

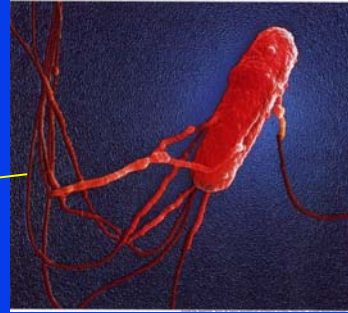
# **Adaptive Immunity to Flagellin in IBD**

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# Background

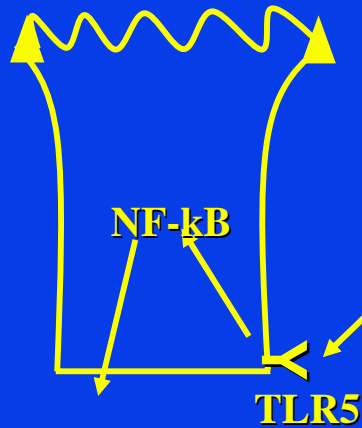


**E. Coli**

**Flagella**

**Flagellin monomers (About 70,000 per flagella)**

**Intestinal epithelial cell**



**?**

**Adaptive Immunity**

**Innate Immunity**

**Acute Inflammation**

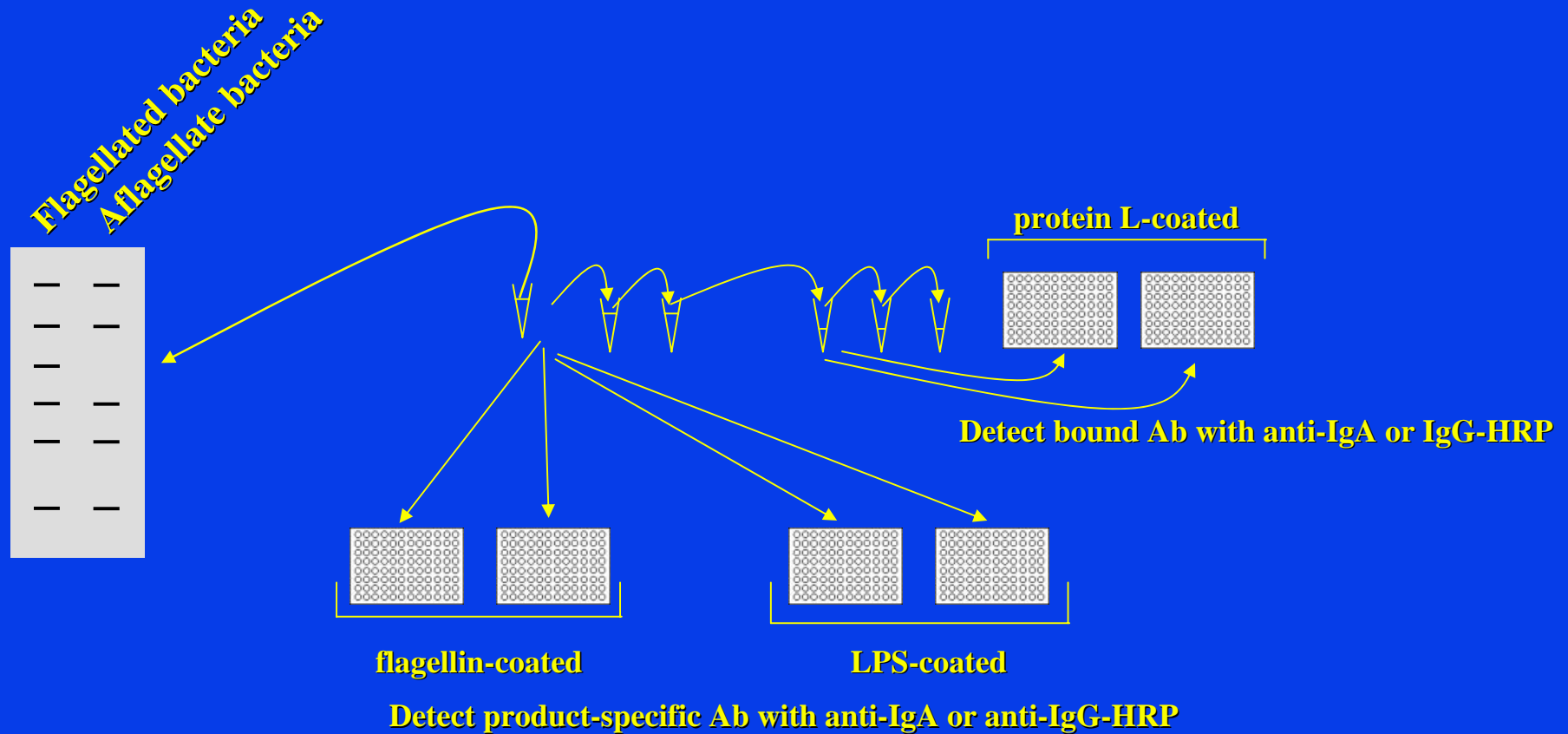
**Cytokines**

**Neutrophil Influx**

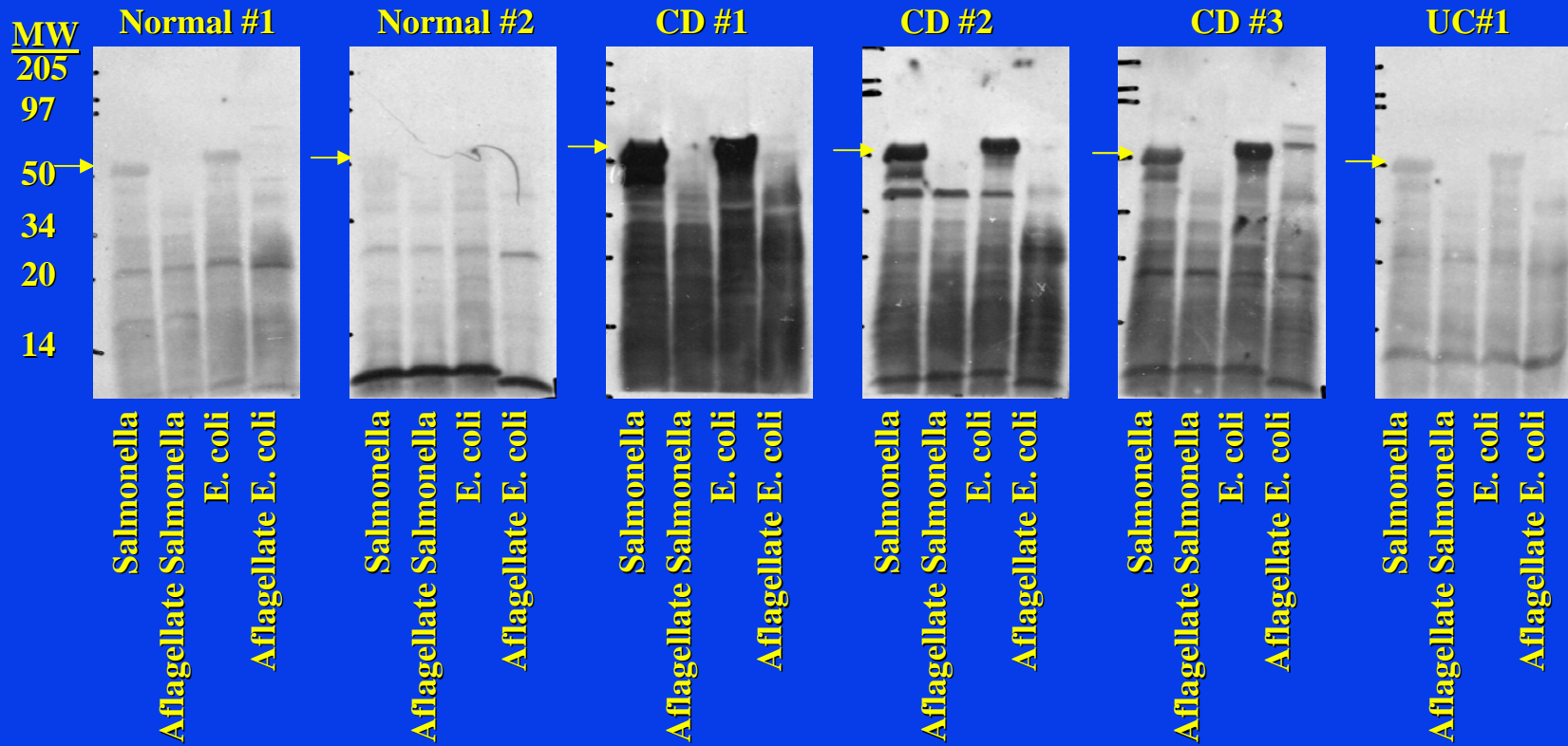
**Hypothesis: Flagellin may be a target and promoter of adaptive immunity in IBD**

