Methylmalonic acidemia (MMA) (mRNA-3705)

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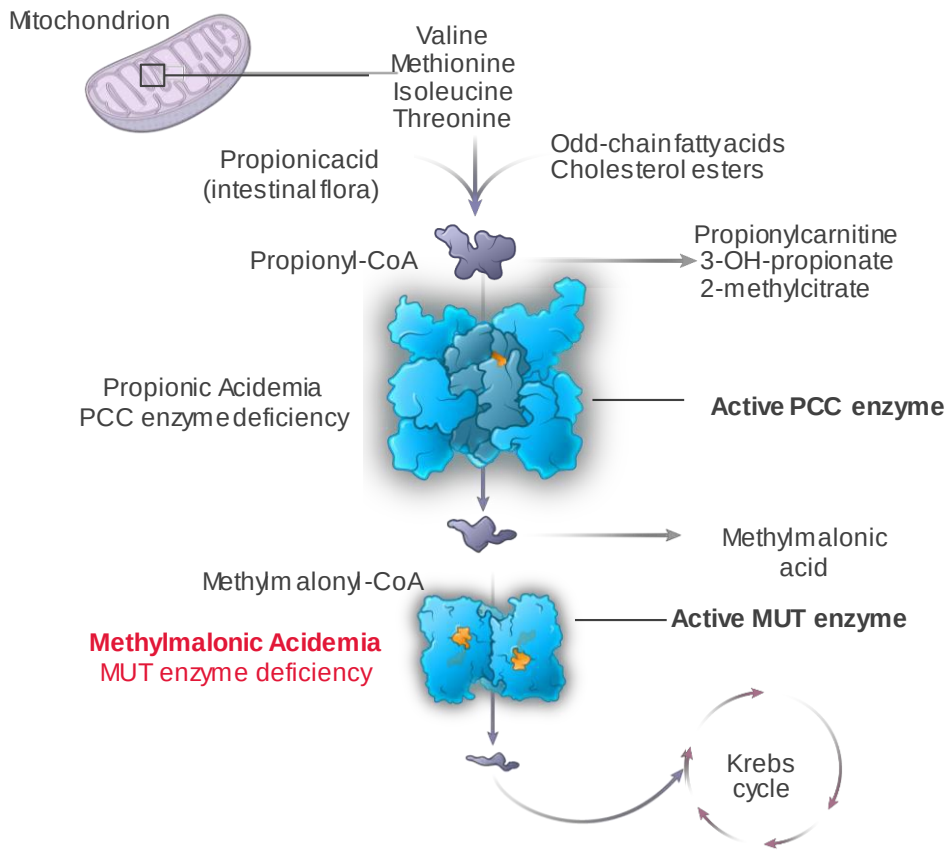
Modality	Program	ID #	Preclinical development	Phase 1	Phase 2	Phase 3	Commercial	Moderna rights
Systemic secreted & cell surface therapeutics	Relaxin *Heart failure*	**mRNA-0184**						Worldwide
	PD-L1 *Autoimmune hepatitis*	**mRNA-6981**						Worldwide
	Personalized cancer vaccine (PCV)	**mRNA-4157**						50-50 global profit sharing with **Merck**
Cancer vaccines	KRAS vaccine	**mRNA-4671**						Worldwide
	Checkpoint vaccine	**mRNA-4359**	Open IND					Worldwide
Intratumoral Immuno-oncology	OX40L/IL-23/IL-36γ (Triplet) *Solid tumors/lymphoma*	**mRNA-2752**						Worldwide
	IL-12 *Solid tumors*	**MEDI1191**						50-50 U.S. profit sharing; **AZ** to pay royalties on ex-U.S. sales
Localized Regenerative Therapeutics	VEGF-A *Myocardial ischemia*	**AZD8601**						Worldwide
	Propionic acidemia (PA)	**mRNA-3927**						Worldwide
	Methylmalonic acidemia (MMA)	**mRNA-3705**						Worldwide
Systemic Intracellular Therapeutics	Glycogen storage disease type 1a (GSD1a)	**mRNA-3745**						Worldwide
	Phenylketonuria (PKU)	**mRNA-3283**						Worldwide
Inhaled Pulmonary Therapeutics	Crigler-Najjar syndrome type 1 (CN-1)	**mRNA-3351**						Provided to **ILCM** free of charge
	Cystic fibrosis (CF)	**VXc-522**						**Vertex** to pay milestones and royalties

MMA therapy (mRNA-3705) encodes for the MUT enzyme

- Methylmalonic acidemia (MMA) refers to a rare, autosomal recessive acidemia
  - Affects 1/100,000 in various regions of the world (except in Middle East where it affects 6/100,000)
- It is caused by a defective or missing MUT enzyme (methylmalonic CoA mutase)
- **Changes in the *MMUT gene* causes methylmalonic acidemia**
  - Gene provides instructions for making an enzyme called methylmalonyl CoA mutase
  - Changes in the gene disrupt the function of the enzyme and prevent the normal breakdown of molecules



