FINAL STUDY REPORT

Date: 30/09/2019

Name:

Nicola Scott (2017PRONicola Scott)

Project Title:

Phosphodiesterase 9 inhibition as a novel therapeutic strategy in heart failure

1. *Please copy the "Specific Objective(s)" statement, entered on your application form, in the space below.*

Our aims are to explore inhibition of Phosphodiesterase 9 (PDE9) as a novel treatment strategy in heart failure (HF).

We will investigate for the first time the integrated effects of acute PDE9 inhibition (PDE9-I) in normal (**Objective 1**) and HF sheep (**Objective 2**), as well as sustained PDE9-I over the development of HF to determine the impact on disease progression (**Objective 3)**.

(NB: Research Objectives were unchanged)

2. *Briefly describe how successful you were in achieving the stated objective(s). If the objective(s) was not achieved, explain why that is the case and describe what you did manage to achieve.*

PROJECT OBJECTIVES.
Objective 1: *Acute PDE9-I dose response in normal sheep* **- Study completed and published.**
Objective 2: *Acute PDE9-I dose response in heart failure sheep* **- Study completed and published.**

The data generated by Objectives 1 and 2 was combined and accepted for publication in one of the top cardiovascular journals - *Journal of the American College of Cardiology* (Impact factor 16.8). Below is the published abstract from Scott *et al*, JACC 2019;74(7): 889-901, https://doi.org/10.1016/j.jacc.2019.05.067.

Hemodynamic, Hormonal, and Renal Actions of Phosphodiesterase-9 Inhibition in Experimental Heart Failure.

Nicola J.A. Scott, Miriam T. Rademaker, Christopher J. Charles, Eric A. Espiner, A. Mark Richards.

BACKGROUND: Phosphodiesterase-9 (PDE9) reduces natriuretic peptide (NP) signaling and may be involved in the pathophysiology of heart failure (HF).
OBJECTIVES: This study investigated for the first time the integrated hemodynamic, endocrine, and renal effects of phosphodiesterase-9 inhibition (PDE9-I).
METHODS: A total of 8 normal sheep and 8 sheep with pacing-induced HF received incremental intravenous boluses of PDE9-I (30, 100, and 300 mg PF-04749982 at 1-h intervals).
RESULTS: PDE9-I dose-dependently increased plasma cyclic guanosine monophosphate (cGMP) in normal sheep ($p < 0.05$) while concurrently reducing circulating atrial natriuretic peptide levels ($p < 0.01$). Similar trends were evident in HF, resulting in significant elevations in the cGMP/NP ratio in both states ($p < 0.001$ and $p < 0.05$, respectively). PDE9-I also produced progressive falls in arterial pressure (HF: $p < 0.001$), atrial pressure (Normal: $p < 0.001$; HF: $p < 0.001$), and peripheral resistance (HF: $p < 0.001$), and transiently increased cardiac output at the top dose (Normal: $p < 0.05$; HF: $p < 0.001$). Inhibition of PDE9 had a negligible effect on circulating hormones at the lower doses, but post–high dose, acutely increased renin activity (Normal: $p < 0.001$; HF: $p < 0.05$), vasopressin (Normal: $p < 0.001$; HF: $p < 0.01$), and cyclic adenosine monophosphate (HF: $p < 0.001$). Plasma aldosterone increased briefly after high-dose
PDE9-I in normal sheep, and fell following the top dose in HF. PDE9-I dose-dependently increased urinary cGMP in both states (both $p < 0.001$). In HF, this was associated with increases in urine volume ($p < 0.01$), sodium excretion ($p < 0.01$), and creatinine clearance ($p < 0.001$).
CONCLUSIONS: PDE9-I improves NP efficacy in conjunction with beneficial hemodynamic and renal effects in experimental HF. These results support a role for PDE9 in HF pathophysiology and suggest its inhibition may constitute a novel therapeutic approach to this disease.

The quality and importance of this work is further evidenced by the publication of an accompanying editorial comment (McMurray & Docherty, *JACC* 2019;74:902-904, https://doi.org/10.1016/j.jacc.2019.07.008)
In addition, our work has spearheaded Phase-1 Clinical trials currently underway evaluating PDE9-I safety/tolerability in patients with HF.

Objective 3: *Chronic PDE9-I during HF development* **– Study incomplete*.***

***Methods & Protocol*:**
Instrumented sheep (as for Objective 2) will undergo two separate periods of rapid LV pacing (@~220 bpm) for 4 days to instigate cardiac overload and subsequent development of HF, with ten days without pacing between phases to allow recovery to a normal pre-pacing state. On initiation of pacing, the animals will receive a constant 4-day i.v. infusion of a vehicle control or the PDE9-I PF-04749982 (50mg loading dose + 500mg/day infusion) in a crossover design. Serial hemodynamic, hormonal and urine sampling will be performed throughout.

Results: Unfortunately, only one animal has successfully completed this protocol due to problems experienced with the PDE9-I compound (PF-04749982) coming out of solution during the overnight infusion period. We are currently exploring alternate vehicle options that will provide a safe and stable infusate formulation.

3. *Financial Summary.*
This project has provided salary support for Dr Nicola Scott at 0.5FTE for 2-years. The research funds have been used as outlined in the original application.

4. *Briefly describe any interesting outcomes which might not have been considered in your original objectives (if any).*

Large animal studies such as these are essential in understanding the combined effects of any potential new treatment, and are a requisite step preceding human investigations. The findings to date have expanded our understanding of the role of PDE9 inhibition in normal physiology and HF. The striking renal response, consistent with previous reports that renal PDE9 activity is markedly increased in heart failure, supports further investigation in acutely decompensated HF. Further research into PDE9-I, possibly in combination with other agents, has real therapeutic potential in the treatment of HF. In addition, we are also considering administration of PDE9-I post-myocardial infarction - a setting of cardiac injury which often leads onto the development of HF.