



Chemical & Physical Sciences

UNIVERSITY OF TORONTO

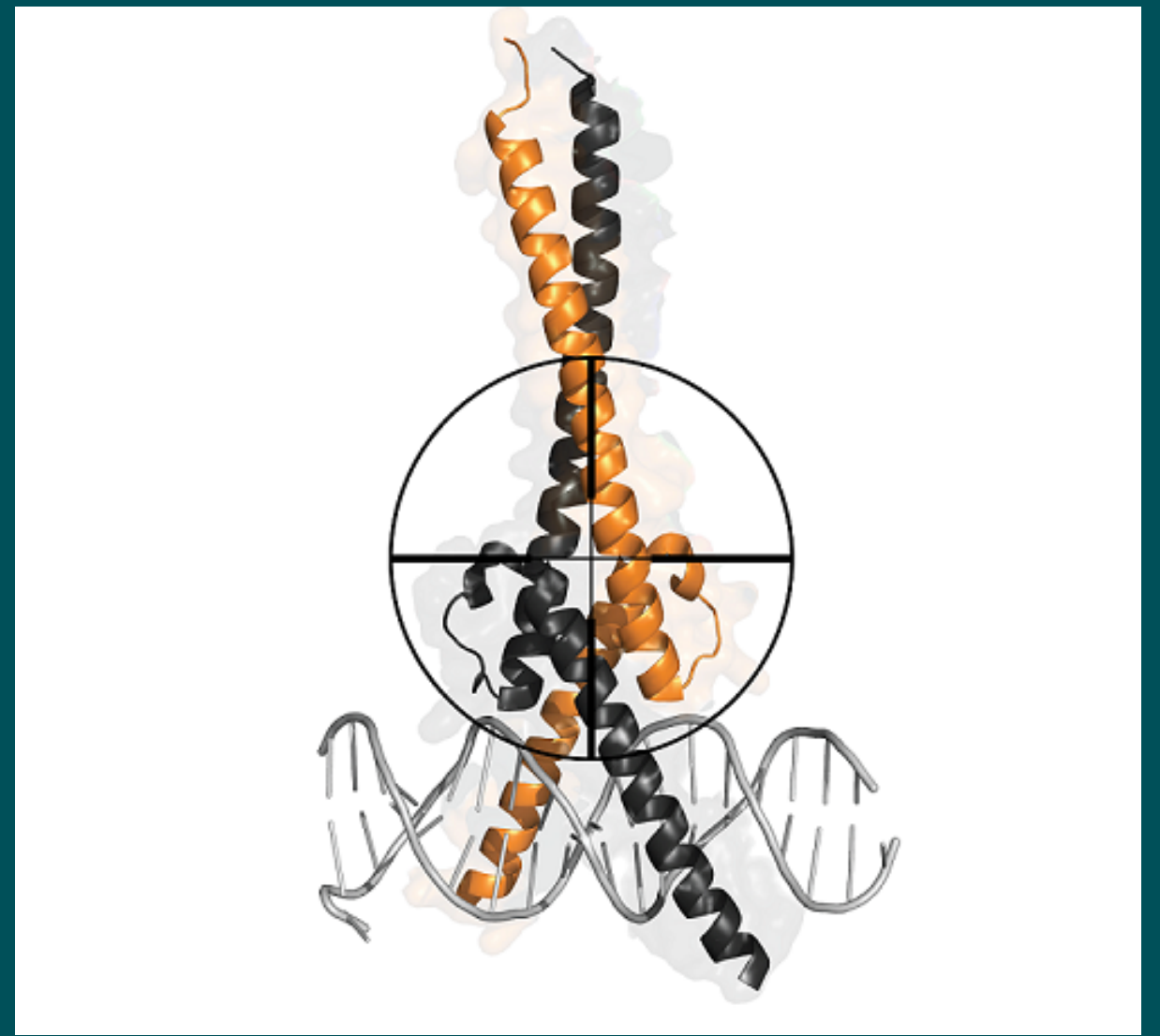
MISSISSAUGA

COLLOQUIUM SEMINAR SERIES

HITTING CANCER: NEW THERAPIES BY REPROGRAMMING THE CELLULAR DEGRADATION MACHINERY



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CeMM Research Center for Molecular
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Targeted protein degradation (TPD) is a new therapeutic modality based on drugs that destabilize proteins by inducing their proximity to E3 ubiquitin ligases. In my presentation, I will first discuss how we leverage TPD to understand transcriptional processes at a high kinetic resolution. Moreover, I will discuss how we develop phenotypic drug screens to find novel small molecule degraders that function as “molecular glues”. Molecular glues are of particular interest as they can degrade otherwise unligandable proteins by orchestrating direct interactions between target and ligase. I will describe a scalable strategy toward glue degrader discovery that is based on chemical screening in hyponeedylated cells coupled to a multi-omics target deconvolution campaign. This approach led us to identify compounds that induce ubiquitination and degradation of cyclin K by prompting an interaction of CDK12–cyclin K with a CRL4B ligase complex. Notably, this interaction is independent of a dedicated substrate receptor, thus functionally segregating this mechanism from all described degraders. Collectively, our data outline a versatile and broadly applicable strategy to identify degraders with nonobvious mechanisms and thus empower future drug discovery efforts particularly for proteins that are historically considered to be undruggable, such as transcription factors.

Colloquium Seminar Series

Wednesday, November 3, 2021

Join us on Zoom at 3:10pm

<https://utoronto.zoom.us/j/84409166490>