Congress Interviews

EMJ spoke with leading early-career researchers to discuss the future of infectious diseases research, from macrophage host defence and host-directed therapies to viral transmission, infectiousness testing, and pandemic preparedness. Featuring insights from Young Investigator Awardees at the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), these interviews explore how translational science, clinical medicine, and public health are shaping new approaches to antimicrobial resistance, respiratory virus transmission, and personalised infection management.

Featuring: Clark Russell and Daniel Pan

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Clark Russell

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> **Studying immune-adaptive pathogen variants is a tool to cut through some of the complexity of host responses**

Q1 How did you first become interested in infectious diseases and microbiology, and what path led you to this field?

I've been interested in infectious diseases and microbiology since I was a medical student, particularly after an intercalated Bachelor of Medical Sciences degree in infectious diseases.

My specific interest in *Staphylococcus aureus* and macrophages comes from a patient I saw as a medical student on a 'medicine of the elderly' rotation, which I still remember very clearly. They had *Staphylococcus aureus* bacteraemia, and I remember learning about the pathogenesis of this infection in the context of that patient, and how diverse it could be.

Staphylococcus aureus has the capacity to infect almost any organ in the body, and the idea that it can do this by surviving inside phagocytes, the very cells meant to protect us, really stayed with me. Ever since that patient, I've been very interested in this area.

Q2 Your Young Investigator Award at the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Global 2026 recognises your work on macrophage antibacterial defence. What do you see as the key scientific findings that led to this recognition?

My interest in macrophage antibacterial defence lies in therapeutically augmenting it through host-directed therapies, as an alternative or an adjunct to conventional antibiotics, both in response to antibiotic resistance and to address intrinsic limitations of antibiotics, such as harm to the microbiome and failure to target intracellular bacteria.

A particular challenge in identifying targets for host-directed therapies is the complexity of immune responses *in vivo*. There's a lot of redundancy and many layers of regulation. Identifying appropriate mediators to target is difficult, and that might be one of the reasons why there are so few examples of host-directed therapies in clinical practice.

So, we took a different perspective on this problem and tried to take a pathogen's perspective on the host response.[1] We aimed to test the hypothesis that macrophage antibacterial mechanisms that a successful pathogen variant has evolved to escape might be particularly important in host defence and could be good targets for host-directed therapies.

We studied clinical isolates of bacteria using primary human macrophages and identified bacterial isolates that were resistant to macrophage intracellular killing. We then identified some of the macrophage responses that differed during challenge with these resistant isolates and validated, both *in vitro* and *in vivo*, some of these responses.

Overall, this approach of taking a pathogen's perspective allowed us to identify new mechanisms by which macrophages kill bacteria and to identify targets for host-directed therapies, including repurposing an existing drug, an old antihistamine called clemastine.

I think what this study adds is that studying immune-adaptive pathogen variants is a tool to cut through some of the complexity of host responses.

