



SPACEFLIGHT AND THE MOUSE EYE: RESULTS FROM EXPERIMENTS ON SHUTTLE MISSIONS STS-133 AND STS-135

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Problem

Vision alterations associated with globe flattening, choroidal folds and papilledema, shown in some crew members returning from long duration missions (Mader, et al. Ophthalmology 2011)



Hypothesis

Ocular neuroanatomical changes observed in the VIIP syndrome are accompanied by retinal changes at the molecular and cellular level that may affect retinal health and physiology

Previous work

Scarce evidence from animal flight experiments, showing cell loss in retina of rat neonates aboard STS-72 (Tombran-Tink & Barnstable, 2005) and cell disruption in retina of rats aboard Cosmos 782 and 936 (Philpott, et al. 1978, 1980)

Experimental design

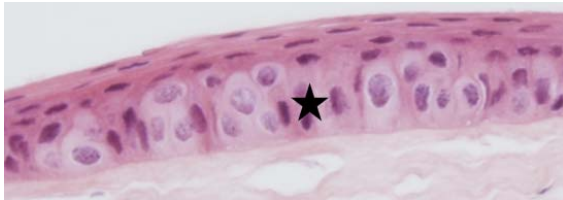
- Tissue sharing
- STS-133 Balb/cJ mice, 10-12 week old (albino)
Conditions: vivarium (VIV), AEM, flight (FLT) 
Duration of flight: ~13 days
Tissue collections: R+1, R+5, R+7
- STS-135 C57BL/6 mice, 9-11 weeks old 
Conditions: AEM, flight
Duration of flight: ~13 days
Tissue collections: R+1

Objective

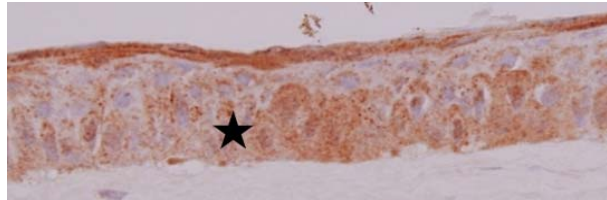
Investigate evidence of ocular (retinal) changes associated with spaceflight:

- ✓ histological markers of cellular death and damage
- ✓ molecular markers of oxidative stress
- ✓ gene expression markers of stress

