Erythropoietic Protoporphyria (EPP) and Bitopertin

April 25, 2023

disc medicine

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01 **Welcome and Introduction**
John Quisel, J.D., PhD, CEO

02 **EPP Disease Background and Pathophysiology**
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05 **Q&A Session**

Disc is Building a Leading Company Dedicated to Treating Hematologic Diseases

Focus on Hematologic Disorders

Immense medical need across a wide spectrum of disorders

Predictive, objective endpoints

Fundamental & Validated Pathways

Fundamental to red blood cell biology: iron and heme

Clinical and genetic evidence of target mechanism in humans

Multiple Clinical Programs with Broad Potential

Bitopertin in Phase 2

DISC-0974 in Phase 1b/2

MWTX-003 is Phase 1-Ready

Multiple Near-Term Catalysts

Data expected 2023:

Bitopertin in EPP

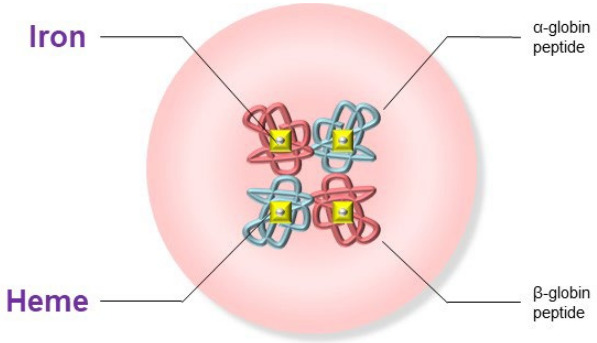
DISC-0974 in MF and NDD-CKD

Initiate Ph 1 MWTX-003

EPP (Erythropoietic Protoporphyria); XLP (X-linked Protoporphyria); MF (myelofibrosis); NDD (non-dialysis dependent);CKD (chronic kidney disease)

Targeting Fundamental Pathways that Impact the Biology of Red Blood Cells

Iron and heme formation play a central role in erythropoiesis



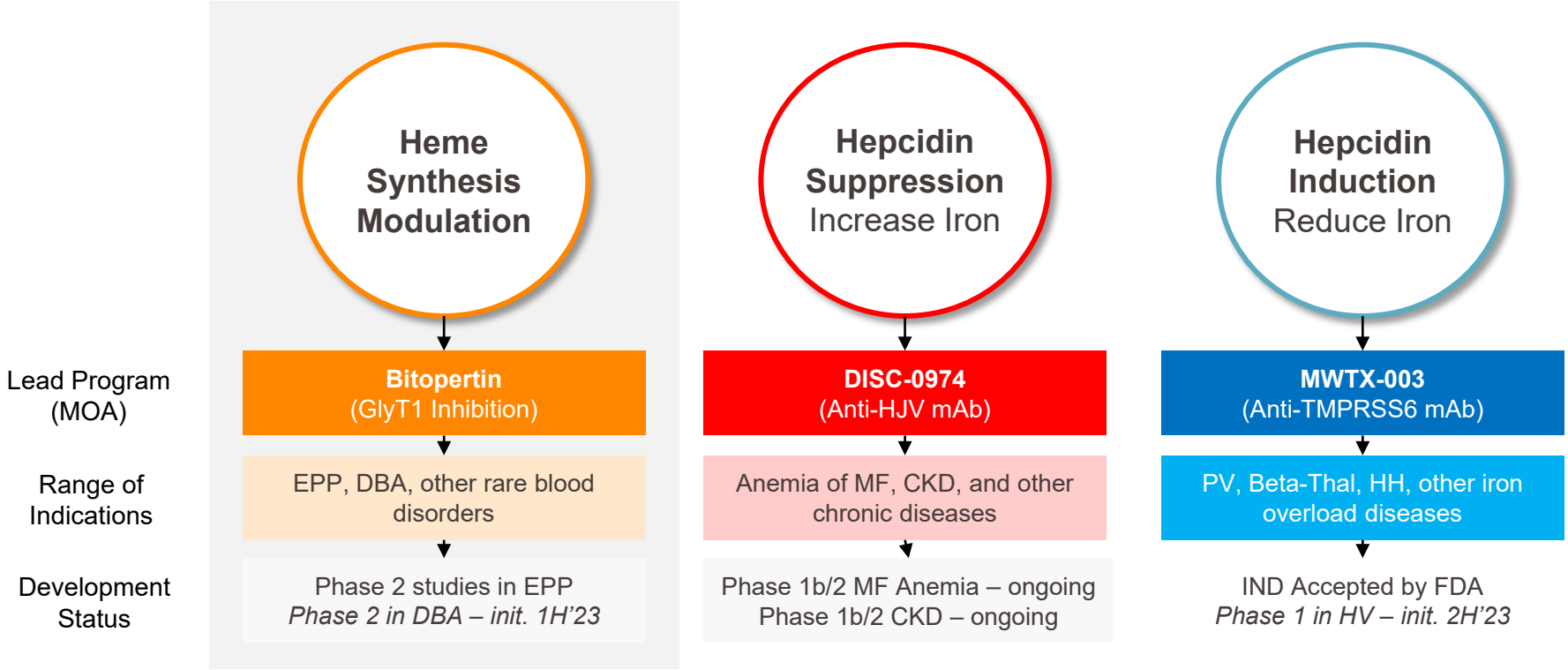
Critical points of intervention across multiple hematologic diseases

