Five Years of Prostate Cancer Research and Collaboration

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“Collaborative research is crucial if Ireland is to increase its contribution to the acquisition of new knowledge about prostate cancer...”
The Irish Cancer Society is delighted to have been instrumental in bringing the Prostate Cancer Research Consortium (PCRC) into existence, and it is a pleasure to be penning this message as we celebrate five years of true collaboration and progress in prostate cancer research.

Prostate cancer is a serious problem in Ireland with approximately 2,500 cases and over 550 deaths annually. When the Irish Cancer Society, under the auspices of Cancer Research Ireland invited applications from prostate cancer researchers, it was with the aim of getting Ireland to make a very real contribution to research in this cancer.

We were delighted when four clinical sites and four research institutions decided to work together and submit an application for funding in a competitive review process.

Collaborative research is crucial if Ireland is to increase its contribution to the acquisition of new knowledge about prostate cancer, and it has been an exciting development to see such a co-ordinated research effort take place across different institutions, medical and scientific disciplines. It has been a pleasure to watch the PCRC grow and develop, and to see its participants raise more funding in their own right to fund research carried out in the Consortium.

I congratulate Professor Mark Lawler and Professor William Watson, co-founders of the Consortium and I pay tribute to their leadership. I applaud all the members of the PCRC on their achievements, and wish them every success in the next phase of the Consortium’s development.

John McCormack
Chief Executive, Irish Cancer Society
Message from Dr Ruth Barrington  
CEO, Molecular Medicine Ireland

On behalf of Molecular Medicine Ireland, I would like to congratulate the Prostate Cancer Research Consortium on its achievements over the past five years.

One of the great achievements of the Consortium has been to establish a standardised bioresource of over 550 samples donated by patients treated for prostate cancer in the participating hospitals. This bioresource has not only provided an invaluable resource for research on prostate cancer, but has also provided the prototype for the kind of bio-repositories needed for research in many other disease areas. The sophisticated information management system designed for the bioresource has also broken new ground in Ireland and the Consortium has generously offered the system to other groups engaged in storing and managing specimens and clinical information.

The Consortium’s research output has been most impressive and includes over 30 publications in international peer reviewed journals and has leveraged funding of over €4m. The research of those involved in the Consortium has impacted on patients through the identification of new biomarkers of early disease and of the most aggressive form of the disease. It has opened up the possibility of new therapies through the development of novel anti-cancer compounds. The Consortium has helped to build expertise in cancer research through its mentoring and training of 33 scientists and medical graduates at PhD and MD level.

There are great opportunities for the Consortium in the next five years. With the support of MMI and now the Dublin Centre for Clinical Research, the Consortium can develop into a national collaboration, involving scientists and clinicians in NUI Galway and University College Cork. The Consortium can also strengthen its international partnerships in North America, Europe and Australia and play a role in the global challenge of more effective control of prostate cancer. I would like to wish the Consortium every success in the next phase of its development and offer the continuing support of MMI in strengthening and deepening the collaboration.

Dr Ruth Barrington  
CEO, Molecular Medicine Ireland
Message from Co-Principal Investigators
Prostate Cancer Research Consortium

How do you do truly collaborative research? It is a question that challenges all scientists, clinicians and allied health care professionals, as we strive to make new discoveries that will impact on human health. We chose to address the challenges of prostate cancer by engaging like-minded individuals who could work together, linking different skill sets which would complement rather than compete, in a collaborative environment that made sense and provided increased capacity to engage in high quality research.

A critical component which led to the establishment of the Prostate Cancer Research Consortium (PCRC) was the leadership of the Irish Cancer Society (ICS). The ICS recognised the need to support high quality research in prostate cancer in Ireland and issued a call for prostate cancer research applications. We were successful in this competitive call which provided funding for a programme of research in prostate cancer and allowed the establishment of a prostate cancer biobank. The ICS also realised that the PCRC would take time to grow and establish itself and issued a second call in 2006/2007 in which the PCRC was also successful. We cannot over-emphasise our gratitude to the ICS for their foresight. Their initial support has allowed this Consortium to leverage significant additional funding in competitive peer review from other funding agencies, and publish our findings in international peer review journals. It has also provided us with the profile to establish a number of important international partnerships.

The Dublin Molecular Medicine Centre (DMMC), now Molecular Medicine Ireland (MMI), facilitated the establishment of the PCRC at an inter-institutional level and we would like to take this opportunity to thank the former CEO of the DMMC, Dr Pierre Meulien and his team for their support in the establishment of the PCRC.

However, it was the enthusiasm of the researchers and the clear benefits that started to emerge as we worked together, which really provided the impetus for growth and development of this Consortium.

However, a consortium is not merely about structures, it is about people, in particular the young researchers who have been and continue to be the lifeblood of this initiative, working together in the true spirit of collaboration, delivering on the aims of the Consortium and developing as the researchers and academic leaders of the future.

We provide to you a report of the activities of the PCRC on their behalf, while also looking forward to improving research quality and its translation for the cancer patient over the next five years and beyond.

Professor Mark Lawler
Associate Professor of Experimental Haematology, Trinity College Dublin and Chief Molecular Geneticist, St. James’s Hospital

Professor William Watson
Associate Professor of Cancer Biology, School of Medicine and Medical Science, University College Dublin
Executive Summary

“The Prostate Cancer Research Consortium (PCRC) was established... with the stated aim of linking ‘like minded’ researchers from different academic institutions and hospitals in a co-ordinated approach to maximise research potential in this disease.”

Prostate cancer is a common cancer and a frequent cause of death in Irish males. Critical to improved diagnosis and better treatment, is the requirement for a more complete understanding of

(i) what makes prostate cancer cells different from normal prostate cells
(ii) why some patients get very aggressive cancer while other men have a mild slow growing form of the disease
(iii) how to exploit the abnormal biology of the disease to devise new treatment strategies.

Understanding what genes and pathways may be damaged in prostate cancer cells can help us to translate this information to earlier diagnosis and better treatment options for men with prostate cancer.

The Prostate Cancer Research Consortium (PCRC) was established at the end of 2003, through a significant competitive grant from the Irish Cancer Society, with the stated aim of linking “like minded” researchers from different academic institutions and hospitals in a co-ordinated approach to maximise research potential in this disease. Bringing together researchers from different centres and different disciplines with complementary “added value” skills provides an excellent environment to tackle important questions in relation to prostate cancer diagnosis, prognosis and new therapies. Our aspiration was to make a significant contribution to prostate cancer research, with a clear focus on the cancer patient, while providing a teaching and mentoring environment that would encourage young scientists and clinicians to flourish.

Key events and discoveries within the PCRC include:

- Establishing the first Irish prostate cancer bioresource, licensed by the data protection commissioner, containing samples taken from prostate cancer patients with their informed consent. Samples from over 550 patients have been collected, providing a valuable resource for specific projects within the programme of research.
- Publication of a comprehensive survey of male urological patients’ attitudes to the collection of biological material, which showed a greater than 85 percent positive response and emphasises the patient-centred approach of the Consortium.
- Achieving more than 30 new research findings, many of which have been recognised by research awards at national and international conferences and published in high impact international journals.
“These promising advances have been achieved by the truly collaborative nature of the Consortium and the quality of the young researchers who have been nurtured through the programme.”

- Novels genetic changes have been identified, which may increase your risk of getting prostate cancer.
- Increased expression of specific combinations of different proteins have been detected in the serum of cancer patients indicating more extensive and aggressive forms of the disease.
- Potential new targets have been found and new experimental approaches developed, which may allow new treatment approaches to be devised.
- PCRC researchers have been increasingly successful in attracting research funding from national and international agencies (e.g., Science Foundation Ireland, Health Research Board, Enterprise Ireland, Irish Cancer Society, Irish Research Council for Science, Engineering and Technology, British Urological Foundation).
- Mentoring of a cohort of young scientists, clinicians and allied healthcare professionals as future leaders, who have demonstrated their ability through significant national and international awards including:
  - Best Oral Presentation, Irish Association for Cancer Research 2006
  - American Association for Cancer Research, AstraZeneca International Scholar-in-Training Award, 2009

These promising advances have been achieved by the truly collaborative nature of the Consortium and the quality of the young researchers who have been nurtured through the programme, delivering science that has been recognised as high quality by international leaders and key journals in cancer research.

The PCRC is setting an ambitious agenda for the next five years, to ensure that the quality of the research continues to improve, that the learning experience for young researchers makes a key contribution to their career development and that the patient continues to be at the centre of a collaborative, disciplinary research effort.
Establishment of the Prostate Cancer Research Consortium

Background

Prostate cancer is the most common malignancy among men in Ireland (see Figure 1) and is associated with significant morbidity and mortality. In the Republic of Ireland, the current annual incidence is approximately 2,500 with a mortality in excess of 550 cases per annum. With the increased ageing of the population, it is predicted that prostate cancer will increase by 275%, with figures approaching 6,000 new cases on the island of Ireland by the year 2020.

This projected increase is of major concern, especially when there are dilemmas associated with both the detection and treatment of prostate cancer. Current early detection strategies for prostate cancer are inadequate due to poor specificity, while there is controversy concerning the effectiveness of screening programmes due to the poor specificity of the current biomarker, prostate specific antigen (PSA), with one-third of men with prostate cancer having a normal PSA.

In addition, due to the heterogeneity of prostate cancer, biopsies may not represent the overall pathobiology of the tumour, with only one in four men with a PSA of greater than 4.0 ng/ml having biopsy proven disease.

Annual number of cases/deaths are given in brackets after the cancer site.


Prostate cancer is a major health issue for patients, physicians, healthcare providers and policy makers and it is imperative to convert knowledge of the disease process into tangible benefits through clinical research initiatives. This requires translation of current fundamental discovery to clinically applicable diagnostic tools and new therapeutic approaches.

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2 Kattan M.W. Judging new markers by their ability to improve predictive accuracy J Nat. Cancer Inst. 95(9): 634-635.
A critical bridge for enabling this translational research is the establishment of a collaborative infrastructure from the clinic to the research bench and the availability of bioresources or biobanks of clinically relevant samples from patients at different stages of disease (Figure 6, page 16). The careful examination of this valuable bioresource, in meaningful hypothesis-driven research, represents the best way forward to impact on patient outcomes with prostate cancer.

