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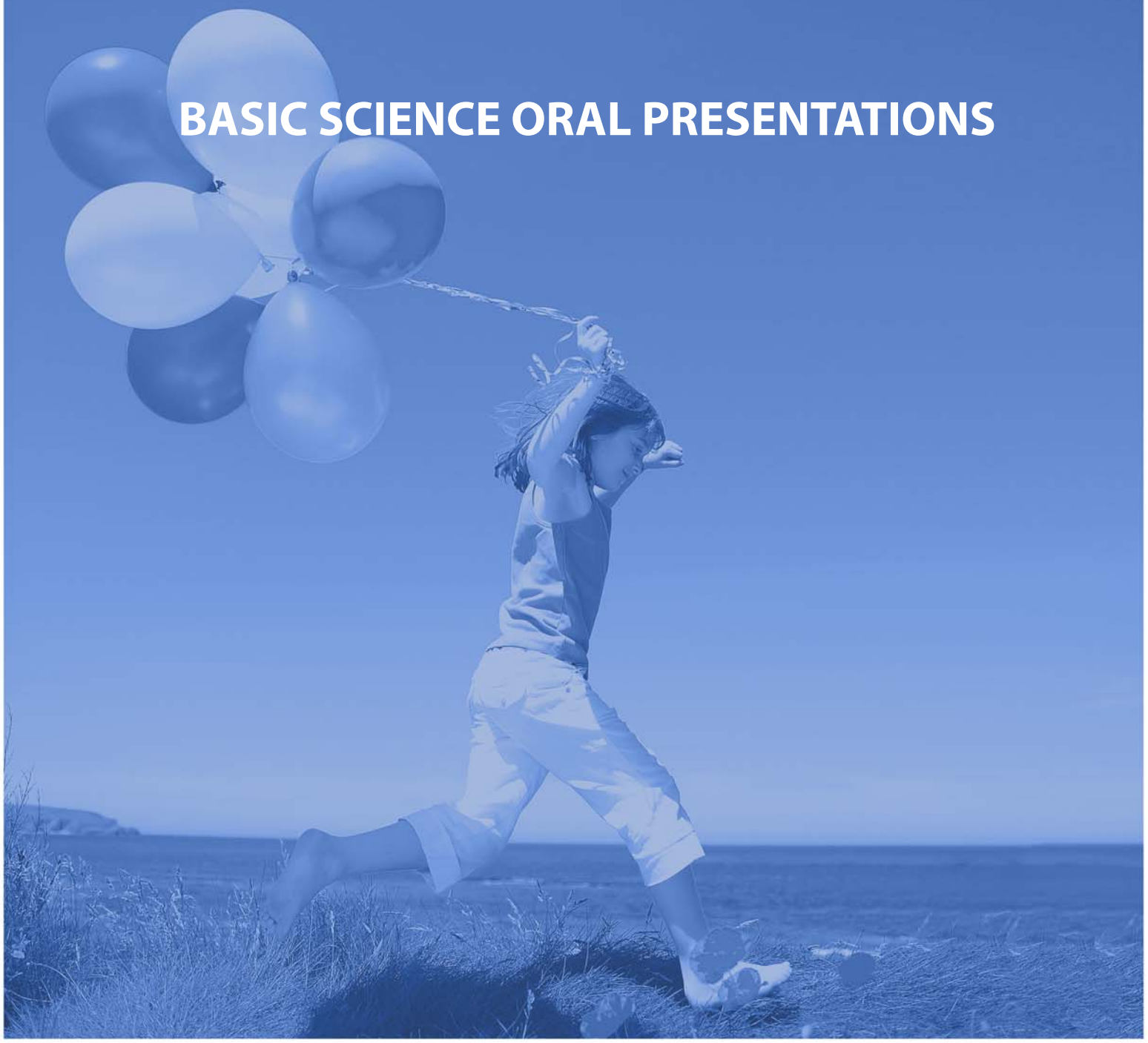
BASIC SCIENCE ORAL PRESENTATIONS



P-008. HIF prolyl hydroxylase inhibition reverses disease symptoms in established TNBS colitis.

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Hypoxia-inducible factor (HIF) prolyl-hydroxylation inhibition has been shown to reduce disease severity in murine models of colitis[1,2]. The observed mucosal protection is a consequence of pharmacological stabilization of the HIF pathway and ameliorates disease on several levels of clinical scoring. This mucosal protection is likely a consequence of both compensatory barrier protection at the epithelial level[3] and promotion of restitution and wound healing[4]. However, previously investigated prolyl hydroxylase inhibitors (PHDi; DMOG and FG-class compounds) suffer from poor solubility and low drug efficacy, resulting in excessive doses (4-40g per treatment). In addition, previous studies have focused on pre-treatment with PHDi's before disease onset, a context unlikely to be relevant to clinical situations. In this study we examined a new class of PHDi which preferentially target HIF-1 over HIF-2; AKB-4924, as a treatment for TNBS colitis. Mice were treated from either Day -1 (pre-treatment) or day 3 (post-treatment) with respect to induction of TNBS colitis and received AKB-4924 daily at either 0.3, 1.0 or 5.0 mg/kg doses. Disease progression was measured by core body temperature and weight loss. All groups receiving AKB-4924 recovered weight at a rate significantly faster than vehicle controls. Treated animals showed no changes in hematocrit (HIF-2-specific response) as a result of PHDi administration. In post mortem examination, PHDi treated mice displayed less colon shortening and lower disease activity index (DAI) than vehicle controls in both pre-treatment and post-treatment groups. In addition, all PHDi treated animals showed lower colon tissue cytokine levels at both protein and mRNA transcript levels and reduced NOD-2 induction. Mice pre-treated with AKB-4924 showed resistance to an early hyperthermic response to the TNBS treatment. In addition, these pre-treated animals showed a reduction in mucosal tissue and MLN leukocyte infiltration. Taken together, these data suggest that AKB-4924 is a potent HIF-1 specific prolyl hydroxylase inhibitor that may be employed after disease onset to reduce clinical disease measurements of TNBS colitis at lower concentrations that previously employed PHDi's. In addition, prevention of the early TNBS hyperthermic response and reduced leukocyte infiltration may hint at a previously unappreciated mechanism of protection by prolyl hydroxylase inhibition.

References:

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