



The MUSC Drug Discovery Core



Patrick M. Woster, Ph.D. SmartState® Endowed Chair in Drug Discovery

Yuri Peterson, Ph.D. Research Associate Professor







History of the MUSC Drug Discovery

-Center created by SmartState[®] Endowed Chairs Charles Smith and John Lemasters in 2008 as the SmartState[®] Center for Cancer Drug Discovery. -A facility was created to perform high-throughput screening of commercial compound libraries.

-Patrick M. Woster hired as SmartState[®] Endowed Chair in Drug Discovery in 2011 to provide chemical synthesis and medicinal chemistry support for the Center.

-Yuri Peterson oversaw the transfer of a 100,000 compound proprietary library to the Center from the German pharma company Aeterna Zentaris.

-Patrick Woster appointed Director of the SmartState® Center for Cancer Drug Discovery in 2017. -Reorganized the Center to provide high-throughput screening capabilities for MUSC faculty -Invested \$175,000 for the purchase of upgraded instrumentation.

-Center was approved as a MUSC Core facility in January of 2020.

-Idea Elan for DDC went live in August of 2020.





Primary Goals of the MUSC Drug Discovery Core (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.



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MUSC Drug Discovery Core

Administrative and Technical Structure

Core Director	Patrick M. Woster, Ph.D., Professor and SmartState® Endowed Chair in Drug Discovery
Associate Director	Yuri K. Peterson, Ph.D., Research Associate Professor
Computational Chemistry Artificial Intelligence	Pieter Burger, Ph.D. Research Assistant Professor
Chemical Synthesis	lvett Piña Research Scientist II

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 SC³ 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. All synthetic operations are housed in DD 421-422.





Instrumentation

Instrument Name	Short Name	Instrument Location
Search here X	Search here X	Search here X
Molecular Devices SpectraMax iD3 Plate Reader	Molecular Devices SpectraMax iD3 Plate Reader	DD 420
Eppendorf epMotion 5075 high-throughput liquid handler	Eppendorf epMotion 5075 high-throughput liquid handler	DD 420
Waters Acquity H-series UPLC	Waters Acquity H-series UPLC	DD 422
Waters UPLC/MS	Waters UPLC/MS	DD 420
NanoTemper Tycho N.6 protein analyzer	NanoTemper Tycho N.6 protein analyzer	DD 420
Biotage Selekt Chromatographic Purification System	Biotage Selekt Chromatographic Purification System	DD 422
Applied Biosystems QuantStudio 3 RT-qPCR	pPCR	DD421
Azure Biosystems c600 Imager	Blot & Gel Imager	DD421
Hermes WiScan Cell Imaging System	WiScan	DD421
Eppendorf epMotion 96-well pipettor	Eppendorf epMotion 96-well pipettor	DD 420







Screening Services

Tier 1 (\$500.00): Virtual (computational)-based screen of SC³, assisted deconvolution of data.

Tier 2a (\$650): Virtual (computational)-based screen of SC³, assisted deconvolution of data, preparation of investigatorderived 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 SC³, assisted deconvolution of data, preparation of investigatorderived 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 SC³ 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 SC³ 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.



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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.









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Ongoing Projects

Therapeutic Area	PI	Target	MTA_Status	Activity	Internal Status	Second Indication	Title	Library
Oraclass	Ogretman/	057	Target	Lifeture	Libbs load		Inhibitors of SET	
Oncology	Peterson	SEI	Validation	Hiatus	Hit to lead		Oncoprotein	SC3
Cardiomyopathy	Norris	CDK/Aurora/ MEK	l arget Validation	Active	Hit to lead			PKIS
Oncology	Maldonado	HDAC	Target Validation	Active	Preliminary screen completed, hit validation, biology		Small molecule modulators of mitochondrial membrane potential	SC3
Sickle_Cell Disease	Patrick Woster	KDM1A	Hit	Active	Lead development	Re- expression of tumor suppressor genes	Small molecule inhibitors of the histone demethylase KDM1A	commerical, SC3 & macrocycle
Periodontal Disease/ Inflammation	Patrick Woster	KDM4B	Hit	Active	Lead	Inflammation in cancer	Inhibitors of the histone demethylase KDM4B	commerical, SC3 & macrocycle
Oncology - Chemoprevention	Patrick Woster	Spermine oxidase	Hit	Active	Hits identified and now being evaluated			
Hepatic disease/ Hypercholesterolemia	Duncan	iPSC-FH	Lead	Active	Lead Optimization	Lipid Lowering	Small molecule inhibitors of ApoB secretion	SC3
Oncology	Ogretman/ Roth	SPNS2	Target Validation	Active	Screening			SC3
Oncology	Ogretman/ Mehrotra	PPARγ	Target Validation	Hiatus	Screening			Sc3
Oncology	O'Bryan	Ras	Target Validation	Active	Screening			SC3
Oncology	Dolloff	TXNDC5	Target Validation	Active	Screen completed - poor quality hits			SC3
Oncology	Gemmill	NRP2b	Lead identified, optimization in progress	Active	Synthesis of macrocycles in progress			ChemBridge macrocycle Library

