Chemical & Physical Sciences
UNIVERSITY OF TORONTO
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COLLOQUIUM SEMINAR TALK
WEDNESDAY, JANUARY 17, 2018
3:10PM
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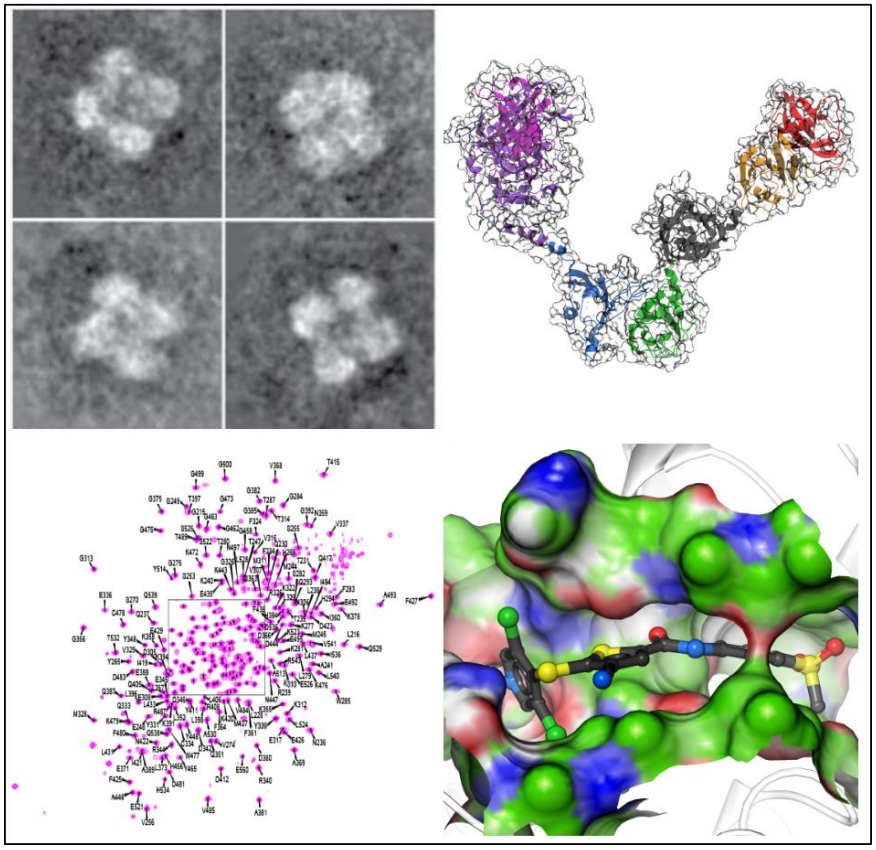
How to Rescue a Tumor Suppressor: Structure, Function, and Inhibition of USP7



USP7 is a deubiquitinating enzyme that plays a pivotal role in multiple oncogenic pathways and therefore is a desirable target for new anti-cancer therapies. However, the lack of structural information about the USP7-inhibitor interactions has been a critical gap in the development of potent inhibitors. USP7 is unique among USPs in that its active site is catalytically incompetent and is postulated to rearrange into a productive conformation only upon binding to ubiquitin. Surprisingly, we found that ubiquitin alone does not induce an active conformation in solution. Using a combination of NMR, mass spectrometry, computational modeling and cell-based assays, we found that DUB inhibitors P22077 and P50429 covalently modify the catalytic cysteine of USP7 and induce a conformational switch in the enzyme associated with active site rearrangement. This work represents the first experimental insights into USP7 activation and inhibition and provides a structural basis for rational development of potent anti-cancer therapeutics.