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Invited Review

Translatability of helminth therapy in inflammatory bowel diseases

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ABSTRACT

Modern hygienic lifestyles are associated with the emergence of inflammatory bowel disease (IBD) which now afflicts millions of people in highly-developed countries. Meticulous hygiene interrupts conduits of transmission required for ubiquitous exposure to parasitic worms (helminths). We proposed that loss of exposure to helminths permits development of IBD. Early clinical trials suggested that exposure to helminths such as *Trichuris suis* or *Necator americanus* can improve IBD. Over the last several years, processes to "medicinalize" *T. suis* have been developed and use of this helminth is now being studied in large multi-center clinical trials. Concurrently, we and others have identified some of the immune regulatory mechanisms elicited by helminth exposure that suppress inappropriate intestinal inflammation. These efforts could soon result in new therapies for patients with IBD.

1. Introduction

Inflammatory bowel disease (IBD) are conditions of unknown cause that usually start in people during the second or third decade of life. The patients frequently experience continuous or intermittent diarrhoea, abdominal pain, rectal bleeding and fatigue due to aberrant intestinal inflammation, probably resulting from inappropriately vigorous immune responses to components of our natural intestinal faecal stream (Maloy and Powrie, 2011). For lack of a thorough understanding of the causes of IBD, the condition is categorised as either ulcerative colitis (UC) or Crohn's disease based on the location and duration of the inflammation, the microscopic pathology and the lack of identifiable inciting factors such as infection with enteric pathogens.

Variations in more than 160 distinct genes can either increase or decrease the risk of acquiring either UC or Crohn's disease (Van et al., 2011; Vermeire et al., 2011). Many of these genes influence innate immunity, intestinal epithelial cell barrier function, bacterial clearance, immune regulation and effector cytokine pathways such as Th17/IL23/Stat3. While these genes affect disease susceptibility, they are not the cause of the rapid spread of IBD in industrialised countries over the last 75 years.

IBD are diseases that emerged in the latter half of the 20th Century. Once considered quite rare, the frequency of IBD is about one in every 250 people in some regions of developed countries (Molodecky et al., 2012). Although there are a small number of published papers on the incidence of IBD in underdeveloped countries, the existing publications and the experience of regional health care professionals suggest that these diseases are spreading into underdeveloped countries experiencing rapid improvements in lifestyle.

In the early 1990s, we proposed the "IBD hygiene hypothesis" to explain changing IBD prevalence (Elliott et al., 2000). It stated that modern day living changed intestinal flora and fauna that have impaired the development of the immune regulatory circuits that previously protected us from IBD and other such immune-mediated diseases. It also was proposed that loss of helminthic infections was particularly important due to their especially strong stimulatory influence on host immune regulatory circuits. Animal experimentation as well as clinical and epidemiological studies support this concept (Weinstock and Elliott, 2009; Kabeerdoss et al., 2011). Translation of helminthic infections into therapeutic vaccines to promote immune regulation and control of IBD was the logical consequence of such studies (Table 1).

2. Clinical trials using helminth therapy in IBD

Supportive epidemiological observations and recognition that helminths can both protect mice from IBD and stop ongoing disease activity, led our group to explore whether a helminthic infection could alter the course of disease in patients with either active UC or Crohn's disease. To accomplish this task, we first needed to identify a helminth species producible in the laboratory and that likely could be safely administered to patients. The authors,

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Table 1
Translational research phases of helminthic therapy.

Phase of Research[a]	Brief definition	Examples and current status of helminths in IBD
T0	Identification of novel approach to care for patients with IBD	Epidemiological study of inverse associations of helminthes and IBD – ongoing Studies of the effects of helminthes in animal models of IBD – ongoing Case studies of the effects of helminth infection in patients with IBD – ongoing
T1	Discovery of a specific application in patients with IBD	Identification of *Trichuris suis* and *Necator americanus* as potential therapeutic agents – done Phase I and II clinical trials of *T. suis* in IBD – done Phase I and II clinical trials on *N. americanus* in IBD – done
T2	Develop and apply discovery to evidence-based practice	Development of production protocols to 'medicinalize' *T. suis* – done Phase IIb and Phase III clinical studies of *T. suis* in IBD – ongoing[b]
T3	Development of practice guidelines to incorporate into standard of care	Phase IV ('diffusional') clinical studies of *T. suis* – future Implementation research – identification of barriers to use - future
T4	Identification of health impact of discovery in patients with IBD	Outcomes study of helminthes in IBD – future Cost/risk/benefit (QALY) analysis – future

[a] Translation of biomedical discovery into apparatus promoting human health moves through five stages (T0–T4) (Khoury et al., 2007).
[b] Use of helminths to enhance immune regulatory pathways and treat inflammatory bowel disease (IBD) is now solidly in phase T2.

together with Dr. Robert Summers (University of Iowa, USA) sought the advice of Dr. Joseph Urban at the US Department of Agriculture, USA who is an authority on intestinal helminths.

