Developing new therapies for Batten Disease

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

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 666918

Generating human cell models of Batten disease (BD)

Lorna FitzPatrick PhD.

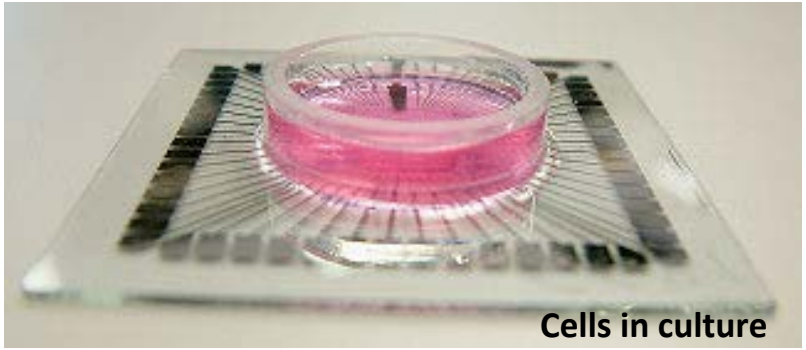
Overview

- What is a model and why do we need new ones for BD?
- Generating induced pluripotent stem cells from patient skin cells
- Genome editing in human embryonic stem cell to mimic patient cells

Disease models

- A model of disease is either an animal or cells that display some or all of the symptoms that are found in the actual human disease.

Animal models



Cells in culture

Disease models

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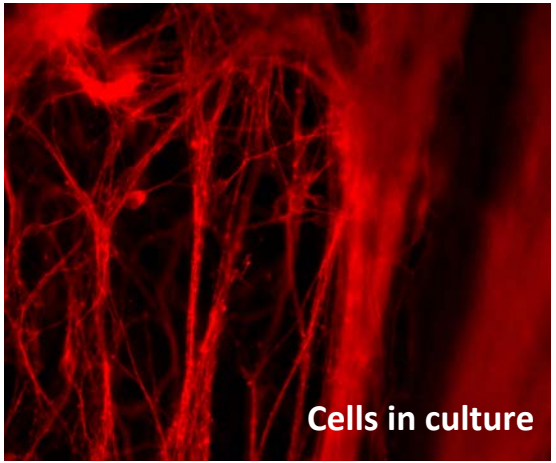
Animal models



Cells in culture

Which is best for Batten disease?

- Behavioural and motor skills

- Long time to display symptoms
- Costly
- Does not display retinal pathology
- Difficult to do large scale drug screening

- Quick development

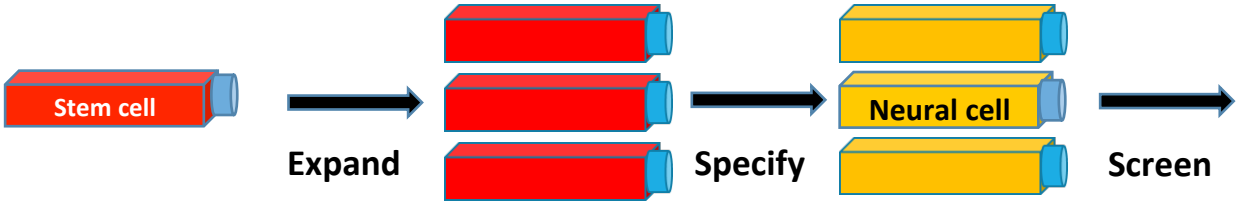
- No lysosomal build up
- Simple organism
- Low throughput
- Large culling

Could stem cells be an ideal replacement model?

- The aim of my funding is to generate stem cell models of Batten disease.
- The cells are shipped to other partners funded by Horizon 2020 for drug screening and functional analysis.