STS-133 Histology

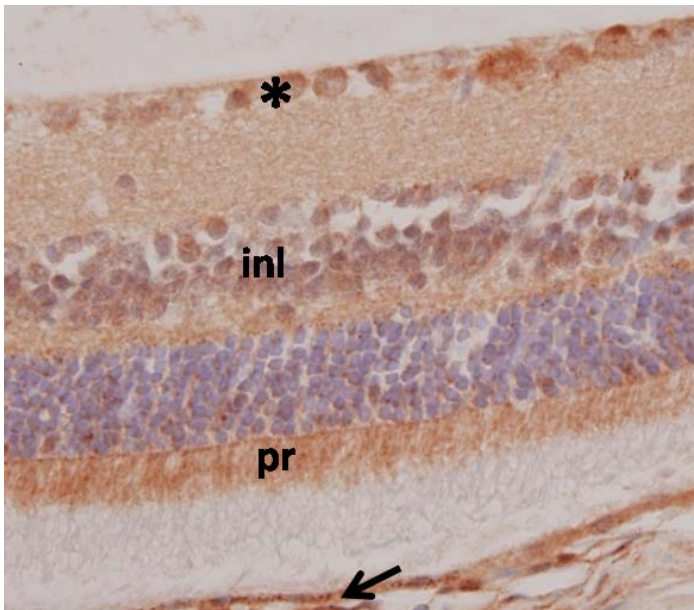


AEM R+7-Basal edema and acanthosis



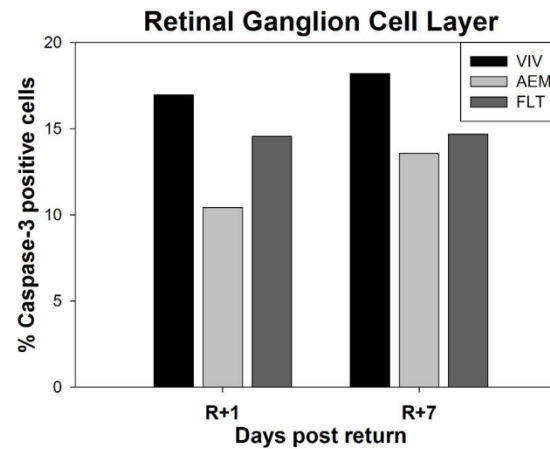
FLT R+1 - Caspase 3 positive

Corneal epithelium

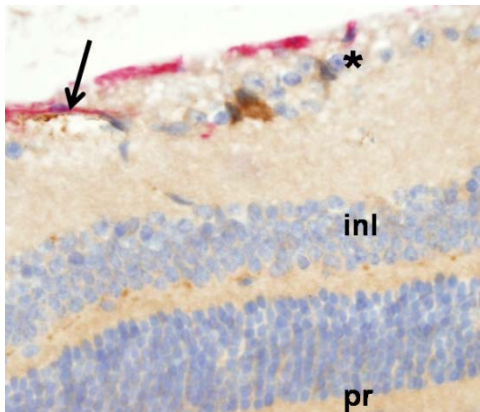


FLT R+1 Caspase-3 positive

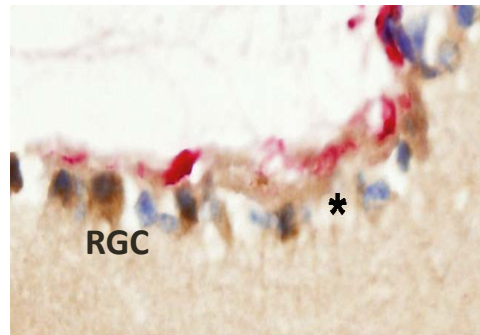
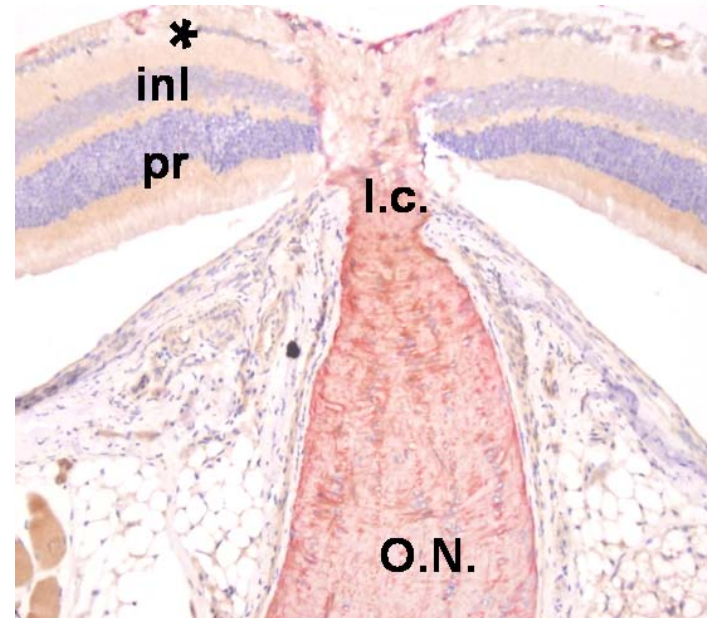
Retina



STS-133 Histology

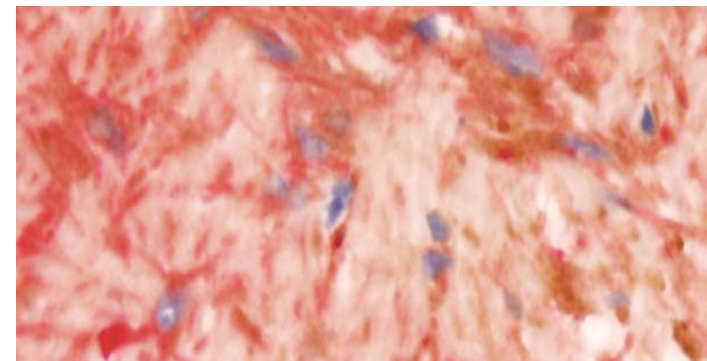


FLT R+1



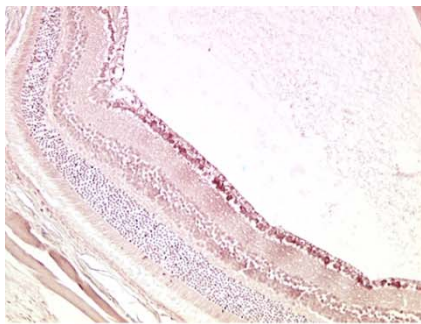
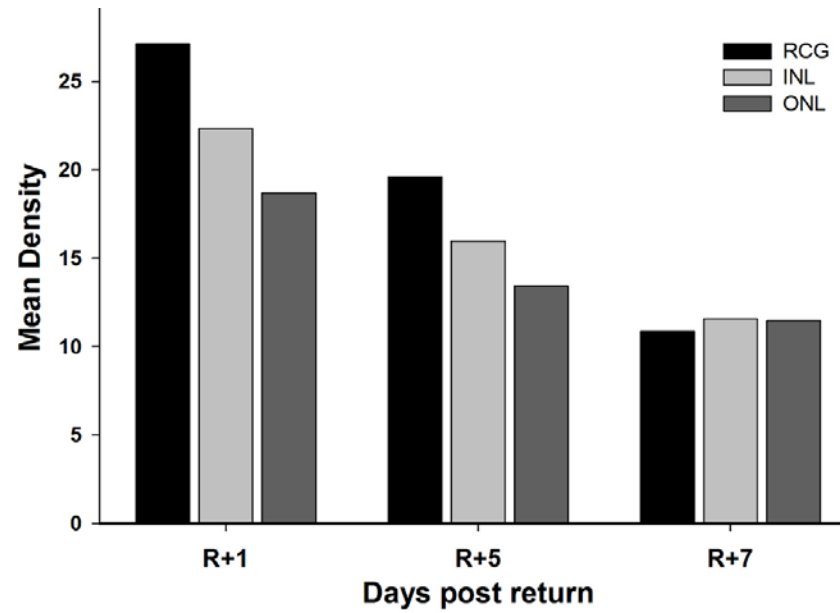
GFAP: glial fibrillary acidic protein (glial activation)