Wide Spectrum of Hematologic Diseases Addressable by Disc Portfolio

Severe Rare (000s) — Moderate Prevalence (100K+) — Widely Prevalent (MMs)

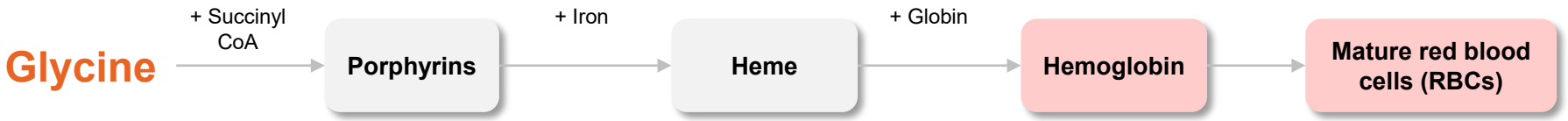
Diamond-Blackfan Anemia	Erythropoietic Porphyrias	Beta-Thalassemia	Anemia of Myelofibrosis	Myelodysplastic Syndromes	Sickle Cell Disease	Polycythemia Vera	Hereditary Hemochromatosis	IBD Anemia	CKD Anemia

Disc's Portfolio Addresses Broad Spectrum of Hematologic Disorders



Dysregulated Hemoglobin Synthesis Drives Disease

Inhibiting heme synthesis with bitopertin has potential to address a wide range of hematologic diseases



Porphyrin Toxicity

Erythropoietic Protoporphyria
X-Linked Protoporphyria
Congenital Erythropoietic Porphyria
Hepatic Porphyrias

Heme Toxicity

Diamond-Blackfan Anemia
Myelodysplastic Syndromes

Globin Toxicity

Beta-Thalassemia
Sickle Cell Disease

Excess RBCs

Polycythemia Vera

bold (trial ongoing) / **bold (trial planned)**

Bitopertin: Oral, Selective GlyT1 Inhibitor

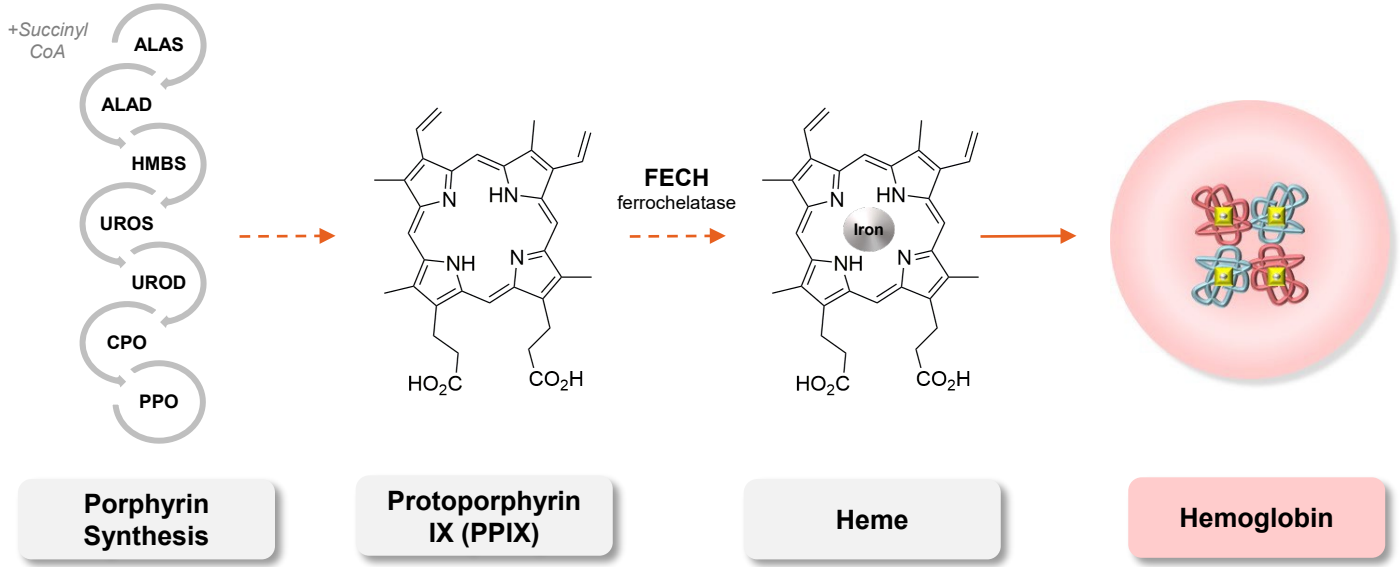
In multiple clinical trials by Roche, bitopertin was observed to modulate heme biosynthesis by blocking uptake of glycine in erythrocytes

Glycine

Critical and initiating precursor for heme biosynthesis and is supplied by **GlyT1 transporter**

Bitopertin

Blocks glycine uptake in RBCs by inhibiting GlyT1



Heme Biosynthesis Pathway

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Bruce Wang, M.D.

