Rensselaer Polytechnic Institute.
Workshop Attendees

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Dr. Nico de Jong graduated from the University of Technology in Delft, the Netherlands, where he got his MSc in the field of pattern recognition. Since 1980, he has been a staff member of Erasmus MC and Interuniversity Cardiology Institute of the Netherlands. At the Department of Biomedical Engineering, he first was involved in the development of linear and phased-array ultrasonic probes for medical diagnosis and he later received his PhD for the thesis ‘Acoustic properties of ultrasound contrast agents’. Currently, he is interested in the development of three-dimensional transducers and ultrasound contrast imaging. Together with Dr. Folkert Ten Cate, he is organizer of the annual European Symposium on Ultrasound Contrast Imaging, held in Rotterdam. For the past three years, he has worked with the Physics of Fluids Group from the University of Twente. The combination has resulted in the construction of the Brandaris fast framing camera to study bubbles at frame rates on the order of 25 million frames per second. Dr. de Jong is now a part time professor at the University of Twente on Medical Ultrasound and Therapy.

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Dr. Mark Dewhirst is the Gustavo S. Montana Professor and the Director of Tumor Microcirculation Laboratory in the Department of Radiation Oncology at Duke University Medical Center. He also holds appointments in the Departments of Pathology and Biomedical Engineering at Duke and in the Department of Anatomy Pathology and Radiology at the School of Veterinary Medicine at North Carolina State University. Dr. Dewhirst directs a clinical program grant to study the use of hyperthermia in the treatment of cancer. This program has four main themes: (1) Establishment of robust methods to measure hyperthermia treatment delivery (i.e. thermal dosimetry), (2) Investigate novel therapeutic opportunities afforded by the use of hyperthermia. In particular, the program is currently focusing on use of novel thermally sensitive nanoparticles (called liposomes) to deliver high concentrations of cancer drugs to tumors. This concept has been translated from the bench to human clinical trials. (3) Conduct human clinical trials testing the value of hyperthermia when combined with radiation and/or chemotherapy and (4) Understand the physiologic and metabolic consequences of hyperthermia treatment. Dr. Dewhirst also has research interests in tumor hypoxia, angiogenesis and drug transport.

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Dr. Christian Diederich received his BS in Bioengineering from the University of California, San Diego, and his PhD in Electrical Engineering from the University of Arizona. He is a Professor in Radiation Oncology and Director of the Thermal Therapy Research Group at the University of California at San Francisco (UCSF), and his primary research activities include the development of ultrasound devices and treatment delivery strategies for targeted hyperthermia and thermal ablation therapies. This includes integration of devices with MR and US imaging techniques to guide and monitor therapy delivery. Areas of expertise include theoretical and experimental techniques, including in vivo experiments, to develop and evaluate thermal therapy devices prior to clinical implementation. Catheter based ultrasound devices and a delivery system developed by his group are currently being used in an NIH sponsored clinical study at UCSF for applying hyperthermia in conjunction with HDR brachytherapy for the treatment of locally advanced prostate and cervix cancer. Clinical experience includes the treatment planning and
Matt Dreher, PhD
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Dr. Matthew Dreher is a Staff Scientist for the Interventional Radiology Research Laboratory at the National Institutes of Health (NIH). He earned his undergraduate degree in Biomedical Engineering from Rensselaer Polytechnic Institute and then a Masters Degree and PhD in Biomedical Engineering from Duke University. He then went on to complete a postdoctoral fellowship in the Department of Radiation Oncology in the Duke University Medical Center. In 2007, he went to the NIH to work in the Interventional Radiology Research Laboratory, which focuses on minimally invasive image guided therapies. He now focuses on novel drug and device combinations to improve local-regional therapies. His background is well suited for emerging therapies in Interventional Oncology. His specific research interests include: 1) Temperature sensitive liposomes combined with radiofrequency ablation (RFA) or high intensity focused ultrasound (HIFU), 2) RFA combined with antiangiogenic or antivascular therapy, and 3) Development of image-able drug eluting beads (DEB) for transcatheter arterial chemoembolization (TACE). Dr. Dreher’s expertise in drug delivery allows him to partner with Interventional Radiology and Interventional Oncology Clinical Investigators to facilitate development and translation of novel approaches to minimally invasive, image guided therapies at the Clinical Center.

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Matt Eames is the Brain Program Senior Project Engineer and joined the Focused Ultrasound Surgery Foundation in December 2009. Dr. Eames earned his PhD in Biomedical Engineering at the University of Virginia performing research in the design, modeling, fabrication, and characterization of combined diagnostic/therapeutic ultrasound transducers. In conjunction with John Snell PhD, he supports the technical component of the Brain R&D Program and establishes and maintains collaborative relationships with members of the ultrasound industry and research communities who share a common interest in advancing the Foundation’s Research Programs.

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Dr. Keyvan Farahani is a Program Director in the Image-Guided Interventions (IGI) Branch, Cancer Imaging Program of the National Cancer Institute (NCI). In this capacity he is responsible for the development of NCI initiatives that address diagnosis and treatment of cancer through integration of advanced imaging and minimally invasive therapies. Since 2009 Dr. Farahani has lead the NCI initiatives in image-guided drug delivery in cancer, small business as well as early phase clinical trials in oncologic IGI. He has led a series of NCI workshops that promote an open science model to develop, optimize and validate platforms for IGI. These initiatives have engaged other agencies of the federal government namely NIH IC’s, NIBIB, FDA, NIST and CMS. Prior to joining NCI in fall of 2001, Dr. Farahani was a faculty of the department of Radiological Sciences at the University of California, Los Angeles, where he obtained his MS (’89) and PhD (’93) degrees in Biomedical Physics. Dr. Farahani is a member
of the American Association of Physicists in Medicine, the Scientific Program Committee of the Radiological Society of North America, and a past president of the Interventional MR study group of the International Society of Magnetic Resonance in Medicine.

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Dr. Katherine Ferrara received her PhD in 1989 from the University of California, Davis. Following an appointment as an Associate Professor in the Department of Biomedical Engineering at the University of Virginia, Charlottesville, Dr. Ferrara served as the founding chair of the Department of Biomedical Engineering at UC Davis. She is currently a Professor of Biomedical Engineering at UC Davis with research interests in imaging and drug delivery. She is a fellow of five societies, including the Institute for Electrical and Electronic Engineers, the American Association for the Advancement of Science, the Biomedical Engineering Society, the Acoustical Society of America and the American Institute of Medical and Biological Engineering and is currently a member of the National Advisory Council for the National Institute of Biomedical Imaging and Bioengineering.

