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Bringing curative gene therapies to patients with rare, undertreated diseases

Systemic Delivery of AAV9.LAMP2B for the Treatment of Danon Disease: Toxicology Studies in Mice and Cynomolgus Monkeys

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Disclosure Information

- Pavan Battiprolu, David Ricks, Simon Moore, Sanchali Kasbekar, Kinnari Patel, Jonathan D. Schwartz, Gaurav Shah, and Annahita Keravala are employees of Rocket Pharmaceuticals, Inc.
- Ana-Maria Manso is a consultant for Rocket Pharma
- Eric Adler is a shareholder in Rocket Pharma

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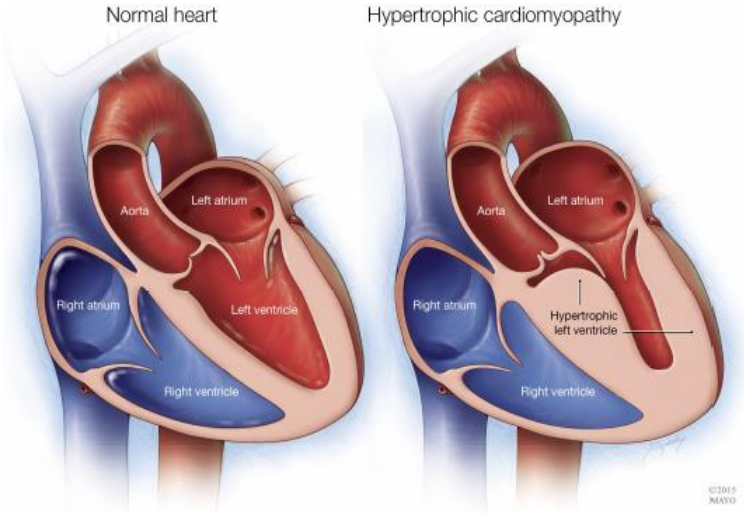
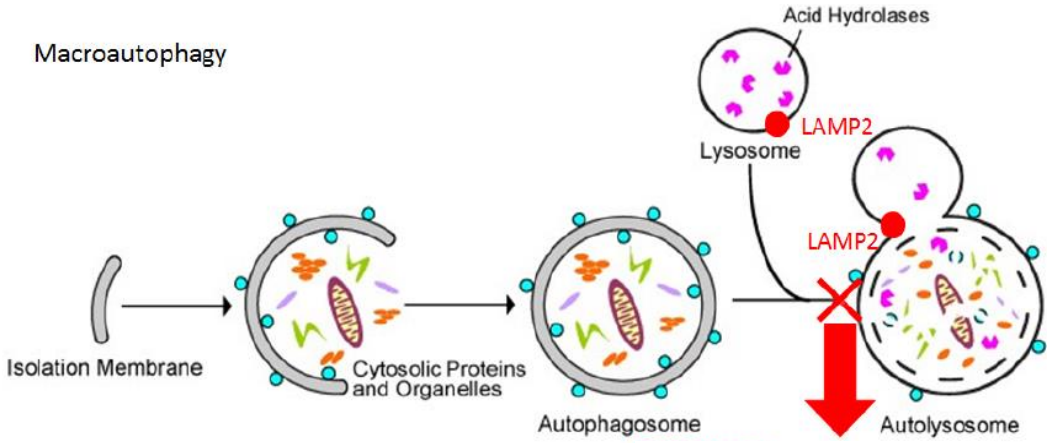
Danon Disease (DD)



- Danon disease is a devastating multi-system disorder primarily affecting cardiac tissue
  - 95% of patients have severe cardiomyopathy and die from progressive heart failure
  - Heart transplant is a treatment option, which is not curative & is associated with considerable morbidity & mortality
- Other clinical manifestations include skeletal myopathy, ophthalmic abnormalities, and mild cognitive impairment
- Estimated prevalence of 15,000 – 30,000 in US + EU

