Research Highlight #303

Lewis Francis, Ph.D.
Swansea University

From the Basics to Complexities—Unraveling Cell and Tissue Characteristics

The Human Genome Project was a remarkable scientific feat where researchers came together to map the entire human genome—providing countless biological insights, including into the various ways genetics can impact human anatomy and physiology. This project was also one of the driving forces that started Dr. Lewis Francis on his path to becoming a Professor at Swansea University. Lewis has always been interested in how genetic drivers (e.g., mutations) and changes in transient gene regulatory networks can lead to changes in protein complementation and cellular function across the spectrum of diseases. He explored this as an undergraduate student at Swansea University studying Medical Genetics, and in industry, where he performed technical work to underpin (epi)genetic discovery and understanding.

Cellular and Molecular Drivers of Infertility

Wanting more of a challenge and an opportunity to dive deeper into the tradeoff between gene regulation and cellular phenotype, Lewis pursued a Ph.D. in Cell and Molecular Biophysics from Swansea University. During this time, he studied how the surface lining of the womb (the endometrial tissue) changed and developed throughout the menstrual cycle to prepare for receiving a developing embryo and establishing pregnancy. This provided Lewis with an exciting opportunity to study a dynamic differentiation environment at the molecular, cellular, and tissue levels:

> "The overarching research question was, can we better understand potential cellular and/or molecular features of the endometrial epithelium that may be driving infertility? I had the fundamental question about progesterone signaling and the secretory phase of the reproductive window, in the wider context of assisted reproductive techniques, IVF, and on the human side of things. So, I thought about bringing the multiple resolutions of biology together, from the nucleus to the tissue surface."

ABOUT THE RESEARCHER

Professor Lewis Francis is a Professor in Functional (Nano)Biology and is a lead academic in the Reproductive Biology and Gynecological Oncology Research Group (RBGO) at Swansea University. He obtained his Bachelor of Science in Medical Genetics and a Ph.D. in Cell and Molecular Biophysics from Swansea University. Within RBGO, he leads the Biophysics and Epigenetics research programs with a range of research focusing on cellular and molecular heterogeneity in tissue micro-environments. Lewis works with global collaborators to champion cross-discipline research and delineate complex systems, focusing primarily on solid tumor cancers.

RBGO Website:
https://sites.google.com/view/rbgo/home

Lots of women suffer from infertility due to several reasons that can include infertile pathology, egg defects, underlying pathologies (polycystic ovarian syndrome or endometriosis), or even for unexplained reasons. His Ph.D. involved a lot of work with cell surface glycoproteins, familiarizing him with atomic force microscopes (AFMs). They used AFMs and in vitro models to track cellular differentiation at high resolution and mimic the molecular interactions that underpin embryo attachment to the maternal surface. Future work would bring him and his collaborators to develop other biotechnologies and techniques in this space, focusing within the context of infertility and, more recently, gynecological cancers.

Combining Fundamentals with New Biotechnology Tools

Lewis feels he was lucky to undertake postdoctoral training in an industrial-academic program with "Active Motif" in Belgium. Here, they worked to develop biotechnology tools for the epigenetic market, looking at the nuclear patterns of gene regulation and histone modification. He describes this as a great experience:

> "I was working at that interface between fundamental biology and translational biotech development. I was always thinking about better understanding the regulatory systems in cells while focusing on scalable biotechnology development and the research market, aiming to help other scientists develop their understanding of fundamental systems as well. So, I have a BioAFM heart and used basic training in epigenomics technologies very early in my career to shape links between nuclear signaling and cellular differentiation. Since then, and in my academic career, I've been trying to put those two together."

Scientific research has come a long way with the development of research tools and techniques that allow scientists to spend more of their time exploring different questions in the lab. For example, Lewis mentions the positives of kit-based protocols for routine experiments in the laboratory, freeing up time to develop upstream complex pseudo-tissue models or downstream skill development in analytical assays. Understanding the fundamental biology, chemistry, and /or physical aspects of disease phenomena informs the development of research questions and new products or product applications for the market, helping Lewis and his collaborators to expand their research:

> "Understanding begins from the ground up and really gives you an opportunity to think about how you might apply novel analysis methods and techniques in physiologically relevant contexts. This is particularly important with a reductionist approach, where we try to limit our reliance on animal models. In animal models, we need more complex in vitro models, in 3D. Then, how do we apply everything that was developed in 2D to a 3D model? I really like the development side of science that we do with our collaborators, such as Bruker. This is highlighted by some of the strategic partnerships we have in Swansea and with the Houston Methodist Research Institute in the US."

