

Project closing report of NKFIH FK 124483: “The role of transient receptor potential channels in fever and hypothermia associated with systemic inflammation.”

1. Summary of the results, their importance and impact

During the four years and three months of the project, we published 39 scientific articles in peer-reviewed journals (24 ranked Q1) and 5 book chapters. The total cumulative impact factor of the published full articles is 159.315. The total number of citations of the articles published from the project is 690 based on Google Scholar (12/27/2021). I gave 4 oral presentations as an invited speaker and participated at national and international conferences with several poster presentations. Student researchers involved in the project, presented the results of the supported research at several local, national, and international conferences and wrote their diploma theses in association with the project. Among the PhD students under my supervision, Dr. Eszter Pakai successfully defended her thesis, while Drs. Alexandra Csenkey, Patrik Keringer, and Zoltan Rumbus, as well as Mr. Leonardo Kelava passed their complex PhD exams. Dr. Patrik Keringer and Ms. Eموke Olah submitted their PhD theses to the Doctoral School at the University of Pecs to initiate the defense of their doctoral degree.

According to the workplan, we conducted the experimental investigation of the thermoregulatory role of temperature-activated transient receptor potential (TRP) channels in different animal models. With thermoregulatory measurements we studied the exact mechanisms of the thermal effects of ligand-induced activation of the TRP vanilloid-1 (V1) channel. We showed that potentiation of the proton activation mode of TRPV1 decreases body temperature in rats and mice (Garami et al., 2018). Surprisingly, we found that the fall in body temperature is triggered through the reverse modulation of the same physiological mechanisms which cause an increase in body temperature when the proton activation mode of TRPV1 is blocked. Our results are of high importance for understanding the physiological mechanisms of thermoregulation as well as for drug development. The study was published in a leading (Q1) physiology journal, *Acta Physiologica* (Oxford).

We studied the importance of proton-induced activation of the TRPV1 channel with meta-analysis and mathematical modeling of human data, and by comparing these novel results with data obtained in animal experiments. The results of these complex analyses supported the thermoregulatory importance of the proton activation mode of the TRPV1 channel and revealed species-dependent differences between rodents and humans in the role of the heat activation mode of the channel in the thermoregulation system. The paper (Garami et al. 2020) was published in the journal *Pharmacology & Therapeutics*, which ranks 4/263 in SJR's *Pharmacology (Medical)* category with an impact factor of 12.310.

In further thermophysiological experiments, we studied the thermoregulatory role of neurotransmitters which are released from TRPV1-expressing sensory nerve endings upon their activation. We demonstrated that substance P can evoke a fever-like response. We found that the absence of the neurokinin-1 receptor of substance P leads to the attenuation of endotoxin-induced fever via suppressed cyclooxygenase-2 expression on the periphery (i.e., outside of the blood-brain barrier) (Pakai et al., 2018). Our findings can promote the identification of the neurokinin-1 receptor as a target for antipyretic therapy. The study was published in a top ranking immunology journal, *Frontiers in Immunology*.

We developed a mouse model of systemic metabolic acidosis (Rumbus et al., 2018) to study the effect of increased proton concentration on thermoregulation and systemic inflammation. In this model, we investigated the relationship between metabolic acidosis and the outcome of acute pancreatitis-induced systemic inflammation and discovered the

existence of a vicious cycle between low systemic pH and the severity of pancreatic inflammation, in which acidosis worsens the outcome of systemic inflammation, while severe pancreatic inflammation augments the decrease of blood pH (Rumbus et al., 2018). A unique feature of our study was that in a translational scientific manner, in addition to the basic research experiments, we simultaneously validated the human relevance of our results by showing the same association between acidosis and pancreatitis in human patients with the use of meta-analysis (Rumbus et al., 2018).

With regards to TRPA1, we investigated whether it is involved in the mediation of the thermoregulatory response to hydrogen-sulfide. We showed that hydrogen-sulfide evokes a fall in deep body temperature via the inhibition of brown adipose tissue thermogenesis and the induction of cutaneous heat dissipation. The hypothermic effect was triggered from the central nervous system and it was markedly attenuated in TRPA1 knockout mice. In our experiments, we also performed PCR and RNAscope measurements for the detection of TRPA1 channels in brain neurons located in thermoregulatory pathways and found modest expression of the TRPA1 channel in several thermoregulation-related nuclei. Our findings suggest that hydrogen-sulfide, which is produced in severe forms of systemic inflammation, triggers its hypothermic effect via TRPA1 channels expressed in the central nervous system, presumably in the hypothalamus. The paper describing these results was published in the journal *Pharmaceuticals* (Olah et al. 2021) during the 3-month extension of the project.

