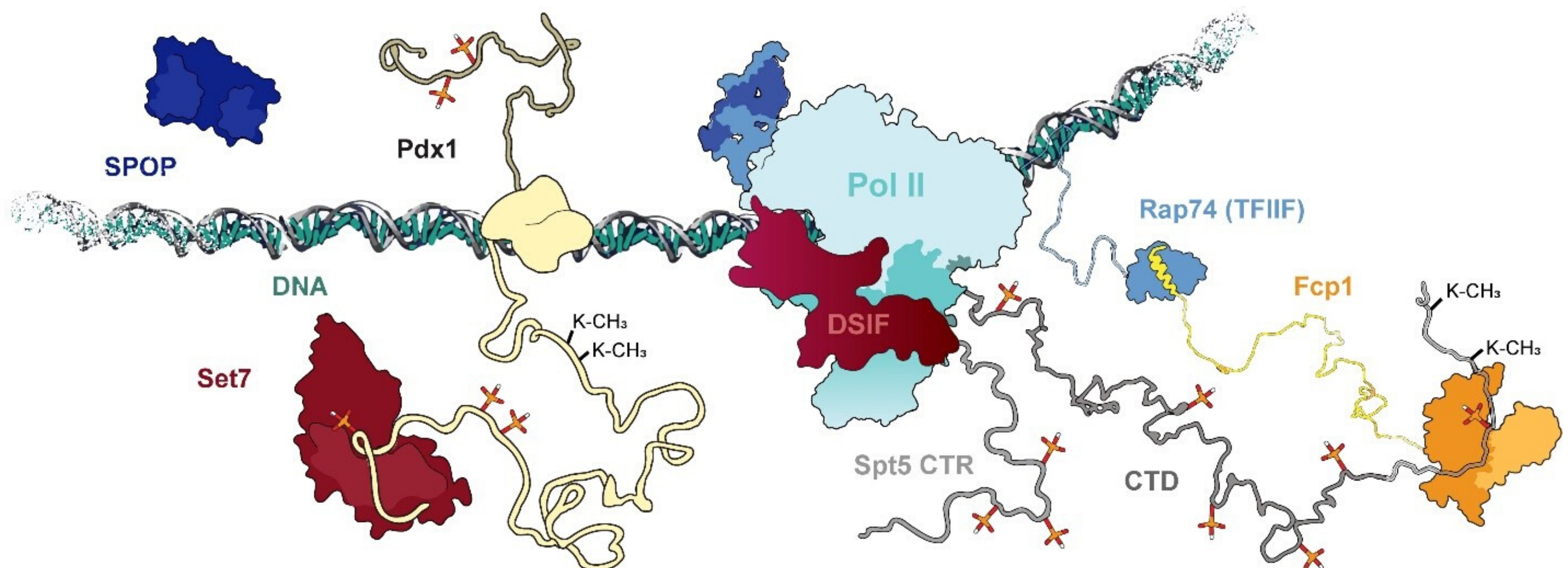




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### (Un)Structural Biology and the Mechanisms of Regulated Gene Expression



Nearly every cell in a multicellular organism possesses the same genetic information, yet each cell type utilizes that information in profoundly different ways. Regulating access to the genome requires the participation of a wide array of transcription factors, enzymes, and scaffolding proteins that must interact in temporally dynamic complexes, controlled by metabolic signals. Although structural biology and molecular biophysics have given us deep insight into DNA binding mechanisms and the catalytic functions of enzymes, how the multi-protein complexes that regulate transcription form and dissociate has remained more elusive. A significant driver of this knowledge gap is the over-representation of Intrinsically Disordered Proteins (IDPs) in the transcription machinery, which confound traditionally defined structure-function relationships. IDPs partially or completely lack a co-operatively folded structure under native conditions, making their equilibrium state very different from that typically described through high-resolution structural biology. Our view is that IDPs do possess native structure that is responsible for imparting their specific functions; describing these structures simply requires a broadening of the traditionally narrow structure-function paradigm. To better understand how IDPs regulate gene expression, our laboratory has developed a suite of  $^{13}\text{C}$  direct-detect nuclear magnetic resonance (NMR) experiments capable of providing the comprehensive and quantitative structural information required. Here, we will focus on several new directions for our laboratory, which have the common theme of addressing how covalent protein modifications change the structures and interactions of IDPs. Examples will be drawn from both transcription factors and the enzymes they partner with to regulate transcription.