Lab-on-a-Chip technologies for precision medicine

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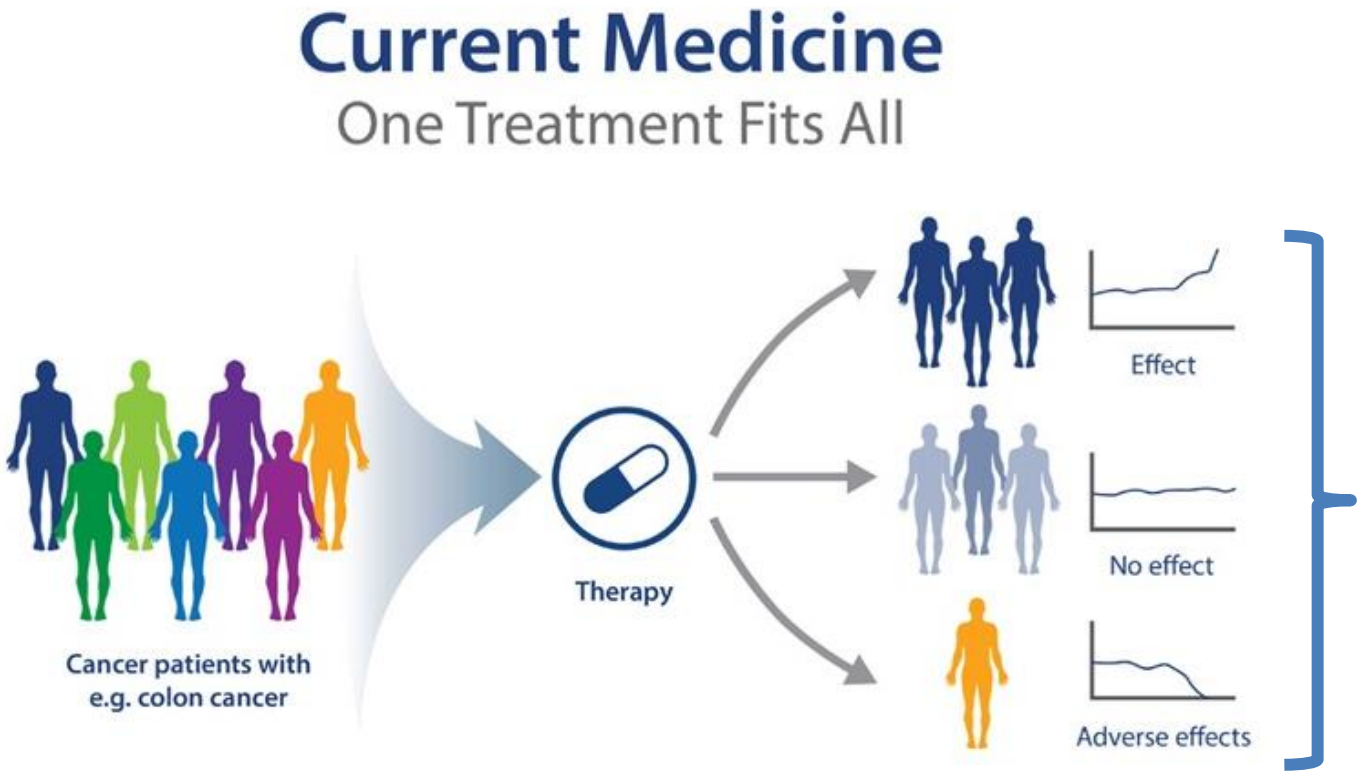
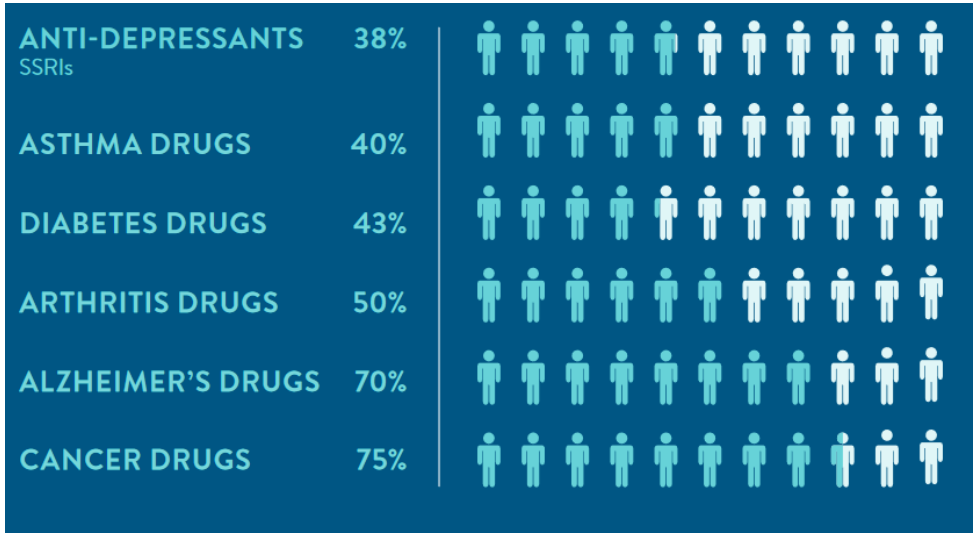
What about precision/personalized medicine?

Personalized medicine is the use of information from a patient's genotype to:

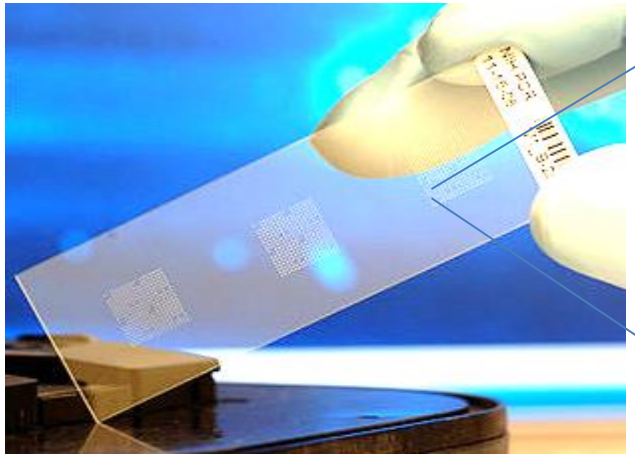
- initiate a preventative measure against the development of a disease or condition, or
- select the most appropriate therapy for a disease or condition that is particularly suited to a patient.

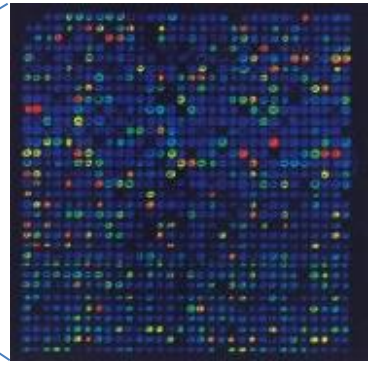


drug performance/ effectivity analysis



Personalized DNA diagnostics – does it work?

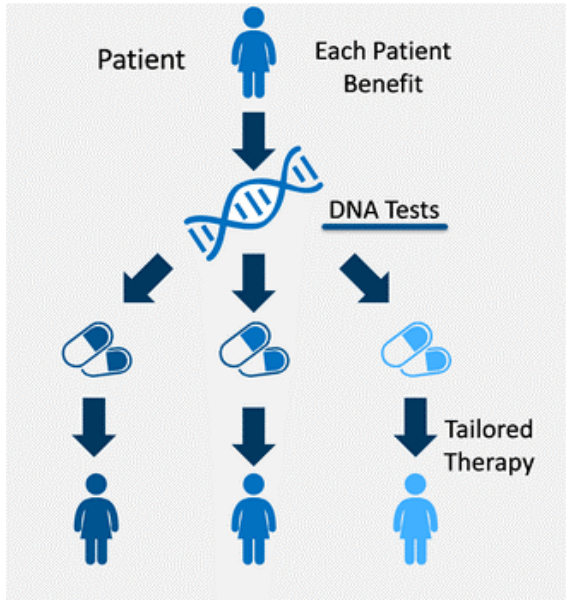




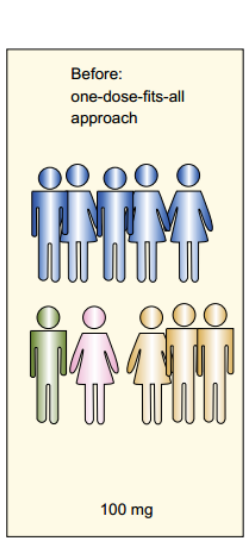
Data Mining and analysis

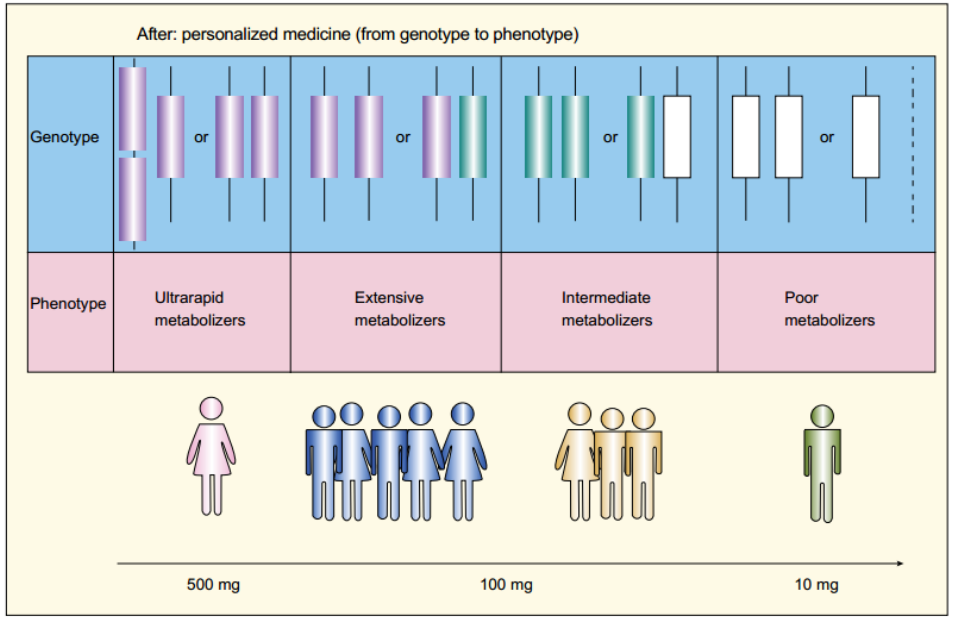
Gene	Value
D26528_at	193
D26561_cds1_at	-70
D26561_cds2_at	144
D26561_cds3_at	33
D26579_at	318
D26598_at	1764
D26599_at	1537
D26600_at	1204
D28114_at	707

prediction



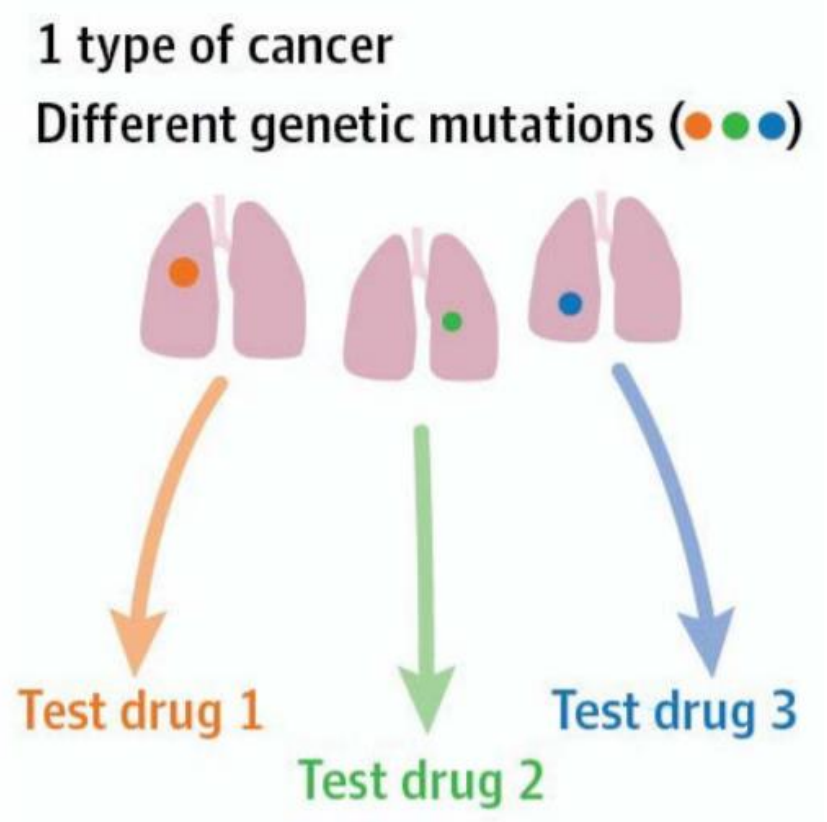
prediction on how cells and tissue respond based on a patient's individual genetic profile

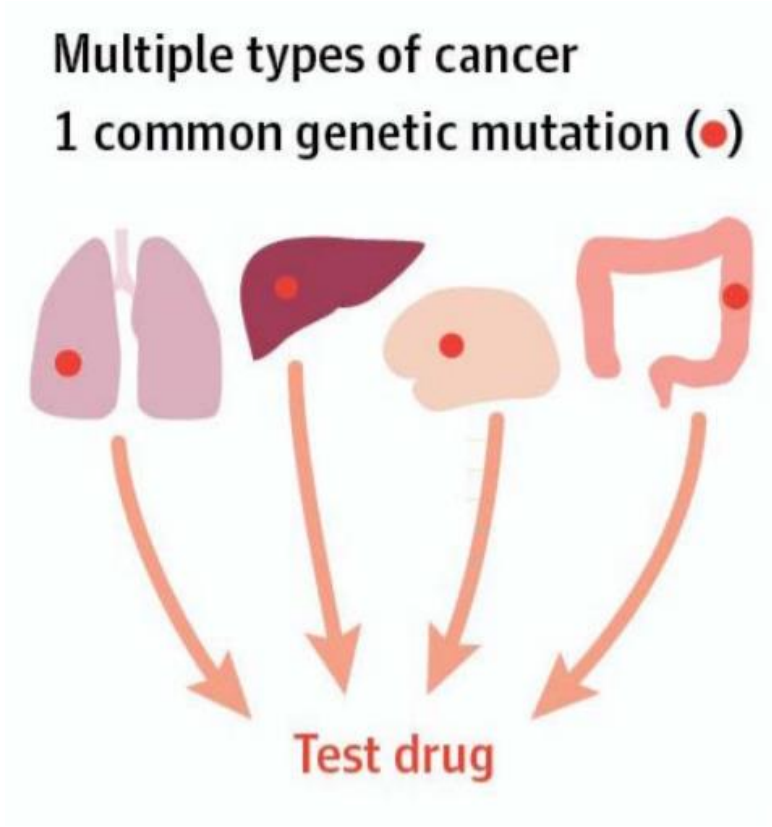




- Incorrect DNA analysis
- Gene variations are too numerous
- Environmental factors and life-style
- demographic, age and gender effects

