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Buccal delivery of the GLP-1 against exenatide using ArisCrown technology

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Arisgen has developed a novel lipid based formulation technology that can concomitantly promote permeation and overcome poor peptide oral bioavailability. This technology is called ArisCrown and is based on the selective and reversible masking of peptide functional groups by novel and proprietary biodegradable cyclic (BCC) compounds. The BCC/peptide complex is combined with a range of known GRAS lipidic components and the final formulation optimized to maintain peptide stability, solubility and conformation. Our first clinical application of the technology will be a formulation of exenatide that can be delivered as a sub-lingual fast-melt tablet to replace the need for daily injections. We have demonstrated in mice that sub-lingual administration of ArisCrown Exenatide (ARG011) is able to control glycaemia, as determined by glucose and insulin regulation, as well as food intake, in a manner equivalent to i.p. injection of unformulated peptide. In addition in monkey studies we have demonstrated that ARG011 combined in a buccal patch is able to deliver the peptide and control PD markers of glycaemia equivalent to s.c. injected peptide. We are concluding our pre-clinical assessment of the technology. Data on pre-clinical safety and tolerability will be presented as well as our immediate clinical plans.

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Ruboxistaurin reduces myocardial ischemia/reperfusion injury via a caveolin-3-dependent mechanism in diabetic rats

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Background: Activation of PKCβ has been shown to exacerbate myocardial ischemia/reperfusion (I/R) injury. Caveolin-3 (Cav-3) specifically expressed in cardiomyocytes is critical in signal transduction of PKCβ in cardiomyocytes. The present study tested the hypothesis that ruboxistaurin (RBX), a selective PKCβ inhibitor, may attenuate myocardial I/R injury in Diabetes through a Cav-3-dependent mechanism.

Methods: Sprague-Dawley rats were treated with RBX (1 mg/kg/day) for 4 weeks, starting from 1 week after streptozotocin injection. Diabetic hearts were subjected to I/R achieved by the left descending coronary artery ligation followed by reperfusion. Cardiac function was measured using a pressure-volume conductance catheter. Cardiac H9C2 cells were exposed to high glucose (30mM) and subjected to hypoxia followed by reoxygenation (H/R) in the presence or absence of PKCβ2 siRNA and Cav-3 siRNA. Cell apoptosis and mitochondrial injury were assessed by TUNEL and JC-1 staining respectively.

Results: RBX significantly decreased myocardial infarct size from 35±5% in the control groups to 49±3% and cardiac dysfunction and increased Cav-3 and phosphorylated Akt (p-Akt) in diabetic rats (All $P<0.05$ vs. control). PKCβ2 siRNA significantly decreased H/R-induced H9C2 cell injury in vitro under high glucose conditions evidenced as decreased TUNEL-positive and JC-1 monomeric cells, whereas Cav-3 siRNA significantly increased H/R-induced H9C2 cell injury (All $P<0.05$ vs. control). Interestingly, Cav-3 siRNA significantly reduced p-Akt and increased post-hypoxic mitochondrial injury, concomitantly with a reduction in PKCβ2 phosphorylation.

Conclusions: PKCβ2 plays an obligatory role in myocardial I/R injury in Diabetes. The Cav-3-dependent Akt activation contributes to RBX-induced cardio protection against I/R.

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