**Prostate Cancer Research Consortium – How it Started**

There were a number of key events that led to the beginnings of the PCRC. It was, no doubt, helpful that long-standing interactions existed between key prostate cancer investigators and clinicians in Dublin (namely ourselves, Professor Donal Hollywood and Professor John Fitzpatrick). In addition to these existing connections, at the time, there was an emerging awareness in the public domain of the debate about prostate cancer screening.

The publicity generated by the PSA screening debate highlighted the urgent need for a better understanding of the disease, and there was a real desire by the Irish Cancer Society to take action in some way. In December 2001 the then Minister for Finance, Charlie McCreevy, announced that €320,000 would be allocated for prostate cancer research and the Irish Cancer Society agreed to match that amount. The Irish Cancer Society invited research applications to be specifically of a collaborative nature. We were successful in our bid for research funding to develop a consortium of prostate cancer researchers, and thus the PCRC began.

The initiation of any collaborative effort is not without obstacles, and one such obstacle was the co-ordination of a group of individuals across competitive institutions. This was where the guidance of Pierre Meulien of the DMMC (now MMI) came into play, by mediating the initial discussions to develop the Consortium. Importantly, the DMMC also provided a neutral ground where individuals from different institutions could set aside their differences.

**Comments from Professor John Fitzpatrick**

Professor of Surgery, Mater Misericordiae University Hospital

“There are many challenges in the diagnosis and treatment of prostate cancer. The PCRC aims to address many of these, and is particularly focused on identifying better biomarkers of the disease. The surgeons, pathologists and research nurses are centrally important to these research efforts, not only by facilitating the collection of biological samples for the bioresource, but also by ensuring that the research remains focused on addressing clinical needs and the needs of the patient.”
institutional roles, and work as equal partners to address the considerable challenges of prostate cancer.

When the PCRC was launched in 2004 (Figure 2), this brought together for the first time clinicians, pathologists, scientists, research nurses and allied health care professionals with a common goal of understanding the molecular and cellular basis for prostate cancer development and progression. The stated aim of the Consortium was to translate this information to improve detection, prognosis and treatment of this common disease.

**Participating Research Centres and Hospitals**

The Consortium includes four clinical sites; Mater Misericordiae University Hospital, St James’s Hospital, Beaumont Hospital and the Adelaide & Meath incorporating the National Children’s Hospital and four research institutions; Conway Institute of Biomolecular and Biomedical Research, University College Dublin; Institute of Molecular Medicine, Trinity College Dublin; RCSI-Education and Research Centre, Royal College of Surgeons in Ireland and National Centre for Sensor Research, Dublin City University (see Figure 3).
Governance

The Consortium has a governance structure as detailed below which manages and develops each aspect in the Consortium. The governance structure was developed using the management structures of MMI as a model.

Executive Management Committee

Professor Mark Lawler
Professor William Watson
Mr John McCormack
Professor John Fitzpatrick
Professor Elaine Kay
Professor Donal Hollywood
Professor John O’Leary
Professor Richard O’Kennedy
Dr Jan Guerin (representing Dr Ruth Barrington)

The Executive Management Committee receive input from the Data Protection/Security Group, chaired by Dr Geoff Bradley, the Bioresource Management Implementation Group, chaired by Professor William Watson, the Biomarker Discovery/Validation Group, chaired by Professor William Watson, and the Molecular Therapeutics Group, chaired by Professor Mark Lawler. These groups are informed by the BIMS Development Group, chaired by Dr Darach Golden, the Research Nurse Group, chaired by Ms Maureen Brenan and the Pathology Review Group, chaired by Professor Elaine Kay.

These groups allow discussion of protocols, results and other highly specific information relating to the area of interest of the research group. Each group Chair presents summary reports at the quarterly Consortium group meetings.

Comments from External Advisor

Professor Stephen Hewitt, Director, Tissue Array Research Programme, National Cancer Institute, USA

“The PCRC is an excellent example of leveraging the resources of Ireland to enable high-level molecular research in cancer. The PCRC brings together a population-based cohort of prostate cancer specimens with deep clinical annotation and puts them in the hands of a young and dynamic research Consortium. The Consortium approach is essential, as the groups bring different skills to bear in the process of biomarker development. Individual research groups are able to focus their efforts independently to pursue a broad spectrum of questions in prostate cancer using state of the art technologies including genomics, transcriptomics and proteomics.”
to all PCRC members and the executive management committee. These Consortium group meetings provide a platform for both junior and senior members of the PCRC to exchange ideas, provide expert advice and create opportunities for continuous collaboration.

**External Scientific Review**

A crucial component of the PCRC is external review.

The initial application to the Irish Cancer Society was recommended for funding through a competitive peer-review process. This core grant was renewed after an additional open call and international peer review in 2007. Comments from these international reviewers included:

“This collaborative research group is a tremendous asset to the research infrastructure on prostate cancer in Ireland. Although specific examples of areas of more detailed research are provided, much of the application focuses on expanding the infrastructure and adding new technologies to be applied to specimens obtained.”

“Biomarker discovery and tumour repository in a collaborative environment is essential to making discoveries important to unravelling prostate cancer pathogenesis”

“The group appears to be addressing the changing research environment and investing in new technologies that allow for continued scientific advancement.”

In addition to these two formal peer-review processes, we have engaged a number of international scientific advisors to provide expert critique of the research and to advise on future directions of the Consortium. We invite these international advisors to attend the Consortium group meetings, review the presentations of the group and provide feedback. This has been a very important component of the research process. Details of previous and current scientific advisors are provided in Appendix 1.
Comment on the Importance of Young Researchers

Professor Cliona O Farrelly, Chairperson, Cancer Research Committee, Irish Cancer Society

“The education and training of young cancer researchers is hugely important to any cancer research programme, and has contributed significantly to the success of the PCRC. These young people bring a wealth of new and fresh ideas, as well as the enthusiasm, commitment and drive to tackle complex research questions. The PCRC has also nurtured important collaborative opportunities between young scientists, clinicians and nurses to establish a strong research focus within the clinical environment which will ultimately benefit cancer patients.”

Focus of Research

The research focus of the PCRC has been primarily driven by the need to address urgent clinical questions. The limitations of PSA as a marker of prostate cancer have highlighted the need for new and multiple biomarkers of this heterogenous disease. Also, upon diagnosis of prostate cancer, both clinicians and patients face dilemmas about treatment choice.

To address these clinical questions, the PCRC has undertaken a focus of research which aims to

1. identify novel cancer biomarkers which will permit early diagnosis of disease and provide critical information for risk stratification and clinical intervention.
2. determine potential targets and new approaches to kill prostate cancer cells.

The approach taken by the PCRC to achieve these aims is based on the expertise within the Consortium, including significant input from the collaborating clinicians and the technologies available to undertake the research. State-of-the-art research infrastructure and technologies have been made available through the Programme of Research in Third Level Institutions (PRTLI). This has enabled a comprehensive approach utilising genomic, transcriptomic and proteomic platforms to accomplish the Consortium’s objectives.
The objectives of the PCRC are to:

1. Establish a prostate cancer tumour bioresource to support ongoing research and evaluate patient attitudes to collecting tumour samples
2. Apply genomic, transcriptomic and proteomic technologies to identify novel biomarkers for early detection and improved prognosis of prostate cancer cases
3. Validate the novel biomarkers and correlate these molecular characteristics with disease progression phenotypes
4. Evaluate novel therapies in pre-clinical and potentially Phase I and Phase II studies

In addition to the specific research aims, the PCRC also has an educational focus, particularly in the training of research students and the mentoring of postdoctoral researchers at an early stage in their career. The PCRC places the patient at the centre of the research process, with significant levels of interaction, particularly through the research nurses. It also facilitates patients and patient advocacy groups to visit the research facilities, talk to the researchers and learn more about the work of the Consortium.

People Focus 1

Yue Fan
PhD Student, University College Dublin

I came to Ireland from China in 2007. I applied for a PhD through the UCD Bioinformatics PhD programme. They have a list of all the projects related to bioinformatics/statistics and I was very interested in the prostate cancer project in Bill Watson’s lab. I travelled from China to do an interview with Bill and got accepted. Before I came to Ireland, I completed a BSc in Bioscience at the College of Life Sciences, Agricultural University of Hebei and an MSc in Bio-Health informatics at the School of Computer Science, University of Manchester.

Since I started my PhD, I have been working on biomarker discovery for prostate cancer through analysing proteomics and metabolomics data, and I also offer statistical analysis advice to other researchers within the Consortium.

The benefits of working within the PCRC are that resources such as patient samples and clinical data have been made available for my research, and I am inspired by other peoples’ work progress seen at the Consortium group meetings. At these meetings, I have also been given valuable suggestions by other PCRC members.

The thing I most enjoy about working in the PCRC is the team work shown by different prostate cancer research groups through sharing information and resources, and discussing the results together.
People Focus 2

Maureen Brenan
Research Nurse, Beaumont Hospital

Without patients, medical research would be very limited. My role is to meet patients, provide them with clear information regarding the study and obtain an informed consent for their participation into the study.

What attracted me to the role of a research nurse was the challenge of something new and different, the high requirements to be employed as a research nurse, the flexibility of the job, and maintaining some patient contact.

I approach each patient by giving them clear information about the study being undertaken in a friendly yet professional manner, outlining potential risks such as breach of confidentiality etc. I listen attentively to each patient and give them the opportunity to ask any questions.

My biggest achievements include putting in place an efficient system for being informed of potential patients for the study and for the collection of samples for research. We have a very high recruitment rate which could not have been achieved without the help of the collaborators within the hospital.

Establishment of a Prostate Cancer Bioresource

The first objective of the PCRC was to develop a prostate cancer tumour bank or bioresource.

The PCRC established a multi-site or federated prostate cancer bioresource at its hospital sites, following ethical approval by each of the hospital’s ethics committees. Using the federated collection model, agreed standard operating procedures (informed consent, sample collection and initial processing) are implemented across the different sites by dedicated research nurses, ensuring uniformity of the resource.

