

Searching for enigmatic biomarkers to address a devastating degenerative disease

Friedreich's ataxia is a genetic disorder that damages the nervous system and dramatically reduces life expectancy. It is caused by low levels of an elusive protein called frataxin. Innovative treatments aim to boost frataxin levels, but measuring the success of these treatments is not easy. Fortunately, **Professor Ian Blair** and his team of pharmacologists at the **University of Pennsylvania** in the US are on the case. They are using powerful mass spectrometry techniques to identify biomarkers – other molecules that correlate with frataxin levels but are easier to measure. Their discoveries could accelerate the development of new treatments for Friedreich's ataxia.



Professor Ian Blair

Department of Systems Pharmacology and Translational Therapeutics, Perelman School of Medicine, University of Pennsylvania, USA

Fields of research

Pharmacology, translational therapeutics

Research project

Using mass spectrometry to analyse frataxin proteins as biomarkers to improve treatments for Friedreich's ataxia

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Talk like a ...

pharmacologist

Biomarker — a measurable characteristic that indicates the state of a biological process

Biopsy — an examination of tissue removed from a living body

Frataxin-M — a protein found in mitochondria that is essential for the assembly of other proteins required for mitochondria to function properly

Friedreich's ataxia — a rare neurological disease that causes progressive damage to the nervous and cardiovascular systems

Gene therapy —

a treatment for genetic diseases that involves providing the patient with the correct gene to supplement the malfunctioning gene that is responsible for the disease

Mass spectrometry —

an analytical technique used to identify and quantify the molecules in a sample

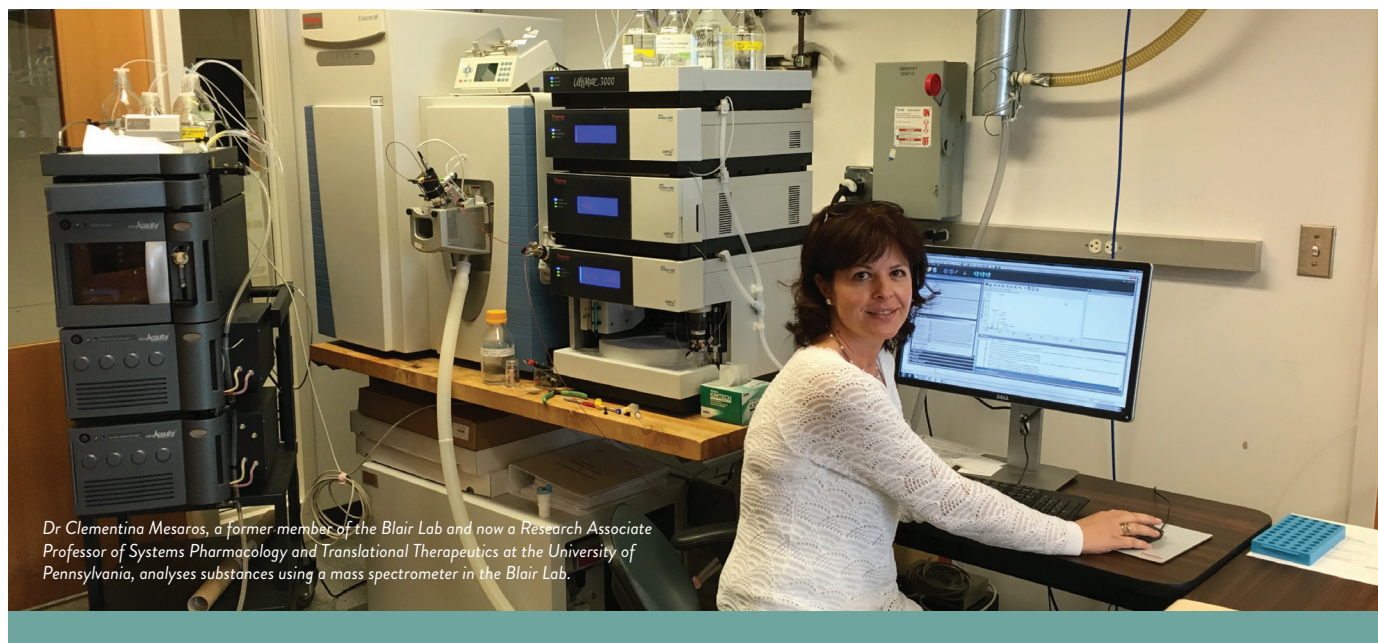
Mitochondria — small

structures in all cells (except red blood cells) that provide the cell with energy

Friedreich's ataxia affects roughly one in 50,000 people in the US. "It is a disorder that progressively damages neurons and other tissues over a period of years," says Professor Ian Blair, a pharmacologist at the University of Pennsylvania. "Most patients

progress to wheelchair dependency within twenty years of diagnosis in childhood, and most die in their thirties from heart disease." Ataxia refers to poor muscle control, which leads to difficulties with co-ordination, balance and speech – and in Friedreich's ataxia these symptoms get worse over time. Friedreich's ataxia also causes heart problems and other complications. There is currently no cure for

Friedreich's ataxia. "There is one approved treatment that slows its progression, but it is far from a cure," says Ian. "Alternative therapeutic approaches are in development, but challenges in measuring their effectiveness are slowing progress." To address this, Ian and his team in the Blair Lab are using innovative laboratory techniques to improve methods for determining the success of treatments.



