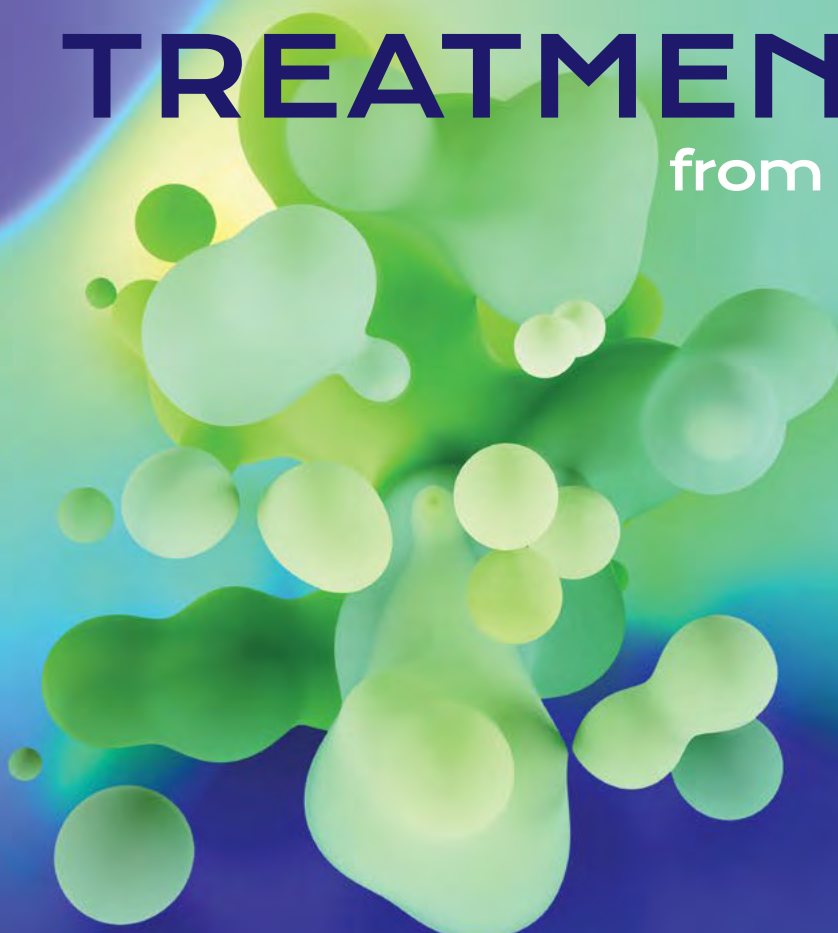


Identifying novel

LEUKAEMIA TREATMENTS

from nature



Author: **Christian Keszthelyi**

*University of Malta research has shown that polyphenols, chemical compounds naturally found in plant foods such as fruits, legumes, and olive oil, exhibit anti-leukaemia activity. Can these compounds give us insight into better leukaemia treatments? **THINK** talks to **Prof. Marion Zammit Mangion** and **Neil Cutajar** to find out more about the Agent NovoBio Project.*

The human body is a complex structure composed of many different types of cells with specialised functions. As most cells have only a relatively short lifespan, they must replicate continuously to replace themselves before they die. This requires each cell to form exact copies of itself. Unfortunately this replicating process is not perfect, and the resulting cells may not carry out the exact functions required. When this happens, it may lead to dysfunction of the cell, which in turn may ultimately result in a malignant cancerous growth. In cancer treatments, scientists try to find molecules that affect the malignant cells while limiting the harm to healthy cells. Professors Marion Zammit Mangion and Pierre Schembri Wismayer (Associate Professor, Faculty of Medicine & Surgery, University of Malta), research support officer Neil Cutajar, and Dr Lucienne Vassallo Gatt are working on the NovoBio Project, which examines natural bioactive agents from Maltese endemic plants for the treatment of leukaemia. But before we jump into that, we need to understand some basic biology — cellular differentiation.

