Clinical Translation of Activated Optical Fluorescence Methods and Technologies for Sensitive Cancer Detection *In Vivo*

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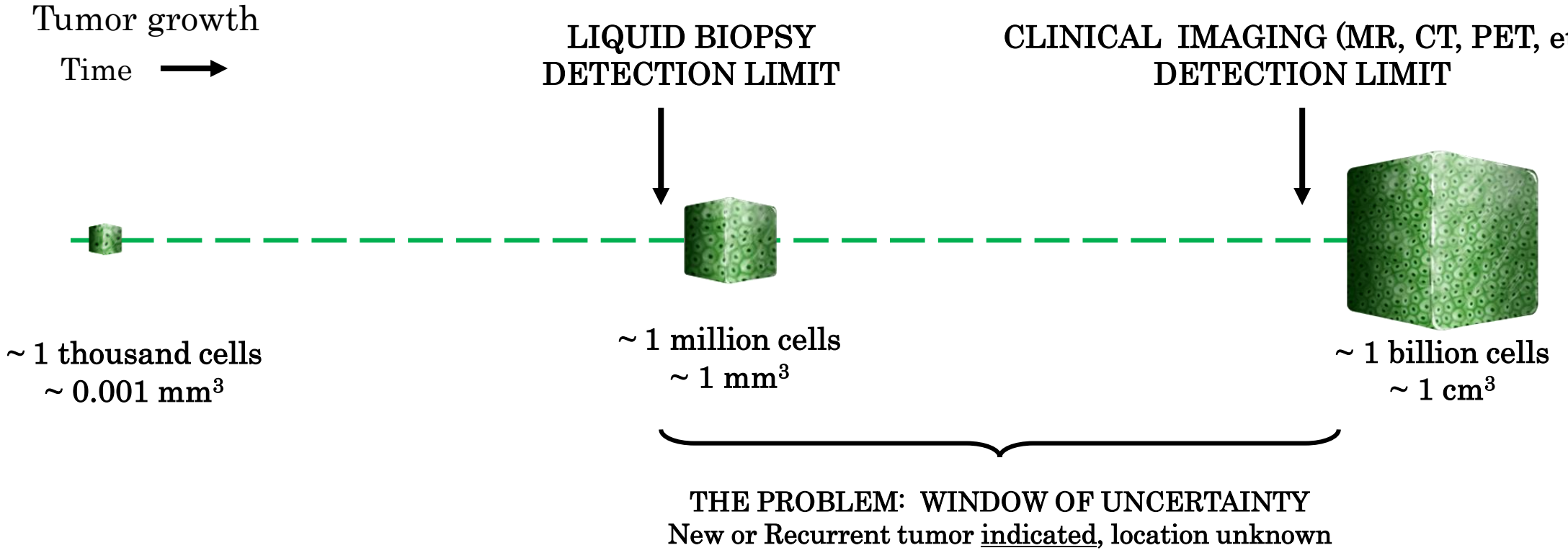
Harness High Sensitivity Imaging for Locating Very Small Volume Cancers



Goal of the Project

Demonstrate enhanced sensitivity of imaging that will enable physicians to locate small tumors indicated by fluid-based diagnostic results…

…and to do this within the framework of the Moonshot program.

Budget constraints.
Ten years of progress in a five year period.

Why is Greater Imaging Sensitivity Important?

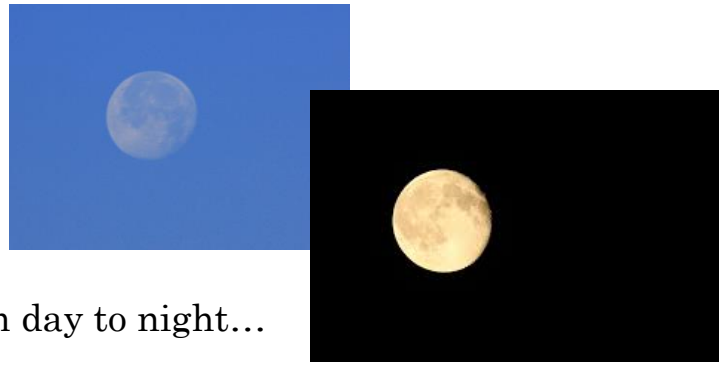
- Early detection
- Anatomic staging and treatment planning
- Detection of residual disease or metastatic disease
- Reduced patient anxiety
- More…

