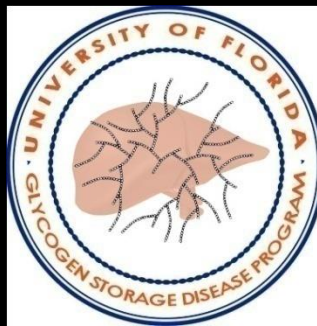




# ***Gene Therapy in the Canine Model of GSD Ia***

**David A. Weinstein, M.D, M.M.Sc.  
Director; Glycogen Storage Disease Program  
Milan Italy  
October 2, 2010**



# The GSD dogs



- Naturally occurring in maltese
- Mutation 1 codon away from human mutation
- Associated with no enzyme activity
- Clinically identical to humans
- Prior to study, no dog had survived more than 4 weeks

# Gene Therapy in Dogs with GSD



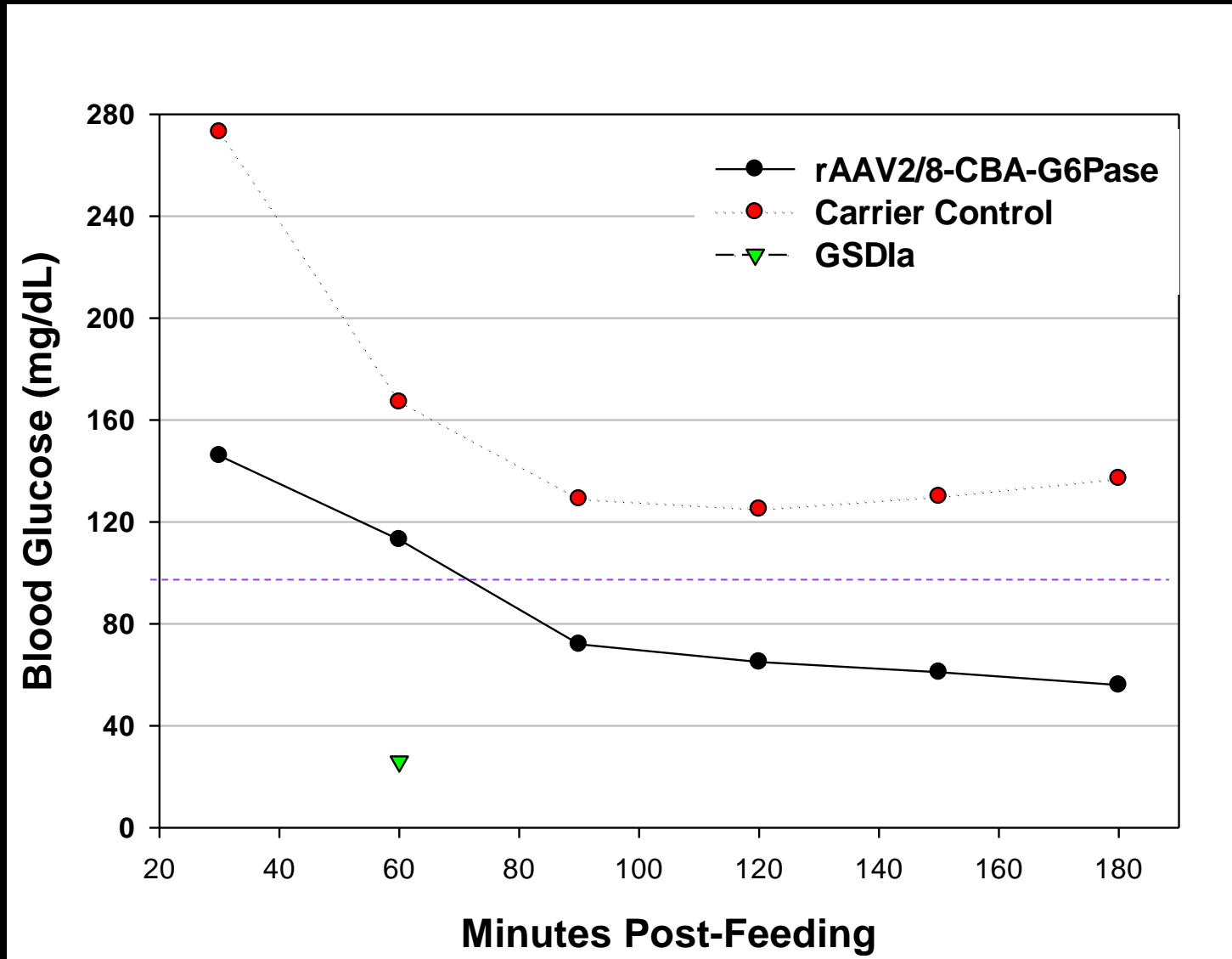
- Undetectable glucose at birth
- Confirmed by mutation analysis on DOL #1



