Mitosis in all eukaryotic cells is accompanied by a near-complete shutdown of transcription due to highly compacted chromatin and dissociation of transcription factors, chromatin remodelers and components of the basal transcription machinery from mitotic chromosomes. Upon exit from mitosis, transcription resumes and gene expression patterns must be restored faithfully in order to maintain cellular identity. However, as most components of the transcription and chromatin-modifying machinery are either displaced or degraded when entering mitosis, timely and accurate reactivation of the genes necessary for cell cycle progression and maintenance of cell fate poses a significant challenge. How cells remember the transcriptional program that defines their lineage and identity during mitosis remains a key question in chromatin biology.

e emerging concept of gene bookmarking unifies potential mechanisms by which genes are marked for post-mitotic re-activation or re-silencing so that their transcriptional state is accurately passed on to progeny cells [1]. In a recent elegant study, Zhao *et al.* [2] employed real-time quantitative fluorescence microscopy to assess the kinetics of transcriptional reactivation after mitosis. eir findings support a bookmarking mechanism centered on bromodomain protein 4 (BRD4), a member of the bromodomain and extraterminal (BET) family of proteins, and a promising target for cancer therapeutics.

the locus at the onset of mitosis, and no transcripts were detectable throughout mitosis, as expected from the general mitotic shutdown of transcription. After mitosis, Pol II was re-recruited to the reporter locus with much faster kinetics than those of the initial induction, a behavior that was reflected in the kinetics of the nascent transcripts. e locus was thus not only marked for post-mitotic reactivation, it also gained a kinetic edge in passage through mitosis that led both to a faster onset and steeper rise of recruitment.

Importantly, the Tet-On activator was lost from chromatin at the onset of mitosis, precluding the possibility that the bo[illegible]

JQ1, the second prototypical BET domain inhibitor, has an a nity comparable to I-BET, and likewise displaces acetylated histone peptides from the BRD4 bromodomains and from fluorescently tagged versions of both BRD4 and the BRD4-NUT fusion from chromatin in cells [7]. Proliferation of cells derived from BRD4-NUT-dependent midline carcinoma was diminished upon JQ1 treatment, leading to tumor regression and prolonged survival in mouse models [7]. Several strands of evidence, from a number of patient-derived cancer cell lines and xenograft models, have further shown that JQ1 has potent antitumor e cacy on *myc*-dependent cancer cells, and it has been proposed that this is due to reduced expression of c-*myc* and its downstream transcriptional programs [8,9]. An elegant, recent study from the Kouzarides laboratory uncovered interactions of BET proteins with mixed lineage leukemia (MLL) fusion proteins as part of the super elongation complex and the polymerase-associated factor (PAF) complex [10]. BET inhibitors had strong antiproliferative e cacy against cell lines harboring MLL fusions and had profound benefits in mouse models of MLL [10], expanding the therapeutic spectrum of BET inhibitors from midline carcinoma and c-*myc*-dependent cancers to MLL fusion-driven cancers.

e finding by Zhao *et al.* that BRD4 functions as a gene expression bookmark prompts the question of whether the mode of action of BET inhibitors extends to the disruption of gene bookmarking in addition to the impairment of transcriptional nant cZha