TargetMI:

Unravelling the Molecular Roots of Heart Attacks

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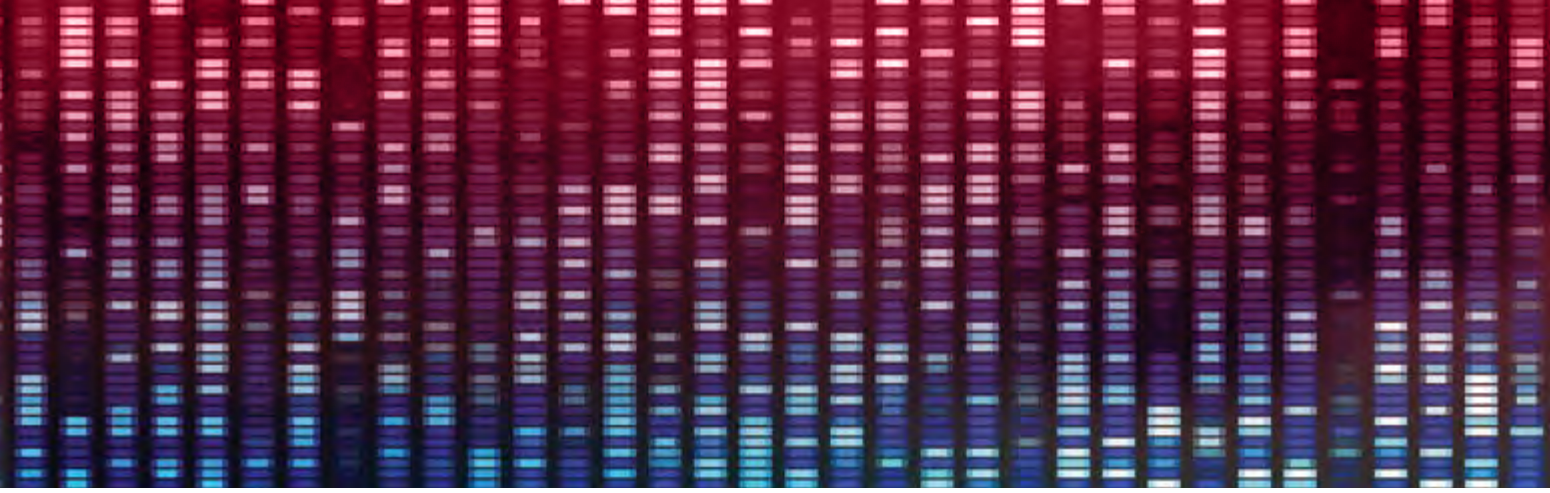
Cardiovascular disease remains a leading cause of death worldwide, claiming millions of lives each year. Across Europe alone, over 60 million potential years of life are lost annually to cardiovascular deaths. At the University of Malta, ***Prof. Stephanie Bezzina Wettinger*** *and her team are leading TargetMI, an EU-funded project that aims to examine the molecular pathways behind myocardial infarction, commonly known as heart attacks, and pave the way for targeted prevention and treatment.*



For Prof. Stephanie Bezzina Wettinger, the project's principal investigator and coordinator, TargetMI is the culmination of nearly two decades of collaboration and research.

The idea for TargetMI developed from her earlier work with Prof. Pieter Reitsma and Prof. Frits Rosendaal in the Netherlands. 'We first worked together on the SMILE Project – the Study of Myocardial Infarction in Leiden. When I returned to Malta, I set up the Maltese Acute Myocardial Infarction (MAMI) Study in 2008 so that we could study heart attacks in the Maltese population.' That partnership laid the groundwork for TargetMI, which now bridges clinical medicine, genetics, and metabolism in an effort to reveal who is most at risk and why.

Unlike traditional genetic studies that focus solely on one aspect of biology, TargetMI takes a *multiomic approach* – it combines genomic, proteomic, and metabolomic data to reveal how different biological systems interact in heart disease. Each 'omic' layer tells a different story: genes are related to inherited risks, proteins reflect active biological processes, and metabolites capture how genetics, lifestyle, and environment influence health. By integrating these layers, researchers can uncover patterns invisible to single analyses, building a more complete understanding as to why some individuals develop heart disease while others, even those with similar lifestyles, do not.

