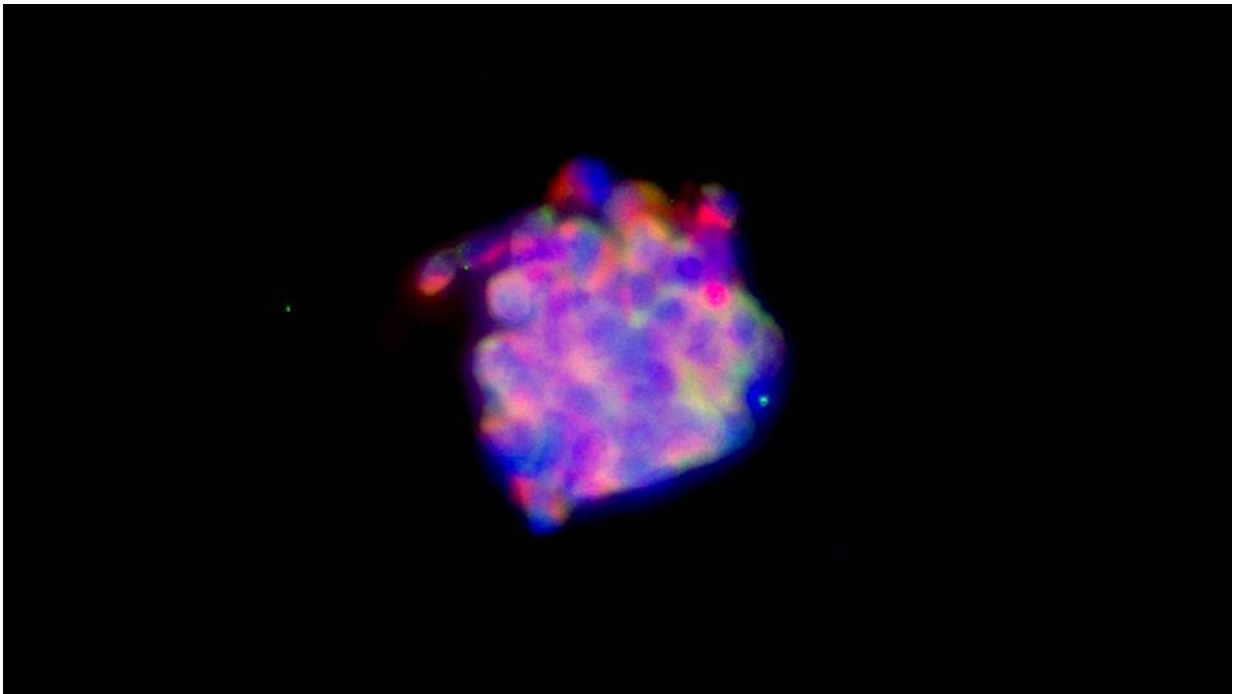


Researchers show potential liver cancer treatment by targeting cancer stem-like cells

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Liver cancer stem-like cells grown as tumourspheres that are sensitive to JAK/STAT small molecule inhibitors. Credit: National University of Singapore

Liver cancer is the second leading cause of cancer-related deaths worldwide. The most common primary liver cancer in adults is known as hepatocellular carcinoma (HCC), and accounts for approximately 780,000 deaths every year. Even with advanced surgical treatments or transplantation, the 5-year survival rate for HCC patients remains poor

due to frequent recurrence.

Now, a new study from National University of Singapore (NUS) researchers has demonstrated a potential method for treating advanced liver cancers like HCC. Led by Associate Professor Edward Chow, who is a Principal Investigator with the Cancer Science Institute of Singapore (CSI) at NUS and Dr. Toh Tan Boon, who is Head of the Translational Core Laboratory at NUS N.1 Institute for Health (N.1), a team of NUS scientists showed that a class of small molecule drugs that target the JAK/STAT signalling pathway could be used to fight against the disease.

"Targeting molecular mechanisms that drive chemoresistance has shown success in clinical trials for other diseases. Therefore, such targeted approaches can be potentially useful as adjuvant therapies to improve clinical outcomes of HCC patients," explained Assoc Prof Chow.

Their results were published in the Journal of *Hepatology* on 18 September 2019.

Inhibiting the JAK/STAT signalling pathway

The JAK/STAT signalling pathway is an important set of proteins that control a wide range of biological functions, including immune responses and cellular development. This pathway typically responds to external cellular cues to turn on specific sets of genes that help [cells](#) properly develop or allow the immune system to fight off infections. As such, if the JAK/STAT signalling pathway somehow goes awry, it can lead to the formation of tumours.

In their study, the NUS team targeted the JAK/STAT pathway to inhibit its action in tumour formation. They showed that a subpopulation of [cancer](#) 'stem-like' cells are sensitive to a class of small molecule drugs that inhibit the JAK/STAT pathway. These stem-like cells can self-

renew and are responsible for causing the [cancer cells](#) that comprise the tumour.

Dr. Toh Tan Boon, who is Head of the Translational Core Laboratory at N.1 and the co-lead author of the study, explained the significance of these findings, "We can now potentially use small molecule compounds to target these specific small population of cancer stem-like cells that are often the cause of tumour recurrence."

Small molecule drug candidates effective in reducing cancer progression

The researchers were able to isolate these tumour-initiating cancer cells that are often the culprits of therapy resistance that leads to cancer relapse. They found that an important cancer pathway, known as the JAK/STAT signalling pathway, was enriched in this cancer stem-like population of cells.

In this study, JAK/STAT inhibitors targeting cancer stem-like cells were able to effectively reduce cancer progression in preclinical models of [liver cancer](#). The NUS team found that the tumour forming ability was reduced by 50 percent after drug treatment.

Miss Lim Jhin Jieh, a doctoral student at CSI and co-first author of the paper, said, "This study highlights a novel strategy in treating liver cancer patients whose tumours show aberrant activity of important cellular pathways. Blocking the activity of an alternative [pathway](#) with small molecule drugs could effectively eradicate the cancer at its roots and prevent a relapse."

Next steps

These findings provide increased support that JAK/STAT-based therapies targeting cancer stem-like cells are important for more effective treatment outcomes against liver cancer.

Assoc Prof Chow said, "The immediate next step is to validate this concept in our collection of clinically relevant patient-derived tumour xenografts and organoids." JAK/STAT inhibitors are also now being tested in clinical trials for the treatment of other solid cancers.

More information: Tan Boon Toh et al. Targeting Jak/Stat pathway as a therapeutic strategy against SP/CD44+ tumorigenic cells in Akt/ β -catenin-driven hepatocellular carcinoma, *Journal of Hepatology* (2019). DOI: [10.1016/j.jhep.2019.08.035](https://doi.org/10.1016/j.jhep.2019.08.035)

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