Endurance Training in a TAZKD Mouse Model of BTHS

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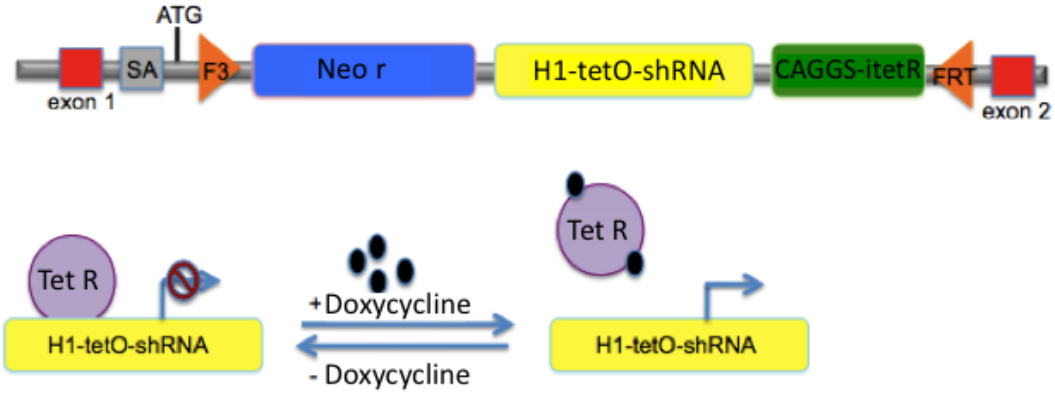
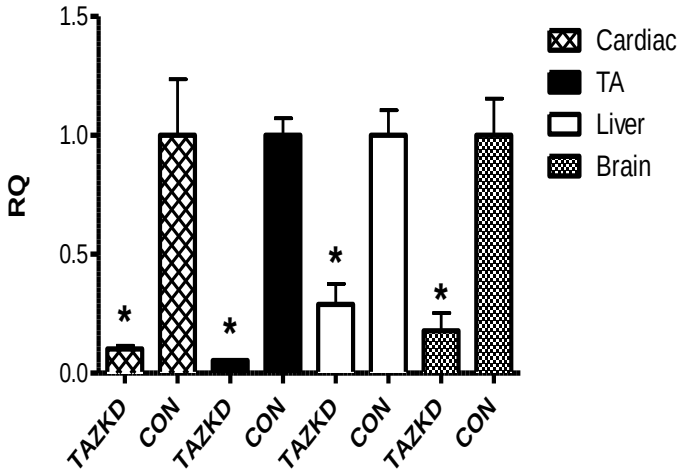
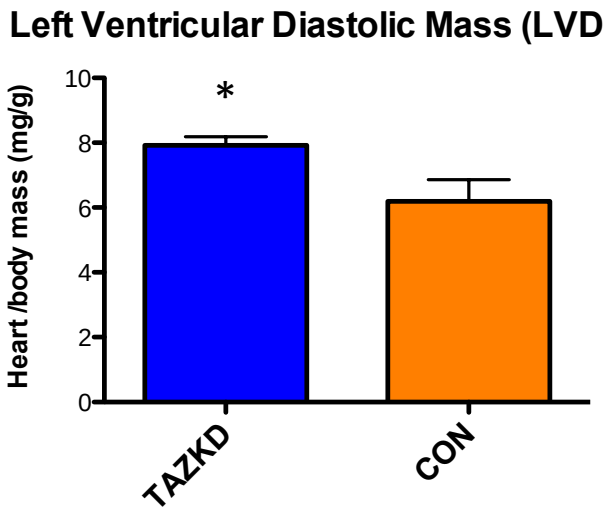
Outline

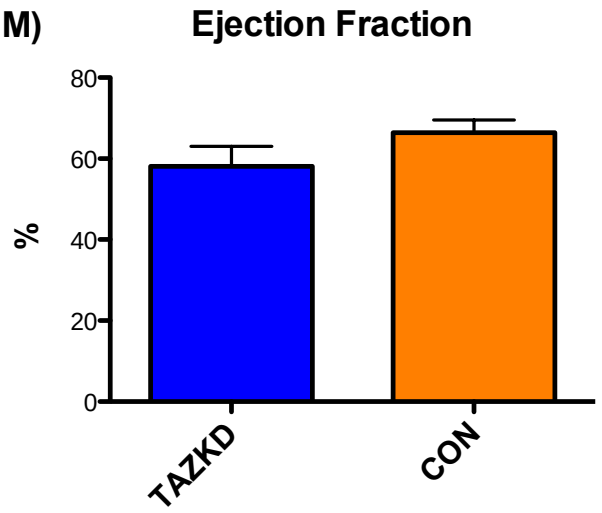
- Review TAZKD Mouse Model
- Endurance Training in TAZKD Model
  - Protocol
  - Results
- Gene Therapy
  - Background
  - Preliminary data
  - Future directions
- Final Summary

