

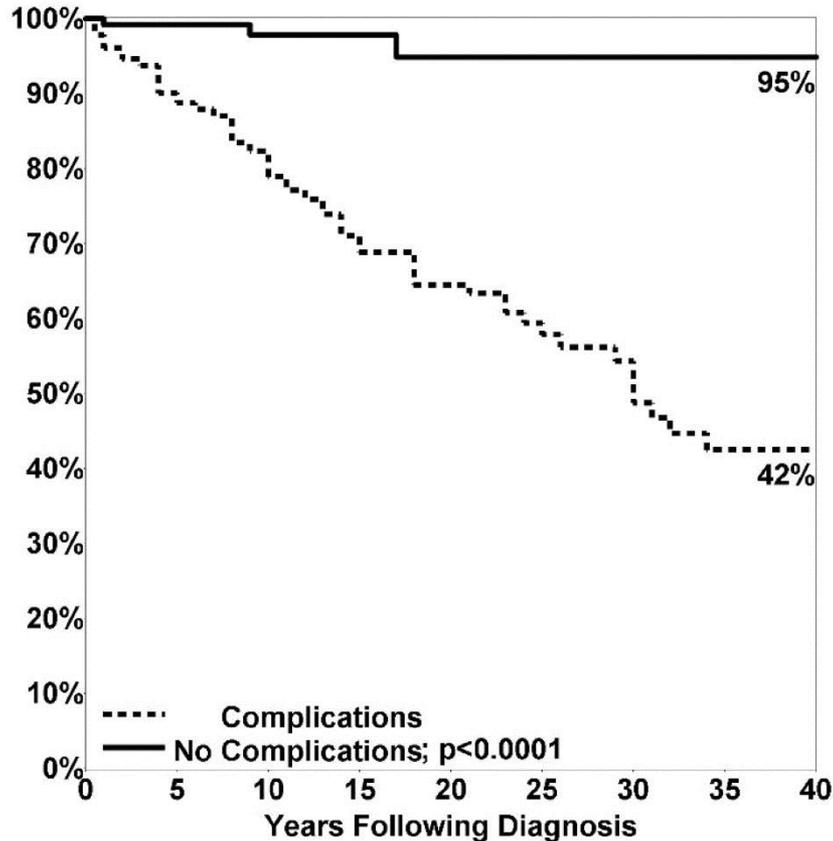
# **Amplification of NF- $\kappa$ B-driven type 1 cytokines promotes common variable immunodeficiency inflammatory complications**

PJ Maglione, MD, PhD

Assistant Professor  
Pulmonary Center  
Boston University School of Medicine

# CVID patients with complications have worsened survival

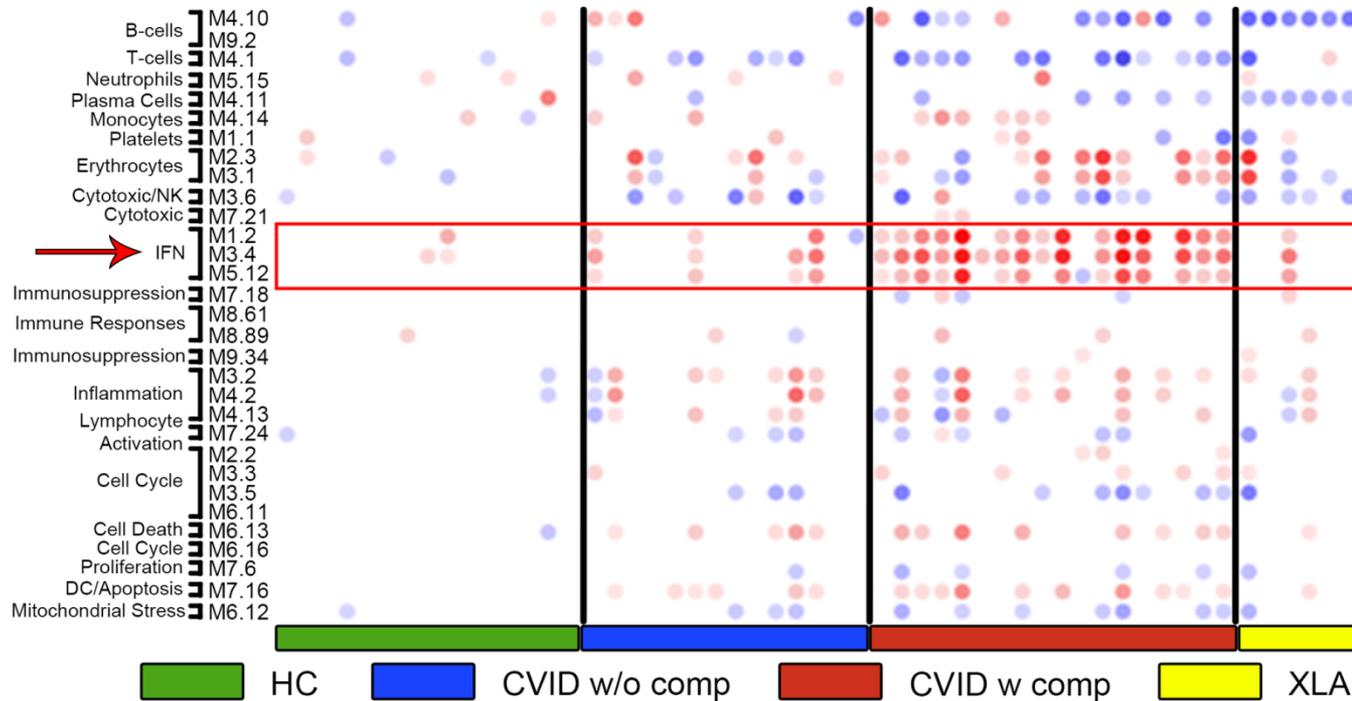
## CVID patient survival over time



**IgG replacement (IVIG)  
antibiotics**

Associated condition (N = 473)	n	Percentage
Infections only (no complications)	151	31.9
Chronic lung disease (functional/structural)	135	28.5
Autoimmunity	134	28.6
Gastrointestinal disease	73	15.4
Granulomatous disease	46	9.7
Liver disease/hepatitis	43	9.1
Lymphomas and other lymphoid malignancies	39	8.2
Splenectomy	39	8.2
Other cancers	33	6.9

# Interferon gene signature defines CVID with complications



Park et al. 2013. *PLoS One*. 17: 8.