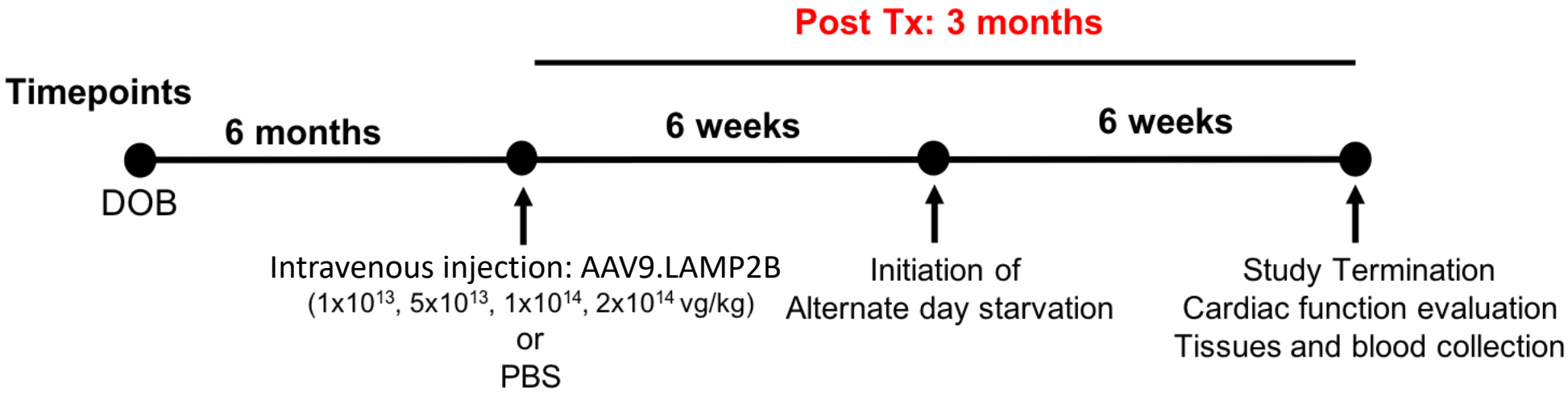
- DD is an X-linked monogenic disease
- Mutations in the lysosomal associated membrane protein 2B (LAMP2B) result in impaired autophagy



AAV9 Vector Shows Consistent & Strong Cardiac Tropism In Several Studies Across Different Species

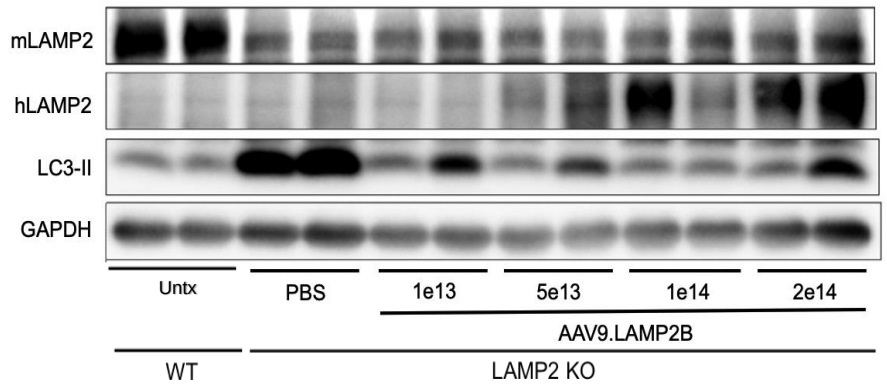
Disorder & Vector	Dose	Species	Results	Sponsor	Reference
LGMD2A AAV9.hCAPN3	3E+13 vg/kg	NHP	8-80-fold higher transduction in cardiac vs. skeletal muscle	Genethon	Lostal et al (ASGCT 2018)
Non-specific AAV9.Luc	3E+12 vg/kg	NHP	~ 10-fold higher transduction in cardiac vs. diaphragm; and comparable to other muscles	UNC	Tarantal et al 2016
Pompe AAV9.hGAA	1E+11 vg/mouse	Mouse	~ 10-fold higher transduction in cardiac vs. diaphragm	U. Florida	Falk et al 2015
DMD AAV9.μDys	1.9–6.2E+14 vg/kg	Dog	2-3 fold higher transduction in cardiac vs. skeletal muscle	U. Missouri	Yue et al 2015
SMA AAV9.SMN	3E+14 vg/kg & 1E+13 vg/kg	Mouse & NHP	~ 100-fold higher transduction in cardiac vs. skeletal muscle (mouse)	Nationwide Children's	Meyer et al 2014
MPSIIIB AAV9.hNAGLU	1–2E+13 vg/kg	NHP	≥ 10-fold higher transduction in cardiac vs. skeletal muscle in majority of animals	Nationwide Children's	Murrey et al 2014
Non-specific AAV9.Luc	5E+10 vg/mouse	Mouse	5-10-fold higher transduction in cardiac vs. skeletal muscle	UNC	Pulicherla et al 2011
Non-specific AAV9.LacZ	1E+11 vg/mouse	Mouse	~ 8-12-fold higher transduction in cardiac vs. skeletal muscle or diaphragm	U. Florida	Pacak et al 2006

