# Repurposed for Hope

## *How Existing Cancer Drugs Point to an Alzheimer's Breakthrough*

Last July, scientists at the University of California, San Francisco (UCSF) and Gladstone Institutes flipped the script on the traditional drug-discovery process with their groundbreaking study published in *Cell*.

Traditional drug discovery is a time-consuming process that involves researching a single disease mechanism in lab studies and then designing a drug to address it. Instead, using computational tools to mine human data first and then validating their findings with lab studies, these scientists identified two cancer drugs with the potential to slow or even reverse Alzheimer's disease (AD) symptoms.

Mind Over Matter® spoke with lead author Dr. Yaqiao Li, a post-doctoral scholar at Gladstone, to learn more about how the study came about, their methods, what they found, and what's next. Dr. Li also shared her bold vision for how this novel research method may one day lead to personalized drug discovery for AD.

### WHAT INSPIRED YOU TO RESEARCH AD?

My interest in neuroscience began when I was a teenager. I noticed my mother's personality and cognitive ability changed after she had surgery for brain cancer, and I wondered if the surgery or the cancer medications caused the changes.

That sparked my interest in neuroscience and led me to choose it as my college major. Dr. Li Gan at UCSF was doing a lot of basic science work, exploring the mechanisms of various neurodegenerative diseases, which I found very interesting.

*I learned that Alzheimer's is a complex, multifactorial disease with few treatment options.*

I recognized that the traditional drug-discovery method of focusing on a single gene or protein might not be the best way to treat and cure the disease. When I started graduate school, I knew I wanted to work on a new approach to drug discovery.

At the same time, I was exposed to new computational tools and the first few studies on single-cell analysis in Alzheimer's patients were published. These things all came together, leading me to think that instead of studying single targets like amyloid-beta or tau, we might be able to identify existing drugs that alter the way specific cells behave by manipulating their gene expression.

## THIS STUDY WAS A COLLABORATION BETWEEN UCSF AND THE GLADSTONE. WHO WERE THE KEY PLAYERS?

The senior researchers were Dr. Marina Sirota, the interim director of the USCF Bakar Computational Health Sciences Institute and professor of pediatrics, and Dr. Yadong Huang, a senior investigator and Director of the Center for Translational Advancement at Gladstone, and professor of neurology and pathology at USCF.

I worked on the computational predictions of this project in Dr. Sirota's lab and the experimental validations in Dr. Huang's lab as part of my graduate degree and was the lead author on the *Cell* paper. Now, as a postdoctoral scholar, I am working in Dr. Huang's lab, and I am very excited to continue this research.

## WHAT DID YOUR DATABASE MINING REVEAL?

First, we analyzed publicly available data from three studies that measured single-cell gene expression in brain cells from deceased people with and without Alzheimer's.

We used the data to learn how genes behave in neurons and glia affected by Alzheimer's. These patterns of gene activity are like disease signatures showing what goes wrong in each cell type. Next, we compared the signatures to the effects of thousands of existing drugs, using a database known as the Connectivity Map, which records how different drugs change gene activity in human cells.

Among 1,300 drugs, we identified 86 that reversed the Alzheimer's disease gene expression signature in one cell type, and 25 that reversed the signatures in several brain cell types. Within that list, ten of those drugs had already been approved by the U.S. Food and Drug Administration for use in people with cancer or other diseases.

A typical drug discovery process involves investigating one drug at a time. Our big data approach allowed us to analyze 1,300 drugs at once.

From there, we combed the UC Health Data Warehouse, a databank of anonymous health records of 1.4 million people over the age of 65. We discovered that five of the ten drugs on our shortlist were associated with a significantly lower risk of developing Alzheimer's.

## WHAT WERE THE TWO MOST PROMISING CANCER DRUGS, AND HOW DID YOU CONFIRM THEY HAD THE POTENTIAL TO ADDRESS ALZHEIMER'S?

We chose to conduct lab studies on two drugs – letrozole and irinotecan. From our previous work, we predicted that letrozole would reduce Alzheimer's gene expression signatures in neurons and that irinotecan would address glia.