β-amyloid (neuronal injury)

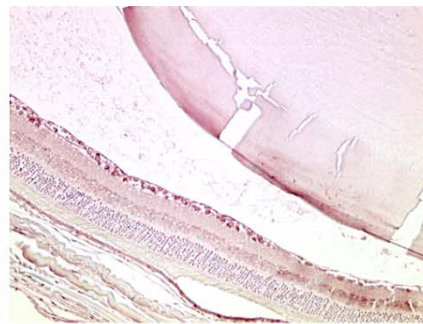


Post -laminar β-amyloid + region

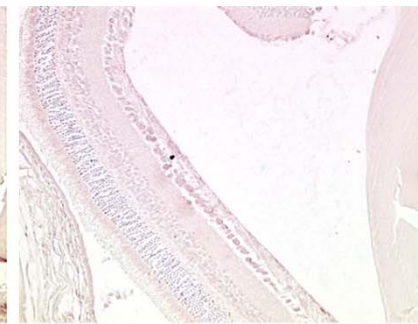
STS-133 Oxidative stress DNA damage (8OHdG)



FLT R+1

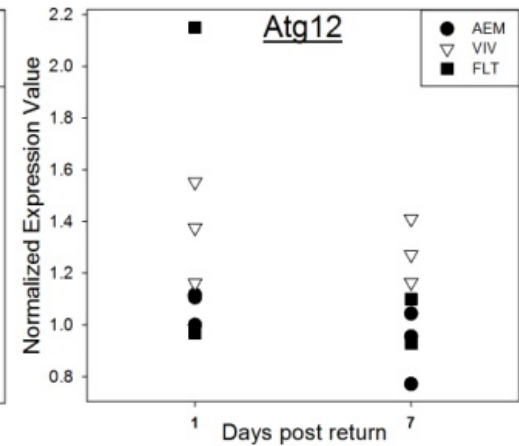
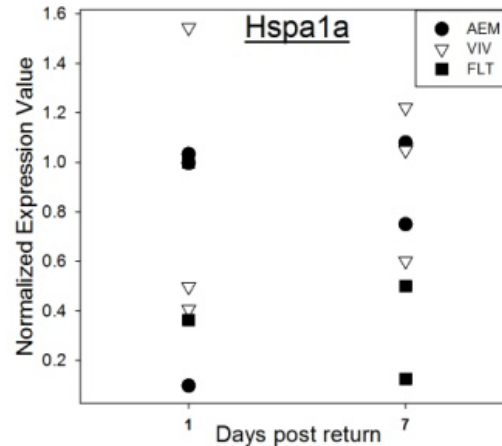
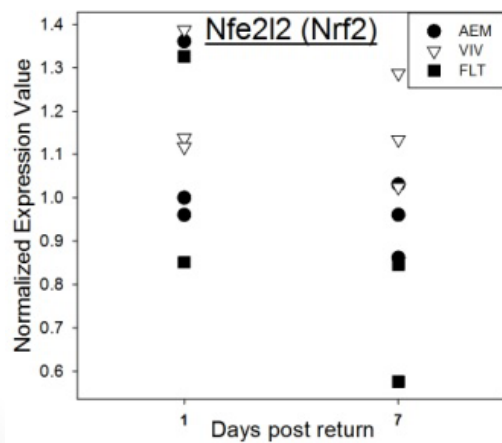
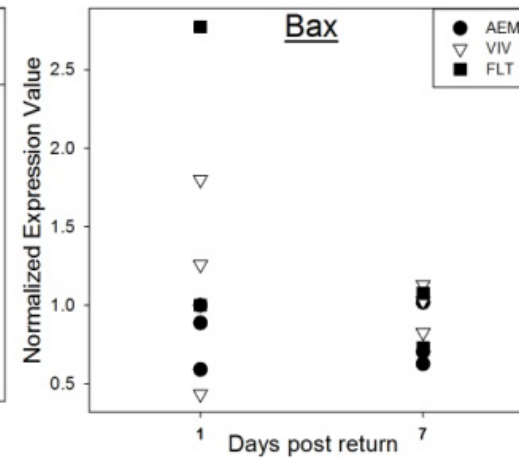
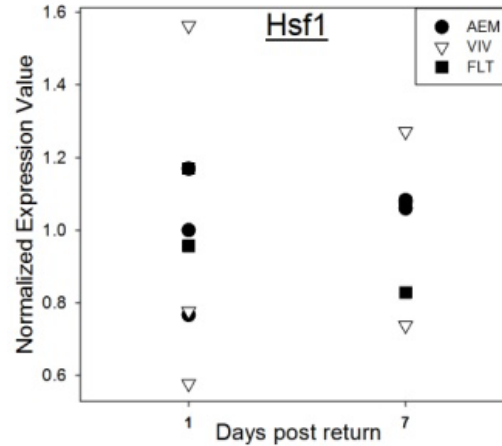
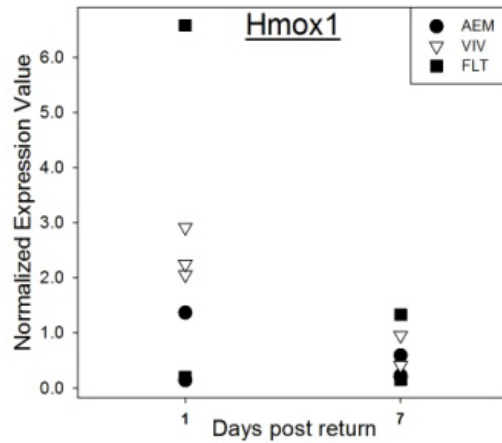


