LASERLAB-EUROPE

The Integrated Initiative of European Laser Research Infrastructures V

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Work package 8 – NA7 – Innovation Management and Industry Relations

Deliverable D8.1
First workshop on innovation and industry relations

Lead Beneficiary: 30 – LLE-AISBL

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Deliverable Type		
R	Document, report	OTHER
DEM	Demonstrator, pilot, prototype	
DEC	Websites, patent fillings, videos, etc.	
OTHER		
ETHICS	Ethics requirement	
ORDP	Open Research Data Pilot	
DATA	data sets, microdata, etc.	
Dissemination Level		
PU	Public, fully open, e.g. web	PU
CO	Confidential, restricted under conditions set out in Model Grant Agreement	

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1 Objectives

The objectives of WP 8 are to foster Laserlab-Europe's relations with industry and the medical sector and to implement supporting measures that will promote the use of advanced laser technology for industrial and medical applications. Further objectives are to promote the use of laser RIs by industrial researchers, to enhance technology and knowledge transfer and help to fully exploit the innovation potential of the participating research infrastructures.

Under Task 2, Laserlab-Europe maintains an Innovation Forum, with support from the Industrial Advisory Committee, in order to facilitate exchange between stakeholders from academia, industry and the medical sector. Workshops are held to enhance interaction of laser facilities with industry and medical centres, in particular with a view to exploit the innovation potential resulting from the JRAs.

2 First workshop on innovation and industry relations

Laserlab-Europe Symposium "Lasers Fighting Cancer", 25 May 2021, online event

Medical and industrial application of lasers in the diagnosis and treatment of cancers

Laserlab-Europe provides outstanding laser-based cancer research performed by its members, often in interdisciplinary collaboration with medical institutions, as well as a unique innovation potential for disruptive technologies. These activities showcase the role lasers play from understanding cancer to advanced diagnostics up to treatment modalities - on the level of fundamental or pre-clinical research up to the clinical application. On the other hand, there is a huge global market for medical applications, e.g. for optical and radiological medical imaging technologies, minimal-invasive individualised treatment techniques and optical drug monitoring.

Based on these framework conditions, the first workshop on innovation and industry relations focused on medical and industrial application of lasers in the diagnosis and treatment of cancers. With support from the Industrial Advisory Committee, in particular from Anchored In Ltd, an ambitious programme was designed with the aim to raise awareness of the opportunities for laser technologies, to inform about barriers that new technologies face when being deployed in the medical/pharmaceutical sector – and what needs to be done to overcome them, to showcase Laserlab-Europe's activities and expertise to the broader community, and to initiate discussion on joint R&D activities.

Due to the Covid-19 pandemic, the symposium took place as a web conference. It was attended by more than 140 participants (out of about 200 registrations), comprising scientists from Laserlab-Europe laboratories, from European and international medical institutions and representatives from several companies developing medical laser systems and looking for new technologies. The symposium was very successful, even though the meeting was held as virtual meeting with less opportunities for discussion and interaction as compared to a meeting in person. A much higher number of participants could attend, as no travelling was required. The event created a unique opportunity for interaction between academia and industry in the field of application of lasers in the diagnosis and treatment of cancers.

Feedback, collected after the event through an online questionnaire, showed a high level of appreciation from the participants and broad interest in specialised follow-up events focusing on targeted issues related to laser science in cancer diagnosis and treatment, ranging from different forms of cancers to specific techniques, to clinical translation of photonic developments and also to applications of ultrashort laser systems to other medical areas. Based on this feedback, and with support of the more than 20 labs in Laserlab-Europe that are active in the field of cancer research, targeted follow-up workshops will be planned.

