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High Throughput Screening Operations at the University of Kansas

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Abstract

The High Throughput Screening Laboratory at University of Kansas plays a critical role in advancing academic interest in the identification of chemical probes as tools to better understand the biological and biochemical basis of new therapeutic targets. The HTS laboratory has an open service policy and collaborates with internal and external academia as well as for-profit organizations to execute projects requiring HTS-compatible assay development and screening of chemical libraries for target validation, probe selection, hit identification and lead optimization.

Keywords

Biochemical and Cell based Assays; compound libraries; drug discovery; High Throughput Screening Laboratory; instrumentation.

INTRODUCTION

The High Throughput Screening Laboratory (HTSL) at the University of Kansas (KU-HTS) laboratory is an integral component of the university's integrated cross campus multi-institutional drug discovery and development program. The drug discovery program is managed by the professionals with extensive biopharmaceutical experience in the office of Institute for Advancing Medical Innovation (IAMI) (<http://www.kumc.edu/iami>) under the leadership of Dr. Scott Weir. The management and execution of projects follows the "pharma" paradigm and brings industry best practices to university drug discovery. The program is driven by highly collaborative project teams through effective planning and management and seeks industry partners to advance projects and strengthen the program. The KU drug discovery and development program which encompasses the broad spectrum from early discovery to late stage drug development played a key role in establishing KU Medical Center as NCI designated cancer center in 2012. The major focus of the IAMI lies in channeling drug discovery research activities towards innovative and improved products for the prevention and control of diseases. KU has also set up expertise to identify and commercialize intellectual property, and has created a highly collaborative, entrepreneurial

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CONFLICT OF INTEREST

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environment which attracts other academic institutions, industry and disease-focused non-profit organizations into partnership with the KU.

The projects within the scope of drug discovery have several entry points into the program, depending on whether they have a new target or already have compounds that need optimization and further development (Fig. 1). The projects come from local academic centers, institutes and hospitals as well as from out-of state academia and industry. The early stage programs characterized by novel target discovery are funneled through the KU-HTS lab. The hits identified by the HTS lab are optimized further by Medicinal Chemistry and Synthesis Laboratories (Director: Dr. Jeffery Aube) located at the KU-Lawrence campus. The optimized molecules are characterized further for animal and pre-clinical studies at the BioCenter (Biotechnology Innovation and Optimization Center) (Director: Dr. Michael Baltezor). The Institute for Advanced Medical Innovations (IAMI) under the leadership of Dr. Scott Weir focuses on leveraging relationships with other institutions and industry partners to advance clinical projects and promote product development.

KU-HTS: MISSION AND GOALS

The KU HTS core was established in 2002 at the University of Kansas with support from an NIH-COBRE (Center of Biomedical Research Excellence) grant to create the CCET (Center for Cancer Experimental Therapeutics) awarded to Dr. Gunda Geog. The KU-HTSL is also a shared resource of the university Medical School's Cancer Center headed by Dr. Roy Jensen [1]. The KU HTS core was reorganized in 2008 under the new director, Dr. Rathnam Chaguturu, and relocated to the Del Shankel Structural Biology Center, a new addition to the University of Kansas. The HTS core infrastructure was further strengthened by recruitment of highly skilled scientific staff and industry-trained project managers. The HTS support team also included services for informatics, chemoinformatics, administration/budgeting, and marketing aspects of the screening core. In addition to the KU HTS staff, director, and project managers, the KU HTS core also benefits from collaborations with the protein purification/molecular biology core, and HTS works in close association with the highly skilled medicinal chemistry and compound synthesis facilities at the University of Kansas.

The High Throughput Screening Laboratory provides a fee for service support for screening and identification of compounds/siRNAs that modulate biochemical and cell based assays. The academic HTS lab also provides a platform to address disease targets that are either financially risky or scientifically impractical to implement in big Pharma settings. The HTS laboratory focuses on being a strong long-term collaborative partner in drug discovery and to help advance the early stage projects to hit to lead optimizations and late stage drug discovery.

