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EDITORIAL

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At every active gene in any genome, there is a transcription cycle, defined as the collective set of biochemical reactions that control RNA polymerase activity, from promoter binding to polymerase recycling. The transcription cycle serves as a command center where multiple sources of information are integrated to ensure that RNA synthesis across genomic loci is tailored precisely to the needs of the cell and organism. Despite its critical importance, our understanding of the transcription cycle is limited, and this lack of knowledge hampers our ability to manipulate transcriptional activity for myriad purposes, both in basic research and the applied sciences. Within this framework, in this issue of Transcription, we are excited to publish a series of reviews focused on key regulators of the transcription cycle: the transcriptional cyclin-dependent kinases or tCDKs.

CDKs are a distinct class of serine-threonine protein kinases that share a core set of features, including the requirement of a cyclin partner and phosphorylation of their 'activating T-loops' by a CDK-activating kinase (CAK). In vertebrates, a distinct set of CDKs have clear roles in the regulation of cell cycle progression (CDK1, −2, −4, −6), while a different subset is involved mostly in transcriptional control (tCDKs: CDK7, −8, −9, −12, −13, −19) (ref 1–3). Our understanding of tCDKs has evolved rapidly in the last decade, yet for some of these proteins, our knowledge is still minimal, as in the cases of CDK12, CDK13, and CDK19. Even for the more well-studied tCDKs, such as CDK7 and CDK9, recent discoveries have changed our view of their mechanism of action and their roles in cell biology. Thus, we felt at *Transcription* that the time was right to have an updated view of the field, with a focus on recent discoveries and future venues for research. The need for these reviews is further justified by the increasing recognition that tCDKs could be valid targets of pharmacological intervention for the management of a number of human pathologies.

In this issue of *Transcription*, Robert Fisher gets us started with an entertaining and thorough update on the state of affairs for CDK7, arguably the most multifaceted of the tCDKs, describing unanticipated roles for this enzyme in capping, termination, and polymerase recycling, while also sharing promising news about the therapeutic value of CDK7 inhibitors [4]. Then, Bacon and D'Orso bring us up to speed on CDK9, which they accurately describe as a "signaling hub" for transcriptional control, providing detailed descriptions of the mechanisms regulating CDK9 activity, as well as the roles of CDK9 in gene and enhancer transcription, RNA processing, chromatin regulation, and its roles in human disease [5]. Next, Fant and Taatjes provide an expert testimony about the Mediator-associated kinases, CDK8 and CDK19, introducing new and intriguing roles in enhancer-promoter communication, transcriptional memory, metabolism, and, in the case of CDK19, kinase-independent roles in transcriptional control [6]. They are followed by Arno Greenleaf, who provides a detailed account of the history behind the discovery of CDK12 and CDK13, arguably the least understood members of this family, as well as a summary of current facts, including tantalizing roles for these tCDKs in mRNA processing and genome stability [7]. Then, Andrew Rice brings us back to the "big picture" by integrating what is known about the role of diverse CDKs in transcription of the HIV genome [8]. Repeatedly, study of the HIV life cycle has produced major insights about control of the transcription cycle in general, proving to be a great model system to study tCDKs. Finally, the review by Galbraith et al. takes us on a tour-de-force about the development of pharmacological inhibitors of multiple tCDKs, explaining the existing rationale for testing these molecules for the treatment of various human pathologies, mostly in the area of oncology [9].

We are grateful to all authors for their expert contributions and hope that the readers of *Transcription* will treasure this issue focused on tCDKs.

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