Three Types to Help Them All:

# HOW BIOLOGICAL PATTERNS IN SEPSIS COULD IMPROVE PATIENT TREATMENT

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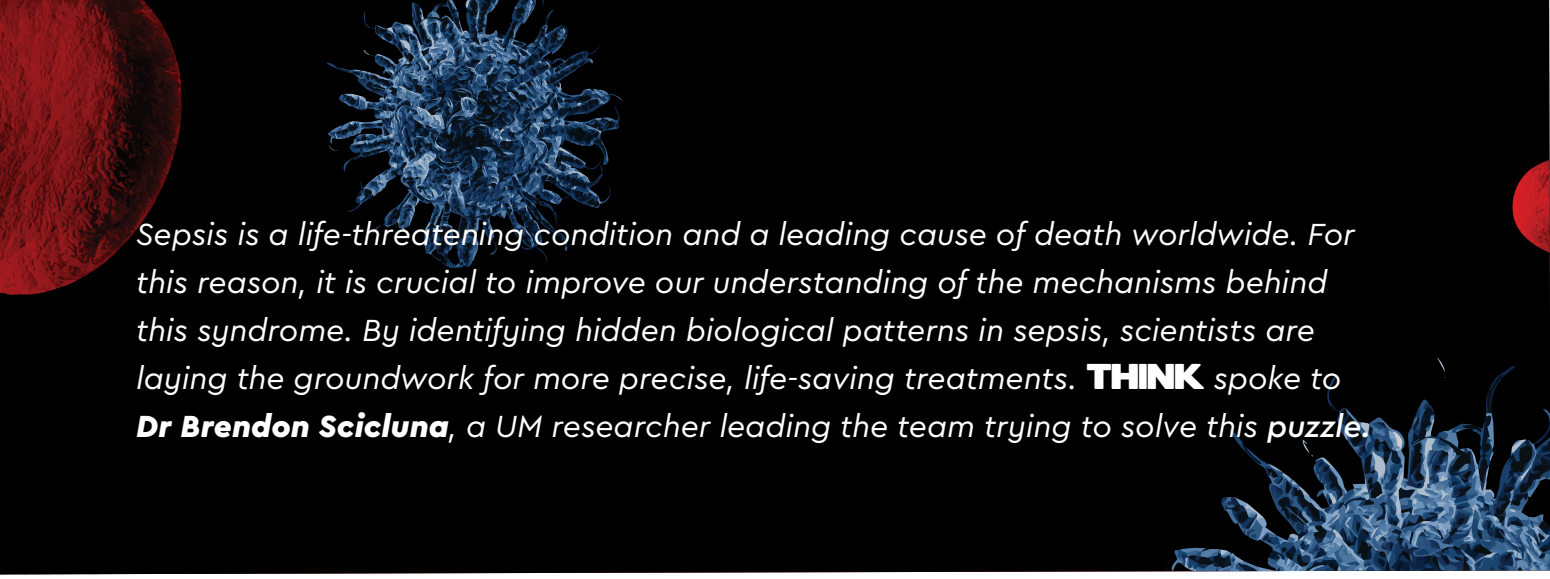
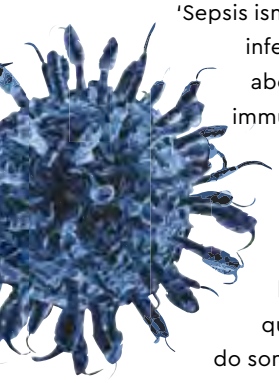


*Sepsis is a life-threatening condition and a leading cause of death worldwide. For this reason, it is crucial to improve our understanding of the mechanisms behind this syndrome. By identifying hidden biological patterns in sepsis, scientists are laying the groundwork for more precise, life-saving treatments.* **THINK** *spoke to* ***Dr Brendon Scicluna****, a UM researcher leading the team trying to solve this* ***puzzle.***

Sepsis is one of the most formidable challenges that modern medicine faces. Each year, it kills millions of people worldwide and remains one of the leading causes of death in our hospitals. Despite decades of research and hundreds of clinical trials, doctors still struggle to treat sepsis patients effectively.

That challenge is exactly what motivates Dr Brendon Scicluna (Department of Applied Biomedical Science, Faculty of Health Sciences).



'Sepsis isn't just about the infection itself; it's about the body's own immune system launching a dysregulated response that ends up damaging its own tissues and organs,' he explains. 'The question is this: Why do some patients recover while others, with a similar infection, decline so rapidly? My inspiration comes from trying to solve that puzzle.' The problem, says Scicluna, is that sepsis has been treated as a single disease for too long. 'Right now, treatment remains largely supportive, where antibiotics are prescribed to fight the infection, and other measures like fluids, mechanical ventilation, and vasopressors are used to keep organs functioning. But, this doesn't address the root of the problem – the patient's specific immune response that has become dysregulated,' he says.

