אוניברסיטת בר-אילן
Bar-Ilan University

The 15th international conference in Israel

18 – 20 Nov. 2018

Faculty of Engineering
Bar-Ilan University

LALS

Laser Applications in Life Sciences

Track C: Treatment

KEYNOTE C1:

Optical Dosimetry in Radiation Therapy with Scintillation & Cherenkov Imaging

Brian W. Pogue

Dartmouth, USA

A fundamentally new way to visualize radiation dose delivery in real time is demonstrated with Cherenkov light imaging and Scintillation light imaging, using time gated intensified cameras that synchronize to the pulses of radiation delivered. Linear accelerators are used to deliver radiotherapy to patients, with photon or electron beams at MegaElectron Volt (MV & MeV) energies, and the electrons resulting from this generate Cherenkov light when passing through tissue. This light emission can be imaged from the surface of patients, and the images provide a real time optical image of the radiation delivery as it happens dynamically. Cherenkov imaging is being translated into a a system that would allow for verification of delivery in radiation oncology. Examples of video capture of radiotherapy will be shown in total breast irradiation and total skin electron therapy, where dosimetry is challenging and inaccurate. Additionally, point dose measurements can be taken with high accuracy by placing small scintillator badges on the patient, and imaging with the same camera systems. The benefit of these scintillating dosimeters is that the images are highly linear with dose and independent of body site or tissue properties. The benefits of both Cherenkov imaging and scintillator dosimetry will be outlined, and examples shown with tissue phantoms and patient treatments. Further use of Cherenkov or scintillation as a light activator for molecular sensing is feasible, and in vivo pre-clinical studies have shown the value of this in lymph node sensing for oxygen and EGFR receptor status.

KEYNOTE C2:

Clinical Biophotonics: Pushing the Technical Solutions into the Hospital

Juergen Popp[a,b,c]

[a]*Leibniz Institute of Photonic Technology Jena, Germany, Member of the Leibniz Research Alliance Leibniz Health Technology Technology, Albert-Einstein-Straße 9, 07745 Jena, Germany*

[b]*Institute of Physical Chemistry & Abbe-Center of Photonics, Friedrich-Schiller University Jena, Germany, Helmholtzweg 4, 07743 Jena, Germany*

[c]*InfectoGnostics Research Campus Jena, Philosophenweg 7, 07743 Jena Germany*

Photonic approaches have shown their potential to meet current diagnostic challenges in various fields of medical need. In this context, spectroscopic approaches like e.g. Raman spectroscopy are especially noteworthy. Within this contribution, we will highlight our efforts in utilizing spectroscopic approaches with focus on Raman spectroscopy towards routine clinical applications for an early diagnosis and targeted therapy of infectious diseases and cancer, since these types of diseases represent unmet medical needs with respect to diagnosis and therapy. Addressing this question requires new spectroscopic instrumentation, which can be applied out of specialized labs in a clinical environment (e.g. operation theatre, bedside or in a doctor's practice).

Infectious diseases are one of the major reasons of deaths worldwide. Successful treatment of infection relies on timely identification of the pathogen and its antibiotic resistance pattern in order to select the appropriate antibiotic treatment as early as possible. Classical microbiological analysis methods rely on time-consuming overnight cultures. Fast culture-independent analysis methods could thus lead to huge improvements and help save lives because an early and targeted treatment improves the prognosis of the patients. It will be shown that Raman spectroscopy in combination with chemometric strategies and chip-based sampling show great promise for a fast and targeted identification of pathogens together with their antibiotics resistance pattern and plays a key role in turning this vision into reality.

In addition, we will highlight the potential of multimodal spectroscopy as a sensitive and selective tool to potentially solve challenges currently faced by clinical pathology in cancer diagnosis. We will amongst other introduce a compact CARS/SHG/TPEF (coherent anti-Stokes Raman spectroscopy/ second harmonic generation/ two-photon excited autofluorescence) multimodal nonlinear microscope in combination with novel fiber laser sources for use in clinics. The system offers great potential to complement established clinical pathological diagnostic tools and to augment standard intraoperative clinical assessment with multimodal images to highlight functional activity and tumor boundaries.

Overall, here we report on innovative technological concepts for bringing multispectroscopic approaches closer to clinical use and on what is still needed in order to apply these approaches in clinical routine diagnostics. The latter is only possible via a close interaction of technologists with experts from clinics and the industry. A suitable new way of such an interaction is to work in a public-private partnership e.g. in the form of a research campus.

Acknowledgment

Financial support of the EU, the "Thüringer Ministerium für Wirtschaft, Wissenschaft und Digitale Gesellschaft", the "Thüringer Aufbaubank", the Federal Ministry of Education and Research, Germany (BMBF), the German Science Foundation, the Fonds der Chemischen Industrie and the Carl-Zeiss Foundation are greatly acknowledged.

KEYNOTE C3:

Shedding New Light on Old Diseases

Prof. Abraham Katzir,

Physics, Tel Aviv University, ISRAEL

Modern optics has made a revolution in medicine. Lasers and their use for diagnosis and therapy, optical fiber sensors, endoscopy, novel imaging techniques, new spectroscopic techniques and other methods, have made enormous impact on medical practices. As an example, in surgery, these methods opened the way for least invasive surgery and minimally invasive surgery.

One may get the impression that all these advanced methods are linked only to the advent of a novel medical devices such as lasers and fibers and digital cameras and to the extensive use of powerful computation techniques. This is not true.

Medicine is as old as mankind. The roots of modern medicine are in prehistoric medicine. Since ancient times optics has been used for the diagnosis of diseases and even for some medical treatments.

For example, in ophthalmology Optical Coherent Tomogrphy (OCT) is used as screening before laser assisted cataract surgery. The origin of this surgical procedure is the cataract treatment carried out in Ancient Egypt in 3000BC. Another example is modern photochemotherapy, the combined use of chemicals and light for the treatment of disease. A common method in dermatology is PUVA (psoralen and ultraviolet A), a light therapy treatment for vitiligo, psoriasis, eczema etc. The ancient Egyptians used an identical method in 1500BC. Endoscopy is another example. Endoscopy was first described by Hippocrates in Greece around 400BC. He was the first to describe a rectal speculum.

In conclusion, the advances in today's medicine, including biomedical optics, stem from 10000 years of continuous developments.

INVITED C1:

ALA-mediated cancer photo-therapy and fluorescence-guided surgery

Zvi Malik
The Mina and Everard Goodman Faculty of Life Sciences
Bar-Ilan University, Ramat-Gan 5290002, Israel
Zvi.Malik@biu.ac.il

Amino-levulinic acid (ALA) is a precursor of Protoporphyrin (PpIX) biosynthesis, a potent photo-sensitizer activated by light irradiation producing singlet oxygen used for phototherapy of in malignant tissues. ALA induces preferential tetra-pyrrole synthesis in transformed cells due to reduced ferrochelatase enzymatic activity and disturbed onco-metabolism. ALA-photodynamic therapy (PDT) of cancer is clinically used in oncology and surgery after decades of research. Topical ALA-PDT application enables the treatment of multiple non-melanoma skin lesions simultaneously with excellent cosmetic results. No acquired multidrug resistance was reported, and the treatment can be repeated with the same efficacy each time in the event of tumor recurrence which is of major significance in oncology. ALA-PDT is a well-established treatment pre-cancerous lesions of actinic keratosis, and inflammatory microbial disease such as acne vulgaris.

Most importantly PpIX fluorescence-guided resection of high-grade glioblastoma tumors is a practical and simple tool that provides intraoperative visualization of lesions with mm accuracy, a method recently approved by the FDA. ALA photo-diagnosis is increasingly utilized in fluorescence-guided surgery for diverse malignant lesions, such as bladder tumors associated with a significantly improved extent of resection and progression-free survival. Moreover, the recent introduction of combinatory concepts of multi-functional ALA prodrugs that maximize sensitizer biosynthesis and affect multiple subcellular targets might open new modalities in PDT. The current status, significance, limitations, and future perspectives of ALA in cancer therapy and diagnosis will be discussed.

INVITED C2:

Multi-Photon Processes in Cancer Diagnostics and Therapy

Ricardas Rotomskis

Biophotonics Group, Laser Research Center, Vilnius University, & Biomedical Physics laboratory, Nacional Cancer Institute, Vilnius, Lithuania

The simultaneous absorption of two photons by the same molecule was first analyzed theoretically in the 1930s by Gppert-Mayer, and was first demonstrated experimentally in 1961, soon after the invention of the laser. Nowadays the simultaneous and consecutive absorption of two or more photons by atom, molecule or ions in upconverting nanoparticles shows promising application in different areas of biomedicine, especially in cancer therapy and diagnostics.

Presentation is devoted to the explanation of two-photon, two-step and upconverting processes in biological active molecules and upconverting nanoparticles with special emphasis on the cancer therapy and diagnostics. Different types of multiphoton excitation will be summarized in detail as well as the perspectives of application in photodynamic cancer therapy and diagnostics will discussed. Exceptional attention will be paid on the application of upconverting nanoparticles for multimodal imaging and theranostics.

INVITED C3:

The use of lasers in the treatment of soft and hard tissues in veterinary medicine

M. Wąsowicz [1,2]

[1]Department of Morphological Sciences, Faculty of Veterinary Medicine, Warsaw University of Life Sciences, Nowoursynowska 159, 02-776 Warszawa, Poland.
[2]Praktyka Weterynaryjna. Michał Wąsowicz, Osowska 70/72 m 3, 04-332 Warszawa, Poland.

In modern veterinary medicine, innovative technologies are increasingly used for treatment. One of them is a laser that uses the phenomenon of forced emission. It is a device emitting electromagnetic radiation in the range of infrared, ultraviolet and visible light. The name LASER is a commonly used acronym meaning in English: Light Amplification by Stimulated Emission of Radiation. Laser radiation used in medicine is consistent, polarized and has a beam with very little discrepancy. Due to the wide variety of lasers in the world, practical aspects of lasers of different powers will be presented. Different dimensions of the functioning of devices depending on the spectrum of radiation, active medium and application in veterinary medicine will be shown. Clinical cases will be presented based on various species of animals from the world of veterinary practice. The topics will include the treatment of soft and hard tissues. Among the diseases of soft tissues, changes in the skin and mucous membranes are distinguished. Some cases include fairly frequent changes in diseases that include mucocutaneous tissue. They are a great challenge for people who are taking treatment. Diseases of hard tissues constitute the second group in the order of described cases. These include lesions involving small-fiber and thick-tissue tissue. The characteristics of individual lasers and the impact on individual tissues of the animal body will be the subject of the lecture. This study was partially supported by the Leading National Research Centre Scientific Consortium “Healthy Animal-Safe Food” Faculty of Veterinary Medicine, Warsaw University of Life Sciences,

Poland, decision of Ministry of Science and Higher Education No. 05-1/KNOW2/2015.

INVITED C4:

Application of the laser techniques for in vitro and in vivo evaluation of the interaction of nanoparticles with blood components and their effect on blood microrheology

A.E. Lugovtsov[1,2*], V.I. Kochubey[3,4], E.A Shirshin[1,2], V.V. Tuchin[3,4,5], C.L. Cheng[6], A.V. Priezzhev[1,2]

[1]International Laser Center and [2]Department of Physics of M.V. Lomonosov Moscow State University,
Leninskye Gory 1-62, 119991 Moscow, Russia
[3]Research-Educational Institute of Optics and Biophotonics, Saratov State University, Astrakhanskaya 83, 410012 Saratov, Russia
[4]Interdisciplinary Laboratory of Biophotonics, Tomsk State University, Lenin's av. 36, 634050 Tomsk, Russia
[5]Laboratory of Laser Diagnostics of Technical and Living Systems, Institute of Precision Mechanics and Control of the RAS,
Rabochaya 24, 410028 Saratov, Russia
[6]Department of Physics, National Dong Hwa University, Da-Hsueh Rd. 1-2, Shou-Feng, 974 Hualien, Taiwan

** anlug@biomedphotonics.ru*

In the last decade, usage of different types of nanoparticles (NP) in many fields of life sciences rapidly grows due to non-toxicity and biocompatibility of many of these particles. In particular, iron (iii) oxide nan oparticles (Fe_2O_3) and carbon nanoparticles - nanodiamonds (ND), nanotubes and fullerenes - have been p roposed for using in various biological and biomedical applications. For example, Fe_2O_3 particles are promising for biomedical imaging and photodynamic therapy (PDT) of oncologic diseases. Recently, the Fe_2O_3 nanoparticles with surface functionalization by porphyrins (Fe_2O_3-POR) were proposed as more efficient for PDT since they strongly absorb light, which is then converted to energy and heat in the illuminated areas. Fullerenes and NDs can potentially be used for treatment, diagnostics as bio-labeling tool of living organs because they do not destroy vitally important organs, tissues and cells. Nowadays, many studies are conducted on the application of carbon nanoparticles for direct drug delivery. It is presumed that in order to reach the target these particles would be intravenously administered into blood. However, so far there is little information on the interaction of NP with major blood components: cells and plasma proteins. It can be assumed that NP can affect the red blood cells (RBCs) properties such as their ability to reversibly aggregate and deform in shear flow when propagating along blood vessels and capillaries. These alterations can impair blood rheology and, as a result, increase the risk of development of cardiovascular diseases and even mortality during medical application of NP. The aim of our work was to study *in vitro* and *in vivo* effect of ND, fullerenes and Fe_2O_3 particles on blood microrheology – aggregation and

deformability properties of the cells.

Measurements were performed by means of the laser diffractometry and aggregometry techniques by using the commercially available Rheoscan system (Rheomeditech, Korea). These techniques based on laser interaction with blood, in particular diffuse light scattering and diffraction, are convenient, fast and relatively simple for *in vitro* measurement of the deformability and aggregation properties of RBC in blood samples. To further investigate the interaction between the NPs and RBCs, namely, to study sorption onto the membrane and cellular penetration, we performed experiments using the fluorescence laser confocal microscopy. Our experimental results were obtained on EDTA stabilized human and rat blood samples incubated with NP of different sizes and surface functionalization in different concentrations in cases of *in vitro* and *in vivo* conditions.

