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The Role of Cell Cycle Mediators in the Progression of Non-alcoholic Steatohepatitis in Male and Female Murine Models

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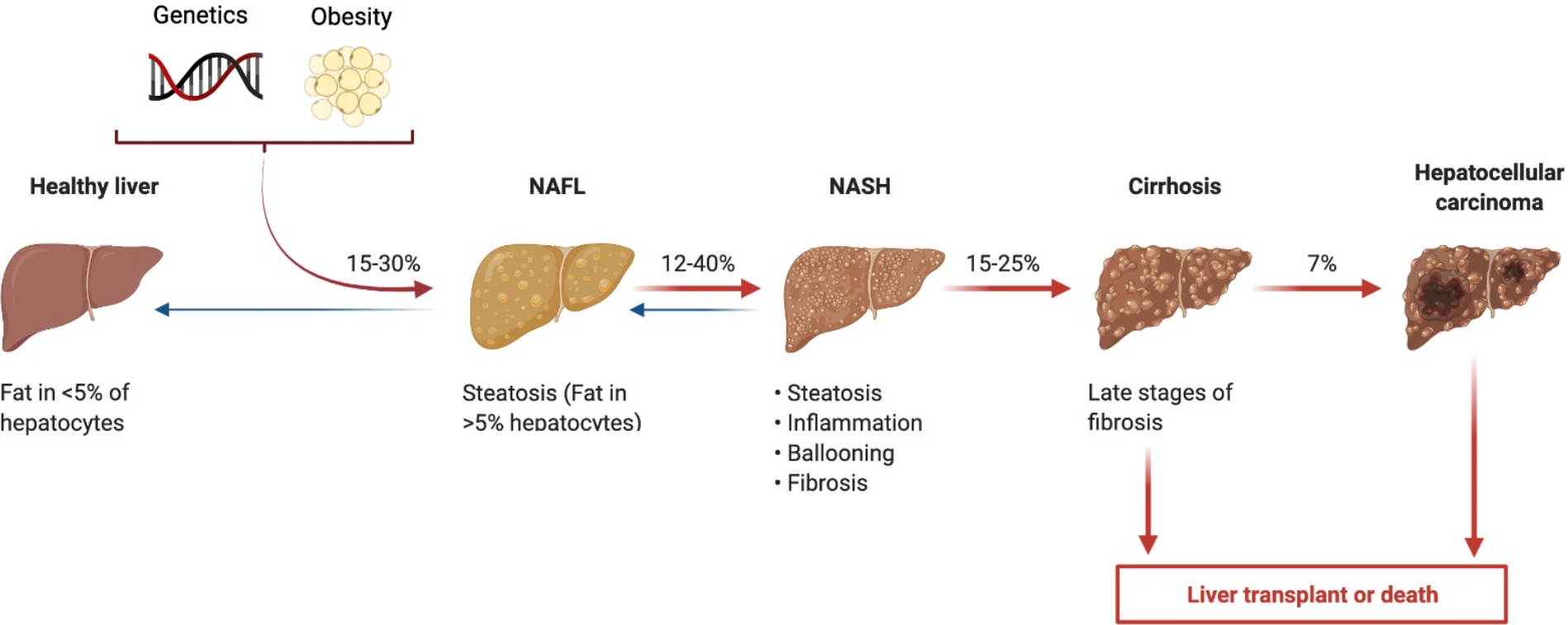
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The Role of Cell Cycle Mediators in the Progression of Non-alcoholic Steatohepatitis in Male and Female Murine Models

