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Professor Louis Burton Nabors III
Dr Natalia Filippova

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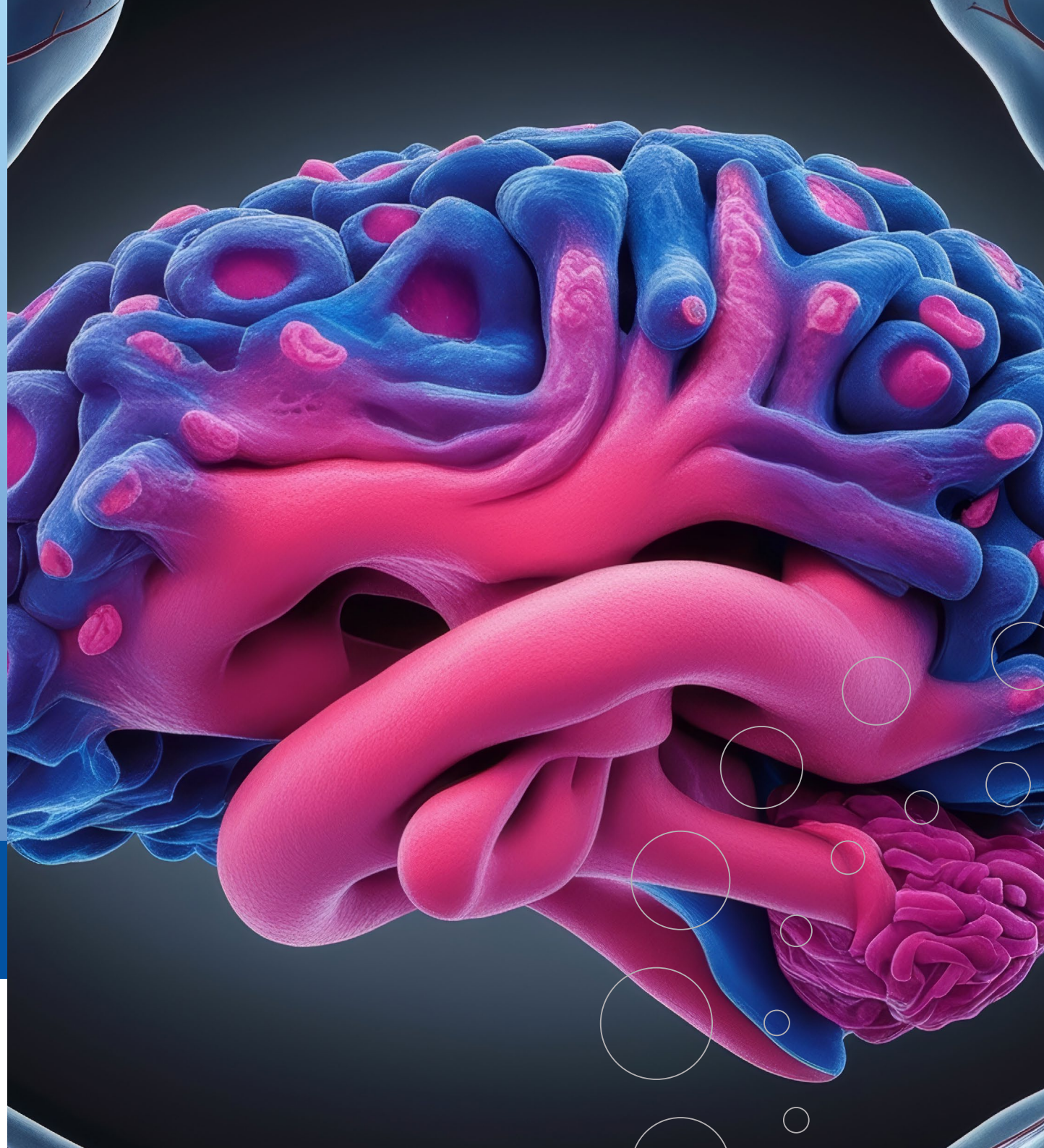
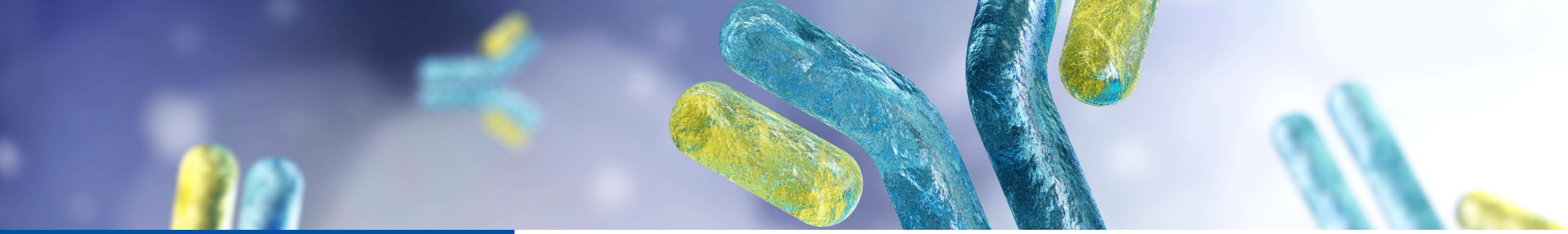




