Disruptive imaging spectroscopy for minimal-invasive cancer diagnostics: 3D-CANCER-SPEC

Martin M. Roth[1*], Philippe Godefroy[2], Vincent Lapere[2], Rafael Bernardi[1], Christer Sandin[3], Elmar Schmälzlin[1]

[1]Leibniz-Institut für Astrophysik Potsdam (AIP), An der Sternwarte 16, 14482 Potsdam, Germany; [2]Winlight System, 135 rue Benjamin Franklin, ZA Saint Martin, 84120 Pertuis, France; [3]Sandin Advanced Visualization, Tylögränd 14, 12156 Johanneshov, Sweden
*Corresponding author: mmroth@aip.de

ABSTRACT

The 3D-CANCER-SPEC design study has provided the blue-print for a demonstrator that shall be used as a precursor for a future medical instrument for minimal-invasive optical cancer diagnostics, using imaging Raman spectroscopy. The demonstrator will be extensively tested in clinical studies and validated for the certification needed for commercialization as a medical instrument.

Keywords: cancer diagnostic, minimal-invasive, imaging Raman spectroscopy

1. INTRODUCTION

Cancer is the second-most relevant reason for mortality worldwide in countries of all income levels. The number of cancer cases and deaths is expected to grow rapidly as populations grow, age, and adopt lifestyle behaviors that increase cancer risk [1]. However, diagnoses at an early stage can have a high impact to improve the chances to cure the disease. Minimal-invasive optical methods can be used to this end in about 2/3 of all cases.

It has been shown that fiber-coupled Raman spectroscopy allows to differentiate between malign and benign tissue to reduce the need of biopsy [2], thus to reduce the risk of metastasis growth, to achieve high sensitivity and specificity, and to even distinguish between different stages of tissue lesion. Ideally, one would want to employ a *2-dimensional spectroscopic imager* to allow the surgeon to optically identify malign tissue and its boundary, and to immediately extract the cancer in one step [3]. Current state-of-the-art instruments are single-channel spectrographs that can merely investigate one tiny spot at a time. Scanning with such devices across a 2-dimensional area of tissue leads to extremely long exposure times, which is impractical for medical doctors, their patients, and the clinical routine. However, the technology transfer program "*Multiplex Raman Spectroscopy (MRS): from Astrophysics to Medicine*" has addressed the challenge to adapt a MUSE-clone spectrograph module, originally developed for the ESO Very Large Telescope [4], to an optical fiber bundle for the purpose of imaging biological tissue with Raman spectroscopy, i.e. to map the characteristic fingerprint of molecules when illuminated with laser light [5], [6]. A first major breakthrough has been the recent publication of the successful validation of this imaging technique for cancer diagnostics using real clinical samples [7]. However, these first experiments (Fig. 1, Fig. 2) were very much limited with regard to size, weight, and volume of the astronomical spectrograph and not suitable for clinical studies, which would be the next important step towards a medical device.

3D-CANCER-SPEC will enable the development of minimal-invasive optical cancer diagnostics through imaging Raman spectroscopy with a novel medical device that is suitable to perform clinical studies. We have completed a design study of an imaging Raman spectroscopy demonstrator including software, with management plan and costing, to become the blue-print for follow-up commercialization, suitable for fund-raising in a public-private partnership, from venture capital, or other financial resources, and subsequent realization.

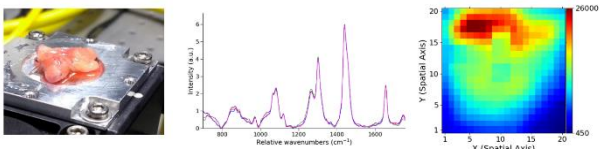

Fig. 1. Cancerous tissue investigated in previous feasibility study that has led to successful validation of imaging Raman spectroscopy for minimal-invasive cancer diagnostics. Left: tissue after resection, placed on optical sensor, middle: Raman spectra, right: Raman image.

