Structure guided inhibitor discovery targeting a membrane receptor involved in atherosclerosis

Arockiasamy Arulandu[1], Akanksha Tomar[1], Azeem Khan[1], Sibasis Sahoo[1], Muthu Sankar Aathi[1], Shobhan Kuila[1], Anmol Chandele[1], Jawahar L Mehta[2], Kottayil I Varughese[3]

[1]International Centre for Genetic Engineering and Biotechnology, Aruna Asaf Ali Marg, New Dlehi-110067. India,
[2]Department of Internal Medicine, University of Arkansas for Medical Sciences and the Central Arkansas Veterans Healthcare System, Little Rock, Arkansas, AR 72205. United States,
[3]Department of Physiology and Cell Biology University of Arkansas for Medical Sciences, Little Rock, Arkansas, AR 72205, United States.

sam@icgeb.res.in

Atherosclerosis is a major cause of cardiovascular diseases and stroke. Oxidized low-density lipoprotein (Ox-LDL) plays a key role in the initiation and progression atherogenic process. Lectin-like ox-LDL receptor-1 (LOX-1) [1], a scavenger receptor present on vascular endothelial cells, macrophages, smooth muscle cells, and platelets, facilitates internalization of ox-LDL leading to atherosclerotic plaque formation. Existing data points towards LOX-1 as a potential target for novel anti-atherosclerosis therapy [2-3]. However, no approved therapeutics targeting LOX-1 are known. Using computational tools, we first identified a potential druggable site on the extracellular C-terminal domain (CTLD) of LOX-1. Then, using structure-based screening and molecular dynamics we have identified and short-listed molecules from chemical libraries for further validation with a combination of surface plasmon resonance, cell-based ox-LDL uptake assay and complex crystal structures. Our data clearly shows that LOX-1 is druggable. Further studies will be performed to decipher mechanistic details of ox-LDL uptake inhibition.

[1] Sawamura, T., Kume, N., Aoyama, T., Moriwaki, H., Hoshikawa, H., Aiba, Y., ... & Masaki, T. (1997). *Nature*. **386**(6620), 73.

[2] Mehta, J. L., Sanada, N., Hu, C. P., Chen, J., Dandapat, A., Sugawara, F., ... & Sawamura, T. (2007). *Circ. Res.* **100**(11), 1634.

[3] Pothineni, N. V. K., Karathanasis, S. K., Ding, Z., Arulandu, A., Varughese, K. I., & Mehta, J. L. (2017). *J. Am. Coll. Cardiol.* **69**(22), 2759.

Keywords: Atherosclerosis; ox-LDL receptor; drug discovery; LOX-1, scavenger receptor