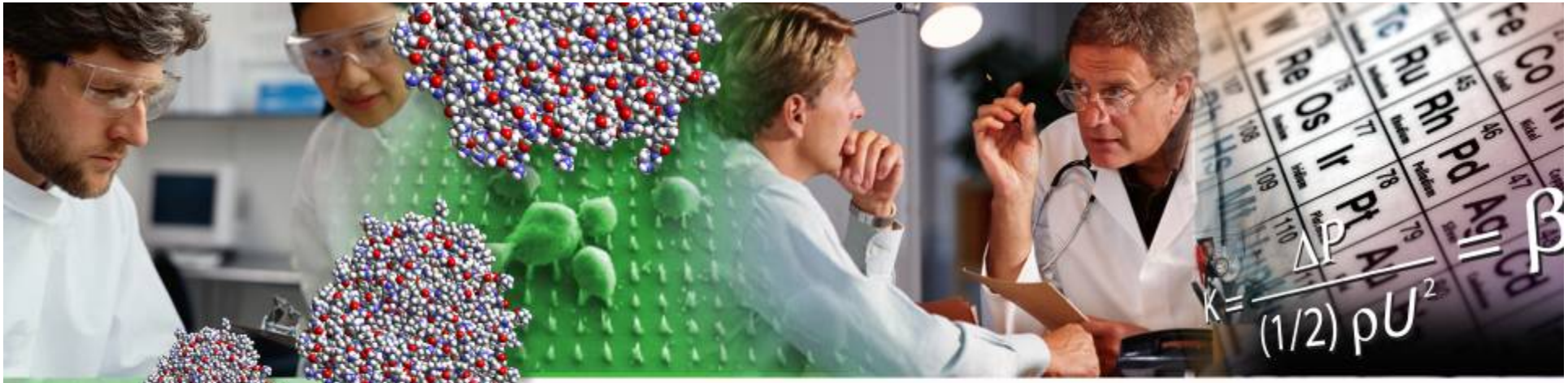


NATIONAL INSTITUTES OF HEALTH

NATIONAL CANCER INSTITUTE

NCI Alliance for Nanotechnology in Cancer

Driving the Future of Biomedical Applications with Nanoelectronics

Larry Nagahara, Ph.D.

Nanotechnology Projects Manager

National Cancer Institute

Arizona Institute for Nanoelectronics Kickoff Meeting

April 4, 2008

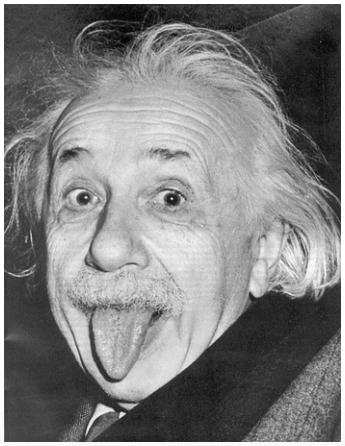
Presentation Outline

NCI Alliance for Nanotechnology in Cancer

"In the middle of difficulty lies great opportunity"

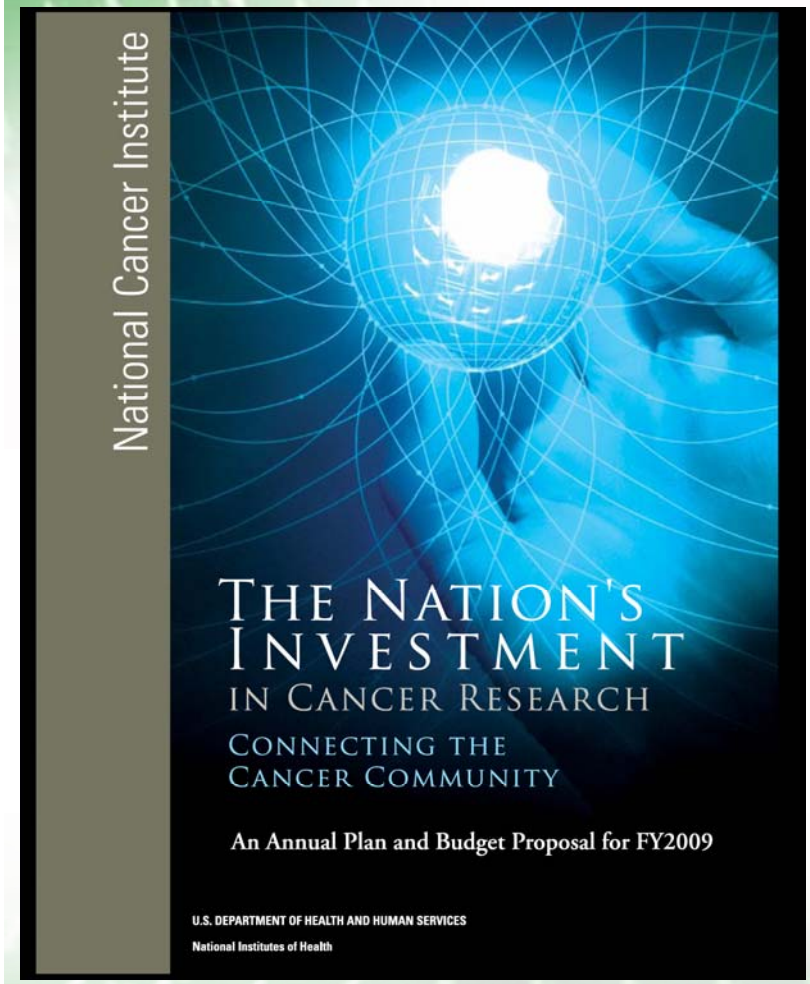
– Albert Einstein

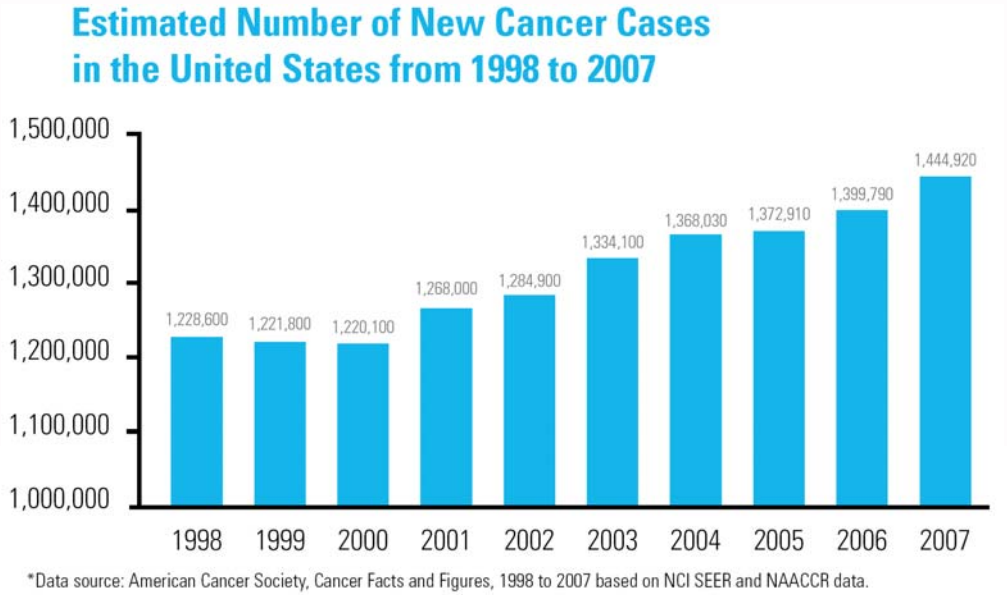
- **Biomedical Community Trends**
  - **Healthcare Cost**
  - **Big Pharma's Dilemma**
  - **Personalize Medicine**
- **Niches for Nanotechnology**
  - **Oncologist's Wish List**
  - **Diagnostic, Imaging, & Therapy**
  - **Biospecimen Challenge**



The Human and Economic Burden of Cancer

NCI Alliance for Nanotechnology in Cancer



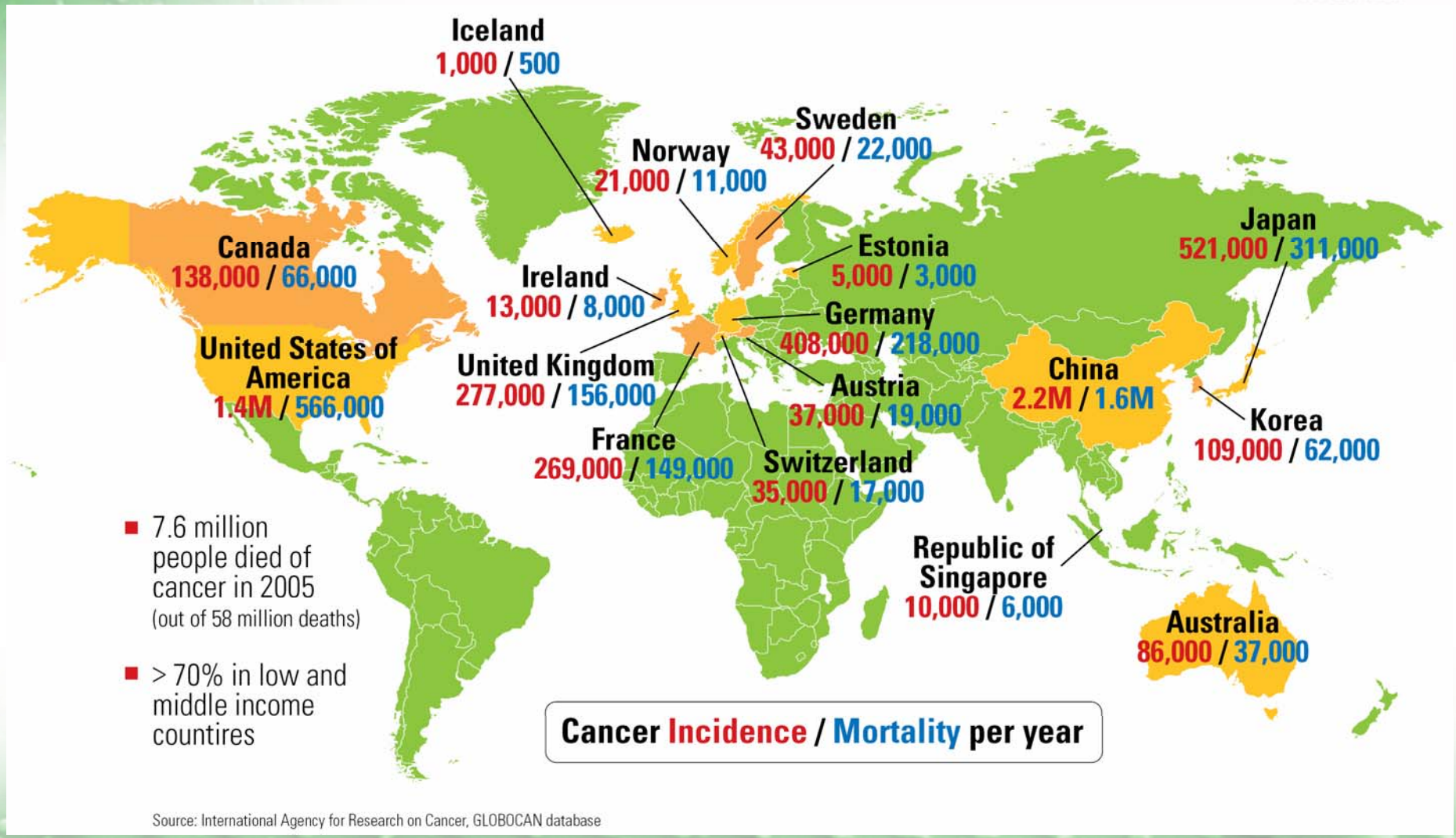


*Data source: American Cancer Society, Cancer Facts and Figures, 1998 to 2007 based on NCI SEER and NAACCR data.