Scicluna's research aims to change that by moving sepsis treatment into the era of precision medicine, by understanding the different biological subgroups of sepsis patients. 'We can see that Sepsis Patient A is very different biologically from Sepsis Patient B. This reasoning will pave the way for new clinical trials where we don't just give a new drug to a thousand random sepsis patients.' Instead, these clinical trials will allocate specific treatments to subgroups of patients who are most likely to benefit from them.

## DECODING THE IMMUNE RESPONSE

To make sense of these differences, Scicluna and an international team of researchers compiled data from two large patient cohorts, comprising over a thousand sepsis cases in total. Their findings, published in *Nature Medicine* in October 2025, revealed three distinct Consensus Transcriptomic Subtypes, or CTSs.

'"Transcriptomic" refers to gene activity happening inside a cell at a specific moment,' Scicluna explains. 'Think of it as a snapshot of our approximately 20,000 genes that are switched "on" or "off", and of how the dial of gene activity is turned up or down. We analysed this gene activity in the white blood cells of sepsis patients.'

The result was striking: the patterns of gene activity were not random. Instead, they clustered into reproducible biological groups that emerged across data from multiple countries. 'We call these "Consensus Transcriptomic Subtypes" because our findings were validated against the independent work of several other international research groups, including those in the UK, USA, and Africa,' he says. 'It proved that we weren't just seeing a pattern in our own data, but a real, reproducible biological signal that others were also seeing.'

## THREE BIOLOGICAL "PERSONALITIES"

Each subtype tells a different biological story, and this is the core aspect of sepsis-related research. 'We found that the patient subtypes have distinct biological "personalities", so to speak,' says Scicluna.

- CTS1, an inflammatory subtype, is characterised by an immune system in overdrive with high activation of inflammatory

Dr Brendon Scicluna

**Dr Brendon Scicluna (far right) with members of the Translational Immunology and Infection Lab at the University of Malta, investigating immune responses in sepsis and ageing**
***Photo courtesy of the Translational Immunology and Infection Lab***

pathways. This is accompanied by a "cytokine storm", which is a pathological reaction involving the uncontrolled and excessive release of inflammatory signalling molecules, called cytokines, by the innate immune system.

- CTS2, the blood-clotting subtype, shows 'marked disturbances in blood clotting,' says Scicluna. He notes specifically the breakdown of blood clots, which is a crucial part of wound healing called fibrinolysis. 'If this process is not properly regulated, it can lead to numerous complications. This subtype of patients is the most severe and has the highest risk of death,' he adds.
- CTS3, the adaptive immune subtype, displays a relatively more balanced immune response. 'Biologically, they appear to have a lymphocyte-centred response compared to the other two subtypes with signs of a more "normal" response to infection, though they are still stressed,' Scicluna notes.

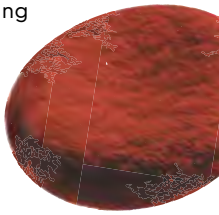
Identifying these subtypes required immense collaboration and data harmonisation between research groups, which presented a significant challenge in this research. 'Every hospital, every lab, every country has slightly different protocols, divergent treatment approaches, different machines, and different patient populations,' says Scicluna. 'When you put all that data together, the biggest challenge is filtering out this "noise" so that you can hear the true biological signal coming from the patients themselves.'

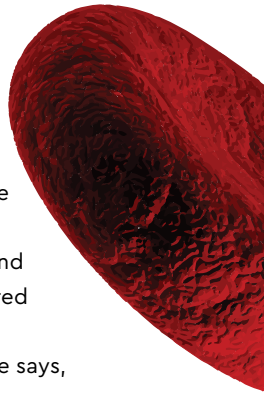
The team compared three classification methods developed independently by research groups in the Netherlands (Scicluna's lab prior to relocating to Malta), the UK, and the USA, finding a common overarching signal. To ensure their findings were robust, Scicluna and his team validated the findings in a cohort from Uganda, Africa, as well as an independent randomised controlled trial in the UK. 'It's like three different maps, drawn by different cartographers, all pointing to the same hidden treasure,' says Scicluna. 'It gave us enormous confidence that these molecular subtypes aren't a statistical fluke, but represent true, distinct biological states.'

## WHEN A TREATMENT CAN HELP OR HARM

Perhaps the most significant clinical insight came when the team revisited data from a previous corticosteroid clinical trial – a common anti-inflammatory treatment used in sepsis. Classifying patients by their CTSs revealed a concerning pattern.

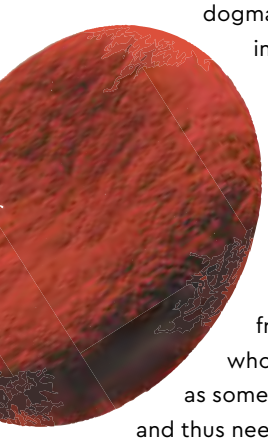
Corticosteroids are harmful to CTS2 patients. 'For decades, clinical trials for promising sepsis drugs have failed, one after another. Our work, and the work of others in this field, strongly suggests why,' Scicluna points out. 'These trials were enrolling all sepsis patients without considering the immune status of the patient. It's very likely that a drug helped one subtype (e.g., an anti-inflammatory helping CTS1 patients) while simultaneously harming another (e.g., the same drug making CTS2 patients more immunocompromised). In the final analysis, these opposing effects would cancel each other out, and the trial would be declared a failure.'





