# How can microsystems help to improve our health?

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Obuda University, Budapest, August 2019

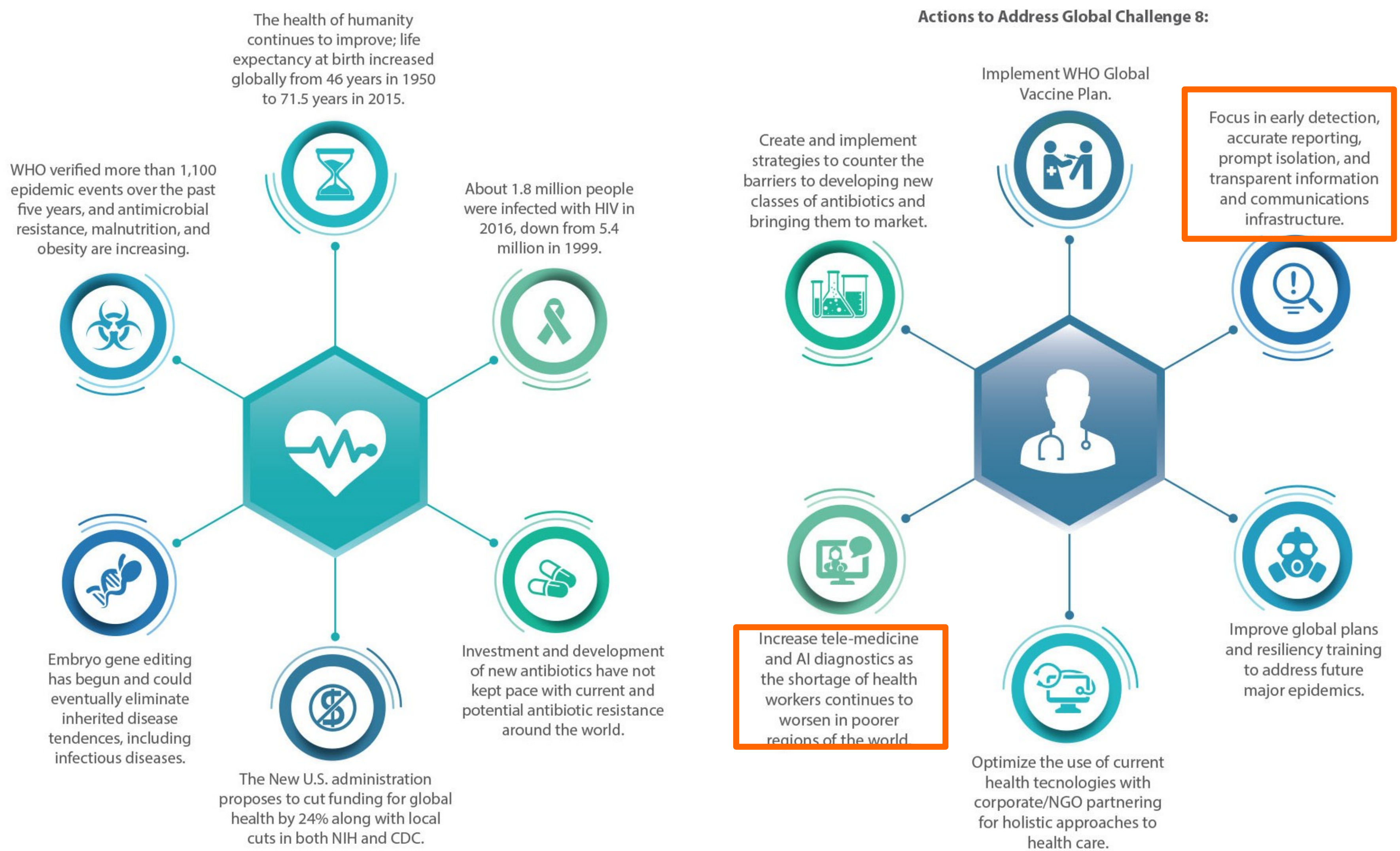
# Contents

- Microsystems, MEMS and BioMEMS
- Production of radiopharmaceuticals at the microscale
- Organ surrogates on chips

# About myself

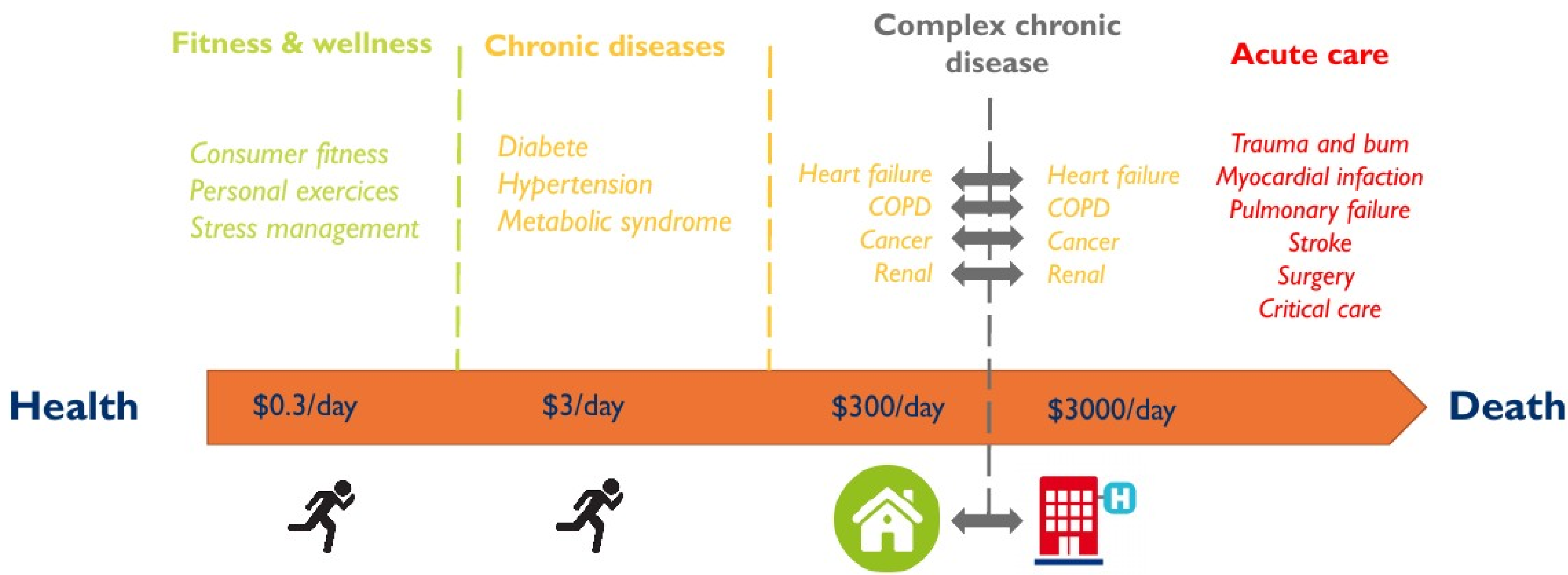
- Associate Professor at the Department of Electronics Engineering, University of Seville, Spain
- Research group on microsystems. 5 faculty, 6 undergraduate, graduate and PhD students
- Research lines on microfluidics, lab on chips, microfluidics, IoT

# Global Challenge #14




The Millennium Project, Washington D.C.

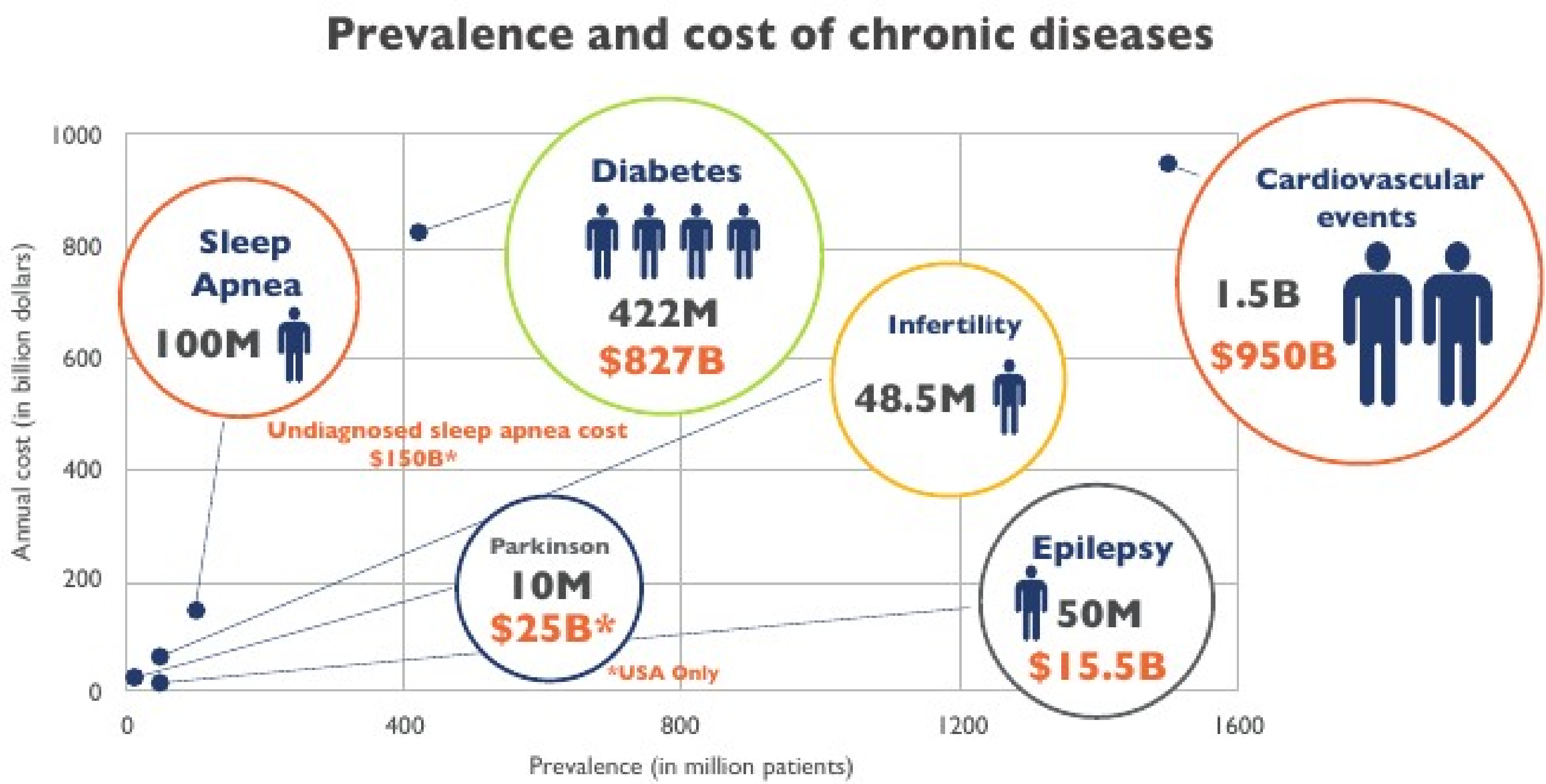
# Cost of care




Cost of care is exponentially increasing from people managing their health to complex chronic disease and acute care. If acute disease are not manageable, chronic disease need to be controlled.

The challenge for health organizations is to make people staying on the left side.

# Cost of diseases



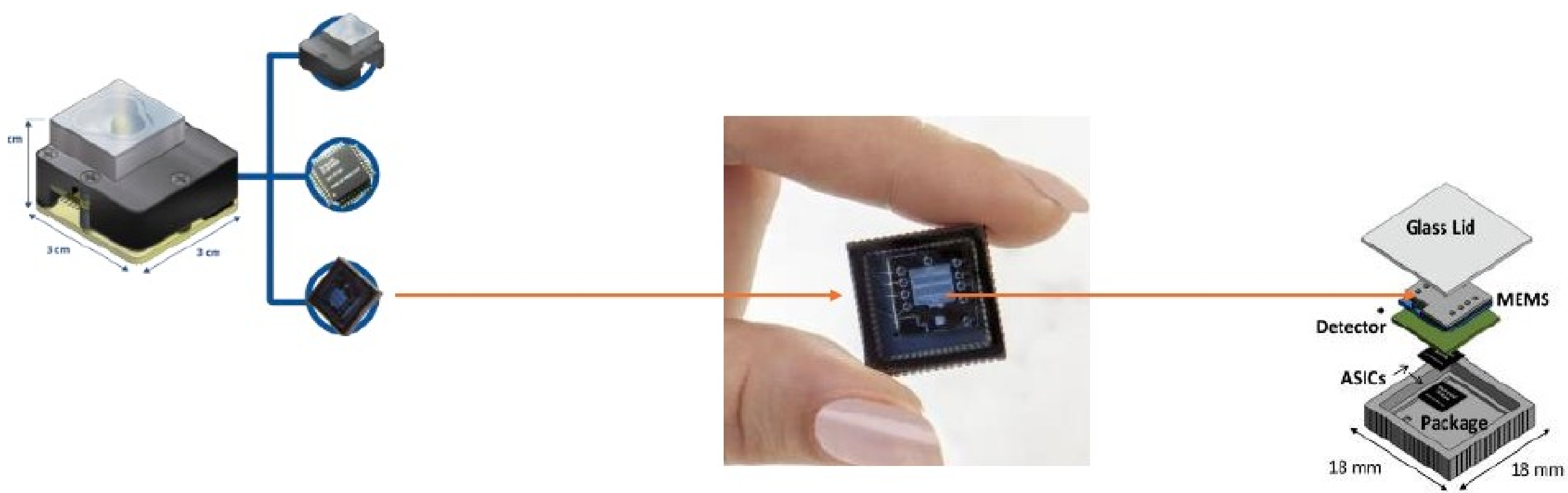

Source: Reports from World Health Organization

(Yole Développement, August 2018)

# Microsystems or MEMS

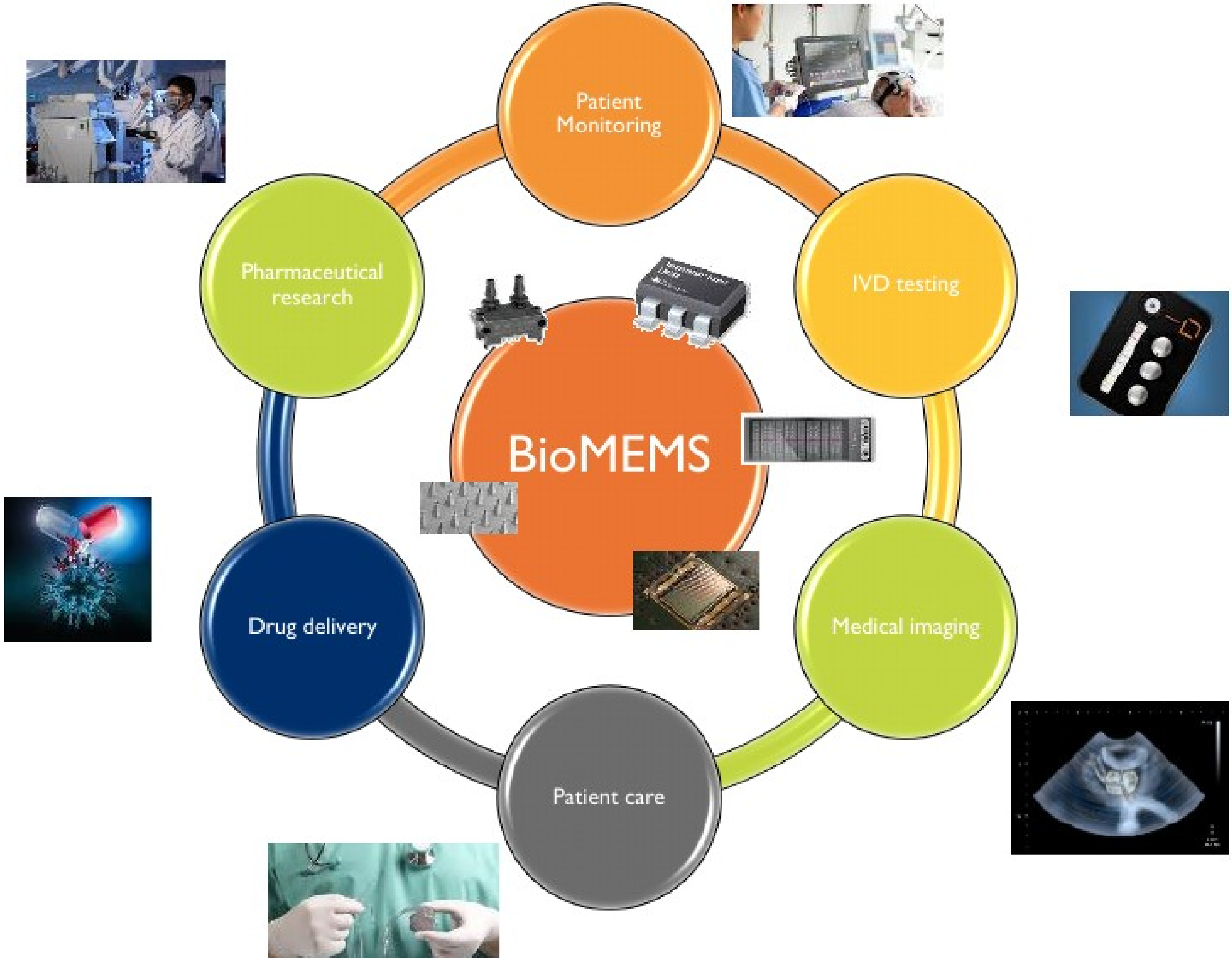
A MEMS device – Micro ElectroMechanical Systems – is a component made by semiconductor processes with successive photolithography and etching process steps on silicon, glass or quartz substrates.

A BioMEMS device is a MEMS device involved in life science and healthcare applications. A specific focus is made on medical-grade products integrating bioMEMS devices.



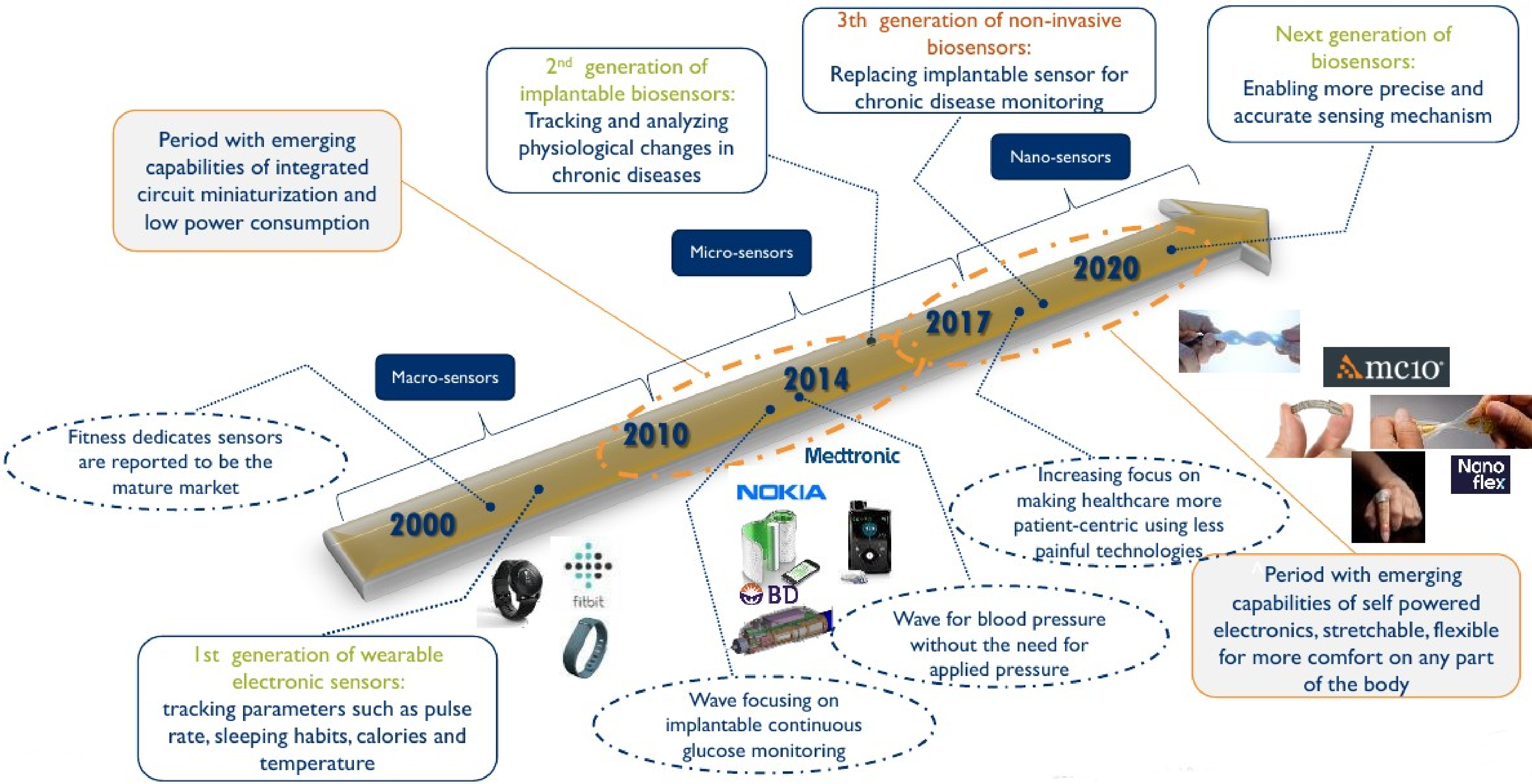

MEMS Spectrometer used for point of care testing: illustration of the MEMS dies, MEMS chip and Spectrometer module. *Source: Si-Ware*

# BioMEMS

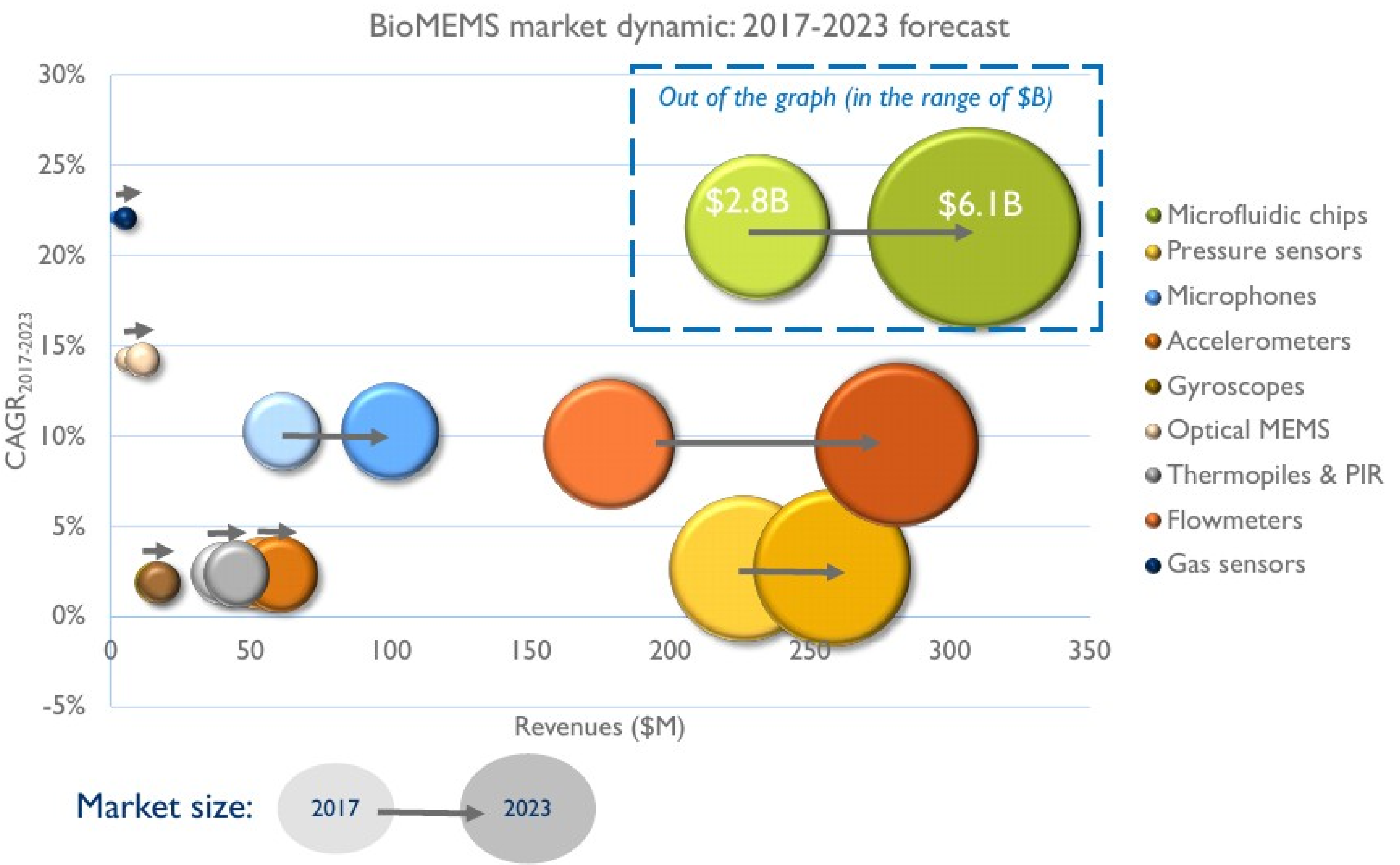


Patient Monitoring
IVD testing
Medical imaging
Patient care
Drug delivery
Pharmaceutical research
BioMEMS