Organizationally, the business strategy of the HTS Laboratory is based along the lines of a contract research organization with an educational mission. The laboratory focuses on university priorities, academic drug discovery, and providing unmet regional needs. The HTSL in Lawrence sits in the MidWest where there are no comparable screening facilities within the 275 mile radius of the Lawrence campus. The niche for KU-HTS lies in serving

the academics and small/mid-sized existing local companies and future start-ups in the Midwest corridor.

KU-HTS SERVICES IN TRANSLATIONAL RESEARCH

HTS is an essential enabling technology for translational research and is one of several steps required in transition of basic research from bench to bedside. The KU-HTS workflow begins with the identification of a druggable target or a pathway of clinical relevance through basic research (Fig. 2). An assay that interrogates the target or pathway is optimized and miniaturized for screening in 384-well plate 'HTS-ready' format by addressing assay parameters that reduce variability, and maximize signal to background ratios. The intra-day and inter-day plate to plate uniformity of maximum, mid and minimum signals is tested across three days to evaluate statistical parameters to define plate acceptance criteria. The assay is further validated through screening a small collection of few thousand compounds to establish assay performance, screening statistics and hit rates. Once the assay characteristics are established, larger compound collections are screened with the goal of identifying few hundred active compounds. In general, compound library screens are performed using one compound per well in a 384-well microplate format at a single concentration. For some projects, quantitative HTS is performed at eight compound concentrations [2]. The activity of hits is reconfirmed at this stage by cherry-picking hits and testing them in a dose-response experiment using the primary assay. Data sets from reconfirmed hits are analyzed by chemoinformatics and compounds are rank ordered after identification of structure activity clusters. Further optimization of compound activity and selectivity by medicinal chemistry synthesis should result in ten or less chemical series. This stage culminates into one of the endpoints for translational research, probe discovery where a molecule which is relatively novel, has sub-uM activity and reasonable target selectivity could serve as a chemical tool to dissect a biological mechanism of a target. Some of the chemical series identified at the probe discovery stage can serve as starting points for further medicinal chemistry and metabolism optimizations for the long-term goal directed towards development of drug candidates. Drug discovery is a long term endpoint of translational research which involves diverse skill sets and stringent characterization of chemical leads before the molecules can be progressed to the steps leading to a marketable drug. The probe discovery aspect of translational research is more prevalent on academic campuses and is compatible with the cost and time considerations for the academic faculty.

KU-HTS SERVICES IN GRANT APPLICATION SUPPORT

In addition to compound screening services, the HTS lab at KU also actively provides pre-grant mentoring. HTS helps define what preliminary data is required based on the type of drug/probe discovery grant submission announcements (exploratory/assay development/screening grants), advice on opting for core facilities on a fee-for-service basis and provide input on how to reach the goals of a grant, for example, on how to develop an HTS-ready assay. The HTS also provides work flow charts and assists the academic project investigators hone in on HTS and secondary screen work flows required for handling of HTS hits, chemoinformatics and medicinal chemistry aspects of advancing the project. The HTS laboratory also helps generate preliminary pilot data for grant applications on a fee-for-

service basis. This may include developing and optimizing an assay to a miniaturized, automated, HTS-ready format, then providing sufficient pilot screening data to the application. As proof of principle, the HTS lab screens upto 7000 compounds from validation library to acquire HTS screening parameters. The pilot data may also identify several compound hits, which could be tested further in secondary assays which are distinct from the primary screening assay. Since validation pilot screening is often done using compounds with known mechanisms of action, the type of screening hits can immediately validate the assay and target.

KU-HTS CAPABILITIES: ASSAY FORMATS

The KU-HTS team has extensive background in assay formats compatible with high throughput and high content screening with siRNAs and compounds. The KU-HTS laboratory routinely performs both biochemical and cell-based assays in homogeneous as well as heterogeneous formats [3]. A vast majority of assays are homogeneous and involve one or two steps based on a wide variety of assay platforms: absorbance, fluorescence (fluorescence intensity, FRET, fluorescence polarization and time-resolved FRET), luminescence, and AlphaScreen. The heterogeneous formats include label-free, ELISA assays, flow cytometry assays and high content phenotypic assays. The biochemical screens include the enzyme assays (direct/indirect coupled assays), protein-protein, protein-peptide, protein-nucleic acid (RNA/DNA) interaction assays. Cell-based screens include cell growth and viability screens, reporter modulation assays, apoptosis assays, ion channel assays, phenotypic screens (viability, nuclear-cytoplasmic translocation, expression of cancer cell markers, etc.).