## Expansion of inflammatory innate lymphoid cells in patients with common variable immunodeficiency



Montserrat Cols, PhD,<sup>a,b</sup> Adeb Rahman, PhD,<sup>b</sup> Paul J. Maglione, MD, PhD,<sup>a,b</sup> Yolanda Garcia-Carmona, PhD,<sup>a,b</sup> Noa Simchoni, PhD,<sup>a,b</sup> Huai-Bin M. Ko, MD,<sup>d</sup> Lin Radigan,<sup>a,b</sup> Andrea Cerutti, MD, PhD,<sup>a,b</sup> Derek Blankenship, PhD,<sup>c</sup> Virginia Pascual, MD,<sup>c</sup> and Charlotte Cunningham-Rundles, MD, PhD<sup>a,b</sup> *New York, NY, and Dallas, Tex*

## BAFF-driven B cell hyperplasia underlies lung disease in common variable immunodeficiency

Paul J. Maglione, ... , Andrea Cerutti, Charlotte Cunningham-Rundles

*JCI Insight*. 2019;4(5):e122728. <https://doi.org/10.1172/jci.insight.122728>.

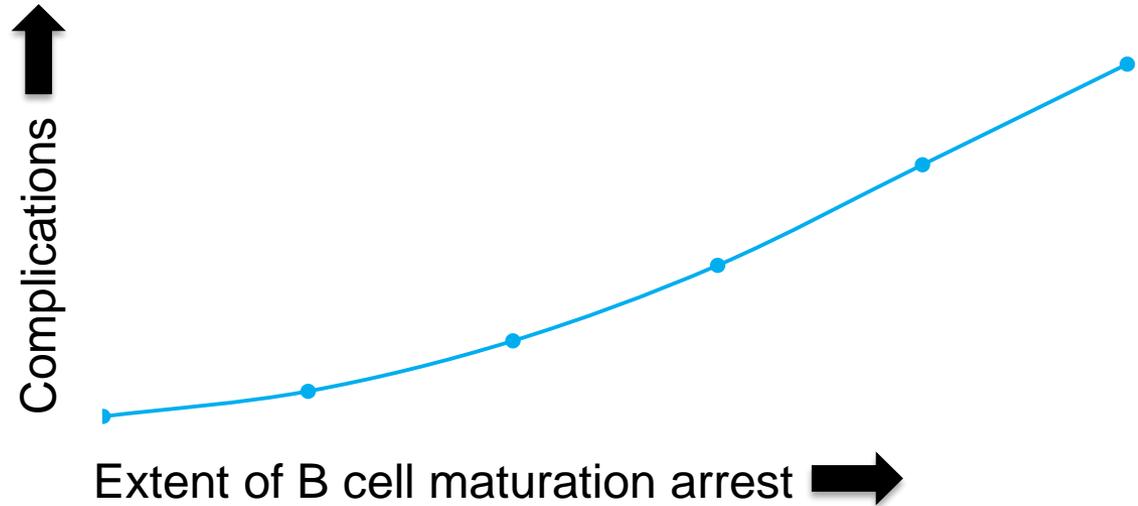
## The T<sub>H</sub>1 phenotype of follicular helper T cells indicates an IFN- $\gamma$ -associated immune dysregulation in patients with CD21<sup>low</sup> common variable immunodeficiency

Unger et al. 2018. *J Allergy Clin Immunol*. 141: 730-740.

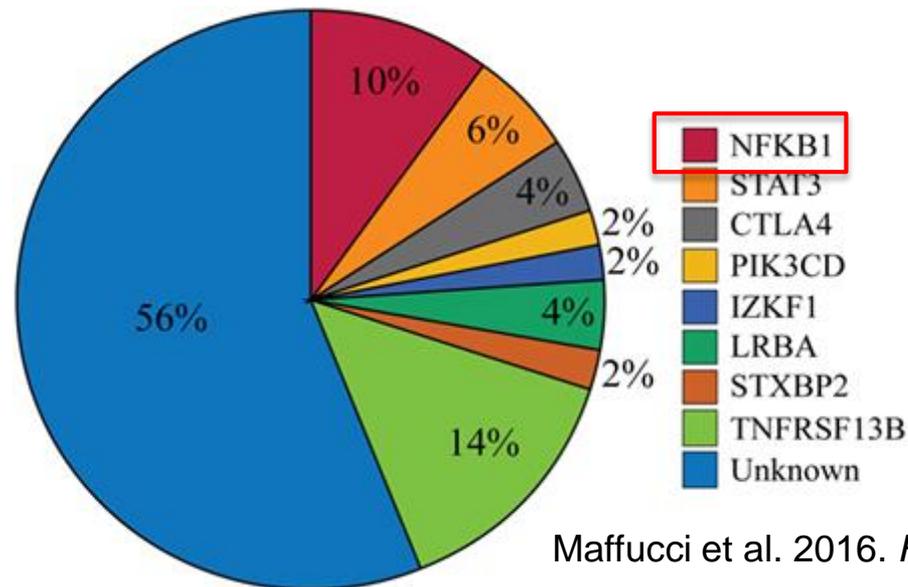


# Why do a subset of CVID patients develop this IGS?

**Extent of B cell maturation arrest contributes**



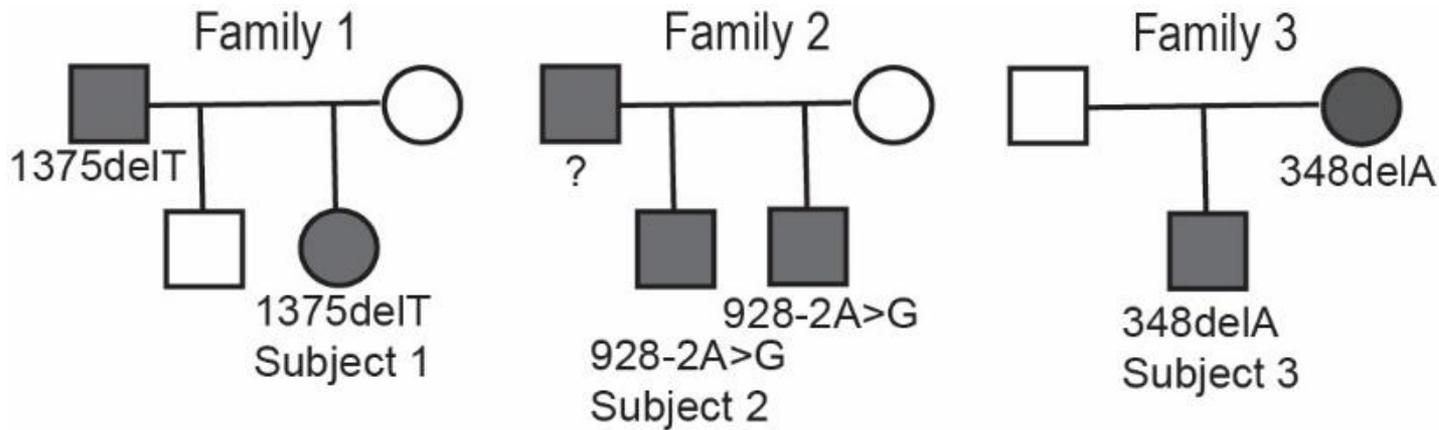
**Genetics contributes**



Maffucci et al. 2016. *Front Immunol.* 13: 7220.

