Clinical Lab of Biosensors

Never Stand Still | Faculty of Engineering | Graduate School of Biomedical Engineering

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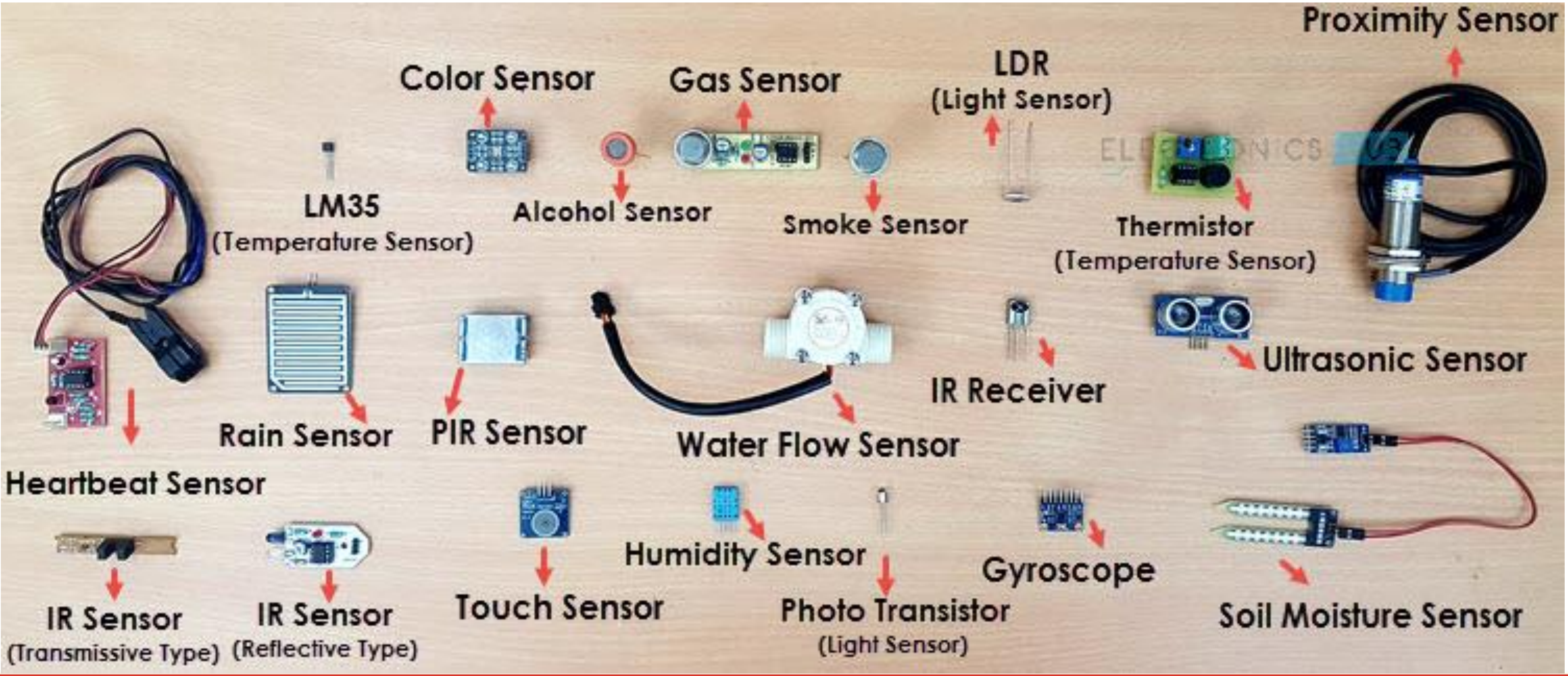
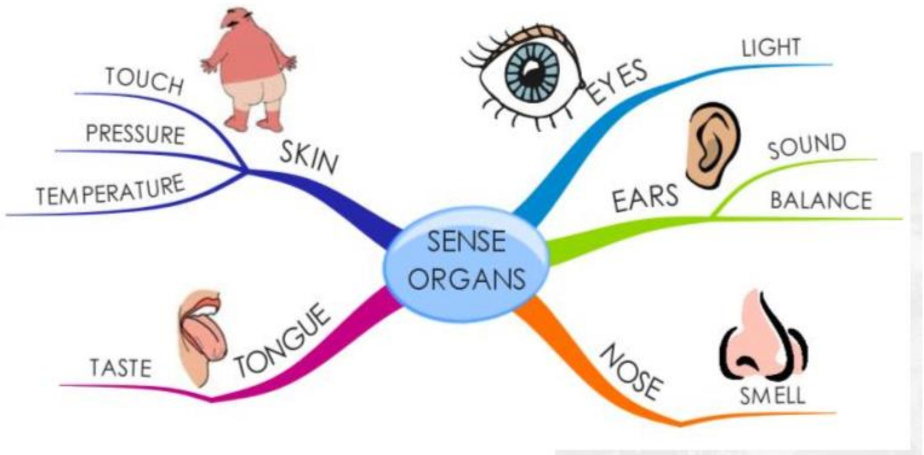
What are sensors?

A **sensor** is a device that detects and responds to some type of input from the physical environment.

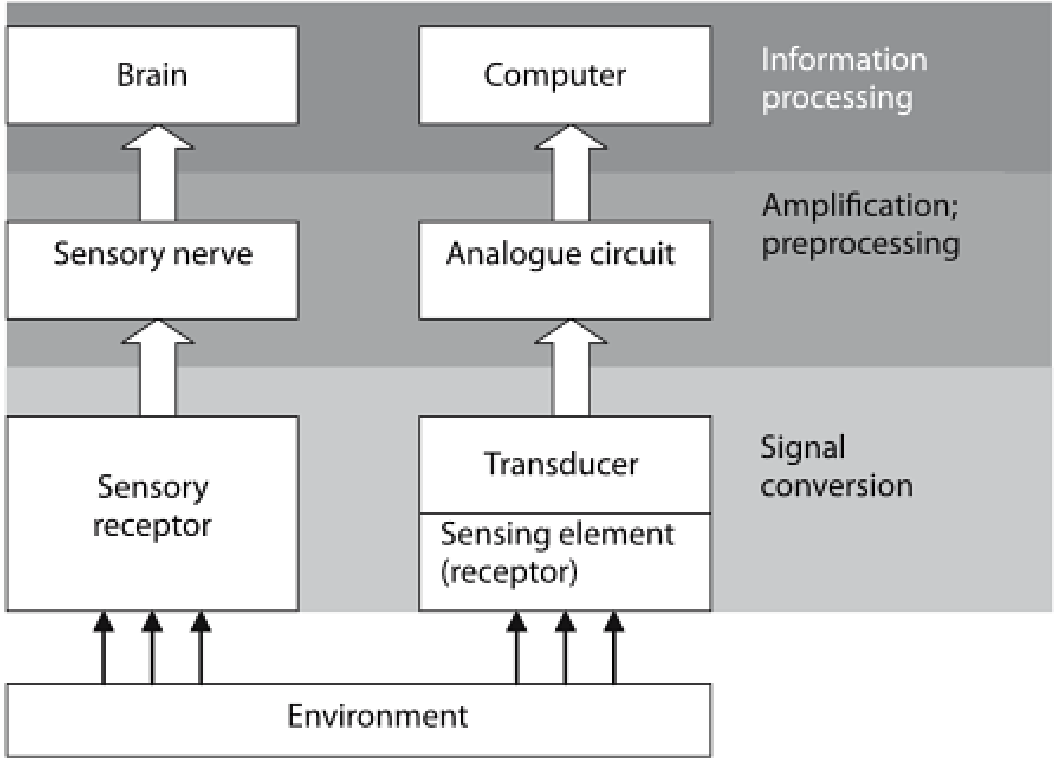
We live in a world of sensors!



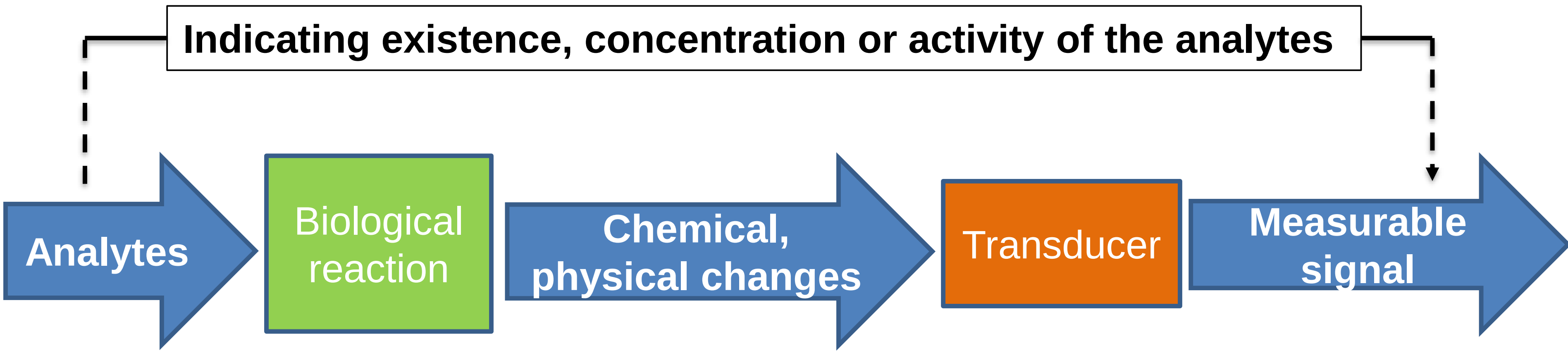


Human senses

General signal processing

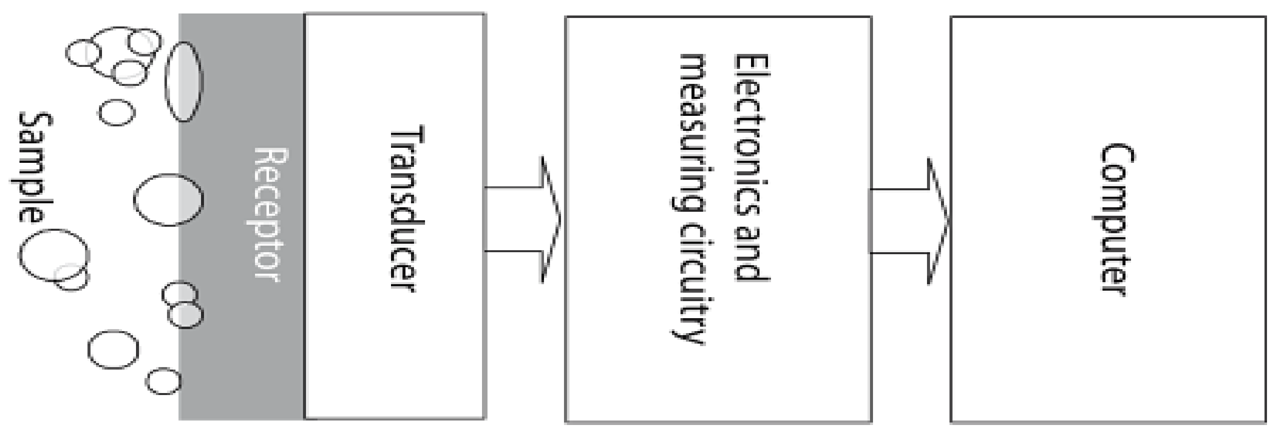


What are biosensors?



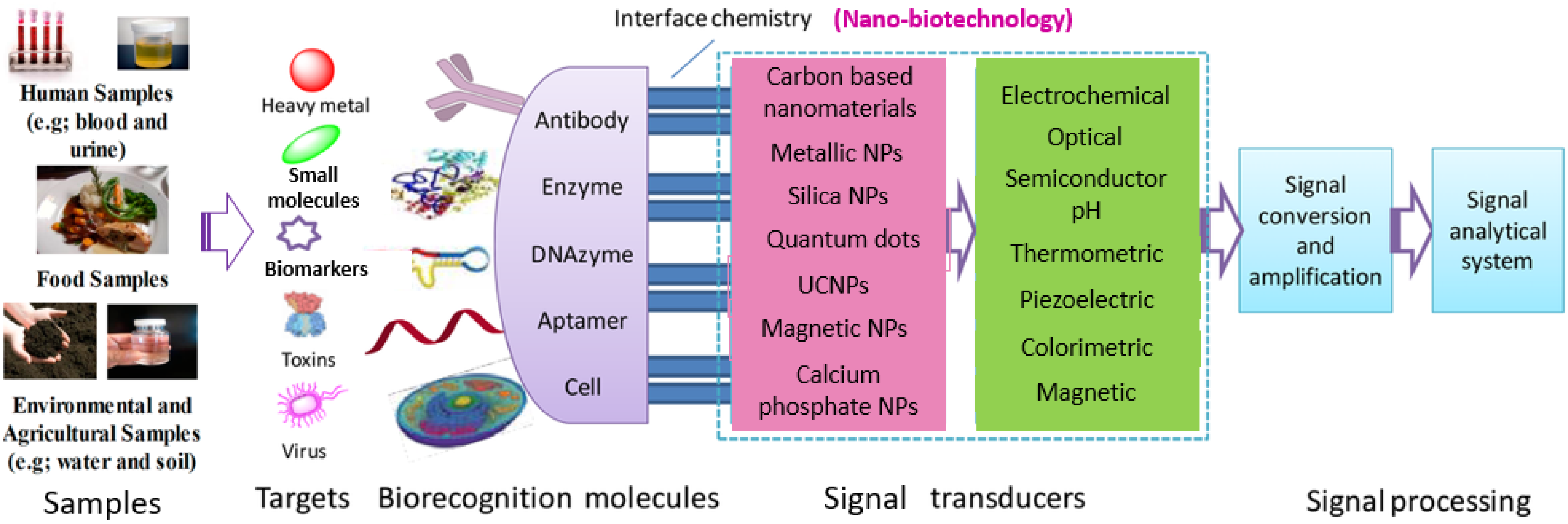
Biosensors comprise:

- Recognition element
- Transduction element
- Signal processor



What are biosensors?

Biosensors comprise: **Recognition element; Transduction element; Signal processor**



Classification of biosensors

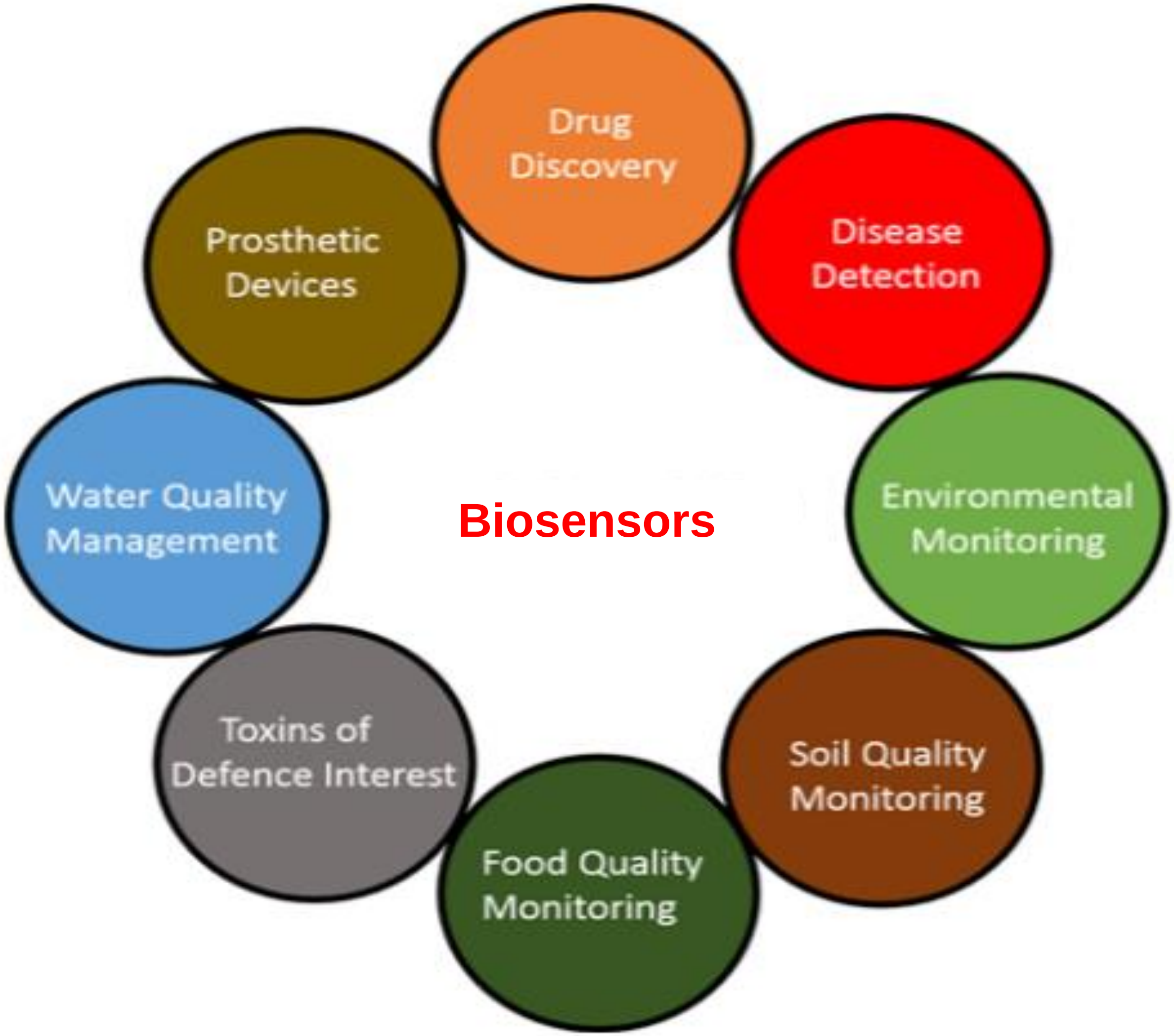
According to recognition molecules:

- **Enzyme sensors**
- **Immunosensors**
- **DNA/RNA sensors**
- **Molecular imprinted polymer based sensors**
- **Whole cell sensors**
- **Tissue sensors**
- **Intact sensors**
- **Microbial sensors**

According to Transducers:

- **Elelctrochemcial sensors**
- **Optical sensors**
- **Thermal sensors**
- **Magnetic sensors**
- **Mechanical sensors**
- **Acoustic sensors**
- **Piezoelectric sensors**
- **Semiconductor based sensors**

Application of biosensors



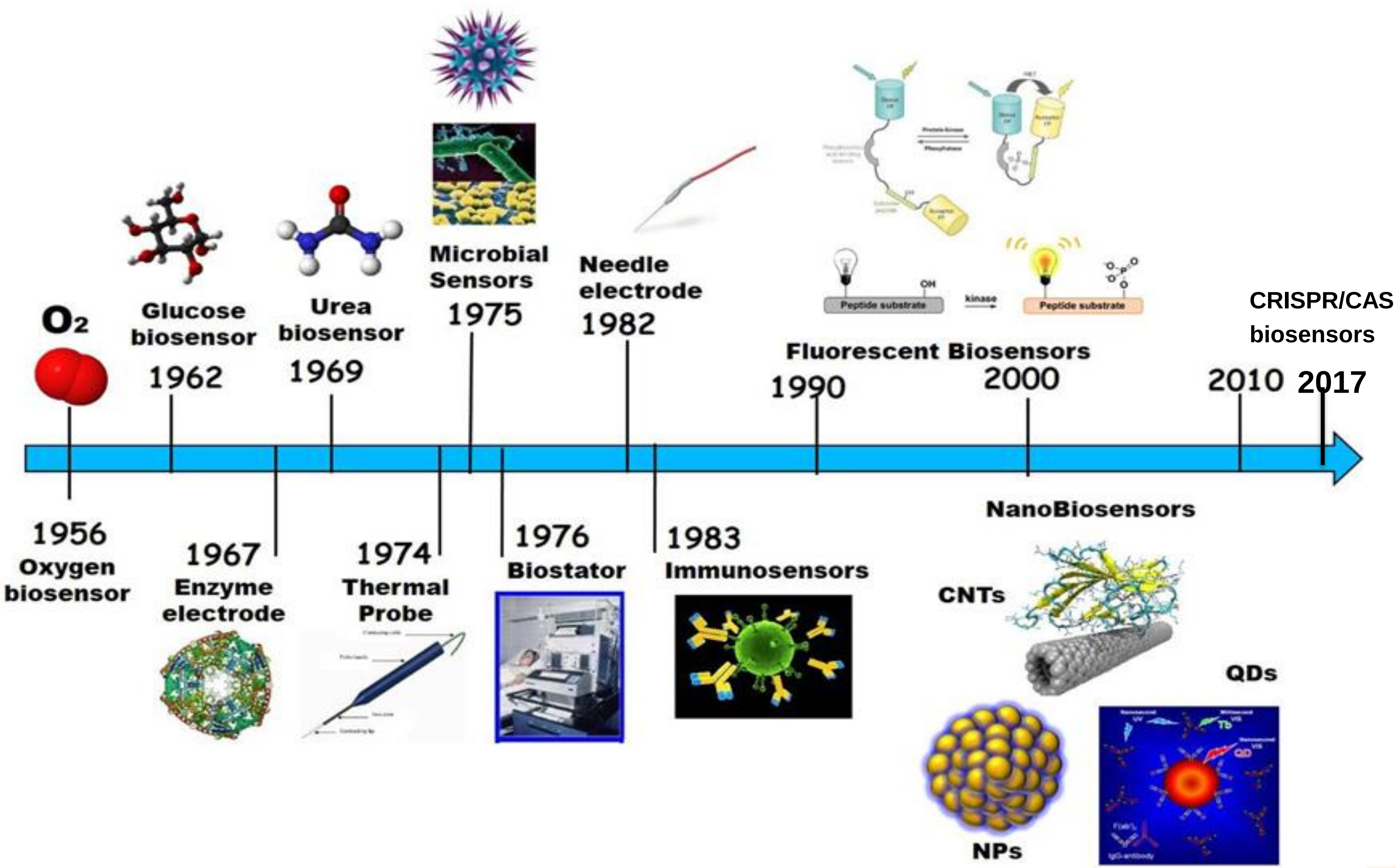
The most successful biosensors on the market

GLUCOSE METER

CGM

PREGNANCY TEST

Biosensor development timeline



Key performance of a biosensor

Sensitivity

Stability

Response time

Specificity

Selectivity

Linearity

Accuracy

Detection limit

Resolution

Characteristics of biosensors

The most important characteristics of biosensors are sensitivity, selectivity, accuracy and precision:

Sensitivity – relates to the change in measurement unit per concentration unit of the analyte. If concentration is low and variation is small measurement must be reliable, i.e. large change in signal.

Selectivity – relating to the analyte which is being measured. Only the analyte gives a signal, no interference by other species.

Reproducibility - the ability of the biosensor to generate identical responses for a duplicated experimental set-up.

Accuracy – an expression of the agreement between the measured result and the true result. Mean measured C = true C, no interference, no bias.

Precision – indicates that many values measured around a mean value have a small standard deviation.

Characteristics of chemical biosensors

Other important characteristics of chemical sensors include:

Detection limit – the lowest concentration value which can be measured by a given sensor under defined conditions.

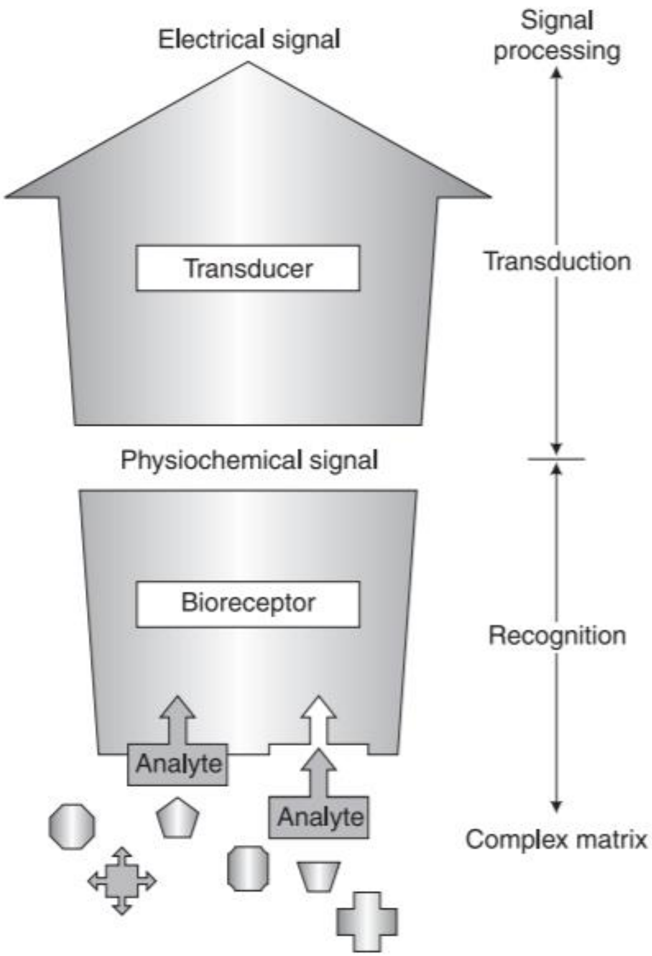
Dynamic range – the concentration values between the detection limit and upper limiting analyte concentration.

Resolution – the lowest concentration difference which can be distinguished when concentration is varied.

Response time – the time for a sensor to respond from a steady state concentration to a step wise deviation in concentration.

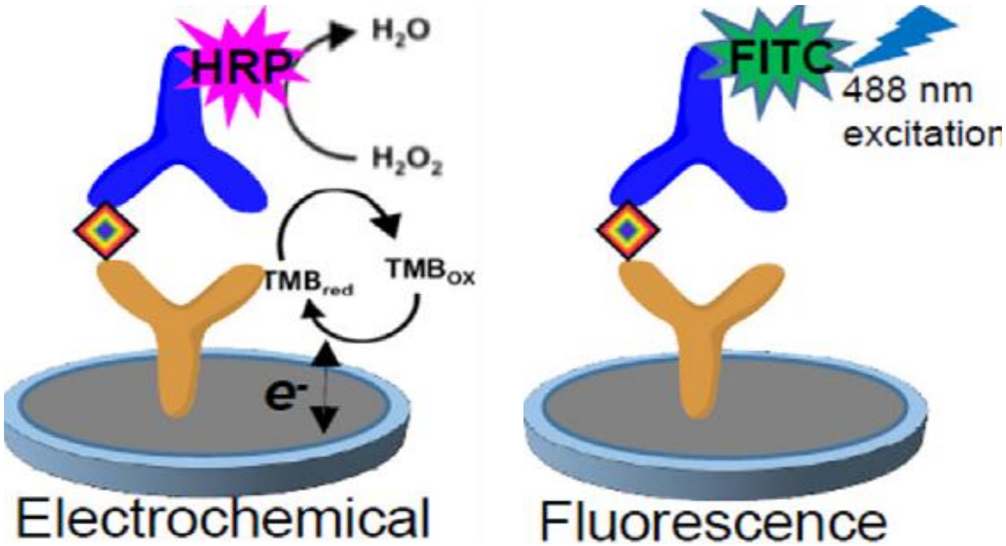
Stability – the ability for a sensor to maintain its performance for a given time, ie. without drift.

Sensing interface



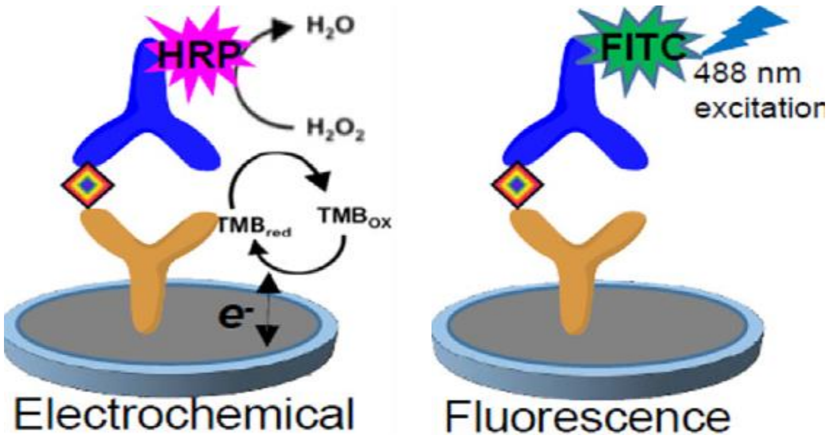
An effective sensing interface is expected to have have the following characteristics:

- select the bioreceptor
- be compatible with surface chemistry
- have good biocompatibility
- have big surface area to load large number of biorecognition molecules
- resist the non-specific protein adsorption
- provide the quick and selective signal response

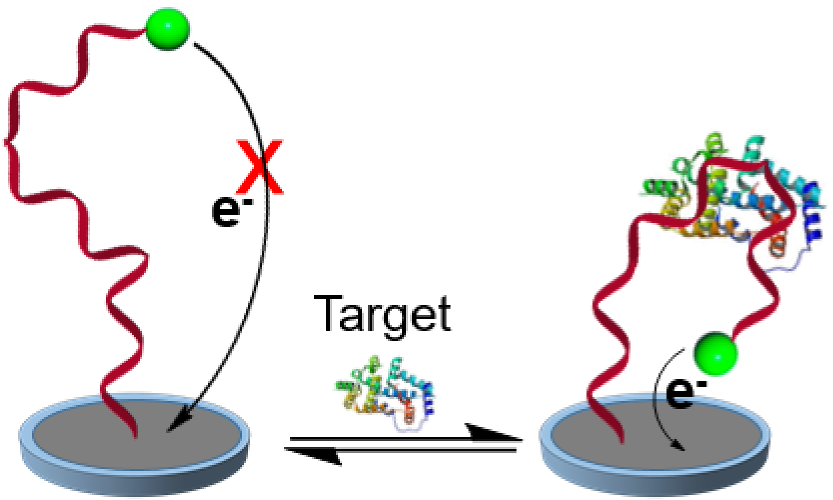


Structure switching signaling molecules for real-time sensing

Sandwich assay



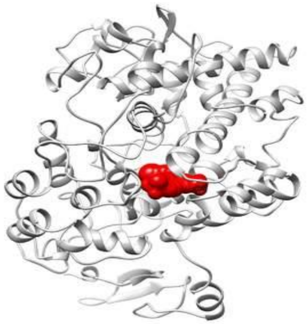
Real-time in vivo assays



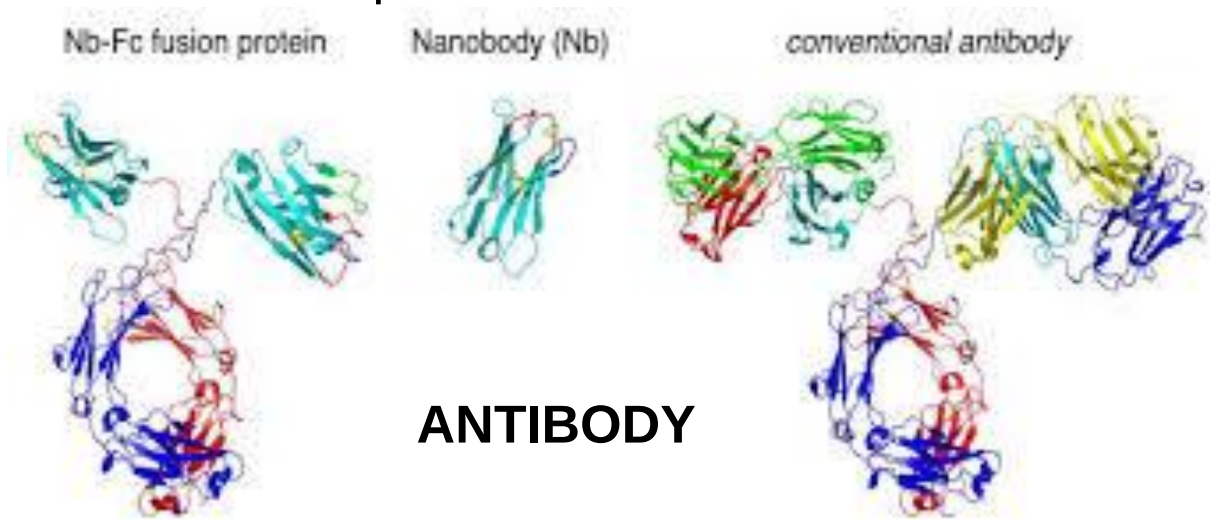
Plaxco, K.W., et al, Trends Biotechnol., 2011, 29(1), 1-5
White, R.J., et al. Annu. Rev. Anal. Chem. 2016. 9:163–81

Biorecognition molecules

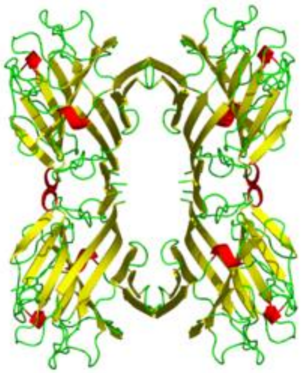
Bioreceptor molecules may be a protein such as an enzyme, antibody; a nucleic acid (DNA or RNA), antibody fragment, a whole microbial cell, even a plant or an animal tissue and microbial products.