Frataxin: an elusive protein

Friedreich's ataxia is caused by a genetic mutation that leads to low expression of a protein called frataxin. The mitochondrial form of frataxin (frataxin-M) is essential for mitochondria to function properly and supply cells with the energy they need to stay alive and healthy. Emerging therapies for Friedreich's ataxia aim to boost levels of frataxin via different means. Gene therapy, for example, would modify patients' genes to increase frataxin expression, while pharmacological approaches include developing drugs to modify the activity of transcription factors – proteins designed to boost the transcription, and therefore expression, of genes that produce frataxin.

But measuring whether these therapies are working is difficult because tracking disease progression by observing clinical symptoms can take months or even years. To detect changes over shorter timeframes, thereby enabling faster development of new treatments, it is necessary to look at molecular activity. As therapies for Friedreich's ataxia aim to increase frataxin levels in the body, frataxin would be the most obvious molecule to measure to determine whether the therapy is effective. However, it is not an easy molecule to measure.

"Frataxin is not secreted by cells into the bloodstream or other body fluids," says Ian. This means it is challenging to collect samples. Instead of a simple blood test, patients require a biopsy (usually from the heart) to remove tissue that can be analysed, a process that is both costly and invasive. "Also, frataxin levels are naturally very low – only a few nanograms per millilitre,"

Ian continues. This means it is challenging to detect and quantify changes in frataxin levels.

Mass spectrometry: ultra-sensitive molecular detection

To overcome these challenges, Ian and his team use a powerful technique called mass spectrometry. "Mass spectrometry is an analytical technique used to identify and quantify molecules," Ian explains. It can precisely and sensitively detect even very low levels of frataxin protein – something no other technique can do.

"The most powerful mass spectrometers now enable us to quantify frataxin levels from very small samples – as small as only one milligram of heart biopsy tissue," says Ian. "I anticipate that future advances in mass spectrometry technology will continue to push the limits of sensitivity, which will make it possible to quantify proteins from even smaller samples."

Using mass spectrometry, Ian has shown that frataxin levels increase after gene therapy, indicating the treatment is effective. The technique has also highlighted a strong correlation between frataxin levels and the severity and progression of Friedreich's ataxia in patients. However, highly sensitive mass spectrometers are expensive, uncommon and require specialised knowledge to use them effectively. This means this method cannot be used to monitor the disease and therapeutic effectiveness for every Friedreich's ataxia patient. So, Ian and his team are using mass spectrometry to pave the way for more accessible techniques – specifically by searching for biomarkers.

Biomarkers: correlating with frataxin

Ian wanted to find other molecules whose concentrations correlated with frataxin concentrations, but which were easier to quantify. "A biomarker is any measurable characteristic that indicates the state of a biological process," he explains. "In our case, we sought a molecular biomarker – a molecule whose levels correlate with frataxin levels." Mass spectrometry provided a tool that was sensitive enough to detect such correlations. During their search, Ian and the team made an unexpected discovery. They found a different form of frataxin, which they named 'isoform E', that is present in red blood cells, which do not contain mitochondria.

The purpose of isoform E remains mysterious, but it adds a highly useful tool in Friedreich's ataxia diagnosis and monitoring. "The isoform E version of frataxin provides a precise, sensitive and physiologically relevant biomarker for Friedreich's ataxia," says Ian. Most importantly, isoform E is found in the blood, meaning it can be measured from a blood test rather than an invasive heart biopsy, and it is present in much higher concentrations than frataxin, meaning it can be detected by less sensitive equipment.

"Our mass spectrometry measurements of frataxin and isoform E expand the biomarker landscape, improve clinical trial outcomes and advance research for Friedreich's ataxia treatments," concludes Ian. "Our comprehensive approach is crucial for supporting ongoing and future research into therapeutic strategies for Friedreich's ataxia."

About *pharmacology*

Pharmacology is the branch of science and medicine that focuses on how drugs, chemicals and gene products interact with the body. “Pharmacology is a hybrid science encompassing chemistry, biochemistry and molecular biology,” says Ian. “This means that diverse careers are available in academia, the pharmaceutical and biotechnology industries, and instrumentation development.”

