Preclinical Studies on New Treatments for Cystinosis in Cystinotic Rats

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The only treatment available for cystinosis is the cystine-depleting drug Cysteamine. With early intervention and strict compliance of an intense dosing schedule (up to four times a day), this drug can delay end stage kidney disease (ESKD) by six to ten years. Despite its ability to reduce cystine, Cysteamine has many disadvantages, such as a need for large doses due to its short half-life, its foul taste and resulting nausea, unpleasant body odour, and gastrointestinal damage, which all negatively affect drug adherence. Thus, there is an **urgent need for better therapies** that 1) address the side-effects of Cysteamine and 2) address the fact that cystine depletion alone does not result in prevention of ESKD. To address 1), our collaborator Professor Newell with the late Prof Roz Anderson, developed a cysteamine prodrug called CF10 that has comparable cystine-depleting activity as Cysteamine (as measured in cell models) but far less side-effects (low odour, weak taste, no gastrointestinal damage). To address 2), we discovered that a drug combination of cysteamine and the mTOR inhibitor, Everolimus, can correct the cystinotic cell phenotype in stem cell and kidney organoid models.

To evaluate the therapeutic potential of new therapies *in vivo* we have developed a rat model of cystinosis that very closely recapitulates the human disease and is an excellent model for preclinical drug studies. Using this model, we performed 6-month drug studies to compare equal doses of Cysteamine and CF10 at reducing cystine levels and to evaluate the potential of a combination treatment to prevent kidney dysfunction. For each study body weight was measured weekly, and urine and blood were collected monthly for analysis. Tissues were collected for cystine measurements and histology at the end of the study.

In our CF10 vs Cysteamine study, we have found that delivery of CF10 for 6-months to cystinotic rats is therapeutically equal to delivery of Cysteamine at the same dose for 6-months. Specifically, we found that CF10 was equal to Cysteamine in its ability to reduce cystine levels and preserve kidney function when measuring urine output, water intake and Fanconi syndrome markers and in preserving kidney health at a histological level. These results suggest that CF10 has the potential to replace Cysteamine as a treatment for cystinosis and improve the quality of life of patients by offering the same benefits of Cysteamine without the negative side effects.

In our combination treatment study, we found that combination treatment of Cysteamine and Everolimus resulted in a superior reduction in tissue cystine levels, urine output, water intake and a superior improvement in gross kidney health compared to Cysteamine or Everolimus treatment alone. These results demonstrate the potential of a Cysteamine/Everolimus dual therapy to improve the treatment of cystinosis.

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