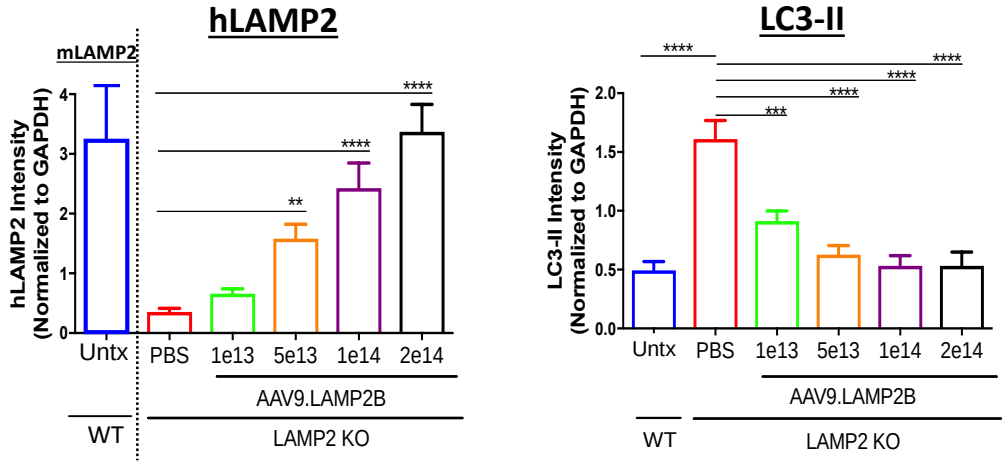
Study To Assess Efficacy of AAV9.LAMP2B (RP-A501) in *LAMP2* Knockout Mouse Model of Danon Disease



