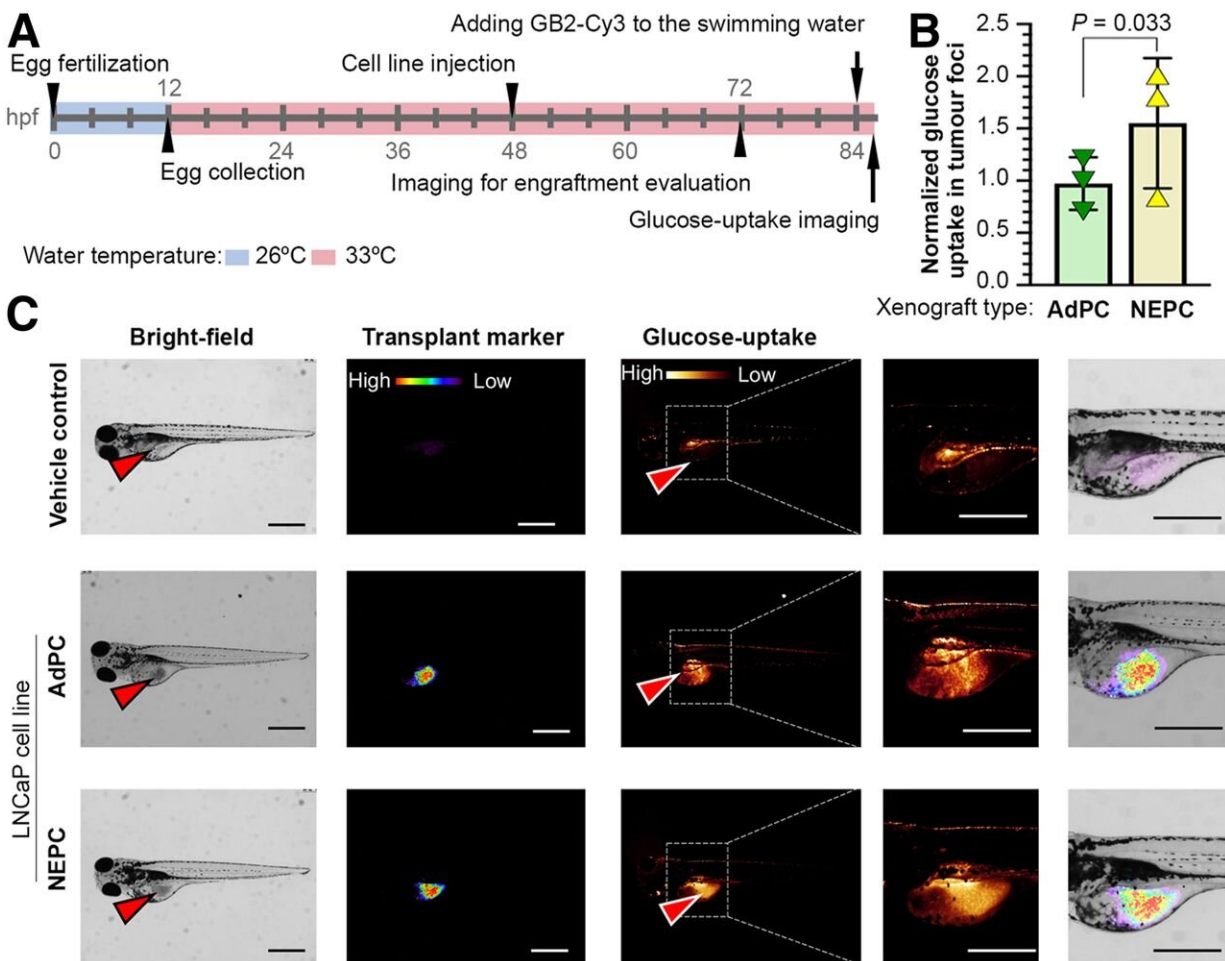


Genomic signature explains FDG-avidity of PSMA-suppressed prostate tumors

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Neuroendocrine-induced LNCaP cell line xenografts represent higher glucose uptake in zebrafish model. (A) Schematic of experiment. (B and C) Quantification of GB2-Cy3 uptake and representative images of embryos injected with different LNCaP cells. Arrowheads show injection sites. Scale bar 500 μm. Credit: Society of Nuclear Medicine and Molecular Imaging

