Characterization of Small Molecules that Degrade YAP1 Protein in Cancer
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Background
The Hippo Pathway is a signaling pathway that regulates various essential biological processes including cellular proliferation, cell survival, differentiation, organ size, and tissue homeostasis. YAP1 is a transcriptional co-activator and downstream effector in the Hippo pathway¹.

If overexpressed, YAP1 can become a highly potent oncogene that plays a major role in tumorigenesis and metastasis in various types of cancer. This gene is overexpressed in 10% of all cancers and seen in many solid tumors either by genetic copy number amplification or by unknown pathways.

YAP1 activation also leads to resistance to common cancer therapies such as cytotoxic chemotherapy, molecular targeted therapy and radiotherapy². Thus, targeting YAP1 requires nontraditional drug and cancer technology.

Methods
Below is a flow chart outlining the general procedures used in this study to discover and verify the PROTACs most effective in degrading YAP1 proteins.

Results
Primary screening followed by secondary validation identified about 32 molecules with potential reduction of GFP levels tagged to the YAP1 protein. Some hits were further validated by YAP1 western blot which suggested that some of the identified compounds degraded YAP1.

CIDD-015087, was identified as a lead compound in degrading YAP1. Through qSAR analysis of this compound three PROTACs, CIDD-0162266, CIDD-0162288, and CIDD-0162289, were synthesized. The efficacy of these four compounds was measured in YAP1 independent and YAP1 dependent cell lines after 4 hours of treatment.

Conclusion
Our data show that these four novel molecules that can significantly reduce YAP1 protein levels in different cell lines. This data suggests that these compounds could be useful agents to target YAP1-dependent cancers and could offer significant improvements in a short amount of time.

Future Direction
Our future steps include conducting proliferation assays using all the drugs on YAP1 independent and dependent cell lines. After this we hope to validate these results through in vivo studies.

References