New aspects of negative regulation of RNA polymerase III in yeast *Saccharomyces cerevisiae*

Control of transcription in an eukaryotic cell is the main mechanism of gene expression regulation, basic for growth and differentiation, and critical for oncogenic transformation. Yeast *Saccharomyces cerevisiae* is an excellent model organism for the genetic and molecular analysis of regulatory relationships that control transcription. The planned studies will focus on the regulation of tRNA transcription directed by RNA polymerase III (Pol III). Specific elements of the Pol III machinery are: the general transcription factors TFIIIB and TFIIIC, and Maf1, the negative regulator. These regulatory factors are strictly controlled and regulate Pol III transcription in response to environmental signals. Recent years have provided the knowledge about various mechanisms regulating Pol III transcription and allowed to create new research hypotheses which currently require experimental verification. The aim of the proposed project is to explain new aspects of Pol III transcription regulation by the TFIIIC transcription factor and the Maf1 repressor. Our recent research has shown that the TFIIIC transcription factor necessary for initiation of tRNA synthesis, plays also role in the negative regulation of Pol III. The function of TFIIIC in repression is observed upon the switch of yeast metabolism from fermentation to respiration, yet the respective molecular mechanism that stands behind such effect has not been recognized yet. Therefore, the aim of the proposed research is to explain the unknown elements of the negative regulation of transcription by TFIIIC in response to changes in yeast metabolism.

The repression of Pol III transcription by Maf1 under stress conditions as well as changes of yeast metabolism has been widely documented. Maf1 repression has been shown to be associated with its dephosphorylation, nuclear location and direct interaction with Pol III. The aim of the proposed research will be to analyze the mechanism of the negative regulation of Pol III by small molecules identified through the screening of a chemical library. The library contained marketed drugs that suppress the growth defect of a yeast strain carrying a deletion in the Maf1-encoding gene. We will focus on compounds that specifically affect Pol III, by substituting Maf1 and selectively inhibiting yeast Pol III via a direct interaction, yet compounds that act on Pol III indirectly, by affecting other cellular processes, will also be investigated. The Pol III machinery is conserved from yeast to man. Thus, it is possible that the newly discovered inhibitors of tRNA transcription will turn out to be specific both for yeast and humans. It is well established that transcripts produced by Pol III are overexpressed in a variety of cancers. Therefore, in the future, the newly discovered Pol III inhibitors could be implemented as therapeutic agents in cancer treatment.