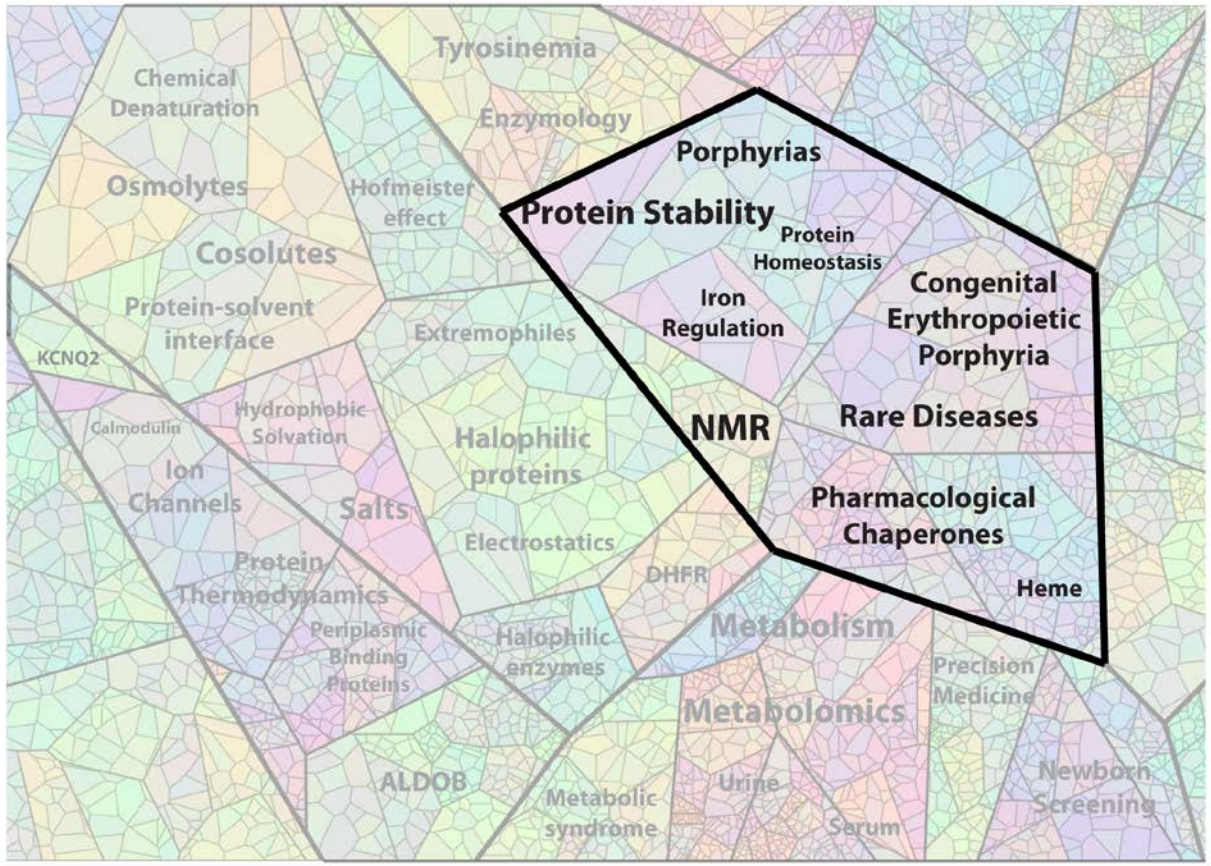
atlas molecular pharma

Pharmacological Chaperones for the treatment of rare and ultra rare diseases

Orphan Drug Designation for Ciclopirox against Congenital Erythropoietic Porphyria

Oscar Millet



2006 **Arola Fortián** (Research Associate, UCL, London, UK)
Oscar Millet
Xavier Tadeo (Scientific Editor, BCN)

2007 **Ana Laín**
Blanca López-Méndez (Group Leader, Univ. Copenhagen, Denmark)
David Castaño (Research Associate, AAAS Star, Singapur)

2008 **Gabriel Ortega** (Post-doc, UCSD, San Diego, US)

2009 **Paula Pluta** (Staff Scientist, Roche, Poland)

2011 **Fredj ben Bdira** (Ph. D., Univ. Leiden, Netherlands)
Idoia Iturrioz (Technician, CIC bioGUNE)

2013 **Ganeko Bernardo** (Staff Scientist, ATLAS Molecular Pharma)
Nieves Embade
Arantza Sanz-Parra

2014 **Pedro Urquiza** (Post-doc, EEUU)
Sivanandam Veeramuthu (Post-doc, CIC bioGUNE)

2015 **Iratxe Macías** (Researcher, bioCRUCES)

2016 **Laura de la Cruz**

2017 **Xabier Cendoya**
Itxaso San Juan
Luca Unione (Post-doc, Univ. Utrech, Netherlands)

2018 **Chiara Bruzzone**
Rubén Gil
Beatriz González
Nicanor Zalba

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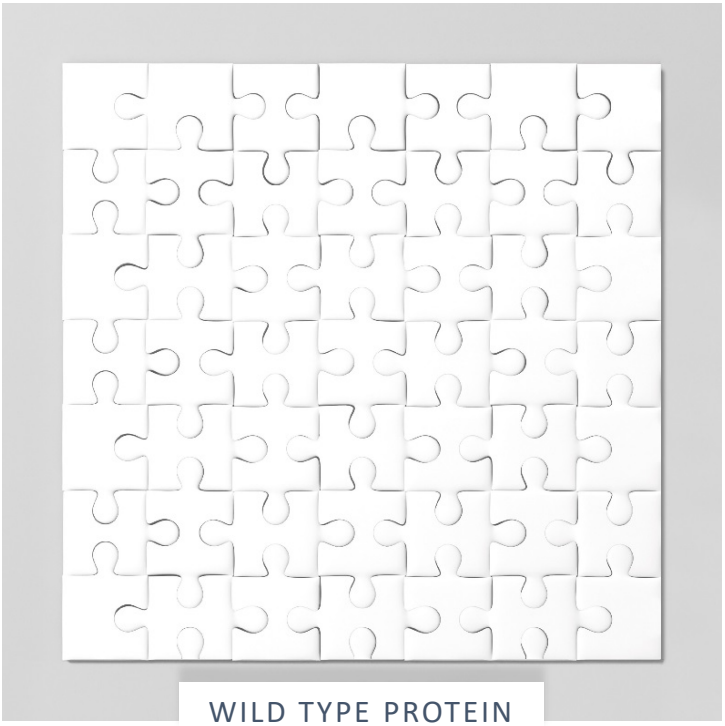
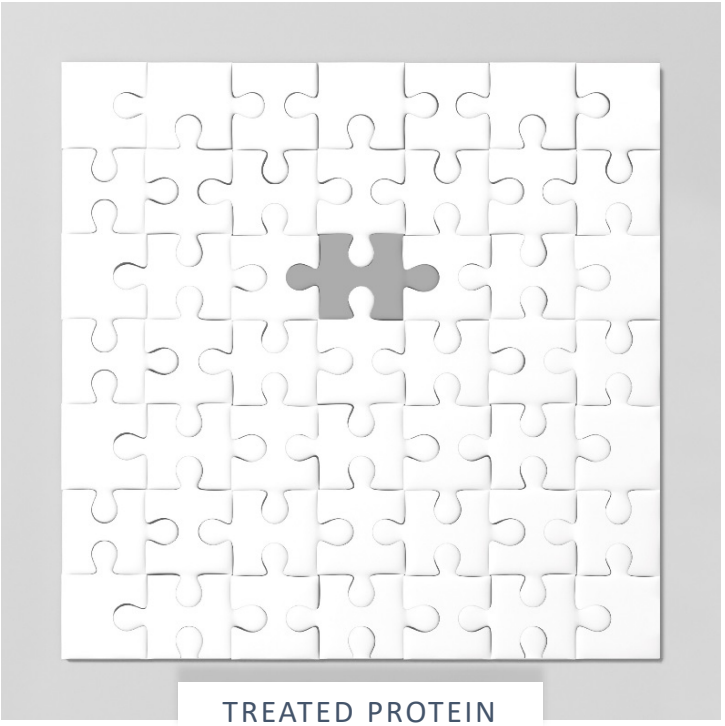
Pharmacological Chaperones for the treatment of rare and ultra rare diseases

A **rare disease** affect only to a small percentage of the population, the reason why they have been neglected for years.
Yet, a **common mechanism** is shared by many: an inherited mutation that ultimately results in the **destabilization** of a protein.

Our goal is to tackle this common pathogenic mechanism with the design of disease-specific **pharmacological chaperones**.
This strategy may be able to correct the phenotype for a plethora of rare syndromes.