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Dr. Craig Fischer is currently the Chief of the Division of Surgical Oncology at the Methodist Hospital. He attended Tulane University, where he graduated from the Department of Biology. He attended the University of Texas in Houston, graduating with a combined MD, MPH degree and publishing his thesis entitled “Racial and Socioeconomic Contributors to Trauma Mortality”. In 2005, Dr. Fischer joined Weill Cornell Medical College and its new primary teaching hospital in Houston, The Methodist Hospital. Dr. Fischer performed the first laparoscopic right hepatectomy in the State of Texas, the first laparoscopic Whipple in the Texas Medical Center and the first laparoscopic total pancreatectomy in the world. He has developed a leading pancreatic islet cell laboratory and transplant program, offering donor and autologous auto transplant options to patients. The program recently performed the world's first completely laparoscopic pancreatic resection and islet cell transplant. Dr. Fischer’s research interests focus on clinical studies to evaluate novel treatments for perioperative soft tissue bleeding.

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Dr. Wladyslaw Gedroyc was born and educated in London. His radiology training was at Guy’s Hospital London followed by one year at Penn State University at Hershey Medical Center. For the past 19 years he has been a radiology consultant at St. Mary’s Hospital and medical director of the MR unit during that time. Today he is the Personal Chair at Imperial College London and is a Consultant Radiologist for Imperial College Healthcare NHS Trust. He has over 80 papers published in peer reviewed journals, mostly on MR related topics. These include multiple research papers on interventional MRI and the development of MRgFUS in various clinical situations. He is an international expert on MR-guided interventional techniques. The widespread use of MR-guided focused ultrasound treatment for fibroids has directly evolved from his initial research work in this area. He has multiple projects currently underway investigating the use of MR-guided focused ultrasound in the treatment of liver tumors, bone secondary tumors, back pain, prostate cancer, and fertility.
Workshop Attendees

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Dr. Neil Glossop is a medical technology industry executive with over 22 years of experience in medical research and the medical device industry. This includes over 15 years in company building, leadership and executive management. He has both worked for large diverse medical device companies and led a medical device company through a complete life-cycle from founding and startup through to purchase by a multinational device company. The product was focused on computer-assisted image guidance of minimally invasive devices for biopsy and cancer therapy. In addition to chief executive responsibilities, he defined and led the R&D activities of the company throughout this period. He has a developed a deep network of luminary clinical and scientific contacts at leading institutions through the world. Dr. Glossop is a recognized expert in the field of image guided surgery and the author of over 50 publications. He has 12 issued US patents and 15 US patents-pending in addition to numerous foreign applications and patents. He was awarded 3 NIH grants and co-authored the “ISG Viewing Wand” software, the first commercial and FDA cleared image-guided neurosurgery application. He completed his PhD in Aerospace Engineering at the University of Toronto in 1989. During this time, he was active in research at several local hospitals primarily in biomechanical engineering and orthopaedics. He also spent time at research institutes in Basle, Switzerland and at the Swiss National Research Institute (ETH) in Zürich. His post-doctoral work was done in Toronto and at Baylor University Medical Center in Dallas, with a focus on minimally invasive arthroscopic repairs, treatments using Excimer lasers and other novel arthroscopic devices.

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Dr. Timothy Greten received his medical training at Christian Albrechts University in Kiel, Germany in 1993. He did his internship in Munich, followed by a 3-year postdoctoral fellowship at the Johns Hopkins University in Baltimore in the laboratory of Drew Pardoll and Liz Jaffee, where he initiated his work in the field of tumor immunology. In 1999, Dr. Greten returned to Hannover Medical School, where he finished his training in internal medicine in 2003, medical oncology in 2004, and gastroenterology in 2007. He held an associate professor position in the Department of Gastroenterology, Hepatology and Endocrinology. In February 2010, he joined CCR's Medical Oncology Branch as the program director of the Gastrointestinal Malignancy Section. Dr. Greten has published more than 70 peer-reviewed papers on basic tumor immunology and translational research studies in hepatocellular carcinoma (HCC), as well as clinical trials in different gastrointestinal malignancies, including HCC. He has also headed the Group for Hepatobiliary Carcinoma from 2006 until 2010, where he coordinated and directed the German Clinical Trial Group (AIO). Currently, Dr. Greten is the chair of the NCI Gastrointestinal Malignancy Faculty and Immunology Faculty.

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Dr. Holger Grüll studied chemistry in Cologne, Germany, where he obtained his PhD in 1996 in chemical physics for research on interfacial phenomena in critical mixtures. After his PhD, Dr. Grüll received a Feodor-Lynen Fellowship of the Alexander von Humboldt Society and stayed until 1999 at the National Institute of Standards and Technology (NIST), where he specialized on surface and interfacial phenomena in polymer thin films and biomimetic membranes. From 1999 to 2000, a post-doctoral stay followed at the Ben-Gurion University of Be’er Sheva, Israel, with research on polymer coatings and Langmuir-Blodgett layers. In 2000, Dr. Grüll started at Philips Research in the area of molecular diagnostics. Since 2004, Dr. Grüll is scientifically responsible
for research projects on molecular imaging and drug delivery. In 2007, Dr. Grüll was appointed part-time professor in the group of Biomedical NMR at the Faculty of Biomedical Engineering at Eindhoven University of Technology. His chair is focusing on molecular imaging and image guided interventions. Most of the research effort is devoted to pressure and temperature-induced drug delivery using focused ultrasound under image guidance.

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Dr. Dieter Haemmerich is Associate Professor in the Department of Pediatrics at the Medical University of South Carolina and Adjunct Faculty in the Department of Bioengineering at Clemson University. His research interests are in the areas of thermal ablation applied to treatment of cancer and cardiac arrhythmia. This includes computational modeling, measurement of thermal and electrical tissue properties, as well as device design and testing ex-vivo and in animal models. Recent work includes computational modeling of targeted drug delivery via temperature-sensitive liposomes and focused ultrasound. He has co-authored ~60 peer-reviewed journal publications, and has served as reviewer of ~30 scientific journals. He is currently serving as Editorial Board Member on eight journals, including Critical Reviews in Biomedical Engineering, International Journal of Hyperthermia, and the Open Biomedical Engineering Journal, and is Associate Editor of the IEEE Transactions in Information Technology and Biomedicine.

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Dr. Arik Hanannel received his MD and Bachelor of Computer Science from Tel-Aviv University in Israel and is currently working on his Executive MBA through the Recanati International School of Business Program, which will be complete in July 2011. After completing his medical internship at Tel-Aviv Medical Center in 1999, Dr. Hanannel joined InSightec and is now the Director of International Clinical Research and the Manager of the Bone Program. He has also held the following positions at InSightec: Global Manager of Advanced Applications; Clinical Research and Development Manager; Application Manager; and Programmer and Communication Team Leader. He has experience in research, development and collaboration in basic science, pre-clinical and clinical work, (including global FDA pivotal trials), in the development of a non-invasive thermal ablation system using MR-guide, HIFU for multiple clinical indications. He is also ranked as a Medical Officer on reserve and fluent in Hebrew.