It was shown that 45 min-long incubation of RBCs with NP at high concentrations of the latter does negatively affect both aggregation and deformability of the cells, the effect being dependent on the particle concentration, size and surface functionalization. The alterations in the microrheological properties are more significant for higher NP concentrations and more pronounced for non-functionalized particles in comparison with Fe_2O_3 particles functionalized with porphyrin and carboxylated ND. Basing on the results one can conclude that the ND, fullerenes and Fe_2O_3 NP can be administered into blood in ambient conditions at low concentrations (33 μg/ml), without significant complication of the blood rheological conditions. However, controlling the RBCs microrheological properties is necessary during treatment.

The work was supported by the RFBR grants № 16-32-50128 and 17-02-01200.

INVITED C5:

Digital capillaroscopy in scientific research and in clinical practice, new approaches

Yury Gurfinkel[1], Alexander Priezzhev[2,3], Evgeny Shirshin[2,3]

1 – Medical Research and Education Center, Lomonosov Moscow State University, Russia
2 - International Laser Center, Lomonosov Moscow State University, Moscow, Russia.
3 - Physics Faculty, Lomonosov Moscow State University, Moscow, Russia.
yugurf@yandex.ru

Capillaries play an essential role in fluid exchange between blood and tissue providing delivery of gases and nutrients. A typical adult has about 10^{11} blood vessels. More than 99% of these vessels are in the microcirculation (Schmid-Schonbein, 2000). The microcirculation is organized into three principal section s, arterioles, capillaries and venules; each has unique structure and function. The arterioles with vascular smooth muscle are primarily responsible for delivery of blood to localized tissue areas and regulation of the rate of delivery. The network operates with numerous control mechanisms, and there are many ways in which such a delicate system may break down, leading to cardiovascular disease. However, on the other hand, the microcirculation system has various mechanisms that allow it to adapt to the needs of tissues and organs in conditions of worsening contractility of the heart muscle. As an example is the removal of excess fluid from the vascular bed and its deposition in the perivascular zones (PZ), which we showed in patients with heart failure (HF). The technique of digital capillaroscopy of nailfold capillaries with high resolution, which we developed, allows us to quantify the degree of the tissues edema in patients suffering from HF. We performed in vivo imaging of the blood capillaries and the (PZ) around them with this technique.
For the first time we have shown that the PZ size is governed by the accumulation of interstitial fluid in the epidermis. The results of *in vivo* nail fold multiphoton tomography combined with fluorescence lifetime imaging support this hypothesis. Hence, we suggest a novel quantitative and very sensitive non-invasive indicator of HF and its severity. The use of vital digital capillaroscopy also makes it possible to detect the presence of remodeling of the microvascular bed in patient with arterial hypertension. The tortuosity of the capillary bed, which is one of the characteristic signs of diabetes mellitus, reflects the pathophysiological mechanism caused by a decrease in the permeability of the capillary wall due to the deposition of glycoproteins in it.
Our studies have shown the possibility of determining the presence of aggregates in the capillary bed. This allows monitoring the effectiveness of treatment of coronary heart disease with platelet antiaggregation drugs and new oral anticoagulants. Also results of scientific researches in the field of space medicine, performed together with the Institute of Space Researches of the Russian Academy of Sciences will be presented.

This work was supported by the grant of the Russian Science Foundation № 18-15-00422.

References:

[1] Schmid-Schonbein, G. W. What is the relevance of microcirculation in cardiovascular disease? (eds Struijker Boudier, H. and Ambrosio, G.) 1–12 (Lippinkott Williams & Wilkins, 2000).
[2] Shirshin, E. A., Gurfinkel, Y. I., Priezzhev, A. V., Fadeev, V. V., Lademann, J., & Darvin, M. E. (2017). Two-photon autofluorescence lifetime imaging of human skin papillary dermis in vivo: assessment of blood capillaries and structural proteins localization. Scientific Reports, 7: 1171, Doi: 10.1038/s41598-017-01238w (2017).

[3] Gurfinkel, Y. I., Sasonko, M. L. & Priezzhev, A. V. Digital capillaroscopy as important tool for early diagnostics of arterial hypertension. Proc. SPIE 9448, 944804, Doi: 10.1117/12.2180259 (2014).
[4] Gurfinkel, Y. I.,Sasonko, M. L. Potentialities of digital capillaroscopy in the diagnostics of oedema syndrome // Journal of Biomedical Photonics & Engineering, 3(3), Doi: 10.18287/JBPE17.03.030401 (2017).

[5] E.A. Shirshin, Y.I. Gurfinkel, S.T. Matskeplishvili, et al. In vivo optical imaging of the viable epidermis around the nailfold capillaries for the assessment of heart failure severity in humans. J. Biophotonics. e201800066. Doi: 10. 1002/jbio.2018000 (2018).

INVITED C6:

Smart nanomaterials for synergistically enhancing photodynamic therapy efficiency

Ming Wu, Da Zhang, Xiaolong Liu*

The United Innovation of Mengchao Hepatobiliary Technology Key Laboratory of Fujian Province, Mengchao Hepatobiliary Hospital of Fujian Medical University, Fuzhou 350025, P.R. China.

Tel. /fax: +86 591 8370 5927; Email address: liuxl@fjirsm.ac.cn

Photodynamic therapy (PDT), as a very promising treatment modality for cancer, has several advantages over conventional therapies because of its noninvasive nature, the fast healing process, and none ionizing radiation. However, the clinical efficacy of PDT needs to be further improved, and there are many obstacles still existed, such as the limited tumor selectivity of the clinically used photosensitizers, severe tumor hypoxia which has been associated with resistance to therapy, tumor recurrence and distal metastasis after oxygen consumption by PDT. In addition, single photodynamic therapy modality can not completely eliminate the tumor cells. To solve the above mentioned problems, our group has developed a smart nanosystem for tumor micro-enviroment triggered programmable in demand photodynamic therapy, aggregation induced photothermal therapy and hypoxia-activated chemotherapy. This nanosystem is composed of HCC cell specific targeting aptamers (TLS11a), monodispersed gold nanoparticle (GNP), photosensitizer (Ce6), and hypoxia activatable prodrug (AQ4N). In normal physiological conditions, the fluorescence and ROS generation ability of Ce6 are quenched by GNPs via resonance energy transfer (RET); but in cancerous cells, the fluorescence and the ROS generation of Ce6 could be recovered by cleavage of Au-S bond through high level of intracellular GSH for real-time imaging and in demand PDT. Meanwhile, the prodrug AQ4N release could be triggered by acid-cleavage of coordination bonds, then accompanied by a release of Cu(II) that would induce the electrostatic aggregation of GNPs for photo-thermal ablation; furthermore, the significantly enhanced chemotherapy efficiency could be achieved by PDT produced hypoxia to reduce AQ4N into AQ4. Taken together, here described nanoplatform with tumor cell specific responsive properties and programmable PDT/PTT/chemotherapy functions, might be an interesting synergistic strategy for HCC treatment.

INVITED C7:

Event-related Activities in the Dorsolateral Prefrontal Cortex Associated with Playing A Multiplayer Online Battle Arena Game "League of Legends"

Kehong Long[1], Yue Li[1,2], Lei Zhang[2], Hui Gong[2], Hao Lei[1,2*]

1. National Center for Magnetic Resonance in Wuhan, State Key Laboratory of Magnetic Resonance and Atomic and Molecular Physics, Wuhan Institute of Physics and Mathematics, Chinese Academy of Sciences

2. Wuhan National Laboratory for Optoelectronics, Huazhong University of Science and Technology

Frequent video game (VG) playing can have both positive and negative effects on cognition and brain [1-6]. Dorsolateral prefrontal cortex (DLPFC) is a key brain region involved in VG-related brain plasticity [7, 8]. In this study, functional near infrared spectroscopy (fNIRS) was used to record dynamic hemodynamic/oxygenation changes in bilateral DLPFC of subjects playing a massively multiplayer online battle arena (MOBA) VG, League of Legends (LOL).

Twenty four experienced LOL players (19.7 ±1.4 years old) played one round of Matching mode LOL game wearing an fNIRS device, which recorded real-time oxyhemoglobin (HbO_2)/deoxyhemoglobin (Hb) changes in bilateral DLPFC [9]. In LOL, a player can control his/her game figure (i.e., champion) to slay (S) an enemy champion (EC) or assist (A) his/her teammate's champion to slay an EC. After killing the EC virtually, the player's champion can either be kept on the battle ground continuing to play (C) or be recalled (R) to the nexus for replenishment. The HbO_2/Hb time series 20 s before and after the S+C, S+R, A+C and A+R events were clipped and analyzed. It was observed that under the A+C scenario, event-related ΔHb was significantly higher in the right DLPFC than in the left DLPFC (paired t-test, $p<0.05$); S+R was associated with significantly higher ($p<0.05$) event-related ΔHb, relative to S+C and A+R. Event-related ΔHbO_2 appeared to be lower in S+R than in S+C and A+R, but the differences did not reach statistical significance.

The lateralized DLPFC responses in A+C are consistent with the notion that higher demands on extraction of task-relevant information led to stronger activation in the left DLPFC, whereas higher demands on integration of interdependent information into a coherent action sequence entailed stronger activation of the right DLPFC [10]. In the S+R scenario, defeating the EC was associated with significantly higher ΔHb and relatively lower ΔHbO_2. The results were consistent with a recent report showing that violent game events in a car driving video game (i.e., killing pedestrians virtually) was associated with negative blood oxygenation level-dependent (BOLD) signals in the lateral prefrontal cortex, relative to the non-violent game events [11].

References:

[1] J.A. Anguera et al., Nature, 501 (2013) 97-101; [2] A.J. de Kloet et al., Brain Inj, 26 (2012) 1021-1029; [3] R. Nouchi et al., PloS One, 8 (2013) e55518; [4] C.H. Ko et al., Psychiatry Res, 175 (2010) 121-125; [5] X. Qi et al., Front Behav Neurosci, 9 (2015) 296; [6] D.J. Kuss et al, Int J Ment Health Ad, 10 (2012) 278-296; [7] S. Kuhn et al., PloS One, 9 (2014) e91506; [8] H. Takeuchi et al, Mol Psychiatry, 21 (2016) 1781-1789; [9] Y. Li et al., J Biophotonics, DOI 10.1002/jbio.201700308(2018) e201700308; [10] C.P. Kaller et al., Hum Brain Mapp, 34 (2013) 36-51; [11] D. Wolf et al., Brain Struct Funct, DOI 10.1007/s00429-018-1693-2(2018).

INVITED C8:

Is the direct vHPC–mPFC information transfer requisite for spatial working memory?

- An application of Optogenetic technologe to inhibite vHPC–mPFC input in rat

Tiaotiao Liu, Wenwen Bai, Xin Tian[CA]

School of Biomedical Engineering and Technology, Tianjin Medical University, Tianjin, 300070, China

Spatial working memory (SWM) is a fundamental element of cognition. Previous research has established that both the ventral hippocampus (vHPC) and medial prefrontal cortex (mPFC) are central nodes for SWM function, and spatial information transfer between the mPFC and vHPC plays a vital role during spatial working memory tasks. There is still a question has not yet been known:whether the direct vHPC–mPFC information transfer plays the same role as the direct mPFC-vHPC for successful execution of SWM? If not, which direct input plays the major role? The aim of this study is to explore this question. An optogenetic inhibition (OI) of vHPC terminals in rat is used to interfere vHPC–mPFC input[1] for the OI group. Local field potentials (LFPs) were extracted from multi-channel signals recorded in both vHPC and mPFC while rat performed a delay-alternation working memory task in Y-maze. Information flow (IF) calculted from LFP network in direction from vHPC to mPFC describes the vHPC–mPFC input quantificationally. The value of IF for the OI group significantly was less than the control group statistically with OI SWM dysfunction. This finding indicates that the direct vHPC–mPFC information transfer is requisite for spatial working memory in rat.

Key words: spatial working memory; information transfer; optogenetics; light-sensitive rhodopsin; rat

Refercence:

1 Spellman T, Rigotti M, Ahmari SE, *et al*. Hippocampal-prefrontal input supports spatial encoding in working memory.Nature. 2015 Jun 18;522(7556):309-14.

INVITED C9:

Interaction of red blood cells incubated with engineered nanoparticles assessed by optical tweezers and SEM imaging

Alexey Popov*, Tatiana Avsievich, Alexander Bykov, Igor Meglinski

Optoelectronics and Measurement Techniques Unit, University of Oulu, Oulu 90570, Finland
** correspondence to: alexey.popov@oulu.fi*

Whilst different types of nanoparticles have been extensively used as drug carriers, the application of red blood cells (RBC) as natural transport agents for systemic drug delivery either encapsulated in the cell's inner volume, or coupled to the surface of RBC is considered a new paradigm in modern medicine that possesses a great potential. To reveal possible undesirable effects in routine delivery of nanoparticles by RBC in a day-to-day clinical practice an ultimate understanding of nanoparticles influence on the cells mutual interaction is required. We applied optical tweezers to quantitatively assess adhesive interaction of RBC incubated with nanoparticles, whereas scanning electron microscopy (SEM) was used to direct observe localization of nanoparticles on the membranes of interacting RBC. The experiments were performed in a platelet-free blood plasma mimicking natural environment for RBC interaction. Here, we show that among all considered nanoparticles only nanodiamonds influenced the RBC interaction forces and energy, which resulted in larger cell aggregates. The results emphasize importance of the optical tweezers application for studying cell interaction with nanomaterials.