Imaging Small Tumors: Requirements

- Reduced noise in the system
- Increase resolving power
- Sufficient field of view

These are design changes in the imaging device

Increasing contrast in the image can greatly increase sensitivity without requiring costly hardware improvements



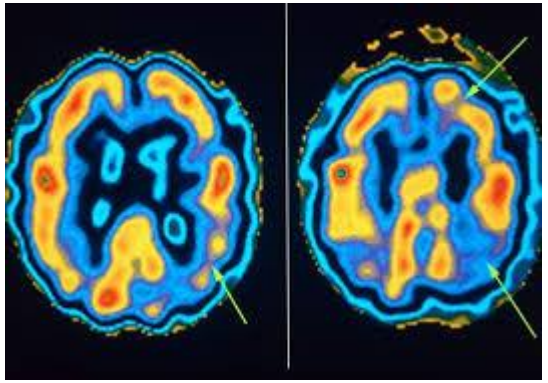
The moon does not get brighter from day to night…

…the contrast increases.

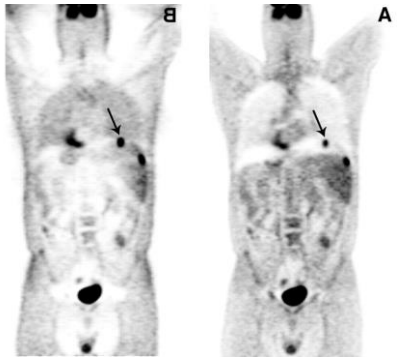
Contrast Enhancement by Imaging Agents

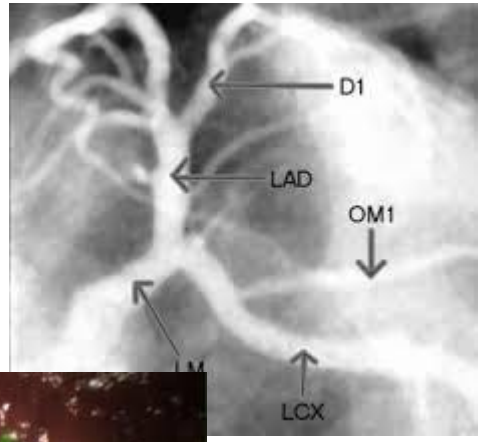
Virtually every *in vivo* clinical imaging modality can be improved through contrast enhancement

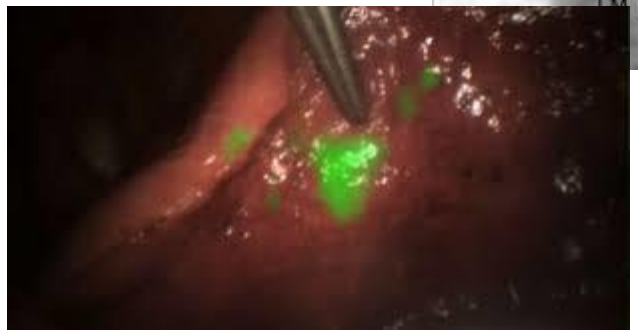
- Magnetic Resonance Imaging: Gadolinium for DCE
- PET: Radiotracers of various kinds
- Ultrasound: Microbubbles
- Optical: Variety of dyes from visible to near IR



