Biophotonic Strategies of Measurement and Stimulation of the Cranial and the Extracranial Lymphatic Drainage Function

Oxana Semyachkina-Glushkovskaya, Dmitry Postnov, Anastasia Lavrova, Ivan Fedosov, Ekaterina Borisova, Vladimir Nikolenko, Thomas Penzel, *Senior Member, IEEE*, Jürgen Kurths, and Valery Tuchin, *Member, IEEE*

***Abstract*—In this review, we discuss the crucial role of cranial and the extracranial lymphatics in keeping the central nervous system (CNS) health. We talk about the important lymphatic mechanism of removal of metabolites and toxins from the brain, which orchestrates the regenerative processes in CNS. We debate a novel knowledge about the lymphatic mechanism responsible for maintaining the balance between the exit and the entrance of molecules and cells from and into CNS. Finally, we highlight the pioneering technologies of biophotonic stimulation of lymphatic drainage function that can open a new era for the development of novel bedside, readily applicable and commercially viable technologies for the treatment of brain diseases.**

***Index Terms*—The cranial and the extracranial lymphatics, brain diseases, photostimulation of the lymphatics.**

Manuscript received October 6, 2020; revised November 29, 2020; accepted December 16, 2020. Date of publication December 18, 2020; date of current version February 9, 2021. This work was supported in part by Grants of Russian Science Foundation: under Grant 20-15-00090, in part by th O.S-G. and J.K., Sections I, II, III, VI under Grant 18-75-10033, in part by the I.F.and M.K., Section V under Grant 19-15-00201, in part by the D.P. and A.L., Section VI RFBR under Grant 19-515-55016, 20-015-00308-a, and in part by the RF Government under Grant 075-15-2019-1885. *(Corresponding author: Oxana Semyachkina-Glushkovskaya.)*

Oxana Semyachkina-Glushkovskaya is with the Department of Human and Animal Physiology, Saratov State University, Saratov 83410012, Russia, and also with the Physics Department, Humboldt University, 12489 Berlin, Germany (e-mail: glushkovskaya@mail.ru).

Dmitry Postnov and Ivan Fedosov are with the Department of Optics and Biophotonics, Saratov State University, Saratov 410012, Russia (e-mail: postnov@info.sgu.ru; fedosov_optics@mail.ru).

Anastasia Lavrova is with the Department of Optics and Biophotonics, Saratov State University, Saratov 410012, Russia, with the Saint-Petersburg State Research Institute of Phthisiopulmonology, Saint-Petersburg, Russia, and also with the Saint-Petersburg State University, Saint Petersburg, Russia (e-mail: aurebours@googlemail.com).

Ekaterina Borisova is with the Institute of Electronics, Bulgarian Academy of Sciences, Sofia 1784, Bulgaria, and also with the Department of Human and Animal Physiology, Saratov State University, Saratov 83410012, Russia (e-mail: ekaterina.borisova@gmail.com).

Vladimir Nikolenko is with the N. V. Sklifosovsky Institute of Clinical Medicine, FSAEI HE I. M. Sechenov First Moscow State Medical University (Sechenov University), Moscow 119435, Russia, and also with the Lomonosov Moscow State University, Moscow 119991, Russia (e-mail: vn.nikolenko@yandex.ru).

Thomas Penzel is with the Department of Human and Animal Physiology, Saratov State University, Saratov 83410012, Russia, with the Advanced Sleep Research GmbH, 12489 Berlin, Germany, and also with the Charité-Universitätsmedizin Berlin, Sleep Medicine Center, 10117 Berlin, Germany (e-mail: thomas.penzel@charite.de).

Jürgen Kurths is with the Physics Department, Humboldt University, 12489 Berlin, Germany, with the Potsdam Institute for Climate Impact Research, 14473 Potsdam, Germany, and also with the Department of Human and Animal Physiology, Saratov State University, Saratov 83410012, Russia (e-mail: juergen.kurths@pik-potsdam.de).

Valery Tuchin is with the Department of Optics and Biophotonics, Saratov State University, Saratov 83410012, Russia, with the Institute of Precision Mechanics and Control, Russian Academy of Science, Saratov, Russia, and also with the Tomsk State University, Tomsk, Russia (e-mail: Tuchinvv@mail.ru).

Color versions of one or more figures in this article are available at https://doi.org/10.1109/JSTQE.2020.3045834.

Digital Object Identifier 10.1109/JSTQE.2020.3045834

I. Introduction

THE lymphatic door from and into the brain is Yin and Yang in the cerebral homeostasis. Over the last few decades, the crucial role of the cerebral lymphatics in keeping the central nervous system (CNS) health has been actively debated [1]–[17]. The lymphatic mechanisms of removal of metabolites and toxins from the brain tissues orchestrate recovery processes in the CNS [17]. The lymphatic abnormalities are accompanied by suppression of the cerebral spinal fluid (CSF) outflow that contributes the elevation of intracranial pressure (ICP) [18]. Because CSF production is actively regulated to maintain normal ICP [19], damage to the outflow pathways could drive compensatory decreases in CSF production and turnover [20] or altered patterns of CSF flow. Either of these could result in decreased waste and toxin clearance, as is seen in aging and some neurological diseases.

The cribriform plate is a center of lymphatic pathway of metabolic clearance and is connective bridge between CSF and the cervical lymphatic system [1]–[3], [21]–[26]. The cribriform plate is a fenestrated bony plate of the ethmoid bone that separates the cranial and nasal cavities. Once through the plate, CSF is absorbed by the lymphatic vessels (LVs) in the nasal mucosa and drained into the cervical lymph nodes (cLNs) [27]. There has been speculation that the interstitial fluid (ISF) and CSF leave the brain via the extracellular space between the olfactory sensory nerve (OSN) axon bundles [28], as the intercellular space between axon bundles provide low-resistance directed pathways for fluid flow [29]. Fig. 1 illustrates the cribriform-lymphatic anatomical connection.

The disruption of cribriform-lymphatic connection is a key mechanism underlying development of various neurological disorders. Indeed, acute blockage of CSF outflow by surgically obstructing the cribriform plate results in an increase in ICP [30] and outflow resistance [31], [32] in adult [33] and neonatal

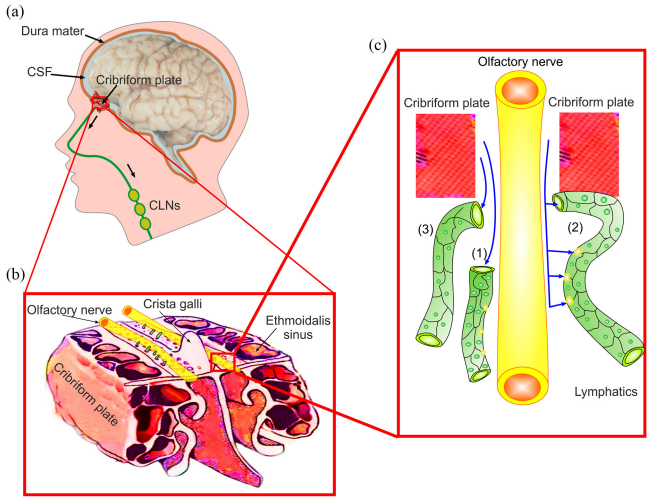


Fig. 1. The cribriform-lymphatic anatomical connection: (a) – Anatomical connection between the cribriform plate and the cervical lymphatics; (b) – anatomical structure of the cribriform plate; (c) – the schematic illustration of location of LVs in the cribriform plate. In schema (1) LVs tightly surround the olfactory nerve and the lymphatic endothelium fuses the nerve. In schema (2) LVs join with the cribriform plate and LVs follows the nerve some distance. In both scenarios (1) and (2) LVs collect CSF and direct it into cLNs; no CSF enters into the submucosal interstitium. In (3) LVs are not connected directly with the cribriform plate and the nerve but are interspersed throughout the olfactory submucosa. In this proposal, CSF enters first into the submucosal interstitium from which it is absorbed into entering LVs. The schemes were modified from [1].

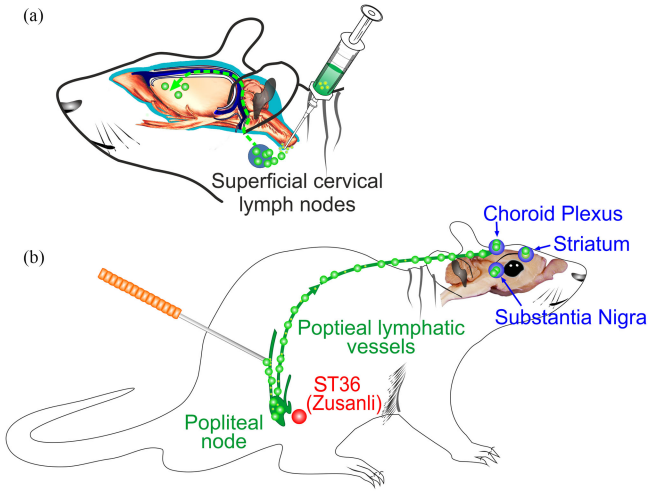


Fig. 2. Schematic illustration of lymphatic door into the brain: (1) nanoparticles brain delivery via MLVs bypassing the blood-brain barrier (BBB) [63]; the choroid cells injected into acupuncture point ST36 transfer to the striatum, the choroid plexus and the substantia nigra [61].

sheep [34]. Surgical procedures in humans and mice that ablate the olfactory nerves provides the development of hydrocephalus in the immediate post-surgical period. The obstruction of the nasal lymphatics due to inflammation could lead to a viral invasion and infection of the brain [35]. The surgical removal of the deep cervical lymph nodes (dcLN) – the first anatomical station of CSF exist from the brain, leads to cognitive impairment in mice [36] and necrotic changes in neurons with infiltration of phagocytes in rabbits [37]. The cerebral edema, elevation of the intracranial pressure (ICP), abnormalities of electrical activity of the brain and behavior alterations have been observed after chronic blockade of the cervical lymphatics in dogs [38], [39]. Ligation of the cervical lymphatic vessels (cLVs) results in the brain edema with an increase in concentration of proteins in the cerebral spinal fluid (CSF) in cats and rabbits [40], [41]. The blockade of this lymphatic pathway aggravates the severity of brain edema and contributes to an elevation of ICP after stroke and subarachnoid hemorrhage [11], [42], [43].

Intriguingly, there may be a connection between the patency of the clearance pathway through the cribriform plate and neurodegenerative diseases [26], [44]. The neurons whose axons make up the nerve bundles that traverse the cribriform plate, such as the olfactory sense nerve (OSN), are exposed to environmental toxins and air pollutants [45], which epidemiological studies have associated exposure to neurodegenerative diseases. Furthermore, anosmia and decreased acuity in the sense of smell, which will result from OSN damage, reliably precede many neurological disorders [47]. The reduction in smell and taste one of the first and mystery symptoms of COVID-19 [46]–[48] is accompanied by various neurological manifestations [49]. One of hypothesis explains that the virus infiltrates the brain, possibly from the nose, and affects olfactory centers (olfactory bulb and cortex), thereby reducing smell sensations [50]. This scenario has been considered by several investigators [51]–[56].

A lymphatic-CSF relationship is an important mechanism of immune communication. Indeed, the injection of blood in the different brain regions causes a humoral immune response in mice generated mainly by dcLNs [57]. Similarly, the injection of serum albumin in the subarachnoid space induces antibody production by cLNs in cat [58], [59]. Interestingly, serum antibody titer was reduced after obligation of cLNs [58]. Thus, cLNs may act to prime immune cells to target the brain. There has been speculation that lymphatic drainage of brain antigens could contribute to the pathogenesis of Alzheimer's disease and multiple sclerosis [60].

However, lymphatic pathway of CSF outflow is not one-way trip, there is evidence that lymphatic window is opened also into the brain. Just recently, it was shown that the injection of choroid plexus cells into the ST36 acupuncture point (Zusanli) causes neuroprotective effect in mice with Parkinson's disease due to delivery of injected cells to the brain that was associated with a decrease in tyrosine hydroxylase expression, activation of inflammatory and apoptosis factors [61]. The injected cells were present in the striatum, the choroid plexus and in the substantia nigra one week after administration. There is hypothesis that injected cells enter the popliteal LVs surrounding ST36 acupuncture point and transfer into the brain through the lymph (Fig. 2). The confirmation of possible lymphatic entrance into the brain was found recently [61]. Zhao *et al.* demonstrate that injection of fluorescent nanoparticles subcutaneously close to dcLNs is accompanied by nanoparticles brain delivery through the meningeal lymphatic vessels (MLVs) [62].

