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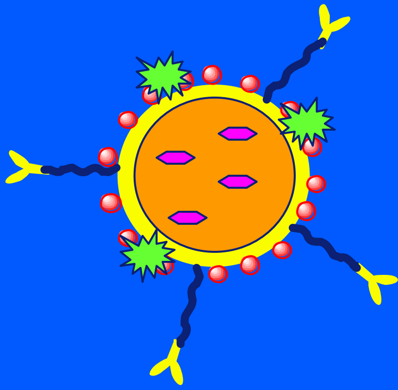
Nanomaterials for Healthcare



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Outline

- Introduction
  - Promises of nanotechnology
- Nanotechnology at Philips
  - Using nanotechnology for real applications
  - Focus on Healthcare applications:
    - Nanomaterials enabling Molecular Medicine
- Examples
  - GMR biosensors for Molecular Diagnostics
  - Targeted nanoparticles for Molecular Imaging
- Summary

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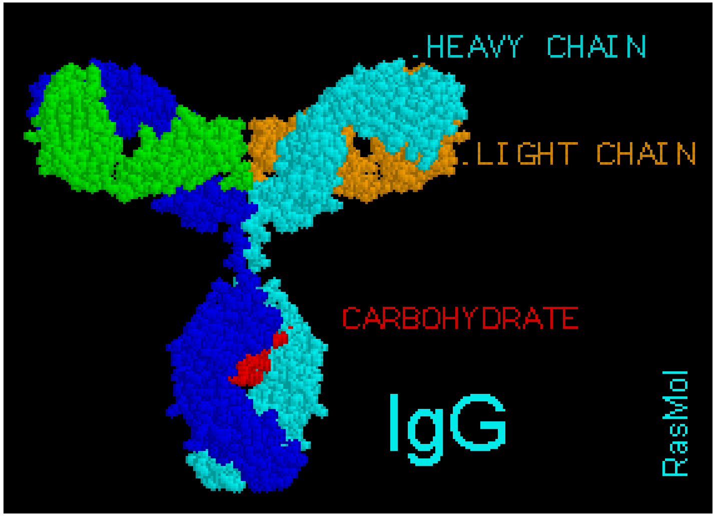
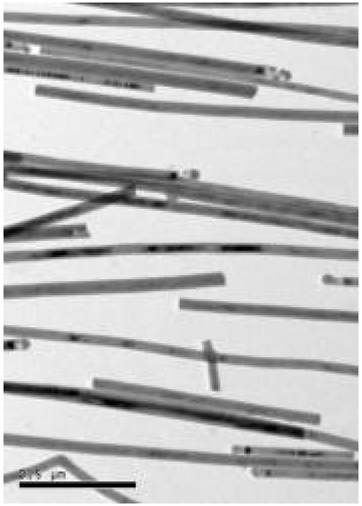
Nanotechnology - Introduction

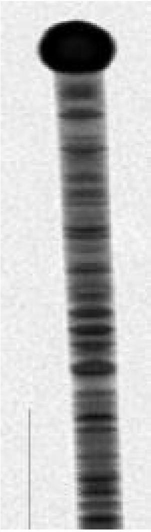
New materials & structures for new applications

A definition of nanotechnology

Nanotechnology refers to the top-down and bottom-up manipulation of matter down to the atomic level, ranging from atoms, molecules and biomolecules, to particles and (structured) thin films, to arrive at functional building blocks of sub-nm size.







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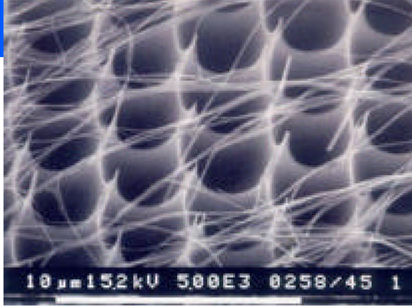
Nanotechnology @ Philips: focus on real applications



- Nanotechnology with an eye on the application
  Not nanotechnology for nanotechnology's sake

- Taking advantage of unique properties of nanomaterials and nanostructures, e.g.:
  - Semiconductors: towards 10-nm MOSFET
  - Lighting: InP, Quantum Dots
  - Sensors: Si nanowires, magnetic nanoparticles
  - Analysis: Carbon Nanotubes as field emitters in EM
  - Displays: functional optical films and "rollable" displays
  - Healthcare: (targeted) contrast agents

- Considering manufacturability issues
  - Integrated approach: upscalable, connected nanotechnology

Key in manufacturing: patterning techniques

Top-Down

< 100 nm (nano)

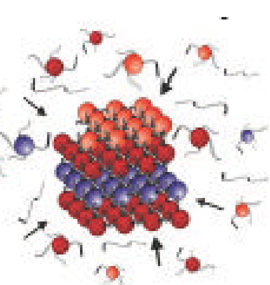
Extreme UV lithography
Water immersion litho
E-Beam lithography
Serial, 5-10 nm limit, $$
Nanoimprint lithography*
Parallel,10 nm limit
Dip-pen lithography
Direct transfer,
15 nm resolution

> 100 nm (micro)

Photolithography (DUV)
- Parallel, resist based
- Practical limit ≈ 100 nm
- $$$

Soft Lithography*
- Parallel, direct transfer
- Limit ≈ 50-100 nm

Bottom-up



Self-assembly
- Supramolecular chemistry
- Combination with top-down technology always required

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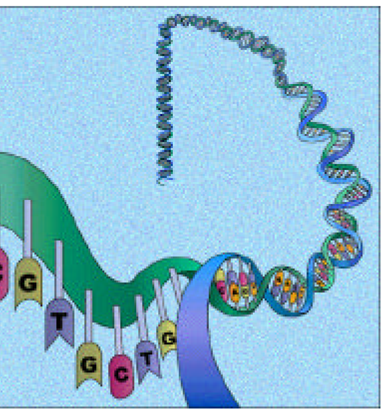
Example:
Nanomaterials for Molecular Medicine

Very small, “multifunctional”, high surface area particles for sensitive and specific diagnosis, and for targeted therapy

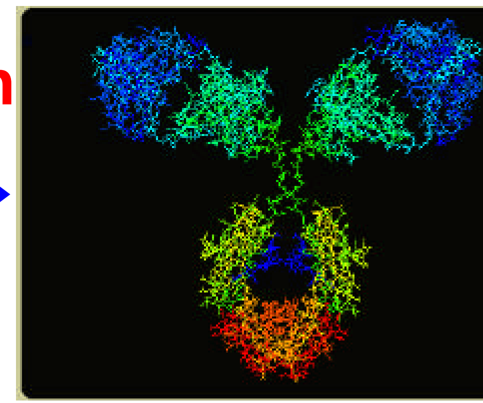
Molecular Medicine

- Genomic information becomes ***the primary basis*** for diagnostics and for day-to-day treatment decisions in healthcare

The flow of Genetic Information



transcription → RNA → translation



The Code

The Functio

- *Exploiting knowledge on the genetic, molecular and cellular basis of disease*

The Impact of Molecular Medicine:

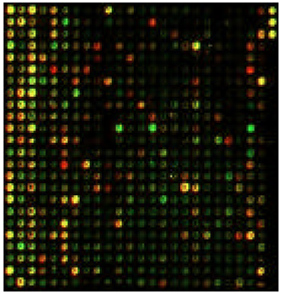
Improving the Health of the Nation (NIH position statement)