TAZKD Mouse

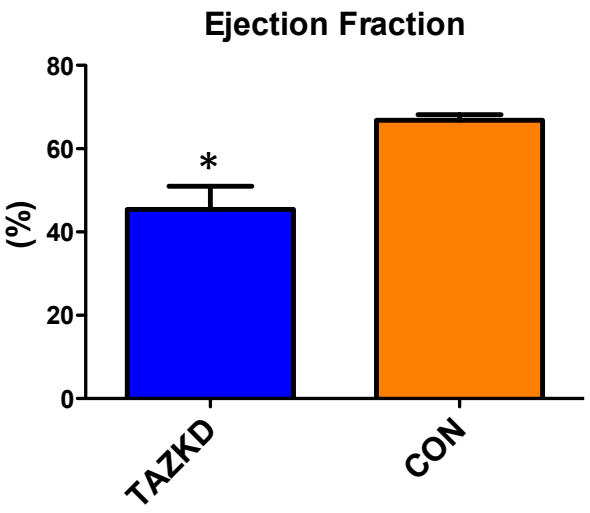






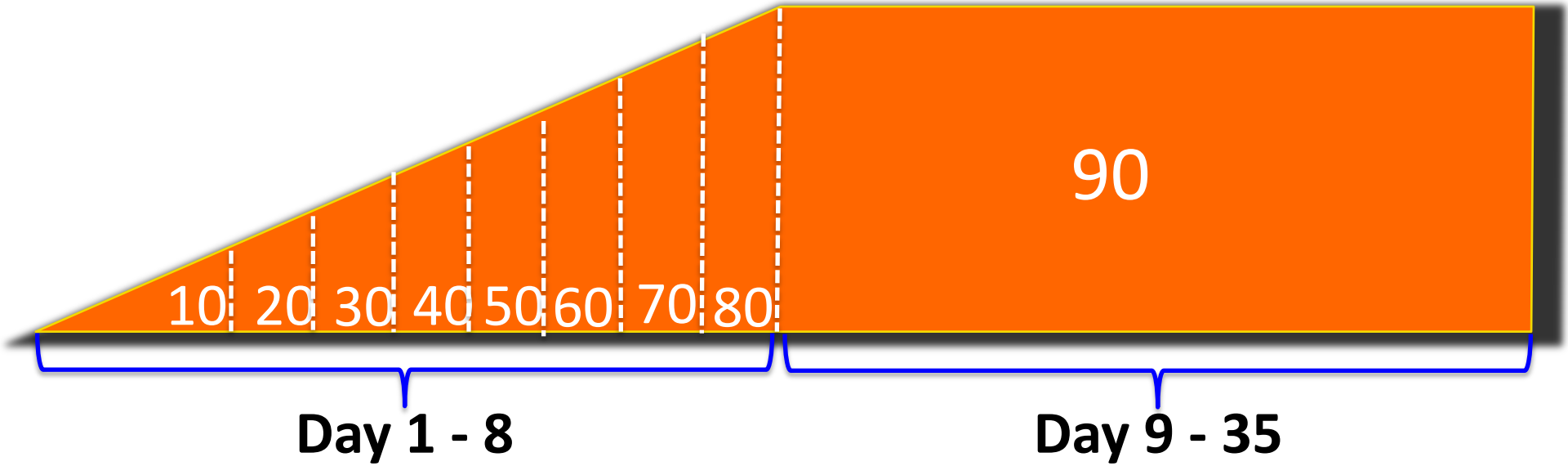


3 months



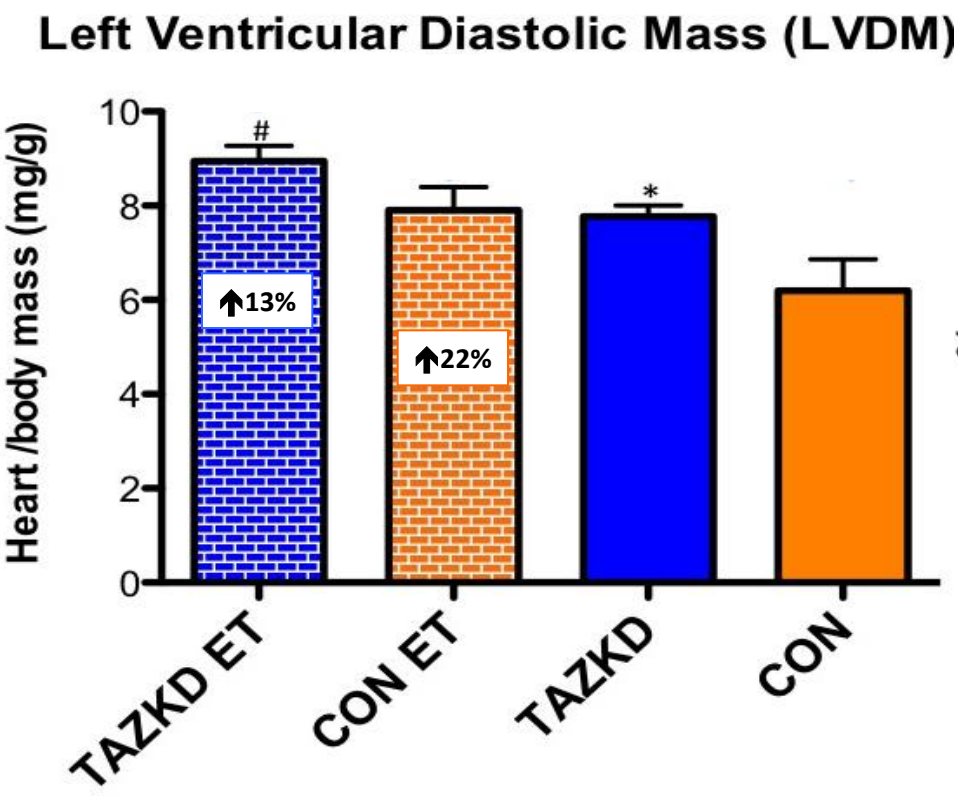
10 months

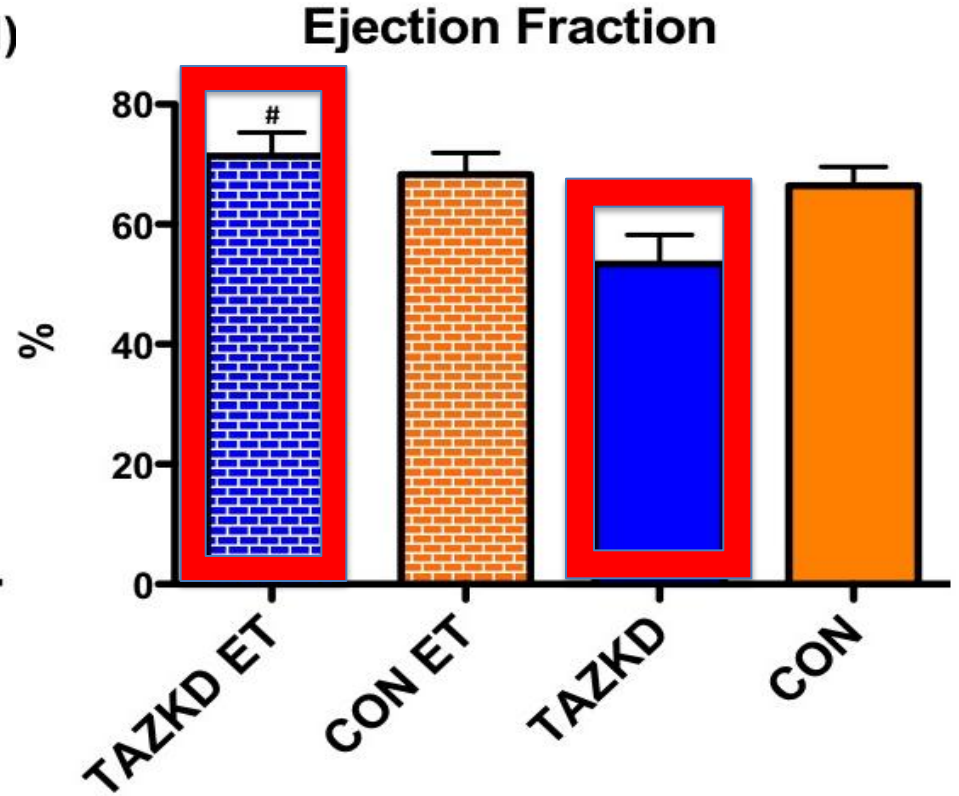
Endurance Training Protocol



