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Surface Polymer Imprinted – Closed Loop Optical Patient Sensors (SPI-CLOPS)

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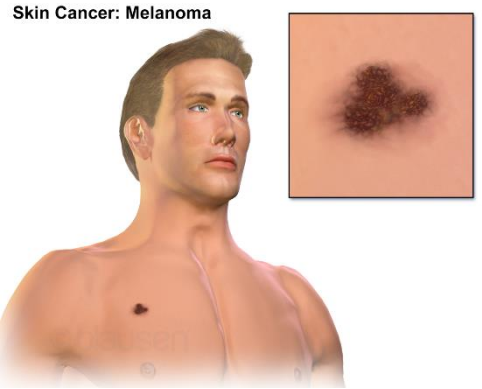
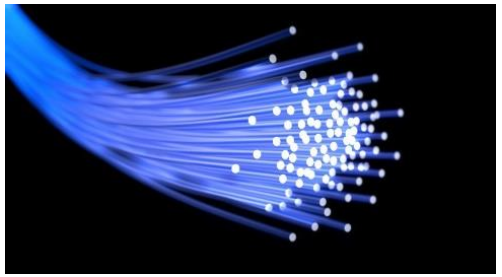
OUTLINE

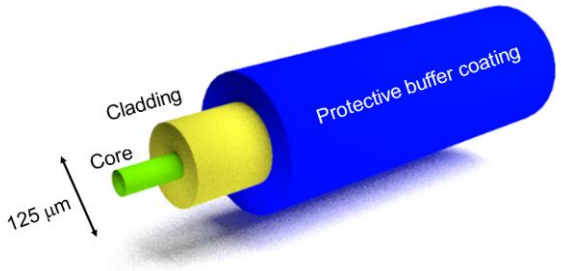
- Background to the project
- Background of Technology
- Demonstration case of study
- Progress to date
- Conclusions and future plans

Background to the project

- Lead BRAF inhibitors has dramatically improved outcomes for melanoma (Dabrafenib, Vemurafenib).
- Sub-populations of patients treated with these drugs can become resistant.
- No current way to predict which patients will develop resistant cancers.
- No method to detect whether a patient's tumour is receiving a therapeutic dose of drug.
- Urgent need to evaluate in real time the molecular events occurring in tumours.







Optical fibre

Aims:

- Accurate monitoring of dose and detection of resistance in cancer.
- Develop an ambitious new healthcare technology, applicable to areas far beyond melanoma.

Objectives for the project

(O1) Develop polymer-coated optical fibre long period gratings to detect Dabrafenib in serum.

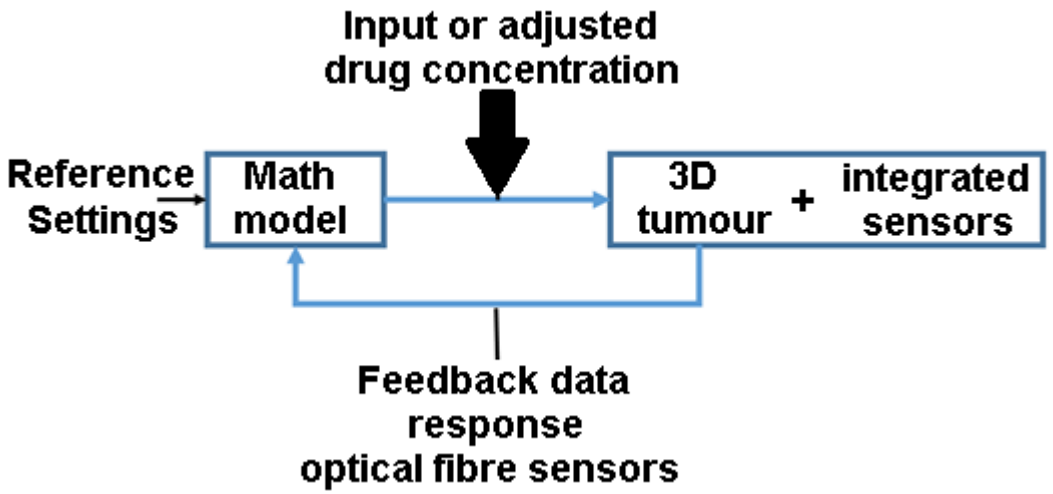
(O2) Derive 2D and 3D cultures of BRAF sensitive cells and validate Dabrafenib monitoring in extracellular milieu.

(O3) Interface recognition polymers with optical fibre based sensors which can detect local changes in pH, and test readouts from fibres in 3D tumour spheroids.

