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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

REVIEW

Gastrin and Gastric Cancer

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SUMMARY

The gastrointestinal peptide, gastrin, stimulates growth of gastric adenocarcinoma (gastric cancer) through the cholecystokinin-B receptors that are overexpressed in this malignancy. Serum gastrin levels may be increased secondary to chronic administration of proton pump inhibitors, atrophic gastritis, *Helicobacter pylori* infection, or from de novo gastrin expression from the gastric cancer epithelial cells. Strategies to interrupt the interaction of gastrin at the cholecystokinin-B receptor may provide a novel approach to the treatment of gastric cancer.

Gastric cancer is the third leading cause of cancer-related mortality worldwide. Despite progress in understanding its development, challenges with treatment remain. Gastrin, a peptide hormone, is trophic for normal gastrointestinal epithelium. Gastrin also has been shown to play an important role in the stimulation of growth of several gastrointestinal cancers including gastric cancer. We sought to review the role of gastrin and its pathway in gastric cancer and its potential as a therapeutic target in the management of gastric cancer. In the normal adult stomach, gastrin is synthesized in the G cells of the antrum; however, gastrin expression also is found in many gastric adenocarcinomas of the stomach corpus. Gastrin's actions are mediated through the G-protein–coupled receptor cholecystokinin-B (CCK-B) on parietal and enterochromaffin cells of the gastric body. Gastrin blood levels are increased in subjects with type A atrophic gastritis and in those taking high doses of daily proton pump inhibitors for acid reflux disease. In experimental models, proton pump inhibitor–induced hypergastrinemia and infection with *Helicobacter pylori* increase the risk of gastric cancer. Understanding the gastrin:CCK-B signaling pathway has led to therapeutic strategies to treat gastric cancer by either targeting the CCK-B receptor with small-molecule antagonists or targeting the peptide with immune-based therapies. In this review, we discuss the role of gastrin in gastric adenocarcinoma, and strategies to block its effects to treat those with unresectable gastric cancer. *(Cell Mol Gastroenterol Hepatol 2017;4:75–83; http://dx.doi.org/10.1016/j.jcmgh.2017.03.004)*

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Gastric adenocarcinoma (gastric cancer) is a common malignancy and is the world's second leading cause of cancer mortality worldwide.[1] Novel therapeutic targets desperately are needed. The meager improvement in the approximately 10% cure rate realized by adjunctive treatments to surgery is unacceptable because more than 50% of patients with localized gastric cancer die as a result of their disease.[2] The prognosis of those with advanced gastric cancer is poor, with a 5-year survival of only 20%–30%.[3,4] The only curative option in the treatment of gastric cancer is surgery, and for metastatic disease conventional chemotherapy has shown only a modest benefit, with an average survival of approximately 10 months.[5] Unfortunately, however only marginal improvements in patient outcomes have been achieved with chemotherapy despite extensive phase 3 testing.[6] The current standard of care for advanced gastric cancer in the first-line setting remains a combination of a fluoropyrimidine (eg, 5-fluorouracil) and a platinum (eg, cisplatinum)-containing chemotherapeutic agent. Targeted therapy may offer new possibilities for the treatment of gastric cancer. Because human epidermal growth factor receptor 2 (HER2) receptors are found in approximately 20% of gastric cancers, the addition of a HER2-receptor antibody to standard chemotherapy may be beneficial, as shown in the Trastuzumab for Gastric Cancer study, in which trastuzumab (Herceptin; Genentech, South San Francisco, CA) was beneficial in subjects with HER2-positive gastric cancer.[7] However, clinical trials studying the value of other targeted therapies, such as with epidermal growth factor receptor (EGFR) or vascular endothelial growth factor, yielded disappointing results.[8,9]

Histologic and Molecular Classifications of Gastric Cancer

In the West, most of those with gastric cancer typically present with advanced or metastatic disease, whereas in several Asian countries, gastric cancer usually is identified early and cure rates are higher.[10] Other regional differences in gastric cancer are readily identifiable; for example,