- **Early diagnosis/prevention/selection**
  - Big 3: Cardiovascular, Cancer, Stroke
- **Disease mechanisms**
  - e.g., islet *beta cell* mass in diabetes, detection of inhaled pulmonary pathogens, cellular effectors of (auto)immune diseases, neuro(psychiatric) disorders (amyloid, etc.)
- **New therapies**
  - Receptor-targeted drug/gene therapy
  - Stem cell imaging/tracking
  - Organ/tissue transplantation: function/rejection
- **Surrogate endpoints for clinical trials**
- **Bioterrorism: early warning**

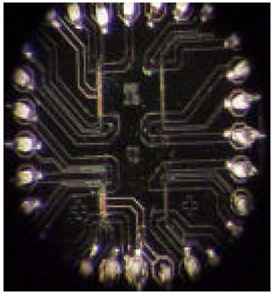
The paradigm shift in healthcare

2005: symptom → diagnosis → therapy

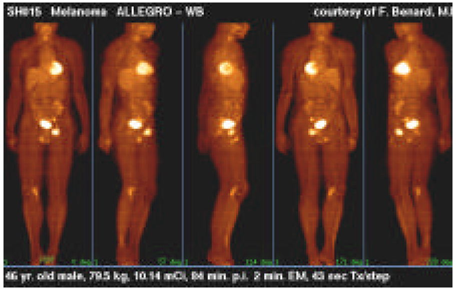
2020: predisposition → focused screening / EARLY detection → individualized therapy → therapeutic monitoring



