

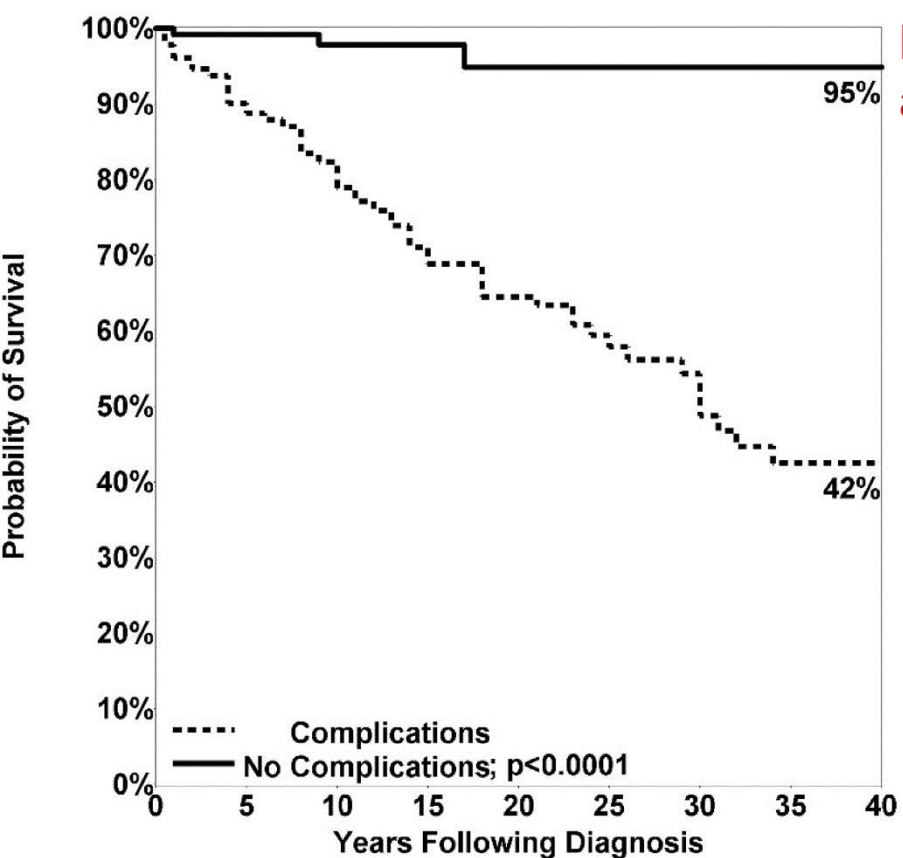
Amplification of NF-kB-driven type 1 cytokines promotes common variable immunodeficiency inflammatory complications

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CVID patients with complications have worsened survival

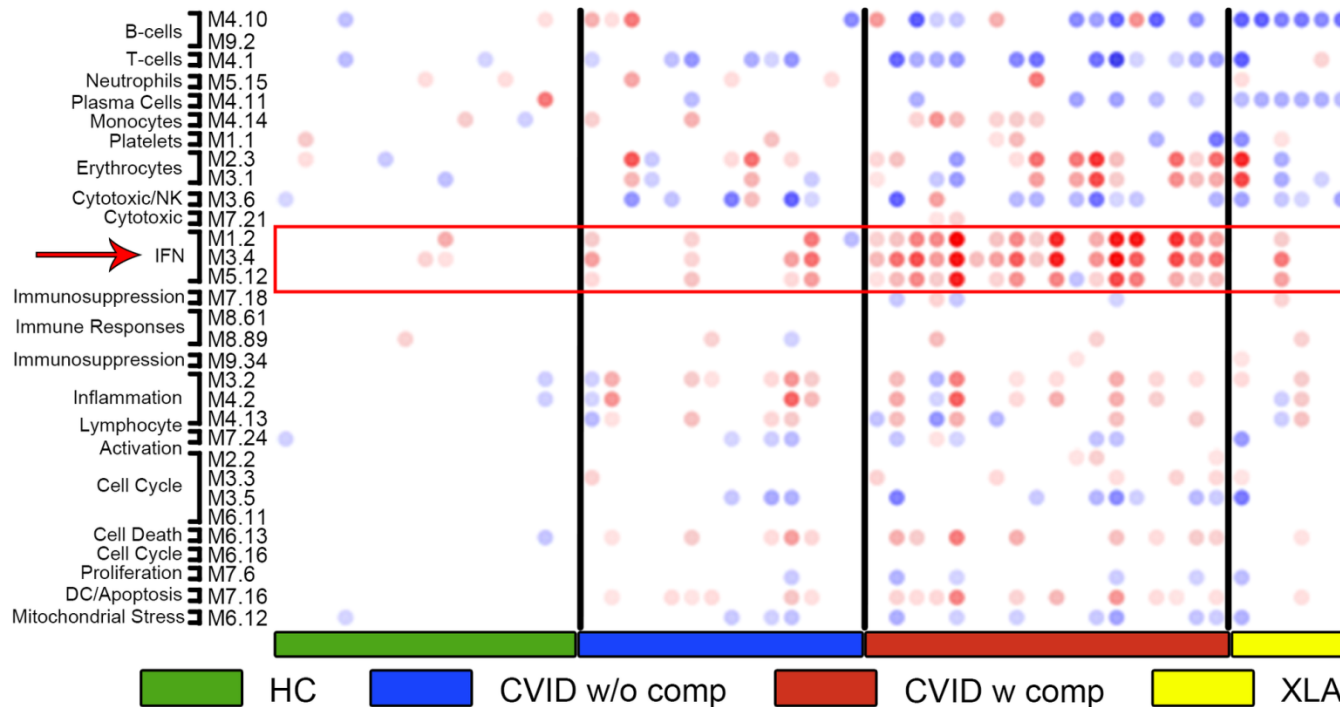
CVID patient survival over time



**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 immune deficiency



Montserrat Cols, PhD,^{a,b} Adeeb Rahman, PhD,^b Paul J. Maglione, MD, PhD,^{a,b} Yolanda Garcia-Carmona, PhD,^{a,b} Noa Simchoni, PhD,^{a,b} Huai-Bin M. Ko, MD,^d Lin Radigan,^{a,b} Andrea Cerutti, MD, PhD,^{a,b} Derek Blankenship, PhD,^c Virginia Pascual, MD,^c and Charlotte Cunningham-Rundles, MD, PhD^{a,b} *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>.