Gene therapy was performed on our dogs with GSD type Ia for the first time on September 11, 2007

- Vector: AAV-8
- Dose:  $5 \times 10^{13}$  vector genomes/kg
- Method: IV injection into the jugular vein

# Fasting Blood Glucose 2 wks post-injection of rAAV2/8





**Untreated GSDIa affected dog**

•18 days old



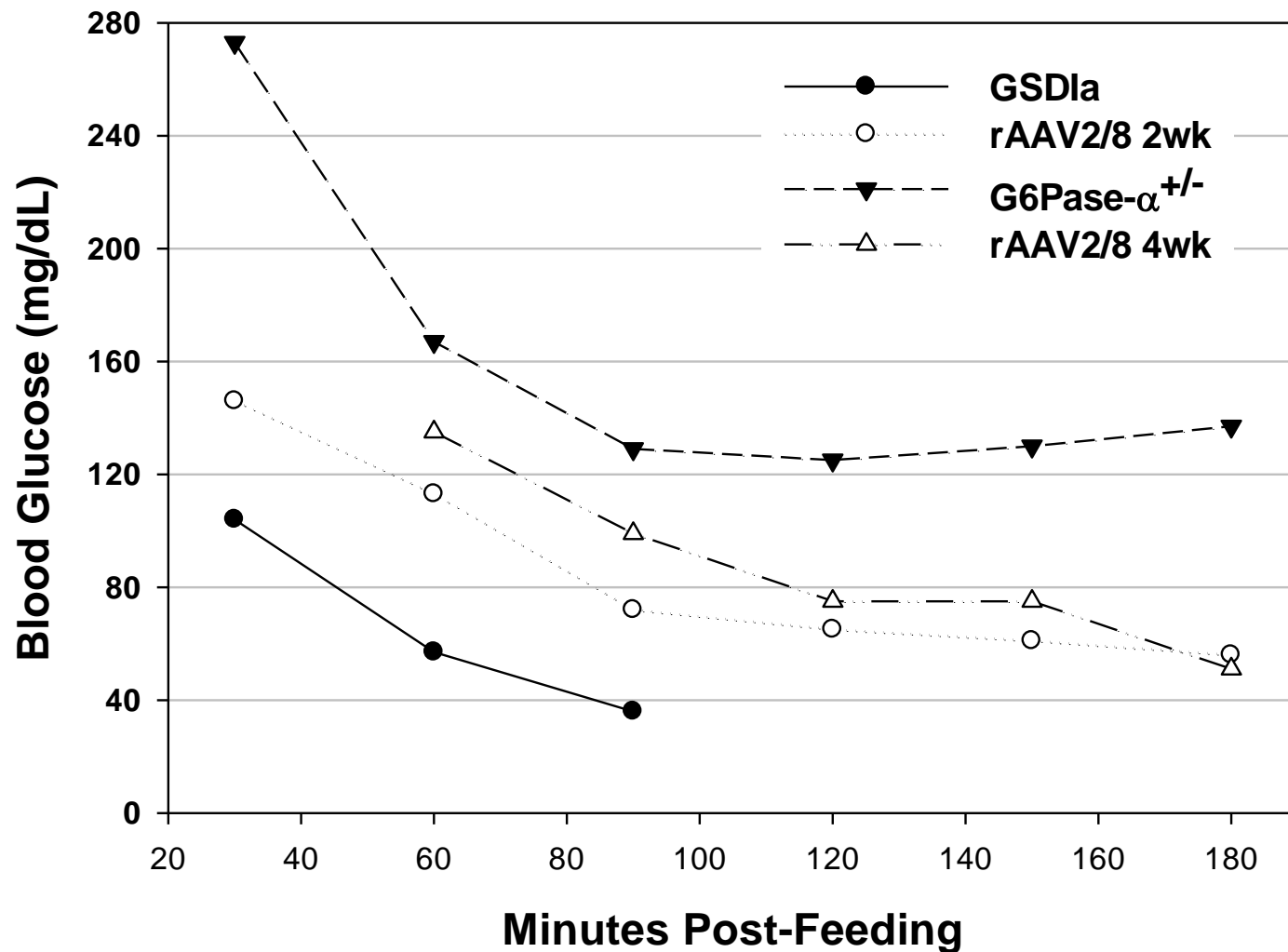
**Treated GSDIa affected dog**

•17 days old

