

The role of TNF in a high fat diet stroke model and the influence on inflammation, stroke size and functional outcome

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INTRODUCTION

- Obesity is a major risk factor of stroke, a leading cause of death and disability worldwide. People who are obese are 64% more likely to have a stroke.
- Today, the only approved treatments for stroke are thrombolysis and mechanical thrombectomy, but they fail to prevent the neurotoxic components of post-ischemic inflammation. Some neuroinflammation is necessary to clear dead tissue, however excess neuroinflammation enlarges the stroke and worsens functional outcomes in obesity.
- Tumor necrosis factor (TNF) is a promising target for reducing obesity-exacerbated stroke sizes and functional decline. Studies have found that it modulates the amount of ischemic damage, and it is found to be elevated in obesity, where it is a critical mediator of inflammation and glucose intolerance/insulin resistance.

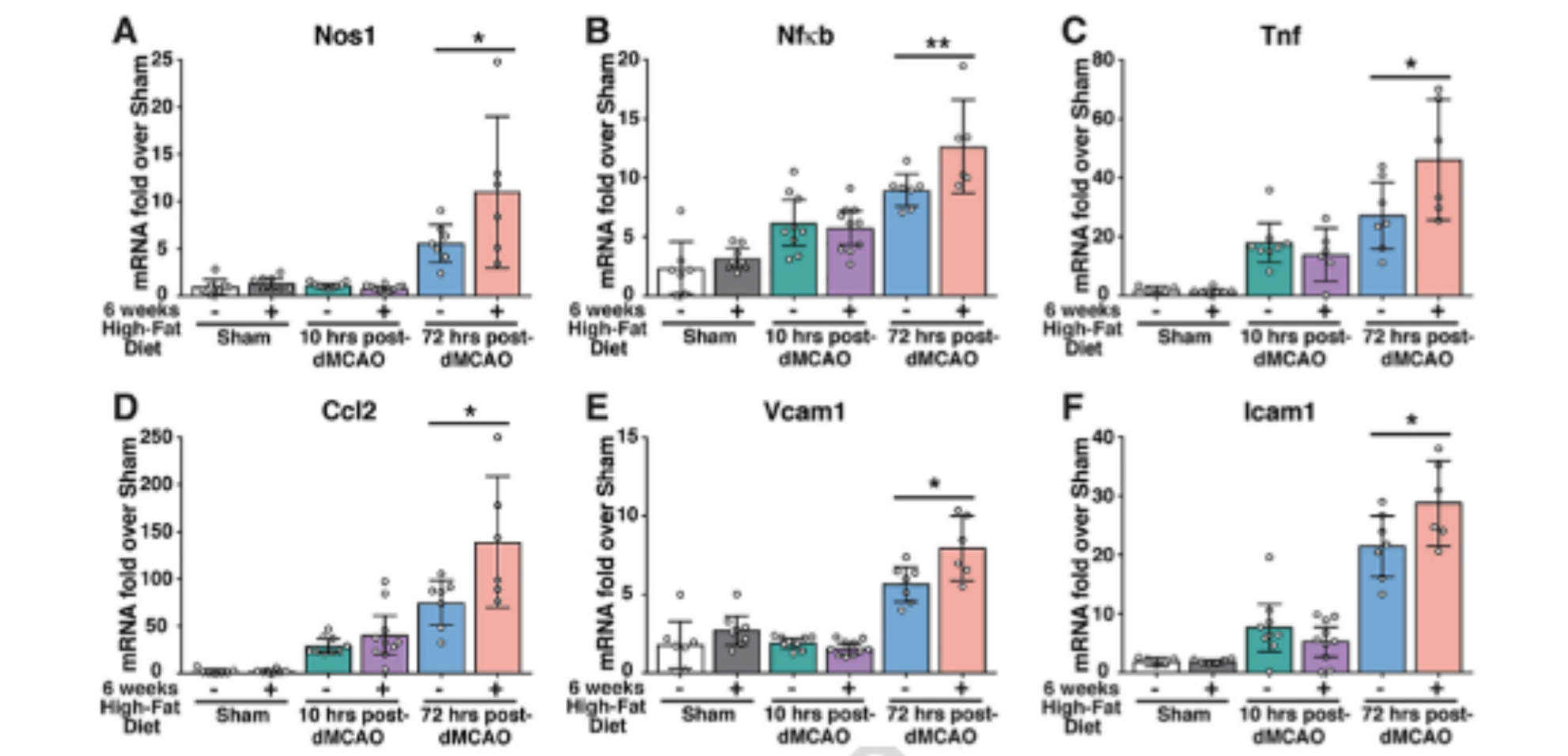
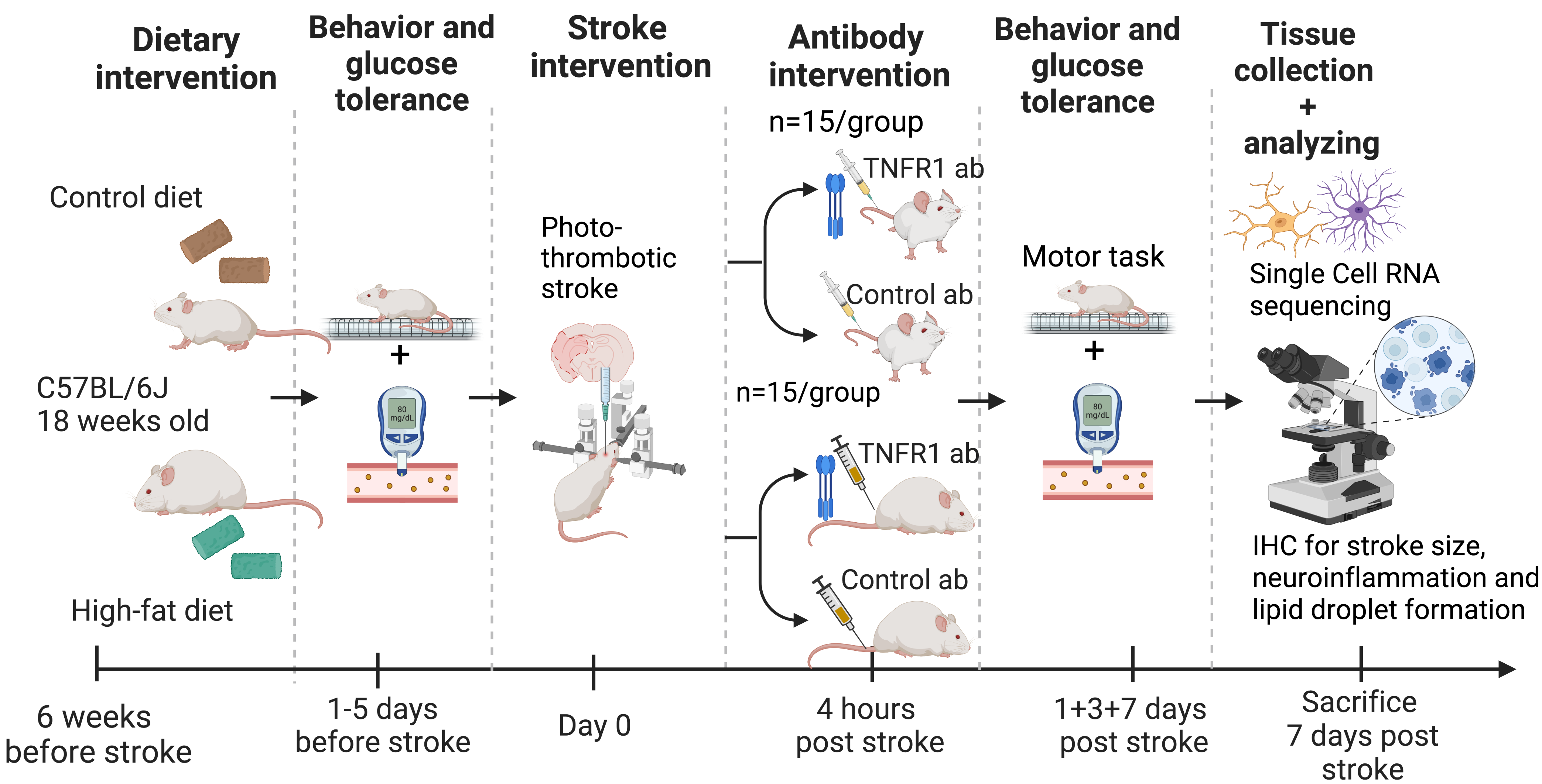