Abbreviations used in this paper: **CCK-BR, cholecystokinin-B receptor; ECL, enterochromaffin-like; EGFR, epidermal growth factor receptor; ERK, extracellular signal–regulated kinase; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; PAS, polyclonal antibody stimulator; PPI, proton pump inhibitor; TCGA, The Cancer Genome Atlas.**

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proximal gastric cancers are more prevalent in Europe and the Americas than in Asia.[11] Histologically, gastric cancer has been categorized according to the Lauren[12] classification as either diffuse or intestinal-type. The intestinal-type is characterized by chronic *Helicobacter pylori* infection; is more prevalent in high-incidence areas such as Japan, Korea, and Eastern Europe[13]; and the more aggressive diffuse type has been associated with genetic variations (single nucleotide polymorphisms) of the prostate stem cell antigen.[14] The Cancer Genome Atlas (TCGA) Research Network described 4 groups of gastric cancer based on molecular classifications including Epstein–Barr virus, microsatellite instability, genomically stable, and chromosomal instability.[15] With the TCGA classification, 73% of the genomically stable were the diffuse type histologically according to Lauren's criteria and systematic differences in distribution were not observed between East Asian and those of Western origin. The Asian Cancer Research Group[16] further characterized the molecular classification with the incorporation of the tumor protein 53 activity and epithelial-to-mesenchymal transition and found some unique differences compared with the TCGA analysis.

Risk Factors for Gastric Cancer

Factors associated with an increased risk of gastric cancer include nutrition, such as high salt and nitrate intake, a diet low in vitamins A and C, the consumption of large amounts of smoked or cured foods, lack of refrigerated foods, and poor-quality drinking water.[17] Occupational exposure to rubber and coal also increase the risk.[18] Other risk factors that have been implicated include the following: cigarette smoking, *H pylori* infection, Epstein–Barr virus, radiation exposure, and prior gastric surgery for benign ulcer disease.[18] More recently, a number of investigators have shown that polymorphisms in inflammatory genes can be associated with gastric cancer risk.[19,20] Genetic risk factors include type A blood group, pernicious anemia, family history of gastric cancer, hereditary nonpolyposis colon cancer, and Li–Fraumeni syndrome.[18] Most cases of gastric cancer are sporadic, and gastric cancer associated with an inherited syndrome occurs in only a limited number of patients (1%–3%). E-cadherin mutations occur in approximately 25% of families with an autosomal-dominant hereditary form of diffuse gastric cancer.[21]

The gastrointestinal peptide gastrin is involved physiologically in secretion of gastric acid[22] and growth of the gastrointestinal tract.[23] Gastrin is an important growth factor for the developing[24] and adult[25] digestive system, and is trophic to the entire gastrointestinal tract.[26,27] Gastrin is released from G cells in the stomach antrum during normal physiologic digestion of food and serves as a major stimulator of gastric acid secretion from the stomach parietal cells (Figure 1).[28] In human beings the majority of gastrins are amidated and gastrin-17 is the most abundant circulating gastrin in the peripheral blood.[29] Proton pump inhibitors (PPIs) have been developed to facilitate healing of peptic ulcer disease and gastroesophageal reflux disease. Because this class of medications is very effective in suppressing acid, a consequence of long-term acid suppression can be the increase of serum gastrin levels[30,31] resulting from the interruption of the normal feedback mechanisms. One PPI, omeprazole, causes a 2- to 6-fold increase in serum gastrin levels in 80%–100% of patients receiving chronic therapy.[30,32,33] Up to 30% of patients on chronic PPI therapy may have gastrin blood levels greater than 500 ng/L or more than 6-fold greater than the upper limit of normal.[30,31,33] Even short-term administration of omeprazole has been shown to increase serum gastrin levels,[34] however, levels return to normal after discontinuation. Although raised as a potential issue at the time of their initial approval 25 years ago, the concern regarding PPI-induced hypergastrinemia has not disappeared completely.[35,36]