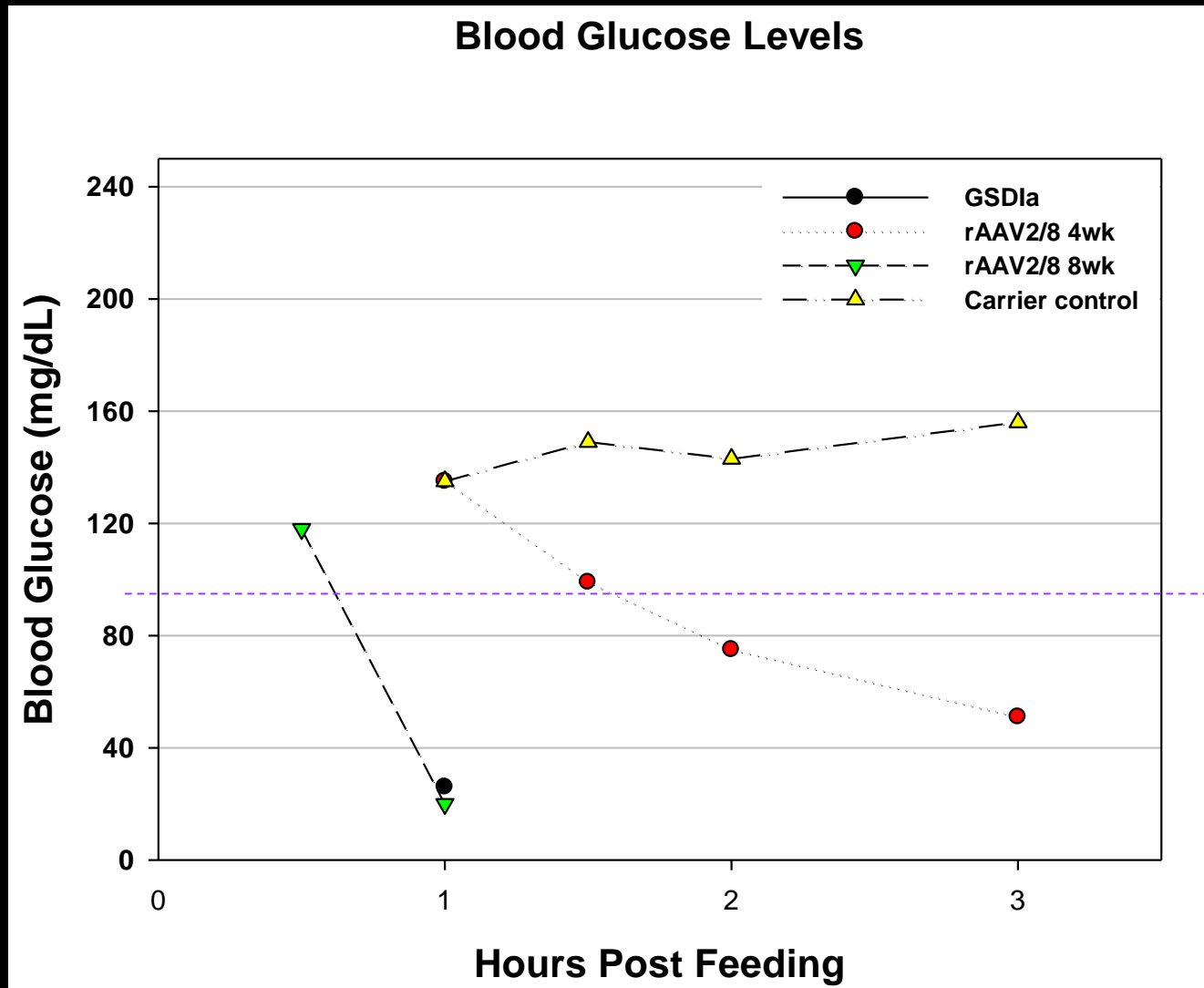
•16 days post AAV8 treatment

# Blood Glucose Levels

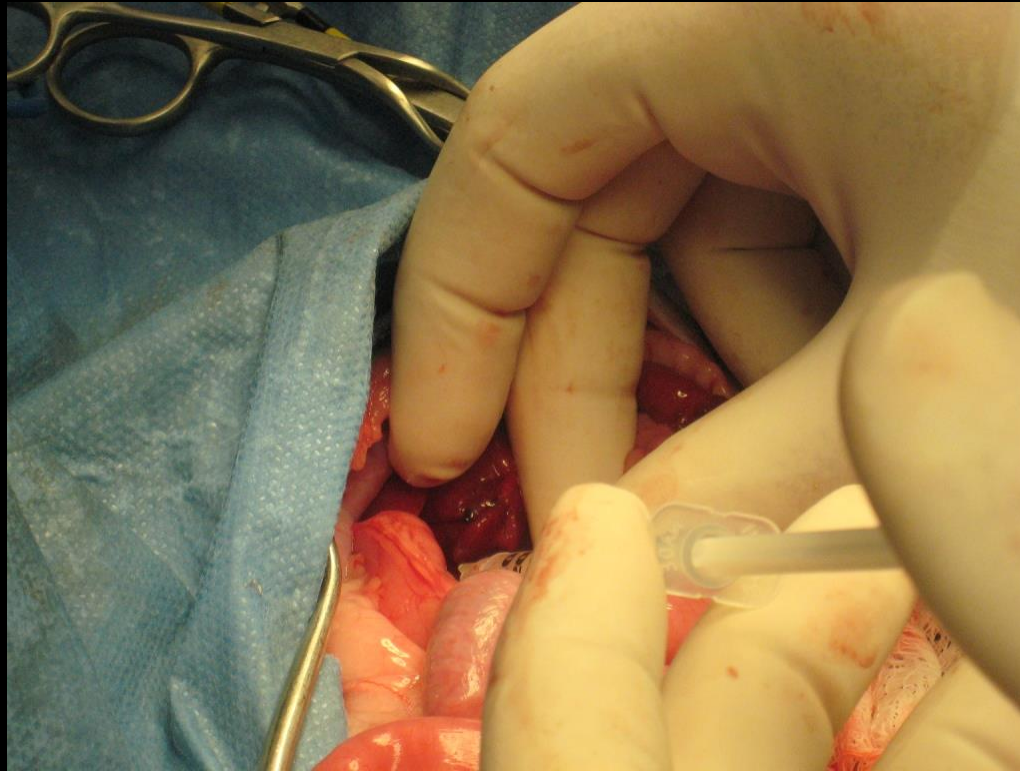
4wks post administration of  $5 \times 10^{13}$  vg/kg AAV8-CBA-mG6Pase



