Amyotrophic lateral sclerosis (ALS) is a type of neurodegenerative disease characterized by motor neuron death1. Approximately 5% of Familial ALS cases have mutations located in the fused in sarcoma (FUS) gene which leads to reduced muscle mass and impaired motor movement1,2. Mutations in *FUS* concentrate in the non-conventional nuclear localization signal region (NLS), near the C-terminal domain. This region has been shown to result in severe juvenile onset occurring as young as 11 years old compared to other regions of FUS 2,3. *FUS* functions in mediating regulation for transcription, translation, and DNA repair mechanisms4,5,6. Although it is known that impaired DNA damage response mechanisms help create FUS mislocalization and aggregation of proteins, it is *unknown* *how the FUS-related DNA repair pathways interact and their specific downstream effect on neurodegeneration remains unclear*7,8*.*

The **objective** of this study is to determine which amino acids in FUS are necessary for DNA repair mechanisms and motor neuron function. I **hypothesize** that alterations in the NLS segment will disrupt DNA repair mechanisms and result in earlier neuron death compared to other regions. *D. rerio* will be used to test this hypothesis due to conserved homology, transparency during development, opportunity for ploidy manipulation, and anatomical similarity of motor neurons in the spinal cord7. The **long-term goal** of this research is to determine the effect on neurodegeneration due to these alterations, while providing a comprehensive mechanism for the FUS-related DNA repair pathways.

References:

1. Shang, Y. & Huang E.J. (2016, September). Mechanisms of *FUS* mutations in familial amyotrophic lateral sclerosis. *Brain Research* 1647:65-78.
2. Zou, Z.Y., Liu, M.S., Li, X.G., Cui, L.Y. (2015, September). Mutations in *SOD1* and *FUS* caused juvenile-onset sporadic amyotrophic lateral sclerosis with aggressive progression. *Ann Translation Medicine* 3(15):221
3. Conte, A., Lattante, S., et al. (2012, January). P525L FUS mutation is consistently associated with a severe form of juvenile Amyotrophic Lateral Sclerosis. *Neurology Genetics* 2:63
4. Wang, H., Guo, W., et. Al. (2018, September). Mutant FUS causes DNA ligation defects to inhibit oxidative damage repair in Amyotrophic Lateral Sclerosis. *Nature Communications* 9:3683
5. Zhou, Y., Liu, S., et al. (2013, October). ALS-associated *FUS* mutations result in compromised *FUS* alternative splicing and autoregulation. *Nature Communications* 9:3683
6. Naumann, M., Pal, A., et al. (2018, January). Impaired DNA damage response signaling by *FUS*-NLS mutations leads to neurodegeneration and FUS aggregate formation. *Nature Communications*9:335
7. Penndorf, D., Witte, O., et al. (2018, February). DNA plasticity and damage in amyotrophic lateral sclerosis. *Neural Regeneration Research* 3(2): 173–180.
8. McGown, A., McDearmid, J.R., et al. (2012, October). Early interneuron dysfunction in ALS: Insights from a mutant *sod1* zebrafish. *Annals of Neurobiology* 73(2):246-258.