Novel "Sensor-in-Fiber" optical probes for molecular sensing in the gastro-intestinal tract of murine models of cardiometabolic diseases

V. Azzi[1,2], A. Grégoire[1], JP. Bérubé[1], J. Lapointe[1], A. Sepulveda[1,2], R. Vallée[1], A. Marette[2], D. Boudreau[1]
[1]Centre d'Optique, photonique et laser (COPL), [2]Institut Universitaire de Cardiologie et de Pneumologie de Québec (IUCPQ), Université Laval, Québec, QC, Canada

Introduction

The gut microbiota has recently been determined to be a key player of one's health where a disruption in its balance can cause numerous detrimental effects.[1] The progressive increase in obesity and cardiometabolic diseases in northern populations and around the globe is being driven by various environmental factors, such as changes in diet, that are also generating important changes in the gut microbiome. It is hypothesized that proper analysis of key biomarkers in the microbiota could be used reliably for predictive diagnostics of these prevalent disorders.

Current analysis of the gut microbiota, being made *in vitro* through feces, is time consuming, expensive and requires qualified personnel. The medical field presently lacks proper tools for rapid and efficient monitoring of these host-bacteria interactions, that could lead to a better understanding of these diseases.

We propose a "Sensor-in-Fibre" optical probe that uses evanescent fields generated on the peripheral interface to interact with elements in its vicinity through the use of fluorescent species-selective surface-grafted sensing nanomaterials. This technology holds promise for a flexible and reliable *in vivo* sensor capable of responding to various biomarkers.

Background

Gut Microbiota

Modulated by

- Birth type
- Environment
- Genetics
- Diet
- Antibiotics

Effects

- Inflammation
- Obesity/Diabetes
- Allergies
- Mental Health
- Cardiovascular risks

Figure 1. Key effects and modulators of the gut microbiota.[2]

Optical Fibre and Evanescent waves

Light propagates through the core by total internal reflection and can generate evanescent fields on its periphery.

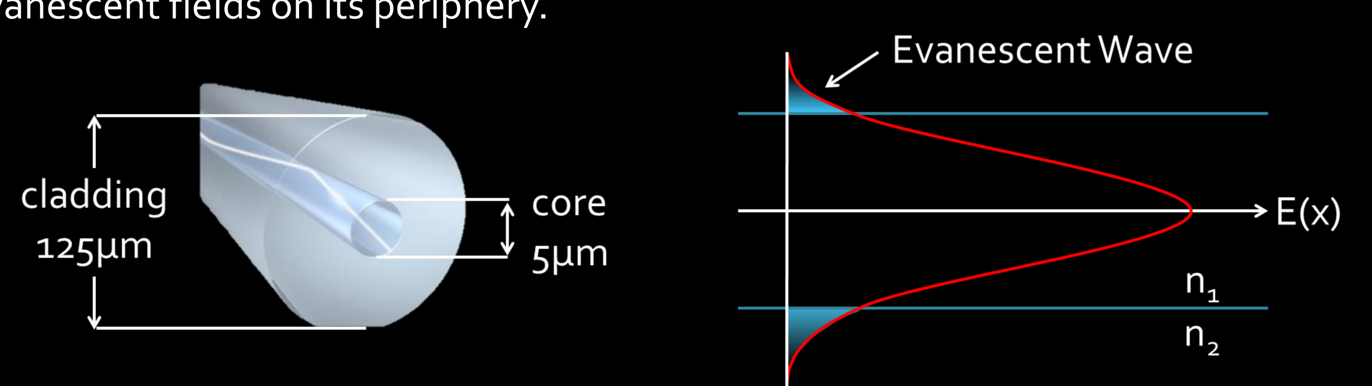

Figure 2. Left: Basic anatomy of a commercial optical fiber
Right: Typical electromagnetic field profile when propagating through a fibre core.[3]

Exploiting this energy can be done using a variety of methods such as removing cladding, approaching the core to the edge, having no core at all etc.[4]

