Baker IDI
HEART & DIABETES INSTITUTE

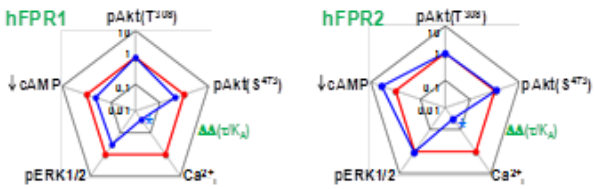
Formyl Peptide Receptor Agonists for the Treatment of Myocardial Ischemia-Reperfusion Injury

- More than 1.2 million hospitalisations due to MI in 2015 in the 7MM
- Reperfusion injury accounts for up to 50% of the final size of a myocardial infarct
- Biased small molecule FPR1 agonists provide novel triple shield therapy against myocardial reperfusion injury

SUMMARY OF INVESTMENT OPPORTUNITY:
Myocardial infarction (MI or "heart attack") is a major cause of death and disability worldwide. In patients with MI, the treatment of choice for reducing acute myocardial ischemic injury and limiting MI size is timely and effective myocardial reperfusion using either thrombolytic therapy or primary percutaneous coronary intervention. However, the process of reperfusion can itself induce cardiomyocyte death, known as myocardial reperfusion injury, for which there is still no effective therapy.
A/Prof Rebecca Ritchie has a distinguished track record with respect to annexin-A1 (ANX-A1) cardioprotection from ischemic insults. The GPCR family of formyl peptide receptors (FPRs) and activation of the cell survival kinase Akt, are both integral to ANX-A1 cardioprotection. Her work revealed that the ANX-A1/FPR system represents an exciting "druggable" target for MI, abrogating cardiomyocyte necrosis, infarct size, left ventricular (LV) inflammation, remodeling and LV contractile dysfunction in vivo. A/Prof Ritchie's team at Baker IDI, in collaboration with Monash Institute for Pharmaceutical Sciences, synthetized small molecule FPR agonist prototypes that exhibit clear, biased signaling, favoring cell survival mechanisms whilst blunting potentially deleterious pathways. Of clinical relevance, ANX-A1/FPR cardioprotection is preserved even when treatment is delayed until reperfusion. These compelling observations provide the basis for targeted development of biased, small molecule FPR agonists as a novel strategy for treating MI. We have constructed a unique set of drug screening tools and, in collaboration with the Monash Institute for Pharmaceutical Sciences, we are engaged in a program of drug discovery based on the unique biological properties of a probe compound.

TECHNOLOGY:
We discovered that *biased* signalling by the FPR1 provides cardioprotection in the context of ischaemia-reperfusion injury. We then identified a small-molecule drug candidate, BIDI-001, which acts as an FPR1 agonist with the requisite bias and shown this candidate does indeed provide cardioprotection in well-characterised animal models of ischaemia-reperfusion injury.

Figure 1: Biased profile for BIDI-001(blue), away from calcium mobilisation, compared with Cmpd 43 (red).



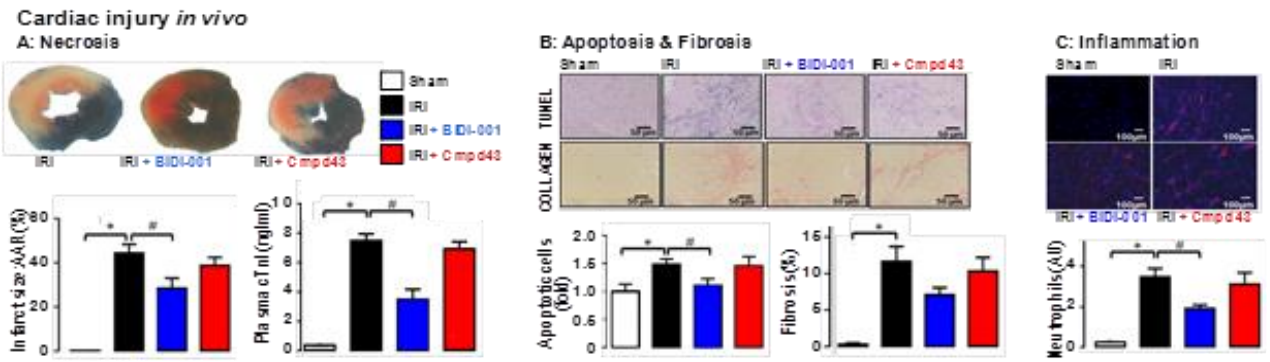


Figure 2: BIDI-001(50mg/kg/day IP) limits LV injury after IRI in mice in vivo. A) LV necrosis after 24h reperfusion, on infarct size (white, red and dark blue staining represents non-viable, ischaemic but viable, and non-risk zones, respectively) and plasma troponin; B) LV apoptosis and fibrosis after 7days reperfusion; C) LV neutrophil content after 48h reperfusion