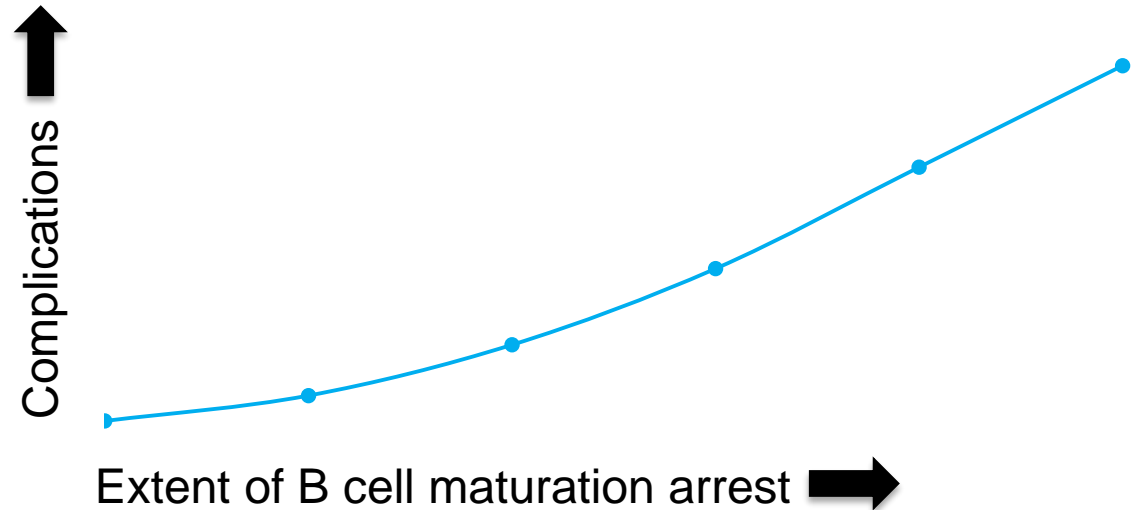
The T_H1 phenotype of follicular helper T cells indicates an IFN- γ -associated immune dysregulation in patients with CD21^{low} common variable immunodeficiency

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

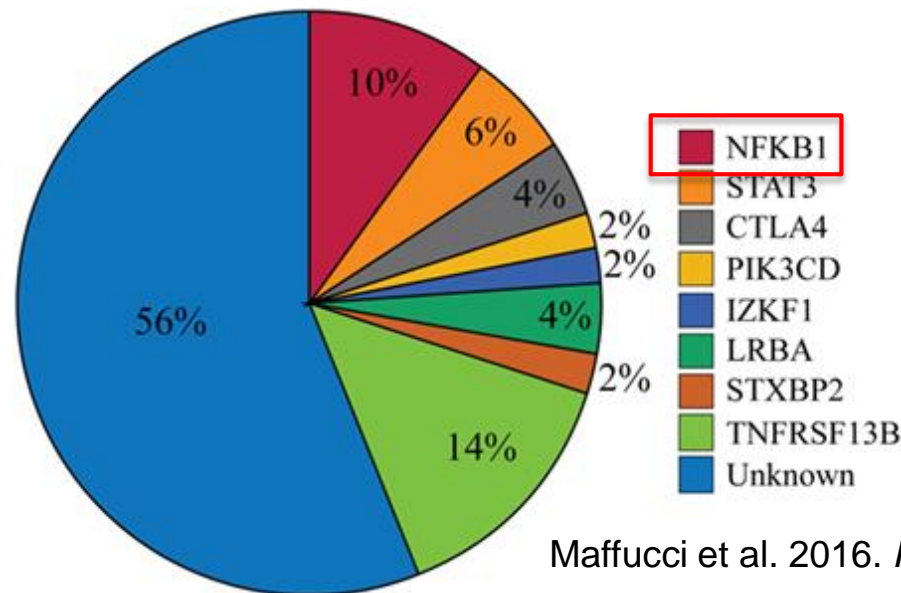


Why do a subset of CVID patients develop this IGS?