Gene Chip



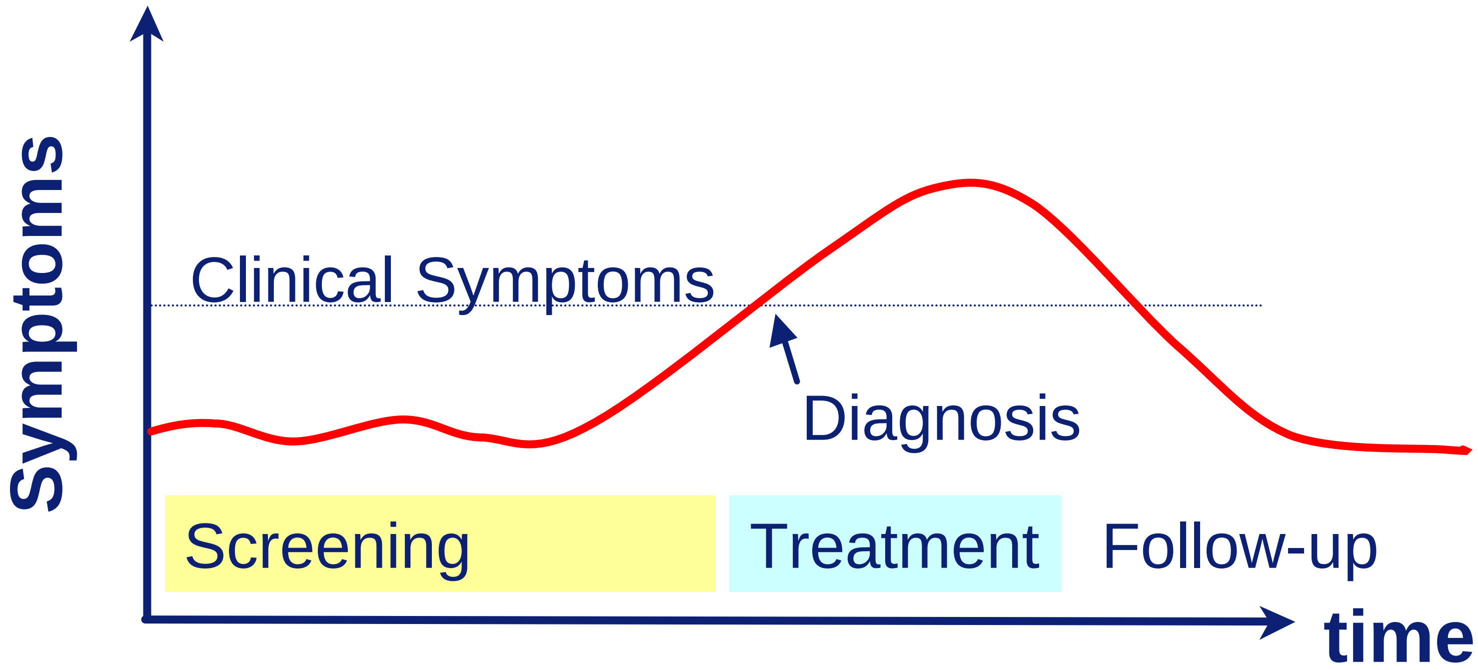
Biosensor



Molecular Imaging

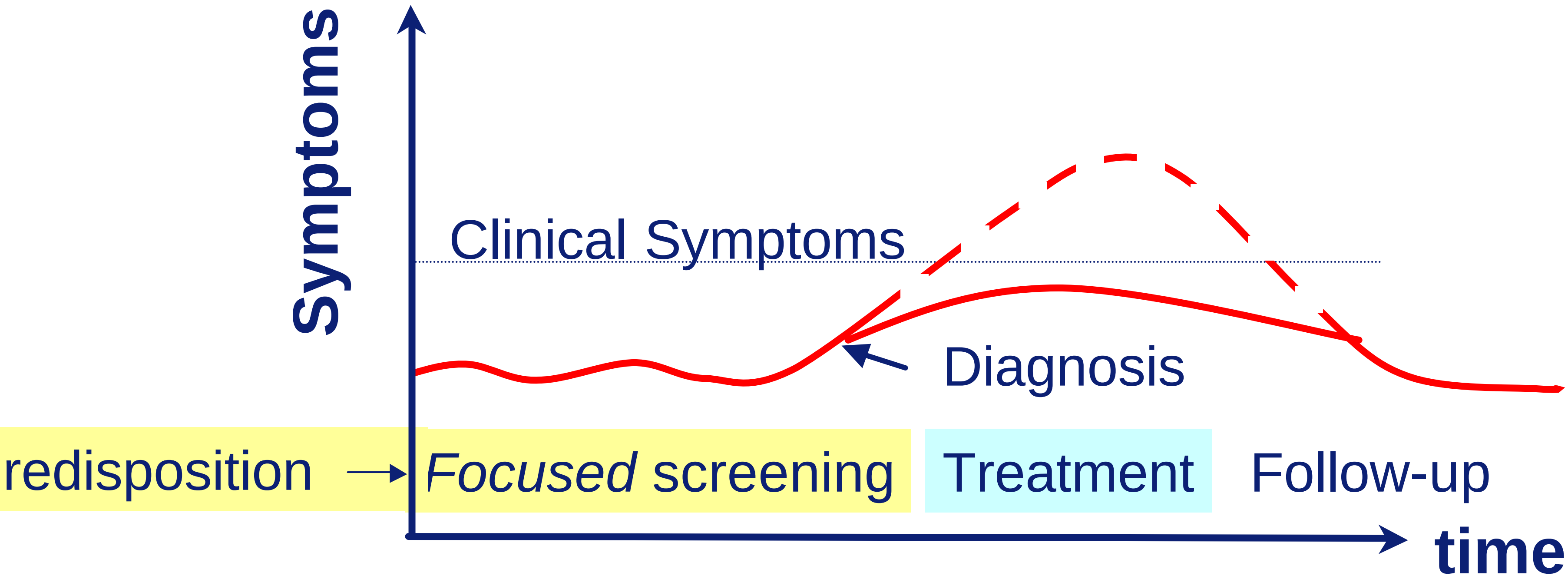
Tool: **Genetics** | **Biomarkers**

Disease Progression



Today, in all phases Medical Diagnostics and Medical Imaging are applied

Disease Progression

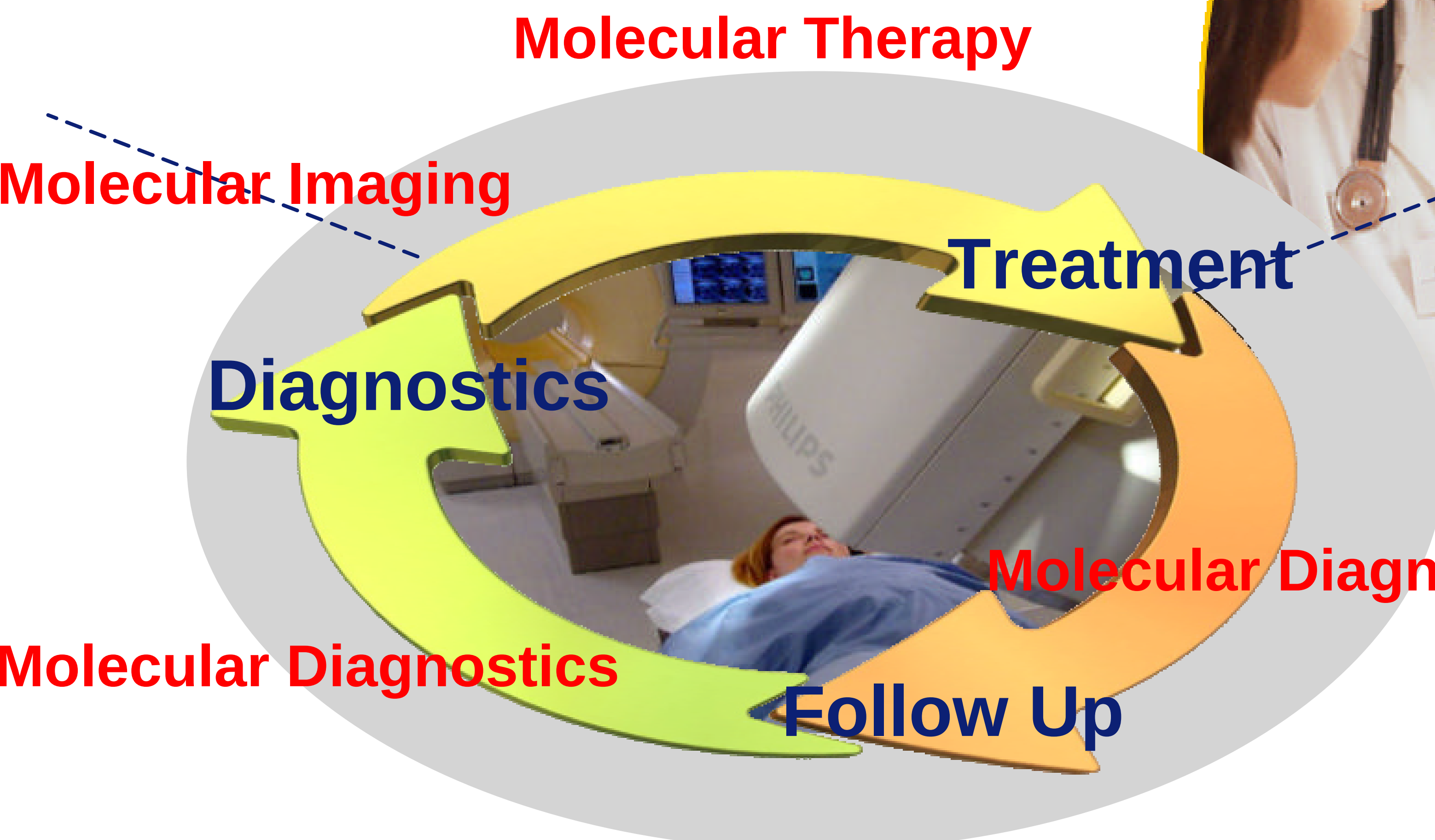


Tomorrow, *Molecular* Diagnostics and *Molecular* Imaging and Therapy will be used

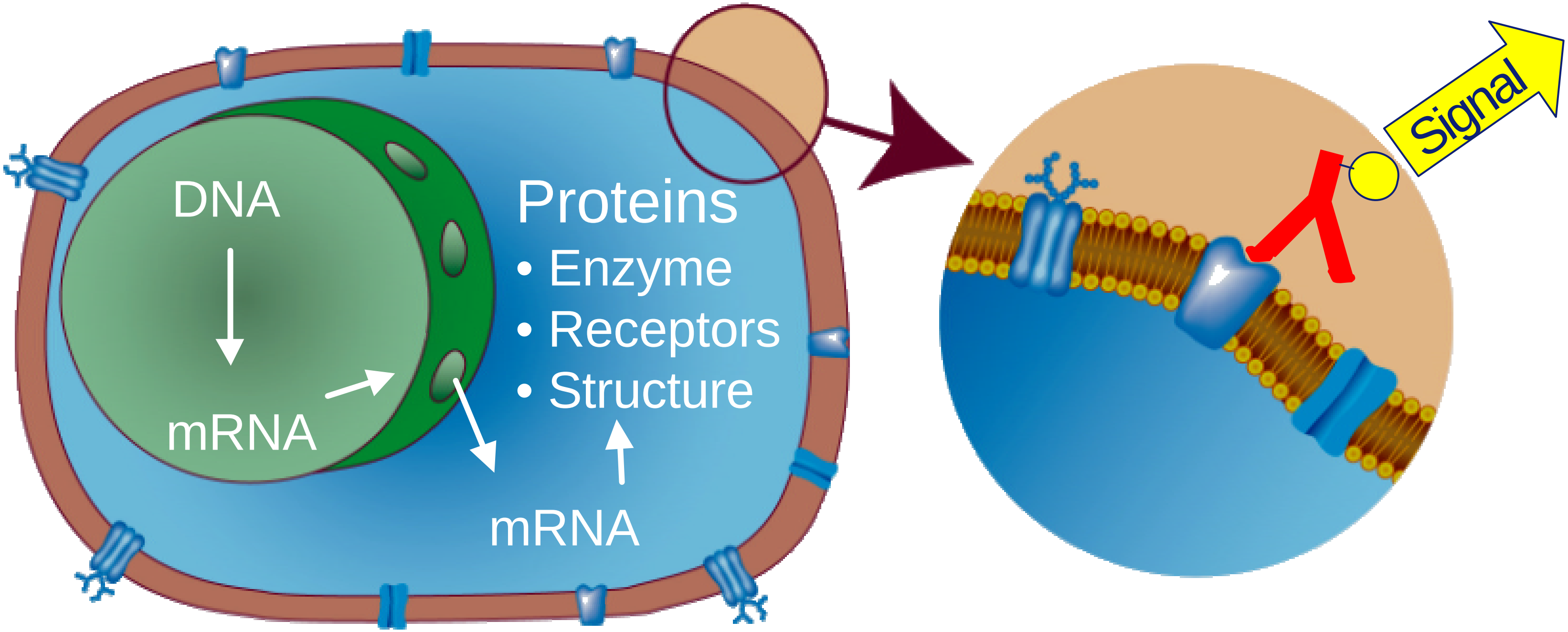
The Care Cycle in Molecular Medicine

Our Vision:

“Healthcare without Boundaries”



Possible Targets and Markers for MDx and MI

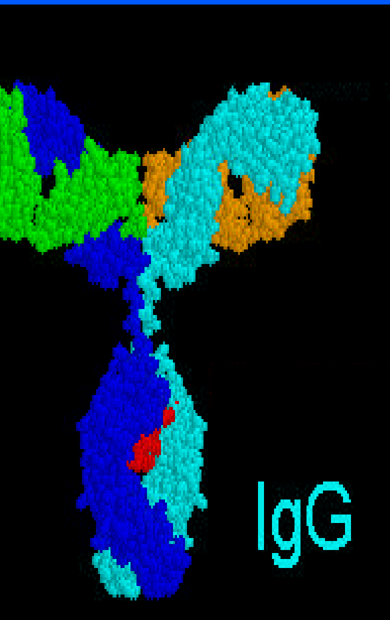


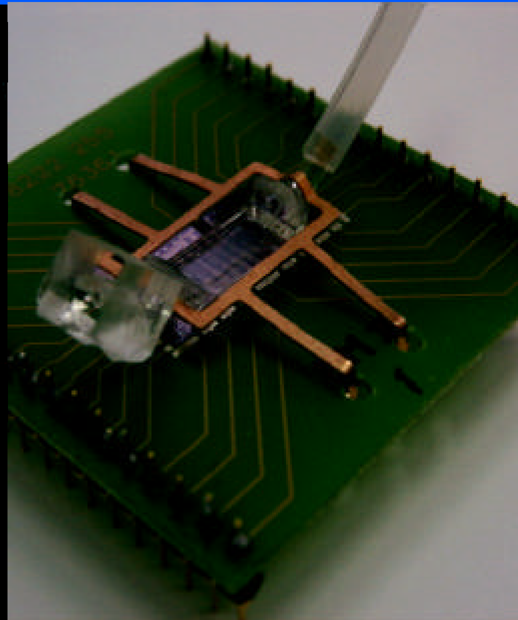
Molecular Diagnostics

- **In vitro** tests of specific molecules associated with a disease
- Use of biosensors

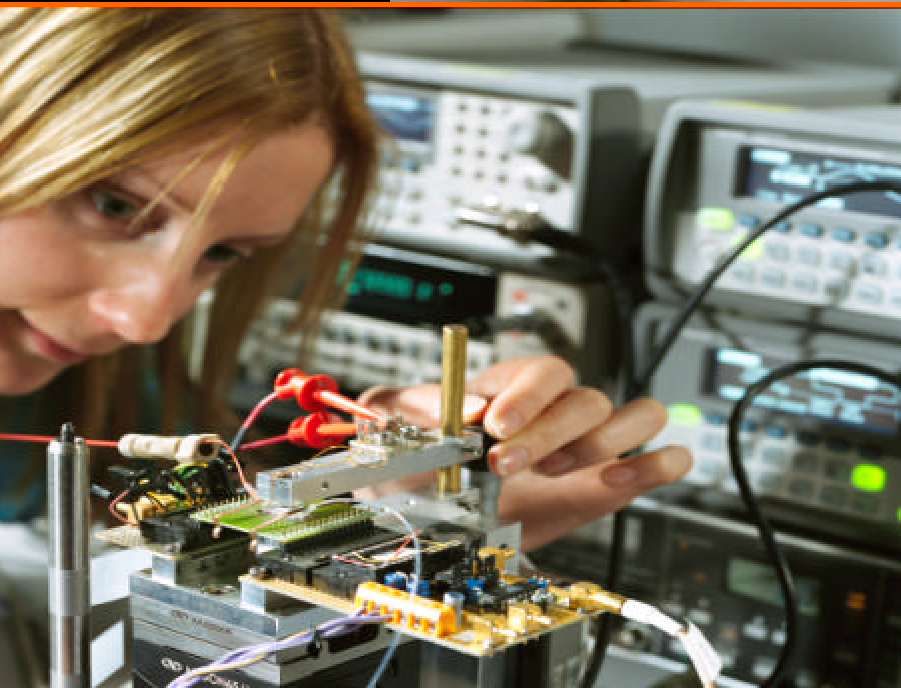
Molecular Imaging

- **In vivo** “measurement” of specific molecules associated with a disease
- Using medical imaging equipment and specific contrast agents



