BioFrontiers - Biology Seminar

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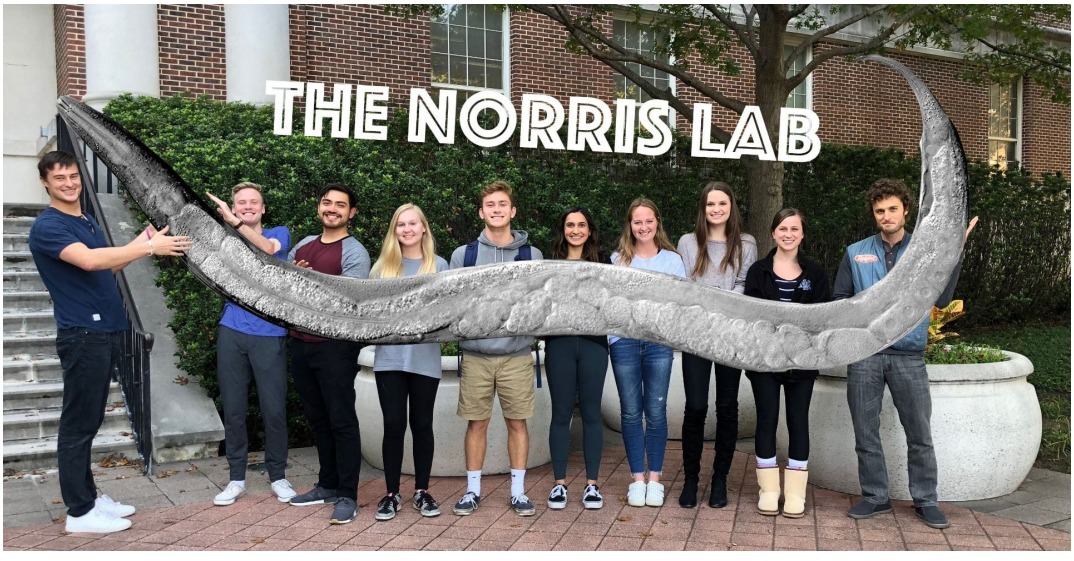
Multi-layered control of gene expression in single neurons

Single-cell transcriptomes are established by transcription factors (TFs), which determine a cell's gene-expression complement. Post-transcriptional regulation of single-cell transcriptomes, and the RNA binding proteins (RBPs) responsible, are more technically challenging to determine, and combinatorial TF-RBP coordination of single-cell transcriptomes remains unexplored. We use fluorescent reporters to visualize alternative splicing in single *Caenorhabditis elegans* neurons, combined with single-neuron transcriptomics to identify the entire transcriptome of individual neurons. We recently identified complex splicing patterns in the conserved neuronal kinase *sad-1*. Most neurons express both isoforms, but the ALM mechanosensory neuron expresses only the exon-included isoform, while its developmental sister cell the BDU neuron expresses only the exon-skipped isoform. We identified a cascade of three cell-specific TFs and two RBPs combinatorially required for *sad-1* exon inclusion. Mechanistically, TFs coordinately ensure expression of the RBPs, which interact directly with *sad-1* pre-mRNA. Thus, a combinatorial TF-RBP code controls single-neuron *sad-1* splicing. Additionally, we find 'phenotypic convergence,' previously observed for TFs, also applies to RBPs: different RBP combinations generate similar splicing outcomes in different neurons. We are now using single-cell RNA-Seq to extend these findings to other transcripts in single neurons, and using CRISPR/Cas9 technology to identify functional and behavioral consequences for neuron-specific splicing patterns.



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