# Introduction to Lab-on-a-chip

Paper-based microfluidic sensors

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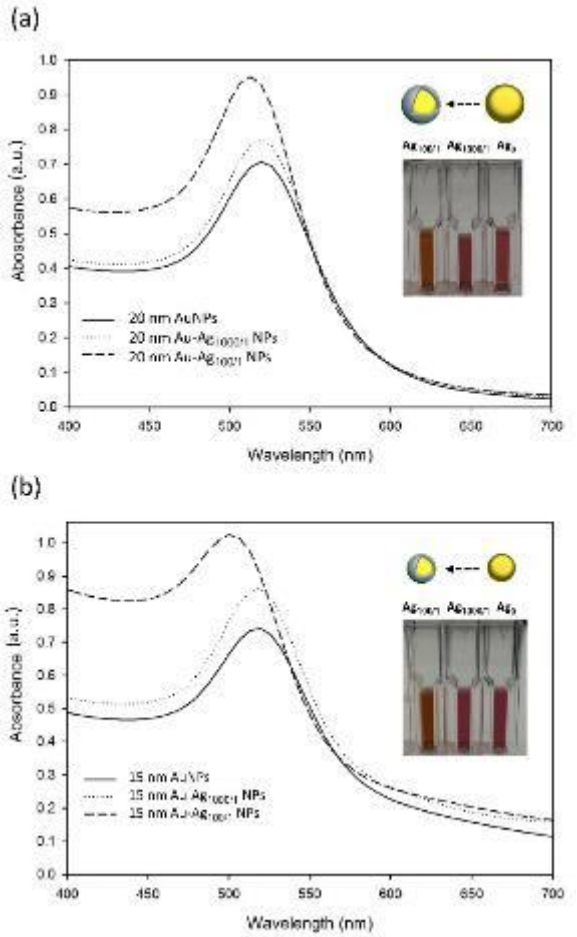
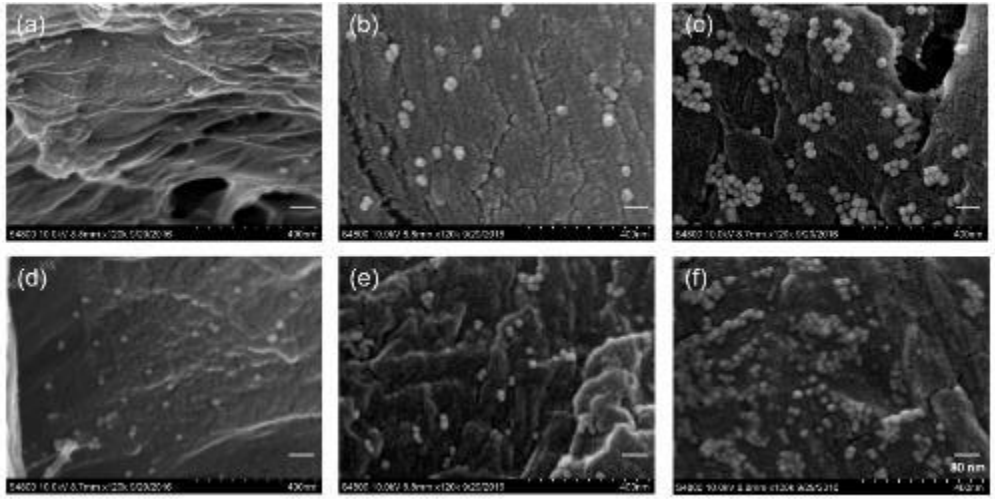
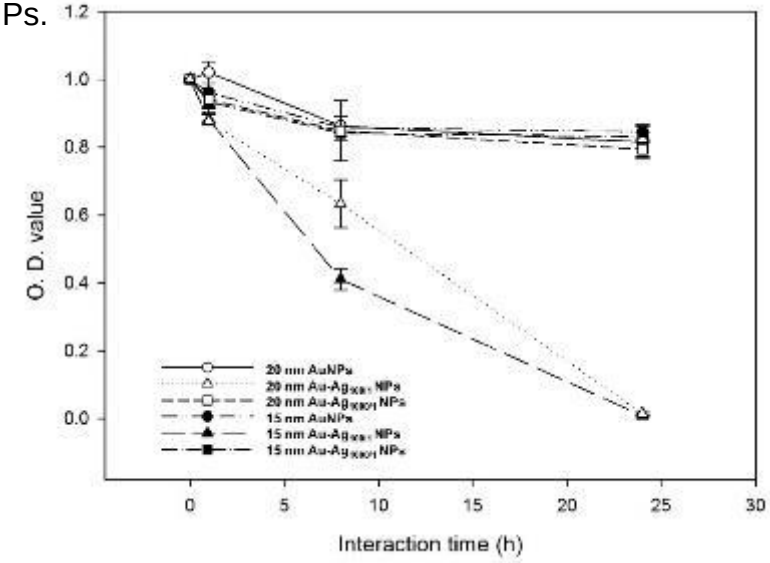
# Antibacterial Cellulose Paper Made with Silver-Coated Gold Nanoparticles




UV-Vis absorption spectra of different diameter Au and Au-Ag NPs. The plot shows the (a) 20 nm and (b) 15 nm Au and Au-Ag NPs at different ratios of Ag enhancement.




SEM images of the different Au and Au-Ag NPs on cellulose paper. The bright spots in the images are NPs, specifically (a) 20 nm Au NPs, (b) 20 nm Au-$Ag_{1000/1}$ NPs, (c) 20 nm Au-$Ag_{100/1}$ NPs, (d) 15 nm Au NPs, (e) 15 nm Au-$Ag_{1000/1}$ NPs, and (f) 15 nm Au-$Ag_{100/1}$ NPs.




The survival curve of *E. coli* exposed to Au and Au-Ag NPs. *E. coli* were continuously exposed to different NP-coated cellulose paper for 24 h.

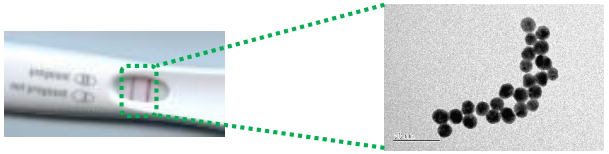
***Scientific Reports*, 7 (1), 3155**

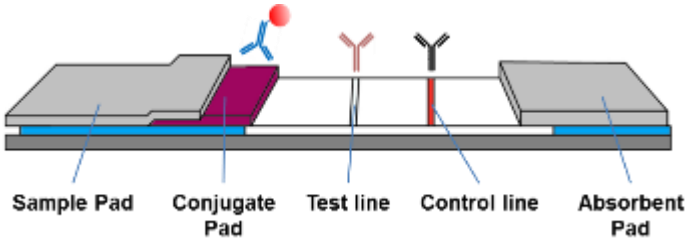
# Paper Devices

- **The wettability**
- **White**
- **Simple fabrication**
- **Cost effective**
- **Portable**
- **Disposable**
- **Flexible**
- **Easy to store and delivery**
- **Scalable**

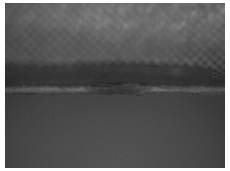
## Dipstick


## Lateral Flow Immunoassay (LFA)



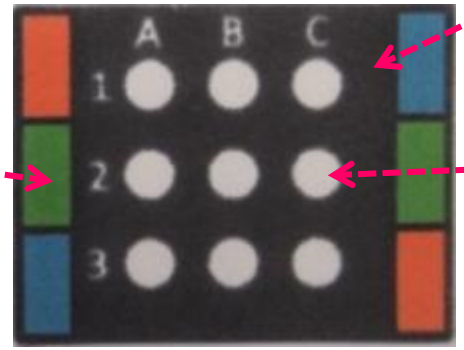




## Microfluidic Paper-Based Analytical Devices (µPADs)



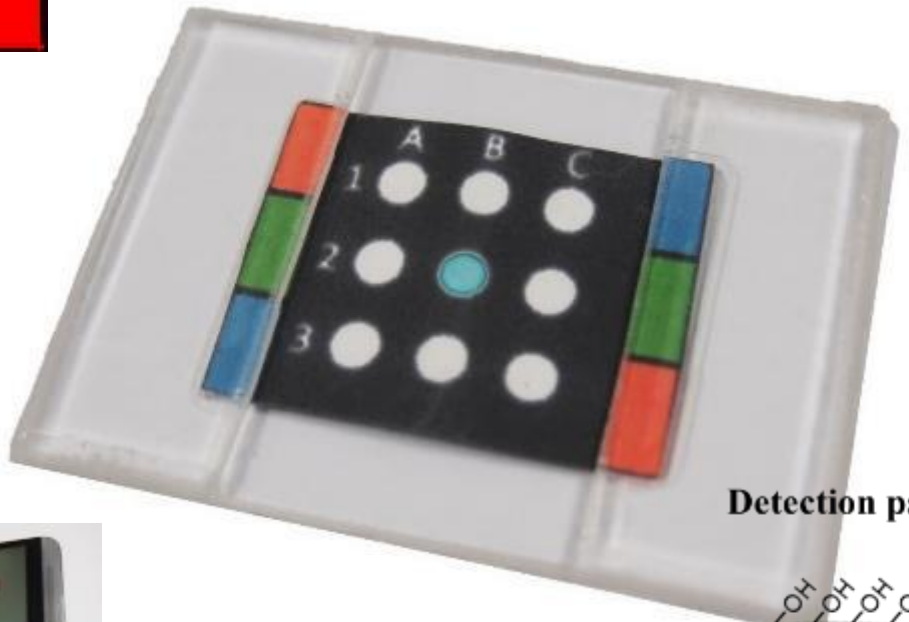
**Hydrophobic wax** for detection area definition

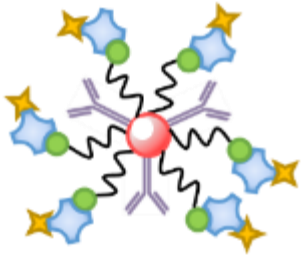
**Color bar** for light condition adjustment




**Hydrophilic area** for colorimetric detection

## Colorimetric or Electrical Sensing (capacitance or electrochemical)

## System Integration

## Signal Amplification

Result readout

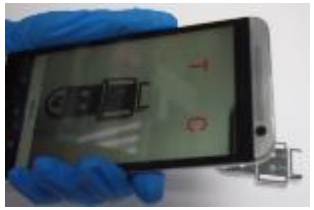
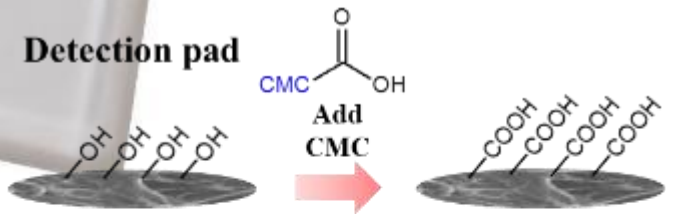


Image capture




## Surface Modification

# Smartphone Based Colorimetric Detection/Diagnosis


App for medical care

Selection of detection target

Selection of detection platform


Processes notice

Incubation

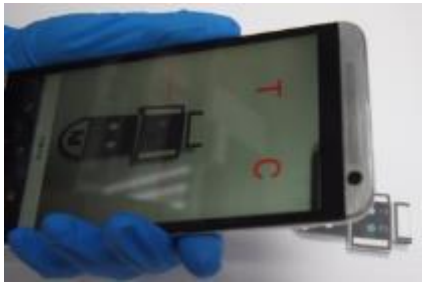
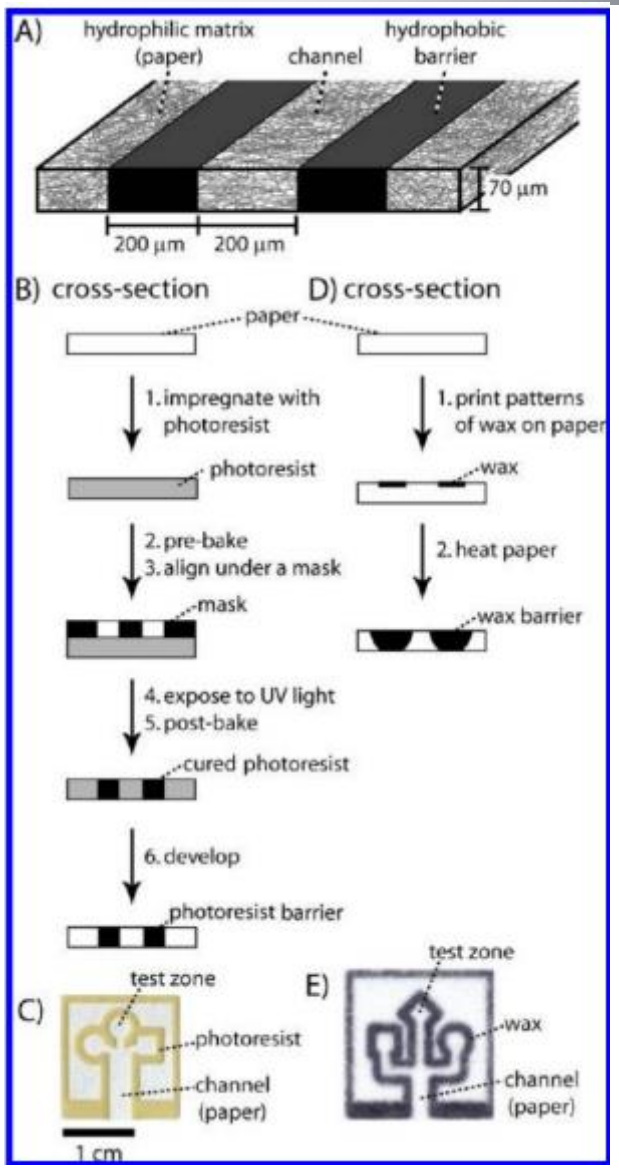