Details about the event, the speakers and presentations of the talks are available at
https://www.laserlab-europe.eu/events-1/laserlab-events/2021/lasers-fighting-cancer-25-may

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3 Agenda

Session 1 – Lasers in Cancer Diagnosis Chaired by Prof. Luis Arnaut

Opening address

Dr Sylvie Jacquemot – Coordinator Laserlab-Europe

Clinical Translational Laser Spectroscopy for an Improved Cancer Diagnosis and Therapy

Prof. Juergen Popp – Director Leibniz Institute of Photonic Technology

Quantitative OCT signal analysis for tumor detection

Prof. Ton van Leeuwen – Academic Medical Center, University of Amsterdam

Raman spectroscopy for cancer diagnosis: adding a new molecular dimension

Dr Mónica Marro – ICFO - The Institute of Photonic Science

Vibrational imaging approaches for cancer diagnosis:
status, needs and perspectives

Dr. Renzo Vanna – Italian National Research Council, Institute for Photonics and Nanotechnologies IFN-CNR

The SOLUS project: smart optical and ultrasound diagnostics of breast cancer

Prof. Paola Taroni – Politecnico di Milano

Real time widefield TCSPC imaging of a model tumour system

Dr Graham Hungerford – Horiba

Q&A with the speakers from session 1

Session 2 – Lasers in Cancer Treatment Chaired by Paola Taroni

Very high energy electron beams for cancer radiotherapy

Prof. Dino Jaroszynski – Director of the Scottish Centre for the Application of Plasma-based Accelerators, SCAPA

High dose rate in vivo proton irradiation based on a laser plasma accelerator

Prof. Ulrich Schramm – Director Institute for Radiation Physics and Head Laser Particle Acceleration Division, HZDR

Translating optical systems into surgery & radiation oncology: academic & industry

Prof. Brian Pogue – Thayer School of Engineering and Geisel School of Medicine at Dartmouth

Translation of a combination between a laser device and a medicinal agent, from bench to bedside

Prof. Luis Arnaut – Chemistry Department, University of Coimbra

Photonics research in cancer therapy and industrial spin-off

Prof. Katarina Svanberg – Department of Clinical Sciences and Lund Laser Centre; Board member, SpectraCure

Q&A with the speakers from session 2

Closing Statements

Dr Anke Lohmann – Anchored In

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4 Abstracts

Abstract: Clinical Translational Laser Spectroscopy for an Improved Cancer Diagnosis and Therapy

Prof. Juergen Popp – Director, Leibniz Institute of Photonic Technology

Due to an aging society an increase of cancer is observed representing unsolved medical needs with respect to early diagnosis and therapy. Thus, in tumor surgery, there is a great need for new technologies that are able to localize the tumor exactly in order to remove it as complete as possible as the specific detection of malignant tissue during curative surgery is the most important precondition for complete tumor removal. Thus, new diagnostic approaches, which can be applied intraoperatively, i.e. in-vivo or near in-vivo (e.g. as frozen section analysis approach) are required.

The recent progress in the development of high intensive ultrashort laser sources has revolutionized microscopy by utilizing non-linear optical phenomena to create a higher microscopic contrast. It emerged to be very advantageous to combine several non-linear spectroscopic contrast mechanisms in a multimodal approach. In this contribution it will be shown that multi-contrast nonlinear imaging, using different spectroscopic methods such as coherent anti-Stokes Raman scattering (CARS), two-photon excited autofluorescence (TPEF) and second harmonic generation (SHG) represents a powerful tool for the label-free characterization of the molecular composition of biological tissue and allows to reliably assess tumor tissue and the success of an operation directly in the operating theatre. Here we will highlight our recent efforts in translating this CARS/TPEF/SHG approach towards routine clinical applications by researching and developing compact clinically usable automated instrumentation with high TRL levels. We have transferred the aforementioned approach into a compact and portable microscope for an intraoperative frozen section analysis. In order to further extend the applicability of this multimodal microscopy approach for *in vivo* tissue screening, different endospectroscopic probe concepts are also presented. Besides innovative multicontrast spectroscopic technologies, the presentation will also introduce innovative image evaluation algorithms for the translation of multimodal images into quantitative diagnostic markers. Finally, it will be shown that the presented CARS/SHG/TPEF multimodal imaging approach can be combined with laser tissue ablation for tissue specific laser surgery.

