

# ADVANCES IN THE TREATMENT OF MMA : CAN GENE THERAPY WORK?

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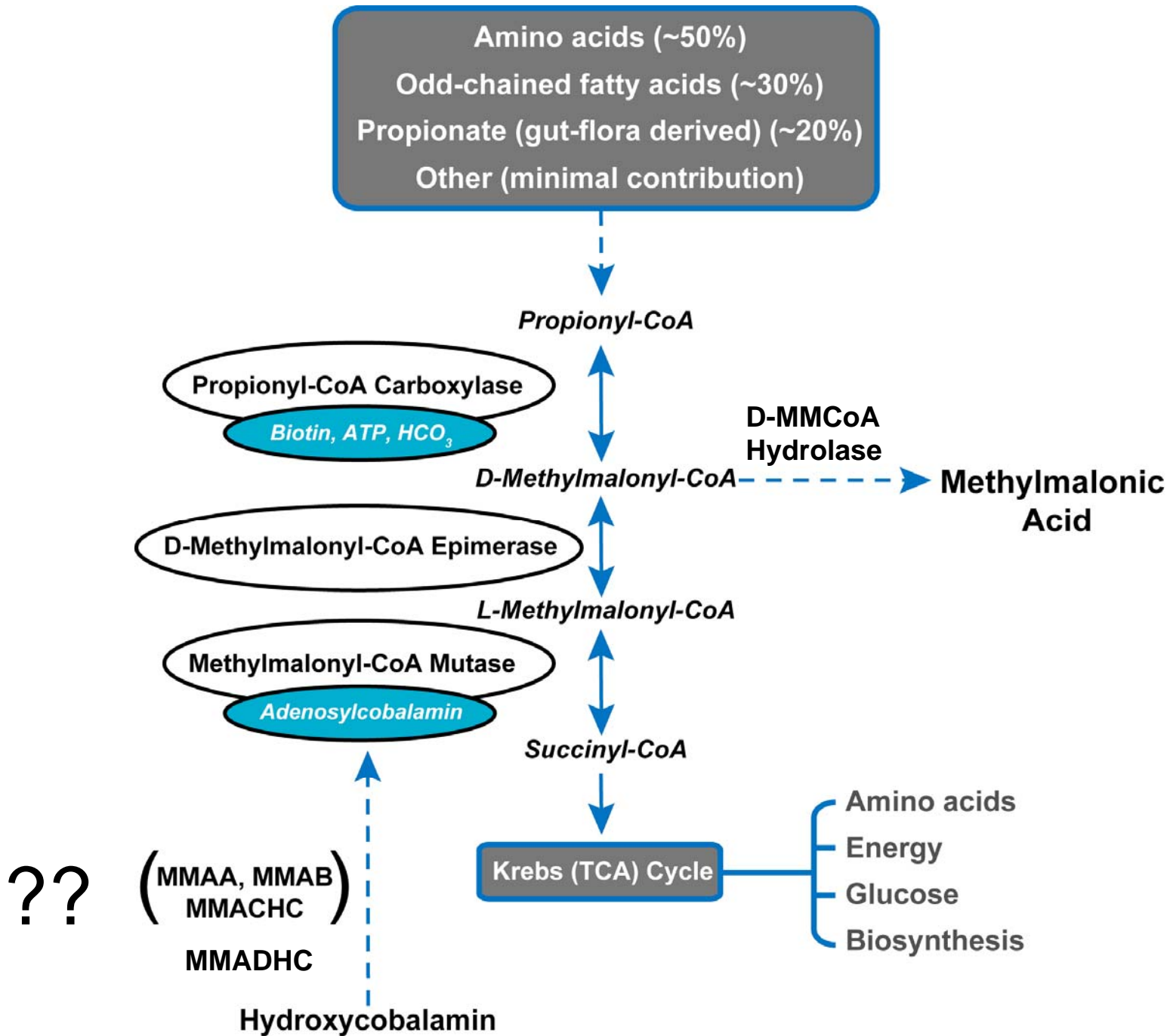
# NIH

QuickTime™ and a  
TIFF (Uncompressed) decompressor  
are needed to see this picture.

