Tuberculosis POCT: An Integrated Photonic Biosensor for Tuberculosis Detection


Goal: Point of care test for tuberculosis

- In 2014, TB killed 1.5 million people (1.1 million HIV-negative and 0.4 million HIV-positive).
- In 2014, 6 million new cases of TB
- TB now ranks alongside HIV as a leading cause of death worldwide.
- Resistance
  - MDR-TB (3.3% of new TB cases and 20% of previously treated cases have MDR-TB)
  - XDR-TB
  - TDR-TB
- Burden of latent infection

Goal: Point of care test for tuberculosis

- Tuberculosis is a global disease
- Current methods for the detection of TB are either time consuming or require expensive instruments (not point of care) and no rapid tests for diagnosis of active TB are available
- World market for Tuberculosis diagnosis: more than 1 billion US$.
- HIV and TB is a deadly combination killing the maximum number of people worldwide due to any infectious diseases.

A point of care photonic transducer

- Silicon nitride waveguides to use 850 nm light for reduced water absorption.

Preliminary detection of LAM with photonic biosensor

- Different concentrations of LAM are successfully detected.
- Successful detection of 250 pg/ml.
- Sufficient Limit of Detection for real urine.

<table>
<thead>
<tr>
<th>[LAM] (pg/ml)</th>
<th>Δλ(nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 pg/ml</td>
<td>0.16</td>
</tr>
<tr>
<td>500 pg/ml</td>
<td>0.34</td>
</tr>
<tr>
<td>1 ng/ml</td>
<td>0.49</td>
</tr>
<tr>
<td>50 ng/ml</td>
<td>0.69</td>
</tr>
<tr>
<td>1 pg/ml</td>
<td>4.89</td>
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</tbody>
</table>

Novel and highly selective TB biomarker developed

- Kinetics characterization of one monoclonal anti-LAM antibody using APS sensors on octet platform.
- High-quality antibodies with KD around $10^{-8} - 10^{-9}$.

Ex-situ functionalization procedure

- Incubation with 2 mM of OVA in PBS.
- Incubation with 100 μg/ml of anti-HBs in PBS.
- Incubation with ethanethiol.
- SA blocking (1 mg/ml).

- Glass slide
- 10 μl anti-LAM
  - 250 μl LAM 1 pg/ml ON
  - 250 μl LAM 1 pg/ml OFF
- 1 μl ON
- Signal: 1-2
Development of low-cost point-of-care test for Tuberculosis Diagnosis

- 750 dies/hp for IBIS
- 150 dies/hp per wafer
- 1000 dies/30 channels

Measurement procedure

- The camera captures the output from all spectral filter channels
- The intensities from different channels are continuously monitored

Point of care: The ultimate goal of photonic biosensors

- A device that can be taken to the patient and operated by non-specialists

**Application level**
- Limited/no sample preparation

**Device level**
- Easy to use
- Operational under a range of conditions

**Sensor level**
- Cheap
- Disposable
- Adequate limit of detection
Microfluidic chip as transfer medium

Integrate the silicon nitride chips directly in a polymer fluidic cartridge, while leaving parts of the chip exposed for easy optical access.

POCKET POCT

- No sample preparation
- Easy to use
- Cheap
- Adequate limit of detection

Development of low-cost point-of-care test for Tuberculosis Diagnosis

POCKET POCT

Silanisation and 2nd generation of devices
Imec, Germany

Biofunctionalisation and bioanalytical application
ICN2, Barcelona

Antigen and antibodies for the detection TB (TB biomarker)
LIONEX, Germany

Microfluidics
MFCS, Germany

Towards an industrial process

Functionalisation at wafer level

Spotting of the antibodies

Implementation of capillary pumps

Packaging of the biochip
Conclusion and outlook

- Point-of-care photonic sensor with bulk potential for multiplexing:
  - Limit of detection of $7 \times 10^{-7}$ RIU and
  - Successful detection of $250 \text{ pg/mL}$ LAM, a biomarker for TB found in urine

- Field tests planned in 2017

Thanks
Abstracts CPOCT Symposium

AACC CPOCT INTERNATIONAL SYMPOSIUM

The Benefits and Challenges of Point-of-Care Testing Across the Clinical Spectrum
September 21-24, 2016, Copenhagen, Denmark
Accepted Abstracts

Poster Submitting
Author/Title

SESSION 1: POCT IN THE INTENSIVE CARE SETTING

P1 Allon Reiter: Diagnosis of Infection Utilizing Accellix CD64

P2 Paloma Oliver: Precision and agreement of 266 strip-based glucose meters without the involvement of the laboratory medicine

P3 Hanneke Buter: Plasma glutamine levels before cardiac surgery are related to post-surgery infections; an observational study.