Thus, the lymphatic system is a door from and into the brain, which maintains balance between the exit and the entrance

of molecules and cells from and into CNS contributing Yin and Yang in the cerebral homeostasis. Since the obstruction of cribriform-lymphatic route contributes the development of various neurological disorders, augmentation of lymphatic drainage function can open a new era for therapy of brain diseases associated with reducing CSF outflow from the brain.

II. Photostimulation of the Lymphatic System

The transcranial photostimulation (tPS) is considered as a possible novel nonpharmacological and non-invasive promising strategy for prevention or delay of AD [63]–[69], depression [70]–[75], Parkinson's disease [76], stroke [77], [78], traumatic brain injuries [79], [80], post-mastectomy lymphedema [81], [82], and post-surgical swelling [82]–[84]. The PS, known as low-level laser therapy, was first proposed by Endre Mester in 1967 for stimulation of hair growth [85] and in 1971 for wound healing [86]. The PS has broadened to include near-infrared wavelengths 600–1200 nm. The better tissue penetration properties of near-infrared light, together with its good efficacy, made it the most popular wavelength range.

The PS-mediated stimulation of lymphatic drainage and clearing function might be one of the mechanisms underlying an important role of PS in neurorehabilition [87]. Due to a good penetration of PS into the brain cortex, tPS can stimulate MLVs. In our recent pilot study on mice with the injected AD model, we have clearly demonstrated that 9 days course of tPS (1267 nm, 32 J/cm^2) strongly reduces Aβ plaques in the brain which is associated with improving of the memory and neurocognitive deficit [63]. Based on our data on the real time monitoring of lymphatic clearance of gold nanorods (GNRs) from the cortex, the hyppocampus, the right ventricle, and the cisterna magna, we have proposed that the tPS-mediated stimulation of lymphatic drainage might be a possible mechanism underlying the tPS-elimination of Aβ from the brain. These results open breakthrough strategies for a non-pharmacological therapy of AD and give strong evidence that tPS might be a promising therapeutic target for preventing or delaying AD.

We investigated possible mechanisms of tPS-stimulation of lymphatic drainage and clearance [88], [89]. Our results demonstrate that already low PS doses (1267 nm, 5 and 10 J/cm^2) cause relaxation of the mesenteric LVs and increase their permeability to fluorescent macrophages via a decrease of expression of the tight junction proteins and the transendothelial resistance. We hypothesized that a PS-mediated increase in the permeability of the lymphatic endothelium might be the mechanism of transport of macromolecules and cells in the narrow cerebral LVs. The increasing of permeability of the lymphatic endothelium is the key factor underlying lipids diffusion and macromolecules from the tissues to the LVs, which may help to explain why the adipose tissue is always located adjacent to collecting lymphatics and the lymph nodes [90]–[92].

The transport of macromolecules across the collecting LVs is coupled to water flux and sensitive to lymph pressure [90]. The inherent permeability of LVs is sufficient to broadcast antigens, passing within lymph to the cLNs [91]. Kuan *et al.* clearly demonstrated that the delivery of soluble antigens, such as FITC-conjugated endogenous proteins and Eα-GFP is possible due to the permeability of the LVs [91].

This process exposes a large community of endocytic and phagocytic cells, particularly dendritic cells and macrophages. Physiological mechanisms underlying the lymphatic permeability to macromolecules remain, however, unknown. The possible role of Lyve-1 and CCL-21 might be involved in the regulation of migration of immune cells through the lymphatic endothelium. The Lyve-1 is a transmembrane receptor of hyaluronan, which regulates cell migration in the course of wound healing, inflammation, and embryonic morphogenesis [93]. This protein is expressed primarily on both the luminal and abluminal surface of the lymphatic endothelium [93], [94] and plays an important role in hyaluronan transport providing for migration of immune cells [95]. The CCL is secreted by the lymphatic endothelial cells and is involved in activation of T-lymphocyte movement, migration of the lymphocytes to other organs, and dendritic cells into the lymph nodes [96].

Nitric oxide (NO) can be another modulating factor of lymph flow [97]–[102]. There are multiple sources of NO that could influence on the LVs funtions: 1) NO production from the endothelial nitric synthase in the lymphatic endothelium; 2) NO generation from the inducible nitric synthase in immune cells; 3) NO release from neural nitric synthase in the parenchyma or the perivascular lymphatic nerves [100], [102]–[105], 4) countercurrent exchange of NO from adjacent arteries or veins. The predominant NO production in the LVs occurs in the valve-bulb region [106], [107]. The high-shear force of lymph flowing through the open valve leaflets contributes to elevating of NO levels near the valve. The NO-mediated modulation of valves closing and opening coordinates the flow of lymph in the LVs [108]. In sum, the data above open new strategies for an alternative non-pharmacological therapy of brain diseases via photomodulation of the lymphatic mechanisms of drainage and clearance of CNS tissues.

III. Noninvasive Technologies of Stimulation of the Extracranial Lymphatics

Photostimulation of the cerebral lymphatics has significant limitation to be clinically applied due to low penetration of light via the skull, which provides significant scattering effect. Therefore, photostimulation of the extracranial lymphatics can be a promising candidate for modulation of the brain lymphatic system via the cribriform-lymphatic connection. The intranasal irradiation might be most effective method for therapeutic stimulation of CSF outflow.

At the beginning of 1990's in Russia [109]–[111] and in China, [112], [113] experiments were started to study the irradiation of bloodstream of nasal cavity. Many Russian studies were focused on treatment of rhinitis [109], sinusitis [110], and ischemic heart diseases [114], while the Chinese investigations were dedicated mainly to neurological diseases, such as stroke [115]. The technique of intranasal irradiation of blood and LVs involves a diode laser device (mainly at 650–660 nm, 810–830 nm) with 10–30 mW of power, attached inside the nose.

The treatment duration varies from 15 min to 30 min per day for 10–14 days (consecutively or not). There are four suggested pathways discussed in the literature, that mediating the intranasal low-level laser/light therapy: the olfactory nerves, blood cells, meridians in traditional Chinese medicine, and the autonomic nervous system. The special treatment was called intranasal low intensity laser therapy (ILILT) and started to be clinically applied broadly on patients in the end of 1990's [113], [116].

ILILT might be a promising candidate for effective treatment of obstruction of the cribriform-lymphatic route and an improving of CSF outflow. The mechanism by which ILILT can affects obstruction of the cribriform plate has not been adequately explored, although it makes sense that it should because NO modulates the LVs contraction and subsequent the lymph flow [117]. Photostimulation causes the light-stimulated release of NO [118]–[120]. NO is produced by the endothelial nitric oxide synthase in the lymphatic endothelial cells, which in turn affects the dilation and force of LVs contractions [121], [122]. NO is a well known vasodilator that acts via stimulation of the soluble guanylate cyclase to form the cyclic-GMP (cGMP). cGMP activates the protein kinase G, which causes re-uptake of Ca2+ and the opening of calcium-activated potassium channels. The fall in concentration of Ca2+ prevents the myosin light-chain kinase from phosphorylating the myosin molecule, leading to relaxation of the smooth muscle cells in the lining of blood and LVs [123]. There are several other mechanisms by which NO could conduct signaling pathways, including the activation of the iron-regulatory factor in macrophages [124], modulation of proteins such as the ribonucleotide reductase [125] and aconitase [126] stimulating the ADP-ribosylation of glyceraldehyde-3-phosphate dehydrogenase [127] and the protein-sulfhydryl-group nitrosylation [128]. The successful clinically application of ILILT for therapy of the brain diseases shown in several studies. ILILT is used for treatment of patients with Alzheimer' disease [129] and improves insomnia problems [130]–[132]. The mechanisms of therapeutic effects of ILILT are not clear, but there is evidence that ILILT modulates blood circulation and drainage function of the lymphatic system [133]. Fig. 3 schematically illustrates a possible mechanisms of ILILT of the obstruction of the cribriform-lymphatic pathway of CSF outflow.

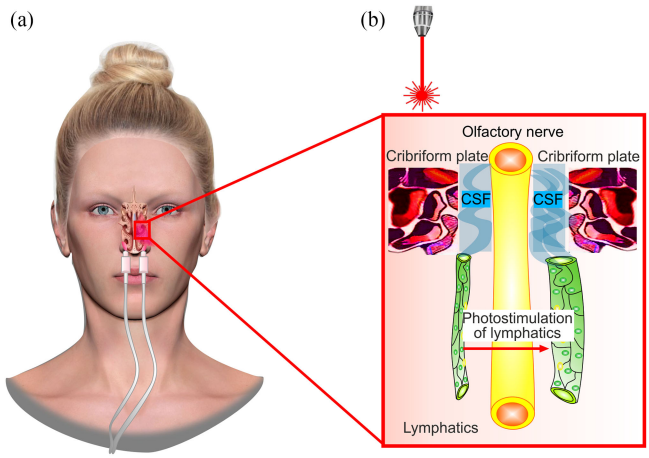


Fig. 3. Schematic illustration of ILILT of the cribriform plate and the olfactory nerve that provides the stimulation of CSF outflow via the extracranial lymphatics.

IV. Optogenetics as Selective Photo-Technology for the Study of Mechanisms Underlying ILILT

Optogenetics (from Greek optikós 'seen, visible') is a technique that involves the use of light to cause or inhibit well-defined events in specific cells of living tissue and behaving animals [134], [135]. In 2010, optogenetics was chosen as the "Method of the Year" across all fields of science and engineering by the interdisciplinary research journal Nature Methods [136]. At the same time, optogenetics was highlighted in the article on "Breakthroughs of the Decade" in the academic research journal Science [137], [138].

The field of optogenetics has furthered the fundamental scientific understanding of how specific cell types contribute to the function of biological tissues such as neural circuits in vivo [134], [135]. Moreover, on the clinical side, optogenetics-driven research has led to insights into Parkinson's disease [139], [140] and other neurological and psychiatric disorders [141]–[144].

Optogenetis is also pioneering tool that has recently been crafted to modulate spontaneous vasomotion and manipulation of the lymphocyte trafficking, the inflammasome activation, the dendritic cell maturation, and antitumor immunity through the photoactivation of the engineered chemokine receptors and Ca2+ release via light-activated the calcium channels [145]–[148].

Therefore, this technology could be implemented in the development of new strategies of a targeted photo-stimulation of lymphatic drainage and clearing functions. For example, recent genetic screening reveal that patients with mutations in GJC2 or GJA1, encoding the gap junction proteins Cx (connexin) 47 and Cx43, respectively, develop primary lymphedema [149]–[152]. Possible mechanisms include defects in 1-way endothelial valves that minimize lymph back-flow or impairment of the spontaneous contractions of the lymphatic muscle cells, both of which are critical for efficient lymph transport. Castorena-Gonzalez *et al.* found that lymphatic contractions are highly coordinated along LVs segments because of the rapid conduction of pacemaking signals between the Cx-coupled lymphatic muscle cells [153]. Using transgenic mouse models to delete specific Cx isoforms, this research group show that each of the 3 major endothelial Cxs (Cx47, Cx43, Cx37) are dispensable for the initiation and entertainment of spontaneous lymphatic contractions. However, the smooth muscle–specific Cx45 deficiency results in the disruption of both electrical and contraction waves. Lymph transport is impaired in the intact hindlimbs of Cx45-deficient mice only when a gravitational load is imposed [154]–[156]. These findings suggest that lymphedema in the dependent extremities of human patients with Cx47 or Cx43 mutations is related to reduced valve density and competency rather than contractile dysfunction or dyssynchrony. Therefore, the development of transgenic animals expressing both a light-gated photon channel (channelrhodopsin 2, ChR2),

which is widely used in optogenetics, and Cx in the lymphatic endothelium might be a promising tool to examine possible targets of optogenetic photostimulation of lymphatic drainage for therapeutic purposes [157], [158].

Among the optogenetic methods, a technique called "optogenetic noise-photostimulation" [157], [158] could be useful to determine the optimal light intensity of light for lymphatic photostimulation. For instance, Mabil *et al.* demonstrated that a light intensities below 0.67 mW allows to avoid opto non-genetics related responses due to light-induced temperature changes [159].