**Hypothesis:** CVID patients with genetic or immunological characteristics that amplify NF-kB signaling have increased type 1 cytokines and inflammatory complications.

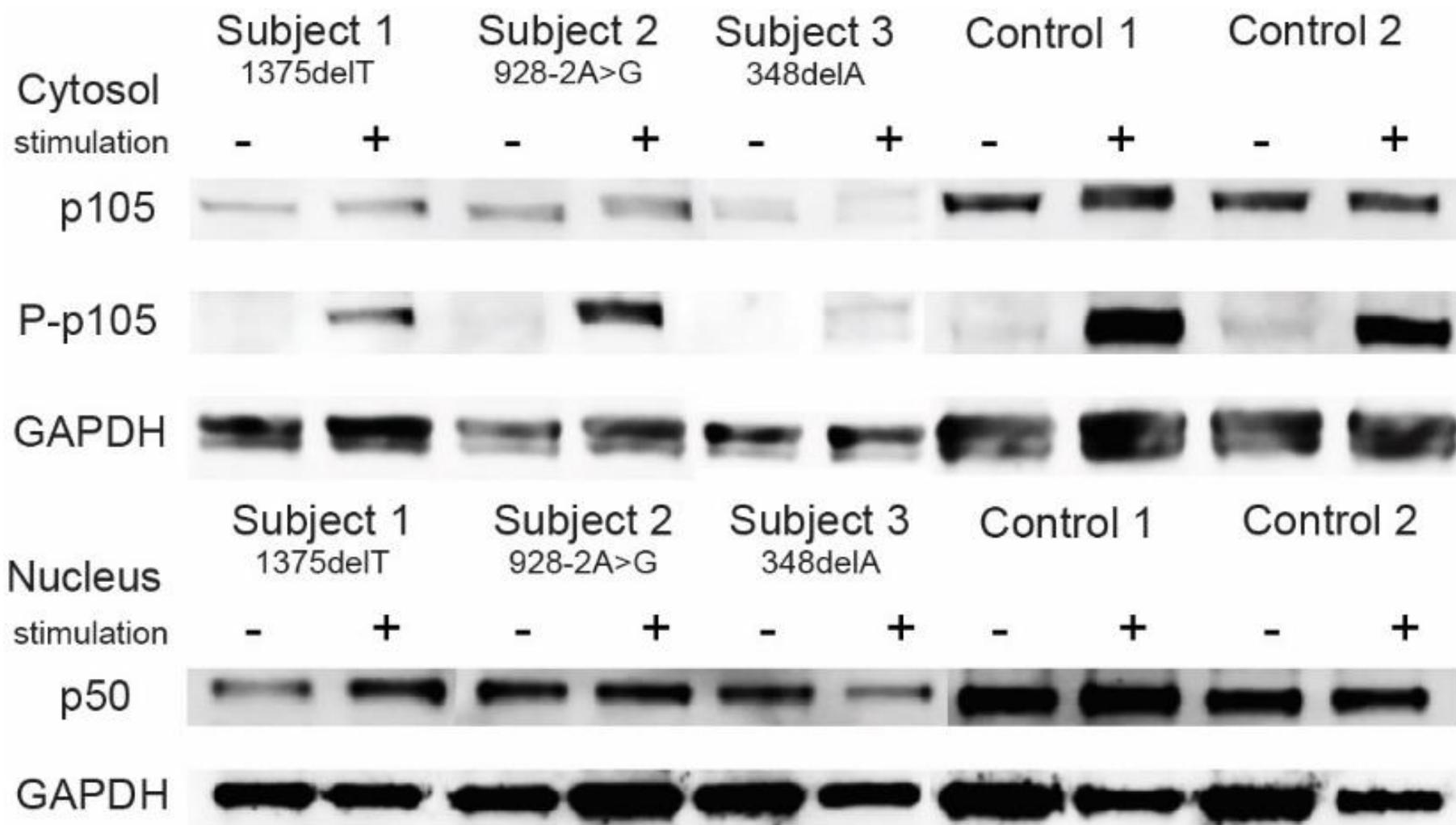
# Not all CVID with *NFKB1* variants develop complications



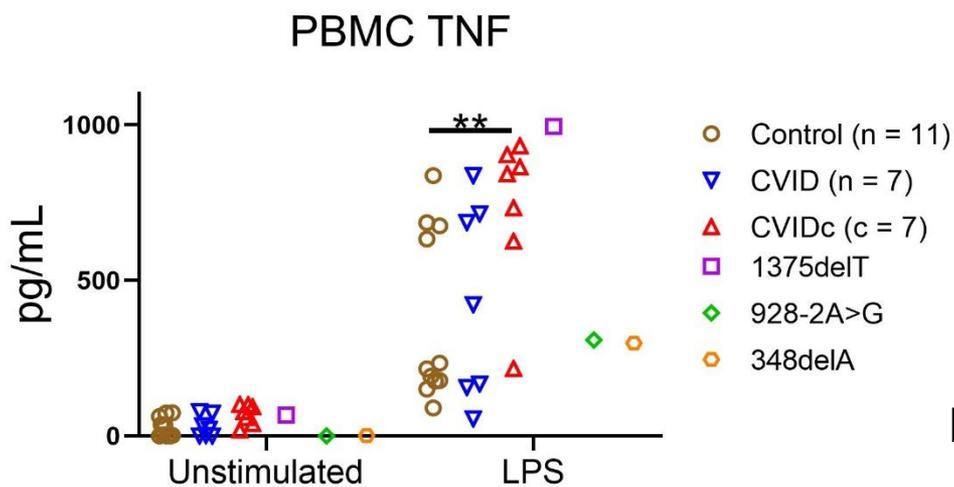
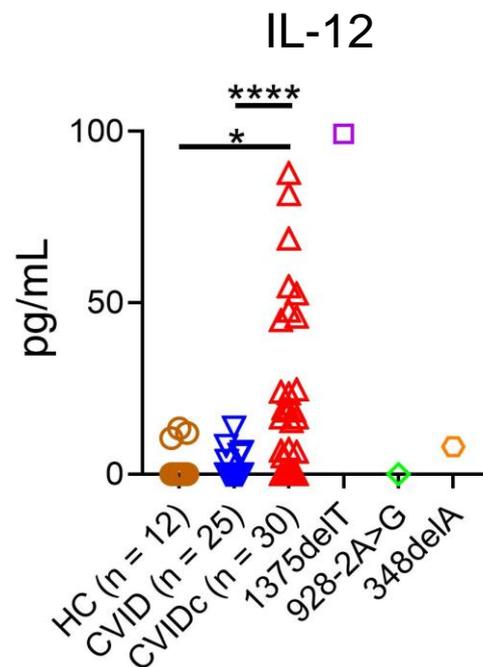
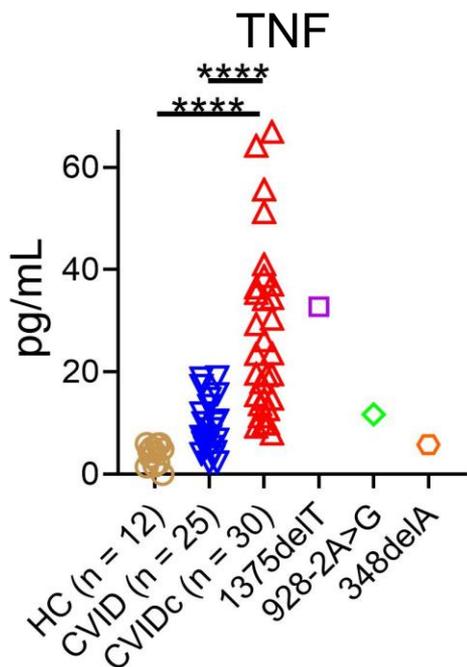
Variant	DX Age	GI Disease	ITP	ILD	Bronchiectasis	Pneumonia
1375delT	11	erosive esophagitis and gastritis, enteritis, and colitis	Y	N	Y	Y
928-2A>G	16	none active (mild intraepithelial lymphocytosis)	Y	N	Y	Y
348delA	27	none active (mild intraepithelial lymphocytosis)	N	N	N	N

