

STAT5b Promotes Mucosal Tolerance in Crohn's Disease and Murine Colitis

- NIH, CCFA, BMRP
- NIH DDRDC
- CHRF TRTO
- Centocor, Genentech



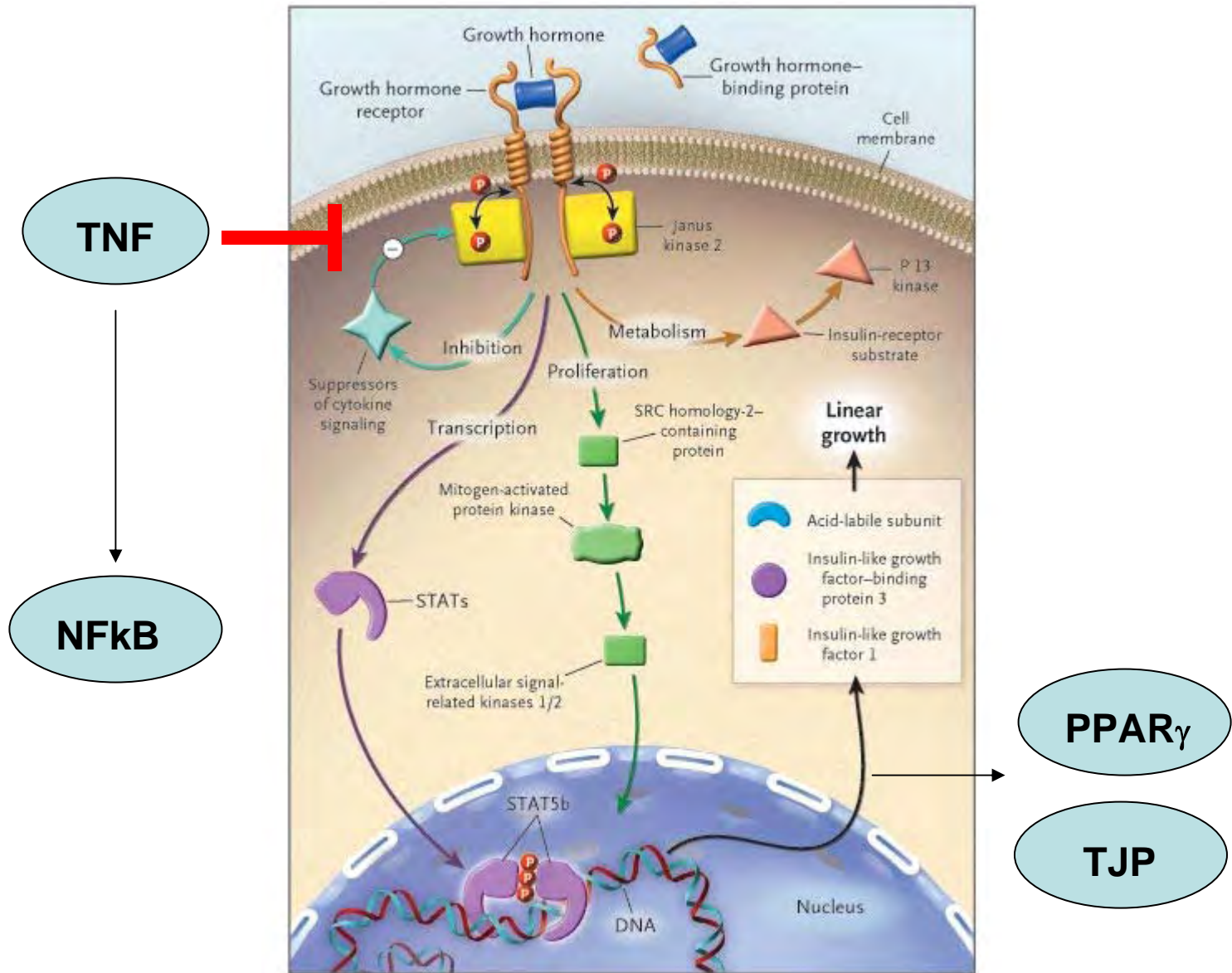
Background

- Growth failure is common in children with CD
- Current therapies do not consistently restore normal growth
- Inflammatory cytokines including TNF suppress the GH:IGF-1 axis in children and adults with CD
- TNF neutralization restores systemic GH signaling in CD and murine colitis due to IL-10 deficiency
- The GH receptor is expressed on epithelial cells and lamina propria immune cells of the gut
- GH administration relieves symptoms in CD and reduces mucosal inflammation in murine colitis

