Donnelly Centre
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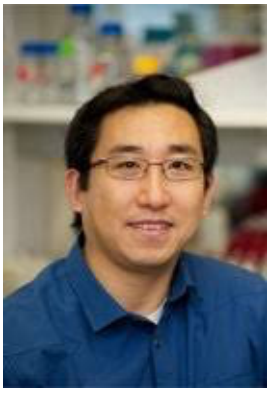
Zhang Lab Seminar Announcement

"Novel technologies to dissect dynamics of protein machineries and gene regulation on the whole proteogenomic scale"



Professor Haiyuan Yu

Dept of Computational Biology
Weill Institute for Cell and Molecular Biology
Cornell University, Ithaca, New York

Friday, June 28, 11:00 a.m.
Donnelly Centre, Yip / Friesen Red Seminar Room
160 College Street, Toronto

Protein-protein interactions facilitate much of known cellular function. While simply knowing which proteins interact with each other provides valuable information to spur functional studies, far more specific hypotheses can be tested if the spatial contacts of interacting proteins are known. However, co-crystal structures and homology models cover only ~10% of all known human interactions. To solve this issue, we developed ECLAIR (Ensemble Classifier Learning Algorithm to predict Interface Residues), a unified machine learning framework that we used to create the first multi-scale whole-proteome structural interactome in human for all experimentally-determined binary interactions reported in major databases. Furthermore, we established Interactome INSIDER (INtegrated Structural Interactome and genomic Data browsER), an information center for genomic studies and for functional exploration of human disease within this structurally resolved human interactome.

Cross-linking mass spectrometry (XL-MS) has the unique capability to detect protein-protein interactions at a large scale along with spatial constraints between interaction partners. We have optimized an MS2-MS3 XL-MS workflow using a novel MS-cleavable cross-linker, DSSO, to carry out a proteome-wide 3D human interactome screen in K562 cells. However, the conventional MS2-centric cross-link search algorithms show sub-optimal performance in terms of both sensitivity and specificity. Thus, we developed a novel MS3-centric cross-link search algorithm named MaXLinker with significantly better performance than the current state-of-the art approaches. In total, our XL-MS screen yielded 9,319 unique cross-links (8,051 intraprotein and 1,268 interprotein) at 1% FDR.

Distal enhancer elements remain one of the least understood genomic entities despite decades of research demonstrating their pivotal roles in development and disease. Recently, we developed the PRO-cap assay that is capable of detecting transcription start sites (TSSs) genome wide with at least an order of magnitude higher sensitivity than other assays. Since numerous chromatin features have been proposed to mark distal enhancer elements, we performed systematic and functional comparisons of enhancer predictions using our improved eSTARR-seq assay. Our results indicate gene-distal divergent TSSs detected by PRO-cap are a robust predictor of enhancer activity, with higher specificity than histone modifications. We propose a model of regulatory elements defined by divergent TSS boundaries, validate that these boundaries are necessary and sufficient to capture enhancer activities genome wide.

Host: Zhaolei Zhang