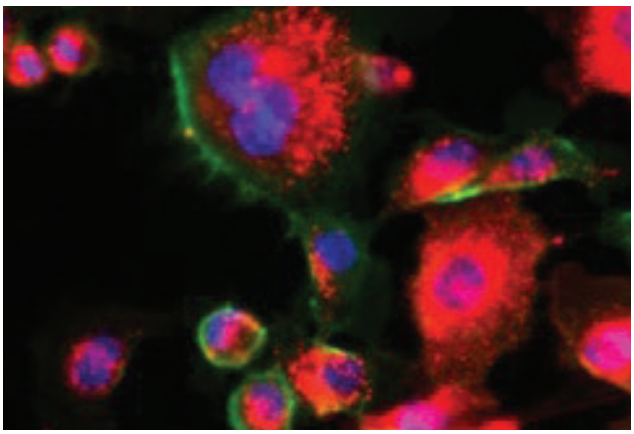
Focusing on the fundamentals of science has taken Lewis a long way in his research and continues to be his approach to the work done at home at Swansea University or abroad with collaborators. A large portion of his job as a professor in the medical school at Swansea is co-leading a diverse research team and postgraduate teaching as the program director for the Nanomedicine Master's program. Along with ten other academic colleagues, this program lets students explore the best approach to developing tools and applications at the nanoscale level. Lewis shares an example, saying;

> "We try to understand how we use assays that look at the nanoscale, like BioAFM, to characterize cell-cell and cell-matrix interactions that may be driving disease differentiation stages. Then, we can target different stages of disease for downstream therapeutic development. We also work with clinical colleagues who will tell us what the unmet clinical need is to focus our efforts on in a given area."

Currently, Lewis is focusing much of his time on teaching and helping students find their niche research focuses, rather than going into the lab. On top of this, his current area of study is solid tumor cancer, and more specifically, ovarian cancer.

Ovarian Cancer and a Pharmacological Research Agenda

Ovarian cancer is characterized by heterogeneous cell types and populations that communicate with each other and their surrounding matrix-rich environments. Because of this heterogeneity, it can be described as a "collection of diseases," which makes studying the advanced-stage disease very difficult. It requires a host of microscopy tools and multiomic techniques, including epigenomics, transcriptomics, and bio-mechanical assays.



Dr. Francis and his team use AFMs to study cellular and molecular interactions in live cells and tissues at the nanoscale.

Lewis uses what he's learned from many different stages of his schooling and professional career to:

- Look at which genes are expressed at different stages of the metastatic cascade and their epigenetic and regulatory context;
- Understand the underlying stromal and penetrating immune cell environment with single-cell transcriptomics; and
- Measure changes in physical presentation between cells and the matrix with BioAFM.

He is very motivated to explore this disease in depth:

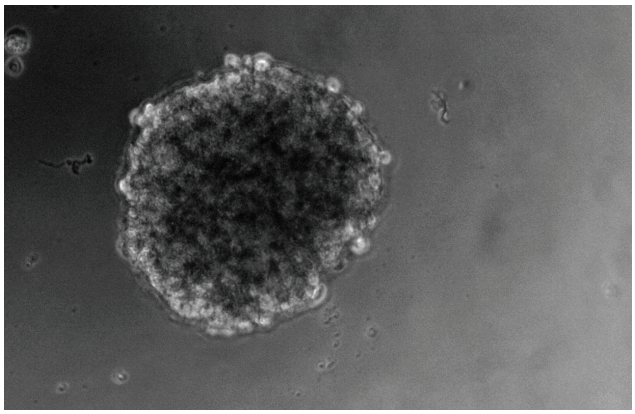
> "What drives my passion is understanding these processes to a point where we can manipulate and target them. Therefore, we have this kind of pharmacological research agenda in our team at the moment. So, what are the disease's metastatic processes? How do we delineate those so we can understand the key players? That way, we can match them to pharmaceutical and therapeutic approaches, which may drive innovative compound combinations that allow us to rewire these processes."

This innovative combination of techniques is employed with the hopes of providing multiple levels of contrast to delineate heterogeneity and characterize the subtle variations of the disease. This enables the group to start considering how this information can be used to make personalized therapeutics for cancer patients.

