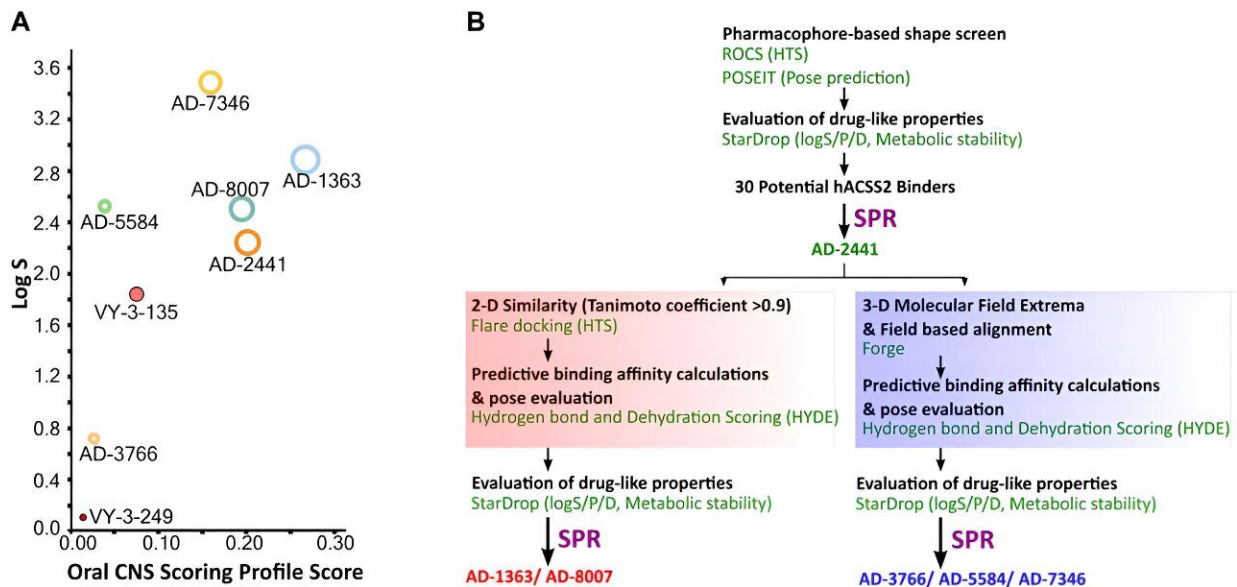


Drug-like molecules show early success in targeting breast cancer brain metastases

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Computational pipeline and predicted drug-like properties for the discovery of AD-2441 and its analogs. Credit: *Frontiers in Pharmacology* (2024). DOI: 10.3389/fphar.2024.1394685

Researchers from Drexel's College of Medicine have identified new drugs that show early success in shrinking breast cancer tumors that have metastasized in the brain. The discovery marks the first time that targeting a key metabolic enzyme in cancer cells in the brain has shrunk tumors in a mouse model. The findings, which could develop into more effective therapies for breast cancer brain metastases, were published in

the journal [*Frontiers in Pharmacology*](#).

Brain tumor growth depends on converting an energy source for the brain known as acetate, to acetyl-CoA—a molecule involved in biochemical reactions in carbohydrates, proteins and in metabolism and that aids in energy production—using an enzyme known as acetyl-CoA synthetase 2, or ACSS2.

With this knowledge, the Drexel team used computer models to identify stable drug compounds that can break through the [blood-brain barrier](#)—a major obstacle plaguing many existing drug options for cancer patients—bind to ACSS2, block its function and shrink tumors in the brain.

"Currently available inhibitors aren't very good, or don't get to the brain," said senior author Mauricio Reginato, Ph.D., a professor and chair of the department of Biochemistry & Molecular Biology in the College of Medicine.

"This work is still in very early stages, but we're finding that these novel compounds are crossing the blood-brain barrier and effectively starving tumors of a key energy source."