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Abstract: Quantitative OCT signal analysis for tumor detection

Prof. Ton van Leeuwen – Academic Medical Center, University of Amsterdam

With OCT high resolution images can be obtained of tissue in patients. This morphological information can be used to detect superficial tumors. Furthermore, by quantitative analysis of the OCT signals, optical properties that reflect the microstructure of the tissue can be determined. We demonstrate that the scattering coefficient can be related to the grade of the tumor.

Abstract: Raman spectroscopy for cancer diagnosis: adding a new molecular dimension

Dr Mónica Marro – ICFO - The Institute of Photonic Science

Raman spectroscopy is a promising optical technique that enables the investigation of the molecular content of biological samples in a rapid, non-invasive, label-free and multiplexed

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approach. In the medical field, it is of special interest because the device can be portable and cost-effective.

In this seminar, I will show how Raman spectroscopy coupled with appropriate data science methods can represent a step forward into cancer diagnosis, enabling the extraction of new molecular information and therefore improving current cancer diagnosis and patient stratification. I will show some examples of ongoing and recently published work in areas like breast cancer, dermatology, and cancer exosomes detection.

Overall, I will show how Raman spectroscopy coupled with data science could revolutionize cancer diagnosis and research in the next years, providing new and other-wise inaccessible molecular information, and giving a step towards a more rapid, accurate, personalized diagnosis and treatments.

Abstract: Vibrational imaging approaches for cancer diagnosis: status, needs and perspectives

Dr. Renzo Vanna - Italian National Research Council, Institute for Photonics and Nanotechnologies IFN-CNR

Despite the introduction of promising blood-based cancer biomarkers and of revolutionary imaging approaches (including MRI, PET and CT scan) for cancer assessment, tissue biopsies and their microscopic assessment - after slicing and staining - remain a fundamental diagnostic step before therapeutic or surgical interventions.

This is what we call “histopathology” and nowadays, similarly to 150 years ago, it is performed by the visual inspection of thin tissue slices under the bright field microscope after producing sufficient contrast by two or more stains able to bind only specific biological structures. This approach can be accompanied by human errors, subjectivity, reproducibility, and long manual procedures. The very recent introduction of Digital Pathology partially solved the subjectivity issue but, still, the information we get from the tumour is the same coming from typical staining procedure.

Conversely, ideal and modern tools should be able to detect and image the intrinsic biochemical and biomolecular features of tissue - and related malignancies – without necessarily using chemical stains and subsequent subjective interpretation. In the last thirty years, vibrational spectroscopies, including Raman and Infrared-based approaches, aimed to reach this ambitious goal by taking advantage from recent technological improvements, comprising advanced new detectors, fast computational approaches, and efficient light sources, where the role of lasers has been fundamental.

In this talk I will give a brief overview of major advances in the field of vibrational imaging for cancer diagnosis mainly focusing on spontaneous Raman imaging, FT-IR imaging, coherent Raman imaging and photothermal imaging approaches. Contextually, I will try to underline current clinical and technological needs, also considering the importance of a close interaction between laser experts, spectroscopists and pathologists.

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Abstract: The SOLUS project: smart optical and ultrasound diagnostics of breast cancer

Prof. Paola Taroni – Politecnico di Milano

The H2020-funded project SOLUS aims at improving non-invasively the diagnosis of breast cancer through the development of an innovative multimodal imaging system that combines cutting-edge developments in diffuse optics, ultrasound and shear wave elastography.

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Each of the three techniques provides useful diagnostic information: tissue morphology is obtained from B-mode ultrasound imaging, stiffness from shear wave elastography, and composition (oxy- and deoxyhemoglobin, lipid, water and collagen) from diffuse optical tomography. Multiparametric analysis of all results will be performed to improve the discrimination between lesions that are borderline between malignant and benign ones.

While for the ultrasound techniques, the project relied on state-of-the-art technology, to allow time domain diffuse optical tomography to be performed at 8 wavelengths all needed components were specifically developed to combine high performance with small footprint: Eight picosecond pulsed laser diodes (635-1064 nm), a wide area fast-gated Silicon PhotoMultiplier (SiPM) detector, and an integrated Time-to-Digital-Converter. They all fit within few cm^3, and can also be exploited as a stand-alone device (called “smart optode”) for diffuse optical spectroscopy.

