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Preface to DMR special edition “Cannabinoid Receptors and Ligands: Therapeutic Drug Development and Abuse Potential”

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Evidence following decades of research into ligands acting at cannabinoid type-1 (CB₁) and type-2 (CB₂) receptors suggests that development of drugs in this class may exhibit potential therapeutic use for a diverse range of clinical indications including chronic pain (Lynch and Ware, 2015), cancer (Guzman, 2003), nausea (Parker et al., 2011), stroke (Fernandez-Ruiz et al., 2015), heart disease (Steffens et al., 2005) and epilepsy (Friedman and Devinsky, 2015). Cannabinoid receptors are seven transmembrane receptors that couple to G-proteins and are characterized into two subtypes, CB₁ and CB₂ receptors (Matsuda et al., 1990; Howlett et al., 2002). CB₁ receptors are ubiquitously expressed in the central nervous system (Vogel et al., 1993; Kano et al., 2002) and CB₂ receptors are found in greatest abundance peripherally on circulating immune cells (Di Marzo, 1999; Walter et al., 2003). Both cannabinoid receptor subtypes bind a structurally diverse range of ligands that are endogenously produced (endocannabinoids) (Martin et al., 1999), plant-derived (phytocannabinoids) (Hanus et al., 2016) and synthesized (synthetic cannabinoids) (Di Marzo and Petrocellis, 2006). Drug development in this area has been significantly limited by potential abuse liability and psychotropic effects produced by activation of cannabinoid receptors in the CNS by compounds such as ⁹-tetrahydrocannabinol (⁹-THC) present in marijuana (*Cannabis sativa*) (Bostwick, 2012) and synthetic cannabinoids found in the emerging drugs of abuse known as K2 and spice (Fantegrossi et al., 2014).

The purpose of the current special issue “Cannabinoid Receptors and Ligands: Therapeutic Drug Development and Abuse Potential” is to present articles that review current literature related to novel aspects of (1) cannabinoid receptor signaling, (2) cannabinoid receptor ligands (endocannabinoids, phytocannabinoids and synthetic cannabinoids), (3) drug development of cannabinoid ligands for therapeutic use, and (4) potential cannabinoid abuse and toxicity.

The initial two articles in this special issue presented by Dopart *et al.* and Alaverdashvili and Laprairie provide excellent reviews of recent progress made concerning CB₁ receptor allosteric modulators, and discuss the future promise of this research in the field of therapeutic drug discovery of cannabinoid receptor ligands. Schwarz *et al.* next presents an extensive review of targets associated with the extended endocannabinoid network

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considered to possess antitumorigenic effects, thus providing valuable information for development of cannabinoid ligands for potential use as anti-cancer agents.

Potential abuse liability and reported adverse effects of synthetic cannabinoids present in the emerging drugs of abuse known as K2 and spice are reviewed in the next two articles. Zanda and Fattore provide a detailed overview of animal studies employing self-administration and reinstatement models, drug discrimination and conditioned place preference to examine potential abuse potential of first, second and third generation synthetic cannabinoids. These behavioral studies importantly indicate that synthetic cannabinoids likely possess abuse potential that occurs due to activation of brain reward circuits and induction of positive subjective and reinforcing effects. Subsequently, Fantegrossi *et al.* present an excellent review of published studies concerning CB₁ receptor interactions with dopamine, serotonin and glutamate systems, three neurotransmitters that are well-established in the pathophysiology of schizophrenia and psychosis. The information presented will help explain, and potentially lead to clinical interventions for, pro-psychotic effects produced by synthetic cannabinoids.

The final article by Morales *et al.* reviews current literature related to characterization of three orphan G-protein coupled receptors (GPR3, GPR6 and GPR12) that share a high percentage of homology with CB₁ and CB₂ receptors and lipid receptors such as the lysophospholipid receptors sphingosine 1-phosphate and lysophosphatidic acid receptors. Specifically, the role of these receptors in brain function, and in particular association with neurological conditions such as Parkinson or Alzheimer's disease, is presented. This information will allow for a better understanding of the pathophysiological role of these poorly understood orphan receptors, and thus for future therapeutic exploitation of these promising targets.

Collectively, review articles presented in this special issue provide novel and important information necessary to advance research in the rapidly expanding field of therapeutic drug development and abuse potential of cannabinoid receptors and their ligands.

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