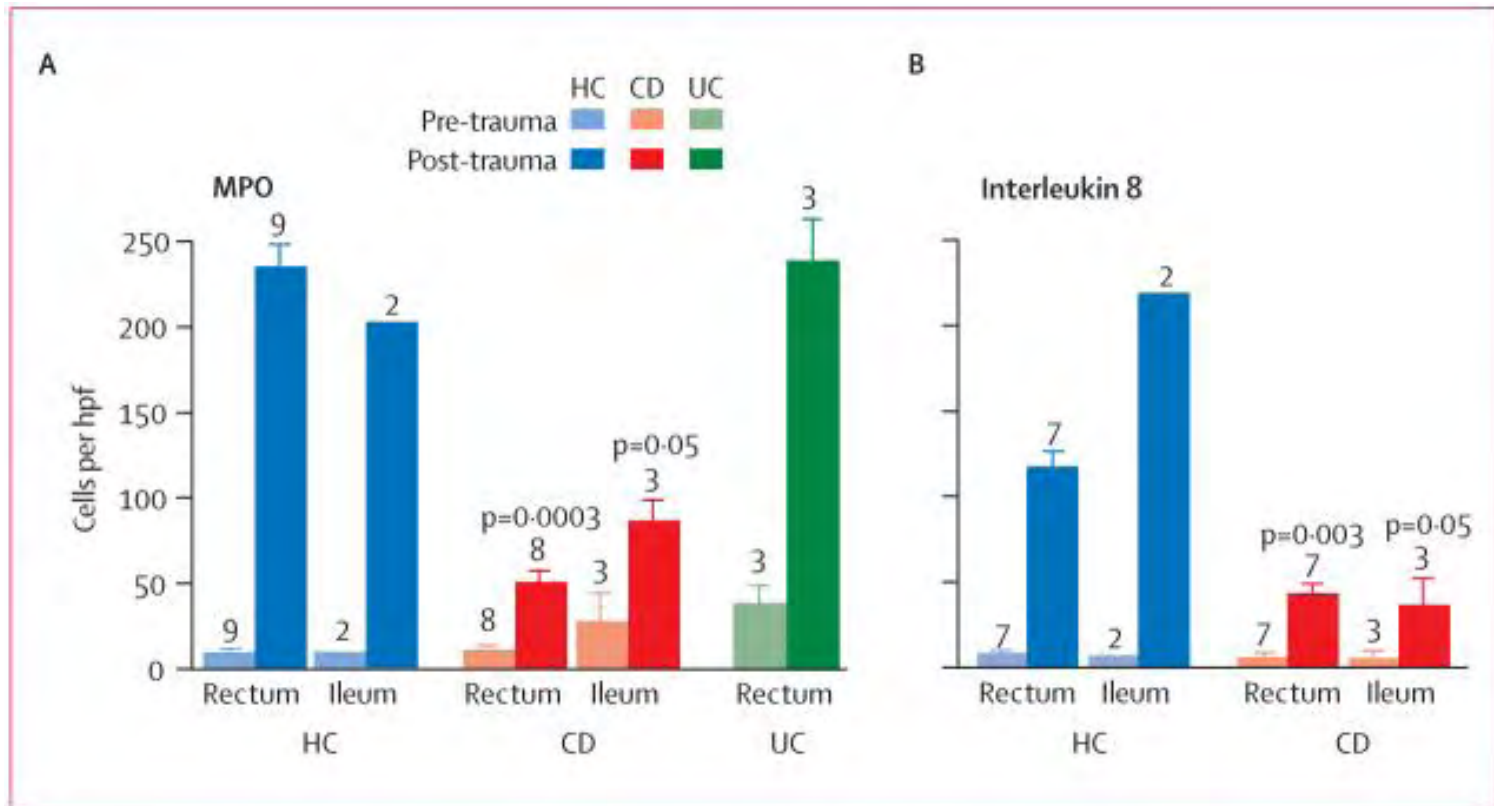


GM-CSF Bioactivity and IBD Phenotype

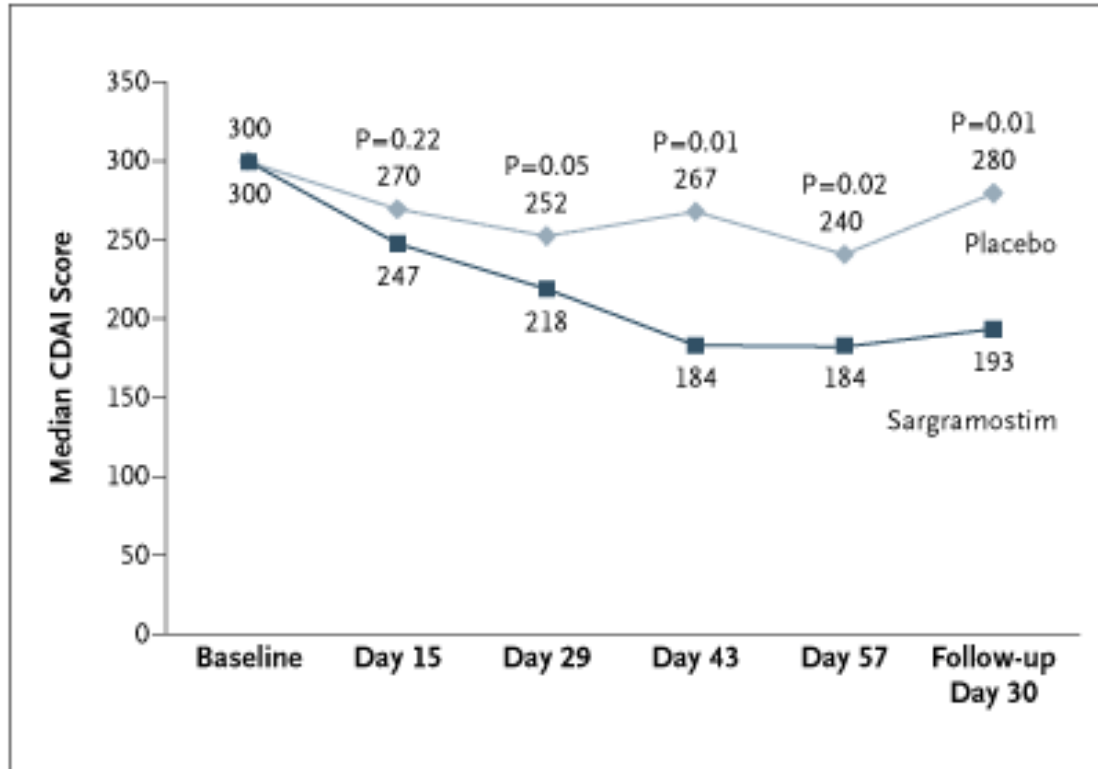
- NIH, CCFA, BMRP
- NIH DHC
- Trapnell Lab
- Kugathasan/Plevy Labs
- MiOk Kim, PhD