# Methylmalonic Acidemia/uria

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- A group of inborn errors of metabolism, first described in the late 1960s
- Genetic heterogeneity
- Phenotype of metabolic instability and multiorgan system pathology
- Guarded prognosis in severe cases
- Most (>95%) US newborns screened for MMA
- ? TRADITIONAL THERAPY INEFFECTIVE IN SEVERE CASES



# CLINICAL MANIFESTATIONS

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**METABOLISM: SEVERE INSTABILITY/FRAGILITY**

**GROWTH: STUNTED**

**GI: VOMITING, PANCREATITIS, ANOREXIA**

**NEUROLOGICAL: STROKE SYNDROME**

**RENAL: KIDNEY FAILURE**

**HEMATOLOGICAL: CYTOPENIAS**

**IMMUNE: FUNGAL AND GRAM NEGATIVE  
INFECTIONS**

**FAMILY/SOCIAL: DISRUPTIVE TO FAMILY LIFE**

# ACMG Panel - Used by 95% USA

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## CORE PANEL

10 Organic Acidemias (**MUT, MMAA, MMAB**; IVA, GA I, HMG, MCD, 3-MCC, PROP, BKT)

5 FAO

6 AA

## SECONDARY TARGETS

6 Organic Acidemias (**MMACHC, MMADHC**; MAL, IBG, 2M3HBA, 2MBG, 3MGA)

8 FAO 8

AA

# Research Goals

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- CLINICAL SPECTRUM OF MMA/CBL
- DISEASE MECHANISMS
- THERAPEUTIC INTERVENTIONS

# Approaches to Study Hereditary Methylmalonic Acidemia and Cobalamin Metabolic Disorders

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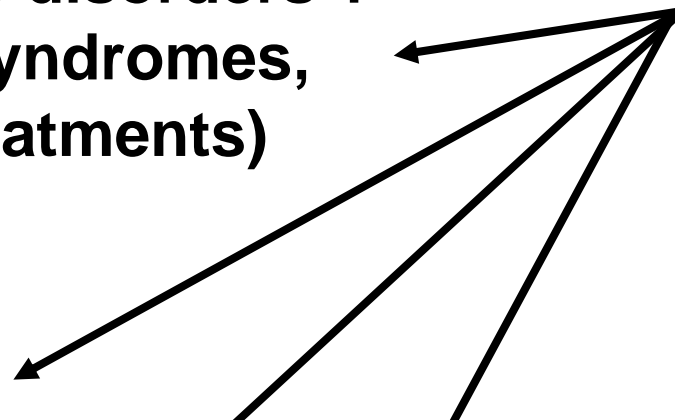
## Questions

## Model System

What is natural history of the disorders ?  
(metabolic instability, CNS syndromes,  
renal failure, pancreatitis, treatments)

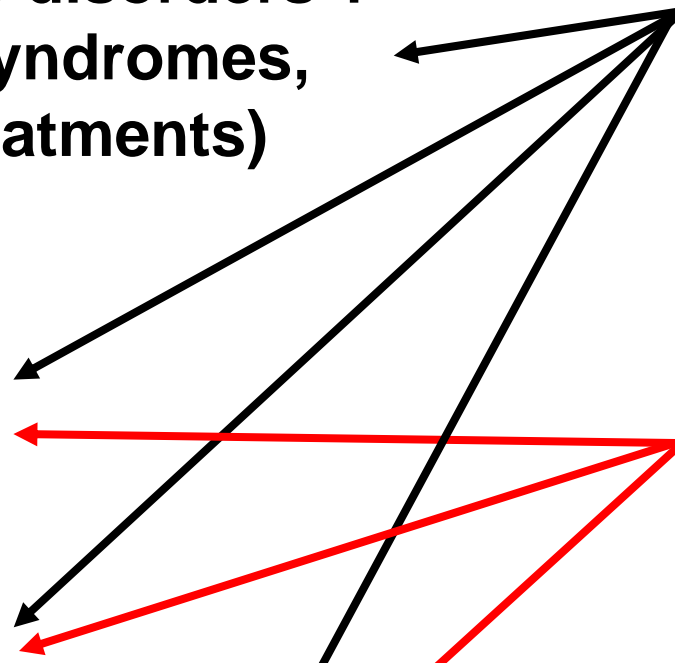
**Human**

What causes the pathology?



