

# PMI-2020-10

Thi Tran-Nguyen

08/19/20

## Participant Information

- Sex & birth: Male, 2002
- Diagnosis: Ulcerative Colitis (UC) at 3 yo. 13 yo in remission but flared again.
- Symptoms/phenotype:
  - slight/mod/severe pan-colitis (confirmed through many colonoscopies)
  - current: chronic active UC, intermittent pain and limitation from thrombosed hemorrhoids.
- Point of Contact/relationship to participant: dad is Dr. Might's referral, [REDACTED]
- Molecular data: (no actual report, I got these info from a word.doc)
  - **Whole Exome sequencing (trio):**
    - de novo mutation: ANTXR1, MUC20, CCZ1, ATP6V02, DMBT1, OR4C46, ZNF740, DPF3
    - inherited missense variants: AGER (dad), DMBT1 (mom), IL1R1 (mom), NELL1 (dad)
    - known disease associated variants: (all are heterozygous missense variant): HPS5, ATM, GABRB3, ECI1, NQO1, MYH3, TGIF1, FKRP, HNF4A, PRODH, F11, TBXAS1
  - **Expression data:** IL1R1 is massively upregulated and the downstream genes such as IRAK3, TAK1 and NEMO were much higher than other UC patients.
  - IL1 cytokine is normal
  - Treg genes (such as FOXP3 and IL-10) and other downstream of Treg genes such as SOCS3 are up-regulated.
  - High level of CD34 (suggests active wound/repair processes)
- **In vitro data:** show IL1 secretion in macrophage cells in response to LPS and ATP stimulation is higher than his parents. His IL-10-mediated suppression results were normal.

### **Past Meds**

- initially good response with sulfasalazine and fish oil when he was in remission but then flared again in 2015
- steroids, 6-mercaptopurine (6MP) and infliximab (no effect)
- vancomycin tried in 2016, initial improvement but reverted
- Rifaximin temporarily worked but then stopped
- PR meds (medication administered per rectum) : no effects, such as including cortisone enemas, cortifoam, canasa suppos. uceris.

### **Current Meds**

- Vedolizumab 300mg q 4-8 weeks (not much effect)
- Tacrolimus: 2.5 bid (improve symptoms a lot but didn't produce remission)
- Balsalazide: 3 capsules tid (750 mg each)
- Hydrocortisone Acetate suppositories 25mg: bid
- IC Sulfamethoxazole-TMP DS: one capsule three times a week

### **Complementary Meds**

- Indigo: 3 capsules bid
- Curcumin: 4 capsules bid
- Fish oil: one capsule once a day (1280 mg)
- Flaxseed oil: one capsule once a day (1000 mg)
- Probutyrate: 6 capsules bid (300 mg per capsule)
- L-carnitine: one capsule once a day (680 mg per capsule)
- Vitamin D3: one capsule per day (1,000 IU)
- CoQ10: one capsule once per day (100 mg)

# Current Status

- No blood in stools since ~ January 2017
- 4-6 BM/day
- Intermittently painful hemorrhoids (not active past 2 weeks except for mild/mod discomfort with BMs)
- Uses medical marijuana for appetite and decreased frequency (very effective), although has had some allergic symptoms (nasal congestion)
- Exercises--rigorous daily routine (has been somewhat intermittent past month with increased discomfort)
- He made it through senior year with help of a 504, enabling him to have flexibility in attending classes, and to not have early morning classes

# Diet

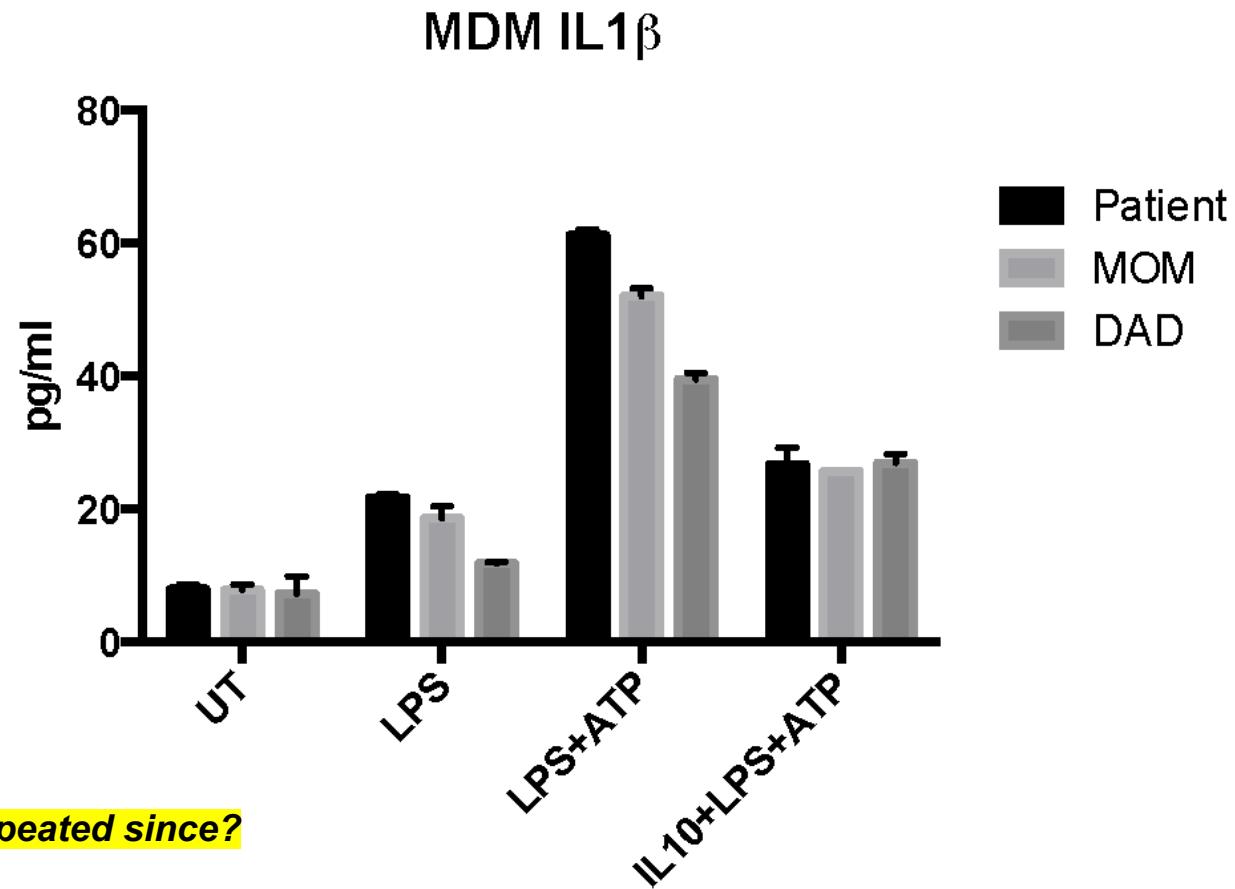
- Diet is impeccable--olive oil only, no fried foods, virtually no prepared foods, fruits, vegetables, protein, nut butter smoothies

# Labs

Showing results from (2/3/2020 - 5/14/2020) [Show more results](#)

Lab View	2/3/2020 18:34 EST	2/3/2020 18:48 EST	3/3/2020 17:48 EST	4/1/2020 17:00 EDT	5/14/2020 19:05 EDT
<b>Hematology</b>					
WBC	12.48 H		15.15 H	15.08 H	15.02 H
Hemoglobin	11.2 L		12.8	12.5	13.0
Hematocrit	33.2		38.4	36.9	38.1
Platelet	346 H		381 H	353 H	353 H
MPV	9.9 H		9.2 H	9.9 H	9.5 H
RBC	3.82		4.36	4.22	4.51
MCV	86.9		88.1	87.4	84.5
MCH	29.3		29.4	29.6	28.8 L
MCHC	33.7		33.3 L	33.9	34.1
Red Cell Distribution with CV	12.2		12.3	12.1	12.2
Nucleated Red Blood Cell %	0.0		0.0	0.0	0.0
Nucleated Red Blood Cell Count	0.00		0.00	0.00	0.00
Absolute Neutrophil Count	3.51 L		6.51	7.72 H	7.61 H
Absolute Lymphocyte Count	7.76 H		6.24 H	4.86 H	5.57 H
Absolute Eosinophil Count	0.44 H		1.45 H	1.52 H	0.83 H
Absolute Basophil Count	0.00 L		0.27 H	0.07 H	0.08 H
Absolute Monocyte Count	0.66		0.53	0.86 H	0.88 H
Absolute Immature Granulocyte Count				0.05	0.05
Neutrophil/Band	28.1 L		43.0 L	51.2	50.7
Immature Granulocytes				0.3	0.3
Lymphocyte	62 H		41 H	32.2	37.1 H
Monocyte	5.3		3.5 L	5.7	5.9
Eosinophil	3.5		9.6 H	10.1 H	5.5 H
Basophil	0.0		1.8 H	0.5	0.5
Atypical Lymphocyte	0.9		0.9		
Cells Counted, Manual Differential	114		114		
Microcytosis, RBC	1+				
Ovalocytes, RBC	1+				
ESR (Erythrocyte Sedimentation Rate)	16		27	24	31 H
<b>Chemistry</b>					
BUN	20 H		14	20 H	17
Creatinine	0.58 L		0.83	0.65	0.85
AST (Aspartate Aminotransferase)	39 (f)		22	30	26
ALT	12 (f)		9	14	13
GGTP (Gamma Glutamyl Transpeptidase)	11 (f) L		13 (f)	15 (f)	13 (f)
Vitamin B12	723				
C-Reactive Protein	0.05		0.04	0.07	0.10
<b>Therapeutic Drug Monitoring/Toxicology</b>					
Ferritin	27.8				
TIBC (Iron Binding Capacity, Total)	346				
Transferrin	247				
Iron, Plasma	71 (f)				
Zinc		61			
<b>Endocrinology</b>					
25-Hydroxy Vitamin D		33.5			

# *in-vitro* data



*Scott Snapper's 2017 Studies*

**note: perhaps this assay has been repeated since?**

# Whole Exome Sequencing findings

## De novo mutation candidates

CHROM	POS	MOTHER_GT	FATHER_GT	CHILD_GT	GENE	COMMENT
2	69420574	GTC/GTC	GTC/GTC	GTC/G	ANTXR1	Splice site
3	195452980	T/T	T/T	T/C	MUC20	
7	5941354	C/C	T/T	C/C	CCZ1	one copy loss?
7	5941411	G/G	A/A	G/G	CCZ1	one copy loss?
7	5944687	C/C	A/A	C/C	CCZ1	one copy loss?
8	87126039	CTA/CTA	CTA/CTA	CTA/C	ATP6V02	Frameshift deletion
10	124345796	C/C	G/G	G/G	DMBT1	one copy loss?
10	124351954	G/G	A/A	A/A	DMBT1	one copy loss?
11	51515546	G/G	G/G	G/T	OR4C46	
12	53581456	C/C	C/C	C/CCGG	ZNF740	
14	73159872	A/A	A/A	A/C	DPF3	Coding

### Gene level: Are there evidence that these genes are associated with UC?

- none of these genes have been curated by Clingen (gene-disease relationship), or Clingen dosage sensitivity map
- transcript search: none of these variants in Clinvar
- OMIM: MUC20 gene expression is correlated with UC (need to check this gene in his microarray data)

# Whole Exome Sequencing findings

## De novo mutation candidates:

### ANTXR1 (splice site)

**ANTXR1** ANTXR cell adhesion molecule 1

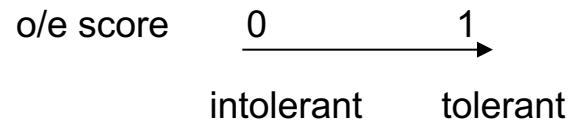
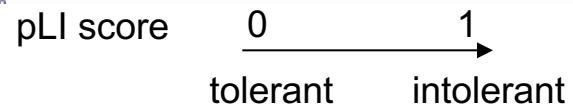
Dataset gnomAD v2.1.1 ▾ gnomAD SVs v2.1 ▾ ?