WHAT HAPPENS DURING A HEART ATTACK

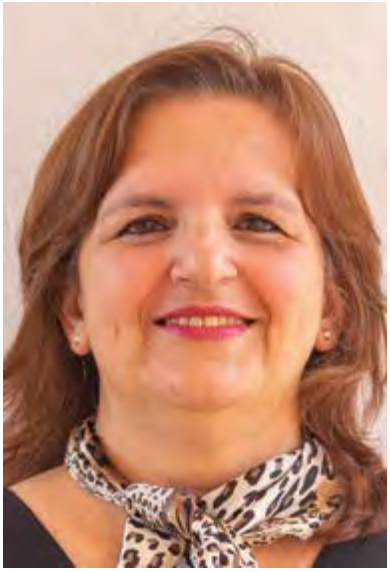
The heart, a powerful muscular pump, supplies oxygenated blood to all organs around the body. To accomplish this, it depends on its own network of vessels – the coronary arteries, for oxygen. When one of these arteries becomes blocked, blood supply to a portion of the heart muscle is cut off, leading to tissue damage or death. The most common culprit is atherosclerosis, the gradual build-up of fatty deposits within arterial walls. When this plaque ruptures, it can trigger clot formation and block blood flow, leading to a heart attack.

TargetMI focuses mainly on Type I myocardial infarction, the form caused by such plaque rupture. Yet, even within this category, molecular subgroups may exist. The team aims to identify these molecular 'signatures', so that doctors will one day be able to group patients according to their biological profiles and offer more precise, tailored treatments. This is a core principle of personalised medicine.

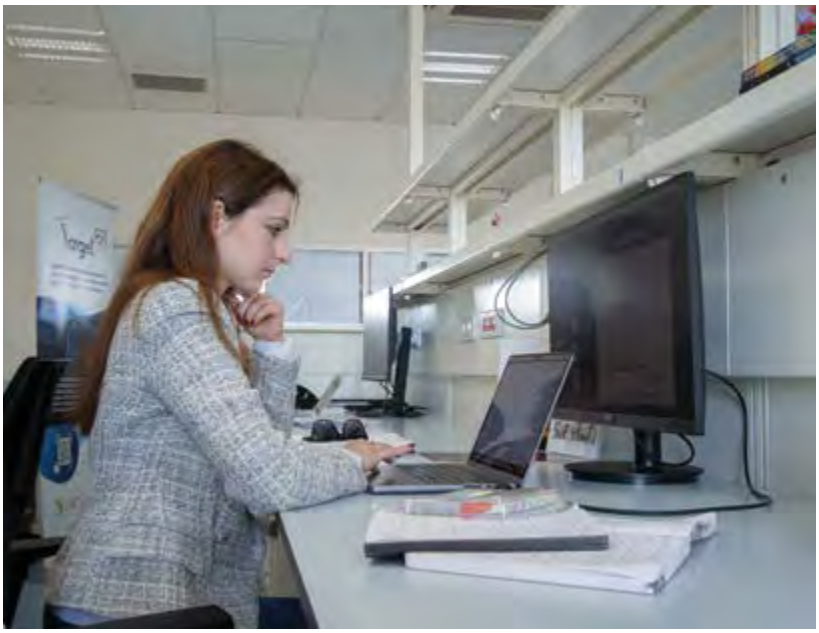
Bezzina Wettinger adds that sex-based differences play an important role. 'Men are more likely to develop plaques with a higher fatty content and thinner linings, which makes them more prone to rupture,' she explains. 'After menopause, women's risk catches up as the protective effect of oestrogen diminishes. This is why it is important to conduct separate data analyses for men and women.'