# Methods

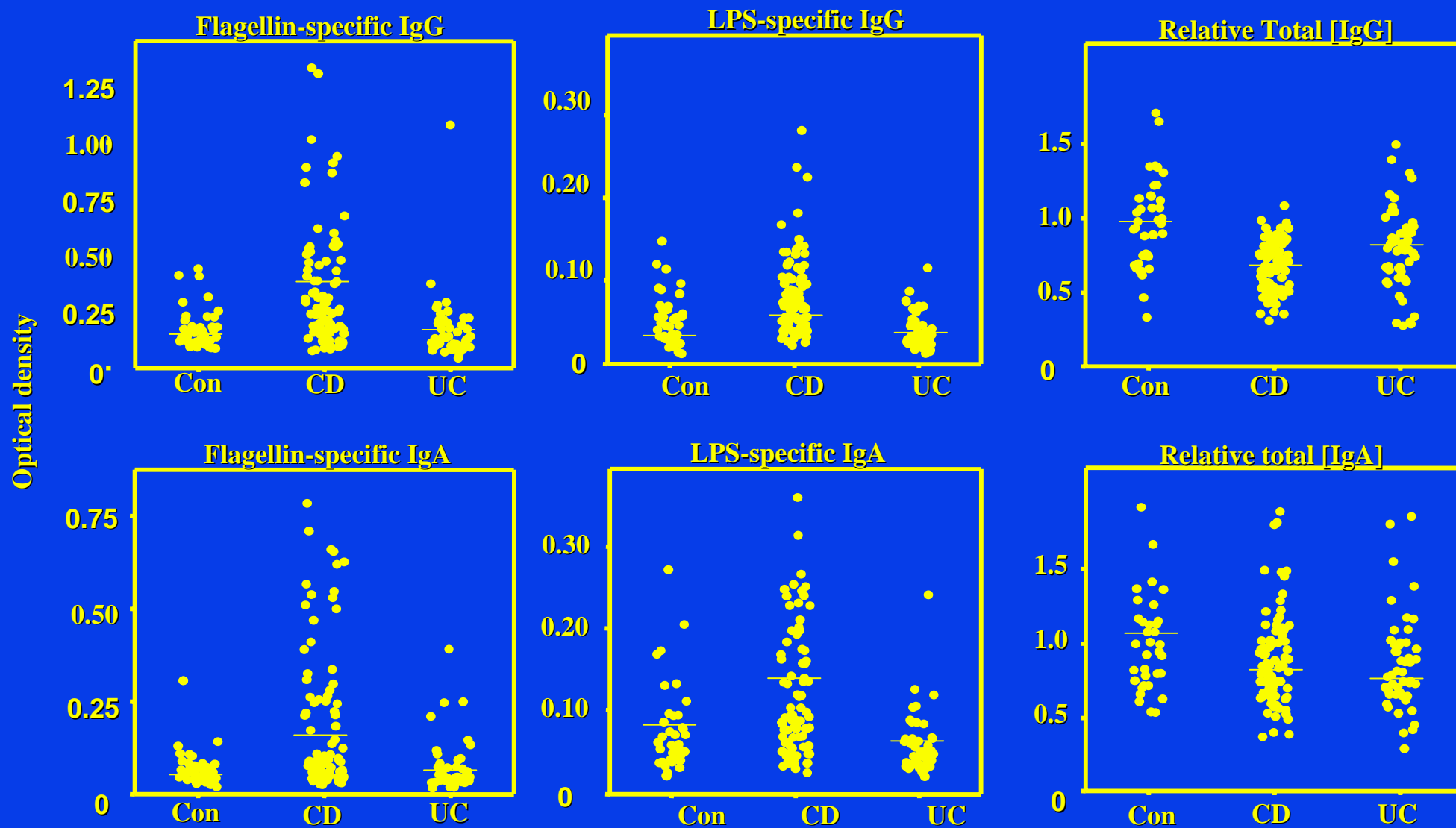
1. Isolate Serum from IBD patients and control subjects
2. Assess immunoreactivity to flagellins via western blotting or ELISA.