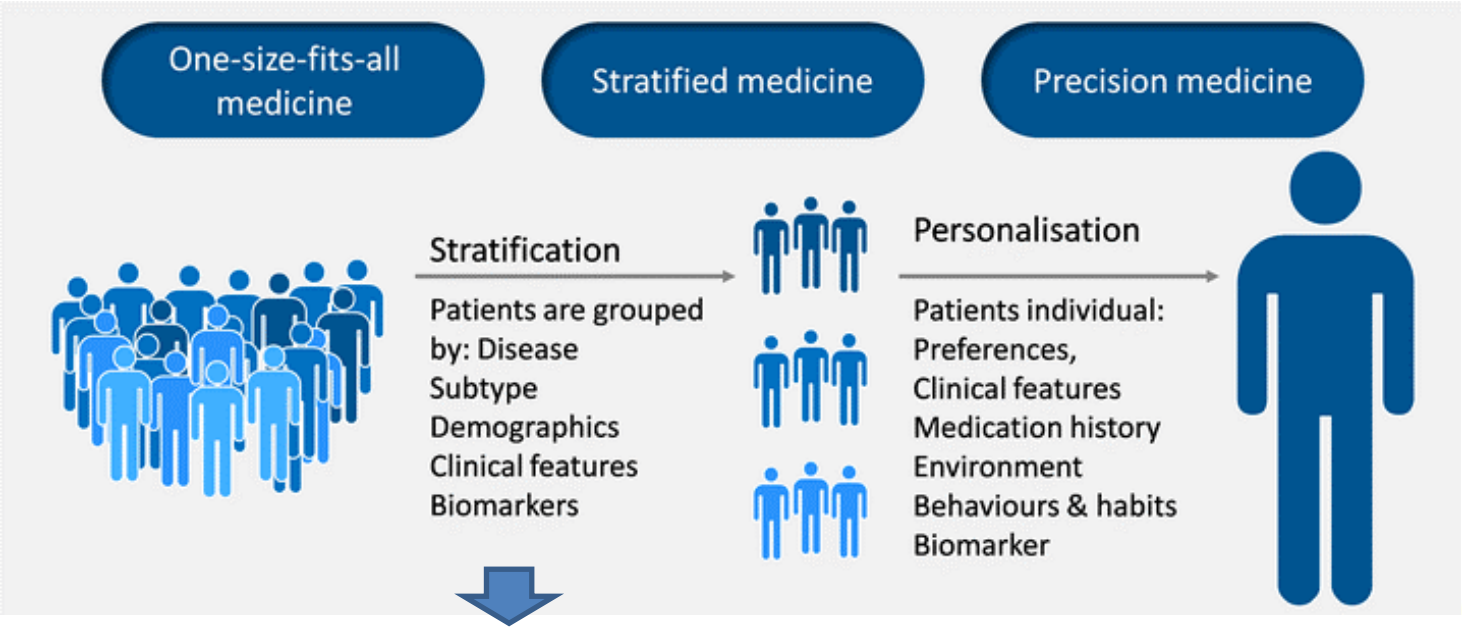
Other problems with genetic profiling

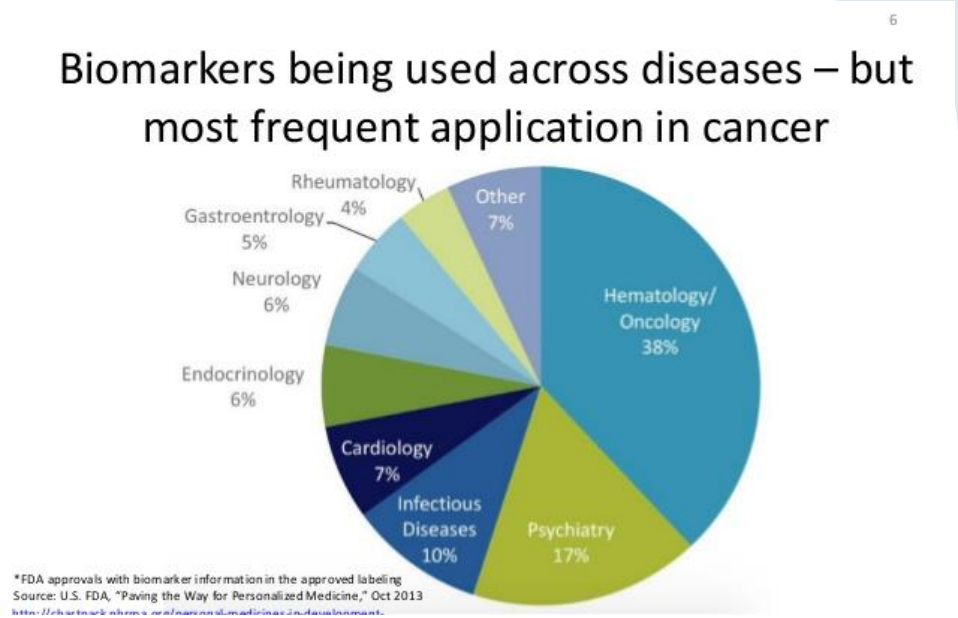




What about multi-factorial diseases ?

Companion diagnostics in precision medicine

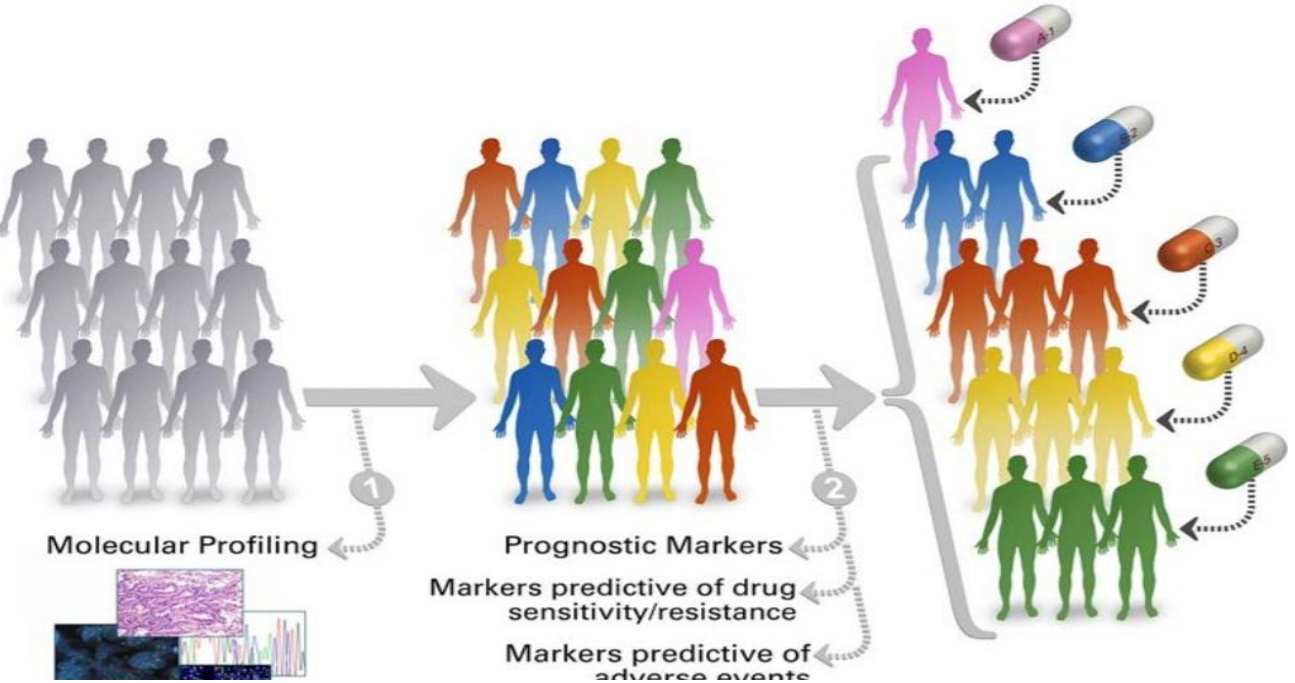




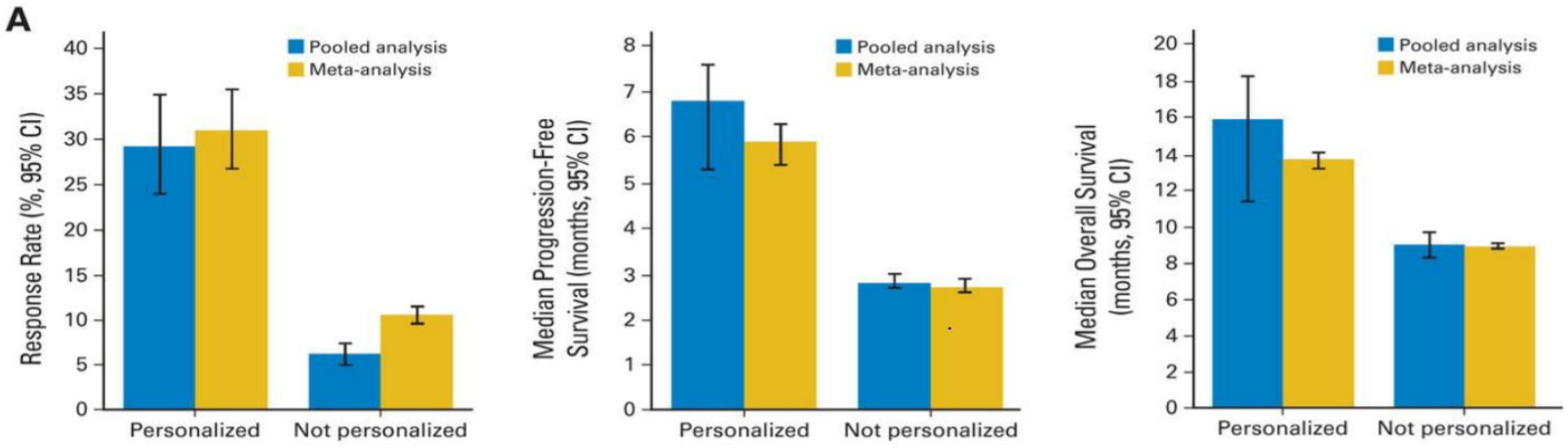
Companion diagnostics are necessary tests that select patients before a medicine is given. They may:

- show who is likely to respond to the medicine ('responders' and 'non-responders');
- identify patients at high risk for adverse reactions;
- and help the doctor to select an appropriate dose that is both safe and effective.

How good are precision medicine approaches?



- An advantage of developing targeted medicines is the increase in the efficiency of clinical trials.
- Fewer new medicines should fail at each stage of the development process if they are targeted at a known cause of the disease.
- The use of biomarkers will be central to personalised medicine.
- Validation of unique and predictive biomarkers measuring treatment outcomes will need to be in place before medicines developed in this way can be authorised.



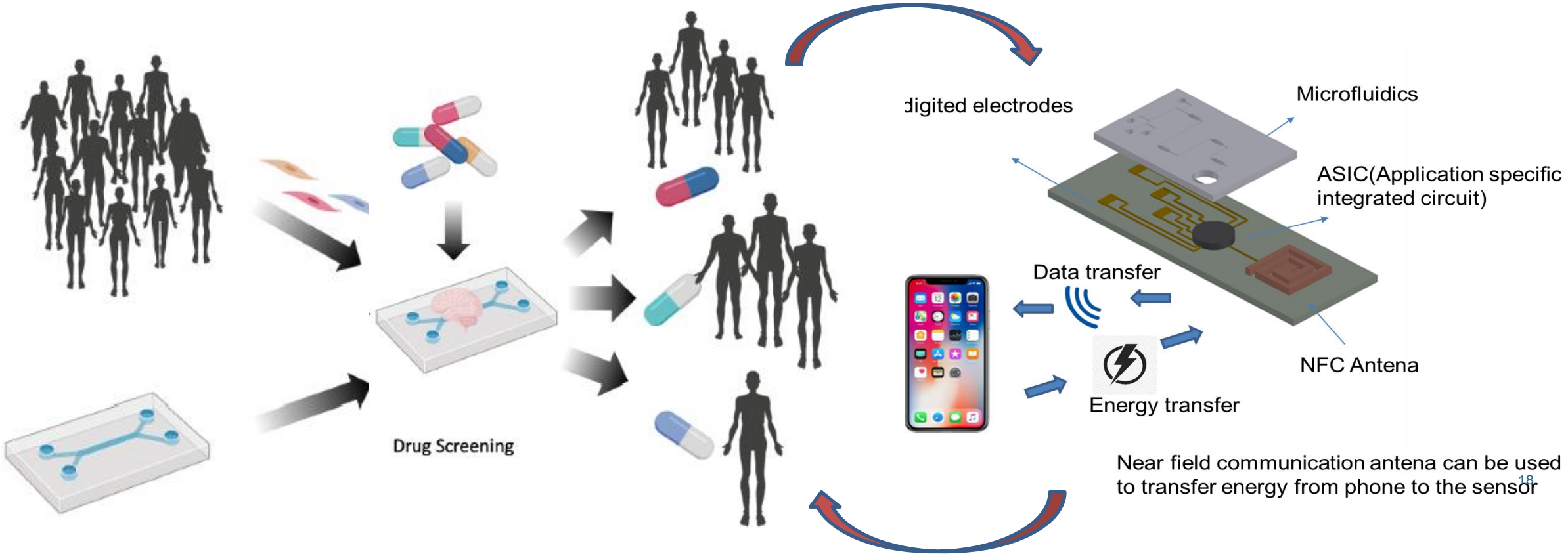
So what's next?

Future personalized medicine is based on information from a patient's own cells:

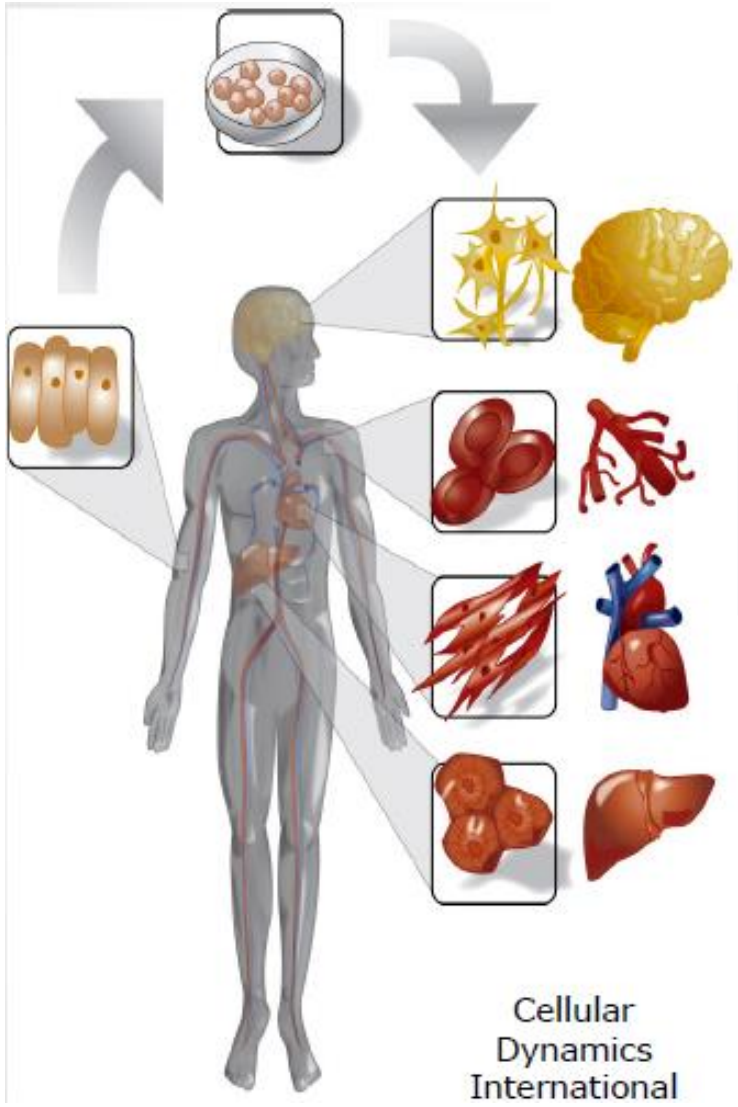
- initiate a preventative measure against the development of a disease or condition, or
- select the most appropriate therapy for a disease or condition that is particularly suited to that patient.

