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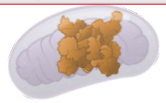
Propionic acidemia (PA) (mRNA-3927)

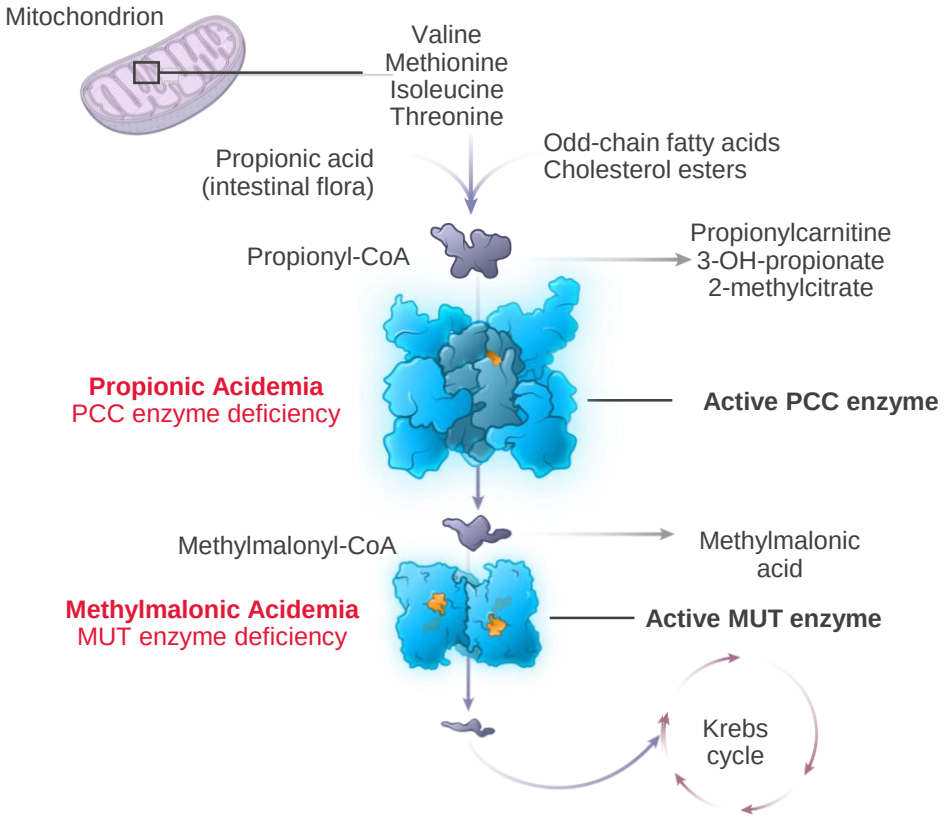
Last updated: December 6, 2018

Modality	Program #	Program *Indication*	Preclinical development	Phase 1	Phase 2	Phase 3 and commercial	Moderna rights
Systemic intracellular therapeutics	mRNA-3704	MUT *Methylmalonic acidemia, MMA* 					Worldwide
	mRNA-3927	PCCA+PCCB *Propionic acidemia, PA* 					Worldwide
	mRNA-3283	PAH *Phenylketonuria, PKU* 					Worldwide

mRNA-3927 is in IND-enabling GLP toxicology studies

Organic acidemias

Multiple candidates targeting same metabolic pathway



MMA and PA

- Similar biology and disease pathology
- Shared KOLs and centers of excellence
- Relative prevalence in any given locale is a function of local founder effects/ consanguinity
  - MMA: ~500-2,000 patients in the US*
  - PA: ~325-2,000 patients in the US*

mRNA advantages

*Ability to encode for **intracellular** proteins, **localized** to mitochondria*

*Potential to treat during **acute** metabolic decompensations*

*Based on estimated birth prevalence (MMA: 0.3-1.2:100,000 newborns; PA: 0.2-1.2:100,000 newborns) and mortality rates

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Propionic acidemia (PA) (mRNA-3927)

