of Wedbush Securities in San Francisco estimates that peak US sales of linaclotide will reach $2.4 billion by 2019. "It is eventually going to be a pretty large drug," he says.

Testing the water

Linaclotide seemed to be the right drug for Felicia Avella. But a chloride channel activator that draws water into the intestines won't be the solution for everybody. "There will be some patients for whom the problem of constipation is caused by this lack of sufficient fluid in the colon," says Michael Camilleri, a gastroenterologist at the Mayo Clinic in Rochester, Minnesota, who has led trials investigating many experimental anticonstipation agents, including linaclotide. "On the other hand, there will be some other patients for whom the problem is one of the nerves and muscles not stimulating the propulsion of content through the colon, and there, flushing it from above with water, as it were, might not be sufficient."

For this second group of patients, a drug called prucalopride could help. Like tegaserod, prucalopride stimulates serotonin 5-HT_4 receptors in the gut to induce colonic contractions that help with defecation. But prucalopride's increased selectivity for its target is thought to shield the drug from the problematic cardiac effects observed with tegaserod.

Prucalopride was developed by New Jersey's Johnson & Johnson and has been marketed by Belgium's Movetis (now part of Ireland's Shire) in Europe as Resolor since 2009 for the treatment of long-term constipation. Shire acquired the US rights to the compound in January and is currently "working with the FDA to determine a regulatory path forward," according to company spokesperson Gwen Fisher. Two similar serotonin receptor agonists—naronapride and velusetrag, both from small Northern California companies—have also completed phase 2 testing.

To determine the right course of therapy, Camilleri advocates using an imaging technique called 'scintigraphic colonic transit' in which patients swallow a radioactive marker that can be tracked to give an indication of the type of constipation they are suffering from (*Clin. Pharmacol. Ther.* **87**, 748–753, 2010). "We actually measure how fast things move through the colon," he says. "If they're very slow then we're more likely to use a secretagogue agent, and if they're really, really slow we're more likely to use something that stimulates the colon."

But the therapeutic picture could be complicated by the arrival of another anticonstipation drug class. The Swedish company Albireo has a compound called elobixibat that modulates a transporter protein involved in delivering bile acids to the gut. Bile acids loosen stool consistency, allowing for easier defecation and reduced straining. In a phase 2 trial involving 190 people with CIC, elobixibat was found to increase the frequency of bowel movements two- to sixfold, depending on the dose, over the course of eight weeks (*Am. J. Gastroenterol.* **106**, 1803–1812, 2011).

Meanwhile, Synergy Pharmaceuticals has its own GC-C agonist currently in phase 3 testing in 880 people with CIC. According to Gary Jacob, president and chief executive of the New York–based firm, Synergy's compound, called plecanatide, doesn't hang on to the GC-C receptor for as long as linaclotide does, suggesting that the drug might be less prone to causing diarrhea. Preliminary phase 2 data presented at this year's Digestive Disease Week meeting seems to bear out that molecular inference: none of the 58 people who received a two-week course of plecanatide experienced diarrhea, the company reported.

Larger clinical studies will be needed to confirm whether plecanatide's safety profile is indeed superior. In the meantime, Jacob is cheering for his competitor's product to pave the way for other drugs in the same class. "We believe they've got a great drug in linaclotide," Jacob says. "I think it's going to be approved, and it's going to change the whole landscape for treating gastrointestinal disorders."

Elie Dolgin

NIH aims to facilitate extramural research through new grants

The challenges of reaching across organizational and geographical lines to collaborate on research are numerous. Investigators who work with or within the US National Institutes of Health (NIH) know this better than most. While so-called 'extramural' NIH grantees at various universities may be eager to team up with their 'intramural' counterparts within the government agency, they have a tough time keeping tabs on people and projects within the NIH. It is for this reason that scientists are hopeful that a recently launched program may make such partnerships run smoother.

In July, the government agency formally announced a grant program, the first of its kind, to compel scientists who work in academia on translational science projects to partner with its scientists at the NIH Clinical Center in Bethesda, Maryland. Both current and prospective extramural researchers may begin applying in October 2012 and must list an intramural NIH scientist as lead or co-investigator of the study. The projects must also make use of the Clinical Center, the largest US hospital dedicated only to clinical studies, a place that has only rarely been used by extramural researchers.

To foster this collaborative work, the agency unveiled a new website on 13 July that allows external investigators to search the types of assays and biomedical tools available at the center; it also lists the contact information of the scientists who work there. "Collaborations did occur in the past but were restricted to people who knew each other," says John Gallin, director of the NIH Clinical Center.

"This is a special type of grant that would allow extramural and intramural investigators who have special patient populations, special reagents and special technologies to be brought together," says Phillip Gorden, a senior investigator at the NIH's National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK). Extramural investigators who receive a grant could, for example, have priority access to NIDDK's metabolic chambers—small rooms that measure how much energy a patient burns while eating, sleeping and performing everyday activities. Before this new grant program, extramural investigators specializing in obesity research may have had to wait for months or longer before receiving clearance to use equipment at the Clinical Center.

The new grant program may make collaboration easier, but it is limited to projects that include the 444 principal investigators at the Clinical Center, who make up 37% of all intramural researchers at the NIH. Gallin says a future challenge will be to figure out how to maintain these intra- and extramural relationships and expand collaborations throughout all of the NIH.

Kathleen Raven