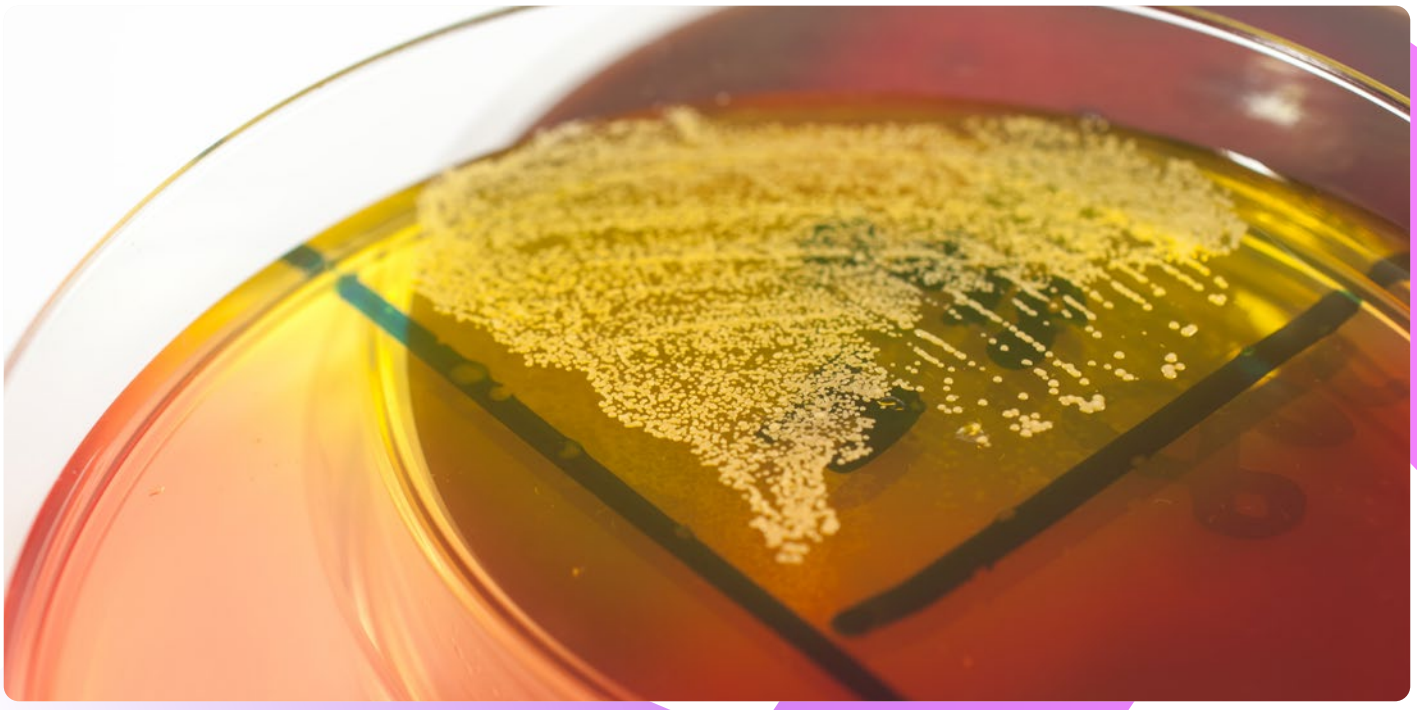
Q3 Much of your research focuses on how macrophages kill Gram-positive bacteria like *Staphylococcus aureus*. What have we recently learned about these immune mechanisms that we didn't understand a few years ago?

Staphylococcus aureus, *Streptococcus pneumoniae*, and enterococci are all major Gram-positive pathogens. Classically, they're considered extracellular bacteria. However, more recently, the importance of their intracellular phase in disease pathogenesis has been recognised.

In particular, survival within professional phagocytes, cells that in health might be able to kill the bacteria, can fail in certain disease states. This intracellular survival is important in the pathogenesis of the diseases that they cause.

I think this represents a shift in the relative importance of extracellular versus intracellular defence mechanisms. In the past, intracellular defence was mainly thought to be important for pathogens like mycobacteria or intracellular fungi. That's the new perspective.

What remains to be established is what the key mechanisms are that should control the intracellular phase of these Gram-positive bacteria, how and when they fail, and most importantly, what can be done



about it to recalibrate host responses in infection.

Q4 In your ESCMID presentation, you link host-directed therapies with patient stratification in *Staphylococcus aureus* bacteraemia. Can you walk through the central idea of this approach and why it matters clinically?

Currently, in clinical practice, clinical trials, and studies of disease pathogenesis, *Staphylococcus aureus* bacteraemia, like other bacterial infections, is usually considered a single entity. In reality, it's intrinsically very heterogeneous.

There's variation in the host, like age, sex, comorbidities, prosthetic material, there's variation in the pathogen, and there's variation in the extent of infection in an individual.

The patient stratification element came from some studies where we used routine clinical data to reproducibly identify clinical sub-phenotypes of *Staphylococcus aureus* bacteraemia.[2,3] This has potential value in clinical practice for prognostication, and we identified potential differential treatment effects of an existing therapy.

However, this is based only on observable features (age, sex, comorbidity), so it's just the starting point. The next step is to understand how disease mechanisms differ between patients. What are the pathophysiologic differences between these subphenotypes?

That's where the link to host-directed comes in. It's likely that different patient groups there have different problems. Some patients might have defective intracellular killing; others might have issues with immunometabolism or abnormal platelet-thrombotic responses.

