IDENTIFICATION OF POTENTIAL URINARY BIOMARKERS FOR THE MANAGEMENT OF PATIENTS WITH FABRY DISEASE

Manwaring Victoria[1], Mills Kevin[1], Heywood Wendy[1], Bainbridge Katie[2], Winchester Bryan[2], Vellodi Ashok[1], Burke Derek[2] and Heales Simon[1, 2]

[1]Clinical and Molecular Genetic Unit, UCL Institute of Child Health, London
[2]Enzyme Unit, Inherited Metabolic Diseases Section, Great Ormond Street Hospital for Children, London.
v.manwaring@ich.ucl.ac.uk

Fabry Disease (FD)

UCL

Pathophisiology

- X-linked Lysosomal Storage Disorder (LSD)
- Deficiency of the enzyme *α*-galactosidase A (*α*-GAL).
- Intracellular accumulation of ceramidetrihexoside (CTH)

Epidemiology

- Incidence is reported to range from 1/40,000 to 1/117,000
- Distribution is panethnic

Clinical Presentation

- Symptoms are variable developing in childhood, progressing with advancing age

Diagnosis

- *α*-GAL activity measured using the fluorogenic substrate 4MU

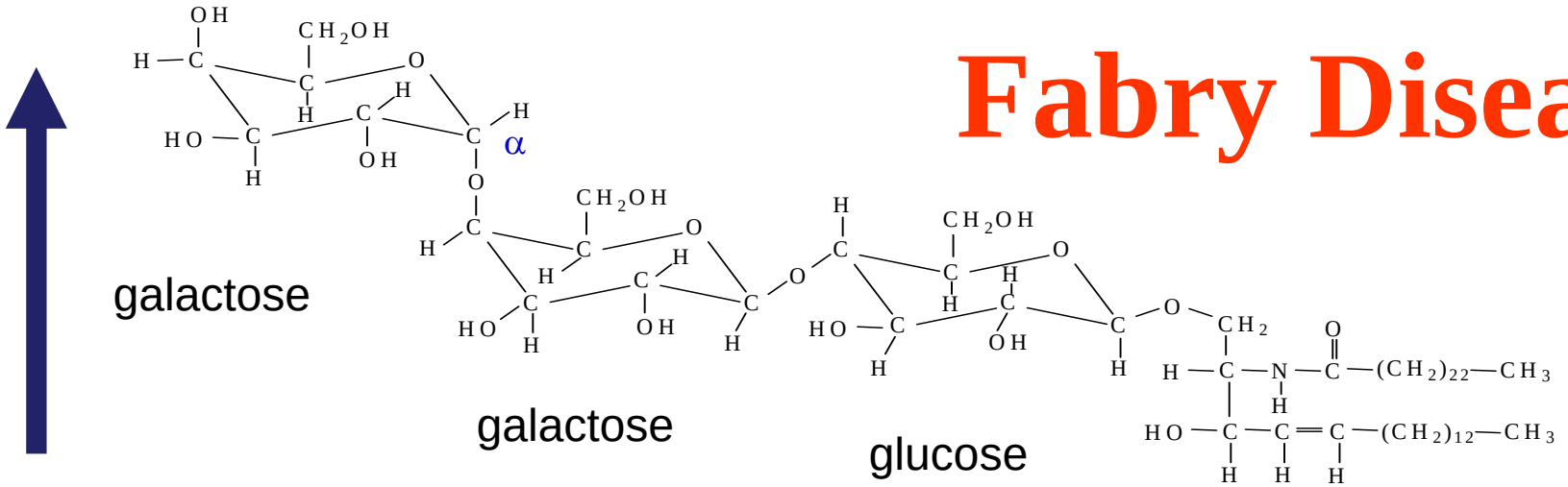
Treatment

- Enzyme Replacement Therapy (Fabrazyme, Replagal)

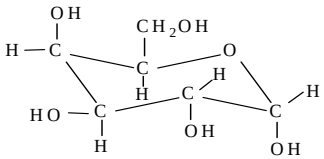
Monitoring

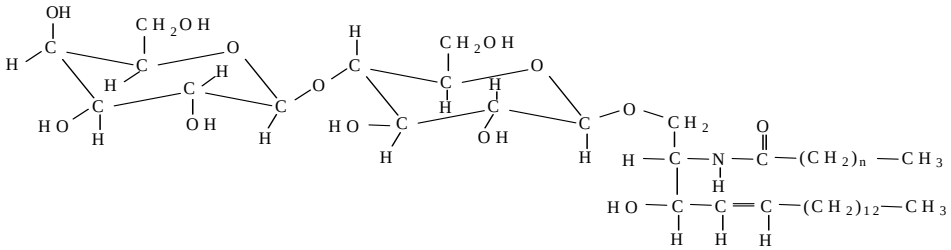
- Urine or plasma CTH assay

Fabry Disease



α-galactosidase





Fabry Disease (FD)

