

**Table S1.** Participant characteristics. \*, Note that patients can present with more than one cancer type. Sd, standard deviation; Sd, syndrome; MMR, mismatch repair; CRC, colorectal cancer; LD, Low-Dose; HD, High-Dose.

	Total		Placebo		LD Naproxen		HD Naproxen		P
	N	(%)	N	(%)	N	(%)	N	(%)	
<b>Total</b>	80	100	28	35	27	33.8	25	31.3	
<b>Age</b>									0.819
Mean (sd)	44.61	12.33	44.44	13.49	45.65	13.14	43.67	10.3	
<b>Age group</b>									0.294
20-29	14	17.5	7	25	5	18.5	2	8	
30-39	11	13.8	2	7.1	2	7.4	7	28	
40-49	25	31.3	8	28.6	8	29.6	9	36	
50-59	22	27.5	9	32.1	8	29.6	5	20	
60-69	7	8.8	1	3.6	4	14.8	2	8	
70-79	1	1.3	1	3.6					
<b>Gender</b>									0.092
Male	50	64	15	53.6	15	55.6	20	80	
Female	30	36	13	46.4	12	44.4	5	20	
<b>Race</b>									0.3
White	70	87.5	27	96.4	21	77.8	22	88.4	
Other	7	8.8	1	3.6	4	14.8	2	8	
Unknown	3	3.8			2	7.4	1	4	
<b>Ethnicity</b>									0.352
Not Hispanic or Latino	76	84.4	27	96.4	21	77.8	22	88.4	
Hispanic or Latino	7	8.1	1	3.6	4	14.8	2	8	
Not Reported	3	3.75			2	7.4	1	4	
<b>Type of MMR</b>									1
Lynch-Like Syndrome	4	5	2	7.4	1	3.7	1	4	
Lynch Sd Positive	76	95	26	92.6	26	96.3	24	96	
Germline									
<b>MMR gene</b>									0.775
<i>MLH1</i>	27	35.5	11	38.5	9	34.6	8	33.3	
<i>MSH2</i>	25	33	7	26.9	9	34.6	9	37.5	
<i>MSH6</i>	14	18.5	3	11.5	6	23.1	5	20.8	
<i>PMS2</i>	7	9	4	15.4	2	7.7	1	4.2	
<i>EPCAM</i>	3	4	2	7.7			1	4.2	
<b>History of cancer</b>									

Negative	42	53	14	50	16	59.2	12	48	0.923
Cancer diagnosis	38	47	14	50	11	40.8	13	52	
<b>Type of cancer (n)*</b>									
CRC	23		8		8		7		
Endometrial	7		2		3		2		
Urothelial	2		1		1		0		
Ovarian	2		0		1		1		
Other	20		6		7		7		
<b>Accrual</b>									
Site									0.542
Brigham	22	27.5	7	25.0	5	18.5	10	40.0	
Huntsman	9	11.3	3	10.8	4	14.8	2	8.0	
MDACC	30	37.5	9	32.1	13	48.2	8	32.0	
Michigan	19	23.8	9	32.1	5	18.5	5	20.0	

**Table S2.** Demographic and genetic information of Lynch syndrome patient-derived organoids (PDOs). Female, F; Male, M; Normal mucosa, NM; MMR, mismatch repair.

Patient ID#	Condition	Age	Gender	MMR gene	Mutation	Type of Tissue	Colon Location	mRNAseq	qPCR validation
1	DMSO Naproxen	37	F	MSH2	c.1034G>A	Normal Mucosa	Sigmoid	✓	✓
2	DMSO Naproxen	43	M	MLH1	c.306G>A	Normal Mucosa	Sigmoid	✓	✓
3	DMSO Naproxen	73	M	MSH2	c.1906G>C	Normal Mucosa	Sigmoid	✓	✓
4	DMSO Naproxen	56	M	MLH1	del Exon 15	Normal Mucosa	Sigmoid	✓	-
5	DMSO Naproxen	47	M	PMS2	c.137G>T	Normal Mucosa	Sigmoid	✓	✓
6	DMSO Naproxen	70	F	MSH6	c.663_667delAGATAinsTAC	Normal Mucosa	Sigmoid	✓	-