Samples are stored at the collection centres using monitored storage facilities as part of the Clinical Research Centres, developed by Molecular Medicine Ireland through the Programme of Research for Third Level Institutions (PRTLI). The bioresource currently has 558 tissue samples with corresponding serum, plasma and DNA isolated from blood samples and 318 urine samples. Comprehensive clinical information is also collected for each patient and their samples including full pathology of the initial biopsy and radical prostatectomy, pre and post PSA and subsequent follow-up of the patient.

Bioresource Information and Management System (BIMS)

Central to the federated bioresource is an IT system known as the Bioresource Information and Management System (BIMS), which accommodates the collection and tracking of samples and integration of clinical information.
In 2006, the PCRC received funding from the Health Research Board to unify access to the bioresource by developing a BIMS. The BIMS system development was undertaken by the Trinity Centre for High Performance Computing (TCHPC) and the PCRC partners. Following a tendering process, SlidePath was awarded the contract to build a system using their Distiller software.

The BIMS web-based system stores all the de-identified data from the patients and their samples. This allows investigators to identify what samples are available and where they are located, as well as linking the relevant clinical data in a completely confidential way. The BIMS is a central data repository for the clinical and research information, however, the samples themselves remain stored in the hospital sites of the Consortium.

The data which is entered into BIMS originates from two sources:

- **Hospital sites:** De-identified clinical, sample and pathology data is uploaded to the BIMS system, via a web browser, by clinical research nurses at the hospital sites. The hospital sites maintain the identifiable data linked to a study number which links the identified and de-identified data so that appropriate patient follow up information, such as post-operative PSA, can be uploaded on to BIMS.

- **Research Institutes:** Research results such as genomic and proteomic data, produced by further analysis of samples at the research laboratories, is uploaded to the BIMS by PCRC researchers via a secure web browser.

"Biomarker discovery and tumour repository in a collaborative environment is essential to making discoveries important to unravelling prostate cancer pathogenesis."

**Figure 5** Structure of the BIMS database
Ethical Requirements

Ensuring the confidentiality of participants’ data is considered one of the major requirements of bioresources and their associated data management systems. Based on national, European and international regulations, best practices were identified, defined and adhered to in the construction of BIMS. Among the measures which are implemented for the PCRC BIMS are:

- **Informed Consent:** Donors are fully informed of the uses to which their biological samples and clinical data will be put and appropriate permission is requested and granted by each individual patient. Clear and unambiguous information leaflets on what the samples will be used for and consent forms are made available to the participants before any sample is obtained.

- **Standard operating procedures (SOPs):** SOPs have been designed for all procedures from consent management to sample collection, storage, retrieval and tracking so that inappropriate or identifiable data will not be inadvertently revealed.

- **De-identification of all data:** Data stored in BIMS contains no information which allows identification of individual patients.

- **Access:** Donors are allowed access to their data and may request that it be removed from the BIMS at any time.

- **Secure environment:** Restrictions are in place to keep all data safe from unauthorised access and all access is monitored and recorded.

The Consortium’s BIMS is the first biobank database that has been approved and licensed by the Data Protection Commissioner and fully complies with all National and European regulations. The system has been registered as a separate entity for the purposes of data protection. The bioresource and BIMS are monitored by the Bioresource Management and Implementation Committee (see Figure 4) which also reviews access to the resource.

BIMS offers the potential to accelerate knowledge discovery significantly by greatly increasing the study population size for both discovery and most importantly validation of novel biomarkers and treatment strategies which is required before clinical utilisation.

PCRC researchers are also continuously striving to improve existing procedures for sample identification and tracking. One research project at the Trinity Centre for High Performance Computing aims to develop a novel prototype system for tracking samples across multiple sites which ensures the integrity and security of the data and samples which complies with regulations governing biobanks.
Comments from patients on prostate cancer research and the work of the Consortium

“The two questions I had were – how did I get it and will I survive it? As far as I can see, research is the key to understanding how people get cancer and maybe if we know what the cause is, it might lead to discovering how to prevent it or deal with it better”.

“Men in particular are poor at looking after their healthcare and getting check-ups unless they have a friend who gets a serious illness. For example, friends of mine who had never heard of the prostate blood test (as I hadn’t) have all had at least 1 test since I had my operation. I am sure a huge amount of research goes into finding cures but research to educate people on how to prevent or identify an illness early also has an important role”.

“I believe that medical research is the start of saving lives. Each patient brings different medical family history and symptoms to the research team. These patterns may help to diagnose the cancer at an early stage and so save lives”.

“Medical research is a “must” as without it we cannot progress to find cures for all type of illness”.

(On participating in the PCRC) “I think it is very worthwhile and everybody should participate, there is absolutely nothing to lose and I think a lot to gain”.

“This project is worthwhile because it gives an insight into the pattern of prostate cancer. I would encourage all men over 50 and other younger men who may have a family history of prostate cancer to participate in this study. This may help others so that early diagnoses can be identified”.

Patients’ Attitudes to Biobanking

In the PCRC we feel it is very important to work closely with our patients. When establishing the objectives of the Consortium, our first priority was not solely to establish a prostate cancer bioresource, but also to evaluate for the first time Irish male patients’ attitudes to collecting biological material. Patients and the availability of clinically relevant patient samples are at the crux of the PCRC and so the success of the Consortium relies heavily on the goodwill and co-operation of Irish men who are diagnosed with prostate cancer. We commissioned a comprehensive survey of male patients’ attitudes to collecting biological material and tissue donation for research purposes and we were overwhelmed with the level of support. This study, which was published in BJU International, was the first survey of Irish mens’ attitudes to the collection of biological material and as such is a landmark in Irish cancer research.

In addition to this survey we are also interested in hearing the ongoing thoughts and responses of patients in relation to research in general and the work of the Consortium. A number of comments from prostate cancer patients are included below.

In a unique study, PCRC researchers surveyed male patient’s attitudes to biobanking and donating tissue for research purposes. A total of 259 patients attending tertiary referral urology clinics in 2 Dublin hospitals participated in the study. Key findings were:

- Very high level of willingness to donate tissue for research (84.5% agreed/strongly agreed).
- Older patients (>55 years), and those who had generally positive attitudes about genetic advances were even more favourably disposed to donating their tissue.
- High degree of trust in medical researchers to act ethically with regard to tissue samples.

Patient Focus

Sean White

from Artane, Dublin 5, is a prostate cancer survivor. Sean donated tissue to the Prostate Cancer Research Consortium’s biobank.

When it was confirmed to me that I had prostate cancer, I was faced with various treatment options but I knew straight away that I wanted to have surgery. My attitude is to live for today and to deal with things, and having surgery was my way of talking control again.

My son was getting married during the summer of 2008, so I put off having my operation until the following November. My wife and I didn’t tell our children about my diagnosis until shortly before the operation as I did not want them worrying and fretting about me.

On November 7th I had my operation, and my doctor told me that he was happy with how it went. My family got a shock that evening when they saw me hooked up to all these tubes, but by the following day I was looking and feeling much better. I was fitted with a bag which I had to wear for about a month but I just got on with it. I have to say that the care and attention shown to me by the nurses and doctors in Beaumont Hospital was excellent.

When I went back for my check-up the following March, I was very happy to hear that my PSA level was completely normal. I have since had a number of check-ups, and it has only been good news.

About a month after my diagnosis, Maureen Brenan, the Research Nurse at Beaumont, contacted me to ask me if I would take part in research on prostate cancer and I did not hesitate to say yes. Maureen was extremely nice and respectful, and explained everything very clearly. She was always very open about everything, and has a great sense of humour!

I was very happy to take part in the research and donate tissue to the biobank. I believe that medical research is the first step on the road to saving lives. Without it we will never find a cure.

Links to International Bioresources

The current resource contains significant numbers of samples for biomarker discovery and first phase validation. However larger bioresources are required for the large scale validation of appropriate biomarkers. For this reason, the PCRC has established a number of international collaborations (Figure 7). These include: Professor Helmut Klocker, Innsbruck Medical University and the Tyrol Prostate Cancer Screening programme; Professor David Horsfall, Australian Prostate Cancer Bioresource; Dr Sudhir Srivastava, Early Detection Research Network (EDRN) of the National Cancer Institute. The Consortium is also part of the International Cancer Biomarker Consortium – established by Professor Lee Hartwell.

Currently negotiations are underway with Professor Martin Gleave, Vancouver General Hospital and University of British Columbia, Canada and Professor Coleen Nelson, Queensland University of Technology, Institute of Health and Biomedical Innovation, Princess Alexandra Hospital, Brisbane, to establish an Australian-Irish Alliance in Prostate Cancer similar to the Australian-Canadian Prostate Cancer Research Alliance.

1 www.urolab-ibk.at
2 www.apccbioresource.org.au
3 www.edrn.nci.nih.gov
4 www.fhcrc.org/science/international_biomarker/teams
In addition, the Consortium has a number of active international research collaborations, including Queens University Belfast (Professor David Hirst, Dr Tracy Robson, Dr David Waugh), the National Cancer Institute (Dr Karen Woodson, Dr Mike Emmert Buck) and the UC Davis Cancer Centre (Professor Ralph DeVere White) and Innsbruck Medical University (Professor Helmut Klocker).

Figure 7  International Bioresource and Research collaborations established by the Prostate Cancer Research Consortium.
Comments from International Collaborators

Professor Ralph DeVere White, Director, UC Davis Cancer Center and Codman-Radke Chair in Cancer Research, USA

“Since its inception in 2003, the PCRC has built a large extremely well annotated and managed prostate cancer bioresource. In addition to this, they have gathered a very talented collaborative team and are developing the next generation of prostate cancer researchers. Both the bioresource and the developing scientists who utilise this resource promise to make great strides in this disease in the years to come.”