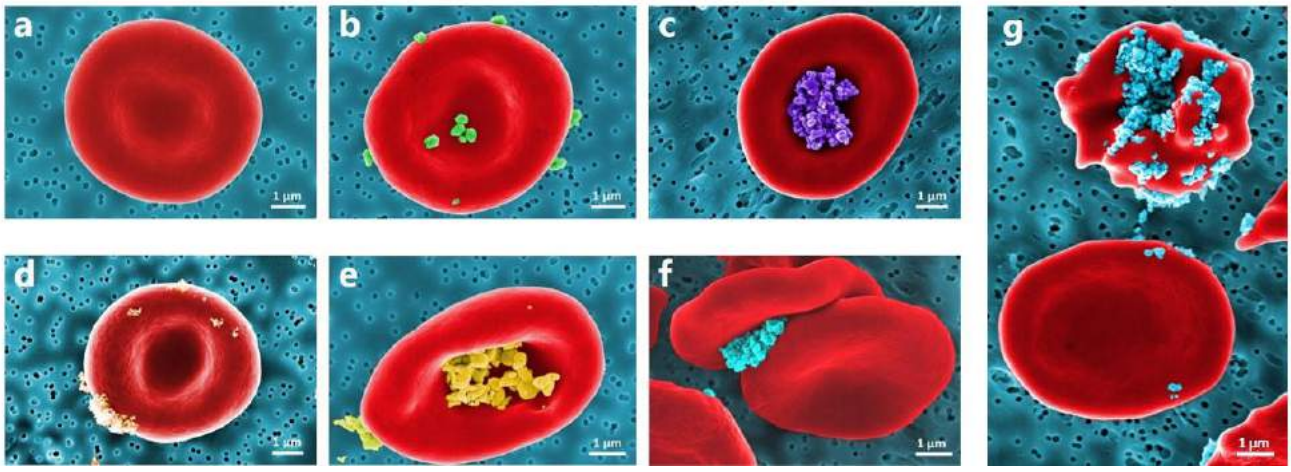


Fig. 1. Coloured SEM images of RBC obtained after incubation with NP demonstrate a variety of RBC-NP complexes. RBC under normal conditions (a), RBC incubated with TiO_2 RODI (b), TiO_2 Hombitan AN (c), TiO_2 15 nm (d), ZnO NP (e), a RBC aggregate with nanodiamonds (f) and RBC with the shape severely deformed due to adhesion of nanodiamonds (g).

Acknowledgement: authors acknowledge the support of the Academy of Finland (grant 290596) and EDUFI Fellowships (TM-17-10370, TM-18-10820).

INVITED C10**:**

Unpconversional nanoparticle for deep tumor PDT

Zhiyu Qian*, Yamin Yang, Liuye Yao, Weitao Li

Department of Biomedical Engineering, College of Automation Engineering, Nanjing University of Aeronautics and Astronautics, 29 Jiangjun Road, Nanjing, China, 211106

**zhiyu@nuaa.edu.cn*

Photodynamic therapy (PDT) is a minimally invasive cancer modality for a variety of diseases including cancer. Two major challenges of current PDT for treating deep tumor are the limited tissue penetration of irradiating light and poor tumor-selectivity of currently available photosensitizer (PS). Advances of new nanotechnologies hold potentials to improve PDT performance, among which upconversion nanoparticles (UCNPs) have attracted much attention. Attributed to their distinct photon upconverting feature, UCNPs are known with capability of emitting high-energy visible light under near-infrared (NIR) light excitation, which can activate nearby PS to produce singlet oxygen and lead to cell death. With the incorporation of UCNPs, a wide variety of NIR excitation sources, which permits to penetrate deeper into tissue, can therefore be employed as an effective light source in PDT, allowing for deep tumor treatment. Hexagonal lanthanide ion codoped sodium yttrium fluoride (NaYF4) nanoparticles have been successfully employed for deep tumor treatment using PDT providing the highest photon upconversion efficiencies with desirable tumor cell destruction demonstrated both *in vitro* and *in vivo*. In addition to their active role in PDT as sensitizing agents, UCNPs also enable strategies for enhanced PS loading, as well as NIR light-triggered release of additional imaging or therapeutic drugs. UCNPs-assisted PDT in deep tumor will benefit more from better design of materials with increased upconversion quantum yield, tumor specific targeting surface modification, and in-depth understanding of the interaction between UCNPs and biological environments.

INVITED C11:

Multimodal monitoring of the brain, glymphatic and cardiovascular system

Teemu Myllylä

University of Oulu

Recent findings on dementia propose that a malfunction of the brain clearance mechanism called glymphatic system leads to slow accumulation of proteins and finally, neuronal degeneration. The term glymphatic (glial lymphatic) system was first used in 2013 to describe a pathway for removal of protein waste products from the central nervous system (CNS). It involves arterial pulsations to push cerebrospinal fluid (CSF) into brain interstitium via glial aquaporin 4 (AQP4) water channels in astrocyte endfeet. For studies of the glymphatic circulation, we develop advanced scale free multimodal techniques, which enable simultaneous recording of cardiovascular, blood pressure and respiratory signals as well as CSF and brain hemodynamics measurement, to be combined with both micro and macroscopic neuroimaging tools. In addition, most of our techniques can be used also simultaneously with different modes of magnetic neuroimaging, particularly with magnetic-resonanceencephalography (MREG). One of the optical neuroimaging techniques that we utilise is near-infrared spectroscopy (NIRS), which is safe, and can be used non-invasively also as a portable solution for long-term measurements. NIRS based imaging techniques allow the possibility to monitor blood flow-related metabolism. It has not yet been applied to imaging of the glymphatic system, but we recently demonstrated that it can be potentially utilized for this purpose. In addition, by using NIRS combined with electroencephalogram (EEG), we have pioneered in monitoring human blood brain barrier disruption (BBBD), which is used in Oulu University Hospital in treatment of patients with primary CNS lymphoma (PCNSL). Monitoring BBBD is of great interest in terms of brain drug delivery and maybe in the future in other diseases like dementia. Clinical PCNSL therapy and BBBD techniques that are currently in preclinical development provide us models to investigate the effects of BBB opening and its relation to glymphatic brain clearance.

INVITED C12:

Thermo-Optical Nonlinearity of a Single Metallic Nanoparticle

Ieng-Wai Un[1, 2] and Yonatan Sivan[1*]

[1] *Unit of Electro-optics Engineering, Faculty of Engineering Sciences, Ben-Gurion University of the Negev, Israel*

[2] *Taiwan Israel Institute (TIX), National Tsing-Hua University, Taiwan*

[*] *sivanyon@bgu.ac.il*

The optical nonlinearities are intrinsically weak in most common materials. Many efforts have been devoted to the enhancement of optical nonlinearity by local field engineering [1]. In this analysis, quite different from many previous studies of nonlinear effects of composites or uniform film in the ultrafast region, we consider the nonlinear scattering from a single metallic nanoparticle due to the thermal effects under continuous-wave (CW) intensive illumination. Specifically, the thermal effect [2,3] is known to be one of the strongest mechanism of optical nonlinearity but is usually avoided in the ultrafast region. It was shown [2,3] to be able to qualitatively explain the experimental results of the strong nonlinear scattering from sufficiently small Au nanoparticle [4,5].

By using the best experimentally measured data of the temperature dependent permittivities of bulk gold, going beyond the quasi-static approximation, approximately modeling by Mie theory with spatial independent parameters as well as exactly modeling by simulation, we calculate the temperature and scattering cross section of the nanoparticle of finite size. We show that, quite counterintuitively, the particle temperature changes with its size non-monotonically, as shown in Fig. 1 (a). Such non-monotonic behavior can be understood by the redshift of electric dipole resonance and the quadrupole mode kicking in as the particle size increases. Further, we demonstrate that the nonlinear scattering coefficient of the second order depends on the particle size significantly as shown in Fig. 1 (b), which is somehow related to the non-monotonic dependence of the particle temperature on the particle size. Furthermore, our numerical model also shows much better agreement with the nonlinear scattering measurement results than the previous studies as shown in Fig. 1 (c).

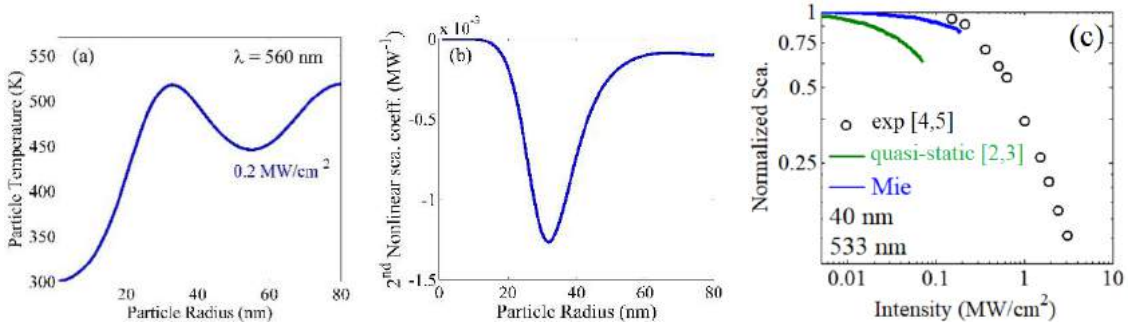


Figure 1. Size dependence of (a) the particle temperature at fixed incident intensity and (b) 2nd nonlinear scattering coefficient. (c) Comparison among measurement [4,5], Mie (blue) and the quasi-static (green) model [2,3].

The comparison among various modeling methods allows us to further quantitatively identify the most relevant physical effects contributing to the thermo-optical nonlinearity of many other systems of finite size such as silicon and graphene. This study also provides a comprehensive design of highly thermal-optical metamaterials for applications such as photothermal imaging and all-optical switching.

References:

[1] M. Lapine, I. V. Shadrivov, and Y. S. Kivshar, Reviews of Modern Physics **86**, 1093 (2014).
[2] I. Gurwich and Y. Sivan, Physical Review E **96**, 012212 (2017).
[3] Y. Sivan and S.-W. Chu, *Nanophotonics* **6**, 317 (2017).
[4] Y.-T. Chen *et al.*, ACS Photonics **3**, 1432 (2016).
[5] S.-W. Chu *et al.*, Physical Review Letters **112**, 017402 (2014).

INVITED C13:

Theranostic activity-based probes-Development and Applications

Georgia Sotiropoulou*, Evangelos Bissyris, Georgios Pampalakis

Department of Pharmacy, School of Health Sciences, University of Patras, Rion-Patras 265 04, Greece

**E-mail: gdsotiro@upatras.gr*

In vivo, enzymes are regulated at multiple levels (activation, deactivation by cleavage or inhibitor binding, aberrant subcellular localization, *etc*), consequently, protein abundancies determined by antibody-based methods or proteomics do not always reflect actual enzymatic activities underlying (patho)physiology. Such discrepancies often complicate drug development and could be linked to drug failure. The levels of active enzymes, such as the serine proteases, can be determined using activity-based probes (ABPs), small molecules that bind selectively to the catalytic site of the active enzyme enabling detection *via* a reporter tag which is adaptable to versatile analytical platforms (fluorescence, *in vivo* imaging, chromogenic). Kallikrein-related peptidases (KLKs), on the other hand, are emerging diagnostic and therapeutic targets for different human disease including inflammatory and overdesquamating skin disorders, where their unopposed activities are directly linked to the severe, often fatal, clinical phenotype. We designed a new ABP (B24P) and used it to develop a quick, easy-to-perform and versatile histochemical technique named “activography” (Pampalakis et al. Chem Commun 53:3246-3248, 2017) that we used to quantify and spatially localize active serine proteases/KLKs in tissue biopsies. We will present on a novel ABP with discriminating specificity for a selected KLK enzyme that accommodates dual properties on the same scaffold, *i.e.* it binds specifically and selectively to the active form of the target enzyme and can also inhibit its activity, irreversibly. Thus, it could be exploited both in molecular diagnosis and as a candidate drug compound for pharmacological targeting (theranostic). We proof-of-concept validated the potential therapeutic effect of this KLK-ABP in a preclinical (mouse) model of a rare disease for which no therapy exists, thus, such ABP inhibitors would represent a breakthrough.

INVITED C15:

Novel developments and biomedical applications of multi-spectral optoacoustic tomography

X. Luís Deán-Ben and Daniel Razansky
Technical University of Munich and Helmholtz Center Munich, Germany
Email: dr@tum.de

Optoacoustic imaging is increasingly attracting the attention of the biomedical research community due to its excellent spatial and temporal resolution, centimeter scale penetration into living tissues, versatile endogenous and exogenous optical absorption contrast. State-of-the-art implementations of multi-spectral optoacoustic tomography (MSOT) are based on multi-wavelength excitation of tissues to visualize specific molecules within opaque tissues. As a result, the MSOT technology can noninvasively deliver structural, functional, metabolic, and molecular information from living tissues [1]. Our recent efforts in the field of optoacoustic functional and molecular imaging have established new technological platforms employing spherical matrix arrays, parallel acquisition hardware, GPU-based data processing and fast-tuning laser systems in order to enable acquisition and visualization of spectroscopic information from entire tissue volumes at video rates [2]. This has set the stage for the so-called five dimensional (real-time three-dimensional multi-spectral) optoacoustic imaging that offers unparalleled capabilities among the existing bio-imaging modalities. Biomedical applications are explored in the areas of functional neuro-imaging, fast tracking of agent kinetics and biodistribution, cardiovascular research, monitoring of therapies and drug efficacy as well as targeted molecular imaging studies. Handheld optoacoustic systems are further transforming optical imaging by offering novel precision in clinical observations of patients, demonstrating high diagnostic efficacy in a number of indications, such as breast cancer, inflammatory bowel disease and lymph node metastases.

References:

[1] X. L. Deán-Ben, S. Gottschalk, B. McLarney, S. Shoham, D. Razansky. Advanced optoacoustic methods for multi-scale imaging of in vivo dynamics. *Chem Soc Rev* 46, 2158-2198 (2017)

[2] X. L. Deán-Ben and D. Razansky. Adding fifth dimension to optoacoustic imaging: volumetric time-resolved spectrally-enriched tomography. *Light Sci Appl* 3, e137 (2014)

ORAL C1:

Optimization of photodynamic effects on the blood-brain barrier permeability

A. Terskov[1], N. Navolokin[2], A. Shirokov[3], A. Bodrova[1], N. Shushunova[1], A. Khorovodov[1], I. Agranovich[1], T. Iskra[1], A. Mamedova[1], O. Semyachkina-Glushkovskaya[1]

[1]Saratov State University, Astrakhanskaya Str. 83, Saratov, 410012, Russia
[2]Saratov State Medical University, Bolshaya Kazachaya Str. 112, Saratov 410012, Russia
[3]Institute of Biochemistry and Physiology of Plants and Microorganisms, Russian Academy of Sciences, Prospekt Entuziastov, 13, Saratov, 410049, Russia

Corresponding authors: Semyachkina-Glushkovskaya Oxana – glushkovskaya@mail.ru
Terskov Andrey - terskow.andrey@gmail.com

In our previous work we clearly show that photodynamic effects (PD) causes a significant increase in the permeability of blood-brain barrier (BBB) in healthy mice (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5695951). Here using laser radiation (635 nm, 10-40 J/cm^2) and photosensitizer (5-aminolevulinic acid – 5-ALA, i.v.), we studied effects of different laser doses on the BBB with the aim to optimize the PD-related opening of the BBB and minimize negative consequences of this procedure.