Genome build GRCh37 / hg19  
Ensembl gene ID ENSG00000169604.15  
Ensembl canonical transcript ⓘ ENST00000303714.4  
Region 2:69240310-69476459  
References Ensembl, UCSC Browser, and more

#### Constraint ⓘ

Category	Exp. SNVs	Obs. SNVs	Constraint metrics
Synonymous	118	142	Z = -1.74 o/e = 1.2 (1.05 - 1.38) 0 → 1
Missense	316.1	240	Z = 1.52 o/e = 0.76 (0.68 - 0.84) 0 → 1
pLoF	35	5	pLI = 0.99 o/e = 0.14 (0.07 - 0.3) 0 → 1

exome  genome Metric: Mean



# Whole Exome Sequencing findings

## De novo mutation candidates:

### ANTXR1 (splice site)

**gnomAD browser**

gnomAD v2.1.1 | Search

gnomAD collection published in Nature!

**Deletion: 2-69420574-GTC-G (GRCh37)**

Filter	Exomes	Genomes	Total
Alliee Count	4918	26	4944
Alliee Number	148810	24696	173506
Alliee Frequency	0.03305	0.001053	0.02849
Popmax Filtering AF (95% confidence)	0.04690	0.001814	
Number of homozygotes	0 *	0	0 *

**Warning** Up to 1 individuals called as heterozygous for this variant have a skewed allele balance which suggests that some may actually be homozygous for the alternative allele. [More details](#).

**Note** This variant is found in a low complexity region.

This variant is multiallelic. Other alt alleles are:

- 2-69420574-G-GTC
- 2-69420574-G-GTCTC
- 2-69420574-G-GTCTCTC
- 2-69420574-G-GTCTCTCTC
- 2-69420574-GTCTC-G

#### Population Frequencies

Population	Allele Count	Allele Number	Number of Homozygotes	Allele Frequency
Overall	3036	75052	0	0.04045
Swedish	1094	13962	0	0.07836
Southern European	441	6556	0	0.06727
Bulgarian	80	1518	0	0.05270
▼ European (non-Finnish European)	760	18966	0	0.04007
North-western European	656	30182	0	0.02173
Estonian	5	3868	0	0.001293
Male	1762	41884	0	0.04207
Female	1274	33168	0	0.03841
▼ European (Finnish)	553	14330	0	0.03859
▼ Ashkenazi Jewish	213	5542	0	0.03843
▼ South Asian	399	18608	0	0.02144
▼ Other	93	4436	0	0.02096
▼ Latino	452	22282	0	0.02029
▼ East Asian	102	14808	0	0.006888
▼ African	96	18448	0	0.005204
Male	2788	93578	0	0.02979
Female	2156	79928	0	0.02697
<b>Total</b>	<b>4944</b>	<b>173506</b>	<b>0</b>	<b>0.02849</b>

Include:  Exomes  Genomes

# Whole Exome Sequencing findings

## De novo mutation candidates

### MUC20 (missense)

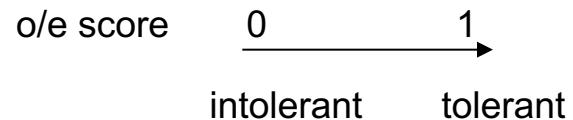
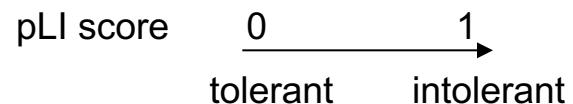
MUC20 mucin 20, cell surface associated

Dataset gnomAD v2.1.1 ▾ gnomAD SVs v2.1 ▾ ?

Genome build GRCh37 / hg19  
Ensembl gene ID ENSG00000176945.12  
Ensembl canonical transcript ⓘ ENST00000447234.2  
Region 3:195447753-195467994  
References Ensembl, UCSC Browser, and more

#### Constraint ⓘ

Category	Exp. SNVs	Obs. SNVs	Constraint metrics
Synonymous	121.2	136	Z = -1.05 o/e = 1.12 (0.97 - 1.29) 0 ⚡ 1
Missense	271.6	268	Z = 0.08 o/e = 0.99 (0.89 - 1.09) 0 ⚡ 1
pLoF	9.6	5	pLI = 0 o/e = 0.52 (0.27 - 1.1) 0 ⚡ 1



# Whole Exome Sequencing findings

## De novo mutation candidates

### CCZ1 (one copy loss)

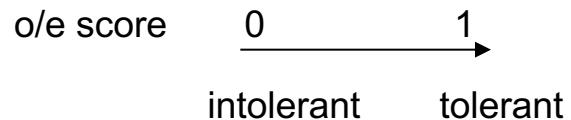
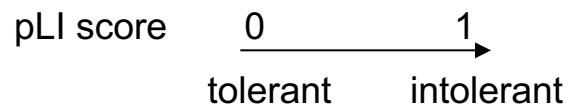
**CCZ1** CCZ1 homolog, vacuolar protein trafficking and biogenesis associated

Dataset gnomAD v2.1.1 ▾ gnomAD SVs v2.1 ▾

Genome build GRCh37 / hg19  
Ensembl gene ID ENSG00000122674.8  
Ensembl canonical transcript ⓘ ENST00000325974.6  
Region 7:5938356-5965605  
References Ensembl, UCSC Browser, and more

#### Constraint ⓘ

Category	Exp. SNVs	Obs. SNVs	Constraint metrics
Synonymous	69.8	79	Z = -0.87 o/e = 1.13 (0.94 - 1.36) 0 ⚡ 1
Missense	191.5	199	Z = -0.19 o/e = 1.04 (0.93 - 1.17) 0 ⚡ 1
pLoF	21.1	12	pLI = 0 o/e = 0.57 (0.36 - 0.92) 0 ⚡ 1



# Whole Exome Sequencing findings

## De novo mutation candidates

### ATP6V0D2 (frameshift deletion, het)

**ATP6V0D2** ATPase H<sup>+</sup> transporting V0 subunit d2

Dataset gnomAD v2.1.1 ▾ gnomAD SVs v2.1 ▾ ⓘ

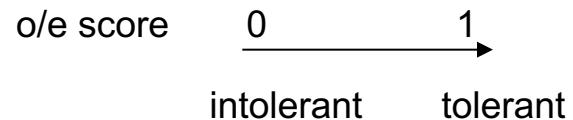
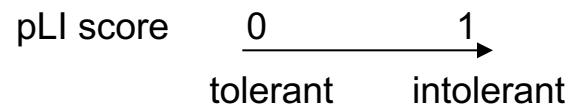
Genome build GRCh37 / hg19  
Ensembl gene ID ENSG00000147614.3  
Ensembl canonical transcript ⓘ ENST00000285393.3  
Region 8:86999552-87166457  
References Ensembl, UCSC Browser, and more

#### Constraint ⓘ

Category	Exp. SNVs	Obs. SNVs	Constraint metrics
Synonymous	74.3	82	Z = -0.7 o/e = 1.1 (0.92 - 1.33) 0 → 1
Missense	192	222	Z = -0.77 o/e = 1.16 (1.04 - 1.29) 0 → 1
pLoF	18.1	17	pLI = 0 o/e = 0.94 (0.64 - 1.4) 0 → 1

exome genome Metric: Mean Save plot

00 →



# Whole Exome Sequencing findings

## De novo mutation candidates

### ATP6V0D2 (frameshift deletion, het)

#### Deletion: 8-87126039-CTA-C (GRCh37)

Dataset gnomAD v2.1.1

Filter	Exomes Pass	Genomes No variant	Total	References
Allele Count	1		1	<ul style="list-style-type: none"> <li>dbSNP (rs766037901)</li> <li>UCSC</li> </ul>
Allele Number	251298		251298	
Allele Frequency	0.000003979		0.000003979	
Popmax Filtering AF ⓘ (95% confidence)	—			
Number of homozygotes	0		0	

#### Annotations

This variant falls on 2 transcripts in 2 genes.

Gene	Type	Location	Effect
ATP6V0D2	frameshift	Exons	frameshift deletion, het
ENST00000285393.3	frameshift	Introns	frameshift deletion, het
Ensembl canonical transcript for ATP6V0D2			
HGVSp: p.Cys79TrpfsTer4			
pLoF: ● High-confidence			

#### Population Frequencies ⓘ

Population	Allele Count	Allele Number	Number of Homozygotes	Allele Frequency
African	1	16254	0	0.00006152
Latino	0	34556	0	0.000
Ashkenazi Jewish	0	10074	0	0.000
East Asian	0	18392	0	0.000
European (Finnish)	0	21648	0	0.000
European (non-Finnish)	0	113648	0	0.000
Other	0	6128	0	0.000
South Asian	0	30598	0	0.000
Male	1	135818	0	0.000007363
Female	0	115480	0	0.000
<b>Total</b>	<b>1</b>	<b>251298</b>	<b>0</b>	<b>0.000003979</b>

# Whole Exome Sequencing findings

## De novo mutation candidates

### DMBT1 (one copy loss?)

DMBT1 deleted in malignant brain tumors 1

Dataset gnomAD v2.1.1 ▾ gnomAD SVs v2.1 ▾ ⓘ

Genome build	GRCh37 / hg19
Ensembl gene ID	ENSG00000187908.11
Ensembl canonical transcript ⓘ	ENST00000368909.3
Region	10:124320181-124403252
References	<a href="#">Ensembl</a> , <a href="#">UCSC Browser</a> , and more

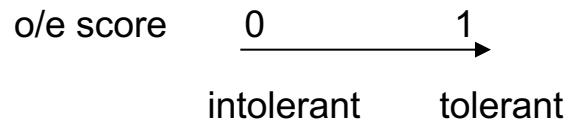
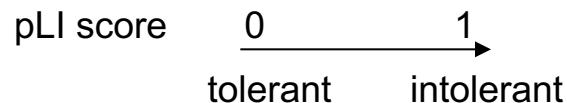
#### Constraint ⓘ

Category	Exp. SNVs	Obs. SNVs	Constraint metrics
Synonymous	408.2	550	Z = -5.52 o/e = 1.35 (1.26 - 1.45) 0 ⚡ 1
Missense	1020.5	1217	Z = -2.19 o/e = 1.19 (1.14 - 1.25) 0 ⚡ 1
pLoF	110.3	101	pLI = 0 o/e = 0.92 (0.78 - 1.08) 0 ⚡ 1

**Note** More missense variants than expected

**Note** More or fewer synonymous variants than expected

See the [FAQ](#) for more information on constraint flags.