UCL

Pathophisiology

- X-linked lysosomal storage disorder
- Deficiency of the enzyme *α*-galactosidase A (*α*-GAL).
- Intracellular accumulation of neutral glycosphingolipids (primarily ceramidetrihexoside, CTH) in multiple cell types.

Epidemiology

- Incidence is reported to range from 1/40,000 to 1/117,000
- Distribution is panethnic

Clinical Presentation

- Symptoms are variable developing in childhood, progressing with advancing age

Diagnosis

- *α*-GAL activity measured using the fluorogenic substrate 4MU

Treatment

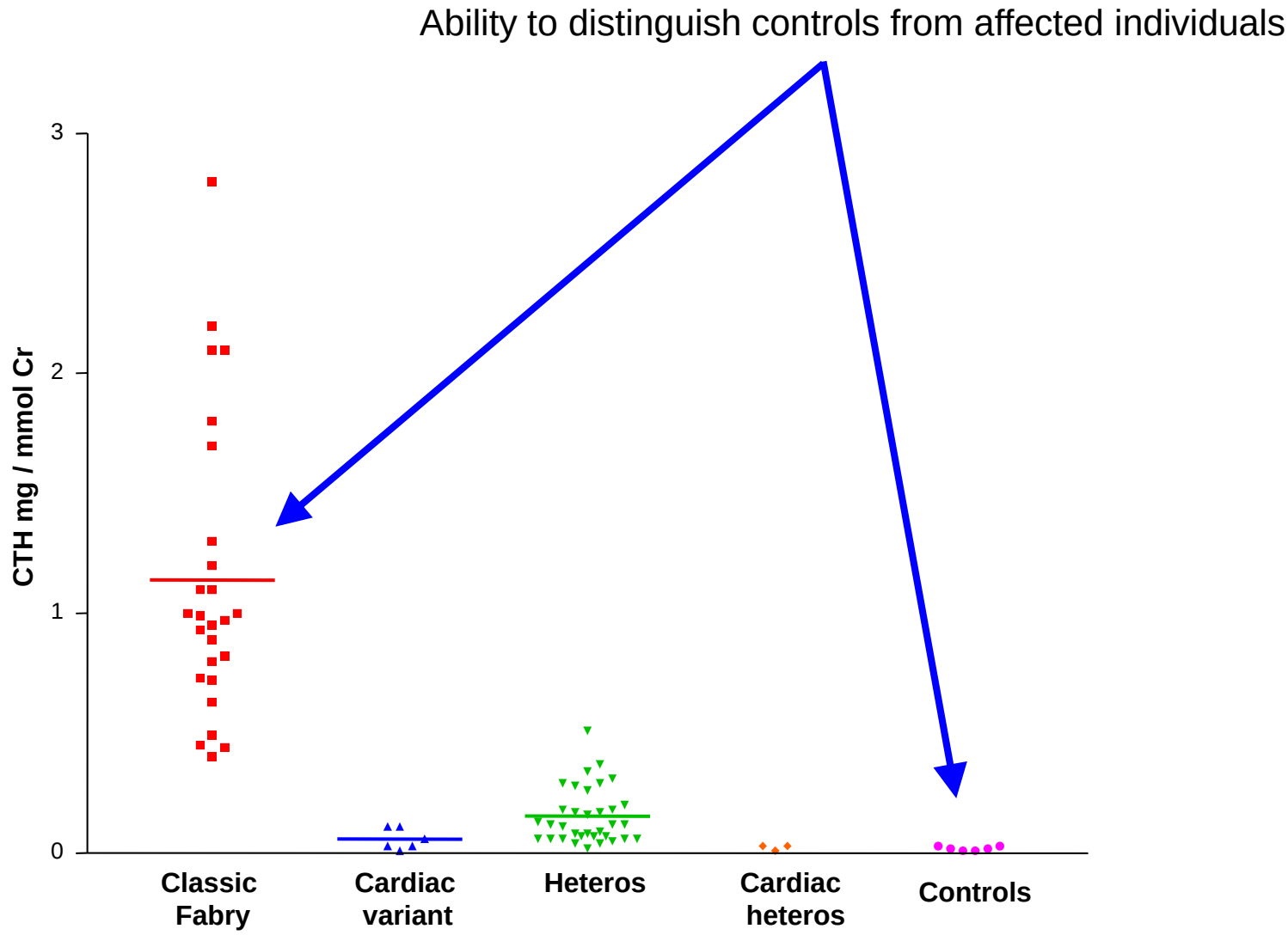
- Enzyme Replacement Therapy (Fabrazyme, Replagal)

