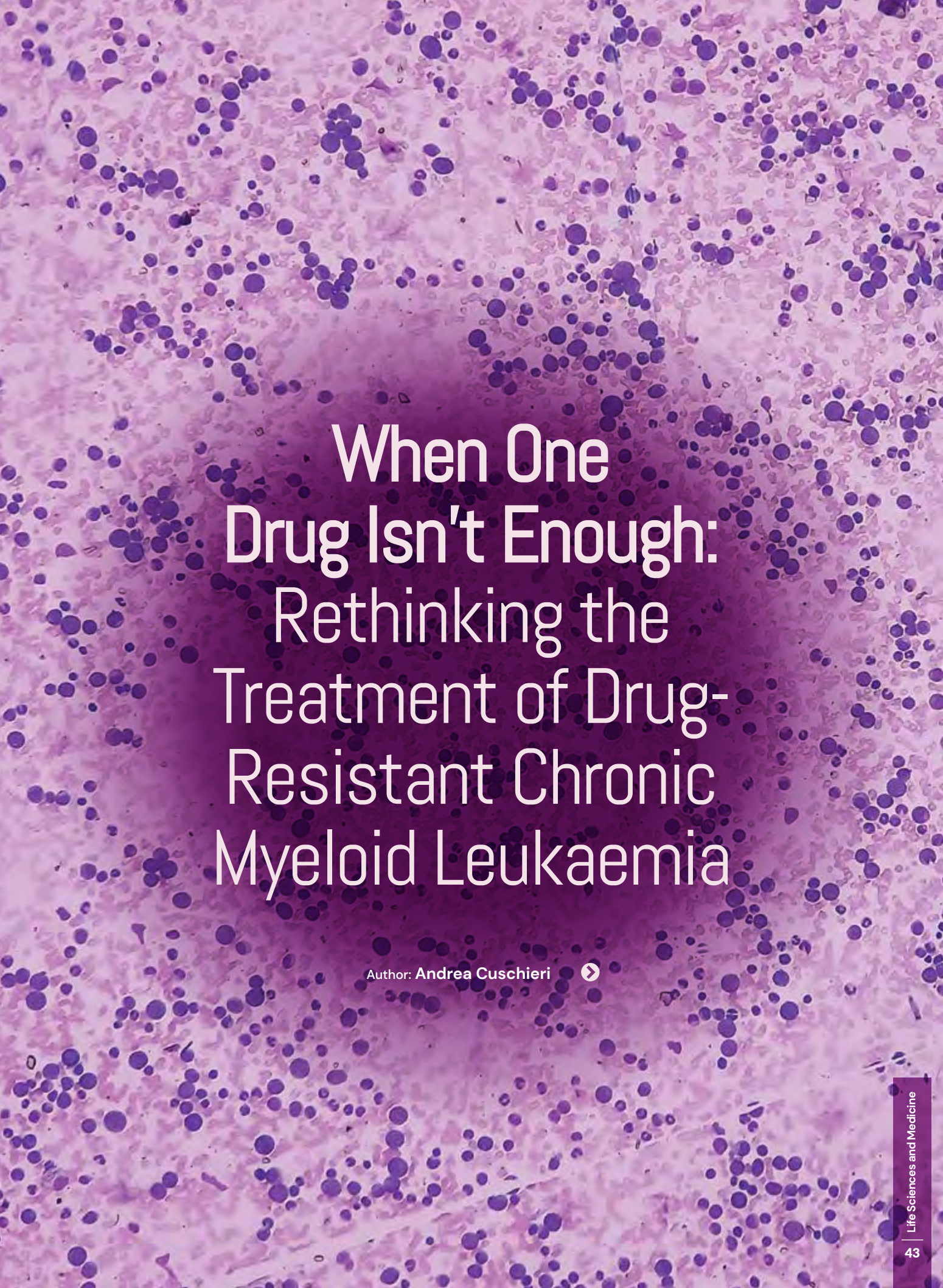


# When One Drug Isn't Enough: Rethinking the Treatment of Drug-Resistant Chronic Myeloid Leukaemia

Author: **Andrea Cuschieri**

*When art meets science, the result can be something extraordinary. For one Maltese researcher, that intersection has become the foundation of a career dedicated to creativity, curiosity, and compassion. From tutoring students and conducting research in the lab, to painting with oils and curating art exhibitions,* ***Antonio Polidano Vella****'s life has been a balance of expression and exploration. Looking into his scientific work, particularly his research on drug-resistant Chronic Myeloid Leukaemia, one can see how this could reshape how we think about cancer treatment.*

**An intracellular voyage**
***Artwork by Antonio Polidano Vella***

Leukaemia broadly speaking, is a cancer of the blood. But what is particularly worrisome about Chronic Myeloid Leukaemia (CML) is its increasing prevalence in an ageing society – a time when patients have other comorbidities. CML starts in the bone marrow, the body's tissue responsible for creating cells present within our blood. Defective production of these cells leads to leukaemia.