BIOLOGY 101: CELLULAR DIFFERENTIATION

Cellular differentiation refers to a process during which a cell changes from one type to another. Think of foetal

development. As the cells divide, they gradually become more specific (hence differentiation) with new daughter cells taking on more specialised roles. A similar process occurs within our blood-forming tissue. Special cells called stem cells will divide and mature into the different cells that make up our blood in a process referred to as haematopoiesis or 'blood cell formation'. Leukaemia or blood cancer occurs when this complex differentiation process is halted or blocked at an early stage of the differentiation cycle. When this happens, new unspecialised cells that lack the specialised structures of healthy cells form. These new, malignant cells may be described as 'out of control' in terms of their behaviour, cell division, and appearance.

TREATING LEUKAEMIA

Project Agent NovoBio studies the use of bioactive agents from Maltese endemic plants, specifically how these may be used to treat leukaemia. The project builds upon previous work performed by the team in the laboratories at the University of Malta, who noted that on addition of a crudely purified plant extract, differentiating activity was observed, and the leukaemia cells reverted back to healthy blood cells and died naturally. This is a very interesting scenario, where the malignant cells were induced to develop some of their lost structures and to slow down the rampant cell division. ➤



From left to right: Prof. Pierre Schembri Wismayer, Dr Lucienne Vassallo Gatt, Neil Cutajar, Prof. Marion Zammit Mangion
Photo by Sarah Zammit

Logically, there had to be a specific molecule or molecules within the extract that was responsible for this. This is where the first challenge to separate this mixture of compounds into single components was encountered. For this, the researchers, primarily Dr Vassallo Gatt, used a preparative high-pressure liquid chromatography (prepHPLC), the only one of its kind on the island. By separating the extract into its singular components, the team could test each one individually to see which would trigger differentiation.

In a painstakingly long process, the team behind the Agent NovoBio research managed to identify a single component out of the ten different compounds that showed marked differentiation on specific leukaemia cell lines. The next step is to see whether the component can be used on other types of leukaemia as well as other cancer cell lines and explore the molecular pathways by which the bioactive component acts.

Cutajar explains how this chemical component may help fight off leukaemia cells. 'What we would like to do with this bioactive molecule is to help encourage the process of differentiation – this component would be introduced to the differentiation process at the early stage of maturation and cause malignant cells to stop dividing and die off naturally.' Essentially, leukaemia cells do not usually fully differentiate and are immortal. However, when exposed to the treatment, these cells would differentiate and then die off.

Cutajar explains his current research phase: 'I am now testing the different components of the extract on different leukaemia cell lines. Once I have investigated whether differentiation is also occurring in these cells,

I will do more precise tests to establish how far along the maturation process differentiation occurs in practice.'

Prof. Zammit Mangion underlines the importance of Cutajar's work, who is not only testing these agents to see their reaction with malignant cells but also working on characterising these components. 'If you want commercialisation of your research results, you have to showcase a highly purified, preferably single component that is fully characterised. You need to fully understand how it behaves in different types of leukaemia and cancer models to ensure it can be further developed as a pharmaceutical with follow-up investment,' the lead researcher says.

The next phase of the research will be to see what changes the molecule induces in leukaemia cells on a micro-molecular level, which is indispensable for commercial development. In fact, Zammit Mangion emphasises how MCST funding is critically important to act as a bridge between downstream research and the commercialisation of scientific discoveries.

The research is in its early stages and still far from being available to patients, as like all treatments, a very long process of rigorous experimentation and testing is needed. However, the team sounds optimistic about the results they have achieved so far. **T**