About Atlas

Company Overview

An innovative and efficient proprietary Platform Technology approach

Chassys Platform
Chaperone Seeker System

Lead project in Congenital Erythropoietic Porphyria

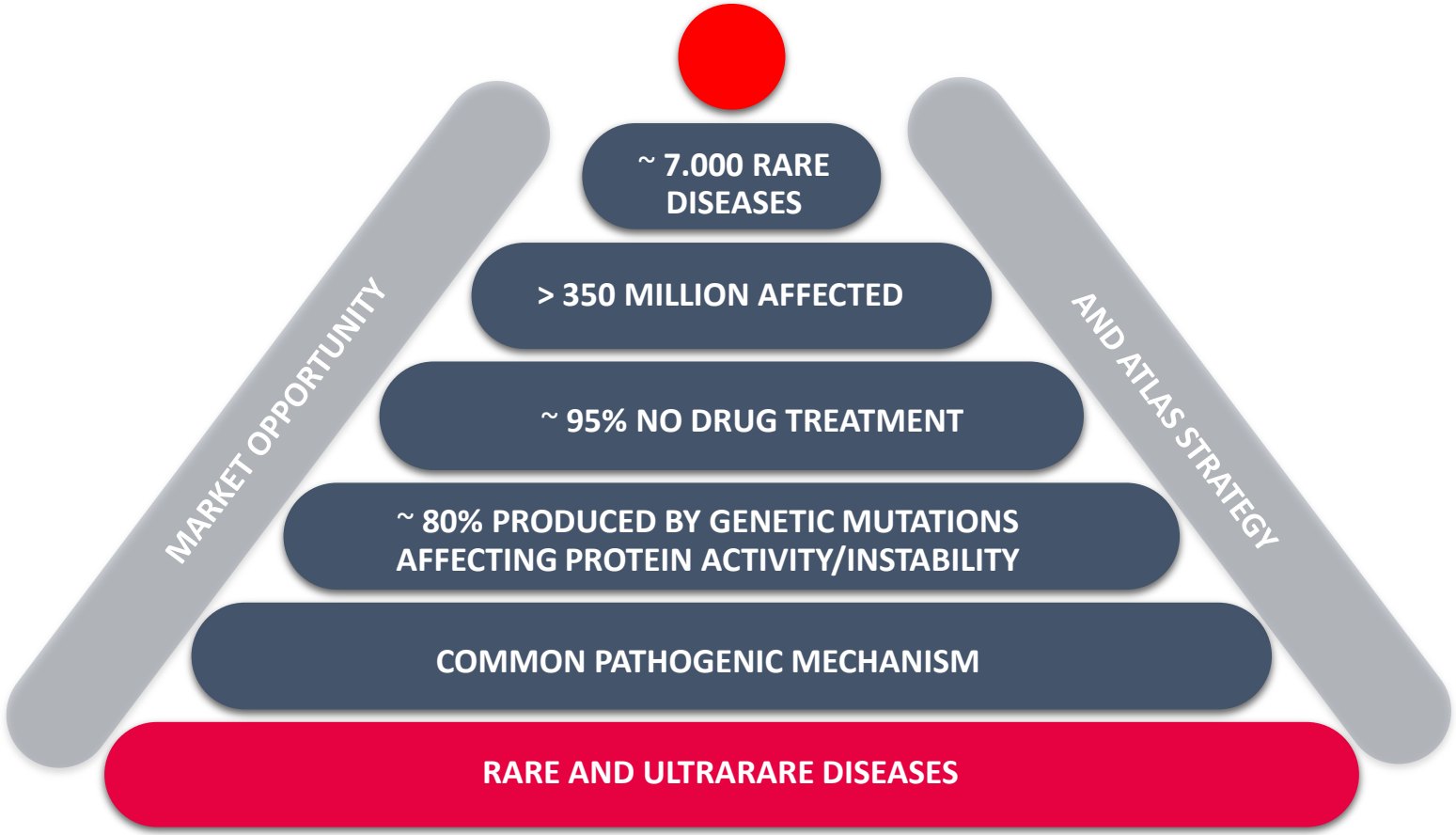
- Efficacy Proof of Concept in animal model
- Orphan Medicinal Product Application Aproval 1Q 2018

Spin-out from CIC **bioGUNE** end 2015.
Centre for Cooperative Research in Biosciences.
Bilbao · Spain

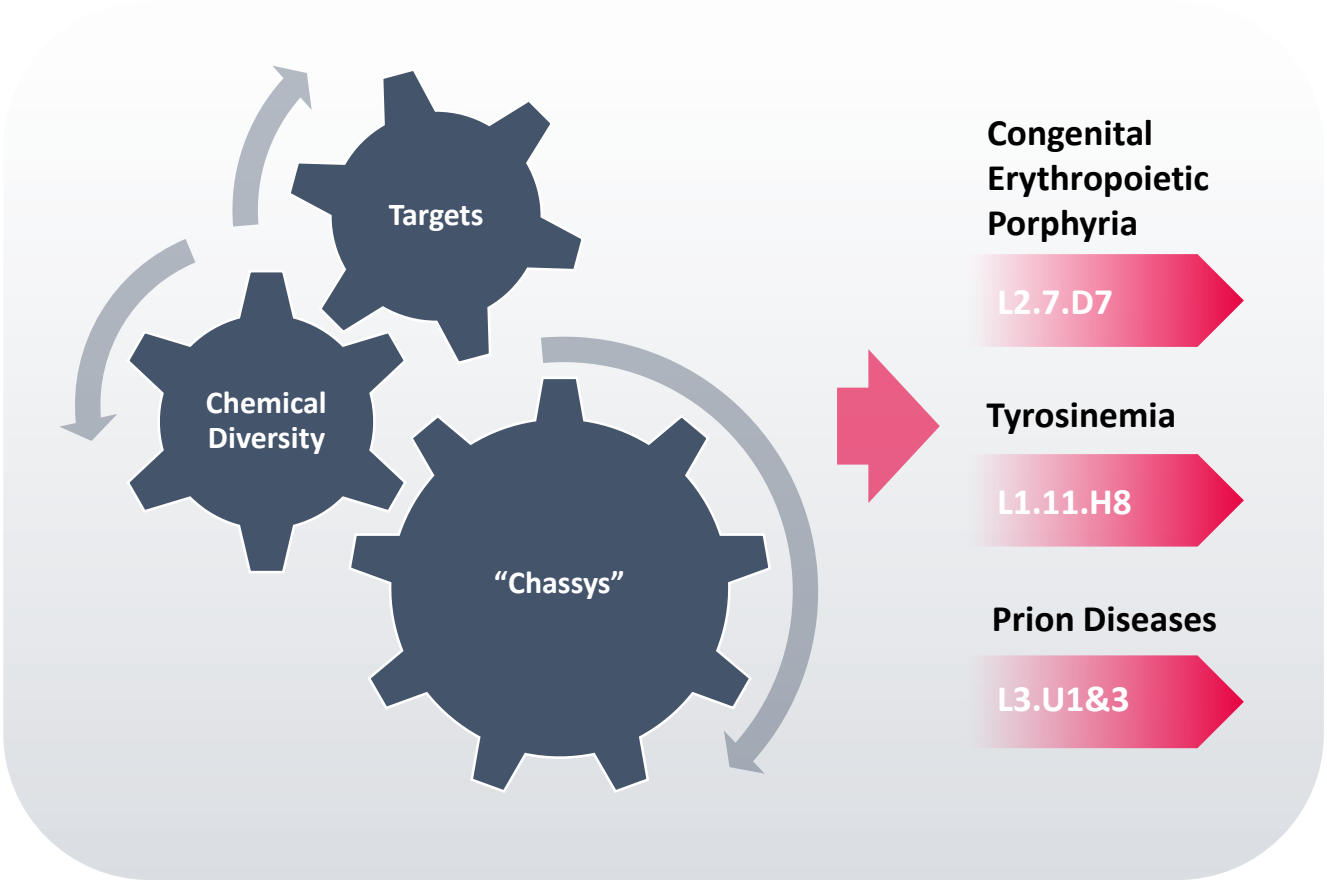
Licensing of projects at the Pre-clinical or Clinical Stage

€2M Series A round in 2019-2020

The opportunity



The technology and the portfolio



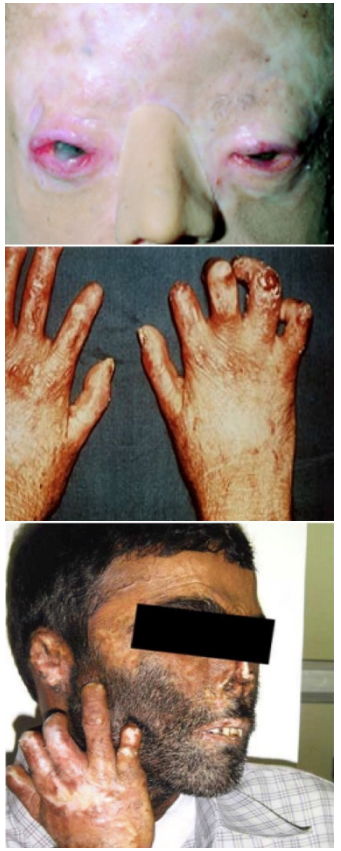
Chassys® Platform
Chaperone Seeker System

- A successful platform for the identification of small molecules that bind and stabilize mutated proteins that are the cause of rare and ultra-rare diseases.
- A platform based on a smart combination of screening technologies for the identification of protein chaperones.
  - NMR based STD and CSP
  - Isothermal calorimetry
  - Cell-based protein stability
  - Biochemical binding and functional assays

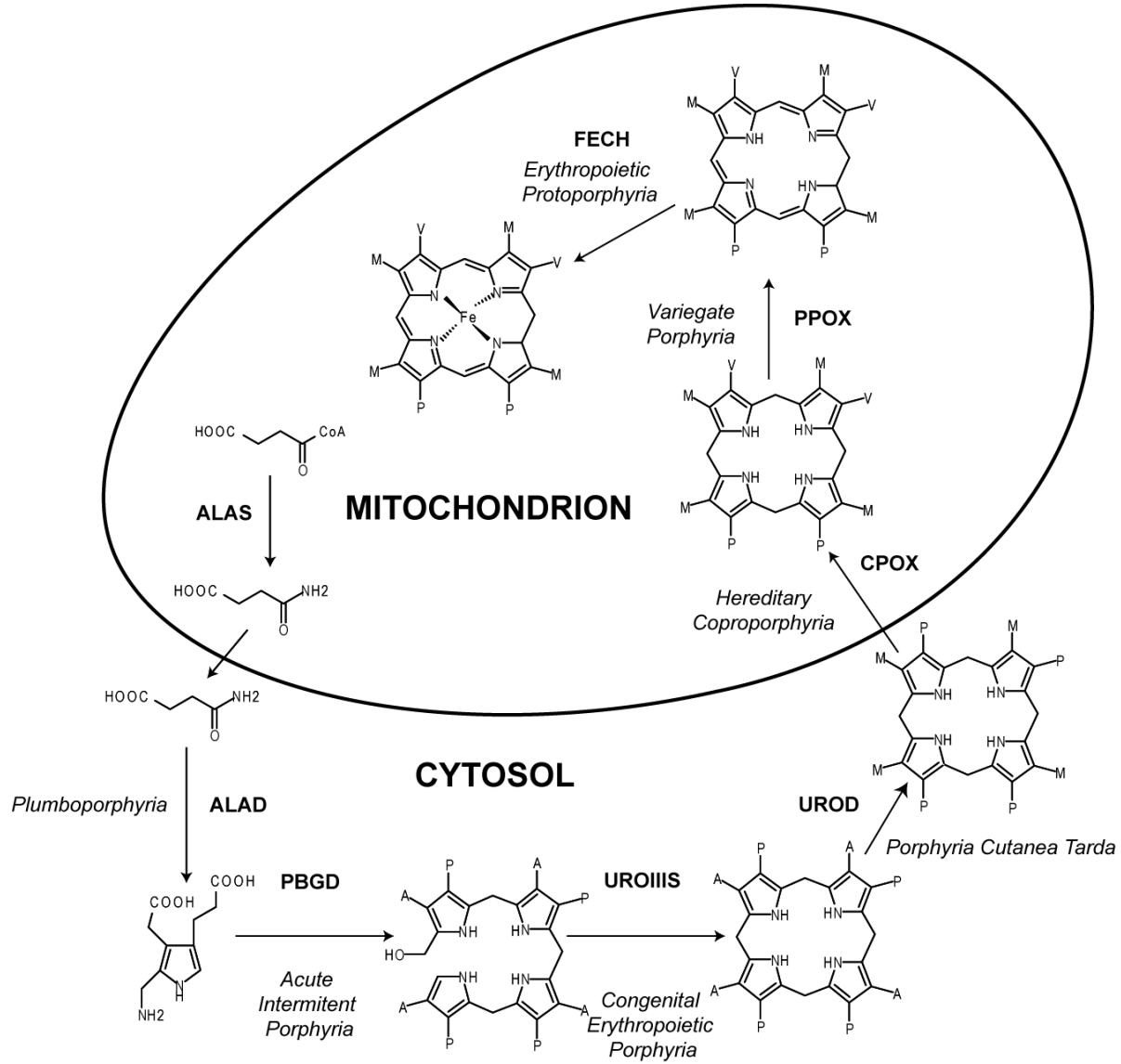
Project: Congenital Erythropoietic Porphyria

Devastating disease for which there are no effective treatments currently marketed

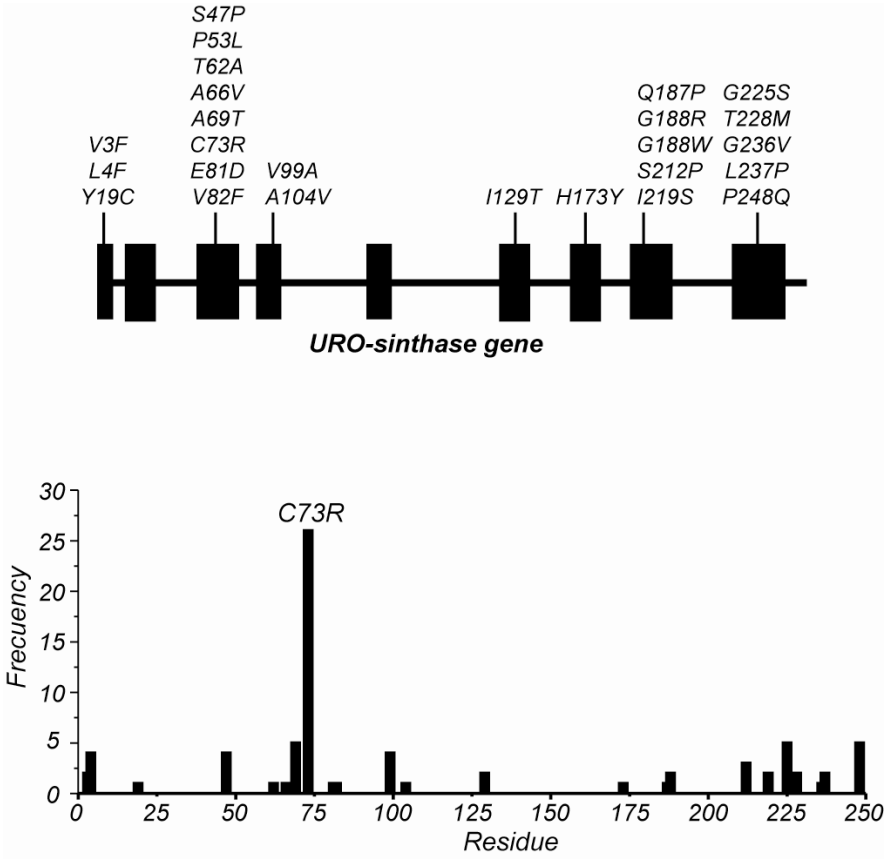
- <1 in 1 000 000 (affecting males, females and ethnic groups equally)
  severe prognosis - death in early life to an extremely disfiguring, debilitating and lifelong disease
- Deficiency in UROIIIS enzyme leading to a build-up in the body of toxic porphyrins resulting in extreme skin photosensitivity - blistering, severe scarring and loss of facial features and fingers
- We have identified a pharmacological chaperon for Congenital Erythropoietic Porphyria (CEP) that demonstrated *in vitro* activity as a chaperone molecule and efficacy in CEP animal model
  re-positioned approved drug – Orphan Medicine Product Application

