Inhibition of protein-protein interactions and transcription factors by small organic molecules

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According to current thinking, only one in seven human proteins can be targeted by small organic molecules. Since most biological processes are performed by protein complexes, inhibitors of specific protein-protein interactions are likely to influence the functions of most proteins. Therefore, the inhibition of protein-protein interactions represents a powerful approach by which to expand the proportion of proteins that can be targeted by small organic molecules. In support of this notion, we have previously demonstrated that dimeric transcription factors can be efficiently and selectively inhibited by small molecules that interfere with the protein-protein interactions required for their activity. Moreover, small-molecule inhibitors of protein-protein interactions can provide alternative methods by which to interfere with the function of established small-molecule targets, i.e. protein kinases. In collaboration with Prof. K. Strebhardt (University of Frankfurt, Germany), we have provided proof-of-principle that the serine/threonine kinase Plk1 can be targeted by small-molecules which do not target its ATP binding pocket, but instead inhibit the protein-protein interactions required for correct intracellular localization of the enzyme.

Stimulated by our discoveries of small molecules which inhibit protein-protein interactions and transcription factors, we hypothesized that known bioactive molecules could possess similar activities. In the course of these studies, we have identified hitherto unknown activities of certain natural products and FDA-approved drugs on transcription factors and protein-protein interactions, which will be detailed in the presentation. Our data give new insights into the molecules' biological activities. In addition, they highlight the role of known bioactive compounds as a prominent source of lead structures for the development of inhibitors of protein-protein interactions and transcription factors.