Future of companion diagnostics is based on miniaturized, automated and integrated analysis tools:

- Rapid, reliable and portable point-of-care devices that perform data transfer and telemedicine

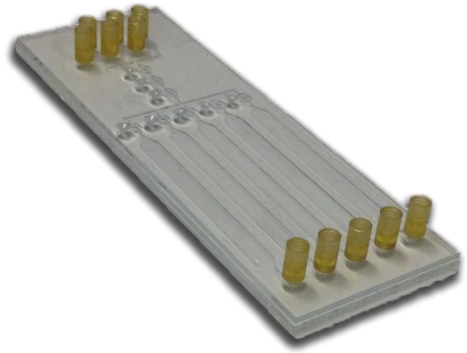


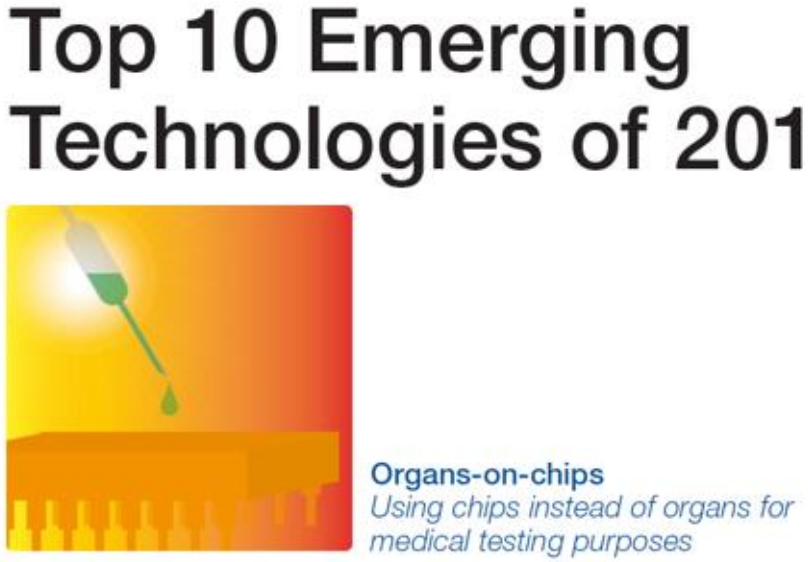
Organ-on-a-Chip technology



Nobel Prize in Medicine (2012)

Combination of complex biology with microchip technology





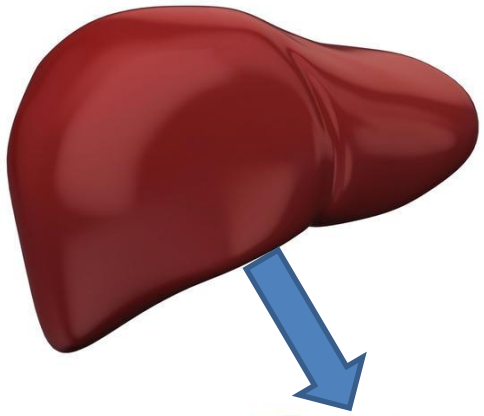
Advantages of Organ Chips:

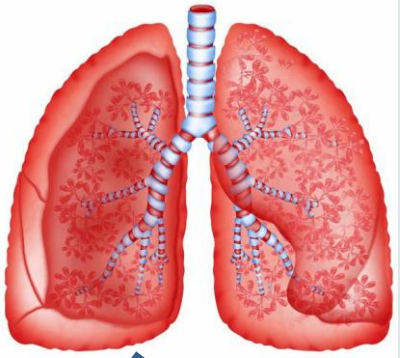
- Biomimetic tissue architecture
- Perfusion simulates vascular system (dynamic culture)
- Preservation of cell phenotype and genotype *in vitro*
- Heterotypic cell-cell, cell-matrix interactions
- Engineering of biochemical and biophysical microenvironments
- Increased predictive capabilities (screening tool)

What about Organ-on-a-Chip???

Scaling laws

- Smallest functional unit of a tissue structure





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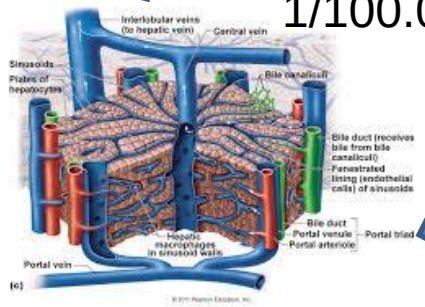
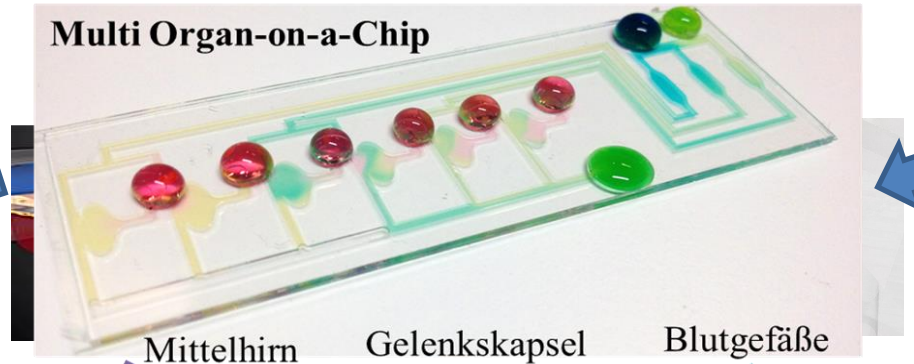
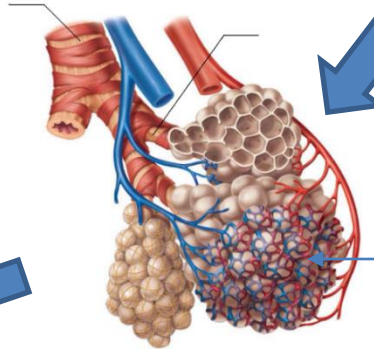






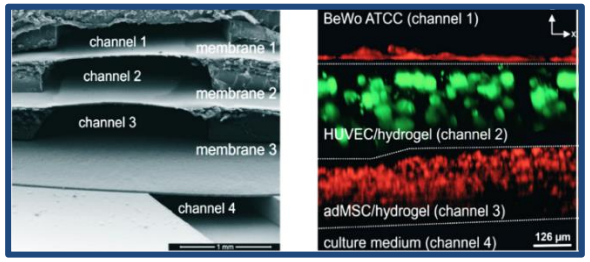
200 µm
alveolus

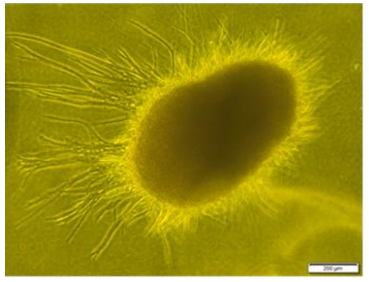
Mittelhirn

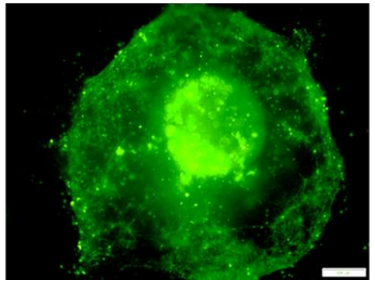
Gelenkskapsel

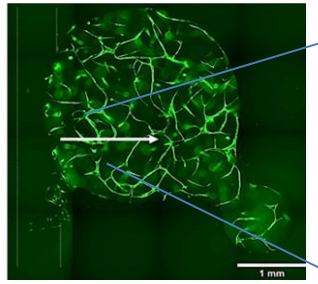
Blutgefäße

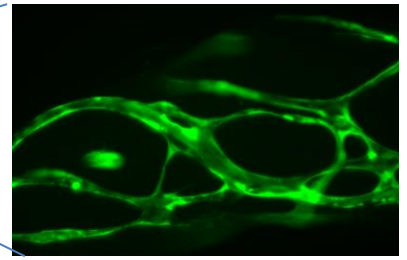
Plazenta











Who needs advanced biochip technology?

POTENTIAL STAKEHOLDERS OF ORGAN-ON-CHIP TECHNOLOGY

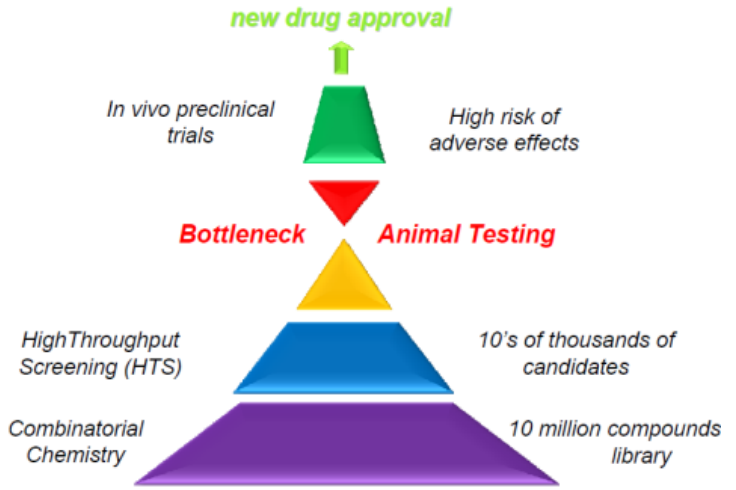
- Patient groups
- Medical centers
- Health foundations
- Insurance companies
- Pharmaceutical companies
- Biotechnology companies
- High-tech companies
- Agrifood companies
- Cosmetics companies
- Environmental institutes
- Regulatory agencies
- Advocacy groups

- 39% fundamental research
- 28% pharmaceutical R&D
- 10% toxicity testing
- 10% quality control
- 3% education and training
- others

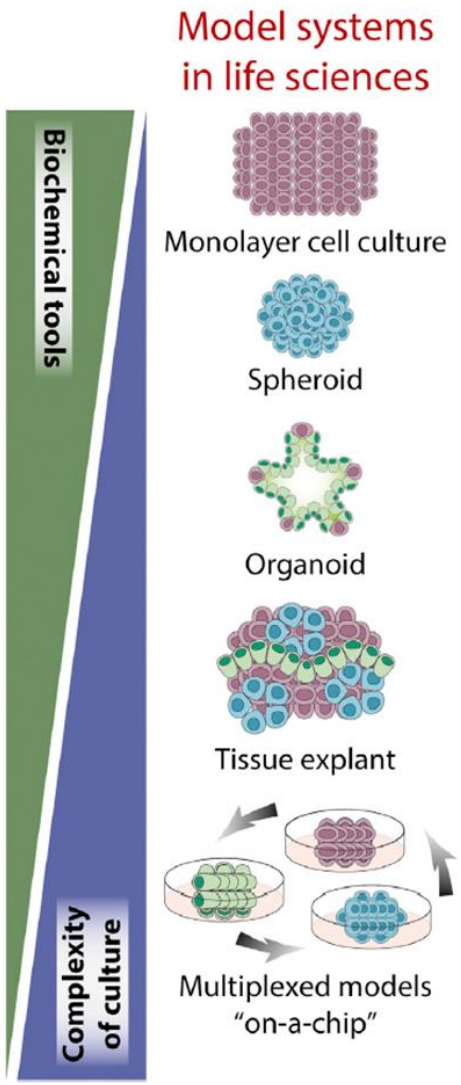
R R R → **Approx. 10 million animal test per year**

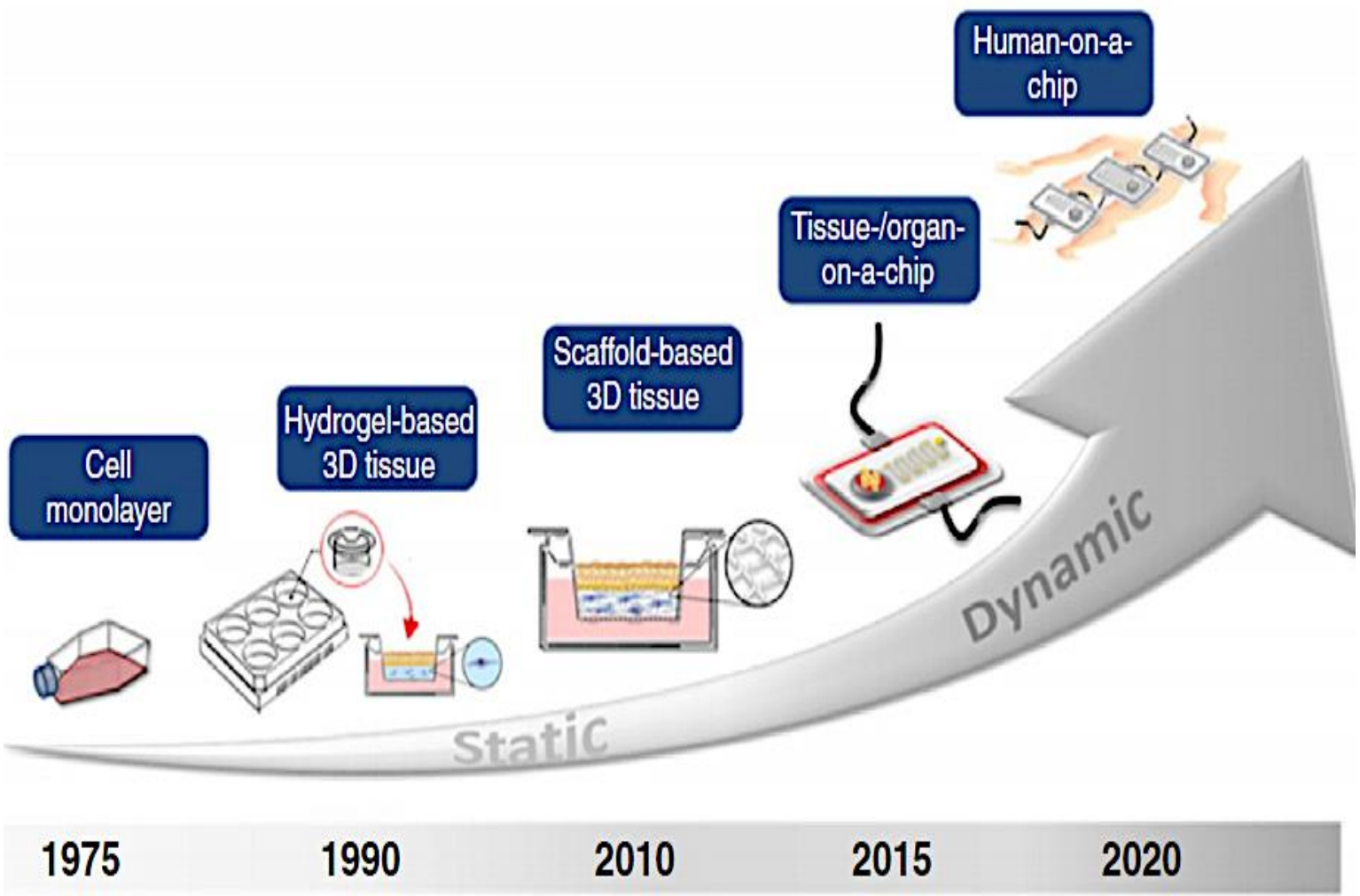
POTENTIAL APPLICATIONS OF ORGAN-ON-CHIP MODELS

- Mechanistic insights
- Drug development (target discovery & screening)
- Drug toxicity
- Personalized medicine
- Exploring technology for regenerative medicine
- Personalized food
- Environmental contaminant screening
- Cosmetic safety testing



