Clinical Imaging of Human Body: For Health, Visualization and Predictive Analytics

Pratik Shah, Mrinal Mohit, Tristan Swedish and Ramesh Raskar

Pratik Shah. Ph.D.
pratiks@mit.edu

Outline of Tutorial

9:00–9:10	Introduction
9:10–9:40	Overview of Image Acquisition Modalities
9:40–10:00	Breakouts
10:00–10:40	Deep Learning in Healthcare
10:40–11:00	Breakouts
11:00–11:40	Case Study: Deploying Automated Screening
11:40–12:00	Q&A and Discussion

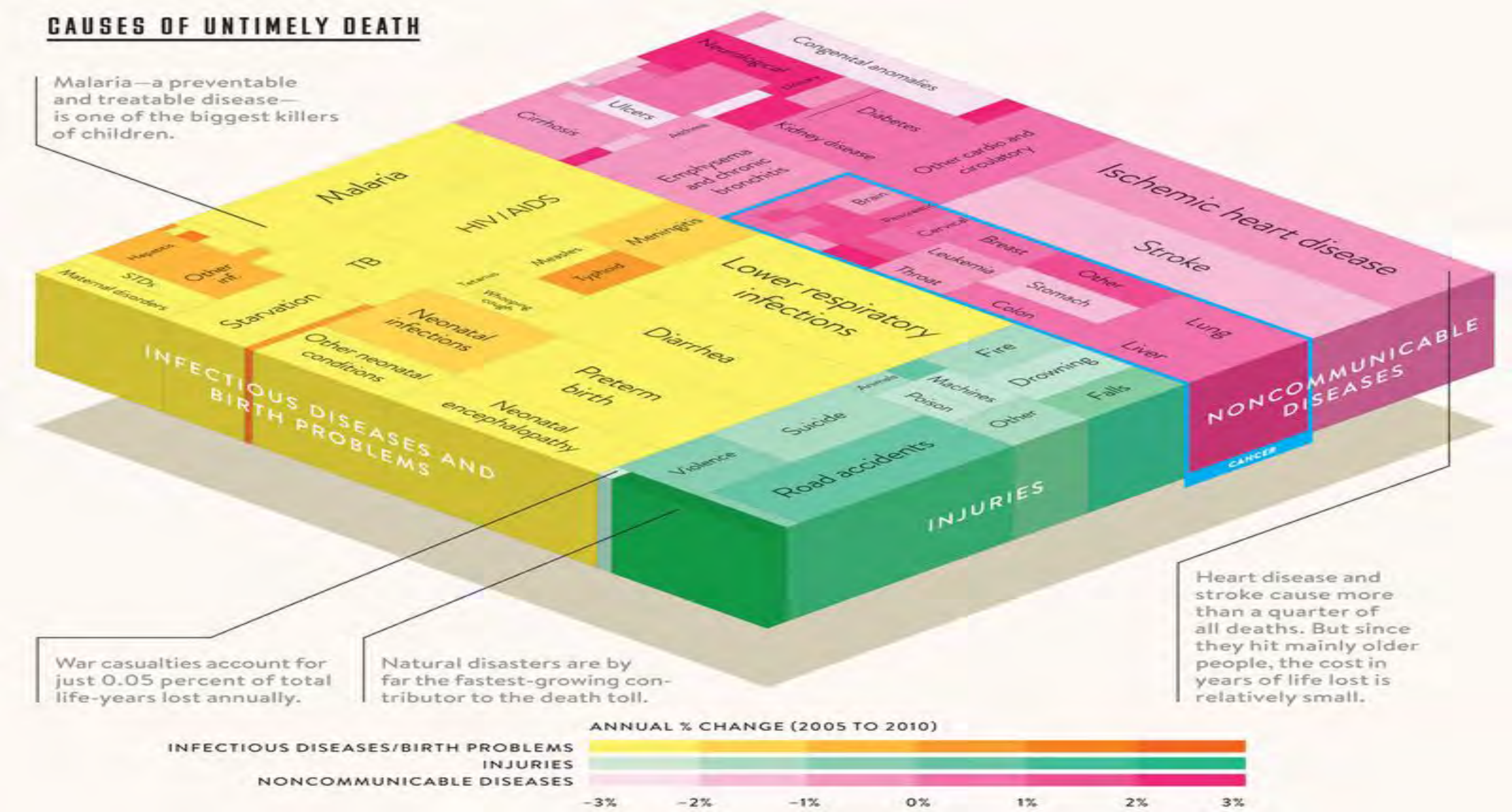
Pratik Shah. Ph.D.
pratiks@mit.edu

Automated image processing platforms for medical and biological data

Pratik Shah, Ph.D*

***Co-Principal Investigator, Camera Culture Group, MIT Media Lab**

Causes of untimely death



Pratik Shah. Ph.D.
pratiks@mit.edu

Outline of presentation / ANI vs. AGI

Diagnostic Imaging Modalities

In-class exercises

Deep learning approaches

In-class exercises

What next?

In-class exercises

Biological Imaging Modalities

In-class exercises

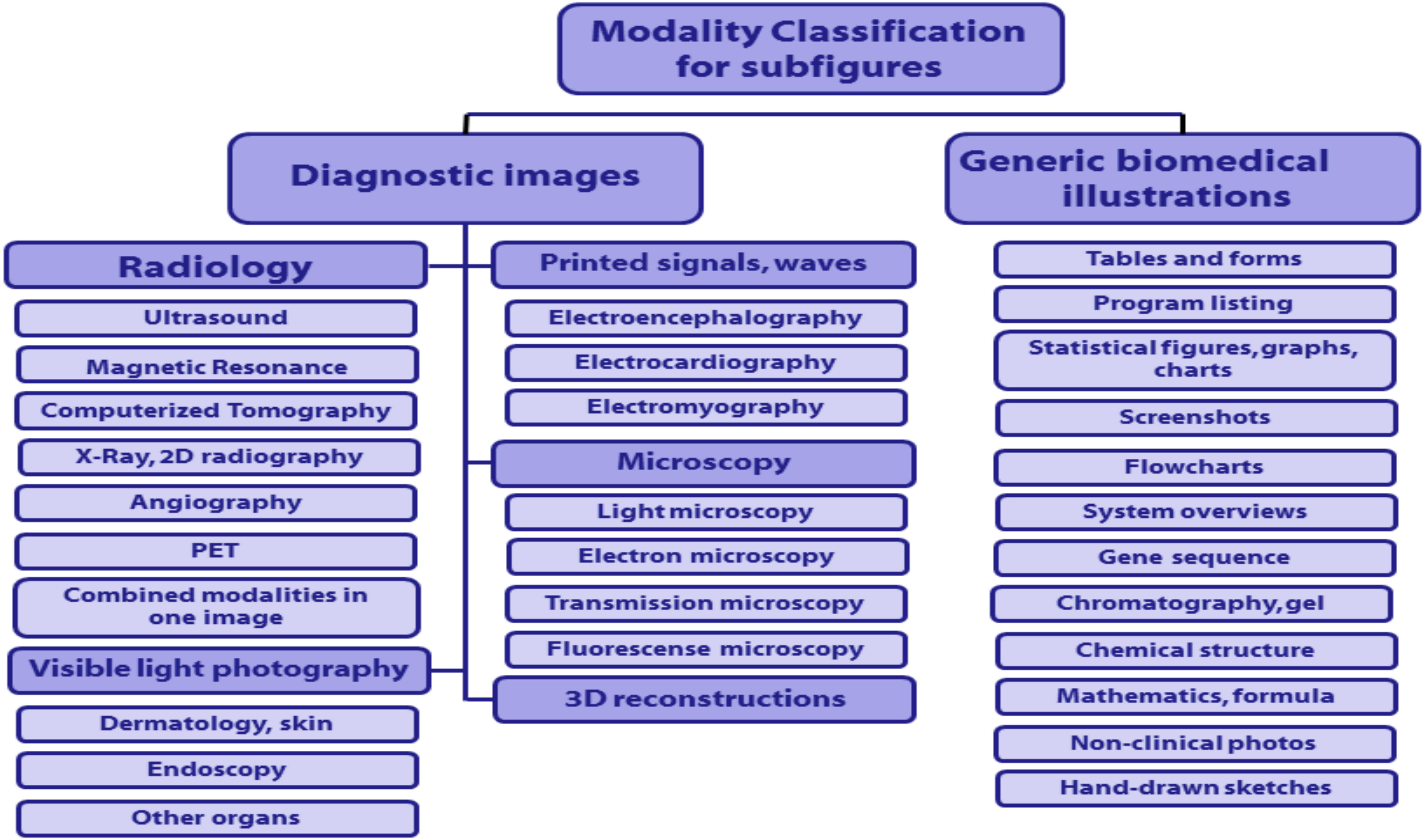
Deep learning approaches

In-class exercises

What next?

In-class exercises

Pratik Shah. Ph.D.
pratiks@mit.edu



Modality Classification for subfigures
Diagnostic images
Generic biomedical illustrations
Radiology
Ultrasound
Magnetic Resonance
Computerized Tomography
X-Ray, 2D radiography
Angiography
PET
Combined modalities in one image
Visible light photography
Dermatology, skin
Endoscopy
Other organs
Printed signals, waves
Electroencephalography
Electrocardiography
Electromyography
Microscopy
Light microscopy
Electron microscopy
Transmission microscopy
Fluorescense microscopy
3D reconstructions
Tables and forms
Program listing
Statistical figures, graphs, charts
Screenshots
Flowcharts
System overviews
Gene sequence
Chromatography, gel
Chemical structure
Mathematics, formula
Non-clinical photos
Hand-drawn sketches

Molecular Imaging

- Create methods to image the underlying biological processes or functional state of living cells, tissues, and organs.
- In vivo imaging of living organisms
- Can use MRI, PET, SPECT, or optical imaging modalities
- Applications:
  - Detect disease in humans
  - Quantify disease in small animals for drug development
  - Better understand biological processes in living animals

Pratik Shah. Ph.D.
pratiks@mit.edu

Medical Imaging

Medical imaging refers to several different technologies that are used to view the human body in order to diagnose, monitor, or treat medical conditions. Each type of technology gives different information about the area of the body being studied or treated, related to possible disease, injury, or the effectiveness of medical treatment. (www.fda.gov)

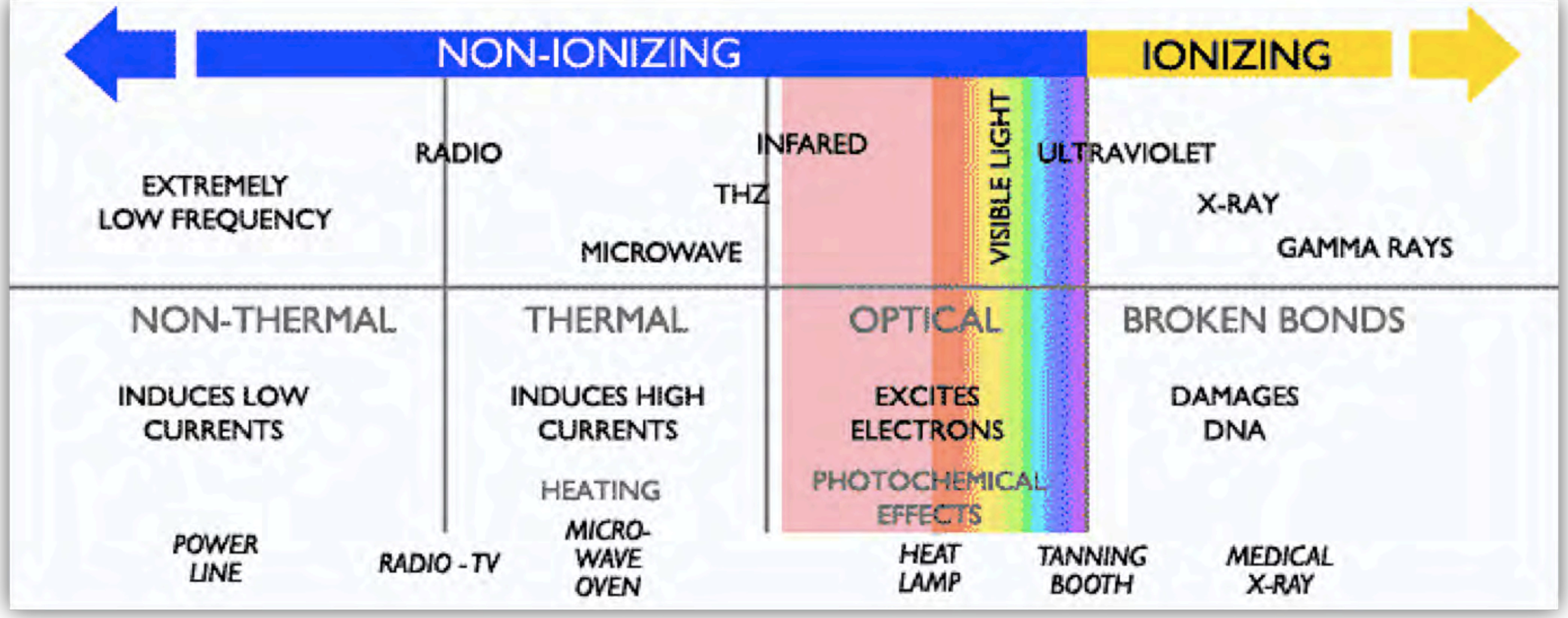
IONIZING

- X-rays Radiography
- Fluroscopy
- Computed Tomography
- Cone-beam Computed Tomography

NON IONIZING

- UV
- Visible
- Infrared
- Magnetic Resonance Imaging

Pratik Shah. Ph.D.
pratiks@mit.edu



http://www.radiologyandphysicalmedicine.com/

X-rays radiography

X-ray radiography: Detects bone fractures, certain tumors and other abnormal masses, pneumonia, some types of injuries, calcifications, foreign objects, dental problems, etc.

Bones

Fat

Tissues

Air

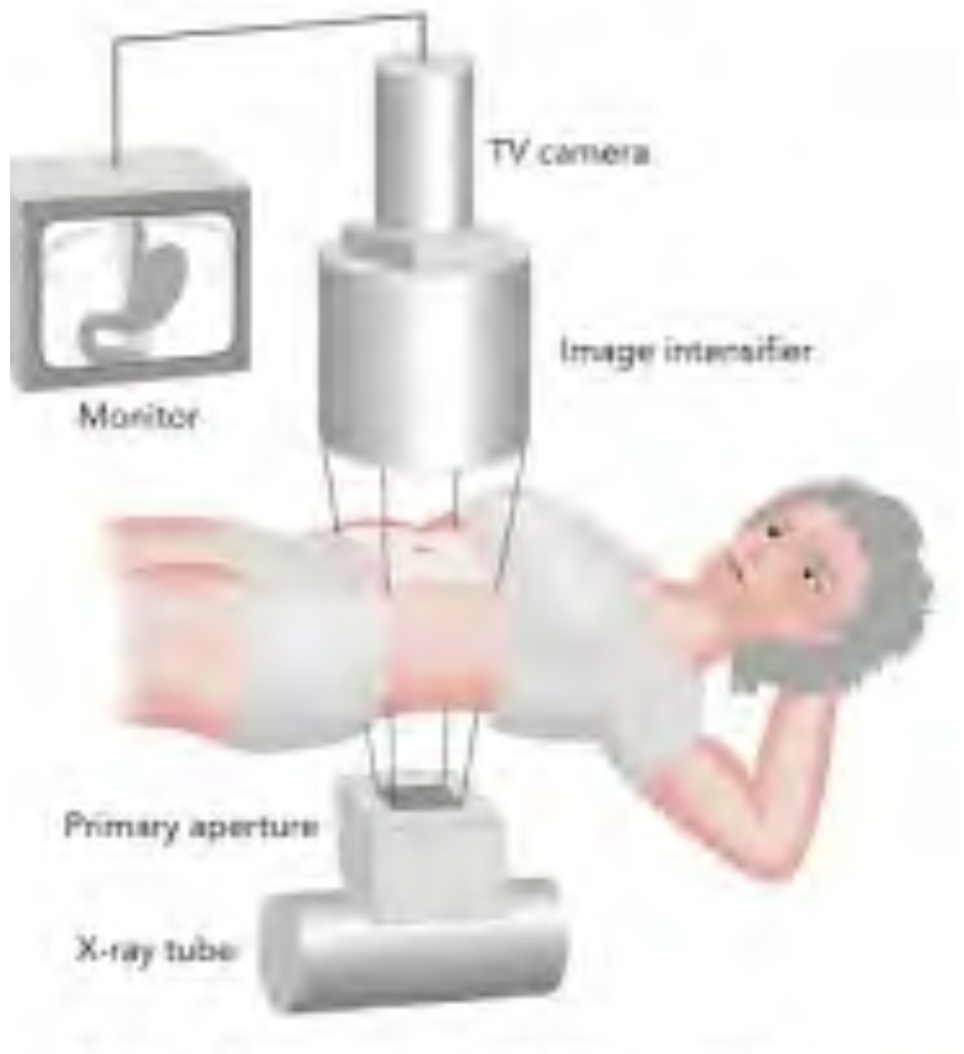
Barium / Iodine

https://www.nibib.nih.gov/science-education/science-topics/x-rays

Pratik Shah. Ph.D.
pratiks@mit.edu

Fluroscopy

Barium X-rays and enemas
Catheter insertion and manipulation
Placement of devices within the body, such as stents
Angiograms
Orthopedic surgery



