BIOANALYTICAL AND BIOMEDICAL MICROSENSORS

Gerald A. URBAN

Laboratory for Sensors

IMTEK
Freiburg/Germany
DISTINGUISHING FEATURES

- Unique combination of Computer Science and Microsystems Engineering
- One of the largest university based MEMS institution worldwide
- First curriculum in MEMS
- Extensive state-of-the-art cleanroom facilities
- 1400 students
- 22 Million external research funding
- 3. Place ranking of german “Wissenschaftsrat”
- ~ 40 patent applications /a (2005 – now)
OUTLINE

- History: Where we are going?
- Megatrends - Personalized Medicine
- Biomarker Analytics
- Microbiosensors/Lab-on-Chip
HISTORY

ADVANCEMENTS IN MEDICAL TREATMENT

1750 -
Industrialization: food production, goods,…

1850 -
Hygienic concepts
Anesthesiology - surgery

1900 -
ECG / X-ray

1930 -
BioMedical Engineering / Antibiotics

1990 -
Computerization - Molecularization - Miniaturization

- Imaging
  Anesthesiology, ICU
  Dialysis

- Biomaterials
  Molecular imaging

- Implants
  Minimal invasiv surgery
MEGATRENDS

- Lifestyle diseases – cardiovascular, diabetes,..
- Aging population – cancer, neurodegenerative diseases
- EMERGING DISEASES: New infectious diseases – Multiple antibiotic resistance of bacteria (MRSA)

NEW MEGATRENDS:

- Personalized Medicine - „Biologization“ - Nanomedicine
- Biomarker
- Systems biology
- from micro to nano
AGING POPULATION

G. Urban, VDE Positionspapier „Theranostische Implantate“ 2011
Tailor therapy and manage a patient’s disease better through use of molecular insights (Systems Biology) and diagnostic tests.

Today most patients are treated the same:
- 25–80% of patients receive effective treatment¹
- >100,000 deaths/yr from adverse drug reactions in US²

Increasingly, treatment will be tailored to selected patient groups defined by biomarkers.

Adapted from T. Gutjahr, Roche

¹ Spear et al., Trends Mol Med, 2001
² Lazarou et al., JAMA, 1998
Biomarker development
Most likely to benefit / most effective treatment

Healthy
Asymptomatic disease
Symptomatic disease
Chronic disease cured

Risk assessment
Screening/Diagnosis
Prognostic
Predictive
Monitoring

Predisposition for developing disease
Early detection
Predict probable disease course
Predict therapy likely response to a drug
Monitor efficacy/recurrence

G. Urban, VDE Innovationsreport 2012
PERSONALIZED MEDICINE

PHARMA COMPANY

MARKET CONCEPT / NEED

Sell Pharmaka with "Companion diagnostics" tools as a complete system

ECONOMIC/ADDED VALUE

Very high

BUT

It’s not only big pharma!
Biomarker development

Most likely to benefit / most effective treatment

- Healthy
- Asymptomatic disease
- Symptomatic disease
- Chronic disease cured

- one time
- often
- frequently
- continuous
- implanted

Risk assessment

Screening/Diagnosis

Prognostic

Predictive

Monitoring

MONITORING

Centralized lab

IVD

Near patient

POC

ICU

HomeCare

disease
disease course
to a drug or therapy
recurrence

Gen tests

Mutation
Protein assays
Glucose
Blood pressure

Genotyping
Mutation analysis
Protein marker
Pathogen analysis

Blood pressure
Glucose
Tumor Marker

G.Urban, VDE Innovationsreport 2012
Systems Biology

Investigation of the origin of diseases by basic biological research: Scientific description of complex, dynamic biological pathways

ANALYTICS OF BIOMARKER

Description/Expression of Genes (\(\sim 10^4\))

Monitoring of Proteins (\(\sim 10^5\))

Monitoring chemical and physical metabolic parameters (\(\sim 10^3\))
PATHWAY ANALYSIS:
Bioanalytics of Biomarker using LAB on CHIP and SENSORS

- Analysis of Human Genom
- Mutation analysis
- Gen expressions/RNA

- Lab-on-Chip
- Oligonucleotide Arrays
- Gensequencing

- Protein analytics

- in-vivo monitoring of blood pressure and small molecules with microbiosensors

- Biochip-Array
- e.g. SEPSIS marker
BIOMARKER

OLIGOCHIPS - Sequencing of 4th generation

Primer with replication-stopping or facilitating Oligonucleotides
Complementary bases (A,C,G,T)

Analysis of the whole human genome < 10^4 US$

Company: IonTorrent
Sequencing with pH Sensors

Analysis of the whole human genome
< 10⁴ US$

Company: IonTorrent

Ion-sensitive layer

Micro-machined wells

Proprietary Ion sensor

pH-Sensor array

ISFET
Next generation: Nanopore sequencing / Nanotechnology

The harvard nanopore group

Courtesy of Paul Montie Design
SEQUENCING MARKET

GLOBAL VALUE OF SEQUENCING PRODUCTS AND SERVICES BY TYPE,

Oligonucleotide μArray Market: ~1.5 Billion/a (2012)