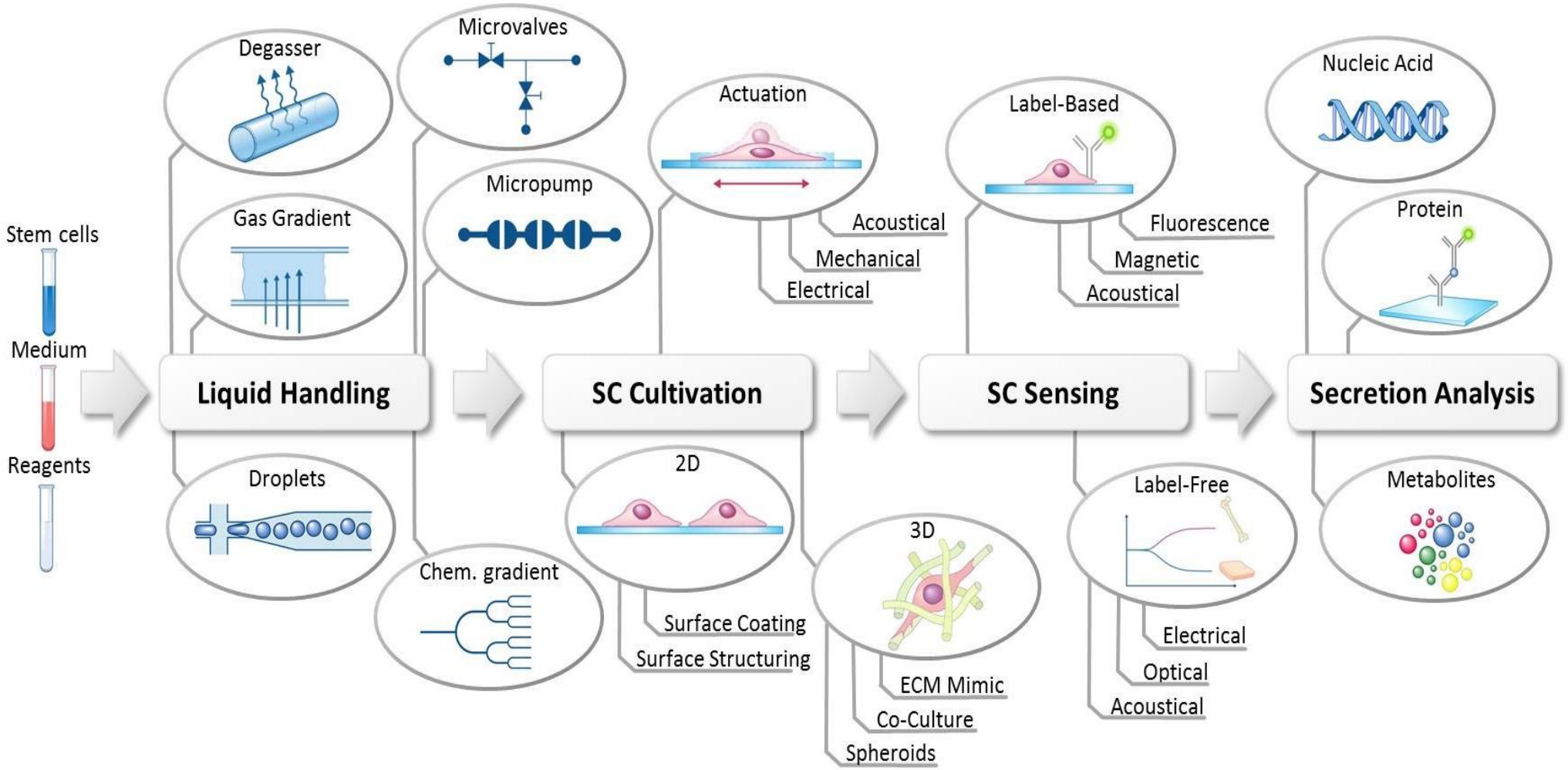
Trends towards better *in vitro* models





(Cho and Yoon, 2017)

Biology-on-chip needs technology



P. Ertl et al. *Trends in Biotechnology*, **32**(5): 245-253, 2014

TU Vienna Technology platforms

- Lab-on-a-chip Technologies in BioSciences – devices and applications

1. " Hydrogel Condensation Guide und Hydrogel Stopper on Chip " **EP 20173705.3** filed May 2020
   - Reliable and reproduceable establishment of 3D biological structures (*joint-on-a-chip*)
2. "Microfluidic device-midbrain" **EP 20173702.0** filed May 2020
   - Biochip for long-term cultivation and maturation of human midbrain organoids (*Parkinson's-on-a-Chip*)

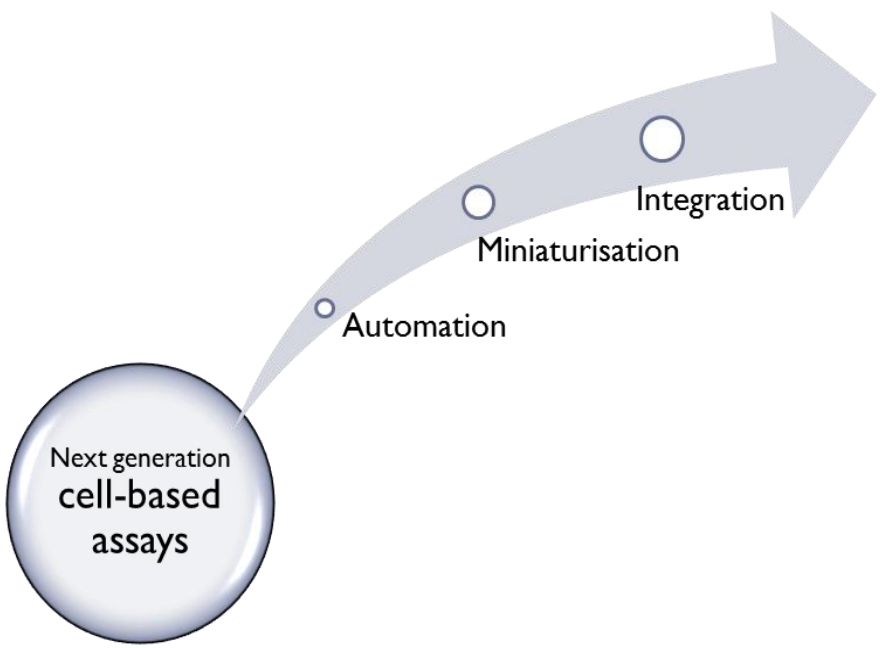
3. "Microfluidic device for applying pressure to a cell assembly" **EP18183978.8** was filed July, 2018 and **EP16165229.2** was filed April 2016
   - Method and device to induce mechanical injuries and stimuli on 2D and 3D cell cultures (*wound healing chip*)
4. "Microfluidic device comprising electrodes" **EP Nr. 19168889.4** was filed Nov 2019
   - Method for multi-parametric and multi-cell barrier integrity analysis using membrane-embedded electric microarrays (*TEER-ECIS chip*)

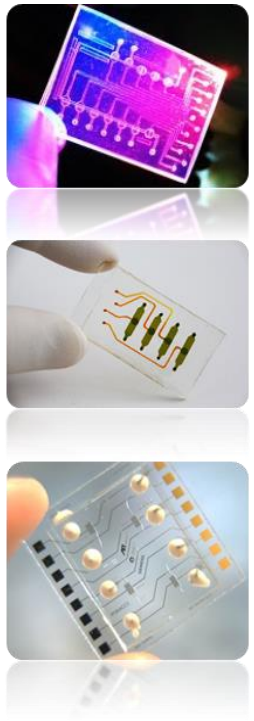
5. "Tensile and shear strength measurement" PCT appl Nr. **PCT/AT2019/060362 w**as filed Oct, 2020;
   - Methods and adapter to test tensile and shear strength by applying pressure for microfluidic composite manufacturing process Technologies (*QC tool*)

6. „Self-powered microfluidic sensor system" **EP 20189436.7** filed August 2020
   - Fast, reliable and portable detection of viral infections (<5 min) using an embedded nanosensor array (*Sars-Cov-2 detection system*)

TU Vienna Technology platforms

NextGen cell-based analsys systems – automation, miniaturization and integration





µpumps

µactuator

µsensors

Applications:

- quality control of stem cells
- pharmaceutical screening
- lead optimization studies
- toxicology tests (REACH)
- replacing animal testing
- cell-based therapies
- personalized diagnostics
- functionality studies
- cell-based biosensors
- biocompatibility
- investigating drug mechanisms
- ….

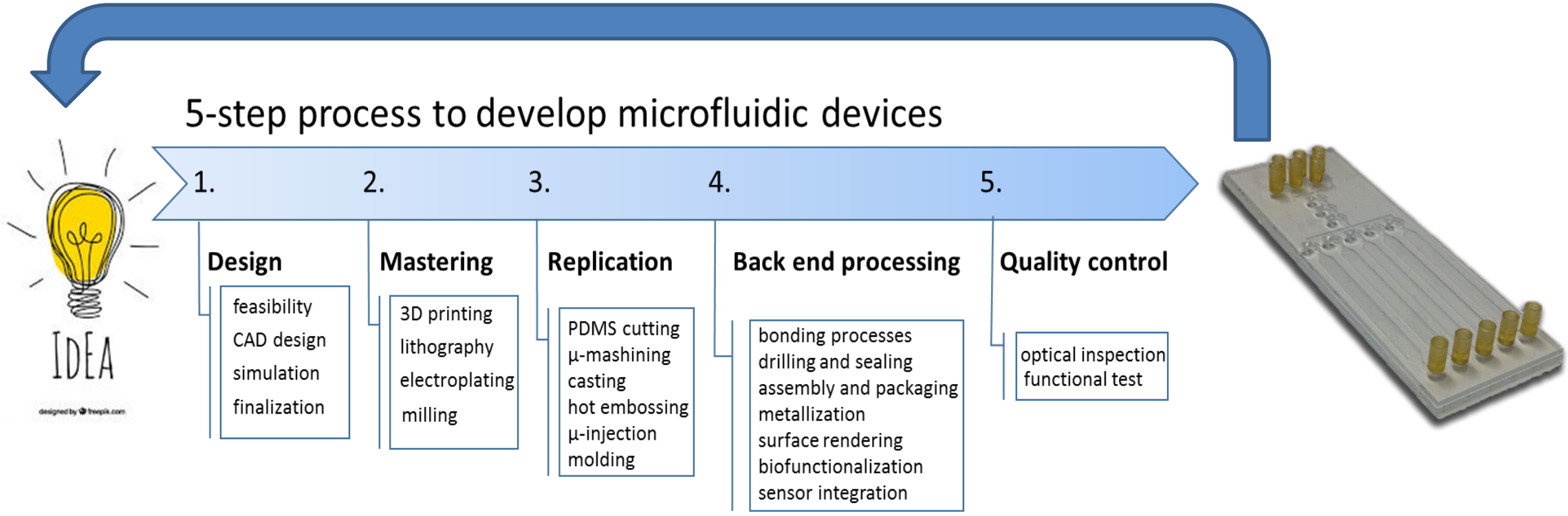
Regenerative medicine

Chronic inflammation

Drug development

From idea to functional prototype

Long and expensive development of industrial-relevant prototypes and small scale production



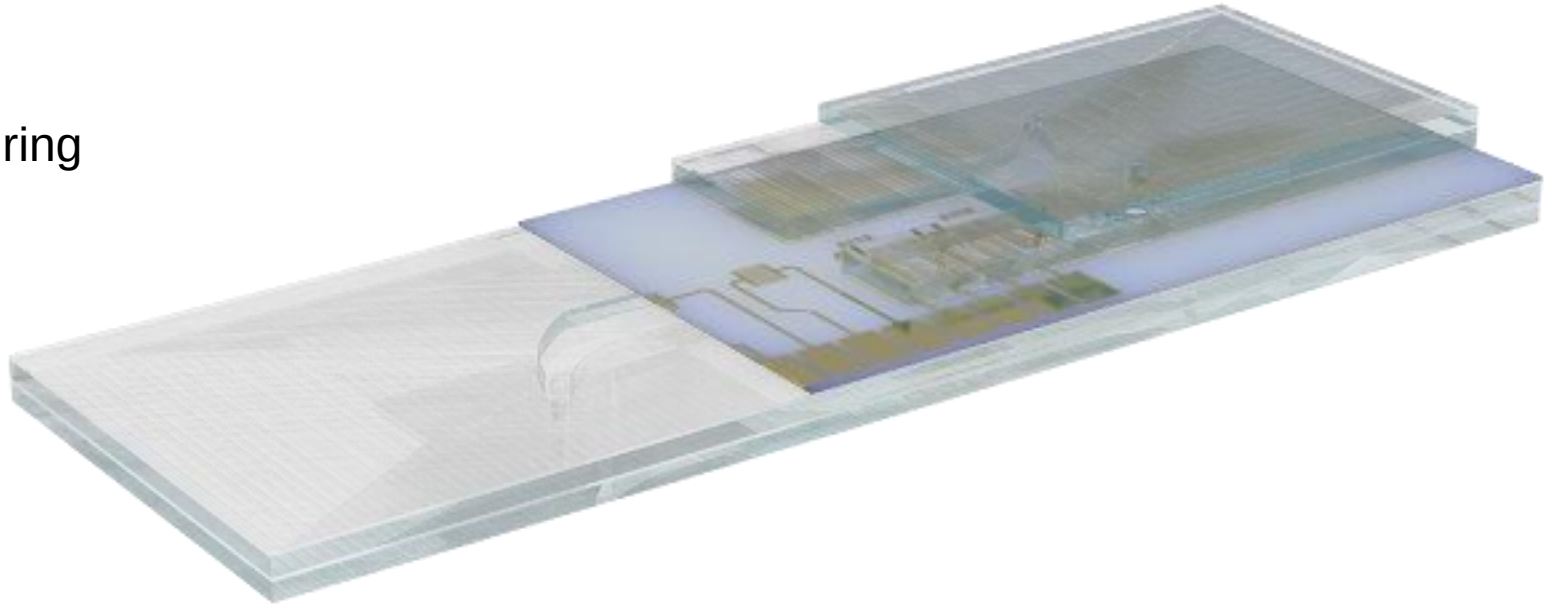
1 to 5 iterations to a functional prototype