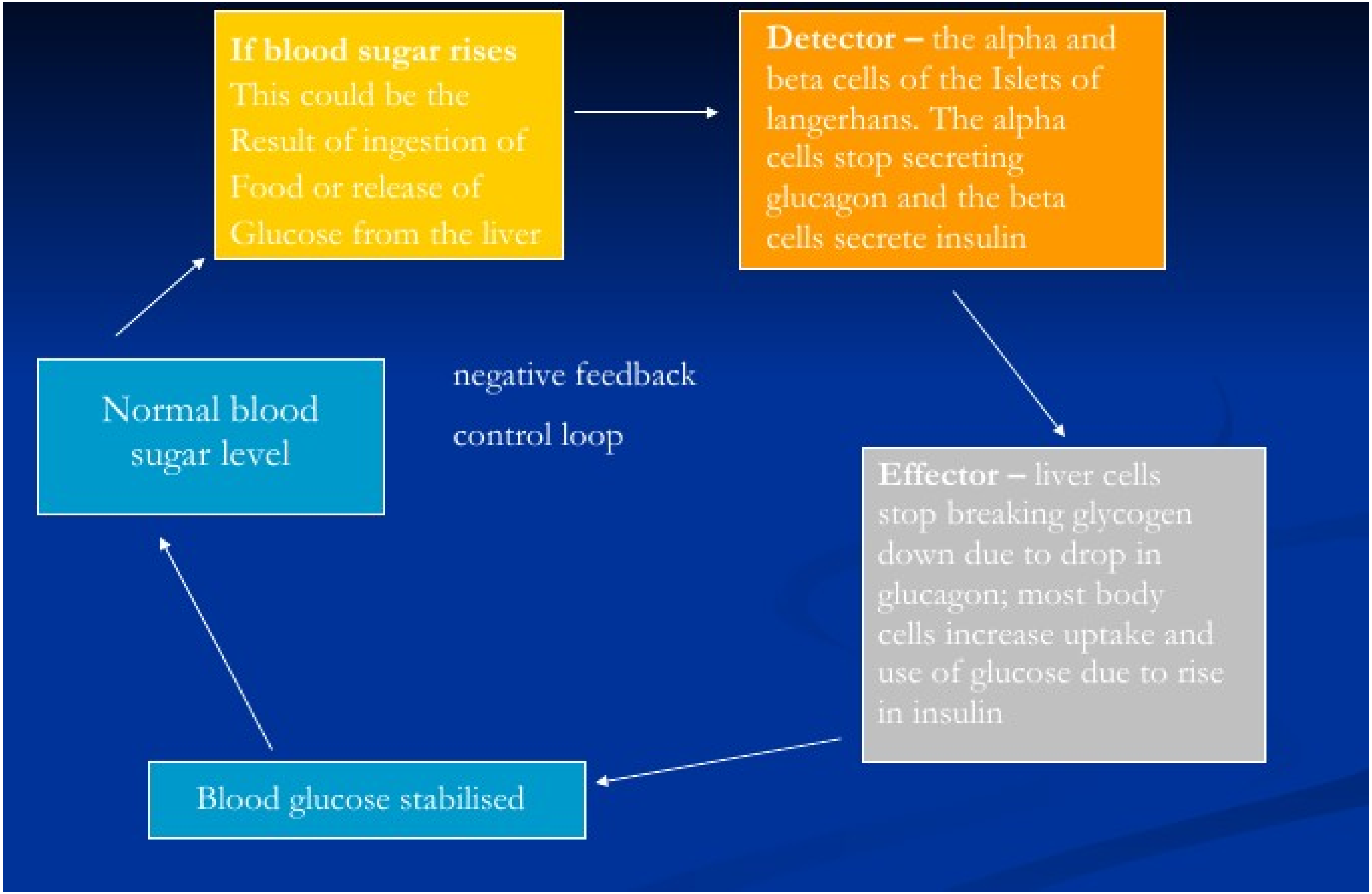
# Evolution of BioMEMS



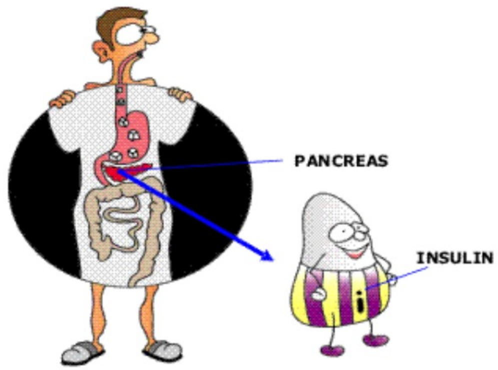
# BioMEMS market forecast

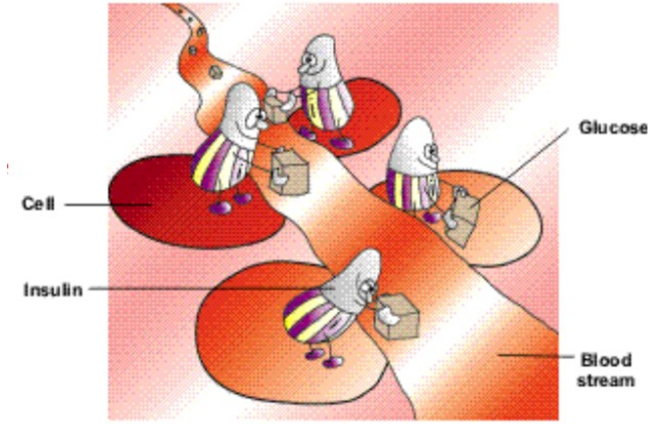


# Typical example: diabetes and glucose measurement



# Diabetes

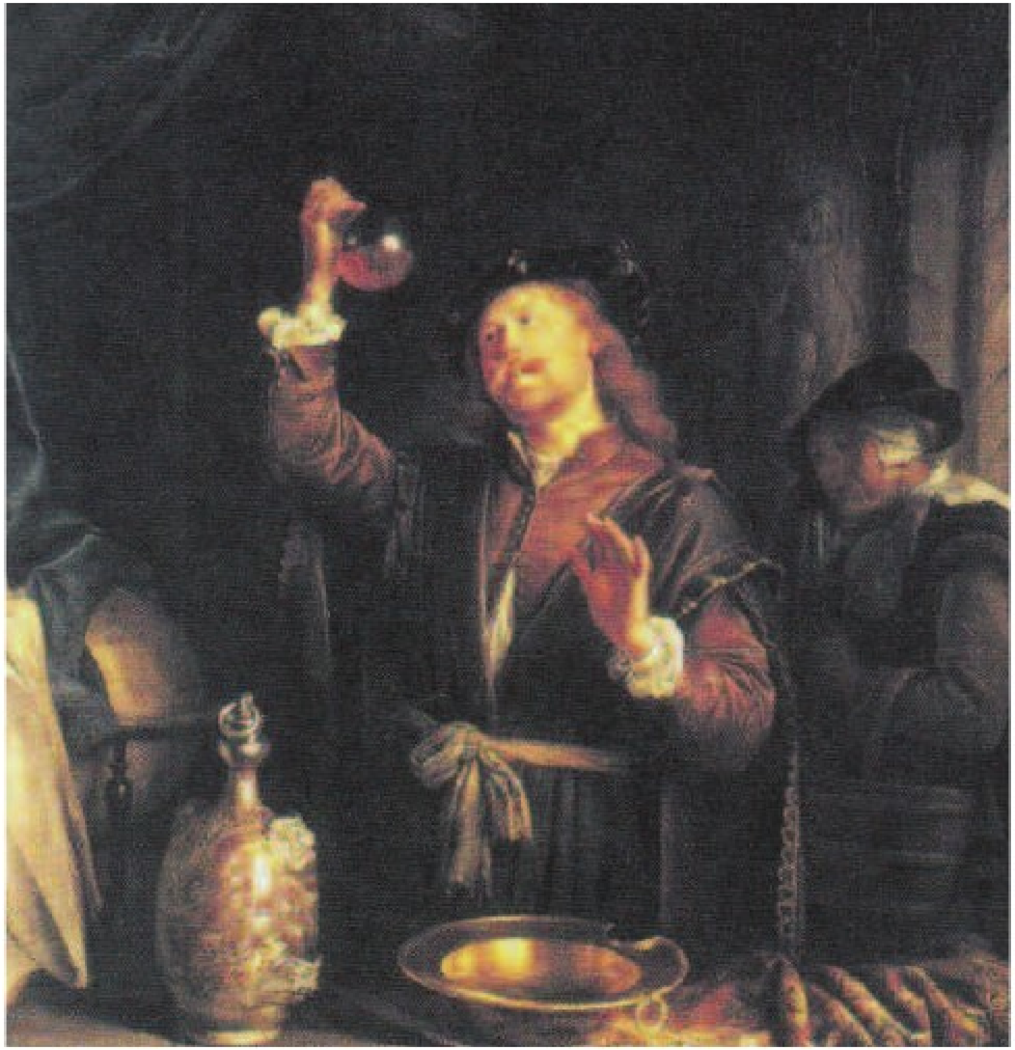




- Normal glucose level in blood is about 5 to 5.5 mmol·dm$^{-3}$
- If this level rises too high it would affect the water content of the body.
- If glucose appears in the urine (glycosuria) water reabsorbtion in the kidney will be reduced.
- If glucose level in the tissue fluid is high, water will be lost from cells by osmosis.
- If levels fall below 3 mmol·dm$^{-3}$ (hypoglycaemia) this would lead to a loss of consciousness (coma).
- If level goes above 10 mmol·dm$^{-3}$ (hyperglycaemia ) glucose will appear in the urine, the pH of the blood would fall and this also leads to coma.
- Both conditions are a feature of **diabetes mellitus**.

# Glucose monitoring

| Glucose Test | Person without diabetes | Person with diabetes |
|---|---|---|
| Fasting Test | 70-110mg/dL | $\geq$ 140mg/dL |
| 2 hours after eating | $\leq$110mg/dL | $\geq$ 200mg/dL |

# Historical developments



A physician looking at a container of urine, using his senses of sight, touch, hearing, smell and taste to make a diagnosis.

# Historical developments



Clinitest was introduced by Ames in 1945, and utilised a copper reagent tablet that contained all the reagents required for a urine glucose test.

# Historical developments


Boehringer Mannheim introduced the Reflomat in 1974 and the Reflolux in 1984.

# Historical developments


With the 21st century came a number of different electrochemical glucose meter systems, including the OneTouch Ultra (top right) from Johnson & Johnson.

# More recent developments

Warn like a wristwatch, the GlucoWatch Biographer measures glucose every ten minutes through the skin.

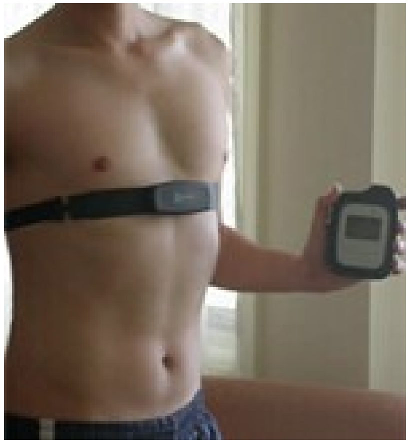
First noninvasive glucose monitor

Provides glucose readings every ten minutes. Very helpful at showing patterns of glucose levels

The HypoMon® System noninvasively detects low blood sugar in diabetes throught skin contact. The HypoMon® includes a battery power pack worn on the chest and a wireless receiver where the readings are sent to and can be read.

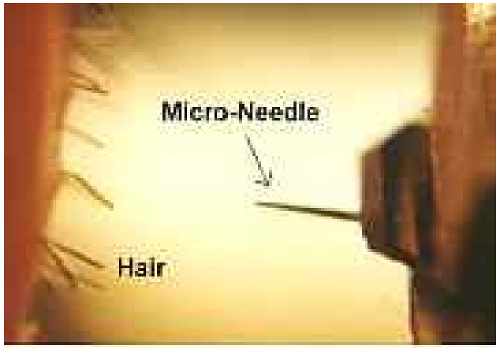
Enables monitoring during the day and night.

Alters allow the diabetic to treat hypoglycemia at an earlier stage.



Silicon Micro Needle consists of a hand-held battery-powered electronic monitor which holds a cartridge loaded with 10 disposable sampling devices. Each disposable consists of the micro-needle and a receptacle into which the blood sample is drawn.

Pain free testing and the amount of blood required is 1/100th of a drop of blood

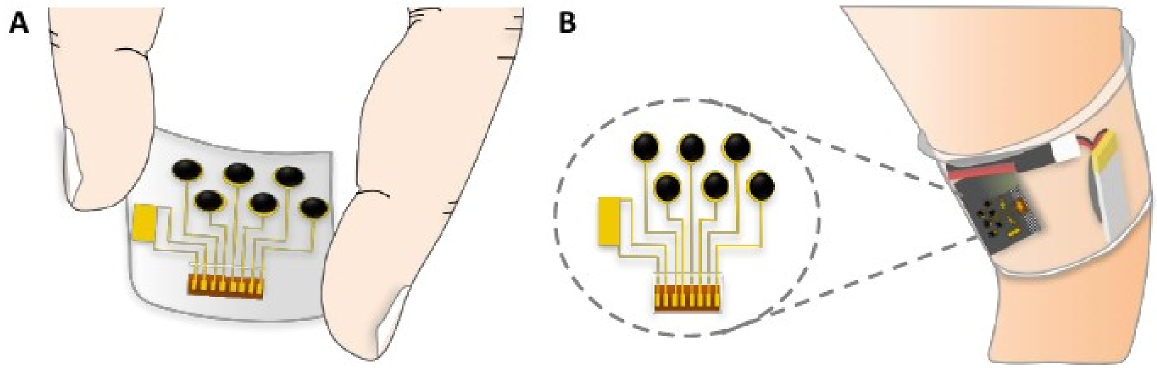


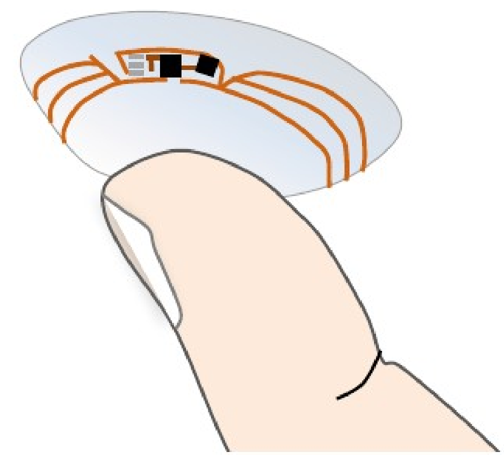

**Lasette.** A laser lancing device that uses a laser beam to draw a drop of blood rather then using a steel lancet.

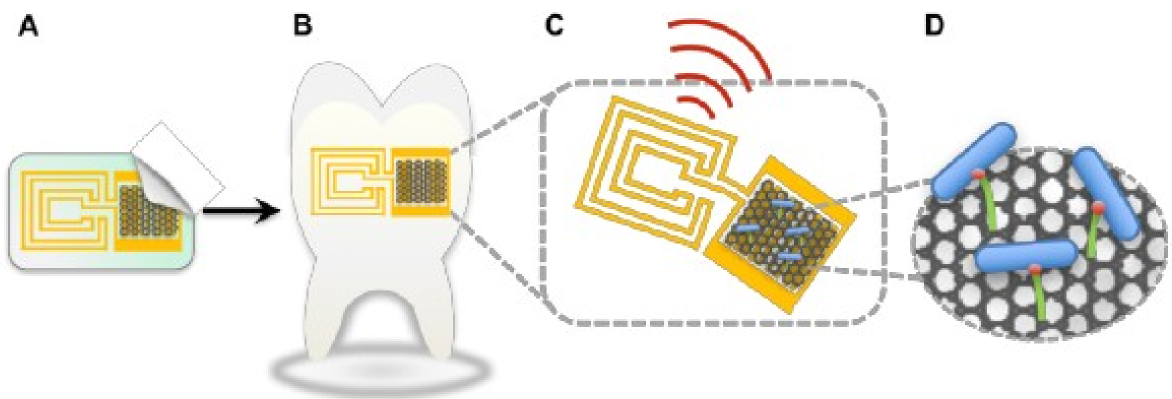
Virtually painless

No more finger pricking

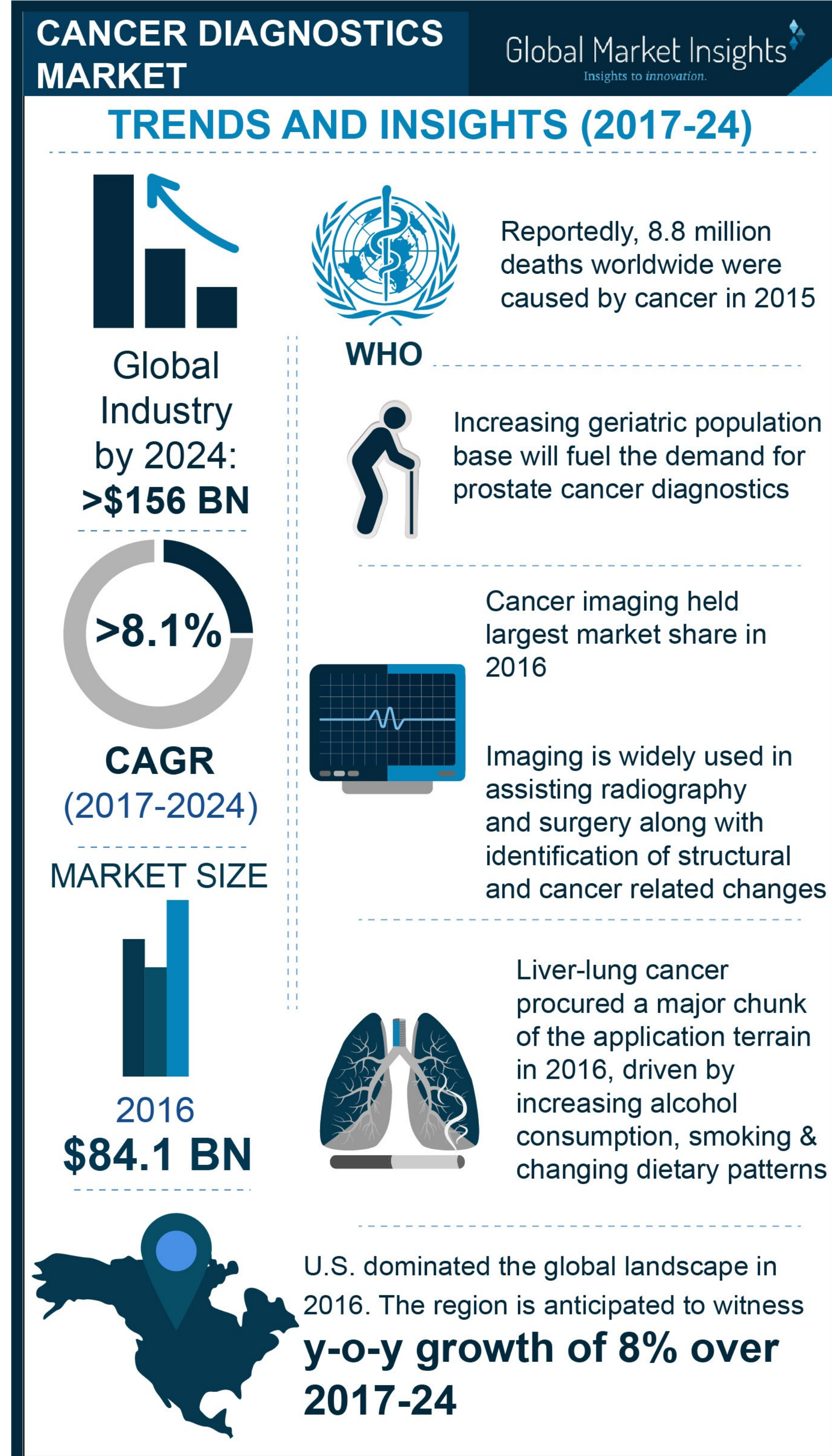
# Research and ideas



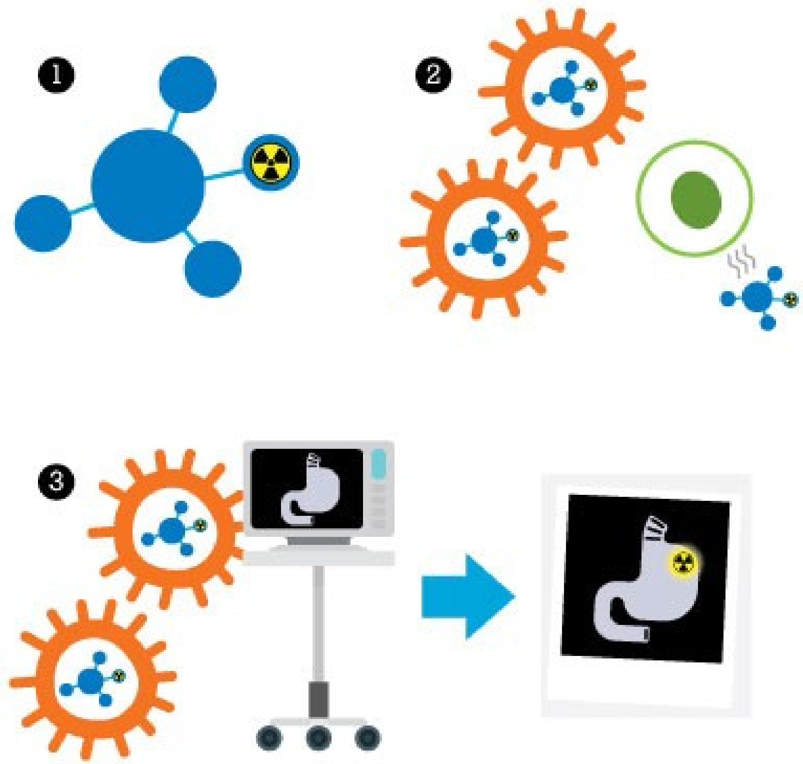





# Tumor and cancer diagnostics



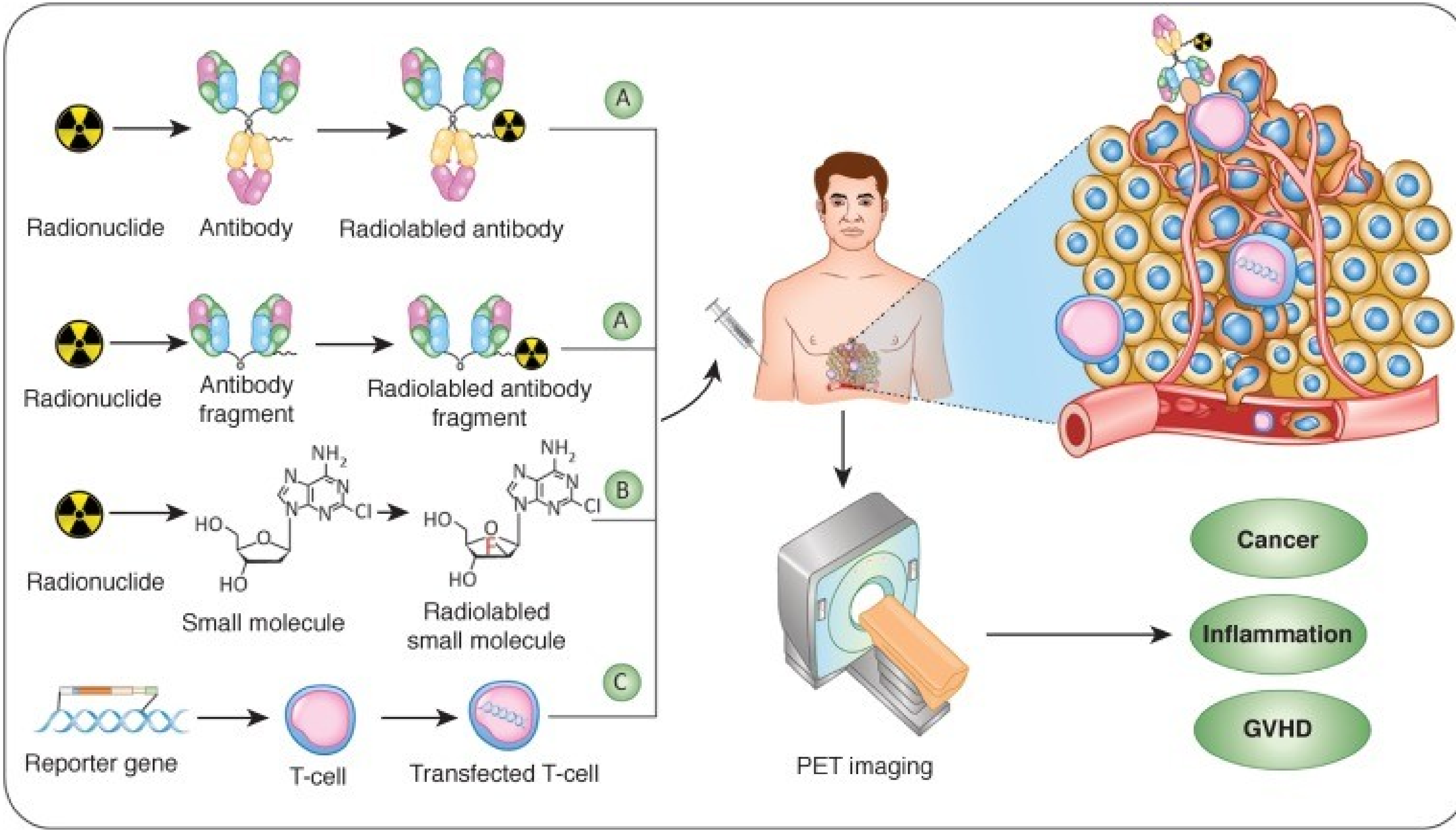
# PET imaging




## PET imaging

1. A molecule, usually glucose, is tagged with a radioactive signal.
2. Cancer cells absorb the tagged molecules but healthy cells do not.
3. Specialized equipment detects the radioactive signal and creates an image showing where the cancer cells are.