Each with very different clinical roles to play

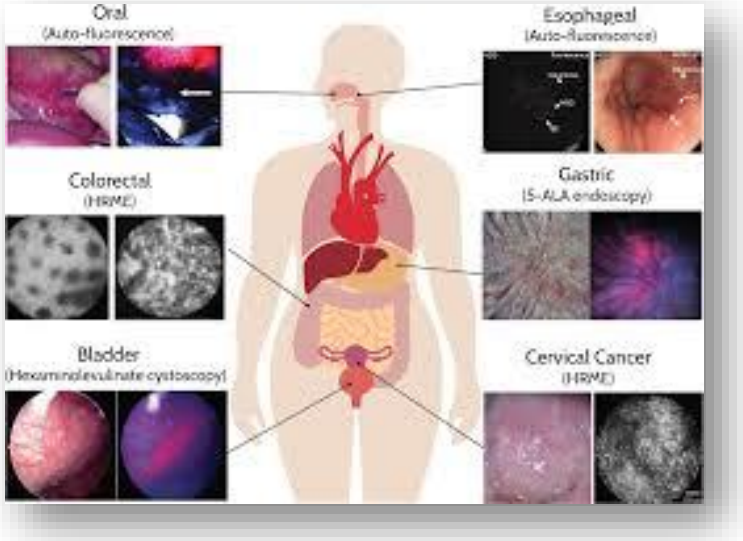






Important Uses of Optical Fluorescence Imaging

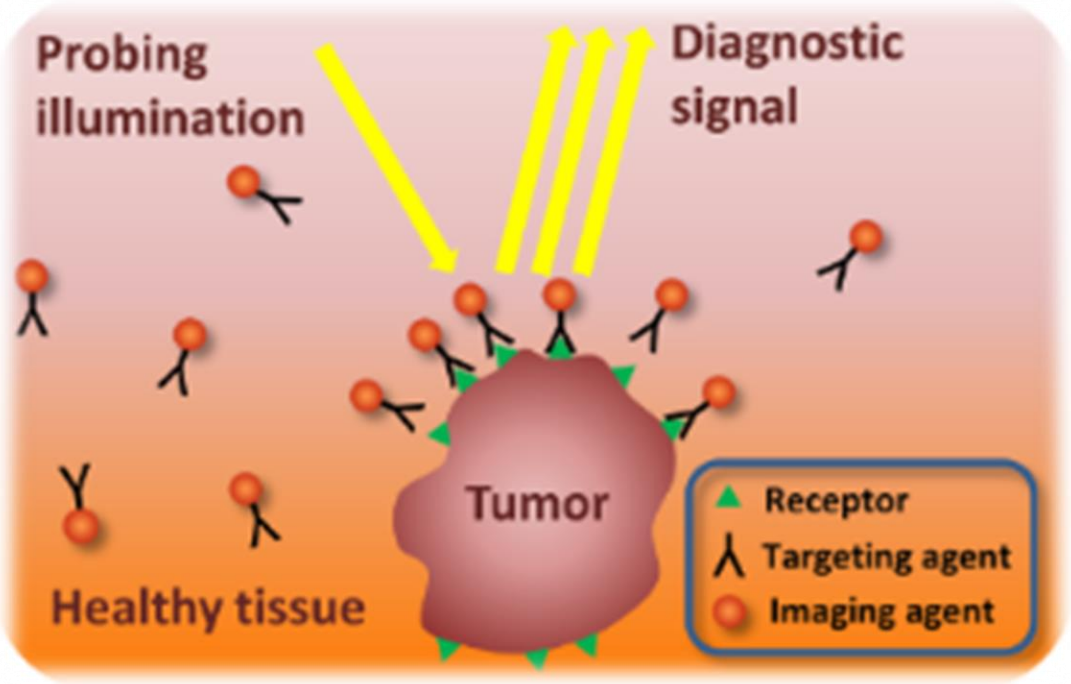
A variety of body lumens and organs



- Probe technology (dyes) is well developed and understood
  - Many emission wavelengths and excitation wavelengths
    - Visible through near infrared
  - Toxicities are known
- Non-invasive
  - Low-energy photons used
  - High resolving power achievable
  - Tissue penetration depths up to several cm.
- Relatively low cost in medical imaging arena

Easily incorporated in robotic surgical suites

Fluorescence Contrast Can Be Increased With Targeted Probes



Indocyanine Green and
5-Aminolevulinic Acid (5-ALA)

A reporter dye is conjugated with an affinity ligand (e.g. antibodies, peptides, labeled small molecules) selected for the specific tumor being sought.