# Increased Immunoreactivity to Bacterial Extracts in Crohn's Disease



# Flagellin is a Target of Adaptive Immunity in Crohn's Disease



# Measuring immune responses to flagellin in mice

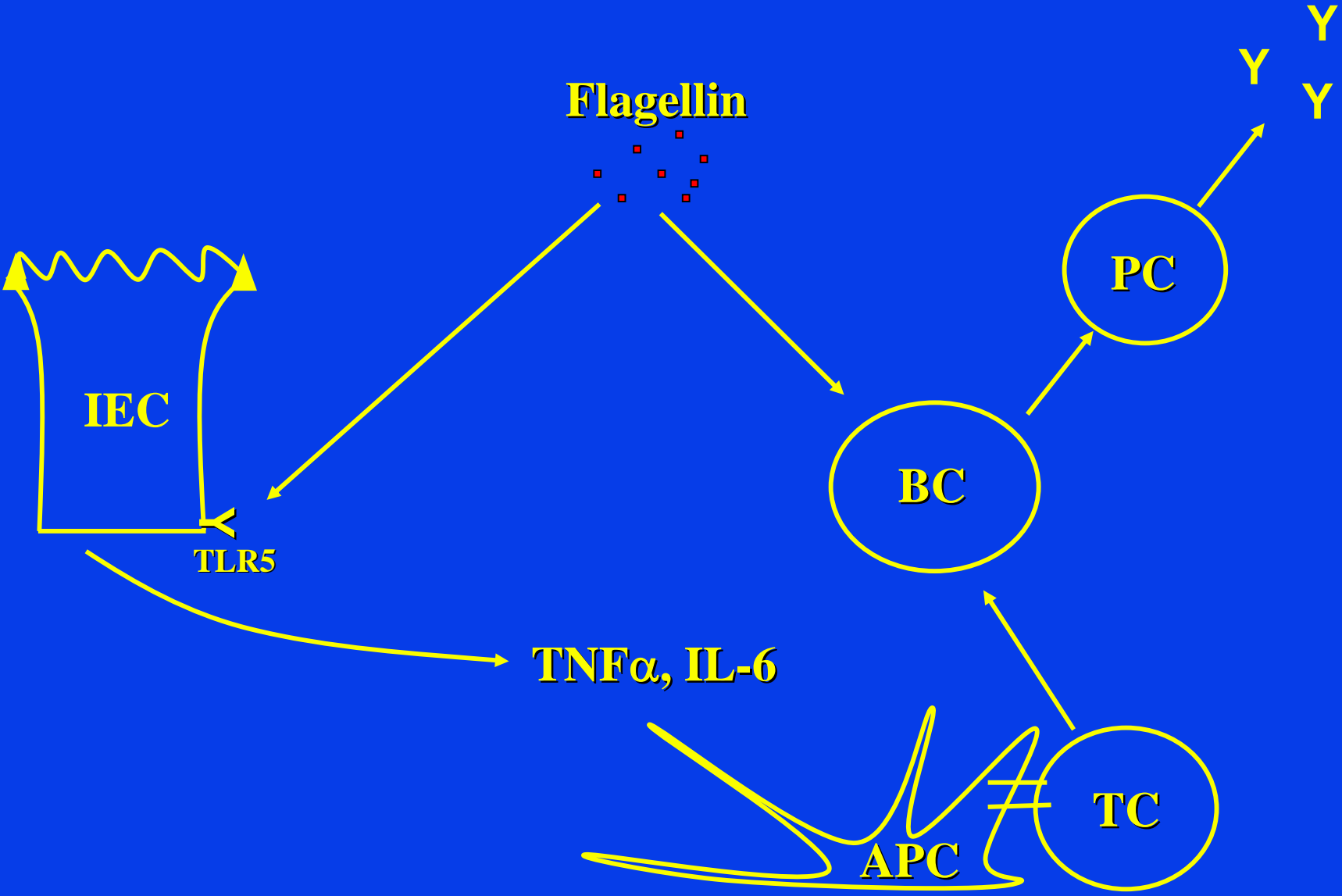
Inject flagellin (or controls) intraperitoneally