Dose-dependent Expression of LAMP2 and Decreased LC3-II in Heart

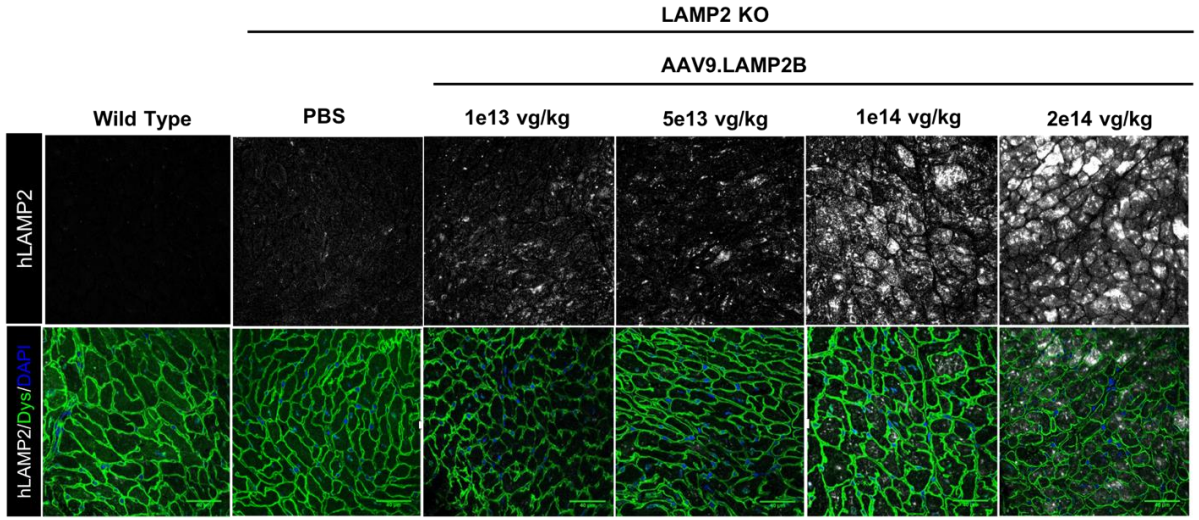
Western Blot





*p<0.05, **p<0.01, ****p<0.0001

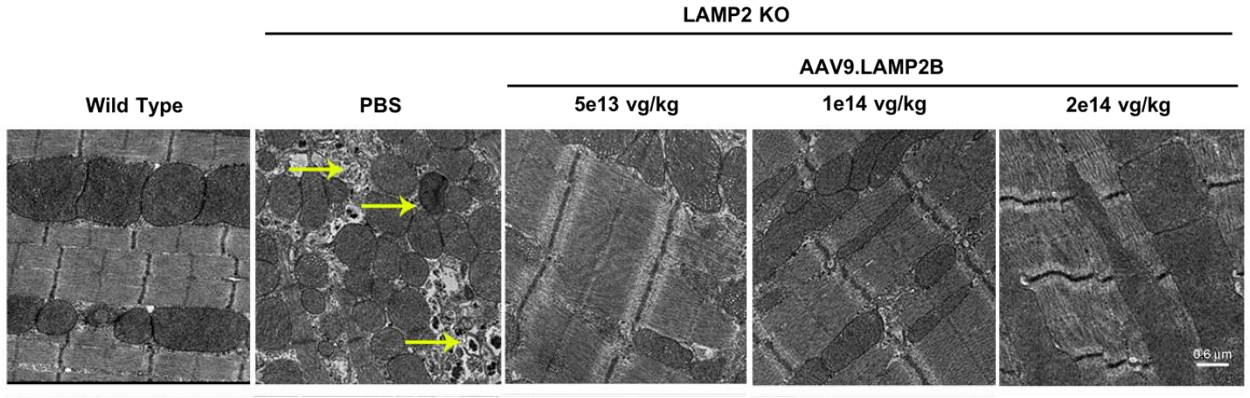
Immunofluorescence



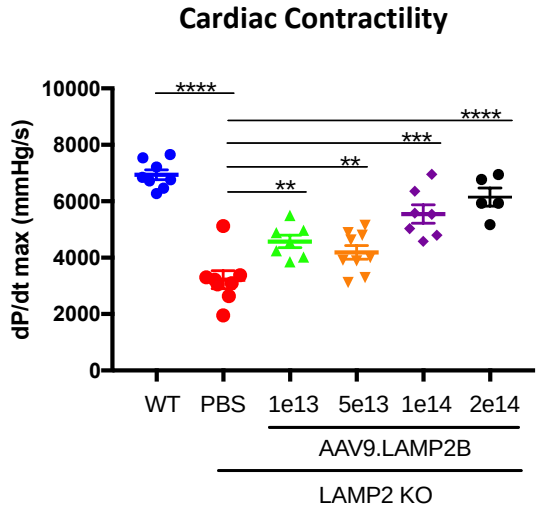
Manso et al. Unpublished data

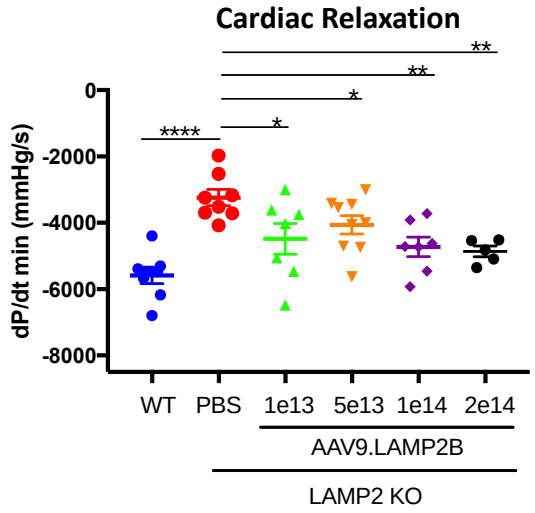
Restoration of Cardiac Ultrastructure and Systolic & Diastolic Function

