Allosteric modulators of protein-protein interactions

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Most essential cellular functions are accomplished by dynamic macromolecular assemblies comprised of least one enzymatic component surrounded by non-enzymatic moieties that enforce timing, location and specificity. In the case of transcription, transcriptional activators direct the assembly of the RNA polymerase II holoenzyme at specific gene promoters at particular time points; once the polymerase is engaged, the complex disassembles as transcription initiates. This is accomplished through transient protein-protein interactions (PPIs) between conformationally dynamic binding partners. Mis-regulation of activator-transcriptional machinery assembly events is at the heart of many human diseases and the PPIs that direct these dynamic processes are critical for probe development and for therapeutic targeting. We will discuss two new strategies for the discovery of small molecule modulators of activator-transcriptional machinery PPIs, strategies that have produced molecules with unique potency and specificity profiles due to their allosteric mechanism.