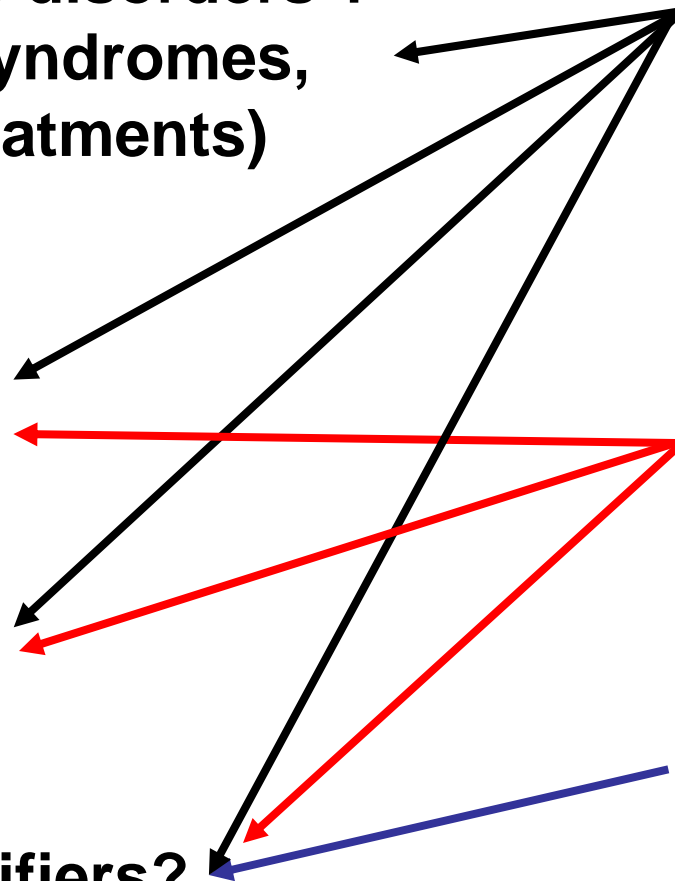
**Mouse  
Zebrafish**

How effective are therapies?



**Mouse  
C. elegans**

What are the genes and modifiers?



# Clinical Research: Natural History Studies

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- **Since June 2004, >100 visits for 68 patients and families**
- **Areas of focus**
  - **enzymatic/genotype/phenotype correlations**
  - **MMA transplantation**
  - **CNS manifestations in MMA/cbl syndromes, esp the MMA stroke syndrome**
  - **clinical and ophthalmologic correlations (cblC)**

# Research Goals

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- CLINICAL SPECTRUM OF MMA/CBL
- DISEASE MECHANISMS
- THERAPEUTIC INTERVENTIONS
  - GENE THERAPY

# Why should we consider gene therapy for MMA?

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- Traditional therapies not effective for severely affected patients
- Enzyme replacement not feasible/available
- LT and L(K)T pts display a drastically ameliorated phenotype
- Gene therapy will not eliminate other treatment options
- MAJOR UNKNOWN - CAN IT WORK ??

# Outcome of B12 Non-Responsive MMA

## STUDY

## MORTALITY

<ul style="list-style-type: none"><li>• NEJM (1983) 308:857<ul style="list-style-type: none"><li>• 45 pts total (15 mut<sup>o</sup>, 5 mut<sup>-</sup>)</li></ul></li></ul>	60% mut <sup>o</sup> , 40% mut <sup>-</sup>
<ul style="list-style-type: none"><li>• J Ped (1994) 125:903<ul style="list-style-type: none"><li>• 26 B12 non-responsive</li></ul></li></ul>	53%
<ul style="list-style-type: none"><li>• Arch Dis Child (1998) 78:508<ul style="list-style-type: none"><li>• 28 B12 non-responsive</li></ul></li></ul>	50%
<ul style="list-style-type: none"><li>• Ped Res (2007) 62:225<ul style="list-style-type: none"><li>• 83 pts total, (42 mut<sup>o</sup>, 11 mut<sup>-</sup>)</li></ul></li></ul>	47% mut <sup>o</sup> , 45% mut <sup>-</sup>