Up to 12 iterations to go from functional prototype to industrial pilot plant production

Requirements for new methods of rapid prototyping for organ-on-a-chip systems

- resolution in micro structuring
- optical transparency
- oxygen permeability
- vapor permeability
- biocompatibility

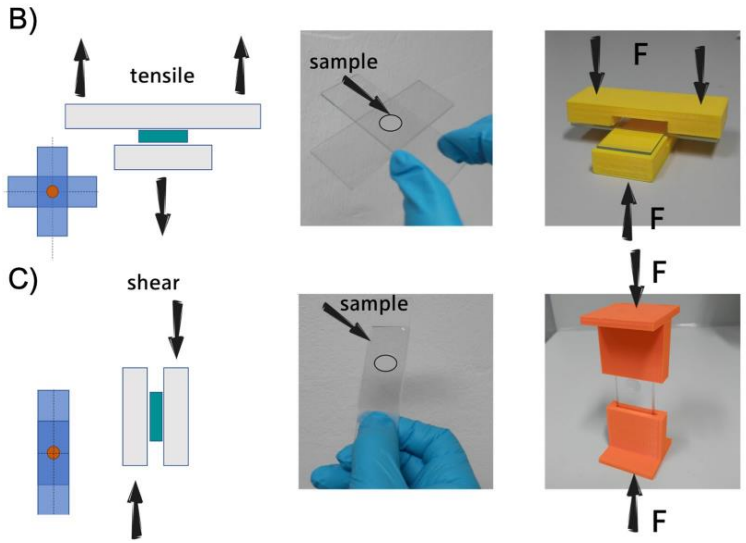
- **bonding strength**



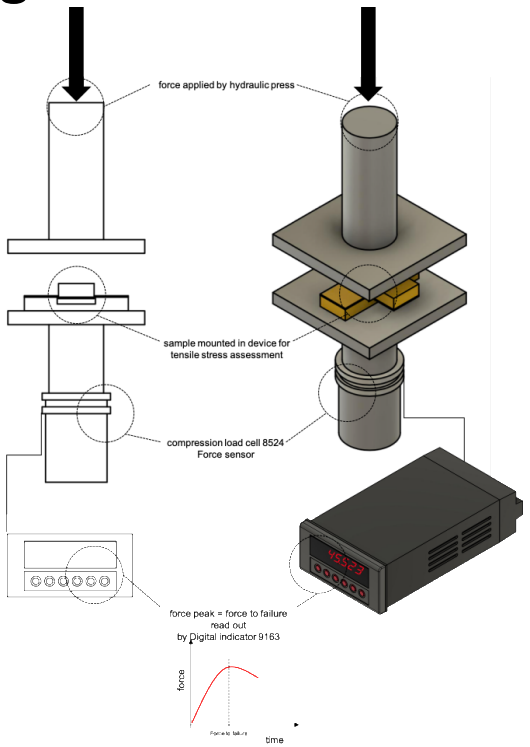
QC tool for microfluidics

AT patent Nr. A 50933/2018
PCT appl Nr. PCT/AT2019/060362

Method and adapter to test tensile and shear strength by applying pressure for microfluidic composite manufacturing process Technologies



Standardized sample layout



Sample set up

Common bonding protocolls:

- Adhesive, plasma, solvent, silanization

Common materials:

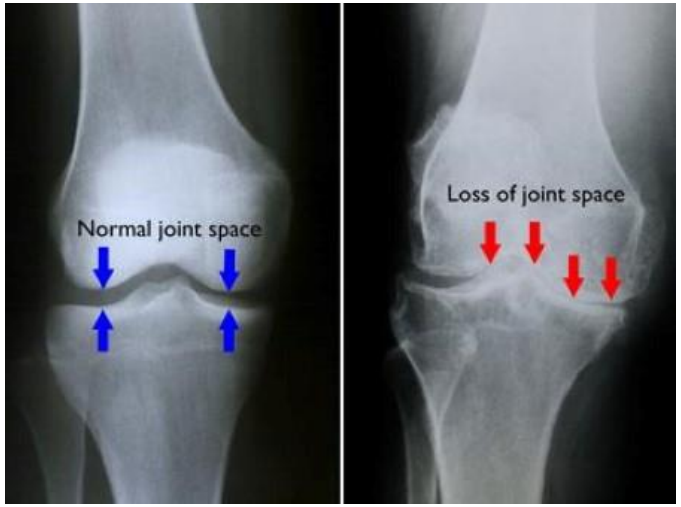
- thiol-ene-epoxy, glass, biocompatible adhesive, polydimethylsiloxane (PDMS) and polymers (PC, PMMA, COC/COP, PET)

Chip-based personalized arthritis model

- Musculoskeletal disorder
- Progressive joint destruction
- Joint pain → limitations in movement and daily activities
- Over **100 different types** of arthritis – 2 very common types:

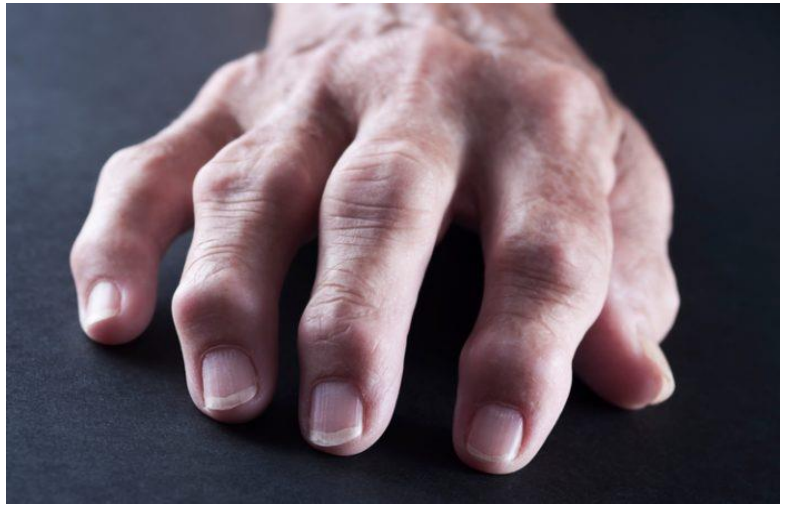
Inflammatory arthritis affects 325 million people worldwide and costs the US alone $185 billion annually.

- **Osteoarthritis**



- Degenerative joint disease affecting articular **cartilage**
- One of the most frequent disorders and associated with ageing
- Prevalence* (worldwide, age over 60)
  - 10 % men & 18 % women

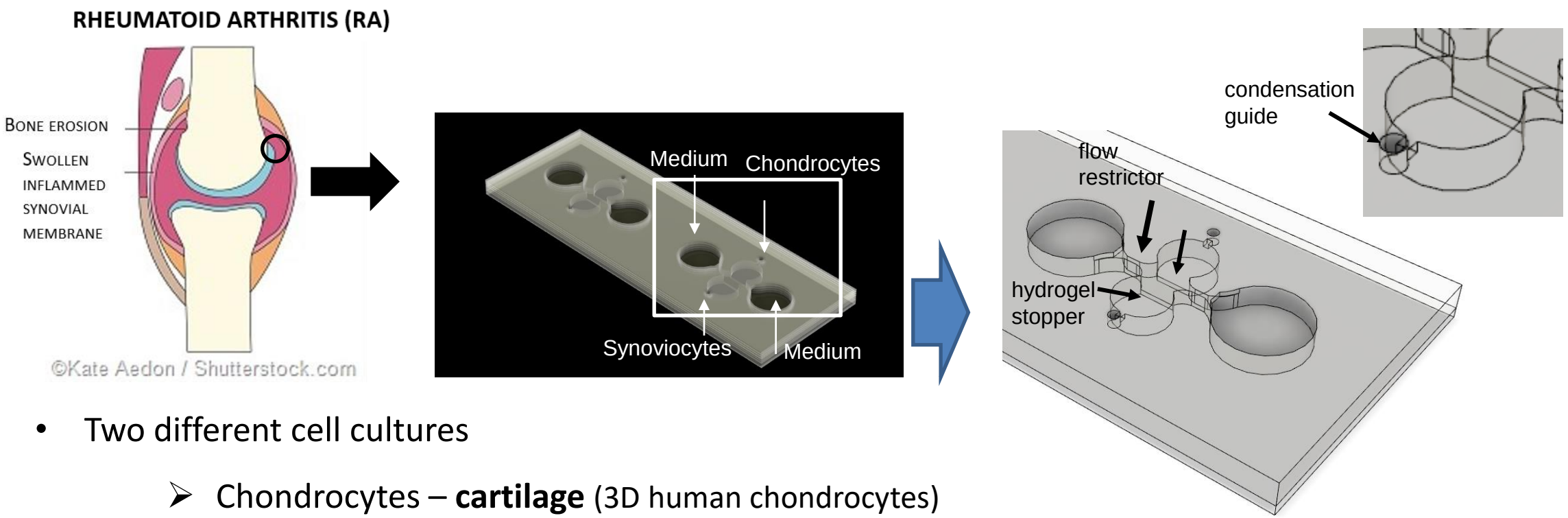
- **Rheumatoid Arthritis**



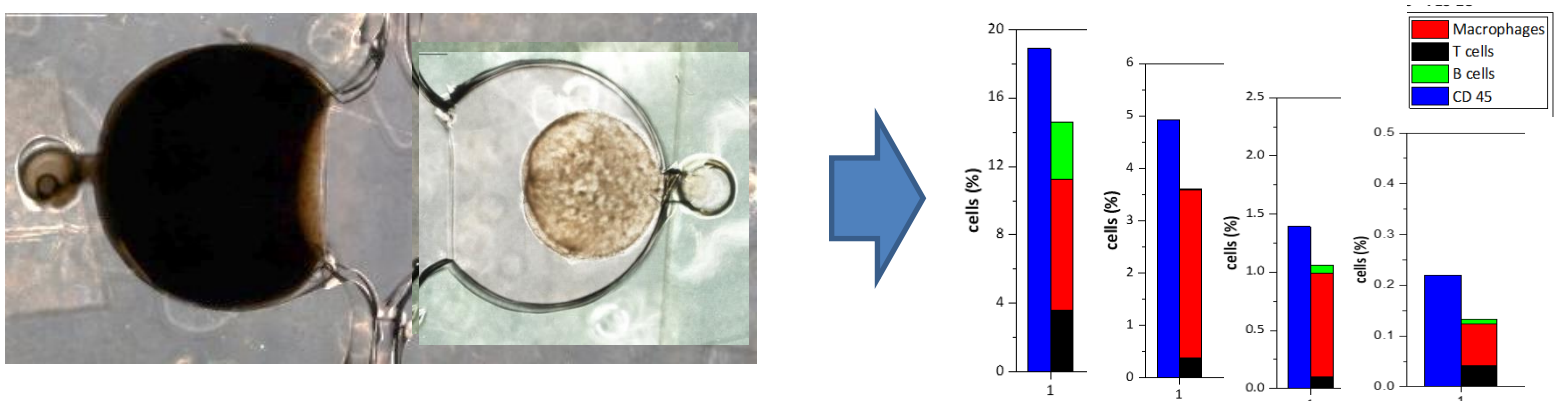
- Chronic systemic auto-immune disease
- Inflammatory, targets the **synovium**
- Deformity of joint (more common in women)
  - Prevalence 0.3 % - 1 % (worldwide)

Joint-on-a-Chip design

EP 20173705.3

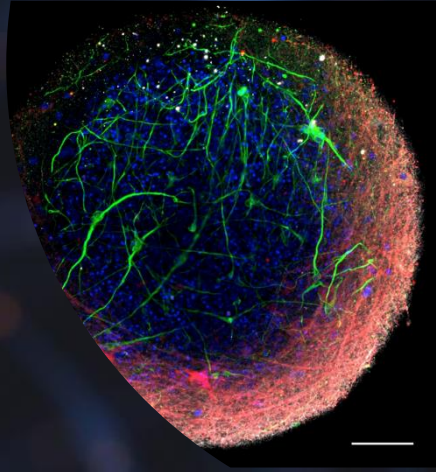


- Two different cell cultures
  - Chondrocytes – **cartilage** (3D human chondrocytes)
  - Fibroblast like synoviocytes – **synovium patient biopsies**

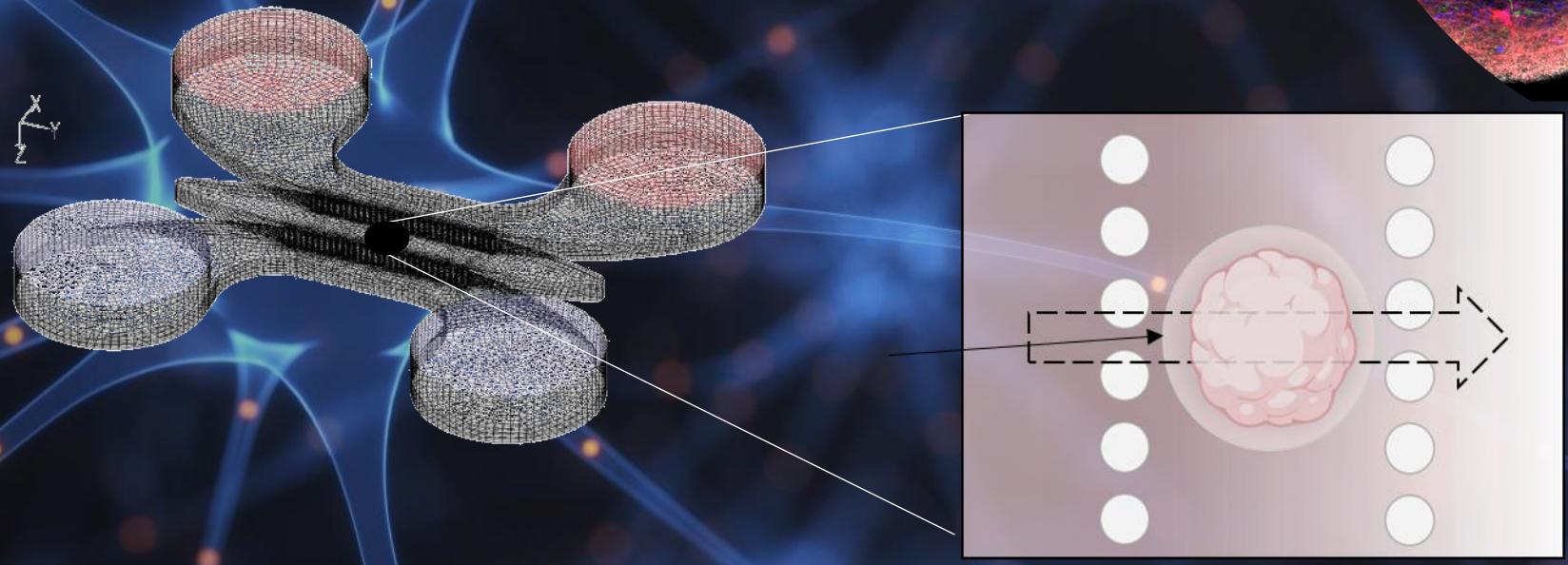


Parkinson's-on-a-Chip:

Unravelling the Complexity of Neurodegenerative Diseases Using a Chip-based Midbrain Organoid Model



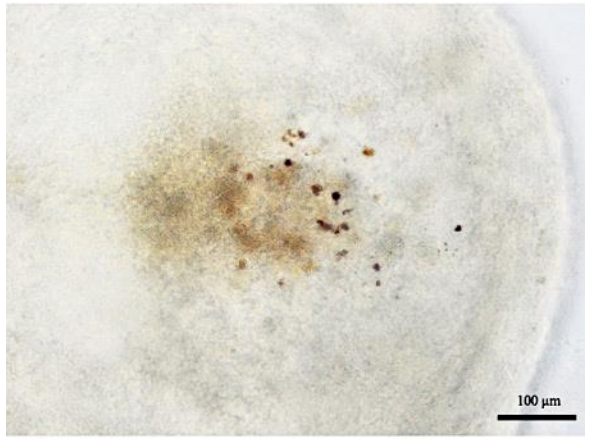
- **Motor symptoms**
  bradykinesia, akinesia, tremor, rigidity..
- **Non-motor symptoms**
  depression, hallucinations,..

