TECHNOLOGY PROFILE

Methods, Treatment and Compositions for the Treatment and/or Prevention of Bowel Disorders Particularly in Treatment and Prevention of Inflammatory Bowel Disease.

Technology Overview

Inflammatory bowel disease (IBD) is characterized by chronic or relapsing immune activation and inflammation within the gastrointestinal (GI) tract that markedly alters GI function. IBD includes Crohn’s disease (CD) and Ulcerative Colitis (UC). CD can affect any part of the intestine, from mouth to anus, and is characterised by skip lesions (inflamed parts of the intestine interspersed by healthy tissue), but preferentially involves the ileum and colon, whereas UC is specific to the colon. CD has an early onset and commonly affects people aged 15-35. Both of these conditions are chronic disorders with persistent spontaneous reoccurrence that contribute significantly to morbidity. IBD patients suffer from diarrhoea (with blood or mucus), abdominal pain, fever, weight loss, nausea, vomiting and fatigue. Frequent complications in CD include abscess and stricture formation, intestinal obstruction and fistulas (Baumgart & Sandborn 2007). Biopsy specimens from inflamed gut mucosa typically show transmural inflammation, including submucosal oedema, ulcerations and fibrosis.

The choice of medical treatment depends on the location of disease, its severity, and response to earlier therapy. Immunosuppressive therapy (such as 6-mercaptopurine, azathioprine and methotrexate), corticosteroids and biologic anti-TNF-α therapies (such as infliximab and adalimumab) are used to treat active disease and prevent relapses. However, corticosteroids and immunosuppressants are very toxic and cause severe adverse effects (Scribano 2008; Triantafillidis et al 2011). While biologic therapy demonstrates less toxicity and fewer side-effects, many patients fail to respond to this treatment (Stallmach et al 2010). Unfortunately, 70%–90% of IBD patients eventually undergo surgery during the course of the disease because patients respond less to medical therapies over time. Approximately 39% of the patients with CD require repeated surgery (Lewis & Maron 2010), thus the search for novel effective therapeutics for the treatment of IBD is crucial.

Gastrointestinal functions are mostly controlled by the enteric nervous system (ENS) embedded in the gut wall. Biopsies from IBD patients, and samples of intestine from animal models, have provided evidence of enteric neuronal death and axonal damage of enteric neurons in intestinal inflammation (Boyer et al 2005; Linden et al 2005; Sarnelli et al 2009). Victoria University researchers have demonstrated that axonal damage and neuronal death which occur during the acute stage of intestinal inflammation contribute to triggering mechanisms of persistent neuronal hyperexcitability (Nurgali et al 2007, 2011). These structural and functional changes in the ENS, as well as invasion of the immune cells into the myenteric and submucosal plexuses (plexitis), are prognostic of disease progression and may play a role in recurrence of IBD and development of post-inflammatory Irritable Bowel Syndrome (IBS). It was found that increased number of eosinophils correlate with persistent neuronal hyperexcitability and changes in intestinal motility long after the resolution of acute inflammation. Thus, the data implied that eosinophils and their released products such as eosinophil-derived neurotoxin (EDN) might be factors contributing to long-term functional changes in enteric neurons resulting in persistent gut dysfunction.
State of Development

To date, Victoria University researchers have tested the relationship between eosinophils and EDN with the enteric neurons in inflamed animal intestine, and the effects of specific inhibitors of eotaxin-1 and CCR3 receptors on attenuation of neuronal damage and intestinal dysfunction following induction of inflammation in the colon.

A highly potent and selective CCR3 receptor antagonist which can also inhibit eotaxin-1 at higher doses was tested in an animal model of trinitrobenzene sulfonate (TNBS)-induced inflammation in the colon. The drug was administered intraperitoneally prior to and after induction of inflammation; the effects were studied at Day 1 (acute stage) and Day 7 (chronic stage) post-TNBS injection. Both high and low doses of CCR3 antagonist prevented accumulation of activated eosinophils within the myenteric plexus and lamina propria (Figure 1), significantly improved survival of enteric neurons (Figure 2) and reduced axonal damage, reduced gross inflammatory score and alleviated colon motility (Figure 3). There were no differences found between groups of animals treated with CCR3 antagonist prior to and after TNBS administration.