As part of the project, we also contributed to certain preclinical drug development experiments. As a translational research approach, first we demonstrated the diagnostic and prognostic value of macrophage migration inhibitor factor in septic and noninfectious systemic inflammation based on the meta-analysis of published human data (Toldi et al., 2021). Then, by going from “bed to bench”, in preclinical experiments we showed that the inhibition of the enzymatic activity of the same factor enhances the magnitude of hypothermia in a mouse model of severe systemic inflammation (Garai et al. 2021). Taken together, our findings can pave the road towards the identification of macrophage migration inhibitor factor as a therapeutic target in patients suffering from systemic inflammation. Furthermore, we contributed to the development of a novel analgesic and anti-inflammatory drug candidate, which is also an antagonist of TRPV1, by the investigation of its thermoregulatory effects in mice (Horvath et al., 2021).

In addition to the *in vivo* experiments, we took another approach (*viz.*, meta-analysis) to study the importance of thermoregulation in systemic inflammation in human patients. We analyzed whether the outcome of the systemic inflammatory response syndrome induced by severe head trauma can be improved by therapeutic hypothermia (Olah et al., 2018). We showed that external cooling is beneficial in head trauma only if the extent of the hypothermia (*i.e.*, cooling index) is big enough. We provided a recipe for the most optimal cooling parameters in head injury and proposed hypothermic TRPV1 antagonists (*see above*) for pharmacological induction of hypothermia. These results were published in the official journal of the International Neurotrauma Society, *Journal of Neurotrauma*. Later, in a paper published in the same journal we further supported the benefits of therapeutic hypothermia in severe traumatic brain injury by extending our former analysis of the cooling index with inclusion of a new multicenter trial (Olah et al. 2021).

We also used the meta-analysis method to complement our animal experiments with human data. We found that dietary supplementation of TRPV1 agonists alone or in combination with other active ingredients significantly reduces the levels of serum cholesterol and low-density lipoprotein (LDL), however it does not influence the concentrations of high-density lipoprotein (HDL) and triglycerides. These findings provide novel quantitative evidence for the beneficial effects of dietary capsaicinoid consumption on the serum

cholesterol and LDL levels in humans and underlie its usability in the prevention of atherosclerosis, which is characterized by low-grade, chronic inflammation. We published this meta-analysis in *Critical Reviews in Food Science and Nutrition* (Kelava et al. 2021), which is in D1 category in food sciences (9/332) with an impact factor of 11.176 in 2020.

We also studied the thermoregulatory role of the menthol receptor (a cold-sensitive TRP channel, TRPM8), and found that its activation enhances the sport performance in athletes without compromising warmth-defense responses during physical exercise, thereby without increasing the risk of heat-related illnesses such as heat stroke (Keringer et al. 2020). We used a similar meta-analysis approach to determine whether systemic antibiotic prophylaxis prevents inflammatory complications in thermal injuries of children (Csenkey et al., 2019). We showed that systemic antibiotic prophylaxis as a routine has no benefits for the prevention of local and systemic infectious complications in pediatric patients with burn injuries (Csenkey et al., 2019).

The meta-analysis approach was also successfully applied in the assessments of influencing factors of the outcome in different inflammatory and metabolic diseases (e.g., pancreatitis, obesity, diabetes mellitus, metabolic syndrome, inflammatory bowel diseases, gastritis, esophagitis, eosinophilia, hepatic alloimmune reactions, and age-related cytokine changes), which are widely related to the project (Szabo et al., 2017; Solymar et al., 2018; Eross et al., 2018; Kiss et al., 2018; Cazacu et al., 2018; Miko et al., 2018; Tenk et al., 2018; Szilagyi et al., 2018; Miko et al., 2019; Varju et al., 2019; Ottogy et al. 2020, Szebenyi et al. 2020, Balint et al. 2021, Wobbe et al. 2021).

To summarize the current scientific understanding of the researched topic and to highlight the importance of thermoregulation to basic scientists and clinicians, as an associate editor I contributed to publication of two volumes in the *Handbook of Clinical Neurology* series. In one of these books, we also published a chapter about the systemic inflammation-associated changes in body temperature (Garami et al., 2018). We summarized the importance of translational medicine and its scientific aspects with the support of the *Academia Europaea* in the *Journal of Clinical Medicine* (Hegyí et al. 2020) for experts in the field, as well as, in a chapter of a textbook for medical students (Garami et al. 2019). We also wrote a chapter in Hungarian and in English about pain, including the TRPV1 channel, and about blood, including inflammatory cells, in the pathophysiology textbook for medical students.

