Derek Gilroy

Head of Department of Experimental & Translational Medicine, University College London, UK

Citation: EMJ. 2026;11[3]:74-79. https://doi.org/10.33590/emj/P5D58UMJ

Q1 Your research has focused on understanding how inflammation resolves rather than simply how it starts. What first drew you to the concept that resolution is an active biological process rather than a passive one?

During my PhD, we came across a serendipitous observation using rat pleuritis. If I remember correctly, we made an error and created an extra group of rats which were left to run for a couple of days. We were normally interested in the acute inflammatory phase: how the heat, redness, oedema, and pain occur. This normally occurs within the first 24 hours. It was serendipity! A group of rats were euthanised and we examined their pleural cavity. Despite expecting that everything would have gone away, there was still immune activity, that, we now know, is associated with clearing up debris and helping to switch off inflammation.

That made us curious, thinking "we know a lot about the heat, redness, oedema, and pain that occurs during inflammation. How does that switch off? Does it just passively switch off or are there other things that actively help the pain to go away, vascular redness to reverse, oedema to disappear, immune cells to die and be eaten up and cleared in an anti-inflammatory manner?" It was in the late 1990s when we began to ask these questions, considering that there must be more happening at the site of inflammation, but logically there must also be things able to help reverse that process. That was the catalyst.

Q2 You've argued that many chronic inflammatory diseases may result from failures in the body's natural resolution pathways. How has our understanding of these pathways changed over the course of your career, and what do you think are the biggest unanswered questions today?

When I first entered the field, our view of inflammation was relatively straightforward. Immune cells arrived at the site of infection or injury, eliminated the threat, and then simply disappeared. We knew they had to die, but we didn't really appreciate that how they died was just as important as what they had done while they were alive.

Over the past 25–30 years, we've learnt that resolution is an extraordinarily active and tightly regulated process. Immune cells don't just disappear, they undergo a carefully orchestrated form of cell death and are then cleared by other immune cells in a way that actively suppresses further inflammation and promotes tissue repair. At the same time, tissues produce specialised mediators and activate intracellular signalling pathways that restore normal function and establish immune tolerance. Remarkably, all of this happens almost silently, without us ever noticing.

One of the biggest advances has been recognising that resolution isn't a single universal programme. Different organs resolve inflammation differently. The pathways operating in the skin may be quite distinct from those in the lung, liver, or brain. Resolution also varies depending on the trigger, whether it's an infection, trauma,

"By using human skin as a window into the immune system, we can safely induce a controlled inflammatory response"

or autoimmune disease, and is influenced by age, sex, and an individual's overall health. In other words, there isn't one resolution programme; there are many.

The really exciting challenge now is understanding what goes wrong in disease. In chronic inflammatory conditions, these natural healing pathways become dysregulated or fail altogether. Instead of restoring tissue health, inflammation persists, causing progressive damage. We now need to identify precisely why resolution fails in one disease, one organ, or one group of patients, and why those mechanisms differ from another. I think that's where the future lies.

If we can understand the specific pathways that fail in individual diseases, we can move beyond simply suppressing inflammation. Instead, we could develop therapies that actively restart the body's own healing programmes, restoring health rather than just dampening the inflammatory response. I think that's one of the most exciting opportunities in medicine today.

Q3 Your answer has made me think about how we typically explain chronic pain through mechanisms like peripheral and central sensitisation, as well as persistent inflammation. However, we don't often discuss the role of immune cells interacting directly with sensory nerves. Do you think that understanding those neuroimmune interactions, particularly during the resolution of inflammation, could fundamentally change the way we think about chronic pain and why it persists in some people?

Absolutely. In fact, I think this is one of the most exciting frontiers in inflammation research.

Historically, we've tended to think about chronic pain in terms of changes within the nervous system; peripheral sensitisation, central sensitisation, and persistent inflammation. But we've paid surprisingly little attention to how immune cells and sensory nerves communicate directly, particularly during the phase when inflammation is naturally resolving.

One of the great advantages we've had in our laboratory is being able to study inflammation directly in humans. By using human skin as a window into the immune system, we can safely induce a controlled inflammatory response, follow the development of heat, redness, swelling, and pain over time, and then watch the entire process resolve. Importantly, we can repeatedly sample the tissue as this happens. That gives us an opportunity that very few models can offer, namely to see how immune cells, blood vessels, stromal cells, and, potentially, sensory nerves interact in real time in human tissue.

The reality is that we still know remarkably little about what happens around sensory nerves during the resolution phase. We have hundreds of archived tissue samples in the laboratory that contain this information, but we've barely begun to explore it. The obvious next question is: at the peak of pain, which immune cells are sitting alongside sensory nerve endings, what signals are they exchanging, and how do those interactions change as pain resolves?