Abstract: Real time widefield TCSPC imaging of a model tumour system

Dr Graham Hungerford – Horiba

Protoporphyrin IX (PpIX) occurs naturally as part of the haem pathway. It is localised within cells and in relation to cancer diagnostic/ treatment can be induced by the metabolism of 5-aminolevulonic acid (5-ALA). As well as labelling cancerous tissue, its photophysics exhibit potential in photodynamic therapy. Therefore its study and the ability to rapidly image its localisation is important, especially in the growing field of fluorescence guided surgery. However, simply measuring the intensity of its fluorescence emission may not be straightforward, as this can be influenced by both aggregation and the formation of photoproducts. The use of the fluorescence lifetime imaging (FLIM) can, in this case, be advantageous. For practical purposes imaging needs to be rapid and preferably in real time. Recent advances in CMOS based technology has enabled sensor arrays with in-pixel timing to allow for the Fluorescence Lifetime Acquisition by Simultaneous Histogramming (FLASH) to acquire widefield fluorescence lifetime images in real time. Here we use PpIX in a tissue mimic construct imaged using FLASH – FLIM on a commercial widefield TCSPC camera based on a sensor chip with 192 x 128 pixels; each containing both detection and photon timing. The potential use in visualising tumour boundaries in a model system using FLIM is shown.

References: Methods Appl. Fluoresc. 9, 015002 (2021), IEEE J. Solid-State Circuits, 54, 1907-1916 (2019)

Abstract: Very high energy electron beams for cancer radiotherapy

Prof. Dino Jaroszynski – Director of the Scottish Centre for the Application of Plasma-based Accelerators, SCAPA

In the talk we present studies of VHEE beams for radiotherapy. We show theoretically and experimentally that VHEE beams can be focussed to a very small volumetric element that can be scanned over a tumour. We also present experimental study where we produce VHEE beams from laser-plasma accelerators. Finally, we have set up a medical beamline at the SCAPA facility at Strathclyde to investigate radiotherapy using VHEE beams using in vitro and in vivo methods.

Abstract: High dose rate in vivo proton irradiation based on a laser plasma accelerator

Prof. Ulrich Schramm – Director Institute for Radiation Physics and Head Laser Particle Acceleration Division, HZDR

Since the first demonstration of laser acceleration of intense proton bunches two decades ago applications of such compact laser accelerators in radiation therapy have been

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discussed. Though in principle well matched, so far insufficient reliability and control of beam paramaters has prevented the further developing of this idea. The continuous generation of proton beams at energies exceeding 60 MeV at repetition rate supporting laser parameters at the Dresden platform recently opened the door to systematic radiobiological studies of tumor response to the corresponding high dose rate irradiation (10^8 Gy/s) and individual pulse dose of up to 20 Gy, reviving the concept. Combined with pulsed magnet based energy selecting beam transport and online dosimetry a first full scale in-vivo irradiation campaign was performed at the Draco laser at HZDR.

Scientific Reports 10, 9118 (2020)
Scientific Reports 11, 7338 (2021)

Abstract: Translating optical systems into surgery & radiation oncology: academic & industry

Prof. Brian Pogue – Thayer School of Engineering and Geisel School of Medicine

Academic biomedical engineers today must differentiate themselves by their discipline, as tool-based or disease-based professionals, making an impact through scientific discovery, engineering inventions, and creating enterprising translation. This work must be done in a collaborating iterative environment where there is both stimulus and feedback are possible from the needs in biomedicine and healthcare and the possibilities in venture and industry. Evolution, testing and maturation of discoveries can maximize impact each branch of science or medicine, which may not exactly fit a singular definition of BME. Along the way, it is imperative that the impact be measured by creation of research that is: i) productive, ii) quality, iii) reproducible, iv) shared, and v) translated.