Difedele et al Gastroenterology 2005

Vespasiani et al Aliment Pharmacol Ther 2005

Growth Hormone & Mucosal Inflammation in CD



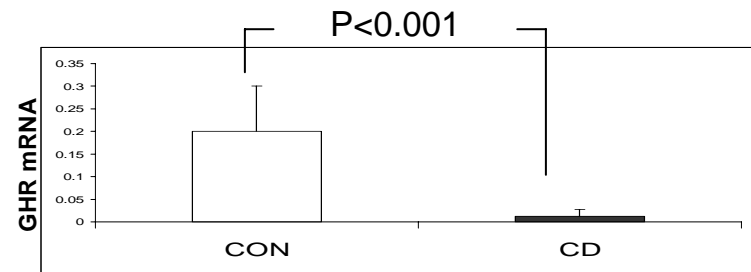
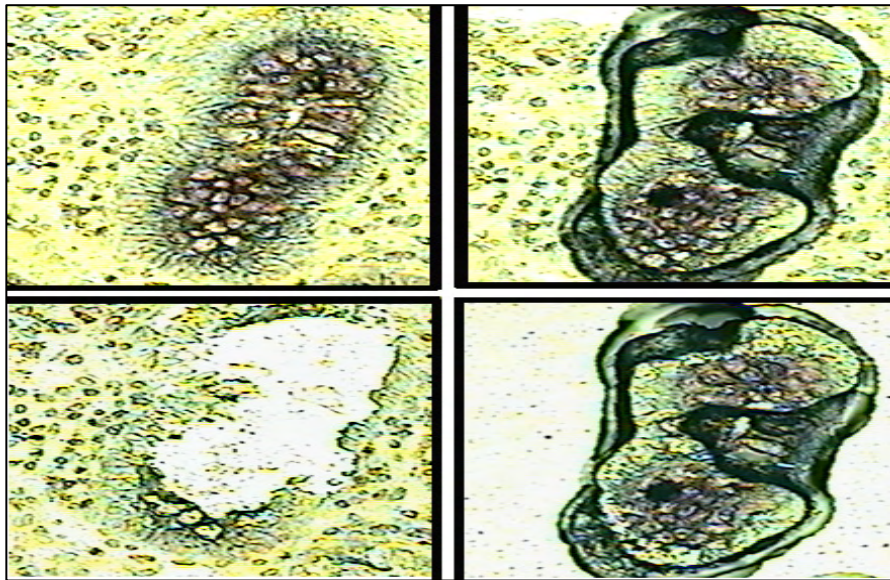
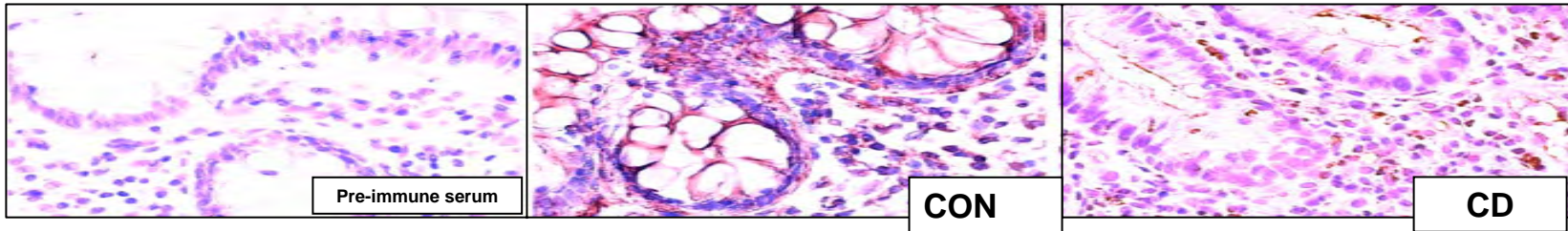
Hypothesis