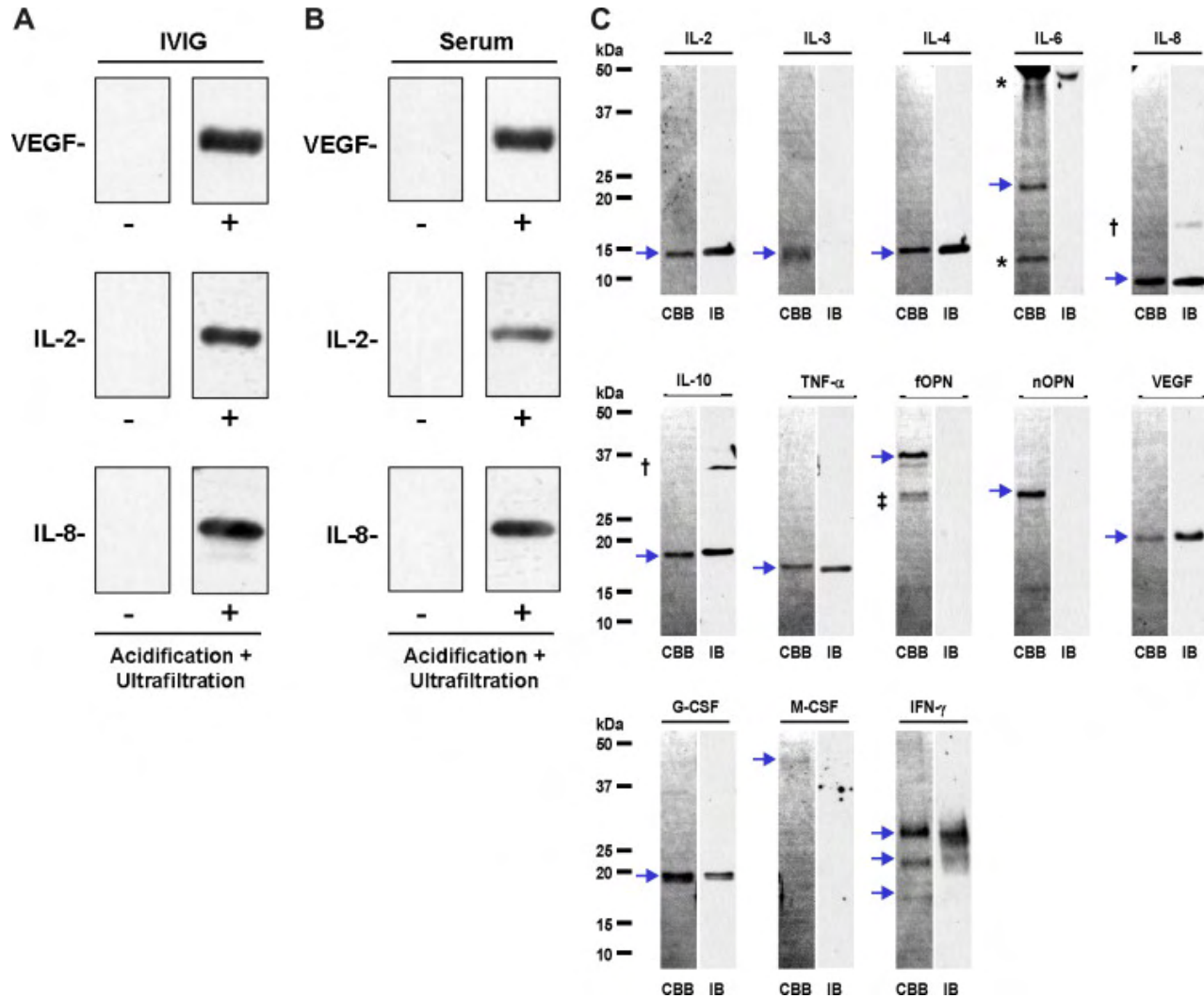
Defective Neutrophil Function in Crohn's Disease



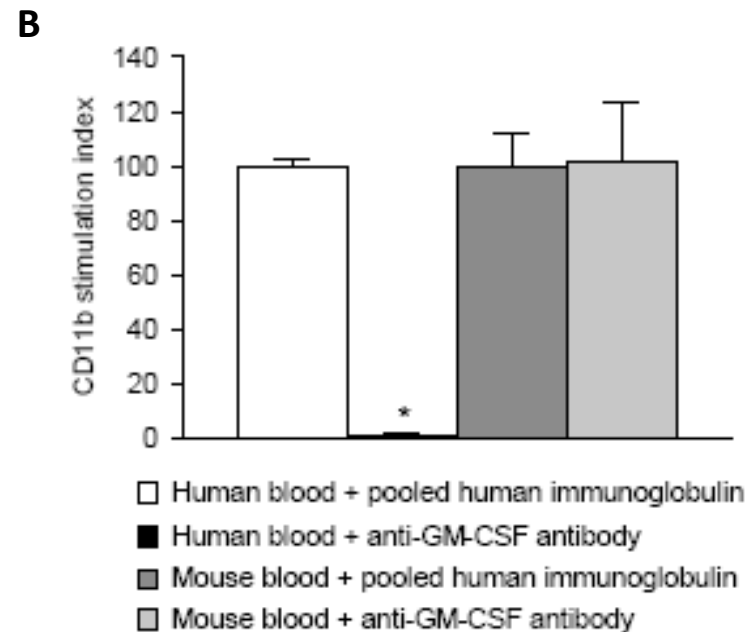
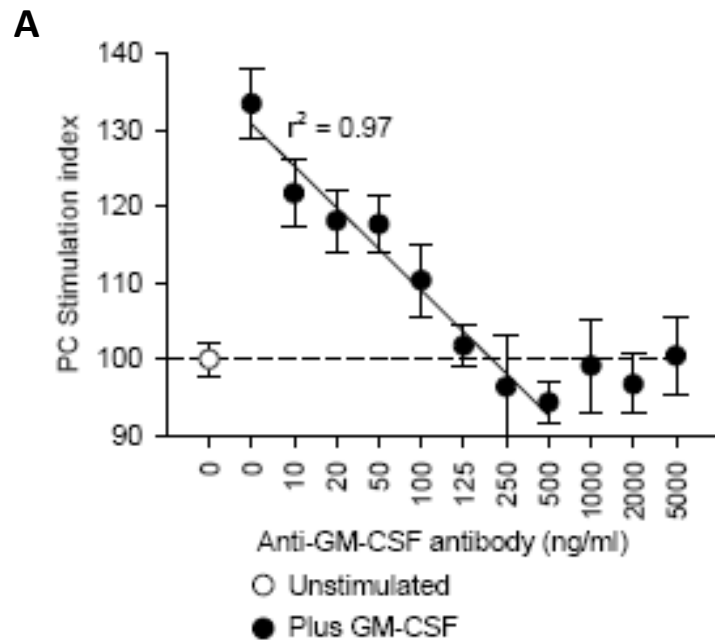
GM-CSF in Active Crohn's Disease



