WELCOME

Dear Colleagues,

We are pleased to welcome you at the scientific event "Liver-Brain interface - implications for lifestyle-related diseases". The bidirectional communication between the liver and the brain impacts lifestyle-related diseases, including metabolic-associated fatty liver disease (MAFLD), obesity, diabetes, and might lead to neurodegeneration. Unlike the highly studied brain-gut link, liver-brain interaction has received less attention thus far. However, the multiple neural pathways and hormonal signals (hepatokines) involved imply a highly regulated axis, the dysfunction of which can lead to a range of disorders.

The present meeting brings together clinicians and basic researchers working on the pathways linking liver and brain, and how these pathways are preformatted in disease. A special focus of the meeting will be to highlight how lifestyle choices can influence both the liver and brain and contribute to chronic health conditions.

We hope that the interdisciplinary profile of the participating researchers will contribute to the translational impact of the fundamental discoveries that will be reported through the event. We further hope our meeting will promote building new partnerships between the participants.

Yours sincerely,

Antonia Atanassova
Irina Ivanova
Anton B. Tonchev

Varna, Bulgaria, November 2025

PROGRAMME

Friday, November 14th 2025

15:00 Registration

16:00 Welcome address and opening

16:30 – 17:15 **Tetsumori Yamashima** (Kanazawa, Japan)
Implication of vegetable oil-derived hydroxynonenal for lifestyle-related diseases

17:15 – 18:00 **Hirofumi Tanaka** (Austin, Texas, USA)
Vascular dysfunction at the nexus of cognitive decline and Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): implications for exercise-based prevention

18:30 – Reception

Saturday, November 15th 2025

09:00 – 09:45 **Andreana P. Haley** (Austin, Texas, USA)
Dietary modulation of the Liver-Brain Axis in Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): proof-of-concept and future directions

09:45 – 10:30 **Alessandro Pinto** (Rome, Italy)
Modulation of Liver-Brain Axis: the diet's role, with particular reference to the Mediterranean dietary pattern

10:30 – 11:00 Coffee break

11:00 – 11:30 **Krasimir Antonov** (Sofia, Bulgaria)
Wilson disease - a diagnostic challenge

11:30 – 12:00 **Irina Ivanova** (Varna, Bulgaria)
Shear wave dispersion: do we have new noninvasive methods to study liver injury?

12:00 – 12:30 **Marco Fiore** (Rome, Italy)
Liver-Brain Interface - implications for lifestyle-related diseases: the neglected role of alcohol abuse

12:30 – 13:00 **Manlio Vinciguerra** (Varna, Bulgaria)
Beyond the nucleus: MacroH2A1 links hepatic metabolism to social cognition

13:00 – 15:00 – Lunch break

15:00 – 15:45 **Rita Businaro** (Rome, Italy)
Treatments promoting innate immune cells polarization towards an anti-inflammatory phenotype

15:45 – 16:15 **David Lutz** (Varna, Bulgaria)
Small Hydra-derived peptide pedin promotes nerve regeneration

16:15 – 16:40 **Andon Mladenov** (Kanazawa, Japan)
Species-specific effects of hydroxynonenal on progenitor proliferation in mice and monkeys

16:40 – 17:00 **Andreas Kontny** (Varna, Bulgaria)
Effects of hydroxynonenal on mammalian cornea – a pilot study

17:00 – 17:20 **Martin Ivanov** (Varna, Bulgaria)
Effects of hydroxynonenal on a putative primate neurogenic niche – a pilot study

18:00 – Official dinner

Sunday, November 16th

10:00 – 10:30 **Sabrina Venditti** (Rome, Italy)
Brain-Liver Axis and disease: a field in need of epigenetic studies

10:30 – 11:00 **Veronica Peneva** (Sofia, Bulgaria)
Therapeutic strategies for Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) and their influence on the liver–brain axis

11:00 – 11:30 **Stefka Kuzmanova** (Varna, Bulgaria)
Association between metabolic dysfunction-associated fatty liver disease, insulin resistance and cognitive performance. Effects of Aronia melanocarpa

11:30 – 12:00 **Anton B. Tonchev** (Varna, Bulgaria)
Round table discussion

12:00 Concluding remarks

12:30 – Lunch

Implication of vegetable oil-derived hydroxynonenal for lifestyle-related diseases

