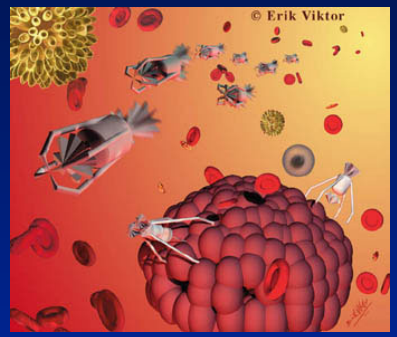
Nanotechnology in medical research: where, when and why?



Marc Baumann

Protein Chemistry/Proteomics Unit
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Biomedicum Helsinki

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(http://research.med.helsinki.fi/corefacilities/proteinchem)

Nanoscience IV

Nanomedicine

Five lectures:

- Nanomedicine prospectives
- Nanoscience and lipids
- Nanoscale enegy production
- Nanoscience and immunology
- Nanoscience and virology

Contact:

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P.O.Box 63, 00014 UH
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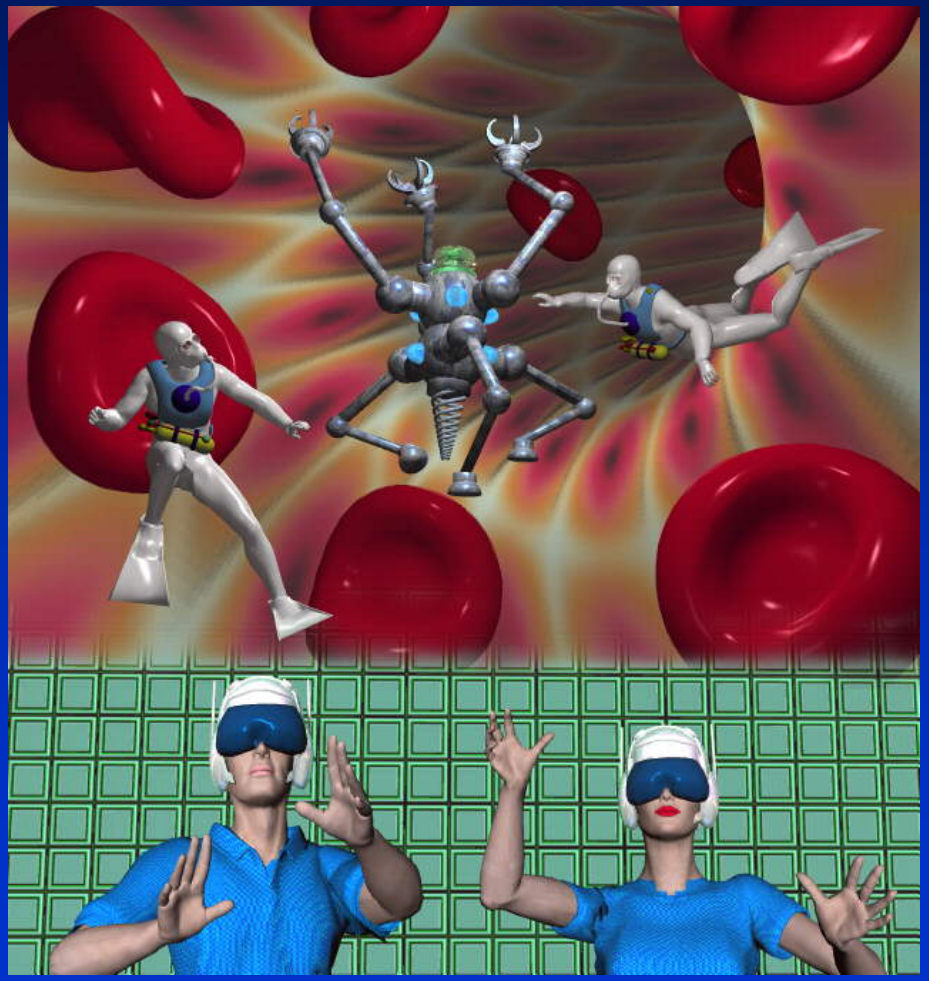


MAJOR BIOLOGICAL MACROMOLECULES IN NANOSCALE

What are the major biological macromolecules in NANOSCALE?

MAJOR BIOLOGICAL MACROMOLECULES IN NANOSCALE

What are the major biological macromolecules in NANOSCALE?

→ Philosophical question with no answer!!

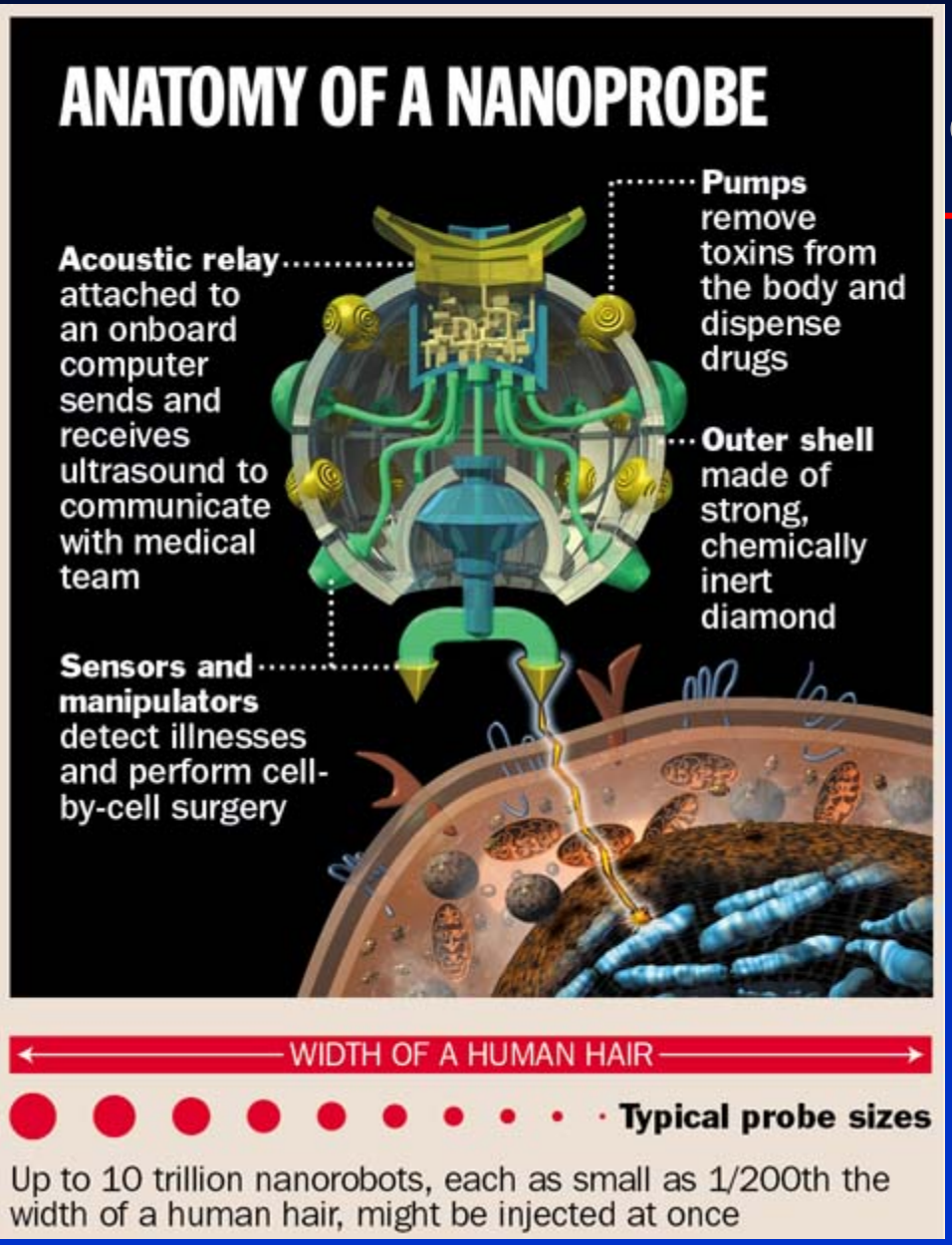
Every biomolecule is in nanoscale and all they are equally important…

Nanomedicine, what is all about?

Nanom about?

Our dream!

1999
(J. Lertola)



Nanomedicine…

Like primitive engineers faced with advanced technology, medicine must `catch up' with the technology level of the human body before it can become really effective. What is the technology level? Since the human body is basically an extremely complex system of interacting molecules (i.e., a molecular machine), the technology required to truly understand and repair the body is the molecular machine technology -- nanotechnology. A natural consequence of this level of technology will be the ability to analyze and repair the human body as completely and effectively as we can repair any conventional machine today."

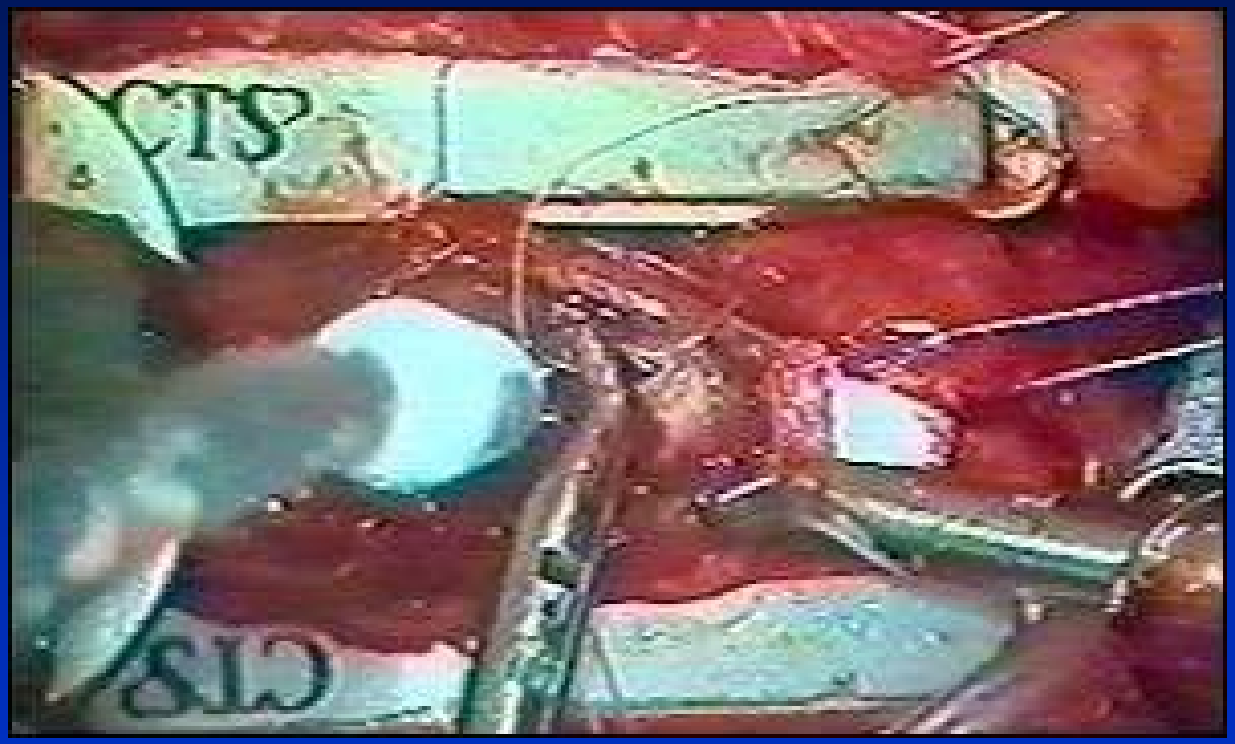
Nanomedicine…

"Surgeons have advanced from stitching wounds and amputating limbs to repairing hearts and reattaching limbs. Using microscopes and fine tools, they join delicate blood vessels and nerves. Yet even the best microsurgeon cannot cut and stitch finer tissue structures. Modern scalpels and sutures are simply too coarse for repairing capillaries, cells, and molecules. Consider `delicate' surgery from a cell's perspective. A huge blade sweeps down, chopping blindly past and through the molecular machinery of a crowd of cells, slaughtering thousands. Later, a great obelisk plunges through the divided crowd, dragging a cable as wide as a freight train behind it to rope the crowd together again. From a cell's perspective, even the most delicate surgery, performed with exquisite knives and great skill, is still a butcher job. Only the ability of cells to abandon their dead, regroup, and multiply makes healing possible."

K.E. Drexler Engines of Creation (1950's): The Coming Era of Nanotechnology, Anchor Press/Doubleday, New York, 1986.

Medical microchips' massive potential

2mm



Robotic techniques could revolutionize heart surgery

Nanomedicine

Nanomedicine may be defined as the monitoring, repair, construction and control of human biological systems at the molecular level, using engineered nanodevices and nanostructures.

Nanotechnology Thorough, inexpensive control of the structure of matter based on molecule-by-molecule control of products and byproducts; the products and processes of molecular manufacturing, including molecular machinery.

Nanomedicine cont…

Nanosurgery A generic term including molecular repair and cell surgery.

Nanodentistry The maintenance of comprehensive oral health by employing nanomaterials, biotechnology including tissue engineering and dental nanorobotics.

Bio-nanomaterial science Materials which are in direct contact with biological fluids or living tissue, with minimal adverse reaction or rejection by the body.

Nanomachine An artificial molecular machine of the sort made by molecular manufacturing.

(**Nano-**: A prefix meaning one billionth (1/1,000,000,000).)

For what do you think medicine could use nanotechnology?

What do you think medicine could use nanotechnology for?