Extent of B cell maturation arrest contributes



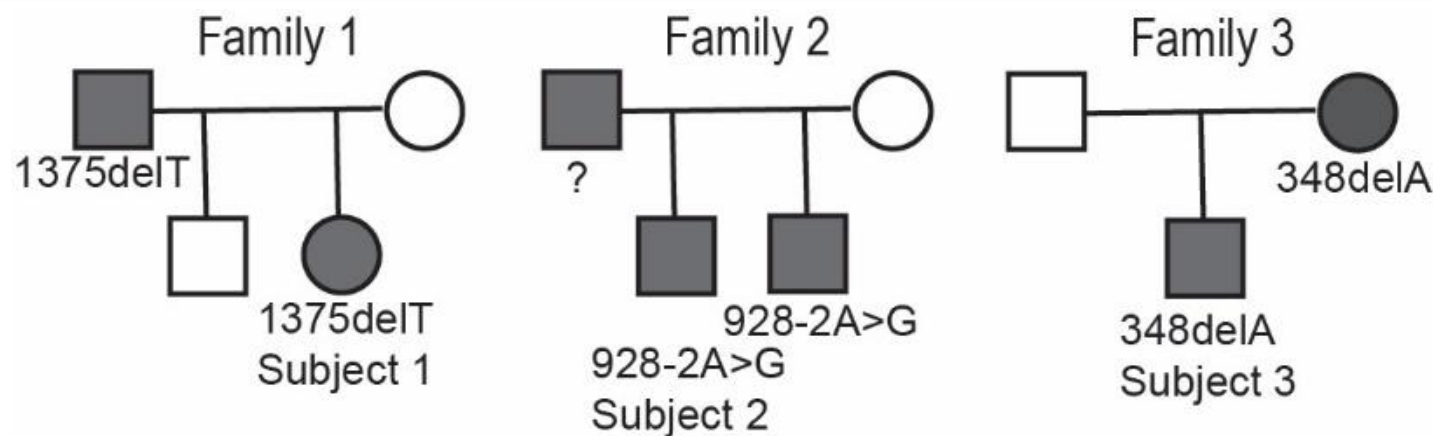
Genetics contributes



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

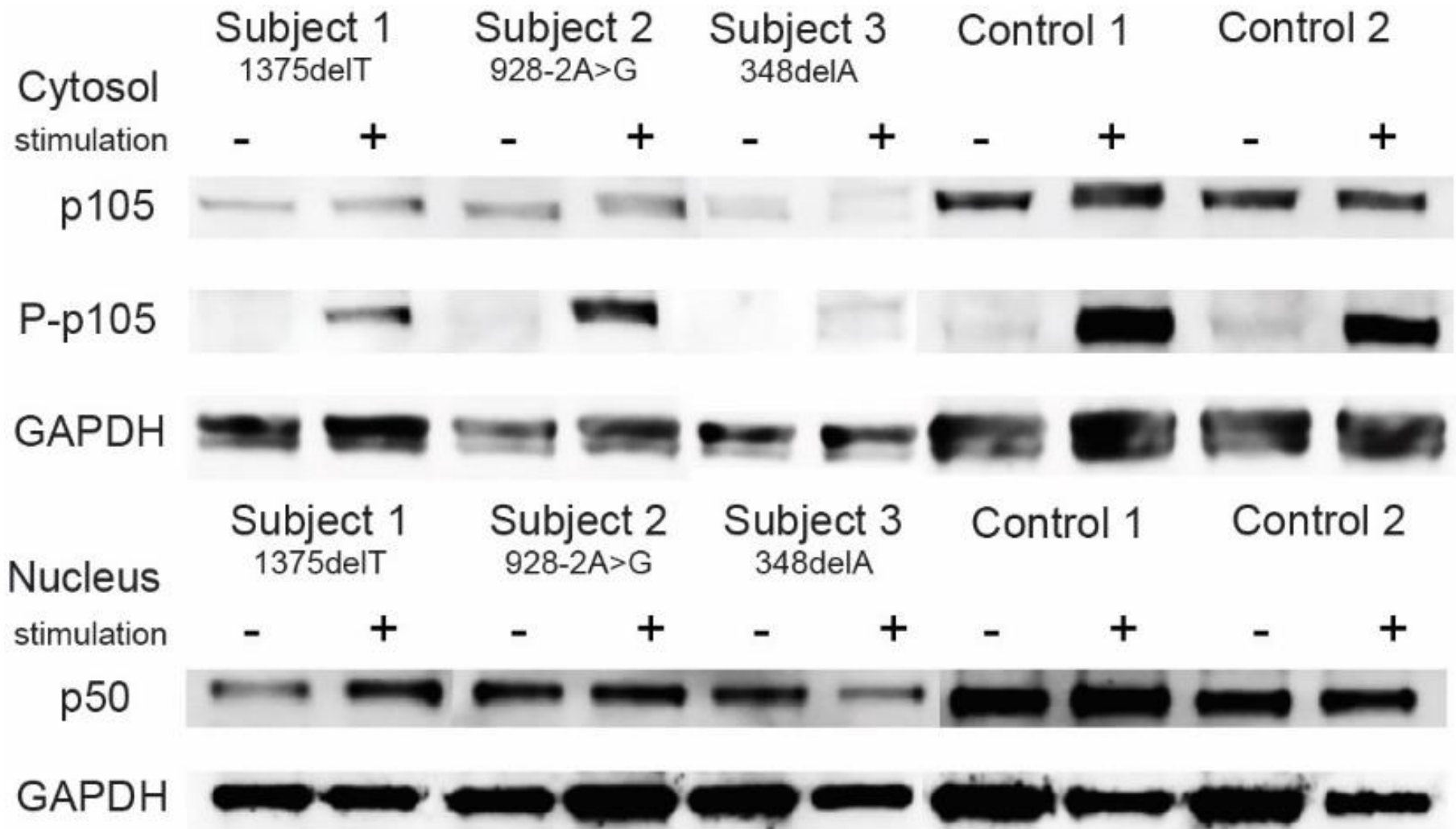
Hypothesis: CVID patients with genetic or immunological characteristics that amplify NF-kB signaling have increased type 1 cytokines and inflammatory complications.

Not all CVID with *NFKB1* variants develop complications

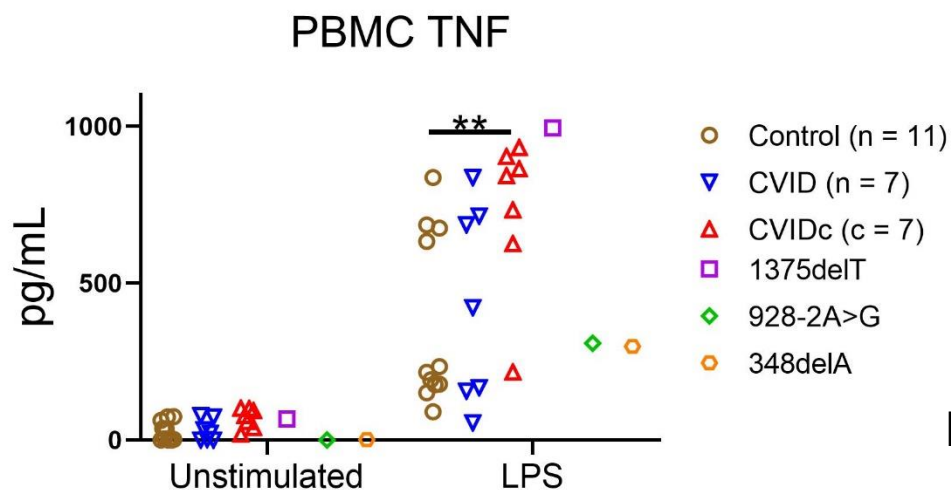
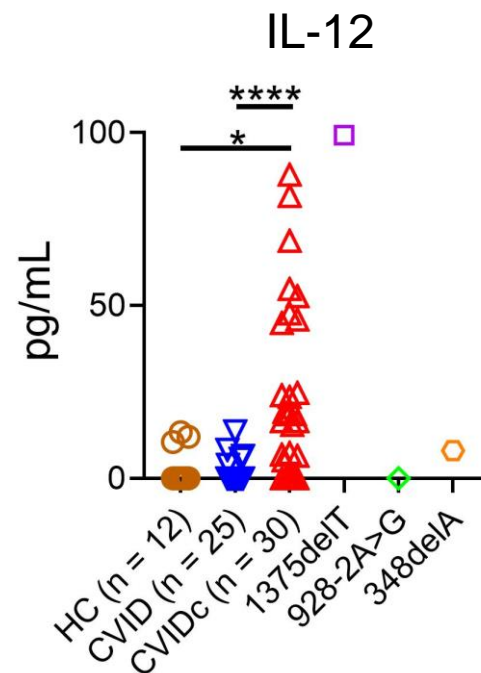
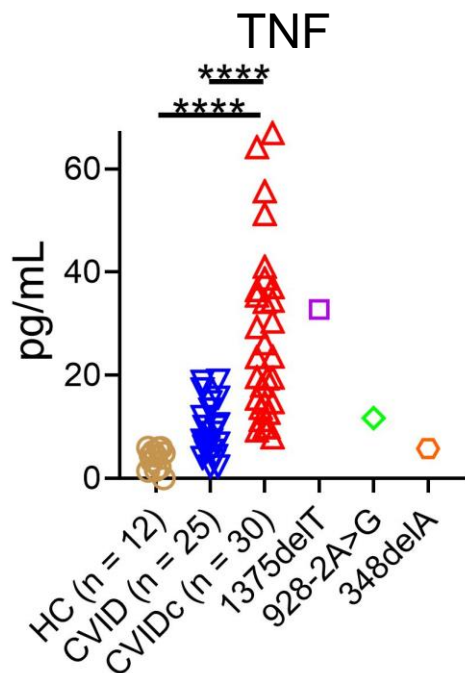