Tetsumori Yamashima

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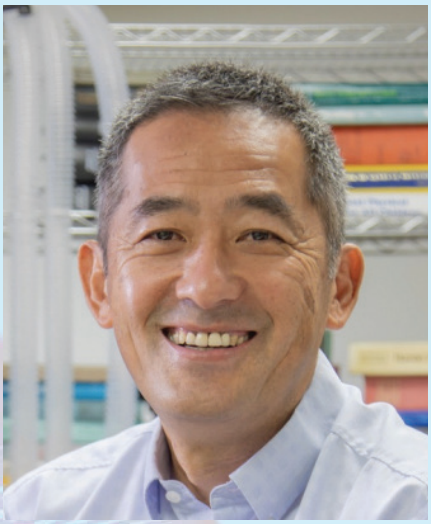
Lysosomes mediate degradation and recycling of aged/damaged macromolecules within the cell. For ensuring the place of degradation within the acidic organelle, the integrity of the lysosomal-limiting membrane is critical in order to not injure the cell. As lysosomes fade away in response to acute intense insults or long-term mild insults, dissolving lysosomes are hardly detected during the phase of cell degeneration. In both the experimental and clinical materials, the author found evidence of rupture and/or permeabilization of the lysosomal-limiting membrane. Regardless of insults, cell types, organs, diseases, or species, leakage of lysosomal content occurs in the early phase of necrotic cell death.

Lipid peroxidation product, 4-hydroxy-2-nonenal (HNE), is incorporated into the serum by the intake of linoleic acid-rich vegetable oils (exogenous), and/or is generated by the peroxidation of mitochondrial inner membranes due to the oxidative stress (intrinsic). Exogenous and intrinsic HNE may synergically oxidize the heat-shock protein Hsp70.1, which has dual functions as a 'chaperone protein' and 'lysosomal stabilizer'. HNE-mediated carbonylation of Hsp70.1 facilitates calpain-mediated cleavage to induce lysosomal membrane rupture/permeabilization, autophagy failure, and cell death. Currently, vegetable oils such as soybean and canola oils are the most widely consumed cooking oils worldwide. Accordingly, high linoleic acid content may be a major health concern, because cells can become damaged by its major end product, HNE. By focusing on dynamic changes of the lysosomal membrane integrity at both ultrastructural and molecular levels, implications of its rupture/permeabilization on cell death are discussed as an etiology of various lifestyle-related diseases such as Alzheimer's disease, Type 2 diabetes, and Non-Alcoholic Steatohepatitis.

https://www.researchgate.net/profile/Tetsumori-Yamashima

Vascular dysfunction at the nexus of cognitive decline and Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): implications for exercise-based prevention



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Cognitive decline, most notably manifested as dementia, and liver disease, exemplified by metabolic dysfunction-associated steatotic liver disease (MASLD), are rising at an alarming rate worldwide. These conditions, once considered distinct, share several overlapping risk factors for cardiovascular disease such as obesity, insulin resistance, hypertension, and sedentary lifestyle. A growing body of evidence highlights vascular dysfunction as a pivotal pathophysiological mechanism linking both brain and liver disorders. Indeed, vascular dysfunction appears to be one of the earliest detectable events driving the onset and progression of cognitive impairment and hepatic steatosis, thereby suggesting a common underlying pathway. Despite these emerging insights, it remains unclear whether vascular dysfunction constitutes the "missing link" that explains the parallel global rise in liver fat accumulation and age-related cognitive decline. Given this shared vascular origin, preventive strategies targeting vascular health may provide dual protection for both the brain and liver. Among such strategies, habitual physical activity stands out as one of the most accessible and effective interventions. Regular exercise improves vascular function, reduces systemic inflammation, enhances insulin sensitivity, and promotes cerebrovascular as well as hepatic health. This raises the intriguing possibility that regular exercise may simultaneously attenuate the development of MASLD, preserve cognitive performance, and counteract dementia risk. In this context, the presentation will focus on the role of vascular dysfunction in the pathogenesis of both cognitive decline and liver disease, and the potential of habitual exercise as a multifaceted preventive strategy capable of addressing these interconnected conditions.

https://liberalarts.utexas.edu/caps/faculty/tanaka

Dietary modulation of the Liver-Brain Axis in Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): proof-of-concept and future directions