Bones

Fat

Tissues

Air

Barium / Iodine

Pratik Shah. Ph.D.
pratiks@mit.edu

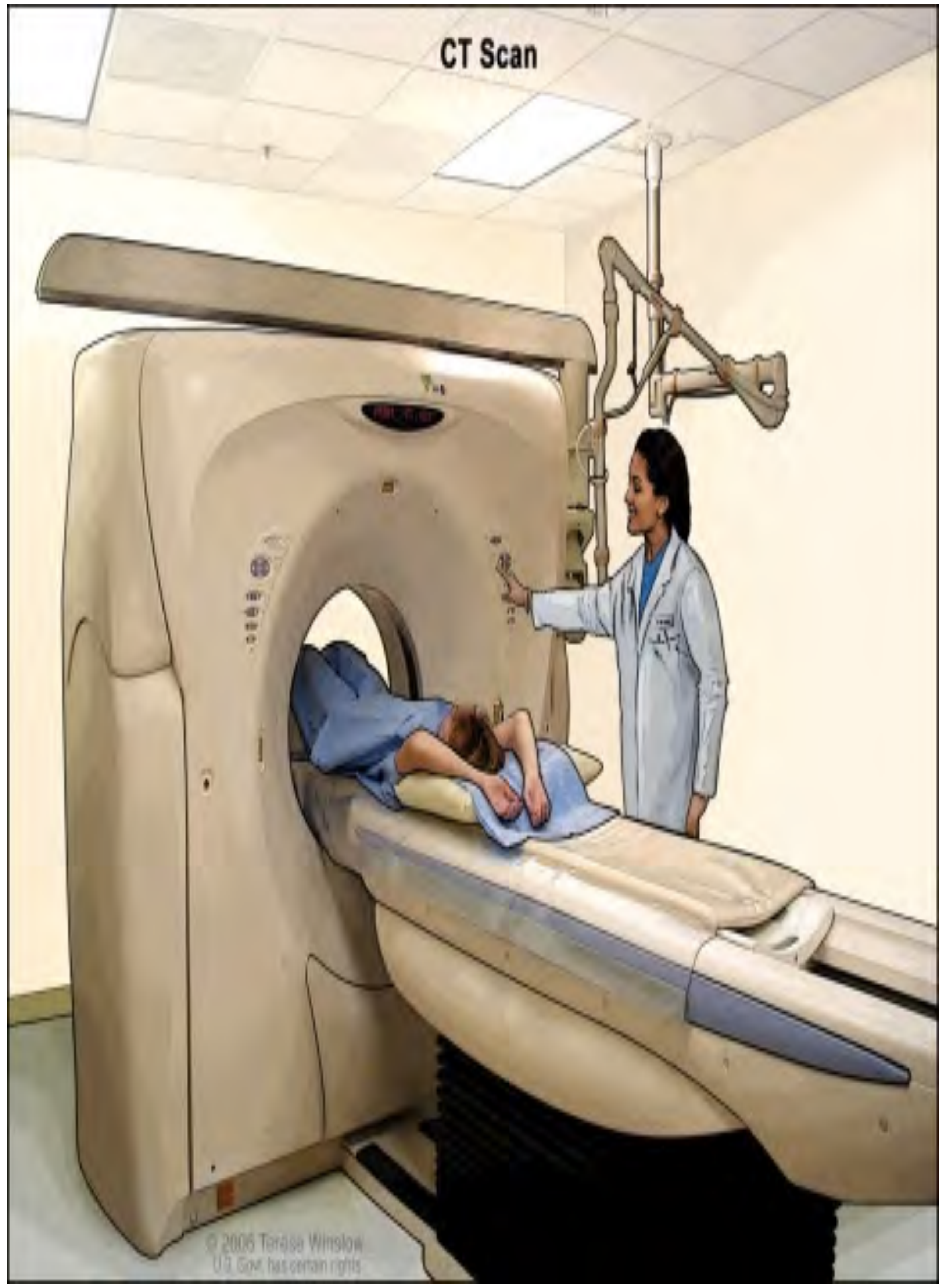
http://www.fda.gov

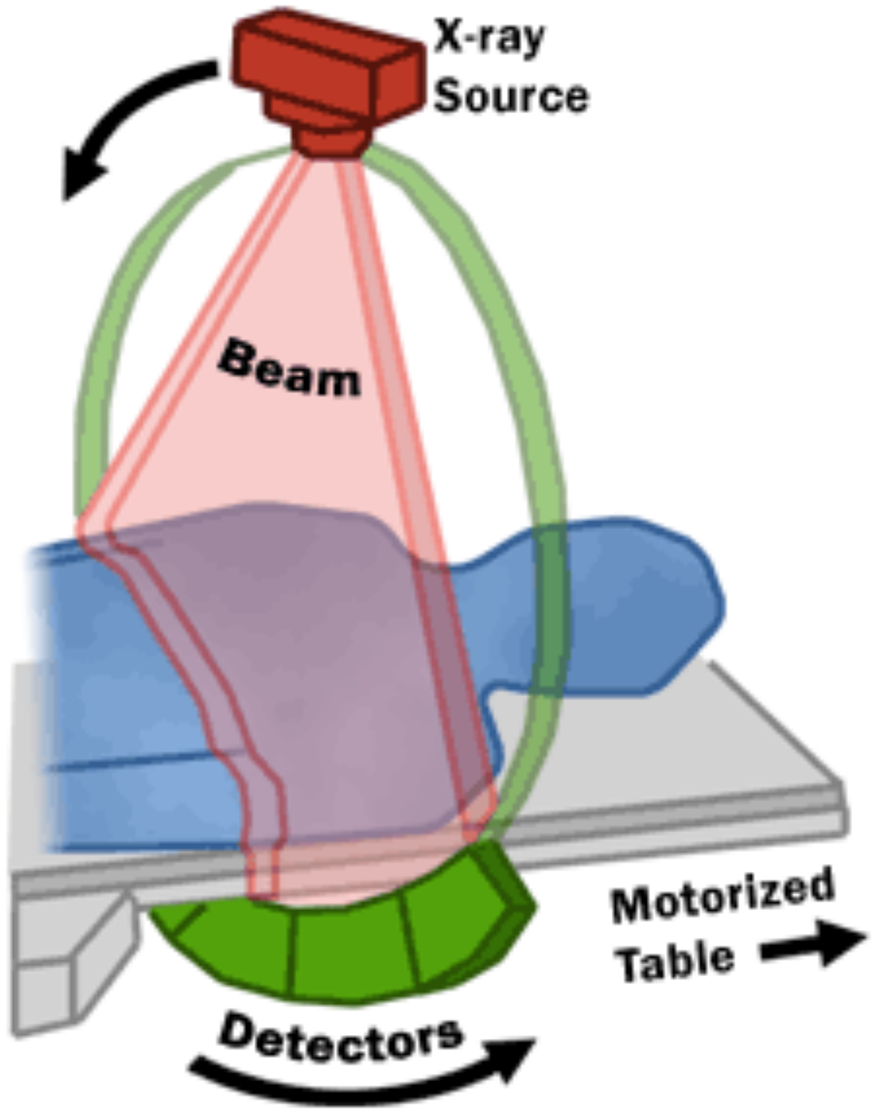
Computed tomograpy

Stomach: Lesions, tumors of abdomen

Head: Injuries, tumors, clots leading to stroke, hemorrhage

Lungs: Tumors, pulmonary embolisms (blood clots), excess fluid, and other conditions such as emphysema or pneumonia





Bones

Fat

Tissues

Air

Barium / Iodine

https://www.nibib.nih.gov/science-education/science-topics/x-rays

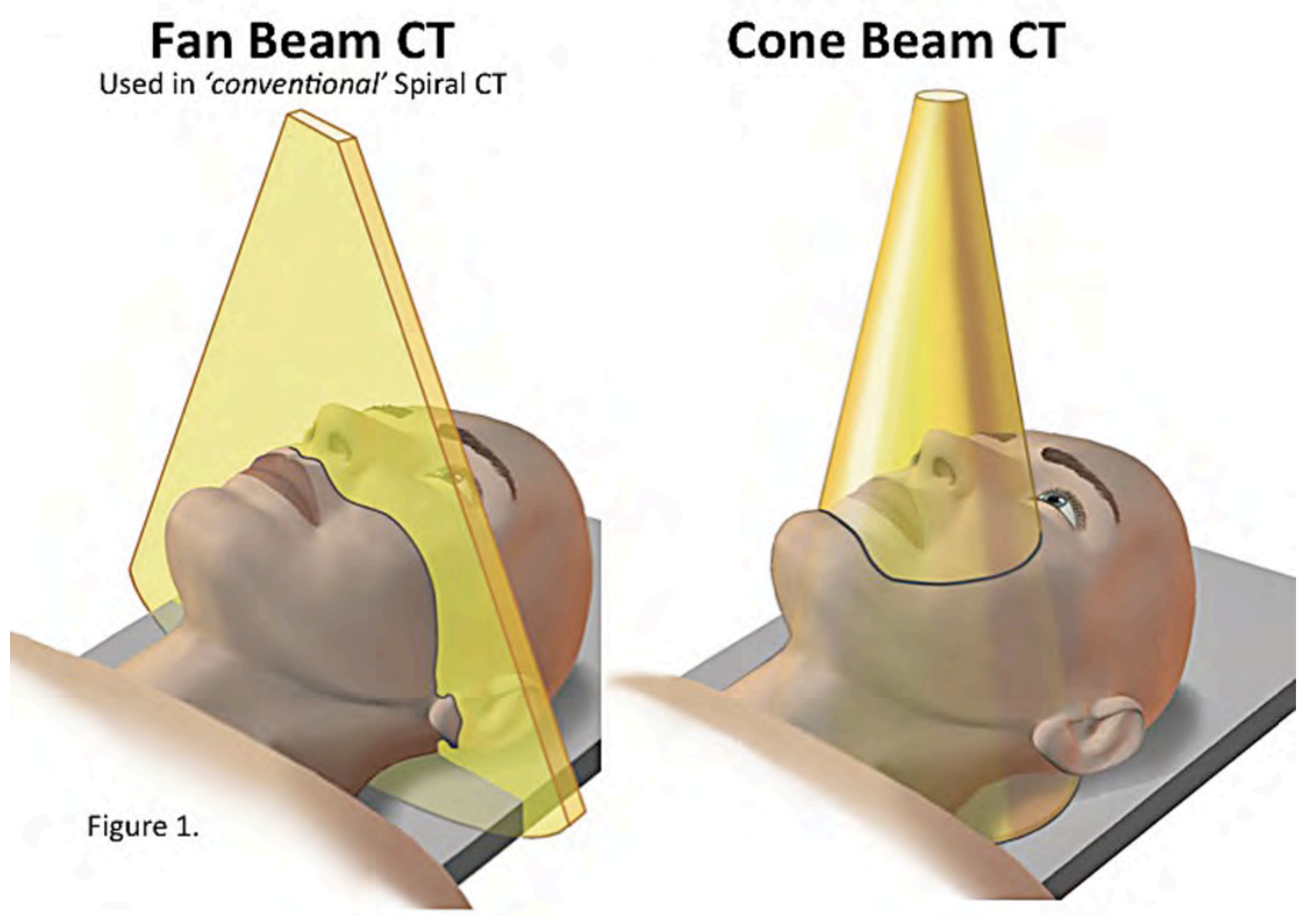
Pratik Shah. Ph.D.
pratiks@mit.edu

Pratik Shah. Ph.D.
pratiks@mit.edu

Pratik Shah. Ph.D.
pratiks@mit.edu

Cone-beam Computed Tomography

Reconstruct a three-dimensional (3D) image of: dental (teeth); oral and maxillofacial region (mouth, jaw, and neck); and ears, nose, and throat ("ENT").



https://www.nibib.nih.gov/science-education/science-topics/x-rays

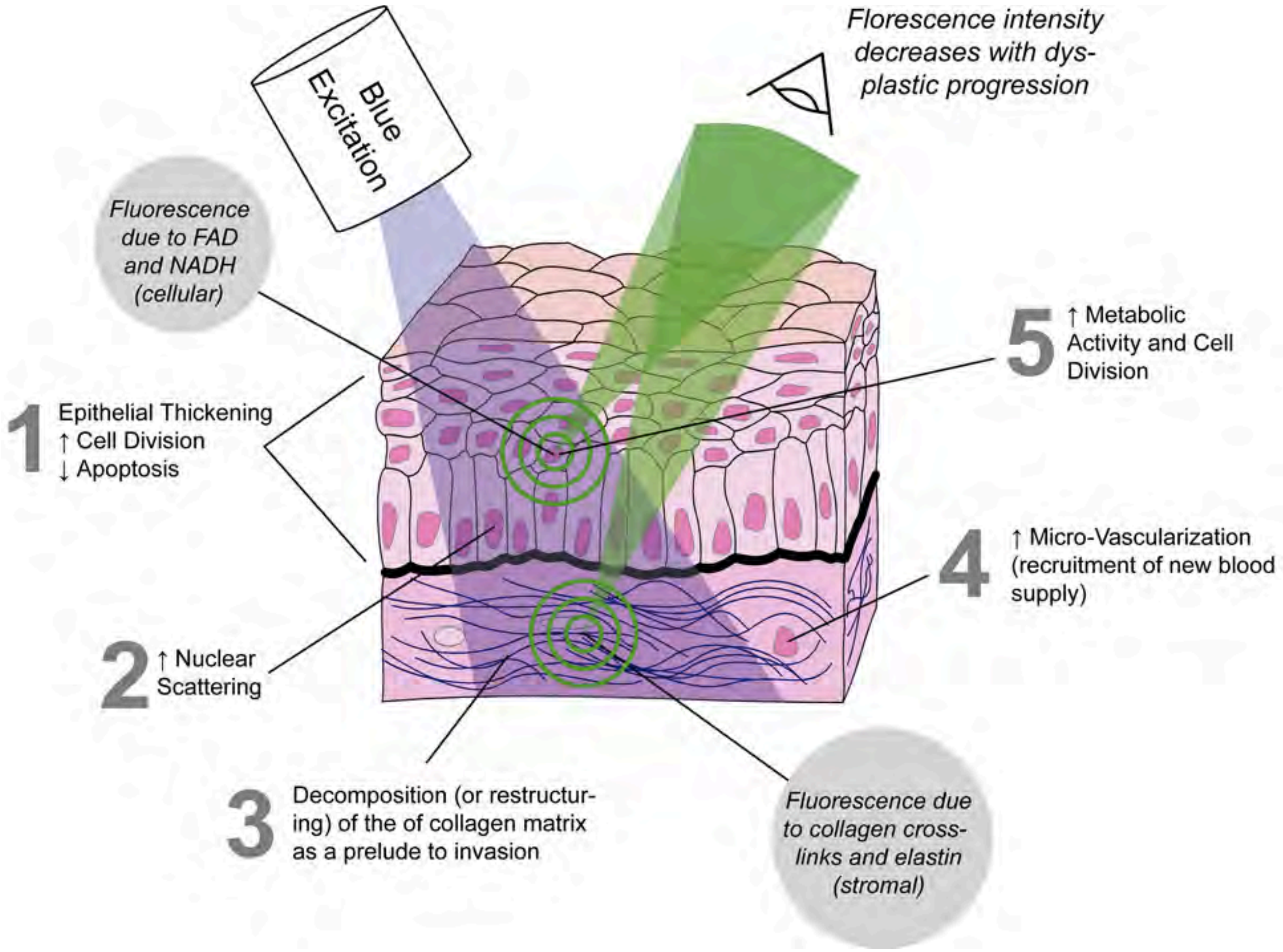
https://canaray.com

Pratik Shah. Ph.D.
pratiks@mit.edu


Clinical practice
PET
MRI
Ultrasound
X-rays and CT
PET
PET-CT
MRI
LN-MRI
Diffusion MRI
Ultrasound
Interventional ultrasound
X-rays
X-rays
CT
MSCT
MSCT
1900
1920
1940
1960
1970
1980
1985
1990
1995
2000
2001
2002
2003
2004
2005
2006
2007
2008
Optical development
Macroscopic reflectance
Tomography
Microscopy
Diaphanoscopy
Fibre optic
FRI
BLI
HR-FRI
Lifetime FRI
DOT
FMT
FPT
FMT-CT
FMT-MRI
Bright field
Bright field
Epifluorescence
OCT, OFDI
Confocal
MPM
Microendoscopy

UV Light Diagnostic Imaging

Autofluroscence of human cellular structures used for oral and skin cancer screening



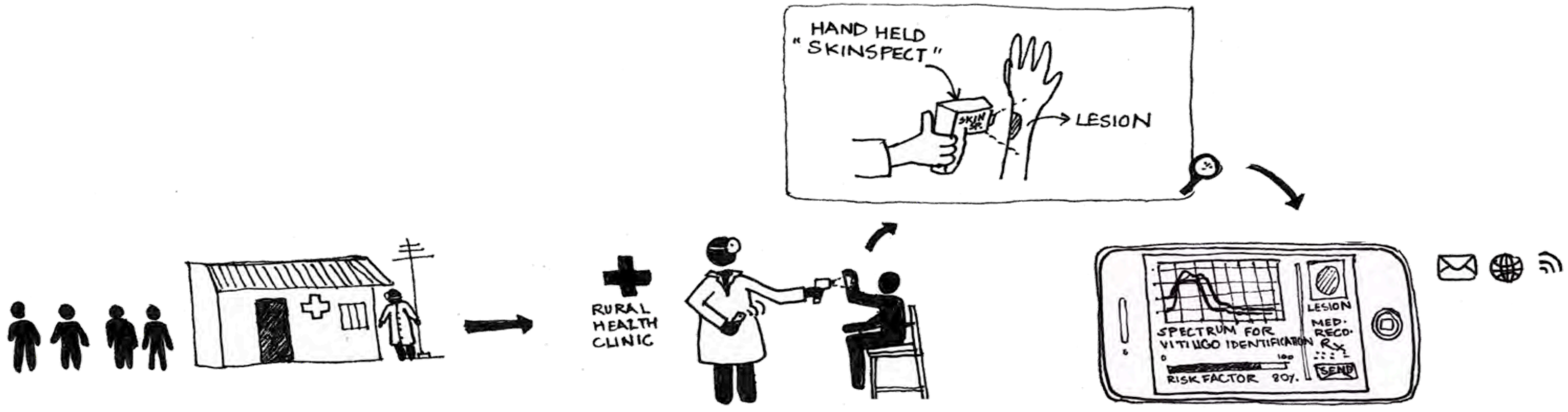
Label free

Pratik Shah. Ph.D.
pratiks@mit.edu

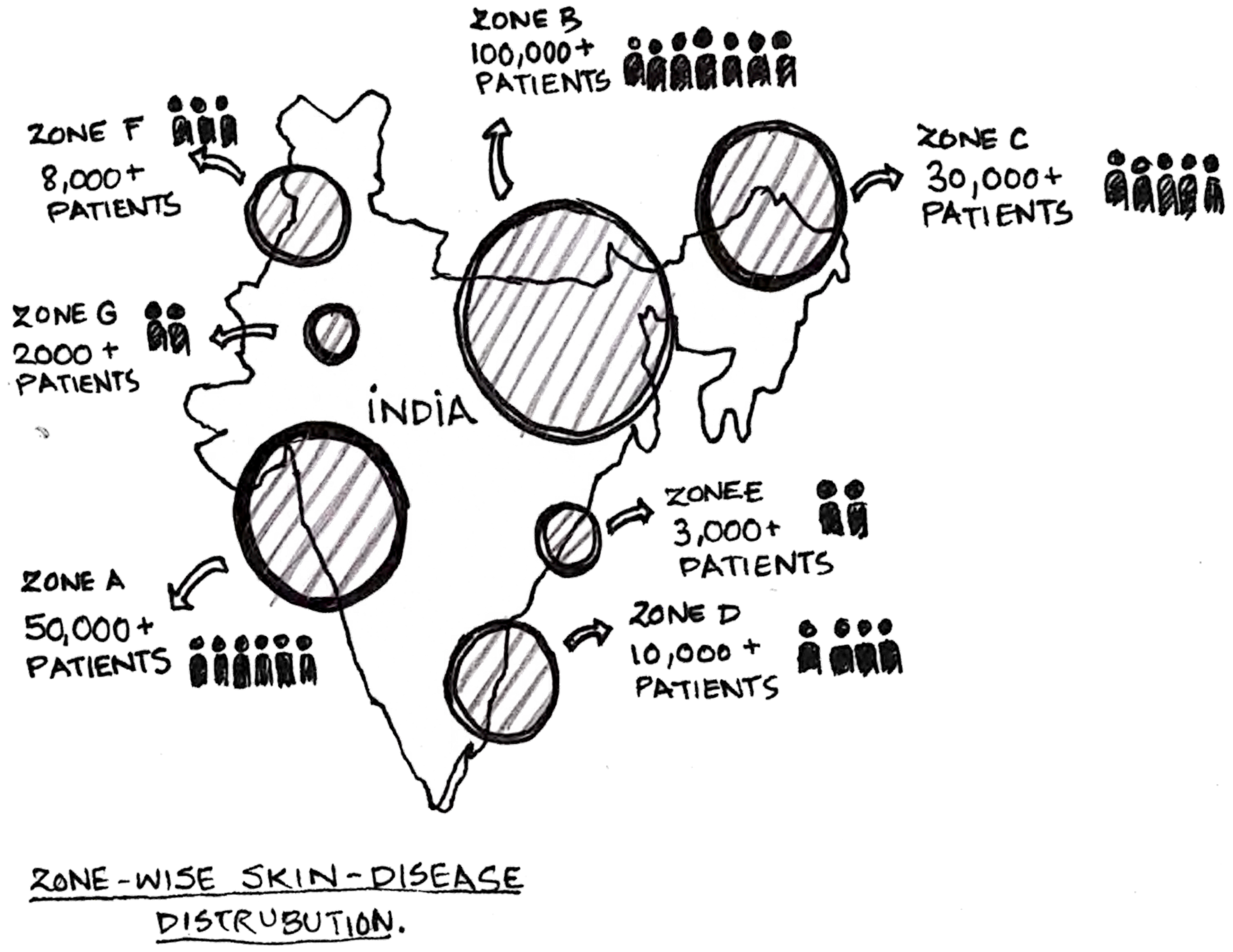
www.velscope.com

Pratavieira, S., et al. Optical imaging as auxiliary tool in skin cancer diagnosis., 2011.

SkinSpect



RURAL
HEALTH
CLINIC
HAND HELD
"SKINSPECT"
LESION
SPECTRUM FOR
VITILIGO IDENTIFICATION
LESION
MED.
RECO.
Rx
SEND
RISK FACTOR 80%

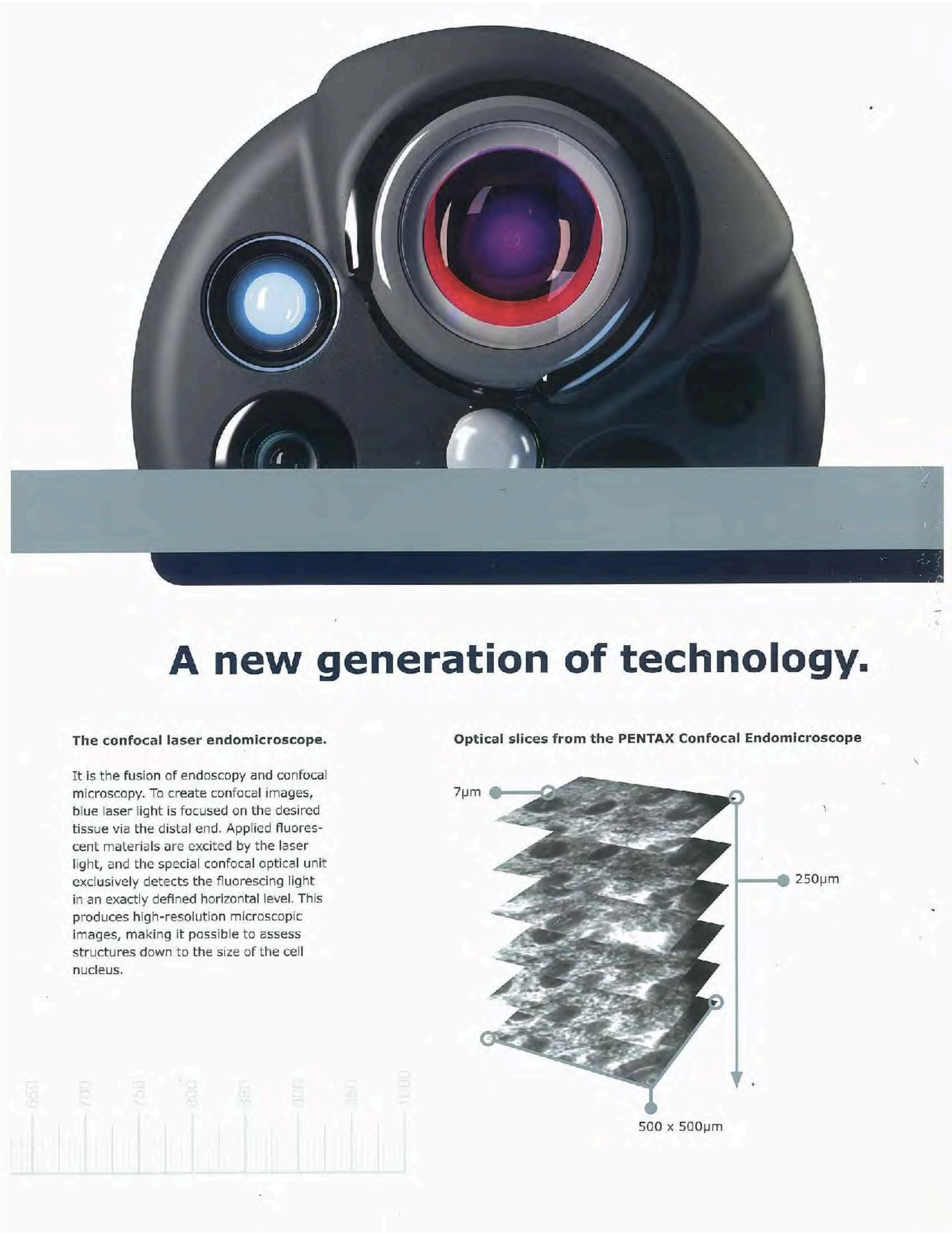


ZONE B
100,000+
PATIENTS
ZONE F
8,000+
PATIENTS
ZONE C
30,000+
PATIENTS
ZONE G
2000 +
PATIENTS
INDIA
ZONE E
3,000+
PATIENTS
ZONE A
50,000+
PATIENTS
ZONE D
10,000 +
PATIENTS
ZONE-WISE SKIN-DISEASE
DISTRUBUTION.