# Whole Exome Sequencing findings

## De novo mutation candidates

### OR4C46 (missense)

**OR4C46** olfactory receptor family 4 subfamily C member 46

Dataset gnomAD v2.1.1 ▾ gnomAD SVs v2.1 ▾ ⓘ

Genome build GRCh37 / hg19  
Ensembl gene ID ENSG00000185926.1  
Ensembl canonical transcript ⓘ ENST00000328188.1  
Region 11:51515282-51516211  
References Ensembl, UCSC Browser, and more

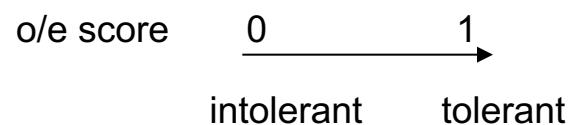
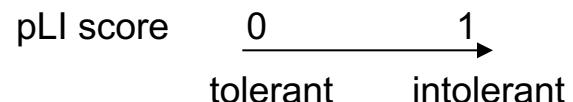
#### Constraint ⓘ

Category	Exp. SNVs	Obs. SNVs	Constraint metrics
Synonymous	59.8	123	Z = -6.42 o/e = 2.06 (1.7 - 1.99) 0 ⬅ 1
Missense	158.1	354	Z = -5.54 o/e = 2.24 (1.89 - 2) 0 ⬅ 1
pLoF	2.2	8	pLI = 0 o/e = 3.72 (1.22 - 1.98) 0 ⬅ 1

**Note** More missense variants than expected

**Note** More or fewer synonymous variants than expected

See the FAQ for more information on constraint flags.



# Whole Exome Sequencing findings

## De novo mutation candidates

### OR4C46 (missense-deletion)

#### Single nucleotide variant: 11-51515546-G-T (GRCh37)

Filter	Exomes <span style="background-color: green; border: 1px solid black; padding: 2px;">Pass</span>	Genomes <span style="background-color: red; border: 1px solid black; padding: 2px;">No variant</span>	Total	References
Allele Count	16		16	<ul style="list-style-type: none"><li><a href="#">dbSNP (rs61890419)</a></li><li><a href="#">UCSC</a></li></ul>
Allele Number	251052		251052	
Allele Frequency	0.00006373		0.00006373	
Popmax Filtering AF <span style="color: blue;">?</span> (95% confidence)	0.0001298			
Number of homozygotes	0		0	<ul style="list-style-type: none"><li><a href="#">Report this variant</a></li><li><a href="#">Request additional information</a></li></ul>

This variant is multiallelic. Other alt alleles are:

- 11-51515546-G-A
- 11-51515546-G-C
- 11-51515546-GCC-G

#### Annotations

This variant falls on 1 transcript in 1 gene.

#### missense

- [OR4C46](#)

- [ENST00000328188.1](#)

Ensembl canonical transcript for OR4C46

HGVSp: p.Ala89Ser

Polyphen: benign

SIFT: deleterious\_low\_confidence

#### Population Frequencies ?

Population	Allele Count	Allele Number	Number of Homozygotes	Allele Frequency
South Asian	8	30616	0	0.0002613
European (Finnish)	2	21648	0	0.00009239
African	1	16256	0	0.00006152
East Asian	1	18382	0	0.00005440
European (non-Finnish)	4	113370	0	0.00003528
Latino	0	34582	0	0.000
Ashkenazi Jewish	0	10076	0	0.000
Other	0	6122	0	0.000
Male	10	135668	0	0.00007371
Female	6	115384	0	0.00005200
<b>Total</b>	<b>16</b>	<b>251052</b>	<b>0</b>	<b>0.00006373</b>

Include:  Exomes  Genomes

# Whole Exome Sequencing findings

## De novo mutation candidates

### ZNF740 (missense)

**ZNF740** zinc finger protein 740

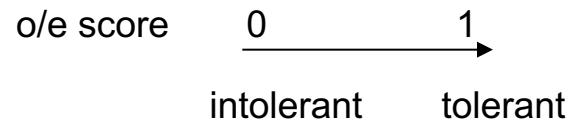
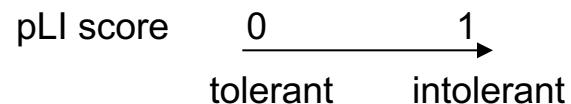
Dataset: gnomAD v2.1.1 ▾ gnomAD SVs v2.1 ▾ ?

Genome build	GRCh37 / hg19
Ensembl gene ID	ENSG00000139651.9
Ensembl canonical transcript	<a href="#">ENST00000416904.3</a>
Region	12:53574484-53584596
References	<a href="#">Ensembl</a> , UCSC Browser, and more

**Constraint** ⓘ

Category	Exp. SNVs	Obs. SNVs	Constraint metrics
Synonymous	40.1	35	$Z = 0.64$ o/e = 0.87 (0.67 - 1.16) 0 <input checked="" type="radio"/> 1
Missense	113.4	78	$Z = 1.18$ o/e = 0.69 (0.57 - 0.83) 0 <input checked="" type="radio"/> 1
pLoF	10.9	3	$pLI = 0.19$ o/e = 0.27 (0.12 - 0.71) 0 <input checked="" type="radio"/> 1

Legend: exome (blue square), genome (green square). Metric: Mean ▾ Save plot



# Whole Exome Sequencing findings

## De novo mutation candidates

### DPF3 (coding)

DPF3 double PHD fingers 3

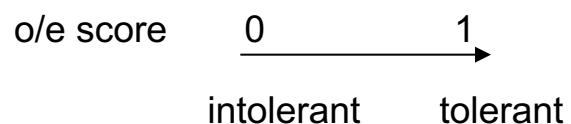
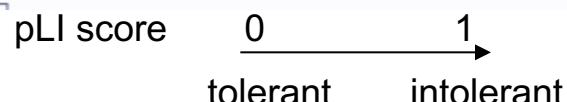
Dataset gnomAD v2.1.1 ▾ gnomAD SVs v2.1 ▾ ⓘ

Genome build GRCh37 / hg19  
Ensembl gene ID ENSG00000205683.7  
Ensembl canonical transcript ⓘ ENST00000541685.1  
Region 14:73086004-73360809  
References Ensembl, UCSC Browser, and more

#### Constraint ⓘ

Category	Exp. SNVs	Obs. SNVs	Constraint metrics
Synonymous	875	93	Z = -0.46 o/e = 1.06 (0.9 - 1.26) 0 ⚡ 1
Missense	230	181	Z = 1.15 o/e = 0.79 (0.7 - 0.89) 0 ⚡ 1
pLoF	22.1	7	pLI = 0.02 o/e = 0.32 (0.18 - 0.59) 0 ⚡ 1

exome genome Metric: Mean Save plot



# Candidate genes of Crohn's disease, UC, IBD (N=134 genes)

P

NM_001136	AGER	snp	chr6	32150086	32150086 C	G	heterozygous	5.50E-03
NM_001136	AGER	snp	chr6	32150356	32150356 A	T	heterozygous	5.50E-03
NM_004406	DMBT1	snp	chr10	124358475	124358475 T	A	heterozygous	-1.00E+01
NM_000877	IL1R1	snp	chr2	102791994	102791994 G	A	heterozygous	-1.00E+01
NM_006157	NELL1	snp	chr11	20968970	20968970 G	A	heterozygous	7.50E-03

F

NM_006157	NELL1	snp	chr11	20968970	20968970 G	A	heterozygous	7.50E-03
NM_0012562	KRT8	snp	chr12	53298579	53298579 T	C	heterozygous	-1.00E+01
NM_001136	AGER	snp	chr6	32150086	32150086 C	G	homozygous	5.50E-03
NM_001136	AGER	snp	chr6	32150356	32150356 A	T	homozygous	5.50E-03

M

NM_004406	DMBT1	snp	chr10	124358475	124358475 T	A	heterozygous	-1.00E+01
NM_0011721	IL16	snp	chr15	81571990	81571990 G	A	heterozygous	6.50E-03
NM_000877	IL1R1	snp	chr2	102791994	102791994 G	A	heterozygous	-1.00E+01

# Candidate genes of Crohn's disease, UC, IBD (N=134 genes)

## 2 NM\_001136 (AGER) variants

### NM\_001136.5(AGER):c.902G>C (p.Cys301Ser)

**Interpretation:** Conflicting interpretations of pathogenicity  
Benign(1);Uncertain significance(1)

**Review status:** ★☆☆☆ criteria provided, conflicting interpretations

**Submissions:** 2 (Most recent: Jul 6, 2020)

**Last evaluated:** Jul 21, 2018

**Accession:** VCV000710266.5

**Variation ID:** 710266

**Description:** single nucleotide variant

### NM\_001136.5(AGER):c.811T>A (p.Trp271Arg)

**Interpretation:** Conflicting interpretations of pathogenicity  
Benign(1);Uncertain significance(1)

**Review status:** ★☆☆☆ criteria provided, conflicting interpretations

**Submissions:** 2 (Most recent: Jul 6, 2020)

**Last evaluated:** Jul 21, 2018

**Accession:** VCV000710267.5

**Variation ID:** 710267

**Description:** single nucleotide variant

Interpretation (Last evaluated)	Review status (Assertion criteria)	Condition (Inheritance)	Submitter	Supporting information (See all)
Benign (Jul 21, 2018)	criteria provided, single submitter ( <a href="#">Invitae Variant Classification Sherloc (09022015)</a> ) Method: clinical testing	not provided Allele origin: germline	<a href="#">Invitae</a> Accession: SCV001025000.1 Submitted: (Mar 14, 2019)	<a href="#">Evidence details</a>
Uncertain significance (May 01, 2016)	criteria provided, single submitter ( <a href="#">Praxis fuer Humangenetik Tuebingen - Variant Classification Criteria</a> ) Method: clinical testing	not provided Allele origin: germline	<a href="#">CeGaT Praxis fuer Humangenetik Tuebingen</a> Accession: SCV001154704.4 Submitted: (Jul 06, 2020)	<a href="#">Evidence details</a>

Interpretation (Last evaluated)	Review status (Assertion criteria)	Condition (Inheritance)	Submitter	Supporting information (See all)
Benign (Jul 21, 2018)	criteria provided, single submitter ( <a href="#">Invitae Variant Classification Sherloc (09022015)</a> ) Method: clinical testing	not provided Allele origin: germline	<a href="#">Invitae</a> Accession: SCV001025001.1 Submitted: (Mar 14, 2019)	<a href="#">Evidence details</a>
Uncertain significance (May 01, 2016)	criteria provided, single submitter ( <a href="#">Praxis fuer Humangenetik Tuebingen - Variant Classification Criteria</a> ) Method: clinical testing	not provided Allele origin: germline	<a href="#">CeGaT Praxis fuer Humangenetik Tuebingen</a> Accession: SCV001154705.4 Submitted: (Jul 06, 2020)	<a href="#">Evidence details</a>

## ClinVar

<https://www.ncbi.nlm.nih.gov/clinvar/variation/710266/>

<https://www.ncbi.nlm.nih.gov/clinvar/variation/710267/>

Candidate genes of Crohn's disease, UC, IBD (N=134 genes)

## NM\_006157 (NELL1) variant

### NM\_006157.5(NELL1):c.1160G>A (p.Arg387His)

<b>Interpretation:</b>	Benign
<b>Review status:</b>	    criteria provided, single submitter
<b>Submissions:</b>	1 (Most recent: Mar 14, 2019)
<b>Last evaluated:</b>	Jun 28, 2018
<b>Accession:</b>	VCV000713988.1
<b>Variation ID:</b>	713988
<b>Description:</b>	single nucleotide variant

Candidate genes of Crohn's disease, UC, IBD (N=134 genes)

## NM\_006157 (NELL1) variant

### NM\_006157.5(NELL1):c.1160G>A (p.Arg387His)

<b>Interpretation:</b>	Benign
<b>Review status:</b>	    criteria provided, single submitter
<b>Submissions:</b>	1 (Most recent: Mar 14, 2019)
<b>Last evaluated:</b>	Jun 28, 2018
<b>Accession:</b>	VCV000713988.1
<b>Variation ID:</b>	713988
<b>Description:</b>	single nucleotide variant

*IL1R1 Gene* (Interleukin 1 Receptor Type 1) - HGNC:5993  
aka IL1R, IL1RA, CD121A ,

- **Genetic Report Information**

- IL1R1 gene variant, HGNC:5993, located at 2q11.2-q12.1.
- heterozygous (inherited from mom) for a missense variant chr2-124358475 (G>A)

- **Wild type Protein Function**

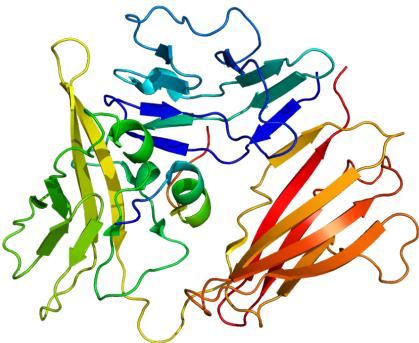
- UniProtKB: P14778
- innate immune signaling/inflammatory response

- **Suspected Variant Impact**

- possibly a gain of function? but could be a loss of function as well.
- supporting evidence: microarray expression data showed upregulation of IL1R signaling pathway in colonoscopy.

