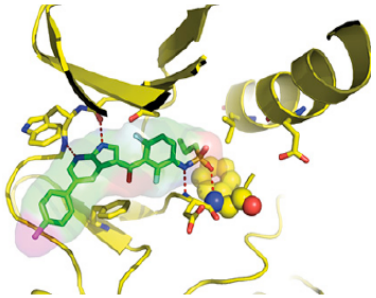
The MUSC Drug Discovery Core

Drug Discovery Building
Room DD420, MSC 139
Charleston, SC 29525

MUSC



Drug Discovery Core

Core Director: Patrick M. Woster, Ph.D. Professor and SmartState® Endowed Chair in Drug Discovery

Assistant Director: Yuri K. Peterson, Ph.D. Research Associate Professor

The MUSC Drug Discovery Core (MUSC DDC) is a specialized resource providing tools, facilities, and expertise for early drug discovery and chemical biology. We employ virtual and physical screening, medicinal chemistry, chemical synthesis and chemoinformatics to study of the effects and properties of small molecules and proteins. As such, we are the only drug discovery resource in South Carolina with the ability to identify high-affinity ligands for a variety of biological targets.

Primary Goals of the MUSC DDC

The primary goals of the MUSC DDC are:

- to facilitate the discovery of new therapeutic agents and chemical probes with the focused vision of creating new chemical entities and optimizing their structures.

- to provide chemical and medicinal chemistry support to synthesize hits identified by physical or virtual screening, and to optimize these hits through structure-based generation of analogues.

-to assist investigators with the creation of new intellectual property, and to collaborate with the MUSC Foundation for Research and Development to commercialize potential therapeutics.

- to keep MUSC abreast of and competitive in the areas of academic drug discovery, medicinal chemistry, target engagement, and cheminformatics.

Facilities

The MUSC Drug Discovery Core screening facility occupies approximately 900 sq. ft. of laboratory space located in Room 420 of the Drug Discovery Building at the Medical University of South Carolina. This space is adequate to house the entire screening operation (sample prep, plate prep, bar-coding, liquid handling, plate reader), compound library, and 2 Waters LC/MS instruments. These instruments are available for individual use for a nominal fee. The computational chemistry and bioinformatics center is housed in 90 sq. ft. of laboratory space assigned to Dr. Woster (DD-422A). All data and structural information for the SC^3 is stored in a secure compound database (the MUSC Vault) which is accessible to DDC staff and individual PI's. All proprietary data are stored securely and are unavailable outside the MUSC firewall. The MUSC DDC is also well equipped for chemical synthesis, and can generate libraries of analogues based on optimization of screening hits and lead compounds.

Expertise

Patrick M. Woster is Professor and Chair of the Department of Drug Discovery and Biomedical Sciences at MUSC, and also serves as MUSC SmartState® Endowed Chair in Drug Discovery. He has more than 30 years of experience in drug discovery, including virtual and physical screening, compound synthesis, hit-to-lead studies, lead optimization and bioassay procedures. He assumed directorship of the MUSC NMR Core in July of 2018, and will oversee all operations in the MUSC Drug Discovery Core.

Yuri Peterson is Research Associate Professor of Drug Discovery and Biomedical Sciences. Dr. Peterson is well versed in computational chemistry, assay development and bioinformatics, and manages the CDD Vault secure compound data repository.

Bioassay Procedures

Biological assay procedures will typically be provided by faculty researchers and adapted for high-throughput screening in 96- or 384-well format. The MUSC DDC closely collaborates with faculty researchers to automate assays for specific targets of interest.

Services

Tier 1 ($500.00):

Virtual (computational)-based screen of SC^3, assisted deconvolution of data.

Tier 2a ($650):

Virtual (computational)-based screen of SC^3, assisted deconvolution of data, preparation of investigator-derived bioassay (96-well format), physical screen of up to 25 compounds, consultation concerning proposed synthesis and hit-to-lead. Synthetic procedures would be priced separately based on cost of starting materials, number of synthetic steps, etc.

Tier 2b ($850):

Virtual (computational)-based screen of SC^3, assisted deconvolution of data, preparation of investigator-derived bioassay (96-well format), physical screen of up to 100 compounds, IC_{50} determination for top 3 compounds, consultation concerning proposed synthesis and limited derivatization. Synthetic procedures would be priced separately based on cost of starting materials, number of synthetic steps, etc.

Tier 3a ($2,250):

Initial consultation and assay development, preparation of investigator-derived bioassay (96-well format), physical screen of the 1,000-member screening set, assisted deconvolution of data, IC_{50} determination for top 10 compounds, similarity search of entire SC^3 for structural analogues, validation screen for 75 compounds from screen and/or similarity search, preliminary pharmacophore determination, consultation concerning proposed synthesis and limited derivatization. Synthetic procedures would be priced separately based on cost of starting materials, number of synthetic steps, etc.

Tier 3b ($6,000):

Initial consultation and preparation of assay for high-throughput screening, (96-well format), physical screen of the 10,000-member screening set, assisted deconvolution of data, IC_{50} determination for top 5 compounds, similarity search of entire SC^3 for structural analogues, validation screen for 50 compounds from screen and/or similarity search, preliminary pharmacophore determination, consultation concerning proposed synthesis and limited derivatization. Synthetic procedures would be priced separately based on cost of starting materials, number of synthetic steps, etc.

Compound Library

The MUSC DDC houses the South Carolina Compound Collection (SC^3), comprised of over 150,000 fully annotated, drug-like molecules collected from industry and academic donations, or produced in-house (see above). 100,000 of these molecules are proprietary. Two representative screening sets of 1,000 or 10,000 compounds selected through cheminformatic analysis from the SC^3 are available to MUSC faculty.

The 100,000 compounds in the MUSC SC^3 have been donated to MUSC under an existing contract that requires the Core to consult with Aeterna-Zentaris concerning any findings in specific therapeutic areas under an existing confidentiality agreement. In these cases, A-Z may choose to pursue the technology after licensing from MUSC, or to release the IP to the university.

The MUSC DDC also conducts virtual screens for targets with high-resolution X-ray structures, or can develop homology models for use in virtual screening where appropriate. For virtual or physical hits, we conduct a similarity search to identify additional congeners form the SC^3 for evaluation. Similarity searches may also utilize search engines for multiple compound databases (ChemSpider, ChemBridge, Maybridge and PubChem). For each search, compounds will be selected based on a Tanimoto coefficient[2] $\geq$ 90%. From these results, we select 30-40 congeners of each parent, and these compounds will be evaluated in vitro.

We use the tools and expertise of the Core to deconvolute screening results to create structure activity relationship (SAR) compound sets. Available tools include similarity-, fragment-, QSAR-, pharmacophore- and molecular docking-based searching, as well as physical property prediction (solubility, drug metabolism, pharmacokinetic parameters, and toxicity).

Synthesis and Optimization Capabilities

The MUSC DDC will design a synthetic pathway to produce hit compounds and a limited number of derivatives in high yield, and with sufficient flexibility to introduce chemical diversity. As analogues are produced and evaluated, data from biological studies are used to design more effective analogues, often guided by structure-based design. Our two-fold goal is to maximize efficacy and calculated pharmacokinetic parameters, and to generate new chemical entities (NCEs) that constitute new intellectual property. Thus, faculty and other clients are provided with potential clinical candidates that can be patented and commercialized.