# Effect of Gene Therapy Waned by 8 Weeks

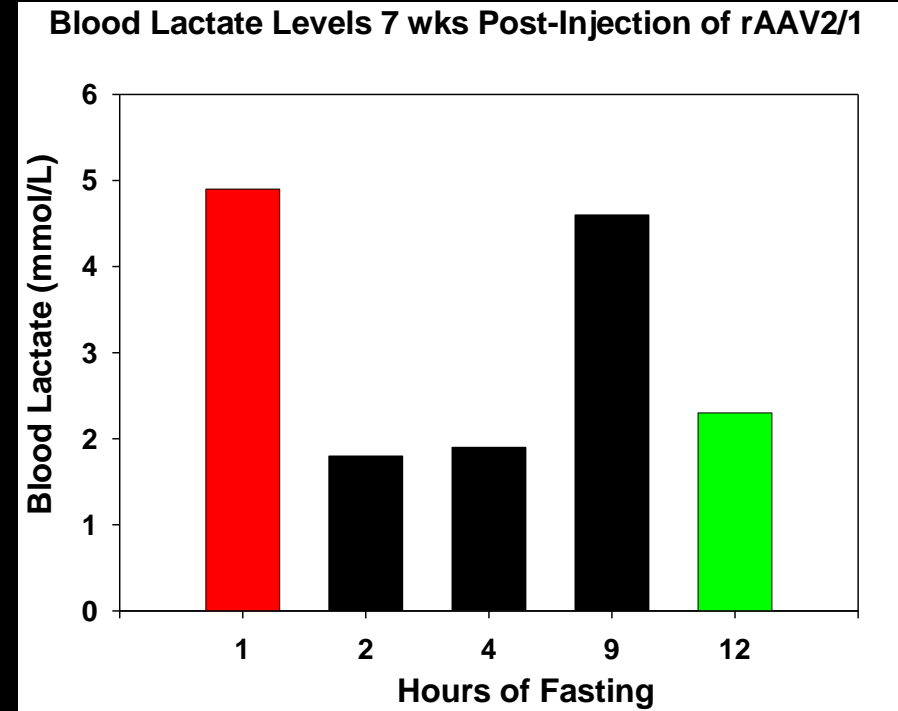
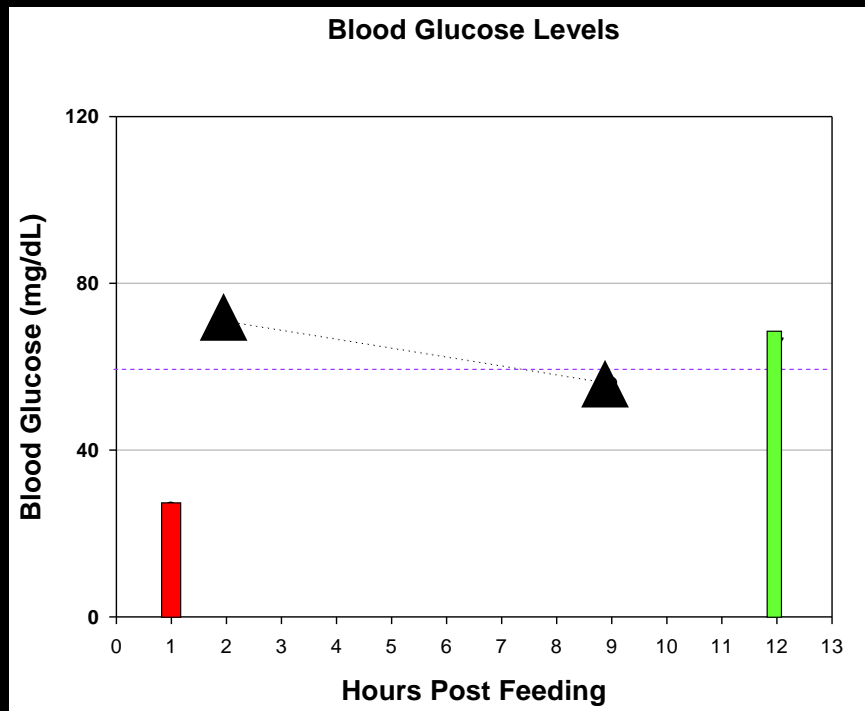


# Second Gene Therapy Treatment at 4-1/2 months of age



- $1 \times 10^{12}$  viral genomes/kg injected into the hepatic portal vein using AAV-1 as the vector