2. STATE OF THE ART

Raman spectroscopy hast been demonstrated to provide label-free, non-destructive insight into the biochemical composition of organic samples. It can be used for the pathological assessment of biological samples like cells and tissues [8–12], and, in particular, for the purpose of minimal-invasive optical cancer diagnostics [2,3]. A major limitation has consisted in the fact that conventional Raman spectrographs are single-channel instruments, whereas the sample that needs attention, e.g. an area of skin to diagnose skin cancer, is spatially extended. Therefore, in order to measure across a meaningful area of the sample, a scanning process must be used to raster scan the object, which is a sequential, i.e. time-consuming process. As the Raman scattering cross-section is a very small number, few photons are being scattered from the excitation laser beam, meaning that the exposure time per sample spot cannot be made arbitrarily short. Unlike inorganic samples, medical applications of in vivo human tissue measurements must also observe stringent limits on laser beam power, such that short exposures would provide inadequate signal-to-noise ratios. As a result, sequential scanning techniques take too much time to be practical for a diagnostic medical device.

However, observational Astronomy, being a photon-starved science that has to live with extremely low intensities of distant galaxies, has developed a solution for this problem. Integral field spectroscopy is a technique that is capable of obtaining simultaneously hundreds and thousands of spectra over a 2-dimensional field-of-view in a single exposure. MUSE at the Paranal Observatory of the European Southern Observatory (ESO) is the most powerful instrument of this kind world-wide (Fig. 3). It was designed by an international consortium of research institutes with significant contributions from AIP (Potsdam, Germany). The optical components of this hugely complex instrument were manufactured by Winlight System (Pertuis, France).

Fig. 3. Installation of MUSE, the Multi Unit Spectral Explorer, on the Nasmyth platform of the 8.2m UT4 telescope of the Paranal Observatory in Chile. MUSE has a total mass of 7 tons.

AIP and Winlight have teamed up in 2012 to build a copy of one of the 24 MUSE spectrograph modules for the purpose of the MRS project (Fig. 2). In collaboration with the Charité Clinic (Berlin, Germany), the MUSE spectrograph was coupled with a Raman microscope and validated with real cancer samples as a tool for cancer diagnostics (TRL-4) [6,7].

3. BREAKTHROUGH CHARACTER OF THE PROJECT

Building on the successful outcome of the MRS project, AIP and Winlight System have put forward a concept of developing a new spectrograph that would be optimized for Raman spectroscopy and medical applications. The 3D-CANCER-SPEC project has delivered a design study that enables the manufacture of a prototype instrument for achieving technology readiness levels TLR-5 and TRL-6, that would be critical to conduct clinical studies as required for certification according to European legislation) [13]. After publication of technical details and first results from the MRS experiment [6] and of the final