Variant	DX Age	GI Disease	ITP	ILD	Bronchiectasis	Pneumonia
1375delT	11	erosive esophagitis and gastritis, enteritis, and colitis	Y	N	Y	Y
928-2A>G	16	none active (mild intraepithelial lymphocytosis)	Y	N	Y	Y
348delA	27	none active (mild intraepithelial lymphocytosis)	N	N	N	N
Immunoglobulins		Subject 1	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



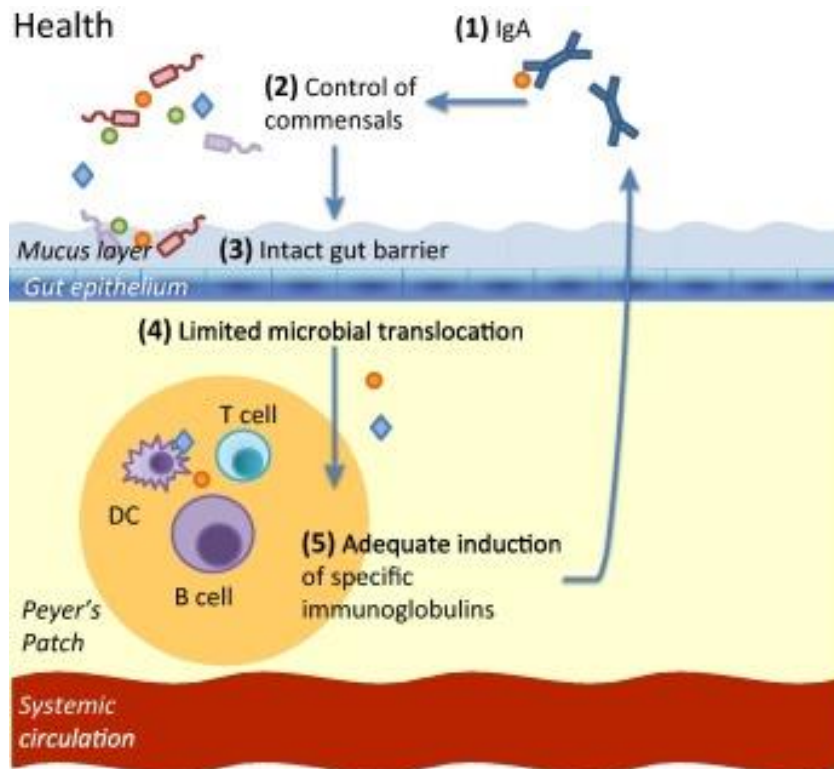
NF- κ B-driven type 1 cytokines are increased in CVID with complications



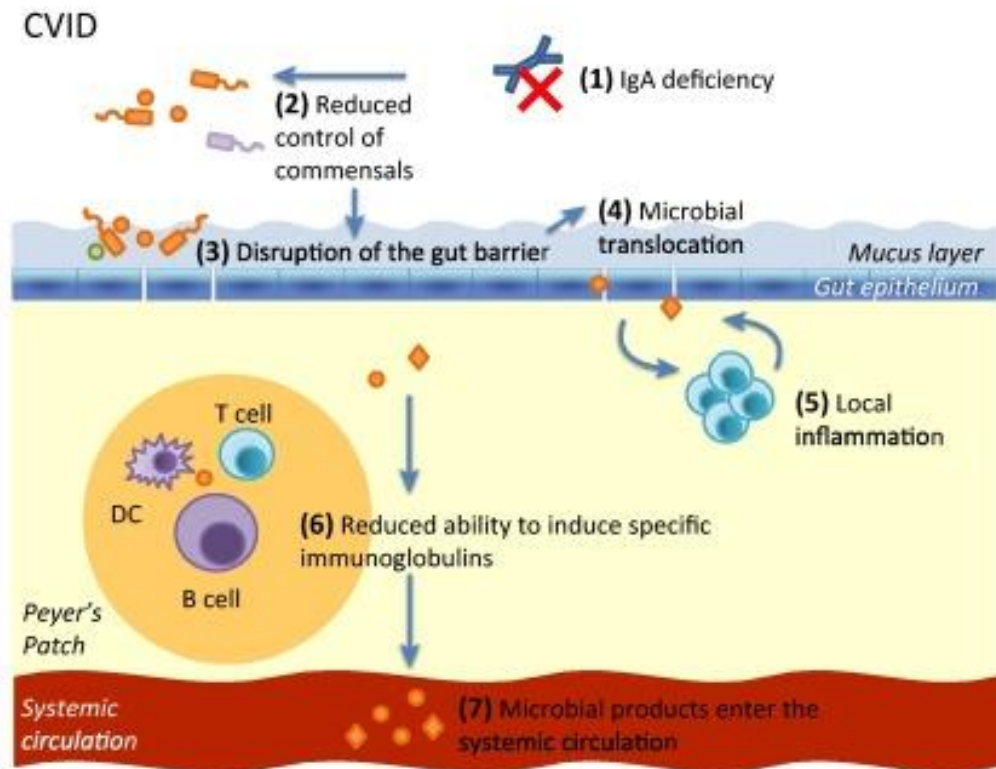
IL-12/IL-18/TNF
ISG \uparrow ← Pattern recognition receptor signaling \uparrow ← ?