As proposed in the workplan, our findings were also presented as oral and poster presentations at national and international conferences, such as the FENS Regional Meeting (Pécs, 2017); Conference of the Hungarian & Eastern and Central European Pancreatic Study Groups (Budapest, 2017); Membrane Transport Conference (Sümege, 2018); Meeting of the Hungarian Physiological Society (Szeged, 2018); the 7th International Conference on the Physiology and Pharmacology of Temperature Regulation (Split, Croatia, 2018); the 28th Congress of the Hungarian Society of Clinical Nutrition (Mátraháza, 2018); the Joint Conference of the Hungarian Pharmacology, Anatomy, Microcirculation and Physiological Societies (Budapest, 2019); and the Virtual 8th International Conference on the Physiology and Pharmacology of Temperature Regulation (vPPTR) 2020 (North Vancouver, Canada, October 26-29, 2020).

In summary, 39 scientific articles were published during the project (total impact factor: 159.315). Of these, 17 are closely related to the funded project (Garai et al., 2017; Garami et al., 2018a; Garami et al., 2018b; Jozsa et al., 2018; Olah et al., 2018; Pakai et al., 2018; Rumbus et al., 2018; Csenkey et al., 2019; Garami et al., 2020; Keringer et al., 2020; Hegyí et

al., 2020; Garai et al., 2021, Horvath et al., 2021, Kelava et al., 2021, Olah et al., 2021a, Olah et al., 2021b; Toldi et al., 2021) with a total impact factor: 80.898. Manuscripts reporting our unpublished data are being processed for peer-reviewed scientific journals. Among them, 1 paper is under revision in *J Infect Public Health*, and 2 manuscripts are in preparation (targeted journals: *Life and Temperature*).

2. Setbacks during the research project

Because of COVID-19 we experienced some delays in the project, therefore we asked a 3-month extension to the project's end date, which enabled us to complete final experiments and publish further results (Olah et al. 2021; Pazmany et al. 2021; Lorincz et al. 2021). We also presented our newest findings at an international scientific conference during the extra time [11th International Symposium on Cell/Tissue Injury and Cytoprotection/Organoprotection (ISCTICO), joint meeting of the Hungarian Society for Experimental and Clinical Pharmacology (HUPHAR) and the International Union of Basic and Clinical Pharmacology (IUPHAR), Pécs, October 27-30, 2021].

During the 4th year, with permission of the NKFI Hivatal (NRDI Office), Ms. Nikolett Szabo joined the project as a parttime researcher in order to facilitate the molecular biology measurements.

3. Selected publications during the research project

3.1 Articles in peer-reviewed scientific journals

- * Balint, A., L. Hanak, P. Hegyi, Z. Szakacs, S. Eitmann, **A. Garami**, M. Solymar, K. Marta, Z. Rumbus, and A. Komocsi (2021). Increased risk of adverse events in patients with low-on clopidogrel platelet reactivity after percutaneous coronary intervention: A systematic review and meta-analysis. *Cardiol J*. doi:10.5603/CJ.a2021.0084
- * Cazacu, I. M., N. Farkas, **A. Garami**, M. Balasko, B. Mosdosi, H. Alizadeh, Z. Gyongyi, Z. Rakonczay, Jr., E. Vigh, T. Habon, et al. (2018). Pancreatitis-Associated Genes and Pancreatic Cancer Risk: A Systematic Review and Meta-analysis. *Pancreas* 47 (9):1078-86. doi:10.1097/MPA.0000000000001145
- Csenkey, A., G. Jozsa, N. Gede, E. Pakai, B. Tinusz, Z. Rumbus, A. Lukacs, Z. Gyongyi, P. Hamar, R. Sepp, A. A. Romanovsky, P. Hegyi, P. Vajda, and **A. Garami** (2019). Systemic antibiotic prophylaxis does not affect infectious complications in pediatric burn injury: A meta-analysis. *PLoS One* 14 (9):e0223063. doi:10.1371/journal.pone.0223063
- * Eitmann, S., D. Nemeth, P. Hegyi, Z. Szakacs, **A. Garami**, M. Balasko, M. Solymar, B. Eross, E. Kovacs, and E. Petervari (2020). Maternal overnutrition impairs offspring's insulin sensitivity: A systematic review and meta-analysis. *Matern Child Nutr* 16 (4):e13031. doi:10.1111/mcn.13031
- * Eross, B., N. Farkas, A. Vincze, B. Tinusz, L. Szapary, **A. Garami**, M. Balasko, P. Sarlos, L. Czopf, H. Alizadeh, et al. (2018). *Helicobacter pylori* infection reduces the risk of Barrett's esophagus: A meta-analysis and systematic review. *Helicobacter* 23 (4):e12504. doi:10.1111/hel.12504
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- Garai, J., M. Kreko, L. Orfi, P. B. Jakus, Z. Rumbus, P. Keringer, **A. Garami**, E. Vamos, D. Kovacs, V. Bagone Vantus, et al. (2021). Tetralone derivatives are MIF tautomerase inhibitors and

