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Drugging the Redox Switch in the Transcription Factor ΔFosB - a potential therapeutic target for neuropsychiatric and neurological disorders.

ΔFosB is an unusually stable transcription factor that accumulates uniquely to very high levels in specific regions of the brain following insults such as chronic exposure to drugs of abuse. ΔFosB accumulation drives locomotor responses to drugs of abuse, drug reward, drug self-administration and relapse. ΔFosB also accumulates in brain in response to Alzheimer's disease where it contributes to cognitive decline, and Parkinson's disease where it is involved in mediating dyskinesia. ΔFosB is an attractive drug target. However, it is also a highly challenging one because it lacks typical 'druggable' molecular features like a deep active site found in enzymes, and because it is generally difficult to identify compounds that can interfere with DNA binding. In addition, the molecular basis for ΔFosB action is not understood well yet.

We are delineating the molecular mechanism of ΔFosB and de-risking ΔFosB as a highly novel drug target. We have characterized molecular and structural features of ΔFosB, in particular its DNA binding site, and discovered a redox switch that controls DNA binding. The redox switch renders ΔFosB susceptible to small molecule binding, and we have leveraged it to identify compounds that disrupt ΔFosB's ability to bind to DNA, demonstrating that ΔFosB is indeed 'druggable'. By manipulating ΔFosB with small molecules, it may be possible to exert selective effects on gene transcription, and guide neural and behavioral outcomes in a therapeutically beneficial manner, for example, following exposure to drugs of abuse. We will report on our recent progress.