FLT R+5



FLT R+7

STS-133 Gene Expression

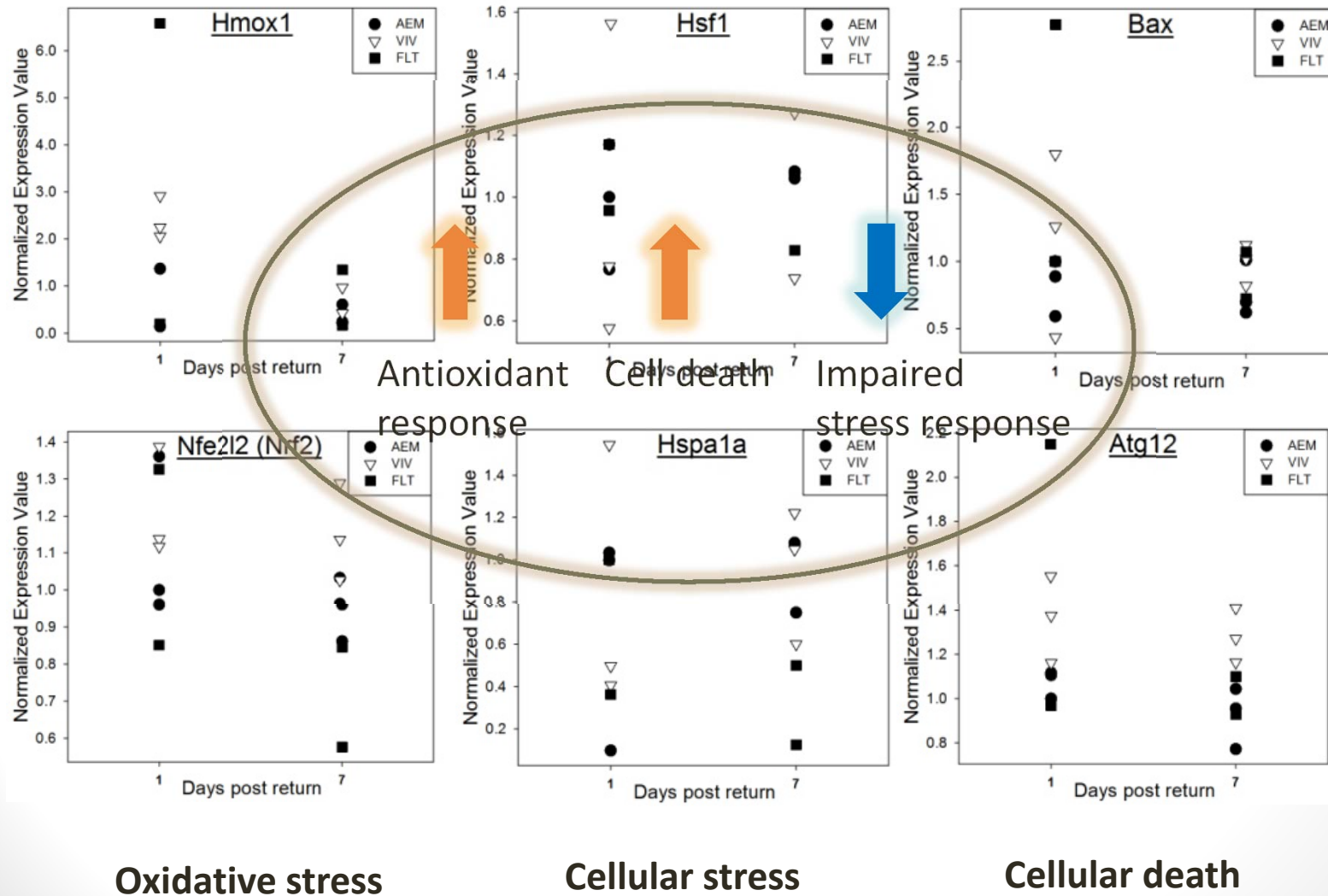


Oxidative stress

Cellular stress

Cellular death

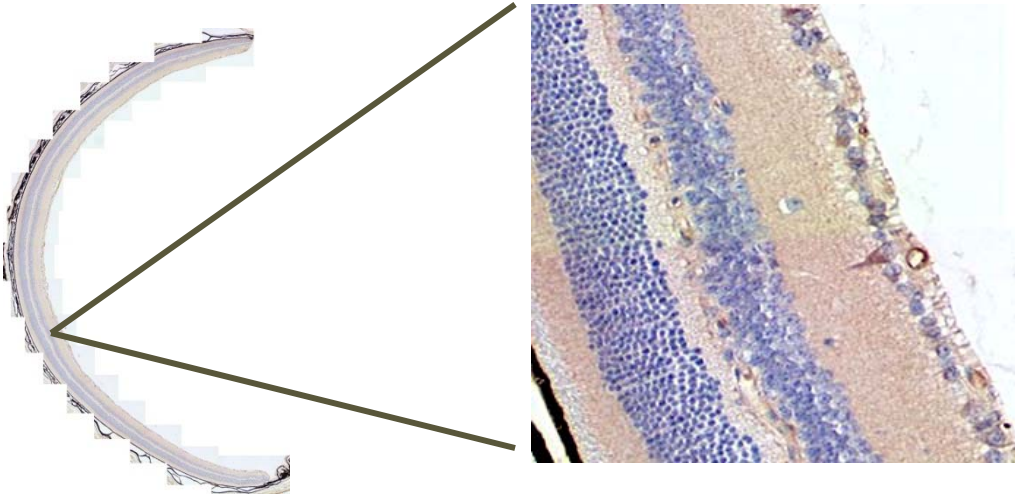
STS-133 Gene Expression