Initial 6 months: Basic technology

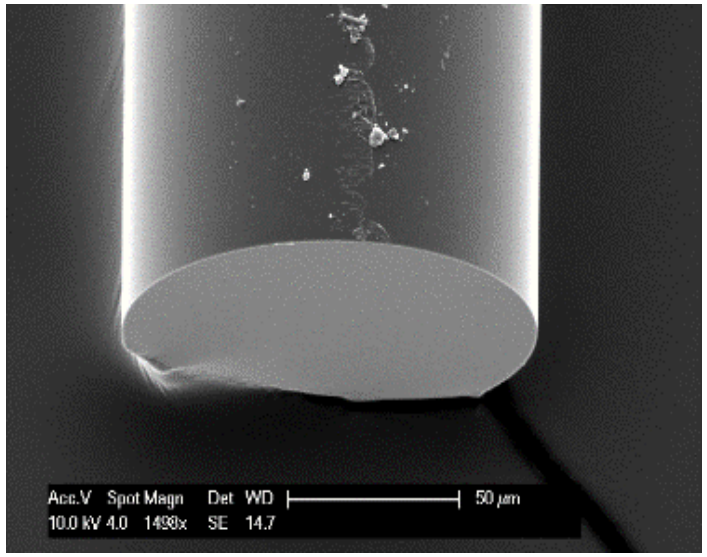
- Detect BRAF inhibitors and suitability for models linking drug concentration.
- BRAF suppression and extracellular pH.
- Testable hypotheses relating dosing to cell response and resistance.