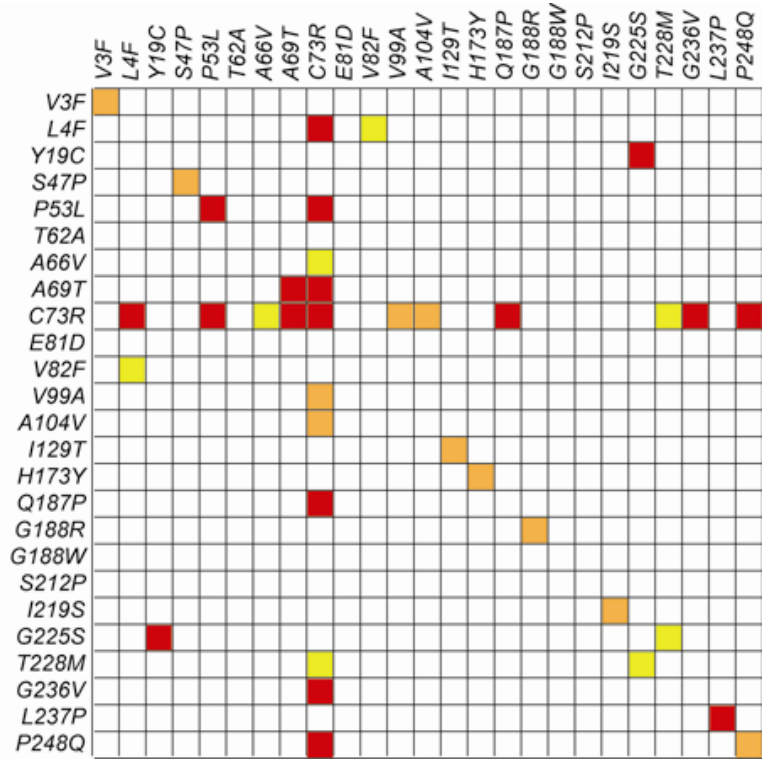


The Heme Pathway



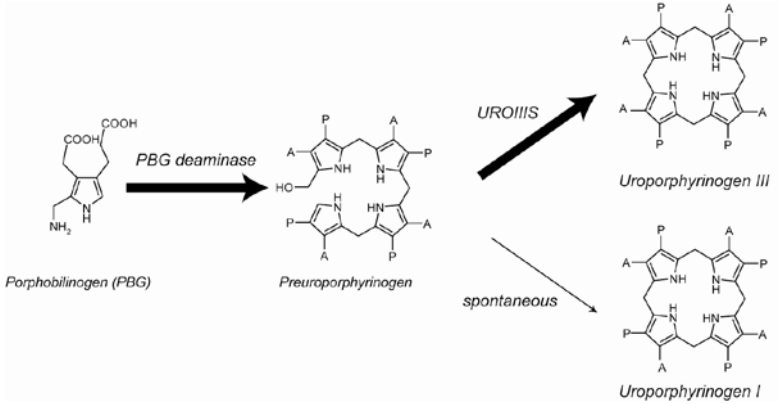
The Genetic Defect

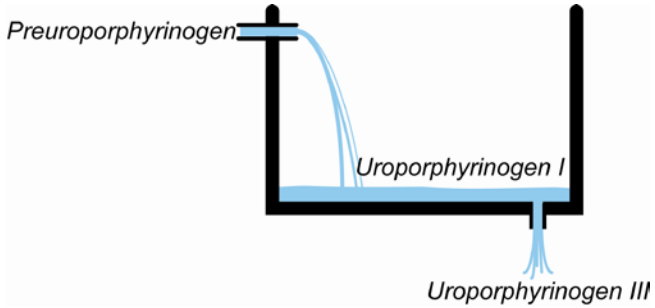




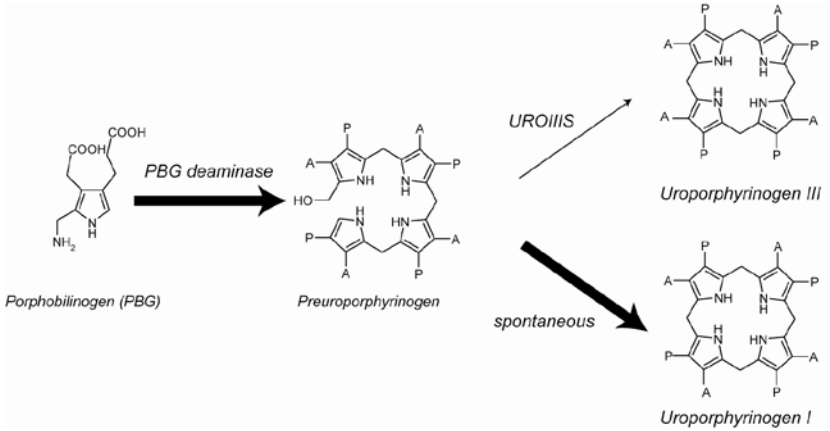
The Metabolic Defect

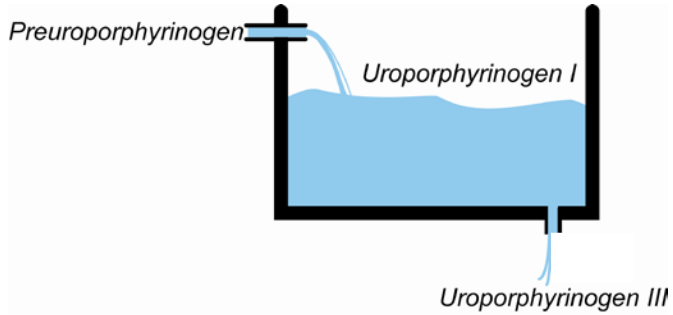
HEALTHY



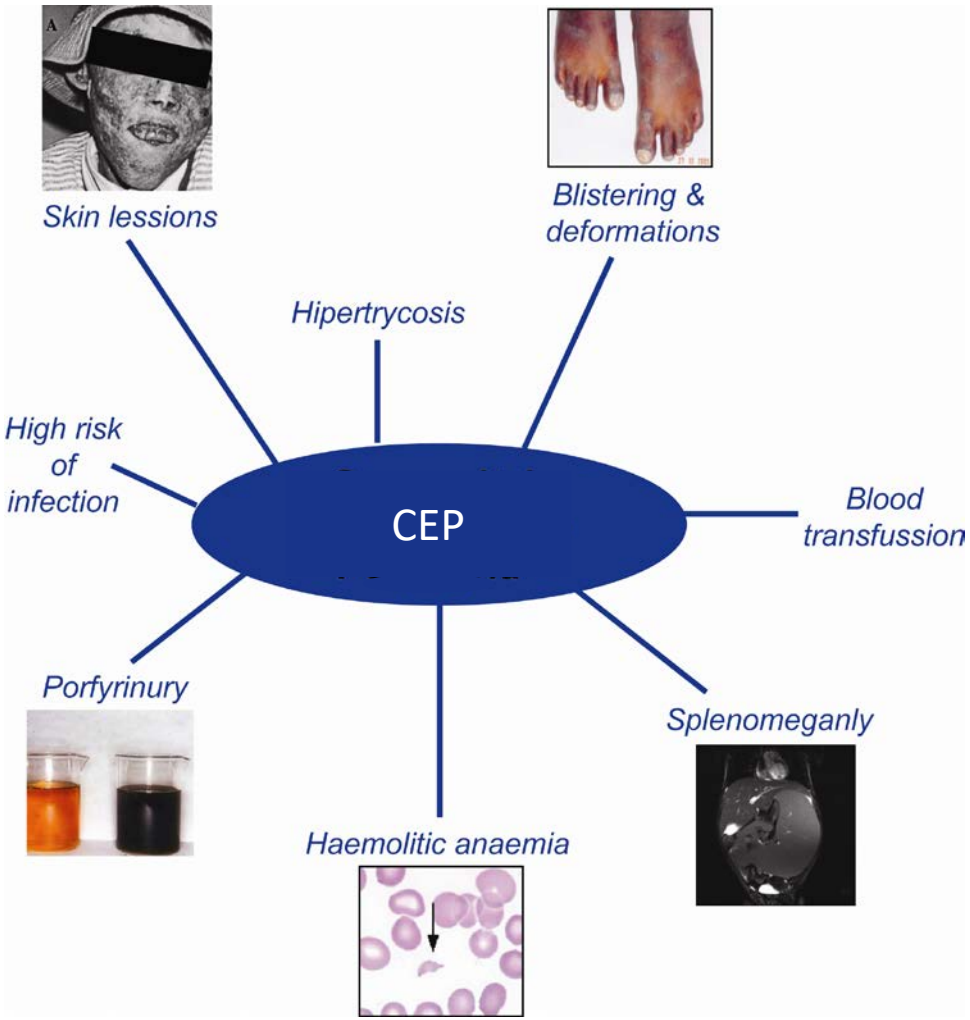


CEP



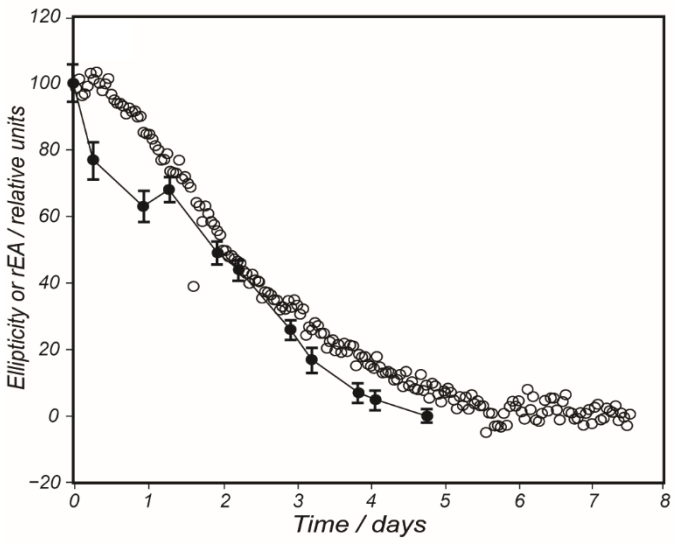


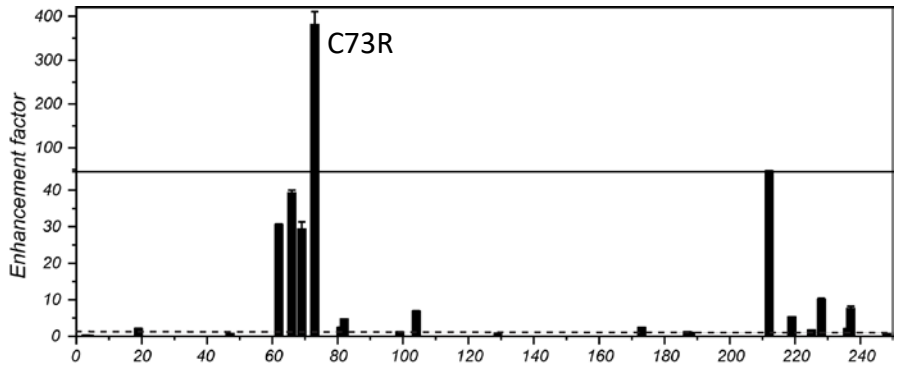
