PRESS RELEASE

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Scientists use microcellular drones to deliver lung cancer-killing drugs

In a study led by researchers at the NUS Yong Loo Lin School of Medicine, extracellular vesicles (EVs) loaded with customisable anti-cancer antisense oligonucleotides suppressed cancer growth

Singapore, *11 November 2024* – Lung cancer, specifically Non-Small Cell Lung Cancer (NSCLC)–the most common subtype of cancer contracted by patients who do not smoke, is a leading cause of cancer mortality and the second most diagnosed cancer globally. The rapid and inevitable emergence of drug resistance mechanisms caused by mutations in cancer severely outpaces the development of small molecule drugs. This phenomenon adds urgency for a new, customisable, safe, and effective anti-cancer therapeutic that could be designed, screened, and validated in a short amount of time.

A team of researchers, led by Assistant Professor Minh Le from the Institute for Digital Medicine (WisDM) and Department of Pharmacology at the Yong Loo Lin School of Medicine, National University of Singapore (NUS Medicine), has successfully demonstrated that nano-sized particles released by cells, such as red blood cells, could be repurposed to function as drug delivery platforms to carry antisense oligonucleotide (ASO) molecules targeting cancer cells in the lungs, thereby suppressing cancer progression. This study was conducted in collaboration with the Cancer Science Institute of Singapore (CSI Singapore) at NUS, Agency for Science, Technology and Research (A*STAR), National Cancer Centre Singapore (NCCS), and Duke-NUS Medical School.

Asst Prof Minh Le said, “Mutant Epidermal Growth Factor Receptors (EGFRs) are the most common driver of lung cancer among the Asian population. Therefore, we focused on targeting lung cancer caused by the mutant EGFR. Currently, drugs known as tyrosine kinase inhibitors are the standard of treatment, and they work by inhibiting the mutant EGFR protein to stop cancer progression. As the cancer cells may further mutate and resist these drugs, we sought to find a more effective way to target the cancer.”

In the study published in *eBioMedicine*, the authors looked toward ASOs to not only overcome the issue of drug resistance but also contribute to the development of precision medicine. Precision medicine tailors the treatment to individual patients and their disease, as compared to a “one-size fits all” broad spectrum therapy. ASOs are molecules that can stick to a specific part of a ribonucleic acid (RNA) and inhibit irregular activity. ASOs are a flexible tool that can be easily redesigned to target and fix problems in different genes. This advantage is critical in the context of NSCLC which is known to develop resistance against tyrosine kinase inhibitors. Furthermore, the ASOs can be customised to target unique mutations based on the cancer

profiles of each individual patient. However, some disadvantages of ASOs are that they are easily degraded in the bloodstream, which results in diluted treatment at the tumour sites. This can be remedied with a method to hold the ASOs and deliver them directly to the tumour site.

To achieve that, the researchers utilised extracellular vesicles (EVs) derived from human red blood cells as a natural carrier to deliver the anti-cancer ASOs to the tumour site. To direct the ASO-loaded EV towards the tumour site, EGFR-targeting moieties were engineered onto the surface of the EVs. This primed the EV to home in on the cancerous cells. Furthermore, the ASO-loaded EVs were shown to exhibit a potent anti-cancer effect in various models of lung cancer, including patient-derived cells. The specific design of the ASOs allows them to suppress mutant EGFR, while leaving the normal EGFR unaffected. They also demonstrated that the ASO-loaded RBCEVs possessed potent anti-cancer effects against TKI-resistant cancer cells.

Associate Professor Tam Wai Leong, Deputy Executive Director of A*STAR Genome Institute of Singapore (A*STAR GIS), and co-corresponding author of the study, said, “The innovative use of extracellular vesicles as a delivery vehicle for nucleic acid therapeutics added a potentially powerful treatment modality for treating malignancies. The ability to precisely eliminate mutant EGFR cancer cells while sparing normal tissues will enable customised treatment for individual patients. This is a significant step towards addressing cancer drug resistance and advancing the application of personalised cancer medicine.”

Professor Goh Boon Cher, Deputy Director of CSI Singapore, Professor of Medicine at NUS Medicine and one of the authors of the study added, “This work is instrumental in breaking new ground for precise delivery of therapeutic RNA to tumour cells to destroy them by targeting their vulnerabilities. It is a proof of concept that can be broadly applied in other areas of cancer treatment.”

For media enquiries, please contact:

Shaun Yee
Yong Loo Lin School of Medicine, Communications Office
National University of Singapore
DID: +65 9012 1928
Email: medv3719@partner.nus.edu.sg

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Our multidisciplinary and real-world approach to education, research and entrepreneurship enables us to work closely with industry, governments, and academia to address crucial and complex issues relevant to Asia and the world. Researchers in our faculties, research centres of excellence, corporate labs and more than 30 university-level research institutes focus on

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Through a dynamic and future-oriented five-year curriculum that is inter-disciplinary and inter-professional in nature, our students undergo a holistic learning experience that exposes them to multiple facets of healthcare and prepares them to become visionary leaders and compassionate doctors and nurses of tomorrow. Since the School's founding in 1905, more than 12,000 graduates have passed through our doors.

In our pursuit of health for all, our strategic research programmes focus on innovative, cutting-edge biomedical research with collaborators around the world to deliver high impact solutions to benefit human lives.

The School is the oldest institution of higher learning in the National University of Singapore and a founding institutional member of the National University Health System. It is one of the leading medical schools in Asia and ranks among the best in the world (Times Higher Education World University Rankings 2024 by subject and the Quacquarelli Symonds (QS) World University Rankings by subject 2023).

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