Stem cells as a model of BD

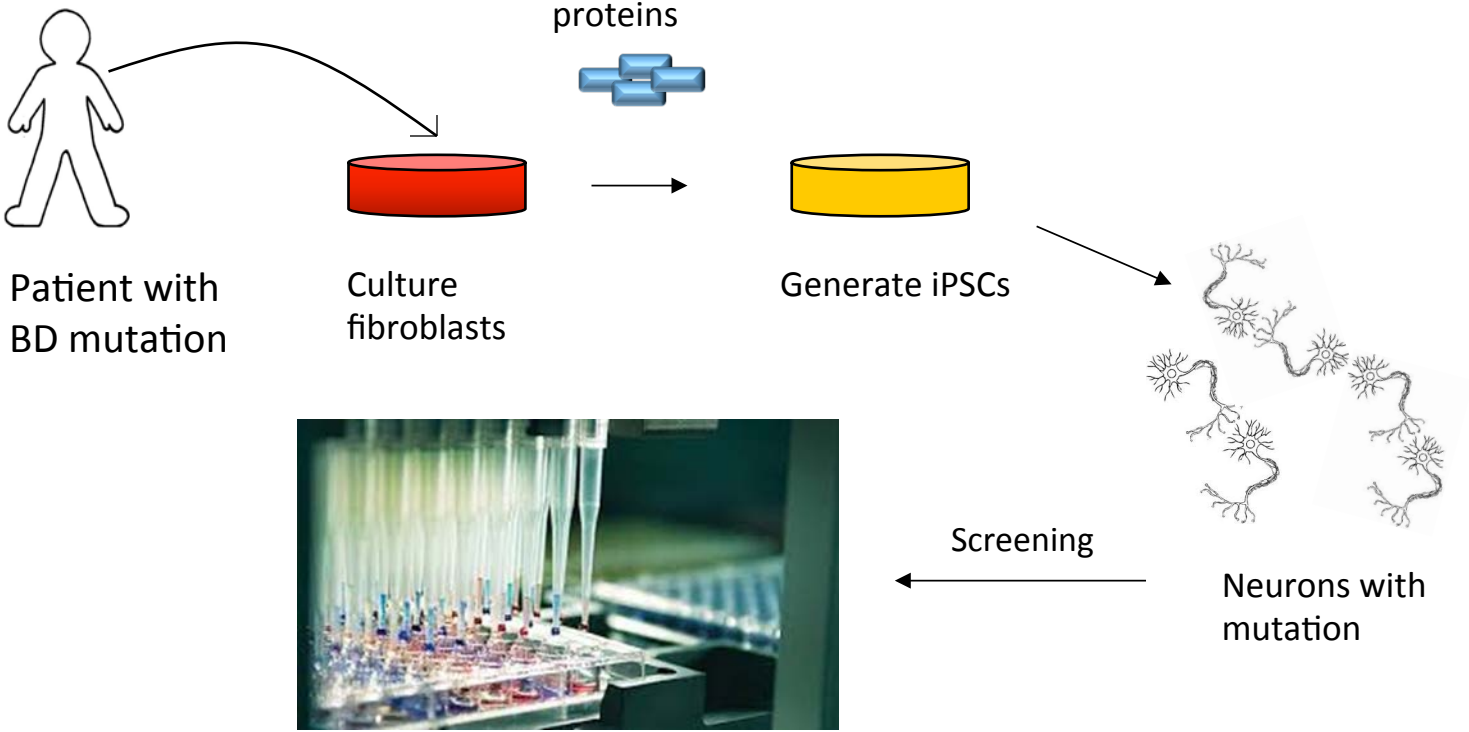
- Stem cells have the capacity to generate any cell type in the body, including those affected by BD.
- Can generate a large number of neurons rapidly.
- Lower costs, higher throughput for drug screening.