# Gene Therapy Experiments

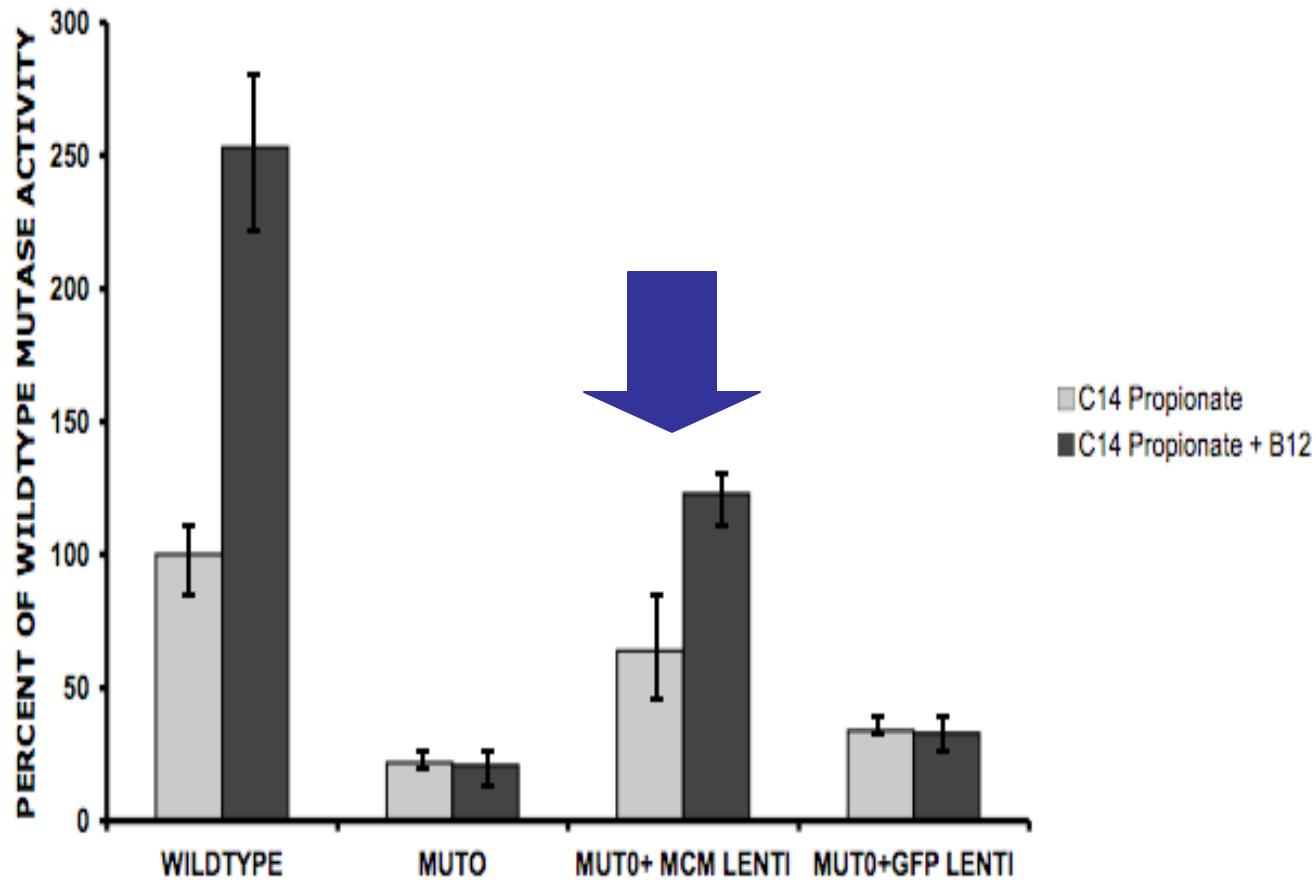
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- Lentiviral
- Adenoviral

# Lentiviral Vector and Correction Studies

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Vector : pLENTI, CMV-murine Mut gene, also carries Blast<sup>R</sup>