Spectrum
Cancel
Save

Visible Light Diagnostic Imaging

Label-free Endoscopy, Endomicroscopy (optical biopsy) and Fundus photography



ACM SIGGRAPH 2015. Transactions on Graphics 34(4).

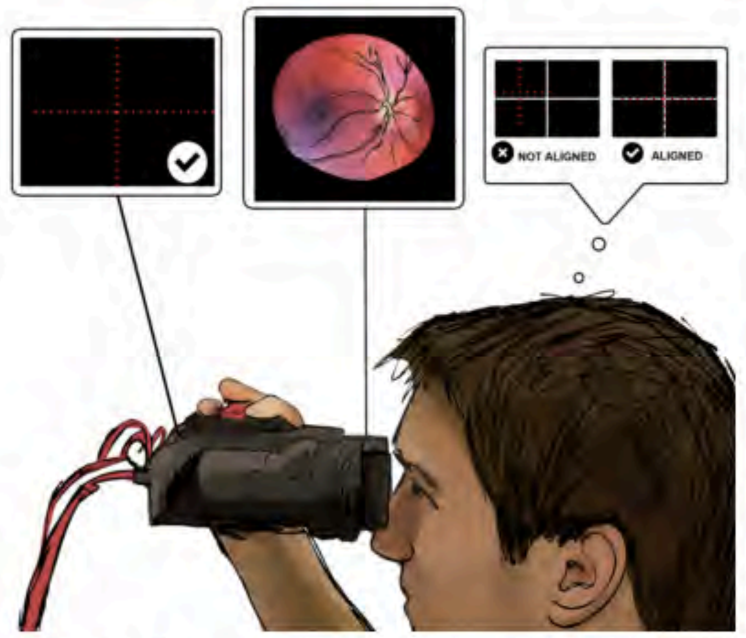
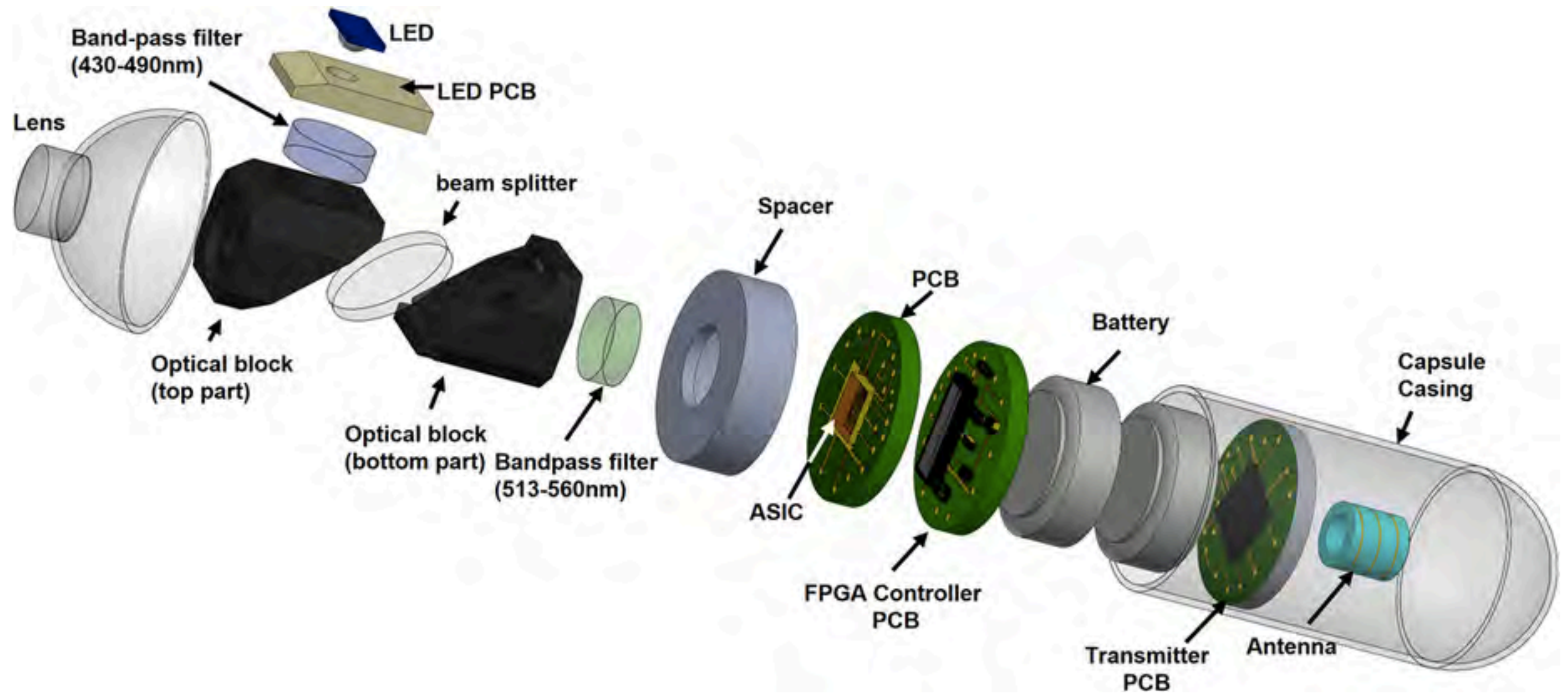


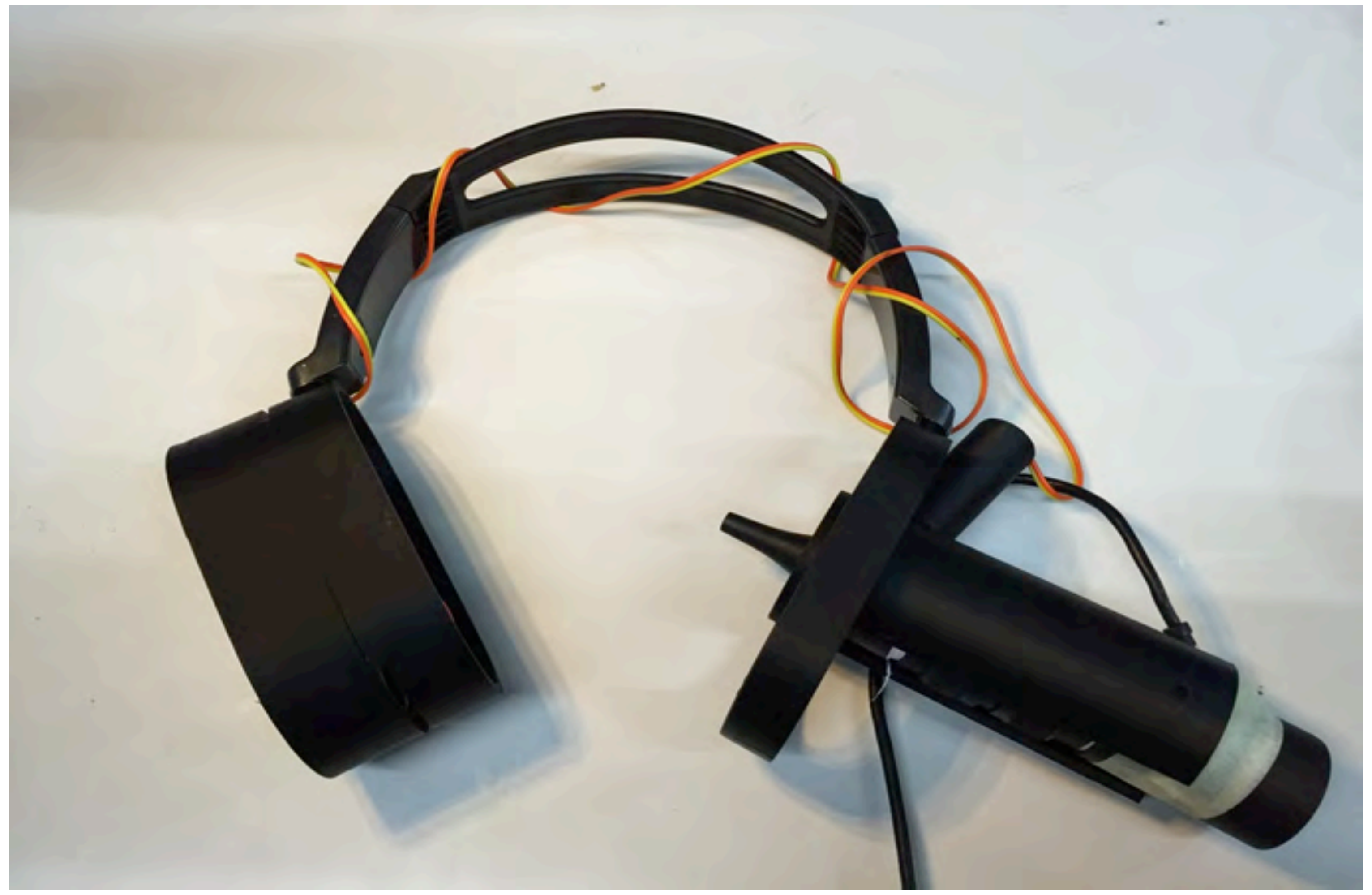
Figure 1: Self-aligned, mobile, non-mydriatic Fundus Photography. The user is presented with an alignment dependent fixation cue on a ray-based display. Once correctly aligned, a self-acquired retinal image is captured. This retinal image can be used for health, security or HMD calibration. Illustration: Laura Piraino

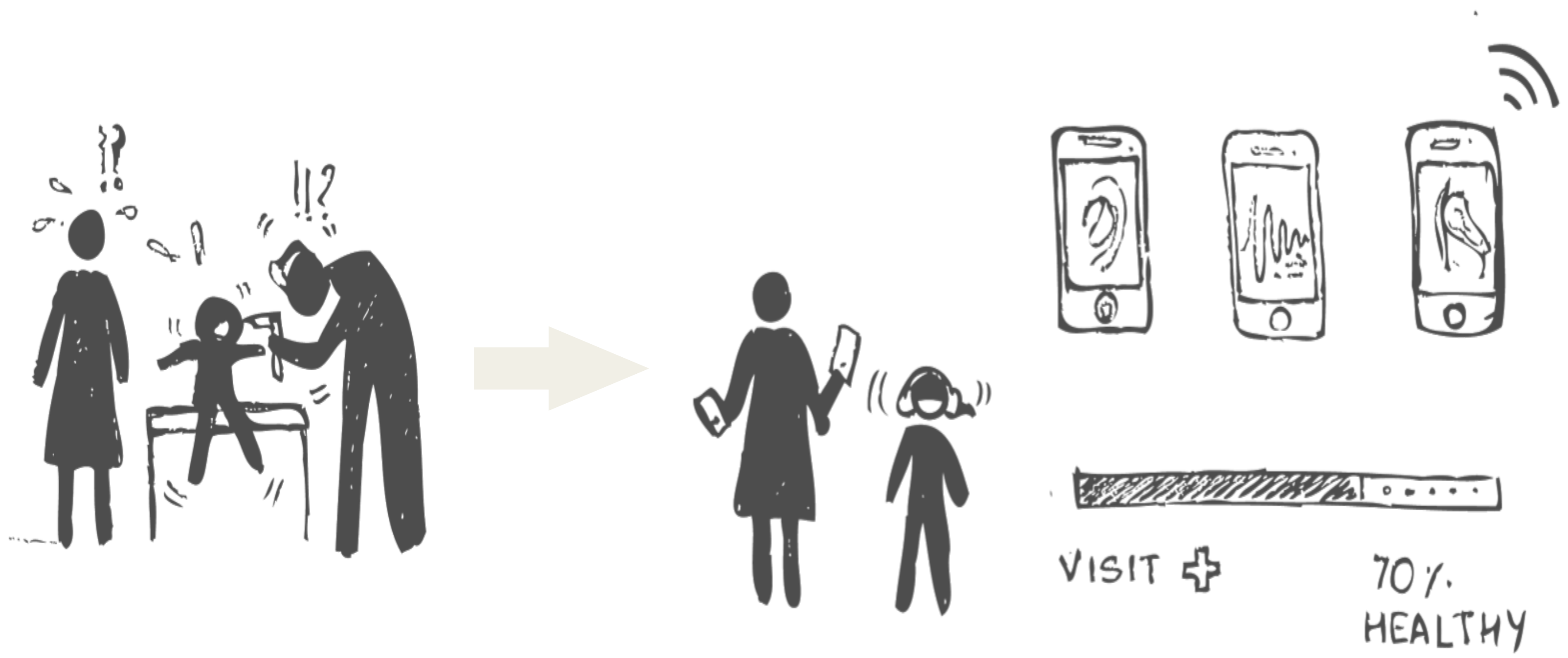
Commercially available clinical endomicroscopes can achieve a resolution on the order of a micrometre, have a field-of-view of several hundred µm, and are compatible with fluorophores which are excitable using 488 nm laser light. The main applications are currently in imaging of the gastro-intestinal tract.

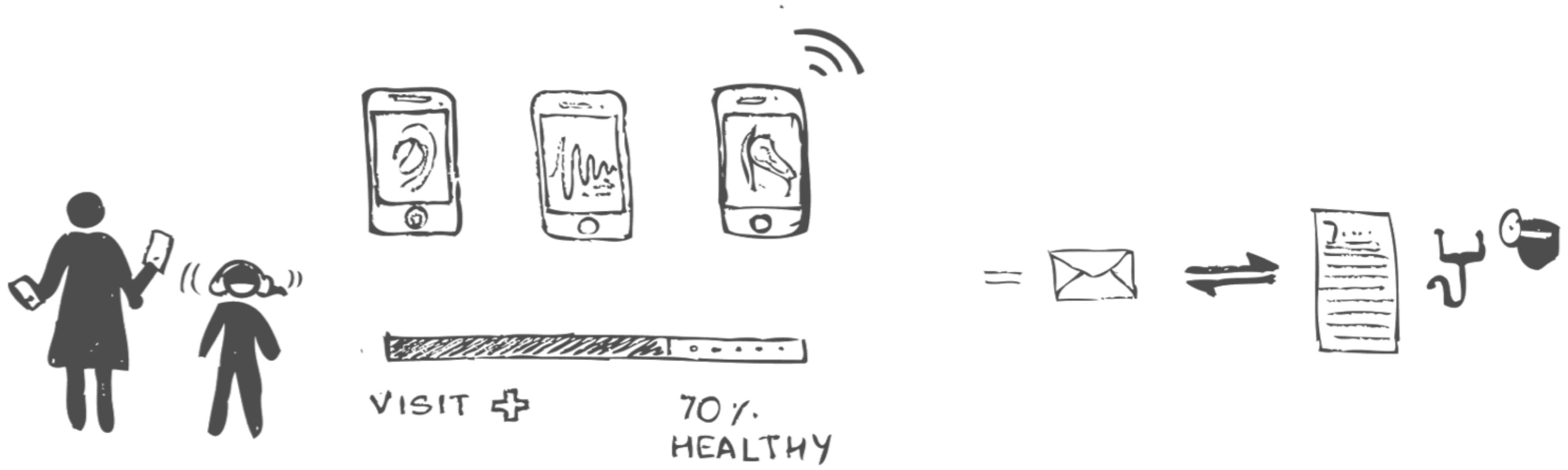


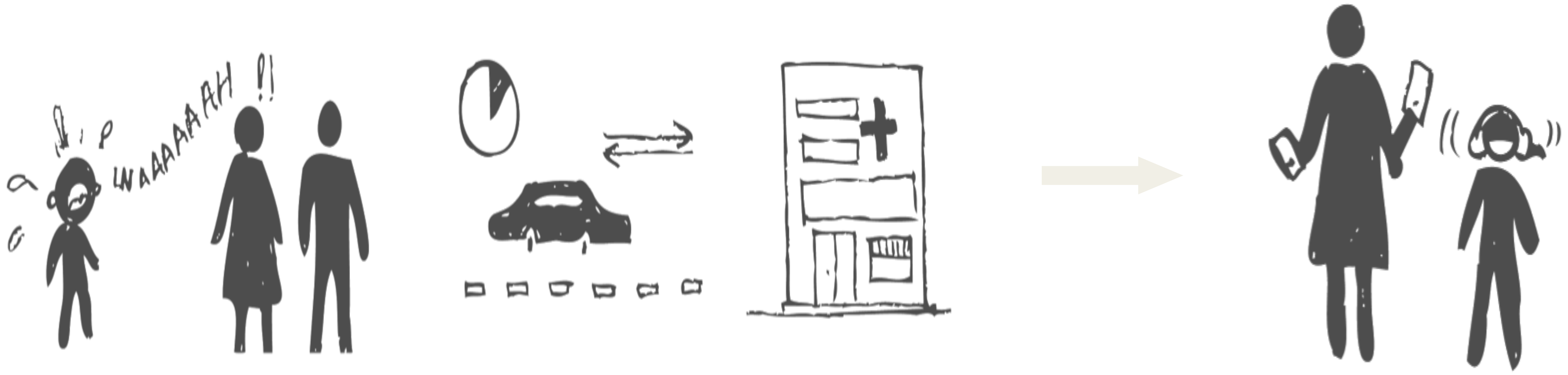
. http://www.fda.gov, *Scientific Reports 5, Article number: 18591 (2015)*, www.hoya.com

LightEar









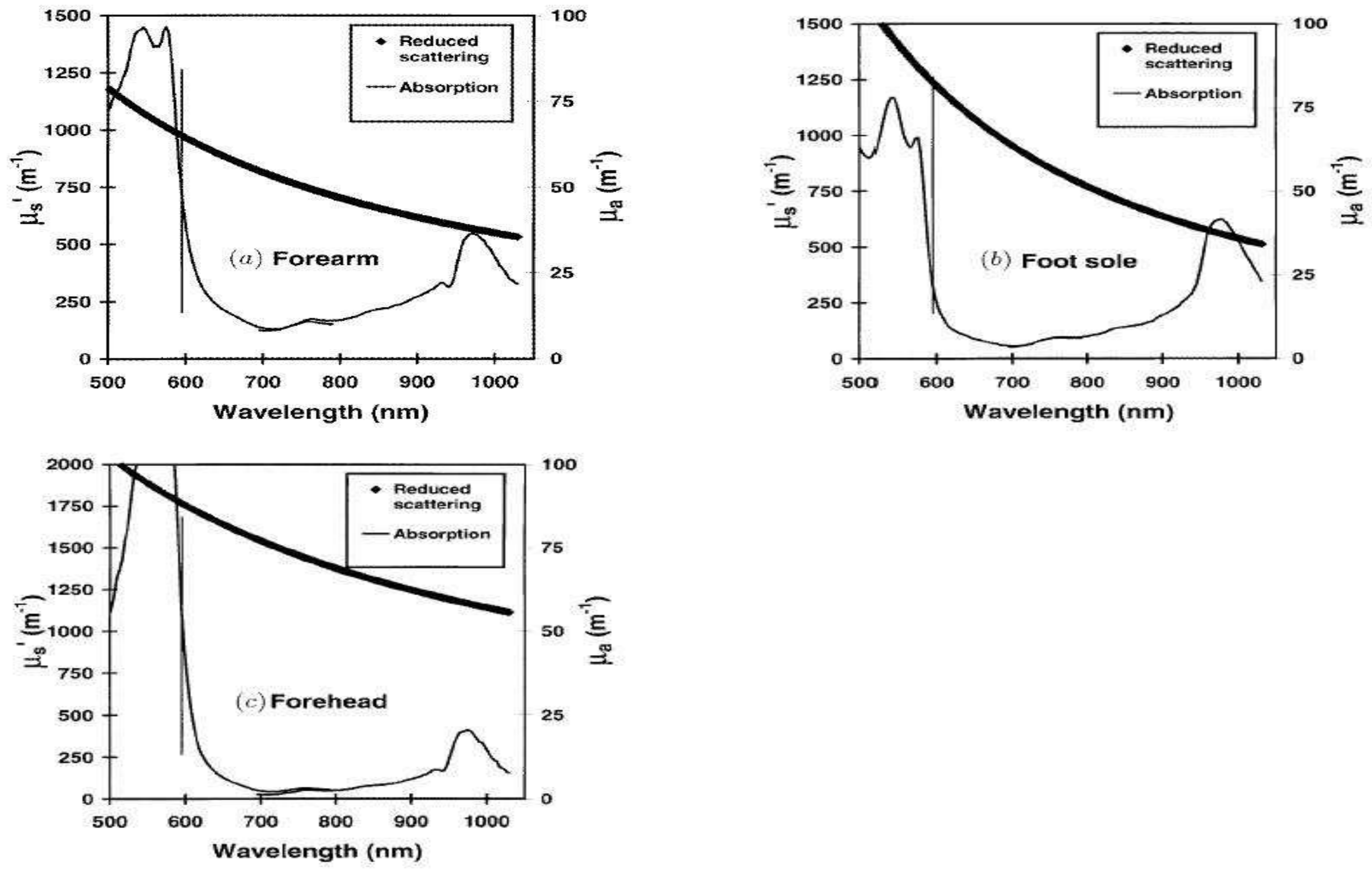
Pratik Shah, Ph.D.
pratiks@mit.edu

EyeNetra

(Source: mit.edu)