- Biomaterials
- Bone
- Teeth
- Cells
- Cartilage
- Immune system
- Viral and bacterial attack
- Drug delivery
- Diagnostics

Bionanomaterials

1) orthopedic prostheses such as total knee and hip joint replacements, spinal implants, bone fixators, and tendon and ligament prostheses;

2) cardiovascular implants such as artificial heart valves, vascular grafts and stents, pacemakers, and implantable defibrillators;

3) neural implants (e.g., cochlear implants) and cerebrospinal fluid drainage systems (e.g., hydrocephalus shunts);

4) plastic and reconstructive implants such as breast augmentation or reconstruction, maxillofacial reconstruction, artificial larynx, penile implants, and injectable collagen for soft tissue augmentation;

5) dental implants to replace teeth/root systems and bony tissue in the oral cavity;

6) ophthalmic systems including contact and intraocular lenses;

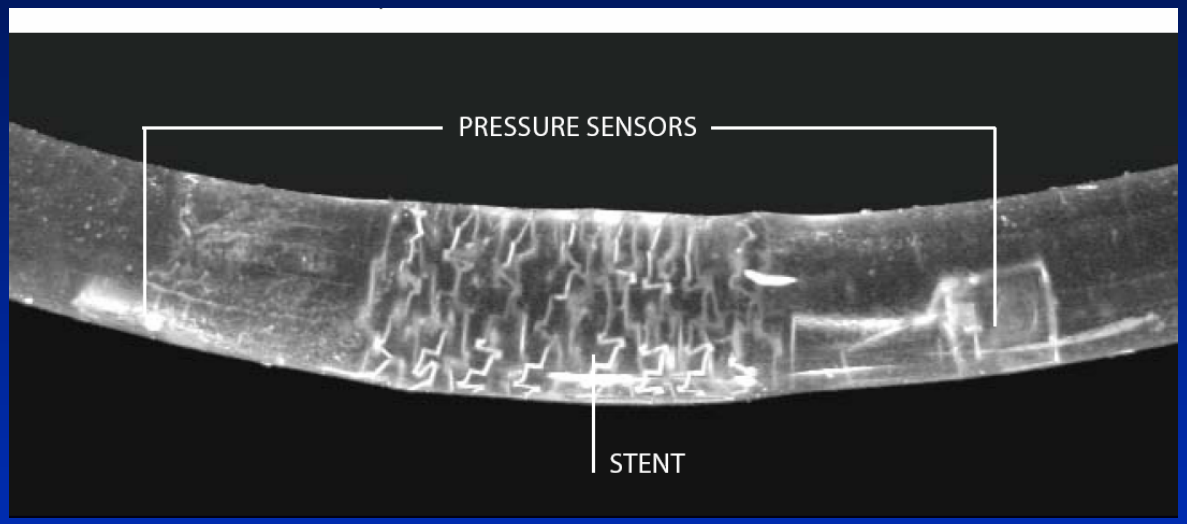
7) catheters and bladder stimulators;

8) drug-dispensing implants such as insulin pumps;

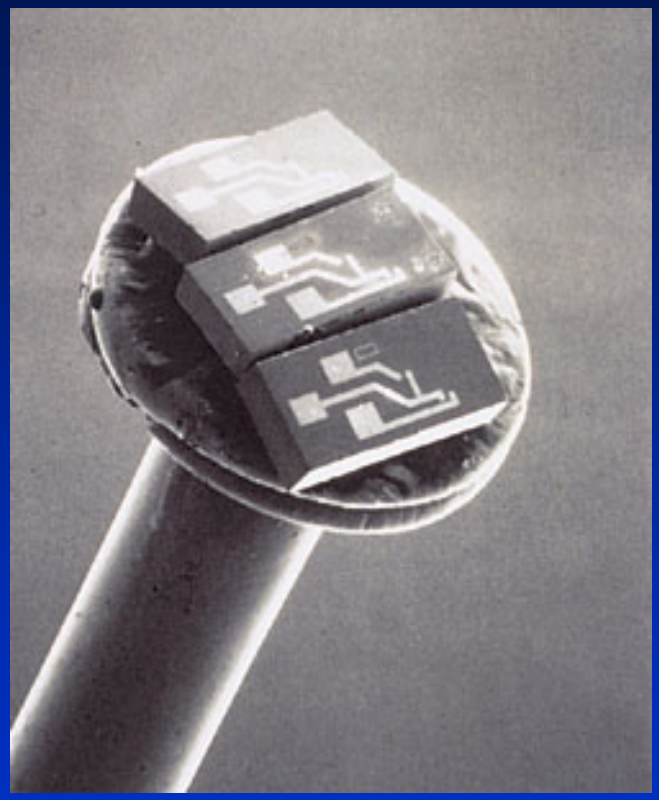
9) general surgical systems such as sutures, staples, adhesives, and blood substitutes.

Stent and Catheter Developments

- Biodegradeable, Drug-Eluting Stents (DES)
- BioMEMS sensor stents and catheters



Stentenna – transmits blood flow and pressure data
Courtesy U. of Michigan



BioMEMS Catheter Technology

Heart Valve biomaterials

Two types of materials (hard man-made and soft bioprosthetic) are commonly used for artificial heart valves, though a third type – polymer valves – were also being Investigated (Graphite/diamond coated with pyrolytic carbon, 2.1 billion cycles, 52 years; denatured Porcine aortic valves, 5-15 years; bovine or autologous pericardium, human homografts).

>> The principal problems with mechanical heart valves are thrombosis or Hemorrhaging (life long antithrombosis treatment required), and with biomaterials their short lifespan.

Bioactive materials

1) Chemically inert materials (e.g. Titanium, tantalum, polyethylene, alumina)

>> Are not inert but get a fiborous tissue capsule around them

2) Bioresorbable materials (e.g. tricalcium phosphate, polylacti-polyclycolic acid copolymers)

>> Used as drug delivery applications, biodegradable implants (sutures, stents, screws etc.)

Here we will see the nanofibres come up!! (Star Inc. Electrospun nanofibers; eSpin Tech. Nanofibers of organic and biological polymers)(150nm fibers).

3) Bioactive materials (e.g. Glass, ceramics, glass-ceramics, plasma-sprayed Hydroxyapatide, oxidized silicon, sodium, calcium, phosphorus etc.)

Bioactive materials cont...

The goals is to alter the surface material by changing the atomic structure and chemistry e.g. Ceramic is not very bioactive but when treated with Ion beam surface modification it become bioactive.

Cells align themselves to nano-scale features on a titanium surface, and the size and shape of features can control the behavior of different cells.

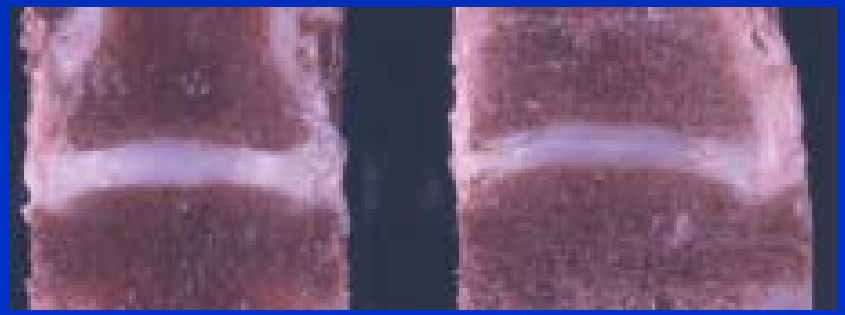
For instance, fibroblasts (responsible for new collagen fiber deposition during wound healing) migrate along the nano-sized grooves, while macrophages (white blood cells responsible for digesting foreign matter) can become trapped within these features. Biomaterial scientists can exploit such topographical controls to provide new ways to guide regeneration and healing.

Orthopedic biomaterials

Artificial joints consist of a plastic cup made of ultrahigh molecular weight polyethylene, placed in the joint socket, and a metal (titanium or cobalt chromium alloy) or ceramic (aluminum oxide or zirconium oxide) ball affixed to a metal stem.

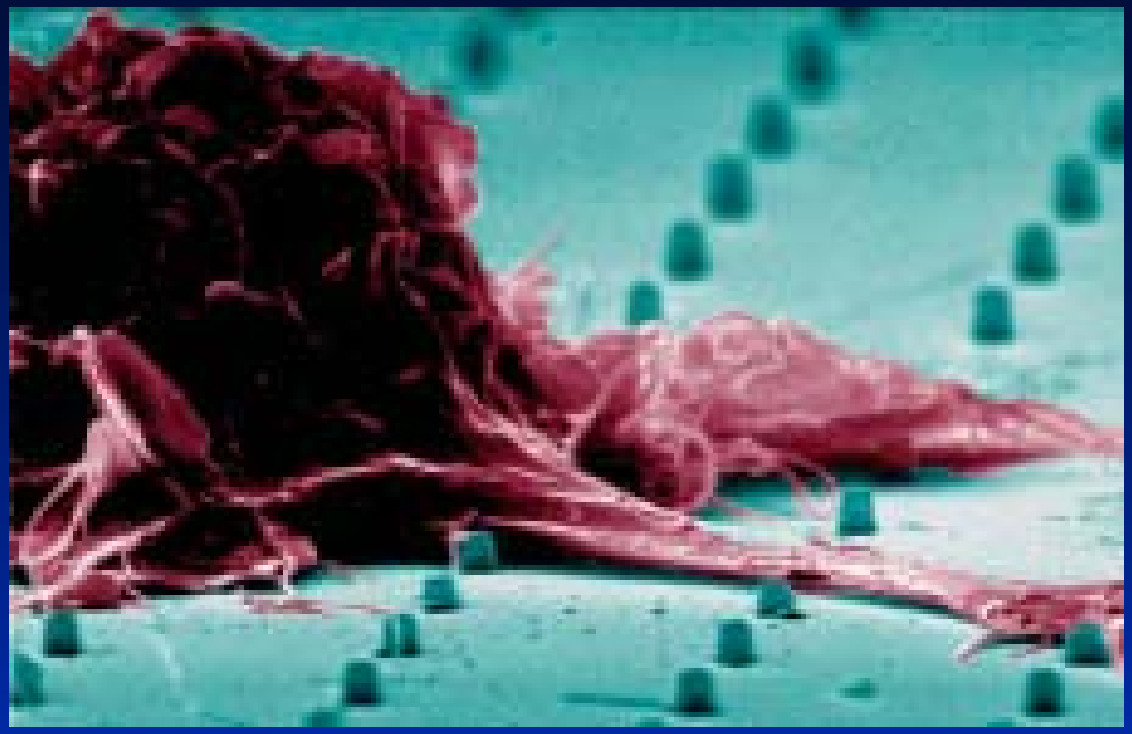
Billion of tiny polymer particles are shed into the surrounding synovial fluid and tissues during the life time of the AJ (8-12 Years).

>> Inflammatory cells lack receptors for ultrahigh-density polyethylene or fragments thereof, yet are able to recognize these utterly foreign objects as such and attack them.



Left: intervertebral disc, 12 months after treatment with autologous disc chondrocytes

Right: untreated intervertebral disc
Regenerated discs mimic native disc morphology; autologous treatment promotes tissue regeneration.

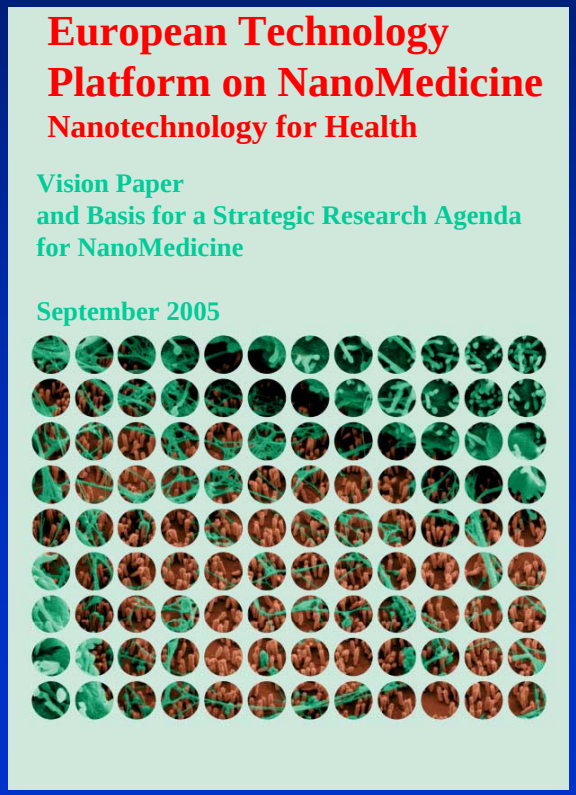


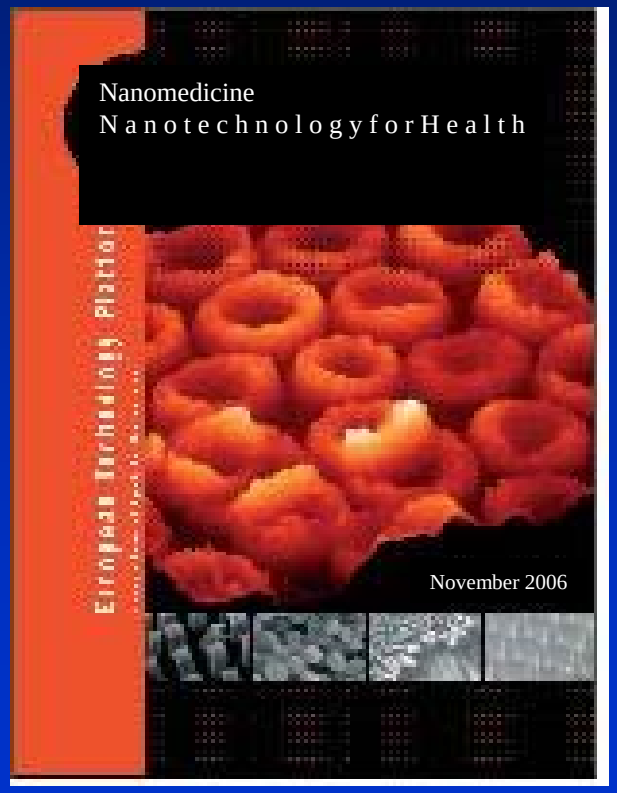
Fibroblast cell on a nanostructured surface

Note: that in many nanomedical applications, tissue integration with the implant is desirable!! For other applications such as hemodynamic systems, a nonadhesive inert nanodevice surface is desirable!!

Nanotechnology in medical research: where, when and why?

