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Towards Integrated Molecular Diagnostics:

Biomedical Sensors – the Missing Link?

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Corporate Technology
Siemens AG

Tampere, June 7, 2006

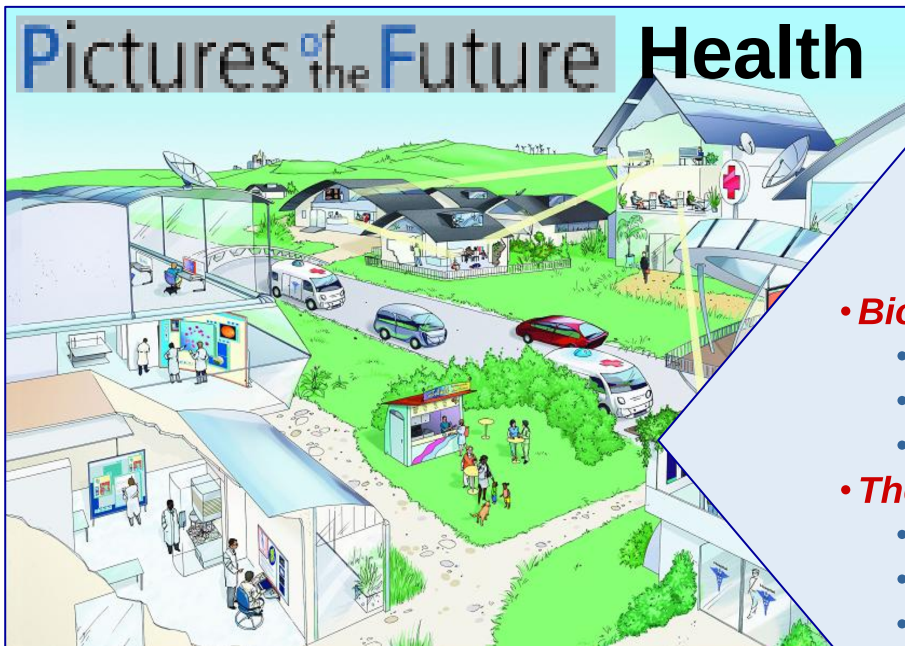
What are the Trends for Future Medicine?

A Few Theses:

- ❑ **Fusion of diagnostic tools (… and data)**
- ❑ **Diagnostics and therapeutics at the molecular level**
- ❑ **Preventive and earliest recognition**
- ❑ **Individualized and home based diagnostics & therapy**
- ❑ **Fully ICT supported**
- ❑ **Highly cost effective: Point of care, home care**
- ❑ **…**

What are the Trends for Future Medicine?

- ➔ From reactive to proactive, predictive, preventive
- ➔ Combination of in-vitro and in-vivo diagnostics
- ➔ Completion of diagnostics towards therapy and progress tracking



Molecular Medicine

- *Bio-, Nano-, Info- Technologies*
  - *Bio-Medical Knowledge Fusion*
  - *Molecular Diagnostics*
  - *Personalized Medicine*
- *Theranostics*
  - *Computer-aided Diagnosis & Treatment*
  - *Molecular Imaging*
  - *Imaging for Drug Effectiveness*

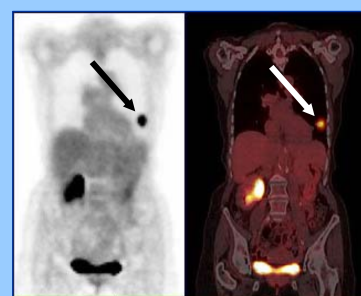
Diagnostics and Therapeutics at the Molecular Level

Molecular Medicine

In-Vitro Diagnostics

New molecular technologies for preventive disease diagnosis and therapy

Molecular Imaging



In vivo visualization of molecular processes for diagnosis und therapy

Knowledge based IT Systems

Integrated medical data base provides IT-based, clinical decision assistance

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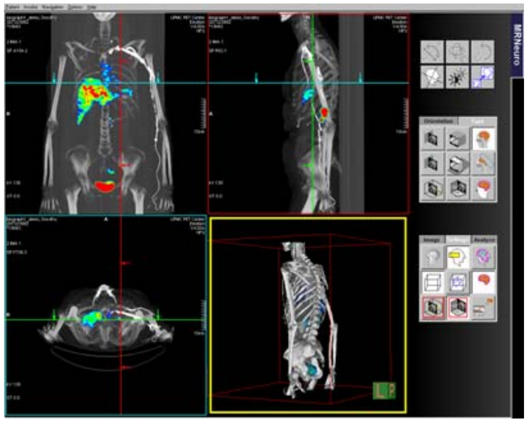
Towards Molecular Diagnostics:
Molecular Imaging (MI)

Status & Goals

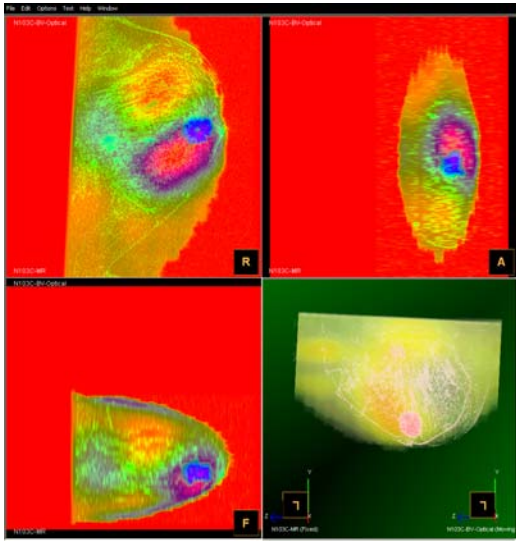
- … approaches the cell level
- … uses of molecular agents
- … fuses various imaging techniques

▪Use of new contrast agents / molecular probes with existing equipment (today's MI, image fusion)

- Specialized protocols for data acquisition and analysis
- Introduction of new equipment:
  - Hybrid modalities (PET&CT, PET&MR…)
  - Modalities for small animal imaging (e.g. micro-PET/CT) for drug discovery / development
  - Optical imaging
  - …