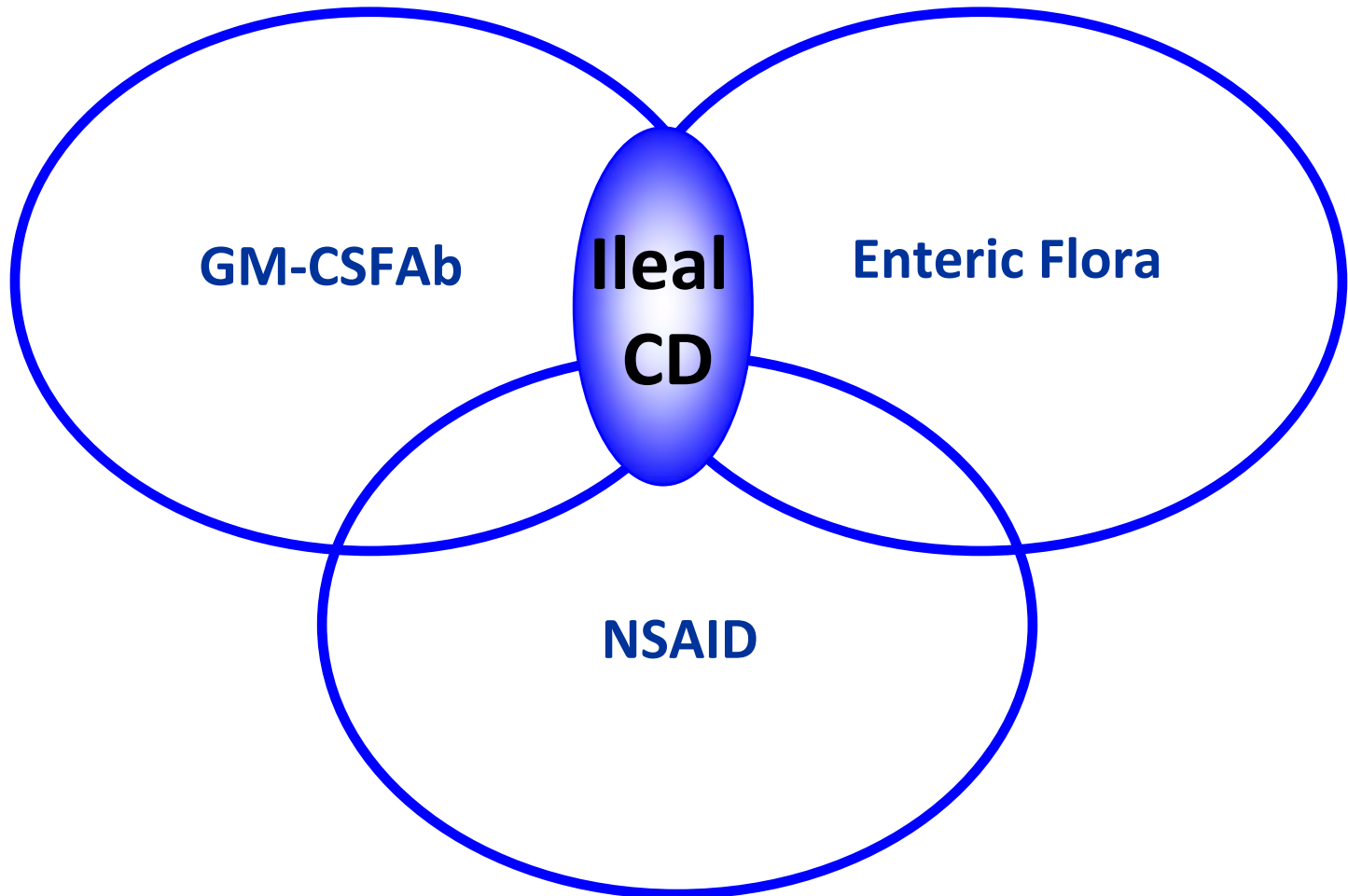
Neutralizing Cytokine Auto-antibodies in Healthy Individuals