Andreana P. Haley

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Metabolic dysfunction–associated steatotic liver disease (MASLD) and age-related cognitive decline represent two converging epidemics, yet their mechanistic links remain incompletely understood. The concept of a liver–brain axis suggests that metabolic and inflammatory signals originating in the liver may influence brain vulnerability. To probe this connection in humans, we conducted a short-term proof-of-concept study in adults with MASLD who followed either a low-carbohydrate or a low-calorie diet for two weeks. Despite the brief duration, participants demonstrated meaningful reductions in liver fat accompanied by decreases in brain metabolites associated with neurotoxicity and inflammation, specifically glutamate and myo-inositol. These findings provide preliminary support for the hypothesis that dietary modulation of liver health can translate into measurable changes in the brain, even over a short timescale. Building on this early evidence, we are developing a large-scale clinical trial to test whether age moderates the brain and cognitive response to longer dietary interventions. Such work will benefit from international collaborations that integrate advanced neuroimaging, neuropsychological testing, and metabolic assessments. Together, these studies advance the view of MASLD as a systemic condition with implications for both brain and hepatic health and highlight the potential of dietary strategies as accessible tools for modulating the liver–brain axis across the lifespan.

https://liberalarts.utexas.edu/psychology/faculty/aph355

Modulation of Liver-Brain Axis: the diet's role, with particular reference to the Mediterranean dietary pattern

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Nutrients and bioactive compounds derived from food digestion or gut microbiome metabolism, neurotransmitters, hormones, cytokines, antigens, and endotoxins (when intestinal permeability increases) are transported to the liver and involved in the regulation or dysregulation of hepatic metabolism and the liver-brain axis (LBA). The Mediterranean diet (MedD), thanks to its high content of polyphenols and other bioactive plant compounds, omega-3 fatty acids, fiber, and its beneficial impact on the gut microbiome, may positively influence the LBA, both directly (as ligands for brain receptors) and indirectly, through protective effects against neurodegenerative diseases, Metabolically Associated Fatty Liver Disease (MASLD) and Non-alcoholic Fatty Liver Disease (NAFLD). The effects are due to the antioxidant and anti-inflammatory activity of polyphenols, particularly found in fruits such as berries (strawberries, blueberries, blackberries, cranberries, etc). Natural pentacyclic triterpenoids extracted from plants (e.g., oleanolic acid from Olea europaea and nomilin from citrus fruits) influence neuronal activity in various brain regions as agonists of the TGR5 receptor. MedD supports the production of short-chain fatty acids (SCFAs) by the microbiome, which activates vagal afferent neurons, suppresses food intake, crosses the blood-brain barrier (six SCFA receptors have been identified in the brain), modulates CNS immune responses by regulating microglia and T cells, and contributes to maintaining the integrity of the intestinal epithelium and the brain barrier. Although the literature highlights the need for further in vivo studies and human clinical trials, it is possible to conclude that current evidence supports the positive role of MedD on LBA.

https://scholar.google.com/citations?user=OgOCIfEAAAAJ&hl=it

Wilson disease – a diagnostic challenge

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The progressive lenticular degeneration is a familial lethal neurological disease associated with cirrhosis. Copper (Cu^{2+}) metabolism is impaired, resulting in excess Cu^{2+} accumulation in the liver and central nervous system, as well as in other tissues. Wilson's disease (WD) is an inherited disease with an autosomal recessive mode of transmission. The absence or impaired function of ATP7B reduces the biliary excretion of copper from hepatocytes into bile, reducing the biosynthetic binding of Cu^{2+} to ceruloplasmin in hepatocytes. When the storage capacity of Cu^{2+} in hepatocytes is exceeded, hepatic copper is deposited via the circulation in other organs, especially brain, kidneys and cornea. WD should be considered in any patient with unexplained liver disease accompanied by neurological or psychiatric abnormalities. A search for WD is critical in patients with recurrent, self-limiting, nonimmune hemolysis.

The clinical manifestations of WD may involve organs and systems other than the liver and the nervous system (such as renal, musculoskeletal, cardiac or endocrine). Serum ceruloplasmin (<5 mg/dL) is a strong indicator of WD, and in some patients, serum Cu^{2+} levels are also strong indicators. A 24-hour urinary Cu^{2+} excretion of over 1,6 μmol/100 μg might indicate WD. Slit-lamp or anterior segment optical coherence tomography (AS-OCT) examination of the eyes for Kayser-Fleischer (KF) rings are used to confirm WD. In the presence of neurological abnormalities, it is advisable to perform a radiological examination of the brain, preferably MRI. Molecular genetic testing of ATP7B can confirm the diagnosis when biochemical tests are uncertain and is suitable for screening first-degree relatives. Diagnostic scoring systems (Leipzig score) can assist clinicians in establishing or ruling out the diagnosis of WD in patients who do not fit the classic descriptions of the disease. Prognostic scoring systems (New Wilson Index) can help determine the potential for successful medical treatment of WD.