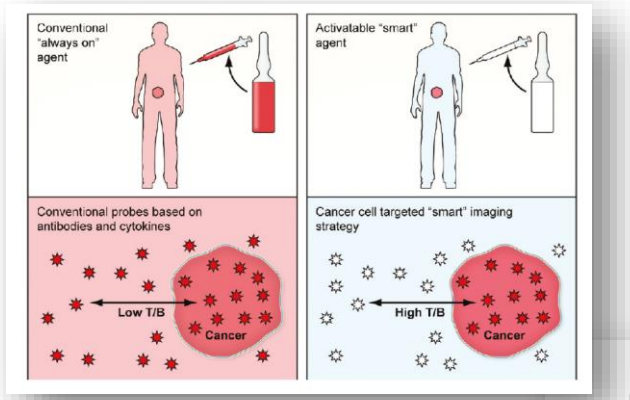
Accumulation of the dye at the tumor site

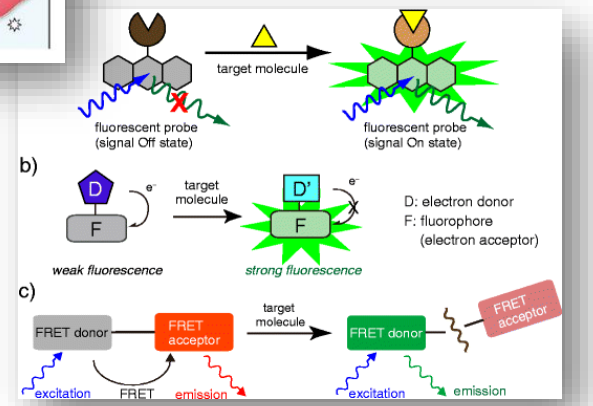
- Unbound probes must be eliminated from region
  - This requires sufficient circulation time
  - Bound probes can disengage

Contrast enhancements on the order of 3.4 to 10

Next step up from Targeted Probes

Smart probes
Optical switches
Activated probes



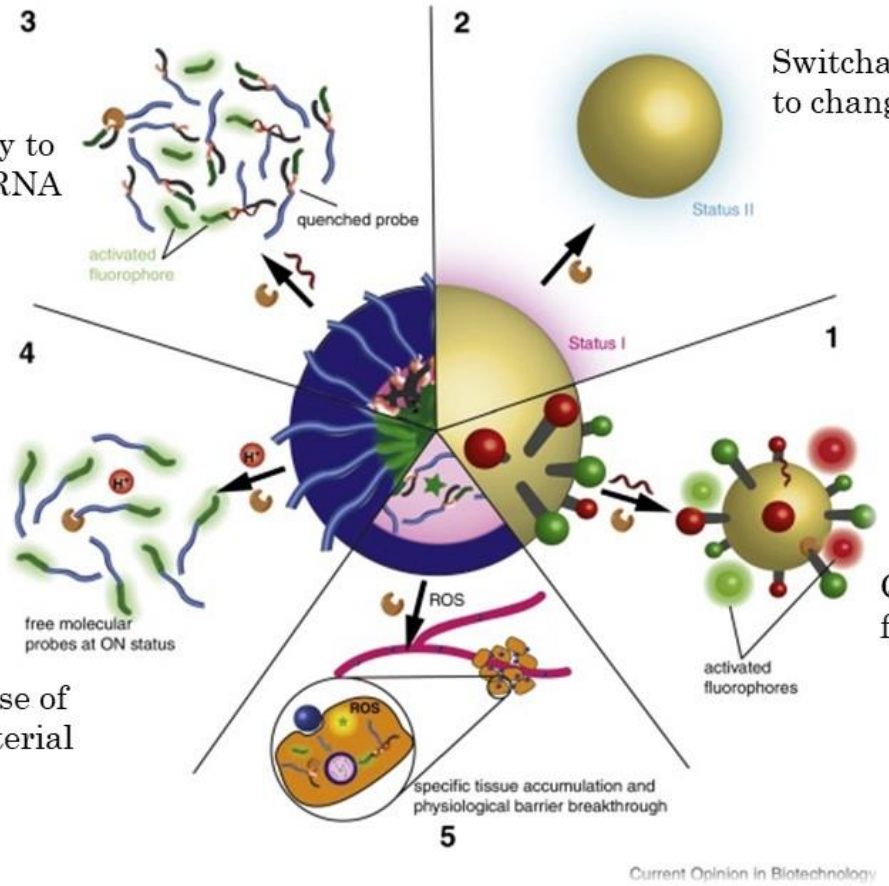


A number of activated probe operation designs
- Quenched-fluorophore
- Enzyme activated
- Fluorescence resonance energy transfer (FRET)
- Self-quenching
- Photon-Induced Electron Transfer (PeT)