GM-CSF Autoantibodies and Neutrophil Function



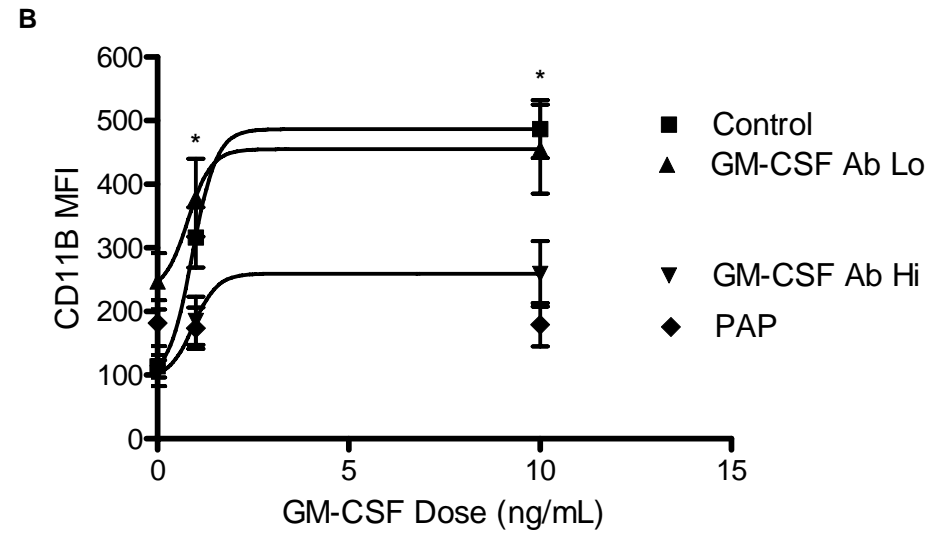
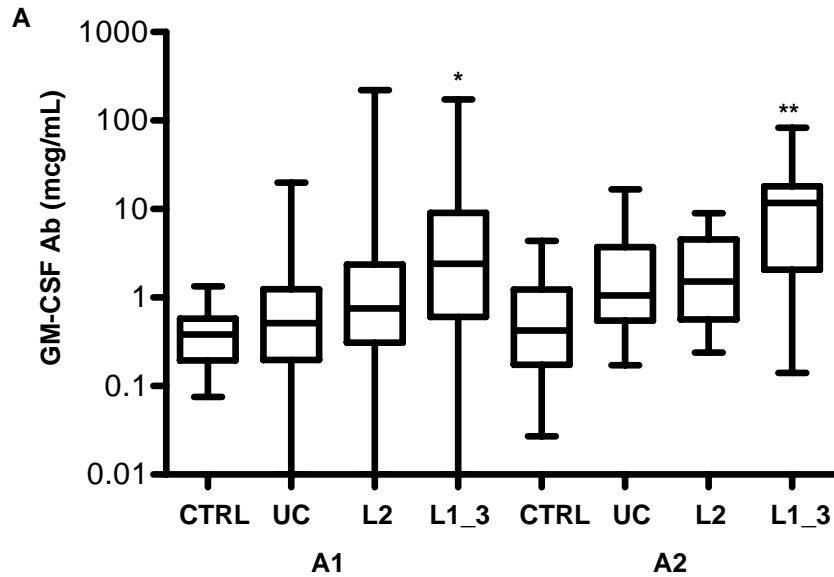
Do GM-CSFAb Regulate Barrier Function and CD Behavior?



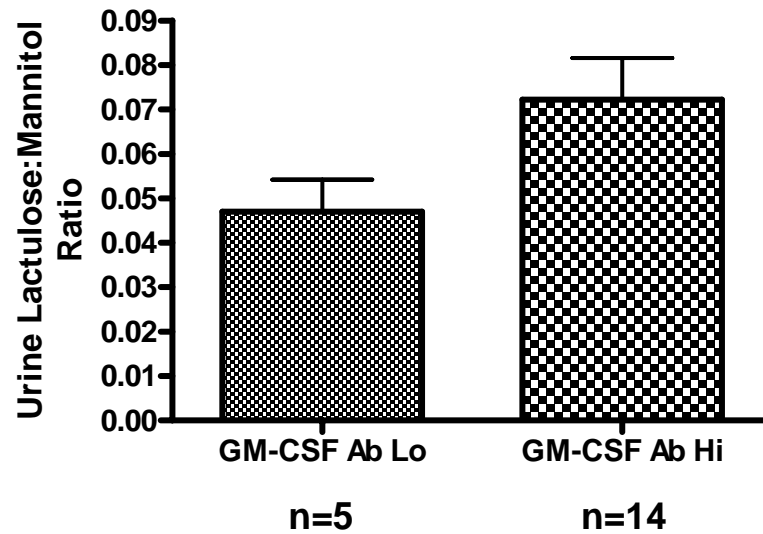
Pediatric Onset IBD Cohort

Diagnosis	n	Age of Onset Median(range)	Gender (male)	Duration Median(range)	GM-CSF Ab Median(25 th ,75 th)
Ileal CD	27	12(5,18)	78	27(1,94)	2.5(1,6.7)^
Ileo-colonic CD	143	12(2,17)	57	28(1,160)	2.2(0.8,8.3)^
Colonic CD	76	12(3,18)	61	31(1,298)	1(0.4,2.1)
Ulcerative Colitis	43	12(2,16)	61	48(1,192)	0.7(0.2,1.3)
CD Subset*	21	12(4,17)	76	23(6,96)	3.4(1.4,11.5)^
Healthy Controls	20	13(10,16)	70	NA	0.6(0.4,1)

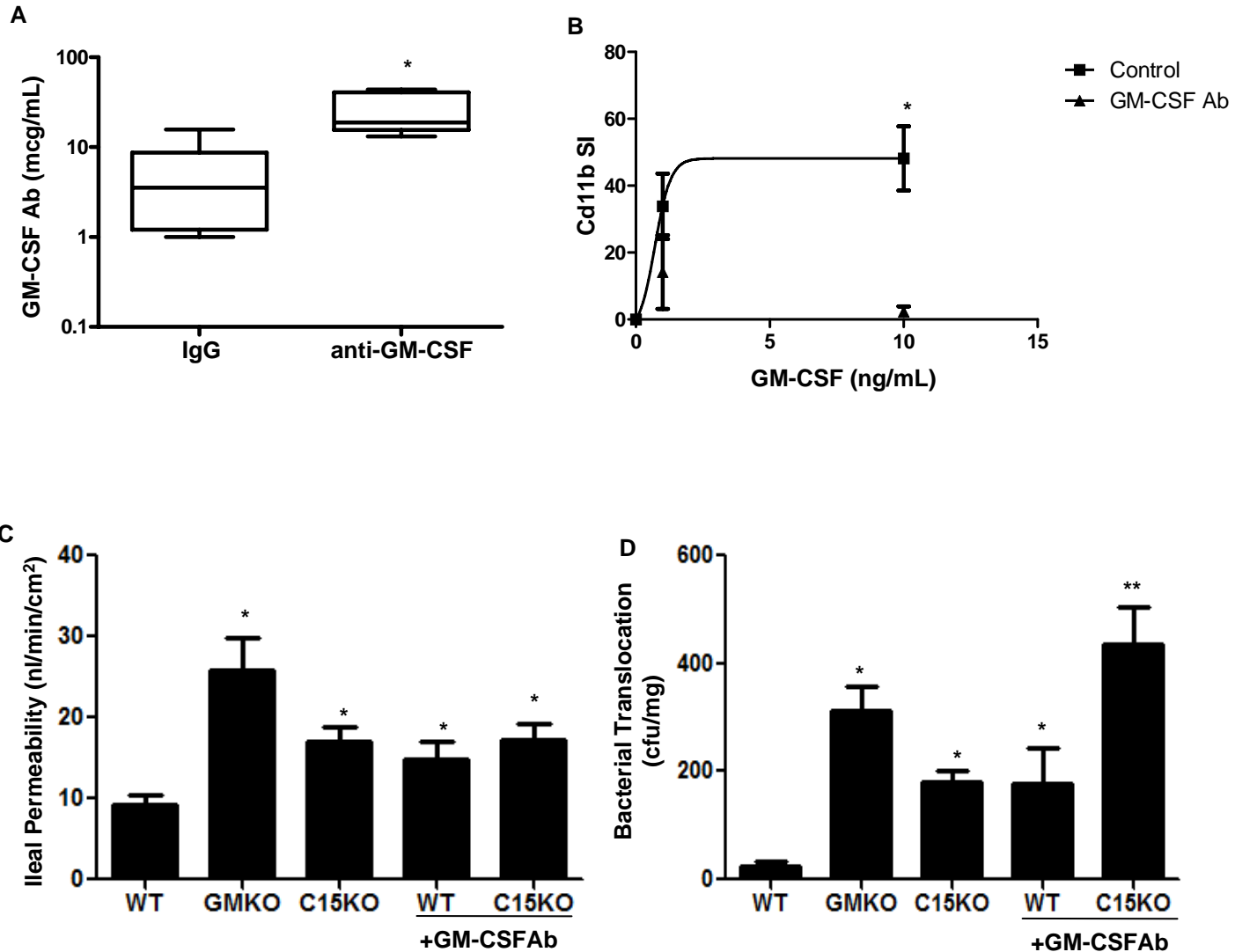
GM-CSF Ab Are Increased in Ileal CD and Reduce GM-CSF Activation of CD11B