One concern in regard to hypergastrinemia and PPIs has been the potential relationship between gastrin and gastric cancer. When gastrin is administered in animal models, there is a marked increase in parietal cell mass and the enterochromaffin-like (ECL) cells of the stomach body.[37] Increased gastrin levels in rats[38] and human beings[39] have been associated with gastric carcinoid tumors arising from the ECL cells. In cell culture, gastrin has been shown to stimulate the growth of human gastric cancer cell lines.[40,41] Several reviews and meta-analyses have been performed concerning the association between PPI use and risk for gastrointestinal cancers without confirmatory results.[42,43] Ahn et al[44] reported a significantly increased risk of gastric cancer in a large systematic search with a cohort of nearly 6000 subjects; however, Lundell et al[45] did not find an increased risk in a cohort of 1920 subjects. Han et al[46] even suggested that PPI use may decrease the risk of gastric cancer by antagonizing the proliferative and anti-apoptotic effects of gastrin.[46]

Gastrin Mediates its Effects Through the Cholecystokinin-B Receptor

Gastrin mediates both its acid-releasing and growth properties on the gastrointestinal tract through a G-protein–coupled receptor called the cholecystokinin (CCK) or CCK-B receptor (CCK-BR).[47] After interacting with the CCK-BR on parietal or ECL-like cells, downstream signaling occurs through the activation of the phospholipase C–β/diacylglycerol/Ca^{2+}/protein kinase C cascade[48] (Figure 1). CCK-B receptors are overexpressed in gastric cancers,[40,49] and stimulation with exogenous gastrin promotes growth of this malignancy.[40] CCK receptors also induce other signaling pathways through tyrosine kinase receptors. CCK-BR signaling also has been shown to transactivate the EGFR[50] through Src and Matrix metalloproteinase releasing transforming growth factor-α from its precursor protein causing EGFR tyrosine phosphorylation.[50] The EGFR phosphorylates phosphoinositide 3-kinase, activating PDK1, Protein kinase B (PKB), and mammalian target of rapamycin. The EGFR interacts with adaptor proteins Grb2 and SOS, activating Ras and Raf, followed by phosphorylation of Mitogen-activated protein kinase/ERK and extracellular signal–regulated kinase (ERK). Gastrin also has been shown to mediate its actions by up-regulating phosphorylation of ERK