'Imagine your bone marrow as a factory that makes blood cells,' explains Antonio Polidano Vella (a Doctoral researcher with UM's Department of Anatomy). 'In CML, that factory makes an error in the production line and starts overproducing certain cells.' The system that should be carefully making red and white blood cells just stops listening to the rules.

The main culprit behind CML is a genetic accident known as the BCR-ABL1 fusion gene, which drives the abnormal cell growth. Fortunately, medical science has developed drugs called Tyrosine Kinase Inhibitors (TKIs), the most famous being *Imatinib*, that specifically target the cellular pathways that result from this rogue fusion gene. 'Patients typically take Imatinib as a daily oral medication,' he says. 'It's not a cure, but for many, it keeps the cancer under control.'

However, as with many cancers, there's a catch: resistance. Over time, some people living with CML stop responding to the drug as their cancer cells learn to evade the effects of treatment, leaving them with few treatment options.

Many resistances are due to further mutations within the BCR-ABL1 fusion gene, but other genes may also be involved in these changes.

## WHY CML RESEARCH MATTERS

CML is not like cancers caused by smoking, diet, or inherited mutations. 'It's one of those cancers that doesn't commonly have a direct environmental or lifestyle-related cause,' he explains. 'It isn't something you can easily prevent or see coming.'

That virtual inability for prevention and the suddenness of diagnosis, Polidano Vella says, is what motivated him to act. 'This reality motivated me to find alternative medications for this cancer. In particular, I wanted to find new treatments which could overcome resistance, meaning that they would work even on types of this leukaemia that no longer respond to medicines currently given in the clinic.'

His passion isn't just scientific – it is deeply humanitarian. 'Everything I did during my research had a direct goal: to make the lives of those suffering from CML better and give hope to patients who no longer respond to publicly available drugs. That's what makes the long hours and sacrifices worth it.'

## A NEW HORIZON: COMBINING FORCES AGAINST CANCER

Polidano Vella's latest study was part of the Cancer Therapeutics laboratory of the Centre for Molecular Medicine & Biobanking, supervised by Dr Analisse Cassar, herself a UM Ph.D. graduate, and co-supervised by Prof. Pierre Schembri-Wismayer. Polidano Vella's latest work pushes forward the therapeutic strategy for how resistant cancers are treated. His studies show that combining Imatinib with another class of drugs called epigenetic modifiers can resensitise resistant cancer cells, making them vulnerable to treatment once again.

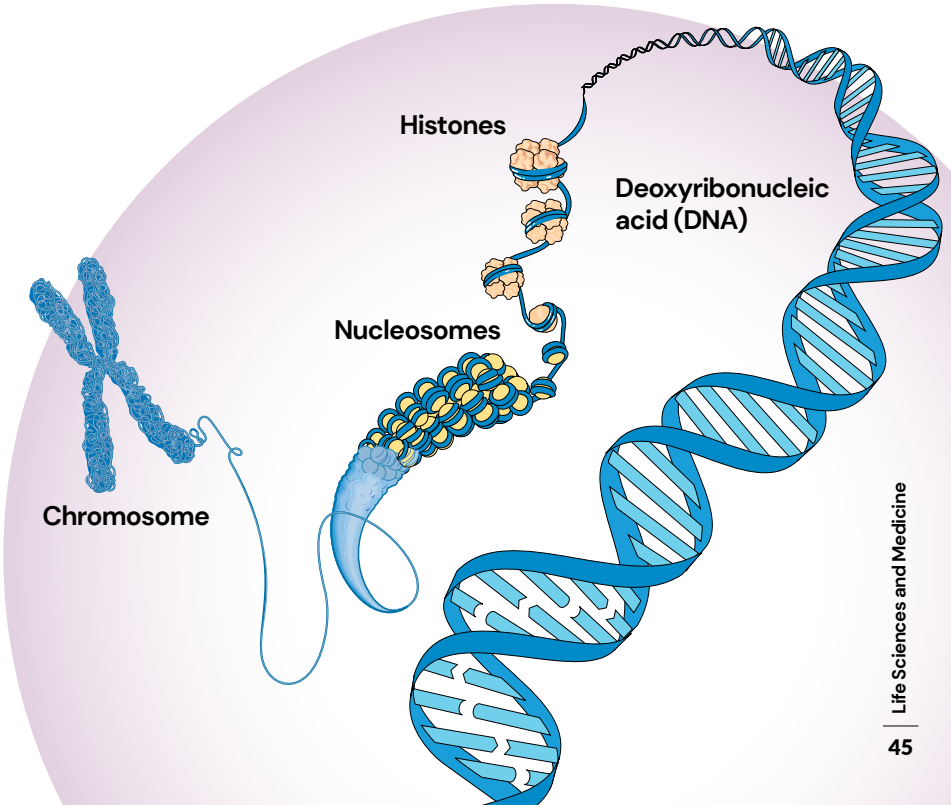
'Epigenetic-modifying drugs change the availability of DNA by influencing how your DNA is packaged inside a cell,' he explains. DNA is an extremely long chain of molecules, acting as a code that contains all the instructions for the cell. To keep things organised, the cell wraps and folds this code into structures called chromosomes. By modifying how tightly or loosely that DNA is packed, these drugs can control which genes are turned on or off.

