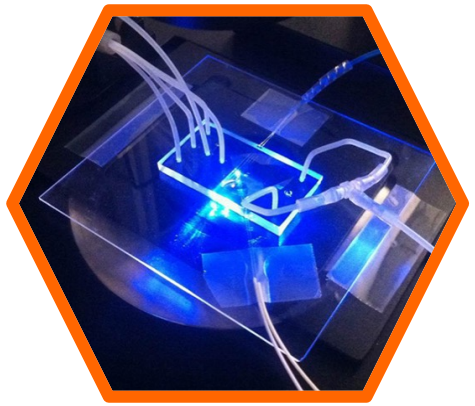
Biomaterials for MX

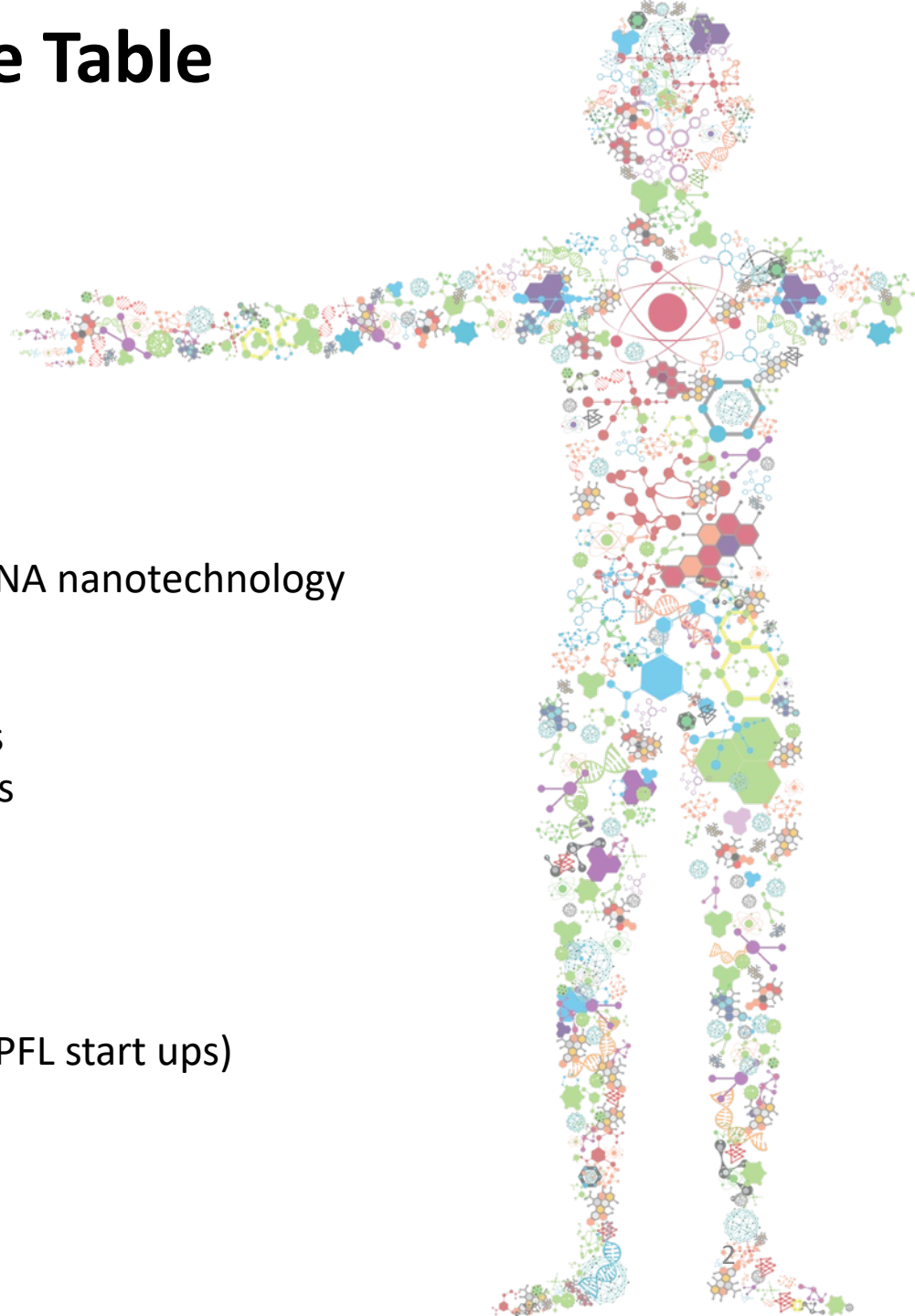
MSE – 471

Maartje Bastings



Course 11: Sensors and Diagnostic Devices

Course Content & Time Table



BLOCK 1: Introduction and materials overview

11-9	Lecture 1.	Intro to biomaterials and biology
18-9	Lecture 2.	Naturally derived biomaterials
25-9	Lecture 3.	Implants and metals
2-10	Lecture 4.	Polymers, Particles, and Surfaces

BLOCK 2: Interactions and specific applications

9-10	Lecture 5.	Materials for drug delivery and targeting: DNA nanotechnology
16-10	Lecture 6.	Materials for cell adhesion: scaffolds
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30-10	Lecture 7.	Materials for immune engineering: vaccines
6-11	Lecture 8.	Materials for tissue engineering: heartvalves

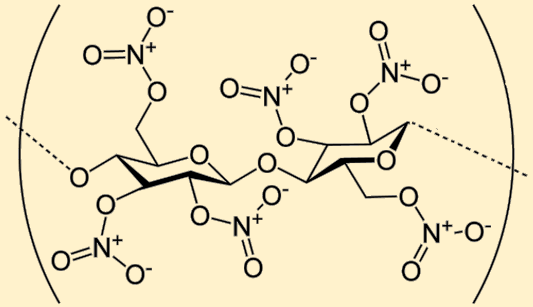
BLOCK 3: Measurements, regulation and translation

13-11	Lecture 9.	Characterization and performance
20-11	**Lecture 10.**	**Sensors and diagnostic devices**
27-11	Lecture 11.	Translation to industry, patents, spin-offs (EPFL start ups)
4-12	Lecture 12.	Regulatory aspects and trials (EPFL TTO)
11-12	Lecture 13.	Revision and conclusion
18-12	Open discussion and hand in of lab papers	

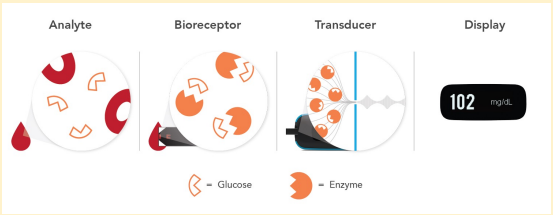
Sensors and Diagnostics

Electronics

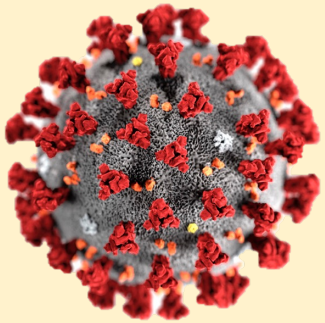
Paper



Sensors

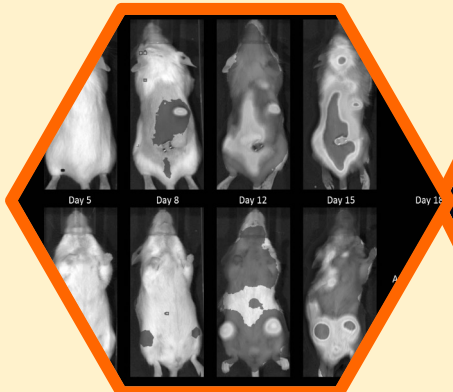


Fast Diagnostics

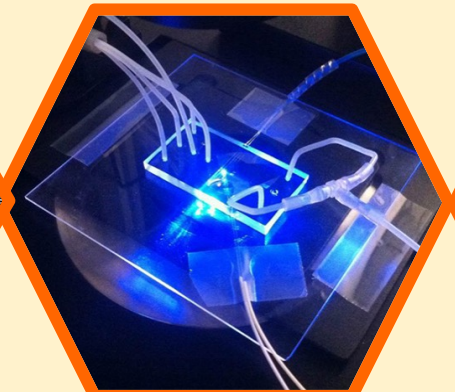


BLOCK 3: Quantification

Characterization



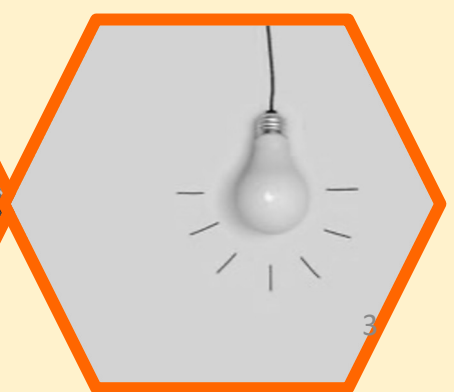
Sensors



Translation

Regulation

Conclusion



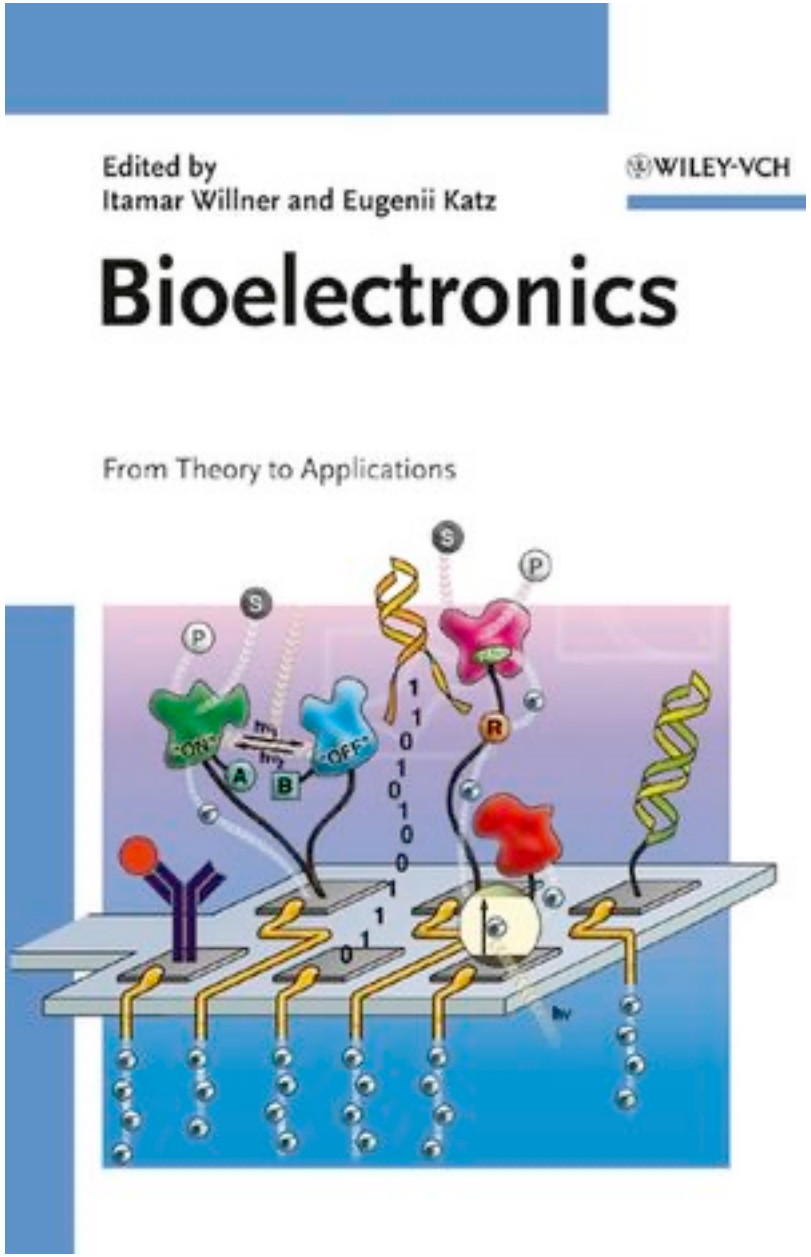
Bioelectronics

Bioelectronics is an interdisciplinary research field that aims to integrate biomolecules and electronic elements into functional systems.

The ability to control the shape and structure of biomolecules, such as proteins and DNA, and the evolution-optimized chemical functions of biomaterials including binding, catalysis, ion-pumping and self-assembly, make **biomolecules** attractive building blocks for functional devices.

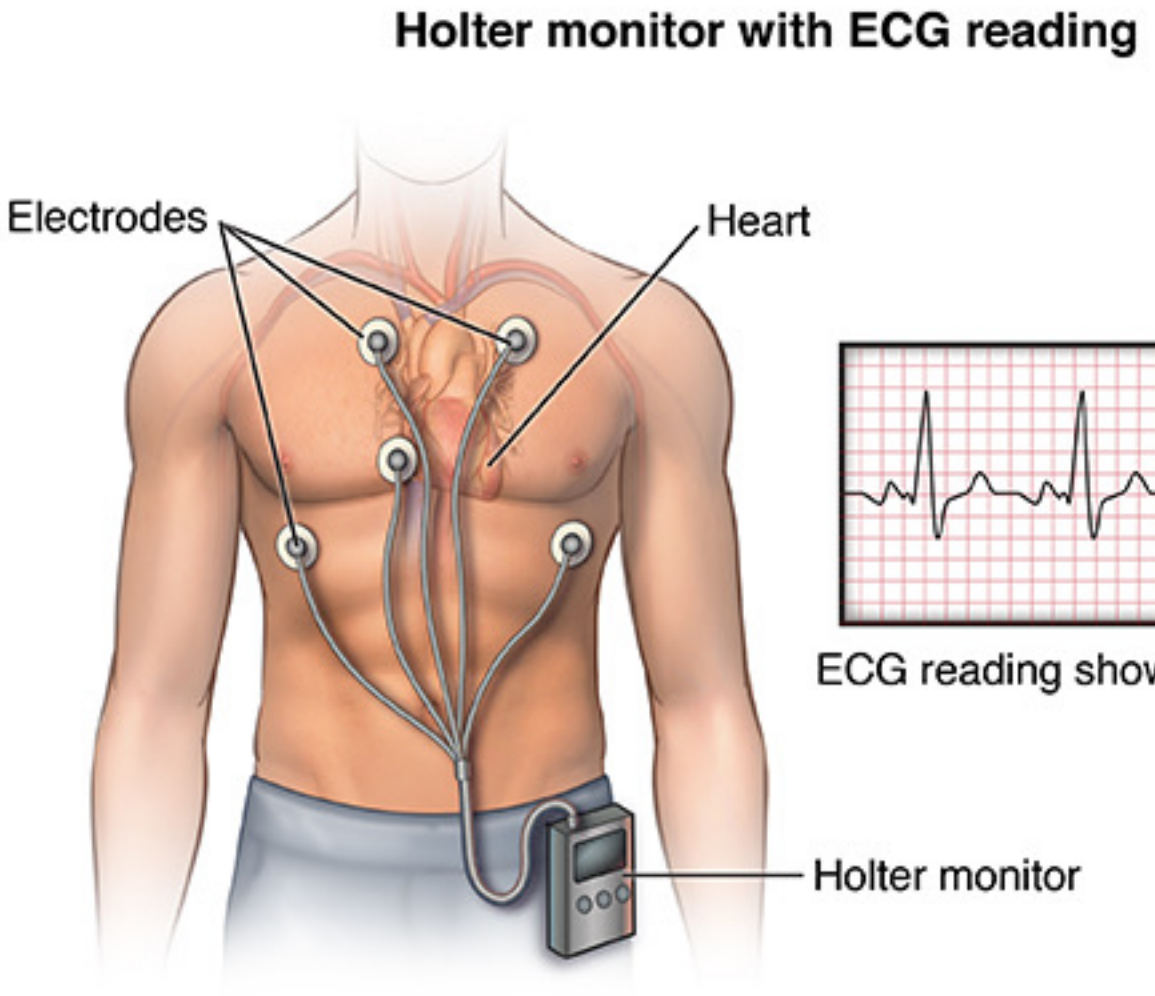
Hybrid systems formed by the integration of biomolecules with electronic elements, such as electrodes, or transistors enable the electronic read-out detection of biomolecular functions, the transformation of biocatalyzed processes into electrical power, and the templating of nanosized circuitry.