Image capture

Result readout

# Diagnostics for the Developing World: Microfluidic Paper-Based Analytical Devices



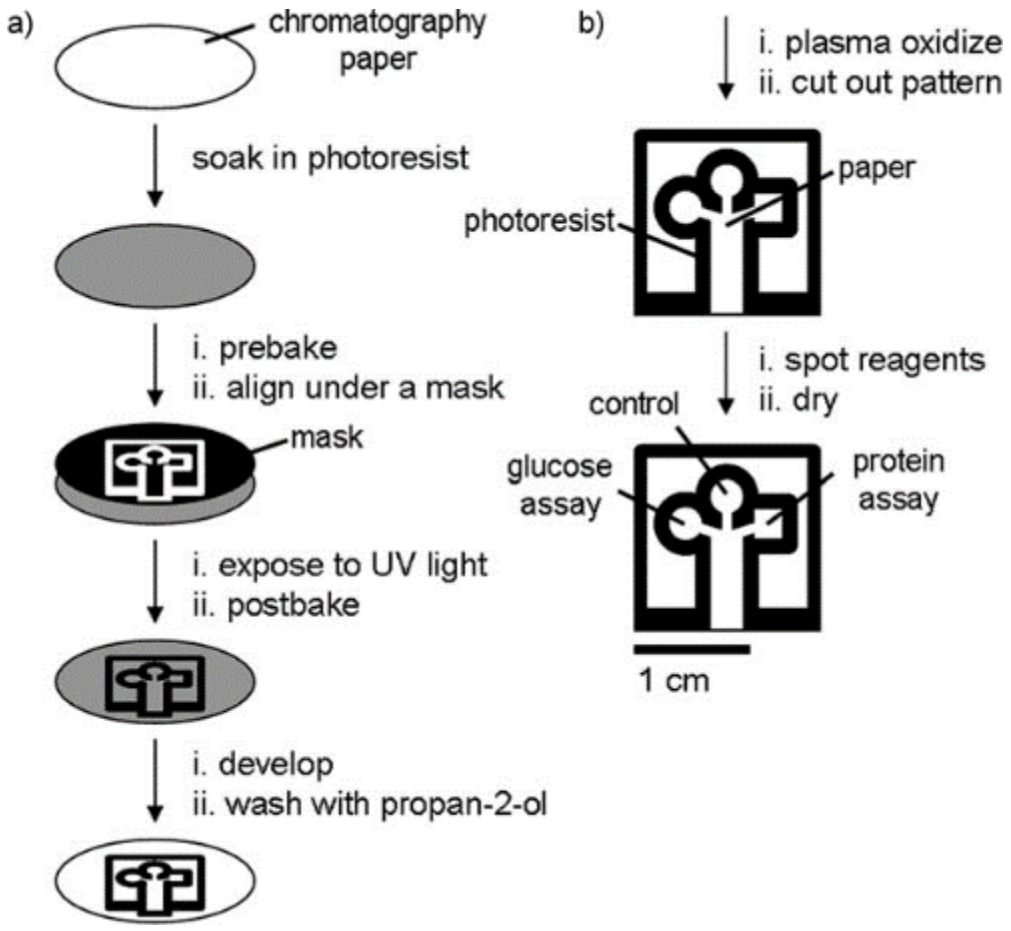




Diagram depicting the method for patterning paper into millimeter-sized channels

# Patterned Paper as a Platform for Inexpensive, Low-Volume, Portable Bioassays

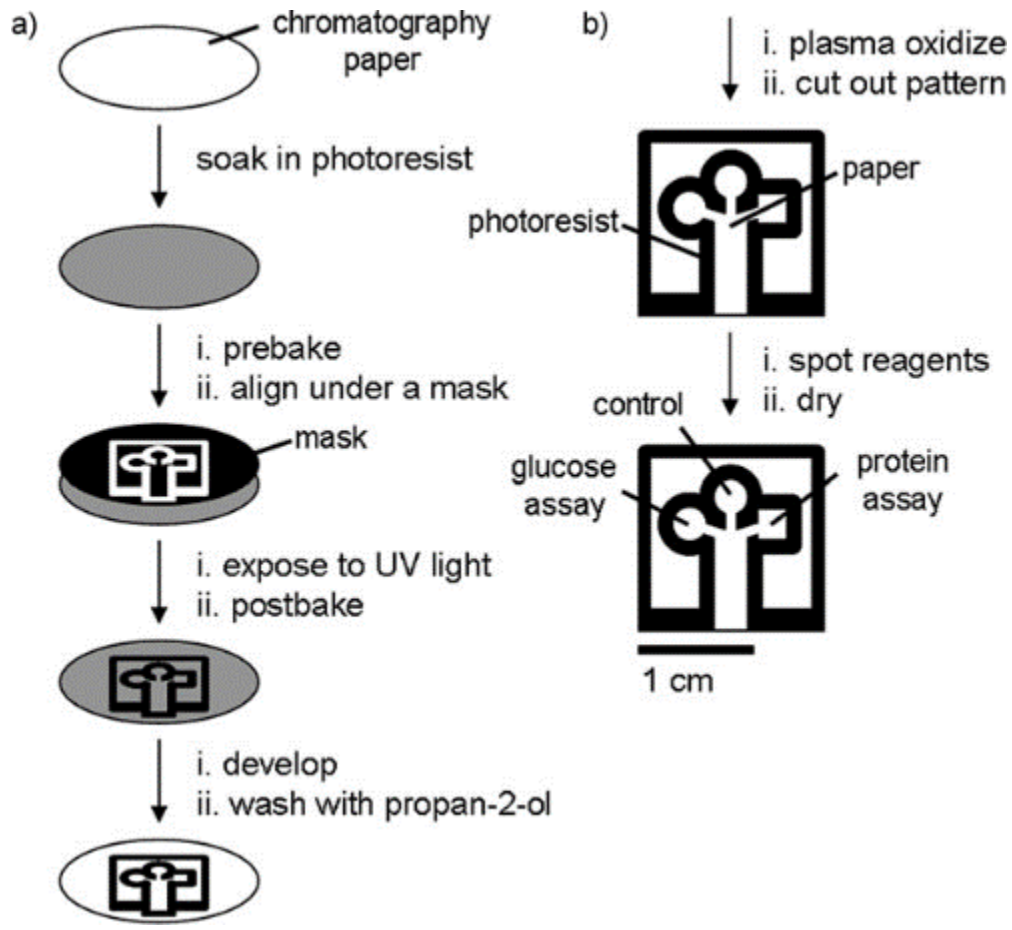
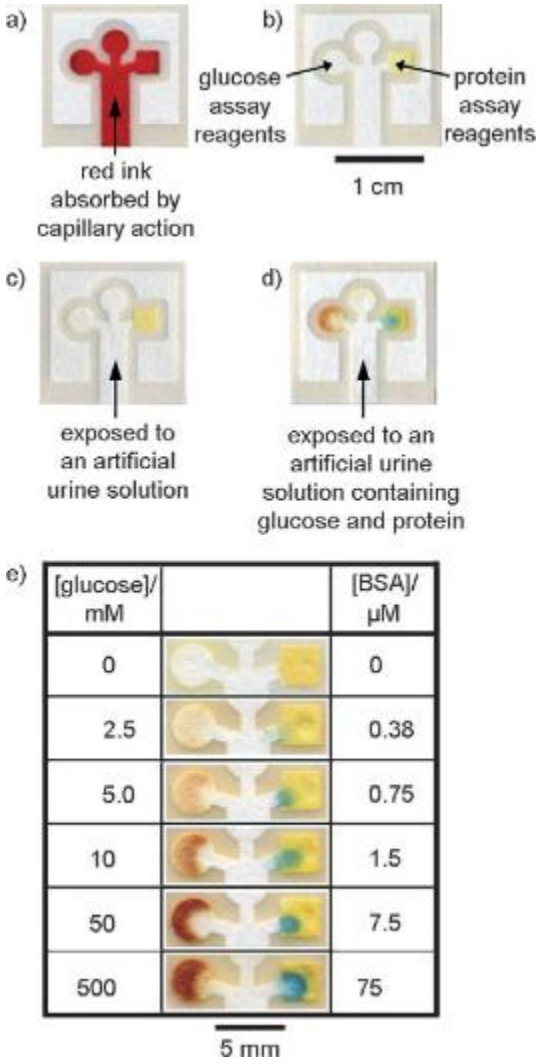



Diagram depicting the method for patterning paper into millimeter-sized channels



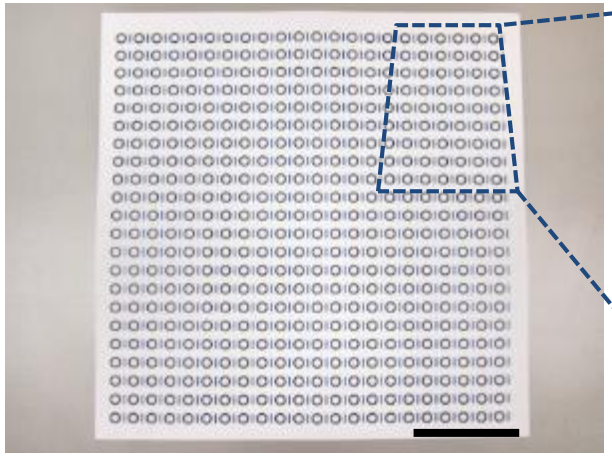

Chromatography paper patterned with photoresist. The darker lines are cured photoresist, whereas the lighter areas are unexposed paper.

# Paper-Based Devices Fabrication

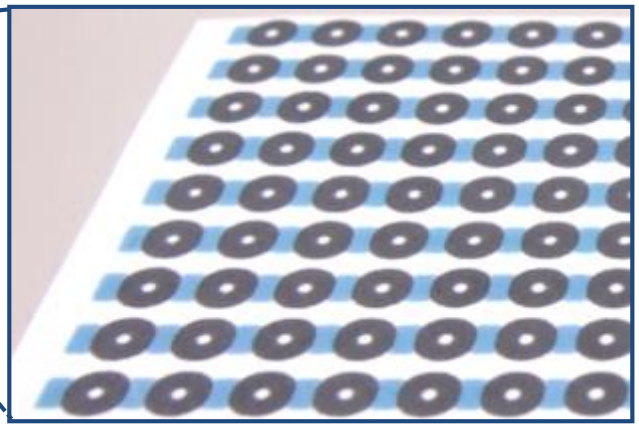
Device layout

Wax printing

Spot area formation



5 cm

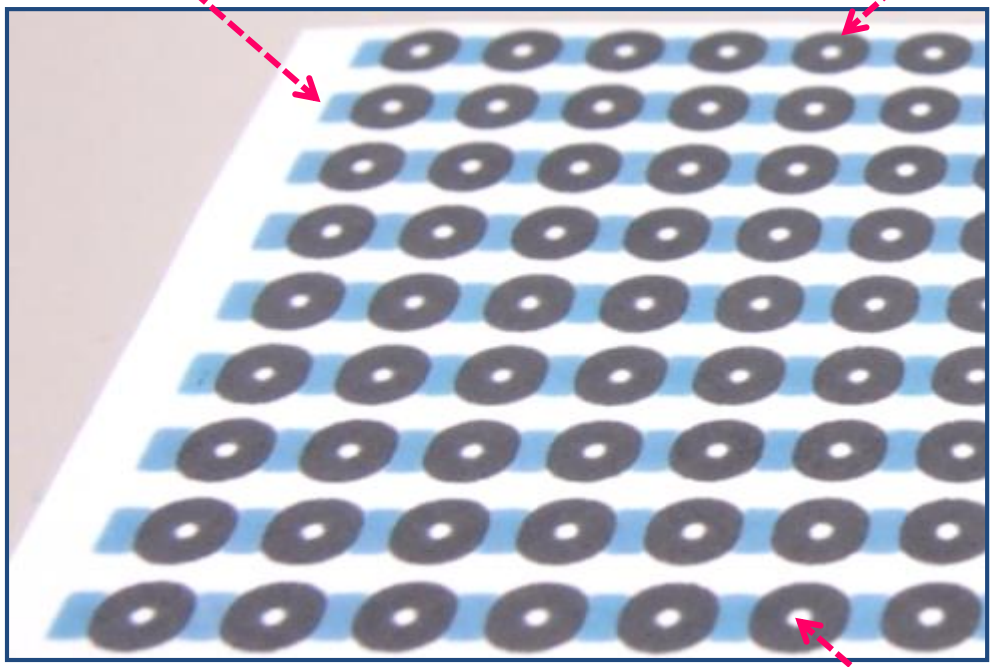


Microfluidic Paper-Based Analytical Devices (μPADs)