Monitoring

- Urine or plasma CTH assay

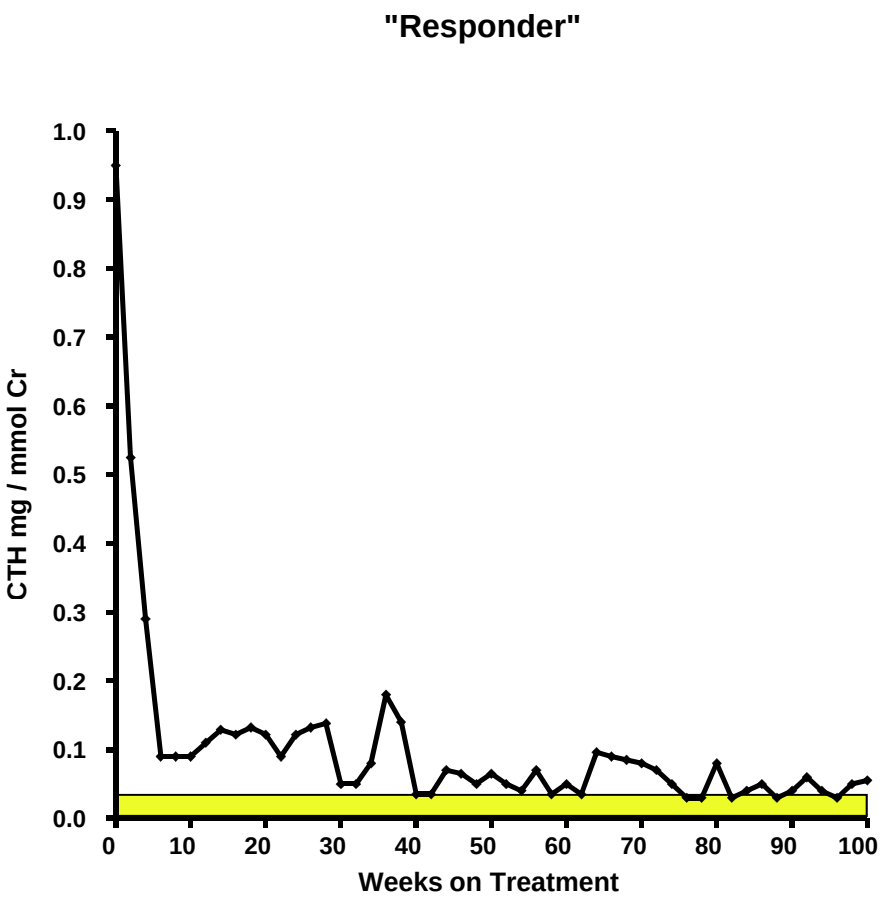
Analysis of Fabry and Control Urine Using LC-MS/MS