**Table S3.** Primer sequences used for assessment of gene expression using qRT-PCR in organoid lines.

Gene	Forward primer	Reverse primer
LGR5	TCAGTCAGCTGCTCCCGAAT	CGTTTCCCGCAAGACGTAAC
ASCL2	GGCACTGCTGCTCTGCTA	GTTACGCTCCCTTGAAGA
KRT20	TGTCCTGCAAATTGATAATGCT	AGACGTATTCCTCTCTCAGTCTCATA
LYZ	GGCCAAATGGGAGAGTGGTTA	CCAGTAGCGGCTATTGATCTGAA
MUC2	GAGGGCAGAACCCGAAACC	GGCGAAGTTGTAGTCGCAGAG
TOP2A	TGGCTGTGGTATTGTAGAAAGC	TTGGCATCATCGAGTTTGGGA
PPIA	ATGGTCAACCCACCGTGT	TCTGCTGTCTTTGGGACCTTGTC
CDKN1C	AGCACATCCACGATGGAGC	ACCGTCTCGCGGTAGAACGC
CDKN2A	CAGCAGAGGAAGACCATGTG	GGCGTTTGGAGTGGTAGAAA
E2F1	ACGTGACGTGTCAGGACCT	GATCGGGCCTTGTTTGCTCTT
BIRC5	AGTGAGGGAGGAAGAAGGCA	TTCACTGTGGAAGGCTCTGC
MKI67	TGAATTTCCAAGAAAAATACGTGA	TCAGGGTCAGAAGAGAAGCTAGA
NGFR	CCTACGGCTACTACCAGGATG	CACACGGTGTTCTGCTTGT

**Table S4.** Summary of adverse events by grade and relation to the treatment as assigned by study investigators.

Grade	Relationship	Placebo	LD Naproxen	HD Naproxen	Total
3 - Severe	Unrelated	3	5	0	8
	Unrelated	21	16	19	56
2 - Moderate	Unlikely	3	2	0	5
	Possible	2	2	2	6
	Probable	0	0	2	2
1 - Mild	Unrelated	18	19	13	50
	Unlikely	8	7	7	22
	Possible	11	10	11	32
	Probable	0	0	5	5

**Table S5.** Adverse events experience by participants with possible or probable relation to the treatment. The table displays the total number of events. Note that no grade 3 events related to the study intervention were reported among the participants. LD, Low-Dose; HD, High-dose.

	Placebo		LD Naproxen		HD Naproxen		Total
	1 Mild	2 Moderate	1 Mild	2 Moderate	1 Mild	2 Moderate	
Allergic Reaction	0	0	0	1	0	0	1
Anxiety	0	0	0	0	1	0	1
Bruising	1	0	0	0	3	1	5
Chest Pain	0	0	1	0	0	0	1
Constipation	0	0	0	1	2	0	3
Cough	0	0	0	0	1	0	1
Diarrhea	2	0	0	0	0	0	2
Dysphagia	1	0	0	0	0	0	1
Gastroesophageal Reflux	2	0	1	0	1	0	4
Gastrointestinal Bleeding	0	0	3	0	5	0	8
Hypertension	0	1	0	0	0	0	1
Insomnia	0	0	0	0	0	2	2
Neuropathy	0	0	0	0	1	0	1
Migraine	1	0	0	0	0	0	1
Nausea/Vomiting	2	1	2	0	2	0	7
Changes in urine color	1	0	0	0	0	0	1
Palpitations	0	0	0	0	0	1	1
Rash	0	0	2	0	0	0	2
Tinnitus	0	0	1	0	0	0	1
Vivid dreams	1	0	0	0	0	0	1

**Table S6.** Changes in levels of PGE2 in normal colorectal mucosa in absolute values and comparisons between treatment groups. P-values have been calculated applying Wilcoxon rank sum test.