Professor Helmut Klocker, Department of Urology, Innsbruck Medical University, Austria

“The establishment of the Irish Prostate Cancer Research Consortium is an important collaboration for the exchange of ideas, cell lines and patient samples in the European network of prostate cancer researchers. We are convinced that joining our efforts has speeded up the progress in prostate cancer diagnosis, treatment and patient care and will have an important impact on future projects and developments.”
Biomarker Discovery and Validation

Research Programme 1

While management of cancer patients has improved significantly, early cancer detection is the most important parameter in contributing to increased survival. Appropriate diagnosis also allows the doctor and patient to decide on the best treatment. In prostate cancer, it has become increasingly important to have reliable ways to diagnose disease, as aggressive therapies can lead to significant risk of treatment-related side effects which will impact on the patient’s quality of life. The PCRC has undertaken two approaches – epigenetics and proteomics – in the discovery of novel biomarkers for prostate cancer which utilise both tissue and bio-fluids from the bioresource (Figure 8).

Within the biomarker discovery strand of research, nine separate research projects have been undertaken by PCRC researchers. These range from the identification of DNA methylation biomarkers, proteomic analysis of urine and serum from early stage prostate cancer, multivariate analysis integrating metabolomic and proteomic patient data, and microRNA profiling of prostate cancer and prostate cancer progenitor cells.

Epigenetics and Prostate Cancer

In addition to the classical models of oncogene activation and tumour suppressor gene suppression in cancer, recent evidence indicates that epigenetic regulation of genes also contributes significantly to development of malignancy. “Switching off” genes through a process of increased methylation of critical control regions (hypermethylation), where a chemical change in the structure of DNA in the control region of certain genes leads to their inactivation, is now a common mechanism underpinning the development of malignancy. Our hypothesis, for which we have now accumulated a significant body of evidence, is that epigenetic changes are a frequent event in prostate cancer development and progression.

Figure 8 Biological samples (biopsy tissue, blood and urine) collected as part of the PCRC BioResource

Analysis of the biopsy tissue of the patient may identify novel epigenetic, genetic or protein changes. These changes may also be present in the blood/urine, allowing a simple diagnostic or prognostic test to be developed.

FROM PCRC BIOMARKER DISCOVERY RESEARCH...

8 out of 9 projects have used the bioresource

On average, each project has involved the use of 95 patient samples

Results have been presented through 16 oral presentations and 39 poster presentations

Findings have been published in 11 papers
In epigenetic studies, PCRC researchers have identified increased methylation of genes in prostate cancer cells from the bioresource in a number of important cellular pathways including IGFBP-3, an important pathway in regulating the growth of cells. Methylation of IGFBP-3 was not only a novel marker of increased risk of developing early prostate cancer (Perry et al, 2007a), but also helps us to understand how the cancer might develop.

Technology development is an important part of epigenetic research and PCRC researchers, in collaboration with researchers at the National Cancer Institute Washington, USA and the biotechnology company Transgenomics have developed a novel epigenetic screening approach using denaturing high performance liquid chromatography (dHPLC) (Perry et al, 2007b). Employing a combination of bioinformatic in silico and wet lab discovery tools, PCRC researchers are exploring the epigenetic control of genes that regulate the ways in which prostate cancer cells evade cell death.

Another epigenetic mechanism for regulation of gene expression is through a new class of molecules called microRNAs. PCRC researchers are investigating expression of these molecules in prostate cancer tissue from the bioresource. A microRNA profile of prostate cancer cells will provide novel insights into prostate cancer development and uncover new biomarkers.

People Focus 3
Antoinette Perry
Postdoctoral Researcher, Trinity College Dublin

I started working in the area of prostate cancer in 2002, when I started my IRCSET PhD with Professor Mark Lawler, working on novel targets of DNA hypermethylation in prostate cancer.

When I joined Mark’s laboratory I had a degree in Human Genetics from Trinity College Dublin and had worked as a research assistant for 1 year in the Smurfit Institute of Genetics, TCD. For me, one of the highlights of working in the PCRC has been the opportunity to establish partnerships with other scientists with different skill sets working on other avenues of prostate cancer research. Quarterly meetings of the PCRC provide a forum for me to present my findings and gain valuable feedback, ensuring that I am focused on targeting important clinical problems.

I have contributed to prostate cancer research by demonstrating hypermethylation of several novel genes in prostate cancer and my biggest research achievement to date was the development of Denaturing High Performance Liquid Chromatography as a novel DNA methylation screening platform (published in the journal Epigenetics in 2007).

During my PhD, I was fortunate to complete two research stays in Dr Karen Woodson’s laboratory at the National Cancer Institute in Washington, USA, as part of the PCRC international collaboration. This contributed significantly to my career development. Recently, in a competitive grant process, I was awarded a prestigious Irish Cancer Society Research Fellowship Award. It is my hope that my Irish Cancer Society Fellowship will enable me to perform high quality epigenetic cancer research and bring methylation biomarkers into the clinic.
Serum and Urine Proteomic Biomarker Discovery

Having identified specific (epi)genetic changes in the tumour tissue, PCRC researchers are testing serum and urine samples from patients to see if these biofluids harbour the same and additional changes. Bio-fluids are much easier to sample and monitor on a regular basis and so would be an ideal sample source for a routine diagnostic/prognostic test.

Using proteomics and metabolomics, PCRC researchers have identified changes in the presence of proteins in the serum and urine which are specific to men with early stage prostate cancer (Figure 9). Changes in 64 proteins were detected, unveiling a number of novel targets which are being investigated in greater detail (Byrne et al, 2009). Advanced bioinformatic tools have been developed to analyse this complex dataset, allowing predictive models to be generated for early stage disease.

This collaborative approach, utilising different technologies across the Consortium in the same cohort of patients provides added value, allowing comprehensive evaluation and validation of potential markers identified through our discovery process. Crucially, these studies funnel into the validation phase of the research programme, allowing exploration of their clinical utility.

Figure 9  Proteomic analysis of serum samples from a benign and high grade disease

Serum samples from benign (stained with Blue Fluorescent Dye) and Gleason 7 (Stained with Green Fluorescent Dye) are separated in two-dimensional gels (2D-DIGE) based on the protein charge and size giving individual spots representative of individual proteins. Overlaying of images identifies protein spots up or down regulated in disease which can be subsequently identified by mass spectrometry.

Adapted from the research published in Byrne et al, J. Proteome Res 2009; 8(2): 942-957.
Central to the identification of novel biomarkers of disease is their validation in larger groups of patient samples. Unfortunately, this represents the largest bottleneck in bringing novel biomarkers from the research laboratory into clinical use. The Consortium’s bioresource will significantly help in speeding up this process as it has access to nearly 550 samples, representing a significant sample base for first stage validation. International collaborations will allow further access to additional samples for international validation studies required to determine the clinical usefulness of the new biomarkers.

Serum Validation Studies

PCRC researchers have performed validation studies on the expression of proteins identified from the methylation and proteomics discovery phase in the serum and urine of larger groups of men with early stage prostate cancer. These studies have identified a panel of five serum biomarkers that can predict with a high degree of reliability the presence of high or low grade disease. These findings have been made possible through the development of a unique software package by Mr Yue Fan called DIGER (Fan et al, 2009) which can analyse the complexity of protein expression data to identify panels which predict disease. Importantly, they have identified a second panel of four proteins that can help to determine if the cancer is localised to the prostate gland or has spread beyond the capsule of the gland.

People Focus 4

Deirdre Fanning
Urology Surgeon in training, (research completed in UCD)

I graduated from medicine in 2004 (MB BCh BAO NUI (Honours)) and undertook my basic surgical training in the RCSI (2005-2007). I decided on urology as my surgical speciality and was awarded an RCSI scholarship and subsequently a British Urological Foundation scholarship to undertake an MD under the supervision of Professor William Watson.

My research focused on the identification and validation of panels of serum biomarkers in the detection of clinically significant prostate cancer to inform appropriate treatment strategies.

As a surgical trainee, my time within the PCRC allowed me to develop many and varied research skills, which I feel positively impact upon my clinical practice. With an ever-increasing emphasis on the practice of evidence based medicine and continuing professional development, it is critical that all doctors are capable of both understanding and critically appraising the contemporary scientific literature.

My greatest research achievement to date was the receipt of an International Scholar-in-Training Award from the American Association for Cancer Research (AACR) in 2008. I received this award at the AACR Advances in Prostate Cancer Research Conference in San Diego, USA.

A memorable event for me was the award of my MD in December 2009 from University College Dublin.

I am currently completing my urological training in Ireland, after which I would love to progress to an international urology fellowship programme. Ultimately I plan to work in Ireland, ideally in a university-affiliated hospital allowing me to combine my clinical and research interests.
This significant result has undergone initial validation (Fanning et al, 2009) and will help the clinician to determine the most relevant therapeutic strategy that will benefit the outcome of the patient.

**Tissue Validation Studies**

PCRC researchers are validating potential serum biomarkers in the patient’s corresponding tissue. This is to determine if these biomarkers are coming directly from the tumour or are released from other organs of the body as a consequence of the tumour. Tissue microarrays have been developed from the individual tumour samples, available from the bioresource, which represents a faster way of looking for the expression of these proteins in the cancer tissue. Significant changes in a number of the identified proteins have been detected (O’Hurley et al, Best Poster Presentation, CANCER 2009).

Computer scanning and machine learning approaches are also being developed by PCRC researchers to automatically read pathology slides and more accurately measure the changes in the presence of biomarker proteins, thus assisting the pathologist in the grading of the disease. One such project at the UCD School of Computer Science and Informatics is investigating the use of hierarchical computer aided diagnosis and supervised machine learning techniques to assist pathologists in Gleason scoring of prostate histopathology slides (see Figure 10).

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**People Focus 5**

**Gillian O’Hurley**

PhD Student, Royal College of Surgeons in Ireland

I achieved a double Honours Degree in Biology and Statistics and a Masters Degree in Immunology and Global Health, both from NUI Maynooth. I was successful in obtaining a PhD scholarship within the PCRC, funded by the Irish Cancer Society and am now in the final year of my doctorate in the Royal College of Surgeons in Ireland under the supervision of Professor Elaine Kay (Beaumont Hospital/RCSI) and co-supervisor Professor Richard O’Kennedy (DCU).

My project involves tissue validation of potential markers forwarded from the protein discovery projects within the PCRC and generation of antibodies to the discovered proteins.