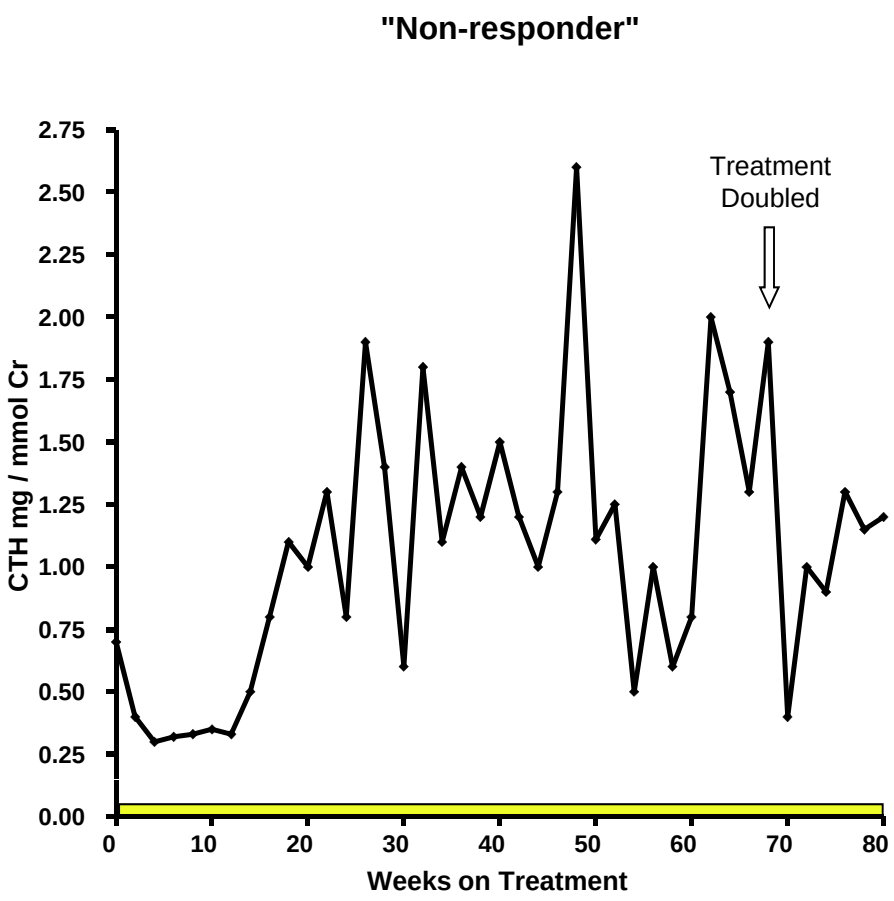
UCL



Response to Enzyme Replacement Therapy

UCL

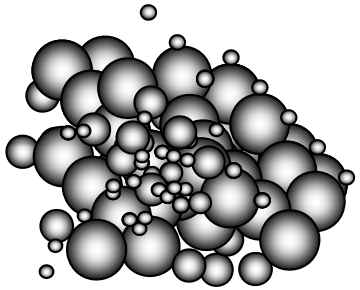




Proteomics

UCL

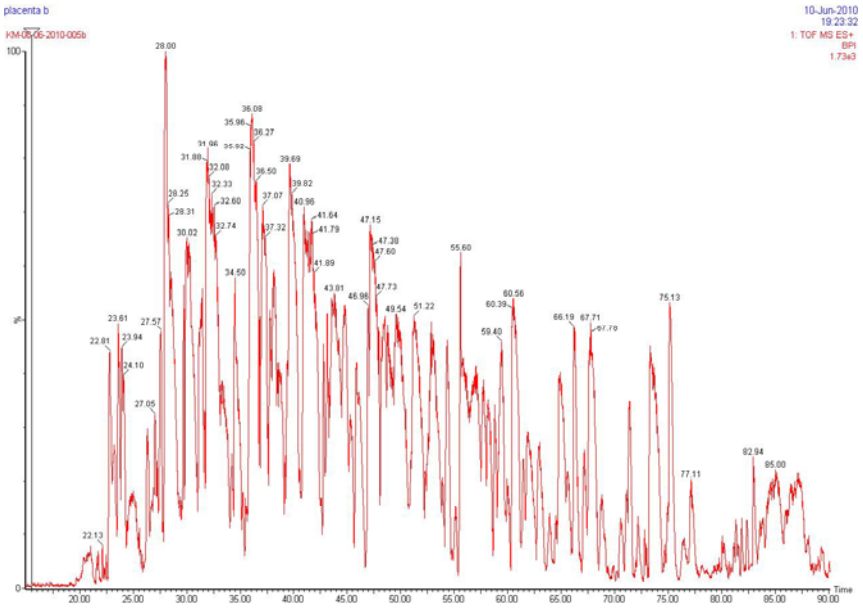
Protein
Purification (4ml)