KU-HTS RESOURCES

Research at the KU-HTS is enabled by its collection of cutting edge instrumentation for compound handling, liquid dispensing platforms and plate readers. The HTS facility houses five robotic liquid handling robotic platforms and ten multimodal detection systems, six bulk dispensers, two label-free technological platforms and confocal automated microscopy for high content screening. The KU-HTS facility also has an expanding collection of compounds, plant extracts, siRNA library and, an automated compound storage and retrieval system, and activity base for storage of information and data management (www.hts.ku.edu).

COMPOUND LIBRARY COLLECTION

The compound library at the KU HTS core includes over 200,000 diverse compounds, 1,000 natural products, a large number of legacy compounds synthesized in-house by the medicinal chemistry faculty members and a small interfering RNA (siRNA) library of 2,157 siRNA duplexes. The small molecule scaffolds were carefully selected for their adherence to Lipinski's 'Rule of Five' and their drug like characteristics from several of the commercial vendors to maximize successful identification of active compounds for use in screening projects. The HTS core benefited from the vast drug discovery experience of professors in the Medicinal Chemistry department at the University of Kansas in selecting these compounds. This library of compounds is optimized for structural diversity (30,000 unique

scaffolds) with minimal overlap across libraries and drug-like properties. The compounds were drawn from ChemDiv, ChemBridge, Prestwick, Microsource Spectrum and Life Chemicals. The Center for Chemical Methodology and Library Development (CMLD) directed by Dr. Jeffery Aube has enabled use of their 5000 novel compounds for screening against incoming targets. The HTS laboratory also has access to 104,000 compounds formatted into orthogonal compressed libraries by Dr. Melvin Reichman from The Lankenau Institute for Medical Research (LIMR) Chemical Genomics Center (LCGC). The HTS laboratory has also collected a set of 2320 FDA approved compounds from various sources including compounds from the NIH clinical collection. The FDA collection of compounds have been clinically tested, are highly drug-like and are associated with safety profiles, providing invaluable starting points for drug combination studies, compound optimization and application to new disease targets [4]. The FDA approved library is extensively used in the KU-HTS laboratory for screening assays addressing intractable adult and childhood cancers with the goal of identifying approved drugs or combinations thereof for fast track drug repurposing projects for treatment of new indications. The KU-HTS library also houses A collection of 15,000 unique information rich molecules synthesized by the world-class KU medicinal chemist Joseph Burckhalter, an inductee in the National Inventors Hall of Fame (<http://www.acsmedchem.org/burckhalter.html>). The collection is currently being cataloged by the Medicinal Chemistry laboratory under the directorship of Dr. Jeffery Aube.

KU-HTS INSTRUMENTATION

The instrumentation for the KU-HTS laboratory falls under three categories: (1) Instrumentation for compound storage and processing; (2) Robotic liquid dispensing platforms and bulk reagent dispensers (3) Multimodal plate readers (Table 1). The HTS laboratory is also equipped with standard routine laboratory instrumentation and has automated plate delidders, sealers, electronic multichannel pipettes, western blot apparatus, RT-PCR systems. The laboratory is also equipped with cell culture facility, microscopes, and other instrumentation necessary for high throughput and high content screening.

Instrumentation for Compound Storage and Processing

The Nexus Labstore (Nexus Biosystems), a 590 cubic foot compound storage system, facilitates storage and retrieval of chemical compounds in a nitrogen purged environment at -20°C and 10% oxygen. The compound integrity is maintained by pumping nitrogen into the system which displaces oxygen to reduce humidity (2%) and prevent hydration of DMSO samples. The Labstore is equipped with robotic systems for sample management, imaging devices, a large -20°C freezer storage area, a heated 30°C storage area, computer controllers, user interfaces, external condensers, and sensors and alarms to alert and regulate safe temperatures and oxygen levels. The high resolution camera captures and reads entire racks of 384 individual 2-D barcoded tubes. The labstore is modular and the system software defragments available space to maximize storage capacity of various combinations of 384-well plates, tubes, and dram vials. The compounds are thawed under highly controlled environmental conditions which minimizes moisture uptake and compound dissolution. The DMSO-solvated compound libraries at the KU-HTS facility are stored in 384 well polypropylene plates as well as Labcyte Echo COC plates and are thawed at 37°C . After the

