For years, peptides were largely overlooked by large pharmaceutical companies, who argued that these molecular entities lacked drug-like properties. However, specificity, potency and low toxicity are the main features of peptides as drugs, although their poor oral bioavailability and low biological stability, and as a consequence their short half-life in the body, cannot be disregarded [1]. Peptide therapeutics, many of them containing 10–30 amino acids and with one, two, sometimes even three disulfide bonds, are now synthetically manageable at large scales under regulatory compliance. This achievement, along with the dramatic reduction in the cost of synthesis over the past decade, has helped advance peptides as therapeutic agents. To date, hundreds of synthetic therapeutic peptides are in clinical trial processes, and even more are in advance stages of preclinical studies [2].

Recently, after a long journey of preclinical studies and clinical trials, linaclotide, a first-in-class GC-C receptor peptide agonist, has received the approval in the USA and Europe for the treatment of IBS-C and CIC. This article provides an overview of clinical, economic and biological aspects of IBS-C and CIC and covers the current and emerging therapeutic agents for treating these conditions. Particularly, the pharmacodynamic and pharmacokinetic properties of linaclotide, a small, disulfide-rich peptide, and its implications in the future of peptide drug discovery and development are discussed.

**Functional gastrointestinal disorders: a major health & social problem**

Functional gastrointestinal disorders are a heterogeneous group of symptomatically-defined clinical entities characterized by chronic or recurrent gastrointestinal disorders in the absence of any known structural or biochemical abnormalities. Functional gastrointestinal disorders are influenced by multiple factors, including genetic predisposition, environmental influence, as well as by psychological and social factors. According to Rome III criteria [3], CIC and IBS-C are two distinct functional bowel disorders associated with constipation [4]. IBS-C is distinguished from CIC based on the presence of any abdominal pain or discomfort associated with disturbed defecation. Thus, these two clinical entities share a number of symptoms, such as straining, hard or lumpy stools, decreased frequency of bowel movement and the sensation of incomplete evacuation; however, only those patients experiencing abdominal pain or discomfort are most likely to suffer from IBS-C. Nevertheless, there has been some evidence to suggest a degree of overlap between these two conditions, and an absence of stability in either diagnosis during follow-up, thereby indicating that IBS-C and CIC may not be entirely separate conditions [5].

The worldwide impact of these two functional bowel disorders is frequently underestimated because of the restricted associated mortality. However, CIC and IBS-C have a significant...
negative impact on the patient’s quality of life, and an elevated prevalence in the population, which has a significant direct healthcare cost because of the number of physician visits, unnecessary diagnostic tests, procedures and surgeries, along with indirect expenses as a result of absenteeism and presenteeism, thereby making these conditions a major health and social problem [6–8]. A recent meta-analysis revealed a global prevalence of 11.2% for IBS [9], whereas a previous study disclosed a 14% for CIC, along with a significantly elevated presence of CIC individuals with IBS, thus, suggesting an overlap between these two conditions [10]. Specifically, IBS may affect up to one in five people at some point in their lives [11] and its prevalence in Europe is estimated at 11.5% of the population, although only 4.8% are formally diagnosed [12]. Thus, approximately 27 million Europeans suffer from this condition, of which just 11 million are officially diagnosed. Total costs relating to IBS have been estimated at €700–1600 per person per year in Europe [13,14], while in the USA, the annual costs of IBS are similar to, or greater than the cost of other common chronic conditions, such as asthma and congestive heart failure [15].

Emerging therapeutic targets for chronic constipation disorders: current & prospective therapeutic agents for the treatment of CIC & IBS-C

Multiple factors have been considered to play a role in the complex pathophysiology of IBS and CIC disorders [16,17]. Although recent studies have proposed that CIC and IBS-C are enteric neuropathies [18], precise pathophysiological mechanisms underlying these disorders remain incompletely understood, and patients not responding to diet and lifestyle changes require effective and safe long-term therapies. As our knowledge of the pathophysiology of these disorders increases, one of the most important things the pharmaceutical industry can offer patients is the development of compounds with proved global symptom relief and minimal side effects. Traditional therapies are often of limited efficacy in addressing the overall symptom complex and are usually insufficient in terms of patient satisfaction [19]. Among nonspecific laxatives available, osmotic laxatives, such as PEG and lactulose, have shown efficacy for chronic constipation, although they may not alleviate pain in IBS-C, whereas stimulant laxatives, such as diphenylmethanes (e.g., bisacodyl and sodium picosulfate), have demonstrated effectiveness for chronic constipation. However, no randomized controlled clinical trials have assessed the effectiveness or long-term safety of these drugs [20].