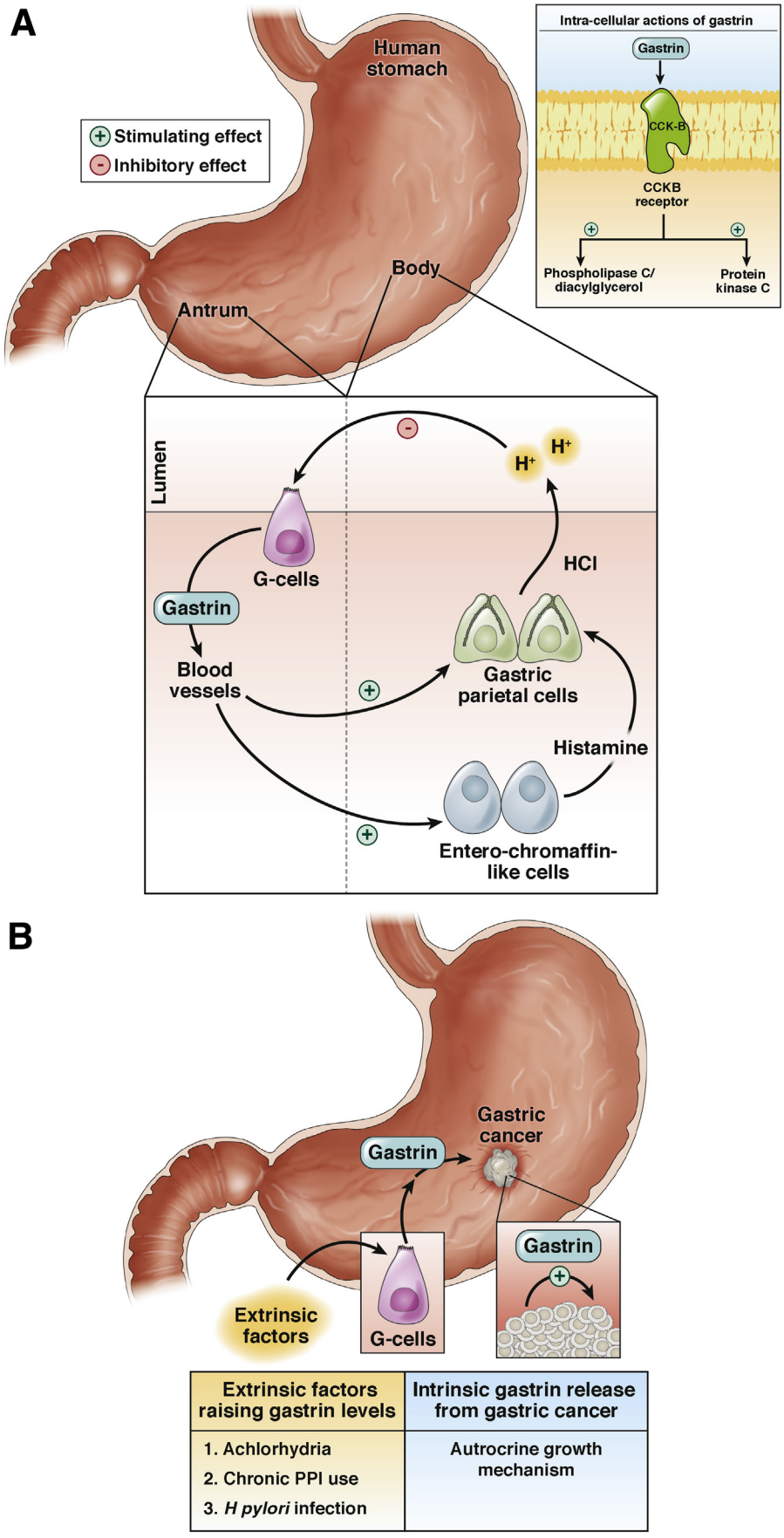

Figure 1. Physiologic and pathologic role of gastrin. (*A*) Under physiologic conditions gastrin is released from antrum G cells in response to food, decreased acid, and gastric distension. Gastrin circulates in the peripheral blood and binds to the CCK-B receptors on the parietal and ECL cells of the body. The ECL cells release histamine, which activates the H2 receptors on parietal cells and HCl (H^+) is released. The increased H^+ feeds back to the D cells of the antrum to release somatostatin to turn off the gastrin release. Gastrin also is responsible for basal growth and renewal of the gastric epithelium. Normal signaling through the CCK-B receptor occurs through the activation of the phospholipase C-β/diacylglycerol/Ca^{2+}/protein kinase C. (*B*) Increased gastrin levels can result from achlorhydria, chronic use of PPIs, or *H pylori* infection. Gastric cancer epithelial cells that express CCK-B receptors also produce their own gastrin de novo, which in turn stimulates growth and metastases of gastric cancer by an autocrine mechanism.

and K-Ras through the Ras-Raf-MEK1/2-ERK1/2 pathway.[51,52] Gastrin also has been shown to induce other EGFR ligands such as heparin-binding EGF,[53–55] as well as trefoil family factor 2 expression.[56,57] The end result of CCK-BR signaling involves motility,[58] secretion,[59] and migration,[60] as well as growth and proliferation.[26] In addition, gastrin has shown angiogenesis and anti-apoptotic characteristics in several malignancies including gastric cancer.[61–63]