# IL1R1 function (Wild-type)

<https://www.rcsb.org/pdb/protein/P14778>

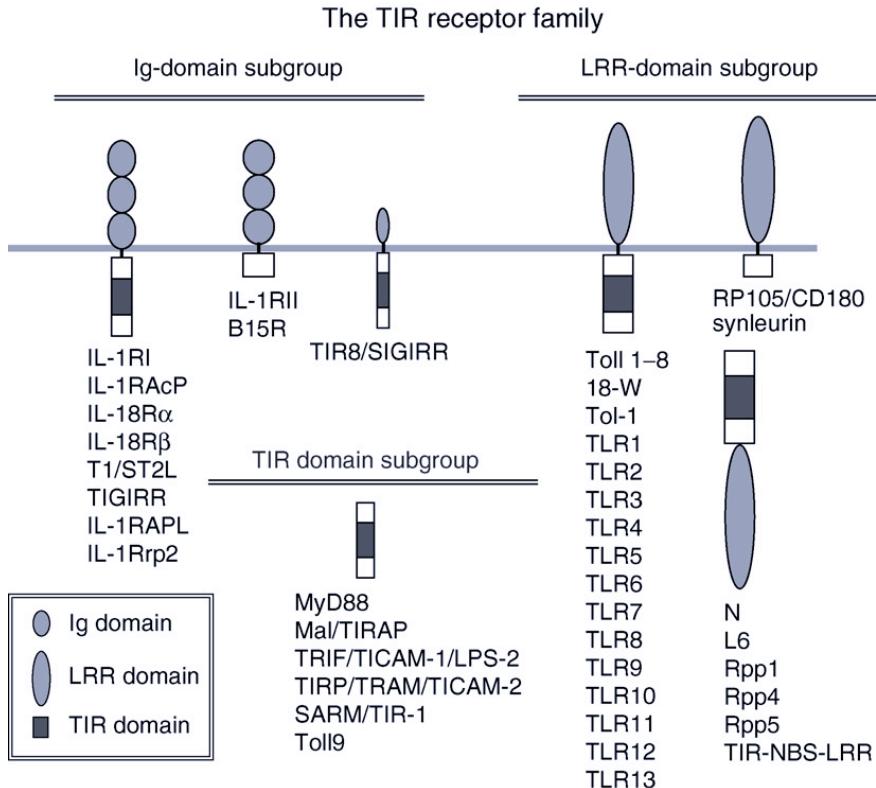


552 aa, transmembrane  
with 213 cytoplasmic tail  
80kDa

- cytokine receptor belongs to the Interleukin 1 -receptor family (type I receptors activate inflammatory response upon IL-1 binding while type II receptor (decoy) suppresses it.)
- Due to shared intracellular signaling TIR structure with the TLR family, they also grouped -> TLR/IL1R receptor superfamily
- receptor for IL1A (higher affinity), IL1B and IL1 receptor antagonist (IL1RA)
- induces potent pro-inflammatory signaling/response
- tightly regulated via decoy receptors (type II) and antagonist ligand (IL1RA)

# Patient's mutation:

- in the TIR (intracellular signaling domain)
- perhaps is a gain of function?
- TIR domain is ancient, shared across different taxonomic kingdoms (plants, fish, avian, mammalian etc)
- important inflammatory signaling moiety that trigger complex + potent signaling pathways  
->increase multiple other inflammatory genes
- aberrant activation promotes autoimmune disease



[https://doi.org/10.1016/S0083-6729\(06\)74009-2Get](https://doi.org/10.1016/S0083-6729(06)74009-2Get)

# PMI Working Hypothesis- a T-cell imbalance?

- patient responded well to therapies that block T cell activity such as steroid + tacrolimus (calcineurin inhibitor), so perhaps T cells should be the main target
- Th17/Treg lineages imbalance in colitis has been well-established to play major role in UC/IBD
- Naïve CD4+ T cells can differentiate into Th1/Th2/Th17 or Tregs depending on the cytokine environment.
- IL-1 $\beta$  is known to lead to a Th17 signature (<https://www.frontiersin.org/articles/10.3389/fimmu.2019.01266/full>).
- Increased IL-1R signaling in T cells also predisposes them to Th17 lineage (PMC3136902)
- if IL-1R signaling in T cells is the main cause of his UC, we can specifically block IL-1R signaling pathway
- Many drugs that block IL-1R signaling (PMC3644509)

# strategies:

## 1. Directly block IL1R signaling

Human literature search founded these FDA-approved therapies: (PMC3644509)

- a/ IL-1 receptor antagonist (compete with IL-1) such as **anakinra** (FDA-approved to treat RA and NOMID)
- b/**Rilonacept**: soluble IL-1 receptor that binds IL-1 $\beta$  > IL-1 $\alpha$ > IL-1Ra (FDA-approved to treat cryopyrin-associated periodic syndrome (CAPS) such as Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS).
- c/ anti IL-1 $\beta$  mAb (block the cytokine and therefore blocking this IL-1R signaling pathway), such as **canakinumab**, which has been FDA approved to treat FCAS and MWS.

# strategies:

## 1. Directly block IL1R signaling

mediKanren queries

Since participant has higher IL1R1 expression in his colonoscopy biopsy -> find **drugs that reduce IL1R1 expressions.**

CURIE	synonyms	thoughts
"CHEBI:15367"	all-trans-retinoic acid	great evidence to inhibit TH17 and promote Treg
"CHEBI:28918"	(R)-adrenaline, ephinephrine	may aggravate TH17
"CHEMBL1201570"	IL-1 receptor antagonist	anakinra
"CUI:C0002658"	Amphetamine	drug-induced colitis? harmful
"CUI:C0012854"	Deoxyribonucleic acid	DNA?
"CUI:C0022614"	ketamine	anesthesia, sedation
"CUI:C0035339"	Retinoids	
"CUI:C0041385"	Tunicamycin	ER-stress inducer, may aggravate it
"CUI:C0084183"	(S)-Pyrrolidinecarbodithioic Acid	selective NFkB inhibitor, antioxidant, antiapoptotic effects
"CUI:C0376202"	Isopregnanolone	sepranolone
"CUI:C0684163"	membrane bound receptors	irrelevant

# all-trans-retinoic acid for UC/IBD

*Blood*. 2008 Feb 1; 111(3): 1013–1020.

Prepublished online 2007 Oct 19. doi: [10.1182/blood-2007-06-096438](https://doi.org/10.1182/blood-2007-06-096438)

Chemokines, Cytokines, and Interleukins

PMCID: PMC2214761

PMID: [17951529](https://pubmed.ncbi.nlm.nih.gov/17951529/)

Retinoic acid inhibits Th17 polarization and enhances FoxP3 expression through a Stat-3/Stat-5 independent signaling pathway

- all-trans RA = primary vitamin A metabolite
- suppress IFN- $\gamma$  and IL-4, and IL-17 and promote Treg
- *in vitro* T cell polarization assays
- *in vivo* adoptive transfer cells to OT mice
- Binds to transcription factor RAR $\alpha$  and influences ROR $\gamma$ t expression



Immunology Letters

Volume 162, Issue 1, Part A, November 2014, Pages 34-40



All-trans retinoic acid attenuates experimental colitis through inhibition of NF- $\kappa$ B signaling

- dampens inflammation-induced macrophage activation.
- attenuates experimental colitis through inhibition of NF- $\kappa$ B signaling.

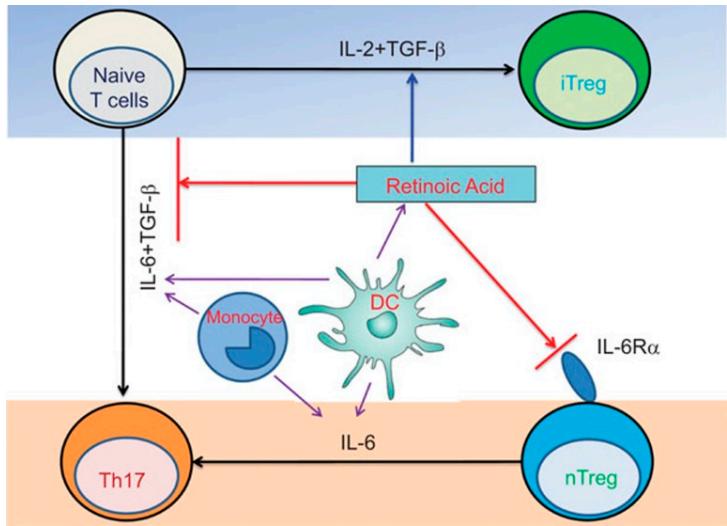
*Cell Mol Immunol*. 2015 Sep; 12(5): 553–557.

Published online 2015 Feb 2. doi: [10.1038/cmi.2014.133](https://doi.org/10.1038/cmi.2014.133)

PMCID: PMC4579645

PMID: [25640656](https://pubmed.ncbi.nlm.nih.gov/25640656/)

The role of all-trans retinoic acid in the biology of Foxp3 $^{+}$  regulatory T cells



<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4579645/>

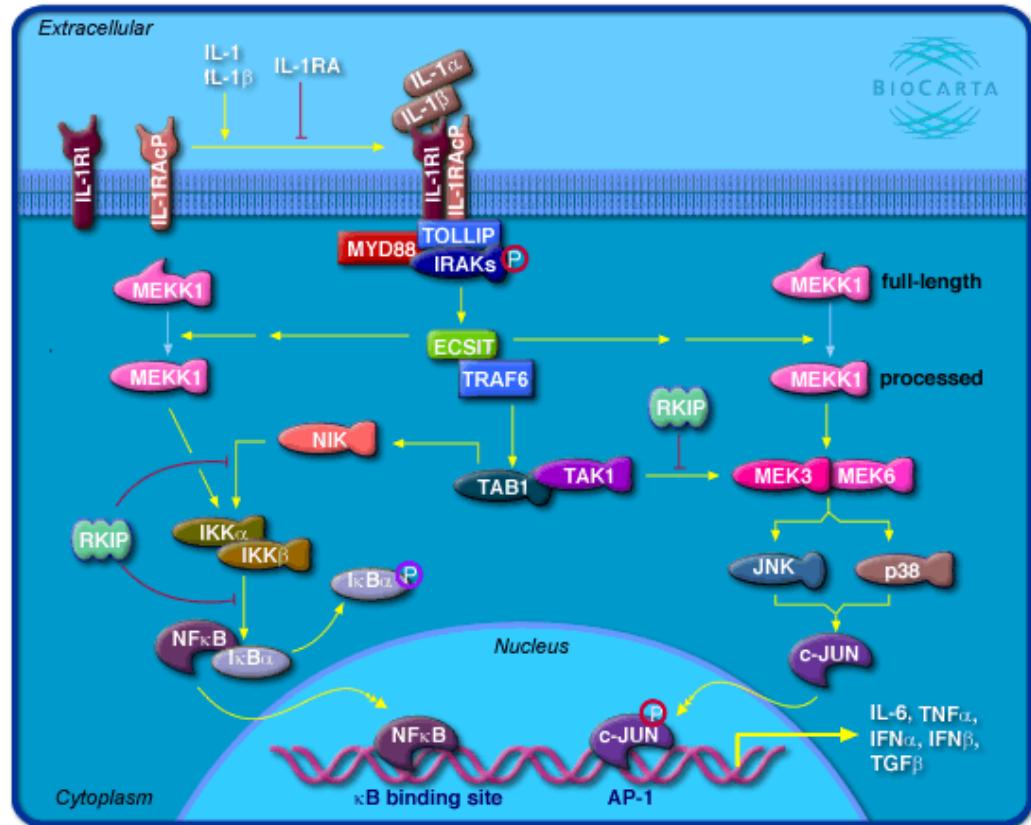
# Ketamine for UC

- Intravenous (IV) ketamine infusion therapy treats a variety of chronic pain conditions, anesthesia since 1970
- suppress inflammatory cytokines TNF- $\alpha$ , L-6, IL-8 and IL-1 $\beta$
- <https://rsds.org/wp-content/uploads/2015/02/ketamine-Peripheral-inflammation.pdf>
- <https://www.ivketamine.com/crohns-disease/>
- IV or oral (or other?) route would work best? Ideally, we don't want too much sedative effect, as the participant is returning to school