Swim time (mins): 5x per week; twice a day

Cardiac Function



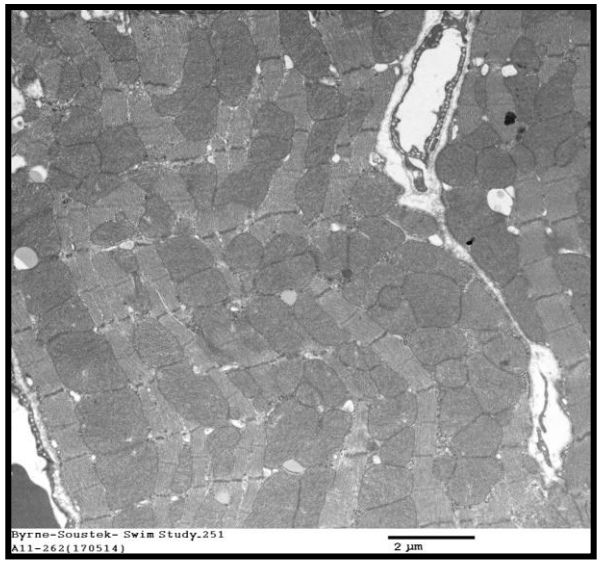


= TAZKD vs TAZKD ET; $p<0.05$

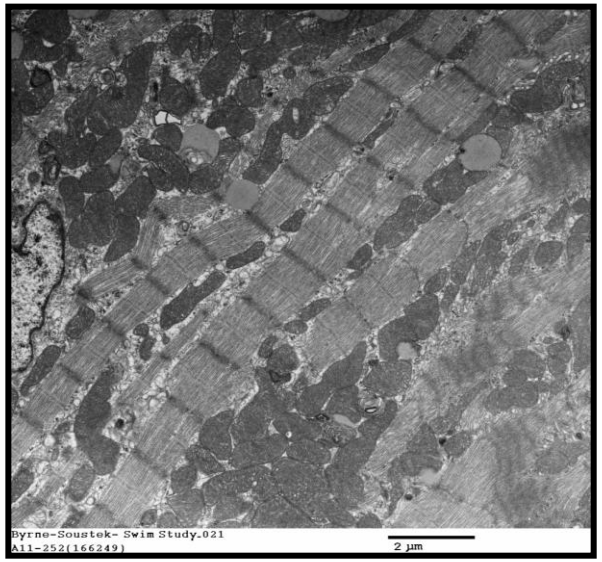
* = TAZKD vs CON; $p<0.05$

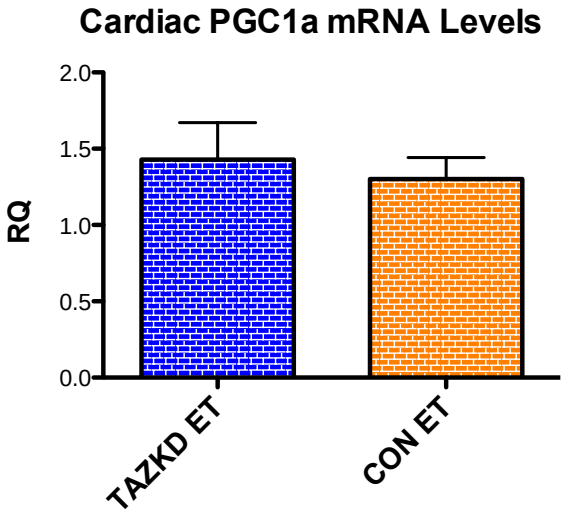
