

MITHUN R. RAJE, Ph.D.

12 East Madison St, #2B
Baltimore, MD 21202

Cell: 540-577-6656
mraje@umbc.edu

EDUCATION

Virginia Tech

Blacksburg, VA

PhD (Chemistry), Advisor: Prof. Webster L. Santos

08/06 – 05/12

Dissertation: "Design, synthesis, and biological evaluation of selective sphingosine kinase inhibitors"

Developed cell permeable small-molecule libraries as probes for defining the roles of sphingosine kinases (SphKs) in hyperproliferative diseases and validating the enzyme as a therapeutic target. This work resulted in 4 publications and a patent and also provided the foundation for the launch of SphynKx Therapeutics, a biotechnology company focused on developing SphK inhibitors for the treatment of fibrosis.

Institute of Chemical Technology

Mumbai, India

B.Tech (Chemical Technology)

09/02 – 05/06

RESEARCH EXPERIENCE

University of Maryland

Baltimore, MD

Research Associate, Chemistry

09/14-present

- Developed flexible analogues of the antiviral drug Acyclovir as novel inhibitors of SARS-CoV replication. Inhibitors were tested in virus replication assay, CPE assay, and plaque assay. Prodrugs were synthesized to improve cell permeability and conversion to active monophosphate. Nucleoside triphosphate helped elucidate mechanism of action.

Research Associate, Pharmaceutical Sciences

- Dual inhibitors of the oncoproteins Bcl-xL and Mcl-1, based on a thiazolidine-2,4-dione (TZD) scaffold that mimicked the Bim-BH3 α -helix, were synthesized and tested for activity in multiple cancer cell lines. Direct binding of inhibitor to Mcl-1 was confirmed by ^1H - ^{15}N HSQC NMR studies.
- Conducted successful lead optimization of Brd4 inhibitors with improved binding affinity and PK properties in terms of increased half-life and better intestinal permeability. Research resulted in the selection of a group of compounds that went on to an advanced stage of *in vivo* studies.

Brain Science Institute, Johns Hopkins School of Medicine

Baltimore, MD

Research Associate, NeuroTranslational Drug Discovery Program

09/12-08/14

- Optimized potency and PK properties of a high throughput screening hit with focused structural modifications to provide lead molecules. Lead compounds crossed blood brain barrier and affected glutamate release in cultured microglia.

- Performed an effective multi-iterative lead optimization program that led to the development of potent D-amino acid oxidase inhibitors. Conducted molecular modeling on the enzyme inhibitors.
- Designed and synthesized a series of small molecule glutaminase inhibitors that were tested against several breast cancer cell lines. In addition, they were also evaluated for the treatment of neurological disorders associated with glutamate excitotoxicity.

HIGHLIGHTS

- Expertise in synthetic organic chemistry, protein biochemistry, and analytical chemistry
 - **Synthetic organic chemistry:** Multi-step small molecule organic synthesis, air free techniques like glove box and Schlenk lines, microwave and pressure reactors, electronic notebooks, automated column chromatography.
 - **Protein sequence and structure analysis:** Visualization and analysis of protein structures (Swiss-PDB Viewer, PyMol), homology modeling (Swiss-Model), sequence alignment (ClustalW), protein-small molecule docking (AutoDock Vina).
 - **Analytical Chemistry:** 1D and 2D NMR, IR, UV-Vis spectroscopy, HPLC, ion exchange chromatography, size exclusion chromatography, and Mass Spectrometry (ion trap, single quad, triple quad, and MALDI-TOF)
- Demonstrated excellent written and oral communications, proven success in a collaborative environment and published results in scientific journals