ENZYME

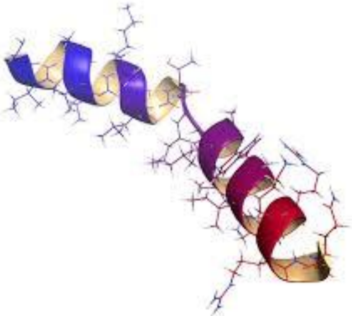


ANTIBODY

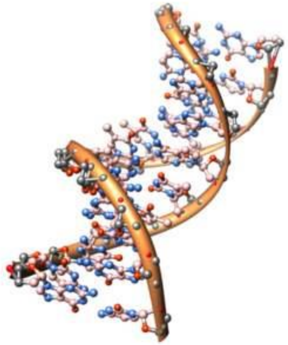


LECTIN

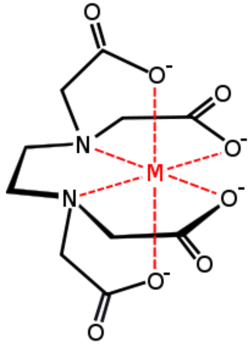
APTAMER



PEPTIDE

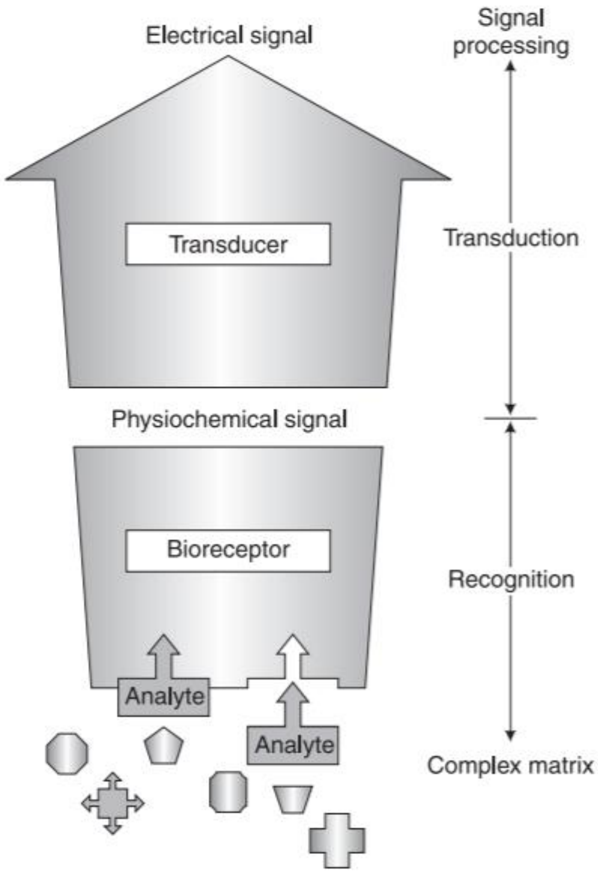


NUCLEIC ACID



LIGAND

Transducers



Transducer is a device that converts energy from one form to another form, for example, telephone companies use transducers to convert sound energy into electrical energy to be carried by long distance through telephone lines and then another transducer at the receiving end to convert the electrical energy back into sound.

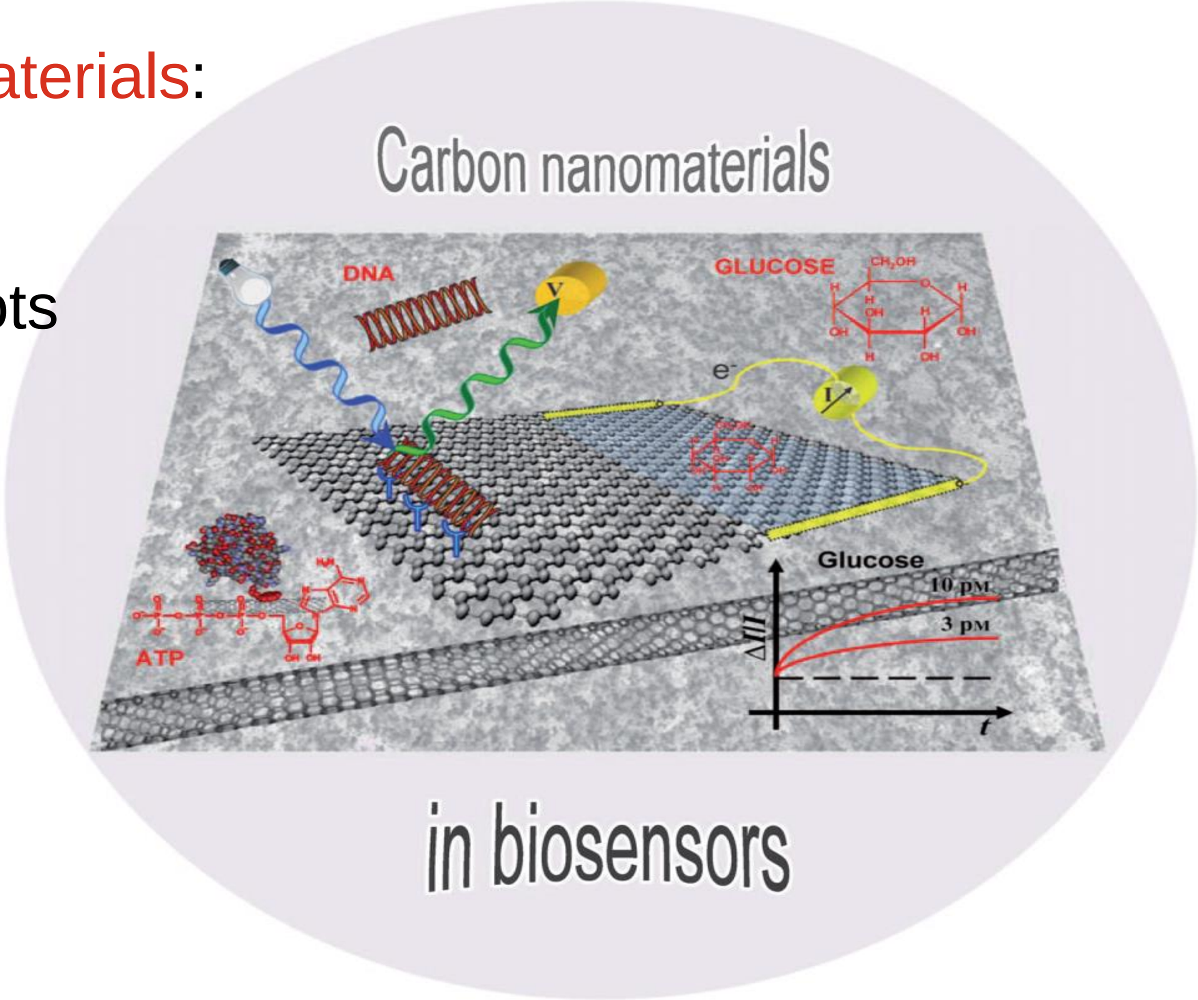
In biosensors transducers convert the biochemical activity into electrical energy. The transducer converts a biorecognition event into a measurable signal that correlates with the quantity or presence of the chemical or biological target.

… and the method of signal transduction allows the following groups to be defined:

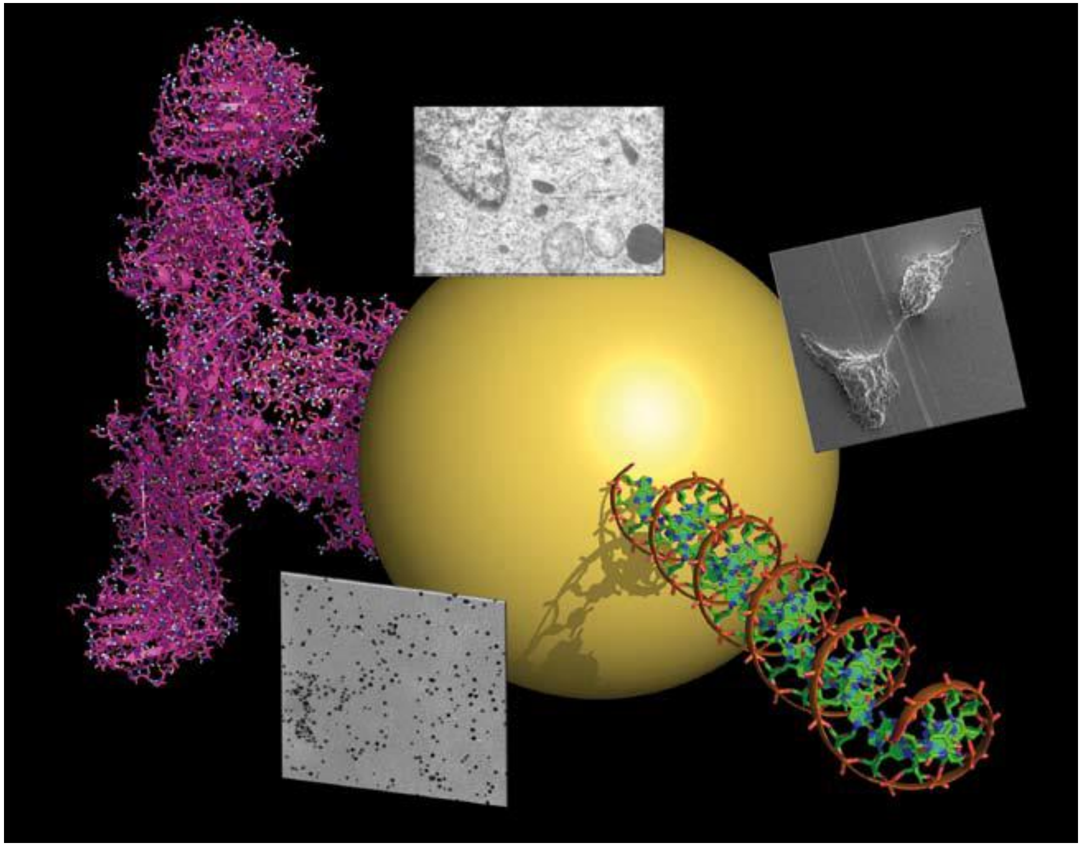
- **Optical sensors**
- **Electrochemical sensors**
- Mass sensitive sensors
- Magnetic sensors
- Thermometric sensors

Nanobiofabrication of sensing interface to load functional molecules

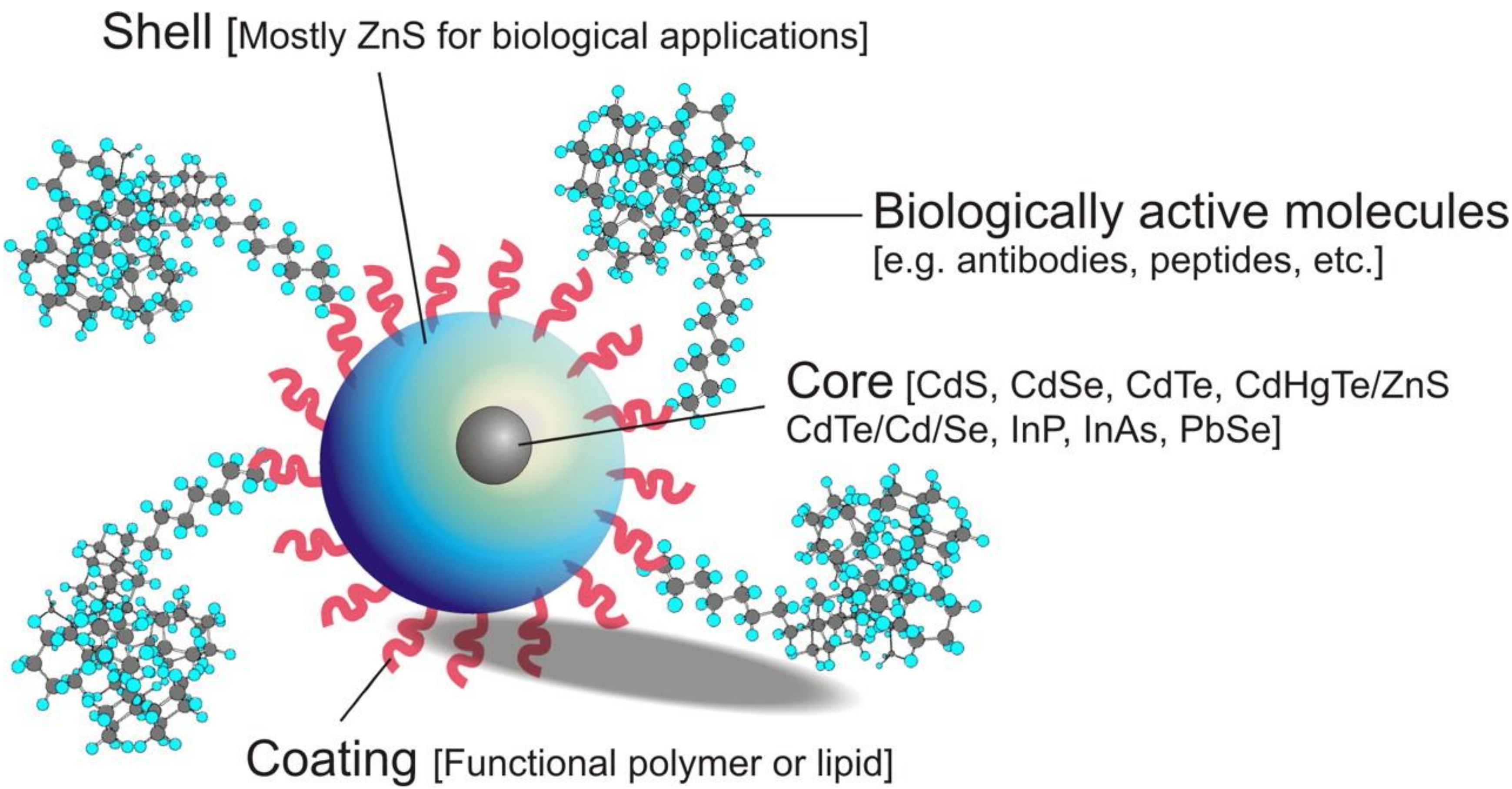
Carbon based nanomaterials:
Carbon naotubes
Graphene oxide
Graphene quantum dots
Carbon dots



