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# DISRUPTING THE NFAT-AP-1 TRANSCRIPTIONAL COMPLEX USING SMALL MOLECULES

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The physical interaction between the transcription factors NFAT and AP-1 is pivotal for both the effector immune response and for the exacerbated response that happens during autoimmune and inflammatory diseases. In the absence of AP-1, NFAT directs another program of gene expression, which resembles T cell tolerance, where the cells lose their effector function. We have screened ~200,000 small drug-like compounds using a FRET assay that allows identifying inhibitors of the NFAT-AP-1 complex on DNA. We identified 960 candidate inhibitors in the initial screen. 24 compounds were evaluated and one of them actually inhibits the *in vitro* assembly of the NFAT-AP-1 complex on DNA with no effect on the binding of NFAT or AP-1 individually to their consensus binding sites. This compound also inhibits the induction of cytokine genes that depend on NFAT-AP-1 interaction, such as IL2, but not of those regulated independently of NFAT-AP-1 cooperation, such as TNF. The differential effect on IL2 and TNF gene expression indicates that selective inhibition of NFAT-AP-1 complexes in preference to other NFAT transcriptional complexes may be achievable by small molecules. One caveat is that further experiments have shown that this compound binds directly to DNA and not to the interface between NFAT and AP-1 as desired. We are currently developing an ELISA assay to pinpoint inhibitors that bind at the NFAT-AP-1 interface, and plan to re-test the other 936 compounds identified in the initial high-throughput screen. A proper inhibitor targeting NFAT-AP-1 complexes might redirect T cell transcription from an effector program to a tolerance program, and might find practical applications in the treatment of autoimmune and inflammatory diseases.

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