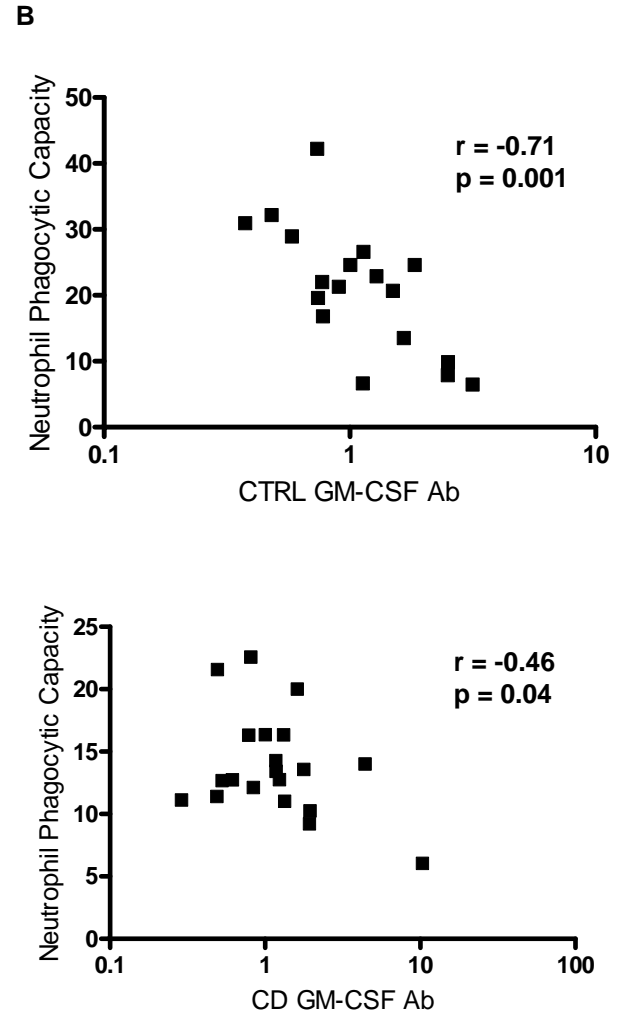
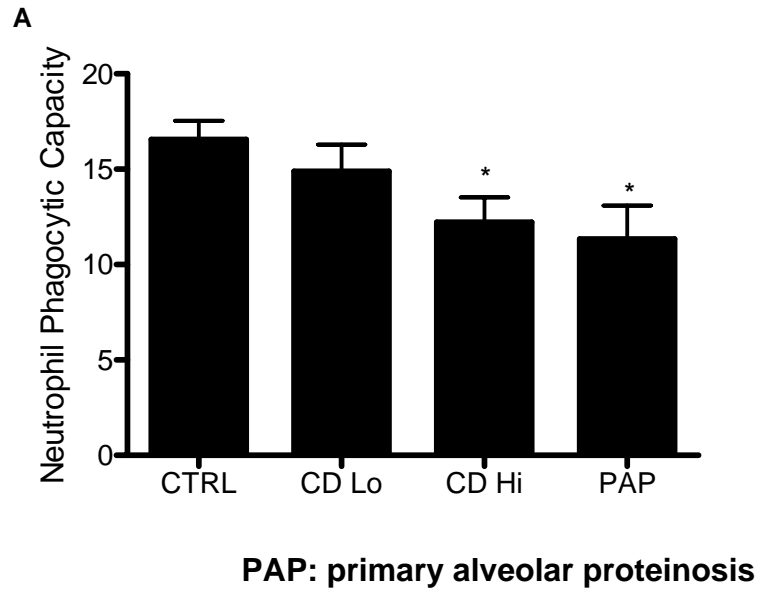
GM-CSF Ab and Intestinal Permeability in CD: Preliminary Results