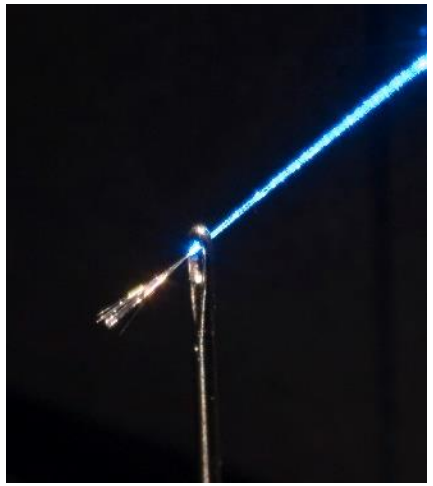
Long term: 2nd Cyclops round



Background – size and working principle of technology

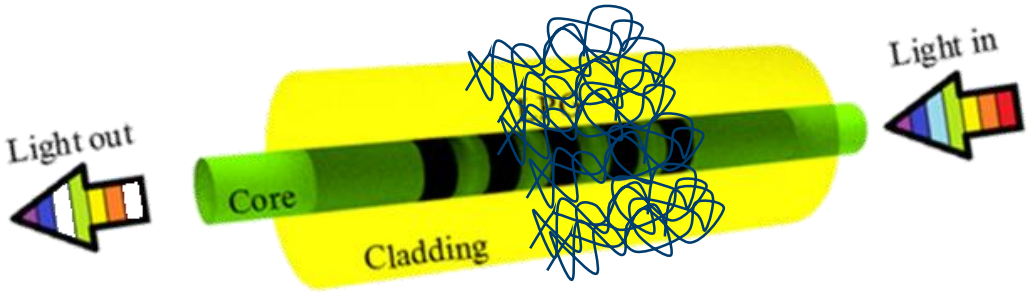
SEM optical fibre



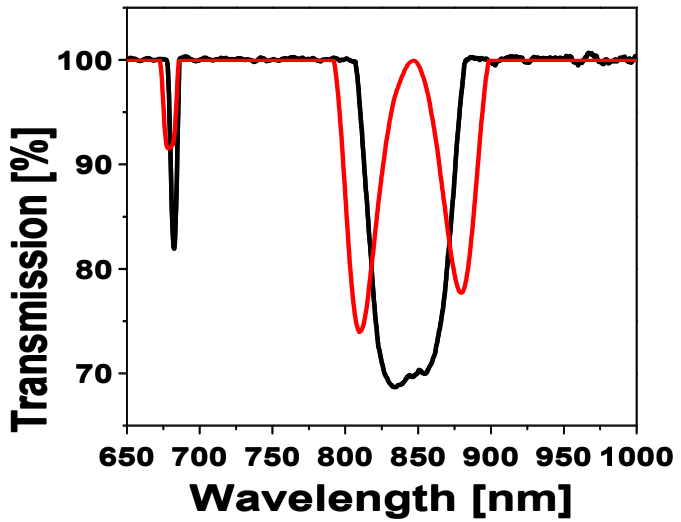


Bundle
optical fibres

Long Period Grating (LPG):
A wavelength encoded sensitive sensor

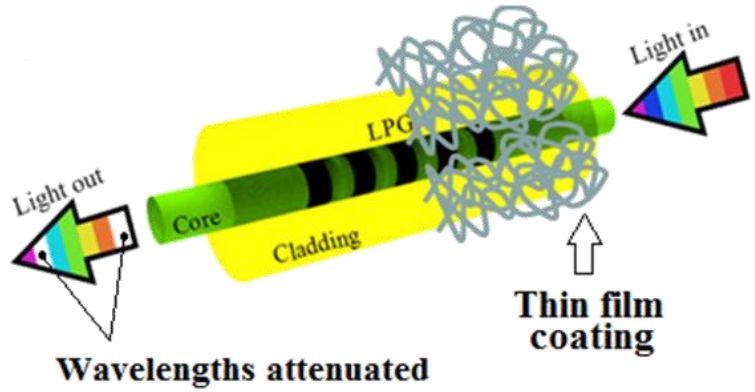


Wavelengths attenuated



Novelty of the research

Advanced fibre-optic sensors with polymer coatings



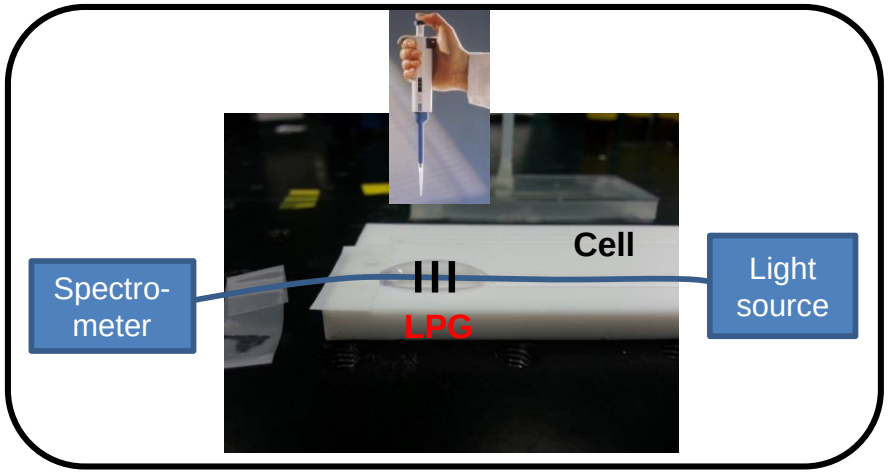
- No current sensor material for drugs BRAF inhibitors.
- No existing technology for online monitoring (real time).

Current offline methods for quantification:*

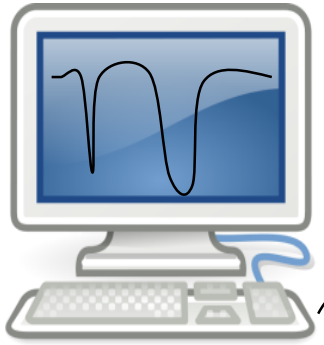
1. HPLC / UV (200 ml plasma sample).
2. LC / MS (50 or 10 ml plasma sample).