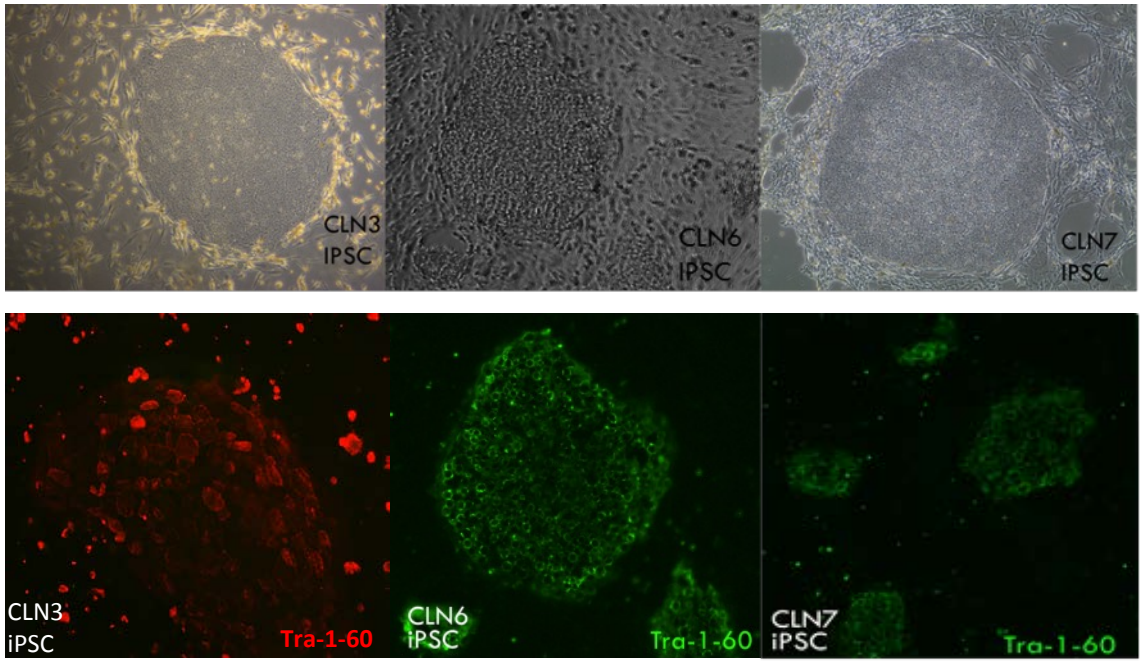
What type of stem cells should we focus on?

- 2 options :
  - 1. Stem cells generated from patients that contain BD mutations (CLN3,CLN6 and CLN7)
  - 2. Embryonic stem cells genetically engineered to introduce the BD mutation.

