Research Strategy

The Need

There is an urgent need to develop new effective treatments for men with prostate cancer, particularly advanced prostate cancer, and to carry out the underpinning research to achieve this.

Improvements in therapies have been developed in the past decade, but one man still dies of prostate cancer every 45 minutes in the UK, and 250,000 men die each year from prostate cancer world-wide. Innovative thinking and new approaches are required to solve this problem, and existing treatments need to be applied more effectively.

Our Vision

Our vision is to improve survival and quality of life for men who already have prostate cancer, and to find treatments for prostate cancer for the next generation of men.

Our Research Strategy describes how we aim to engage and empower scientists and clinicians to achieve this goal. Prostate Cancer Research Centre recognises that many new treatment approaches, new targets and drugs need to be discovered and translated to patient benefit.

We understand that the probability of a scientific breakthrough and achievement of our stated goals will quicken if we broaden the base of the research we fund. Our focus is on finding therapies for advanced disease but we recognise that important research is needed to develop classification systems that can be applied when treating metastatic and non-metastatic disease. We acknowledge that clues relevant to men with advanced prostate cancer may be found in the early evolution of the disease.

We are committed to the goals of health resource equality and understand that the resources of the National Health Service are finite and would encourage research that aims to reduce the cost of prostate cancer treatment in the long term for the patients in the UK, primarily, but also around the world.

Targeting with a single drug or treatment currently does not cure the disease. Multiple treatments may need to be integrated for the treatment of a single prostate cancer patient. We are therefore committed to co-operating with other organisations to combine approaches, to support single outstanding projects, and to promote the careers of young scientists, who can carry the research forward with ever increasing improvements in advancement of knowledge and technologies. We are committed to continually researching and reviewing at which stage scientists find it hardest to get funding, and to considering how to adjust our strategy to improve impact across the sector.

Within the current Prostate Cancer Research Centre, scientists and clinicians from around the UK are working together and sharing ideas to solve critical problems relevant to men with advanced prostate cancer.

We are committed to ethically conducted research, and a robust but rapid process of scientific peer review, allowing support to be quickly directed to innovative projects with fewer non-essential or administrative encumbrances.

Our Scientific Approach

'We only fund research as it is only through research that we will find treatment.'

Definition of Advanced Prostate Cancer

Prostate Cancer Research Centre (PCRC) is dedicated to funding research that will improve the lives of and/or cure men with prostate cancer, particularly advanced prostate cancer. By advanced prostate cancer we mean disease that has spread outside the prostate and that may become, or is already, life threatening. We will fund research that demonstrates a clear intellectual relevance to the betterment of advanced prostate cancer patients.

Funding by Prostate Cancer Research Centre

Our ambition is to become a world centre of excellence for prostate cancer research through funding excellent scientists and clinicians. Prostate Cancer Research Centre researchers will be expected to carry out world leading research recognised for its originality, significance and rigour.

In assessing the scientific rigour of a proposal we follow AMRC guidelines and those of established funding organizations such as the Medical Research Council, UK and established cancer charities such as the Cancer Research UK. Areas of investigation should span one or more of the fields outlined in Table 1.

All funded teams, whatever their location, are considered to be part of the core Prostate Cancer Research Centre (PCRC). PCRC grantees are expected to work as part of a collegial academic group combining resources to target important problems relevant to men with advanced disease. Over the next two years we will work on new ways to support scientists funded by PCRC. New grantees will be required to develop strategically important areas of research, to build solid links to existing groups, and to add new expertise. For a detailed list of the expectations of new members see Appendix: For New Members.

We know that objective peer review in reputable scientific journals is the life blood of any research activity. We are also committed to the Open Access philosophy adopted by all established research funders in the UK and elsewhere and also by the Research Excellence Framework in the UK.

Scientific Peer Review

Each research proposal will be assessed by a Grants Review Committee, incorporating a broad range of views with patient participation. Three main criteria will be used. First, scientific merit as judged against our Research Strategy. Secondly, collaboration with others supported by PCRC. Thirdly, intellectual innovation and when appropriate, the formulation of a path to translation.