** Jean-Claude Alvarez et al. Journal of Pharmaceutical and Biomedical Analysis. 97 (2014) 29-32*

Demonstration of the Layer-by-Layer method

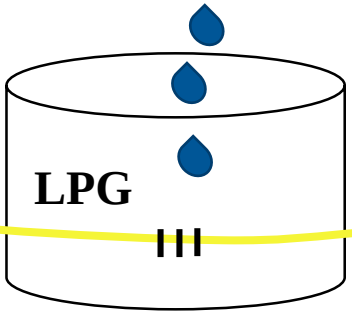


Experimental set-up



Spectrometer

Light source

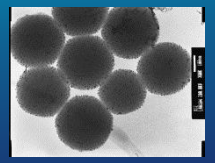


Visualization in PC

Deposition cell

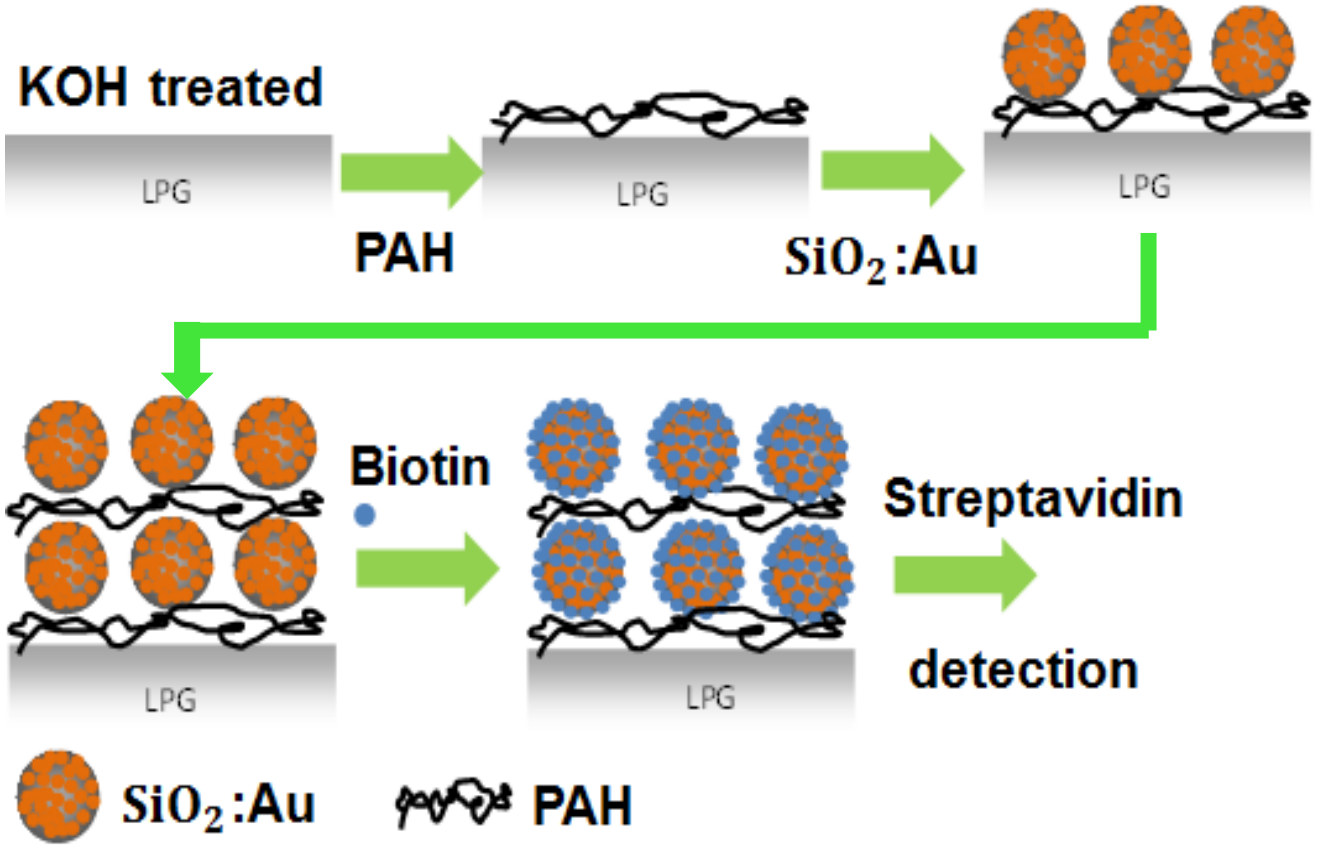
Optical fibre

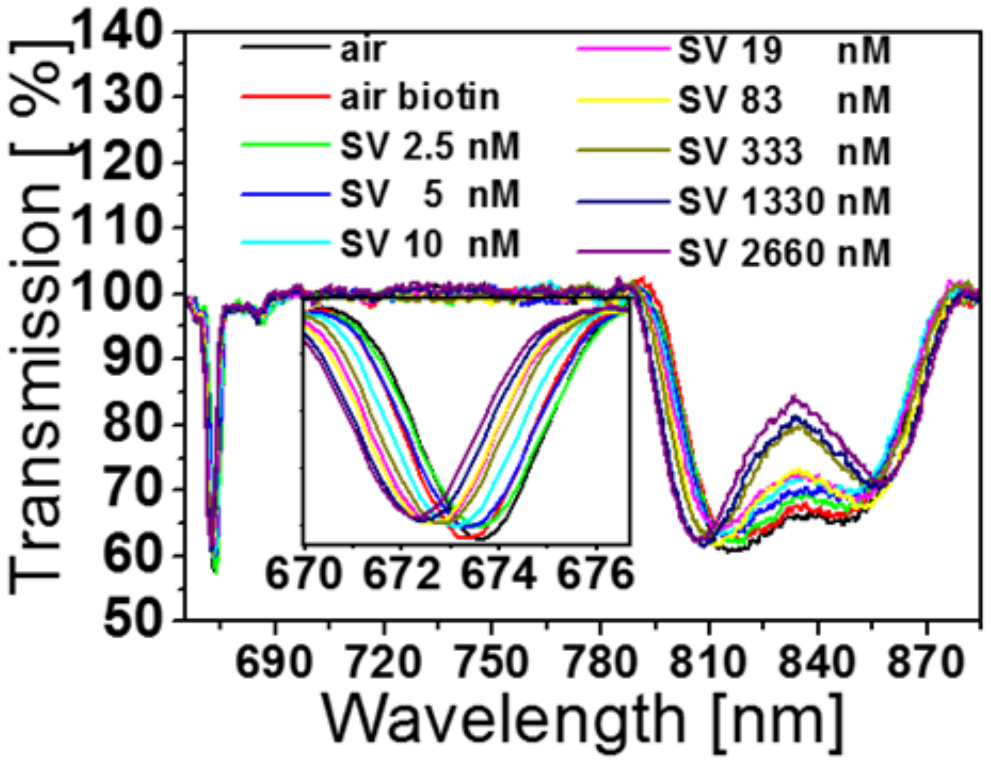
Demonstration of the Layer-by-Layer method



