Atlas of Science
another view on science
https://atlasofscience.org

PEPITEM: Helping the body's natural defence against arthritis

Rheumatoid arthritis (RA) and psoriatic arthritis (PsA) are diseases where the body's immune system attacks the joints by mistake. White blood cells move into the joints, causing swelling, pain and stiffness. Over time, this can damage the cartilage and bone. Current medicines help reduce inflammation once it has started, but they cannot repair damage that has already happened.

Our bodies also have natural ways of keeping inflammation under control. One of these uses a natural substance called adiponectin, which tells white blood cells to produce another small molecule called PEPITEM. PEPITEM acts like the body's own brake, helping to stop too many white blood cells entering the joints and causing damage.

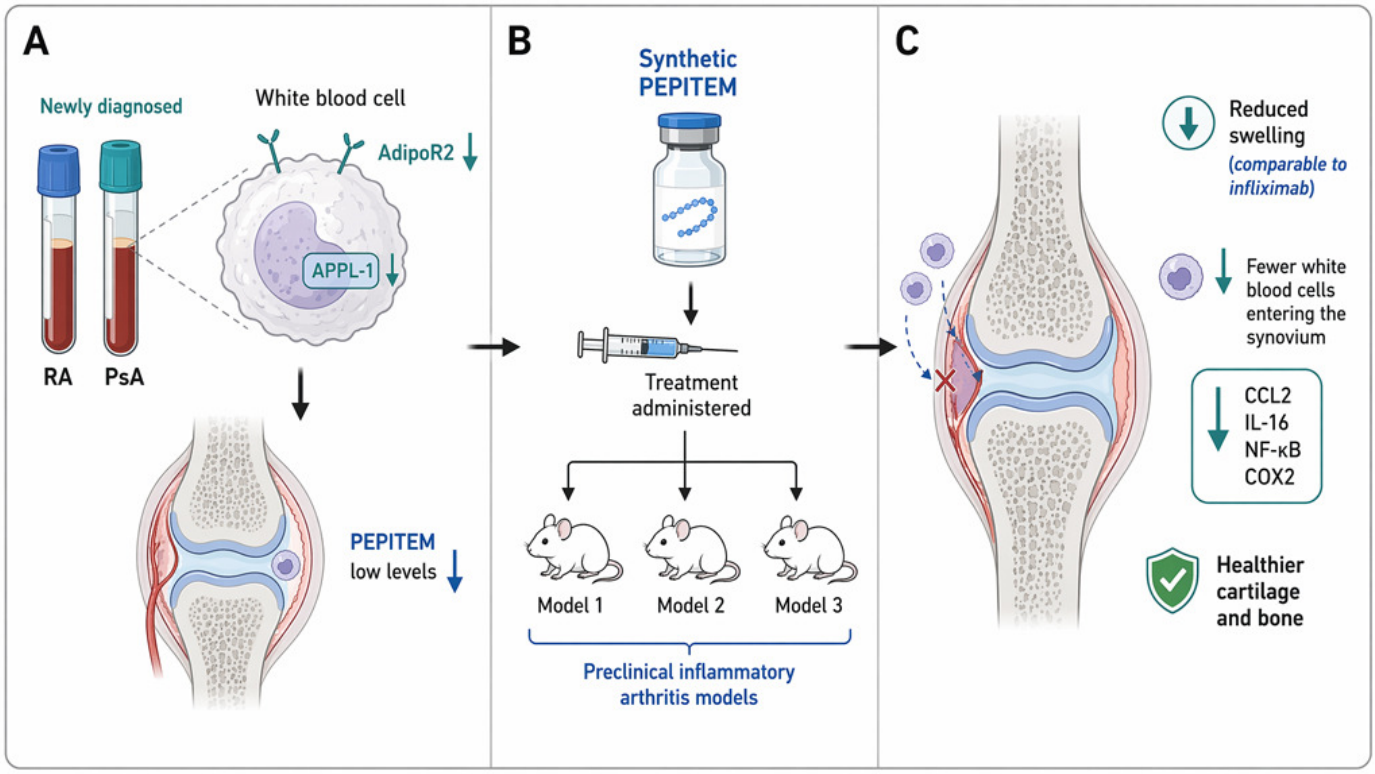

Fig. 1. Changes in the PEPITEM pathway and the effects of PEPITEM treatment in inflammatory arthritis. (A) Blood samples from people with newly diagnosed rheumatoid arthritis or psoriatic arthritis showed lower levels of the receptor needed to produce PEPITEM, resulting in reduced PEPITEM levels. (B) A laboratory-made version of PEPITEM was tested in three different mouse models of inflammatory arthritis. (C) PEPITEM treatment reduced joint swelling, changed gene activity within cells in the joint, reduced inflammatory proteins, decreased the number of white blood cells entering the joints, and reduced cartilage and bone damage.

In this study, we found that this natural control system was not working properly in people who had recently been diagnosed with Rheumatoid arthritis or psoriatic arthritis. Their white blood cells showed lower levels of the receptor for adiponectin, leading to them being much less able to produce PEPITEM than those from

healthy people (Fig. 1A). Without enough PEPITEM, the body's natural brake becomes weaker, allowing more white blood cells to enter the joints and drive inflammation.

As patients had lower levels of PEPITEM, we wanted to find out whether replacing it could reduce arthritis. We tested a laboratory-made version of PEPITEM in different mouse models of inflammatory arthritis (Fig. 1B). Mice treated with PEPITEM had less joint swelling, less damage to their cartilage and bone, and fewer white blood cells entering the joints. The treatment worked as well as infliximab, a medicine already used to treat arthritis.

We also wanted to understand how PEPITEM protects the joints. We used single-cell sequencing, a technique that shows which genes are switched on or off in thousands of individual cells. This allowed us to examine cells taken directly from the inflamed joints of mice with arthritis. We found that PEPITEM changed the transcriptional profile of these cells – that is, the pattern of genes they were using. The cells became less likely to promote inflammation and more likely to help control it. We also found a similar change in the proteins present within the joint. PEPITEM reduced proteins that drive inflammation and increased those that help calm it (Fig. 1C). Together, these changes shifted the joint environment away from a damaging, pro-inflammatory state and towards a more controlled, anti-inflammatory one. In other words, PEPITEM helped restore a healthier balance in the joint, allowing the immune system to control inflammation instead of causing damage.

Our findings suggest that some people with rheumatoid arthritis and psoriatic arthritis have a problem with one of the body's natural systems for controlling inflammation. Rather than simply blocking inflammation, PEPITEM may help restore the body's own ability to keep the immune system in balance. In the future, this approach could be used alongside existing treatments, especially early in the disease, to reduce inflammation and help protect joints from long-term damage.

Mussarat Wahid and Helen McGettrick
Rheumatology Research Group, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, B15 2TT, United Kingdom

Publication

PEPITEM Regulates the Synovial Microenvironment During Immune-Mediated Inflammatory Arthritis to Limit Disease
Mussarat Wahid, Samuel Kemble, Oladimeji Abudu, Anella Saviano, Christopher Mahony, Jonathan W. Lewis, Thomas A. Nicholson, Anna Schettino, Noemi Marigliano, Kathryn Frost, Jenefa Begum, Alyssa M. Urbanowski, Marion Limo, Rakesh Jha, Sandra Martinez Jarquin, Laleh Pezhman, Abbie E. A. Degan, Amy E. Anderson, Charlotte G. Smith, Armaiti Batki, Holly Adams, Francesco Caso, Raffaele Scarpa, Iain McInnes, Stefan Siebert, Arthur G. Pratt, Andrew Filer, Karim Raza, Adam P. Croft, Myriam Chimen, Felicity de Cogan, G. Ed Rainger, Asif J. Iqbal, Francesco Maione, Helen M. McGettrick
Arthritis Rheumatol. 2026 Jul