The experience I have gained in Beaumont hospital working with Professor Elaine Kay and Dr Tony O’Grady in a medical environment, getting to see first hand what is involved in diagnosing prostate cancer and learning what goes on in a histopathology lab has been an invaluable experience that all the reading of literature in the world could not substitute for. It is very rare a PhD student gets the opportunity to translate their scientific knowledge into a medical environment.

At the moment, I am enjoying working in DCU with Professor Richard O’Kennedy generating an antibody to a novel protein discovered in my project. Here I am gaining enormous experience in biotechnology and also getting the opportunity to integrate my immunology experience from my Masters Degree into my project.

I am completely focused on finishing my PhD which is due to be submitted in September 2010. After that I would hope to stay in research and would love to do a post doctorate if the right opportunity presented itself particularly in the field of prostate cancer.
Central to these studies are availability of suitable antibodies to detect the proteins of interest. Novel antibodies for prostate specific antigen have been generated by PCRC researchers (Townsend et al, 2006) and similar approaches will develop antibodies for target analysis.

The rapid validation of targets identified in the biomarker phase of the programme will allow these markers to be more quickly moved towards clinical utilisation.

**Novel Antibodies for Biomarker Validation**

FROM PCRC BIOMARKER VALIDATION RESEARCH...

5 out of 5 projects have used the bioresource

On average, each project has involved the use of 82 patient samples

Results have been presented through 7 oral presentations and 13 poster presentations

Findings have been published in 4 papers

**Figure 10 Automated Image Analysis in Histopathology**

Digital grading of tissue sections would represent an important tool for pathologists in the diagnosis of the different grades of disease. Novel machine learning techniques have been shown to identify high grade disease in digitised sections. Prostate cancer Gleason Grades 3 and 4 can be differentiated with accuracy as high as 80% using multi-channel co-occurrence features, but the classification accuracy depends on the consistency of staining between the test and training data. Adapted from research published by DiFranco in Proceedings of International Workshop on Microscopic Image Analysis with Applications in Biology (MIAAB’08).

The identification of biomarkers can also be achieved by having a fundamental understanding of the molecular mechanisms of prostate cancer. The Consortium has undertaken a number of studies to understand the molecular mechanism by which prostate cancer initiates and progresses.

**Hypoxia and Prostate Cancer**

A particular focus of the PCRC is the role of hypoxia, or low oxygen concentrations, in prostate cancer, including the potential for hypoxia as a therapeutic target. Increasing levels of tissue hypoxia have been reported as a natural feature of the aging prostate gland and may be a risk factor for the development of prostate cancer. In order to study hypoxia in cancer, it is important to have relevant biomarkers of hypoxia. In a trans-institutional study that highlights the strengths of the PCRC and the importance of the bioresource, PCRC scientists have identified markers of hypoxia (Foley, Marignol et al, 2009) that will aid in identifying hypoxic regions within tumours for a number of related studies within the Consortium. The cellular response to hypoxia is governed by the transcription factor, hypoxia inducible factor-1 alpha (HIF-1 alpha) which is overexpressed in prostate cancer. Given the importance of HIF-1 alpha in hypoxia, PCRC researchers also demonstrated that a polymorphism within this gene may predispose to clinically localised prostate cancer (Foley, Marignol et al, 2009) (see Figure 11).

Additionally, a novel link between epigenetics and hypoxia has been demonstrated in the normal prostate (Watson et al, Hum Mol Genet, 2009). In this study, PCRC researchers demonstrated genome-wide epigenetic changes under chronic hypoxic conditions in the prostate, which may represent a mechanism of adaptation to hypoxia with a potential role in tumour development.

**Hypoxia and Cell Death**

Resistance to cell death is a fundamental hallmark for cancer development and represents an excellent marker of the disease. PCRC researchers have identified changes in the genes and proteins that regulate cell death following exposure to low levels of oxygen. Clinical hypoxia and oxidative stress are important features of prostate tumours and are implicated in the tumour’s resistance to chemotherapy. Using hypoxia chambers, PCRC researchers investigated the effect of hypoxia on the apoptotic (programmed cell death) pathway of normal and cancerous cells. The investigators demonstrated that lowering of oxygen results in the resistance of normal prostate epithelial cells to cell death and may represent an early “trigger” for prostate cancer development. PCRC researchers have shown that when prostate epithelial cells are exposed to hypoxia, the expression of “survival” proteins is increased, which facilitates the resistance of these cells to toxic damage (Walsh et al, 2009).

**Figure 11**

DNA sequence of the HIF-1 alpha gene in prostate cancer patient samples

The C1772T single nucleotide polymorphism (SNP) is present in sample B but not sample A. Adapted from Foley et al, 2009.
Infection and Prostate Cancer

Prostatitis is a common occurrence in prostate cancer patients, raising the possibility that infection may play a role in the development of prostate cancer. Based on published literature, PCRC investigators attempted to identify potential association with exposure to a virus called xenotropic murine leukemia virus-related virus (XMRV) and risk of prostate cancer. In particular, patients whose samples exhibited a particular polymorphic variant in the RNAseL gene, a gene which regulates the cellular response to viruses were examined. While the polymorphic variant was significantly more common in samples from prostate cancer patients than controls, there was no evidence for increased presence of XMRV in samples from prostate cancer patients.

The discovery, validation and translational biomarker studies described here have allowed PCRC researchers to define panels of novel biomarkers (genetic/epigenetic/protein based) which have demonstrated significant relevance in tumour tissue and may also have utility in serum and urine.

Androgen Independent Prostate Cancer

In prostate cancer, tumour aggressiveness is associated with progression to androgen independent disease. Therefore it is important to identify potential markers of androgen or castrate independent prostate cancer. PCRC investigators looked at changes in the androgen receptor (AR) gene and risk of progression and identified variation in a region of the AR gene that was linked to more aggressive AIPC.
Research Programme 3
Cancer Drug Development and Cancer Therapeutics

In prostate cancer, there is a need to understand in more detail why certain patients respond to therapeutic intervention and which patients should be scheduled for specific therapies. Furthermore, standard treatments fail to prevent disease progression in some prostate cancer patients and therefore it is hoped that a more complete understanding of the cellular and molecular processes in prostate cancer cells can help identify new therapeutic targets, or novel approaches to killing prostate cancer cells. Working in an interdisciplinary way with input from the key areas of chemistry, computational biology, radiation oncology, biochemistry and translational medicine, PCRC researchers have used the knowledge that they have generated of the cellular and molecular biology of prostate cancer to drive a cancer drug discovery and development programme of research. This research programme focuses on key problems in prostate cancer including tumour hypoxia, radiation response, androgen independence, and apoptosis resistance.

Hypoxia as a Therapeutic Target in Prostate Cancer

As discussed, tumour hypoxia is emerging as a common feature of prostate cancer which is associated with resistance to cell death, making this pathway a target for new therapeutic strategies.

An area of significant interest to PCRC researchers is the use of gene therapy as a novel approach to killing prostate cancer cells. PCRC researchers have previously developed a suicide gene therapy approach that is prostate specific, leading to targeted killing of prostate cancer cells (Foley et al, 2004). These researchers have now developed a novel suicide gene therapy approach which overcomes tumour hypoxia, priming the specific killing of prostate cancer cells (Marignol et al, 2005, 2009). This gene therapy approach has been achieved by developing vectors incorporating HIF-1 transcriptional control elements together with additional PSA promoter/enhancer elements.

PCRC researchers have also begun to investigate the role of hypoxia in the response of prostate cancer cells to microtubule targeting agents, including novel agents that have been developed in collaboration with the School of Biochemistry and Immunology TCD and the University of Siena, Italy.

Figure 12 Effects of Resveratrol (a constituent of red wine!) on prostate cancer cell death
Pre-incubation of the androgen independent prostate cancer cells, PC-3, with Resveratrol for 24 hours increases their sensitivity to TRAIL induced cell death. Adapted from Gill et al, Prostate 2007; 67(5): 1641-1653.

Figure 13 Growing Prostate Cancer cells in 3-dimensional culture systems for experimental therapeutic studies
Adapted from current work.
Radiation therapy is routinely used in prostate cancer management and PCRC researchers aim to exploit the molecular characteristics of prostate cancer cells to enhance the radiosensitivity of these cells. The use of radiotherapy and the development of radiation response gene therapy promoters can enhance the therapeutic response of other prostate-specific gene therapy vectors (Marignol et al, 2007, 2008). PCRC researchers have also demonstrated that gene therapy approaches can be effective in 3-dimensional prostate cancer culture models (Figure 13).

Allied to the development of radioresponsive gene therapy vectors, PCRC researchers are also investigating the role of low dose hyper-radiosensitivity (HRS). Low dose HRS is the phenomenon whereby cells exposed to radiation doses less than 0.5 Gy exhibit increased cell kill relative to the linear quadratic model. This research has shown the importance of O6MeG lesions and Mismatch Repair Proficiency in HRS in prostate cancer (Martin et al, 2009). It has also highlighted the potential relevance of DNA mismatch repair in the progression to hormone independent prostate cancer (Martin et al, 2009(b)).

Manipulating Apoptosis in Prostate Cancer

As in other tumours, understanding the apoptotic phenotype is an important component of testing both existing and novel drug approaches in prostate cancer. PCRC researchers have shown that inhibitors of apoptosis (IAP) proteins are upregulated in prostate cancer cells and manipulation of these proteins, either using siRNAs (Gill et al, 2009) or by treatment with naturally occurring agents such as Resveratrol (Gill et al, 2007) can sensitise prostate cancer cells to apoptosis and may be employed with other agents to achieve effective prostate cancer cell kill (see Figures 12 and 15).

PCRC researchers demonstrated that agents such as dutasteride could induce apoptosis in androgen dependent and androgen independent cell lines and overcome hypoxia in model systems (McCrohan et al, Cancer 2006).

Novel titanocene analogues, developed in collaboration with the Centre for Synthesis and Chemical Biology, UCD were shown to induce apoptosis both in cell line and animal studies (O Connor et al, 2006, Dowling et al, 2008). Sublines of prostate cancer cells resistant to standard therapy with docetaxel have been established and the novel analogues induce apoptosis in these cells. These resistant cell lines are also a useful resource for other research projects within the cancer drug development arm of the PCRC Programme of Research.