**Reduced GH dependent STAT5
activation contributes to mucosal
inflammation in Crohn's disease**

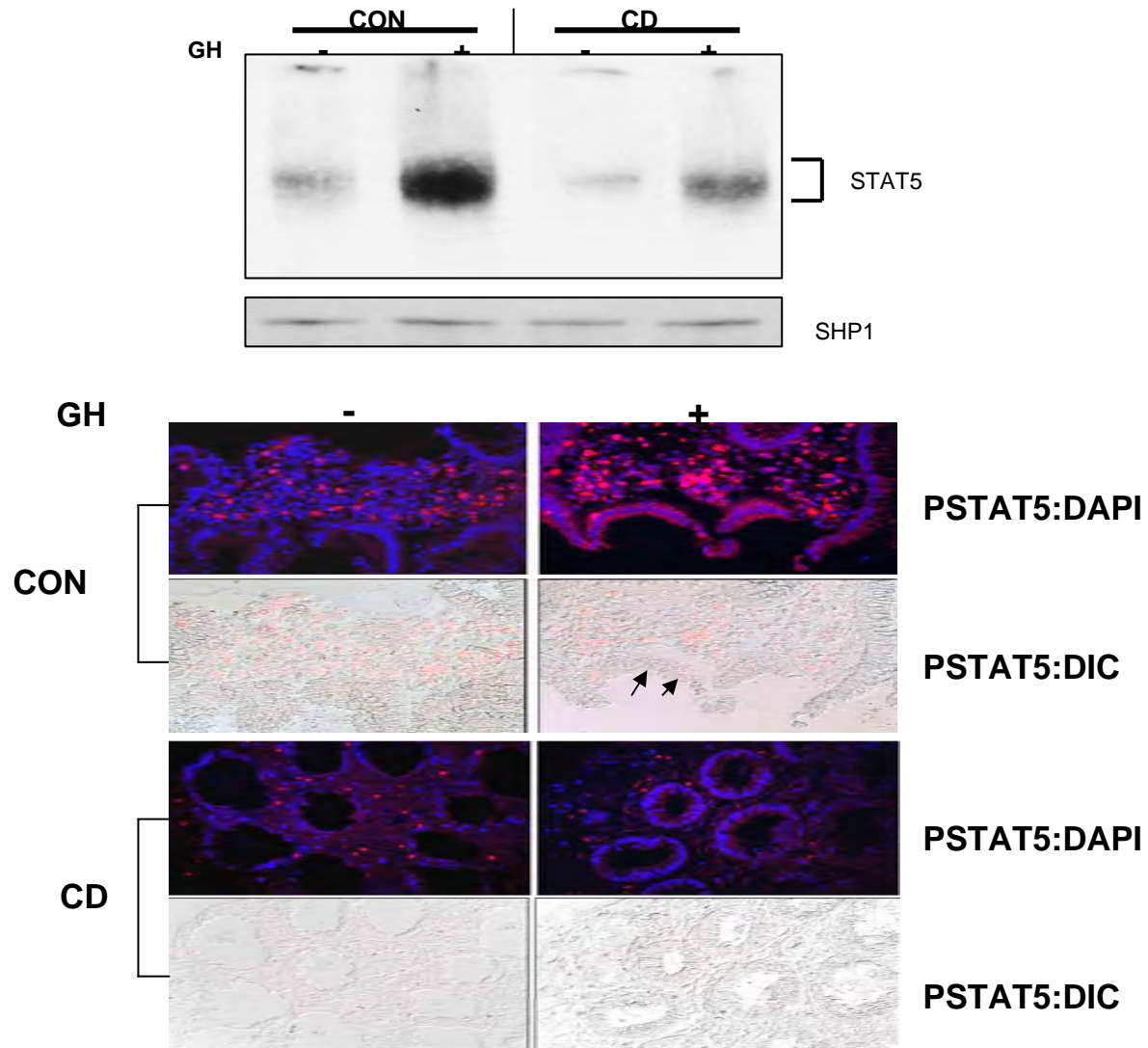
Methods

- **CD colon biopsies : laser capture micro-dissection for GHR expression and GH stimulation in culture for STAT5b activation**
- **Micro-array & real time PCR for GH target gene expression**
- **GH and TNF treatment of T84 colon cancer cells with STAT5b RNA interference**
- **GH treatment of wild type and STAT5b deficient mice with TNBS colitis**
- **GH and anti-TNF treatment of IL-10 deficient mice with colitis**

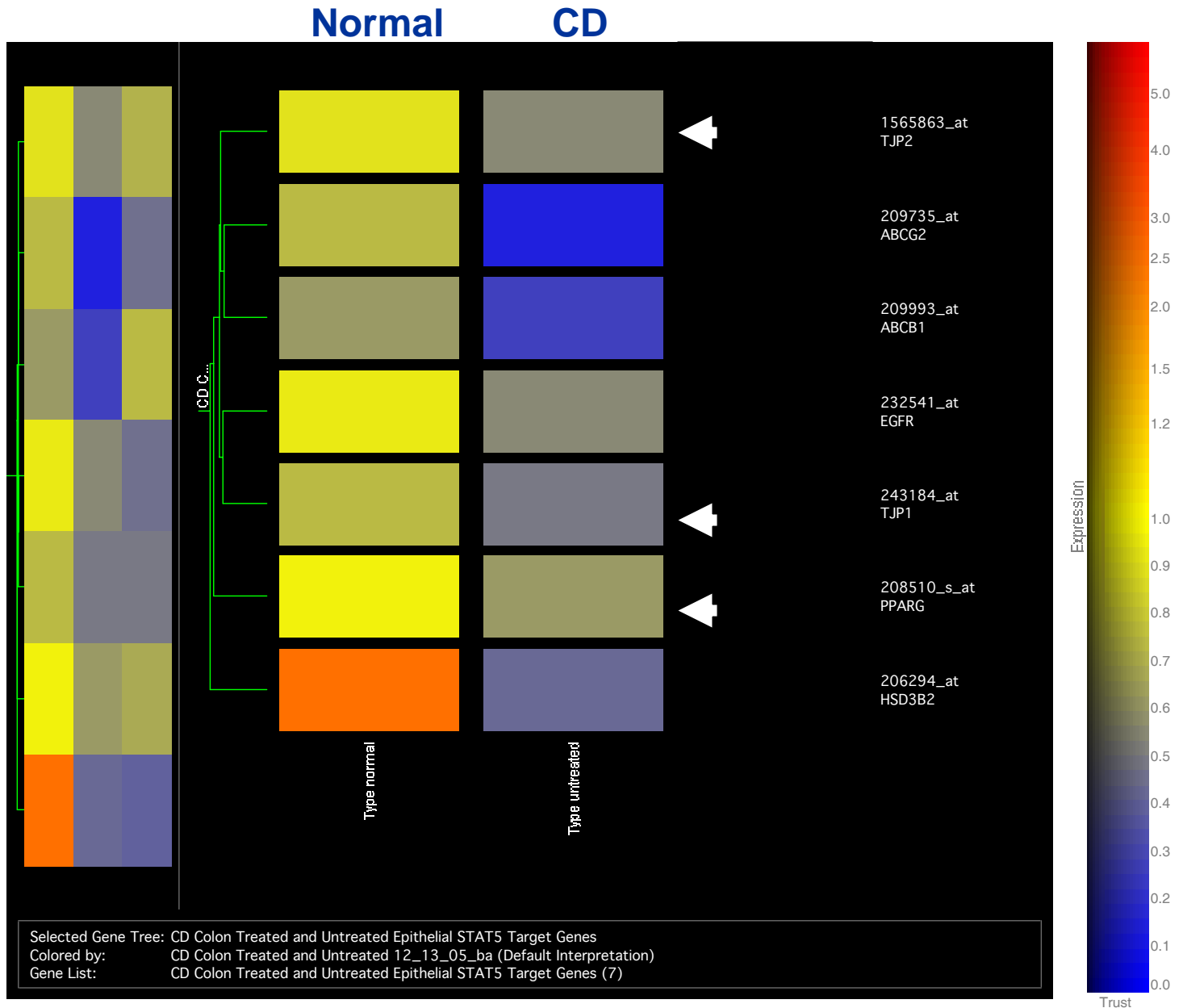
GH Receptor Expression is Reduced in CD Colon



