A Novel Approach to Optimize Sensitivity in Ultrasound Molecular Imaging

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Background

- Ultrasonic Molecular Imaging
  - Uses targeted contrast agents
  - Attachment of specific ligands
    - Antibodies
    - Peptides
    - Polysaccharides
  - Bind to cellular receptors
  - Recognize disease antigens
- Targeted Pathologies
  - Tumors
  - Inflammation
  - Thrombus
Targeted Ultrasound Contrast Agents

- Blood doesn’t scatter US well
- Microbubble: A contrast agent
- Filled with gas: High echogenicity compared to liquid based particles or blood cells
- Diameters of the order of 1 to 5 µm
- Smaller than Red Blood Cells (6-8 µm)
- Improve the sensitivity of 2-D and 3-D ultrasound imaging

Hettiarachchi et al., Lab Chip, 2007
Structure of Microbubbles

- A monolayer amphiphilic phospholipid shell
- The water insoluble hydrocarbons
- Charged phosphate head groups
- Use of PEG:
  - Coalescence
  - Phagocytosis
  - Physical barrier to enzymatic agents, adsorption of blood proteins
Current Contrast Agent Production

- produced by mechanical agitation of lipid solution
- polydisperse size distribution

Large Size Variance:
Problems with Current Contrast Agents & Ultrasound Systems for Molecular Imaging

- Size distribution
- The resonant frequency
- Limited frequency bandwidth
- Only a small percentage of the contrast agents have diameters which result in resonant frequencies optimized for the limited bandwidth
- Fewer contrast agents retained
- Filtering does not work on lipid-shelled bubbles
The Problem

- Bubble size: $1.8 \pm 1.5$ microns
- $F_{\text{receiver bandwidth}} = 5.0 \pm 1.5$ MHz
- Detectable bubbles: 18%

A Solution

- Bubble size: $1.8 \pm 0.2$ microns
- $F_{\text{receiver bandwidth}} = 5.0 \pm 1.5$ MHz
- Detectable bubbles: 92%
Monodisperse Microbubble Production

• Use of Microfluidic Flow Focusing Device

Talu, et al., Langmuir, 2006
Hettiarachchi et al., Lab Chip, 2007
Why use a Microfluidic System?

- Relatively cheap, simple, and easy to multiplex


Stable monodisperse 10 µm lipid shell-based PFC microbubble generation in a microfluidic flow-focusing device with expanding nozzle geometry.
Tailoring the Size Distribution Microbubbles

Lipid Encapsulation for Stability

Cell Targeting

Incorporate Targeting Ligand
Ultrasound Imaging System

Acoustical System

Arbitrary Waveform Generator → Trigger → Amplifier → Transmitting Ultrasound Transducer → Receiving Ultrasound Transducer

Computer with LabView & Photron Software → Oscilloscope → Panametrics Receiver

Microbubble Generation

PFC Gas Tank → Microfluidic Flow-Focusing Chamber → Syringe Pump

Optical System

Monitor → High Speed Camera → Microscope
- Ultrasound Transducers
- Transmitter 2.5 MHZ / Receiver 5 MHz
- Liquid flow rate: 35 ul/min
- PFC flow rate: ~2-4 psi
Acoustic Studies of Monodisperse Contrast Agents

- Standard deviation of echo amplitude is smaller
- Correlation coefficient 0.95 vs. 0.70
- Improved Signal Response of Monodisperse Contrast Agents
Detection of Monodisperse Agents

Monodisperse

Polydisperse

Matched filter detection threshold

Mono

Definity *
Summary & Conclusions

• Successful production of monodisperse contrast agents
• Monodisperse microbubble contrast agents have the potential to increase sensitivity in ultrasound molecular imaging
• More sensitive detection of monodisperse contrast agents compared to polydisperse agents
• Production rate of contrast agents is one of the challenges (in comparison to $10^{10} \mu l$ with polydisperse)
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