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Shear wave dispersion: do we have new noninvasive methods to study liver injury?

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Liver ultrasound elastography is an established and essential non-invasive method for assessment of chronic liver diseases. The frequency-dependent variation of the speed of the secondary waves generated during two-dimensional ‚shear wave' elastography, known as shear-wave dispersion (SWD), provides information about tissue viscosity and likely complements biomechanical data in the direction of studying inflammatory activity. In an experimental model of acute liver injury, it has been found that: SWD corresponds to the severity of liver necrosis; SWD is higher in inflammatory activity, unlike in vivo models with predominantly liver fibrosis, where the change in liver stiffness (LS) dominates; SWD of the spleen does not change with liver injury. An example of SWD assessment as part of 2D-SWE is embedded in the Aplio ultrasound equipment (Canon) for calculating SWD speed (SWDS in (m/s)/kHz) or the Vi.Plus software, which calculates a viscosity index (Supersonic Shear Imaging). SWDS in healthy individuals (right liver lobe) averages 10 (m/s)/kHz. In recent years, there has been an increasing number of clinical studies on the measurement and dynamics of SWD in liver diseases. A direct proportional relationship between SWD and morphological activity and liver stiffness (LS) is reported; there is a weak association with transaminase activity; a moderate relationship is found between SWD and the level of cholestatic enzymes in primary biliary cholangitis. Although in its early stages, observations of high SWD values in liver iron overload, acute fatty liver of pregnancy, and acute rejection of the transplanted liver are interesting. Thus, presentation will be focused on the role of SWD as a quantitative biomarker for liver tissue remodeling in injury, though further studies are needed to identify co-factors and confirm the clinical applicability of that promising method.

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Liver-Brain Interface - implications for lifestyle-related diseases: the neglected role of alcohol abuse

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The liver–brain interface is a pivotal nexus in maintaining metabolic and neurological homeostasis. While diet, physical inactivity, and smoking have dominated research on lifestyle-related diseases, alcohol abuse, including during pregnancy, remains a critically neglected disruptor of this axis. Sustained ethanol exposure precipitates hepatic steatosis, inflammation, and oxidative stress, altering cytokine and neurotrophin profiles and compromising blood–brain barrier integrity. These insults propagate neuroinflammation, disrupt neurotransmitter balance, and impair cognitive and emotional regulation, thereby amplifying the risk of cardiovascular disease, metabolic resistance, and neurodegeneration.

Molecular mediators—including tumor necrosis factor-α, interleukin-6, nerve growth factor and brain-derived neurotrophic factor may bridge hepatic dysfunction to neural circuits governing reward, stress response, and metabolic regulation. Altogether, these parameters could be considered novel biomarkers for early detection of liver–brain axis perturbation.

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Beyond the nucleus: MacroH2A1 links hepatic metabolism to social cognition

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MacroH2A1 was identified in the early '90s as the largest histone variant in nature, present only in vertebrates. Originally associated with the functional inactivation of X chromosome, it was subsequently involved in the efficient inhibition of cell pluripotency, as shown by the work of Nobel prize awardees (2012) Yamanaka and Gurdon. MacroH2A1 exists in two alternative exon-spliced isoforms, macroH2A1.1 and macroH2A1.2, which have both opposite and redundant roles in the regulation of gene expression in a variety of settings, including cancer. The histone variant macroH2A1.1 contains a macrodomain capable of binding NAD+-derived metabolites, which is not present in macroH2A1.2 and is thought to mediate some of its specific cellular functions, such as gene expression and modulation of mitochondrial respiration. We recently generated a mouse model where the histone variant isoform macroH2A1.1, but not macroH2A1.2, was depleted in the whole body by means of the Cre/LoxP technology. These mice appear normal under unchallenged circumstances. However, they present a phenotype at the level of social behaviour. Also, we have shown, using the same mouse model, that ablation of macroH2A1.1 exacerbated obesity and hepatic dysmetabolism (fatty liver) induced by a high fat diet (HFD), and affected as well hematopoietic processes. In this talk, I will thus summarize the existing evidence of a new macroH2A1.1-dependent epigenetic link connecting liver disease and cognition in vivo.