# strategies:

2. Target downstream of IL-1R signaling pathways:

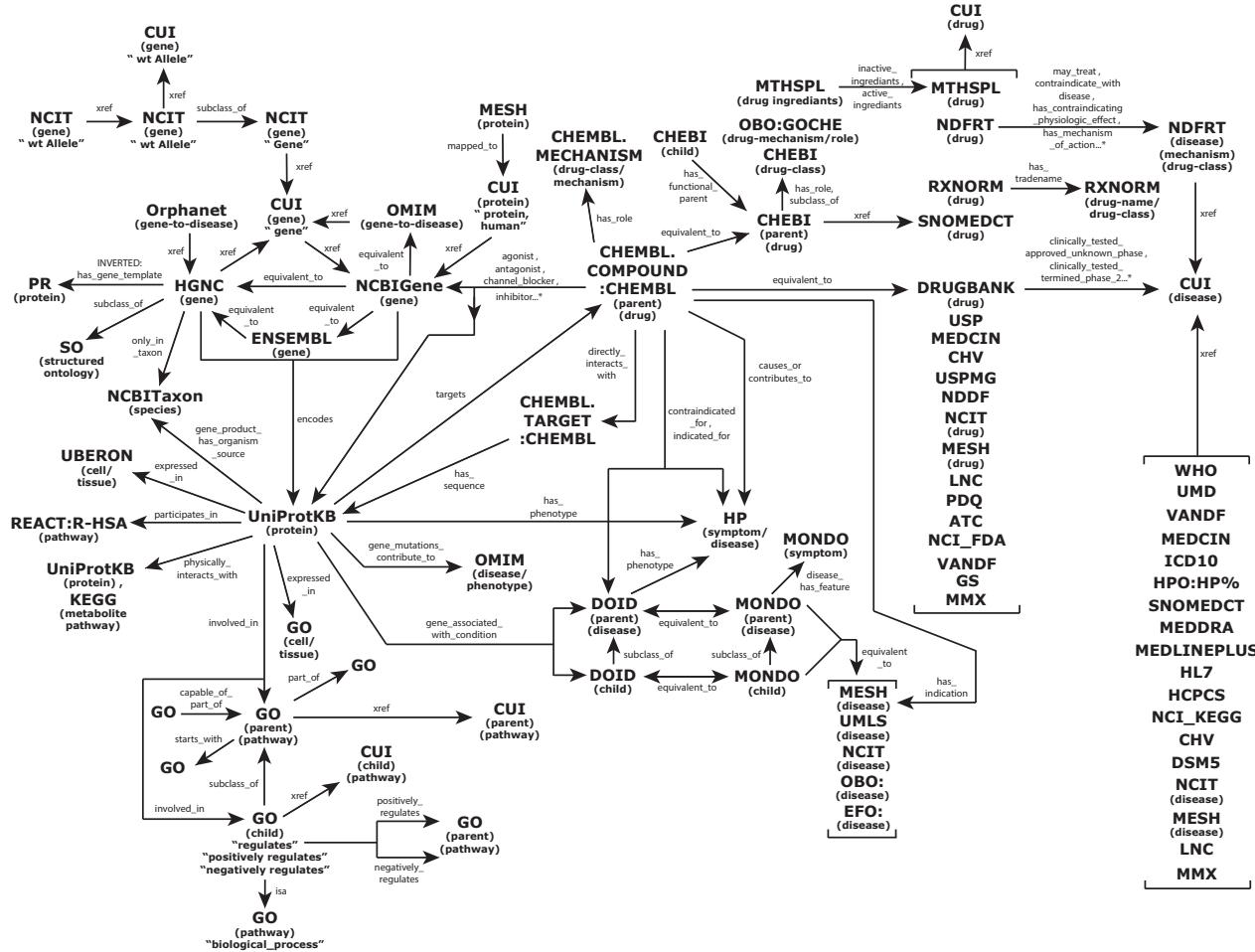
such as MyD88, TAK1, NEMO, IRAKs,  
TRAF6, MEKK1, MEK3, MEK6, IKK $\alpha\beta$ ,  
NF $\kappa$ B, JNK, p38, c-JNK.



[https://data.broadinstitute.org/gsea-msigdb/msigdb/biocarta/human/h\\_il1rPathway.gif](https://data.broadinstitute.org/gsea-msigdb/msigdb/biocarta/human/h_il1rPathway.gif)

RTX2-KG Map

Michael Patton  
2/19/2020



# strategies:

## 2. Target downstream of IL-1R signaling pathways:

mediKanren queries

- (define targets (list myD88 TAK1 NEMO IRAK1 IRAK2 TRAF6 MEK1 MEK3 MEK6 NFkB JNK p38 c-JNK))
- all of these genes have been synonymized (thanks to Nada + Will for the updated synonym codes!),
- use query/graph + one-hop approach, with ranking of pathways members (members with the most inhibitory drugs) and drugs (drugs that target the most members of this pathways = polypharmacy?)
- note, remove drugs with CUI prefixes because they contain useless drug recommendations

# Results of mediKanren 1-hop query/graph with ranked results

## IL1-R1 pathway members with the most drugs available to target them in ranked orders

'(((HGNC:6881" . "mitogen-activated protein kinase 8") . 233)	<b>c-JNK : 233 drugs</b>
((HGNC:6876" . "mitogen-activated protein kinase 14") . 188)	<b>p38/MAPK : 188 drugs</b>
((HGNC:7794" . "nuclear factor kappa B subunit 1") . 97)	<b>NFkB : 97 drugs</b>
((HGNC:7562" . "myeloid differentiation primary response 88") . 28)	<b>MYD88 : 28 drugs</b>
((HGNC:6859" . "mitogen-activated protein kinase kinase kinase 7") . 20)	<b>TAK1 : 20 drugs</b>
((HGNC:6846" . "mitogen-activated protein kinase kinase 6") . 16)	<b>MEK6 : 16 drugs</b>
((HGNC:6112" . "interleukin 1 receptor associated kinase 1") . 11)	<b>IRAK1 : 11 drugs</b>
((HGNC:5961" . "inhibitor of nuclear factor kappa B kinase subunit gamma") . 10)	<b>NEMO : 10 drugs</b>
((HGNC:12036" . "TNF receptor associated factor 6") . 9)	<b>TRAF6 : 33 drugs</b>
((HGNC:6861" . "mitogen-activated protein kinase kinase kinase 9") . 8)	<b>JNK 9 : drugs</b>
((HGNC:6848" . "mitogen-activated protein kinase kinase kinase 1") . 8)	<b>MEK1 : 8 drugs</b>
((HGNC:6843" . "mitogen-activated protein kinase kinase 3") . 7)	<b>MEK3 : 7 drugs</b>
((HGNC:6113" . "interleukin 1 receptor associated kinase 2") . 0))	<b>TAK2 : 0 drugs</b>

note: remove CUI prefix

# Results of mediKanren 1-hop query/graph with ranked results

- 444 drugs that target >=1 members of the IL1R signaling pathways
- top 15 drugs target >=5 members of the IL1R signaling pathways

drugs	targets
'(("CHEBI:3962" "curcumin")	8
("CHEBI:16243" "quercetin")	7
("CHEBI:45713" "trans-resveratrol")	6
("CHEBI:39867" "valproic acid")	6
("CHEBI:4806" "epigallocatechin gallate")	6
("CHEBI:52717" "bortezomib")	6
("CHEBI:90695" "anthra[1,9-cd]pyrazol-6(2H)-one")	5
("CHEBI:15551" "prostaglandin E2")	5
("CHEBI:38701" "delphinidin chloride")	5
("CHEBI:76004" "dimethyl fumarate")	5
("CHEBI:46024" "trichostatin A")	5
("CHEBI:45863" "paclitaxel")	5
("CHEBI:8899" "rottlerin")	5
("CHEBI:41879" "dexamethasone")	5
("CHEBI:37537" "phorbol 13-acetate 12-myristate")	5

# Explore the side effects of the top 15 drugs which targets >=5 members of IL1R signaling pathway

Hard filter with one predicate "contraindicated\_for"

## Drugs with the most contraindications (30)

```
'(((("CHEBI:45863" . "paclitaxel")
  ("CUI:C0002792" . "Anaphylaxis")
  ("CUI:C0002871" . "Anemia")
  ("CUI:C0003811" . "Cardiac rhythm irregular")
  ("CUI:C0004096" . "Asthma")
  ("CUI:C0004331" . "P and QRS complexes dissociated")
  ("CUI:C0011581" . "Dysthymia")
  ("CUI:C0011847" . "Diabetes")
  ("CUI:C0020435" . "Hyperbilirubinemia, Hereditary")
  ("CUI:C0020615" . "Blood glucose level below normal")
  ("CUI:C0020649" . "Systemic hypotension")
```

## 2<sup>nd</sup> drug with the most contraindications( 21)

```
('(("CHEBI:15551" .
  ("CUI:C0002871" . "Anemia") "prostaglandin E2")
  ("CUI:C0004096" . "Asthma")
  ("CUI:C0007222" . "Disorder of cardiovascular system")
  ("CUI:C0007860" . "Inflammation of cervix")
  ("CUI:C0011847" . "Diabetes")
  ("CUI:C0012739" . "Disseminated intravascular coagulation")
  ("CUI:C0014544" . "Seizure disorder")
  ("CUI:C0017601" . "Glaucoma")
  ("CUI:C0019342" . "Genital herpes simplex")
  ("CUI:C0020538" . "Elevated blood pressure")
```

## 3<sup>rd</sup> drug with the most contraindications (19)

```
'(("CHEBI:52717" . "bortezomib")
  ("CUI:C0007222" . "Disorder of cardiovascular system")
  ("CUI:C0011175" . "Dehydration")
  ("CUI:C0011847" . "Diabetes")
  ("CUI:C0020542" . "Pulmonary hypertension")
  ("CUI:C0020649" . "Systemic hypotension")
  ("CUI:C0020651" . "Orthostatic hypotension")
  ("CUI:C0021843" . "Intestinal obstruction")
  ("CUI:C0023895" . "Hepatic disease")
```

## 4<sup>th</sup> drug with the most contraindications (18)

```
('(("CHEBI:39867" . "valproic acid")
  ("CUI:C0001339" . "Acute pancreatitis")
  ("CUI:C0011581" . "Dysthymia")
  ("CUI:C0018939" . "Disease of blood AND/OR blood-forming organ")
  ("CUI:C0020672" . "Hypothermia")
  ("CUI:C0022658" . "Kidney disease")
  ("CUI:C0023895" . "Hepatic disease")
  ("CUI:C0027720" . "Kidney disease")
```

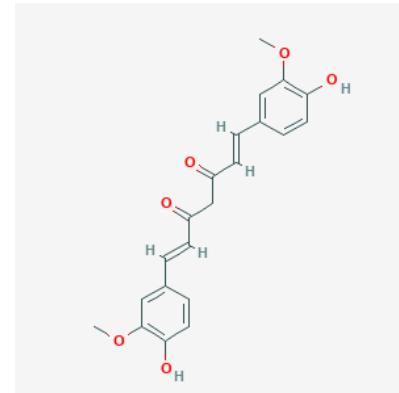
the rest has no contraindications

# Curcumin as a great supplement

- rank no. 1<sup>st</sup> in mediKanren's query

- Curcumin (diferuloylmethane) is a yellow polyphenolic compound extracted from turmeric.
- Curcumin targets many important pathways above and many more such as NF- $\kappa$ B, AP-1, JNK, MTOR/AKT... Even extremely high doses are very well tolerated (2200mg/day for ~ 4 months).
- However, naturally curcumin's bioavailability is poor, so perhaps other drug delivery approaches (such as liposomal curcumin) ) are necessary to maximize its therapeutic effects.