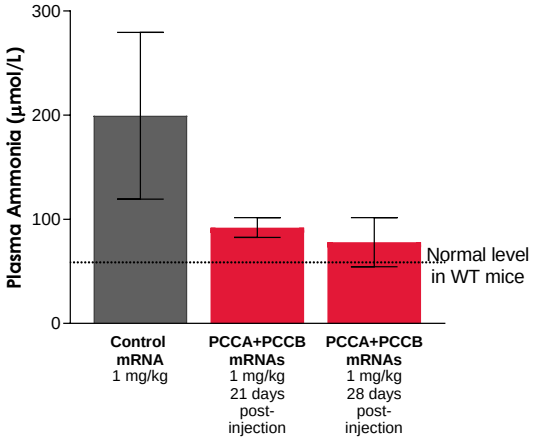
Pre-clinical data show restoration of enzyme activity

Study Design:

Species: **Mouse**

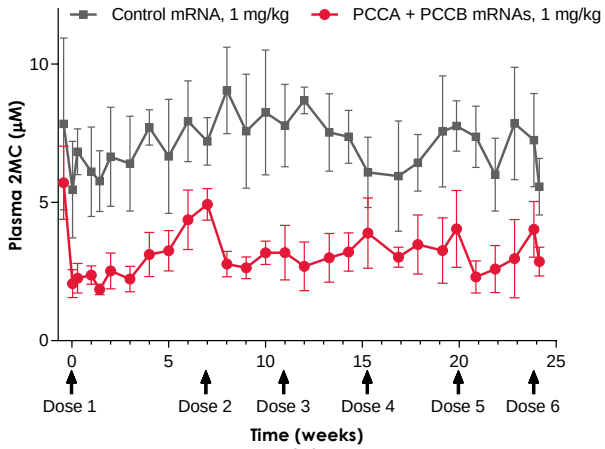
- Animals: PA^
- Dose: 1 mpk (A); 1 mpk (B); 0.5-1 mpk (C)
- Dosing Schedule: Single (A); approximately monthly for doses 2-6[1] (B,C)
- Injection Route: IV
- Sample Size: 4-5/group (A); 6/group (B,C)

Reduction in plasma ammonia with PCCA+PCCB mRNA



(A)

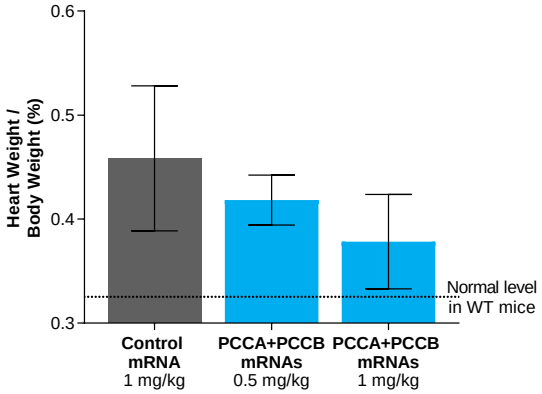
Reduced plasma 2-methylcitrate levels with repeat dosing of PCCA+PCCB mRNA



(B)

Data presented as mean ± standard deviation.

Decrease in heart weight with PCCA+PCCB mRNA in 6 month repeat dose study



(C)

Data presented as mean ± standard deviation.

We have demonstrated preclinical proof-of-concept for the combined PCCA and PCCB mRNA therapy in in vivo studies

^Pcca-/-(A138T) mice (Guenzel et al Mol Ther 2013)

[1] Biomarkers monitored for 7 weeks after first dose to determine duration of response, then approximately monthly dosing

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Clinical development plan

Combined natural history study, and two phase 1/2 MAD studies in pediatric MMA and PA patients

Global natural history study:

- First patients enrolled in global natural history study for MMA and PA
- Identifying and correlating clinical and biomarker endpoints
- Global, multi-center, non-interventional study:
  - Patients confirmed with MMA due to MUT deficiency or PA
  - Up to 60 MMA patients and up to 60 PA patients in the US and Europe will be followed prospectively for 1-3 years
  - Retrospective data to be collected as available

2 Phase 1/2 clinical trials, for mRNA-3704 in MMA and mRNA-3927 in PA:

- Open-label, multi-center, dose escalation Phase 1/2 study (US and Europe)
- **Objectives**
  - Evaluate safety and tolerability
  - Characterize the pharmacodynamic response
  - Characterize the pharmacokinetic profile
  - Assess clinical incidence and severity of clinical events

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