Fluorescence

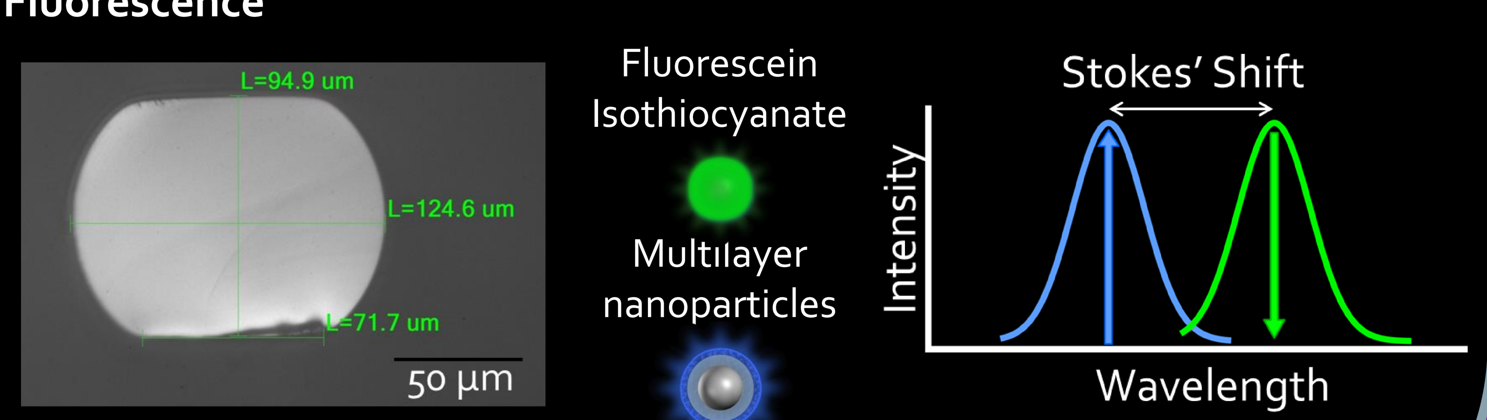

Figure 3. Left: : Custom coreless *DoubleD* optical fiber
Middle: Sample fluorescent particle structures with varying complexity
Right: Sample fluorescence excitation and emission spectra

Experimental Approach & Results

Attempt to combine all concepts to generate optical sensor capable of detecting a factor of interest surrounding the fibre with the use of murine models relevant to cardiometabolic diseases. As a proof of concept, pH measurement was determined as the first factor of interest.

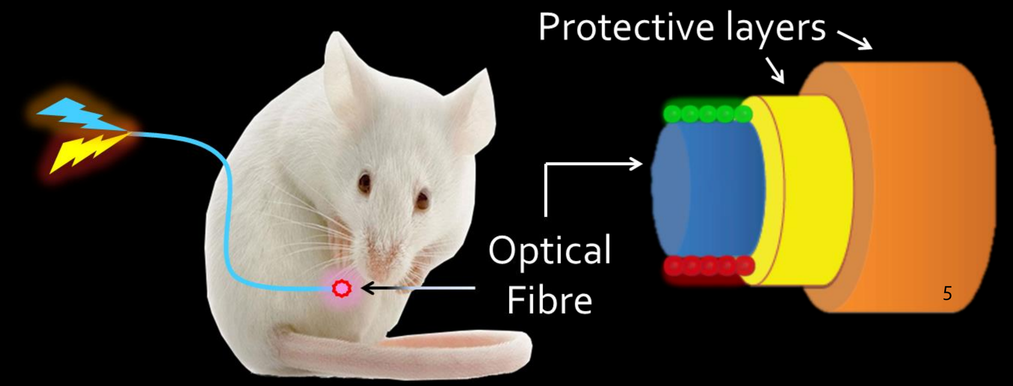

Figure 5. Representation of optical sensor a murine model

A) Creation of the optical sensor

Functionalizing FITC with aminopropyltriethoxysilane (APS) permits the creation of a monolayer of the pH sensing fluorophore on the periphery of the coreless fibre. Splicing the sensor section with a commercial fibre permits the transmission of information over moderate distances. Capping with black paint and medical silicone avoids noise due to transmitted light and reduces mechanical stresses when implanted.