Professor at UCSF

Principal Investigator in US Porphyrias Consortium

Disclosures

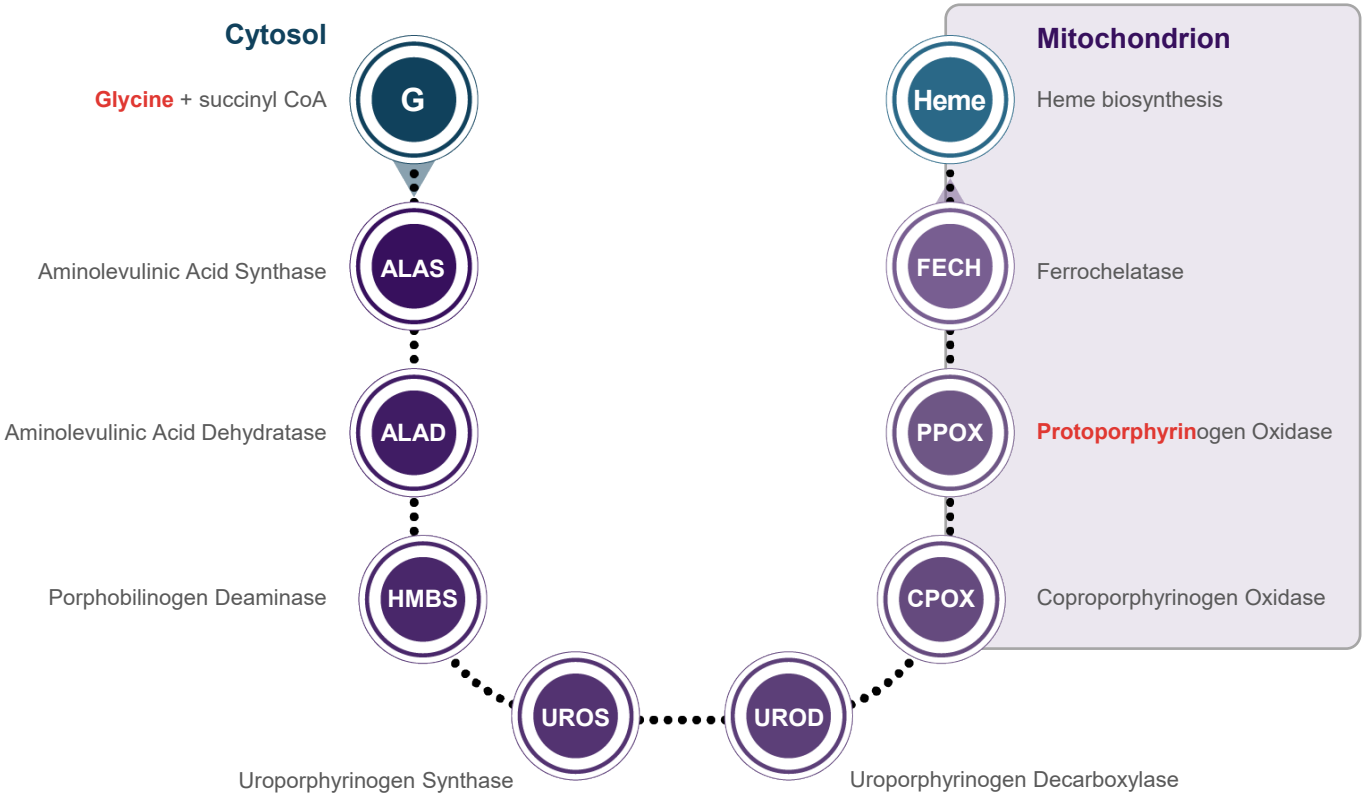
- Alnylam (consultant, investigator in clinical trial, grant funding)
- Disc Medicine (consultant, investigator in clinical trial)
- Mitsubishi-Tanabe (consultant, investigator in clinical trial, grant funding)
- Recordati Rare Diseases (consultant)

Heme synthesis is a complex process underlying the processes of erythropoiesis

- Erythropoiesis is a high-volume and dynamic process that produces 2 million **erythrocytes per second** and consumes the highest amount of body iron for heme synthesis
- Heme is the structural component of hemoglobin and is synthesized in developing erythrocytes
- Heme synthesis occurs in a multi-step process and requires glycine as a critical initial substrate
  - One atom of iron and **8 molecules of glycine** are required for each molecule of heme
- Glycine is supplied by glycine transporter-1 (GlyT1)

Zivot et al. Molecular Medicine (2018) 24:11; Chiabrando et al. Haematologica (2014) 99(6):973-983; Yoshida et al. Blood Transfus (2019) 17(1): 27–52; Garcia-Santos et al. Haematologica 2017; 102(8):1314-1323