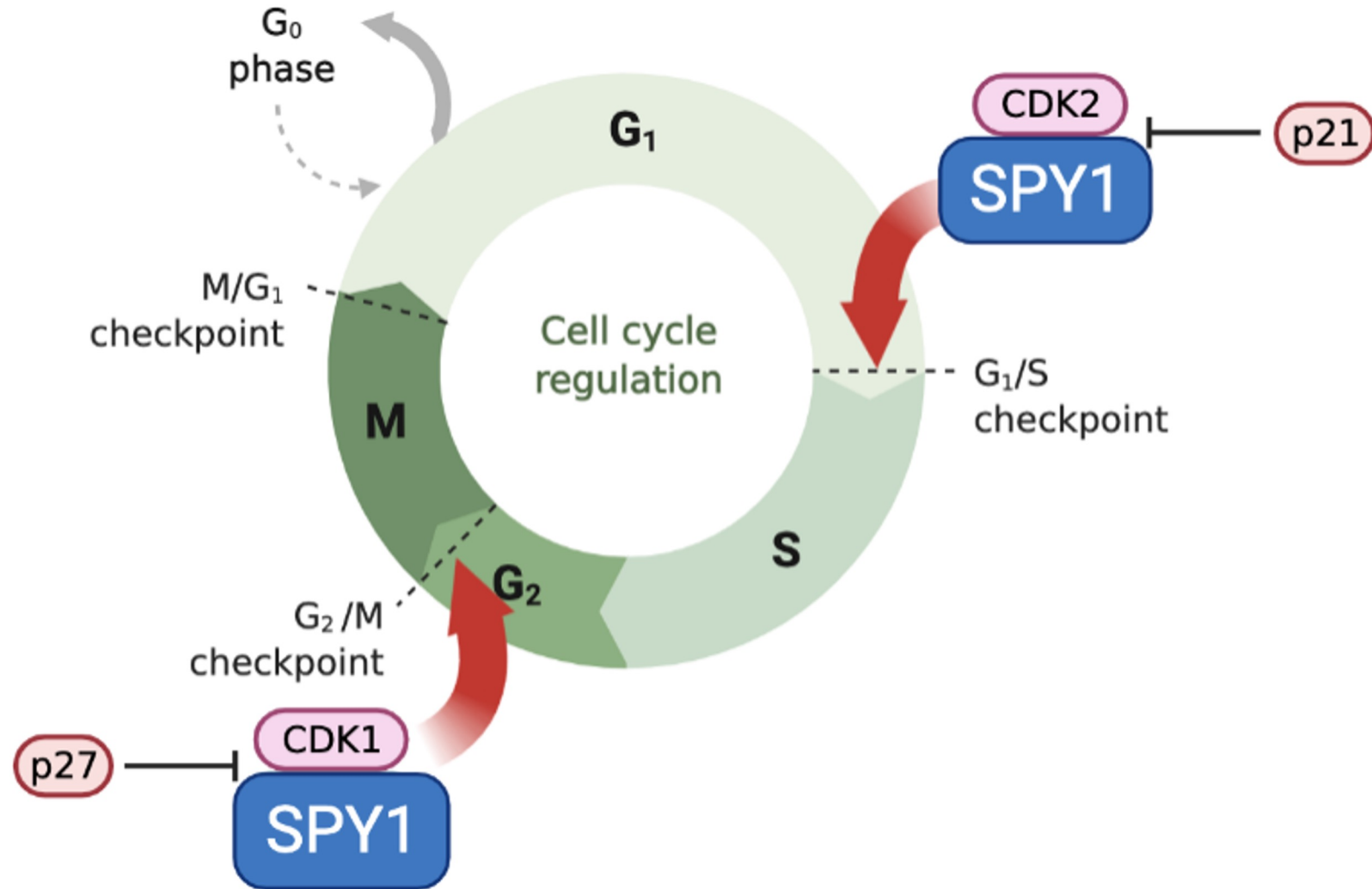
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Liver cancer: Hepatocellular carcinoma (HCC)

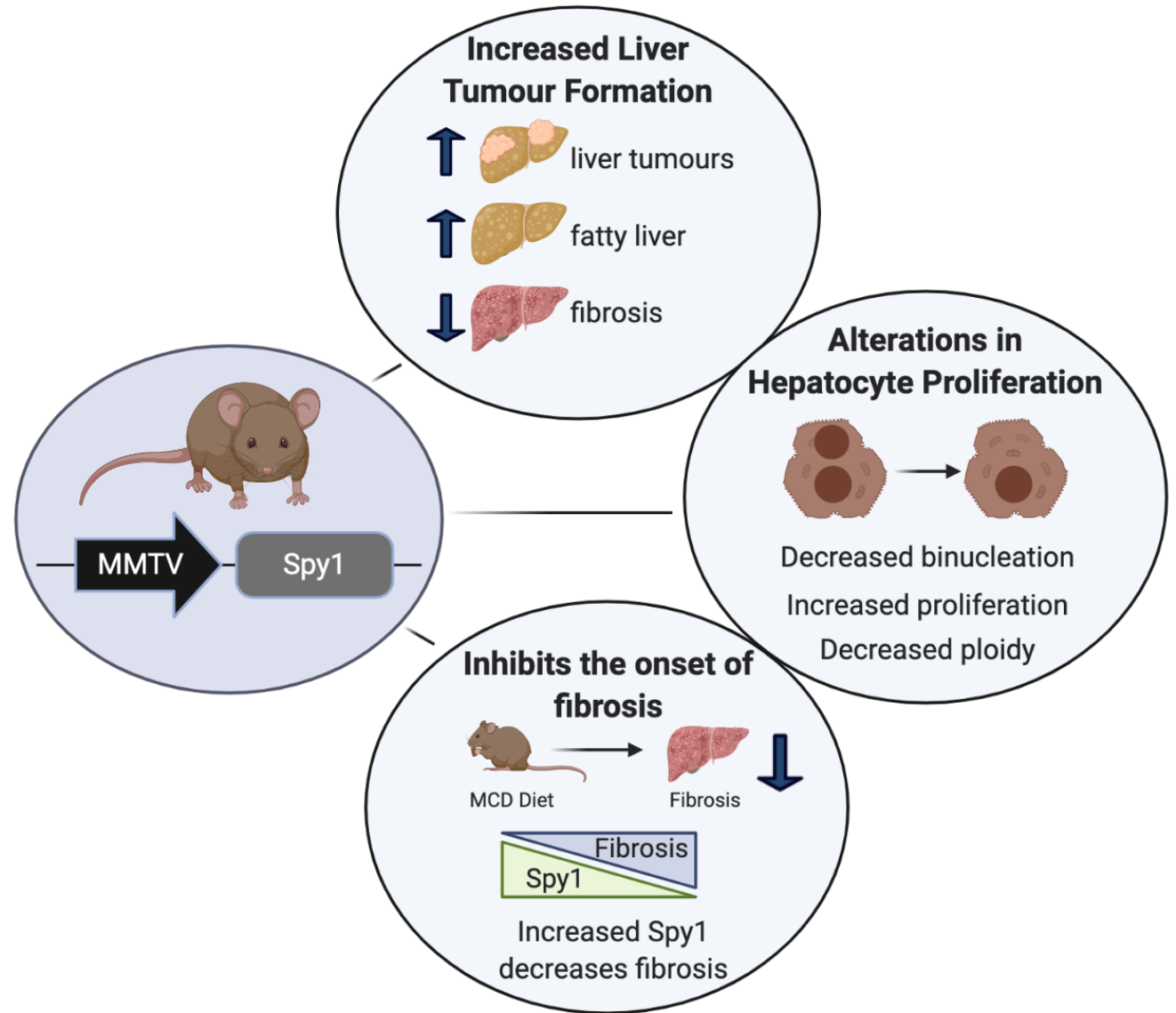


Men are 3-5x more susceptible to developing HCC!