It was found that the laser fluence (15 J/cm^2) is optimal for opening of the BBB without serious disorders of cerebral tissues and vessels. The laser fluence of 20-40 J/cm^2 did not cause a more pronounced increase in the BBB permeability, however, high laser fluences induced severe vasogenic edema and changes in the shape of cerebral vessels.

These results are an informative platform for further studies of new strategies in brain drug delivery and for better understanding of mechanisms underlying cerebrovascular effects of PD-related fluorescence guided resection of brain tumor.

This study was supported by a grant from the Russian Science Foundation (Grant No. 17-75-20069)

ORAL C2:

Evanescent wave dynamic light scattering by proteins in mixed saliva under influence of electric field

Ekaterina Savchenko

Engineer of Higher school of Applied Physics and Space Technologies
Institute of Physics, Nanotechnology and Telecommunications,
Peter the Great St. Petersburg Polytechnic University, Russia

Mixed saliva of a human is a unique biological liquid that has a great opportunity for use in fundamental research and in the early diagnosis, prognostication, and monitoring post therapy status [1]. Mixed saliva has been considered for monitoring diseases like cancer, autoimmune, viral, bacterial, cardiovascular, and metabolic, hormonal analysis and drug level monitoring [1]. At present, mixed saliva is investigated by various biochemical, chromatographic and optical methods. With the advent of the laser and advances in electronics, optical methods, such as scanning electron microscopy, sedimentation analysis, nephelometry, static and dynamic light scattering, have become the most universal and accurate tools for estimating the parameters of proteins [2]. One of the most informative and promising techniques for studying bimolecular fluids and in particular, protein molecules is evanescent wave dynamic light scattering (EWDLS).

The advantages of EWDLS are as follows [3]:

- Non-invasiveness and availability (as compared with the atomic force and electron microscopic techniques);
- A wide range of particles that can be investigated in a liquid medium (sizes from units to thousands of nanometers);
- A small amount of the object required for the study (less than a few microliters);
- The near surface dynamics investigation;
- Observation of fast time-dependent phenomena and kinetic fluctuations.

The typical scheme of EWDLS experiment consists of laser, glass prism, photomultiplier, analog-to digital convertor, computer. Semiconductor laser (650 nm) with 2.5 mW power was used in this work because in the red spectral range a saliva's absorption was minimal. In the experiments of EWDLS, only the region of the sample close to the boundary is illuminated, as the electric field strength of an evanescent wave decays with distance z away from the wall as exp(kz/2) [3]. The characteristic length scale 2/k, called the penetration depth, is typically of the order of several hundred nanometers. Using this feature, we can obtain information on the effects of hydrodynamic interactions with the surface on the dynamics of suspended colloids. Also EWDLS allows us to measure translational diffusion and radius of proteins.

Mixed saliva is multicomponent liquids and it need to separate mixture into fractions or individual substances before studying. In this work the mixed saliva from a healthy patient and patient with diseases was studied under influence of electric field. We modified experimental setup by adding two electrodes on the top side of the prism. In this case the proteins of mixed saliva migrates to the opposite charge electrode and it begins to separate into its constituent components due to differences in their electrophoretic mobility. This mobility is converted into zeta potential to enable comparison of molecular solution under different

conditions [4]. In the case of proteins, the measurement of protein mobility allows us to calculate the protein charge, which in turn is related to factors such as activity and kinetics of chemical reaction.

The experimental results confirmed possibilities of the EWDLS under influence of electric field to determine parameters of proteins (size, zeta-potential) and separate them by electrophoretic mobility in mixed saliva. It was shown that the difference of parameters between healthy patient and ill patient can be registered. Obtained results were compared with results from blood plasma.

References:

1. Malathi N., Sabesan M., Hannah R.V., "Salivary diagnostics: a brief review," ISRN dentistry, 2014.
2. Jachimska B., Wasilewska M., Adamczyk Z., "Characterization of globular protein solutions by dynamic light scattering, electrophoretic mobility, and viscosity measurements," Langmuir vol. 24, no 13, pp.6866-6872, 2008.
3. Lisicki M., Cichocki B., Rogers, S., Dhont J., Lang P., “Translational and rotational near-wall diffusion of spherical colloids studied by evanescent wave scattering,” Soft Matter. vol.10. pp. 4312–4323, 2014.
4. Makino K., Ohshima H., “Electrophoretic mobility of a colloidal particle with constant surface charge density,” Langmuir. vol. 26. no 23. pp. 18016–18019, 2010.

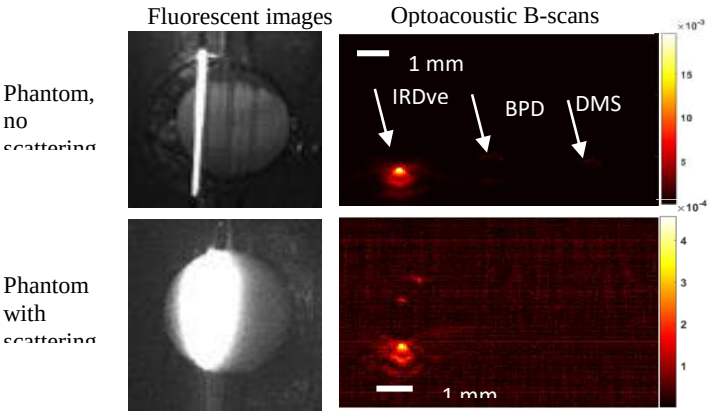
ORAL C3:

Complementary bimodal approach to monitoring of photodynamic therapy with target nanoconstructs: numerical simulations and phantom study

I.V. Turchin[1], M.Yu. Kirillin[1], D.A. Loginova[1], V.V. Perekatova[1], A.G. Orlova[1], E.A. Sergeeva[1], V.I Plekhanov[1], A.V. Khilov[1], P.V. Subochev[1], S. Mallidi[2] and T. Hasan[2]

[1] Institute of Applied Physics of the Russian Academy of Science,603950, Nizhny Novgorod, Russia
[2]Wellman Center for Photomedicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114

We propose a new approach to monitoring of photodynamic therapy (PDT) of glioblastoma with the use of targeted nanoconstructs containing a photosensitizer (PS) benzoporphyrin derivative (BPD) and IRDye800 dye, antibodies for efficient accumulation of the drug in a tumor, and a chemotherapeutic agent for combined effect on tumor cells. Monitoring of PDT is based on the simultaneous fluorescent and optoacoustic (OA) imaging. Fluorescent imaging provides visualization of fluorescence agents with high molecular sensitivity, and monitoring of the effectiveness of PDT by PS photobleaching. OA allows to examine the vascular pattern of the tumor environment, as well as assess the tumor depth . IRDye800 is a better contrast agent in comparison to BPD due to red shifted spectral characteristics and higher fluorescence quantum yield. Monte Carlo simulations combined for OA imaging with K-wave modeling allowed to study the feasibility of the complementary approach and demonstrated that this combination allow one to localize a tumor with a size of 2 mm at depths from 100 μm to 2 mm. The results of numerical simulations have been verified in phantom studies using fluorescence and optoacoustic experimental setups and an agar phantom with optical characteristics similar to those of murine brai



Fluorescent images (left) and OA-B-scan of a phantom with plastic 400 micron tubes containing IRDye in DMSO, BPD in DMSO and pure DMSO with (upper row) and without (bottom row) turbid medium mimicking murine brain tissue. Images were obtain under 785 nm laser excitation.

The work was carried out as part of the RFBR project 17-54-33043 onko-a.

ORAL C4:

Interaction of nanostructured gold with light and bioapplications of gold- and gold-shell nanoparticles

E. Perevedentseva[1,2], O. Bibikova[3,4], N.Ali[3], A. Karmenyan[1], Y.C. Lin[1], C.C. Chang[1], I. Skovorodkin[3], R. Prunskaite-Hyyryläinen[3], S. Vainio[3], C.L. Cheng[1*], M. Kinnunen[4]**

[1]Physics Department, National Dong Hwa University, Hualien, Taiwan

[2]P.N. Lebedev Physics Institute of Rus. Acad. Sci., Moscow, Russia

[3]Biocenter Oulu, University of Oulu, Oulu, Finland

[4]Opto-Electronics and Measurement Techniques Research Unit, Faculty of Information Technology and Electrical Engineering, University of Oulu, Oulu, Finland

elena@gms.ndhu.edu.tw, *clcheng@gms.ndhu.edu.tw, **matti.kinnunen@oulu.fi

Interaction of nanostructured surfaces of noble metals with electromagnetic radiation is in large degree based on surface plasmons - collective oscillations of the electrons of conductivity. The effects of local field enhancement resulting in an increased absorption or scattering of light by noble metal nanostructures and nonradiative energy transfer from fluorophore to the nanostructure leading to a decrease of the quantum yield and luminescence quenching that are competing in such system. Plasmonic properties of these metallic nanostructures offer possibilities for developing novel methods of biosensing, based on detection of plasmonic resonance and surface enhanced Raman scattering (SERS). Additionally, other physical properties of such nanostructures, particularly nanoparticles (NP) of various size, shape and structure, allow using them for bioimaging, including 2-photon excitation and photoacoustics; photothermal and other treatments; for combining sensing and imaging functionalities with drug delivery.

In present work Au NP (Au nanostars, AuNS [1]) are considered in terms of their multifunctional applications in biomedical research and theranostics. The NP interaction with cell, tissue and 3D tissue model, zebrafish embryo *in-vivo* is demonstrated and analyzed using the 2-photon imaging, fluorescence lifetime imaging (FLIM), optical coherence tomography (OCT), and fluorescence confocal imaging. We also discuss the penetration and distribution of NP and into target, and how the NP influence the biosystem of the target. Moreover, prospective of theranostic applications are suggested and compared with other kinds of plasmonic or hybrid [2] NP.

[1] O. Bibikova, A. Popov, A. Bykov, A. Fales, H. Yuan, I. Skovorodkin, M. Kinnunen, S. Vainio, T. Vo-Dinh, V. Tuchin. Plasmon-resonant gold nanostars with variable size as contrast agents for imaging applications. IEEE J Selected Topics in Quantum Electronics 22(3), 2016, DOI 10.1109/JSTQE.2016.2526602.

[2] L. Minati, C.L. Cheng, Y.C. Lin, J. Hees, G. Lewes-Malandrakis, C.E. Nebel, F. Benetti, C. Migliaresi, G. Speranza. Synthesis of novel nanodiamonds–gold core shell nanoparticles. Diamond Relat Mater 53 23-28, 2015

ORAL C5:

Fiber optic solutions for laser delivery and spectroscopy in medical applications

O. Bibikova,[1] E. Zherebtsov,[2] I. Usenov,[1] T. Sakharova,[1] U. Zabarylo,[3] E. Oleneva,[4] S. Sokolovski,[2] O. Minet,[5] D. Kirsanov,[4,6] E. Rafailov,[2] V. Artyushenko[1]

1. art photonics GmbH, Berlin, Germany
2. Aston Institute of Photonic Technologies, Aston University, Birmingham, United Kingdom
3. Berlin-Brandenburg School for Regenerative Therapies, Charité – Universitätsklinikum Berli n, Campus Virchow Klinikum, Berlin, Germany
4. Laboratory of artificial sensory systems, ITMO University, St. Petersburg, Russia
5. Medical Physics & Optical Diagnostics, CC6 Campus Benjamin Franklin, Charité Universitätsmedizin Berlin, 12203 Berlin, Germany
6. Institute of Chemistry, St. Petersburg State University, St. Petersburg, Russia

Fiber optics is a key technology for the photonics applications, providing a flexible mechanism for delivering the output from laser sources in biological and medical applications. As an example, high power cables based on Mid-IR-fibers are widely used in combination with CO and CO_2 lasers for welding and coagulation of biotissues during surgery. To compare the effectiveness of tissue welding and coagulation for fiber equipped CO and CO_2 lasers, several types of animal tissues were treated in comparable conditions. In all cases, CO_2 laser shows the best cutting ability with greater deepness, while CO laser produces larger coagulation zone both measuring next to the cut (side coagulation) and measuring below the cut (vertical coagulation). For deeper understanding of physical processes in the biotissue under laser treatment, the fluorescence parameters in fresh samples were measured before and after thermal exposure by IR lasers. Specially developed needle probe with diameter 1.2 mm were used to allow penetration in some depth of tissue and collection of the most reliable spectral information both under and on the tissue surface.

Fiber optic based spectroscopy, being reagent free, can rapidly and non-invasively detect changes in the biochemical composition of cells and tissues at the molecular level, which is extremely important in brain studies. As an illustration, we present the results of *in vitro* fluorescence and NIR spectra measurements of archived paraffin blocks with rat glioma C6 biopsy materials. A particular interest of this work was to study the fiber optic probe performance in case of heterogenic surrounding of a tumor: ventricles, cerebellum, etc. Investigations of the fluorescence lifetime in fresh sections of the mice brain is presented as well.

Diffuse NIR-reflection, Raman and fluorescence spectroscopy as the key spectroscopic techniques were used and compared for investigation of surgically removed brain tissue samples (normal and tumour samples). Obtained spectral data were evaluated by multivariate discrimination analysis to enable clear separation of different types of malignant tissues.

