Novel Approaches and Assays in Drug Discovery

Thursday, May 23, 2013
Herman Auditorium, MBRB (Molecular Biology Research Building)
900 South Ashland Avenue, Chicago, IL 60607

8:30 Registration and Check-in

8:45 Welcome
Bernard D. Santarsiero, Translational Technology Resources, CCTS

9:00 Characterization of HDAC Isoform Selective Inhibitors Using Caliper LabChip EZ Reader
Jennifer Gale, Broad Institute of MIT and Harvard

10:00 Applying Affinity CE Technology to Fragment-Based Screening
Dallas Hughes, Selcia Discovery

11:00 Extracting Rich Information From Biological Images to Tackle World Health Problems
Anne Carpenter, Broad Institute of MIT and Harvard

Noon Lunch (provided)

1:00 Activity-Based Protein Profiling
Ken Hsu, Scripps Research Institute

2:00 Modern Phenotypic Drug Discovery is a Viable Pharma Strategy
Jonathan Lee, Eli Lilly and Company

3:00 Reception

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Characterization of HDAC Isoform Selective Inhibitors Using the Caliper LabChip EZ Reader

Jennifer Gale, Senior Research Associate, Broad Institute of MIT and Harvard

Histone deacetylases, HDACs, are a class of enzymes associated with many important biological functions. HDACs have been linked to a variety of diseases, including psychiatric disorders such as Alzheimer’s, Schizophrenia, and depression. Modulation in HDAC activity via selective compound inhibitors is a viable strategy for the understanding and treatment of these diseases. A non-coupled HDAC Caliper assay has been optimized for evaluating and screening inhibitors of full-length DHAC isoforms. The Caliper assay format has replaced the original protease-coupled format where enzyme could be inactivated by trypsin digestion. Inhibition kinetics is an important process for evaluating an inhibitor's efficacy, safety, differentiation, and duration of action. We developed a methodology utilizing Caliper’s EZ Reader bench top instrument to support lead compound characterization and late-stage lead optimization. Direct radiometric measurement of fluorescently-labeled acetylated substrate and deacetylated product formation were monitored for each reaction. Experiments were conducted in real-time kinetic mode, allowing for precise and rapid determination of compound mechanism of action. Several selective HDAC isoform inhibitors have been identified, optimized, and characterized using this method.

Applying Affinity CE Technology to Fragment-Based Screening in Drug Discovery

Dallas Hughes, Consultant, Selcia Discovery

Fragment-based drug discovery (FBDD) is a recognized and successful complementary approach to high throughput screening. FBDD requires techniques that can detect weak affinity fragment/target interactions. An affinity capillary electrophoresis method is described that detects weak fragment binding interactions with soluble protein targets in solution, without the need to immobilise the target protein(s). Affinity capillary electrophoresis is a microscale, high resolution, separation technique that can be used either as a primary screen or as an orthogonal screening tool to confirm fragment hits obtained by other methods. The technique detects a reduction in the interaction of a probe ligand with its target protein in the presence of a binding fragment. The competitive nature of this interaction ensures that fragment “hits” bind in a defined manner and avoids the problem of false positives caused by non-specific binding. Case studies of screening several different targets, including Hsp90 and the MDM2:p53 protein-protein interaction will be presented.
Extracting Rich Information From Biological Images to Tackle World Health Problems

Anne Carpenter, Director, Imaging Platform, Broad Institute of MIT and Harvard

Microscopy images contact rich information about the state of cells and organisms, and are an improtant part of experiments to address a multitude of world health problems. Our laboratory works with dozens of collaborators around the world to design and execute high-content screens using chemical libraries or genetic perturbations, in order to identify the causes and potential cures of disease. For instance, we are working to identify novel drugs for various forms of leukemia and infectious diseases, regulators of DNA damage, distinctions between human isoforms of cancer-relevant histone deacetylase proteins, mechanisms of hepatotoxicity, and diagnostics for bipolar disorder and schizophrenia. Biologists are developing model systems that are more physiologically relevant, yet still compatible with automated instrumentation. Such systems include co-culturing two different cell types to better mimic functional tissue and culturing whole organisms, such as Caenorhabditis elegans, to study entire organ systems. Machine-learning approaches, guided by biologists’ intuition, have been particularly successful for measuring subtle phenotypes in these increasingly complex model systems.