**Figure 1:** Increased number of activated eosinophils (EDN-positive) in the lamina propria and in the myenteric plexus at Day 7 post-TNBS injection was reduced significantly after administration of the CCR3 antagonist.

**Figure 2:** Both low and high doses of CCR3 antagonist prevented neuronal death in the myenteric plexus. *P<0.05, significantly different compared to sham and CCR3 treated groups.
Figure 3: CCR3 antagonist restored the length of propulsive colon contractions in animals with TNBS-induced inflammation. *P<0.05, significantly different compared to sham and CCR3 treated groups.

**Intellectual Property Position**

The technology is protected by the following patent:

**Methods and Compositions for the Treatment and/or Prevention of Bowel Disorders**

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<tr>
<th>PATENT/APPLICATION NUMBER</th>
<th>JURISDICTION</th>
<th>STATUS</th>
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<td>PCT/AU2012/001414</td>
<td>PCT Signatory Countries</td>
<td>Filing Date: 15 November 2012</td>
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**Market Overview**

**Inflammatory bowel disease (IBD)**, comprising two main pathologies (UC and CD) affects more than 60,000 Australians, costs our economy $2.7B per year while another 1600 Australians are diagnosed with CD or UC every year (Access Economics Report, 2007). Although considerable progress has been made in recent years in understanding IBD’s pathophysiology, current treatment aims to suppress symptoms rather than to effect a cure. Most IBD patients undergo surgical removal of the damaged intestinal tissue, thus the search for novel therapies for the treatment of IBD is crucial.

As IBD rates continue to rise, so too public awareness spreads and as more thorough diagnostic procedures identify a greater number of affected patients, the demand for IBD drugs will increase. The world market for intestinal anti-inflammatories was worth over $2.4B in 2008, and had grown at 9% over the previous year. The value of other types of drugs used to treat IBD, including immunosuppressants and monoclonal antibodies, approached $12B. Visiongain\(^1\) predicts that the market for intestinal anti-inflammatories and IBD drugs will continue to expand based on rising disease rates and evolving diagnostic methods. IBD is under-diagnosed, especially in developing countries; however as governments and health services address chronic illnesses like IBD, the market for IBD drugs will expand into previously untreated countries/regions. Continuing studies and surveys indicate that IBD is spreading globally, with an especially high prevalence rate in India. In addition, sales of IBD drugs in Latin American countries increased by 14% in 2012, and this is set to account for an increasingly large share of the world market in years to come.

**Irritable Bowel Syndrome (IBS)** is a chronic, fluctuating and debilitating condition that involves changed properties of neurons and affects 10 to 20 percent of the population in developed countries (Camilleri, 2012) with overall prevalence of IBS in the USA of 14.1%, with only 3.3% being medically diagnosed (Ibid.). In Australia 1 in

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\(^1\) [https://www.visiongain.com](https://www.visiongain.com)
10 people experience symptoms associated with IBS at some time (Boyce et al 2006), however, not all seek medical treatment (AIHW, 2012). The probability of IBS occurring in an individual is increased about 10 fold following an episode of severe gastroenteritis (Chadwick et al. 2002; Spiller, 2004), with IBS often manifesting after the gastroenteritis has subsided. Consistent with this association, 57% of patients with CD who were in remission reported IBS-like symptoms (Simren et al., 2002). Current treatment for IBS is based on dietary and lifestyle adjustments. Development of therapies aimed at mechanisms underlying the IBS is therefore crucial.

Opportunities for Technology Co-development

An opportunity exists for licensing of the technology and for investment and/or a partnership agreement to further develop the technology. Victoria University is seeking partners to test the technology in other animal models (such as animal models of spontaneous chronic intestinal inflammation which are available at Victoria University and currently are the best animal models for IBD) and later on, the development of clinical trials of the invention.

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