STS-135 Histology

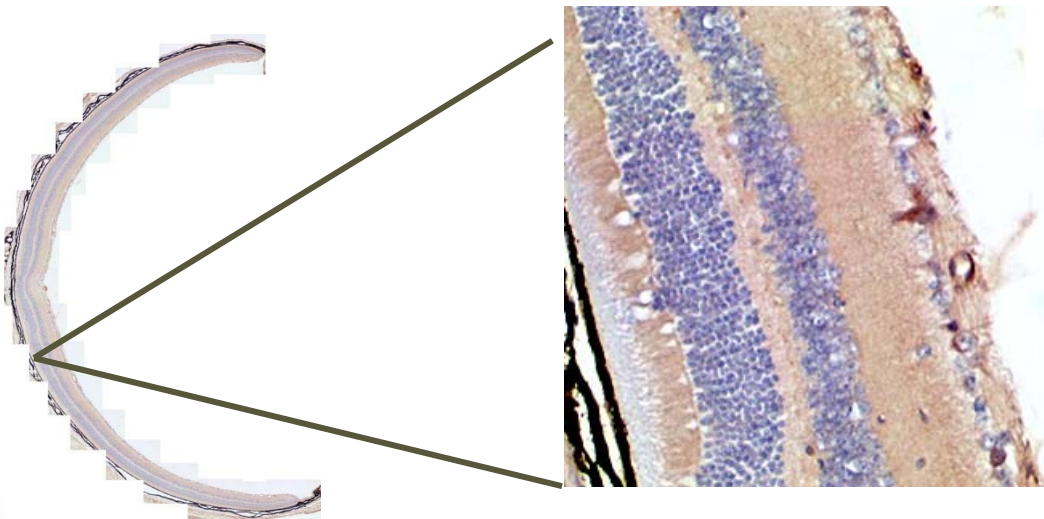
**CASPASE-3
MEDIATED
APOPTOSIS**

#16 AEM

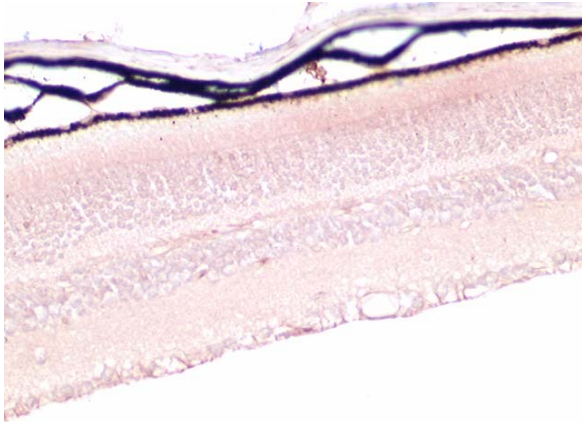


...% more caspase-3
+ RGC in FLT vs AEM
(n=3)

