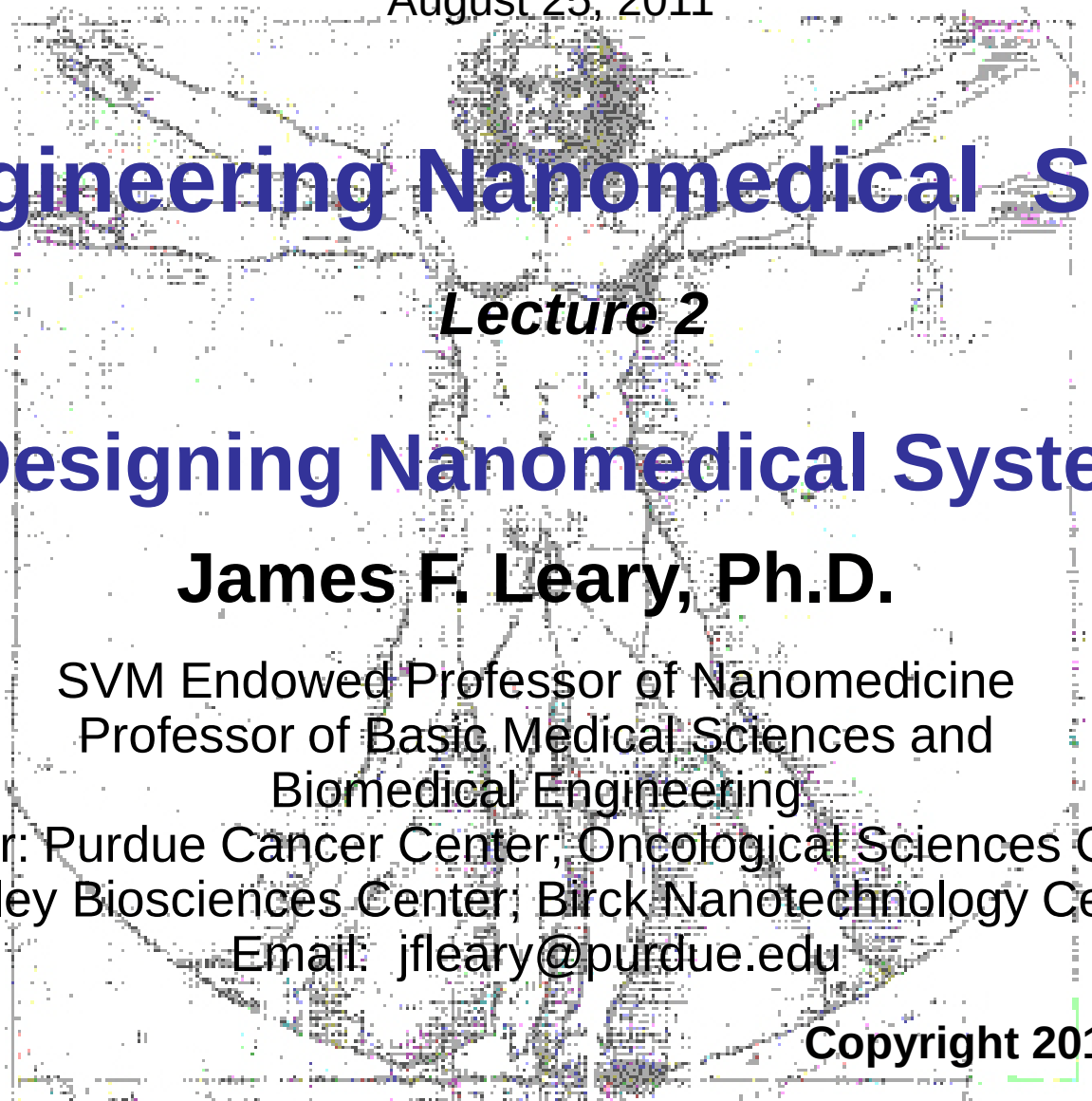
PURDUE UNIVERSITY

Weldon School of Biomedical Engineering

The Convergence of Differences, The Future of Excellence

BME 695

August 25, 2011



Engineering Nanomedical Systems

Lecture 2

"Designing Nanomedical Systems"

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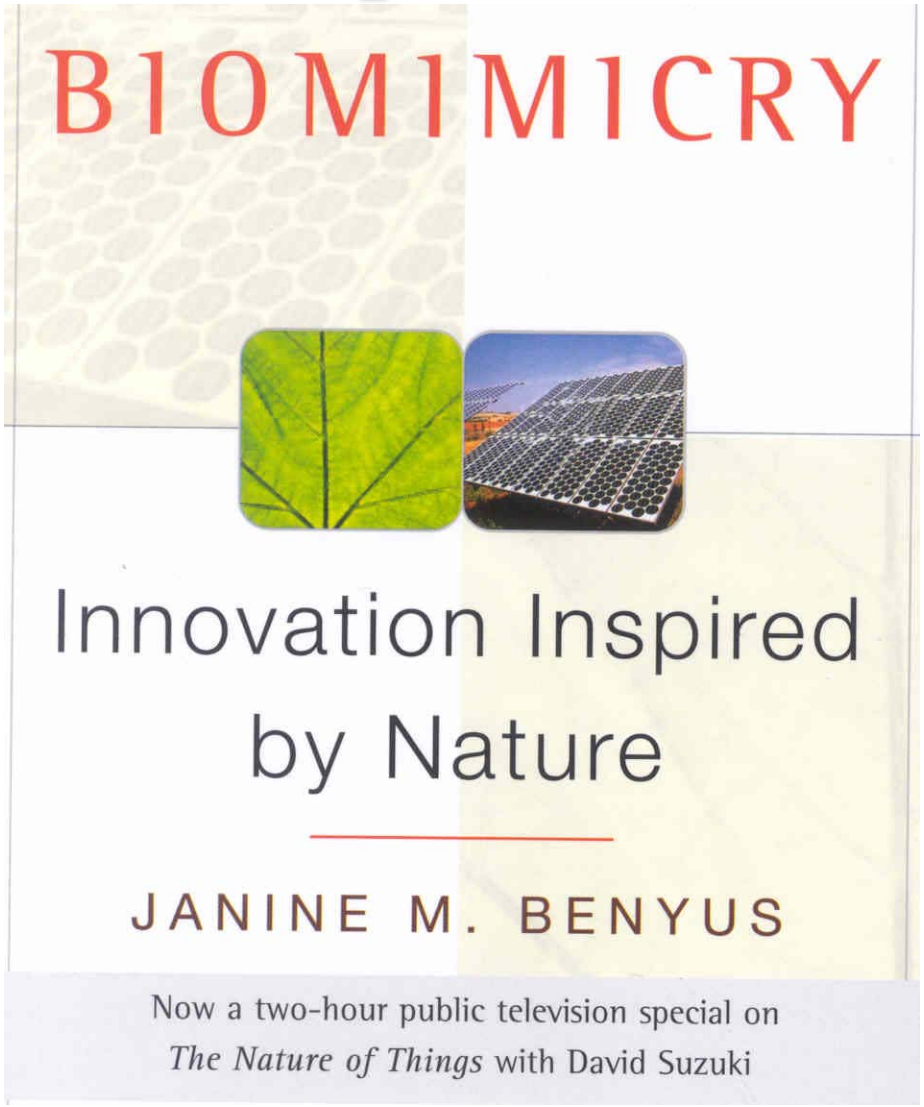
Some Elements of Good Engineering Design Applicable to the Design of Nanomedical Systems

Principle 1: Whenever possible, use a general design that has already been tested!

Biomimicry – Nature has already developed some successful designs!



From the Greek “bios” = life and “mimesis” = imitation…

“Biomimicry (or Biomimetics) is a new science that studies nature’s models and then imitates or takes inspiration from these designs and processes to solve human problems.”

[from the preface of Biomimicry]

Nature has already solved similar problems with “Nature’s nanoparticle”, the virus. We are making artificial, non-biological viruses in the form of nano-machines but with some capabilities and features not present in biological viruses.