Critical role of Spy 1 in tumor initiation

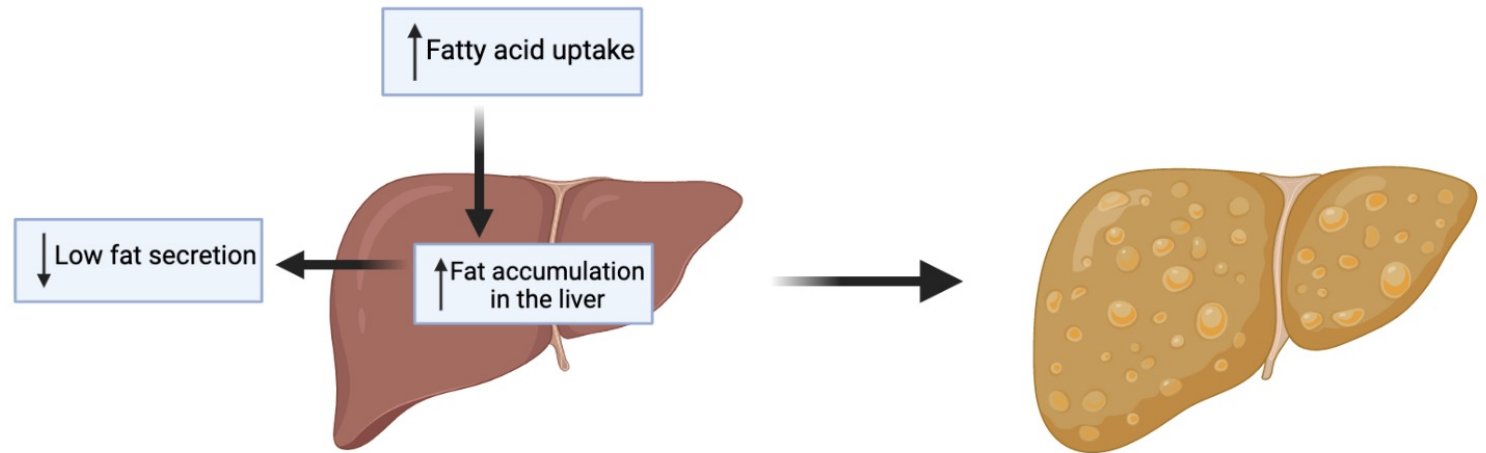


An Unforeseen Discovery



The Methionine-Choline Deficient (MCD) Diet

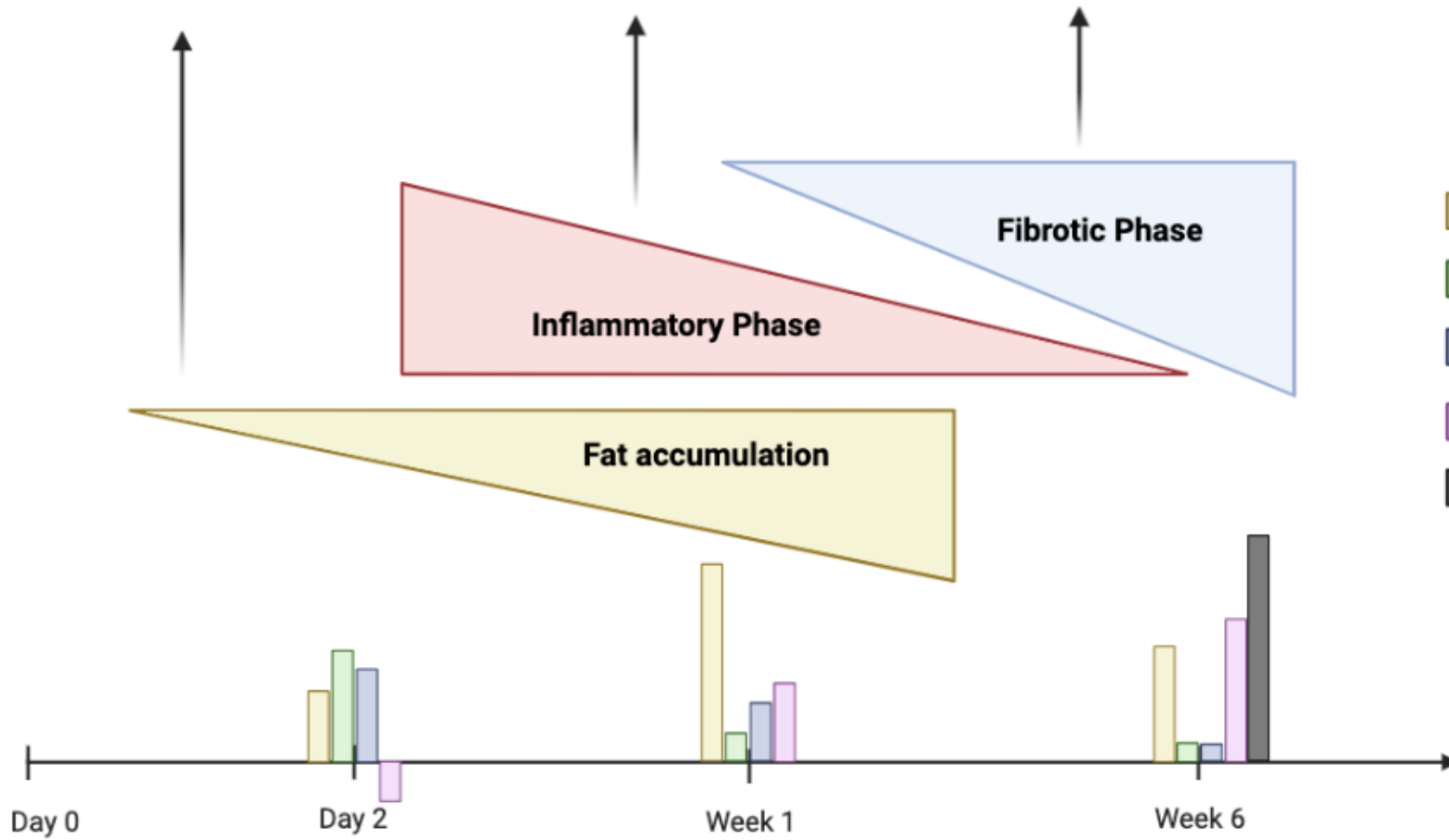
- Induces NASH phenotype in short timeframe
- It causes:
 - Increase of fat in hepatocytes
 - Inflammation
 - Oxidative damage
 - Fibrosis