freeze-thaw, to ensure full dissolution of all compounds retrieved from Nexus Labstore, the Covaris L8 system based on adaptive focused acoustics (AFA) is used to mix and dissolve compounds in DMSO in their original 384-well storage plates. The high-powered acoustic waves aid in dissolution of compounds that may have come out of DMSO. The compound plates are sealed using Agilent plate sealer which flushes the plates with nitrogen prior to sealing of compound plates.

Robotic Liquid Dispensing Platforms and Bulk Reagent Dispensers

The liquid dispensing platforms facilitate assay execution by transferring varying volumes of liquids into the assay plates. Several of the automated liquid handling instruments are coupled to plate loading devices and robotic arms to load microwell plates. The volumes of reagents required for transfer dictates the choice of the liquid handling system. Nanoliters of the compound library are transferred using the Labcyte Echo 550, which utilizes acoustic technology for transferring compounds in precise 2.5 nanoliter increments into the destination assay plate placed inverted, directly above the source plate. The Echo mediated transfer minimizes waste of solvated compound stocks for an assay. The touch-less acoustic transfer eliminates the need for robotic tips, eliminates compound carryover and also minimizes environmental plastic waste. The majority of compound library screens performed at KU HTS rely on solvated compound dispensing by the Labcyte ECHO 550, an acoustic liquid handler. The ECHO allows transfer of any source well to any destination well and can dispense to any plate format, including 1536 and 3456-well plate formats. The Echo cherry-picking module allows for cherry-picking compounds directly from mother plates without a need for intermediate plates.

Larger microliter volumes are dispensed with the conventional bulk dispensing cartridges, disposable tips, and stainless steel 384-head syringes. The KU-HTS lab has BioMek FX and PlateMate 2X3 (ThermoScientific Matrix) with interchangeable 96- and 384 well heads. These robotic platforms utilize robotic tips which add to the cost of consumables in the assay. These liquid dispensing systems are largely employed for plating new compound libraries into daughter plates and are generally avoided for use in routine screening assays. The Platemate Plus (ThermoScientific Matrix) with a 384 well head of stainless steel positive displacement reusable tips is equipped with two peristaltic pumps support active reagent replenishment and pipette tip washing. The TTP Mosquito is used in some assays to perform serial dilutions, which are performed at extremely short periods of time. The Thermo Scientific Matrix WellMates and multidrop dispensers are used for bulk transfer of assay reagents (1 μ l to 60 μ l).

Multimodal Plate Readers

The KU HTS core executes screening campaigns using both biochemical and cell based assays, requiring label-based signal detection platforms. The laboratory has at least nine plate readers which are multi-modal and can read 96/384 well plates for absorbance, fluorescence, fluorescence polarization, TR-FRET, luminescence, AlphaScreen assay formats. The direct binding of proteins to peptides or of proteins and cells to small molecule compounds can be read directly using the Enspire label-free module. The Roche

Excelligence system is impedance based platform that is used to study effects of compound on growth rates of various cell-lines.

The plate readers include a filter based reader (Perkin Elmer Envision) and three monochromator based plate readers namely Tecan Safire2, BioTek Synergy H1 and Perkin Elmer Enspire for measuring absorbance, fluorescence (FI, FP, TR-FRET), luminescence, and AlphaScreen assays. The HTS lab also has two Spectramax 340PC384 Absorbance and Spectramax Gemini Fluorescence (Molecular Devices) microplate readers for absorbance and fluorescence measurements. All plate readers are used for reading kinetic as well as end point biochemical and cell based assay types. A Hamamatsu FDSS 7000 functional drug discovery system, an imaging-based plate reader with fluorescence (including FRET) and luminescence capabilities for use in ion channel and G-protein coupled receptors (GPCRs) research. The instrument is equipped with high resolution cameras that allow data capture for reading extremely fast kinetics assays (for example peptidyl prolyl cis-trans isomerase assays), as well as for GPCR assays, calcium immobilization, membrane potential, ion influx, and Aequorin and luciferase assays in mammalian cells. The system is equipped with two robotic arms that help dispensing robots that enable rapid addition of substrates/agonists/antagonists and simultaneous endpoint/kinetic capture of luminescence or fluorescence signals in all wells of a 384 well plate.

