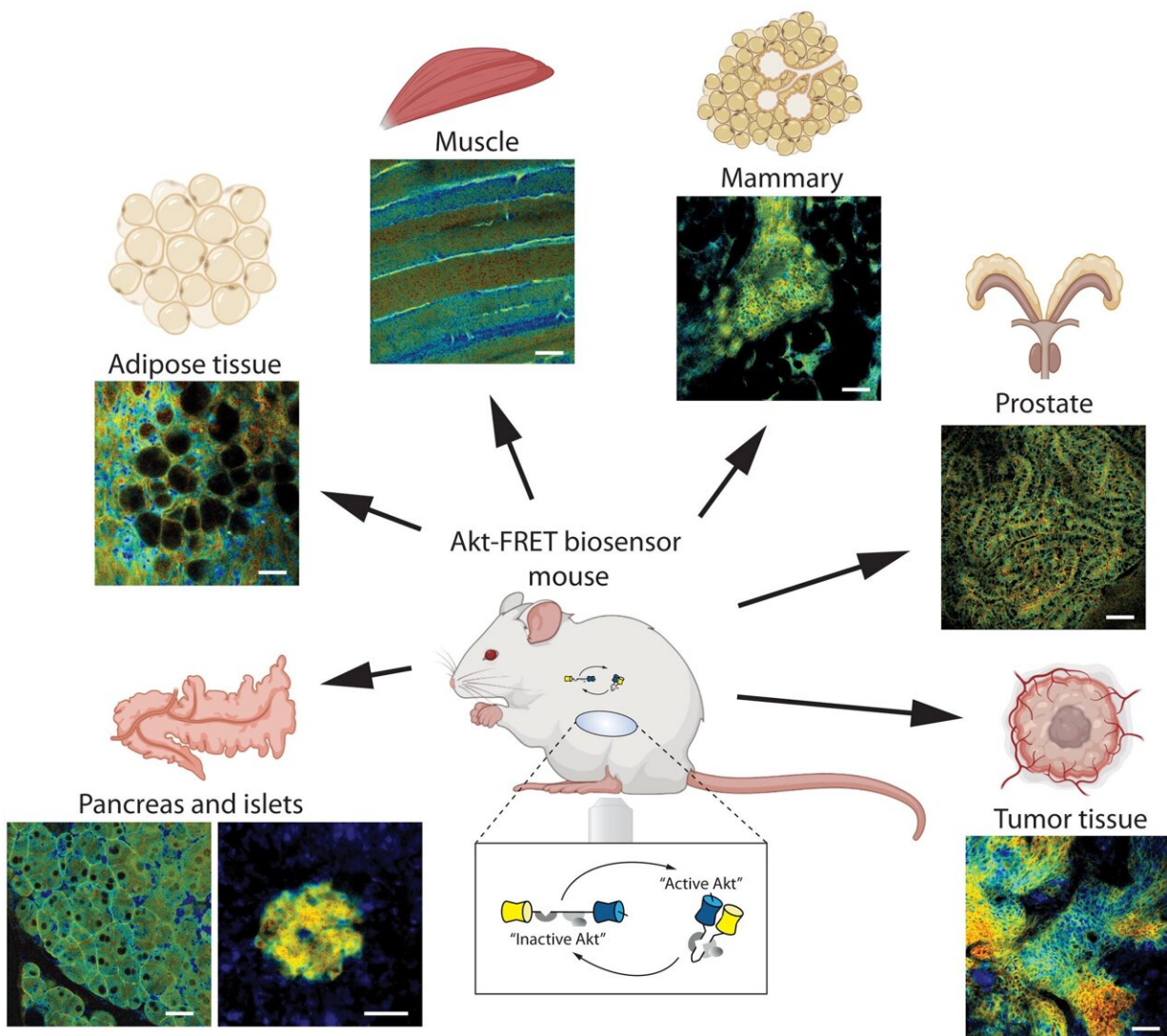


Researchers image live drug response and resistant 'pockets' in pancreatic cancer

April 28 2023



Schematic of spatiotemporal AKT activity mapping in several organ systems in vivo. Optical window-mediated intravital assessment of metabolic and

malignancy-mediated AKT signaling in a variety of organs including pancreas, adipose tissue, muscle, mammary, prostate, muscle, and tumor tissue. Scale bars, 50 μm . Credit: *Science Advances* (2023). DOI: 10.1126/sciadv.adf9063

Pancreatic cancer drug response and resistance has been uncovered in unprecedented detail, thanks to a research tool developed at the Garvan Institute.

