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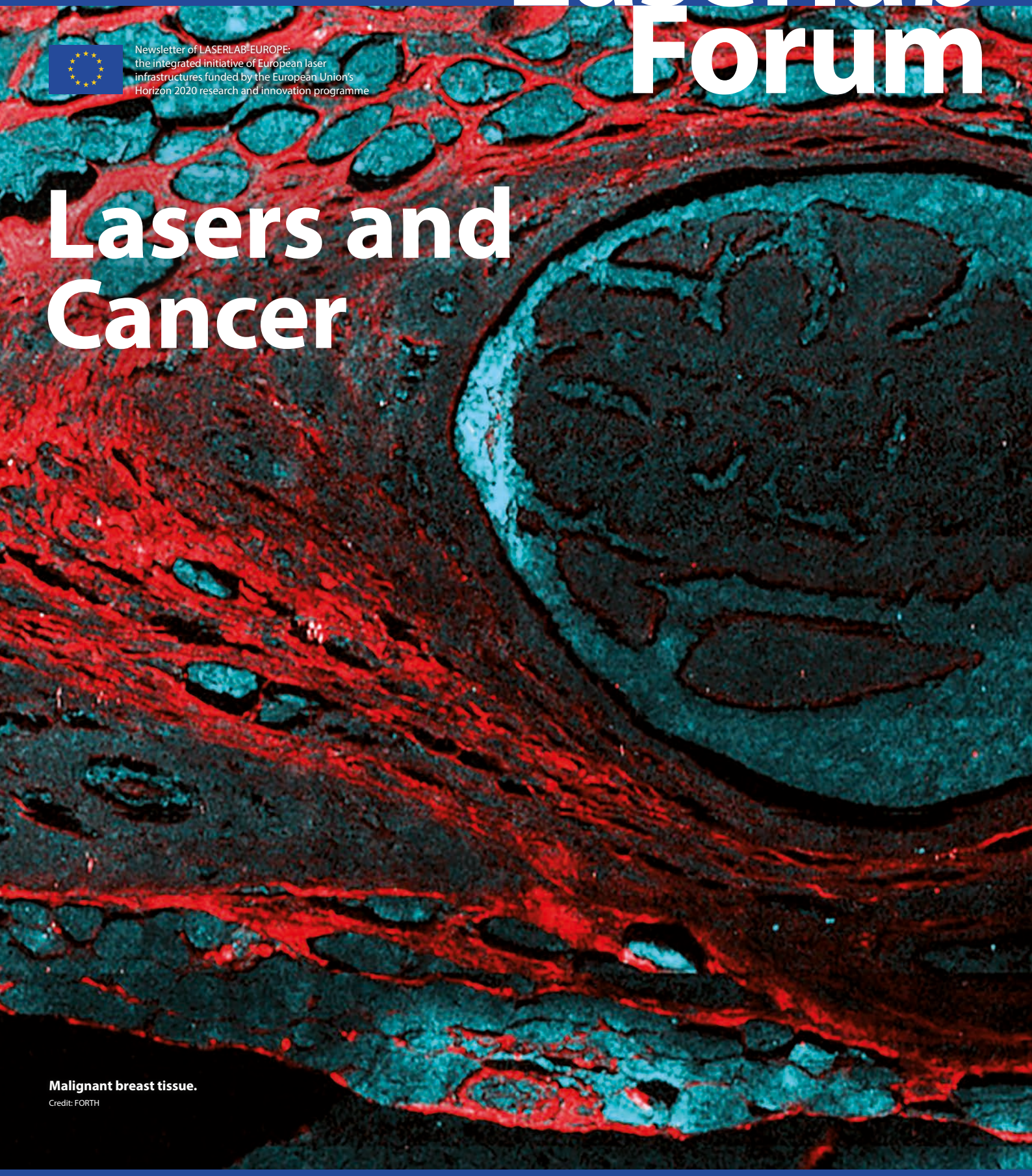
Laserlab Europe

Laserlab Forum

Newsletter of LASERLAB-EUROPE:
the integrated initiative of European laser infrastructures funded by the European Union's Horizon 2020 research and innovation programme

Lasers and Cancer



Malignant breast tissue.
Credit: FORTH

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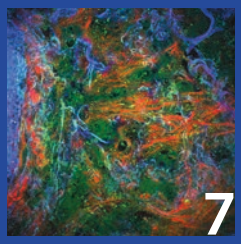
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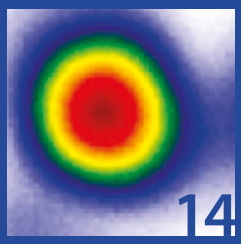
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Editorial

Rebecca Davenport

There have been many changes since the last Laserlab newsletter. Laserlab-Europe has been successful in acquiring EC funding for the next four years, Sylvie Jacquemot has taken over as new Coordinator, and so has Ludger Wöste as new chair of the Access Selection Panel.

There has also been a substantial new challenge in the form of COVID-19, which has caused major disruptions to everyday life as well as to science and research, from the need for new teaching methods, to the loss of conferences and meetings, to the suspension of access to laboratories.

The focus of this newsletter is on another big challenge facing our society: cancer. Every year, more than 3.5 million new cancer diagnoses are made, and that number has been increasing steadily. This has been recognized by the European Commission, who has designated cancer a "Mission" area over the next ten years. Lasers are a crucial tool for tackling cancer, from diagnosis to treatment.

Also in this issue are a brief presentation of recent ERC Consolidator and Advanced grant recipients, an access highlight from LOA, an overview of four new facilities now offering transnational access, and an introduction to CARLA, a new project encouraging people to make their careers in photonics.

This issue also marks my start as new editor of Laserlab Forum. I am taking the place of Tom Jeltes, who has been responsible for the newsletter since 2008, and now has taken a new step in his career path. On behalf of all Laserlab-Europe members, I would like to thank Tom for his impressive work and wish him all the best with his future endeavours! Please enjoy this edition of our newsletter.

Rebecca Davenport

News

New Laserlab-Europe Coordinator Sylvie Jacquemot

Sylvie Jacquemot, from the Laboratoire pour l'Utilisation des Lasers Intenses (LULI, France), has been elected as the new Coordinator of Laserlab-Europe. She takes over from Claes-Göran Wahlström from Lund University (Sweden), who had led the consortium since 2012. The consortium now comprises 36 partner institutions, across 19 European countries.

Following more than 16 years as Deputy Director of LULI, Sylvie Jacquemot is now Officer in Charge of European Affairs in the lab. Her background includes plasma physics and related high-energy-density applications, in particular inertial fusion sciences and X-Ray laser physics.

Laserlab-Europe congratulates Sylvie Jacquemot on this election and wishes her all the best in the future coordination of the network. The Consortium thanks Claes-Göran Wahlström for his commitment and successful leadership in promoting laser science and collaboration on a European scale.

Happy birthday lasers!

In May 1960, the first optical laser was demonstrated at Bell Labs in the USA, based on the previously demonstrated maser. Referred to by some as "a solution without a problem", others could see its potential with notes on a patent application from 1959 suggesting spectrometry, interferometry and nuclear fusion as possible uses. Over the last 60 years, improved designs and new applications have been reshaping our lives and earning the laser, as part of the photonics sector, "Key Enabling Technology" status. On its diamond anniversary, the future looks bright for lasers!

ARIE joint position paper

Seven European networks, including Laserlab-Europe, have joined forces in the Analytical Research Infrastructures in Europe (ARIE) working group and released a common position paper highlighting how their complementary approach will help addressing the societal challenges, defined as "Missions" in the Horizon Europe framework programme, starting in 2021.

The ARIEs are centres of scientific and technological excellence, delivering services, data and know-how to a growing and diverse user

community of more than 40,000 academic and industrial researchers, across a range of domains: physical sciences, energy, engineering, environmental and earth sciences, as well as medicine, health, food and cultural heritage. To address the Missions, the ARIEs will collaborate amongst themselves and with the Mission specialists at unprecedented levels, accelerating research and driving solutions for Europe's citizens.

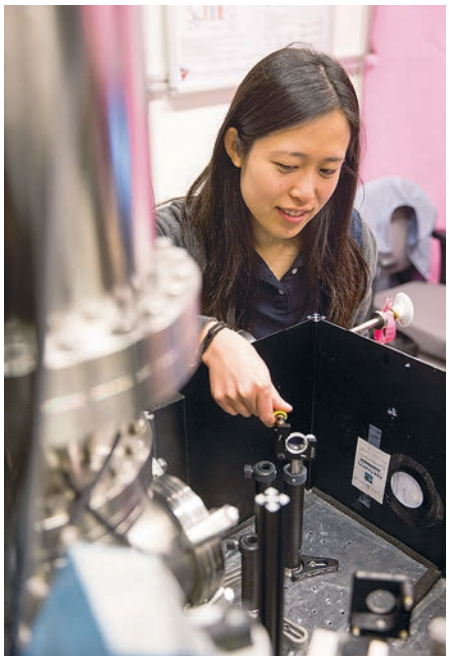
What is Laserlab-Europe?

Laserlab-Europe, the Integrated Initiative of European Laser Research Infrastructures, understands itself as the central place in Europe where new developments in laser research take place in a flexible and co-ordinated fashion beyond the potential of a national scale. The Consortium currently brings together 35 leading organisations in laser-based inter-disciplinary research from 18 countries. Additional partners and countries join in the activities through the association Laserlab-Europe AISBL. Its main objectives are to maintain a sustainable inter-disciplinary network of European national laboratories; to strengthen the European leading role in laser research through Joint Research Activities; and to offer access to state-of-the-art laser research facilities to researchers from all fields of science and from any laboratory in order to perform world-class research.

