PRESS RELEASE

Lower Dose, Less Toxic Radiopharmaceutical Produces Better Outcomes

NUS and Peking Union Medical College Hospital (PUMCH) researchers successfully trial new, improved treatment for neuroendocrine cancers

Singapore, 9 March 2021 — Neuroendocrine tumours are cancers that begin in specialised cells called neuroendocrine cells. These cells have traits similar to those of nerve cells and hormone-producing cells. Neuroendocrine tumours, while rare, can occur anywhere in the body. Most affect the cardiothoracic region, eg lungs, appendix, small intestine, pancreas as well as the rectum. There are many types of neuroendocrine tumours: some grow slowly while others develop very rapidly.

Neuroendocrine tumors are characterised by abundant production of somatostatin receptor 2, a naturally circulating hormone that is an important target for scientists studying new treatment approaches.

Peptide Receptor Radionuclide Therapy (PRRT) is the most commonly used treatment for refractive neuroendocrine cancers, delivering cancer-killing radioactive substances directly to tumour sites. This treatment provides symptomatic relief, stopping or slowing tumour growth and improving overall survival for patients. It is a form of molecular therapy that features a protein (called a peptide) which targets cancer cells and which is similar to the naturally circulating hormone, somatostatin. The peptide is mated with a small amount of radioactive material, or radionuclide. They form a radiopharmaceutical called a radiopeptide (177Lu-DOTA-EB-TATE). Injected into a patient, this radiopeptide travels in the bloodstream, finds and then binds to neuroendocrine tumor cells, before delivering a targeted high dose of radiation directly to the cancer cells.

PPRT pharmacokinetics, pharmacodynamics improved

Together with collaborators at the Peking Union Medical College Hospital, the Chinese Academy of Medical Science, Professor Shawn Chen Xiaoyuan of the Department of Diagnostic Radiology, Yong Loo Lin School of Medicine at the National University of Singapore (NUS), has managed to improve the pharmacokinetics (i.e. the absorption and movement of drugs into, through and out of the body) and effectiveness of PPRT, while reducing its dosage and toxicity. The researchers did this by introducing a truncated Evans blue molecule onto octreotate peptide (denoted as 177Lu-DOTA-EB-TATE).

“The EB part allows reversible binding of 177Lu-DOTA-EB-TATE to blood albumin and extends its half-life in the blood, and thus provides an extended therapeutic time window, and improved treatment efficacy over Lutathera,” said Prof Chen, who holds concurrent appointments at the NUS Departments of Chemical and Biomolecular Engineering, and the

Department of Biomedical Engineering, Faculty of Engineering. Lutathera is a radioactive medication used to treat neuroendocrine cancers.

Clinical trial results

Thirty-two patients at Peking Union Medical College Hospital (PUMCH) with histologically confirmed neuroendocrine tumours were recruited for a clinical trial with the new technology. The patients were randomly divided into three escalating dose groups. The treatments were planned for up to three cycles, repeated at eight-to 12-week intervals. Hematologic parameters, liver function, and kidney function were tested at baseline, one week, and four weeks after each cycle of treatment. The patients were scanned at the start of the trial, some days before the second and third cycles of treatment, and two to three months after their last PPRT cycle.

The patients tolerated 177Lu-DOTA-EB-TATE well, with good tumor response with almost no side effects. The study was published in the 2021 March issue of the Journal of Nuclear Medicine[1].

"177Lu-DOTA-EB-TATE with longer circulation half-life and high tumor accumulation appears to have more potent anti-cancer efficacy than Lutathera, and at a much lower dose. We hope reversible albumin binding through Evans blue derivatives will create various novel therapeutic radiopharmaceuticals that can be effective for not only NET patients but also other types of cancer patients overexpressing different molecular targets," Prof Chen said.

Associate Professor Quek Swee Tian, Head, Department of Diagnostic Radiology at the National University Hospital, said PRRT has been shown to confer a longer progression-free survival and a significantly higher response rate in patients with advanced neuroendocrine cancers as compared to first line medical therapy. "The development of 177Lu-DOTA-EB-TATE, with its improved pharmacokinetics, has further advanced the PRRT therapeutic technology and holds promise for even better therapeutic efficacy and a more efficient workflow for our patients with a drug infusion time a fraction of standard PRRT."

The technology has been licensed to Molecular Targeting Technologies, Inc. (MTTI) and an Investigational New Drug (IND) application has been approved by the U.S. Food and Drug Administration (FDA).

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[1] "Peptide Receptor Radionuclide Therapy of Late-Stage Neuroendocrine Tumor Patients with Multiple Cycles of 177Lu-DOTA-EB-TATE", *Journal of Nuclear Medicine,* March 2021 (https://pubmed.ncbi.nlm.nih.gov/32826319/))

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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, 31 university-level research institutes, research centres of excellence and corporate labs focus on themes that include energy, environmental and urban sustainability; treatment and prevention of diseases common among Asians; active ageing; advanced materials; as well as risk management and resilience of financial systems. Our latest research focus is on the use of data science, operations research and cybersecurity to support Singapore's Smart Nation initiative.

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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 Asia's leading medical school and ranks among the best in the world (Times Higher Education World University Rankings 2019 by subject and the Quacquarelli Symonds (QS) World University Rankings by Subject 2019).

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