Oil Red O Staining

TNF-alpha levels

Trichrome stain



- Fat accumulation → Stress response
- Spy1 protein → Proliferative response
- p53 protein → Tumor suppressor
- TNF-alpha gene expression → Inflammation
- Collagen deposition → Fibrosis

MCD start date



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Objectives

1



Measure endogenous cell cycle mediator gene expression and protein levels

2



Uncover the link between cell cycle regulation and NASH disease progression to HCC

3



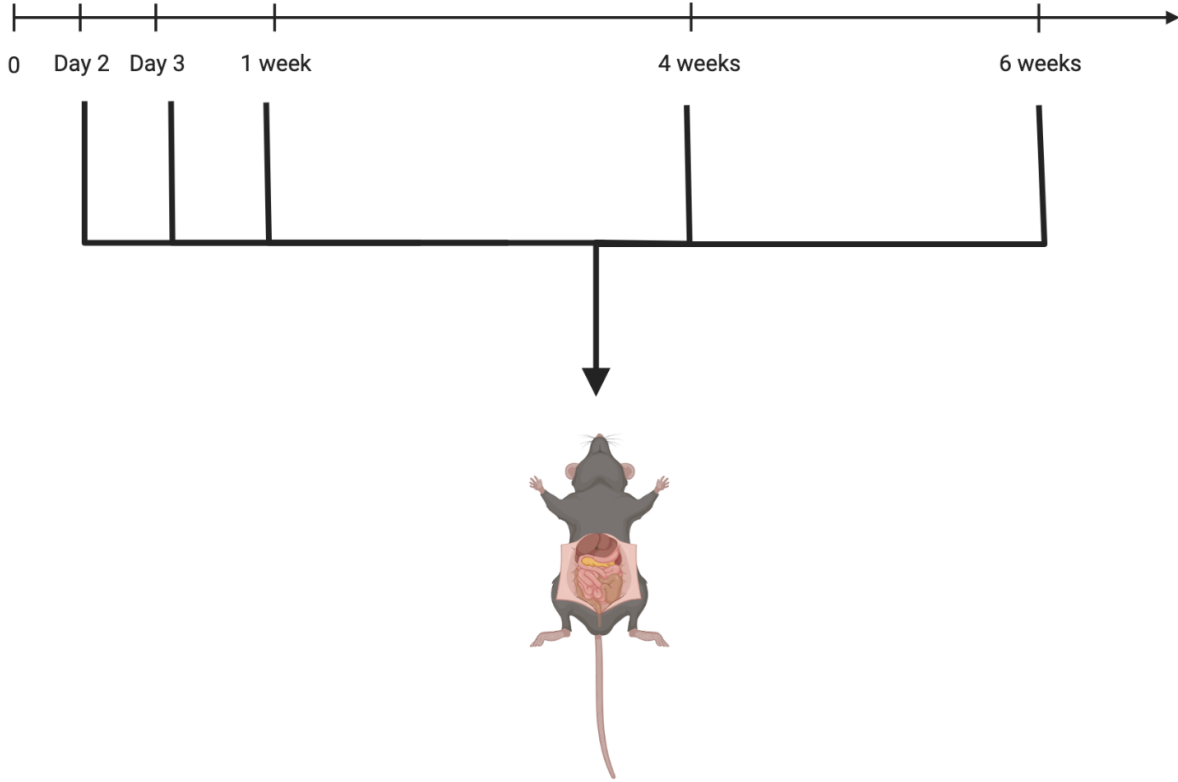
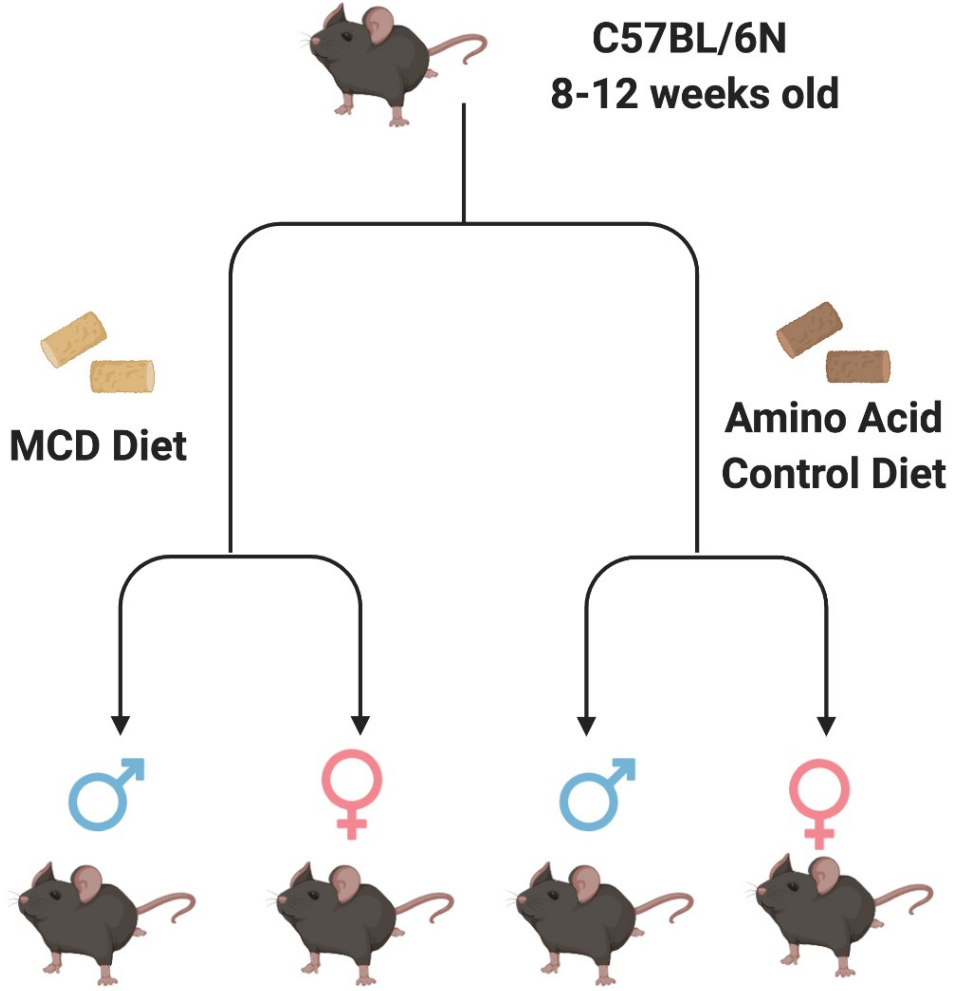
Discover differences between female and male mouse responses to the diet with respect to cell cycle regulation