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Dr. Gerald Harris received a bachelor's degree in electrical engineering in 1967 from the Georgia Institute of Technology, Atlanta, an MS degree in biological engineering in 1971 from the Rose-Hulman Institute of Technology, Terre Haute, Indiana, and a PhD degree in electrical engineering in 1982 from the Catholic University of America, Washington, DC. Since 1967, he has been employed by the U.S. Public Health Service. Currently he is a research engineer and ultrasonics laboratory leader with the U.S. Food and Drug Administration's Center for Devices and Radiological Health, Silver Spring, Maryland. His main activities comprise the experimental and theoretical evaluation of medical ultrasound transducers and systems. He is a Fellow of the Institute of Electrical and Electronics Engineers, Acoustical Society of America, American
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Dr. John Hossack is a Professor of Biomedical Engineering at the University of Virginia. He earned his undergraduate degree and his doctorate from the University of Strathclyde, UK. In his lab at UVA his research encompasses ultrasound transducer design, modeling and fabrication, beamforming methods, 3D acquisition, 2D / 3D image quantification. He has also investigated mouse heart ultrasound imaging with an emphasis on developing new metrics for heart function, while accounting for ventricular dysynchrony. He has also explored the use of microbubbles in dual diagnostic and therapeutic applications. The laboratory has been working extensively on the use of antiproliferative drug-loaded microbubbles dispensed from a catheter as a potential treatment for preventing in-stent restenosis as a replacement or augmentation for drug eluting stents. This work has involved microbubble design, microbubble modeling (including nonlinear and asymmetric 3D effects), ultrasound parameter optimization for simultaneously achieving efficacy and safety, and catheter transducer design. His laboratory has investigated several techniques for achieving tighter control over microbubble radius, which he believes will result in improved efficacy with optimized safety.

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Dr. Joo Ha Hwang is an Assistant Professor in the Department of Medicine in the Division of Gastroenterology at the University of Washington with adjunct appointments in the Departments of Radiology and Bioengineering. He is board certified in Internal Medicine and Gastroenterology. His clinical practice is in Gastroenterology with a focus on performing endoscopic ultrasound (EUS) for diagnosing and staging pancreatic cancer. In addition, he has a PhD in Bioengineering and maintains an active lab performing high-intensity focused ultrasound (HIFU) research. Current research activities in his lab include ultrasound-enhanced drug delivery, ultrasound-mediated vascular bioeffects, ultrasound-enhanced tumor specific immune response and optimization of HIFU ablation.

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Dr. Kullervo Hynynen is currently a Professor in the Department of Medical Biophysics and Institute of Biomaterials & Biomedical Engineering (IBBME) at the University of Toronto and a Senior Scientist and director of Imaging Research at Sunnybrook Research Institute, and the appointed Canada Research Chair in Imaging Systems and Image-Guided Therapy (Tier 1). He also directs the Centre for Research in Image-guided therapeutics at Sunnybrook. He received his BSc and MSc in Physics from the University of Kuopio in Finland and his PhD in Biomedical Physics and Biomedical Engineering from the University of Aberdeen, United Kingdom. Most of his current research interests are centered in utilizing focused ultrasound in medicine. One of the most published and cited researchers in the field; Dr. Hynynen has investigated the use of focused ultrasound for noninvasive surgery, vascular surgery, targeted drug delivery and gene therapy. Currently, he is exploring new ultrasound imaging methods for therapy delivery and
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Mr. Jonathan Kahan is a Co-director of Hogan Lovell’s food, drug, medical device, and agriculture group and has been practicing in FDA law for 35 years. His practice focuses primarily on assisting medical device companies in navigating the U.S. Food and Drug Administration (FDA) regulatory process. He also has an extensive practice in combination products, which includes combinations of drugs, devices and biologics. In addition to the daily counseling of clients in FDA-related matters, he represents many clients in administrative hearings and trials, and in the federal courts. Mr. Kahan has published numerous law review and other articles concerning FDA regulatory issues, and is the author of Medical Device Development: Regulation and Law (Parexel 2009) and Medical Devices: Obtaining FDA Market Clearance (Parexel 1995). He is also a co-editor of Food and Drug Law and Regulation published by the Food and Drug Law Institute in 2008. Mr. Kahan is a member of the Dean’s Advisory Board of the George Washington University Law School. He is the former Chairman of the Federal Bar Association Section on Health and Human Services, which includes the Food, Drug and Cosmetic Law Committee. He is a member of Phi Beta Kappa and Order of the Coif. After receiving his law degree, Mr. Kahan served as a clerk to The Honorable Oliver Gasch of the U.S. District Court for the District of Columbia.

Dr. Neal Kassell is a Distinguished Professor of Neurosurgery at the University of Virginia, and the Founder and Chairman of the Focused Ultrasound Surgery Foundation. Prior to UVA, Dr. Kassell served on the faculty at the University of Iowa. Dr. Kassell is a founder of numerous private ventures including Interax, Inc, the Virginia Neurological Institute, Multimedia Medical Systems, the Neuroclinical Trials Center, Neuroventure Fund, and MedSpecialist. He currently serves as a director of the Virginia National Bank and the La Gesse Foundation, and is on the editorial board of Neurosurgery and Stroke. Dr. Kassell has been a recipient of the McKenzie Memorial Award of the Canadian Neurosurgical Society and the Grass Award of the Society of Neurological Surgeons. He has published over 450 scientific papers. Dr. Kassell received his undergraduate and medical education at the University of Pennsylvania.

Dr. Alexander Klibanov is an Associate Professor in the Department of Internal Medicine at the University of Virginia (UVA). He earned his MS in Chemistry at Moscow State University in Russia and earned his PhD in Biochemistry from the U.S.S.R. Cardiology Research Center. He has held research positions at the University of Pittsburgh in Pennsylvania, UVA, and Mallinckrodt, Inc. in Missouri. Dr. Klibanov’s research interests include targeted delivery of...
therapeutic and diagnostic imaging agents, the design of ultrasound contrast materials and the attachment of targeting ligands to contrast materials, colloid-based delivery systems such as microbubbles and liposomes, and long-circulating liposomes and particulates.

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Dr. Elisa Konofagou is an Associate Professor of Biomedical Engineering and Radiology at Columbia University in New York. She earned her BS in Chemical Physics from Universite de Paris in 1992, her MS in Biomedical Engineering from Imperial College at the University of London in 1996, and her PhD in Biomedical Engineering from University of Houston and University of Texas Medical School in 1999. In 2007, Dr. Konofagou won the Career Award from The National Science Foundation, which supported her research on non-invasive methods to facilitate drug delivery for neurodegenerative diseases.

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Dr. Twan Lammers studied Pharmacy at the University of Utrecht. He obtained a DSc degree in Radiation Oncology from Heidelberg University in 2008, and a PhD degree in Pharmaceutics from Utrecht University in 2009. Since 2007, he has been appointed as a postdoctoral fellow at the Department of Pharmaceutics at Utrecht University, where he predominantly works on the MediTrans project (FP6: ‘Targeted delivery of nanomedicines’). Since 2009, he has also been appointed as a group leader at the Department of Experimental Molecular Imaging at the University of Aachen (RWTH) and the Helmholtz Institute for Biomedical Engineering. In 2010, he co-edited a theme issue on HPMA copolymers for Advanced Drug Delivery Reviews, and he was elected to the editorial boards of Theranostics, the Journal of Nanomedicine and Biotherapeutic Discovery and the Journal of Controlled Release. His primary research interests include drug targeting to tumors, image-guided drug delivery and tumor-targeted combination therapies.