Nanoparticles

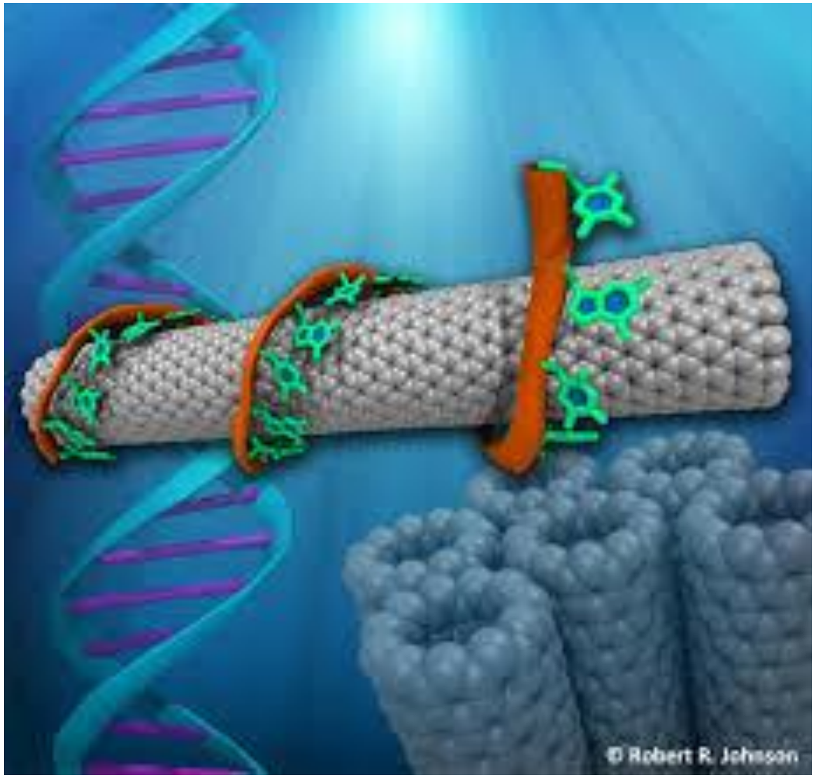


Gold nanoparticles

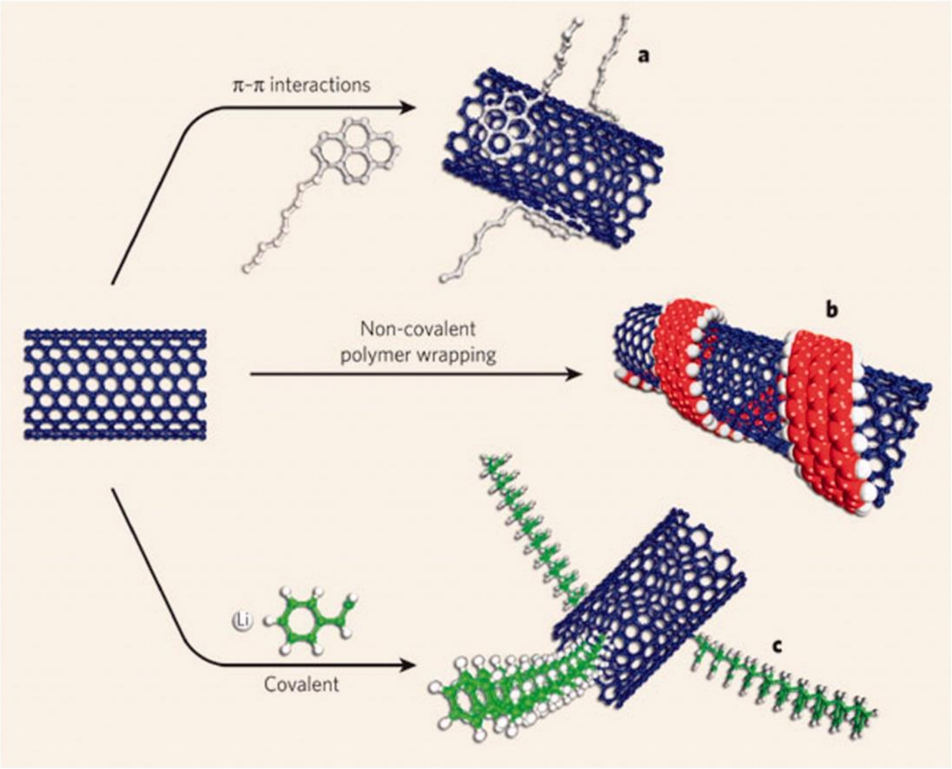


UNSW THE UNIVERSITY OF NEW SOUTH WALES

Carbon nanotubes

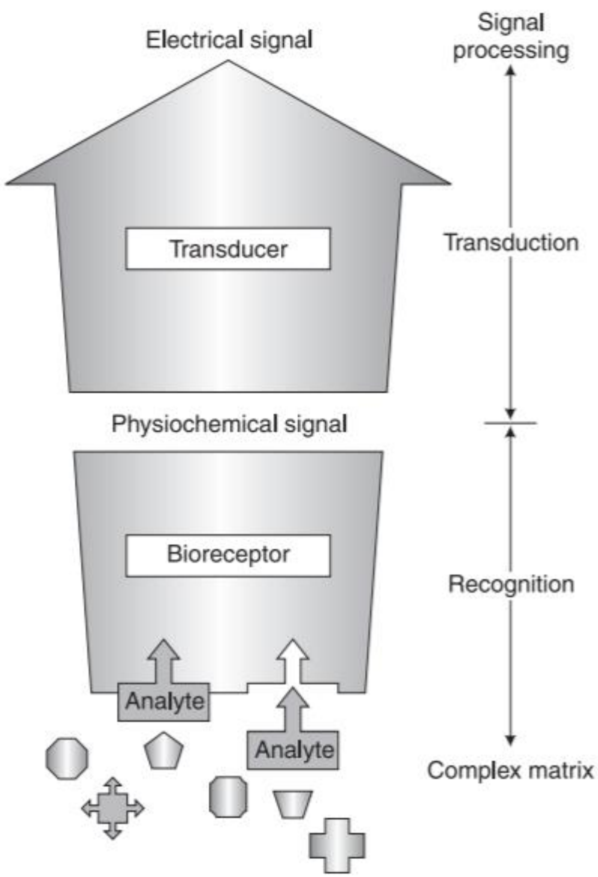


Surface modification of carbon nanotubes



Signal reporting in biosensors

Signal reporting



How can we measure concentration?

There are many ways to measure concentration, but the most important biomedical applications are:

Spectrophotometry (Optical): Measure analyte X directly through its interaction with light, such as fluorescence or color

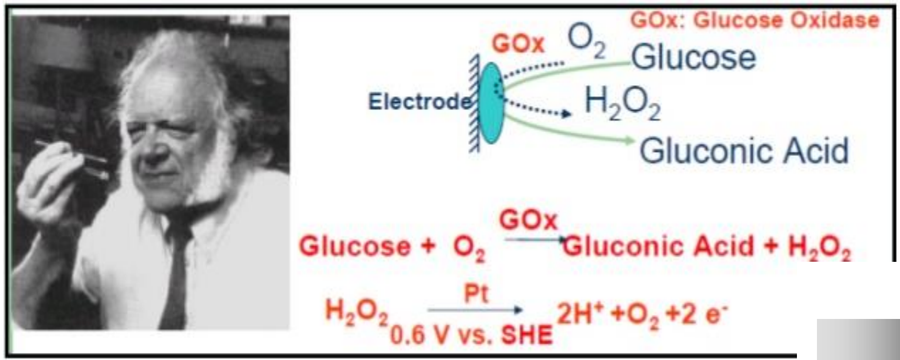
Potentiometry (Electrochemical) - Measuring the electromotive force (EMF) which is related to the concentration of X

Amperometry (Electrochemical) - Measuring the current related to the rate of oxidation or reduction of X at an electrode which is related to the concentration of X

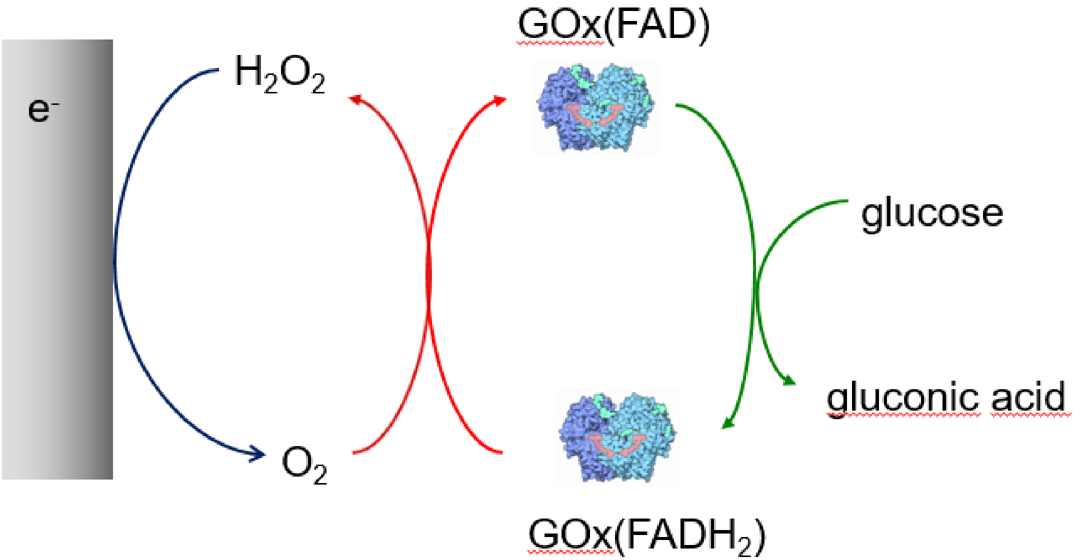
Amperometric glucose sensor

FATHER OF BIOSENSORS

Professor Leland C Clark (1918–2005)



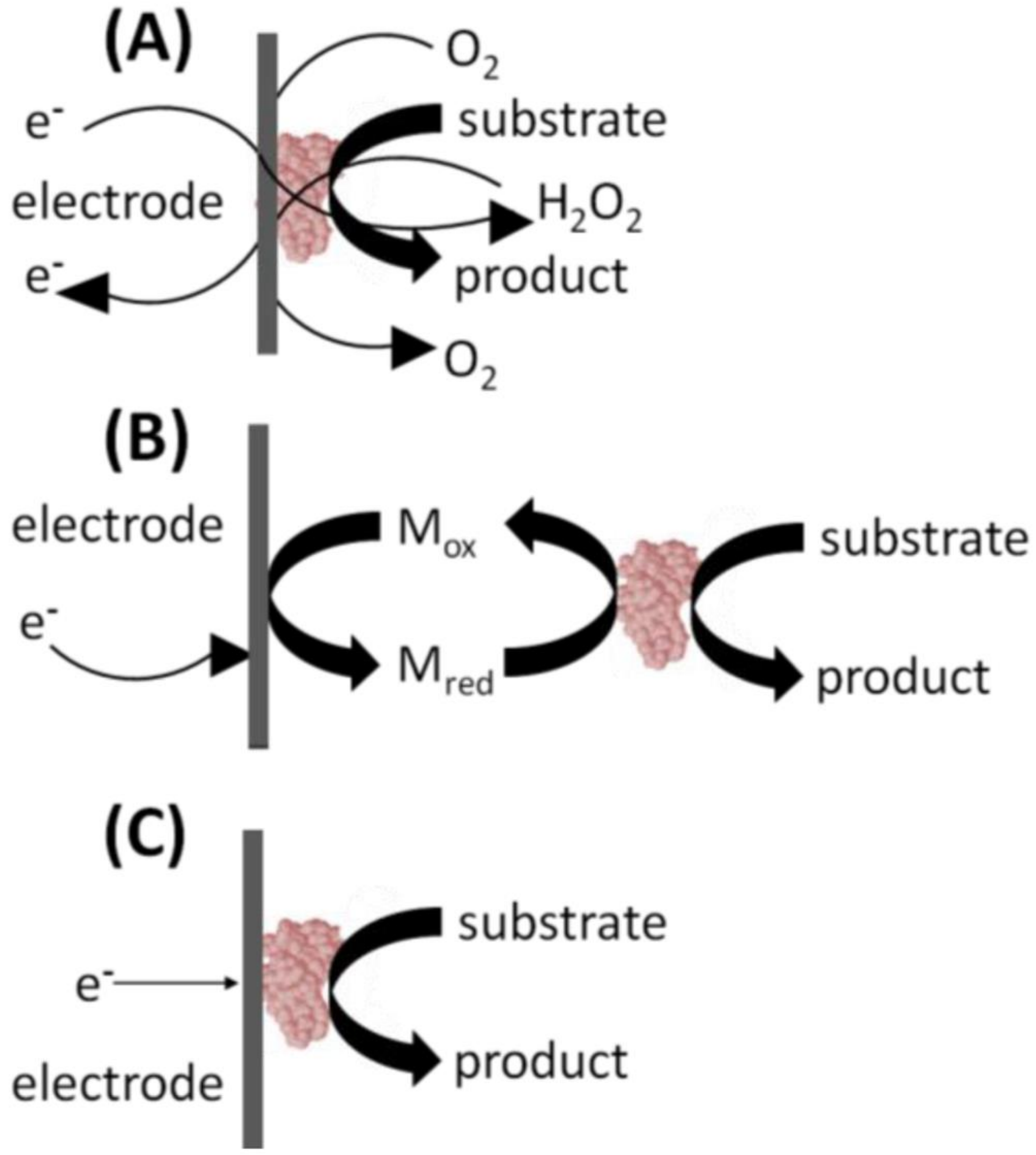
The first and the most widespreadly used commercial biosensor: the glucose biosensor – developed by *Leland C. Clark in 1962*



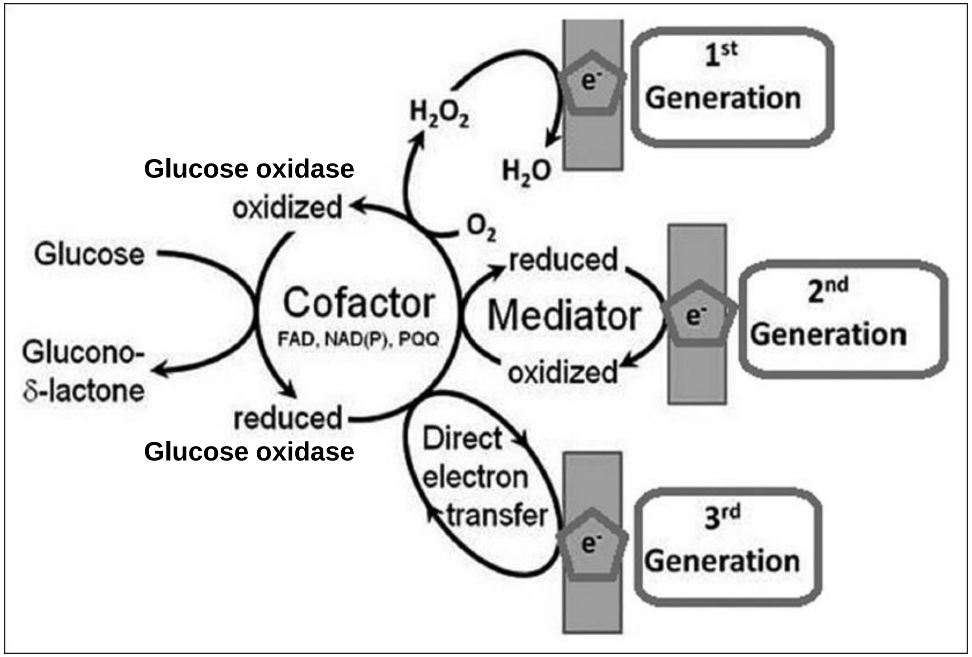
+0.7 V vs Ag/AgCl

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3292132/

Three generation of glucose biosensors:



Glucose biosensors



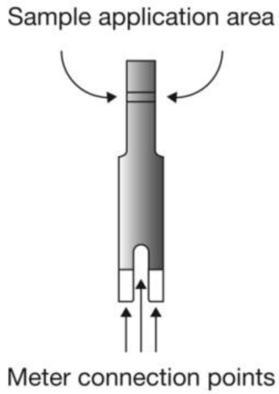
Major drawbacks of the 1st generation glucose biosensor

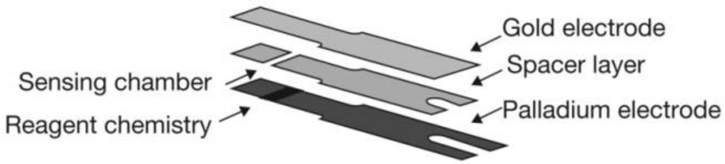
- Amperometric measurement of hydrogen peroxide required a high operating potential (0.6 V) for high selectivity.
- Restricted solubility of oxygen in biological fluids, which produced fluctuations in the oxygen tension.
- Deactivation of the enzyme due to the production of hydrogen peroxide.

Major drawbacks of the 2nd generation glucose biosensor

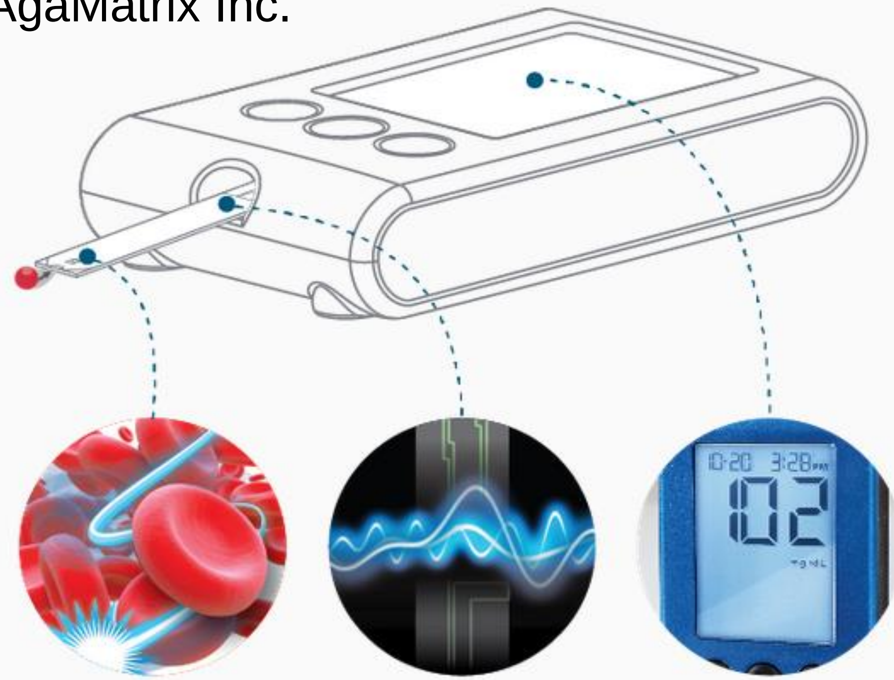
- High competition between redox mediator and oxygen.
- Interference of other electroactive species lead to false and inaccurate results.
- Small size and highly diffusive nature of mediators poses problem of leaching of mediator from intermediate region between enzyme and electrode surface.