A design tested by Mother nature…*

One good biomimetic design that has been well tested is that of a virus. But in the case of a nanomedical device we might instead construct a non-replicating, artificial virus made of well-defined molecular components that we can manufacture in a reproducible manner suitable for human in-vivo use.

* *Not necessarily the best design, but one that works at least moderately well !*

Some Elements of Good Engineering Design Applicable to the Design of Nanomedical Systems

Principle 2: Something that is a good general purpose design means that it is not particularly good for any particular function.

N.B. Instead, design systems containing collections of specific designs to do each specific function well.

A nanomedical device must do several functions well, so it must contain specific molecules that do these functions well:

1. Cell targeting
2. Cell entry
3. Intracellular targeting
4. Controlled drug delivery

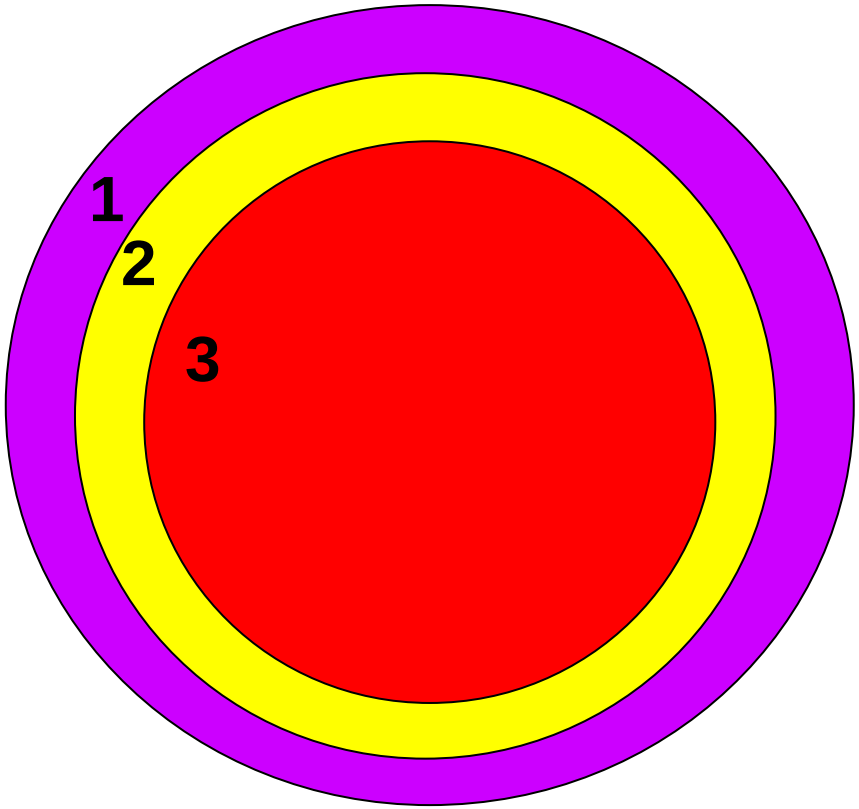
N.B. It is possible, but rare, for a single molecule to do two or even more functions. For example, we are currently using a single peptide sequence which does pretty good cell targeting, cell entry, and intracellular targeting to the nucleus of that cell. But that is unusual!

Some Elements of Good Engineering Design Applicable to the Design of Nanomedical Systems

Principle 3: By controlling the order of molecular assembly one can control the order of those specific molecular functions, leading to a "programmable" nanodevice*.

* *Where "programming" simply means controlling the order of events*

By controlling the order of molecular assembly one can control the order of those specific molecular functions, leading to a “programmable”* nanodevice.



** Whereby Step 1 must occur before Step 2 can happen, and Step 3 will not happen unless it is preceded by Steps 1 and 2*

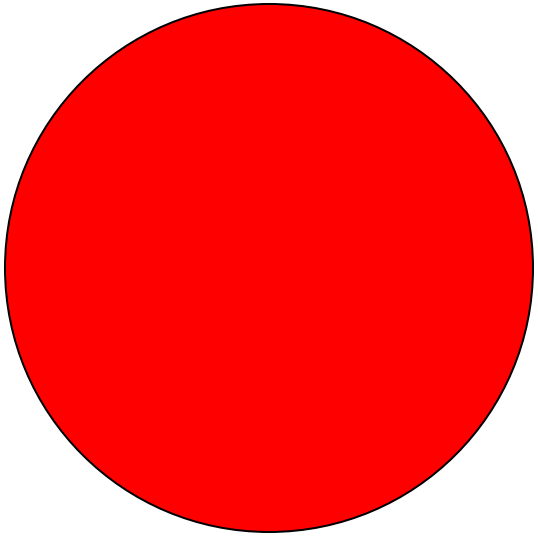
Order of nanoassembly

Consequently we usually construct a multi-component nanomedical system in reverse order of controlling events, namely from the inside out. The outer components are the first to be used. The inner components are the last.

"The first shall be last, and the last shall be first…"

