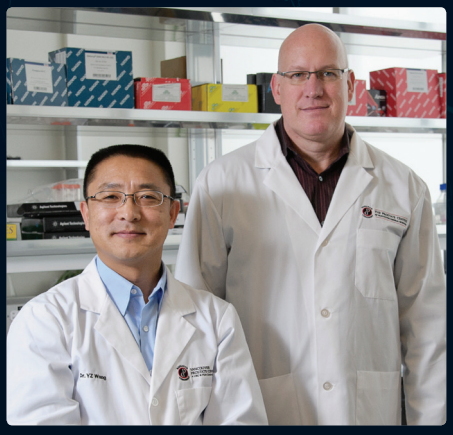
The detection and management of cancer is poised for a revolution. At the forefront are **Drs Colin Collins** and **Yuzhuo Wang** who outline how their unique and translational studies are changing the face of cancer research

Getting personal with cancer treatment



Why is oncology poised for a revolution in the detection and management of cancer, and how might your work contribute to this breakthrough?

The sequencing of tumour genomes and transcriptomes is rapidly revealing the genomic landscapes of cancer. In turn, the various and distinct subtypes of each cancer are being delineated, as well as the mechanisms driving their initiation and progression. This knowledge is leading to the identification of biomarkers and therapeutic targets. And the pace is accelerating due to the confluence of clinical science, massively parallel sequencing and computer science.

The addition of patients' tumours growing in murine hosts enables rapid prediction and testing of therapies in the setting of personalised oncology. At the same time, such patient-derived xenograft models provide a uniquely powerful platform for discovery of new therapeutic targets and their validation. The same system allows for cost-effective, multi-tiered drug development of single agents and combinatorial strategies.

What proportion of cancer patients do not benefit from current anticancer regimens, would you say?

Unfortunately, many cancer therapies ultimately fail due to adaptive response and the evolution of resistant clones; consequently, cures remain elusive. The challenge is to bottleneck the cancer so that patients live with the disease and do not die of it, just as is the case with HIV now. Prostate cancer serves as an informative example. It is a complex disease of the genome driven by evolutionary pressures so that it manifests and progresses differently in each patient, and we believe that personalised therapy will improve outcomes by allowing tailored therapies to attack targets specific to each patient.

What sets your study apart from conventional diagnostic and therapeutic approaches?

The combination of next-generation sequencing (NGS) of a patient's tumour to predict a therapy, then functionally test that drug on the patient's tumour in mice is unique and timely. Most excitingly, the experimental efficacy results are particularly well correlated with patient outcomes.

How would quantitative genomics take full advantage of this system for drug development and personalised oncology?

It is becoming routine to sequence tumour genomes and transcriptomes. This process, coupled with computer science, enables identification of all sequence variants and mutations in the tumour. Sequencing the transcriptome makes quantitative analysis of gene expression possible, and identification of novel isoforms resulting from alternative splicing. Pathway and subnetwork analyses can then place all of these into signalling pathways and protein interaction subnetworks.

In terms of drug development, the identification of mutated genes, gene fusions, aberrantly expressed genes and, most interesting to us, splice variants can form the basis of targets for new therapeutics. Because exon splice variants introduce novel domains into proteins, these offer the possibility of tumour-specific or restricted targets that can be specifically pinpointed with therapeutic antibodies, antisense and small molecules.

You and your collaborators at the BGI (formally Beijing Genome Institute) are exploring development of a joint institute. What are the implications for prostate cancer treatment and cancer therapies on the whole?

BGI is the largest genome center in the world and the VPC is a leading translational prostate cancer center with very large tissue banks, unique living tumour bank, a large patient population, and an efficient discovery pipeline. Together BGI and the VPC have an opportunity to combine their complementary strengths to focus on and accelerate translational oncology and personalised medicine.

Finally, could you offer a snapshot of the key findings you have made to date?