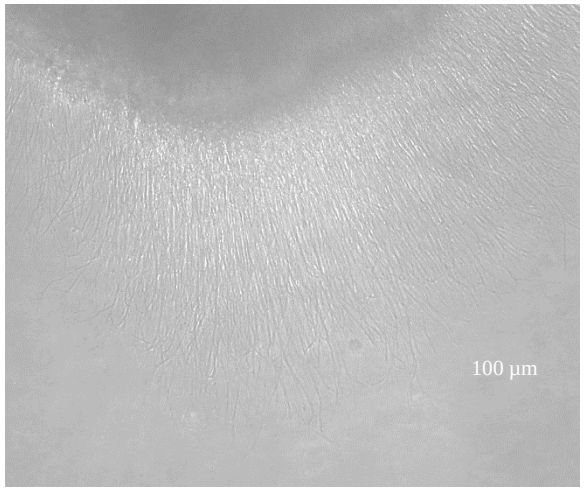


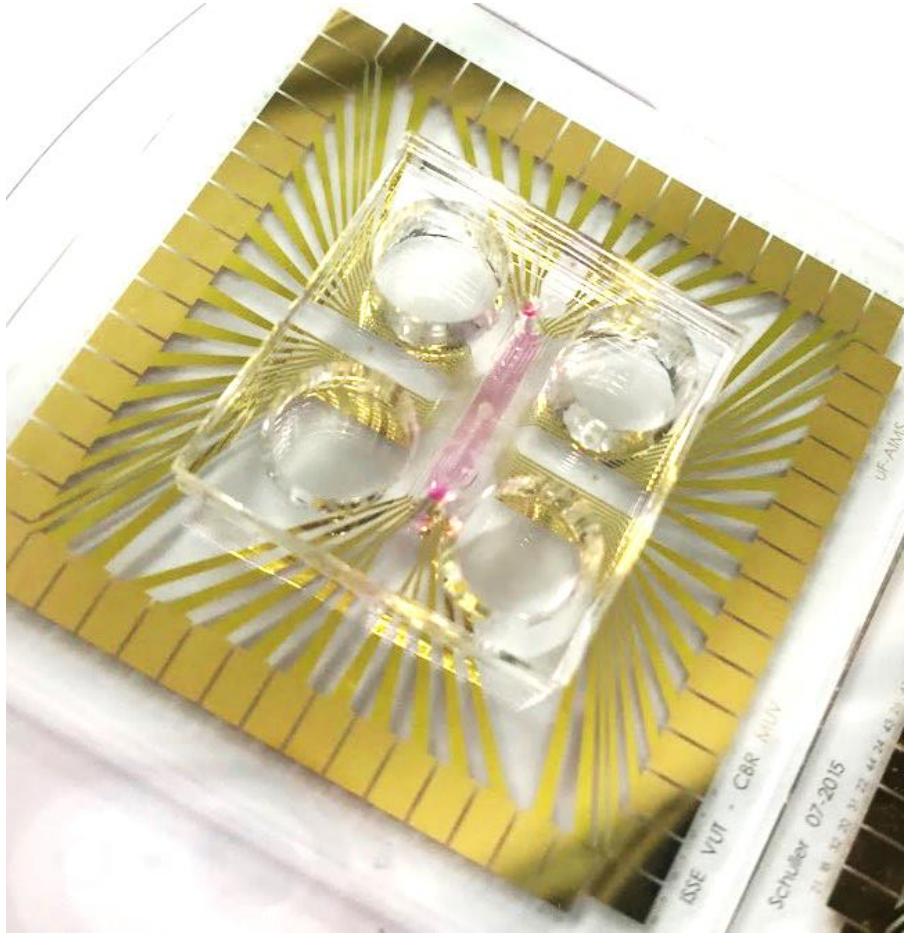
Annual health care costs associated with Parkinson's are estimated to be EUR 13.9 billion in Europe alone and includes recurrent direct costs per patient for symptomatic treatments summing up to 2,500 or 13,000 EUR per three months, depending on the disease stage of the patient

Organoid maturation-on-chip

EP 20173702.0



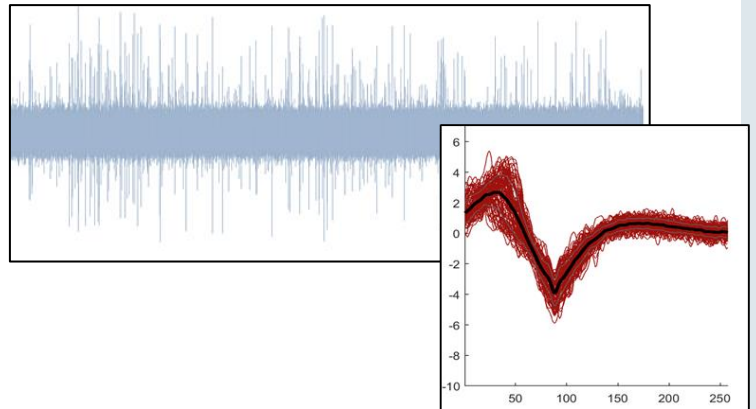




Neuromelanin production detected after 30 days in culture

Intra- and extracellular neuromelanin deposition

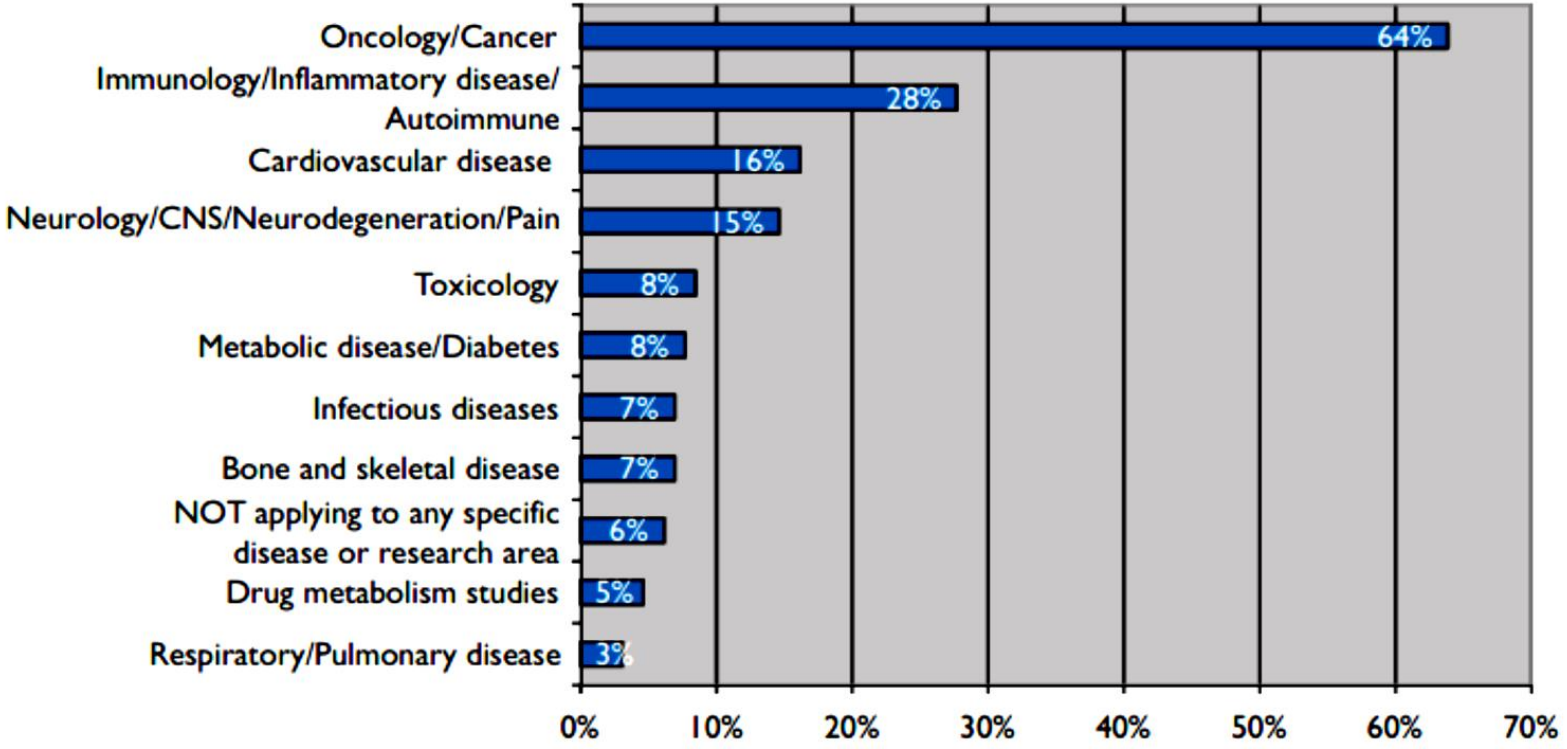
hMOs display **spontaneous** electrophysiological activity



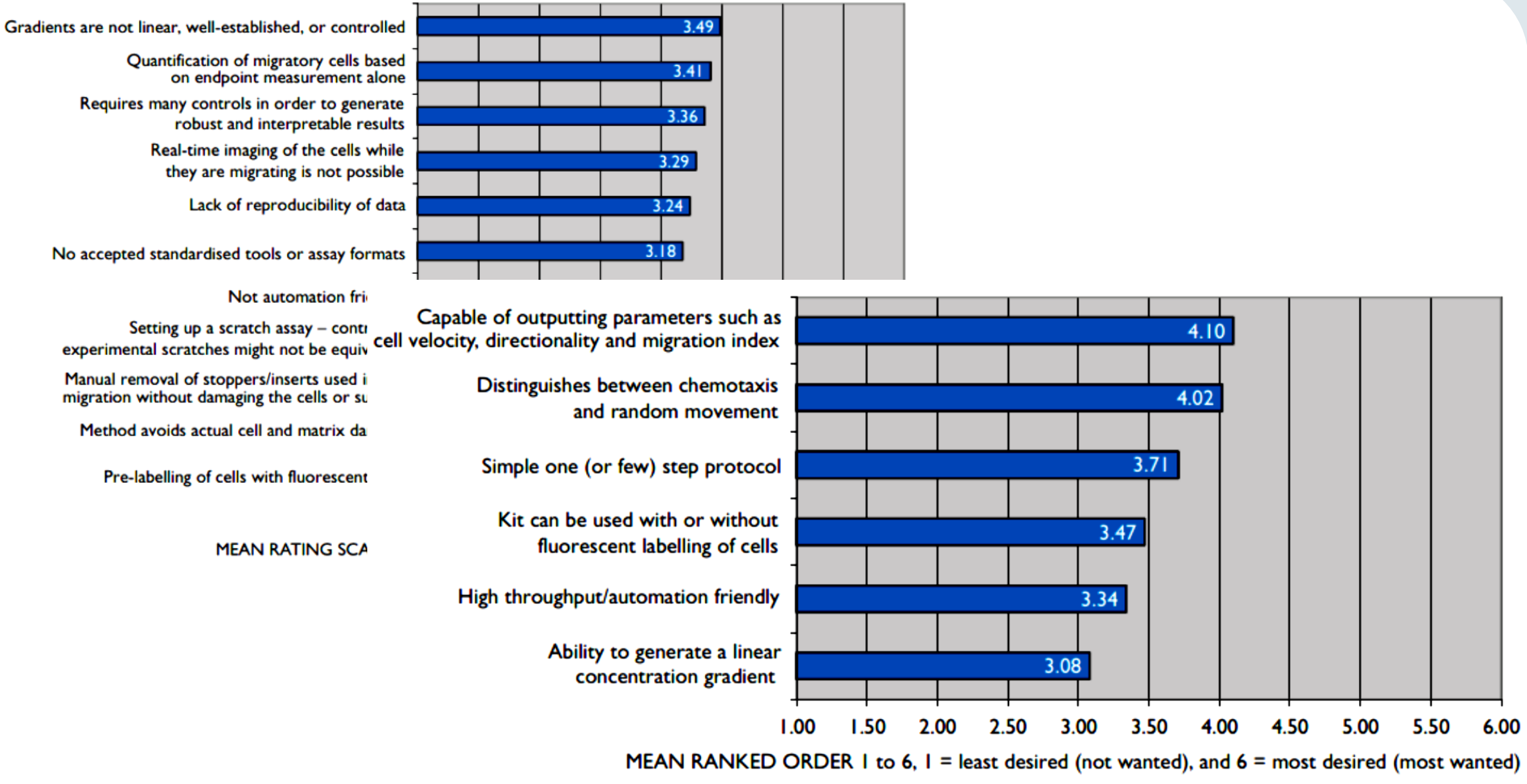
Cell migration market and wound healing assays

Region/Country	2013	2014	2015	2016	2017	2018	2019	2020	% CAGR
US	786.8	917.6	1,106.9	1,355.5	1,669.0	2,034.3	2,442.6	2,878.1	20.4
Japan	181.3	213.1	255.1	308.4	374.2	449.6	533.0	621.4	19.2
Europe	883.8	1,057.3	1,305.8	1,655.5	2,120.8	2,689.9	3,381.9	4,192.2	24.9
Rest of World	35.3	39.7	46.2	54.4	64.4	75.6	87.7	100.1	16.1
Total	**1,887.2**	**2,227.7**	**2,714.0**	**3,373.8**	**4,228.4**	**5,249.4**	**6,445.2**	**7,791.8**	**22.5**