https://transtem.org/en/manlio-vinciguerra/

Treatments promoting innate immune cells polarization towards an anti-inflammatory phenotype

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The pathogenic mechanisms underlying a broad spectrum of liver disorders are multifactorial, involve the gut-liver-brain-axis and include oxidative stress, inflammatory cascades, mitochondrial impairment, and disturbances in immune homeostasis. Our research has been focusing on CNS innate immunity cells, microglia, analyzing bioactive compounds able to promote their homeostatic balance after the addition of a pro-inflammatory stimulus.

We analyzed the anti-inflammatory as well anti-oxidant activity of plant extracts, increased endocannabinoid tone, probiotics to drive microglia polarization towards an anti-inflammatory phenotype. Endocannabinoids have attracted great interest for their ability to counteract the neuroinflammation underlying Alzheimer's disease. Our study aimed at evaluating whether this activity was also due to a rebalance of autophagic mechanisms in cellular and animal models of AD. We supplied URB597, an inhibitor of Fatty-Acid Amide Hydrolase (FAAH), the degradation enzyme of anandamide, to microglial cultures treated with Aβ25-35, and to Tg2576 transgenic mice, thus increasing the endocannabinoid tone. The addition of URB597 induced microglia polarization toward an anti-inflammatory phenotype, as shown by the modulation of pro- and anti-inflammatory cytokines, as well as M1 and M2 markers; moreover microglia, after URB597 treatment released higher levels of Bdnf and Nrf2, confirming the protective role underlying endocannabinoids increase.

Moreover, we showed that wheat extracts polarize microglia cells towards an anti-inflammatory phenotype, even after the addition of LPS and that the probiotic Milmed yeast, obtained from S. cerevisiae after exposure to electromagnetic millimeter wavelengths, induces a reversal of LPS-M1 polarized microglia towards an anti-inflammatory phenotype, decreasing the mRNAs of IL-1β, IL-6, TNF-α and the expression of iNOS. Moreover, Milmed stimulated the secretion of IL-10 and the expression of Arginase-1, cell markers of M2 anti-inflammatory polarized cells.

https://www.vita365.it/prof-ssa-rita-businaro/

Small Hydra-derived peptide pedin promotes nerve regeneration

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Biologically immortal cnidarians possess an abundant system of small bioregulatory peptides that govern ontogenetic, homeostatic and restorative processes, including formation and maintenance of the neural nets. However, whether these molecules can stimulate neuroregeneration in higher organisms remains unclear. Here, we identify the Hydra-derived morphogenic epitheliopeptide pedin as a potent promoter of nerve fiber regrowth and remyelination in mice. Pedin induces neurite sprouting and branching in dorsal root ganglia and cerebral cortex neurons. The peptide stimulates Schwann cells to form processes, proliferate and migrate. Pedin regulates neuronal electric impedance and calcium flux. Complementarily, the morphogen enhances neuron-glia coverage and neurite-glial process alignment, and facilitates in vitro myelination, accompanied by reshaping of the Golgi apparatus in Schwann cells. Furthermore, in mice with gap-transected femoral nerves, pedin treatment supports axonal regrowth, gap bridging, and motor reinnervation, resulting in a nearly complete functional recovery. Our findings reveal that cnidarian-derived molecules can counteract demyelination, augment neurorepair, and offer a potential therapeutic strategy for nervous system injuries and degenerative diseases.

https://www.researchgate.net/profile/David-Lutz-2

Species-specific effects of hydroxynonenal on progenitor proliferation in mice and monkeys

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4-hydroxy-2-nonenal (4-HNE) is a highly reactive, toxic peroxidation product of ω-6 polyunsaturated acids (PUFA). It is generated endogenously by reactive oxygen species and exogenously during the deep frying of most commercially available cooking oils. 4-HNE has well-established effects on cell death in different organs, including the liver, pancreas, and brain. Less is known, however, of its effects on cell proliferation, including the maintenance of progenitor cell populations in stem cell niches.