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Dr. King Li graduated from Faculty of Medicine, University of Toronto in 1981 and finished his residency in 1986 at University of Texas. Dr. Li is currently a Professor of Radiology at Weill Medical College of Cornell University and M.D. Anderson Foundation Distinguished Chair of Radiology at the Methodist Hospital in Houston, Texas. Before joining the Methodist Hospital, he was the Associate Director of the NIH Clinical Center and the Chief of Radiology and the Imaging Sciences Program. Dr. Li was on faculty in Stanford University for 10 years prior to joining the NIH. Dr. Li’s main research interest is in molecular imaging, molecular image guided therapy, and integrating imaging with tissue analysis for studying systems biology. He has 9 issued and 6 pending patents, has won over ten different awards from four different professional organizations and has given numerous invited lectures. He has published over 100 scientific articles, 5 book chapters and 1 monograph and has received grants from government, industry and private sources.
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Dr. Hao-Li Liu was born in Taichung, Taiwan. He received a BS degree in electrical engineering from the National Taipei University of Technology located in Taipei, Taiwan in 1996 and received the MS and PhD degrees in Electrical Engineering in 1998 and 2003, respectively, from National Taiwan University in Taipei, Taiwan. In 2004-2005, he was the research fellow of the Department of Radiology at Brigham and Women’s Hospital. He is currently an Associate Professor for the Department of Electrical Engineering at Chang-Gung University, which is located in Taoyuan, Taiwan, and the Adjunct Assistant Researcher of Division of Medical Engineering Research at the National Health Research Institutes located in Miaoli, Taiwan. He is currently continuing research in ultrasound thermal therapy and its treatment planning and simulation, ultrasound-induced blood brain barrier (BBB) disruption for brain drug delivery, and ultrasound phased array design. Dr. Liu is a member of IEEE and International Society of Therapeutic Ultrasound (ISTU).

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Dr. Todd Mainprize is an Arthur and Sonia Labatt Brain Tumour Research Centre Associate Scientist at Sunnybrook Health Centre in Toronto. His clinical and academic focus is Neuro-Oncology. Currently, he is focusing on the translational applications of MRI-guided focused ultrasound in the treatment of both primary and metastatic brain tumours. He is also looking at the role of blood brain barrier disruption for the delivery of novel therapeutic agents in recurrent glioblastoma.

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Dr. Ernst Martin became a professor in Pediatrics and Pediatric Neuroradiology in 1996. In addition, he managed several research projects on higher cognitive brain functions in children using multimodal imaging techniques, e.g. EEG and functional MRI. His current experimental and clinical research interests include BBB opening and targeted drug delivery, and neurosurgical interventions for brain tumors and for various functional brain disorders, such as neuropathic pain, movement disorders, epilepsy and neuro-psychiatric disorders, in children and adults using transcranial MR-guided FUS.

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Dr. Nathan McDannold received his BS in Physics from the University of Virginia in Charlottesville and his PhD in Physics from Tufts University in Boston. He is currently an Associate Professor in Radiology at Harvard University. He has been working in the Focused Ultrasound Laboratory at Brigham & Women’s Hospital since June 1996. His work has been primarily concerned with the development and implementation of MRI-based thermometry methods, animal experiments testing MRI and ultrasound related work, and clinical focused ultrasound treatments of breast tumors, uterine fibroids, and brain tumors. In recent years, a main focus of his work has been studying the use of ultrasound for temporary disruption of the blood-brain barrier, which may allow for targeted drug delivery in the brain.
Workshop Attendees

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Dr. Yoav Medan is currently the Vice President and Chief Systems Architect at InSightec and is responsible for developing new platforms for the Magnetic Resonance guided Focused Ultrasound technology. Prior to joining InSightec in 1999, Dr. Medan spent 17 years in various senior research and management positions at the IBM Research Division and was elected to the IBM Academy of Technology. In addition to technical and managerial experience, Dr. Medan has academic experience as well, teaching at the EE department at the Technion, Israel Institute of Technology, in addition to serving as a lecturer for Avionic Systems at the Aeronautical Engineering faculty. He is also a Senior Member of the Institute of Electrical and Electronics Engineers. Dr. Medan has widely published and holds nine IBM as well as several other patents. He received his DSc and BSc (Summa Cum Laude) in Aeronautical Engineering from the Technion, Israel Institute of Technology, and an MBA diploma from Bradford University, UK.

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Dr. Andreas Melzer is Professor of Medical Technology, Head of Division and Director of the Institute for Medical Science and Technology, founded in 2006 as a joint venture of the Universities of Dundee and St Andrews, Scotland. Among various other projects he is coordinating three MRgFUS related EU grants www.nanoporation.eu, www.HIOS.eu and www.fusimo.eu (medical coordinator) with a total budget exceeding $15 Mio. He has 20 years of experience in the development of medical technology for laparo-endoscopic surgery, interventional radiology, interventional and intraoperative magnetic resonance imaging, image-guided robotics, surgical instrumentation, surgical robotics and Nitinol devices. Dr. Melzer is named inventor on more than 100 patents and on over 500 publications, including oral and poster presentations. He has served as Co-Editor of five medical journals, co-founder and partner of six start-up companies in the medical technology business and a consultant for major vendors in medicine. He organizes or is Chairman of various medical conferences, and has been Board Member of six medical and technical societies. Dr. Melzer qualified in dentistry in 1989 and in medicine in 1993.

Chrit Moonen, PhD
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Dr. Chrit Moonen studied Molecular Sciences at the University of Wageningen, where he also obtained a PhD in Biophysics. After spending a year at the University of Oxford, he moved to the University of California. From 1987-1996 he was director of the ‘In-Vivo NMR Research Center’ at the National Institutes of Health. He is currently a CNRS Research Director in France, a director of the ‘Laboratory for Molecular and Functional Imaging’ (CNRS/University Bordeaux, France) and a part-time visiting professor of radiology at the University Medical Center Utrecht. Professor Moonen was the president of the ‘International Society of Magnetic Resonance in Medicine’ in 2006, and the president of the ‘Society for Molecular Imaging’ in 2009.
Workshop Attendees

Ghulam Nabi, MD
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Dr. Ghulam Nabi is Senior Clinical Lecturer (Associate Professor) and consultant urological surgeon at Ninewells Hospital and Medical School in Dundee. He qualified in India and had urology training at prestigious All India Institute of Medical Sciences, New Delhi before moving to the United Kingdom. He held Clinical Lecturer position at the University of Aberdeen and was trained in advanced laparoscopic surgery in France and Germany. Dr. Nabi has published more than 100 papers in basic and clinical research and is on the editorial board of many journals. He has been instrumental in raising more than 5 million £ of research money over the past few years. His special research is focused ultrasound treatment in urological cancers.

