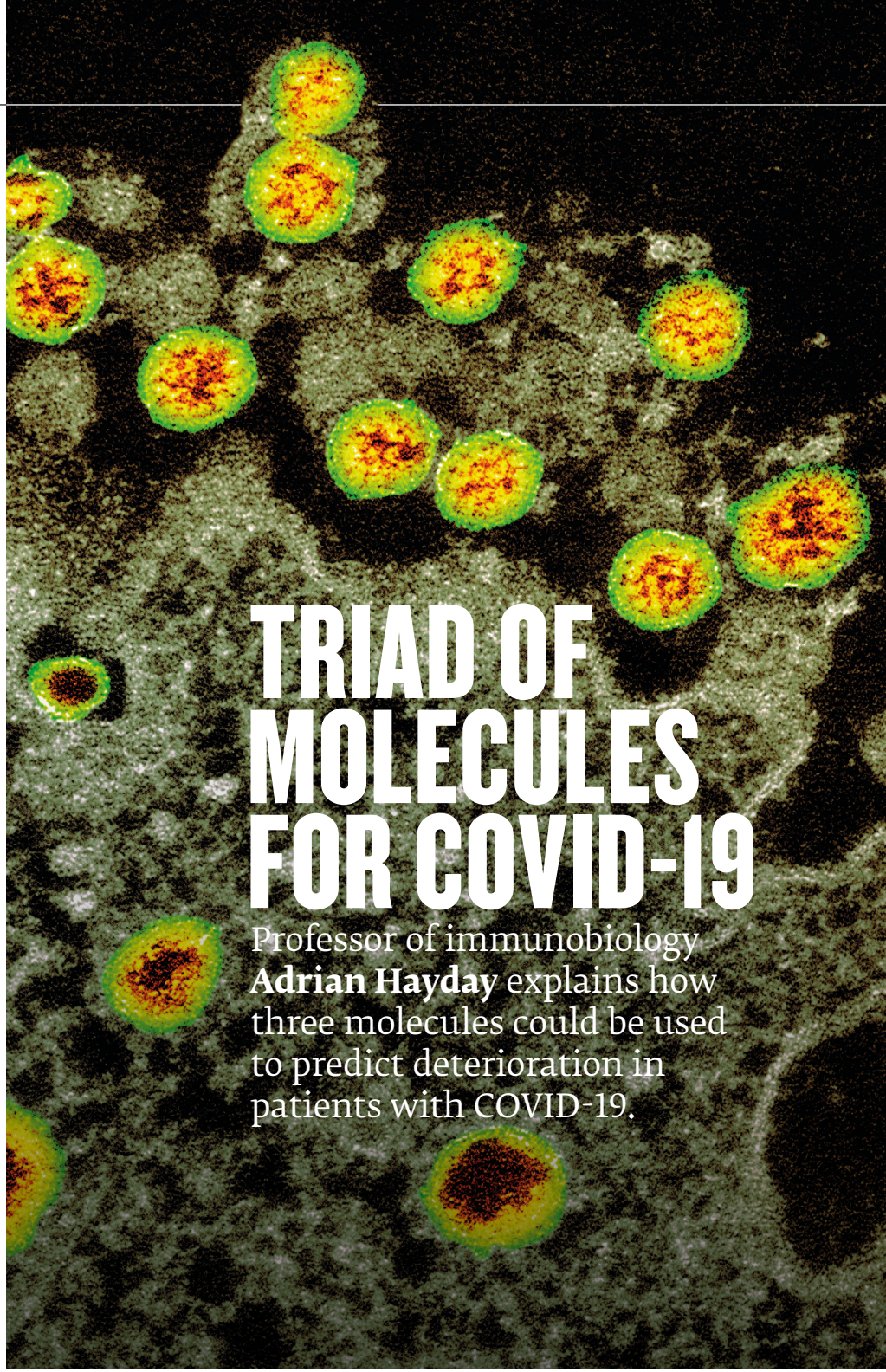


TRIAD OF MOLECULES FOR COVID-19

Professor of immunobiology **Adrian Hayday** explains how three molecules could be used to predict deterioration in patients with COVID-19.