Basic Science and Target Discovery

The conversion of a normal prostate cell into a life-threatening cancer cell is a complex process involving alterations in expression of thousands of many genes and changes in multiple control pathways. We seek to support projects where there is clear evidence that the target or process under investigation is central to progression from early to advanced disease, rather than a subsidiary or supporting event. Or alternatively where a specific change in the advanced cancer cell can be used as an Achilles Heel to develop a new therapy.

Re-tasking of existing drugs is another possible strategy. Based on these principles several new treatments have been cultivated over the last decade (Table 2). The new therapies relieve symptoms and prolong life, but seldom cure. There is therefore a need both (A) to enhance existing treatments to further extend life

and relieve symptoms and (B) to discover and develop completely novel therapeutic approaches that have the potential to result in cancer cure.

The PCRC currently funds the following basic science and drug discovery projects:

1. Translating fundamental knowledge of stem cells and cancer biology into therapies *(Dr Ahmed, Kings College. London)*, with particular emphasis on the Wnt pathway.
2. The development of a novel new way to harness immunotherapeutic properties of IL-15 *(Dr Galustian, Kings College London)*
3. Preventing the spreading of the cancer cells by investigating the role of plexin proteins in underpinning metastasis *(Dr Williamson, Kings College London)*
4. The re-tasking of off-label Membrane Potential Regulating Compounds (ion channel and calcium store modulators) (*Dr Ahmed, Kings College London)*

https://www.prostate-cancer-research.org.uk/our-research

Classification and Drug Targeting (Personalised Medicine)

Prostate cancer is a clinically and molecularly heterogeneous disease. However, no clear classification framework has been developed. The lack of a classification framework represents a major problem for the targeting of new therapies and in the development of personalised medicine. Stratifications have been proposed based on the presence of specific genetic alterations (e.g. *ERG, ETV1, ETV4, FLI1, SPOP, FOXA1,* and *IDH1*) and a number of rarer cancer subgroups have been defined (e.g. cribriform carcinoma, basal cell prostate cancer, neuroendocrine prostate cancer).

The clinical utility of these divisions in managing advanced disease is still under investigation, although the tailored targeting of patients with specific classes of genetic alteration (stratified medicine) represents a promising area of investigation, as illustrated by the use of PARP inhibitors in the treatment of patients harbouring BRCA mutation.

None-the-less there still is an urgent requirement for better classification frameworks that can used to assist targeting of therapies for advanced cancers, and for the development of linked tests that can be applied in the clinic, which we will consider funding.

Clinical Trials and Trial Support

A large number of clinical trials are underway aimed at testing new treatments for prostate cancer. We would like to support and develop links to existing clinical trials and help develop new clinical trials where this will allow the testing of discoveries made within Prostate Cancer Research Centre.
We would also consider funding:

A. The development and use of model systems where these are required to test hypotheses and help devise new treatment as illustrated by our work at Cardiff; and

B. The development of new approaches for tracking and imaging cancer where improvements in monitoring the effectiveness of therapeutic approaches can be demonstrated, such as the use of PMSA staining for cancer imaging.

Our vision is to improve survival and quality of life for men who already have prostate cancer, and to find a cure for prostate cancer for the next generation of men. Accordingly we would consider supporting studies aimed at reducing the side effects of current therapies or focused on developing improved palliative care. In exceptional cases we would consider funding sociological and qualitative studies, particularly when they would lead to observations that could be subsequently tested by quantitative research.

We recognise the value of biobanking samples from men with advanced disease and developing databases. Would welcome proposals where there a well-defined benefit can be demonstrated and where there is an established link to existing PCRC projects.

The PCRC currently funds the following Clinical Trials and Trial Support projects:

1. Models for testing new prostate cancer treatments *(Professor Matt Smalley, Cardiff)*

https://www.prostate-cancer-research.org.uk/our-research

Germline and Early Disease

We would normally not fund research into early organ confined prostate cancer, germline alterations or the aetiology of prostate cancer. However, for outstanding studies where a strong link to advanced prostate cancer can be demonstrated we may make exceptions. We are specifically interested in research that will impact on the treatment of patients with advanced disease.