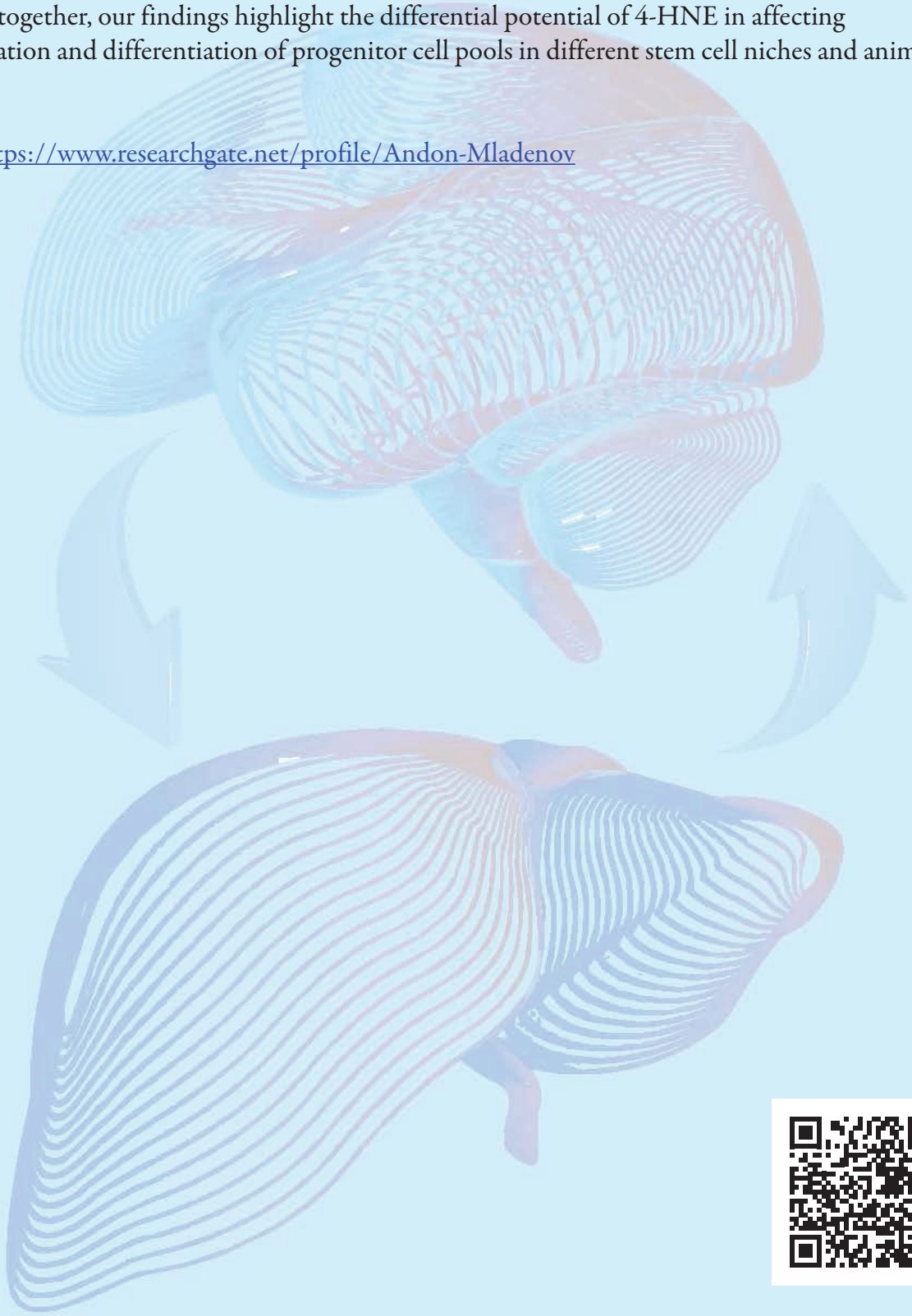
To address the latter, we examined the effects of a chronic 4-HNE exposure on the proliferation in stem cell niches of two different organs (liver and brain), in two different species (mice and monkeys). Adult mice C57BL/6J received intraperitoneal injections of 5mg/kg/day synthetic 4-HNE for 2 months or an equivalent volume of PBS as a vehicle control. Adult Japanese macaque monkeys received intravenous injections of 5 mg/week of 4-HNE for 6 months. Liver and brain were resected from controls and treated animals, and were examined by immunohistochemistry.

