Years in Optoacoustics: 70th Anniversary of Prof. Vladimir P. Zharov

The guest editors introduces this Special Issue of the [Journal of Biomedical Photonics & Engineering](#) in honor of **Vladimir P. Zharov**, PhD, DSc, who is considered one of the pioneers of the modern era of biomedical engineering associated with novel integrations of laser diagnostics and therapy called laser theranostics with focus on photoacoustic and photothermal targeted theranostics using conjugated nanoparticles as the photoacoustic and photothermal molecular contrast agents. He has the extraordinary influence on this field. **Vladimir Zharov's** research interests are exceptionally broad and his contributions to the field fall into many distinct areas including laser spectroscopy, photoacoustics (called also optoacoustics), analytical chemistry, nanomedicine and biophotonics, and their multiple applications for theranostics (diagnosis + therapy) and prevention of cancer, infection and cardiovascular disorders (e.g., stroke) which are major killers in the world [1-27].

Prof. Zharov pioneered a high resolution photoacoustic spectroscopy with tunable lasers [1, 2] and invented photoacoustic flow cytometry [5, 6, 9-16] and pulsed nanophototherapy of infections and cancers targeted by gold nanoclusters [17-24], photoacoustic and photothermal tweezers for manipulation of nanoparticles and cells even in blood [26], photothermal super-resolution confocal and multiplex imaging [16], photothermal-gene therapy [24], noninvasive ultrasensitive blood test [15, 27] and *in vivo* multicolor flow cytometry [9-11]. In particular, **Prof. Zharov** pioneered (2002) one of the first applications of nanotechnology for cancer treatment using pulse laser-induced photothermal and accompanied nanobubble-formation phenomena around gold nanoparticles and, especially, their clusters targeted cancer cells [17-24].

He discovered ultrasharp (~ 1 nm) photothermal and photoacoustic spectral resonances in plasmonic nanostructures and their red and blue spectral shifting [7], which were named after him by others as “*Zharov splitting*.” [25]

He leaded the group of interdisciplinary researches to demonstrate the first clinical application of in vivo theranostics of circulating tumor cells (CTCs) in melanoma patients with the ~1000-fold sensitivity improvement and simultaneous laser killing of early CTCs that open way to prevent the development of deadly metastasis [15]. His team demonstrated also first biomedical application of spasers (nanolasers) as the brightest labels for advancer targeted single cell theranostics [8].

For his innovations, **Prof. Zharov** was many prestigious awards including the State Prize (1989), one of the Russia's highest scientific award for laser monitoring of pollution in atmosphere, and the United States' Maiman Award (1993), named after the inventor of the first laser (**Vladimir Zharov** was the first recipient of this award) for first combination of ultrasound and laser for microsurgery using optical fibers as the waveguide for both acoustic waves and laser radiation. **Vladimir Zharov** richly deserves to be called a photoacoustic flow cytometry "pioneer," and not just of a single methodology.

In the eighties, **Vladimir Zharov** received unique interdisciplinary education and skills in physics (degree from Moscow State University), optical engineering (degrees from Moscow State Technical University), photobiology and biochemistry (fellowship at the Lawrence Berkeley National Laboratory at the University of California in 1984-1985) and business management (Diploma certificate from the U.S. Educational Center in Moscow in 1993). Through serving as the Chairman of largest in Russia Biomedical Engineering Department (1989-2000) at the Moscow State Technical University named after N.E. Bauman and as a president of the private company "Yainvest" in Moscow at the end of the 1980s and into the 1990s, **Vladimir Zharov** was focused on both fundamental research and commercialization. Based on his broad interdisciplinary background in biomedical engineering he organized commercial productions of novel hybrid medical technologies and apparatuses for LED-vacuum, magnetic-laser and electro-laser therapies. These systems have been successfully used in many Russian medical centers and clinics to treat several thousand patients who suffered from infected wounds, postmastectomy lymphedema, and urological disorders (e.g., chronic prostatitis).