The European way:



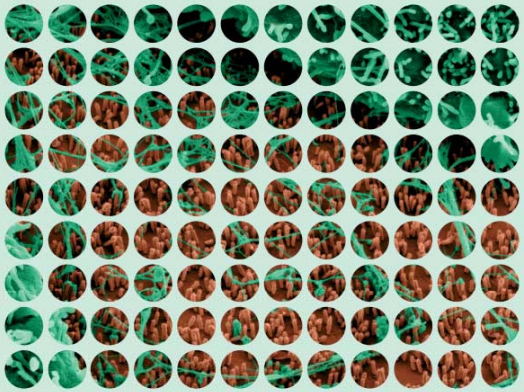


EUROPEAN COMISSION

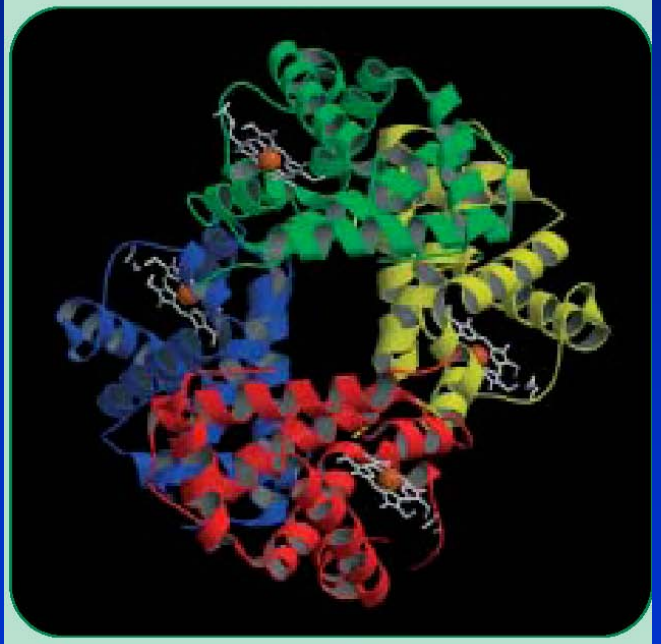
European Technology Platform on NanoMedicine
Nanotechnology for Health

Vision Paper
and Basis for a Strategic Research Agenda for NanoMedicine

September 2005

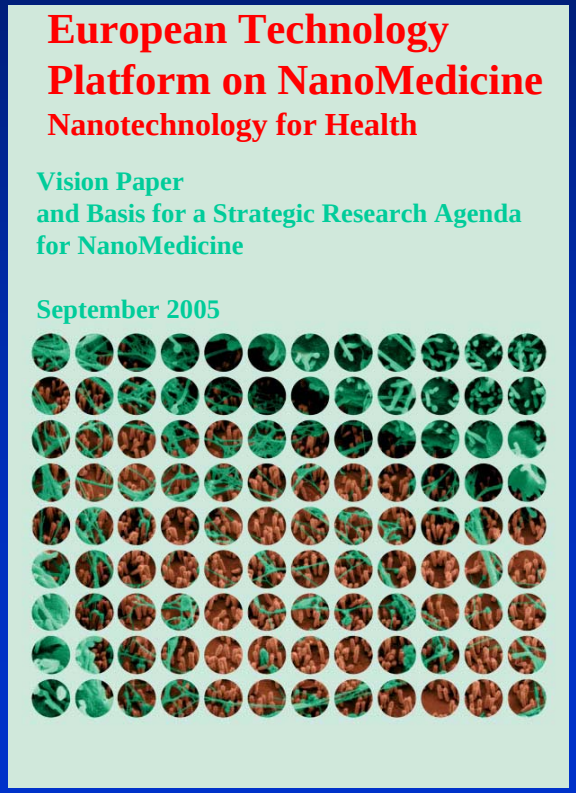


This European Technology Platform addresses ambitious, responsible research, development and innovation in Nanotechnology for Health to strengthen the competitive scientific and industrial position of Europe in the area of NanoMedicine and improve the quality of life and health care of its citizens.



Crystal structure of human deoxyhaemoglobin
© InformationsSekretariat Biotechnologie, 2005

Definition: NanoMedicine, for the purpose of this vision document, is defined as the application of Nanotechnology to Health. It exploits the improved and often novel physical, chemical, and biological properties of materials at the nanometric scale. NanoMedicine has potential impact on the prevention, early and reliable diagnosis and treatment of diseases.



Nanomedical developments range from nanoparticles for molecular diagnostics, imaging and therapy to integrated medical nanosystems, which may perform complex repair actions at the cellular level inside the body in the future.

Mastering Artificial Nanostructures

Scanning Tunneling Microscopy (STM)

Scanning Force[1] Microscopy (SFM)

Electron Beam Lithography

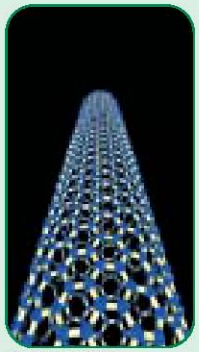
Photo Lithography

Dendrimers

Liposomes

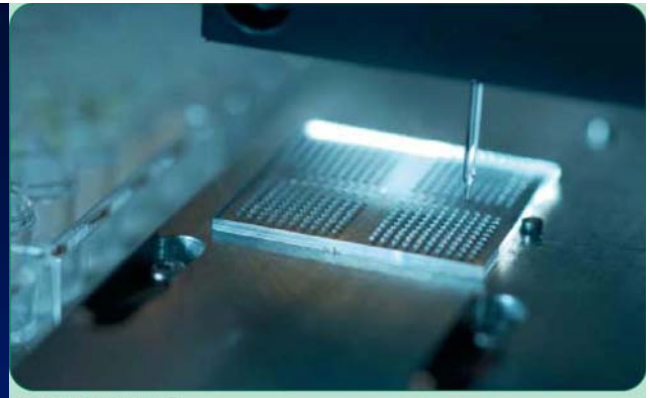
Nanoparticles (nanotubes[2], fullerenes[3], quantum dots, etc.)

1 Scanning Force Microscopy (SFM)

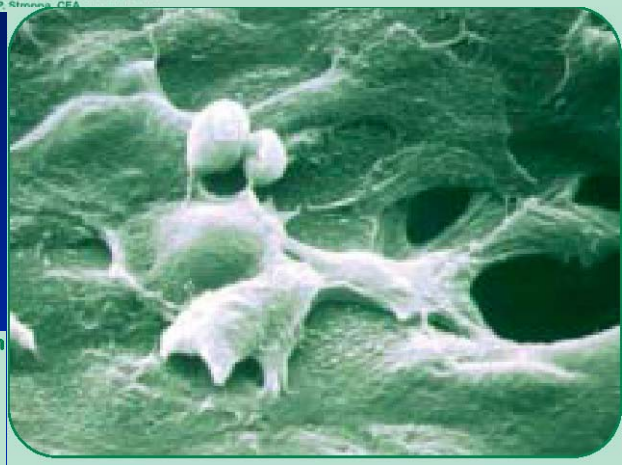


2 Carbon nanotube © Chris Ewels

3 Fullerene



Droplets (50nl) dispensing robot © P. Simone, CEA



Tissue engineered epithelium © Fidia Advanced Biopolymers

1 | 1 | 10^1 | 10^2 | 10^3 | 10^4 Size, nm

DNA[1]

Haemoglobin

Lipid bilayer surrounding cells

Proteins

Typical virus[2,3,4]

Human cell nucleus

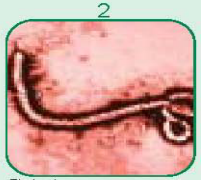
Staphylococcus

Lymphocyte, Red blood cell[5]

Fibroblast cell[6]

1 

DNA © PhotoDisc Inc 1996

2 

Ebola virus © Digital Stock 1996

3 

Marburg virus © H. Oberleithner, University of Münster

4 

Influenza virus © Roche, 2005

5 

Red blood cell

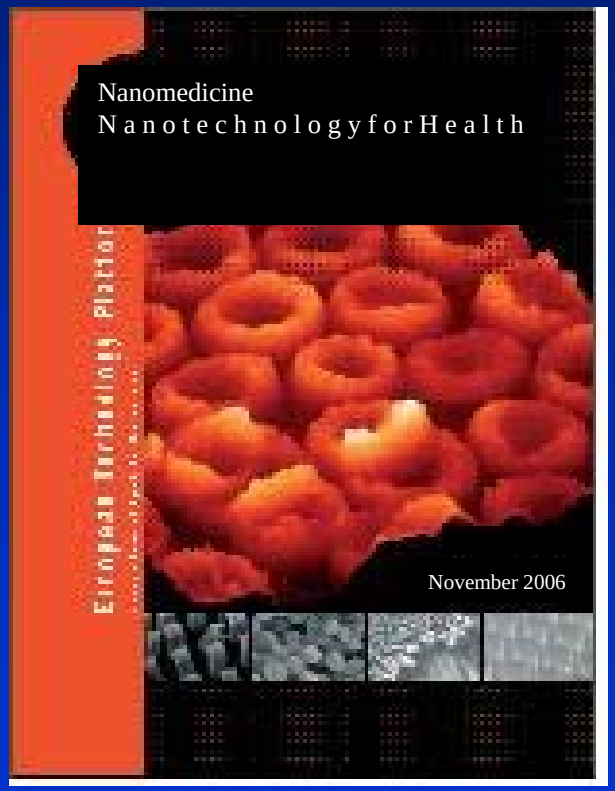
6 

Fibroblast cell © Roche, 2005

Biological Nanostructures

EUROPEAN SCIENCE FOUNDATION

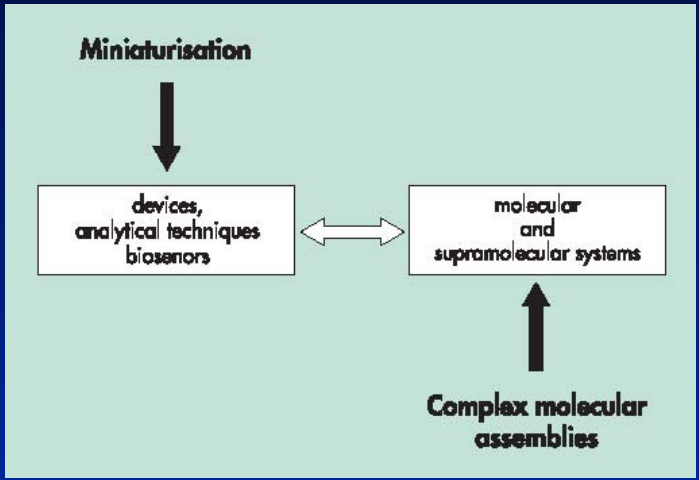
The field of 'Nanomedicine' is the science and technology of diagnosing, treating and preventing disease and traumatic injury, of relieving pain, and of preserving and improving human health, using molecular tools and molecular knowledge of the human body. It was perceived as embracing five main sub-disciplines that in many ways are overlapping and underpinned by the following common technical issues.

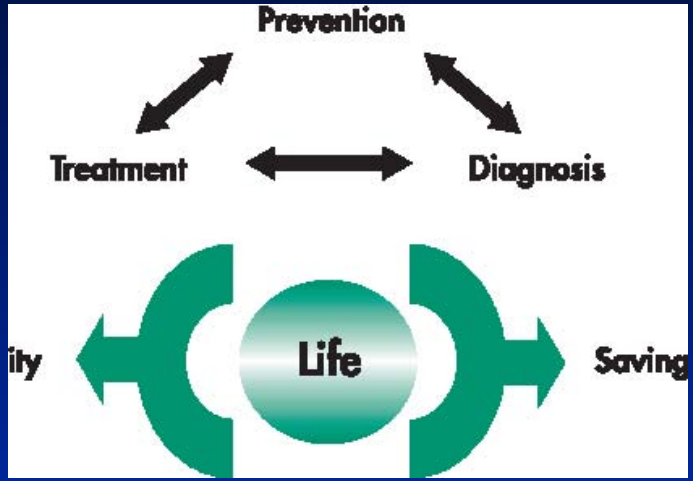


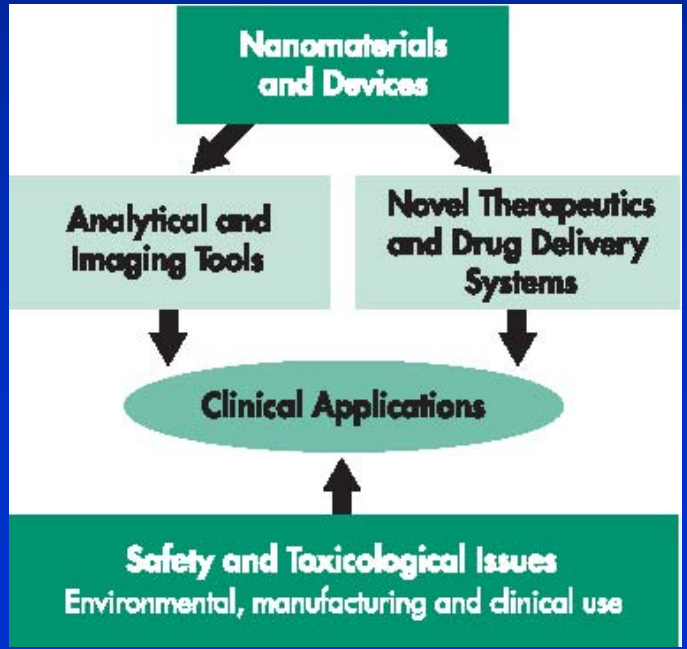
Analytical Tools

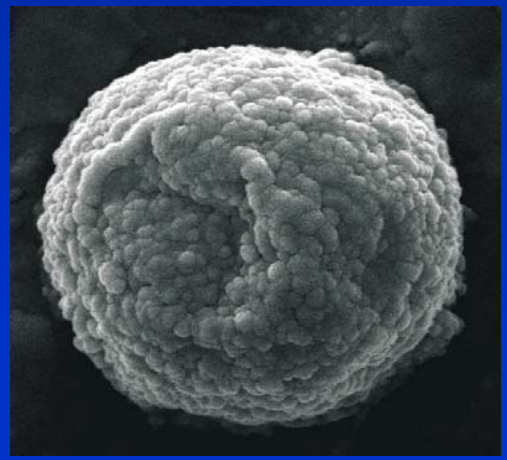
- Nanoimaging
- Nanomaterials and Nanodevices
- Novel Therapeutics and Drug Delivery Systems
- Clinical, Regulatory and Toxicological Issues

