Grant Type
Project Grant

Grant Round
Project Grants 2013

Reference Number
PG13-021

Lead Applicant
Dr Rich Williams

Research Title
Development of Legumain based therapeutic for the treatment of advanced prostate cancer

Total Research Cost
£384,126.00

Lay title of project
Development of Legumain based therapeutic for the treatment of advanced prostate cancer

What are you proposing?
Legumain is a cancer associated enzyme that is over-expressed in prostate cancer and has been implicated in both cancer cell proliferation and invasion. We have observed that inhibition of Legumain activity has dramatic effects on prostate cancer cells, suggesting that targeting Legumain represents a significant opportunity to develop a novel treatment for men suffering from prostate cancer. We have designed, synthesized and tested a novel series of drugs which specifically target Legumain. These Legumain inhibitors now require optimisation in order to deliver a new treatment specifically for poor outcome prostate cancers. This project grant will use a medicinal chemistry and biomarker development approach to:

(1) Deliver a potent and selective Legumain inhibitor, which will be optimized from the series of drugs we already have.

(2) Develop and validate a series of biomarkers that will a) stratify patients that will respond to a Legumain based therapy; and b) monitor the effectiveness of this therapy in patients. This work will be underpinned by collaborators who have expertise in each of the following fields; biomarker development, tumour pathology, medicinal chemistry, animal models and cell signalling.

Why are you proposing it?
Legumain has been identified as a key marker in a number of poor prognosis cancers, including breast, glioma, pancreatic and prostate. The expression level of Legumain has also been observed to increase with the severity of the disease. We have performed a series of studies to prevent Legumain either being produced or working properly, and have shown that both approaches result in pronounced inhibition of cell growth. The loss of Legumain is poorly tolerated by prostate cancer cells with >90% cell death being observed 72h post treatment. This effect is also cancer cell specific with no effect being observed in normal cell lines. In addition we have observed that use of small molecule Legumain inhibitors has a significant impact on the ability of cancer cells to invade and metastasise, a hallmark of poor prognosis prostate cancers. Due to the dual role of
Legumain in prostate cancer, cell growth and invasion, the development of Legumain based therapy would provide a powerful new therapeutic option against prostate cancer. To that end, we have identified a series of Legumain inhibitors with drug-like features, they can be used at very low concentrations and have exquisite selectivity, as the basis of developing a clinically relevant therapeutic.

**How are you proposing to do it?**

We have developed a series of highly potent, selective and patentable Legumain inhibitors, with potent in vitro biological effects (on proliferation, wound-healing and cell invasion). Here we aim to further optimise the properties of these inhibitors using animal models. We will develop models of Legumain-dependent prostate cancers in mice and test the effect of our drugs on tumour proliferation and metastasis. We will also test any potential off-target effects through post mortems of treated mice.

We have already identified a number of biomarkers to assist in the selection of tumours which could be Legumain inhibitor responsive. These include overexpression of Legumain and loss of a protein called Cystatin 6 (CST6), the natural inhibitor of Legumain (and a gene commonly downregulated in prostate and other cancers). Further studies will be conducted to identify additional biomarkers by further analysis of the other proteins involved in regulating Legumain. In addition, from studies in cell lines we have also identified potential biomarkers of Legumain inhibition which will now be tested in our vivo models. Real time imaging of the live mice and post mortem assessment will help to tell us how potent the inhibitors are along with how useful the biomarkers will be.

**How long will it take?**

36 months

**What are the expected outcomes?**

We envisage that during the course of this project we will identify potent and selective Legumain inhibitors which will be able to inhibit the proliferation and invasion of Legumain-dependent prostate cancers. We will be able to evaluate any off-target effects of these inhibitors in animal models, although currently this does not appear to be an issue using our existing drugs in cell line models). We will also test a series of biomarkers that will act as companion diagnostic tests to support future clinical applications of this project.

**How could it make a difference to the lives of men affected by prostate cancer?**

Prostate cancer is second leading cause of death in men in the US. There are currently several treatment options, such as radical prostatectomy, androgen deprivation and Docetaxel-based chemotherapies. The efficacy of these treatments is somewhat limited with a substantial number of patients experiencing reoccurrence with metastatic disease. New therapeutic options are required to target prostate cancer more effectively. Legumain has been identified as a key driver of many poor prognosis cancers, including prostate. We aim to generate potent Legumain inhibitors alongside proof of concept biological data to support a clinical drug development application.

**Please write a summary of the project in one sentence only.**

Development of a novel therapeutic for the treatment of advanced prostate cancer