MONASH University

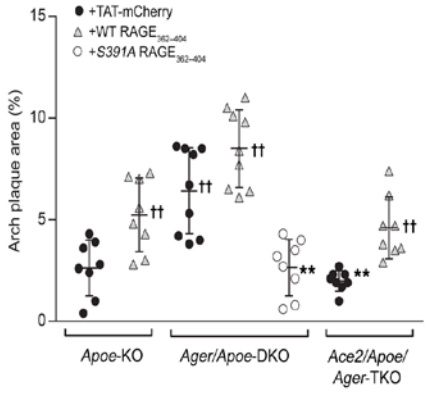
RAGE Modulator

THERAPEUTIC: Inflammation & Immunity

Product Type	Peptide-based drug
Indication/ROA	Broad application in inflammatory diseases such as diabetes, atherosclerosis, dementia, respiratory disease, sepsis and malignancy.
Target/MoA	Cytosolic tail of receptor for advanced glycation end products (RAGE). Activation of G-Protein coupled receptors (GPCRs) leads to transactivation of the co-located cytosolic tail of RAGE, and downstream pro-inflammatory signaling. Blocking this transactivation may have a beneficial therapeutic effect.
Development Stage	Lead series
Brief Description & Differentiation	The receptor for advanced glycation end products (RAGE) is a cell surface receptor implicated in many aspects of disease. We have identified a novel mechanism whereby activation of GPCRs leads to transactivation of the co-located cytosolic tail of RAGE, and downstream pro-inflammatory signaling. We have developed and tested proof-of-principal peptide-based RAGE inhibitors that attenuate Angiotensin II-dependent inflammation and atherogenesis. • Our novel finding might explain the failed attempts to drug RAGE by targeting the extra-cellular domain. • GPCRs are the single most common target for disease-preventing therapies in modern medicine. Currently blocking GPCR signaling without disrupting the homeostatic role of these GPCRs or triggering feedback pathways is problematic. By blocking RAGE transactivation selectively, there is no feedback/escape or disruption of physiological regulation. • Our novel finding highlights the need for a dual blockade strategy i.e. blocking both transactivation and ligand mediated direct activation for effective therapeutic targeting of RAGE activation.
Research Team	Prof Merlin Thomas (Monash) and Prof Kevin Pfleger (University of Western Australia)
Intellectual Property	PCT patent application (PCT/AU2018/050883) covering peptide based modulators of RAGE activity induced by an active co-located GPCR, methods for screening and identifying RAGE modulators and method of use of the modulators for treatment have been filed.
Key Publications	Pickering et al. (2019) Transactivation of RAGE mediates angiotensin-induced inflammation and Atherogenesis. *J Clin Invest.*; *129*(1):406-421.
Future	Progress the optimization of existing peptide RAGE modulator and generate PoC in preclinical disease models. Thereafter, launch a formal preclinical and clinical drug development program.

➢ Key Data

Our novel RAGE modulator has demonstrated PoC *in vitro* and *in vivo*. They are effective in reduces plaque accumulation and renal damage in Atherosclerosis-prone apolipoprotein E-deficient mice (Apoe-KO) in both normal and diabetic setting.



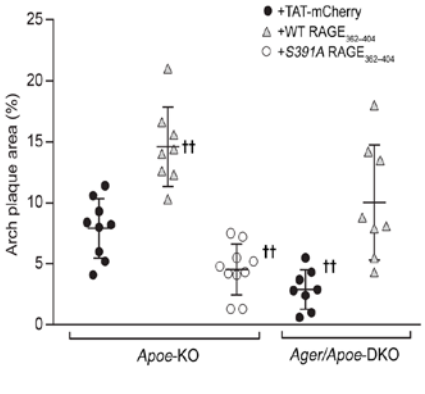


Figure 1*: In vivo* treatment effect of RAGE Modulator. Normal mice: Plaque area in aortae from Apoe-KO, Ace2/Apoe-DKO and Ager/Ace2/Apoe-TKO mice in presence or absence of mCherry-RAGE362–404 or mCherry-S391A RAGE362–404 (10 µg/kg i.p. every other day).
Diabetic mice: Plaque area in aortae from diabetic Apoe-KO and Ager/Apoe-DKO mice in presence or absence of mCherry-RAGE362–404 or mCherry-S391A-RAGE362–404 (10 µg/kg i.p. every other day).
Ager: Advanced Glycosylation End-Product Specific Receptor, Ace2: Angiotensin I Converting Enzyme 2, S391A RAGE362-404: RAGE