UNIVERSITY OF LEEDS

This is a repository copy of *Placental Homing Peptide-microRNA-145 Inhibitor Conjugates for Targeted Enhancement of Placenta Growth*.

White Rose Research Online URL for this paper:
http://eprints.whiterose.ac.uk/92247/

Version: Submitted Version

**Article:**
Beards, F, Jones, L, Charnock, J et al. (2 more authors) (2015) Placental Homing Peptide-microRNA-145 Inhibitor Conjugates for Targeted Enhancement of Placenta Growth. Reproductive Sciences, 22 (S1). 77A - 78A. ISSN 1933-7205

https://doi.org/10.1177/1933719115579631

**Reuse**
Unless indicated otherwise, fulltext items are protected by copyright with all rights reserved. The copyright exception in section 29 of the Copyright, Designs and Patents Act 1988 allows the making of a single copy solely for the purpose of non-commercial research or private study within the limits of fair dealing. The publisher or other rights-holder may allow further reproduction and re-use of this version - refer to the White Rose Research Online record for this item. Where records identify the publisher as the copyright holder, users can verify any specific terms of use on the publisher's website.

**Takedown**
If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.

White Rose university consortium
Universities of Leeds, Sheffield & York

eprints@whiterose.ac.uk
https://eprints.whiterose.ac.uk/

**Placental homing peptide-microRNA 145 inhibitor conjugates for targeted enhancement of placenta growth**

F Beards, L Jones, J Charnock, K Forbes, LK Harris
Maternal and Fetal Health Research Centre, University of Manchester, Manchester, UK

## Introduction

A major cause of pregnancy complications is suboptimal placental growth, but no treatments are currently available. We have previously shown that microRNA (miR)-145 regulates human cytotrophoblast (CTB) proliferation and that the homing peptide sequence CCGKRK is capable of selectively delivering payloads to the placental surface. To reduce the risk of detrimental side effects associated with systemic drug administration in pregnancy, we have developed a novel placental homing peptide-miR145 inhibitor conjugate for targeted manipulation of intrinsic placental growth signalling. Here we test whether this small molecule therapeutic can enhance placental growth in-vitro and in-vivo.

## Methods

Scrambled- or miR-145 inhibitor-CCGKRK conjugates were synthesised from peptide nucleic acids. Human placental explants were cultured with vehicle, scrambled conjugate or miR-145 inhibitor conjugate (50nM); miR expression was measured after 24h by qPCR and CTB proliferation was quantified after 48h, by immunostaining for Ki67. C57 mice were injected with scrambled- or miR-145 inhibitor conjugates on embryonic (E) day 12.5, E14.5 and E16.5 of pregnancy; fetal and placental weights were assessed on E18.5.

## Results

miR-145 expression was reduced (n=3) and CTB proliferation was significantly increased in first trimester human placental explants treated with the miR-145 conjugate, compared to the scrambled control (n=5, $P<0.05$; Friedman test). No effect was seen in term placental explants, which was as expected as basal miR-145 expression was low at this gestation. miR-145 expression was detected in the mouse placenta (E12.5-E18.5) and was significantly reduced by miR-145 inhibitor conjugates. Preliminary data from the treatment study (n=5/group) showed that miR-145 inhibitor conjugates did not cross the placenta and did not alter litter size or number of resorptions compared to scrambled control, suggesting that these drugs are safe in pregnancy. Whilst placental and fetal weights were not significantly altered by the miR-145 inhibitor conjugate, frequency distribution curves showed fewer fetuses and placentas falling below the $5^{th}$ centile after treatment.

**Discussion**

Here we show that a homing peptide-miR-145 inhibitor conjugate can enhance CTB proliferation in the first trimester of human pregnancy and alter placental and fetal weight distribution in mice. miR-145 inhibitor conjugates may represent a novel strategy for treating suboptimal placental growth.

**Key words:** placenta, microRNA, drug therapy