PUBLICATIONS

1. "Design, Synthesis, and Biological Activity of Sphingosine Kinase 2 Selective Inhibitors" Raje, M.R., Knott, K., Kharel, Y., Bissel, P., Lynch, K.R., and Santos, W.L. *Bioorg. Med. Chem.* **2012**, *20*, 183.
2. "Effect of Alkyl Chain Length on Sphingosine Kinase 2 Selectivity" Knott, K., Kharel, Y., Raje, M.R., Lynch, K.R., and Santos, W.L. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 6817.
3. "Sphingosine Kinase Type 2 Inhibition Elevates Circulating Sphingosine-1-phosphate" Kharel, Y., Raje, M.R., Gao, M, Gellett, A.M., Tomsig, J.L., Lynch, K.R., and Santos, W.L. *Biochem. J.* **2012**, *447*, 149.
4. "Synthesis of Kojic Acid Derivatives as Secondary Binding Site Probes of D-Amino Acid Oxidase" Raje, M., Hin, N., Duvall, B., Ferraris, D.V., Berry, J.F., Thomas, A.G., Alt, J., Rojas, C., Slusher, B.S., Tsukamoto, T. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3910.
5. "Molecular Mechanisms of 5-HT₃ and NK₁ Receptor Antagonists in Prevention of Emesis" Rojas, C., Raje, M., Tsukamoto, T., Slusher, B. *Eur. J. Pharmacol.* **2014**, *722*, 26.

6. "Structure-Activity Relationship Studies and In Vivo Activity of Guanidine-Based Inhibitors of Sphingosine Kinase 2" Patwardhan, N. N., Morris, E. A., Kharel, Y., Raje, M. R., Gao, M., Tomsig, J. L., Lynch, K.R., Santos, W. L. *J. Med. Chem.* **2015**, *58*, 1879.
7. "Brd4 Structure-Activity Relationships of Dual PLK1 Kinase/Brd4 Bromodomain Inhibitor BI-2536" Chen, L., Yap, J. L., Yoshioka, M., Lanning, M. E., Fountain, R. N., Raje, M., Scheenstra, J. A., Strovel, J. W., Fletcher, S. *ACS Med. Chem. Lett.* **2015**, *6*, 764.
8. "Towards more drug-like proteomimetics: Two-faced, synthetic α -helix mimetics based on a purine scaffold" Lanning, M. E., Wilder, P. T., Bailey, H., Drennen, B., Cavalier, M., Chen, L., Raje, M., Fletcher, S. *Org. Biomol. Chem.* **2015**, *13*, 8642.
9. "Synthetic, of HIV-1 protease structural mimetics of the β -hairpin flap inhibit enzyme function" Chauhan, J., Chen, S., Fenstermacher, K., Reingewertz, T., Salmo, R., Lee, C., Raje, M., Sandberg, E., DeStefano, J. J., Friere, E., Fletcher, S. *Bioorg. Med. Chem.* **2015**, *23*, 7095.
10. "Novel Bromodomain Inhibitors Suppress Proliferation of Multiple Myeloma Cells" Ashihara, E., Oki, R., Imayoshi, N., Yoshioka, M., Strovel, J., Honjo, A., Sakai, Y., Takada, T., Chauhan, J., Raje, M., Fletcher, S., Takata, K. *Blood*, **2015**, *126*, 4432.

PATENT

1. Santos, W.L., Raje, M.R., Lynch, K.R., Kharel, Y., Macdonald, T.L., Kennedy, A.J. "Long Chain Base Sphingosine Kinase Inhibitors", PCT/US2013/025341, February 8, 2013.

CONFERENCE PROCEEDINGS

1. "Structure-activity relationship studies of sphingosine kinase inhibitors" Raje, M. R., Kharel, Y., Lynch, K. R., Santos, W. L., 240th National Meeting of the American Chemical Society, Boston, August 22-26, 2010. MEDI-163.
2. "Structure-activity relationship studies of sphingosine kinase inhibitors" Raje, Mithun, ACC Interdisciplinary Forum for Discovery in Life Sciences, Blacksburg, October 3-6, 2010.
3. "Design, synthesis, and biological activity of isoform-selective sphingosine kinase inhibitors" Raje, M., Santos, W., Kharel, Y., Lynch, K., Joint 66th SW and 62nd SE Regional Meeting of the American Chemical Society, New Orleans, December 1– 4, 2010. SESW-795.
4. "Sphingosine kinase inhibitors: Potential anti-cancer agents" Raje, Mithun, Virginia Tech Cancer Research Symposium, Blacksburg, April 29, 2011.
5. "Structure-activity studies and biological activity of guanidine-based isotype-selective sphingosine kinase inhibitors" Raje, Mithun, GSA Research Symposium, Blacksburg, March 29, 2012.