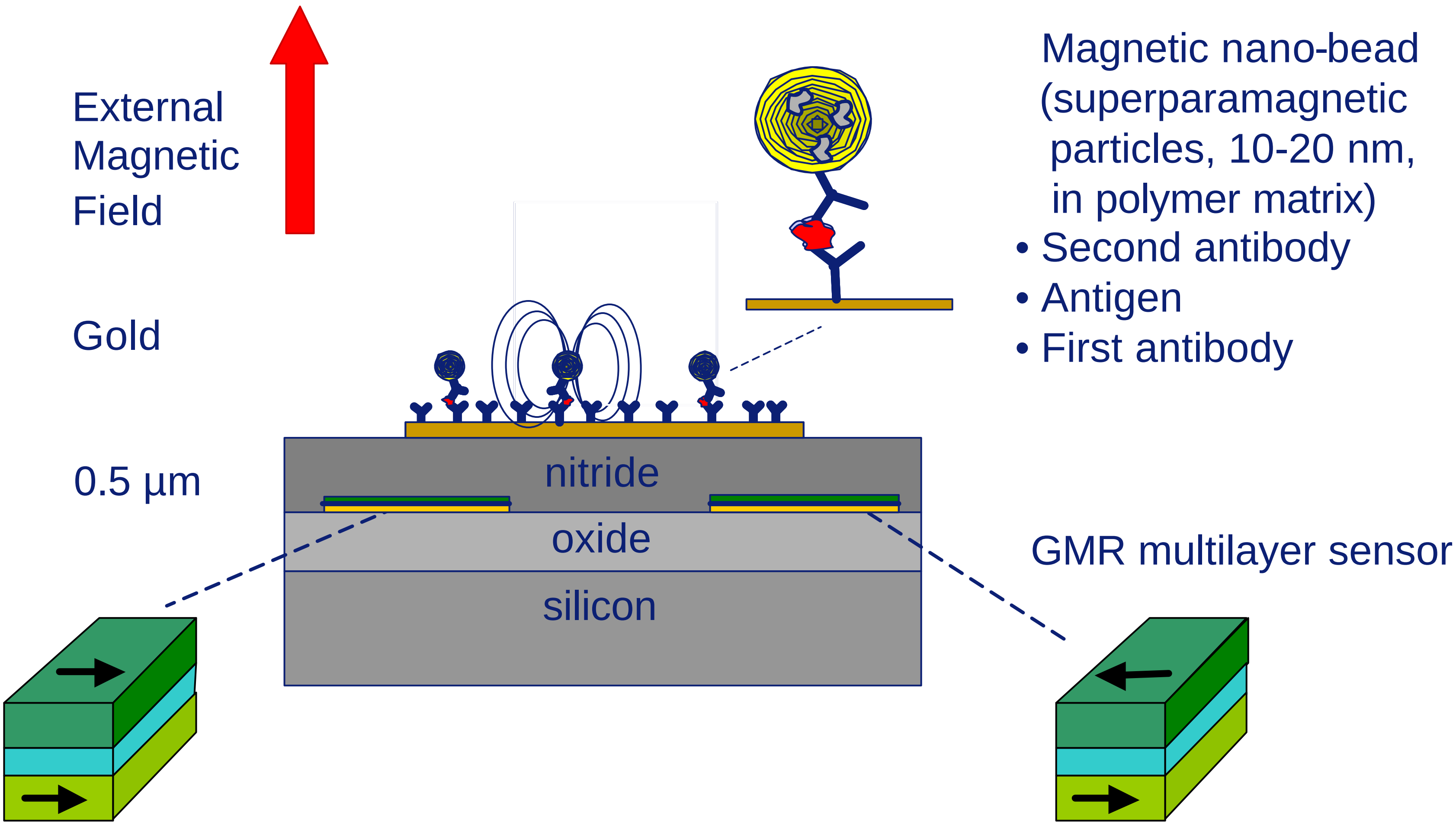


Molecular Diagnostics

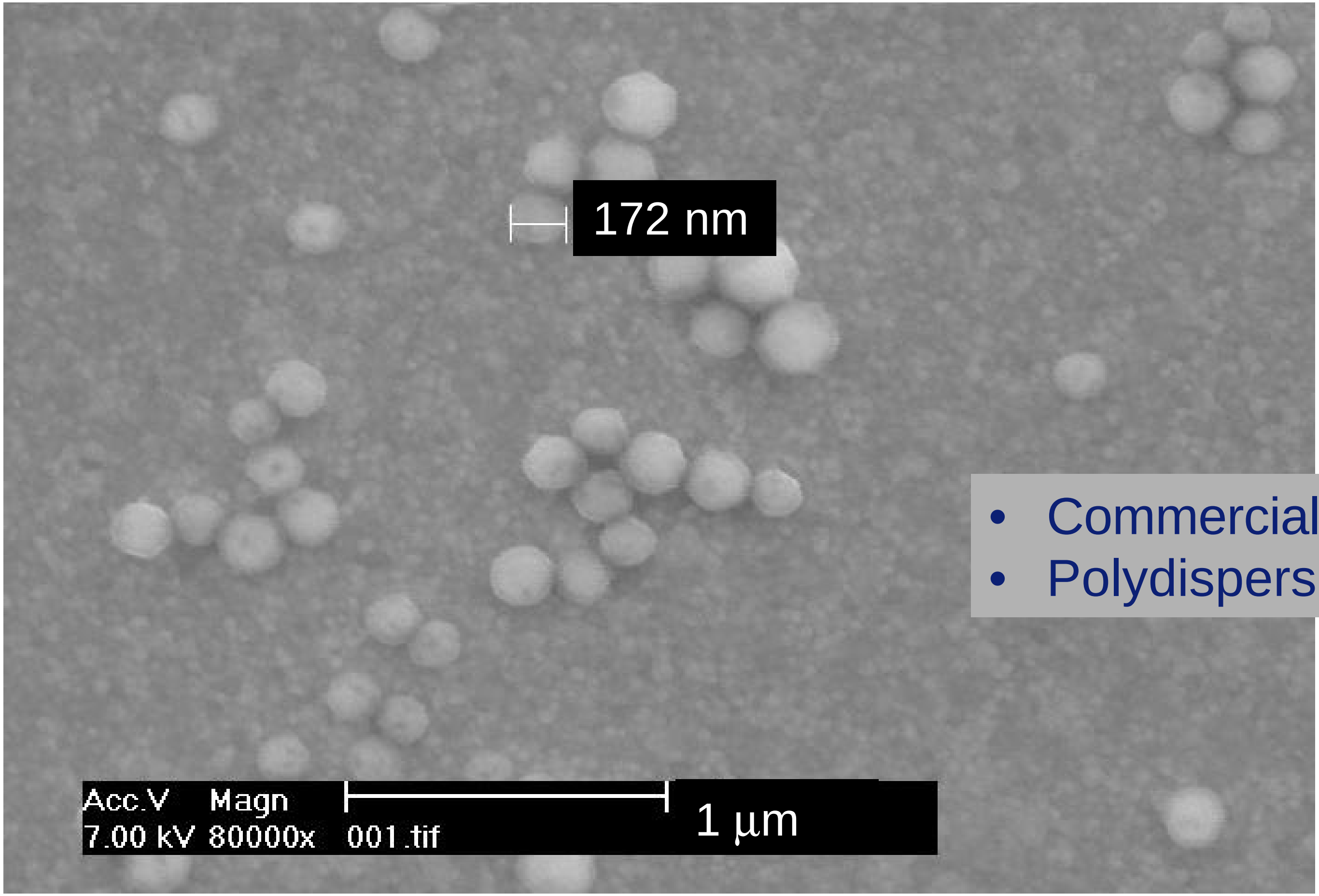


- Biosensors
  - Multi-analyte
  - fMol/l sensitivity
- Sensors that can measure non-invasivel
  - Blood
  - Breath

Molecular Diagnostics: GMR biosensor (Giant Magneto Resistance)