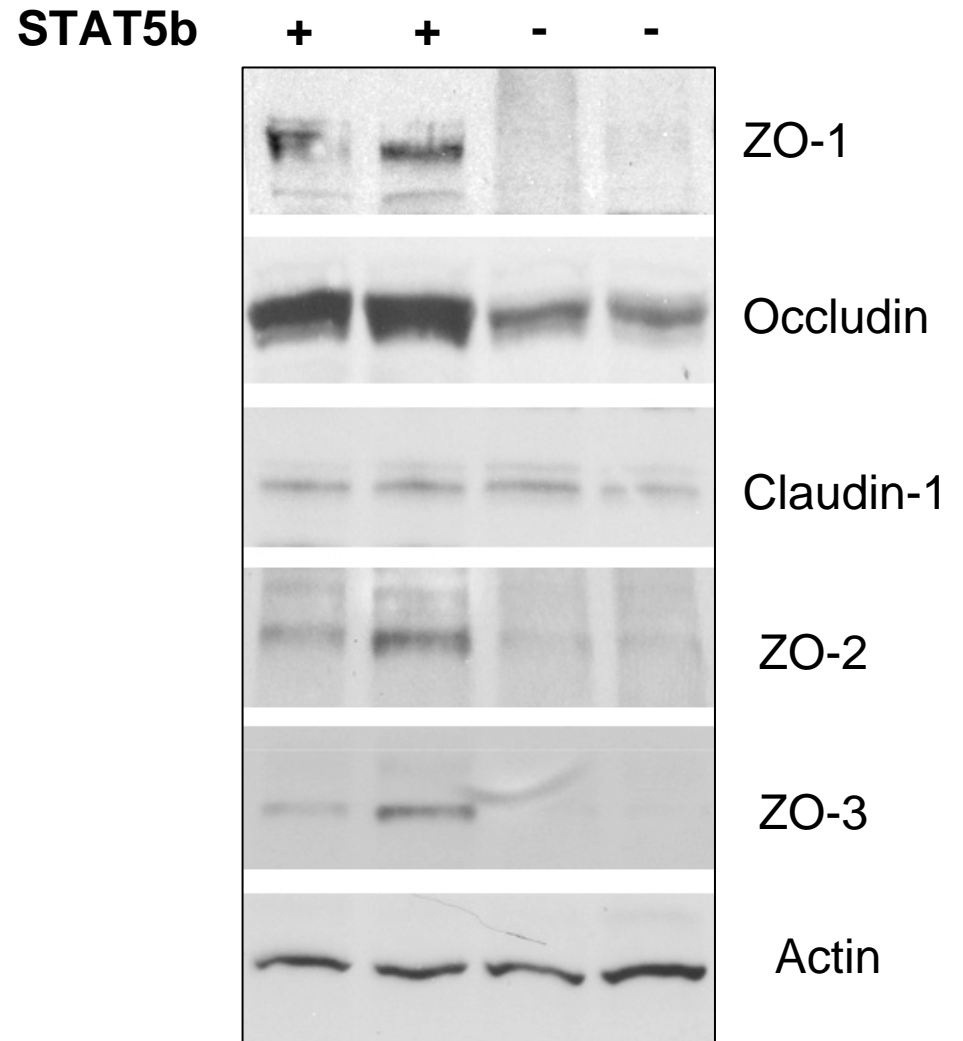
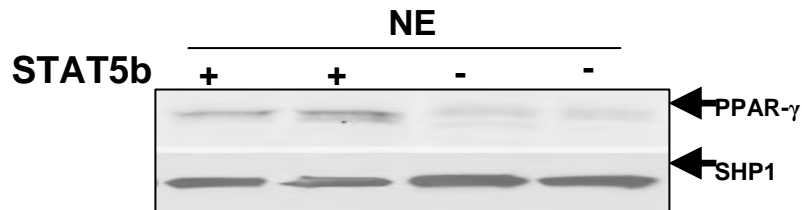
GH Activation of STAT5b is Reduced in CD Colon