EUROPEAN SCIENCE FOUNDATION









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Bioarrays and Biosensors	Nanofabrication	Nano-objects	Detection
DNA chips	lab on chip	nanotubes	electrochemical detection
protein-chips	pill on chip	nanowires	optical detection
glyco-chips	nanofluidics	nanoparticles	mechanical detection
cell-chips		nanostructured surfaces	electrical detection - by scanning probes - by mass spectrometry - by electronmicroscopy
biosensors for single and multiple analytes		nanodevices and nanoelectronics	

An ideal near-patient diagnostic system	
• **Fast**	Minimise consultation time (<1 minute)
• **Simple**	Lay person (nurse's aid) can use
• **Portable**	Take the test to the patient
• **Storage**	Room temperature for consumables
• **Painless**	Minimally invasive blood sampling

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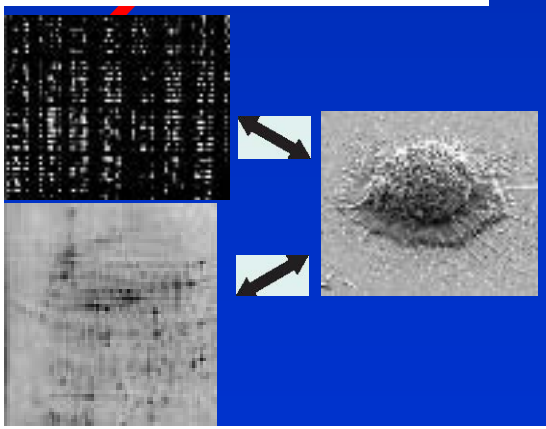
What do we have



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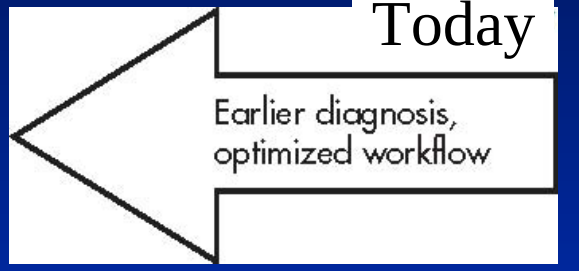
What do we want

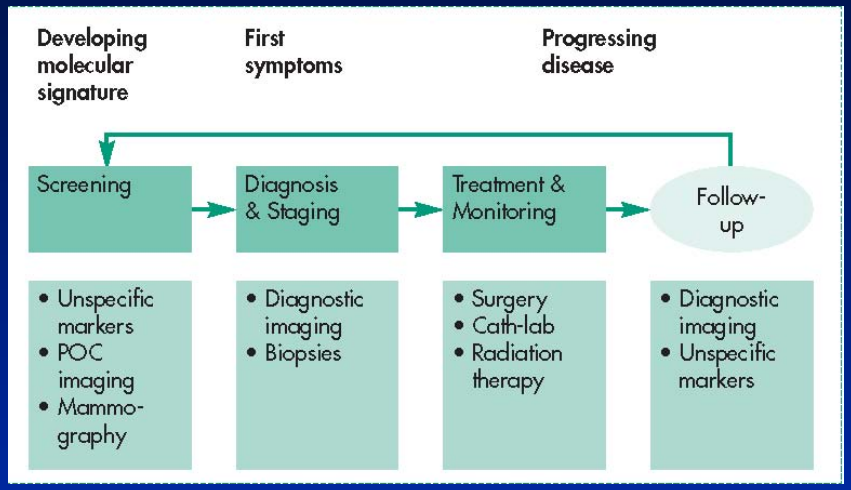
Molecular Imaging Diagnostics (MDx): Impact on healthcare in the future

Genetic disposition

DNA Mutations

Today

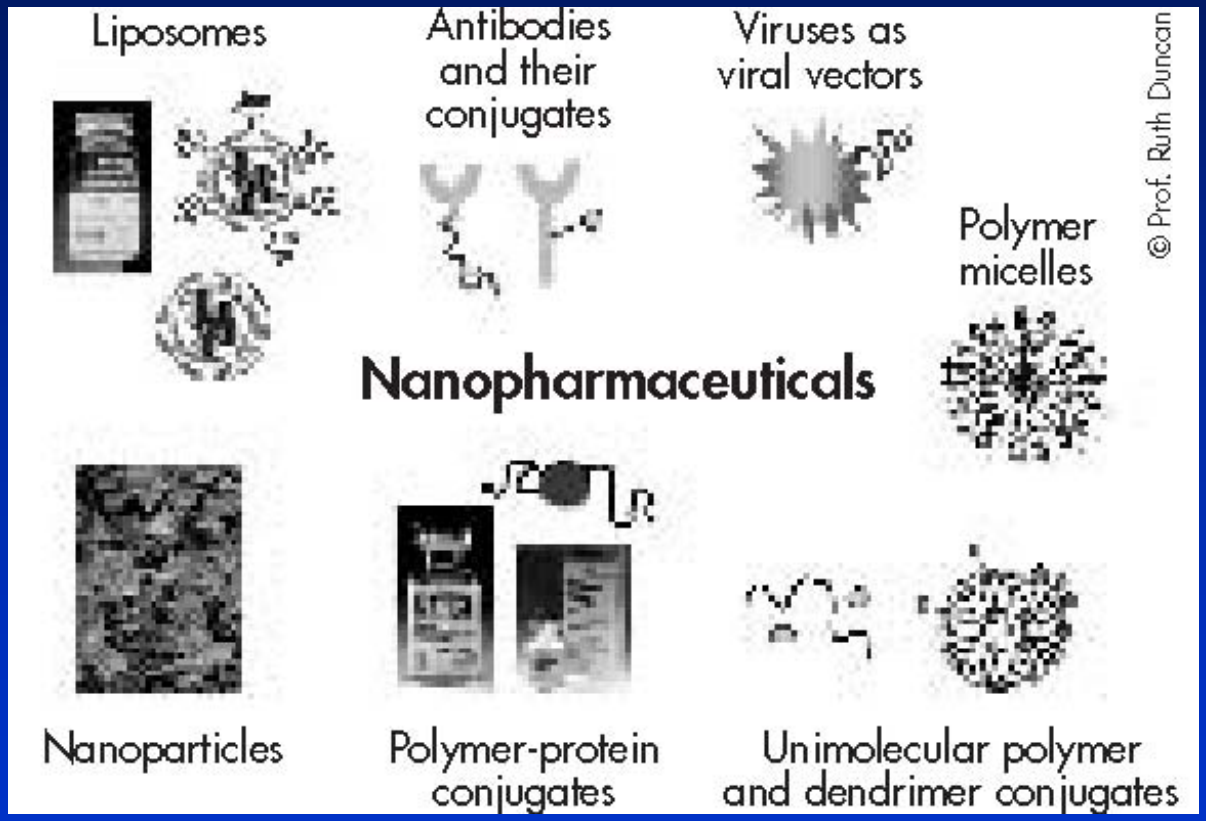




Future

• Specific	• Molecular	• Mini-invasive	• MI, MDx
markers	imaging:	surgery	• Non-invasive,
(MDx)	quantitative,	• Local/target-	Quantitative
	whole-body	ed drug	imaging
	• CA Diagnosis	delivery &	
		tracing	
		• Tissue analy-	
		sis (MDx)	

Drug delivery and Pharmaceutical development



Nanotechnologies

- Supramolecular chemistry-Self assembling drug carriers and gene delivery systems
- Nanoparticles and nanocapsules
- Antibody technologies
- Polymer-drug conjugates
- Polymer-protein and antibody conjugates
- Nano-precipitation, nanocrystals
- Emulsification technologies
- Liposome technology
- In situ polymerisation
- Tissue engineering and repair
- Dendrimer technologies
- Molecular imprinting

Nanotechnologies

Technology	Application
Nanopharmaceuticals in current use or Entering routine use in the short-term future (within 5 years)	Cancer Antiviral agents Arteriosclerosis Chronic lung diseases Diabetes
Nanopharmaceuticals with potential clinical applications in the longer term future (10 years)	Gene therapy Tissue engineering Tissue/cell repair
Nanodevices	Delivery of diagnostic and therapeutic agents

At the Doctors Office

Examination and Diagnosis of a Patient

The first step in any treatment process is the examination of the patient, including the individual's medical history, personal functional and structural baseline, and current complaints.

Advancing technology has also brought a plethora of tests that contribute to accurate diagnosis, including auscultation, microscopy and clinical bacteriology in the 19th century, and radiological scanning, clinical biochemistry, genetic testing, and minimally invasive exploratory surgery in the 20th century.

In the 21st century, new tools for nanomedical testing and observation will include clinical in vivo cytography; real-time whole-body microbiotic surveys; immediate access to laboratory-quality data on the patient.

An Example

A patient presents in the clinic with mild fever, nasal congestion, discomfort, and cough. A swab of his throat is taken.

What do we do now?

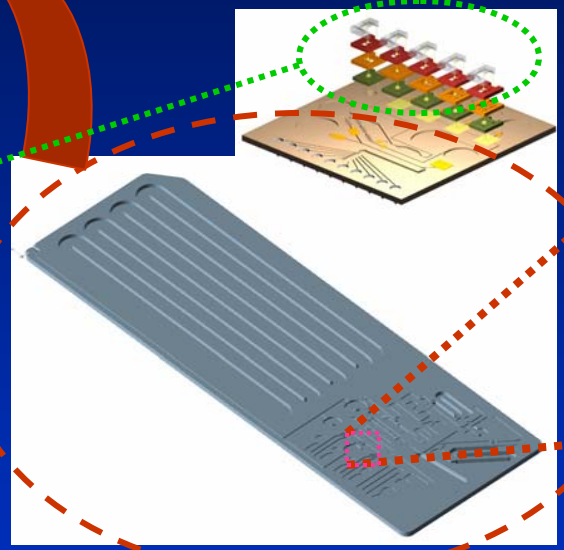
The sample is analyzed by recombinant DNA techniques.
The cotton throat swab is mixed with a cocktail of DNA probes.
(In approx. 24 hours we will have the first answers for the pathogen!)

What do we do in the future?

The physician faces the patient and pulls from his pocket a lightweight handheld device resembling a pocket calculator…

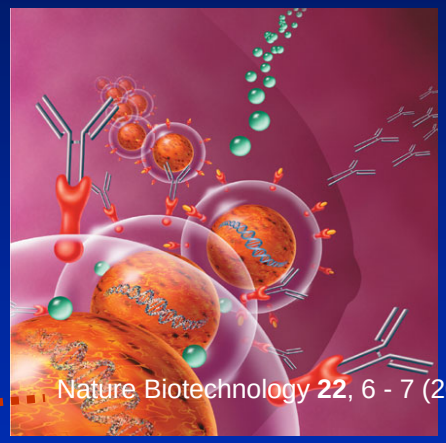
MD (Molecular Diagnostics) Chip for Preventive & Personalized Medicine

Biomedical analysis & communication system



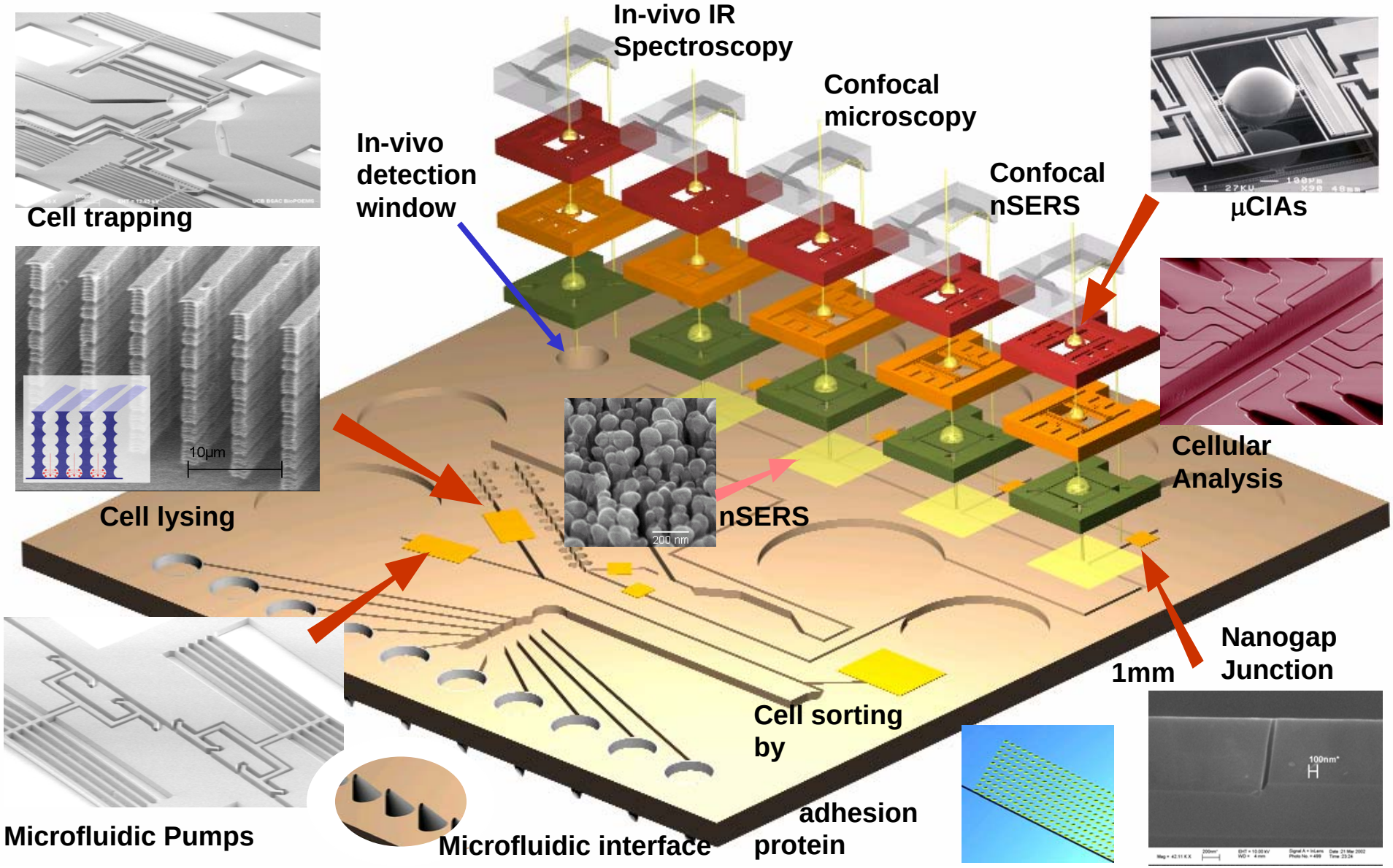
Disposable Diagnostic Biochip

Prof. Luke P. Lee, Berkely

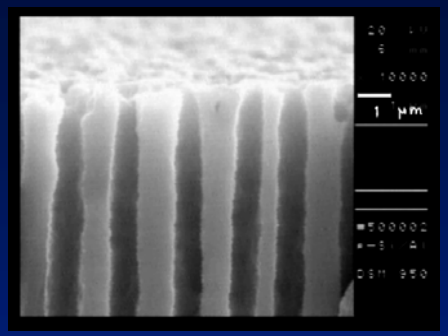


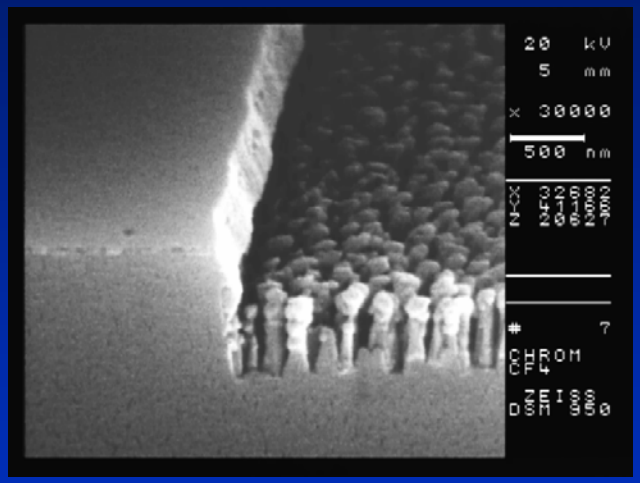
Nature Biotechnology **22**, 6 - 7 (2004)