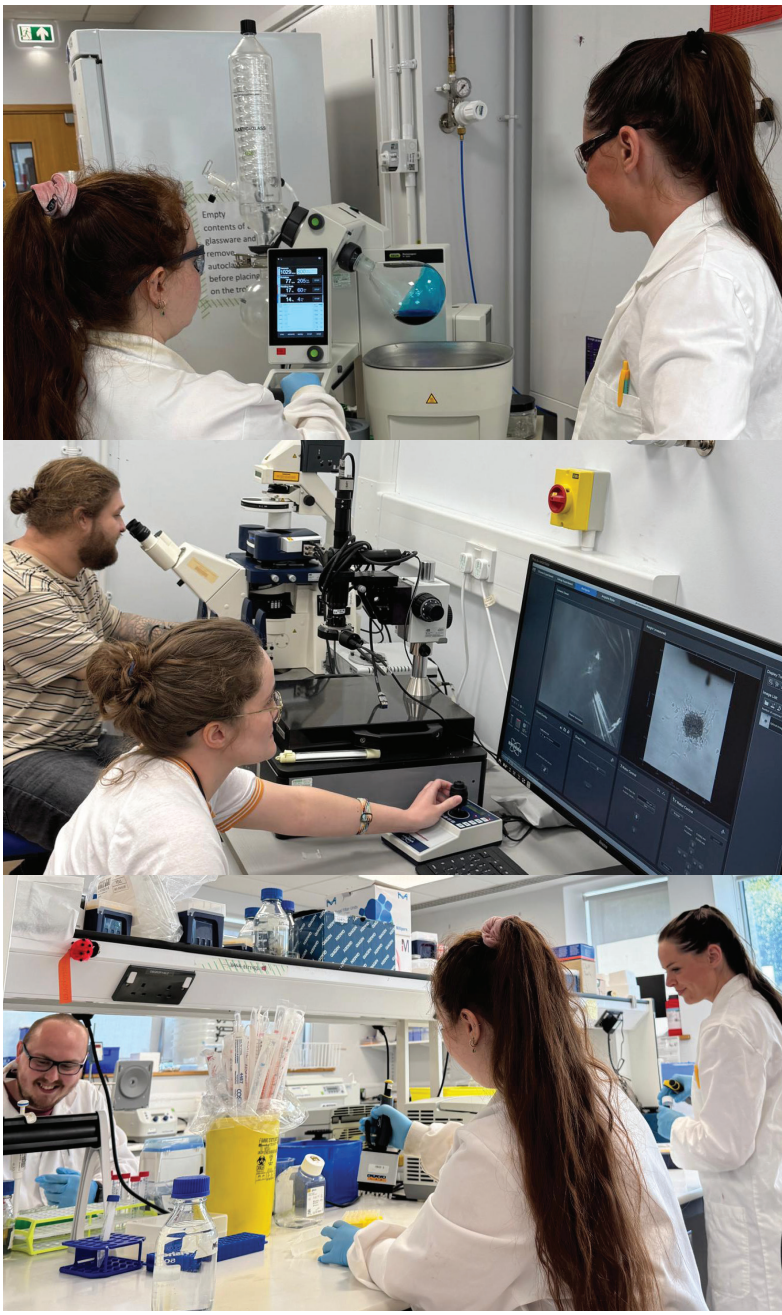
Tool Development to Tackle Real-World Problems

In addition to understanding the fundamentals and dynamic processes of cancers in the lab, Lewis and his team conduct patient advocacy work with local cancer charities and patient groups. This allows them to not only understand what these patients may be going through, but also educates them on the disease and facilitates sample donation and support, enabling patients to actively participate in research activities. Their work and this industrial-clinical-academic axis grant them access to samples from local hospitals across Wales.

Lewis's work dives into the intricacies of reproductive biology, cell and molecular analyses, as well as personalized medicine. His research starts with the basics and spans several disciplines to develop tools and gain a more holistic view of some of the very aggressive and diverse diseases that affect individuals around the world.



3D spheroid models are created from cells extracted from tumor tissues. They are being used to evaluate epigenetic nanoparticle and antibody-drug conjugate therapeutics.



Lewis and his students perform real-world research aiming to help patients tackle their diseases with emerging tools and data.

Learn More

Complementary Publications

Francis, L., Taraballi, F., et al. "Studying Activated Fibroblast Phenotypes and Fibrosis-Linked Mechanosensing Using 3D Biomimetic Models." *Macromolecular Bioscience 22*, no. 4 (2022): 2100450. https://doi.org/10.1002/mabi.202100450.

Francis, L., Mcculloch, P., Taraballi, F., et al. "Biomimetic Scaffolds Modulate the Posttraumatic Inflammatory Response in Articular Cartilage Contributing to Enhanced Neoformation of Cartilaginous Tissue In Vivo." *Advanced Healthcare Materials 11*, no. 1 (2022): 2101127. https://doi.org/10.1002/adhm.202101127.

Francis, L., Powell, L., et al. "Cisplatin resistance alters ovarian cancer spheroid formation and impacts peritoneal invasion." *Frontiers in Cell and Developmental Biology* Volume 13-2025 (2025). https://doi.org/10.3389/fcell.2025.1450407

Francis, L., et al. "In Silico Enhancer Mining Reveals SNS-032 and EHMT2 Inhibitors as Therapeutic Candidates in High-Grade Serous Ovarian Cancer." *British Journal of Cancer* 129, no. 1 (2023): 163–74. https://doi.org/10.1038/s41416-023-02274-2

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Author
Melissa Martin
Bruker, Life Science Writer
Melissa.martin@bruker.com

Bruker Nano Surfaces and Metrology

Bruker Nano GmbH
Berlin • Germany

productinfo@bruker.com

www.bruker.com/BioAFM