Supplementary Material

Table S1. Proteins identified in involved gastric mucosa of Ménétrier's disease patients by shotgun proteomic analysis.

Protein	Gene Name	Full Gene Name	Pre-Treatment counts	Post-Treatment counts	Fold-change	p-value
Proteins with higher spectral counts post-treatment						
IPI00027350.3	PRDX2	peroxiredoxin 2	0	16	∞	0.002309
IPI00032851.1	COPZ1	coatomer protein complex, subunit zeta 1	0	14	∞	0.002309
IPI00025100.1	BCKDHA	branched chain keto acid dehydrogenase E1, alpha polypeptide	0	10	∞	0.002309
IPI00293867.7	DDT	D-dopachrome tautomerase	0	10	∞	0.002309
IPI00418262.4	ALDOC	aldolase C, fructose-bisphosphate	0	10	∞	0.002309
IPI00550021.4	RPL3	ribosomal protein L3	0	10	∞	0.002309
IPI00291328.3	NDUFV2	NADH dehydrogenase (ubiquinone) flavoprotein 2, 24kDa	0	9	∞	0.002309
IPI00012119.1	DCN	decorin	0	10	∞	0.013969
IPI00024915.2	PRDX5	peroxiredoxin 5	0	10	∞	0.013969
IPI00006114.4	SERPINF1	serpin peptidase inhibitor, clade F (alpha-2 antiplasmin, pigment epithelium derived factor), member 1	0	9	∞	0.013969
IPI00017526.1	S100P	S100 calcium binding protein P	0	9	∞	0.013969
IPI00018246.5	HK1	hexokinase 1	0	9	∞	0.019652
IPI00015141.4	CKMT2	creatine kinase, mitochondrial 2 (sarcomeric)	0	8	∞	0.019652
IPI00003734.1	LOC347701	calgizzarin-like	0	8	∞	0.019652
IPI00006721.3	OPA1	optic atrophy 1 (autosomal dominant)	0	8	∞	0.013969
IPI00026665.2	QARS	glutaminyl-tRNA synthetase	0	8	∞	0.015987
IPI00604664.4	NDUFS1	NADH dehydrogenase (ubiquinone) Fe-S protein 1, 75kDa (NADH-coenzyme Q reductase)	0	14	∞	0.024941
IPI00401776.9	MUC6	mucin 6, oligomeric mucus/gel-forming	0	11	∞	0.045686
IPI00026087.1	BANF1	barrier to autointegration factor 1	0	10	∞	0.029086
IPI00216694.3	PLS3	plastin 3 (T isoform)	2	26	7.978694	0.020992
IPI00009893.1	LIPF	lipase, gastric	5	47	5.769210	0.043437
IPI00075248.11	CALM2	calmodulin 2 (phosphorylase kinase, delta)	5	34	4.173471	0.044332
IPI00010896.3	CLIC1	chloride intracellular channel 1	3	19	3.887056	0.044332
IPI00645078.1	UBE1	ubiquitin-activating enzyme E1	9	52	3.546086	0.013969
IPI00456969.1	DYNC1H1	dynein, cytoplasmic 1, heavy chain 1	6	32	3.273310	0.040341
IPI00218919.7	ATP4A	ATPase, H+/K+ exchanging, alpha polypeptide	7	36	3.156406	0.048786
IPI00009342.1	IQGAP1	IQ motif containing GTPase activating protein 1	10	48	2.945979	0.025964
IPI00419237.3	LAP3	leucine aminopeptidase 3	5	23	2.823230	0.029700
IPI00022200.2	COL6A3	collagen, type VI, alpha 3	23	105	2.801883	0.012067
IPI00306959.10	KRT7	keratin 7	9	40	2.727759	0.036465
IPI00218414.5	CA2	carbonic anhydrase II	98	384	2.404881	0.007074
IPI00017855.1	ACO2	aconitase 2, mitochondrial	22	83	2.315495	0.016882