Microbial Translocation in CVID may drive inflammation

CVID without complications

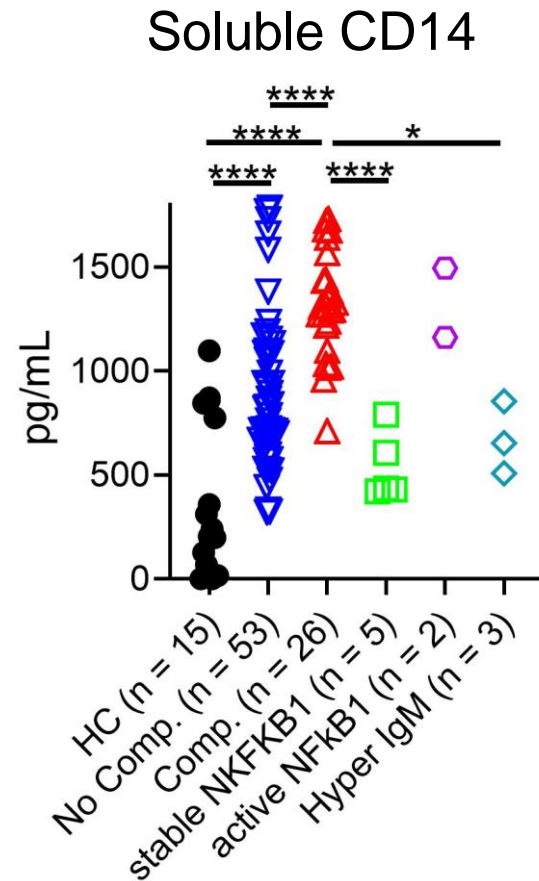
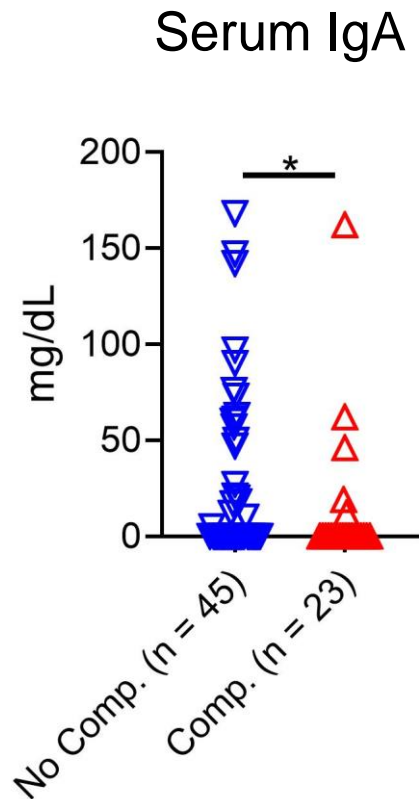


CVID with complications



Trends in Immunology

Increased bacterial translocation in CVID with complications



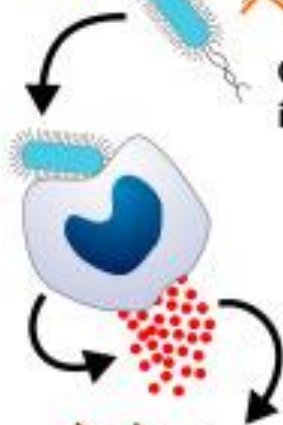
The extent of B cell maturation defect in CVID determines susceptibility to inflammatory complications

(supported by NIAID K23 and AAAAI Foundation Grant)

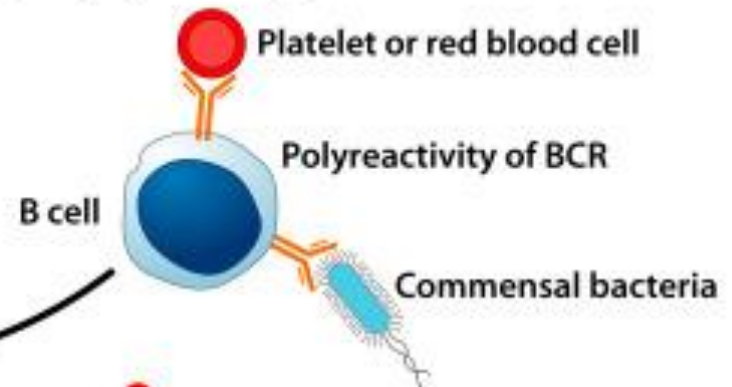
Impaired IgM neutralization
of translocating bacteria



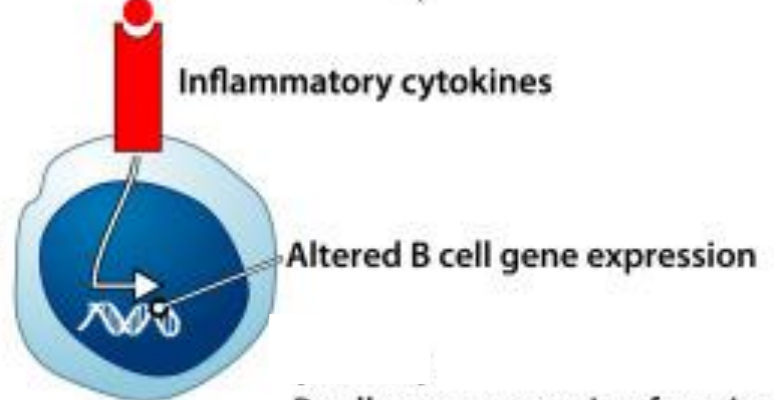
Circulating bacteria stimulate
inflammatory cytokine production



