

# PREETPAL SINGH SIDHU

Department of Chemistry and Biochemistry

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## EDUCATION

- Bachelor of Pharmacy (2006) Rajiv Gandhi University of Health Science, India
- Doctor of Philosophy (2011) Dept. of Medicinal Chemistry, Virginia Commonwealth University  
Thesis title: *Designing Allosteric Inhibitors of Thrombin*

## CERTIFICATION

- Industry Diploma in Contract Research & Clinical Trial (2006)
- Certificate in Pharmaceutical Patents (2006)
- Six Sigma Green Belt (April, 2012)
- Six Sigma Project Management (May, 2012)

## AWARDS AND HONORS

- Gordon Research Seminar Scholarship
- Gordon Research Conference Travel Grant
- 2010 Graduate School Mentorship Award for recognition for mentorship in graduate school mentorship program at Virginia Commonwealth University
- AAiPS 2009 Scholar Award for recognition of excellence in pharmaceutical research

## WORK EXPERIENCE

### **University of Wisconsin, Milwaukee**

- *Post-Doctoral Associate* Aug 2012 – Present  
*No. of Hours/week - 40*

### **Department of Medicinal Chemistry, Virginia Commonwealth University, Richmond**

- *Post-Doctoral Fellow* Nov 2011 – July 2012  
*No. of Hours/week - 40*
- *Graduate Research Assistant* Aug 2011 – Nov 2011
- *Graduate Teaching Assistant* Aug 2008 – Aug 2011
- *Graduate Research Assistant* Jan 2008 – Jun 2008

## INVENTION DISCLOSURE

- *Vitamin D Receptor-Coregulators Inhibitors*. PS Sidhu, P Nandhikonda, A Arnold, R Singh; *PCT Int. Appl.* (2013) WO 2013032960 A2 20130307.
- *Sulfated Indole and Thiazole Based Inhibitors of FXIa*. UR Desai, PS Sidhu; VCU Invention (July, 2012).
- *Sulfated Benzofurans as Anticoagulants*. UR Desai, Q Zhou, PS Sidhu; VCU Invention (Nov, 2011).

## PUBLICATIONS

1. Allosteric Regulation of Dual Function of Thrombin. **Preetpal S Sidhu**. *Journal of Pharmacy and Pharmacology*. **Accepted 2013**

2. PT19c, Another Nonhypercalcemic Vitamin D<sub>2</sub> Derivative, Demonstrates Antitumor Efficacy in Epithelial Ovarian and Endometrial Cancer Models. Nada Kowar, Shannon Maclaughlan, Timothy C. Horan, Alper Uzun, Thilo S. Lange, Kyu K. Kim, Russell Hopson, Ajay P. Singh, **Preetpal S. Sidhu**, Kyle A. Glass, Sunil Shaw, James F. Padbury, Nicholi Vorsa, Leggy A. Arnold, Richard G. Moore, Laurent Brard, and Rakesh K. Singh. *Genes and Cancer*. In press (DOI: 10.1177/1947601913507575).
3. Designing Allosteric Regulators of Thrombin. Exosite 2 Features Multiple Sub-Sites That Can Be Targeted By Sulfated Small Molecules for Inducing Inhibition. **Preetpal S. Sidhu**, May A. Hamdy, Akul Y. Mehta, Qibing Zhou and Umesh R. Desai. *J. Med. Chem.* **2013**, 56, 5059-5070.
4. PPAR  $\delta$  agonist GW0742 interacts weakly with multiple nuclear receptors including the vitamin D receptor. Premchendar Nandhikonda, Adam Yasgar, Athena M. Baranowski, **Preetpal S. Sidhu**, Kelly Teske, Belaynesh Feleke, Megan M. McCallum, Nina Y. Yuan, Chinedum Kevin, Daniel D. Bikle, Steven D. Ayers, Paul Webb, Ganesh Bantukallu, Anton Simeonov, Ajit Jadhav, David Maloney, Leggy A. Arnold. *Biochemistry*, **2013**, 52, 4194-4203.
5. *On Scaffold Hopping: Challenges in the Discovery of Sulfated Small Molecules as Mimetics of Glycosaminoglycans.* **Preetpal S. Sidhu**, Philip D. Mosier, Qibing Zhou and Umesh Desai. *Bioorg. Med. Chem. Lett.* **2013**, 23 (1), 355–359.
6. *Identification of Novel Binding Site for Allosteric Regulation of Thrombin.* May A. Hamdy, **Preetpal S. Sidhu**, Aiye Liang, Philip D. Mosier, Qibing Zhou, David H. Farrell and Umesh R. Desai. *J. Med. Chem.*, **2012**, 55 (15), 6888–6897.
7. *Rational Design of Potent, Small, Synthetic Allosteric Inhibitors of Thrombin.* **Preetpal S. Sidhu**, Aiye Liang, Akul Y. Mehta, May A. Hamdy, Qibing Zhou and Umesh R. Desai. *J. Med. Chem.* **2011**, 54(15), 5522-5531.
8. *First Step in Synthetic, Allosteric, Direct Inhibitors of Thrombin and Factor Xa.* Jenson Verghese, Aiye Liang, **Preetpal S. Sidhu**, Qibing Zhou, Michael Hindle, and Umesh R. Desai. *Bioorg. Med. Chem. Letters*, **2009**, 19(15), 4126.
9. *An Efficient Synthesis of Highly Functionalized Benzofuran Ring in One Step.* **Preetpal S. Sidhu**. Manuscript submitted to *JPSR*.
10. Designing Inhibitors of Thrombin and Factor XIa as Newer Anticoagulants. **Preetpal S. Sidhu**, Qibing Zhou and Umesh Desai. Manuscript Submitted to *Bioorg. Med. Chem. Lett.*
11. Development of the first nanomolar inhibitor of the Vitamin D Receptor–Coactivator interaction. **Preetpal S. Sidhu**, Premchendra Nandhikonda, Nicholas Nassif, Megan M. McCallum, Kelly Teske, Belaynesh Feleke, Nina Y. Yuan, James M. Cook, Rakesh K. Singh, Daniel D. Bikle, Leggy A. Arnold. Submitted to *J. Med.Chem.*
12. Understanding the Mechanism of Anticancer Effect of PS121912. Manuscript in Preparation.