**Enzymatic**

**Correction**

# Gene Therapy Experiments

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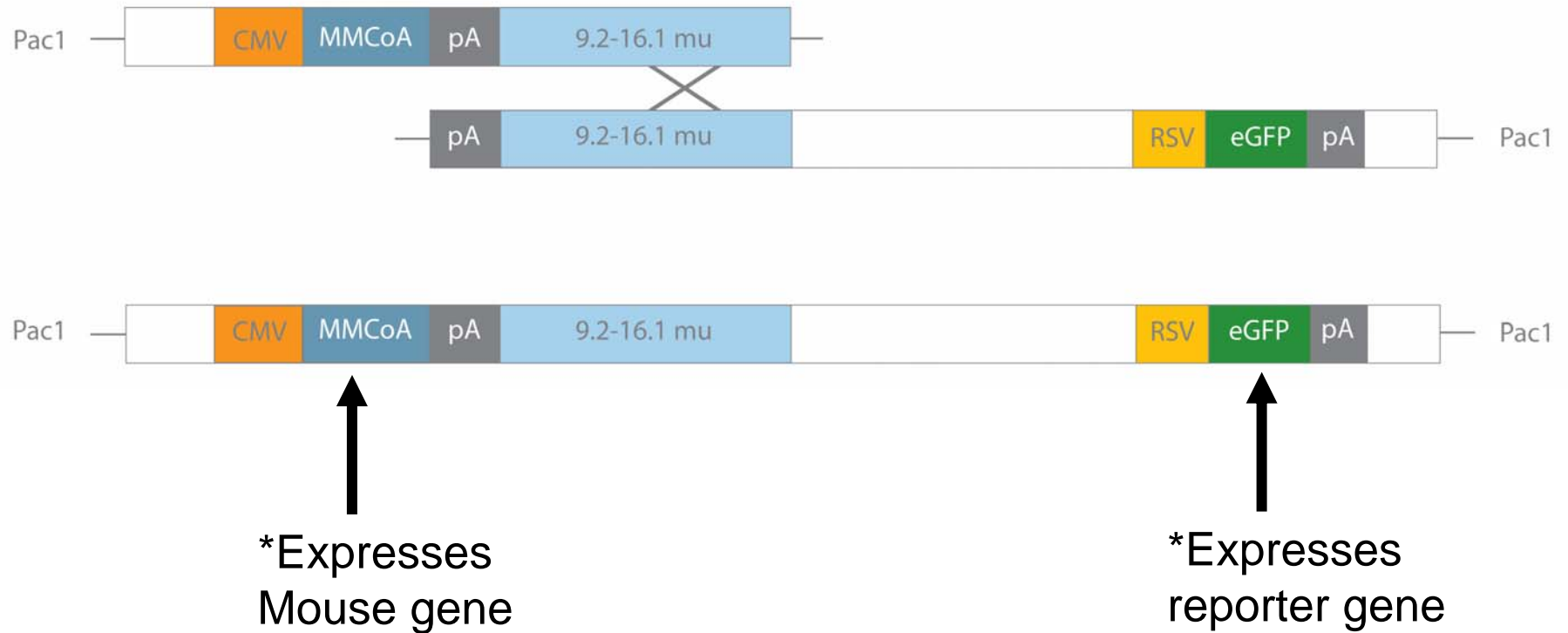
- Lentiviral
- Adenoviral

Chandler et al 2007 BMC Medical Genetics 8:24

Chandler and Venditti 2008 Hum Gene Therapy 19:53

# Adenoviral Vector Construction

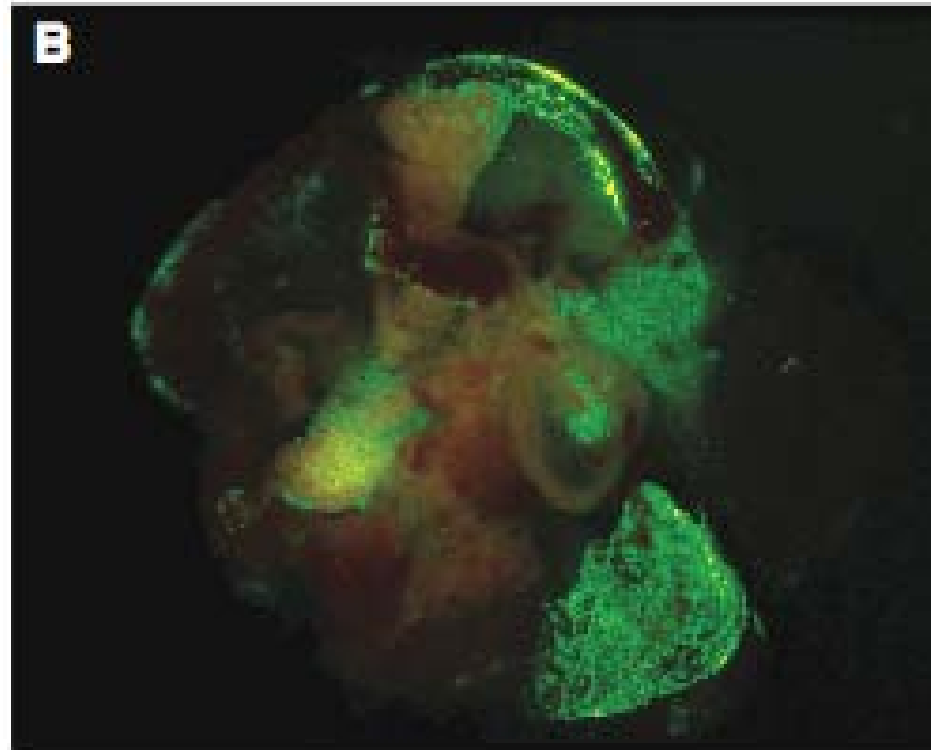
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# Adenoviral Vector and *In Vivo* Expression Studies