The potential market for IBS-C and CIC drugs is large but under-penetrated by the global pharmaceutical industry with only a few effective therapeutic agents are available to mitigate the predominant bowel symptoms. According to Decision Resources Group, the IBS drug market will experience a dramatic growth, increasing from US$611 million in 2010 to $3.1 billion in 2020 [103].

In the last decade, the discovery of novel therapeutic targets has helped to identify the underlying pathology (e.g., abnormal gastrointestinal motility and secretion in CIC and IBS-C individuals, and visceral hypersensitivity in IBS-C patients) and promote the development of prospective therapeutic agents. Among others, novel therapeutic targets identified for the treatment of chronic constipation disorders include the 5-HT4 receptor, CLC2, CCK1 or CCKA, the GC-C receptor, IBAT, and NHE3 channel [21,104].

The pharmaceutical industry is highly incentivized to invest in the development of more efficacious therapies for CIC and IBS-C. In this regard, several clinical trials are currently evaluating the effectiveness of molecular entities directed at new targets for the treatment of these two conditions (Table 1). Furthermore, many pharmaceutical companies are now in the process of developing drugs with indications for both men and women, which is a major improvement for male IBS-C patients because, until now, most new medications have been tested and approved only for use in women.

The first serotonergic agent for the treatment of chronic constipation disorders was tegaserod [22], an indole carbazimidamide agonist with high affinity for 5-HT4 receptor, which received approval from the FDA in 2002 for the treatment of IBS-C in women and CIC. However, this drug was withdrawn from the US market in 2007 after postmarketing analysis demonstrated increased serious cardiovascular effects in some patients [23]. Prucalopride [24,25], another 5-HT4 agonist, was approved by the European Medicines Agency (2009), Australia (2011) and Canada (2011). However, the FDA has recently refused its marketing in the USA. At present, diverse pharmaceutical companies are carrying out clinical trials to evaluate potential 5-HT4 receptors.
receptor agonists, including velusetrag \[\text{26,27}\], HCP–0613 (a combination of Mosapride, Bacillus subtilis and Streptococcus faecium) \[\text{104}\], TD–8954 \[\text{28}\] and DSP–6952 \[\text{105}\]. What is clear is that future 5-HT\(_4\) receptor agonists have to provide greater selectivity and safety.

As a unique representative of a CLC2 activator, lubiprostone \[\text{29,30}\], an analog of prostaglandin E1, was approved by the FDA in 2006 for the treatment of CIC, and later, in 2008, received FDA approval for the treatment of IBS-C in women. Lubiprostone is a selective CLC2 activator that stimulates chloride-fluid secretion into the GI tract, softening stools and accelerating transit time. Unfortunately, common side effects reported for this drug include nausea, headaches and diarrhea.

Given the significant role of CCK1 in gastrointestinal motility, CCK1 antagonists have emerged as potential pharmaceutical agents for the treatment of chronic constipation disorders. Thus, dexloxiglumide \[\text{31}\], a CCK1 receptor antagonist, underwent clinical trials for the treatment of IBS-C in females. Nevertheless, during Phase III studies, statistically significant efficiency was not demonstrated. Hence, the development of this drug for the treatment of IBS-C was discontinued in the USA in 2003, although Phase III clinical trials are still being pursued in Europe.

Linaclotide \[\text{32,33}\], an orally administered peptide, is a GC-C receptor agonist that acts locally in the intestine. It shows minimal oral bioavailability to the systemic compartment, eliminating mechanism (GC-C)-independent and off-target adverse effects. In August 2012, linaclotide received the approval from the FDA, and then, 1 month later, in September, was approved by the European Medicines Agency in Europe.

Plecanatide \[\text{106–108}\], another GC-C receptor agonist, is currently undergoing Phase II clinical trials.

