Laboratory of Molecular Cell Metabolism

Department of Endocrine Neurobiology

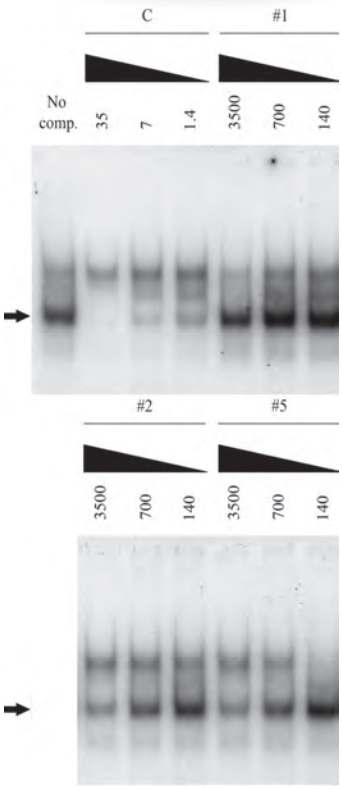
Head of Laboratory:
Balázs Gereben, DVM, PhD

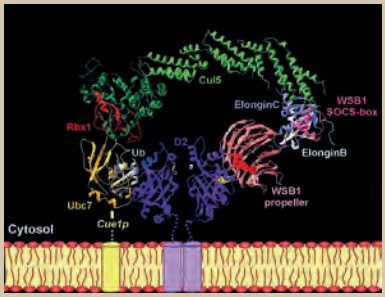
Mission statement

The major goal of the Laboratory is to understand how cell-type specific thyroid hormone (TH) regulation affects brain function and nervous system-controlled peripheral events under physiological and pathophysiological conditions, and to identify the underlying cellular and molecular pathways.

TH is a master regulator of cellular metabolism and proliferation, and exerts a fundamental impact on brain development and function. Despite its relatively stable plasma level, intracellular concentration of TH undergoes rapid and turbulent changes to meet the current needs of specific cellular conditions. The hypothalamo-hypophyseal-thyroid (HPT) axis dominates plasma TH levels via its stable prohormone, thyroxin (T4). Therefore, the axis is unable to perform quick and cell-type specific regulation of intracellular TH levels. This is achieved by cell-type specific TH metabolism catalyzed by deiodinase enzymes, allowing rapid activation and inactivation of TH. In the brain, the type 2 deiodinase (D2) selenoenzyme catalyzes TH activation in the glial compartment by activating T4 to T3, the compound that can effectively bind TH receptors. In contrast, type 3 deiodinase (D3) is responsible for T3 degradation in neurons.

The Laboratory contributed to the description of a complex molecular network allowing temporally and spatially controlled regulation of TH-dependent gene expression. They combine methods of cellular and molecular neurobiology with cell-type specific *in vivo* modulation of gene expression in transgenic mice. They aim to understand how neuro-glial TH economy mediates the function of hypothalamic hypophysiotropic neurons and cell proliferation in adult neurogenic brain niches.





Dissecting the molecular regulation of deiodination

The Laboratory studies molecular regulation of D2 and D3 at multiple regulatory levels including transcriptional and post-transcriptional

Ph.D. students: Péter Egri, Petra Mohácsik
Junior scientist: Zsuzsanna Kvarta-Papp
Technician: Andrea Juhász
Undergraduate student: Richárd Sinkó

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events. These efforts involve the identification of molecular elements and protein-protein interactions allowing the rapid regulation of T3 generation via ubiquitination using fluorescence resonance energy transfer and recombinant protein studies. They also investigate the regulation of the D2-encoding *dio*2 gene during hypothalamic response to inflammation, a phenomenon they described as a component of the nonthyroidal illness syndrome.

Understanding neuron-glial coupling in thyroid hormone metabolism

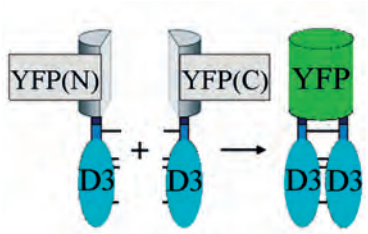
They study the mechanism and molecular components of neuron-glial coupling of TH metabolism and the biological impact of this process. They revealed a novel pathway regulating hypothalamic HT signaling and investigate how local TH affects the regulation of the HPT axis and the intracellular energy homeostasis of hypothalamic neurosecretory neurons. They also aim to identify TH dependent pathways in the regulation of cell proliferation and differentiation in adult neurogenesis.