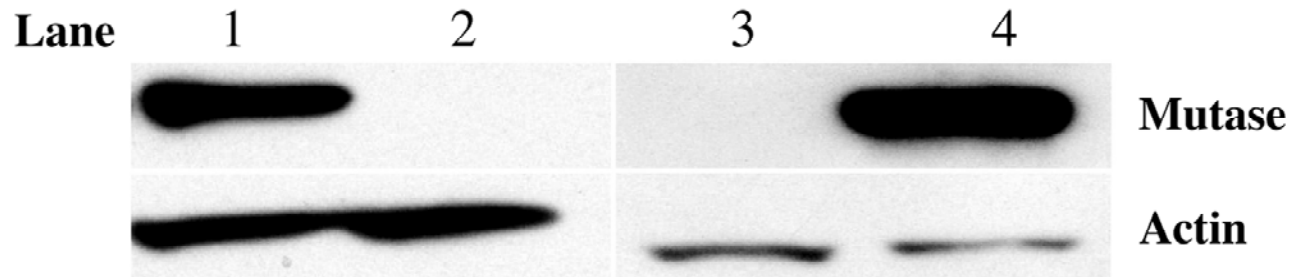
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Ad-Mut-eGFP delivered by  
direct-hepatic injection  
at birth

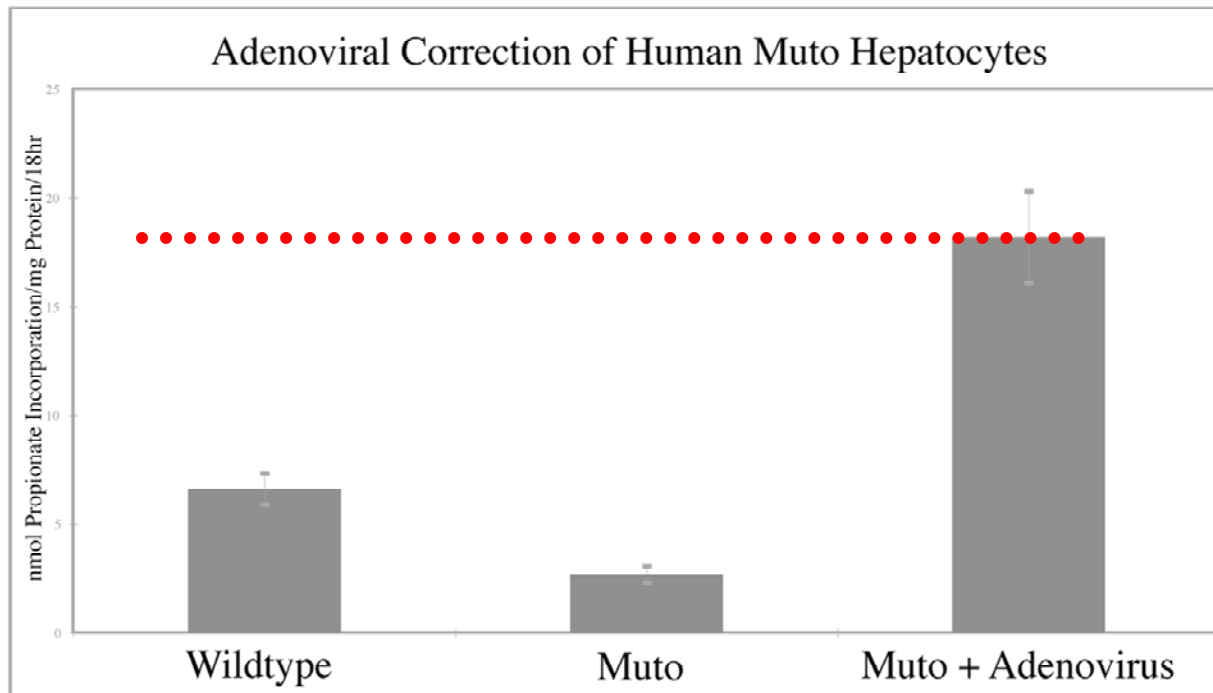


