**In Vitro Evaluation of Novel Cysteamine Prodrugs Targeted to γ-Glutamyl Transpeptidase**

**R.J. Anderson, S. Cannell, P.W. Groundwater, P. Suryadevara, W. van’t Hoff**

Sunderland Pharmacy School, University of Sunderland, Sunderland, SR1 3SD, UK and 4Great Ormond Street Hospital, London, UK

**Aims**

The overall aim of this work is to create novel prodrugs for cysteamine to increase tolerability, efficiency and patient compliance by:

- Diminishing the side effects associated with standard cysteamine treatment
- Improving the absorption and bioavailability of cysteamine and thus decreasing the quantity and frequency of dosing
- Adequately controlling cellular cystine levels to diminish the serious complications associated with disease progression

This will be achieved by:

- Preserving the basic structure of cysteamine, which is essential to its mode of action
- Targeting the prodrugs to γ-glutamyl transpeptidase (GGT), an important enzyme in the glutathione cycle, with high expression on the surface of particular cells (e.g., kidney, liver and pancreatic cells).

**BACKGROUND**

Cystinosis, a rare autosomal recessive disorder, is characterised by the accumulation of cystine in the lysosomes of most tissues. The condition has been linked to mutations in the CTNS gene found on chromosome 17p13, which encodes for cystinosin, a lysosomal membrane transport protein responsible for the passage of cystine from the lysosome back into the cytosol where cystine can be recycled for protein synthesis and the glutathione cycle. As a result, the cystine content of leukocytes and cultured fibroblasts from cystinotic patients is 50 to 100 times the normal levels.  

**RESULTS & DISCUSSION**

**Figure 1:** A Overlaid of L-lysine with L-cysteine-cysteamine dimer showing similarity in shape, size and relative position of functional groups.

**Figure 2:** Prodrugs (1-9) structure – esterification of the free thiol and carboxyl groups of γ-glutamyl-cysteamine derivatives, such as γ-glutamyl derivatives, which are more resistant to proteolytic degradation due to the unusual amide linkage through the γ-carboxyl group, may further address these concerns. In fact, γ-glutaryl derivatives are expected to survive enzymatic attack hydrolysis because of enzymes specific for γ-glutaryl derivatives, such as glutathione (GGT), an essential enzyme of the glutathione cycle.

GGT is found on the surface of most cells and is found in high concentrations on the surface of kidney, liver, skin and pancreatic cells, thus it provides a suitable target for γ-glutamyl-cysteamine prodrugs. Interactions of the prodrugs with GGT is expected to result in the internalisation of the prodrugs and intracellular release of glutathione and cysteamine.

**REFERENCES**

- **Acknowledgements**

We are indebted to the Cystinosis Foundation UK for their financial support and to PS.