Aim:
Goal of this research project is the development of ligands acting at the cannabinoid (CB) receptors subtype 1 and subtype 2, which can be switched in their biological activity by light.

Background / Methodology:
The property of a ligand to be switched by UV light is achieved by incorporation of an azobenzene group, chemical modification of which can be applied to achieve higher photoconversion as well as by higher wavelengths. At the receptor level there are two possibilities of such photochromic switching: the photoisomer reversibly formed after irradiation shows a different affinity to the receptor and/or it (de)activates the receptor to a different degree. Depending on the ligand the receptors can either be switched on or off. Based on our previous work on highly selective ligands for both subtypes, and on computational investigations into the binding modes of these ligands in the CB2 receptor we have developed first ligands that bind stronger after irradiation (“affinity- on switches”). For advanced pharmacological studies this property is to be optimized using different classes of chemical templates, and selective photochromic ligands for both subtypes are planned that do not interact with other targets of the endocannabinoid system of the human body, such as ion channels. Another focus of the project is the development of ligands that change intrinsic activity (efficacy) upon irradiation (“efficacy switches”). Such compounds are of particular relevance for investigations into the modes and temporal processes of receptor signaling cascades. These aims will be achieved by collaboration of computational (PD Strasser, U Regensburg) and pharmacology groups. By collaboration with groups from the Universities of Camerino (Italy), Aberdeen (UK), and Barcelona (Spain) the compounds will be applied in studies of more elaborate and complex nature, such as biased signaling, in order to use these molecular tool compounds to unravel the largely unknown processes of activation and dynamics of GPCRs.

International Collaborators:
James N. Hislop (Aberdeen, UK)
Massimo Nabissi (Camerino, Italy)

Key Publications:

