SELECTED OPPORTUNITIES IN NEUROSCIENCE

Increasing Tfr1 palmitoylation as a novel therapeutic strategy for Neurodegeneration with brain iron accumulation (BIO16340)

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Product factsheet

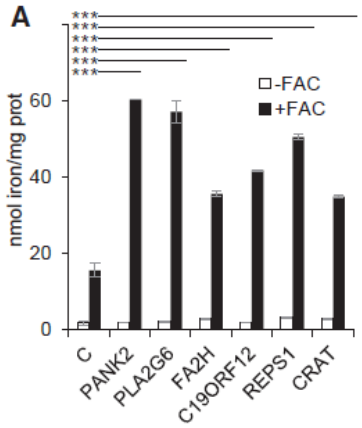
Stage in vitro PoC

- **Target:**
  - Transferrin receptor 1 palmitoylation
- **Product:**
  - Artesunate
- **Application:**
  - Neurodegeneration with Brain Iron Accumulation (NBIA)
- **Technology:**
  - Drug repurposing
- **Rational / POC:**
  - An abnormal iron content and homeostasis is observed in cultured fibroblasts of NBIA subjects
  - TfR1 amount is increased at the cell surface of NBIA subject fibroblasts irrespective of the mutation associated to the disease
  - TfR1 palmitoylation is reduced in NBIA subject fibroblasts irrespective of the mutation associated to the disease
  - Artesunate enhances TfR1 palmitoylation in NBIA subject fibroblasts and lowers iron content
- **Patent and publication:**
  - Patent: “Methods And Pharmaceutical Compositions For The Treatment Of Neurodegeneration With Brain Iron Accumulation” PCT/EP2017/083642 – priority date: 20th November 2016
  - Publication: “Impaired Transferrin Receptor Palmitoylation and Recycling in Neurodegeneration with Brain Iron Accumulation” Drecourt et al. **The American Journal of Human Genetics** 102, 266–277, February 1, 2018

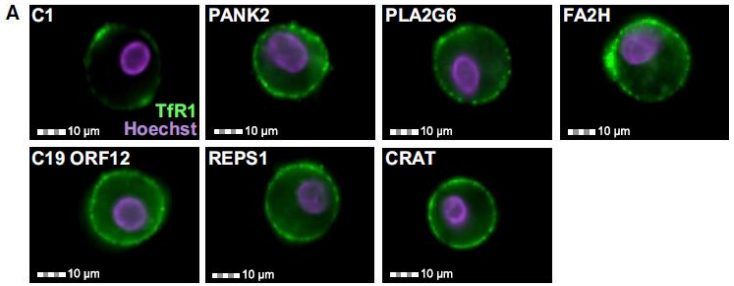
Proof of concept

- **Title : Abnormal iron content in cultured NBIA subject fibroblasts**

Figure 1: Iron quantification using the ferrozine based colorimetric assay in control and NBIA subject fibroblasts carrying mutations in different NBIA-causing genes



- **Title: Increase of TfR1 at the cell surface of NBIA subject fibroblasts**



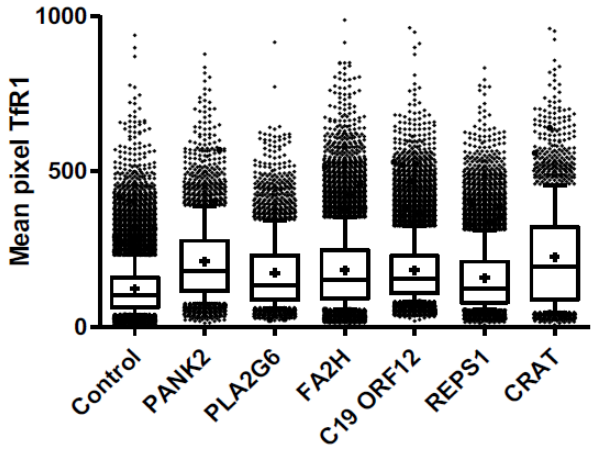


Figure 2: Immunostaining-based quantification of TfR1 at the cell surface of control and NBIA subject fibroblasts carrying mutations in different NBIA-causing genes.

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Proof of concept

- **Title : TfR1 palmitoylation reduction in NBIA subject fibroblasts can be rescued by artesunate treatment**

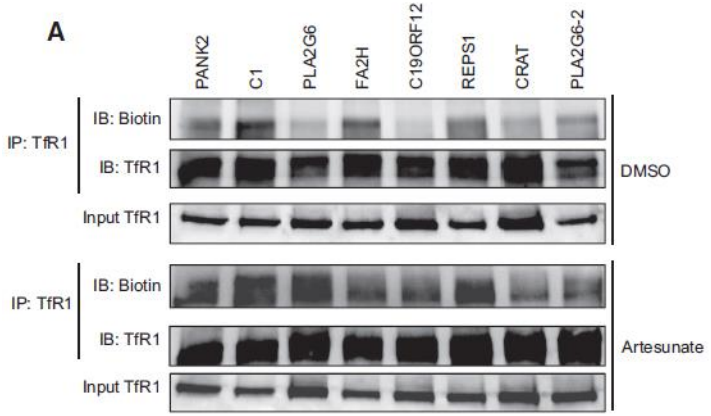


Figure 3: Quantification of palmitoylated TfR1 in subject fibroblasts and control. Palmitoylation defect is observed in patient fibroblasts for all mutations. Artesunate treatment (25µM) alleviates this defect.