Esben Nilssen, PhD
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Dr. Esben Nilssen is the CEO of the Norwegian drug delivery company Epitarget AS. He holds an MPhil degree in molecular virology from the University of Cambridge (UK) and a PhD degree in cell biology from the University of Oslo. He has also obtained a Mag. Art. degree in philosophy from the University of Oslo, as well as completed training at the Copenhagen group of Centre for International Industrial Property Studies (Strasbourg) to qualify as a European Patent Attorney. Earlier appointments include intellectual property rights consulting and biotech equity analysis.

Brian O’Neill, PhD
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Dr. Brian O’Neill is an Assistant Member of the Methodist Hospital Research Institute. After he received his doctorate in Applied Physics from the University of Windsor in Windsor, ON, he was awarded a research fellowship by the National Research Council of the United States Academy of Sciences. Under this program, he spent over two years studying the biophysical effects of pulsed high intensity focused ultrasound for application in targeted drug delivery, first at the Boulder, Colorado campus of the National Institute for Standards and Technology, and then at the National Institutes of Health. Much of Dr. O’Neill’s current research involves the use of externally applied physical energies with the goal of promoting local drug delivery and uptake. He seeks to do this in two ways. First is to reversibly and locally manipulate tissue transport and gene expression to enhance drug penetration or produce targets for pharmaceuticals, thus altering the biodistribution and pharmacokinetics of the therapeutic agent. Second is to manipulate the properties of drug carrying vehicles, such as liposomes, to promote drug release once they have accumulated in the target area. Possible physical energies include ultrasound, light, RF, and magnetic. Other research involves the synergistic interaction of ultrasound and drugs, novel photo-acoustic contrast agents, and ultrasound-based molecular imaging.

Anil Patri, PhD
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Dr. Anil Patri leads a multi-disciplinary research team in his role as the Deputy Director of the Nanotechnology Characterization Laboratory (NCL) at the National Cancer Institute at Frederick. His research interests are in the translation of nanotech-derived drugs, diagnostics and imaging agents to clinic. He interfaces with many sponsors and collaborators from federal agencies, academia and private companies on projects related to nanotechnology to conduct pre-
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Clinical assessment and standards development. He directs a chemistry lab at NCL and serves regularly on scientific panels and advisory boards to review nanotechnology related concepts and proposals. Prior to joining NCL, Dr. Patri served at the Center for Biologic Nanotechnology, (now MNIMBS) University of Michigan Medical School, and developed multifunctional nanomaterial for targeting, imaging and drug delivery application for cancer. He received his PhD in Chemistry from the University of South Florida followed by post-doctoral research training at the University of Michigan. Prior to graduate school, Dr. Patri worked as a lecturer in Chemistry and at AstraZeneca in India.

Venu Pillarisetty, MD
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Dr. Venu Pillarisetty is an Assistant Professor in the Department of Surgery at the University of Washington and a surgical oncologist who cares for patients with pancreatic cancer and other gastrointestinal malignancies. He received his BS from the University of Michigan in 1994 and his MD from the Columbia University College of Physicians and Surgeons in 1999. He completed his General Surgery Residency at the University of Massachusetts, as well as Research and Clinical Surgical Oncology Fellowships at Memorial Sloan-Kettering Cancer Center. Dr. Pillarisetty’s research interests include basic and translational studies into the importance of immune dysregulation in facilitating the progression of pancreatic cancer, with a goal of developing novel immunotherapies.

Peter Pinto, MD
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Dr. Peter Pinto is an internationally recognized author and lecturer on the targeted registration of genitourinary tumors and minimally invasive treatment of urologic malignancies. He currently holds the title of Senior Surgeon and Clinical Investigator in the Urologic Oncology Branch of the National Cancer Institute, National Institutes of Health, in Bethesda, Maryland. He is also Director of the Urologic Oncology Fellowship Program at the NCI. Dr Pinto came to the NIH after completing a minimally invasive urologic-oncology surgical fellowship at Johns Hopkins Brady Urologic Institute. Dr. Pinto is a fellow of the American Urologic Association, the Society of Urologic Oncology, the Society of Urology and Engineering and the Society of Endourology. He also serves on the National Cancer Institute’s Center for Cancer Research Advisory Board. Dr Pinto is a contributing editor for Canadian Journal of Urology and performs manuscript reviews for the Journal of Urology, The Cancer Journal, Journal of Endourology, Urologic Oncology and Urology. He has published more than 100 original medical articles and textbook chapters and has been involved with the development of several image guided systems and robotic surgical techniques that are now commonly used throughout the world. His clinical and research interests are focused on image guided registration of genitourinary tumors for molecular targeted therapies and novel minimally invasive treatments.

Joy Polefrone, PhD
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Dr. Joy Polefrone is the Program Director for the Foundations internally driven research initiative in focal drug delivery, which was launched in early 2010. Prior to filling this role, Dr. Polefrone served as the Director of Patient Support Organizations at the FUS Foundation, a position she held from May 2008 to January 2010. While in this role, Dr. Polefrone founded the Foundation's first patient support organization, Fibroid Relief, and served as its Executive Director.
Director from October 2008 - February 2010. Prior to joining the Foundation, Dr. Polefrone worked as a biotech equity analyst at CRT Capital Group in Stamford, Connecticut. She earned her PhD in Chemistry at the University of Virginia in the fall of 2006 in the Laboratory of Donald F. Hunt, PhD. The focus of her doctoral dissertation was the use of mass spectrometry to interrogate research questions related to cancer immunology and immunotherapy.

Rachel Pollard, DVM, PhD, DiplACVR
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Dr. Rachel Pollard attended Washington State University for her Doctorate of Veterinary Medicine. She then moved to New York for a 1-year internship at the Animal Medical Center. Dr. Pollard moved to Davis, California in 1997 to complete the 4-year residency in Diagnostic Imaging at the University of California, Davis School of Veterinary Medicine. She then completed a PhD in Comparative Pathology and is currently an Associate Professor of Diagnostic Imaging at UC Davis. Her areas of research focus primarily on quantitative imaging techniques using both dynamic contrast enhanced computed tomography and contrast enhanced ultrasound to evaluate tumor blood flow and assess for response to different therapeutics. She also has a research interest in radiofrequency heat ablation for the treatment of head and neck tumors in dogs. Dr. Pollard is particularly interested in translational medicine by using spontaneously occurring animal diseases in the veterinary arena to evaluate novel quantitative imaging and treatment modalities.