Recently, it was reported that a light in the visible range can affect the neuronal physiology in a cell-specific manner. Ait Ouares *et al.* demonstrated that a light by itself modulates ion channels by changing the temperature from 0.1 to 0.4 °C associated with the generation of a hyperpolarizing current and a modification of action potential shape [160]. Tissue temperature linearly increases with a light power reaching an average value of 0.03 °C at 1 mW and 0.4 °C at 13 mW. In contrast, optogenetic photostimulation can produce physiological responses in cells in the brain not associated with light-induced temperature changes, at least at a range below 0.67 mW [159]. We expect that all these selective techniques could allow more detailed research the specific mechanisms underlying ILILT as effective photostimulation treatment in the cribriform-lymphatic-plate obstruction".

V. Measurement of the Lymph Flow

The development of promising technologies of the cerebral and the extracranial lymphatics strongly depends on the non-invasive methods of measurement of the lymph flow.

The volumetric flow rate of the lymph as well as the concentration of cells in the flow are the key parameters characterizing the lymph perfusion in tissue [161]. The increasing of the relative lymph flow rate indicates regulatory response of the lymphatic system to external or internal factors. In a long term temporal scale the increase of local lymphatic perfusion could indicate LVs growth as compensatory response to external factors [162]–[164].

Current interest to the physiology and the functionality of MLVs demands for non-invasive techniques for a label-free assessment of the lymphatic perfusion. Even a qualitative detection of the lymph perfusion in the brain tissues could potentially revolutionize the understanding of the brain physiology and in particular MLVs [162]–[164].

However the detection of the lymphatic perfusion is not a trivial procedure that currently can be performed only with very specific animal models like the rat intestine mesentery lymphatic [88], [89] or the mouse ear skin [165]–[170], but no label-free detection of the lymph flow through MLVs has been reported yet. Both of these models represent the peripheral lymphatic system and provide the advantage of intravital optical imaging of the LVs structure and function [161], [168].

The rat mesentery is a transparent structure with the averaged refractive index 1.38 that consists of two thin (approx 10 μ m both) layers of conjunctive tissue with a single layer of the blood and well developed LVs between them. It provides an ideal condition for both a transmitted light and fluorescent microscopy with highest possible numerical resolution. That makes it possible to track the movement of individual cells with the lymph flow [168] as well as injection of a fluorescent dye to visualize the lymph flow itself [161].

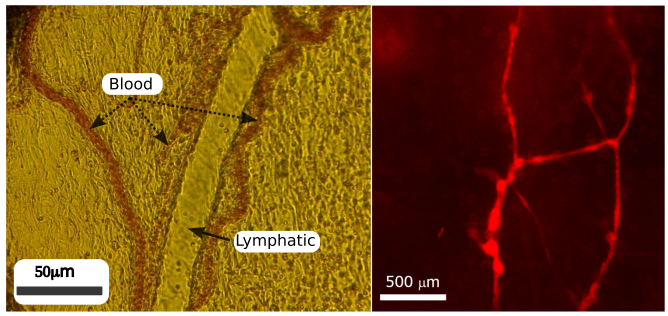


Fig. 4. Transmission light microscopy image of LV of the rat mesentery (a) and Evans Blue dye fluorescence in LVs of the mouse ear (b).

The disadvantage of the rat mesentery model is its invasiveness. To overcome this issue, a mouse ear model is also used for studies of the lymphatic system [161], [165], [167], [168]. Thin ear skin with single layer of LVs makes it possible to perform microscopic imaging of LVs and the blood vessels with fluorescent techniques. While individual cells in the lymph flow are hard to be resolved, fluorescent angiography enables mapping of LVs and the lymph flow velocity measurements [161], [167], [169].

A typical image of the rat mesentery LV is shown in Fig. 4(a). The LV appears as a light band filled with rare circulating cells in the center of the image. Digital tracking of these cells can be performed to measure the lymph flow velocity and to estimate the cell concentration. Fig. 4(b) represents fluorescence of Evans blue dye into LVs of the mouse ear.

In contrast to these animal models non-invasive optical imaging of MLVs is impossible even in mice due to light scattering of the non transparent skull and the skin, under which MLVs are localized. Currently dynamic MRI of contrast enhanced CSF is capable for estimation of the flow rate trough MLVs [162], while the structure and the anatomy of MLVs can be reconstructed with ex vivo fluorescent microscopy [162], [163].

Earlier we have demonstrated the use of coherent laser light scattering for measurements of the lymph flow velocity in the rat mesentery vessels [171], [172]. The schematic diagram of the instrument is presented in Fig. 5(a). The measurements were performed using the rat mesentery LVs. Laser light was focused at distance z above the vessel in order to produce a translating speckle field resulting from light scattering on the moving cells. Within the mesentery plane laser, the diverging laser beam overlaps the entire cross-section of LVs. Coherent light scattered with the moving cells produces a dynamic speckle field. It is a characteristic diffraction pattern consisting of randomly distributed bright spots, namely speckles Fig. 5(b). The speckle pattern translates in the same direction as the lymph cells and its velocity is directly proportional to these cells with the factor of L/z (Fig. 5(a)) [171], [172]. Translation velocity of the speckle

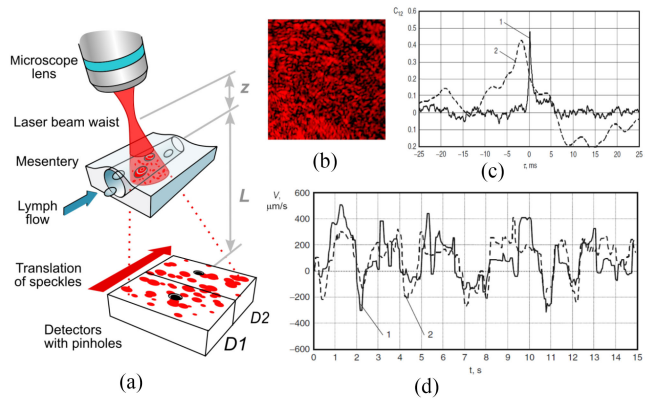


Fig. 5. Laser speckle technique for the rat mesentery lymph flow velocity measurements [171], [172]. The instrument (a); laser speckles within the detector plane, (b); cross-correlation of photodiode signals due to translation of speckles (c), and (d) comparison of the lymph flow velocity measured with laser speckle technique (solid line) with results of digital tracking of cells. In panel (a): D1, D2 are the photodiode detectors; z is the separation between laser beam waist and the lymph vessel plane; L is the distance between the object and the detection plane.

pattern $V_{speckles}$ can be measured by the analysis of the mutual correlation of photocurrent fluctuations from two photodiodes D1 and D2 (Fig. 5(a)), as it is shown in Fig. 5(c).The peak of the mutual correlation is displaced by the time interval required for moving speckle pattern to cover the separation between detectors.

Fig. 5(d) shows the lymph cells velocity measured with the laser speckles technique (solid line) and that measured with direct tracking of the cells on video sequence recorded simultaneously. The advantage of the use of coherent laser radiation is that the laser speckle contrast is close to 1 even when the cell image could not be resolved because the cell is out of focus or because the light scattering tissue covers LV. Namely the laser speckle technique allows to detect the cell movement even when the cells are not visible. In the case of high scattering of light by tissues translation of speckle pattern can be destroyed and speckles will "boil" but anyway movement of cells results in detectable fluctuations of a speckle pattern. That principle has been successfully applied for visualization of LVs of the mouse ear with laser speckle contrast analysis technique [167], which allows for full field visualization of speckle fluctuations. The fluctuating speckle field appears blurred when captured with long exposure although its "instant" contrast is close to 1 because of the high coherence of laser light. The fast moving cells, like the red blood cells produce rapidly fluctuating speckle field. It is blurred even at short exposure time about several ms. A longer exposure time is suitable to detect the slowly moving cells, e.g. the capillary blood flow. The higher contrast corresponds to the slower movement of cells. Fig. 6(a) and (b) show the distribution of the speckle field contrast over the nude mouse ear.

Fig. 6(a) corresponds to exposure time of 33 ms and (b) to that of 650 ms. On the Fig. 6(b) a white pattern corresponding to a vessel-like structure is visible. The white area corresponds to the higher contrast, namely to the cells moving slower than the background. Thus this is a "negative" image of the moving cells within the tissue. These regions could be interpreted as

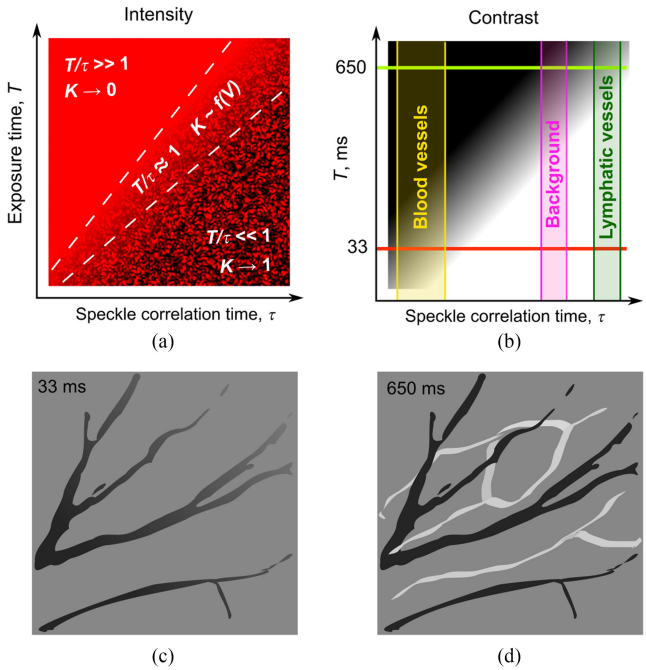


Fig. 6. Principles of laser speckle imaging of LVs. Contrast of laser speckle image depends on the blood flow velocity within so called sensitivity interval confined within dashed lines (a). Short exposure time (red line) enables to detect fast variations of speckle contrast, while longer exposure times (green line) discover background circulation (b). Short exposure time of laser speckle imaging enables the blood vessel imaging (c); long exposure time of laser speckle imaging reveals LVs as a light shaded regions with low background circulation (d) [167].

regions without blood microcirculation e.g. LVs. Figs. 6(c) and (d) show fluorescent intravital microscopy image of LVs and its superposition with a LASCA image respectively.

The laser speckle contrast technique is useful for the detection of the superficial vessels. The deep circulation manifests itself as an average of fluctuations of coherent light scattered by living biological tissue. Because no structure of the vessels could be resolved at a depth of several millimeters the resulting speckle field fluctuations represent only the averaged velocity and concentration of the moving cells. The technique based on the detection of averaged fluctuations is referred to as laser Doppler flowmetry [161], [173]. Typically laser Doppler flowmetry is aimed to detect fast fluctuations of laser speckles, related with the circulation of red blood cells. But it is possible that a slow movement of the lymph also contributes into the laser Doppler flowmetry signal at low frequencies. The averaged velocity of the lymph does not exceed 0.1 mm/s, while the averaged velocity of the red blood cells is within the range 0, 1–5 mm/s. Thus laser speckle fluctuations related with the lymph microcirculation can be detected at low frequencies. The problem of detection is challenging because of the interference of involuntary movements of an object, cardiac and respiratory activity as well vasomotor reaction.

VI. The Driving Mechanisms of CSF Outflow

The other limiting factor for the progress in the development of technologies of stimulation of brain drainage is the not

well-established connective bridge between ISF and CSF flow as well as the driving mechanisms of CSF outflow from the brain.

The presence of arterial pulsations in the brain vasculature can be regarded as a proven fact. Hadaczek *et al.* [174] investigated the movement of the interstitially infused macromolecules within the brain at different combinations of the blood pressure and the heart rate including cardiac arrest. Iliff *et al.* [175] showed that the perivascular pulsations accelerate the spread of dye and suggested that they provide a kind of pumping mechanism through the parenchyma, being one of the key elements of the glymphatic hypothesis. Later, this statement was criticized [176]–[178].

