



ScienceNatters

In this episode of Science Natters, we learn about a recent study authored by **Professor Lali Medina-Kauwe** from **Cedars-Sinai Medical Center** in the US.

In this study, Professor Medina-Kauwe and her team show that a new bioengineered protein that they have created, called HPK, is able to cross the blood-brain barrier and deliver targeted cancer drugs directly to brain tumours. This new therapeutic method could revolutionise the treatment of aggressive cancers and improve outcomes for patients with brain tumours.

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Reference: Alonso-Valenteen, F., Mikhael, S., Wang, H. et al. Systemic HER3 ligand-mimicking nanobiotoparticles enter the brain and reduce intracranial tumour growth. *Nat. Nanotechnol.* 20, 683–696 (2025).

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Brain tumours are particularly difficult to treat due to an extraordinary, evolutionary defence: the blood-brain barrier. This tightly regulated wall of endothelial cells shields the brain from harmful substances circulating in the blood. However, this protective shield doesn't discriminate; it also blocks most therapeutic molecules, including some of medicine's most advanced cancer drugs.

For years, researchers have been asking the same question: how do we get effective drugs into the brain to target and treat tumours? Although scientists have made remarkable progress with targeted therapies elsewhere in the body, the moment that tumours spread to the brain, the success stories often stop. Why? Because the blood-brain barrier simply refuses to let most drugs through.

This issue can affect patients suffering from many kinds of cancer. As a cancer grows and spreads, it can metastasise, forming tumours in other parts of the body, including the brain. Therefore, patients with breast, lung and skin cancers can all suffer from brain tumours. For example, triple-negative breast cancer is fast-moving, aggressive and has a dangerous tendency to metastasise in the brain. It also lacks the hormone receptor targets that make other breast cancers treatable with targeted drugs. So, when triple-negative breast cancer reaches the

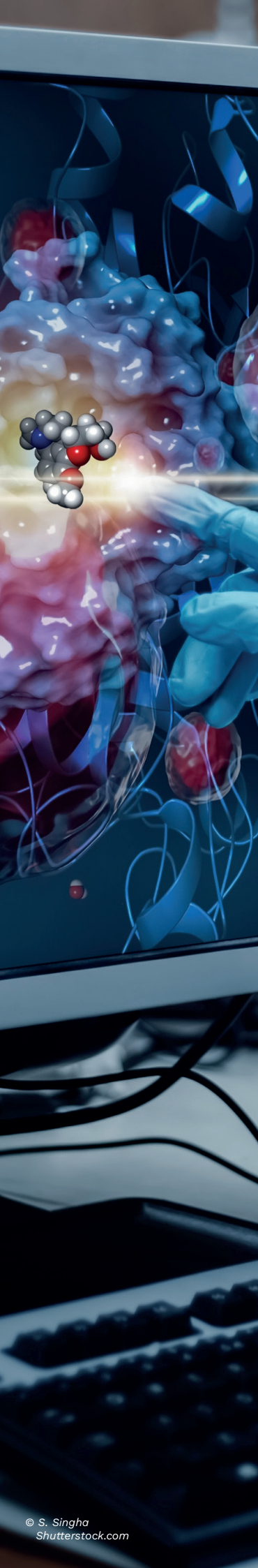
brain, the options are limited. Median survival is often less than a year, and the treatments we do have — chemotherapy and radiation — are blunt tools, bringing heavy side effects with limited precision.

At Cedars-Sinai Medical Center in the US, biomedical scientist Professor Lali Medina-Kauwe has been developing a new therapeutic method that targets triple-negative breast cancer brain tumours. Lali and her team have been using bioengineering techniques to create a new protein molecule that can pass through the blood-brain barrier, find brain tumours, and deliver cancer drugs with exceptional precision.

Professor Medina-Kauwe created this new protein, called HPK, by piecing together different segments of other proteins that have desirable characteristics. For example, HPK features a ligand that binds to human epidermal growth factor receptor 3, or HER3, which is present on the endothelial cells of the blood-brain barrier and is associated with many metastatic tumour cells. As a result, HPK is pulled across the blood-brain barrier and is then attracted to aggressive brain tumour cells.

Another bioengineered feature of HPK is its ability to enter cancerous cells. Using a protein from the common cold virus, HPK allows itself to be swallowed by the





tumour cells and then uses an escape mechanism to avoid being digested. Finally, a short positively-charged peptide allows HPK to carry other molecules, including therapeutic treatments such as cancer drugs.

So, armed with a bioengineered synthetic protein that can pass through the blood-brain barrier, enter cancerous cells and deliver therapeutic cargo to destroy them, Professor Medina-Kauwe and her team began testing their new technique.