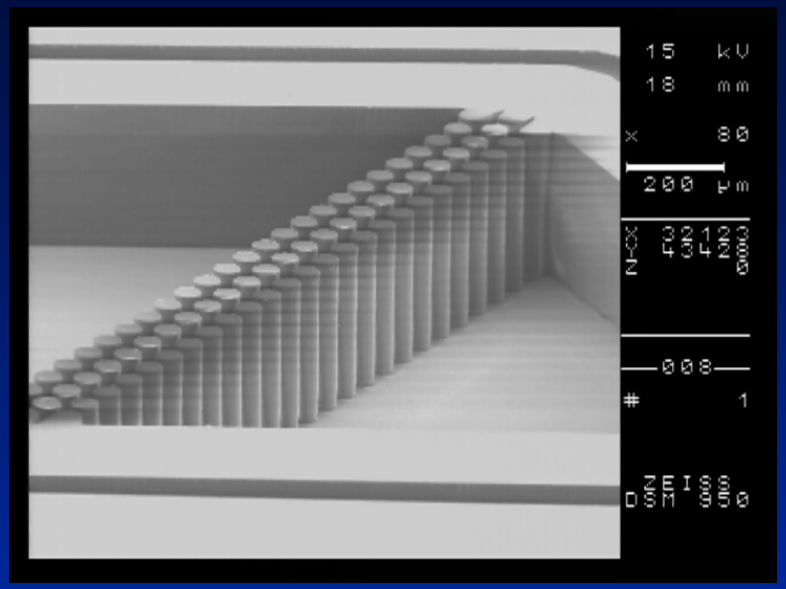
Info Bio Nano

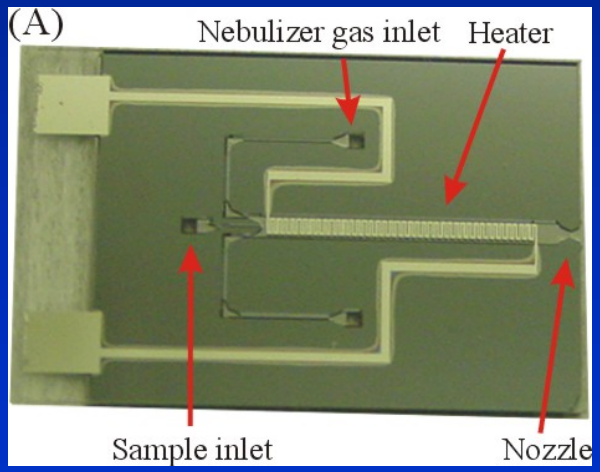

In-vivo IR Spectroscopy
Confocal microscopy
Confocal nSERS
In-vivo detection window
Cell trapping
µCIAs
Cellular Analysis
Cell lysing
10µm
nSERS
200 nm
Nanogap Junction
1mm
Cell sorting by adhesion protein
Microfluidic Pumps
Microfluidic interface

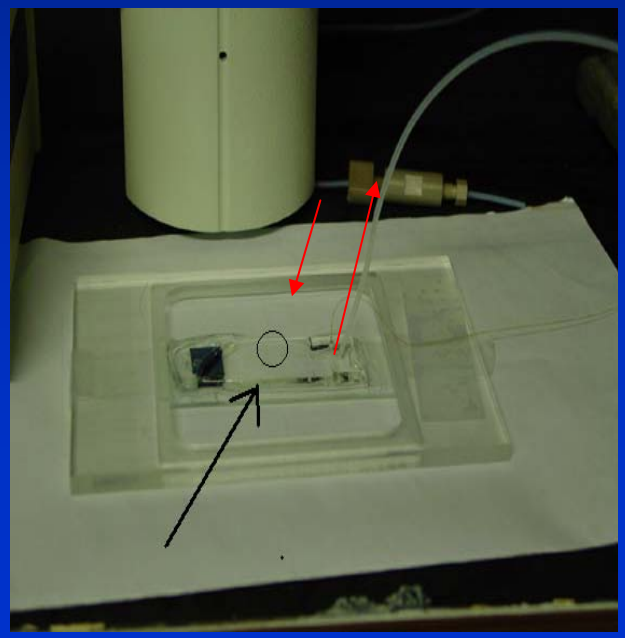
Protein Microarray Chip structures



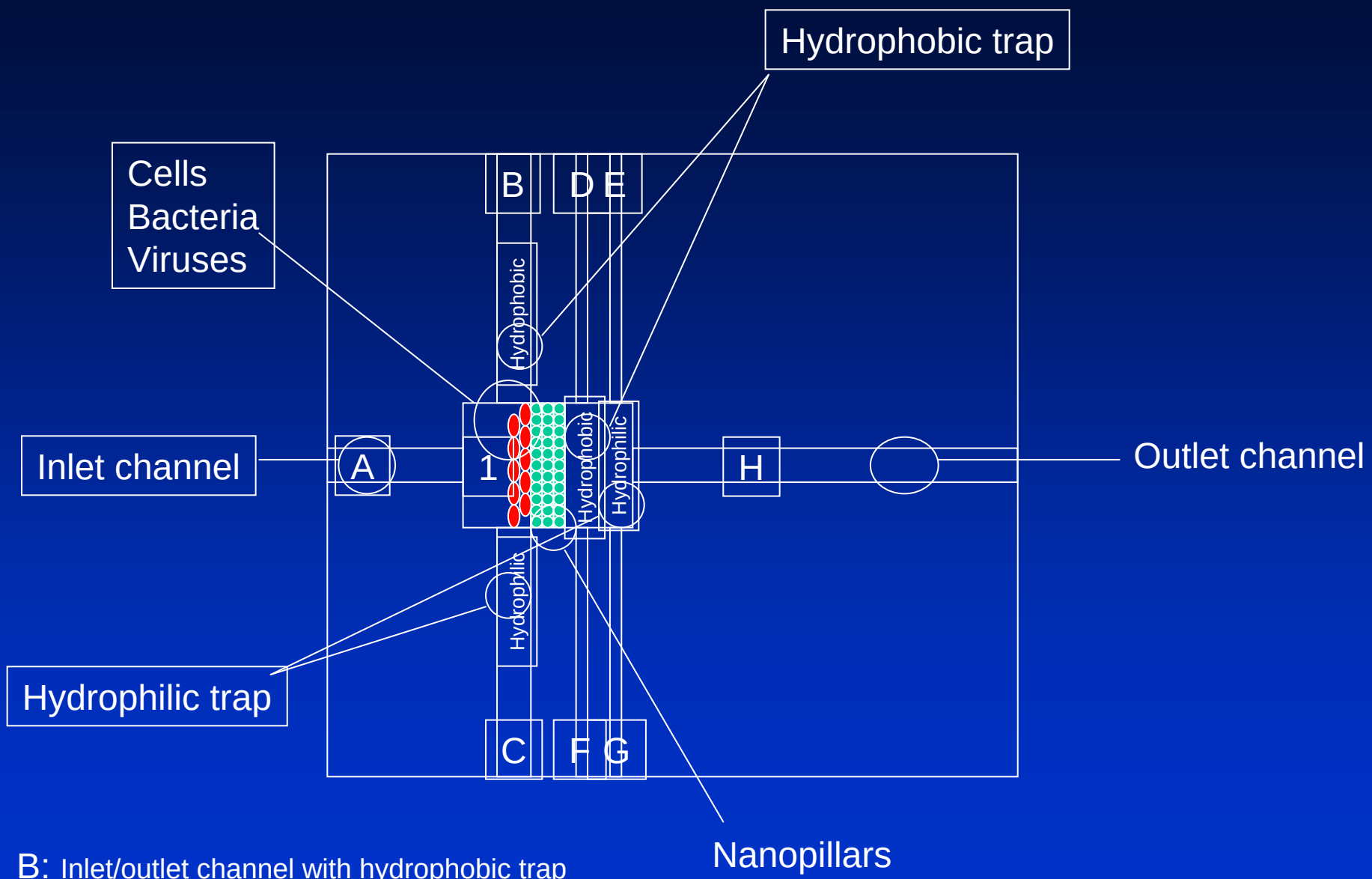








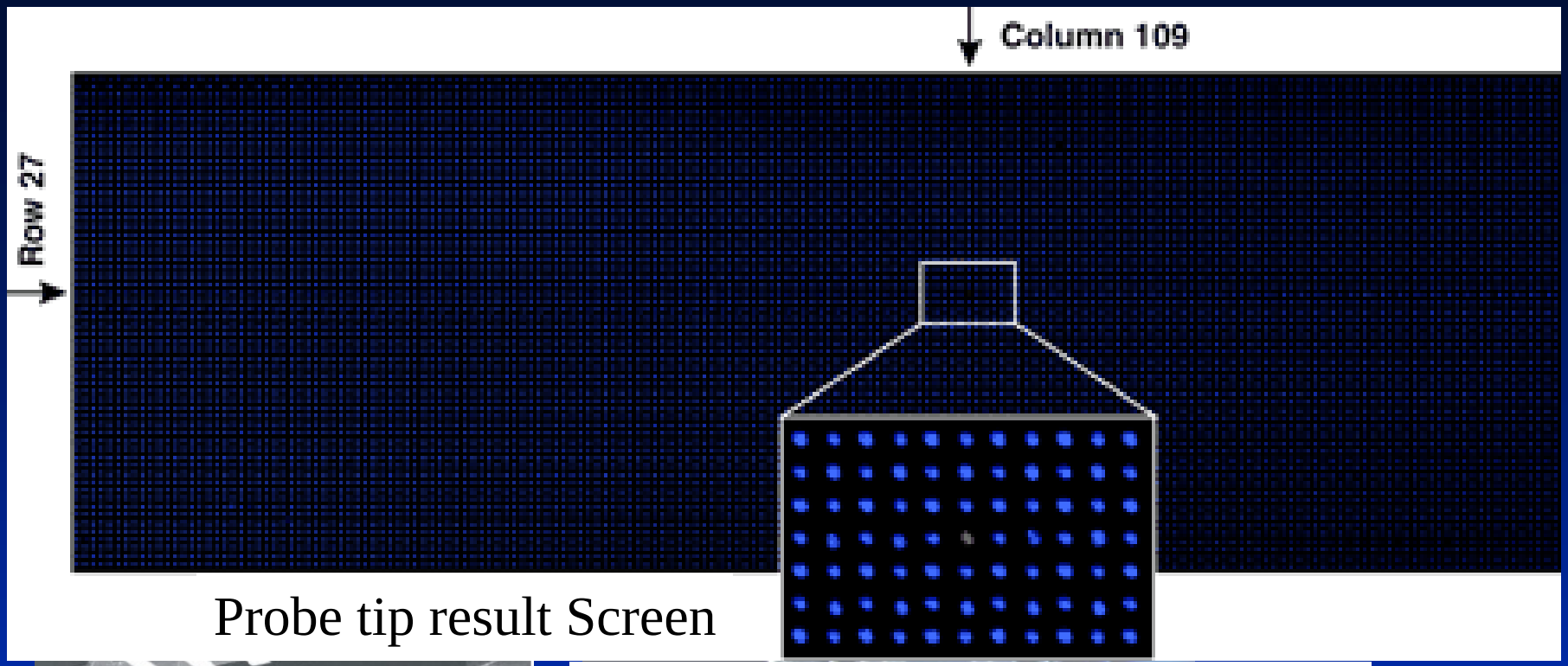
Development of Integrated Nanoliter Analysis Devices (DDTC-Viikki, Microtechnology Center-HUT, Biomedicum Helsinki)



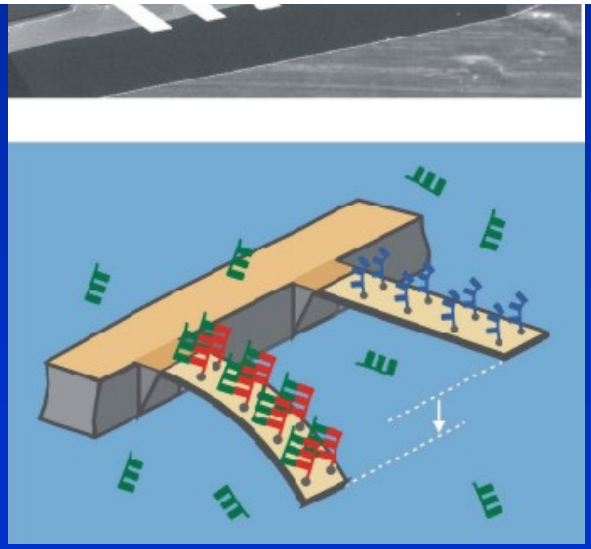
B: Inlet/outlet channel with hydrophobic trap