The Roche Lightcycler 480 in KU-HTSL is used for quantitative RT-PCR based assays for screening compounds that modulate expression levels of targets of interest. The compound treated cells in 384 well are lysed directly in wells and the cell lysates are used to prepare cDNA. A low volume qRT-PCR plate is used to amplify target cDNAs using multiplexed primer sets or *via* SYBR Green detection of unlabeled individual primer sets.

The high content BD Pathway 855 platform for automated microscopy and analysis is used extensively for phenotypic screens and provides high resolution plate reading at a subcellular level. The reader detects fluorescence based signals allowing quantification of biomarkers and activity at single cell level, and requires use of fluorophore labeled antibodies, peptides or substrates, and fluorescent proteins. While the high content screening is used for primary screening, the HCS assays can also be designed to obtain detailed mechanistic information of primary screen actives using secondary assays. The BD pathway is used for several types of cell based imaging based assays which include viability, nuclear-cytoplasmic translocation, calcium flux assays, GFP reporter expressing cells etc. The HTS laboratory has also acquired the ImageXpress Micro (Molecular Dynamics) for rapid automated cellular imaging in fluorescent, transmitted light, and phase-contrast modes for fixed- or live-cell phenotypic screens. ImageXpress software also allows rapid processing of information captured from images in the phenotypic assays.

The KU-HTS facility is also equipped with plate readers that use changes in spectral and other biophysical properties to measure direct binding of small molecules and peptides to the target of interest. The direct binding measurements facilitated by label free technology allows screening for modulators of orphan targets for which very limited functional information is available in literature but which are known to be up/down regulated in clinical settings. The Perkin Elmer Enspire is equipped with a label free module that allows 384-well

plate screening of binding interactions between immobilized proteins /peptides with each other or with small molecules. The label free module based on Corning Epic technology also allows measurement of binding interactions between small molecules and cellular monolayer in 384-well format.

CELL CULTURE FACILITY

The KU HTS laboratory has five biosafety level 2 cabinets which are used predominantly for culture of mammalian cell lines and primary cells. The engineered as well as the primary cell cultures transferred from academic client labs are first processed and maintained in the quarantine hood and quarantine incubator, which are housed in a room separate from the main cell culture facility. The cell cultures are tested for presence of mycoplasma first before these are transferred to regular biosafety cabinets and used for screening operations in the main cell culture facility. In general majority of the assays are performed on cell lines purchased from ATCC to confirm validity, prevent contamination and have a better handle on passage numbers. Also one of the bulk Well Mate dispensers is kept in a safety cabinet for sterile dispensing of cells.

DATABASE MANAGEMENT

The information on compounds, their structures and the biological data from all assays were previously stored in the locally developed laboratory information management system (LIMS) system, K-Screen, for high throughput screening database management, data mining, and visualization. K-Screen was developed based on the standard open source Linux/Apache/MySQL/PHP platform, utilizing a number of open source software programs and supports a diverse array of plate readers and has an automated statistical analysis routine [5]. Recently the KU-HTS acquired Activity Base (IDBS), which is an industry standard for high volume data processing and management. The raw data generated from various plate readers is imported into Activity Base and is processed based on data analysis specifications specified by the designer. All required analysis such as z' factors, medians of positive/negative controls, coefficient of variation, are performed within the IDBS software. The data are used to define screen actives and reports are generated through SAR view and SARgen. The promiscuity of hits is assessed *via* comparison with previous data sets and also by comparison to the PubChem datasets. Large datasets of captured images from high content automated fluorescence microscopes in cell-based screening campaigns are stored and processed utilizing large storage space provided by the KU Information and Telecommunication Technology Center (ITTC) supercomputer clusters, thus providing an efficient workflow for data storage and management.