Behind the Barrier: Targeting Immune Signals in Glioblastoma

Glioblastoma is one of the most aggressive and deadly forms of brain cancer, known for its rapid progression and resistance to treatment. Professor Louis Burton Nabors and Dr Natalia Filippova at the University of Alabama have highlighted the role of the immune system in this cancer, and in particular, a receptor called TREM1, which is involved in disease severity and progression. They developed a novel compound called SRI42127, which can block this pathway and reduce tumour growth in laboratory experiments. Their work shows that targeting the tumour's immune support network may offer a promising new approach to developing effective therapies.

Glioblastoma: Fast-growing and Aggressive

Glioblastomas are the most common type of cancerous brain tumours in adults. They are also typically fast-growing and aggressive, with patients often surviving only 12 to 18 months following diagnosis. Current treatment options include surgery, chemotherapy, and radiotherapy. But as glioblastomas grow quickly and are able to invade deep into brain tissue, they are difficult to remove completely with surgery, and even with chemotherapy and radiation, the tumours often rapidly return, making effective treatment a major challenge.

Glioblastomas often have a high degree of heterogeneity – meaning that the tumour contains multiple different cell types, which can further increase difficulties in treating the cancer as some of the cell types in the tumour may be more resistant to therapies or have stem cell-like properties, allowing them to cause the tumour to grow again.

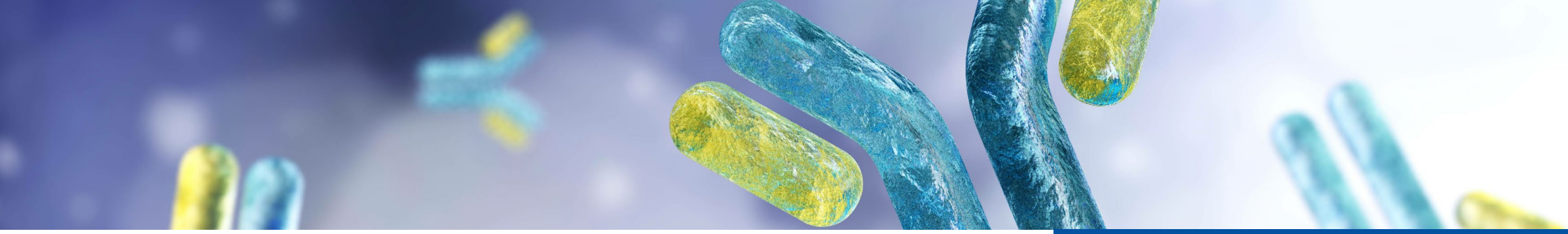
As a fast-growing, low survival rate cancer, it is vital to understand the biological mechanisms that drive tumour growth and treatment resistance. By identifying the key signals, molecules, and pathways that allow these tumours to grow and spread, researchers may be able to develop new, more effective therapies that could extend patient survival and improve quality of life. Professor Louis Burton Nabors and Dr Natalia Filippova are experts in the study of brain cancers and conduct cutting-edge research into the development and spread of these tumours to give insights into novel treatments.

Hijacking the Immune System

The brain is usually protected by a natural barrier called the blood-brain barrier, which keeps harmful substances and immune cells out. However, when something goes wrong – like when a tumour is present – this barrier becomes weaker and allows immune cells to enter the brain. Some of these cells belong to a group called myeloid-derived immune cells, which normally help fight infections and repair damage. But in the case of glioblastoma, these immune cells may actually be helping the tumour instead of stopping it.

One of the ways glioblastoma hijacks the immune system is through a protein called TREM1 (Triggering Receptor Expressed on Myeloid Cells 1), which is produced by certain immune cells. TREM1 is normally involved in boosting the body's immune response during infections by helping immune cells, and the body's inflammatory system become more active. However, researchers have discovered that TREM1 can actually promote cancer growth; TREM1 can reduce the impact of other immune cells which act against the cancer and can cause cells to release molecules which help glioblastoma grow.