Heme synthesis is a tightly regulated process

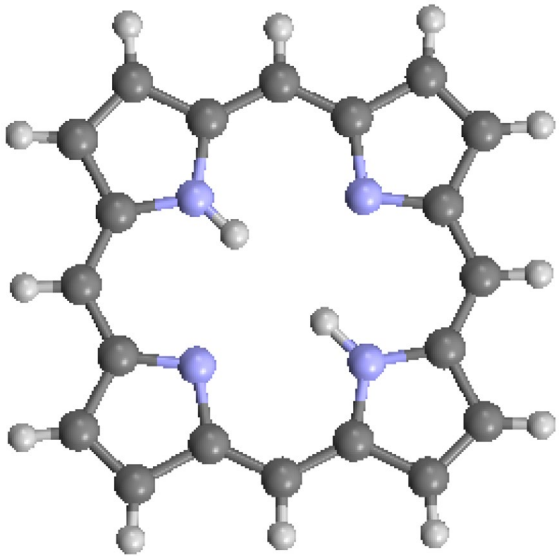


Dysregulation of heme synthesis leads to disease

- Disruptions in heme-synthesis can cause accumulation of porphyrin, giving rise to the family of disorders known as the porphyrias
  - The porphyrias are a group of eight distinct disorders resulting from impaired heme synthesis

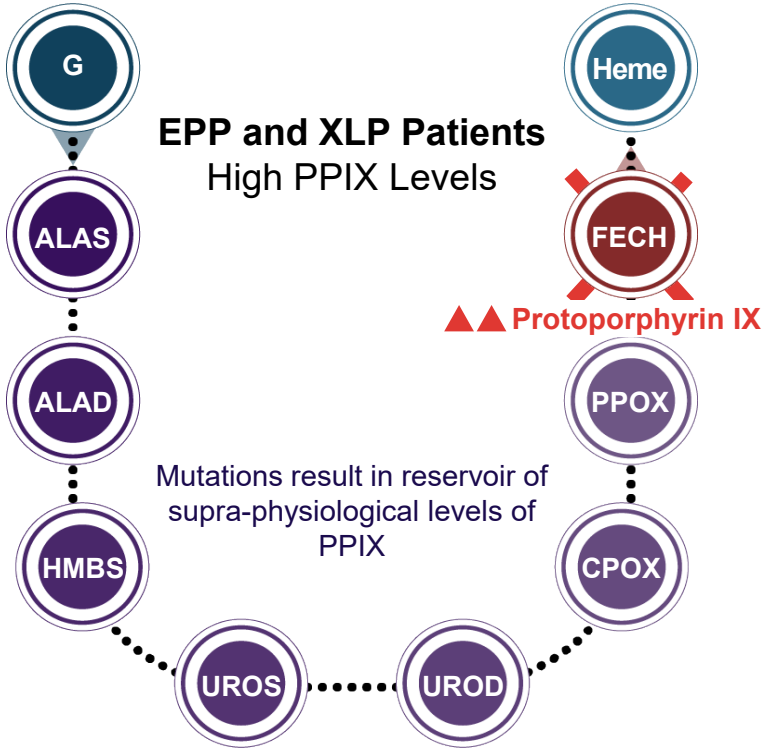
- Porphyria can be acute or chronic, and primarily impact the skin, nervous system, and liver

- Porphyrias can be classified by which body system becomes overactive
  - **Erythropoietic porphyrias** – bone marrow produces excess porphyrins
  - **Hepatic porphyria** – the liver produces excess porphyrins and porphyrin precursors



In EPP, a genetic mutation leads to the buildup of protoporphyrin IX (PPIX)

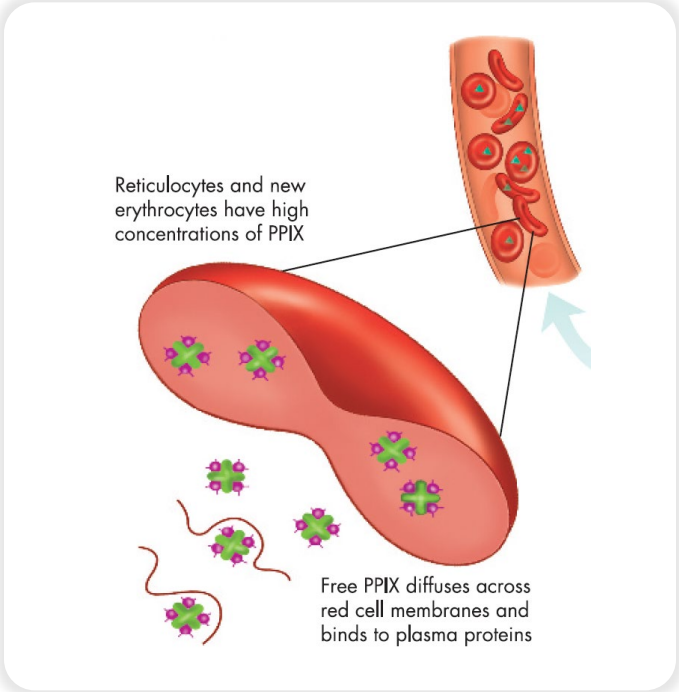
- EPP is caused in most patients by deficient ferrochelatase activity due to mutations of FECH gene
- The deficiency causes a failure to convert protoporphyrin IX (PPIX) into heme in the terminal step of heme synthesis
- PPIX substantially accumulates in erythrocytes, plasma, skin, and liver