Glucose test strips





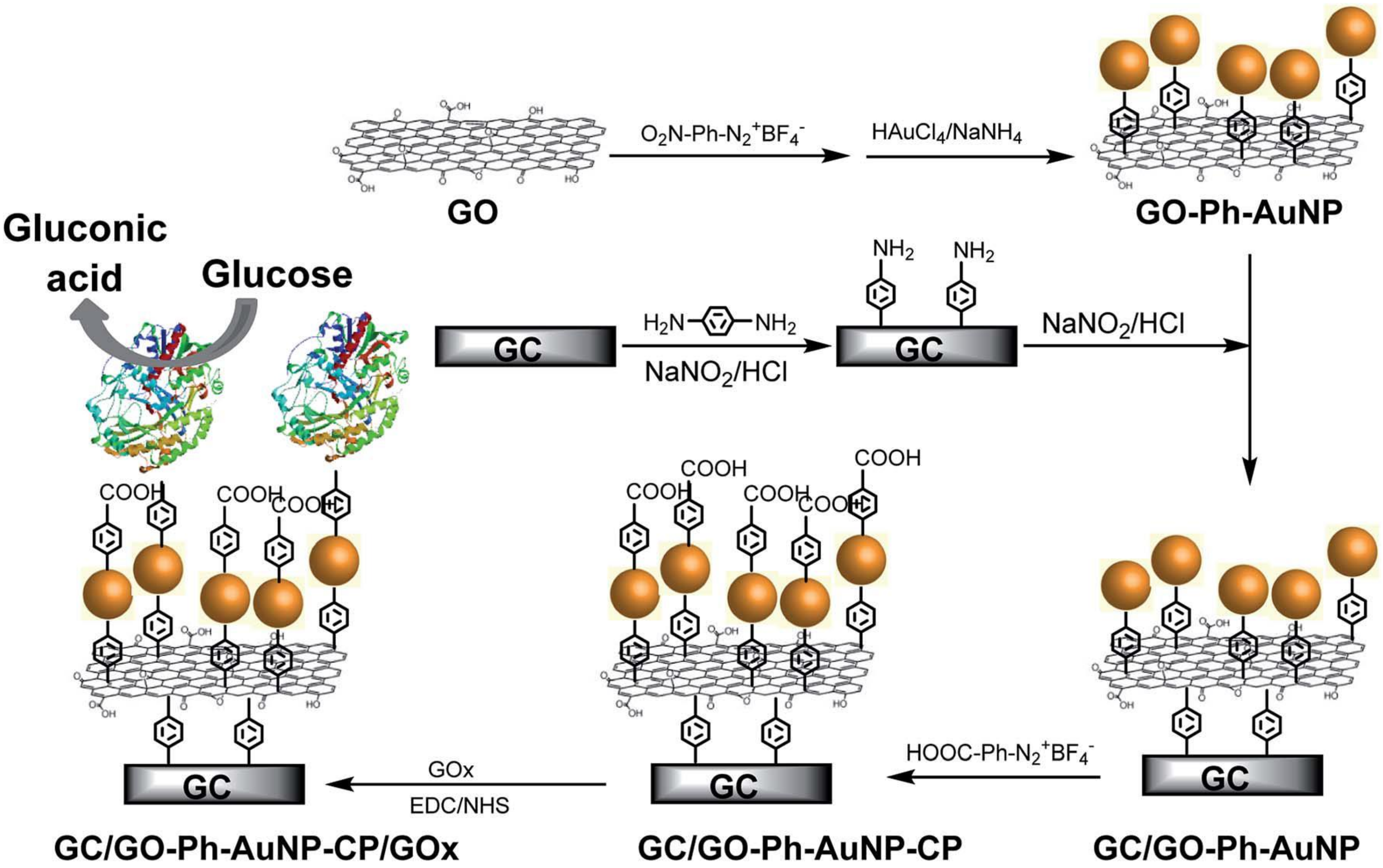
AgaMatrix Inc.



How WaveSense Works

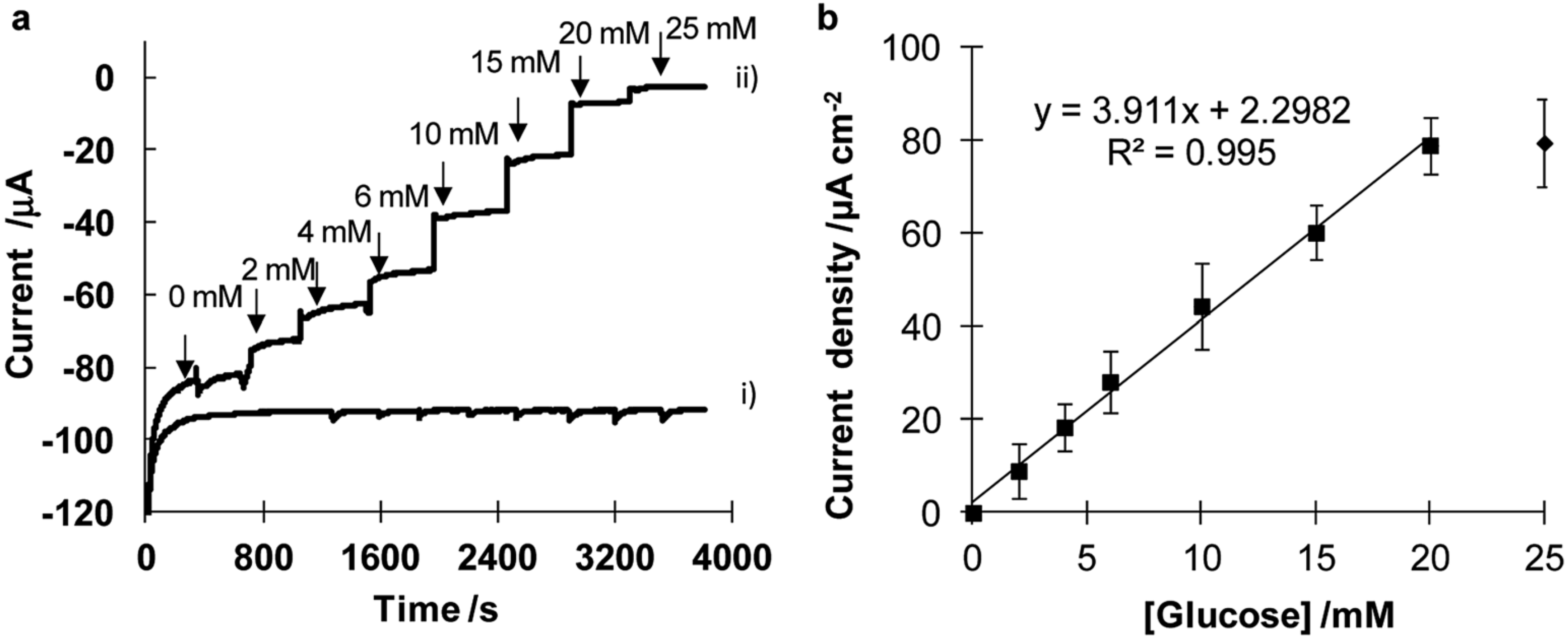
1. Glucose reacts with an enzyme in the test strip.
2. Complex electrical signals are sent from the meter into the test strip and back.
3. The meter accurately detects the glucose signal by removing common sources of interference and displays a result.

An example of a glucose biosensor



G. Liu, et al. RSC Adv., 2016, 6, 39180–39187

An example of a glucose biosensor



G. Liu, et al. RSC Adv., 2016, 6, 39180–39187

Nanoparticle based biosensors

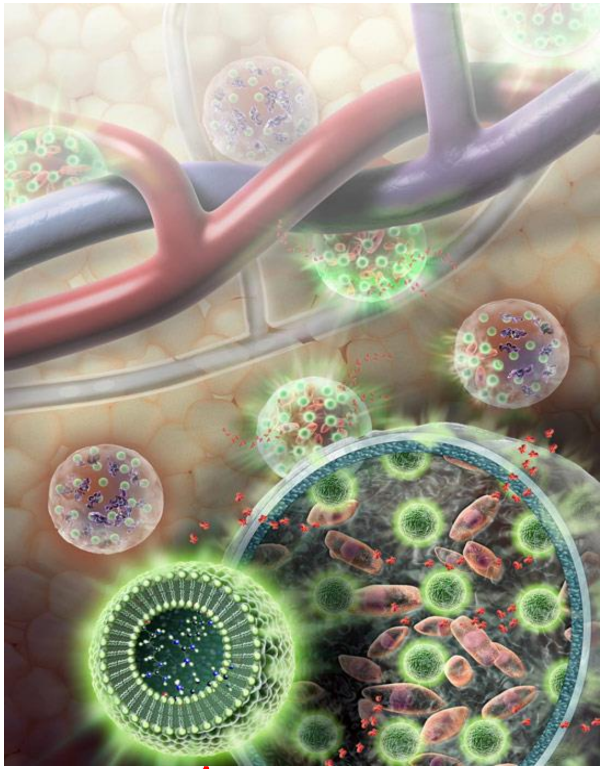
Nanosensors: the future of diagnostic medicine?

✓What are nanosensors?

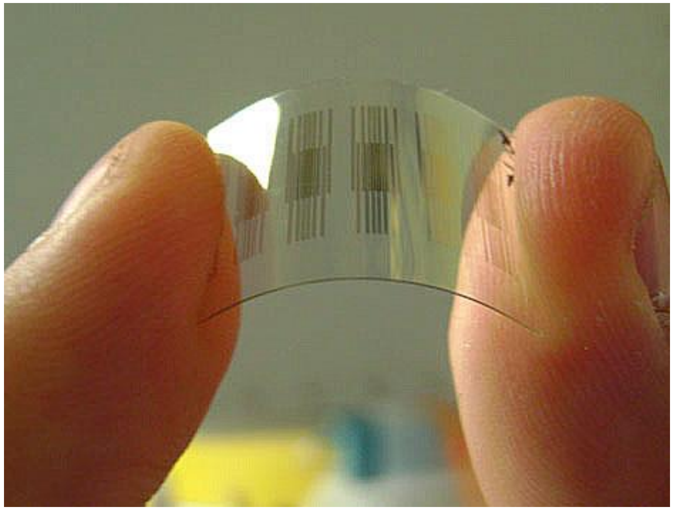
- Biological, chemical, or physical sensory points used to convey information about nanoparticles to the macroscopic world

✓Why nanosensors?

- Small size (<100 nm)
- Able to monitor physical and chemical phenomena in regions difficult to reach
- Able to detect biochemicals in cellular organelles
- Less power required to work
- Greater sensitivity
- Better specificity



A nanosensor



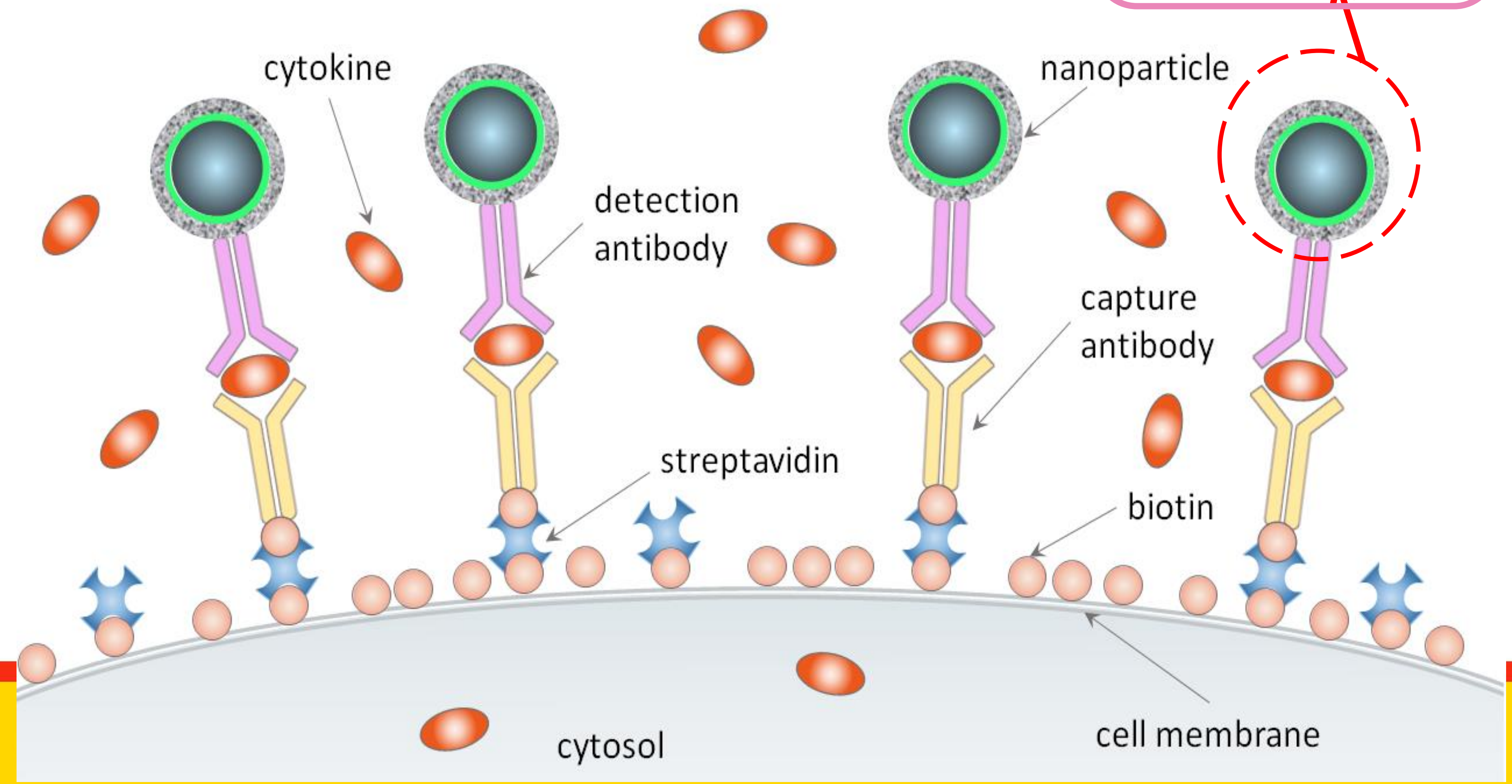
A nanosensor based device

P. D. Howes et al, Science, 2014, 346:1247390, 1-9.

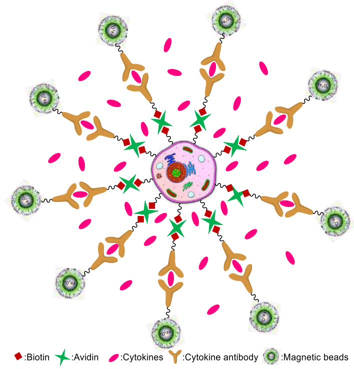
The on cell surface ELISA (OnCELISA)

✓Big surface area
✓Carboxylated
✓Fluorescent
✓ being magnetic
✓Commercial available

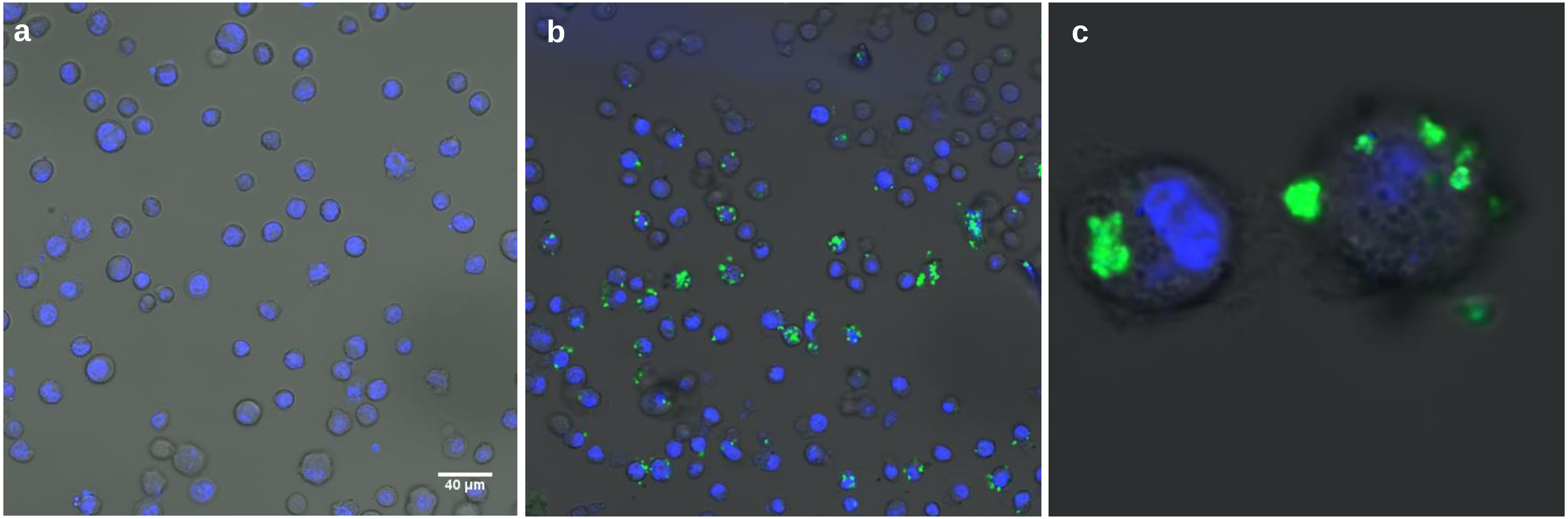
G. Liu, E. Goldys, A. Anwer, Australia Patent (2015904826)