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Project Advancement Overview

Project	Indication	Target Validation	Hit	Lead	Lead Optimization
SD-1: FH	Hyper– cholesterolemia				
PW-1/2: KDM	Sickle Cell				
RN-1: MEK	Cardiomyopathy				
BO-1: SET	Oncology				Completed
ND-2: TXNDC5	Oncology				Underway
JO-1: Ras	Oncology				Terminated
EM-1: VDAC	Oncology				

PW-1/2: KDM

Hit Stage Requirements						
Target Validation	i. In vitro assays	ii. EC50/IC50	iii. Purity > 75%	iv. Structure & Composition	3 rd Party Rights	Patent?
complete	complete	ln progress			Ν	Y

Title	Title	
PI	Pat Woster	ME ME<
Target	KDM1A, KDM4B	$\begin{array}{c c} \hline \\ \hline $
Lead Indication	Sickle cell	H-S1-G-R3-G-K5-GG-K8-GL-G-K12-GGA-K18-RHR-K20-VLRDN+QG+T-KPA+RRLAR-O-H4 P P P P H-S1-GRG-K5-QGG-K9-A-RAKAKSRSSR-AGLQFPVGRV-HRLLRKGNY-O-H2A 08
Other Indications	Cancer; Periodontal disease	H-PEPA-K5-SAPAP-K-K12-G-S14-KKAVTK-AQKKDSKKRK-RSRKESYSV-O-H2B-UB
Estimated Completion of Stage	February 2021	$\begin{array}{cccccccccccccccccccccccccccccccccccc$

Key Points

- Long standing leader in epigenetics
- Epigenetics is a hot target
- No suitable treatment available for sickle cell or periodontitis
 Some compounds are chemoprotective SMOX inhibitors

Sierra, J.C. et al., *Oncogene* **2020**, epub PMID 32350444 Holshouser et al., *MedChemComm* **2019**, *10*, 778–790 Kutz et al., *MedChemComm* **2014**, *5*, 1863–1870.

7(X = H)

MUDDC-PW-1 - Low risk on hepatotoxicity

KDM1A screen against SC3 top hits



Key Points

First in class inhibitors and indication



Bench Assays

Enzyme end-point and kinetics

Metabolic stains/ Viability

Luminescent

Fluorescent

ELISA

and more...





High-Content Microscopy

End point and time resolved live cell

Multi-label

Object detection and tracking

Protein trafficking

Rare event detection

and more...





Methodology for Virtual Screening Using QSAR



Comparison of 4 versus 5 pt Pharmacophore and Montelukast versus Nelfinavir







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ChemInformatic*s*

Small Molecule Libraries

Library	# compounds
NCI AOD9 approved oncology Set VIII	133
PKIS (published kinase inhibitor set)	367
LOPAC	1,280
National Tox Program (NTP)	1,353
Drug Bank	4,886
Chembridge Macrocycle	6,676
Asinex Macrocycle	31,500
Chembridge DiverSet	50,000
World Drug Index	53,000
MUSC SC ³	120,000
Enamine Macrocycle	150,000
ZINC-Clean Leads	1,442,716
ZINC–Everything	21,603,031
PubChem – Everything	98,000,000





The South Carolina Compound Collection (SC³)





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The South Carolina Compound Collection (SC³)



Physiochemical properties of the South Carolina Compound Collection. Similarity was calculated pairwise using MAACS keyed Tanimoto coefficient. Red lines show drug-likeness thresholds.





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