1. Stem cells from BD patient skin samples

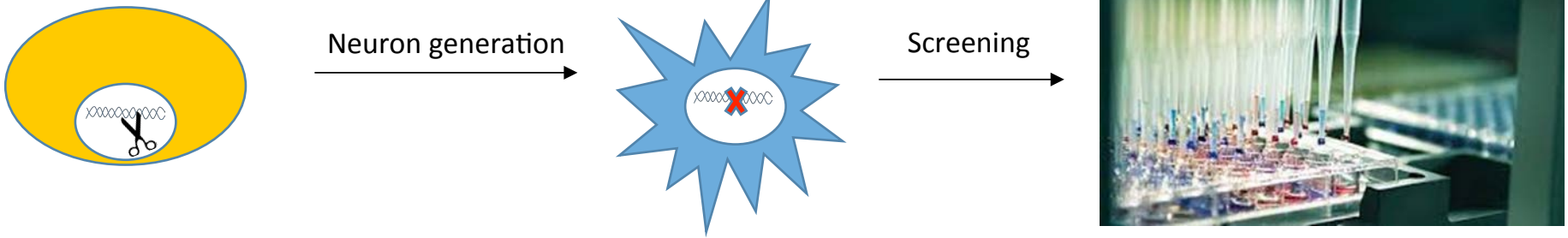


BD patient iPSC lines



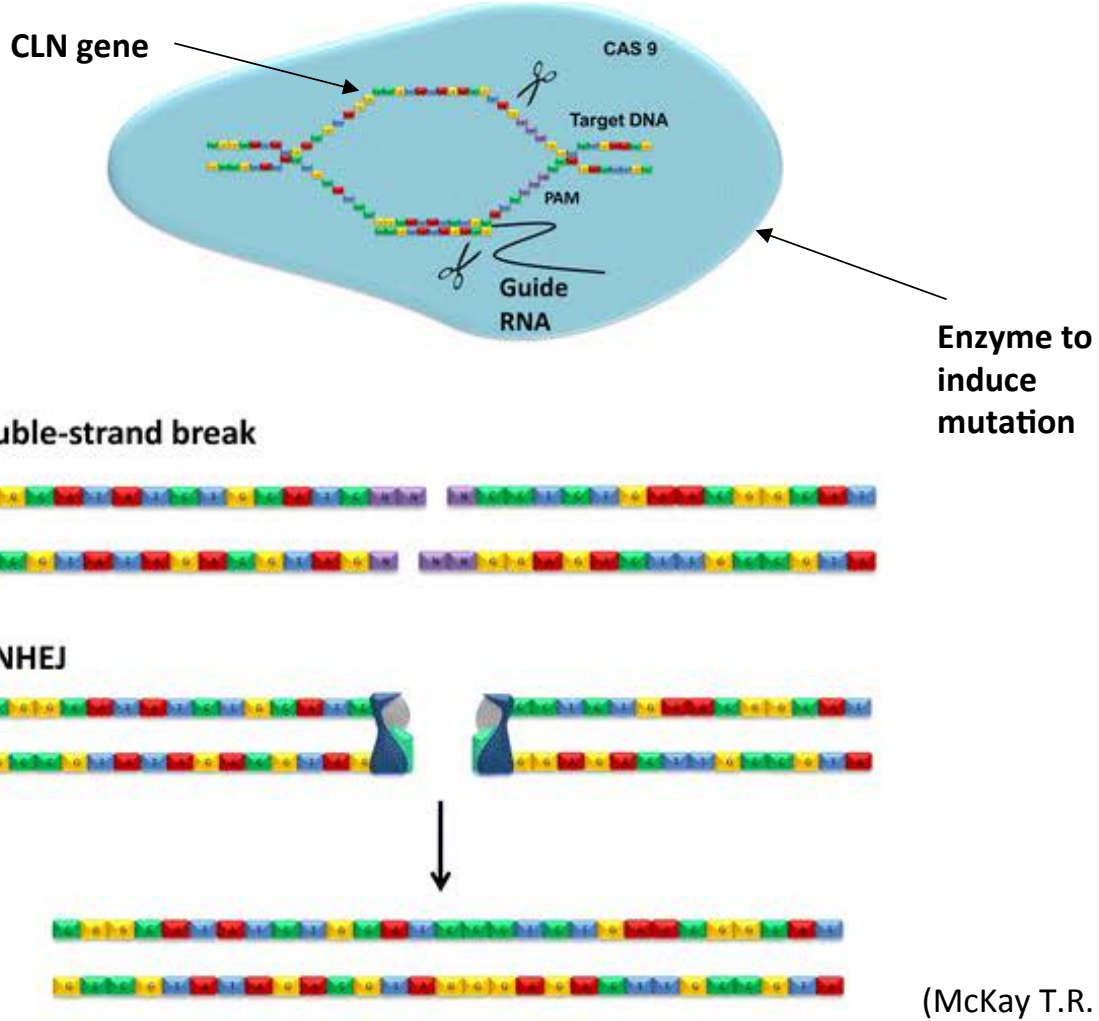
2. Genome editing human embryonic stem cells to create cell lines similar to BD patients

- General principle



Genome editing using the CRISPR Cas system to generate BD stem cells

- The CRISPR Cas system is an innovative way to induce site specific mutations in the genome.
- A guide nucleic acid directs the Cas enzyme to a target site to induce a mutation.



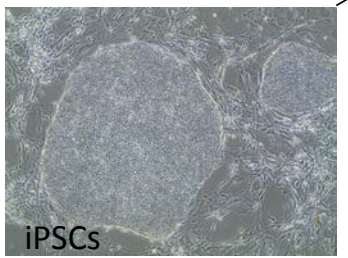
(McKay T.R. and FitzPatrick L.M., 2015)

What next?

- To date, we have successfully developed this system for the CLN3 mutation and are currently generating the stem cell lines

What next?

Dr. Emyr Lloyd-Evans
Function of CLN3



Prof Juan Bolanos
Metabolism studies

Dr. Thomas Kirkegaard
Mechanism of action of candidate drugs

Dr. Stephan Storch
Characterise dysfunctional pathways

Our plans for the stem cells

- We are also interested in understand the mechanisms of the disease
- We know that the problem is with the lysosome so can we track the process of lysosome production?