Basic Design – Building a Nanodevice

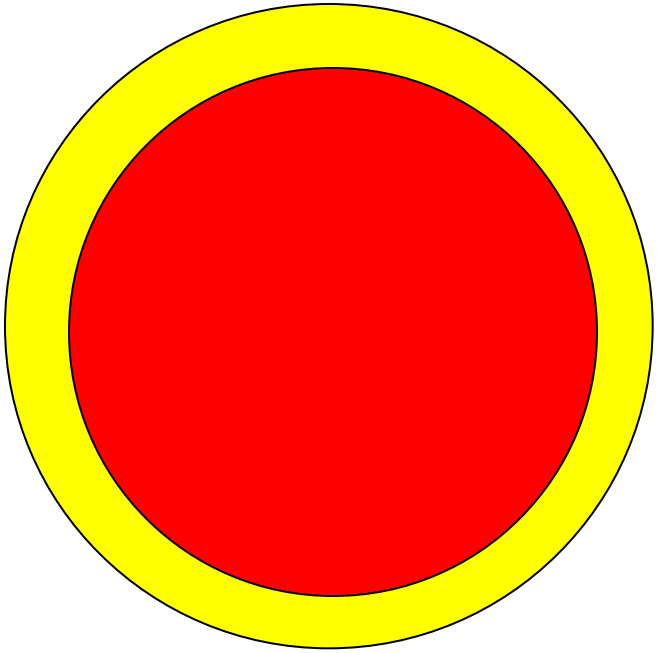
Step 1: Choice of Core Materials



Commonly used core materials include: gold, ferric oxide, silica, Qdots,

Basic Design – Building a Nanodevice

Step 2: Add drug or therapeutic gene

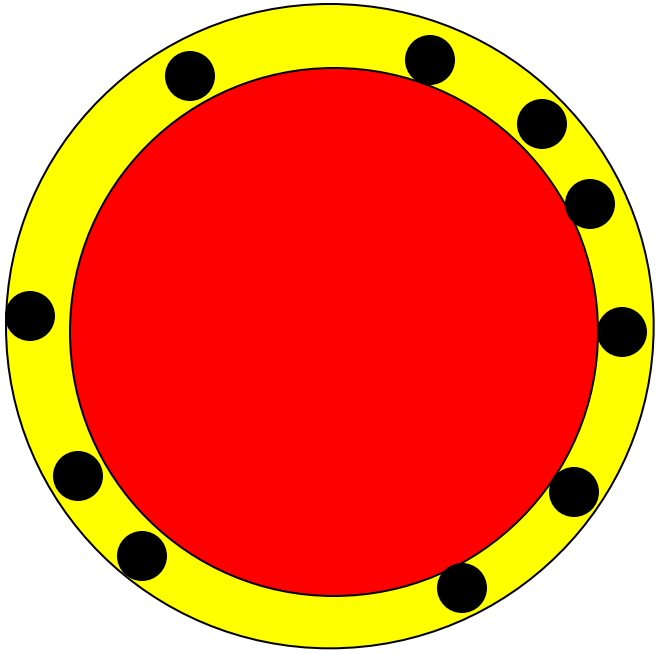


Drugs or therapeutic genes

Commonly used core materials include: gold, ferric oxide, silica, Qdots,

Basic Design – Building a Nanodevice

Step 3: Add Molecular Biosensors



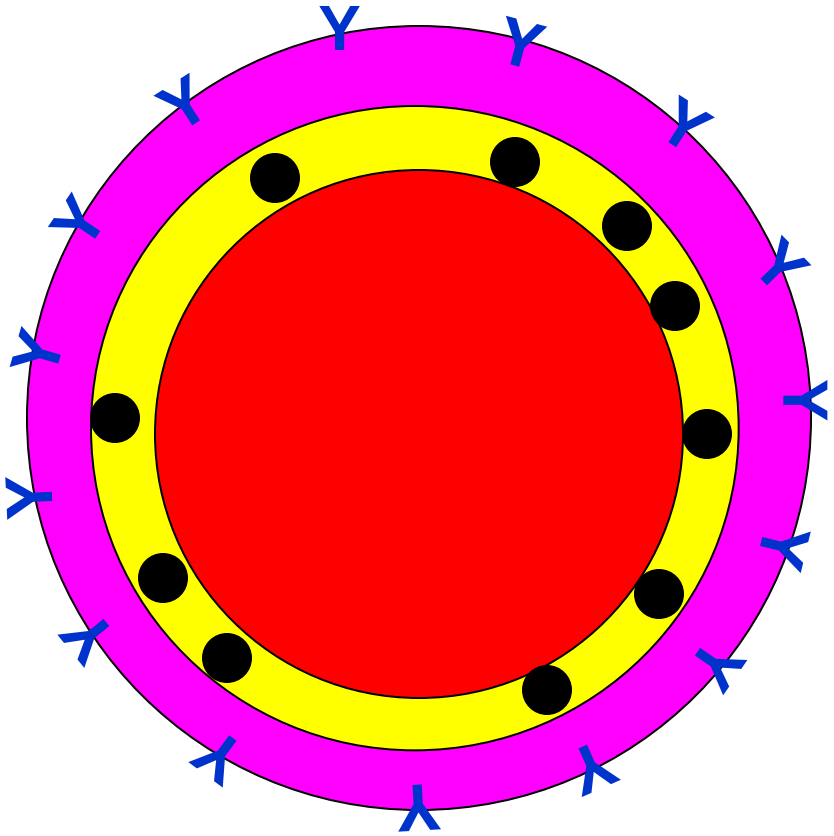
Therapeutic drugs or genes

Commonly used core materials include: gold, ferric oxide, silica, Qdots,

Biomolecular feed-back control sensors (can also provide error-checking and/or gene switch)

Basic Design – Building a Nanodevice

Step 4: Add Intracellular targeting molecules



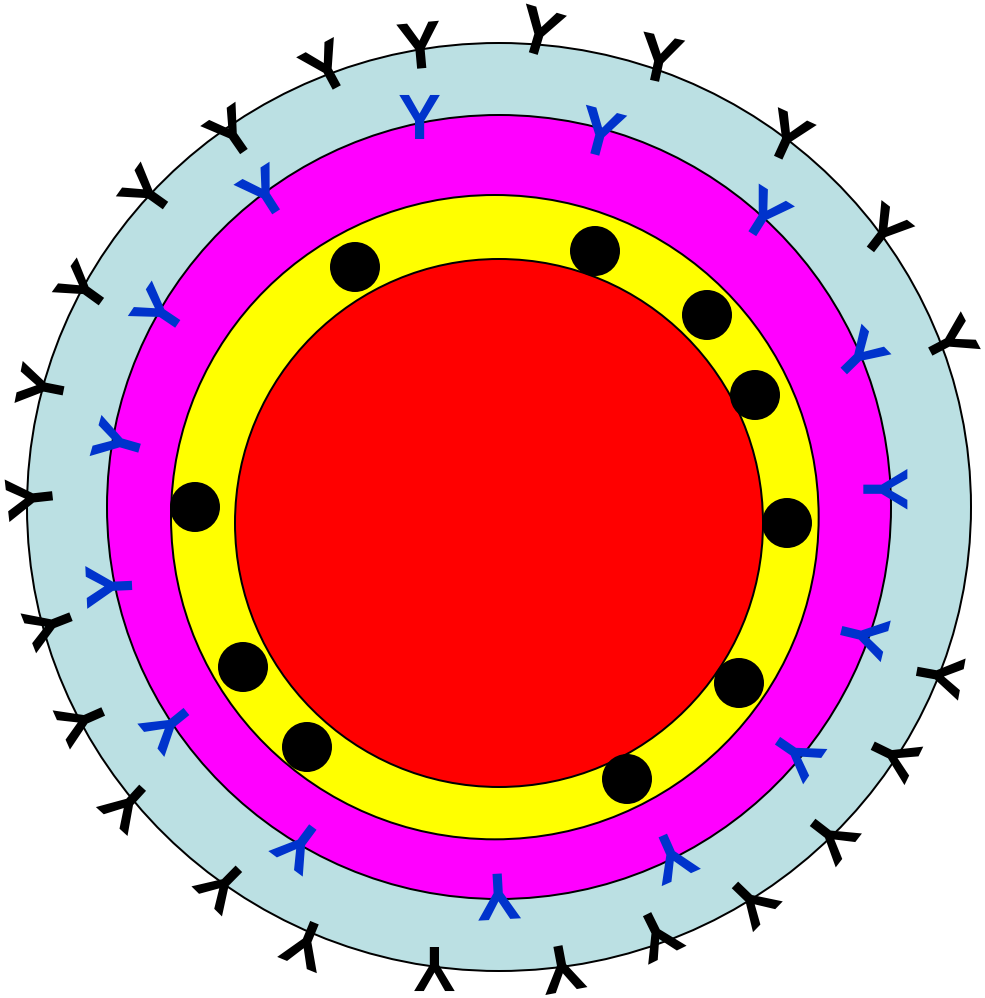
Intracellular targeting

Therapeutic genes

Commonly used core materials include: gold, ferric oxide, silica, Qdots,

Biomolecular sensors (for error-checking or ON/OFF gene switch)

Result: A Multi-component, Multi-functional "Programmable" Nanodevice or Nanosystem