Pratik Shah. Ph.D.
pratiks@mit.edu

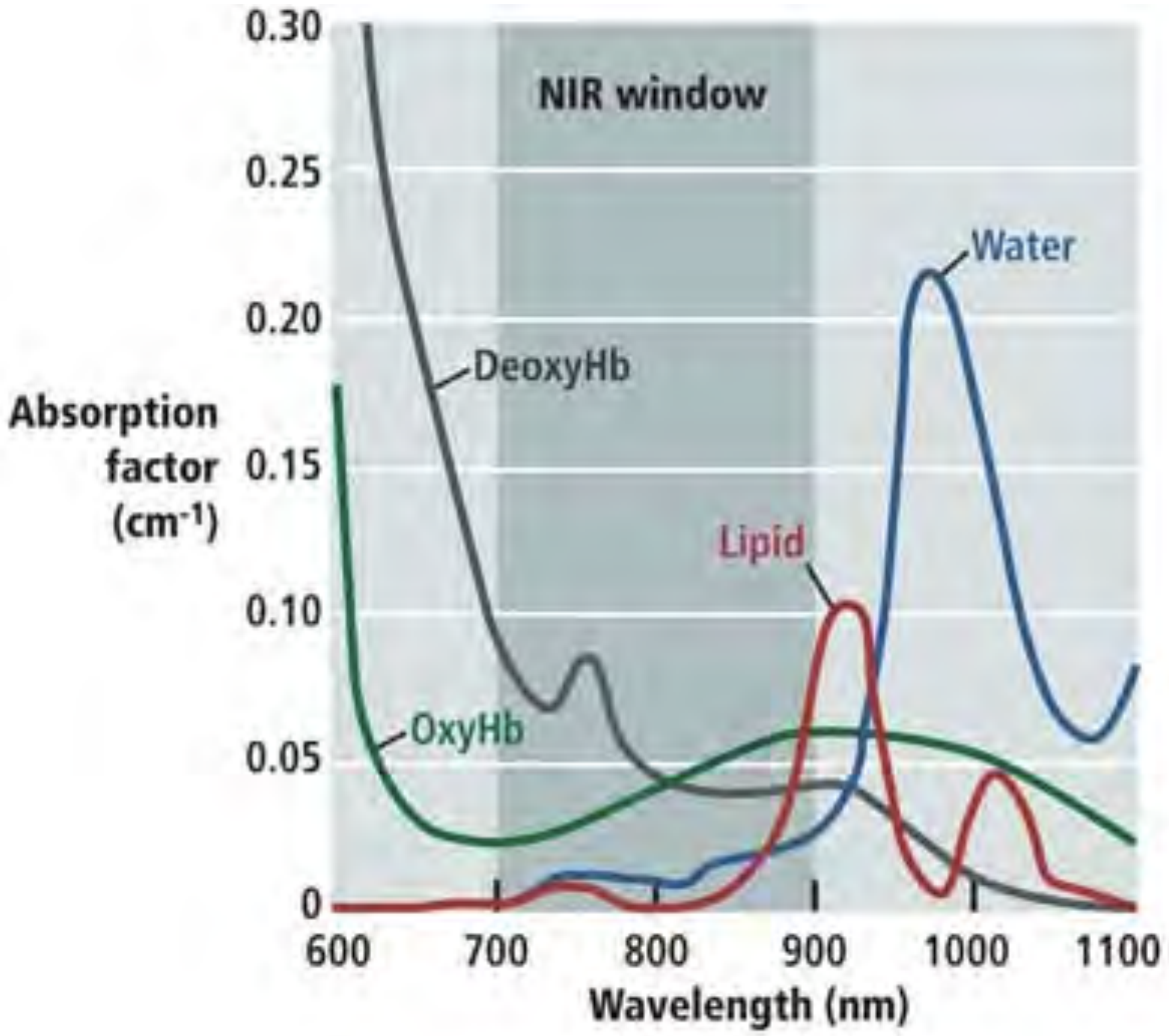
Transparency Of Tissue in Near IR Light

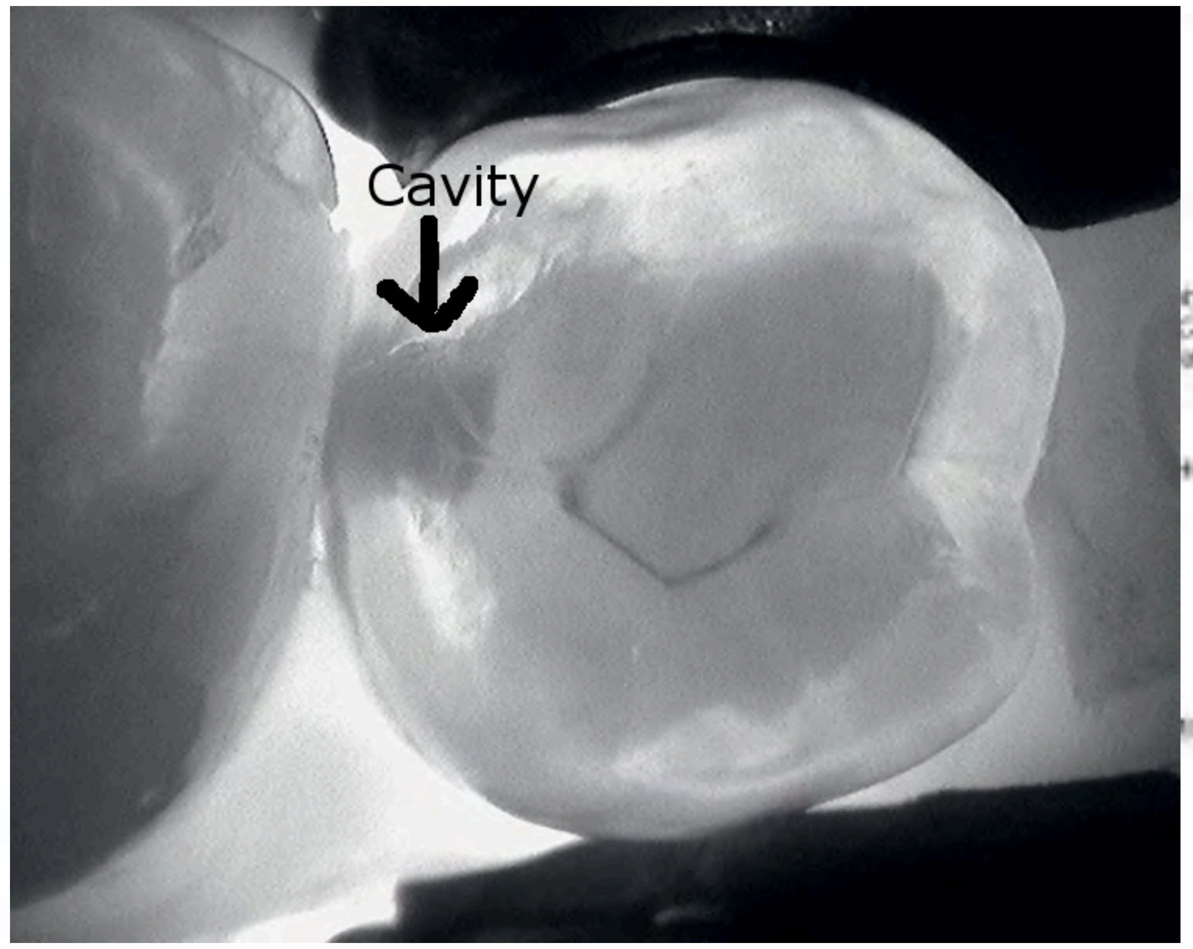


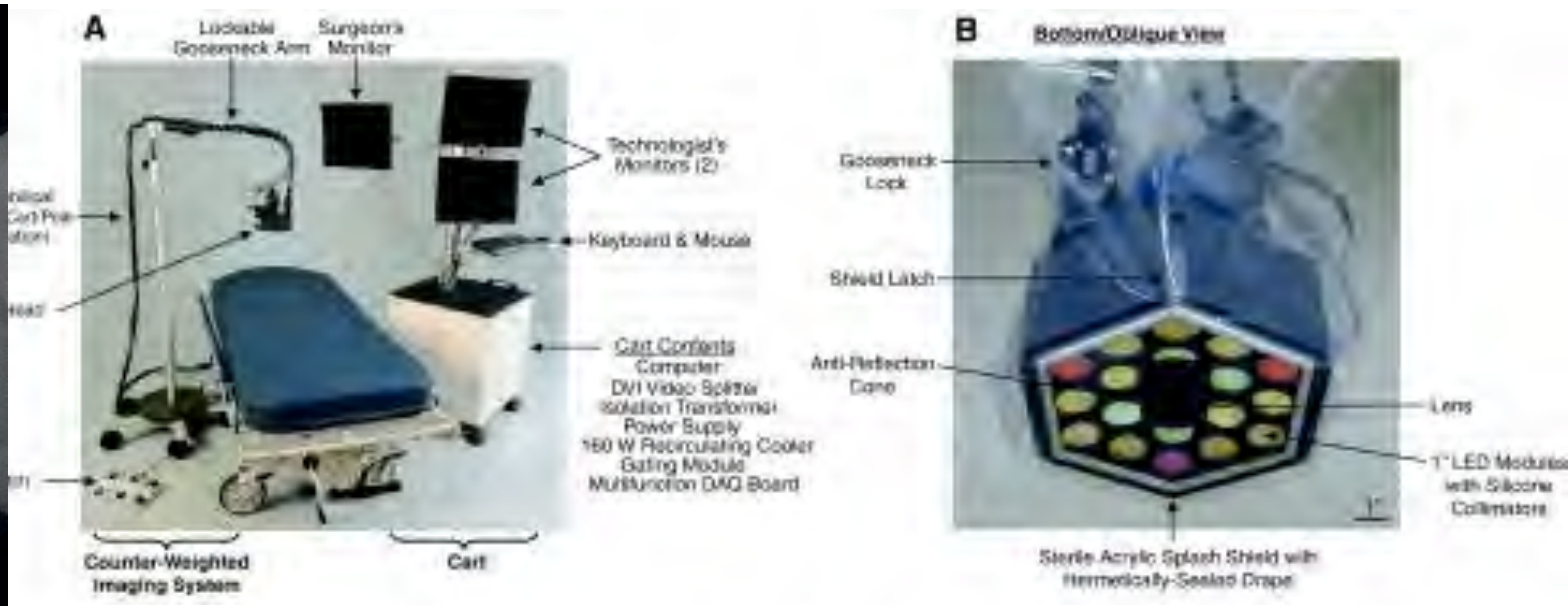
R. M. P. Doornbos *et al.*, *Phys. Med. Biol.*, 1999.)

Pratik Shah. Ph.D.
pratiks@mit.edu

Infrared Light Diagnostic Imaging





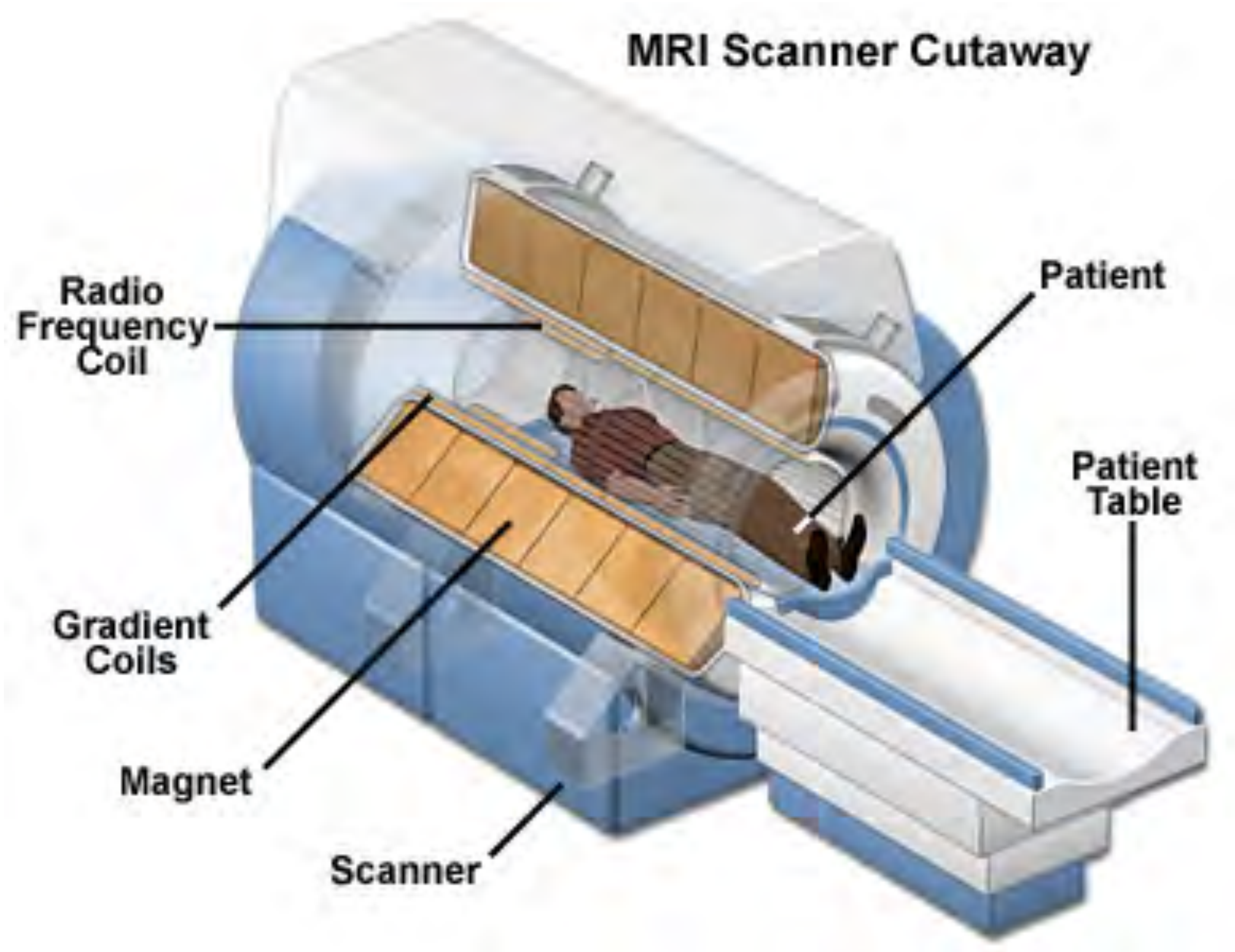


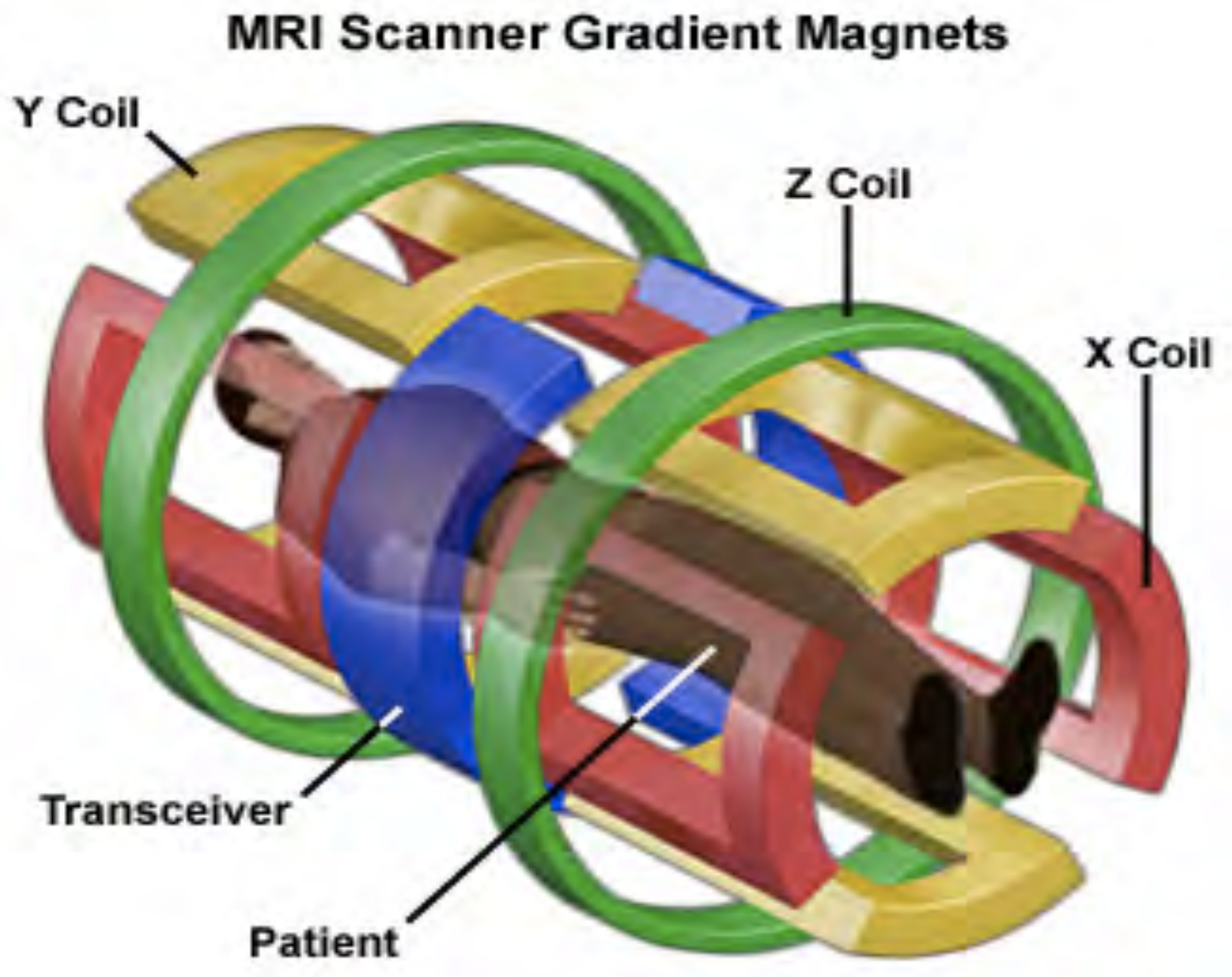
Near-infrared (NIR) fluorescent light in the wavelength range of 700–900 nm is invisible to the human eye. It is also capable of penetrating millimeters into living tissue and is not obscured by autofluorescence. For these reasons, NIR fluorescent light is ideal for image-guided surgery and scatter-free illumination of inaccessible tissues.