Back in March the fight against COVID-19 set in motion a vast mobilisation of biological research resources around the world, and barely six months later this unprecedented effort has yielded a multitude of discoveries and insights, not least the results of the work published in *Nature Medicine* by a team drawn from the Francis Crick Institute, King's College London, and Guy's and St Thomas' NHS Foundation Trust.

Looking at blood samples from 63 patients treated for COVID-19 in London, they found a common immune signature, which could help doctors predict how ill individuals might become and how long they might need to stay in hospital. This immune signature contains high levels of three molecules in particular: IP-10, interleukin-10 and interleukin-6, which the researchers have collectively dubbed the "triad".

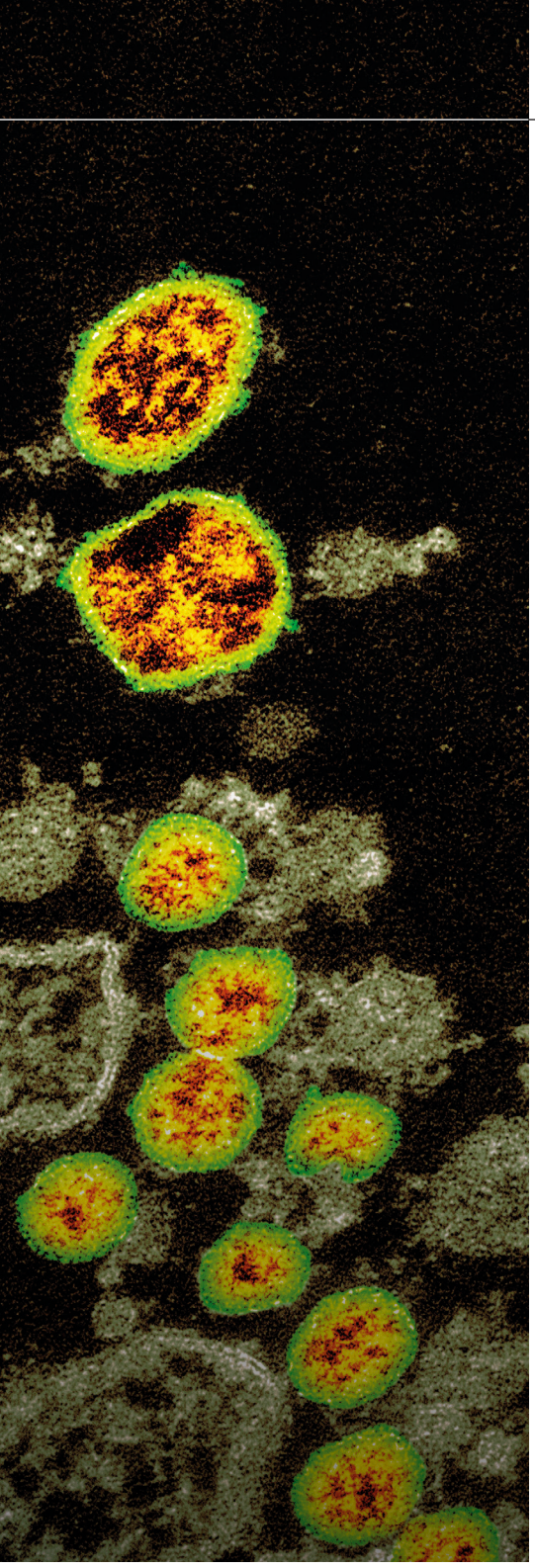
Immune system

Project leader Adrian Hayday, head of the immunosurveillance laboratory at the Francis Crick Institute and professor of immunobiology at King's College London, says the team didn't set out with any great expectations. "We are not virologists or vaccine developers, but we are pretty good at trying to track what the immune system is doing in patients who are suffering from the worst consequences of this infection. We figured that as long as we don't get in the way of other groups, we're not competing for samples or other more proximal needs, then finding out what the immune system is doing could be useful in trying to understand why certain individuals gets sick and others do not."