PET-CT
Image Registration & Fusion

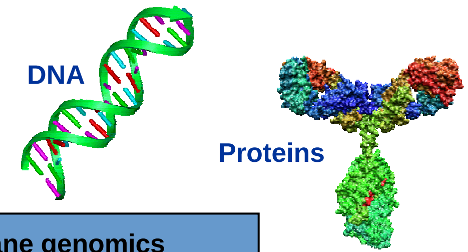


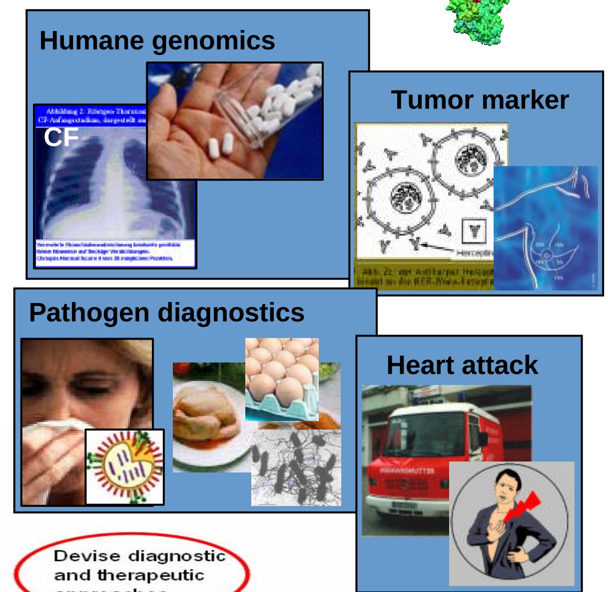
Diffuse Optical Tomography – MRI Fusion for Breast Cancer Diagnosis

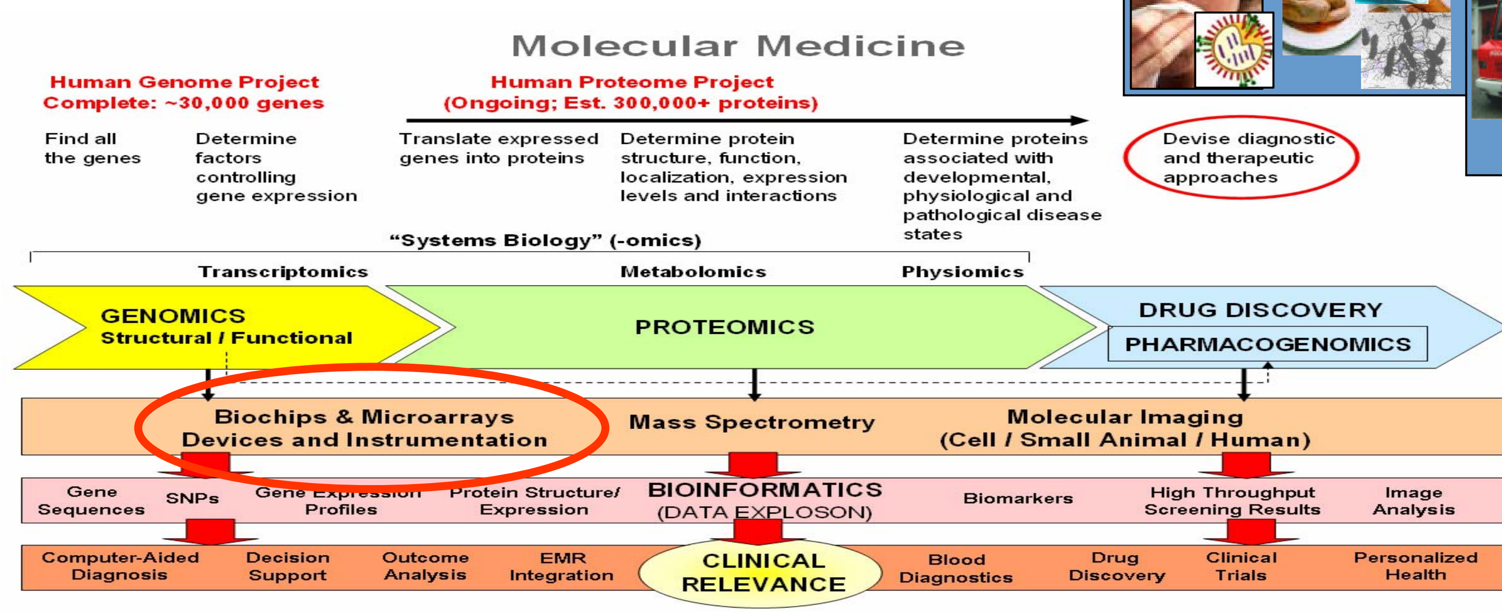
Towards Molecular Diagnostics:
In-Vitro Diagnostics (IVD)

Status & Goals

- … handles individual molecules
- … detects genes and proteins
- … based on biochemical sensors
- … integrated biochemical systems
- … link to MI (identification, selection, prediction)