#### **POSTER AND ORAL PRESENTATIONS**

1. Gordon Research Conference – Medicinal Chemistry, Colby-Sawyer College, New London, NH.
2. Gordon Research Seminar – Medicinal Chemistry, *Selective, Irreversible VDR-coactivator Inhibitors and Their Evaluation In Vivo Using an Ovarian Cancer Animal Model*, Colby-Sawyer College, New London, NH.
3. 245<sup>th</sup> ACS National Meeting and Exposition, *Chemical improvement of pharmacological properties of irreversible VDR-coactivator inhibitors*, New Orleans, Louisiana.
4. 244<sup>th</sup> ACS National Meeting and Exposition, *Allosteric Modulation of Thrombin; Design, Synthesis, and Inhibition Properties of Sulfated Benzofuran Trimers*, Philadelphia, PA.

5. SERMAC-2011, *Design & Synthesis of Allosteric Inhibitors of Thrombin*, ACS Regional Meeting, Richmond, VA.
6. Virginia Academy of Science-2011, *Design, Synthesis and Interaction Studies of Sulfated Allosteric Modulator of Thrombin*, VAS Annual Meeting, Richmond, VA.
7. SERMAC/SWRM-2010, *Synthesis and Interaction Studies of Benzofuran Based Allosteric Modulator of Thrombin*, ACS regional meeting, New Orleans, LA.
8. SERMAC/SWRM-2010, *Exploring Larger Chemical Space to Design Small, Aromatic, Sulfated Allosteric Modulators Of Thrombin*, ACS regional meeting, New Orleans, LA.
9. The Twenty Seventh Annual Daniel T. Watts Research Poster Symposiums 2010, *Structure Based Design Of Allosteric Inhibitors Of Thrombin*, Virginia Commonwealth University, Richmond, VA.
10. School of Pharmacy's Research and Career Day 2010, *Exploring Larger Chemical Space to Design Small, Aromatic, Sulfated Allosteric Modulators of Thrombin*, Virginia Commonwealth University, Richmond, VA.
11. Graduate Student Association Twelfth Annual Research Symposium and Exhibit 2010, *Structure Based Design Of Allosteric Inhibitors Of Thrombin*, Virginia Commonwealth University, Richmond, VA.
12. School of Pharmacy's Research and Career Day 2009, *Design, Synthesis and Interaction Studies Of Dual, Direct Non-saccharide Allosteric Modulators Of Thrombin And Factor Xa*, Virginia Commonwealth University, Richmond, VA.
13. The Twenty Sixth Annual Daniel T. Watts Research Poster Symposium 2009, *Design, Synthesis and Interaction Studies Of Dual, Direct Non-saccharide Allosteric Modulators Of Thrombin and Factor Xa*, Virginia Commonwealth University, Richmond, VA.

