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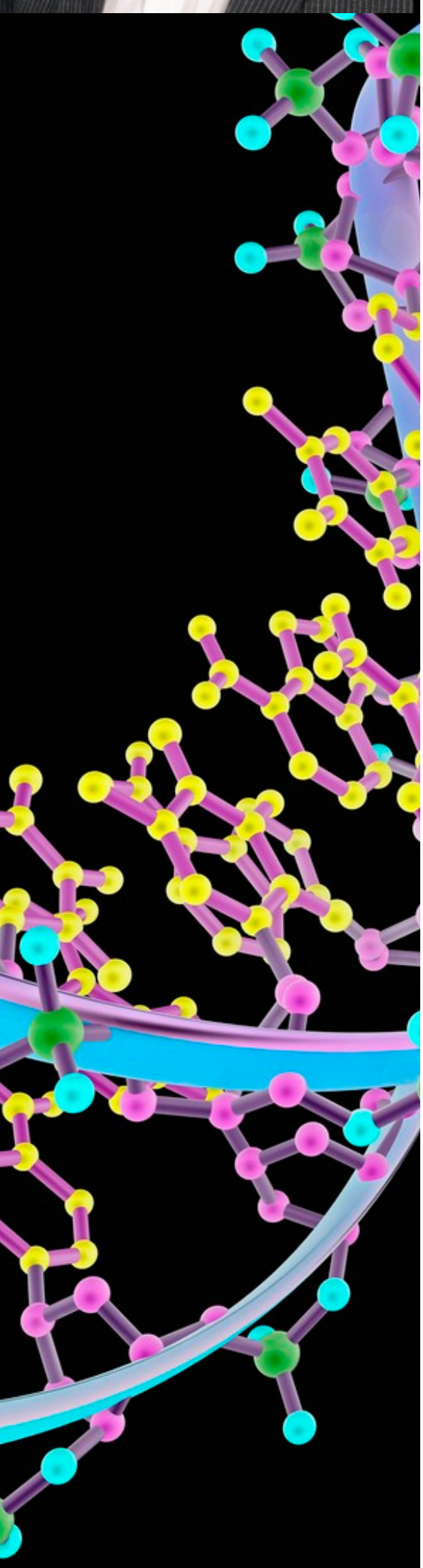
miRNA and RNA Alternative Polyadenylation



MicroRNAs (miRNAs) are small regulatory RNAs that pair with 3'UTRs and repress mRNA translation into proteins. Because these recognition elements are degenerated, and small, miRNA targets are generally difficult to identify, thus the vast majority are still unknown. Defining these targets is the ultimate goal in the field of miRNA biology since misregulation of miRNAs, and their known target genes have been observed in almost all human diseases, including cancer, Alzheimer's, and muscular disorders.

Alternative Polyadenylation (APA) is an elusive process observed in virtually all metazoans that produces genes with different mRNA 3'end isoforms. While it is routinely detected in normal states and often altered in disease, its biological role in cells and tissues is still a mystery. Since genes with longer 3'ends possess more sequence real estate containing potential regulatory sites, an attractive hypothesis is that APA allows genes to change their 3'UTR length and escape the negative regulation exerted by miRNAs and RNA binding proteins. Given that APA is very abundant, this model could explain why there is no direct correlation between cellular transcriptomes and proteomes.

APA is achieved because of the presence of multiple polyadenylation signal (PAS) elements in the same 3'UTR, which are differentially recognized and cleaved by the RNA cleavage and polyadenylation complex. In humans, this complex is composed of at least 17 different subunits. However, we still do not entirely understand its exact composition, how it is assembled, how it recognizes the termination sequences on the pre-mRNAs, how it discriminates between multiple PAS elements, the role of each of the subunits, and the dynamics of how this process is executed in detail.

In this seminar, I will cover three short stories describing how miRNA regulatory networks evolved their target specificity, how they interface with APA and mechanistic insights on how APA is achieved in metazoans.

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