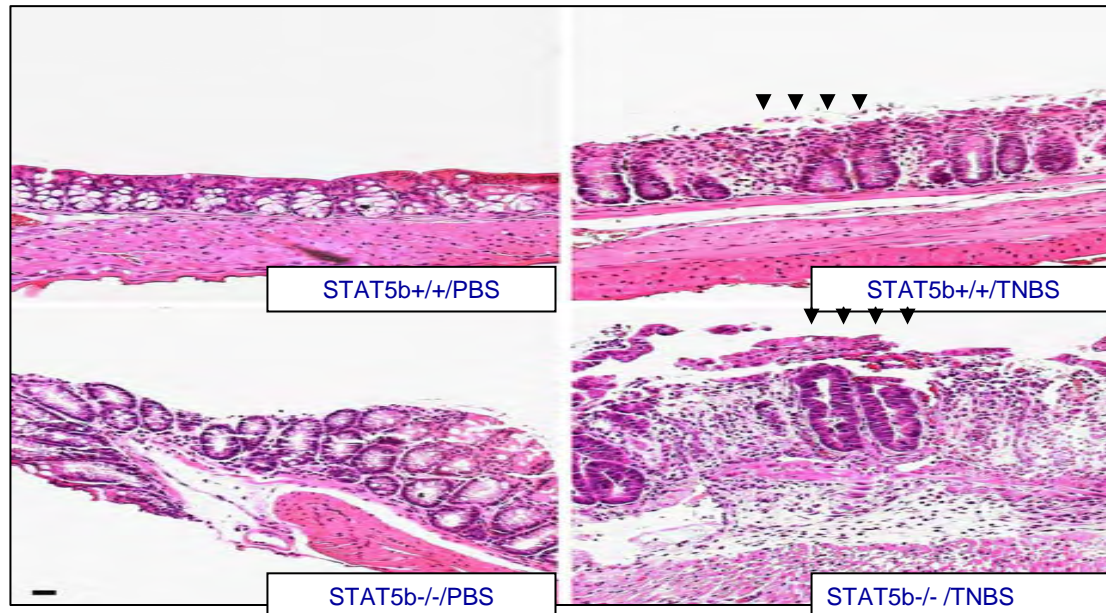
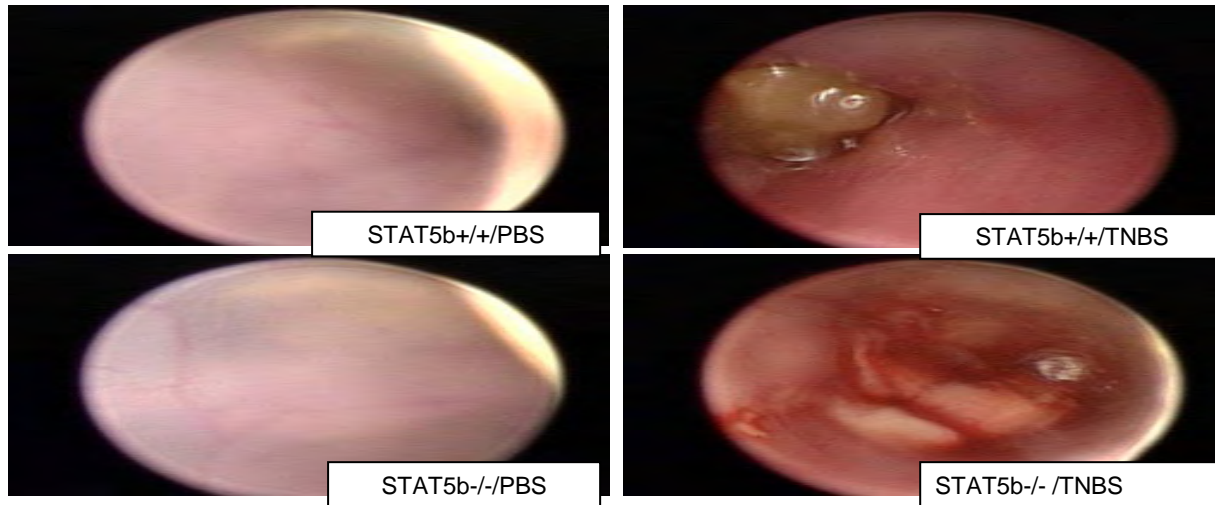
STAT5b Target Genes are Down Regulated in CD Colon