Figure 1. Gene expression of pro-inflammatory genes at 10 hours and 3 days after stroke. Peterson TC, Lechtenberg KJ, Piening BD, Lucas TA, Wei E, Chaib H, et al. Obesity Drives Delayed Infarct Expansion, Inflammation, and Distinct Gene Networks in a Mouse Stroke Model. Transl Stroke Res. 2021;12(2):331-46.

Mice fed a high fat diet have larger strokes and deficits in motor coordination as well as an increase in inflammatory genes after stroke that are not present prior to stroke. The late appearance of neuroinflammation and infarct expansion indicates that there may be a therapeutic window between 10 hours and 3 days after stroke where obesity-specific inflammation could be targeted.

Experimental plan



Preliminary results

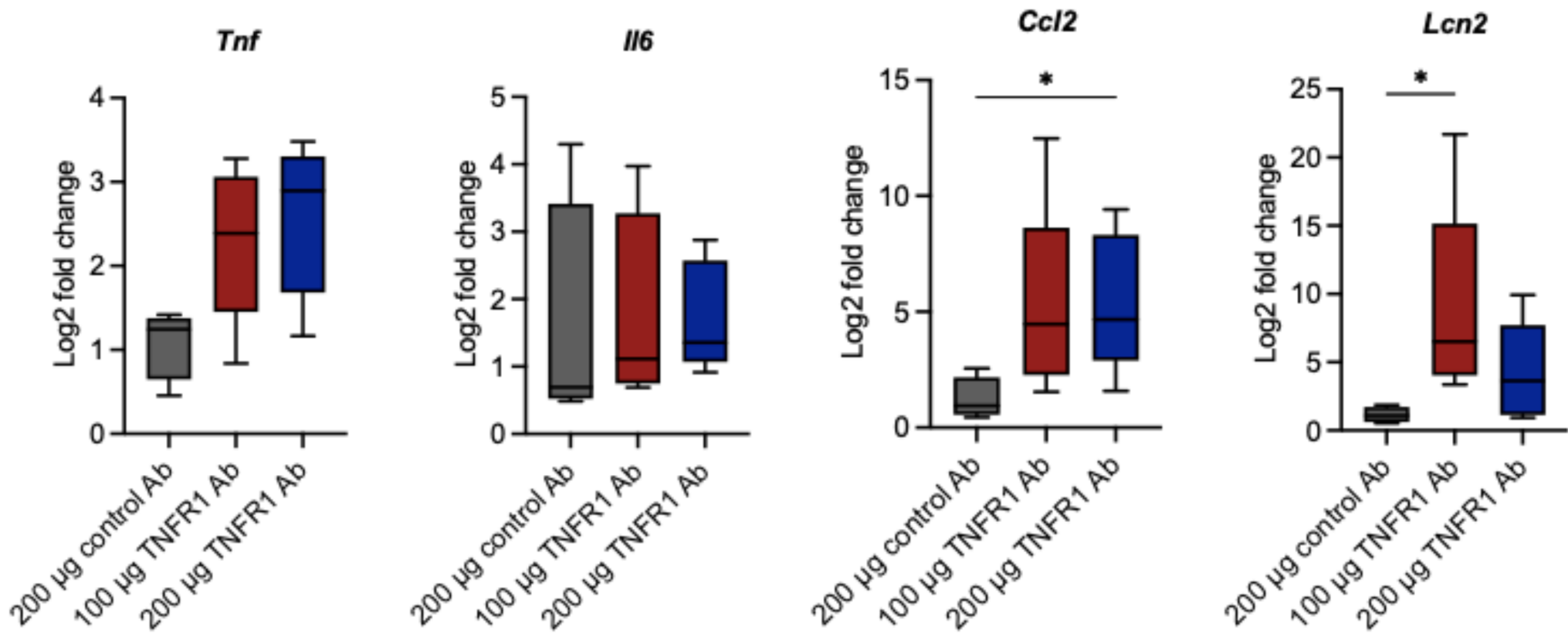


Figure 2. Changes in gene expression after stroke in TNFR1 or control antibody injected mice.