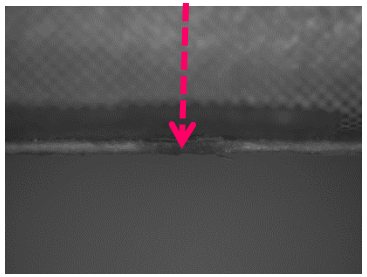
| Method (References) | Channel (μm) | Barrier (μm) | Advantages | Disadvantages |
|---|---|---|---|---|
| Photolithography (10) | 186 ± 13 | 248 ± 13 | Can pattern a wide variety of papers up to 360 μm in width. | Hydrophilic areas exposed to polymers and solvents. |
| Plotting (30) | ~1000[a] | ~1000[a] | Hydrophilic channels not exposed to polymers or solvents; hydrophobic barriers are flexible. | Requires a customized plotter. |
| Inkjet etching (31) | 420 ± 50 | —[a] | Reagents can be inkjet printed into the test zones using the printer. | Requires a customized inkjet printer; hydrophilic areas exposed to polymers and solvents. |
| Plasma etching (32) | ~1500[a] | —[a] | Useful for laboratories equipped with a plasma cleaner that wish to make many replicates of a few simple patterns. | Hydrophilic areas exposed to polymers and solvents; metal masks must be made for each pattern; cannot produce arrays of free-standing hydrophobic patterns. |
| Cutting (29) | 1000[b] | 700[b] | Hydrophilic channels not exposed to polymers or solvents. | Devices must be encased in tape; cannot produce arrays of free-standing hydrophilic patterns. |
| Wax printing (33,34) | 561 ± 45 | 850 ± 50 | Rapid (~5 minutes); requires only a commercially available printer and hot plate; hydrophilic channels not exposed to polymers or solvents. | The design of the patterns must account for the spreading of the wax in the paper. |

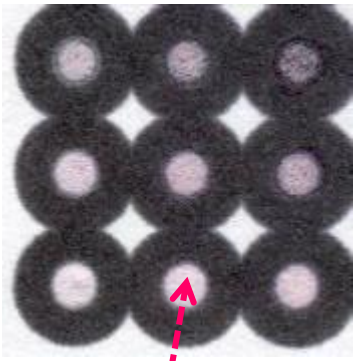
# Introduction to Microfluidic Paper-Based Analytical Devices (µPADs)

**Color bar for light condition**

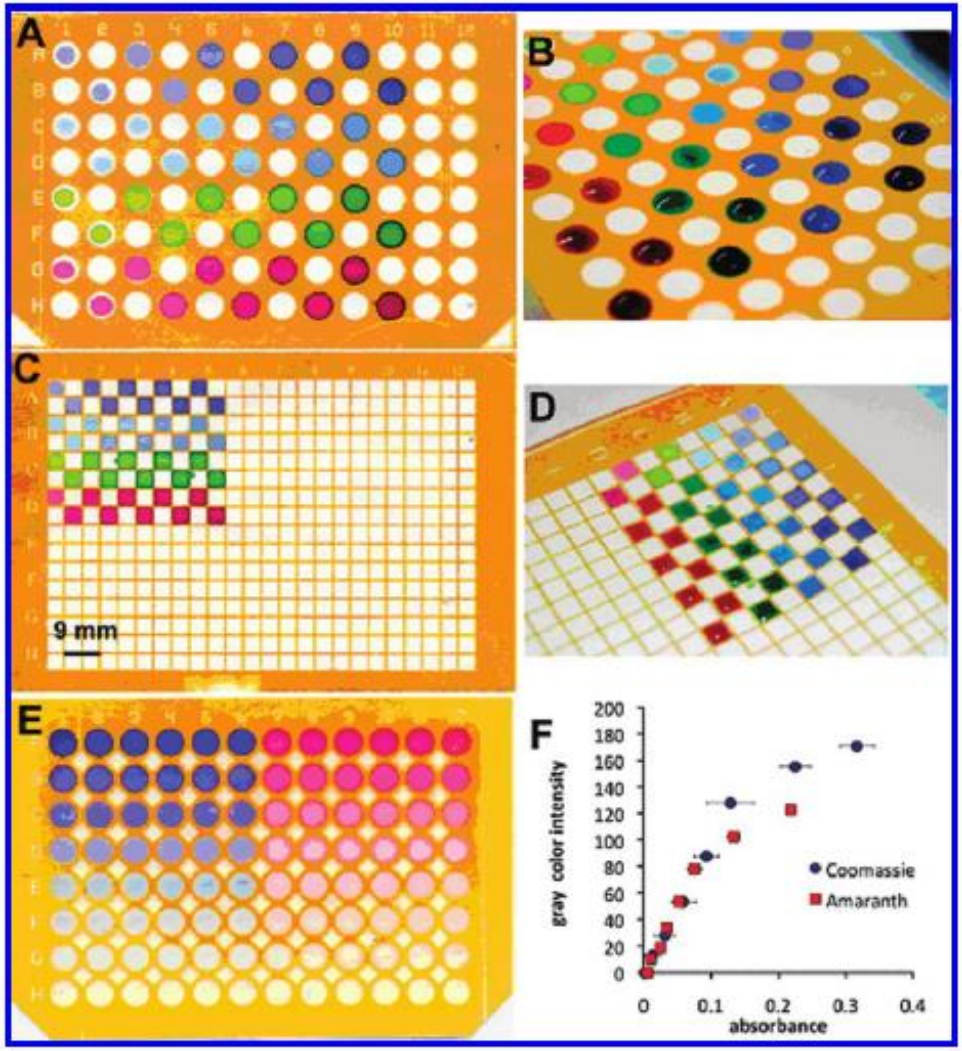


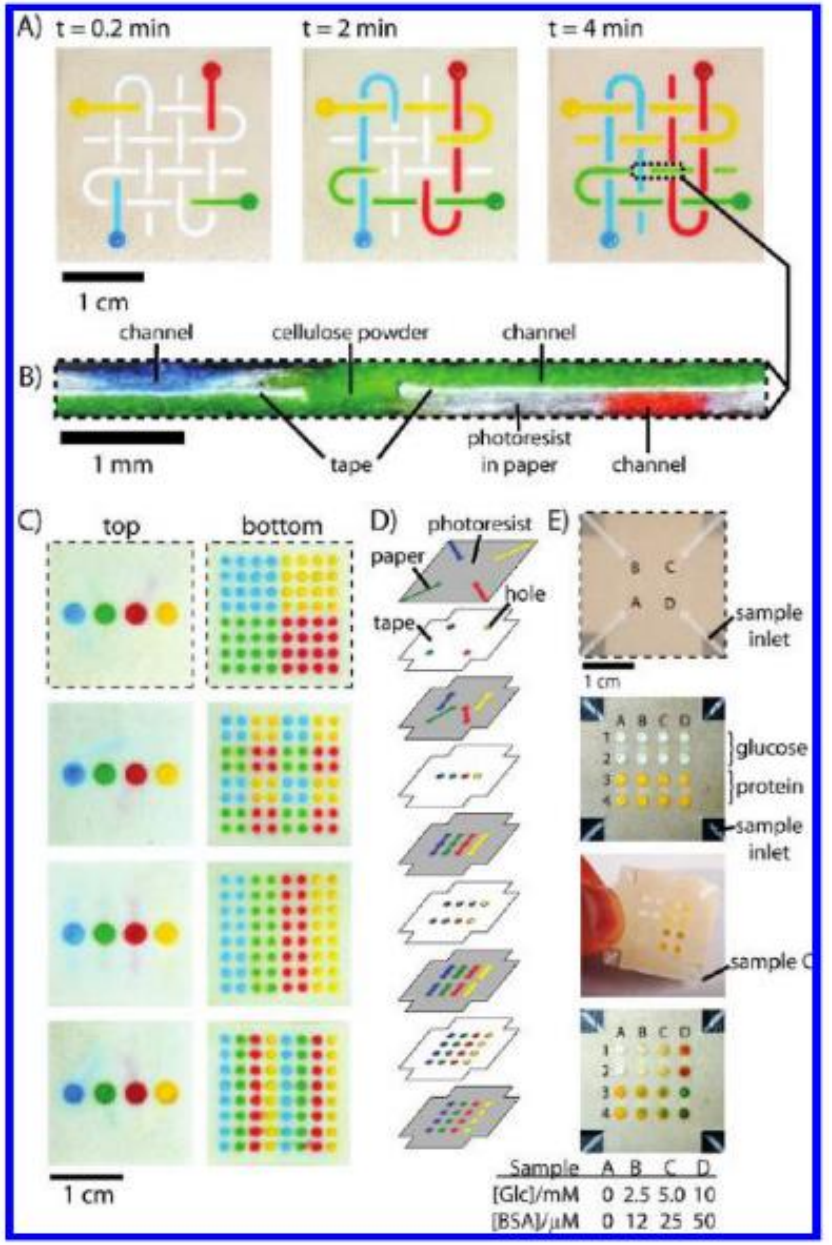
**Hydrophobic wax for detection area definition**





**Hydrophilic area for colorimetric detection**



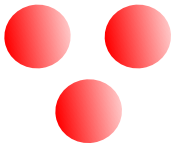




A) Image of a 96-zone plate after application of a range of volumes (1-55 μL) of solutions of aqueous dyes in alternating zones. B) Image showing the 96-zone plate with volumes of liquid up to 55 μL that were completely contained by the hydrophobic barrier. C) Image of a 384-zone plate after application of 1-10 μL of the same solutions as in (A). D) Image showing the 384-zone plate with volumes of fluid up to 10 μL that were contained by the hydrophobic barrier. E) Image of a 96-zone plate with a serial dilution. F) Correlation of the absorbance values from a microplate reader and the gray scale values from an image acquired using a desktop scanner for the paper plate shown in (E).

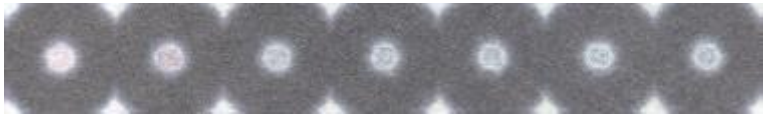
# Colorimetric Quantitative Detection on a Paper Device