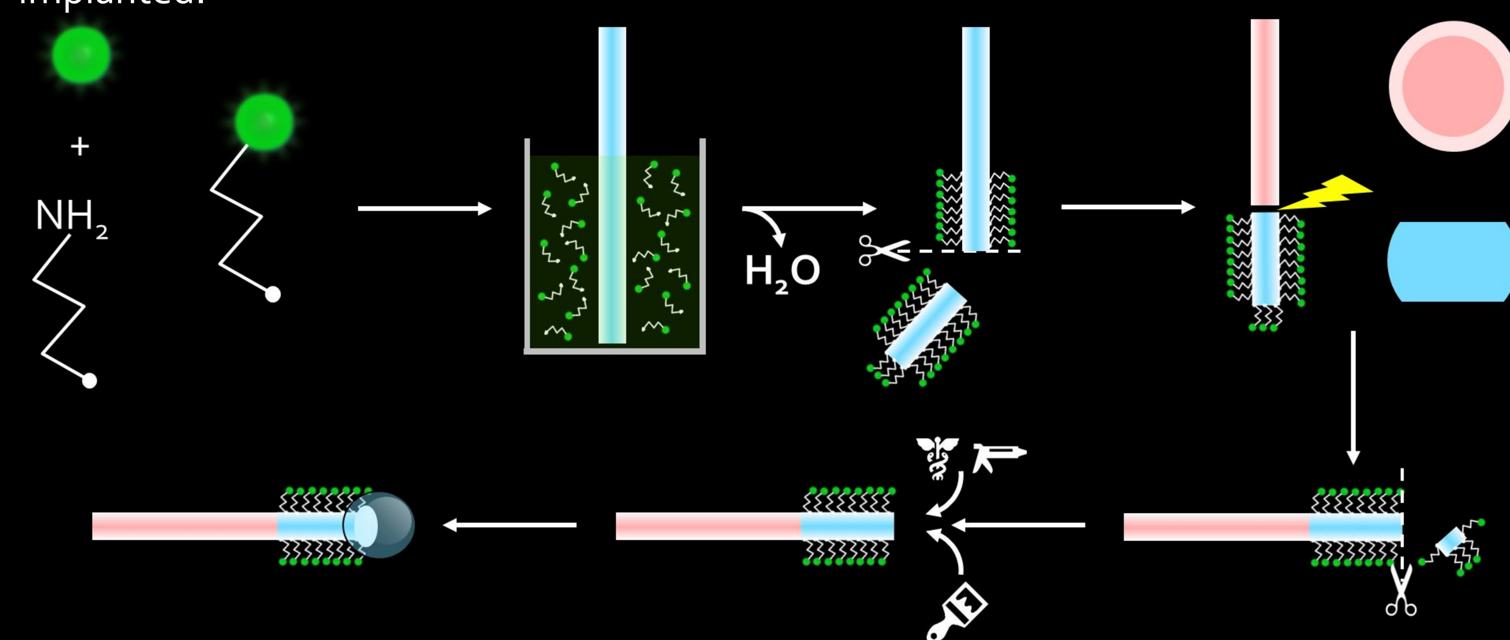

Figure 5. FITC functionalized with APS is used to graft fluorophores to the fiber surface. It is then cleaved, spliced with a multimodal 105/125 fiber, cleaved to appropriate length and capped with medical silicone and paint.