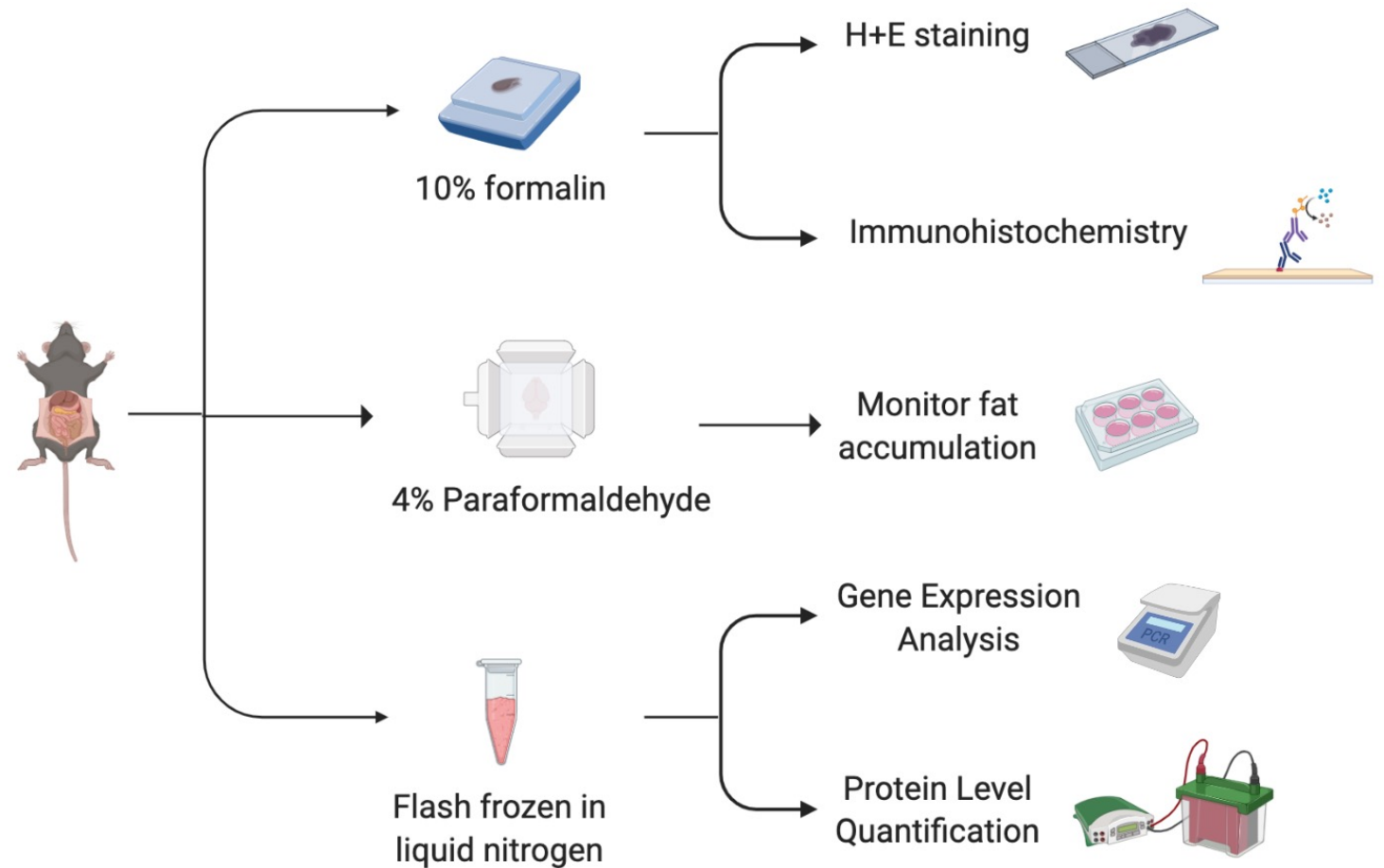
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Experimental Design