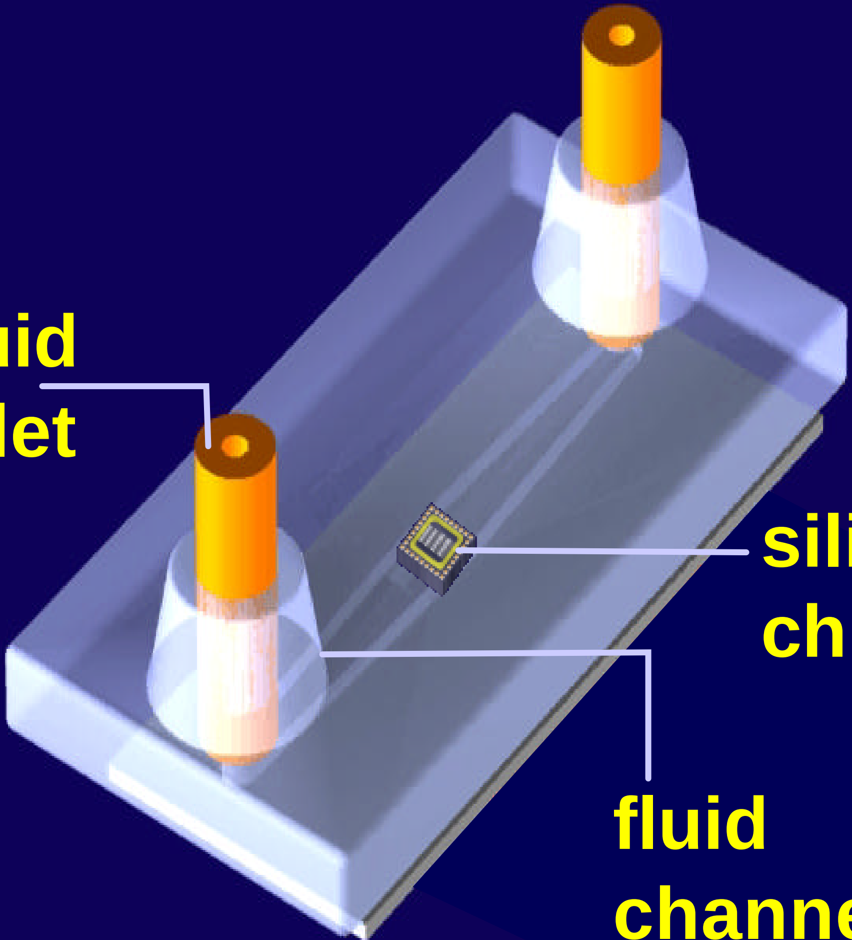


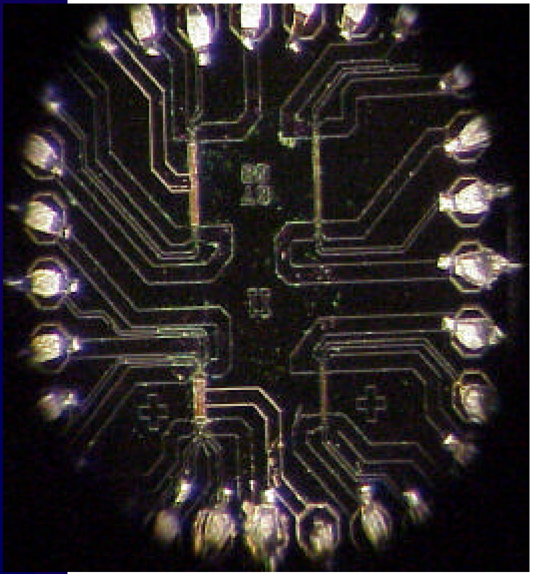
Magnetic nanoparticles



- Commercial beads
- Polydisperse

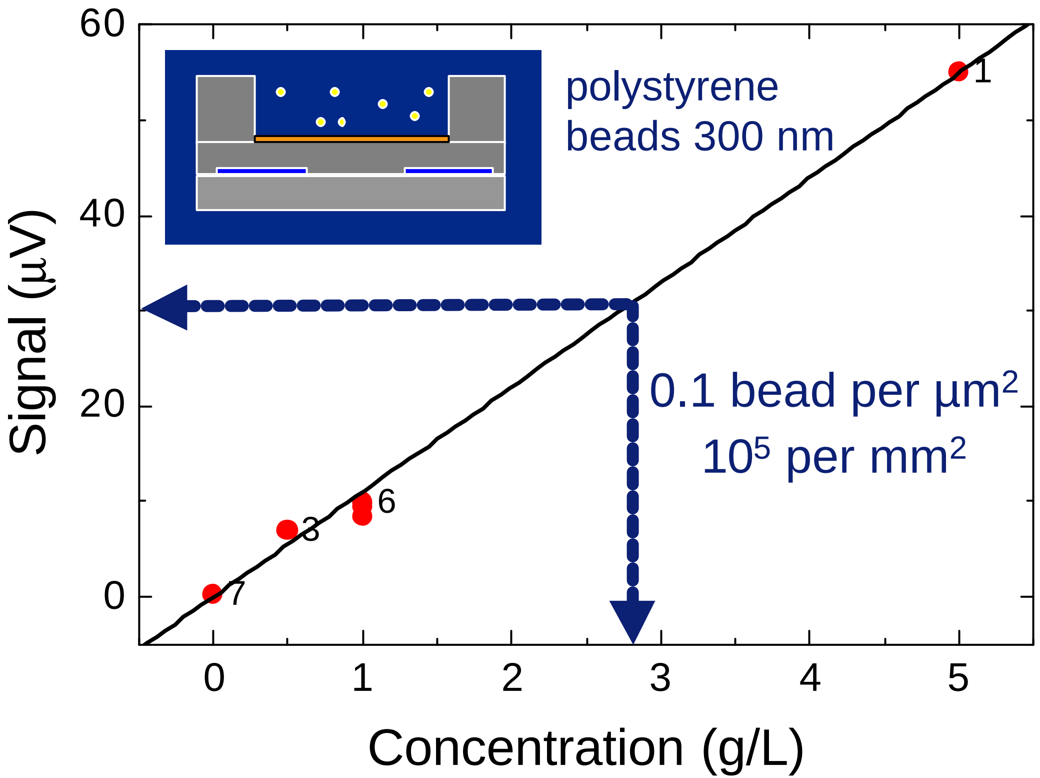
Biomarker detection in magnetic biochip





Millimeter ? micrometer ? nanometer

Signal from magnetic beads



Sensor technology seems suitable for 0.001 beads/µm^2 and fmole/L detection, which would be a breakthrough.

Low concentrations: examples

- **Cardiac markers in blood ? 1 picomole/L**
- **Needle biopsy with 5000 cells concentrate into 50 ml ? 0.2 femtomole/L**
- **30 bacteria in 50 ml ? 1 attomole/L**

Detection limit benchmark

- Fluorescence: ~ 1 fluorescent label per μm^2
  ~ picomole/L for proteins
  (a grain of salt in an Olympic swimming pool)
- New detection technologies & new labels needed
- Magnetic biosensor technology is expected to bring cardiac marker detection within reach!

Developing very sensitive detection techniques for routine use

Key in screening and monitoring

- Ultra-sensitive protein detection

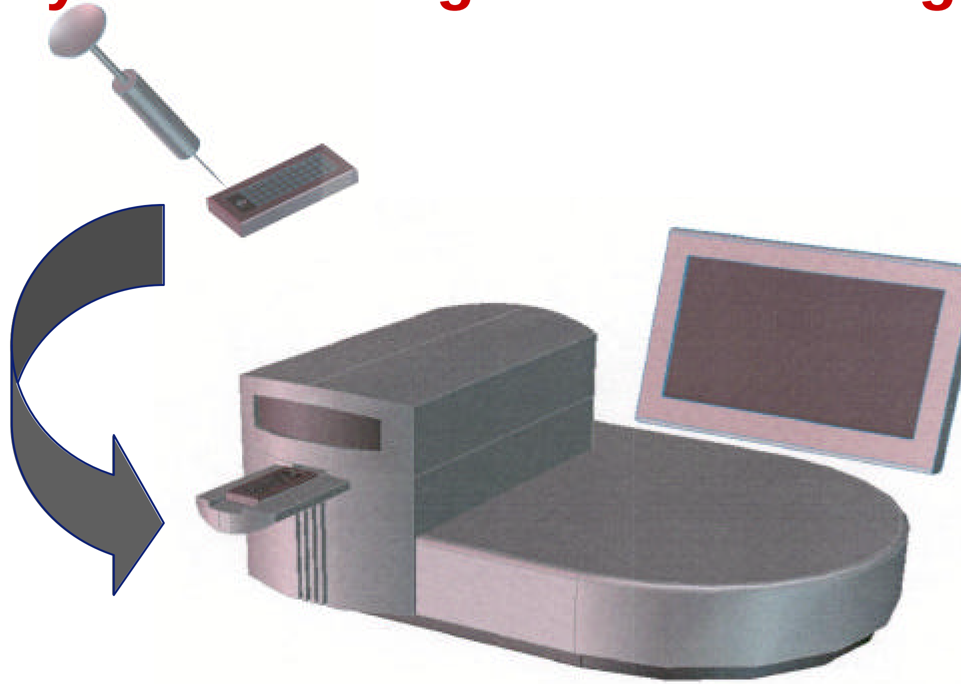
  e.g. tumor markers (point-of-care, lab)