<https://store.amymyersmd.com/products/liposomal-curcumin>



Roll over image to zoom in

Optimized Liposomal Curcumin  
Liquid 250 mg, High Absorption  
Turmeric, from Non-GMO  
Sunflower, Soy Free - Powerful  
Antioxidant Supplement

[Visit the IV for Life Store](#)

82 ratings | 15 answered questions

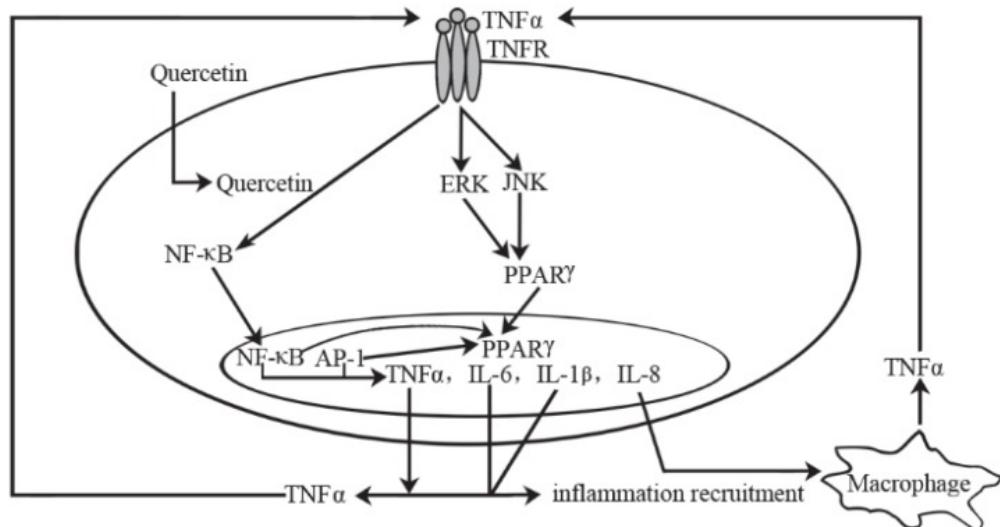
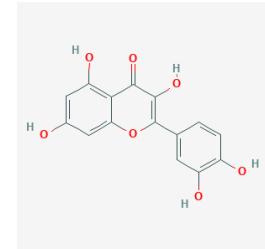
**Currently unavailable.**

We don't know when or if this item will be back in stock.

- **POWERFUL ANTI-INFLAMMATORY:** Curcumin is a natural alternative to over-the-counter pain relief products. Persistent inflammation is thought to be the root cause of many illnesses. However, it can cause a host of other chronic, medical issues that can lead to cardiovascular disease, poor blood sugar control and accelerated aging. By taking our joint and arthritis support supplement, you may be able to also mitigate some of these health risks.

# Quercetin inhibits many components of the IL1R1 signaling ranked no. 2<sup>nd</sup> in mediKanren's query

- safe as dietary supplement
- quercetin glycoside (rutin) is a more efficient form
- many research support (*in vitro*, *in vivo*, clinical)
- anti-carcinogenic, anti-inflammatory, antiviral, antioxidant, psychostimulant
- inhibit lipid peroxidation, platelet aggregation, capillary permeability, stimulate mitochondrial biogenesis
- regulates mast cells + has gastrointestinal
- cytoprotective activity



# Quercetin for UC-many evidences

Nature and Science 2019;17(6)

<http://www.sciencepub.net/nature>

## The Impact of Quercetin on Sirtuin1, High Mobility Group Box 1 and Selected Oxidative Stress Indices in Ulcerative Colitis Induced by Oxazolone in Rats

*Cell Cycle.* 2018; 17(1): 53–63.

Published online 2018 Jan 2. doi: [10.1080/15384101.2017.1387701](https://doi.org/10.1080/15384101.2017.1387701)

PMCID: PMC5815442

PMID: [29376231](https://pubmed.ncbi.nlm.nih.gov/29376231/)

Dietary quercetin ameliorates experimental colitis in mouse by remodeling the function of colonic macrophages via a heme oxygenase-1-dependent pathway

### ORIGINAL RESEARCH ARTICLE

Front. Microbiol., 16 May 2019 | <https://doi.org/10.3389/fmicb.2019.01092>



## Dietary Quercetin Increases Colonic Microbial Diversity and Attenuates Colitis Severity in *Citrobacter rodentium*-Infected Mice

*Interdiscip Toxicol.* 2013 Mar; 6(1): 9–12.

Published online 2013 Mar. doi: [10.2478/intox-2013-0002](https://doi.org/10.2478/intox-2013-0002)

PMCID: PMC3795315

PMID: [23540771](https://pubmed.ncbi.nlm.nih.gov/23540771/)

Efficacy of quercetin derivatives in prevention of ulcerative colitis in rats

## Natural Therapies of the Inflammatory Bowel Disease: The Case of Rutin and its Aglycone, Quercetin

January 2017 · *Mini Reviews in Medicinal Chemistry* 17(999)

DOI: [10.2174/138955751766170120152417](https://doi.org/10.2174/138955751766170120152417)

## The effects of dietary curcumin and rutin on colonic inflammation and gene expression in multidrug resistance gene-deficient (*mdr1a*<sup>-/-</sup>) mice, a model of inflammatory bowel diseases

Katia Nones<sup>(a1)</sup>, Yvonne E. M. Dommels<sup>(a1) (a2)</sup>, Sheridan Martell<sup>(a1)</sup>, Christine Butts<sup>(a1)</sup> ...

DOI: <https://doi.org/10.1017/S0007114508009847> Published online by Cambridge University Press: 02 September 2008

### Research Article | Open Access

Volume 2018 | Article ID 8343052 | 7 pages | <https://doi.org/10.1155/2018/8343052>

## Effect of Quercetin Monoglycosides on Oxidative Stress and Gut Microbiota Diversity in Mice with Dextran Sodium Sulphate-Induced Colitis

# Resveratrol for UC – many evidences

- natural polyphenol, phytoalexin (plant antimicrobial + antioxidative)
- grapes, blueberries, raspberries and peanuts
- increases SIRT1 and AMPK activation
- suppress NF- $\kappa$ B

Randomized Controlled Trial > Arch Med Res. 2015 May;46(4):280-5.

doi: 10.1016/j.arcmed.2015.05.005. Epub 2015 May 20.

## Anti-Inflammatory Effects of Resveratrol in Patients with Ulcerative Colitis: A Randomized, Double-Blind, Placebo-controlled Pilot Study

Maryam Samsami-Kor <sup>1</sup>, Naser Ebrahimi Daryani <sup>2</sup>, Parisa Rezanejad Asl <sup>3</sup>, Azita Hekmatdoost <sup>4</sup>

- 6 weeks, 500 mg resveratrol decreases colitis
- effects are partially dependent on gut microbiota

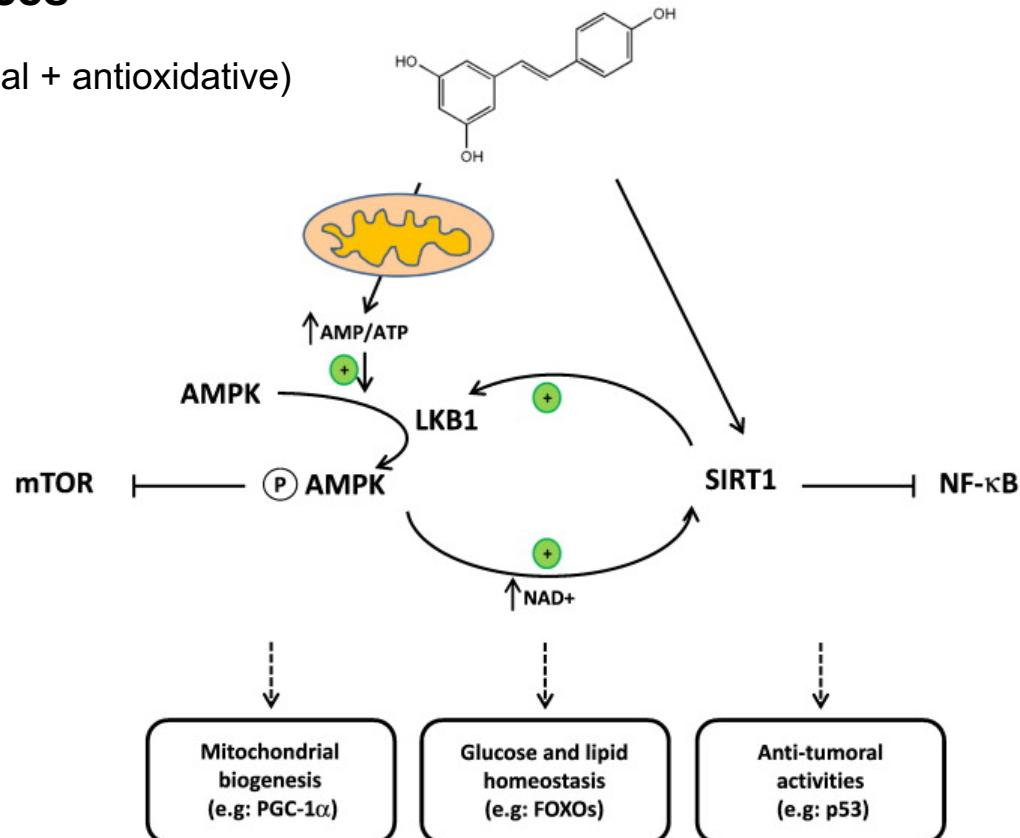
Biomed Res Int. 2019; 2019: 5403761.