In the lab, the compounds, known as AD-5584 and AD-8007, selectively killed cancer cells and blocked tumor growth in animal models, as well as reduced acetyl-CoA and lipids that cancer cells depend on for survival and growth.

"Our predictive computational models helped us identify two ACSS2 inhibitors that exhibited stability and important drug-like properties from a pool of other molecules," said senior author Alexej Dick, MBA, Ph.D., an assistant professor in the College of Medicine.

"We could verify our computational pipeline's success and predictive power in the lab and saw a good correlation with our predictions. This is critical and very helpful for further developing those drugs into a clinically relevant range."

Reginato, who is also Program Leader of the Translational and Cellular Oncology Program at the Sidney Kimmel Cancer Center Research Consortium, reached out to Nicole Simone, MD, a professor and radiation oncologist at Thomas Jefferson University's Sidney Kimmel Cancer Center, to test the combination of these inhibitors with radiation in brain slices containing cancer cells. The colleagues found that the inhibitors work well in concert with radiation to both destroy tumors and block tumor growth.

About [10-15%](#) of stage IV [breast cancer patients](#) develop brain metastasis, a term used when cancer cells spread into the brain, and more than eight out of 10 patients with brain metastasis are diagnosed with end-stage disease [within a year](#) following their diagnosis.

Treating these growths through surgery, radiation and/or chemotherapy can damage healthy brain tissue and doesn't destroy the tumor entirely. Aside from a few chemotherapy drugs, there are few effective cancer drugs that can cross the blood-brain barrier. This same barrier of blood vessels and tissue that protects a healthy brain from infection-causing bacteria is also the largely impenetrable obstacle for existing cancer-fighting drugs.

The authors are working on optimizing these compounds with the hopes of running a clinical trial in patients in the next few years to determine possible toxicities of these new ACSS2 inhibitors, proper dosing, and see if using this drug allows patients to use less radiation. The research team currently holds a patent, is in pursuit of another for newer compounds and is exploring the creation of a startup to further develop the

inhibitors.

In 2022, 42,211 women died from breast cancer, according to the [Centers for Disease Control and Prevention](#). One in eight women will develop breast cancer, according to the [National Breast Cancer Foundation](#).

The current work builds on [earlier research](#) from Reginato and colleagues on the critical role for this ACSS2 protein for tumors in the brain.

"We knew these drugs were killing the cancer cells, but the mechanism we discovered was quite exciting," said Reginato.

"It's causing [ferroptosis](#), a relatively new form of cell death, discovered only about a decade ago, and causes damage to the membrane of a cell, causing it to leak everything out and cause an immune response. The immune cells see the contents of the cell leaking out and any drug that causes this type of cell death and [immune response](#) may also sensitize to radiation or immune therapy."

Currently available FDA-approved immune therapy works well in "hot" cancers, thanks to antigens on the surface of the cancer cells that make it easier for immune cells to recognize and attack tumors. In contrast, "cold" cancers prevent [immune cells](#) from entering tumors, so adding these drugs could someday fulfill a critical need in breast and other cancers.

"We are currently planning to test whether these [new drugs](#) can turn breast cancer brain metastasis into a 'hot' tumor and thus synergize with immune therapy and radiation in preclinical models," Reginato said.

In addition to Reginato and Dick, additional authors on the paper include

lead author Emily M. Esquea, Lorela Ciraku, Riley G. Young, Jessica Merzy, Alexandra N. Talarico, Nusaiba N. Ahmed, Mangalam Karuppiah, Anna Ramesh, Adel A. Rashad, Simon Cocklin and Joris Beld from Drexel, Adam Chatoff, Claudia V. Crispim, and Nathaniel W. Snyder from Temple University and Nicole L. Simone from Thomas Jefferson University's Sydney Kimmel Cancer Center.

More information: Emily M. Esquea et al, Selective and brain-penetrant ACSS2 inhibitors target breast cancer brain metastatic cells, *Frontiers in Pharmacology* (2024). [DOI: 10.3389/fphar.2024.1394685](https://doi.org/10.3389/fphar.2024.1394685)

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