Medical Xpress

Could blocking or deleting a protein help prevent common oral cancers?

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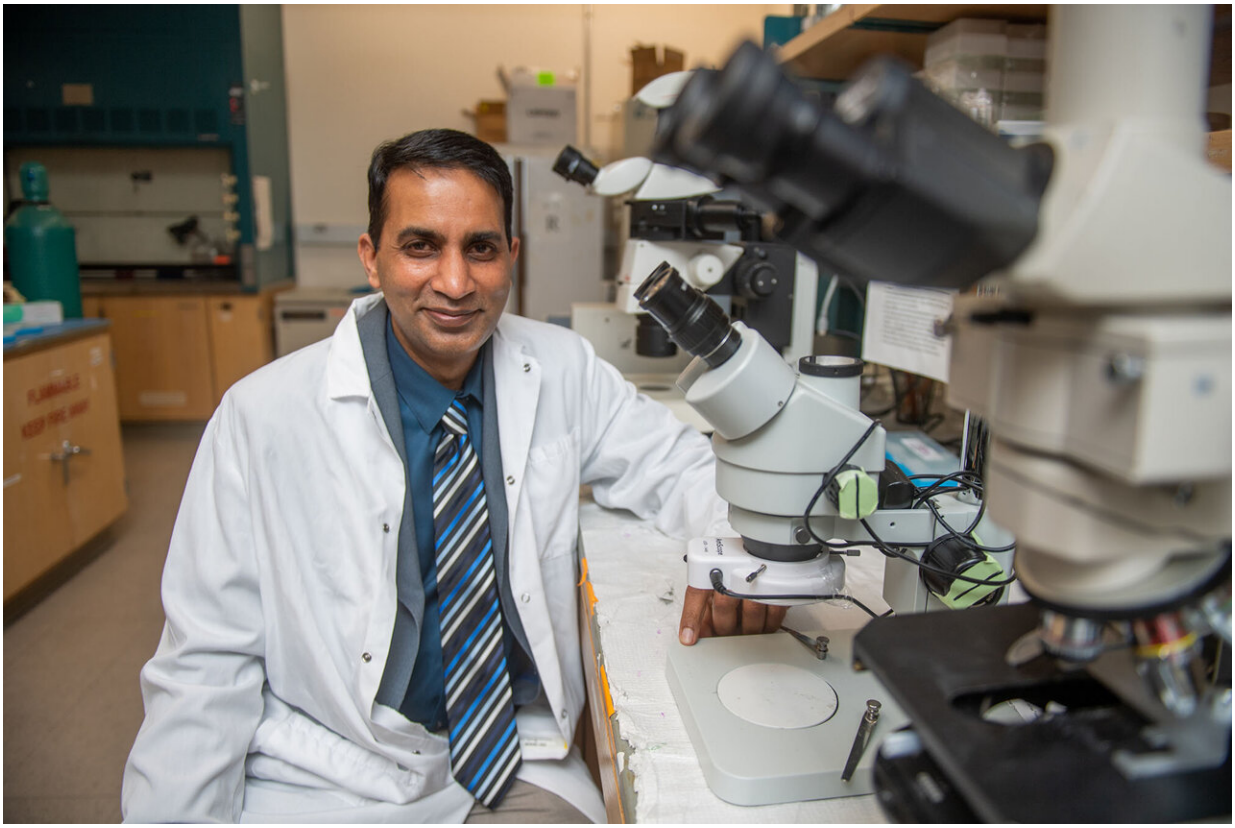

Manish V. Bais, a BU Goldman School of Dental Medicine assistant professor of translational dental medicine, has found the lysine-specific demethylase 1 protein is a potential oral cancer “druggable target,” knowledge that may one day help doctors take down tumors. Credit: Cydney Scott for Boston University Photography

The most common head and neck cancer—oral squamous cell carcinoma—often starts off, as many other cancers do, quite innocently. Perhaps as a little white patch in the mouth or a small red bump on the gums. Easy to ignore, to downplay. But then something changes, and the little blotch becomes more ominous, starts growing, burrowing into connective tissue.

Patients who are lucky enough to see a dentist before things take a nasty turn have a shot at being able to prevent the lesions from turning cancerous—or can at least make sure treatment starts when it's most effective. But for those who aren't that lucky, the outlook can be bleak: the five-year survival rate of oral squamous cell carcinoma (OSCC) is around 66 percent. More than 10,000 Americans die of oral cancer every year; smokers and drinkers are hardest hit.

Now, researchers at Boston University's Henry M. Goldman School of Dental Medicine have found that dialing back—or even genetically deleting—a protein that seems to spur the cancer's growth might help limit a tumor's development and spread. They say their findings make the protein, an enzyme called lysine-specific demethylase 1, a potential "druggable target"—something that doctors could aim chemo and immuno-oncology therapies at to take down a tumor. The study was published in February in *Molecular Cancer Research*.

Given that at least one-third of Americans don't visit a dentist regularly, according to the Centers for Disease Control and Prevention, the discovery could be a future lifesaver for those who miss out on preventative care.

"These findings have significant implications for new and potentially more effective therapies for oral cancer patients," says Manish V. Bais, a lead author on the study and SDM assistant professor of translational dental medicine. "This study is an important step toward the

development of novel groundbreaking therapies to treat oral cancer."

