Good morning everyone. This project will hopefully reveal mechanisms in fundamental cellular biology, particularly that relating to miRNAs.

These microRNAs are small non-coding RNAs that mediate cellular activity by gene regulation. Traditionally, this gene regulation occurs by complementary binding to protein transcripts, where through recruitment of RNA induced silencing complex, argonates and dicer proteins degrade the transcript. Thus limiting that proteins activity and potentially impacting on entire pathways. Hereby, tight spatial and temporal regulation is required to prevent dysregulation of vital cellular processes. Recently, an exciting finding had shown that miRNAs are able to be exported from the host cell, via extracellular vesicles, and integrated into recipient cells to perform this regulatory function.

These extracellular vesicles are composed of microvesicles and exosomes, which encompass various protein, RNAs and DNA. Typically the extracellular space is rife with RNase activity that would rapidly degrade miRNAs, however, packaging into extracellular vesicles increases its stability. This allows the miRNAs to move between cells. Hereby detailing a novel and recently discovered mechanism for intracellular communication.

However, the mechanisms surrounding the miRNA sorting into the extracellular vesicles is still mostly unknown. Originally, miRNAs were previously considered to be packaged into vesicles non-selectively, where the miRNAs contained in EVs were merely representative of their cellular concentration. Yet now there is a stream of evidence emerging that reveals that certain miRNAs can be over or underrepresented in extracellular vesicles given a change in condition. Hereby indicating a selective export mechanism for some the miRNAs into EVs. In attempts to elucidate the mechanism, a single protein was found. This was found to bind a subset of 30 miRNAs to mediate the subcellular localisation and exosomal export. However, how this is regulated is still unknown.

Fortunately, recent studies had revealed that lipid rafts may regulate cargo export. Lipid rafts are small microdomains of membrane enriched in specific lipids and proteins that act as signalling hubs. In particular, cholesterol, sphinolipid and ceramide enriched lipid rafts are known to be present on the surface of extracellular vesicles. In order to investigate their function in extracellular vesicles a series of deletion studies were completed. Individually depleting ceramide, cholesterol and sphingolipid had a dramatic effect on protein sorting into extracellular vesicles.