Protein	Gene Name	Full Gene Name	Pre-Treatment counts	Post-Treatment counts	Fold-change	p-value
Proteins with lower spectral counts post-treatment						
IPI00644766.3	TOR1AIP1	torsin A interacting protein 1	8	4	3.258679	0.013969
IPI00021891.5	FGG	fibrinogen gamma chain	20	10	3.258679	0.018157
IPI00045511.1	CLCC1	chloride channel CLIC-like 1	10	5	3.258679	0.024913
IPI00410714.5	HBA1	hemoglobin, alpha 1	314	166	3.082003	0.013969
IPI00032293.1	CST3	cystatin C	15	8	3.055011	0.013969
IPI00157820.3	TXNRD2	thioredoxin reductase 2	7	4	2.851344	0.027473
IPI00217468.3	HIST1H1B	histone cluster 1, H1b	20	12	2.715566	0.027473
IPI00025333.4	CIAPIN1	cytokine induced apoptosis inhibitor 1	11	7	2.560390	0.036465
IPI00640417.1	HP1BP3	heterochromatin protein 1, binding protein 3	18	12	2.444009	0.024941
IPI00007334.1	ACIN1	apoptotic chromatin condensation inducer 1	16	11	2.369948	0.027473
IPI00021885.1	FGA	fibrinogen alpha chain	70	50	2.281075	0.008418
IPI00010675.1	TFF2	trefoil factor 2	104	75	2.259351	0.004005
IPI00011695.8	PRSS2	protease, serine, 2 (trypsin 2)	12	9	2.172452	0.020737
IPI00180240.2	TMSL3	thymosin-like 3	19	15	2.063830	0.013969
IPI00008418.6	DIABLO	diablo homolog (Drosophila)	10	8	2.036674	0.009594