Future applications of bioelectronic systems may include computation devices and prosthetic units.

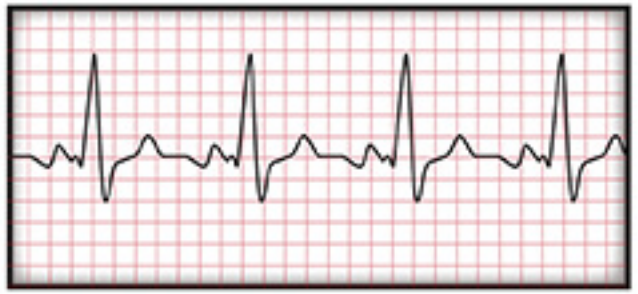


Science 20 Dec 2002:
Vol. 298, Issue 5602, pp. 2407-2408
DOI: 10.1126/science.298.5602.2407

Electrodes

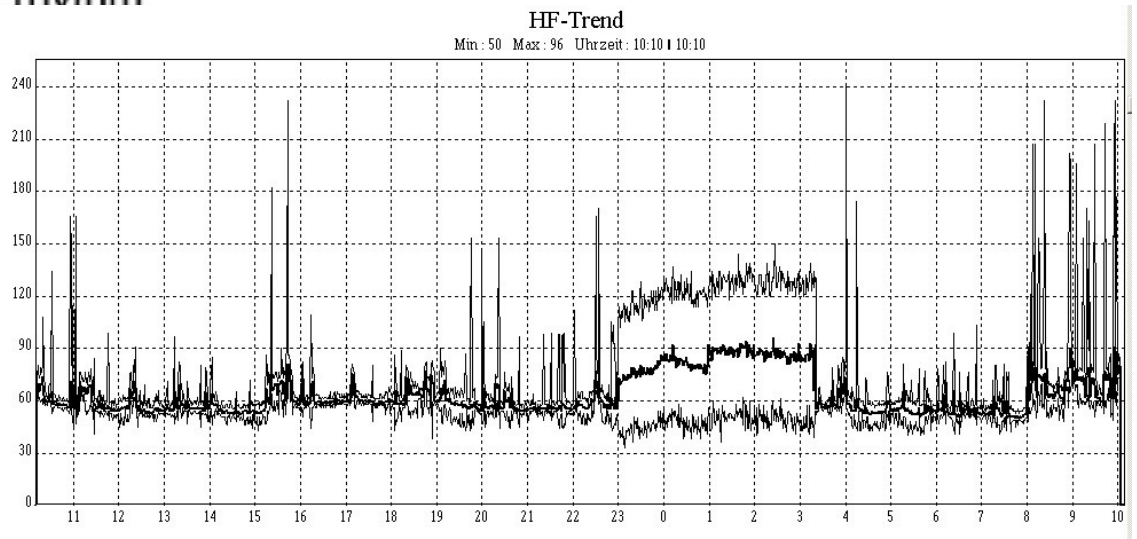


ECG records the electrical activity generated by heart muscle depolarizations, which propagate in pulsating electrical waves towards the skin. Although the electricity amount is in fact very small, it can be picked up reliably with **ECG electrodes** attached to the skin (in microvolts, or µV).



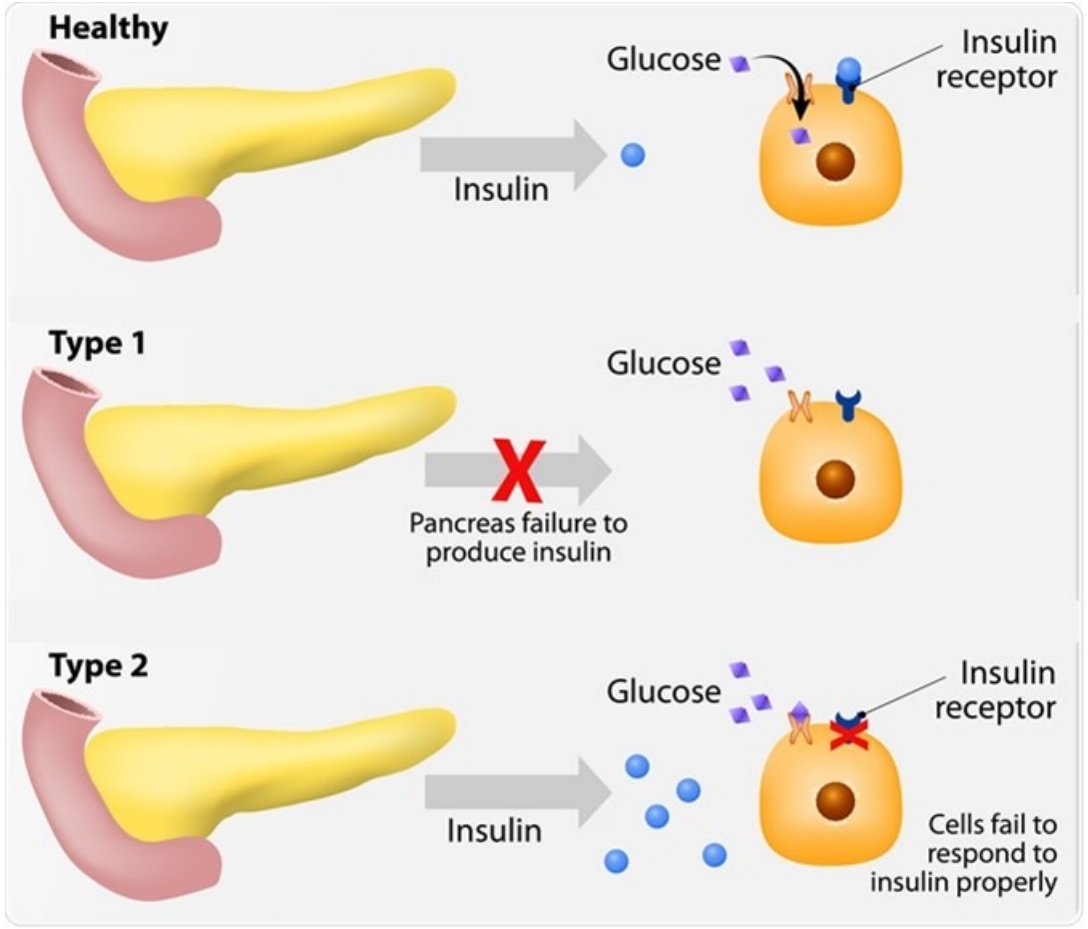
ECG reading showing heart rhythm

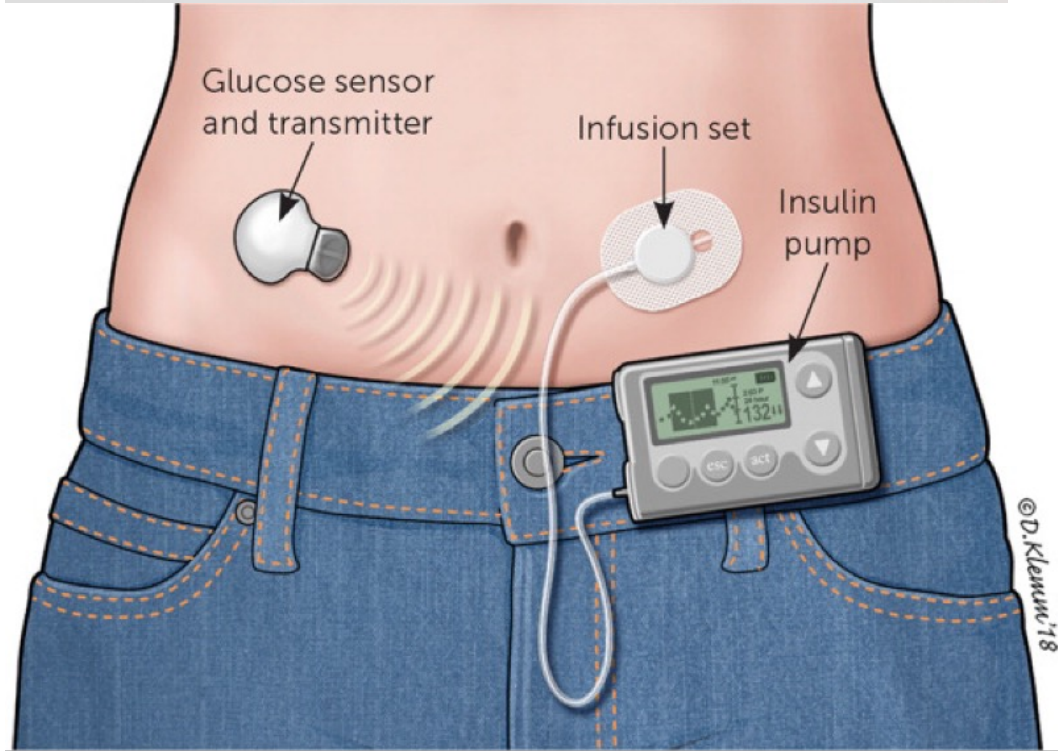
A Holter monitor records electrical signals from the heart via a series of electrodes attached to the chest. Electrodes are placed over bones to minimize artifacts from muscular activity.



Diabetes

Diabetes is a metabolic disease that causes high blood sugar. The hormone insulin moves sugar from the blood into your cells to be stored or used for energy. With **diabetes**, your body either doesn't make enough insulin or can't effectively use the insulin it does make.





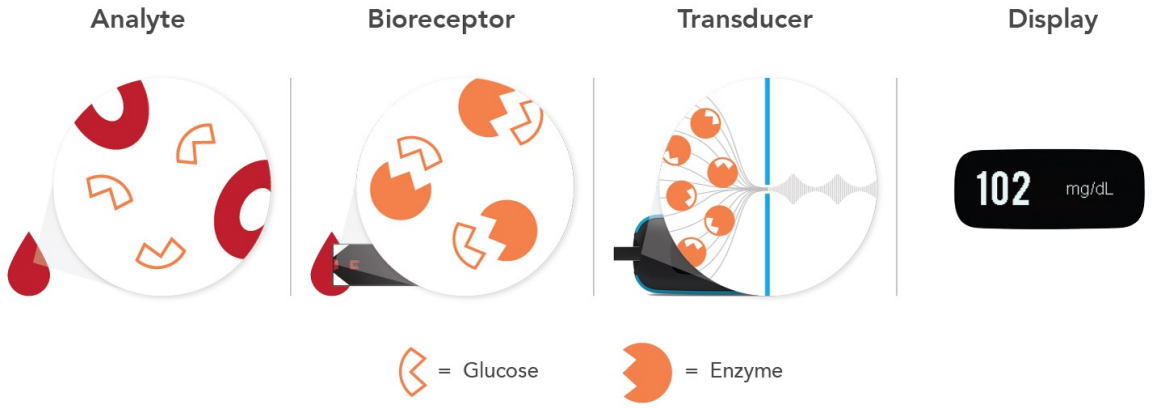
Glucose Sensor

Analyte: A substance with chemical constituents that are being identified and measured. In this instance, glucose is the analyte that the biosensor is designed to detect.

Bioreceptor: This is a molecule that specifically recognizes the analyte. For the detection of glucose, specific enzymes are used, which are proteins that facilitate a chemical reaction. For example, the test strip for a blood glucose test contains the enzyme that interacts with the analyte in the drop of blood.

Transducer: This part of the biosensor converts one form of energy into another. Specifically, it converts the recognition of the bioreceptor into a measurable signal. Most modern-day glucose meters and continuous glucose monitors measure electrical signals, although earlier generations of glucose meters used a colorimetric process (color change) that was measured optically.

Electronics and display: These components process the transduced signal and prepare it for display. The processed signals are then quantified and shown on either the glucose meter's display or the receiver for a continuous glucose monitor (or compatible app).



In order to create the chemical reaction that allows glucose to be detected in a bodily fluid, different bioreceptors can be used. The most common type of **glucose sensor is enzyme-based.** The enzyme coating on the glucose sensor allows it to react with the analyte and produce a **secondary species that can be measured electrochemically.** Common enzymes (bioreceptors) that are used to detect glucose include:

- Glucose oxidase (GOx)
- Glucose dehydrogenase nicotinamide adenine dinucleotide (GDH-NAD)
- Glucose dehydrogenase flavin adenine dinucleotide (GDH-FAD)

Skin Electrodes

A group of researchers at the University of Tokyo developed an ultra-thin biomedical device that securely stick to the human skin.

It has a stretchable display that shows the patient's electrocardiogram waveform as well as temperature and blood pressure recorded by an integrated on-skin electrode sensor.

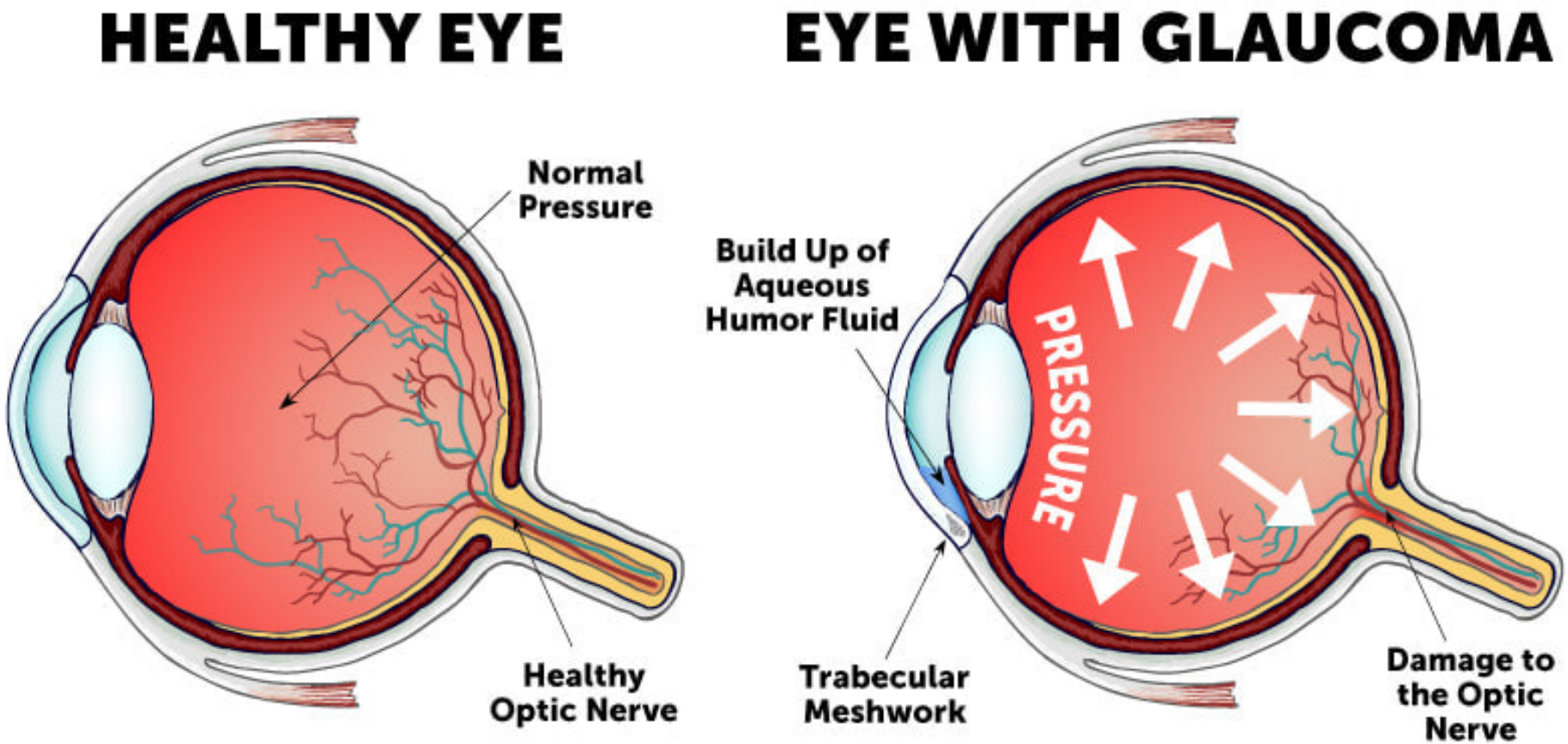
The results will then be transmitted immediately to a smartphone for self-monitoring or through a cloud that enables the doctors to remotely access the data, minimizing the need for hospital visits.

