

## Small Molecule Inhibitors of Transcription Factors: Evaluation as a Drug

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Cell proliferation, differentiation, and transformation are regulated via intracellular signals in response to cell surface stimuli. At the final step of regulation, transcription factors play important roles in the expression of genetic information. A few transcription factors have been found to be overactive in many human cancer cells; thus, these factors are likely targets for the development of anticancer drugs. Such transcription factors include activator protein 1 (AP-1),  $\beta$ -catenin/Tcf, NF $\kappa$ B, and the signal transducer and activator of transcription (Stat) family. These transcription factors offer the most promising targets for treating cancer due, in part, to the widespread effects of these transcription factors on the cancer process as there are many more signaling pathways than there are oncogenic transcription factors.

Activated  $\beta$ -catenin/Tcf signaling as evidenced by the accumulation of  $\beta$ -catenin in the nucleus has been implicated in human carcinogenesis, including colorectal cancer (CRC), melanoma, hepatocellular carcinoma, and gastric carcinoma. In addition, enhanced expression of c-Jun and c-Fos, which dimerize to form AP-1, as well as of AP-1-dependent genes is found in tumors derived from *in vivo* and *in vitro* transformation. In addition, c-Jun is known to be over-expressed between 4- and 12-fold in 40% of human small-cell lung cancers and 20% of non-small cell lung cancers. C-Jun may be involved in leukemia. Activation of c-Jun appears to be crucial for transmitting cancer-promoting signals. Disruption of Fos-Jun dimerization has been shown to impair transcriptional activation and cell transformation regulated by these proteins. Thus, the dysregulation of transcription factors plays a crucial role in some cancer cells. Therefore, we hypothesized that

reduced  $\beta$ -catenin/Tcf transcriptional activity may lead to suppressed tumor growth in types of cancer with activated  $\beta$ -catenin. Given that small-molecule inhibitors of an overactive process are thought to be the most useful mechanism for tumor inhibition, antagonists that bind directly to the "hot spot" of a protein-protein interface or to allosteric sites distal to the protein-protein interface of the transcription factors are the most logical targets. Further investigation is required to determine exactly how specific transcription factor activity can be inhibited by these small-molecule inhibitors.

Over the last few decades, significant interest has been generated for developing therapeutics and chemical probes that inhibit specific protein-protein interactions. Although it has been challenging to develop small molecules that are capable of interrupting the large, often relatively featureless protein-protein interaction interface, an increasing number of small molecules that are shown to function in this manner are emerging. Specific interruption of the DNA binding of a particular transcription factor may not be achieved; however, interruption of the function of this limited number of transcription factors by other mechanisms still offers ample opportunity for extensive pharmacological searches. Some transcription factor inhibitors, such as Stat5a/b inhibitors, are currently in pre-clinical development and under phase I/II clinical trials. Importantly, identification of the correct target and design of a potent inhibitor against interactive types of transcription factors will provide clues to develop personalized medicine strategies for each cancer associated with activation of specific transcription factors.

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