Tyrone Porter, PhD
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Dr. Tyrone Porter is a tenure-track Assistant Professor in the Department of Aerospace and Mechanical Engineering and Department of Biomedical Engineering at Boston University. He is building a research program focused on medical applications of ultrasound, including molecular imaging and targeted drug delivery. The Medical Acoustics Laboratory (MedAL), led by Dr. Porter, is developing acoustically responsive nanoemulsions to nucleate cavitation and enhance MRI-guided focused ultrasound cancer therapy and using microfluidics to produce monodispersions of targeted ultrasound contrast agents for molecular imaging applications. Additionally, the group is formulating ultrasound-triggerable drug carriers for localized delivery of chemotherapy. Dr. Porter received the 2008 R. Bruce Lindsay Award from the ASA in recognition of his contributions to medical acoustics as a young investigator and the BRIGE award from the National Science Foundation for studies on bubble-enhanced heating and tumor ablation.

Rich Price, PhD
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Dr. Richard Price is an Associate Professor of Biomedical Engineering at the University of Virginia and the Research Director of the UVa Focused Ultrasound Center. His primary research interests are in the regulation of microvascular growth and remodeling by hemodynamics and bone marrow-derived cells and in the development of therapeutic approaches based on interactions between focused ultrasound and microbubbles. Within the ultrasound-microbubble field, Dr. Price has studied the molecular mechanisms through which ultrasonic microbubble destruction stimulates skeletal muscle angiogenesis. He has also developed methods that use ultrasound and microbubbles for stimulating therapeutic arteriogenesis through growth factor-bearing nanoparticle delivery. More recent work has focused on using ultrasound and
Workshop Attendees

microbubbles for brain tumor therapy, including targeted drug-bearing nanoparticle delivery and mechanical tumor ablation.

Natalya Rapoport, PhD
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Dr. Natalya Rapoport is currently a Research Professor for the Department of Biomedical Engineering at the University of Utah. She earned her MSc at Moscow State University, her PhD at the Karpov Institute of Physical Chemistry, and her DSc at the Institute of Chemical Physics in the Russian Academy of Sciences. She has done research in Materials Science and Engineering as well as Biomedical Engineering at the University of Utah, and has held the W.W. Clyde Distinguished Chair in the College of Engineering. Dr. Rapoport's research interests in the field of nanomedicine are focused on the application of ultrasound-mediated drug delivery for drug targeting to solid tumors using ultrasound-activated perfluorocarbon nanoemulsions/microbubbles as drug carriers.

Robert Reed, PhD
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Dr. Robert Reed joined Celsion on May 11, 2009 as Executive Director, CMC and Technological Operations. In this position Dr. Reed oversees the CMC, QA and Technical Operations functions for Celsion. He most recently was Vice President, Pharmaceutical Operations at XenoPort, Inc., has 18+ years of experience & responsibility across XenoPort, Inc, Merck & Company, Inc., and The Liposome Company, Inc., with extensive scientific and regulatory experience in the design and development of pharmaceutical products. He holds a PhD in Analytical Chemistry from The University of North Carolina at Chapel Hill and was the recipient of a 3-year NIH Postdoctoral Individual Award at Princeton University.

Dan Schultz, MD, FACS
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Dr. Daniel Schultz joined Greenleaf Health following a distinguished 35-year career as a physician, teacher, Food and Drug Administration (FDA) official and member of the U.S. Public Health Service (USPHS). As the Senior Vice President for Medical Devices and Combination Products at Greenleaf he provides strategic consulting services and works to bring innovative devices to patients. He was the Director of the Center for Devices and Radiological Health (CDRH) at FDA from 2004 to 2009, where he led the development, implementation and evaluation of regulatory policies concerning medical devices and radiation-emitting products. He also established national goals and policies to ensure that FDA and U.S. Department of Health and Human Services (HHS) objectives were met. He began his FDA career in 1994 as a Medical Officer in the General Surgery Devices branch of the CDRH’s Office of Device Evaluation. In 1995 he advanced to the Chief Medical Officer in the division of Reproductive, Abdominal, ENT, and Radiological Devices. He served as division Director from 1998 to 2001. Dan became Deputy Director for Clinical and Review Policy in the Office of Device Evaluation in 2001 and Director of the Office of Device Evaluation the following year. He was the Director of CDRH from 2004 to 2010. He provided medical care for people living in the Navajo Nation and Indian Pueblos and received multiple awards for his service, including the Public Health Service Outstanding Service Medal. In addition to his role at Greenleaf, he is the Assistant Professor of Surgery at the Uniformed Services University of the Health Sciences and a member of the Surgical Staff at the National Naval Medical Center. Dr. Schultz is a fellow of the...
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American College of Surgeons, a member of the Commissioned Officers Association (COA). He received his medical degree from the University of Pittsburgh and is Board-certified in Surgery and Family Practice.

John Snell, PhD
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jsnell@fusfoundation.org

Dr. John Snell is the Technical Director of the FUS Foundation's Brain Program, having joined the Foundation in October 2009. He received a PhD in Biomedical Engineering from the University of Virginia in 1994 and brings a depth of academic and commercial experience in the areas of medical image analysis, neurosurgical planning, surgical navigation, radiation therapy and radiosurgery planning. He has served on the faculty of the University of Virginia Neurological Surgery Department and has made contributions to commercial medical device development with several companies including Multimedia Medical Systems, Medical Numerics and Varian Medical Systems. Dr. Snell is responsible for the definition and coordination of Brain Program technical research projects as well as providing engineering support to participating research sites.

Sham Sokka, PhD
Philips Healthcare, Andover, Massachusetts
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Dr. Sham Sokka is currently the CTO & Director of Research & Clinical Science for the Philips Healthcare MR-HIFU group. In this role, he has responsibility for all research, clinical activities, and business development in the MR-guided HIFU area. He received his masters in Electrical Engineering from the Massachusetts Institute of Technology (MIT) in 1999 and then his PhD in 2004 in Electrical & Medical Engineering from the Harvard-MIT Health Sciences & Technology Program. His dissertation topic was in the area of MR-guided HIFU, specifically on cavitation and heating mechanism critical to thermal ablation and HIFU-mediated drug delivery. In 2003, he joined Philips Research as a Senior Scientist in the area of ultrasound-mediated drug delivery. This work focused more specifically on ultrasound methods with bubble and nanoparticle agents for drug delivery. While at Philips Research, he also managed projects in the area of multi-modality imaging for clinical electrophysiology interventions. Dr. Sokka has over 20 publications and pending patents in the area of HIFU, ultrasound imaging, and multi-modality image guidance for interventions.

