Moriconi A, Cunha TM, Souza GR, Lopes AH, Cunha FQ, Carneiro VL, Pinto LG, Brandolini L, Aramini A, Bizzarri C, Bianchini G, Beccari AR, Fanton M, Bruno A, Costantino G, Bertini R, Galliera E, Locati M, Ferreira SH, Teixeira MM, Allegretti M. (2014). Targeting the minor pocket of C5aR for the rational design of an oral allosteric inhibitor for inflammatory and neuropathic pain relief. *Proc Natl Acad Sci USA* 111:16937-42.

Chronic pain resulting from inflammatory and neuropathic disorders causes considerable economic and social burden. Pharmacological therapies currently available for certain types of pain are only partially effective and may cause severe adverse side effects. The C5a anaphylatoxin acting on its cognate G protein-coupled receptor (GPCR), C5aR, is a potent pronociceptive mediator in several models of inflammatory and neuropathic pain. Although there has long been interest in the identification of C5aR inhibitors, their development has been complicated, as for many peptidomimetic drugs, mostly by poor drug-like properties. Herein, we report the de novo design of a potent and selective C5aR noncompetitive allosteric inhibitor, DF2593A, guided by the hypothesis that an allosteric site, the "minor pocket," previously characterized in CXC chemokine receptors-1 and -2, is functionally conserved in the GPCR class. In vitro, DF2593A potently inhibited C5a-induced migration of human and rodent neutrophils. In vivo, oral administration of DF2593A effectively reduced mechanical hyperalgesia in several models of acute and chronic inflammatory and neuropathic pain, without any apparent side effects. Mechanical hyperalgesia after spared nerve injury was also reduced in C5aR(-/-) mice compared with WT mice. Furthermore, treatment of C5aR(-/-) mice with DF2593A did not produce any further antinociceptive effect compared with C5aR(-/-) mice treated with vehicle. The successful medicinal chemistry strategy confirms that a conserved minor pocket is amenable for the rational design of selective inhibitors and the pharmacological results support that the allosteric blockade of the C5aR represents a highly promising therapeutic approach to control chronic inflammatory and neuropathic pain.