Challenges bringing CB_2R medicine to bedside

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Drug hunters explain how to overcome pitfalls on the way to CB_2R medicine and therapeutics

Type-2 cannabinoid receptor (CB_2R) is a key element of the endocannabinoid system (ECS) and an important pharmacological target which was referred to as a 'hidden treasure trove for treating inflammatory diseases' [1]. Preclinical data suggest that activation of this G-protein-coupled receptor (GPCR) holds great potential for treating a plethora of pathological conditions in humans e.g. cardiovascular, gastrointestinal, liver, kidney, lung, neurodegenerative/ neuroinflammatory, skin pathologies, rheumatoid arthritis, endometriosis, and eye diseases [2]. Despite this enormous therapeutic potential, no selective CB_2R agonist has reached the market so far as CB_2R medicine.

This can be linked to four main reasons:

1. Expression & detection of CB_2R;
2. Quality of early tool compounds;
3. Profile of first development candidates;
4. Translatability of preclinical efficacy data toward humans.

All these elements are highly relevant for any drug discovery program but proved to be particularly challenging for CB_2R (Figure 1).

How to detect CB_2R?

The detection of CB_2R relies on assays of messenger RNA (mRNA) expression or methodologies which can detect the protein itself. Meanwhile, sophisticated mRNA techniques such as quantitative real-time polymerase chain reaction (qRT-PCR), droplet digital PCR (ddPCR) and RNAscope have revealed that CB_2R is under healthy conditions primarily expressed in immune cells and detailed information has been reported in multiple databases such as Genotype-Tissue Expression (GTEx) and the ImmGen Web Page [3].

Various states of a disease can lead to robust induction of CB_2R. Due to a paucity of specific antibodies, the detection of CB_2R protein remained for a long time challenging. Only recently highly selective labelled chemical probes such as radiotracers and fluorescent ligands have been developed that allow for more reliable detection of CB_2R protein [4].