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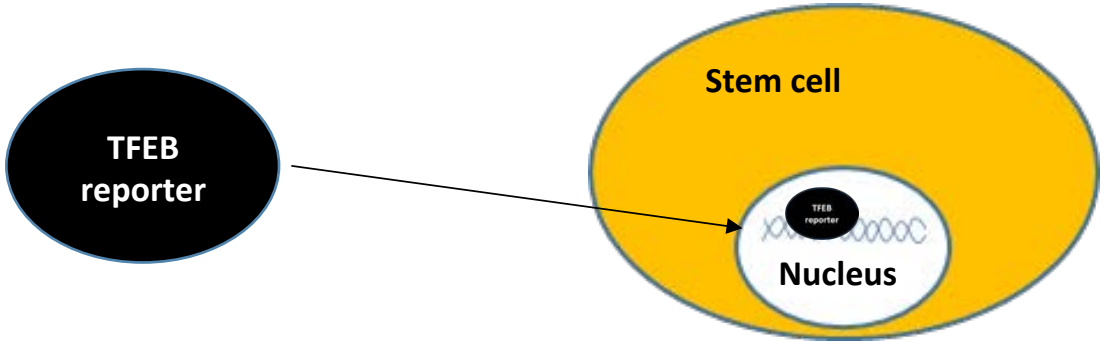
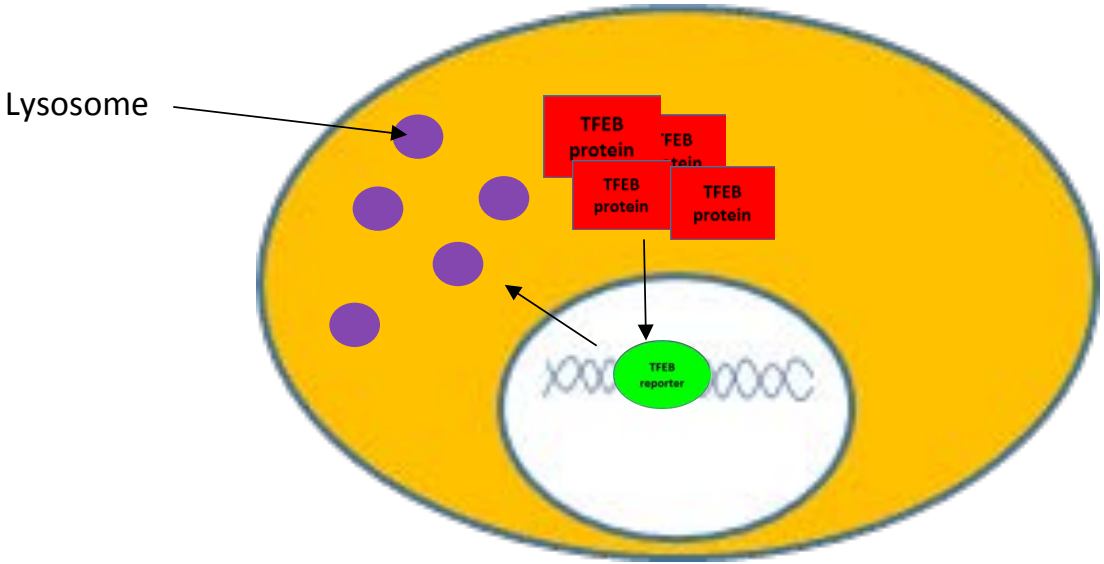
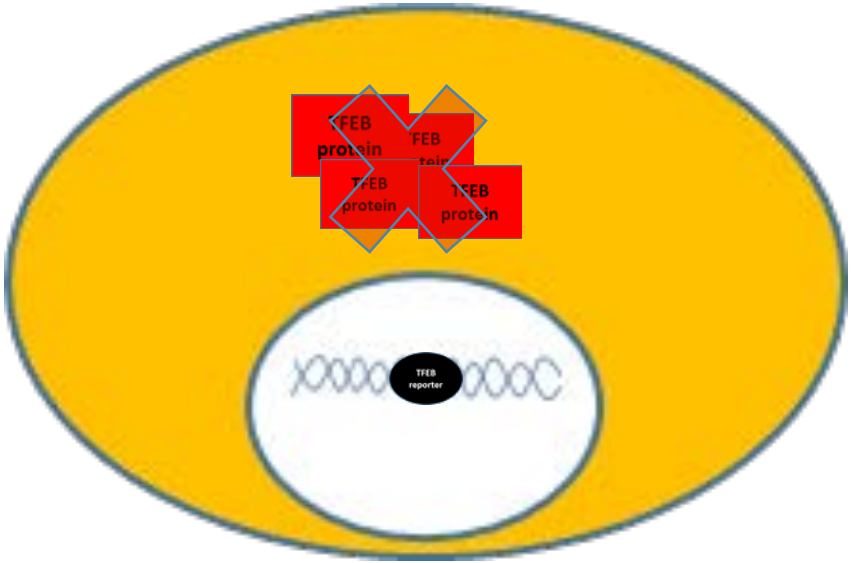
- Yes!
- Reporter tool