Zach Taylor, MBA
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Mr. Zachariah Taylor is the Director of Business Development at Philips Research focusing on technologies in the biopharmaceutical space. He is the business lead for Philips’ image-guided drug delivery activity within Philips Research, responsible for development planning, collaborations, and the overall business strategy for the technology. Prior to Philips, he worked at Millennium Pharmaceuticals, an oncology focused biotech now owned by Takeda, in the role of Director of Corporate Development where he chaired the inlicensing committee. Additionally, he served as a drug development project leader in the R&D organization, leading several oncology drug candidates in their clinical development, including both small molecules and antibody-based drugs. Prior to Millennium, he spent 3 years at Parke-Davis pharmaceuticals (now owned by Pfizer) in their commercial organization and has also worked as a management consultant. He has an MBA from Kellogg School of Management, Northwestern University and a BS in Physics from Cornell University.
Workshop Attendees

Maya Thanou, PhD
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Dr. Maya Thanou is a Senior Lecturer in the Institute of Pharmaceutical Science, King’s College London and Honorary Research Fellow at Imperial College London. She is a drug delivery scientist and is currently focusing on the design and development of nanoparticles. Her research interests are: understanding the diffusion of nanoparticles in biological samples, engineering cancer targeted nanoparticles, and developing carbon nanomaterials as novel drug delivery devices. She works in collaboration with Professor Andrew Miller and Professor Nick Quirke and has published a variety of academic articles on these topics.

Shuki Vitek, PhD
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Dr. Shuki Vitek, Vice President of Research and Development at InSightec, oversees the development of systems for noninvasive treatments using MRI guided Focused Ultrasound. Such systems are commercially available for noninvasive treatment of uterine fibroids and others are being developed and clinically tested to treat cancer in various organs including breast, bone, prostate, liver, brain. He has been at InSightec since it was founded in 1999 and has been one of the prime innovators of this technology. As part of this, he has issued 14 patents, accepted in the USA. Before joining InSightec, Dr. Vitek spent 21 years at Rafael in a variety of positions, from a research engineer in the field of guidance & navigation to the chief scientist of the Missiles Division. He was also awarded twice the Rafael Prize. Dr. Vitek received his PhD in Mathematics from the Technion, Israel Institute of Technology, where he also graduated and received BSc degrees in Mathematics and in Electrical Engineering.

Beat Werner, PhD
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Dr. Beat Werner graduated from the faculty of physics of ETH Zürich, Switzerland in 1988 and started working at the University Children’s Hospital Zürich on C-13 MR-spectroscopy. He left MR-research in 1990 and worked for several years in software developing and marketing communications with new media. In 2002, he joined again the MR-Center at University Children’s Hospital. Since 2005, he is involved in the Brain Project for technical and physical aspects of the related research activities.

Samuel Whiting, MD, PhD
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Dr. Samuel Whiting is an Assistant Professor for the Department of Medical Oncology at the University of Washington School of Medicine and is an Assistant Member of the Clinical Research Division of the Fred Hutchinson Cancer Center. The areas of his clinical expertise are as follows: clinical trials, liver and lung metastases, chemoradiotherapy, neoadjuvant treatment approaches, adjuvant chemotherapy and surveillance. He earned his BS in Chemistry from Lewis and Clark College in Portland and his MD and PhD from the University of Washington School of Medicine. He completed his residency in internal medicine at the University of Washington as well and completed a four-year residency on medical oncology at the Fred Hutchinson Research Center. Dr. Whiting’s initial focus was on laboratory research aimed at how patient data informs medical research. He studied how retroviruses such as the HIV virus replicate within cells and...
Brad Wood, MD
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Dr. Bradford Wood is Director of the Center for Interventional Oncology at the National Cancer Institute, Chief of Interventional Radiology in the Clinical Center, and a Senior Investigator at the National Institutes of Health (NIH). He earned both his undergraduate and graduate degrees from The University of Virginia and completed an Internship in Internal Medicine, followed by Residency in Diagnostic Radiology at Georgetown University, where he was Chief Resident. He went on to do double fellowships at Massachusetts General Hospital at Harvard in Abdominal Imaging and in Intervention and Vascular & Interventional Radiology. He stayed on staff at Massachusetts General Hospital / Harvard after training, and holds his Certificate of Added Qualifications in Vascular and Interventional Radiology. Dr. Wood has practiced at the NIH in Interventional Radiology since 1998. He directed the Interventional Radiology Research Lab from 2004 to present, and was Acting Chief of Radiology - Science and Research and Acting Director of the Molecular Imaging Lab from 2006 to 2008, when he became a Tenured Senior Investigator. He also is an Adjunct Investigator in the National Cancer Institute, and is credentialed in surgery and radiology. He has received both the Clinical Center Director’s Award and the NIH Director’s Award, and has published widely in the field of Interventional Radiology and the emerging discipline in Interventional Oncology. Dr. Wood’s research interests include drug and device combination therapies, heat deployed nanoparticle vectors, GPS-smart medical devices, minimally invasive & image-guided tumor ablation, high intensity focused ultrasound, molecular interventions, and the Operating Room of the Future. He was the first physician to perform radiofrequency ablation mono-therapy for kidney tumors in humans in the mid-1990’s, the first to use ablation devices plus heat deployed drugs, and the first to guide ablation with GPS-enabled devices.

Feng Yan, PhD
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Dr. Feng Yan works currently as a senior scientist for Bracco Suisse (Geneva), a company dedicated to R & D of diagnostic contrast media. He received his MSc in Polymer Chemistry at the Sichuan University in 1982 and he obtained his PhD in 1987 at the University of Louis Pasteur in Strasbourg (France), specializing in Biopolymer and Bio-surface for medical application. He joined Bracco Suisse in 1990 and works on ultrasound contrast agents (gas microbubbles) for diagnostic and therapeutic applications. His research effort contributed to the development and commercialization of SonoVueTM, a second generation of ultrasound contrast agents. His current interests are focused on ultrasound molecular/targeted imaging, ultrasound-mediated gene and drug delivery (BBB opening), clinical application of SonoVueTM, nanocarriers for drug delivery and sonothrombolysis (use of rt-PA, ultrasound and microbubbles intended to treat ischemic stroke patients and brain diseases). He has filed a dozen patents in the contrast ultrasound field and ultrasound-mediated drug delivery and published about 20 scientific articles.
The Collaborative Research Network

The Foundation has developed an online tool to aid one of the tenants of our mission: to accelerate the development of focused ultrasound. This website, called the Collaborative Research Network (www.fusfoundation.org/crn), has been established with the goal of allowing researchers and clinicians at disparate institutions to collaborate with one another on shared research projects and receive the most up to date information in their field.

The Collaborative Research Network (CRN) is a secure section of our website available only to registered members. There, users can

- Join existing groups established around specific research topics
- Create new groups open to all CRN researchers or private groups for research projects of their choice
- Search a full bibliography on focused ultrasound related literature
- Connect with other members of the focused ultrasound research community
- Stay up to date on the latest publications and news about their research interests
- Search job, fellowship, and research positions in the focused ultrasound community

Research groups on the CRN can

- Exchange documents, images, and videos with other members
- Post questions and project updates on the group forum
- Receive notifications via email of new information posted to the group

The Foundation is committed to developing the CRN into a tool that serves the needs of the focused ultrasound research community and we welcome your participation and input.