National Roadmap grant for HMFL-FELIX

The Dutch research infrastructure HFML-FELIX has been awarded a grant of 15.1 million euros by the Dutch Research Council. The grant is part of the National Roadmap for Large-Scale Research and aims to develop novel instrumentation and new experimental techniques to strengthen science and technology with IR/THz free-electron lasers (FELs) and high-field magnets.

The developments cover several areas of instrumentation: adding microscopic imaging capabilities to mass spectrometry with infrared spectroscopy and magnetic levitation, creating a platform for THz dynamics experiments using the combination of the brightness of the THz FELs and magnetic fields of up to 45T, and creating new experimental capabilities at extreme conditions such as ultralow temperatures. This will enable breakthroughs in a wide range of fields and contribute to solving societal challenges in the areas of health, energy and smart materials.



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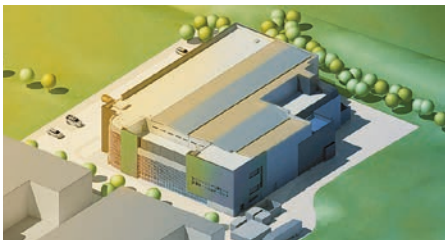
FELIX Laboratory.



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Impression of the EPAC building.

Ground breaking ceremony for new EPAC facility

The Central Laser Facility in the UK has broken ground for the Extreme Photonics Application Centre (EPAC). The facility will house a 10 Hz PW laser configured for the production and application of a wide range of radiation types. The system is intended to be very versatile, with applications from imaging to fundamental research into laser-matter interactions, and is intended to come online in 2024. Some early suggestions for projects include high-rate imaging of mechanical components under dynamic loading, enhancing corrosion resistance through surface hardening and shock peening, and imaging of fluid flow in closed systems. This £82 million project has been funded by the UK Government.

CREMLINplus inaugurated

In February of this year, the CREMLINplus project, a successor to the highly successful CREMLIN project, officially began. The Horizon 2020 project, coordinated by DESY, Germany, will continue to promote cooperation between large-scale research infrastructures in Russia and the European Union. Over the next four years, the partners will advance five Russian megascience projects, including the XCELS Exawatt Centre for Extreme Light Studies, a planned 200 PW laser facility in Nizhny Novgorod. In addition, procedures will be developed for international access to a set of Russian research infrastructures. Laserlab-Europe is part of the CREMLINplus consortium of 35 partners, 10 from Russia and 25 from the EU and associated countries, and will focus primarily on supporting the XCELS project with networking, training and staff exchange. The project has received 25 million euros from the EU.

CREMLIN PLUS

Laboratory operations during COVID-19

The on-going COVID-19 pandemic has strongly impacted the operations of analytical facilities. To protect staff and users, many research infrastructures (RIs) have either closed or severely reduced operations. Others have implemented specific protective measures, and some have maintained limited user access specifically for COVID-19-related investigations. In response to travel limitations, several RIs are expanding the provision of remote access to their instrumentation.

To assist RIs with re-opening their facilities, the Association of European-Level Research Infrastructures Facilities (ERF) has published a report on working practices of experimental facilities in Europe open to international users, mainly European synchrotrons, neutron sources and laser research infrastructures.

Ludger Wöste new chairperson of the Access Selection Panel

Ludger Wöste, former professor of physics at the Freie Universität in Berlin, has been elected the new Chair of the Laserlab-Europe Access Selection Panel. His driving passions are lasers and teaching. Topics he has worked on include femtosecond spectroscopy and coherent control; structure and dynamics of metal clusters; and white-light plasma channels in air. He is taking over after Wolfgang Demtröder, who has chaired the Selection Panel and directed the selection process with outstanding enthusiasm since the start of Laserlab-Europe.

ERC Grants

Each year, Laserlab-Europe researchers are awarded prestigious grants by the European Research Council. Here, we highlight two recently granted Consolidator projects, and two Advanced Grant projects – worth up to 2 and 2.5 million Euro, respectively – for a period of five years.

Stefan Witte (LLAMS): Seeing the invisible: Light-based 3D imaging of opaque nanostructures

Lenseless imaging, in which an image of the desired object or feature is digitally reconstructed based on the diffraction pattern of light through the object, offers a solution in situations where traditional imaging optics cannot be used. This is of particular significance to UV and X-ray imaging, in which the development of suitable lenses has been extremely difficult.

By using lenseless imaging techniques on a combination of soft x-rays and acoustic waves, produced by ultrafast laser pulses, it is possible to gain a complete 3-D picture of the interior of structures which are entirely opaque to visible light, with an improved resolution compared to optical microscopes. Associate Professor Stefan Witte has been awarded an ERC Consolidator Grant to extend this technique to the study of nanostructures, following on from his ERC Starting Grant award in 2014.

The project is targeted specifically at nanostructures because of their increasing centrality to everyday life, from smartphones to novel medical devices. As such, an accurate picture of their structure and function is crucial to improvements in design for the next generations of devices.

Anne L'Huillier (LLC): Quantum Physics with Attosecond Pulses

© Erika Weiland

Using attosecond laser pulses as a "camera flash", it is possible to study the fundamental interactions of our physical world, such as the motion of an electron as an atom is ionised. With her new ERC Advanced Grant, Anne L'Huillier intends to push this incredible technique even further, directly studying and observing new quantum physical phenomena for the first time. This is the third time that Anne L'Huillier has received an ERC Advanced Grant.

Instead of using an ion or a photon, the new project will use an attosecond laser pulse to generate an electron "wave packet", which can then be entangled or interfered with other electron-waves, deepening our understanding of the wave nature of matter.

Since matter only behaves in a wave-like manner under very particular physical conditions, this state has typically been harder to study than particle-like behaviour. By using a laser pulse to generate electron wave-packets, they will have a well-defined energy. It is hoped that this will enable a much more detailed study of entanglement and matter-wave interference, shedding new light on these little-understood corners of the microcosmos.

"I am very pleased. It is a very, very nice feeling to be awarded this grant. It will be both demanding and exciting", says Anne L'Huillier.

Gijs Wuite (LLAMS): Mechanically mapped chromosomes

© Anne Reitsma

Optical tweezers are a tool for manipulating microscopic objects using a beam of light. When the light diffracts through the object, it imparts a force which acts to center it in the beam. This has enabled extremely precise manipulation of microscopic objects, which can be combined with precision microscopy to give new insight into their exact shape.

Gijs Wuite has used this technique to attach microscopic spheres to specific points on complex molecules, such as DNA which has been extracted from a cell and kept in physiological buffer, enabling them to be moved and deformed in very precise ways.

Chromosomes (the compact organisation of DNA just before cells divide) are found in every cell, and in diseased cells (cancer in particular) they will have an abnormal composition and structure. By imaging and mechanically mapping chromosomes, it is possible to learn about these abnormal structures. Wuite plans to use his new ERC Advanced Grant to expand his research group to address this question. "There are currently only two of us working on this project. The grant gives us the opportunity to hire five extra researchers and considerably expand our line of biophysics of chromosome research."

Norbert Schuch (MPQ): Symmetries and Entanglement in Quantum Matter

© Jan Greune (MPQ)

Symmetries are at the heart of quantum many-body phenomena in quantum chemistry, condensed matter, and high energy physics. The discovery of new and unconventional phases, such as the fractional quantum Hall effect, has challenged this view because these phases display a global ordering in their entanglement rather than a local symmetry, which hinders their characterization.

This new ERC Consolidator Grant will allow Norbert Schuch and his team to develop a comprehensive, symmetry-centred framework for the study of quantum many-body systems across physics based on the structure of their entanglement. It is at the interface between Quantum Information and Quantum Many-Body Physics. He has previously been awarded an ERC Starter Grant in 2014.

Using Tensor Networks, it is possible to "transform" the model between physical space, with its local symmetries, and entanglement space, which gives rise to larger-scale ordering. By mapping back and forth, it is possible to study the ways in which the entanglement order manifests physically, and obtain a spectrum of powerful analytical, numerical, and experimental probes for unconventional phases.

This framework can then be applied to a wide range of systems which appear in condensed matter and high energy physics, and the results of the project will give a unified understanding of unconventional phases, based on physical symmetries and the resulting entanglement order. This understanding will in turn provide numerical probes for their detection and simple ways to realise and probe these models in experimental scenarios, thereby significantly advancing our ability to understand, study, and realize complex quantum phases.

New access opportunities in Laserlab-Europe

In the fifth phase of its existence, four labs have joined the transnational access programme, offering their facilities to users across the whole range of laser applications. HZDR specialises in laser accelerators, Lacus offers a range of spectroscopic techniques, HiLASE adds materials science expertise and CLPU provides ultra-fast, high-intensity secondary sources. The addition of these facilities enriches the access programme and the opportunities offered to users. Full details of the programme, including how to apply, are found on the Laserlab-Europe website.

Helmholtz-Zentrum Dresden-Rossendorf (HZDR)

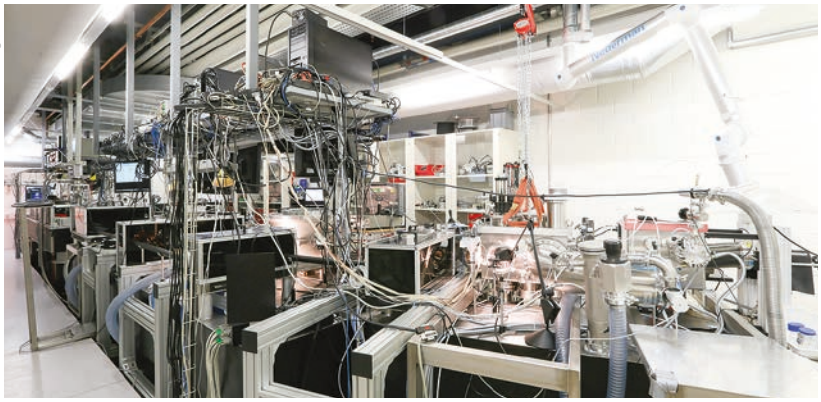
With proven performance in plasma proton acceleration in the 60 MeV energy range, HZDR's petawatt laser DRACO in Dresden, Germany, offers an ideal environment for advanced accelerator development and application. Multi-parameter diagnostics and independent optical probes ranging from few-cycle through multicolour to 100 TW driven sources enable an unprecedented probing of solid target interaction. Dedicated and case-optimised settings, together with typically collaborative access, facilitate the effective use of the facility. Medical physics and radiobiology related experiments at the highest dose rates benefit from a pulsed magnet driven proton beamline that includes a biology lab and reference irradiation instrumentation. In a separate area, long focal lengths enable effective electron acceleration at the highest nC bunch charges, driving radiation sources and subsequent accelerator stages. Multi-beam combinations can in principle be applied for pump-probe experiments of laser heated matter.