6. "Discovery and in vivo activity of sphingosine kinase 2 selective inhibitors" Santos, W. L., Raje, M., Knott, K., Kharel, Y., Lynch, K. R., Gao, M., 244th National Meeting of the American Chemical Society, Philadelphia, August 19-23, 2012. MEDI-26.
7. "Structure-activity relationship studies of novel guanidine containing inhibitors of sphingosine kinase 2" Patwardhan, N, N., Raje, M. R., Morris, E. A., Knott, K., Congdon, M., Gao, M., Kharel, Y., Lynch, K. R., Santos, W. L., 91st Annual Meeting of the Virginia Academy of Science, Blacksburg, May 2013.
8. "Synthesis of kojic acid derivatives as secondary binding site probes of D-amino acid oxidase" Raje, M. R., Hin, N., Duvall, B., Ferraris, D. V., Berry, J. F., Thomas, A. G., Alt, J., Rojas, C., Slusher, B. S., Tsukamoto, T., 246th National Meeting of the American Chemical Society, Indianapolis, September 8-12, 2013. MEDI-85.
9. "Structure-activity relationship studies of novel guanidine based inhibitors of sphingosine kinase 2" Patwardhan, N, N., Raje, M. R., Morris, E. A., Knott, K., Congdon, M., Gao, M., Kharel, Y., Lynch, K. R., Santos, W. L., 246th National Meeting of the American Chemical Society, Indianapolis, September 8-12, 2013. MEDI-17.
10. "Potent Mcl-1/Bcl-xL dual inhibitors based on a thiazolidine-2,4-dione (TZD) scaffold" Mithun Raje et al., 8th Frontiers in Chemistry and Biology Interface Symposium, University of Maryland, Baltimore County, May 2015.
11. "Targeting MERS-CoV with flexible nucleosides" Mithun Raje et al., 22nd International Round Table on Nucleosides, Nucleotides, and Nucleic Acids, Institut Pasteur, Paris, July 2016.

AWARDS

- Poster Prize, 8th Frontiers in Chemistry and Biology Interface Symposium, University of Maryland, Baltimore County, May 2015.
- Travel Grant Award, 22nd International Round Table on Nucleosides, Nucleotides, and Nucleic Acids, Institut Pasteur, May 2016.

PROFESSIONAL ACTIVITIES

- Member of the American Chemical Society, 2010-present
- Member of the International Society of Nucleosides, Nucleotides, and Nucleic Acids, 2016-present
- Peer reviewer of manuscripts
 - *Chemical Reviews*
 - *Bioorganic and Medicinal Chemistry*

- *Bioorganic and Medicinal Chemistry Letters*
- *Journal of Medicinal Chemistry*
- *Chemical Communications*
- *Nucleosides, Nucleotides and Nucleic Acids*
- *Frontiers in Chemistry*
- *Medicinal Chemistry*
- *Mini Reviews in Organic Chemistry*
- *Perspectives in Medicinal Chemistry*
- *South African Journal of Chemistry*
- *Open Chemistry*
- Poster Session Judge, 18th Annual Undergraduate Research Symposium in Chemical and Biological Sciences, University of Maryland Baltimore County, October 2015
- Poster Session Judge, 9th Frontiers in Chemistry and Biology Interface Symposium, Johns Hopkins University, May 2016

TEACHING AND MENTORING EXPERIENCE

- Served as mentor for beginner graduate students and undergraduate research assistants
 - Wesley Morris, Chemistry, Virginia Tech (2008)
 - Leah Heist, Chemistry, Virginia Tech (2011)
 - Julie Ta, Biochemistry, Virginia Tech (2012)
 - Forrest Bowling, Chemistry, University of Maryland (2014)
 - Alexander Vega, Chemistry, University of Maryland (2015)
 - Mary Yates, Chemistry, University of Maryland (2016)