The Chemical Genomics Core Facility (CGCF) facilitates the identification of chemical tools to study pathological pathways and the discovery of lead compounds for the development of novel therapeutics. The CGCF strives to provide excellence and innovation in high throughput screening and medicinal chemistry. The first shared resource facility of its kind to be established in an academic setting in India, the CGCF is providing screening and medicinal chemistry expertise and service to Indian University Medlen and Biren Simon Cancer Center (IUSCC) and other cancer research groups in India and beyond. The CGCF provides IUSCC investigators with cutting edge technologies and cost-effective access to large-scale, high throughput screening, medicinal chemistry, drug-like small molecules, IC50 confirmation and resupply, and to help lead optimization chemistry to furnish research tools to identify new experimental small molecule therapeutics.

This shared resource has been designated to be highly flexible in order to meet the needs of multiple users employing a range of different types of assays. The facility staff works closely with each user throughout all stages of the drug discovery process, providing an opportunity for cancer center investigators to gain experience and training in high throughput screening and medicinal chemistry at the facility. The CGCF became fully operational in July 2006 and has been a shared resource for IUSCC since 2007. The number of investigators utilizing the CGCF increases every year, from 10 in FY 2007 to 48 in FY 2012, a 480% increase in user base. The majority of CGCF users are Cancer Center investigators. Of the 48 CGCF users in FY 2013, 28 of them are peer-review funded (58%) IUSCC and 20 of them (42%) are non-IUSCC members. As a shared resource, the CGCF has assisted Cancer Center members in their research by providing quality services to enable numerous high throughput screening and medicinal chemistry projects aimed at identifying small molecule probes and potentially new therapeutics against novel cancer targets.

New Science – Examples of the projects supported by the CGCF

Small Molecule Inhibitors Target the Translational GmRNA shuttle and Fibroblast Growth Factor 23

PI: Jia-Tong Zhang, PhD (EDP Program)

Translational growth factors (TGF) mediate protein crosslinking through generation of a glycine/glycine isopeptide bond and promotes cell adhesion interaction with interaction (TGIF) and integrins. Cell adhesion to the pericellular matrix regulated by TGFs facilitate ovarian cancer dissemination. Therefore, developing a small molecule that inhibits cell adhesion and metastasis in the Core has helped Dr. Malte’s group developing a novel high throughput screening (HTS) assay based on AlphaScreen technology to measure the formation of a complex between His-TGF and a biotinylated FN fragment. Among the hits, several compounds were selected and evaluated at the CGCF to discover small molecules that inhibit this protein-protein interaction. Several hits were identified and validated in ELISA and other cell based assays measuring cell adhesion, migration, invasion, and proliferation. The top candidate (TG30) was found to inhibit interaction with integrins and partly interfere with cell invasion (sees figures below) and could be further developed as a potential inhibitor for ovarian cancer dissemination. Further lead optimization is planned at the core facility.

Development of Selective Inhibitors for Human Aldoldehydes for Targeting Cysteine Protease (Cathepsin C)

PI: Thomas D. Hurley, PhD (EDP Program)

Aldoldehydes are known to regulate normal and pathological cellular processes, including cancer-related pathways. The CGCF has helped Dr. Hurley’s group develop a novel high throughput screening assay at the CGCF using a kinetic assay measuring the enzymatic activity of the aldolase C domain (ALDH). The assay is highly predictive for Cathepsin C (CatC) inhibition and its derivatives can become novel agents that increase chemosensitivity towards Cathepsin C inhibitors.

Screening for Selective Retinolactones Cell Cytoskeleton

PI: Tiemo Cordes, PhD (EDP Program)

Retinolactones is a pediatric ocular cancer, responsible for 1% of childhood cancer death and 5% of childhood blindness. Despite this disease burden, there has been limited research that has led to successful treatments in development of novel therapeutics specific for this blinding childhood cancer. Dr. Conner and his collaborators believe that the first step toward targeted therapies for retinoblastoma is to find small molecules that have an effect on retinoblastoma cell lines with varied genetic profiles and provide a mechanism of action.