- Rapid finger-prick protein detection in blood

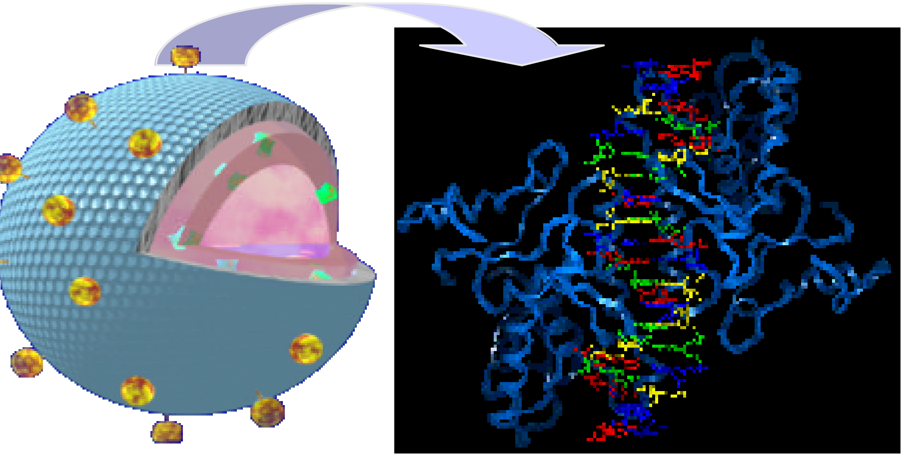
  e.g. cardiac markers (point-of-care, ambulance)

- Rapid and compact system for DNA detection

  e.g. bacterial infection (point-of-care, small lab)



Contrast agents for Molecular Imaging (MI)



Molecular Imaging

DNA → RNA → Protein

Molecular Imaging

Assessment of biological processes in vivo, at the cellular and molecular level

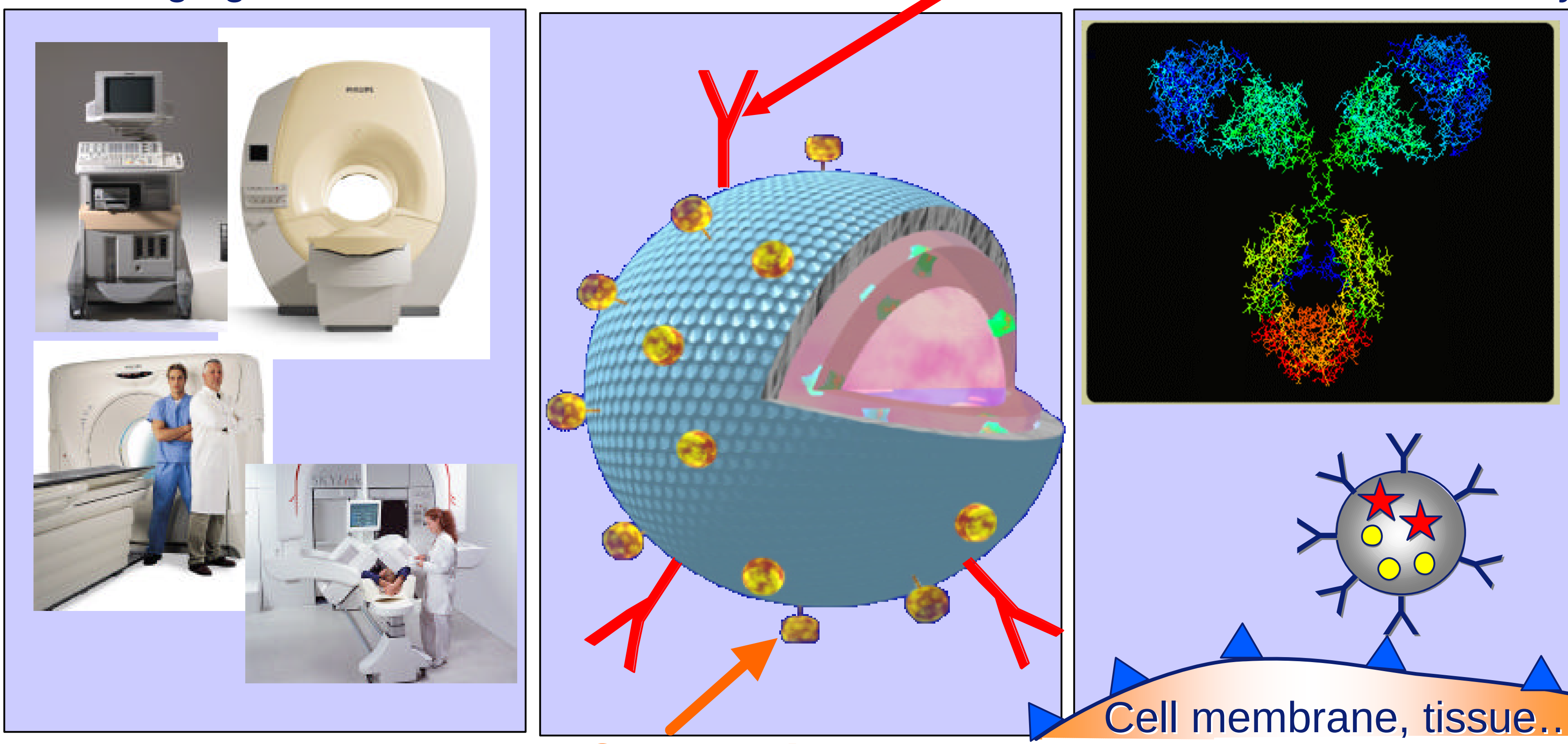
- **Earlier detection and characterization of disease**
  - **Much faster than invasive conventional techniques such as histologic analysis**
- **Evaluation of treatment**
  - **Assess therapeutic effectiveness at the molecular level, long before phenotypic changes occur**
- **Understanding of biology**
  - **Study pathogenesis in intact microenvironments**

Molecular Imaging:

Targeted contrast agents & dedicated imaging equipment

Targeting bio-molecule, e.g. protein

Imaging Modalities | Contrast Media | Bio-molecules Pharmacy



Contrast Agent,
e.g., Gd(MRI), ^{99m}Tc(SPECT), ^{18}F(PET)

Why Target?

- Reduce Side Effects and “Collateral” Damage
- Reduce Dosage
- Reduce Repetition
- Create New Opportunities
- Increase Overall Efficacy

“Personalized Medicine”

Potential Targets

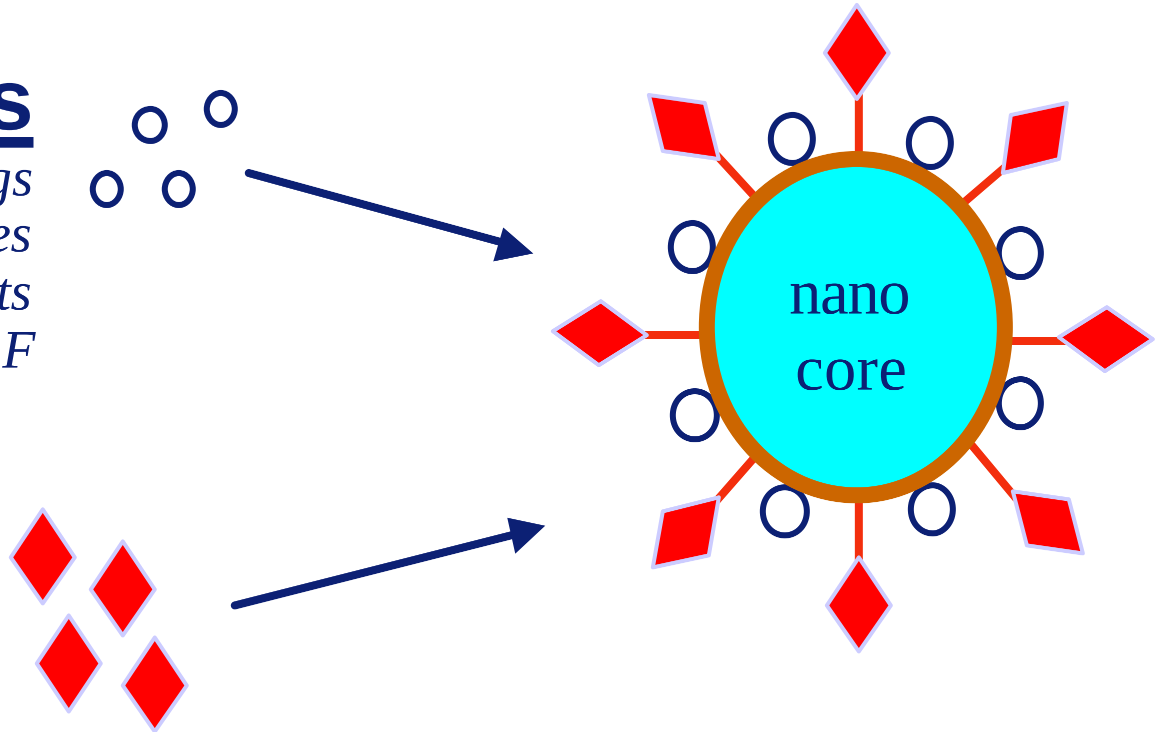
- Cancer
- Vascular Disease
- Heart Attack
- Stroke
- Many, many more…

