CUTTING-EDGE RESEARCH FOR BETTER DIAGNOSIS AND TREATMENT

Discoveries made by researchers at THE CHINESE UNIVERSITY OF HONG KONG (CUHK)'S FACULTY OF MEDICINE are leading to biomedical innovations improving people's lives.

Unravelling the pathway to organ scarring

A CUHK research team has uncovered a signalling mechanism that leads to tissue scar formation and cancer progression by studying transforming growth factor-beta (TGF-β), a set of proteins that play an essential role in the immune system.

Led by Hui Yao Lan, a professor of biomedical sciences in CUHK's Department of Medicine & Therapeutics, the team found that Smad3, a key molecule downstream of TGF-β signalling, is the 'bad guy' and is over-activated in scar tissue and tumour microenvironments. In contrast, Smad7, another protein in TGF-β signalling, plays the 'good guy' role, countering the functions of Smad3. When Smad7 is lost, as in scar and tumour tissues, Smad3 overrides, causing scarring.

"I am proud of our new discovery," said Lan, who has devoted his academic efforts to the battle against tissue scarring and tumour inflammation. "The finding leads to the identification of a new pathway of tissue scarring."

In the context of the scarring of connective tissues, called fibrosis, Smad3 binds to fibrosis genes and mediates tissue scarring in chronic heart, kidney, liver, and lung diseases. Targeting the molecules regulating gene expression can combat tissue fibrosis.

Importantly, 'bad guy' Smad3 can also bind to many check-point genes on immune cells and can cause tissue scarring by converting macrophages to fibroblasts and can promote cancer progression by dysregulating immune system responses to cancer in the tumour microenvironment. Even more recently, Lan's team discovered that Smad3 plays an essential role in the disease procession of type-2 diabetes and diabetic complications, and deletion of Smad3 corrects the diabetic phenotype in diabetic mice.

These discoveries have led to novel therapies for diseases associated with fibrosis, diabetes, and cancer by rebalancing TGF-β/Smad signalling.

Cracking inflammatory bowel disease

When inflammatory bowel disease (IBD), a lifelong and debilitating gastrointestinal condition, began to increase in Asia two decades ago, the causes were still a mystery. When Siew Ng joined CUHK in 2010 after obtaining her PhD at Imperial College London, she witnessed the explosion of this 'western' disease in Asia and began her quest to crack it.

Ng's team was the first to launch the Asia-Pacific Crohn's and Colitis Epidemiology Study (ACCESS), which, for the past five years, has tracked several thousands of new cases of Crohn's disease and ulcerative colitis — the two major forms of IBD — across 15 countries in Asia, as well as Australia. Their studies have revealed that the disease progression of IBD, in both the West and the East, is driven by the interplay of an abnormal immune response and gut microbes. Having identified specific microorganisms that may contribute to the disease, Ng and her collaborators also suggested environmental exposures that can be modulated for disease prevention. These revelations are now being used to develop targeted therapies for IBD.

The ideal time to tease apart the complex web of environmental triggers and genetic associations, says Ng, is before the IBD incidence peaks, when urbanization is happening. "We are going into rural areas of China where IBD is still rare," says Ng. "We are studying how the environment, diets and gut microbes of rural people differ from those living in China's megacities."

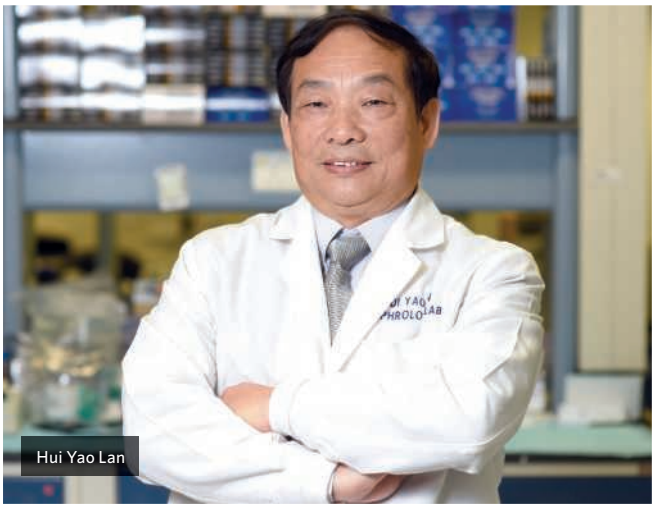
Ng's team is using new approaches, such as genomics and microbiomics, to unlock the aetiology, or set of causes, underlying IBD. "The golden time for identifying the cause of the disease is the next ten years," says Ng. "We need to seize this golden opportunity now".