Application of OnCELISA for BV2 cells

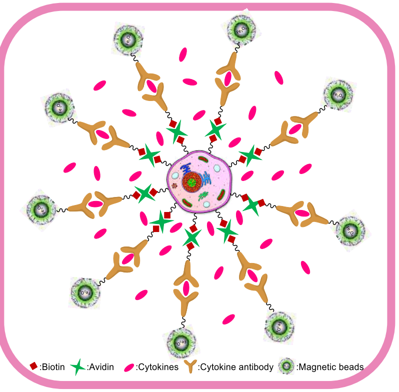


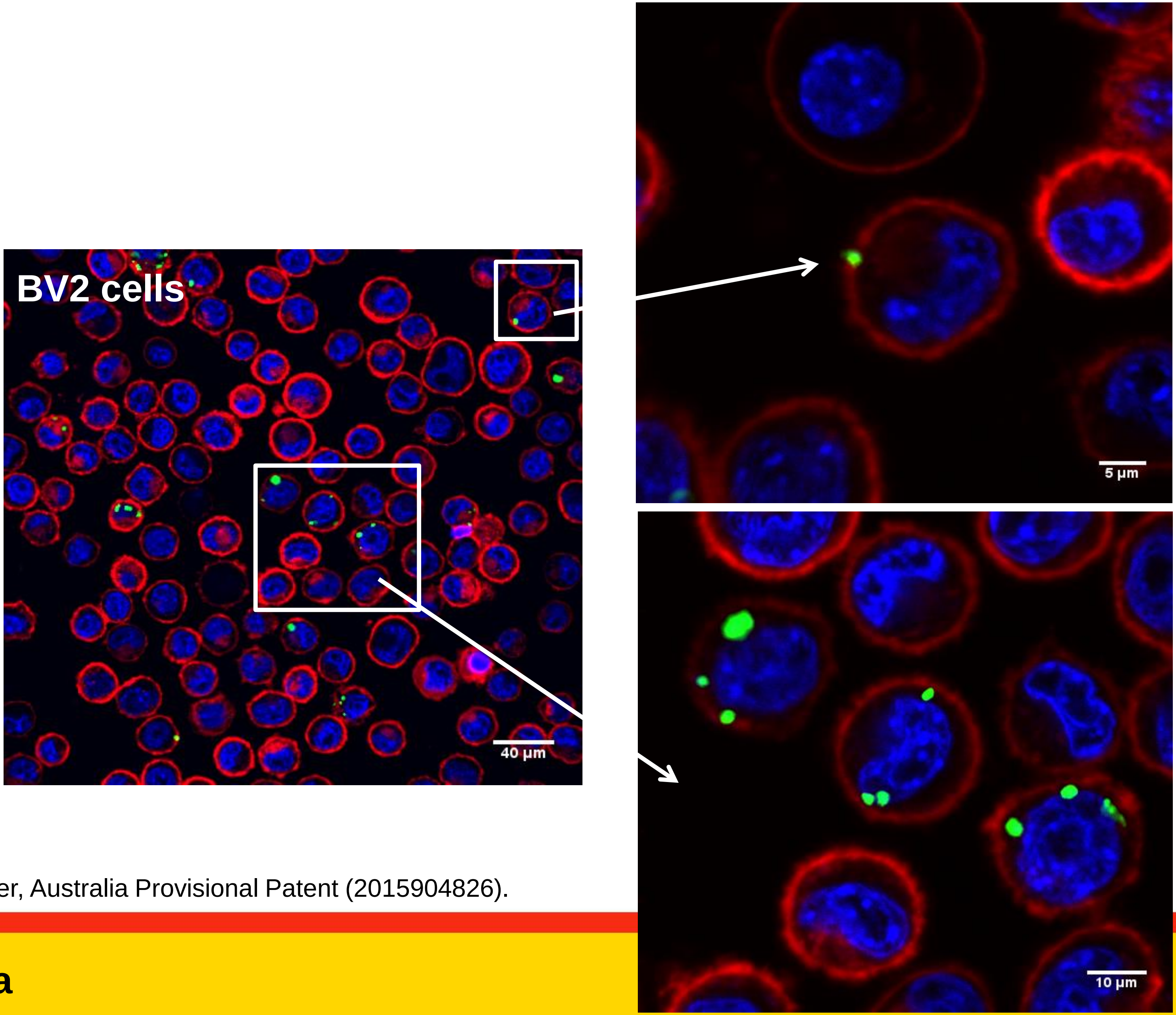
OnCELISA



Application of OnCELISA to BV2 cells with 6 h LPS stimulation (a) before and after treatment with (b,c) DG SPIO_IL-6_Ab at different magnifications

Does OnCELISA happen on the cell surface?





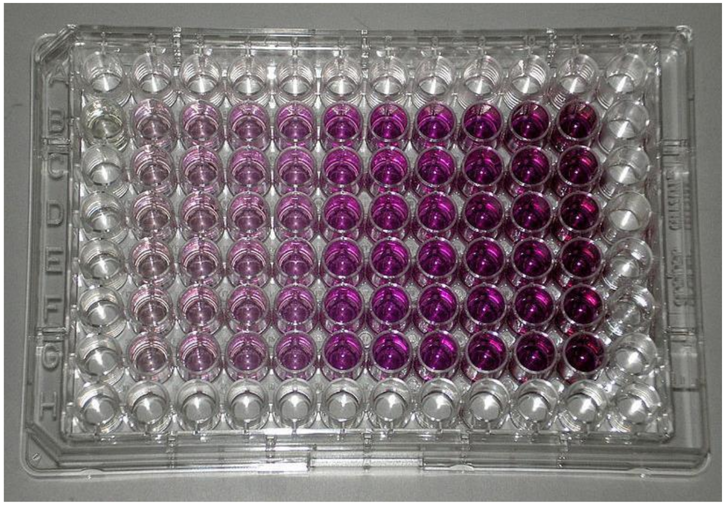
G. Liu, E. Goldys, A. Anwer, Australia Provisional Patent (2015904826).

Unpublished data

Disposable biosending devices

Paper based deployable devices

ELISA



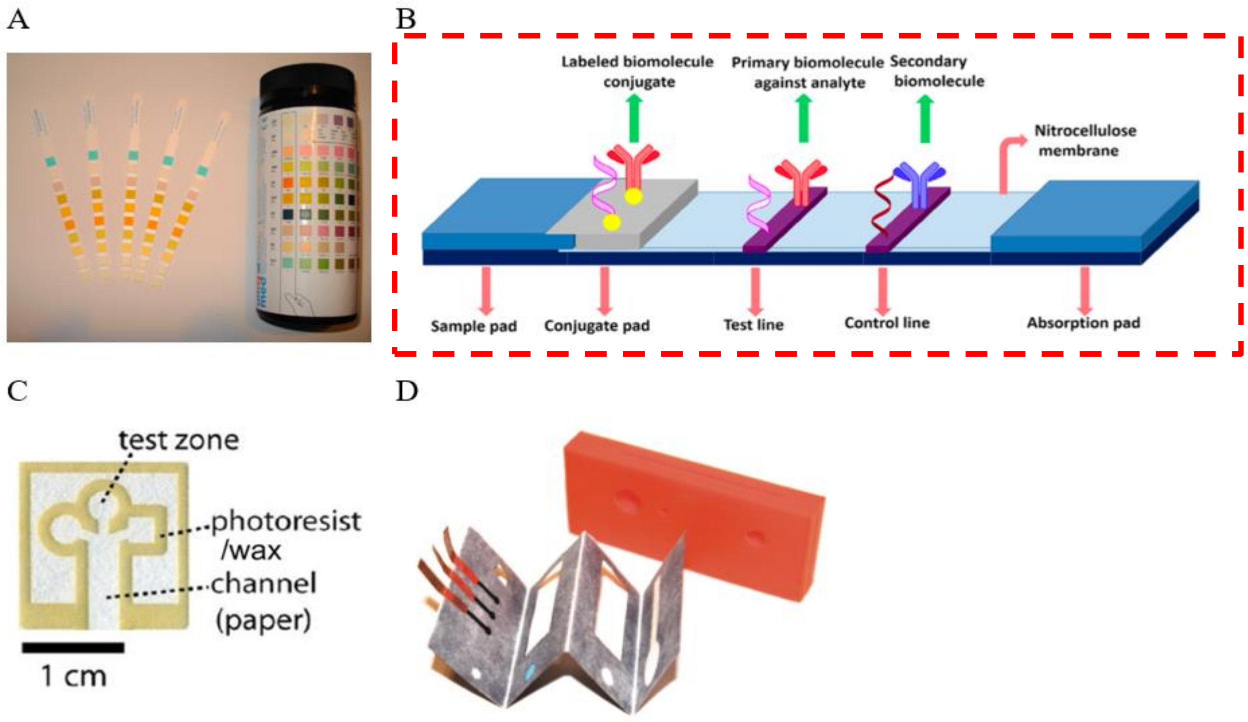
Paper based device

Smartphone
or
Glucose meter
Readout

Human
vs
Animal

Health care
Environment monitoring
Food safety and Security

Different types of paper based analytical devices (PADs)

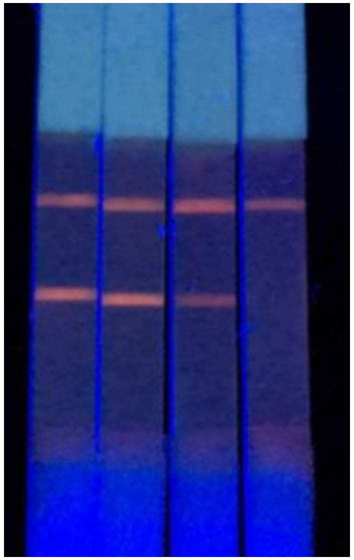


A: Photo of dipstick assays. B: The structure of a basic lateral flow assay in a sandwich format. C: Photo of a 2D μPAD. D: Photo of an electrochemical μPAD called NoSlip and its 3D-printed holder.

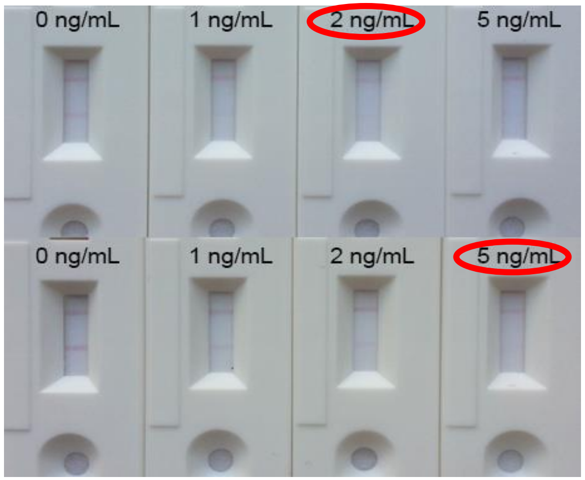
Paper based lateral flow assay

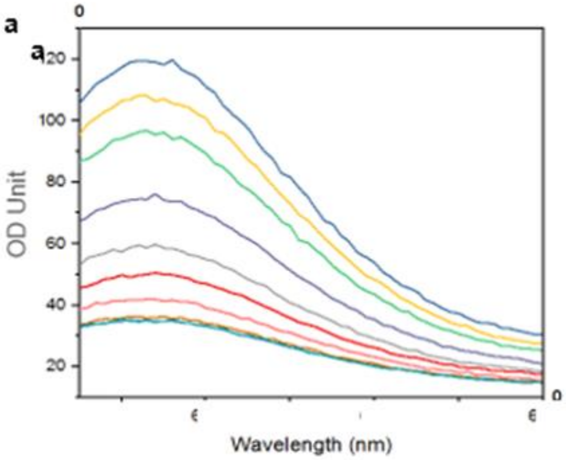
Emerged for the first time at the end of the 1960s for the first time, being used of monitoring of serum proteins. The first homemade LFA was performed in 1976 to detect human choronic gonadotropin (hCG) in urine.

