

CB₂R ligands to treat inflammatory diabetes

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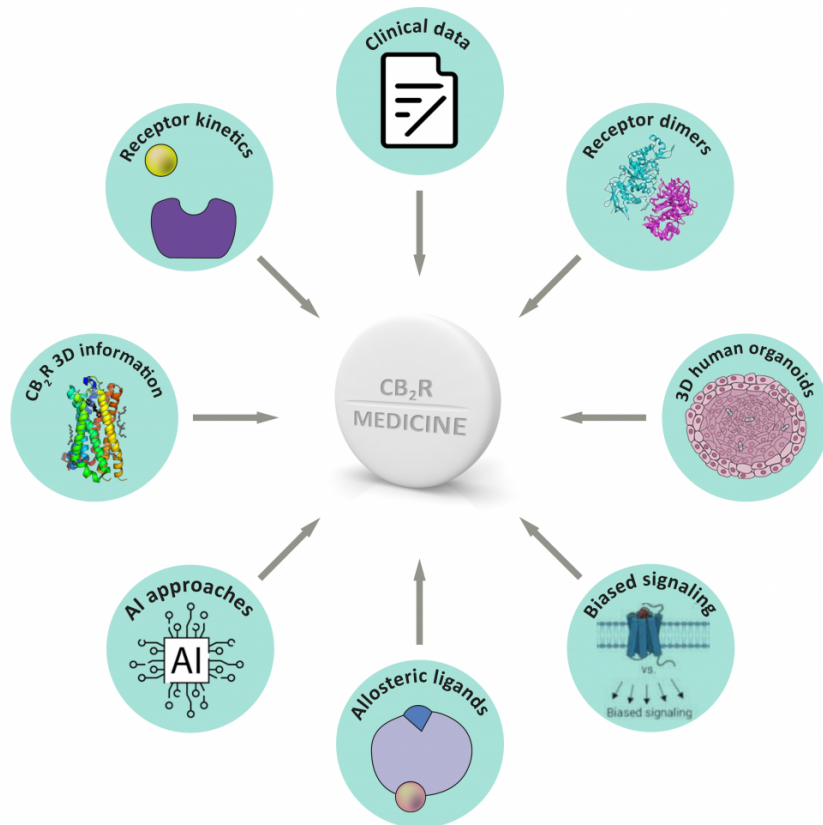


Figure 1: Scientific innovations in ECS research and drug discovery that will strongly impact the future discovery of improved and tailor-made CB₂R medicines.

Researchers discuss how scientific innovations might influence the discovery of future tailor-made CB₂R-based anti-inflammatory treatments

The G-protein-coupled receptor (GPCR) type-2 cannabinoid receptor (CB₂R) is a highly promising pharmacological target for novel anti-inflammatory medicines. (1) CB₂R is an essential component of a vital lipid signaling system that tremendously influences multiple

human health and disease states ranging from metabolic disorders to neurodegenerative diseases and is termed endocannabinoid system (ECS). Few CB₂R-activation-based drugs have been launched. ⁽²⁾

Several candidates are under active clinical development, aiming at treating diseases in which inflammatory processes play a significant role or are the underlying reason. Recent scientific innovations in ECS research and drug discovery in general (Figure 1) are now being incorporated into the design, synthesis and evaluation of novel ligands targeting CB₂R. They will impact the generation of further improved tailor-made medicines for inflammatory diseases.

From homology models to 3D structures of CB₂R

Only recently, there was more understanding of how CB₂R ligands interact with its target protein due to the lack of reliable information about the 3D structure of the CB₂R. The design of novel molecules depended on site-directed mutagenesis data or homology models based on the crystal structure of the somewhat distantly related β₂-adrenergic receptor.

Recent elucidation of CB₂ receptor structures bound to agonists and inverse agonists by x-ray crystallography and cryogenic electron microscopy provided deep insights into the multiple essential protein-ligand interactions and underlying receptor dynamics of the activation process. ⁽³⁾ This information allows for rationalising structure-function relationships and will tremendously impact and accelerate the design of future ligands.

Novel artificial intelligence approaches for drug discovery

Computational methods support the discovery of CB₂ ligands since several years. Novel machine learning methods, e.g., quantitative structure-activity relationship models and de novo molecular design, led to numerous valuable applications in drug discovery. ⁽⁴⁾

Recently introduced techniques such as geometric deep learning or de novo drug design applying chemical language models offer further opportunities to accelerate drug design and discovery.

These innovative artificial intelligence-based approaches enable researchers to conceive and select better molecules faster. Thus, the number of necessary design-make-test cycles to arrive at optimal molecules will significantly reduce.

Better understanding of receptor pharmacology

While recently developed high-quality labelled CB₂R fluorescent and PET probes have significantly contributed to a better understanding of CB₂R expression and function, numerous unanswered questions remain to be addressed regarding the receptor's mechanism of action and how this translates to a clinical benefit.

For example, the biased signaling induced by different ligands elicited by the existence of different ligand-dependent CB₂R conformations is yet poorly understood but highly relevant as it results in distinct pharmacological responses ⁽⁶⁾. Furthermore, determining binding kinetics, i.e., residence time of a ligand, may provide essential insights and rationalisation for in vivo efficacy and might even influence signaling bias. (7)

Alternatively, allosteric ligands that bind to a site that is topographically distinct from the orthosteric site of the endogenous ligand might provide a superior therapeutic solution as they can modulate affinity and/or efficacy of endogenous ligands.

Lastly, balancing the association equilibria of CB₂R receptors homo and heterodimers might translate into different functional properties and ultimately address different receptor populations for arriving at tailor-made CB₂R therapeutics.

Incorporation of translational knowledge

Development candidates often fail in phase 2 clinical trials where the focus is on establishing a preliminary efficacy of the drug in patients, usually against a placebo control group [2b]. The main reason is the lack of translatability from promising preclinical in *vivo* efficacy studies toward the human situation.

Thus, a feedback loop and back-translation of clinical data and knowledge from patients or human 'systems' toward preclinical research will tremendously increase the chance of being successful. Therefore, steady feeding of discovery activities with the most recent clinical data and information on biomarkers are instrumental.

Furthermore, bioinformatics approaches that help bridge between species can contribute to clinical success. The recently introduced use of human stem cell-derived three-dimensional multi-cellular microtissues that closely mimic the complex structure and functionality of human organs, so-called organoids, became increasingly important for drug discovery. They allow, e.g., drug screens and toxicity evaluations in human systems.

Overall, the recently elucidated 3D structures of CB₂R, novel artificial intelligence approaches for drug discovery, an improved understanding of receptor pharmacology, and last but not least, the incorporation of the accumulated translational knowledge will enable the discovery of more potent, effective and safe CB₂R medicines for indications with a dire or even unmet medical need, eventually leading us to much more significant benefits for patients in the treatment of inflammatory diseases.

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