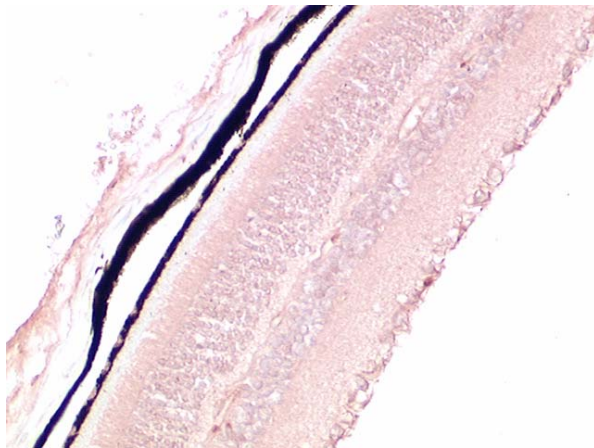
#52 FLT



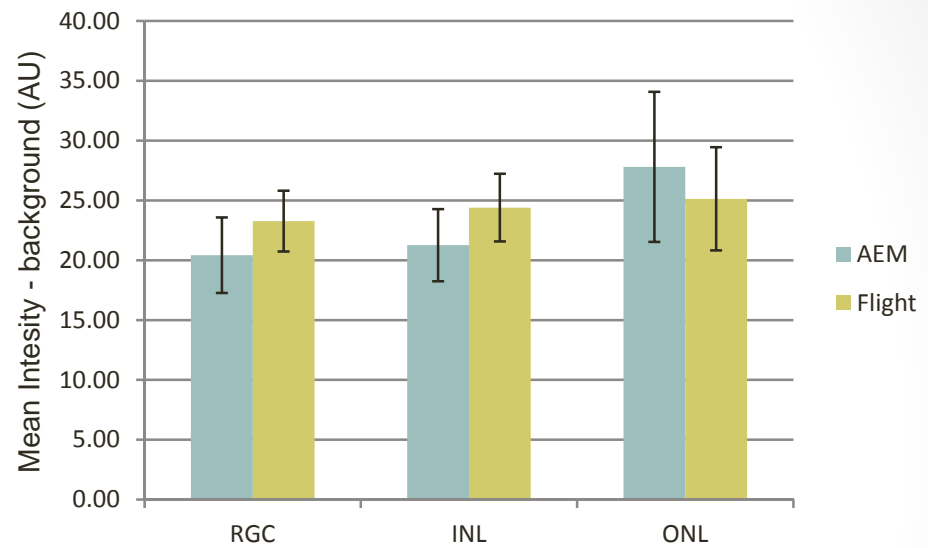
STS-135 Histology



AEM



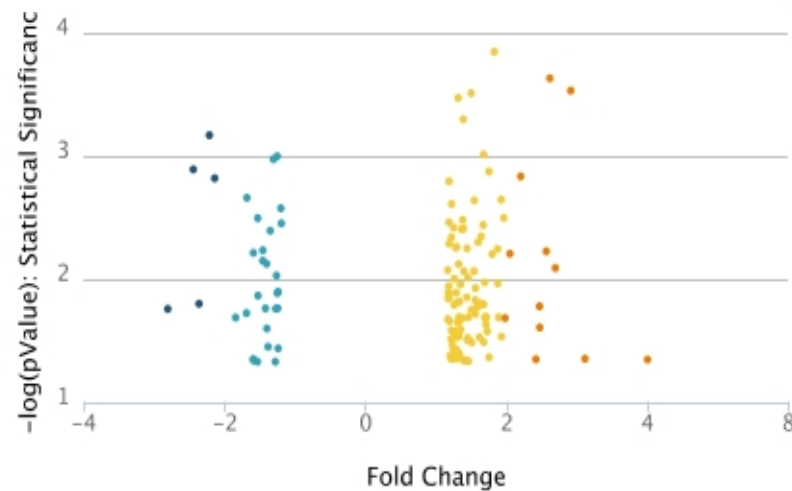
FLT



80HdG

STS-135 Microarray

- Microarray processing and analysis performed at the UTMB Genomics Core Laboratory (n=3)
- Ingenuity systems iReport generated
- Affymetrix mouse expression array:
40,000genes
- Differentially expressed genes: 139