ORAL C6:

Fractional laser treatment of soft oral tissues: in vivo and ex vivo study

Karabut Maria[1], Shatilova K.[2], Aloian G.[3], Snopova L.[1], Ryabova V.[1], Yaroslavsky I.[4], Altshuler G.[4]

[1] Privolzhsky Research Medical University, Nizhny Novgorod, Russia,
[2] NTO IRE-Polus, One Vvedenskogo Sq., Fryazino, Russia;
[3] Moscow Institute of Physics and Technology, Moscow, Russia;
[4] IPG Medical Corp., Marlborough, MA, USA

Regeneration of periodontal soft tissues is an important objective in periodontal therapy. In this study, a minimally invasive microsurgical approach, also known as fractional laser treatment, has been used to initiate gingival or oral mucosa tissue regeneration. Two lasers were used: a diode laser (wavelength 980 nm, peak power 20 W) and an Er fiber laser (wavelength 1550 nm, peak power 25 W).

In vivo animal study with diode laser has shown that regeneration of tissue structure is completed 28 days after laser treatment; no undesirable side effects in the zone of local laser damage and surrounding tissues occurred. Observation at 3 months follow up of fifteen patients with peridontitis after a single fractional treatment showed a significant decrease in the depth of periodontal pockets ($p=0.015$) in the treatment group compared with controls. Moreover, the first clinical case of hyperpigmentation removal using fractional laser treatment was demonstrated.

The first ex vivo animal study using porcine tissue model and NBTC staining with fractional Er fiber laser investigated effects of pulse energy, beam diameter, and beam divergence in detail. It has been demonstrated that under optimal conditions columns up to 800 μm in depth could be reliably produced with 130 mJ pulses. Clinically, 2 subjects were treated and 4 punch biopsies were collected. It was found that Er fiber 1550 nm laser can produce coagulation columns with the histological characteristics close to those created with 980 nm diode laser. Combined with the positive clinical experience of using the 980 nm diode laser for fractional treatment of gums, results of this study provide a reasonable ground for a future clinical research directed at elucidating clinical benefits of using the fractional 1550 nm Er fiber laser in dental setting.

ORAL C7:

Optical biopsy of abdominal tissues in mini-invasive surgery

Viktor V. Dremin[1], Evgeny A. Zherebtsov[1], Elena V. Potapova[1], Ksenia Yu. Kandurova[1], Andrian V. Mamoshin[1,2], Alexander L. Alyanov[1,2], Andrey V. Dunaev[1]

[1]Research and Development Center of Biomedical Photonics, Orel State University, Orel, Russia
[2]Orel Regional Clinical Hospital, Orel, Russia

The recent development of the instrumental methods for two- and three-dimensional imaging allows one to upgrade minimally invasive surgical methods for the abdominal organs to a new level. This type of surgical interventions makes possible to achieve recovery with minimal trauma, reducing the incidence of complications, effectively maintaining and restoring affected organs functions. This leads to an improvement of quality and life expectancy of patients, optimizing the economic component of the treatment process.

Currently, the general problem of available diagnostic methods for a surgeon, performing minimally invasive interventions, is the inability to monitor perfusion and metabolic processes in the biological tissue in real-time mode during the surgery intervention. Microcirculatory disorders play a central pathogenetic role in the progression of various diseases of abdominal organs. Therefore, the measurements of microcirculation have the potential to become a new tool for the optical image-guided surgery. Newly emerging methods for optical biopsy are one of the most promising directions to provide the surgeon with vital information about the state of tissues in operative site.

This work presents recent results on the development and validation of the optical biopsy technique based on the multimodal approach and applied for both optical fiber probe measurements and imaging.

At first stage, a fiber optic system has been developed to be applied in minimally invasive surgical interventions and allows for assessing the vitality of biological tissues during the procedures. The method combines data obtaining by fluorescence spectroscopy and laser Doppler flowmetry in one diagnostic classifier. The sensitivity of the tool has been assessed for several types of pathological changes in abdominal tissues. The technology augmented by the measurements of the diffuse reflectance has been implemented in a form factor of a fine-needle optical probe for the optical biopsy. The probe is of 1 mm outer diameter, and has been developed to be compatible with the 17.5G biopsy needle. The studies have been combined with the standard procedure of the biopsy sampling. The obtained results demonstrate a significant increase in the specificity and sensitivity for the classifier based on the multimodal approach compared with ones based on the two optical measurement techniques applied separately.

To test the approach for imaging, a setup combining hyperspectral imaging and laser speckle contrast measurements through standard minimally invasive surgical tools has been developed and tested in an animal model. In trials in the animal model of acute pancreatitis, the technique has demonstrated to be a useful tool for the mapping of the necrotic areas of the pancreas.

The proposed techniques promise to be a robust, useful tool in diagnostics of the profound changes in tissue perfusion and metabolism for the practice of guided surgery to objectify the criteria for selecting surgical tactics.

The study was funded by the Russian Science Foundation according to the research project №18-15-00201.

ORAL C8:

The effectiveness of interventional procedures in patients with tumor lesion of bile ducts

Andrian V. Mamoshin[1,2], Alexander L. Alyanov[1,2], Ksenia Yu. Kandurova[1], Alexey V. Borsukov[3], Yuriy V. Ivanov[4], Vadim F. Muradyan[2]

[1]Research and Development Center of Biomedical Photonics, Orel State University, Orel, Russia
[2]Orel Regional Clinical Hospital, Orel, Russia
[3]Problem Scientific-Research Laboratory "Diagnostic researches and miniinvasive technologies" of Smolensk State Medical University, the Ministry of Health of Russian Federation, Smolensk, Russia
[4]Federal Scientific and Clinical Center for Specialized Medical Service and Medical Technologies, Moscow, Russia

In recent decades, there has been an increase in patients with malignant tumors of hepatopancreatoduodenal organs complicated by obstructive jaundice. The problems of diagnosis and treatment of patients with this pathologies continue to be relevant at the present time. Use of interventional procedures to solve these issues is increasing along with endoscopic ones. However, these procedures still require more methods of acquiring of diagnostic information during intervention.

The aim of the work is evaluation of the effectiveness and study of the results of interventional procedures application in diagnostic and treatment of malignant tumors of hepatopancreatoduodenal organs complicated by obstructive jaundice.

Interventional procedures were used in 277 patients with mechanical jaundice syndrome. The causes of mechanical jaundice were: pancreatic head cancer - 160 patients, cholangiocarcinoma - 60 patients, gallbladder cancer - 13 patients, bile papilla cancer - 11 patients, regional metastasis - 32 patients, duodenal cancer - 1 patient. All patients underwent antegrade access to the bile-excreting tracts under ultrasound and X-ray control.

Through the drainage channel, fluorescence spectroscopy and laser Doppler flowmetry methods were used as well. These methods were aimed at assessing metabolic processes, blood microcirculation parameters and pathological changes and condition of tissues blocked and not blocked by tumor.

In each case percutaneous transhepatic cholangiography with percutaneous transhepatic cholangiostomy was performed for closer definition of level and degree of the block. After bilirubin level lowering, further examination and stabilization of patients, the questions of the possibility of performing open surgical treatment, transfer of external cholangiostoma into external-internal one or antegrade endobiliary stenting were decided. For several patients, this type of intervention was the final surgical tool aimed at improving the quality of life. A total of 370 interventional procedures were performed. Complications after the interventions occurred in 64 cases. Lethal outcomes occurred in 21 patients due to the progression of underlying disease and multi-organ failure.

The results of measurements by optical methods showed the sensitivity to the state of tissues, which will be used later for development of new diagnostic criteria and special tooling to provide additional diagnostic information during interventional procedures.

In general. interventional procedures are important modern surgical strategy for treating obstructive jaundice

caused by malignant tumors of hepatopancreatoduodenal organs. Thus, the use of interventional technologies makes it possible to early clarify the nature of bile duct obstruction, effectively reduce biliary hypertension, improve the overall condition of patients, and determine a further treatment process.

The study was funded by the Russian Science Foundation according to the research project №18-15-00201.

ORAL C9:

Surface chemistry controls the uptake of Gold nanorods by macrophages

Ruchira Chakraborty[1], Dorit Leshem-Lev[2], Dror Fixler[1]

1 Faculty of Engineering and Institute of Nanotechnology and Advanced Materials, Bar-Ilan University, Ramat-Gan, 5290002, Israel.

2 Cardiac Research Laboratories at the Felsenstein Medical Research Center and the Cardiology Department, Rabin Medical Center, Petah-Tikva, Israel.

In recent days gold nanorods (GNR) catch the eyes not only with their unique optical behavior, but also for a wide variety of application in the field of the diagnostics and therapy. When it comes to the case of *in vivo* studies, monitoring the pattern on interaction of nanoparticles with the immune cells are very important. Macrophages, the proficient phagocytic immune cells, differentiated from monocytes, play a major role in our innate immunity. Recently macrophages after uptake of nanoparticles are used as vehicle for drug delivery for cancer or, as diagnostic tool for atherosclerosis. Though macrophages can internalize the GNRs by phagocytosis, still the surface charge and presence of particular linker can bring a huge change in the uptake and cytotoxicity pattern of GNRs. In this study we took three different types of macrophages – macrophages isolated from blood of healthy donor, macrophages differentiated from THP1 human monocyte cell lines and RAW 264.7 murine macrophage cell line, and compared their change in viability and uptake of GNRs. We chose GNRs of same aspect ratio with different zeta potential. GNRs with positive zeta i.e. cetyl trimethylammonium bromide (CTAB), poly allylamine hydrochloride (PAH) internalized more than the GNRs with null i.e. poly ethylene glycol (PEG) or negatively charged surface i.e., poly sodium 4-styrenesulfonate (PSS), citrate. But because of high toxicity CTAB GNRs effect on cell viability, whereas PAH GNRs showed less toxicity. Over all RAW 264.7 showed more uptake than macrophages from PBMC. This study draws an idea on how surface modifications of GNRs affect their uptake by macrophages.

Keywords: Macrophages, Gold nanorods (GNRs), zeta potential, cellular uptake, viability.

ORAL C10:

Comparative analysis of regimes in single and dual-wavelength photodynamic therapy assisted by optical monitoring

M.A. Shakhova[1,2], A.V. Khilov[1], D.A. Loginova[1], O.A. Orlova[1], E.A. Sergeeva[1], A.E. Meller[1,2], A.V. Shakhov[1,2], N.Yu. Orlinskaya[2], I.V. Turchin[1], and M.Yu. Kirillin[1]

1 - Institute of Applied Physics RAS, Nizhny Novgorod, Russia
2 – Privolzhsky Research Medical University, Nizhny Novgorod, Russia

Main author email address: maha-shakh@yandex.ru

Photodynamic therapy (PDT) is a modern minimally invasive multifactor treatment technique. Its efficiency was demonstrated in treatment of oncologic pathologies, inflammatory diseases of various localizations, and in aesthetic medicine due to photodynamic reactions. The basic photodynamic effects inducing the PDT mechanism are cytotoxic impact on cells, tumor vasculature damage and immune response. Employment of chlorine E6 based photosensitizers (PS) allows for optimization and personification of a PDT procedure due to two pronounced absorption peaks in blue and red optical ranges (402 nm, 662 nm). However, efficient personification of PDT treatment requires for treatment monitoring. Employment o non-invasive optical diagnostics techniques allows to improve PDT protocols. Fluorescent properties of photosensitizers ensure additional diagnostic abilities. Dual-wavelngth fluorescence imaging allows for monitoring of PS accumulation, distribution and photobleacing prior to and in course of PDT procedure [1,3]. Monitoring of structural and functional changes in tissue with optical coherence tomography (OCT) provides evaluation of immediate and long-term response to the procedure. It is worth to note, that recent OCT-angiography modality allows to monitor microcirculation in course of PDT treatment [4].

In present paper we study the effects of different PDT regimens with topically applied chlorin e6 base PS (“Revixan derma” (Revixan Ltd., Russia) on structural and functional properties of intact and tumor tissues in laboratory animals in vivo. Fluorescence imaging (Fluovizor, IAR PAS, Russia) was employed to monitor PS photobleaching in course of procedure while OCT (OCT-1300E device, IAP RAS, Biomedtech, Russia) was employed to acquire structural and functional images to monitor immediate and long-term tissue response. Tissue temperature measurements prior to and after procedure was performed with IR thermometer Optris. Biopsy for morphological verification was taken in 1, 3, and 7 days after the procedure. Standard histopathologic study (hematoxyline-eosine staining) was accompanied by immunohistochemical study (Ki-67 staining) allowing to evaluate proliferative activity in vessels endothelium that serves an indicator for angiogenesis.

In experiments on intact tissue PDT regimens with irradiation at 405 and 660 nm were studied with the light doses of 75, 100, and 150 J/cm^2 together with combo regimen with a total dose of and 150 J/cm^2 (75 J/cm^2 at 405 nm and 75 J/cm^2 at 660 nm). The chosen doses agree with typical doses employed for antimicrobial action and in aesthetic medicine [1,2]. Morphological and functional alterations (edema, plethora, stasis, neoangigenesis) are demonstrated to be dependent of the chosen PDT regimen.

Experiments with tumor tissues were conducted on Balb/c laboratory mice with Colo-26 tumor models. The regimens with the total dose of 200 J/cm^2 at the wavelength of 405 nm was studied for different

irradiation intensities and tumor localizations. The PDT response was demonstrated to be highly dependent both on the intensity and tumor localization.

The optical diagnostics data are in good agreement with the results of histopathology studies.

The study is supported by Russian Science Foundation, project 17-15-01264.

[1] A. Khilov et al, Two-Wavelength Fluorescence Monitoring and Planning of Photodynamic Therapy, CTM, 9, 96–105 (2017).
[2] M. Shakhova et al, Photodynamic therapy with chlorin-based photosensitizer at 405 nm: numerical, morphological and clinical study, J. Biomed. Opt., , 23(9), 091412 (2018).
[3] M. Kleshnin et al, Compact and fully automated system for monitoring photodynamic therapy, based on two LEDs and a single CCD. Laser Phys. Lett.; 12, 115602 (2015).
[4] A. Moiseev et al, OCT-based angiography device with real-time angiography B-scans visualization and hand-held probe for everyday clinical use, J. Biophotonics, e201700292 (2018).