Symptomathology

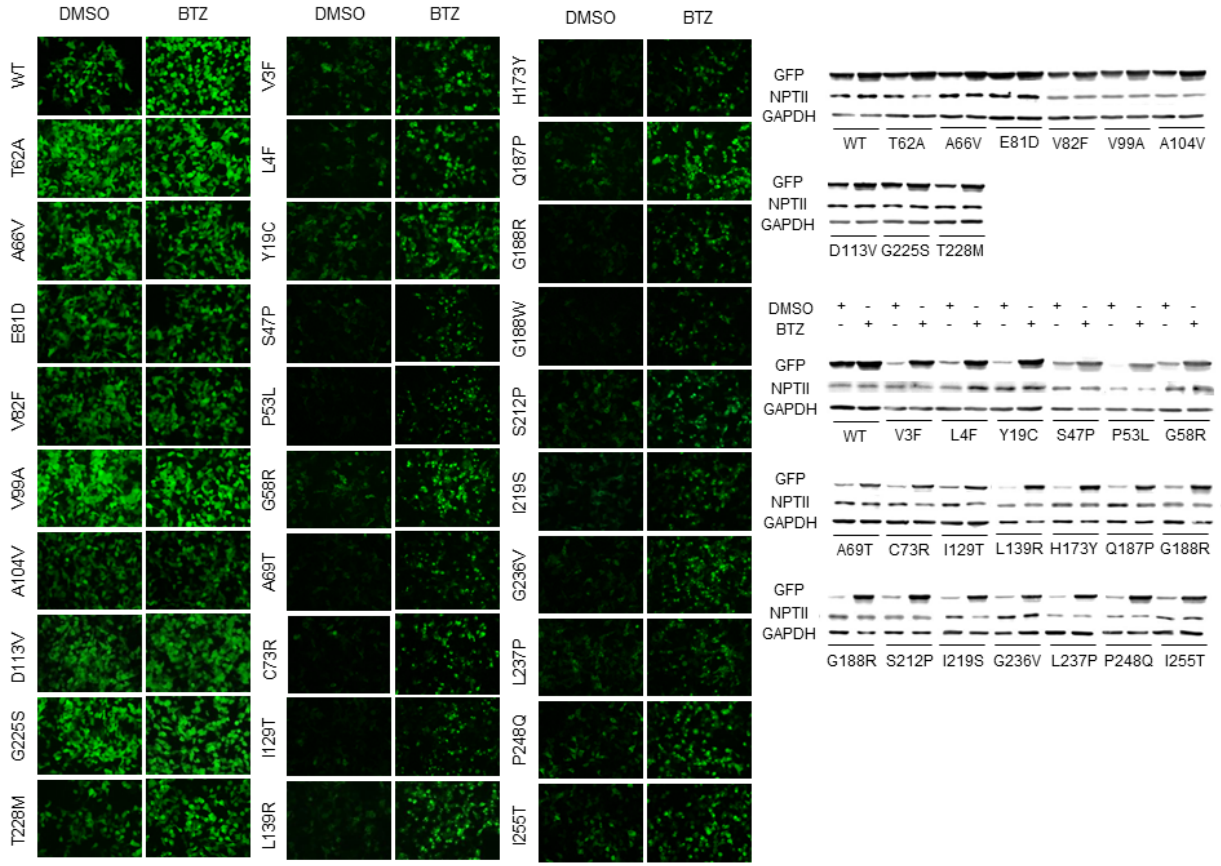


Abdominal pain - **Alopecia** - Anemia - **Back Pain** - Behavioral change - **Constipation** - Dysphasia - **Fatigue** - Fever - **Gastrointestinal spasms** - Hallucinations - Irritability - **Muscle pain** - Nausea - **Paralysis** - Photosensitivity Skin lesions - **Seizures** - Urine changes - **Vomiting** - Weakness - **…**