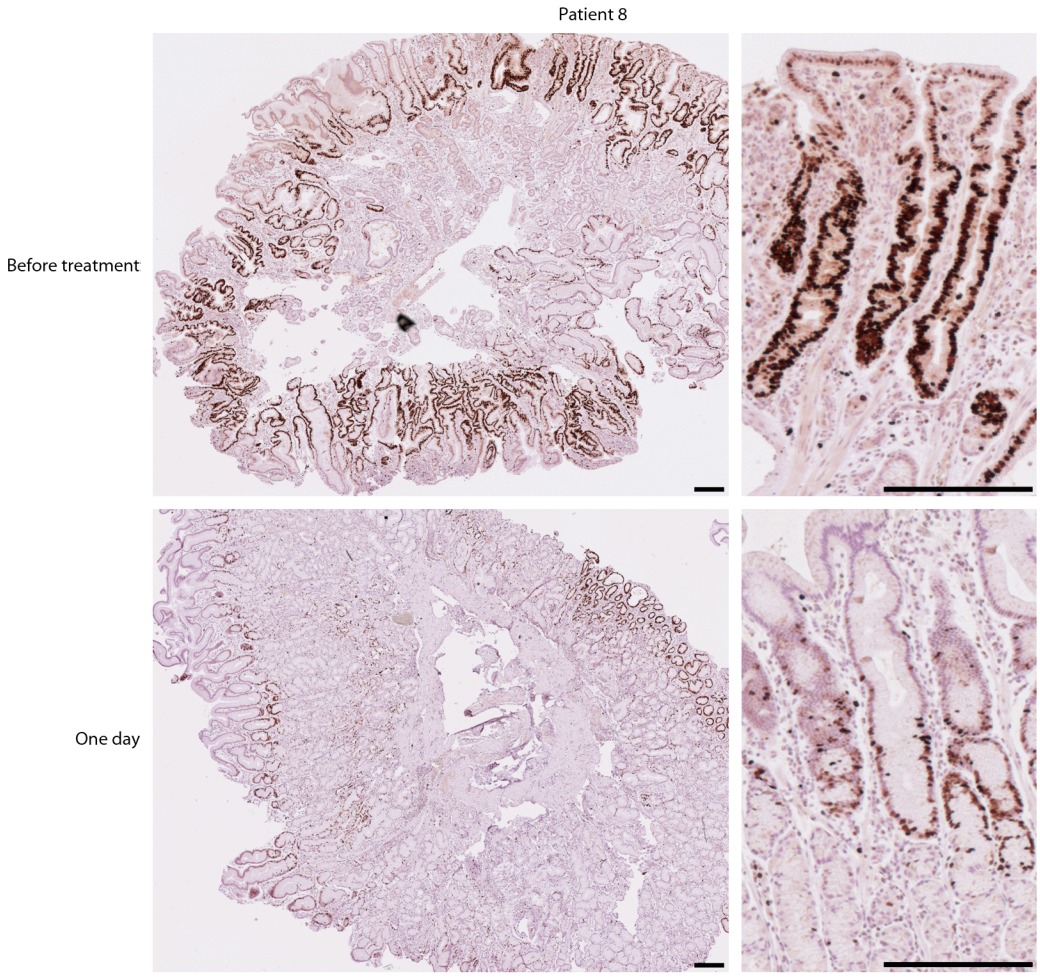

Fig. S1. Decreased proliferation in gastric mucosa of patient 8 one day after first dose of cetuximab. Although this patient opted to leave the trial after one treatment, there was a marked decrease in Ki-67 staining in the involved gastric mucosa. Scale bar is 250 microns.

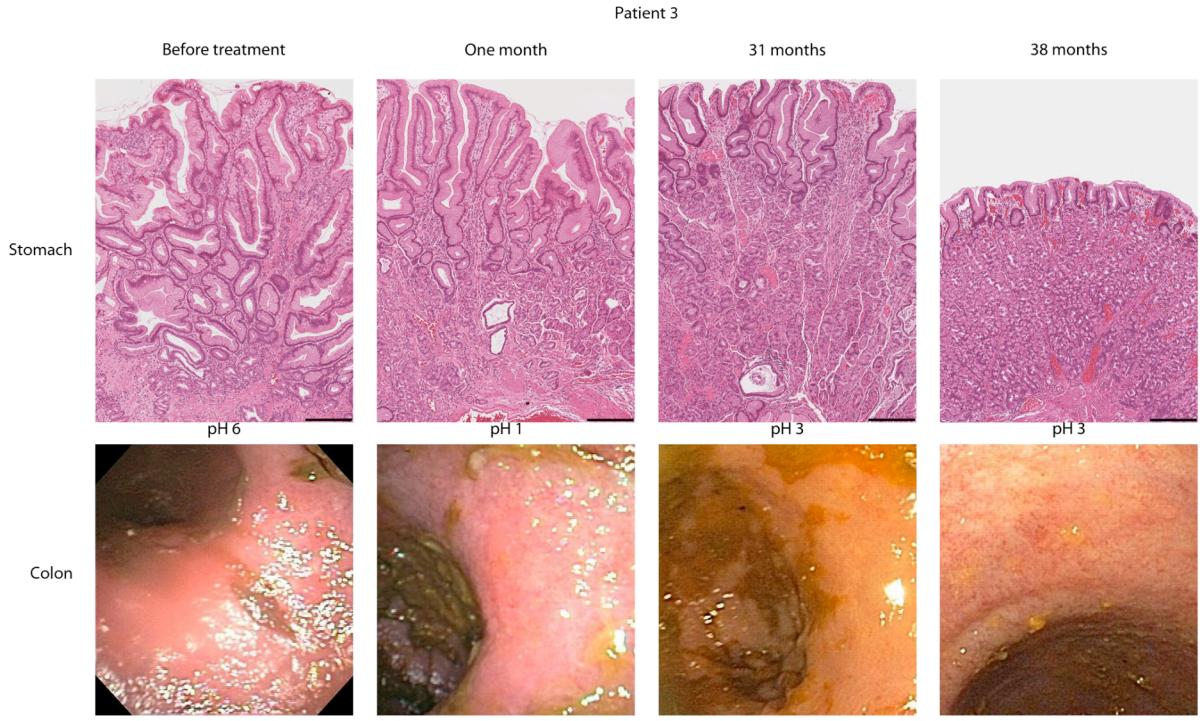

Fig. S2. Long term changes in the stomach and colon of patient 3. (A) Patient 3 demonstrated partial improvement in foveolar hyperplasia after one month of treatment (top panel). Fovelar hyperplasia continued to regress further with long term cetuximab therapy, along with restoration of normal gastric glandular architecture and improved gastric acidity. Scale bar is 250 microns. (B) There was no evidence of increased severity of ulcerative colitis with long term cetuximab as determined by gross and microscopic (data not shown) examination of the colon at sigmoidoscopy.