The Future of Skin Electronics

https://www.youtube.com/watch?v=zpGujcLRHNw&feature=emb_logo

Glaucoma

Office hours vs peak in pressure



https://www.wolfeeyeclinic.com/medical-services/glaucoma

https://www.sensimed.ch

About SENSIMED Triggerfish®

The SENSIMED Triggerfish® continuous ocular monitoring system is a CE marked and FDA approved device that provides insights into the ocular volume changes throughout the day and night. The device includes a smart contact lens that captures spontaneous changes in the eye providing physicians with valuable information that can help guide glaucoma treatment.

Diagnosis First

Healthcare Professionals' Advantage

What Patients can Expect

The SENSIMED Triggerfish® Advantage

SENSIMED Triggerfish

Glaucoma diagnosis technology has seen many advancements,
none can provide a complete picture of the eye, unlike the SENSIMED Triggerfish®

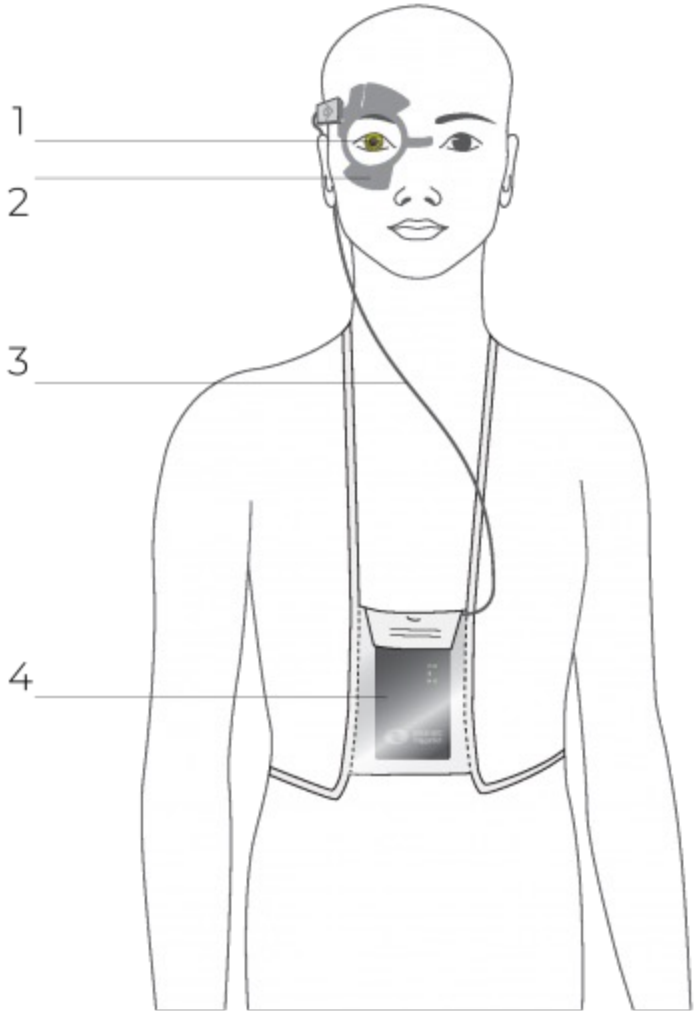
While SENSIMED Triggerfish® is a highly innovative technology, how it works is very simple
The patient wears the SENSIMED Triggerfish® system up to 24 hours and assumes normal activities including sleep periods.

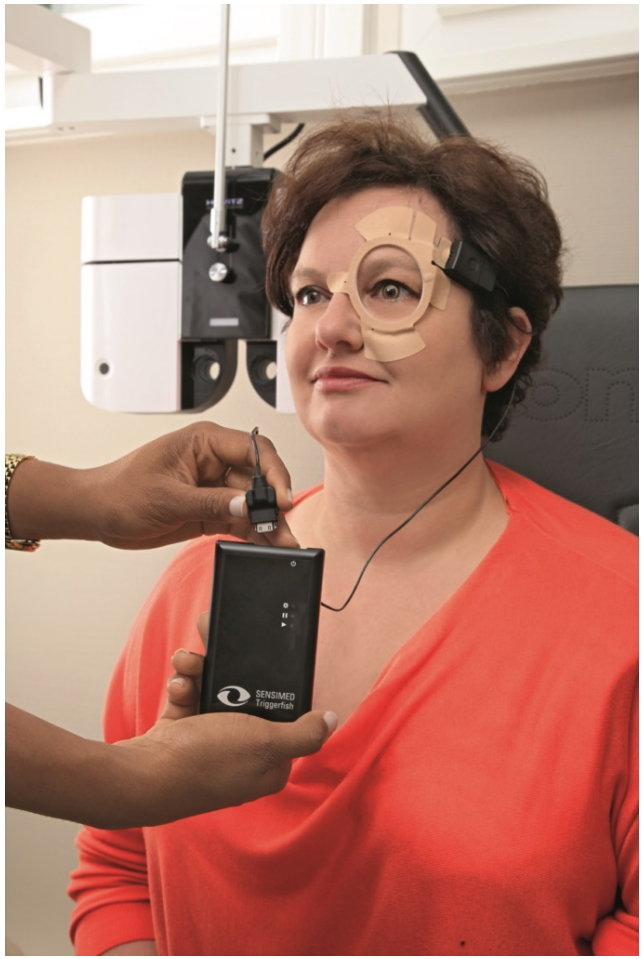
The SENSIMED Triggerfish Sensor is a soft disposable silicone contact lens embedding a micro-sensor that captures spontaneous circumferential changes at the corneoscleral area. (1)

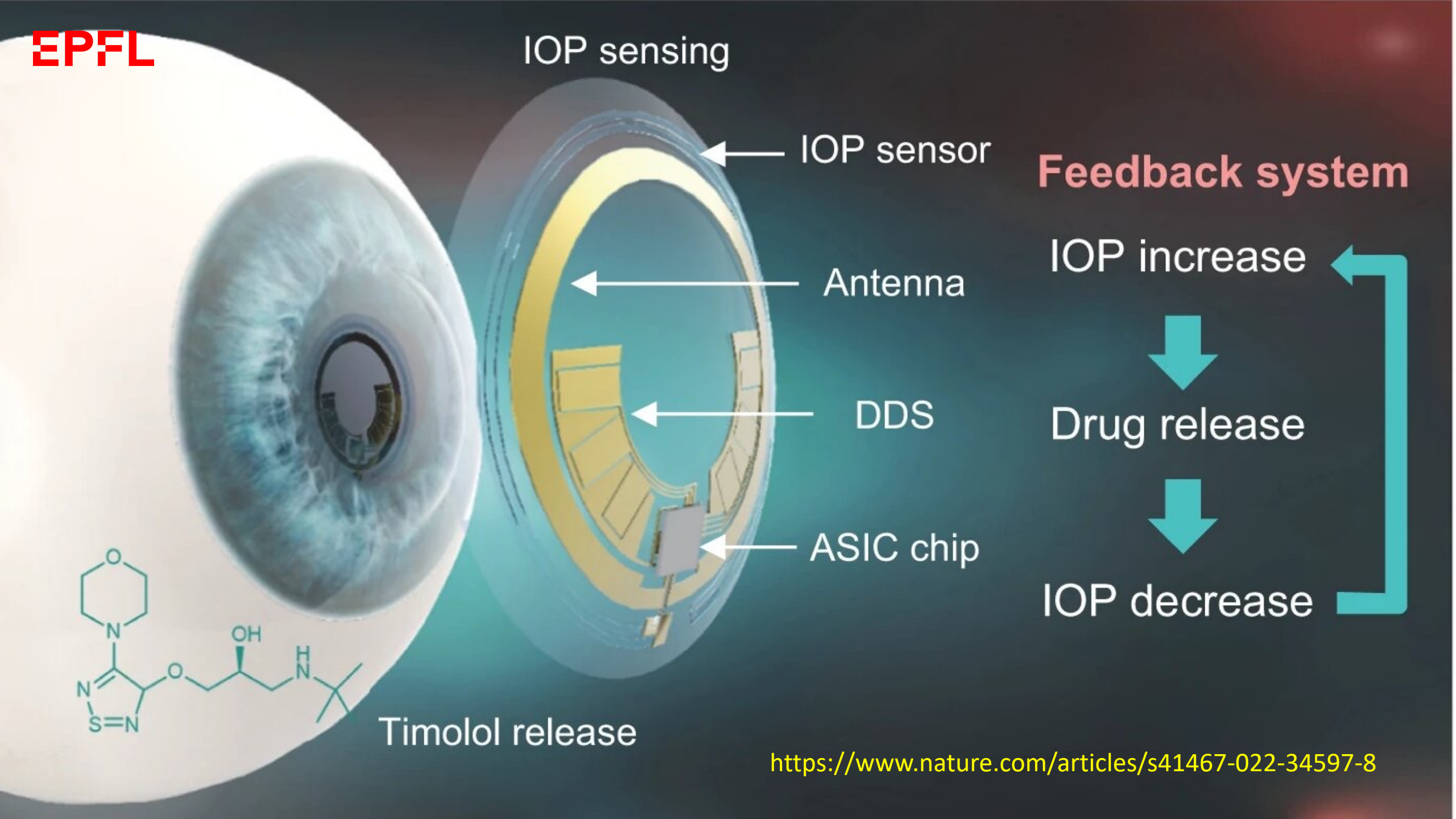
The adhesive SENSIMED Triggerfish Antenna, which is placed around the eye, receives wirelessly the information from the contact lens. (2)

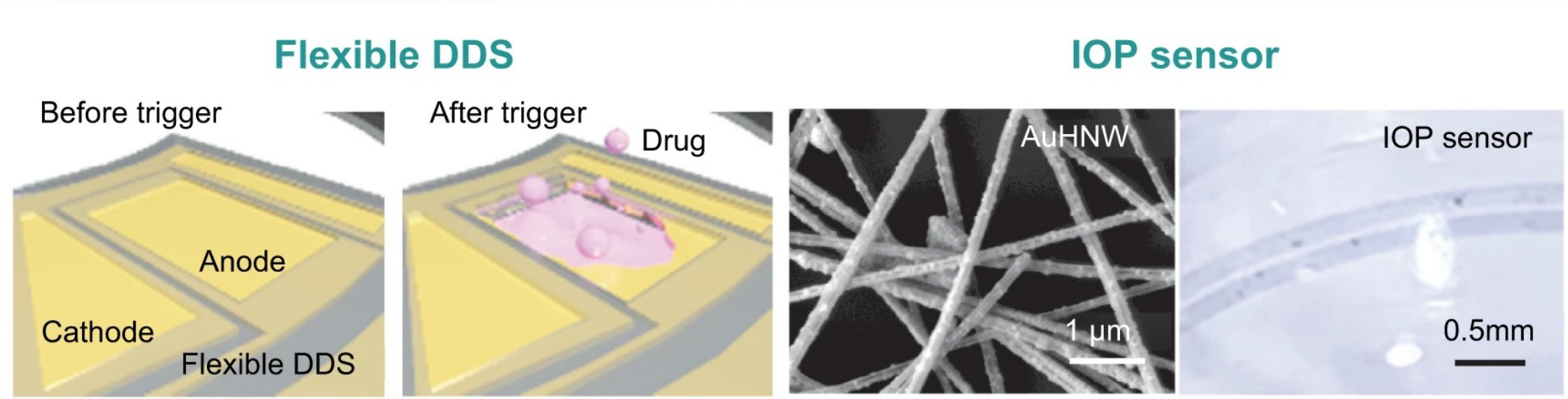
The data is transmitted through a thin flexible cable from the Antenna to the portable recorder. (3)

The recorder, worn by the patient, stores the acquired data during the monitoring session. At the end of the recording period, the data is transferred via Bluetooth from the recorder to the software previously installed on the practitioner's computer. (4)