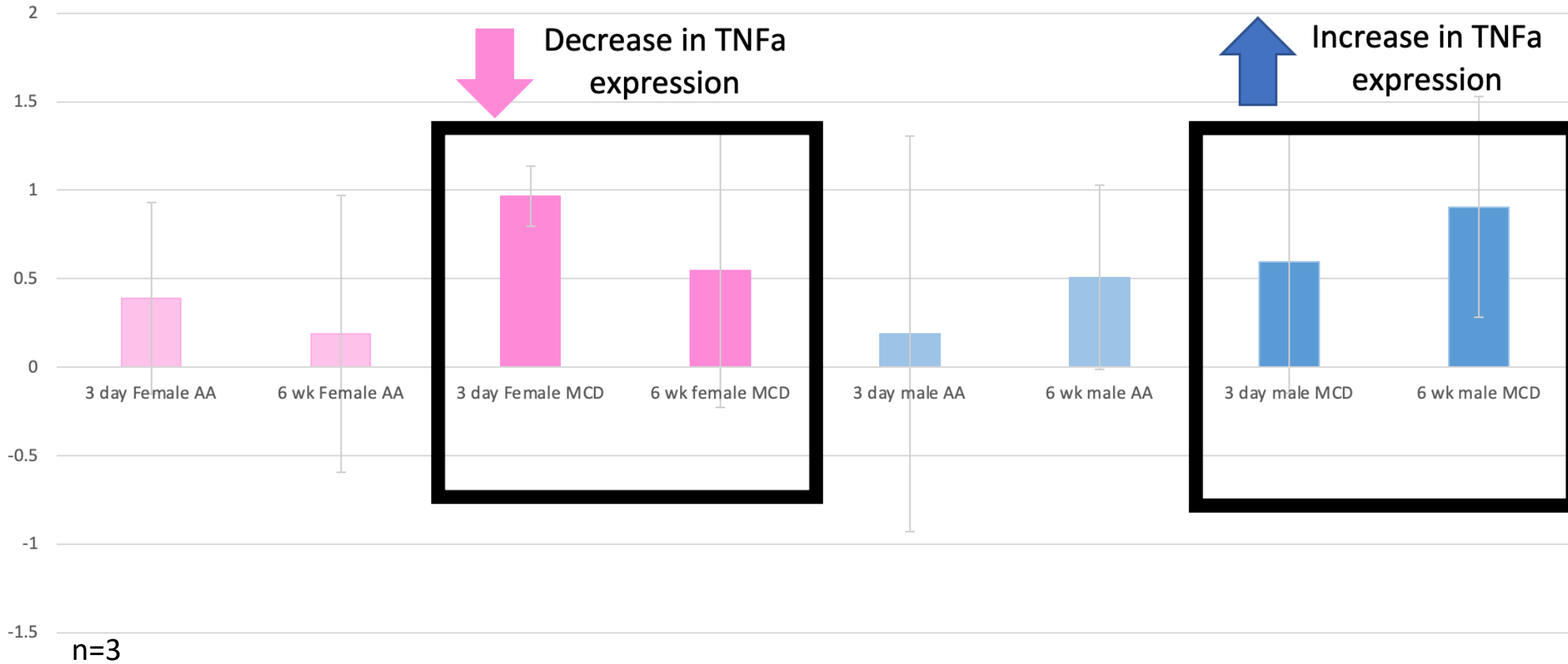


Tissue Collection and Analysis



Sex specific TNFa expression in MCD mice

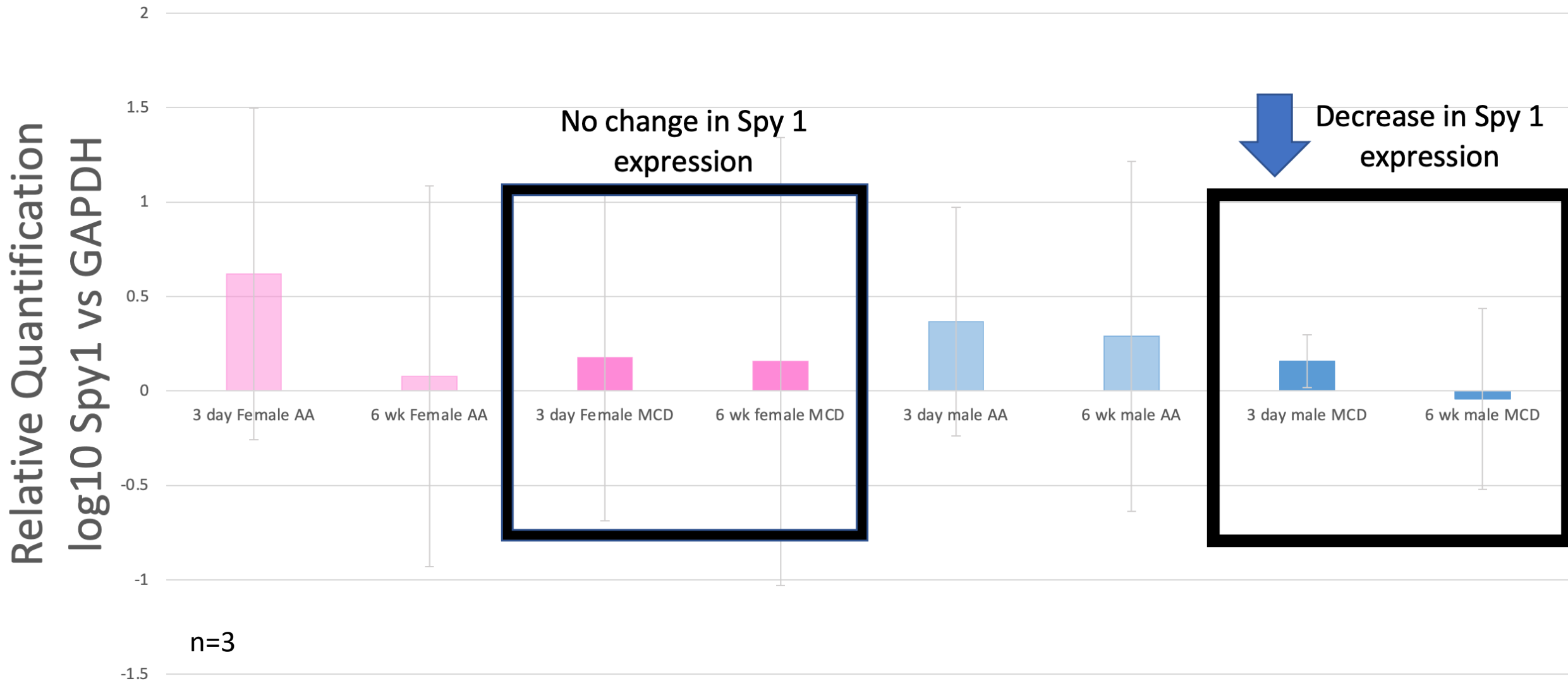
Relative Quantification
log10 TNFa vs GAPDH



