Spectral fiber sensors for cancer diagnostics *in-vitro*

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Introduction:

According to the world cancer report in 2014 cancer is one of the leading causes for morbidity and mortality worldwide. Around 14 million new cases and 8.2 million cancer related deaths were registered in 2012, and the number of new cancer patients diagnosed each year will rise by 20% between 2002 and 2020. Reports in the literature show that up to 30% of surgical procedures result in irradical (incomplete) removal of the tumor. The task to define tumor margins *in-vivo* is a great challenge, and optical spectroscopy may solve this problem.

Malignant and healthy tissues may be differentiated by fluorescence or molecular spectroscopy methods: Raman scattering, IR-absorption or diffuse reflection. To select the best method or their best combination we have already started to apply them all to the same samples of normal and cancer tissues *ex-vivo* and to find the best one in sensitivity, specificity and accuracy.

Looking for the future clinical applications all systems (Fig.1) or sensors must be used with flexible and tiny fiber probes – to be disposable or sterilizable.

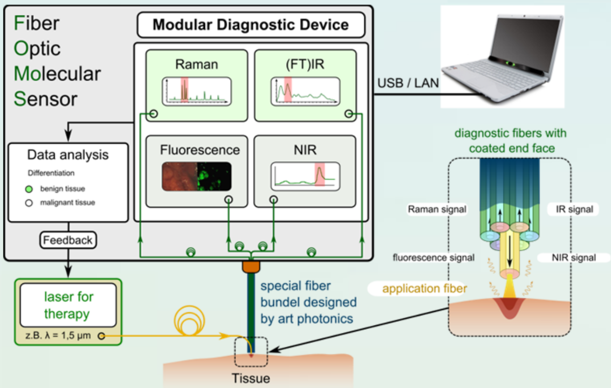

Fig.1 MultiSpectral fiber system to analyze tissue *in-vivo*

Mid IR-spectroscopy

Mid IR-absorption spectroscopy is the most informative for molecular tissue analysis as the absorption bands for organic molecules are dense in "finger-print region" from 2 to 16µm. Recent development of Mid IR fiber optics for this range makes biomedical applications of FTIR-spectroscopy possible not only for *in-vitro*, but for *in-vivo* diagnostics. The latest fiber coupled FTIR-spectrometers with effective fiber couplers can be used in clinics with room temperature DTGS-detectors (Fig.2).

Fig.2 FTIR-spectrometer iS5 with ATR-fiber probe

Fig.3 Needle ATR-PIR-fiber probe

ATR-Fiber probes

Polycrystalline PIR-fibers from Silver Halide crystals and Chalcogenide glass CIR-fibers are used for assembly of ATR-probes of various designs, including needle probe (Fig.3) to enable tissue puncture for 3D tumor margins definition. PIR-fiber probes can be used for ATR-tissue spectroscopy in-vivo as they can fit tiny needle diameter in mono-fiber probe design (*US Patent US 7,956,317 B2*).

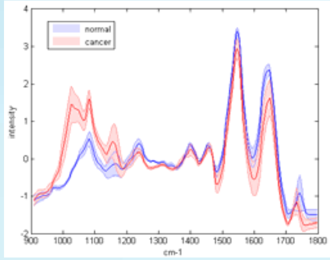

Fig.4 ATR-spectra of kidney

Tissue spectra in Mid IR-range

ATR-Absorption spectra collected to distinguish between normal and cancer kidney tissue in the range 900-1800cm^{-1} with ATR PIR-fiber probe are shown in Fig. 4. This method was tested before for the colonic inflammation diagnostics with sensitivity, specificity and accuracy of 92%, 88% and 90% respectively (V. K. Katukuri et al., Biomedical Optics Express 1014, v.1, No.3, 1 October 2010).

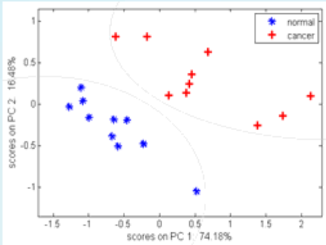

Fig.5 PCA on Mid IR ATR-spectra

Diffused Reflection spectroscopy

Diffused reflection spectroscopy in Near IR-range enables to control water to lipid ratio – considered as specific biomarker in definition of breast cancer margins by the team of Netherlands Cancer Institute & Philips (Lisanne de Boer, EPIC Workshop in Rotterdam on July 2-3rd, 2014). Fig. 6 & 7 illustrates similar feature in NIR-spectra for 3 samples of kidney cancer- with one sample very different from 2 others - with its score outside 95% confidence level.

NIR-Silica fiber probe was made with a tiny bundle of illumination & signal collection fibers - coupled with NIR-source & NIR-spectrometer/ sensor.

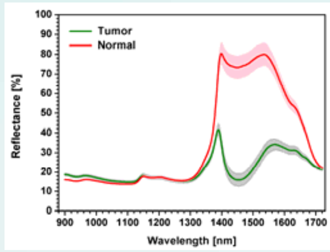

Fig.6 NIR-DRS-spectra of kidney tumor & normal tissue – for the saline used as background

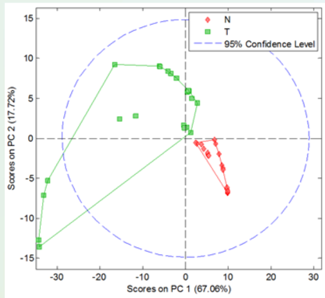

Fig.7 PCA on NIR spectra

Raman scattering spectroscopy

This method is complimentary to Mid IR-absorption, needs laser excitation and must detect very low signal of non-linear scattering much weaker vs laser power. The innovative design of Raman probe was developed based on patented process of special filters deposition at fiber ends - for a small probe diameter and possibility to analyze spectra in fingerprint and high wavenumber regions (using lasers at 785nm & 690nm).

Raman probes for high wavenumber range needs no filters and can control increase of water ratio at 3100-3700cm^{-1} to CH_3 at 2946cm^{-1} (Fig.8) - as it can be also cancer biomarker (S. Duraipandian et al., Anal.Chem. **84**, 5913-19, 2012)

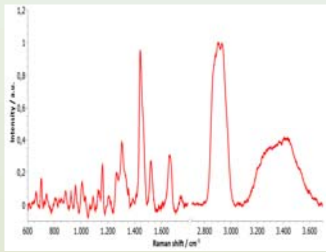

Fig.8 Raman spectrum of kidney cancer (in FP + HW regions)

Summary: Fiber probes are developed to investigate the possibility to define tumour margin *in-vivo* using key spectroscopy methods: Mid IR-absorption, NIR-reflection & Raman scattering