Failure to broaden BCR repertoire
beyond polyreactivity



Inflammatory cytokines

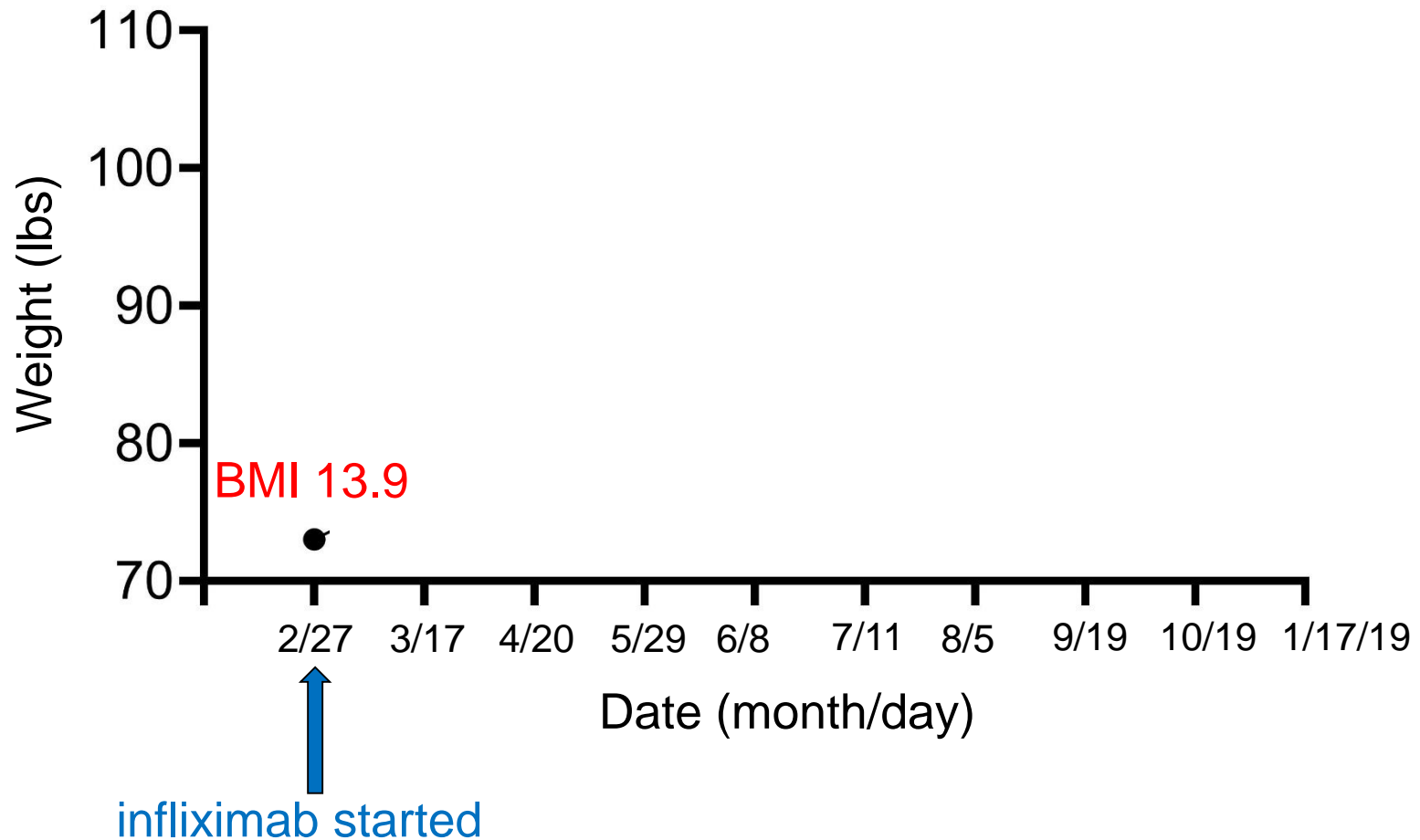


B cell gene expression favoring
proliferation and survival

↑ Autoimmune Cytopenias
↑ Lymphoid Hyperplasia in lungs
and mucosal sites



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



Thank you!