Statistical LoD=15.1 nm

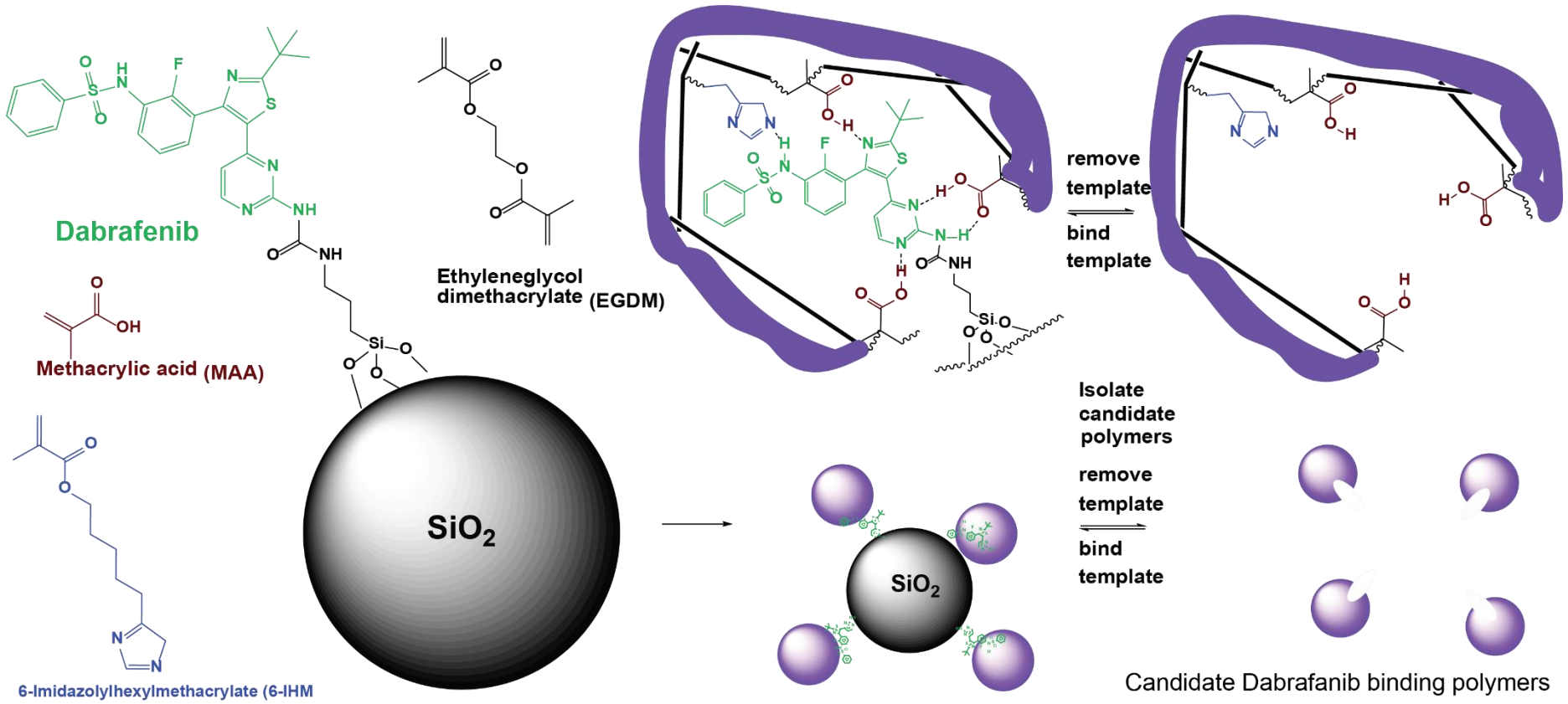
Theoretical LoD=$18.9\ \mathrm{p\,g/mm^2}$