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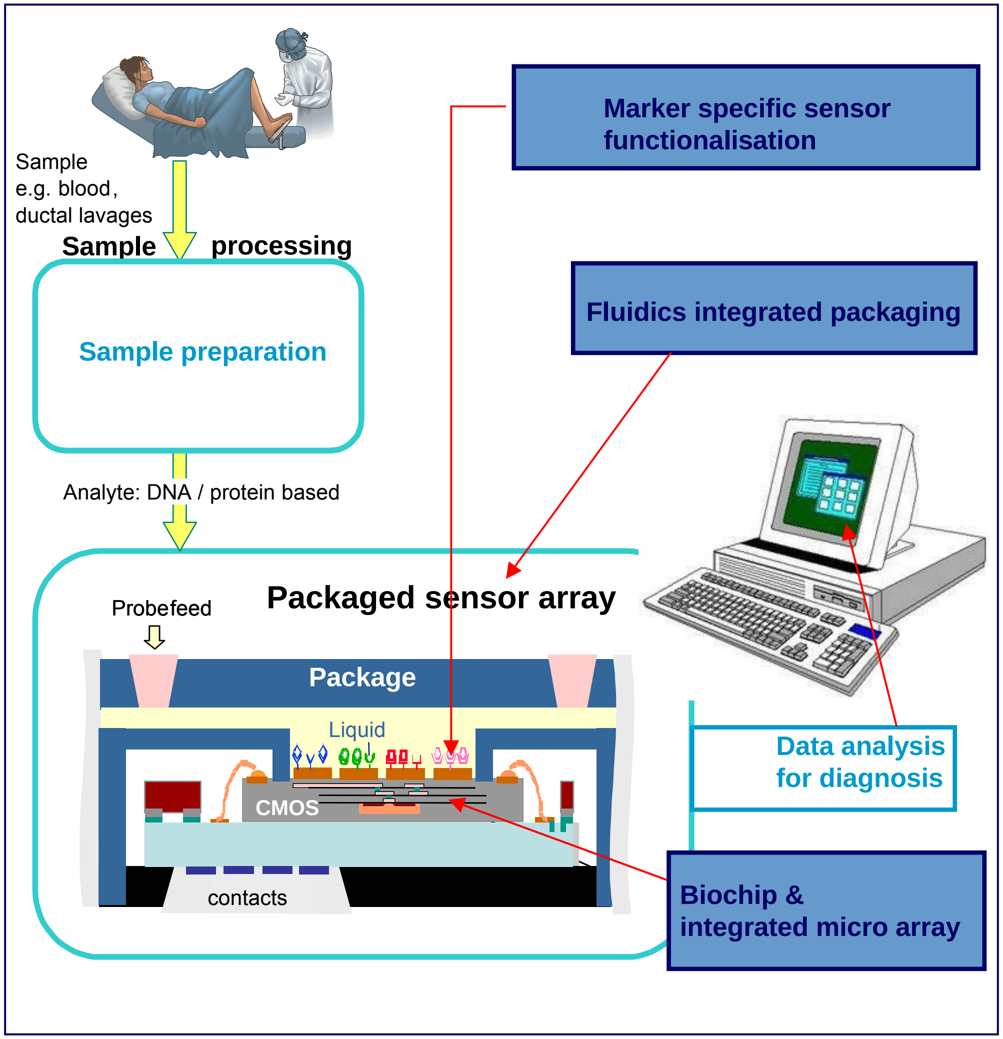
Lab-on-a-Chip based IVD by integrated biosensor systems

- ▶ Integration and miniaturization of multiple lab functions:
  - sample preparation
  - fluidic- & reagent-handling
  - analysis & detection
- ▶ No manual steps
- ▶ Small sample volume
- ▶ Short measurement time, ~30 min
- ▶ Small size (laptop format)
- ▶ DNA & protein detection
- ▶ Local application („Point of Care“)

Simpler, quicker, cheaper and new applications!



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IVD: The quicklab®- technology

The First Fully Integrated Lab-on-a-Chip System

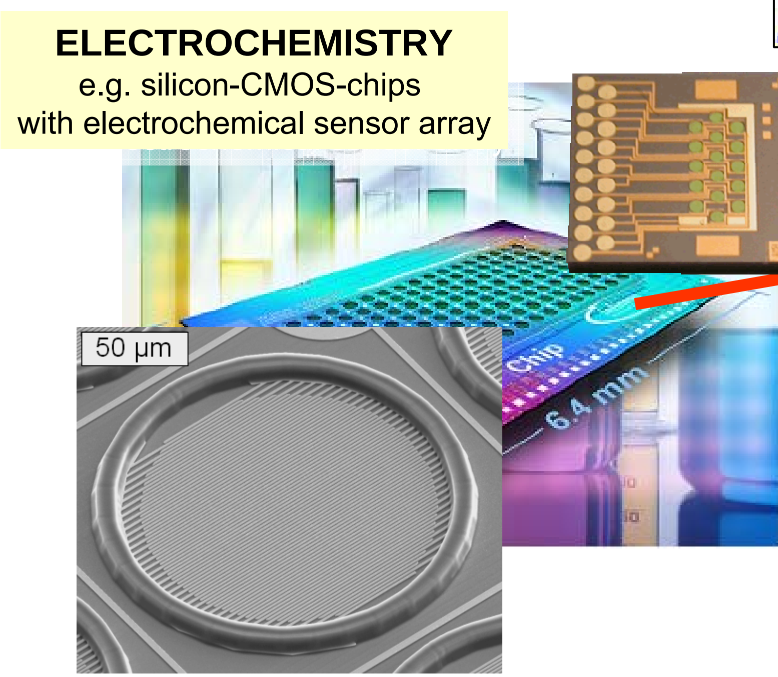
Detecting Genetic, Infections Diseases from a Drop of Blood