ORAL C11:

He-Ne laser irradiation stimulates anabolism in cultured chondrocytes by enhancing subcellular ultrastructure and increasing extracellular matrix secretion

Xiaohong Yanga, Shaojie Liua, Timon Cheng-yi Liub, Weicong Zhua, Peihong Lianga and Shuliang Cuiaa

Guangzhou Institute of Traumatic Surgery, Guangzhou Red Cross Hospital, Jinan University School of Medicine, Guangzhou, P R China; bCollege of Sport Science, South China Normal

Background/Aims: Both physiologic remodeling and pathologic regeneration of cartilage tissue rely upon secreting activities of the only resident cell type, chondrocytes, which are particularly changed profoundly in many aspects, including their capability of growth and secretion when cultured ex vivo. Factors that promote viability and inhibit apoptosis of the chondrocytes, and associated mechanisms, would be important stimuli for modulating chondrocytic viability and secretion, including highly accessible laser irradiation. This study examined the effect of low intensity He-Ne laser irradiation (HNL) on ultrastructural enhancement and secretion of extracellular matrix cultured chondrocytes.

Methods:
Chondrocytes isolated from 3-week old rabbit cartilage were cultured and treated by an output intensity of low level HNL (5.74 mW/cm2) for 30 minutes daily for 6 days, then cultivated in nutrition-deficit medium for a week. The synthesis of type II collagen was estimated by measurement of hydroxyproline (Hpr) at the time points of day 2, 4, 6, 8, 10, and 12 in the cultured chondrocytes. The DNA synthesis in chondrocytes detected using acridine orange staining combined with confocal laser scanning microscope (CLSM) on day 9 after irradiated for the first 6 days by applying the above intensity daily. The details of cellular morphology and ultrastructure were observed using the scan electron microscope (SEM) and a transmission electron microscope (TEM), respectively.

Results: The synthesis of type II collagen was increased steadily in HNL treated chondrocytes. The level of DNA content and secreted matrix proteins of type II collagen and aggrecan in the cultured chondrocytes were increased by the HNL irradiation for the first 6 days as detected on day 9 of cultivation compared to untreated control cells. The HNL treated chondrocytes showed clearer structure of endoplasmic reticulum than that in control group.

Conclusion/Implication: HNL treatment ameliorates endoplasmic reticulum stress in chondrocytes generated by culture conditions in vitro, increases the secretion of matrix proteins such as type II collagen and aggrecan, and ultimately strengthens the viability of the chondrocytes cultured in monolayer in the given treatment and conditions, beneficial to approaches of cell-based therapies for cartilage repair by tissue engineering that demands viable cells expanded ex vivo.

ORAL C12:

Watt-level Tunable Narrow bandwidth Tm:YAP laser using a pair of Etalons for a biomedical applications

Salman Noach[1,#], Uziel Sheintop[1,], Eytan Perez[1], ,

1. *Department of Applied Physics, Electro-optics Engineering Faculty, Jerusalem College of Technology, Havaad Haleumi 21, Jerusalem, Israel*

Watt-level tunable, narrow band, end-pumped Tm:YAP laser is demonstrated. Spectral tunability of $35nm$ ranging continuously between $1917-1951nm$ with a spectral linewidth of $0.15nm$ FWHM was achieved. The tuning and spectral band narrowing were obtained using a pair of YAG Etalons. Watt-level output power was measured along whole laser tunable range, obtaining a maximal output power of $3.88W$ at $1934nm$. A slope efficiency of 44.8% is achieved for a maximal absorbed pump power of $12.1W$. The combination of the narrow bandwidth with tunability at those output power levels makes this laser a promising tool for bio-medical, some laser tissue interaction results will be shown.

Corresponding Author: salman@jct.ac.il

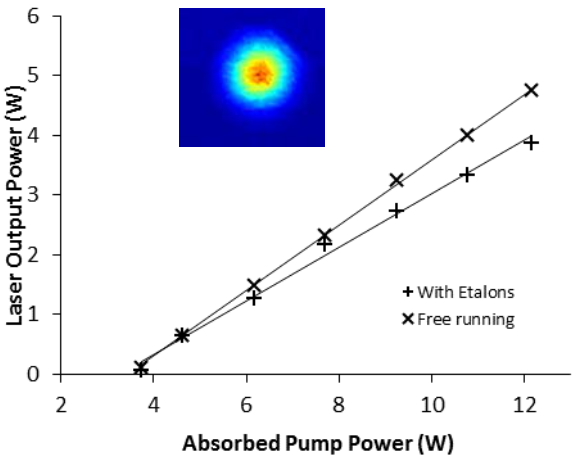


Fig 1. Laser performance and beam profile.

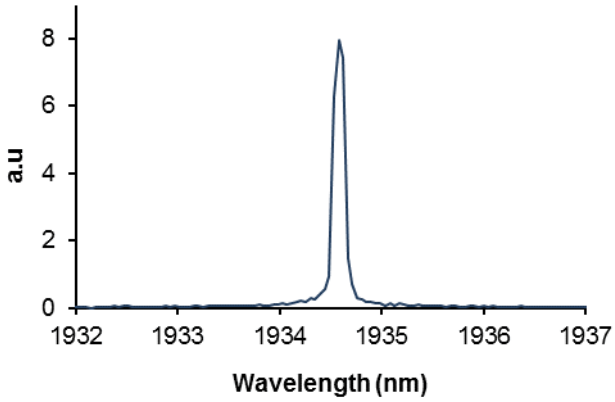
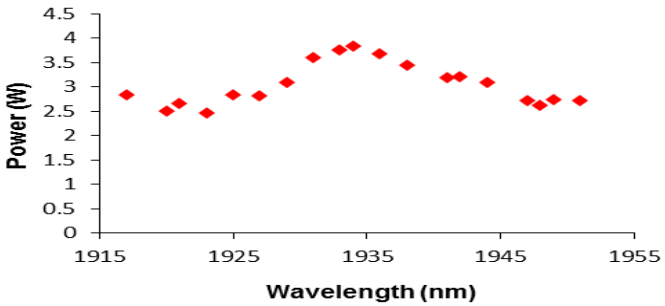


Fig. 2. Spectrum of the Tm:YAP laser using an Etalon pair.



\Fig. 3. Laser tunability performance

ORAL C13:

Cypate-mediated thermosensitive nanoliposome for tumor imaging and photothermal triggered drug release

Yuxiang Ma, Zhihao Han, Yueqing Gu*

(School of Engineering, China Pharmaceutical University, Nanjing, Jiangsu, China)

It is an emerging focus to explore a drug delivery system displayed a photothermal release of entrapped drug for simultaneous cancer imaging and therapy. We synthesized a novel multifunctional nano liposome drug delivery system, the photothermal sensitive liposome(PTSL), with doxorubicin wrapped in the hydropholic layer as the therapeutical agents and cypate dopped in the hydrophobic layer as the diagnostic agents. The physical properties, stabilities and loading properties of the liposomes were tested, the nano composites we synthesized were targeted, stable and delicate, with a drug loading (DL) of 9±1.5% and encapsulation efficiency (EE) of 82.7±2.1%. The Tm value falls on 43.1℃, the temperature of which can be regarded as the proper temperature which can show the thermal therapy effective as well as not burn the normal tissue. It can raise the temperature of liposome to the Tm of thermal sensitive liposome, the liposome cracks and the wrapped chemotherapy drugs release. At the same time, in the level of organelles, the PTSLs mainly located in the lysosomes or endosomes. When exposured to the NIR light, the cypate can incuce the producing of singlet oxygen, causing the crack of the organelle membrane. And the liposome can achieve the functions of target-delivery, enhanced photochemical internalized release, chemotherapy and thremal therapy, indicating that the PTSL is a kind of promising drug delivery system for tumor diagnosis and targeting therapy.

Keywords: Cypate, photothermal sensitive liposome, ERP effect Triggered release, Photothermal conversion

ORAL C14:

Synchronised wearable blood perfusion sensor system for constant microcirculation monitoring

E.A. Zherebtsov[a], I.O. Kozlov[b], E.V. Zharkikh[b], I.E. Rafailov[c], A.I. Zherebtsova[b], V.V. Sidorov[d], S.G. Sokolovski[a], A.V. Dunaev[b], and E.U. Rafailov[a]

[a]Aston Institute of Photonic Technologies, Aston University, Birmingham, UK
[b]Orel State University, Orel, Russia
[c]Aston Medical Technology Ltd., Birmingham, UK
[d]SPE "LAZMA", Moscow, Russia

Timely diagnostics of microcirculatory system abnormalities in many diseases is one of the important problems facing modern health care. Functional anomalies in microcirculation manifest themselves earlier than structural ones, and their registration is the matter of primary importance for early diagnostics. In this regard, optical measurements of blood ow dynamics are demonstrated to be promising methods for in vivo diagnostics of the microvascular blood ow parameters. In modern diagnostics, there are several commonly used optical non- invasive methods to diagnose the functional state of skin microcirculation. One of these methods is laser Doppler owmetry (LDF). At present, the LDF technique has shown promise for applications in the monitoring of cardiovascular parameters, sports and rehabilitation medicine. At the same time, conventional blood owmeters face several challenges, not only due to their large physical dimensions, but also their considerable di_culties in application for blood perfusion monitoring. Recent advances in VCSELs for biomedical applications open the door for implementation of LDF and dynamic light scattering (DLS) measurement techniques in new wearable form factors. The wearable imple-mentation of the techniques can signi_cantly improve the quality of diagnostics. Here, we introduce a novel non-invasive, wireless VCSEL-based diagnostic system for single and multipoint in vivo measurements of blood perfusion. The system comprises one or more wearable devices with an integrated LDF sensor, accelerometer and skin thermometer, and a wireless data acquisition module. Such an approach makes it possible to avoid _bre coupling losses as well as to decrease the movement artefacts. Furthermore, an implemented _ltering technique taking into account the accelerometer data allows the wearable sensor system to signi_cantly increase the signal to noise ratio value and decrease the movement artefacts to an acceptable level. The conducted tests of the system have con_rmed the ability of the LDF sensor to provide the same quality of blood perfusion signal as conventional desktop LDF monitors.The prototypes of the new wireless compact devices have been tested in trials with healthy volunteers of di_erent age and patients with diabetes. Subsequent wavelet coherence analysis of the LDF records has revealed statistically signi_cant age-speci_c di_erence in the synchronisation of blood ow oscillations in the groups under study. The collection of the advantages present in the LDF system introduced into a wearable format demonstrates that this technology can completely replace the conventional LDF monitors in the near future.

Keywords: Laser Doppler owmetry, VCSEL, wearable technologies, wavelet coherence, blood perfusion

Send correspondence to:
E.A.Z.: E-mail: e.zherebtsov@aston.ac.uk, Telephone: +44 121 204 3703

ORAL C15:

Label-free, real-time ultrasensitive monitoring of non-small cell lung cancer cell interaction with drugs

Hailang Dai[1,2], Zhuangqi Cao[1,2] and Xianfeng Chen[1,2,*]

1The State Key Laboratory on Fiber Optic Local Area Communication Networks and Advanced Optical Communication Systems, Department of Physics and Astronomy, Shanghai JiaoTong University, Shanghai 200240, China

2Collaborative Innovation Center of IFSA (CICIFSA), Shanghai Jiao Tong University, Shanghai 200240, China

Abstract: Timely discovery of cancer cell resistance in clinical processing and accurate calculation of drug dosage to reduce and inhibit tumour growth factor in cancer patients are promising technologies in cancer therapy. Here, an optofluidic resonator effectively detects drug interactions with cancer cell processing in real time and enables the calculation of label-free drug-NSCLC EGFR and binding ratios using molecular fluorescence intensity. According to clinical test and in vivo experimental data, the efficiencies of gefitinib and erlotinib are only 37% and 12% compared to AZD9291, and 0.300 μg of EGFR inactivation requires 0.484 μg of AZD9291, 0.815 μg of gefitinib and 1.348 μg of erlotinib. Experimental results show that the present method allows the performance detection of drug resistance and evaluation of dosage usage.

OCIS codes: (170.0170) Medical optics and biotechnology; (170.4580) Optical diagnostics for medicine; (170.6930) Tissue; (140.4780) Optical resonators; (140.0140) Lasers and laser optics.

1. Introduction

Erlotinib and gefitinib tyrosine kinase inhibitors (TKIs) were serendipitously found to be the most effective in advanced non-small cell lung cancer (NSCLC) clinical development [1]. They are reversible small-molecule ATP analogues originally designed to inhibit the TK activity of wild-type EGFR [2]. However, patients ultimately develop disease progression, often driven by the acquisition of a second T790M EGFR TKI resistance mutation [3]. AZD9291 is a novel oral, potent, and selective third-generation irreversible inhibitor of both EGFR-mutant sensitizing and T790M resistance mutants that spares wild-type EGFR [4, 5]. Unfortunately, although patients with EGFR-mutant tumours typically show a good initial response to TKIs, most tumour-tissue patients have a number of mechanisms that mediate EGFR TKI resistance [6-10] after approximately 9 to 14 months of continuous treatment [11-15]. Furthermore, these TKIs are associated with side effects that include skin rash and diarrhoea that are due to inhibition of wild-type EGFR in skin and gastrointestinal organs [16]. In the clinic, the keys of factors of chemotherapy failure are resistance and side effects. As a monotherapy, they have failed to overcome EGFR-mutant mediated resistance in patients, and it is difficult to control the quantity of drugs for inhibition of wild-type EGFR or cell injury in cancer therapy. [17, 18].

Recently, preclinical modeling and analysis of tumor tissue obtained from patients in the study of the disease have been employed. Such genetic technology [19-25] has led to the identification of a number of mechanisms that mediate EGFR TKI resistance. Acquisition of EGFR-mutants is now well established and more than 50% of patients exhibit resistance in tumour cells after disease progression [26,

27]. However, it takes time to detect resistance by genetic technology because the number of resistant tumour cells must accumulate by several orders of magnitude. An optical accelerometer based on the effect of surface plasma resonance (SPR), which can detect drug molecule interactions with EGFR and distinguish EGFR molecule structural changes [28-31]. However, SPR as a probe [32] is problematic due to the limited power portion propagating in the sensing region where the analyte is located, resulting in a relatively wide resonance dip in reflectivity, a limited sensitivity and less luminescent efficiency.