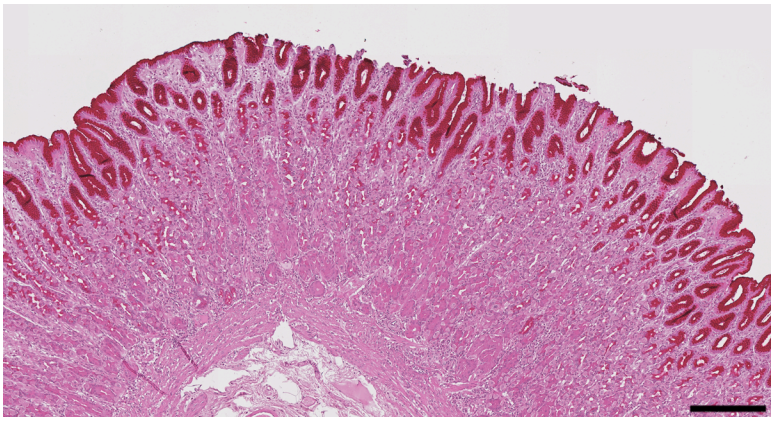

Fig. S3. Patient 4 had histologically normal stomach at gastrectomy. Scale bar is 250 microns.

Case Series

Patient 1

A 79-year-old woman traveled from Lebanon to Vanderbilt University Medical Center to enter the trial. She had experienced one and a half years of severe epigastric pain associated with nausea and vomiting, as well as peripheral edema. During the one-month course of cetuximab, her symptoms and edema resolved. She elected to continue cetuximab infusions without any apparent complications every two weeks for 18 months. At that time, a repeat gastroscopy showed a grossly and histologically normal stomach. As a result, cetuximab was discontinued, and she has continued to be asymptomatic for one year. Nine months after discontinuing cetuximab, the stomach was grossly normal at gastroscopy with a gastric pH of 1, and there was minimal foveolar hyperplasia histologically.

Patient 2

A 48-year-old woman from Tennessee with a history of ankylosing spondylitis presented with six months of nausea and hypoalbuminemia that failed to respond to medical therapy. An upper endoscopy demonstrated findings consistent with Ménétrier's disease, and she was started on cetuximab. The patient noted prompt and significant improvement in her nausea. She continued on long-term therapy, with gradual lengthening of the interval of her infusions from every two to every three weeks. After 16 months of treatment, the gastric mucosa appeared normal with a gastric pH of 2 at gastroscopy, and histologically there was minimal foveolar hyperplasia. As a result, cetuximab was discontinued, and her symptoms have continued to be well controlled for 4 months since stopping treatment.

Patient 3

A 28-year-old male from South Carolina with a two-year history of pancolonic ulcerative colitis presented with burning epigastric pain, along with nausea and vomiting approximately twice per week. He developed lower extremity swelling and hypoalbuminemia. His ulcerative colitis had been previously treated with balsalazide, 6-MP and infliximab, but he was only treated with 6-MP at the time of enrollment in the trial. The patient had a marked reduction in his abdominal pain and nausea after starting cetuximab and has continued maintenance cetuximab infusions for more than 3 years. Follow-up upper endoscopies have revealed continued improvement in the thickened folds and mucous formation. He has also exhibited emergence of parietal cells on gastric biopsy with an associated reduction in his gastric pH from 6 at baseline to between 1 and 3 on follow-up. Histologically, the patient continues to show progressive improvement in the degree of foveolar hyperplasia, even after completing more than three years of treatment. His most recent gastroscopy, performed after 38 months of treatment, showed minimal foveolar hyperplasia and a gastric pH of 3.