Published online 2019 Apr 24. doi: [10.1155/2019/5403761](https://doi.org/10.1155/2019/5403761)

PMCID: PMC6507241

PMID: [31179328](https://pubmed.ncbi.nlm.nih.gov/31179328/)

The Bidirectional Interactions between Resveratrol and Gut Microbiota:  
An Insight into Oxidative Stress and Inflammatory Bowel Disease  
Therapy



# Current available alternative medicine treatments and their effect on UC/IBD

Alternative Medicine	Disease	Effects	Remission	References
Aloe vera gel	UC	Improved histological score	30%	Langmead L, et al. <i>Aliment Pharmacol Ther.</i> 2004;19:739-47
Wheat grass juice	UC/distal	Improved symptoms	90%	Ben-Arye E, et al. <i>Scand J Gastroenterol.</i> 2002;37:444-49.
Germinated barley	UC	Improved diarrhea	—	Kanauchi O, et al. <i>J Gastroenterol.</i> 2002;37: 67-72
Curcumin	UC/CD	Lowered CDAI scores and sedimentation rates	90%	Holt PR et al. <i>Dig Dis Sci.</i> 2005;50:2191-3
Curcumin	UC/CD	Reduced histological sign of inflammation	—	Katia N, et al. <i>Br J Nutr.</i> 2009;101:169-181.
Rutin	UC	Ameliorates DSS induced colitis	—	Ki Han K, et al. <i>Biochem Pharmacol.</i> 2005;69:395-406.
Fresh pineapple juice	UC/CD	Ameliorates colitis and colonic neoplasia	—	Hale LP, et al. <i>Inflamm Bowel Dis.</i> 2010;16: 2012-2021
Pomegranate	UC	Ameliorates DSS induced colitis	—	Singh K, et al. <i>Phytother Res.</i> 2009;23: 1565-1574.
Pomegranate/metabolite	UC	Reduced DSS inflammation	—	Larorosa M, et al. <i>J Nutritional Biochem.</i> 2010;21: 717-725
Epigallocatechin -3-Gallate	UC/CD	Beneficial in colitis	—	Abboud PA, et al. <i>Eur J Phramacol.</i> 2008;579:411-417
Green tea polyphenols	UC	Protect against DSS induced colitis	—	Oz HS, et al. <i>J Nutr Biochem.</i> 2005;16(5):297-304
Green tea polyphenols	UC/CD	Attenuates colon injury and inflammation	—	Mazzon E, et al. <i>Free Radic Res.</i> 2005;39:1017-1025.
Green tea polyphenols	UC/CD	Attenuates colitis	—	Varilek GW, et al. <i>J Nutr.</i> 2001;131(7): 2034-9
Resveratrol	UC/CD	Ameliorates CD	—	Singh UP, et al. <i>Brain Behav Immun.</i> 2012; 26(I):72-82.
Resveratrol	UC	Protect from DSS induced UC	—	Singh UP, et al. <i>J Pharmacol Exp Ther.</i> 2010;332:829-839
Resveratrol	UC/CD	Attenuates colonic inflammation	—	Sanchez-Fidalgo S, et al. <i>Eur J Pharmacol.</i> 2010;633: 78-84
Resveratrol	UC in Rat	Attenuates colonic inflammation	—	Martin AR, et al. <i>Biochem Pharmacol.</i> 2004;67(7): 1399-1410.
Cinnamon extract	UC/CD	Suppress experimental colitis	—	Kwon HK, et al. <i>World J Gastroenterol.</i> 2011;17: 976-986
Freeze-dried black raspberry powder	UC	Potent anti-inflammatory effects	—	Montrose DC, et al. <i>Carcinogenesis.</i> 2011;32: 343-50
American ginseng	UC	Suppress colon cancer associated colitis	—	Cui X, et al. <i>Carcinogenesis.</i> 2010;32: 1734-1741
Ginger extract	UC/rat	Improved inflammation	—	El-Abhar HS, et al. <i>J Ethnopharmacol.</i> 2008;118(3): 367-372

note:

quercetin (rutin) is ranked no. 2nd. in mediKanren query  
resveratrol is ranked no. 3rd

<https://europepmc.org/article/pmc/pmc4138959>

## Valproic Acid, no. 4<sup>th</sup>

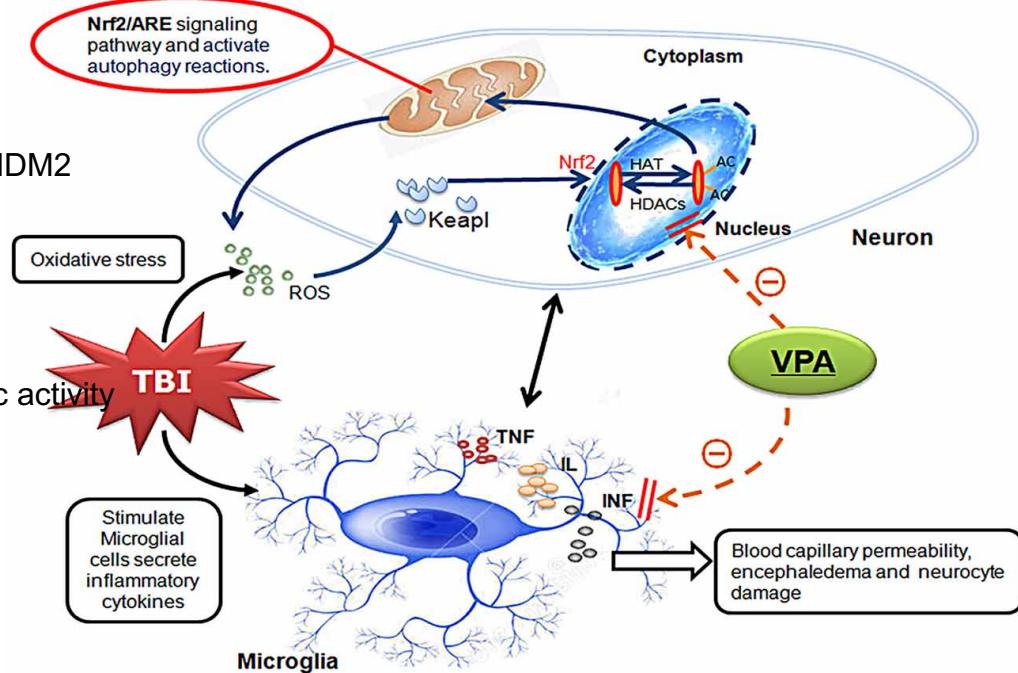


- C<sub>8</sub>H<sub>16</sub>O<sub>2</sub>, 2-propylpentanoic acid, a branched + short chain saturated fatty acid
- antiepileptic, anticonvulsant (via increase GABA in brain)
- antineoplastic and anti-angiogenesis properties (via HDACi activity + inhibition of nitric oxide synthase (NOS) and NO)
- 1<sup>st</sup> drug choice for epilepsy->well-tolerated but has many side effects (mediKanren)
- Also neuroprotective: used in migraines, bipolar + schizophrenia
- Rare but serious complication may occur such as pancreatitis, coagulopathies, bone marrow suppression, hepatotoxicity and encephalopathy

# Valproic Acid inhibit many component downstream of IL1R1 signaling

- Display cell type specific HDACi activity
- inhibit LPS signaling via inhibiting NF- $\kappa$ B, PI3K, Akt and MDM2
- dampen proinflammatory cytokines (IL-6, IL-12, TNF-)
- induce M2 mac polarization, impedes Th17 polarization
- induces neutrophil apoptosis and diminish their phagocytic activity
- diminish mast cell, cytotoxic T cell proliferation
- promote Th2 and Treg and diminish Th1/17

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6437734/>

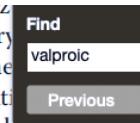


<https://www.frontiersin.org/articles/10.3389/fnmol.2018.00117/full>

# Valproic Acid for UC

- Many evidence about the use of HDACi for UC/IBS  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3105130/>  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3105130/>  
<https://pubmed.ncbi.nlm.nih.gov/16585598/>  
<https://pubmed.ncbi.nlm.nih.gov/21365125/>
- a case report about a 14yo Caucasian with refractory colitis, presented with an acute onset of psychotic  
<https://link.springer.com/content/pdf/10.1186/s13256-019-2106-8.pdf>

...ons, he developed a grossly disorganized thought process, with conceptual disorganization, auditory hallucinations, delusion and suspiciousness, social and emotional withdrawal, somatic anxiety, and tension. Psychopathological assessment was performed by the use of Positive and Negative Syndrome Scale (PANSS). His PANSS total score was 115, while PANSS subscale scores were 29 for positive, 26 for negative, and 60 for general psychopathological symptoms. After proper informed consent, a treatment with antipsychotics and mood stabilizers (risperidone 6 mg/day, levosulpiride 72 mg/day, valproic acid 1000 mg/day) was started, leading to progressive improvement of psychopathological symptoms. During this phase his GI symptomatology remained silent, with 2–3 regular bowel movements/day and no blood or mucus emissions.



- gut-brain axis?



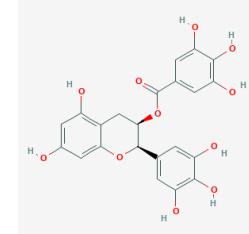
Article | Open Access | Published: 27 September 2019

**Intestinal inflammation increases convulsant activity and reduces antiepileptic drug efficacy in a mouse model of epilepsy**



# Epigallocatechin Gallate (EGCG), no 5<sup>th</sup>

- EGCG (phenolic compound) is the most abundant green tea catechins
- binds to laminin receptor 67LR
- negatively-regulate TLR signaling



## Anti-cancer effects

(Nat. Struct. Mol. Biol. 2004;11:380; Blood 2006;108:2804; J. Biol. Chem. 2008;283:3050; Proc Natl Acad Sci USA 2012;109:12426; Clin. Cancer Res. 2013;19:1116; J. Clin. Invest. 2013;123:787)

## Anti-atherosclerosis effect

(J. Mol. Cell. Cardiol. 2010; 149, 1138)

## Insulin sensing modulating effects

(Planta Med. 2010; 76:1694; Am. J. Physiol. Cell Physiol. 2009; 297:C121; Mol. Nutr. Food Res. (2009), Mol Nutr Food Res. 2012; 56:580)

## Anti-allergic effects

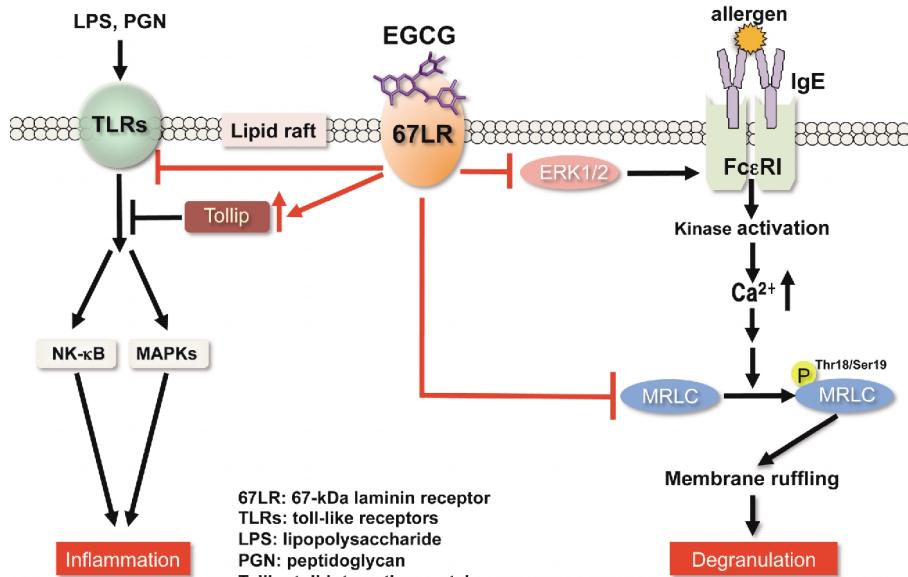
(Biochem. Biophys. Res. Commun. 2005;336:674; Biochem. Biophys. Res. Commun. 2007;364:79)

## Anti-inflammatory effects

(J. Immunol., 2010;185:33; FEBS Lett., 2011;585:814)

## Neuron protective effect

(J. Biol. Chem. 2012;287:34694)