© HZDR / F. Bierstedt

YIG leader Josefine Metzkes-Ng optimising a Draco setup for plasma acceleration.

Lausanne Centre for Ultrafast Science (LACUS)

Located in Lausanne, Switzerland, LACUS combines several ultrafast laser labs across the faculties of basic sciences and engineering of the Ecole polytechnique fédérale de Lausanne (EPFL). It offers a cutting-edge femtosecond VUV High Harmonic source in the 30-110 eV range, allowing users to perform steady-state and ultrafast angle-resolved photoelectron spectroscopy (ARPES) with state-of-the-art detection, a vacuum chamber and in-situ sample preparation as well as steady-state and ultrafast photoelectron spectroscopy of liquid samples with an optional liquid microjet delivery system.



© Alain Herzog (EPFL)

View of the high harmonic generation source "Harmonium" used for ultrafast liquid jet photoelectron spectroscopy and ultrafast ARPES.

Users also have access to ultrafast electron diffraction (with 30-50 keV electron pulses), electron microscopy, Lorenz microscopy and electron-energy-loss-spectroscopy and deep-Ultraviolet (250-380 nm) ultrafast two-dimensional transient absorption spectroscopy and ultrafast circular dichroism.

HiLASE

The HiLASE Centre is a new technological infrastructure in the field of application-oriented laser research and development, commissioned in 2015, and fully operational since 2016. Its main mission is to promote the development of cutting-edge diode-pumped solid-state laser (DPSSL) technology and to offer access, including open access, to external users from both high-tech industry and academia. The HiLASE infrastructure offers laser systems with unique parameters and advanced laser applications stations for laser-induced damage threshold measurements of optical components, laser shock peening, micro/nanostructuring, laser processing, functionalisation of materials, laser propulsion, and ion generation. HiLASE operates the world's current most powerful DPSSL delivering over 1 kW of average power in 105 J, 10 ns pulses at 10 Hz. High-energy second and third harmonic beams are available upon request. Advanced in-house laser development includes PERLA, which is a compact high-average-power thin-disk laser

© HiLASE

The HiLASE laser facility.

platform able to generate < 2 ps pulses in a broad spectral region from DUV (206 nm) to mid-IR (3 microns) at repetition rates from 100 Hz up to 100 kHz. The HiLASE facility is located in Dolni Brezany near Prague (Czech Republic), in the immediate vicinity of ELI Beamlines.

Centro de Laseres Pulsados (CLPU)

Located in Villamayor (Salamanca), CLPU is part of the Spanish Unique Scientific Infrastructure Roadmap. It is a user facility, devoted to highly improving laser-plasma physics, atomic and nuclear physics, materials science, radiobiology, astrophysics, high energy physics, and other applications. All these fields are advancing through the direct employment of the different laser sources and/or through a wide set of ultrafast high peak intensity laser-based secondary sources (e.g. electrons, protons, X-rays, gamma-rays, neutrons, positrons) in an interdisciplinary environment.

The unique equipment at CLPU is the multi-terawatt laser system VEGA composed of three independent and synchronised 30 fs, Ti:Sapphire-based laser pulses: VEGA-3, 1 PW working at a repetition rate up to one Hz; VEGA-2, 200 TW working at a repetition rate up to 10 Hz, and also at 10 Hz, VEGA-1, a 20 TW laser beam. The uniqueness of CLPU is also defined by its radio-protected experimental area.

CLPU can routinely offer users different targets including, for example, a liquid system in three different configurations (column, droplets, and curtain), a specimen under a dense gaseous jet, or a motorized array of solid targets. Several diagnostics are also available to characterize secondary particle and radiation sources.

© Enrique García

General view of the last amplifier in the VEGA-3 PW laser.

Lasers and Cancer

Cancer affects people of all ages and walks of life, with 2.6 million diagnoses and 1.2 million deaths every year in the EU-27. The use of lasers for cancer treatment began in the 1980s, with laser ablation used on tumours. More recent work uses a far broader spectrum of laser applications, from microscopy to manufacturing. This focus showcases laser methods used in fundamental research into tumour pathology, both as microscopes and in fabricating cell scaffolds, the use of laser imaging and laser microscopy as diagnostic instruments, and work improving the efficacy of photodynamic therapy.

Time domain multi-wavelength diffuse optics: Towards a comprehensive approach for breast cancer management (CUSBO, Italy)

Breast cancer is the most frequently diagnosed cancer in the vast majority of countries and is the leading cause of cancer death in over 100 countries worldwide (Global Cancer Statistics 2018: GLOBOCAN). Early diagnosis is key for a high survival rate. Treatment modalities are changing to achieve efficacy, while minimizing invasiveness. In the last years, prevention is also drawing more and more efforts aiming at maximising women's quality of life and the sustainability of healthcare systems.

Diffuse optical spectroscopy (DOS) carried out in the time domain allows the non-invasive assessment of the optical properties (absorption and reduced scattering) of highly diffuse media, like in vivo biological tissues. Measurements performed at repeated wavelengths can then yield the estimate of tissue composition and physiologic parameters, and provide information on tissue microscopic structure. Thus, DOS offers unique potential for non-invasive in vivo pathophysiological investigation.

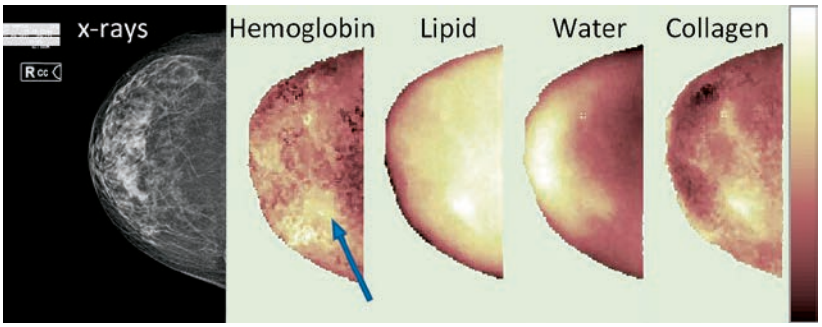
Prevention – Breast density is a major independent risk factor for developing breast cancer. It is currently assessed through the analysis of X-ray mammographic images and thus generally it becomes known at the age of 50 or later. Conversely, knowing it earlier in life would allow designing dedicated diagnostic paths for women at high risk and, even more important, preventive interventions to reduce the risk with drugs or lifestyle changes.

A clinical DOS imaging system, operated in the time domain at 7 discrete wavelengths in the range of 635-1060 nm, was developed by the CUSBO facility at Politecnico di Milano. Applied in a clinical study involving more than 200 patients, it allowed us to show that optically derived parameters correlate to a high degree with both qualitative and quantitative estimates of mammographic density (i.e. BIRADS categories, typically used by clinicians, and percentage density, respectively). Specifically, the instrument developed at Politecnico di Milano, unique at international level, allows the estimate of blood parameters (total volume of hemoglobin and oxygenation level) and of the average composition of tissue not only in terms of water and lipid content, but also of collagen content. The study demonstrated that collagen contributes fundamentally to breast density. Furthermore, collagen amount and type has also been suggested as an independent risk factor for breast cancer. So the approach to DOS followed at Politecnico di Milano may offer unique potential for understanding breast cancer risk and developing prevention strategies.

Diagnosis – Mammographic screening is effective in detecting early cancers, but is affected by limited specificity, often leading to further unnecessary (typically invasive) examinations. In a 2017 clinical study, full-breast images were collected (see figure) that were analysed to identify differences in composition between malignant and benign lesions. A statistical approach based on the Discrete AdaBoost procedure exploiting information derived from optical data and from the patient's history proved able to classify malignant versus benign lesions with sensitivity of 88% and specificity of 79%. Again, optically assessed collagen content was identified as the most important parameter for the discrimination.

Therapy monitoring – Neoadjuvant chemotherapy is becoming more and more widespread to reduce tumor volume (making surgery more conservative) and even achieve pathologic complete response. Unfortunately, a high percentage of women do not respond to therapy, but that becomes known only at the end of several therapeutic cycles. Effective techniques for therapy monitoring and early prediction of pathologic outcome are not available yet in clinical practice, but the ability of DOS to non-invasively estimate tissue composition has already shown interesting potential. In this line, the detection chain of the optical mammograph developed by Politecnico di Milano was recently upgraded, relying on Silicon photomultipliers for photon detection and on high throughput time-to-digital conversion for data acquisition. This improved the signal level, especially at the longest wavelength (1060 nm), which is important for sensitivity to collagen. The instrument has just started an initial clinical study to investigate its potential in therapy monitoring and prediction of pathologic outcome.