Scientists have uncovered the genomic signature to explain why ^{18}F -FDG imaging performs better than PSMA-targeted imaging for prostate cancer patients with low or no expression of the prostate-specific membrane antigen (PSMA). In a study published in the *Journal of Nuclear Medicine*, researchers determined that a neuroendocrine gene signature (common in prostate cancers with low PSMA expression) associates with a distinct differential expression of glucose transporters and hexokinase proteins, which allows for a more favorable uptake of ^{18}F -FDG than PSMA-targeted radioligands. Additionally, the study demonstrated that zebrafish xenograft tumor models are an accurate and efficient preclinical method for monitoring nonradioactive glucose uptake.

"While PSMA-targeted molecular imaging and therapy have transformed the landscape of prostate cancer management, a small minority of [prostate cancers](#) with neuroendocrine prostate cancer may not effectively benefit from PSMA-targeted therapy," said Gi Jeong Cheon, MD, Ph.D., chairman of the department of nuclear medicine at Seoul national University College of Medicine in Seoul, Korea.

"Previous clinical reports indicate that prostate cancers with a phenotype related to [neuroendocrine tumors](#) can be more responsive to imaging with ^{18}F -FDG than PSMA-targeting radioligands. Our research sought to provide a genomic rationalization for this ^{18}F -FDG avidity."

Researchers utilized data-mining approaches, cell lines and patient-derived xenograph models to study the expression levels of [glucose](#)-associated genes, including 14 members of the SLC2A family (encoding glucose transporter proteins), four members of the hexokinase family (genes HK1-HK3 and GCK) and PSMA (FOLH1 gene) after androgen-directed therapy and in correlation with neuroendocrine hallmarks. A neuroendocrine-like subset was characterized among a

group of primary and metastatic prostate cancer samples with no neuroendocrine histopathology. Glucose uptake was measured in a neuroendocrine-induced in vitro model and a zebrafish model by nonradioactive imaging of glucose uptake using a fluorescent glucose bioprobe.

Upon statistical analysis, researchers found elevated expression of GCK and decreased expression of SLC2A12, which demonstrates that a neuroendocrine gene signature associates with differential expression glucose transporters and hexokinase proteins. In accordance with this expression, the suppression of PSMA in neuroendocrine prostate cancer is associated with elevated glucose uptake.

"Early detection of neuroendocrine prostate [cancer](#) development is critical for patients as these tumors do not respond to standard of care and require alternate therapies," noted Cheon. "Our data demonstrate that these tumors express genes that are in favor of higher uptake of glucose, providing genomic data to support that ^{18}F -FDG positron emission tomography is an attractive imaging tool for these patients."

In addition to studying the expression levels of glucose uptake-associate genes, researchers sought to determine the feasibility of using nonradioactive in vivo imaging of glucose uptake in a zebrafish model. Using a fluorescent glucose bioprobe to image embryo-larval zebrafish, researchers demonstrated that zebrafish xenograft tumor models are a rapid and cost-effective method to monitor nonradioactive glucose uptake.

"The use of FDG imaging in mice can be limited by several factors, such as operating cost and short half-life of the radioactive substance and nonradioactive glucose probes, which are of particular interest. Human xenografts in mice also present challenges in engraftment rate and are both costly and time-consuming," noted Lisa A. Porter, Ph.D., professor

at the University of Windsor in Ontario, Canada. "From technical perspective, this work indicates the zebrafish model as a promising avenue to accelerate [molecular imaging](#) in vivo experiments."

More information: Martin K. Bakht et al, Differential Expression of Glucose Transporters and Hexokinases in Prostate Cancer with a Neuroendocrine Gene Signature: A Mechanistic Perspective for 18F-FDG Imaging of PSMA-Suppressed Tumors, *Journal of Nuclear Medicine* (2019). [DOI: 10.2967/jnumed.119.231068](https://doi.org/10.2967/jnumed.119.231068)

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