Market groth rate of almost 25%

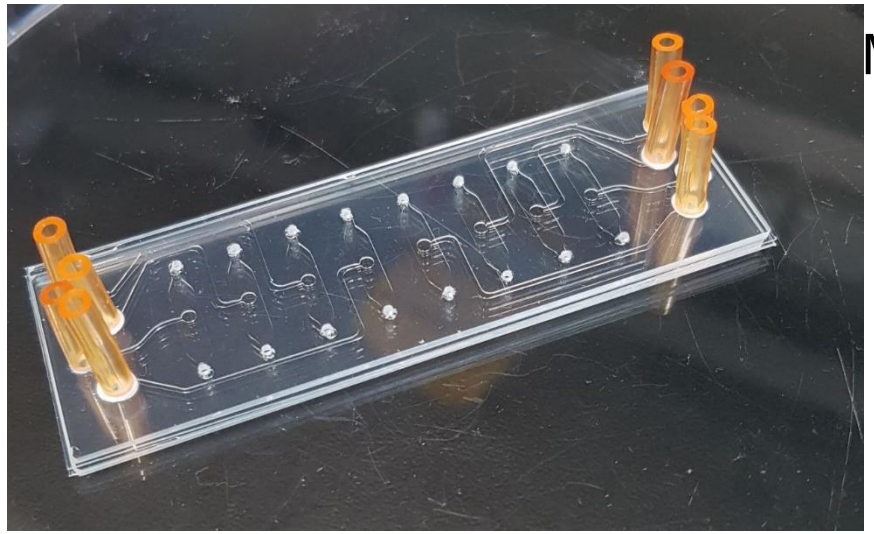


Main limitations of existing cell migration assay products



Automation, miniaturization and integration

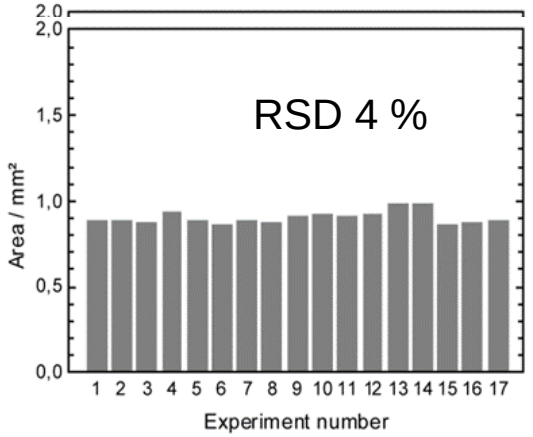
EP 18183978.8
EP16165229.2

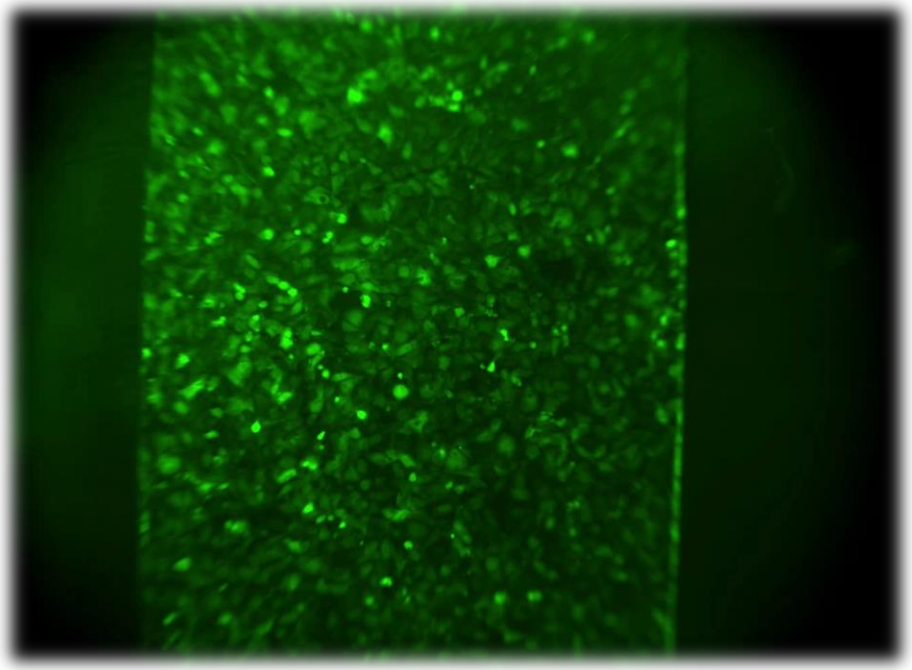


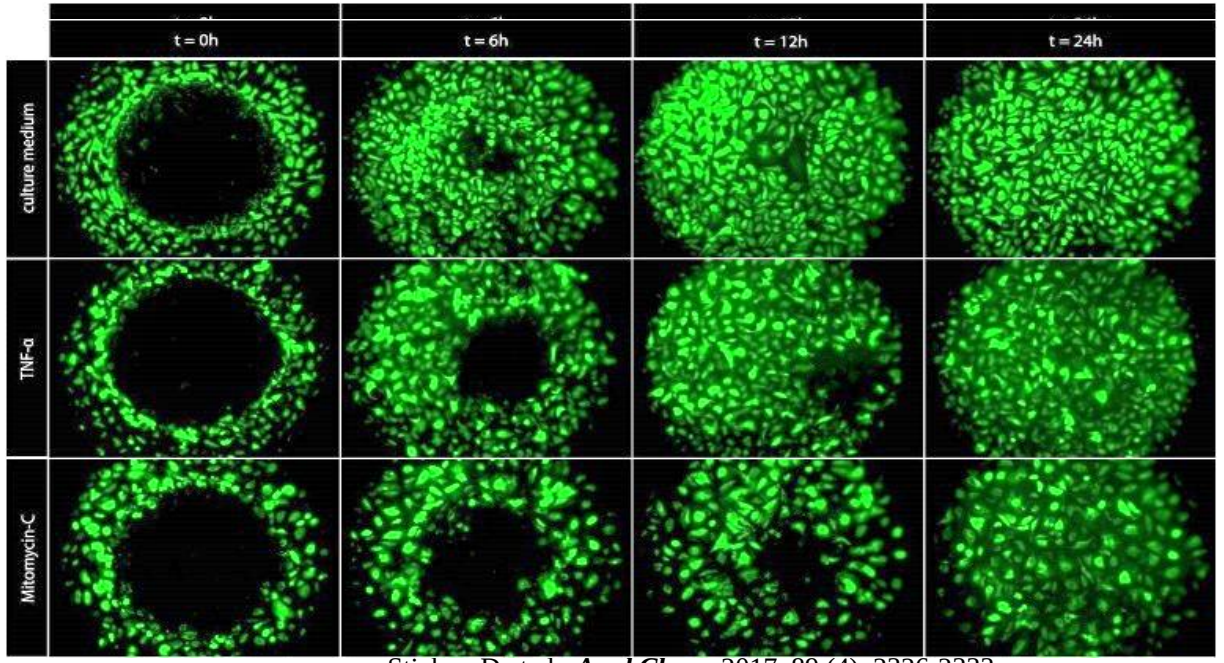
Microfluidic wound healing & migration assay

All advantages & no short comings:

1. Automated mechanically inducing wounds
2. Creation of high reproducibility cell-free areas
3. Repeatable wounding without ECM removal
4. Reduction of injured cell along the edge
5. Removal of cell debris during perfusion



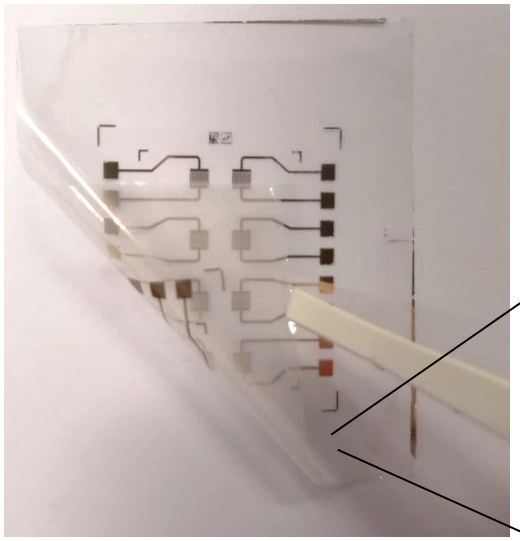


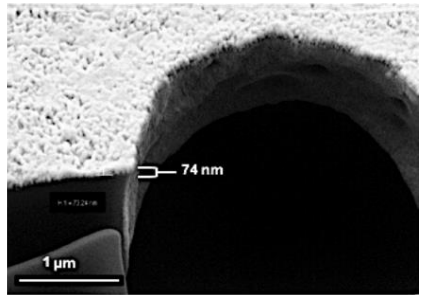


Sticker, D et al. ***Anal Chem,*** 2017, 89 (4), 2326-2333

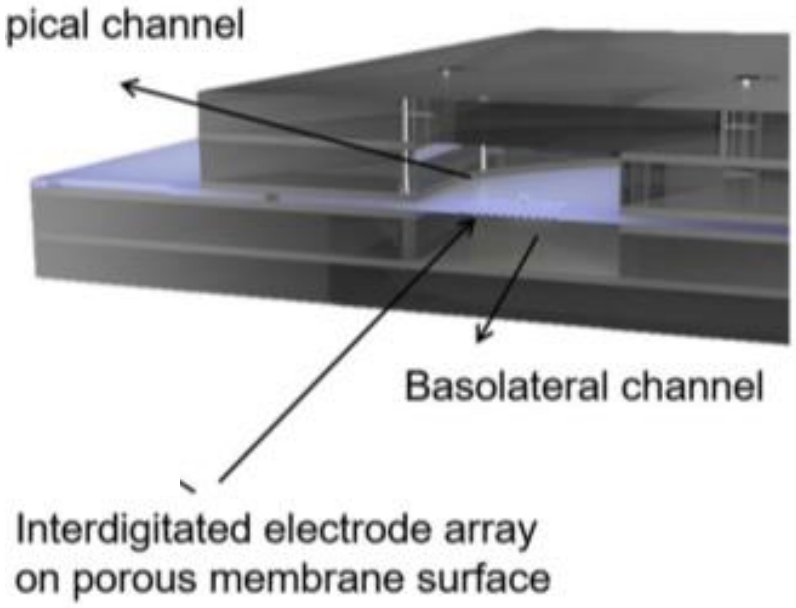
Membrane-integrated bioimpedance sensor

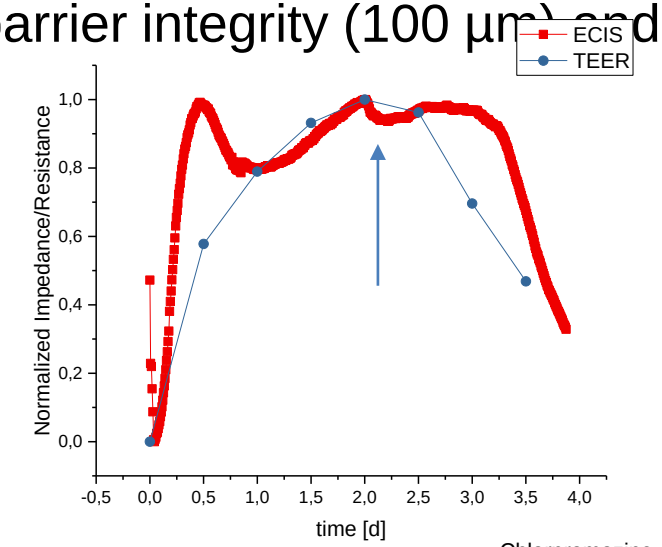
EP Nr. 19168889.4



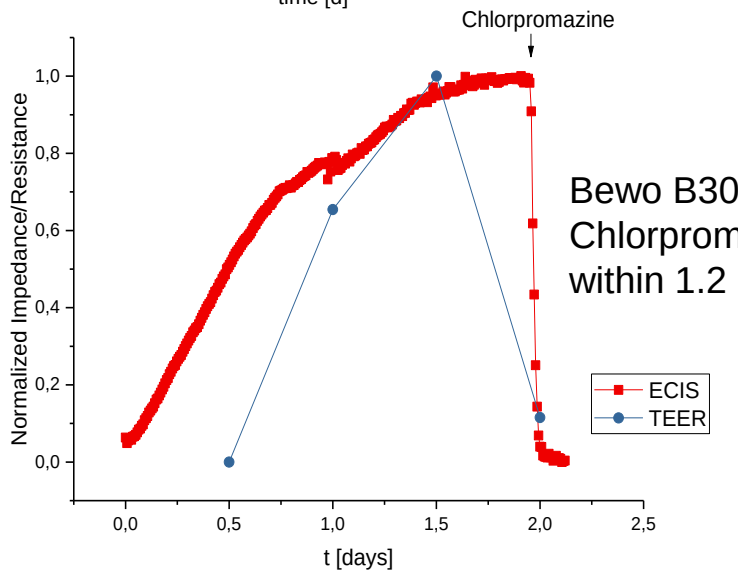


Device and method for multi-parametric, multi-cell barrier integrity analysis using a different-sized (e.g 10 µm and 100 µm pitch) membrane-integrated IDES sensors to detect barrier integrity (100 µm) and surface coverage (10 µm)