In Butler [179], pulsations were studied at the micro-level: the shape and phases of a single pulse wave in the arterial and venous vessels in response to injection were evaluated. A phase lag in the venous vessel relative to arterial was detected. In Postnov D. D. *et al.* [180] the speckle flowmetry method was used to build a map of the intensity of vascular pulsations. The relative powers of pulsations in the arteries, the veins, and the parenchyma are estimated. In contrast to the previous work, no significant phase shift from the arteries to the veins was found. In addition, it was shown that the pulsations in the parenchyma are spatially homogeneous.

Gao *et al.* [181] used two-photon microscopy to image the vascular dynamics in the somatosensory cortex of awake behaving mice. They showed that the mechanism of intracortical vessel dilation by brain tissue sculpts the hemodynamic response. Bedussi B. *et al.* [182] observed that microspheres move preferentially in the perivascular space of the arteries rather than in the adjacent subarachnoid space or the veins. The perivascular flow was pulsatile, generated by the cardiac cycle, with the net antegrade flow. The paper [183] shows that the direction of flow in the cerebral aqueduct can change during one cardiac cycle.

Kiviniemi *et al.* [184] showed that the spectral power of the respiratory rhythm in the signal obtained by ultra-fast magnetic resonance is not inferior to the one of cardiac pulsations. It looks counter-intuitive, since the respiratory rhythm is recorded throughout the body, but its power is usually much lower than that of the heart. Why is this not so for the brain? Recently, Vinje V. *et al.* [185] possibly answered this question. In their work, they evaluated the contribution of heart and respiratory rhythms to CSF movement. It was found that pressure gradients underlying CSF flow are dominated by cardiac pulsations, but induced CSF flow volumes are dominated by respiration. No significant differences were found for this relationship between sleep and wakefulness.

The third type of pulsation reported in [184] was very low frequency (VLF 0.001–0.023 Hz). The VLF pulsations were found as the most complex in the spatiotemporal dynamics. Recently, Fultz N. E. *et al.* [186] reported the results of the sophisticated multimodal study that revealed the formation of ultra-slow synchronized electrophysiological, hemodynamic, and CSF oscillations in human sleep. In contrast to [184], here the ultra-slow oscillations have a very simple, globally synchronized pattern which appear specifically during non-REM sleep. The important new feature revealed is the phase lags between the EEG, BOLD, and CSF signals, which allow drawing the conclusions about the causal chain. Specifically, it is shown that a very slow EEG wave precedes the changes in cerebral blood flow that, in turn, is followed by CSF peak.

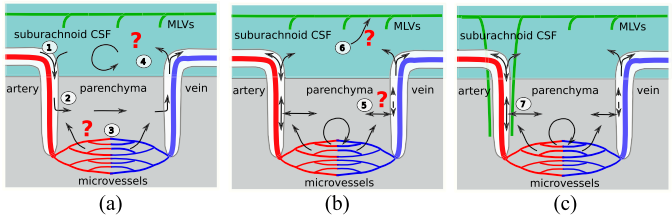


Fig. 7. The plausible schemes of brain drainage. (a) based on glymphatic hypothesis, (b) based on arterial pulsations with zero bulk flow, and (c) pulsation-powered mechanism exploiting the hypothesised small LVs. Digits in circles denote the key issues to discuss, see text.

Since CSF movement plays an important role in the brain drainage mechanisms, it is important to mention that there are alternative points of view on the main sources of CSF and, therefore, on the way it moves. According to the usual point of view, CSF formation occurs mainly in brain ventricles, in choroid plexuses. The CSF formation, together with CSF absorption and circulation, represents the so-called classic hypothesis of CSF hydrodynamics. However, there is also an alternative point of view known as Orešković and Klarica hypothesis [187], [188]. According to this alternative hypothesis, CSF is permanently produced and absorbed in the whole CSF system as a consequence of filtration and reabsorption of water volume through the capillary walls into the surrounding brain tissue.

We can see how different hypotheses play, both long known and newly emerging ones. After 2012, the proposed glymphatic hypothesis caused such a revision. In particular, Hladky and Barrand [189] reviewed the playability of glymphatics and its alternatives, in which there are pulsations, but they do not create bulk flow. The variants of proposed mechanisms provided the basis for a number of model studies comparing them to each other [190].

Fig. 7 shows the most interesting flow management options under various assumptions. Panel (a) shows how flows flow according to the glymphatic hypothesis [191], [192]. This glia-mediated transport occurs through the brain extracellular space and deliver of wastes to the venules for clearance along perivenous spaces. The mechanism to major extent relies on the fact that arterial pulsations create a directed bulk flow of CSF from the pial membrane (1) to the parenchyma region near PVS (2). However, this pumping is a weak point of the hypothesis and has caused the main criticism of the hypothesis as a whole, as we mentioned above [17], [178], [193], [194]. Also, this mechanism makes impossible the fast release substances from the opened blood-brain barrier (BBB) (3), and especially the erythrocytes to the meningues, since they cannot move freely through the parenchyma, and in the periarterial space they would have to move upstream. Additionally, one may wonder how efficiently metabolic waste can reach MLVs by exiting the venous PVS (4). The fact that LVs, rather than the veins, are the major outflow pathway for both large and small molecular tracers in mice was demonstrated by Ma *et al.* [195].

Panel (b) of the figure displays the mechanism of "pulsation-assisted diffusion", which many critics of the glymphatic hypothesis suggest as the more likely mechanism [17], [177], [178], [196]. According to this mechanism, the rapid transport of substances in any direction is possible due to the fact that arterial pulsations create oscillations of fluid, which dramatically accelerates diffusion even at zero net flow. This mechanism works equally well in both directions along PVS. It is not very clear how much it takes place for the venous vessels (5), but this is possible, since a number of works reported rather strong pulsations of blood flow in them [179], [180]. However, just as for the glymphatic hypothesis, it is difficult to explain the facts of the fast and approximately simultaneous transport of macromolecules and the cells in MLVs (6).

Panel (c) of Fig. 7 shows a variant that could be plausible if the small perivascular LVs would be found. In this case, the role of pulsations would be even more important, since the weak directed flow of CSF into hypothesized LVs together with local pulsations of the brain fluid, which accelerate the exchange with the parenchyma, can provide effective short-distance movement of metabolic waste into LVs from the surrounding parenchyma (7). This could work equally well for: (i) transfer of substances from the subarachnoid space to the parenchyma; (ii) washing out of amyloids from the parenchyma and transfer of substances from the opened BBB, in a certain proportion, to the meninges, to the parenchyma, and also to hypothetical perivascular LVs. (3) the transfer of the red blood cells mainly to LVs, since arterial PVS seems narrower and more difficult to pass through.

VII. Conclusion

Taking together, photomodulation of the cranial and the extracranial lymphatics might be a promising candidate for therapy of brain diseases associated with CSF outflow disorders. Latest discoveries suggest that the infrared laser irradiation significantly affects the drainage and clearing function of the lymphatics in the brain meninges and in the cribriform plate, which is main station of CSF exist from the brain. In this aspect, ILILT can be the effective noninvasive technique for therapy of obstruction of the cribriform plate leading the development of various brain pathologies due to the blocking of CSF drainage. The pilot results of several research groups clearly demonstrate that the lymphatic system is door not only from the brain but also into it. It sheds light on the development pioneering strategies in drug delivery into the brain bypassing the BBB. However, photostimulation of MLVs is limited by low penetration of laser through the skull, which provides significant scattering effects. Most likely that photostimulation of MLVs can be clinically applied only in neonates via the fontanels. In adults, ILILT is a more promising approach for modulation of the extracranial lymphatics. But, there are no well-recognized guidelines and protocols for ILILT. The photostimulation of the lymphatic mechanisms of restorative functions of the brain is still in infancy. Nevertheless, these promising technologies might be progressive step in neurorehabilitation medicine opening a new era for the development of novel bedside, readily applicable and commercially viable and non-pharmacological technologies for the treatment of brain diseases.

Acknowledgment

We thank Saranceva Elena for preparation of figures for this review.

References

[1] L. Koh, A. Zakharov, and M. Johnston, "Integration of the subarachnoid space and lymphatics: Is it time to embrace a new concept of cerebrospinal fluid absorption?" *Cerebrospinal Fluid Res.*, vol. 2, no. 1, pp. 1–11, 2005.

[2] H. F. Cserr and P. M. Knopf, "Cervical lymphatics, the blood-brain barrier and the immunoreactivity of the brain: A new view," *Immunol. Today*, vol. 13, no. 12, pp. 507–512, 1992.

[3] M. Bradbury, "Lymphatics and the central nervous system," *Trends Neurosciences*, vol. 4, pp. 100–101, 1981.

[4] E. Mezey and M. Palkovits, "Forgotten findings of brain lymphatics," *Nature*, vol. 524, no. 7566, pp. 415–415, 2015.

[5] R. O. Weller, E. Djuanda, H.-Y. Yow, and R. O. Carare, "Lymphatic drainage of the brain and the pathophysiology of neurological disease," *Acta Neuropathologica*, vol. 117, no. 1, pp. 1–14, 2009.

[6] A. Aspelund *et al.*, "A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules," *J. Exp. Med.*, vol. 212, no. 7, pp. 991–999, 2015.

[7] A. Louveau *et al.*, "Structural and functional features of central nervous system lymphatic vessels," *Nature*, vol. 523, no. 7560, pp. 337–341, 2015.

[8] W. His, "Ueber ein perivasculäres canalsystem in den nervösen centralorganen und über dissen beziehungen zum lymphsystem," *Zeitschr. F. Wiss. Zool., Bd*, vol. 15, 1865, Art. no. 1874.

[9] G. Schwalbe, "Der arachnoidalraum, ein lymphraum und sein zusammenhang mit dem perichorioidalraum," *Zentralbl. Med. Wiss.*, vol. 7, pp. 465–467, 1869.

[10] L. H. Weed, "Studies on cerebro-spinal fluid. no. iii: The pathways of escape from the subarachnoid spaces with particular reference to the arachnoid villi," *J. Med. Res.*, vol. 31, no. 1, pp. 51–91, 1914.

[11] M. Caversaccio, O. Peschel, and W. Arnold, "Connections between the cerebrospinal fluid space and the lymphatic system of the head and neck in humans," in *Proc. Intracranial Intralabyrinthine Fluids.*, 1996, pp. 123–128.

[12] B. Engelhardt, R. O. Carare, I. Bechmann, A. Flügel, J. D. Laman, and R. O. Weller, "Vascular, glial, and lymphatic immune gateways of the central nervous system," *Acta Neuropathologica*, vol. 132, no. 3, pp. 317–338, 2016.

[13] F. Bucchieri, F. Farina, G. Zummo, and F. Cappello, "Lymphatic vessels of the dura mater: A new discovery?" *J. Anatomy*, vol. 227, no. 5, 2015, Art. no. 702-3.

[14] O. Semyachkina-Glushkovskaya *et al.*, "Photodynamic opening of the blood-brain barrier and pathways of brain clearing," *J. Biophotonics*, vol. 11, no. 8, 2018, Art. no. e201700287.

[15] O. Semyachkina-Glushkovskaya *et al.*, "Application of optical coherence tomography for in vivo monitoring of the meningeal lymphatic vessels during opening of blood-brain barrier: Mechanisms of brain clearing," *J. Biomed. Opt.*, vol. 22, no. 12, 2017, Art. no. 121719.

[16] S. Da Mesquita *et al.*, "Functional aspects of meningeal lymphatics in ageing and alzheimer's disease," *Nature*, vol. 560, no. 7717, pp. 185–191, 2018.

[17] O. Semyachkina-Glushkovskaya, D. Postnov, and J. Kurths, "Blood-brain barrier, lymphatic clearance, and recovery: Ariadne's thread in labyrinths of hypotheses," *Int. J. Mol. Sci.*, vol. 19, no. 12, 2018, Art. no. 3818.

[18] M. Kosteljanetz, "Intracranial pressure: Cerebrospinal fluid dynamics and pressure-volume relations," *Acta Neurologica Scandinavica. Supplementum*, vol. 111, pp. 1–23, 1987.

[19] A. Marmarou, K. Shulman, and J. Lamorgese, "Compartmental analysis of compliance and outflow resistance of the cerebrospinal fluid system," *J. Neurosurgery*, vol. 43, no. 5, pp. 523–534, 1975.

[20] M. Czosnyka, Z. H. Czosnyka, P. C. Whitfield, and J. D. Pickard, "Cerebrospinal Fluid Dynamics," in *Pediatric Hydrocephalus* Berlin, Germany: Springer, 2005, pp. 47–63.

