



**Donnelly Centre**  
for Cellular + Biomolecular Research  
UNIVERSITY OF TORONTO



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## “No target left behind: developing inhibitors for undruggable proteins”



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### **Abstract:**

Targeting protein-protein interactions can provide plentiful opportunities for the discovery of novel drug candidates and powerful chemical biology tools. However, the majority of these interactions are “undruggable” and we still know very little about the structural mechanisms and functions for the vast majority of them. We have developed a rational approach that allows for the straightforward development of cell-permeable metabolically stable inhibitors of protein-protein interaction. The approach is based on structural stabilization of protein fragments by membrane anchoring. General applicability of this method was confirmed by generation of selective and highly potent dominant negative inhibitors of RAS oncogenes, b-catenin, STAT1, STAT3 and STAT5 N-domains, and other non-druggable targets. The use of the approach allowed uncovering two previously unknown regulatory mechanisms for the product of the worst known oncogene, K-Ras and a new function of STAT3 transcription factor. High throughput generation of selective chemical biology tools allows for effective interrogation of protein-protein interactions leading to discovery of mechanistic details of molecular signaling that could not be obtained with the help of genetic approaches.

**Host: Dr. Philip M. Kim**