Case of study: Biotin-streptavidin (SV) interaction

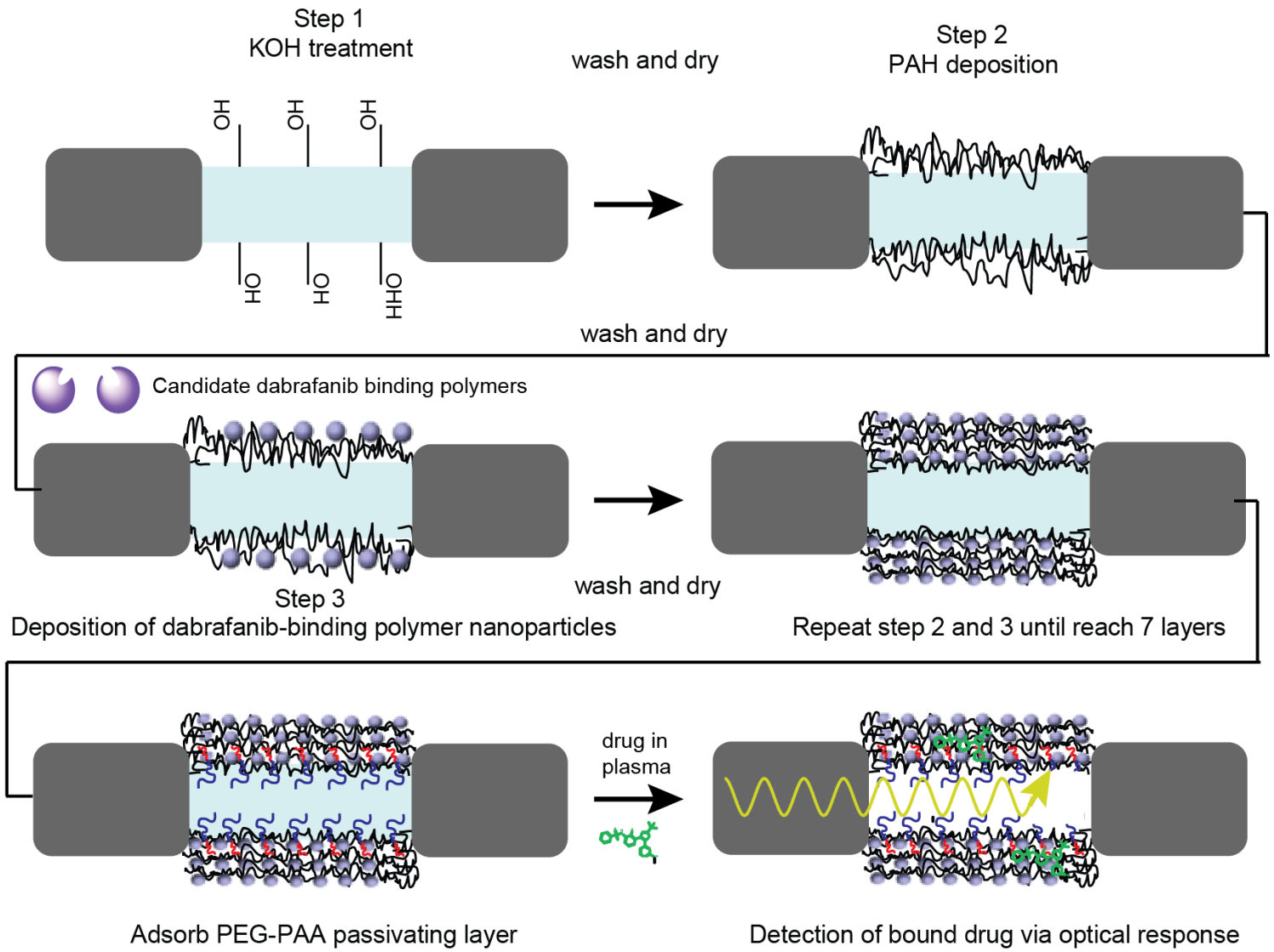
Concept for the project & experimental plan



1. Polymers prepared to bind Dabrafenib using molecular imprinting and related techniques based on methods developed in the Alexander, Korposh and Piletsky labs.

2. Resultant polymers immobilised on surfaces of optical fibres with LPGs from the Morgan lab.

Experimental plans



1. Passivation with poly(ethyleneglycol)-co-poly(methacrylic acid) will provide a hydrophilic ‘steric shield’ resistant to protein adsorption but permeable to dabrafanib.

2. First generation fibre sensors tested for detecting drug levels in buffer solutions, serum with extracellular matrix components and in blood.

3. Cancer cell lines susceptible to BRAF inhibitors and those known to have acquired resistance will be cultured as 3D spheroids.

4. Fibres will be inserted into the spheroids and in situ monitoring of dabrafenib carried out following drug infusion to the spheroids.

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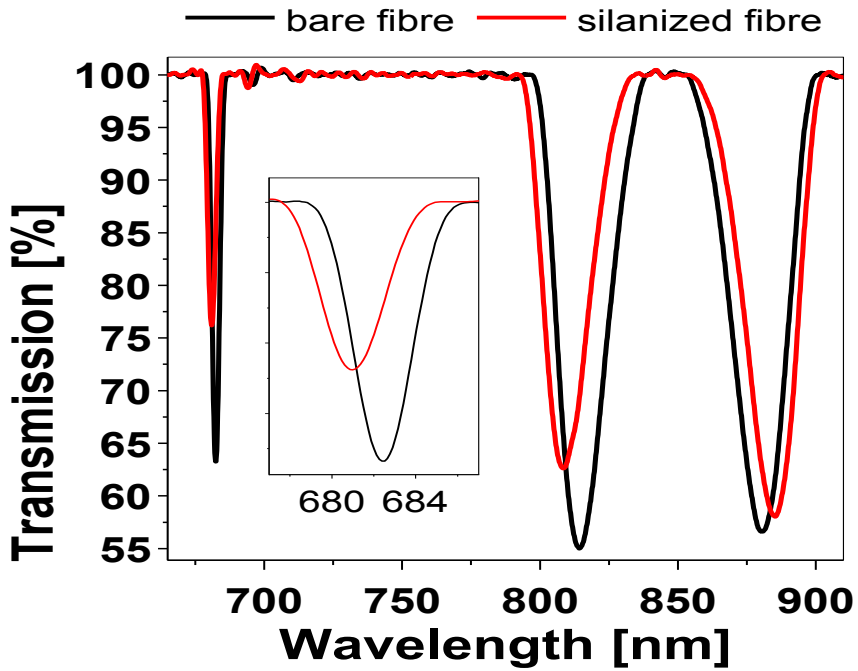
Progress to date