[21] A. Zakharov, C. Papaiconomou, L. Koh, J. Djenic, R. Bozanovic-Sosic, and M. Johnston, "Integrating the roles of extracranial lymphatics and intracranial veins in cerebrospinal fluid absorption in sheep," *Microvascular Res.*, vol. 67, no. 1, pp. 96–104, 2004.

[22] Q. Ma *et al.*, "Rapid lymphatic efflux limits cerebrospinal fluid flow to the brain," *Acta Neuropathologica*, vol. 137, no. 1, pp. 151–165, 2019.

[23] R. O. Weller, S. Kida, and E.-T. Zhang, "Pathways of fluid drainage from the brain-morphological aspects and immunological significance in rat and man," *Brain Pathol.*, vol. 2, no. 4, pp. 277–284, 1992.

[24] S. Kida, A. Pantazis, and R. Weller, "Csf drains directly from the subarachnoid space into nasal lymphatics in the rat. anatomy, histology and immunological significance," *Neuropathol. Appl. Neurobiol.*, vol. 19, no. 6, pp. 480–488, 1993.

[25] M. Johnston, A. Zakharov, C. Papaiconomou, G. Salmasi, and D. Armstrong, "Evidence of connections between cerebrospinal fluid and nasal lymphatic vessels in humans, non-human primates and other mammalian species," *Cerebrospinal Fluid Res.*, vol. 1, no. 1, pp. 1–13, 2004.

[26] M. J. De Leon *et al.*, "Cerebrospinal fluid clearance in alzheimer disease measured with dynamic pet," *J. Nuclear. Med.*, vol. 58, no. 9, pp. 1471–1476, 2017.

[27] M. Bradbury and D. Cole, "The role of the lymphatic system in drainage of cerebrospinal fluid and aqueous humour," *J. Physiol.*, vol. 299, no. 1, pp. 353–365, 1980.

[28] I. Szentistvanyi, C. S. Patlak, R. A. Ellis, and H. F. Cserr, "Drainage of interstitial fluid from different regions of rat brain," *Amer. J. Physiol.-Renal Physiol.*, vol. 246, no. 6, pp. F835–F844, 1984.

[29] E. Syková and C. Nicholson, "Diffusion in brain extracellular space," *Physiol. Rev.*, vol. 88, no. 4, pp. 1277–1340, 2008.

[30] R. Mollanji, R. Bozanovic-Sosic, A. Zakharov, L. Makarian, and M. G. Johnston, "Blocking cerebrospinal fluid absorption through the cribriform plate increases resting intracranial pressure," *Amer. J. Physiol.-Regulatory, Integrative Comp. Physiol.*, vol. 282, no. 6, pp. R1593–R1599, 2002.

[31] I. Silver, C. Kim, R. Mollanji, and M. Johnston, "Cerebrospinal fluid outflow resistance in sheep: Impact of blocking cerebrospinal fluid transport through the cribriform plate," *Neuropathol. Appl. Neurobiol.*, vol. 28, no. 1, pp. 67–74, 2002.

[32] C. Botel *et al.*, "A species comparing study of lymphatic absorption of cerebrospinal-fluid," *Lymphol.*, vol. 27, pp. 688–691, 1994.

[33] R. Mollanji *et al.*, "Intracranial pressure accommodation is impaired by blocking pathways leading to extracranial lymphatics," *Amer. J. Physiol.-Regulatory, Integrative Comp. Physiol.*, vol. 280, no. 5, pp. R 1573–R1581, 2001.

[34] C. Papaiconomou, R. Bozanovic-Sosic, A. Zakharov, and M. Johnston, "Does neonatal cerebrospinal fluid absorption occur via arachnoid projections or extracranial lymphatics?," *Amer. J. Physiol.-Regulatory, Integrative Comp. Physiol.*, vol. 283, no. 4, pp. R869–R876, 2002.

[35] R. T. Jackson, J. Tigges, and W. Arnold, "Subarachnoid space of the cns, nasal mucosa, and lymphatic system," *Arch. Otolaryngol.*, vol. 105, no. 4, pp. 180–184, 1979.

[36] A. Radjavi, I. Smirnov, N. Derecki, and J. Kipnis, "Dynamics of the meningeal cd4 t-cell repertoire are defined by the cervical lymph nodes and facilitate cognitive task performance in mice," *Mol. Psychiatry*, vol. 19, no. 5, pp. 531–532, 2014.

[37] C. Xing, X. Lu, W. Sun, J. Wang, and D. Xiang, "The effect of blocking the cervical lymphatic drainage of rabbit on its cerebral structure and function in the acute lymphostasis stage," *LYMPHOLOGY*, vol. 27, pp. 742–746, 1994.

[38] M. Földi, B. Csillik, and Ö. Zoltán, "Lymphatic drainage of the brain," *Experientia*, vol. 24, no. 12, pp. 1283–1287, 1968.

[39] M. Foldi, "*Lymphogenous Encephalopathy*," *Lymph Lymphatic Syst.*, 1968, pp. 169–198.

[40] J. Casley-Smith, L. Clodius, E. Földi-Börcsök, J. Grüntzig, and M. Földi, "The effects of chronic cervical lymphostasis on regions drained by lymphatics and by prelymphatics," *J. Pathol.*, vol. 124, no. 1, pp. 13–17, 1978.

[41] J. Casley-Smith, E. Földi-Börsök, and M. Földi, "The prelymphatic pathways of the brain as revealed by cervical lymphatic obstruction and the passage of particles," *Brit. J. Exp. pathol.*, vol. 57, no. 2, pp. 179–188, 1976.

[42] B.-L. Sun *et al.*, "Effects of blockade of cerebral lymphatic drainage on regional cerebral blood flow and brain edema after subarachnoid hemorrhage," *Clin. Hemorheol. Microcirculation*, vol. 34, no. 1, 2, pp. 227–232, 2006.

[43] Z.-L. Xia *et al.*, "The effect of cerebral lymphatic blockage on cortex regional cerebral blood flow and somatosensory evoked potential," *Clin. Hemorheol. Microcirculation*, vol. 29, no. 3, 4, pp. 345–349, 2003.

[44] D. W. Ethell, "Disruption of cerebrospinal fluid flow through the olfactory system may contribute to alzheimer's disease pathogenesis," *J. Alzheimer's Dis.*, vol. 41, no. 4, pp. 1021–1030, 2014.

[45] G. S. Ajmani, H. H. Suh, and J. M. Pinto, "Effects of ambient air pollution exposure on olfaction: A review," *Environ. Health Perspectives*, vol. 124, no. 11, pp. 1683–1693, 2016.

[46] A. A. Agyeman, K. L. Chin, C. B. Landersdorfer, D. Liew, and R. Ofori-Asenso, "Smell and Taste Dysfunction in Patients With covid-19: A Systematic Review and Meta-Analysis," in *Mayo Clinic Proceedings.* New York, NY, USA: Elsevier, 2020.

[47] P. C. Passarelli, M. A. Lopez, G. Mastandrea Bonaviri, F. Garcia-Godoy, and A. D'Addona, "Taste and smell as chemosensory dysfunctions in covid-19 infection," *Amer. J. Dent.*, vol. 33, no. 3, pp. 135–137, 2020.

[48] A. Printza and J. Constantinidis, "The role of self-reported smell and taste disorders in suspected covid-19," *Eur. Arch. of Oto-Rhino-Laryngology*, vol. 277, pp. 2625–2630, 2020.

[49] V. Montalvan, J. Lee, T. Bueso, J. De Toledo, and K. Rivas, "Neurological manifestations of covid-19 and other coronavirus infections: A systematic review," *Clin. Neurol. Neurosurgery*, vol. 194, 2020, Art. no. 105921.

[50] R. Butowt and C. S. von Bartheld, "Anosmia in COVID-19: Underlying mechanisms and assessment of an olfactory route to brain infection," *Neuroscientist*, Sep. 2020, Art no. 1073858420956905.

[51] M. d. F. V. V. Aragão *et al.*, "Anosmia in covid-19 associated with injury to the olfactory bulbs evident on mri," *Amer. J. Neuroradiol.*, vol. 41, no. 9, pp. 1703–1706, 2020.

[52] A. M. Baig, A. Khaleeq, U. Ali, and H. Syeda, "Evidence of the covid-19 virus targeting the cns: Tissue distribution, host-virus interaction, and proposed neurotropic mechanisms," *ACS Chem. Neurosci.*, vol. 11, no. 7, pp. 995–998, 2020.

[53] M. Briguglio *et al.*, "Disentangling the hypothesis of host dysosmia and sars-cov-2: The bait symptom that hides neglected neurophysiological routes," *Front. Physiol.*, vol. 11, 2020, Art. no. 671.

[54] S. Gilani, R. Roditi, and M. Naraghi, "Covid-19 and Anosmia in Tehran, Iran," *Med. Hypotheses*, vol. 141, 2020, Art. no. 109757.

[55] M. Karimi-Galougahi, A. Yousefi-Koma, M. Bakhshayeshkaram, N. Raad, and S. Haseli, "18fdg pet/ct scan reveals hypoactive orbitofrontal cortex in anosmia of covid-19," *Academic Radiol.*, vol. 27, pp. 1042–1043, 2020.

[56] N. M. Beeraka *et al.*, "Strategies for targeting sars cov-2: Small molecule inhibitors-the current status," *Front. Immunol.*, vol. 11, 2020, Art. no. 552925.

[57] H. Widner, G. Möller, and B. Johansson, "Immune response in deep cervical lymph nodes and spleen in the mouse after antigen deposition in different intracerebral sites," *Scand. J. Immunol.*, vol. 28, no. 5, pp. 563–571, 1988.

[58] C. Harling-Berg, P. M. Knopf, J. Merriam, and H. F. Cserr, "Role of cervical lymph nodes in the systemic humoral immune response to human serum albumin microinfused into rat cerebrospinal fluid," *J. neuroimmunol.*, vol. 25, no. 2, pp. 185–193, 1989.

[59] J. L. Vega, D. Ganea, and G. M. Jonakait, "Acute down-regulation of antibody production following spinal cord injury: Role of systemic catecholamines," *J. Neuropathol. Exp. Neurol.*, vol. 62, no. 8, pp. 848–854, 2003.

[60] R. O. Weller, "Pathology of cerebrospinal fluid and interstitial fluid of the cns: Significance for alzheimer disease, prion disorders and multiple sclerosis," *J. Neuropathol. Experimental Neurol.*, vol. 57, no. 10, pp. 885–894, 1998.

[61] J. Song, S.-S. Lee, S. Lim, and S. Yeo, "Mechanism of the neuroprotective effect of injecting brain cells on st36 in an animal model of parkinson's disease," *Neurosci. Lett.*, vol. 717, 2020, Art. no. 134698.

[62] P. Zhao, Z. Le, L. Liu, and Y. Chen, "Therapeutic delivery to the brain via the lymphatic vasculature," *Nano Lett.*, vol. 20, pp. 5415–5420, 2020.

[63] E. Zinchenko *et al.*, "Pilot study of transcranial photobiomodulation of lymphatic clearance of beta-amyloid from the mouse brain: Breakthrough strategies for non-pharmacologic therapy of alzheimer's disease," *Biomed. Opt. Express*, vol. 10, no. 8, pp. 4003–4017, 2019.

[64] Y. Lu *et al.*, "Low-level laser therapy for beta amyloid toxicity in rat hippocampus," *Neurobiol. Aging*, vol. 49, pp. 165–182, 2017.

[65] S. Grillo, N. Duggett, A. Ennaceur, and P. Chazot, "Non-invasive infrared therapy (1072 nm) reduces β-amyloid protein levels in the brain of an alzheimer's disease mouse model, tastpm," *J. Photochemistry Photobiol. B: Biol.*, vol. 123, pp. 13–22, 2013.

[66] S. Purushothuman *et al.*, "Near infrared light mitigates cerebellar pathology in transgenic mouse models of dementia," *Neurosci. Lett.*, vol. 591, pp. 155–159, 2015.

[67] C. da Luz Eltchechem *et al.*, "Transcranial led therapy on amyloid-β toxin 25-35 in the hippocampal region of rats," *Lasers Med. Sci.*, vol. 32, no. 4, pp. 749–756, 2017.