The stability defect



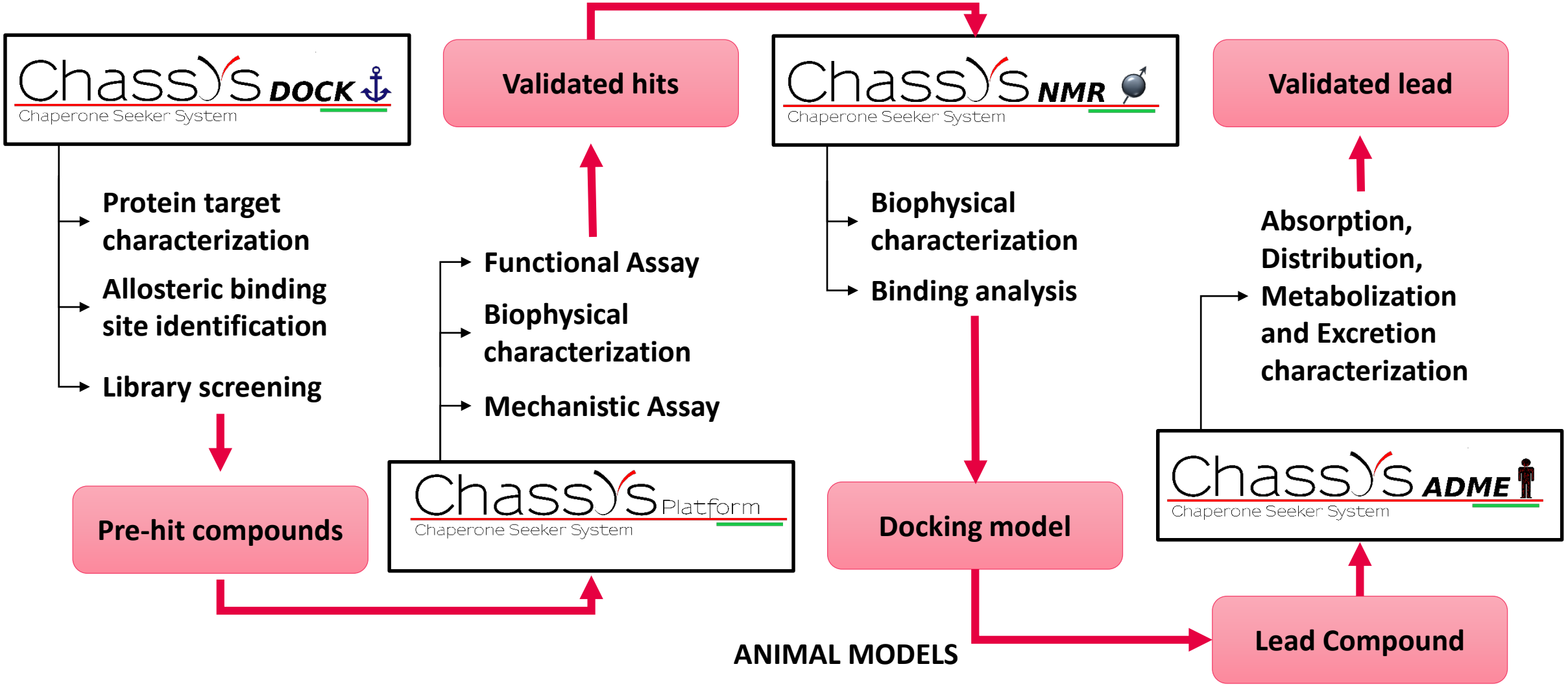


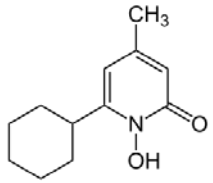


Chassys Platform

Research Strategy and Scientific approach

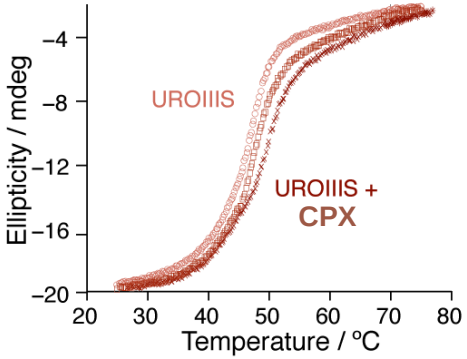
Pharmacological Chaperones for the Treatment of Rare and Ultra Rare Diseases