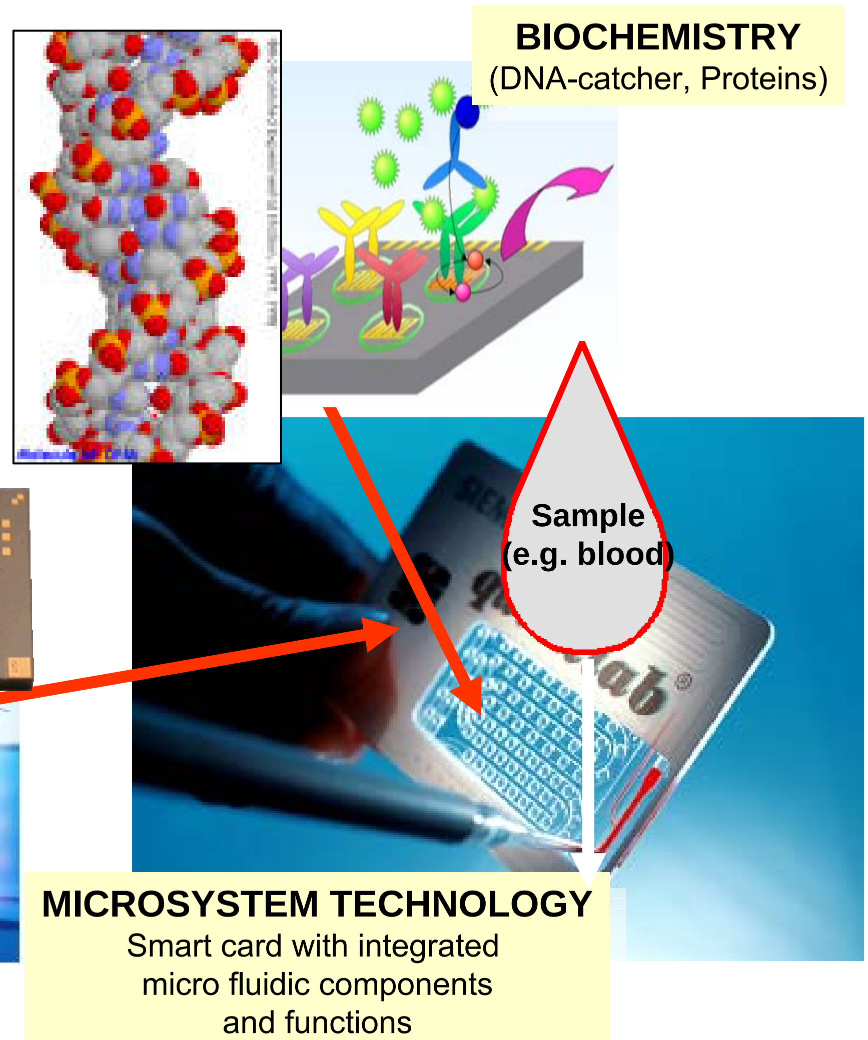
- DNA, Protein and Small Molecule Detection Systems
- ASIC Design of Biochips
- Microfluidics

IVD : The quicklab® - technology

Integration of:

- Sample preparation
- DNA Amplification
- Electrical detection





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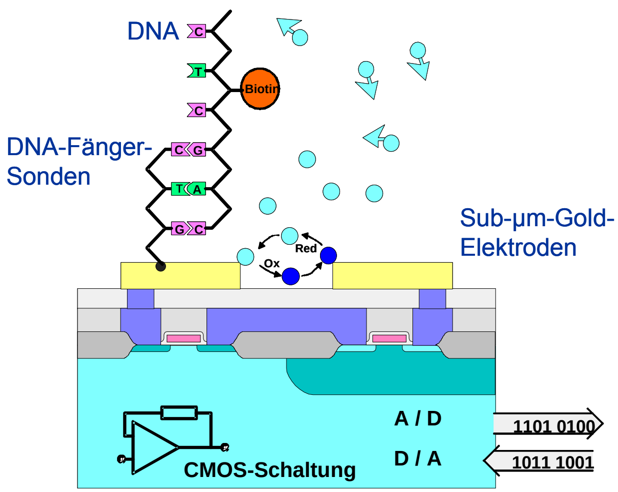
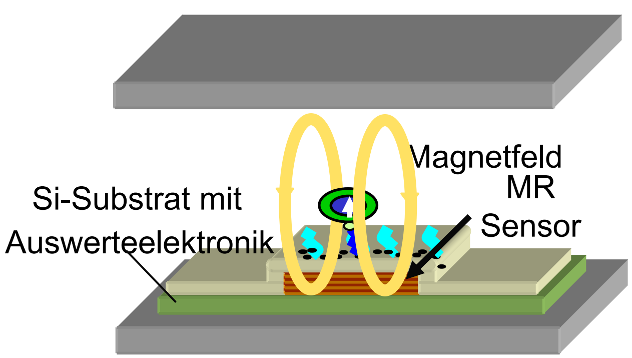
IVD : Innovative concepts for biomedical sensors

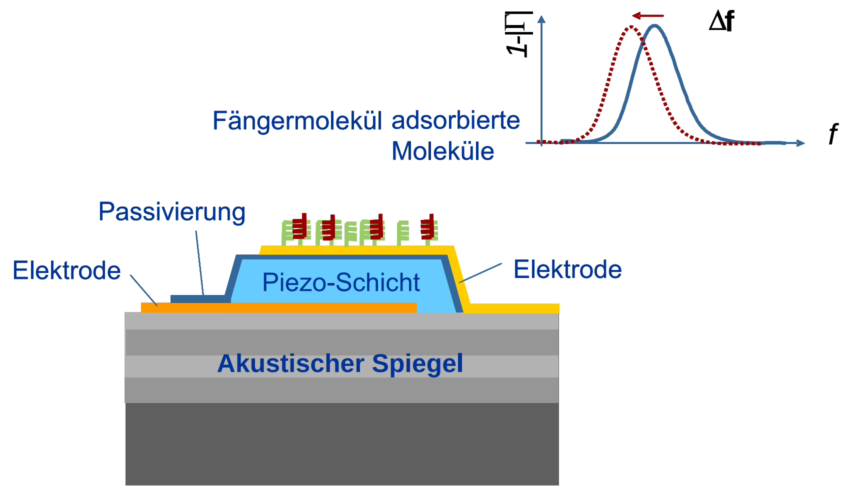
Electro-chemical principle



Magnetic principle



Gravimetric principle



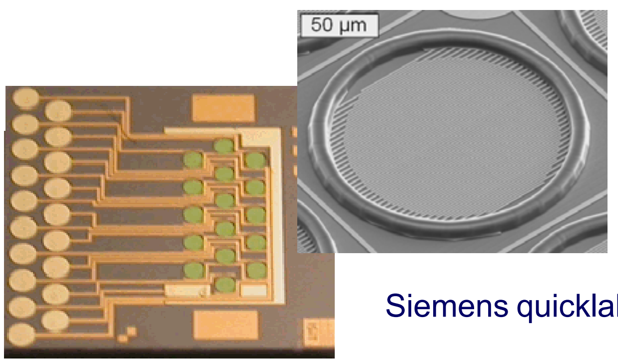
- No label necessary
- High sensitivity and comparable mass resolution to QCM: < 10ng/cm² proved
- Integrable with CMOS-readout addressing large no. of pixels
- Application in liquid and gaseous surroundings

