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. Obesity is a global health crisis and control of excess body fat is one of the greatest healthcare challenges of our time. The global obesity prevalence has nearly tripled since 1975 and, with detrimental effects on all organ systems leading to worsening disease state and rising costs of care. Obesity has an estimated heritability of~40–70% and genetic variation in FKBPL is a novel factor in determining body mass index.

- **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
- FKBPL regulates BMI independent of food intake by modulation of adipogenesis and inflammation
- FKBPL based therapeutics have potential efficacy in inflammatory disorders such as psoriasis and rheumatology

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.**

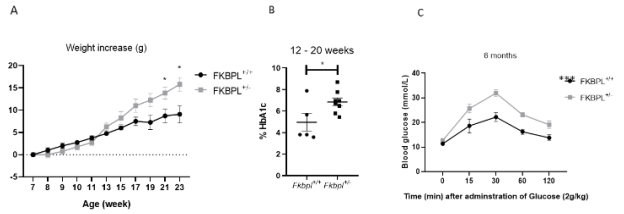

Fig 1. **Loss of one allele of FKBPL predisposes mice to obesity and metabolic syndrome on a normal chow diet. A)** - FKBPL$^{+/-}$ mice weigh more than WT counterparts, **B)** - FKBPL$^{+/-}$ mice have a higher %HbA1c and **C** -reduced glucose tolerance (n >5 mice/ group)

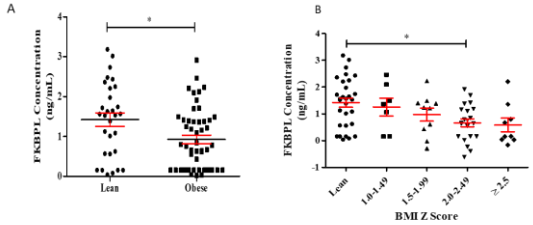

Fig 2. **Figure 1 Serum FKBPL concentration in obese children, aged 7-18 years, and correlated to BMI Z Score and serum leptin levels A)** Serum FKBPL concentrations (ng/mL) for obese children, aged 7-18 years, (n=48), assessed via ELISA. **B)** Serum FKBPL concentrations (ng/mL) for lean (n=30) and 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). FKBPL regulate body mass index independent of food intake and through regulation of adipogenesis and inflammation (Fig. 5).

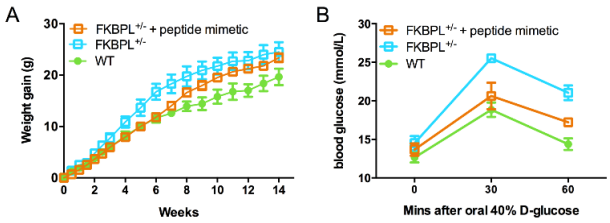

Fig 3. **A peptide mimetic of FKBPL protects from diet-induced obesity .and metabolic syndrome A**) FKBPL$^{+/-}$ mice gain weight more quickly than WT; this weight gain is partially reversed by a peptide mimetic of FKBPL. **B)** FKBPL$^{+/-}$ mice display intolerance to glucose, which is revered by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

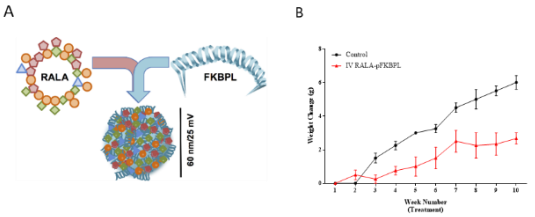

Fig 4. **Gene therapy delivery of plasmid FKBPL protects from diet induced obesity. A)** RALA/FKBPL nanoparticles are formulated by mixing cationic RALA with anionic FKBPL DNA, producing nanoparticles suitable for cellular delivery. **B)** Wild type C57/6N mice treated with RALA/FKBPL nanoparticles have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

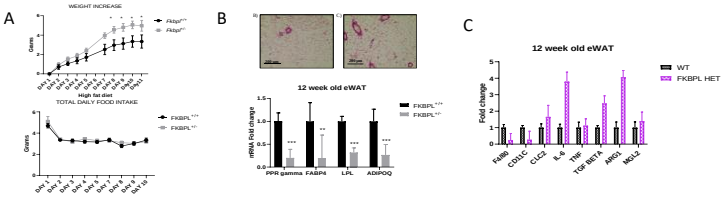

Fig 5: **FKBPL regulates body mass index independent of food intake through regulation of adipogenesis and inflammation. A)** *Fkbpl*$^{+/-}$ fed a high fat diet have a significant increase in weight compared to *Fkbpl*$^{+/+}$ despite having similar food intake. **B)** Adipose tissue from *Fkbpl*$^{+/-}$ mice displays hypertrophic adipocytes and decreased expression of gene associated with adipogenesis compared to *Fkbpl*$^{+/+}$ mice. **C)** Adipose tissue from *Fkbpl*$^{+/-}$ mice has enhanced expression of genes associated with inflammation compared to *Fkbpl*$^{+/+}$ mice.

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INTELLECTUAL PROPERTY

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

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