Following surgery, a patient's neuroendocrine prostate tumour was analysed using NGS. A xenograft model was also generated from the tumour. Both the patient's original tumour and the tumour-derived xenograft had a homozygous deletion on chromosome 9p21 spanning the 5'-deoxy-5'-methylthioadenosine phosphorylase (MTAP) gene. Deletion of the MTAP gene occurs in a wide range of common tumours at frequencies ranging between 10-70 per cent. We then combined methylthioadenosine (MTA) and high 6-thioguanine (6-TG) to treat the mice bearing the xenografts. The treatment caused regression of the MTAP-deficient neuroendocrine tumour; they were also protected from toxicity by MTA from 6-TG. Subsequently, we discovered that about 10 per cent of human prostate cancers carry deletions of the MTAP locus and/or express decreased levels of MTAP mRNA, and this is a prognosticator for shorter disease-free survival.

The elusive 'Holy Grail'

Following vital breakthroughs in genomics, a collaborative study at the **Vancouver Prostate Centre** in Canada is using patient-derived xenograft models to test personalised and combinatorial treatment strategies – the elusive Holy Grail of oncology

CANCER IS A DISEASE of the genome driven by evolution, and research is revealing that substantial structural and genetic variations exist – even within the same tumour. Consequently, it is increasingly recognised that patients are receiving incongruous treatments that are unable to target the specific molecular characteristics of the malignant growth.

The complexity of tumour management is exemplified in the fight against prostate cancer. Representing the most common cancer for men, particularly in older age, it is estimated that half of the male population over 60 years old have cancer cells in their prostate. Despite this alarming statistic, the disease will often stay dormant for a number of years and commonly develops very slowly. In these cases, patients may be able to live with the cancer and delay, or even avoid, therapy.

As with other cancers, there are numerous forms – or subtypes – of prostate cancer, however, including particularly aggressive types. Each has its own pathology, growth dynamic and genome structure, and all respond differently to the various treatment modalities. Identifying the safest and most effective treatment option therefore presents a significant challenge. This combination of factors means that prostate cancer research provides investigators with an important platform from which to explore and evaluate recent innovations in genomics – studies which can both lead to the development of cutting-edge tumour modelling technologies and drive radical new approaches to cancer treatment.

A MODEL PARTNERSHIP

Drs Colin Collins and Yuzhuo Wang are two leading scientists in the oncology field who have forged a working partnership that is it as the forefront of a revolution in cancer research. United by a shared passion for treating prostate cancer, the two researchers were drawn to the Vancouver Prostate Centre (VPC) at the University of British Columbia (UBC) in Canada because of its state-of-the-art infrastructure, visionary leadership and clinical excellence. Collins is Director of The Laboratory for Advanced Genome Analysis at the VPC and Professor in the Department of Urologic Sciences at UBC; while Wang is an Associate Professor at UBC, VPC Senior Scientist and founder of the Living Tumor Laboratory. Their combined expertise is paving the way for personalised oncology.

Wang has dedicated much of his career to developing unique methods for growing human tumours in mice. Known as patient-derived xenografts, the patient's own tumour is grafted into immune-compromised mice. These 'high fidelity' mouse models retain the same genomic and pathological profiles as the donor tumour, opening the door for testing personalised and even combinational drug therapies predicted to be efficacious from the tumour's sequence. The possibility of these 'tailored' treatment options is coming to fruition thanks to recent leaps in genomics.

A REVOLUTION

In 2003, preceding the advent of next-generation DNA sequencing (NGS), Collins and his colleague Dr Stanislav Volik invented paired-end sequencing (PES). By sequencing just the two ends of a DNA molecule, PES provides enough sequence information to map the partially sequenced DNA molecule onto a fully sequenced reference genome. PES has emerged as the predominant method used in NGS. Defined as translational genomics, Collins' work incorporates mathematics, computer and clinical science. This interdisciplinary approach enables him to build on Wang's xenograft system to accurately identify the specific genomics of the tumour and, in turn, predict single agent and combinational therapeutics that might target the cancer in question. Collins expands on the pair's collaborative work: "When I was recruited to the VPC, I directed a portion of my start up funds to sequence the genomes and transcriptomes of Dr Wang's models, and to characterise them in depth using a combination of computer science and bioinformatics. Together, we have a tremendous and palpable synergy that inspires and accelerates our research".

It is this very synergy that is making waves in the field of oncology. By deciphering the genome sequence of the patient's tumours and the matched high fidelity xenografts, Collins is able to identify abnormalities that provide growth and survival advantages for the tumour. Moreover, through his ability to simultaneously sequence and examine all of the estimated 23,000 coding genes, the investigators are able to analyse gene mutations, gene expression, as well as uncover gene fusions and amplified or deleted genes that can form the basis of therapies. The duo believe their work will accelerate the coming revolution in cancer treatment, when it will be possible to give the right therapy to the right patient at the right time.