A first-in-class IBAT inhibitor developed for the treatment of CIC and IBS-C, elobixabat \[\text{34}\], acts locally in the gut with minimal systemic exposure and modulates the enterohepatic circulation of bile acids by partial inhibition of IBAT, which increases colonic fluid secretion and motility. Elobixabat is currently undergoing Phase II trials for the treatment of IBS-C and Phase III for CIC.

Another novel therapeutic target for the treatment of chronic constipation is the NHE3 channel, a sodium transporter channel present on the surface of intestinal epithelia. RDX5791 \[\text{109–110}\] is a potent and selective inhibitor of NHE3 and

---

Table 1. Current and prospective therapeutic agents for chronic idiopathic constipation and irritable bowel syndrome with constipation.

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Drug name (brand names)</th>
<th>Indication</th>
<th>Company</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT(_4) agonist</td>
<td>Tegaserod maleate (Zelmac\textsuperscript{TM}, Zelmorm\textsuperscript{®})</td>
<td>IBS-C, CIC</td>
<td>Novartis Bristol-Myers Squibb</td>
<td>Withdrawn 2007 (USA)</td>
</tr>
<tr>
<td>5-HT(_4) agonist</td>
<td>Prucalopride (Resotran\textsuperscript{TM}, Resolor)</td>
<td>CIC</td>
<td>Janssen</td>
<td>Launched 2009 (EU)</td>
</tr>
<tr>
<td>5-HT(_4) agonist</td>
<td>Velusetrag</td>
<td>IBS-C, CIC</td>
<td>Theravance</td>
<td>Phase II</td>
</tr>
<tr>
<td>5-HT(_4) agonist</td>
<td>HCP–0613</td>
<td>IBS-C</td>
<td>Hanmi Pharmaceuticals</td>
<td>Phase II</td>
</tr>
<tr>
<td>TD–8954</td>
<td>IBS-C, CIC</td>
<td>Theravance</td>
<td>Phase I</td>
<td></td>
</tr>
<tr>
<td>DSP–6952</td>
<td>IBS-C</td>
<td>Dainippon Sumitomo Pharma</td>
<td>Phase I (JP)</td>
<td></td>
</tr>
<tr>
<td>CLC2 activator</td>
<td>Lubiprostone (Amitiza)</td>
<td>IBS-C, CIC</td>
<td>Sucampo Takeda</td>
<td>Launched 2006 (USA)</td>
</tr>
<tr>
<td>CCK1 antagonist</td>
<td>Dexloxiglumide</td>
<td>IBS-C</td>
<td>Rottapharm</td>
<td>Phase III (EU)</td>
</tr>
<tr>
<td>GC-C receptor agonist</td>
<td>Linaclotide acetate (Linzess\textsuperscript{TM}, Constella\textsuperscript{TM})</td>
<td>IBS-C, CIC</td>
<td>Forest-Ironwood Almirall Synergy</td>
<td>Registered 2012 (USA, EU)</td>
</tr>
<tr>
<td>IBAT inhibitor</td>
<td>Elobixabat</td>
<td>IBS-C, CIC</td>
<td>Albireo</td>
<td>Phase II</td>
</tr>
<tr>
<td>NHE3 inhibitor</td>
<td>RDX5791</td>
<td>IBS-C</td>
<td>Ardelyx</td>
<td>Phase II</td>
</tr>
</tbody>
</table>

CIC: Chronic idiopathic constipation; IBS-C: Irritable bowel syndrome with constipation.

Data taken from \[\text{21,41,111}\].

---

Constella\textsuperscript{TM}(EU)–Linzess\textsuperscript{TM}(USA): the last milestone in the long journey | Special Report
is currently undergoing Phase II clinical trials. It has proved to be well tolerated and produces a significant improvement of IBS-C symptoms.

**GC-C receptor: a specific target for the treatment of CIC & IBS-C**

The GC-C receptor is a member of the guanylyl cyclase family [35], predominantly expressed in the luminal aspect of intestinal epithelial cells. GC-C is a multidomain enzyme composed of an extracellular ligand-binding domain, a single transmembrane region, a domain similar to that of protein tyrosine kinases and a C-terminal GC-C catalytic domain, responsible for producing cGMP by ligand-mediated activation (Figure 1).