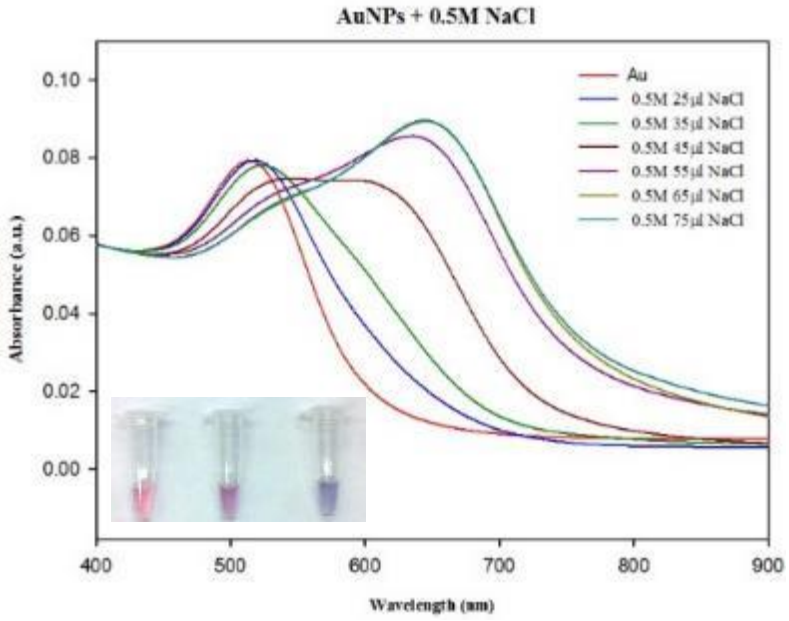
**$ 20 K**

**$ 0.2 K**

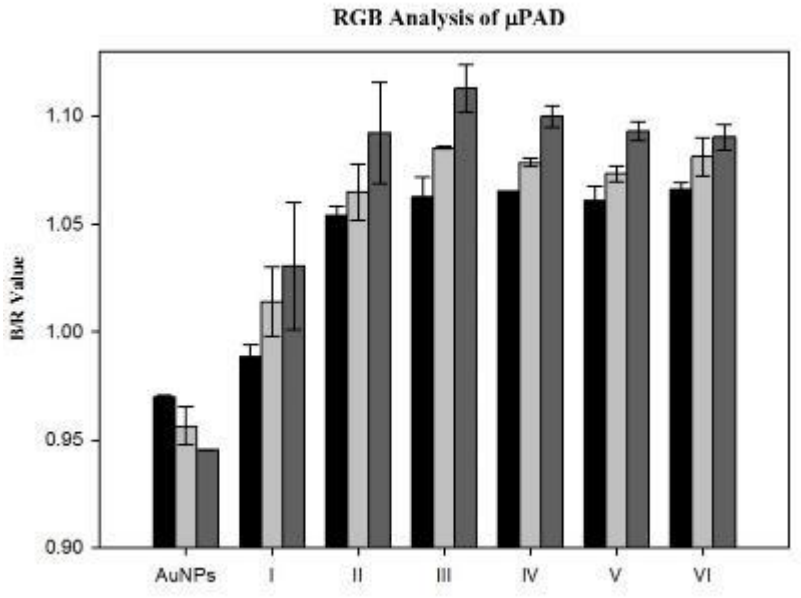


Surface plasmon resonance effect





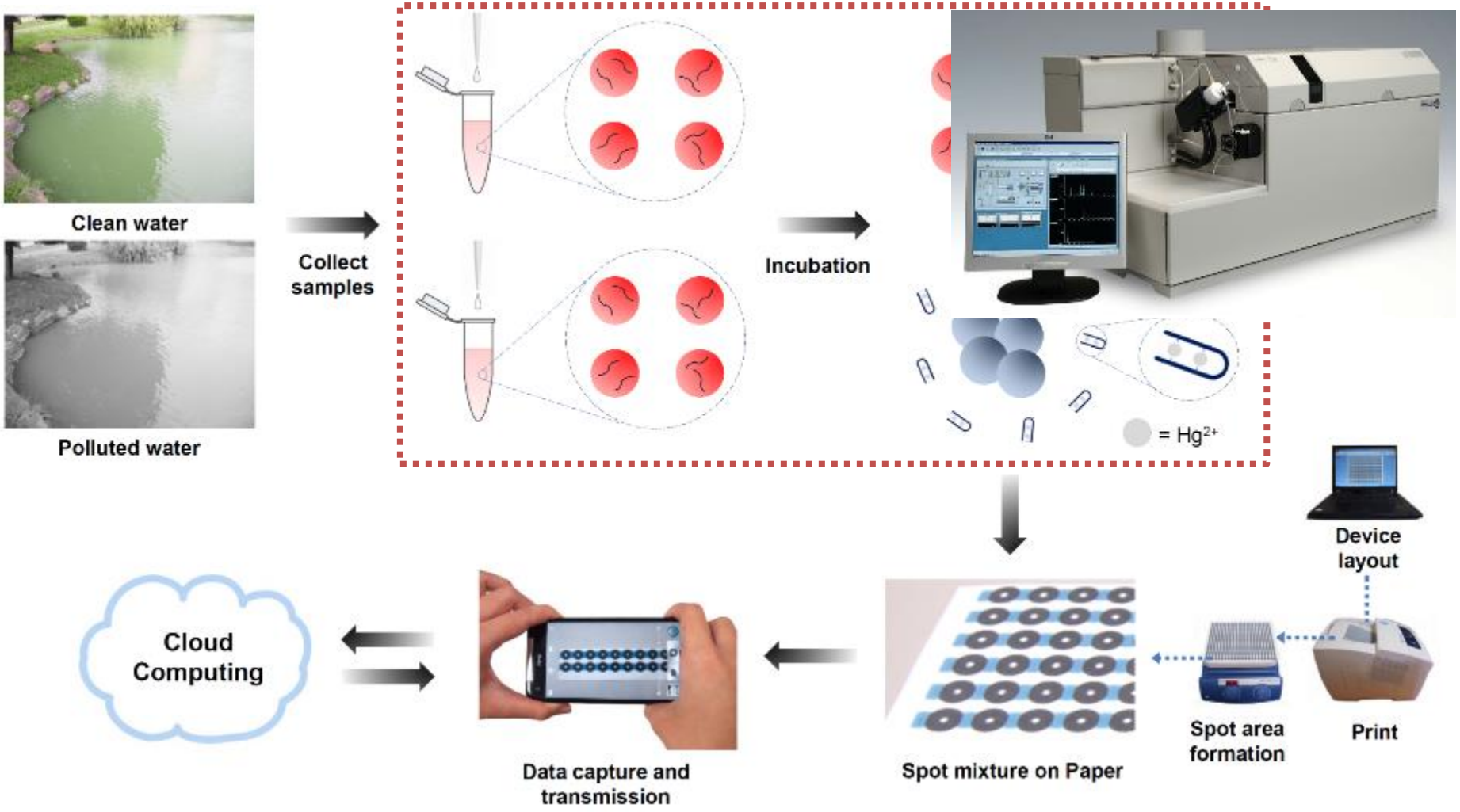

**UV-Vis absorbance spectra**




**Colorimetric results readout of PADs**

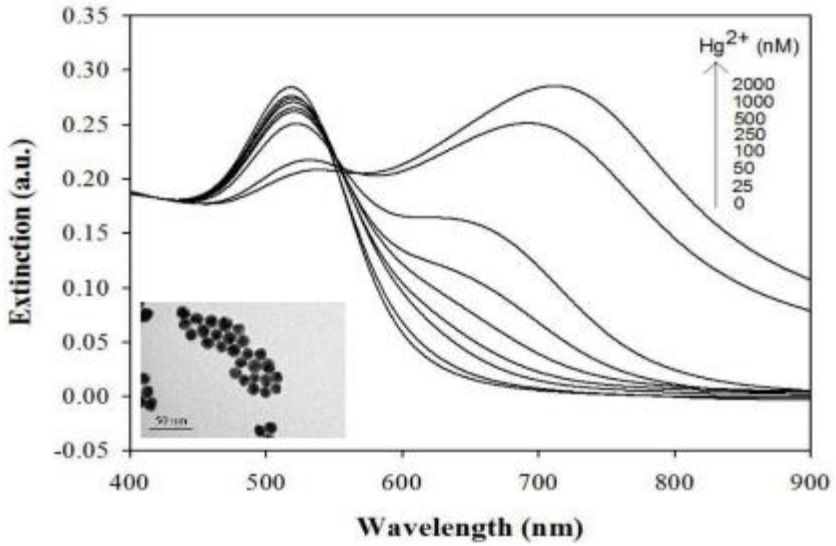
# A On-Site $Hg^{2+}$ Sensing Strategy

- **Mercury affects the nervous, immune, and digestive systems and causes damage to the brain as well as kidneys and lungs of human beings.**

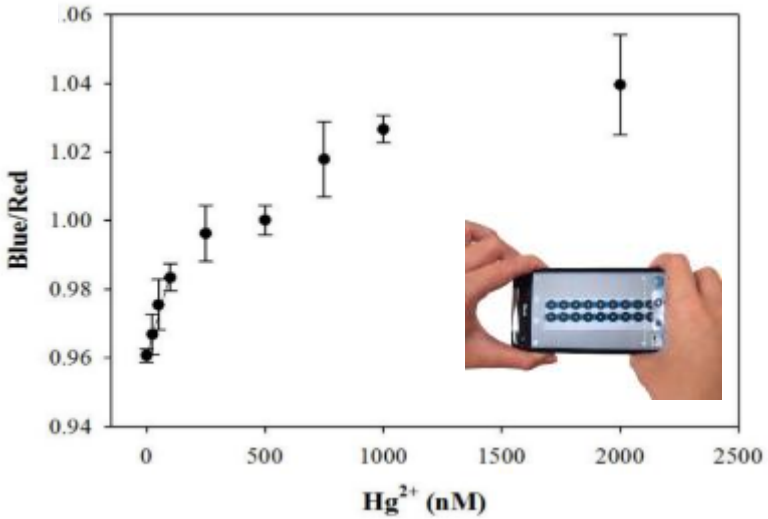



*Analytical Chemistry,* 2014, 86, 6843−6849

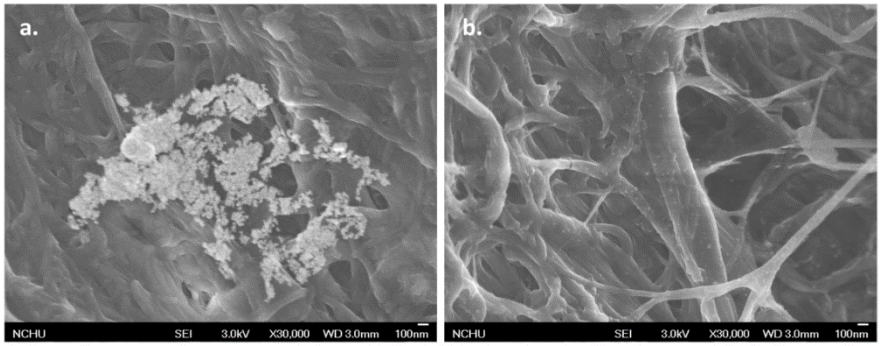
# UV-Vis Spectrometer VS. Smartphone for $Hg^{2+}$ Sensing




UV–Vis absorbane spectra of colorimetric AuNPs and $Hg^{2+}$-ssDNA complex-based $Hg^{2+}$ sensing.



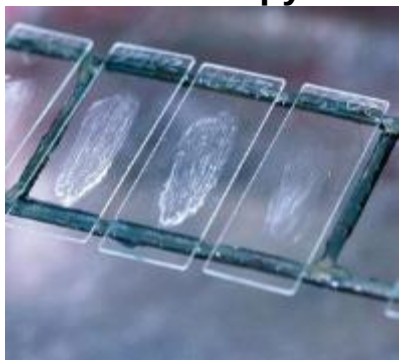

The colorimetric results for mercury ion detection on cellulose paper and the analytical blue/red color values of the spots.




SEM images of spots of detected AuNP mixtures (a) with and (b) without $Hg^{2+}$ on cellulose paper.

# Conventional Detection Methods of Tuberculosis

**Sputum Smear Microscopy**

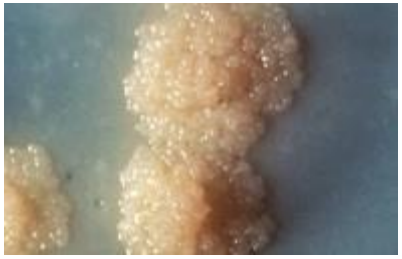


**Chest X-ray and CT scan**

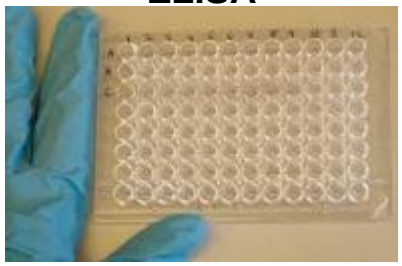
**LC-MS/MS**

**Tuberculin Purified Protein Derivative，PPD test**

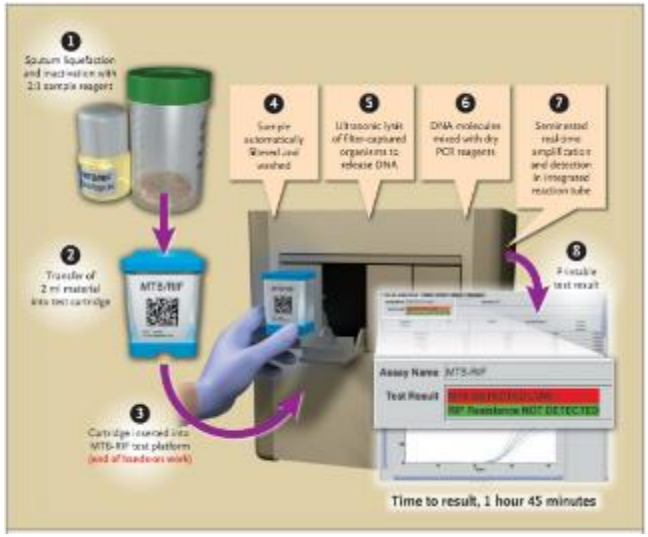
**Cell Culture**



**ELISA**



**Cepheid GeneXpert MTB/RIF**

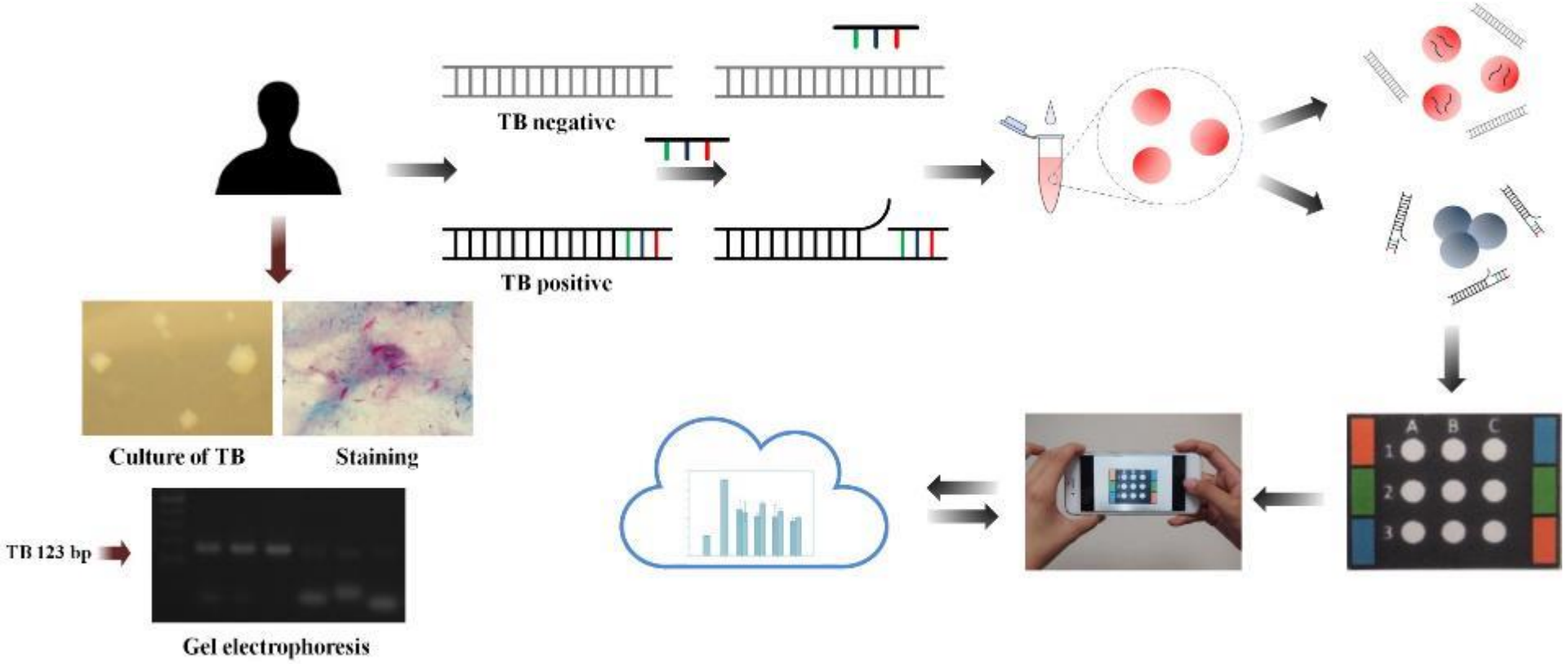



- Expensive
- Time consuming processes
- Trained technician
- Bulky size of equipment
- Sensitivity and specificity?