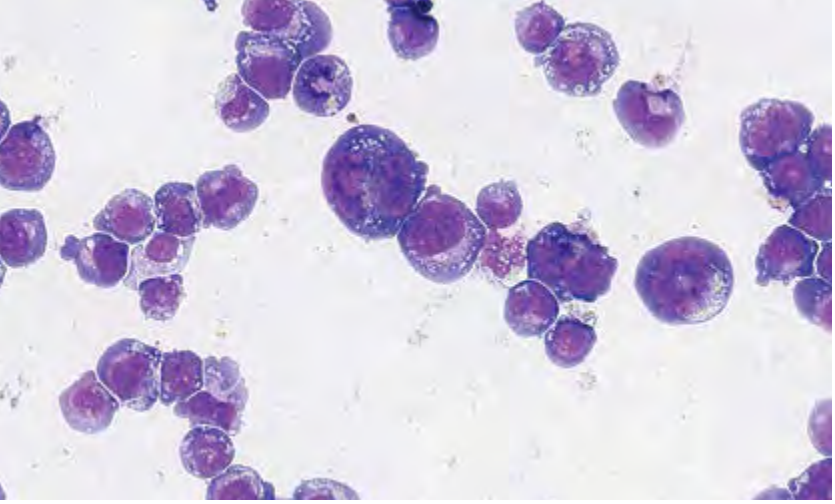
This might sound abstract, but the results are concrete: when these drugs are paired with Imatinib, the previously resistant cancer cells start responding again. 'It sheds light on combination therapy,' he says, 'where more than one drug is used together to target the cancer.'

## WHY ONE DRUG ISN'T ENOUGH

In medicine, there has long been a search for the magic bullet – a single, perfect drug that could cure a disease. But as cancer research evolves, that vision is being replaced with a more nuanced approach.

'Cancer cells are chaotic,' Polidano Vella says. 'There is usually more than one process going wrong at the same time. Combining drugs allows scientists and clinicians to target multiple weak spots in the cancer. It makes therapy more





**Lab CML cells**
***Image courtesy of Antonio Polidano Vella***

**Antonio Polidano Vella**

effective and reduces the risk of resistance, since cancer cells struggle to adapt to multiple drugs at once.'

This principle isn't unique to CML. It's becoming a cornerstone of modern oncology. Combination therapy has improved outcomes in other cancers too, from breast cancer to melanoma. While Polidano Vella's research focused on CML, it fits into this modern era of oncological management. He explains, 'This became a natural next step in the battle against cancer after numerous cases of cancers, not just CML, became resistant to treatments, especially when only one drug is used.' Thus, research is 'moving away from the current "one-size-fits-all" approach' to keep on innovating and improving the lives of people living with cancer.

## THE POWER OF PERSONALISATION

Another crucial insight from his research lies in personalised medicine – the idea that each person's cancer behaves differently, even if diagnosed with the same disease.

In his studies, Polidano Vella found that 'resistant CML cell colonies cultivated from a common CML sample respond differently to the same treatments. This supports the idea that the "one-size-fits-all" approach doesn't always work. Personalised therapy means tailoring treatment to each patient's unique cancer genetics and behaviour.'

Interestingly, his research also suggested that not all TKI-drug resistance stems from additional mutations in the BCR-ABL1 gene. 'Together with my supervisors, Cassar and Schembri-Wismayer, we discovered that even without additional mutations in that fusion gene, some cancer cells still behave differently,' he says. 'This suggests other genes are influencing resistance, thus adding another layer of complexity, but also opportunity, to how we understand CML.'

## CHALLENGES ON THE ROAD TO THE CLINIC

Despite the promise of his findings, bringing new cancer treatments from the lab to the clinic is no easy feat. 'Cancer research is very expensive and demanding,' Polidano Vella admits. 'There's always more to do and more questions to answer, but funding and workforce are limited. Additional support and better research networks would help push projects like mine forward.'

Even when the science works, the translation into clinical use can be a long and difficult journey. 'Going from an idea to the laboratory bench and then to the clinic are two separate, time-consuming and expensive paths,' he explains. 'There are hurdles at every stage – legal, regulatory, and commercial. Even when everything works scientifically, moving into the clinic becomes an entrepreneurial challenge as much as a medical one.'

## THE HUMAN SIDE OF SCIENCE

For all the data, chemicals, reagents, and microscopes, the heart of this research is profoundly human. 'I urge the general public to notice and appreciate the hard work being put into cancer research,' he says passionately. 'The treatments we take for granted are the result of years of effort and billions of euros in investment worldwide.'

He's also proud of what's being achieved locally. 'Malta, while comparatively humble in its size and scientific workforce, is the cradle of many bright scientists who are well-deserving of further funding and resources to bring their ideas to life, and improve the lives of suffering patients.'

***Antonio Polidano Vella's research into treating drug-resistant Chronic Myeloid Leukaemia (CML) using combination therapy is funded by the Ministry of Education and Xjenza Malta, and guided by his primary supervisor, Dr Analisse Cassar, and co-supervisor, Prof. Pierre Schembri-Wismayer.***