The CTS framework, he says, 'gives us a new lens to re-analyse that old trial data, as well as potentially repurposing treatments that were shelved. More importantly, it provides a blueprint for designing new trials that are smarter, safer, and targeted to the right patients from the start.'

## RETHINKING INFLAMMATION



This breakthrough involves challenging outdated medical dogmas that have, for instance, contributed to the inconsistent and sometimes inappropriate use of corticosteroids. 'Medical teaching still draws heavily on 19th-century ideas from Rudolf Virchow, who viewed inflammation as something inherently harmful and thus needed to be suppressed,' says Scicluna. 'But inflammation is not uniformly bad. In fact, in many acute illnesses, specific inflammatory pathways are crucial for recovery.'

Scicluna contrasts this with the work of Elie Metchnikoff, who saw inflammation as a core element of the body's housekeeping and repair system. 'When that balance is disturbed, the immune system mounts an inflammatory response to restore order,' he says. 'In the case of CTS2, our research suggests that this subtype reacts poorly to corticosteroids for several biological reasons,' from oxidative stress to clotting disturbances and hormone-related mechanisms. 'Altogether, these findings help explain why a one-size-fits-all approach to corticosteroid therapy can be risky. The biology of each patient subgroup matters, and that's what CTS classification aims to reveal,' he concludes.

## A ROADMAP FOR THE FUTURE: TOWARDS FASTER AND SMARTER DIAGNOSIS

The challenge now is translating this knowledge into clinical practice. 'A full transcriptome analysis takes days, and in sepsis, you have hours,' says Scicluna. 'The solution is to develop a "classifier" – a much simpler, faster test that looks for a small handful of key biomarkers. Instead of measuring 20,000 genes, we identify the two or five that can accurately predict which subtype a patient belongs to.'

Scicluna's team and several international partners are working on rapid diagnostic tools based on the same principle as PCR or blood protein tests. 'The goal is to get a result in under an hour,' Scicluna explains. 'We are not there yet, but this is the most active area of development. Widespread implementation is likely still a few years away, but it's the critical next step.'

At the Translational Immunology and Infection Lab, based at UM's Centre for Molecular Medicine and Biobanking, the next phase of work is already underway. 'First, we are refining and validating the rapid diagnostic classifier. Second, we are working to better understand the biological mechanisms that drive each CTS subtype,' says Scicluna.

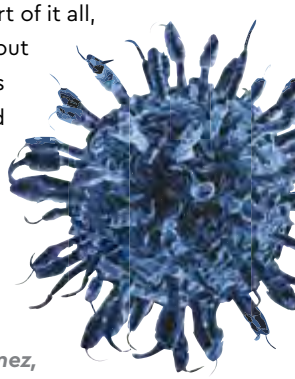
This includes a new collaboration with Jilin University in China, through a project funded by the Xjenza Malta Internationalisation Fund (SINO-MALTA-2024–40) as part of the IMMUNO-P Project. 'We're exploring how generative AI and other machine-learning tools can predict which treatments are most likely to work for each subtype, focusing particularly on immune and metabolic pathways,' he explains. 'The early results are extremely promising.'

Ultimately, the team aims to launch a randomised controlled trial in which sepsis patients are classified as CTS1, CTS2, or CTS3 within the first hour of hospitalisation and treated accordingly. Scicluna adds that 'this is the only way to definitively prove that a subtype-driven approach can save lives.'

## AN IMPORTANT MILESTONE

For Scicluna, the success of this project and its publication in *Nature Medicine* represents a significant milestone for science and patient care. 'This kind of work is only possible through a massive global collaboration,' he emphasises. 'It brings together clinicians, immunologists, microbiologists, data scientists and, most importantly, the thousands of patients who selflessly consent to take part in these studies.'

After decades of slow progress, Scicluna believes that the field is finally turning a corner. 'We are moving away from a one-size-fits-all approach towards truly personalised treatment – one that recognises every patient's unique biology,' he says. 'Because at the heart of it all, this research isn't just about data or classifications. It's about giving patients and their families a better chance at recovery and hope for the future.'



*Further Reading:*

*Scicluna, B. P., Cano-Gamez, K., Burnham, K. L., Davenport, E. E., Moore, A. R., Khan, S., Hinds, C. J., Cremer, O. L., Khatri, P., Sweeney, T. E., Knight, J. C., & van der Poll, T. (2025). A consensus blood transcriptomic framework for sepsis. Nature Medicine, 31, 4119–4130. https://doi.org/10.1038/s41591-025-03964-5*