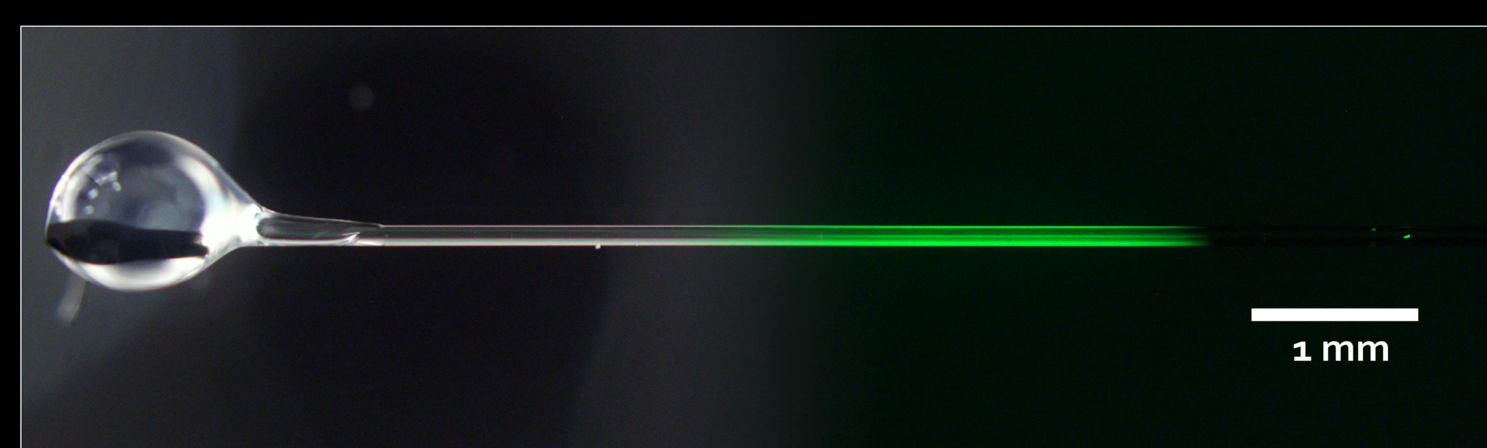

Figure 6. Single sensor fiber tip seen under microscope with 4x magnification taken at ambient light (left) and in epifluorescence with excitation at 488 nm and emission at 515 nm (right).