# PET imaging




Trends in Cancer

# Production of PET tracers

- Radioisotope production
- Radiolabeling, purification and formulation
- Quality control

# Production of PET tracers

- **Radioisotope production**
- Radiolabeling, purification and formulation
- Quality control

Nuclear reaction

# Production of PET tracers

- Radioisotope production
- **Radiolabeling, purification and formulation**
- Quality control

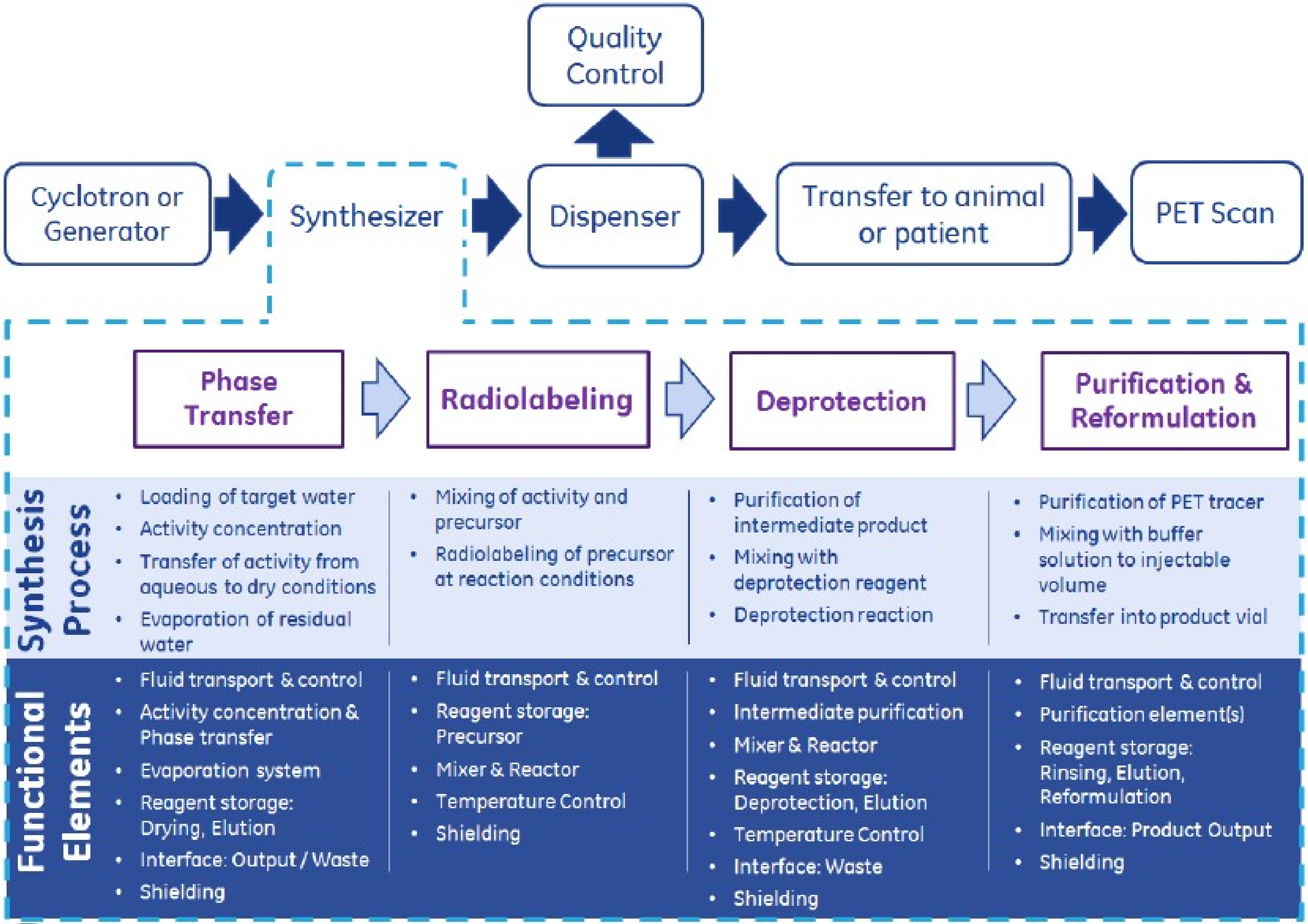
Chemical reaction

# Production of PET tracers

- Radioisotope production
- Radiolabeling, purification and formulation
- **Quality control**

Analytical chemistry

# Production of PET tracers

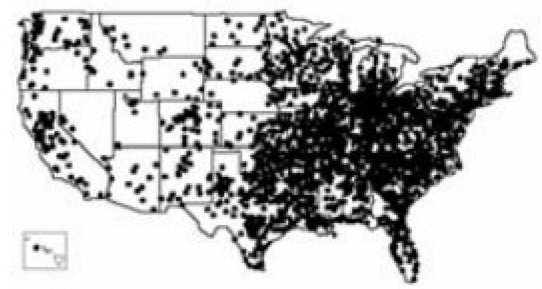


# Production costs

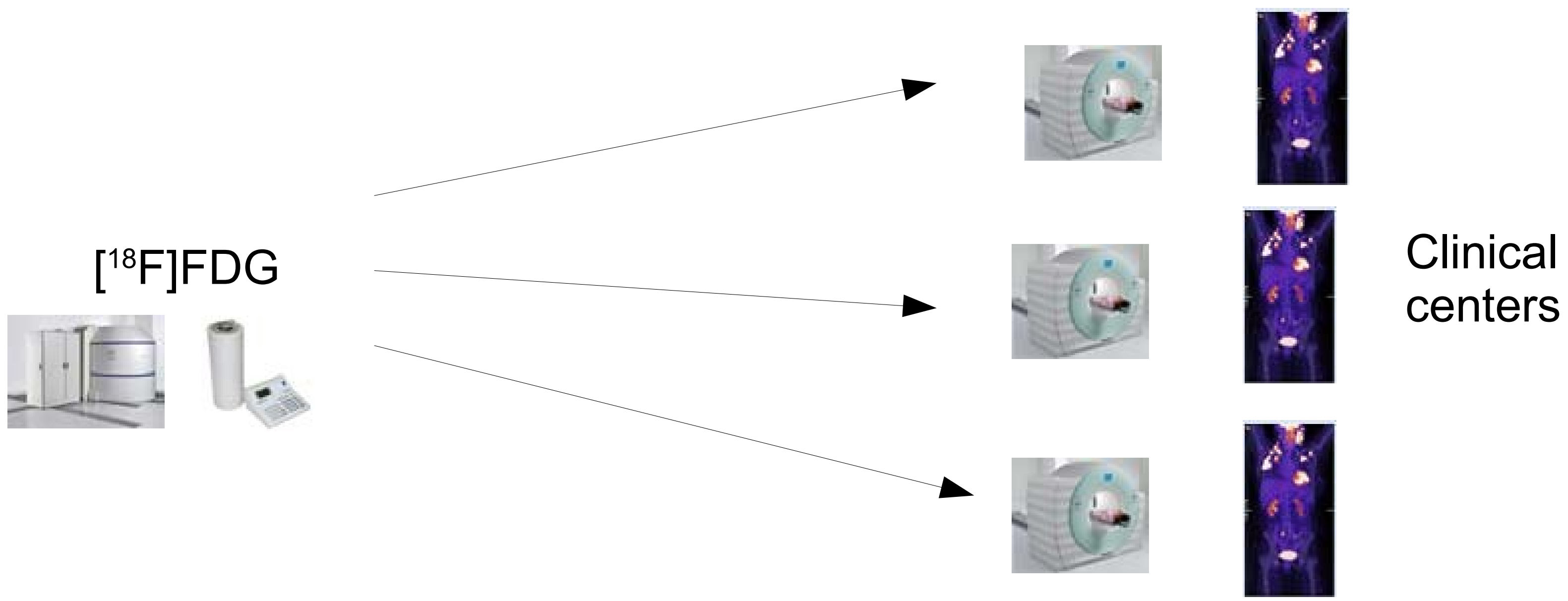
- Equipment costs
  – Radiosynthesizer and HPLC purification
  – Dedicated synthesizer for each tracer
  – Analytical equipment for QC
- Infrastructure costs
  – Radiation hazard requires use of expensive hot cells
  – Size/weight of hot cells requires site planning
- Operating costs
  –Maintenance and repairs for each equipment
  –Personnel with specialized expertise
  – Synthesizer setup and operation
  – Quality control testing
  –Reagents and consumables

# Centralized production

PET Radiopharmacies

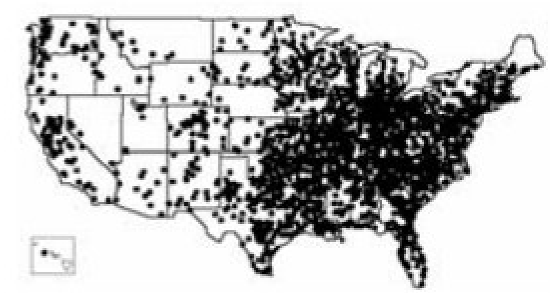


PET Centers

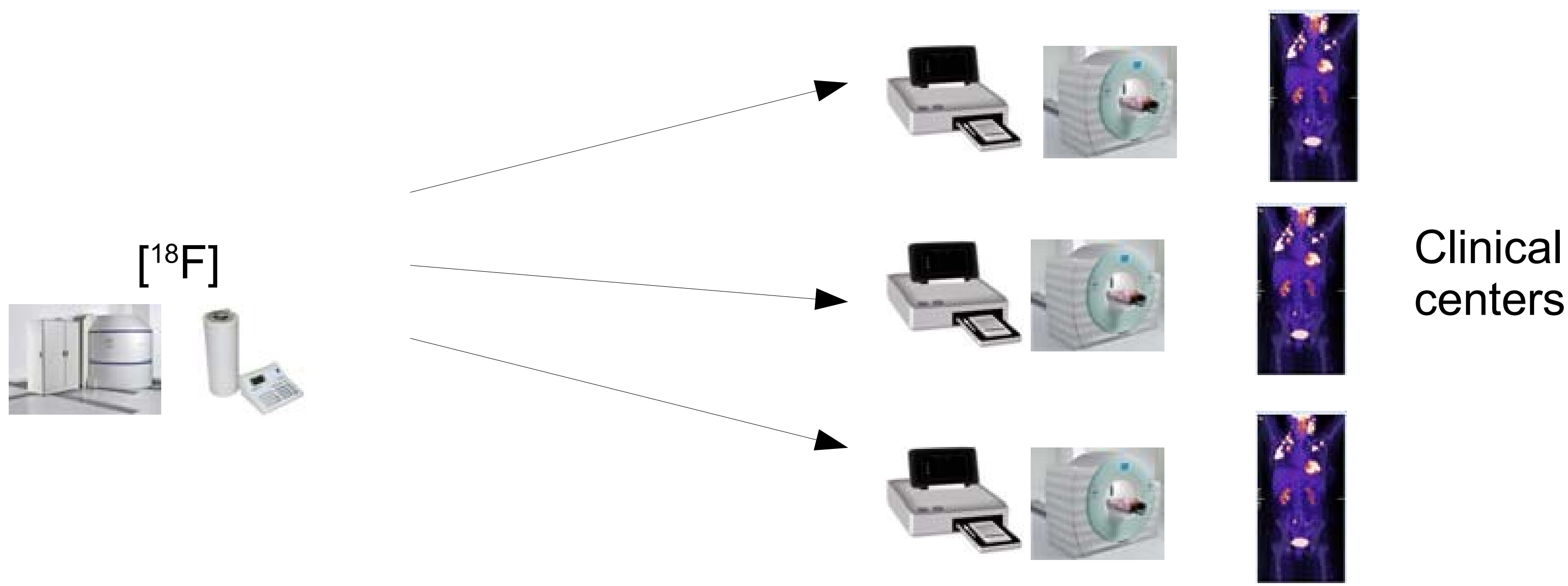


# Distributed production

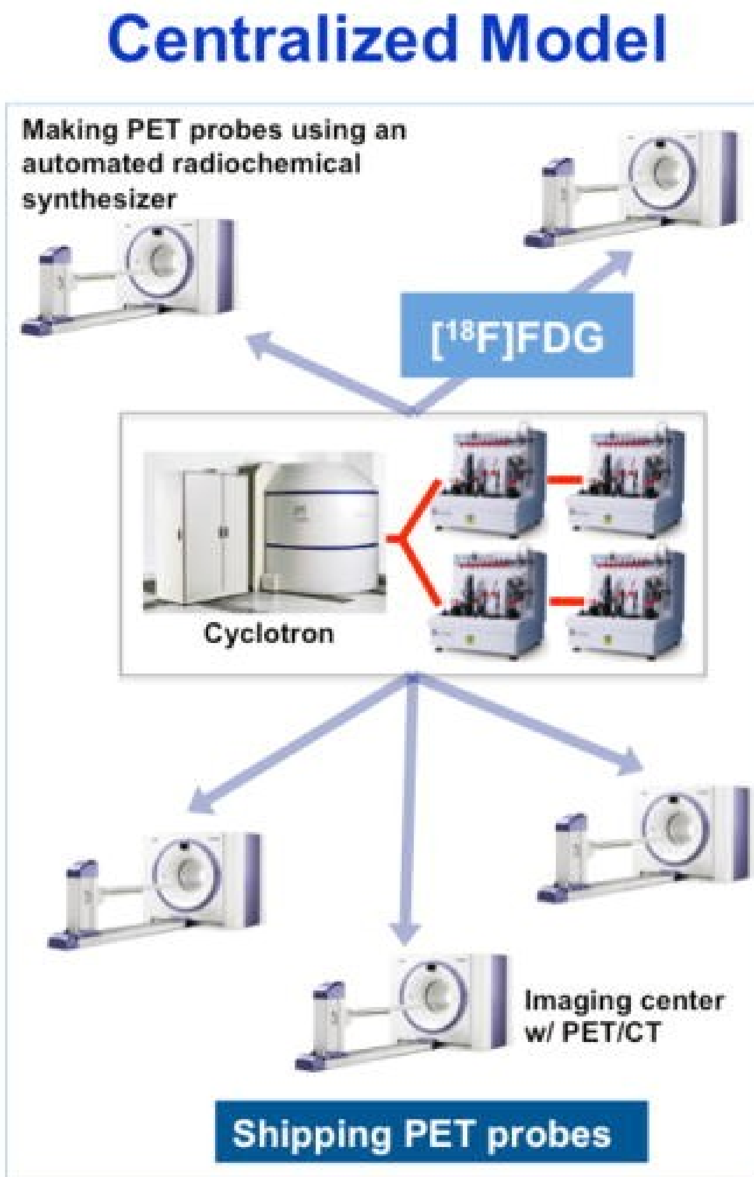
PET Radiopharmacies

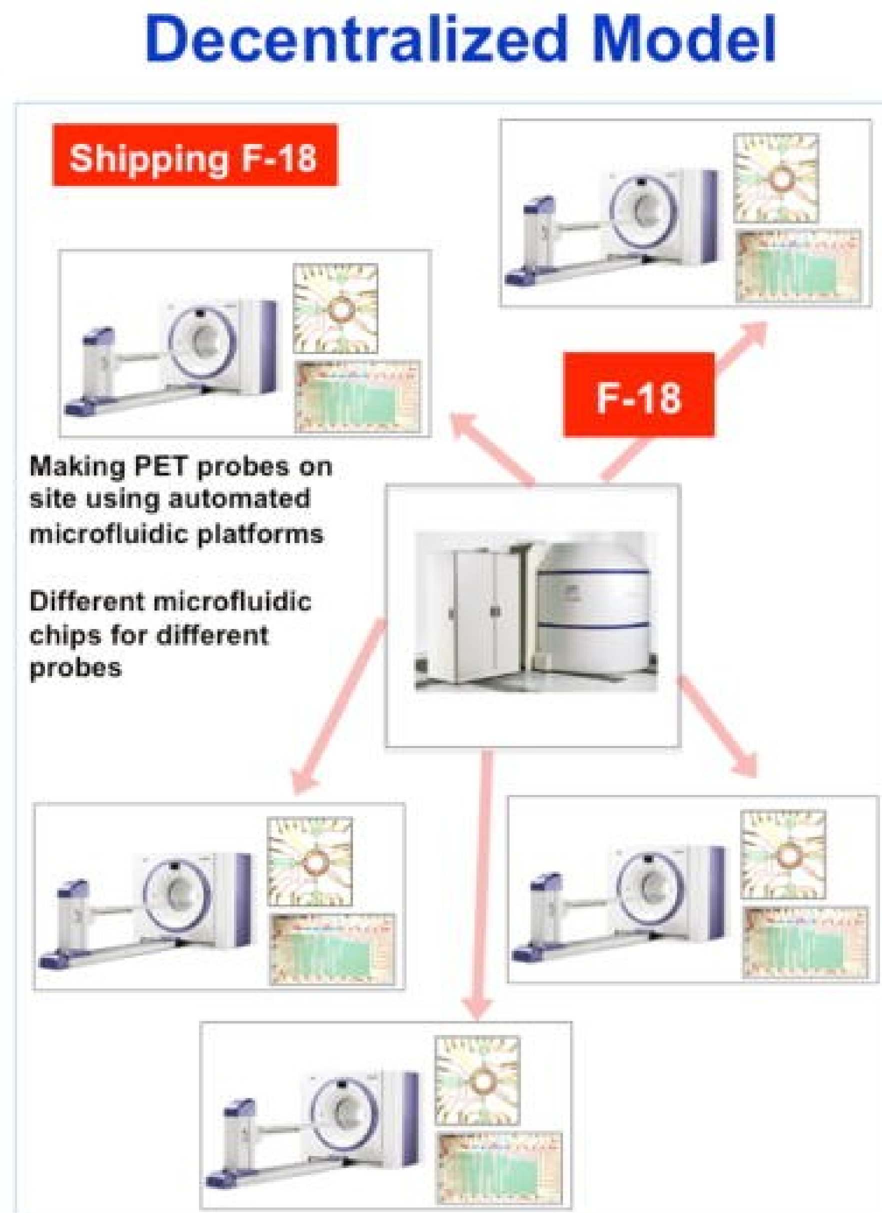


PET Centers



# Centralized vs. Distributed



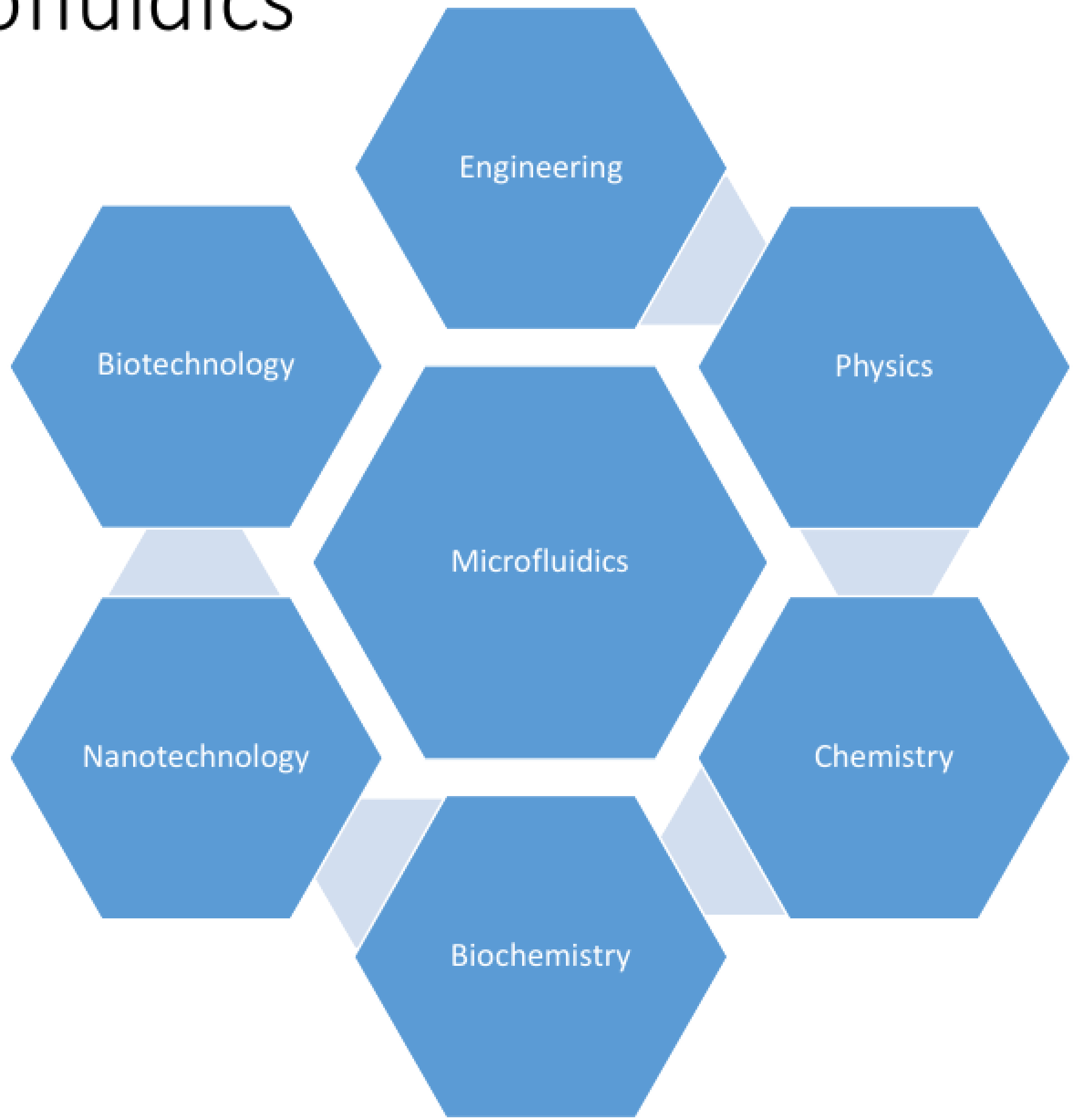



# Research objective

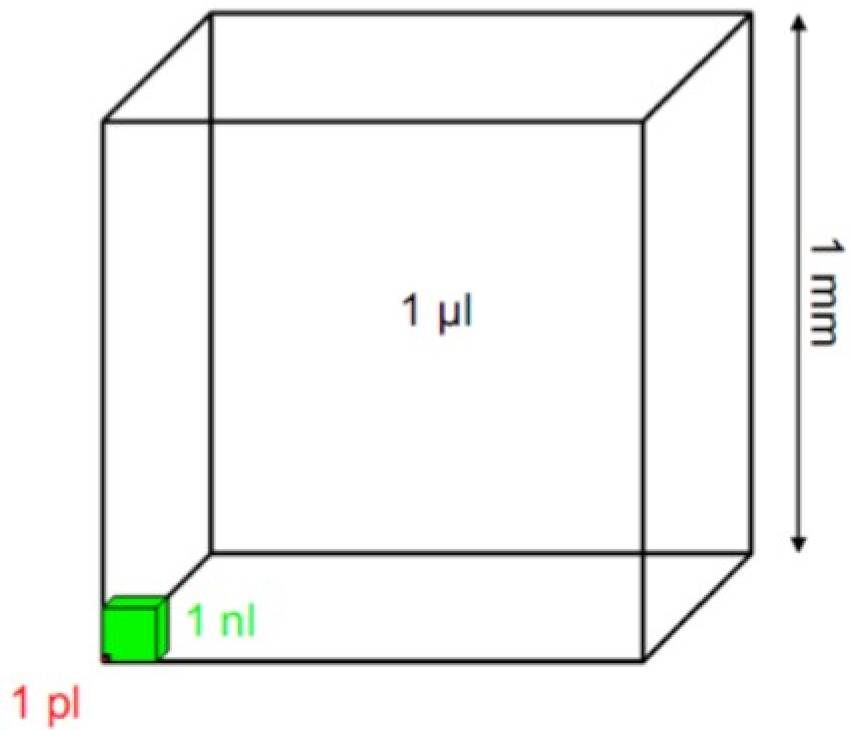
Developing a technology that makes decentralized PET production affordable and efficient

Microfluidics can be a good option

# Where microfluidics lies



# Microfluidics




$$1l = 1dm^3$$

$$1\mu l = 1mm^3$$

$$1nl = 100\mu m^3$$

$$1pl = 10\mu m^3$$

$$1fl = 1\mu m^3$$

- A typical microfluidic channel is about the same width as a human hair (60-80 um)

# Advantages of microfluidics

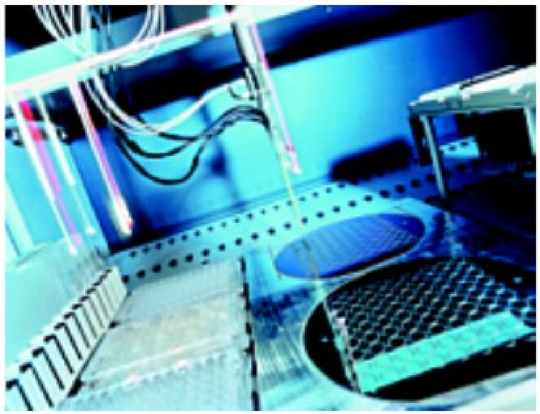
- Micro scale = laminar flow
- Laminar flow allows controlled mixing
- Low thermal mass
- Efficient mass transport (speedy diffusion)
- Good (large) ratio of channel surface area: channel volume
- Single cell and molecule manipulations
- Protection against contamination and evaporation
- Kinetics easy to study
- Parallelization and high throughput

# Mixing

A good lab technician or scientist

**Advantage:** Highly flexible

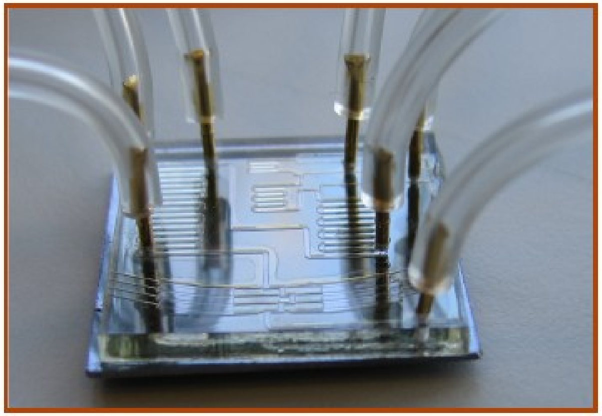
**Disadvantage:** Low through-put



A pipette based Sample-mixing robot

**Advantage:** High-throughput, High reproducibility

**Disadvantage:** Not very flexible

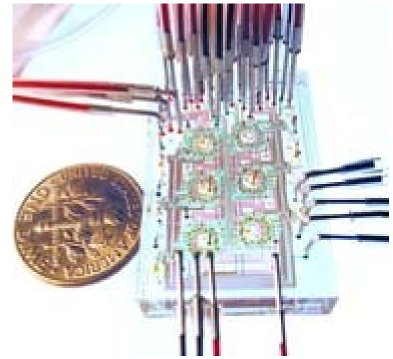


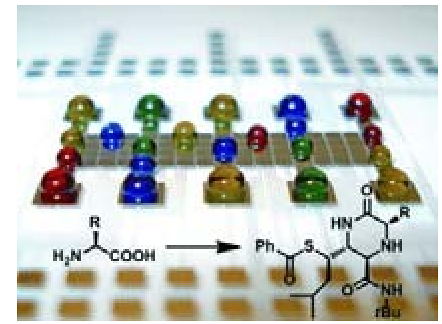
A microfluidic device

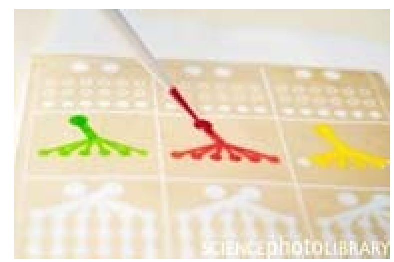
Has the potential to combine the best of both worlds?