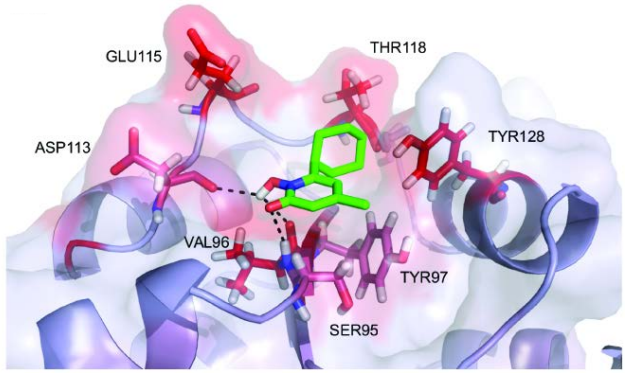


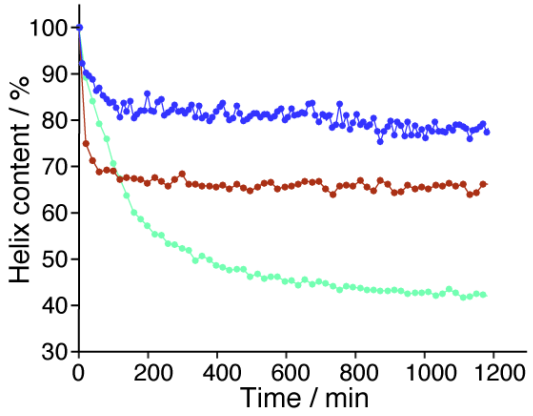


Biophysical characterization

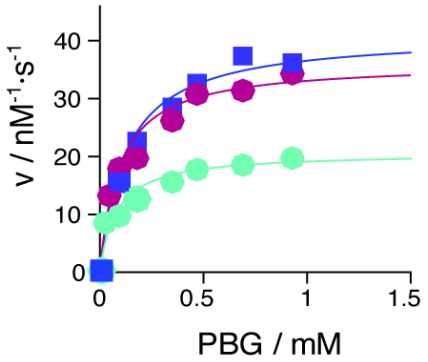
Thermodynamic



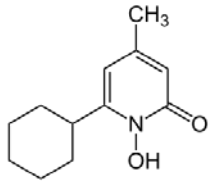




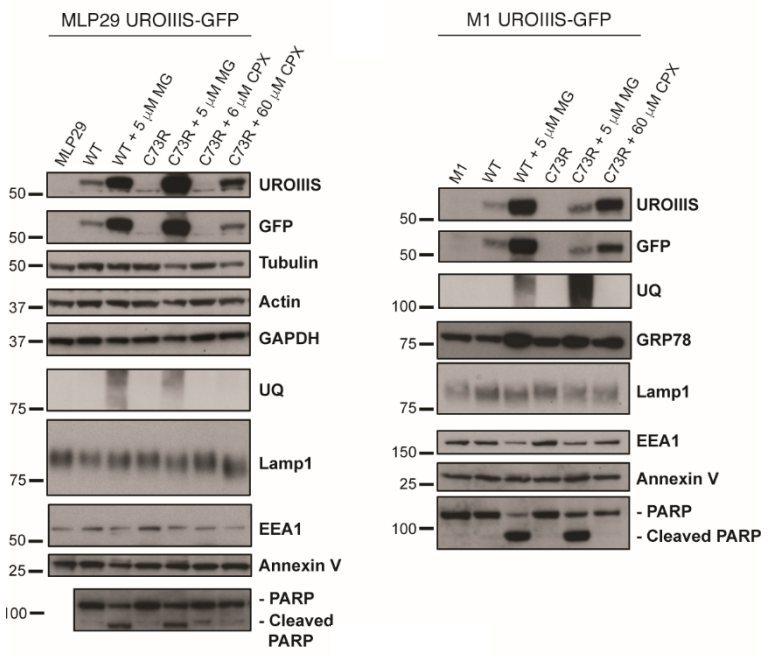
Kinetic

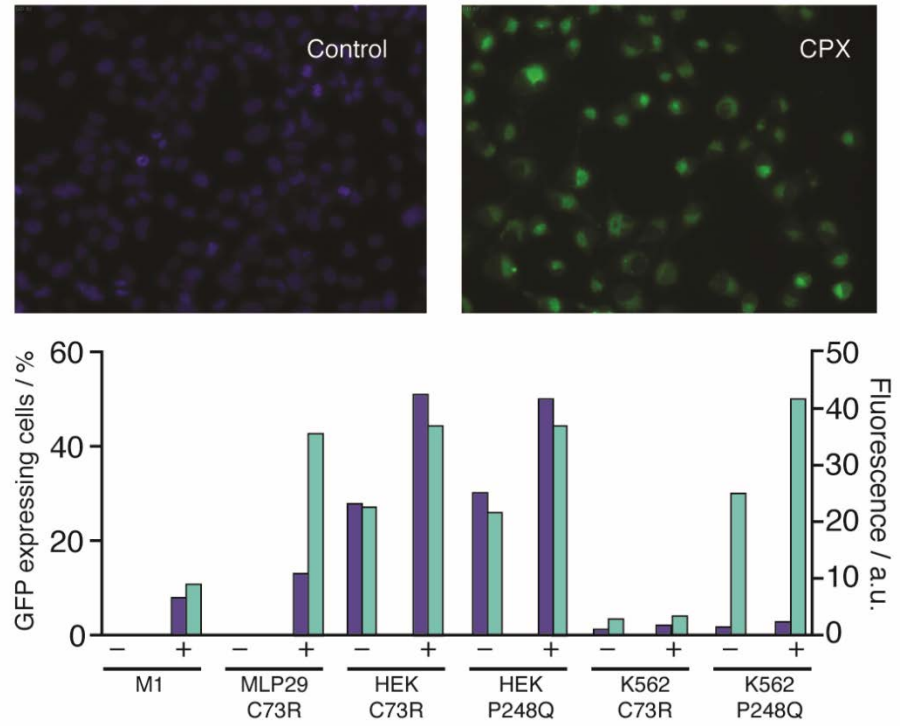


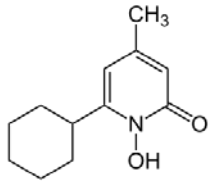
Enzymatic



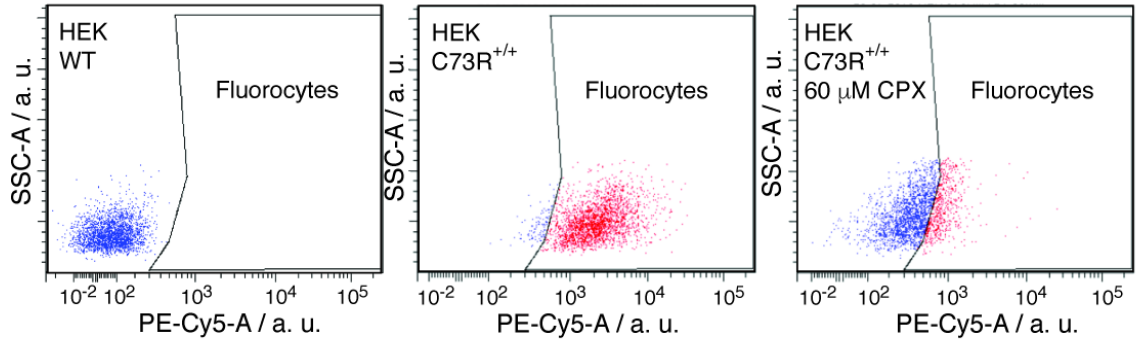
Biochemical characterization

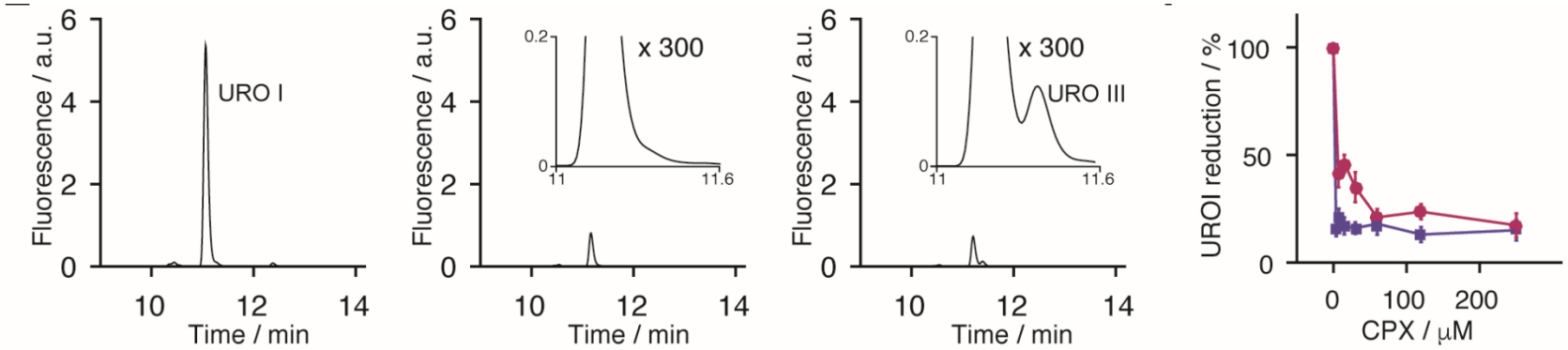


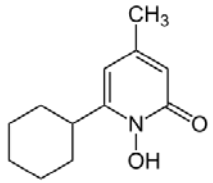




CRISPR/Cas9 cellular CEP models







Pre-application to the Orphan Drug Designation

4Q 2016

- Format: file submission (no specific format) + phone call with two EMA delegates.
- The conclusions are not binding but useful

- Outcome:

  Very promising BUT,

  Data using animal models has to be provided, when the model is available.

  Find a proper estimation of the disease prevalence.

Chassys
Chaperone Seeker System

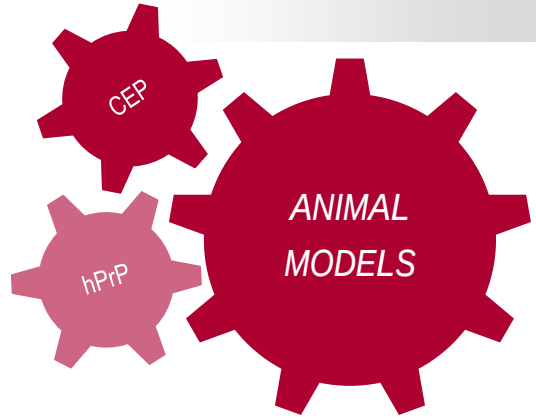
ANIMAL MODELS

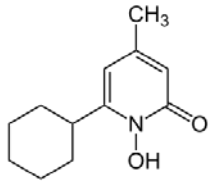
→ Congenital Erithropoietic Porphyria

Same disease-associated mutation as in humans.

