The Cramer laboratory unraveled the structural basis of eukaryotic gene transcription and cellular mechanisms of gene regulation.

Patrick Cramer determined the first structure of a eukaryotic RNA polymerase, Pol II, with Roger Kornberg (Cramer, Science 2001). Over the last two decades, the Cramer laboratory used a combination of crystallography, cryo-EM, and chemical crosslinking to determine structures of Pol II in many functional complexes (reviewed in Osman, Annu Rev Cell Dev Biol 2020). These include the Pol II pre-initiation complex with the coactivator Mediator, a 46-protein assembly that provides the basis for transcription initiation and regulation. The Cramer lab also developed methods for integrated structural biology of macromolecular assemblies and for functional multi-omics. They established biological concepts such as the tunability of the polymerase active site (Kettenberger, Cell 2003), indirect promoter recognition (Engel, Nature 2013), or elongation-limited initiation regulation of genes (Gressel, eLife 2017).

Recently, the Cramer lab reported structures of mammalian Pol II (Bernecky, Nature 2016) and paused and activated complexes (Vos et al., Nature 2018a, 2018b). This elucidated the mechanisms of transcriptional regulation during elongation. Cramer further pioneered structural studies of alternative RNA polymerases. They recently solved the structure of the polymerase of the coronavirus SARS-CoV-2 (Hillen, Nature 2020) and clarified the mechanism of the polymerase inhibitor remdesivir, the only FDA-approved drug for COVID-19 (Kokic, BioRxiv 2020). The Cramer group also resolved first structures of Pol I (Engel, Nature 2013) and the mitochondrial RNA polymerase (Ringel, Nature 2011), and initiation and elongation complexes for both (Engel, Cell 2017; Hillen Cell 2017). This led to molecular movies for these alternative transcription systems that reveal differences to Pol II.

Cramer also pioneered the mechanistic analysis of chromatin transcription. His laboratory reported the structure of Pol II in complex with the nucleosome (Farnung et al., Nature Comm 2018), and the first structure of a complete chromatin remodeling enzyme on a nucleosome (Farnung, Nature 2017). This enabled studies of transcription on chromatin, including first nucleosome complex structures of a pioneer factor (Dodonova, Nature 2020), the cofactor SAGA (Wang, Nature 2020) and a SWI/SNF remodeller (Wagner, Nature 2020).

In complementary functional studies, the Cramer laboratory also developed functional genomics methods. They 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 (Miller, Mol Syst Biol 2011). Cramer was also amongst the first to introduce robust global normalization methods to transcriptomics, leading to the discovery of ‘mRNA buffering’, a cellular mechanism that maintains mRNA levels (Sun, Genome Res. 2012; Sun, Mol. Cell 2013).

The Cramer lab also developed ‘transient transcriptome sequencing’ (TT-seq), which monitors human gene activity and dynamic changes in enhancers (Schwalb, Science 2016). They further combined TT-seq with occupancy profiling and kinetic modeling to uncover the nature of transcriptional regulation genome-wide (Gressel, eLife 2017). This multi-omics approach showed that transcription elongation can control initiation during gene activation (Gressel, Nature Comm 2019). TT-seq can also be used in labeling time series to derive also the rates of pre-mRNA splicing in human cells (Wachutka, eLife 2019), and can be adopted to enable sequencing of native mRNA isoforms (Schwalb, Genome Res 2020). Together, this work defines some of the key molecular switches that regulate gene activity in eukaryotic cells.