# CORRECTION OF HUMAN MUTO LIVER CELLS

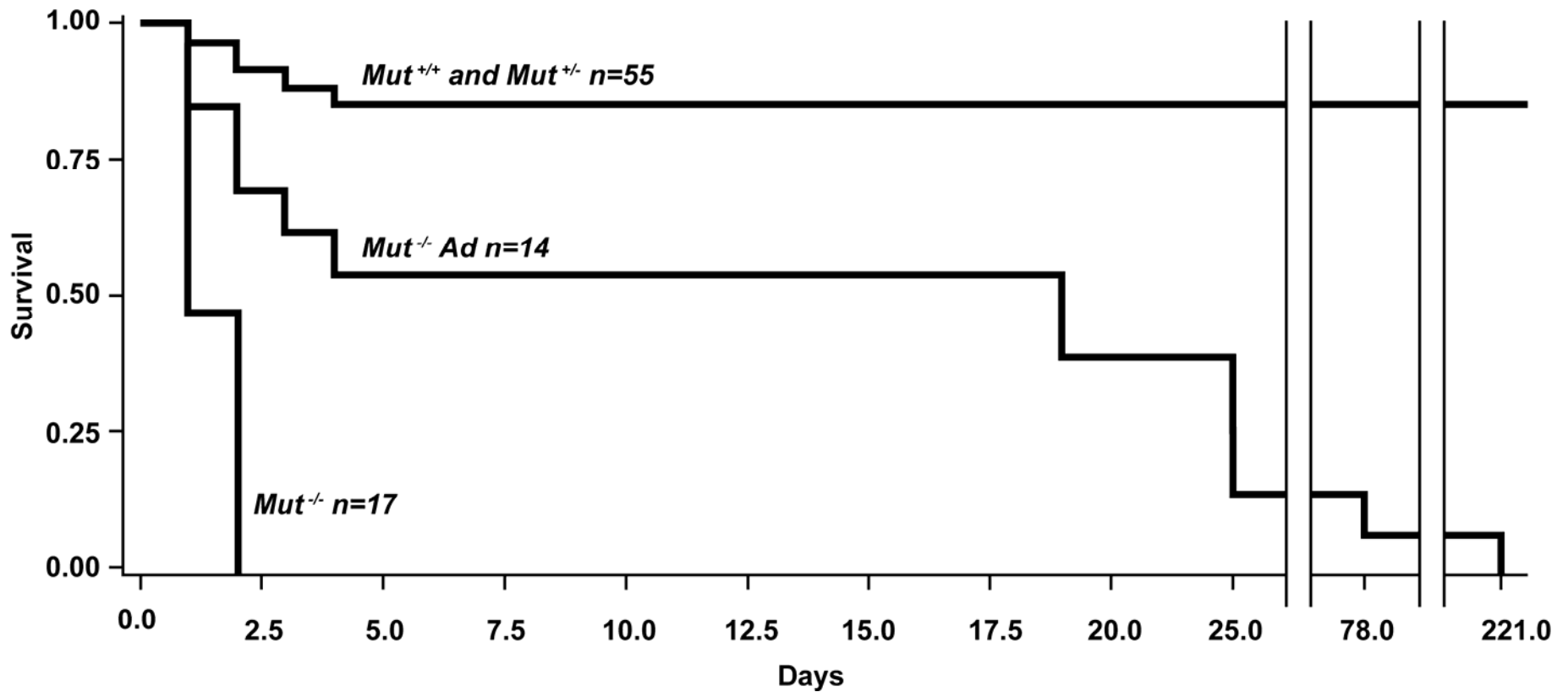
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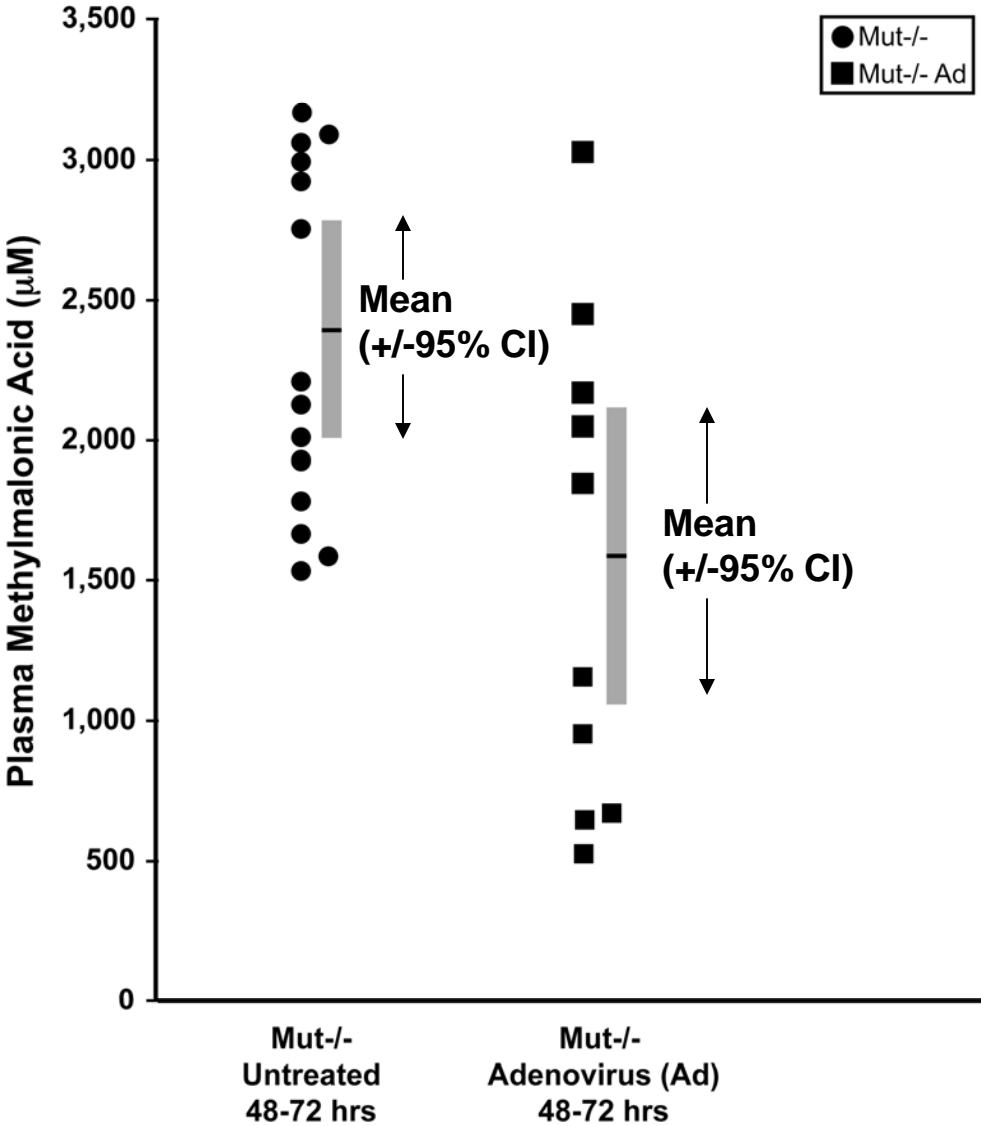
**B**



