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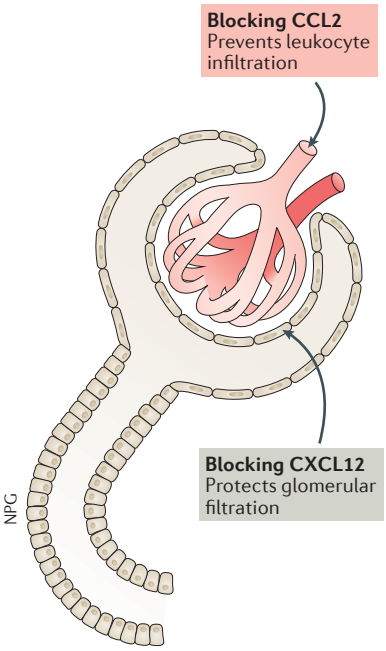
LUPUS NEPHRITIS

Mirror RNAs might reflect better therapy

> Dual blockade of [CCL2 and CXCL12] is as effective as high-dose cyclophosphamide

Dual blockade of CC-motif chemokine 2 (CCL2, also known as MCP1) and stromal cell-derived factor 1 (also known as CXC-motif chemokine 12 (CXCL12)) is as effective as high-dose cyclophosphamide monotherapy in the MRL/lpr mouse model of proliferative lupus nephritis, a new report suggests. The researchers blocked CCL2 and CXCL12 using RNA aptamer agents built from mirror-image (L-enantiomeric) nucleotides — emapticap pegol and olaptesed pegol, respectively. Mirror RNAs, unlike other oligonucleotides, are highly nuclease-resistant and do not stimulate pattern-recognition receptors. "Such therapy would be feasible also in humans," opines Hans-Joachim Anders, corresponding author of the paper.

Earlier studies had failed to show additive effects of dual chemokine-blocking therapy, probably because chemokines or chemokine receptors of the same class were targeted. "We started out to combine agents targeting chemokines of different classes: proinflammatory and homeostatic," describes Anders, who goes on to explain that CXCL12 blockade targets autoimmunity by disrupting germinal centre formation, whereas CCL2 blockade has no effect on autoimmunity but instead selectively blocks intrarenal inflammation.



Treatment of proliferative lupus nephritis in humans currently requires potent immunosuppression with steroids plus either high-dose cyclophosphamide or mycophenolate mofetil. "Remember that we used a steroid-free regimen in the present study, which is currently the major objective to address in lupus clinical trials," Anders highlights. "Our finding that this approach has equivalent efficacy to high-dose cyclophosphamide implies that the dual cytokine-blocking aptamer therapy is very potent, despite (probably) not having any severe immunosuppressive effects," he asserts.

Although clinical trials of these agents in lupus nephritis are not yet underway, Anders notes that a drug blocking the CXCL12 receptor is already FDA-approved, and human trials have validated inhibition of CCL2 and its receptor as a treatment for diabetic nephropathy.

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ORIGINAL ARTICLE Devarapu, S. K. *et al.* Dual blockade of the pro-inflammatory chemokine CCL2 and the homeostatic chemokine CXCL12 is as effective as high dose cyclophosphamide in murine proliferative lupus nephritis. *Clin. Immunol.* http://dx.doi.org/10.1016/j.clim.2016.07.003 (2016)