Ann Surg Oncol. 2011 Sep; 18(9): 2483–2491. www.dexis.com,

http://www.vision-systems.com/articles/print/volume-17/issue-10

Magnetic Resonance Imaging





The brain, spinal cord and nerves, as well as muscles, ligaments, and tendons are seen much more clearly with MRI than with regular x-rays and CT; for this reason MRI is often used to image knee and shoulder injuries.
In the brain, MRI can differentiate between white matter and grey matter and can also be used to diagnose aneurysms and tumors.

https://nationalmaglab.org

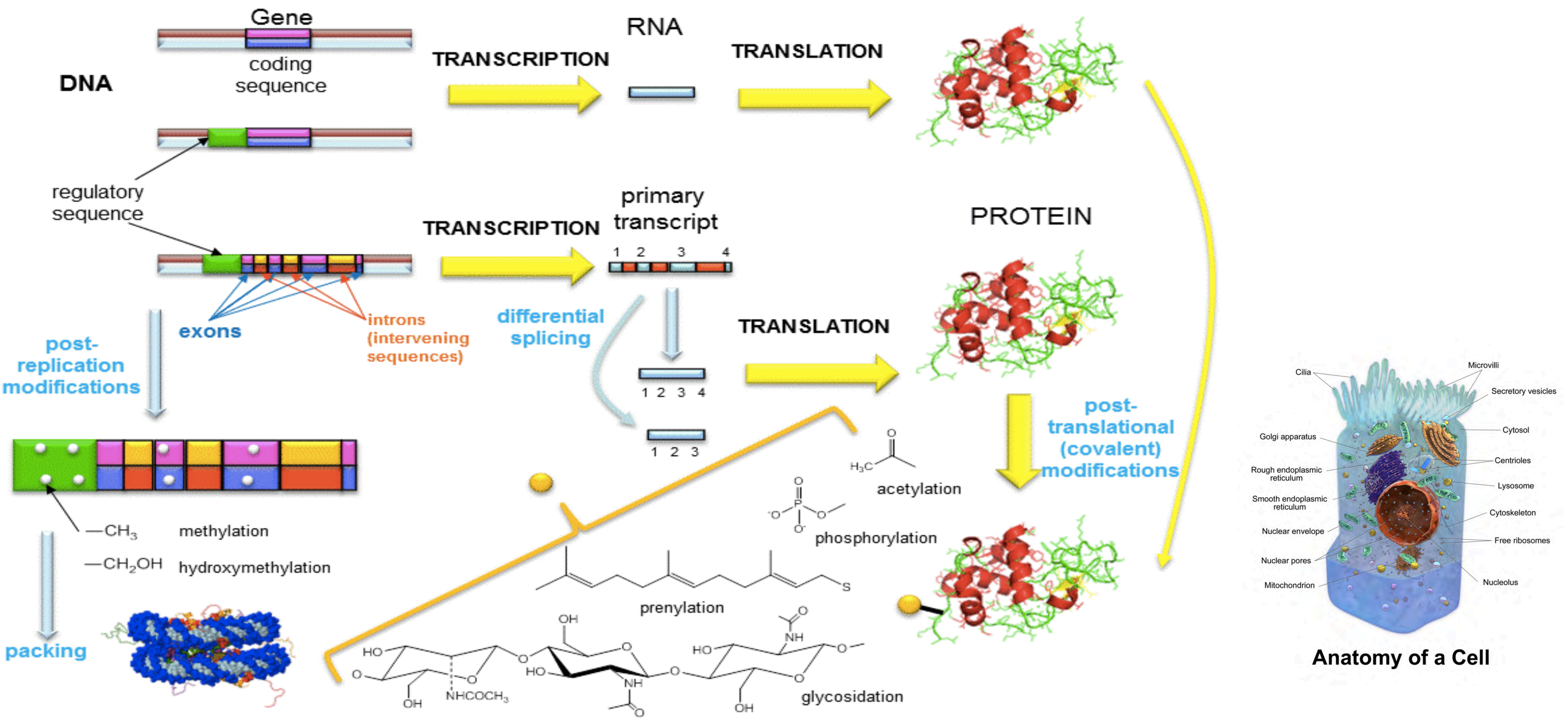
Crossover Imaging Modalities

Imaging Technique	Resolution References	Spatial Resolution	Scan Time	Contrast Agents and Molecular Probes	Key Use
Multi-photon Microscopy	[29, 38]	15 – 1000 nm	Secs	Fluorescent proteins, dyes, rhodamine amide, quantum dots	Visualization of cell structures
Atomic Force Microscopy	[104]	10 – 20 nm	Mins	Intermolecular forces	Mapping cell surface
Electron Microscopy	[41]	~5 nm	Secs	Cyrofixation	Discerning protein structure
Ultrasound	[29]	50 μm	Secs	Microbubbles, nanoparticles	Vascular imaging
CT/MicroCT	[29, 70]	12 – 50 μm	Mins	Iodine	Lung and bone tumor imaging
MRI/MicroMRI	[29, 76]	4 – 100 μm	Mins – Hrs	Gadolinium, dysprosium, iron oxide particles	Anatomical imaging
fMRI	[105]	~1 mm	Secs – Mins	Oxygenated hemoglobin (HbO_2) deoxygenated hemoglobin (Hb)	Functional imaging of brain activity
MRS	[106, 107]	~2 mm	Secs	N-acetylaspartate (NAA), creatine, choline, citrate	Detection of metabolites
PET/MicroPET	[29, 108]	1 – 2 mm	Mins	Fluorodeoxyglucose (FDG), ^{18}F, ^{11}C, ^{15}O	Metabolic imaging

The various micro versions of the imaging modalities (MicroCT, MicroMRI, MicroPET) as well as the microscopy techniques (Fluorescence, Multi-photon, Atomic, Electron) are primarily used in either cellular or animal studies. The remaining modalities (Ultrasound, CT, MRI, MRS, PET) are more widely used clinically.

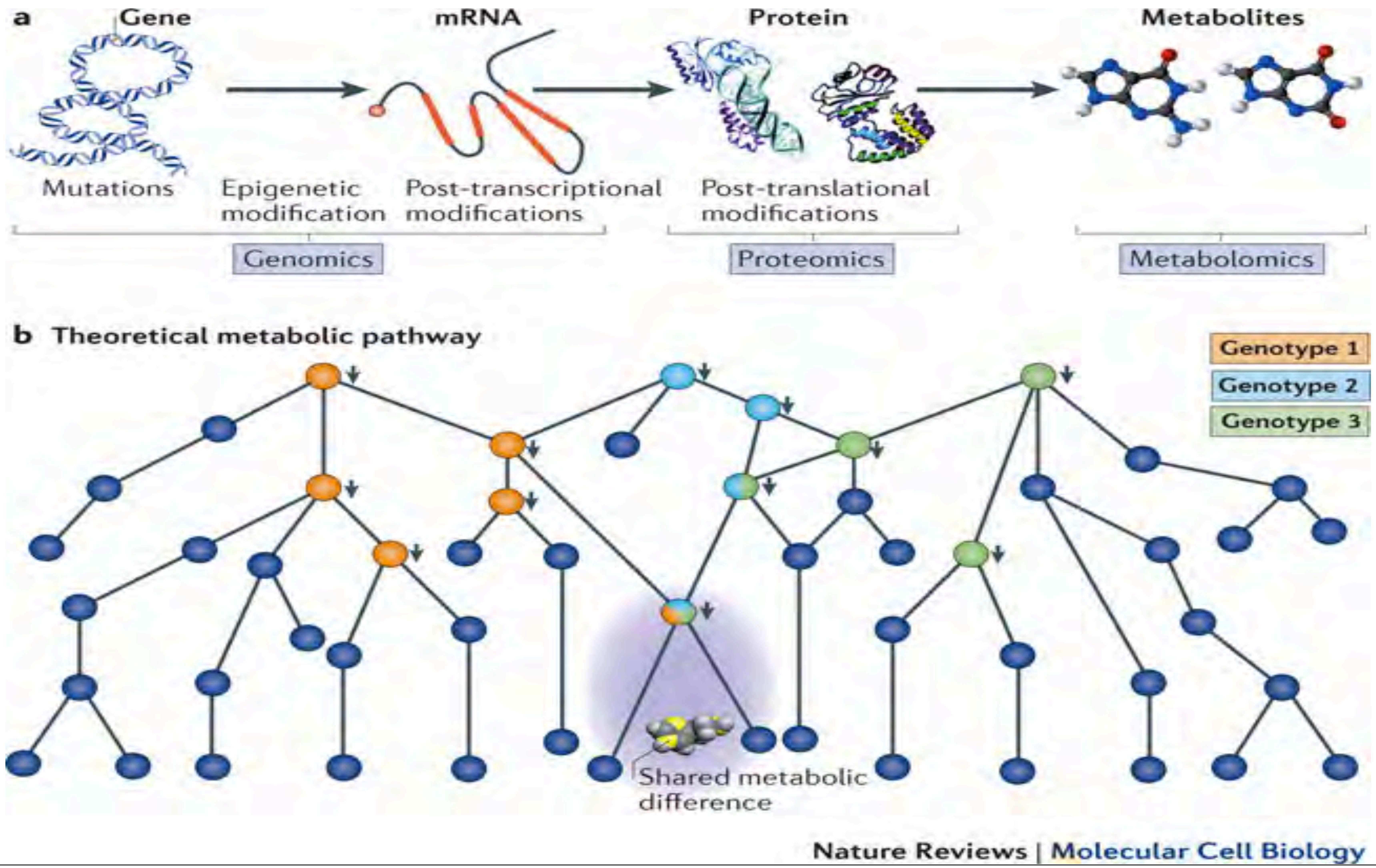
BMC Systems Biology 2008 2:74

AN EXPANDED CENTRAL DOGMA OF BIOLOGY:
GENES - Simple to Complex Models



http://biowiki.ucdavis.edu/

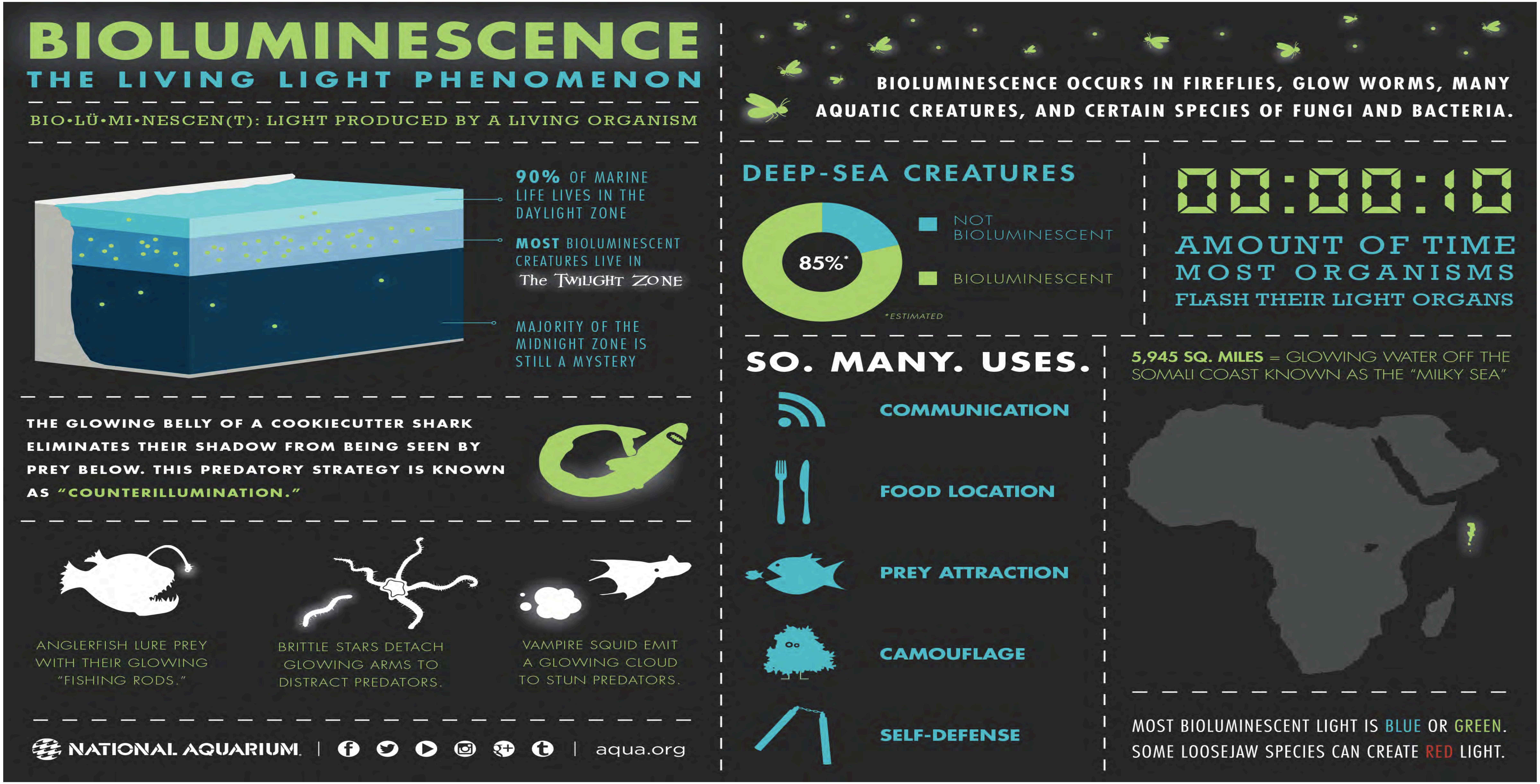
New Technologies in Research



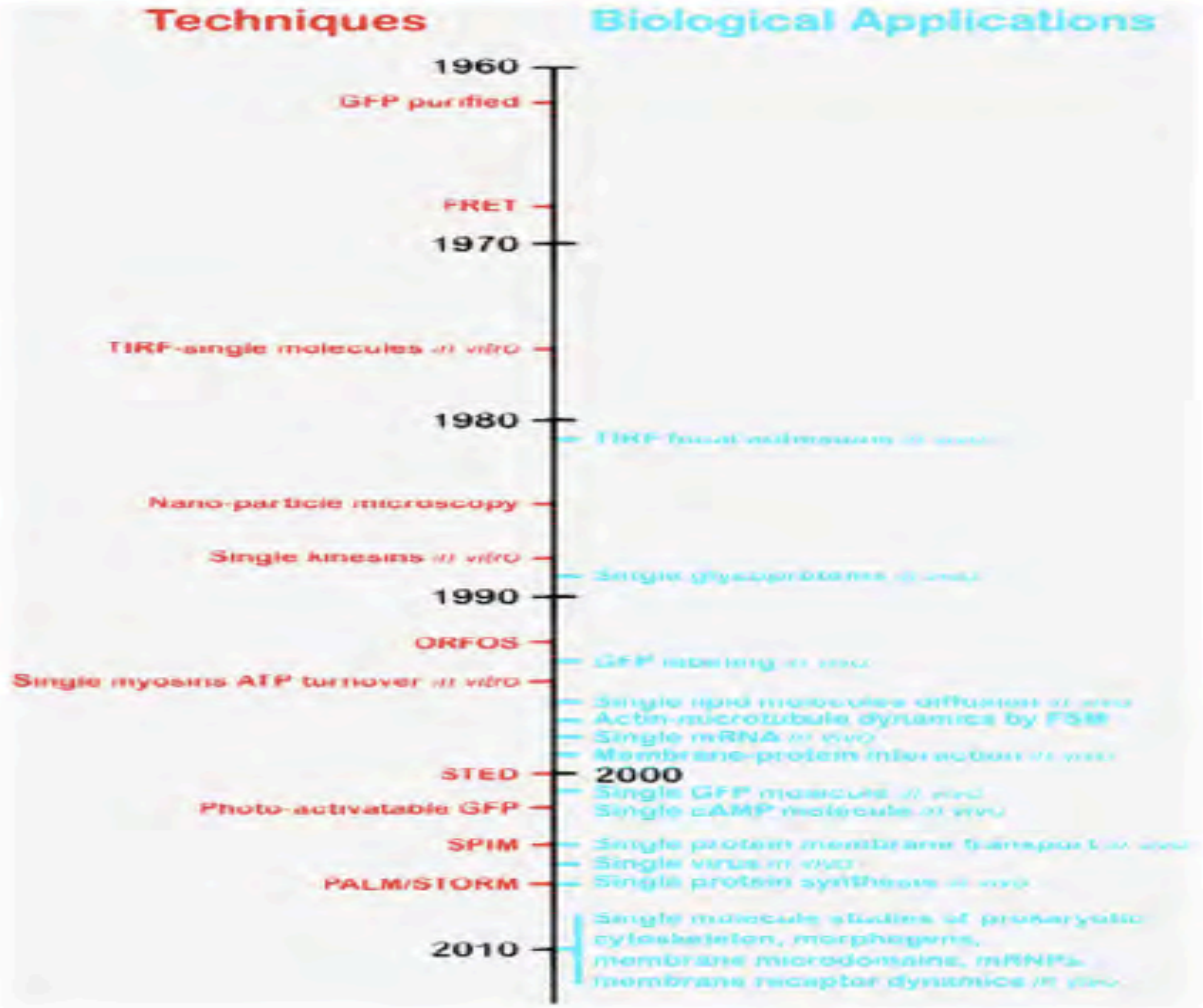
Pratik Shah. Ph.D.
pratiks@mit.edu

New Technologies in Research

	Transcriptomics (microarray, SAGE)	Proteomics (abundance, post-translational modification)	Metabolomics (metabolite abundance)	Protein–DNA interactions (ChIP–chip)	Protein–protein interactions (yeast 2H, coAP–MS)	Fluxomics (isotopic tracing)	Phenomics (phenotype arrays, RNAi screens, synthetic lethals)
Genomics (sequence annotation)	• ORF validation • Regulatory element identification[74]	• SNP effect on protein activity or abundance	• Enzyme annotation	• Binding-site identification[75]	• Functional annotation[79]	• Functional annotation	• Functional annotation • Biomarkers[125]
Transcriptomics (microarray, SAGE)		• Protein: transcript correlation[23]	• Enzyme annotation[109]	• Gene-regulatory networks[78]	• Functional annotation[81] • Protein complex identification[82]		• Functional annotation[101]
Proteomics (abundance, post-translational modification)			• Enzyme annotation[95]	• Regulatory complex identification	• Differential complex formation	• Enzyme capacity	• Functional annotation
Metabolomics (metabolite abundance)				• Metabolic-transcriptional response		• Metabolic pathway bottlenecks	• Metabolic flexibility • Metabolic engineering[109]
Protein–DNA interactions (ChIP–chip)					• Signalling cascades		• Dynamic network responses[54]
Protein–protein interactions (yeast 2H, coAP–MS)							• Pathway identification activity
Fluxomics (isotopic tracing)							• Metabolic engineering

