A pain in the neck

Expert molecular biologist and cancer researcher Dr Muy-Teck Teh shares his opinions on the field and gives details of his work towards developing early warning systems for head and neck cancer.

How did you develop an interest in head and neck cancer?

Cancers of the head and neck are among the most challenging cancer types to deal with, as they affect the most important part of our body. The head and neck region is made up of some highly complex anatomical structures and organs. Surgical treatment often leads to debilitating consequences that not only affect one’s key physiological functions – such as feeding, speech and vision – but may also destroy the face, disrupting one’s personal identity. Hence, it can be a highly devastating disease both physically and mentally for many cancer patients. Early treatment intervention can lead to significant improvements in patient morbidity and long-term reductions in healthcare cost.

Could you introduce the ‘cancer stem cell’ hypothesis and explain how it relates to your work?

The cancer stem cell hypothesis states that a tumour is created and sustained by a subpopulation of stem cells with the ability to proliferate indefinitely. My work has found that forkhead box protein M1 (FOXM1) plays an important role in controlling a stem cell’s ability to proliferate. We have used a 3D organotypical culture system to demonstrate that FOXM1 stimulates hyperproliferation by inducing stem cell proliferation, resulting in a pathological phenotype resembling hyperplasia – a premalignant condition prior to cancer initiation.

What efforts have you made to develop a clinically useful tool or drug that targets FOXM1 expression?

My research mainly focuses on finding biomarkers to spot cancer early; therefore, my priority has been on understanding the mechanism of cancer initiation. As FOXM1 is essential for normal cell cycle function and cell fate determination, simply eliminating FOXM1 will also kill normal cells due to nonspecific toxicity. The key objective is either to target the oncogenic signals triggered by FOXM1 or to prevent FOXM1 from overactivation.

In 2009, you led a study that made headlines due to its finding that nicotine may be linked with mouth cancer. What is the impact of this study?

The finding that FOXM1 can be activated by nicotine led the manufacturers of tobacco...
cessation products such as nicotine gum to re-examine the nicotine doses in their products. This discovery also helped promote anti-smoking campaigns around the world, and sparked the development of a FOXM1 diagnostic test (qMIDS) for head and neck cancer diagnosis and prognosis.

Can you outline the primary challenges associated with the effective translation of basic science into clinical application? How can these difficulties be circumnavigated?

The primary challenges of bench-to-bedside research development are that a tool or drug must have high clinical demand, be backed up by a robust science, have proven clinical benefit over conventional methods and bring cost saving advantages. These challenges can be compensated to some extent; for example, a niche product may be compensated by having a high clinical value or benefit, and vice versa.

What barriers must be overcome if we are to successfully enter an era of personalised medicine based on a combination of patients’ genetic, epigenetic and gene expression signatures?

The greatest barrier at the moment is finding a robust, accurate and sensitive biomarker, or biomarkers, in a highly heterogeneous disease – cancer. In addition, we also have a challenge to tailor specific treatments to patients following molecular diagnosis. Having a test alone is useless unless we can provide patients effective treatment options according to their test results.

To what extent do your investigations rely on cutting-edge techniques and technologies?

As we are currently investigating the potential of detecting epigenetic biomarkers in saliva samples, we are constantly looking into novel techniques and technologies to advance the field of biomarker detection in small biological specimens.

Are there any forthcoming events, conferences or workshops related to your work that you would like to highlight? Do you have any future projects in the pipeline?

We will be hosting workshops in China to promote international collaboration and translation of research work to the clinic using qMIDS as an example. We aim to expand our international collaboration network to facilitate the translation of basic research into clinical benefits.

Additionally, we are working on future projects that will focus on finding and validating genetic, epigenetic and gene expression markers in saliva samples, with the ultimate aim of developing a non-invasive screening test for detecting cancer in asymptomatic individuals.

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CANCER IS OFTEN an unpredictable affliction for individual patients, and even in general terms, many elements of its initiation and progression are still not very well understood. However, one thing is certain: medical professionals are better able to deal with cancer the earlier it is caught. For example, when patients with head and neck cancer are diagnosed and treated at early stages of the disease, their five-year survival rates increase significantly from less than 20 per cent to over 80 per cent. As a disease, cancer is highly heterogeneous and difficult to treat at late stages – but this problem could be alleviated by focusing on early detection and prevention.

The key to both early diagnosis and the eventual development of preventive methods is identifying molecules associated with oncogenesis. Over the last few years, many proteins have been implicated in the development and growth of various cancers – but few with as much promise as forkhead box protein M1 (FOXM1). Studies have shown that FOXM1 expression is not only upregulated in one or two forms of cancer, but the majority of human cancer types including liver, brain, prostate, lung, colon, oesophageal, stomach, kidney, breast, pancreas, testicular, ovary, uterus and cervix. However, there is a hitch: because FOXM1 is also a vital part of many cells in their everyday function, simply blocking its expression would only cause nonspecific cytotoxicity, killing normal cells alongside the cancerous ones.

Molecular biologists at Queen Mary University of London have been investigating the FOXM1 protein with the hope of using it to prevent cancer. Now, their work has produced a new way of quantifying cancer aggressiveness linked its overexpression with resistance to chemotherapeutic drugs. The protein was named Molecule of the Year by the International Society for Molecular and Cell Biology and Biotechnology Protocols and Research in 2010 because of the potential of FOXM1 being a target for new studies into cancer.

