FKBPL: NOVEL TARGET FOR OBESITY AND METABOLIC SYNDROME

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The obesity pharmaceutical market is projected to grow from $407m in 2012 to $8.4b by 2022. 40–70% of inter-individual variability in BMI is attributable to genetic factors. Although treatment strategies are available, the side effects associated with their use necessitates development of novel therapies.

- **FK**506 **b**inding **p**rotein **l**ike – FKBPL is a member of the immunophilin protein family
- Mice lacking one FKBPL allele are highly susceptible to obesity and metabolic syndrome
- A deficiency of serum FKBPL is associated with childhood obesity
- Preliminary data indicates that treatment with an FKBPL peptide mimetic or FKBPL gene therapy are novel therapeutic options for obesity and metabolic syndrome

VALUE PROPOSITION

We have had a long-standing interest in the **FKBPL** gene. Using funding from BBSRC, we developed a heterozygous FKBPL$^{+/-}$ mouse (loss of both alleles was embryonically lethal) to improve our understanding of the role of FKBPL in normal development. FKBPL$^{+/-}$ mice began to develop obesity on a normal diet between 2-6 months (Fig. 1) and metabolic syndrome (Fig. 1 b,c). In addition, a deficiency in serum FKBPL is significantly associated with childhood obesity (Fig. 2).**Together, this data are indicates that FKBPL is a promising novel drug target for obesity and metabolic syndrome.**

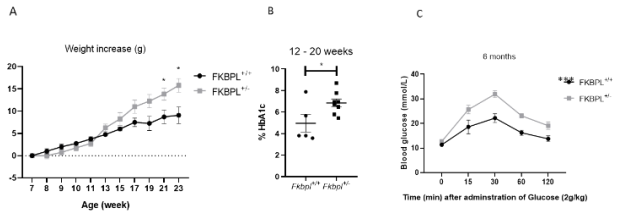

Fig 1. **Loss of one allele of FKBPL predisposes mice to obesity and metabolic syndrome on a normal chow diet. A** - FKBPL$^{+/-}$ mice weigh more than WT counterparts, **B** - FKBPL$^{+/-}$ mice have a higher %HbA1c and **C** -reduced glucose tolerance (n >5 mice/ group)

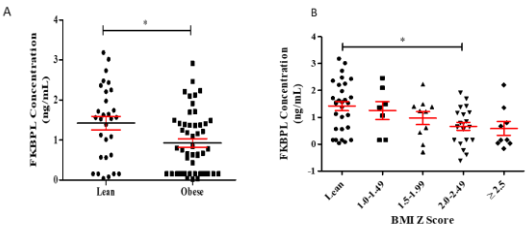

Fig 2. **Figure 1 Serum FKBPL concentration in obese children, aged 7-18 years, and correlated to BMI Z Score and serum leptin levels A)** Serum FKBPL concentrations (ng/mL) for obese children, aged 7-18 years, (n=48), assessed via ELISA. **B)** Serum FKBPL concentrations (ng/mL) for lean (n=30) and obese children, aged 7-18 years, with a BMI Z Score in the range 1.0-1.49 (n=7), 1.5-1.99 (n=10), 2.0-2.49 (n=21) or ≥ 2.5 (n=9).

To investigate if FKBPL could be used therapeutically as an anti-obesity agent a peptide mimetic and nanoparticle gene therapy has been utilised. A peptide mimetic of FKBPL inhibits diet-induced weight gain in FKBPL$^{+/-}$ mice, and improves glucose intolerance (Fig. 3). Furthermore, delivery of plasmid of FKBPL is also inhibits diet induced weight gain (Fig. 4)

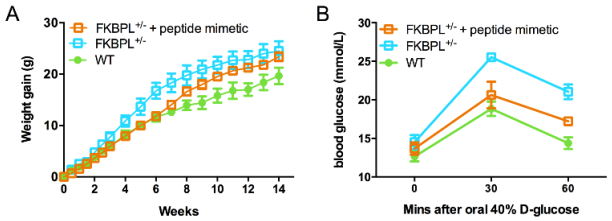

Fig 3. **A peptide mimetic of FKBPL protects from diet-induced obesity .and metabolic syndrome A** - FKBPL$^{+/-}$ mice gain weight more quickly than WT; this weight gain is partially reversed by a peptide mimetic of FKBPL. **B** - FKBPL$^{+/-}$ mice display intolerance to glucose, which is revered by treatment with the FKBPL peptide.

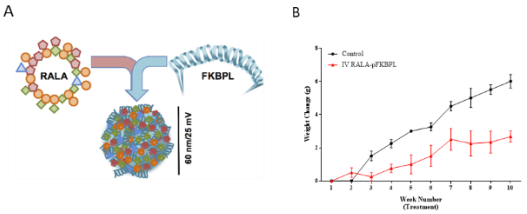

Fig 4. **Gene therapy delivery of plasmid FKBPL protects from diet induced obesity. A** - RALA/FKBPL nanoparticles are formulated by mixing cationic RALA with anionic FKBPL DNA, producing nanoparticles suitable for cellular delivery. B – Wild type C57/6N mice treated with RALA/FKBPL nanoparticles have reduce weight gain following high fat diet. (n>5 mice/group)

INTELLECTUAL PROPERTY

- Use of RALA for the delivery of anionic cargo is protected under patent WO 2014087023 A1.
- Use of FKBPL in oncological/ocular conditions is protected by patent WO 2007141533.
- A patent that describes a role for FKBPL in obesity has been filed (UK patent application no. 1617726.3).

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