Immunoglobulins	Subject 1	Subject 2	Subject 3	Reference Range
IgA	< 5	< 7	< 5	70 - 400 mg/dL
IgG	838 (on IgG replacement)	330	50	700 - 1,600 mg/dL
IgM	< 5	27	10	40 - 230 mg/dL

# *NFKB1* protein expression by 3 CVID variants



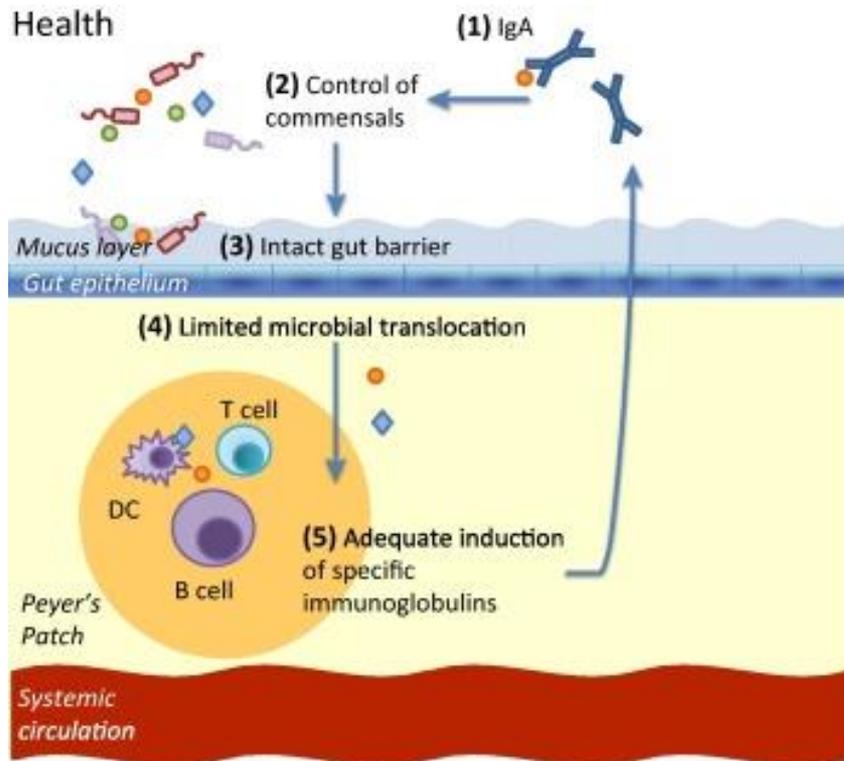
# NF-κB-driven type 1 cytokines are increased in CVID with complications



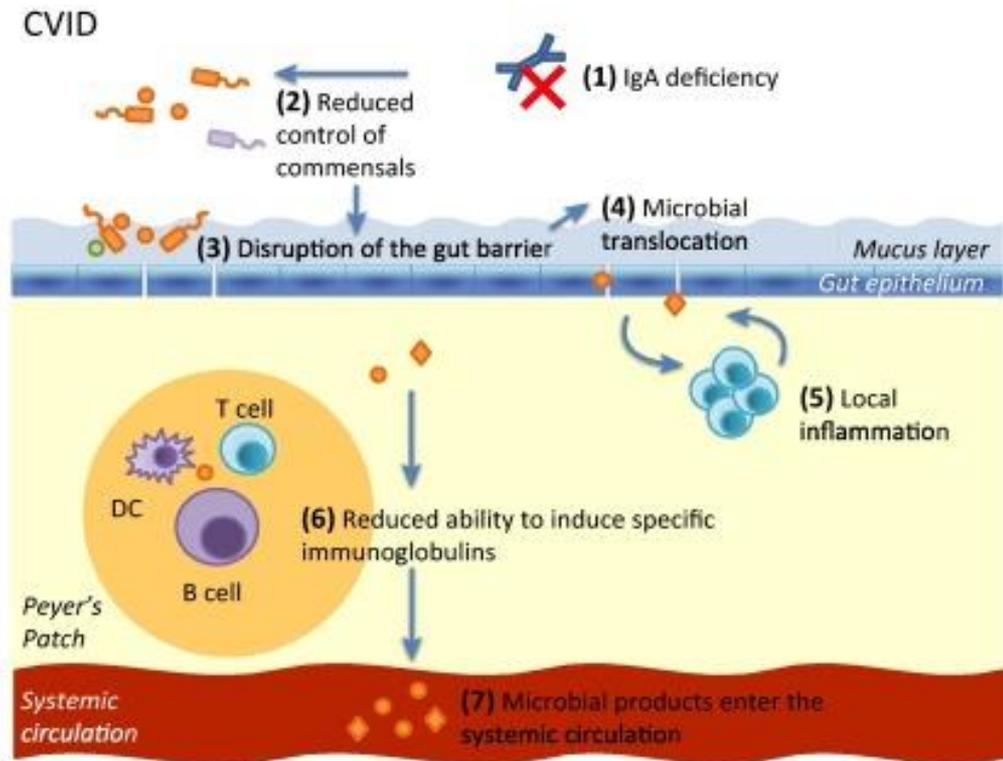
IL-12/IL-18/TNF  
Pattern recognition receptor signaling ↑ ← ?  
ISG ↑ ←

