

X-ray-activated drug treatments for pancreatic cancer

- Pancreatic cancer is difficult to treat, with some tumours becoming resistant to treatment.
- Treatments often affect healthy cells too, causing unwanted side effects.
- Dr Jennifer Shell, assistant professor at the South College School of Pharmacy in Knoxville, USA, has collaborated with researchers to develop a novel, targeted alternative by joining a light-sensitive compound to a drug which slows tumour cell growth.
- The results showed that the drug could be activated at the site of action using light, reducing tumour size in pancreatic cancer models.
- This research provides a new hope for targeted treatment to pancreatic tumours with fewer side effects than traditional methods.

Pancreatic ductal adenocarcinoma (PDAC) is a type of cancer that affects the pancreas – the organ responsible for helping hormones to digest food and to control blood sugar levels. Sadly, there is a very low survival rate for patients diagnosed with this form of cancer and in many cases, the cancer can return after initial treatment. Globally, there were almost half a million cases of pancreatic cancer diagnosed in 2020, making it the 12th most common cancer worldwide.

The global burden of pancreatic cancer and the low survival rates for PDAC mean that there is a critical need to develop new treatment strategies for this form of pancreatic cancer. Jennifer R Shell, assistant professor at the South College School of Pharmacy, Knoxville, USA has collaborated with fellow researchers to explore a new therapy for pancreatic cancer.

X-ray-activated chemotherapy

Shell explains that delivery of drugs to pancreatic tumours can be challenging. Chemotherapy drugs are often administered into the bloodstream and reach their site of action by moving through the network of blood vessels within the tumour. PDAC tumours tend to contain fewer blood vessels and higher

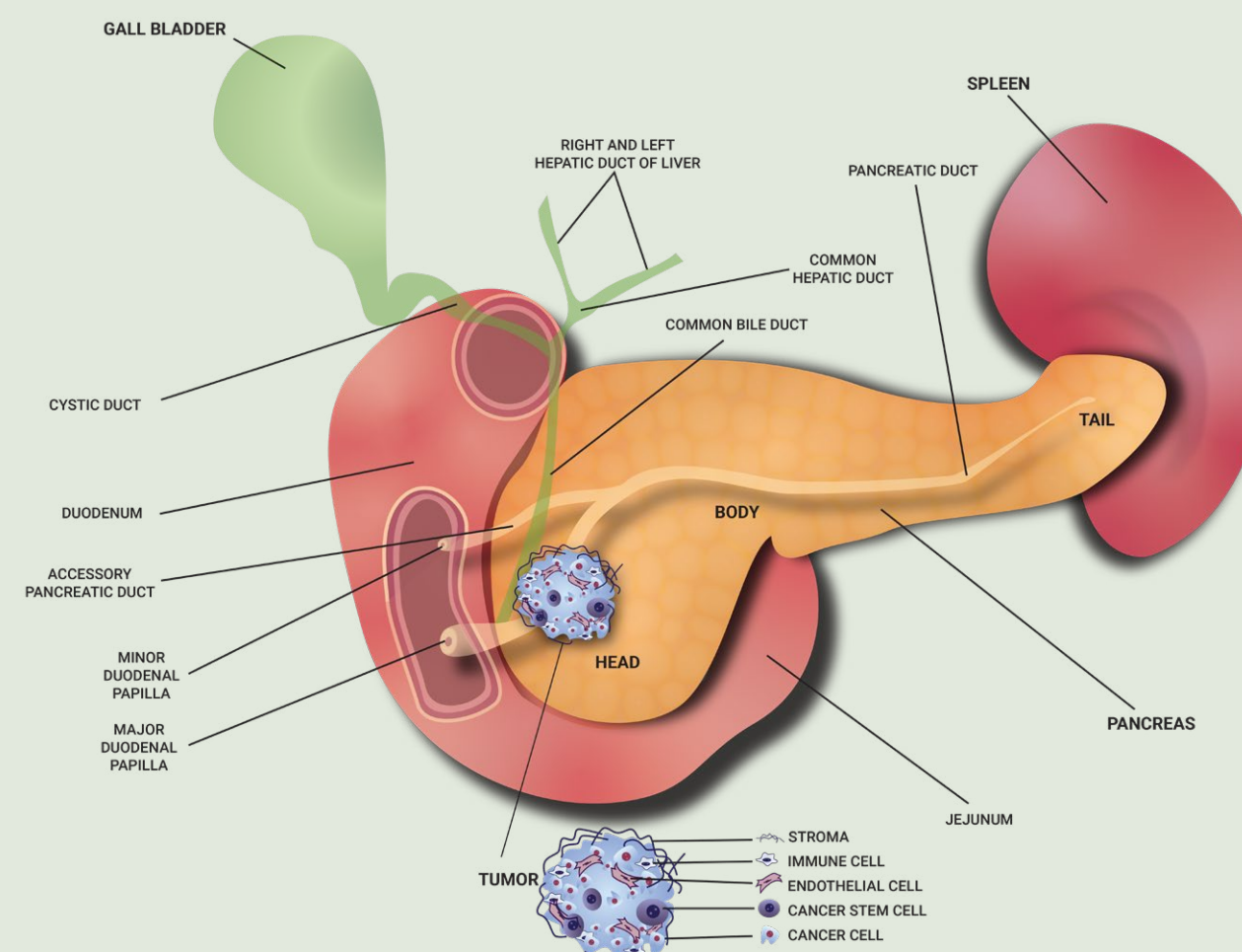
levels of other tissues, which makes it difficult to deliver sufficient amounts of a drug close to the tumour cells.