B) Optical Apparatus

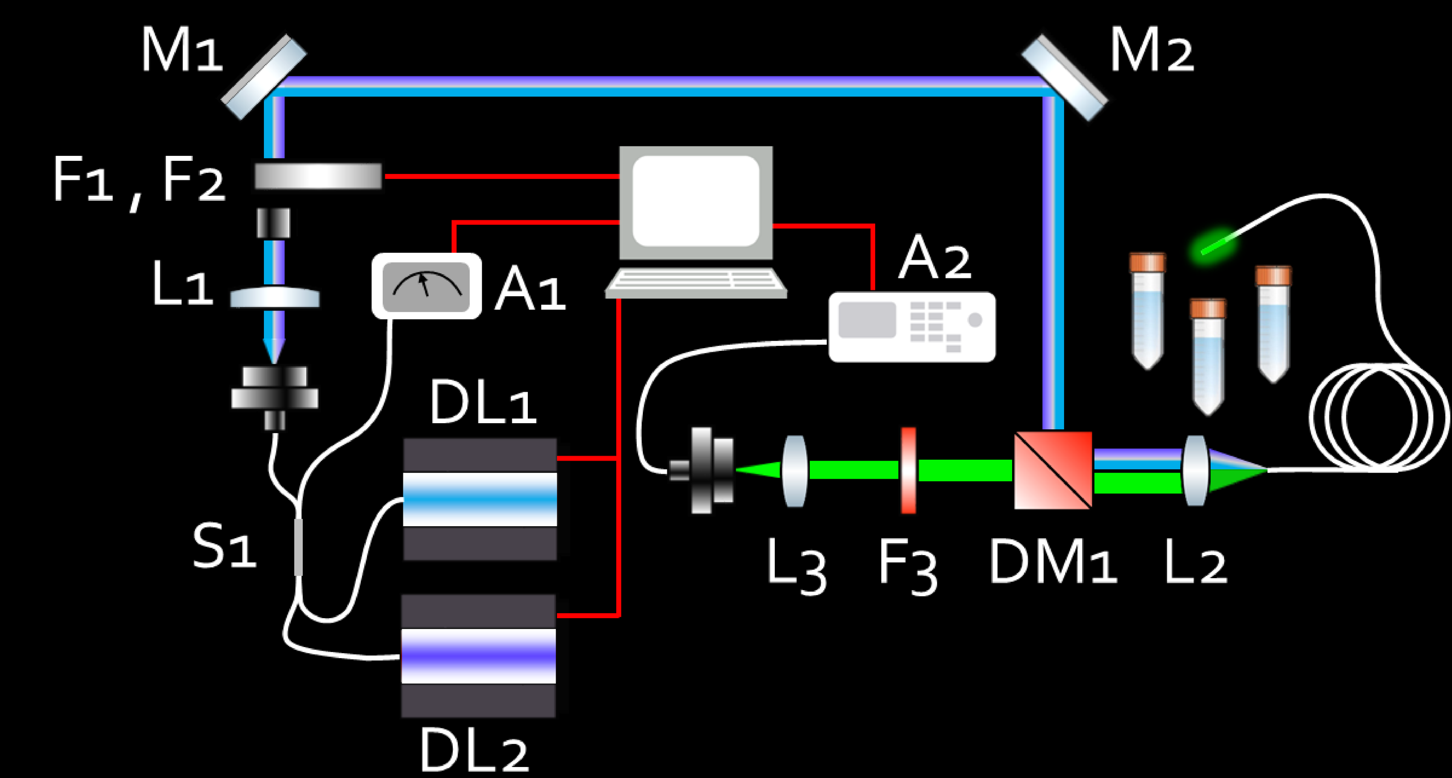

Figure 7. Experimental set-up used to detect pH variations. The system is controlled through a central computer. DL1, DL2: 488 nm and 450 nm diode lasers, respectively. S1: 50/50 coupler. L1, L2, L3: f40mm, 10x objective, f150mm lenses, respectively. F1,F2: Bandpass filters on a filter changer, 488/4 nm and 450/10 nm respectively. F3: 488 nm longpass filter. DM1: 506 nm dichroic mirror. M1, M2: mirrors. A1,A2: powermeter and spectrometer,

