CENTER FOR RNA BIOMEDICINE

RNA Faculty Candidate Seminar
Wednesday, March 13th at 4:00pm
Willard H Dow Chemistry & Laboratory
Room 1400
930 UNIVERSITY AVE

Thomas Gonatopoulos-Pournatzis, PhD
Postdoctoral Fellow, Blencowe Laboratory
Donnelly Centre, University of Toronto

"Uncovering post-transcriptional regulatory mechanisms underling human diseases Through CRISPR-based screening strategies"

Abstract: Alternative splicing generates vast transcriptomic and proteomic complexity and is implicated in numerous diseases and disorders. An overarching challenge is to develop a comprehensive knowledge of the function of the myriads of uncharacterized alternative exons and of the regulatory networks that control them. During my postdoc I have identified and functionally characterized a neuron-specific exon in the translation initiation factor EIF4G which promotes associations with cytoplasmic mRNP granule components resulting in ribosome stalling. Strikingly, this microexon regulates the translation of synaptic receptors and impacts animal behavior and memory. In addition, I have developed a genome-wide CRISPR screening strategy for the systematic exploration of factors and pathways that regulate alternative splicing. Application of this approach revealed a common mechanism for the definition of neuronal microexons, which are commonly disrupted in autism (Gonatopoulos-Pournatzis et al., Mol Cell, 2018). Finally, I will present the development of a novel CRISPR- based dual-guide screening approach for efficient combinatorial genetic targeting and systematic deletion of sizeable genetic elements. This constitutes the first screening platform with single-exon resolution and its application has uncovered a network of alternative exons underlying cell fitness. Overall, these novel tools pave the way for the exploration of the regulatory and functional complexity of AS and the systematic identification of transcript variants with critical roles in normal physiology and disease-state.

BIOSCIENCES

umichrna.org