7-2015-3171 | Novel Indoline Derivatives as Anti-Inflammatory Agents for the Treatment of Diabetes

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Categories
- Small molecules, anti-inflammatory treatment

Development Stage
- In-vivo proof of concept

Patent Status
- Patent application filed

Market
- Inflammation indications: acute pancreatitis, acute liver damage, fatty liver damage, diabetic nephropathy

Background

- Chronic activation of the immune system occurs in a variety of pathological conditions and is associated with the release of pro-inflammatory cytokines, TNF-α, IL-6, IL-1β and an increase in reactive oxygen species (ROS). Although TNF-α antagonists may produce a marked improvement in conditions such as rheumatoid arthritis and ulcerative colitis, they can also cause serious adverse effects.

Our Innovation

We have developed a family of indoline derivatives which prevent cytotoxicity induced by ROS and the release of pro-inflammatory cytokines from lipopolysaccharide (LPS) activated macrophages.

Pre-Clinical Results:

- Acute pancreatitis - In a mouse model, 2 mg/kg of the compounds bring about almost complete prevention of rise in serum amylase and TNF-α, reduction by >50% of edema, necrosis and neutrophil infiltration and degradation of IκB-α in the pancreas after 4 h.
- Acute liver damage - In a mouse model of acute liver damage, a dose of 0.25 mg/kg of the compounds brings about a >60% reduction of the increase in serum ALT and liver apoptosis, and reduction from 90% to 20% in the lethality in mice after 72 hr.
- Fatty liver damage - In a fatty liver in-vivo model, 1 mg/kg/day causes significant reduction of the liver/body weight ratio, p<0.01, plasma ALT and liver fat content (oil red).
- Diabetic Nephropathy - In a mouse model of type 1 diabetes, treatment with 0.25 mg/kg bid for 3 months abolishes the damage to the glomerular area and mesangial expansion. One of the compounds decreases the rise in serum and urine glucose, and urine urea (p<0.01), while another one reduces the albumin/creatinine ratio (p<0.01). Both compounds abolish the rise in gene expression of collagen 1 and 3, lipocalin 2 and fibronectin in the kidney. One compound also prevents the rise in TIMP1 and TGFβ.

Key Features

- Some of the compounds are also active through the oral route at about 2-5 times higher doses.
- No adverse effects were seen during a 3-day observation period in mice after the injection of three of the compounds at doses of 25 mg/kg.
- The compounds, which are readily prepared from commercially available compounds, are achiral. They are isolated as water soluble, crystalline salts.
- The compounds are stable for extended periods, both in solid form as well as in aqueous solution.
- These compounds and their biological activities have been patented.
Development Milestones

- Seeking investment in new company or industrial collaboration for product development and clinical studies.

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