However, before new drugs and treatments can be devised, researchers must attend to the task of discovering more about the exact role of FOXM1 in cancer initiation and progression. Thankfully, among the research groups investigating this problem, one has shown itself time and again to be up to the task. More than 10 years ago, Dr Muy-Teck Teh of Queen Mary University of London was responsible for linking FOXM1 and cancer for the first time, and since then he has been working – along with his collaborators – towards understanding the function and mechanism of this enigmatic protein. Teh’s specialism is in cancers of the head and neck, but in general, the team’s work is concerned with discovering the earliest activator of cancer initiation. This “cancer switch,” Teh notes, “would have huge clinical implications for early cancer detection and prevention” – and it could also translate into less debilitating surgical treatment and better patient outcomes.

PROLONGED PURSUIT

Teh published the first evidence linking FOXM1 to cancer in 2002. Since then, this revelation has led other investigators to identify the protein at work in many forms of the disease. Although he considers this his “greatest contribution to the field of cancer research”, in 2009, Teh and his collaborators were also responsible for producing evidence demonstrating that FOXM1 is an early biomarker in head and neck cancer, playing a part in initiating cancer by disrupting the stem cell renewal and differentiation mechanisms. Using adult human stem cells engineered to produce excessive FOXM1, the
OBJECTIVES

• To delineate the mechanisms and identify molecular markers to understand the earliest 'switch' that initiates cancer
• To personalise cancer treatments based on an individual’s molecular profile

KEY COLLABORATORS

Professor Iain Hutchison; Professor Ian Mackenzie; Dr Matt Parker; Dr Caroline Brennan; Queen Mary University of London, UK • Professor Eric Lam, Imperial College London, UK • Professor Allan Hackshaw, University College London, UK • Professor Daniela Costea, University of Bergen, Norway • Professor Simon Christian, University of Lausanne, Switzerland • Professor Andrew Yeudall, Virginia Commonwealth University, USA • Professor Ma Hong, Guiyang Medical University, China

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CONTACT

Dr Muy-Teck Teh
Principal Investigator
Barts & the London School of Medicine & Dentistry
Queen Mary University of London
The Blizard Institute
4 Newark Street
London E1 2AT
United Kingdom
T +44 20 7882 7140
E m.t.teh@qmul.ac.uk
www.dentistry.qmul.ac.uk/centres/clinical-and-diagnostic-oral-sciences

MUY-TECK TEH obtained both his Biomedical Science BSc Hons degree (1996) and PhD in Physiology (2000) from King’s College London. Following two postdoctoral trainings funded by Wellcome Trust and Cancer Research UK, he is now a tenured lecturer at Barts & the London School of Medicine & Dentistry, Queen Mary University of London. He currently leads a number of research programmes in clinical translational of cancer biomarker discovery, molecular diagnostics, molecular re-programming of adult epithelial stem cell renewal, differentiation and senescence. He was awarded ‘Molecule of the Year 2010’ for his research on FOXM1.

QMIDS

The qMIDS test is the first molecular test based on FOXM1, and it measures the levels of expression in 16 target genes within a tissue sample, detecting whether the lesion from which it was derived is likely to become cancerous. Using a unique algorithm, the test combines the gene levels into a single malignancy index, which gives a good indication of how a cancer is likely to behave. Early tests indicate that the new system can achieve a cancer detection rate of 91-94 per cent, and it is currently the first and only multi-biomarker based test for squamous cell carcinoma undergoing clinical validation. It will be a particularly useful tool once it reaches the bedside because there is currently no test capable of detecting whether or not a mouth lesion will become cancerous.

So far, Teh has validated the test in 359 specimens from 299 patients in two independent cohorts of head and neck squamous cell carcinoma patients, one based in the UK, the other in Norway. The test quantitatively diagnosed and objectively stratified cancer aggressiveness with high accuracy. The scientists also tested qMIDS on vulva and skin squamous cell carcinomas, yielding further promising results. The experiment suggested the method might be applicable to other cancers beyond those of the mouth. Further multi-cohort trials are required to establish its use in the clinic, but so far the results have been very promising indeed.

FUTURE DIAGNOSES

The group’s more recent studies and research endeavours focus on developing the qMIDS system and other diagnostic tools with the goal of creating non-invasive predictive tests for cancer initiation.

In 2012, the team published a paper presenting further evidence as to how FOXM1 causes normal cells to start behaving like cancer cells. Using a gene-chip microarray, the investigators examined DNA memory patterns in normal mouth cells – and their results were very revealing. The memory function is produced by masking or unmasking different portions of the DNA strand and these so called ‘epigenetic’ patterns are inherited by cells from their progenitors.

FOXM1, the team found, disrupts this epigenetic memory pattern, changing it into the pattern found in cancer cells in a process Teh likens to ‘brainwashing’. Since this DNA memory is important to normal cell function, any alteration to it can cause the cell to begin behaving strangely – as is the case with cancer cells.

This discovery had a number of important implications for early cancer diagnostics and represented a potential lead for subsequent biomarkers with cancer predictive value.

Ultimately, the achievements of Teh and his collaborators will help medical professionals to identify and diagnose cancer in earlier phases, achieving a more positive patient outcome and a greater survival rate.