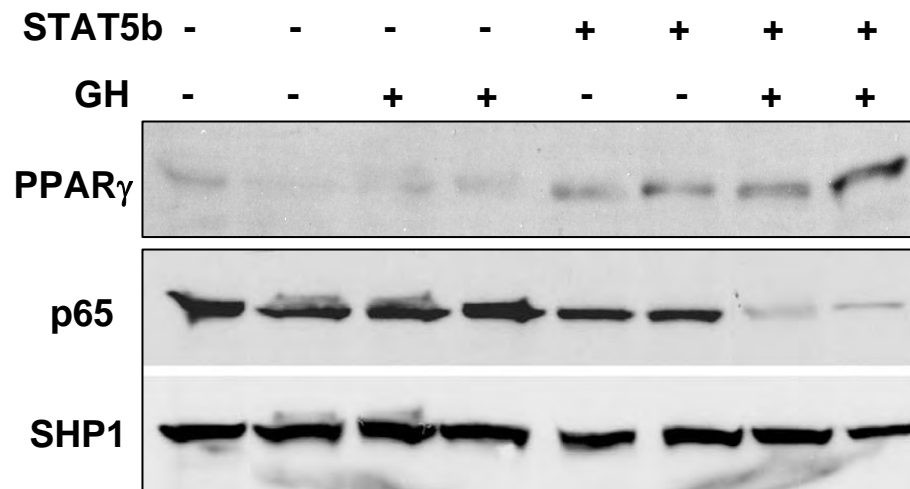
STAT5b Deficient Mice Have Reduced Colonic PPAR γ and TJP Abundance



STAT5b Deficient Mice are More Susceptible to TNBS Colitis



GH Does not Reduce NFkB Activation in STAT5b Deficient Mice

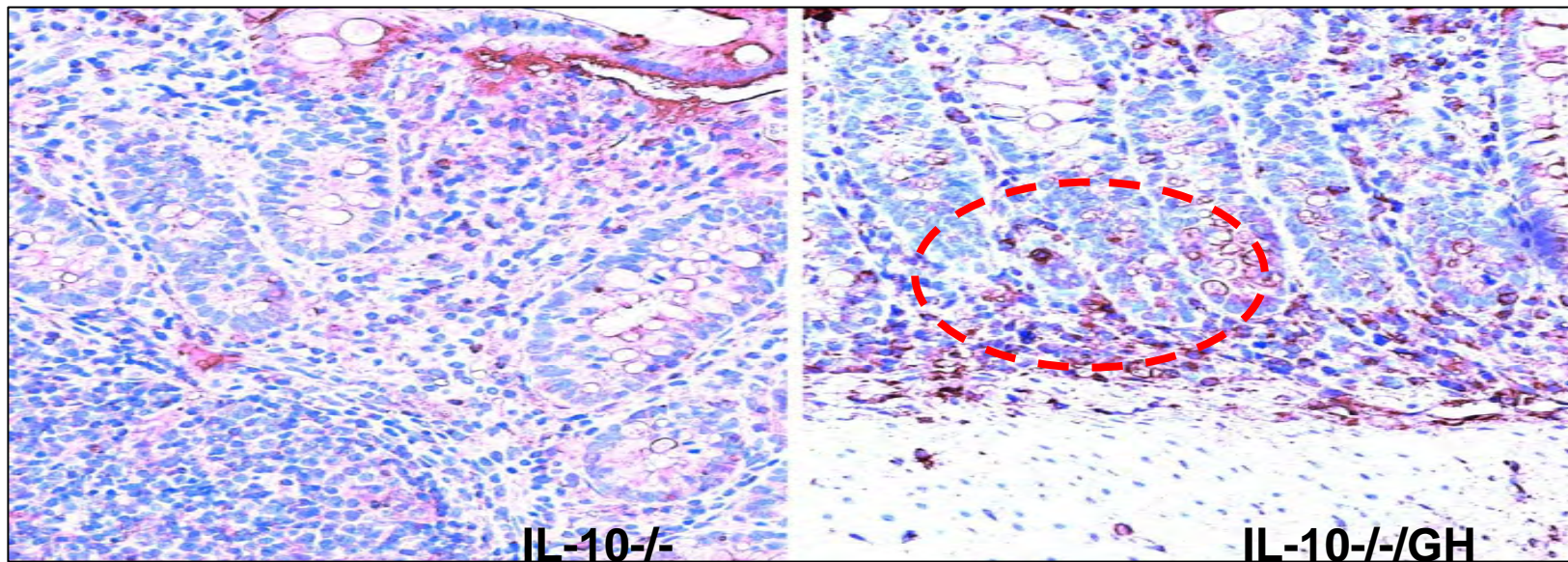
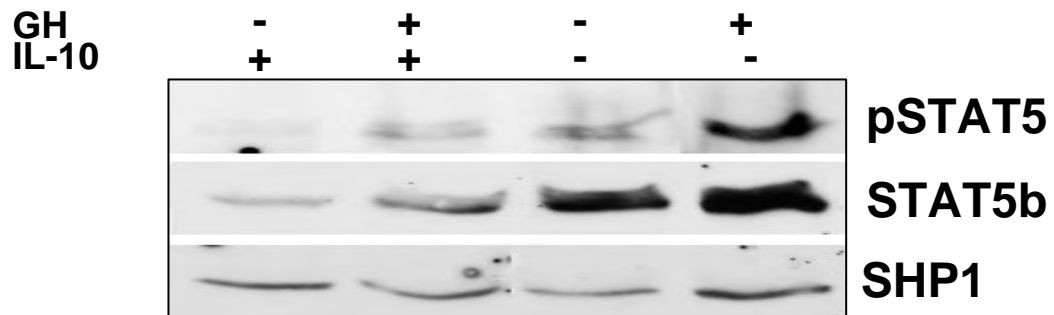


