Foreign body response from implanted cortical-neuro probes in the spiny mouse (*Acomys*)

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INTRODUCTION

- Spiny mice (*Acomys* species) have emerged as an exciting research organism in the field of regenerative medicine owing to their remarkable ability to regenerate a wide range of tissues. They can perfectly regrow damaged tissues, such as skin, muscle, kidney, and spinal cord, with minimal or no scarring. (1), (2), (3)
- Scarring or fibrosis share similar characteristics with the foreign body response (FBR), an inflammatory response elicited by the host to materials implanted in the body that ultimately leads to the failure of implanted devices.
- Whether the "fibrosis-free" healing outcome as observed in peripheral tissues/organs of *Acomys* translates to biomedical implants-induced scarring remains unknown.
- We investigated *Acomys'* response to the injury model of cortical implant.

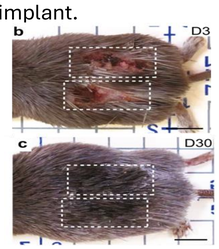

Figure 1. *Acomys* fully regrow skin wounds within 30 days. (1)

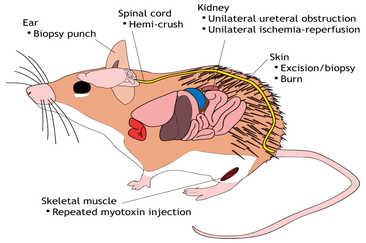

Figure 2. *Acomys* regrow various tissues and organs after a wide range of injuries. Figure adapted from (2).

METHODS

All animal work carried out in this study was approved by Institutional Animal Care and Usage Committee (IACUC) at the University of Florida.

- Animals: Spiny mice (*Acomys*) and Mice (CD1 Strain); Both sexes
- Surgery: Cranial surgery to implant silicon microelectrode implant (NeuroNexus Ann Arbor, MI) in the cortex
- Time points: 1-, 4-, 14-, 21-, and 28-days post implant (DPI)
- Histological assessment: Perfusion using phosphate buffered saline followed by 4% paraformaldehyde solution, processed for cryosectioning, and stained with antibodies for microglia/macrophages (Iba1), astrocytes (GFAP), and neuronal nuclei (NeuN). Stained sectioned were imaged using a confocal microscope.
- RNA sequencing: Immediately after CO2-induced euthanasia, cortex was harvested and frozen in liquid nitrogen. Stored at -80 °C until RNA extraction and sequencing.

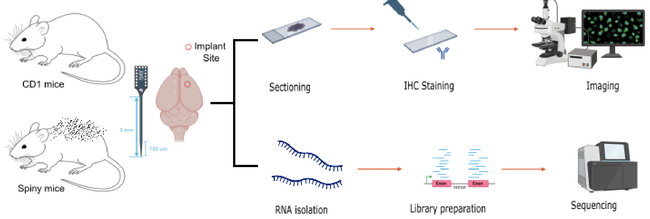

Figure 3. Overview of methods

RESULTS – Histological Assessment

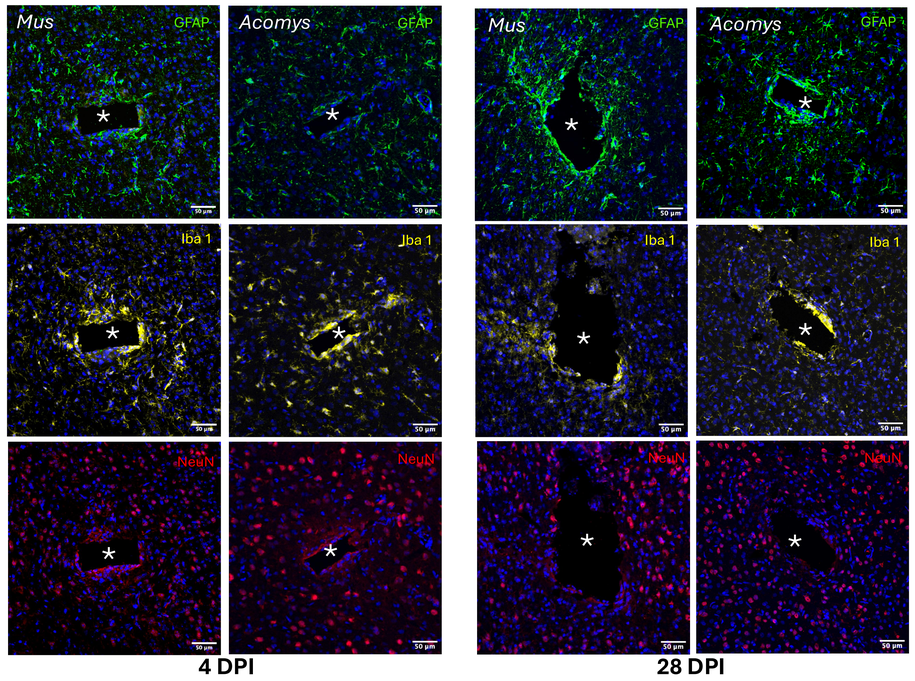

Figure 4. Representative histological images of cortical (brain) sections from CD1 mice and *Acomys* stained with markers for astrocytes (GFAP, green), microglia/macrophages (Iba, yellow), and neuronal nuclei (NeuN, red) at 4- and 28- days post implant (DPI). All nuclei were counterstained with DAPI (blue). Asterisk (*) represent implant location). N≥3