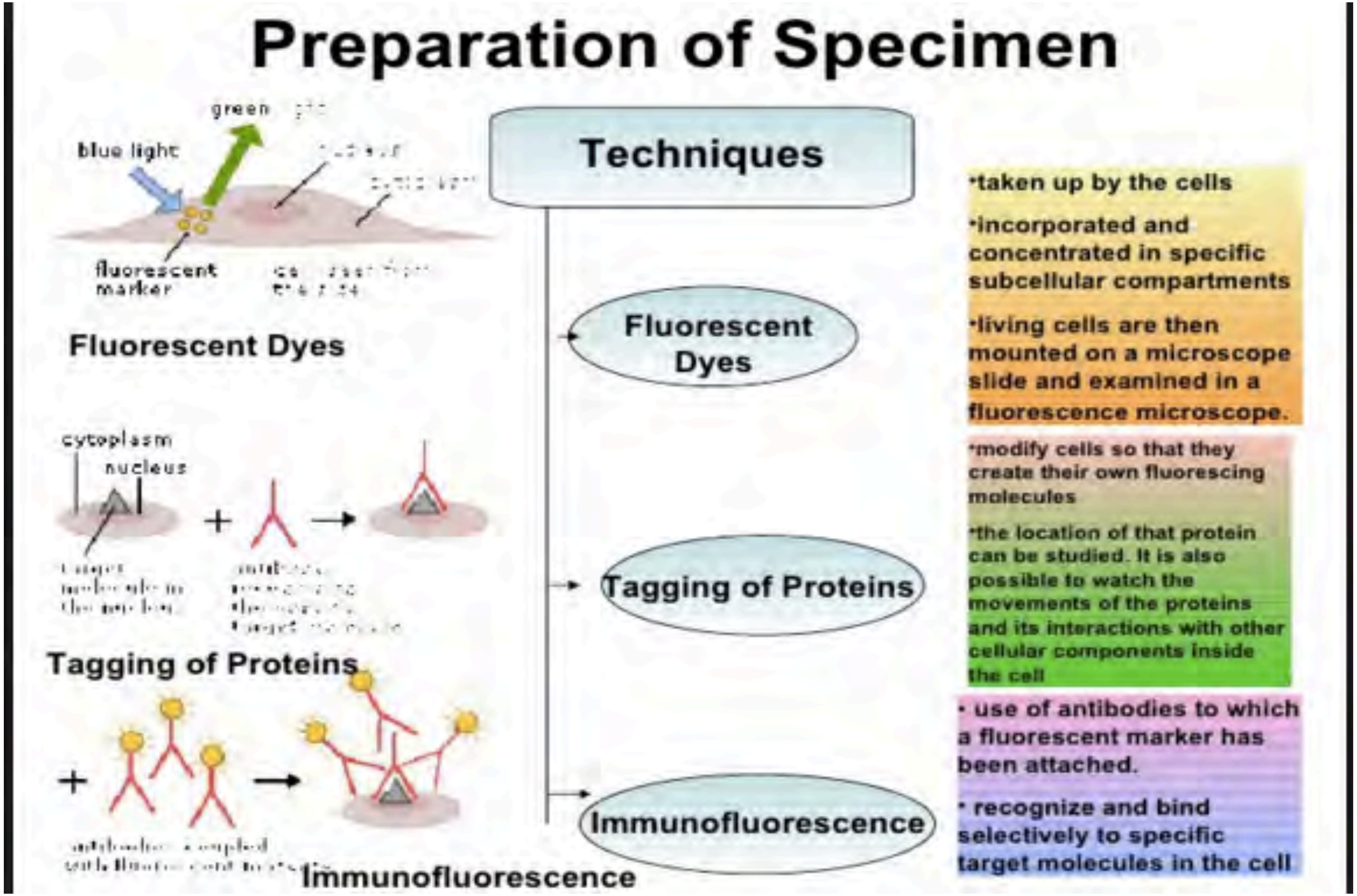


Pratik Shah. Ph.D.
pratiks@mit.edu



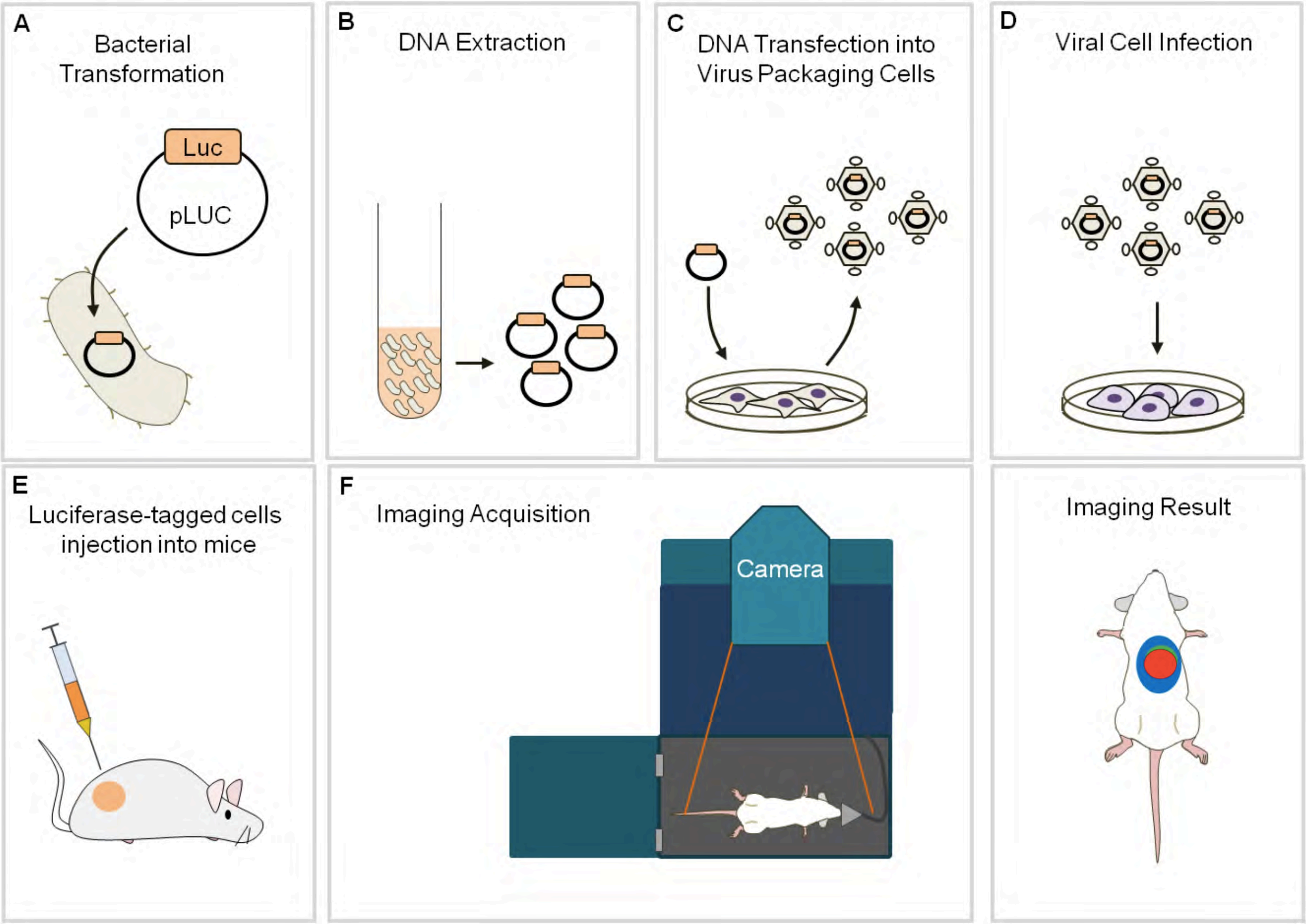
DOI: 10.1039/C3IB40018B (Tutorial Review) Integr. Biol., 2013, 5, 748-758

Pratik Shah. Ph.D.
pratiks@mit.edu



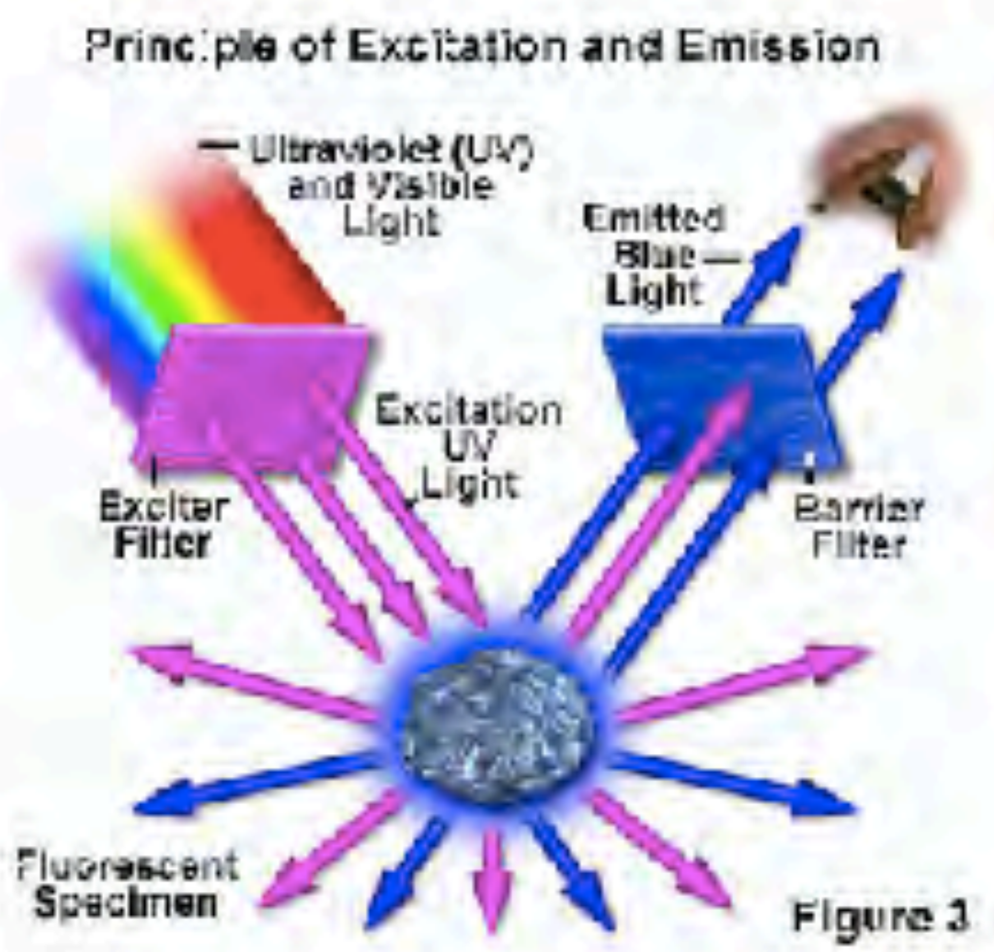
PLoS One. 2013; 8(2): e57708.

Molecular Imaging for Biological Research



PLoS One. 2013; 8(2): e57708.

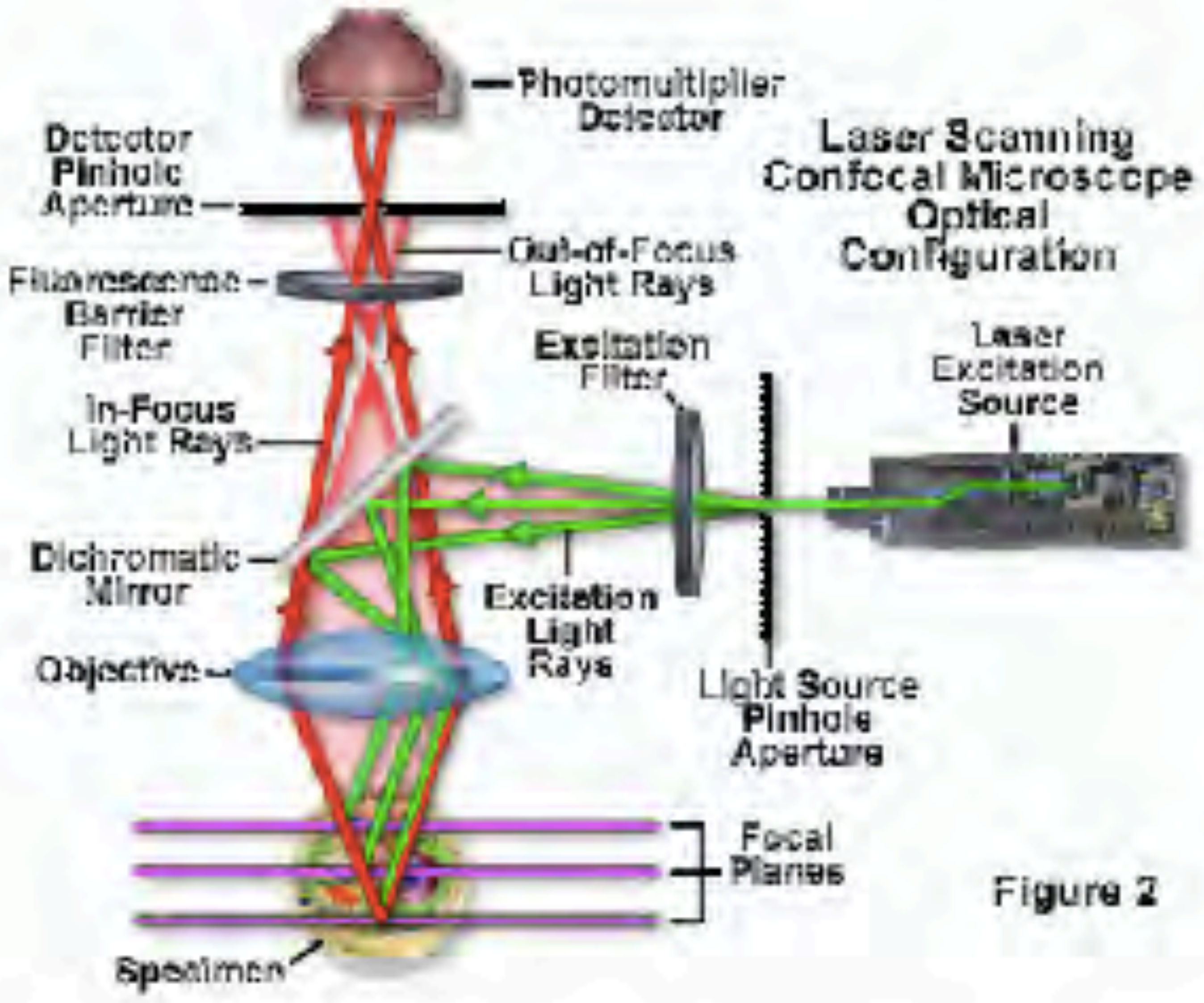
Fluorescence Microscopy



- Based on the principle of absorption and re-radiation of light by fluorophores (like the Green Fluorescence Protein) in a specimen
- Provides higher contrast than conventional optical microscopies
- Resolution is diffraction limited
- Image is further blurred due to fluorescence from out-of-focus region of the specimen

(Reproduced from| www.olympusmicro.com/primer/lightandcolor/fluorointroduction.html)

Confocal Microscopy

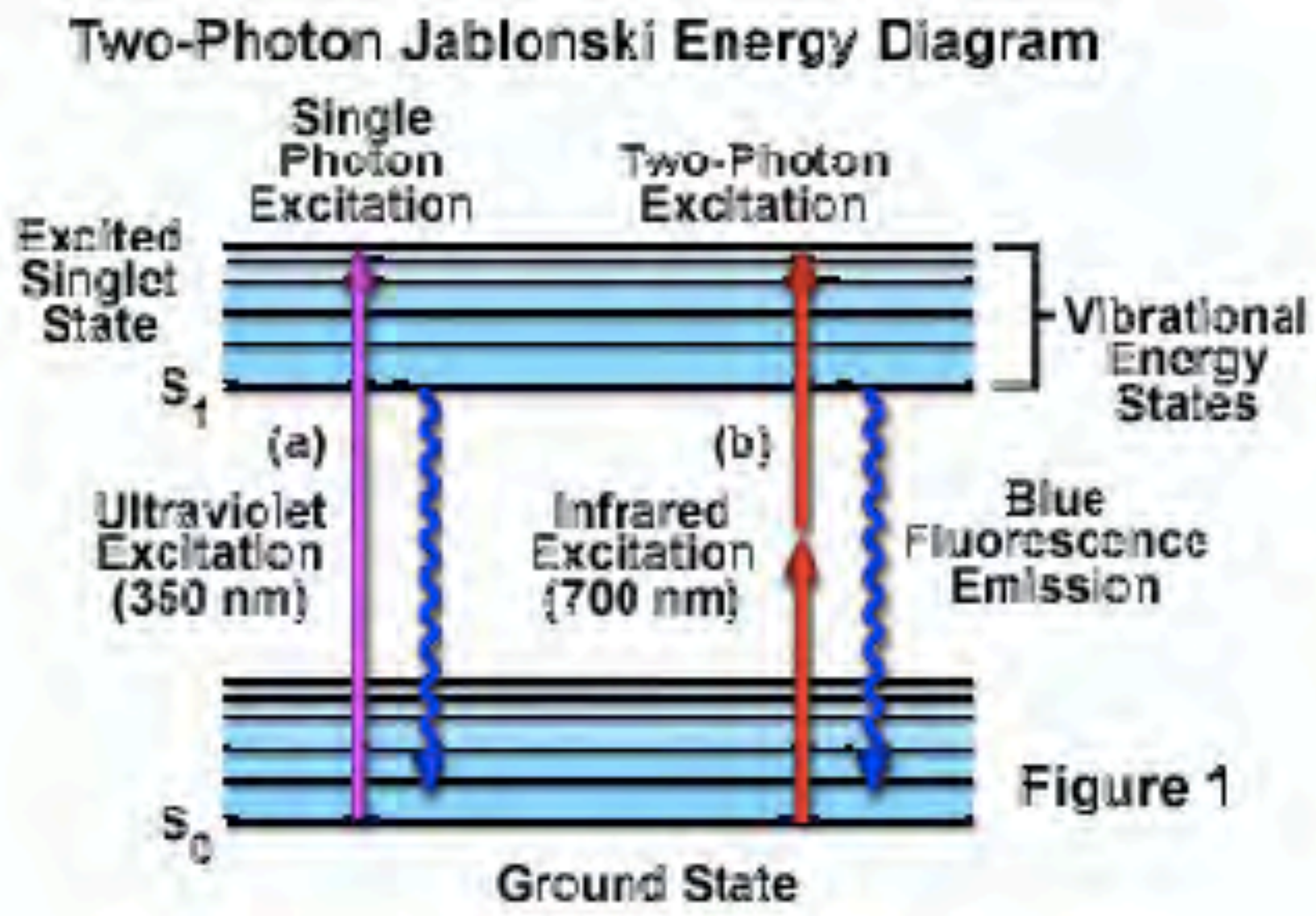


- Conventional fluorescence microscopes have poor resolution due to secondary fluorescence from out-of-focus regions.
- In a confocal microscope, a focused beam is scanned across the specimen. Both the excitation and reemitted light are focused through lens.
- The fluorescence emission that occurs above and below the focal plane is not confocal with the Pinhole aperture. Thus only the fluorescence emission from the laser focal point reaches the detector.
- The confocal microscope facilitates the collection of three dimensional data

(Reproduced from www.olympusfluoview.com/theory/confocalintro.html)

Pratik Shah. Ph.D.
pratiks@mit.edu

Two Photon Excited Fluorescence (TPEF) Microscopy

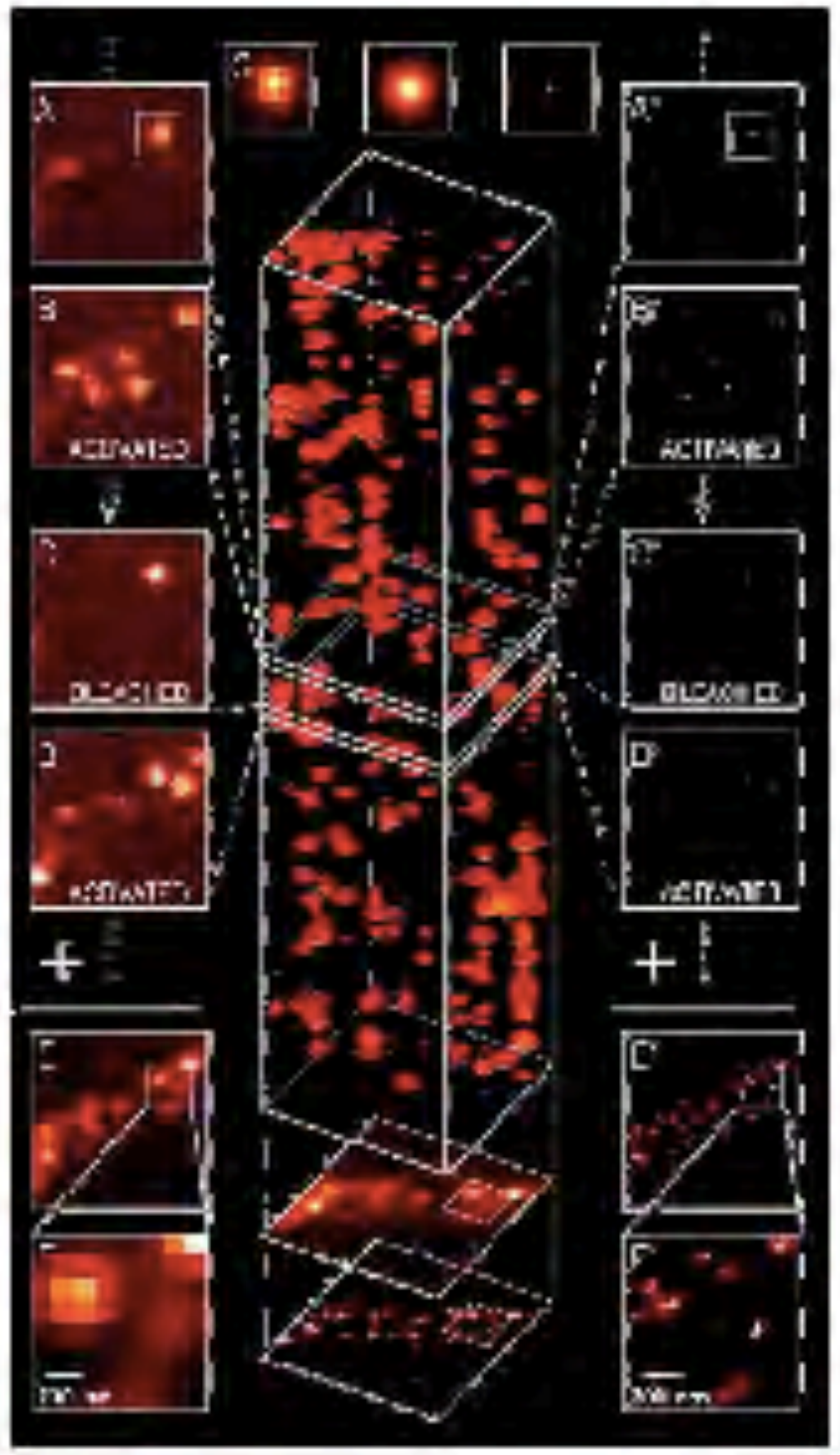


- Two low energy photon absorption
- Emission wavelength is shorter than excitation wavelength.
- Typical fluorophore emission wavelength is in the 400-500 nm range.
- Typical laser excitation wavelength is in the 700-1000 nm range.