# Fasting Study 7 weeks after AAV-1 infusion



■ GSDIa    ■ rAAV2/8+rAAV2/1    ■ Carrier Control

# All glucose support was stopped at 6 months of age

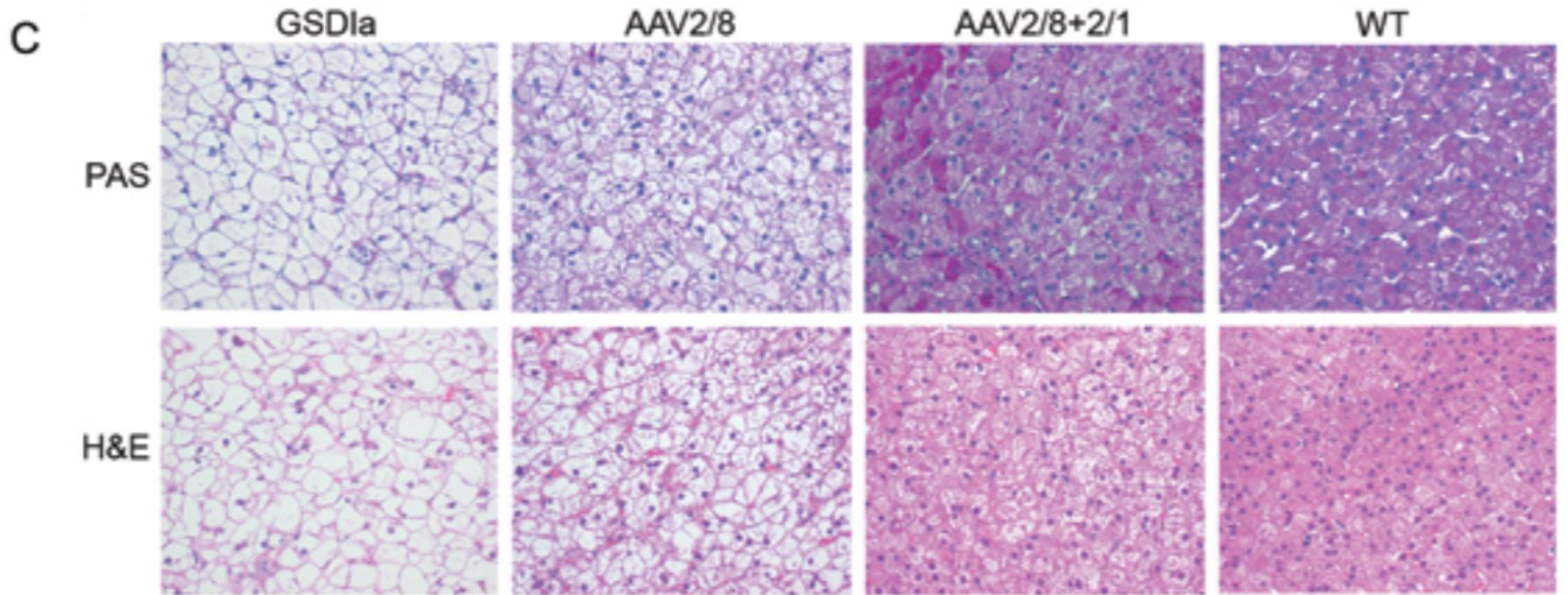
- No problems clinically while weaning off therapy
- On the day after all support was stopped, dog went 22 hours without food yet remained clinically well

**Dulce:** Off Therapy for 19 months  
(21 months following last gene therapy treatment)



*Liver biopsy 6 months after the 2<sup>nd</sup> gene therapy dose  
demonstrated 7% activity*

# H & E Staining



# Gene Therapy Update

- No adenomas or evidence of complications 3 years after initial therapy
- While the 2 year metabolic lipids and liver function tests have continued to improve, lactates have begun to rise with stress
- Third gene therapy treatment performed in Feb 2010

# Introducing the New Puppies

## Born April 9, 2010



**Tucker**



**Jasmine**

# Gene Therapy Update

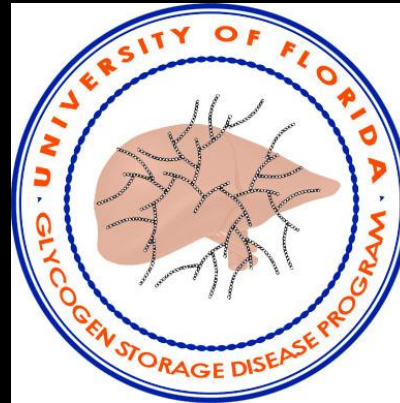
- Gene therapy performed at 36 hours of life
- By 2 weeks, puppies able to fast for 6 hours (baseline 45-60 minutes)
- Glucose support discontinued at 3 weeks



# Gene Therapy Summary

- Gene therapy appears to be a promising therapy for the future
- Planning to treat 5 other dogs this year using G-6-pase regulated by the human promoter
- If successful, same technique could be used to treat many other genetic diseases of the liver

# Thank you



*For more information on the research, please visit our  
website [www.glycogenstoragedisease.com](http://www.glycogenstoragedisease.com)*