C: Inlet/outlet channel with hydrophilic trap

D-G: Inlet/outlet channels for liquid transfer and wash



Probe tip result Screen



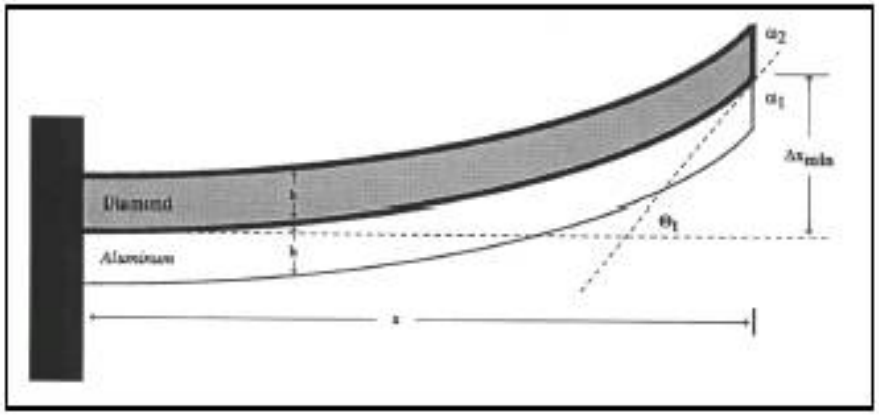
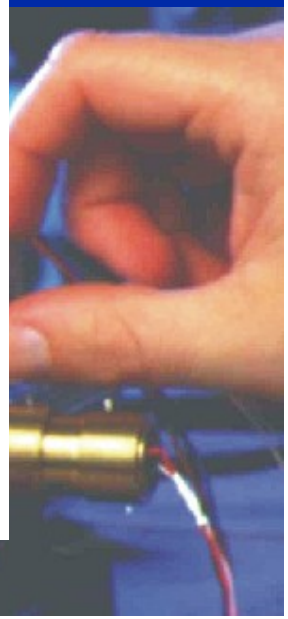
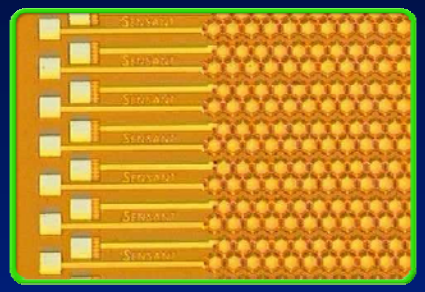


Fig. 4.8. Thermal expansion temperature sensor (schematic representation only).



Probe tip contains billions of nanoscale molecular assay receptors

Solid State Ultrasound



cMUT MEMS Array
Capacitive micro-fabricated ultrasonic transducers

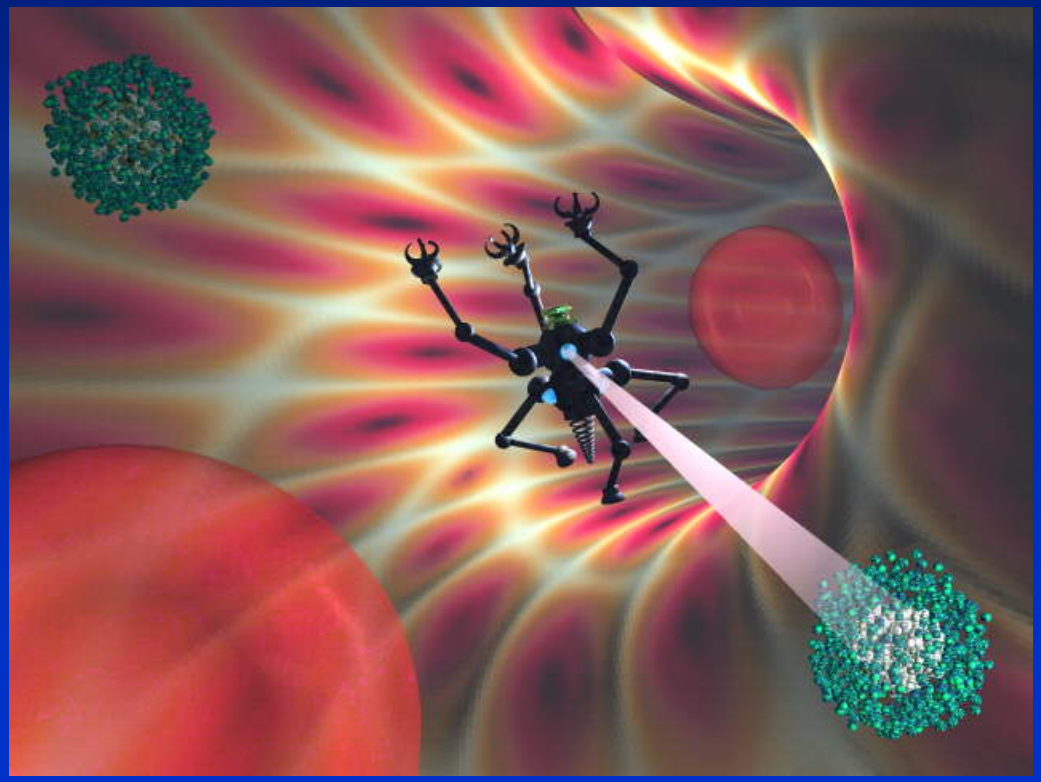
- Enabling Technologies
- Integration
  - MEMS transducer and electronics in the same miniature circuit
- Miniaturization
  - Highest density, performance interconnect & packaging

- Benefits
- Portable applications
- Flexible sheet-like “probe”
- Low-cost manufacturing

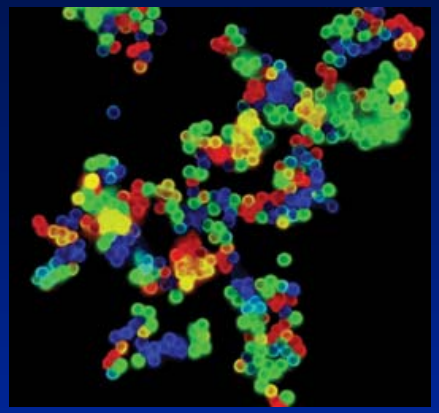
The diagnosis is completed in a few seconds, the infectious agent is Promptly Exterminated and a resurvey with the probe several minutes afterwards reveals no evidence of the pathogen.

Key words:

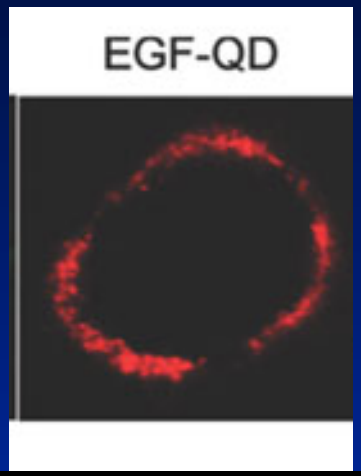
- Diagnostic
- Treatment



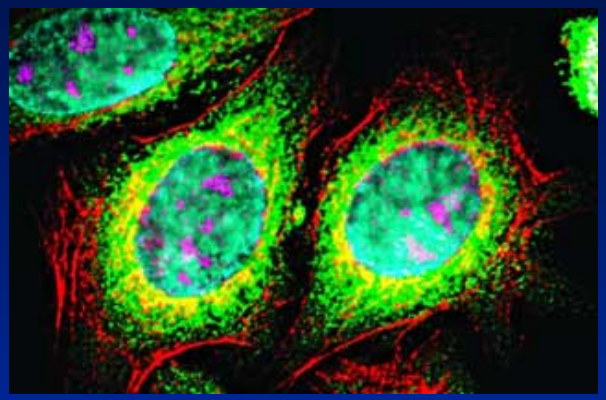
Quantum Dot Applications in Cancer Management



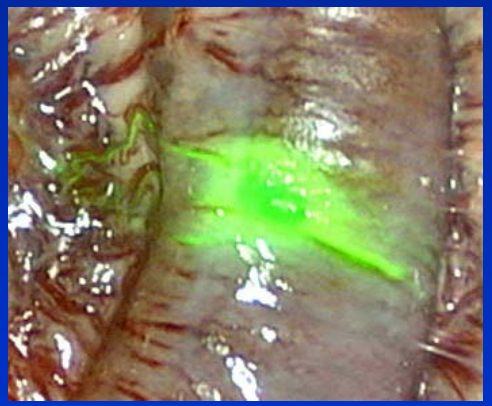
Quantum dots



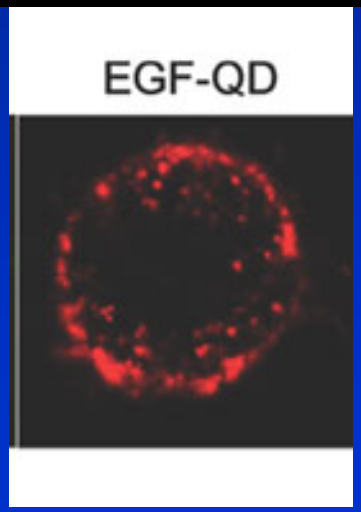
Protein binding & internalization

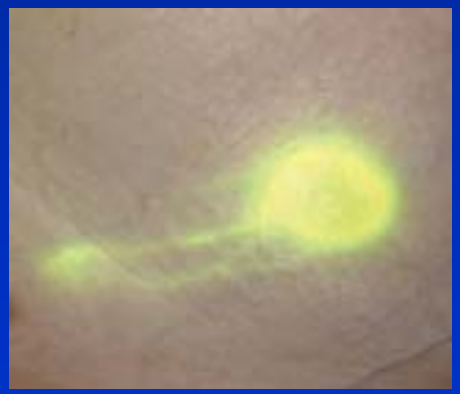


Laboratory diagnostics



Quantum dot labelling of mouse colon cancer



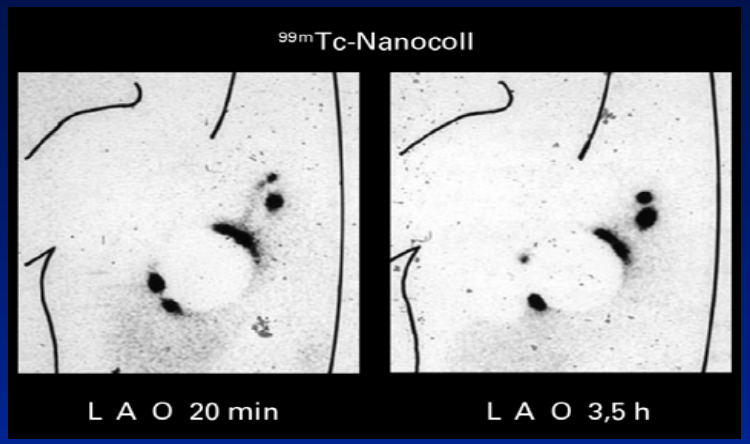


Sentinel node visualization for breast cancer through 1 cm of tissue

Intra-Operative Imaging

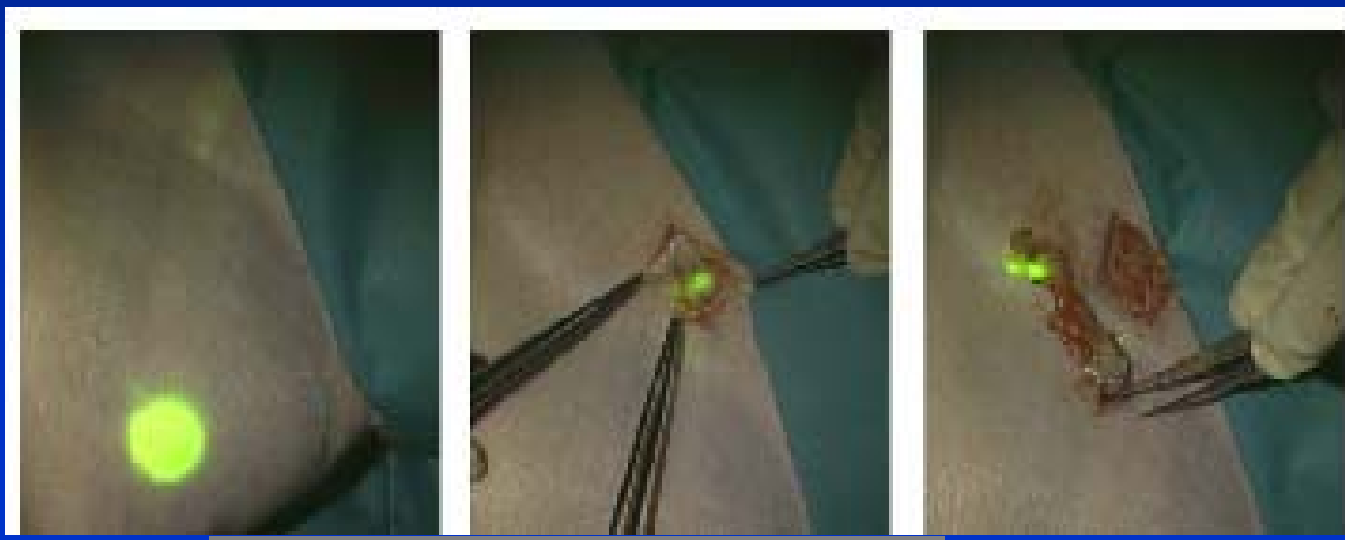
Sentinal lymph node evaluation and tumour extent

99mTc
NanoColloid



Zentralklinikum Augsburg, Nuklearmedizin

Quantum Dot
Nanoparticle
Fluorescence



Beth Israel Deaconess Medical Center

Nanomedicine will offer in the doctors office…

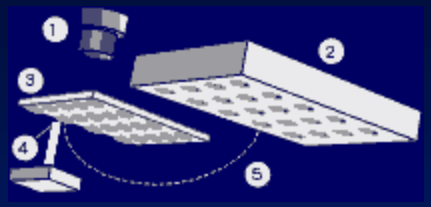
- in-office comprehensive genotyping

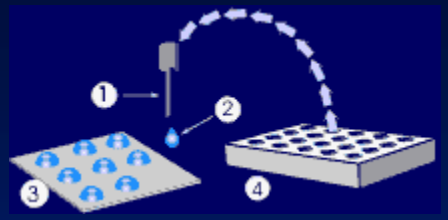
- real-time whole-body scans for particular bacterial coat markers, tumor cell antigens, mineral deposits, suspected toxins, hormone imbalances of genetic or lifestyle origin, and other specified molecules

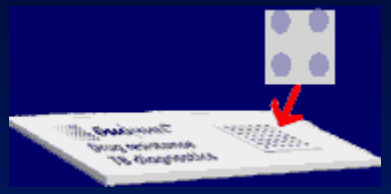
- producing three-dimensional maps of desired targets with submillimeter spatial resolution.