Partnerships and the Funding of Young Researchers

To fulfil our goal of establishing Prostate Cancer Research Centre as a world leading organisation for curing men with advanced prostate cancer strategic, partnerships with other organisations would be welcomed. Partnerships could allow us to combine approaches or provide resources that are essential for achieving our research goals but currently missing from the PCRC portfolio.

We are committed to promoting the careers of young researchers. Currently we are seeking to provide this support in partnership with other organisations.

Further Information:

Funding our research

PCRC intends to fund research using funds raised through various fundraising activities, including events, trusts and foundations, major donors and companies.

In addition, PCRC intends to partner and collaborate with other prostate cancer research and support organisations to maximise the amount of prostate cancer research that is carried out globally.

Details of grants provided by PCRC

PCRC intends to provide grants for research projects which are typically 3-5 years in duration.

Grants can include salary support, on costs and consumables. PCRC will also be prepared to fund and support collaborations and conferences for its researchers. Additional support could be provided to improve efficiency and effectiveness of the initial grant.

Researchers supported by PCRC are expected to work as part of a single collegial academic group combining resources to target important problems relevant to men with advanced disease. For a detailed list of the expectations of new members see Appendix: For New Members.

Who PCRC will fund

PCRC intends to fund research at highly-rated research institutions. This is assessed primarily through the Research Excellence Framework ("REF"), a periodic measurement of research quality in universities and other higher education institutions in the UK against international standards of excellence.

Applicants for major grants should at least have PhD qualification and the support of a senior researcher at their institution.

PCRC intends to focus its resources on funding research in the UK initially, but would consider any research globally as the amount of research that we fund grows.

How PCRC awards its grants

PCRC will request interested scientists and researchers submit a short expression of interest. These will be reviewed by a Grant Review Committee and a shortlist selected. Shortlisted candidates will be asked to submit a full application which will be peer reviewed by international reviewers. Based on this, the Grant Review Committee will select successful applicants to be presented to the board for final approval. Further information can be found on our website.

APPENDIX

Table 1 - Science and Clinical Translation for Advanced Disease

Basic Science and Target Discovery	Prostate Cancer Classification and Drug Targeting (Personalised Medicine)
• Discovery and Development of New Drug targets • Immunotherapy • Stem Cell Research • Analytical Studies (Genomics, Proteomics, • Metabolomics) • Understanding Development and Progression • Bioinformatics Analysis of Large Datasets • New Imaging Approaches • Development of Newer and Cheaper Therapies	• New and improved Classifications based upon molecular basis of the disease • Distinguishing indolent vs aggressive cancer • Test Development • Stratified Medicine and Personalised Treatments

Clinical Trials and Trial Support	Germline and Early Disease
• New and Improved Treatments (Drugs, Radiotherapy, Immunotherapy) • Trials testing the re-tasking of Existing Drugs • Clinical Models for Drug Testing • Improved Imaging and Tracking • Reducing Side Effects • Better Palliative Care • Sociological Studies Including Qualitative Research • Biobanking and Databases	• Information Relevant to Advanced Prostate Cancer • Relationship to Environment and Diet

Table 2 - New Therapies for Advanced Prostate Cancer

The standard treatment for metastatic prostate cancer is androgen withdrawal by orchiedectomy or drug treatment. On average this controls the cancers 18 to 36 months before castration-resistant disease develops. New treatments presented in this table can prolong life through targeting of newly presenting or castration resistant disease.

Drug	Putative Method of Action	Patient Target
Docetaxel *(Taxotere, Sanofi)*	Microtubule inhibition Inhibition of AR transport	Administer with Androgen Depravation Therapy
Cabazitaxel *(Jevtana, Sanofi)*	Microtubule inhibitor Overcomes resistance to docetaxel	Second-line treatment following docetaxel
Mitoxantrone *(Novantrone, Immunex)*	Topoisomerase inhibitor	Symptom relief
Abiraterone *(Zytiga, Johnson & Johnson)*	Irreversible CYP17 inhibitor Androgen ablation	Castration recurrence
Enzalutamide *(Xtandi, Pfizer)*	Prevents AR action	Castration recurrence
Radium-223 *(Xofigo, Bayer)*	Selectively binds to areas of high bone turn over	Bony metastases
Sipuleucel-T *(Provenge)*	Autologous Cellular Immunotherapy	Castration recurrence with minimal symptoms
PARP Inhibition *(Lynparza, AstraZeneca; Rubraca, Clovis)*	Inhibits repair of single strand Inhibits repair of single strand	Cancers with BRCA1/2 DNA breaks and PALB2 mutations
Platinum-Based Chemotherapy	Induce Double Strand Breaks and Cross-linking in DNA	Cancers with DNA repair defects
Immune Checkpoint Targeting *(Keytruda, Merck)*	High mutation rate leading to enhanced immune reaction	Cancers with mismatch Repair Defects