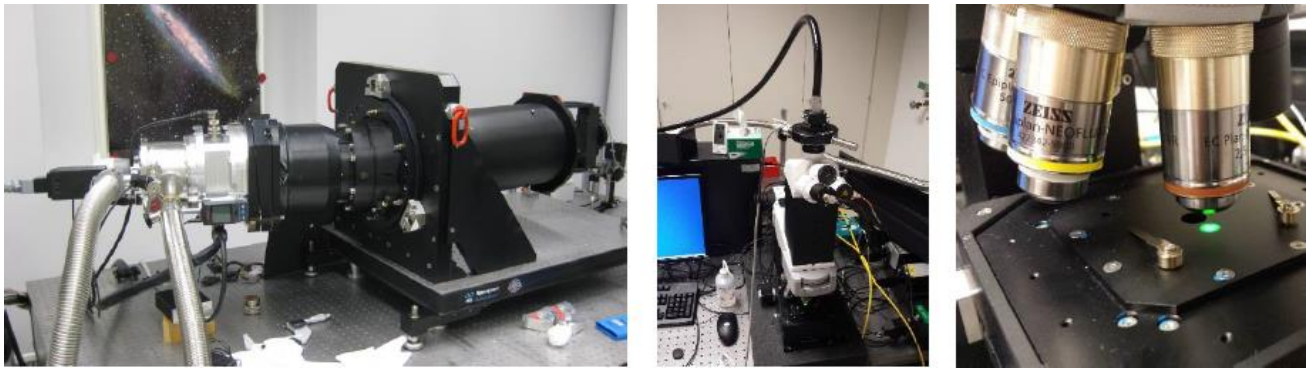

Fig. 2. Laboratory experiment to validate imaging Raman spectroscopy as a tool for minimal-invasive optical cancer diagnostics.

validation paper [7], the team was approached by medical research experts from several institutions, requesting either to transfer the equipment to their places, or otherwise making copies of the instrument in order to allow operation directly in a clinical environment. Providing cancer tissue for testing purposes is a complicated process, involving endorsement of ethical committees, proper timing (when a biopsy has occurred), fast transportation and immediate follow-up measurement since tissue tends to degrade rapidly. Therefore, external labs are not an option, such that intense testing and use with real cases in a clinical environment is a critical step for further development towards a certified medical device. However, the current experimental setup (Fig. 2) is not at all suitable for that task. The spectrograph system was optimized for high throughput and stability needed for astronomical observations. However, it is far too large, bulky, heavy and complicated to operate in a hospital, also actually an expensive overkill in terms of wavelength coverage and detector technology.

► Building a prototype on the basis of the blueprint provided by the 3D-CANCER-SPEC design study would mean a unique breakthrough for imaging Raman spectroscopy and a future medical device.

4. PROJECT RESULTS

The initial requirements and specifications of the spectrograph optical system are listed in Tab. 1. It was assumed that the parameters would be subject to a trade-off and optimized for the future application. An important top-level requirement was compatibility with the clinical environment, involving a self-contained system within an enclosure that would meet hygienic conditions and no need for direct human interaction. Fig. 4 shows a sketch of the complete system mounted in an industrial 19’ rack. The fiber-coupled spectrograph optical design is fully dioptric, consisting of a collimator, a volume phase holographic grating (VPHG), and a camera that illuminates a cooled science grade CCD detector system.

Tab. 1. Requirements and Specifications

	Value
Fiber input	telecentric, Ø 100 µm
Fiber probe	20 x 20 square matrix
Pseudoslit length	75 mm
Detector, pixels	CCD, 2Kx2K, 13.5 µm
Image scale	0.5
Image quality	D80 ≤ 13.5 µm
Collimator, camera optics	f/3, f/1.5
Dispersive Element	VPH grating
Free spectral range	530… 880 / 600…950 nm
Linear dispersion	0.171 nm/pixel

The design is composed of 10 lenses with two aspheric surfaces and can be separated in three parts:

- The collimator part is made of 5 lenses (a slit lens and 4 regular lenses) and has a wide space (about 900 mm) to fit a folding flat mirror.
- The VPHG with an incident angle of 5.2°, for a circular useful area of Ø 174 mm with 0,273 lines/µm.
- The camera part composed of 5 lenses with 2 aspheric surfaces.

The spectrograph is connected to a commercial CCD camera system. Data analysis has been demonstrated with simulated images using the p3d code [16].