Expression of Gastrin and the CCK-B Receptors in Gastric Cancer and Stem Cells

Unlike the normal expression of gastrin in G cells of the stomach,[64] the gastrin gene also becomes overexpressed de novo in nonendocrine epithelial cells of gastric cancer[65] and, likewise, the CCK-B receptor becomes overexpressed in cancer cells.[40] The mechanisms involved with gastrin gene activation or gastrin peptide re-expression are unknown, however, several mechanisms have been proposed. EGFR ligands have been shown to induce gastrin gene transcription in a human gastric cancer cell line, through an EGF response element that has been mapped to the gastrin promoter.[66] The gastrin promoter activation is mediated in part by the Ras–Erk signaling cascade that targets Sp1, a zinc finger transcription factor that is involved in regulating expression of a large number of genes that contribute to the "hallmarks of cancer."[67] Goetze et al[68] analyzed 20 resected human gastric cancers and found that all expressed CCK-B receptors and gastrin messenger RNA by real-time reverse-transcription polymerase chain reaction. They confirmed gastrin peptide expression in 16 of 20 gastric cancers by Western blot analysis and immunohistochemistry (IHC). Henwood[69] examined 90 archival tissue samples of gastrin cancer and also identified the de novo presence of gastrin peptide by IHC. Hur et al[70] examined 279 human gastric cancers and found gastrin peptide expression by IHC in 47.7% and the CCK-B receptor in 56.6%; the CCK-B receptor detection was significantly greater in tumors characterized as intestinal-type by the Lauren[12] classification. Hypergastrinemia in animal models has been shown to promote gastric carcinogenesis of proximal gastric tumors,[71] whereas deficiency of gastrin (ie, in gastrin knock-out mice) has been associated with antral tumors.[72] An explanation for these dissimilarities may be related to gastrin's actions on the stem cells in the antrum compared with the corpus. Through lineage tracing experiments, Hayakawa et al[73,74] reported that the CCK-B receptor expression in the stomach antrum is expressed in position 4+ of antral stem cells and responds to progastrin rather than gastrin-17. In the gastric cardia CCK-B receptors are found on position 4+ stem cells, but unlike the antral stem cells these cells respond to the proliferative actions of amidated gastrin-17.[74,75] In the body of the stomach, the CCK-B receptors on the parietal cells, ECL cells, and cells in the isthmus also respond to gastrin-17.[48,75,76]

There is a well-known association between *H pylori* infection and gastric cancer.[77,78] Although many investigators had thought that the mechanism solely due to chronic inflammation induced by *H pylori*, studies now have shown that *H pylori* also induces genetic and epigenetic changes that lead to genetic instability in gastric epithelial cells.[79] Cover[80] recently described strain differences in *H pylori* in regard to the presence or absence of a 40-kb chromosomal region known as the *cag* pathogenicity island. Current evidence suggests that the risk of gastric cancer is very low among persons harboring *H pylori* strains that lack the *cag* pathogenicity island. A relationship between gastrin and *H pylori* infections has shown that gastrin messenger RNA is upregulated by *H pylori*–cytotoxin–associated protein A.[81]