Elder et al. Cell Mol Biol (Noisy-le-grand). 2009 Jul 1;55(2):118-26

PPIX is highly toxic and photoreactive

- PPIX molecule absorbs light radiation
- Absorption increases energy content and enables excess energy to be transferred to oxygen, resulting in reactive oxygen species (ROS)
- These oxygen species can injure tissue by membrane lipid peroxidation, complement activation, and mast cell degranulation
- PPIX is also highly toxic independent of the photosensitizing reactions, particularly impacting the liver



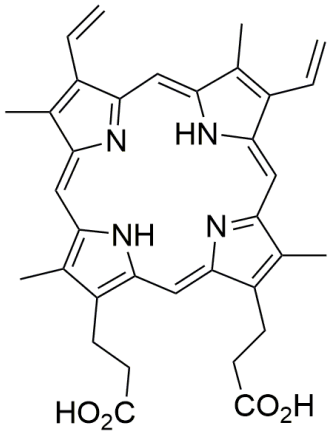
The accumulation of this toxic metabolite can cause a variety of symptoms

Skin

- Porphyrin ring absorbs light and **emits energy and heat**
- Oxidative damage to endothelial capillaries and surrounding tissue, perivascular edema, complement activation
- Pain, burning sensation, swelling, inflammation, chronic skin lesions

Psychosocial

- Issues with focus and concentration
- Lack of sleep, physical and social isolation
- Significant lifestyle modification, fear and anxiety



Protoporphyrin IX

Hepatobiliary

- PPIX accumulation in bile canaliculae, causing oxidative damage
- Cholelithiasis requiring surgery or impaired liver function (~25%) and end-stage liver disease requiring transplant (2-5%)
- Clinical and biochemical surveillance

Other Complications

- Nutritional deficiency resulting in osteoporosis and propensity for fractures, chronic alterations to skin (e.g., fragile), mild anemia

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Jean-Charles Deybach, M.D., PhD

Professor emeritus at Paris Diderot University, France

Past head of the French reference center for porphyria

Past president of the European Porphyria Network (EPNET)

Consultant for Alnylam Pharmaceuticals, Recordati Rare Diseases, Mitsubishi Tanabe, and Disc Medicine

EPP the most recently described inherited porphyria

62 years ago…

«Erythropoietic protoporphyria. A new porphyria syndrome with solar urticaria due to porphyrinaemia»

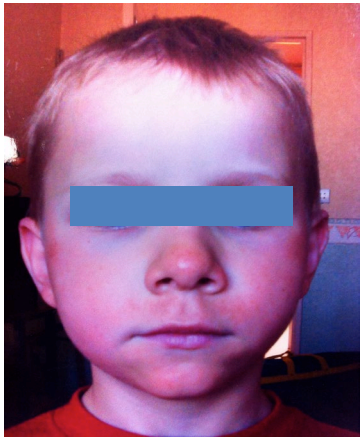
Magnus IA, Jarret A, Prankerd TA, Rimington C, The Lancet 1961

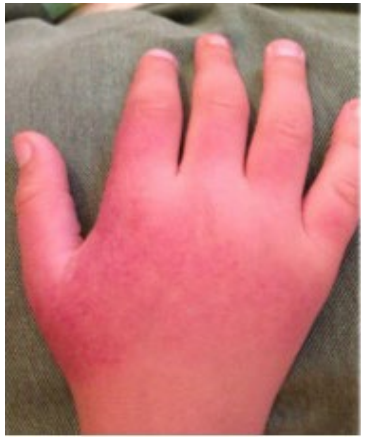
What did we learn about EPP in the past 62 years?

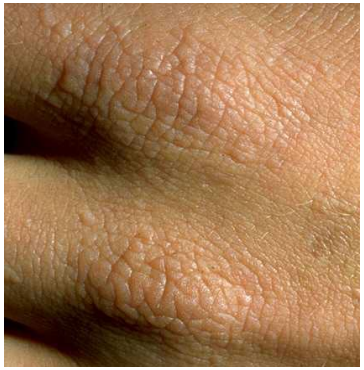
A multi-faceted, multi-gene, multi-organ disease that still has unmet needs

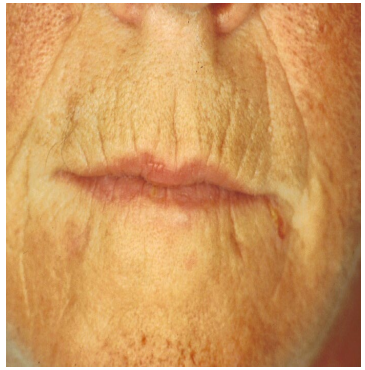
EPP: A distressing painful skin photosensitivity

- **Extreme intolerance to sun, wind and temperature variation**
  - Early childhood
  - Minutes of exposure
  - Painful: tinging, needles stuck into the skin, hands +++
  - Relief by cold material (water…)
  - sleep disrupted
- **Acute phototoxic reaction : Burning, itching, swelling, oedema, erythema, sometimes purpura or vesicles**
- **Chronic lesions: thickened waxy skin, linear scars**