We observed a significant decrease of proliferating (Ki-67+) cells in the mouse liver, following 4-HNE treatment. To understand the mechanism behind the reduced proliferation, we performed bulk RNA-seq analysis on 4-HNE-treated hepatocellular carcinoma-derived cell line (HEPG2), which revealed that 4-HNE significantly upregulated p53 and its downstream target, p21, genes that are strong inhibitors of cell cycle progression. In alignment with these data, we observed downregulation of key checkpoint kinases, including the Cyclin D/CDK4-6 and Cyclin B/CDK1 complexes, contributing to cell cycle arrest at both the G1/S and G2/M checkpoints.

In contrast to the mouse liver and human carcinoma cell line, in the adult monkey hippocampal dentate gyrus stem cell niche, the Subgranular zone (SGZ), 4-HNE did not induce an alteration of cell proliferation as measured by Ki-67 immunostaining. However, chronic 4-HNE application led to a significant reduction of the SGZ stem cell pool (SOX2+/GFAP+/S100b- cells), which was accompanied by an increased quantity of immature neurons (DCX+/CALR+), suggesting that in the primate SGZ, 4-HNE induces effects on cell differentiation rather than on cell proliferation.

Altogether, our findings highlight the differential potential of 4-HNE in affecting proliferation and differentiation of progenitor cell pools in different stem cell niches and animal species.

https://www.researchgate.net/profile/Andon-Mladenov



Effects of hydroxynonenal on mammalian cornea – a pilot study

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4-hydroxy-2-nonenal (HNE) is a lipid peroxidation product known to induce cellular stress and exert cytotoxic effects. It is naturally present in the photoreceptors of the retina, where its accumulation is tightly regulated and eliminated by the retinal pigment epithelium. Disruption of this balance can lead to cellular dysfunction and tissue damage. In this study, we present the first data on the morphological and cellular changes observed in the retina and cornea following experimental HNE treatment in mice. Our findings demonstrate that exposure to HNE triggers a pronounced activation of retinal Müller glia, which are essential for maintaining retinal homeostasis and responding to injury. Additionally, preliminary evidence suggests that the integrity of the corneal mucin layer may be compromised after HNE exposure, potentially affecting corneal barrier function and ocular surface health. These results highlight the dual vulnerability of both retinal and corneal tissues to oxidative stress mediated by HNE and underscore the importance of endogenous detoxification mechanisms. Understanding the cellular responses to HNE in ocular tissues may provide new insights into the pathogenesis of retinal and corneal diseases associated with oxidative stress and inform the development of targeted therapeutic strategies.

https://transtem.org/en/andreas-kontny/

Effects of hydroxynonenal on a putative primate neurogenic niche – a pilot study

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The septum pellucidum is a thin midline structure located between the cerebral lateral ventricles, traditionally regarded as a simple membrane separating the ventricular cavities. It encloses a small cavity known as the cavum septi pellucidi. Here, we address the issue whether the septum pellucidum exhibits features of a stem cell niche in the adult brain.

Anatomically, the septum pellucidum can be delineated using Sudan Black B (SBB), while Nissl staining confirms the presence of cellular elements. Notably, neurofilament H immunostaining did not reveal axonal or dendritic fibers, suggesting an absence of mature neuronal processes. To assess neuronal maturity, we performed NeuN immunostaining combined with lipofuscin autofluorescence. NeuN-positive neurons lacking lipofuscin granules were identified, indicating an immature neuronal phenotype. Double immunostaining for doublecortin (DCX) and NeuN revealed both $DCX^+/NeuN^-$ and $DCX^+/NeuN^+$ cells, consistent with distinct stages of neuronal maturation. Additional staining for neural stem cell (NSC) markers demonstrated the presence of NSC-like cells, some of which were located along the structure's borders, further supporting the hypothesis of ongoing postnatal neurogenesis in this region.

Our ongoing work aims to characterize these cells in the monkey brain and to investigate the effects of 4-hydroxy-2-nonenal (HNE) on their viability and differentiation.

https://transtem.org/en/martin-n-ivanov/

Brain-liver axis and disease: a field in need of epigenetic studies

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The brain–liver axis is a crucial bidirectional communication system involving metabolic, neural, and immune pathways. Disruption of this crosstalk has been associated with hepatic encephalopathy, non-alcoholic fatty liver disease (NAFLD), and neurodegenerative conditions. While increasing evidence highlights the importance of this axis, the epigenetic mechanisms underlying its regulation remain largely unexplored.