In collaboration with the colleagues from the Institute of Spectroscopy RAS, Moscow State University, and Bauman Moscow State Technical University there were developed and studied [1-4]: optoacoustic (OA) spectroscopy (named later photoacoustic) of the excited molecule states using heated OA detector (1977); OA nonlinear and multiphoton absorption using strong-focused laser beams with high spatial resolution OA detector (1978); OA isotope analysis (1976-1982); laser-acoustic drug injection and delivery through syringe needle (1986-1987); the influence of laser-acoustic effects on cells using nanosecond and picosecond pulses (1986-1989), laser-OA scalpel (1986); destruction of gall bladder stones by using "internal" and "external" OA effects (1986); principle and the first demonstration of OA tomography of large beam profiles (1988-1989); biophotophone for diagnostic of ear's diseases with an ear as natural acoustic sensor of acoustic waves generated by light in different internal ear's zones (1987); OA-chromatographic detectors for early diagnostic of some diseases including detection of vitamin A in blood plasma (1986) and some organic substances in exhaled air associated with tuberculosis (1989); the first application the remote pulsed photothermal radiometry for study tissue properties and as a feedback in laser medicine (1986-1987). His team also developed the first integration of laser and low-

frequency (20-50 kHz) ultrasound technology for microsurgery using the same optical fiber for delivery optical and acoustic waves that increased the cutting and drilling speed (5-10-fold) of soft and hard tissues with simultaneous self-cleaning the surgical tip.

In 1997-2000 they tested in clinical condition novel photo-ultrasonic treatment of infected wounds by integration photodynamic therapy (PDT) and ultrasonic (US) therapy with antibiotics (A) as tools for effective killing bacteria. The delivery into wound both photosensitizer (PS) and A and followed up light irradiation and US low-frequency application brought new advantages: effective mixing of A and PS in solution; enhanced diffusion A in tissue; increasing penetration of PS in bacteria; US clearing of surface from necrotic adjournment; additional US-induced bactericidal effect; increasing efficacy of light irradiation of non-transparent wound; and additional activation of immune system. The clinical trials with over 200 patients with different post-operation infectious complications of different origin demonstrated advantage of new technology [4].

At that time **Zharov's** team also developed [4]: photo-bactericidal patch as integration of LED-based thin film chip with PA to provide PDT of local skin infected areas; photo-electrical autonomous capsule of elliptical shape with size $\varnothing$ 8×16 mm for therapy in endoscopy; implantable electrooptical module $\varnothing$ 4×0.8 mm with remote power supply using pulse magnetic field and miniature coil inside module (these micro-modules during clinical trials in Institute of Eye's Surgery in Moscow in 1996-1999 were implanted in eyes of 175 patients with different vision problems caused mostly by atrophied optic nerve; LED-based strip with remote pulse magnetic power source for treatment of chronic generalized parodontitis (20 patients were treated in Moscow State University of Medicine and Dentistry in 1998-2000).

Prof. Zharov broad interdisciplinary background and experience in biomedical engineering helped him to organize commercial productions of novel hybrid medical technologies. Specifically in 1992-1999, **Zharov's** team commercialized several combined therapeutic technologies for treatment of chronic prostatitis [4]: 1) electro-laser apparatus integrating near-infrared therapy and electrostimulation that provided increasing of blood microcirculation, improving drug delivery, and reducing infections (it has been used in 140 Russian clinics for successful treatment of many thousand patients); 2) "photo-vacuum" therapy integrating powerful LED array and so-called "vacuum" therapy (decompression); 3) photo-magnetic therapy integrating relatively high intensity of pulse magnetic field and laser thermal therapy with infrared pulse laser diode. Phototherapy of lymphedema after mastectomy (breast cancer surgery) using powerful LED array and compression was used with the high efficacy (87%) for treatment 128 patients in Moscow State University of Medicine and Dentistry (1997-1999). **Zharov's** team presented the first experimental evidence of mechanism of phototherapy with powerful LED array as photochemical transformation IgG antibody from a low-acid state to a high one that was used in 1998-2000 for treatment of 18 patients with atopic dermatitis [4].

Since 2000 as the Director of the Laser Research at Winthrop Paul Rockefeller Cancer Institute at the University of Arkansas for Medical Science (UAMS), he established Arkansas Nanomedicine Center (ANC), which is currently one of the best in the USA in the field of Nanotechnology, Nanomedicine, and Biophotonics and their clinical applications. He was one of the researchers who

clearly saw the potential of integration of photoacoustics, nanotechnology, and laser optics for biomedicine. Specifically, he became interested in the biomedical applications of these technologies to answer a question: how to help people with severe diseases like cancer, heart attack, stroke and severe infections? His curiosity and wide spanning intellectual interests enriched these fields and propelled them in many ways.