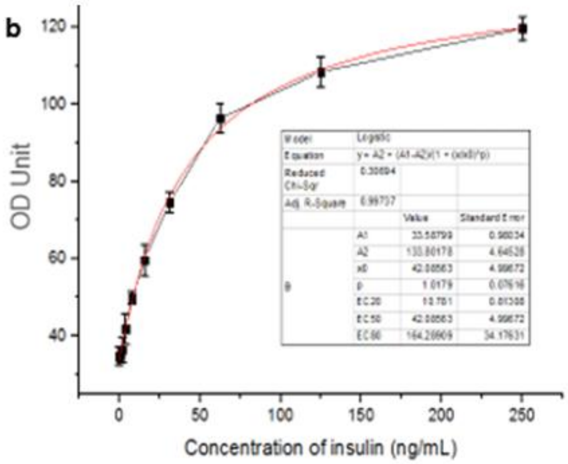
Fluorescent



Colorimetric

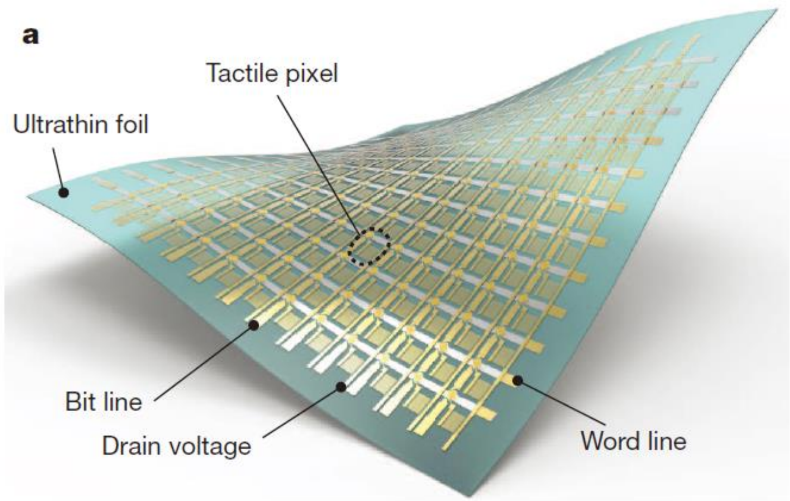


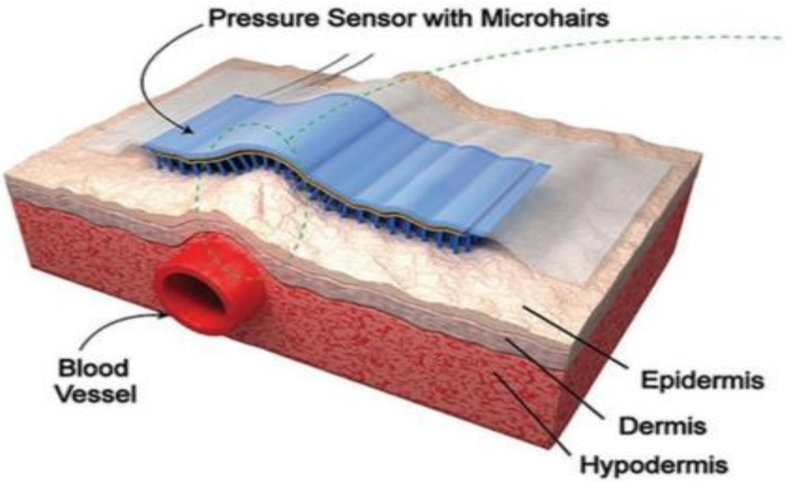




Wearable biosending devices

Wearable biosensing devices





1. Test heart rate to diagnose heart disease

2. Test the chemical materials contents in sweat to diagnose Various diseases

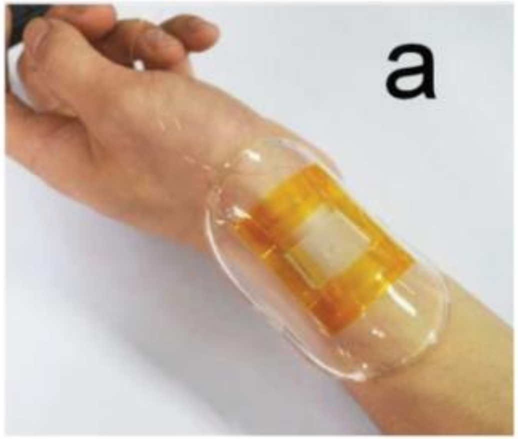
Wearable biosensing devices

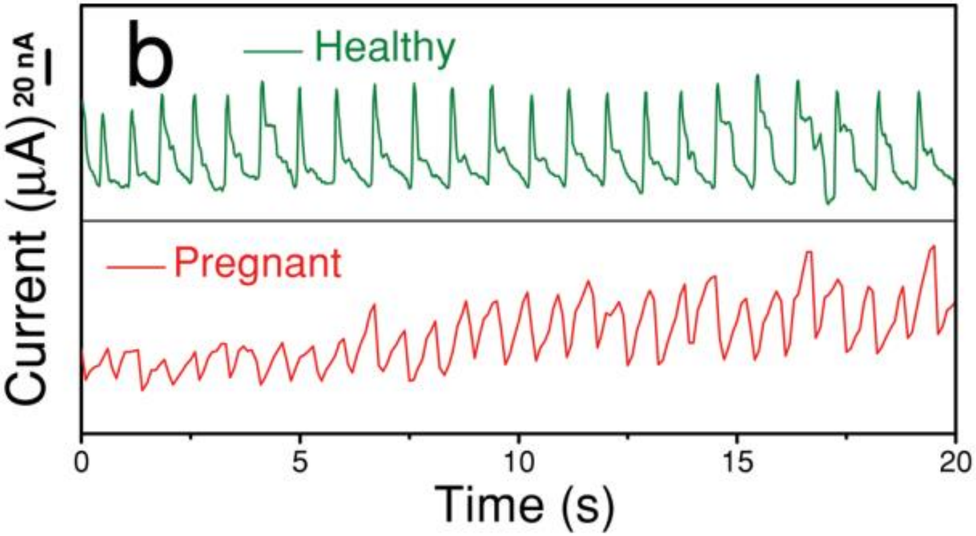
a)Thin and Weable
b) Portable
c) Real-time detection

Benefits

d) No-Invasive
e) Accuracy

No-Invasive & Accuracy

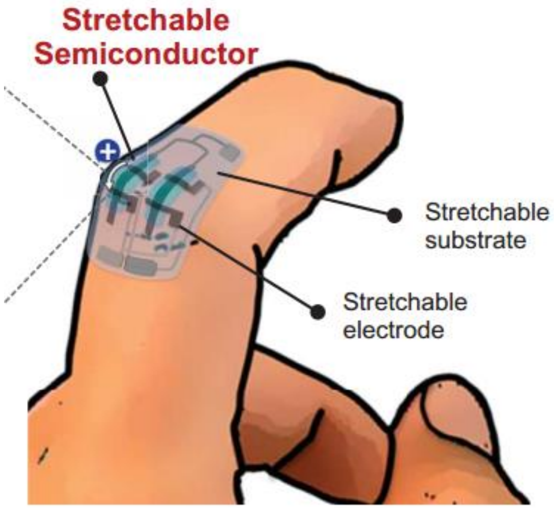




Malter, L & Kekitani T 2015, ‘ An ultra-lightweight design plastic electronics’, nature, pp.152-163, accessed 25 May 2018

Wearable biosensing devices

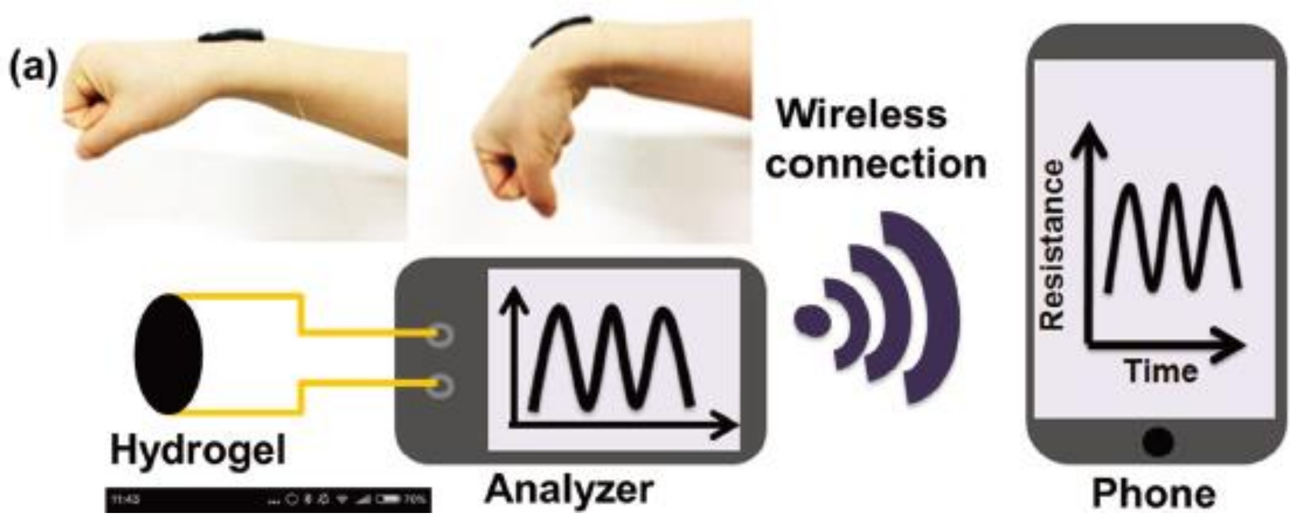
Thin and Weable



Kaltenbrunner, L & Sekitani T 2015, '5. Kaltenbrunner, L & Sekitani T 2015, ' An ultra-lightweight design for imperceptible plastic electronics', *nature*, vol. 5, pp.152-163, accessed 31 May 2018

Wearable biosensing devices

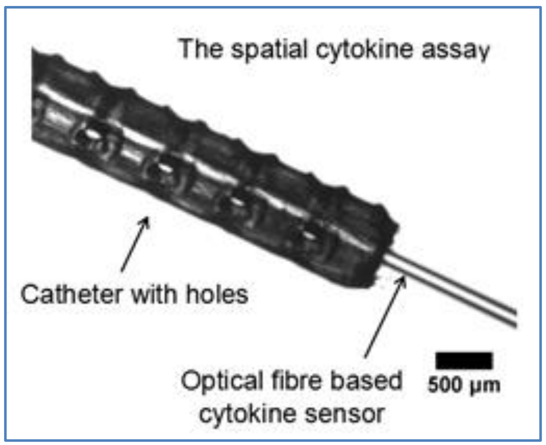
Real-time detection

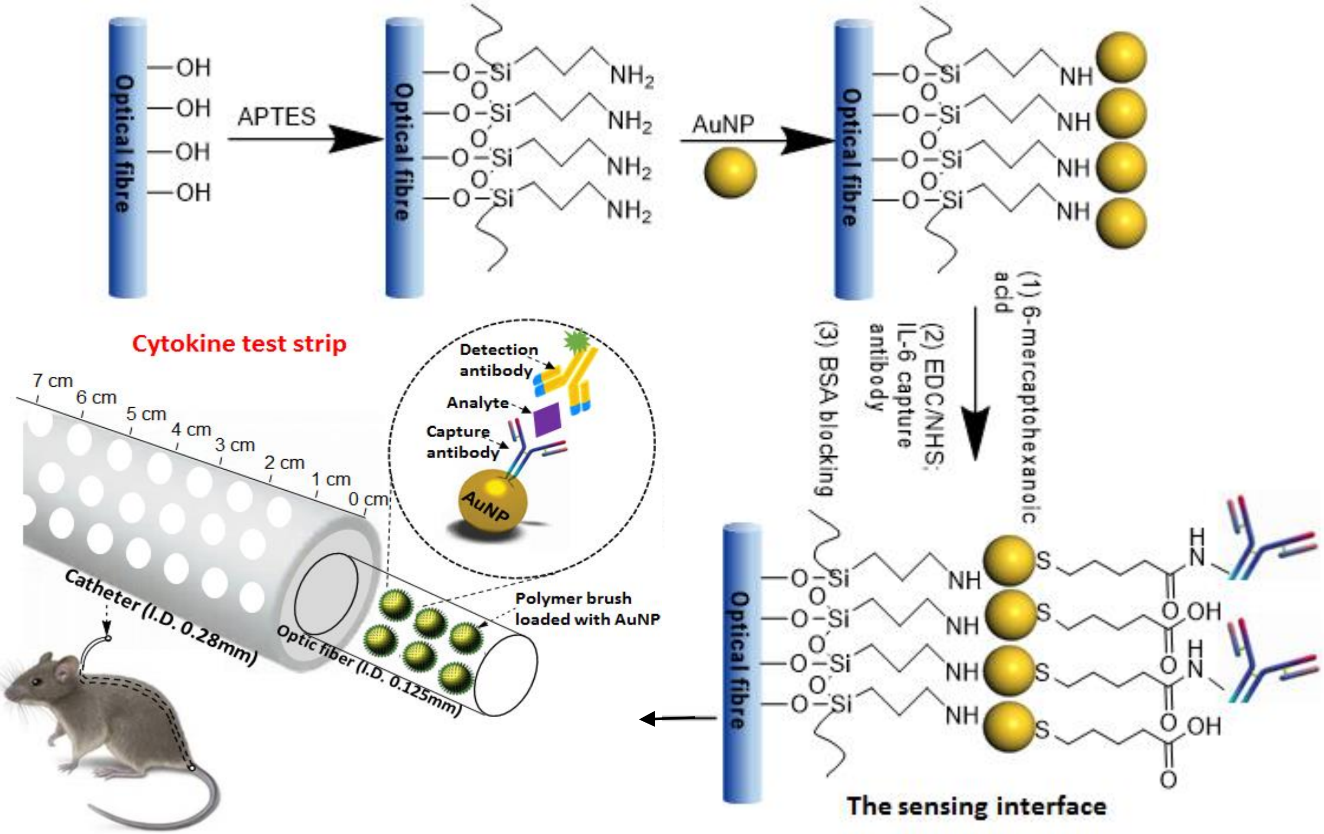


Zhang, L 2015, ' A Bioinspired Mineral Hydrogel as a Self-Healable, Mechanically Adaptable Ionic Skin for HighlySensitive Pressure Sensing', Advced Material, vol. 12, no. 2, pp. 1250-1260, accessed 25 May 2018.

Implantable biosending devices

In vivo medical device development



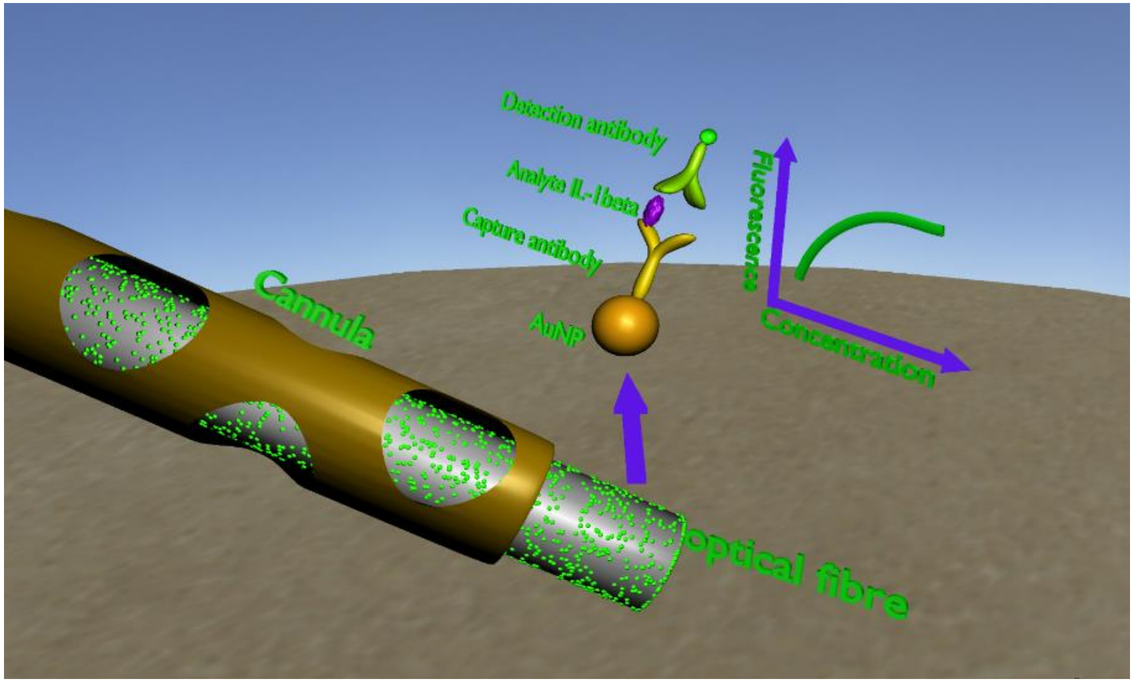


G. Liu, E.M. Goldys, patent No.: PCT/AU2016/000401

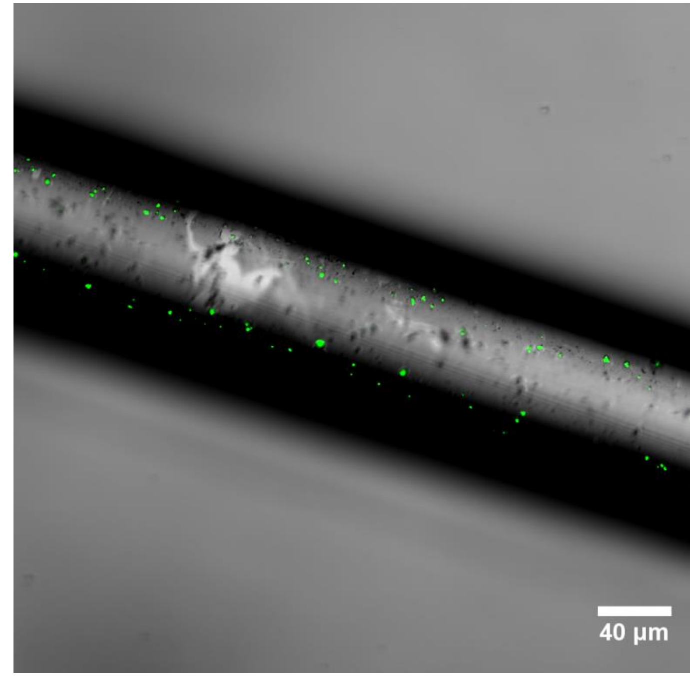
It aims to provide a solution to monitor spatially localised concentration of cytokines in specific location of the body, such as the spinal cord, reproductive tract, cancer stroma etc.