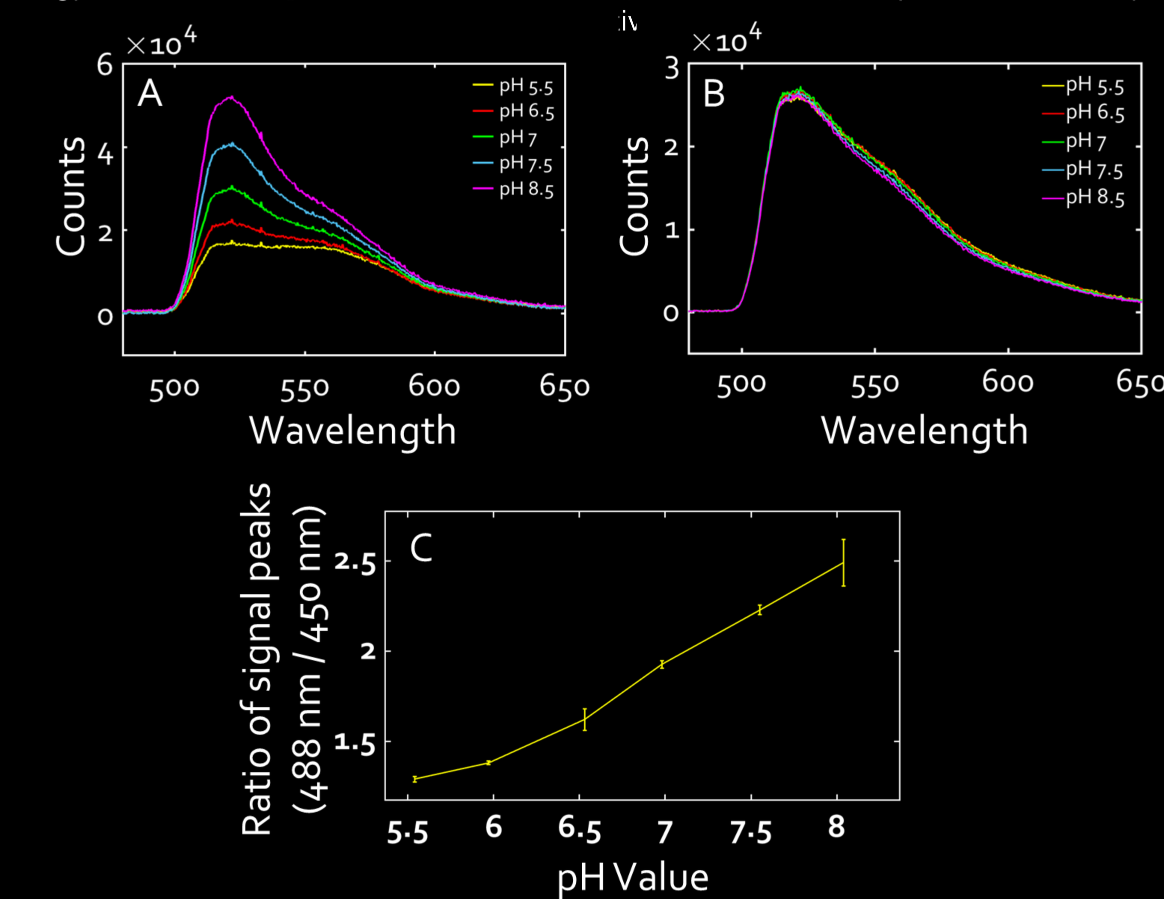

Figure 7. Sample spectra and ratios of a fiber placed in solutions with different pHs. A, B: Emission spectra when excited at 488 nm and 450 nm, respectively. C: Ratio of peaks from A & B with respect to the pH of the fluid.

Future Works

- *In vivo* validation in murine models relevant to cardiometabolic diseases
- Optimization of excitation and collection through the use of femtosecond laser photoinscription and fibre microstructures (JP. Bérubé, J. Lapointe, R. Vallée)
- Use of specialized fluorescent nanoparticles for detection of metabolites relevant to cardiometabolic diseases (N. Fontaine)

Conclusion et perspectives

The pH dependent optical properties of FITC were exploited in a coreless fibre model system through the generation of a covalently bonded fluorescent monolayer on a biologically relevant length. Rapid and accurate detection of environing pH through evanescent wave excitation and signal collection by backscatter were demonstrated. In time, multichannel fibre architecture can be combined with specialized fluorescent sensors hence making this a minimally invasive and flexible tool for *in vivo* measurements.

Bibliography

(1) O'Callaghan, Amy, and Douwe van Sinderen. "Bifidobacteria and their role as members of the human gut microbiota." Frontiers in microbiology 7 (2016): 925.
(2) Guasto, Jeffrey S., Peter Huang, and Kenneth S. Breuer. "Evanescent wave microscopy." Encyclopedia of Microfluidics and Nanofluidics. Springer US, 2008. 638-644.
(3) Quigley, Eamonn MM. "Gut bacteria in health and disease." Gastroenterology & hepatology 9.9 (2013): 560.
(4) Hale, Z. M., and F. P. Payne. "Fluorescent sensors based on tapered single-mode optical fibres." Sensors and Actuators B: Chemical 17.3 (1994): 233-240.
(5) Modified from: Dakin, John, and Brian Culshaw. "Optical fiber sensors: Principles and components. Volume 1." Boston, MA, Artech House, 1988, 343 p.

Acknowledgments

NSERC CRSNG
Fonds de recherche Nature et technologies Québec
Fonds de la recherche en santé Québec
INNOVATION.CA
CANADA FIRST RESEARCH EXCELLENCE FUND
APOGÉE CANADA
André Marette & Denis Boudreau's research groups