## **LABORATORY SKILLS**

### *Bio-analytical and Microbiology Techniques*

- Mass Spectroscopy: Plasma and Microsomal Studies, metabolomics, Vitamin D receptor digestion studies.
- Protein Expression and Purification, Cell-Based Transcription Assay, Toxicity Studies, Transcription Assay, Formulation Assay, stability studies and Permeability Studies.
- Enzyme Assay, Plasma and Blood Studies.
- Western Blot, ELISA, RT-PCR, Cell Culture, Proliferation Studies, and Plasmid, DNA and RNA Purification.
- ADME: Solubility Studies, Membrane Permeability Studies, Liver Microsomal Stability Studies, and Half-life and Clearance Rate measurement.
- Metabolomics.

### *Synthetic Chemistry Techniques*

- Organic synthesis including anhydrous reaction, Microwave-based reactions, transition metal catalyzed reactions, polymer synthesis and characterization.
- Synthesis of extensive libraries of molecules for discovery of allosteric inhibitors of thrombin (VCU) and VDR-Coregulators inhibitors (UWM).
- Scale-up of lead molecule for *In-vivo* studies.

### *Analytical Techniques*

- NMR (Proton, Carbon and 2D), Mass Spectroscopy, Chromatography Techniques (Flash System, Cation Exchange, Size Exclusion), HPLC (Quantitative and Preparative), UV, IR.

### *Computational Techniques*

- Sybyl, legion Library Builder, HINT, GOLD Docking Software, MDL, Virtual Screening Techniques and QSAR.

## **RESEARCH PROJECTS**

- MS-based Microsomal Stability Studies

Project involves development of MS-based stability study protocol in plasma and microsomal studies. In-vitro pharmacokinetics studies were used to access in-vivo stability of the drug. The potential metabolites formed are quantified by MS.

- MS-based Trypsin Digestion Studies of Vitamin D Receptor

Project aims at identifying the binding site of PS121912 on VDR. The VDR and VDR-PS121912 conjugate samples were digested with trypsin enzyme. The peptides generated from both the samples were analyzed and compare to identify peptide containing PS121912.

- Understanding the Biology of PS121912

Project involves the understanding of mechanism of effect of lead compound PS121912 in various cancer cell lines. RT-PCR studies were performed to observe the effect on various VDR regulated and oncogenes. NCI 60-Cell line screen were performed to study the effect on various cell lines.

- Formulation Studies for inhibitors pBBG and PS121912 for *In Vivo* studies.

Project involves the designing of formulation for IP and slow dissolution using osmotic pump for *In Vivo* studies in mice models. Along with formulation, stabilities studies were performed to assess stability of inhibitors in the designed formulation for extended time period.

- Large Scale Synthesis of 3d, pBBG and 31b inhibitors for *In Vivo* studies.

Gram scale synthesis of potent inhibitors for preclinical studies.

- Metabolomics Studies to Identify the Metabolites of VDR-Coregulators interactions inhibitors in *In Vivo* studies (Aug2012-Present).

The project involves the metabolomics studies to identify the major metabolites using LCMS. The lead molecule 31b is used for *In Vivo* studies in mice. The organ samples were collected and metabolites were extracted and identified by LCMS.

- Discovery of VDR-Coregulators Interaction Inhibitors for Cancer Treatment (Aug2012-Present).

The project involves the synthesis of library of inhibitors to disturb the interaction between VDR-Coregulators for treatment of cancer. The SAR studies were performed to optimize the activity of lead molecules. The synthesized library of inhibitors was biochemically analyzed using FP assay, Transcription and toxicity studies, solubility and permeability studies.

- Design, Synthesis and Biochemical Studies of Sulfated Allosteric Inhibitors of Thrombin Identified by Scaffold Hopping (Jan2012-June2012).

The project involves the design of *In Silico* library of sulfated molecules based on sulfated benzofuran inhibitors by scaffold hopping method. The library is docked and hits were identified. These hits were synthesized and tested for thrombin inhibition studies. These inhibitors are allosteric in nature and potent inhibitors in blood.

- Synthesis of 2<sup>nd</sup> Generation Benzofuran-Based Sulfated Allosteric Inhibitors of Thrombin (Sept 2010 – Oct 2011).

The project involves the synthesis of pilot library of novel sulfated benzofuran-based trimer and biological evaluation for inhibition of thrombin. These molecules were found to be potent allosteric inhibitors of thrombin. The library was also screened against the panel of other proteases involved in coagulation cascade and identified the lead structures for designing the inhibitors for Factors VIIa, IXa, Xa and XIa. The manuscript is ready for submission to *J. Med. Chem.*

- Design, Synthesis and Interaction Study of novel Allosteric Modulators of Thrombin (Jan 2008 - Sept 2010).

