PRESS RELEASE

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Scientists grow liver cancer cells in lab

Recreating liver tumours as organoids for faster, more accurate drug screening

Singapore, 28 February 2018 — Liver cancer (hepatocellular carcinoma or HCC) is the fourth leading cause of cancer death worldwide. Here in Singapore, the disease is the third and fourth leading cause of cancer deaths for men and women respectively. It is often detected only at an advanced stage when cure is no longer possible.

A major challenge in developing effective drugs for liver cancer is the inability of current pre-clinical tumour models to accurately replicate features of the cancer and the environment in the human body in which the tumour is located. This has led to many potential drugs to fail in clinical testing.

Seeking to more accurately mimic the tumour environment to grow liver cancer cells, researchers have developed models of such cancerous growths, called patient-derived xenografts (PDX). Although these models provide a more accurate picture of how effective potential cancer drugs would be when they are used in humans, they are also expensive and time-consuming for drug screening.

Growing these PDX cancer cells in the laboratory (*in vitro*) would thus be a more cost effective and faster way to test for drug efficacy. However, attempts to culture these cells robustly have been largely unsuccessful.

Now, an interdisciplinary team of researchers from the National University of Singapore's Departments of Physiology and Biomedical Engineering, the Cancer Science Institute of Singapore, the Institute of Bioengineering and Nanotechnology, A*STAR and the National Cancer Centre Singapore has devised a new method to grow PDX liver cancer cells. Their success was documented in a recent paper in the leading bioengineering journal *Biomaterials.*

Led by Dr Eliza Fong and Dr Toh Tan Boon, the team managed to grow cancer cells derived from 14 liver cancer PDX on a synthetic 3D scaffold made of a plant-based porous hydrogel. The researchers engineered the spongy scaffold with optimised biochemical and mechanical properties, to help liver cancer cells maintain their proper shape and function and grow as organoids. By effectively recreating the tumour environment in the liver, cancer cells from PDX can now be grown in the petri dish for drug testing.

After growing the cells as organoids for one to three weeks, the team verified that the liver cancer cells in the organoids were alive and reproducing. Additionally, liver cancer cells usually

contain specific genetic changes that are absent in healthy liver cells. Most of the organoids retained the same key genetic changes that were in the source PDX cells.

They also maintained an important feature of liver tumours – intra-tumoural heterogeneity. Not all cancer cells within a tumour are the same; distinct populations of liver cancer cells exist within the same tumour and may affect its response to treatment. The presence of this feature is another advantage that the organoids have over traditional cell culture methods as a pre-clinical model for drug screening. In the latter's case, all cells are identical.

Another attractive feature of the 3D organoids in scaffold is their small size – a mere 100 microns. These organoids in scaffold can easily fit inside the well of a 96-well microtiter plate (a flat plate with numerous "wells" that are used as small test tubes). The microplate has become a standard tool in analytical research and clinical diagnostic testing laboratories. This is a standard platform that is used for high-throughput drug screening, and enables many drugs to be tested at the same time.

Through this technology, one PDX can be used to produce tens to hundreds of such scaffolds containing organoids. Combined with their ability to recapitulate the genetic features and heterogeneity of the original liver tumours, these tumour avatars have the potential to revolutionise the screening and development of liver cancer drugs for patients.

Said Professor Hanry Yu, Group Leader at the Institute of Bioengineering and Nanotechnology, A*STAR, and Department of Physiology at NUS, "The spongy scaffolds were developed to keep normal liver cells happy and also preserve the important properties of liver cancer for drug testing. This could one day allow patients to choose the best treatment based on the drug testing results of their own liver cancer cells."

Added Dr Eliza Fong, "As a bioengineer, this study truly epitomises the positive synergy we can achieve in growing patient tumours outside the body by marrying advances in tissue engineering with cancer biology."

And the availability of a reliable platform to grow liver cancer patient-derived cells is a major step in personalised medicine, said Dr Toh Tan Boon. "We can now use them for increased throughput drug sensitivity testing."

Commenting on the potential impact of the team's work, Associate Professor Dan Yock Young, Head, Department of Medicine at the Yong Loo Lin School of Medicine and the National University Hospital said, "Liver cancer is the second most lethal cancer in the world with few chemotherapy options. This is in part due to our inability to customise effective therapy for individual HCC. The ability to grow cancer cells *in vitro* affords us the ability to conduct high throughput drug testing to validate drug efficacy before they are used on patients. This is a key step in guiding the use of effective chemotherapy and minimising treatment futility."

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NUS has 17 faculties and schools across three campuses. Its transformative education includes a broad-based curriculum underscored by multidisciplinary courses and cross-faculty enrichment. Over 38,000 students from 100 countries enrich the community with their diverse social and cultural perspectives. NUS also strives to create a supportive and innovative environment to promote creative enterprise within its community.

NUS takes an integrated and multidisciplinary approach to research, working with partners from industry, government and academia, to address crucial and complex issues relevant to Asia and the world. Researchers in NUS' Schools and Faculties, 30 university-level research institutes and centres, and Research Centres of Excellence cover a wide range of themes including: energy, environmental and urban sustainability; treatment and prevention of diseases common among Asians; active ageing; advanced materials; risk management and resilience of financial systems. The University's latest research focus is to use data science, operations research and cybersecurity to support Singapore's Smart Nation initiative.

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Established in 1905, the NUS Yong Loo Lin School of Medicine is the first institution of higher learning in Singapore and the genesis of the National University of Singapore.

The School offers one of the finest undergraduate medical programmes in the Asia Pacific region and enjoys international recognition and respect. The Times Higher Education World University Rankings 2016 by subject and Quacquarelli Symonds (QS) World University Rankings by Subject 2017 list NUS Medicine as a leading medical school in Asia.

It admits 300 students to the MBBS degree programme annually and its principal missions are to educate and train the next generation of healthcare professionals, and foster research that will help to advance the practice of medicine.

The 18 NUS Medicine departments in the basic sciences and clinical specialties work closely with the Centre for Medical Education, the Centre for Biomedical Ethics, the Centre for Healthcare Simulation as well as the restructured public hospitals to ensure that teaching and research are aligned and relevant to Singapore's healthcare needs. The School is a founding institutional member of the National University Health System.

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