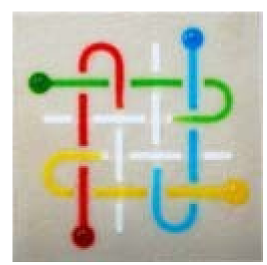
# Advantages of microfluidics

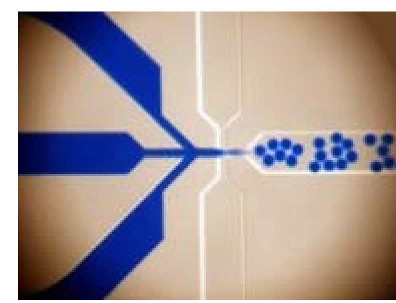
- Down-sizing of reactors is typical of organic chemistry industry
- Increased Surface-to-Volume Ratio (SVR)
- Quicker and more efficient transfer of reagents
- Improved energy transfer
- Efficient control of reaction by adjusting reagent ratio and reaction time
- Reduced shielding and overall size and weight







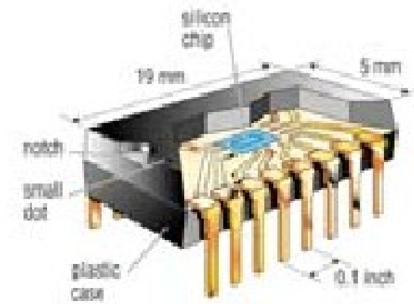




G. Pascali et al. “Microfluidics in radiopharmaceutical industry”, *Nuclear Medicine and Biology*, 2013

# Microfluidics revolution

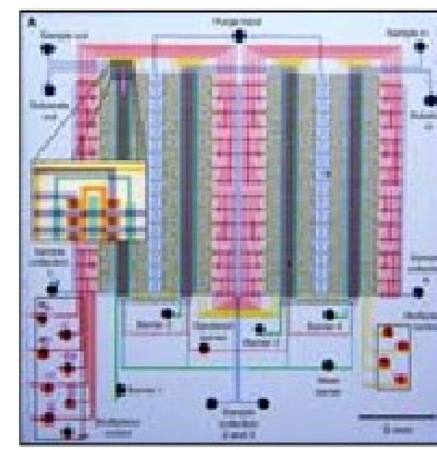
Microelectroncs
Revolution




Parallel fabrication of many transistors

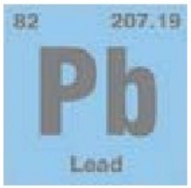
Microfluidics
Revolution
(Lab on a chip)


Parallel fabrication of many microvalves



# Reduction of shielding size

During production of PET probes, shielding is needed to protect operator from gamma radiation




11.34 g/cm$^3$

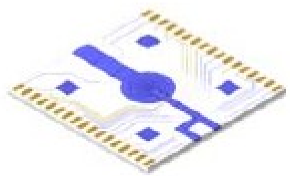
$T_H$(Pb): 4.1mm

**If synthesizer is size of a hot cell:**
50" x 37" x 47" rectangular interior, 3" thick
Mass of Pb = 7600 kg

Minimum size can be considered a "shell" around the synthesizer

**If size of mini cell**:
27" x 20" x 24" rectangular interior, 3" thick
Mass of Pb = 2400 kg

Thus mass of shielding scales as $R^2$

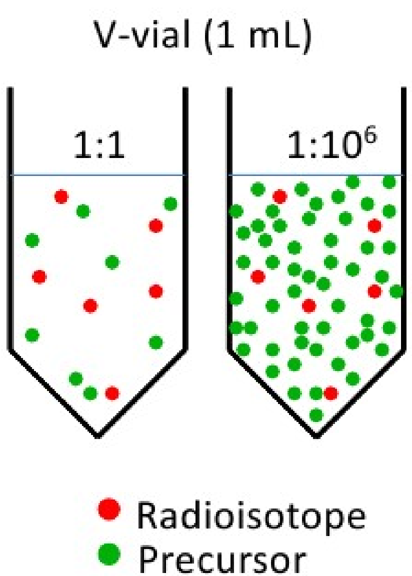


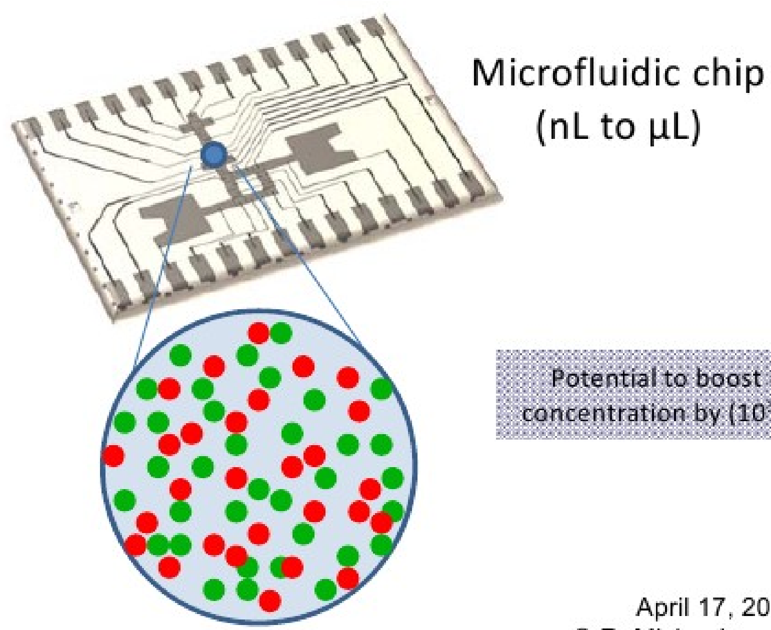
**Hypothetical future microfluidic system:**
2" x 2" x 2" rectangular interior, 3" thick
Mass of Pb = <u>90 kg</u> (BENCHTOP!)

# Micro-scale reaction

- Example: F-18

| | |
|---|---|
| Theor. Max. Specific activity: | 1710 Ci/µmol |
| Number of F-18 in 1 Ci | 0.6 nmol |
| Concentration (1 mL): | 0.6 µM |
| Human image needs ~10 mCi: | 6 nM |
| Mouse image needs ~100 µCi: | 60 pM |

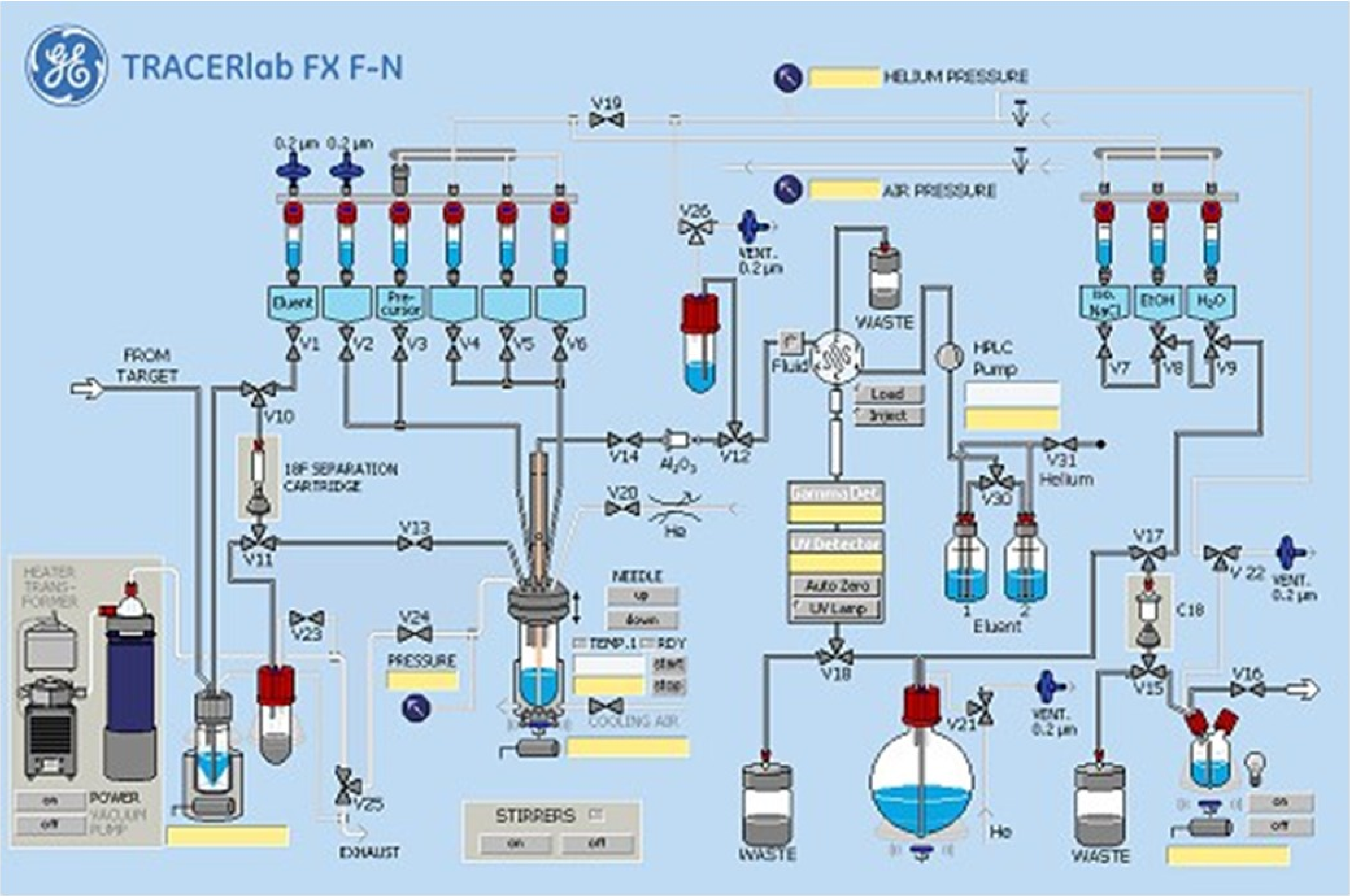


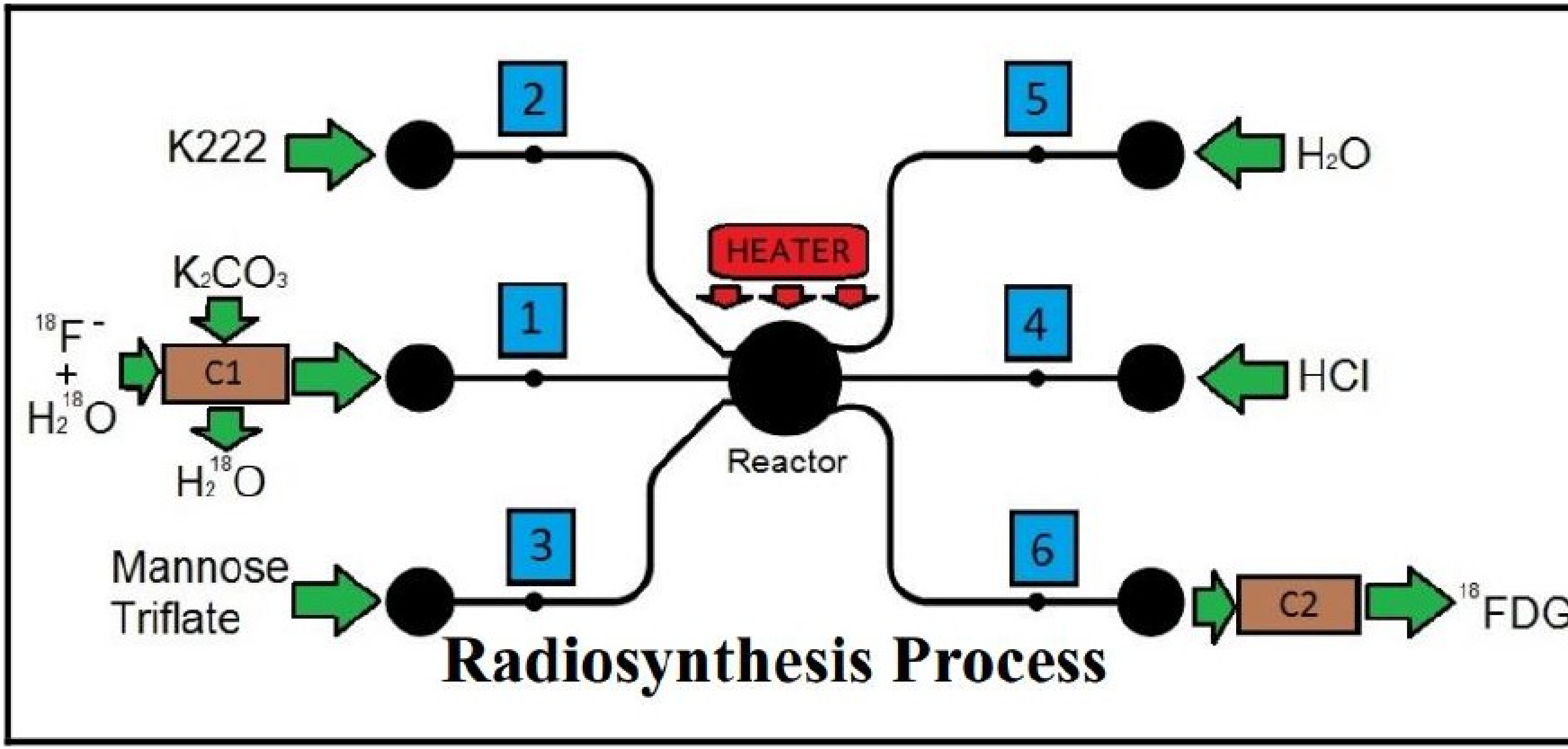

Potential to boost F-18 concentration by ($10^3$-$10^6$ x)

April 17, 2013 (START)

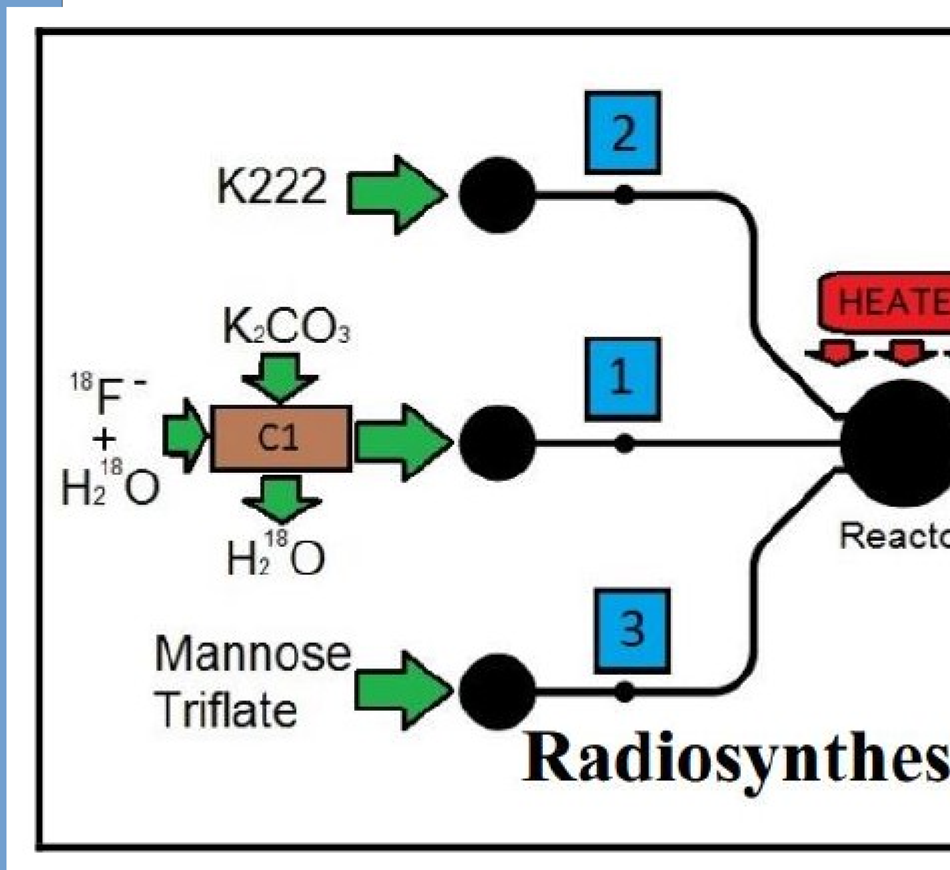
# [$^{18}$F]FDG synthesis. Macro level



# [$^{18}$F]FDG synthesis. Micro concept



# [$^{18}$F]FDG synthesis




Soluted $^{18}$F dissolved in water passing through C1. NOTE C1 is not integrated

Concentration of $^{18}$F in $K_2CO_3$ through C1 and entering the chamber in 1

Valves closing and evaporation of water in the reactor by applying heat

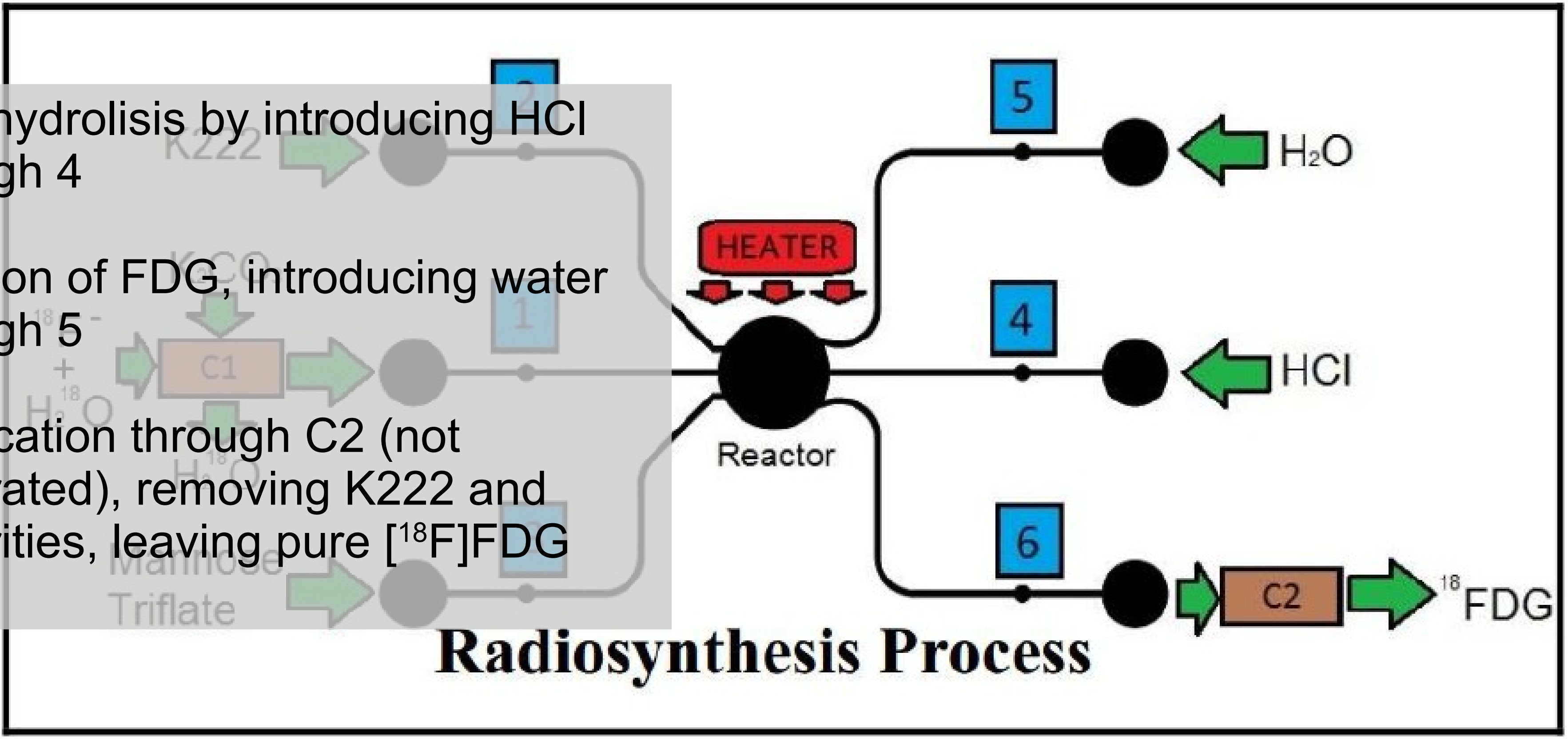
Introduction of K222 and MeCN through 2

Evaporation of MeCN. Dry residue remains

Introduction of mannose triflate (MT) through 3

Fluorination in the chamber at 75ºC.