Paola Taroni
(CUSBO-Politecnico di Milano)

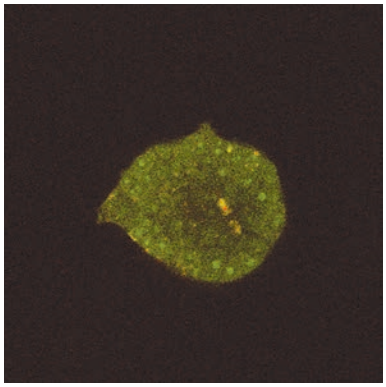


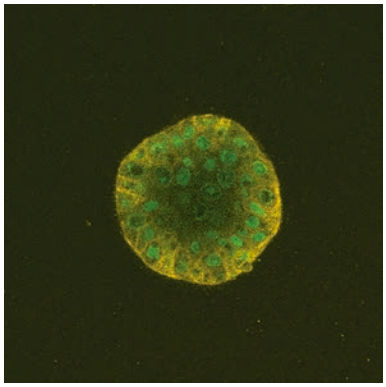
X-ray mammogram and optically derived composition maps of a breast with a 10-mm fibroadenoma (adapted from Taroni et al., Sci. Rep. 7: 40683, 2017).

Two-photon lithography in cancer research (ILC, Slovakia)

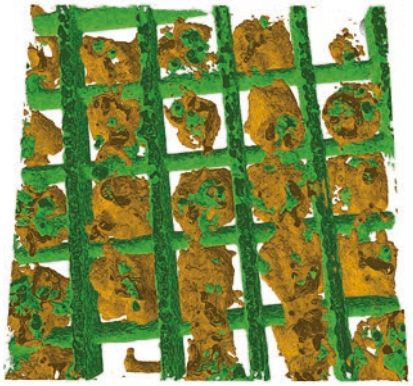
The complexity and dynamic nature of cancer pose many challenges for the experimental designer who wishes to efficiently decipher some of the unknowns in cancer development and progression and pave the way to new prospective anti-cancer therapies. Experimental research on cancer has for many years relied on *in-vitro* models consisting of cancer cells grown in 2D monolayers, typically on plastic flat surfaces. However, many studies have shown that these models are too simplified to represent the many key factors involved in tumor progression. There is a clear need for *in-vitro* models better mimicking the physiological conditions seen in native cancer tissues. *In-vitro* models based on 3D cell cultures seem to meet this requirement, and recently they started to be extensively utilised in experimental cancer research.

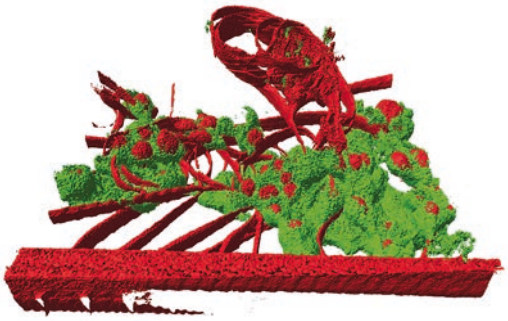
To study processes occurring at the single-cell scale, the scaffold structure is often required to have comparable dimensions, which is not trivial. One suitable fabrication technique is two-photon lithography. The technique exploits the two-photon absorption (2PA) process to solidify a liquid photosensitive polymeric material by photo-polymerisation. 2PA occurs if the spatial and temporal density of the photon flux is sufficient to induce a simultaneous absorption of two photons by a molecule of the photosensitive material. This is usually achieved in the focus of a femtosecond pulsed laser. 2PA activates radical initiation and propagation reactions in the exposed polymer, resulting in the resist polymerisation. The volume in which polymerisation occurs is proportional to the size of the laser focus. The movement of the laser focus through a volume of polymeric material progressively photo-polymerises the liquid material and finally creates a solid 3D structure. The non-polymerised (unexposed) material is then washed out with an appropriate solvent and the photo-polymerised solid structure is prepared for the next application. Any polymer comprising monomers that are able to photo-polymerise in the presence of a suitable photo-initiator can be used in 2PA lithography [1].





Morphology of 3D clusters of KYSE 450 cells in collagen type I (left) and Matrigel matrices (right) imaged by confocal microscopy. The cells were stained with Acridine orange (green) to visualise intracellular organelles and Cell mask to visualise cellular membranes (orange).





Top: 3D morphology of clusters of KYSE 450 cells (orange) grown on the scaffold structure (green). The scaffold structure was fabricated from OrmoComp (Micro Resist Technology GmbH) by direct laser writing utilising a 2-photon photopolymerisation process. The cells were stained with cell mask to visualise cellular membranes, scaffold visualisation was done thanks to inherent autofluorescence of OrmoComp., Bottom: Reconstructed 3D image from stack of confocal 2D images of tumor cells (red nuclear and green membrane fluorescence) adhered to OrmoComp polymer fibers (red fluorescence). Dimension of both imaged volumes was 225 x 225 x 109 µm (XYZ).

The biocompatibility of the scaffold material and maintaining the properties of cells residing in resulting 3D scaffolds are the main clues when investigating cellular processes in 3D space. Freshly prepared scaffolds often lack proper surface chemical properties and are toxic to cells, so further surface functionalisation of the scaffold need to be performed to achieve an optimal combination of chemical and morphological characteristics for cell seeding, which is one of the research areas of the ILC group in this field [2].

2PA lithography offers a number of advantages over other fabrication techniques, particularly if the ultimate resolution of fabricated structures plays a key role. A high degree of control over the shape and porosity of fabricated structures allows the preparation of near-biomimetic structures with feature sizes in micrometers and overall dimensions on the order of millimeters. 2PA can create microenvironments with highly controlled and reproducible porosity, by intersecting polymeric rods to create scaffolds with different pore sizes. This 3D geometrical assembly, known as a woodpile structure, can be obtained in a single fabrication step with 2PA, while a similar complexity is difficult to achieve with planar micro-fabrication approaches. Woodpiles fabricated with 2PA have been used for various appli-

cations, including the study of cell motility and migration in 3D, a process highly influenced by the mechanical interaction between the cell and the extracellular environment. In conclusion, 2PA technology seems to be apromising tool to generate in-vitro 3D models for analysis of tumor-immune system interactions in highly controlled conditions, considering the recognised roles of several factors of tumor architecture and microenvironment in tumor biology [3].

Anton Mateašík, Dusan Chorvát, Beáta Čunderlíková (ILC) and Tibor Teplický (Comenius University)

[1] T. Teplicky et al., Proc. SPIE 10142: 101420C-1-8, 2016
[2] T. Teplický et al., Biointerphases 13: 041009, 2018
[3] T. Teplicky et al., Proc. SPIE 11271: 1127111, 2020

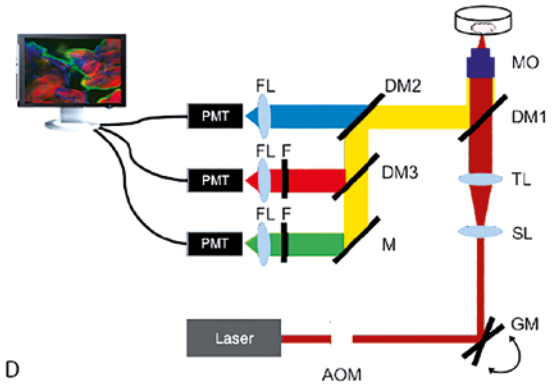
Lasers and cancer detection: Label free nonlinear microscopy for tumour cell visualisation (LaserLaB Amsterdam, The Netherlands)

Distinguishing tumour from normal tissue is important to improve surgical results. Researchers at Laserlab-Europe partner LaserLaB Amsterdam use second- and third harmonic generation microscopy to identify tumour cells in brain and lung tissue within seconds.

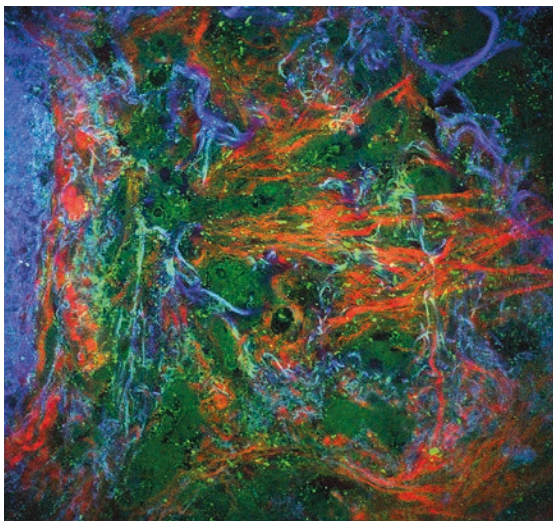
A rapid and reliable histological typing can reduce operation time and potentially improve surgical patient outcomes. The currently used intra-operative technique for providing fast feedback about the nature of the excised tissue and resection margins is frozen section analysis, which takes 45-60 minutes. Surgical results could be improved when having a faster pathological grade diagnosis of tissue available during surgery.

Second and third harmonic generation microscopy (SHG and THG) combined with 2- and 3-photon excited auto-fluorescence microscopy shows great potential as a clinical tool for the real-time assessment of the pathological state of tissue during surgery: the relative speed of the imaging modalities approaches 'real' time, and no preparation steps of the tissue are required.

THG and SHG are coherent multiphoton processes. The efficiency of THG depends mainly on the third-order susceptibility $\chi^{(3)}$ of the medium and the phase-matching conditions. In practice, cell membranes and cell nuclei are clearly displayed with THG microscopy, since they contain lipids which are known to have a high $\chi^{(3)}$. SHG contrast depends on the second-order susceptibility, $\chi^{(2)}$. Only media with a non-centrosymmetric molecular organization have a non-zero $\chi^{(2)}$. For example, a strong SHG source is collagen. Since the THG nonlinear signals are proportional to the cube of the applied laser intensity (I^2 for SHG), femtosecond laser pulses are required to generate a high peak power, while keeping a low average power. As the nonlinearity of the optical signals ensures they are only efficiently generated in the laser focal spot, this provides intrinsic confocality. A small focal spot volume results in a high submicron resolution and provides direct depth sectioning resulting in full 3D images of the tissue.