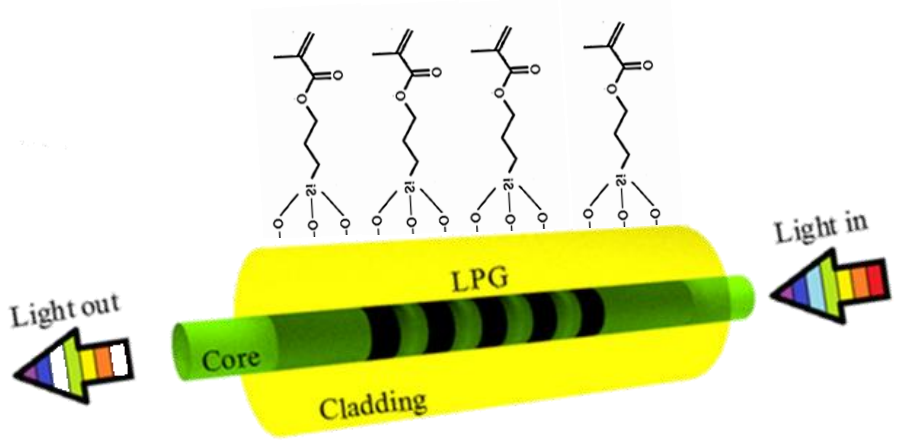
Experiments October-December 2017

First stage of the project

Silanized optical fibre

Silanization homogeneity influences surface polymer imprinting





2 steps silanization protocol:

Hydroxilation + silane agent (3-(trimethoxysilyl) propyl methacrylate) at 5 % (v/v) in solvent (MetOH/H_2O, 95 : 5).

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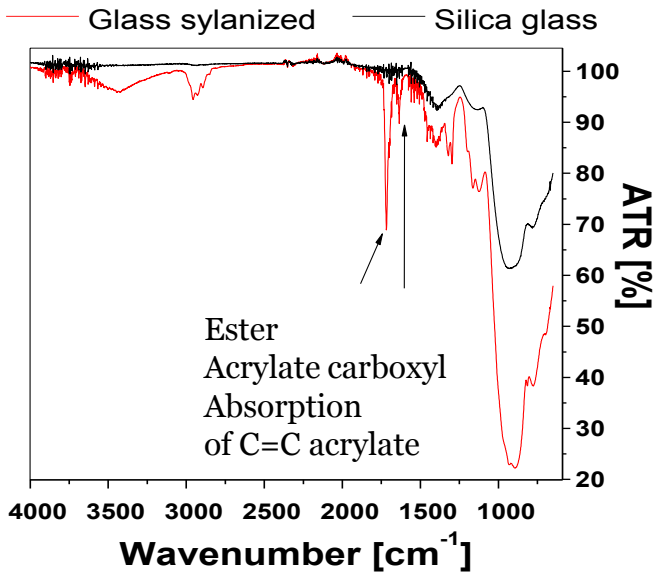
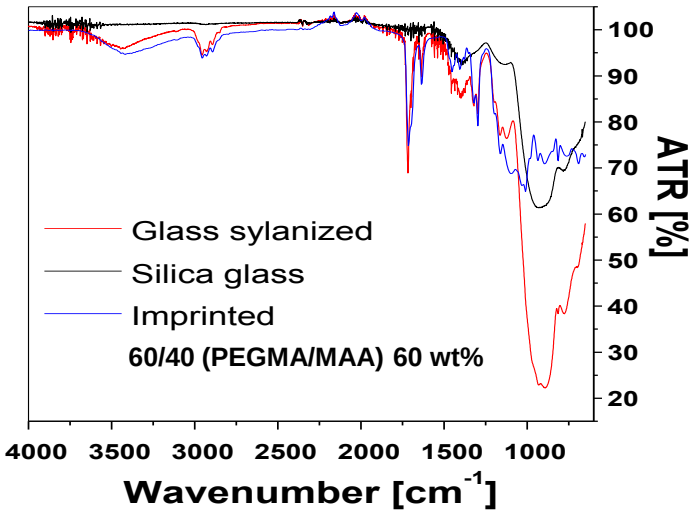
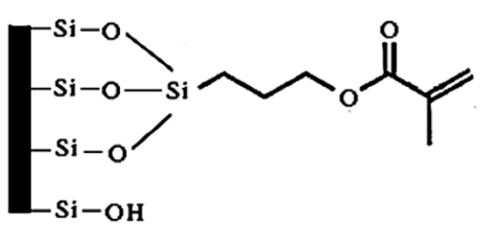
First stage of the project: Surface imprinting (photopolymerization)

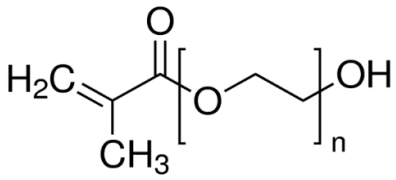






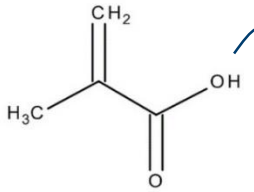
Silanated glass surface

+



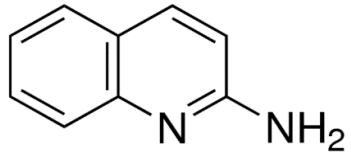
Poly(ethylene glycol) methacrylate (PEGMA)

