Urine: Liquid Gold for Prostate Cancer Detection and Monitoring

Written by Antoinette Perry PhD

UCD epiCaPture team: Dr Antoinette Perry, Asia Jordan and Adele Connor. Photograph taken by Vincent Hoban (Vincent.hoban@ucd.ie).

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Dr Antoinette Perry is Assistant Professor of Cell Biology and Genetics at the School of Biology and Environmental Science, UCD. She trained at Trinity College Dublin, where she studied Human Genetics, before undertaking a PhD and has worked in the field of prostate cancer for more than 15 years. Her research focuses on translational prostate cancer epigenetics; understanding the role of epigenomic aberrations in the pathogenesis of prostate cancer and harnessing these aberrations to develop prognostic and predictive biomarkers. Dr Perry has a particular interest in studying DNA methylation changes in "liquid biopsies" that can act as surrogates for non-invasive tumour detection and monitoring. Her research has also highlighted the importance of epigenetic dysregulation of the Wnt and IGF axis in prostate cancer, and has identified a number of potential biomarkers for aggressive disease. Other research avenues involve the exploration of chemopreventive and therapeutic properties of marine and terrestrial plant compounds. Dr Perry's research is supported by the Irish Cancer Society, Movember, Science Foundation Ireland, Enterprise Ireland, the Irish Research Council, the Health Research Board and the Prostate Cancer Foundation.

Prostate cancer is the most common non-skin cancer in men in Ireland and the Western world. More than 1.1 million new cases are diagnosed annually, approximately 3,500 of which are in Ireland.[1]

Prostate cancer is on the rise, overtaking colorectal cancer, and is now the second most common cause of male cancer deaths in Europe, killing 108,000 men in 2018.[2] In Ireland, more than 500 men die every year from this disease.[1] Today there are more than 35,000 men living with prostate cancer in Ireland and it's estimated that 1 in 7 men will develop this cancer by the age of 85. As well as being potentially lethal, the disease and its treatments can cause a range of co-morbidities, emotional and social difficulties for patients and their families. Research into the causes, prevention, detection and treatments of prostate cancer is needed to reduce the pain and suffering from this prevalent, often chronic, disease.

For several years, November has become fondly known as MOvember, due to a global initiative involving the growing of moustaches (or MOs) throughout the month to raise awareness of men's health issues including, but not limited to, prostate cancer.[3] An estimated 5 million MOs have been grown around the world since 2003, funding 1,250 men's heath projects, including a number of research projects carried out by scientists and urologists in Ireland. The success of Movember is phenomenal, not only because of the funds raised and collaborative research supported, but also because it has made it socially acceptable to talk openly about prostate cancer and the importance of getting checked early. On MOvember 17th this year, the European Association of Urology is hosting Prostate Cancer Awareness day, via a free online event.[4]

For most men, their journey with prostate cancer begins with a PSA (prostate specific antigen) blood test. While the PSA test has been the gold standard for prostate cancer detection for almost 30 years, it has numerous limitations. It is not specific to prostate cancer; only 25% of men with a PSA >4ng/ml (upper normal limit) are diagnosed with cancer, while the remaining 75% undergo unnecessary invasive transrectal biopsies. Conversely, cancer is also sometimes detected in men with PSA levels <4ng/ml.[2] In those men diagnosed with cancer on biopsy, recent

estimates of overtreatment levels are as high as 67%, due to the high prevalence of slow growing indolent tumours that are unlikely to ever impact a patient's life. This over-diagnosis and over-treatment is not economically viable and causes severe co-morbidities and anxiety for patients.

The availability of multiparametric Magnetic Resonance Imaging (mpMRI) has made a substantial impact on the diagnostic paradigm of localised prostate cancer. Performance of mpMRI before prostate biopsy can improve detection of a higher proportion of clinically-significant tumours compared to random needle biopsies. Evidence suggests that mpMRI can reduce the over-diagnosis of insignificant disease by at least 10% and lead to a 30% reduction in the number of unnecessary biopsies.[2]