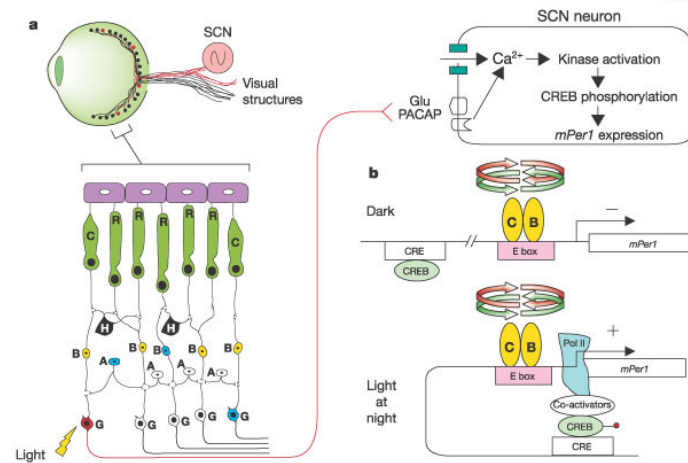
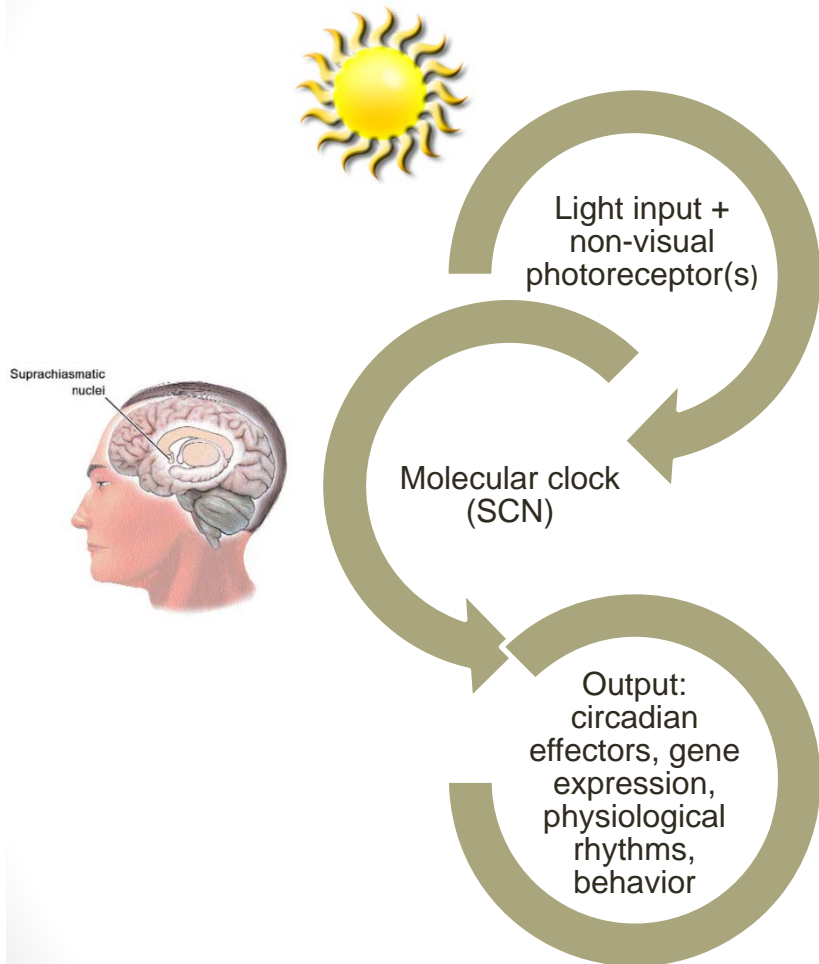


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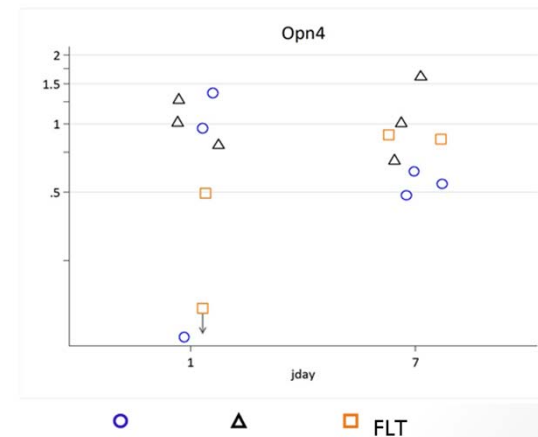
STS-135 Pathway analysis

PATHWAYS	PROCESSES	DISEASES
ER stress	RNA processing (mRNA splicing)	Cancer
Pyrimidine metabolism	Cell death of sensory neurons and RGC	Neurodegeneration of nerves and nervous tissue
Cytokine production and signaling (IL-1, IL-6, IL17)	Apoptosis of microglia and neuronal cells	Degeneration of optic nerve
Sphingosine-1-P signaling	Stabilization and assembly of desmosomes	Reactivation of herpes virus
Axonal guidance and actin cytoskeleton	Axon branching	
Molecular mechanisms of cancer	ER stress response	