Kinase inhibitors are a class of drugs used to treat PDAC as the tumours often contain high levels of protein kinases. Kinases are a type of enzyme, therefore, blocking their activity using inhibitors can stop cancer cells from carrying out the functions they need to grow, in turn slowing down the tumour growth. However, other healthy tissues also rely on kinase proteins to function, meaning that they are inadvertently affected by the cancer drugs.

Light-activated chemotherapy enables drug release to be tightly controlled, as the drug isn't activated until it reaches the region of interest. This means that the side effects are reduced. This approach has already been used for other types of cancer, such as brain, lung, and head and neck cancer. Shell investigated whether this delivery approach could be used for pancreatic tumours.

While traditional light-activated chemotherapy is only effective up to a depth of a few millimetres, another form of radiation – external beam radiation

Light-activated chemotherapy enables drug release to be tightly controlled, as the drug isn't activated until it reaches the region of interest.



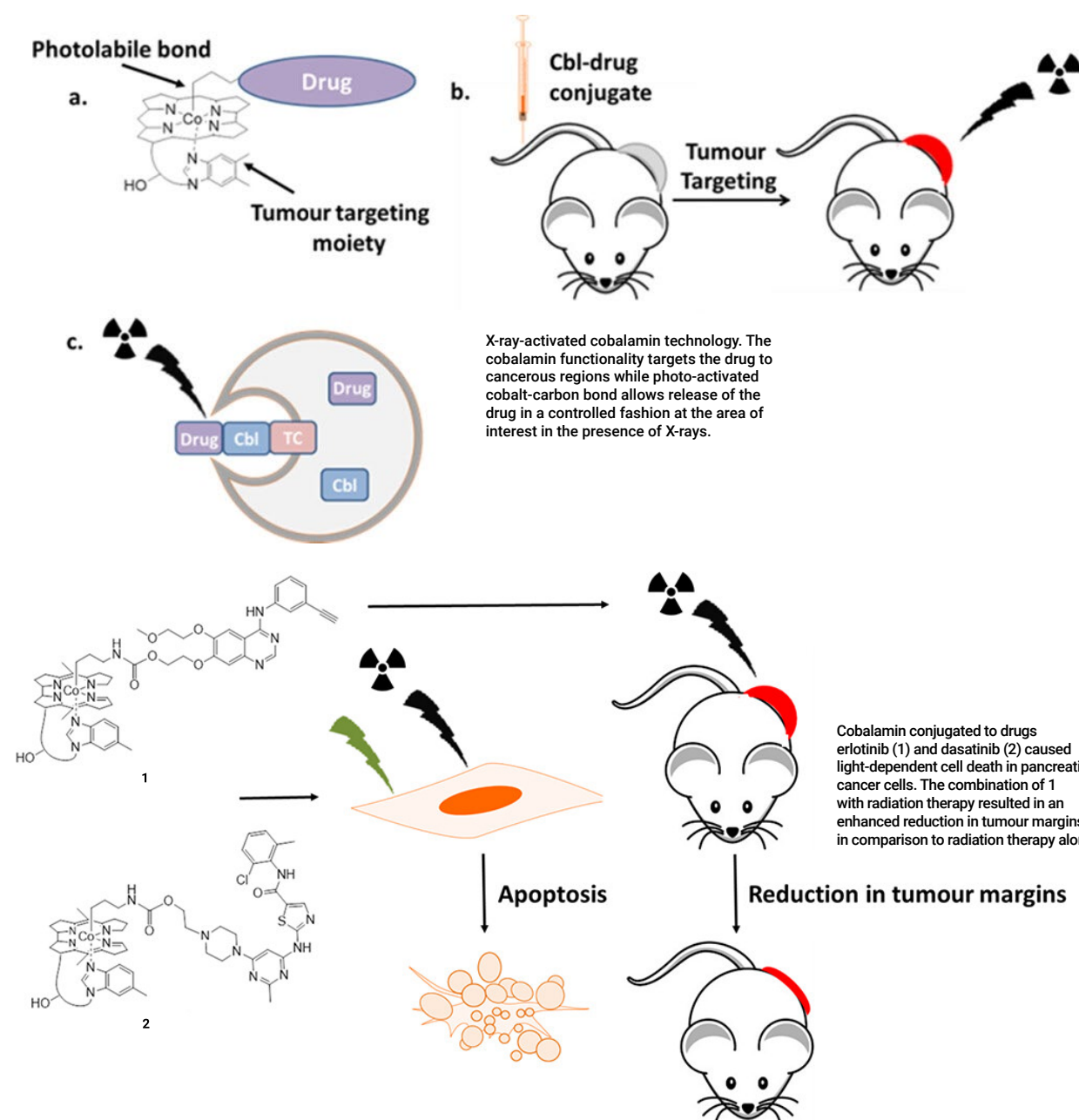
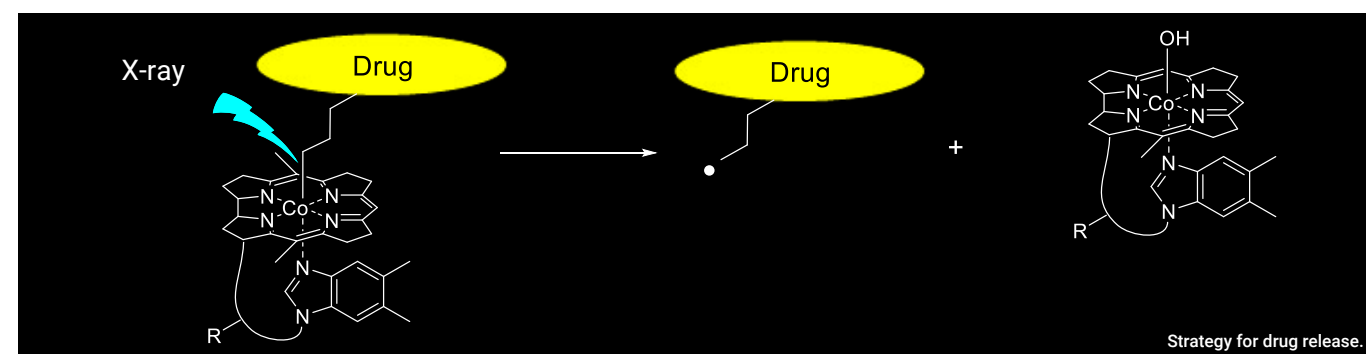


Photo credit: Modified from Gendron, et al. doi.org/10.1021/acs.molpharmaceut.3c00667

The researchers have shown that X-ray-activated, B12-kinase inhibitor technology can be used to reduce the size of pancreatic tumours.

therapy – can reach tumours that are located deeper within organs. This X-ray activated chemotherapy approach shows promise for targeting deep-seated tumours, such as those seen in PDAC.

Reaching the target

Shell and colleagues synthesised two novel drugs, each comprised of a kinase inhibitor (erlotinib, Cbl-Erl, or dasatinib, Cbl-Das) attached to a B12 platform. This means

that the drug attaches to cancer cells which have a receptor for vitamin B12 (the transcobalamin receptor). This platform was selected because B12 derivatives are known to be photosensitive, and thus, a good candidate for light-activated chemotherapy.