For New Members[1]

Summary

The research groups funded by the charity are required to work as part of a collegial academic group, the Prostate Cancer Research Centre (PCRC). The research groups are expected to combine both intellectual and material resources, where possible, to target important problems relevant to men with advanced prostate cancer. New grantees are required to develop strategically important areas of research, to build solid links to existing and new groups, and to add new expertise. This structure differs from that of many other research charities where projects may be funded at a single or small number of institutions.

Existing Groups

Stem Cells and Prostate Cancer
Dr Aamir Ahmed, King's College London
Dr Ahmed's group is investigating the mechanisms of Wnt pathway, a key cell signaling network that is critical during development and in diseases such as cancers. Their group have made fundamental discoveries regarding the role of Wnt signaling in prostate cancer. They discovered that the Wnt signaling pathway is electrogenic, i.e. it is regulated by the cell electrical potential. They are using this insight to repurpose drugs, termed membrane potential regulating compounds, for prostate cancer therapy. By focusing on the role of the Wnt signaling genes and proteins in prostate cancer, Dr Ahmed and his team are also developing new computational approaches (e.g. quantitative image analysis through machine learning) to develop biomarkers for prognostication of prostate cancer.

Immunotherapy for Prostate Cancer
Dr Christine Galustian, King's College London
Dr Galustian is interested in developing immunotherapy for prostate cancer. This group is working with a naturally-occurring protein called IL-15 that's causes the immune system to identify and attack cancerous cells. The group has devised an innovative new way to harness IL-15's immunotherapeutic properties that involves attaching chemical tail to specifically anchor IL-15 at the cancer site. The drug is relatively easy to manufacture and has the potential reduce treatment side effects.

The Spread of Prostate Cancer
Dr Magali Williamson, King's College London
Dr Williamson discovered novel mutations in Plexin B1 in prostate cancer. This team now works on the role of Plexin B1 in the development of metastasis in prostate cancer. They've shown that metastasis can be reduced by inhibiting Plexin B1 with antibodies. However, because Plexin B1 has healthy functions as well, it doesn't make sense to completely block it from working. The team are working on improving our understanding of which functions of the protein are relevant to metastasis, so that they can develop a more specific, targeted therapy.

Modelling Prostate Cancer
Professor Matthew Smalley and Dr Boris Shorning, Cardiff University
This team is developing innovative, world-first models for metastatic prostate cancer that are essential to test the effectiveness of novel treatments. The models have already been used to assist the research of Drs Williamson and Ahmed, and are additionally providing new insights into the mechanism of prostate

cancer development. Thus, better models are increase our understanding of the disease, and helping development of better therapies.

Detailed Expectations

Detailed requirements of PCRC members are as follows:

1. Liaising with other PCRC teams to achieve clearly defined and achievable joint goals(these may have been stated in your grant application) .

2. Sharing expertise and resources to assist other PCRC teams

3. Joining monthly PCRC telephone conferences.

4. Attending joint annual PCRC meetings[2].

5. Attending PCRC workshops and conferences where required[2].

6. Help to publicise PCRC research

7. To join fundraising groups and events to present your PCRC funded work as requested by the PCRC charity.

8. Develop new collaborative programs of research and consortia to address important translational questions and approaches

Whilst not a requirement, new members may also be invited to become participants in working groups set up to target specific problems. Such groups may have more regular communications.

[1]These are the expectation for scientific membership of PCRC that are separate from the detailed agreement between the PCRC and your organisation that has to be agreed and signed prior to the release of research funds.
[2]Please include costings to attend these meetings in your grant applications.