Gavin Gyimesi

Immunology Institute

Minji Byun

Charlotte Cunningham-Rundles

Pathology

Mabel Ko

Patients and Families



Miranda Abyazi

Kayla Bell

Luke Wallace

Pulmonary Center

David Center

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Department of Microbiology

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Tom Kepler

Center for Regenerative Medicine

Darrell Kotton

Gustavo Mostoslavsky

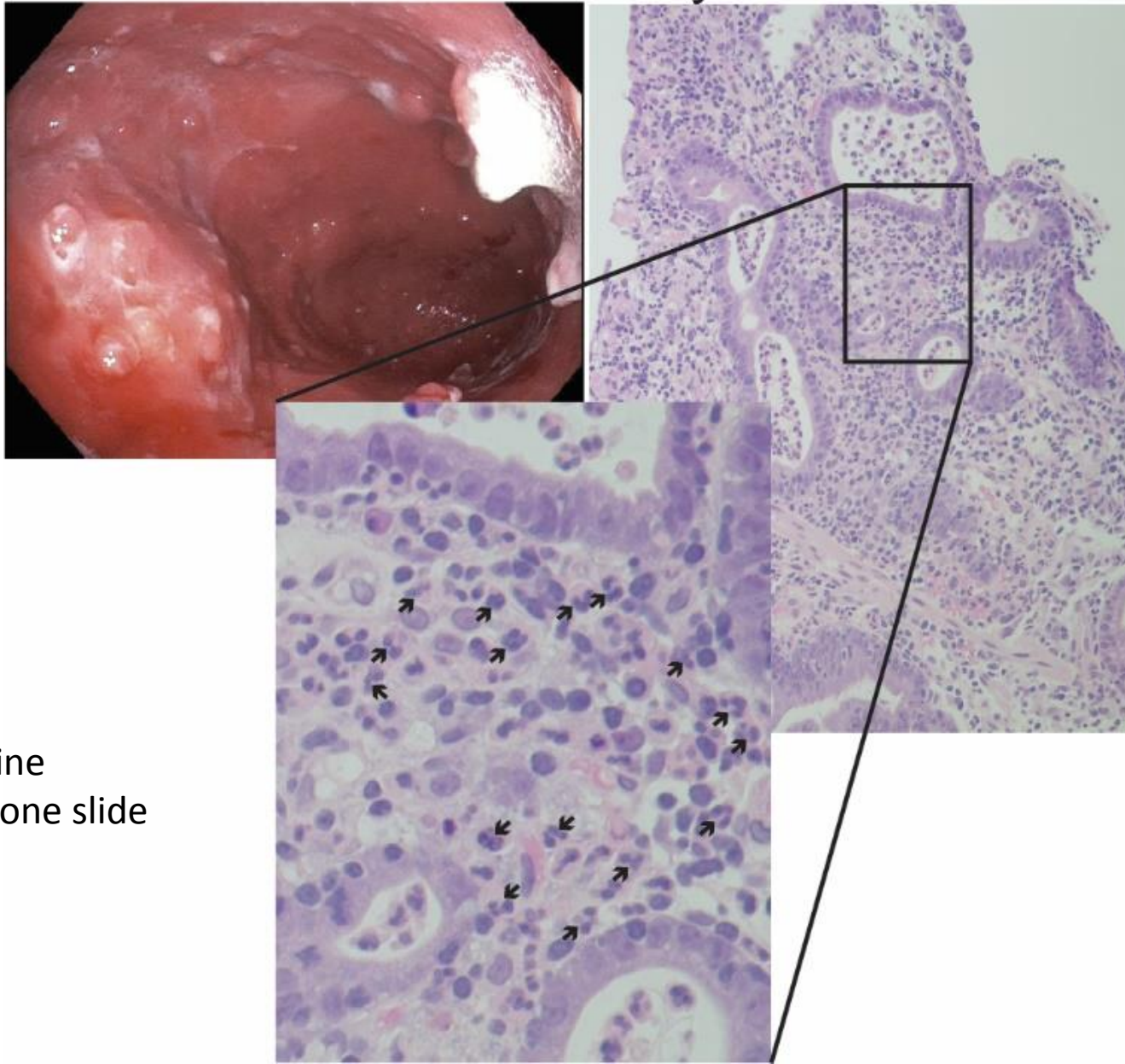
Funding



Boston University
Evans Junior Faculty Award

Neutrophilic gastritis in CVID with 1375delT *NFKB1*

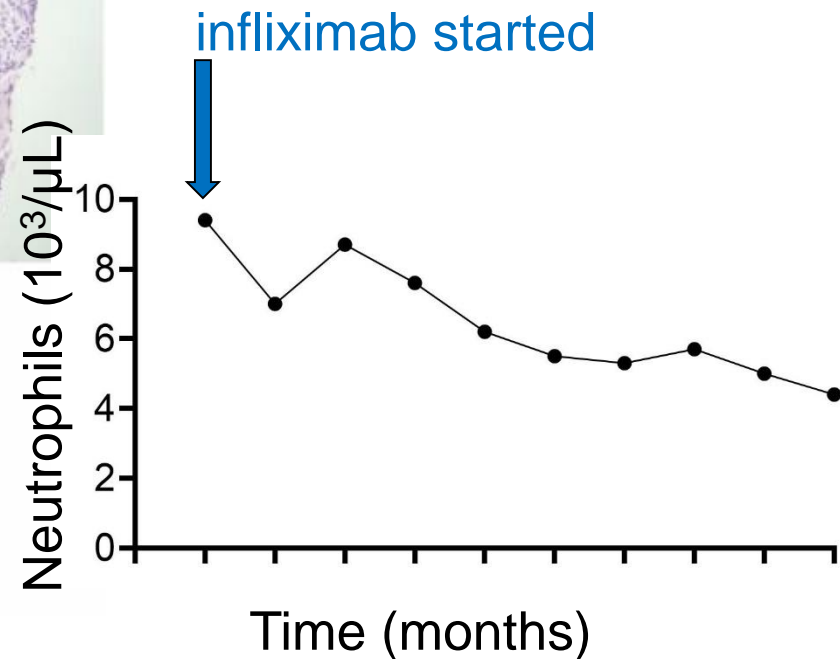
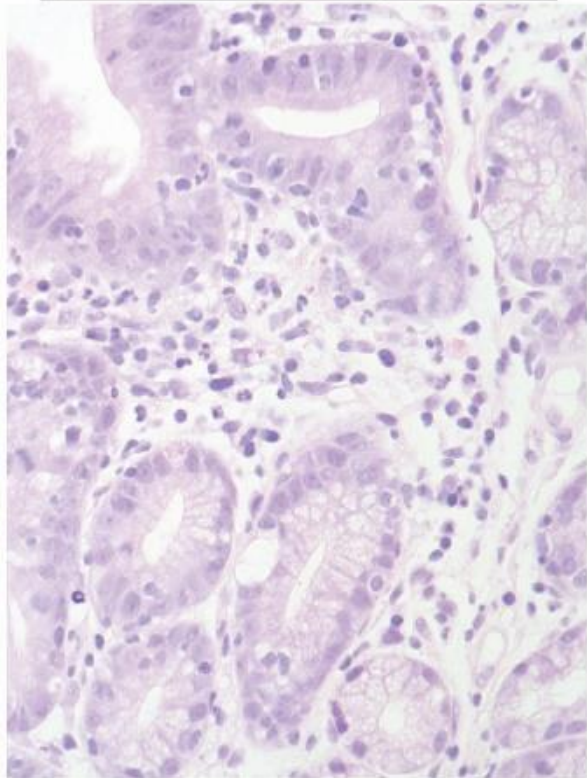
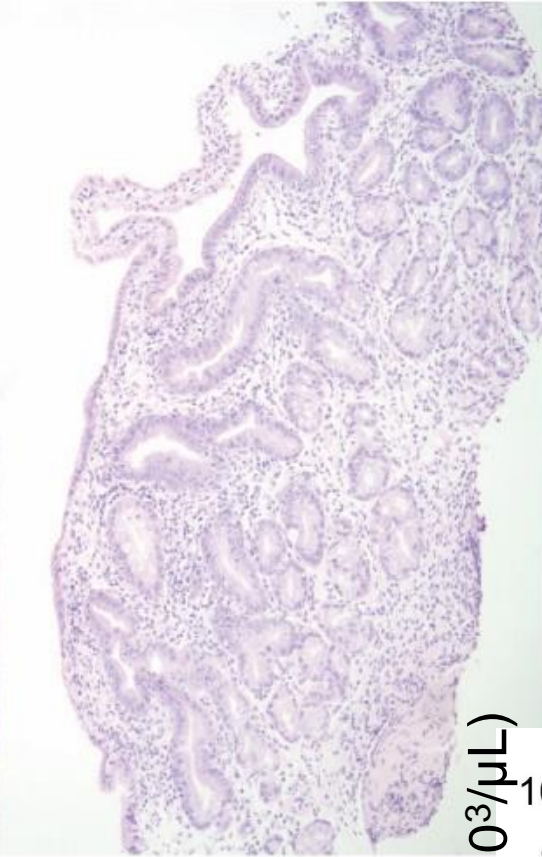
Gastric Body