The first ligand identified for GC-C was a member of the heat-stable (ST) enterotoxin family (STa), produced by bacteria that colonize the intestine, including *Escherichia coli*, *Enterobacter* sp., *Klebsiella* sp., and *Yersinia enterocolitica*, and one of the most common causative agents of secretory diarrhea [36]. Later, two endogenous intestinal paracrine hormones, first guanylin [37], expressed mainly in duodenum and proximal small intestine, and then uroguanylin [38], abundant in the colonic epithelium, were identified. The signaling cascade mediated by these two peptide hormones in the intestine is identical to that described for STa. Thus, after binding to the external domain of GC-C at the apical membrane of enterocytes, the ligands stimulate intrinsic guanylyl cyclase catalytic activity, initiating a cascade in which an accumulation of the second messenger cGMP occurs first. This leads to a stimulation of the membrane-associated PKGII, or inhibition of the activity of a cAMP-specific PDE3. The latter hydrolyzes cAMP, thus, its inhibition provokes a cAMP accumulation, which, in turn, activates cAMP-dependent PKA. Next, the phosphorylation of the cystic fibrosis transmembrane conductance regulator by PKGII or PKA kinases triggers an increase in bicarbonate and chloride-secreting activity, thereby prompting net secretion of salts and water into the intestinal lumen. In addition, cGMP enhances duodenal bicarbonate secretion through an unknown channel in a cystic fibrosis transmembrane conductance regulator-dependent manner and inhibits NHE3, through interaction with PKGII and the regulatory cofactor NHERF2. NHE3 inhibition leads to a marked reduction in Na+ absorption and consequently decreased fluid uptake by the intestinal cells. cGMP can also directly activate cyclic nucleotide-gated channels, thereby causing Ca2+ influx. Finally, GC-C signaling is terminated by hydrolysis of cGMP into guanosine monophosphate by cGMP-dependent PDE5 (Figure 1) [39].

Overall, the GC-C receptor plays a crucial role in fluid homeostasis, pH control and electrolyte balance. Thus, it has been proposed that the endogenous ligands guanylin and uroguanylin...
regulate intestinal fluid and electrolyte homeostasis involving cGMP as a second messenger, a fundamental phenomenon for the maintenance of gut physiology. Moreover, various studies suggested that administration of STs stimulates intestinal smooth muscle [40], thereby altering gut motility, and GC-C activation by STs diminishes afferent pain fiber firing [41], presumably through the release of a specific mediator that stimulates surrounding dendritic nerve endings, thus, modifying neural firing rates.

Therefore, given the participation of the GC-C receptor in the maintenance of fluid and ion homeostasis in the intestine as well as its alleged implication in intestinal motility and attenuation of afferent pain, and based on the emerging molecular-targeted therapeutic approach, this receptor has become a potential therapeutic target for the treatment of chronic constipation disorders such as CIC and IBS-C. These observations, along with the discovery of the molecular mechanism of action of ST peptides and the endogenous hormones guanylin and uroguanylin, have lead to the development of innovative prosecretory drugs, such as linaclotide [42] and plecanatide [43]. These bonds stabilize the tertiary structure and are required for full biological potency and efficacy [45]. The 13-amino acid sequence from Cys6 to Cys18 of STh enterotoxin was determined as the minimal fragment responsible for full biological activity, referred to as the toxin domain (Figure 2) [46]. However, a truncated STh variant lacking the N-terminal residues Asn-Ser-Ser-Asn was reported to exhibit tenfold reduction of potency compared with the full-length STh, thereby suggesting that the extra N-terminal residues, although required for full potency, are not essential for the biological activity of this peptide [47]. Moreover, the receptor-binding region of STh was identified in the highly solvent-exposed β-turn formed by amino acids Asn11-Pro12-Ala13 [48]. Point mutation in this region dramatically reduces the receptor binding activity of ST, thus, demonstrating the relevance of these residues for interaction with the GC-C receptor [49].