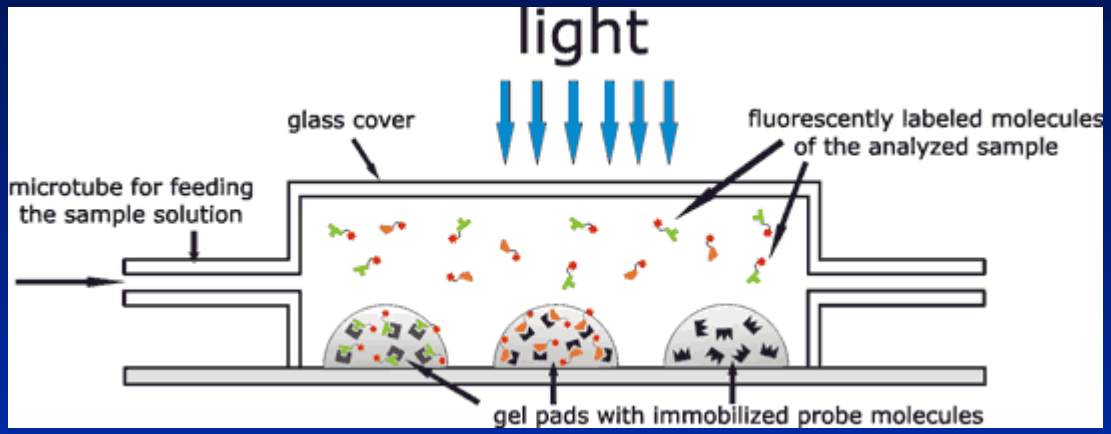
- Treatment of various symptoms at the spot

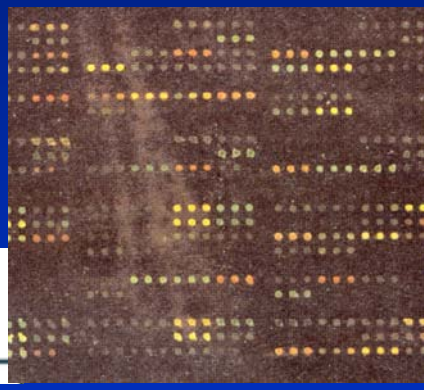
Microfluidics in a Chip with nanosurfaces

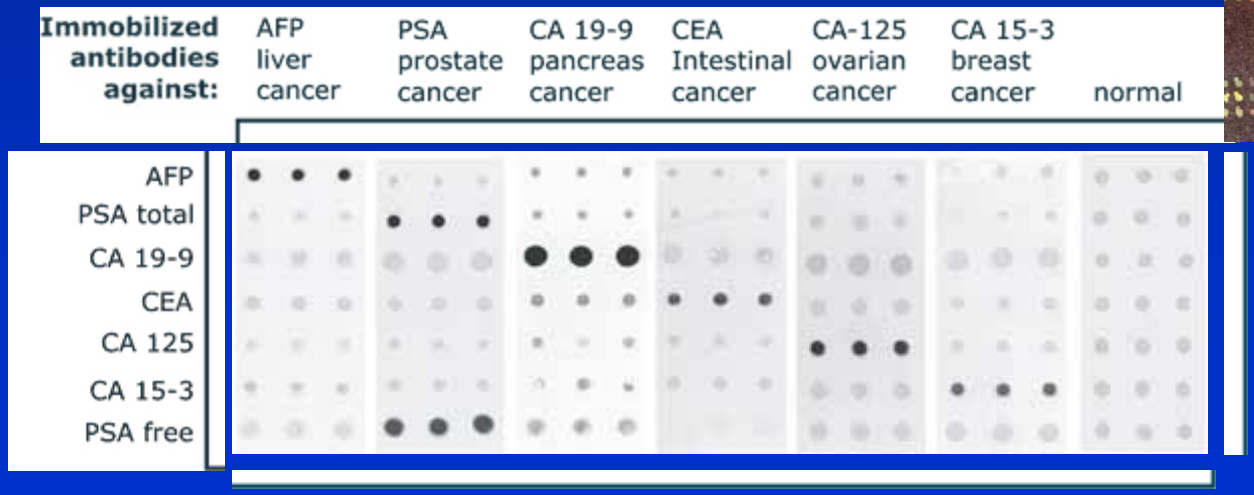







light
glass cover
fluorescently labeled molecules of the analyzed sample
microtube for feeding the sample solution
gel pads with immobilized probe molecules




Immobilized antibodies against:
AFP liver cancer
PSA prostate cancer
CA 19-9 pancreas cancer
CEA Intestinal cancer
CA-125 ovarian cancer
CA 15-3 breast cancer
normal
AFP
PSA total
CA 19-9
CEA
CA 125
CA 15-3
PSA free

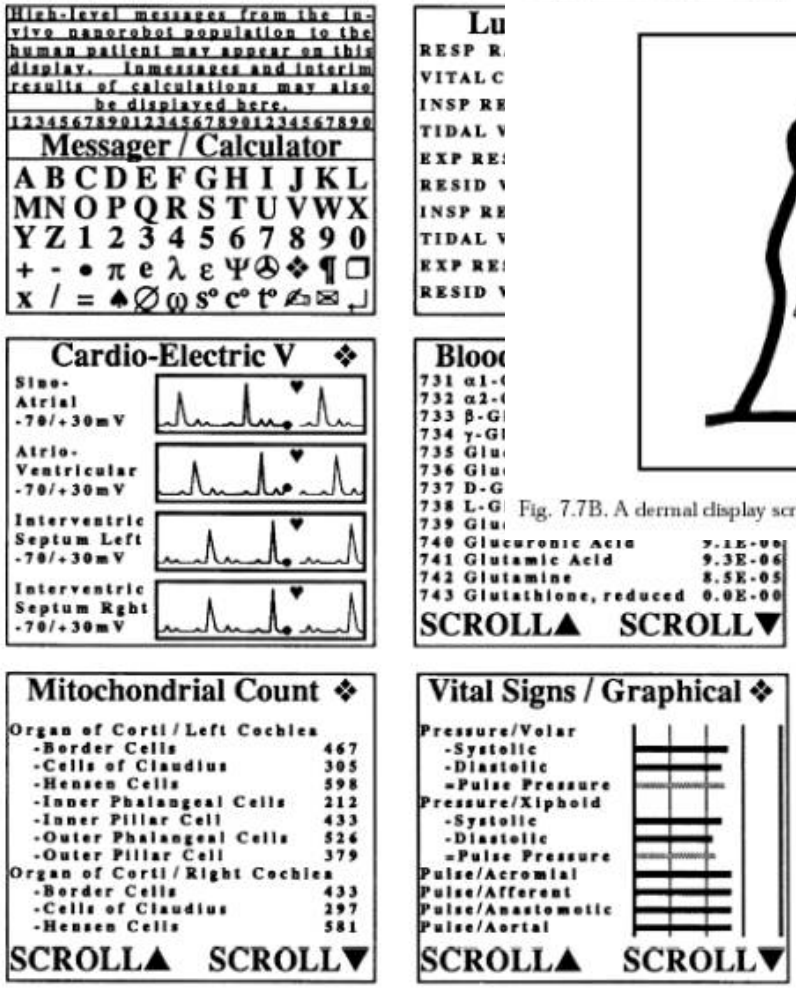


Fig. 7.7A. A selection of possible dermal display screens.

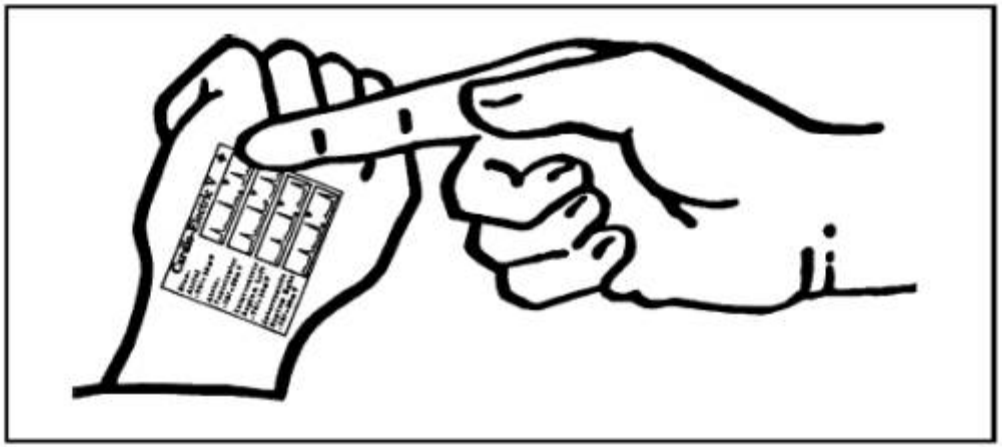
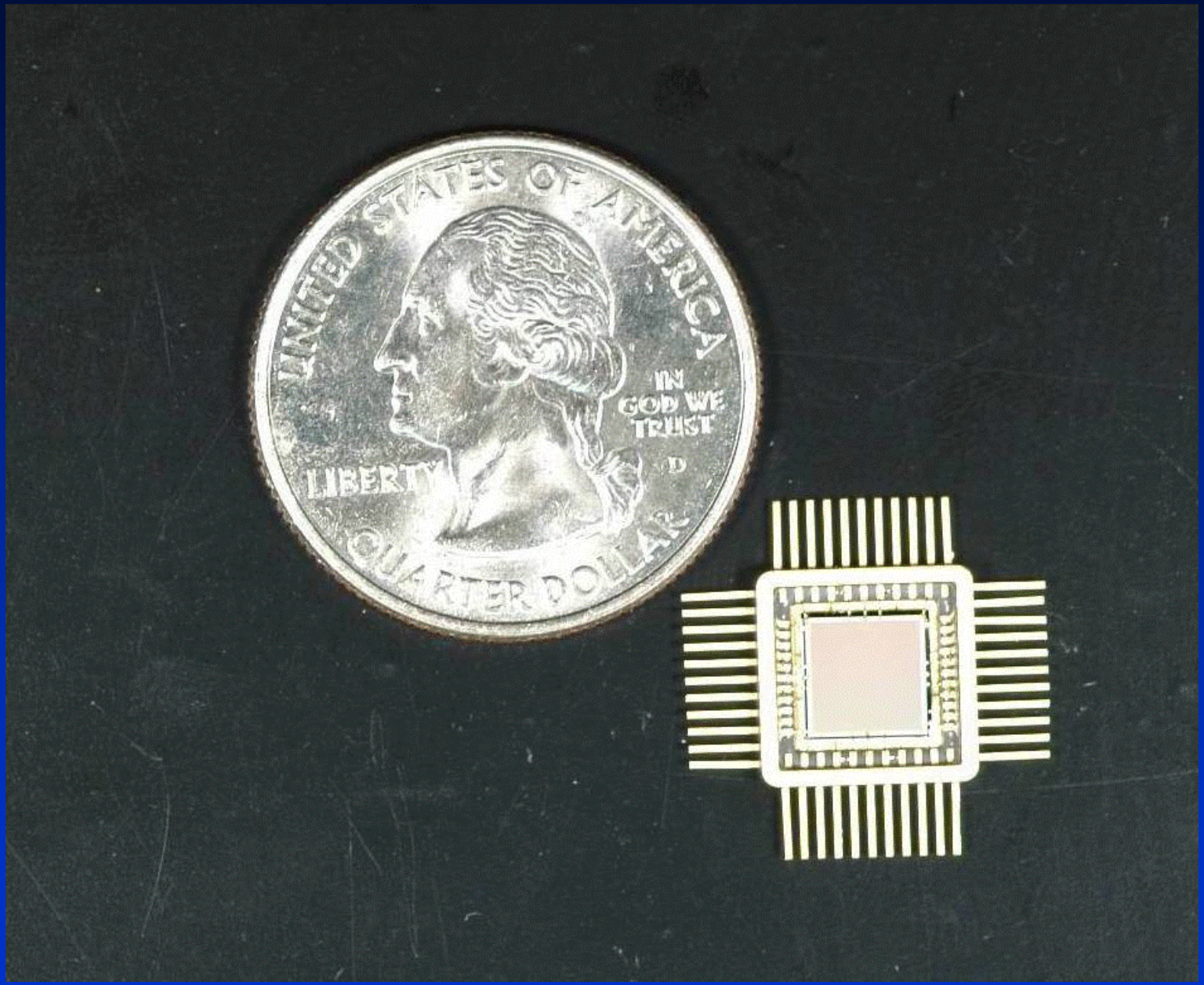
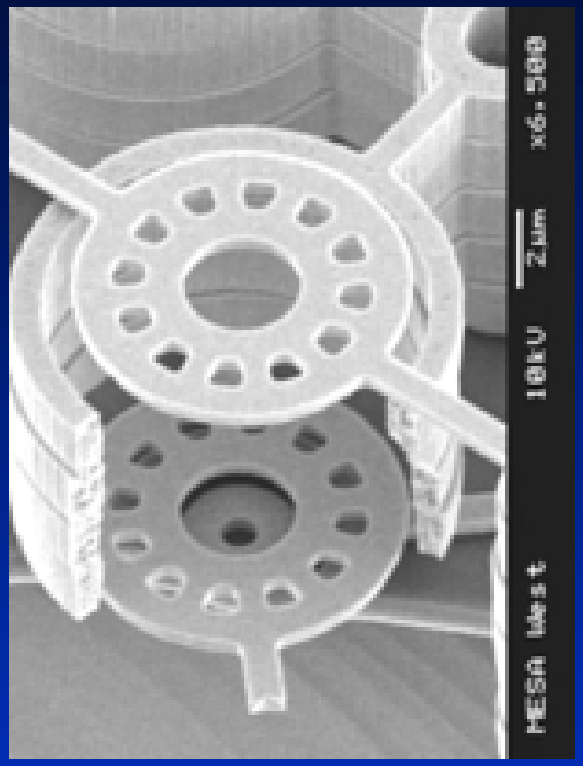
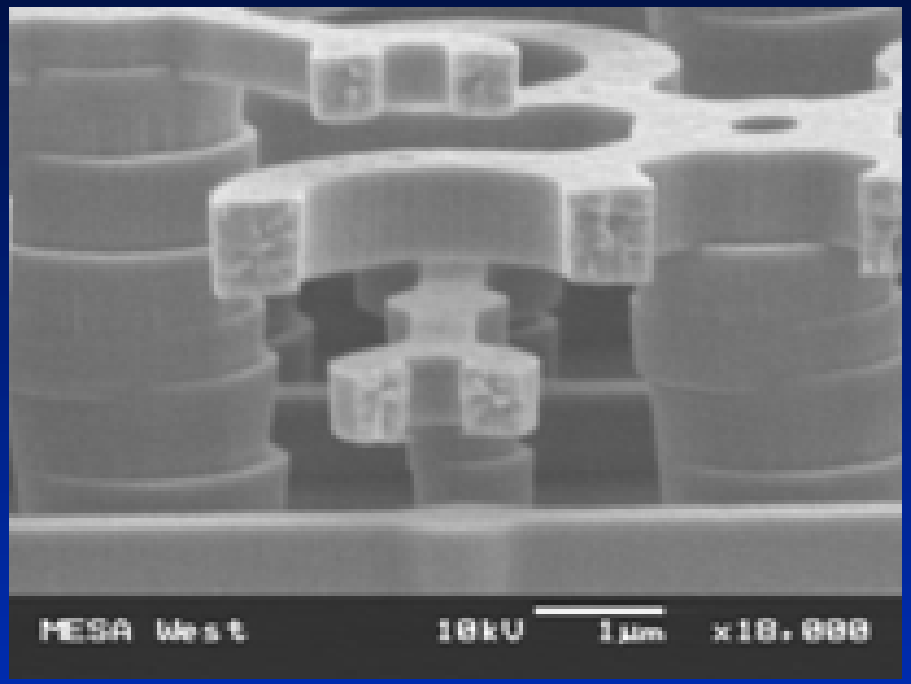