# Microbial Translocation in CVID may drive inflammation

## CVID without complications

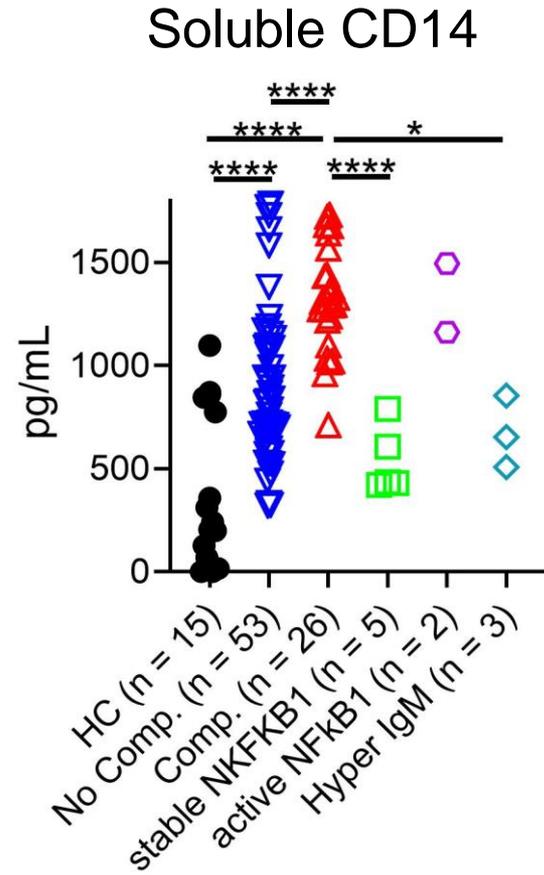
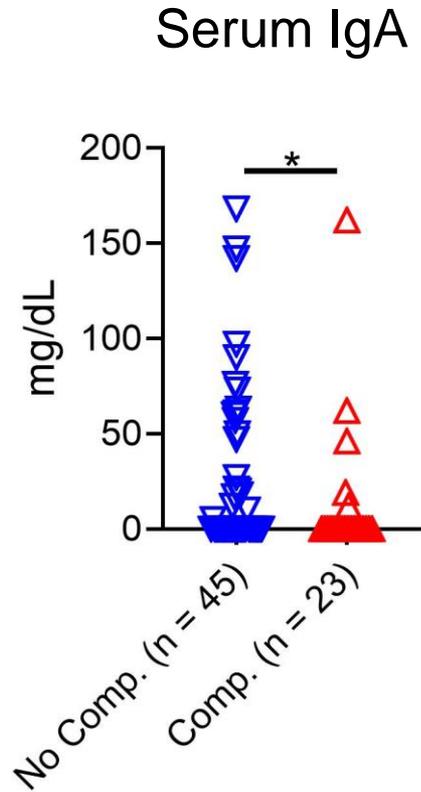


## CVID with complications



Trends in Immunology

# Increased bacterial translocation in CVID with complications



# The extent of B cell maturation defect in CVID determines susceptibility to inflammatory complications

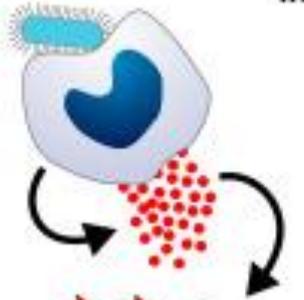
(supported by NIAID K23 and AAAAI Foundation Grant)

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Impaired IgM neutralization of translocating bacteria