IVD : Enabling factors for biomedical sensors

Sensor detectivity and selectivity is basically determined by:

⇨ Sensor characteristics

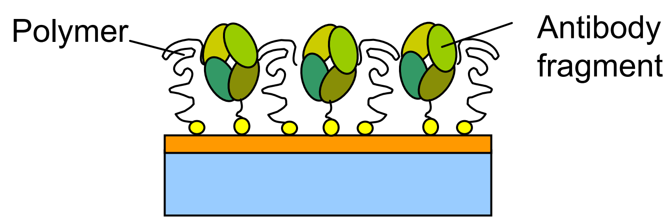
- ▶ High detectivity
  meeting application requirements
- ▶ Low cross-talking
- ▶ Sufficient # of pixels
- ▶ Robust
- ▶ Inexpensive
  - • Fabrication
  - • Application process



Siemens quicklab® -chip

⇨ Functionalisation properties

- ▶ High specificity to marker
- ▶ Blocking of unspecific binding
- ▶ Oriented receptors for higher sensitivity
- ▶ Sufficient stability in time (>1 year)
- ▶ Reliable and fast deposition process
  - • Speed
  - • Parallel processing
  - • Dispensing volume (<1nl)
  - • Quality management



Site-directed immobilisation of
Fab´-fragments and pTHMMAA

IVD : Comparison of gravimetric biosensors

Sensor Type	Frequency Range (Hz)	Sensitivity (Hz cm² / ng)	Pixel Size (m^2)	CMOS Circuit Integration	Liquid Biosensing	Mass resolution in liquid (ng/cm²)
QCM	10^6-10^7	1.3	10^{-5}	NO	YES	5.2
SAW	10^8-10^9	14.2*	10^{-7}	NO	YES	2 – 7*
FBAR	**10^9-10^{10}**	**800**	**10^{-9}**	**YES**	**YES**	2.3
Cantilevers	10^3	**~10^{-3}****	10^{-5}	**YES**	NO	-

*Values for SAW from: Josse Bender: "Guided SH-SAW Sensors for Liquid-Phase Detection"
**Values for Cantilevers from: Zhang Shea: "Tuning forks as micromechanical mass sensitive sensors for bio- or liquid detection"

Advantages of FBARs: → High sensitivity
→ Sensor and electronics on same wafer
→ High packaging density through photolithographic processability
→ Quantitative and time dependent measurements

The FBAR is the first gravimetric (acoustic) sensor that works in liquid and can be integrated into CMOS circuitry!

EU-funded Project Biognosis (www.biognosis-info.de)

Fully integrated gravimetric biosensor

Consortium - European interdisciplinary network of competences

Biognosis 2005-2008

Siemens Aktiengesellschaft (D)
Biosensor Application (S)
VTT Finland (FIN)
Cranfield University (GB)
Medizinische Universität Innsbruck (A)
Uppsala Universitet (S)
Perlos OYJ (FIN)

Objectives

► Development of a unique resonator based **integrated DNA and protein detection system** for applications in **medical diagnostics**.

► Due to its **easy to use** and **cost-effective nature**, the system will allow fast and reliable **DNA and protein based in-vitro testing.**

► Aiming for **point of care** and **doctor's office applications**, e.g. **early cancer recognition**, this approach will help **improve public health.**

► DNA and protein based **markers for breast cancer** will be identified and applied for **a final clinical validation** of the sensor system.

EU-funded Project Biognosis (www.biognosis-info.de)

Fully integrated gravimetric biosensor

…and critical issues beyond

- ► Transducer properties
- ► **Functionalisation – Quality and processing**
- ► **Fast and cheap sample preparation**
  e.g. Serum modification for DNA
- ► Systems for **quantitative** measurements
  - Transducer
  - Integrated processing
    e.g. **quantitative LoC-PCR**
- ► **Marker identification and adapted bio-interface**
- ► Cost reduction
  - Fabrication
  - Handling & Use

EU-funded Project Biognosis (www.biognosis-info.de)

Fully integrated gravimetric biosensor

… and challenges for tumor marker development

Sophisticated marker development process needs:

- Standards for analytical and clinical validation
- Coordination of identification, validation and screening programs
- Establishment and application of informative data bases

Requirements on (tumour) markers:

- Sensitive and specific!
- Predictive!
- Robust and reproducible!
- Abundance!
- Stability!
- Available in body fluids!
- Not byproduct of inflammation!

So far not a single candidate in the literature matches all criteria!....

Towards Molecular Diagnostics …

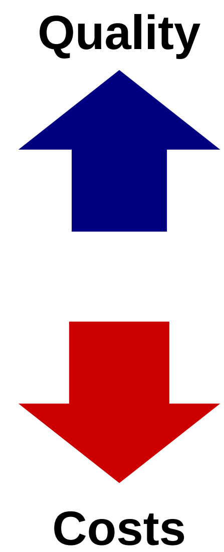
… Challenges and Needs

- Improvement of processing (resolution, precision, reliability, yield)
- Essential role of biochemistry
- Increase multi-functionality by integration and miniaturization
- Interface to medicine, chemistry, electronics and IT
- Integration of wireless data transfer & self-sustaining power supply
- Full leverage of interdisciplinary added value

The Mission of Siemens

… to shape the future of healthcare by

- identification of risk patients and preventing disease outbreak
- diagnosing diseases early at their onset
- enabling efficient therapies with measurable outcomes