Transcription factor E box (TFEB) a master regulator of lysosomal production

- We can track its activity using a fluorescent protein responsive to TFEB activity…




Lysosome
TFEB protein
TFEB protein
TFEB protein
TFEB reporter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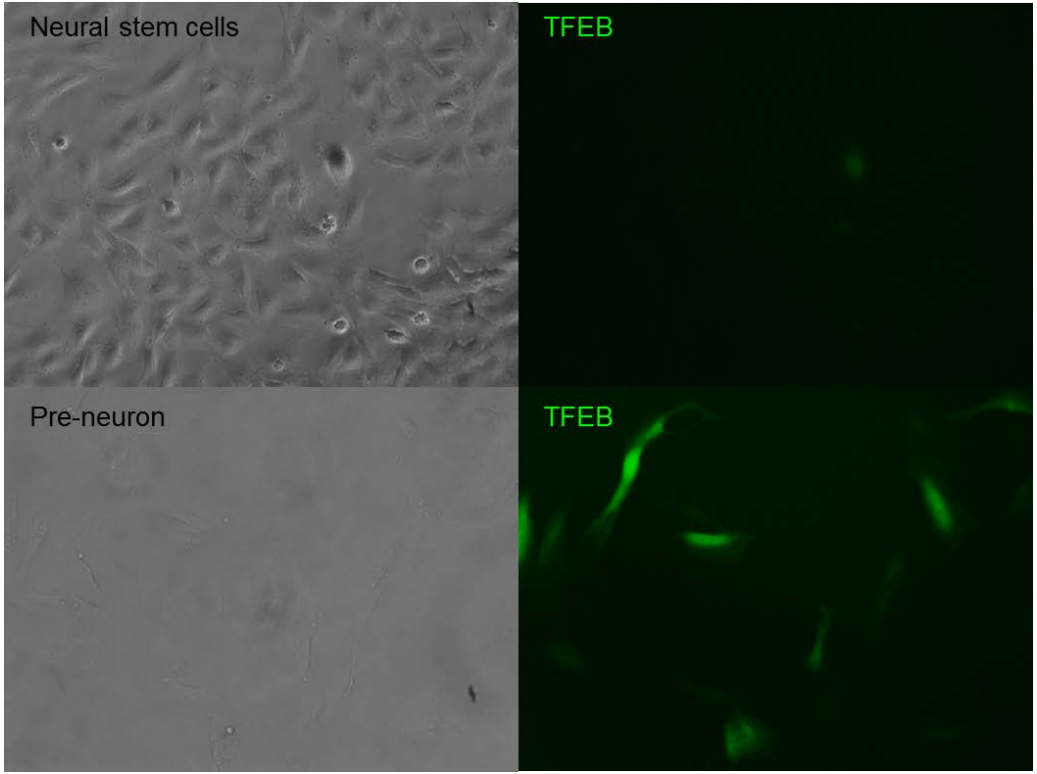
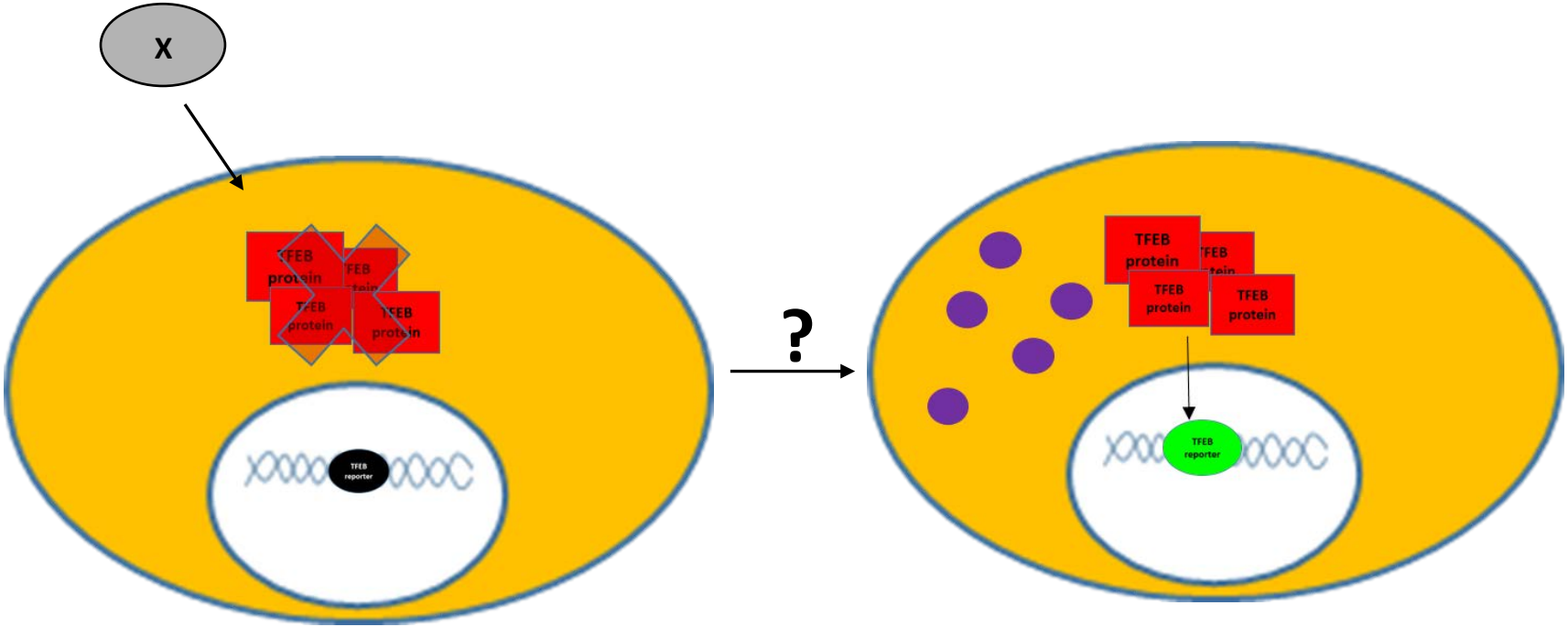

Neural stem cells
TFEB
Pre-neuron
TFEB

A readout for drug screening?



Conclusions

- We have successfully generated iPSC lines from CLN3, CLN6 (x2) and CLN7 (x2)
- Distributed these to other members of the BATCure Consortium
- Optimised genome editing using CRISPR Cas
- Have begun studying the mechanism of the disease also using the reporter system.

Who we are

- Prof. Tris McKay
- Dr. Lauren Harkin
- Louise Bullen
- Chip Thornton
- Alysha Burrows

- Dr. Emyr Lloyd Evans

- Prof. Sara Mole

- Dr. Angela Schulz

WP LEADER & PARTNERS INVOLVED

No.	Acronym	P/Ms
1	UCL	15.00
2	AcureO	2.00
3	OSI	6.00
4	CU	4.00
5	FTLELE.IGM	4.00
6	UKE	4.00
7	PRONEXUS	4.00

No.	Acronym	P/Ms
8	MMU	6.00
9	RVC	2.00
10	USAL	4.00
11	Orphazyme	4.00
12	KCL	5.00
13	LEITAT	4.00
14	BDFA	12.00
	TOTAL	76.00

Thank you for your attention

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