Cardiac Morphology

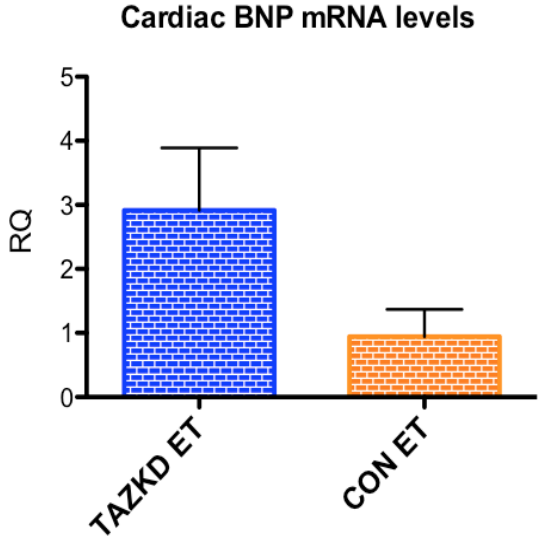
CON ET



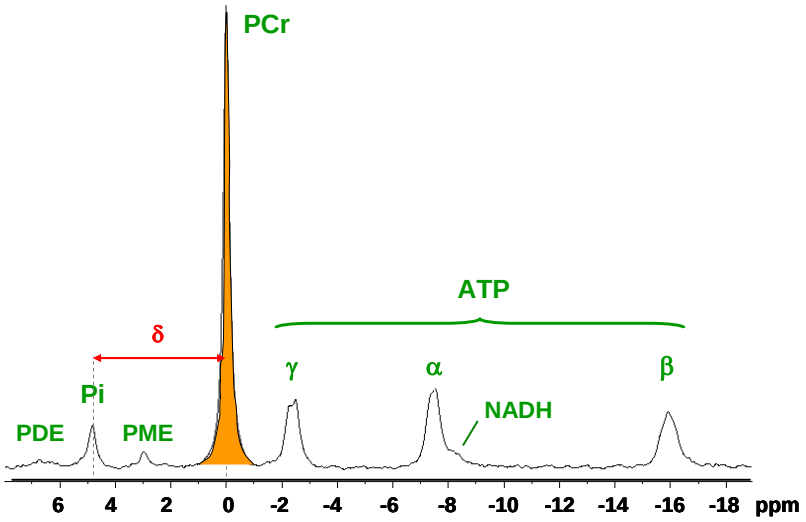
TAZKD ET

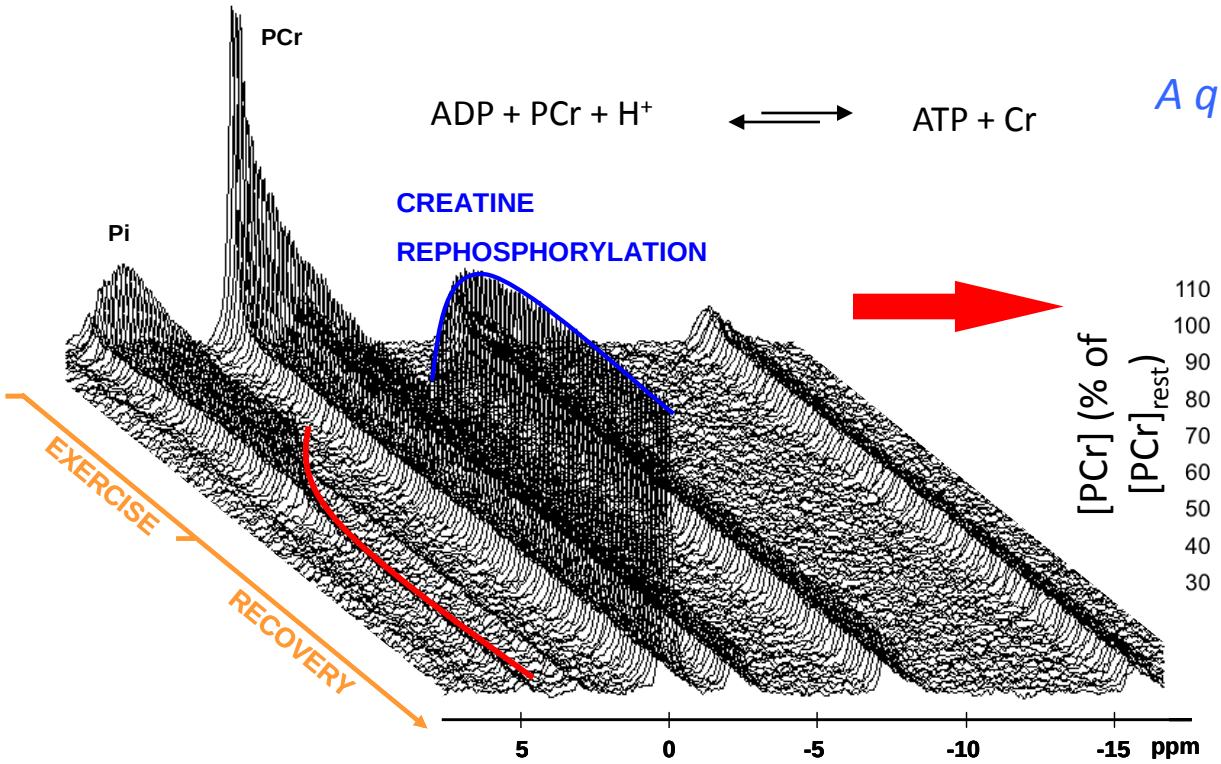






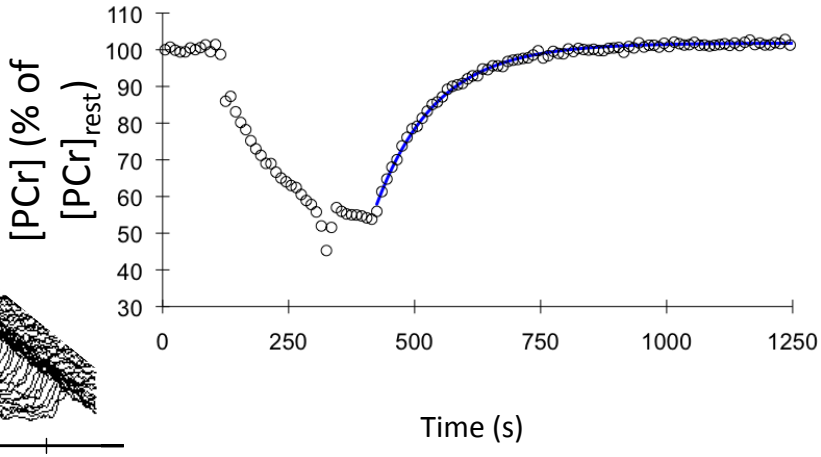
Assessing Mitochondrial Function *in vivo*