Electron Microscopy



Invasive Hemodynamics





*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001

Manso et al. Unpublished data

IND-Enabling Studies to Assess Safety of AAV9.LAMP2B (RP-A501)

Toxicology/Biodistribution studies were conducted:

I. A GLP study performed in wild-type C57BL/6 mice
   - Doses: 3×10^{13}, 1×10^{14}, 3×10^{14} vg/kg
   - Assessment timepoints: 30, 91, and 180 days post infusion

II. NHP study performed in cynomolgus monkeys
   - Dose: 3×10^{14} vg/kg
   - Assessment timepoint: Through 102 days post infusion

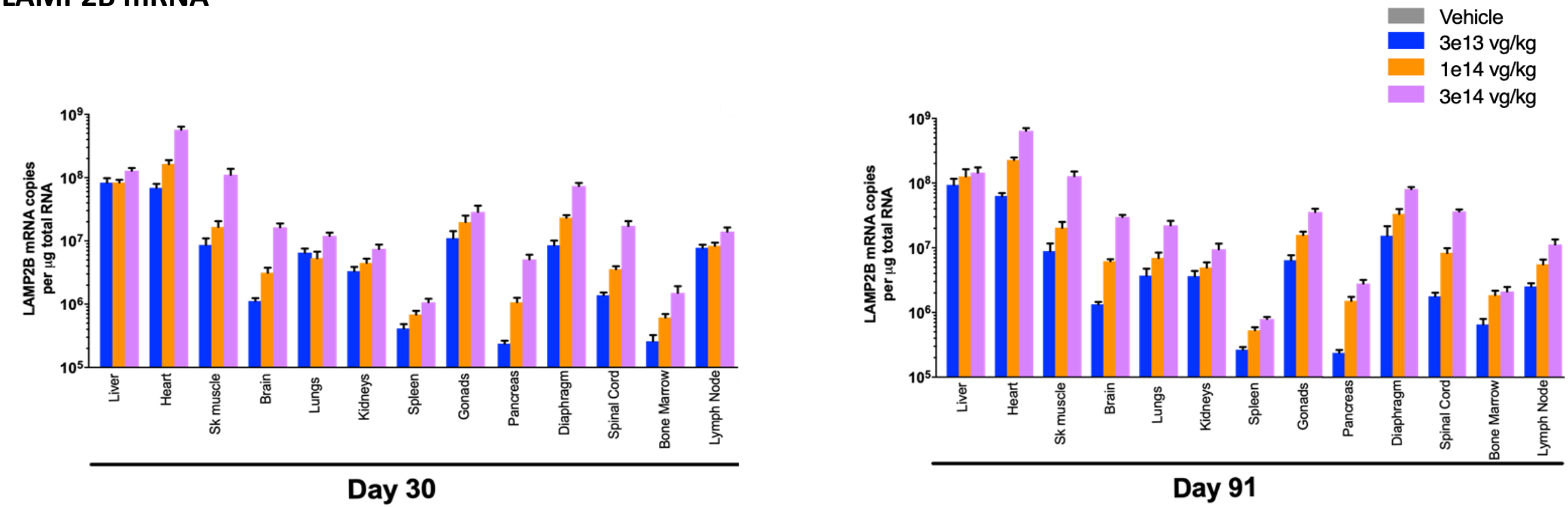
Toxicology Assessment of RP-A501 in Mice at Days 30, 91, and 180

Assessment	Outcome
Clinical blood chemistry	No relevant dose-related findings in clinical chemistry panel
Hematology	No relevant dose-related changes at any time-point
Organ weight	No adverse organ weight changes related to dosing
Histopathology	No noteworthy treatment-related microscopic findings
Immune response	▪ Dose-dependent increase in neutralizing antibodies (NAbs) ▪ Characteristic strong total antibody (TAb) response to capsid ▪ No significant anti-drug antibody (ADA) response to transgene