Using mouse models of aggressive Alzheimer's, we found that the combination of letrozole and irinotecan addressed many disease processes. It reversed the gene expression signatures in both neurons and glia, and reduced the accumulation of amyloid plaques and brain degeneration.

## DID YOUR RESEARCH ACCOUNT FOR SEX-RELATED DIFFERENCES, AND IF SO, WHAT WERE THE FINDINGS?

The main difference with our research compared to traditional drug discovery is that we started by mining human data first to identify potential drug candidates and then validated our findings in mouse models.

In our human data analysis, letrozole was associated with a 56% lower relative risk of AD overall and 57% lower in women. The ratio of women: men in the data was 33:1, which makes sense because letrozole is used primarily to treat breast cancer. There were not enough men included in the data for us to draw any conclusions for letrozole.

**Single-cell gene expression is a modern method for measuring gene activity in individual cells, providing a better understanding of cell functions within a tissue or sample than older "bulk" methods that averaged the activity of all cells together.**

**A gene expression signature is a unique pattern of gene activity that may be used to help diagnose diseases and determine whether treatments are working.**

For irinotecan, we found a relative risk reduction of 80% for developing AD overall. In this case, the finding applied to both sexes as there was a balanced representation of women and men in the data with enough in each group. We did not look at sex-related differences in AD with the combination of letrozole plus irinotecan because there were not enough people who had taken the combination.

Next, to test our hypotheses from the human data, we used a total of 80 AD-model mice, with an equal split of 40 females and 40 males. We observed some sex-related differences but we didn't investigate them further because our goal was to validate our approach to drug discovery.

The combination of letrozole-irinotecan worked better than either drug alone or the placebo in both male and female mice. The male mice seemed to have better results with the combination than females, but I suspect that may have been because the females tended to have worse pathology than the males.

It's essential to take the animal study results with a grain of salt because they might not necessarily reflect what exactly happens in the human body in either biology or mechanism. In my opinion, the human data findings may carry more weight.

## WHAT ARE THE SIDE EFFECTS OF THESE CANCER DRUGS?

These drugs come with a long list of side effects, including nausea, hot flashes, and bone pain. As a combination therapy for treating Alzheimer's disease, we may be able to use lower doses because they work synergistically. However, that would need to be established in clinical trials.

## WHAT HAPPENS NEXT WITH THESE TWO DRUGS?

We are actively seeking partners to start a clinical trial of the letrozole and irinotecan combination in people with Alzheimer's.

**THESE DRUGS ALREADY HAVE ESTABLISHED SAFETY PROFILES, WHICH MAY HELP ACCELERATE APPROVALS FOR A CLINICAL TRIAL. HOWEVER, VENTURE PARTNERS MAY BE LESS INTERESTED BECAUSE THESE DRUGS ARE ALREADY ON THE MARKET AND PRODUCED BY TWO DIFFERENT MANUFACTURERS.**

We have two ideas for overcoming these challenges. The first is that we could identify similar drugs with a similar mechanism of action but are not yet FDA-approved. The ability to patent another novel combination might generate the needed financial interest from venture partners. Another approach would be to seek academic research partners interested in collaborating on a clinical trial.

**YOU ALSO IDENTIFIED THREE OTHER POTENTIAL DRUG CANDIDATES: METHOTREXATE, A TREATMENT FOR CANCER AND AUTOIMMUNE CONDITIONS LIKE ARTHRITIS AND PSORIASIS; CICLOPIROX, AN ANTIFUNGAL MEDICATION FOR TREATING FUNGAL INFECTIONS IN FINGERNAILS AND TOENAILS; AND SIROLIMUS, AN IMMUNOSUPPRESSANT USED TO PREVENT REJECTION OF ORGAN TRANSPLANTS. DO YOU PLAN TO STUDY THESE DRUGS TOO?**

Yes, we are definitely still interested in these three other drugs that we identified in our shortlist of five and plan to study them in the lab.

Our focus, though, will be to build a much larger drug response library in human neuronal cell lines. We're aiming to include 10,000 compounds, either FDA-approved or previously investigated. Since the new database will be more specific to neurological diseases, we hope to identify even more targets than were possible with the Connectivity Map, which was originally built using cancer cell lines.

