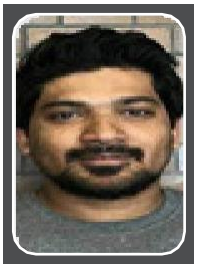
Journal of Pharmaceutical Chemistry and Chemical Science



Targeted Degradation of Transcription Factors by TRAFTACs: TRAnscription Factor Targeting Chimeras

Kusal Samarasinghe

Yale University, USA

Abstract

Many diseases, including cancer, stem from aberrant activation or overexpression of oncoproteins that are associated with multiple signaling pathways. Although proteins with catalytic activity can be successfully drugged, the majority of other protein families, such as transcription factors, remain intractable due to their lack of ligandable sites. In this study, we report the development of TRAnscription Factor TArgeting Chimeras (TRAFTACs) as a generalizable strategy for targeted transcription-factor degradation. Herein, we show that TRAFTACs, which consist of a chimeric oligonucleotide that simultaneously binds to the transcription factor- of-interest (TOI) and to HaloTag-fused dCas9 protein, can induce degradation of the former via the proteasomal pathway. Application of TRAFTACs to two oncogenic TOIs, NF-κB and brachyury, suggests that TRAFTACs can be successfully employed for the targeted degradation of other DNA-binding proteins. Thus, TRAFTAC technology is potentially a generalizable strategy to induce degradation of other transcription factors both *in vitro* and *in vivo*.

Biography

Kusal Samarasinghe completed his PhD in 2017 from the department of Chemistry, Wayne State University, MI. Then, he joined the laboratory of professor Craig Crews at Yale University as a postdoctoral fellow. His research interest focusses on developing new therapeutic modalities, like targeted protein degradation or TPD. TPD by Proteolysis Targeting Chimeras or PROTACs, was developed in his current laboratory and two candidates have already found the way to clinic. His prior work successfully demonstrated several advantages of TPD such as targeting scaffolding roles of kinases and spatiotemporal control of TPD by light activatable PROTACs. As an effort to expand the druggable space by TPD, Kusal Samarasinghe has successfully developed a generalizable method to target transcription factors (TFs) for degradation by coopting the DNA binding ability of TFs. With this strategy, many undruggable TFs could be targeted for proteasomal degradation.

Publications

Dhanusha A. Nalawansha, Kusal T. G. Samarasinghe “ACS Pharmacology and Translational Science”, 2020:3(5).

Kusal T. G. Samarasinghe, Dhanushka N. P. Munkanatta Godage, Yani Zhou, Fidelis T. Ndombera, Eranthie Weerapana and Young-Hoon Ahn “Molecular Biosystems”, 2016: 8

2nd International Conference on Pharmacology and Pharmaceutical research
Webinar | April 21, 2021

Citation: Kusal Samarasinghe, *Targeted Degradation of Transcription Factors by TRAFTACs: TRAnscription Factor Targeting Chimeras*, Euro pharma 2021, 2nd International Conference on Pharmacology and Pharmaceutical research, Webinar, April 21, 2021, 05:02-10