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What's Next for Gastrointestinal Disorders: No Needles?

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ABSTRACT

A myriad of pathologies affect the gastrointestinal tract, citing this affected area as a significant target for therapeutic intervention. One group of therapeutic agents, antisense and oligonucleotides and small interfering RNAs, offer a promising platform for treating a wide variety of diseases ranging from cancer to auto-immune diseases. Current delivery methods are carried out either systemically or locally into diseased areas, both of which involve needles. The challenge in orally administering this type of treatment lies in the complications that arise due to the vast environmental extremes found within the gastrointestinal tract, owing to the fact that, as the drug travels down the gastrointestinal tract, it is subjected to pH changes and interactions with bacteria and a variety of digestive and protective enzymes including proteases, DNAses, and RNAses. Overcoming these challenges to allow the practical application of these drugs is a priority that has invoked a multitude of research in the chemical, biological, and material sciences. In this review, we will address common gastrointestinal pathologies, the barriers to oral-based therapies and antisense-interfering technologies, the approaches that have already been applied for their delivery, and the current status of antisense drug therapy clinical trials for gastrointestinal-related disorders.

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1. Introduction

Antisense oligonucleotides and related small interfering RNAs modulate target messenger RNA, preventing or reducing the translation of specific proteins, and therefore, serve as promising potential treatments for a variety of conditions. Although strides have been made in the intravenous administration and implementation of these molecules, oral administration permits close juxtaposition of the molecules to the luminal tissue that is affected by many diseases [1,2]. Developing the ability to administer the drugs orally is a top priority for the biomedical community, as the systematic delivery of these molecules, small and capable of penetrating the mucosal barrier, orally provides great anatomical advantage and remains the preferred route by patients and physicians [3].

The oral route and travel through the gastrointestinal (GI) system, however, poses a significant challenge. The GI tract, a hollow viscus starting at the oral cavity and ending at the anus, ranges from 5 to 10 m in length. It has various, unique environments, subjecting its migrants to drastic pH changes of 5–6 units, varying bacterial loads, and interactions with diverse forms of protective and digestive enzymes. In each unique environment, a host of pathologies can be appreciated, including malignancies, autoimmune diseases, and infections, which manifest themselves in distinct forms based on the local environment and tissue architecture.

Exploiting the particular characteristics of each segment in the GI tract is one of the ways in which specific therapies can be targeted to specific pathologies. For example, enteric coating may be applied to deliver mesalazine specifically to the terminal ileum and colon to treat inflammatory bowel disease. Several examples of these technologies have reached clinical studies [4–9]. Despite promising achievements, the previous year has witnessed a significant drop in the application of this treatment approach, possibly due to financial reductions of federal government funding in biotechnology/pharmaceutical industries that include over $1 billion in spending cuts specifically in this field [10,11]. The greatest challenge facing the implementation of these treatments remains in delivering the molecules specifically to the target cells within the complex gastrointestinal (GI) system. Here, we review the use of various antisense and siRNA technologies in treating GI pathologies, the physiological barriers to its luminal delivery, as well as the materials being applied to achieve the successful delivery of this promising therapeutic treatment.

2. The gastrointestinal tract — anatomy

The GI tract is involved in a variety of essential functions. Primarily, it ensures the proper digestion and absorption of nutrients, which requires a complex set of enzymes (e.g. proteases for protein digestion) and unique environments (e.g. acidic environment of the stomach to aid directly in digestion [12] as well as in intestinal villous architecture designed to maximize surface for the absorption of food). The GI tract also serves as a barrier from the directly contiguous external environment and is coated in a protective milieu of molecules, comprised of immunoglobulins, mucus, DNAses, and RNAses, which protects the body from pathogens. One of the most important barriers presented by GI tract along with blood, vascular endothelium and liver is first-pass effect or first-pass metabolism. It greatly affects bioavailability of orally administered drugs as its active concentration that reaches systemic circulation is decreased. The reasons behind this phenomenon stem from the presence of active enzymes, plasma proteins and blood cell binding, and GI motility [13]. Furthermore, recent studies have suggested that the GI tract is one of the largest endocrine organs and plays a critical role in the regulation of satiety and weight control [14]. Every one of these functions is expressed in a different manner along the GI tract and contribute to the biomolecular idiosyncrasies of the system, as demonstrated by Table 1, which summarizes the basic physiologic function of each segment of the GI tract and the distinct physiologic barriers challenging both pathogens and site-directed delivery, and Table 2, which outlines specific enzymes and their corresponding reactions. Careful consideration of these factors is essential to the successful luminal delivery of oligonucleotide-based therapeutics.

3. Gastrointestinal tract disorders

Gastrointestinal pathology describes a large number of diseases, some of which are inflammation-related, such as Inflammatory Bowel Disease (IBD), Crohn's disease (CD), and Ulcerative Colitis (UC). Irritable Bowel Syndrome (IBS), chronic diarrhea, constipation, and intestinal pain are less acquainted with inflammation and more commonly described as functional disorders. For a list of most common GI disorders, their physiologic barriers, and challenges, please refer to Table 3. Out of the numerous GI-related diseases, here, we introduce three of the most prevalent, Barrett's esophagus, inflammatory bowel disease, and colon cancer. As these diseases are caused by genetic alterations, they present possible targets for antisense oligonucleotide therapies.

3.1. Barrett's esophagus

Barrett's esophagus (BE) is characterized by a chronic inflammation of the esophagus caused by either refluxed stomach acid or internal pressure buildup [43]. BE is strongly correlated with gastroesophageal reflux disease (GERD), which is caused by a failure in the valve that connects the esophagus to the stomach (cardia valve). It is estimated that about 10–15% of patients with GERD will develop Barrett's esophagus, which, in turn, drastically increases the risk of developing cancer in the esophagus. The progression from the inflammatory phase to the development of cancer begins with damage of the squamous epithelium, continues with various stages of columnar metaplasia, low- and high-grade dysplasia, and, ultimately, results in carcinoma. For a comprehensive review on BE and its therapy, please refer to Quante [44].

3.2. Inflammatory bowel disease (IBD)

Inflammatory bowel disease (IBD) is a chronic condition of the digestive tract and consists of two subclasses, namely ulcerative colitis (UC) and Crohn's disease (CD). It is characterized by a chronic and