# [$^{18}$F]FDG synthesis

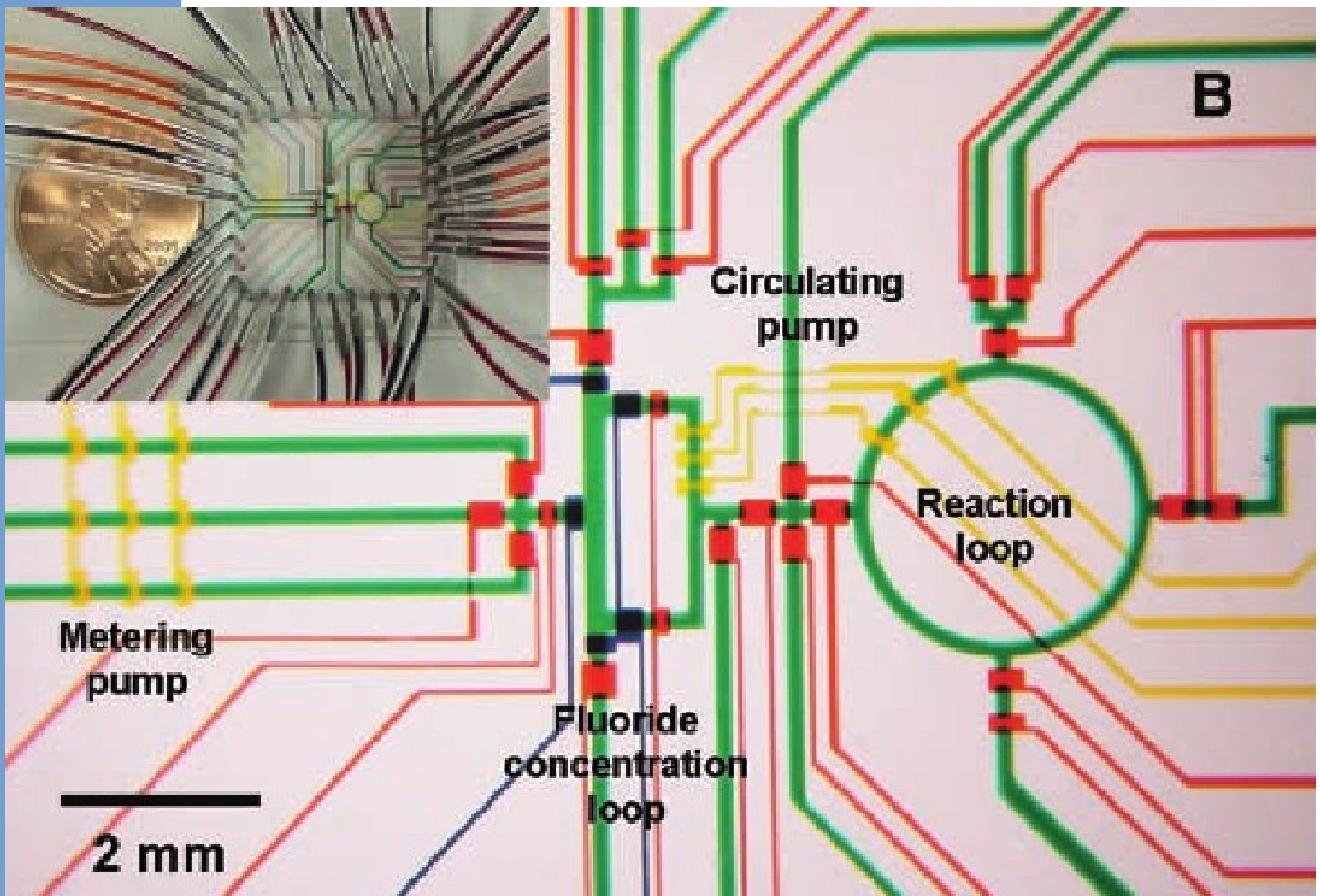



Acid hydrolisis by introducing HCl through 4

Solution of FDG, introducing water through 5

Purification through C2 (not integrated), removing K222 and impurities, leaving pure [$^{18}$F]FDG

# Microsynthesis of [$^{18}$F]FDG




Low yield (38% vs 70% standard in macro)

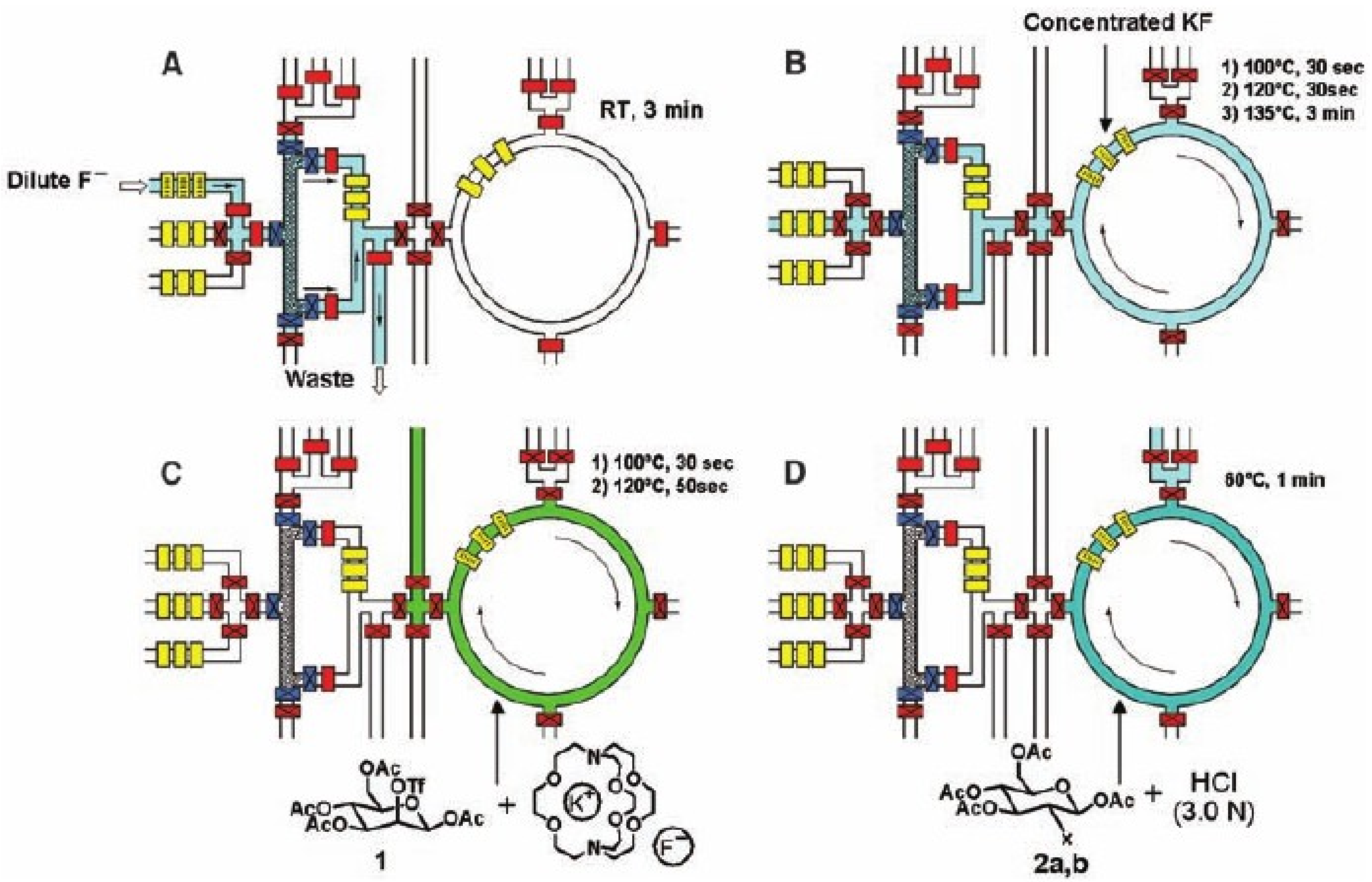
Small final dose

PDMS chip presented swelling of organic solvents

But PDMS allowed easy creation of valves

Lee C-C, et al. Multistep synthesis of a radiolabeled imaging probe using integrated microfluidics. Science 2005

# Steps of the process



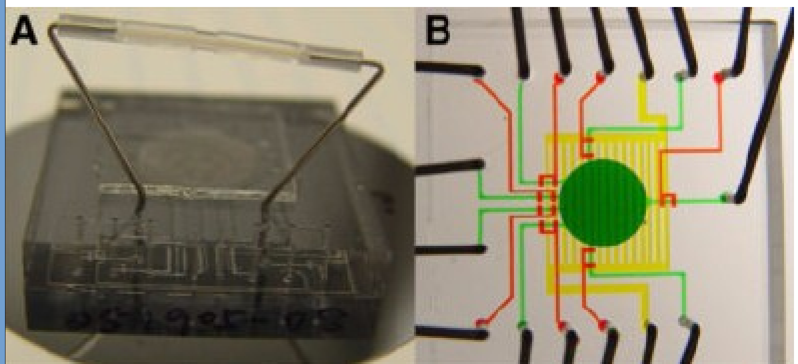

A. Concentration of fluoride ion

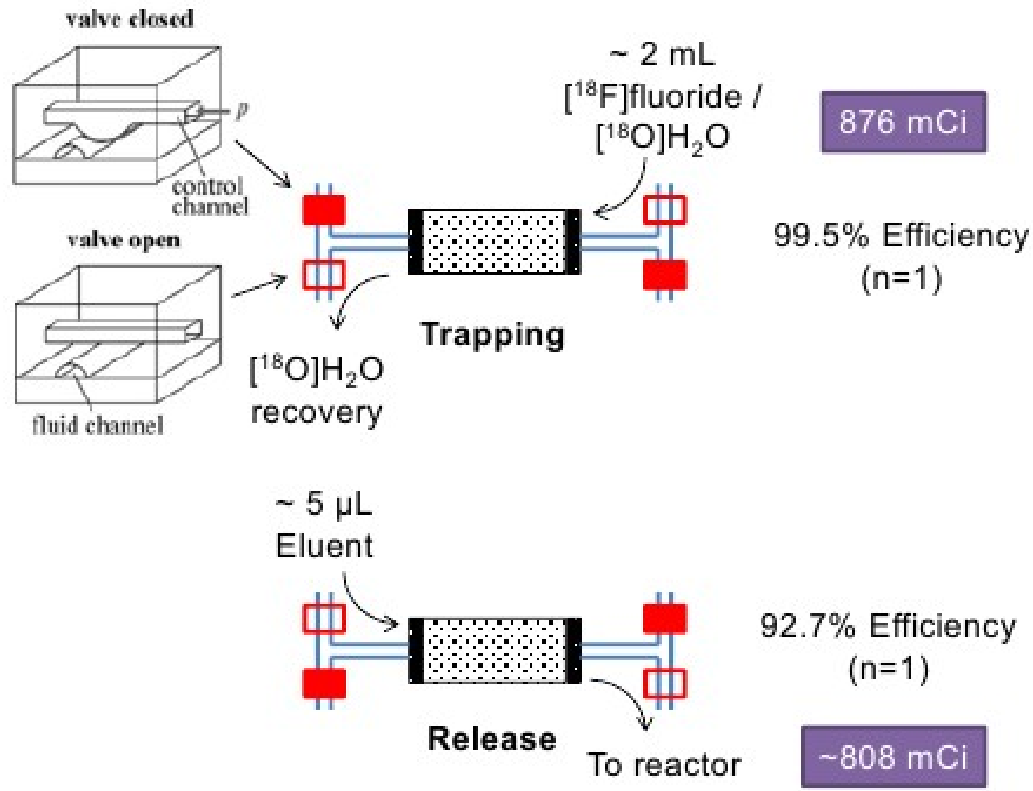
B. Evaporation of water

C. Fluorination reaction

D. Hydrolisis reaction

# Coin-shaped reactor




Ion exchange columns are not integrated

PDMS had to be coated and still some $^{18}$F is lost

Yield of 96% in 14min (vs macro 75% in 35-45min)

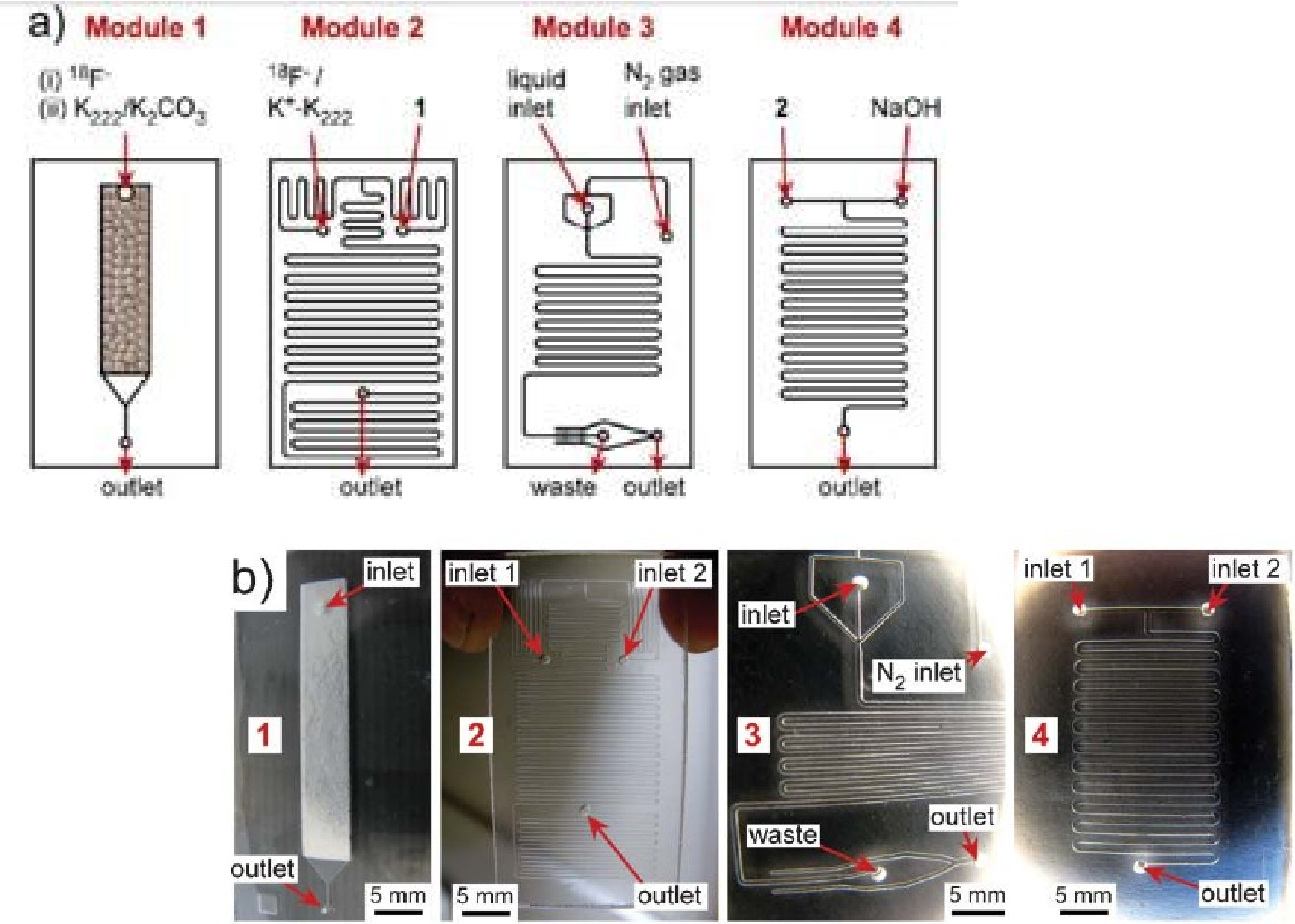
# Commercial reactors


Advion Nanotek
4 parallel mixers
Volume hundreds of uL

Veenstra / Future Chemistry D-500

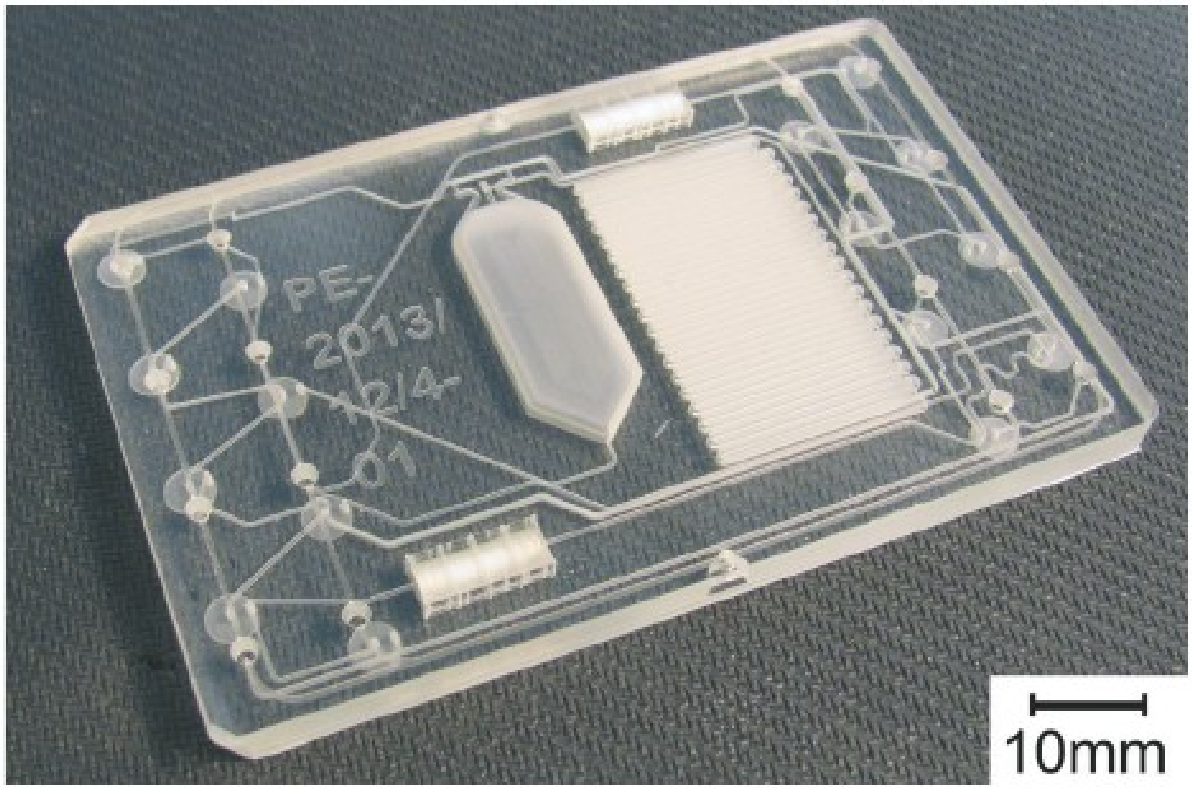
Scintomics u-ICR

# Radiochemistry-on-chip



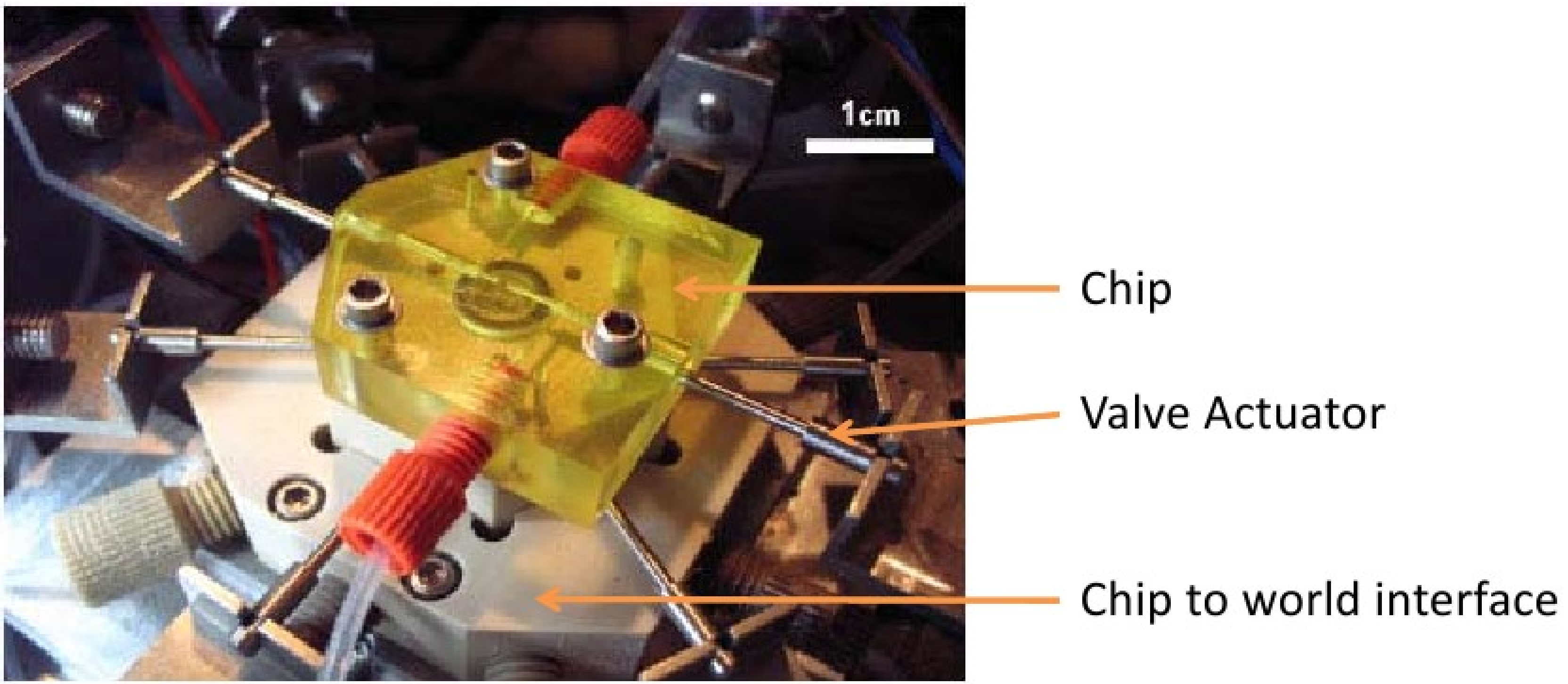

Arima et al. 2013. Lab on a Chip. DOI: 10.1039/C3LC00055A

# Microfluidic chip




Microfluidic chip for complete [$^{18}$F]PESIN synthesis with valves, reactors, QMA and SPE resins integrated on-chip.

# Microbatch reactor

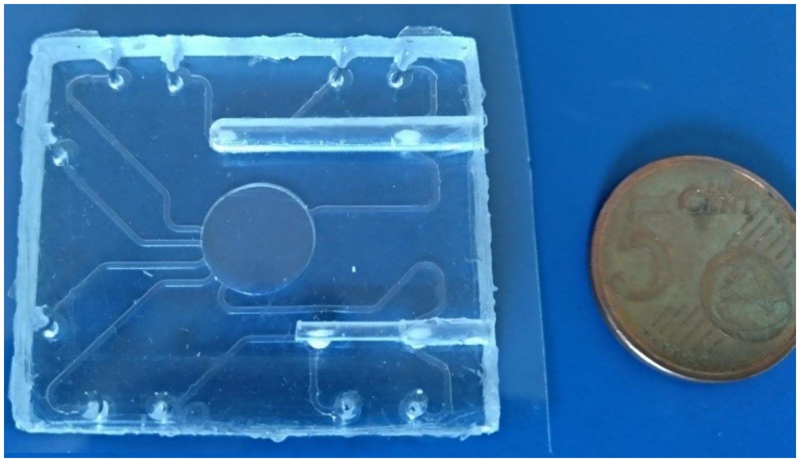


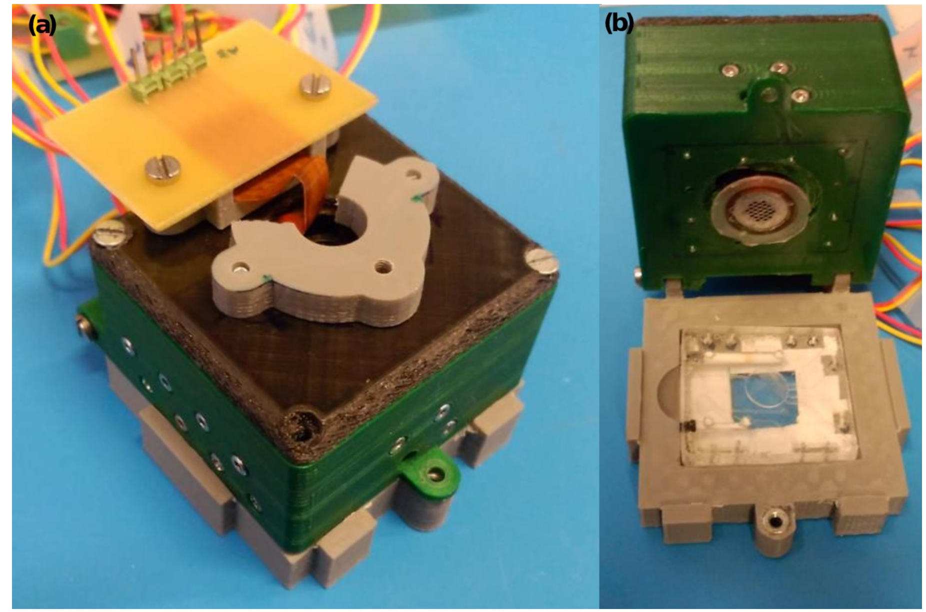

Bejot R, et al. Batch-mode microfluidic radiosynthesis of N-succinimidyl-4-[18F]fluorobenzoate for protein labelling. J Label Compd Radiopharm 201

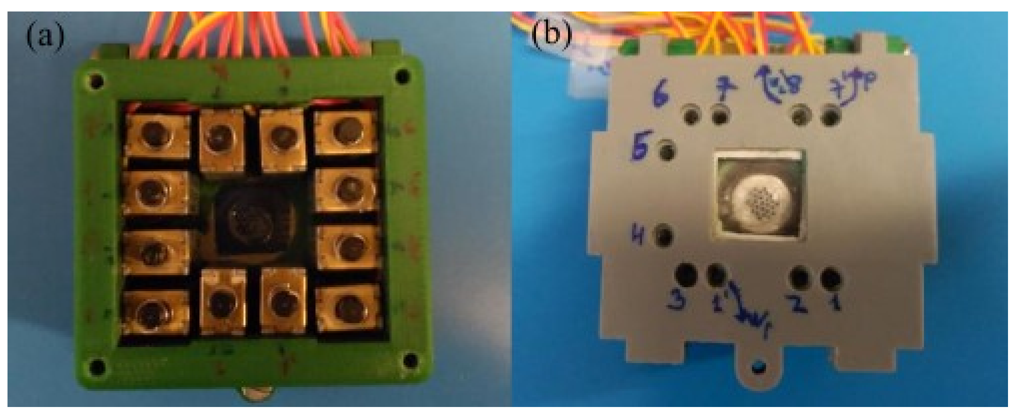
# MicroRad project

- Public Research Project, Andalusian Government, Spain, 2014-2018
- Aim: developing a complete smart radiosynthesis system
- Disposable chips, made of unexpensive material
- Integrated cartridges
- Fast, efficient gas extraction
- Smart monitoring by use of integrated sensors