> The scientists foresee a future where patient tumours will be sequenced, as well as grown in mice, to select and test the most appropriate treatment

THE HARD GRAFT

Wang is the first scientist to have grown 'prostate needle biopsies' from different regions of the prostate by taking several small samples of tissue from the prostate gland. The technique allows the heterogeneity in tumour foci, from benign to aggressive, to be characterised and understood. He has grown five biopsies from a single cancerous prostate, each displaying different characteristics, which is of great significance, as Wang explains: "Patient stratification is important because some men can safely live with their cancer whereas others require aggressive intervention and biopsies are a critical component of this. It is essential that heterogeneity is functionalised to improve prognosis and thus stratification. Moreover, we are convinced that the genomes and transcriptomes of the grafted biopsies will reveal key mechanisms of progression for prostate cancer".

Crucially, the unique mice models allow the team to accurately determine the mechanisms behind the development of resistance of tumours to therapy, and to test the effectiveness of existing and experimental single agent or combinational therapeutics that can be predicted from their results. Presently, the researchers are identifying numerous potential drug targets and, as Wang elucidates, their research has room for wider scope: "We can leverage knowledge from other tumour types that share common targets and mechanisms because it is becoming clear that some drugs work across tumour types and should be considered to be 'broader spectrum'."

BRAVE NEW WORLD

The scientists foresee a future where patient tumours will be sequenced, as well as grown in mice, to select and test the most appropriate treatment sanctioned by the US Food and Drug Administration (FDA), or the most appropriate clinical trial. This means many patients will avoid toxic and sometimes painful therapies that provide no benefit. Certainly, their work is already moving in this direction. For example, sequencing the tumour from a patient with prostate cancer suggested an experimental therapy based on the absence of a gene. This experimental strategy worked well when tested on the patient's tumor growing in the mouse. In another example, the researchers uncovered a potential treatment for a woman diagnosed with ovarian cancer, which has yet to be approved: "Sequencing revealed the tumour to be a relatively rare subtype that expresses a receptor, which can be targeted by a therapeutic antibody that is currently under review for approval by the FDA. Accordingly, the patient could possibly benefit from this finding," elaborates Collins.

By combining NGS of patient tumours with functional drug testing in the matched patient-derived tumour xenografts, Wang and Collins' believe that their ability to quickly turn around experimental efficacy results will ultimately expand the repertoire of available therapies, and improve patient outcomes and quality of life. Moreover, the xenografts are leading the way for combinatorial therapeutics, which the two scientists describe as "the elusive Holy Grail of oncology. Just as with HIV, which requires a cocktail of drugs, cancer will similarly require a combination of therapies to contain it".

INTELLIGENCE

COMBINING SEQUENCE-BASED MOLECULAR PROFILING OF PATIENT TUMOURS WITH PATIENT-DERIVED TUMOURS IN MICE FOR ADVANCING PERSONALISED ONCOLOGY

OBJECTIVES

To identify new biomarkers for improved diagnosis and prognosis of human cancers, including cancers of the prostate, bladder, ovary, kidney and lung; and to develop novel, more effective therapies for cancer based on personalised oncology – tailoring the right drug to the right patient at the right time.

KEY COLLABORATORS

Dr Martin Gleave, **Dr Larry Goldenberg**; **Dr Paul Rennie**; **Dr Kim Chi,** Vancouver Prostate Centre • **Dr Marco Marra**, Canada's Michael Smith Genome Sciences Centre • **Dr Jun Wang**; **Yingrui Li**, BGI • **Dr Cenk Sahinalp**, Simon Fraser University

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DR COLIN COLLINS is a Professor at the University of British Columbia (UBC) and Senior Scientist at the Vancouver Prostate Centre where he directs The Laboratory for Advanced Genome Analysis (LAGA).

DR YUZHUO WANG has a dual appointment as a Senior Scientist at the Vancouver Prostate Centre and the BC Cancer Agency. He is also an Associate Professor at UBC, and founder of the Living Tumor Laboratory.