GH Inhibits NFκB Activation in T84 Cells via STAT5b

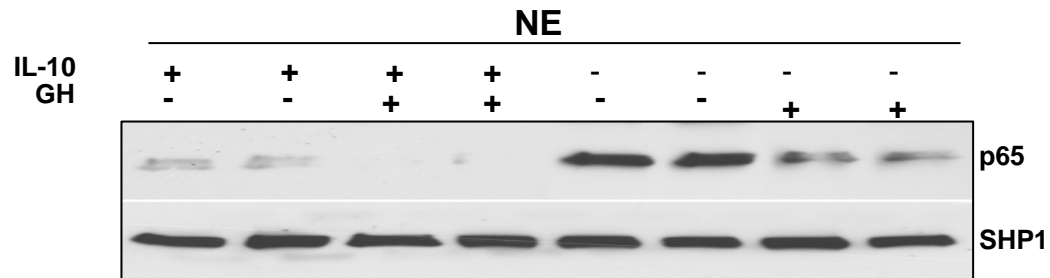
STAT5b RNAi	-	-	-	-	+	+	+	+
GH	-	-	+	+	-	-	+	+
TNF-α	-	+	-	+	-	+	-	+



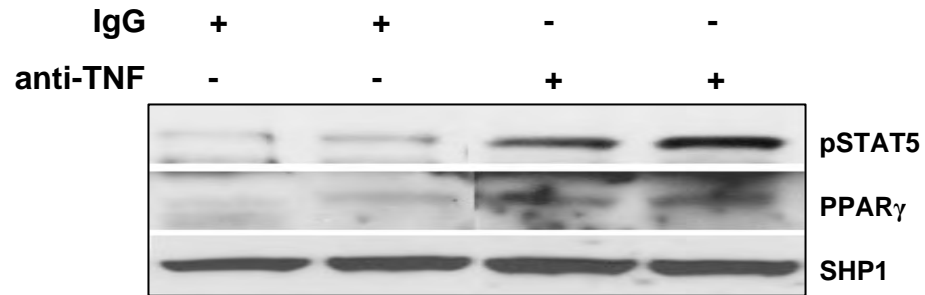
GH Activates STAT5b in IL-10 Deficient Mice



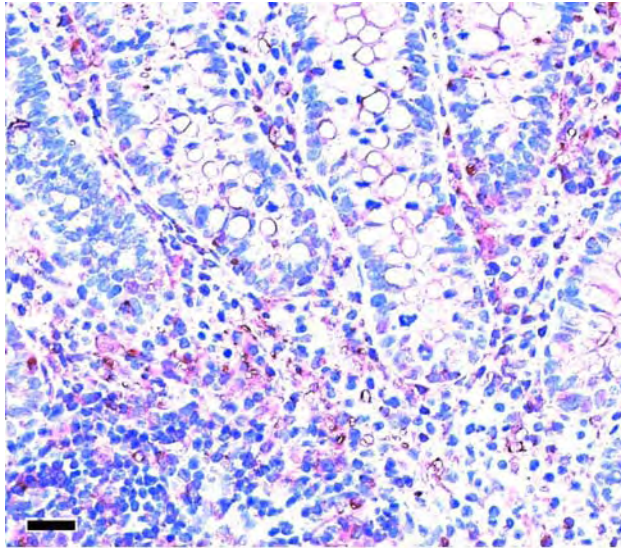
GH Reduces NFkB Activation in IL-10 Deficient Mice



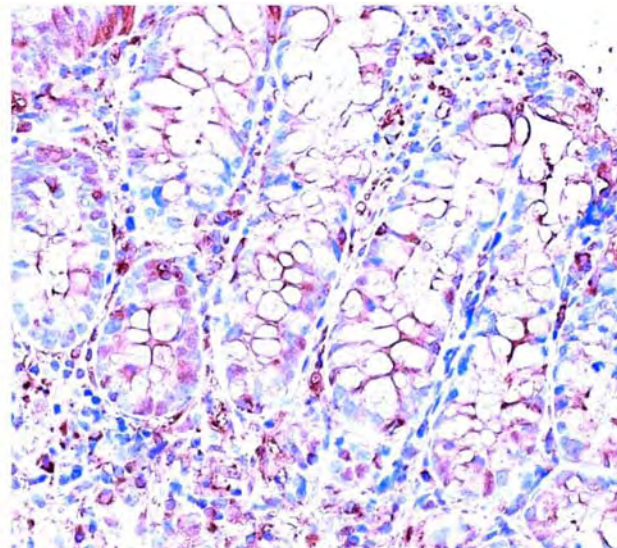
TNF Blockade Up Regulates pSTAT5:PPAR γ in IL-10 Deficient Mice