There is an urgent need for accurate and cost effective diagnostic platform to end the disease spread.


http://oxfordimmunotec.com/international/products-solutions/healthcare-professionals/tuberculosis/
The CIBA Collection of Medical Illustrations. Vol. 7, pp. 205
http://www.visualphotos.com/image/1x6006724/sputum_sample_slides_for_tb_diagnosis_ethiopia
http://www.pasthorizonspr.com
*N. Engl. J. Med.,* vol. 363, pp. 1005-1015, 2010.

# Diagnosis of Tuberculosis Using Colorimetric Gold Nanoparticles on a Paper-Based Analytical Device




*ACS Sensors*, 2017, 2, 1345−1354

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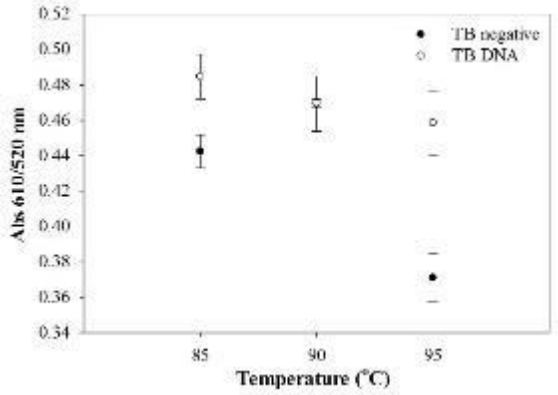
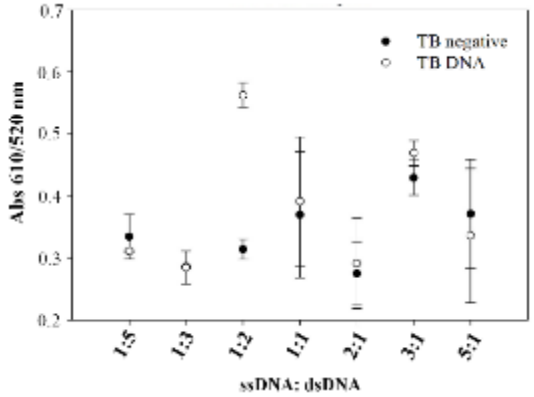
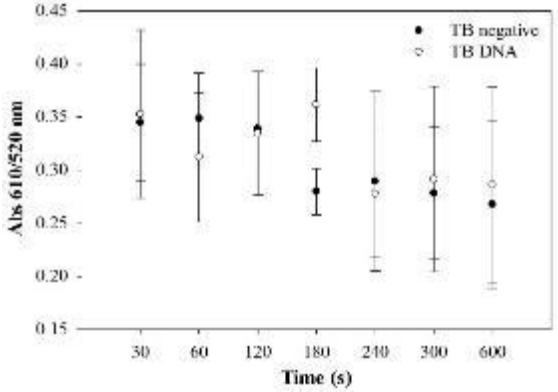
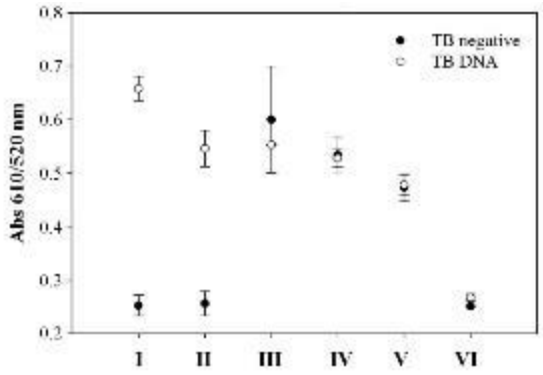
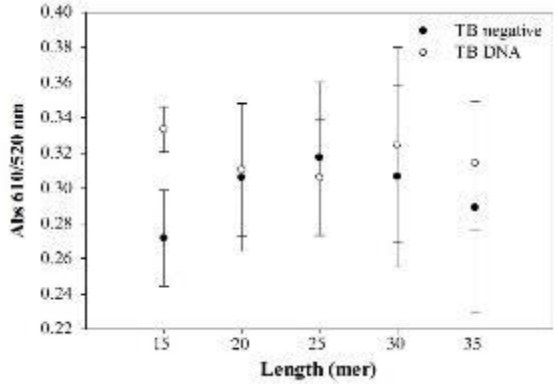
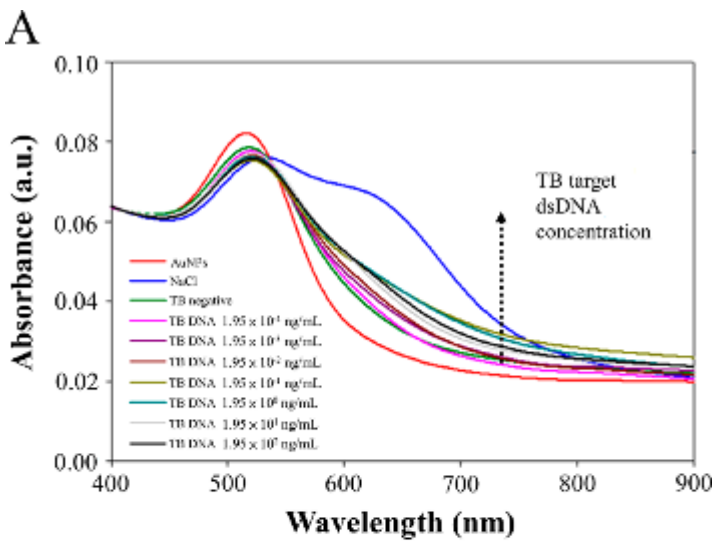


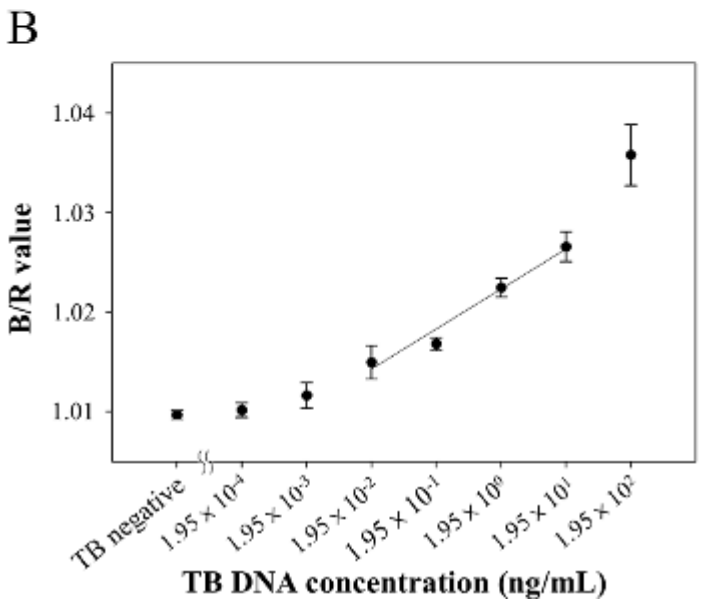



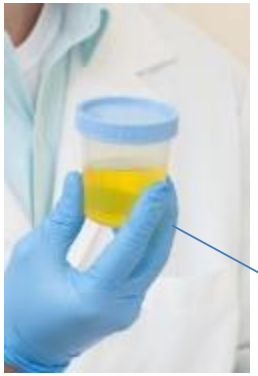



# On-Site Drug Detection

❖ **In 2012, the Food and Drug Administration of Taiwan reported that 60% of reported drug abusers aged below 19 years old were addicted to ketamine.**

Blood test[1]

- **Invasive**
- **Infection risk**
- **Need trained and licensed personnel**



Urine test[2]

- **Adulteration**

Sample preparation[3]

LC-MS/MS[4] or GC-MS/MS

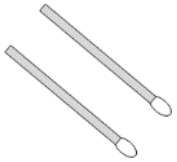
- **Expensive**
- **Time consuming processes**
- **Bulky size of equipment**
- **Power sources requirement**

There is an urgent need for frontline officers to identify drug-impaired drivers at the roadside.

1. jessefeatonby.blogspot.com
2. www.wisegeek.org
3. www.skalar.com
4. agilent.com

# Proposed Operation Processes

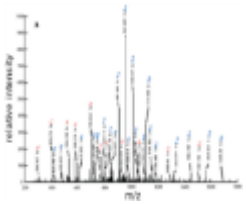
Suspect



Oral fluid (OF) sampler

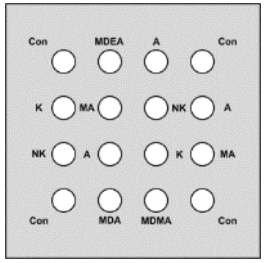
Put the OF samplers at the suspect's mouth

LC-MS/MS[2]

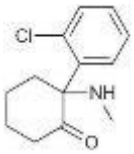


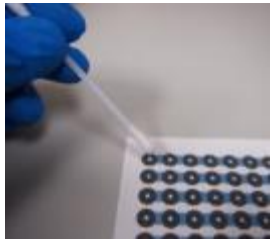
MS data

Pull over[1]

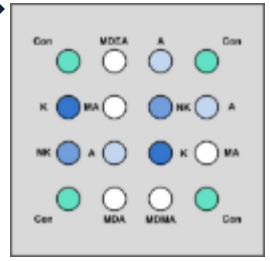



Microfluidic Paper-Based Analytical Devices (μPAD)