Conclusion

In summary, this cancer drug discovery and development programme of research has identified a number of promising targets and developed a number of novel compounds and approaches which may allow specific killing of prostate cancer cells. The most promising of these candidates are currently being tested in relevant models of prostate cancer.
Conclusions and Future Directions

The PCRC has made significant advances since its formation at the end of 2003. A clinically annotated bioresource has been established, providing a crucial bridge between basic biology discoveries and translational research. Harmonisation of the methodologies for collection, processing, storage and annotation of this material has been achieved across the participating academic teaching hospitals. A premier quality informatics architecture has been created to ensure proper management of the resource, maximising its potential in investigator-led research projects within the Consortium. Promotion of inter-institutional and cross-discipline collaboration has provided clear “added value” as judged by the relevant metrics of joint publications in high quality international journals and joint research projects achieving competitive peer review funding. Nurturing of PhD students and junior staff has been recognised by numerous research awards at national and international conferences. Capacity building achieved through the establishment of the Consortium has allowed the brokering of a number of significant international collaborations.

Looking back over the genesis and initial achievements of the PCRC is the spur required to set ambitious goals for the next five years of the Consortium.

Future Directions

Significant programmatic funding will be sought to increase the competitiveness and research output of the Consortium with a strong focus on addressing clinically relevant questions that will impact on patient diagnosis and treatment. There are three specific objectives to be undertaken:

1. Validate our tissue and serum biomarkers so as to develop a panel of markers that could distinguish patients with different pathological grades and features of disease which would better stratify them into appropriate treatment strategies.

2. Validate the epigenetic signature for the initial stages of prostate cancer which will identify sites of therapeutic manipulation to prevent both the initiation and progression of the disease.

3. Investigate the role of hypoxia in the regulation of resistance of the cancer to radiotherapy and chemotherapy.

Premier international journals will be targeted to increase the impact of PCRC research publications which again will be the measure of the Consortium’s success in addition to patents of new diagnostics with clinical utilisation.

Central to the success of the Consortium has been the PCRC bioresource. Recently the PCRC has been accepted by the Dublin Centre for Clinical Research (DCCR) as a Prostate Cancer DCCR Thematic Group, providing the infrastructure and the motivation to advance PCRC discoveries into the clinical arena. This collaboration will ensure the continued development of this vital resource supporting research nurses in each of the clinical sites and the continued development of the BIMS database which is key to linking the individual clinical and research sites.

For updates on the progress of the Consortium, check out https://pcrc.tchpc.tcd.ie

“Looking back over the genesis and initial achievements of the PCRC is the spur required to set ambitious goals for the next five years of the Consortium.”
We are extremely proud of our achievement of collecting tissue samples from 90 percent of radical prostatectomies at participating hospital sites.

We plan to triple the number of patients enrolled into the bioresource to over 1500. It has always been the vision of the Consortium to expand this valuable resource nationally. During the course of the next five years discussions with other interested institutes will be undertaken so as to establish a national bioresource in line with the Health Research Boards “Recommendations for the Establishment of a National Cancer Biobank”. We believe that the Consortium’s bioresource can act as a template to deliver this National Cancer Biobank and in so doing establish itself as a key player in the European Biobanking and Biomolecular Resource Research Infrastructure (BBMRI). This will allow Ireland to be a key contributor to international cancer research initiatives and also gain from international collaborations required to bring scientific discoveries from the bench into clinical utilisation.

The Consortium has recently received funding as part of the Molecular Therapeutics for Cancer Ireland, a Science Foundation Ireland-funded Strategic Research Cluster which aims to discover and develop new anti-cancer drugs. This represents an important collaboration in the area of therapeutic development and access to additional clinical collaboration in the area of oncology.

The PCRC will continue to nurture students and young researchers to fulfill their potential as future senior investigators and academic/clinical leaders and will develop, lead and contribute to educational initiatives in basic, translational and clinical.

Finally, recognising that our most important constituency is our patients, the PCRC will continue to engage with patients and patient advocates and seek to enhance outreach activities that will benefit the public.
Acknowledgements

“Most importantly we wish to thank all the patients that kindly agreed to participate in the bioresource and have allowed us to ‘build’ this prostate cancer collection.”

The Prostate Cancer Research Consortium (PCRC) comprises 22 senior investigators leading teams of clinicians and research scientists from four major Irish Hospitals; the Mater Misericordiae University Hospital, St Vincent’s University Hospital, St James’s Hospital, Beaumont Hospital and the Adelaide & Meath incorporating the National Children’s Hospital and four research institutions; Conway Institute of Biomolecular and Biomedical Research, University College Dublin; Institute of Molecular Medicine, Trinity College Dublin; RCSI-Education and Research Centre, Royal College of Surgeons in Ireland and National Centre for Sensor Research, Dublin City University.

In addition to the individual members of the Consortium already mentioned in the Report, there are a significant number of other clinical, pathological, nursing and scientific members that make up the Consortium. These professionals contributed greatly to different aspects of the bioresource and programme of research at its partner sites. We would therefore like to take this opportunity to thank them all sincerely for their outstanding contributions and for making the work of the Consortium so successful. We look forward to continuing these collaborations over the coming years.

We would also like to thank two of our key partners, the Irish Cancer Society and Molecular Medicine Ireland, and the other funding organisations for their peer review and generous funding of this initiative (please see Appendix 3).

Most importantly we wish to thank all the patients that kindly agreed to participate in the bioresource and have allowed us to ‘build’ this prostate cancer collection. They are contributing greatly to advances in the detection and treatment of this common male cancer on an international scale.
Highlights of PCRC
Prostate Cancer Research Consortium

Key Achievements 2004-2009

Creation of a vibrant inter-institutional, trans-disciplinary Consortium comprising 4 academic institutions and 4 affiliated hospitals

Recruitment 558 patients to the prostate cancer bioresource

Publication of over 30 articles in international peer review journals

Peer review grant funding of over €4m secured from 18 research grant calls

PCRC researchers received 19 awards recognising the quality of the research at national and international conferences

Creation of Bioresource Informatics Management System, the first in Ireland to receive a license from the Data Protection Commissioner

Publication of first survey of Irish men’s attitudes to cancer biobanking

Identification of novel biomarkers of early prostate cancer

Determination of epigenetic signatures of key processes in prostate cancer including hypoxia and apoptosis

Identification of novel markers of aggressive disease

Development of novel anti-cancer compounds and approaches that target the biology of the disease

Mentoring and training of 33 students at PhD and MD levels (18 completed, 15 in progress)
Appendix 1: PCRC International Visitors and Reviewers

In keeping with maintaining the highest international standards of the Consortium, we have undertaken to invite international leaders in the field of prostate cancer to visit and review the work of the Consortium.


January 2005: Professor David Neal: Professor of Surgical Oncology, Department of Oncology, University of Cambridge. http://www.oncology.cam.ac.uk/Neal.html


July 2008: Professor Alan Partin: David Hall McConnell Professor and Chair of the Department of Urology, John Hopkins University Hospital. http://urology.jhu.edu/about/faculty.php?id=57

Appendix 2: Details of Peer Review Publications by the PCRC

Fanning DM, Kay E, Fan Y, Fitzpatrick JM, Watson RW.
Prostate cancer grading: the effect of stratification of needle biopsy Gleason Score 4 + 3 as high or intermediate grade.
*BJU Int.* 2010 Mar 1;105(5):631-5
PMID: 19732053

Generation of an epigenetic signature by chronic hypoxia in prostate cells.

Fanning DM, Yue F, Fitzpatrick JM, Watson RW.
Novel predictive tools for Irish radical prostatectomy pathological outcomes: development and validation.

The HIF-1alpha C1772T polymorphism may be associated with susceptibility to clinically localised prostate cancer but not with elevated expression of hypoxic biomarkers.
*Cancer Biol Ther.* 2009 Feb 1;8(2). PMID: 19106642

Gill C, Dowling C, O’Neill AJ, Watson RW.
Effects of cIAP-1, cIAP-2 and XIAP triple knockdown on prostate cancer cell susceptibility to apoptosis, cell survival and proliferation.
PMID: 19549337

Perry AS and Lawler M.
The epigenome as a therapeutic target in prostate cancer.

Walsh S, Gill C, O’Neill A, Fitzpatrick JM, Watson RW.
Hypoxia increases normal prostate epithelial cell resistance to receptor-mediated apoptosis via AKT activation.
*Int J Cancer.* 2008 Apr 1;124(8):1871-8
PMID: 19142871

2D-DIGE as a Strategy To Identify Serum Markers for the Progression of Prostate Cancer.
PMID: 19093873

Hypoxia response element-driven cytosine deaminase/5-fluorocytosine gene therapy system: a highly effective approach to overcome the dynamics of tumour hypoxia and enhance the radiosensitivity of prostate cancer cells in vitro.
The tissue plasminogen activator gene promoter: a novel tool for radiogenic gene therapy of the prostate?
*J Gene Med.* 2008 Sep;10(9):1032-8. PMID: 18615772

Byrne JC, Downes MR, O’Donoghue N, Fitzpatrick JM, Dunn MJ, Watson RW.
Fasting status as a consideration for human serum collection and preparation prior to depletion and analysis.

Floyd MS Jr, Teahan SJ, Fitzpatrick JM, Watson RW.
Differential mechanisms of bicalutamide-induced apoptosis in prostate cell lines.

Marignol L, Coffey M, Lawler M, Hollywood D.
Hypoxia in prostate cancer: a powerful shield against tumour destruction?

Murphy TM, Perry AS, Lawler M.
The emergence of DNA methylation as a key modulator of aberrant cell death in prostate cancer.

Perry AS, Liyanage H, Lawler M, Woodson K.
Discovery of DNA hypermethylation using a DHPLC screening strategy.

Gill C, Walsh SE, Morrissey C, Fitzpatrick JM, Watson RW.
Resveratrol sensitizes androgen-independent prostate cancer cells to death-receptor mediated apoptosis through multiple mechanisms.
*Prostate.* 2007 Nov;67(15):1641-53. PMID: 17823925

Global mRNA analysis to determine a transcriptome profile of cancer stemness in a mouse model.

