

Towards the development of selective LIMK degraders for the treatment of pathological actin dynamic dysfunction

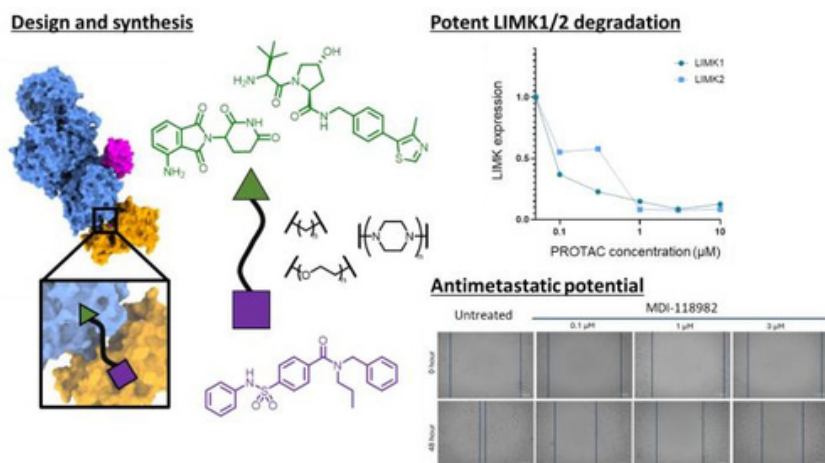
Angus Muller^a, Alex Baldwin^b, Simon Ward^b, Christopher Hyland^a

^a School of Science, University of Wollongong, NSW, Australia

^b Medicines Discovery Institute, Cardiff University, Wales, United Kingdom

Abstract

Abnormal regulation of actin remodelling has been identified as a key driving force in both neurological and oncological disorders, being particularly prevalent in various metastatic cancers.¹ A common mediator of this dysfunction is the hyperactivity of LIM kinases (LIMKs) which manifests as altered cell morphology and increased propensity for invasion and migration. Despite significant work investigating LIMK inhibitors, identification of an effective antagonist remains elusive.² Application of targeted protein degrader technology to LIMK represents a promising strategy to utilise this target where traditional inhibition has proven ineffective.³ This presentation will describe the design, synthesis and analysis cycle of selective LIMK degraders over multiple generations. A click-reaction-based synthetic strategy has been developed to efficiently prepare a diverse series of degraders containing a highly selective allosteric LIMK ligand. The lead compound potently impedes migration and invasion in metastatic breast cancer through selective LIMK knockdown. Promising results from early biochemical characterisation of the candidate supports the in vivo assessment of both the DMPK profile and efficacy against metastatic disease.



1. Villalonga et al. Cells, 2023, 12(5), 805
2. Berabez et al. Cells, 2022, 11(13), 2090
3. Békés et al. Nat Rev Drug Discov, 2022, 21, 181-200

Biography

Angus completed his PhD at the University of Wollongong, where his research focused on developing PROTACs to address cytoskeletal dysfunction in metastatic cancer. He has since joined MedChem Australia and the Australian Translational Medicinal Chemistry Facility at MIPS, where he works across multiple drug discovery projects with a focus on translating research to commercialisation.