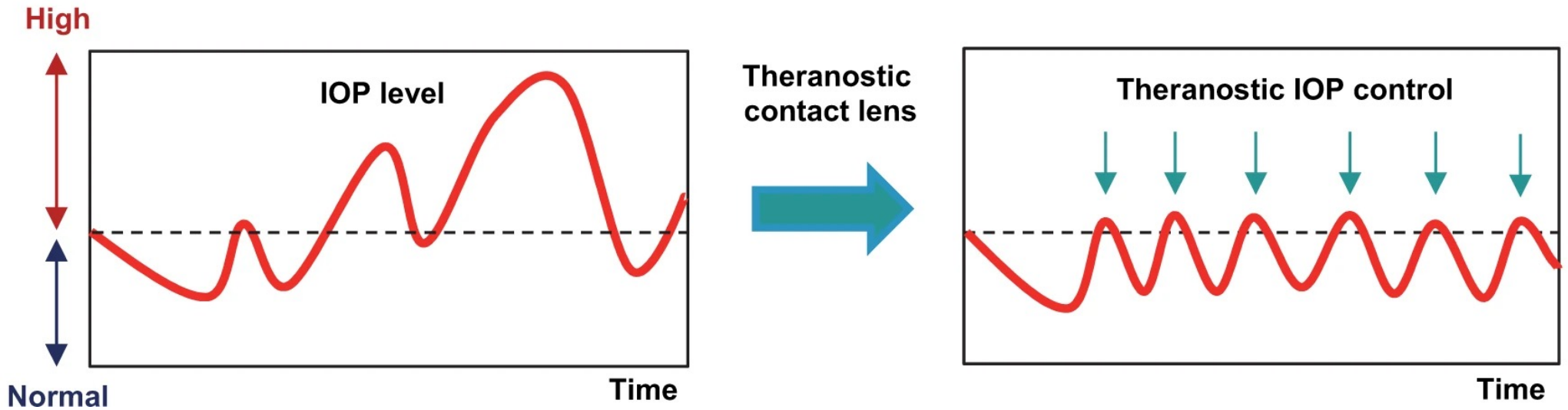


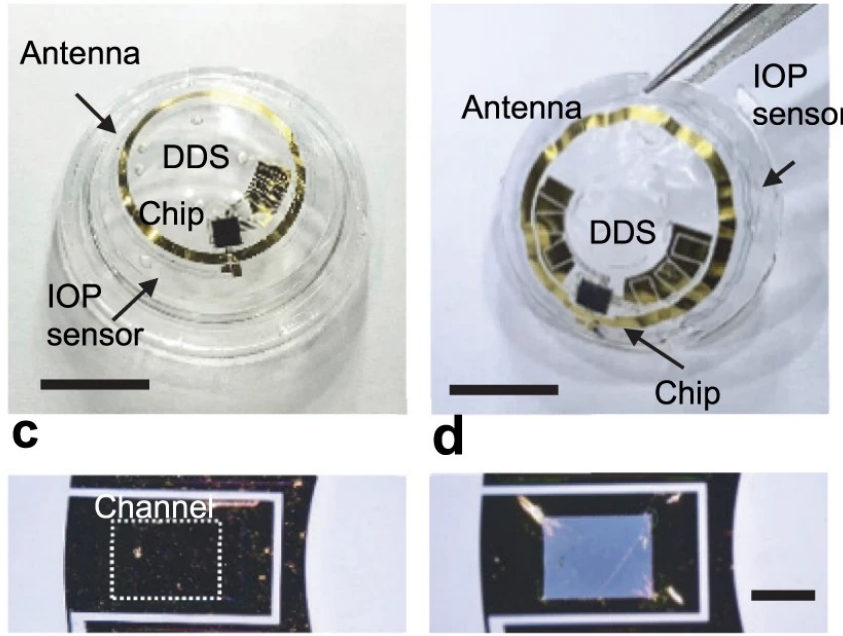


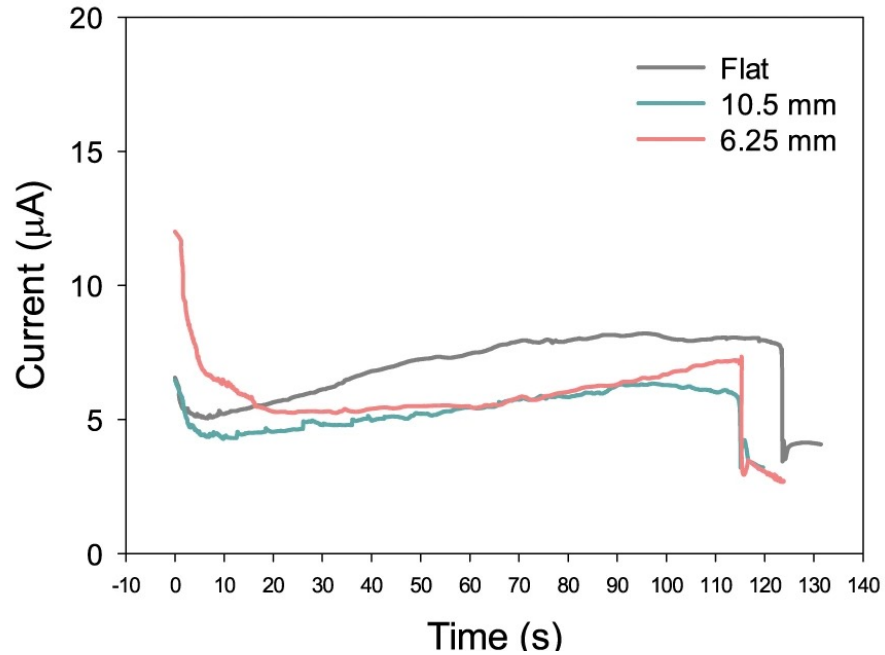

EPFL
IOP sensing
IOP sensor
Antenna
DDS
ASIC chip
Feedback system
IOP increase
Drug release
IOP decrease
Timolol release
https://www.nature.com/articles/s41467-022-34597-8

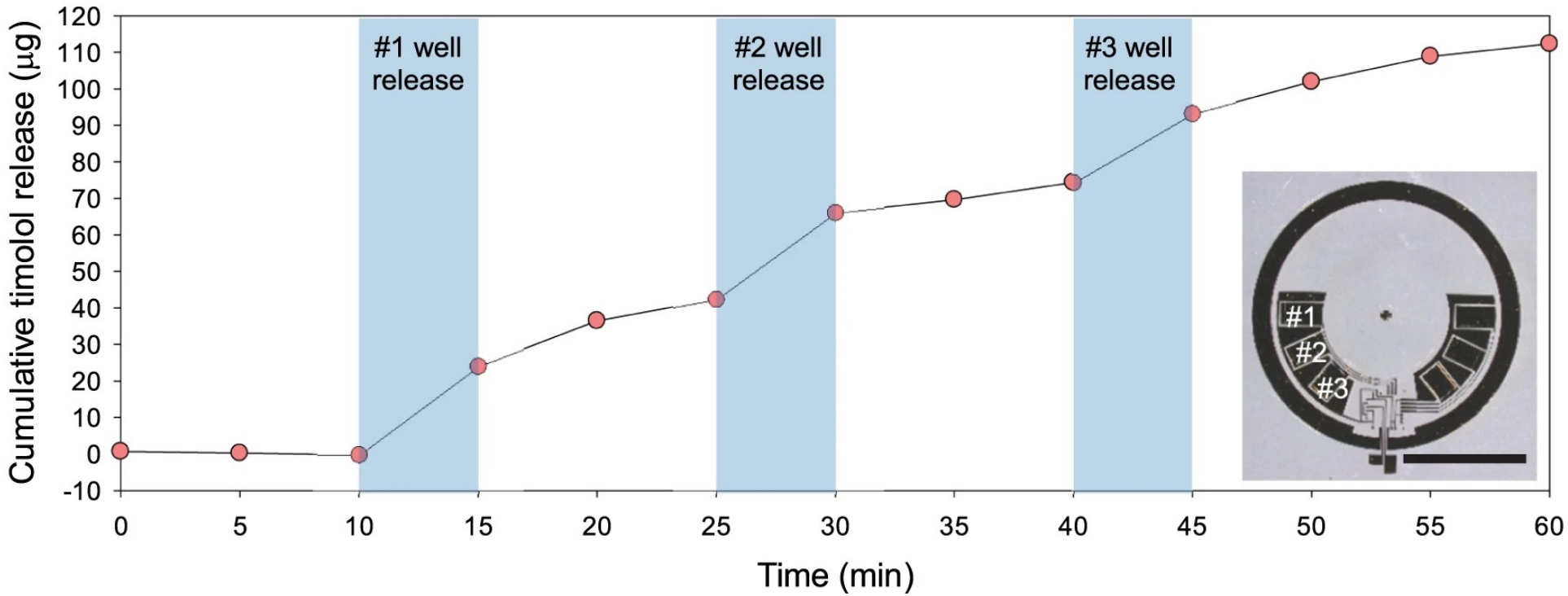

Flexible DDS
IOP sensor
Before trigger
After trigger
Drug
Anode
Cathode
Flexible DDS
AuHNW
1 μm
IOP sensor
0.5mm

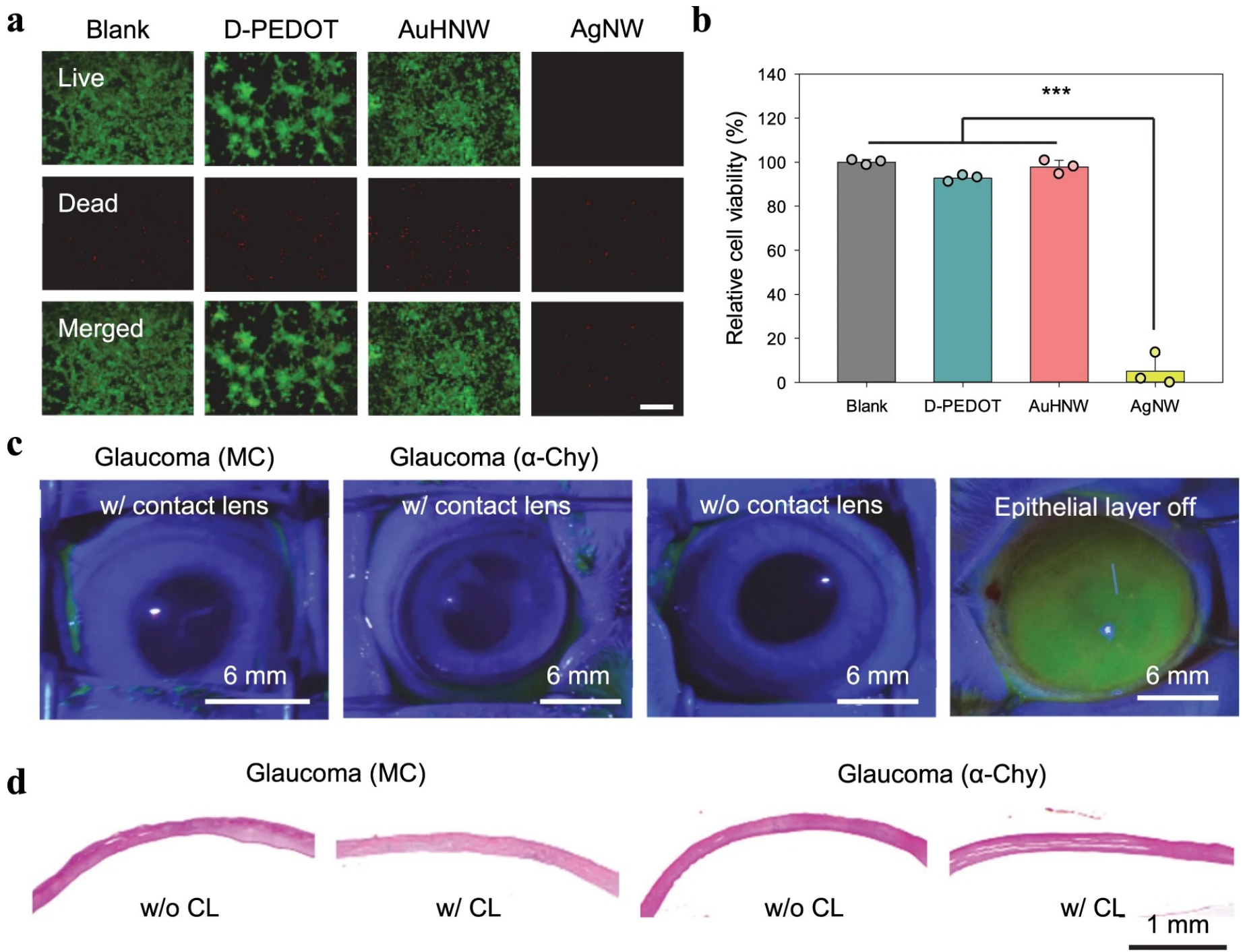
b


High
IOP level
Normal
Time
Theranostic
contact lens
Theranostic IOP control
Time


Antenna
DDS
Chip
IOP
sensor
Antenna
IOP
sensor
DDS
Chip
c
d
Channel


Flat
10.5 mm
6.25 mm
Current (μA)
Time (s)


#1 well
release
#2 well
release
#3 well
release
Cumulative timolol release (μg)
Time (min)
#1
#2
#3


a
Blank
D-PEDOT
AuHNW
AgNW
Live
Dead
Merged
b
Relative cell viability (%)
140
120
100
80
60
40
20
0
***
Blank
D-PEDOT
AuHNW
AgNW
c
Glaucoma (MC)
Glaucoma (α-Chy)
w/ contact lens
w/ contact lens
w/o contact lens
Epithelial layer off
6 mm
6 mm
6 mm
6 mm
d
Glaucoma (MC)
Glaucoma (α-Chy)
w/o CL
w/ CL
w/o CL
w/ CL
1 mm

Cheap, accessible, fast…

Motivation:

Existing diagnostic strategies for (viral) infections are expensive and time-consuming.

Hence, there is a significant interest in developing portable and inexpensive diagnostic platforms for various viral diseases and testing at point-of-care (POC) settings.

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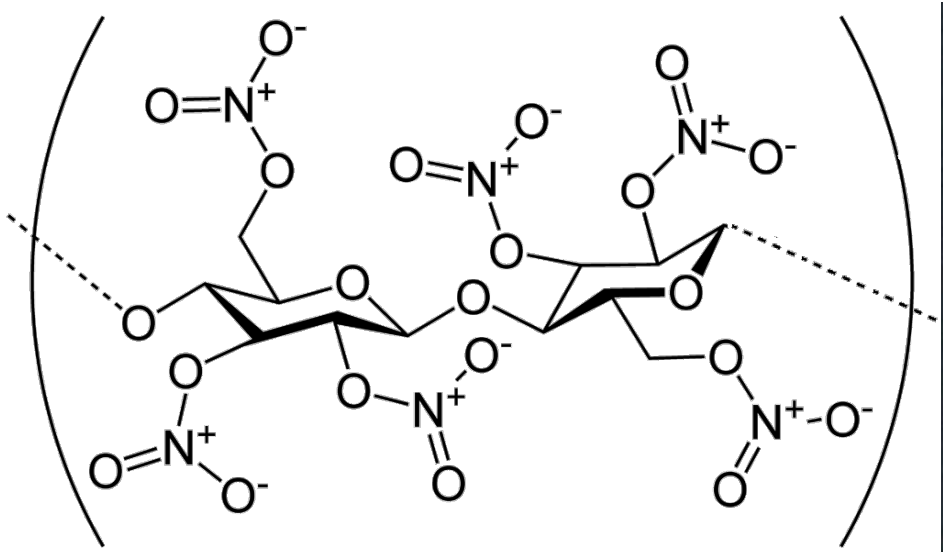
PAPER! (NitroCellulose)



Cheap, accessible, fast…

Motivation:

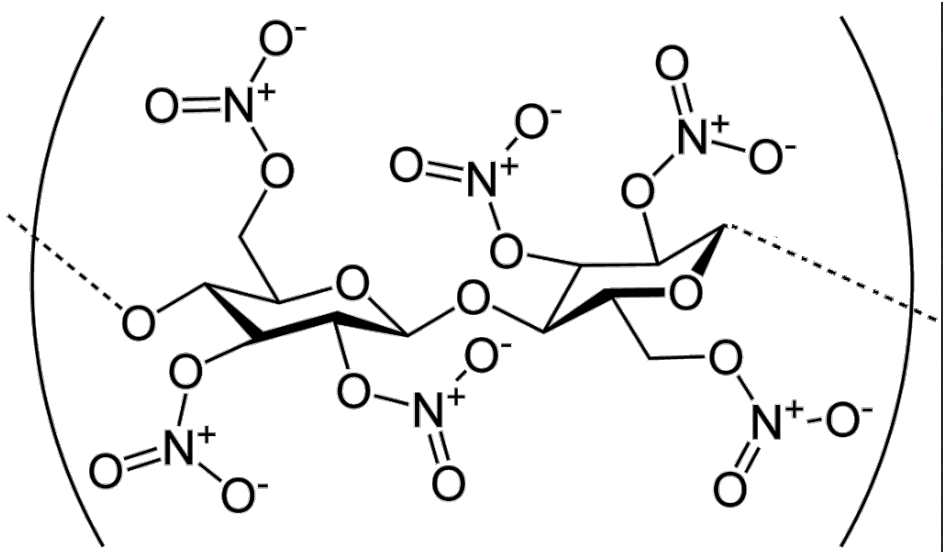
Existing diagnostic strategies for (viral) infections are expensive and time-consuming.