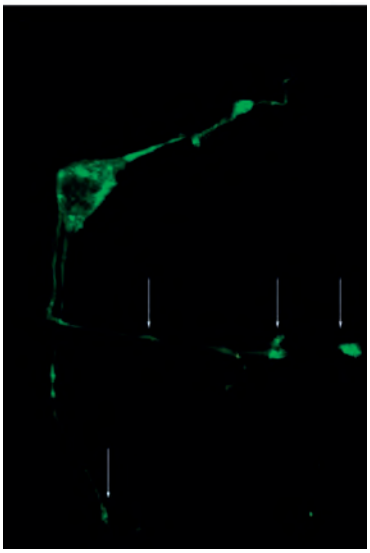
In vivo assessment of thyroid hormone signaling in the brain

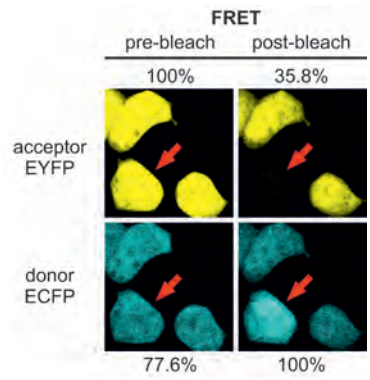
The Laboratory is involved in the generation of transgenic mouse models for cell-type specific modulation and assessment of TH signaling.

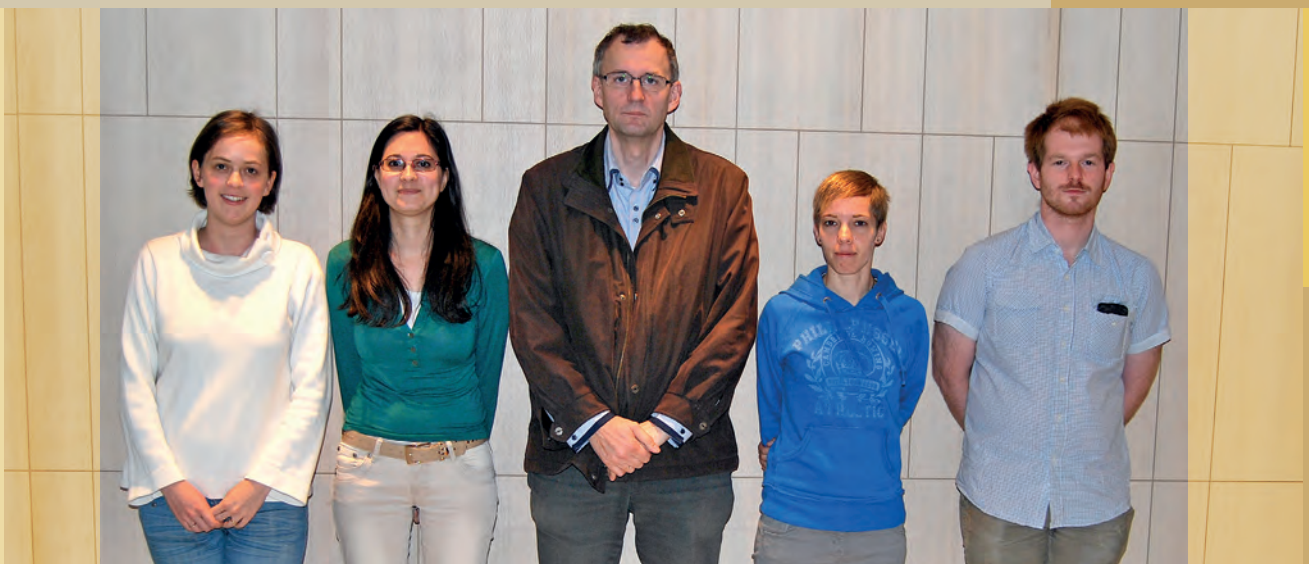
Selected publications from the last 10 years:

- Egri P., Gereben B. Minimal requirements for ubiquitination mediated regulation of thyroid hormone activation. J MOL ENDOCRINOL. 53(2):217-26 (2014)
- Kalló I., Mohácsik P., Vida B., Zeöld A., Bardóczi Z., Zavacki A. M., Farkas E., Kádár A., Hrabovszky E., Arrojo E Drigo R., Dong L., Barna L., Palkovits M., Borsay B. A., Herczeg L., Lechan R. M., Bianco A. C., Liposits Z., Fekete C. and Gereben B. A novel pathway regulates thyroid hormone availability in rat and human hypothalamic neurosecretory neurons. PLOS ONE. 7(6):e37860. doi: 10.1371/journal.pone.0037860 (2012)
- Gereben B., Zavacki A. M., Ribich S., Kim B. W., Huang S. A., Simonides W. S., Zeöld A. and Bianco A. C. Cellular and Molecular Basis of Deiodinase-Regulated Thyroid Hormone Signaling. ENDOCRINE REVIEWS 29 (7): 898-938 (2008)
- Zeöld A., Pormüller L., Dentice M., Harney J. W., Curcio-Morelli C., Tente S. M., Bianco A. C., and Gereben B. Metabolic instability of type 2 deiodinase is transferable to stable proteins independently of subcellular localization. J. OF BIOLOGICAL CHEMISTRY. 281(42):31538-43 (2006)