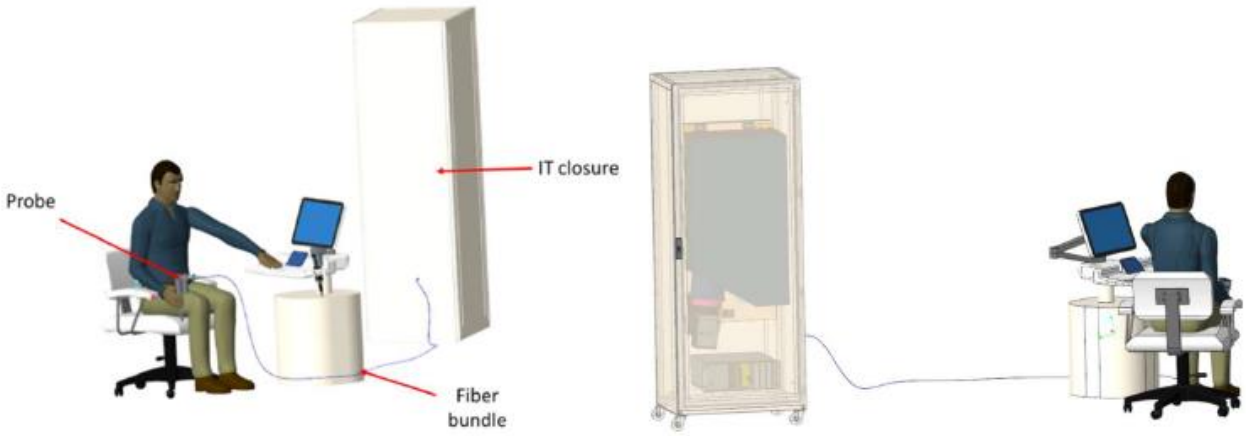

Fig. 4. 3D-CANCER-SPEC instrument ready as a turnkey system for use in a clinical environment.

5. FUTURE PROJECT VISION

The 3D-CANCER-SPEC study has already attracted considerable attention, both in the general public, as well as by potential future users of the new technology. A number of follow-up projects to the MRS study with institutes such as IPHT (Jena), FBH (Berlin), Fraunhofer IIS (Erlangen), also SMEs like Schölly Fiber Optic (Denzlingen), Oberon (Wildau), Becker&Hickl (Berlin), as well as clinical partners, e.g. in Freiburg, Berlin, but also encouraging interest extended from the Leibniz Health Technology Network in Germany, present convincing evidence for a dire need to make the next step. The results from the current design study show that the optical design is indeed feasible for manufacturing.

5.1. Technology Scaling

As explained in Section 2, the current state of the art has been set by the MRS experiment at TRL-4, i.e. validation in the lab. Moving toward TRL-5/6 is critical in order to be able to conduct clinical studies with sufficiently large cohorts of patients to enable statistically meaningful conclusions that are necessary for certification as a medical product.

STEP 1: Manufacture of the spectrograph with imaging fiber optical sensor. The feasibility has been shown in the completed 3D-CANCER-SPEC design study. This phase would include as major work packages: creating requirements and specification document (R&S), predesign, final design, manufacture, integration, and test. Each of those activities would be followed by a gate review to assess the level of completion and compliance with R&S. The deliverable would be a demonstrator, ready for clinical tests. At this stage, it would be possible to manufacture even several identical copies for different clinical collaborators who might want to do independent tests in parallel, perhaps also different applications (skin, bladder, cervix, etc.). The demonstrator would be supported by an updated version of the existing data reduction and analysis software package p3d that has already been used for the MRS project.

STEP 2: Use of demonstrator(s) in clinical tests. The results would be evaluated by experts and published in scientific journals. As pointed out above, we have already established good collaborations with several institutions who are definitely interested – however for reasons related to funding, for the time being only in Germany. It would be a goal at this stage to involve a larger number of competent players across Europe.

STEP 3: With the outcome of clinical studies, the opto-mechanical design as well as the data analysis software would be critically reviewed and a comprehensive report drafted, including requirements and specifications for a follow-up prototype of a commercial medical product.

STEP 4: Manufacture of prototype(s) to reach TRL-7. The validation would be accomplished by the collaborating institutions involved from STEP 2. At this stage, the development of a multimodal software package with augmented reality capabilities will replace the current p3d open source software [16]. For a commercial product, it will be preferable to deliver a proprietary software along with the instrument.

STEP 5: Commercialization. Stage 4 and 5 would follow after a possible projected funded under Attract Phase 2 and involve commercial companies of sufficient size and weight, or raising venture capital and creating a spin-off company. It is plausible to assume that such options would emerge by the interplay of partners over the course of Phase 2.