The project involves the design and synthesis of library of novel sulfated monomers and dimer as inhibitors of thrombin. The enzyme assay and mechanistic studies suggested as potent allosteric inhibitors of thrombin. This work is published in *J. Med. Chem.*

- Structure Based Virtual Screening to Explore Larger Chemical Space (Jan 2010 - Jul 2010).

The pharmacophore was generated from the library of sulfated benzofuran dimers to identify the new lead molecules. Using virtual screening, the vast chemical space in ZINC database was explored to find the new core structures as allosteric inhibitors of thrombin. *In silico* study was combination of ligand-based and docking-based approach using GOLD docking suite. The hit was evaluated experimentally. The manuscript is ready for submission to *Bioorg. Med. Chem. Letters*.

- QSAR Model of Direct Factor Xa Inhibitors (Sep 2009 - Dec 2009).

The QSAR studies were carried out for direct factor Xa inhibitors using MDL QSAR software to find relationship between enzyme inhibition activity and various physical descriptors.

- *In silico* Designing of Factor Xa and Thrombin Inhibitors (Mar 2008 - Jun 2008).

The project involves the designing of *in silico* library of molecules and docking it on the target protein using GOLD docking software. The virtual library was docked on crystal structure of thrombin and factor Xa and GOLDScore function was used to identify molecules having high binding affinity.

## **REVIEWING**

### **Editor**

- Journal of Postdoctoral Research

### **Journal Reviewer**

- Journal of Pharmacy and Pharmacology
- International Journal of Carbohydrate Chemistry
- Biochemistry Research International
- Mini-Reviews in Medicinal Chemistry
- Journal of Medicinal Chemistry
- Arabic Journal of Chemistry
- Chemico-Biological Interactions
- Bioorganic and Medicinal Chemistry

### **Symposium**

- Judge for 15<sup>th</sup> Annual Research Symposium and Exhibit, Graduate Student Association, Virginia Commonwealth University, Richmond, VA, USA.

- Abstract Screener for DDDI Section at 2012 AAPS Annual Meeting and Exposition, American Association of Pharmaceutical Scientists, Chicago, IL, USA.
- Judge for 2012 VJAS Research Symposium, Virginia Academy of Science, Norfolk, VA, USA.
- Judge for 2012 Undergraduate Research Symposium at University of Wisconsin, Milwaukee, WI, USA.
- Abstract Screener for DDDI Section at 2013 AAPS Annual Meeting and Exposition, American Association of Pharmaceutical Scientists, San Antonio, TX, USA.

## **TEACHING**

Teaching assistant for following courses:

- PHAR-524 (Foundation II)
- PHAR-534 (Foundation III)
- PHAR-640 (Foundation V)
- MEDC-543 (Clinical Chemistry for Pharmacists)
- MEDC-310 ( Medicinal Chemistry and Drug Design)
- MEDC-541 (Survey of Molecular Modeling Methods)
- MEDC-670 (Advanced Molecular Modeling)

## **MENTORSHIP**

- Miten Patel (June 2010- Dec 2010) – Undergraduate Student
- Swathi Bobby (Aug 2010-May 2011) – Graduate Mentorship Program
- Susana Ayad (June 2011- Jul2012) – Undergraduate Student
- Amal Shanker ( Nov 2011 – Jul2012) – Graduate Student

## **EXTRACURRICULAR LEADERSHIP INVOLVEMENT**

- Student Advisor and Member of VCU Honor System, Office of Judicial Affairs & Academic Integrity, Virginia Commonwealth University, 2010 – 2011.
- Graduate Mentor, VCU Graduate School Mentorship Program, Virginia Commonwealth University, 2010 – 2011.
- Vice President, TIRANGA-Indian Nationals at VCU, Virginia Commonwealth University, 2009 – 2010.
- Treasurer, TIRANGA-Indian Nationals at VCU, Virginia Commonwealth University, 2010 – 2011.

## **MEMBERSHIPS**

- American Association of Pharmaceutical Scientists (AAPS)
- American Chemical Society (ACS)
- American Association of Indian Pharmaceutical Scientists (AAiPS)

## **REFERENCES**

1. Dr. Umesh R. Desai  
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2. Dr. Qibing Zhou  
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3. Dr. Alexander Arnold  
Assistant Professor  
Department of Chemistry and Biochemistry  
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