## WHAT SETS YOUR WORK APART FROM OTHER DRUG REPURPOSING STUDIES?

There are several studies similar to ours as drug repurposing has become a hot field of inquiry. But many other drug discovery studies begin with animal testing

**Letrozole** is primarily used to treat breast cancer. It works by blocking the enzyme aromatase, lowering estrogen levels and inhibiting the growth of estrogen-dependent breast cancer cells. It is sometimes used to treat infertility in men by blocking the conversion of testosterone to estrogen.

**Irinotecan** is a chemotherapy drug used to treat metastatic colorectal cancer and advanced small cell lung cancer. It causes DNA breaks that cannot be repaired, causing cancer cells and other rapidly dividing cells to die.

and then face challenges when trying to translate their findings to humans.

Our study was the first to identify drug targets based heavily on human data, validated extensively in mouse models, and supported by more human evidence that they are associated with a reduced risk of Alzheimer's in people who take them to treat cancer.

## WHAT'S YOUR BOLD VISION FOR THE FUTURE OF DRUG DISCOVERY FOR AD?

Our study analyzed the cellular disease processes that occur in Alzheimer's across many people. However, as your readers know, some groups are disproportionately affected by the disease: women and people with the *APOE4* genetic marker have an increased risk and a faster disease progression.

We can apply the same method we used in our study to identify the most promising drugs for subgroups of people. Part of my future work will be trying to identify the best drug candidates for women with or without the *APOE4* mutation.

***I'm passionate about finding a cure for Alzheimer's, and I think finding a cure will require a precision medicine approach because the disease is so complex.***

Biological data available to us is growing at an exponential rate. Ultimately, we can apply our method to individual patients by defining their specific molecular profiles and then using artificial intelligence to pinpoint the drug or drugs with the greatest potential to make a difference for each person.

## OTHER PROMISING DRUGS FOR ALZHEIMER'S

### STATINS

Statins are common treatments for lowering cholesterol levels and are given to people who have an increased risk of heart attack or stroke. A team of researchers at Monash University in Australia, led by Dr. Joanne Ryan, is conducting a clinical trial to determine whether statins may also help prevent dementia over a period of five years.

They are analyzing blood samples and brain imaging to see if statins affect proteins related to Alzheimer's disease. The study is funded by the Alzheimer's Drug Discovery Foundation.

### A BLOOD PRESSURE & DIURETIC COMBINATION

A team of researchers at Harvard Medical School, Rutgers University, and the Johns Hopkins University School of Medicine is leading the Drug Repurposing for Effective Alzheimer's Medicines (DREAM) study, sponsored by the National Institute on Aging.

In their paper, published in *Clinical Pharmacology & Therapeutics* in February 2025, they reported that the combination of the blood pressure medication hydrochlorothiazide and the diuretic drug amiloride was associated with a lower risk of Alzheimer's and related dementias, according to population-based data. The research team concluded this combination merits further investigation.

### UPDATE: GLP-1 DRUGS

The glucagon-like peptide-1 (GLP-1) drug Ozempic (semaglutide) was initially approved for treating type 2 diabetes. Recently, it was also approved for lowering the risk of worsening cardiovascular disease and kidney disease in people with diabetes. Wegovy, which also contains semaglutide, was approved as a weight-loss medication for people with obesity and also for reducing risk of major cardiovascular events in adults with heart disease and obesity.

In our story "Ozempic & Brain Health," published in Mind Over Matter® Volume 20 (Spring 2025), we spoke with one researcher who was studying semaglutide as a potential treatment for early Alzheimer's and mild cognitive impairment. On November 24, 2025, the manufacturer announced that while semaglutide improved Alzheimer's-related disease markers in both the EVOKE and EVOKE Plus Phase 3 clinical trials, there was no measurable change in delay of disease progression compared to placebo.

We also spoke with another researcher studying semaglutide for potential smoking cessation benefits in people with overweight or obesity. The Phase 2 clinical trial for that indication continues, with an estimated completion date of mid-2026.