RamanSense: Metabolomics based on Enhanced Stimulated Raman Microscopy

Motivation: *Imagine you could position yourself inside an individual cell to observe its interior workings, visualize organelles and the complex interplay of signaling molecules and corresponding metabolic changes. Imagine how powerful you could be in the diagnostics of lifestyle diseases and hence their treatment.*

[1]

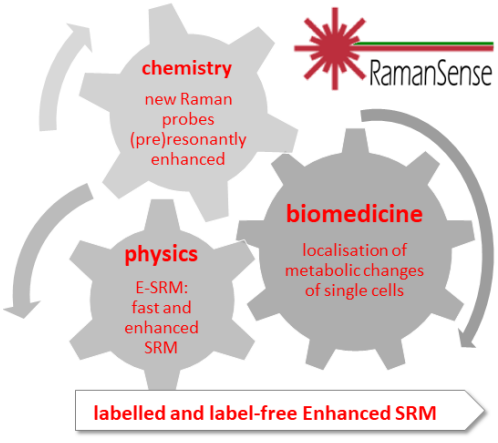
RamanSense is a multidiciplinary project where a new spectroscopic technique is developed. It is a combination of newly developed Enhanced Stimulated Raman Microscopy (E-SRM) and newly designed Raman probes, targeting specific subcellular structures and their functions, to be applied to study the metabolic state of cells.

New *omic* approaches, based on genomics, transcriptomics, proteomics and metabolomics, can help define the multiple cellular and humoral interactions that regulate normal and abnormal cell development and their response to stress or pathogens that are hallmarks of disease. While genomics reveals what a cell is capable, transcriptomics gives a view what is planning to do, metabolomics shows what is cell actually doing. One of the important elements for accurate diagnosis or efficient identification of biomarkers for personalized therapy that cannot be delivered by standard diagnostic methods is assessing the metabolic state of cells, i.e. their function or phenotype.

Raman spectroscopy is a method of breakthrough potential for the development of innovative *omic* technologies. Raman spectroscopy is one of the cornerstones of molecular analysis, especially since the advent of the first Raman microscope in the 1970s, followed by the possibility of high-resolution measurement in 2 and 3 dimensions. It is among the most powerful tools available for *in situ* analysis of molecular organisation of living cells. It allows identification of concentrations of different molecular groups, which collectively contribute to the Raman spectrum of the sample. Stimulated Raman Spectroscopy is a several orders of magnitude more sensitive than Raman microscopy based on spontaneous scattering, but still not enough sensitive and specific to study complex processes going in the cells.
Hence, the main goal of *RamanSense* is to overcome methodological and technical limits of optical imaging in detecting small organelles and specific molecules within cells by harnessing physics, chemistry, medicine, pharmacology, biology, engineering, and data analysis, to use these advanced technologies in life sciences. I propose to break the stereotype: Raman imaging does not have to be label-free. Furthermore, one can force the signal to be enhanced by adding selected dyes to the sample. So, the measurements can be performed both in labelled and label-free way using E-SRM.

The research will be conducted on two types of cells of the vascular system studied *in vitro*: adhesive endothelial cells and non-adhesive leukocytes. Dysfunction of endothelium is associated with the development of many lifestyle diseases, while leukocyte phenotyping is crucial in the proper diagnosis of haematopoietic proliferative diseases.

In this multidisciplinary project the research will connect: *i) chemistry:* design and synthesis of new Raman probes for highly specific and sensitive subcellular detection (due to specific bonding to individual molecules inside cells and containing a Raman tag), *ii) physics:* development of a new Enhanced Stimulated Raman Microscopy technique, capable of rapid measurements in (pre)resonance conditions, hence of real diagnostic potential (by using specific dyes in electronic (pre)resonance with excitation wavelength), *iii) biomedicine:* development of methodology for studying single cell metabolism (of endothelium and leukocytes) in selected models (dysfunction, stress, phenotyping) to follow cell metabolism and hence understand the cellular origin of lifestyle diseases, also leukemia, and improve their treatment.



The novel Raman technique I will develop is not only better than the current state of art but will allow analysis of living cells to track processes and is essential to the better understanding of the respective diseases and improved treatment strategies.

[1] https://www.scientistlive.com/sites/scientistlive/files/amsbiopr187-image.png; https://pl.freepik.com/premium-zdjecie/czlowiek-z-lupa_5443460.htm.