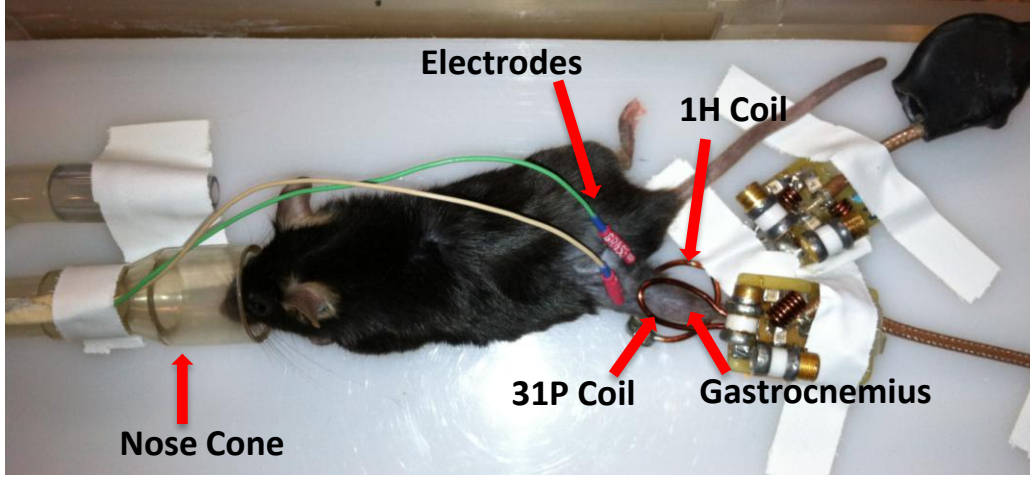


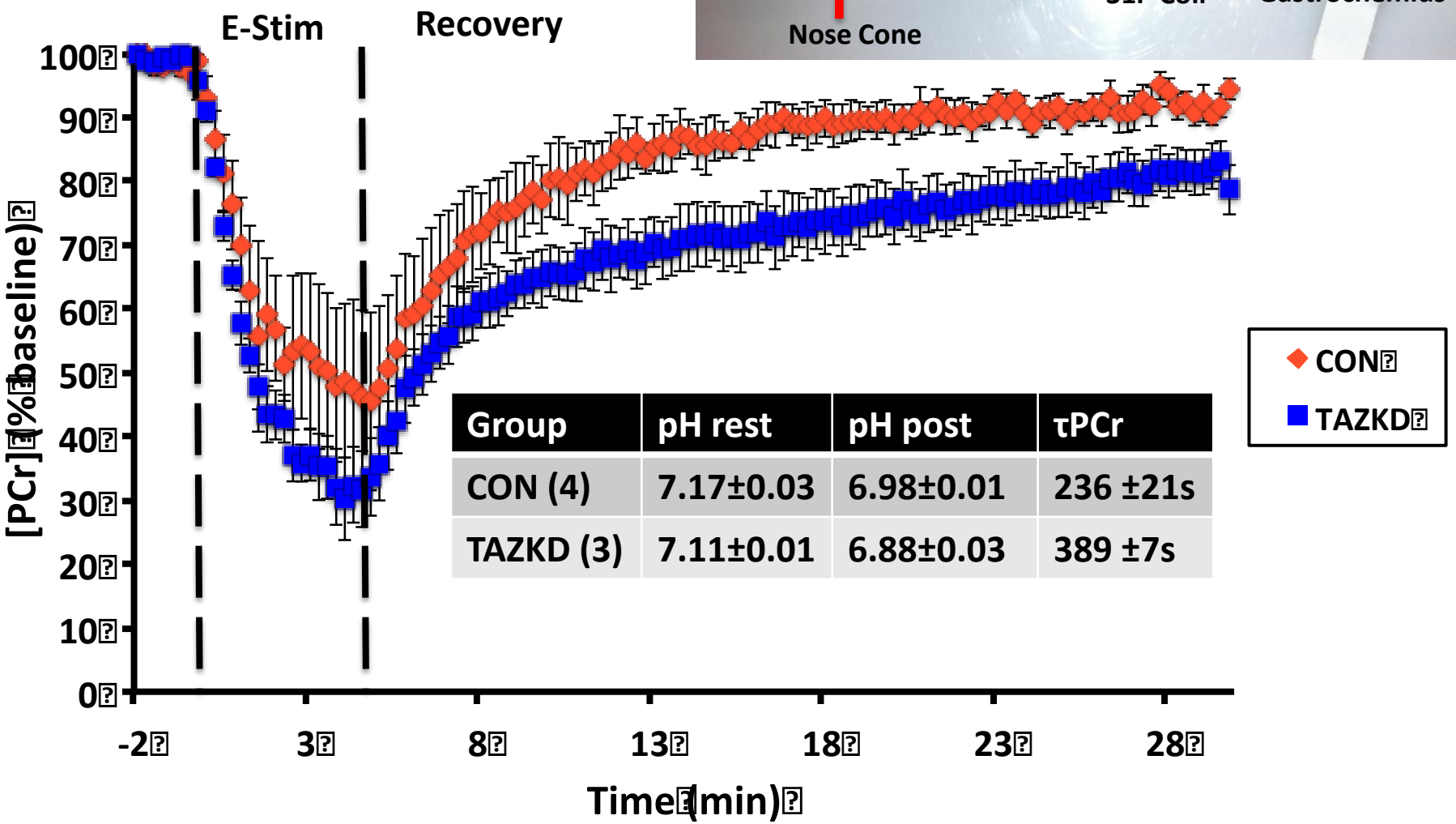
A quantitative index of mitochondrial oxidative capacity.