[68] A. Oron and U. Oron, "Low-level laser therapy to the bone marrow ameliorates neurodegenerative disease progression in a mouse model of alzheimer's disease: A minireview," *Photomedicine Laser Surgery*, vol. 34, no. 12, pp. 627–630, 2016.

[69] D. Farfara *et al.*, "Low-level laser therapy ameliorates disease progression in a mouse model of alzheimer's disease," *J. Mol. Neurosci.*, vol. 55, no. 2, pp. 430–436, 2015.

[70] J. Chang *et al.*, "Transcranial low-level laser therapy for depression and alzheimer's disease," *Neuropsychiatry*, vol. 8, no. 2, pp. 477–483, 2018.

[71] M. R. Hamblin, "Photobiomodulation for traumatic brain injury and stroke," *J. Neurosci. Res.*, vol. 96, no. 4, pp. 731–743, 2018.

[72] F. Salehpour *et al.*, "Brain photobiomodulation therapy: A narrative review," *Mol. Neurobiol.*, vol. 55, no. 8, pp. 6601–6636, 2018.

[73] P. Cassano *et al.*, "Near-infrared transcranial radiation for major depressive disorder: Proof of concept study," *Psychiatry J.*, vol. 2015, 2015, Art. no. 352979.

[74] Z. Xu *et al.*, "Low-level laser irradiation improves depression-like behaviors in mice," *Mol. neurobiol.*, vol. 54, no. 6, pp. 4551–4559, 2017.

[75] H. S. Mohammed, "Transcranial low-level infrared laser irradiation ameliorates depression induced by reserpine in rats," *Lasers Med. Sci.*, vol. 31, no. 8, pp. 1651–1656, 2016.

[76] S. Purushothuman, C. Nandasena, D. M. Johnstone, J. Stone, and J. Mitrofanis, "The impact of near-infrared light on dopaminergic cell survival in a transgenic mouse model of parkinsonism," *Brain Res.*, vol. 1535, pp. 61–70, 2013.

[77] B. N. Huisa *et al.*, "Transcranial laser therapy for acute ischemic stroke: A pooled analysis of nest-1 and nest-2," *Int. J. Stroke*, vol. 8, no. 5, pp. 315–320, 2013.

[78] P. A. Lapchak and P. D. Boitano, "Transcranial near-infrared laser therapy for stroke: How to recover from futility in the nest-3 clinical trial," in *Brain Edema XVI* Berlin, Germany: Springer, 2016, pp. 7–12.

[79] W. Xuan, T. Agrawal, L. Huang, G. K. Gupta, and M. R. Hamblin, "Low-level laser therapy for traumatic brain injury in mice increases brain derived neurotrophic factor (bdnf) and synaptogenesis," *J. Biophotonics*, vol. 8, no. 6, pp. 502–511, 2015.

[80] L. D. Morries, P. Cassano, and T. A. Henderson, "Treatments for traumatic brain injury with emphasis on transcranial near-infrared laser phototherapy," *Neuropsychiatric Dis. Treat.*, vol. 11, 2015.

[81] B. Smoot, L. Chiavola-Larson, J. Lee, H. Manibusan, and D. D. Allen, "Effect of low-level laser therapy on pain and swelling in women with breast cancer-related lymphedema: A systematic review and meta-analysis," *J. Cancer Survivorship*, vol. 9, no. 2, pp. 287–304, 2015Art. no–2159.

[82] A. Dirican, O. Andacoglu, R. Johnson, K. McGuire, L. Mager, and A. Soran, "The short-term effects of low-level laser therapy in the management of breast-cancer-related lymphedema," *Supportive Care Cancer*, vol. 19, no. 5, pp. 685–690, 2011.

[83] A. Landucci, A. Wosny, L. Uetanabaro, A. Moro, and M. Araujo, "Efficacy of a single dose of low-level laser therapy in reducing pain, swelling, and trismus following third molar extraction surgery," *Int. J. Oral Maxillofac. Surg.*, vol. 45, no. 3, pp. 392–398, 2016.

[84] A. Markovic and L. Todorovic, "Effectiveness of dexamethasone and low-power laser in minimizing oedema after third molar surgery: A clinical trial," *Int. J. Oral Maxillofac. Surg.*, vol. 36, no. 3, pp. 226–229, 2007.

[85] E. Mester *et al.*, "Effect of laser on hair growth of mice," *Kiserl Orvostud*, vol. 19, no. 7, 1967, Art. no. 621.

[86] E. Mester, T. Spiry, B. Szende, and J. G. Tota, "Effect of laser rays on wound healing," *Amer. J. Surg.*, vol. 122, no. 4, pp. 532–535, 1971.

[87] M. R. Hamblin, *Low-Level Light Therapy: Photobiomod-ulation*, SPIE Press, 2018, p. 388.

[88] O. Semyachkina-glushkovskaya *et al.*, "Photobiomodulation of lymphatic drainage and clearance: Perspective strategy for augmentation of meningeal lymphatic functions," *Biomed. Opt. Express*, vol. 11, no. 2, pp. 725–734, 2020.

[89] O. Semyachkina-Glushkovskaya *et al.*, "Photostimulation of cerebral and peripheral lymphatic functions," *Transl. Biophotonics*, vol. 2, 2020, Art. no. e201900036. [Online]. Available: https://www.onlinelibrary.wiley.com/doi/abs/10.1002/tbio.201900036

[90] J. P. Scallan and V. H. Huxley, "In vivo determination of collecting lymphatic vessel permeability to albumin: A role for lymphatics in exchange," *J. Physiol.*, vol. 588, no. 1, pp. 243–254, 2010.

[91] E. L. Kuan *et al.*, "Collecting lymphatic vessel permeability facilitates adipose tissue inflammation and distribution of antigen to lymph node-homing adipose tissue dendritic cells," *J. Immunol.*, vol. 194, no. 11, pp. 5200–5210, 2015.

[92] N. L. Harvey, "The link between lymphatic function and adipose biology," *Ann. New York Acad. Sci.*, vol. 1131, no. 1, pp. 82–88, 2008.

[93] S. Banerji *et al.*, "Lyve-1, a new homologue of the cd44 glycoprotein, is a lymph-specific receptor for hyaluronan," *J. Cell biol.*, vol. 144, no. 4, pp. 789–801, 1999.

[94] D. G. Jackson, "The lymphatics revisited: New perspectives from the hyaluronan receptor lyve-1," *Trends Cardiovasc. Med.*, vol. 13, no. 1, pp. 1–7, 2003.

[95] D. G. Jackson, R. Prevo, S. Clasper, and S. Banerji, "Lyve-1, the lymphatic system and tumor lymphangiogenesis," *Trends Immunol.*, vol. 22, no. 6, pp. 317–321, 2001.

[96] S. Liao and P.-Y. von der Weid, "Lymphatic System: An Active Pathway for Immune Protection," in *Seminars in Cell & Developmental Biology*, vol. 38. New York, NY, USA: Elsevier, 2015, pp. 83–89.

[97] A. A. Gashev, M. J. Davis, and D. C. Zawieja, "Inhibition of the active lymph pump by flow in rat mesenteric lymphatics and thoracic duct," *J. physiol.*, vol. 540, no. 3, pp. 1023–1037, 2002.

[98] R. Elias and M. Johnston, "Modulation of lymphatic pumping by lymph-borne factors after endotoxin administration in sheep," *J. Appl. Physiol.*, vol. 68, no. 1, pp. 199–208, 1990.

[99] M. K. Ferguson and V. J. DeFilippi, "Nitric oxide and endothelium-dependent relaxation in tracheobronchial lymph vessels," *Microvascular Res.*, vol. 47, no. 3, pp. 308–317, 1994.

[100] Y. Shirasawa, F. Ikomi, and T. Ohhashi, "Physiological roles of endogenous nitric oxide in lymphatic pump activity of rat mesentery in vivo," *Amer. J. Physiol.-Gastrointestinal Liver Physiol.*, vol. 278, no. 4, pp. G551–G556, 2000.

[101] P. Von der Weid, M. Crowe, and D. Van Helden, "Endothelium-dependent modulation of pacemaking in lymphatic vessels of the guinea-pig mesentery," *J. Physiol.*, vol. 493, no. 2, pp. 563–575, 1996.

[102] S. Yokoyama and T. Ohhashi, "Effects of acetylcholine on spontaneous contractions in isolated bovine mesenteric lymphatics," *Amer. J. Physiol.-Heart Circulatory Physiol.*, vol. 264, no. 5, pp. H1460–H1464, 1993.

[103] O. Y. Gasheva, D. C. Zawieja, and A. A. Gashev, "Contraction-initiated no-dependent lymphatic relaxation: A self-regulatory mechanism in rat thoracic duct," *J. physiol.*, vol. 575, no. 3, pp. 821–832, 2006.

[104] J. Hagendoorn *et al.*, "Endothelial nitric oxide synthase regulates microlymphatic flow via collecting lymphatics," *Circulation Res.*, vol. 95, no. 2, pp. 204–209, 2004.

[105] S. Liao *et al.*, "Impaired lymphatic contraction associated with immunosuppression," *Proc. Nat. Acad. Sci.*, vol. 108, no. 46, pp. 18 784–18 789, 2011.

[106] H. G. Bohlen, W. Wang, A. Gashev, O. Gasheva, and D. Zawieja, "Phasic contractions of rat mesenteric lymphatics increase basal and phasic nitric oxide generation in vivo," *Amer. J. Physiol.-Heart Circulatory Physiol.*, vol. 297, no. 4, pp. H1319–H1328, 2009.

[107] H. G. Bohlen, X. Zhou, J. L. Unthank, S. J. Miller, and R. Bills, "Transfer of nitric oxide by blood from upstream to downstream resistance vessels causes microvascular dilation," *Amer. J. Physiol.-Heart Circulatory Physiol.*, vol. 297, no. 4, pp. H 1337–H1346, 2009.

[108] H. G. Bohlen, O. Y. Gasheva, and D. C. Zawieja, "Nitric oxide formation by lymphatic bulb and valves is a major regulatory component of lymphatic pumping," *Amer. J. Physiol.-Heart Circulatory Physiol.*, vol. 301, no. 5, pp. H1897–H1906, 2011.

[109] R. Tulebaev, S. Sadykov, V. Romanov, and G. Khalitova, "Indicators of the activity of the immune system during laser therapy of vasomotor rhinitis," *Vestnik otorinolaringologii*, no. 1, pp. 46–49, 1989.

[110] I. Kruchinina, L. Feniksova, S. Rybalkin, and F. Pekli, "Therapeutic effect of helium-neon laser on microcirculation of nasal mucosa in children with acute and chronic maxillary sinusitis as measured by conjunctival biomicroscopy," *Vestnik Otorinolaringologii*, no. 3, pp. 26–30, 1991.

[111] B. Shevrygin, S. Rybalkin, F. Pekli, and L. Feniksova, "Correction of microcirculatory disorders with low-energy laser radiation in children with vasomotor rhinitis," *Vestnik Otorinolaringologii*, no. 2, pp. 31–33, 2000.

[112] C. Xu, L. Wang, J. Liu, Y. Tan, and Q. Li, "Endonasal low energy he-ne laser treatment of insomnia," *Qian Wei J. Med. Pharm.*, vol. 18, no. 5, pp. 337–338, 2001.

[113] D. T. Meneguzzo *et al.*, "Intravascular laser irradiation of blood," in *Low-Level light therapy: photobiomodulation.* United States: SPIE, 2017, pp. 978–981.

[114] A. Volotovskaia, V. Ulashchik, and V. Filipovich, "Antioxidant action and therapeutic efficacy of laser irradiation of blood in patients with ischemic heart disease," *Voprosy Kurortologii, Fizioterapii, I Lechebnoi Fizicheskoi Kultury*, no. 3, pp. 22–25, 2003.

[115] X. Xuechang *et al.*, "Effects of low power laser irradiation in nasal cavity on cerebral blood flow perfusion of patients with brain infarction," *Chin. J. Phys. Med.*, vol. 27, no. 7, pp. 418–420, 2005.

[116] C. Liu and P. Zhu, "Intranasal low intensity laser therapy," Beijing, China: People's Military Medical Press, 2009.

[117] S. Chakraborty, M. J. Davis, and M. Muthuchamy, "Emerging trends in the pathophysiology of lymphatic contractile function," in *Seminars in Cell & Developmental Biology*, vol. 38. New York, NY, USA: Elsevier, 2015, pp. 55–66.