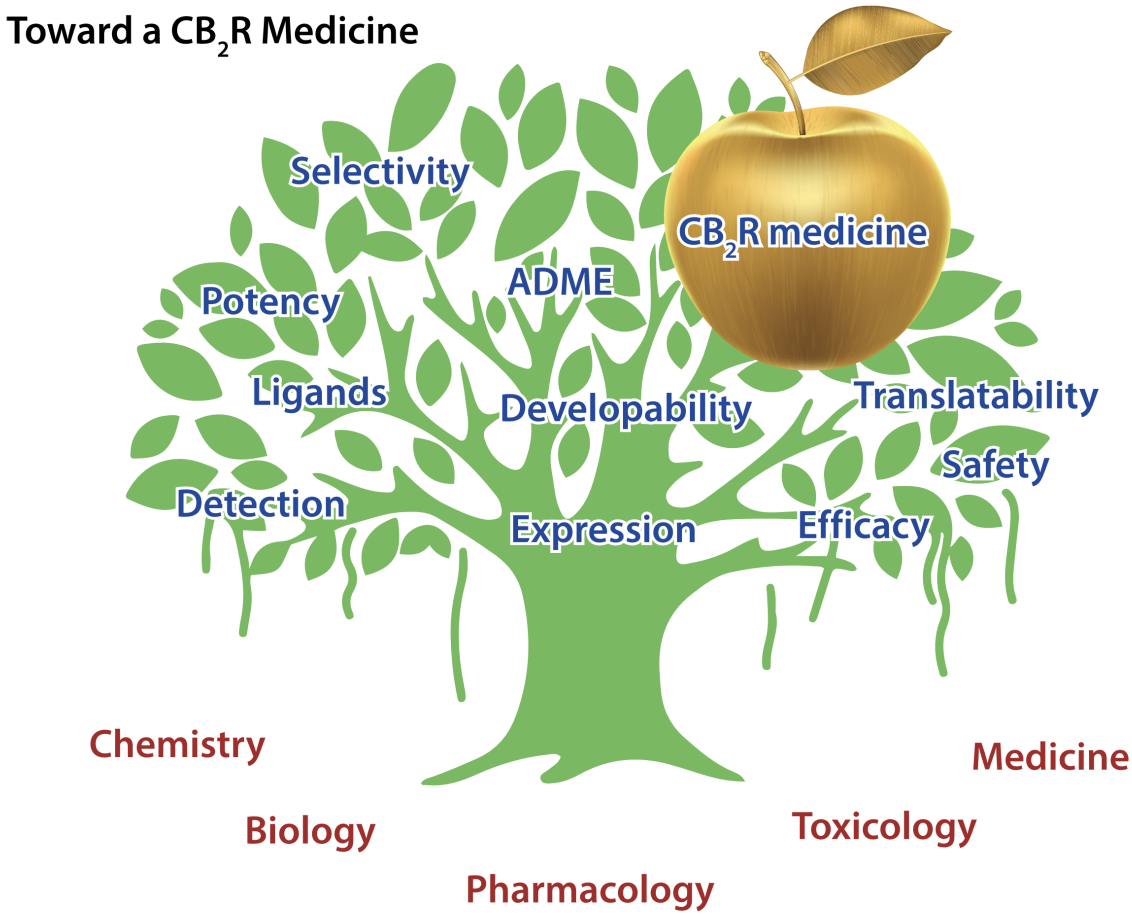

Figure 1: Drug discovery is routed in scientific disciplines such as chemistry, biology, pharmacology, toxicology, and medicine. For harvesting, the golden apple, a CB2R medicine, the target protein needs to be thoroughly evaluated. For this purpose, tools to detect CB2R and study its expression are required. Hit structures have to be elaborated and optimized toward a development candidate which should be potent, selective and exhibit a favourable absorption, distribution, metabolism and excretion (ADME) profile translating into a safe and developable medicine. Furthermore, the drug candidate must be efficacious in preclinical disease models which translate toward the human situation.

The importance of high-quality chemical tools for studying CB_2R pharmacology

Target validation is an essential element of drug discovery and requires tool compounds. Such chemical tools need to fulfil a multitude of criteria, e.g., high potency on the target and excellent selectivity regarding off-targets. If applied in vivo, tool compounds need to be bioavailable meaning they must be able to reach the target protein within the relevant diseased tissue compartment in sufficient concentration to trigger a pharmacological effect.

For extrapolation toward the human situation potency and selectivity profiles of chemical probes must be comparable in the species in which an in vivo efficacy study is conducted and in humans. Initial CB_2R probes were lacking one or 2 more of the above-mentioned criteria leading to misinterpretations of in vivo efficacy data. To address this issue, an extensive molecular pharmacology characterization of the most widely used CB_2R ligands

in a collaborative effort between multiple academic and industry laboratories was conducted, reaching a consensus on which CB_2R molecules to use for studying the role of CB_2R in biological and diseases processes [5].

Profile of early development candidates

Due to the huge therapeutic potential of CB_2R multiple ligands have been developed by both academic institutions and the pharmaceutical industry [6]. These ligands can be divided into endogenous cannabinoids and related fatty acid derivatives, phytocannabinoids and synthetic cannabinoids. Besides the abovementioned criteria for chemical tools, drug candidates need to fulfil a multitude of further requirements, e.g., regarding their ADME, safety and developability properties. Early development candidates often suffered, e.g., from high lipophilicity and poor solubility, contributing to unfavorably low oral bioavailability. Furthermore, their therapeutic index was limited due to insufficient selectivity against CB_1R. Meanwhile, more than 20 new molecular entities activating CB_2R have been evaluated in clinical trials and in particular, most recent ligands have overcome deficiencies of the early ligands, possess excellent ADME properties translating into favourable pharmacokinetic profiles and are devoid of centrally mediated CB_1R-driven psychotropic or other toxicological side effects.

Translatability of preclinical efficacy data toward human situation

Insufficient selectivity against CB_1R could partially explain why some of the early clinical trials with CB_2R agonists failed. At high concentrations, such ligands also trigger CB_1R activation, which counteracts beneficial CB_2R effects in multiple pathological conditions or lead to cardiovascular and other side effects [7].

Furthermore, past clinical trials often looked at the wrong illnesses such as osteoarthritis and third molar extraction, which didn't match with what preclinical results suggested to be a good patient population. Recent studies put a strong focus on peripheral indications with an inflammatory/immunomodulatory and/or fibrotic background [6] for which there is ample proof of concept in rodent disease models.

Although some uncertainties still surround CB_2R and CB_2R medicine, researchers made significant progress and are now better armed to solve them. High-quality biological and labelled chemical probes will facilitate a better understanding of CB_2R expression and mechanism of action. Chemical tools with suitable property profiles for interrogating CB_2R, pharmacology and drug candidates with ideal target compound profiles have been developed to aid preclinical research. Ongoing clinical trials mimic disease conditions which are matching preclinical proof of concept studies and thus hold great potential for unlocking CB_2R's promise for the treatment of inflammatory diseases.

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