Multiphoton microscope setup: Femtosecond laser; GM – X-Y galvo-scanner mirrors; SL – scan lens; TL – tube lens; MO – microscope objective; DM1 – dichroic mirror.



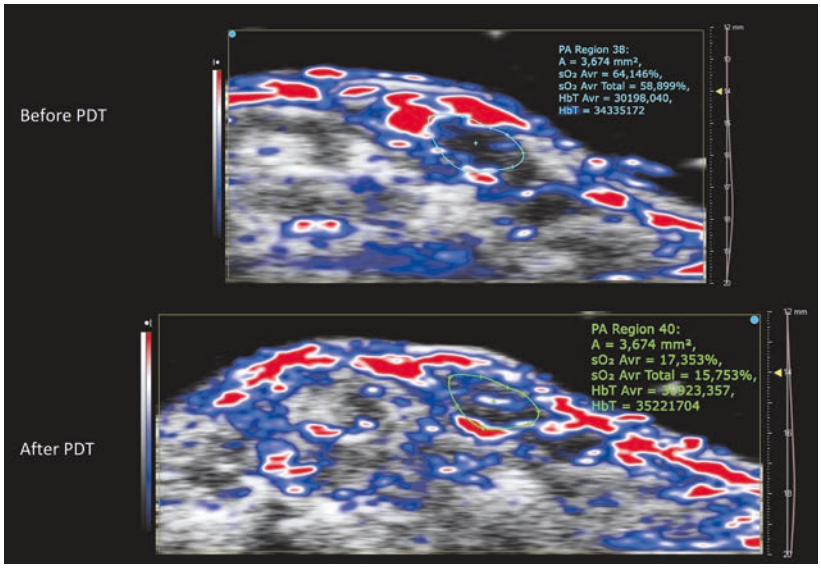
Multiphoton images of lung tumor tissue, mixed mucinous and non-mucinous adenocarcinoma with lepidic and acinar growth pattern with abundant amount of inflammatory cells that contain bright THG spots. THG (green)/SHG (red)/2PEF (blue) Acquisition time 3.5 seconds per image, power 5 mW.

THG and SHG microscopy were used in combination to detect healthy and diseased states in fresh excised brain and breast tissue. Normal and malignant human brain tissue were successfully discriminated, based on histopathological hallmarks such as increased cellularity and nuclear pleomorphism. Glioma infiltration has also been qualitatively detected by applying automated image analysis (see *Zhang et al.*).

These experiments have been performed in the laboratory, with the excised tissue brought to the lab within 20 minutes after surgery. The next step is to explore the added value of instant feedback on the nature of excised tissue *during* surgery. The VU spin-off company Femto Diagnostics B.V. has developed a mobile version of the THG/SHG microscope. This machine has been brought into the lung endoscopy suite of the Amsterdam Universities Medical Center for a first test, and a study with this microscope was completed on ex-vivo fresh unprocessed lung tissue (submitted for publication). Alveolar structures and histopathological hallmarks, cellular structures (THG), collagen (SHG), and elastin (2PEF), were imaged within 1-3 seconds using a power of only 5 mW (see figure). Comparing the generated images of tumorous and non-tumorous lung tissues with the corresponding standard histology showed excellent agreement.

Laura van Huizen, Zhiqing Zhang and Marloes Groot (LaserLab Amsterdam)

Z. Zhang et al.: Adv. Sci. 6: 1900163, 2019



Photoacoustic tomography of CT26 tumors subcutaneously implanted in BALB/c mice before and after photodynamic therapy with redaporfin when this photosensitiser is in the vasculature. Red: oxyhemoglobin; blue: deoxyhemoglobin. The average amount of oxyhemoglobin in the region of interest is reduced with PDT as a result of the destruction of the tumour vasculature. Under these conditions ca. 95% of the mice are cured.

Photodynamic Therapy and Cancer (CLL, Portugal)

Photodynamic therapy (PDT) consists in the administration of a dye (referred to as a photosensitiser) and its subsequent activation with light. The photosensitiser does not have any pharmacological effect in the dark, but when electronically excited rapidly undergoes intersystem crossing to the lowest triplet state, from which it has time to react with nearby oxygen molecules, either by energy transfer (Type II process) to form singlet oxygen or by electron transfer (Type I process) to form a superoxide ion. Other reactive oxygen species (ROS) are subsequently formed by dark processes and then react with biomolecules within a radius of 200 nm before being deactivated. Hence, PDT produces a localized oxidative stress that triggers various cell death mechanisms. PDT is a major use of laser sources to treat cancers, and has also been used in the inactivation of bacteria, fungi and viruses.

The origins of PDT can be traced back to 4000 years ago when ancient Egyptians ingested plants containing light-activated psoralens and exposed themselves to sunlight to treat vitiligo. The photodynamic effect was first reported in the scientific literature in the beginning of the 20th century after the observation by Oscar Raab, working in the laboratory of Hermann von Tapiener, that illuminating microbial cultures in the presence of acridine compounds induced microbe death. The initial interest in the photodynamic effect was offset by the success of antibiotics in the treatment of bacterial infections. The current era of PDT began with studies by R. L. Lipson and S. Schwartz at the Mayo Clinic in 1960 who observed that injection of crude preparations of hematoporphyrin led to the fluorescence of neoplastic lesions visualised during surgery. Schwartz realized that a purified fraction of hematoporphyrin derivatives could be used as a photosensitising agent to destroy tumour tissue. Thomas Dougherty identified and purified the most active derivatives to obtain a photosensitiser named Photofrin®, and led the first clinical study that showed conclusive clinical benefits of PDT in the treatment of solid tumours.

Photofrin® was first approved for clinical treatments in Canada in 1993 and other approvals in major markets followed rapidly. Today, dozens of photosensitisers have been approved, or are in active clinical trials, for the treatment of solid tumours. One of these photosensitisers, named redaporfin, was issued from the Coimbra LaserLab. PDT also enjoys widespread use in the treatment of skin lesions such as actinic keratosis and basal cell carcinoma. Interestingly, the dramatic increase in antibiotic resistance has led to a revival of antimicrobial PDT in the last decade. Its use in periodontal diseases and in the treatment of acne is becoming popular. More recently, the PDT community joined many other efforts to control Covid-19. The remarkable range of application of PDT can be explained by its fundamental mechanism: the ability to produce controlled oxidative stress when and where desired by simply controlling a laser confers specificity in the destruction of tumour cells, bacteria/fungi or virus.

Cancer remains the major focus of PDT. The challenges ahead are related to the limited penetration of light in human tissues and to the specificity of the photosensitisers to the elected targets. Light penetration in tissues increases with the wavelength of light in the visible and near-infrared but it is difficult to prepare photosensitisers with strong electronic absorptions in the infrared. Two-photon absorption may be the solution in the future, and medical lasers for such applications are needed.

Luis G. Arnaut (CLL)

Radiobiology experiments with laser-accelerated ion beams (LULI, LOA, France, CLF, UK and collaborators)

Investigations of the response of biological samples to irradiation with laser-accelerated ion beams have been carried out in the last few years in the frame of a collaboration between different European partners, namely the LULI, LOA, Laboratory for Optics and Biosciences (LOB) in France, the Queen's University Belfast and the Central Laser Facility (CLF) in the UK, and the University of Naples Federico II and the LNS-INFN laboratory in Italy. These studies are of relevance to assess the potential viability of hadron-therapy applications for laser-driven ion sources.

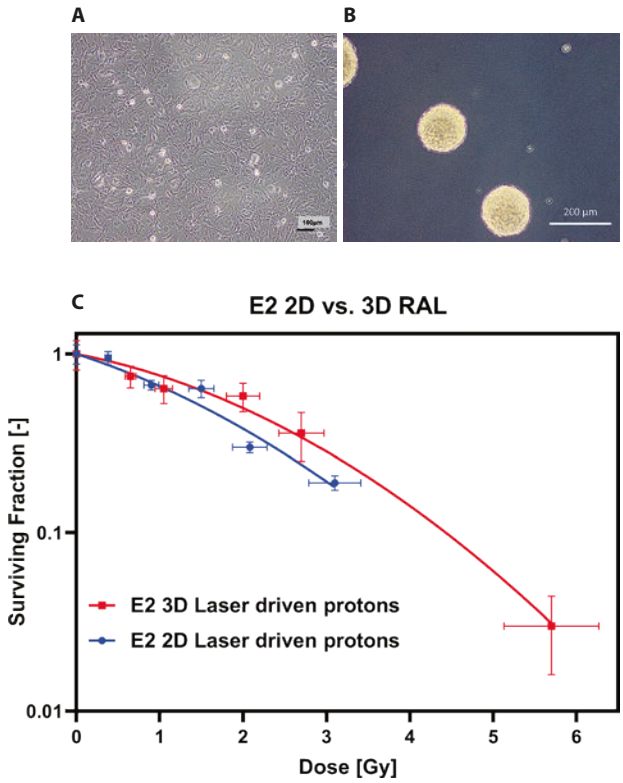
Since the completion of the first clinical facilities in the early 90s, hadron therapy has become a well-established methodology for cancer treatment, the main advantage in comparison to photon-based radiotherapy lying in the ability of ion beams to deliver peak radiation doses at the tumour while minimising damage of the surrounding healthy tissues. The size and the considerable costs of cyclotron and synchrotron accelerators, however, have so far hampered a wider diffusion of hadron therapy clinical fa-

cilities [1]. Hence, there is a growing interest towards finding viable compact and cost-effective alternatives to accelerate particles for medical applications, and laser-driven particle accelerators have recently been proposed as a possible candidate. Clearly, before any medical application can be realistically considered, the radiobiological effectiveness of irradiation at the considerably higher dose rates provided by these short pulse sources must be assessed.