Innate Response  
Cytokines at 90 min

Adaptive Response  
Antibodies at 2 weeks

# Mouse results/interpretation

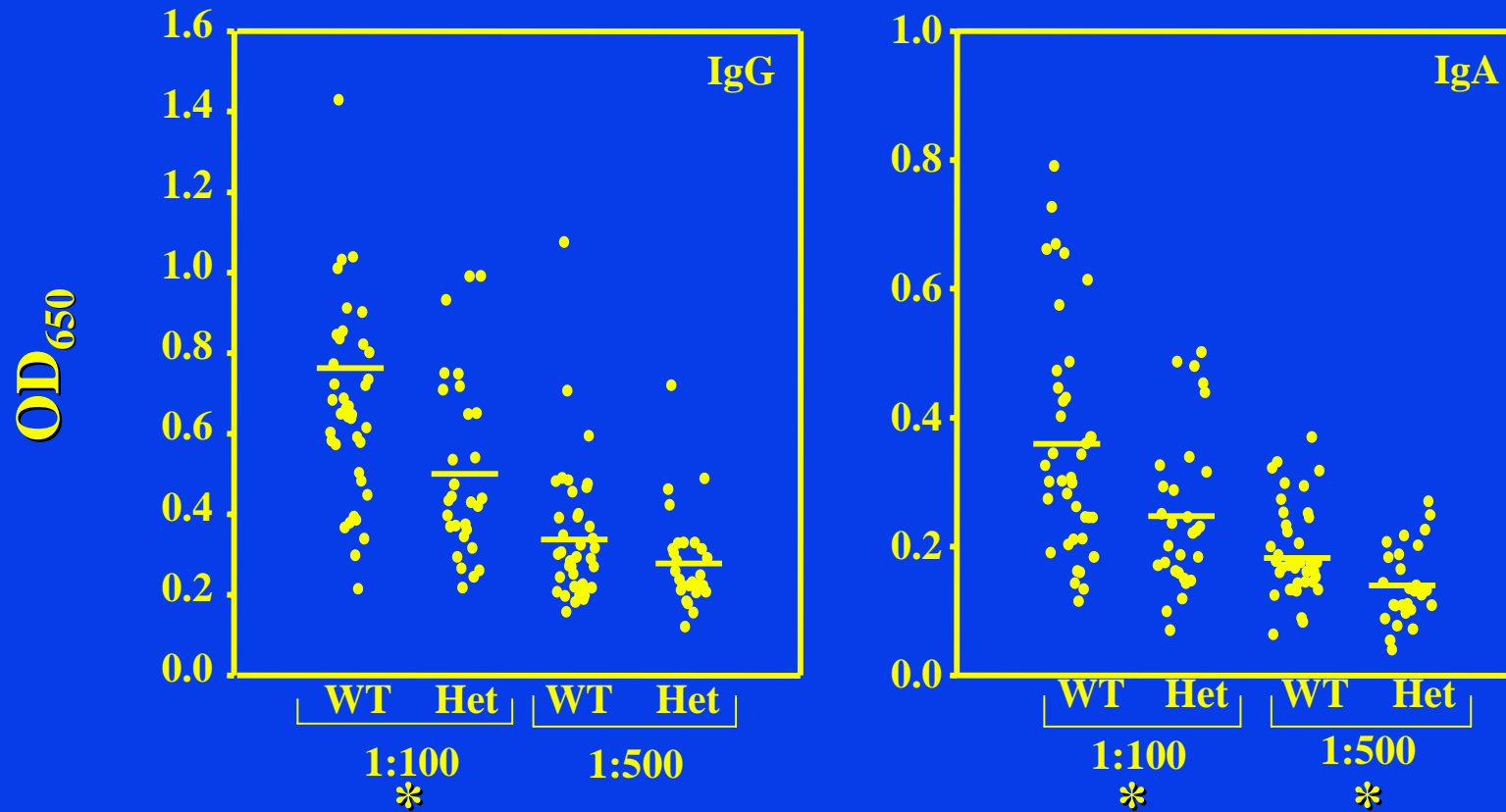


## **A Common Dominant TLR5 Stop Codon Polymorphism Abolishes Flagellin Signaling and Is Associated with Susceptibility to Legionnaires' Disease**

Thomas R. Hawn,<sup>1,2</sup> Annelies Verbon,<sup>3,4</sup> Kamilla D. Lettinga,<sup>3</sup> Lue Ping Zhao,<sup>5,6</sup> Shuying Sue Li,<sup>5</sup> Richard J. Laws,<sup>5</sup> Shawn J. Skerrett,<sup>1</sup> Bruce Beutler,<sup>7</sup> Lea Schroeder,<sup>2</sup> Alex Nachman,<sup>2</sup> Adrian Ozinsky,<sup>2</sup> Kelly D. Smith,<sup>1,2</sup> and Alan Aderem<sup>2</sup>

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# Carriage Of TLR5-stop Reduces Natural Acquisition Of Adaptive Immunity To Flagellin



\*: p<0.01

# Reduced Rate of Crohn's Disease In Persons Carrying TLR5-stop (Jewish Cohort)

	<u>Number of subjects</u>	<u>Het-TLR5-stop # (%)</u>
Healthy Relatives	296	16 (5.4%)
Crohn's Disease	215	2 (0.9%)
Ulcerative Colitis	185	11 (6.0%)
Ethnic Controls	416	27 (6.5%)

# Conclusions

- 1. Common gram-negative flagellins (i.e. *E. coli*) are antigenic targets of the elevated adaptive immune response in Crohn's disease.**
- 2. Adaptive immunity to flagellin is regulated by TLR5-mediated innate immunity.**
- 3. Cytokines (e.g. IL-6 and TNF $\alpha$ ) produced by non-hematopoietic cells, may link mucosal detection of flagellin to adaptive immune response.**
- 4. Adaptive immunity to flagellin may promote development of Crohn's Disease.**

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