I suspect those answers could fundamentally change how we think about chronic pain. Rather than viewing pain simply as a consequence of inflammation, we may discover that the failure to restore healthy communication between immune cells and sensory nerves is one of the reasons pain persists long after the original injury or inflammation should have resolved.

Ultimately, we'd like to take those discoveries into chronic inflammatory and autoimmune diseases. If we can identify the cellular conversations that normally switch pain off, we may

be able to design therapies that don't simply block pain signals but instead restore the body's own natural mechanisms for resolving pain. I think that's an exciting prospect, and to be honest, we've only just begun to scratch the surface.

Q4 A recurring theme in your work is the idea of developing therapies that actively drive tissues back towards resolution of inflammation. What are the biggest challenges in translating pro-resolution biology into treatments that can benefit patients?

I think the biggest challenge is recognising that there isn't a single 'resolution pathway'. Biology simply isn't that straightforward.

For many years we've searched for universal anti-inflammatory drugs, but resolution biology is much more nuanced. The mechanisms that restore tissue health after a bacterial infection are likely to be very different from those that resolve autoimmune inflammation in lupus or rheumatoid arthritis, or fibrosis in the lung. Even within the same disease, different biological pathways can be driving pathology in different patients.

Take lupus as an example. We increasingly recognise that lupus isn't one disease, it's probably four or five distinct biological endotypes that happen to produce similar clinical symptoms. That helps explain why some patients respond remarkably well to a particular treatment, while others with an apparently identical diagnosis derive little or no benefit. The same principle applies to many inflammatory diseases, including sepsis.

There are also important biological differences between people. Autoimmune diseases are far more common in women than in men, suggesting that both the mechanisms driving disease and those responsible for restoring immune balance are likely to differ. Age, ethnicity, genetics, and the affected organ all add further layers of complexity.

So, I would always be cautious when someone claims they have a single pro-resolution therapy that could treat every inflammatory disease. I simply don't think biology works that way. Resolution pathways are likely to be disease-, organ-, and patient-specific.

To me, the future lies in precision resolution medicine. Rather than asking, "How do we treat inflammation?", we should first ask, "Why has this particular patient's inflammation failed to resolve?" Once we understand the specific pathways that have become impaired in that disease, or even that endotype of disease, we can develop therapies that reactivate the body's own healing mechanisms. That's a much more rational approach, and I think it's where the field is heading over the next decade.

Once we understand the specific pathways that have become impaired in that disease, we can develop therapies that reactivate the body's own healing mechanisms

Q5 In your recent work you've highlighted intermediate monocytes as potentially important drivers of tissue damage in diseases such as lupus and leishmaniasis. What makes these cells so interesting, and how close are we to being able to therapeutically target them?

Serendipity is a very important word in science. It isn't quite the same as luck. Luck simply lands in your lap; serendipity usually follows hard work, careful observation, and being prepared to notice something unexpected. As the saying goes, the harder you work, the luckier you get.

Our interest in intermediate monocytes began in exactly that way. We were studying an enzyme called soluble epoxide hydrolase, or sEH, which regulates a group of bioactive lipid mediators. Our initial experiments in mice suggested that blocking this pathway could alter inflammation, and we were then fortunate to have access to a clinically tested sEH inhibitor that could be studied in our human skin inflammation model.

We began the study with a clear hypothesis about what the drug would do. In fact, it produced almost the opposite result. But when we looked carefully through the data, we found something much more interesting than we had originally expected: blocking sEH had a profound effect on the appearance of intermediate monocytes during inflammation.

Human blood monocytes are commonly divided into three populations: classical, intermediate, and non-classical monocytes. Classical monocytes make up the great majority, whereas intermediate monocytes represent only a small proportion of the cells circulating in healthy blood.

However, during inflammation, the intermediate population can expand substantially.

What we discovered was that the sEH pathway appears to regulate the transition from classical to intermediate monocytes. Importantly, this process begins in the circulation. Following infection or injury, intermediate monocytes increase in the blood and, although they remain relatively few in absolute terms, they are disproportionately represented among the monocytes that subsequently enter inflamed tissues.

That is what makes them so interesting. When we isolate these cells and compare them with other monocyte populations, they have a remarkable capacity to release inflammatory mediators, degrade extracellular matrix, and damage surrounding cells and tissues. They may be relatively rare in the blood, but once recruited into tissue they can have an outsized biological effect.

This is particularly relevant to diseases characterised by repeated episodes of flare and remission, such as lupus and rheumatoid arthritis. Each flare can bring another wave of inflammatory cells into the skin, joints, kidneys, or other organs. Over time, that repeated and often insidious process contributes to cumulative tissue damage. Intermediate monocytes are also persistently expanded in a range of chronic inflammatory, infectious, and metabolic diseases, which suggests that they may represent a common pathogenic component in at least some patient groups.