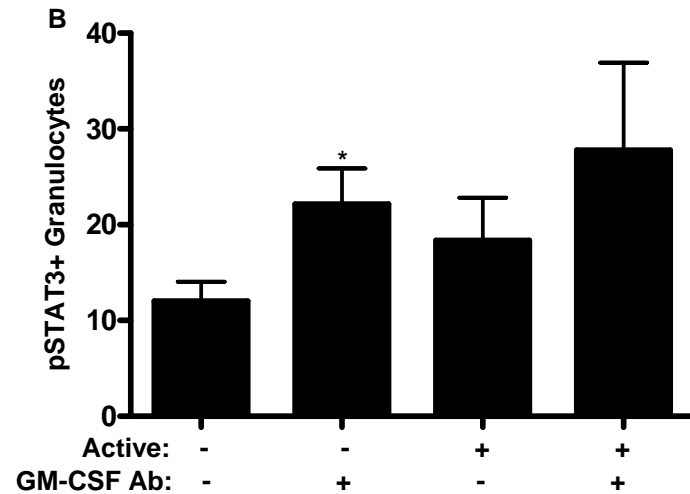
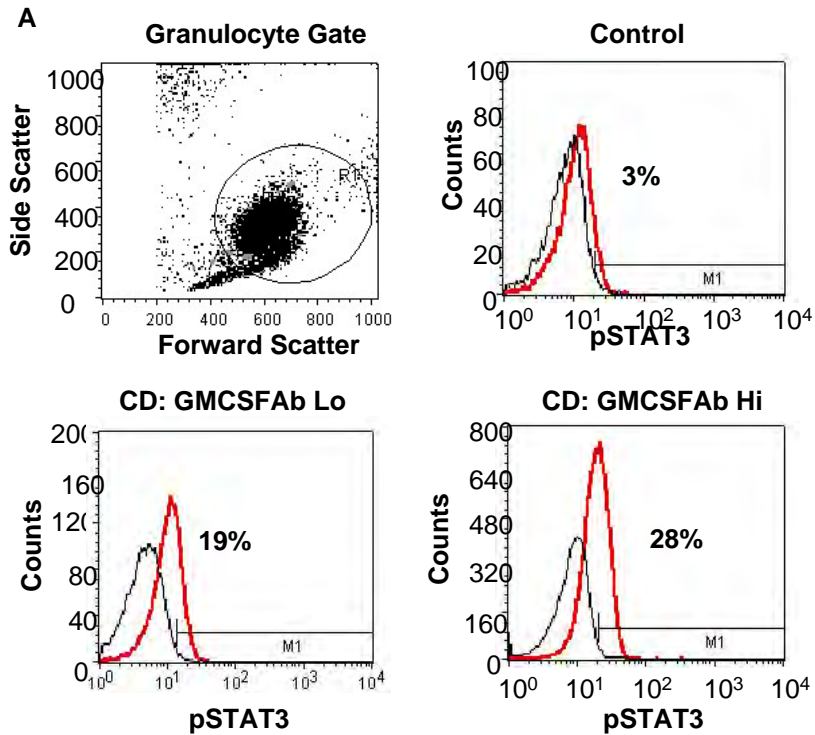
GM-CSF Ab and Murine Intestinal Permeability