Unpicking these differences opens the door to mechanism-targeted, host-directed therapies. The specific approach I am interested in is augmenting antibacterial immune responses.

Q5 Your research also explores why *Staphylococcus aureus* bacteraemia varies so widely between patients. What biological or clinical factors appear to drive that variability?

The studies in which we identified these subphenotypes were based on routine clinical data. These included patient factors like age, sex, and comorbidity, infection factors like the presence or absence of metastatic infection, whether the infection was community-acquired, and how the bacteria entered the bloodstream.

Using these variables, we identified five distinct sub-phenotypes of bacteraemia. The main factors driving the separation between sub-phenotypes were age, certain comorbidities, route of infection, and the presence or absence of dissemination (metastatic infection).

A limitation of these studies was the exclusive use of routine clinical variables. We didn't include biomarkers or experimental

assays such as readouts of immune function or pathogen virulence traits. So, the answer is constrained by the data available.

From a biological perspective, something that interests me is the impact of age. The biggest differences in survival between sub-phenotypes correlated very closely with age. Younger people, who predominantly acquire *Staphylococcus aureus* bacteraemia as a complication of injection drug use, can have a high burden of infection with metastatic spread, but, fortunately, they tend to have high survival rates. In contrast, elderly patients with multiple comorbidities have very poor survival rates.

I think the impact of age on mechanisms of host defence is relatively underexplored. Mechanisms aren't well understood but are increasingly important epidemiologically.

Q6 Looking beyond your own talk, are there particular sessions or themes at ESCMID Global this year that you're particularly looking forward to?

I think one of the most exciting things for me, as someone interested in *Staphylococcus aureus*, will be Asha Bowen, University of Western Australia, Perth, Australia, presenting results from the adjunctive clindamycin arm of the *Staphylococcus aureus* Network Adaptive Platform (SNAP) trial, the large international platform trial. I'm really looking forward to that.

Part of my work is clinical as well as research, and I really enjoyed a session on the first day about interpreting antibiograms. It was very helpful in addressing challenges related to new and emerging resistance mechanisms, as well as some of the newer drugs that are now available. That was an excellent session.

Q7 As a Young Investigator awardee, how important has mentorship been in your career so far, and what makes a good mentor in your experience?

Mentorship has been essential. I've been fortunate to have excellent mentors.

Some of the traits that make a good mentor include a willingness to challenge you and help you identify areas where you need to improve or develop. Another helpful trait is being able to step back and support pursuing your own interests, even if they diverge from theirs, so that you can develop some independence and create your own research niche.

Q8 For early-career researchers or clinicians attending ESCMID, what advice would you give on building a path that combines clinical work with research?

I can only speak from my own experience, and I recognise that I've been very fortunate to have protected research time through an External Quality Control of Diagnostic Assays and Tests (ECAT)/Wellcome PhD training fellowship and now through a lectureship from the Scottish Chief Scientist Office.

First, if you are in such a fortunate position to have protected, funded research time, it's important to recognise how lucky you are, because it's a huge advantage in terms of achieving research productivity.

Second, identify specific skills that align with the questions you want to answer, and learn to do them very well, so that you have a unique selling point. Whether in data science, epidemiology, or wet lab science, identifying and learning specific research and technical skills is very important, and this often requires focusing on one area, rather than spreading yourself too thin.

Finally, collaborate and embrace team science. This has been essential for all my work. It's allowed me to work with brilliant people, learn a great deal, and it's also been fun. As a clinician scientist, where time is always pressured, having a network of collaborators is key to getting things done.

Q9 Finally, what's next for you in terms of your research?

I am coming towards the end of my clinical training; I'll finish in around 1 year. I'm now planning an application for a research fellowship, which I hope to start after I finish my training.

I want to stay in the macrophage host defence field and continue working on *Staphylococcus aureus* as a model pathogen. I'm interested in investigating the mechanisms by which ageing increases both the risk of invasive bacterial infection and the risk of death in people who become infected.

This is a clear clinical observation and epidemiologically robust, but the underlying mechanisms remain unknown. As a result, there are currently no therapies to modify age-related susceptibility to infection, and that's something I'd like to address.