MicroRNA-Targeting Therapeutics for IBD and Colon Cancer

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SUMMARY

Dr. Dimitrios Iliopoulos in UCLA Department of Medicine has identified a novel biomarker, microRNA-214 (miR-214), that predicts, at near 100% specificity, an ulcerative colitis patient's risk for developing colon cancer.

BACKGROUND

Ulcerative colitis is characterized by inflammation in the digestive tract and together with Crohn's disease is the most common type of Inflammatory Bowel Disease (IBD). Current IBD therapies systemically target the immune system with poor efficacy and safety profiles. For example immunomodulators take a long time to act and have a high infection risk. Similarly, biologics such as anti-TNFα and anti-integrin antibodies have a 40-60% non-response rate and approximately 45% of patients develop resistance to anti-TNFα therapies.

In order to develop more targeted and effective IBD therapies, a UCLA team of researchers is taking a systems biology view of the gut, which is a complex network consisting of epithelial cells, immune cells, fibroblasts, adipocytes & bacteria. Their aim is to develop therapies that regulate the balance of the entire gut network involved in IBD and not just the immune cells.

One of the key targets in this project are microRNA's which are epigenetic factors that mediate interactions between bacterial, immune and epithelial cells. To identify these targets, the UCLA team undertook a two-year study and analyzed 401 colon tissue samples from patients in the United States and Europe with IBD, IBS, sporadic colorectal cancer, and colitis-associated colon cancer. The most advanced program to arise from this study is around microRNA-214. This target is highly elevated in patients with ulcerative colitis relative to healthy controls and is involved in regulating a host of immune targets (such as IL6, IL1B, TNFA, STAT3, IL17) as well as gut epithelial tight junction cell structure (including claudins and occludins).

The UCLA team then developed potent and selective chemically-modified antisense oligonucleotides towards this target and validated their activity and safety in two IBD animal models and a colitis-induced colon cancer model. A companion diagnostic using a three-gene signature that serves as a biomarker of the miR-214 inhibitor response is also in development using an ex-vivo colon tissue biopsy system. Initial liver and kidney toxicity assays have been performed and the program is approximately one year away from an IND filing. A second antisense compound targeting microRNA-133, which is also up-regulated in ulcerative colitis, is about to begin IND-enabling studies.

APPLICATIONS

Inflammatory bowel diseases (Crohn's and ulcerative colitis) and colon cancer patients with a history of IBD

ADVANTAGES

- Can be used for both prognosis and diagnosis
- Highly Specific to UC and not other inflammatory bowel disease
- Drug target for two diseases (UC, colon cancer)
- Rapid test to identify potential responders to the miR-214 inhibitor

STATE OF DEVELOPMENT

miR-214 expression has been reliably found in patients with ulcerative colitis and is shown to correlate with the development of colon-cancer. Therapeutics targeting miR-214 have also been shown to alleviate colitis and colon cancer in mouse models. Currently, Dr. Iliopoulos is

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OTHER INFORMATION

KEYWORDS

MicroRNA, Biomarker, Cancer, Colon Cancer, Risk Factor, Ulcers, Chronic Inflammation, Therapeutics, Treatment

CATEGORIZED AS

- **Biotechnology**
  - Genomics
- **Medical**
  - Diagnostics
  - Disease: Cancer
  - Disease: Digestive System
  - Gene Therapy
  - Research Tools
  - Screening

RELATED CASES

2015-113-0

developing additional antisense miR-214 inhibitors that have different chemical modifications to improve stability and biodistribution.

PATENT STATUS

Country	Type	Number	Dated	Case
European Patent Office	Issued Patent	3218517	11/03/2023	2015-113
United States Of America	Published Application	20170333468	11/23/2017	2015-113

Additional Patents Pending

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