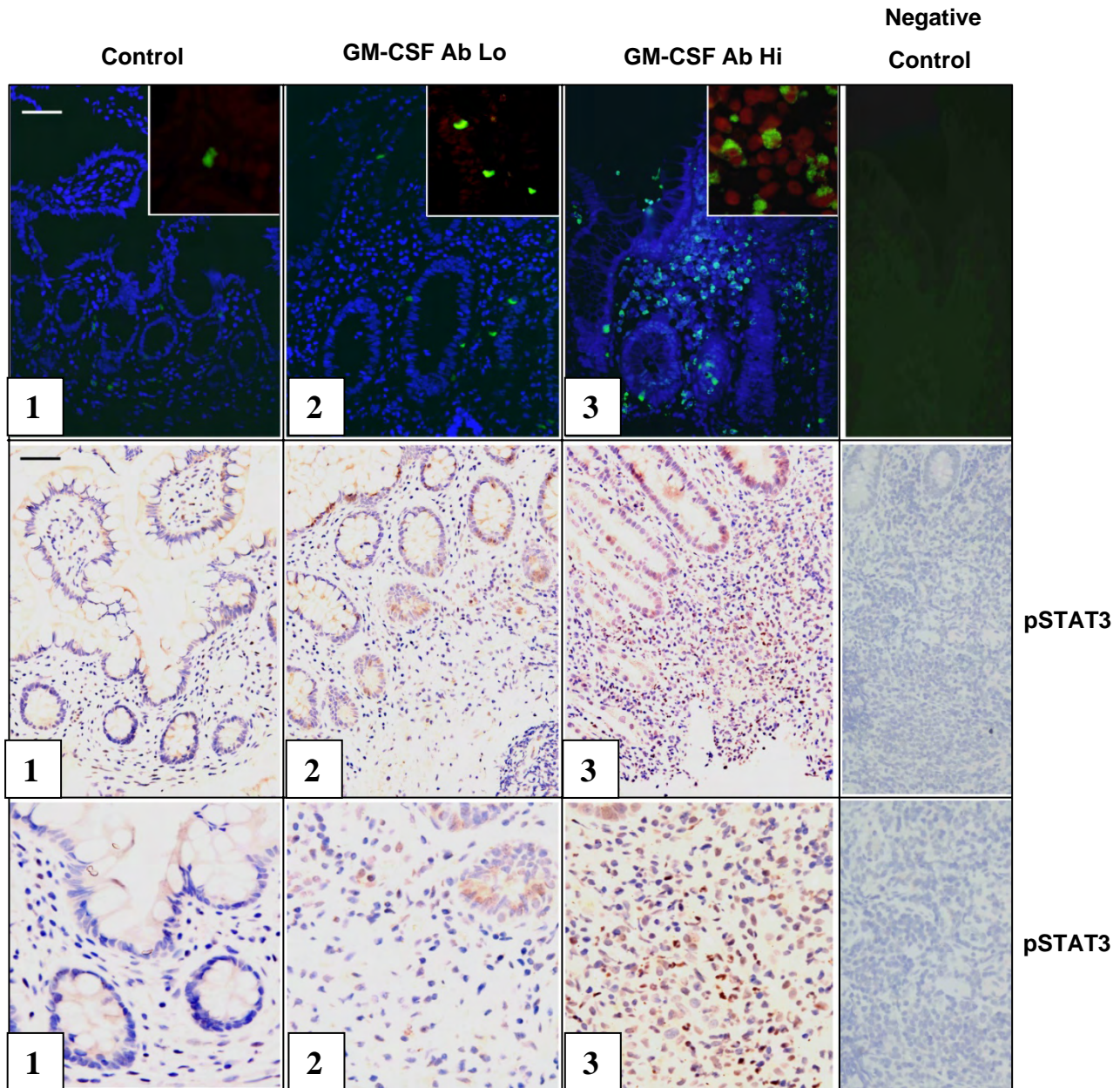


Neutrophil Phagocytosis is Reduced in GM-CSF Ab Hi CD

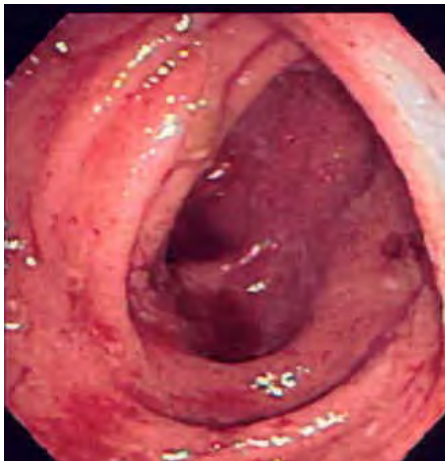
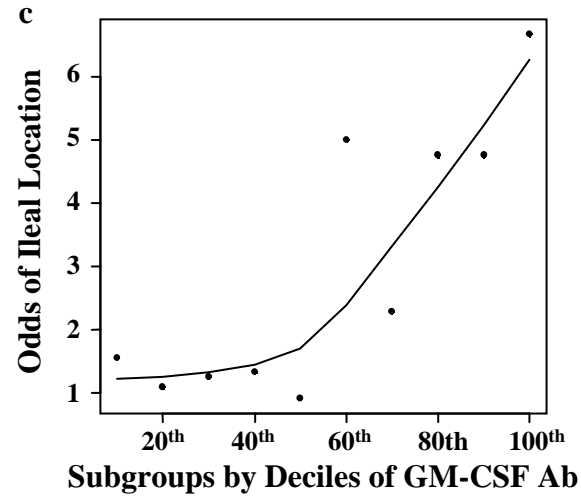


Neutrophil STAT3 Activation is Increased In GM-CSF Ab Hi CD





GM-CSF Ab Are Increased in Ileal CD



Ulcerative Colitis

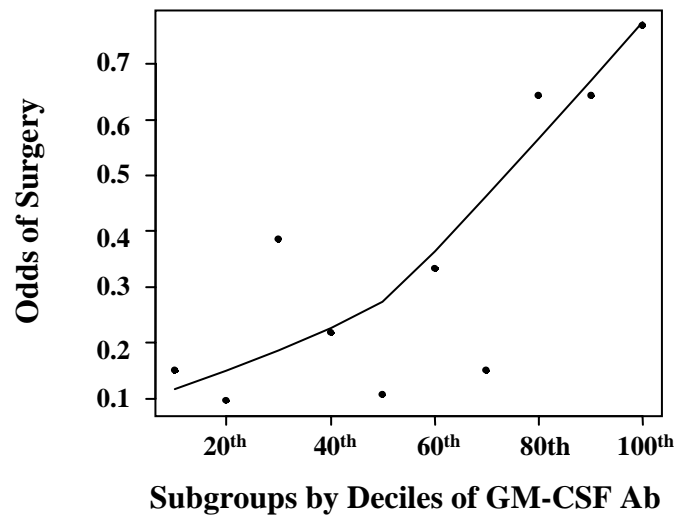
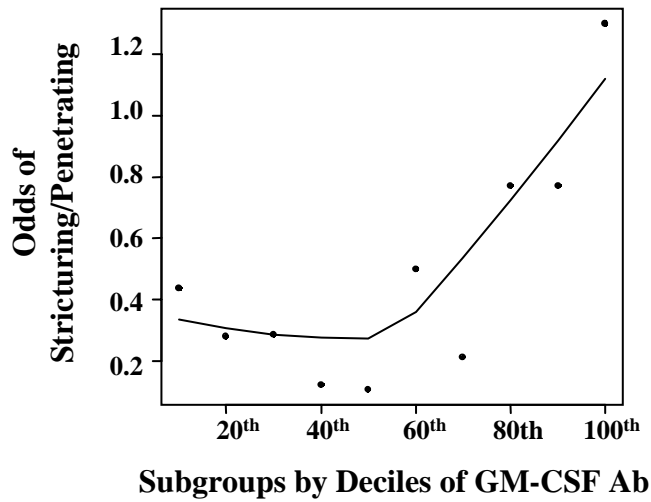


Crohns Colitis

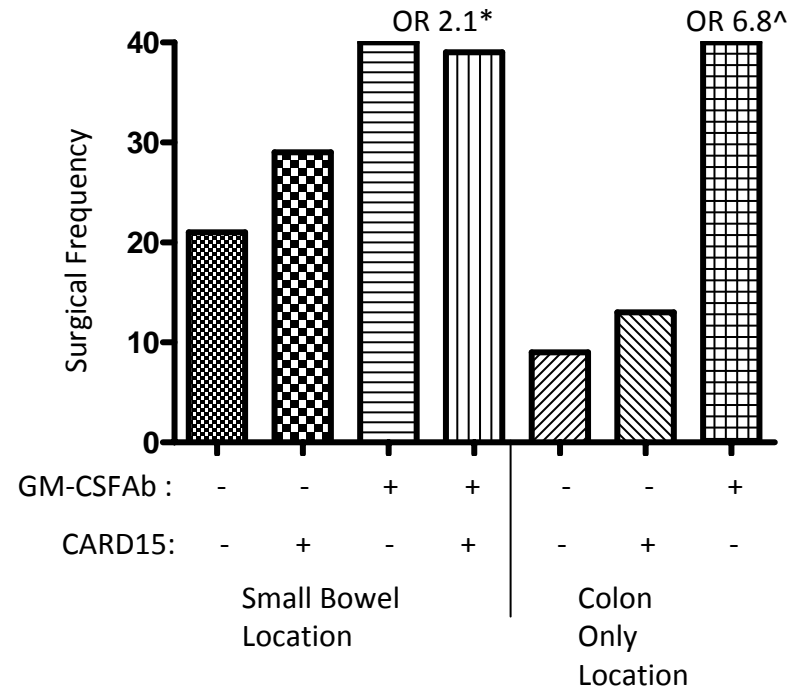
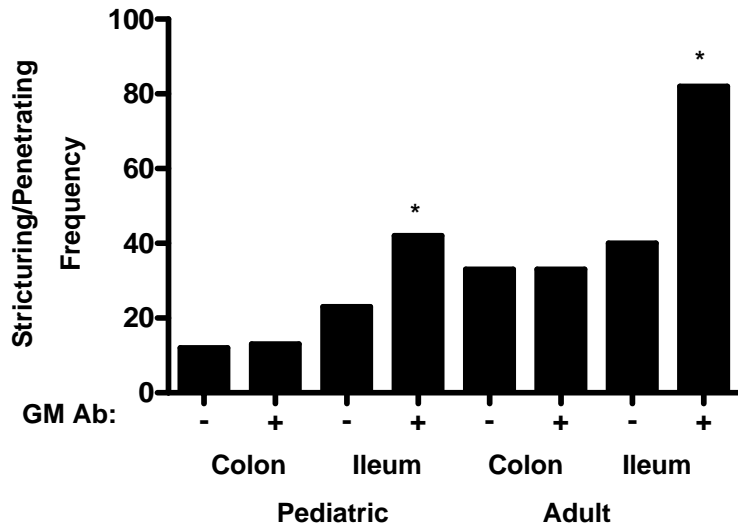