(Reproduced from www.microscopyu.com/articles/fluorescence/multiphoton/multiphotonintro.html)

Pratik Shah. Ph.D.
pratiks@mit.edu

Photoactivated Localization Microscopy (PALM)

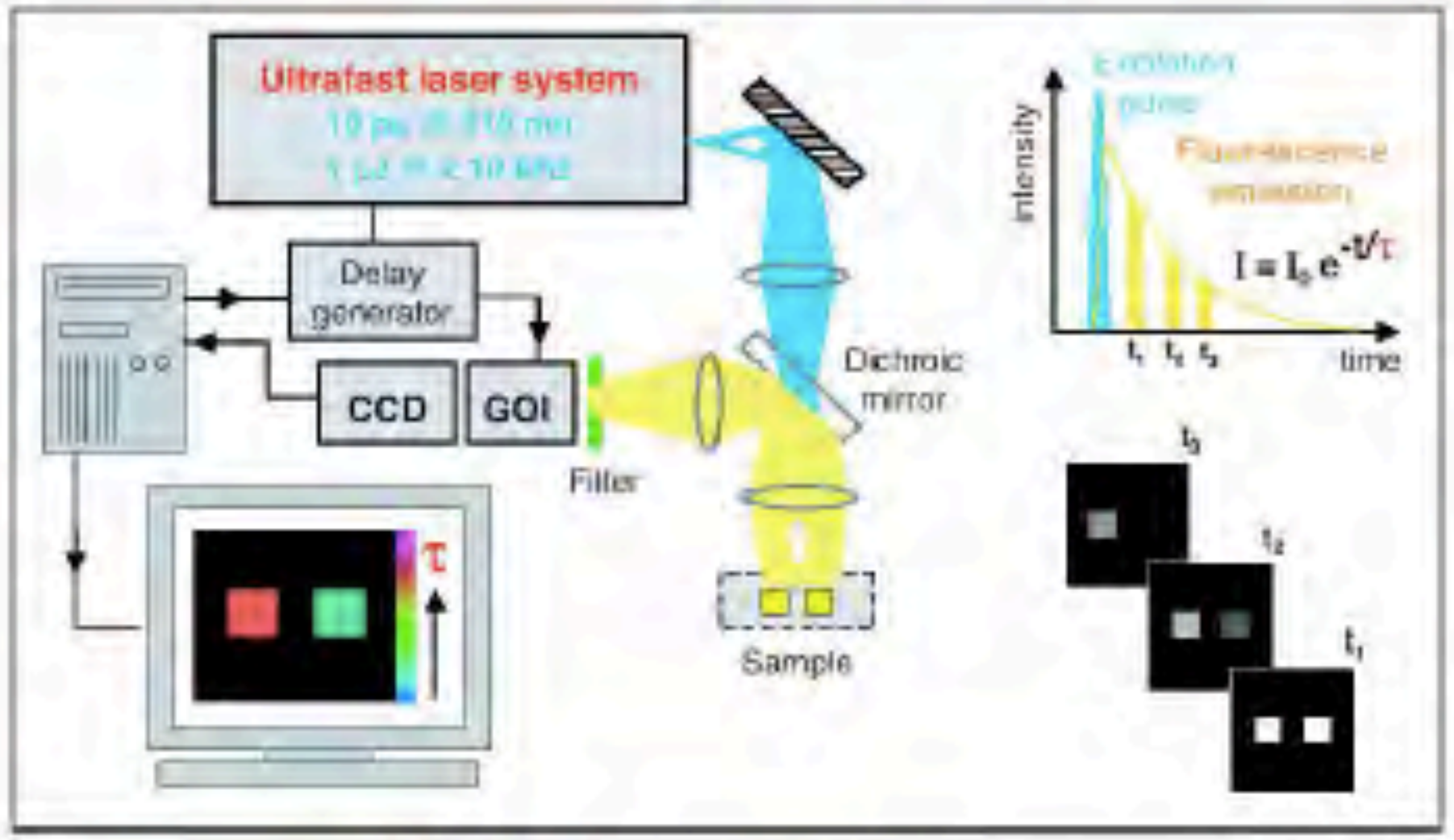


- In PALM, small sets of photoactivable fluorescent protein (PA-FP) that are attached to the protein of interest are photoactivated selectively and then bleached.
- A small area of the molecule is imaged at a time.
- The process is repeated many times until all the PA-FP have been activated and bleached.
- Using an estimated point spread function (PSF) of the microscope, the blurred image is deconvolved and replaced with a point source resulting in a very high resolution image.

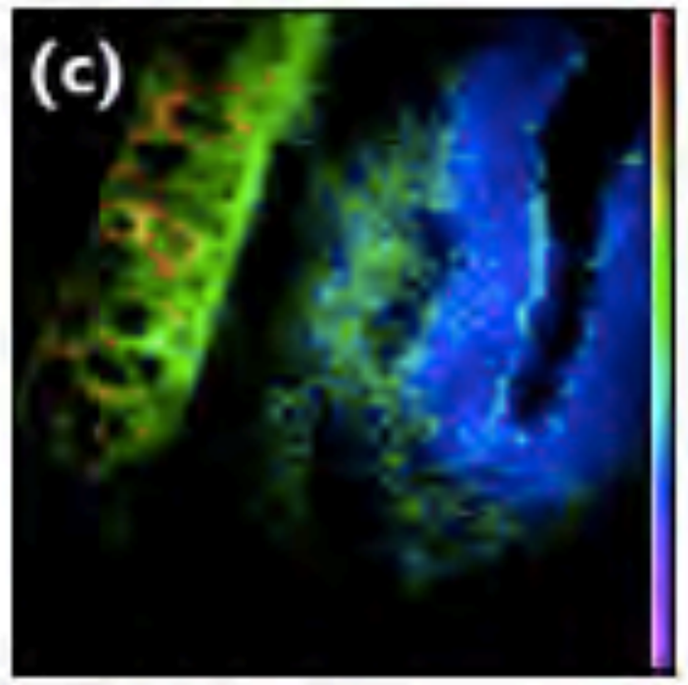
(Reproduced from [21] Betzig *et al.*, "Science", Vol. 313, 1642-1645, 2006)

Pratik Shah. Ph.D.
pratiks@mit.edu

Fluorescence Lifetime Imaging Microscopy (FILM)



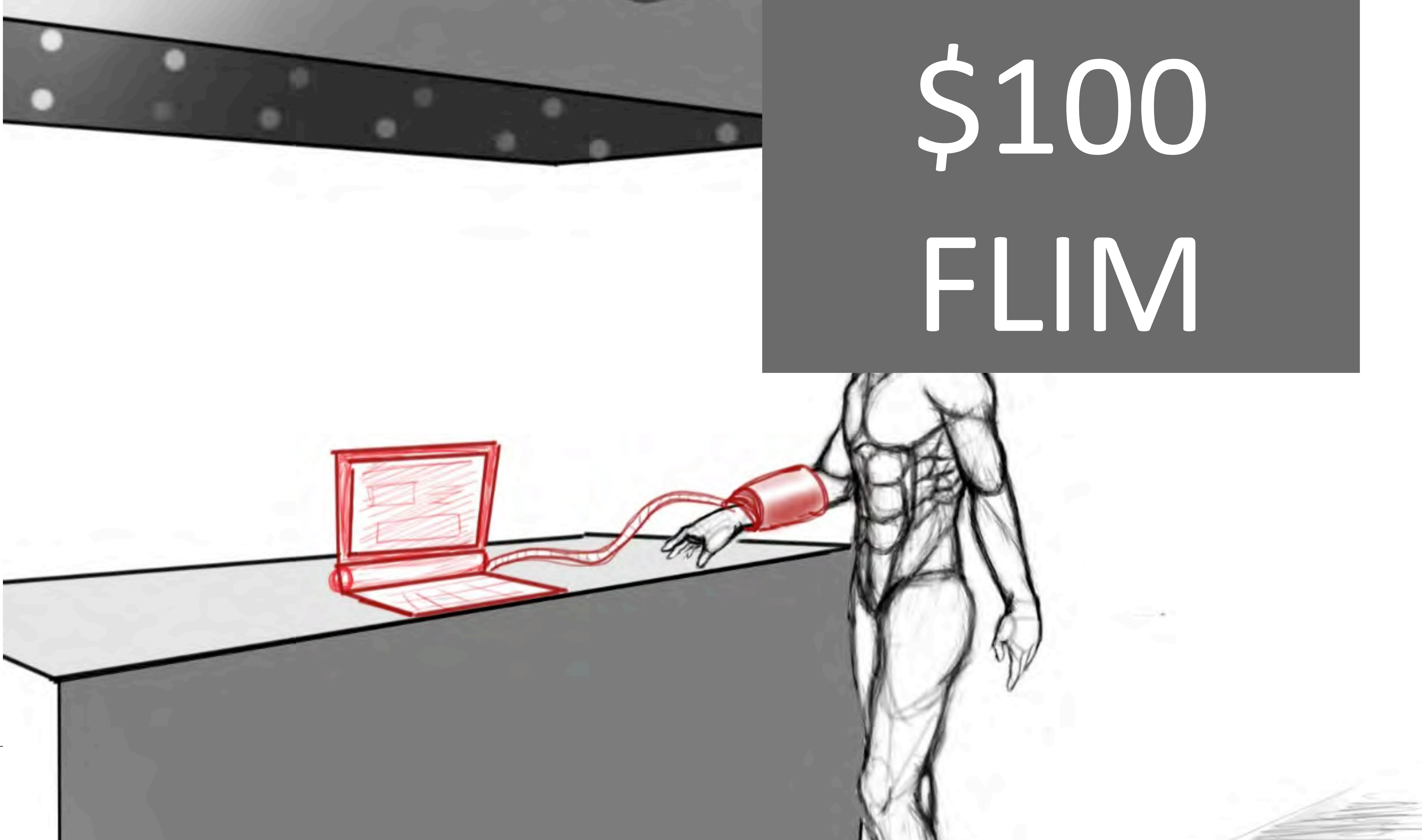
FLIM experiment



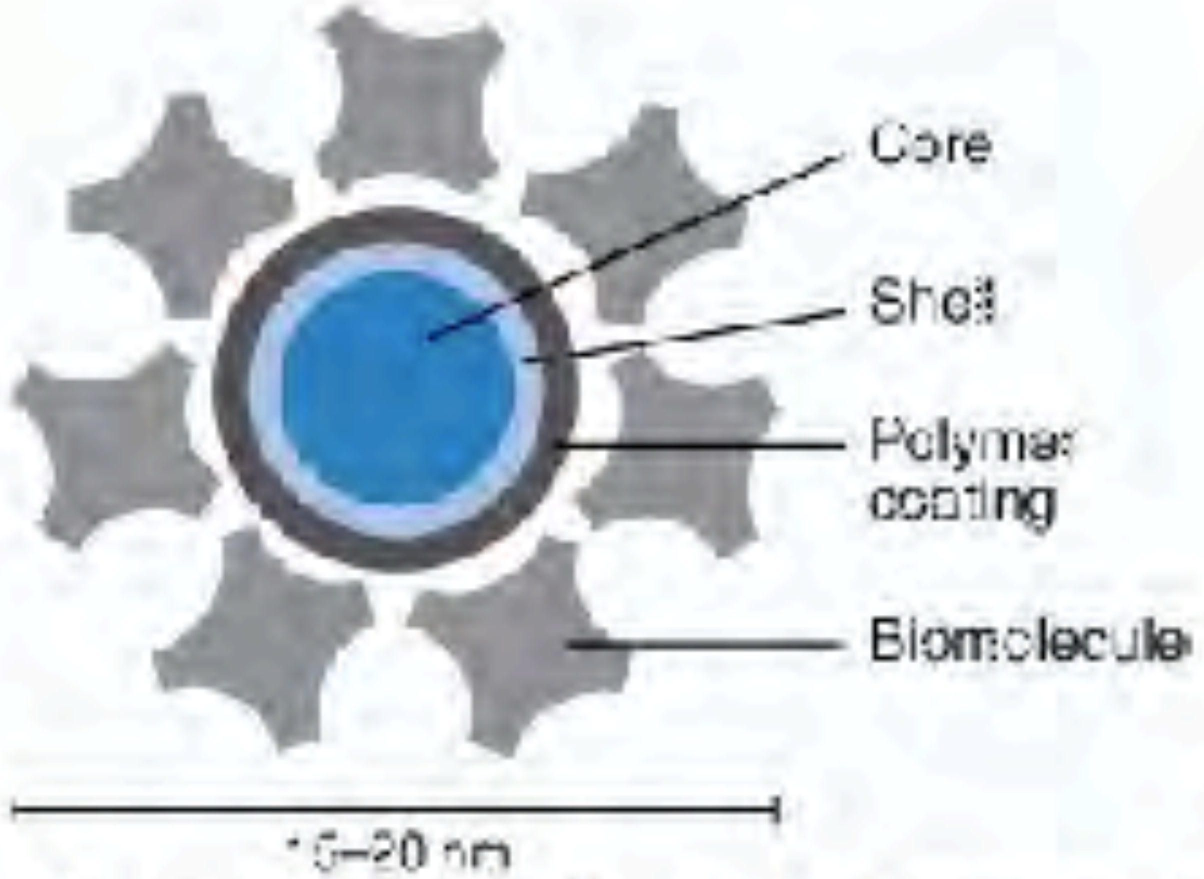
FLIM image of rat ear autofluorescence

- Time- or frequency-resolved fluorescence is recorded, and decay rate is represented as an image
- Tunable mode-locked laser and gated image intensifier can be used
- Fluorescent lifetime may provide information about tissue [24]

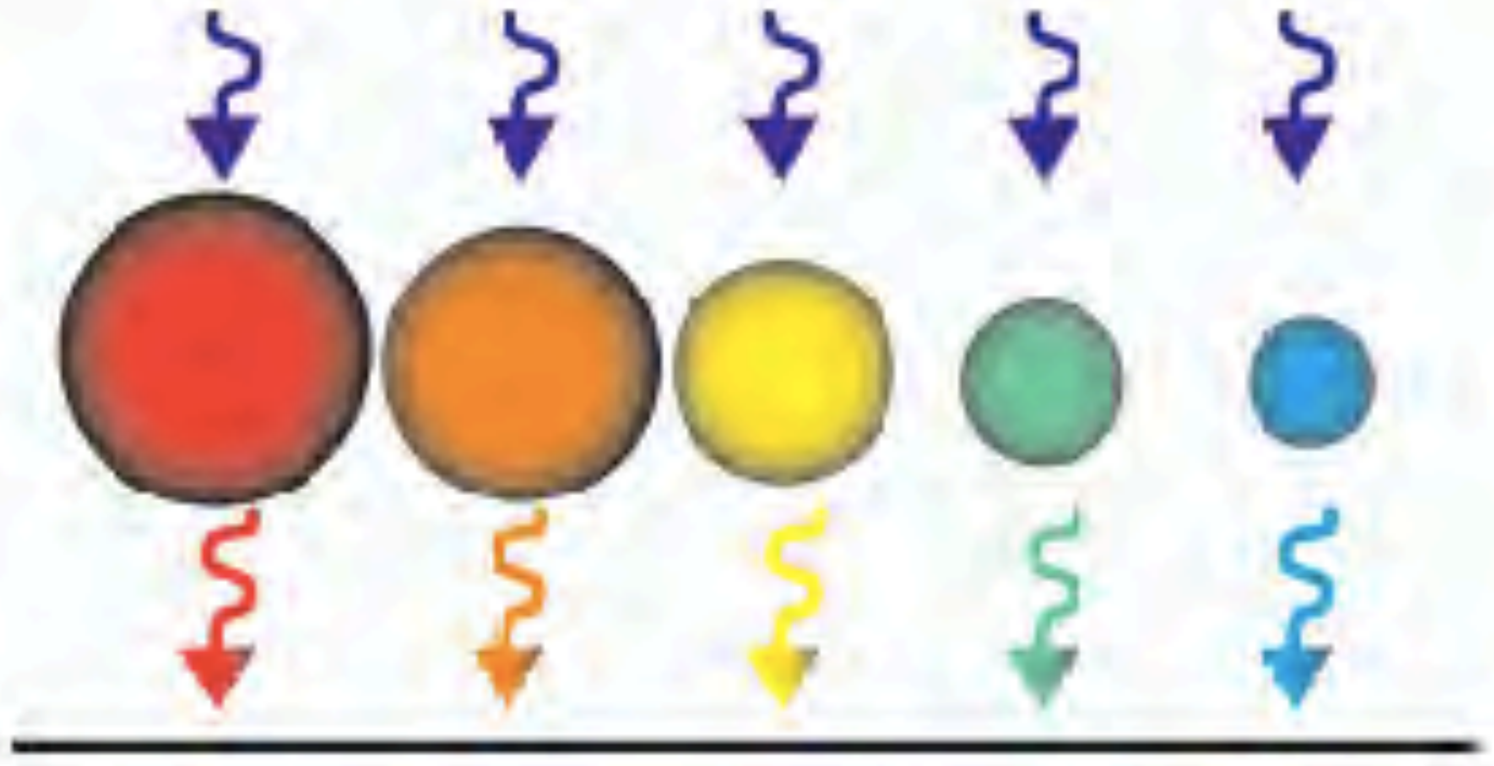
(Reproduced from [22] Paul French group, *Opt. Phot. News*, 2002)


$100
FLIM

Quantum Dots for Imaging Living Cells



Quantum dot structure



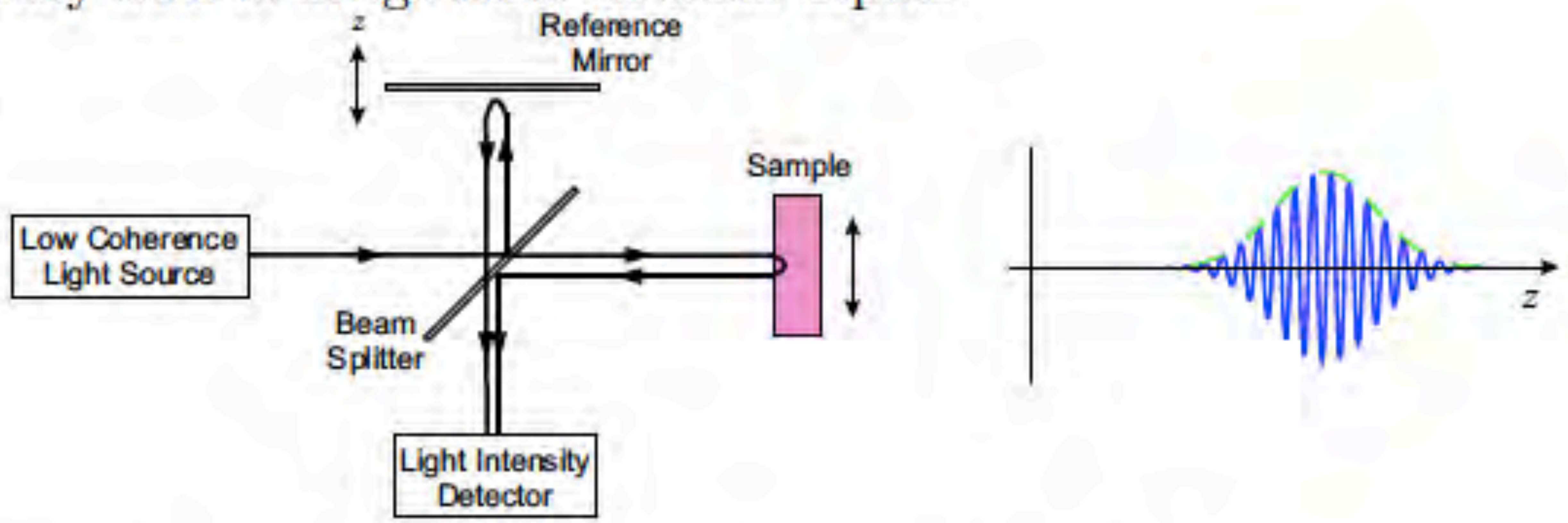
Tuneability of quantum dot

- High quantum yield (90%)
- Tunable emission wavelength by changing the Qdot size
- Resistance to bleaching- useful for 3-D imaging.
- Broadband absorption spectrum compared to standard flurophores

(Reproduced from http://probes.invitrogen.com/products/qdot/overview.html)

Optical Coherence Tomography (OCT)

- 2-D or 3-D image is made by using interferometric measurement of optical backreflection or backscattering from internal tissue microstructures
- Similar in principal to RADAR ranging with optical signal
- Negligible scatter assumed
- Typically used to image tissue at small depths



