CANCER

NEW DUAL THERAPY TARGETS LUNG TUMOURS & SECONDARIES IN THE BRAIN

by Cliff Dominy PhD

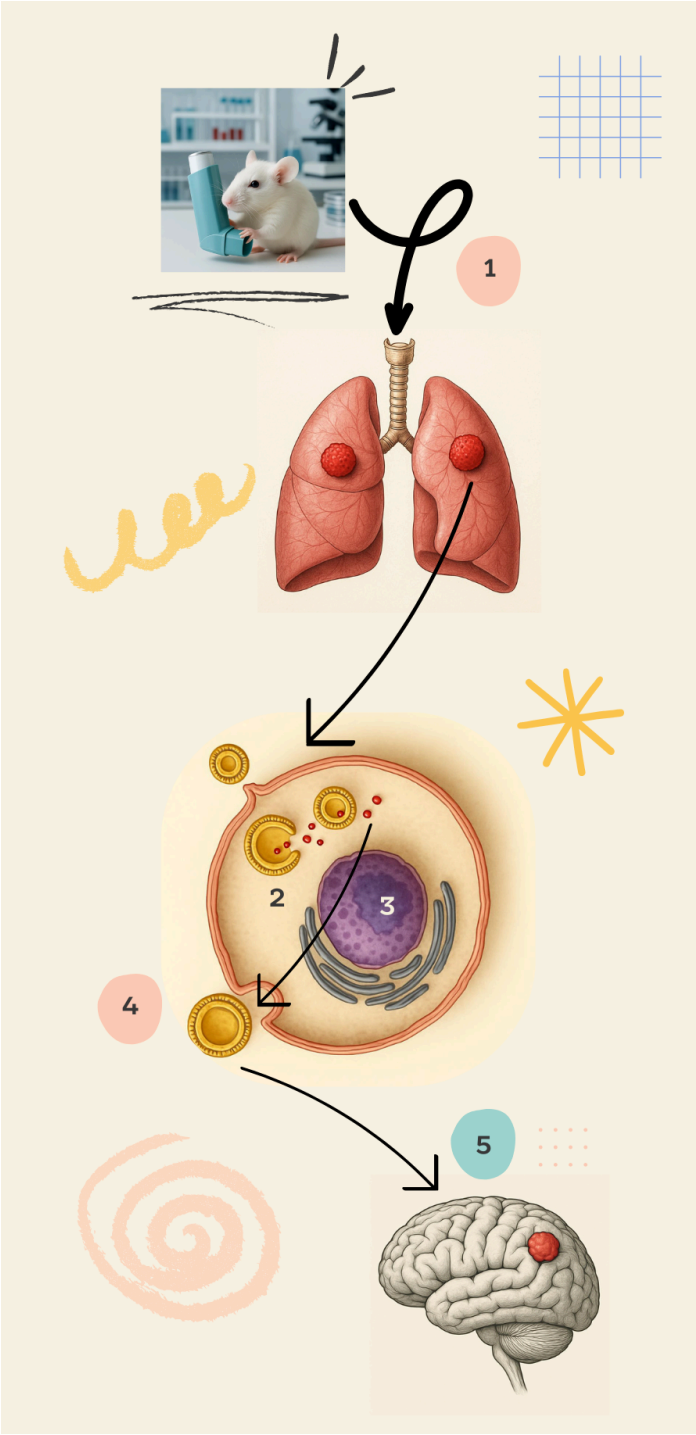
Scientists have developed a novel inhalable drug delivery system that could revolutionize the treatment of stage 4 non-small cell lung carcinoma 1. The study, conducted in mice appeared safe and effective, with a significant survival benefit seen in animals with the disease.

The paper was published in Nature Communications in April 2025 by scientists at Shandong University in China. The researchers tested an aerosolized liposome preparation in mice with non-small cell lung carcinoma (NSCLC) and brain metastases.

NSCLC is the most common form of lung cancer, and its spread to the brain marks a critical and often fatal progression of the disease in humans. Indeed, the Global Cancer Observatory estimates that every year 1.5 million people die from the disease globally. By the time the cancer spreads to the brain (Stage 4), life expectancy is less than a year.

Their innovative approach to tackling NSCLC can be broken down into five discrete steps (shown in the diagram opposite).

1. The chemotherapeutic payload is delivered to the lungs inside an aerosolized liposome particle.
2. Inside the particle, the primary drug, osimertinib, actively inhibits tumour growth. A fellow passenger, a small DNA molecule, is released into the cell and provides the genetic blueprint for the production of a second gene inhibitor.
3. The new DNA takes control of the tumour and forces the mass production of a small gene-silencing RNA molecule.
4. The molecular hijackers exit the lung in a tumor-provided escape pod, called an exosome, and use it to travel through the bloodstream to the brain.
5. The tumour-derived exosome is readily transported across the blood-brain barrier, where it binds to neurons and unleashes the gene silencing therapy on the secondary growths in the brain.



The challenge of cancer ... challenge accepted

Cancer is a complex disease, and cancer therapies often need to overcome several challenges. With brain tumours, obstacles include selective delivery of the drug to the target organ (to minimize side effects), and getting the drug across the impenetrable blood-brain barrier to access the tumours. The new Shandong therapy addressed both problems.

The researchers turned to liposomes - microscopic droplets engineered to mimic cell membranes. Because liposomes are composed of naturally occurring molecules, they are easily absorbed by the body. These laboratory-made particles can be loaded with the drug or gene therapy of choice - in this case, the scientists used both technologies.

The cargo ...

The scientists loaded the liposomes with four key ingredients ...