- ***1,444,920 Americans were diagnosed with cancer in 2007***
- ***559,650 Americans died of cancer in 2007***
- ***$206.3 billion was spent on healthcare cost for cancer in 2006***

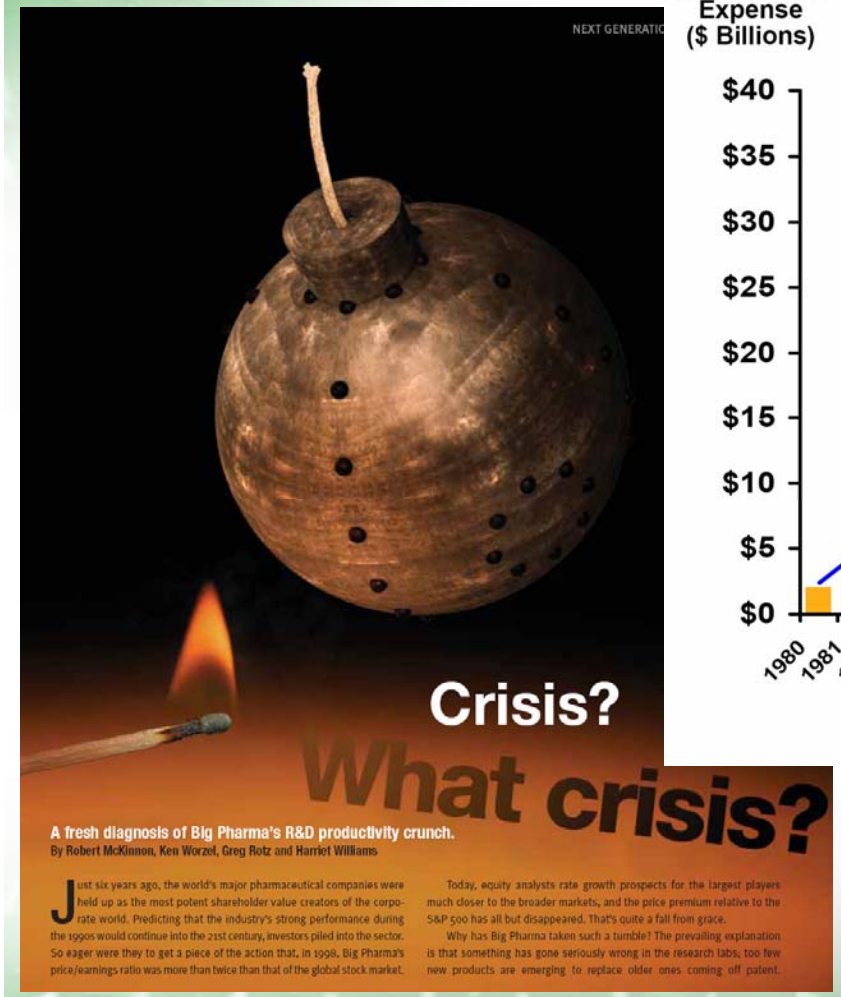
Global Cancer Incidence and Mortality

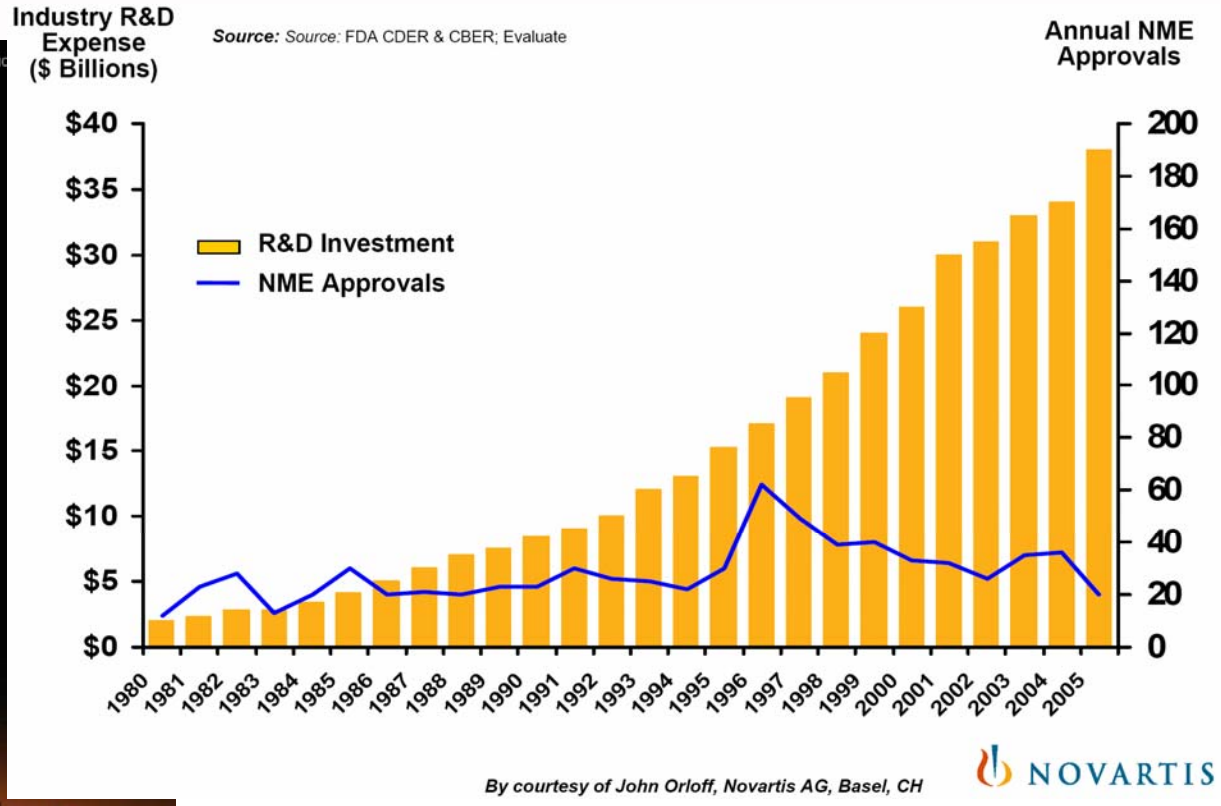
NCI Alliance for Nanotechnology in Cancer



Big Pharma's Dilemma

NCI Alliance for Nanotechnology in Cancer



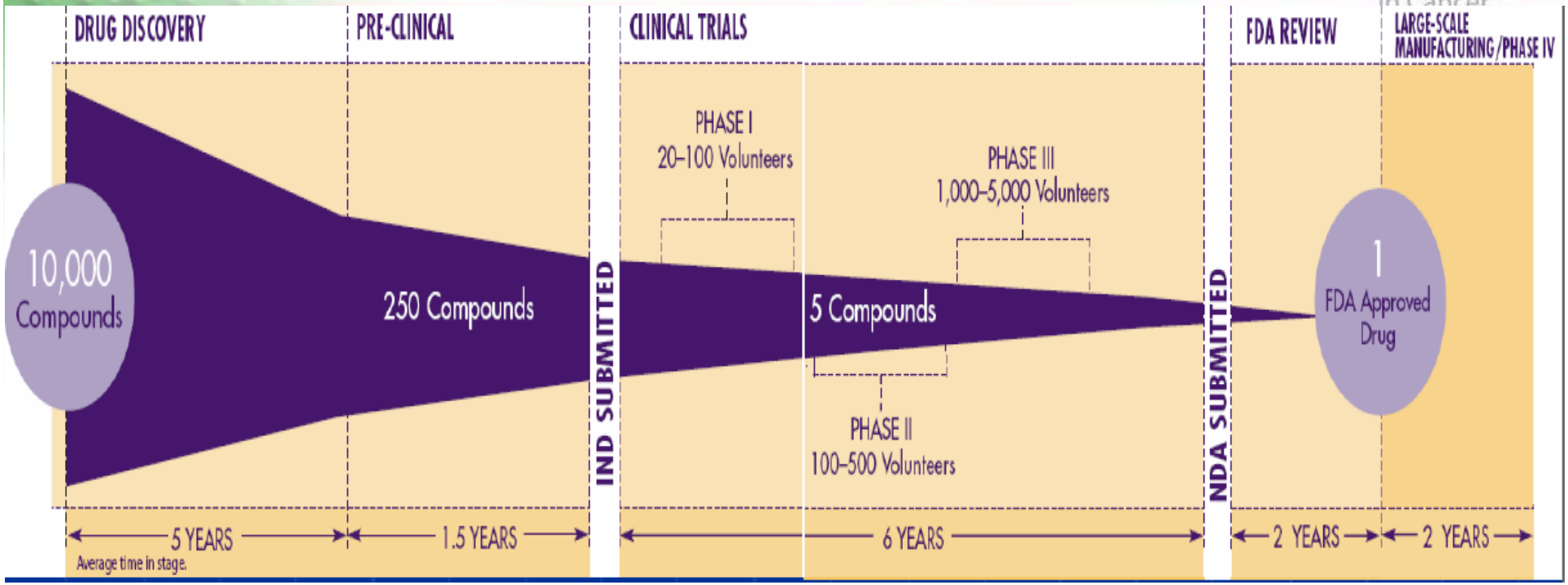


By courtesy of John Orloff, Novartis AG, Basel, CH

NOVARTIS

Time is Really Mucho Dinero

NCI Alliance for Nanotechnology in Cancer



Trend:

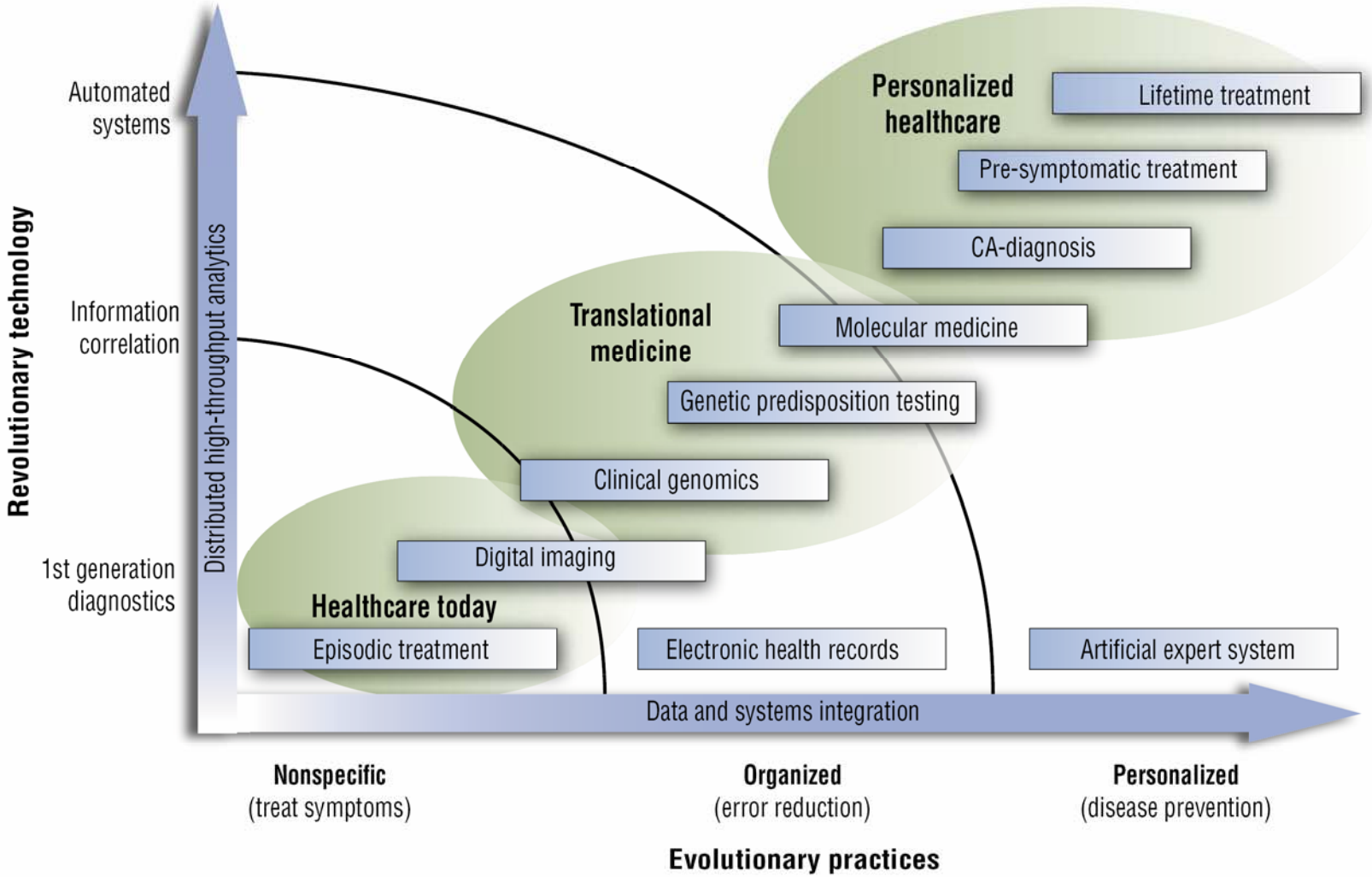
More patients and clinical trials required per NDA