In silico mining identifies IGFBP3 as a novel target of methylation in prostate cancer.
*Br J Cancer.* 2007 May 21;96(10):187-94. PMID: 17453001

Low-level TOP2A amplification in prostate cancer is associated with HER2 duplication, androgen resistance, and decreased survival.

Healy DA, Hayes CJ, Leonard P, McKenna L, O’Kennedy R.
Biosensor developments: application to prostate-specific antigen detection.
Downes MR, Byrne JC, Pennington SR, Dunn MJ, Fitzpatrick JM, Watson RW.
Urinary markers for prostate cancer.
BJU Int. 2007 Feb;99(2):263-8. PMID: 17092277

Downes MR, Byrne JC, Dunn MJ, Fitzpatrick JM, Watson RW, Pennington SR.
Application of proteomic strategies to the identification of urinary biomarkers for prostate cancer: a review.

Perry AS, Foley R, Woodson K, Lawler M.
The emerging roles of DNA methylation in the clinical management of prostate cancer.
Endocr Relat Cancer. 2006 Jun;13(2):357-77. PMID: 16728568

Effects of the dual 5 alpha-reductase inhibitor dutasteride on apoptosis in primary cultures of prostate cancer epithelial cells and cell lines.
Cancer. 2006 Jun 15;106(12):2743-52. PMID: 16703599

O’Connor K, Gill C, Tacke M, Rehmann FJ, Strohfeldt K, Sweeney N, Fitzpatrick JM, Watson RW.
Novel titanocene anti-cancer drugs and their effect on apoptosis and the apoptotic pathway in prostate cancer cells.
Apoptosis. 2006 Jul;11(7):1205-14. PMID: 16699961

Topoisomerase II-alpha expression increases with increasing Gleason score and with hormone insensitivity in prostate carcinoma.

S. Townsend, WJ.J. Finlay, S. Hearty and O’Kennedy R.
Optimising recombinant antibody function in SPR immunosensing: The influence of antibody structural format and chip surface chemistry on assay sensitivity.
Biosensors and Bioelectronics. 2006 22, 268-274. PMID: 16487701

Watson RW, Fitzpatrick JM.
Targeting apoptosis in prostate cancer: focus on caspases and inhibitors of apoptosis proteins.
BJU Int. 2005 Dec;96 Suppl 2:30-4. PMID: 16359436

P. Dillon, A. Killard, S. Daly, P. Leonard and O’Kennedy R.
Novel assay format allowing the prolonged use of regeneration-based sensor chip technology.

Foley R, Hollywood D, Lawler M.
Molecular pathology of prostate cancer: the key to identifying new biomarkers of disease.
Endocr Relat Cancer. 2004 Sep;11(3):477-88. PMID: 15369449

Foley R, Lawler M, Hollywood D.
Gene-based therapy in prostate cancer.
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<td>2009-2014</td>
<td><strong>Professor John Crown</strong></td>
<td><strong>Professor Liam Gallagher, Dr Judy Harmey, Professor Joe Duffy, Professor William Watson</strong></td>
<td><strong>€5,600,000 (of which €510,000 granted to Professor William Watson for prostate cancer research, with access to further funding for core and support facilities)</strong></td>
</tr>
<tr>
<td>Unmasking epigenetic signatures in prostate cancer</td>
<td>Irish Cancer Society Career Fellowship</td>
<td>2009-2011</td>
<td><strong>Dr Antoinette Perry (Mentor Professor Mark Lawler)</strong></td>
<td></td>
<td><strong>€220,000</strong></td>
</tr>
<tr>
<td>Validation of Prostatic secretory proteins as Biomarkers of Prostate Cancer</td>
<td>British Urological Foundation</td>
<td>2008-2010</td>
<td><strong>Professor William Watson (UCD)</strong></td>
<td></td>
<td><strong>€74,000</strong></td>
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<td>Chronic hypoxia in the regulation of Prostate cancer resistance to apoptosis</td>
<td>British Urological Foundation</td>
<td>2008-2010</td>
<td><strong>Professor William Watson (UCD)</strong></td>
<td></td>
<td><strong>€46,000</strong></td>
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<tr>
<td>Biomarkers in Prostate Cancer, a programme of the Prostate Cancer Research Consortium</td>
<td>Cancer Research Ireland</td>
<td>2007-2010</td>
<td><strong>Professor Mark Lawler (TCD), Professor William Watson (UCD)</strong></td>
<td><strong>Professor Donal Hollywood (TCD), Professor John Fitzpatrick (UCD), Professor John O’Leary (TCD), Professor Elaine Kay (RCSI), Professor Richard O’Kennedy (DCU)</strong></td>
<td><strong>€660,000</strong></td>
</tr>
<tr>
<td>Identification of novel methylation biomarkers in prostate cancer</td>
<td>Cancer Research Ireland</td>
<td>2006-2009</td>
<td><strong>Professor Mark Lawler (TCD)</strong></td>
<td></td>
<td><strong>€220,000</strong></td>
</tr>
</tbody>
</table>
Title: Prostate cancer Informatics portal  
Grantee: Health Research Board  
Duration of Grant: 2006-2009  
Principal Investigator: Professor Jane Grimson (TCD)  
Co-investigator: Professor William Watson, Professor Mark Lawler  
Total value: €200,000

Title: Development of A National Centre for Advanced Medical (Functional) Imaging  
Grantee: HRB  
Duration of Grant: 2006-2011  
Principal Investigator: Dr Jim Meaney (St James’s Hospital)  
Co-investigator: Professor Donal Hollywood  
Total value: €4,000,000

Title: HRB equipment award – Cell Irradiation Facility  
Grantee: HRB  
Duration of Grant: 2005  
Principal Investigator: Professor Donal Hollywood  
Co-investigator: Professor Mark Lawler  
Total value: €250,000

Title: Proteomic analysis of urine from prostate cancer patients: translating the proteome to clinical biomarkers.  
Grantee: Cancer Research Ireland  
Duration of Grant: 2006-2009  
Principal Investigator: Professor William Watson (UCD)  
Total value: €172,000

Title: Effects of novel titanocene analogues on DNA stability and subsequent cell death in prostate cancer cells: Pre clinical evaluation  
Grantee: Science Foundation Ireland Research Frontiers Programme  
Duration of Grant: 2006-2009  
Principal Investigator: Professor William Watson (UCD)  
Co-investigator: Dr Matthias Tacke  
Total value: €172,000

Title: Automated system for antibody screening  
Grantee: Science Foundation Ireland  
Duration of Grant: 2005  
Principal Investigator: Professor Richard O’Kennedy (DCU)  
Total value: €500,000
<table>
<thead>
<tr>
<th>Title:</th>
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<tbody>
<tr>
<td>Development of sensor assay formats for PSA testing</td>
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<tr>
<td>Granting Body:</td>
<td>Enterprise Ireland</td>
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<tr>
<td>Duration of Grant:</td>
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<tr>
<td>Principal Investigator:</td>
<td>Professor Richard O’Kennedy (DCU)</td>
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<td>Total value:</td>
<td>€90,000</td>
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<tr>
<td>Altering the anti-apoptotic phenotype of prostate cancer cells by RNA interference</td>
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<td>Granting Body:</td>
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<td>Duration of Grant:</td>
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<td>Principal Investigator:</td>
<td>Professor William Watson (UCD)</td>
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<td>Total value:</td>
<td>€186,000</td>
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<tr>
<td>Development of new diagnostic, prognostic and therapeutic agents in prostate cancer; a programme of the Prostate Cancer Research Consortium</td>
<td></td>
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<tr>
<td>Granting Body:</td>
<td>Cancer Research Ireland</td>
</tr>
<tr>
<td>Duration of Grant:</td>
<td>2003-2006</td>
</tr>
<tr>
<td>Principal Investigator:</td>
<td>Professor Donal Hollywood, Professor Mark Lawler, Dr William Watson</td>
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<td>Total value:</td>
<td>€630,000</td>
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<th>Title:</th>
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<tr>
<td>Development of new procedures for the detection of Prostate Cancer</td>
<td></td>
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<tr>
<td>Granting Body:</td>
<td>Cancer Research Ireland</td>
</tr>
<tr>
<td>Duration of Grant:</td>
<td>2003-2006</td>
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<tr>
<td>Principal Investigator:</td>
<td>Professor Richard O’Kennedy</td>
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<td>Total value:</td>
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<tr>
<td>Molecular Biology of Prostate Cancer</td>
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<tr>
<td>Granting Body:</td>
<td>IRCSET</td>
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<tr>
<td>Duration of Grant:</td>
<td>2003-2006</td>
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<tr>
<td>Principal Investigator:</td>
<td>Professor Mark Lawler</td>
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<tr>
<td>Total value:</td>
<td>€60,000</td>
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<th>Title:</th>
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<tbody>
<tr>
<td>Selective activation of transgenes to enhance radiotherapy in prostate cancer</td>
<td></td>
</tr>
<tr>
<td>Granting Body:</td>
<td>HRB North South Grant</td>
</tr>
<tr>
<td>Duration of Grant:</td>
<td>2000-2003</td>
</tr>
<tr>
<td>Principal Investigator:</td>
<td>Dr Mark Lawler, Professor Donal Hollywood, Professor David Hirst, Dr Tracey Robson</td>
</tr>
<tr>
<td>Total Value:</td>
<td>€180,000</td>
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</table>

In addition the PCRC have active industrial collaborations with the following companies in the area of Prostate Cancer Research:
- Affymetrix
- Almac
- Applied Biosystems
- Astra Zeneca
- GSK
Appendix 4: Awards to Members of the PCRC

Ms Deirdre Fanning (UCD)
O’Connell Medal for Oncology, University College Dublin, October 2009, Dublin, Ireland
“Validation of a novel panel of pre-operative serum-based prostate cancer predictive markers for pathological outcome”

Ms Deirdre Fanning (UCD)
Best presentation. Irish Society for Urology, October 2009, Galway Ireland,
“The development of an Irish Partin table nomogram for predicting outcome for the treatment of prostate cancer”

Ms Lynn Martin (TCD)
Best Poster Award Association for Radiation Research Annual Meeting, June 2009 Glasgow, Scotland.
“Processing of O6MeG lesions by the mismatch repair system may represent a novel mechanism for Low-Dose Radiation Hypersensitivity”