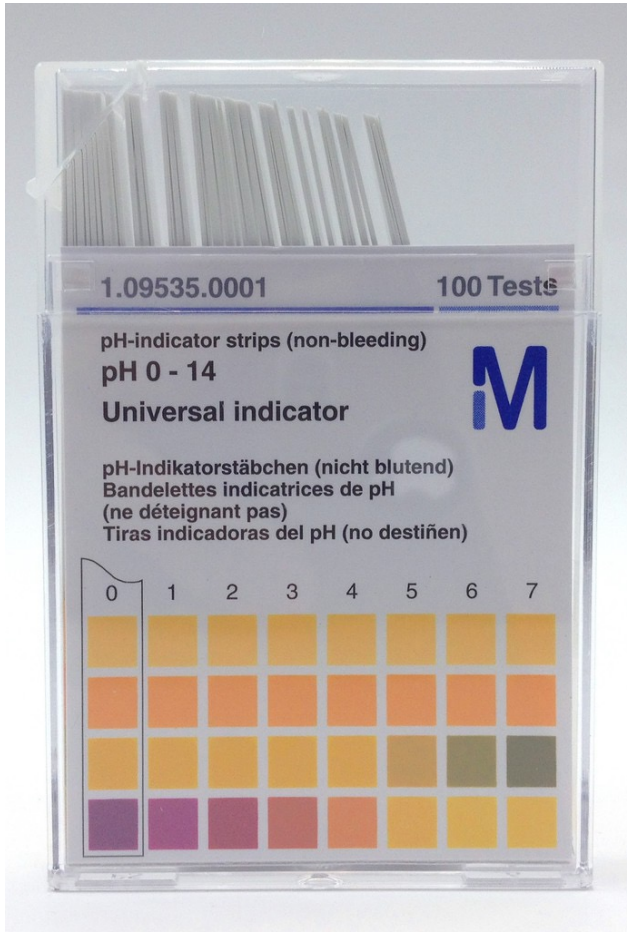
Hence, there is a significant interest in developing portable and inexpensive diagnostic platforms for various viral diseases and testing at point-of-care (POC) settings.

Advantages

- Low cost,
- Easy handling,
- Disposable,
- Transport,
- Storage,
- usable at POC settings.

PAPER! **(NitroCellulose)**





Paper-based sensors were introduced in the seventeenth century for colorimetric **detection of uric acid** through silver-based filter paper (Schiff, 1866).

Over the following years, a few other applications including the detection of **glucose** in urine and **cadmium** were published (Bayley, 1878; Oliver, 1883).

Despite these early implementations, it was only from the 1940s to 1990s that the next generation of paper-based analytic devices gained prominence with developments in **chromatography and analytical chemistry** (Ahmed et al., 2016).

Microfluidic technology has gained precedence in developing point-of-care diagnosis through advanced sensor kits (Hawkins and Weigl, 2010). The popularity of microfluidic paper diagnostic devices increased as it was **cost-effective, easy to use, and disposable.**

Currently, research focused on paper-based platforms, which use colorimetric, fluorometric, and electrochemical approaches, involves diagnosing through the signal received from the analyte (Shafiee et al., 2015).

To **enhance the sensitivity** of paper-based analytic devices, nanoparticles including AuNPs, AgNPs, carbon NPs, liposome, magnetic NPs, and QDs have been used in combination with enzymes and other materials (Lopez-Marzo and Merkoci, 2016).

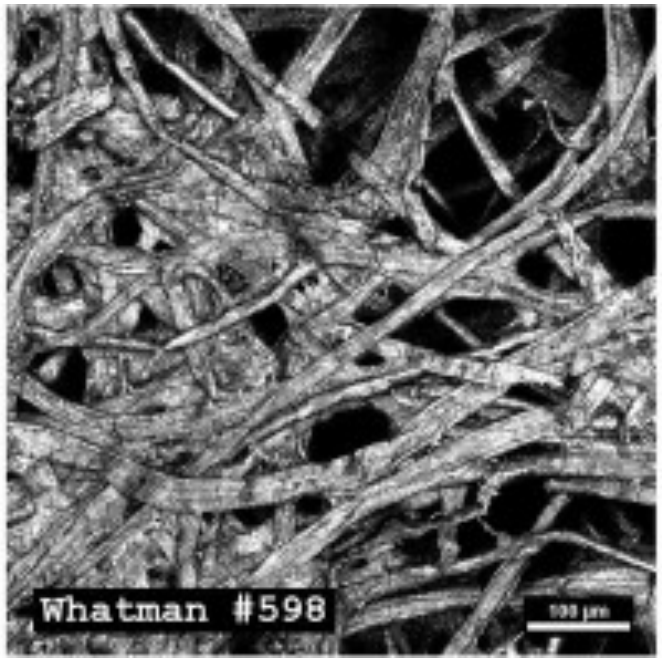
Recent Developments in Applied Microbiology and Biochemistry, 2019, Pages 349-361

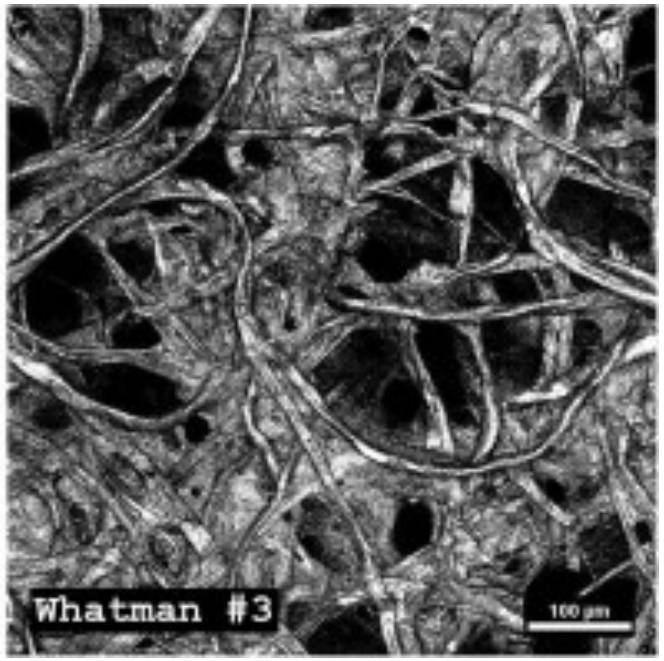
Reagent Storage

Reagent storage plays an important role for paper diagnostics.

Porous materials are capable of storing large amounts of reagents in the dry form over a longer period (Stevens et al., 2008).

Paper with large pores can capture molecules in its dried form and activated by addition of samples (Chong et al., 2013).

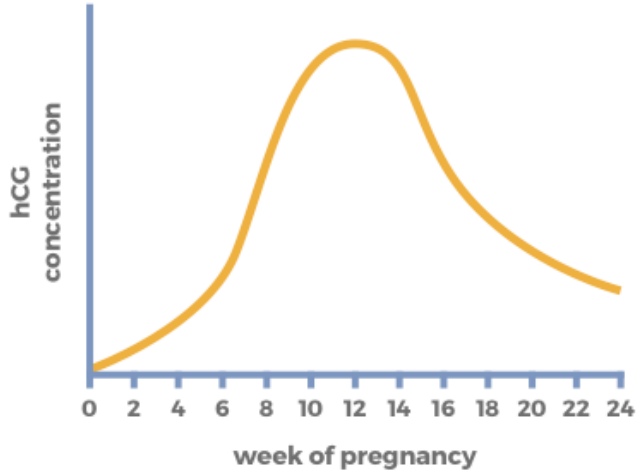




HOW DO PREGNANCY TESTS WORK?

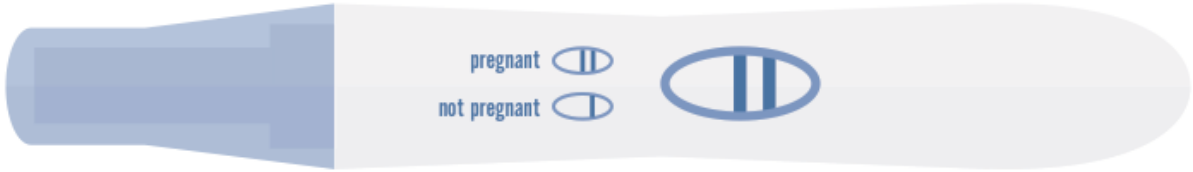
WHAT DO PREGNANCY TESTS DETECT?

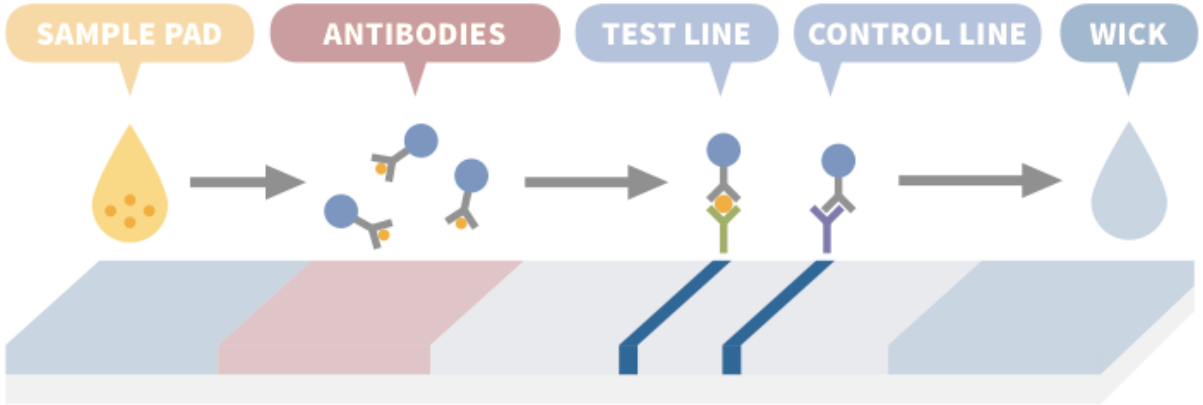
Pregnancy tests detect a hormone called human chorionic gonadotropin (hCG). This hormone is produced by the placenta from the time at which the embryo attaches to the uterus.



hCG is essential for the function of the corpus luteum, a temporary structure in the ovaries that produces the hormones progesterone and estrogen. It has also been linked to early pregnancy symptoms such as nausea and vomiting. hCG is eliminated in urine and can be detected by pregnancy tests around 9 days after fertilisation.

HOW DO PREGNANCY TESTS WORK?





Urine applied to the sample pad. If a woman is pregnant, urine contains hCG.

hCG binds to mobile antibodies. These antibodies also have an enzyme attached to them.

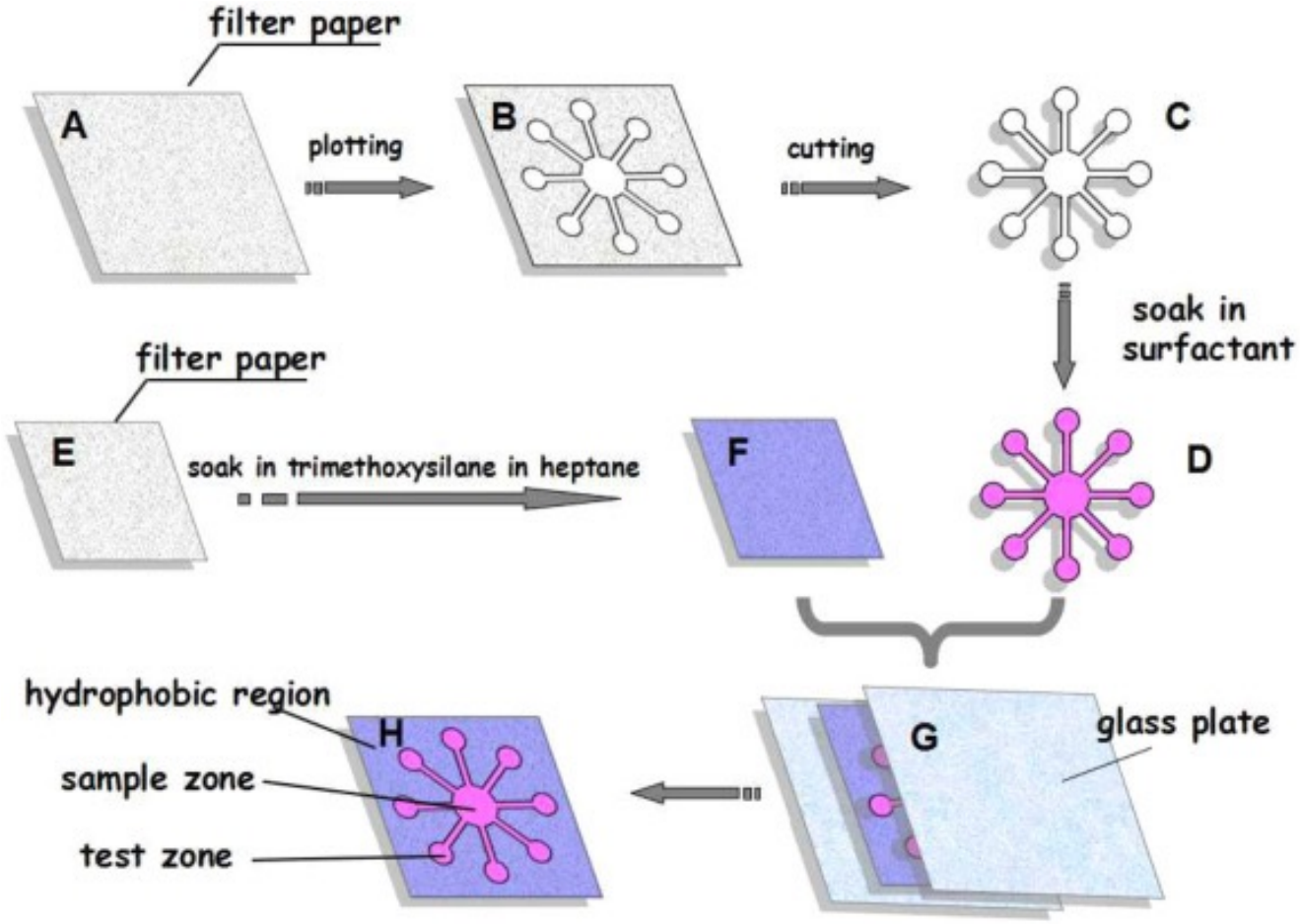
Immobilised antibodies in the test zone bind to hCG. The enzyme on the first antibody changes the test line colour. Excess antibodies bind to immobilised antibodies in the control zone to show the test worked correctly.

Creating reaction chambers

For paper-based device fabrication, the paper device is designed to contain a **hydrophilic pattern**, as **hydrophobic walls** enable the easy flow of liquid onto the device.