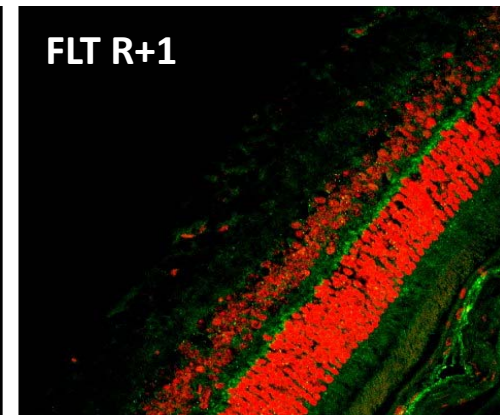
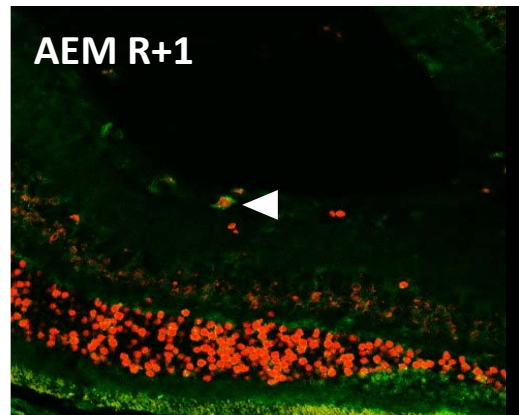
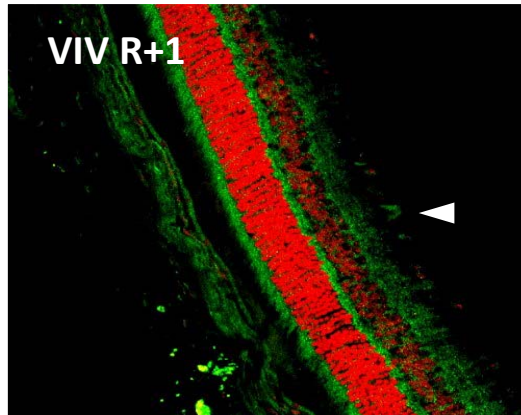
STS-133/135: Melanopsin



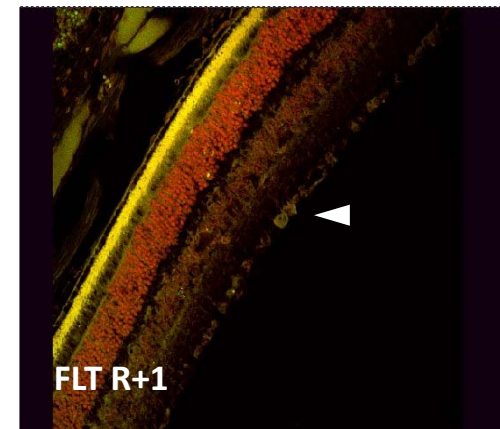
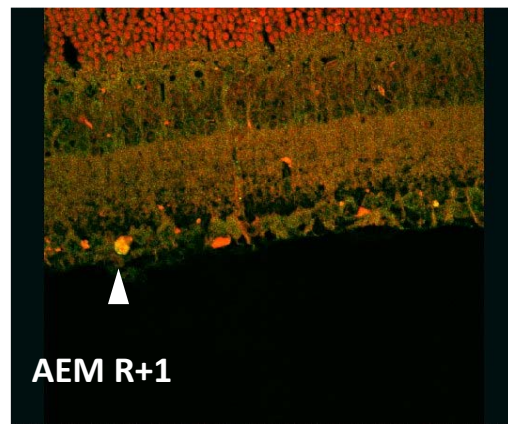
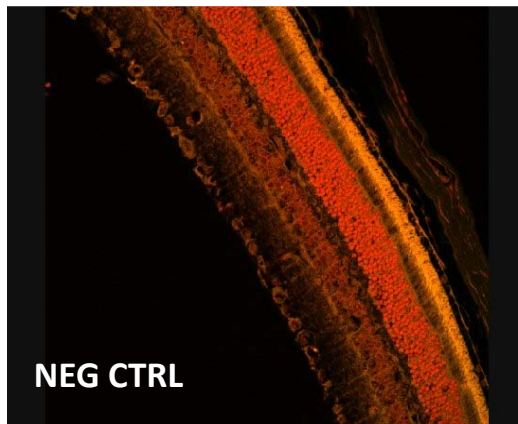
Reppert & Weaver, 2002, Nature 418, 935-941)



STS-133/135: Melanopsin



STS-133-Balb/cJ Albino mice



STS-135 C57BL mice

Summary

These preliminary results suggest that:

- Oxidative stress and neuronal loss occur in the retina of mice exposed to spaceflight
- Damage is preferentially localized in RGC
- Oxidative and cellular stress is reversible upon return to Earth
- Damage is also evidenced by glial activation and neuronal/axonal injury
- ER stress and neuronal/glial cell death pathways are implicated in neuronal cell loss
- Susceptibility to cellular stress may affect the response and resistance to the effects of spaceflight in the retina and thus, the susceptibility to further damage (degeneration)
- Melanopsin expression and/or survival of ipRGC may be compromised under the stress of spaceflight conditions

Acknowledgements

- *Rich Boyle*
- *ARC/KSC tissue sharing*
- *HRP*