Dr Antoinette Perry (TCD)
Best Poster Award 7th International Cancer Conference, May 2009, Dublin, Ireland
“Investigating promoter methylation of wnt signalling antagonists in prostate cancer”

Ms Gillian O’Hurley (RCSI)
Best Poster Award 7th International Cancer Conference, May 2009, Dublin, Ireland
“Zinc-a-2-glycoprotein is a potential biomarker of Prostate Cancer”

Dr Laure Marignol (TCD)
St Lukes Young Investigator Award, Royal College of Physicians in Ireland, January 2009, Dublin, Ireland
“Hypoxia in prostate tumours: detection, consequences and clinical exploitation”

Ms Deirdre Fanning (UCD)
AstraZeneca International Scholar-in-Training Award, American Association for Cancer Research – Advances in Prostate Cancer Research January 2009, San Diego, USA
“Validation of a novel panel of pre-operative serum-based prostate cancer prognosticators”

Ms Therese Murphy (TCD)
Best Presentation Cancer Genomics MasterClass, December 2008, Dublin, Ireland
“Investigating epigenetic regulation of apoptosis controlling genes in prostate cancer”

Ms Gillian O’Hurley (RCSI)
Best Poster Award RCSI Research Day, June 2008, Dublin, Ireland
“Tissue validation of potential biomarkers for Prostate Cancer”

Dr Omer Raheem (TCD)
Best Poster Award, CANCER 2008 The 6th International Cancer Conference, May 2008, Dublin, Ireland
“Investigation into methylation of the secreted frizzled related proteins (SFRPs) family of wnt antagonists in prostate cancer”
Dr Michelle Downes (UCD)
Best Poster Award, 7th World Basic Urological Research Congress, September, 2007, Dublin Ireland.
“Determination of novel urinary biomarkers of prostate cancer using a “D-DIGE proteome platform”

Ms Laure Marignol (TCD)
Best Poster Award, 9th Institute of Molecular Medicine Meeting, November 2007, Dublin, Ireland
“Exploiting a hypoia driven suicide gene therapy approach to kill prostate cancer cells”

Ms Laure Marignol (TCD)
Winner, Young Investigator Award, The Association of Radiation Research Annual Meeting, March 2007 Belfast, NI
“Development of a novel hypoxia-inducible gene therapy strategy for prostate cancer”

Ms Lynn Martin (TCD)
Best Poster Award, Association for Radiation Research, April, 2007 Belfast, N Ireland
“Delivery sequence of partial radiation fractions alters survival response in prostate cancer cells in vitro”

Professor Mark Lawler (TCD)
Recipient of the Graves Medal (Royal Academy of Medicine in Ireland and Health Research Board, 2004)

Ms Antoinette Perry (TCD)
Best Oral Presentation, Irish Association for Cancer Research, April 2006, Galway, Ireland
“Promoter hypermethylation of IGFBP3 is an early event in prostate cancer”

Dr Sinead Walsh (UCD)
Best Oral Presentation and Medal winner, Annual Meeting of the Irish Society Of Urology, September, 2004, Galway, Ireland
“Identification of Novel Genes Associated with Apoptotic Resistance in Prostate Cancer Progression”

Ms Ruth Foley (TCD)
Best Poster Award, Irish Association for Cancer Research March 2003, Kilkenny, Ireland.
“Development of a Tissue-Specific Suicide Gene Therapy approach for Prostate Cancer”

Professor Mark Lawler (TCD)
Awarded FRCPath on the basis of published works (2006)
Appendix 5: Graduate Student Training in the PCRC

**PhD Students**  6 Awarded / 9 in Progress

<table>
<thead>
<tr>
<th>Student:</th>
<th>Project title:</th>
<th>Status:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Ruth Foley (TCD)</td>
<td>Development of a prostate-specific gene therapy approach for prostate cancer</td>
<td>PhD Awarded 2006</td>
</tr>
<tr>
<td>Dr Antoinette Perry (TCD)</td>
<td>Investigating DNA methylation biomarkers for the early detection of prostate cancer.</td>
<td>PhD Awarded 2007</td>
</tr>
<tr>
<td>Dr Laure Marignol (TCD)</td>
<td>Role of hypoxia in prostate cancer</td>
<td>PhD Awarded 2007</td>
</tr>
<tr>
<td>Dr Sinead Walsh (UCD)</td>
<td>The role of apoptosis and its regulation in early stage prostate cancer</td>
<td>PhD Awarded 2007</td>
</tr>
<tr>
<td>Dr Ann Maria McCrohan (UCD)</td>
<td>The effects of dutasteride on prostate cancer cell apoptosis and mechanisms of resistance.</td>
<td>PhD Awarded 2007</td>
</tr>
<tr>
<td>Dr Jennifer Byrne (UCD)</td>
<td>A proteomic approach to identify molecular markers for progression in prostate cancer</td>
<td>PhD Awarded 2008</td>
</tr>
<tr>
<td>Ms Atieh Zaeazadeh (TCD)</td>
<td>Sample Identification and Tracking in Bio-repositories</td>
<td>Submitted 2009</td>
</tr>
<tr>
<td>Ms Therese Murphy (TCD)</td>
<td>Investigation of DNA methylation as a key modulator of aberrant cell death in prostate cancer</td>
<td>Final Year PhD</td>
</tr>
<tr>
<td>Mr Matthew DiFranco (UCD)</td>
<td>Automated Detection and Grading of Prostate Cancer in Digital IHC Slides</td>
<td>Final Year PhD</td>
</tr>
</tbody>
</table>
Student: Ms Sandra Cuffe (UCD)
Project title: Effects of novel titanocene analogues on DNA stability and subsequent cell death in prostate cancer cells
Status: Final Year PhD

Student: Mr Yue Fan (UCD)
Project title: Multivariate analysis integrating metabolomic and proteomic patient data in prostate cancer.
Status: 3rd Year PhD

Student: Ms Yvonne Salley (TCD)
Project title: MicroRNA profiling in prostate cancer and prostate cancer stem/progenitor cells
Status: 3rd Year PhD

Student: Ms Gillian O’Hurley (RCSI/DCU)
Project title: Evaluation of novel targets as prognostic/predictive biomarkers in Prostate Cancer
Status: 3rd Year PhD

Student: Ms Lynn Martin (TCD)
Project title: Mechanisms and Clinical Implications of Low-dose hyper-radiosensitivity
Status: 3rd Year PhD

Student: Ms Alice Vajda (TCD)
Project title: Targeting hypoxia in prostate cancer
Status: 2nd Year PhD

MD/MCh/MSc Students 12 Awarded / 6 in Progress

Student: Mr Michael John Floyd (UCD)
Project title: Apoptotic priming strategies for the treatment of Prostate cancer
Status: MCh Awarded 2005

Student: Mr Rustom Manecksha (TCD)
Project title: Investigating Prostate cancer progression to androgen independence
Status: MD Awarded 2006
<table>
<thead>
<tr>
<th>Student</th>
<th>Project title</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mr Kevin Michael O’Connor (UCD)</td>
<td>Novel titanocene anti-cancer drugs and their effects on apoptosis in androgen independent prostate cancer cells.</td>
<td>MCh Awarded 2006</td>
</tr>
<tr>
<td>Mr Haradikar Varadaraj (TCD)</td>
<td>Exploration of molecular changes in the androgen receptor gene and prostate cancer progression</td>
<td>MD Awarded 2007</td>
</tr>
<tr>
<td>Mr Ivor Cullen (TCD)</td>
<td>The role of the C1772T SNP in the HIF-1α gene in patients with localised prostate cancer.</td>
<td>MCh Awarded 2007</td>
</tr>
<tr>
<td>Ms Michelle Rose Downes (UCD)</td>
<td>Proteomic analysis of voided urine in a prostate cancer cohort</td>
<td>MD Awarded 2008</td>
</tr>
<tr>
<td>Mr Arun Thomas (TCD)</td>
<td>Studying hypoxia markers in prostate cancer</td>
<td>MCh Awarded 2008</td>
</tr>
<tr>
<td>Mr Frank D’Arcy (TCD)</td>
<td>The role of RNASEL SNPs and XMRV infection in prostate cancer</td>
<td>MCh Awarded 2008</td>
</tr>
<tr>
<td>Ms Mary Dillon (DCU)</td>
<td>Antibody-based biosensor assays for the detection of zilpaterol and markers for prostate cancer</td>
<td>MSc Awarded 2008</td>
</tr>
<tr>
<td>Dr Omer Raheem (TCD)</td>
<td>Investigating methylation of SFRP family of Wnt antagonists in prostate cancer</td>
<td>MCh Awarded 2009</td>
</tr>
<tr>
<td>Dr Deirdre Fanning (UCD)</td>
<td>Discovery and Validation of Prostatic Secretory Proteins as Biomarkers of Prostate Cancer</td>
<td>MD Awarded 2009</td>
</tr>
</tbody>
</table>
Student: Dr Catherine Dowling (UCD)
Project title: Characterisation & Manipulation of Hormone Refractory and Chemo-resistant Prostate Cancer
Status: MD Awarded 2009

Student: Dr Ciara Barrett (TCD)
Project title: Investigation of the role of lipid metabolism gene pathways in prostate cancer
Status: 1st Year MD

Student: Ms Lisa Smyth (UCD)
Project title: Chronic Hypoxia in the regulation of prostate cancer resistance to apoptosis
Status: 2nd Year MD

Student: Mr James Forde (TCD)
Project title: The role of HIF-1α and hypoxia in preferential response of prostate tumours to microtubule-disrupting agents
Status: MD Submitted

Student: Mr Derek Hennessy (TCD)
Project title: The impact of the tumour microenvironment on the α/β ratio of prostate tumours and treatment failure after radiotherapy
Status: 1st Year MD

Student: Mr John Keane (TCD)
Project title: Calpain activation interacts with the androgen receptor pathway to promote prostate cancer progression
Status: 1st Year MD

Student: Mr Sheng Oon (UCD)
Project title: Validation of a novel panel of biomarkers for pathological features of prostate cancer
Status: 1st Year MD