ANTAGONIST OF THE NUCLEAR HORMONE RECEPTOR PPARγ FOR SEPSIS THERAPY

Introduction
Sepsis and septic shock in response to infection are life threatening complications and among the leading causes of death in industrial society. Sepsis is characterized by a hyper-inflammatory phase followed by a hypo-inflammatory phase, known also as “immune paralysis”. Here T cells of the adaptive immune system undergo apoptosis and stasis with loss of host defence. Current approaches to treatment focus on inhibition of the hyper-inflammatory phase of the disease in order to suppress disease progression. However, despite recent major advances, the incidence of and mortality due to sepsis continue to increase. There is, therefore, a need for new methods for the prevention and treatment of sepsis.

Invention
The present invention pertains to a new compound (MTTB) and its derivatives. The compounds are selective, competitive peroxisome proliferator-activated receptor gamma (PPARγ) antagonists indicated for the treatment of immune related diseases such as systemic inflammation, sepsis and septic shock. The advantage of PPARγ antagonism is the inhibition of T cell apoptosis and the prevention of “immune paralysis”. The compounds of the invention, in contrast to available agents, are competitive inhibitors, thus facilitating control of parental dosing. The new compounds permit careful timing of sepsis therapy to target hypo- rather than hyper-inflammation during sepsis.

Market Potential
Commercial applications:
• therapy of immune paralysis during sepsis
• adjuvant therapy of viral and neurodegenerative diseases associated with excessive apoptosis

Development Status
The therapy approach has been shown to be effective in a mouse model of sepsis.