Apart from PSA and imaging developments, several molecular biomarkers in liquid biopsies (such as blood and urine) are showing great promise as non-invasive prognostic tools to help stratify patients and identify those men who require a biopsy to histologically diagnose and grade their disease. Urine has been shown to be more sensitive than blood in the early detection and recurrence of urogenital cancers (it is also easier and cheaper to obtain) and so has been the focus of a lot of research into prostate cancer biomarkers. Research in my lab is focusing on urinary biomarkers to improve the early detection of aggressive prostate cancer, while it is still gland confined and potentially curable. Notably, one of the first Global Action Plans initiated by Movember was a prostate cancer urinary biomarker consortium, whose aim was to develop non-invasive biomarkers for aggressive disease. Stemming from this international research partnership, my team at UCD have worked with doctors, nurses, patients and other scientists from around Ireland, the UK, USA and Canada to study urine from almost 500 men. We showed that almost 90% of men with aggressive prostate cancer have changes in their DNA that we could find in their first-void urine following a digital rectal examination. These changes were absent in aged healthy men and men with low-grade disease.[5, 6] Our *in vitro* diagnostic currently in development (epiCaPture) is a prognostic multi-marker qPCR test, which detects changes in DNA methylation at the regulatory regions of six growth regulatory genes involved in prostate cancer. Current research is focusing on a clinical verification of epiCaPture in a large independent cohort, in order to reproduce the results and improve performance by integrating clinical features, such as PSA and patient age.

Further research and prospective clinical trials will determine whether the integration of epiCaPture with the current standard of care, PSA and potentially mpMRI might ultimately serve to provide a simple, accurate, non-invasive approach to triage/screen men at risk of prostate cancer. The goal being to enable early detection and curative action for aggressive disease, whilst sparing the

majority of men the anxiety and long-term effects of unnecessary invasive biopsy and treatment for clinically indolent disease.

In conjunction with technical development of the epiCaPture test in my lab, we are also leading a public-patient outreach project, IMPROVER (Involving men with prostate cancer in engaged research), working with two national cancer charities, the Irish Cancer Society and Breakthrough Cancer Research. We want to engage with key opinion leaders and end-users, including patients living with prostate cancer, patient advocate groups, nurses, doctors (urologists and GPs), hospital managers, health insurers and relevant charity organisations to firstly ensure that development of epiCaPture addresses the unmet needs of each sector, and secondly, to feed-forward end-user opinion into key decision steps in the development of epiCaPture.

If you would like to know more about the epiCaPture or IMPROVER projects or are interesting in getting involved, please contact Dr Antoinette Perry on Antoinette.perry@ucd.ie

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Breast Cancer

Potential new treatment approach for Breast Cancer

A new study by Irish researchers may pave the way to developing a more effective means of treating patients with the most common form of breast cancer.

The promising findings are described in a paper published in the leading journal "Cancer Research", a journal of the American Association for Cancer Research, in a study headed by researchers from RCSI University of Medicine and Health Sciences, and UCD, who led an international team of colleagues from the Netherlands Cancer Institute and Oxford University, among others.

Up to three-quarters of breast cancer patients are diagnosed with what is known as the 'hormone receptor-positive' form of the disease, which affects more than 2,000 women each year in Ireland. While existing hormone receptor-targeting therapies such as tamoxifen are effective for many patients, some do not respond to the treatment or prove resistant to it if their cancer returns. Ultimately, almost half of patients receiving hormone treatments experience a relapse of their disease, and researchers are urgently looking for new treatment options for these patients.

The research team, co-led by Prof Darran O'Connor from RCSI and Prof William Gallagher from UCD, discovered a potential new treatment approach for patients who are resistant to hormone therapy. The study found that a protein called 'USP11' plays a central role in the growth of hormone receptor-positive breast cancer cells, and that targeting this protein may provide a new form of treatment to help stop this growth in a way never attempted previously.

Although studies remain at an early stage, it is hoped this finding could eventually help prompt a significant step forward in treatment options for patients for whom existing hormone therapy has proven unsuccessful.

The study is a result of the Irish Cancer Society-funded BREAST-PREDICT programme which brought experts from around the country together to work on breast cancer research projects. Some of the programme's activities are continuing as part of the ground-breaking Precision Oncology Ireland consortium of 5 universities, 8 companies, and 6 charities, including the Irish Cancer Society, which aims to develop new diagnostics and therapeutics for personalised cancer treatment.