Fig. 7.7B. A dermal display screen in use.

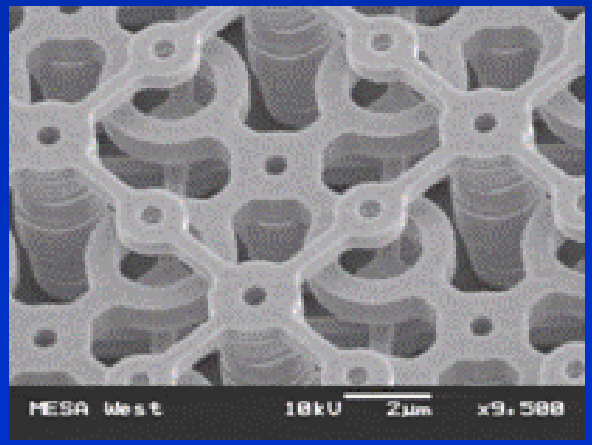
A Dermal Display


UNITED STATES OF AMERICA
IN GOD WE TRUST
LIBERTY
D
QUARTER DOLLAR





A set of thousands of Mass Spectrometers in one chip



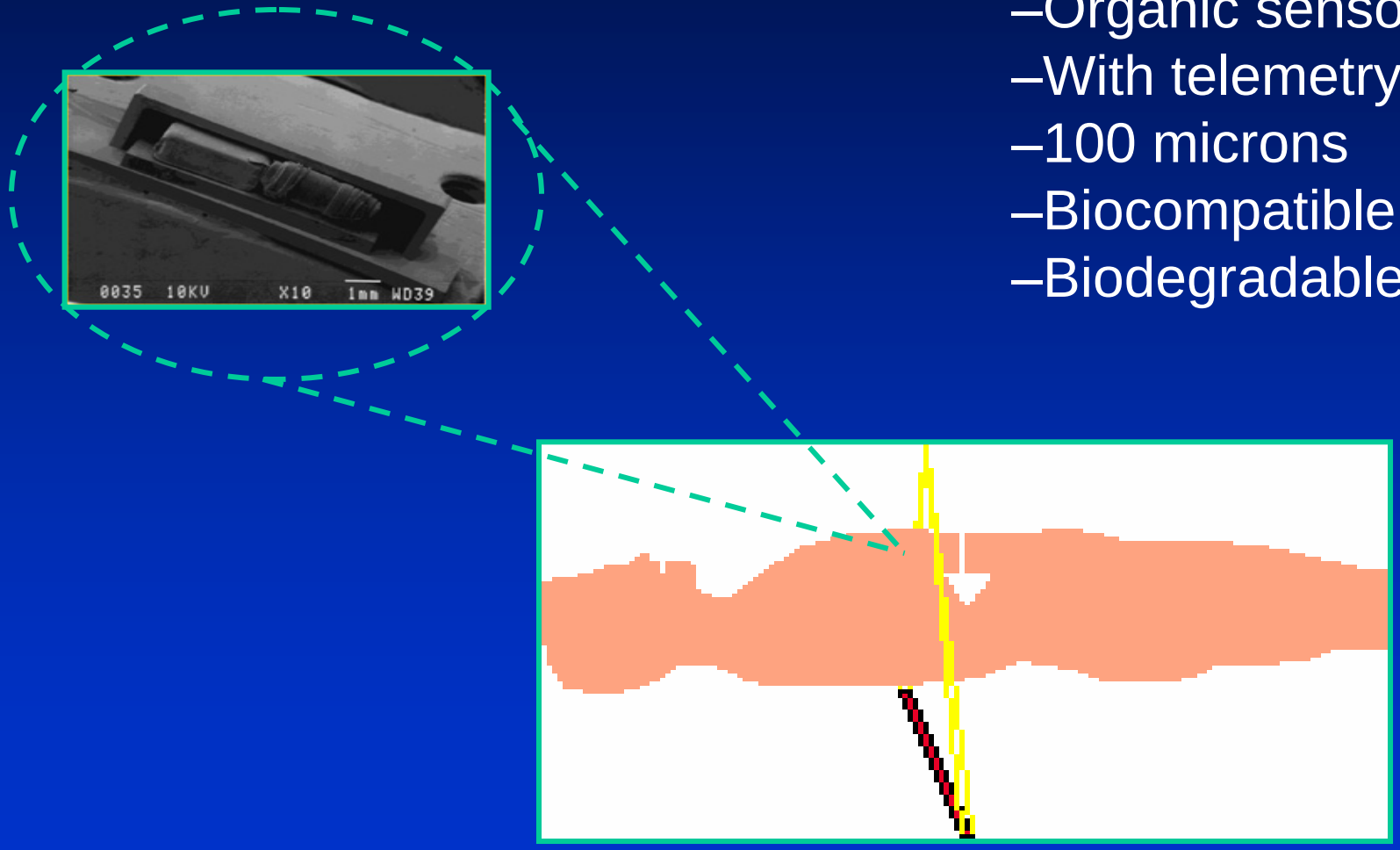
Nanotechnology and Biosensors

- Nanotechnology will contribute to a wide range of diagnostic applications through the development of:
  - Implantable Diagnostic Devices
  - Internal Diagnostics
  - Intracellular Diagnostics
  - Pathogen Detection

Bio-Sensors & Actuators

In-vivo Sensor

- –Organic sensor
- –With telemetry
- –100 microns
- –Biocompatible
- –Biodegradable



New Applications of Biosensors

- Stent Monitor
  - Restenosis
  - Pressure gradients
  - Plaque build-up
  - Artery thickening

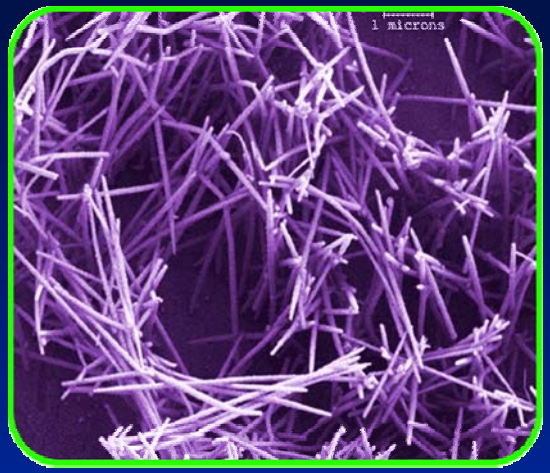
- Smart Catheter
  - Fibrillation Detection
- Post-operative Patient Monitoring

- Drug Delivery
- Radiation Therapy
  - Dynamic Dose Control,
  - Micro-Targeting
  - Reconstruction Aid (angular uncertainty)

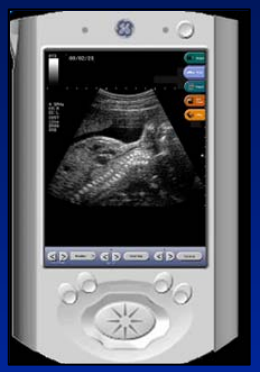
Technology drivers for remote sensing

- MEMS devices
- Sensors and electronic circuitry on same chip
- Low power wireless transmitting devices(100 μWatt)
- Millimetre scale batteries
- Micro-sensor networks using 2.5mm^3 motes
- Transmitter range 20m between motes
- Wireless portable display devices
- Hardware encryption
- Local decision support software

Nano BioSensors in the ER



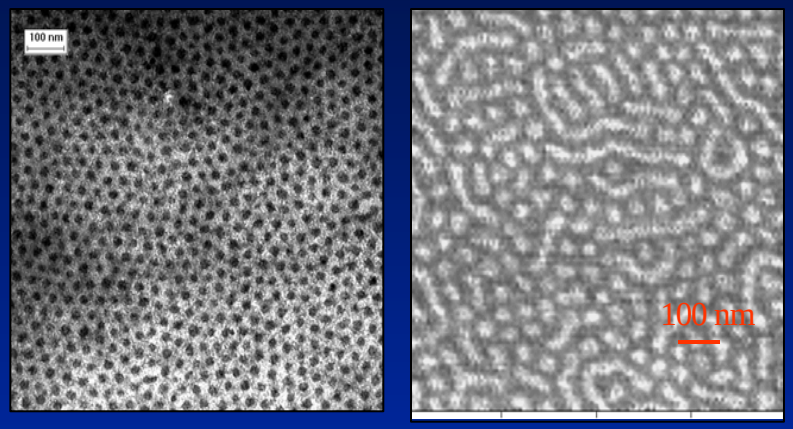
Nanowires
GE Global Research (2002)



- Enabling Technologies
  - Nanotubes & nanowires
  - Quantum dots
  - Hybrid organics/inorganic

- Benefits
  - Real time, in situ reading of biochemical activity
  - Cellular level optical imaging
  - Sensor guided precision surgical tools

Nano BioSensors in the Doctor`s Office



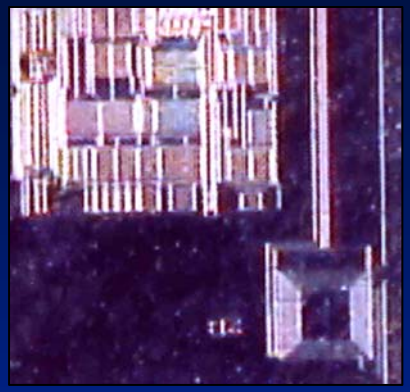
Self Assembled Block Copolymer Thin Films (GE Global Research, 2002)

- Enabling Technologies
  - Molecular recognition
  - High density nano-arrays

- Benefits
  - Total blood analysis in minutes
  - Rapid, accurate disease diagnosis
  - Patient specific disease treatment

Nano BioSensors at Home

Organic Light Emitting Diode (GE Global Research, 2002)



Integrated Hall Effect Sensor (GE Global Research, 1998)

- Enabling Technologies
  - Wireless communications
  - Self powered devices
  - High resolution displays

- Benefits
  - Simple patient administered diagnostic tests
  - Automatic transmission of outpatient data from home to the doctor

Percutaneous Monitoring with Miniature Sensors

- Digital plaster device checks vital signs such as:
  - Temperature
  - Blood pressure
  - Glucose levels
- Results via modem or PDA to a computer
- Out of range readings give alarm
- Based on hybrid analogue/digital CMOS semiconductors

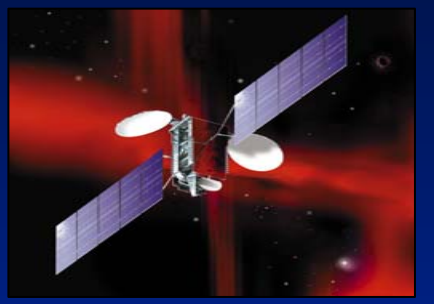
Device 3x5mm

Toumaz Technology

Systems Integration is Key to Success

Point of Decision Application

- In Vitro Analysis
  - Protein targeting fluorescent nanoparticles, Microfluidics Lab on a Chip,Nanowire & Nanocantilever sensors
- Medical Imaging
  - MEMS, Nano Systems
- Communication Satellites
  - 3D, Thin, Low Power Packaging
- Mobile Communications
  - Miniature, High Performance Systems



MEMS based pocket ultrasound system replacing stethoscope

Future Developments of Nanotechnology in Healthcare

- AFM as a nano-scalpel to dissect DNA from regions of a chromosome
- Nanoscale devices on catheter tips
- Single cell diagnosis
- Insertion of molecules into single cell using MEMS devices
- Drug delivery and monitoring devices
- Biomedical lab testing at the point of care
- Synthetic organs

(Special thanks to Leonard Fass Ph.D. GE Healthcare)