If you have any questions, please contact David Moore at dmoore@fusfoundation.org.
Research Funding and Fellowship Opportunities in Focused Ultrasound

**Research Awards**  |  Awards of up to $100K for one year

The FUSF Research Awards Program provides funding for late-stage preclinical research projects and pilot clinical trials that are related to the application or use of MR-guided focused ultrasound technology and that have high potential for rapidly leading to the development of clinical indications. Researchers in all stages of their careers are encouraged to apply. Applications are accepted on a rolling basis.

**Fellowship Awards**  |  Awards of up to $100K for one year

The FUSF Fellowship Awards Program provides funding support for fulltime and part-time clinical fellowships in the field of MR-guided focused ultrasound. Physicians from all clinical specialties are encouraged to apply. Applications are accepted on a rolling basis.

**For more information**

Please click the “Research” tab on the Foundation website at [http://www.fusfoundation.org](http://www.fusfoundation.org)

or contact Hannah Edelen,  
Director of Research and Fellowship Programs, at hedelen@fusfoundation.org.
NCI Funding Opportunities

NCI Funding available for FUS-related Research
For further information please email Dr. Keyvan Farahani at farahani@nih.gov.

PA-09-253: Image-guided Drug Delivery in Cancer (R01)
This initiative encourages innovative translational research in the development of quantitative in vivo imaging characterization of image-guided drug delivery (IGDD) in cancer, including characterizations of the target, delivery validation, and therapy response. It will support research in development of integrated imaging-based platforms for multifunctional and multiplexed drug delivery systems in cancer. Validation studies in non-human primates or large animal models and first in human studies directed towards translation of IGDD technology into the clinic will be considered appropriate for this initiative.

PAR-08-147: Quick-Trials for Imaging and Image-Guided Interventions: Exploratory Grants (R21)*
The goal of this initiative is to support clinical trials conducting preliminary evaluation of the safety and efficacy of imaging agents, as well as an assessment of imaging systems, image processing, image-guided therapy, contrast kinetic modeling, and 3-D reconstruction and other quantitative tools. The rapid translation of promising discoveries in the fields of imaging probes, methodologies, technologies and image-guided therapies to clinical practice requires timely support. This FOA will provide investigators with support for either pilot (Phase I and II) cancer clinical trials, or patient monitoring and laboratory studies.
*This funding opportunity, due to expire on 4/11/2011, will be followed with a similar initiative.

PAR-10-169: Academic-Industrial Partnerships for Development and Validation of In Vivo Imaging Systems and Methods for Cancer Investigations (R01)
This funding initiative encourages applications from research partnerships formed by academic and industrial investigators to accelerate the translation of either animal or human in vivo imaging, image guided, and/or spectroscopic systems and methods designed to solve targeted cancer problems for cancer research, clinical trials, and/or clinical practice. The partners on each application will establish an inter-disciplinary, multi-institutional research team to work in a strategic alliance to implement a coherent strategy to develop and translate the proposed system or methods with potential for significant impact on preclinical, single, or multisite clinical studies. Partnerships must include at least one lead academic and one lead industrial organization large or small among their numbers. For either preclinical or clinical research, funding may be requested for limited additional copies of prototype systems and methods in order to optimize and validate them across different platforms and/or research sites. Each partnership is encouraged to plan to solve its choice of targeted cancer problem within the five year funding period. This initiative supports clinical trials that emphasize optimization and validation of the performance of imaging systems, including devices, agents and/or methods. It will not support commercial production.

PA-10-080 and PA-10-079: Image-Guided Cancer Interventions
These small business-related funding initiatives support the development and clinical validation of systems for image-guided interventions (IGIs) for cancer. Specifically, the goals of this program are to provide support for: the development and optimization of fully integrated cancer imaging, monitoring, and therapy systems; the validation of integrated IGI systems through clinical evaluations; the development of multiple prototype integrated IGI systems as required for multisite clinical evaluations; and partnerships among small business, large business, and academic clinical centers, as well as small business joint ventures, in order to reach the research goals.
Core Stakeholder Meeting
List of Participants

Members of the Core Stakeholder Group:

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*Sander Langereis has been invited to attend in place of Holger Grüll as Holger is unable to attend the first Core Stakeholder face to face meeting.
Core Stakeholder Meeting
List of Participants

Members of the Core Stakeholder Group:

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*Sander Langereis has been invited to attend in place of Holger Grüll as Holger is unable to attend the first Core Stakeholder face to face meeting
Core Stakeholder Meeting
Priority Setting Process

Focal Drug Delivery Clinical Indication & Research Question
Priority Setting Process

Prioritization of Clinical Indications

Clinical Indications submitted to FUSF by Stakeholder Group

Clinical Indication Priority Criteria defined by FUSF and Survey Created

Clinical Indications assessed via Survey by Core Stakeholder Group based on defined Criteria

Clinical Indications Scored with Weighted System Defined by FUSF

Top 2-4 Clinical Indications Reported to Core Group

Survey Results discussed, Clinical Indications Reviewed and Research Questions refined at Face-to-Face Meeting

Prioritization of Research Questions

Research Questions submitted to FUSF by Stakeholder Group

Research Question Priority Criteria defined by FUSF and Survey Created

Research Questions assessed via Survey by Core Stakeholder Group based on defined Criteria

Survey Statistics from Research Questions compiled and analyzed by FUSF

Survey Results Reported to Core Group
**Core Stakeholder Meeting**

Clinical Indications Priority Setting Criteria

**Evaluation Criteria**

*Members of the Core Stakeholder Group used these criteria to rank the clinical indications to determine the priority clinical indications relevant to achieving the mission of the Focused Ultrasound Surgery Foundation.*

*All Indications were assessed for qualification with the Criteria (Yes/No) below:*

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<thead>
<tr>
<th>Criteria Statement</th>
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| 3  | Indication size/population?  
Very small can get HDE  
Very large, larger impact due to population |
| 4  | This indication may be low hanging fruit/will get us to clinic faster.                                                                   |
| 5  | May relate to already approved FUS indications*                                                                                           |
| 6  | Obvious acoustic path to treatment site - easily accessible to FUS (no bone, no air, no problem)                                           |
| 7  | Compassionate use indication - indication with no other treatment available                                                              |

*Core Face-to-Face Meeting discussion lead to a modification of #4 to state: Able to utilize currently available FUS devices and delivery systems, with a preference toward currently approved devices and delivery systems.*
Evaluation Criteria

Members of the Core Stakeholder group used these criteria to rank the research questions to determine the priority research questions relevant to achieving the mission of the Focused Ultrasound Surgery Foundation.

All research questions will be assessed based on alignment with the following criteria:

1. This question can be answered. It is feasible to design an experiment that can produce sufficient data to answer this question.
2. This question can be answered rapidly through one or more defined experimental segments.
3. This question can be answered within reasonable available resources.
4. This question must be answered to lead to successful MR-guided focused ultrasound treatment, it cannot remain unanswered while pursing clinical indications.
5. Answering this research question will contribute to the development pathway for multiple indications.
6. The data provided by performing experiments to answer this question will fill significant gaps in the current body of evidence necessary to achieve a successful clinical application (regulatory).