Cell targeting and entry

Intracellular targeting

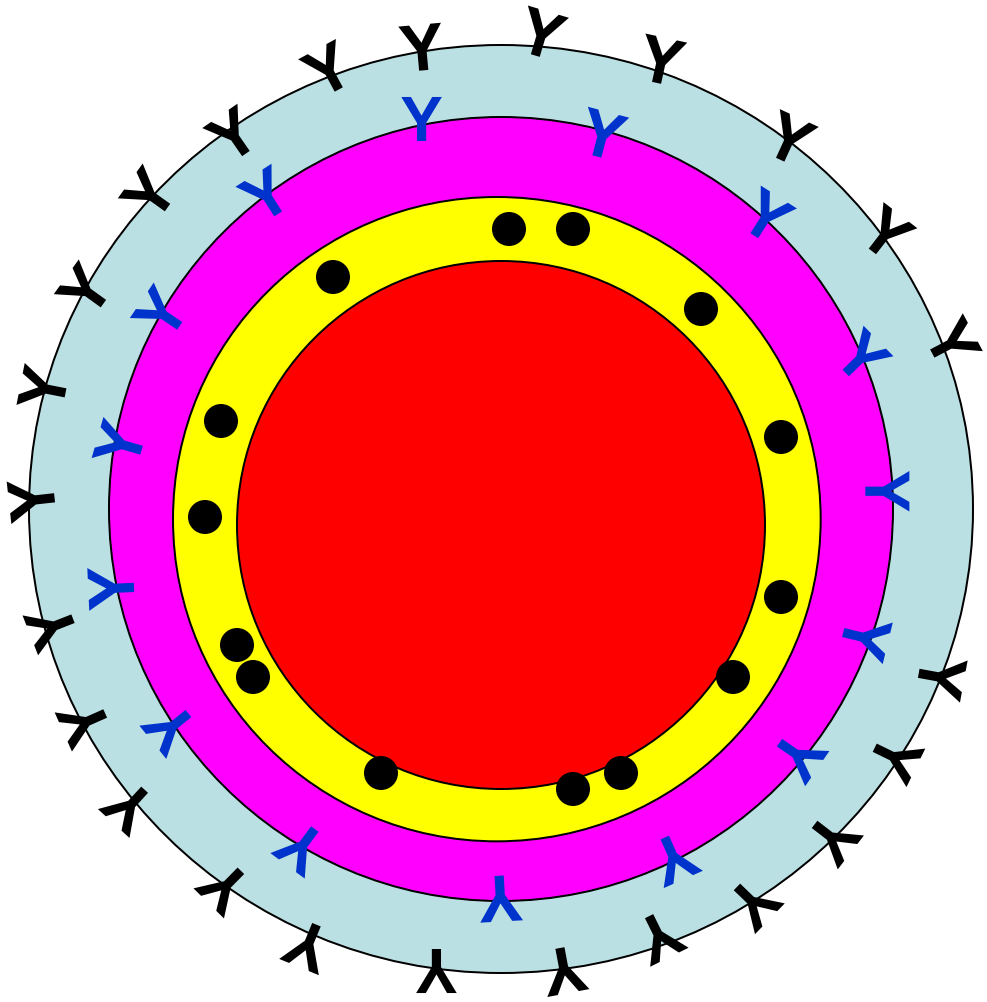
Therapeutic genes

Commonly used core materials include: gold, ferric oxide, silica, Qdots,

Biomolecular sensors (for error-checking and/or gene switch)

Targeting molecules (e.g. an antibody, an DNA, RNA or peptide sequence, a ligand, an aptamer), in proper combinations for more precise nanoparticle delivery

To use, de-layer nanoparticle one layer at a time



Cell targeting and entry

Intracellular targeting

Therapeutic genes

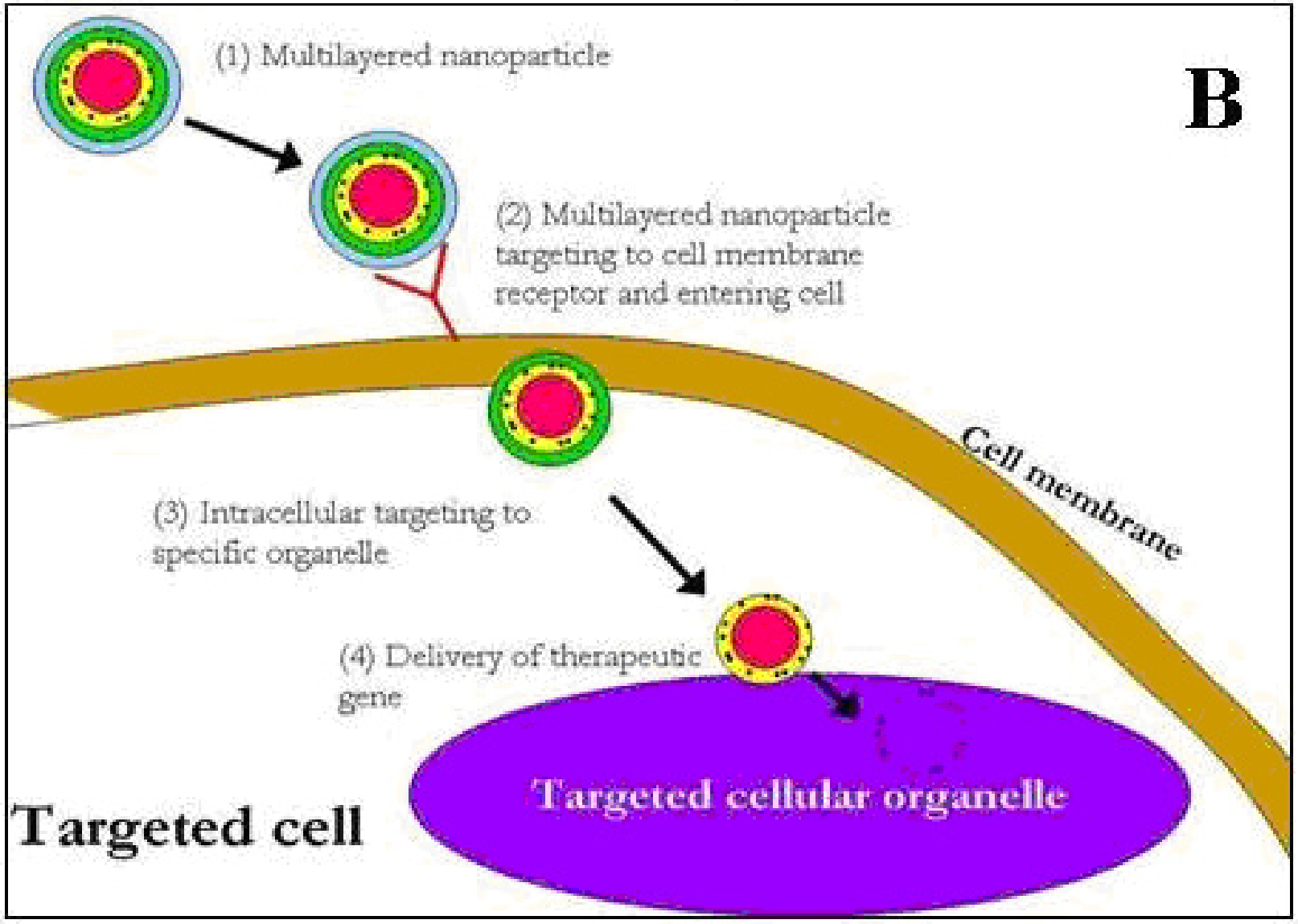
Magnetic or Qdot core (for MRI or optical imaging)

Biomolecular sensors (for error-checking and/or gene switch)

Targeting molecules (e.g. an antibody, an DNA, RNA or peptide sequence, a ligand, an aptamer), in proper combinations for more precise nanoparticle delivery

Leary and Prow, PCT (USA and Europe) Patent pending

The Multi-Step Drug/Gene Delivery Process in Nanomedical Systems



The Challenge

Optimal Drug Delivery to the Right Cells without the “Side Effects”

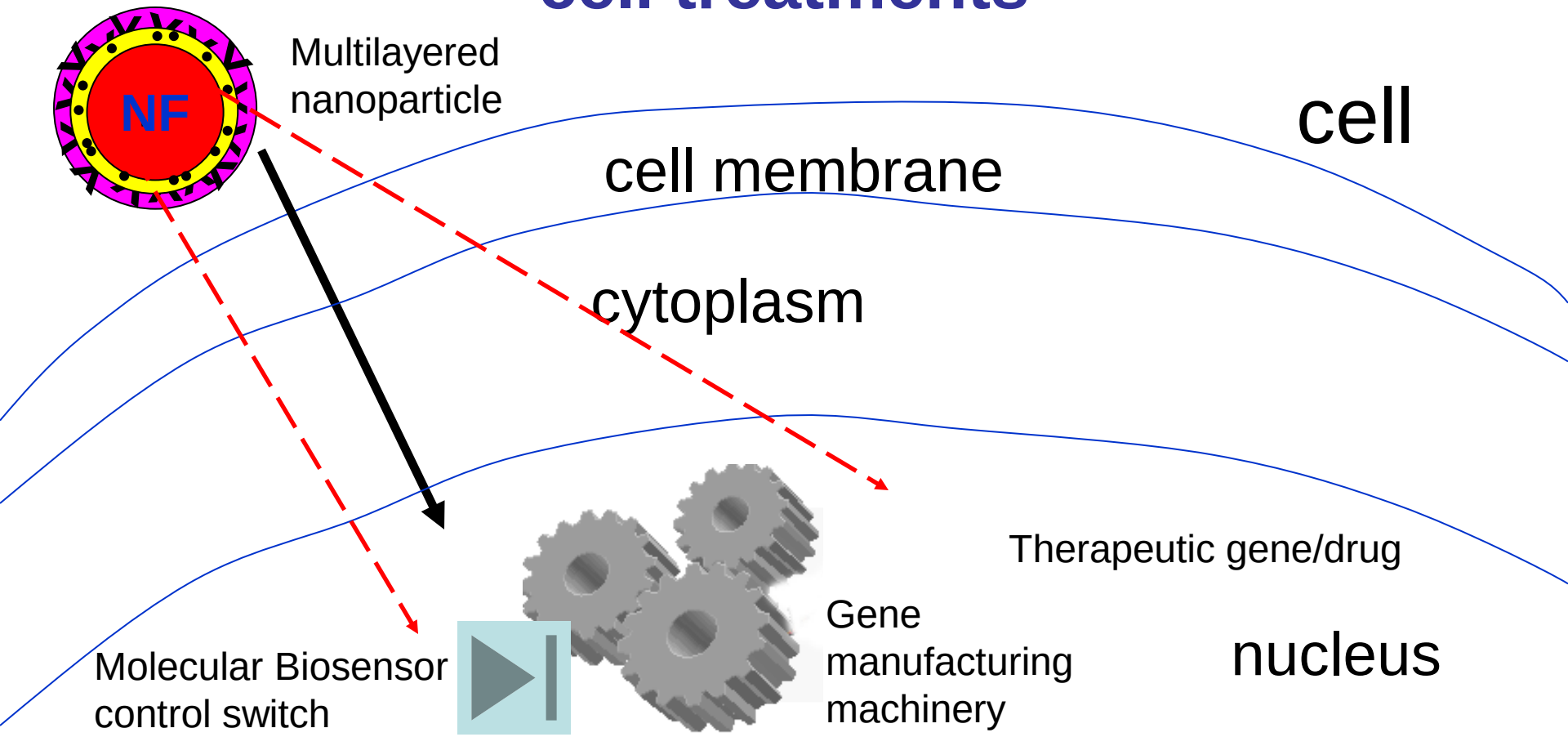
A very tough problem that has been grossly underestimated by most research groups!