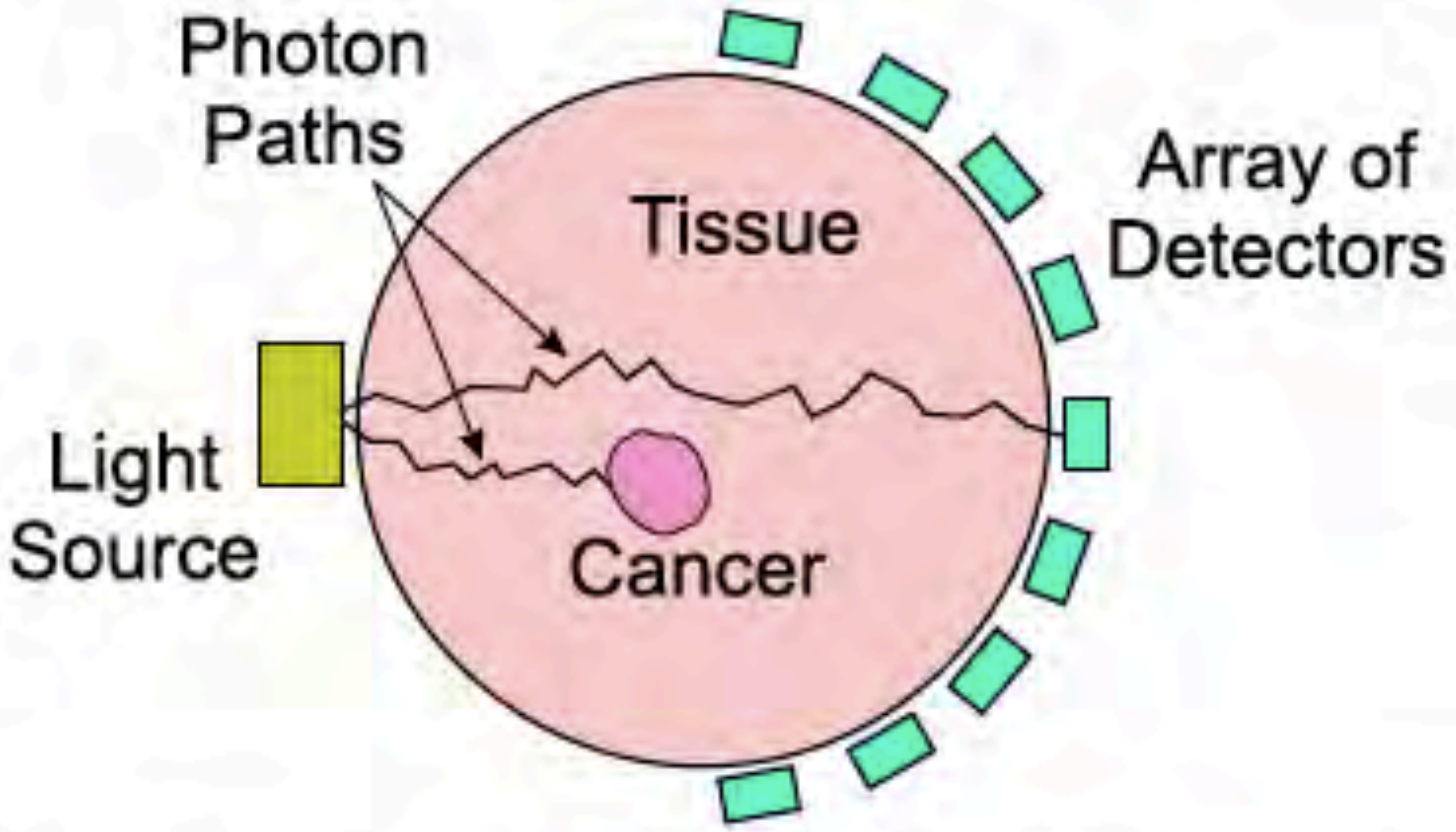
  - z-direction moving of reference mirror → longitudinal scan
  - Beam moving on sample → transverse scan
  - Usually implemented with fiber optic

(Reproduced from [25] Fujimoto Group, *Science*, 1991)

Pratik Shah. Ph.D.
pratiks@mit.edu

Fluorescence Lifetime Imaging Microscopy (FILM)

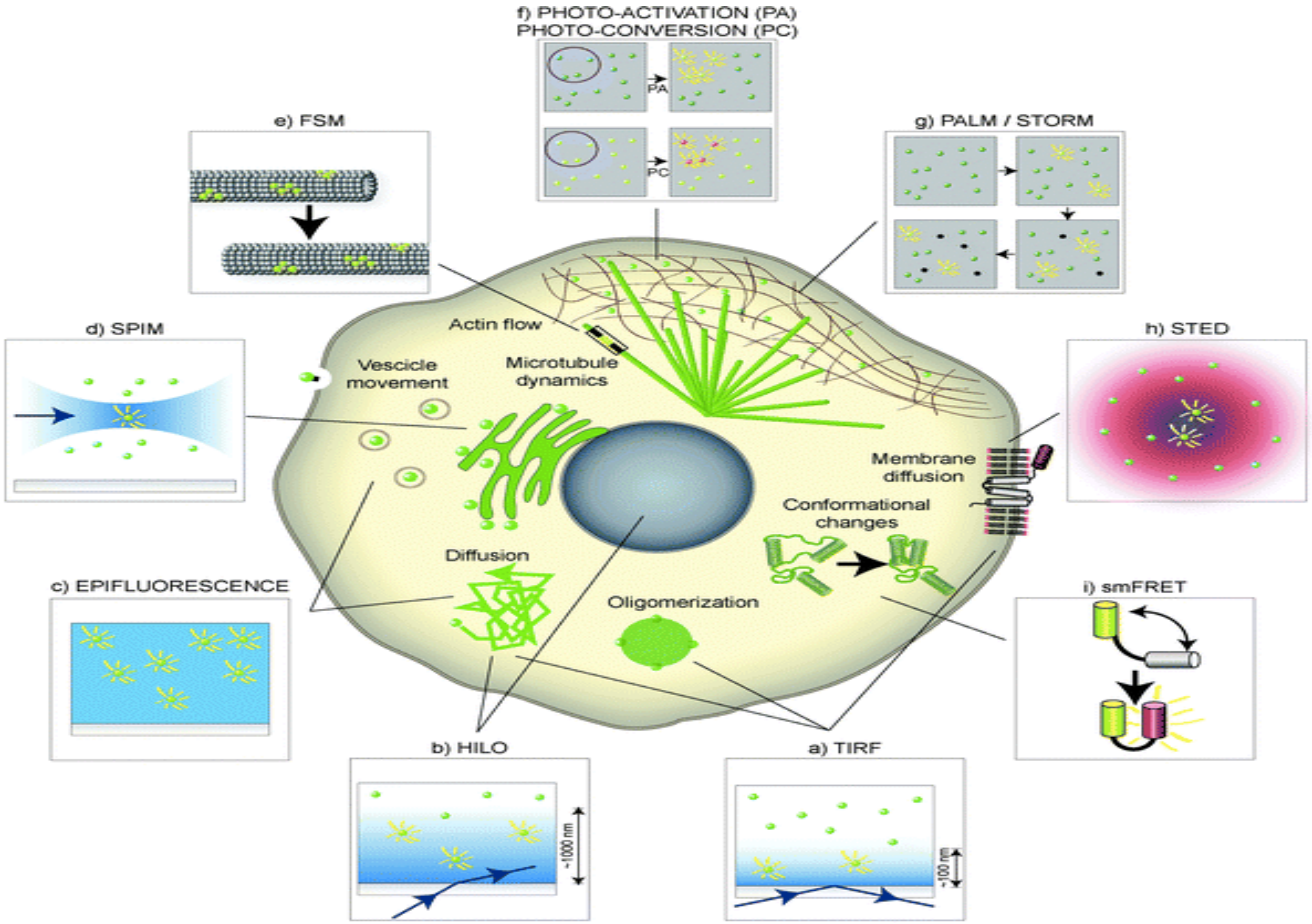
- Measure light that passes through a highly scattering medium
- Determine unknown absorption and/or diffusion cross-section of material



- With K sources and M detectors, there can be KM measurements
- Time domain: Measure delay of light pulse at detector
- Frequency domain: Measure amplitude/phase of modulated light envelope
- Also called "Diffuse Optical Tomography" and "Photon Migration"

Pratik Shah. Ph.D.
pratiks@mit.edu

Single-Molecule Techniques in the Cellular Landscape

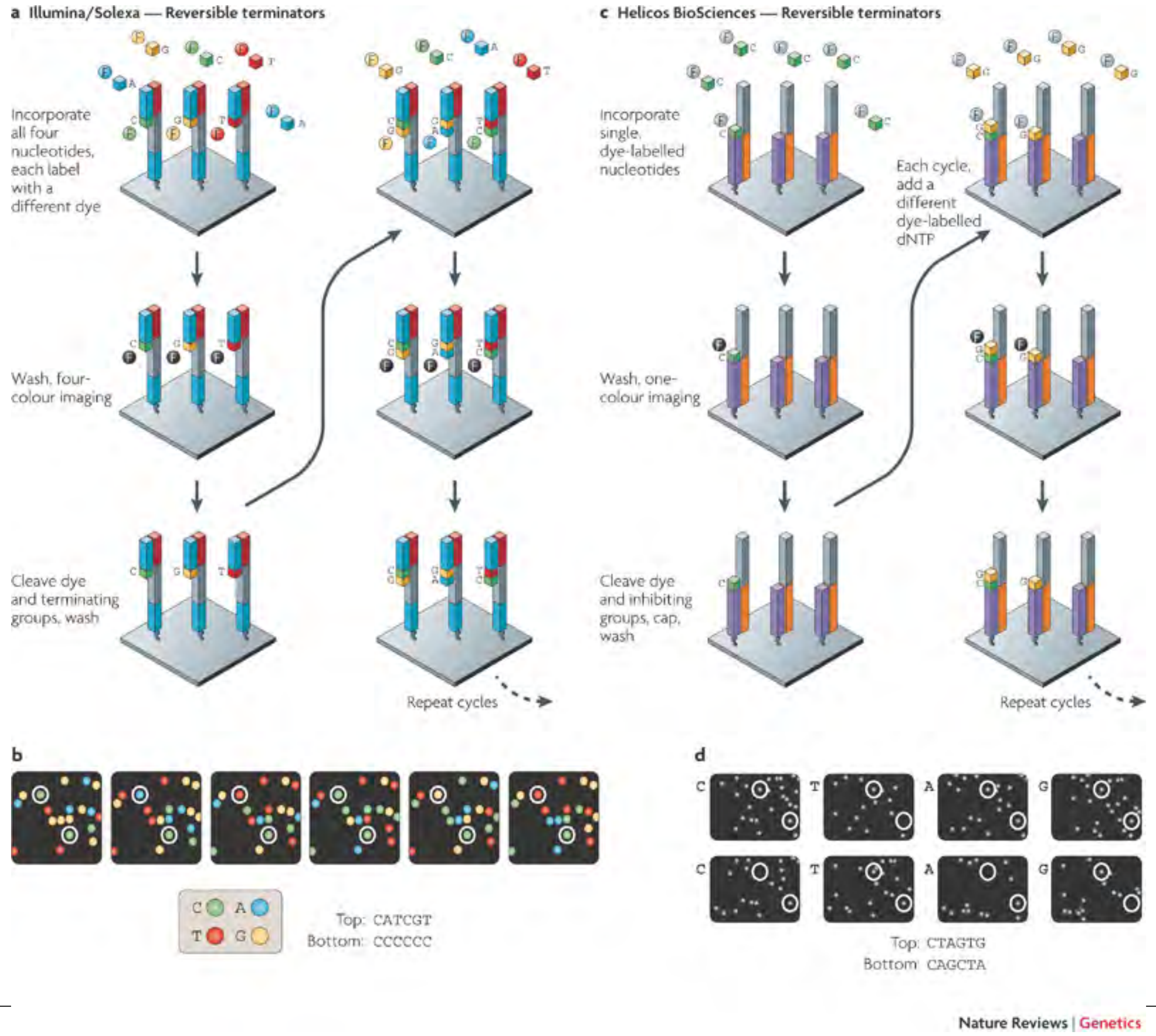


DOI: 10.1039/C3IB40018B (Tutorial Review) Integr. Biol., 2013, 5, 748-758

Technique	Spatial resolution	Time resolution	Photo-toxicity	Measurable physical parameters	Cellular region	Compatible labels	Molecule imaged/label	*In vivo* applications
TIRF	200–250 nm	5 ms	Low	Position and movement	Cover slip interface	FPs, organic dyes	E-cadherin–GFP	Oligomerization dynamics
							cAMP–Cy3	Chemotaxis
							PHD–GFP	Membrane binding
							Telenzepine–Cy3b	Membrane receptors
							G-protein YFP–CIOH-Ras	Membrane microdomains
EPI	200–250 nm	5 ms	Medium	Position and movement	All	FPs, organic dyes, Q-dots, colloidal particles	Glycoprotein–gold	Membrane proteins
							Gly-receptor-Qdot	Neuronal receptors
							Viruses-Cy3/5	Viral infection
SPIM	200–250 nm	5 ms	Low	Position and movement	All	FPs, organic dyes	Kinesin-Qdot	Molecular motors
							Tsr-Venus	Protein synthesis
							Hrp36-ATTO647N	Ribonuclear particles
FSM	200–250 nm	~1 s	Medium	Position and movement	All	FPs, organic dyes	Tubulin–XRhodamine	Microtubule dynamics
							β Actin–EGFP	Actin dynamics
Photo-activation/photo-conversion	200–250 nm	~1 s	High	Position and movement	All	PA-FP, PC-FP, tetracysteine	Igp120–PA-GFP	Membrane diffusion
							Connexin43-Flash/ReAsh	Gap junctions
							Fibrillarin-Dendra2	Nuclear transport
							Nic95-2xDendra2	Nuclear pore segregation
Super resolution	20 nm	~100 ms	High	Position	5–10 μm from the cell surface	Organic dyes, FPs, PA-FP, PC-FP	MreB-PS-EYFP	Prokaryote cytoskeleton

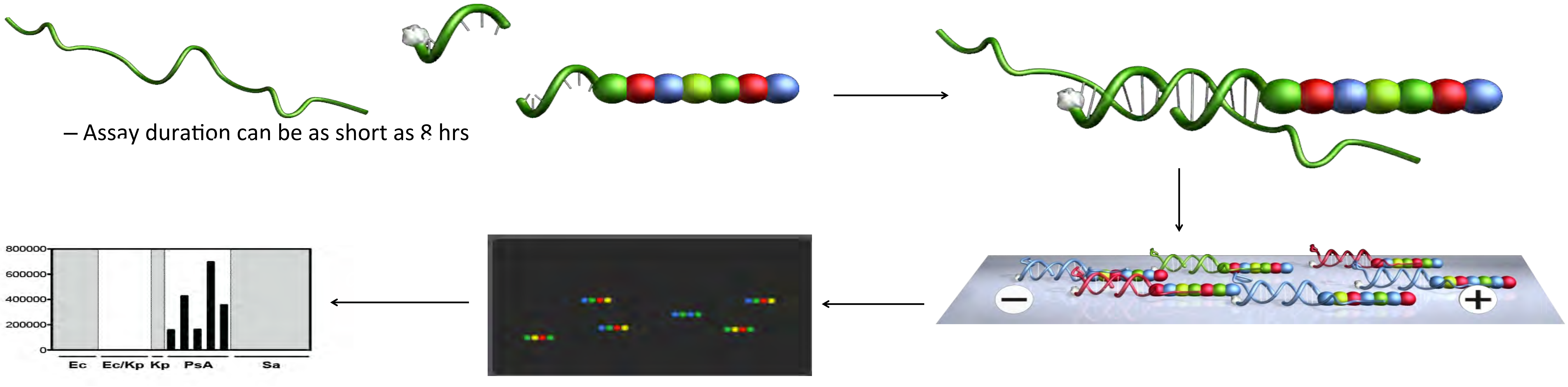
DOI: 10.1039/C3IB40018B (Tutorial Review) Integr. Biol., 2013, 5, 748-758

Solid-State Massively Parallel DNA Sequencing



RNA detection: Nanostring

- Nanostring = a commercial assay for multiplexed, hybridization-based RNA detection from crude lysate
  - Assay duration can be as short as 8 hrs



www.nanostring.com

Pratik Shah. Ph.D.
pratiks@mit.edu

THz pulses: biomedical applications

ACS Chemistry for Life®

ACS Network | Store | Governance | About Us | Contact

Join ACS | Search

Publications | Meetings | Careers | Membership & Networks | Education | Policy | Funding & Awards | Press Room

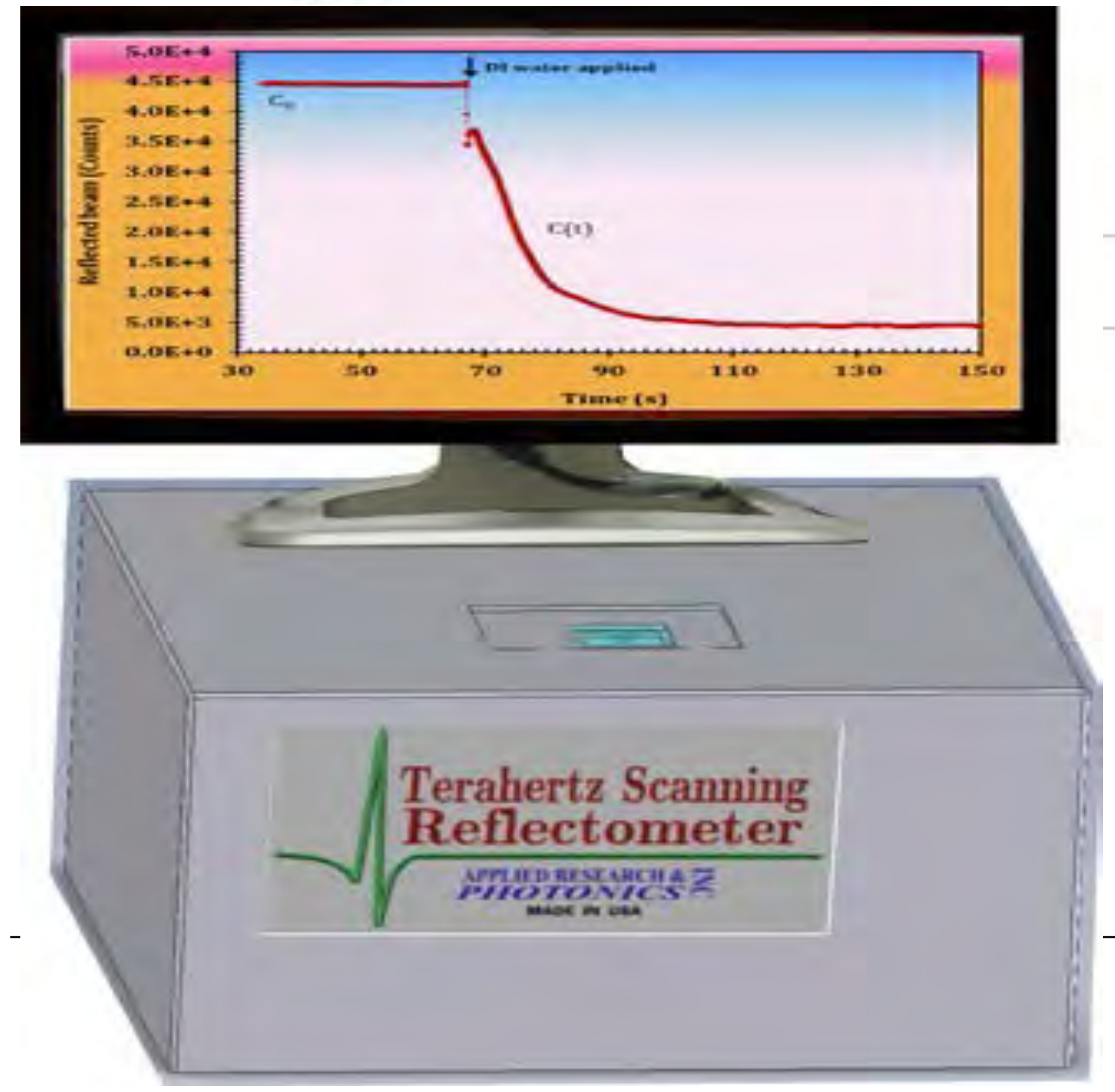
American Chemical Society » Press Room » News Releases » 2013 » September » T-rays offer potential for earlier diagnosis of melanoma

Press Room

Press Pacs

News Releases

2013
2012
2011
2010
2009
2008



EMBARGOED FOR RELEASE | September 11, 2013

T-rays offer potential for earlier diagnosis of melanoma

Note to journalists: Please report that this research was presented at a meeting of the American Chemical Society.

A press conference on this topic will be held Wednesday, Sept. 11, at 1 p.m. in the ACS Press Center, Room 211, in the Indiana Convention Center. Reporters can attend in person or access live audio and video of the event and ask questions at www.ustream.tv/channel/acslive.

INDIANAPOLIS, Sept. 11, 2013 — The technology that peeks underneath clothing at airport security screening check points has great potential for looking underneath human skin to diagnose cancer at its earliest and most treatable stages, a scientist said here today.

The report on efforts to use terahertz radiation — "T-rays" — in early diagnosis of skin cancer was part of the 246th National Meeting & Exposition of the American Chemical Society, the world's largest scientific society. Almost 7,000 reports on new advances in science and other topics are on the schedule for the meeting. It continues here through Thursday in the Indiana Convention Center and downtown hotels.

Anis Rahman, Ph.D., who spoke on the topic, explained that malignant melanoma, the most serious form of skin cancer, starts in pigment-producing cells located in the deepest part of the epidermis. That's the outer layer of the skin. Biochemical changes that are hallmarks of cancer occur in the melanocytes long before mole-like melanomas appear on the skin.

Media Contact

During the national meeting, Sept. 6-11, the contacts can be reached at 317-262-5907.

Michael Bernstein
m_bernstein@acs.org
202-872-6042

Michael Woods
m_woods@acs.org
202-872-6293