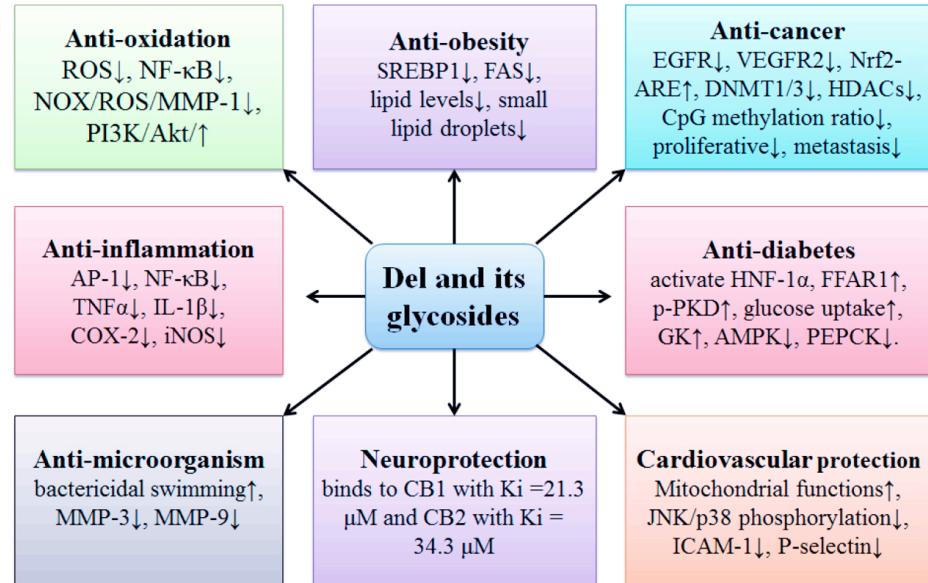
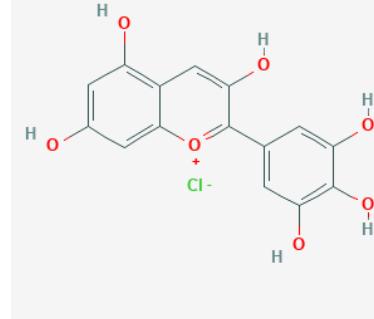
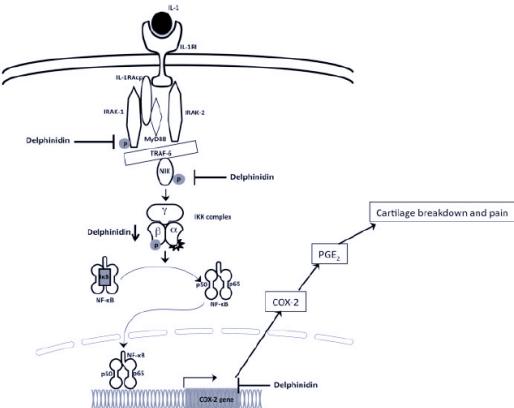
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<https://pubmed.ncbi.nlm.nih.gov/15610077/>

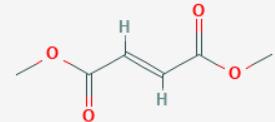
[https://pdfs.semanticscholar.org/02d4/37dc3d11d20a153fb0fd806d0f581f0cc8f.pdf?\\_ga=2.79215188.1997544618.1597853822-2097849337.1597853822](https://pdfs.semanticscholar.org/02d4/37dc3d11d20a153fb0fd806d0f581f0cc8f.pdf?_ga=2.79215188.1997544618.1597853822-2097849337.1597853822)

# Delphinidin, no 9<sup>th</sup>

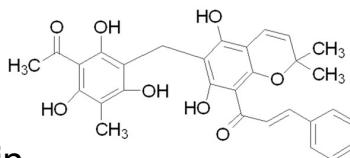
- a dominant anthocyanidin component in red wine and berries
- present in pigmented leaves, fruits and flowers
- strongly inhibit TNF-alpha induced COX-2 expression via inhibiting Fyn kinase
- inhibit TNF-alpha induced phosphorylation of JNK, p38 MAPK, Akt, ERK and thereby blocking AP-1 and NFkB
- can bind directly to MAPKK3 or PI3K and inhibit them



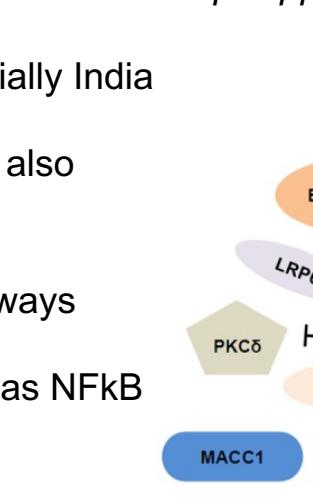
## Dimethyl Fumarate, no 10th



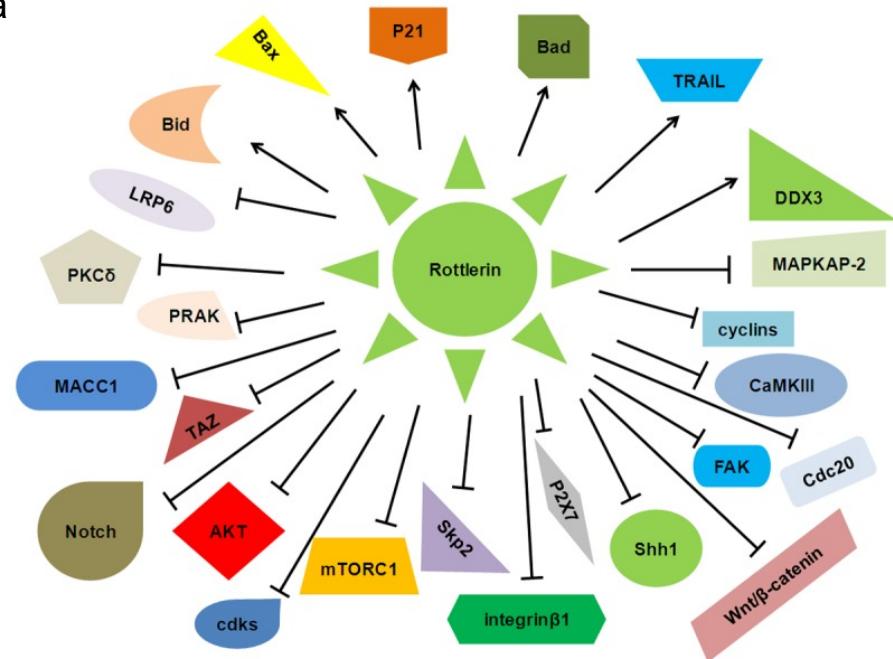
- Trade names: Fumaderm (Germany) for psoriasis, Tecifidera (US) for relapsing MS
- activate Nrf2, and interact with glutathione to inhibit NF- $\kappa$ B
- immunomodulatory: shift from Th1/Th17 to Th2
- reduce immune trafficking in psoriasis plaques
- reduce inflammatory cytokine
- Common side effects: **gastrointestinal symptoms (abdominal pain, nausea, and diarrhea)** flushing, lymphopenia and liver damage
- **However, fumarate has been reported to cause drug-induced colitis so not recommended for this case.**



## Rottlerin, no 13<sup>rd</sup>

- aka Mallotoxin
  - principle phenolic compound of the Kamala plant *Mallotus philippinensis*
  - plant is widely-used in many countries, especially India
  - selective PKC- $\delta$  inhibitor (? controversial) but also affect other PKC- $\delta$  independent pathways
  - activate AMPK, inhibit PI3K/AKT/mTOR pathways
  - affect multiple other signaling pathways such as NFkB
  - anti-tumor, anti-oxidative, anti-inflammatory
  - is it safe? how can we have access?

The diagram illustrates several signaling pathways. At the top right, a yellow triangle labeled 'Box' has arrows pointing to 'Bid' (orange oval), 'LRP6' (purple oval), and 'PRAK' (orange oval). 'Bid' has an arrow pointing to 'PKCδ' (green pentagon). 'PKCδ' has arrows pointing to 'MACC1' (blue oval) and 'TAZ' (red triangle). 'TAZ' has an arrow pointing to 'Box'. 'LRP6' has an arrow pointing to 'PRAK'. 'PRAK' has an arrow pointing to 'Box'. There are also other unlabeled arrows and shapes in the background.



# Fecal transplant to restore intestinal flora

- Fecal Microbiota Transplantation (FMT): introduce faecal material from a highly screened, healthy donor into an unwell recipient's gastrointestinal tract to restore the gut microbiome
- has been proven successful in C. diff for decades
- abnormal intestinal microbiota in UC/IBD (possibly due to inflammation + antibiotics)(PMID: **21073731**)
- FMT may improve symptoms in UC caused by dysbiosis:  
<https://bmcgastroenterol.biomedcentral.com/articles/10.1186/s12876-019-1010-4>  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6624363/>
- Randomized FMT trial in UC steroid-free remission in 12/38 (32%) in FMT vs autologous FMT  
<https://pubmed.ncbi.nlm.nih.gov/30644982/>
- in line with earlier study 38% remission:  
<https://pubmed.ncbi.nlm.nih.gov/28486648/>
- pooled donor FMT seems to have higher effects (possibly more diverse microbes, and sometimes autologous FMT also achieve good results (unknown reasons)

## **Summary as of 08/17/2020**

- heterozygous variant in the TIR domain of the IL1R1 gene, which may lead to aberrant IL1R signaling
- Overactivated T cells, potentially skewed towards Th17 lineages
- Try FDA-approved drugs that dampen IL1R signaling such as anakinra, rilonacept and canakinumab.
- Try all-trans retinoic acid to revert Th17 to Treg (routes of ad?)
- Ketamine (?), liposomal curcumin, FMT

## **Info needed:**

- variant report, other in vitro results?, RNAseq results, medical records (?)

## **Next steps:**

- try targeting downstream signaling and target a number of proteins in one query
- Try to do the drug-safe filter in mediKanren. (target MYD88 leads to 70 drugs!)

## **Summary as of 08/24/2020**

### **Recommendations:**

- drugs: anakinra, all-trans retinoic acid
- supplements: curcumin, quercetin, resveratrol, EGCG, delphinidin, and rottlerin
- FMT

### **Info needed:**

- variant report
- new RNAseq result

### **Next steps:**

- update findings + contact family

## **Summary as of 10/12/2020**

### **Recommendations:**

- drugs: anakinra, all-trans retinoic acid (pill, oral route, been used in )
- anakinra most common side-effects are diarrhea (may not be a good recommendation)
- supplements: curcumin, quercetin, resveratrol, EGCG, delphinidin, and rottlerin
- FMT

### **Thoughts:**

- To validate participant's T-cell dysregulation, can we do his HLA-typing?

### **Next steps:**

- download microarray data and compare T-cell signature or B-cell signature.

# Other references

1. "The Interleukin-1 Receptor Family" by Boraschi et al. *Vitamins & Hormones* 2006
2. "Divergent Roles for the IL-1 Family in Gastrointestinal Homeostasis and Inflammation" by McEntee et al. *Frontiers in Immunology* 2019.
3. " The role of IL-17-producing Foxp3+ CD4+ T cells in inflammatory bowel disease and colon cancer". Li et al. *Clin Immunol* 2013
4. "Targeting TLR/IL-1R signaling in Human Diseases. " by Loiarro et al. *Mediators of Inflammation* 2010.
5. [http://projects.hsl.wisc.edu/SERVICE/modules/18/M18\\_CT\\_Inflammatory\\_Bowel\\_Disease.pdf](http://projects.hsl.wisc.edu/SERVICE/modules/18/M18_CT_Inflammatory_Bowel_Disease.pdf)