PROJECT MANAGEMENT

The HTS projects, as with the late stage drug discovery projects, are managed through project teams led by project managers with pharma and CRO experience. While the PI provides expertise in the biology of his/her target, a project manager documents minutes, action items, go/no go decision points, provides grant support documents, help integrate

with IP management activities. The projects managers also aid in bring in necessary and required expertise in different stages of drug discovery.

RATE STRUCTURE

A three-tier rate structure for the HTS laboratory was developed and approved in consultation with the Service Center Rate Committee. The committee reviews the rate every 2-3 years in consultation with the HTS director to incorporate changes with changing economic and financial landscape. The lowest rate structure is applied to services performed for clients who are KU-Lawrence employees with an increase in rates applied to personnel labor, certain resources and overheads to the projects for external academia and non-profit organizations. A market rate which is greater than the base internal rate is used for services performed for industry/for-profit organizations, within or out-of state. The billable hours depend on the status of incoming project. An HTS ready assay is less expensive than one requiring assay development. A validation screen costs less than a primary large compound screen including hit conformation, assay type (complexities increase pricing), biochemical versus cell-based reporter, viability, cell based imaging or RT-PCR, batch vs kinetic-mode.

SUMMARY

The KU-HTSL in addition to the screening services provides guidance and support for target validation, assay development, purity check, structure confirmation, secondary specificity and counter screens, medicinal chemistry support (hit explosion, structure-activity assessment, chemoinformatics) and intellectual property assessment. The HTS laboratory also maintains momentum in the projects by participating in hit to lead development as well as in the late stage drug discovery and development. The KU-HTS laboratory provides opportunities for the new probe/lead discovery to institutional investigators, and also helps train next generation of drug discovery scientists.

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Biography

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Fig. (1).

Collaborative drug discovery at the University of Kansas. The projects from academic and industry clients can enter the drug discovery work flow at the level of HTS core, medicinal chemistry synthesis, Biocenter (ADME studies) or previously optimized compounds from clients can be advanced through preclinical and clinical studies in collaboration with the IAMI.

Fig. (2).

High throughput screening work flow in translational research. An assay developed to modulate a druggable target identified by basic research is optimized and adapted for screening large compound libraries. The screen actives are modified by medicinal chemistry and several lead series are developed. The lead molecules with sub-uM activity and reasonable selectivity are utilized as chemical probes to study a mechanism of action of the target or to dissect a pathway of interest. The leads can also serve as starting points for drug discovery which requires intense medicinal chemistry and ADME optimizations.

Table 1.**KU-HTSL Equipment**

Function	Equipment	Manufacturer
Compound Storage & Management	Labstore US-200	Nexus
	L8 microplate mixing system	Covaris
	ALPS 300 Automated Sealer	Thermo
	ALPS 50 Plate Sealer	Thermo
	Xpeel	Nexus
	Plate deilidder	Let's Go Robotics
Liquid Handlers	ECHO 550	Labcyte
	PlateMate 2x3	Thermo
	PlateMate Plus	Thermo
	Biomek FX	Beckman Coulter
	Mosquito	TTP Labtech
Plate Readers	Envision with stackers	Perkin Elmer
	Enspire	Perkin Elmer
	BioTek Synergy H1	BioTeck
	SpectraMax 340PC 384	Molecular Devices
	SpectraMax Gemini XS	Molecular Devices
	SpectraMax Plus 384	Molecular Devices
	Victor2 Multilabel reader	Perkin Elmer
	Glomax reader	Promega
	FDSS7000	Hamamatsu
	Lightcycler 480	Roche
	BD Pathway 855 Imager	Becton, Dickinson
	xCELLigence label free	Roche
	MicroXpress	Molecular Dynamics
Bulk Liquid Handlers	WellMates (2)	Thermo
	ELx450 CWS Plate Washers (2)	BioTeck
	Multidrops (6)	Thermo
Miscellaneous	EasyCyte Plus system	Guava
	FPLC for Protein Purification	GE Healthcare
	Iems Microplate Shaker Incubator	Thermo
	KinedX plate loader with stackers	Peak Robotics
	Multichannel Verification System	Artel
	RapidStaks (2)	Thermo
	Titramax 1000 Plate Shaker	Heidolph
	Twister II plate loaders with stacks	Zymark