… whilst increasing efficiency of healthcare delivery

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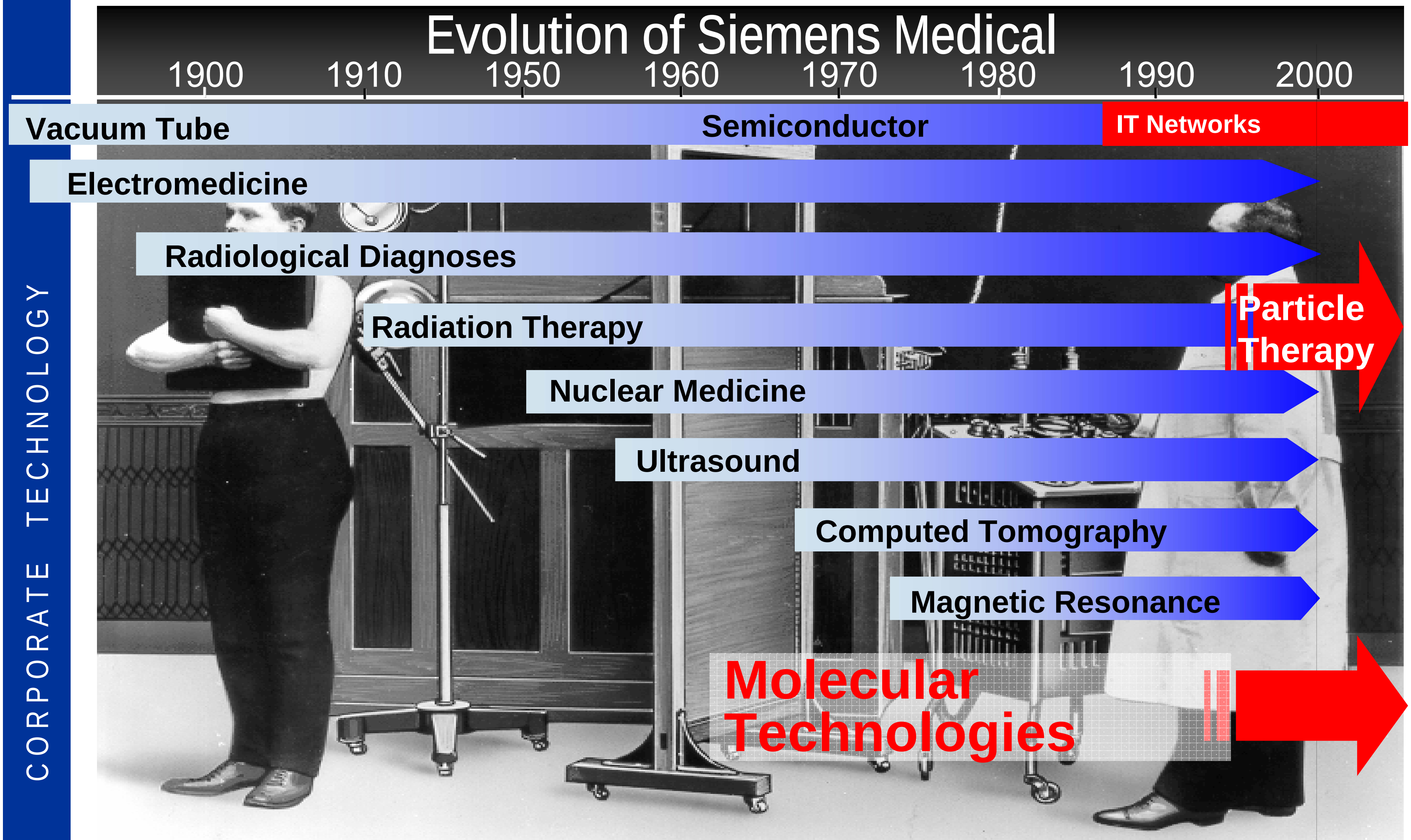
Pictures of the Future Health



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Thank you for your attention!

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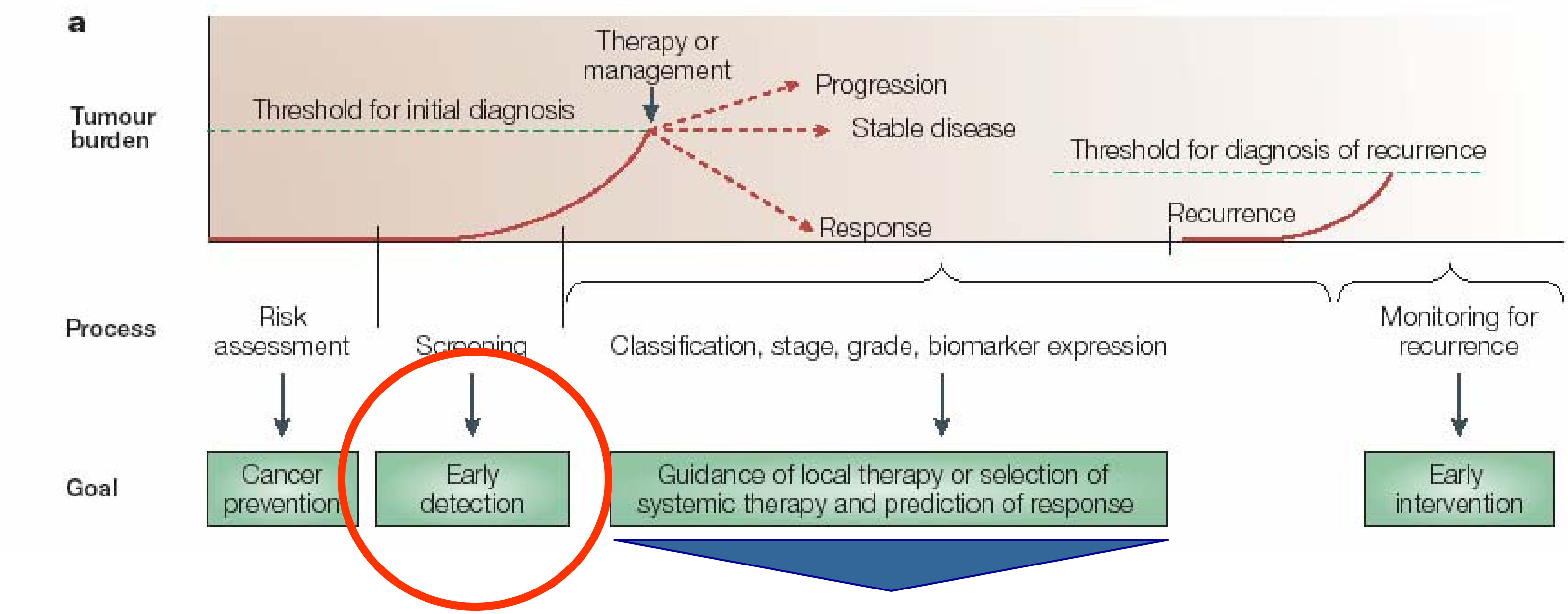
Backup

