Nanotechnology in medical research: where, when and why?

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

Nanomedicine

Five lectures:
- Nanomedicine prospectives
- Nanoscience and lipids
- Nanoscale energy production
- Nanoscience and immunology
- Nanoscience and virology

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What are the 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?
Nanomedicine, what is all about?

Our dream!

1999
(J. Lertola)

ANATOMY OF A NANOPROBE

- **Acoustic relay** attached to an onboard computer sends and receives ultrasound to communicate with medical team
- **Sensors and manipulators** detect illnesses and perform cell-by-cell surgery
- **Pumps** remove toxins from the body and dispense drugs
- **Outer shell** made of strong, chemically inert diamond

**Typical probe sizes**

Up to 10 trillion nanorobots, each as small as 1/200th the width of a human hair, might be injected at once
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."
"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."

Medical microchips' massive potential

Robotic techniques could revolutionize heart surgery
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.
**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?**

<table>
<thead>
<tr>
<th><strong>Biomaterials</strong></th>
<th><strong>Bone</strong></th>
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<tbody>
<tr>
<td><strong>Teeth</strong></td>
<td><strong>Cells</strong></td>
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<tr>
<td><strong>Cartilage</strong></td>
<td><strong>Immune system</strong></td>
</tr>
<tr>
<td><strong>Viral and bacterial attack</strong></td>
<td><strong>Drug delivery</strong></td>
</tr>
<tr>
<td><strong>Diagnostics</strong></td>
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</tbody>
</table>
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 fibrous 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.)
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 Technology Platform on NanoMedicine**
Nanotechnology for Health
Vision Paper
and Basis for a Strategic Research Agenda for NanoMedicine

September 2005

Nanomedicine
Nanotechnology for Health

November 2006
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.
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.
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
### Bioarrays and Biosensors

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

### 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
# EUROPEAN SCIENCE FOUNDATION

## Bioarrays and Biosensors

<table>
<thead>
<tr>
<th>DNA chips</th>
<th>lab on chip</th>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

## What do we have

- Painless
- Room temperature for consumables
- Take the test to the patient
- Lay person (nurse’s aid) can use
- Minimise consultation time (<1 minute)
- Simple
- Portable
- Storage
- Painless

## What do we want

- Minimally invasive blood sampling
Molecular Imaging Diagnostics (MDx): Impact on healthcare in the future

Genetic disposition
DNA Mutations

Today
Earlier diagnosis, optimized workflow

Future

<table>
<thead>
<tr>
<th>Genetic disposition</th>
<th>DNA Mutations</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Screenng</th>
<th>Diagnosis &amp; Staging</th>
<th>Treatment &amp; Monitoring</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>Unspecific markers, POC imaging, Mammo-graphy</td>
<td>Diagnostic imaging, Biopsies</td>
<td>Follow-up</td>
</tr>
<tr>
<td>First symptoms</td>
<td></td>
<td>Surgery, Cuff-lab, Radiation therapy</td>
<td></td>
</tr>
<tr>
<td>Progressing disease</td>
<td></td>
<td></td>
<td>Diagnostic imaging, Unspecific markers</td>
</tr>
</tbody>
</table>

- Specific markers, Imaging: Quantitative, Whole-body
- Molecular imaging:
- Mini-invasive surgery
- MI, MDx
- Non-invasive, Quantitative, Targeted drug imaging
- CA Diagnosis, Delivery & Tracing
- Tissue analysis (MDx)
Drug delivery and Pharmaceutical development

- Liposomes
- Antibodies and their conjugates
- Viruses as viral vectors
- Polymer micelles

Nanopharmaceuticals

- Nanoparticles
- Polymer-protein conjugates
- Unimolecular polymer and dendrimer conjugates
- 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
<table>
<thead>
<tr>
<th>Technology</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nanopharmaceuticals</strong></td>
<td></td>
</tr>
<tr>
<td>in current use or</td>
<td>Cancer</td>
</tr>
<tr>
<td>Entering routine use</td>
<td>Antiviral agents</td>
</tr>
<tr>
<td>in the short-term</td>
<td>Arteriosclerosis</td>
</tr>
<tr>
<td>future (within 5 years)</td>
<td>Chronic lung diseases</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
</tr>
<tr>
<td><strong>Nanopharmaceuticals</strong></td>
<td></td>
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<tr>
<td>with potential clinical</td>
<td>Gene therapy</td>
</tr>
<tr>
<td>applications in the</td>
<td>Tissue engineering</td>
</tr>
<tr>
<td>longer term future</td>
<td>Tissue/cell repair</td>
</tr>
<tr>
<td>(10 years)</td>
<td></td>
</tr>
<tr>
<td><strong>Nanodevices</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Delivery of diagnostic and therapeutic agents</td>
</tr>
</tbody>
</table>
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.
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)
Lab Automation: Sample Prep, SMM, & SMD

1mm Microfluidic Pumps

Cell trapping

In-vivo IR Spectroscopy

Confocal microscopy

Cell sorting by adhesion protein

Cell lysing

nSERS

Microfluidic interface

Confocal nSERS

In-vivo detection window

Nanogap Junction

μCIAs

Cellular Analysis

Microfluidic Pumps

1mm Nanogap Junction
Protein Microarray Chip structures

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

Hydrophilic trap

Nanopillars

B: Inlet/outlet channel with hydrophobic trap
C: Inlet/outlet channel with hydrophilic trap
D-G: Inlet/outlet channels for liquid transfer and wash
The physician faces the patient and pulls from his pocket a lightweight handheld device resembling a pocket calculator…

- **Self-sterilizing cordless pencil-sized probe**
- **Acoustic echolocation transceivers**

Probes tip result Screen

Probe tip contains billions of nanoscale molecular assay receptors

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

Quantum dot labelling of mouse colon cancer

Protein binding & internalization

Laboratory diagnostics

Sentinel node visualization for breast cancer through 1 cm of tissue
Intra-Operative Imaging

Sentinal lymph node evaluation and tumour extent

99mTc NanoColloid

Quantum Dot Nanoparticle Fluorescence

Zentralklinikum Augsburg, Nuklearmedizin
- 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

_Nanomedicine will offer in the doctors office..._
### Immobilized antibodies against:

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Disease</th>
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<tbody>
<tr>
<td>AFP</td>
<td>Liver cancer</td>
</tr>
<tr>
<td>PSA</td>
<td>Prostate cancer</td>
</tr>
<tr>
<td>CA 19-9</td>
<td>Pancreas cancer</td>
</tr>
<tr>
<td>CEA</td>
<td>Intestinal cancer</td>
</tr>
<tr>
<td>CA-125</td>
<td>Ovarian cancer</td>
</tr>
<tr>
<td>CA 15-3</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>Normal</td>
<td></td>
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</tbody>
</table>

### Adjacent Image

- Glass cover
- Microtubes for feeding the sample solution
- Fluorescently labeled molecules of the analyzed sample
- Gel pads with immobilized probe molecules
A Dermal Display

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

Fig. 7.7B. A dermal display screen in use.
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 2.5mm³ motes
- Transmitter range 20m between motes
- Wireless portable display devices
- Hardware encryption
- Local decision support software
Nano BioSensors in the ER

• 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

Nanowires
GE Global Research (2002)
Nano BioSensors in the Doctor`s Office

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

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

Self Assembled Block Copolymer Thin Films (GE Global Research, 2002)
Nano BioSensors at Home

- 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

Organic Light Emitting Diode (GE Global Research, 2002)

Integrated Hall Effect Sensor (GE Global Research, 1998)
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
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)