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

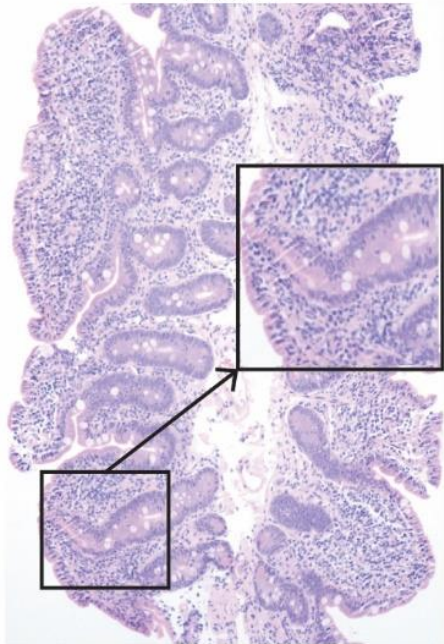
Duodenal Bulb



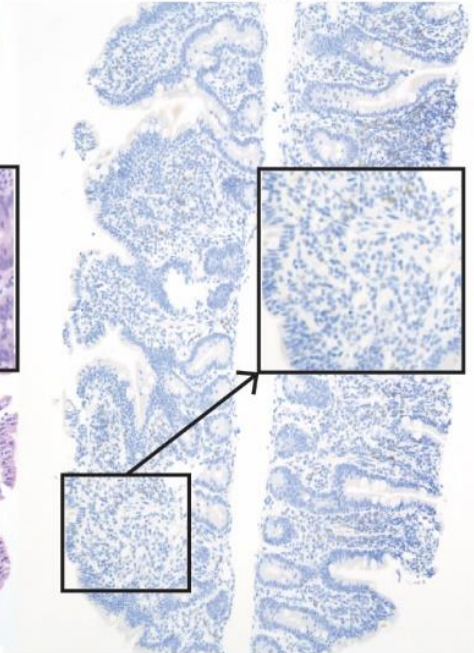
Proximal Jejunum



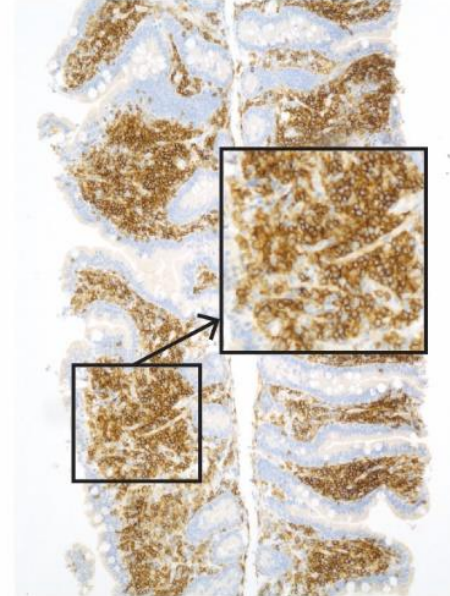
H&E



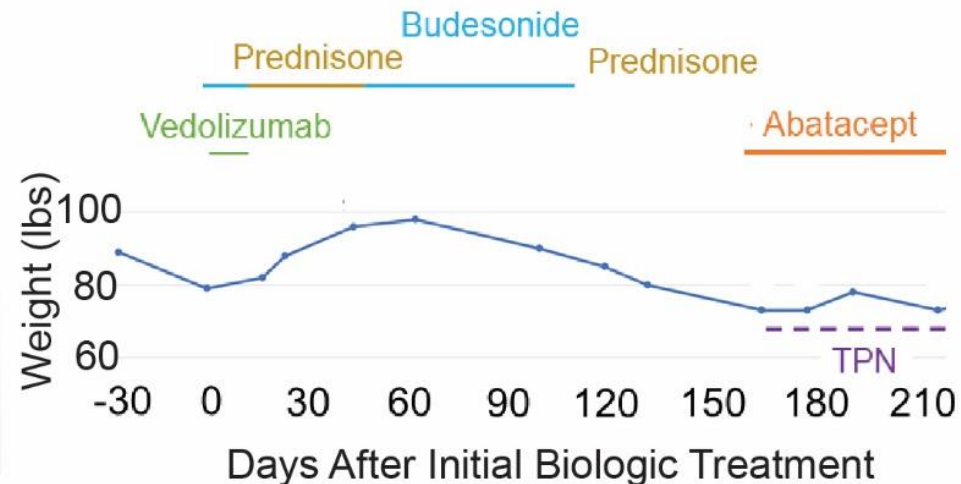
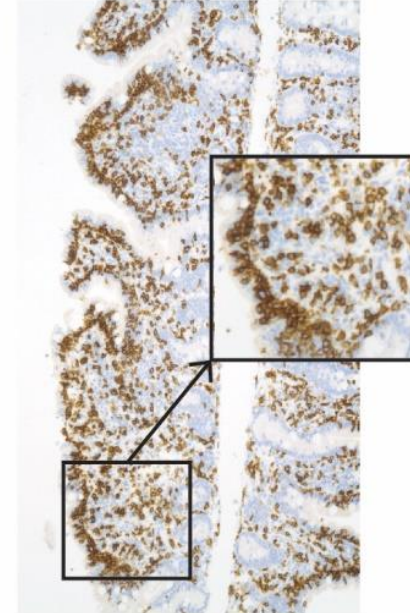
CD20



CD4



CD8



Heterozygous *NFKB1* mutation in CVID

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

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.