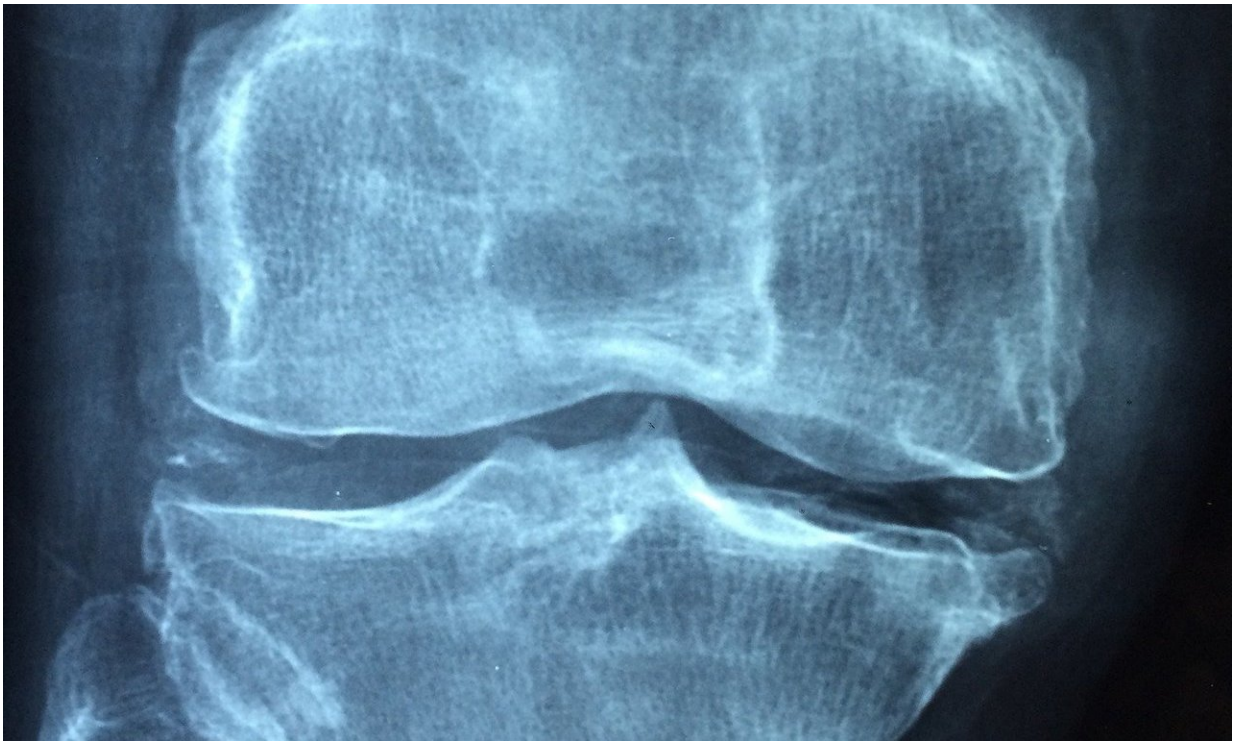
'Locking' an arthritis drug may be key to improving it

June 13 2019



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Attaching a removable lock to an arthritis drug can make it safer and more effective, according to a new study publishing June 13 in the open-access journal *PLOS Biology* led by Wen-Wei Lin of Kaohsiung Medical University, Taiwan. The findings suggest a new way to improve the efficacy of a drug taken by millions of patients throughout the world.

The monoclonal antibodies infliximab and adalimumab have become blockbuster drugs for the autoimmune disease rheumatoid arthritis, because of their ability to block the activity of tumor necrosis factor alpha (TNF-alpha), a key signaling molecule in the autoimmune cascade. But their use comes with two major drawbacks—TNF-alpha blockade in non-arthritic tissues can lead to dangerous immune suppression, and many patients receiving the therapy quickly develop antibodies to the monoclonals themselves, thereby suppressing the activity of the drugs.

The authors set out to mitigate both problems by adding a removable protein "lock" to the infliximab antibody. They attached their lock by chemically linking it to the "business end" of the antibody using a protein tag that can be removed by an enzyme called matrix metalloproteinase (MMP). MMP is abundant at the site of rheumatoid arthritis, where it contributes to the tissue breakdown that is a major consequence of the disease. This high concentration of MMP, the authors hoped, would remove the lock and release active infliximab primarily at the site of disease, while leaving it largely locked and inactive in non-arthritic tissues where MMP levels were lower. At the same time, they hoped that the presence of the lock would alter the shape of the infliximab sufficiently to prevent development of anti-infliximab antibodies.

The locked form worked in both respects. It was equal to infliximab in its ability to treat an experimental form of rheumatoid arthritis in mice, and led to fewer infections in response to a bacterial challenge, an indication that systemic immune suppression had been reduced. Anti-infliximab antibodies bound to the locked form of infliximab with less than 1% of the strength with which they bound to infliximab itself, suggesting it may be less immunogenic and so less likely to lead to development of benefit-neutralizing antibodies.

"The addition of this reversible lock to infliximab has the potential to

improve the risk/benefit ratio for patients with rheumatoid arthritis," Lin said, "and may serve as a model for improvement of other monoclonal antibody therapies as well. Significant further work will be required before the modified form of the antibody can be tested in a clinical trial in patients.

More information: Lu Y-C, Chuang C-H, Chuang K-H, Chen I-J, Huang B-C, Lee W-H, et al. (2019) Specific activation of pro-Infliximab enhances selectivity and safety of rheumatoid arthritis therapy. *PLoS Biol* 17(6): e3000286. doi.org/10.1371/journal.pbio.3000286