The team analysed data from glioblastoma patients and found that the people with higher levels of TREM1 in their tumours had more aggressive tumours and worse survival outcomes. This suggests that TREM1 might be playing a key role in helping glioblastoma resist treatment and come back after therapy. Through laboratory experiments, the team discovered high levels of TREM1 in glioblastoma tumours. The team also used mouse models of glioblastoma to explore how TREM1 interacts with tumour cells. Their results showed that immune cells with TREM1 can fuse with glioblastoma cells, forming hybrid cells that could make the tumour more aggressive and harder to treat.



Development and Testing Novel Compounds

With growing evidence that TREM1 helps glioblastomas grow and evade treatment, the team began exploring whether blocking TREM1 could weaken the tumour. TREM1 is an established drug target in other brain diseases such as Parkinson's and Alzheimer's diseases and so has potential as a therapeutic target in glioblastoma as well. Rather than targeting TREM1 directly, the team focused on a protein called HuR, which helps turn on many inflammation-related genes, including those involved in TREM1 activity. To disrupt this process, Professor Nabors and Dr Filippova designed a new compound called SRI42127, a small molecule that limits the activity of the HuR protein. By stopping HuR from doing its job, the researchers hoped to reduce TREM1 and the harmful signals it sends out indirectly.

The drug was tested in mice models of glioblastoma designed to closely mimic the way the disease behaves in humans. Mice with glioblastoma were treated with SRI42127 twice a day for 20 days. The team then carefully examined the tumours using lab techniques that allowed them to track changes in both the cancer cells and the immune cells inside the tumour.

Early but Promising Results for SRI42127

The results were striking. Mice treated with SRI42127 had smaller, less invasive tumours compared to untreated mice. Importantly, there was also a significant reduction in immune cells producing TREM1 within the tumour microenvironment, particularly the types of immune cells known to help tumours grow. The drug also reduced the number of fused 'hybrid' cells, where glioblastoma cells had merged with immune cells. These hybrids are thought to be especially dangerous as they may help the tumour spread and resist treatment.

While SRI42127 is still in the early stages of development and not yet approved for human use, these findings provide a strong foundation for future studies. The team hopes that combining drugs like SRI42127 with existing therapies could improve treatment outcomes and give patients with glioblastoma a better chance at survival.

Glioblastoma remains one of the hardest cancers to treat, but by targeting its immune-based defences, researchers are uncovering new ways to fight back. Professor Nabors and Dr Filippova's work has exciting implications for glioblastoma patients – the discovery of TREM1's role in tumour growth and spread is a real breakthrough in understanding this disease. If found to be effective, SRI42127 could help improve survival rates for glioblastoma patients worldwide.

Article written by Helen Rickard, PhD

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MEET THE RESEARCHERS

Professor Louis Burton Nabors III
Department of Neurology, University of Alabama, Birmingham, AL, USA

Professor Louis Burton Nabors is a physician-scientist in the field of neuro-oncology. As well as being board certified with the American Board of Psychiatry and Neurology, he leads academic research in primary brain cancer through molecular biology, clinical trials, and population science studies. Professor Nabors serves as Vice-Chair of both Neurosurgery and Neurology and is the Director of the Neuro-Oncology programme at the University of Alabama. He has a particular interest in interdisciplinary and translational research in cancer biology and treatment and, as such, holds secondary appointments with the Department of Biomedical Engineering and the Department of Cell Biology. Professor Nabors has an extensive publication record and has received significant grant funding. His work is at the forefront of primary brain cancer research and aims to alleviate the burden of this disease on patients and caregivers through a neuro-centric approach.

CONTACT

bnabors@uabmc.edu
https://scholars.uab.edu/734-louis-nabors

Dr Natalia Filippova
Department of Neurology, University of Alabama, Birmingham, AL, USA

Dr Natalia Filippova holds a PhD in developmental biology. She furthered her experience and expertise in neurophysiology and neuro-oncology during postdoctoral positions at the Institute Pasteur and the University of Alabama. She is now an Assistant Professor within the Department of Neurology at the University of Alabama where she both teaches and conducts research in the field of neuro-oncology. Her current research focuses on understanding the glioblastoma microenvironment and the drug-discovery axis, leading to the development of novel small molecules with glioblastoma therapeutic potential. Alongside her research, Dr Filippova contributes to the field of neuroscience by acting as a Judge at the University of Alabama Neuroscience Roadmap Conference and Medical Student Research Days, lecturing in the Neurology Grand Rounds lecture series, and serving as a reviewer for multiple journals.

CONTACT

as1999@uab.edu
https://scholars.uab.edu/3720-natalia-filippova

FUNDING

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FURTHER READING

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