In this context, extensive experimental work has been carried out within the research network. A more detailed presentation of the previous work is available in the already published work [2-5], but it is worth mentioning here some of the milestones already achieved by the project:

Part of the investigation has been dedicated to the optimization of laser-driven ion sources for radiobiological applications and to study the feasibility of novel acceleration schemes. This is an open area of research, which will take full advantage of the new high-power laser facilities soon to become operational at different locations in Europe, such as the ELI European laser facilities and the Apollon system in France.

Different schemes for the transport and shaping of laser-accelerated ion beams and integrated dosimetry systems to control the delivered radiation dose have been successfully exploited in these experiments.



Patient-derived glioblastoma stem cells (E2 cells) were irradiated either as (A) 2D monolayers or (B) as 3D neurospheres with 35 MeV laser-accelerated protons. The effect on cell survival was studied using Clonogenic assay, as shown in (C) where the red curve shows the dose response of 3D neurospheres and blue curve shows the dose response of 2D monolayer cells. [Chaudhary et al., in preparation].

Protocols for the manipulation and handling of biological samples in laser facility target areas have been established for a variety of cellular types and irradiation architectures. For instance, in experiments carried out at the CLF and at LULI, the effectiveness of laser-driven proton beams were investigated in the induction of DNA DSB damage in the human normal skin fibroblasts and patient derived-radioresistant tumour Glioblastoma stem cells, both in hypoxic and normoxic conditions, and the radiobiology of laser-accelerated carbon ions in the radiation resistant glioblastoma stem cells were studied. In a recent experiment, methods were exploited for the irradiation of 3D neuro-spheres and 2D monolayers of glioblastoma stem cells (see figure). In experiments performed at the LOA, it was possible to observe both time- and mutation- related resistances to ionising radiation [5] on Human Colo-Rectal Cancer, HCT116 cell lines.

Further investigations are planned for the next few years, with the next collaborative campaign being already scheduled at LULI for the experimental slot 2020-2021. The Laserlab-Europe network has been crucial in supporting such a broad and multidisciplinary collaboration between different European actors, bringing together researchers from 7 different institutes across different countries.

Lorenzo Romagnani (LULI), Marco Borghesi, Pankaj Chaudhary, Kevin M. Prise (Queen's University Belfast), Alessandro Flacco (LOA)

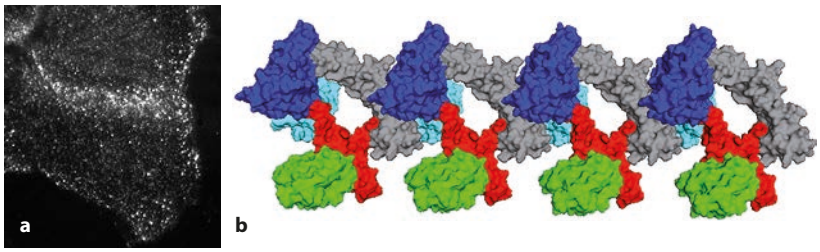
[1] https://www.ptcog.ch/
[2] P. Chaudhary et al., Radiother. Oncol. 118: S24, 2016
[3] L. Manti et al., J. Instrum. 12: C03084, 2017
[4] F. Hanton et al., Sci. Rep. 9: 4471, 2019
[5] E. Bayart et al., Sci. R. 9: 10132, 2019

From molecules to tissue models: Investigating cancer using the *Octopus* imaging cluster (CLF, UK)

The UK Central Laser Facility's Octopus imaging cluster offers a comprehensive range of fluorescence-based optical imaging techniques. These are applied in a vast range of research areas ranging from plant biology to smart materials. Cancer is a complex disease and developing new treatments depends on understanding the disease from its origins at the molecular level through to the way in which it behaves in the multicellular environment of tissues. Octopus techniques have been used to investigate cancer at both ends of this spectrum.

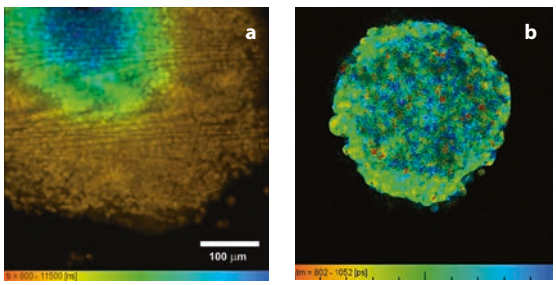
At the molecular level, fluorescence imaging can localise individual molecules with high precision. A method known as Fluorescence Localisation Imaging with Photobleaching (FLImP), developed at the facility, allows to map out the spacing of molecules in complexes with a resolution better than 5 nm. FLImP has been used to characterise the molecular architecture of complexes of Epidermal Growth Factor Receptor (EGFR), the target of a number of drugs in clinical use and under development. Signals from EGFR are responsible for the control of cell growth and EGFR mutations are implicated in many can-

cers. FLImP has shown that the signalling process is more complex than previously thought, and involves the formation of large assemblies of EGFR molecules. Differences can be seen in EGFR complex architecture between wild type receptors and cancer-associated mutations. Anti-cancer drugs have also been shown to influence this molecular architecture. CLF are now working with clinicians with the aim of using FLImP to "fingerprint" biopsies from patients and determine the best course of treatment.



FLImP studies of EGFR. a) Image of cancer cells showing individual EGFR molecules and complexes. b) Model of a multimer of EGFR derived from distance measurements obtained by FLImP. From Zanetti-Domingues et al., Nat. Commun. 9: 4325, 2018.

At the other end of the scale, *Octopus* has been used to look at the metabolism of tumour models with the aim of improving therapies. Solid tumours display varied oxygen levels and this characteristic can be exploited to develop new diagnostic tools to determine and exploit these variations. 3D cultures of cells, such as "spheroids", are a good model for solid tumours. A phosphorescent, low molecular weight platinum (II) complex has been used as an oxygen sensing probe to study the variation in oxygen concentration in a melanoma tumour spheroid using one-photon phosphorescence lifetime imaging microscopy (PLIM). These measurements enabled real time oxygen mapping with high spatial resolution. This gives a valuable tool for optical detection of both physiological and pathological oxygen levels in a live tissue mass and may have the potential for broader clinical application. A related imaging method, fluorescence lifetime imaging microscopy (FLIM), has also been used to investigate the uptake of anticancer drugs into spheroids. In this case, spheroids were exposed to the drug combretastatin. These studies are important for the development of photodynamic therapy, in which inactive drug precursors are delivered to the tumour, and then made active by exposure to light. This new approach (Type IV) minimises side effects as the drug is only toxic in the tumour and not in healthy tissue and does not require oxygen.



Images of melanoma spheroids using PLIM and FLIM. a) PLIM image of spheroid labelled with platinum complexes to show oxygen level. The longer lifetimes (blue) show areas of low oxygen concentration. Raza et al., Sci. Rep. 7: 10743, 2017. b) FLIM image showing Combretastatin uptake in a melanoma spheroid. Scherer et al., J. Biomed. Optics 20: 078003, 2015

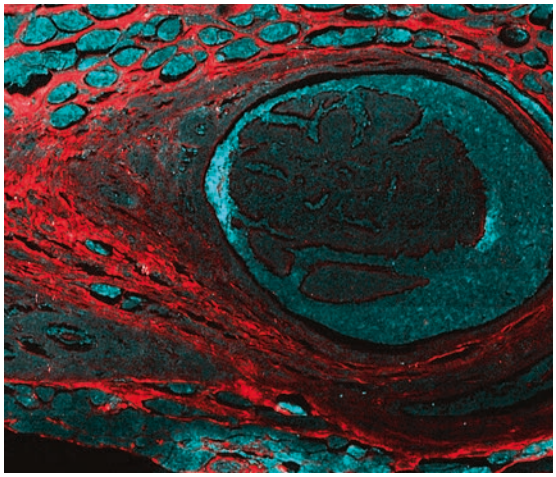
The example projects described above demonstrate the potential for laser-based optical microscopy to investigate different aspects of this complex and difficult disease. These methods will continue to play an important role, as new developments take place in techniques, instrumentation, new chemical probes, and sample preparation. Octopus and its team will continue to work with researchers in this important endeavour.

David Clarke, Stan Botchway, Marisa Martin-Fernandez (CLF)

Non-linear microscopy offers improved tumour biopsies (IESL-FORTH, Greece)

The development of label-free non invasive techniques to be used as new tools in cancer research is of great importance. Non-linear optical imaging techniques, based on the employment of ultrafast lasers as excitation sources, have been widely used to reveal biological structures for accurate diagnosis at the cellular as well as the tissue level [1, 2]. These technologies provide several advantages compared to other optical techniques such as high resolution, label-free imaging capabilities, increased penetration depths and intrinsic three-dimensional sectioning, while the phototoxicity phenomena onto the biological sample are minimized. Non-linear imaging can provide complementary information on autofluorescence, inhomogeneities, as well as collagen distribution of tissue samples at the submicron level. Recently, this approach has been applied on live tissue with very promising results and has therefore been proposed for clinical studies.[3].

At the Non-linear Microscopy lab (*NLM Lab*) of IESL-FORTH qualitative and quantitative information concerning the structure and directionality of collagen fibers in thin breast tissue sections was collected using second-harmonic generation (SHG) and polarisation-dependent SHG (PSHG) imaging measurements. Collagen, which has been considered as cancer biomarker, is an ideal emitter of high SHG signals due to its non-centrosymmetric structure. Collagen fibers that could be detected by SHG imaging showed a well structured continuity in benign tumour tissues, which became less well-structured as the disease became more severe. Moreover, the obtained results indicated that PSHG data analysis can correlate the calculated second-harmonic anisotropy parameter values with tumour progression. Specifically, the analysis suggested that PSHG imaging could provide a quantitative evaluation of the tumour state and the distinction of malignant from benign breast tissues [4]. Furthermore, using a single femtosecond laser beam, label-free third harmonic generation (THG) imaging techniques provided additional important morphological information as to the mean nuclear and cytoplasmic area, cell volume and tissue intensity, which



Multimodal non-linear image of malignant (grade II) breast tissue. SHG depicted in red and THG in blue color. Scale bar depicts 100 μm.

upon quantification could not only distinguish cancerous from benign breast tissues but also define disease severity. Thus, THG signals which arise from breast tissue discontinuities, from multilayered structures detected in membranes and from lipid bodies, can associate the tissue inhomogeneities with the grades of cancer severity [5, 6]. The applied approach has clinical potential, since it could be used for the quick characterisation of newly excised thin biopsy samples.

