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Rare disease therapeutics

Program Pack

Ornithine transcarbamylase deficiency (OTC) (mRNA-3139)

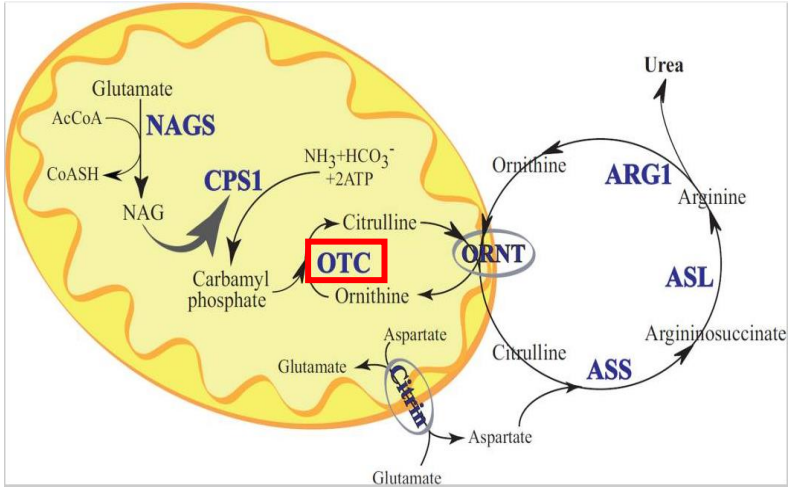
OTC overview

Natural history and clinical course

- Ornithine transcarbamylase (OTC) deficiency is a rare x-linked inherited disorder. Hemizygous males are typically more severely affected than heterozygous females.
  - **Neonatal onset** patients with complete deficiency present with acute hyperammonemia in the first week of life and have more severe disease
    - ➢ Incidence estimated to be 1:57,000 live births
  - **"Late onset"** patients present with symptoms after the first month of life, often in early childhood but sometimes later in adolescence or adulthood
  - ~10% of **heterozygotic female carriers** become symptomatic; this could happen at any time
- Patients who are not well controlled by diet and medications suffer recurrent hyperammonemic crises and accompanying encephalitis, resulting in long term mental impairment, coma, or death
  - Only ~10% of neonatal onset patients survive past 7 years of age; 60% die within the first 7 days of life
  - Except for the most severe cases in the late onset patients and female carrier groups, these patients have a normal life expectancy
- **OTC deficiency can be functionally *cured* via liver transplant**

Pathophysiology

- Encoded by OTC, ornithine transcarbamylase is a mitochondrial enzyme that catalyzes formation of citrulline from ornithine and carbamyl phosphate in the liver and small intestinal mucosa
- Lack of OTC blocks normal ureagenesis, resulting in hyperammonemia and elevated levels of glutamine and orotic acid



Source: Summar. *Mol Genet Metab.* 2013; Brassier. *Orphanet J Rare Dis.* 2015; Batshaw. *Mol Genet Metab.* 2015; Konecki. *GeneReveiws.* 2013; Yamaguchi. *Hum Mutat.* 2006; Cardovic. *J Genet Genomics.* 2015

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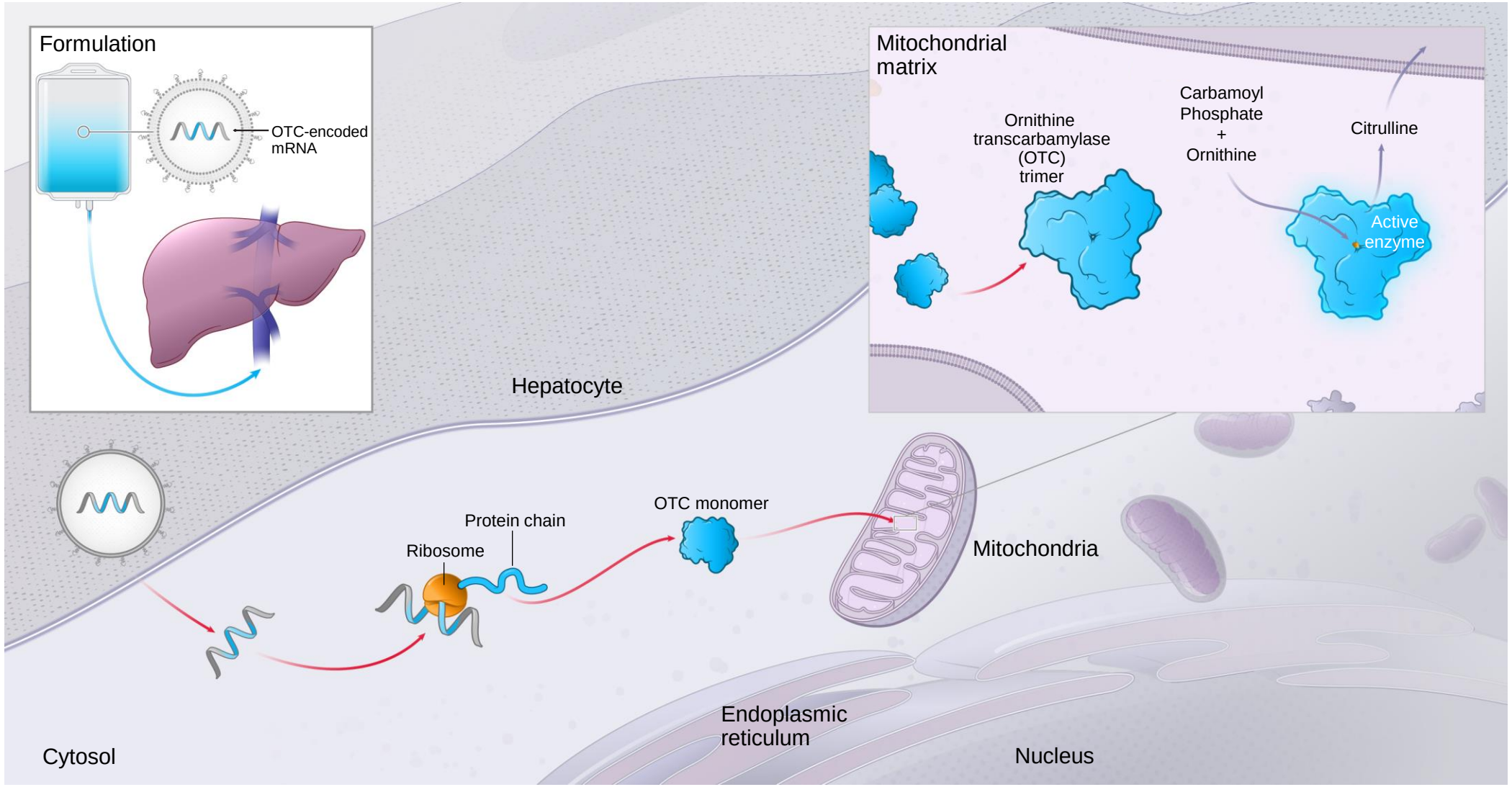
Moderna's OTC program (mRNA-3139)



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