One Solution to the Problem of Targeted Drug Delivery

"Nanofactories"

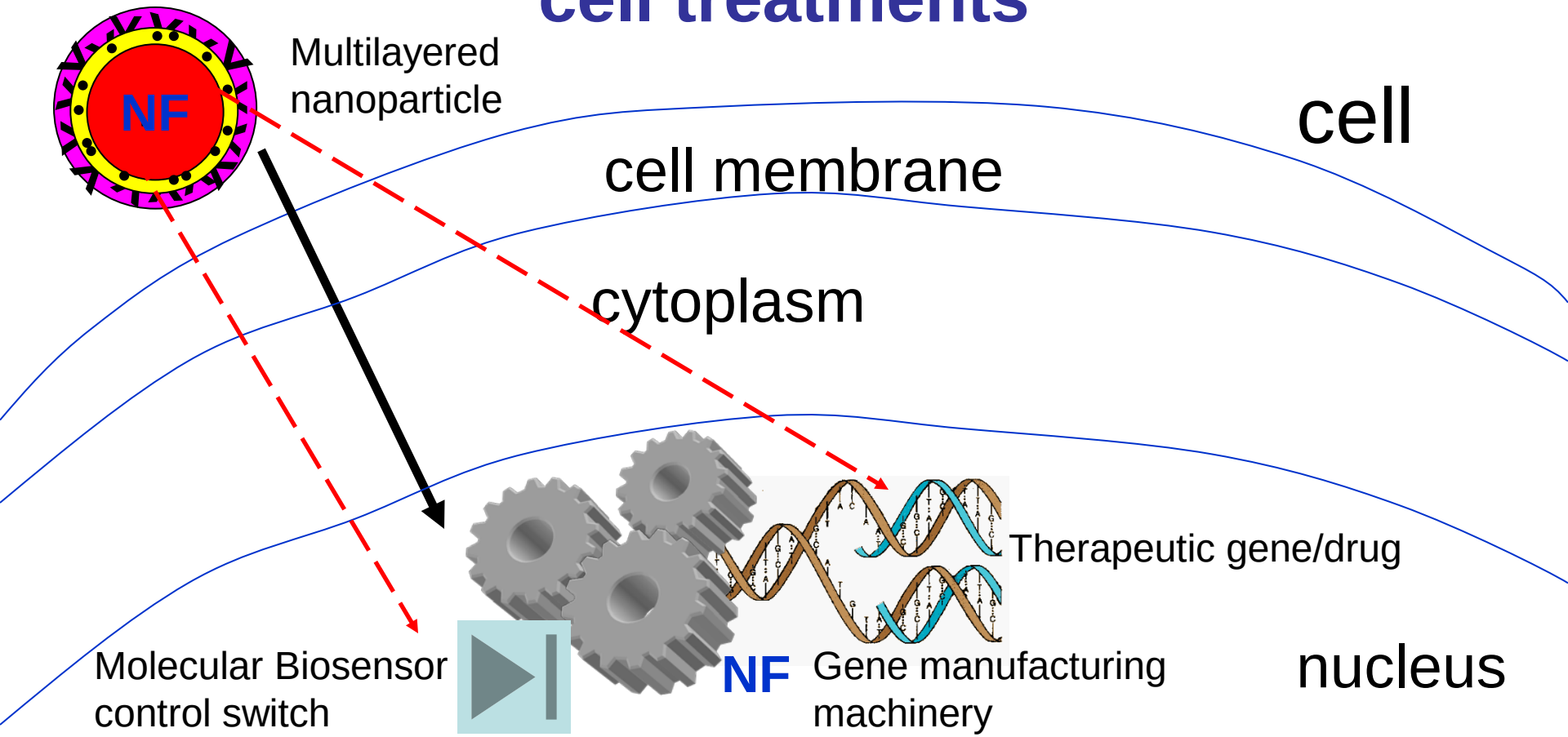
Don't try to guess the proper amount of drug for each cell. Manufacture it to the needs of that specific cell. With upstream biomolecular switches and feedback control, it doesn't matter how many nanoparticles are able to successfully target to a rare cell in-vivo. The total output of therapeutic genes from all targeted nanoparticles will self regulate to the proper dose for that cell.

Concept of nanoparticle-based "nanofactories" (NF) manufacturing therapeutic genes inside living cells for single cell treatments



