# Erectile dysfunction drugs could help in the treatment of esophageal cancer

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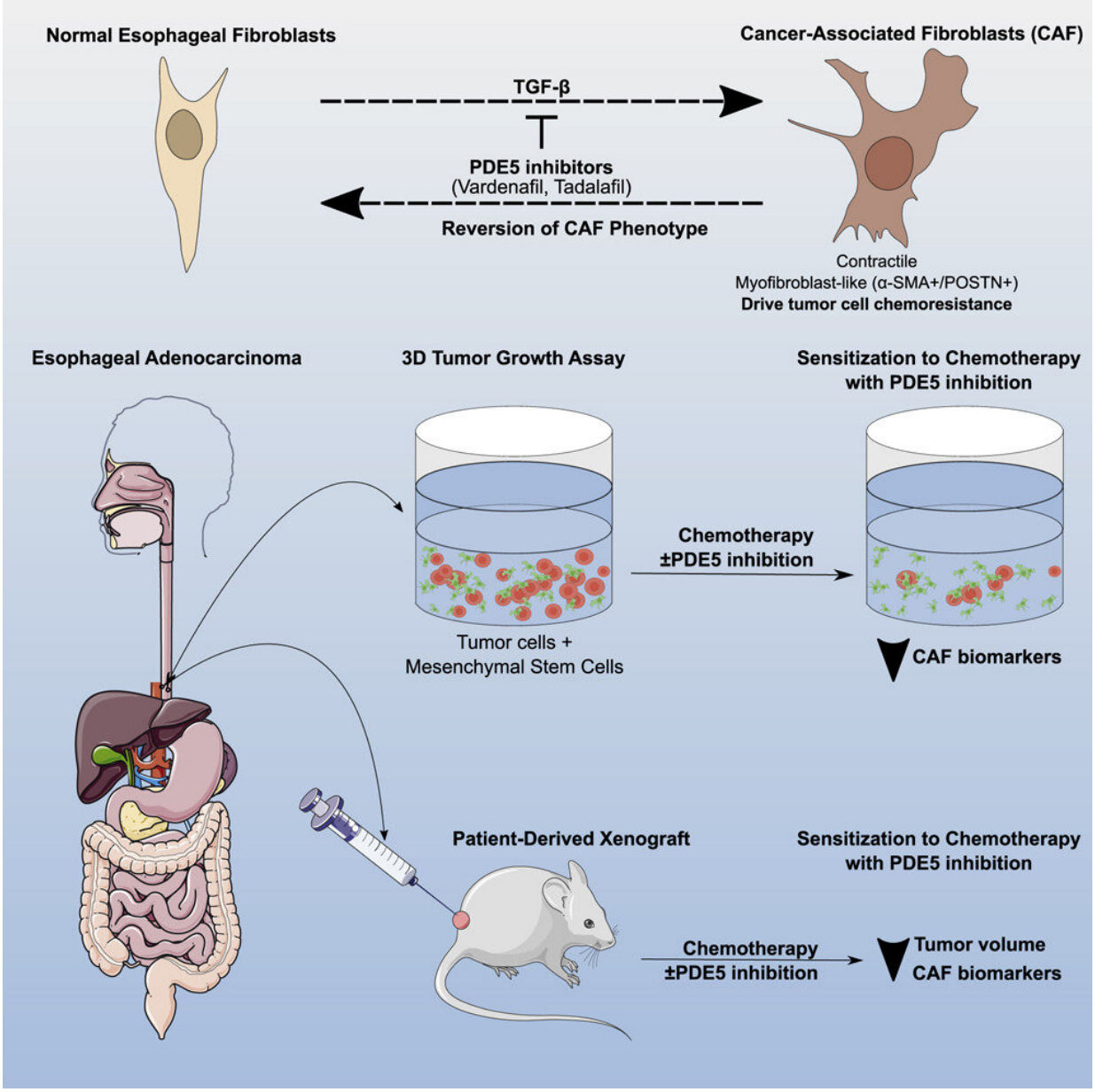

Graphical abstract. Credit: *Cell Reports Medicine* (2022). DOI: 10.1016/j.xcrm.2022.100541

A group of drugs commonly used to treat erectile dysfunction may be able to boost the effect of chemotherapy in esophageal cancer, according to new research.

This research, published today (Tuesday) in *Cell Reports Medicine*, found that the drugs, known as PDE5 inhibitors can reverse chemotherapy resistance by targeting cells called cancer-associated fibroblasts (CAFs) residing in the area surrounding the tumor.

Although this is early discovery research, PDE5 inhibitors combined with chemotherapy may be able to shrink some esophageal tumors more than chemotherapy could alone, tackling chemotherapy resistance, which is one of the major challenges in treating esophageal cancer.