The one of his main achievements in the USA is the developing in 2002-2003 innovative integrations of laser and nanotechnology, which opened new avenues in medicine called laser Nanomedicine for earliest diagnosis and treatment of cancer with focus on metastasis (leading to 90% of cancer death) prevention. He is among those scientists who have made pioneering and contributions in innovative integration of laser, nanotechnology, and medicine. Since then the fields have grown exponentially to become an integral part in many medical disciplines.

Prof. Zharov has provided leadership in many multidisciplinary NIH and NSF research and translational research projects. Quickly adapting to USA's complicated and multilayered funding system, he demonstrated the ability to obtain multiple state and federal grants serving as principal investigator/leader. Overall, **Prof. Zharov** is the principle investigator of 17 grants from the National Institute of Health (NIH), National Science Foundation (NSF), Medical programs of Department of Defense (DOD), and many other agencies, as well as international projects with Samsung, Inc., and European Programme 'EUREKA'. Under his leadership, his self-supporting (i.e., funding from grants) for laboratories have had total nearly \$11 million budget.

Zharov's work in the assessment of the physical properties, toxicity, targeting, and pharmacokinetics of the advanced nanotechnology products (e.g., new bioconjugated nanoparticles) has received significant support from two Nanotechnology centers at the University of Arkansas at Fayetteville and at Little Rock and especially from Nanocore in the FDA-affiliated National Center for Toxicological Research (NCTR) in Arkansas.

Today, **Prof. Zharov** leads several clinical trials of new biomedical technologies including photoacoustic flow cytometry and MRI-guided laser interstitial therapy for the earliest theranostics of metastatic tumors (e.g., melanoma), local tumor and laser treatment of post-resection margins as well as advanced diagnosis of cardiovascular diseases and infections. His 18 years' experience at UAMS with clinical studies allowed him to establish interdisciplinary very productive team of physicist, engineers, chemists, biologists and physicians with publication's rate up to 10-20 papers per year. His communication skills allowed him to establish international collaborations with many universities in different countries (e.g., Russia, Germany, Canada, and Slovenia). He has authored ~200 peer-reviewed publications (including 10 papers in Nature journals), five books, and 55 patents.

The several state medical magazines, and European journal of international innovation have highlighted **Prof. Zharov's** extraordinarily accomplishments, innovations and ability to conduct groundbreaking research in the novel methods of noninvasive disease diagnosis with ultra-high sensitivity. His work has been featured also in several respected sources including NIH website, and journals with the high impact factor such as Nature and Nature Nanotechnology, which highlighted

his the first-of-its-kind clinical trials using photoacoustic flow cytometry for early cancer diagnosis and therapy.

Prof. Zharov is working in the strong collaboration with scientists across the world (e.g., Vladimir Torchilin, Samir Gambhir, Mark Stockman, Valery Tuchin, Vladislav Verkhusha, Markus Frank, Viacheslav Artyushenko, Nikolai Khlebtsov, and Dmitry Gorin) from many universities and companies including IPG Photonics, BrightSolution, Art Photonics, Skolkovo Institute of Science and Technology, Moscow State University, Tomsk State University, Saratov State University, Saratov Medical State University, Institute of Bioorganic Chemistry, Institute of Biochemistry and Physiology of Plants and Microorganisms.

In 2017, **Prof. Zharov** was awarded by the Megagrant given by the Russian Ministry of Science and Higher Education, which allowed him to establish the laboratory of [Biomedical Photoacoustics](#) at Saratov State University in 2018. The main goal of this laboratory is the development of a new concept, approaches, methods and technical solutions for an ultrasensitive analysis of almost the entire blood volume of the patients, and thus to detect rare disease-associated biomarkers, in particular, CTCs, exosomes, bacteria and clots presenting in extremely low concentrations, especially at the early disease stages, for example, down to a few CTCs per 5 liters of blood.

This Special Issue in **Vladimir Zharov's** honor provides a multidisciplinary reflection on his career, indicating the breadth of **Vladimir Zharov's** scientific interests and contributions.

The guest editors of this Special Issue would like to thank all authors for their efforts in preparing their contributions and thank all the reviewers for their help in reviewing these papers. Last but not least, we would like to thank the editorial staff of [Journal of Biomedical Photonics & Engineering](#) for the opportunity to organize this Special Issue.