Crohns Ileitis

GM-CSF Ab Increase Risk for Structuring Behavior and Surgery



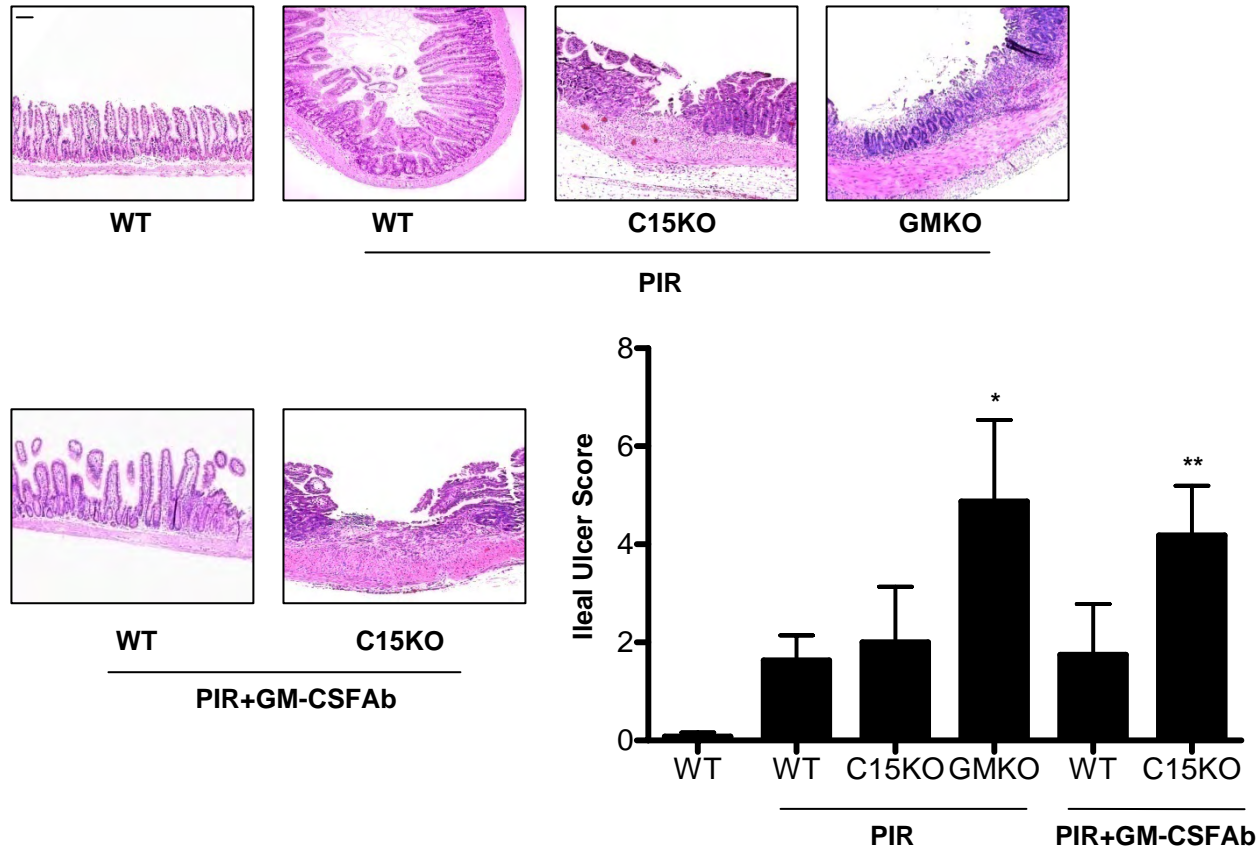
GM-CSF Ab Risk for Strictureing Behavior and Surgery and Disease Location



Regression Analysis

			<i>Odds Ratio</i>	<i>P-value</i>	
Ileal Location					
	Boy vs. Girl		1.04 (0.56,1.92)	0.9126	
	Young vs. Old*		0.75 (0.40,1.41)	0.3748	
	Duration>36 vs. ≤36		1.10 (0.60,2.02)	0.7658	
	CARD15 + vs. -		2.84 (1.42,5.66)	0.0031	
	GM-CSF Ab high vs. low		3.34 (1.80,6.20)	0.0001	
Stricturing/Penetrating					
	Boy vs. Girl		0.70 (0.37,1.30)	0.2572	
	Young vs. Old*		0.76 (0.39,1.48)	0.4168	
	Duration>36 vs. ≤36	with	CARD15 +	0.54 (0.19,1.55)	0.2514
	Duration>36 vs. ≤36	with	CARD15 -	2.64 (1.23,5.67)	0.0124
	CARD15 + vs. -	with	Duration > 36	0.50 (0.18,1.36)	0.1751
	CARD15 + vs. -	with	Duration ≤ 36	2.45 (1.08,5.56)	0.0325
	GM-CSF Ab high vs. low		2.65 (1.42,4.97)	0.0023	
Surgery					
	Boy vs. Girl		0.45 (0.23,0.88)	0.0188	
	Young vs. Old*		1.01 (0.50,2.04)	0.9819	
	Duration>36 vs. ≤36	with	CARD15 +	0.51 (0.17,1.56)	0.2394
	Duration>36 vs. ≤36	with	CARD15 -	3.20 (1.40,7.32)	0.0060
	CARD15 + vs. -	with	Duration > 36	0.47 (0.16,1.34)	0.1594
	CARD15 + vs. -	with	Duration ≤ 36	2.93 (1.19,7.20)	0.0189
	GM-CSF Ab high vs. low		2.59 (1.31,5.11)	0.0061	

Murine Ileitis Due to Loss of GM-CSF Bioactivity



GM-CSF Ab and CD Pathogenesis

- **Neutralizing GM-CSF Ab are increased in ileal CD**
- **Reduce mucosal barrier function**
- **Associated with stricturing/penetrating behavior independent of clinical risk factors or NOD2 genotype**
- **Biomarker for complicated disease course**
- **Identify patients who may benefit from stimulation of innate immunity with GM-CSF**

Current Studies

- **Complete permeability study**
- **Validate GM-CSF Ab as a predictive biomarker for stricturing/penetrating CD**
- **Determine inheritance and genetic contribution to GM-CSF Ab**
- **Determine epithelial mechanisms of GM-CSF Ab**
- **Determine myeloid mechanisms of GM-CSF Ab**

GM-CSF Bioactivity and CD Pathogenesis

