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Next Generation Mass Spectrometry Tools for Characterizing the Protein Interactome

By

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Significant technological advancements in liquid chromatography tandem mass spectrometry (LC-MS/MS) proteomics over the past decade have facilitated the high-throughput and quantitative analysis of proteins, with as many as 10,000 proteins identified in a single sample. However, it is now appreciated that detecting changes in protein abundance alone is insufficient for characterizing disease pathology, and that context-specific molecular interactions between proteins with other biomolecules (i.e. other proteins, nucleic acids and metabolites) are the key drivers in disease development and progression. In order to shed further insight into this protein "interactome", more sophisticated reagents and tools are required that interface with mass spectrometry to fully utilize its potential.

In this work we will present novel MS-based technologies that we have developed for studying different facets of the protein interactome. The first part of the talk will feature a high-resolution approach for mapping sites of small molecule interactions on proteins, and a case study will be used to illustrate how unconstrained sequencing algorithms discovered novel sites of interaction and identified an unanticipated reaction mechanism for a popular class of small molecule probes. The second part of the talk will present MS workflows for identifying protein targets for an important class of enzymes known as histone lysine methyltransferases (HKMTs), which regulate gene expression via protein modifications and are currently of tremendous interest in the pharmaceutical sector [1]. Using these technologies, we have elucidated HKMT targets in human cytomegalovirus (HCMV) infection [2] and made a recent breakthrough discovery in malaria [3]. However, the identification of HKMT targets in higher eukaryotes is confounded by enzyme redundancy as several HKMTs can modify the same protein substrate. To address this problem, we have developed a computational structural biology approach to engineer HKMT-cofactor systems for systematic target identification. Experimental results for a specific HKMT of interest will be presented, where we have validated synthetic cofactor selectivity and utilized this system to unambiguously identify site-specific methylation on histone and non-histone protein targets. The potential for such technologies to bridge apparent "gaps" between complex biological pathways and their impact on transforming target progression in pharma will be discussed.

[1] M. Tcherpakov, "Histone Methyltransferases: Global Markets for Research Tools, Diagnostics and Drug Discovery", *BCC Reports* (2013).
[2] DiMaggio P.A. and O'Connor C. et al., "Quantitative proteomic discovery of dynamic epigenome changes that control human cytomegalovirus infection", *Mol. Cell. Proteom*., 13(9), 2399-410 (2014).
[3] Chen P.B. et al., "*Plasmodium falciparum* PfSET7: enzymatic characterization and cellular localization of a novel protein methyltransferase in sporozoite, liver and erythrocytic stage parasites", *Sci. Reports*, 6, doi:10.1038/srep21802 (2016).

BIO: Dr Pete DiMaggio is a Senior Lecturer in the Department of Chemical Engineering at Imperial College London. Pete was an undergraduate student in the Chemical Engineering Department at URI from 2000-2004, where he worked in Angelo Lucia's research group for three years, resulting in a few publications. He did his PhD research at Princeton University with Chris Floudas from 2004-2010, he was the first to apply optimization tools for solving the peptide and protein identification problem using liquid chromatography tandem mass spectrometry data. As a doctoral student he was the recipient of a number of honors, including the Porter Ogden Jacobus Fellowship (2008-2009), an annual University-wide honorific fellowship awarded to only four students who, in the judgment of the University faculty, demonstrate the highest scholarly excellence.

Following his PhD studies in 2010, Pete continued at Princeton as a Postdoctoral Research Associate funded by a NIH National Research Service Award (2010-2012) in the Department of Molecular Biology to receive complementary experimental training. He worked with Ben Garcia on the development of mass spectrometry platforms for quantitating combinatorial histone modifications and profiling their dynamics of turnover, which was recognized as a breakthrough in the field of proteomics according to the Faculty of 1000 Biology (http://f1000biology.com/article/id/1164285). The data analysis algorithms created by Pete during his postdoc were also licensed to Novartis and Constellation Pharmaceuticals to aid in their search for epigenetic therapeutic targets.

In January of 2012, Pete joined Imperial College London as a Lecturer in the Department of Chemical Engineering, and was promoted to Senior Lecturer in 2015. His main research interests at Imperial are in the development of technologies that interface with mass spectrometry to study how complex molecular interactions regulate biological pathways and are manipulated in disease.

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