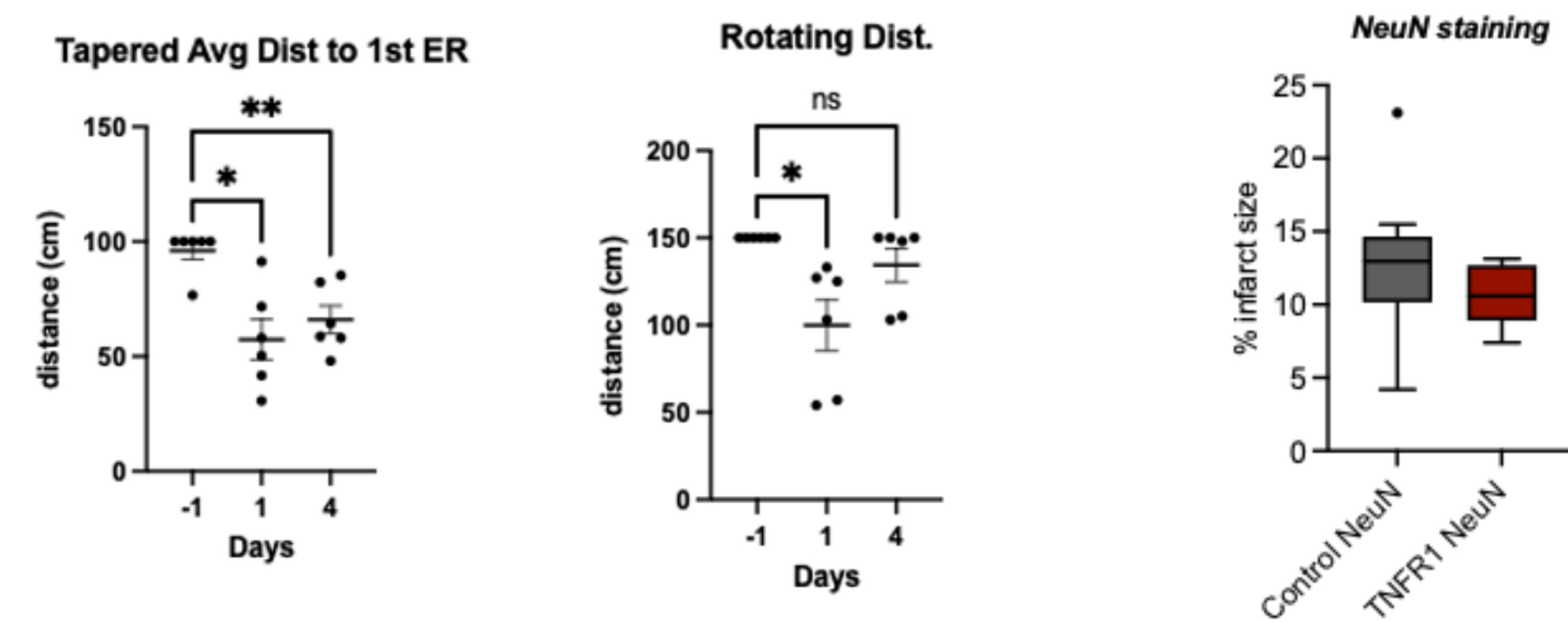


Figure 5. Motor deficits measured on the tapered beam.

Figure 4. Motor deficits after stroke on the rotating beam.

Figure 3. NeuN staining for infarct size in TNFR1 or control antibody.

- Blocking TNFR1 in a regular diet changed Ccl2 and Lcn2 significantly, and a 100ug dose was optimal.
- The infarct size did not change significantly, but there was a tendency to a slight reduction.
- We performed a trial to confirm that the photothrombotic stroke model induced motor deficits after stroke.

Figure 6. Overview of experimental plan for testing the hypothesis that blocking TNFR1 systemically early after stroke improves outcomes 7 days after stroke in high fat diet mice.

