Discovery of the cathepsin S inhibitor RG7625 for the treatment of autoimmune diseases

Wolfgang Haap

Roche Pharma Research & Early Development, Innovation Center Basel,
F. Hoffmann – LaRoche Ltd., Grenzacherstr. 124, CH-4070 Basel, Switzerland
wolfgang.haap@roche.com

The lysosomal cysteine protease cathepsin S plays an important role in antigen presentation by degrading the invariant chain fragment p10 to CLIP. This CLIP fragment is associated to the major histocompatibility complex MHCII. After exchange of CLIP by antigens the MHCII/antigen complex is transported to the surface on antigen presenting cells such as microglia, dendritic and B-cells. This complex may be recognised by e.g. T-cells which subsequently become activated. If this process is disturbed, occasional loading of MHCII by self antigens may occur followed by an autoimmune response. Therefore, inhibition of cathepsin S may be an effective treatment of autoimmune diseases.

This presentation will cover the medicinal chemistry optimization of a series of cathepsin S inhibitors culminating in the identification of RG7625 as a highly potent and highly selective cathepsin S inhibitor. Aspects of structure based design, enzyme kinetics and multi dimensional optimisation will be highlighted. The preclinical profiling of RG7625 and clinical Phase I data will be outlined as well.