Session 2: Identification and production of active pharmaceutical ingredients

Lead optimization: general aspects and MAP kinase inhibitors for psoriasis as an example

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Psoriasis is an immune-mediated inflammatory skin disorder characterized by skin-infiltrating lymphocytes causing hyperproliferation and abnormal differentiation of the keratinocytes. Dependent on the severity of the disease, in addition to phototherapy, several treatments including topically and orally administered small molecules or parenterally administered biological drugs are available. Cytokines, in particular TNF, play a pivotal role during onset and maintenance of the disease, which explains the clinical success of anti-TNF-therapies. The source of TNF in psoriasis is unclear but T-cells, keratinocytes and dendritic cells are involved. Analysis of psoriatic skin has shown, that the activity levels of ERK1/2 and p38 MAP kinase, as well as MAPKAP-2, a protein kinase which is activated by p38 MAP kinase, are increased. Results of immunohistochemical analysis of psoriatic skin and in vitro experiments with keratinocytes indicate an important role of the p38 MAP kinase/MAPKAP-2-signaling pathway in the generation of TNF. Therefore, modulation of this pathway by small molecules represents an attractive approach for development of new anti-psoriatic therapies. However, in other autoimmune diseases, such as rheumatoid arthritis and Crohn's disease, p38 MAP kinase inhibitors failed to demonstrate clinical efficacy. The reasons for the disappointing outcome are not clear. Recent comments on published clinical studies suggest the induction of alternative, p38 MAP kinase circumventing signalling pathways as a potential reason for the disappointing clinical results obtained with p38 MAP kinase inhibitors. Another explanation points to potential drug-induced systemic side effects, particularly in the liver, which may induce pro-inflammatory signalling pathways thereby neutralizing the beneficial anti-inflammatory effects of p38 MAP kinase inhibition. However, data which support these hypotheses are not available.

In this presentation, the discovery of p38 MAP kinase will be reviewed with a focus on the potential use of drug candidates for treatment of inflammatory skin diseases. The different requirements regarding selectivity profile, metabolic stability and physico-chemical properties of clinical candidates which are to be developed either for systemic or topical treatment of psoriasis will be discussed.