After careful deliberation, *Trichuris suis* (pig whipworm) was chosen for use in clinical trials. *Trichuris suis* met the safety requirements. While the pig is the natural host for *T. suis*, it can colonise people but only briefly (Beer, 1976). Farmers raising animals can have pigs infected with *T. suis*, resulting in chronic human exposure. However, this natural exposure to the organism causes no human disease. The organism is transmitted through ingestion of nearly microscopic ova. Thus, it would be easy for patients to receive these ova. The ova can hatch within the human intestine, but do not migrate beyond the gut. In some patients, the larvae may mature into the adult form of the parasite, which theoretically could produce ova. However, the ova require a month-long incubation in moist soil to become infective. Thus, only the number of ova administered to the patient will determine the magnitude of the helminthic infestation, and there ?is no host-to-host transmission under modern living conditions. Because pigs are the natural host, the porcine whipworm can be harvested from pigs reared under pathogen-free conditions, reducing the risk of inadvertent transmission of other infectious diseases. The ova remain viable in the refrigerator for perhaps years, reducing the need for frequent ova production runs. After careful review by our institution's review board, permission was given to proceed with clinical trials.

Initially, the effect of *T. suis* colonisation was studied in a small open-label trial including four patients with Crohn's disease and three patients with UC who each received a single dose of 2,500 viable ova. They demonstrated improvement in symptoms without side-effects (Summers et al., 2003). A second study, which was an open-label trial, tested repeated dosing in 29 patients with Crohn's disease. At week 12, the disease went into remission in 66% of the test subjects (Summers et al., 2005a). Before the end of the Crohn's disease trial, we commenced a randomised double blind placebo-controlled trial of *T. suis* in patients with UC. Those patients were given either 2,500 viable *T. suis* eggs or a placebo every 2 weeks for 12 weeks. This study revealed a significant improvement over a placebo in patients receiving the agent (Summers et al., 2005b,c).

Since the agent showed promise as a useful therapeutic agent, the United States Food and Drug Administration requested that further development proceed down the usual regulatory pathway for drug approval. This required formalisation of good manufacturing procedures (GMP) and appropriate safety testing, which was beyond the capacity of our university based research laboratories. Fortunately, a pharmaceutical company was willing to work with the agent for several years to develop the GMP. They in conjunction with Falk Pharmaceutical Company conducted the safety studies required by both the United States and European drug regulatory agencies. This allowed *T. suis* to re-emerge in the clinic for further testing.

The tolerability and safety of GMP-approved *T. suis* was tested in a multicenter placebo-controlled trial of 36 patients with Crohn's disease (Trial identifier NCT01434693). Patients ingested either a placebo or one of three doses of ova. There were no symptoms or complications associated with *T. suis* exposure (unpublished results).

Currently, there are United States (Trial identifier NCT01576471) and European (Trial identifier NCT01279577) multicenter double-blinded placebo-controlled trials testing the efficacy and safety of *T. suis* for induction of remission in Crohn's disease. The European study passed interim analysis and is projected to conclude sometime in 2013. There also is approval for an investigator initiated study using *T. suis* ova for induction of remission in UC (Trial identifier NCT01433471).

There also has been a small open-label trial using the human hookworm, *Necator americanus*, in nine patients with Crohn's disease (Croese et al., 2006). In natural infection, the larvae enter the skin, migrate into the lungs where they are coughed up and swallowed to enter the gut. In clinical trials, the agent is applied to the skin under an occlusive bandage.

Two patients with active disease treated with 50 larvae applied to the skin reported an improvement in symptoms. The other seven patients had minimal disease and did not display changes in disease activity with helminth exposure. Acute infection with *N. americanus* can cause symptoms such as diarrhoea, nausea, vomiting and abdominal pain in normal volunteers when given 50 or more larvae. Low dose exposure (10 hookworm larvae) is better tolerated (Mortimer et al., 2006) and may prove useful in prolonged clinical trials.

3. Animal models used to elucidate mechanisms of action

IBD is a condition mostly limited to humans. Laboratories have developed several murine models of IBD that simulate the human condition. These models have proven useful for studying the factors which are important for maintaining mucosal immune homeostasis. The growing understanding of the various gene variants that either enhance or diminish our susceptibility to IBD allows us to further exploit these models to gain a deeper understanding of the underlying processes that cause IBD. They also are used to uncover mechanisms of drug action and to help predict potentially useful new therapeutic strategies for control of disease. A few of these models, described below, have been used to test the effects of helminths on intestinal inflammation and to investigate their mechanisms of action.