Even more pressing was the need to discover why the condition of certain individuals deteriorated from severe to catastrophic so unpredictably. "There were wards full of people with the same disease at St Thomas', which is unprecedented in modern history. And among all those individuals, about 20% would go downhill. But there was just no way of telling with any certainty on day one who was going to get worse and who was going to get better. Of course there are a lot of clinical markers that are measured – CRP, ferritin, albumin – but we wanted to look at the immune response and see if there was something that could distinguish what was going on with these patients."

Molecules

Analysing the blood samples of patients versus healthy individuals who had or had not themselves been infected – "a nice set of controls," he says – Hayday and his team detected something related to the "cytokine storm" – the flood of proteins that signal a potentially fatal overreaction by the body's immune system. The molecules associated with this process in inflammatory conditions normally include TNF, interleukin-6 and



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interleukin-1. But what they encountered was more a breeze than a storm. "That is to say we didn't see huge amounts of TNF or interleukin-1, but we did see some other molecules expressed at high levels. Three in particular caught our attention. Interleukin-6 was there, but we also saw interleukin-10 and another one called IP-10, formally a chemokine rather than a cytokine, though they're similar."

The IP-10 molecule is particularly interesting, adds Hayday. "When you look back at the literature for the MERS and first SARS epidemics, everybody reported very high levels of IP-10. So I wonder whether this IP-10 molecule isn't fundamental to the biology of coronavirus infection and pathology? It's speculation, but it's a fascinating speculation."

Robust predictors

Besides noticing that most of the patients had high levels of the "triad" molecules, they also observed that the higher the levels of the molecules, the more severe the disease appeared to be. More than that, they found that the levels were particularly high on the actual day patients were hospitalised. This raises the question of whether these molecules not only correlate with the severity of COVID-19, but actually anticipate that severity in a way that might guide doctors as to which patients are likely to deteriorate. "Of course it's not perfect," says Hayday. "Nonetheless, if you do the maths, if you look at the statistics, those molecules are the most robust predictor of who's going to get worse rather than better. Even to the point that IP-10 levels can pretty much predict how long you're going to be in hospital. If we get to a situation again where there is pressure on hospital beds and resources, it could make a big difference."

But how easily might this be translated into a workable test at the bedside? "These conversations are beginning. I'm not an engineer, but there are some really good engineers out there. I think they will be able to make a fairly routine test for these molecules, a triad-test as it were. Some of the markers that are used in clinical chemistry have been fantastic but they are decades old. With the level of sophistication and understanding we now have, we really ought to be providing doctors with tests that can give a better assessment of a patient's condition."

Spin-off benefits

And what does he make of the whirlwind of research that is swirling around COVID-19? "I've been running a lab for 34 years and I have never seen the speed with which basic research findings are being picked up for clinical bed-proximal translation as we're seeing now. That has to change the way we do science. Once the pandemic is over we can't suddenly go back to how it was. We have to learn."

Part of this learning, he argues, is to reconsider the priorities that inform research funding. "There's never enough money. So funding committees tend to be risk averse. But groups such as ours have just stopped what they were doing and undertook the most adventurous, risky projects, and they have worked. If we were risk averse and conservative, we could never have responded to COVID-19. At all levels, we need to embrace this new era."

There is also huge potential for spin-off benefits in other clinical areas. "We've had an unprecedented opportunity to watch a live immune system response. We've learned huge amounts, and that's going to be hugely informative about the immune response to cancer, for example. The basic fundamental research lessons that we can pick up here are innumerable," he concludes. BMS

ADRIAN HAYDAY

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- ✔ **2009** – Established lab at the London Research Institute, Cancer Research UK
- ✔ **2015** – Group leader, the Francis Crick Institute.