➢ RP-A501 was well tolerated after a single IV injection at all tested doses; 3×10^{13}, 1×10^{14}, and 3×10^{14} vg/kg

Biodistribution of RP-A501 in Mice at Days 30 & 91

LAMP2B mRNA



- Differential distribution of vector genomes (vg) was noted
- Highest levels of mRNA were measured in heart, which were stable between day 30 and 91 timepoints

Toxicology Assessment of RP-A501 in Non-human Primates at Day 102

Assessment	Outcome
Moribundity/mortality	No clinical signs of toxicity manifesting as moribundity or mortality
Electrocardiography	No changes in heart rhythm, ST segment, waveform morphology, MEA, or interval measures
Clinical pathology	No relevant dose-related changes in hematologic, biochemical, or clinical chemistry - mild, transient, increase in liver enzymes at day 7, which self-resolved by day 15
Histopathology	No noteworthy treatment-related findings
Immune response	— Dose-dependent increase in NAbs (expected) — Characteristic strong TAb response to capsid — Mild ADA response to transgene

➢ RP-A501 was well tolerated after a single IV injection of 3×10^{14} vg/kg in NHPs

Immunogenicity Assessment of RP-A501 in NHPs

NAb

Group	Animal ID	AAV9 NAb IC50		
		Pre-Test	Day 30	Day 90
Control	2750	0	443	162
Control	4247	0	229	<5
Treated	0366	0	3050	>5280
Treated	0690	0	>5280	>5280

TAb

Group	Animal ID	Titer (Cut Point of 3.156)		
		Pre-dose	Day 30	Day 90
Control	2750	<10	100	<10
Control	4247	<10	100	<10
Treated	0366	<10	10,000	10,000
Treated	0690	<10	10,000	10,000

ADA

Group	Animal ID	Titer (Cut point of 1.283)		
		Pre-dose	Day 30	Day 90
Control	2750	Negative	Negative	20
Control	4247	Negative	Negative	Negative
Treated	0366	Negative	80	>640
Treated	0690	Negative	>640	>640

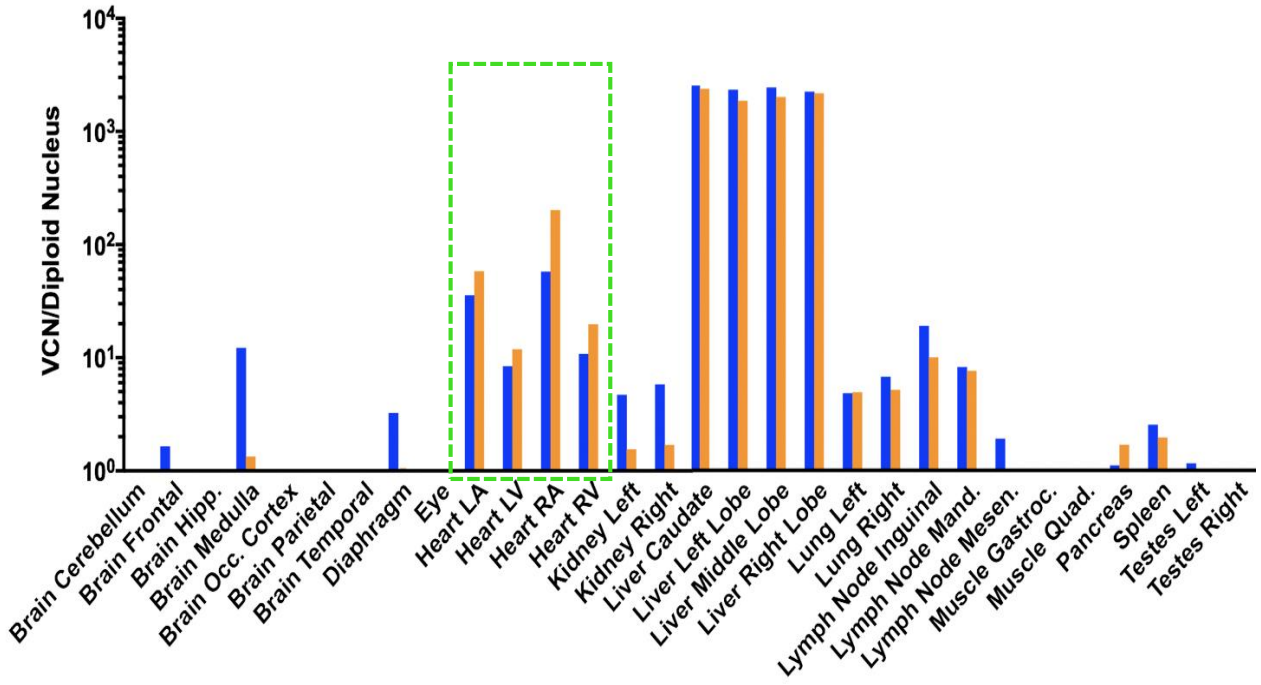
ELISpot (T-Cells)