RESULTS – WGCNA

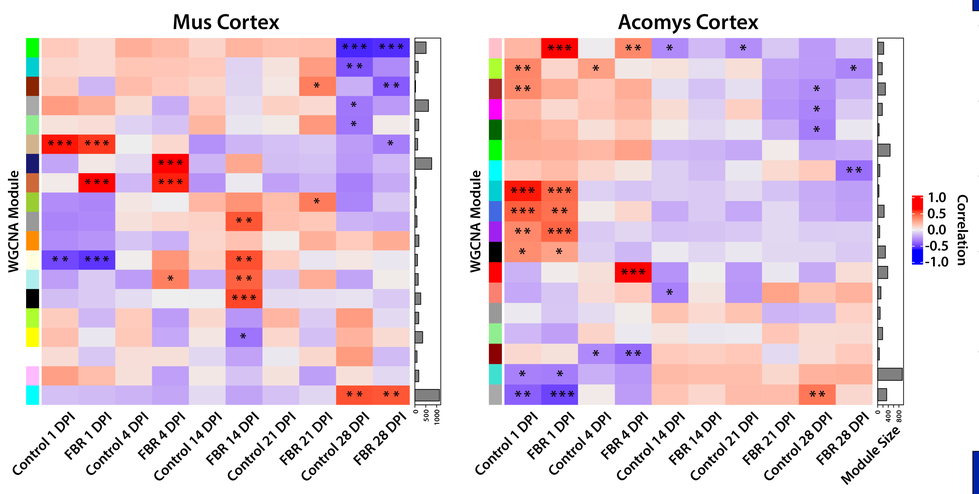

Figure 5. The summary of dataset as visualized by WGCNA plots suggests that *Acomys* has reduced differential gene expression after FBR compared to the *Mus*. After obtaining transcript abundance counts for each sample library, weighted gene co-expression network analysis (WGCNA) was performed to identify modules of transcripts co-expressed between each timepoint for both species. Heatmap coloration represents Pearson correlation between WGCNA modules and sample groups (* = p < 0.05, ** = p < 0.01, *** = p < 0.001; Student's t-test). Control (1 DPI,……, 28DPI) represent uninjured contralateral hemisphere and FBR (1 DPI,…. , 28 DPI) represent the injured/implant site at each timepoint. (n≥4 per group).

RESULTS - Differential Gene Expression

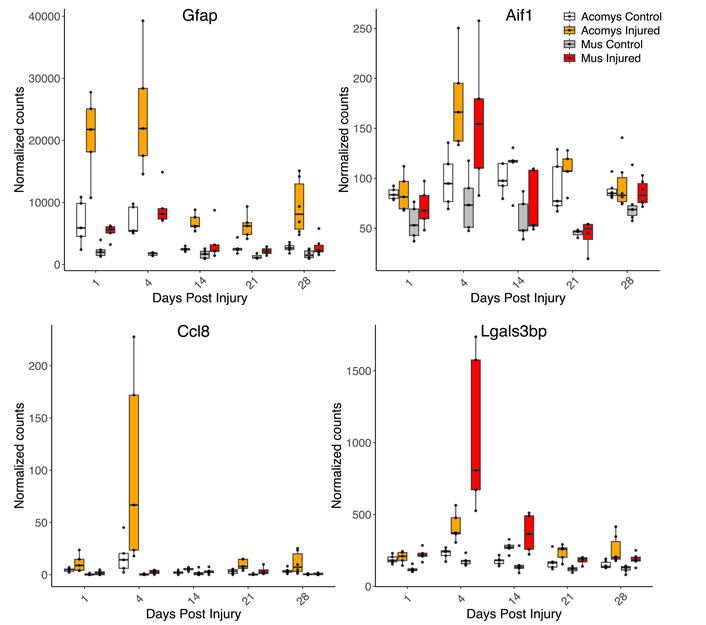

Figure 6. Differentially expressed genes between species and timepoints. When comparing differentially expressed genes, between species and timepoints, many potential therapeutic targets stand out. For example, Gfap and Ccl8 have increased expression in *Acomys* compared to *Mus*, which may suggest a protective state. Conversely Lgals3bp is greatly increased in expression 4 days post FBR, which may suggest its involvement in the *Mus* inflammatory response. Interestingly, Aif1 (IBA1) seems to have similar expression levels between *Acomys* and *Mus*.

CONCLUSION & DISCUSSION

- Histological assessment indicate a subsided inflammatory response (Iba1 and GFAP response) and more neuronal nuclei near the implant site in *Acomys*.
- WCGNA analysis of RNAseq suggests *Acomys* has a more similar transcriptional profile from the injured site than the uninjured site compared to the *Mus* response.
- A subdued inflammatory response in the *Acomys* was evident in the transcriptional profile compared to *Mus*, and several genes of interest emerged as potential therapeutic targets.
- Our findings reveal unique differences in the response of *Acomys* and *Mus* to cortical insult similar to that have been reported in response to other types of injury in *Acomys*, implicating the involvement of similar pathways in fibrosis and FBR.
- Studying non-traditional animal models offer unique biological insights that can uncover novel therapeutic targets and mechanisms not apparent in standard models, potentially accelerating the development of clinically relevant therapeutics.

REFERENCES

(1) Seifert *et al*. 2012; (2) Maden and Varholick. 2020; (3) Gaire *et al*. 2021

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