The toxic domain of STa shows significant homology to the endogenous peptides guanylin and uroguanylin in both amino acid sequence and 3D structure. However, these two hormones contain four Cys residues forming two disulfide bonds with a 1–3/2–4 connectivity (Figure 2). Thus, they lack one of the bonds present in ST enterotoxins. The two disulfide bonds present in guanylin and uroguanylin are structurally equivalent to the 2–5 and 3–6 disulfide bridges of ST, and provide two distinct interconvertible topologies, of which only one isomer, the so-called A-from, is biologically active and meets

**Linaclotide an analog of the GC-C super-agonist STh enterotoxin**

One of the most common STa enterotoxins produced by *E. coli* is STh [44], a 19-amino acid peptide that contains six Cys residues forming three intramolecular disulfide bonds (Cys6–Cys11, Cys7–Cys15 and Cys11–Cys18) (Figure 2). These bonds stabilize the tertiary structure and are required for full biological potency and efficacy [45]. The 13-amino acid sequence from Cys6 to Cys18 of STh enterotoxin was determined as the minimal fragment responsible for full biological activity, referred to as the toxin domain (Figure 2) [46]. However, a truncated STh variant lacking the N-terminal residues Asn-Ser-Ser-Asn was reported to exhibit tenfold reduction of potency compared with the full-length STh, thereby suggesting that the extra N-terminal residues, although required for full potency, are not essential for the biological activity of this peptide [47]. Moreover, the receptor-binding region of STh was identified in the highly solvent-exposed β-turn formed by amino acids Asn11-Pro12-Ala13 [48]. Point mutation in this region dramatically reduces the receptor binding activity of ST, thus, demonstrating the relevance of these residues for interaction with the GC-C receptor [49].

The toxic domain of STa shows significant homology to the endogenous peptides guanylin and uroguanylin in both amino acid sequence and 3D structure. However, these two hormones contain four Cys residues forming two disulfide bonds with a 1–3/2–4 connectivity (Figure 2). Thus, they lack one of the bonds present in ST enterotoxins. The two disulfide bonds present in guanylin and uroguanylin are structurally equivalent to the 2–5 and 3–6 disulfide bridges of ST, and provide two distinct interconvertible topologies, of which only one isomer, the so-called A-from, is biologically active and meets
Figure 3. 3D structure of A-isoforms of human guanylin [1GNA] and uroguanylin [1UYA] peptides. (A) Human guanylin [1GNA] and (B) uroguanylin [1UYA] peptides. Disulfide bonds are highlighted in yellow and the assumed binding cores are colored in green.

Key Terms

**Pharmacodynamics:** Study of the biochemical and physiological effects of drugs and the mechanisms of their actions, including the correlation of their actions and effects with their chemical structure.

**Pharmacophore:** Ensemble of steric and electronic features that is necessary to ensure the optimal intermolecular interactions with a specific biological target structure, and to block or trigger its biological response.

**Patient compliance:** Degree or extent to which a patient’s behavior matches the prescriber’s recommendations, in terms of taking medication, following diets, or executing life style changes.

**Small, disulfide-rich peptides:** Although Cys residues have an occurrence of 2.26% within mammalian proteins, the small, disulfide-rich peptides contain in their sequences more than 10% of Cys residues.

**Pharmacokinetics:** Characteristic interactions of a drug and the body in terms of its absorption, distribution, metabolism and excretion.

the structural requirements to bind and activate GC-C receptor (Figure 3) [50,51]. Interestingly, the 3D structure of this bioactive isomer closely resembles the crystal structure of STa. Hence, the third disulfide bond found in STa enterotoxins appears to freeze the conformation of the biologically active topological A-isomers [52].

The relevance of the conserved disulfide bonds, along with the ST-specific disulfide bridge, was studied by Gariépy and co-workers by preparing ST analogs that lack one or two of the disulfide bonds by replacing the pair of Cys residues with two Ala ones. The Cys7–Cys15 bond was found to be crucial for biological activity, although this bridge alone was not sufficient for binding, while replacement of the Cys6–Cys11 and Cys10–Cys18 bonds resulted in peptides that bind 42,000- and 130-fold less strongly to their receptor, respectively [53]. That study reflected the key structural role of the conserved disulfide bonds and demonstrated that the disruption of ST-specific Cys6–Cys11 diminishes toxicity but is not essential for binding.

Moreover, ST and human uroguanylin share features that distinguish these peptides from the human guanylin hormone. For instance, the presence of an extra residue located after the C-terminal Cys is a common element found in ST and uroguanylin peptides (a Tyr residue and a Leu residue, respectively), but absent in guanylin (Figure 2). Furthermore, human guanylin has a conserved aromatic amino acid Tyr9, instead of the corresponding Asn residue found in ST and human uroguanylin. In the latter two peptides, this residue renders them resistant to proteolytic degradation and inactivation by the endopeptidase chymotrypsine, a digestive enzyme abundant in the intestinal tract (Figure 2). Carpick and Gariépy [54] demonstrated that guanylin is rapidly hydrolyzed in vitro by the action of the enzyme chymotrypsine and proposed that its bioactive form makes it prone to be cleaved by this endopeptidase.