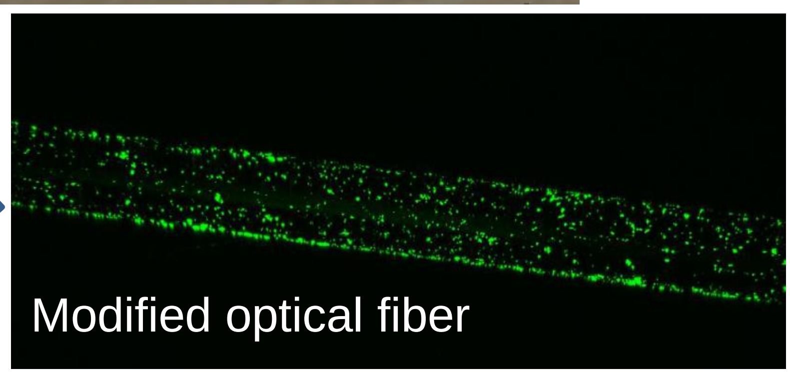
G. Liu, K. Zhang, et al., *ACS Sens.*, 2017, 2(2), 218-226
K. Zhang, G. Liu, E. M. Goldys, *Biosens. Bioelectron*., 2017, 102, 80-86
K. Zhang, G. Liu, et al., Brain Behav. Immun., 2018 under revision

Characterisation of the fibre surface



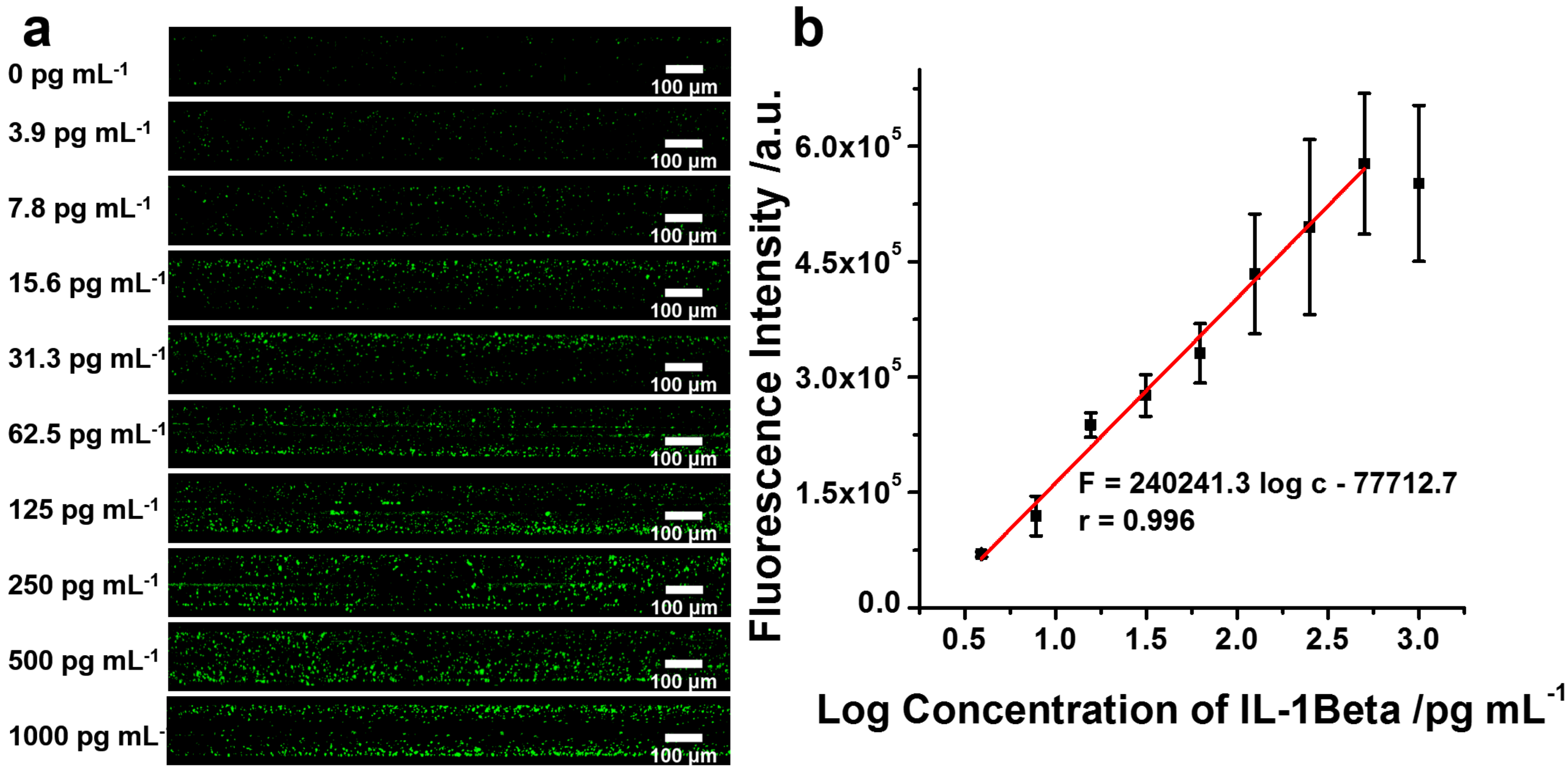
Confocal image of optical fibre





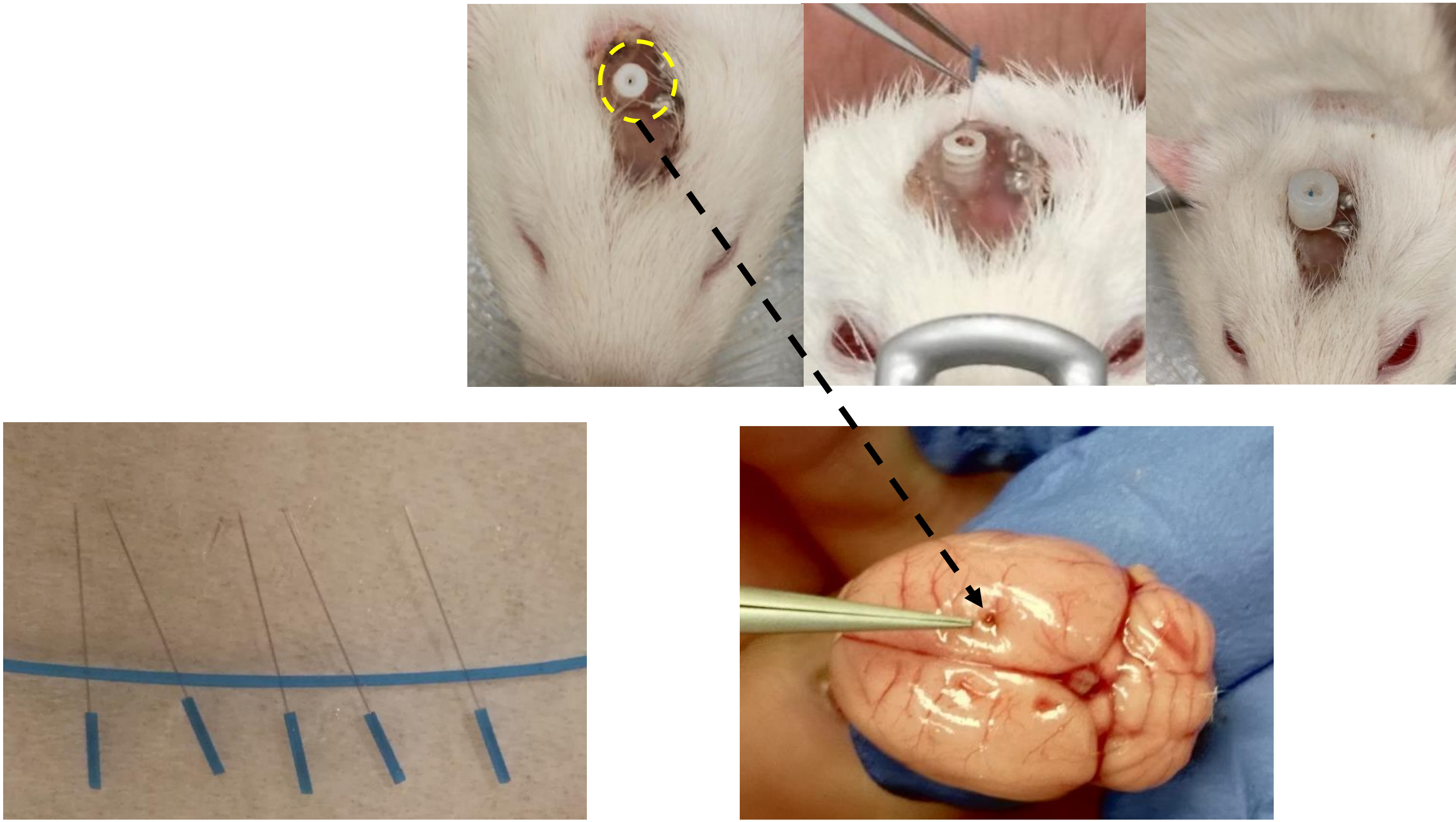
Zoom 1x (FOV 1500 x 1500 micrometer), 10 stacks

Determination of IL-1β in animal serum

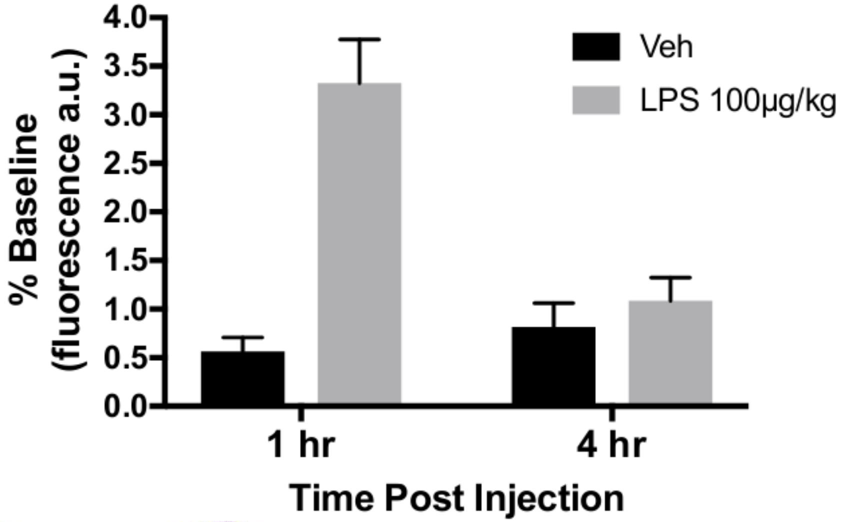


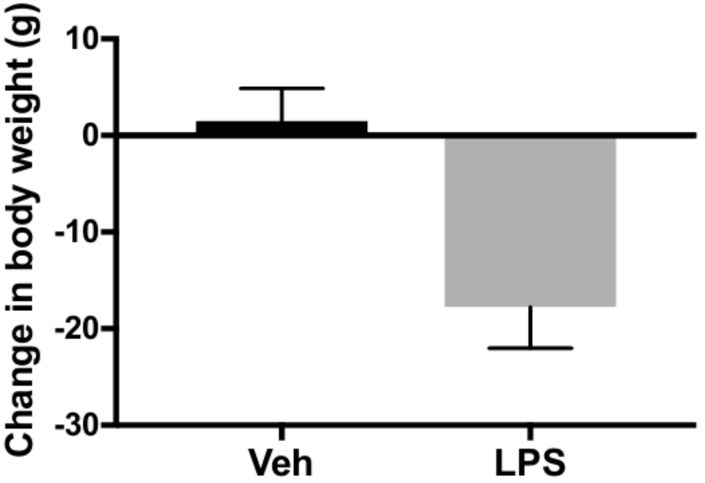
A linear relationship between the fluorescence intensity and the concentration of IL-1β in the range of **3.9 to 500 pg mL^{-1}** was obtained . The lowest detection concentration is **1.2 pg mL^{-1}** .

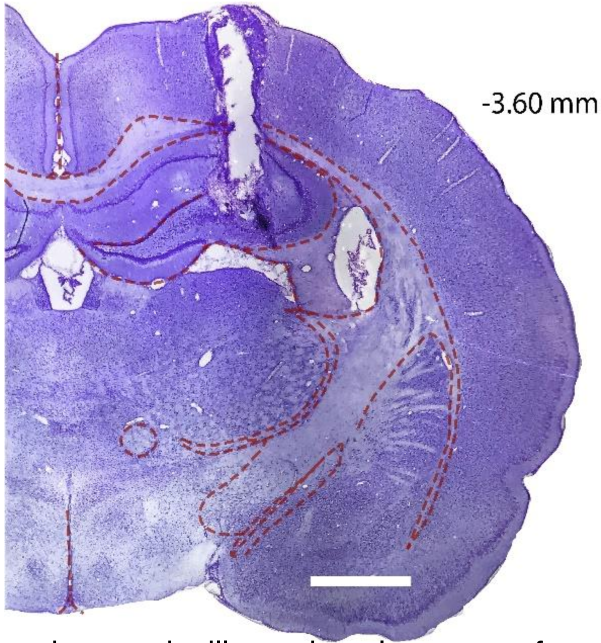
Detection of interleukin-1β in hippocampus



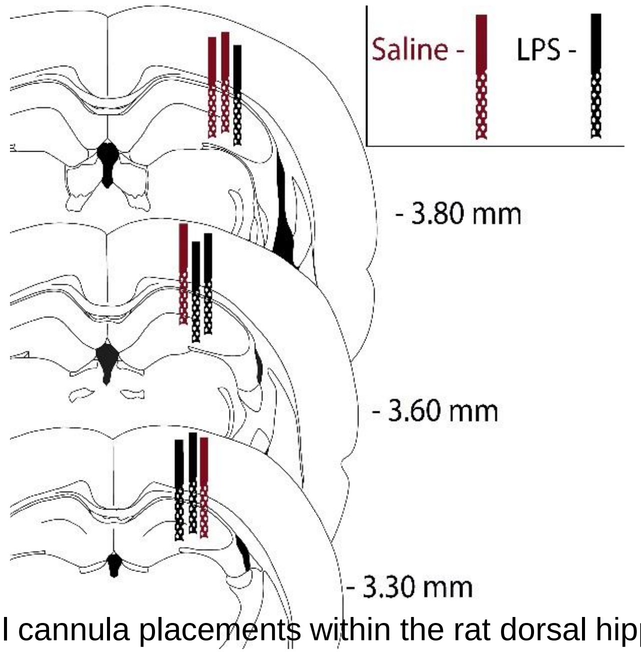
Detection of interleukin-1β in hippocampus







Photomicrographs illustrating placement of cannula in the dorsal hippocampus



All cannula placements within the rat dorsal hippocampus

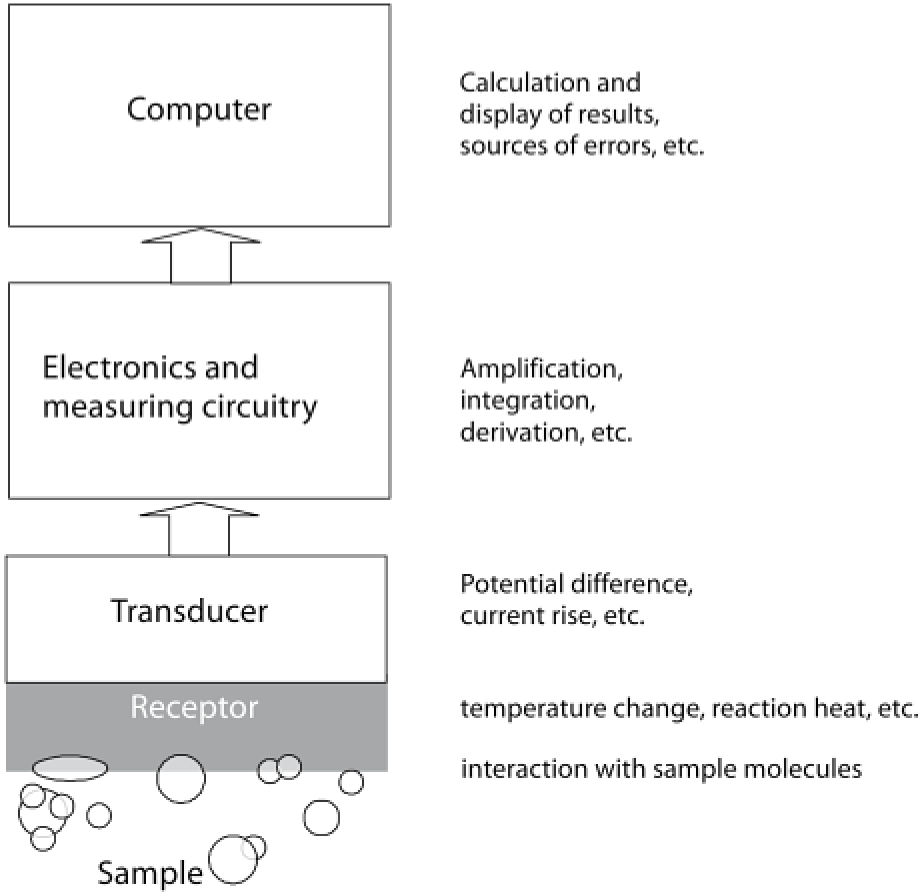
Biosensors

A biosensor is a device which transforms chemical/physical/ information into an analytically useful signal

Comprise:

- Recognition element
- Transduction element
- Signal processor

Information is typically a chemical concentration of a sample component (eg. oxygen in blood), but could also extend to total composition.



Summary

What are biosensors, classification of biosensors?

Performance of a biosensor:

–Precision

–Accuracy

–Sensitivity

–Selectivity

–Detection limit

–Dynamic range

–Resolution

–Response time

–Stability

Examples of biosensors

–Glucose biosensor

–Cytokine biosensor、

–Nanoparticle based biosensor

–Point-of-care biosensor

–In vivo biosensor

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http://info.library.unsw.edu.au/Welcome.html

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