Seeking biodegradable metals for clinical use

CUHK professor Ling Qin heads a research laboratory in the Department of Orthopaedics & Traumatology, focusing on research and development (R&D) of innovative bioactive materials and drugs for orthopaedic use. The lab targets major orthopaedic problems with huge global socioeconomic and healthcare burdens, such as osteoporosis and osteonecrosis.

For example, biodegradable materials, especially those that do not require removal as conventional rigid metal orthopaedic implants do, are highly desirable for fracture fixation. Based on skeletal physiology and pathophysiology, Qin and his group think that magnesium, an essential mineral element of our bone matrix, is an ideal candidate. Collaborating with local and international colleagues, they have developed pure magnesium implants, as well as alloys and hybrid systems for safe application in bone fracture fixation and bone defect repair enhancement.

Qin's multidisciplinary team also looks at the potential healing mechanisms of magnesium ions after implant degradation. In an animal model, they showed, for the first time, that magnesium-induced osteogenesis or bone formation is mediated by local neuronal production of calcitonin gene-related peptide 1 (CGRP1), a calcium-lowering peptide. Joint research with orthopaedic surgeons has led to the very first clinical trial to use magnesium screws for fixation in reconstructive hip surgeries. These findings have been published in *Nature Medicine*, *Biomaterials* and other


Hui Yao Lan


Ling Qin


Siew Ng


Yu Huang

leading journals, and have led to numerous patents and awards.

Qin and his group have concrete plans to take their work forward. These include: furthering experimental work using large animal models; gaining official approval for their innovative implants by licencing and/or spin-off; establishing international standards and guidelines for global R&D of magnesium-based biometals; and advancing innovation of cell- and tissue-specific targeting systems for local or systemic applications in bone regeneration.

Understanding dysfunction in our fat, heart and organ lining

Heart attacks, strokes and kidney failures all originate from dysfunction of endothelial cells lining blood vessels. Deranged performance of these cells triggers a cascade of events in the vessel wall that may ultimately evolve into the narrowing and hardening of arteries and a subsequent blocking of blood flow.

CUHK professor Yu Huang has been committed to analysing the chemical pathways to the malfunction of these endothelial cells for 20 years. He hopes his findings can lead to new drugs that reverse those deleterious effects, protecting our major organs.

Huang's research focuses include: understanding cellular and molecular events involved in the initiation and progression of endothelial dysfunction in hypertension and diabetes; uncovering novel biomarkers for vascular inflammation and atherogenesis; and identifying locations to reverse vascular dysfunction and ageing in animal models of cardio-metabolic diseases.

In recent years, Huang's team has identified key proteins and enzymes that play crucial roles in impairing endothelial function in hypertension, diabetes and ageing. They have also revealed protein hormones essential for the improvement of endothelial function in diabetes, illustrating the potential use of adipocyte-derived cytokines to slow the development of vascular abnormalities related to diabetes. More recently, Huang's team revealed an important signalling cascade in vascular endothelial cells crucial to the development of atherosclerosis, or hardened and narrowed arteries.

As lack of early diagnosis has been the major contributor to the high mortality of vascular diseases such as coronary heart disease and ischemic stroke, Huang's team is setting up a platform for target-specific screening to identify new biomarkers for disease prediction. "We aim to really improve survival and quality of life for patients with cardio-metabolic diseases," says Huang. ■

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