pSTAT5

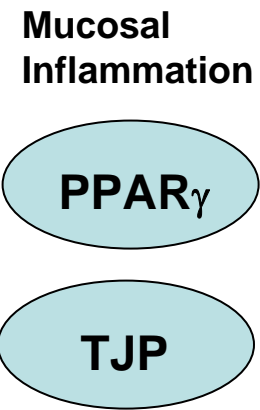
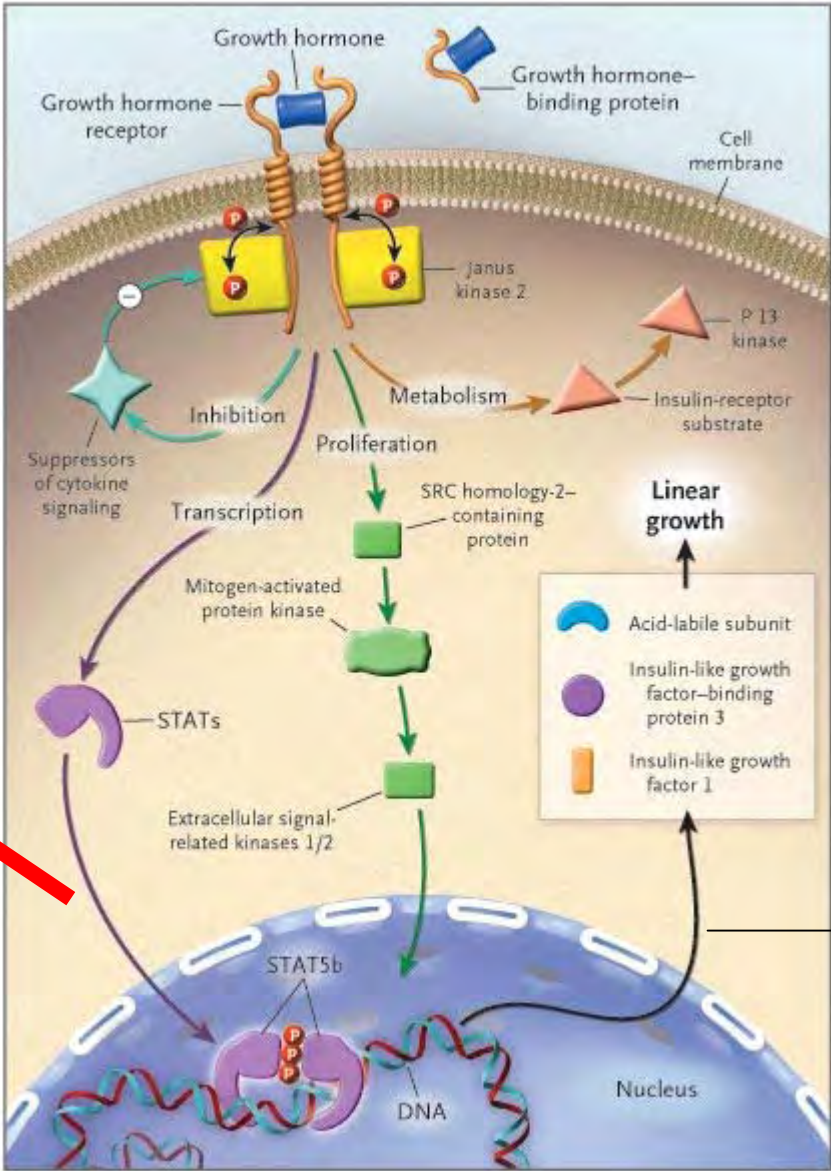
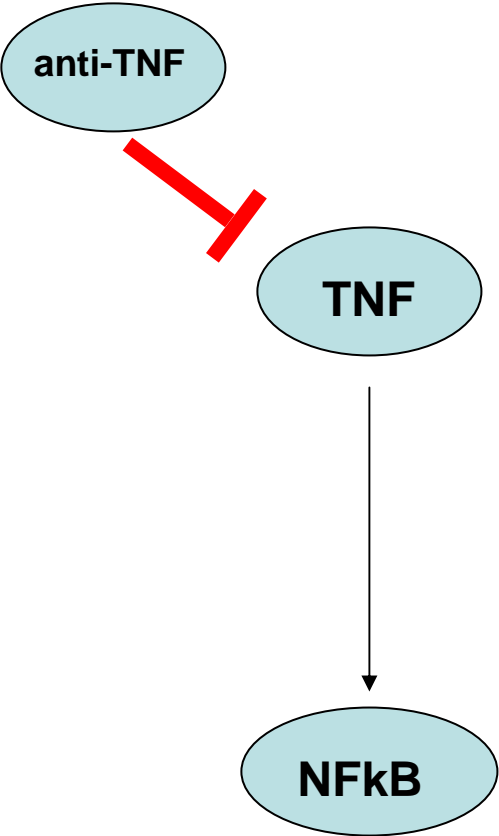


IgG



anti-TNF

STAT5b Regulation of Linear Growth & Mucosal Inflammation in CD



Clinical Implications

- **STAT5b may represent a common molecular target for therapies which will both reduce mucosal inflammation and restore normal growth**
- **GH clinical trial as adjunct therapy in active pediatric CD**
- **Additional mechanistic studies during anti-TNF therapy in children**
- **Combined therapy with anti-TNF followed by GH and immunomodulator may yield better clinical outcomes**