(Development time by Pharma increasing)

(Development cost by Pharma increasing)

Healthcare Trend

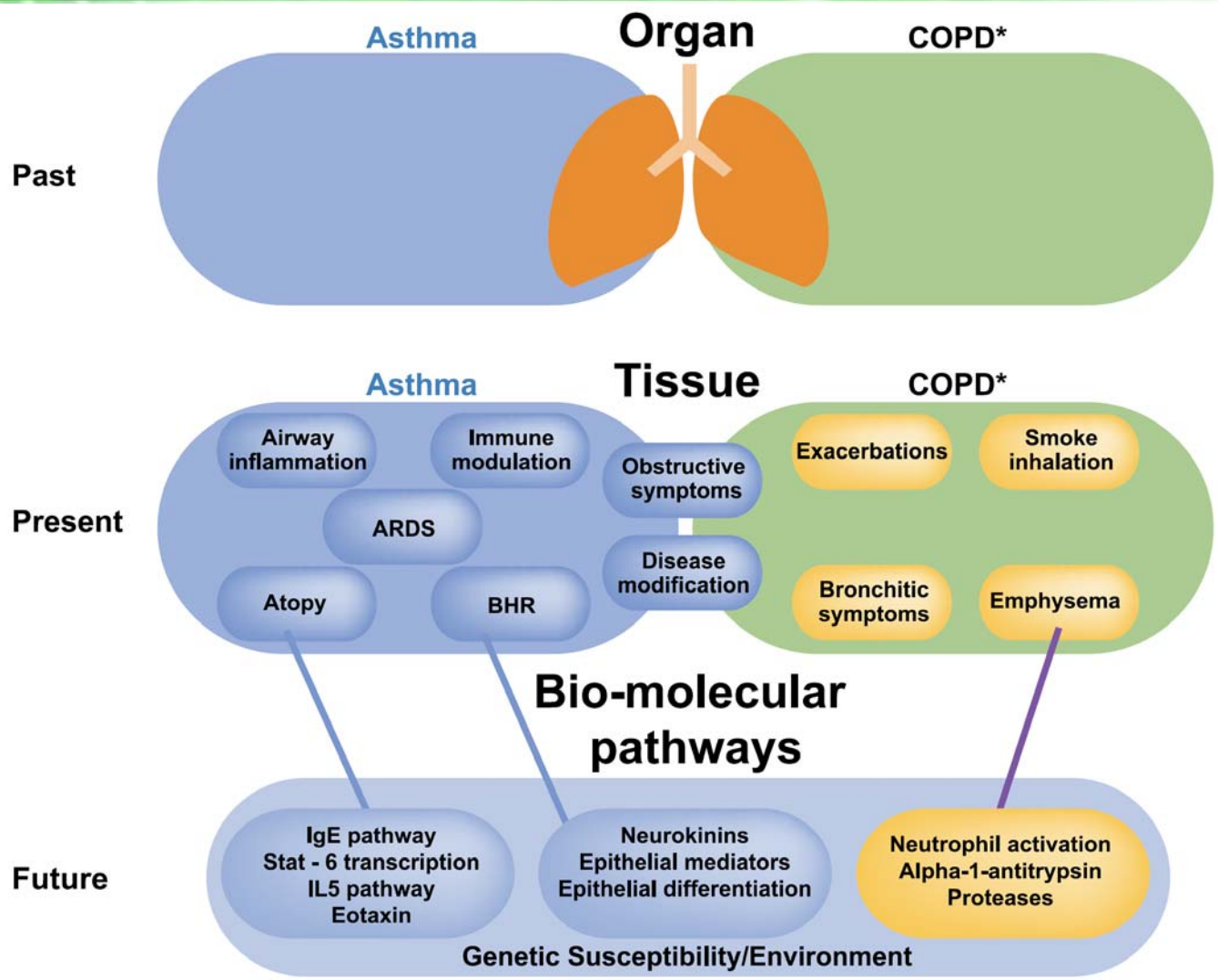
NCI Alliance for Nanotechnology in Cancer



Source: IBM Life Sciences Solutions

From Organs to Pathways

NCI Alliance for Nanotechnology Cancer



*Chronic Obstructive Pulmonary Disease

Oncologist's Imaging Wish List …

NCI Alliance for Nanotechnology in Cancer

NCI Alliance for Nanotechnology in Cancer

National Cancer Institute
National Institutes of Health
U.S. Department of Health and Human Services

Strategic Workshop on Cancer Nanotechnology:
In-vivo Diagnosis and Imaging

March 28, 2008

Bethesda Marriott
Bethesda, Maryland

Jim Olson M.D., Ph.D.
Fred Hutchinson Cancer Research Center
Seattle Children's Hospital

1) ***Early detection***
2) ***Diagnose tumor type***
3) ***Define all metastases***
4) ***Illuminate tumor intraoperatively***
5) ***Nodes & mets too***
6) ***Show therapy delivery***
7) ***Show therapy response***
8) ***Identify resistance emergence***

We Must Accelerate Progress Against Cancer: Early Diagnostics Is Key

NCI Alliance for Nanotechnology in Cancer

Early Diagnostics Is Key

Site	All stages	Local	Regional	Distant
Breast (female)	86.6	97.0	78.7	23.3
Colon and rectum	62.3	90.1	65.5	9.2
Liver	6.9	16.3	6.0	1.9
Lung and bronchus	14.9	48.7	16.0	2.1
Melanoma	89.6	96.7	60.1	13.8
Ovary	53.0	94.7	72.0	30.7
Pancreas	4.4	16.6	6.8	1.6
Prostate	97.5	100.0	--	34.0
Testis	95.5	99.1	95.0	73.1

Source: American Cancer Society

Disease Management

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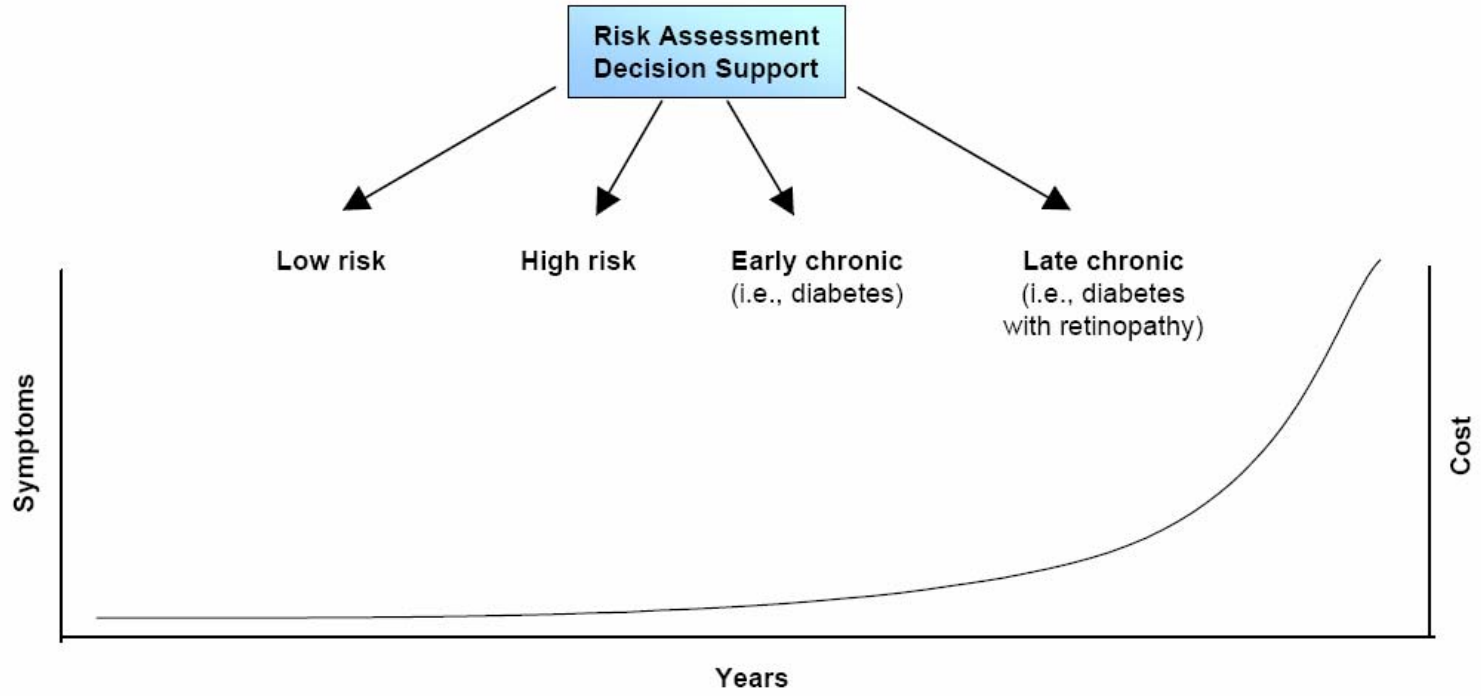
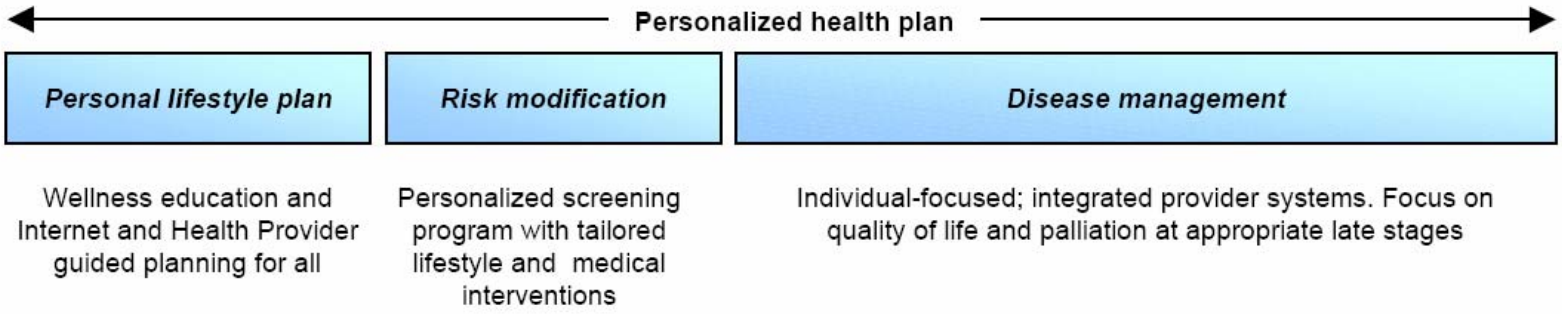