Singularly, human uroguanylin has two Asp residues in the N-terminal region that appear to contribute to biological activity and modulate binding affinity to the GC-C receptor in a pH-dependent manner (Figure 2) [55]. Therefore, a truncated analog of uroguanylin without the last three N-terminal residues resulted in an active peptide, although the potency was markedly reduced compared with the native 15-amino acid form. Regarding the pH-dependency, at acidic pH (5), the potency of uroguanylin increased considerably, while guanylin became ineffective at activating the GC-C receptor. In contrast, at basic pH (8), the potency of guanylin increases substantially while diminishing the potency of uroguanylin, thereby suggesting the possible segmental regulation of the intestine by these two endogenous peptides since the pH of the intestinal lumen varies considerably from the stomach to the rectum. Accordingly, the N-terminal acidic residues of uroguanylin are required for increased binding affinities, thus, the enhanced potency of the hormone for activating the receptor under acidic conditions. Regarding the pH-dependence of ST, although the difference was smaller in comparison to the endogenous homologs, ST exhibited slightly more potency in acidic conditions than in basic pH [55].

Overall, differences in the structural features of ST, guanylin and uroguanylin are reflected in the pharmacodynamic and pharmacokinetic properties of these GC-C receptor ligands. Hence, the reduced conformational space of the constrained ST, compared with that of the endogenous homologues, leads to an enhancement of the receptor-binding affinity and resistance to hydrolytic and enzymatic degradation, and, as a consequence, ST is reported to be more potent than guanylin and uroguanylin, regardless of the pH. It is therefore considered a super-agonist of GC-C [54,55].

Linaclotide is a 14-amino acid peptide homolog of ST that contains the three distinctive disulfide bonds present in enterotoxins, thus conferring the peptide’s higher stability and binding affinity compared with its endogenous two disulfide bond-containing counterparts, guanylin and uroguanylin (Figure 2). It is worth noting the single amino acid substitution (Leu8 in ST is replaced with Tyr4 in linaclotide) and the lack of the five N-terminal residues present in ST, which modulate the pharmacodynamics and
Linaclotide has expanded the range of emerging molecular-based therapeutic options available for the treatment of chronic constipation disorders and is an example of the successful development of a peptide as a therapeutic agent.

**Future perspective**

Although a considerable number of peptide therapeutics are currently in the market for addressing new therapeutic challenges, there is a remaining issue to be resolved: the administration route of peptide drugs. The noninvasive oral route is often the preferred for drugs administration due to the high patient compliance [63], the convenience for self-administration, as well as the wide range of dosage adjustment [64]. However, the oral administration of peptide drugs is well known to be precluded partly by the harsh hydrolytic environment along with the extensive presystemic proteolytic activity in the GI tract, and partly due to their poor absorption across the intestinal epithelium. Thus, most of the approved peptide therapeutics available in the current pharmaceutical market are administered parenterally [65].

**Small, disulfide-rich peptides** [66] are typically constrained architectures with limited and uncommon secondary structure as well as absence of an extensive hydrophobic core, mainly stabilized with two or more disulfide bonds that act as staples. Among others, plant-derived cyclotides [67], venom-derived peptides [68,69], such as conotoxins [70,71], ST enterotoxins [72] antimicrobial defensin peptides [73] and knottins [74] are classified as highly constrained disulfide-rich peptides with many therapeutic applications [66]. Furthermore, besides the inherent biological activity of these particular macromolecules, cyclotides and conotoxins are emerging as promising templates for the grafting of bioactive peptide sequences for the development of novel peptide-based therapeutics. Small disulfide-rich peptides, such as linaclotide, possess an extremely compact and constrained architecture which endows these peptides a remarkable stability to thermal and chemical denaturation and extremely resistance against proteolytic degradation [75]. In addition, the reduced conformational space, distinctive characteristic of the multiple disulfide-containing peptides, enhances the binding affinity of these peptides to the therapeutic target. As a result, it can be said that small, disulfide-rich peptides combine the potency of biologics and the pharmacokinetics of small molecules. These
singular properties allow linaclotide to be orally administered, and the authors envision a promising future for discovering and developing novel peptide therapeutics.

