Developing new therapies for Batten Disease

H2020-PHC-14-2015
New therapies for rare diseases
GA no. 666918

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Academic Partners
University College London – UK
Royal Veterinary College - UK
Manchester Met University – UK
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TIGEM, Naples - Italy

Industry Partners
Pronexus - Sweden
Orphazyme - Denmark
LEITAT - Spain
Acureomics - Sweden
OSI - Latvia
**BATCure Concept**

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<td>Identification of Surrogate Markers</td>
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**CLN3, CLN6, CLN7**

- Transmembrane: CLN3, CLN6, CLN7, CLN8
- Soluble lysosomal: CLN1, CLN2, CLN5
### BATCure work packages

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<td>Induced pluripotent stem cells (iPSC), transgenic zebrafish, transgenic yeast</td>
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**Supporting Work Packages:**
- Patients’ Organisation involvement
- Management
BATCURE CONCEPT

**SMALL MOLECULE**
UCL, AcureO, USAL, Orphazyme
Leads that rescue yeast & zebrafish models
Leads from disease biology

**GENE THERAPY**
UCL
Toxicity CLN3, CLN6
Vectors CLN3, CLN6

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**Disease Models**
**Identification of Surrogate Markers**
**Lead Identification & Optimization**
**Drug & Gene Therapeutic Strategies**
**Prepare for Clinical Trials**
MMU – What do we do?

WP01- New models for Batten disease
Stem cells drive human development
Stem cells drive human development and maintain healthy organs
Stem cell differentiation: A one way street?

Waddington’s epigenetic landscape model
Stem cell differentiation: A one way street?

Waddington’s epigenetic landscape model
induced Pluripotent Stem Cells (iPSC)
Turning pluripotent stem cells into neurons

Embryonic Stem Cell → Neuroepithelial Cell → Neural Stem Cell → Neural Progenitor Cell → Neuron

D0 → D6 → D10 → D13+ → +28D

ESC → NEC → NSC → NPC → Neuron
Developing new therapies for Batten disease using iPSC

CLN3, 6 & 7

- Better understanding of the disease
- Evaluating new drug targets
- Gene therapy efficacy
DNA: The genetic code to make proteins
RNA: A mobile copy of the DNA encoding a gene
Protein: The cells building blocks
Batten disease at the cell level

DNA: The genetic code to make proteins
RNA: A mobile copy of the DNA encoding a gene
Protein: The cells building blocks
DNA codes for genes
Genes to proteins

Promoter

Gene

Transcription

RNA Splicing

mRNA

Translation

Protein
Genes to proteins - CLN

[Diagram showing the process of gene expression]

1. **Promoter**
2. **Gene**
   - **Transcription**
   - **RNA Splicing**
   - **mRNA**
   - **Translation**
   - **CLN**

[Diagram details showing the process of gene expression and the resulting CLN]
Batten disease at the cell level

Lysosome
iPSC derived neurons as a drug screening platform

Patient iPSC-derived neurons

Drug application

Control iPSC-derived neurons

By far the best control iPSC for comparison are from siblings
European collaboration benefits Batten disease research
My own journey in Batten disease research

Genetic Heterogeneity in Neuronal Ceroid Lipofuscinosis (NCL): Evidence That the Late-Infantile Subtype (Jansky-Bielschowsky Disease; CLN2) Is Not an Allelic Form of the Juvenile or Infantile Subtypes
Ruth Williams,* Joui Vesa,† Irma Jarvelä,‡ Tristan McKay,* Hannah Mitchison,* Elna Helseth,† Andrew Thompson,§ David Callen,‖ Grant Sutherland,† David Luna-Battadano,‖ Ray Stalling,‖ Leena Pelkonen,† and Mark Gardiner*†

Journal of Inherited Metabolic Disease, 1993;16(2):342-4. Linkage analysis of late-infantile neuronal ceroid-lipofuscinosis (CLN2) using markers on chromosome 16p.
Williams R†, Mitchison H, McKay T, Jarvelä I, Gardiner RM.


Fine Genetic Mapping of the Batten Disease Locus (CLN3) by Haplotype Analysis and Demonstration of Allelic Association with Chromosome 16p
Microsatellite Loci
Hannah M. Mitchison, Andrew D. Thompson, John C. Mulley, Helen M. Kozman, Rob I. Richards, David F. Callen, Ray L. Stallings, Norman A. Doggett, John Attwood, Tristan R. McKay, Grant R. Sutherland, R. Mark Gardiner
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My own journey in Batten disease research