PERSPECTIVE

LANGER: BACHRACH

Giovanni Traverso (left) and Robert Langer.

Special delivery for the gut

Wanted: biomaterials for a risky journey. **Giovanni Traverso** and **Robert Langer** explain the gastrointestinal frontier.

"Drugs don't work if people don't take them." That succinct analysis by former US surgeon general C. Everett Koop points the way towards the huge contribution that biomaterials technology can make to health care.

The failure of patients to follow instructions for taking medication is a major barrier to effective clinical care. In developed nations, adherence to long-term therapies is only 50%, and it is much lower in developing countries and in people who take multiple drugs with complex dose regimens[1]. Medication non-adherence is estimated to cost more than US$100 billion in avoidable hospitalizations every year in the United States. Technologies that would enable extended drug release — lasting for up to several months — through the gastrointestinal (GI) tract could therefore radically improve delivery of medical therapies. This may be especially useful for patients in areas afflicted by war, regions with poor access to health care, patients suffering from psychiatric illness or dementia, and paediatric populations.

There is good reason to suppose that the gut could host long-acting medication — known as depot formulations — for weeks or even months without significant adverse effects. We know this, for example, from observation of patients with bezoars — indigestible masses trapped in the GI tract that typically pose no problem until they grow quite large[2]. Patients also are generally able to tolerate intra-gastric balloons for several months[3] in their quest to lose weight.

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POTENTIAL CHALLENGES

But translating this possibility into a reality poses a big challenge. To begin with, the gut's typical healthy transit time (from mouth to anus) is about 30 hours. This transit would have to be extended significantly for a drug to achieve weekly or monthly dosing. Furthermore, the GI environment has tremendous variability: pH in different sections ranges from 1 (extremely acidic) to 7 (neutral). Natural variability in the timing and content of meals results in frequent changes in lipid abundance. Then there are the high bacterial loads, 100% humidity, 37 °C temperature and a huge variety of proteases, lipases and other enzymes that work against biomaterial integrity and long-term drug stability. Thus it is imperative to prolong this transit time, which in turn requires developing materials that can withstand extreme conditions while delivering the drug continuously and without compromising safety.

There are two basic engineering approaches to extend transit time. One is to slow a drug's passage through the GI system by using devices that increase friction with the gut's mucosal walls[4]. The other is to prolong retention by loading drugs into devices that are larger than the points in the gut that limit passage of materials beyond a certain size: the pyloric sphincter at the exit of the stomach and the anus[5]. Also crucial to the successful development of such technologies are ways to ensure that drugs survive the harsh GI environment.

Significant efforts have been made using a range of materials, including bioadhesives[4] and swellable polymers[6]. But so far, systems are able to provide extended release times only on the order of hours. It will take a multidisciplinary effort to realize systems that can be safely retained in the GI tract for weeks or months, that deliver drugs continuously and with predictable kinetics during that time.

One big issue is safety. Any drug-delivery system that is intended to work in the gastric environment requires mechanisms that enable it to be automatically disassembled in the event of accidental passage through the pylorus, or if the drug being delivered causes an adverse reaction. Such designs require expertise in physiology, polymer chemistry, chemical engineering and mechanical engineering — plus the ability to design a system for testing in a large animal model.

PROLONGED RELEASE

The clinical applications could be vast. Non-adherence is of particular concern in the treatment of infectious diseases, where it can increase spread of infectious agents as well as rates of multi-drug resistance[7]. Other potential applications include extended-release GI systems for antibodies, DNA and RNA, now available only by injection. Similar technologies could also enable long-term delivery of chemicals that stimulate or inhibit growth of specific bacterial species in the GI tract; such agents are likely to be of significant interest as we learn more about the role of the microbiome in human disease.

We challenge the drug-delivery and medical-device community to unify their efforts in engineering and biomaterials to develop extended drug-release systems that can be orally delivered, as a novel approach to the prevalent and costly problem of medication non-adherence. To achieve this goal, safe, extended GI retention of delivery systems will have to be demonstrated in large animal models to maximize the chances for success in the translation to humans. Extended-release systems that retain their properties in the GI environment and pass without obstruction once they have released their therapeutic payload could revolutionize current clinical-care models and maximize effective treatment for a wide range of diseases in a variety of clinical settings. ■

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