The team developed and tested three prototypes of HPK, their new HER3-homing protein, each carrying a different molecule. The first of these prototypes was called HerOND and carried fluorescently tagged sequences of DNA. HerOND was tested both in mouse models and in a model of the human blood-brain barrier.

When injected into mouse models with breast tumours and healthy brains, HerOND was detected both in the tumours and the brains, showing that it is capable of crossing the blood-brain barrier in mice. In contrast, trastuzumab, a targeted therapy used to treat breast cancer, was only detected in the breast tumours.

The team also injected HerOND into an 'organ chip' model made of human stem cells that formed a blood-vessel-like tube of endothelial cells overlain by neuron cells, thus resembling a blood vessel in the brain and providing an ideal model for testing the human blood-brain barrier. When injected into this model, 42% of HerOND particles passed through the wall of the tube and entered the neuron cells, suggesting that it is capable of passing across the human blood-brain barrier. In contrast, fluorescently tagged pieces of DNA that were not contained within an HPK protein were completely blocked from passing into the neuron cells.

This experiment also shed light on the pathway that HPK uses to cross the blood-brain barrier. Inhibiting human epidermal growth factor receptor 3 on the endothelial cells of the organ chip significantly reduced the amount of HerOND that passed into the neuron cells. As well as this, inhibiting caveolae, small, bubble-like structures that shuttle molecules between cells, also significantly reduced the transport of HerOND. These two findings suggest that HPK makes use

of HER3 and caveolae transport pathways, sliding through the blood-brain barrier via natural vesicle trafficking rather than brute force.

While crossing the blood-brain barrier is an impressive feat, the real question that the researchers needed to answer was: what does HPK do when it enters the brain? To answer this question, Professor Medina-Kauwe created intracranial triple-negative breast cancer models by implanting cancer cells directly into the brains of mice. When her team injected HerOND into these models, they were able to detect it in brain tumour tissue, showing that HPK is able to not only cross the blood-brain barrier, but also to target cancerous cells within the brain.

Having shown that their HPK protein can enter brain tumour cells, Professor Medina-Kauwe and her team then set their sights on testing its therapeutic capabilities. To do this, they used the second of their HPK prototypes, HerDox, which carried a chemotherapy drug called doxorubicin.

Using the intracranial triple-negative breast cancer mouse models from the previous experiment, they compared HerDox with Lipodox, another chemotherapy drug. The results were nothing less than remarkable. Compared to Lipodox, HerDox slowed tumour growth, prevented tumour expansion and, most importantly, left healthy brain tissue unharmed. The effects on the health outcomes for the mice were clear. Lipodox-treated mice were more likely to exhibit weight-loss, reduced mobility and even tumour growth in other parts of the body. Furthermore, 71% of mice treated with Lipodox (and 100% of mice that received no treatment) required early euthanasia, compared to just 43% of HerDox-treated mice.

The researchers also tested their third HPK prototype, HerGa, which carried a toxic gallium-corrole compound that can be used to treat cancer, against more traditional blood-brain barrier transport strategies. Compared to these strategies, HerGa penetrated deeper into tumour cells, caused less damage to healthy tissue, and extended survival more effectively.



What makes these results so impressive is that this isn't just another incremental improvement in drug delivery — it's a potential shift in how we approach brain cancer treatment altogether. The blood-brain barrier has been a significant bottleneck in oncology for many years and, until now, researchers have relied on brute-force strategies, like temporarily opening the blood-brain barrier or flooding the system with high drug doses. But these approaches often cause serious side effects, damaging healthy tissue while barely improving drug penetration.

Professor Medina-Kauwe's study offers something entirely different. By designing a protein that uses the brain's own transport systems, she and her team have found a way to cross the blood-brain barrier safely, precisely, and without chemically modifying the therapeutic drugs. Compared to existing treatments, like Lipodox, the HPK protein offers a higher level of precision and causes less damage to healthy brain tissue.

The versatility of the HPK protein is also impressive. As human epidermal growth factor receptor 3 is found not only on triple-negative breast cancer cells but also in many metastatic cancers, from melanoma to ovarian cancer, HPK could be adapted for a wide range of HER3-positive tumours. HPK can also be loaded with a range of therapies including chemotherapy drugs, RNA therapies, or even gene-editing tools.

Of course, before this therapy can be used to start treating patients, it must go through the rigours of clinical testing. However, with these impressive results in hand, Professor Medina-Kauwe is excited about the HPK protein's potential to target brain tumours and improve outcomes for patients suffering from triple negative breast cancer and other aggressive forms of cancer.