Non-linear microscopy techniques (SHG, PSHG, THG) make it possible to quantitatively differentiate benign from cancerous thin human breast biopsy samples, promising a faster, label-free diagnosis. This work could be a step forward for the development of new, non-destructive optical diagnostic tools, based on ultrafast laser oscillators emitting in the near infrared region of the spectrum, for reducing recalls and unnecessary biopsies, while maintaining or improving cancer detection rates, thus improving the quality of life.

This interdisciplinary study was a collaboration between the Non-linear Microscopy (NLM) group of IESL-FORTH, the Biology Department of University of Crete (Prof. Athanassakis group) and the Medical School of the same University.

George Filippidis (IESL-FORTH)

[1] M.G. Giacomelli et al., Biomed. Opt. Express 9: 2457, 2018
[2] E. Gavgiotaki et al., J. Biophotonics 10: 1152, 2017
[3] S.X. You et al., Nature Communications 9: 1, 2018
[4] V. Tsafas et al., submitted
[5] E. Gavgiotaki et al., Proc. SPIE 11076: 110760I, 2019
[6] E. Gavgiotaki et al., in press Scientific Reports

Photoacoustic imaging – clinical implementation of a novel diagnostic tool for skin tumour delineation (Lund University)

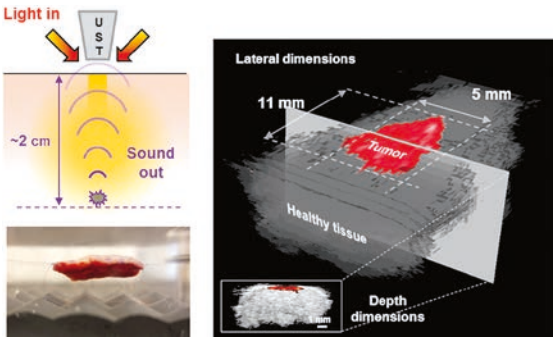
The 'gold standard' method for skin tumour diagnosis requires surgical incision and histopathological analysis to determine the nature of the lesion and the extent to which it may have grown. Patients with non-radical excisions must undergo a second surgery to completely remove the tumour. If the complete dimensions of the tumour, both laterally and at a depth, could be determined non-invasively, it could reduce the number of surgical incisions drastically as well as save time and patient suffering.

Photoacoustic imaging (PAI) is one of the most promising imaging modalities emerging for clinical use as it is capable of generating an image of the tissue down to a depth of 2 cm. This is acquired by sending a train of ns laser pulses into the tissue, which consequently absorb and generate a thermo-elastic expansion that is detected by a high-frequency ultrasound transducer. By tuning the photon energy of each laser pulse, an absorption spectrum is acquired at every point resolved by the ultrasound probe (typically 200 um resolution). At the Lund University, spectroscopists are working in close collaboration with medical doctors to develop PAI for clinical implementation, with particular focus to determine the 3D dimensions of a suspected tumour non-invasively. Specifically, they were among the first to translate the PAI technique into the clinical setting [1], and are therefore uniquely placed to implement it for skin cancer in patients. They were also the first to demonstrate the ability of PAI to discern basal cell carcinoma [2] and squamous cell carcinoma [3].

In an ongoing study, PAI and related spectral imaging analysis methods are being tested on excised skin tumours of different types. As shown in the figure, promising results have been obtained in generating a 3D reconstructed image of the sample in which the dimensions of a melanoma skin tumour can be determined. Ultimately, the project aims at developing a clinically viable method for skin tumour diagnosis capable of identifying and delineating skin tumours within minutes so that the tumour can be removed in a single-stage procedure.

Malin Malmsjö (Lund University)

[1] R. Sheikh et al., IEEE Trans. Ultrason. Ferroelectr. Freq. Control 66: 472, 2019
[2] U. Dahlstrand et al., Photoacoustics 18: 100187, 2020
[3] J. Hult et al., J. Biophotonics 13: e201960212, 2020



Top left: The schematic demonstrates how light from a pulsed tunable laser source penetrates the tissue where absorption of photons generates a thermoelastic response detected by an ultrasound transducer (UST). Bottom left: A picture of an excised tumour that is imaged using PAI from which a 3D reconstructed image can be recreated. Right: Employing spectral unmixing algorithms, the tumour can be distinguished from healthy tissue, and its dimensions can be determined both laterally and at a depth.

Relativistic-intensity 1.5-cycle light waveforms at kHz repetition rate leads to observation of laser waveform effects in laser-plasma accelerator

Generating ultrashort laser transients capable of steering relativistic light forces with sub-cycle precision during laser-plasma interactions has been a long-standing challenge, fuelled by the prospect of developing ultrafast particle and radiation beams for applications. In a recent Transnational Access project performed at French Laserlab-Europe partner LOA, an international team made up of researchers from Berlin, Goettingen and Institut Polytechnique de Paris have developed a source of relativistic-intensity near-single-cycle laser pulses and observed the first evidence of laser waveform effects inside a laser-plasma accelerator. These results have been published in Light: Science & Applications.

There is a push in ultrafast science to merge two distinct classes of lasers: those achieving relativistic intensity and those with pulse durations approaching a single light cycle. While the former laser class traditionally involves large-scale amplification chains, the latter class requires extremely precise spatiotemporal control over the laser field. This feature is at the heart of the recent work done by the Laserlab-Europe collaboration on a laser-plasma accelerator (LPA) driven by near-single-cycle laser pulses (Fig. 1). In order to reach relativistic energies, electrons must be injected into the LPA via field ionisation close to the peak of the pulse, which heavily depends on the carrier-envelope phase (CEP) of the pulse as it determines the final electron beam properties (spectrum and charge). However, the injection event must be highly localised in space and time to avoid field effects being washed out during laser propagation, thereby placing stringent demands on laser stability.

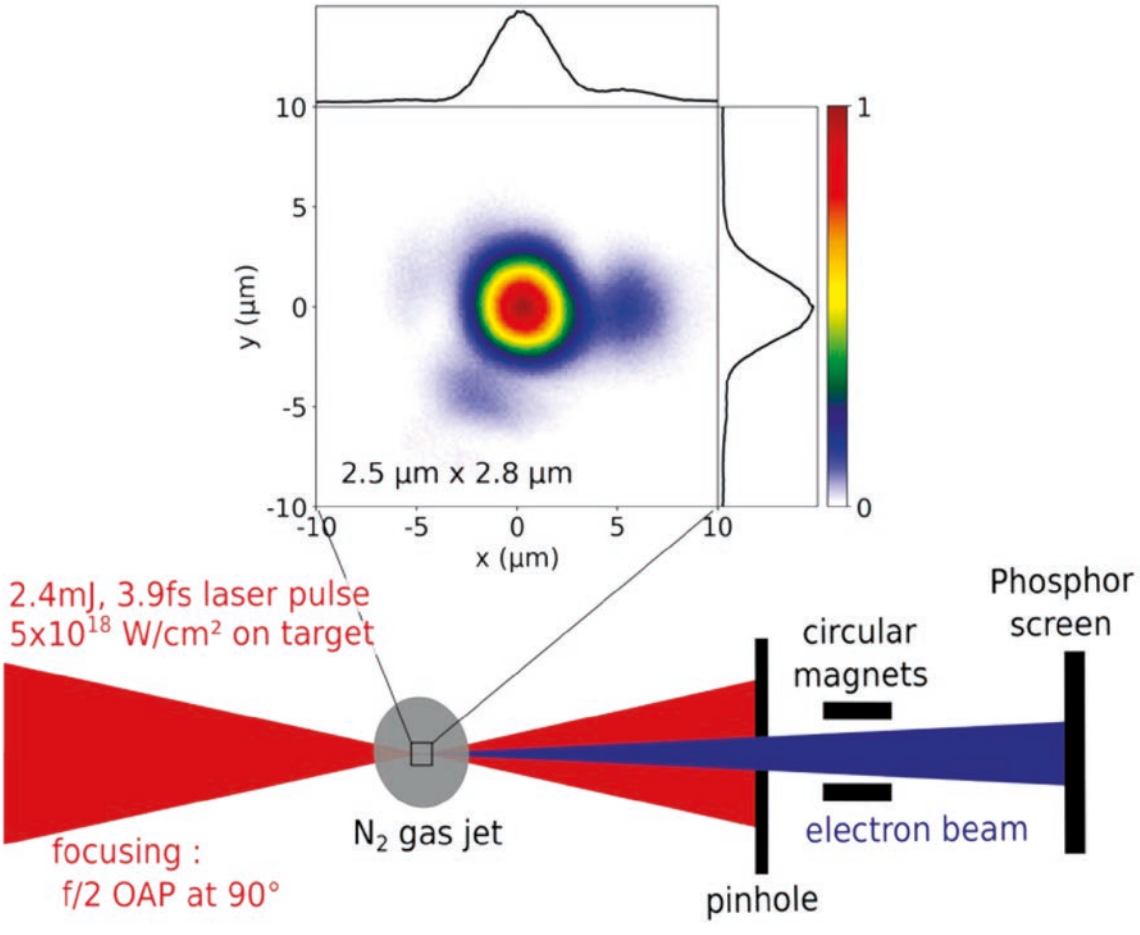


Figure 1: *Schematic top-down view of the electron LPA developed at LOA and snapshot of the 1.5-cycle laser focal spot size (2.5 x 2.8 µm²) resulting in relativistic driving light intensities (5 x 10¹⁸ W/cm²) [3].*

Developing such a stable few-cycle light source was very challenging. The key to success was the adoption of the stretched flexible hollow fiber technology, pioneered by Tamas Nagy (MBI) and Peter Simon (Laser-Laboratorium Goettingen e.V.), to efficiently post-compress the high-energy pulses produced by the CEP-stable Ti:sapphire chirped pulse amplifier built by the LOA team. This would eventually lead to the generation of multi-mJ energy pulses with sub-2-cycle duration and stable CEP for the first time in 2014 [1]. In 2017, increased energy from the laser amplifier and improved integration of the hollow fibre compressor enabled the LOA team to drive a relativistic electron LPA for the first time at kHz repetition rate [2], albeit without CEP control due to insufficient laser stability.

