

## Characterizing Urotensin Receptor Ligands for Potential Signaling Bias

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Urotensin receptors (UT) play a central role in cardiovascular physiology, contributing to vasoconstriction, vasodilation, fibroblast activation, angiogenesis, and cardiac hypertrophy. Expression of the endogenous ligands urotensin II (UII) and urotensin-related peptide (URP) is elevated in patients with chronic kidney and cardiovascular disease, suggesting that modulation of this pathway may hold therapeutic potential. Preclinical studies have proposed that UT inhibition could benefit conditions such as congestive heart failure, atherosclerosis, and pulmonary arterial hypertension. However, despite promising results in rodent models, UT antagonists have not translated into clinical efficacy—likely reflecting interspecies differences between human UT (hUT) and rat UT (rUT), as well as species-specific forms of UII. This work examines the hypothesis that divergent clinical outcomes stem from fundamental biological differences between hUT and rUT, which may yield distinct activation profiles for both endogenous ligands and synthetic antagonists. To address this, we aim to characterize UT signalling using BRET-based biosensors in HEK293 cells expressing either hUT or rUT. Two complementary biosensors will be used: a PKN1-RLucII system to monitor G<sub>12/13</sub>-dependent signaling through Rho recruitment, and a PKC-based biosensor to assess G<sub>q</sub>-mediated activation of phosphoinositide pathways, including PIP3 and DAG production. Responses to UII and URP will be compared across species-specific receptors, followed by evaluation of known antagonists. A comparative understanding of hUT and rUT responses to endogenous ligands and antagonists may clarify the reasons behind previous clinical failures and guide the development of more effective UT-targeting therapeutics capable of slowing the progression of cardiovascular disease.

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