Characterisation of KMT5A, a potential therapeutic target to treat advanced prostate cancer.

Characterisation of androgen receptor epigenetic co-regulators as potential therapeutic targets in castrate resistant prostate cancer.

To provide novel therapeutics to treat patients with advanced castrate resistant prostate cancer (CRPC), who have no other effective drugs available to them, the way in which this resistance develops must be investigated. A major contributor to the development of drug resistance is a protein called the androgen receptor (AR). This protein makes prostate cancer cells grow and most current therapies are designed to prevent this protein from working. The AR becomes faulty as drug resistance develops, which means that it works more efficiently and is not supervised by control mechanisms in the cell. I propose that targeting the proteins that regulate the activity of the AR may be an effective way to treat CRPC. For example, one regulator of interest is called KMT5A. This protein appears to change its role as drug resistance develops and may prove to be not only a therapeutic target but also a way of determining which patients are at greater risk of developing more aggressive disease. I propose to investigate the role of proteins able to regulate AR activity in the development of drug resistance by using KMT5A as an example.

During treatment for advanced prostate cancer, the tumour can begin to overcome the effects of the treatment and continue to grow. This is a significant clinical problem as at this point there are no other effective drugs. Furthermore, 70% of these patients will then begin to develop tumours at other sites in the body as the cancer spreads. Prostate tumour cells most commonly spread into bones, which can lead to a highly painful end of life experience. To minimise this problem, an understanding of how the cancer cell is able to overcome the effects of the therapies used is key. By identifying the cellular components responsible, novel therapeutics can be developed to combat this problem or improve the efficacy of current therapeutics. There is also a need to be able to identify patients who have aggressive disease because the majority of men will only have a very slow growing tumour that will not progress during their lifetime. Again, identifying the cellular components linked to drug resistance may help to predict which patients will quickly become resistant and go on to develop lethal disease that will spread around the body.
**How are you proposing to do it?**

Using state of the art technology an extensive investigation will be carried out to determine how KMT5A works in CRPC. Specifically, I will look at how KMT5A helps AR to attach to the DNA where it instructs the cell to make certain proteins from information held in the DNA. Proteins produced in this way will be identified and the changes they are likely to bring about in the cell can be predicted.

As a protein rarely works alone, KMT5A associated proteins will be identified to determine how they affect KMT5A and AR functionality. One class of proteins well known to influence the activity of other proteins are called kinases. Kinases are already targeted by drugs in a number of diseases. To determine which kinases are important in CRPC, I will remove each kinase individually from the cell and check whether AR activity is affected.

The AR protein can become faulty as drug resistance develops, and so I will also examine whether the interaction between KMT5A and the damaged forms of AR are different to how it interacts with the normal AR protein. Finally, interesting targets identified will be validated in patient samples to confirm their therapeutic value.

**How long will it take?**

5 years

**What are the expected outcomes?**

- New therapeutic targets that indirectly target the AR in CRPC will be identified.
- The value of AR regulatory proteins as novel therapeutic targets will be determined, using KMT5A as an example AR regulator.
- Mechanisms of KMT5A mediated AR regulation will be determined.
- The important cellular pathways regulated by KMT5A in CRPC will be defined.
- New biomarkers will be identified that could be used in preclinical studies of any novel KMT5A targeting therapeutics that should be developed in the future.

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

Currently, there are no effective therapeutic options for men with advanced prostate cancer. Although novel therapeutics are coming to the clinic, it is clear that resistance to these agents will develop. Thoroughly investigating how castrate resistance occurs will allow novel therapeutics to be developed to give these patients increased life-span and importantly a better quality of life if metastatic disease can by reduced or even avoided. It may also enable the identification of those patients who are at greater risk of developing aggressive disease.

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

Identification and validation of novel therapeutic targets for castration resistant prostate cancer.