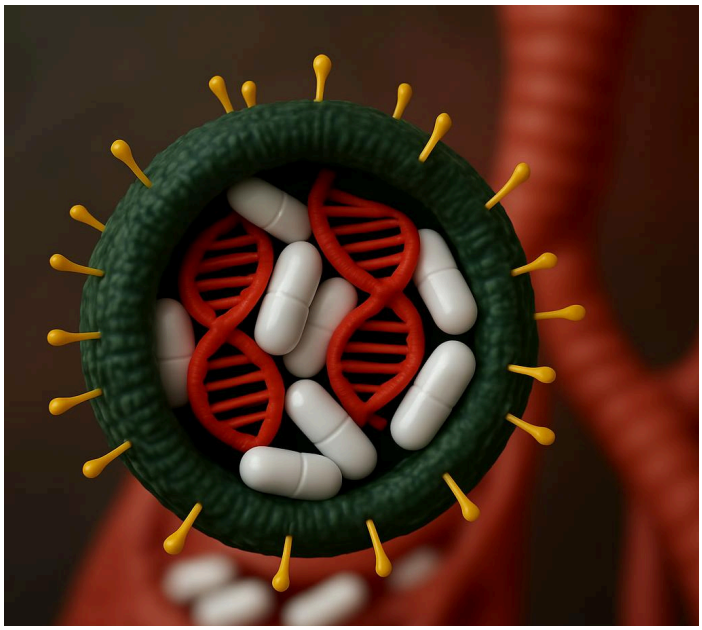
- **Osimertinib** - a third-generation tumor inhibitor. Osimertinib is a potent inhibitor of the growth factor receptor that drives tumour growth. This small molecule is one of the few anti-cancer drugs capable of crossing the blood-brain barrier, making it uniquely suited to treat both primary lung tumours and secondary brain metastases.
- **Surfactant Protein B:** The researchers coated the liposomes with a lung-specific protein called Surfactant Protein B (SP-B). SP-B is found only in lung tissue and plays a critical role in maintaining lung function- it is essential for life. By incorporating SP-B onto the liposome's surface, the team ensured that the drug delivery system would home in specifically on lung cells, effectively guiding the therapeutic cargo to its intended destination.

Genetically modified DNA was included within the liposome. It encoded two very different genes.

- **Gene 1:** A small RNA inhibitor for a second tumour growth factor active in the brain. Gene therapy was considered the best approach to tackle this second growth factor as no drugs exist to inhibit it. Unlike small drug therapy, which inhibits the progression of a physical tumour, gene silencing therapy stops it before it can begin.
- **Gene 2:** The second gene encoded the G-protein from the rabies virus - a surface protein that the virus uses to recognise and attach to neurons in the brain.

Phase 1: Targeting the lung

The aerosolized liposomes were inhaled by mice with NSCLC and secondary tumours in the brain. Guided by SP-B, the liposome entered the lung space and effectively bound to the pulmonary cells on the lung surface. The researchers found no evidence of the liposomes attaching elsewhere in the respiratory tract. They reported the particles were absorbed efficiently by the lung cells, including the tumour cells.



Phase 2: The tumour turns traitor

Once unpackaged inside the tumour, the osimertinib drug was released into the cell. Here, it quickly and efficiently blocked the primary growth factor that drives tumour growth. Meanwhile the DNA payload entered the nucleus of the tumour and took control of its genetic apparatus. It achieved this by overproducing its gene-silencing RNA inhibitor along with its brain guide - the G protein from the rabies virus.

Phase 3: Targeting the brain

The therapy's third phase exploited the tumour's communication network to reach the brain. The osimertinib and its co-conspirator, the RNA inhibitor, escaped the tumour in exosomes. Exosomes are naturally occurring vesicles similar to liposomes, which typically carry signaling molecules around the body. Exosomes have been implicated in spreading cancer to other organs. These exosomes, however, thanks to the G-protein on their surface, had been repurposed to carry their lethal cargo straight to the brain.

The paper had convincing proof that the exosomes, displaying the rabies G protein, were efficiently delivered across the blood-brain barrier and taken up by the secondary tumours in the brain. Effectively, the tumour-derived exosomes acted as a molecular cloak to pass across the impenetrable barrier. The gene-silencing RNA dramatically reduced the tumour growth factor levels in the brain and effectively inhibited tumour growth. Once again, there was no evidence of off-target effects.

Results - Safe & effective ... in mice

The results in mice were highly encouraging, suggesting both the safety and efficacy of this therapeutic approach. By day 70 of treatment, 80% of the treated NSCLC mice were alive, compared to complete mortality in the untreated group by day 42. The therapy showed strong selectivity for lung and brain tissue, with minimal activity in other organs. Importantly, mice treated with the inhalable liposomal form of osimertinib showed no signs of toxicity, whereas some control mice receiving the drug via traditional infusion developed liver damage.

The way ahead ...

While this therapy shows great promise, transferring the technology to humans will be some way off. Further toxicology studies in other animal models are required. Researchers will need to fine-tune the pharmacology of the particles by determining optimal dosage and treatment duration. On the technological front, scaling up liposome production and improving its stability will be critical steps before human clinical trials can begin.

Despite these challenges, the potential impact could be profound. Lung cancer claims 125,000 lives annually in the U.S., with non-small cell lung carcinoma accounting for most of the cases. The Shandong team's innovative dual therapy represents a hopeful advance in the fight against this devastating disease.

Reference

1. Fu X, Shi Y, Wu H, et al. Inhalable liposomal delivery of osimertinib and DNA for treating primary and metastasis lung cancer. Nat Commun. 2025;16(1):3336.