Human Genome Project Makes Virtually Every Cell (Gene Expression) a Potential Target

Generalized Targeting Paradigm

Payloads

Drugs
Radionuclides
Imaging agents
e.g., Gd, Fe, F



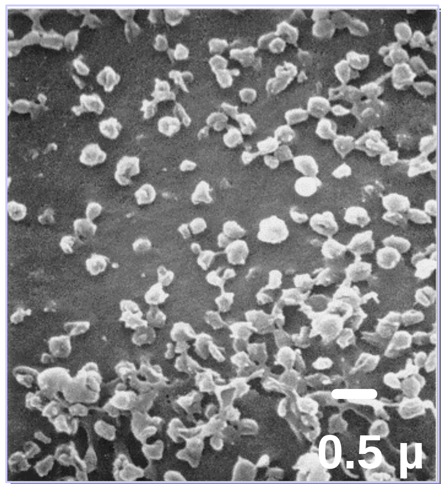
Anti-fibrin
Anti-tissue factor
Anti-** $a_v b_3$**-integrin
(targeted to angiogenesis)

Lanza, Wickline, J Biochemistry, 2003

…Vulnerable Plaque can be imaged, located and quantified

Targeted contrast agent (and drug)

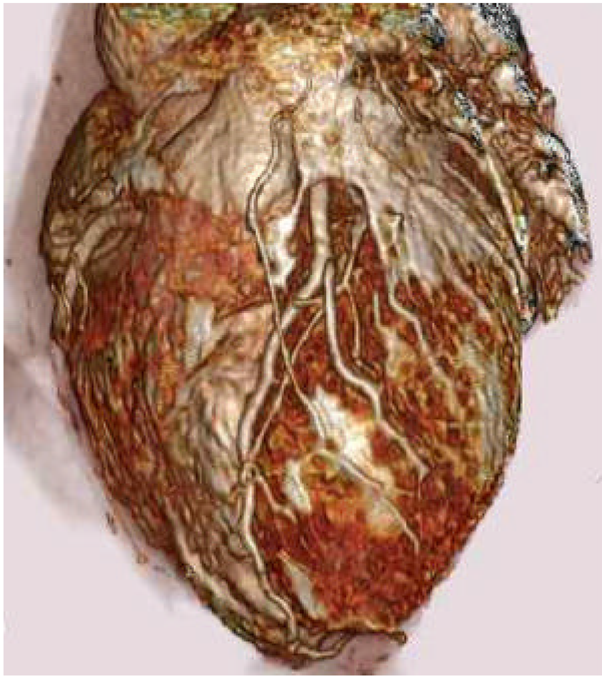
Particles bind to cell surface

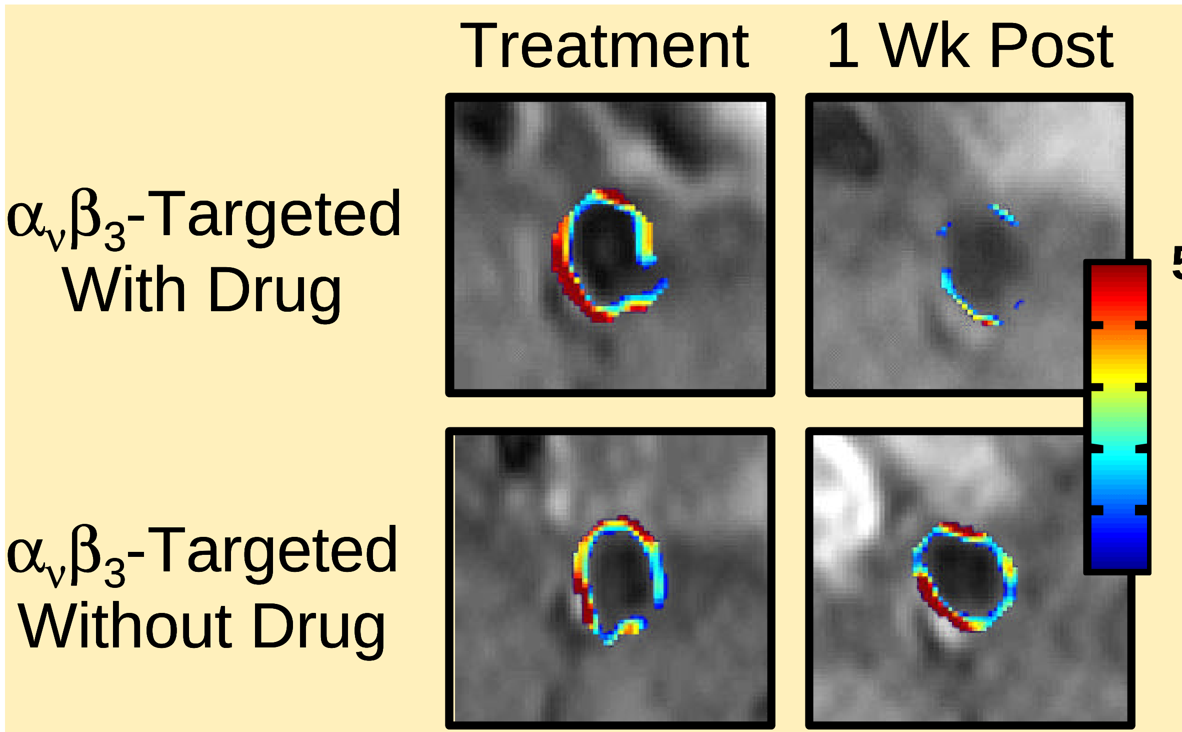


SEM: Tissue factor targeting of SMC with labeled nanoparticles

To locate and image the plaque

And subsequently treated…





Conclusion

Nanometer structures for manufacturable and better devices

Nanotechnology is/becomes reality

- Already “established” in the pigment and additives industry (nanoparticles)
- Still rapid developments in the semiconductor industry
- Much progress and promise in functional organic films, in organic thin-film devices, and in healthcare … first products are becoming commercially available

But there is still a lot to come….

primarily driven by academic research

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Thank you

Contributions from colleagues of Philips Research and our partners are kindly acknowledged