IVD : Application of cancer markers

Representation of biomarkers at different stages in clinical cancer evolution [1]



► Today's main use of tumour markers is limited to response to treatment and check for recurrence; DNA markers are far away from early detection

► Expansion to early detection and diagnosis is expected to be of high socio-economic impact
Successful implementation requires [2]:
- Low rate of "false positive" and "false negative" tests
- Detection before progression to advanced stage
- Distinction between aggressive and harmless lesions
- Inexpensive and accepted by population

► Identification of new suitable markers + application of powerful detection systems needed

[1] Nature review / cancer, vol. 5, Nov. 2005
[2] Nature review / cancer, vol. 3, April 2003

The biotechnology sector can be divided into six segments

Overview over biotechnology applications and business segments

Biopharma/therapeutics	Bioagri	Bioindustrial	Biodefense
Substances with medical/diagnostic use made by biological processes (not chemical synthesis)	Biological compounds and genetically modified organisms for agriculture	Large scale prod. of enzymes and other biological products often for industrial applications	Procedures involved in taking defensive measures against attacks using biological agents

Bioinformatics/Computational Biology

Tools for analysis of biological, medical, health and behavioral data including acquisition, storage, organization, analysis and visualization

Bioservices

Contract research

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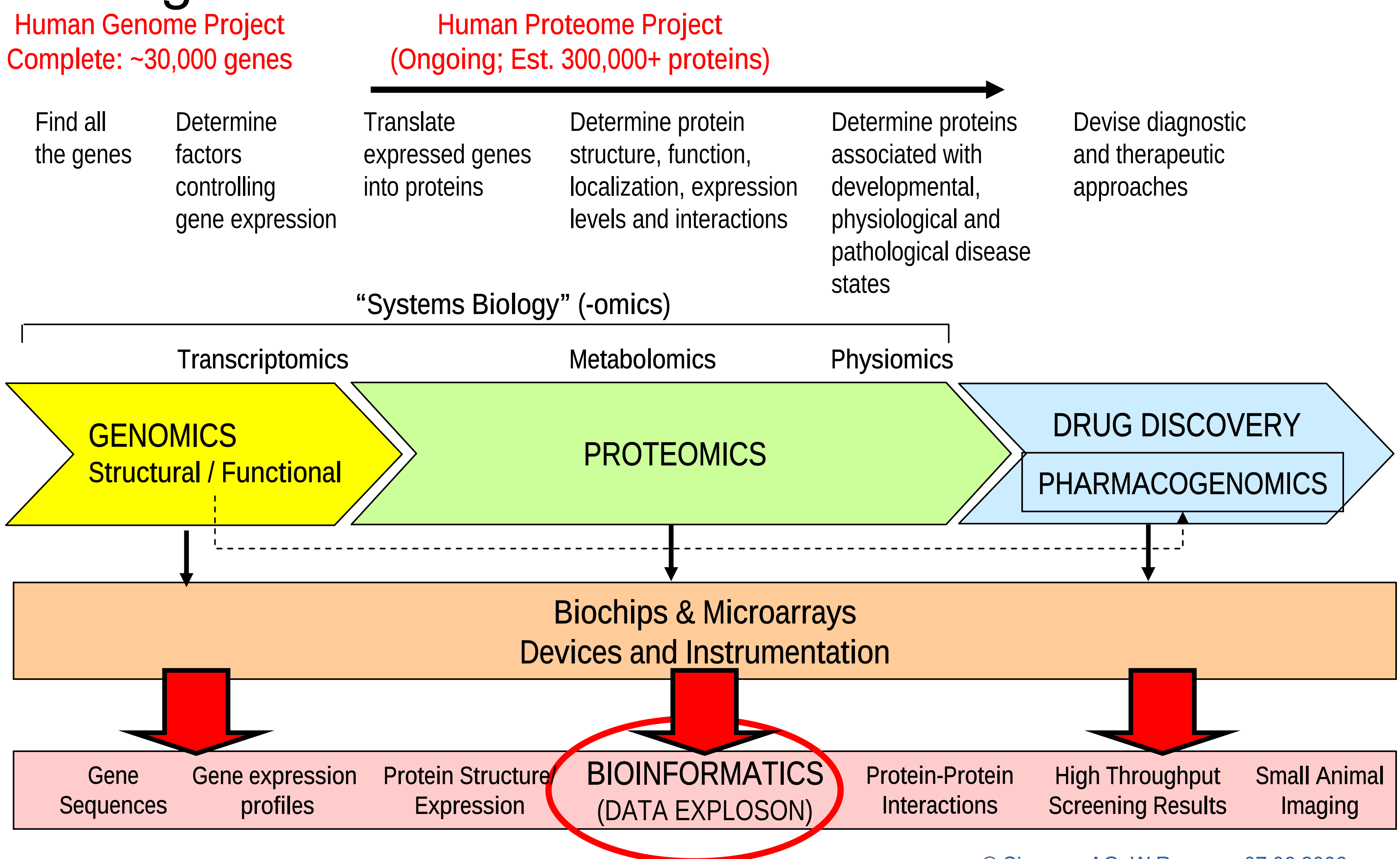
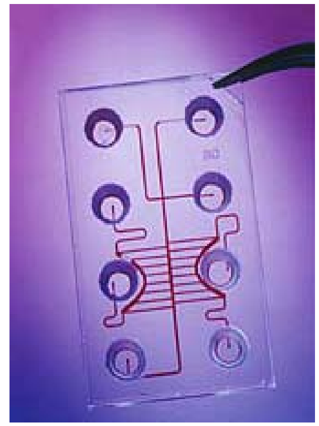
Biotechnology for Healthcare: Putting it all together