[118] U. H. Mitchell and G. L. Mack, "Low-level laser treatment with near-infrared light increases venous nitric oxide levels acutely: A single-blind, randomized clinical trial of efficacy," *Amer. J. Phys. Med. Rehabil.*, vol. 92, no. 2, pp. 151–156, 2013.

[119] N. L. Lohr *et al.*, "Enhancement of nitric oxide release from nitrosyl hemoglobin and nitrosyl myoglobin by red/near infrared radiation: Potential role in cardioprotection," *J. Mol. Cellular cardiol.*, vol. 47, no. 2, pp. 256–263, 2009.

[120] R. Zhang *et al.*, "Near infrared light protects cardiomyocytes from hypoxia and reoxygenation injury by a nitric oxide dependent mechanism," *J. Mol. Cellular cardiol.*, vol. 46, no. 1, pp. 4–14, 2009.

[121] K. A. Samoilova, N. A. Zhevago, N. N. Petrishchev, and A. A. Zimin, "Role of nitric oxide in the visible light-induced rapid increase of human skin microcirculation at the local and systemic levels: Ii healthy volunteers," *Photomedicine Laser Surg.*, vol. 26, no. 5, pp. 443–449, 2008.

[122] S. Benedicenti, I. M. Pepe, F. Angiero, and A. Benedicenti, "Intracellular atp level increases in lymphocytes irradiated with infrared laser light of wavelength 904 nm," *Photomedicine Laser Surg.*, vol. 26, no. 5, pp. 451–453, 2008.

[123] F. Murad, "Discovery of some of the biological effects of nitric oxide and its role in cell signaling (*nobel lecture*)," *Angewandte Chemie Int. Ed.*, vol. 38, no. 13-14, pp. 1856–1868, 1999.

[124] J.-C. Drapier, H. Hirling, J. Wietzerbin, P. Kaldy, and L. Kühn, "Biosynthesis of nitric oxide activates iron regulatory factor in macrophages," *EMBO J.*, vol. 12, no. 9, pp. 3643–3649, 1993.

[125] M. Lepoivre, F. Fieschi, J. Coves, L. Thelander, and M. Fontecave, "Inactivation of ribonucleotide reductase by nitric oxide," *Biochem. Biophysical Res. Commun.*, vol. 179, no. 1, pp. 442–448, 1991.

[126] J.-C. Drapier and J. B. Hibbs, "[3] Aconitases: A Class of Metalloproteins Highly Sensitive to Nitric Oxide Synthesis," in *Nitric Oxide Part B: Physiological and Pathological Processes, ser. Methods in Enzymology*. Academic Press, 1996, vol. 269, pp. 26–36. [Online]. Available: http://www.sciencedirect.com/science/article/pii/S0076687996690065

[127] S. Dimmeler, F. Lottspeich, and B. Brüne, "Nitric oxide causes adpribosylation and inhibition of glyceraldehyde-3-phosphate dehydrogenase," *J. Biol. Chem.*, vol. 267, no. 24, pp. 16 771–16 774, 1992.

[128] J. S. Stamler *et al.*, "S-nitrosylation of proteins with nitric oxide: Synthesis and characterization of biologically active compounds," *Proc. Nat. Acad. Sci.*, vol. 89, no. 1, pp. 444–448, 1992.

[129] T. M. DiMauro, M. Attawia, S. Lilenfeld, and C. Holy, "Intranasal red light probe for treating alzhemers disease," U.S. Patent US 8,734.498 B2, May 2014.

[130] C. Xu, Z. Wu, L. Wang, X. Shang, and Q. Li, "The effects of endonasal low energy he-ne laser treatment of insomnia on sleep eeg," *Prac J. Med Pharm*, vol. 19, no. 6, pp. 407–408, 2002.

[131] Y. Chen and H. Cheng, "Clinical observation of the integrated therapy of intranasal low intensity he-ne laser therapy and herb therapy on insomnia," *J. Tradit. Chin. Med.*, vol. 24, 2004, Art. no. 38.

[132] F. Salehpour *et al.*, "Therapeutic potential of intranasal photobiomodulation therapy for neurological and neuropsychiatric disorders: A narrative review," *Rev. Neurosci.*, vol. 31, no. 3, pp. 269–286, 2020.

[133] T. Moshkovska and J. Mayberry, "It is time to test low level laser therapy in great britain," *Postgraduate Med. J.*, vol. 81, no. 957, pp. 436–441, 2005.

[134] K. Deisseroth, "Optogenetics," *Nat. Methods*, vol. 8, no. 1, pp. 26–29, 2011.

[135] K. "*Deisseroth*, "Optogenetics: 10 years of microbial opsins in neuroscience," *Nat. Neurosci.*, vol. 18, no. 9, pp. 1213–1225, 2015.

[136] E. Pastrana, "Optogenetics: Controlling cell function with light," *Nat. Methods*, vol. 8, no. 1, pp. 24–25, 2011.

[137] N. Staff, "Stepping away from the trees for a look at the forest," *Science*, vol. 330, no. 6011, pp. 1612–1613, 2010.

[138] Nat. Video," "Method of the Year 2010: Optogenetics," [YouTube video], Dec. 2010. [Online]. Available: https://www.youtube.com/watch?v=I64X7vHSHOE

[139] A. V. Kravitz *et al.*, "Regulation of parkinsonian motor behaviours by optogenetic control of basal ganglia circuitry," *Nature*, vol. 466, no. 7306, pp. 622–626, 2010.

[140] V. Gradinaru, M. Mogri, K. R. Thompson, J. M. Henderson, and K. Deisseroth, "Optical deconstruction of parkinsonian neural circuitry," *Science*, vol. 324, no. 5925, pp. 354–359, 2009.

[141] I. B. Witten *et al.*, "Cholinergic interneurons control local circuit activity and cocaine conditioning," *Science*, vol. 330, no. 6011, pp. 1677–1681, 2010.

[142] J. A. Cardin *et al.*, "Driving fast-spiking cells induces gamma rhythm and controls sensory responses," *Nature*, vol. 459, no. 7247, pp. 663–667, 2009.

[143] V. S. Sohal, F. Zhang, O. Yizhar, and K. Deisseroth, "Parvalbumin neurons and gamma rhythms enhance cortical circuit performance," *Nature*, vol. 459, no. 7247, pp. 698–702, 2009.

[144] H.-C. Tsai *et al.*, "Phasic firing in dopaminergic neurons is sufficient for behavioral conditioning," *Science*, vol. 324, no. 5930, pp. 1080–1084, 2009.

[145] A. Bohineust, Z. Garcia, B. Corre, F. Lemaître, and P. Bousso, "Optogenetic manipulation of calcium signals in single t cells in vivo," *Nat. Commun.*, vol. 11, no. 1, pp. 1–10, 2020.

[146] R. A. Hill *et al.*, "Regional blood flow in the normal and ischemic brain is controlled by arteriolar smooth muscle cell contractility and not by capillary pericytes," *Neuron*, vol. 87, no. 1, pp. 95–110, 2015.

[147] P. Tan, L. He, G. Han, and Y. Zhou, "Optogenetic immunomodulation: Shedding light on antitumor immunity," *Trends Biotechnol.*, vol. 35, no. 3, pp. 215–226, 2017.

[148] Y. Xu *et al.*, "Optogenetic control of chemokine receptor signal and t-cell migration," *Proc. Nat. Acad. Sci.*, vol. 111, no. 17, pp. 6371–6376, 2014.

[149] R. E. Ferrell *et al.*, "Gjc2 missense mutations cause human lymphedema," *Amer. J. Hum. Genet.*, vol. 86, no. 6, pp. 943–948, 2010.

[150] P. Ostergaard *et al.*, "Rapid identification of mutations in gjc2 in primary lymphoedema using whole exome sequencing combined with linkage analysis with delineation of the phenotype," *J. Med. Genet.*, vol. 48, no. 4, pp. 251–255, 2011.

[151] D. N. Finegold *et al.*, "Connexin 47 mutations increase risk for secondary lymphedema following breast cancer treatment," *Clin. Cancer Res.*, vol. 18, no. 8, pp. 2382–2390, 2012.

[152] G. Brice, P. Ostergaard, S. Jeffery, K. Gordon, P. Mortimer, and S. Mansour, "A novel mutation in gja1 causing oculodentodigital syndrome and primary lymphoedema in a three generation family," *Clin. Genet.*, vol. 84, no. 4, pp. 378–381, 2013.

[153] J. A. Castorena-Gonzalez *et al.*, "Mechanisms of connexin-related lymphedema: A critical role for cx45, but not cx43 or cx47, in the entrainment of spontaneous lymphatic contractions," *Circulation Res.*, vol. 123, no. 8, pp. 964–985, 2018.

[154] X. Geng *et al.*, "Multiple mouse models of primary lymphedema exhibit distinct defects in lymphovenous valve development," *Devlop. Biol.*, vol. 409, no. 1, pp. 218–233, 2016.

[155] J. D. Kanady, M. T. Dellinger, S. J. Munger, M. H. Witte, and A. M. Simon, "Connexin37 and connexin43 deficiencies in mice disrupt lymphatic valve development and result in lymphatic disorders including lymphedema and chylothorax," *Devlop. Biol.*, vol. 354, no. 2, pp. 253–266, 2011.

[156] A. Sabine *et al.*, "Mechanotransduction, prox1, and foxc2 cooperate to control connexin37 and calcineurin during lymphatic-valve formation," *Devlop. Cell*, vol. 22, no. 2, pp. 430–445, 2012.

[157] N. Huidobro, A. Mendez-Fernandez, I. Mendez-Balbuena, R. Gutierrez, R. Kristeva, and E. Manjarrez, "Brownian optogenetic-noise-photostimulation on the brain amplifies somatosensory-evoked field potentials," *Front. Neurosci.*, vol. 11, 2017, Art. no. 464.

[158] N. Huidobro *et al.*, "Optogenetic noise-photostimulation on the brain increases somatosensory spike firing responses," *Neurosci. Lett.*, vol. 664, pp. 51–57, 2018.

[159] P. Mabil *et al.*, "Noisy light augments the na current in somatosensory pyramidal neurons of optogenetic transgenic mice," *Front. Neurosci.*, vol. 14, 2020.

[160] K. Ait Ouares, C. Beurrier, M. Canepari, G. Laverne, and N. Kuczewski, "Opto nongenetics inhibition of neuronal firing," *Eur. J. Neurosci.*, vol. 49, no. 1, pp. 6–26, 2019.

[161] I. Fedosov *et al.*, "Laser Speckles, Doppler and Imaging Techniques for Blood and Lymph Flow Monitoring," in *Handbook of Optical Biomedical Diagnostics*, V. V. Tuchin, Ed Bellingham, WA: SPIE Press, 2016, vol. 2, p. 688. [Online]. Available: https://doi.org/10.1117/3.2219603

[162] J. H. Ahn *et al.*, "Meningeal lymphatic vessels at the skull base drain cerebrospinal fluid," *Nature*, vol. 572, no. 7767, pp. 62–66, 2019.

[163] P. Yanev *et al.*, "Impaired meningeal lymphatic vessel development worsens stroke outcome," *J. Cereb. Blood Flow Metab.*, vol. 40, no. 2, pp. 263–275, 2020.

[164] X. Hu *et al.*, "Meningeal lymphatic vessels regulate brain tumor drainage and immunity," *Cell Res.*, vol. 30, no. 3, pp. 229–243, 2020.

[165] C. Blatter *et al.*, "In vivo label-free measurement of lymph flow velocity and volumetric flow rates using doppler optical coherence tomography," *Sci. Rep.*, vol. 6, no. 1, pp. 1–10, 2016.

[166] I. V. Fedosov and V. V. Tuchin, "Bioflow Measuring: Laser Doppler and Speckle Techniques," in *Handbook of Coherent-Domain Optical Methods*, V. V. Tuchin, Ed. New York, NY, USA: SpringerNew York, 2013, pp. 487–563.

[167] V. Kalchenko, Y. Kuznetsov, A. Harmelin, and I. V. Meglinski, "Label free in vivo laser speckle imaging of blood and lymph vessels," *J. Biomed. Opt. Express*, vol. 17, no. 5, 2012, Art. no. 0 50502.