Facing the above challenges, it is essential to get as much of the optical power as possible to propagate in the sensing region. Investigation of the mode power distribution suggests us to design a configuration that contains the sample in the guiding layer of the waveguide, where oscillating wave is located and most of the mode power concentrates. Addressed this issue, a hollow-core metal-cladding optofluidic resonator is developed to carry out the experiment. [33] In this design the use of double metal claddings which exhibit negative dielectric constant implies that the effective index of the guided modes can exist in the region of $0 < N < 1$, which is usually prohibited for the conventional guided modes and the surface plasmon resonance. Excitation of the ultrahigh order modes (UOMs) [34, 35] with N~0 hich means group velocity approaches zero maximizes the interaction between tumor cells and the drugs. Furthermore, owing to light power concentrated in the guiding region it give rise to an enlargement of the luminescent efficiency. [36] These two measures make it possible to enhance the sensitivity of the platform. Experiment results have proved that optofluidic resonators provide an effective way to detect drug interactions in real time using EGFR and cancer cells process with CCD real-time monitoring of ATR shifts.

2. Figures and tables

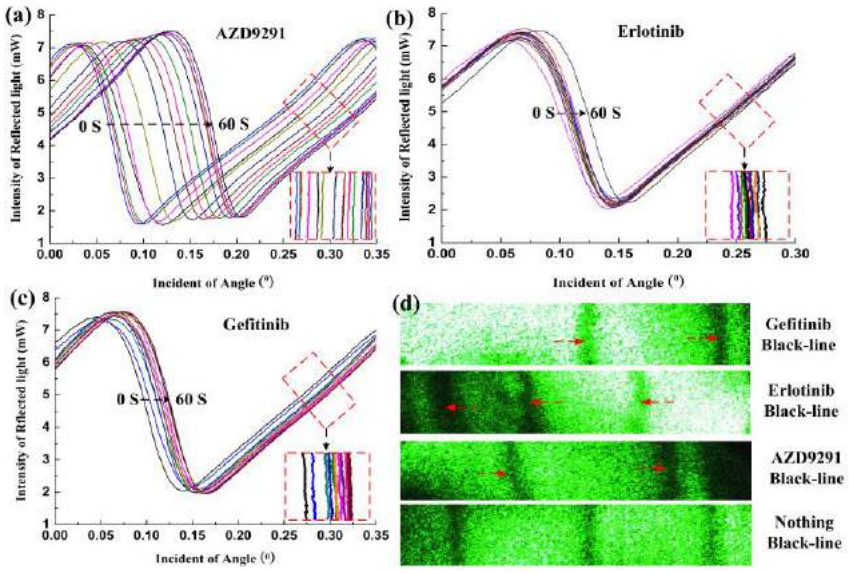


Fig. 1. Drugs, NSCLC-EGFR molecules, and the refraction index of the sample changed in an optofluidic resonator. (a-c) ATR spectrum for different times when drugs were injected into the resonator; c-d present AZD9291, erlotinib and gefitinib, respectively. (d) Different drug ATR dip images.

3. References :

1. Barker A . J . , Gibson K . H . , Grundy W . , et al. , "Studies leading to the identifcation of ZD1839 (IRESSA): an orally active, selective epidermal growth factor receptor tyrosine kinase inhibitor targeted to the treatment of cancer," Bioorg. Med. Chem. Lett. **11,** 1911–1914 (2001).

2. Moyer J . D . , Barbacci E G, Iwata K K, et al. , " Induction of apoptosis and cell cycle arrest by CP-358,774, an inhibitor of epidermal growth factor receptor tyrosine kinase," Cancer Res. **57,** 4838–4848 (1997).

3. Lynch T. J., Bell D. W., Sordella R., et al., "Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to geftinib," N. Engl. J. Med. **350,** 2129–2139 (2004).

4. Paez J. G., Janne P. A., Lee J. C., et al., "EGFR mutations in lung cancer: correlation with clinical response to geftinib therapy," Science **304,** 1497–1500 (2004).

5. Pao W . , Miller V . , Zakowski M . , et al. , "EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to geftinib and erlotinib, " Proc. Natl. Acad. Sci. USA **101,** 13306–13311 (2004).

6. Pao W., Chmielecki J., "Rational biologically based treatment of EGFRmutant non-small-cell lung cancer," Nat. Rev. Cancer **10,** 760–774 (2010).

7. Maemondo M., Inoue A., Kobayashi K., et al., "Geftinib or chemotherapy for non-small-cell lung cancer with mutated EGFR," N. Engl. J. Med. **362,** 2380–2388 (2010).

8. Mitsudomi T . , Morita S . , Yatabe Y . , et al. , " Geftinib versus cisplatin plus docetaxel in patients with nonsmall-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial," Lancet Oncol. **11,** 121–128 (2009).

9. Mok T. S., Wu Y. L., Thongprasert S., Yang C. H., Chu D. T., Saijo N., et al., "Geftinib or carboplatin-paclitaxel in pulmonary adenocarcinoma," N. Engl. J. Med. **361,** 947–957 (2009).

10. Rosell R., Carcereny E., Gervais R., Vergnenegre A., Massuti B., Felip E., et al., "Erlotinib versus standard chemotherapy as frst-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial," Lancet Oncol. **13,** 239–246 (2012).

11. Zhou C . , Wu Y . L . , Chen G . , Feng J, Liu X . Q . , Wang C . , et al. , " Erlotinib versus chemotherapy as frst-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study," Lancet Oncol. **12,** 735–742 (2011).

12. Burtness, B. Anadkat, M. Basti S, Hughes, M. Lacouture, M.E. McClure, J.S., et al. , "NCCN Task Force Report: Management of dermatologic and other toxicities associated with EGFR inhibition in patients with cancer," J. Natl. Compr. Cancer. Netw. **7(1),** S5–21 (2009).

13. Takezawa K . , Pirazzoli V . , Arcila M . E . , Nebhan C . A . , Song X . , de Stanchina E, et al. , "HER2 amplifcation: a potential mechanism of acquired resistance to EGFR inhibition in EGFR-mutant lung cancers that lack the second-site EGFRT790M mutation," Cancer Discovery **2,** 922–933 (2012).

14. Bean J . , Brennan C . , Shih J . Y . , Riely G . , Viale A . , Wang L . , et al. , "MET amplifcation occurs with or without T790M mutations in EGFR mutant lung tumors with acquired resistance to geftinib or erlotinib," Proc. Natl. Acad. Sci. USA **104,** 20932–20937 (2007).

15. Engelman JA, Zejnullahu K, Mitsudomi T, Song Y, Hyland C, Park JO, et al. , "MET amplifcation leads to geftinib resistance in lung cancer by activating ERBB3 signaling," Science **316,** 1039–1043 (2007).

16. Sequist LV, Waltman BA, Dias-Santagata D, Digumarthy S, Turke AB, Fidias P, et al. , "Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors," Sci. Transl. Med. **3,** 75ra26 (2011).

17. Ohashi K, Sequist LV, Arcila ME, Moran T, Chmielecki J, Lin YL, et al. , "Lung cancers with acquired resistance to EGFR inhibitors occasionally harbor BRAF gene mutations but lack mutations in KRAS, NRAS, or MEK1," PNAS **109,** 2127–2133 (2012).

18. de Bruin EC, Cowell CF, Warne PH, Jiang M, Saunders RE, Melnick MA, et al. , "Reduced NF1 expression confers resistance to EGFR inhibition in lung cancer," Cancer Discovery **4,** 606–619 (2014).

19. Ware KE, Marshall ME, Heasley LR, Marek L, Hinz TK, Hercule P, et al. , "Rapidly acquired resistance to EGFR tyrosine kinase inhibitors in NSCLC cell lines through de-repression of FGFR2 and FGFR3 expression," PLoS ONE **5,** e14117 (2010).

20. Kobayashi S, Boggon TJ, Dayaram T, Janne PA, Kocher O, Meyerson M, et al. , "EGFR mutation and resistance of non-small-cell lung cancer to geftinib," N Engl J Med **352,** 786–92 (2005).

21. Pao W, Miller VA, Politi KA, Riely GJ, Somwar R, Zakowski MF, et al. , "Acquired resistance of lung adenocarcinomas to geftinib or erlotinib is associated with a second mutation in the EGFR kinase domain," PLoS. Med. **2,** e73 (2005).

22. Sos ML, Rode HB, Heynck S, Peifer M, Fischer F, Kluter S, et al. , "Chemogenomic profling provides insights into the limited activity of irreversible EGFR Inhibitors in tumor cells expressing the T790M EGFR resista nce mutation," Cancer Res. **70,** 868–874 (2010).

23. Yun CH, Mengwasser KE, Toms AV, Woo MS, Greulich H, Wong KK, et al. , "The T790M mutation in EGFR kinase causes drug resistance by increasing the affnity for ATP," PNAS **105,** 2070–2075 (2008).

24. Li D, Ambrogio L, Shimamura T, Kubo S, Takahashi M, Chirieac LR, et al. , "BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models," Oncogene **27,** 4702–4711 (2008).

25. Engelman JA, Zejnullahu K, Gale CM, Lifshits E, Gonzales AJ, Shimamura T, et al. , " PF00299804, an irreversible pan-ERBB inhibitor, is effective in lung cancer models with EGFR and ERBB2 mutations that are resistant to geftinib," Cancer Res. **67,** 11924–11932 (2007).

26. Ramalingam SS, Blackhall F, Krzakowski M, Barrios CH, Park K, Bover I, et al., "Randomized phase II study of dacomitinib (PF-00299804), an irreversible pan-human epidermal growth factor receptor inhibitor, versus erlotinib in patients with advanced non-small-cell lung cancer, " J. Clin. Oncol. **30,** 3337–44 (2012).

27. Yasushi Sako, Shigeru Minoguchi and Toshio Yanagida, "Single-molecule imaging of EGFR signalling on the surface of living cells," Neture Cell Biology **12,** 168-172 (2000).

28. Jiši Homola, "Surface Plasmon Resonance Sensors for Detection of Chemical and Biological Species," Chem. Rev. **108,** 462–493 (2008)

29. Garnett, M. J. et al., "Systematic identification of genomic markers of drug sensitivity in cancer cells," Nature **483,** 570–575 (2012).

30. Kathrin Heinzmann, Lukas M. Carter, Jason S. Lewis and Eric O. Absagye, "Multiplexed imaging for diagnosis and therapy," Nature Biomedical Engineering **1,** 697-713 (2017).

31. Andrew, P. & Barnes, W. L., "Energy transfer across a metal film mediated by surface plasmon polaritons," Science **306,** 1002-1005 (2004).

32. Wang, Y. et al., "Enhancement of superprism effect based on the strong dispersion effect of ultrahigh-order modes," Opt. Lett. **33,** 1276 (2008).

33. Hailang Dai, et al., "Concentric Circular GratingbGenerated by the Patterning Trapping of Nanoparticles in an Optofluidic Chip," Scientific Reports **6,** 32018-32025 (2016).

34. Yuanlin Zheng, Zhuangqi Cao, and Xianfeng Chen,"Conical reflection of light during free-space coupling into a symmetrical metal-cladding waveguide," Journal of the Optical Society of America **30,** 1901-1904 (2013).

35. R. Horvath, H. C. Pedersen, N. B. Larsen, "Demonstration of reverse symmetry waveguide sensing in aqueous solutions," Appl. Phys. Lett. **81,** 2166 (2002).

36. Cai-Hong Yun, Titus J. Boggon, Yiqun Li, et al., "Structures of Lung Cancer-Derived EGFR Mutants and Inhibitor Complexes: Mechanism of Activation and Insights into Differential Inhibitor Sensitivity," Cancer Cell **11,** 217-227 (2007).

37. Yuan, W. et al., "Wideband slow light assisted by ultrahigh-order modes," J.O.S.A. B. **28,** 968–971(2011).

ORAL C16:

Single-exposure measurement of sperm cell thickness and integral refractive index maps for in-vitro fertilization

Lidor Karako and Natan T. Shaked

Department of Biomedical Engineering, Faculty of Engineering, Tel Aviv University, Tel Aviv 6997801, Israel

We introduce a label-free quantitative imaging modality for refractometry of human spermatozoa during flow, obtained by using phase imaging. Measuring phase provides high contrast when imaging semi-transparent biological cells, where the phase is linearly proportional to optical path delay (OPD) of light passing through the specimen, which encodes both the cell thickness and its integral refractive index (RI). We propose performing a single-exposure quantitative phase imaging and dynamic refractometry of human sperm cells. This refractive-index/thickness decoupling technique is expected to reveal new insights on the morphology and physiology of sperm cells, and to play a major role during in-vivo fertilization (IVF).

This novel method is following by our recent key research results that have shown that stain-free interferometric phase microscopy (IPM) can perform as good as staining microscopy [1]. Next, we have obtained localized measurements of physical parameters within human sperm cells by IPM [2], using which we could identify separate cellular compartments in the OPD map for unstained spermatozoa. We then have shown that sperm cells can be analyzed automatically using machine learning [3], as well as have shown that they can be selected and isolated based on the IPM results using micro-fluidics [4].

Recently, we have also shown the high correlation between stain-free phase imaging recorded by IPM and a DNA fragmentation assay in sperm cells [5]. In this research, the OPD map was not sufficient to determine molecular specificity, and the RI had to be calculated based on pre-measured average sperm cell thickness map performed by atomic force microscopy (AFM) and additional epi-fluorescence microscopy measurements of stained spermatozoa.

Conventional refractometers for biological cells are based point-by-point scanning confocal microscopy, AFM, or tomographic phase microscopy setups, which are either slow, expensive and bulky, invasive, require staining or simply too complex to use in clinical settings. Another integral RI decoupling procedure is to replace the cell-culture medium [6]. However, this cannot be done for highly dynamic samples like sperm cells. To solve this problem, we have constructed a single-exposure dual-wavelength imaging modality, taking into advantage the RI spectral shift of the surrounding perfusion medium of the sperm cell culture. Our setup offers simultaneous measurements of sperm cell integral RI and physical thickness. As far as we know, this is the first time that RI imaging is utilized in dynamic activity of live human sperm cells during flow cytometry.