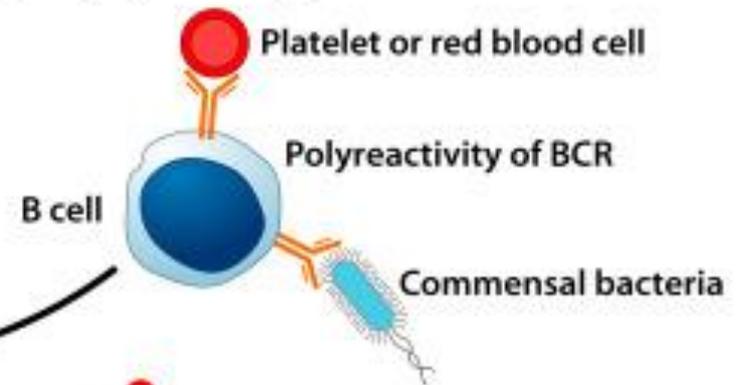


Circulating bacteria stimulate inflammatory cytokine production

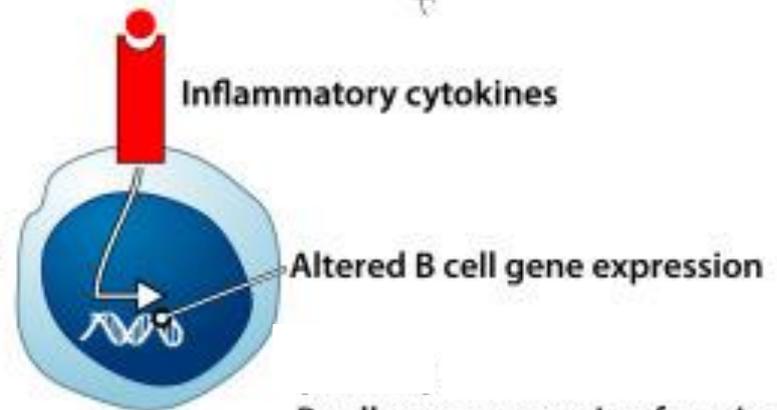


↑ Autoimmune Cytopenias  
↑ Lymphoid Hyperplasia in lungs and mucosal sites

Failure to broaden BCR repertoire beyond polyreactivity



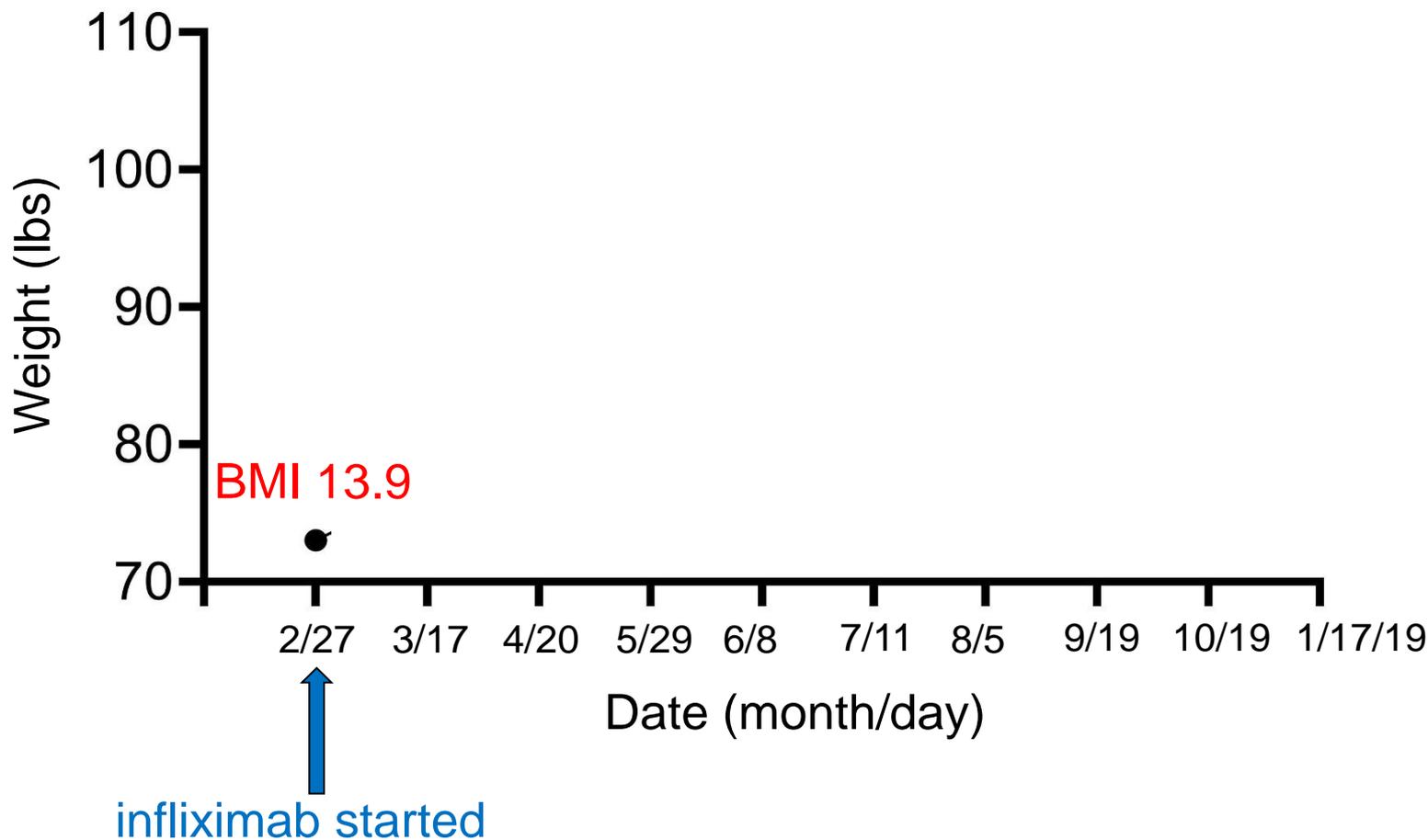
Inflammatory cytokines



B cell gene expression favoring proliferation and survival

# Using TNF antagonism to treat GI disease in a CVID patient with *NFKB1* variant

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# Thank you!

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**Mount  
Sinai**

Gavin Gyimesi

## **Immunology Institute**

Minji Byun

Charlotte Cunningham-Rundles

## **Pathology**

Mabel Ko

Patients and Families



Miranda Abyazi

Kayla Bell

Luke Wallace

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Tom Kepler

## **Center for Regenerative Medicine**

Darrell Kotton

Gustavo Mostoslavsky

## **Funding**

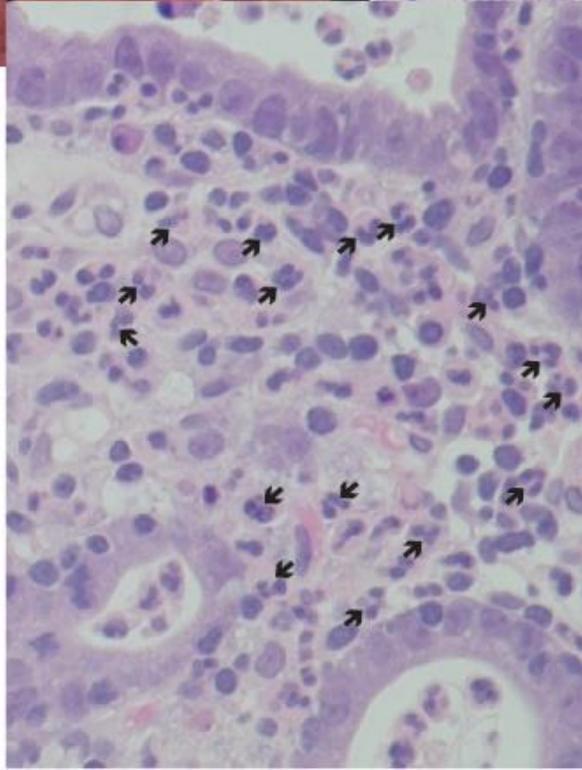
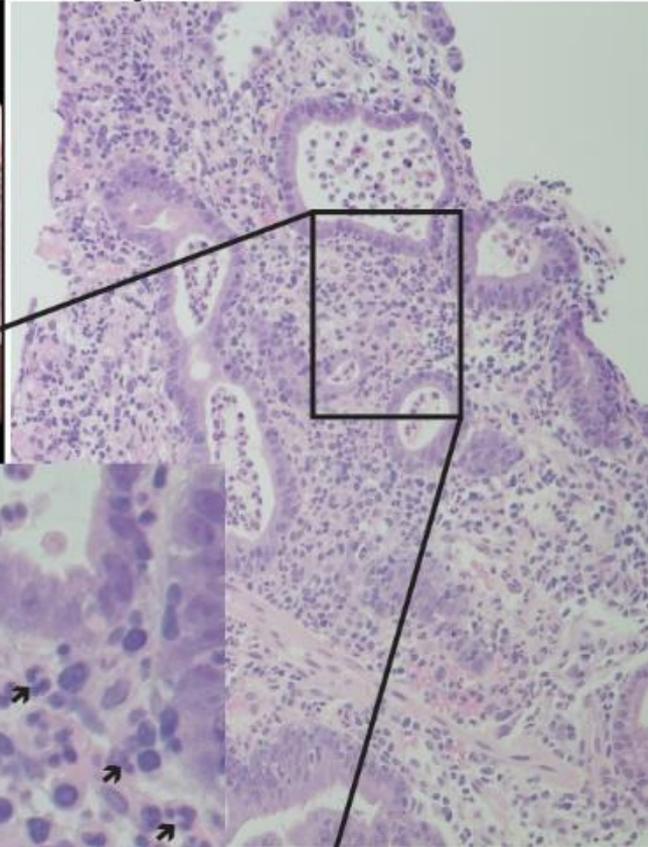
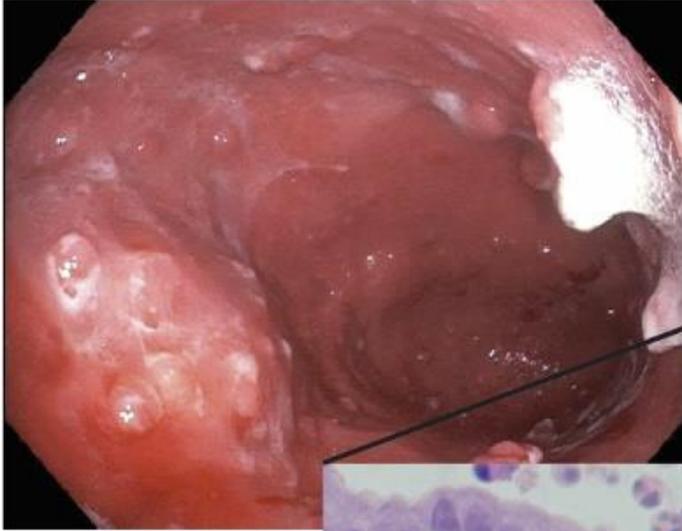