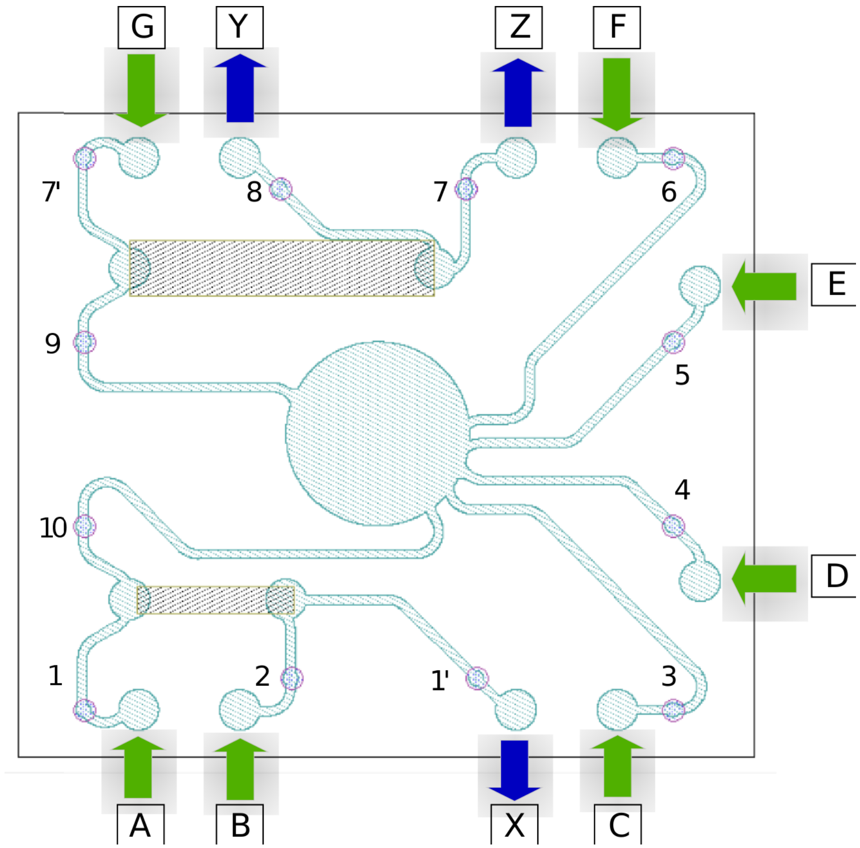
# MicroRad





# Design


G
Y
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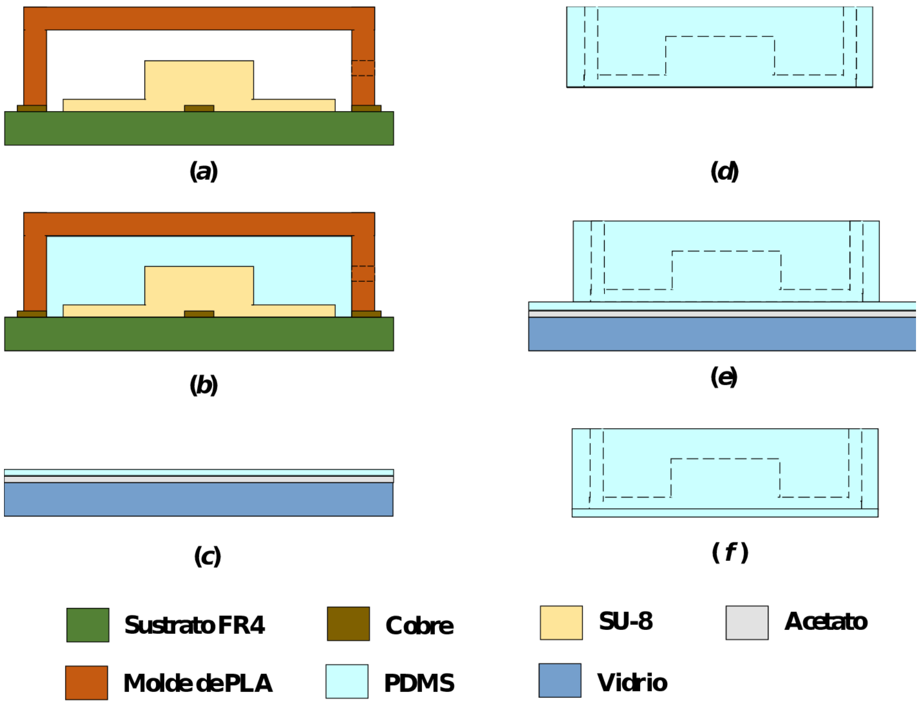
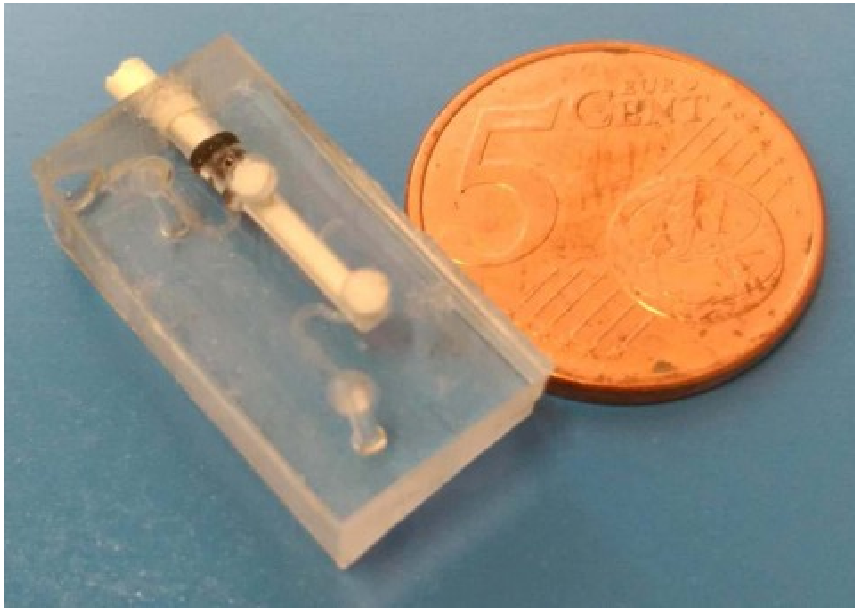

(a)
(d)
(b)
(e)
(c)
( f )
Sustrato FR4
Cobre
SU-8
Acetato
Molde de PLA
PDMS
Vidrio

# Cartridge integration

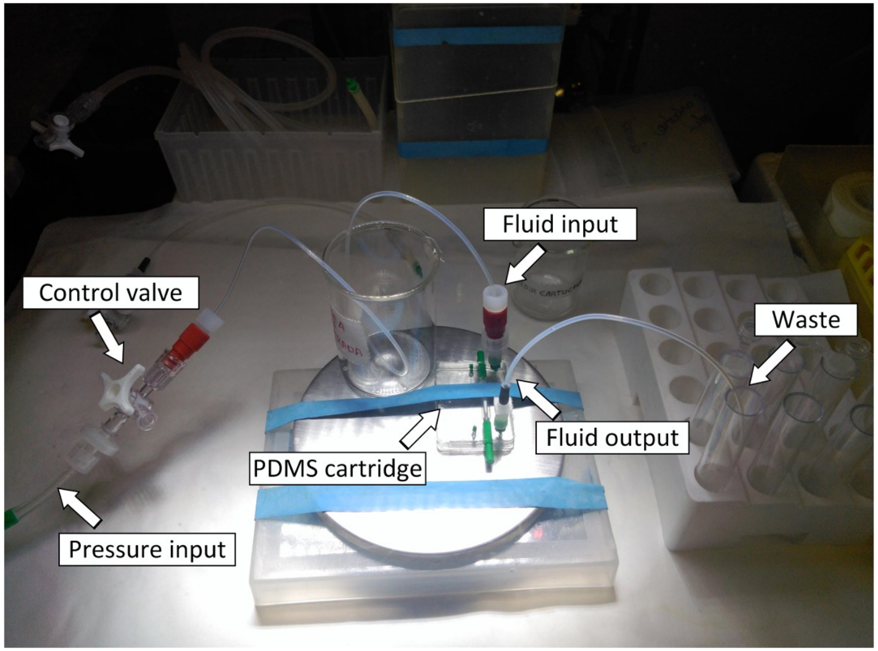



RESULTS FOR DIFFERENT SAMPLE VOLUMES

| Volume (mL) | Retention (%) | Elution (%) |
|---|---|---|
| 0.1 | 100 | 88 |
| 0.1 | 100 | 98 |
| 0.1 | 100 | 98 |
| 2 | 98 | 89 |
| 2 | 98 | 95 |
| 2 | 98 | 79 |

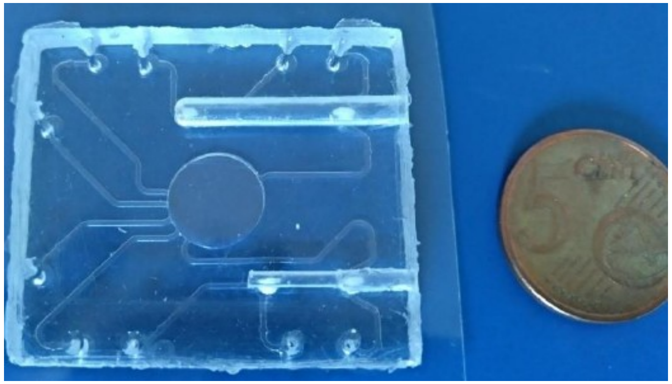
To our knowledge, the first integrated ion-exchange cartridge in PDMS lab-on-chip for PET

B. Salvador, A. Luque, et al. “Disposable PDMS Chip With Integrated [18F]Fluoride Pre-Concentration Cartridge for Radiopharmaceuticals”, *IEEE Journal of Microelectromechanical Systems*, 2017



# Use of PDMS

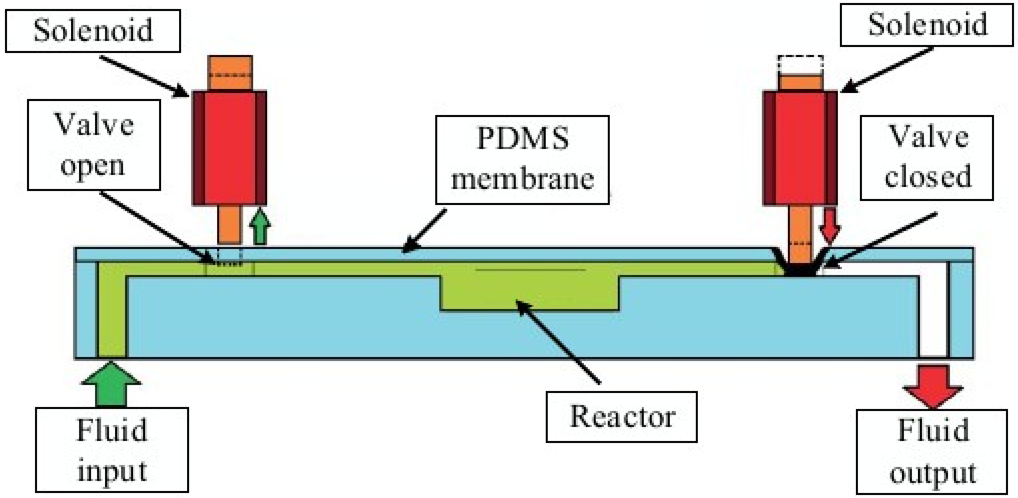
- PDMS is a low-cost, transparent, biocompatible polymer, heavily used for rapid prototyping and disposable devices
- It presents many other advantages for microfluidics, such as flexibility and porosity
- Some authors report that it interacts with [18F], rendering it almost unusable for radiopharmacy
- In our experience, interaction is negligible when parameters are correctly configured

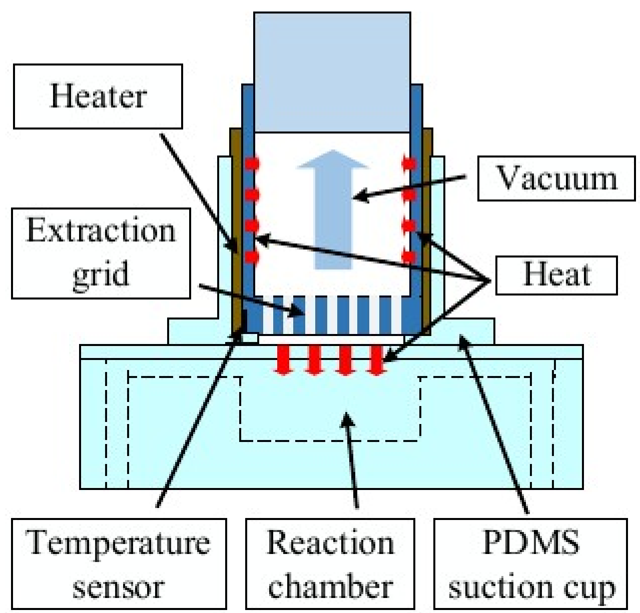


| PDMS Reactor | Loading [$^{18}$F]F- Activity (MBq) | Activity after evaporation (MBq) | Elution Water per injection (MBq) | Residual activity at chip after elution (MBq) | Second chip elution Residual activity (MBq) | Residual Radioactivity at chip (%) |
|---|---|---|---|---|---|---|
| 1 | 8.62 | 8.39 | 7.04 | 0.10 | - | 1.16 |
| 2 | 12.58 | 11.80 | 10.86 | 0.21 | - | 1.66 |
| 3 | 28.12 | 27.98 | 24.07 | 1.09 | 0.3 | 1.06 |
| 4 | 51.80 | 48.84 | 43.35 | 1.81 | 0.5 | 0.96 |
| 5 | 66.60 | 63.15 | 54.21 | 1.91 | 0.5 | 0.75 |
| 6 | 240.05 | 231.77 | 220.27 | 0.78 | - | 0.32 |
| 7 | 802.10 | 774.26 | 716.49 | 19.24 | 2.1 | 0.26 |
| 8 | 925.30 | 856.62 | 756.74 | 7.50 | - | 0.81 |
| 9 | 1257.01 | 1195.85 | 1017.59 | 7.48 | - | 0.59 |
| 10 | 2544.80 | 2526.67 | 2292.26 | 7.88 | - | 0.30 |

L. F. Maza, A. Luque, et al. “Does PDMS really interact with  [18F]fluoride? Applications in microfluidic reactors for 18F-radiopharmaceuticals”. *Micro-nanofluidics*, In press

# Advantages of PDMS

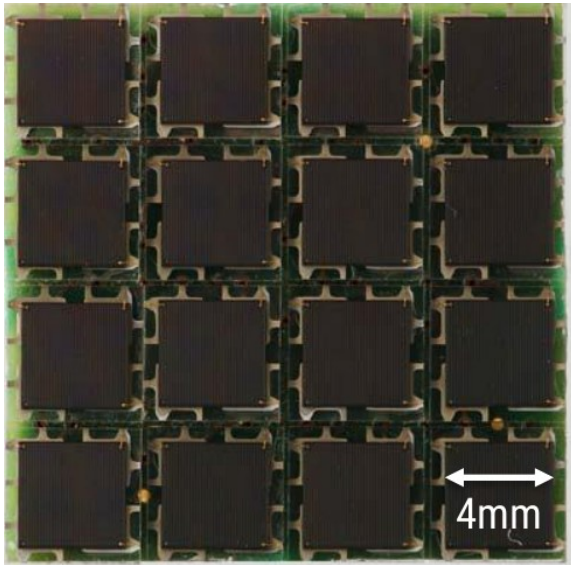


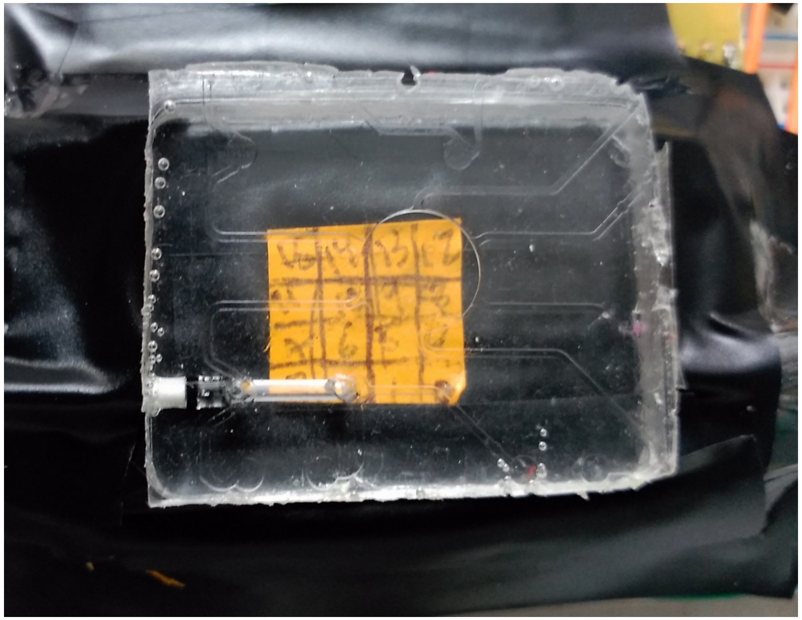

# Integrated sensing and control

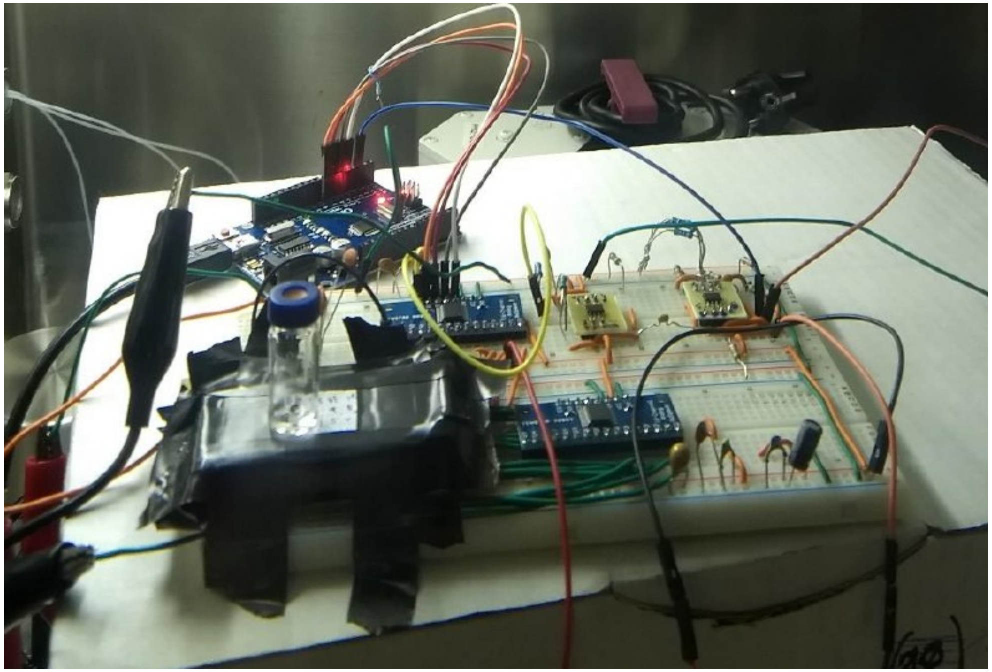
On a disposable chip it is difficult to integrate flow sensors and to understand how is the reaction evolving.

Silicon photomultiplier sensors are used to monitor the sample and reagents flow.

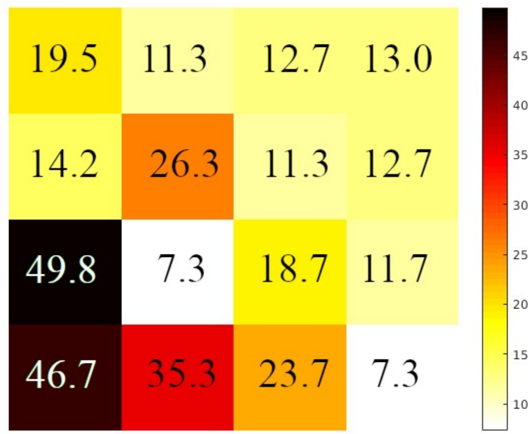


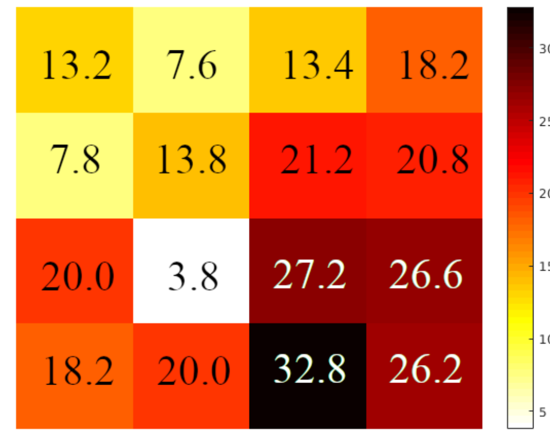

B. Salvador, A. Luque, et al. "Monitoring of Microfluidics Systems for PETRadiopharmaceutical Synthesis Using Integrated Silicon Photomultipliers", *IEEE Sensors*, 2019

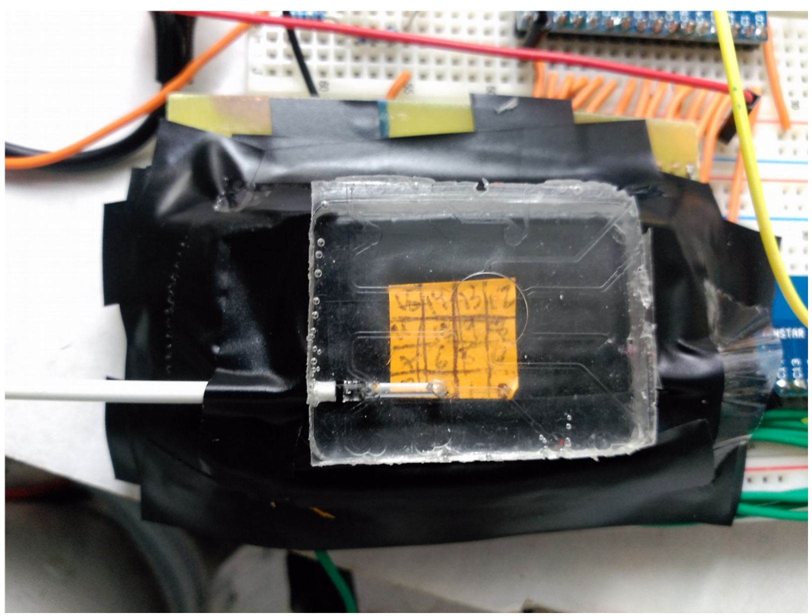


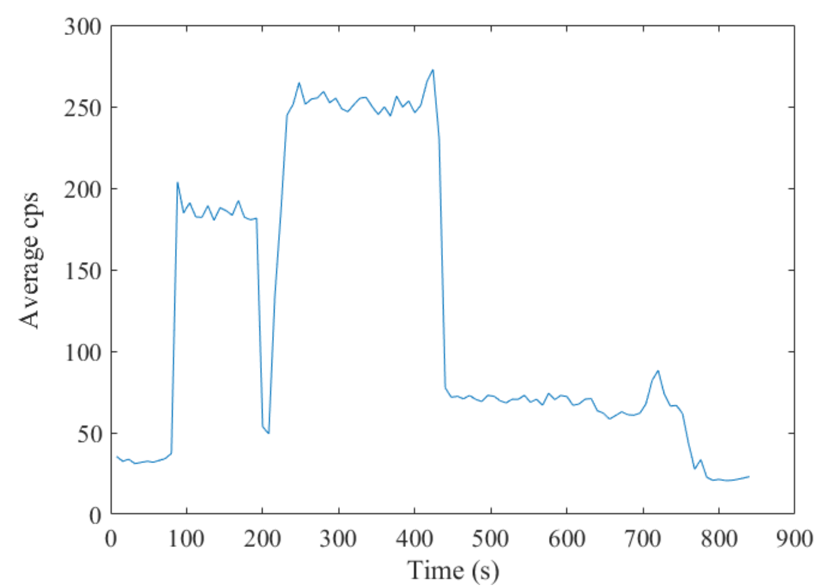


# 16 sensors are enough to monitor

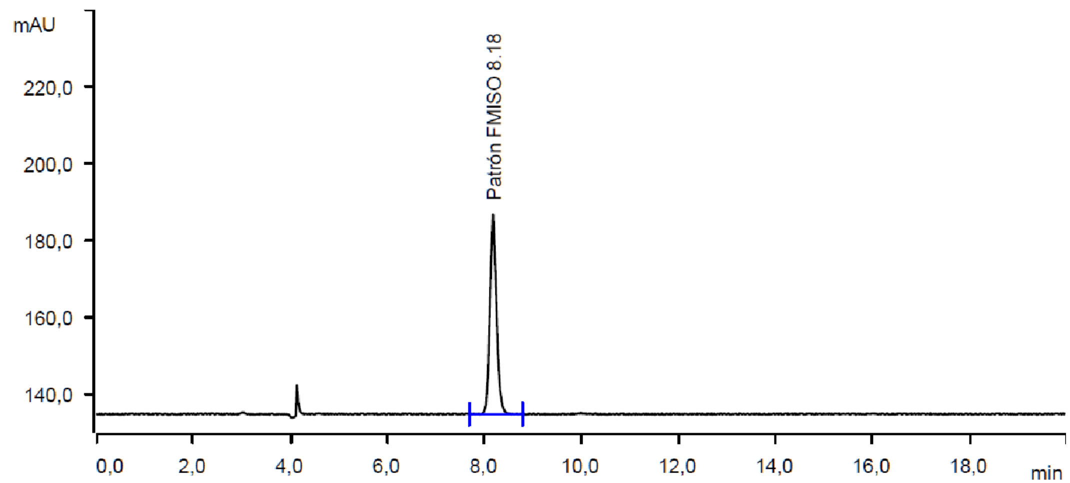


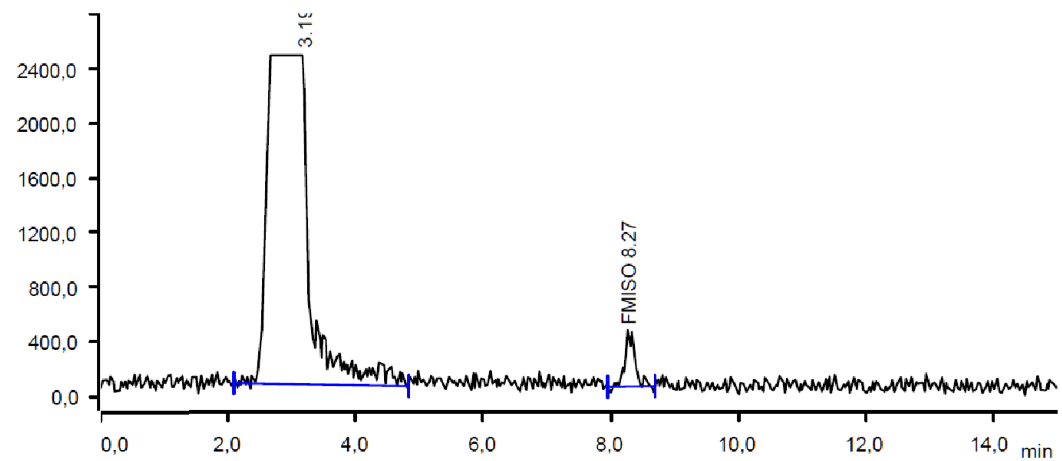





# Results. Synthesis of FMISO




| Peak number | Retention time min | Area (mAU) x min | Area ratio % | Resolution | Height mAU | Concentration ppm | Component name |
|---|---|---|---|---|---|---|---|
| 1 | 8.183 | 8.1415 | 100.00 | invalid | 52.060 | invalid | Patrón FMISO |

