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EXPERIMENTAL ARTHRITIS

Stopping neutrophil migration in its tracks

> Treatment with the anti-G-CSFR mAb … reduced the number of neutrophils in the inflamed joints of mice

Blocking granulocyte colony-stimulating factor (G-CSF) receptor (G-CSFR) halts the progression of established disease in a mouse model of rheumatoid arthritis (RA) by reducing the trafficking of neutrophils to the joints, according to research published in *The Journal of Immunology*. "Our data confirm the important role that the G-CSF signalling pathway has in neutrophil-driven inflammatory arthritis and support the idea of targeting this pathway for the treatment of human diseases, such as RA," states Ian Campbell, corresponding author on the study, which was supported by CSL Limited.

G-CSF, an important growth factor for neutrophil homeostasis and function, binds exclusively to G-CSFR, making it a promising therapeutic target for neutrophil-driven inflammatory diseases. "Our previous studies showed that G-CSF and G-CSFR-deficient mice were protected from various models of RA, while a G-CSF-neutralising monoclonal antibody (mAb) could reduce established disease," asserts Campbell. "Previously, there were no available mAbs that could block mouse G-CSFR and so the effect of G-CSFR blockade on established disease could not be evaluated," he explains.

To address this problem, the research team developed a high affinity mAb to murine G-CSFR using a phage display library. Using this antibody, the team were able to rapidly inhibit joint inflammation in mice with established collagen antibody-induced arthritis (CAIA) when compared with mice with CAIA treated with a control mAb. Treatment with the anti-G-CSFR mAb dramatically reduced the number of neutrophils in the inflamed joints of mice with CAIA without causing the number of circulating neutrophils to drop below levels seen in disease-free mice.

Crucially, when infected with influenza, mice treated with the anti-G-CSFR mAb mounted a normal immune response to the virus. "Given the potentially critical role of G-CSF in neutrophil homeostasis and the importance of neutrophils as first-line defenders against infection, it was important to evaluate the effect of G-CSFR blockade on viral clearance in an influenza model," explains Campbell. "This is an important issue to understand before proceeding to clinical trials in humans," he concludes.

An anti-G-CSFR mAb suitable for use in humans has been developed by CSL Limited, and is currently in a phase I human clinical trial.

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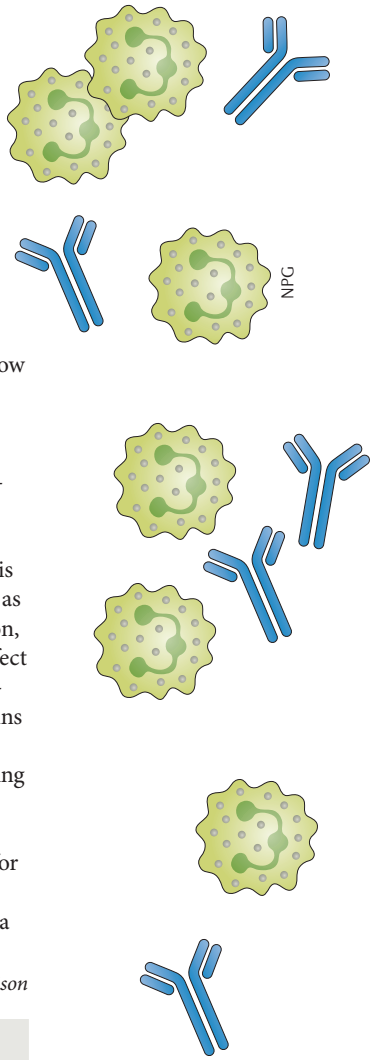

ORIGINAL ARTICLE Campbell, I. K. *et al.* Therapeutic targeting of the G-CSF receptor reduces neutrophil trafficking and joint inflammation in antibody-mediated inflammatory arthritis. *J. Immunol.* http://dx.doi.org/10.4049/jimmunol.1600121 (2016)