Maria Kukuruzinska, SDM's associate dean for research and a coauthor on the study, says it was rare in the past for dental schools to be diving into the science behind head and neck cancers, with most of the research happening in cancer centers. But that's changing and "dental schools have an advantage over traditional cancer centers when it comes to investigating the science behind the development of OSCC," she says, "because we can get access to premalignant lesions, where cancer centers basically just see patients who are presenting with fully developed disease."

Helping the body fight back: Anti-tumor immunity

Once OSCC takes hold, says Bais, there's little chance of eliminating it completely. Clinicians can try chemotherapy and radiotherapy, even cutting out a tumor. "But there is no cure—you can shrink the tumor, but not eliminate it," Bais says.

In previous research, Bais had found that lysine-specific demethylase 1 (LSD1)—an enzyme that typically plays a crucial role in normal cell and embryo development—goes out of control, or is "inappropriately upregulated," in a range of cancers, including in the head and neck, as well as those in the brain, esophagus, liver, and lung.

"The expression of this enzyme goes up with each tumor stage," says Bais, who's also a member of BU's Center for Multiscale & Translational Mechanobiology. "The worse the tumor, the higher the expression of this protein."

In his lab, Bais began testing what would happen to tumors in the tongue if LSD1 was blocked. To restrict the enzyme, the researchers either knocked it out—by manipulating genes so LSD1 is effectively switched

off—or used a type of drug called a small molecule inhibitor, which enters a cell and impedes its normal function. Already in clinical trials for treating other cancers, small molecule inhibitors haven't previously been tested against oral cancer. Bais found that disrupting LSD1 curbed the tumor's growth.

"The aggressiveness, or bad behavior, of the tumor went down," he says. "We found that when we inhibit this protein, it promotes anti-tumor immunity—our body tries to fight by itself."

But LSD1 isn't the only troublemaker in the tumor: when it's upregulated, it messes with a cell communication process—the Hippo signaling pathway-YAP—that normally helps control organ growth and tissue regeneration. Bais says YAP, LSD1, and a couple of other proteins then get stuck in a vicious cycle, each one pushing the other into increasingly aggressive and harmful moves. "We need to break this cycle," says Bais.

To find a new way of doing that, the researchers coupled the effort to inhibit LSD1 by targeting YAP with a different inhibitor, a drug called verteporfin. Originally developed to help treat serious eye conditions like macular degeneration, verteporfin is being tested by other researchers as a potential cancer treatment, including in ovarian cancer. The combination proved effective, according to Bais. He also threw a third drug into the mix. Bais says using the LSD1 inhibitor in combination with a common immunotherapy drug that helps white blood cells in the immune system kill cancer cells—an immune checkpoint inhibitor called anti-Programmed Death 1 ligand antibody—"showed a favorable response."

"Our findings provide a basis for future clinical studies based on the inhibition of LSD1, either as monotherapy or in combination with other agents to treat oral cancer in humans," he says. The work was recently

boosted with a new $2.6 million National Institute of Dental and Craniofacial Research grant. "Although our studies are preclinical, restricted to mice and some human tissue, we want to expand to look at human clinical trial samples."

Predict success in humans

According to Kukuruzinska, Bais' focus on the biology of oral cancer may also help make the development of other future treatments more efficient.

"People get very excited when you have a drug that may show some positive preliminary results, but very frequently, these studies move forward to humans, cost billions of dollars, and then eventually fail," says Kukuruzinska, who's also director of SDM's predoctoral research program and a professor of translational dental medicine. "If you really understand what pathways, what cell processes are impacted by these inhibitors, then it allows you to predict in advance whether something is going to be successful in human patients."

At BU, the dental school has a teaching clinic on site and shares a campus with the BU School of Medicine and its primary teaching hospital, Boston Medical Center. It's also home to BU's Head & Neck Cancer Program—which pairs basic science researchers with clinicians to look at the underlying mechanisms of oral cancers—and Center for Oral Diseases, a multidisciplinary clinical-research collaborative.

"So, we can think about disease interception," says Kukuruzinska. "And perhaps think about preventing the tumor from happening."

With access to a clinic—as well as head and neck surgeons from the neighboring hospital—researchers like Bais can test any new treatments and approaches on human tissue samples.

"It's a holy grail," Kukuruzinska says of the human samples. "We can interrogate them for responses to small molecule inhibitors, by capturing tumor slices and trying to treat them with different inhibitors to see the response."

Eventually, it could also open the door to personalized, precision medicine, with researchers trialing different therapies on tissue from individual patients. "And then it will predict whether this person can be treated with this study," says Kukuruzinska. "This is something we really want to develop."

With students involved in many of the research projects—three were coauthors on Bais' paper and another, Thabet Alhousami (SDM'22), was a lead author—it means future dentists produced at BU will head into the clinic with a sharper eye for potential malicious bumps and blotches.

"They will be able to say, 'This is precancerous or cancerous'—it will impact their diagnoses," says Bais. "Then, in terms of therapy, because they're now aware of what can work, what immunotherapy can work, they can make specific reference to where patients should go next. It can improve the quality of diagnosis and treatment in the long term."

More information: Thabet Alhousami et al, Inhibition of LSD1 attenuates oral cancer development and promotes therapeutic efficacy of immune checkpoint blockade and Yap/Taz inhibition, *Molecular Cancer Research* (2022). DOI: 10.1158/1541-7786.MCR-21-0310

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