P4 Nuha Al Humaidan: Analytical Performance of Point of Care Blood Gas Analyzers In The Operating Theaters

P5 Zachary O'Brien: Novel POC Devices for Testing Procalcitonin (PCT) in ER and ICU Settings

P6 James Nichols: GEM Premier 5000 Clinical Evaluation

P7 Gareth Davies: Development of an External Quality Assessment Scheme for POC Creatinine Whole Blood Meters

P8 Alex Mewis: Organization of an external Quality Control Program for ACT Medtronic

P9 Paloma Oliver: Differences in blood gas results between POCT Neonatal Intensive Care Unit and Emergency laboratory
SESSION 3: POCT IN THE PRIMARY CARE SETTING

P31 Jin Xu  Assessment of the performance of Blood Glucose Monitoring Systems for monitoring glycemic control in non-diabetic patients

P32 Eunice Nai  Clinical Value of the Urinary Albumin-to-Creatinine Ratio Measured Using a Strip Test in Prediabetes and diabetes

P33 Kimi Lutten-Aikma  Nurse-managed Anticoagulation Clinic in Finland: New Point-of-care Testing (POCT) affects TTR in Primary Care Setting

P34 Maurice Larue  Creatinine level in capillary blood: a new tool for estimating glomerular filtration rate at home or in ambulatory care settings

P35 Marijana Vatic Lorenz  Diagnosis performance of a point-of-care glucose analyzer in ambulatory diabetes

P36 Samir van Delhi  Analytical performance, agreement, and user-friendliness of automated POCT urine test strip analysers, and a comparison between man and machine

P37 Krii Lutten-Aikma  Quality Management of Point-of-care testing (POCT) process in nurse-managed anticoagulation clinic

P38 Ayseal Elaziz  Tuberculosis POCT: An Integrated Prediabetes Resource for Tuberculosis Detection

P39 Lisa Harnois  Implementation of quality-assured POCT testing in Dutch general practice

P40 Hans van Pett  Evaluation of three POCT Hematology analyzers for white blood cell analysis

P41 Celine van Johnston  Early more acute treatment after kidney transplantation: adherence to measurement goals of A-dRI in kidney transplanted patients reported data

P42 Angel Jort  Point of care creatinine testing in screening and monitoring of chronic kidney disease

P43 Javier Segarra  New Emergency approaches in primary care efficiency when enhancing the role of POCT
Tuberculosis POCT: A Potential Application of Integrated Photonic Biosensor for Tuberculosis Detection


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Tuberculosis (TB) is an old but re-emerging global health threat caused by the *Mycobacterium tuberculosis* (Mtb). One third of the world’s population is infected with Mtb and new infections occur at a rate of one per second. Despite greatest global health impact of TB, case detection rates are low, posing serious hurdles for TB control. Current methods for the detection of TB are either time consuming or require expensive instruments. Furthermore, these tests have several limitations and perform poorly in populations affected by the HIV epidemic, are thus not suitable for point-of-care diagnosis. Therefore, an accurate, novel, rapid, more sensitive and cost effective diagnostics are urgently needed.

In this respect, the grand goal of the Pocket project is to establish a framework to combine several state-of-the-art concepts for the development of novel and cost-effective point-of-care test for tuberculosis using patients’ urine as non-invasive samples. The new tuberculosis POCT consists of a small photonic chip combined with a microfluidic cartridge (disposable part) and a graphical user interface instrument, used for optical readout and data processing (Figure 1). An integrated label-free photonic circuit is used as biosensor, a low-cost mechanism due to its small size and the compatibility with mature CMOS fabrication technology. The sensing circuit is implemented, combining a highly sensitive Mach-Zehnder interferometer with an on-chip spectral filter, hence replacing the conventional tunable laser by a much cheaper broadband light source. Flood illumination on the input grating couplers was used to reduce the cost and increasing POCT compatibility. The successful development of a POCT TB test depends on an Mtb-specific biomarker. Special focus set to the most promising markers; cell wall lipopolysaccharide lipoolarabinomannan (LAM) and Ag85 complex. A novel, high-quality and selective antibodies were developed against Mtb LAM and Ag85 complex biomarkers. This unique cocktail promises to significantly enhance the sensitivity and specificity far beyond current TB tests. In a preliminary experiment, sensor chips were functionalised using an Azide-ended silane by vapor phase deposition and antibodies were bio-conjugated by click-chemistry using a PEG-based linker. Initial results indicate the successful detection of 250 pg/ml of LAM antigen, thus demonstrating its potential for use in resource-limited area and for the on-line diagnosis of TB. In the new POCT, the safety of sample process has been successfully implemented using microfluidic chip as transfer medium. The designed chip has very low fabrication costs, allowing cost-effective disposable chips to be fabricated in mass production. This chip is plugged into the measurement tool, which contains the required components for optical readouts, an automated system to circulate the urine into the chip as well as a computer for data processing.

Due to rising health-care costs, all health-care stakeholders are forced to shift their onus from a ‘pay for intervention’ to a ‘pay for performance’ model. The highly promising TB POCT need to be evaluated in order to determine a universal threshold, especially in endemic countries as well as performance in the field. Hence, there is a need and justified rationale for performing medium/large evaluation trials which will be our near future step.

Acknowledgement: The Pocket project was funded by the European Commission under grant agreement no FP7 610389.

Attachment: Figure 1: TB POCT Instrument and the disposable chip parts
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