Liza Shrestha, PhD

Research Fellow

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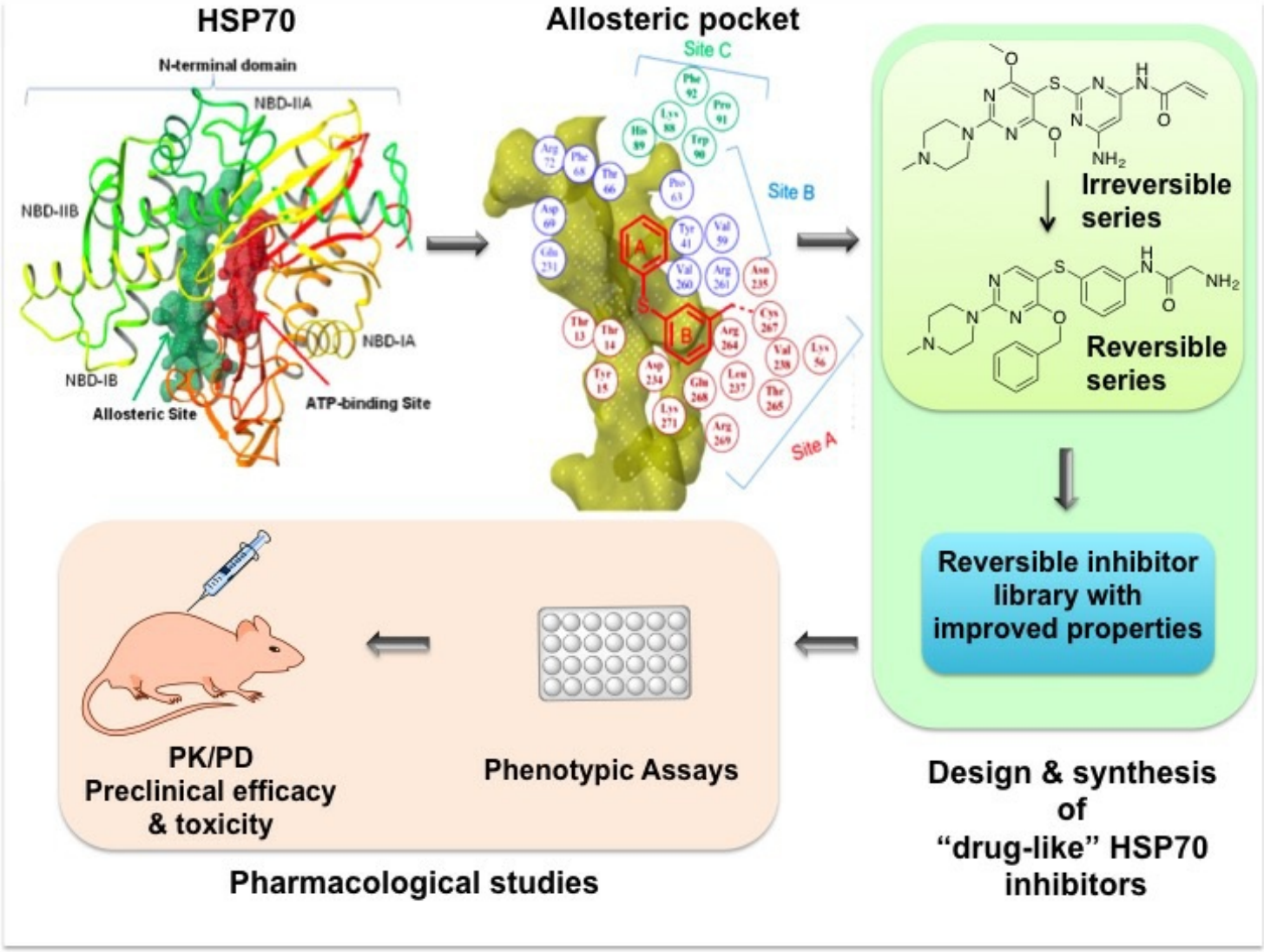
Start Year

2014

I received my PhD in Medicinal Chemistry and Molecular Pharmacology from Purdue University. My dissertation involved substrate-based synthesis of isoprenylcysteine carboxyl methyltransferase (Icmt) inhibitors to combat K-Ras mediated pancreatic

cancer as well as several other neoplasias. During my graduate career, I successfully generated an extensive library of bioactive small molecules, which have strengthened the SAR and resulted in the discovery of low nanomolar inhibitors. These inhibitors exhibit promising antiproliferative effects on pancreatic cancer cells. As a part of my research, I also synthesized benzophenone based photoaffinity probes for effective identification of Icmt active site residues.



At present, I am a postdoctoral research fellow in the Chiosis group. My research involves the rational development of small molecule anticancer therapeutics that target heat shock protein 70 (HSP70). I am involved in the optimization of the potency profile as well as the physicochemical properties of Hsp70 inhibitors. In parallel with our rational strategy to generate allosteric Hsp70 inhibitors, we perform preclinical testing in several xenograft mice models with the ultimate goal of designing a small molecule that can transition into the clinic. My training in the Chiosis lab has allowed me to acquire skill sets required to understand and appreciate the various phases of translational research starting from chemical design to pharmacological assays to preclinical *in vivo* studies.

Patents

Chiosis, Gabriela; Taldone, Tony; Shrestha, Liza; Koren, John; Gomes-Dagama, Erica. Rational synergistic combination therapy for the treatment of cancer using inhibitors of chaperone proteins such as HSP90 inhibitors. WO 2017062520 (A1), Apr 13, 2017.

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Publications

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Shrestha, L.; Young, J. C., Function and Chemotypes of Human Hsp70 Chaperones. *Curr. Top. Med. Chem.* 2016, 16(25), 2812-28.

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Patel, H. J.; Patel, P. D.; Ochiana, S. O.; Yan, P.; Sun, W.; Patel, M. R.; Shah, S. K.; Tramentozzi, E.; Brooks, J.; Bolaender, A.; Shrestha, L.; Stephani, R.; Finotti, P.; Leifer, C.; Li, Z.; Gewirth, D. T.; Taldone, T.; Chiosis, G., Structure-activity relationship in a purine-scaffold compound series with selectivity for the endoplasmic reticulum hsp90 paralog grp94. *J Med. Chem.* 2015, 58 (9), 3922-43.

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Hahne, K.; Vervacke, J. S.; Shrestha, L.; Donelson, J. L.; Gibbs, R. A.; Distefano, M. D.; Hrycyna, C. A., Evaluation of substrate and inhibitor binding to yeast and human isoprenylcysteine carboxyl methyltransferases (Icmts) using biotinylated benzophenone-containing photoaffinity probes. *Biochem. Bioph. Res. Commun.* 2012, 423 (1), 98-103.

Majmudar, J. D.; Hodges-Loaiza, H. B.; Hahne, K.; Donelson, J. L.; Song, J.; Shrestha, L.; Harrison, M. L.; Hrycyna, C. A.; Gibbs, R. A., Amide-modified prenylcysteine based Icmt inhibitors: Structure-activity relationships, kinetic analysis and cellular characterization. *Bioorg. Med. Chem.* 2012, 20 (1), 283-295.

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