OF transferred to the μPAD and LFA




Colorimetric readout


Data capture and on-site analysis


Police station


Cloud Computing

1. 東森新聞
2. agilent.com
3. appleapp.com
4. plustek.com

# Clinical Tests - μPADs and LFAs

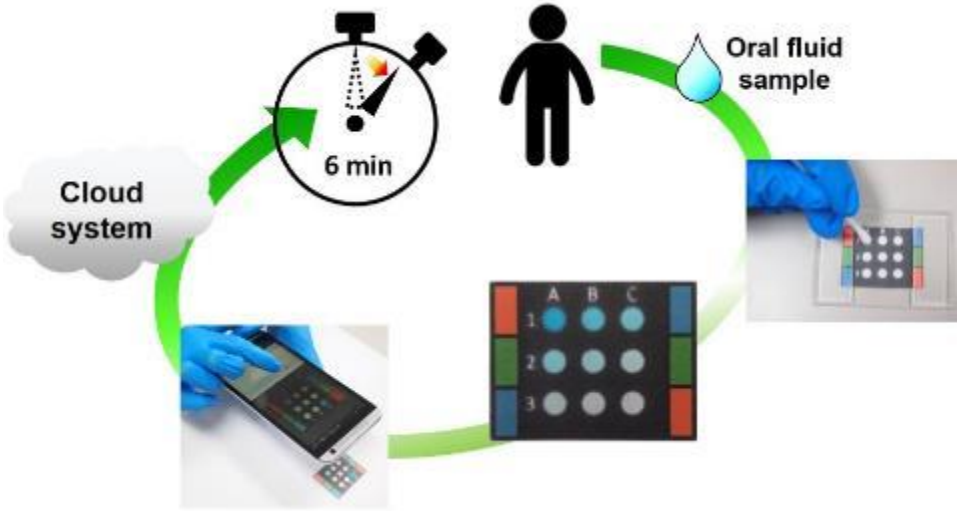
Blood test

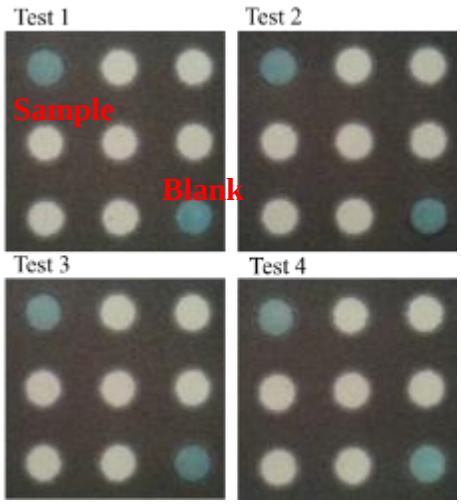
Urine test

- Invasive
- Infection risk
- Need trained and licensed personnel

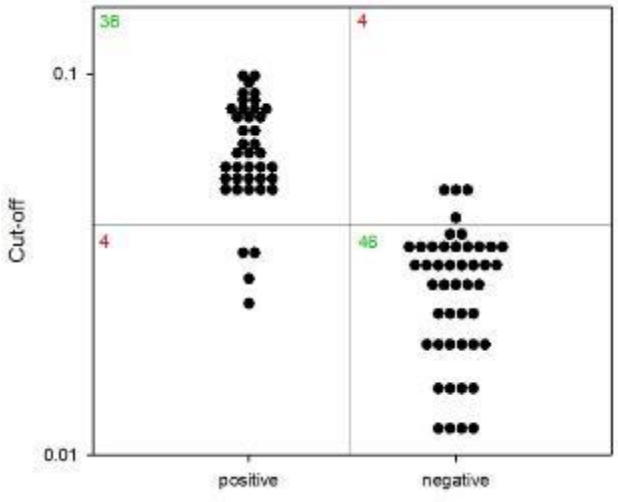
Sample preparation

- Adulteration




**Clinical tests of μPADs**




R/B analysis

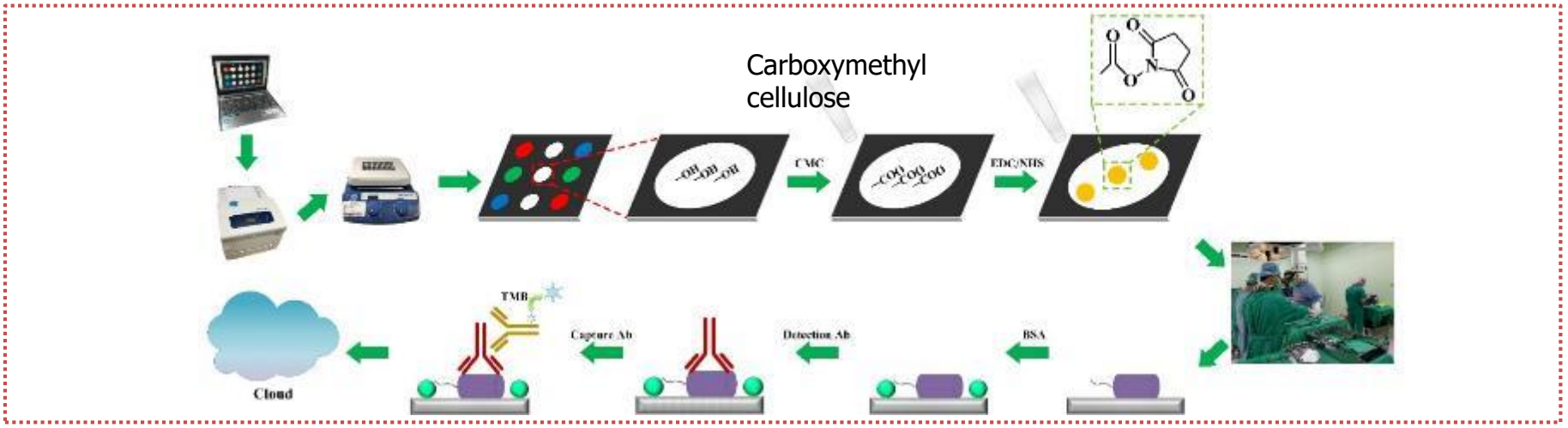
R/B (Sample- Blank) ≧ 0.04 → Positive

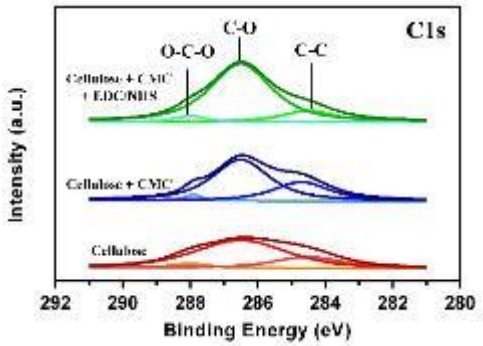
**Sensitivity = 85.7 %**

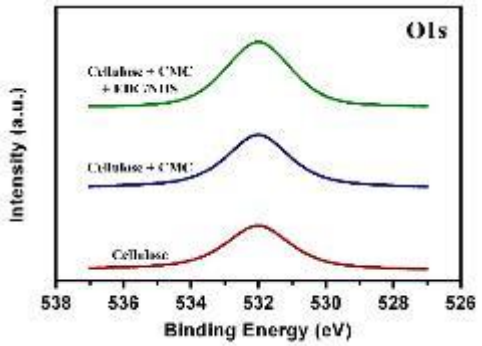
**Specificity = 90 %**

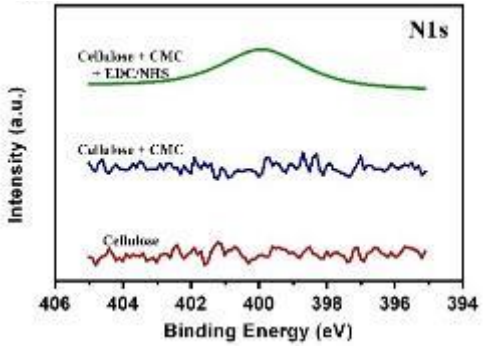
*Sensors and Actuators B: Chemical*, 2019, 282, 251-258.

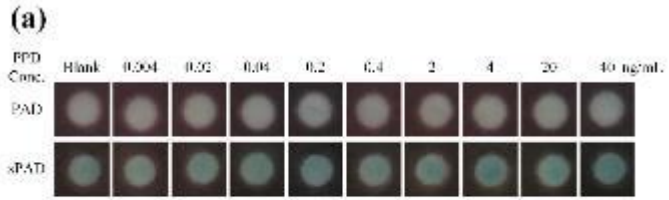
# Surface-Modified Cellulose Paper and Its Application in Disease Diagnosis

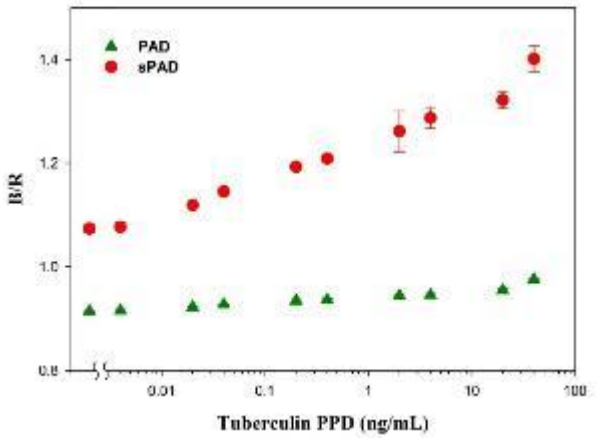


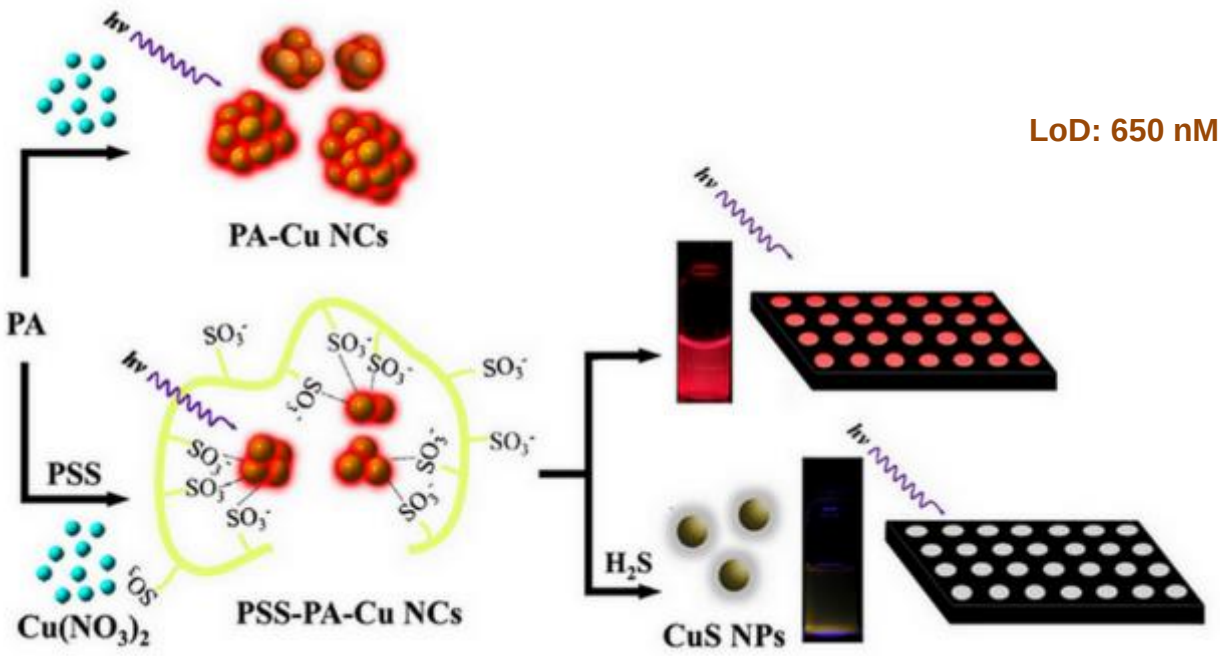



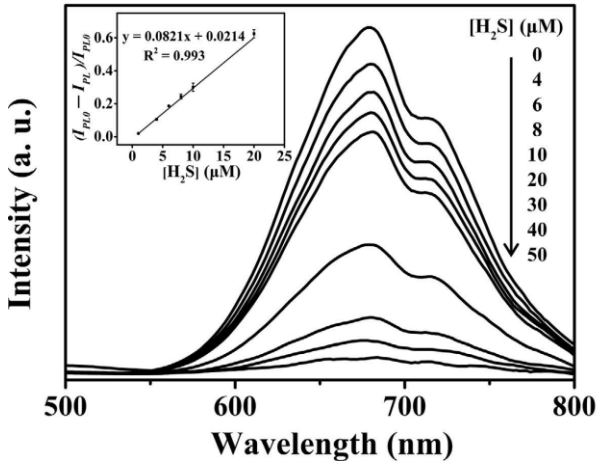



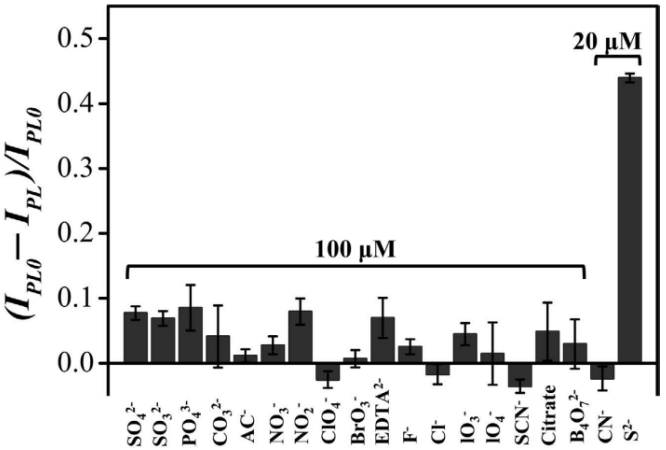

***Sensors and Actuators B: Chemical, 2018, 506-513***

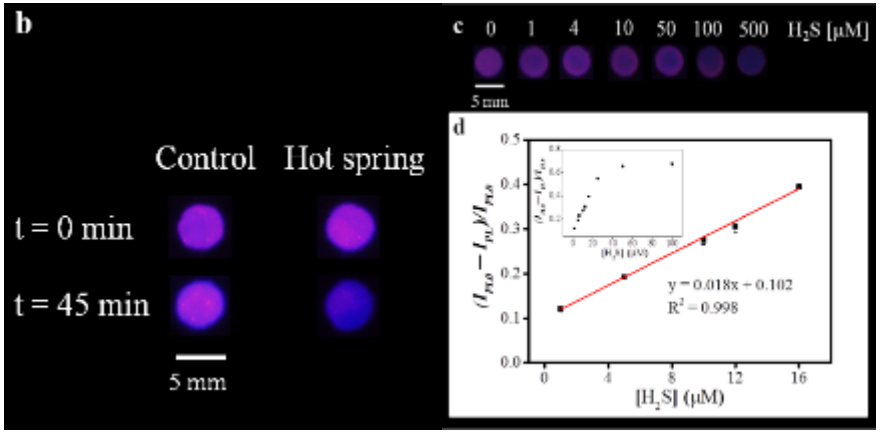
# Polystyrene Sulfonate Penicillamine-Copper Nanocluster Aggregates for $H_2S$ Sensing on PADs