# Survival after Direct Hepatic Ad Injection - Mut KO Mice and Controls



# Plasma MMA levels after Direct Hepatic Ad Injection in the Mut KO Mice



# MMA Gene Delivery Experiments

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- Lentiviral
- Adenoviral

# Summary + Conclusions

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- Proof-of-principle experiments demonstrate effectiveness of gene delivery in cell culture and *in vivo*

# **Future Directions - Therapeutic Interventions RESEARCH**

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- Other delivery systems, viral and non-viral
- Integration vector and hepatocyte transplantation studies

# Future Directions - Therapeutic Interventions

## PRACTICE

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- ? CLINICAL TRIAL OF GENE THERAPY FOR MUT MMA PATIENTS

# **Future Directions - Therapeutic Interventions PRACTICE (CONT'D)**

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**IF A SAFE GENE THERAPY PROTOCOL FOR MMA (or other OA) WAS APPROVED, WOULD YOU ENROLL YOUR CHILD ?**

**COMMENTS APPRECIATED : NOW, SOME TIME IN THE NEXT DAY, OR BY EMAIL TO [VENDITTI@MAIL.NIH.GOV](mailto:VENDITTI@MAIL.NIH.GOV)**

# Acknowledgments

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- U Pitt: Drs Strom and Dorko

?S