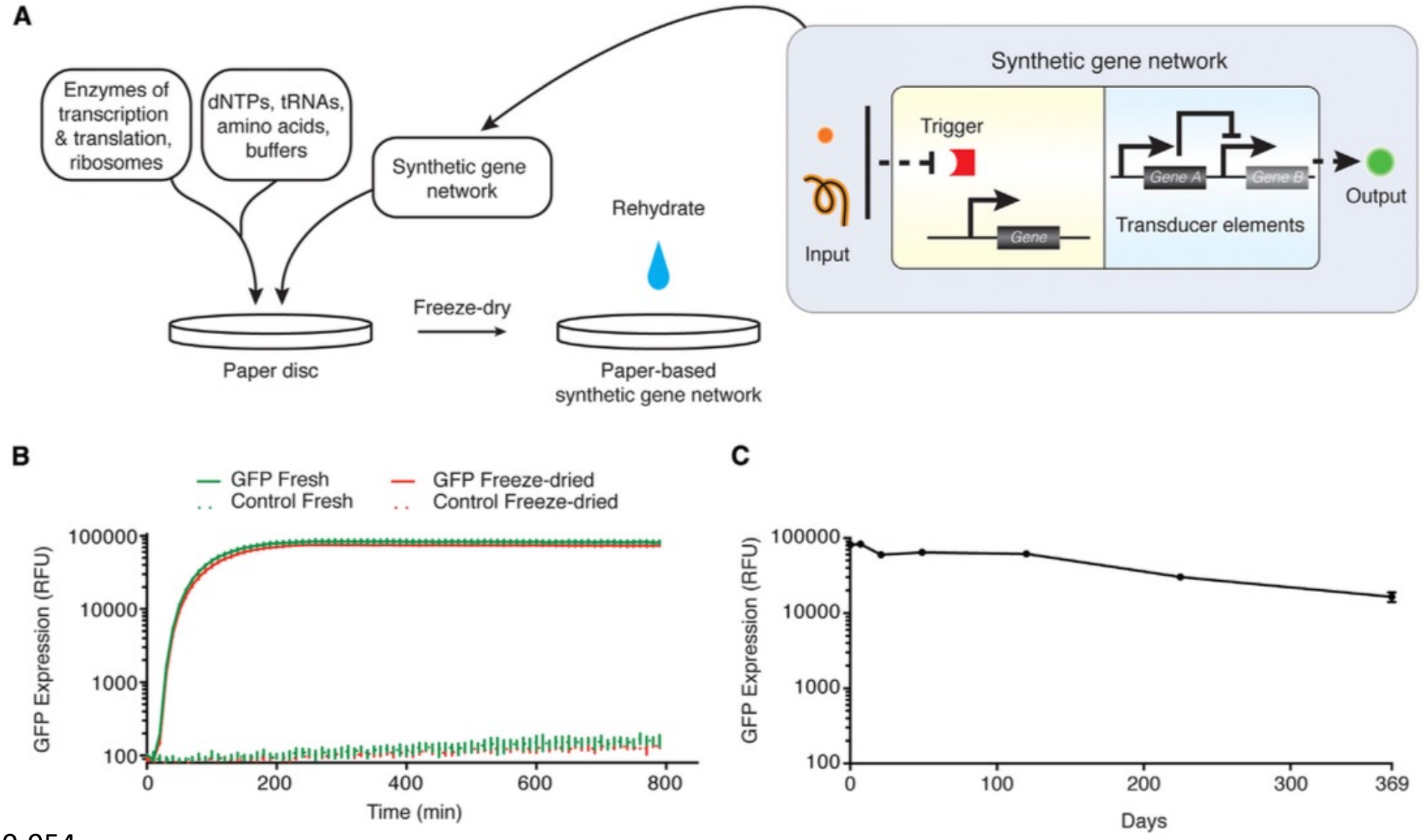
The main role of the pattern is to **avoid the spreading of liquid** in undesired areas, reaction with specific detection areas, or parallelization of multiple reactions in a single device.

Photolithography is often used to make paper-based devices through an inkjet printer, a photocopying machine, and even a hand drawing based on the UV exposure.



Analytical Biochemistry
Volume 525, 15 May 2017, Pages 100-106

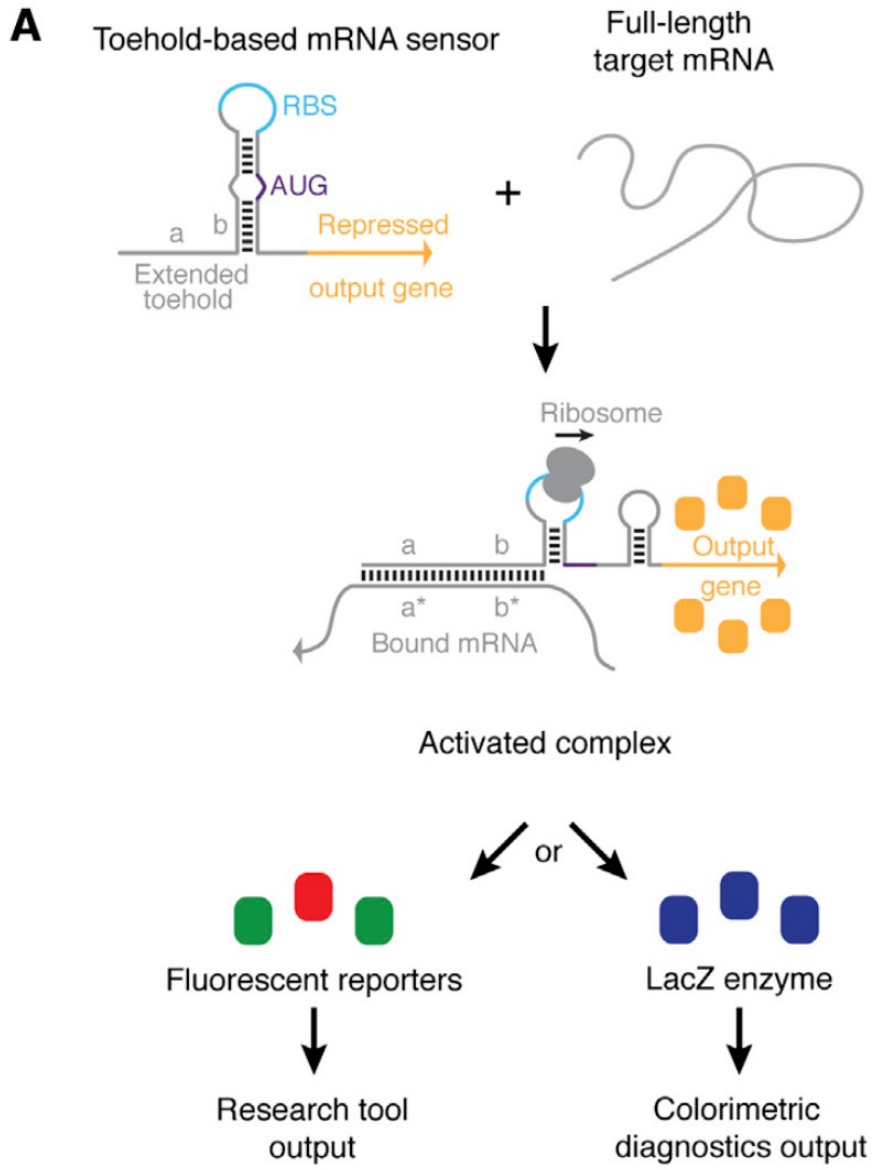
Including Bioreactions to Detect Viruses



Pardee, Cell
159, 4, 2014, 940-954

Including Bioreactions to Detect Viruses

- Virus has long single strand RNA genome
- This can hybridize to the complementary sequence on an RNA sensor
- If the sequence match, the start codon becomes available and transcription can start
- Fluorescent proteins will provide signal or enzymes show reaction output



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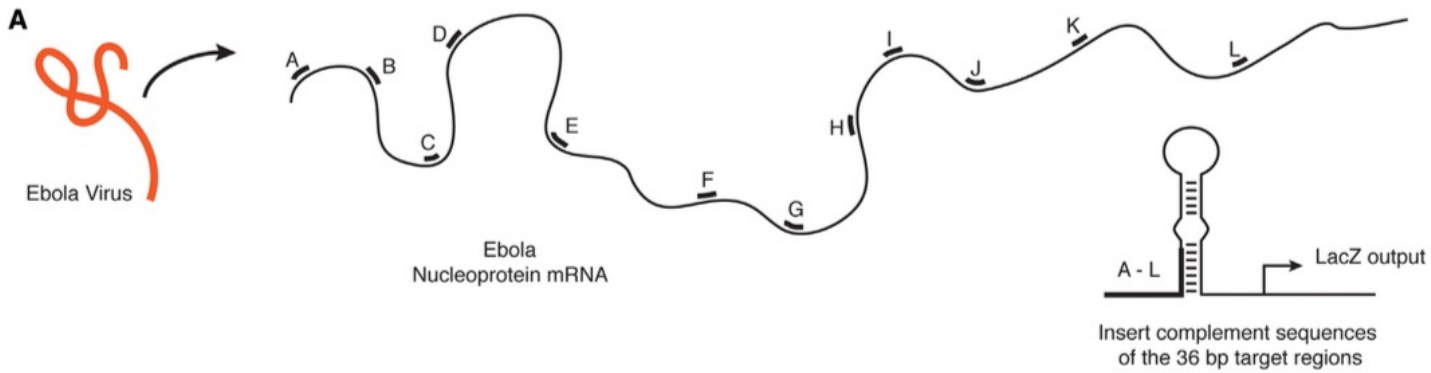
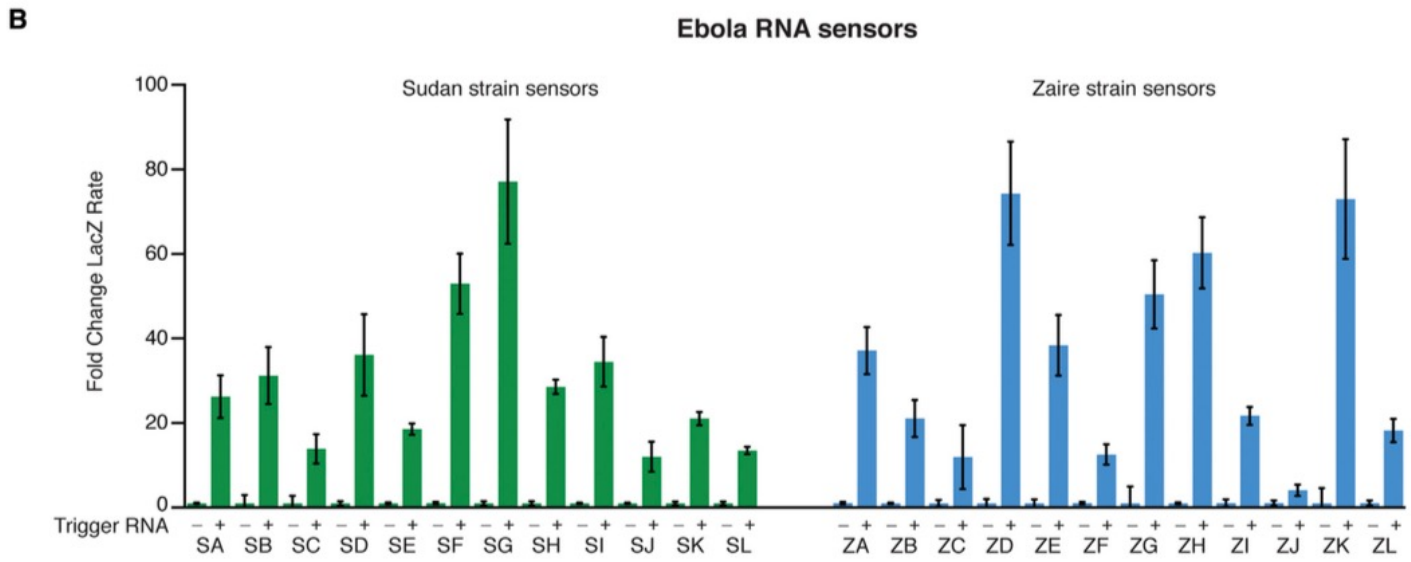
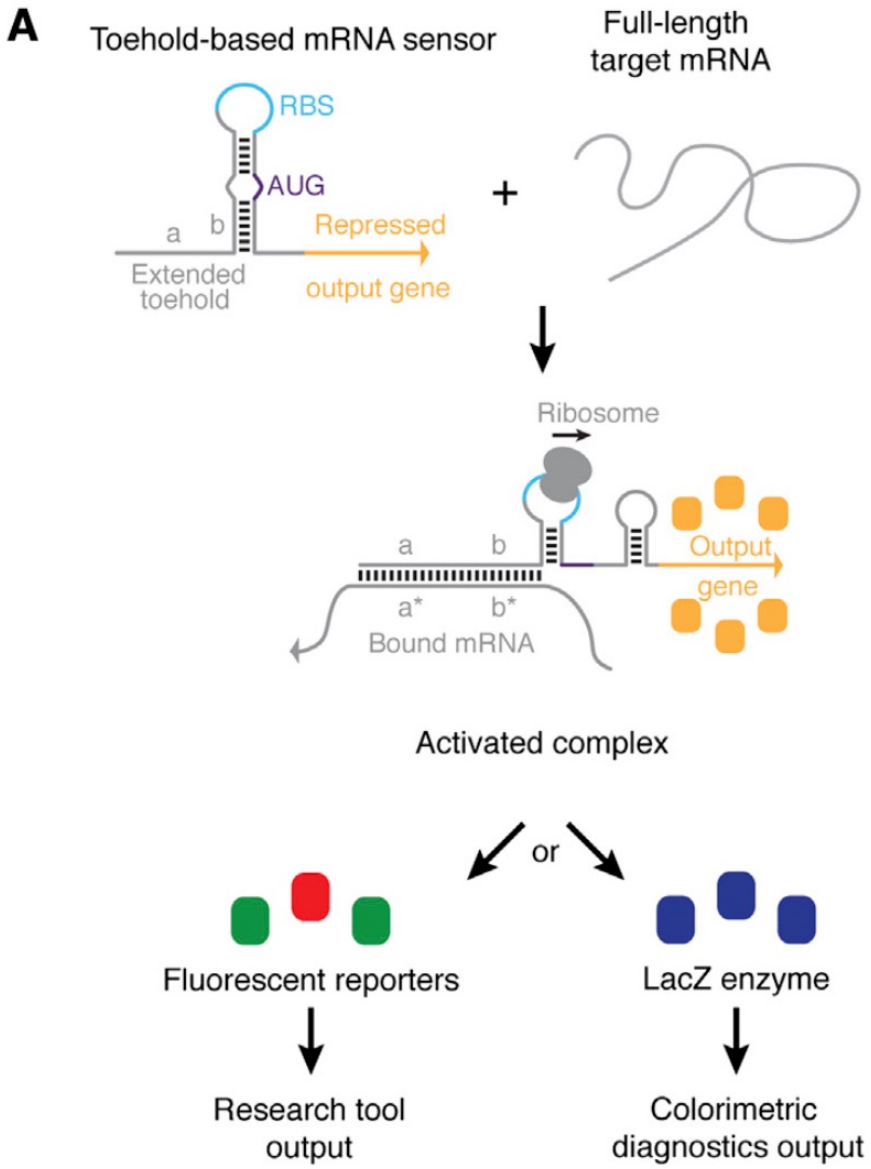
Including Bioreactions to Detect Viruses







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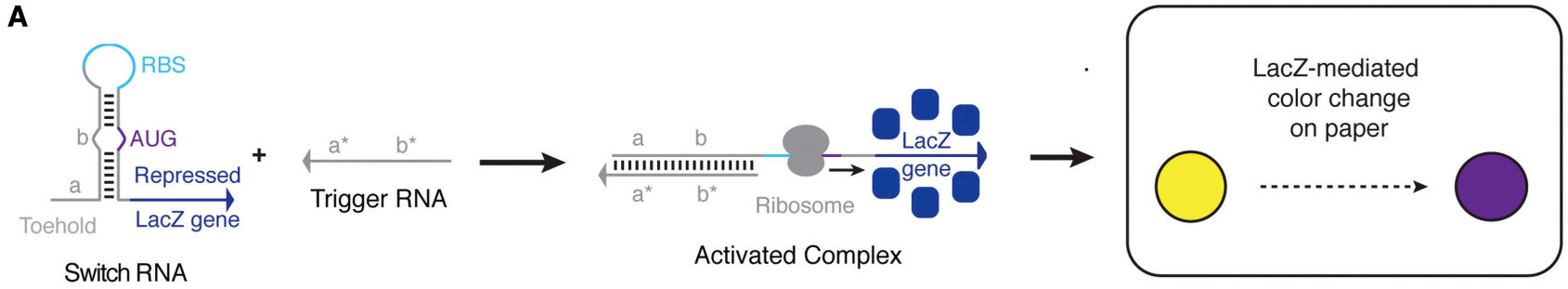
Including Bioreactions to Detect Viruses

(A) A schematic of the modified, LacZ-expressing toehold switches used to generate colorimetric outputs.