Special Issue Editors:

Ekaterina I. Galanzha

Laboratory of Lymphatic Research, Diagnosis and Therapy (LDT),
University of Arkansas for Medical Sciences (UAMS),
Little Rock, AR, USA,
Photoacoustic Laboratory, Saratov State University,
Saratov 410012, Russia
E-mail: egalanzha@uams.edu

Dmitry A. Gorin,

Skolkovo Institute of Science and Technology,
Moscow 143026, Russia
E-mail: d.gorin@skoltech.ru

Valery V. Tuchin

Research-Educational Institute of Optics and Biophotonics,
Saratov State University,
Saratov 410012,
Institute of Precision Mechanics and Control of the RAS,
Saratov 410028,

Tomsk State University,
Tomsk 634050, Russia
E-mail: tuchinvv@mail.ru

Selected publications of Prof. Zharov

- 1 V. P. Zharov, V. S. Letokhov, *Laser Optoacoustic Spectroscopy*, Springer Series in Optical Sciences. Vol. 37, Springer-Verlag, Berlin, Heidelberg, New York (1986).
- 2 V. P. Zharov, "Laser optoacoustic spectroscopy in chromatography," Chap in *Laser Analytical Spectrochemistry*, V. S. Letokhov (ed), The Adam Hilger Series on Optics and Optoelectronics, Bristol, Boston, Mass, 229-271 (1986).
- 3 V. P. Zharov, "Application of power optoacoustic methods and instruments in medicine and biology," Chap. in *Photoacoustics and Photothermal Phenomena*, Springer Series in Optical Sciences. Vol. 58, Springer, Berlin, 533-547 (1987).
- 4 V. P. Zharov, A. S. Latyshev, "[Laser combined medical technologies from Russia](#)," *Journal of Laser Applications* 11(2), 80-90 (1999).
- 5 E. I. Galanzha, V. P. Zharov, "[Photoacoustic flow cytometry](#)," *Methods* 57(3), 280-296 (2012).
- 6 V. V. Tuchin, A. Tárnok, and V. P. Zharov, "[In vivo flow cytometry: A horizon of opportunities](#)," *Cytometry Part A* 79A(10), 737-745 (2011).
- 7 V. P. Zharov, "[Ultrasharp nonlinear photothermal and photoacoustic resonances and holes beyond the spectral limit](#)," *Nature Photonics* 5(2), 110-116 (2011).
- 8 E. I. Galanzha, R. Weingold, D. A. Nedosekin, M. Sarimollaoglu, J. Nolan, W. Harrington, A. S. Kuchyanov, R. G. Parkhomenko, F. Watanabe, Z. Nima, A. S. Biris, A. I. Plekhanov, M. I. Stockman, and V. P. Zharov, "[Spaser as a biological probe](#)," *Nature Communications* 8(1), 15528 (2017).
- 9 J.-W. Kim, E. I. Galanzha, E. V. Shashkov, H.-M. Moon, and V. P. Zharov, "[Golden carbon nanotubes as multimodal photoacoustic and photothermal high-contrast molecular agents](#)," *Nature Nanotechnology* 4(10), 688-694 (2009).
- 10 E. I. Galanzha, E. V. Shashkov, T. Kelly, J.-W. Kim, L. Yang, and V. P. Zharov, "[In vivo magnetic enrichment and multiplex photoacoustic detection of circulating tumour cells](#)," *Nature Nanotechnology* 4(12), 855-860 (2009).
- 11 E. I. Galanzha, E. V. Shashkov, P. M. Spring, J. Y. Suen, and V. P. Zharov, "[In vivo, noninvasive, label-free detection and eradication of circulating metastatic melanoma cells using two-color photoacoustic flow cytometry with a diode laser](#)," *Cancer Research* 69(20), 7926-7934 (2009).
- 12 A. Zerda, J.-W. Kim, E. I. Galanzha, S. S. Gambhir, and V. P. Zharov, "[Advanced contrast nanoagents for photoacoustic molecular imaging, cytometry, blood test, and photothermal theranostics](#)," *Contrast Media & Molecular Imaging* 6(5), 346-369 (2011).
- 13 D. A. Nedosekin, M. Sarimollaoglu, E. I. Galanzha, R. Sawant, V. P. Torchilin, V. V. Verkhusha, J. Ma, M. H. Frank, A. S. Biris, and V. P. Zharov, "[Synergy of photoacoustic and fluorescence flow cytometry of circulating cells with negative and positive contrasts](#)," *Journal of Biophotonics* 6(5), 425-434 (2013).
- 14 Y. A. Menyaev, K. A. Carey, D. A. Nedosekin, M. Sarimollaoglu, E. I. Galanzha, J. S. Stumhofer, and V. P. Zharov, "[Preclinical photoacoustic models: application for ultrasensitive single cell malaria diagnosis in large vein and artery](#)," *Biomedical Optics Express* 7(9), 3643-3658 (2016).
- 15 E. I. Galanzha, Y. A. Menyaev, A. C. Yadem, M. Sarimollaoglu, M. A. Juratli, D. A. Nedosekin, S. R. Foster, A. Jamshidi-Parsian, E. R. Siegel, I. Makhoul, L. F. Hutchins, J. Y. Suen, and V. P. Zharov, "In vivo liquid biopsy using Cytophone platform for photoacoustic detection of circulating tumor cells in patients with melanoma," *Science Translational Medicine* (2019) [in press].
- 16 D. A. Nedosekin, E. I. Galanzha, E. Dervishi, A. S. Biris, and V. P. Zharov, "[Super-resolution nonlinear photothermal microscopy](#)," *Small* 10(1), 135-142 (2014).
- 17 V. Zharov, V. Galitovsky, and M. Viegas, "[Photothermal detection of local thermal effects during selective nanophotothermolysis](#)," *Applied Physics Letters* 83(24), 4897-4899 (2003).
- 18 V. P. Zharov, E. N. Galitovskaya, C. Johnson, and T. Kelly, "[Synergistic enhancement of selective nanophotothermolysis with gold nanoclusters: potential for cancer therapy](#)," *Lasers in Surgery and Medicine* 37(3), 219-226 (2005).
- 19 B. Khlebtsov, V. Zharov, A. Melnikov, V. Tuchin, and N. Khlebtsov, "[Optical amplification of photothermal therapy with gold nanoparticles and nanoclusters](#)," *Nanotechnology* 17(20), 5167-5179 (2006).
- 20 V. P. Zharov, K. E. Mercer, E. N. Galitovskaya, and M. S. Smeltzer, "[Photothermal nanotherapeutics and nanodiagnostics for killing of bacteria targeted with nanoparticles](#)," *Biophysical Journal* 90(2), 619-627 (2006).
- 21 V. K. Pustovalov, A. S. Smetannikov, V. P. Zharov, "[Photothermal and accompanied phenomena during selective nanophotothermolysis with gold nanoparticles and laser pulses](#)," *Laser Physics Letters* 5(11), 775-792 (2008).