Hydroxy Carbonyl Based Inhibitors for Oncogenic Src Homology-2 Domain-Containing Protein Tyrosine Phosphatase-2 (SHP2)

PI: Jia-Ting Zhang, PhD (EDP Program)

The Src homology 2 domain-containing protein tyrosine phosphatases (SHP2) play a role in several signaling transduction downstream of growth factor and cytokine receptors. SHP2 mutations and overexpression are implicated in cancer and other diseases. Potent and selective SHP2 inhibitors may provide new prevention for Noonan Syndrome, leukemia, and cancers. Dr. Z.-T. Zhang’s lab has previously developed a SHP2 inhibitor, II-B08, which has efficacious cellular activity and favorable in vivo anti-leukemia ability; but the potency of this compound is at a low level, which is not adequate for preclinical evaluation. Optimization of II-B08 was performed at the Medicinal Chemistry Core at the CGCF to improve the potency and selectivity. Four focused libraries were designed and synthesized to identify a new SHP2 inhibitor.

Small molecule compounds targeting DNA binding domain of STAT3 for inhibition of tumor growth and metastasis

PI: Jia-Tong Zhang, PhD (EDP Program)

STAT3 is constitutively activated in malignant tumors, and its activation is associated with high histological grade and advanced cancer stage. Thus, inhibiting STAT3 promises an attractive strategy for treatment of advanced tumors with metastatic potential. Dr. J.-T. Zhang’s lab has used a STAT3 reporter cell line for screening a DNA-binding site of STAT3 using an in-silico screening approach. However, the compound was found not to be appropriate for further studies because of low specificity for STAT3 and poor absorbance in mice.

To develop an effective and specific STAT3 inhibitor, the CGCF helps in designing and synthesizing small molecules of analogs of isoxazole-5-carboxaldehyde (A) that as a STAT3 inhibitor is more potent than the parental compound, H354. In addition, A18 can inhibit tumor growth in a xenograft model of human breast cancer cells and an orthotopic model of human breast cancer cells, and a small molecule (H354) is found to be a STAT3 binding domain is a lead compound for the development of anticancer therapeutics.

Facilities and Location

Medical Sciences Building
330 Cripps Drive
Medical Science Complex
IUSCC, MS 105

Personnel

Zhong-Yin Zhang, Ph.D. - Director
Lan Chen, Ph.D. - HTS Director
Vijay Ramamurthy - Manager
Andrea Guzman, Research Analyst

Key Instrumentation

- Freedom EVO Workstations (one using disposable pipette tips, the other for specific tip size and adhesion wash station (reducing the use of a 384- and 50-pin blocks)
- Multiprint 384 Liquid Dispensers (one with robotic stackers and the other placed in biosafety cabinets)
- Precise Minicomputer Sample Processor
- EnviroPlex MALDI Plate Reader (with AlphaScreen® and LANCE® (TRF) upgradable, built-in stackers)
- UTEK MALDI Plate Reader
- VICTOR Light Luminol Cuvette Counter (with dual injectors and stackers)
- Beckman Microplate Reader
- Vidae barcode printing and analyzing station
- PMP-3000 MALDI Plate Reader
- L2C00 Thermal Relaxation Calorimeter
- C18 (3 µm) analytical HPLC
- PEGylated synthetic and microwave reactor
- NMR

Utilization

Small molecule compounds targeting DNA binding domain of STAT3 for inhibition of tumor growth and metastasis

The CGCF has provided over 100 active compounds for high throughput screening (HTS) and a variety of published papers on the respective screening hit compounds.

Future Directions

The following goals reflect an important growth area that will ensure the CGCF continues to be a focal point for state-of-the-art capabilities in chemical biology and drug discovery.

1. Enhanced capability in chemo-informatics: we plan to acquire the SYBYL-X suite for generation of 3D structures and 2D structure-activity relationship models from which to design new lead compounds.

2. Enhanced capability in high throughput screening: we plan to acquire a miniaturized high throughput screen (HTS) system for drug discovery.

3. Enhanced capability in medicinal chemistry: we plan to acquire a high throughput SFC and to expand the medicinal chemistry program.

4. Enhanced capability in data analysis: we plan to acquire additional informatics software to aid in the analysis of HTS data.

5. Enhanced capability in compound handling: we plan to acquire an automated robotic system for compound handling.

6. Enhanced capability in storage: we plan to acquire an automated robotic system for cold storage.

7. Enhanced capability in cell-based assays: we plan to acquire an automated robotic system for cell-based assays.

The CGCF will continue to expand its capabilities to meet the needs of the investigators at IUSCC and beyond. The CGCF will continue to be a focal point for state-of-the-art capabilities in chemical biology and drug discovery.