[168] E. I. Galanzha, V. V. Tuchin, and V. P. Zharov, "Advances in small animal mesentery models for in vivo flow cytometry, dynamic microscopy, and drug screening," *World J. Gastroenterol.*, vol. 13, no. 2, pp. 192–218, 2007.

[169] E. Galanzha, E. Shashkov, V. Tuchin, and V. Zharov, "In vivo multiparameter, multispectral lymph flow cytometry with natural cell focusing, label-free detection and multicolor nanoparticle probes," *Cytometry*, vol. 73, pp. 884–894, 2008.

[170] I. Fedosov, E. Galanzha, A. Solov'eva, and V. Tuchin, "Laser monitoring of the flow velocity in lymphatic microvessels based on a spatiotemporal correlation of the dynamic speckle fields," *Tech. Phys. Lett.*, vol. 28, no. 8, pp. 690–692, 2002.

[171] I. V. Fedosov, V. V. Tuchin, E. Galanzha, A. Solov'eva, and T. Stepanova, "Recording of lymph flow dynamics in microvessels using correlation properties of scattered coherent radiation," *Quantum Electron.*, vol. 32, no. 11, pp. 970–974, 2002.

[172] M. A. Juratli *et al.*, "Dynamic fluctuation of circulating tumor cells during cancer progression," *Cancers*, vol. 6, no. 1, pp. 128–142, 2014.

[173] R. F. Bonner and R. Nossal, "Principles of laser-doppler flowmetry," in *Laser-Doppler blood flowmetry*, A. P. Shepherd and P. A.Öberg, Eds. Berlin, Germany: Springer, 1990, pp. 17–45.

[174] P. Hadaczek *et al.*, "The "perivascular pump driven by arterial pulsation is a powerful mechanism for the distribution of therapeutic molecules within the brain," *Mol. Ther.*, vol. 14, no. 1, pp. 69–78, 2006.

[175] J. J. Iliff *et al.*, "Cerebral arterial pulsation drives paravascular csf-interstitial fluid exchange in the murine brain," *J. Neurosci.*, vol. 33, no. 46, pp. 18 190–18199, 2013.

[176] A. K. Diem *et al.*, "Arterial pulsations cannot drive intramural periarterial drainage: Significance for aβ drainage," *Front. Neurosci.*, vol. 11, 2017, Art. no. 475.

[177] M. Asgari, D. De Zélicourt, and V. Kurtcuoglu, "Glymphatic solute transport does not require bulk flow," *Sci. Rep.*, vol. 6, 2016, Art. no. 38635.

[178] N. J. Abbott, M. E. Pizzo, J. E. Preston, D. Janigro, and R. G. Thorne, "The role of brain barriers in fluid movement in the cns: Is there a 'glymphatic'system?" *Acta Neuropathologica*, vol. 135, no. 3, pp. 387–407, 2018.

[179] W. E. Butler, "Wavelet brain angiography suggests arteriovenous pulse wave phase locking," *PLoS One*, vol. 12, no. 11, 2017, Art. no. e0187014.

[180] D. D. Postnov, S. E. Erdener, K. Kilic, and D. A. Boas, "Cardiac pulsatility mapping and vessel type identification using laser speckle contrast imaging," *J. Biomed. Opt. Express*, vol. 9, no. 12, pp. 6388–6397, 2018.

[181] Y.-R. Gao, S. E. Greene, and P. J. Drew, "Mechanical restriction of intracortical vessel dilation by brain tissue sculpts the hemodynamic response," *Neuroimage*, vol. 115, pp. 162–176, 2015.

[182] B. Bedussi, M. Almasian, J. de Vos, E. VanBavel, and E. N. Bakker, "Paravascular spaces at the brain surface: Low resistance pathways for cerebrospinal fluid flow," *J. Cereb. Blood Flow Metab.*, vol. 38, no. 4, pp. 719–726, 2018.

[183] M. E. Wagshul, P. K. Eide, and J. R. Madsen, "The pulsating brain: A review of experimental and clinical studies of intracranial pulsatility," *Fluids Barriers CNS*, vol. 8, no. 1, 2011, Art. no. 5.

[184] V. Kiviniemi *et al.*, "Ultra-fast magnetic resonance encephalography of physiological brain activity-glymphatic pulsation mechanisms?" *J. Cereb. Blood Flow Metab.*, vol. 36, no. 6, pp. 1033–1045, 2016.

[185] V. Vinje Mardal, "Respiratory influence on cerebrospinal fluid flow-a computational study based on long-term intracranial pressure measurements," *Sci. Rep.*, vol. 9, no. 1, pp. 1–13, 2019.

[186] N. E. Fultz *et al.*, "Coupled electrophysiological, hemodynamic, and cerebrospinal fluid oscillations in human sleep," *Science*, vol. 366, no. 6465, pp. 628–631, 2019.

[187] D. Orešković, M. Radoš, and M. Klarica, "Role of choroid plexus in cerebrospinal fluid hydrodynamics," *Neuroscience*, vol. 354, pp. 69–87, 2017.

[188] D. Orešković *et al.*, "New insight into the mechanism of mannitol effects on cerebrospinal fluid pressure decrease and craniospinal fluid redistribution," *Neuroscience*, vol. 392, pp. 164–171, 2018.

[189] S. B. Hladky and M. A. Barrand, "Mechanisms of fluid movement into, through and out of the brain: Evaluation of the evidence," *Fluids Barriers CNS*, vol. 11, no. 1, 2014, Art. no. 26.

[190] A. D. Martinac and L. E. Bilston, "Computational modelling of fluid and solute transport in the brain," *Biomech. Modeling Mechanobiol.*, vol. 19, no. 3, pp. 781–800, 2020.

[191] J. J. Iliff *et al.*, "A paravascular pathway facilitates csf flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β," *Sci. Transl. Med.*, vol. 4, no. 147, 2012, Art. no. 147ra 111.

[192] N. A. Jessen, A. S. F. Munk, I. Lundgaard, and M. Nedergaard, "The glymphatic system: A beginner's guide," *Neurochemical Res.*, vol. 40, no. 12, pp. 2583–2599, 2015.

[193] A. J. Smith, B.-J. Jin, and A. S. Verkman, "Muddying the water in brain edema?" *Trends Neurosci.*, vol. 38, no. 6, pp. 331–332, 2015.

[194] G. Dupont *et al.*, "Our current understanding of the lymphatics of the brain and spinal cord," *Clin. Anatomy*, vol. 32, no. 1, pp. 117–121, 2019.

[195] Q. Ma, B. V. Ineichen, M. Detmar, and S. T. Proulx, "Outflow of cerebrospinal fluid is predominantly through lymphatic vessels and is reduced in aged mice," *Nat. Commun.*, vol. 8, no. 1, pp. 1–13, 2017.

[196] D. Postnov, E. Postnikov, A. Karavaev, and O. Glushkovskaya-Semyachkina, "On trans-parenchymal transport after blood brain barrier opening: Pump-diffuse-pump hypothesis," in *Proc. Saratov Fall Meeting 2017: Laser Phys. Photon. XVIII; Comput. Biophys. Anal. Biomed. Data IV*, vol. 10717. Int. Soc. Opt. Photon., 2018, Art. no. 107171W.

Oxana Semyachkina-Glushkovskaya is a Head of Interdisciplinary Center of Critical Technologies in medicine, Head of Chair of Physiology of Human and Animals with Saratov Natl. Research State University, Russia.

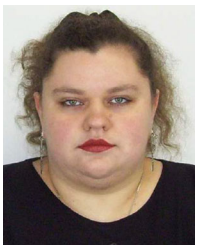
Her research interests include neuroscience with a focus on the development of breakthrough technologies for non-invasive therapy of brain diseases, and the brain drug delivery and monitoring of the immune system of the brain.

She was awarded by Paul Dudley White International Scholar Award (The American Heart Association) and DAAD (M.V. Lomonosov's program). Her research was supported by more than 30 international and Russian projects in fundamental and applied medicine. She is the team member in "Virtual Physiology" educational software.

Dmitry Postnov is a Professor of Optics and Biophotonics Department with Saratov National Research University. He has authored or coauthored about 200 scientific publications, including >120 papers in peer-reviewed journals, two monographs and one book chapters. His research interests include mathematical modeling of brain physiology with focus on neurovascular coupling and fluid movement in tissues, as well as expermental and theoretical study of autoregulation of vascular tone.

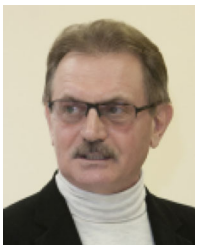
Anastasia Lavrova is a leading Researcher with the Institute of High medical Technologies in Medical Faculty of SPSU, Russia. Her main fields of expertise include the mathematical modeling in Biological and Medical systems (Drug metabolism, Biochemical Modeling and Neuronal networks dynamics) and bifurcation analysis of non-linear systems. She was involved in large range of joined projects of experimentalists and theoreticians in different groups of Russian Federation and Germany.

Ivan Fedosov received the Ph.D. degree in biophotonics from Saratov State University in 2002. Since 2004, he is an Associate Professor with the Department of Optics and Biophotonics of Saratov State University. His current research activities include the field of biomedical imaging, biosensing, laser based blood flow measurements, laser scanning and super resolution microscopy, micro anemometry, and optical micromanipulation.



Ekaterina Borisova received the M.S. degree in medical physics and in laser physics from Sofia University, Bulgaria, in 2000, and the Ph.D. degree in physics from IE-BAS in 2005. She is a Head of Biophotonics laboratory of Institute of Electronics, Bulgarian Academy of Sciences.

She works in the fields of molecular spectroscopy of biological samples, optical biopsy of human tissues and monitoring and detection of their pathological changes, photodiagnosis and photodynamic therapy, different optical techniques for tissue analysis, including fluorescence, reflectance, absorption, Raman spectroscopy, and polarimetry analysis.



Vladimir Nikolenko has been the Doctor of Medical Sciences since 1997. The Ph.D. thesis is "The structure and deformation-strength properties of the hard shell of the spinal cord of a person." The Habilitation thesis is "Morphobiomechanical patterns and individual variability of the construction of the spinal cord." He has published 15 monographs, eight textbooks (some reprinted 5 to 12 times), atlases, 46 patents for inventions and utility models.

Thomas Penzel (Senior Member, IEEE). He has been a Physicist and Physiologist and Scientific Chair with the Sleep Medicine Center, Charite University Hospital Berlin Germany since 2006. His research is on sleep medicine and sleep research with a focus on biosignals and nonlinear analysis of physiological systems. He has authored or coauthored more than 300 Pubmed listed journal papers and book chapters and is an Editor and Editorial Board member of several journals, among them IEEE T-BME, IEEE-JTEHM, IEEE RBME. He is an Adcom Member in IEEE EMBS.

Jürgen Kurths is Director of the working group "Nonlinear Dynamics" of the Max-Planck-Gesellschaft (1992–1996) and of the Interdisciplinary Centre "Dynamics of Complex Systems" with the University Potsdam (1994–2008). His research is related to complex systems theory, nonlinear dynamics as well as applications to the Earth system, the human brain, the cardio-respiratory system and other systems which are characterized by a high degree of complexity and nonlinearity. He is a Member of Board of many Journals and Book Series, including Springer Series of Complexity, CHAOS, *Nonlinear Processes in Geophysics*, *European Journal Physics*, *Nonlinear Biomedical Physics*, and *Journal of Nonlinear Science*. He has the coauthored more than 700 papers with more than 33.000 citations (h-index = 98). He is a Fellow of the American Physical Society.

Valery Tuchin (Member, IEEE) is the Chair of Optics and Biophotonics with Saratov State University and the Head of Laboratory of Laser Diagnostics of Technical and Living Systems of the Institute of Precision Mechanics and Control of the RAS. He is also the Supervisor of Interdisciplinary Laboratory of Biophotonics, National Research Tomsk State University and Laboratory of FemtoMedicine, ITMO University. His research interests include tissue optics, laser medicine, tissue optical clearing, and nanobiophotonics. He is a corresponding member of the RAS, a fellow of SPIE and OSA, he was awarded the Honored Science Worker of the Russia, SPIE Educator Award, Joseph W. Goodman Book Writing Award (OSA/SPIE), and OSA Michael S. Feld Biophotonics Award. His publications were cited more than 28000 times.