Transcription of the genome: from molecular movies to regulatory systems

Our laboratory combines structural biology with functional genomics and computational biology to study the mechanisms of gene transcription and its regulation in eukaryotic cells. Recent work includes structural studies of transcription initiation and regulation (Plaschka Nature 2015, 2016; Nozawa Nature 2017) and the development of transient transcriptome sequencing (TT-seq), which monitors changes in enhancer landscapes at high temporal resolution (Schwalb Science 2016; Demel Mol. Syst. Biol. 2017). I will present our most recent results. After 15 years, our efforts to solve the mechanism of RNA polymerase II initiation have now led to the structure of a 46-subunit, 2 MegaDalton pre-initiation complex that comprises all initiation factors that are essential for cell growth (Schilbach et al., Nature 2017). These results led to a movie of how promoter DNA is opened before RNA synthesis begins. We have also investigated the old question of how regulation at the level of early transcription elongation can lead to changes in gene expression. We used a multi-omics approach to measure the rates of transcription initiation and the duration of RNA polymerase II pausing near the promoter and found that polymerase pausing controls the frequency of initiation (Gressel, Schwalb et al. Leonhardt, Eick, Cramer, eLife 2017). We just solved structures of the polymerase in the paused and the pause-released state, which provide a basis for understanding transcription regulation. Polymerase that has been released from the pause will have to traverse nucleosomes, and I will present structural data that indicate how a chromatin remodeling enzyme may unravel the nucleosome for transcription (Farnung et al., Nature 2017).

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The lecture will be followed by a chalk-board session for PhD students

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