Research Summary Patrick Cramer (2021)

Short version

Patrick Cramer and his laboratory elucidated the molecular mechanisms of gene transcription and its regulation, which underlie cell differentiation and organism development. Cramer pioneered the structural analysis of cellular transcription machineries and described the molecular mechanisms underlying RNA polymerase II initiation, elongation, and regulation. This led to first molecular movies of transcription. The Cramer laboratory also developed functional genomics tools for quantifying transcription kinetics in cells. Cramer provided concepts such as the indirect recognition of promoters, the tunable active site of polymerases, allosteric transcription regulation, cellular buffering of mRNA levels, or elongation-controlled regulation of transcription initiation. Using complementary structural and functional approaches, Cramer defined the cellular switches underlying gene activity, providing the basis for understanding diseases such as cancer.

Long version

Patrick Cramer determined the first structure of a eukaryotic RNA polymerase, Pol II, when working with Roger Kornberg (Science 2001). Over the last two decades, the Cramer laboratory used and developed integrated structural biology methods to determine structures of Pol II in many functional complexes (Annu Rev Cell Dev Biol 2020). These include the Pol II pre-initiation complex with the coactivator Mediator, a 50-protein assembly that provides the basis for transcription initiation and regulation (Nature 2017, 2021a, 2021b, Cell 2021). Cramer developed methods for integrated structural biology of macromolecular assemblies and for functional multi-omics. He established biological concepts such as the tunability of the polymerase active site (Cell 2003), indirect promoter recognition (Nature 2013), or elongation-limited initiation regulation of genes (eLife 2017).

The Cramer laboratory also reported structures of mammalian Pol II (Nature 2016) and paused and activated transcription complexes (Nature 2018a, 2018b). This elucidated regulatory mechanisms during elongation. Cramer further pioneered structural studies of alternative RNA polymerases. His laboratory recently reported the structure of the polymerase of the coronavirus SARS-CoV-2 (Nature 2020) and clarified the mechanisms of the polymerase-targeting antiviral drugs remdesivir and molnupiravir (Nat Comm 2020, NSMB 2021). Cramer also resolved first structures of Pol I (Nature 2013) and mitochondrial RNA polymerase (Nature 2011), and initiation and elongation complexes for both (Cell 2017a, 2017b). This led to molecular movies for these alternative transcription systems that reveal differences to Pol II.

The Cramer lab also elucidated how transcription is mechanistically linked to other nuclear process, including splicing (Science 2021) and DNA repair (Nature 2021). They also pioneered the mechanistic analysis of chromatin transcription. Cramer reported the structure of Pol II in complex with the nucleosome (Nat Comm 2018), and the first structure of a complete chromatin remodeling enzyme on a nucleosome (Nature 2017). This enabled studies of nucleosome transcription (NSMB 2021) and led to first nucleosome complex structures of a pioneer factor (Dodonova, Nature 2020), the cofactor SAGA (Wang, Nature 2020) and a SWI/SNF remodeler (Wagner, Nature 2020).

To complement structural with functional studies, the Cramer laboratory used and developed functional genomics methods. Cramer derived a method that combines RNA metabolic labeling with kinetic modeling and can estimate cellular rates of RNA

synthesis, splicing and degradation, monitoring RNA metabolism for the first time (Mol Syst Biol 2011). His laboratory introduced robust global normalization methods to transcriptomics, leading to the discovery of ‘mRNA buffering’, a cellular mechanism that maintains mRNA levels (Genome Res. 2012; Mol. Cell 2013). Cramer also developed ‘transient transcriptome sequencing’ (TT-seq), which monitors human gene activity and dynamic changes in enhancers (Science 2016). He further combined TT-seq with occupancy profiling and kinetic modeling to uncover the nature of transcriptional regulation in cells genome-wide (eLife 2017). This multi-omics approach recently showed that transcription elongation can control initiation during natural gene activation (Nat Comm 2019). TT-seq can also be used in so-called labeling time series to derive also the rates of pre-mRNA splicing in human cells (eLife 2019), and can be adopted to enable sequencing of native mRNA isoforms (Genome Res 2020).