Ian is an expert in mass spectrometry and its applications to pharmacology and biochemistry. “I am highly motivated to use my expertise to enable better therapeutic development, faster

evaluation of potential treatments and improved prediction of patient outcomes,” he says. “It’s been highly rewarding to help facilitate the development of new therapies for Friedrich’s ataxia and other diseases.” For example, the Blair Lab is also using mass spectrometry to support the development of new therapies for Alzheimer’s disease, a neurological disease that causes memory loss and impaired cognition. Recently, Ian and his team showed how the secretion of a specific protein leads to the death of neurons and other cells, and that preventing this secretion could disrupt this process. “This protein could be a

viable drug target to help restore neuron function,” says Ian.

Techniques such as gene therapy are radically expanding the breadth of pharmacology. “A pharmacologist’s work can range from the study of how tiny molecules can be used as drugs and how they are transformed in the body, through to the analyses of large proteins and how modifying their regulation can help treat genetic diseases,” says Ian. “This makes pharmacology a very exciting scientific discipline to pursue as a career.”

Pathway from school to *pharmacology*

At high school, it would be useful to study chemistry, biology, mathematics, computer science and physics.

At university, study a degree in pharmacology or a related field such as pharmaceutical science, biochemistry or molecular biology. Ian recommends taking modules in organic chemistry, analytical chemistry, medicinal chemistry and mathematics.

Explore careers in *pharmacology*

Ian recommends seeking a research internship in a pharmacology, biochemistry or medicinal chemistry lab at a university or other research institution. Pathways to Science is a useful directory of summer camps, internships and other student opportunities across the US: pathwaystoscience.org/Discipline.aspx?sort=MED-PharmSci_PharmaceuticalSciences

The Perelman School of Medicine at the University of Pennsylvania runs the Teen Research and Education in Environmental Science (TREES) Program, a research and mentorship programme for high school students: ceet.upenn.edu/education-training/high-school

The British Pharmacological Society provides a wealth of educational resources about the range of career opportunities in pharmacology, from academic research and clinical pharmacology to science policy and medicine licensing: bps.ac.uk/careers-in-pharmacology



Meet Jingqi

Dr Jingqi Fan is a research associate in the Blair Lab.

I've loved animals and all kinds of living creatures since my teenage years. I've also always been curious about the origins of life and how life functions. For example, I often wondered things like 'Why doesn't blood flow out of our bodies?' and 'How does our hair regenerate?'

I previously worked as a clinical doctor, and it was my patients who inspired me to pursue pharmacology research. I realised I couldn't clearly answer their questions to explain the specific mechanisms of drug actions, the true causes of diseases, or why drugs work more effectively in some people than others. This sparked my interest in exploring biomarkers, which led me to conduct protein-related research in the Blair Lab.

I had no prior experience with mass spectrometry before joining the Blair Lab. My most memorable day in the lab was when I first used the mass spectrometer to obtain high-quality protein signals. I was thrilled!

Exploring the unknown is the most captivating aspect of pharmacology lab work. When you do research in pharmacology, you will be exposed to many interesting areas of study and technologies. This means you can explore what you are most interested in.

When I'm not working in the lab, I love playing badminton, swimming and travelling.

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Meet Teerapat

Dr Teerapat Rojsajjakul is a research associate in the Blair Lab.

As a teenager, I was interested in science and engineering. I didn't follow a traditional path into pharmacology research. My journey spans multiple institutions and took me from Thailand to Italy to the US. In that time, I have worked as a chemist across multiple disciplines, as a process engineer in the semiconductor industry, and now I use the breadth of my knowledge and experience to contribute to pharmacology research as an analytical and protein chemist.

I enjoy the opportunity to integrate cutting-edge analytical techniques with translational goals. I find it especially rewarding to contribute to projects that have direct therapeutic implications, where our findings can inform drug development and improve patient outcomes.

Pharmacology demands curiosity, precision and creativity – qualities that thrive in young minds. It offers the chance to explore how drugs interact with biological systems, uncover mechanisms of disease and contribute directly to the development of life-changing therapies. For those who want to make a tangible difference in human health while pushing the boundaries of scientific discovery, pharmacology is an incredibly rewarding path.

In my free time, I enjoy activities that help me recharge and stay curious. I love learning about gene therapy as it keeps me inspired and sharp, and I find joy in writing. I also enjoy spending time outdoors, which helps me stay balanced and brings fresh perspective to my work.

Teerapat's top tips

1. Stay curious and never stop learning. Science is constantly evolving, and a commitment to lifelong learning will keep you sharp and relevant.
2. Build strong technical skills. Mastering core techniques, such as mass spectrometry or computational analysis, will open doors for you.
3. Choose work that aligns with your values. When your research contributes to improving lives, it becomes more than a job – it becomes a legacy.