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Including Bioreactions to Detect Viruses

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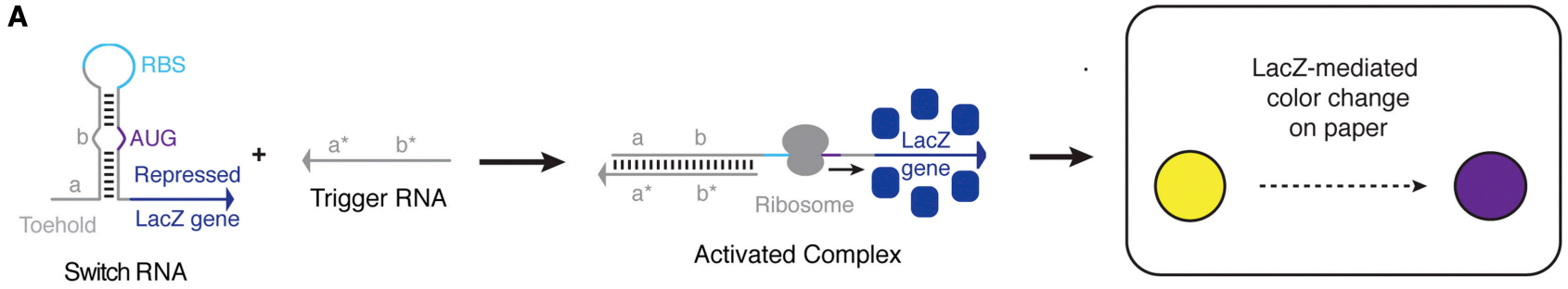
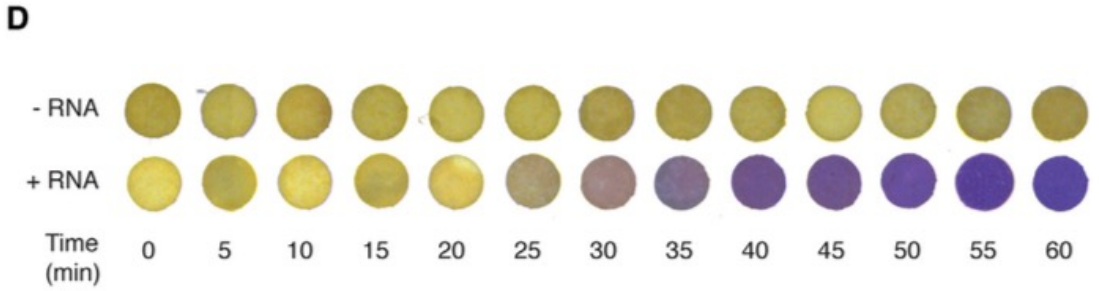
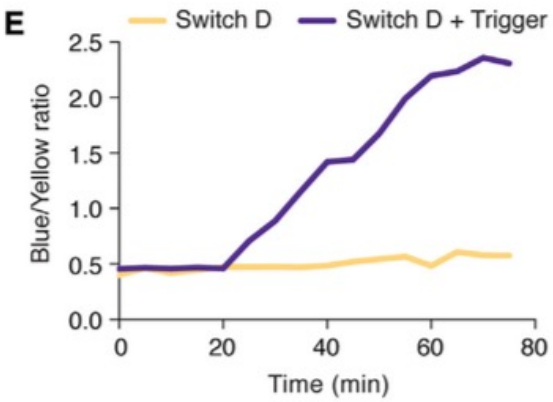


(D) The paper-based development of color from LacZ toehold switch D over 60 min.



(E) Color intensities from (D) were converted to a ratio of blue over yellow (red + green channels) channels and graphed over time.



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Including Bioreactions to Detect Viruses

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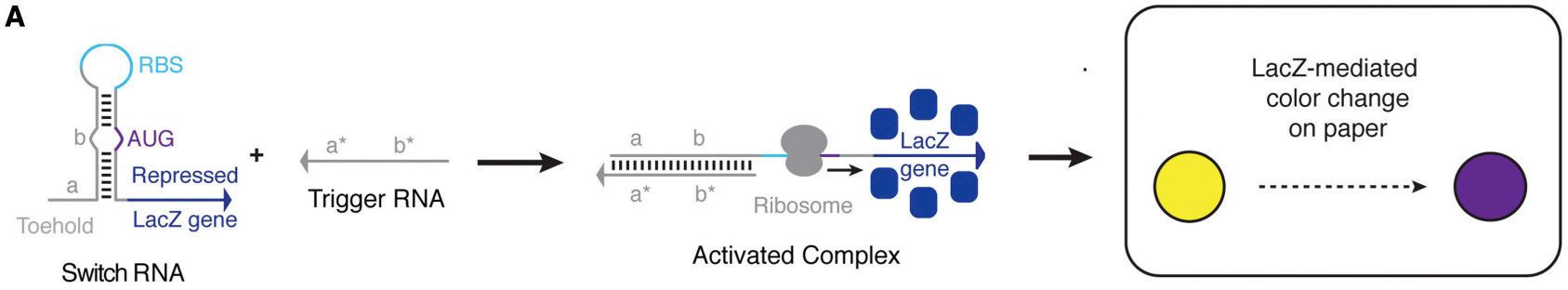

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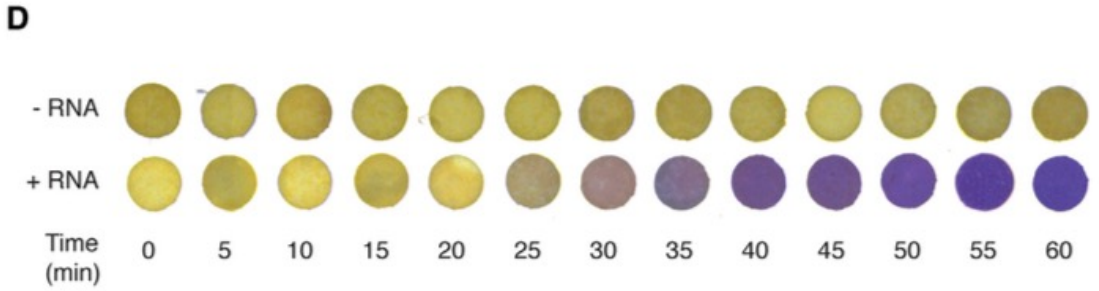

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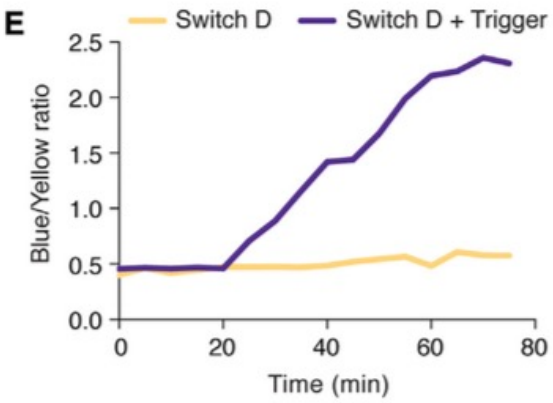
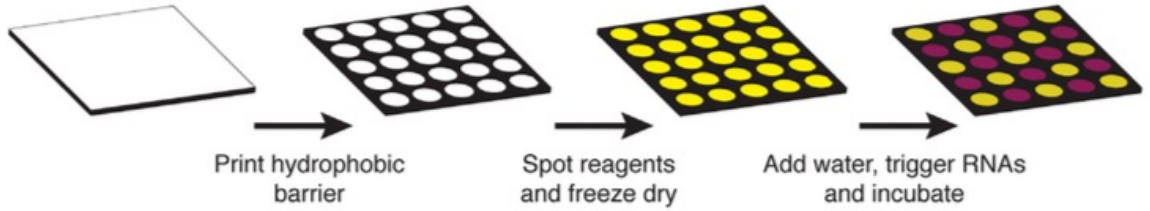
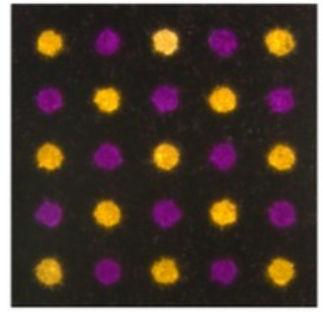


(F) Schematic describing the process of arraying synthetic gene networks on paper using printed arrays.



(G) A 25-reaction printed array (14 × 14 mm) of toehold switch E, containing positive reactions (purple) and negative control reactions (yellow) distributed in a checkerboard pattern following a 2 hr incubation.



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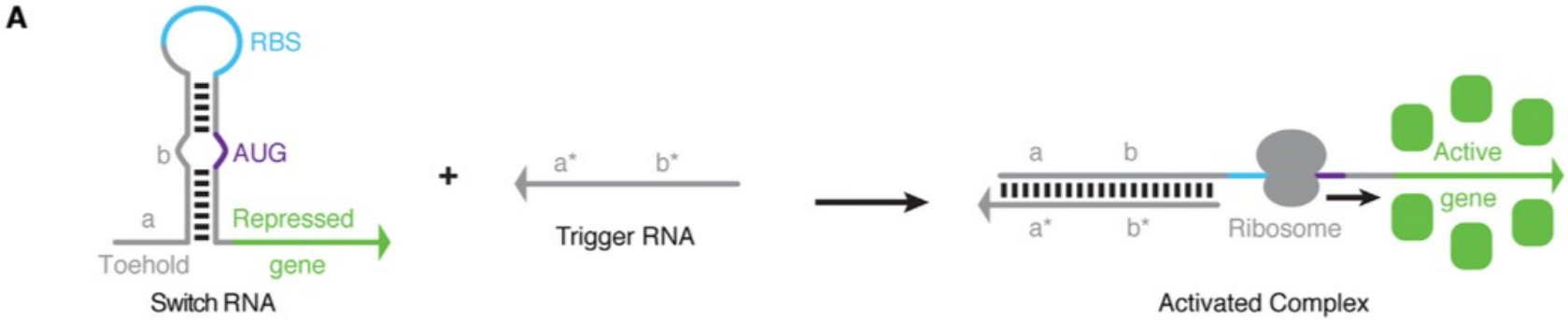
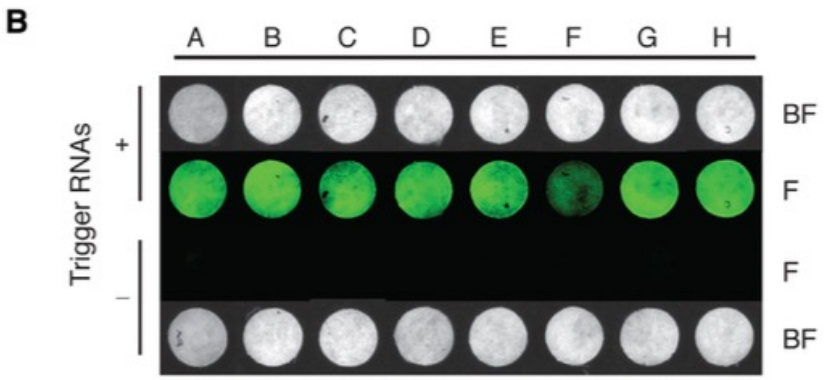
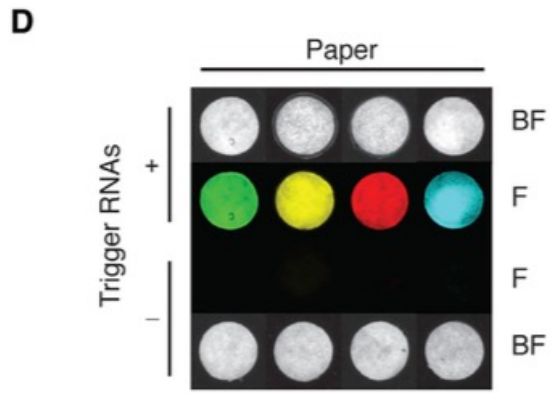
Paper Based Ebola Virus Test

Highlights

- A stable, sterile, and abiotic paper-based platform for synthetic biology
- Enables rapid prototyping for cell-based research and gene circuit design
- Extends laboratory capabilities out of the lab and into the field
- Small-molecule and RNA sensors, including strain-specific Ebola virus sensors
- Cheap: 20USD per sensor







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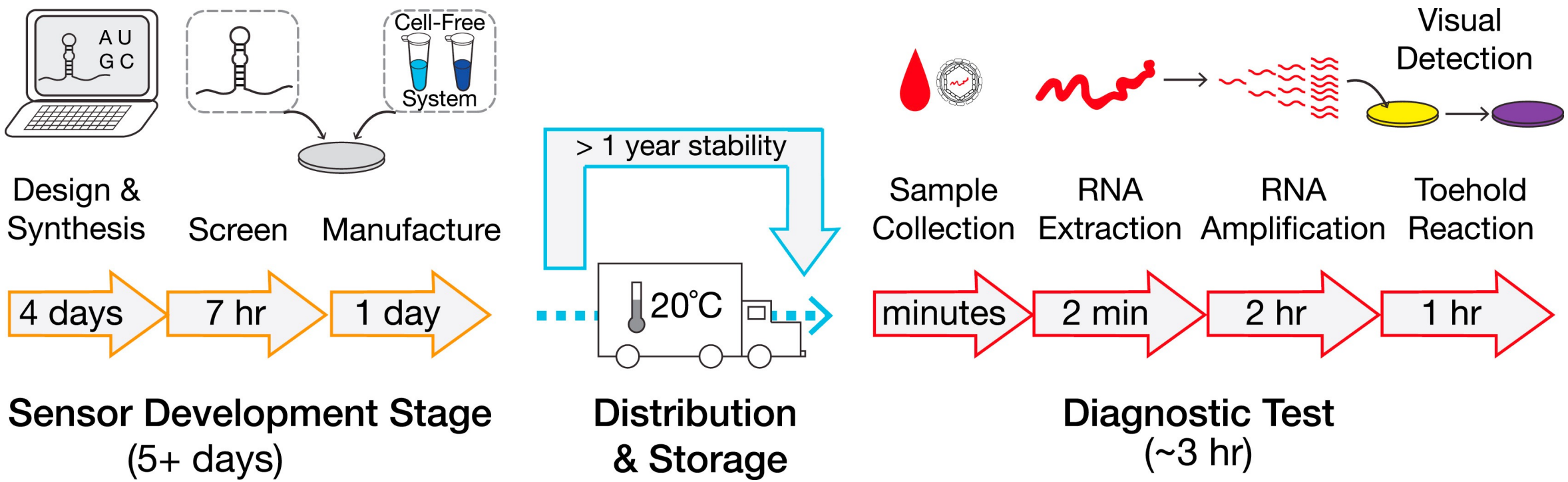
Paper Based Diagnostics Time Line