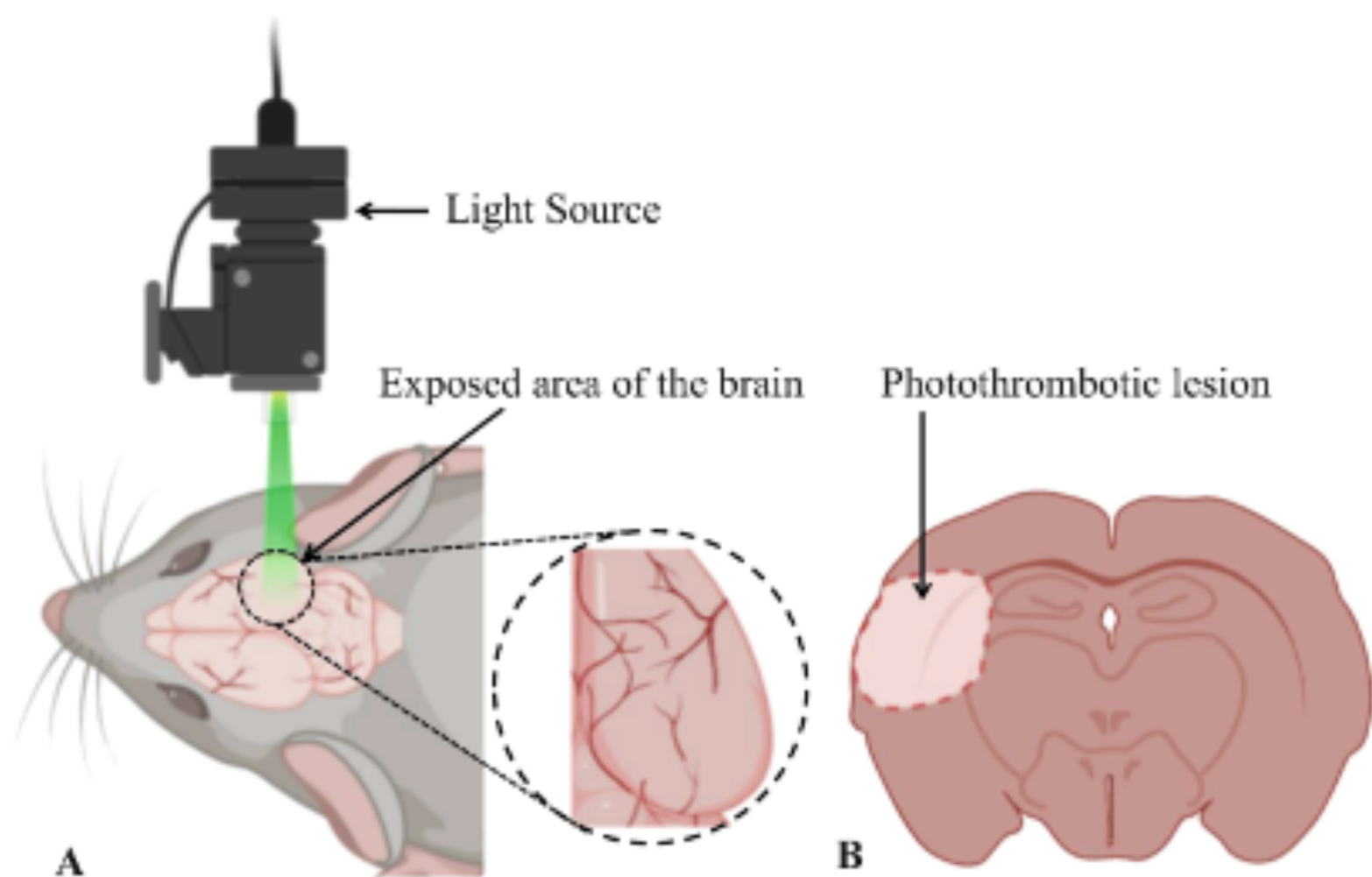


Figure 7. A photosensitive dye, Rose Bengal is injected into the mouse (IP) and enters to the bloodstream. When you shine light on the target brain area, it activates the dye, and it induces a clotting cascade and causes a stroke.

ACKNOWLEDGEMENTS

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