Our latest engineering efforts have now resulted in record pulse duration (1.5 cycle), terawatt peak-power and the pulse stability required to successfully observe field effects inside the LPA (< 0.3 % rms over several hours). Raw electron spectra recorded from the LPA (Fig. 2a) show clear CEP effects although they tend to wash out towards the end of the CEP cycling scan. Nevertheless, the averaged electron spectra for the first two CEP cycles (Fig. 2b) show a correlation for relative CEP changes that clearly outweighs the spectral fluctuations, which naturally occur due to the extreme nonlinearity of the interaction. The next step of the collaboration will focus on enhancing the stability and robustness of the LPA so the electron beam becomes usable for applications downstream.

Rodrigo Lopez-Martens and Stefan Haessler (LOA)

[1] F. Böhle et al., Laser Physics Letters 11: 095401, 2014
[2] D. Guénot et al., Nature Photonics 11: 293, 2017
[3] M. Ouillé et al., Light: Science & Applications 9:47, 2020

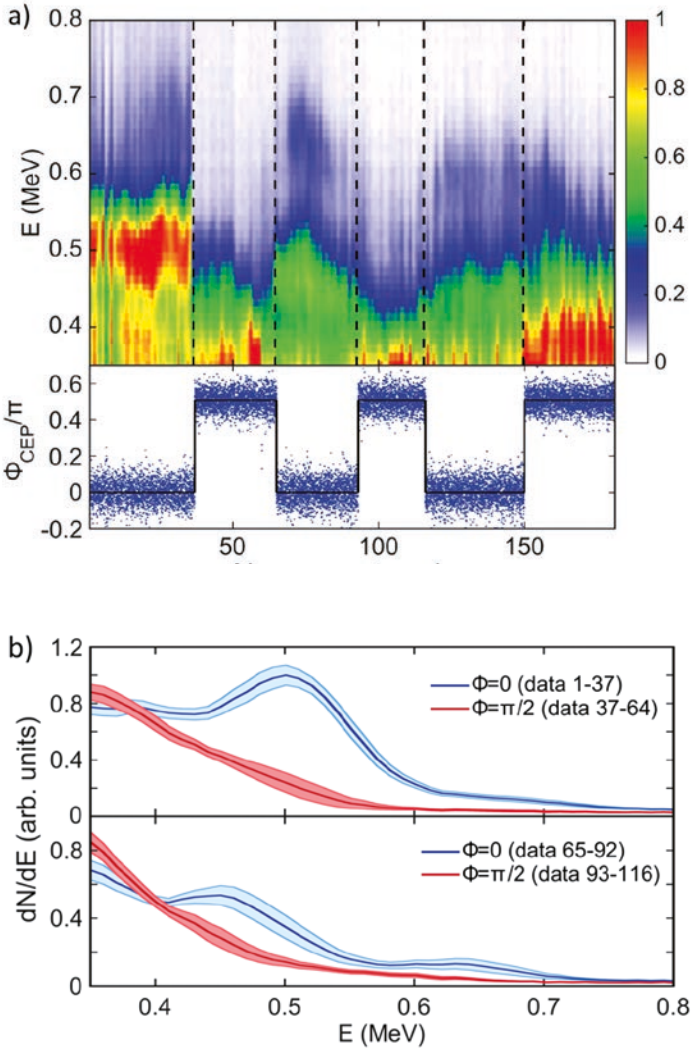


Figure 2: *a) Top: electron spectra dN/dE (arb. units) obtained while varying the CEP of the driving field (each spectrum was obtained by averaging of 500 laser shots). Bottom: the measured CEP (blue dots) and the command CEP values sent to the feedback loop (black line). b) Averaged spectra for the first (top) and second (bottom) CEP cycles. The solid dark lines represent the average spectra, and the light blue areas indicate the standard deviation due to spectral fluctuations [3].*

What is Transnational Access?

Laserlab-Europe offers transnational access to scientists in a wide variety of disciplines, from theoretical physics to life sciences to art conservation. The majority of our users are from the EU, but applications are welcome from anywhere in the world. All access costs are covered, including travel and accommodation. Access is provided on the basis of scientific excellence of the proposal, reviewed by an external and independent Selection Panel. A typical access project lasts for 2 to 4 weeks, with projects longer than this considered highly exceptional.

Young scientists and scientists who have never used lasers in their research before are particularly encouraged to apply. Laserlab-Europe strives to promote gender equality in scientific research and specifically encourages applications from women. Information about proposals and submission can be found on the Laserlab-Europe website.

www.laserlab-europe.eu

Map: CIA World Factbook

CARLA: The European Photonics CAReer LAunch Path

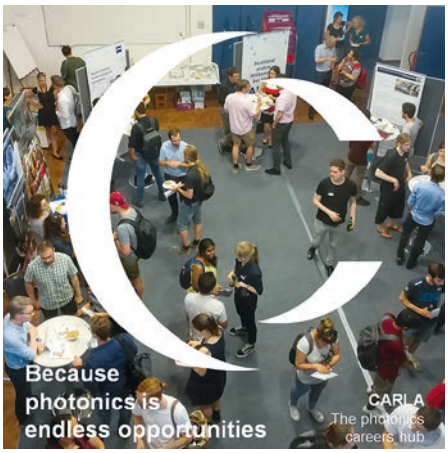
Photonics is a Key Enabling Technology (KET) for Europe's future prosperity according to the European Commission. It is calculated that 20 – 30% of the entire economy and 10% of the workforce in Europe already depends on photonics technologies. However, current skill shortages in this area are already damaging the growth prospects of European companies and the continent's economy.

To support the growth, leadership and innovation potential in this area, Europe needs more well-prepared professionals. CARLA is creating a new instrument to address this need at the source.

CARLA will build a pan-European career camp of excellence that is available to and replicable by the European photonics community, planning to boost the numbers of students and young researchers pursuing careers in photonics, to encourage innovation and entrepreneurship, and to empower diversity across the photonics sector.

The camps will be designed with the input of photonics stakeholders, including industry, academia, entrepreneurs, policymakers, HR and training experts, and the potential users (university students and young researchers). Handbooks will be produced and refined over the 11 camps, providing a tool for other organisers to host a similar programme and summarizing the key lessons for boosting diversity.

If you would like to be involved in a CARLA event local to you, please see the project website *https://carlahub.eu/*.



The Extreme Light Infrastructure takes a major step closer to officially becoming an international organisation

The Extreme Light Infrastructure (ELI) has applied to the European Commission to establish the Extreme Light Infrastructure ERIC (ELI ERIC). The Czech Republic and Hungary, together with Italy and Lithuania, have taken this formal step towards the establishment of the new Pan-European organisation, with The United Kingdom as a founding observer.

The ELI-Beamlines facility in Dolní Břežany, Czech Republic, and the ELI-ALPS facility in Szeged, Hungary, have a complementary portfolio of the world's most intense, shortest-pulse laser systems. Romania is also expected to join in the near future with the ELI-NP Facility.

While the ELI facilities were constructed separately, the aim is to offer them to scientists under one umbrella. They have already begun to open their doors to the research community. The European Commission will review the application and the members expect it to be confirmed in 2020.

Early experiments at ELI Beamlines

The ELI Beamlines Facility invites the scientific community to submit proposals for early experiments using instruments in the E1 Experimental Hall and supporting laboratories for Applications in Molecular, Biomedical and Materials Sciences. Experiments are expected to be scheduled from early September 2020. More info at *https://eli-laser.eu/*.

Allen Weeks (ELI-DC)

Forthcoming events

Science@FELs 2020
14 – 16 September 2020
online conference
Conference in cooperation with Laserlab-Europe

LAPLASS – Laser-Plasma Summer School:
Experimental methods in High-Intensity Laser-Plasma processes
14 – 18 September 2020
online event

To find out more about conferences and events, visit the Laserlab-Europe online conference calendar.

How to apply for access

Interested researchers are invited to contact the Laserlab-Europe website at www.laserlab-europe.eu/transnational-access, where they find relevant information about the participating facilities and local contact points as well as details about the submission procedure. Applicants are encouraged to contact any of the facilities directly to obtain additional information and assistance in preparing a proposal.

Proposal submission is done fully electronically, using the Laserlab-Europe Proposal Management System. Your proposal should contain a brief description of the scientific background and rationale of your project, of its objectives and of the added value of the expected results as well as the experimental set-up, methods and diagnostics that will be used.

Incoming proposals will be examined by the infrastructure you have indicated as host institution for formal compliance with the EU regulations, and then forwarded to the Access Selection Panel (ASP) of Laserlab-Europe. The ASP sends the proposal to external referees, who will judge the scientific content of the project and report their judgement to the ASP. The ASP will then take a final decision. In case the proposal is accepted, the host institution will instruct the applicant about further procedures.

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