Search for dimerization-biased ligands of CCR2: a novel approach to target an elusive receptor family.

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As an important member of the chemokine system, the C-C type chemokine receptor 2 (CCR2) plays a key role in monocyte trafficking and is implicated various diseases including inflammatory and autoimmune diseases, cancer and atherosclerosis [1-3]. Despite the development of several series of antagonists and the availability of detailed knowledge of the receptor 3D structure [4], there has been limited success in showing efficacy in clinical trials.

Here we describe a novel approach to target CCR2 by modulating its dimerization. The project is based on a fine understanding of the structure-activity relationships, defined from complementary data obtained following three axis: (1) modeling of CCR2 homodimers and CCR5/CCR2 heterodimers and their validation by cross-linking experiments, (2) curation of a dataset and docking of known CCR2 ligands to determine their binding modes, (3) experimental testing and MD simulations with a small set of CCR2 ligands representing different binding modes to probe their effect on dimerization.

Establishing the connections between the binding modes and specific functional effects will enable the virtual screening of chemical libraries to discover biased ligands, using machine learning to prioritize compounds based on interaction graph similarity to the MD-trajectories [5].

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