Contrast can be enhanced to over 100:1

Nanoprobes as Activatable Imaging Agents

Molecular self-assembly to Detect intracellular mRNA



Switchable signals in nanoparticle to change wavelength

Quenchers to control fluorescence

Triggered release of fluorescent material

Improve accumulation of probes in target Tissue.

Clinical Translation

Molecular imaging in living subjects: seeing fundamental biological processes in a new light

Tarik F. Massoud[1,3] and Sanjiv S. Gambhir[1,2,4,5]

In 2003, Massoud and Gambhir discussed the challenges of translating molecular imaging

They discussed optical imaging along with other modalities, stating that progress in this area has come form recent developments in targeted bioluminescent probes, near IR fluorochromes, and **activated fluorochromes**.

Yet, despite this early enthusiasm, little translation progress has been made

Translation Plan: R01

- Goal: Clinically focused study of activated fluorescence to demonstrate tumor imaging sensitivity in line with fluid based biopsy results
  - Seek teams with track record in activated fluorescence research for *in vivo* imaging
    - Development challenges mostly solved
  - Emphasize the need for a team approach
    - Clinical input and imaging input both required
    - Technical complexity can be overcome
  - Require clinical trial validation
    - Preclinical research excluded: Toxicity will not be studied in this program

Activated Fluorescence Probes

The Challenge

It is the responsibility of those involved in today's biomedical research to translate the remarkable scientific innovations we are witnessing into health gains for the nation. - E. Zerhouni NEJM 2005

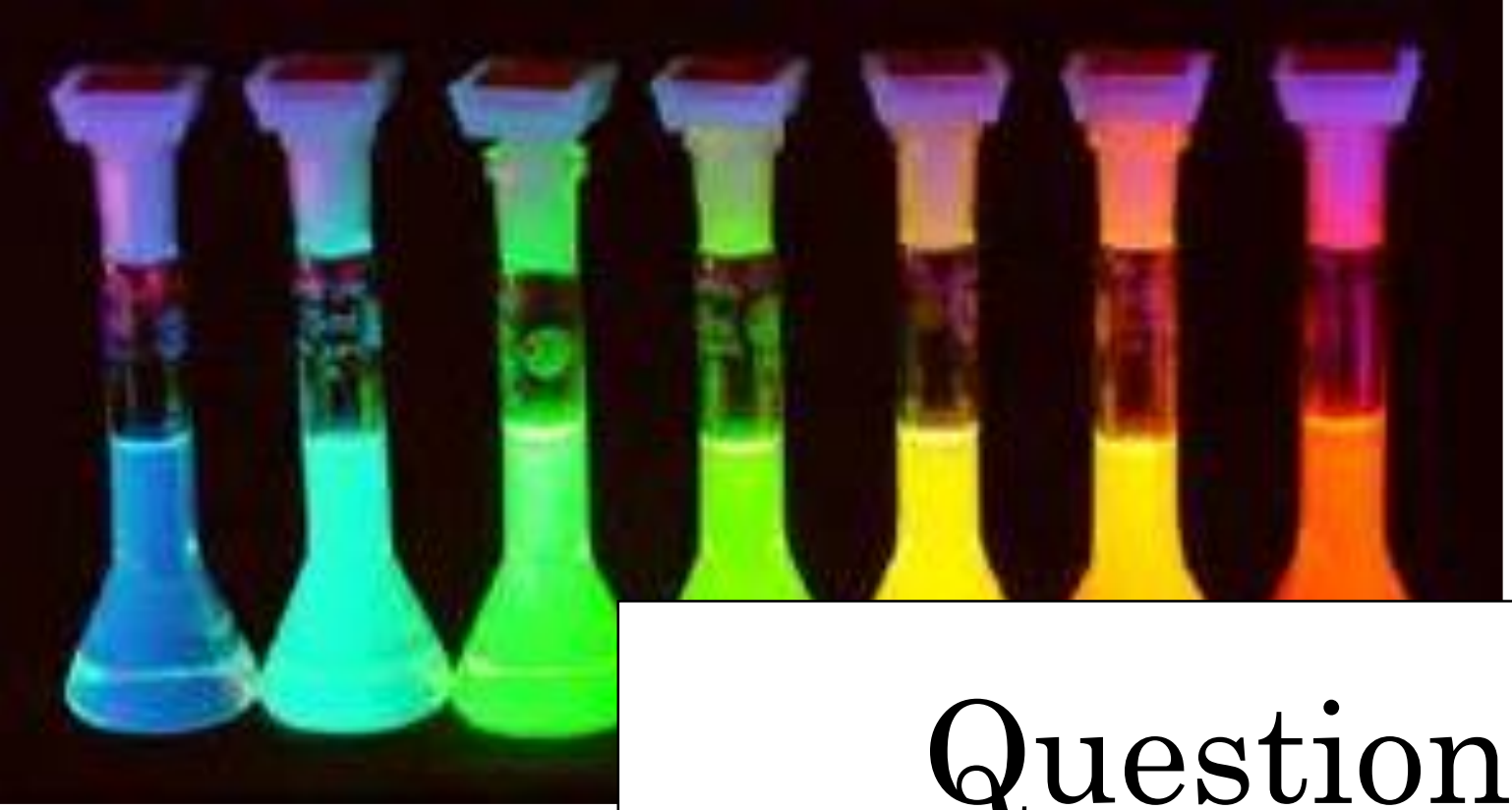
Barriers:

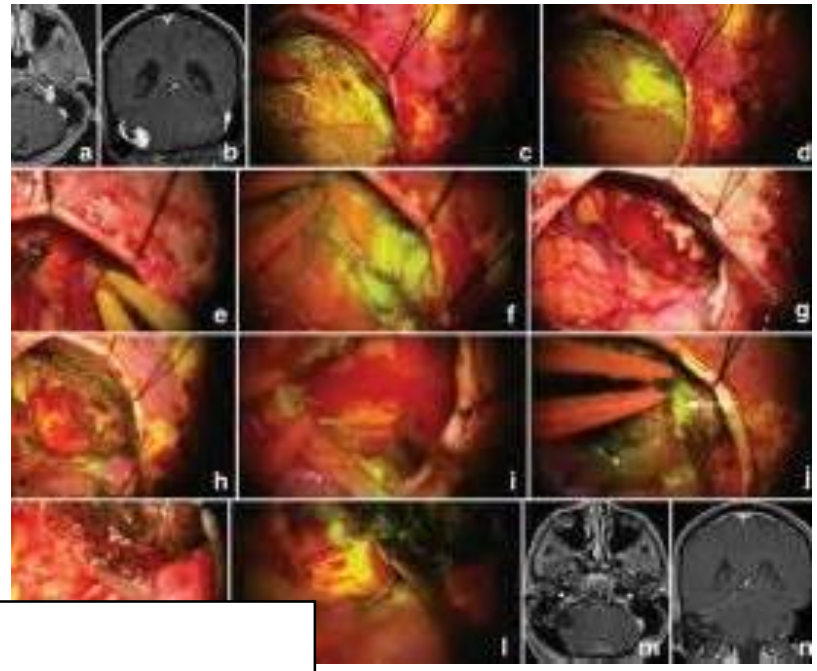
- Language
- FDA regulations
- Perceived needs
- Technology complexity
- Clinical integration
- Many more

Propose:

- 2 - 3R01
  - Translation
  - Clinical validation
  - Workflow integration
- ~ $1M /year for 5 years

Bring sensitive, high-contrast imaging to clinical attention in a pilot project to demonstrate clinical utility in closing the gap between fluid-biopsy indication of tumor and imaging location for anatomic staging and therapy response of imaging.





Questions