Small Molecules Targeting the Endocannabinoid System

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The endocannabinoid system (ECS) consists of endogenous molecules which are termed endocannabinoids (eCBs), their processing enzymes and molecular targets.[1] The ECS is functionally expressed everywhere in mammalian tissues. It controls body homeostasis and many highly critical functions including body temperature, sleep, eating, learning and memory. The relevance of the ECS for the CNS and immunological system is best studied. Due to its high therapeutic relevance, the ECS has been the subject of numerous drug discovery activities.

In this paper, we describe the discovery and evaluation of small molecules targeting enzymes and receptors of the ECS. Therapeutic agents and labelled chemical probes will be discussed. Agonists of the peroxisome proliferator-activated receptors (PPARs) which are nuclear hormone receptors and antagonists of the G protein-coupled receptor (GPCR) type 1 cannabinoid receptor (CB_1R) will be included. Special emphasis will be put on the discovery and evaluation of the highly potent and selective type 2 cannabinoid receptor (CB_2R) agonist RG7774. The ligand is currently under clinical development for providing an innovative oral treatment to patients suffering from moderately severe to severe non-proliferative diabetic retinopathy (NPDR) for whom anti-vascular endothelial growth factor (VEGF) intravitreal injections (IVT) is deferred in clinical practice.

The development of therapeutic ligands has been complemented by the discovery of novel chemical probes. Their relevance for drug discovery programs e.g., to support proof of concept, biomarker and mechanistic studies in which several partners from academia have been involved will be highlighted. Representative examples from the CB_2R program and novel probes targeting the serine hydrolase monoacylglycerol lipase (MAGL) will be shown. MAGL is the key regulator of main eCB 2-arachidonoylglycerol (2-AG) brain concentrations and thus holds great therapeutic potential for treating neuroinflammatory and neurodegenerative diseases.

[1] Mauro Maccarrone, Vincenzo Di Marzo, Jürg Gertsch, Uwe Grether, Allyn C. Howlett, Tian Hua, Alexandros Makriyannis, Daniele Piomelli, Natsuo Ueda, Mario van der Stelt, *Pharmacol. Rev.* **2023**, DOI: 10.1124/pharmrev.122.000600.