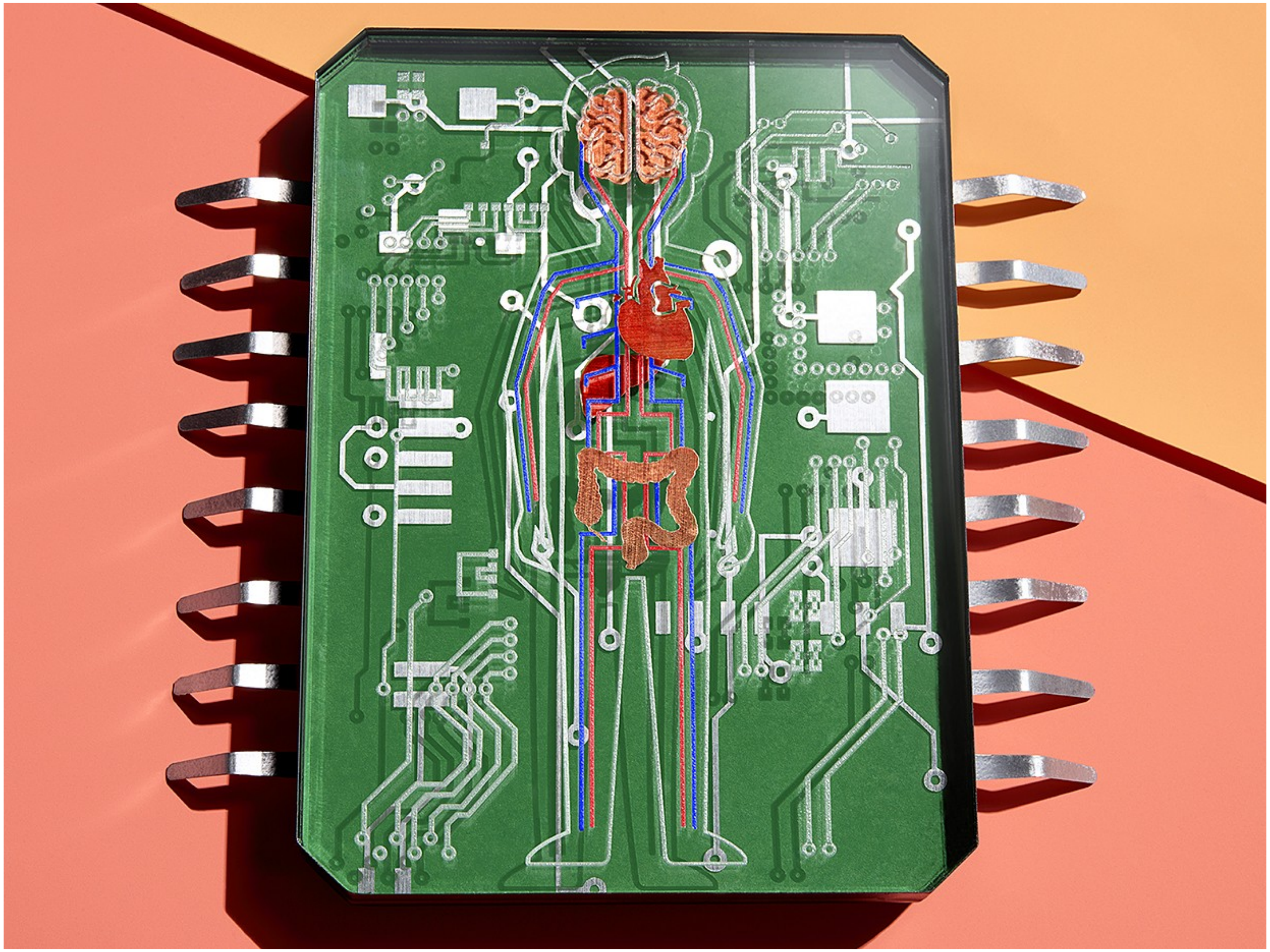



| Peak number | Retention time min | Area (mV) x min | Area ratio % | Resolution | Height mV | Concentration ppm | Component name |
|---|---|---|---|---|---|---|---|
| 1 | 3.192 | 1818.3236 | 96.39 | 12.288 | 2421.795 | invalid | |
| 2 | 8.270 | 68.1043 | 3.61 | invalid | 405.641 | invalid | FMISO |

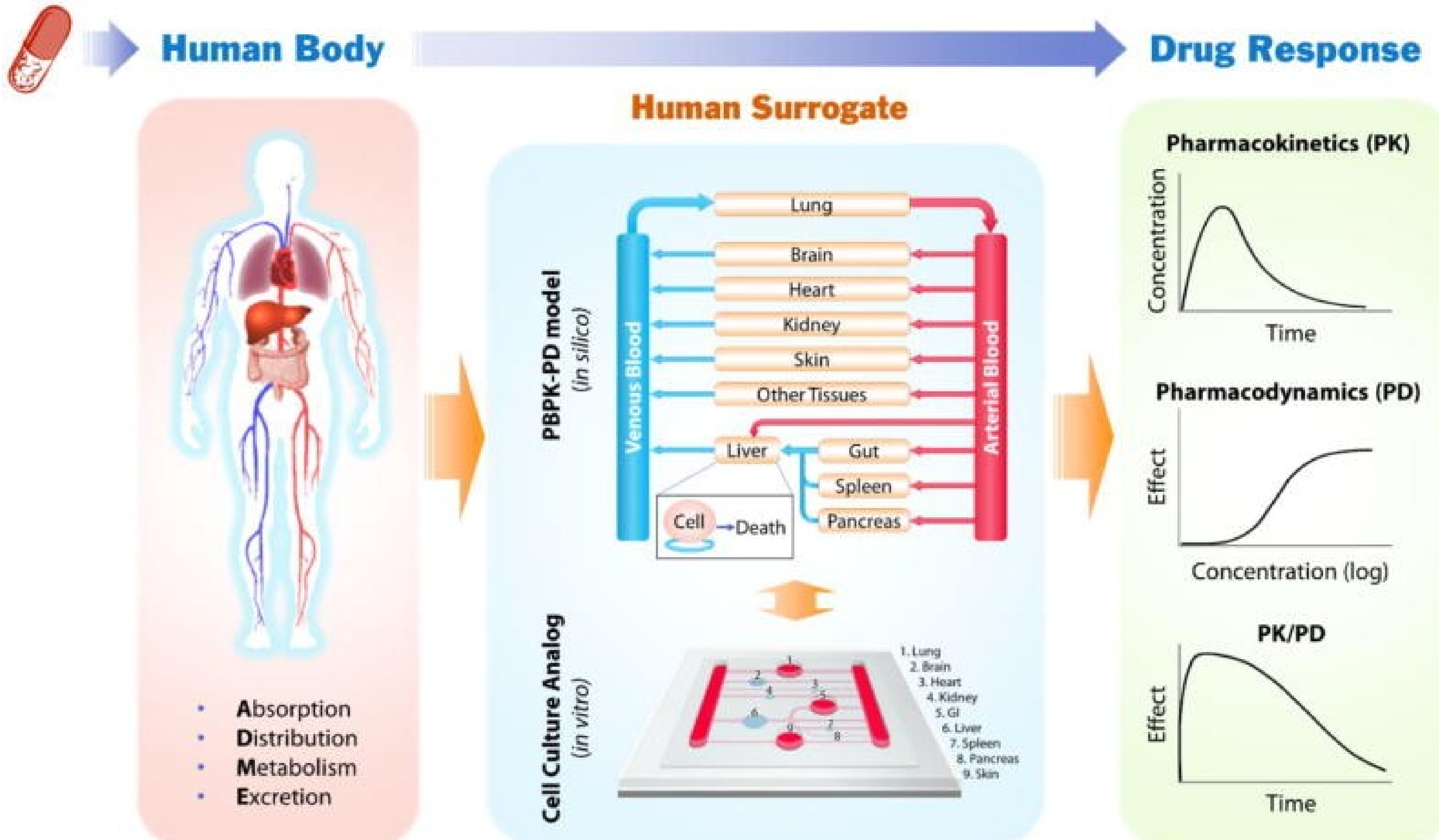
# Conclusions

- Microfluidics can be applied to PET probe generation
- Hot research topic which is expected to provide new developments
- Niche in the intersection between chemistry and electronic technology

# Organs on a chip

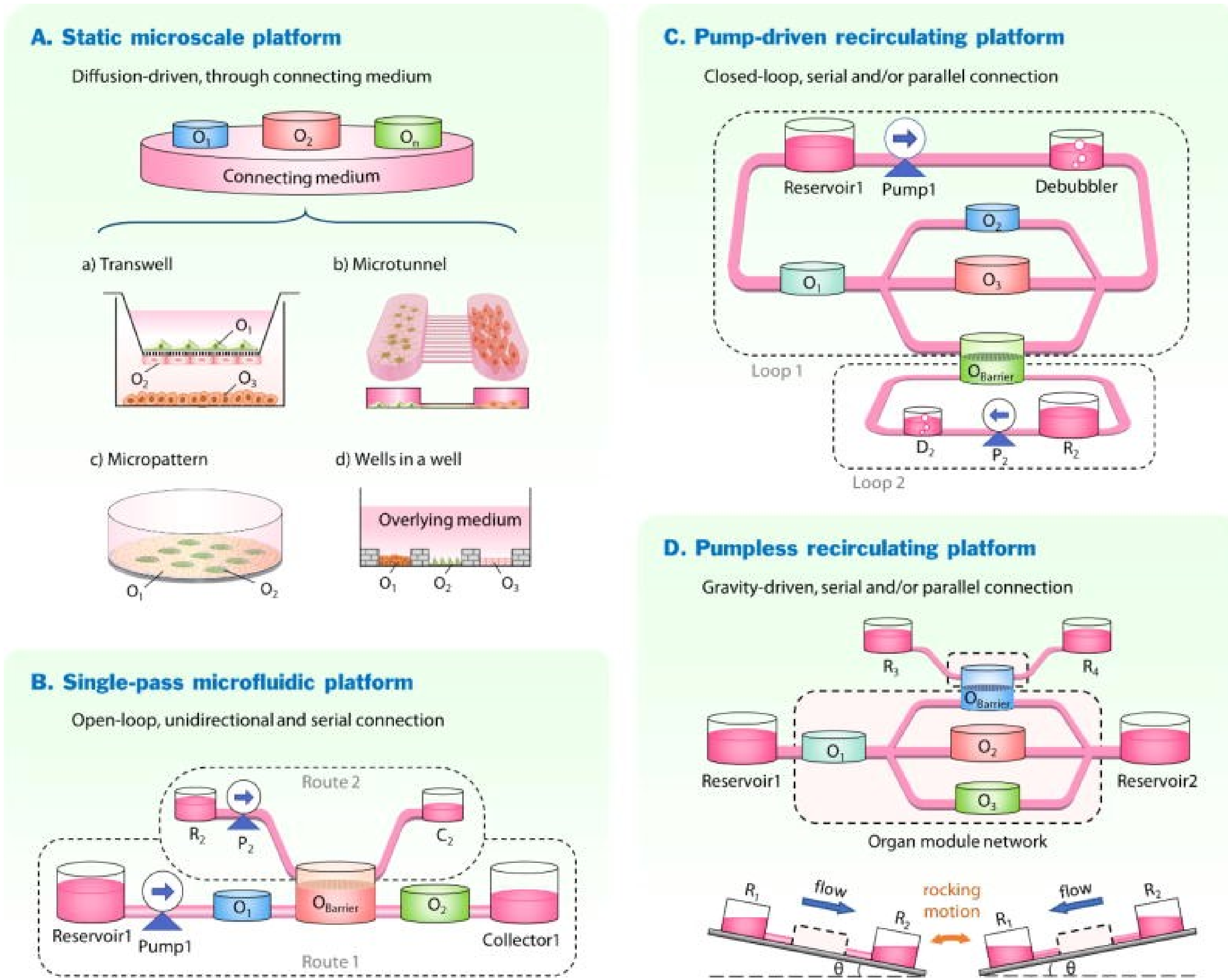


# Organs on a chip



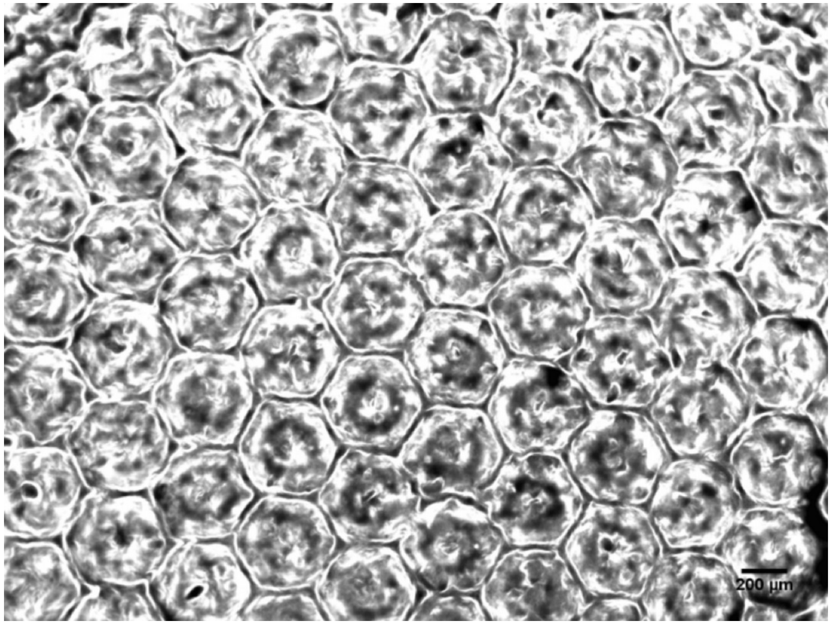

Wang, Y. I., Carmona, C., Hickman, J. J., & Shuler, M. L. (2018). Multiorgan Microphysiological Systems for Drug Development: Strategies, Advances, and Challenges. Advanced healthcare materials, 7(2)

# Organs on a chip



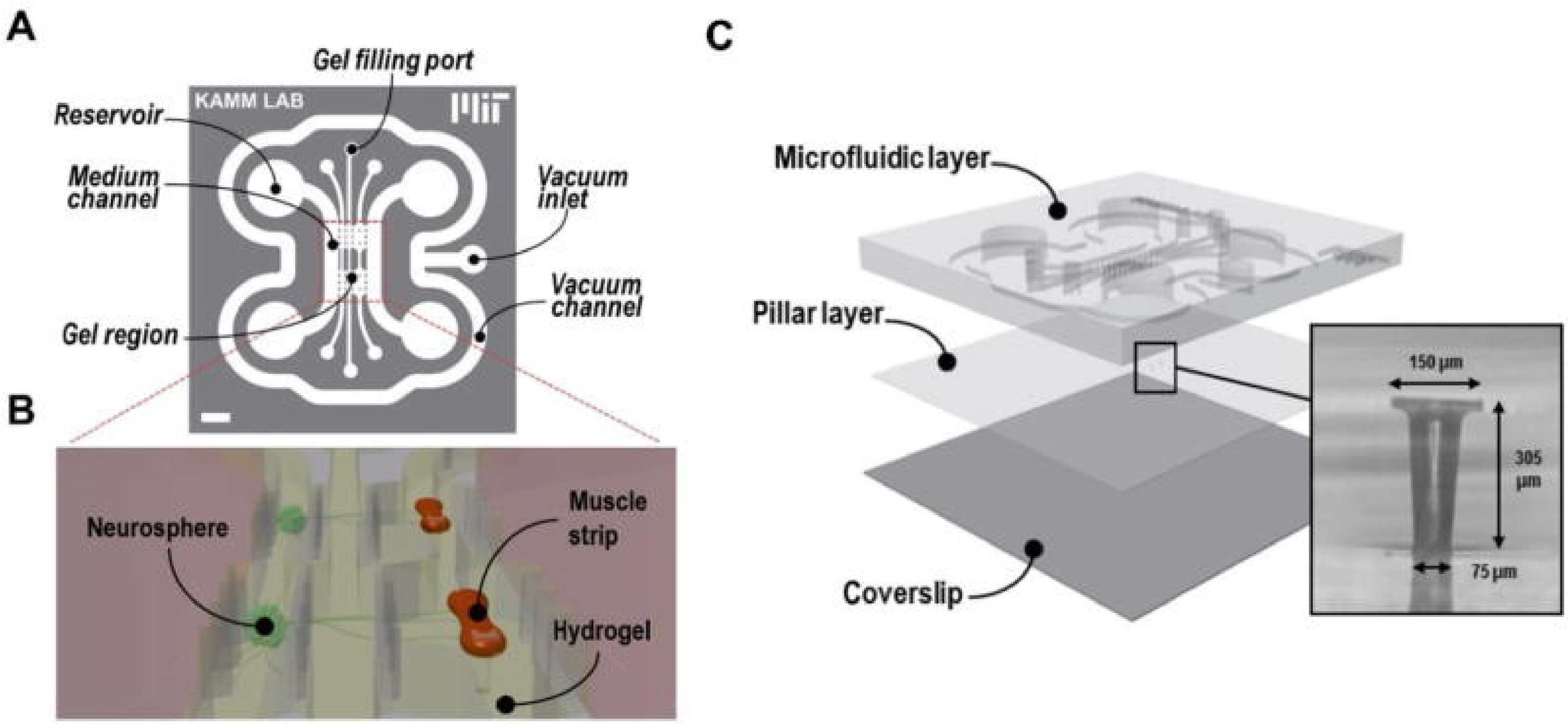
# MEMS for cultivating cells

Aim is to use MEMS techniques to create living cell cultures, tissues, or organs



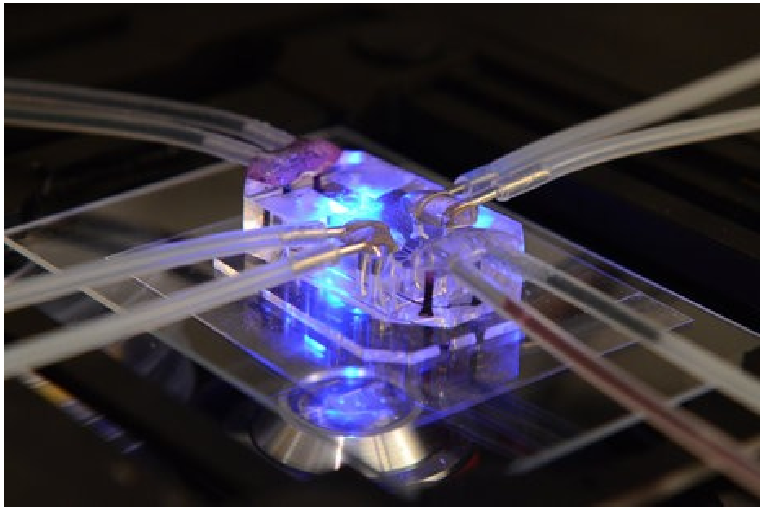

Photolithographically patterned liver cells

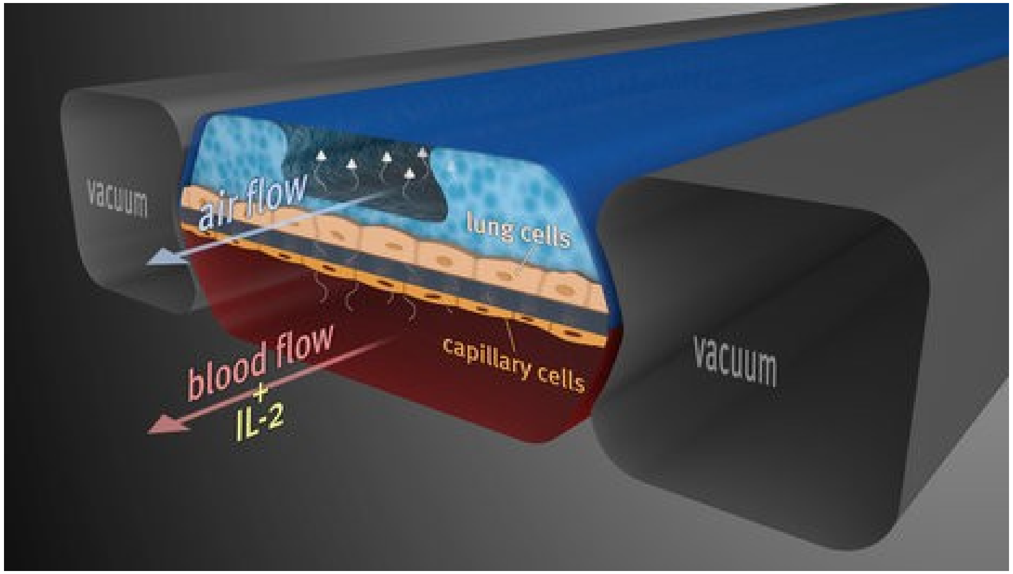
# Muscle on a chip




Uzel SG, Platt RJ, Subramanian V, Pearl TM, Rowlands CJ, Chan V, Boyer LA, So PT, Kamm RD. Sci Adv. 2016;2:e1501429.