Patient 4

A 41-year-old male from New Jersey presented with several years of dull, aching abdominal pain and intermittent lower extremity edema with hypoalbuminemia. Upon treatment with cetuximab, the patient had marked improvement in his abdominal pain, nausea and vomiting. After one month, there was reduced thickness of the gastric folds, regression of foveolar hyperplasia, and emergence of parietal cells with restoration of gastric acidity. He continued on cetuximab infusions for 9 months for control of abdominal pain. He elected to undergo total gastrectomy at that time due to excess fatigue that he attributed to cetuximab and anxiety about

the development of gastric cancer. At the time of gastrectomy, his stomach was grossly and histologically normal (Fig. S3).

Patient 5

A 51-year-old female from California with a long standing history of mild pancolonic ulcerative colitis treated with prednisone presented with one and a half years of progressive nausea and vomiting, anasarca to her waist, and fatigue associated with hypoalbuminemia. Due to her inability to maintain adequate oral intake, she required total parenteral nutrition and regular intravenous albumin infusions. During treatment, her symptoms improved, and parenteral nutrition and intravenous albumin infusions were discontinued. Cetuximab was discontinued after approximately two years of treatment. Approximately one year following discontinuation of cetuximab, a 4-cm gastric lesion containing high grade dysplasia was found at the time of surveillance gastroscopy, and she subsequently underwent total gastrectomy.

Patient 6

A 58-year-old male from California presented with iron deficiency anemia, and subsequent endoscopy demonstrated findings consistent with Ménétrier's disease. Prior to enrollment in the clinical trial, the patient was dependent upon regular packed red blood cell transfusions (despite intravenous iron supplementation), requiring a total of 11 units over the three months prior to enrollment. After the initial two infusions of cetuximab, the patient's hemoglobin stabilized, and he required no further transfusions for the duration of the month-long trial. The patient continued to receive cetuximab infusions every two weeks for approximately 4 months with no need for blood transfusions. Treatment was discontinued when the patient elected to undergo

total gastrectomy because of the premalignant nature of Ménétrier's disease. He did not receive cetuximab infusions for the three months prior to his gastrectomy; during this time, his hemoglobin dropped to 6.6 g/dL, requiring him to receive repeated transfusions.

Patient 7

A 33-year-old man from Arizona with a seven-year history of pancolonic ulcerative colitis presented with abdominal pain, nausea, vomiting, and severe anasarca. His ulcerative colitis had been previously treated with 6-MP and three doses of infliximab prior to the diagnosis of Ménétrier's disease. At the time of enrollment into the cetuximab trial, he was only being treated with prednisone. Due to hypoalbuminemia and an inability to maintain adequate nutritional intake, he had a percutaneous feeding tube placed and was also started on total parenteral nutrition. His nausea and vomiting decreased with cetuximab treatment, and he was able to discontinue total parental nutrition. He continued on therapy for 8 months. However, he had a significant infusion reaction to cetuximab, and elected to proceed to gastrectomy. He tolerated the operation well and had almost immediate improvement in his edema. Since his gastrectomy, he has had no return of symptoms and has returned to an active lifestyle.

Patient 8

A 57-year-old woman from New Jersey with a 30-year history of pancolonic ulcerative colitis presented with lower extremity edema, hypoalbuminemia, and nausea. Her ulcerative colitis had been previously treated with various 5-ASA agents, prednisone, budesonide, cortisone enemas, and 6-MP, but she was only on sulfasalazine and prednisone at the time of enrollment. A diagnosis of Ménétrier's disease was established and the patient elected to enter the clinical trial.

After one infusion, the patient elected to discontinue participation in the trial; however, she had not suffered any objective adverse events or toxicity related to the medication. She ultimately proceeded to gastrectomy, which she tolerated well.

Patient 9

A 54-year-old man from Maryland presented with epigastric abdominal pain that was responsive to non-steroidal anti-inflammatory drugs. An upper endoscopy demonstrated large gastric folds, and histological evaluation showed foveolar hyperplasia with a gastric pH of 7. The patient was enrolled in the clinical trial, and received two infusions of cetuximab with no improvement in his abdominal pain. After the second infusion, his initial baseline biopsies were reviewed by M.K.W. and a focus of gastric cancer was found. As a result, the patient withdrew from the study and returned home for additional treatment of his cancer.