In previous works, Shell and colleagues have shown that B12-based drugs are good options for targeting tumour cells. This is

likely to be because there is an increased demand for B12 in some cancer types, including PDAC, meaning that the receptors used to transport B12 into tumour cells are found at high levels on the tumour surface. As drug delivery to pancreatic tumours has previously been challenging, this B12 delivery platform overcomes some of the challenges associated with traditional chemotherapy treatment of this cancer type.

Shell explains that this is a targeted treatment, meaning that certain types of cancer cells are more affected by the treatment than healthy tissue. Using more targeted treatment approaches can help reduce the side effects associated with off-target use of cancer drugs. The drug is only activated after it has been exposed to energy from radiation therapy, providing another way in which its action can be controlled.

Testing drug candidates

The researchers tested both drug candidates in the laboratory first and found that both drugs successfully killed cancer cells when activated with visible light. Of the two, Cbl-Erl killed cancer cells after being activated with

clinically relevant doses of X-rays, the form of radiation most often used in clinical settings.

Next, Shell and colleagues tested the most promising drug, Cbl-Erl, in a mouse model of pancreatic cancer. They found that tumours shrank more when the dual therapy was used as opposed to using radiation alone. Additionally, there was no reduction in tumour size if radiation was not used to activate the drug. This finding was particularly exciting because this specific tumour model was previously thought to be resistant to erlotinib treatment.

Moving forward

The researchers have shown that X-ray-activated, B12-kinase inhibitor technology can be used to reduce the size of pancreatic tumours that are resistant to other drugs. Furthermore, using a combination of radiation therapy and the new drug was more effective than radiation therapy used in isolation. This may allow more effective treatment of tumours deep within pancreatic tissue with fewer systemic side effects. While the results look promising in lab and animal studies, the researchers maintain that further studies will be required to explore how this treatment approach may translate into human subjects in clinical trials.

Personal response

Could this technology potentially be used to treat other types of cancer?

Yes, any cancers that have been shown to overexpress TCblR, which are numerous due to the enhanced vitamin demand in a variety of cancer types, should respond to this type of treatment. In fact, we are currently working on developing treatments for other cancer types. We hope to use the vitamin B12 scaffold as a general drug delivery strategy to ferry drugs into tumours.

Is it possible to use different wavelengths of light to elicit different actions from the same drug compound?

Yes, the wavelength is tuneable to an attached fluorophore in the visible/

near-IR wavelengths of light, and this has previously been accomplished by us in collaboration with David Lawrence. However, the focus and novelty of this study is the use of X-rays for release of the drug. This is advantageous due to the deep tissue penetration of X-rays in comparison to near-IR light and the potential to release drug in the area of interest in conjunction with radiation therapy.

Do you have any clinical trials planned to test this treatment on human subjects, or are more animal studies needed first?

More animal studies are needed before we plan any clinical trials.

Details



e: jennifer.r.shell@eos-pharmaceuticals.com
 in: www.linkedin.com/in/jenniferrshell

Collaborators

Thomas A Shell is an associate professor in the Department of Chemistry and Physics in the School of Mathematics & Sciences at Lincoln Memorial University in Harrogate, Tennessee.

Bio

Jennifer R Shell is an assistant professor in the Department of Pharmaceutical Sciences in the South College School of Pharmacy in Knoxville, Tennessee, USA. She is also the chief scientific officer of Eos Pharmaceuticals LLC.

Further reading

- Gendron, LN, Sheveland, CG, Gunn, JR, et al, (2024) [Radiation-activated cobalamin-kinase inhibitors for treatment of pancreatic ductal adenocarcinoma](#). *Molecular Pharmaceutics*, 21(1), 137–142.
- Gendron, LN, Zites, DC, LaRochelle, EPM, et al, (2020) [Tumor targeting vitamin B12 derivatives for X-ray induced treatment of pancreatic adenocarcinoma](#). *Photodiagnosis and Photodynamic Therapy*, 30, 101637.
- Shell, TA, Shell, JR, Rodgers, ZL, Lawrence, DS, (2014) [Tunable visible and near-IR photoactivation of light-responsive compounds by using fluorophores as light-capturing antennas](#). *Angewandte Chemie*, 53(3), 875–878.