+

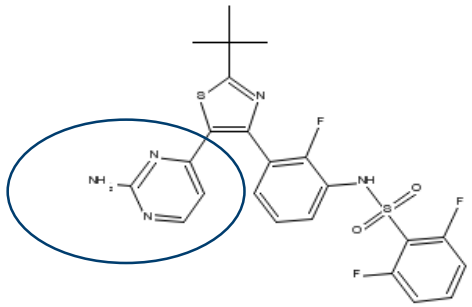


Methacrylic acid (MAA)

+



2-Aminoquinoline



Dabrafenib
BRAF- Inhibitor

Current work:
Exploration of polymer ratios to increase sensitivity

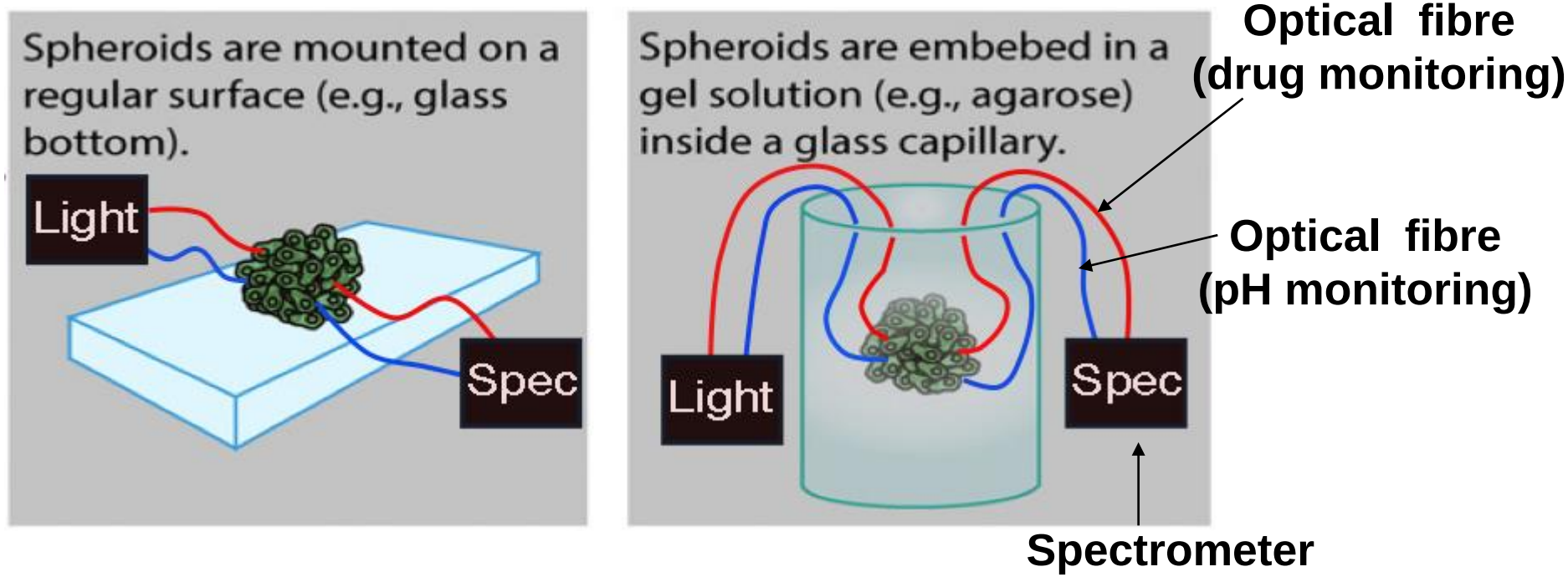
Translation to LPG fibre surface

next trials will include Ethylene glycol dimethacrylate

Extension of the project to monitor in vitro 3D cancer model

Second phase: Monitoring system in 3D tumour mimics.

Drug delivery (dabrafenib concentration) & tumour properties (pH)



"3D tumour spheroids: an overview on the tools and techniques used for their analysis"
Elisabete C. Costa et al. Biotechnology Advances 34(2016) 1427-1441

Summary slide

Conclusions so far:

- **Optical fibres with LPGs readily fabricated in the Faculty of Engineering.**
- **Silanization of silica surfaces.**

Key results and success:

- **Protocol for homogeneous silanization & molecular imprinting of 2-aminoquinoline using photopolymerization.**

Current work:

- **Testing different ratios of PEGMA/MAA for imprinting 2-aminoquinoline and characterization.**

Future plans (April 2018):

Translation to LPGs surface and tests for drug detection in serum.

SiO_2 NPs functionalization and implementation of the Layer-by-Layer Method. Implementation of best sensor system with cell cultures and monitor pH levels vs drug levels.

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cyclops

B15 laboratory
School of Pharmacy

Optics and Photonics
Faculty of Engineering