Script.

So prostate cancer currently rates as the second most diagnosed cancer in men worldwide. While the primary tumour is fairly innocuous, patients with the more advanced prostate cancer face limited treatment options and high mortality rates due to additional comorbidities. For these reasons we need understand and identify biological phenomena and biomarkers that induce the metastatic phenotype to hopefully lower mortalities. (23s)

Caveolin-1 is an important biomarker for cancer progression. In healthy human cells, caveolin-1 is co-expressed and co-localized with putative tumour suppressor, cavin-1, to evoke their canonical function. However, in the case of many cancer types, caveolin-1 is overexpression without corresponding binding partner, which has been linked to many of the hall marks of cancer and cancer progression, though the mechanisms that link caveolin to cancer are still being investigated. Interestingly, knocking down caveolin-1 or adding cavin-1 to a cancer cell line that exerts this activity reduces the oncogenic phenotype induced by the caveolin. (34s)

We’ve used this information previously on the advanced prostate cancer cell line, PC3. This cell line lacks cavin-1 expression, but over expression on caveolin is thought to contribute to many of the aggressive processes. When transfected with cavin-1, our lab determined that this transforms the usually aggressive PC3 cell line to a more placid form by nutralising caveolin-1. BY using this model, we can compare between the aggressive prostate cancer cells and less aggressive cell lines to identify the pathways that caveolin-1 is involved with but also the processes that lead to the increase mortalities associated with advanced prostate cancer. (40s)

Using this model, we focused on the role of extracellular vesicles in these cell lines. These vesicles transfer material from the host cell to the recipient cell, where this content can then evoke their canonical function. This is an import mode of intracellular communication that has been of recent focus in cancer research. Here, the EVs contain content from the host tumour cell that initiate modifications of the microenvironment and establishment of pre-metastatic niche when absorbed into the recipient. Hereby, indicating a role in cancer progression. Primarily this was believed to be due to proteomic content, however our work found that the expression of cavin-1 modulates EV specific concentrations of microRNAs as well as protein. () \*\*Fix up the diagram.

Recently, vesicle contained microRNAs had been implemented in cancer progression. Alike protein, the EV transported microRNAs have been reported to modulate microenvironments and pre-metastatic niche formation, but through their canonical function. MicroRNAs are small non-coding RNAs that mediate post-transcriptional gene silencing through complementary base pairing to target protein transcripts or messenger RNA and recruiting the RNA-induced silencing complex. This is particularly important when you consider that a single microRNA can target hundreds of protein transcripts and therefore modulates many vital cellular pathways. Hereby, being transported between cells could be viable from of intercellular communication, or a major source of disarray in disease states. Previous work using the PC3-cavin-1 cell model found that the prostate cancer cells did secrete oncogenic material, namely mir-148a, whereas the less tumorigenic cell did not. Interesting, this modification was not reflected by a change in cellular expression. This indicates that there is some form of export mechanism that populates the microRNA content of the EVs in prostate cancer.

So, this project basically set out to understand this mechanism. We hypothesize that cavin-1 is attenuating the export of an RNA-binding protein which modulates the miRNA content. This was investigated by looking at the microRNA manipulated in the system, identification of candidates and further though investigation of their activity.

Firstly, we wanted to take a comprehensive look into all of the microRNAs that are manipulated by the proposed export mechanism where previously only a select few microRNAs were investigated. To do this, we wanted to observe microRNAs that change EV levels between cell lines, where this change is not proportional to the cellular change, similar to what was observed for the miR-148a data. In contrast,