BCC research
METABOLIC BIOMARKER

- EMERGENCY ROOM / OP-THEATER / INTENSIVE CARE
- ACUTE MEDICINE / INFECTION MONITORING
- AGING POPULATION / CHRONIC DISEASES

Monitoring of Biomarkers:

- OP/ ICU

- Ambient Assisted living In elderly, chronic ill people

Acute markers, Cardiac markers, Biochemical biomarkers, Blood pressure…LAB on MICROCHIP
Pressure sensors are poised to become the leading type of MEMS device, generating $1.5B in revenue

Monitoring of Blood pressure (High value)
ICP

Disposable (and low-cost) MEMS pressure sensor is the infusion pump, used to introduce fluids, medication, or nutrients into a patient's circulatory system. 60M units of these devices were shipped in 2011.

Worldwide high-value MEMS pressure sensor revenue forecast, in US $M. (Source: IHS iSuppli)
FloTrac sensor attaches to an existing arterial catheter and automatically calculates key flow parameters such as:

- continuous cardiac output
- stroke volume
- stroke volume variation
- systemic vascular resistance
MINIATURIZATION

NICHE MARKET

Additional parameters?
MONITORING BIOCHEMICAL BIOMARKERS

LAB on CHIP
In vitro Diagnostic (IVD)

26 - 46 Billion $ / 2011 (Technology Park, Lacuna AG)

Glucose 9 Billion $
Molecular diagnostics 5 Billion $
POC 4 Billion $
Tumor marker 2 Billion $
**Enzym: GOx Adsorbed**

**Next steps:**
Multianalyte measurements
Monitoring
IVD PERSONALIZED MEDICINE

IVD DIAGNOSTIC COMPANY

MARKET CONCEPT

Sell Devices with multiple diagnostic functions for POC / NP  AAL  ICU/OP

VALUE CHAIN:
Production sensors, electronics, housing /

ECONOMIC/ADDED VALUE

High, but high price pressure
Roche OMNI S for blood gases, electrolytes and metabolites
• POC diagnostics market reached $4 - $13.4 billion (2010) growth rate (CAGR) 3.7%
• Glucose monitoring market $7.6 billion
• Blood chemistry and electrolyte segment $2.2 billion (2010)
POC MONITORING

→ Lab on Chip: Low cost, fast, cheap, reliable

Spin off Company: Jobst Technologies
Chip-based **multianalyte** analyzer

**POC ex-vivo discrete**

For use in the intensive care unit (ICU) and operating room (OR).

A disposable multi-parameter microanalyser is integrated into an existing arterial or venous line on the patient.

When a reading is required, blood is withdrawn from the patient into the device.

All blood is returned into the patient after the measurement.

**Si-chip**: glucose, pH, carbon dioxide, oxygen and potassium ions

510(k) clearance

Duration: 72h
AGING POPULATION:

ELDERLY AND HANDICAPPED PERSONS
HOW WE CAN HELP? USE SMART TEXTILES?

Probably not!!

Solution: Use currently available implants and integrate microsensors

Hypertension monitoring:

Miniaturized implanted pressure sensors

HYPER-IMS
PERSONALIZED MEDICINE
LONG TERM MONITORING

IMPLANT COMPANY
MARKET CONCEPT

Sell Devices with diagnostic and rehabilitative (Theranostic) functions for AAL and ICU/OP
PaceMaker market ~4 Billion $

VALUE CHAIN:
System: production sensors, electronics, housing /

ECONOMIC/ADDED VALUE
High
PaceMaker: Monitoring of biomarkers with Implanted BIOSENSORS

IMPLANTED LAB CHIP

Power management Controller Sensorinterface Battery Interface Packaging Microsensor

Blood pressure Electrolytes Glucose, lactate Kidney biomarkers

Blood

Anti-Biofouling

Semipermeable Membrane

Erkennungskomponente

Transducer Signalverarbeitung Telemetrie

External receiver

VDE Positionspapier „Theranostische Implantate 2011“
IMTEK/Sensors: In vivo array

$pO_2$, pH, glucose, lactate, glutamate, $K$, Cystatin
EMERGING DISEASES : PATHOGENS

POC / Lab-on-Chip: 1 Billion$/a

Biomarker: RNA Detection

Cell sample

Enrichment & cleaning target species

Cell lysis

Nucleic acid purification

Nucleic acid diagnosis

10µl Sample
1. Thermo-electric lysis through Joule heating

2. Electrophoretic purification

3. Detection through real-time PCR

RNA extraction chip

- Lysis electrode
- RNA
- Gel
- Cell sample
- Electrophoresis electrodes
RNA extraction chip

Extraction in 10 minutes: Volume 10µl

Detection Limit: 1 Cell/µl!
THANK YOU FOR YOUR ATTENTION!