Methylmalonic acidemia (MMA) has no approved therapies

- **Primarily a pediatric disease** with onset in early infancy; significant mortality and morbidity
- **Treatment:** There is no approved therapy for MMA
- **Current interventions include:**
  - Dietary restriction, cofactor therapy and carnitine
  - Liver and/or kidney transplant is the only effective treatment, even in infants (but transplant is not curative and is associated with mortality)

MMA Clinical Manifestations

- Recurrent episodes of **life-threatening metabolic decompensations**
- **Progressive multi-organ damage**
  - Brain damage
  - Seizures
  - Intellectual disability
  - Severe vision problems
  - Inflammation of the pancreas (pancreatitis)
  - Chronic renal failure
  - Heart failure (cardiomyopathy); heart rhythm problems
  - Increased risk of having a metabolic stroke as early as a few weeks of age
  - Osteoporosis which can lead to fractures
  - Hematologic: reduced number of cells in blood (anemia, leukopenia, thrombocytopenia, pancytopenia)
  - Growth retardation

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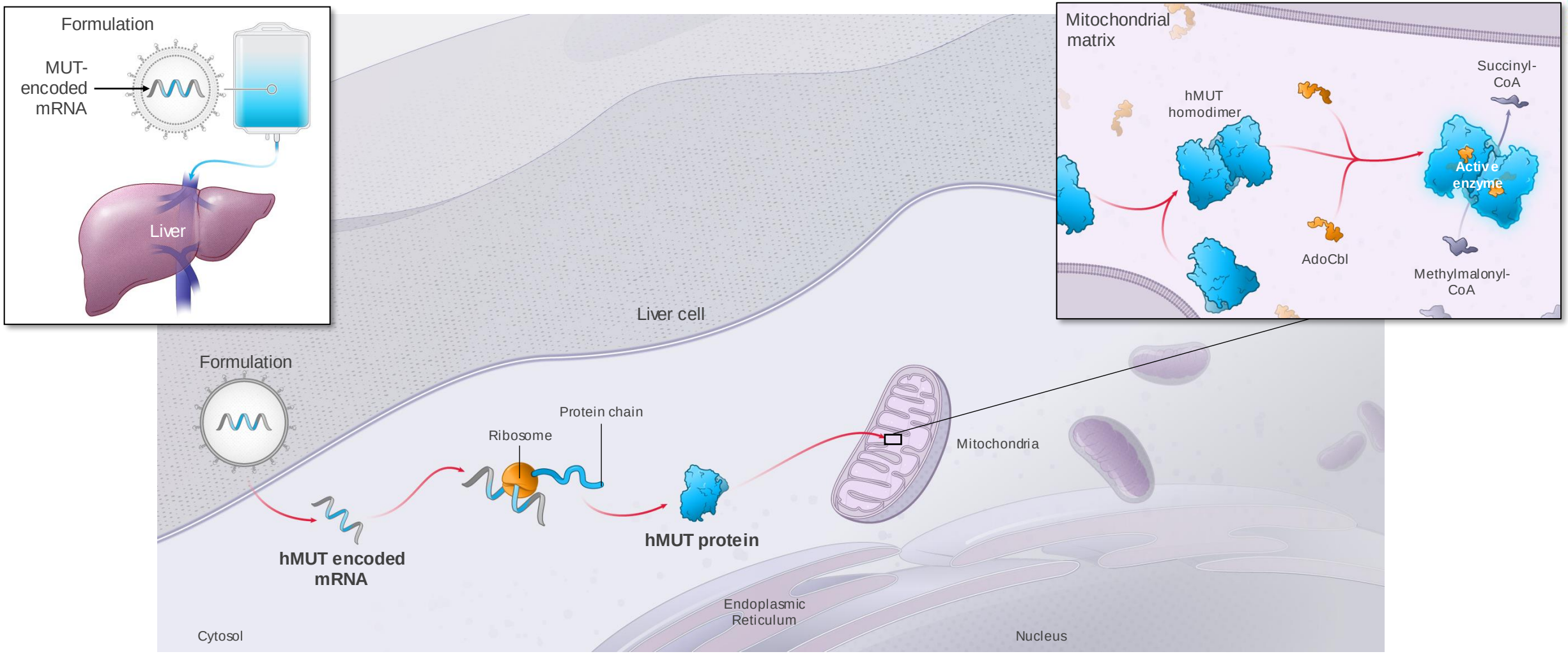

Note: AdoCbl = cofactor adenosylcobalamin

Methylmalonic acidemia (MMA) ongoing in Phase 1/2 study

Key objective
- To evaluate the safety and pharmacology of mRNA-3705 in patients 1 year of age and older with methylmalonic acidemia (MMA)