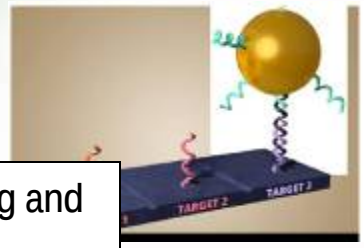


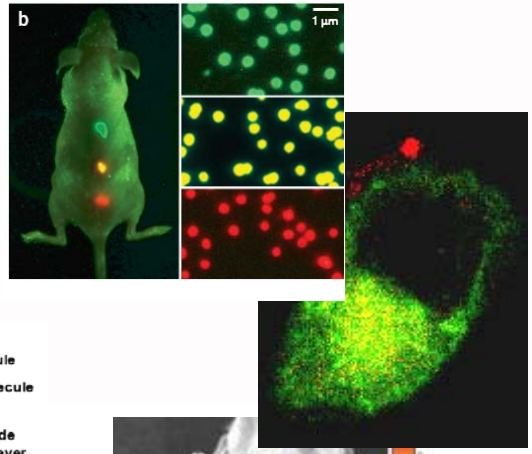
Nanotechnology is an Enabler of New Solutions for Cancer

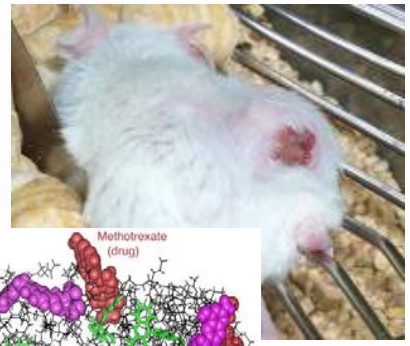
NCI Alliance for Nanotechnology in Cancer

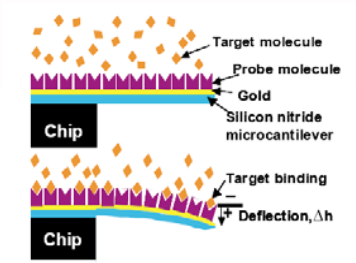
Focus Areas:

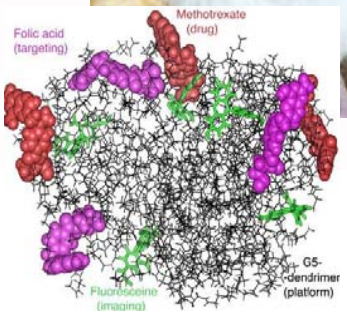
- Molecular imaging and early detection
- In vivo imaging
- Reporters of efficacy
- Multifunctional therapeutics
- Prevention and control
- Research enablers

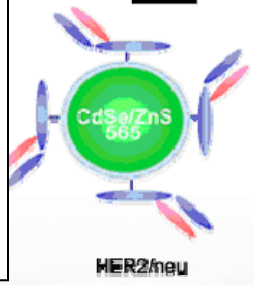


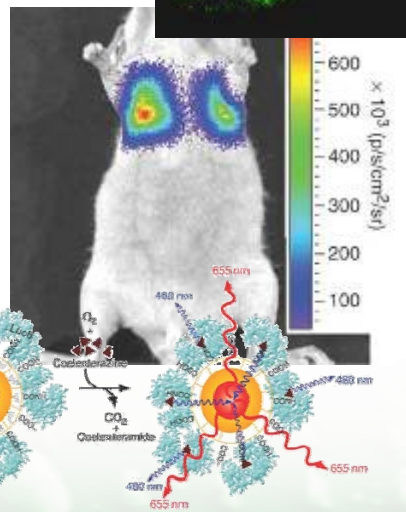


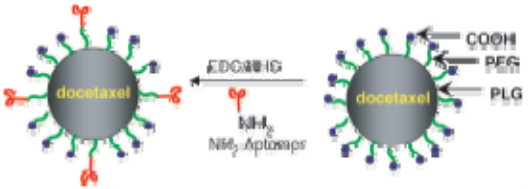












Early detection | Imaging | Therapy

Overview of Project: Magneto-Nano Chips, Magnetic Sifter/Sorter, and Multifunctional Nanoprobes

Objective:

• Quantitative, portable, inexpensive, and high throughput detection of trace amounts of protein tumor markers and relevant protein profiles present in serum or tissue for the determination of appropriate therapies and to follow treatment efficacy.

• Pre-purification and concentration of serum derived analytes with a magnetic sifter and/or multiplexed magnetic sorter.

• Multifunctional nanoprobes (spin-off)

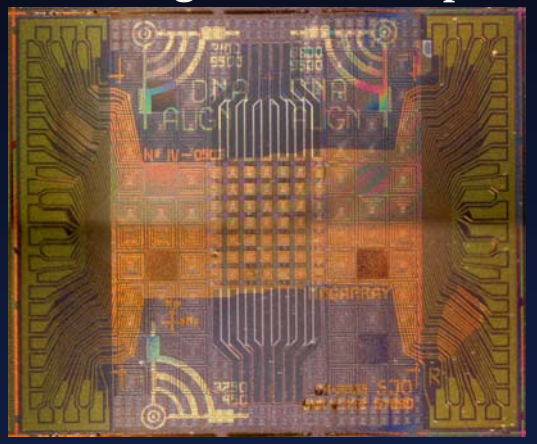
Approach:

• Protein targets are selectively bound to a magneto-nano chip using specific probes above a spin valve sensor

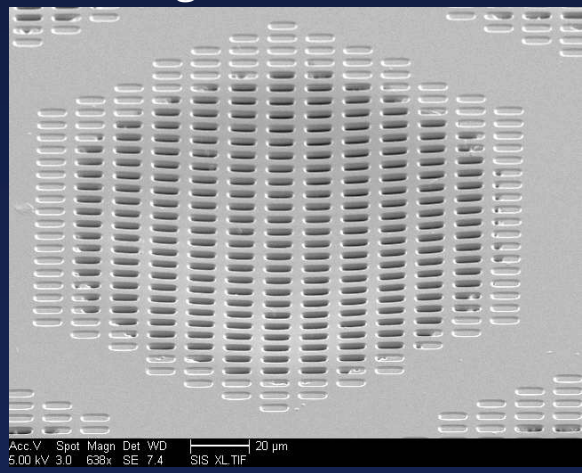
• “Staining” protein targets with magnetic nanotags (~10-100 nm), which are then read out electronically

• The same magnetic nanotags are also exploited for magnetic sample preparation and sorting

Magneto-nano chip



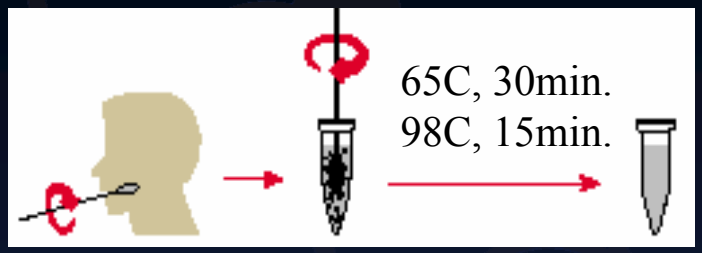
Magnetic sifter/sorter



CCNE-TR

DNA Assay

DNA Sample Preparation

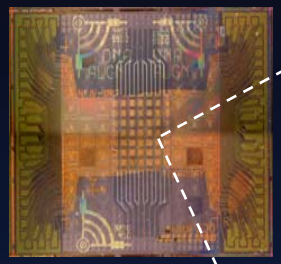


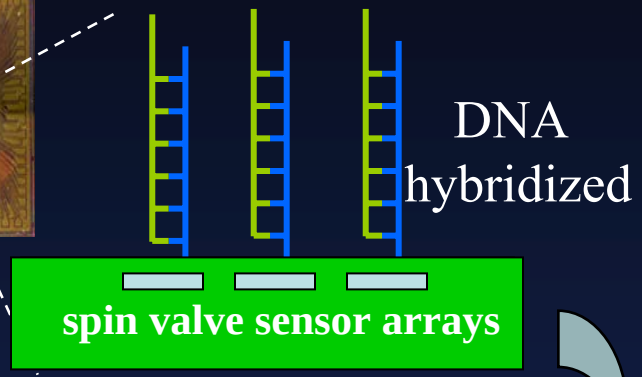
Buccal swab (or Plasma)

QuickExtract™

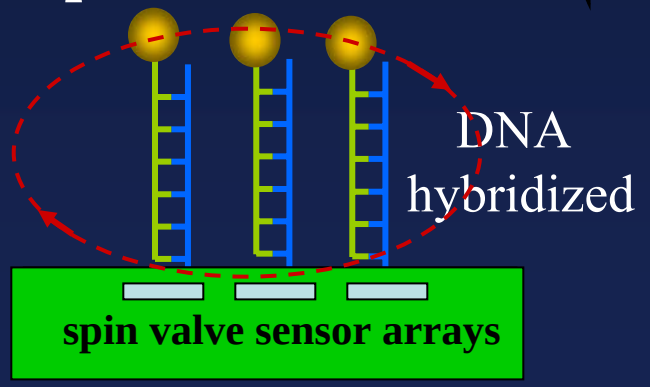
DNA sample

Hybridization Capture of ss-DNA w/ Magnetic Biochip

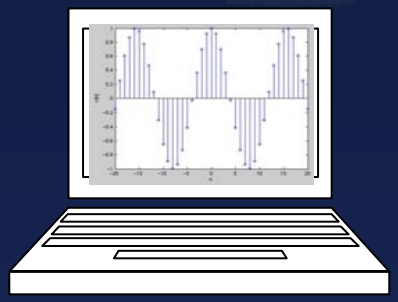




Nanotag Labeling of Captured ss-DNA



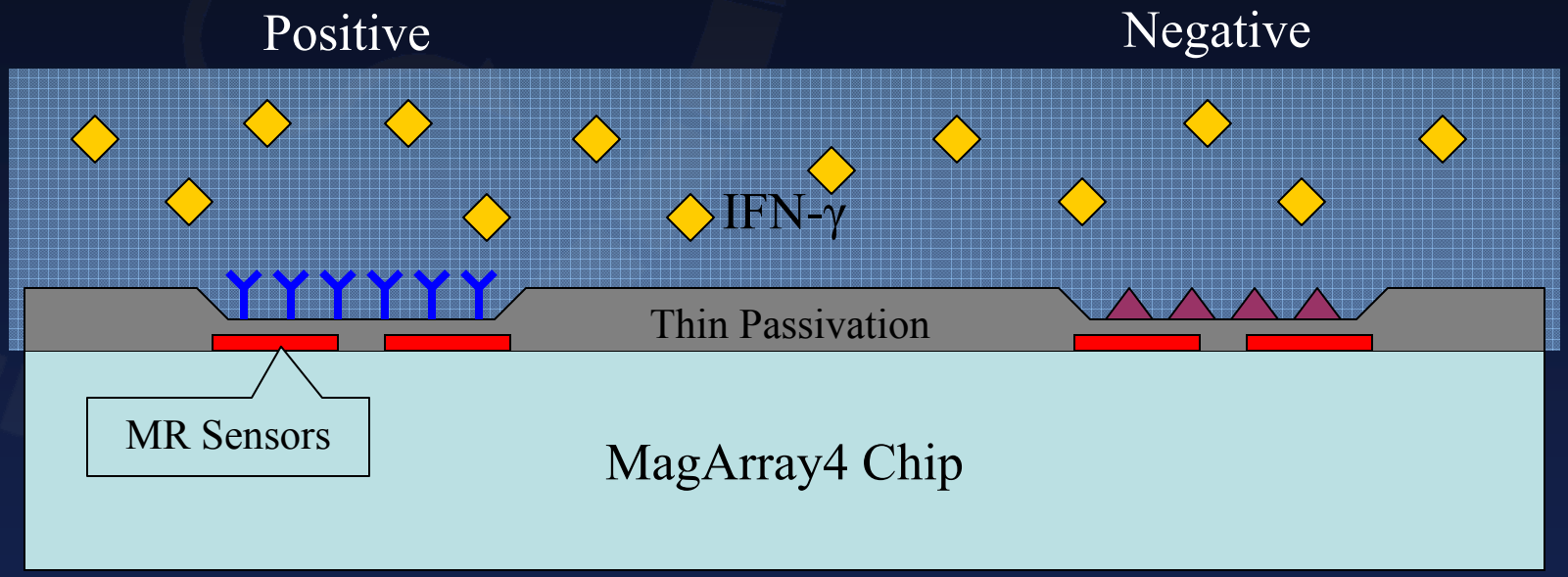
Electronic Readout



(Laptop)