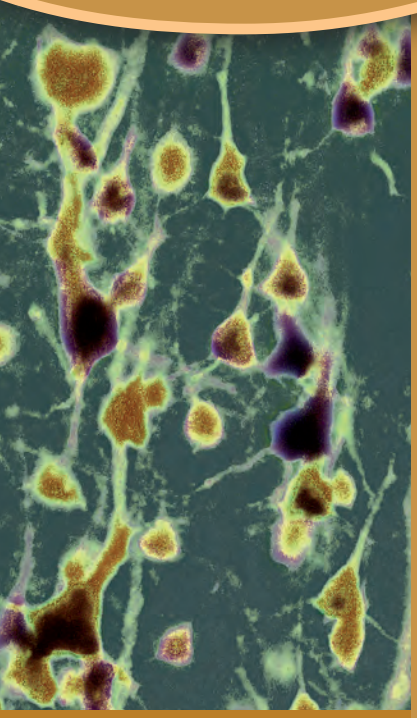
from left: Petra Mohácsik, Zsuzsanna Kvárta-Papp, Balázs Gereben, Andrea Juhász, Péter Egri

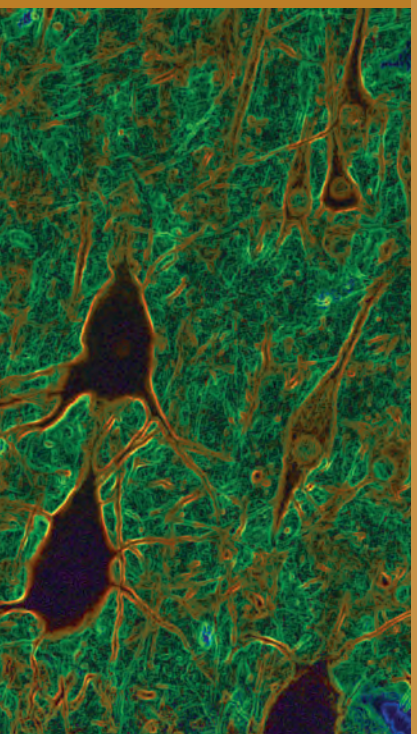
Tamás F. Freund

Laboratory of Cerebral Cortex Research

Department of Cellular and Network Neurobiology

Head of Laboratory: Tamás F. Freund, PhD

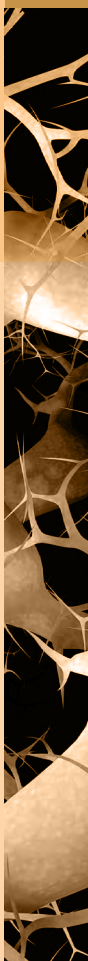




Mission statement

The cerebral cortex consists of billions of cells, which create millions of functional units called neuronal assemblies that operate in a highly sophisticated and organised manner. The concerted action of these cell assemblies or microcircuits form the basis of those neuronal operations that result in the highest level brain functions, including mental operations such as conscious perception, memory, or the generation of thoughts. Studies of Tamas Freund's laboratory over the past 25 years in this Institute represent conceptually novel steps towards uncovering: 1) new molecular pathways in the communication of nerve cells, 2) the identity and principles of connectivity of the nerve cells that build up the circuitry, and 3) the generation of network activity patterns by these circuitries that underlie various stages of information processing and storage in the brain. These findings shed new light not only on the normal operations of the cerebral cortex, but also on several of its disorders at the molecular, cellular or network levels, including epilepsy, schizophrenia, anxiety and ischemic cell death.

In recent years the laboratory has been focusing on the generation of behaviour-dependent population discharge patterns, with particular attention to the theta and gamma oscillations, and hippocampal sharp waves. In addition, we also focus on describing new signaling mechanisms at cortical synapses. Anatomical, *in vitro* and *in vivo* electrophysiological, optogenetic, pharmacological, molecular and modeling techniques are combined to elu-



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Secretary: Katalin Iványi

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