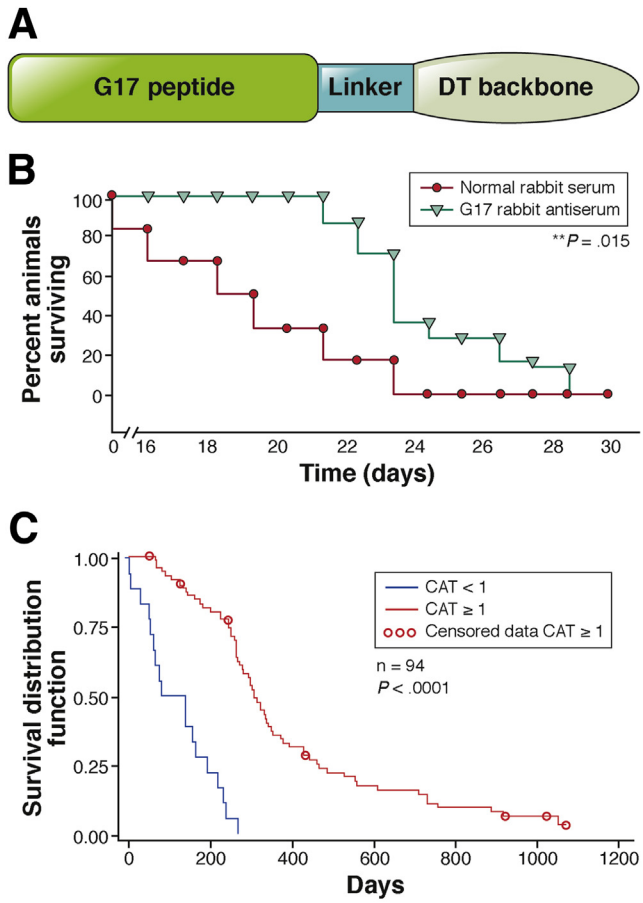

Figure 2. Polyclonal antibody stimulator. (*A*) Diagram showing the structure of PAS with the gastrin epitope linked to diphtheria toxoid with a peptide spacer. Characteristics include a molecular weight of 84 kilodaltons; an appearance that is clear, colorless, to slightly yellow solution; and a pH of 7.0–7.4. PAS is water-soluble and administered as an intramuscular injection. (*B*) Treatment of severe combined immunodeficiency disease mice with gastric cancer showed greater survival compared with mice treated with nonimmune antibody. $^{**}P = .015$.[107] (*C*) Human subjects with gastric cancer treated with PAS vaccination that elicit circulating antibody titers (CAT) have a significantly prolonged survival when compared with subjects who do not elicit an antibody response ($P < .0001$). (Adapted with permission from Ajani JA, Hecht JR, Ho L, et al. An open-label, multinational, multicenter study of G17DT vaccination combined with cisplatin and 5-fluorouracil in patients with untreated, advanced gastric or gastroesophageal cancer: The GC4 study. Cancer 2006;106:1908–1916).

Beales and Calam[82] showed that infection of canine G cells with *H pylori* increased endogenous gastrin secretion from the G cells by 17%–27%. In addition, patients with asymptomatic *H pylori* infection were found to have increased gastrin levels by enzyme-linked immunosorbent assay.[83]

Although hypergastrinemia is associated with the development of gastric neuroendocrine tumors and gastric adenocarcinoma,[84] both animal and human studies have shown the greater incidence of gastric carcinoids in patients with increased gastrin levels. One possible explanation for the more frequent neuroendocrine tumors over gastric adenocarcinoma in patients with hypergastrinemia may be related to the finding that although the CCK-B receptor is present on parietal cells, it is expressed more abundantly in ECL cells of the stomach.[85,86] In addition to responding to the proliferative effects of gastrin, studies also have shown that the parietal cells respond to other trophic factors secreted by the ECL-like cells by a paracrine mechanism including secretion of Reg protein,[87] heparin-binding EGF,[88] and even histamine.[89] With more sophisticated technology using lineage tracing, researchers have confirmed the presence of CCK-B receptors on the antrum stem cells that do not respond to gastrin-17.[73] These studies also help us understand that hypergastrinemia selectively increases the risk of gastric corpus cancers and low gastrin levels may increase the risk for antral cancers. Whether hypergastrinemia enhances the growth of gastric carcinoids more frequently than gastric adenocarcinoma seems irrelevant when the long-term prognosis differs between these 2 lesions, with adenocarcinoma doing more poorly. Clinical investigations in human subjects also have shown that hypergastrinemia adversely affects survival from subjects with stages 2–4 gastric adenocarcinomas.[90] Therefore, strategies to decrease gastrin levels in subjects with gastric cancers may be useful.