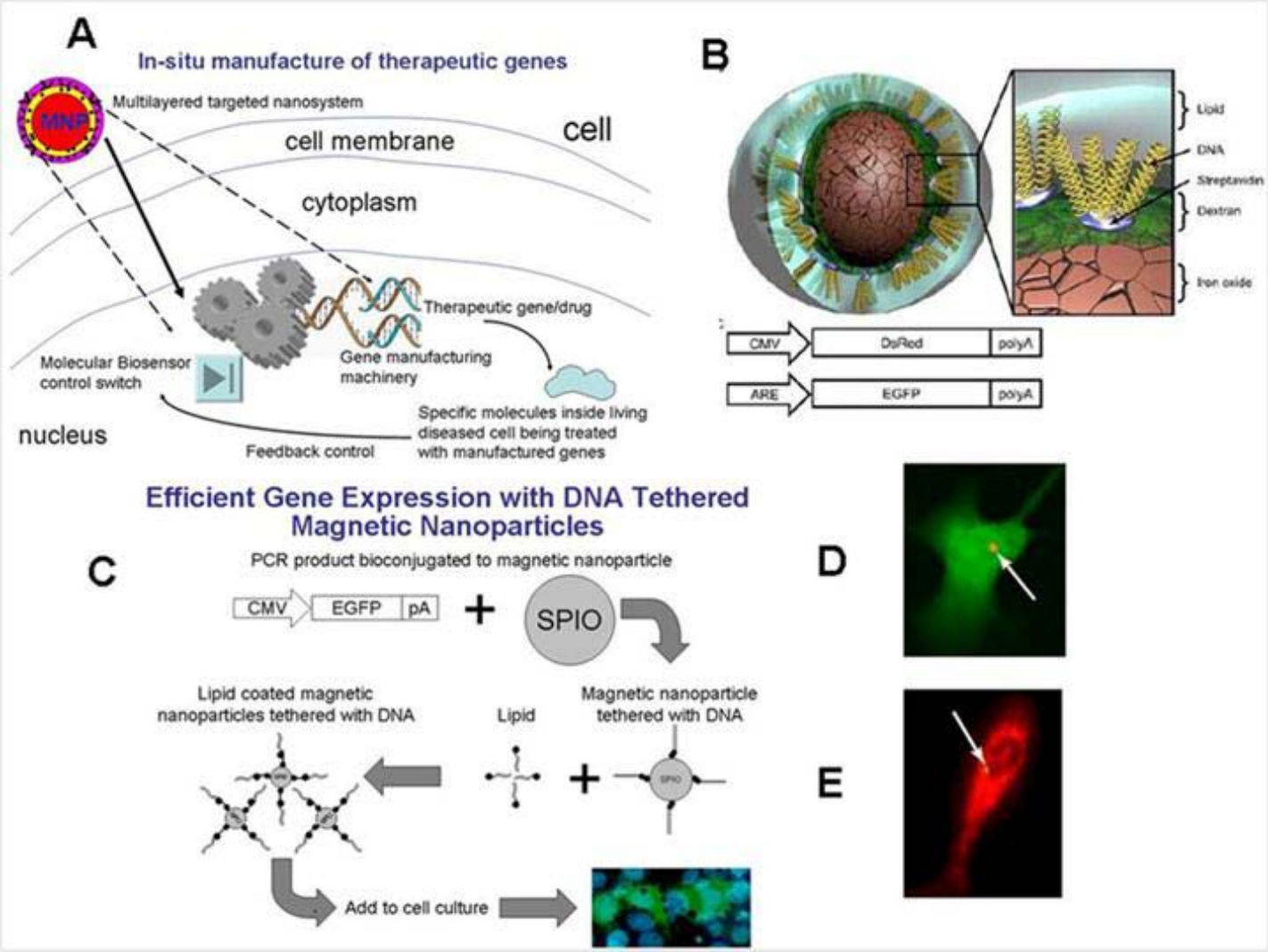
The nanoparticle delivery system delivers the therapeutic gene template which uses the host cell machinery and local materials to manufacture therapeutic gene sequences that are expressed under biosensor-controlled delivery.

Concept of nanoparticle-based "nanofactories" (NF) manufacturing therapeutic genes inside living cells for single cell treatments



The nanoparticle delivery system delivers the therapeutic gene template which uses the host cell machinery and local materials to manufacture therapeutic gene sequences that are expressed under biosensor-controlled delivery.

Example of in-situ manufacture of fluorescent reporter genes



Source: Zarbin, Montemagno, Leary, Ritch "Nanotechnology in Ophthalmology" Canadian Journal of Ophalmology (In Press)

Bridging the gap between diagnostics and therapeutics

A. How conventional medicine is practiced in terms of diagnostics and therapeutics

B. The consequences of separating diagnostics and therapeutics

C. A new approach – "theragnostics" (or "theranostics")

Life Sciences

French clinical diagnostics co. sets up Cambridge shop

Boston Business Journal - July 13, 2007

by Mark Hollmer

Thierry Bernard, a French life sciences executive, is betting Massachusetts will become a lucrative market for a budding life sciences sub-discipline known as theragnostics.

"Theragnostics," also spelled "theranostics," is an emerging field that blends the pharmaceutical industry with clinical diagnostics.

Sure, the word seems made up, even kind of New-Agey. But Bernard, senior executive vice president of commercial operations for bioMerieux SA, is serious about it -- serious enough to open a Kendall Square office for his company to focus on both strategic development and theragnostics programs for the French clinical diagnostics company.

Theragnostics involves coming up with a diagnostic system that tests possible side effects for a given drug, and then can lead to a personalized treatment for an individual that lacks side effects created by some mass market treatments.

It is an important concept in the bid to develop personalized medicine, treatments intended for a specific person's illness best suited for that individual.

http://boston.bizjournals.com/boston/stories/2007/07/16/newscolumn2.html

Examples of current “directed therapy” systems
(Early examples of theragnostic systems)

A. Example: Rituxan ("Rituximab”)
(for Non Hodgkins B-cell (CD20+) Lymphoma)

B. Example 1: Herceptin ("terastuzumab")
(25-30 percent of patients with metastatic breast cancer)

C. Example 2: Iressa ("Gefitinib”)
(patients with small cell lung cancer)

Drug-Test "Theragnostics" Combinations

Table 1. Combination of therapeutic drugs and diagnostic devices

Drug Name	Test Name	Details
Herceptin (Trastuzmab)	HercepTest	Immunohistochemical test is designed to identify metastatic breast cancer patients with overexpression of HER2 protein. HercepTest is used to select breast cancer patients who may benefit from treatment with Herceptin.
Camptosar (Irinotecan)	UTG1A1	UTG1A1 Molecular Assay detects variations in a gene that affects how certain drugs are broken down and cleared by the body. UTG1A1 is used to select colon cancer patients who may benefit from treatment with Camptosar.
Erbitux (Cetuximab)	EGFR Pharma Dx kit	EGFR kit helps the detection of colorectal cancer patients who may benefit from the treatment with Erbitux, which is a monoclonal antibody that targets a protein called the epidermal growth factor receptor (EGFR).
Gleevec (Imatinib)	c-kit	c-kit helps to detect the presence of the c-kit protein in gastrointestinal stromal tumor (GIST). C-kit helps in detecting patients who may benefit from treatment with Gleevec.
Tarceva (Erlotinib)	EGFR pharma Dx kit	EGFR kit helps the detection of non-small cell lung cancer patients who may benefit from the treatment with Tarceva, which is an EGFR inhibitor.
Purinethol (mercatopurine)	TPMT	Patients with inherited little or no thiopurine S-methyltransferase (TPMT) activity are at increased risk for severe PURINETHOL toxicity from conventional doses of mercaptopurine and generally require substantial dose reduction.
Various drugs	AmpliChip CYP 450	AmpliChip test demonstrates if the patient has mutations in a gene that is active in metabolizing many types of drugs, including beta-blockers, antidepressants, antipsychotics, and some chemotherapy drugs.

Ref: Ahn, 2007

How theragnostics relates to Molecular Imaging

A. Conventional imaging is not very specific

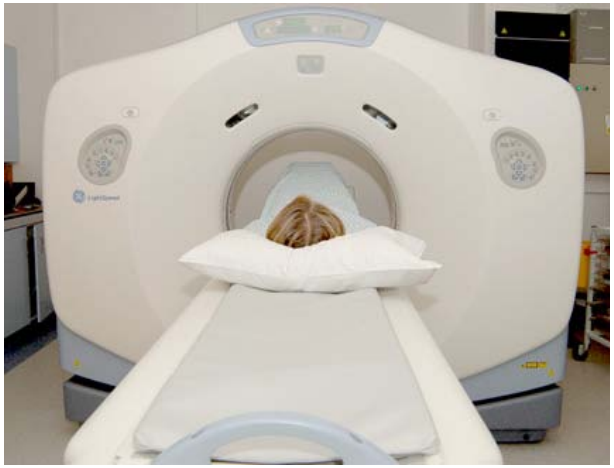
B. Types of In-vivo Imaging
   1. X-rays, CAT (Computed Axial Tomography) scans,
   2. MRI (magnetic Resonance Imaging)
   3. PET (Positron Emission Tomography) scans
   4. In-vivo Optical Imaging

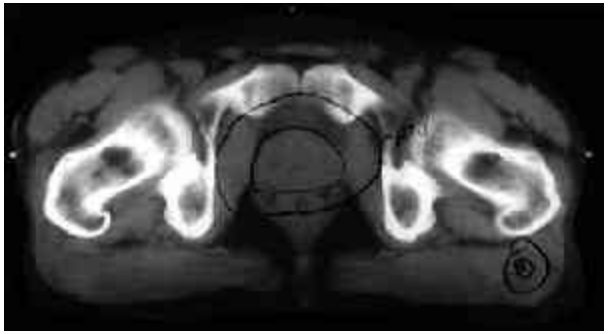
C. "Molecular Imaging"

Types of In-vivo Imaging
1. X-rays

Conventional X-rays (simple, inexpensive)