So, we think these cells may be less like passive biomarkers of inflammation and more like active drivers of tissue injury.

> **Sex isn't simply another variable to record, it's a biological determinant of how inflammation starts, resolves, and leaves tissues protected afterwards**

In terms of therapy, we are at an encouraging but still relatively early stage. We already have a drug capable of modulating the sEH pathway, and it has been given safely to humans. That gives us a major advantage. The next step is to design carefully targeted clinical studies to determine whether altering this pathway can reduce the generation or tissue recruitment of intermediate monocytes and, crucially, whether that translates into less tissue damage.

The opportunity is certainly there, but we still need to identify the diseases and patient endotypes in which these cells are truly pathogenic. If we get that right, intermediate monocytes could become both a useful biomarker and a tractable therapeutic target.

Q6 When we spoke previously, I highlighted the importance of sex-disaggregated data in allergy and immunology research. Do you believe sex stratification of data remains underutilised, and what opportunities are being missed when researchers fail to incorporate it into study design?

Our own work illustrates this very clearly. In our human skin inflammation model, we challenge the forearm skin of healthy volunteers with bacteria and follow the inflammatory response over several days. What we consistently find is that females mount a much more restrained inflammatory response. They develop less redness and swelling, fewer immune cells infiltrate the tissue, and they generally report less inflammatory pain than males.

What's fascinating, however, is that this doesn't represent a weaker immune response. Quite the opposite. Women clear the bacterial challenge more rapidly, and the inflammatory response resolves significantly faster. In other words, they achieve a better outcome with a smaller inflammatory response.

We've also become increasingly interested in what happens after inflammation appears to have resolved. Although the tissue looks normal again, there's still a tremendous amount of immune activity taking place beneath the surface. We believe these processes are crucial for maintaining tissue integrity, restoring immune tolerance, and preventing future tissue damage. Our unpublished work suggests that these post-resolution programmes are fundamentally different between males and females.

To me, this reinforces the idea that sex isn't simply another variable to record, it's a biological determinant of how inflammation starts, resolves, and leaves tissues protected afterwards.

The challenge, of course, is practical. Properly powering studies to detect sex-specific biology usually means recruiting larger cohorts or studying male

and female animals separately. That inevitably increases costs, time, and experimental complexity. Funding agencies such as the Medical Research Council (MRC) and UK Research and Innovation (UKRI) quite rightly encourage researchers to incorporate both sexes into their study designs, but the resources available don't always fully reflect the additional work required.

Nevertheless, I think it's a challenge we have to overcome. If we continue to average male and female data together, we risk overlooking fundamental biology and, potentially, missing opportunities to develop more effective, personalised therapies. Rather than viewing sex as a confounding variable, we should be embracing it as one of the keys to understanding why inflammatory diseases develop differently and why patients respond differently to treatment.

Q7 You've worked with large multidisciplinary collaborations throughout your career. Looking back, what have you learned about building successful research teams and creating environments where younger scientists can thrive?

The first thing I'd say is: employ people who are smarter than you. And, just as importantly, employ people who aren't afraid to disagree with you. Don't be intimidated by that, embrace it. If everyone in the room thinks the same way as you do, you're probably not asking the right questions.

> **Everyone is encouraged to question, challenge, and contribute ideas. Nobody has a monopoly on good ideas**

The second lesson is to create an environment where everyone has a voice. Yes, as Head of Department I may write the grants or set the broad scientific direction, but I've learnt that my presence can sometimes unintentionally inhibit younger scientists. Hierarchy can be surprisingly powerful in academia. Junior researchers may hesitate to challenge an idea simply because it comes from someone more senior. I think that's one of the biggest barriers to innovation.

I've always tried to run my laboratory as a cooperative rather than a hierarchy. Everyone has a voice. Everyone is encouraged to question, challenge, and contribute ideas. Nobody has a monopoly on good ideas, and everyone is equally capable of being right or wrong. Some of our best discoveries have come from conversations where someone junior has questioned an assumption that everyone else had accepted.

I also think it's important to give young scientists what I call 'the freedom to fail'. Science is built on experiments that don't work, hypotheses that turn out to be wrong, and unexpected observations that lead you in entirely new directions. If people become afraid of making mistakes, they stop taking risks, and that's when creativity disappears.

Ultimately, my job isn't to produce clones of myself. It's to help young scientists become independent thinkers with the confidence to develop their own ideas and challenge existing dogma. I see my role as providing the vision, resources, and support, then stepping back and allowing talented people to flourish.