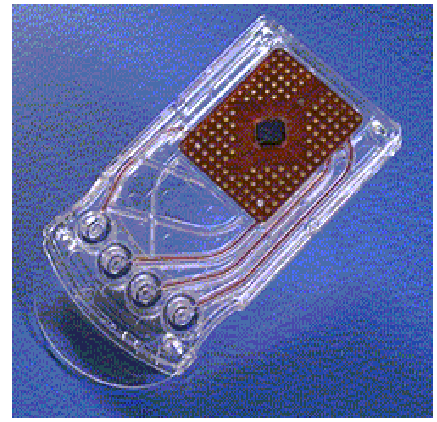
Biochips are currently emerging with different form factors and technologies for applications in research, pharma and healthcare

All biochip concepts are disposables

DNA µArray



µfluidic chip



µfluidic chip
+
DNA µArray

Applications:

- Basic research
- Pharma R&D / Drug development } "Red Biotech"
- Healthcare
- Agriculture and environment — "Green Biotech"
- Industrial and process control — "Grey Biotech"

Biochips have the potential to significantly penetrate the biotech and medical industry

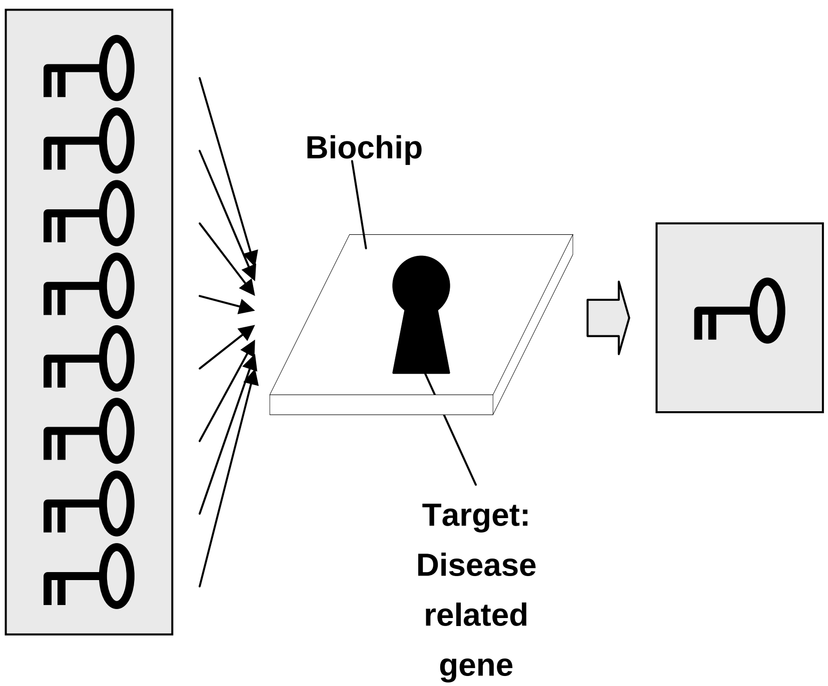
Example

HIGH THROUGHPUT SCREENING

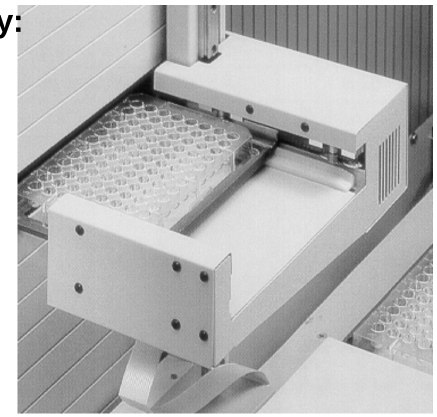
Compound library
Millions of potential drugs

Biochips
Highly parallel screening

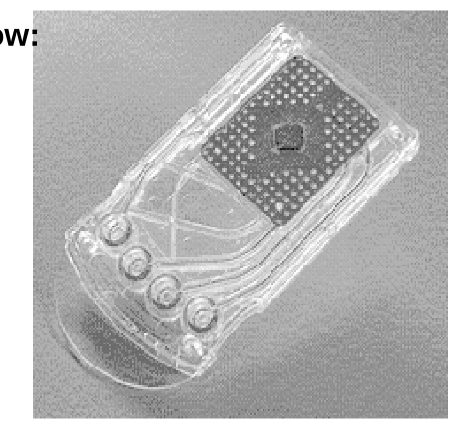
Lead
Identified drug



Today:



Tomorrow:



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Top biochip market trends are genomics research as well as new ways in drug development, diagnosis and therapy driven by cost reduction and lack of performance of conventional medicine

Drivers	Trends	Examples
• Need for cost reduction in healthcare • Progress of diseases that can't be treated with con-ventional medicine	• Consolidation of global genomics knowledge base • Highly efficient development and testing of new drugs • New ways in diagnosis and therapy	• Human genome project: Universal map of genes • Databases matching individual dispositions, risks and susceptibilities • Replacement of time-consuming and expensive animal experiments through biochips • Pharmacogenomics: Drugs designed according to individual dispositions • Prevention: Early detection of diseases enables timely treatment
• More money spendable for life quality improvement	• Genomics migrating into non-specialist environments	• Use of genetic assays in practices and at home
• Threat for health and environment by pollution and genetically modified organisms	• Advance of genomics based environmental and industrial surveillance	• Detection of hazardous substances and germs in air, food and water • Identification of genetically modified crops

Impact of Molecular Medicine on Patients:

Biotechnology Advances are fueling Molecular Medicine

- ➔ More than 325 million people worldwide have been helped by the more than 155 biotechnology drugs and vaccines approved by the FDA. Of the biotech medicines on the market, 70% were approved in the last 6 years.

- ➔ There are more than 370 biotech drug products and vaccines currently in clinical trials targeting more than 200 diseases, including various cancers, Alzheimer's disease, heart disease, diabetes, multiple sclerosis, AIDS and arthritis.

- ➔ Biotechnology is responsible for hundreds of medical diagnostic tests that keep the blood supply safe from the AIDS virus and detect other conditions early enough to be successfully treated.

Source: Bio.org