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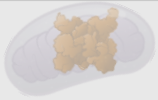
Methylmalonic acidemia (MMA) (mRNA-3704)

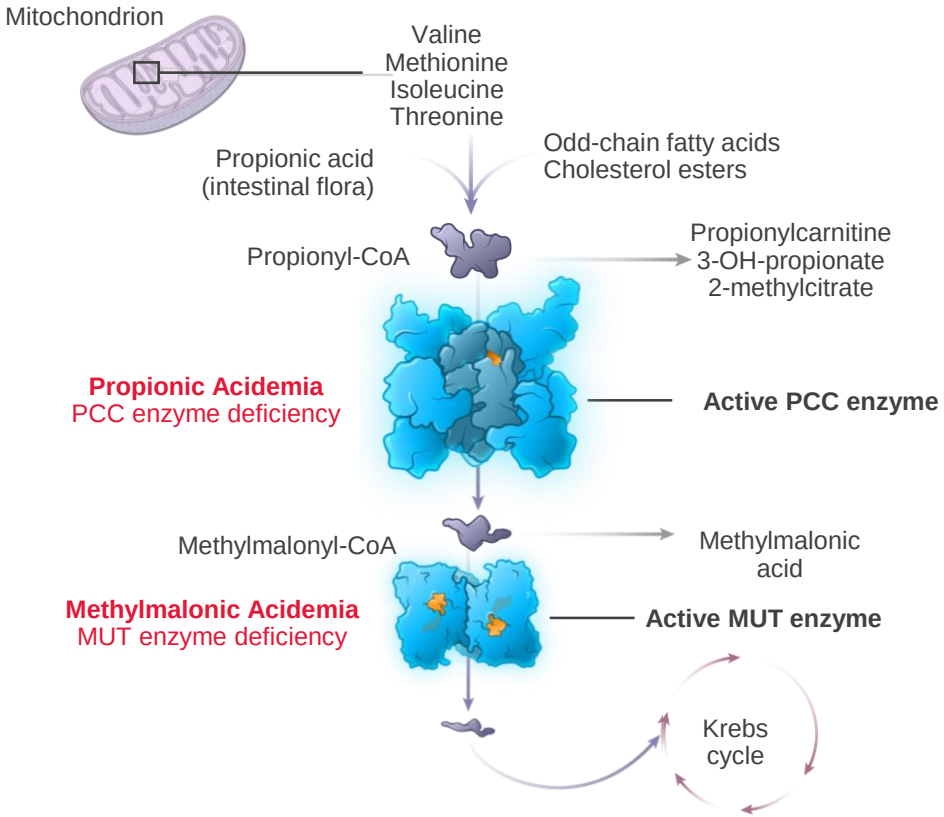
Last updated: January 8, 2019

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

IND filed for mRNA-3704 Phase 1/2 study

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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Methylmalonic acidemia (MMA) (mRNA-3704)

Pre-clinical data show restoration of enzyme activity

Study Design:

Species: Mouse

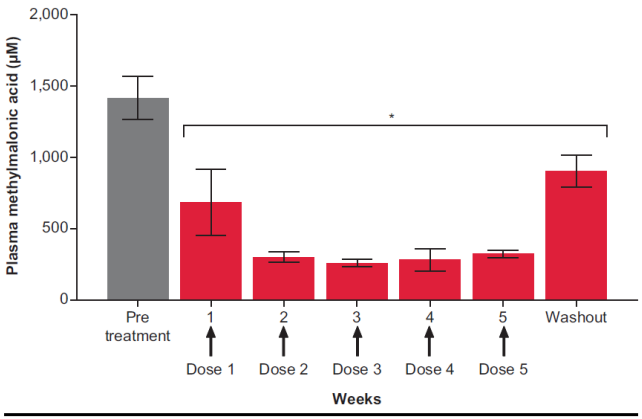
- Animals: mut^0
- Dose: 0.2 mpk
- Dosing Schedule: weekly
- Injection Route: IV
- Sample Size: 6-7/group

Study Design:

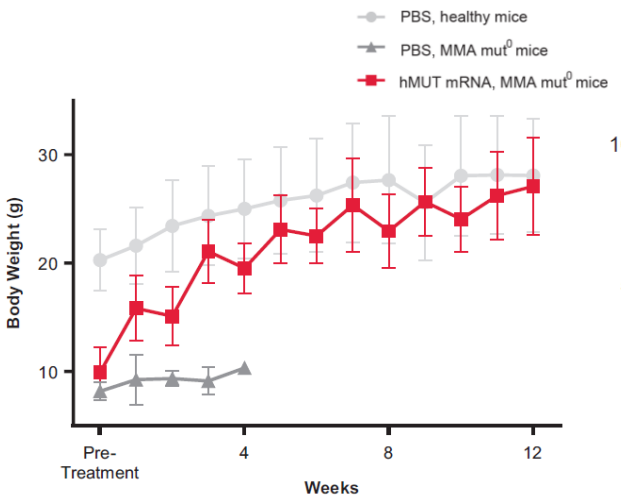
Species: Mouse

- Animals: mut^0
- Dose: 0.5 mpk
- Dosing Schedule: every other week
- Injection Route: IV
- Sample Size: 6/group

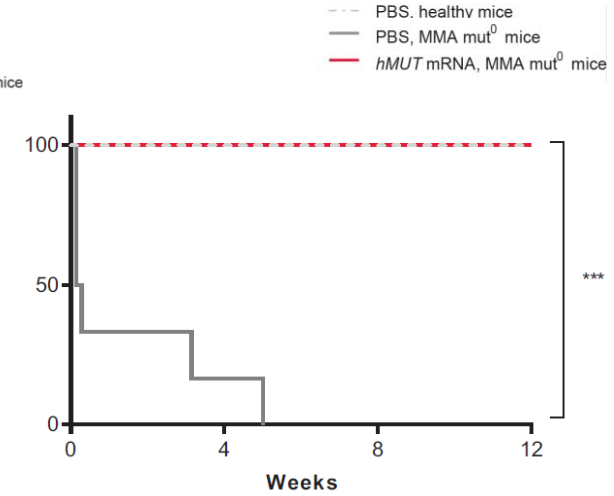
Decrease in plasma methylmalonic acid with in 6-week study in mouse disease model



Increase in body weight in a 12-week study in mouse disease model



Improved survival in a 12-week study in mouse disease model



*p<0.01 from paired t-test of post-treatment vs. pre-treatment levels

MMA mut^0 mice are *Mut*$^{-/-}$;Tg$^{INS\text{-}MCK\text{-}Mut}$ mice

***p<0.001 hMUT mRNA vs. PBS-injected MMA mut0 mice from log-rank test

We have observed pronounced improvement in survival due to mRNA treatment in an MMA mouse model

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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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