- **Title: Increase of TfR1 at the cell surface of NBIA subject fibroblasts**

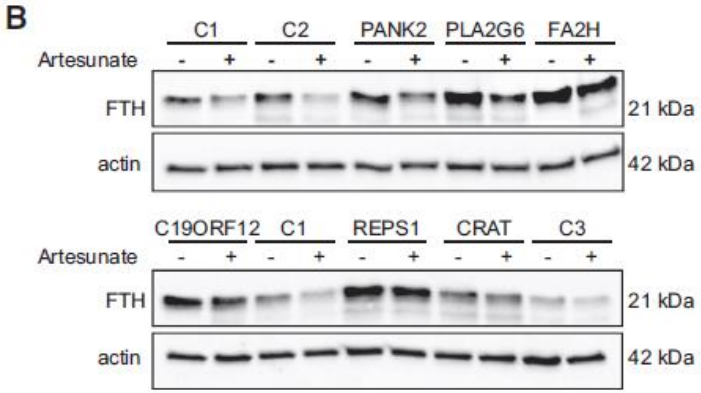
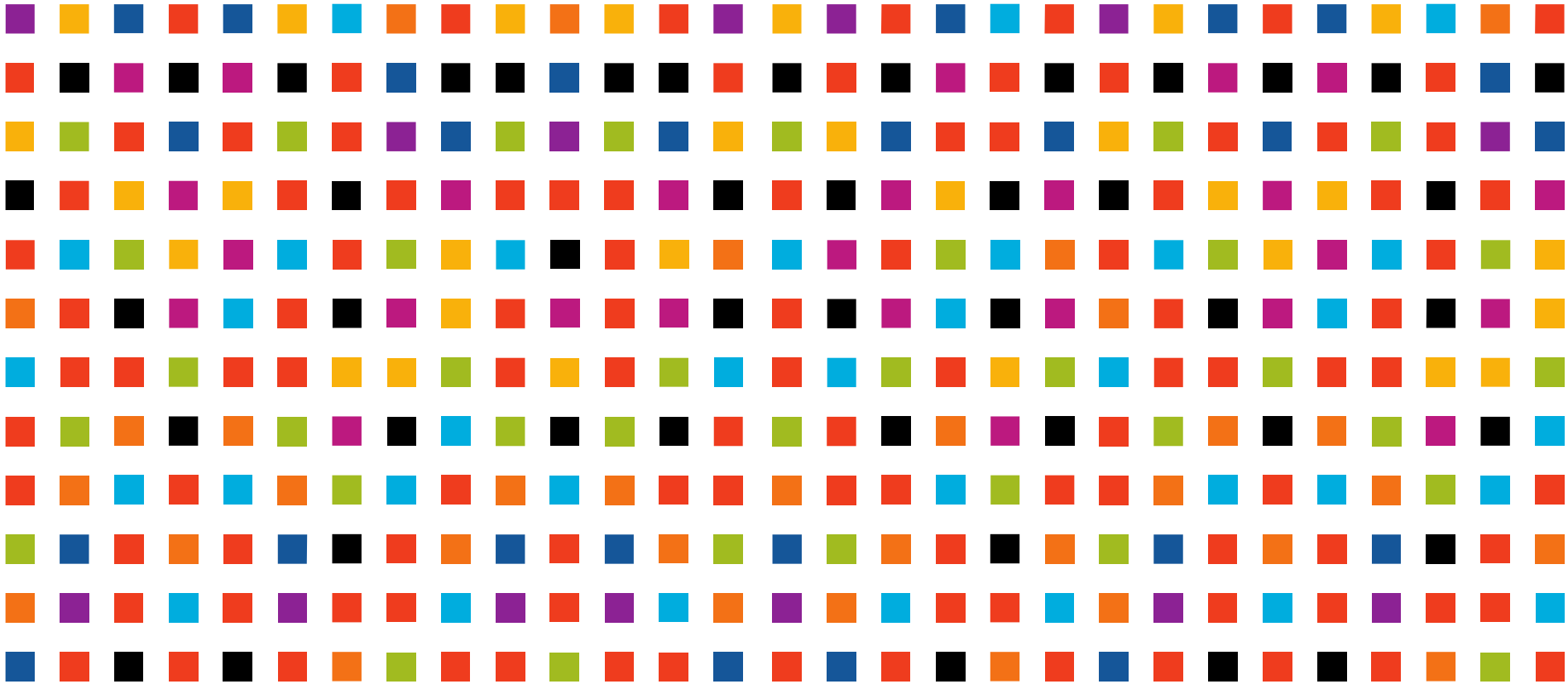


Figure 4: Immunoblot analysis of ferritin (FTH) in control and NBIA subject fibroblasts treated or not with 25µM Artesunate. The treatment lowers steady-state levels of ferritin, reflecting a decrease in total iron content.



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