Turning the lens on LUNG CANCER

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*A lung cancer research team at the University of Malta, jointly led by **Prof. Anthony Fenech** and **Dr Vanessa Petroni Magri**, is exploring a new approach to target lung cancer. **Kimberly Fenech**, who has just started her Ph.D. with the team, will be learning techniques at the very forefront of cell biology to investigate the world's deadliest cancer.*

Gently, Ph.D. student Kimberly Fenech slides the flat plastic plate in her hands under the microscope. Turning the dials with gloved hands, she adjusts the focus until she can see distinct shapes through the red liquid: a layer of living, human cells. They look completely still, though they are actually replicating and growing on the plastic base, and their curved bodies stretch out in different shapes to touch each other.

Your body contains trillions of cells just like these, each a tiny factory adapted to a specific purpose. Cells are the living building blocks of tissues, which fold together to make the organs that keep us functioning. Given the right conditions, however, cells can happily grow on a plastic plate, allowing researchers such as Fenech to find out more about how they function and respond to disease. Fenech is studying lung cancer, and so most of the cells she cultures grow aggressively. Mutations in their genetic code mean that these cells do not die easily, and they divide much more rapidly than normal. When the human body is exposed to carcinogens (such as tobacco smoke), such cells might build up to form a dense mass called a tumour, which left untreated, could spread to other parts of the body and become life-threatening.

A LIFESTYLE RELATED DISEASE?

Lung cancer is the deadliest form of cancer worldwide. Highly aggressive and often difficult to detect in the early stages, the disease has a lower survival rate than most other cancers — only about 18% of patients survive more than 5 years post-diagnosis. Recent research shows that in Maltese males, lung cancer was the second most frequently diagnosed cancer (14.7%) after prostate cancer, while it was the fourth among Maltese women (5.1%). It killed more than any other cancer in both sexes.

The figures are sobering, and even more so when we consider that it took just half a century for lung cancer to go from one of the rarest diseases on the planet to one of mankind's biggest killers. In the 40s, researchers began to notice that lung cancer rates were going through the roof. The reason for the change was not initially obvious, though after World War II, smoking was at an all time-high in the United States and Europe. Companies such as Lucky Strike and Philip Morris were paying doctors to promote cigarettes in medical journals. A seminal paper, published in 1950 by Richard Doll and Austin Hill in the British Medical Journal, changed everything. Doll and Hill had successfully confirmed the suspicions that many researchers were having: the fact

Kimberly Fenech (right) and Nathan Vella (left), Ph.D. students working on the LCeNT Project
Photo by James Moffett

that lung cancer was linked to smoking. Further evidence followed, and in 1965, the US Surgeon General officially advised that tobacco was a leading risk factor for lung cancer.

Unfortunately, it is difficult to assign every case of cancer to a specific initiating cause. Each person's genetics are unique, and how our genes interact with our environment is a crucial element of whether a given disease will develop. Smoking is not responsible for every single case of lung cancer, but research shows it drives around 80% of specific lung cancer cases. Another potential cause is regular inhalation of carcinogens, which could arise from some occupational hazards or air pollution. Nonetheless, 20% of lung cancer cases have no evident lifestyle risk factor.

While current therapies can be initially effective, lung cancer patients may relapse with a tumour that is resistant to treatment. Scientists are urgently searching for new treatment options and a means of detecting the cancer early, before it spreads to other parts of the body and becomes difficult to treat. The team at the University of Malta headed by Dr Vanessa Petroni Magri and Prof. Anthony Fenech is working on the LCeNT Project (Lung Cancer enhanced Novel Therapy), researching new strategies for treating the disease. The team, including Ph.D. students Kimberly Fenech and Nathan Vella, as well as M.Sc. students Rachel Scicluna, Marija Galdes, and Marlene Muscat, have a new idea to target lung cancer. To understand their approach, though, we have to circle back to the contents of those plastic plates: the human cell.

THE SECRET LIFE OF CELLS

In a healthy system, a cell's life cycle is strictly regulated. They are 'born' by division, they grow, they divide, and they die. If we zoom in, each cell is like a miniature factory, bustling with activity from tiny molecular machines which make products or send signals to each other. The cell's 'head office' is the nucleus, a compartment which contains a person's genetic material, which in turn holds all the instructions for life. When everything is ticking along, these instructions provide all the information that keeps those molecular machines, known to biologists as 'proteins', functioning correctly. It is when these instructions become damaged that problems arise. Carcinogens in tobacco smoke or air pollutants can lead to 'typos' in DNA — small mistakes in the instruction manual called mutations. Some people may already have a certain number of these mistakes which they inherited from their parents — a phenomenon known as 'genetic predisposition'.

These errors can happen in any part of the DNA, and if left unchecked or unrepaired, such mistakes will propagate further as the cell continues to divide. Furthermore, if such errors happen in critical genes, they can go into overdrive. A cell might begin to divide much more rapidly than it should, birthing more and more cells with the same faulty DNA. This high-speed build-up of mutant cells eventually develops into a tumour.

Kimberly Fenech
Photo by James Moffett

As a safeguard against this, cells have several checkpoint mechanisms to repair such occurrences, as well as an 'emergency brake'. This triggers them to commit a programmed suicide if they detect enough DNA damage which goes beyond repair. In many cancer cases, however, scientists investigating the tumour will see that these repair mechanisms or the emergency brake itself is often also damaged.

ARE THREE DRUGS BETTER THAN ONE?

To stop the tumour in its tracks, cancer treatments are often agents that are intended to selectively cause the death of cancer cells. This prevents rapid cell growth, but can also be damaging to the healthy cells in the rest of the body. A major problem in cancer treatment is the toxicity of the drugs to normal, non-cancerous cells. The LCeNT team believe that by using a novel combination of carefully selected drugs, they can target specific, cancerous cells while minimising the effects on healthy cells. The team is currently collaborating with a CNRS research team, headed by Prof. Palma Rocchi, to study the outcome of such drugs, while simultaneously also modifying the function of specific genes in order to enhance the result.

The LCeNT team are studying each of the drugs individually and also together, to see how well they kill the cancer cells and how toxic they are to healthy, normal body cells. To carry out these experiments, Fenech will also be obtaining training from collaborators in Nottingham to learn how to culture human lung cells in a new way. Studies have shown that, in the right conditions, lung cells can be coaxed into forming more complex structures that closely resemble lung tissue in the human body. The opportunity is exciting because the drugs can be studied on a model that's much more similar to the microenvironment of lung tissue than a single layer of cells. This approach enables study outcomes which better reflect the real-life situation, producing results which are therefore more relevant.

By working together with Mater Dei Hospital, the team will study patient cancer cells taken from lung cancer surgeries. This allows them to study how actual patient tumour tissue responds to treatment. Through experimentation, the team will see how the drugs' combined effects will impact the malfunctioning proteins. By combining different approaches, they hope to increase the likelihood of success while keeping within parameters which will hopefully not increase the risk of side-effects.

The project is still in its early stages, and it will take a lot of time and experimentation to know if the strategy shows promise. We can take inspiration from the creative approach that the team is taking and the collaborative spirit that is supporting the project. It will surely be needed to challenge the world's deadliest cancer.

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