Esophageal cancer affects the food pipe that connects your mouth to your stomach, and while it is a relatively rare cancer, the UK has one of the higher rates in the world, with 9,300 new esophageal cancer cases in the UK every year.

Currently this disease has much poorer outcomes and treatment options compared to other cancers, with around just 1 in 10 patients surviving their disease for 10 years or more. Part of the reason for this is that, in many cases, it can be resistant to chemotherapy, with around 80% of people not responding.

Resistance to chemotherapy in esophageal cancer is influenced by the tumor microenvironment, the area that sounds the tumor. This is made up of molecules, blood vessels, and cells such as cancer associated

fibroblasts (CAFs), which are important for tumor growth. It feeds the tumor and can act as a protective cloak, preventing treatments like chemotherapy from having an effect.

The team of researchers led by Professor Tim Underwood at the University of Southampton wanted to identify the cells in the tumor microenvironment which protects the tumor from treatment so they could target them.

The researchers found that levels of PDE5, an enzyme originally found in the wall of blood vessels are higher in esophageal adenocarcinoma compared with healthy esophageal tissue. High levels of PDE5 were found in CAFs within the tumor microenvironment. They also found that high expression of PDE5 is associated with worse overall survival, suggesting that PDE5 would be an effective target for treatment.

Following this, the researchers tested a PDE5 inhibitor, PDE5i, on CAFs from esophageal tumors. They found that PDE5i were able to suppress CAF activity and make them look more like normal fibroblasts.

Next, collaborating researchers at the University of Nottingham took samples of tumor cells from 15 tissue biopsies from eight patients, and used them to create lab-grown artificial tumors. They tested a combination of PDE5i and standard chemotherapy on the tumors. Of the 12 samples from patients whose tumors developed a poor response to chemotherapy in the clinic, 9 were made sensitive to standard chemotherapy by targeting CAFs with PDE5i.

The researchers also tested the treatment on mice implanted with chemotherapy resistant esophageal tumors and found that there were no adverse side effects to the treatment, and that chemotherapy combined with PDE5i shrunk the tumors more than chemotherapy alone.

An added benefit of using PDE5 inhibitors is that they are already proven to be a safe and well tolerated class of drug that's given to patients world-wide, even in the high doses that would be required for this treatment. The researchers also say that giving PDE5 inhibitors to people with esophageal cancer would be extremely unlikely to cause erections without the appropriate stimulation.

Professor Tim Underwood, lead author of the study and a professor of gastrointestinal surgery at the University of Southampton, said, "The chemotherapy resistant properties of esophageal tumors mean that many patients undergo intensive chemotherapy that won't work for them. Finding a drug, which is already safely prescribed to people every day, could be a great step forward in tackling this hard-to-treat disease."

With the proven safety of these drugs and the positive results from this research, the researchers next step is a phase I/II clinical trial testing a PDE5 inhibitor in combination with chemotherapy in patients with advanced esophageal cancer.

If successful, this treatment could be helping a significant proportion of the around 9,300 people a year diagnosed with esophageal cancer within the next 5 to 10 years. The study could pave the way for the use of PDE5 inhibitors in other cancer types.

Michelle Mitchell, chief executive of Cancer Research UK, says that "developing new drugs for cancer is incredibly important, but doing so from scratch is a challenging process, and many fail along the way. We've also been keen to explore whether existing drugs, licensed for other diseases, can be effective in treating cancer. If these turn out to be successful treatments, they will also prove to be more affordable and become available to patients quicker."

"Progress in treatment for esophageal cancer over the last 40 years has

seen only limited improvement, which is why we've made it a research priority. We're looking forward to seeing how the combined treatment of PDE5 inhibitors with chemotherapy performs in clinical trials."

Nicola Packer, an HR manager from Basingstoke, was diagnosed with esophageal cancer at age 53. She was being monitored due to her diagnosis of a condition called Barrett's esophagus, which can be a risk factor for esophageal cancer "They found my tumor last February. They caught it at stage 2, which is unusual for esophageal tumors as they often go undetected for a long time and are mostly diagnosed at stage 3 or 4."

"Chemo generally doesn't work that well on my kind of esophageal tumor so I knew it couldn't get rid of the tumor completely, that it could only shrink it with the hopes of making surgery more effective. The chemo was draining and each week they would tell me it was shrinking my tumor, but slowly. The anxiety you feel after going through chemotherapy and then having to wait through the weeks of recovery before you can have surgery, knowing that the chemo could only do so much is overwhelming."

"Research like this that could mean people like me can have a better response to chemotherapy is incredibly important."

**More information:** Benjamin P. Sharpe et al, Phosphodiesterase type 5 inhibitors enhance chemotherapy in preclinical models of esophageal adenocarcinoma by targeting cancer-associated fibroblasts, *Cell Reports Medicine* (2022). DOI: 10.1016/j.xcrm.2022.100541

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