Activity-Based Protein Profiling

Ku-Lung (Ken) Hsu, Hewitt Foundation Fellow, Scripps Research Institute

The human genome contains a vast number of enzymes that lack functional annotation. As a result, our basic understanding of enzymatic pathways that underlie human physiology and pathology has so far remained largely incomplete. Consequently, molecular profiling technologies have emerged as an unbiased means to globally examine the biochemical makeup of cells and tissues and identify genes and proteins associated with pathophysiological states. In contrast, “systems biology” methods for the functional characterization of enzymatic pathways in native biological systems are still lacking. Our lab addresses this problem by integrating functional proteomic and metabolomic technologies to monitor dynamics in enzyme activity directly in living systems. In this presentation, I will describe the application of activity-based protein profiling (ABPP), which utilizes active site-directed chemical probes to determine the functional state of large numbers of enzymes in proteomes, for both inhibitor discovery and confirmation of target engagement in vivo. I will also describe the integrated application of ABPP with complementary functional proteomic/metabolomics methods to discover and show that diacylglycerol lipase-β serves as a key metabolic hub within a lipid-signaling network that regulates proinflammatory responses in macrophages.
Modern Phenotypic Drug Discovery is a Viable Pharma Strategy

Jonathan Lee, Senior Research Advisor, Eli Lilly and Company

The majority of current drug discovery strategies are directed towards specific, molecular targets. However, analysis of FDA approved drugs indicates that the majority of first in class new molecular entities (NMEs) originated from phenotypic and not target-directed screening. Phenotypic drug discovery (PDD) approaches are not commonly used by Pharma, due to concerns about assay performance, difficulties with compound structure-activity relationships (SAR), uncertain applicability of chemoinformatics, and the difficulty/requirement for elucidating a molecular target. We address these perceived issues with PDD by conducting a medium through screen using a co-culture angiogenesis assay. Results indicate that modern phenotypic assays can reliably provide information on compound SAR. Identification of compounds that modulate targets not previously associated with angiogenesis demonstrates that PDD directly interrogates relevant biology without preconceptions of target validation state. These attributes of PDD enabled the identification of compounds that are structurally and mechanistically distinct from current standard of care (SOC) and are active \textit{in vivo}. Modern PDD combines advantages of pharmacology based drug discovery with the high throughput compound testing capacity and operational robustness of targeted approaches.

**UICentre.** A campus-wide initiative, the UIC Center for Collaborative Engagement in Novel Therapeutic Research and Enterprise, was created to foster greater biomedical research collaboration at UIC with a focus on the discovery and development of small molecule therapeutic agents. The CENTRE will fund three rounds of seed grants each year. The mechanism of funding stems from project-based drug discovery proposals that are coupled with invention disclosures filed with UIC/OTM. UIC researchers have traditionally produced a plethora of novel ideas, suitable for translational research, which includes biomolecular targets or non-proprietary small molecules. To add value to these ideas, and to enhance the probability of benefit to society and human health, the CENTRE builds collaborative research teams using core campus resources. This creates an environment that encourages team science and will stimulate the growth of new multi-PI grant applications that translate basic science to the improvement of real health outcomes in the clinic.

**Chicago Drug Discovery Consortium.** The Chicago Drug Discovery Consortium, CDDC, was established in 2010 as an informal biannual gathering of researchers from academia and industry focused on all aspects of drug discovery and development. The UIC Center for Clinical and Translational Science and UIC Center for the Collaborative Engagement in Novel Therapeutic Research and Enterprise co-host the CDDC in collaboration with the CTSA programs at the University of Chicago and Northwestern University. Past symposia included an overview of HTS facilities and methodology in regional academia, the use of nanotechnology in biomedical research, successes in drug discovery from national leaders, and advances in research and therapy on cancer, pain, infectious disease, and neurodegenerative diseases.