TOWARDS A NEW ERA OF PERSONALISED PREVENTION

At its current stage, the project draws primarily on samples from the MAMI Study, which includes



Prof. Stephanie Bezzina Wettinger



Top: Scientific Officer Francesca Borg Carbott working on her computer
Bottom: Samples from the TargetMI collection
Photos by James Moffett

around 1,000 participants of Maltese ethnicity. Certainly, collecting such detailed data was no walk in the park. 'The levels of molecules in blood can change depending on fasting status, time of day, or even whether the participant is seated or lying down,' Bezzina Wettinger says. 'We defined a strict protocol and kept to it for all participants. This consistency is critical.'

Using this dataset, the TargetMI team applies advanced computational analyses to link genetic variants, proteins, and metabolites to cardiovascular risk. As Bezzina Wettinger explains, 'DNA is transcribed into RNA, which is then translated into proteins – the machinery that determines, amongst other things, the levels of metabolites in our body. However, the process isn't always linear. Lifestyle factors such as smoking or diet can modify this. Understanding which biological processes are key in driving a disease helps us identify where we can intervene.'

One of TargetMI's long-term goals is to develop new risk algorithms and drug targets for heart attack prevention. The team has already built a computational tool capable of scanning vast multiomic datasets to identify genes that influence molecular pathways – a framework that could extend well beyond heart

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disease. 'If we can group people based on different molecular causes that predispose them to heart attacks,' she says, 'we could then develop medications that target those specific causes, effectively making prevention far more efficient.'

HAS THE PUZZLE BEEN SOLVED?

Generations of Maltese families trace their ancestry to a small founding population that later expanded in size and caused a phenomenon known as the founder effect. This makes certain genetic variants much more common locally than elsewhere, creating a unique opportunity for researchers. 'By studying the genome in a well-defined population, it becomes easier to uncover molecular clues as to why some people are more likely to suffer from heart attacks than others,' Bezzina Wettinger explains.

Interestingly, through TargetMI, the team has already identified over 35 million genetic variants, of which roughly 10% are novel – not reported in existing databases. One striking example involved a gene previously proposed in international studies as a potential drug target to prevent heart attacks. It was believed that reducing the protein produced by this gene might lower the risk. However, in Malta, the team found a relatively large number of individuals carrying a stop-codon mutation, which is essentially a natural 'off switch' that results in lower protein levels.

Surprisingly, these individuals were not protected from heart attacks. Further analysis revealed that, actually, they had a higher risk of developing diabetes, which in turn increases cardiovascular risk. 'Although some variants may be specific to Malta or neighbouring countries, the conclusions from our findings can be extrapolated more broadly,' Bezzina Wettinger notes. 'Ultimately, we all share the same genes, which have the same function worldwide. Even from a small country, discoveries here can have global implications for preventing heart disease.'

FROM LAB TO LIFE

Unravelling the molecular roots of heart disease is a major scientific milestone, but translating those discoveries into clinical reality is another challenge altogether. Bezzina Wettinger explains that developing a test or medication requires rigorous hospital trials, regulatory approval, and significant investment. Here, the European Innovation Council (EIC) – the EU's flagship Horizon innovation program – plays a crucial role by funding cutting-edge innovations from early stage to market, besides providing mentoring and training to help researchers navigate the pathway from scientific discovery to market-ready innovation.

Despite these hurdles, Bezzina Wettinger remains optimistic. 'Our healthcare professionals are highly skilled,' she says. 'Once these discoveries make it to market, integrating them into Malta's healthcare system would be simpler than it is in larger countries and the payoff would be considerable.' Preventing heart attacks is rewarding on multiple levels, as it not only saves lives but also reduces the economic burden of treatment and long-term complications.

TargetMI's success, Bezzina Wettinger stresses, is the result of a deeply interdisciplinary effort as it brings together experts in bioinformatics, clinical medicine, molecular science, and even ethics and law. It is an excellent example of professionals from different backgrounds using their skills to achieve a shared goal: reducing the cardiovascular burden in Maltese society and beyond.

TargetMI received €4 million in funding from the European Innovation Council (EIC) as part of the EIC Pathfinder Programme.