# NOVEL COMPOSITIONS AND PHARMACEUTICAL COMPOSITIONS THEREOF FOR THE TREATMENT OF INFLAMMATORY DISORDERS

## FIELD OF THE INVENTION

**[0001]** The present invention relates to compositions, useful in the prophylaxis and/or treatment of inflammatory diseases, autoimmune diseases, proliferative diseases, allergic diseases, transplant rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 or interferons. In a particular aspect, the composition comprises a first compound having IRAK inhibitory activity, and a second compound having JAK inhibitory activity. The present invention also provides pharmaceutical compositions comprising the combination of the invention and methods for the prophylaxis and/or treatment of diseases including inflammatory diseases, autoimmune diseases, proliferative diseases, allergic diseases, transplant rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 or interferons by administering the combination of the invention.

## BACKGROUND OF THE INVENTION

**[0002]** Kinases are involved in many essential processes of cell physiology, for example protein phosphorylation. In particular, protein and lipid kinases are involved in the activation, growth, differentiation, and survival of cells. Protein kinases can be divided between those preferentially phosphorylating tyrosine residues, and those preferentially phosphorylating serine and/or threonine residues.

**[0003]** Over the years, kinases have grown to become very important targets for the development of anti-inflammatory drugs (Cohen, 2009) . In particular, Interleukin-1 receptor-associated kinases (IRAK), and more particularly IRAK-4 have been identified as playing a role in inflammation and autoimmune diseases (Ringwood and Li, 2008; Wang et al., 2009).

**[0004]** IRAKs are expressed in many cell types and mediate signals from various cell receptors including interleukin-1 (IL-1) and toll-like receptors (TLRs). In the IRAK family, 4 members have been identified namely IRAK 1-4 (Wang et al., 2009), and IRAK-4, the newest member of the family represents an attractive therapeutic target (Li et al., 2002). Indeed, IRAK-4 is believed to be the key protein kinase activated early downstream of the IL-1 receptor and TLRs (except TLR3), initiating signaling via rapid activation of IRAK-1 and IRAK-2, leading to innate immune responses. Also, other interleukins, such as IL-18 and IL-33, are dependent on IRAK-4 for signaling. As such, diseases for which these cytokines are involved in the pathogenic process (*e.g.*, fibrosis (Li et al., 2014; McHedlidze et al., 2013; Rankin et al., 2010) and atopic dermatitis (Salimi et al., 2013)) are potential target diseases for treatment by IRAK-4 inhibitors.