$$[PCr](t)=[PCr]_{rest}(1-e^{-t/\tau PCr})$$



Mitochondrial Oxidative Capacity



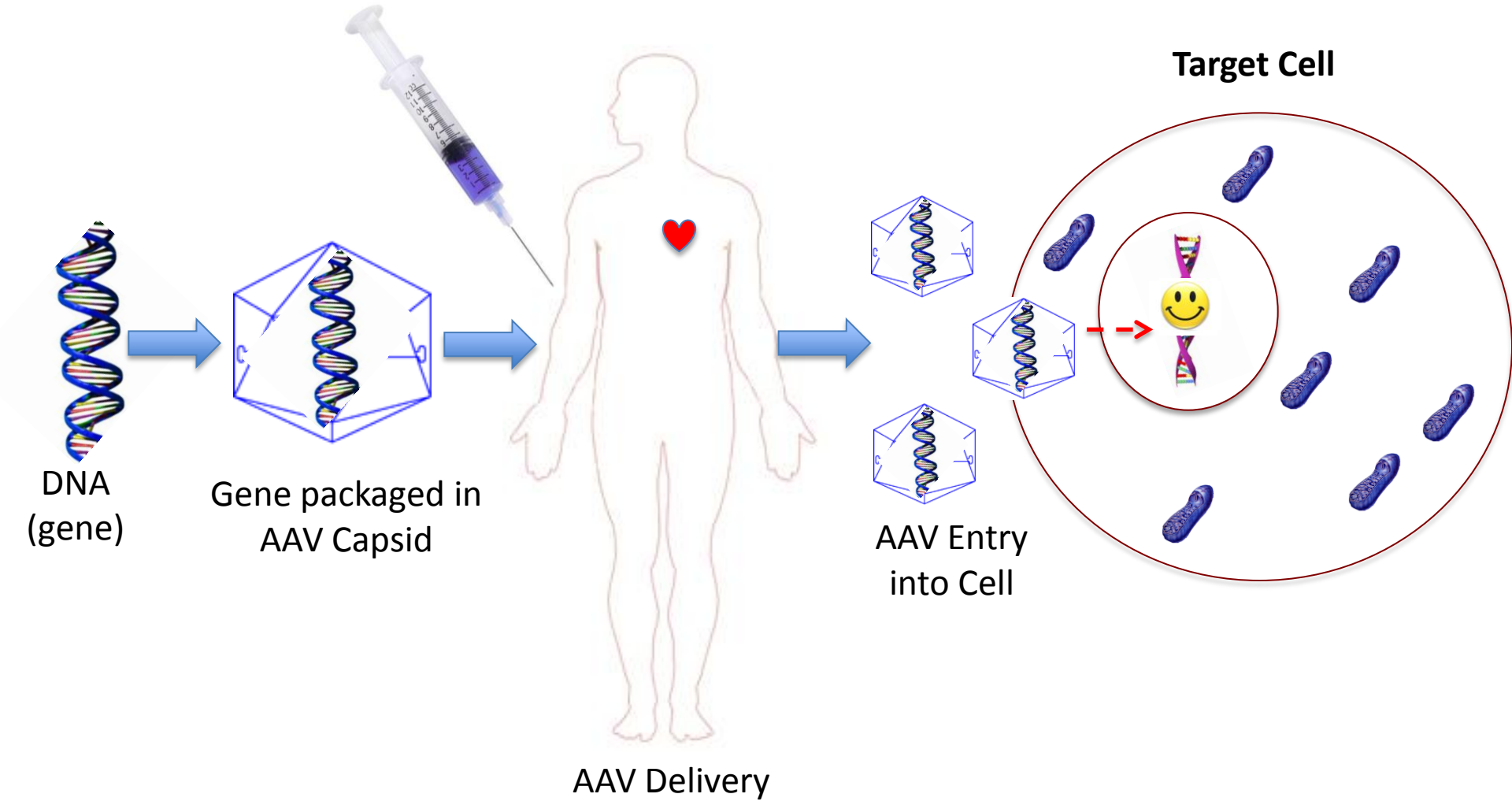


Group	pH rest	pH post	τPCr
CON (4)	7.17±0.03	6.98±0.01	236 ±21s
TAZKD (3)	7.11±0.01	6.88±0.03	389 ±7s

Conclusions

- **Endurance exercise training is not sufficient to accelerate cardiac dysfunction in young TAZKD animals**
- **Endurance training may be beneficial in TAZKD mice in regards to heart function; however, TAZKD mice demonstrate a reduction in oxidative capacity**