Boston University

Evans Junior Faculty Award

# Neutrophilic gastritis in CVID with 1375delT *NFKB1*

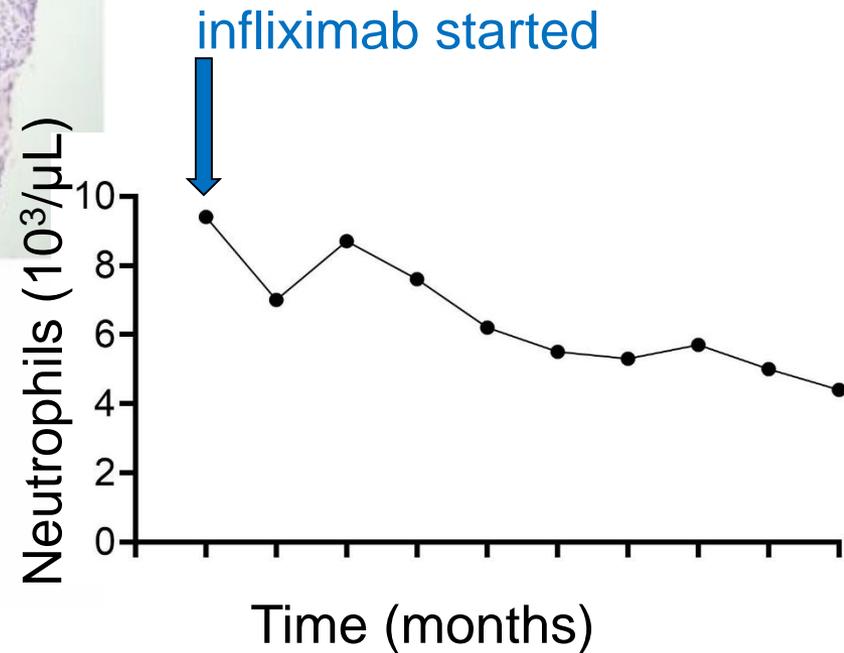
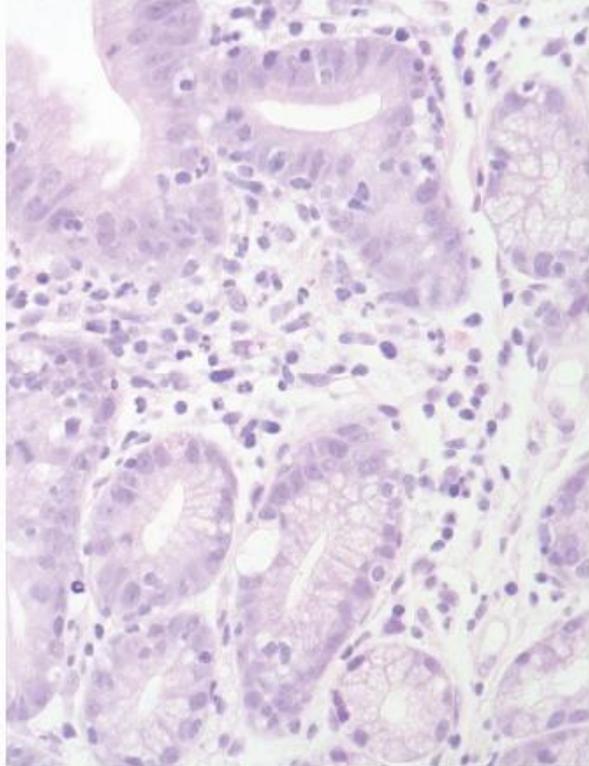
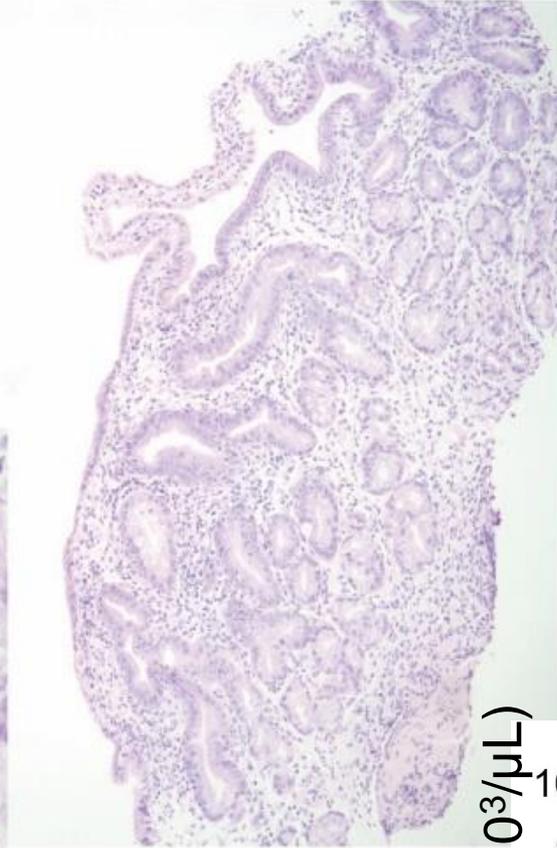
Gastric Body