Epigenetic processes—including DNA methylation, histone modifications, and non-coding RNAs - are known to modulate liver disease progression and may influence systemic signaling toward the brain. Findings from Wilson's disease suggest that hepatic epigenomic changes can mirror neurological manifestations. Moreover, extracellular vesicles and systemic inflammation, both implicated in liver–brain communication, are tightly linked to epigenetic regulation.

Integrating epigenetics into the study of the brain–liver axis could provide novel insights into cross-organ disease mechanisms, identify circulating epigenetic biomarkers for early diagnosis, and uncover therapeutic targets addressing both hepatic and neurological disorders.

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Therapeutic strategies for MASLD and their influence on the liver-brain axis

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Metabolic dysfunction-associated steatotic liver disease (MASLD) represents the most prevalent chronic liver disease globally, reflecting the close link between hepatic steatosis and metabolic risk factors. In addition to liver damage, MASLD affects the central nervous system through systemic inflammation, insulin resistance, and circadian rhythm disruption, contributing to fatigue, impaired attention, and sleep disorders. Evaluating how current treatments act on both liver and brain may broaden our understanding of patient outcomes.

We aimed to review lifestyle and pharmacological therapies for MASLD and explore their potential impact on cognitive performance, mood, and sleep quality. Narrative synthesis of randomized trials, observational cohorts, and mechanistic studies addressing dietary patterns, structured physical activity, and medications such as metformin, pioglitazone, GLP-1 receptor agonists, SGLT2 inhibitors, vitamin E, and probiotics. Outcomes included hepatic endpoints (steatosis, necroinflammation, fibrosis, liver enzymes) and brain-related manifestations (cognition, fatigue, sleep disturbances).

We found that lifestyle interventions, particularly Mediterranean diet combined with regular exercise, consistently reduced hepatic steatosis and are associated with improved subjective well-being and sleep. GLP-1 receptor agonists and SGLT2 inhibitors showed robust hepatic benefits and emerging evidence for neurocognitive improvements. Pioglitazone and vitamin E demonstrated histological improvements in selected patients, whereas metformin exerted modest metabolic and possible neuroprotective effects. Probiotics provided an innovative tool for modulating the gut-liver-brain axis, with preliminary evidence for improved mood and reduced fatigue.

Our results indicate that the therapeutic approaches in MASLD act beyond the liver, influencing cognitive and psychological domains through metabolic and inflammatory pathways. Incorporating neurocognitive outcomes into MASLD research and clinical practice could provide a more comprehensive assessment of treatment efficacy.

https://acibademcityclinic.bg/tokuda/lekari/detaili/d-r-veronika-peneva

Association between metabolic dysfunction-associated fatty liver disease, insulin resistance and cognitive performance. Effects of Aronia melanocarpa

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Background: Calorie-rich diet (CRD) promotes obesity and metabolic dysfunction (MD).

Aim: Polyphenol-rich Aronia melanocarpa fruit juice (AMFJ) was administered to rats fed a CRD with the aim to investigate its effects on metabolic dysfunction (MD)-associated alterations in cognitive performance, insulin resistance and histopathology of the liver.

Methods: Fifty male Wistar rats were allocated in 5 groups: control, MD, MD+AMFJ2.5, MD+AMFJ5 and MD+AMFJ10. In the course of 10 weeks, the control group was on a regular rat chaw and tap water while the other groups received a CRD and 10% fructose solution instead of drinking water. Throughout the whole experiment, groups control and MD were treated daily orally with distilled water and the other three groups – with AMFJ at doses of 2.5, 5.0 and 10.0 ml/kg, respectively. In the 10th week, the novel object location test was performed to evaluate spatial memory. Having the values of the fasting blood glucose and serum triglycerides, the TyG index was calculated as a marker of insulin resistance. Retroperitoneal fat was weighed. Liver samples were evaluated histopathologically.

Results: In MD rats, there was a memory decline, hypertriglyceridemia, visceral obesity and insulin resistance. In the liver, ballooning degeneration, microvesicular steatosis, apoptotic hepatocytes and inflammatory granulomas were observed. AMFJ treatment counteracted the memory decline as well as the development of visceral obesity, hypertriglyceridemia and insulin resistance. It also prevented the occurrence of steatotic, inflammatory, degenerative and pro-apoptotic changes in the liver.

Conclusion: AMFJ prevented CRD-induced metabolic disturbances and associated memory decline, insulin resistance and fatty liver disease probably due to its polyphenolic ingredients with proven antioxidant, anti-inflammatory and metabolic actions.

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