Protein Assay: IFN-γ as Model Analyte

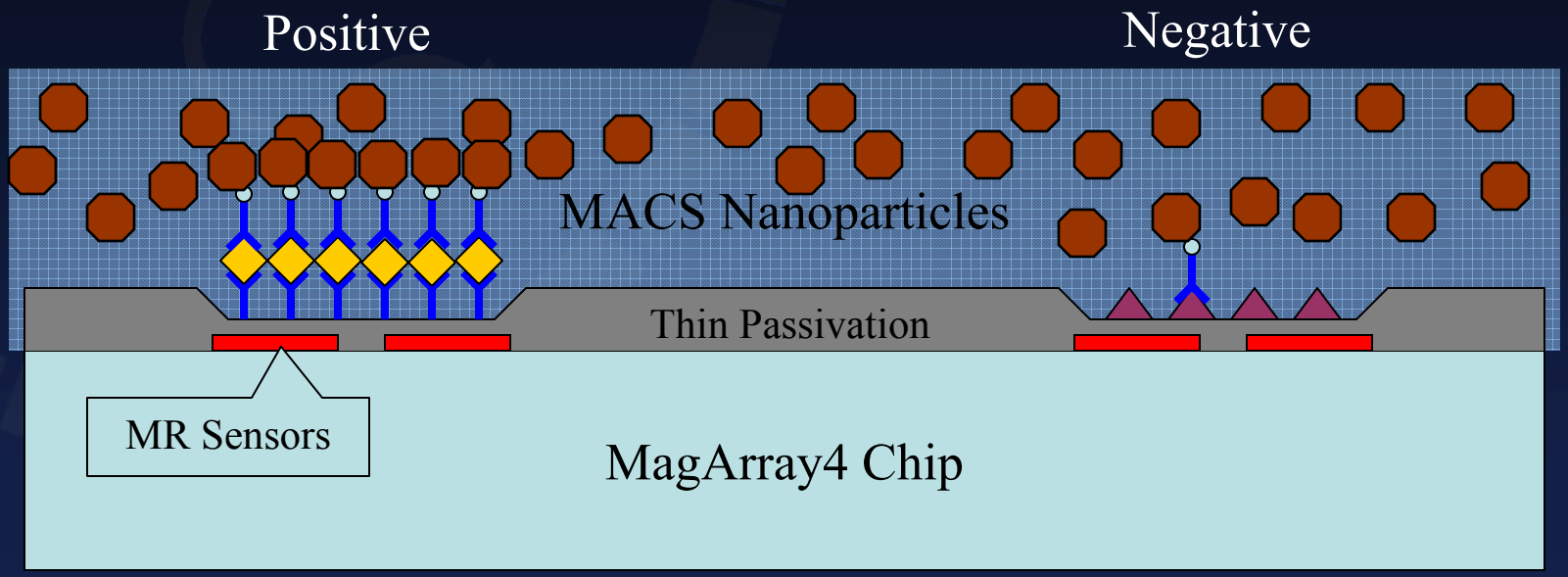
Step 2: Antigen Capture



Osterfeld and Wang, book chapter submitted,
Journal paper in preparation.

Protein Assay: IFN-γ as Model Analyte

Step 4: Live Measurement During Nanoparticle Capture

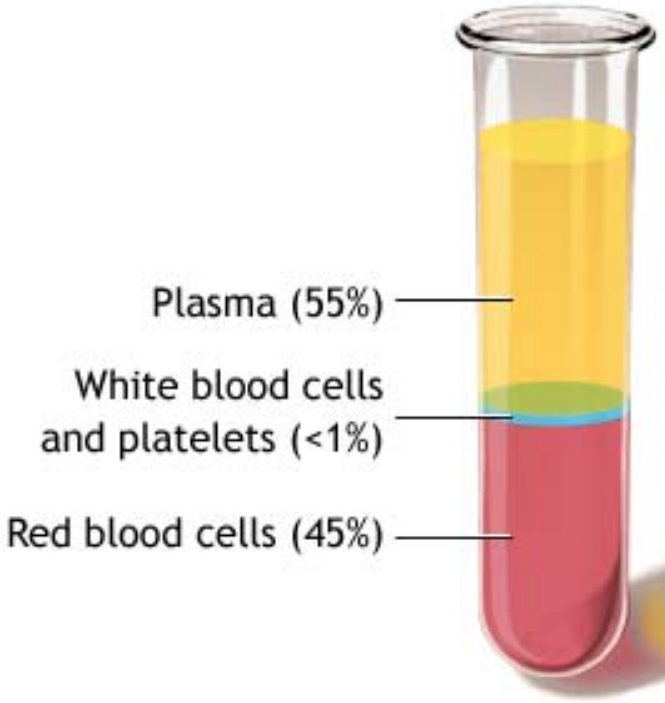


Osterfeld and Wang, book chapter submitted,
Journal paper in preparation.

Blood Chemistry 101: What's in this stuff?

NCI Alliance for Nanotechnology in Cancer

Human body contains ~5 liters of blood



Plasma [= Serum + Clotting Factors]

91% Water

7% Blood Proteins (fibrinogens, albumin, globulin)

2% Nutrients (amino acids, sugars, lipids)

Hormones (erythropoietin, insulin, etc.)

Electrolytes (sodium, potassium, calcium, etc)

Note: This in not nM, µM or mM!!!

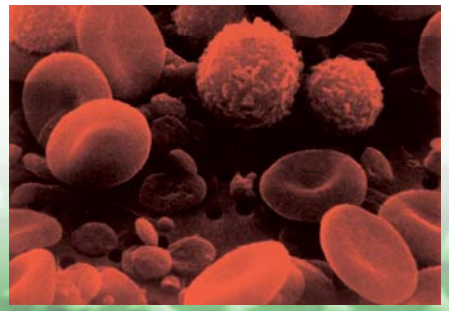
Buffy Coat

White Blood Cells (~7,000,000 – 9,000,000 per cc of blood)

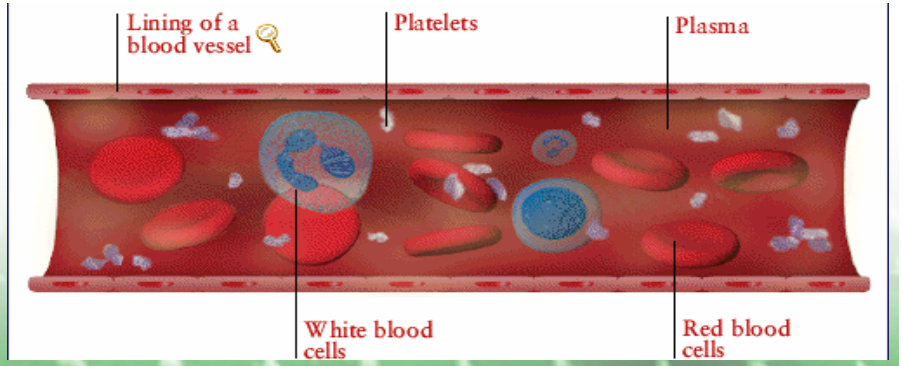
Platelets (~150,000,000 – 350,000,000 per cc of blood)

Red Blood Cells (~5,000,000,000 per cc of blood)

About 10^11 cells produced every day!



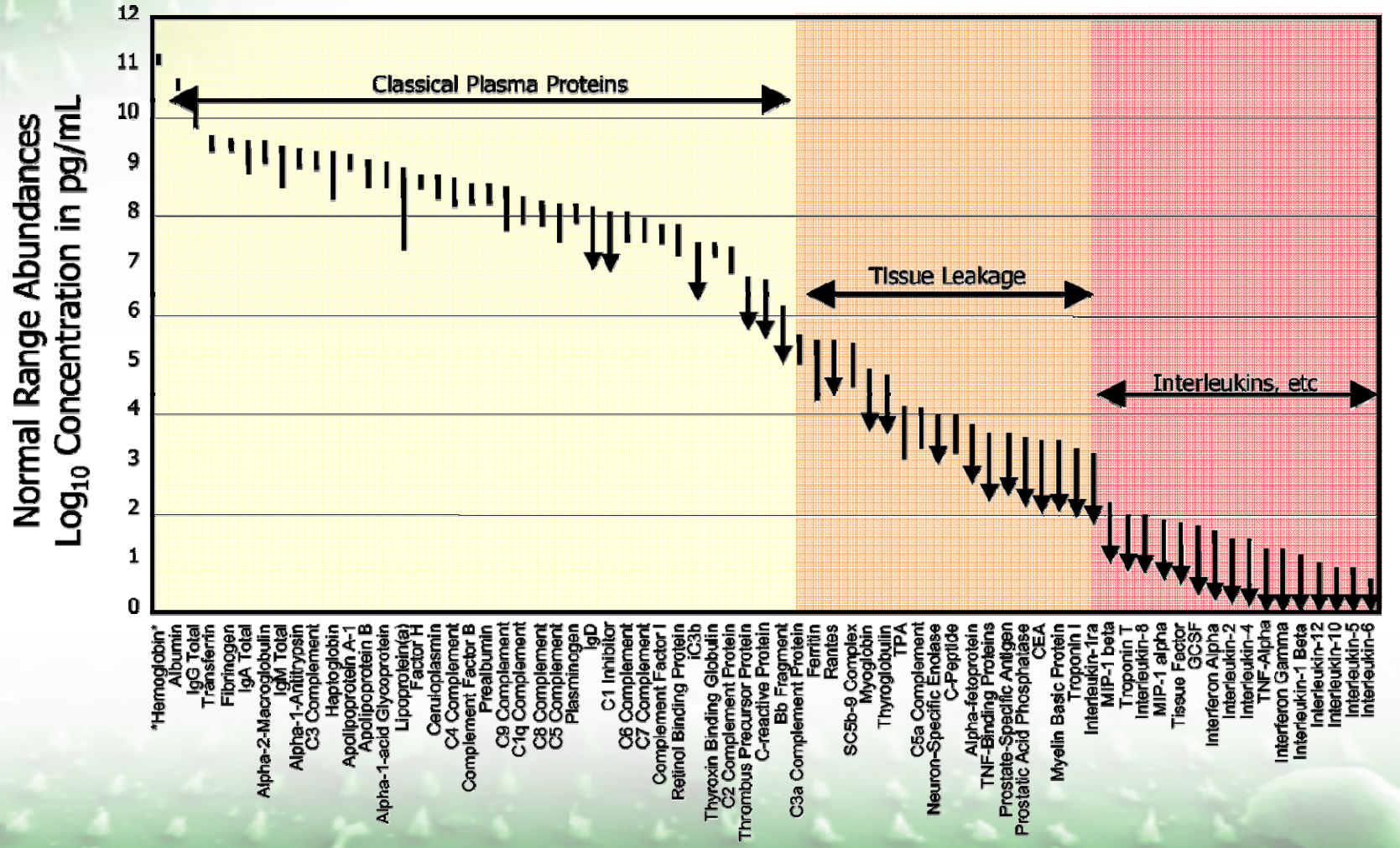
ADAM.