- **Attacks do not respond to pain killers or anti-inflammatory drugs**
- **Diagnosis often delayed**
- **Major impairment of quality of life**
- **Psychosocial complications**

Todd, D.J., Erythropoietic protoporphyria. Br. J. Dermatol. 1994, 1996, 1998

As a result, EPP patients take extreme measures to avoid sunlight

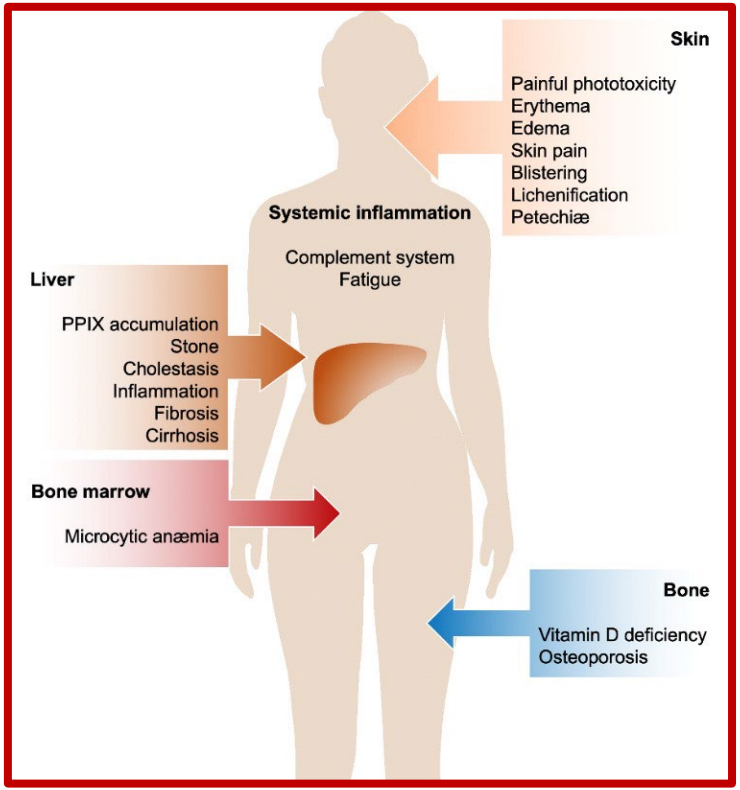
- EPP patients spend most of their time indoors, avoiding the light to prevent a phototoxic reaction
- This can cause patients to miss out on many daily activities and makes attending school or work difficult
- When patients do have to go outside, they may completely cover their skin to avoid sun exposure, wearing long sleeves, hats, and gloves even in summer

However, **EPP is not limited to skin photosensitivity** or a purely dermatological disease with seasonal onset.
It is a **chronic, metabolic, multi-organ disease**

EPP is a multi-dimensional disease

- EPP can result in physical complications affecting:
  - **Skin**: Severe, disabling pain attacks
  - **Hepatobiliary**: gallstones, liver dysfunction or failure
  - **Bone Marrow**: mild microcytic anemia
  - **Bone osteoporosis:** Vit D deficiency
  - **Systemic inflammation**

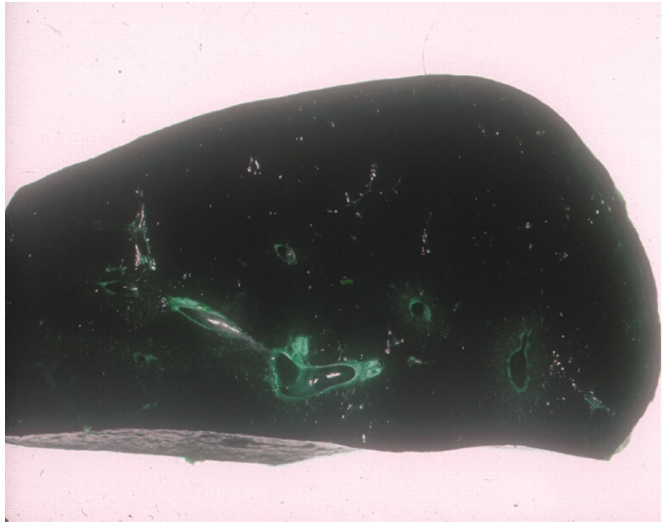
- EPP presents in early childhood and is therefore **a lifelong disease**



Hepatobiliary disease is a potentially severe consequence of liver PPIX accumulation in EPP

Accumulation of protoporphyrin in the liver, as well as porphyrin-induced oxidative stress can lead to liver damage

Over time, excess amount of free protoporphyrin lead to obstruction to bile flow and cholestasis initiating a vicious cycle of worsening cholestasis and reduced protoporphyrin excretion



Patients can experience a variety of hepatobiliary symptoms, ranging from

- **gallstones** (25%)
- **abnormal liver tests** (30%)
- **progressive liver disease and even liver failure** (2-5%) requiring **liver transplantation** with or without combined **bone marrow graft**

The lifestyle modifications required to manage EPP can cause anxiety, depression, and isolation

Due to their condition, EPP patients experience:

- Anxiety (~20% of patients)
- Depression (~10% of patients)
- Social isolation (most patients)
- Fear of future liver disease
- Anger and jealousy about missing out on experiences
- Embarrassment about having to explain the disease

Naik, et al, *Mol Genet Metab*, 2016

The lack of awareness of EPP exacerbates these feelings, as people do not appreciate the severity of the disease

EPP also has a negative impact on the caregivers of EPP patients,
who experience stress and anxiety around ensuring their child is protected from the sun, as well as guilt if other children without EPP miss out on experiences due to their siblings' disease

EPP is a rare disease and often unrecognized

- EPP is the third most common porphyria, and is the most common porphyria in children
- Prevalence for EPP and XLP combined is approximated 1 in 75,000
- This amounts to more than 8,000 patients in the US and EU
- Most patients are diagnosed in early childhood, though some diagnoses take more than a decade from symptoms
- High number of undiagnosed or misdiagnosed EPP patients, likely due to the lack of disease awareness and to recent genetic study suggesting a higher disease prevalence

Lecha, M, et al. Orphanet Journal of Rare Diseases, 2009;4:19

EPP treatment: Unmet needs and emerging therapy

Treatment of patients with EPP has previously built on photoprotection,

e.g., **clothing, physical sunscreen, or afamelanotide**, with some effect on photosensitivity but **no impact on PPIX accumulation**, skin and liver toxicity

Lowering the circulating PPIX by a drug is a novel approach which effects the pathophysiology of the disease

Natural transient improvement in women's EPP life: Pregnancy

Most, if not all, pregnant women with EPP become tolerant to sun exposure after the second trimester

Because of a concomitant

Significant decrease of circulating Protoporphyrin IX

Similar result is therefore expected with Bitopertin treatment

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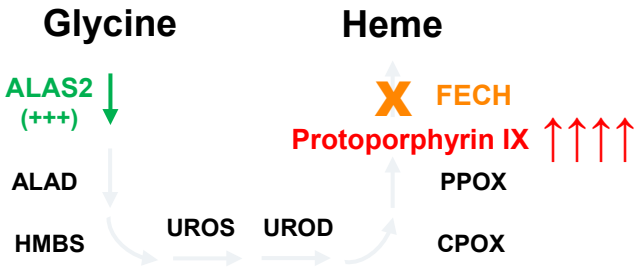
Bitopertin is an investigational agent and is not approved for use as a therapy in any jurisdiction worldwide

Bitopertin: Potential Disease-Modifying Treatment

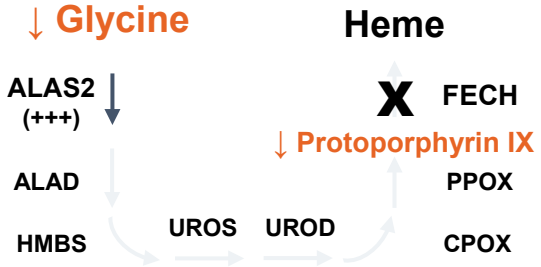
Designed to reduce disease-causing PPIX by limiting uptake of glycine into developing erythrocytes

EPP and XLP Patients
High PPIX Levels



Mutations result in reservoir of supra-physiological levels of PPIX

Bitopertin Treatment
Designed to Reduce PPIX Levels



Potential first disease-modifying treatment for EPP and XLP

Figures adapted from Halloy et al. (2021) Cell Chem Biol

A >30% reduction in PPIX levels has been shown to significantly impact photosensitivity

Pregnant EPP Patients

- During pregnancy, EPP patients experience a **30-50% reduction in PPIX levels**
- This reduction is accompanied by a **marked improvement in light tolerance**

PPIX Photoinactivation Study

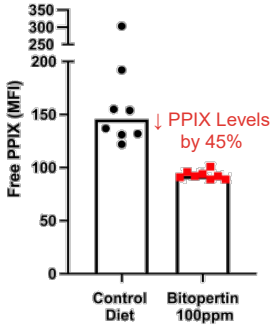
- Patients' blood was exposed to light outside their body then returned to the patient
- The procedure reduced PPIX levels by ~30%
- As a result, **daylight tolerance was increased by 14x** on average (e.g., from 30 minutes at baseline to 7 hours post-treatment)

Poh-Fitzpatrick, J Am Acad Dermatol 1997;36:40-3; Wulf et al. Photodiagnosis Photodyn Ther. 2020;29:101582

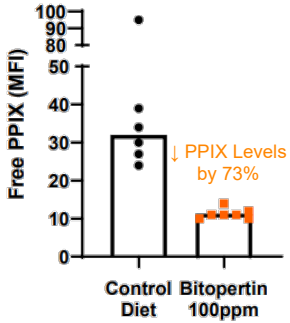
Bitopertin Reduced PPIX in Models of EPP / XLP

Effects on PPIX have the potential to be disease-modifying

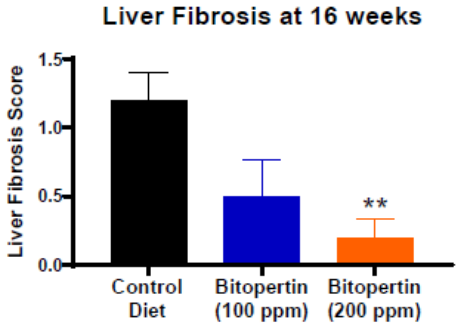
In vivo - EPP Model (Mouse)
FECH^{m1pas} Missense Mutation