References:

1. M. Haifler, P. Girshovitz, G. Band, G. Dardikman, I. Madjar, and N. T. Shaked, "Interferometric phase microscopy for label-free morphological evaluation of sperm cells," *Fertility and Sterility*, Vol. 104, Issue 1, pp. 43-47, 2015.
2. M. Balberg, M. Levi, K. Kalinowski, I. Barnea, S. Mirsky, and N. T. Shaked, "Localized measurements of physical parameters within human sperm cells obtained with wide-field interferometry," *Journal of Biophotonics*, Vol. 10, Issue 10, pp. 1305-1314, 2017.
3. S. K. Mirsky, I. Barnea, M. Levi, H. Greenspan, and N. T. Shaked, "Automated analysis of individual sperm cells using stain-free interferometric phase microscopy and machine learning," *Cytometry Part A*, Vol. 91, Issue 9, pp. 893-900, 2017.
4. P. Jacob Eravuchira, S. K. Mirsky, I. Barnea, M. Levi, M. Balberg, and N. T. Shaked, "Individual sperm selection by microfluidics integrated with interferometric phase microscopy," *Methods*, Vol. 136, pp. 152-159, 2018.
5. I. Barnea, L. Karako, S. K. Mirsky, M. Levi, M. Balberg, and N. T. Shaked, "Stain-free interferometric phase microscopy correlation with DNA fragmentation stain in human spermatozoa," Accepted to *Journal of Biophotonics*, 2018.
6. B. Rappazm, P. Marquet, E. Cuche, Y. Emery, C. Depeursinge, P. J. Magistretti, "Measurement of the integral refractive index and dynamic cell morphometry of living cells with digital holographic microscopy," *Opt. Express*, Vol. 13, pp. 9361-9373, 2005.

ORAL C17:

Implementing biological logic gates using fluorescence lifetime imaging

Eran Barnoy, Rachela Popovtzer, Dror Fixler

There is a paradigm shift in modern medicine from general to personalized treatments. One approach toward this personalized medicine is biological logic gates, which are able to identify and possibly even treat underlying conditions by inherently reacting to patient-specific biological stimuli. Here, we describe recent research in which we explored biologically relevant logic gates using gold nanoparticles (GNPs) conjugated to fluorophores and tracing the results remotely by time-domain fluorescence lifetime imaging microscopy (FLIM).

GNPs have a well-known effect on nearby fluorophores in terms of their fluorescence intensity (FI) as well as fluorescence lifetime (FLT). We have designed a few bio-switch systems in which the FLIM-detected fluorescence varies after biologically relevant stimulation. Some of our tools include Oregon Green which can be activated by either calcium ions or pH, peptide chains cleavable by the enzymes trypsin and caspase 3, and the polymer polyacrylic acid which varies in size based on surrounding pH. After conjugating GNPs to chosen fluorophores, we have successfully demonstrated the logic gates of NOT, AND, OR, NAND, NOR, and XOR by imaging different stages of activation. These logic gates have been demonstrated both in solutions as well as within cultured cells, thereby possibly opening the door for nanoparticulate *in vivo* smart detection.

While these initial probes are mainly tools for intelligent detection systems, they lay the foundation for logic gates functioning in conjunction so as to lead to a form of *in vivo* biological computing, where the system would be able to release proper treatment options in specific situations without external influence.

ORAL C18:

Leucocyte microscopy in patients

Ariel Weigler[1], Matan Hamra[1], Limor Minai[1], Eldad J Dann[2] and Dvir Yelin[1]

[1]Department of Biomedical Engineering, Technion-Israel institute of Technology, Haifa, Israel
[2]Department of Hematology and Bone Marrow Transplantation, Blood Bank and Aphaeresis unit, Rambam Medical Centre, and the Bruce Rappaport Faculty of Medicine, Technion, Haifa, Israel

Detailed classification and counting of leucocytes (white blood cells) is an important part of most blood tests, reliably indicating the status of the immune system. Differentiation between the various types of leucocytes is often required for diagnosing a variety of illnesses, including allergies, various malignancies and immunodeficiency diseases. The most common types of leucocytes in healthy adults are neutrophils and lymphocytes, typically comprising approximately 62% and 30% of the total leucocyte population, respectively. Differentiating between these cell types is often required for identifying sources of infection in ill patients; higher-than-normal neutrophil count may indicate active immune response to bacterial or fungal infection, while high lymphocyte count may indicate viral infection.

In the current study, we employ spectrally encoded flow cytometry (SEFC) for noninvasive imaging and counting of leucocytes in patients, including differentiation between granulocytes and mononuclear cells. By focusing a single transverse line within the cross section of a small blood vessel in a patient lip, and measuring the backscattered light with a high-speed spectrometer, a two-dimensional confocal image of flowing blood cells is acquired which allows the identification of leucocytes among the red cells background. Image data obtained from healthy human volunteers was analyzed and compared to the standard complete blood count for reference. The current study demonstrates the potential of SEFC to noninvasively analyze the immune system status at the point of care and study leucocyte morphology and dynamics *in vivo*.

ORAL C19:

In Depth Flow Inspection using Dynamic Laser Speckle spatial statistics

Mark Golberg[1, +,*] , Ran Califa[2,+] , Sagi Polani[2] , Javier García-Monreal[3] and Zeev Zalevsky[1]

[1]Faculty of Engineering and the Nanotechnology center, Bar Ilan University, Ramat Gan, 5290002, Israel

[2]ContinUse Biometrics Ltd., HaBarzel 32b st., Tel Aviv 6971048, Israel

[3]Departamento de Óptica, Universitat de València, C/Dr. Moliner 50, 46100 Burjassot, Spain

[+]These authors contributed equally to the paper

**Corresponding author: mark.golberg@cu-bx.com*

Abstract: A novel optical approach based on statistical analysis of spatial laser speckle pattern for tissue in-depth flow characteristics is presented. In-vitro experimental results analysis revealed flow in buried pipe from its surrounding intralipid.

1. Introduction

Recent years have seen many studies concerning tissue microfluidic. Common methods include laser doppler velocimetry [1], and dynamic laser speckle patterns analysis [2]. The main novelty in the proposed method is its ability to capture information relating to flow in deep layers in an inspected sample / tissue by analyzing spatial statistics of dynamic speckle pattern generated by a laser point illumination. Analyzing time-domain dynamic speckle statistics from the scattering sample suggest information regarding the particles motion inside the medium. While dynamic laser speckle reflected from particles experience random Brownian motion and can be defined by Lorentzian linewidth with an exponential decaying decorrelation statistic model, an organized particles motion (laminar flow) fits different statistical model and hence a deviation from the exponential model is formed [3]. Figure1.(a) shows result of illumination on bare tube with intralipid inside flowing in different velocities. Decreasing in the fit is shown for higher flow velocity due to stronger effect of laminar flow on scattering statistics.

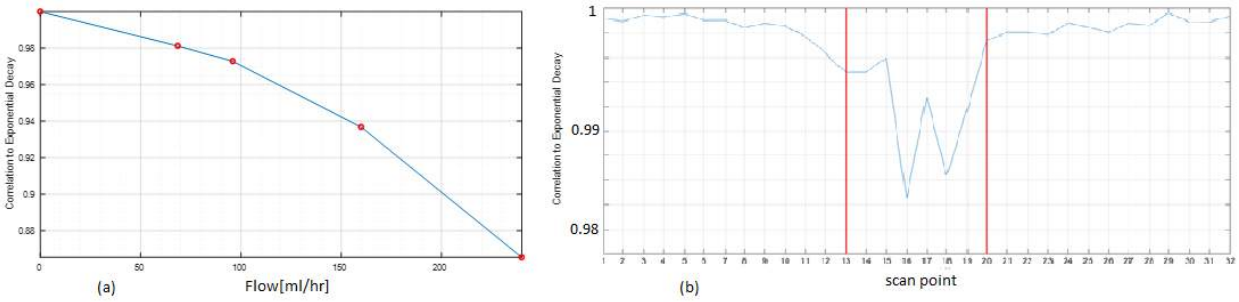


Figure 1. (a)laser speckle autocorrelation fit to exponential model Vs. flow velocity. (b) In-vitro experimental results.

In-depth information of scatters dynamics inside the sample can be achieved by analyzing speckle dynamics from different areas on the sample surface. The in-vitro experiment include phantom, simulating scattering tissue, mixture of intralipid and agarose with a plastic tube inserted through its center. Tube was connected to external pump allowing controlled flow of Intralipid. The sample was illuminated by an IR laser source (780nm, 50mW) with a spot dimeter of 1mm, while video of the dynamic laser speckle pattern was captured by a high-speed camera (100Kfps). Figure2.(b), shows the results of the fit to exponential of correlation coefficient (r) for each scanning point along the buried tube described above. Pipe section enclosed in red lines shows decrease in fit to exponential model in region containing laminar flow.

4. References

[1] J. H. Essex and P. 0. Byrne, "A laser Doppler scanner for imaging blood flow in skin," J.Biomed. Eng., 13, pp. 189-
194, 1991

[2] J. D. Briers and S. Webster, "Laser speckle contrast analysis (LASCA): a non-scanning, full-field technique for monitoring capillary blood flow," J. Biomed. Opt., 1, pp. 174-179, 1996.

[3] D. D. Duncan* and S. J. Kirkpatrick, “Can laser speckle flowmetry be made a quantitative tool?”, J. Opt. Soc. Am. A/Vol. 25, No. 8/August 2008.

ORAL C20:

All-dielectric metasurface engineered absorption in near-infrared

Pavel D. Terekhov [1,2,3,4], Kseniia V. Baryshnikova [4], Yakov Galutin [1,2,3], Arseniy I. Kuznetsov [5], Yuan H. Fu [5], Andrey B. Evlyukhin [4,6], Alexander S. Shalin [4], and Alina Karabchevsky [1,2,3].

[1] Electrooptical Engineering Unit, Ben-Gurion University, Beer-Sheva 8410501, Israel

[2] Ilse Katz Institute for Nanoscale Science & Technology, Ben-Gurion University, Beer-Sheva 8410501, Israel [3] Center for Quantum Information Science and Technology, Ben-Gurion University, Beer-Sheva 8410501, Israel [4] ITMO University, 49 Kronversky Ave., 197101, St. Petersburg, Russia

[5] Data Storage Institute, Singapore [6] Laser Zentrum Hannover e.V., Hollerithallee, D-30419, Hannover, Germany

All-dielectric nanophotonics technology is at the forefront of nanoscience and technology and makes possible to manipulate not only with electric component of electromagnetic radiation but also with its magnetic component. One of the emerging applications of all-dielectric nanophotonics technology is the design of optical devices with tuned absorption. In this work we study the absorption effect in silicon metasurface on bk7 glass substrate. We show, that the absorption of silicon can be enhanced at spectral range in which the silicon experiences negligible absorption. The tuning of the absorption occurs due to the designed and fabricated man-made silicon based metasurface.

To analyze the optical properties such as transmission, reflection and absorption of the metasurface we use multipole decomposition approach. We compare experimental results to the numerical calculations performed with COMSOL. We notice that optical properties of the silicon metasurface relate to the high-order multipoles excitations. We found that resonant electric quadrupole moment leads to the enhanced reflection while resonant magnetic dipole moment enhances the absorption effect. Such multipole excitation provides broadband absorption effect in wavelength range, where silicon does not naturally absorb.

Such metasurfaces are aimed to be utilized in different optical and quantum applications. Our work provides important information for developing 2D optical devices at the nanoscale and tuning optical properties of dielectric metasurfaces.

ORAL C21:

Moving tissue optical clearing to the ultraviolet

Isa Carneiro[1], Sónia Carvalho[1], Rui Henrique[1,2], Luís Oliveira[3,4], Valery V. Tuchin[5,6,7,8,]**

[1]Department of Pathology and Cancer Biology and Epigenetics Group-Research Centre, Portuguese Oncology Institute of Porto, Rua Dr. António Bernardino de Almeida S/N, 4200-072 Porto, Portugal; [2]Department of Pathology and Molecular Immunology, Institute of Biomedical Sciences Abel Salazar – University of Porto (ICBAS-UP), Rua de Jorge Viterbo Ferreira nº228, 4050-313 Porto, Portugal; [3]Physics Department, Polytechnic of Porto, School of Engineering, Rua Dr. António Bernardino de Almeida, 431, 4200-072 Porto, Portugal;
[4]Centre of Innovation in Engineering and Industrial Technology, ISEP, Rua Dr. António Bernardino de Almeida, 431, 4200-072 Porto, Portugal;
[5]Research-Educational Institute of Optics and Biophotonics, Saratov State University, Astrakhanskaya str. 83, Saratov 410012, Russia;
[6]Laboratory of Laser Diagnostics of Technical and Living Systems, Institute of Precision Mechanics and Control Institute of the Russian Academy of Sciences, Rabochaya 24, Saratov 410028, Russia;
[7]Interdisciplinary Laboratory of Biophotonics, Tomsk State University, Lenin's av. 36, Tomsk 634050, Russia;
[8]Laboratory of Femtomedicine, ITMO University, Lomonosova str. 9, St. Petersburg 191002, Russia.

Corresponding author, E-mail: lmo@isep.ipp.pt

The optical clearing (OC) technique was initially proposed in the 1990s and since then it has been used with various measuring and imaging methods. The potential of the OC technique is high for the improvement of noninvasive diagnostic and treatment procedures, since the optical clearing agents (OCAs) used are harmless and turn the tissues clear, allowing to reach higher tissue depths through the decrease of light scattering. Several significant results have been obtained with this technique in the visible and near infrared wavelength ranges. Two examples are the evaluation of the diffusion properties of OCAs in biological materials and pathology discrimination. The OC technique can also be used in other areas, such as organ cryogenics or food industry. With the objective of evaluating the OC technique in the ultraviolet range, we have performed some studies with human colorectal muscle samples. By measuring the collimated transmittance (Tc) spectra during treatment with various concentrations of glycerol in aqueous solutions from 200 to 1000 nm, we observed the creation of two new optical clearing windows between 200 and 250 nm and between 300 and 400 nm. Although the Tc levels are lower in these ranges when compared with the ones seen above 400 nm, the percent increase for the 200-250 nm range is much higher and increases with the glycerol concentration in the treating solution. These are preliminary results and further research is needed to test other OCAs and other biological tissues.