The Human Plasma Proteome
>10 Orders of Magnitude in Abundance

NCI Alliance for Nanotechnology in Cancer

Reference intervals for 70 protein analytes in plasma



Anderson, N. L., and Anderson, N. G. (2002) The Human Plasma Proteome: History, Character, and Diagnostic Prospects. *Molecular & Cellular Proteomics*, 1, 845-867.

Microfluidics as An Enabling Technology for Cancer PET Imaging (Project 3)

Hsian-Rong Tseng
Assistant Professor

NCI NanoSystems Biology Cancer Center (Caltech/UCLA/ISB)
Department of Molecular and Medical Pharmacology
Crump Institute for Molecular Imaging
David Geffen School of Medicine at UCLA

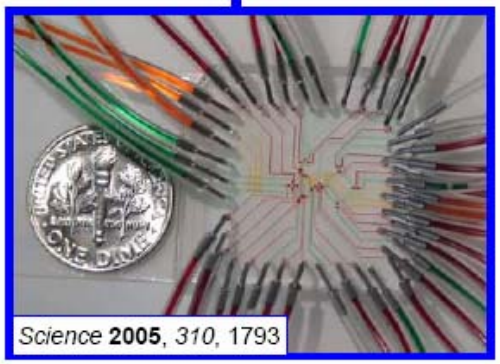
Microfluidic Devices Facilitate Syntheses, Discovery and Evaluation of New PET Probes

Development of PET Probes

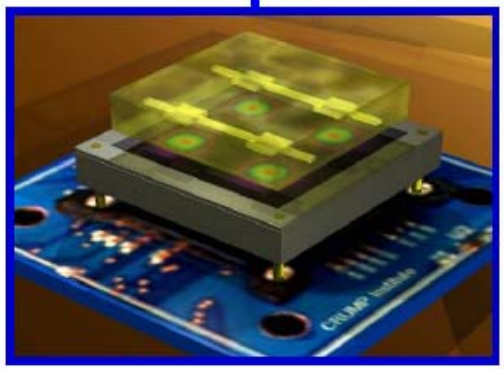
- Synthesis of PET probes
- Discovery of PET probes
- In vitro probe imaging