Assay	Variable	Placebo 23	LD Naproxen 13	HD Naproxen 15	P-value Placebo vs LD Naproxen	P-value Placebo vs HD Naproxen	P-value LD Naproxen vs HD Naproxen
<b>PGE2 (ng/g)</b>	Mean±Std	204.3±335.2	140.3±206.6	134.8±127.1	0.189	0.743	0.295
<b>Baseline</b>	Median (Min,Max)	119.3 (4.5,1641.7)	38.0 (5.4,685.0)	79.0 (19.1,442.3)			
<b>PGE2 (ng/g)</b>	Mean±Std	145.50±171.85	4.88±6.22	6.81±10.94			
<b>Post</b>	Median (Min,Max)	81.3 (1.7,708.1)	2.2 (0.0,19.0)	2.1 (0.0,42.0)			
<b>PGE2 (ng/g)</b>	Mean±Std	-58.83±206.26	-148.31±217.03	-133.51±127.65	0.065	<b>0.005</b>	0.434
<b>Change</b>	Median (Min,Max)	-11.9 (-933.7,112.7)	-37.0 (-683.9,-3.0)	-85.2 (-436.9,-17.2)			

**Table S7.** Changes in levels of PGE-M in normal colorectal mucosa in absolute values and comparisons between treatment groups. P-values have been calculated applying Wilcoxon rank sum test.

Assay	Variable	Placebo	LD Naproxen	HD Naproxen	P-value	P-value	P-value
		23	15	15	Placebo vs LD Naproxen	Placebo vs HD Naproxen	LD Naproxen vs HD Naproxen
PGE-M (ng/mg) Baseline	Mean±Std	11.8±10.7	10.7±4.8	8.3±8.4	0.403	0.259	<b>0.046</b>
	Median (Min,Max)	7.1 (2.1,38.0)	10.5 (2.7,18.6)	4.9 (2.1,30.1)			
PGE-M (ng/mg) Post	Mean±Std	11.80±13.0	5.57±4.70	2.41±2.06	0.029	0.049	0.678
	Median (Min,Max)	6.2 (0.2,44.4)	4.1 (0.9,18.2)	1.5 (0.3,7.7)			
PGE-M (ng/mg) Change	Mean±Std	-0.12±7.16	-5.10±5.43	-6.12±8.75	0.029	0.049	0.678
	Median (Min,Max)	-0.4 (-15.6,12.5)	-3.8 (-14.2,4.5)	-2.8 (-28.7,2.2)			



**Table S8.** Naproxen levels in plasma and normal colorectal mucosa. Levels in patients assigned to placebo were also determined and rendered undetectable levels in all patients.

		<b>LD Naproxen</b>	<b>HD Naproxen</b>
<b>Naproxen concentration plasma</b>	Mean±Std	164.70±37.59	317.61±113.63
	Median (Min,Max)	163.5 (119.7,221.7)	289.0 (160.5,592.1)
<b>Naproxen concentration biopsy</b>	Mean±Std	15.6±11.0	23.8±13.8
	Median (Min,Max)	12.2 (4.0,37.7)	21.3 (3.5,48.8)

**Table S9.** Changes in levels of different Prostaglandins in normal colorectal mucosa in absolute values and comparisons between treatment groups. P-values have been calculated applying Wilcoxon rank sum test.