5.2. Project Synergies and Outreach

As explained in Section 5.1, the success of the development will crucially rely on the collaboration with clinical partners and medical research institutions. We will be open to new partners, but can build already on existing collaborations from three previous projects, also involving industrial partners. Attract has already provided us with significant exposure and visibility, e.g. press releases by ESO, the German BMBF, and various newsletters, to the extent that the team was contacted by healthcare specialized venture capitalists, expressing an interest in helping to commercialize the invention. The team will continue to use Attract as an effective platform for dissemination. Other channels will include the Berlin-Brandenburg Optics Cluster, and EPIC (European Photonics Industry Consortium).

5.3. Technology application and demonstration cases

The 3D-CANCER-SPEC case is obviously associated with the European Societal Challenge *Health, demographic change and wellbeing.* The initial application of the concept of MRS has been demonstrated for skin cancer [7]. Follow-up research projects have focused on bladder cancer [14] (Uro_MDD, BMBF 03ZZ0444C), real-time imaging with Raman video sequences [15] (4D-HTS, BMBF 03ZZ0423ZB), and the suppression of fluorescence and stray light using the nod-shuffle technique (Korinth et al., in prep, HYPERAM, Leibniz Competition). Up to now, three research institutes, two clinics, and three SMEs have been involved in this research. Providing the 3D-CANCER-SPEC instrument, possibly with several replica for different groups, would enable the European research community to achieve a unique breakthrough, similar to how we have accomplished to make European Astronomy a world-wide leader with integral field spectroscopy, by coordinating the Euro3D Research Training Network *"Promoting Integral Field Spectroscopy in Europe"* (*HPRN-CT-2002-00305)*.

5.4. Technology commercialization

The next steps towards commercialization have already been explained as part of the technology scaling roadmap presented in Section 5.1 under STEP 4 and STEP 5. At this stage, we envision various options for implementation that will narrow down in Phase 2. The approach of healthcare specialized venture capitalists has already been mentioned above. Also, Winlight System as a world leader in the area of cutting-edge optical technologies and major manufacturer of advanced astronomical instrumentation has a dedicated interest in expanding into life science and medical applications.

5.5. Envisioned risks

AIP and Winlight System have more than 20 years of experience with professional development of advanced instrumentation, involving proper system engineering, project management, and quality assurance schemes that are necessary to manage complex projects that often have a duration of more than a decade. These schemes include formal risk management and mitigation techniques. The delivered 3D-CANCER-SPEC opto-mechanical design study has already passed a risk analysis, concluding that the proposed optical materials are all commercially available, and that the manufacture of lenses involves no unusual challenges. AIP has provided 78 fiber bundles to the Hobby Eberly Telescope Dark Energy Experiment in Texas, has built the fiber probe for the MRS experiment, and is hosting the innoFSPEC innovation center for fiber-based spectroscopy and sensing[1], such that ample experience exists to keep the risks for building the front-end fiber probe at a minimum.

5.6. Liaison with Student Teams and Socio-Economic Study

The world-leading activities of transferring astronomical integral field spectroscopy to medical Raman imaging were launched by innoFSPEC in 2012. The innovation center is a joint venture between AIP and the Physical Chemistry Department at the University of Potsdam (UP) that has been instrumental to provide the necessary interdisciplinary knowledge transfer. Dr. Elmar Schmälzlin holds a PhD in physical chemistry and brings in years of expertise with Raman spectroscopy. Prof. Martin M. Roth is teaching at UP and entitled to supervision of MSc thesis projects that are being planned to be included in Phase 2.

The innoFSPEC innovation center is very much aware of the challenges of truly interdisciplinary research that is confronted with borderlines between disciplines that are often hard to overcome, and therefore open to participate in the envisaged socio-economic study within Attract.

[1] https://innofspec.de/en/

6. ACKNOWLEDGEMENT

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