Gene Therapy

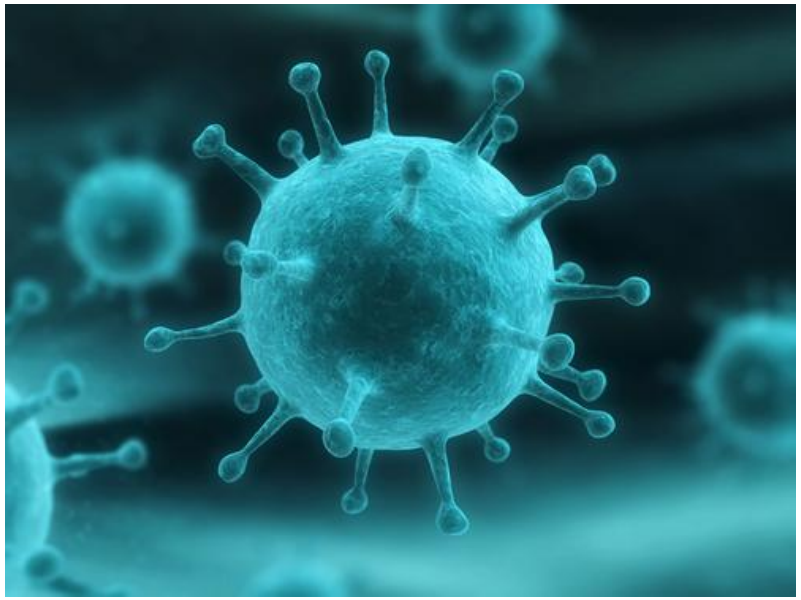


Current AAV Trials

Disease	Transgene product	Serotype	Route of administration	Clinical trial	ClinicalTrials.gov identifier	Refs
AAV clinical trials for inherited diseases						
α1 antitrypsin deficiency	α1 antitrypsin	AAV2	Intramuscular	Phase I/II	NCT00377416	101,102
		AAV1			NCT00430768	
Batten's disease	CLN2	AAV2	Direct intracranial administration	Phase I	NCT00151216	90
		AAVrh10			NCT01161576	
Canavan's disease	Aspartoacylase	AAV2	Direct intracranial administration	Phase I	NA	89
Cystic fibrosis	CFTR	AAV2	Direct instillation to maxillary sinus, bronchoscopy to right lower lobe, aerosol to whole lung	Phase I/II	NCT00004533	154–158
Haemophilia B	Factor IX	AAV2	Intramuscular	Phase I/II	NCT00076557	36,39
			Hepatic		NCT00515710	
		AAV8	Intravenous		NCT00979238	
Leber's congenital amaurosis	RPE65	AAV2	Subretinal	Phase I/II	NCT00643747	4,7,17
					NCT00516477	
					NCT00481546	
LPL deficiency	LPL	AAV1	Intramuscular	Phase I/II	NCT01109498, NCT00891306	12,103,116
Pompe's disease	GAA	AAV1	Series of intradiaphragmatic injections	Phase I/II	NCT00976352	NA (unpublished)
Muscular dystrophy: Duchenne	Microdystrophin	AAV1–AAV2 hybrid	Intramuscular	Phase I	NCT00428935	97
Muscular dystrophy: limb girdle	α-sarcoglycan	AAV1	Two to six separate injections into the selected muscle	Phase I	NCT00494195	95,96
AAV clinical trials for acquired diseases						
Severe heart failure	SERCA2a	AAV1	Antegrade epicardial coronary artery infusion	Phase I/II	NCT00454818	159
		AAV6			NCT00534703	
Parkinson's disease	AADC	AAV2	Intracranial	Phase I/II	NCT00229736	64,65
	GAD				NCT00643890, NCT00195143, NCT01301573	66,69
	Neutrophin				NCT00252850, NCT00985517, NCT00400634	67,68
Age-related macular degeneration	sFLT01	AAV2	Intravitreal injection	Phase I	NCT01024998	NA (unpublished)
Rheumatoid arthritis	TNFR-Fc	AAV2	Intra-articular	Phase I	NCT00617032, NCT00126724	160–162

Mingozzi, Federico, High, Katherine A. Therapeutic in vivo gene transfer for genetic disease using AAV: progress and challenges. Nat Rev Genet

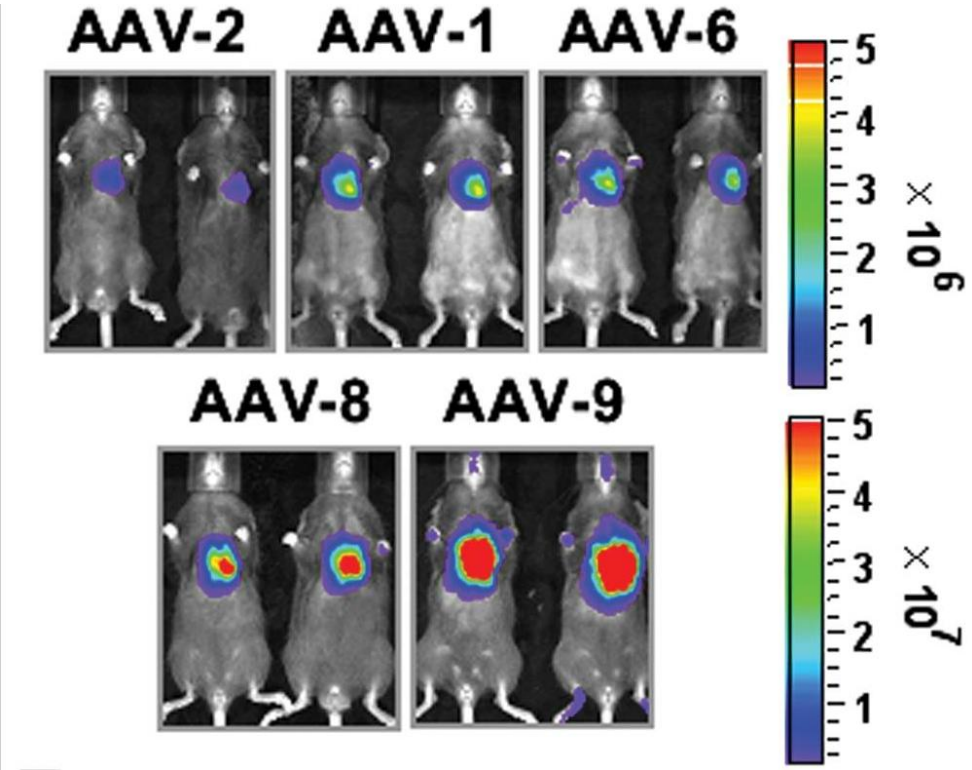
Adeno-associated Virus (AAV)



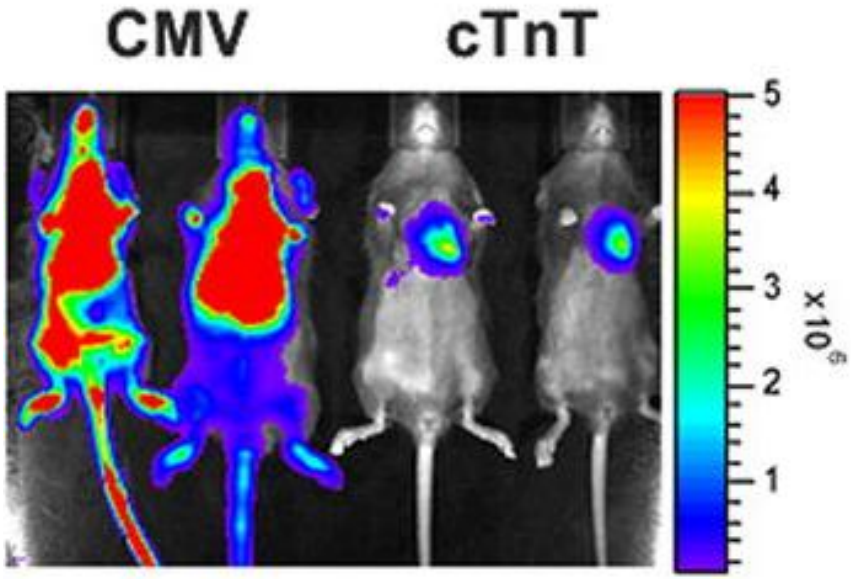
- AAV
  - Small; non-pathogenic
  - Transduces both dividing and nondividing cells
  - Long-term stable gene transfer WITHOUT disrupting genes by insertional mutagenesis

Optimization for Gene Therapy

Serotype:

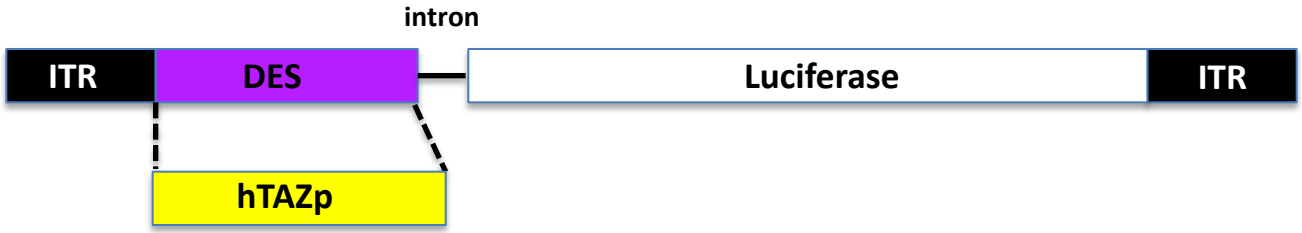


Promoter:

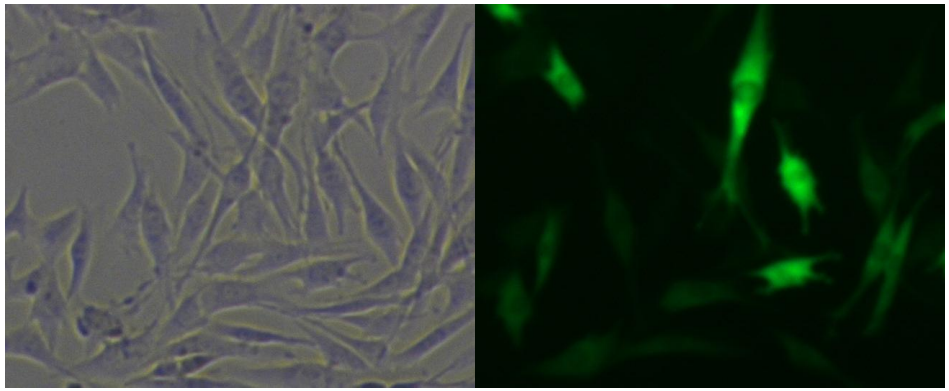


Gene Ther. 2011 January ; 18(1): 43–52. doi:10.1038/gt.2010.105.

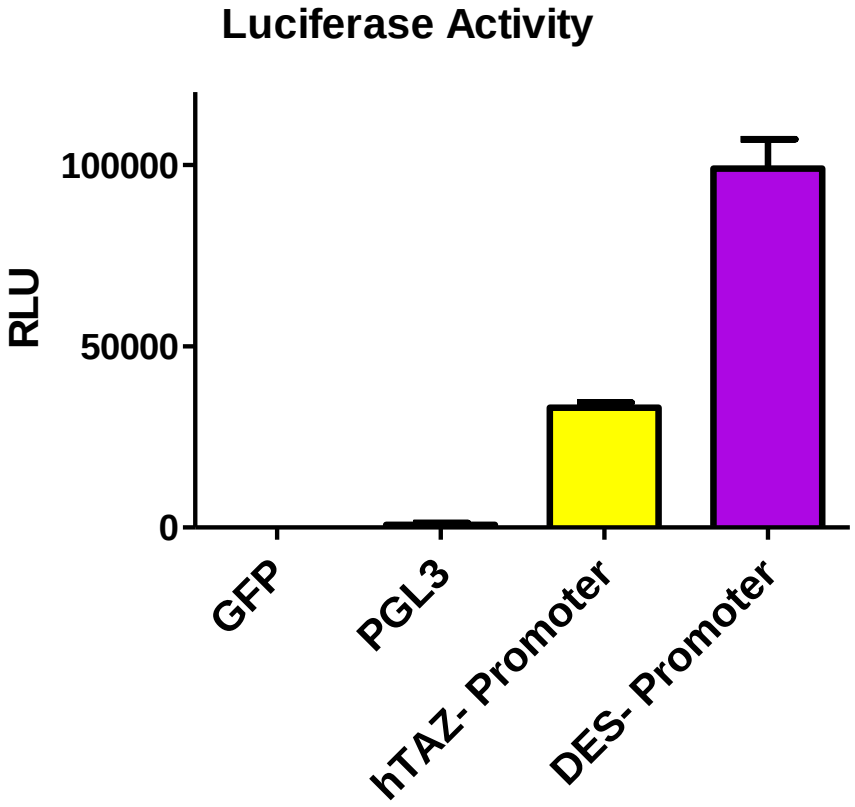
Promoter Expression Levels in C2C12 Cells



C2C12 Cells

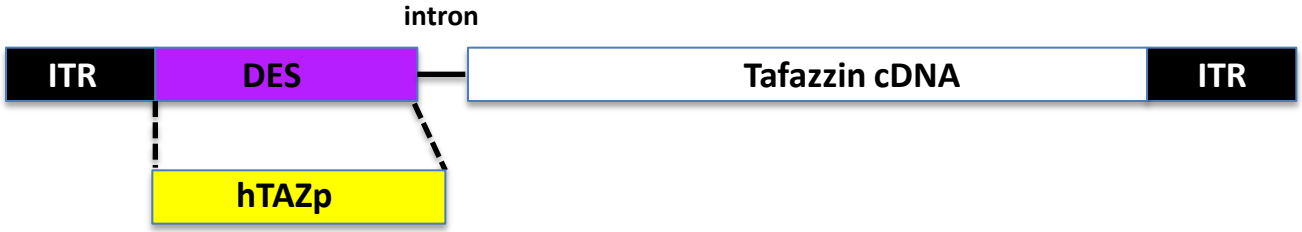


48 hours post Transfection



Future Directions

- Construct Packaging and Delivery



- Test efficacy of construct *in vivo*
  - Protein expression
  - Lipid Profiles

Final Summary

- Endurance Training
  - Does not accelerate cardiomyopathy in TAZKD mice.
  - May be beneficial as seen by an increase in ejection fraction.
- Gene therapy
  - Is a successful therapeutic approach in treating disease.
  - The endogenous promoter along with the preferential tropism of AAV9 will result in appropriate levels of gene expression.

Acknowledgments

UF

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