**LoD: 650 nM**



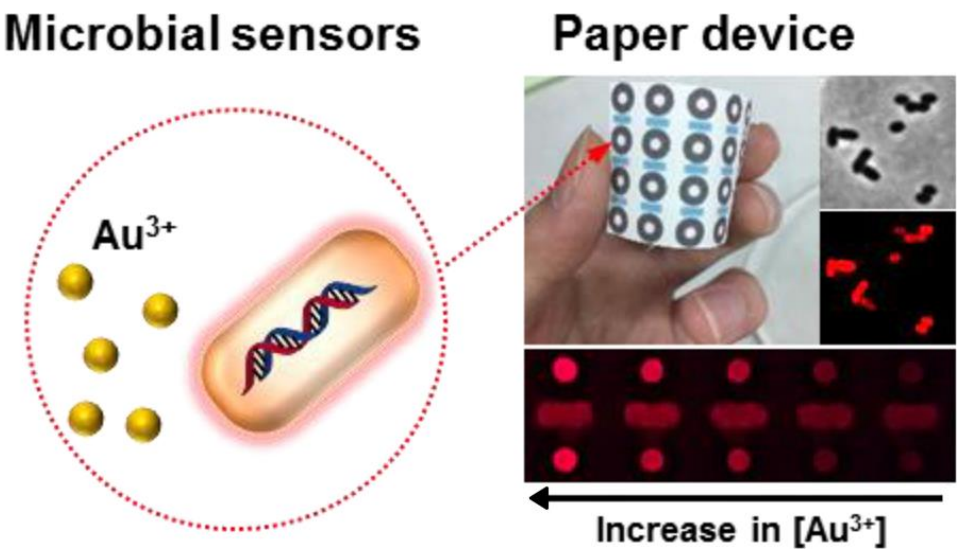



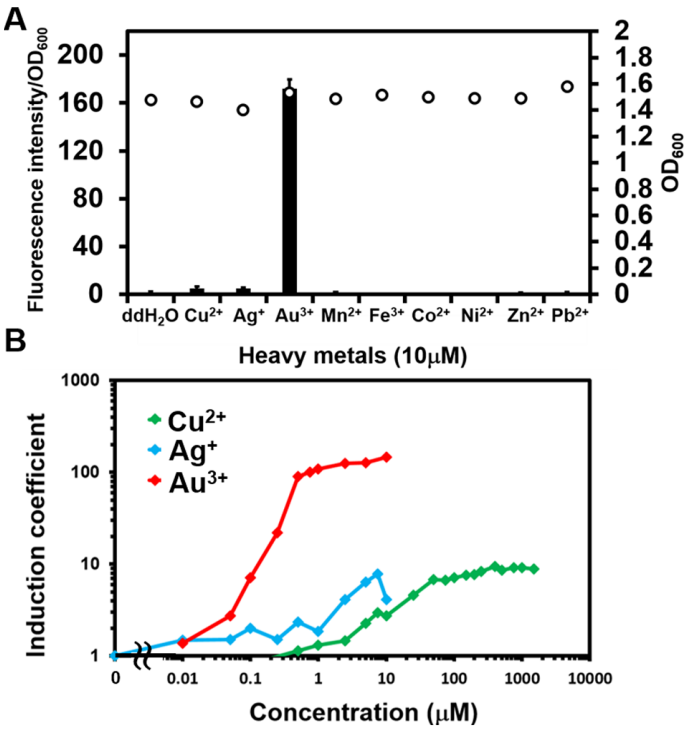




- The PSS-PA-Cu NCs were integrated into a portable μPAD for the on/off determination of $H_2S$ in water samples.

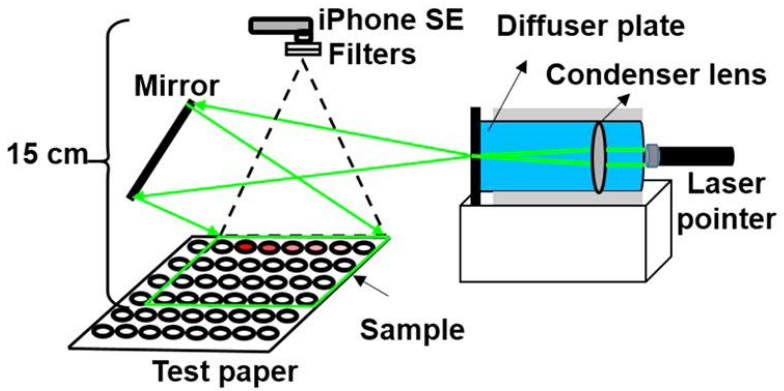
*Scientific Reports*, 2016, 24882

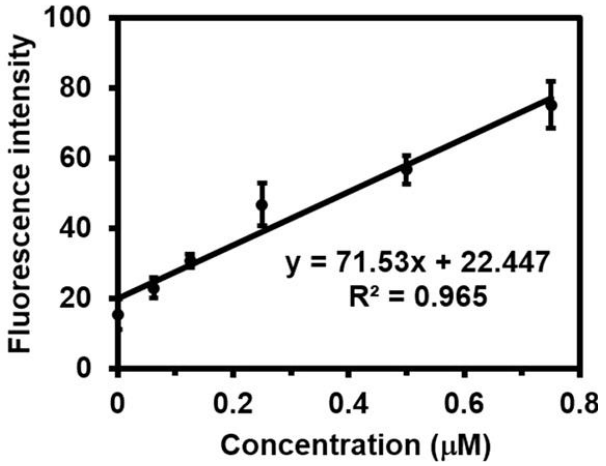
# Determination of Gold Ions in Human Urine Using Genetically Engineered Microorganisms on a Paper Device




The heavy metal-tolerant bacteria *Cupriavidus metallidurans* was genetically engineered for use as a red fluorescent protein (RFP)-based microbial sensor.

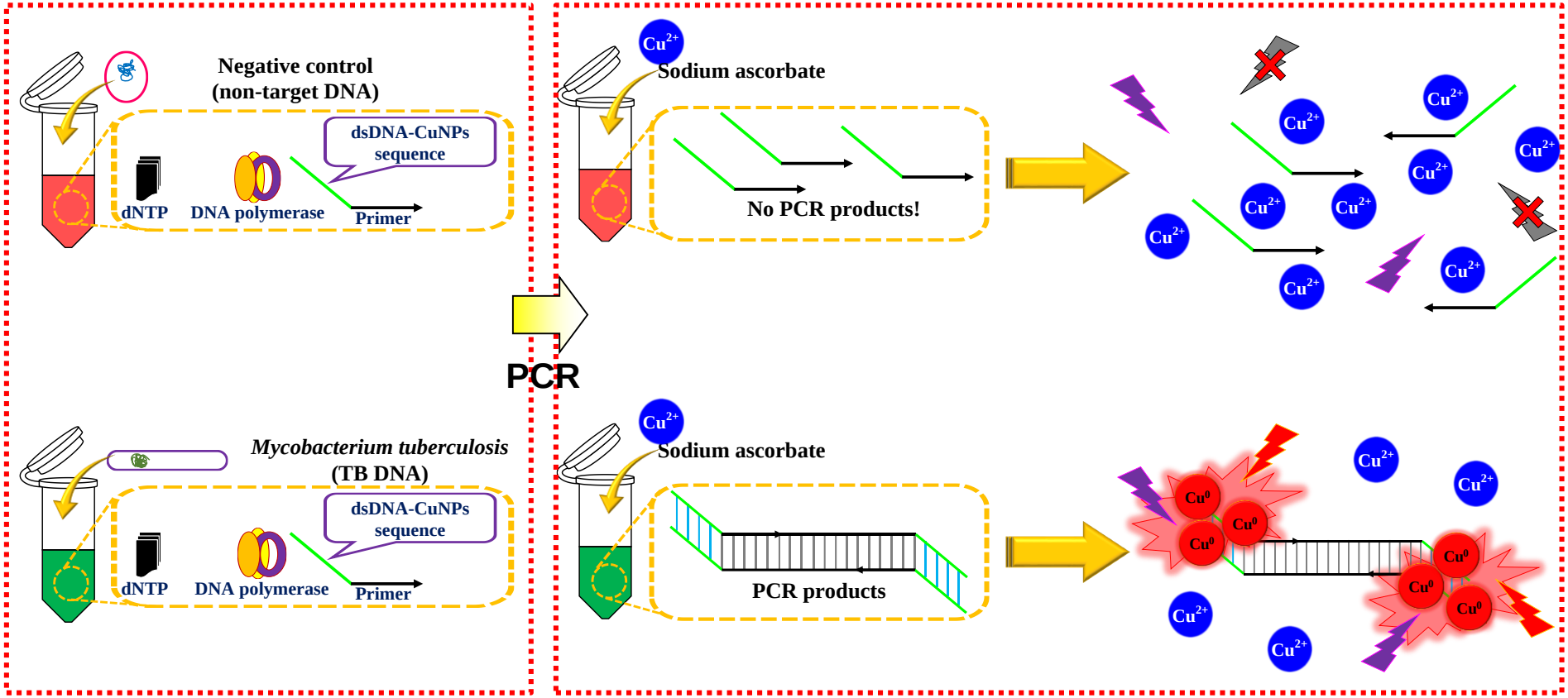



*ACS Sensors*, 2018, 3, 744−748

# Label-Free Fluorescent Copper Nanoclusters for Genotyping Deletion

**Tsung-Ting Tsai**, Chung-An Chen, Natalie Yi-Ju Ho, Yang, and **Chien-Fu Chen**

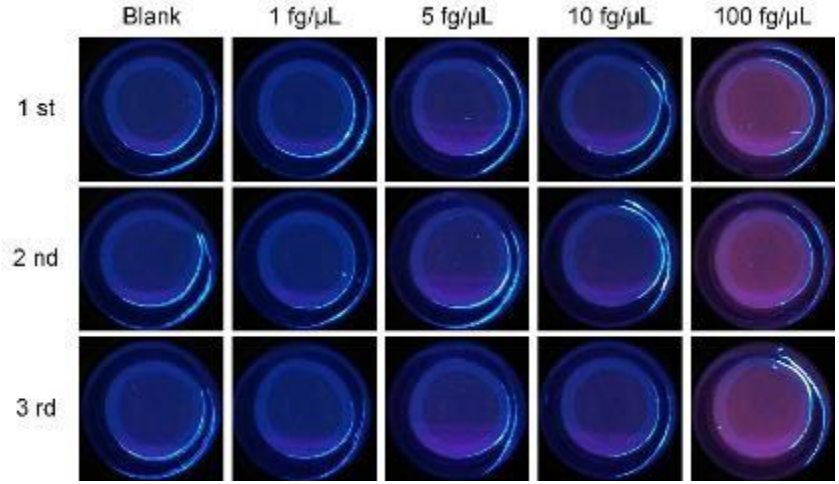



S1: blank-35x
S2: TB negative-35x
S3: TB positive (002)-35x
S4: TB positive (028)-35x
S5: blank-40x
S6: TB negative-40x
S7: TB positive (002)-40x
S8: TB positive (028)-40x

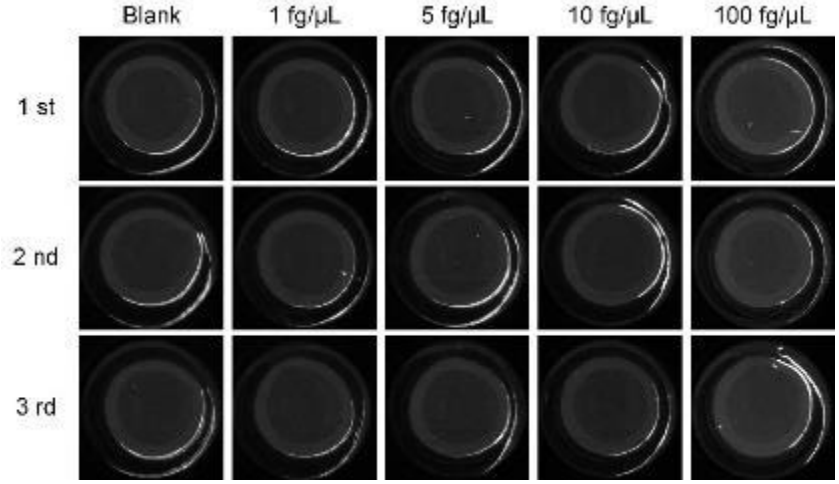

Unpublished.