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- Garami, A.,** E. Pakai, H. A. McDonald, R. M. Reilly, A. Gomtsyan, J. J. Corrigan, E. Pinter, D. X. D. Zhu, S. G. Lehto, N. R. Gavva, et al. (2018). TRPV1 antagonists that cause hypothermia, instead of hyperthermia, in rodents: Compounds' pharmacological profiles, in vivo targets, thermoeffectors recruited and implications for drug development. *Acta Physiol (Oxf)* 223 (3):e13038. doi:10.1111/apha.13038
- Garami, A.,** Y. P. Shimansky, Z. Rumbus, R. C. L. Vizin, N. Farkas, J. Hegyi, Z. Szakacs, M. Solymar, A. Csenkey, D. A. Chiche, et al. (2020). Hyperthermia induced by transient receptor potential vanilloid-1 (TRPV1) antagonists in human clinical trials: Insights from mathematical modeling and meta-analysis. *Pharmacol Ther* 208:107474. doi:10.1016/j.pharmthera.2020.107474
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- Keringer, P., N. Farkas, N. Gede, P. Hegyi, Z. Rumbus, Z. Lohinai, M. Solymar, K. Ruksakiet, G. Varga, and **A. Garami** (2020). Menthol can be safely applied to improve thermal perception during physical exercise: a meta-analysis of randomized controlled trials. *Sci Rep* 10 (1):13636. doi:10.1038/s41598-020-70499-9
- * Kiss, Z., B. Tel, N. Farkas, **A. Garami,** A. Vincze, J. Bajor, P. Sarlos, K. Marta, A. Eros, A. Miko, et al. (2018). Eosinophil Counts in the Small Intestine and Colon of Children Without Apparent Gastrointestinal Disease: A Meta-analysis. *J Pediatr Gastroenterol Nutr* 67 (1):6-12. doi:10.1097/MPG.0000000000001904
- * Kocsis, T., B. Molnar, D. Nemeth, P. Hegyi, Z. Szakacs, A. Balint, **A. Garami,** A. Soos, K. Marta, and M. Solymar (2020). Probiotics have beneficial metabolic effects in patients with type 2 diabetes mellitus: a meta-analysis of randomized clinical trials. *Sci Rep* 10 (1):11787. doi:10.1038/s41598-020-68440-1
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- * Miko, A., N. Farkas, **A. Garami,** I. Szabo, A. Vincze, G. Veres, J. Bajor, H. Alizadeh, Z. Rakonczay, Jr., E. Vigh, et al. (2018). Preexisting Diabetes Elevates Risk of Local and Systemic Complications in Acute Pancreatitis: Systematic Review and Meta-analysis. *Pancreas* 47 (8):917-23. doi:10.1097/MPA.0000000000001122
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- * Miko, A., E. Vigh, P. Matrai, A. Soos, **A. Garami,** M. Balasko, L. Czako, B. Mosdosi, P. Sarlos, B. Eross, et al. (2019). Computed Tomography Severity Index vs. Other Indices in the Prediction

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- * Ruksakiet, K., L. Hanak, N. Farkas, P. Hegyi, W. Sadaeng, L. M. Czumbel, T. Sang-Ngoen, **A. Garami**, A. Miko, G. Varga, et al. (2020). Antimicrobial Efficacy of Chlorhexidine and Sodium Hypochlorite in Root Canal Disinfection: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *J Endod* 46 (8):1032-41 e7. doi:10.1016/j.joen.2020.05.002
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* indicates publications not closely related to the research project

3.2 Book chapters

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