

PI3KC2 α inhibitors as novel anti-thrombotic agents

THERAPEUTIC: CVD/CNS

Product Type	Small molecule
Indication / ROA	Thrombosis/oral
Target / MoA	Inhibitors of the Class II PI3-kinase, PI3KC2 α
Development Stage	Lead series
Brief Description & Differentiation	Arterial thrombosis underlies highly prevalent diseases such as stroke, MI and peripheral arterial disease. The need is for new anti-thrombotics that will reduce vascular events in high-risk patients without causing increases in bleeding. The limitation on current drugs is that they non-specifically prevent platelet function. <ul style="list-style-type: none"> Blocking PI3KC2α is a new approach to preventing thrombosis, whereby platelet inhibition only occurs during pro-thrombotic conditions and global platelet function is not impaired First-in-class
Research Team	Prof Justin Hamilton (Australian Centre for Blood Diseases) & Prof Philip Thompson (Monash Institute of Pharmaceutical Sciences)
Intellectual Property	New compositions of matter, to be filed
Key Publications	Mountford JK <i>et al.</i> (2015) <i>Nature Comm</i> 6, 1-14 Selvadurai MV <i>et al.</i> & Hamilton JR (2019) <i>FEBS Letts.</i> 593, 88-96
Future	Lead series optimization to improve potency and selectivity

➤ Key Data

Target: PI3KC2 α -deficient mice are protected from arterial thrombosis, but do not bleed. The anti-thrombotic effect is independent of effects on platelet activation. Rather, PI3KC2 α -deficient platelets had an altered internal membrane reserve structure that led to impaired adhesion specifically in the setting of thrombosis. This suggests that blocking PI3KC2 α will be an anti-thrombotic mechanism distinct from all other known anti-platelet approaches.

Inhibitors: Monash first-in-class selective PI3KC2 α -inhibitors

- reproduce the ultrastructural defect seen in PI3KC2 α -deficient human platelets associated with protection from arterial thrombosis
- reproduce the antithrombotic effects in human blood
- demonstrate *in vivo* antithrombotic effects in mice