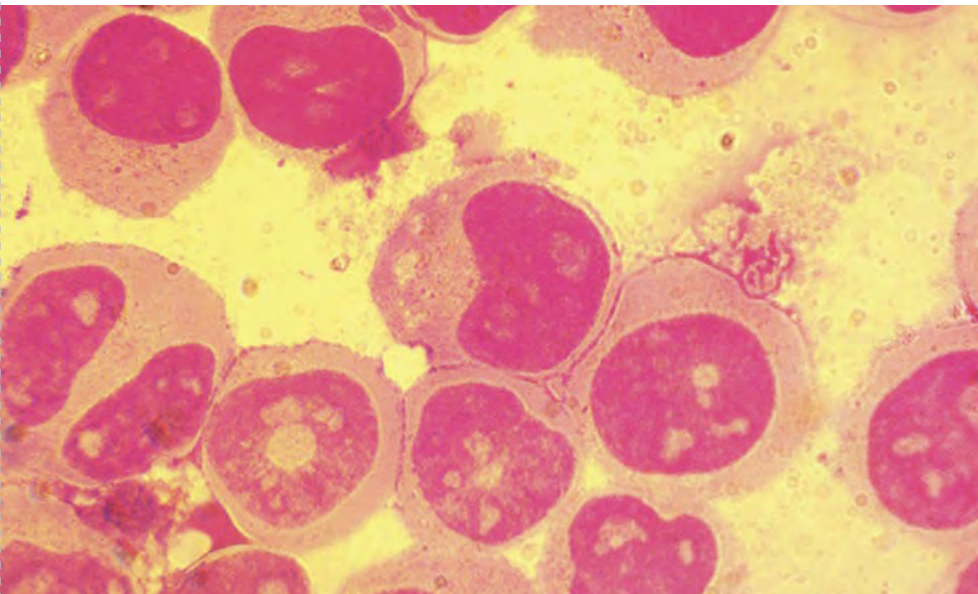
Project Agent NovoBio is financed by the Malta Council for Science & Technology (MCST) through FUSION: The R&I Technology Development Programme 2019



Neil Cutajar
Photo by Sarah Zammit

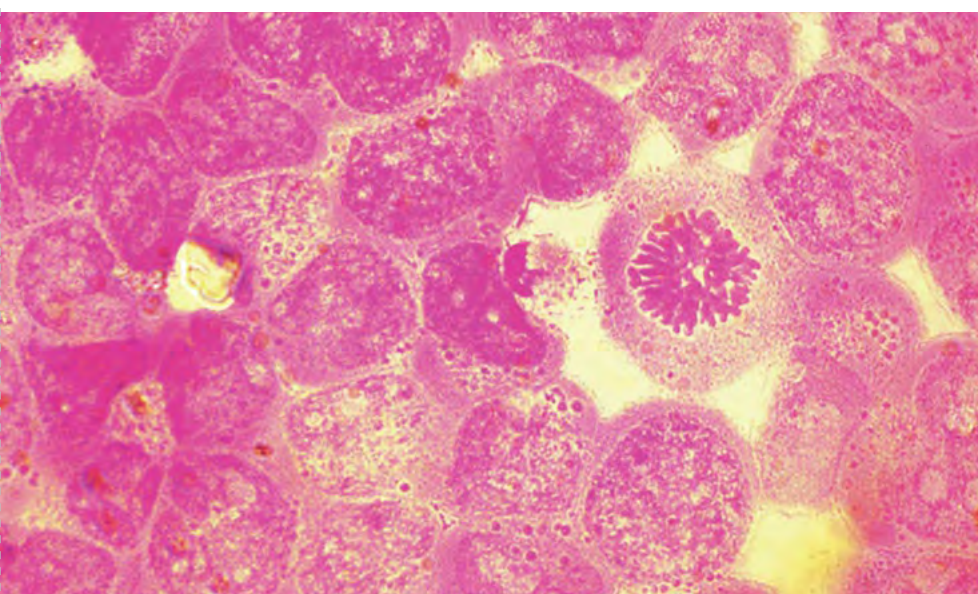


Dr Lucienne Vassallo Gatt
Photo by Sarah Zammit



On addition of a crudely purified plant extract, differentiating activity was observed, and the leukaemia cells reverted back to healthy blood cells and died naturally

Treated (differentiated cells) showing kidney-shaped nucleus and large irregular cytoplasm, showing monocyte-like appearance



Untreated (undifferentiated cells) showing large nucleus with very small cytoplasm in the border, showing immature blast-like appearance

Images courtesy of Neil Cutajar