Project Details	
Project Code	MRCNMH26Ba Licchesi
Title	Tackling Alzheimer's with Smart Protein Removal Tools
Research Theme	NMH
Project Type	Wet lab
Summary	Targeted Protein Degradation (TPD) is a new approach that helps cells remove harmful proteins linked to diseases like Alzheimer's. It uses special molecules that bring the disease-causing protein close to the cell's natural disposal system, triggering its breakdown. This project will use knowledge of how cells tag and remove proteins to design new tools that target mutant Tau, a protein linked to dementia. The student will work across biochemistry and cellular neuroscience to create and test these tools in lab-grown brain cells, studying how removing mutant Tau affects neuron health and brain cell function in models of Alzheimer's disease.
Description	Many brain diseases, like Alzheimer's, are linked to problems with how cells manage their proteins. Normally, cells keep a healthy balance between making new proteins and breaking down old or damaged ones. However, in diseases like Alzheimer's, this balance breaks down, leading to the build-up of harmful protein clumps, such as tangles and fibrils, that damage brain cells, especially neurons. One of the body's natural tools for cleaning up unwanted proteins is a small molecule called ubiquitin. Think of it as a "tag" that marks faulty proteins for disposal. Once tagged, these proteins are sent to cellular recycling centers called the proteasome and the lysosome. New approaches are being developed that use the cell's own natural systems to help remove harmful proteins more effectively, especially those linked to diseases. One promising approach is called Targeted Protein Degradation (TPD). It's already showing success in cancer treatment and could also help with brain diseases like Alzheimer's. A key protein in Alzheimer's is Tau, especially its mutated forms like TauP301L, which is known to cause inherited types of dementia. Mutant Tau proteins can harm neurons and may also disrupt other brain cells, like astrocytes, which normally support healthy brain function. **The BioPROTAC Strategy** This PhD project focuses on a new tool called BioPROTAC. These are specially designed molecules that can find and destroy harmful proteins inside cells. Each BioPROTAC has two parts: A guide that finds the target protein (like a GPS) and a warhead that triggers the protein's destruction. In this case, the guide is a small antibody fragment (called Vhh4) that binds to a protein tagged with GFP and the warhead is an E3 ubiquitin ligase enzyme which adds multiple ubiquitin tags to the target protein, marking it for removal. **Project Goals** **Objective 1: Testing BioPROTAC in Cells** Test how well our new BioPROTACs designs can remove different types of GFP-tagged proteins localised in distinct parts of the cell i.e., the nucleus, cytoplasm, and cell membrane. Protein removal triggered by our BioPROTACs will be quantified using techniques such as flow cytometry, western blotting, and advanced microscopy. In vitro

	biochemical assays will also be carried out to validate the mechanism of action of BioPROTACs molecules. **Objective 2: Targeting Mutant Tau in Brain Cells** BioPROTACs will be evaluated in brain cells, focusing on neurons and astrocytes, to determine their ability to eliminate mutant Tau proteins. Delivery of both BioPROTACs and GFP-tagged TauP301L will be achieved using viral vectors. Microscopy will be used to quantify levels of mutant Tau, and the impact of its removal on cell health will be assessed. In neurons, changes in communication will be measured using microelectrode array technology. In astrocytes, microscopy and biomarker analysis will be used to determine whether normal cellular functions are restored following mutant Tau degradation. **Objective 3: Finding molecules to recruit endogenous warheads** This objective will aim to make our targeted degradation BioPROTAC tools more drug-like. Since no known ligands currently exist for the selected E3 ligase enzymes used in our BioPROTACs, an aptamer library will be used to identify suitable binding partners. Aptamers are short DNA sequences that can bind specifically to proteins and offer advantages over traditional molecules, including better drug-like properties and the ability to cross the blood-brain barrier, an important feature for long-term therapeutic applications. A unique protein domain has already been identified and will serve as bait to isolate aptamers from a library containing approximately 10^{15} different sequences. Once promising aptamers are found, they will be incorporated into new BioPROTAC and PROTAC designs and tested for their ability to degrade GFP-TauP301L in cells.
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