CAT (Computed Axial Tomography) scans (not simple, more powerful, expensive)

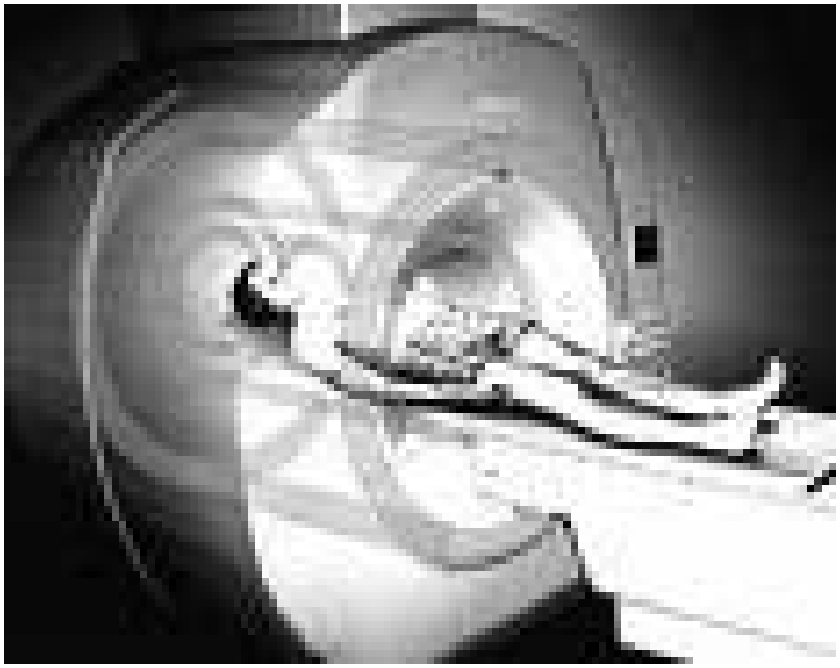


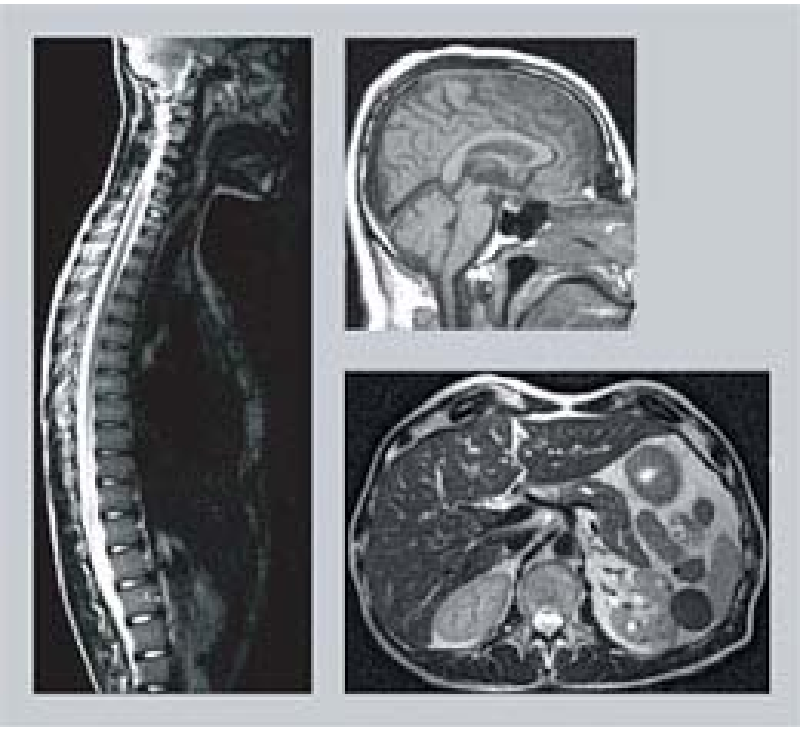


http://www.cancerhelp.org.uk/help/default.asp?page=148

Types of In-vivo Imaging

2. MRI (Magnetic Resonance Imaging)



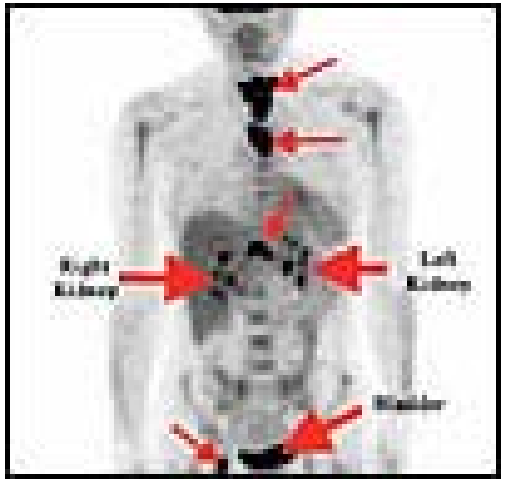


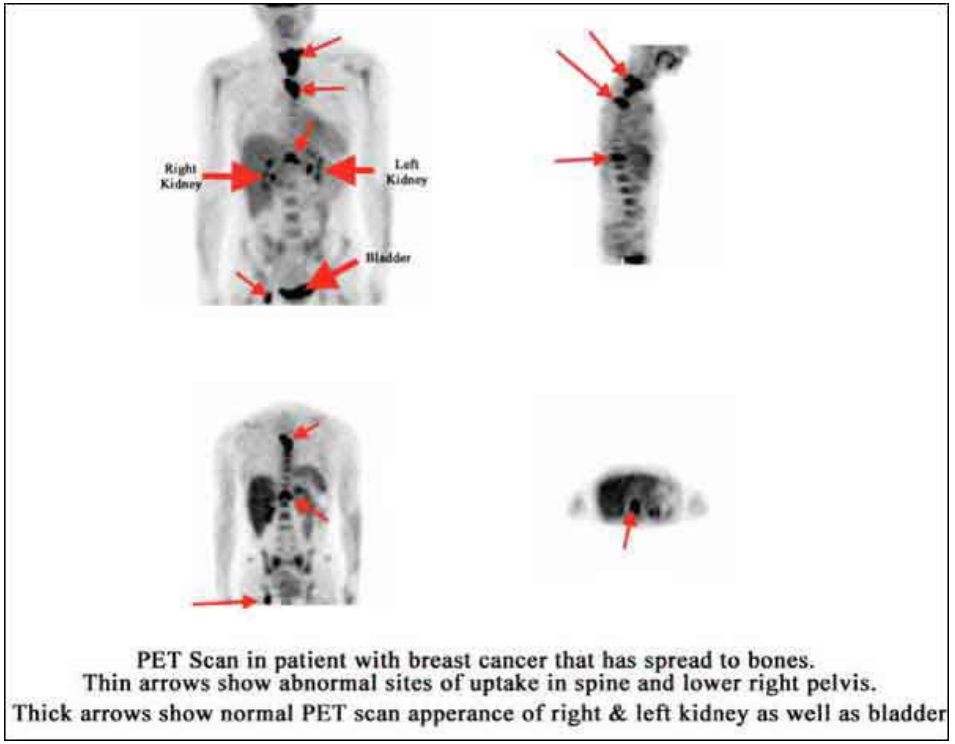
http://nobelprize.org/nobel_prizes/medicine/laureates/2003/press.html