Live microscopy footage of a key cancer driver molecule that is often overly active in pancreatic cancer could be used to reveal new paths to tackling drug resistance with combination therapies.

The team at the Garvan Institute of Medical Research found that the molecule AKT, which causes [cancer cells](#) to multiply and spread, is activated in distinct parts of the tumor, including at the border of a spreading cancer and areas of low oxygen supply where AKT forms pockets of resistance to therapy.

The research was made possible through a 'biosensor' mouse model developed at Garvan that produces a fluorescent version of AKT and provides the first real-time view of a major cancer cell-signaling network within living tissues.

"The AKT pathway has been a target for therapy for decades but drugs targeting this pathway alone have thus far been largely ineffective in the clinic," says Professor Paul Timpson, Head of the Invasion & Metastasis Lab, co-Lead of the Cancer Ecosystems Program at Garvan and co-senior author of the study.

"Thanks to our new imaging model, we can see a clear way forward for how combination approaches could reduce drug resistance, switch off

AKT and help stop tumors from growing and spreading. This research could help significantly improve outcomes for patients with pancreatic cancer."

The research was published in the journal *Science Advances*.

Zeroing in on pockets of drug resistance

Pancreatic cancer has a five-year survival of less than 11%, a rate which drops even further once the cancer has metastasized. Improvements in treatments for this aggressive cancer are therefore urgently needed.

One promising target for therapy is the AKT pathway—a key signaling pathway that in regular cells throughout the body maintains normal cell growth and metabolism. Many cancers, including approximately a quarter of pancreatic cancers, carry an altered version of this pathway that is overly active and fuels cancer growth and spread.

"Our biosensor mouse is the first tool capable of showing us exactly when and where AKT switches on or off in living tissues, providing us with an unprecedented view of its treatment response and resistance," says Professor Timpson.

"Using intravital microscopy at the ACRF INCITe Centre to image our biosensor model, we blocked AKT activity using clinical treatments, but could see, in real time, that AKT remained switched on inside drug-resistant pockets, specifically in areas close to invasive borders or with low oxygen supply," says co-senior author Dr. Max Nobis, Head of the Intravital Imaging Expertise Center at the VIB-KU Leuven Center for Cancer Biology and visiting scientist at Garvan.

"We also saw that as cancer cells got closer to a blood vessel, AKT started to activate. This indicates that AKT not only drives cancer

growth, but it also actively drives the early events of cancer spread to other sites around the body. For the first time, we're able to see these events in a live pancreas."

"Now that we can visualize pockets of treatment response and resistance, our next steps will be to investigate treatments co-targeting AKT in combination with drugs that open up [blood vessels](#) for improved [drug delivery](#), while also breaking down known barriers such as dense fibrotic tissue that often surrounds pancreatic tumors. This could improve drug delivery and switch off AKT inside impenetrable pockets to help reduce [drug resistance](#). Seeing such combination approaches in real-time inside a tumor will be crucial to improving treatments," says Dr. Nobis.

The researchers say their biosensor model will next be used to optimize new combination therapies with AKT pathway inhibitors for [pancreatic cancer](#) and other AKT-driven cancers.

"Our ability to see AKT in cancer cells is taking the guesswork out of the development of new therapies and has broad applications, with AKT contributing to many cancers, including breast and prostate cancers. Our model is a vital new tool in the era of co-targeting the tumor ecosystem in precision medicine, bringing us closer to improved treatment options for patients," says Professor Timpson.

More information: James R. W. Conway et al, Monitoring AKT activity and targeting in live tissue and disease contexts using a real-time Akt-FRET biosensor mouse, *Science Advances* (2023). [DOI: 10.1126/sciadv.adf9063](https://doi.org/10.1126/sciadv.adf9063)

Provided by Garvan Institute of Medical Research

Citation: Researchers image live drug response and resistant 'pockets' in pancreatic cancer (2023, April 28) retrieved 15 May 2024 from <https://medicalxpress.com/news/2023-04-image-drug-response-resistant-pockets.html>

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