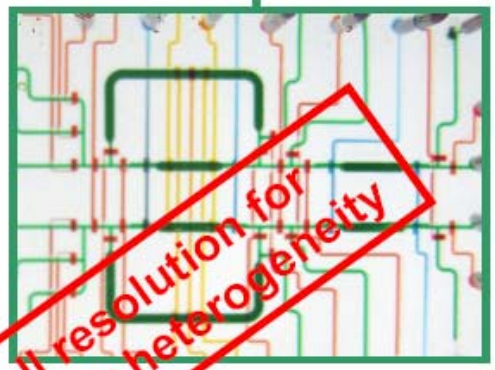
Cancer Diagnosis

- Cancer signaling network
- Kinase assay

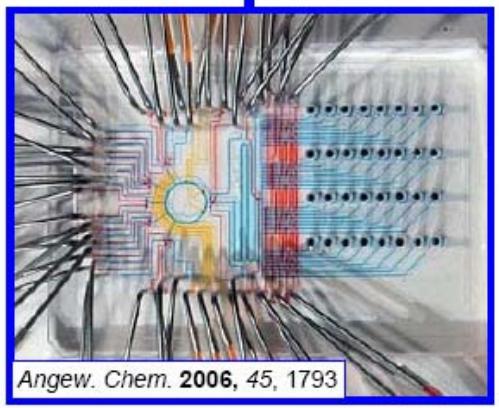


Science **2005**, *310*, 1793

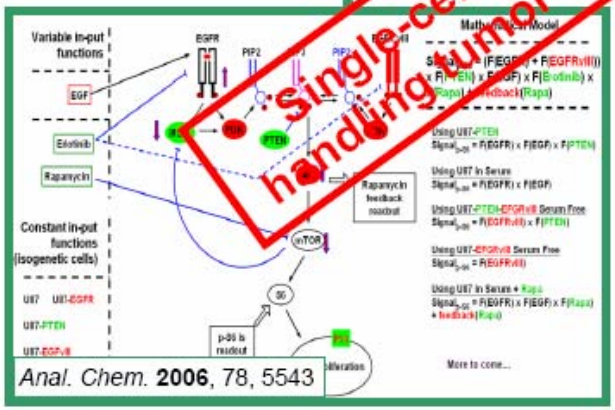




Single-cell resolution for handling tumor heterogeneity

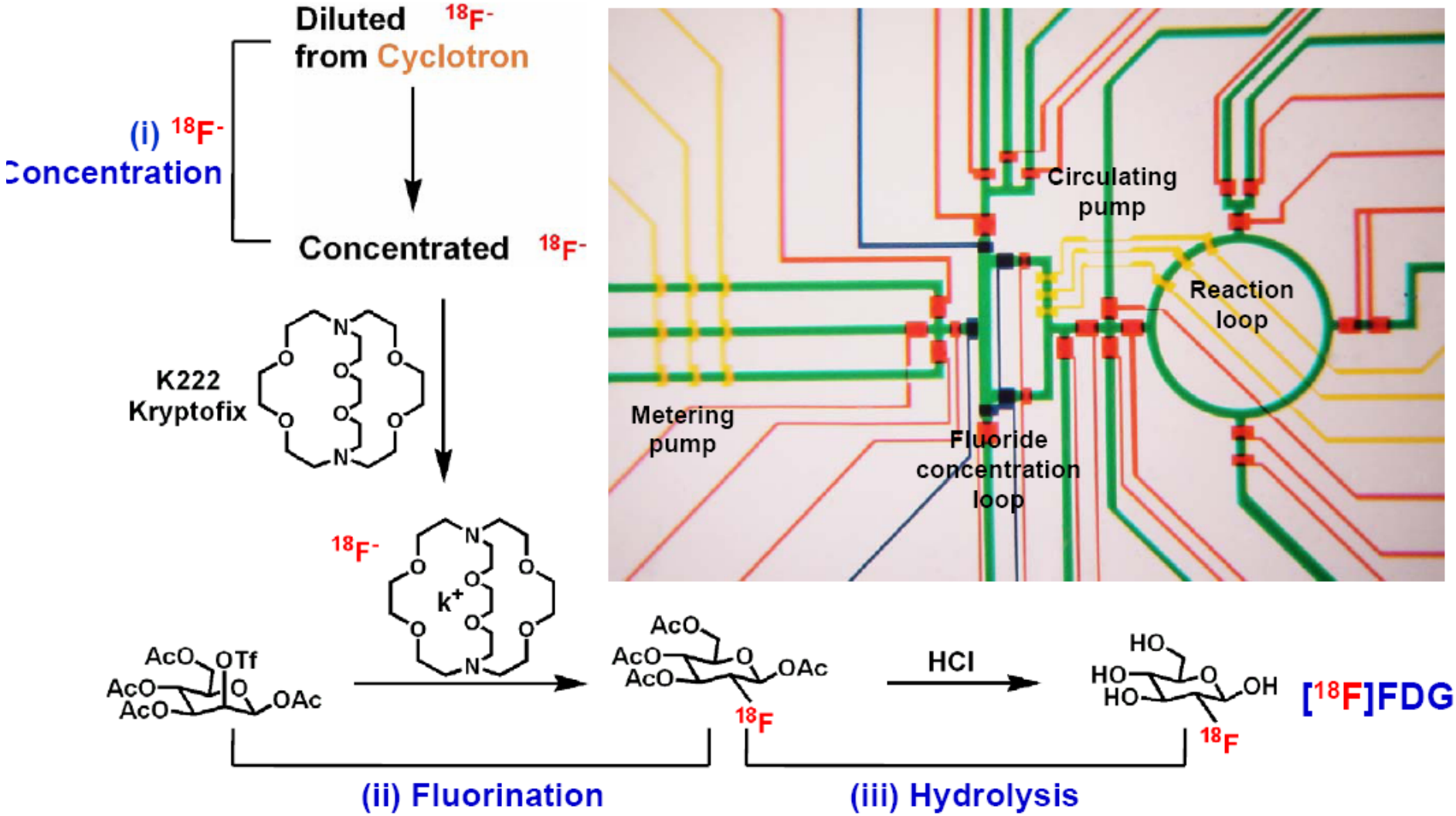


Angew. Chem. **2006**, *45*, 1793

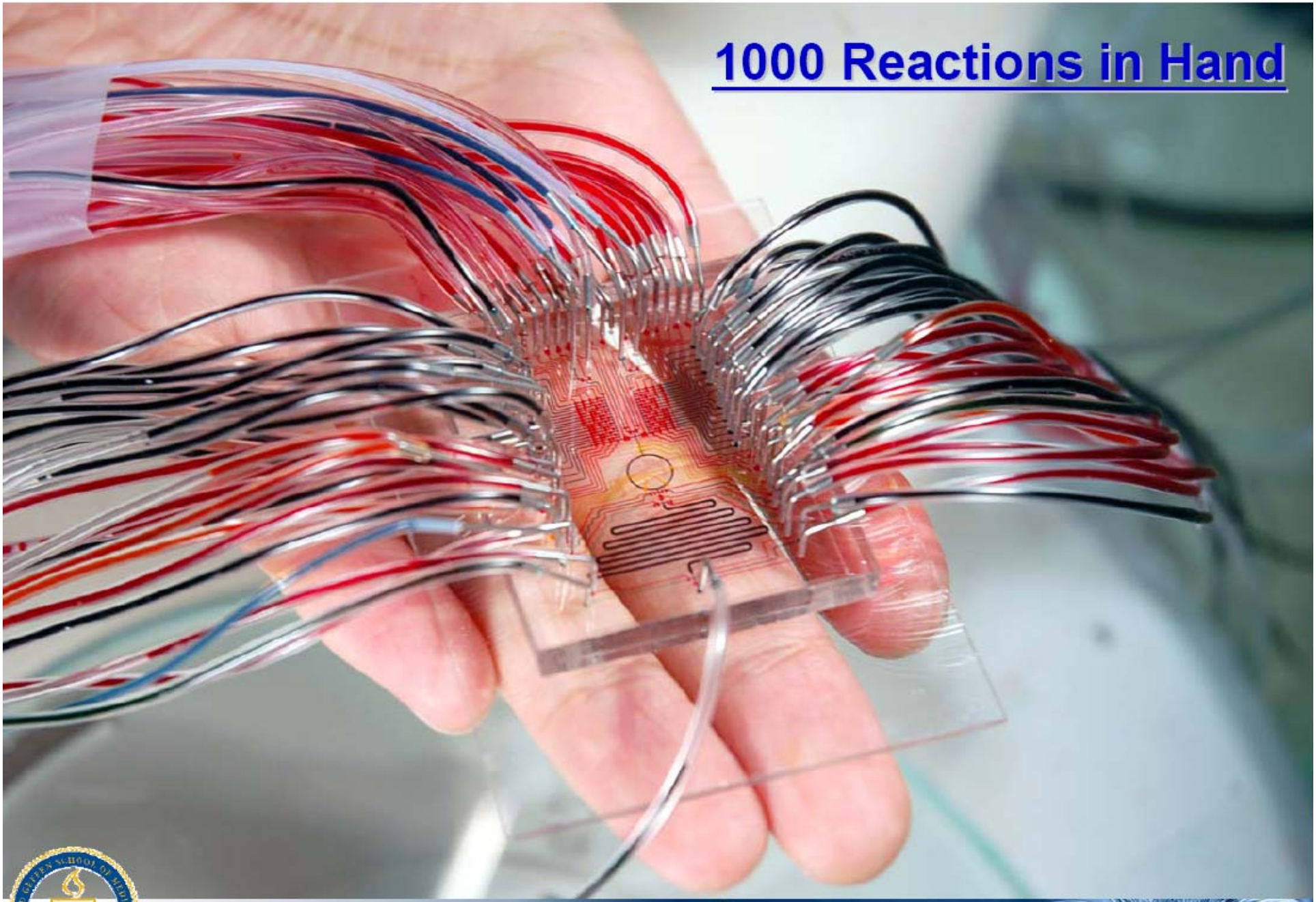


Anal. Chem. **2006**, 78, 5543

[^{18}F]FDG Synthesis in PDMS Microchips



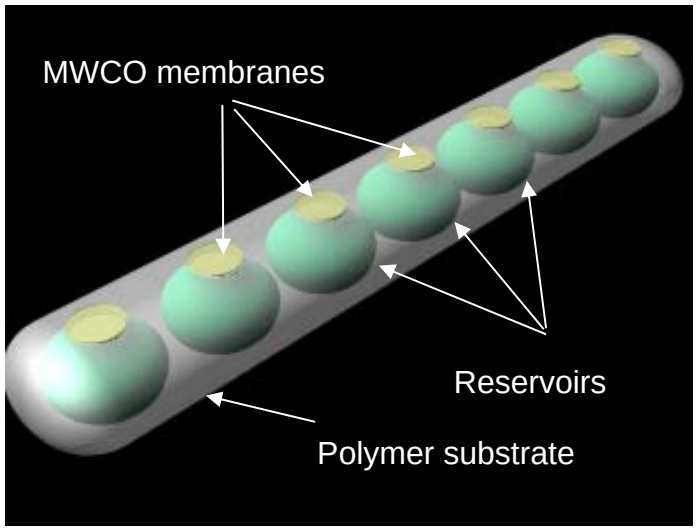
1000 Reactions in Hand



G. Sui, H.-R. Tseng "Reactions in Hand."
Nano Today, **2006**, *1*, 6-7.

Crump Institute for Molecular Imaging

Implantable Diagnostic Device for Cancer Therapy



Grace Y. Kim, Karen D. Daniel, Christophoros C. Vassiliou, Noel Elman,
Robert Langer, Michael J. Cima
Massachusetts Institute of Technology

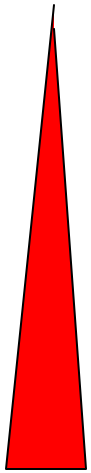
In collaboration with: Lee Josephson (CMIR-MGH), Ralph Weissleder (CMIR-MGH)
Tyler Jacks (CCR-MIT), Al Charest (Tufts, MIT)
Funding: NCI Center for Cancer Nanotechnology Excellence grant

Measuring Soluble Biomarkers *In Vivo*

Hypothesis:

Local biomarker levels are a more sensitive indicator of the state of a solid tumor than systemic concentrations.

LESS INVASIVE



MORE INVASIVE

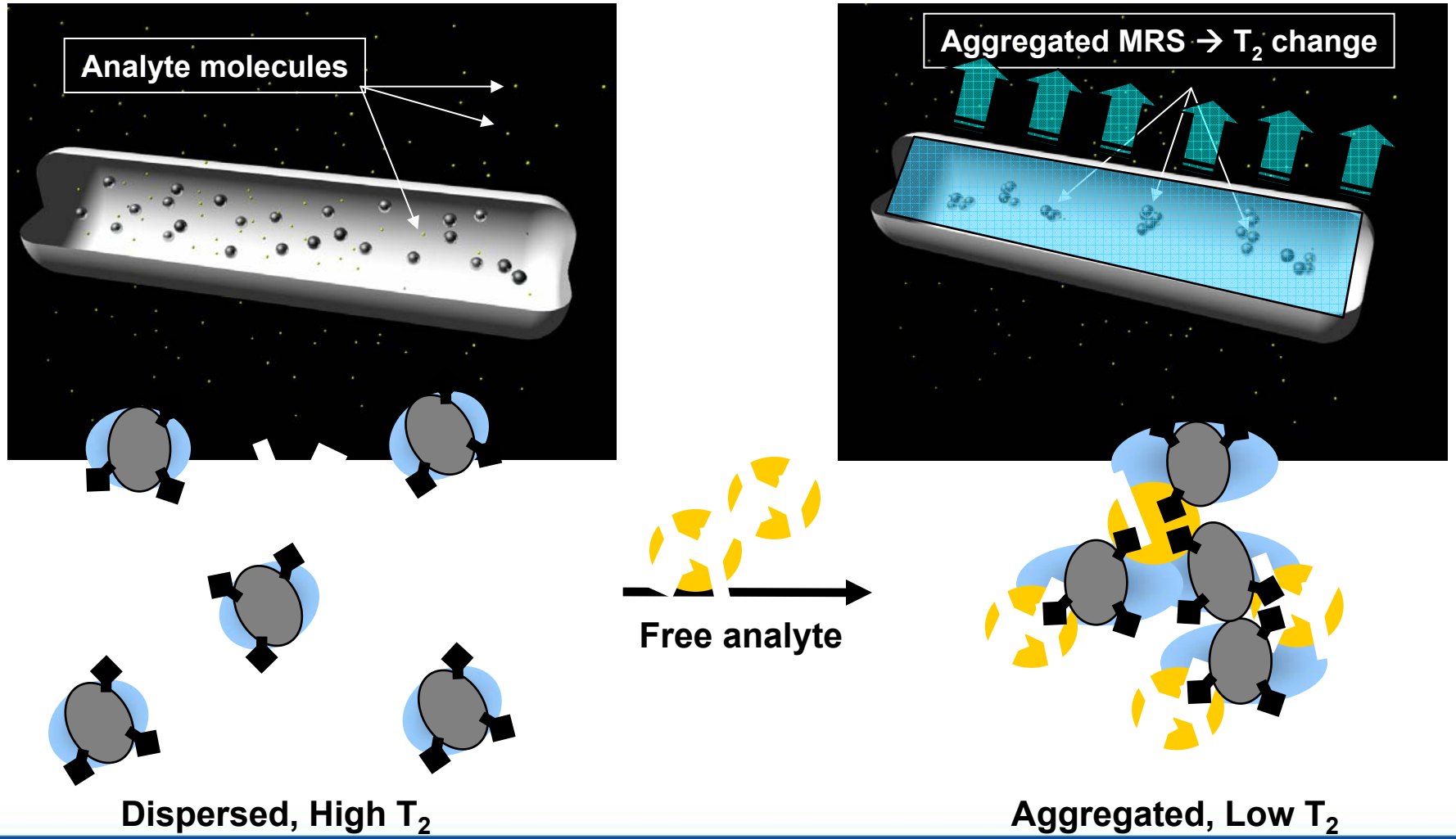
Current Measurement Techniques

- BLOOD TEST (Organ function tests, cancer biomarker concentration, drug concentrations)
- IMPLANT (Reporter of local concentrations, minimally invasive)
- TISSUE (Biopsy, surgical specimens provide most specific information about local state)

Less invasive, faster
Periodic monitoring
Local drug concentrations
Efficacy of therapy
Progression of cancer
Stratify patients for therapy
Detect recurrence

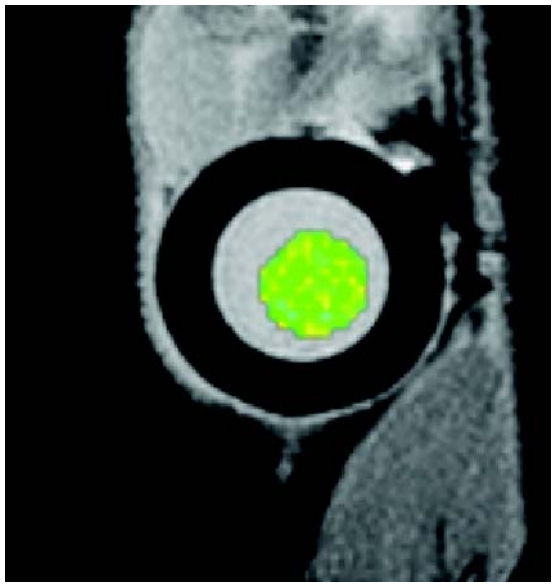
Magnetic Relaxation Switch (MRS) Sensor

Goal: *In vivo*, local detection of soluble cancer biomarkers

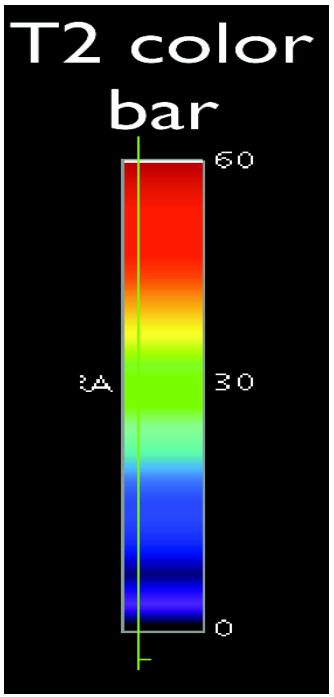


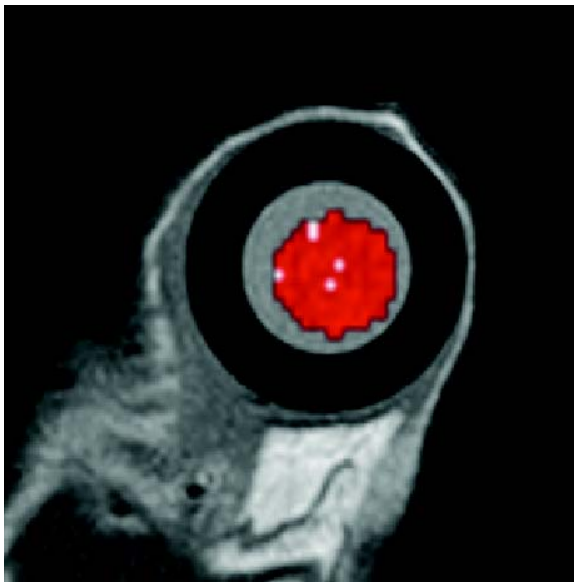
Device-based Sensing ~ in vivo

- Developed tumor model in mice using xenograft tumor cells that secrete HCG
- Device:
  - Polycarbonate membranes on HDPE substrate
  - Low valency nanoparticles
  - Implanted subcutaneously near tumor
- Image by MRI on days one and three after device implantation
- Explant device and read on auto-NMR



Sample Mouse
(device implanted near tumor)





Control Mouse
(no tumor)