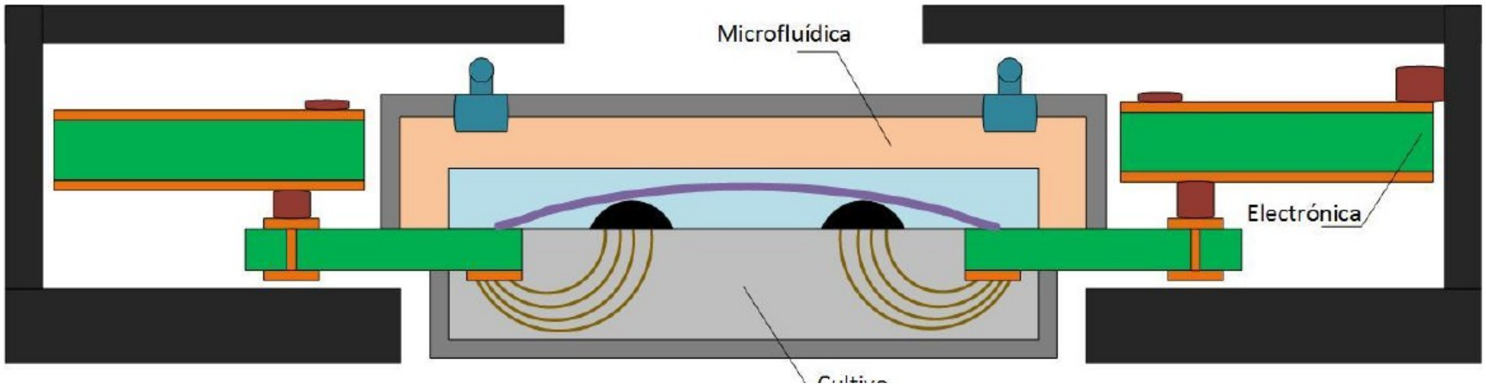
# Lung on a chip

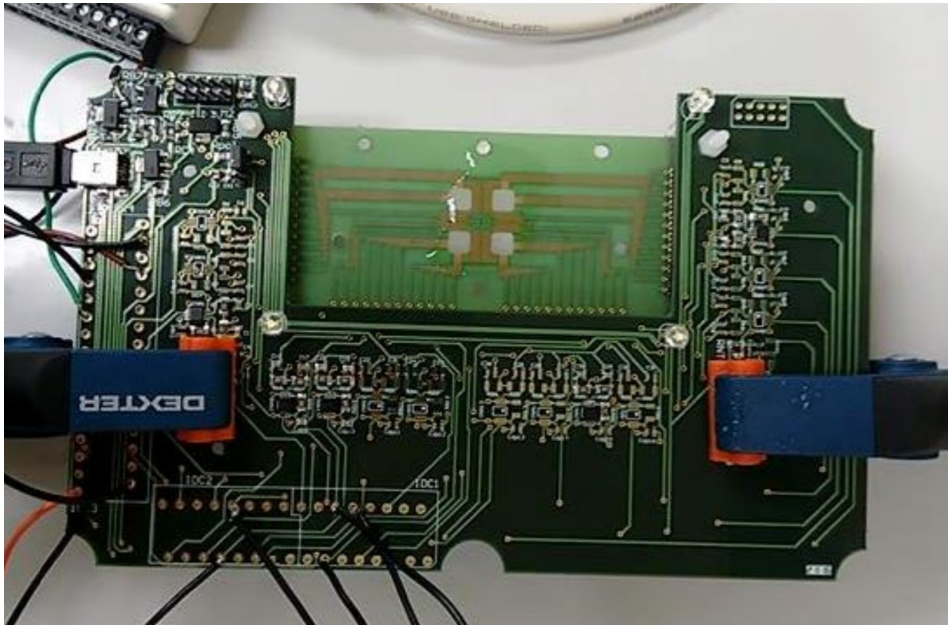


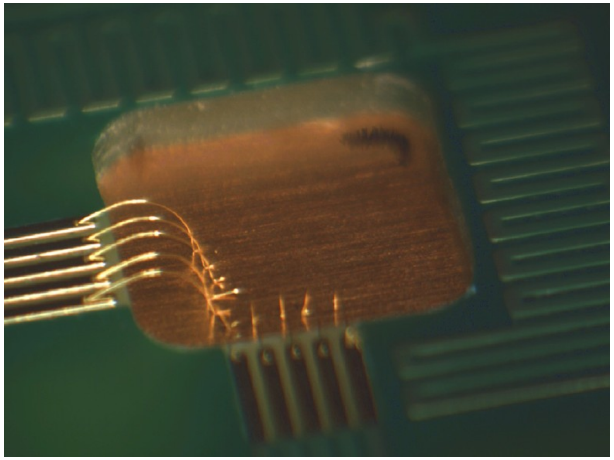



Dongeun Huh *et al.*, A Human Disease Model of Drug Toxicity–Induced Pulmonary Edema in a Lung-on-a-Chip Microdevice, Science Translational Medicine, 07 Nov 2012 : 159ra147

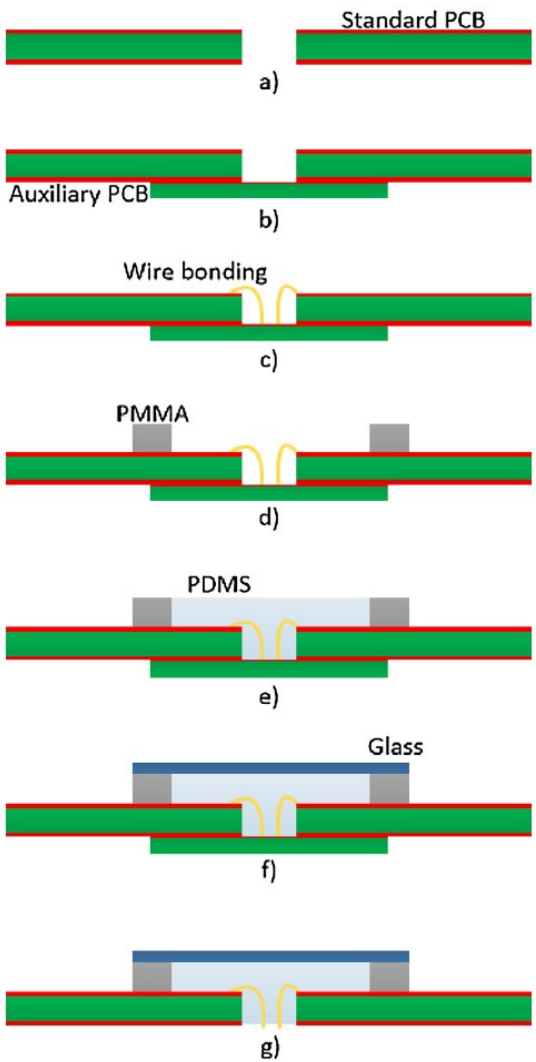
# Labcell: Neuron culture on a chip

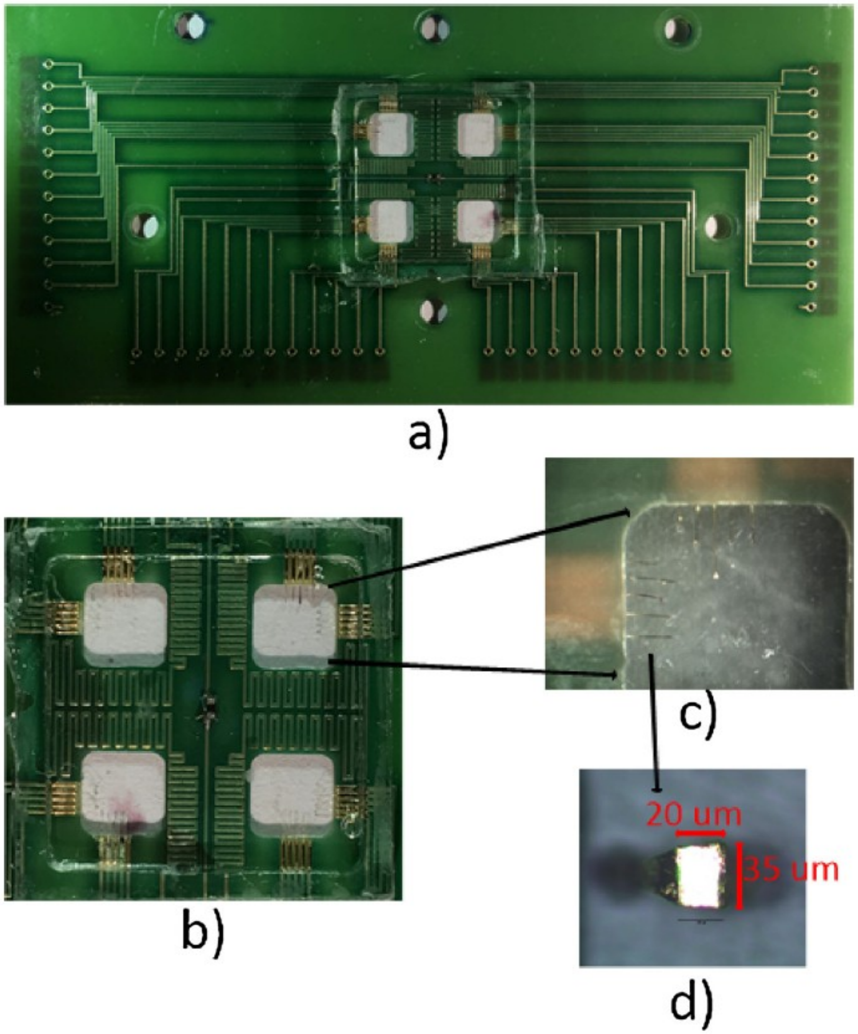


# MEAs embedded in PDMS

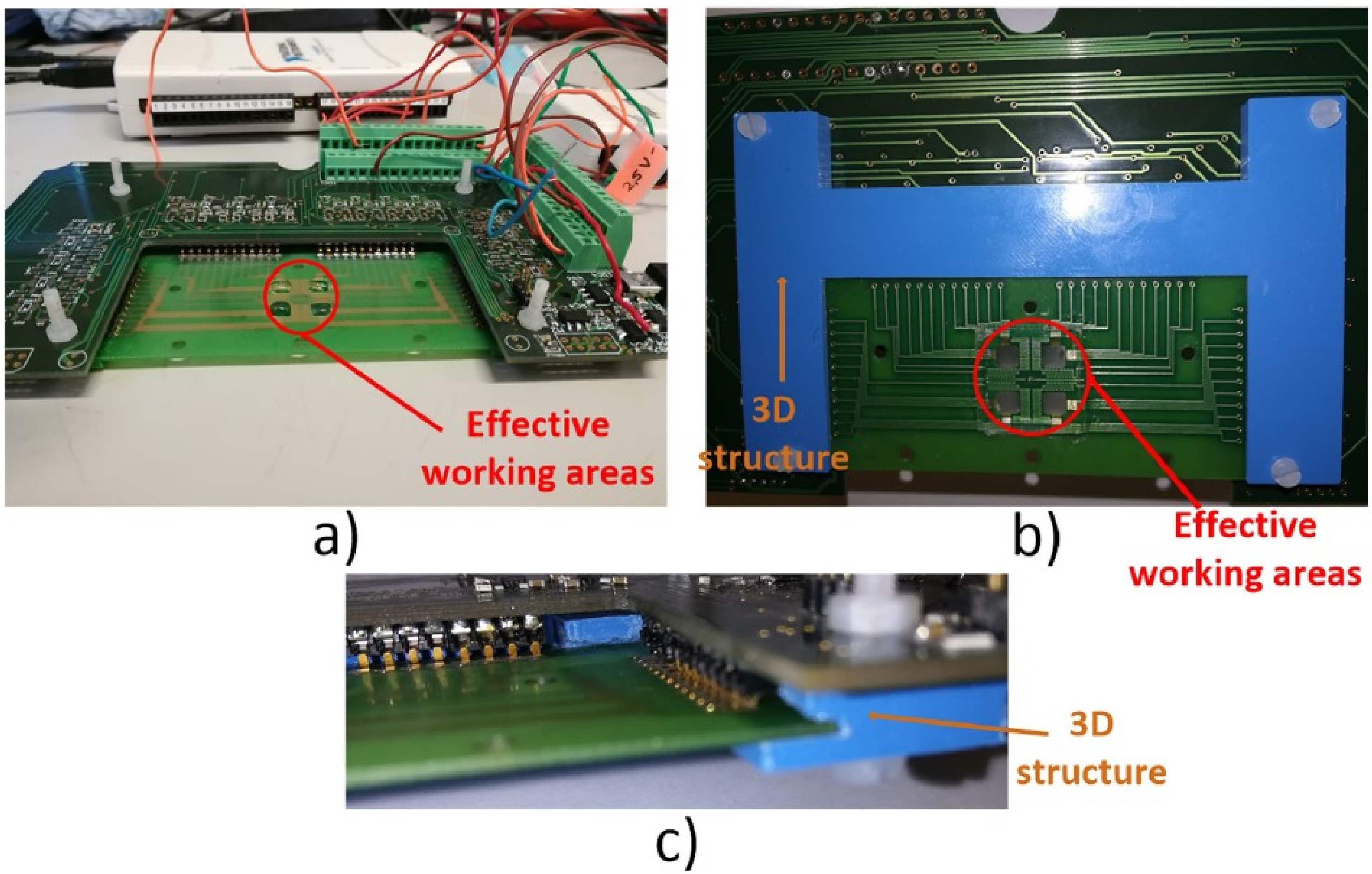


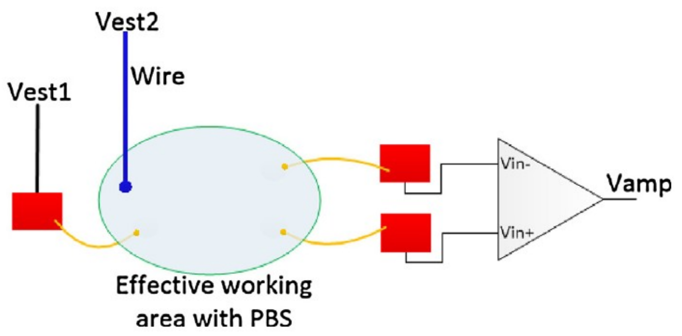

M. Cabello *et al.* Gold microelectrodes array embedded in PDMS for electrical stimulation and signal detection, Sensors and Actuators B 257 (2018) 954–962

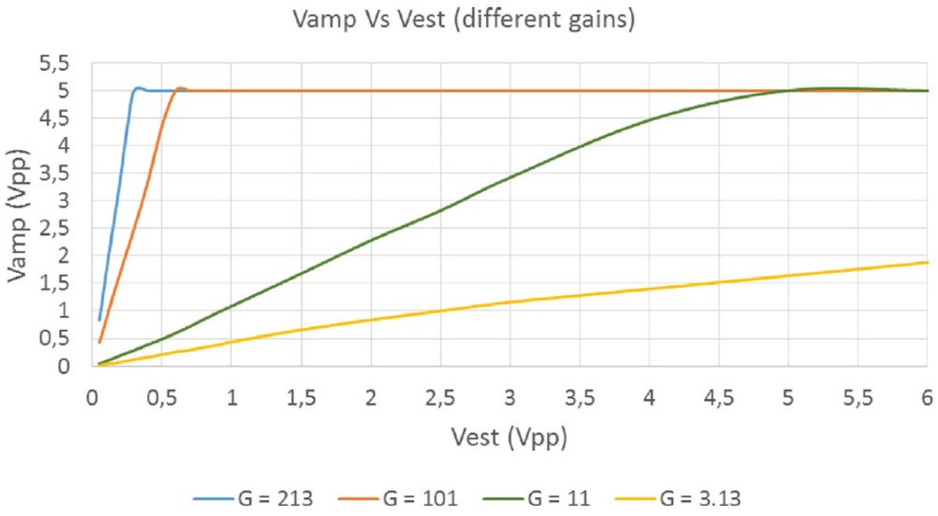
# Integration of electronics and fluidics

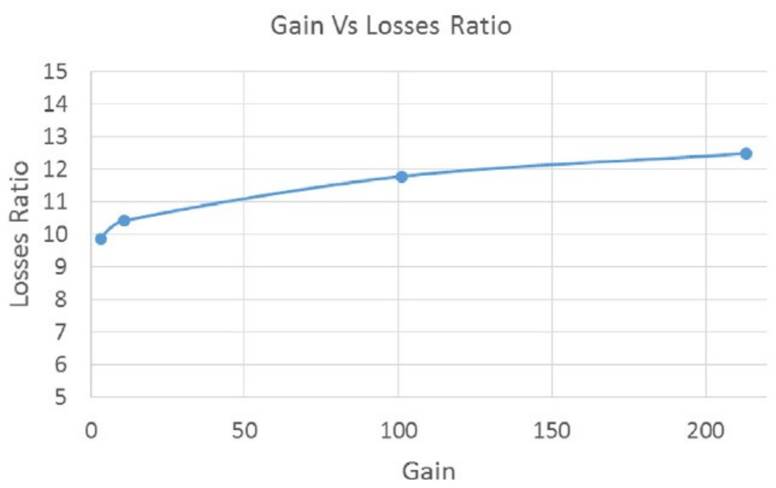
Controlled conditions of temperature, flow rate, and pH

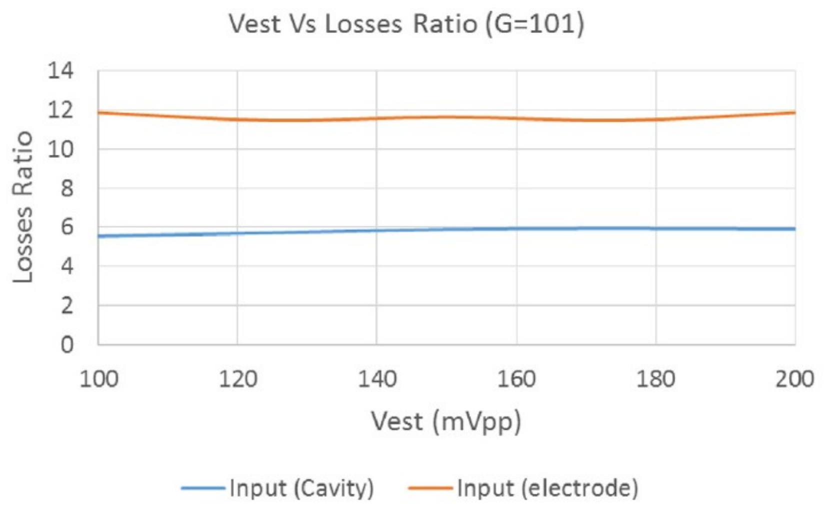


# Experimental results

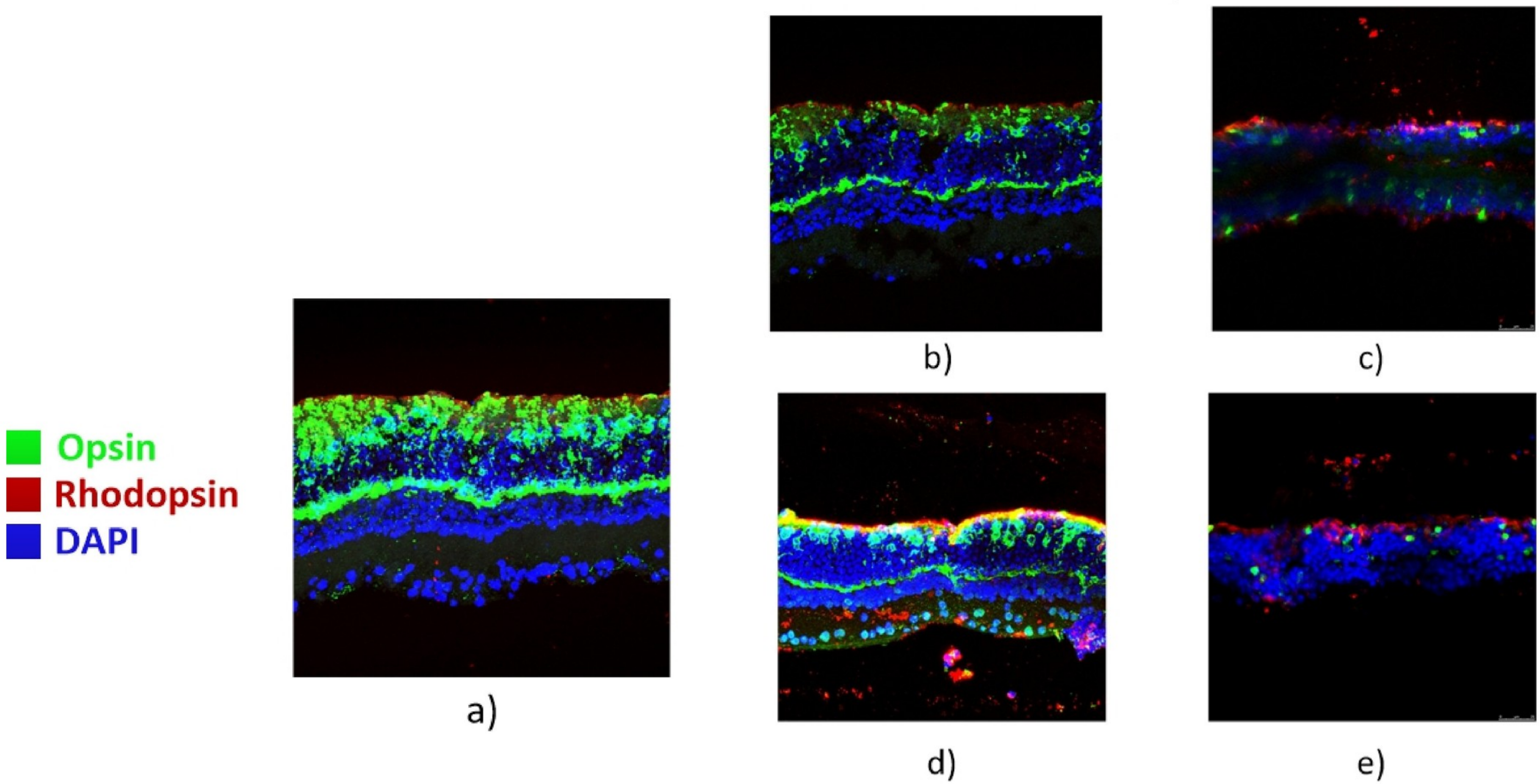


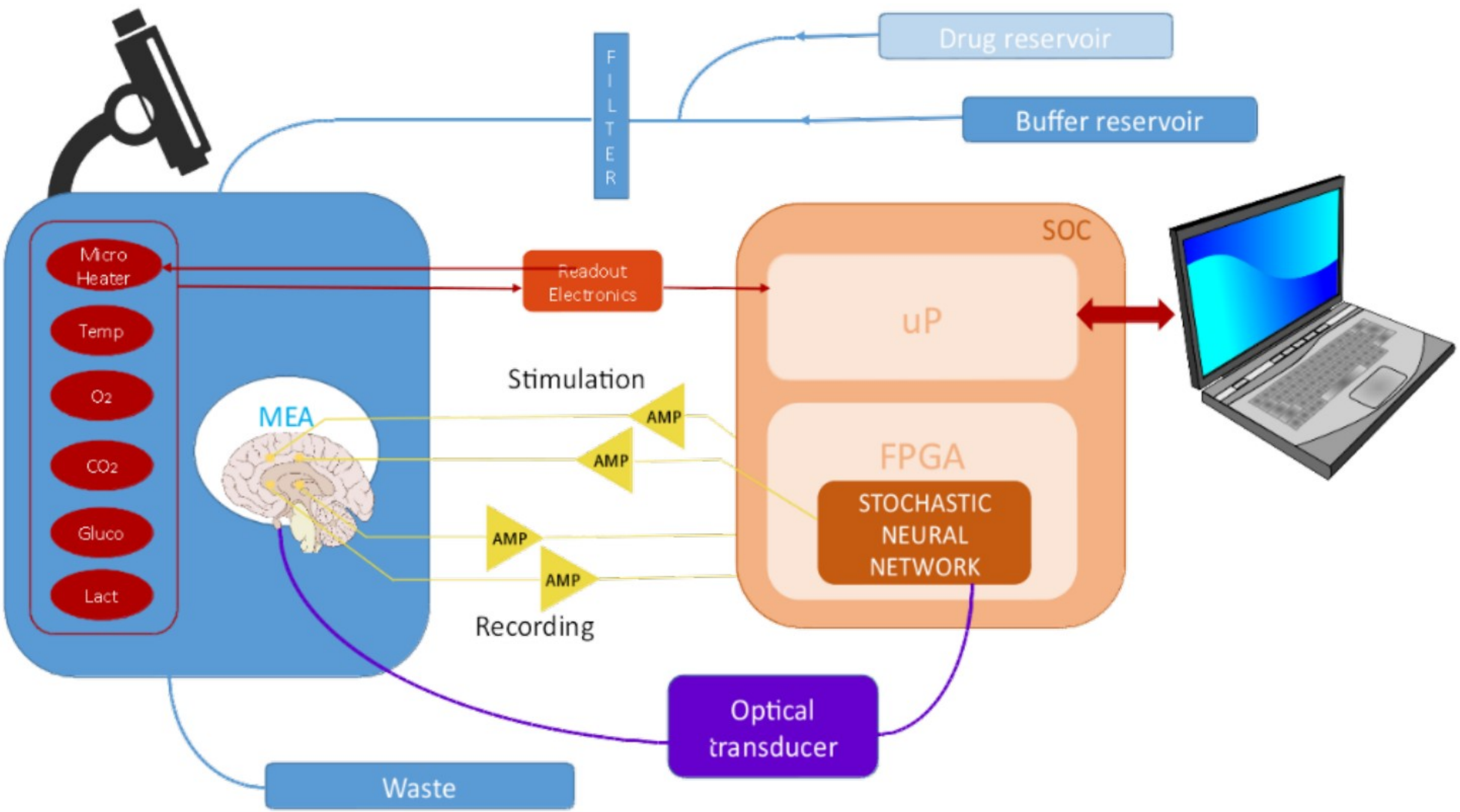



# Experimental results. Mice retina




Immunohistological study: (a) wild-type mice retina after its extraction; (b) wild-type mice retina after seven days of culture in a cell culture plate; (c) albino mice retina after seven days of culture in a cell culture plate; (d) wild-type mice retina after seven days of culture inside the MEA; (e) albino mice retina after seven days of culture inside the MEA.

# Proposed final system



# Conclusions

- It is possible to build simulators of tissues or organs and test drugs on them, using techniques developed for MEMS sensors and actuators
- Next steps:
  - Process signals and communicate with the organs-on-chip
  - Integrate them in half-bio / half-electronics systems
  - Customize to simulate conditions of a specific person

Thank you!