In vivo - XLP Model (Mouse)
ALAS2^{Q548X} Gain-of-Function Mutation



In vivo – EPP Model (Mouse)
FECH^{m1pas} Missense Mutation



In these models, bitopertin reduces PPIX, the driver of disease pathophysiology, and is expected to be disease-modifying

Reductions in PPIX levels of ≥30% reported in literature to have a major impact on photosensitivity in patients†;

Data presented at the 63rd ASH Annual Meeting (December 2021); Studies performed in collaboration with Boston Children's Hospital (PI: Paul Schmidt, Advisor: Mark Fleming)
Sources: † Heerfordt et al. (2016) Br J. Dermatol.; Wulf et al. (2019) Photodiagn and Photodyn Ther; Poh-Fitzpatrick (1997) J Am Acad Derm

BEACON Trial: Open-Label Ph 2 Trial in EPP / XLP

Open-label, parallel-dose trial to establish POC and assess efficacy, safety in patients (N~20)

Study Design

- Open-label, randomized
- EPP and XLP; 18 years +
- Two dose levels, parallel
- Not receiving afamelanotide
- Australia (study open July ‘22)

Treatment Arms

20 mg QD Bitopertin

60 mg QD Bitopertin

Tx Duration: 24 weeks

Study measures: Changes in blood PPIX levels, light tolerance, time to prodromal symptom (TTPS), hepatobiliary markers, QOL, safety / PK

Data availability: Interim, open-label, PPIX data expected 1H 2023

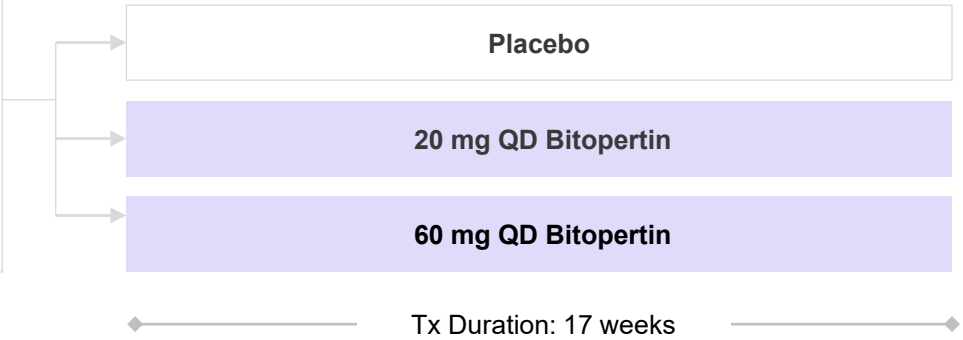
AURORA Trial: Ph 2 Trial in EPP

Randomized, Double-Blind, Placebo Controlled trial to assess efficacy, safety in patients (N~75)

Study Design

- Double-blind, placebo-controlled (1:1:1)
- EPP; 18 years +
- Stratified by light tolerance
- Not receiving afamelanotide
- US (IND cleared, start 2H 2022)

Treatment Arms



Study measures: Changes in blood PPIX levels, time in daylight without pain, light tolerance, time to prodromal symptom (TTPS), hepatobiliary markers, QOL, safety / PK

Data availability: Data expected by 2H 2023

Phase 2 Trial Endpoints

Reduction in PPIX and several measures of light tolerance

Primary Endpoint: Changes in whole blood metal-free PPIX levels from baseline

Key Secondary Endpoints: Multiple measures of changes in light tolerance

01 **Total hours of sunlight exposure on days with no pain from 10:00 am to 6:00 pm**

- This endpoint is measured as the sum of all hours patients have spent in the sun without pain between the hours of 10 am and 6 pm across the entire treatment period

02 **Daily sunlight exposure time to first prodromal symptom associated with sunlight exposure**

- A “prodrome” / “prodromal symptom” are the early signs of a phototoxic reaction, described by patients as burning, tingling, itching, or stinging
- Patients will fill out a sun exposure diary every day during the treatment period, capturing the amount of time a patient has spent in the sun that day, as well as any symptoms they experienced
- Once per week patients are asked to complete a “sun exposure challenge” in which they spend time in sunlight until they experience a prodrome and capture how long they were in the sun

03 **Pain intensity of phototoxic reactions (measured on a Likert scale)**

04 **PRO questions on light tolerance, light sensitivity, and impact of disease on quality of life**

Development Status and Upcoming Milestones

Phase 2 BEACON and AURORA trials initiated; BEACON data expected by 1H'23

Next EPP Milestones

- Interim open label data from the BEACON trial – *to be presented in June 2023*
- AURORA trial data – *topline expected YE 2023*
- BEACON trial data –*topline expected YE 2023*

Additional Milestones

- Phase 2 IIT in Diamond-Blackfan Anemia at NIH – startup expected mid-year 2023
- Planning underway for studies in additional indications

Q&A

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Thank You

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