Tryptic
Digestion

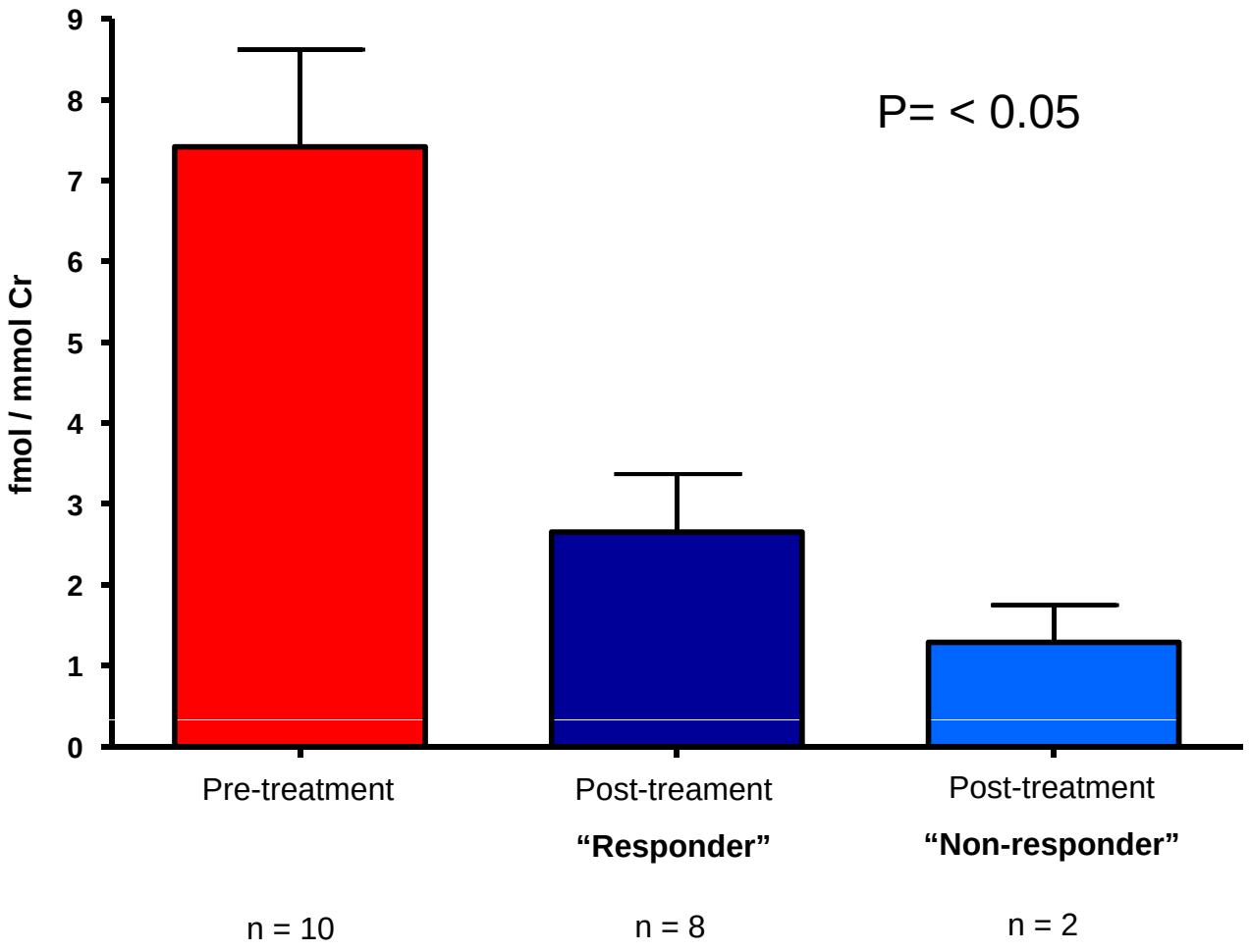
Sequencing
(2 hours)

Quantitation
& Identification



Proactivator Polypeptide – “Prosaposin”

UCL



Conclusions and Future Work

UCL

Conclusions

- Prosaposin may be a useful “biomarker” for monitoring ERT in Fabry disease and perhaps other lysosomal disorders.
- Discovery of several new biomarkers for which have implications for clinical outcomes associated with Fabry disease.
- The presence of proteins in urine without corresponding plasma results requires caution in over interpretation.

Future Work

- Analyse further samples (plasma and urine) to confirm results observed.
- Correlate proteins observed to clinical outcome.
- Develop a rapid, simple test to quantitate prosaposin which can be used in addition to urinary CTH for monitoring therapy.

Acknowledgements

With Many Thanks to

Great Ormond Street Hospital

Derek Burke
Katie Bainbridge
Bryan Winchester
Simon Heales

Institute of Child Health

Wendy Heywood
Ashok Vellodi
Kevin Mills