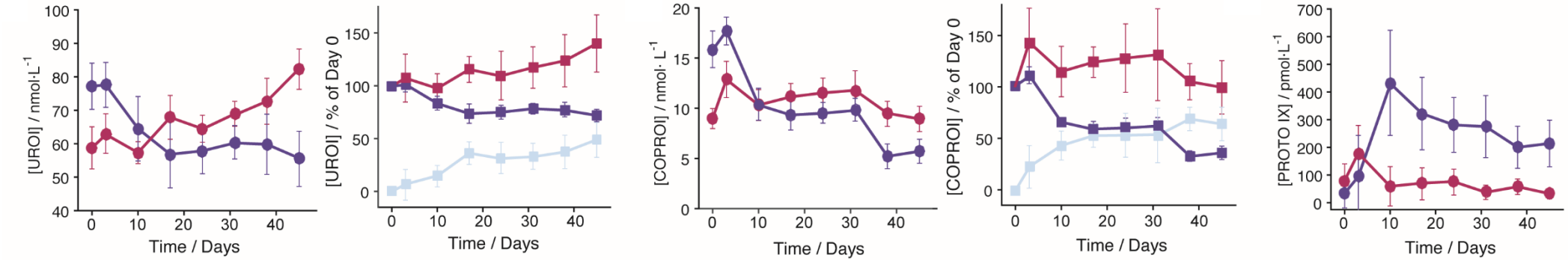
Reproduces all the hallmarks of CEP

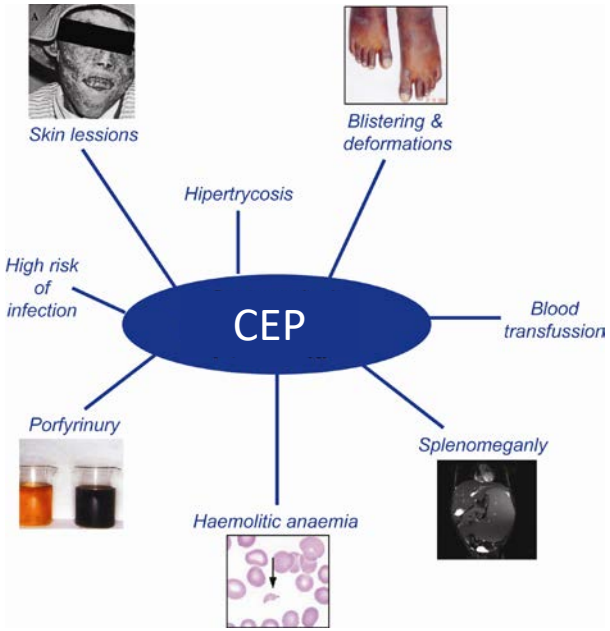
Animal models for rare diseases

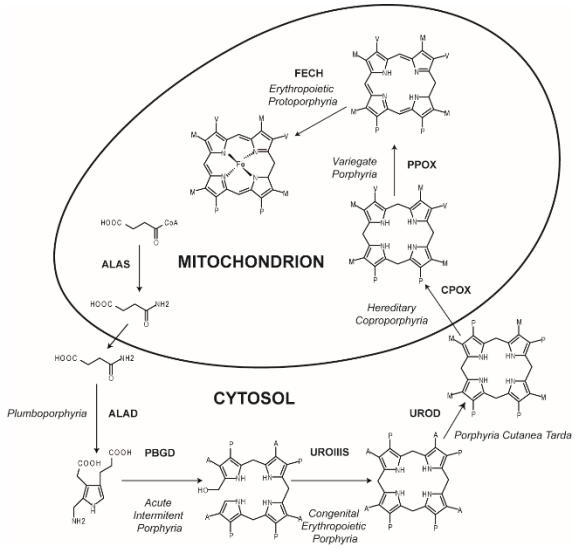


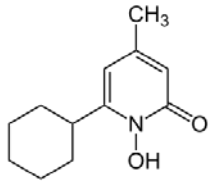


CPX endeavours CEP metabolism

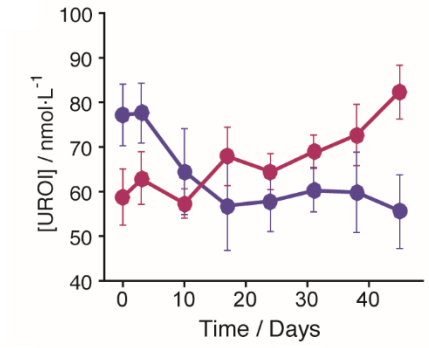


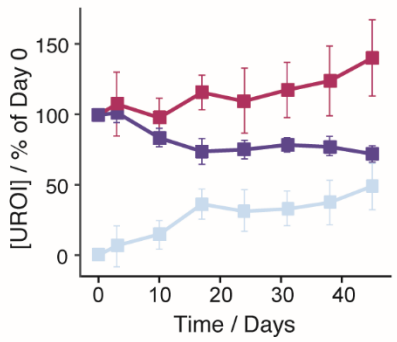


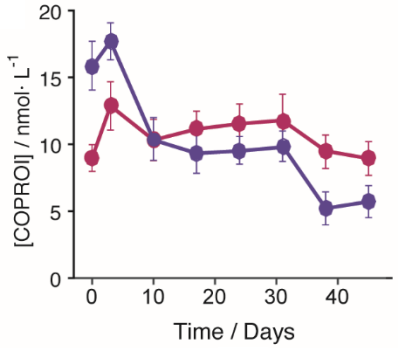


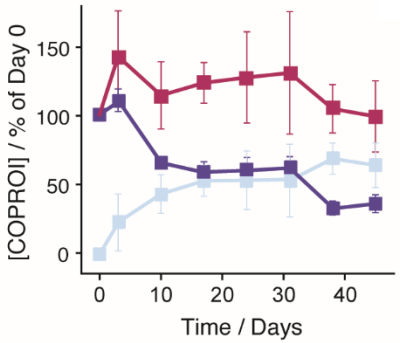


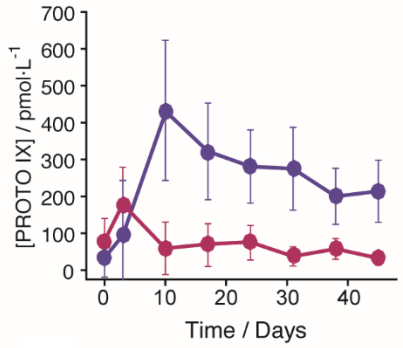
CPX has a systemic benefiton CEP mice

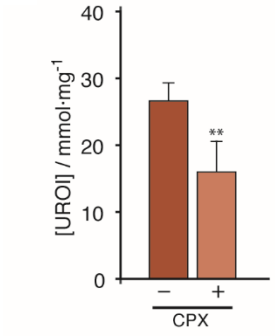


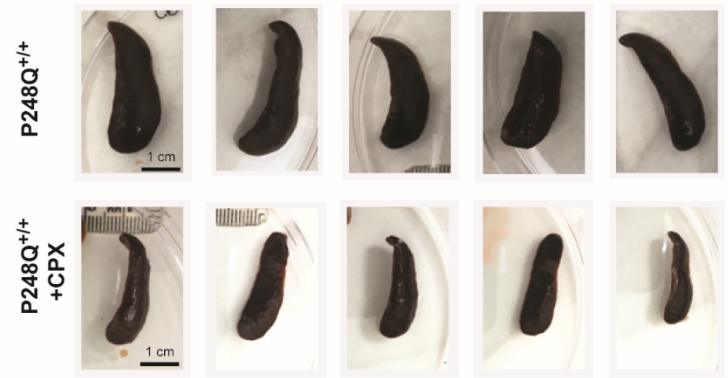


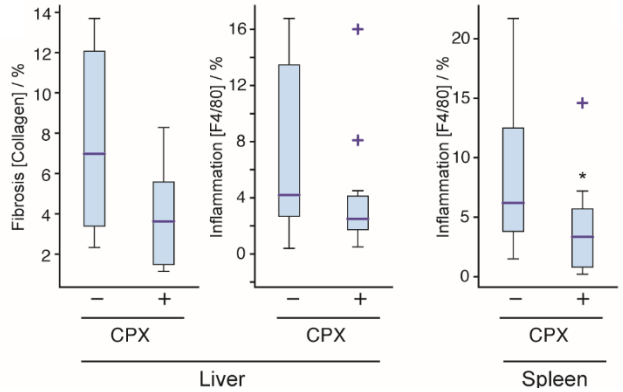


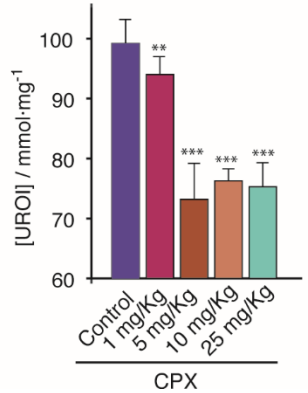


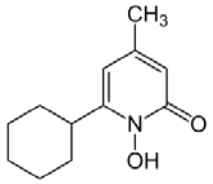












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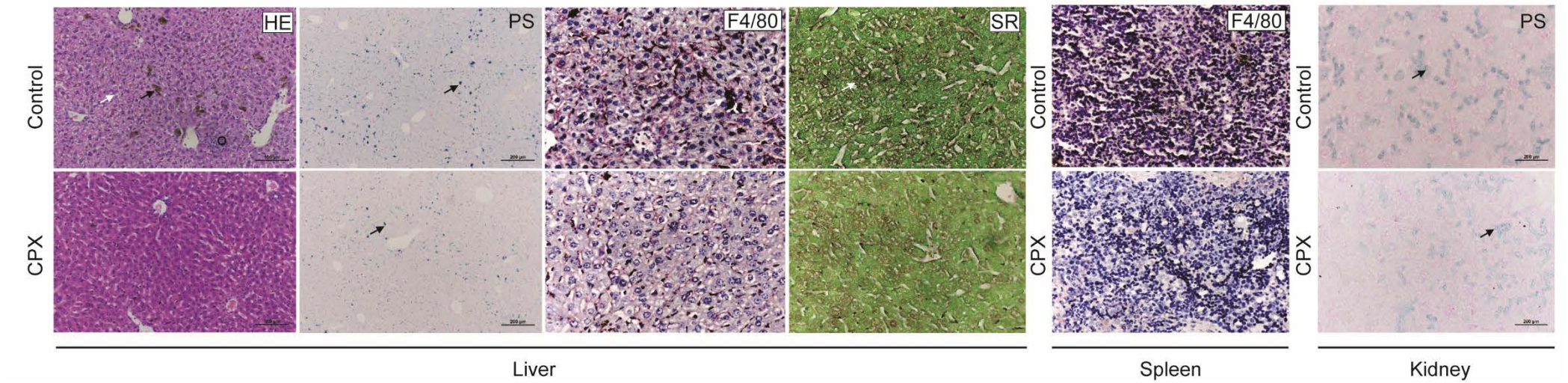

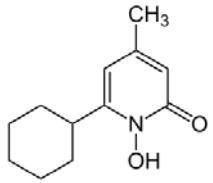

Application to the Orphan Drug Designation

3Q 2017 (September)

- Format: file submission (full dossier).

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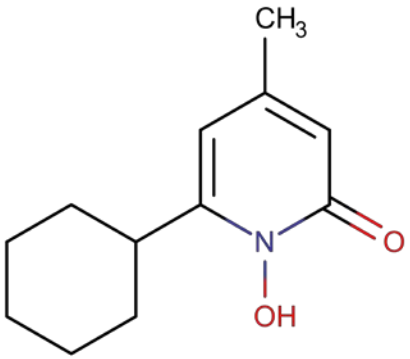
Ciclopirox



Ciclopirox (6-cyclohexyl-1-hydroxy-4-methylpyridin-2-one)
Molecular Weight : 207,269

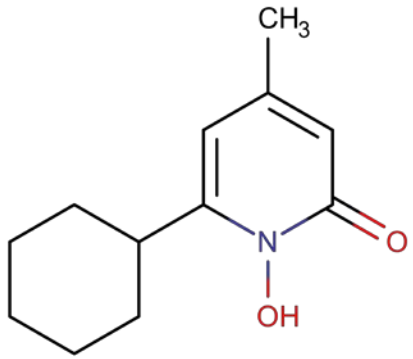
Ciclopirox is an off-patent synthetic antimicrobial agent

- Approved and used for topical treatment of fungal infections
- Our results indicates that ciclopirox is a UROIIIS protein chaperone that stabilise mutated versions of the protein and is partially restoring UROIIIS activity both "in vitro" and "in vivo"

Approval as Orphan Medicinal Product
by the European Commission
January 2018

atlas molecular pharma

Ciclopirox



Ciclopirox (6-cyclohexyl-1-hydroxy-4-methylpyridin-2-one)
Molecular Weight : 207,269

Ciclopirox is an off-patent synthetic antimicrobial agent

- Approved and used for topical treatment of fungal infections
- Our results indicates that ciclopirox is a UROIIIS protein chaperone that stabilise mutated versions of the protein and is partially restoring UROIIIS activity both "in vitro" and "in vivo"

Approval as Orphan Medicinal Product by the European Commission January 2018

Approval as Orphan Drug by the US Food & Drug Administration April 2018