Assay	Variables	Placebo 19	LD Naproxen 12	HD Naproxen 13	P-value Placebo vs LD Naproxen	P-value Placebo vs HD Naproxen	P-value LD Naproxen vs HD Naproxen
<b>9a11b-PGF2a (ng/g)</b>	Mean±Std	8.7±17.2	5.5±7.9	7.3±8.2	0.799	0.439	0.476
<b>Baseline</b>	Median (Min,Max)	2.1 (0.0,74.6)	2.2 (0.0,29.9)	3.9 (0.0,27.5)			
<b>9a11b-PGF2a (ng/g)</b>	Mean±Std	6.68±12.73	0.17±0.26	0.10±0.14			
<b>Post</b>	Median (Min,Max)	2.1 (0.0,48.7)	0.0 (0.0,0.8)	0.0 (0.0,0.3)			
<b>9a11b-PGF2a (ng/g)</b>	Mean±Std	-2.01±10.88	-5.71±8.27	-7.22±8.13	<b>0.034</b>	<b>0.006</b>	0.539
<b>Change</b>	Median (Min,Max)	0.0 (-44.1,21.0)	-2.0 (-29.2,0.0)	-3.9 (-27.5,0.0)			
		<b>23</b>	<b>13</b>	<b>15</b>			
<b>PGF2a (ng/g)</b>	Mean±Std	19.9±35.5	12.7±15.5	13.6±13.4	0.282	0.83	0.465
<b>Baseline</b>	Median (Min,Max)	8.5 (0.6,172.0)	4.9 (0.6,44.3)	7.3 (1.2,43.6)			
<b>PGF2a (ng/g)</b>	Mean±Std	15.07±21.43	62.49±210.12	3.35±4.11			
<b>Post</b>	Median (Min,Max)	7.2 (0.2,74.0)	0.9 (0.1,761.5)	0.7 (0.1,12.8)			
<b>PGF2a (ng/g)</b>	Mean±Std	-4.86±22.79	48.48±214.47	-9.94±11.82	0.188	<b>0.025</b>	0.854
<b>Change</b>	Median (Min,Max)	0.1 (-101.3,30.5)	-6.4 (-38.6,761.0)	-5.7 (-35.6,2.1)			
		<b>23</b>	<b>13</b>	<b>16</b>			
<b>6-Keto-PGF1a (ng/g) Baseline</b>	Mean±Std	45.1±56.8	22.7±36	22.2±22.8	0.179	0.502	0.395
	Median (Min,Max)	18.5 (0.0,186.8)	8.3 (0.0,133.5)	11.5 (2.6,76.5)			
<b>6-Keto-PGF1a (ng/g) Post</b>	Mean±Std	28.44±27.35	0.28±0.80	0.36±0.60			
	Median (Min,Max)	19.3 (0.0,112.1)	0.0 (0.0,2.9)	0.0 (0.0,1.8)			
<b>6-Keto-PGF1a (ng/g) Change</b>	Mean±Std	-16.62±46.10	-22.87±38.49	-21.84±22.66	0.093	<b>0.027</b>	0.392
	Median (Min,Max)	0.1 (-136.8,36.7)	-8.3 (-133.5,1.8)	-11.5 (-76.5,-2.6)			
		<b>23</b>	<b>13</b>	<b>15</b>			
<b>PGD2 (ng/g) Baseline</b>	Mean±Std	135.9±216.1	88.6±76.5	95.4±135.5	1	0.539	0.767
	Median (Min,Max)	48.5 (5.1,1028.4)	62.3 (8.7,224.3)	43.3 (10.2,502.4)			
<b>PGD2 (ng/g) Post</b>	Mean±Std	104.87±112.07	2.65±3.59	3.78±6.18			
	Median (Min,Max)	50.9 (0.0,413.6)	2.0 (0.0,11.5)	0.7 (0.0,19.0)			
<b>PGD2 (ng/g) Change</b>	Mean±Std	-31.08±164.16	-88.17±80.20	-96.55±137.58	<b>0.004</b>	<b>0.004</b>	0.927