Q8 Throughout your career you've received numerous awards and recognitions, published extensively, and helped shape the field of inflammation research. Looking back, which achievement are you personally most proud of and why?

There are probably two things I'm most proud of.

The first is helping to establish the idea that the resolution of inflammation is an active biological process worthy of study in its own right. When I began my career, almost all the emphasis was on understanding how inflammation starts and how to suppress it. Over the years, our work has contributed to shifting that perspective by showing that the body possesses its own highly regulated pathways that actively restore tissue health. I'm also proud that we've translated much of that work from animal models into carefully controlled studies in humans, allowing us to study inflammation and its resolution where it matters most: in people.

But if I'm completely honest, the achievement that gives me the greatest satisfaction has very little to do with papers, grants, or awards.

Over 20 years ago, my good friend Jane Mitchell from Imperial College London, UK, gave me some advice that has stayed with me ever since. She said: "You can never guarantee that you'll cure a disease, discover a receptor, or develop a successful drug. But you can guarantee that you'll help develop the careers of other scientists. That's something you can control."

I've never forgotten those words.

Watching PhD students and postdoctoral researchers grow into independent scientists, establish their own laboratories, and mentor the next generation is probably the most rewarding part of my career. Science is a relay race, not an individual sprint. Each of us makes a small contribution before passing the baton to those who follow.

Scientists often begin their careers dreaming of curing cancer or winning a Nobel Prize. The reality is rather different. Progress usually comes through thousands of small, incremental advances made by people working together over many years. If I've helped move the field forward a little, and at the same time helped others build successful scientific careers, then I'd consider that a career well spent.

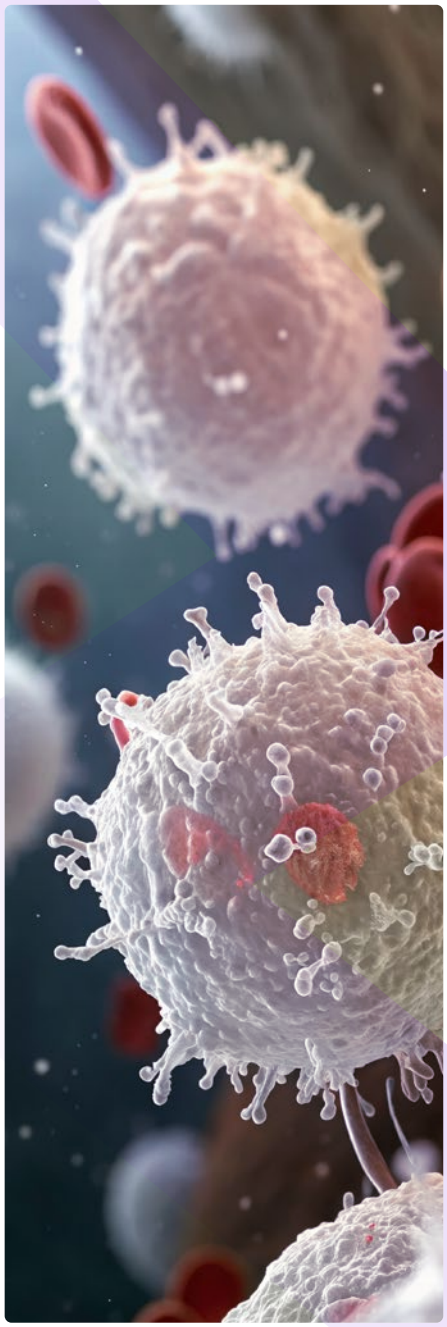
Q9 If we were having this conversation 10 years from now, what discovery or breakthrough in inflammation research would you most like to see happen?

I think it all comes back to precision immunology.

For too long we've tended to think of inflammatory diseases as single entities. I believe the future lies in recognising that every disease is made up of multiple biological endotypes, each driven by different pathways. Rather than trying to develop one treatment for everyone, we'll identify the specific pathway that's gone wrong in an individual patient and target that.

My hope is that, 10 years from now, we'll have moved beyond simply suppressing inflammation. Instead, we'll be able to harness the body's own resolution programmes to actively reset the immune system and restore tissue health.

The ultimate goal would be something even more profound. In many chronic inflammatory and autoimmune diseases, the immune system appears to acquire a maladaptive memory that continually drives tissue damage. I'd love to see us understand how to erase or reprogramme that pathological memory, allowing the immune system to return to



the healthy state it was always designed to achieve.

That's a huge scientific challenge, and we're certainly not there yet. But if we can learn how to restore immune balance, rather than simply dampen inflammation, I think it would fundamentally change the way we treat chronic inflammatory diseases.

For me, that would be the dream. Not just controlling disease, but truly resetting immunity and allowing the body to heal itself.