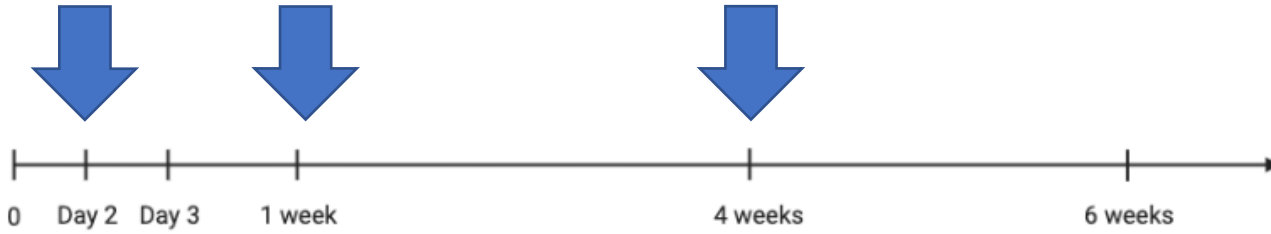
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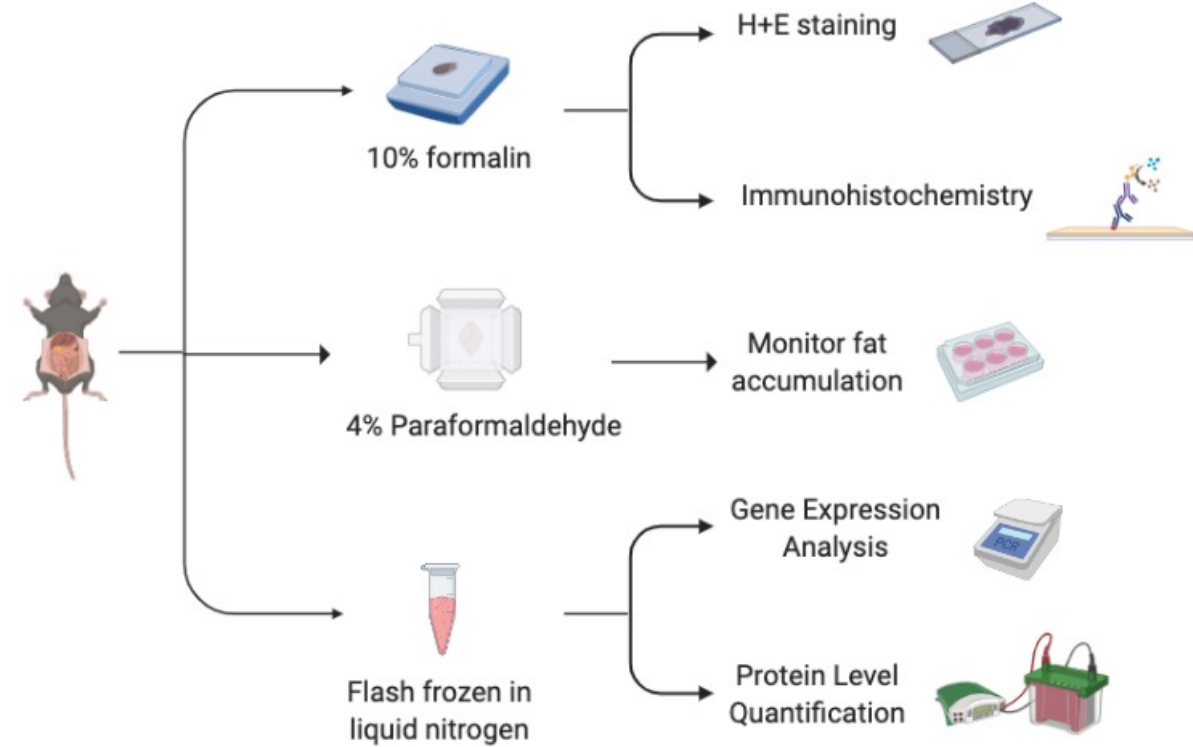
Decrease in Spy1 RNA expression in MCD male mice

