CHEMICAL GENOMICS CORE FACILITY

MELVIN AND BREN SIMON CANCER CENTER
INDIANA UNIVERSITY

Core Director
Zhong-Yin Zhang, Ph.D.

OVERVIEW

The Chemical Genomics Core Facility (CGCF) is a shared facility of the IU Simon Cancer Center and IU School of Medicine. The mission of CGCF is to provide excellence and innovation in high throughput screening and medicinal chemistry. As the first core facility of its kind to be established in an academic setting in Indiana, we have a proven record of providing screening expertise and synthetic service to researchers across Indiana and beyond. This shared facility enables investigators to discover small molecule tools for basic research, therapeutic development and diagnostic applications. The CGCF has been designed to be highly flexible in order to meet the needs of multiple users employing a range of assays. Facility staff work closely with each investigator through all stages of the drug discovery process, providing an opportunity for students and fellows to gain experience and training in high throughput screening and medicinal chemistry at the facility.

Compound Libraries

- 220,000+ diverse small molecules
- 3,680 approved drugs and known bioactives
- 6,000 pure natural products and semi-synthetic natural products

HIGH THROUGHPUT SCREENING ⟷ **MEDICINAL CHEMISTRY**

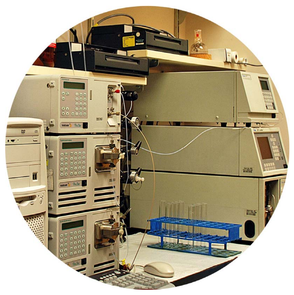
Medicinal Chemistry Capacity

- Targeted synthesis of small molecules and peptides at large scale for cellular and animal studies;
- Design focused library for lead optimization;
- Parallel synthesis of small library for SAR study

Contact for quote

Assay Detection Capability

- Absorbance
- Fluorescence Intensity
- Fluorescence Polarization
- Luminescence
- AlphaScreen /AlphaLISA
- Time-Resolved Fluorescence
- LANCE (HTRF)



Major Equipment of Chemistry

- Chemical hoods for organic synthesis
- LC-MS for small molecule characterization
- Preparative and analytical HPLC
- Flashing systems for large scale purification
- Microwave reactor
- NMR for chemical structure determination

Major Equipment for HTS

- Freedom EVO Workstation
- Multidrop Liquid Dispenser
- Plate Readers
- Isothermal Titration Calorimeter (ITC)

Website: www.chemicalgenomics.iu.edu

Personnel: Zhong-Yin Zhang, (Ph.D., Director), Lan Chen (Ph.D., Director of HTS), Sheng Zhang (Ph.D., Chemist), Lily Wu (MS., Facility Manager), Andrea Gunawan (MS., Research Analyst)

EXAMPLES OF SCREENING PROJECTS

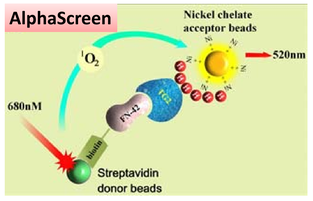
Small Molecule Inhibitors Target the Tissue Transglutaminase and Fibronectin Interaction

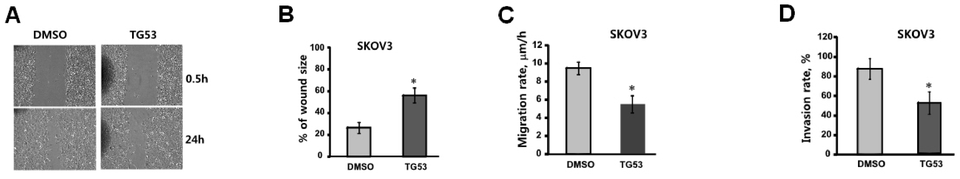
PI: Daniela Matei, MD (IUSM, Dept. Medicine, IUSCC EDT Program)

Tissue transglutaminase (TG2) mediates protein crosslinking through generation of e-(g-glutamyl)lysine isopeptide bonds and promotes cell adhesion through interaction with fibronectin (FN) and integrins. Cell adhesion to the peritoneal matrix is regulated by TG2 facilitates ovarian cancer dissemination. Therefore, disruption of the TG2-FN complex by small molecules may inhibit cell adhesion and metastasis.

The Core has helped Dr. Matei's group developing a novel high throughput screening (HTS) assay based on AlphaScreen™ technology to measure the formation of a complex between His-TG2 and a biotinylated FN fragment.

A HTS of 10,000 compounds was carried out and one of the hits (TG53) was found to inhibit ovarian cancer cell adhesion to FN, cell migration and invasion.





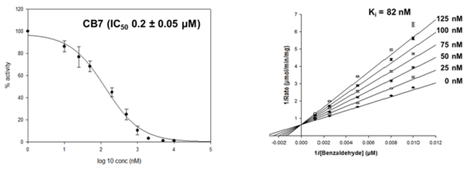
Yakubov, B., Chen, L., Belkin, A. M., Chelladurai, B., Zhang, S., Zhang, Z.-Y., and Matei, D., (2014) *PLOS ONE* 9, e89285.

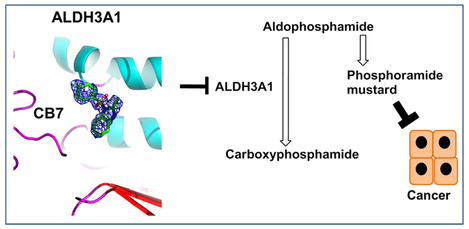
Selective ALDH3A1 inhibition by benzimidazole analogs increase mafosfamide sensitivity in cancer cells

PI: Thomas D. Hurley, PhD (IUSM, Dept. Biochem. Mol. Biol., IUSCC EDT Program)

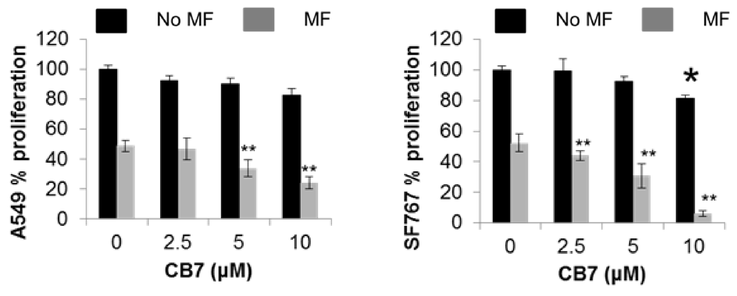
Aldehyde dehydrogenase 3A1 (ALDH3A1) plays an important role in many cellular oxidative processes, including cancer chemo-resistance by metabolizing activated forms of oxazaphosphorine drugs such as cyclophosphamide (CP) and its analogues such as mafosfamide (MF), ifosfamide (IFM), 4-hydroperoxy- cyclophosphamide (4-HPCP). selective inhibition of ALDH3A1 could increase chemosensitivity toward cyclophosphamide in ALDH3A1 expressing tumors.

A HTS of 43,000 compounds was performed at our facility and one of the hit compounds (CB7) was found to bind at the active site of ALDH3A1 and inhibit ALDH3A1 in a competitive mode, and causes the cancer cells more sensitive to the MF treatment.





Dose response of **CB7** for mafosfamide sensitization on lung cancer and brain cancer cells expressing ALDH3A1



Parajuli, B., Fishel, M. L., and Hurley, T. D., (2014). *J. Med. Chem., 57*, 449-461.