Combine  
On to one slide

# Resolution of neutrophilic gastritis after infliximab

Gastric Body



# Severe GI disease unresponsive to lymphocyte-targeted therapy in a CVID patient

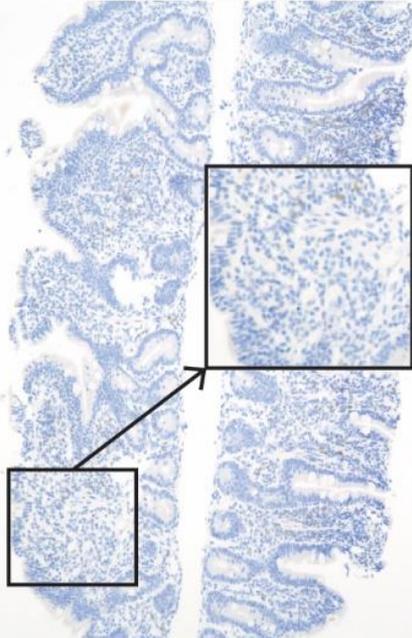
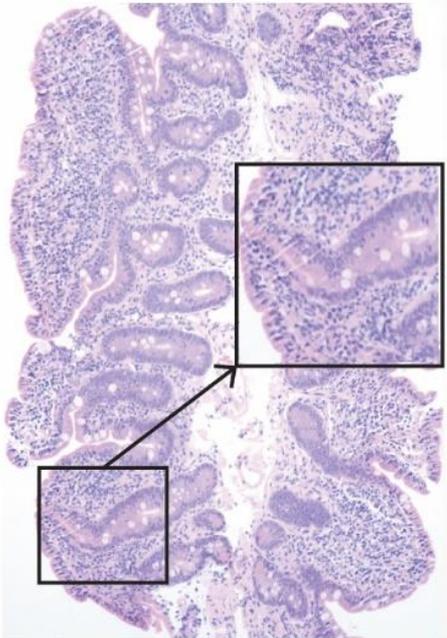
Duodenal Bulb

Proximal Jejunum



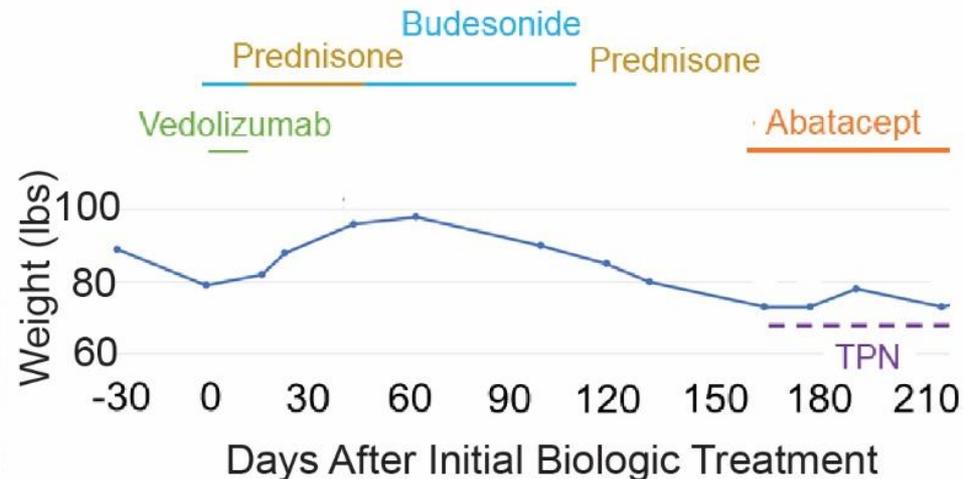
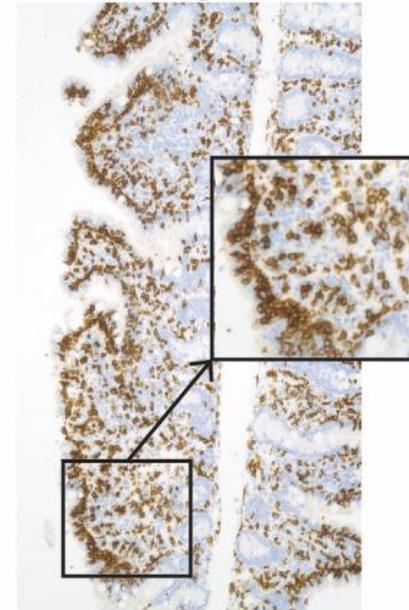
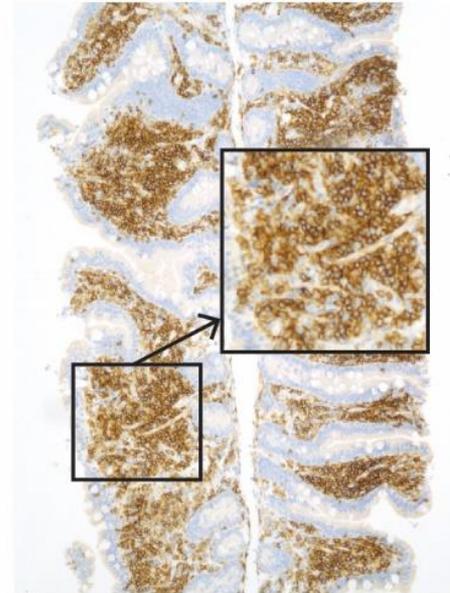
H&E

CD20



CD4

CD8



# **Heterozygous *NFKB1* mutation in CVID**

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Patient was found to have heterozygous mutation of *NFKB1* (1375delT).

*NFKB1* encodes p105 which is processed into p50 to form NF-κB heterodimers that drive inflammatory gene expression. Alternatively, p50 homodimers or unprocessed p105 inhibits NF-κB-mediated transcription.

*NFKB1* mutation has been associated with CVID and severe GI disease.

Dieli-Crimi et al. *Clin Immunol.* 195: 49-59.

*NFKB1* mutations are the among the most common genetic variants found in CVID.

Maffucci et. al. *Front Immunol.* 7: 220.

Tuijnenburg et al. *J Allergy Clin Immunol.* 142: 1285-1296.

Some CVID patients with *NFKB1* mutations develop non-infectious complications, while others do not. There has been no genotype/phenotype correlation defined.

# Summary of results

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CVID patient with 1375delT *NFKB1* variant developed severe GI disease unresponsive to T cell-targeted therapy. Two other CVID *NFKB1* variants were not associated with severe GI disease, but also had severe agammaglobulinemia.

CVID 1375delT *NFKB1* reduced p105 and phosphorylated p105 in association with increased TNF production by PBMCs upon LPS stimulation, to a level corresponding with those produced by PBMCs from CVIDc patients (significantly elevated compared to healthy controls).

Plasma TNF and IL-12 is elevated in 1375delT *NFKB1* CVID at levels comparable to that seen in CVIDc, which is significantly elevated compared to uncomplicated CVID and healthy controls.

TNF antagonism resulted in profound clinical improvement in CVID with 1375delT *NFKB1*, coinciding with reduction of circulating and gastric neutrophils.