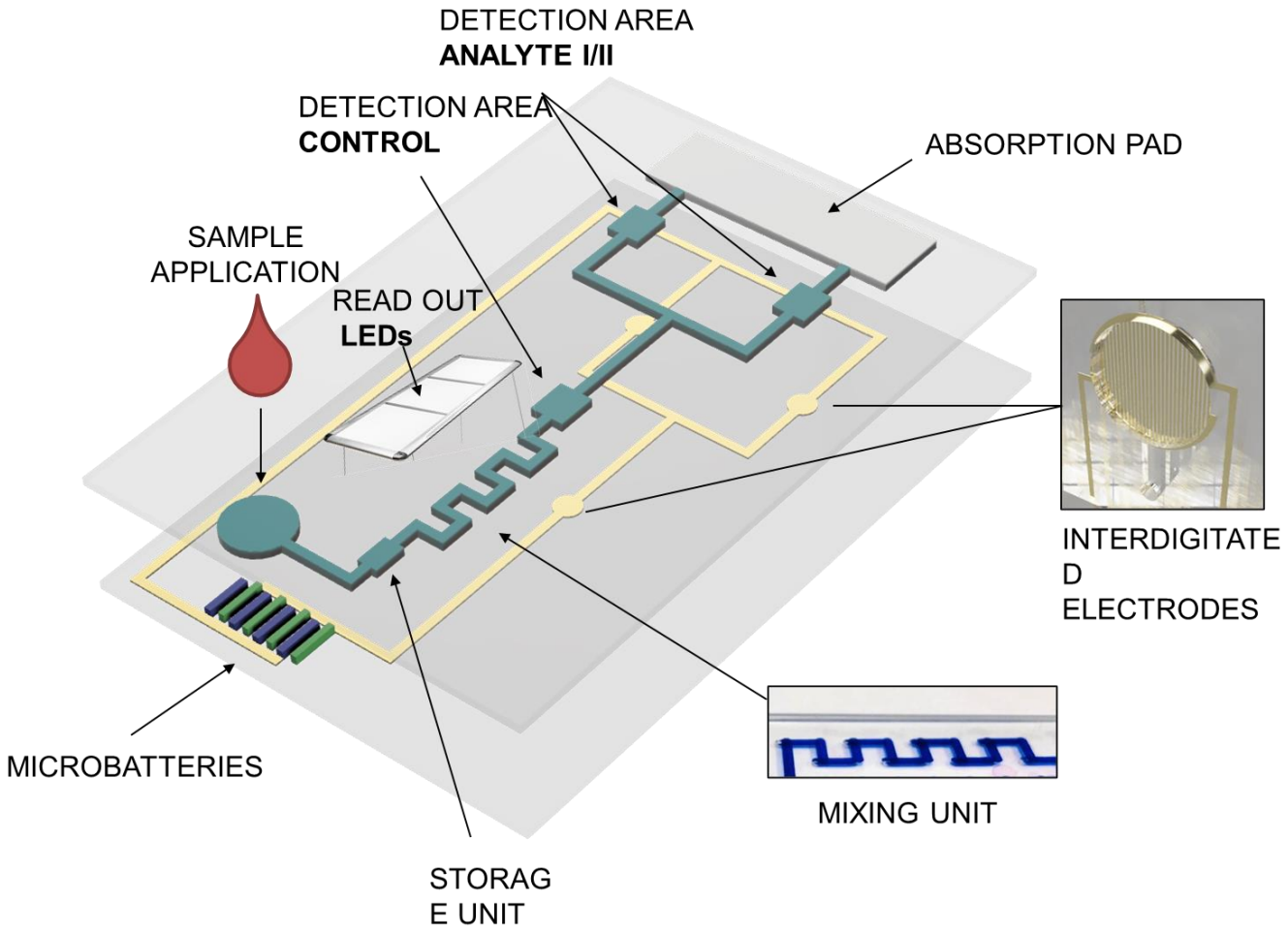
Bewo B30 cultured on membrane based interdigitated electrode sensor for 4 days. Starvation starts around 2.5 days



Bewo B30, addition of 1mM Chlorpromazine at Day 2, cells respond within 1.2 hours

Self-powered biosensor chip

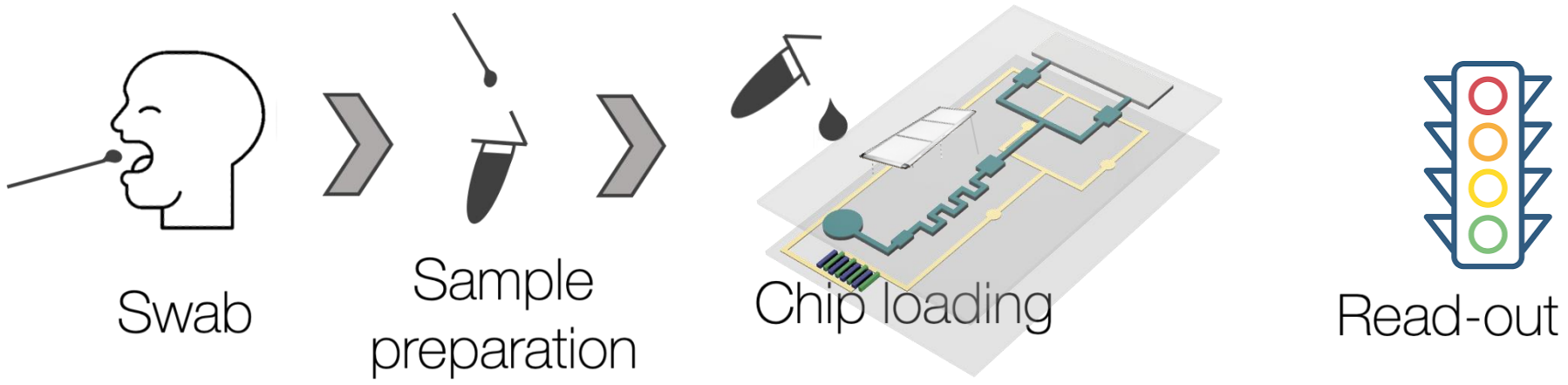
EP 20189436.7



- Rapid ID of pathogens in min
- No false negative results
- Portable and on-site sensing
- Self-powered
- Integrated readout unit
- Data storage & verification
- Multiplexed

Self-powered lab-on-a-chip containing integrated microbatteries, nanosensor array and read out unit with ultra-low detection limit based on nano-labelled immunoassays and silver enhancement chemistry

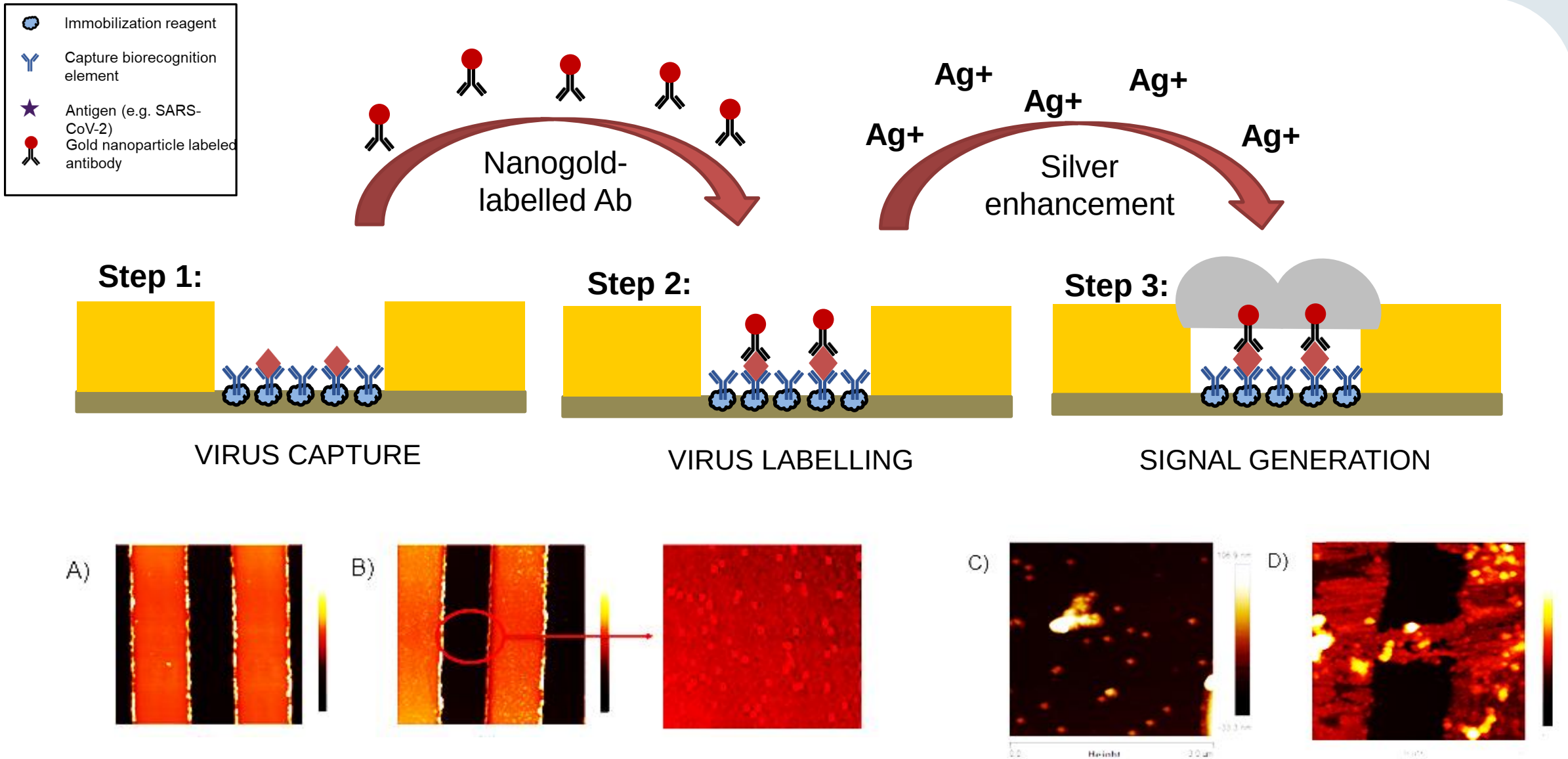
TUW rapid Covid-19 Testing System



Device specifications and development targets:

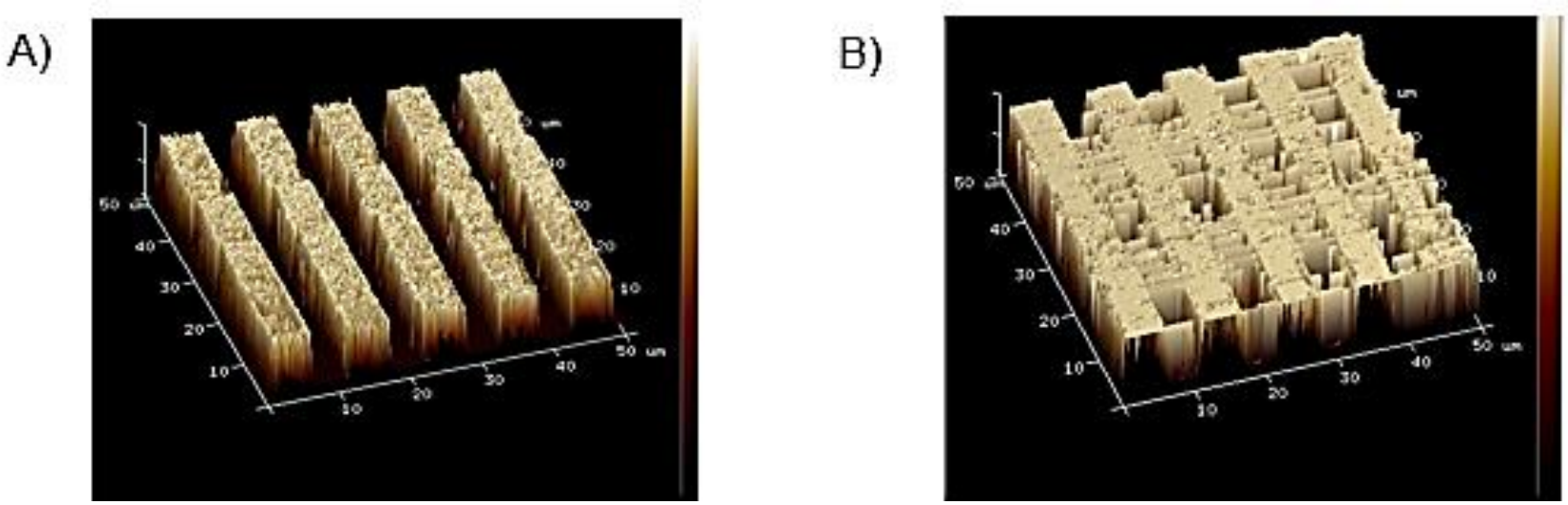
1. Ease of sample loading
2. Integrated sample treatment and handling (automation of fluid handling and assay steps)
3. Ultralow detection limit
4. Elimination of false negative results (high specificity) – 3 readings per sample
5. Quantitative results in less than 5 min (calibration against virus particle count)
6. On-chip power supply (microbatteries and RFID chip) and read out (display unit and wireless data transfer)
7. High throughput to be able detect a large number of samples in a short time while obtaining accurate information

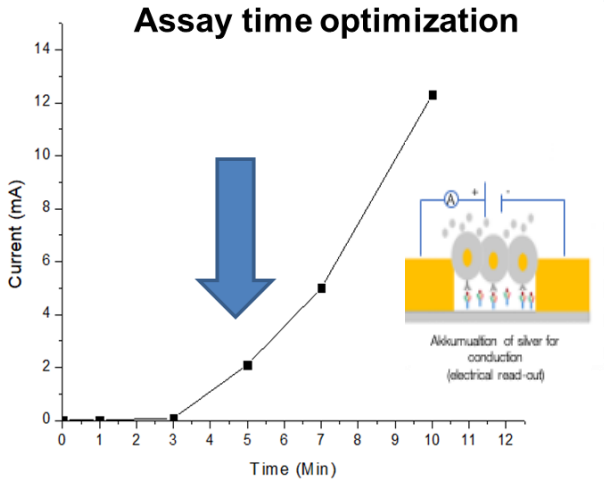
NanoBioAssay Concept



BioSensing principle: formation of conduction silver nanobridges

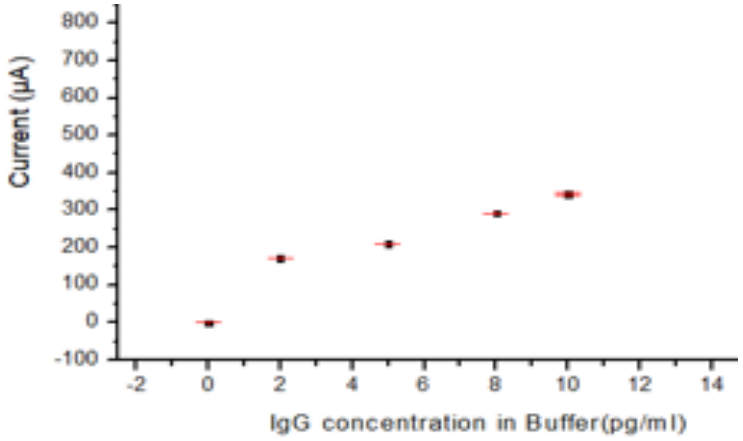
Proof-of-Concept

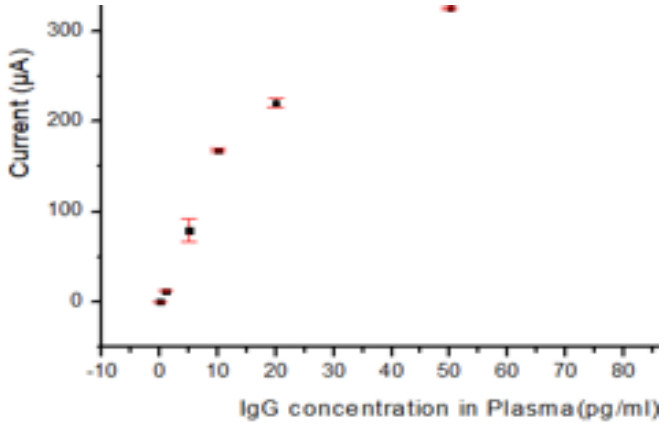




A) Conductive AFM image of the separated interdigitated electrode structures by 5 µm gaps. **B)** Conductive AFM image in the presence of numerous silver bridges formed after immune capture of 10 µg/mL IgG, **nanogold labeling and 5 min silver enhancement chemistry.**

LOD of 2 pg/mL in buffer and plasma





- detection of interleukin 6 cytokine in less than 5 min with ultra low detection limit
- 50 fold improvement of standard ELISA assay

Thank you for your attention