- 22 J. Shao, R. J. Griffin, E. I. Galanzha, J.-W. Kim, N. Koonce, J. Webber, T. Mustafa, A. S. Biris, D. A. Nedosekin, and V. P. Zharov, "[Photothermal nanodrugs: potential of TNF-gold nanospheres for cancer theranostics](#)," Scientific Reports 3(1), 1293 (2013).
- 23 R. R. Letfullin, C. Joenathan, T. F. George, and V. P. Zharov, "[Laser-induced explosion of gold nanoparticles: potential role for nanophotothermolysis of cancer](#)," Nanomedicine 1(4), 473-480 (2006).
- 24 M. Everts, V. Saini, J. L. Leddon, R. J. Kok, M. Stoff-Khalili, M. A. Preuss, C. L. Millican, G. Perkins, J. M. Brown, H. Bagaria, D. E. Nikles, D. T. Johnson, V. P. Zharov, and D. T. Curiel, "[Covalently linked Au nanoparticles to a viral vector: potential for combined photothermal and gene cancer therapy](#)," Nano Letters 6(4), 587-591 (2006).
- 25 A. Mertiri, H. Altug, M. K. Hong, P. Mehta, J. Mertz, L. D. Ziegler, and S. Erramilli, "[Nonlinear midinfrared photothermal spectroscopy using Zharov splitting and quantum cascade lasers](#)," ACS Photonics 1(8), 696-702 (2014).
- 26 E. I. Galanzha, M. G. Viegas, T. I. Malinsky, A. V. Melerzanov, M. A. Juratli, M. Sarimollaoglu, D. A. Nedosekin, and V. P. Zharov, "[In vivo acoustic and photoacoustic focusing of circulating cells](#)," Scientific Reports 6(1), 21531 (2016).
- 27 [Noninvasive Cytophone device detects melanoma in earliest stages, could prevent fatal disease spread.](#)