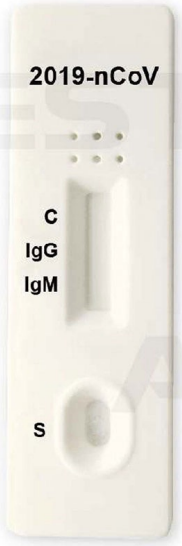


Cell
Volume 165, Issue 5, 19 May 2016, Pages 1255-1266

Paper Based COVID19 tests

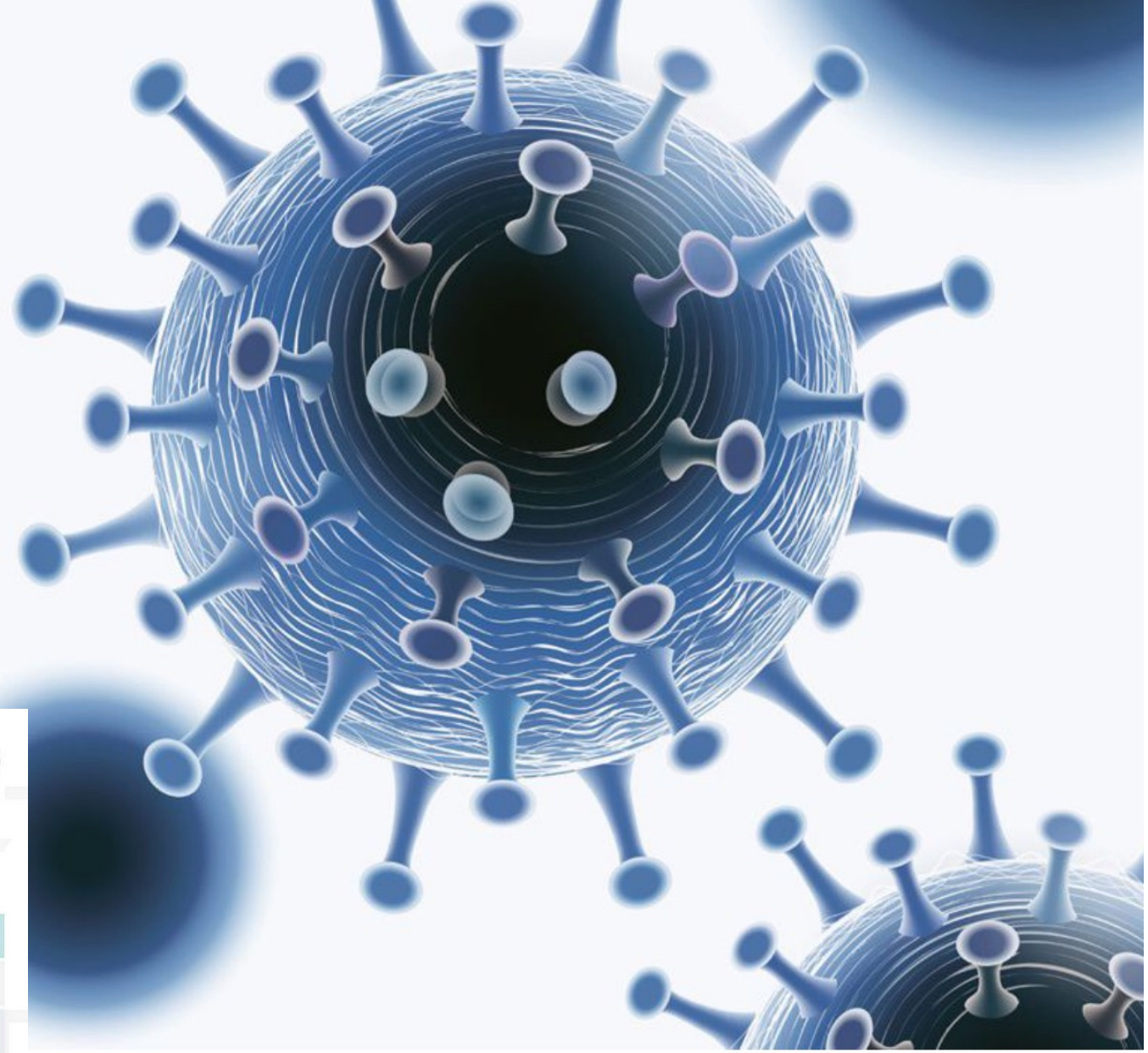
How the SARS-CoV-2 Rapid Antibody Test works[1]

The SARS-CoV-2 laboratory in your pocket. Results within 10 to 15 minutes[1], no analyzer needed and at the point of care.



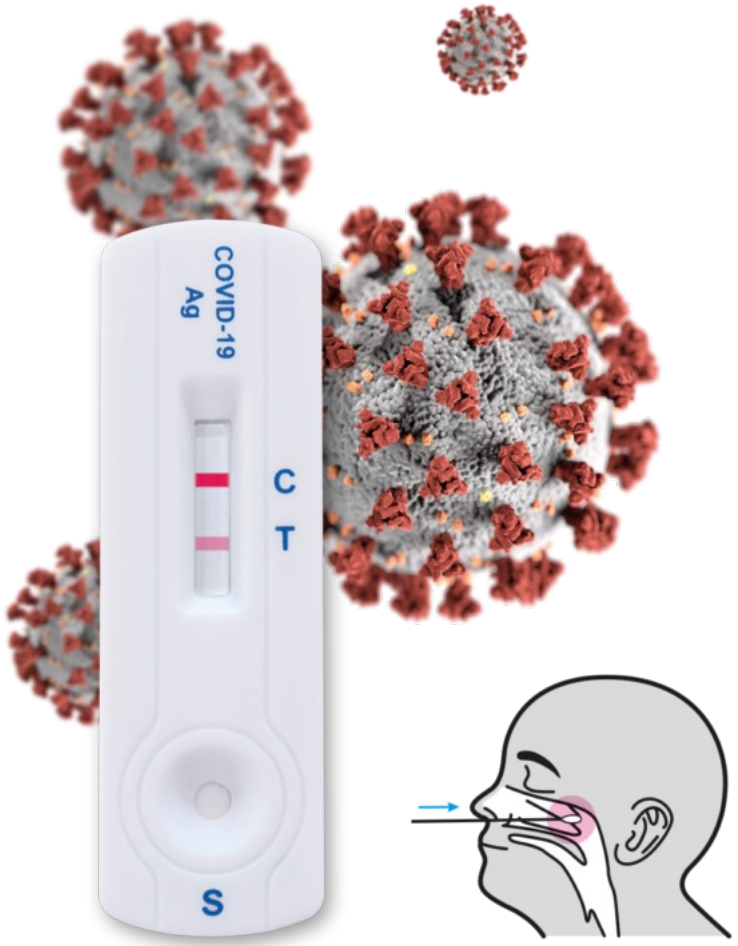
- √ *Fast results (10 mins)*
- √ *Simple operation*
- √ *High accuracy*

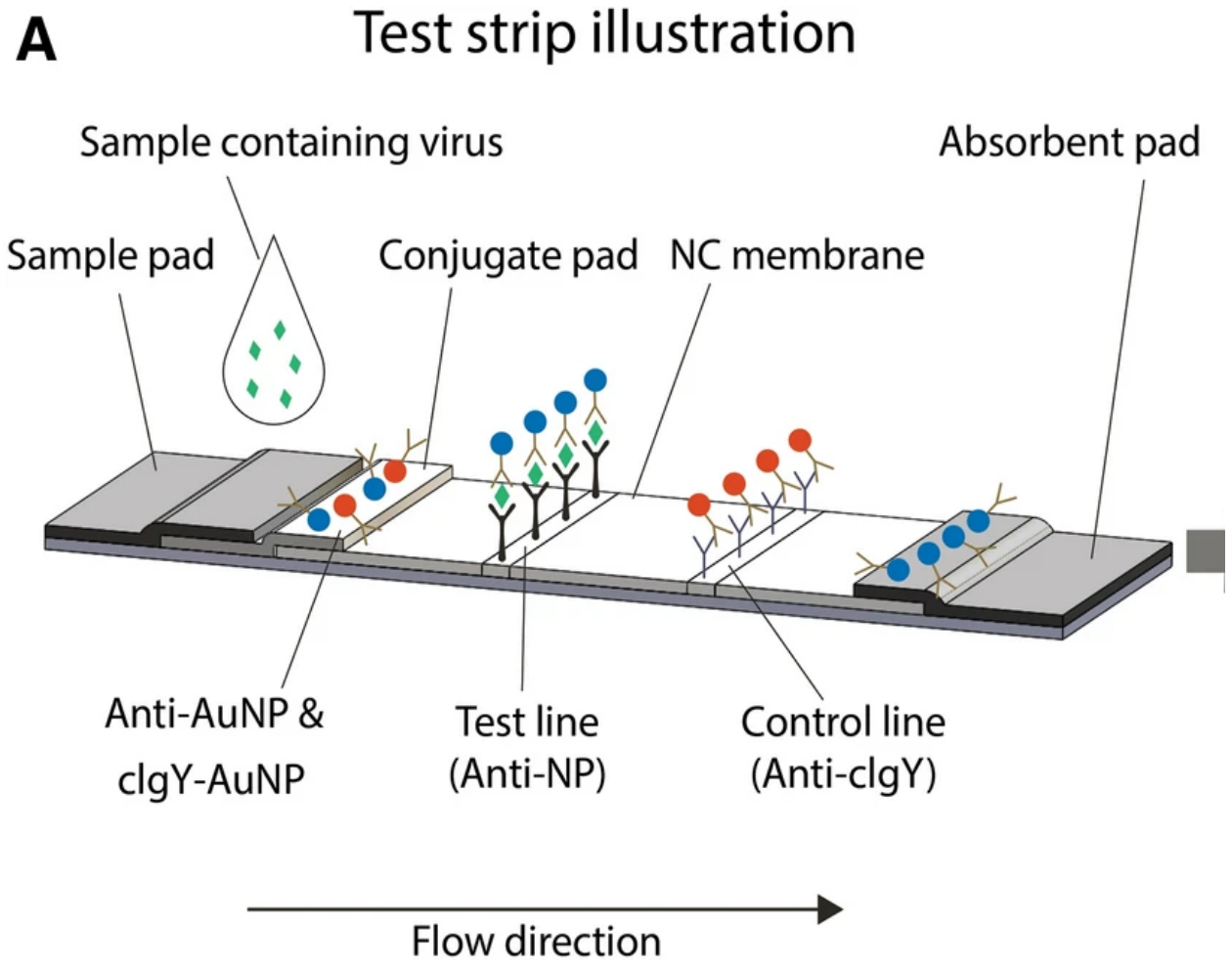
Analytes	2019-nCoV	
	IgG	IgM
Sensitivity	100%	85%
Specificity	98%	96%
Accuracy	98.6%	92.9%



Roche

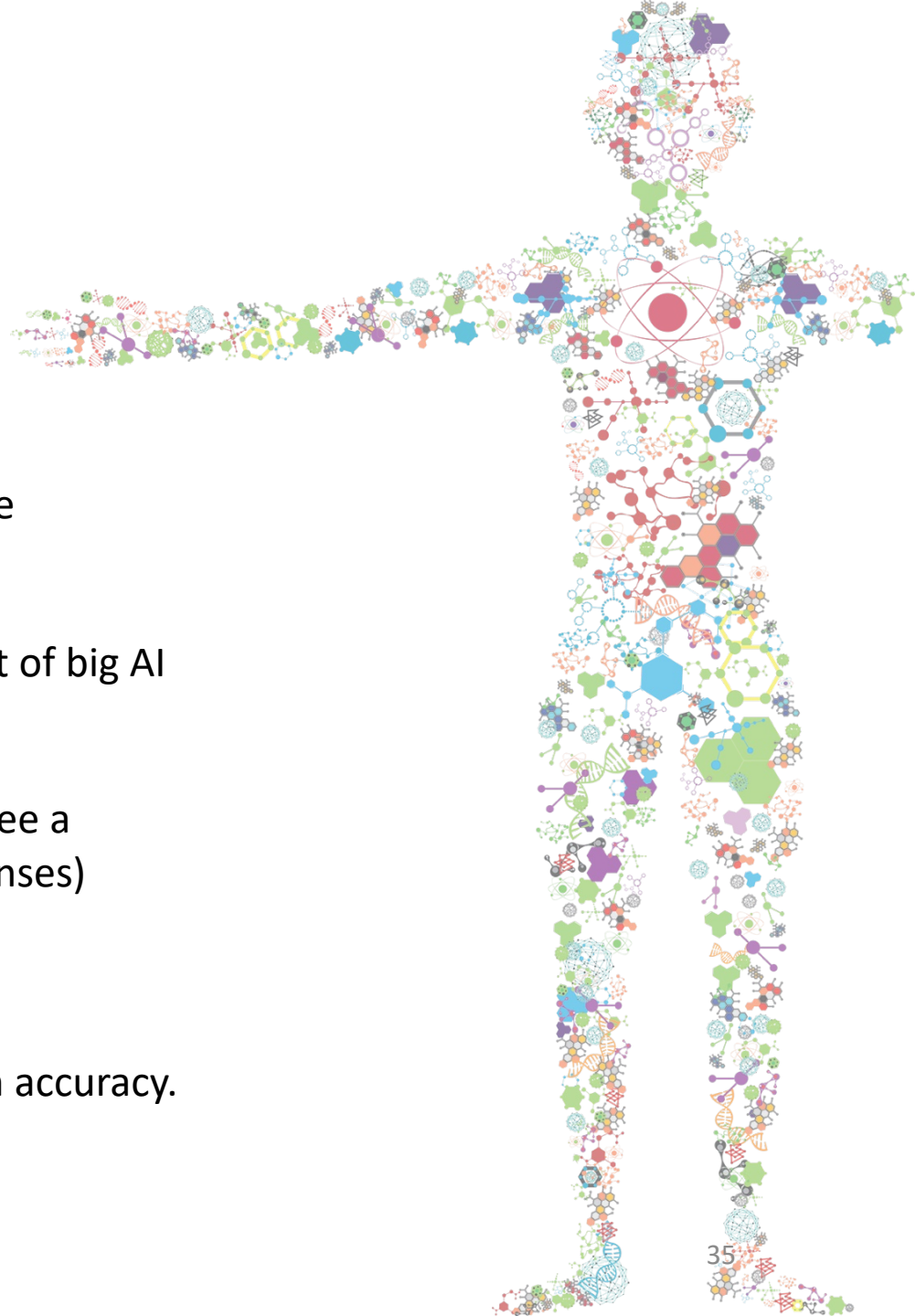
Paper Based COVID19 Fast Test





Frew, E., Roberts, D., Barry, S. *et al.* A SARS-CoV-2 antigen rapid diagnostic test for resource limited settings. *Sci Rep* **11**, 23009 (2021). https://doi.org/10.1038/s41598-021-02128-y

Conclusion



Sensors and Diagnostic Devices, while generally used outside the body, are biomaterials. (see definition in course 1)

They form a forefront field of research, especially with the current interest of big AI companies like Google.

Soft electronics are being integrated in human-contact and we will likely see a “smartification” of everyday objects over the next decade (i.e. contact lenses)

Paper is an excellent substrate for diagnostic tools.

Integration of bio reactions make it possible to detect viral loads with high accuracy.