**Dr. Izhak Michaelevski Research**

More info regarding the lab projects are available on our [**lab homepage**](http://www6.tau.ac.il/michaelevski/).

**Molecular and functional neurobiology of learning and memory and molecular pathogenesis of cognitive impairments are the major research interest of our lab**

***Memory as a physiological entity***

In modern neuroscience memory is discriminated into immediate, short-term and long term forms. Immediate and short term memories have a limited capacity and last only for a period of several seconds to a minute. On the contrary, long-term memory has nearly unlimited capability to store information for unlimited duration. Long-term memory is divided into declarative (explicit) and non-declarative (implicit) types. Declarative memory includes facts whereas non-declarative memory refers to acquisition of skills and habits. These two types of memory are formed by different brain structures, hippocampus along with other medial temporal lobe structures with further consolidation in the neocortex are related to declarative, whereas neostriatum and cerebellum mediate non-declarative memory mechanisms. In addition, amygdale has been shown to mediate emotional memory and being involved in memory consolidation. Declarative memory is divided into episodic memory (the personally experienced event specific to a particular context such as time and place) and semantic memory referred to facts taken independent of the context in which they were learned.

***Synaptic plasticity as a cellular correlate of Memory***

Contemporary understanding of memory formation relies on the initiation and maintenance of long-term synaptic plasticity. On its own, synaptic plasticity is a sequence of alterations in synaptic transmission and strength of post-synaptic response as a sequel of activity changes in the involved neuronal networks. Long-term synaptic plasticity persists hours, days, months, and perhaps, years, in contrast to short-term versions, which end up within seconds and minutes. De novo protein synthesis is a vital requirement for maintenance of long-term synaptic plasticity. De novo protein synthesis itself is secondary to activity-dependent changes in synapses that trigger post-translational modifications of proteins initiating and sustaining multiple signal transduction pathways. In turn, these signaling pathways regulate changes in synaptic strength and connectivity by governing gene expression and protein translation. This regulation is exerted simultaneously by the expression of memory-related genes and de novo protein synthesis, whose peaks are crucial to the initiation of late events in the establishment of synaptic plasticity, which is accompanied by time-bound changes in the cellular ultrastructure. Hence, long-term synaptic plasticity is an extremely intricate phenomenon in which proper timing of consecutive signal transduction events determines the success or failure of memory engram formation. Despite this appealing concept and the volume of research revealing specific sequences of memory-related molecular processes, little is known about gene expression pattern changes incurred during memory formation, or regarding the signal transduction networks leading to these alterations in gene expression. In parallel to genetic mechanisms of regulation, recent studies in different fields of neuroscience have shown a strong epigenetic level of regulation, where noncoding RNAs play one of the most important roles.

Taken together, long-term synaptic plasticity is strictly spatially and temporally controlled that involves a myriad interconnected signaling networks regulating gene expression and protein translation at genetic and epigenetic levels. During the last two decades multiple protein components and their modification have been implicated in memory formation, however despite widespread use of modern high throughput methods in different fields of neurobiology, combined application of proteomics and genomics in study of learning and memory processes is very limited. Hence study of such convoluted processes requires implementation of multilevel interdisciplinary approach step-by-step deciphering its functional components. And certainly, in our laboratory, we attempt to address several of these challenges.

**Our research interest at the current stage includes the following points**

What are the signaling molecules, which deliver signal to the nuclei of neurons and how are they modified? Here we are employing proteomics including mass spectrometry and protein microchip approaches with further target analysis of the identified candidates

What is transcriptional and protein de novo synthesis response involved in memory formation? Here we employ gene microarray and deep sequencing analysis for transcript detection and proteomic approach to identify de novo synthesized proteins.

What is the role of non-coding RNA in regulation of synaptic plasticity? As in previous cases, we combine efforts of deep sequencing analysis of RNA transcripts and proteomic analysis of protein expression with wide support of in silico calculations.

How the signaling molecules regulate protein synthesis elaborated in the memory formation? Here we employ in silico analysis approach to delineate major protein signaling networks with further target specific analysis via up- and downregulation of the corresponding genes in vivo. We will elaborate behavioral, electrophysiological and morphological study for this reason.

How does signal delivery affect the memory formation? Here we test involvement of neuronal transport system via targeted in vivo effect of up- and downregulation of transport proteins genes on the memory formation process.

What are molecular mechanisms elaborating aging related memory impairment? This project will extensively exploit in vivo experiments with proteomic and genomic approaches together with behavioral and electrophysiological studies.

Which changes do appear in the memory formation molecular networks upon stress and how the latter affects the memory formation process? What is the mechanism linking post-traumatic stress disorder and memory? This project will elaborate combination of conventional neurobiological research in PTSD mouse model together with high-throughput study and electrophysiology.

How does transient brain ischemia impact on spatial memory? This project will elaborate animal model of brain ischemia with subsequent behavioral, electrophysiological and high-throughput study.