PRINT Technology

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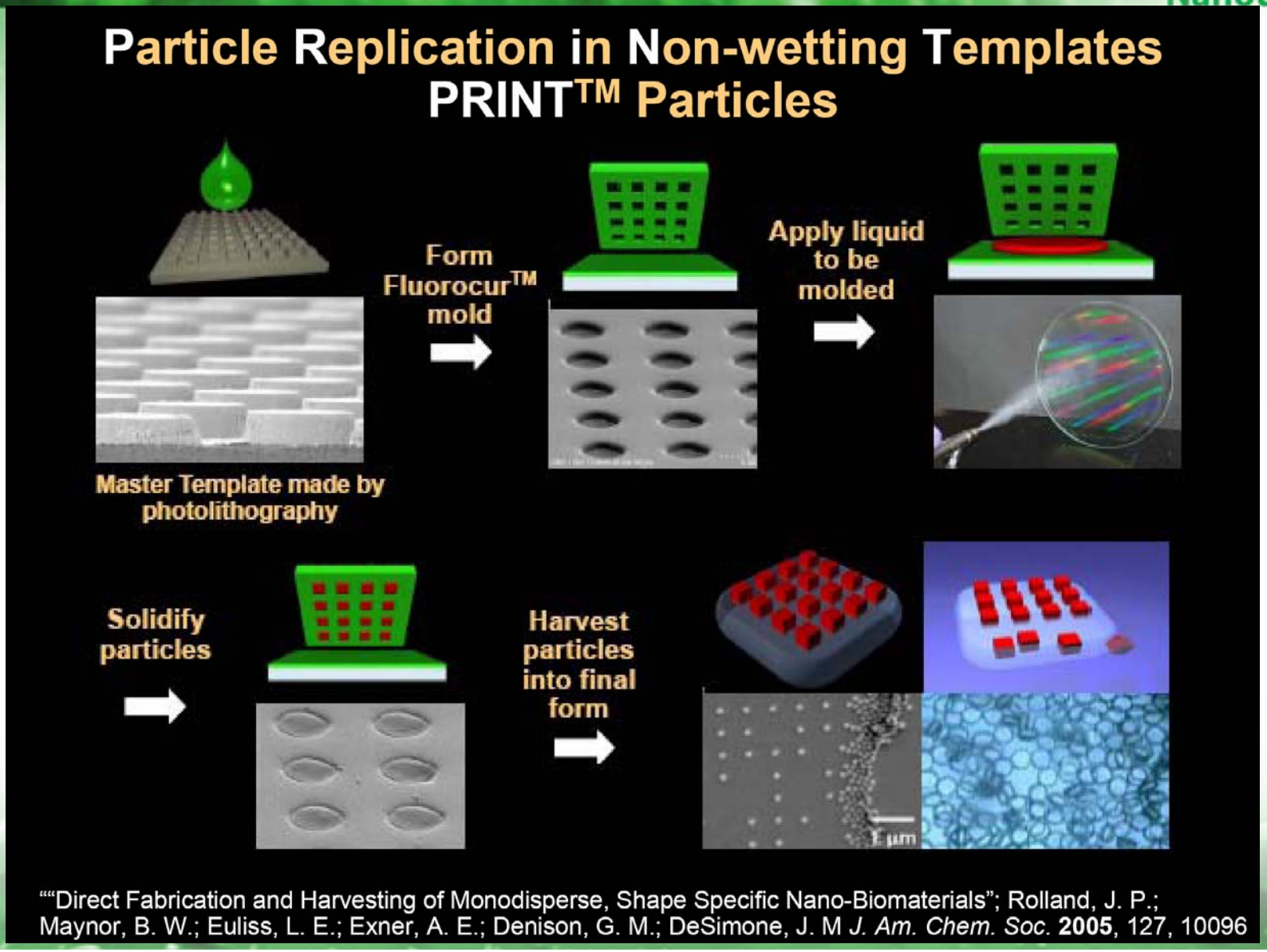

""Direct Fabrication and Harvesting of Monodisperse, Shape Specific Nano-Biomaterials"; Rolland, J. P.; Maynor, B. W.; Euliss, L. E.; Exner, A. E.; Denison, G. M.; DeSimone, J. M *J. Am. Chem. Soc.* **2005**, 127, 10096

Nanoparticle Size and Shape – Biodistribution

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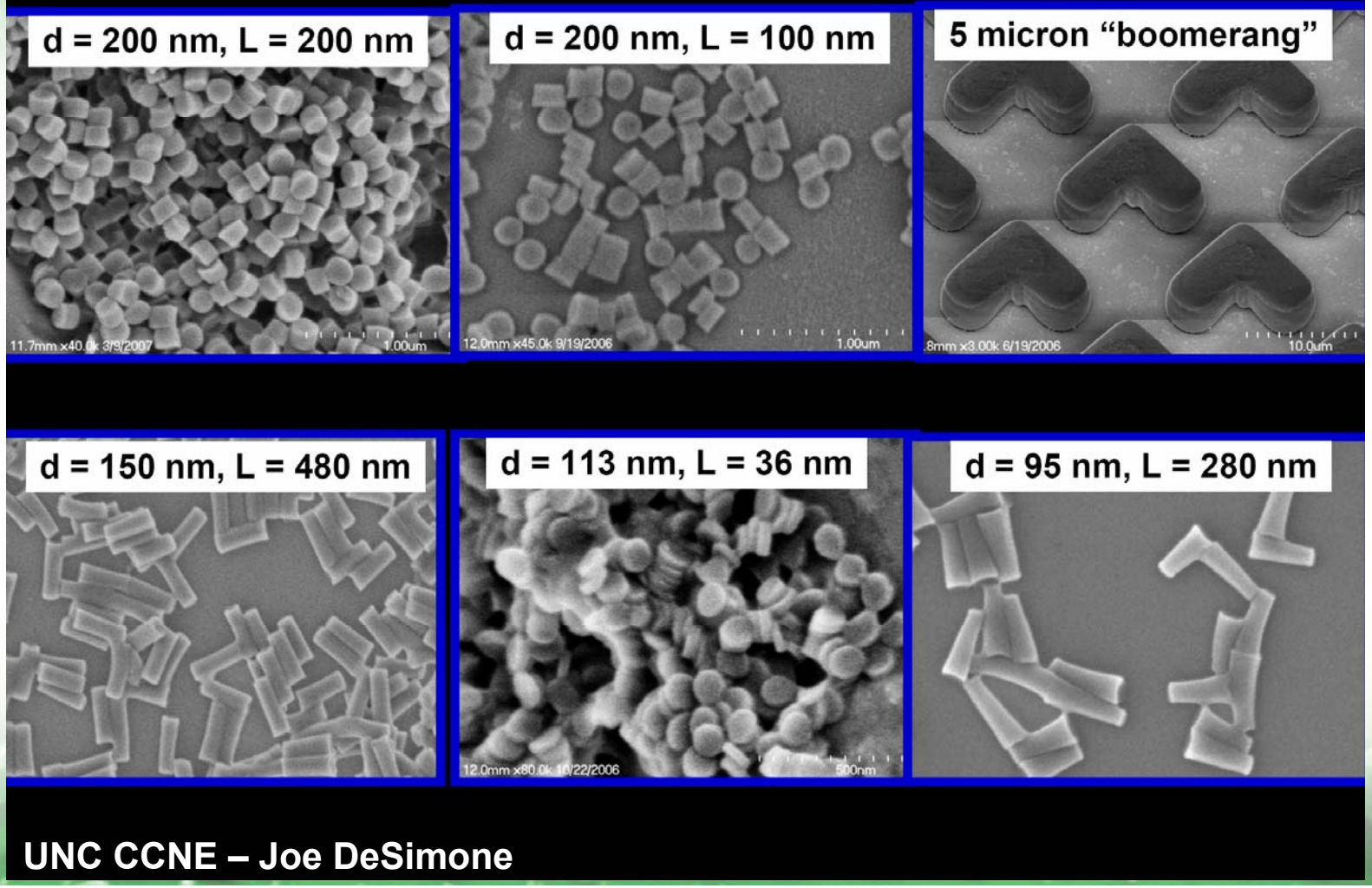
PRINT™ Particles: Shape and Size Range



UNC CCNE – Joe DeSimone

The Alliance Website: http://nano.cancer.gov

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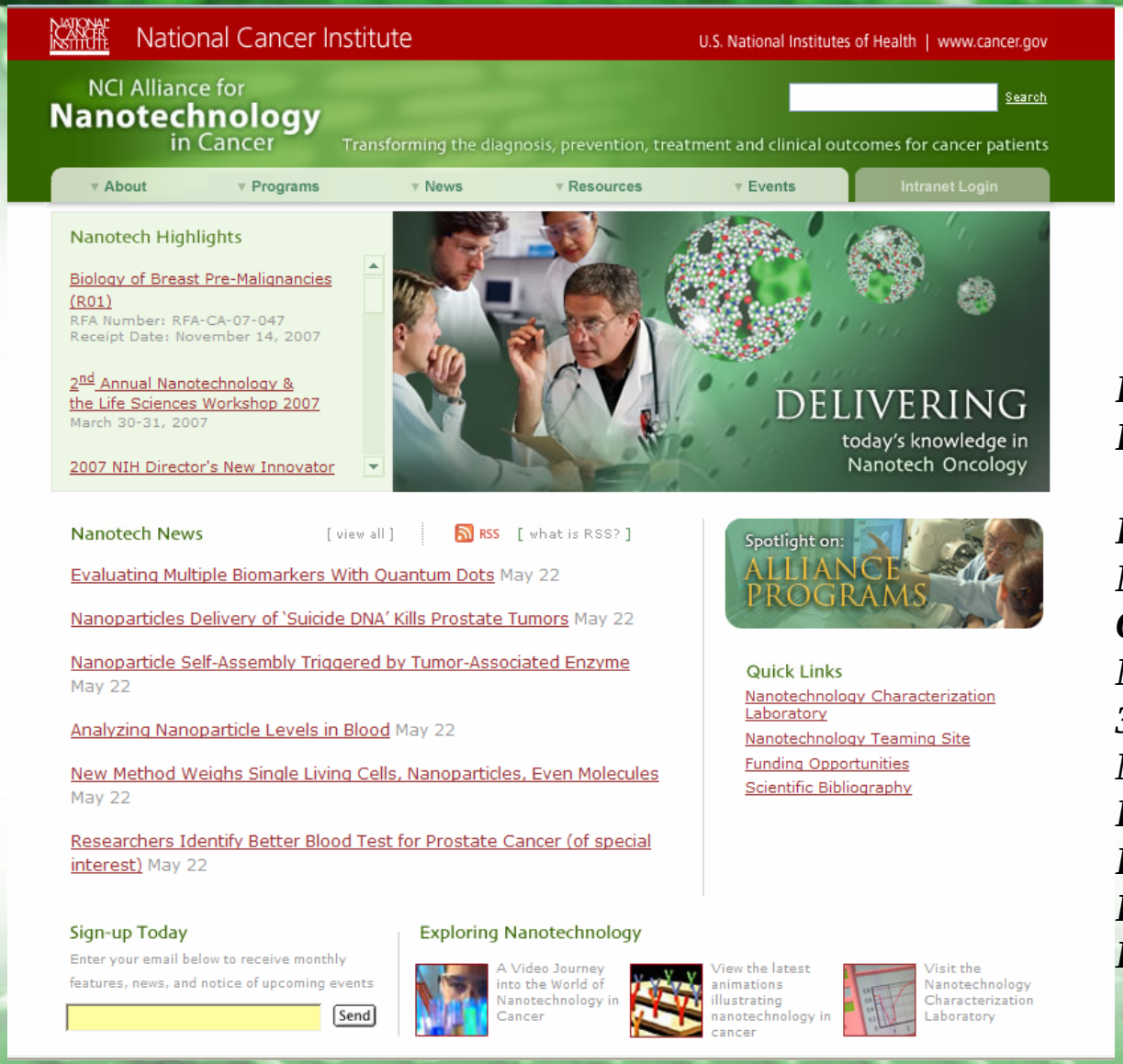

- **More Information**

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