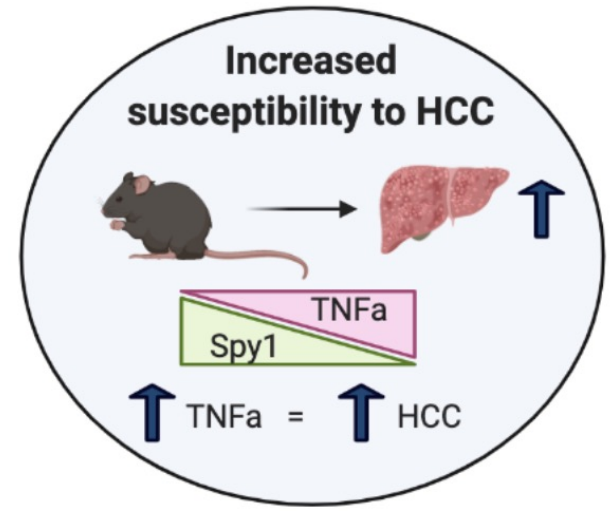
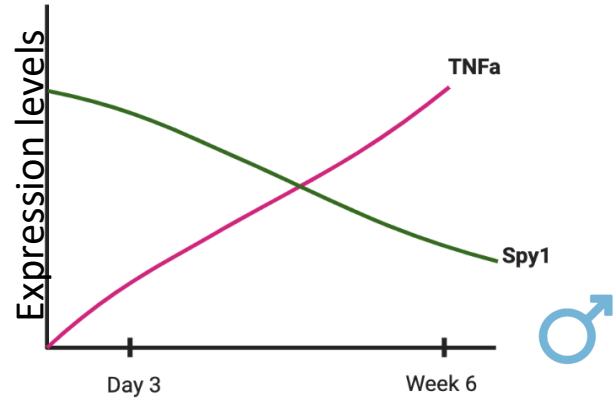


Future Steps:

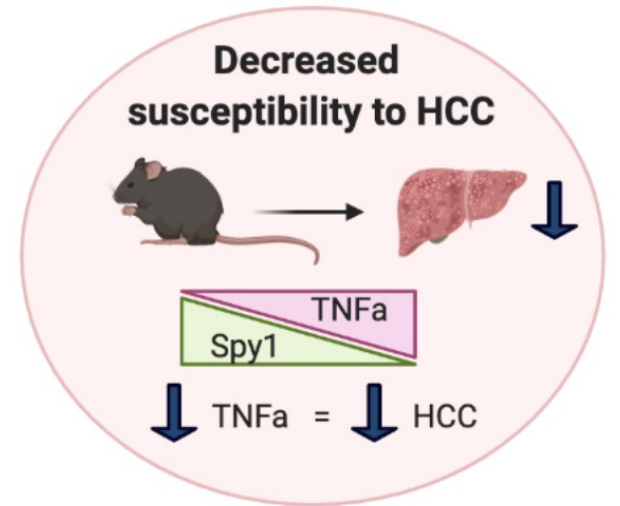
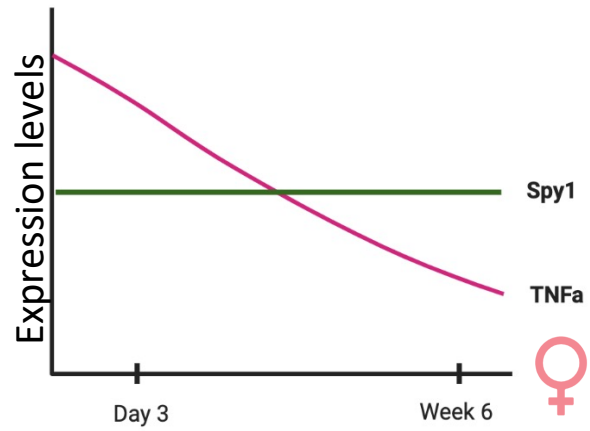


- Cyclin A?
- Cyclin B?
- Cyclin D?
- Cyclin E?
- P53?
- P21?
- CEBPa
- Fat levels?
- Collagen deposition?





MCD start



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CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada



Seeds4Hope



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