Group	Animal ID	Spot Forming Counts per 1E+06 cells day 90	
		α-AAV9	α-LAMP2B
Control	2750	10	125
Control	4247	20	5
Treated	0366	115	25
Treated	0690	125	10

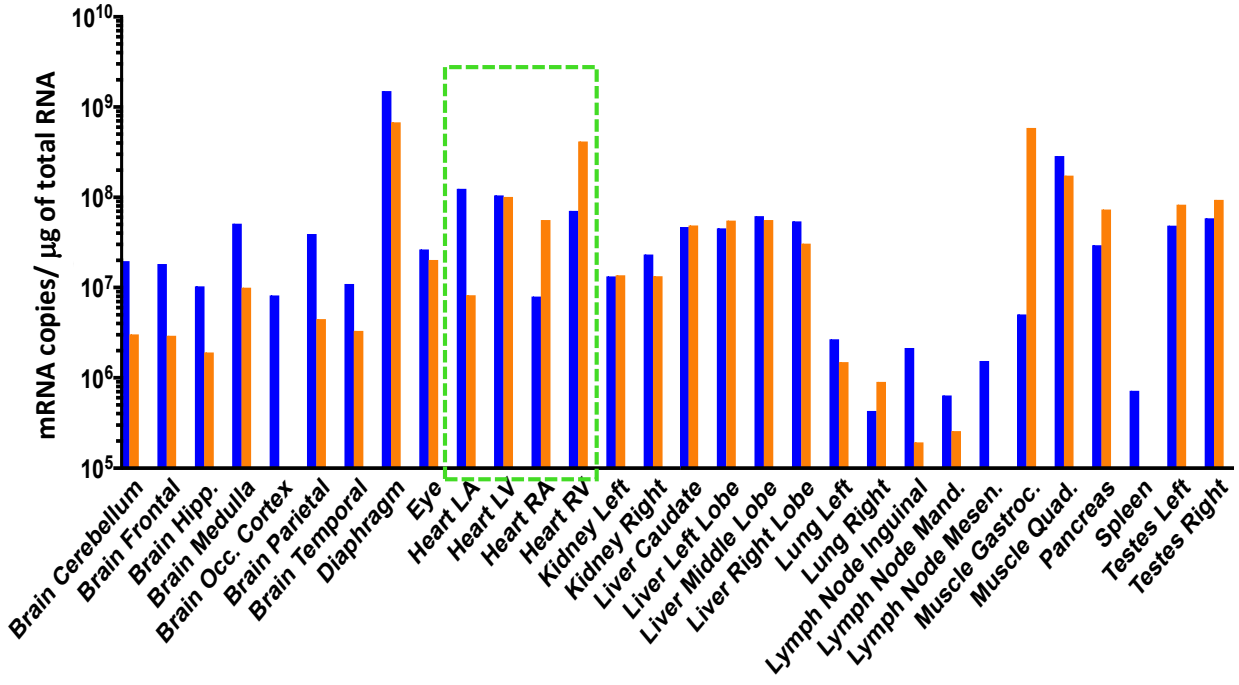
- NAbs to AAV9 capsid developed as expected
- Although robust TAb response to capsid was seen, mild ADA response to transgene was noted
- No significant T-cell response to capsid or transgene (ELISpot) was observed

