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Bringing cures for gastrointestinal disorders within reach

Leveraging an innovative discovery platform, Curileum Discovery is developing an approach based on stem cell drugs that has the potential to cure a wide range of gastrointestinal disorders.

Gastrointestinal problems are among the most commonly reported symptoms in the developed world, affecting up to one-third of individuals in Western countries. Up to three-quarters of diabetic outpatients and one-quarter of elderly individuals report gastrointestinal complaints that may be severe enough to substantially compromise their quality of life. With a market approaching \$35 billion, treatment of the symptoms of serious chronic gastrointestinal disorders is currently the fastest-growing area in medicine.

Curileum Discovery is an emerging London-based regenerative medicine company focused on revealing the underlying causes of serious gastrointestinal diseases. Using an innovative discovery platform, the company is identifying new stem cell therapeutic targets in intestinal mucosal, immune and nerve tissues. Rather than simply treating symptoms, Curileum's stem-cell-drug-based approach holds promise for curing patients with inflammatory bowel disease, colorectal cancer, irritable bowel disease and conditions associated with chronic gastrointestinal complaints.

Regenerative medicine promises to revolutionize patient care by repairing or replacing damaged cells and restoring integrity and function to tissues. Effective tissue regeneration requires activation of endogenous stem cells, rare cells in tissues that are the very source of lifelong tissue renewal. "Harnessing three decades of stem cell drug discovery and development experience, we are unlocking a whole new area of therapeutic targets to kill defective stem cells, control inflammation that surrounds damaged tissues and activate healthy stem cells to restore health to the intestine," said the company's founder and CEO Jeff Moore.

Advanced assays

The gastrointestinal tract is highly vulnerable to damage, with only a single layer of epithelial cells separating the body from adverse factors in the gut environment. Degradation of this mucosal lining leads to tissue inflammation and disease (Fig. 1). Exposure of intestinal stem cells to toxic insults might never lead to overt clinical symptoms, but chronic stress and accumulating stem cell defects can further compromise the integrity and function of the intestinal barrier. A weakened intestinal barrier precedes the onset of type 1 diabetes and inflammatory bowel disease, indicating a genetic predisposition for disease.

Using advanced *in vitro* assays with intestinal mucosal, immune and nerve tissue cells, Curileum is shedding new light on the biological properties and

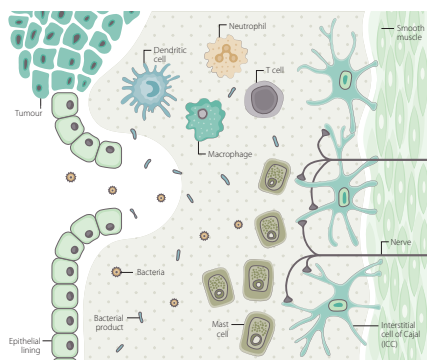


Figure 1: Degradation of the single cell lining of the intestine leads to disease. Bacterial toxins are allowed to permeate mucosal tissue and activate a potent inflammatory response. Chronic inflammation can lead to cancer, seriously disrupt intestinal function, and cause nerve pain.

molecular gene signatures associated with the progression of healthy to diseased intestinal stem cells in the context of chronic inflammation and aging. Endoscopic biopsies of diseased tissue, adjacent inflamed tissue and nearby healthy intestinal tissue in an individual provide a unique opportunity to elucidate by pairwise analyses the steps leading to inflammatory bowel disease and cancer.

Direct comparison of multiple samples collected from an individual over time is particularly informative for understanding disease progression and responses to experimental and standard-of-care drugs. Examination of *in vitro* cultures of intestinal tissue stem cells at the molecular level in time-course experiments can identify the transcriptional signals that trigger stem cell self-renewal, proliferation, differentiation and apoptosis.

Curileum scientists can also use whole-genome sequencing to further analyze genetic variations and defects in intestinal stem cells. These stem cell defects are masked in the presence of the native supporting microenvironment *in vivo*. But the intrinsic growth properties of intestinal stem cells are revealed when the cells are cultured *in vitro*. The company's discovery platform for human disease was previously validated in animal models with the delivery of new stem cell targets in a regenerative medicine collaboration with the Novartis Institutes for BioMedical Research.

Curileum is leveraging this resource and its discovery platform to develop biomarkers to inform patient care and support clinical development. Assessing intestinal stem cell health has the potential

to identify gastrointestinal disease predisposition and early-stage disease, providing opportunities for early intervention. It also would provide health economic benefits by reducing costly follow-up endoscopic monitoring and allowing researchers to more effectively diagnose and select patients for clinical trials.

On course for cures

Curileum's operations are based in northwest London, adjacent to St Mark's Hospital—one of the only hospitals in the world that specializes entirely in intestinal and colorectal medicine, and a national and international referral center for intestinal and colorectal disorders. With access to a large supply of patient tissues and an open innovation model to facilitate collaborations with leading academic clinicians, the company's scientists can rapidly test hypotheses on stratified patient populations to discover and support target development.

Curileum's therapeutic approach to target defective or ineffective intestinal tissue stem cells, control inflammation that surrounds damaged tissues and activate healthy stem cells has the potential to restore the balance in the number and functional properties of cells in intestinal tissues. For example, reducing the overproduction of progenitors of mast cells could be a promising strategy to treat inflammatory bowel disease and abdominal pain associated with irritable bowel syndrome.

Leveraging a front-end drug discovery module that plugs into pharmaceutical companies' development pipeline, Curileum is partnering with such companies to discover and develop new drugs able to restore health to the gut barrier. Curileum has a proven track record of delivery along with streamlined business, legal and project-management capabilities in its discovery and development partnerships with pharmaceutical companies. "Through these collaborations, we expect to unlock a whole new area of stem-cell-focused diagnostic and therapeutic targets in the gastrointestinal tract having broad applications in metabolic disease, aging, chronic inflammation and cancer," Moore said.

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