



Figure 1. I-BET selectively inhibits genes that follow an “analog”-like activation pattern while not affecting the “digital”-like response. In response to an inflammatory stimulus, secondary response genes follow an “analog”-like activation pattern. This activation involves chromatin remodeling and exposure of the nucleosome-covered gene promoter. Next, transcriptional initiation commences with the binding of stimulus-induced transcription factors (SITF) and general transcription factors (GTF) to the accessible DNA. Induced acetylation of histones H3 and H4 (H3/H4Kac, illustrated as cyan triangles) recruits BRD4 and P-TEFb to chromatin. P-TEFb phosphorylates RNA polymerase II (Pol II) on serine 2 (S2) and allows pause-release of Pol II, resulting in elongation of mature RNA. Conversely, primary response genes follow a “digital”-like activation pattern in response to a stimulus. These genes already have relatively high levels of Pol II and the permissive histone marks, H3K4me3 (green hexagons) and H3/H4Kac, before stimulation, indicating a “poised” state that does not require chromatin remodeling. Stimulation results in TF binding and a H3/H4Kac-dependent recruitment of BRD4 and P-TEFb, allowing for the productive transcription of mature RNA. I-BET selectively prevents the transcription of genes that follow the “analog”-like, but not the “digital”-like activation pattern. This specificity suggests that “analog”-like secondary response genes are more dependent on BET protein function than “digital”-like primary response genes.