Primary endpoint
- Safety
- Pharmacokinetics and Pharmacodynamics

Secondary endpoint
- Incidence and severity of adverse events (AEs)
- Change in plasma biomarkers: methylcitric acid (2-MC) and methylmalonic acid

landmark study

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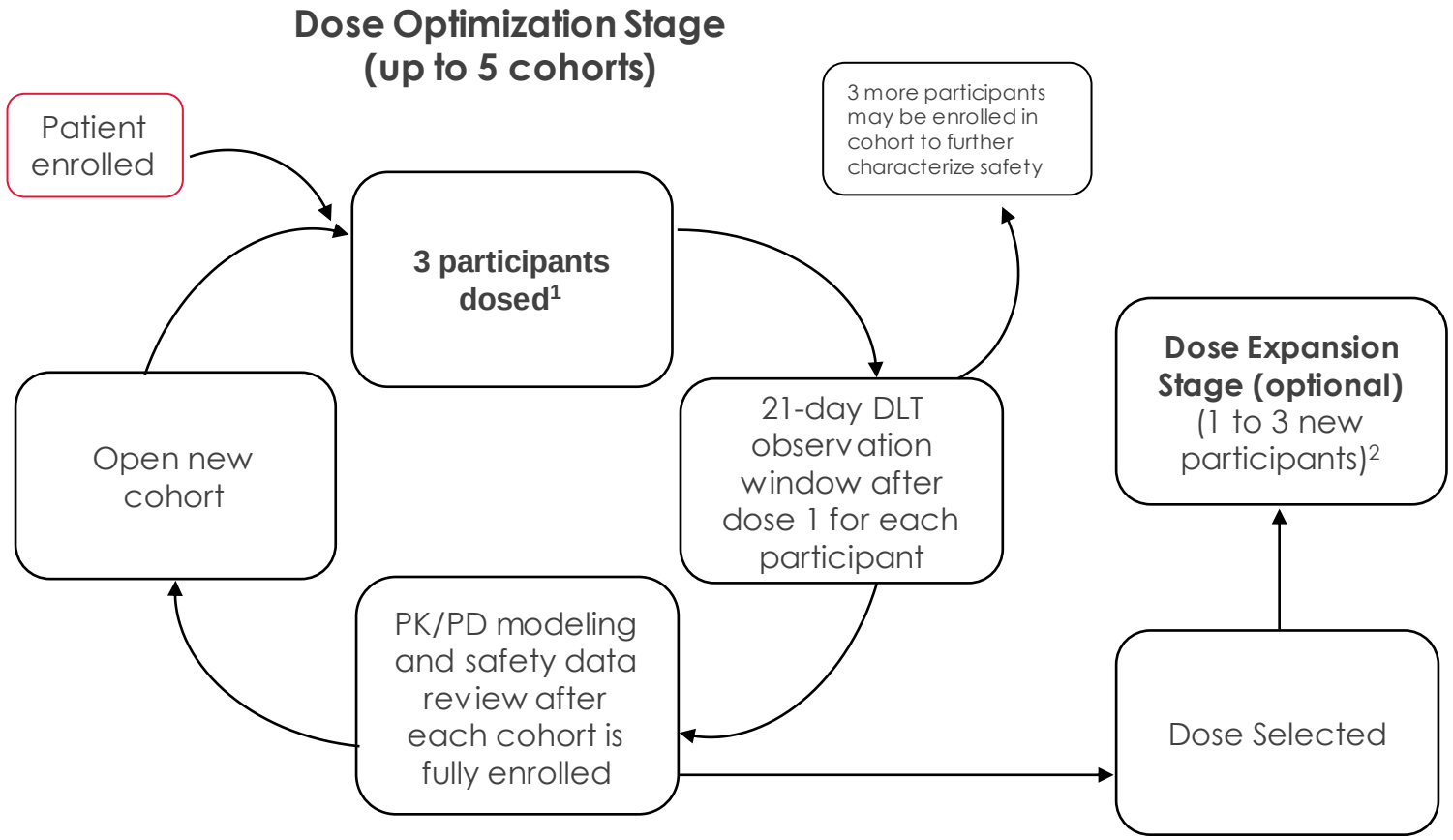

- MMA (mRNA-3705) ongoing in Phase 1/2 study (Landmark study)
- First cohort is fully enrolled and we are enrolling patients into additional cohorts

Abbreviations: DLT = dose-limiting toxicity; PD = pharmacodynamic; PK = pharmacokinetic
A DLT observation window only applies after Dose 1; events occurring thereafter (> 21 days after the first dose and Doses 2 through 10) will be recorded as adverse events (AEs)/serious adverse events (SAEs) but will not be considered DLTs.

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