# Optical Image Analysis Based on Deep Learning

Original figure



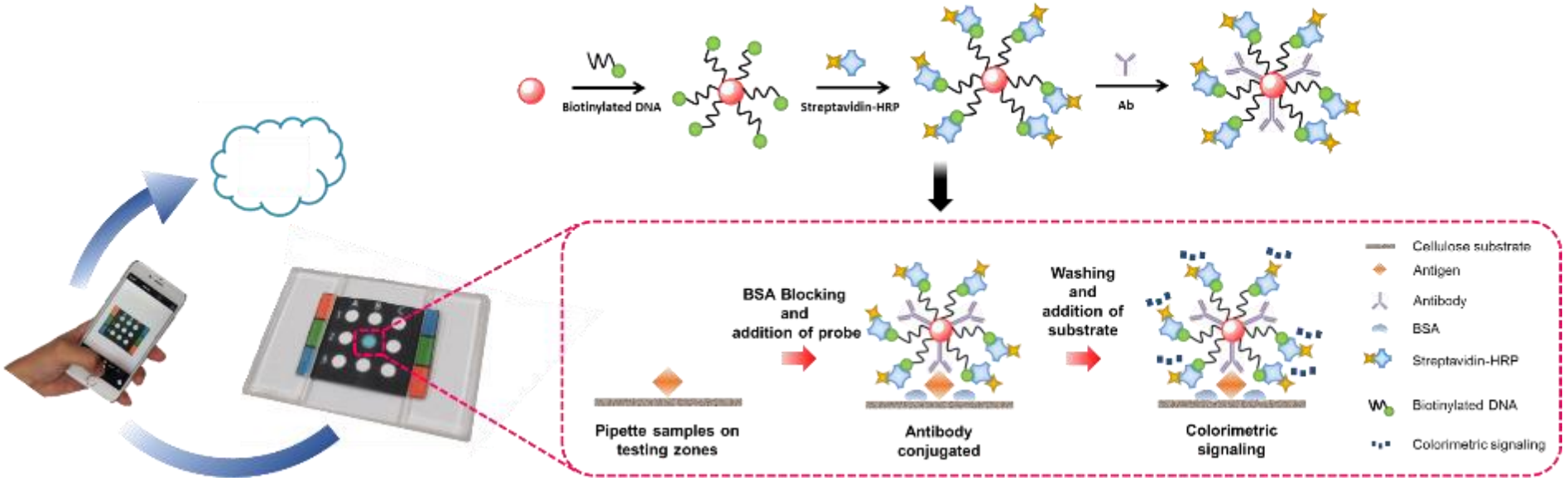

Green split figure

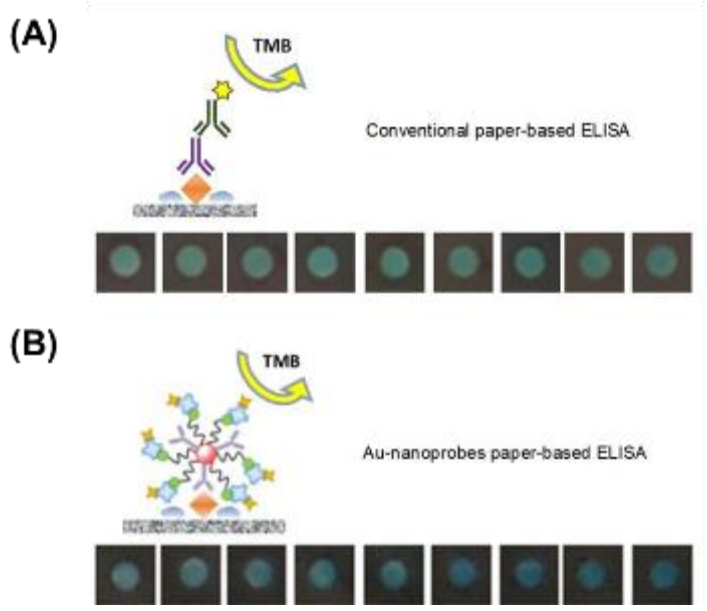


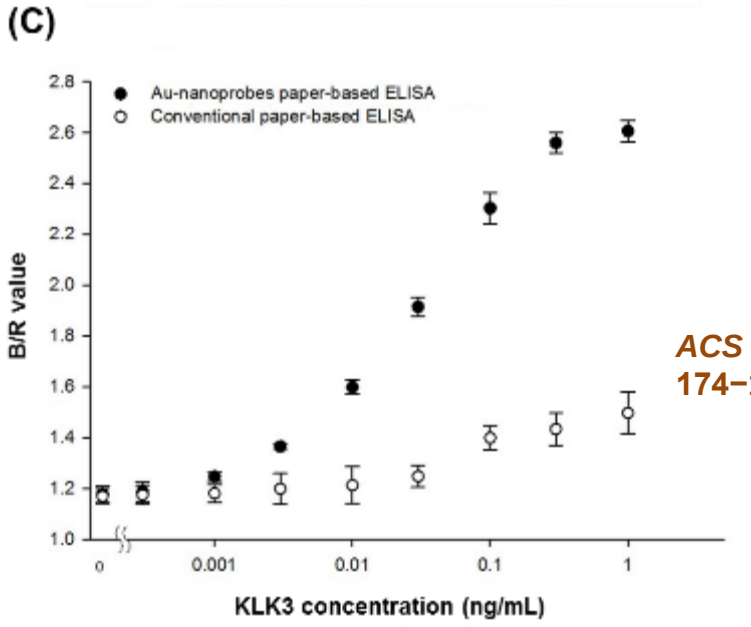

Re


Bl

# Signal Amplified Gold Nanoparticles for Disease Diagnosis on a Paper-Based Analytical Device

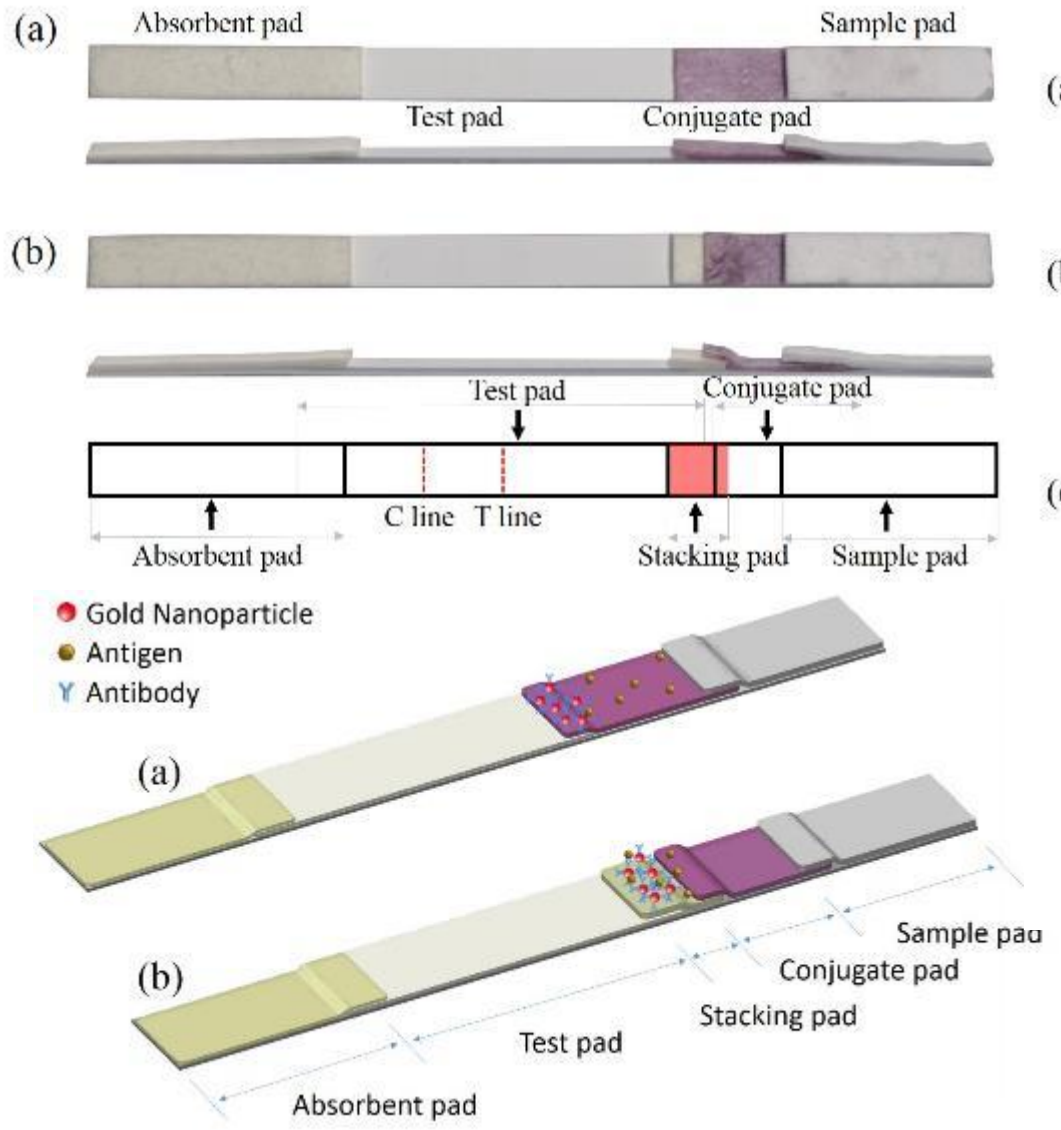


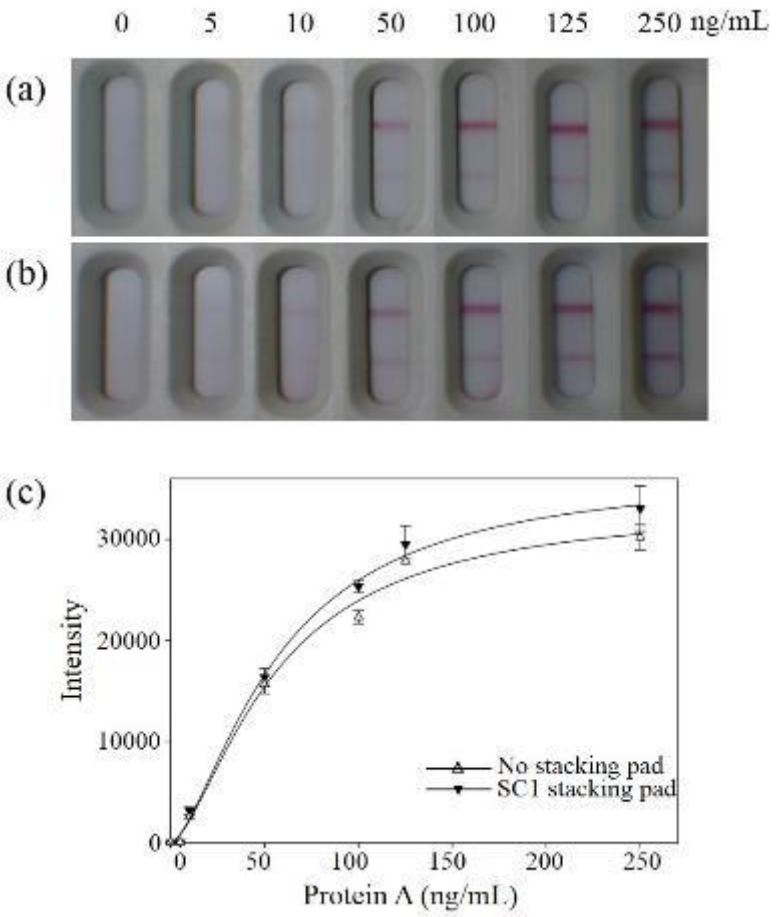




*ACS Sensors*, 2018, 3, 174−182

# Development a Stacking Pad Design for Enhancing the Sensitivity of Lateral Flow Immunoassay



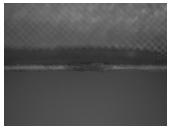



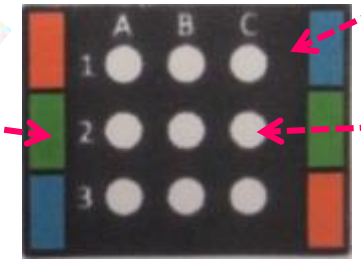

Photographs of the (a) conventional LFIA and (b) sLFIA test strips used to (c) measure synovial fluid spiked with various concentrations of Protein A.

***Scientific Reports*, 2018, 8, 17319**

# Three-dimensional origami paper-based device for portable immunoassay applications

- **Microfluidic Paper-Based Analytical Devices (μPADs)**



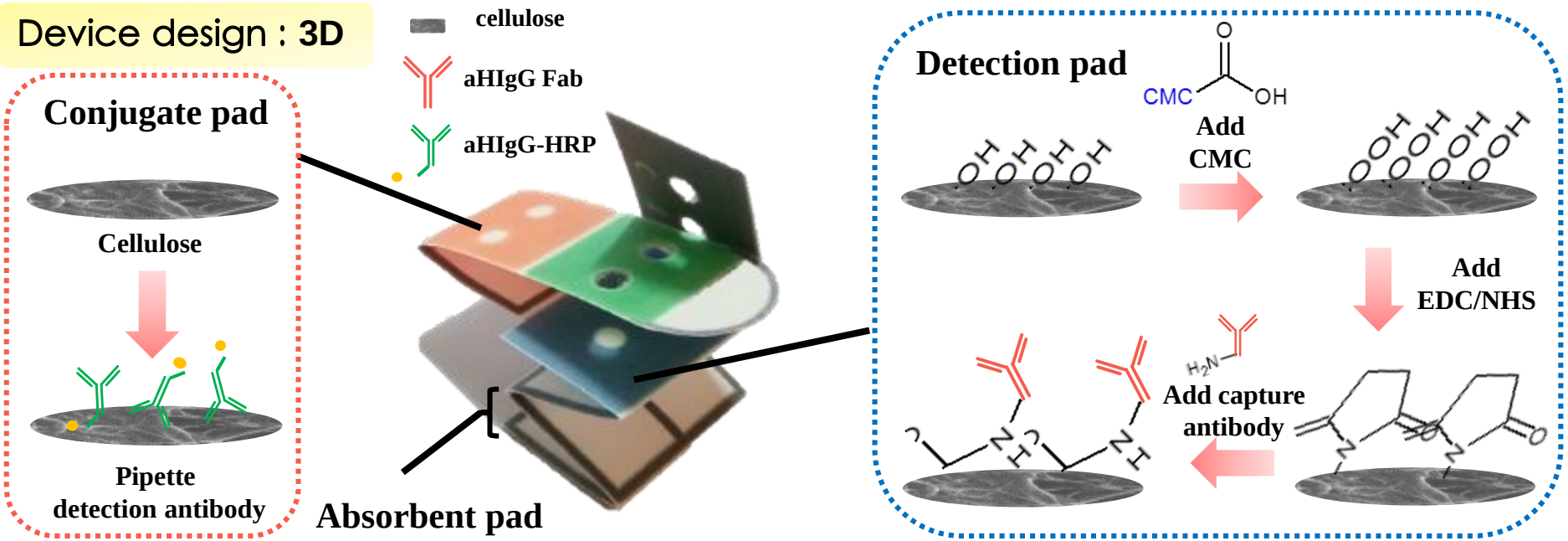



**Hydrophobic wax** for flow area definition

**Color bar** for light condition adjustment

**Hydrophilic area** for colorimetric detection

## Device design : 3D




*Lab on a Chip*, Revision

# Paper-Based Enzyme-linked Immunosorbent Assay