PROBLEM / TARGET MARKET:

After an acute myocardial infarction, early and successful myocardial reperfusion with the use of thrombolytic therapy or primary percutaneous coronary intervention (PPCI) is the most effective strategy for reducing the size of a myocardial infarct and improving the clinical outcome. However, the process of restoring blood flow can induce injury. This form of myocardial injury, which by itself can induce cardiomyocyte death and increase infarct size, may in part explain why, despite optimal myocardial reperfusion, the *rate of death after an acute myocardial infarction approaches 10%*, and the *incidence of cardiac failure after an acute myocardial infarction is almost 25%*. **Studies in animal models of acute myocardial infarction suggest that reperfusion injury accounts for up to 50% of the final size of a myocardial infarct**, and in these models a number of strategies have been shown to ameliorate lethal reperfusion injury. Yet, the translation of these beneficial effects into the clinical setting has been disappointing. These failures have been attributed to a number of factors including the use of inappropriate animal MI models that poorly correlate to human, and poor clinical trial design. We believe that there are animal models which are predictive, and that candidates fail because of a lack of efficacy combined with poor clinical trial design. We can overcome both.

In the US and 5EU, the number of diagnosed prevalent cases of MI will increase from 16.7 million cases in 2015 to 20.2 million cases in 2025. In 2015, the global acute coronary syndrome (ACS, i.e. MI and unstable angina) market was worth $7.8 billion. By 2025, this global market is expected to reach $12.1 billion, at a strong Compound Annual Growth Rate (CAGR) of 4.6%.

STAGE OF DEVELOPMENT:

The single limiting factor of BIDI-001 is poor solubility. Our medicinal chemistry program will provide a pro-drug to progress to manufacture, preclinical toxicology and clinical trials.

COMPETITIVE ADVANTAGE:

- Innovative pharmacotherapy
- Novel "triple shield" therapy against MI:
  - ✓ limiting cardiac inflammation
  - ✓ preserving cardiomyocyte viability
  - ✓ preserving contractile function

INTELLECTUAL PROPERTY:

PCT entitled "a method of treatment and compounds for use therein", priority date 4th Feb 2015, jointly in the name of Baker IDI Heart and Diabetes Research Institute and Monash University.

The application claims BIDI-001, analogues and prodrugs thereof in a method of reducing the extent of ischaemia-induced myocardial tissue damage by selectively upregulating FPR1-mediated ERK signalling (ie a particular FPR1 bias).

TEAM:

Associate Professor Rebecca Ritchie is a NHMRC Senior Research Fellow and Head of the Heart Failure Pharmacology laboratory at the Baker IDI Heart and Diabetes Institute. Over the last 15 years, she has demonstrated a clear commitment to clinically-relevant cardiac research, identifying new therapeutic targets for treating cardiac pathophysiological.

Professor Jonathan Baell is an NHMRC Senior Research Fellow, Monash Larkins Fellow, Co-Director of the Australian Translational Medicinal Chemistry Facility and Full Research Professor of Medicinal Chemistry at MIPS. He is a specialist in medicinal chemistry optimization. He has 19 granted pharmaceutical patent families in a wide variety of diseases, representing compounds in preclinical and clinical development.

Dr Chengxue Helena Qin is a postdoctoral fellow in the Heart Failure Pharmacology laboratory at the Baker IDI Heart and Diabetes Institute.

KEY PUBLICATIONS:

Qin CX, *et al.*, Cardioprotective potential of annexin-A1 mimetics in myocardial infarction. *Pharmacol Ther.*, 2015

Chin KY, *et al.*, New pharmacological approaches to the prevention of myocardial ischemia-reperfusion injury. *Current Drug Targets*, 2015

Qin CX, *et al.*, Reperfusion-induced myocardial dysfunction is prevented by endogenous annexin-A1 and its N-terminal-derived peptide Ac-ANX-A1(2-26). *Br. J. Pharmacol.*, 2013

Bulluck H, *et al.*, Reducing myocardial infarct size: challenges and future opportunities. *Heart*, 2016

Jones SP, *et al.*, The NHLBI-sponsored consortium for preclinical assessment of cardioprotective therapies (CAESAR). *Circulation Research*, 2015

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