It is not surprising that, at present, no less than 12 companies are developing macrocyclic and constrained-peptide synthesis technologies to improve medicinal chemistry properties, including cell-penetrating features and drug-like profile. Since 2007, at least 27 drug development collaborations have been announced for using macrocycle technologies and constrained peptide technologies, with several pharmaceutical corporations assaying more than one technology at the same time [76]. Considering all these facts, there is a promising future for innovative disulfide-rich peptide therapeutics over the coming years.

**Financial & competing interests disclosure**
This work has been financed by the CICYT (CTQ2012-30930), the Generalitat de Catalunya (2009SGR1024), the Institute for Research in Biomedicine Barcelona (IRB Barcelona), and the Barcelona Science Park. The authors have no other relevant affiliations or financial interest in or financial conflict with the subjects matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

---

**Executive summary**

**Background**

- Linaclotide has received the approval of the US FDA and European Medicines Agency agencies for the treatment of irritable bowel syndrome with constipation and chronic idiopathic constipation.

**Functional gastrointestinal disorders: a major health & social problem**

- Irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC) are conditions that have a high prevalence in the worldwide population and a significant negative impact in the patient’s quality of life. It is estimated a global prevalence of 11.2% for IBS and 14% for CIC.
- These clinical entities have a significant direct healthcare cost and indirect expenses, thus, making them a major health, economic, and social problem.

**Emerging therapeutic targets for chronic constipation disorders: current & prospective therapeutic agents for the treatment of CIC & IBS-C**

- Current and prospective therapeutic agents for the treatment of CIC and IBS-C conditions include prokinetic agents such as 5-HT4 receptor agonists, secretagogues including GC-C receptor agonists, ileal bile acid transport inhibitors, CLC2 activators, as well as, CCK1 antagonists and NHE3 channel inhibitors.

**GC-C receptor: a specific target for the treatment of CIC & IBS-C**

- The GC-C receptor is involved in the maintenance of fluid and ion homeostasis in the intestine and, presumably, is implicated in intestinal motility and attenuation of afferent pain.
- Heat-stable enterotoxins and the endogenous hormones guanylin and uroguanylin are natural ligands of this receptor.
- The GC-C receptor has become a potential therapeutic target for the treatment of IBS-C and CIC.

**Linaclotide: an analog of the GC-C super-agonist STh enterotoxin**

- As the super-agonist STh enterotoxin, linaclotide contains three disulfide bridges, which conferred this peptide higher stability and binding affinity compared with its endogenous two disulfide bond homologs, guanylin and uroguanylin.
- Linaclotide is a first-in-class GC-C receptor peptide agonist and has expanded the range of emerging therapeutic options available for the treatment of chronic constipation disorders.

**References**

9. Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome:
49 Carpick, BW, Gariepy J. Structural characterization of functionally important


61 Johnston JM, Kurtz CB, MacDougall JE et al. Linaclotide improves abdominal pain and bowel habits in a Phase 2b study of patients with irritable bowel syndrome with constipation. *Gastroenterology* 139, 1877–1886 (2010).


### Websites

101 US FDA announcement. [www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm317505.htm](http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm317505.htm)


106 Synergy Pharmaceuticals: compounds in development. [www.synergypharma.com/pipeline/overview](http://www.synergypharma.com/pipeline/overview)

107 The plecanatide Chronic Idiopathic Constipation (CIC) study. [www.clinicaltrials.gov/show/NCT01429987](http://www.clinicaltrials.gov/show/NCT01429987)

108 The plecanatide irritable bowel syndrome with constipation study (IBS-C) (CBS). [www.clinicaltrials.gov/show/NCT01722318](http://www.clinicaltrials.gov/show/NCT01722318)


110 A study to evaluate the safety and efficacy of RDX5791 for the treatment of constipation predominant irritable bowel syndrome (IBS-C). [http://clinicaltrials.gov/show/NCT01340053](http://clinicaltrials.gov/show/NCT01340053)

111 Thomson Reuters Integrity. Prous Science. [http://integrity.thomson-pharma.com](http://integrity.thomson-pharma.com)