<b>Change</b>	Median (Min,Max)	-2.1 (- 715.0,143.7)	-45.7 (-222.2,-8.6)	-43.3 (-547.0,-9.0)			
		<b>23</b>	<b>13</b>	<b>16</b>			
<b>TxB2 (ng/g)</b>	Mean±Std	72.6±122.9	51.9±88	52.3±45.1	0.232	0.943	0.228
<b>Baseline</b>	Median (Min,Max)	46.2 (2.5,545.1)	23.0 (0.0,355.2)	36.0 (11.6,136.6)			
<b>TxB2 (ng/g)</b>	Mean±Std	46.21±34.73	1.11±1.58	0.33±1.04			
<b>Post</b>	Median (Min,Max)	37.9 (0.0,135.8)	0.0 (0.0,4.0)	0.0 (0.0,4.1)			
<b>TxB2 (ng/g)</b>	Mean±Std	-26.40±95.51	-53.60±94.10	-52.00±44.50	0.07	<b>0.009</b>	0.211
<b>Change</b>	Median (Min,Max)	-0.3 (-424.6,48.3)	-22.9 (-352.3,0.0)	-36.0 (-159.5,- 11.6)			

**Table S10.** Gene pathways with FDR<0.05 modulated by the naproxen. Results generated by combining genes coming both from HD and LD dose levels. Pathways in bold are consistent with immune deregulation by naproxen treatment.

Pathways	P- adj	NES	No. of genes
<b>IMMUNE ESTIMATE</b>	0.001	2.207	140
<b>IMMUNE RESP GO BP</b>	0.001	2.136	211
<b>KEGG PRIMARY IMMUNODEFICIENCY</b>	0.001	2.127	34
KEGG HEMATOPOIETIC CELL LINEAGE	0.001	2.017	79
<b>KEGG CYTOKINE CYTOKINE RECEPTOR INTERACTION</b>	0.001	2.004	223
KEGG RIBOSOME	0.001	1.998	87
<b>REACTOME CHEMOKINE RECEPTORS BIND CHEMOKINES</b>	0.018	1.988	48
<b>HALLMARK ALLOGRAFT REJECTION</b>	0.001	1.906	197
<b>REACTOME GENERATION OF SECOND MESSENGER MOLECULES</b>	0.041	1.853	26
HALLMARK MYC TARGETS V2	0.02	1.727	58
TGFB 2	0.001	1.686	168
REACTOME PEPTIDE LIGAND BINDING RECEPTORS	0.021	1.651	131
REACTOME CLASS A1 RHODOPSIN LIKE RECEPTORS	0.018	1.634	221
KEGG CELL ADHESION MOLECULES CAMS	0.029	1.555	125
REACTOME GPCR LIGAND BINDING	0.018	1.549	307
REACTOME G ALPHA I SIGNALLING EVENTS	0.048	1.524	155
<b>KEGG CHEMOKINE SIGNALING PATHWAY</b>	0.029	1.495	179
KEGG NEUROACTIVE LIGAND RECEPTOR INTERACTION	0.04	1.431	214
<b>REACTOME GPCR DOWNSTREAM SIGNALING</b>	0.04	1.376	409
REACTOME CELL CYCLE	0.021	-1.457	378
REACTOME CELL CYCLE MITOTIC	0.021	-1.507	302
HALLMARK E2F TARGETS	0.005	-1.582	198
REACTOME MITOTIC M M G1 PHASES	0.021	-1.601	162
REACTOME DNA REPLICATION	0.021	-1.615	182
REACTOME BIOLOGICAL OXIDATIONS	0.021	-1.709	121
REACTOME MITOTIC PROMETAPHASE	0.021	-1.729	79
KEGG RETINOL METABOLISM	0.019	-1.751	52
KEGG DRUG METABOLISM CYTOCHROME P450	0.009	-1.79	62
REACTOME PHASE II CONJUGATION	0.021	-1.809	60
KEGG PORPHYRIN AND CHLOROPHYLL METABOLISM	0.01	-1.85	38
KEGG DRUG METABOLISM OTHER ENZYMES	0.009	-1.872	46
REACTOME GLUCURONIDATION	0.023	-1.882	15

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KEGG STEROID HORMONE BIOSYNTHESIS	0.002	-2.02	48
STARCH SUCROSE METAB KEGG	0.001	-2.09	45
KEGG STARCH AND SUCROSE METABOLISM	0.001	-2.095	45
CRYPT TOP	0.001	-2.103	370

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