Gastrin-CCK-B Receptor Pathway

Treatment of cancer is improved significantly when a cancer-specific target or cell surface receptor is identified. Because gastrin has been shown to stimulate growth of gastric cancer and other gastrointestinal malignancies, researchers have been studying means to block the ligand:receptor interaction in an attempt to slow or arrest tumor growth. Numerous investigations have been conducted in cell culture and animal models of gastric cancer using small-molecule CCK-B receptor antagonists,[91,92] and their use in human trials has been reviewed.[76,93,94]

Clinical trials in human subjects with agents directed to the gastrin:CCK-B–receptor pathway are rare and most studies have investigated agents in other gastrointestinal cancers rather than in gastric cancer, such as gastrazole in pancreatic cancer[95] or netazepide[96] in gastric neuroendocrine tumors.

Polyclonal antibody stimulator (PAS), formerly called *G17DT* and *gastrimmune*, was developed as an immunogen containing a 9–amino acid epitope derived from the amino-terminal sequence of gastrin-17 conjugated to diphtheria toxoid (Figure 2*A*). PAS elicits specific and high-affinity antibodies that bind gastrin-17 and gly-gastrin, thus preventing its trophic activity. Unlike tumor-associated antigen-based vaccines, PAS is unique in that it produces neutralizing antibodies to gastrin with peak titers occurring by week 6 and persisting after vaccination for up to 40 weeks. Preclinical studies were performed in several animal models that have CCK-B receptors,[97–104] including gastric cancer.[40,41] In these animal models, PAS-generated anti-G17 antibodies have been shown to reduce growth and metastases.[105–107] Passive immunization with PAS antibodies raised in rabbits improved survival of severe combined immunodeficiency disease mice bearing gastric cancers compared with diluent-treated controls[108] (Figure 2*B*). To date, 5 open-labeled clinical trials have been conducted using PAS in subjects with gastric cancer in doses ranging from 10 to 500 μg intramuscularly (Table 1).[109,110] One gastric cancer study, GC2,[110] was a dose-finding study and tested 3 doses and analyzed response according to stage of disease. Only 1 study, GC4, evaluated the safety and survival of PAS in combination with standard chemotherapy.[109] The median survival of those with advanced gastric cancer after PAS administration was prolonged significantly (10.8 mo) in subjects who mounted a circulating antibody titer against gastrin (ie, responders) compared with subjects who failed to generate an antibody response (6.2 mo) (ie, nonresponders) (Figure 2*C*). The only notable PAS-related adverse events when compared with placebo were injection-site reaction and pyrexia.

Table 1. Summary of Clinical Trials With PAS in Gastric Cancer

Study name	Study design	Subjects, n	Dose(s), *mcg*	Schedule, *wk*	Results
GC2[110]	Open-label, dose ranging	52	10, 100, 250	0, 2, 6	250 μg gave a 92% Ab response
GC3	Open-label, dose ranging	33	100, 250, 500	0, 1, 3	Dosing schedule was poorly tolerated
GC4[109]	Open-label, combination of cisplatin and 5-fluorouracil in chemotherapy-naive subjects, safety and survival study	103	500	1, 5, 9, 25	67% Ab titers Survival Ab responders 10.3 mo
GC5	Open-label	7	500	0, 2, 6	Stopped prematurely because of poor tolerability
GC12	Open, dosing study	40	125, 250	0, 2, 6	85% Ab response, 250 μg was more effective than 125 μg

Ab, antibody; GC, gastric cancer.

Conclusions

Survival from advanced gastric cancer is poor and new strategies are needed for therapy. CCK-B receptors are overexpressed in many gastric cancers and when these receptors are activated by gastrin, the result is tumor proliferation. Furthermore, many gastric cancers also express gastrin, which stimulates cancer growth by an autocrine mechanism. Understanding the mechanisms and receptor-mediated pathways that regulate the growth of gastric cancer is important. Novel therapeutic agents that target the gastrin:CCK-B–receptor pathways are promising and may help improve survival of advanced gastric cancer.

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Conflicts of interest
These authors disclose the following: Nick Osborne is employed by Cato Research, a company that owns the rights to the polyclonal antibody stimulator; and Jill Smith serves as a consultant to Cato Research. The remaining author discloses no conflicts.