Types of In-vivo Imaging

3. PET (Positron Emission Tomography) scans

Siemen's Petscanner
https://www.smed.com/petct/?gclid=CLf75_LanY4CFRUHWAodsmfYZg



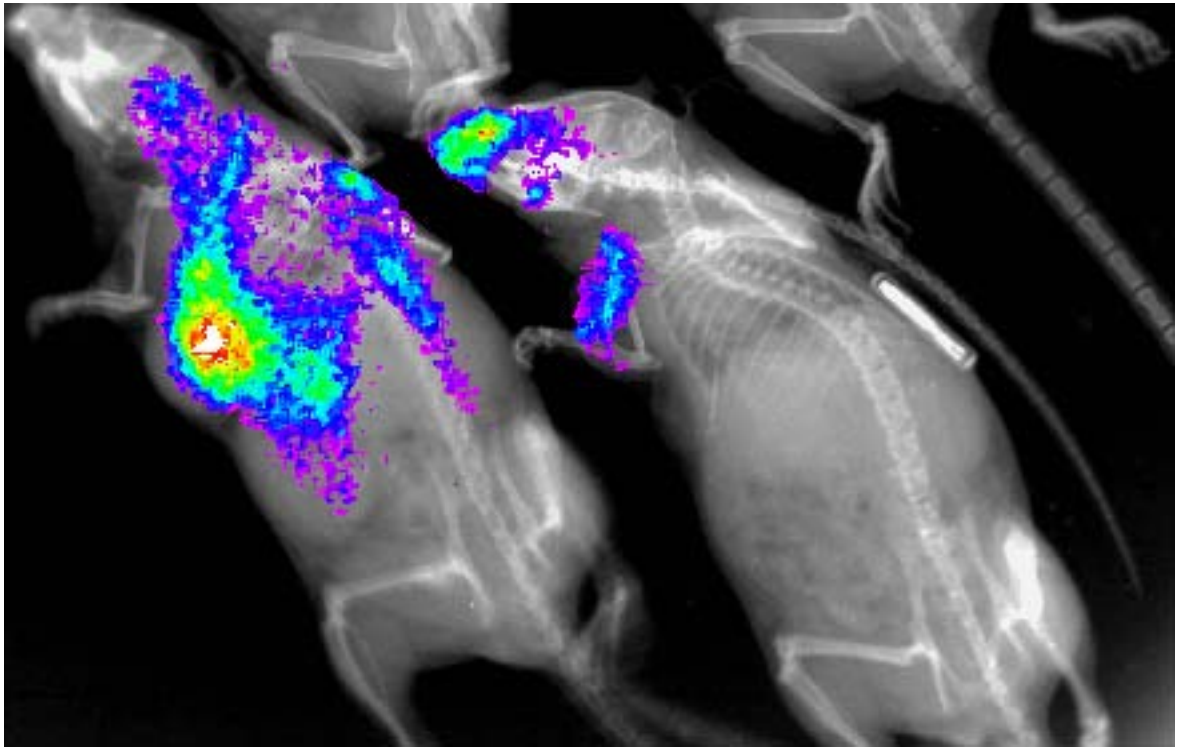


PET Scan in patient with breast cancer that has spread to bones.
Thin arrows show abnormal sites of uptake in spine and lower right pelvis.
Thick arrows show normal PET scan apperance of right & left kidney as well as bladder

http://www.breastcancer.org/pictures/diagnosis/pet_scan/cancer_bones.jsp

Types of In-vivo Imaging

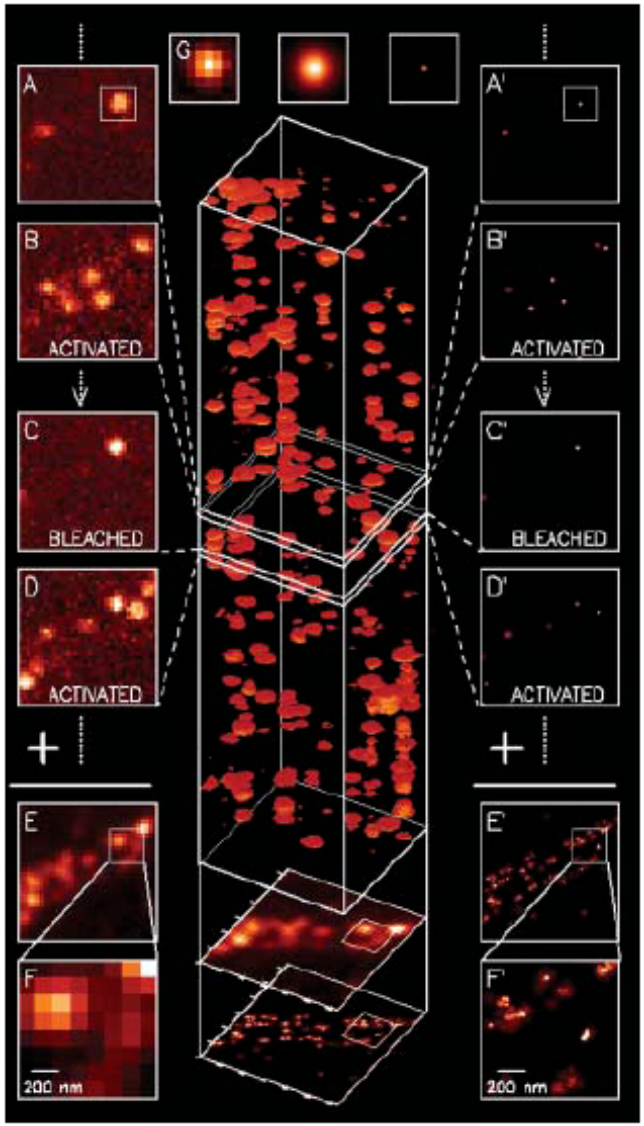
4. In-vivo Optical Imaging



KODAK In-Vivo Imaging Systems FX and F

http://www.kodak.com/US/en/health/s2/products/imgStationXRayImagingModule/index.jhtml

Molecular Imaging on the Nanoscale



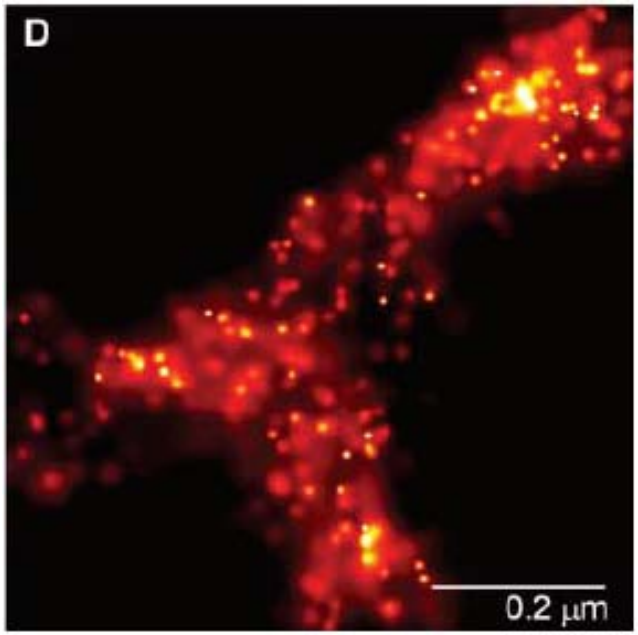


Figure 2D: Tissue distribution of CD63 in lysosomal membrane protein molecules

Fig. 1. The principle behind PALM. A sparse subset of PA-FP molecules that are attached to proteins of interest and then fixed within a cell are activated (A and B) with a brief laser pulse at lact 0 405 mm and then imaged at lexc 0 561 mm until most are bleached (C). This process is repeated many times (C and D) until the population of inactivated, unbleached molecules is depleted. Summing the molecular images across all frames results in a diffraction-limited image (E and F). However, if the location of each molecule is first determined by fitting the expected molecular image given by the PSF of the microscope [(G), center] to the actual molecular image [(G), left], the molecule can be plotted [(G), right] as a Gaussian that has a standard deviation equal to the uncertainty sx,y in the fitted position. Repeating with all molecules across all frames (A¶ through D¶) and summing the results yields a superresolution image (E¶ and F¶) in which resolution is dictated by the uncertainties sx,y as well as by the density of localized molecules. Scale: 1 1 mm in (F) and (F¶), 4 4 mm elsewhere.

Ref: Betzig et al., Science , 2006

Engineering nanomedical systems for simultaneous molecular imaging

A. Using nanomedical systems cores for MRI contrast agents

B. Difficulties in using PET probes for nanomedical devices (short lifetimes!)

C. Using cell-specific probes for molecular imaging of nanomedical devices

Theragnostic nanomedical devices

A. Using nanomedical devices separately to guide choice of therapeutic drug/gene

B. Using nanomedical devices to localize and choose/not choose treatment based on what it sees with biomolecular sensors

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