VCN and mRNA Assessment for RP-A501 Biodistribution in NHPs at Day 102

VCN



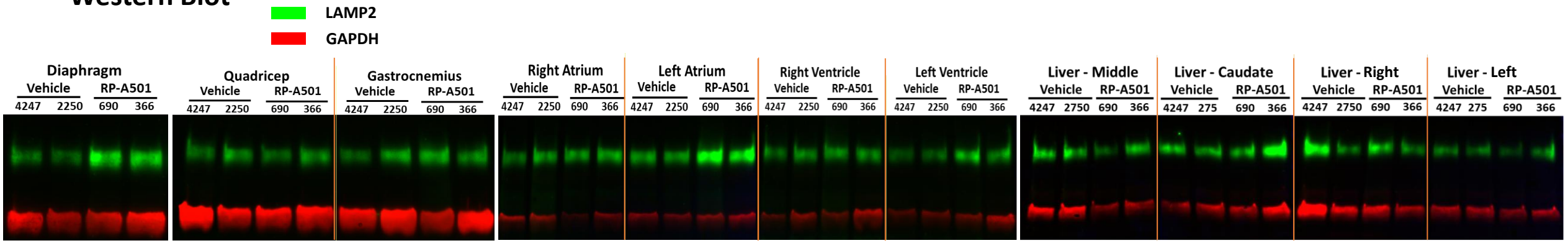
mRNA



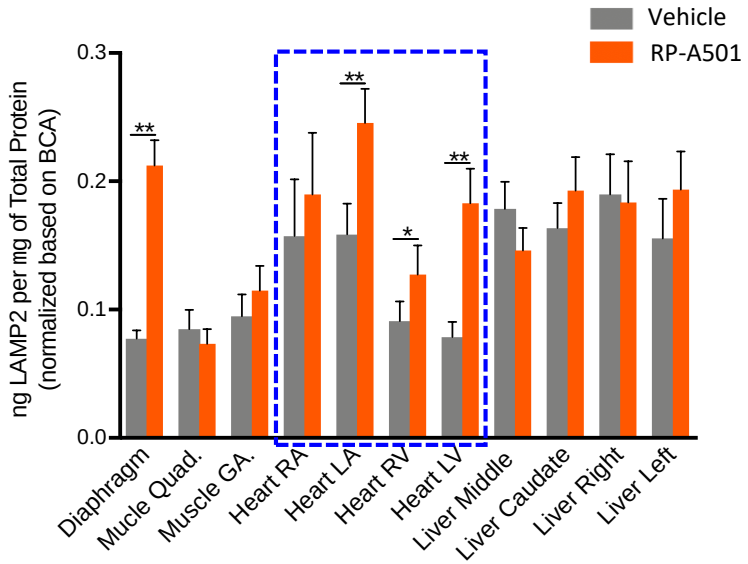
- Differential distribution of vector genomes was observed, with highest VCN measured in liver and heart
- High levels of transduction (mRNA) were observed in the heart

RP-A501-Mediated hLAMP2 Protein Expression in NHPs at Day 102

Western Blot



LAMP2 assessment based on total protein⁺ loaded on gel



*p<0.05, **p<0.01

- Higher levels of transgenic human LAMP2 protein detected over endogenous NHP LAMP2 in most tissues tested, specifically the heart

⁺Normalized to total protein instead of GAPDH, as housekeeping protein levels were variable

Key Takeaways: RP-A501 is Effective & Safe in Preclinical Studies

- ✓ **AAV9.LAMP2B effectively transduces the heart (key target organ for DD).** High VCNs, mRNA, as well as protein were noted in cardiac tissue of dosed mice and NHPs
- ✓ **AAV9.LAMP2B confers direct benefit to cardiac function** and improves ultrastructure at doses of 5×10^{13} vg/kg and higher in the *LAMP2* KO mouse model
- ✓ **AAV9.LAMP2B is safe.** No dose-related adverse events were observed at all tested doses in mice and NHPs

Conclusion: Preclinical data are supportive of RP-A501 gene therapy for Danon disease

https://clinicaltrials.gov/ct2/show/NCT03882437