Examples will be given from the Center for Imaging Medicine, around the invention and development of new optical tools to *Image Medicine.* Translation of novel contrast mechanisms in surgical guidance and radiotherapy that have gone from scientific concept through to technology development and into clinical trials. In the first example, new affibody-based receptor-targeted contrast tools was created and tested with human microdosing, to image receptor phenotype in vivo. This approach to human testing allows for economically feasible assessment of the use of receptor targeted contrast to guide oncology resection. In the second example, radiation dose imaging in radiotherapy was discovered from Cherenkov imaging, and translated to allow capture the real time dose delivery process. Translational delivery via a new venture start up will be discussed. In both cases, economic realities have been a piece of input that drove the decision making, ensuring that the devices created can translate beyond single center clinical trials.

Finally, the role of biomedical engineering is largely to allow for quantitative translational discovery to occur in medicine, and the growth in funding opportunities within this field is extremely strong. While the field of *Medical Imaging* is dominated by radiological devices, the field of *Imaging Medicine* today is dominated by optical devices, and the market sector and growth patterns show that this point-of-care use of imaging is the largest singular technology sector used in medicine.

Abstract: Translation of a combination between a laser device and a medicinal agent, from bench to bedside

Prof. Luis Arnaut – Chemistry Department, University of Coimbra

In 2020, 2.7 million Europeans were diagnosed with cancer, and another 1.3 million of them lost their lives to it. Cancer is estimated to become the leading cause of death in the EU by 2035. In 2020, the overall economic impact of cancer in Europe was estimated to exceed €100 billion. In view of these figures, it is not surprising that cancer research has been able to attract tremendous resources. Already in 2005 it was estimated that the annual global

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spend on cancer research was €14 billion [1]. The "Cancer" mission area of the Horizon Europe framework program will add an extra €1 billion this spending with the objective of saving 3 million lives and improving the quality of life of many more millions.

In this highly competitive and extensively explored research landscape, it is of critical importance to position the resources available in an area of expertise where they can make a difference. We remarked that drug-device combinations (DDC) have been largely oversighted by pharmaceutical and medical technology companies, as well as by regulatory agencies. FDA issued the first GMP regulation for DDC in 2013 and EMA published the first guideline on their quality in 2019. There is an enormous untapped potential in combining innovative drugs with novel technologies.

Photodynamic therapy is probably the most successful DDC in oncology. It combines light (most often, laser light), a dye molecule (named photosensitizer) and oxygen to kill cells in the field of illumination [2]. The photosensitizer absorbs light and interacts with oxygen to generate reactive oxygen species (ROS) that react locally and trigger cell death [3]. This opportunity in DDD motivated research on our labs on the combination of lasers with biomaterials and drugs. We designed and characterized a new photosensitizer (named redaporfin) [4], developed new approaches to perform PDT [5] and contributed to the clinical translation of redaporfin that eventually lead to cures of patients with advanced head and neck cancer that had exhausted approved therapeutic options [6]. This communication presents an overview of this work.

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Disclosure of interest. The Author has patents licensed to Luzitin SA, and owns shares of this company, that sponsors clinical trials with redaporfin.

References

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[2] Photochem. Photobiol. Sc., 14, 1765 (2015)
[3] BBA Rev. Cancer, 1872 188308 (2019)
[4] Chem. Eur. J., 20, 5346 (2014)
[5] Eur. J. Cancer, 51, 1822 (2015)
[6] Case Rep. Oncol. 11, 769 (2018)

Abstract: Photonics research in cancer therapy and industrial spin-off

Prof. Katarina Svanberg – Department of Clinical Sciences and Lund Laser Centre; Board member, SpectraCure

Laser based spectroscopic techniques can be used in the detection and therapy of human diseases. Among threats to mankind the increasing incidence of cancer is of significance and is projected to be doubled until 2040. Has laser spectroscopy and photonics any possibility to meet some aspect of this alarming challenge affecting the whole world? New less-aggressive treatment modalities are of high interest and one such might be minimal invasive photodynamic therapy. The example of prostate cancer will be discussed as being the most common cancer among men only slightly outnumbered by lung cancer.