Published in final edited form as:
Int J Parasitol. 2013 March ; 43(0): 245–251. doi:10.1016/j.ijpara.2012.10.016.

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.

Keywords

Helminths; IBD; Dendritic cells; Mucosa; Colitis

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 diarrhea, abdominal pain, rectal bleeding and fatigue due to aberrant intestinal inflammation, probably resulting from inappropriately vigorous immune responses to components of our natural intestinal fecal stream (Maloy and Powrie, 2011). For lack of a thorough understanding of the causes of IBD, the condition is categorized 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

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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 industrialized 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, together with Dr. Robert Summers (University of Iowa, USA) sought the advice of Dr. Joseph Urban at the U.S. 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 colonize 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* colonization 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 randomized 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 formalization 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 diarrhea, 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.

One of the earlier models of IBD involved the administration of trinitrobenzene sulfonic acid (TNBS) or dinitrobenzene sulfonic acid (DNBS), mixed in alcohol, intrarectally into rodents. TNBS and DNBS induce acute injury and perhaps immune hypersensitivity. In mice, the injury is highly focal, acute and short-lived. In mice, the pathology does not persist without administration of more irritant. The attractiveness of the model is its simplicity, which encourages its continued use. However, there now are more relevant IBD models featuring persistent intestinal inflammation more indicative of human disease.

Humans with defects in the IL10 signaling pathway are prone to IBD (Glocker et al., 2011). Mice with disruption in IL10 production or IL10 receptor signaling develop chronic colitis spontaneously, but sporadically. IL10 is an immune regulatory cytokine important for limiting mucosal immune responses. To enhance expression of disease, mice often are fed a non-steroidal anti-inflammatory drug (NSAID) that triggers the onset of severe colitis. The NSAID disrupts the production of protective arachadonic acid metabolites in the mucosa (Berg et al., 2002) making the animals more prone to IBD. This also is relevant to human IBD, since administration of many types of NSAIDs worsen the disease (Takeuchi et al., 2006; Chan et al., 2011). Another version of the IL10 knockout (KO) model of IBD involves reconstituting Rag mice (mice born without functional T and B cells) with IL10 KO T cells (Blum et al., 2004). These mice also quickly develop severe colitis when fed NSAID. The advantage of this version of the model is that investigators can manipulate the reconstituted T cell compartment, making it more useful for investigating mechanisms of disease.

Another model is the Rag-CD4+CD25- ($CD45^{low}$) T cell transfer model (Maloy and Powrie, 2011). This model involves the transfer of wild-type splenic CD25- or $CD45^{low}$ T cells into Rag recipients lacking T or B cells. The cell transfer reconstitutes the effector T cell compartment. However, unlike the IL10 Rag transfer model, the mice produce few regulatory T cells (Tregs) after T cell reconstitution because such cells come from the $CD45^{high}$, IL25+ T cells, which the animal does not receive. Although they can make IL10, these mice spontaneously develop a persistent colitis, due to the deficiency of Treg cells. The intestinal inflammation develops much more quickly after exposure to a NSAID for the same reasons seen in the IL10 KO model described above.

The intestinal mucosa in these and most other animal models of IBD makes large amounts of IFN_{γ} and IL17. These cytokines are particularly important because they appear to help drive disease in humans and many animal models of IBD (Elliott et al., 2008; Abraham and Cho, 2009; Maloy and Powrie, 2011).

Another animal model of intestinal inflammation involves oral administration of dextran sodium sulfate (DSS) into mice or rats. DSS is toxic to the epithelium, causing epithelial cell death which results in intestinal inflammation. This is mostly an “injury model” that allows the study of factors that promote or inhibit intestinal epithelial healing.

These IBD models are quite different. Their diversity in regards to the mechanisms promoting disease have provided a deeper appreciation of the various complex interactions that happen between helminths and their hosts that can prevent and reverse pathological intestinal inflammation.

4. Potential mechanisms of regulation

Helminths, via their interaction with the host, activate several distinct immune regulatory pathways. This unique property of these organisms could render them highly effective at controlling IBD and other immune regulatory diseases. Over the next few years, we will indeed know if that is the case. The term ‘helminth’ denotes a wide variety of worm-like parasitic organisms, many of which have evolved independently from each other. Various

species can inhabit different regions of the body. While several distinct helminth species can impart protection from IBD in murine models of colitis, it is not established that all helminths do likewise or work to protect the host employing similar immune regulatory strategies.

The first efforts to understand how helminths may work to limit immune mediated disease centered on the observation that the Th2 response can at times inhibit Th1 responses. It is well appreciated that helminths promote the growth of IL4-producing, Th2 cells. Several investigations showed that abrogation of Th2 function promoted both Th1 cell differentiation and persistence of IBD in animal models of this disease, supporting the notion of the importance of worm-induced Th2 cytokines for disease control (Elliott et al., 2003). However, many studies demonstrated that helminthic infections also curtail allergic reactions driven by the Th2 pathway. This led to a search for additional mechanisms of regulation independent of Th2 cytokines.

Regulatory-type T cells help maintain the gut lining in a state of immune tranquility and limit the potential for IBD (Maloy and Powrie, 2011). T cells from the mesenteric lymph nodes (MLN) of *Heligmosomoides polygyrus bakeri*-infected mice transferred into worm-naïve animals can stop colitis, showing the importance of T cells in the control of colitis(Elliott et al., 2004).

Several different T cell subsets can exert regulation. There are T cells that express IL10 and/or TGFβ. A particular type of Treg cell expresses the transcription factor Foxp3. In mouse colon, approximately 20% of lamina propria CD4+ T cells are Foxp3+ Treg. In the colon and terminal ileum at least half of the Foxp3+ T cells also express IL10 and they are perhaps the major source of IL10 in the lamina propria.

The number of Treg cells increases in the MLNs and the intestinal lining during helminthic infection. Lamina propria T cells make more IL10 and TGFβ after *H. polygyrus bakeri* infection (Setiawan et al., 2007). Several different helminthic species such as *H. polygyrus bakeri, Hymenolepis diminuta* and *Schistosoma mansoni* promote IL10 secretion, a regulatory cytokine often from T cells that restrains Th1 responses and colitis in murine models of IBD.

Moreover, *H. polygyrus bakeri* infection expands the number of Foxp3+ Treg cells in the MLNs (Elliott et al., 2004; Grainger et al., 2010) and intestinal lamina propria, although their effect on gut Treg number is modest.

While *H. polygyrus bakeri* infection only modestly expands the number of Foxp3+ T cells in the colon and small bowel, the major effect of this infection on the gut is to “activate” intestinal Tregs making them much more capable of preventing colitis (J. Weinstock, unpublished data). This is readily evident using the Rag/CD25- CD4+ T cell transfer model of IBD in which only the transfer of colonic Foxp3+ T cells from *H. polygyrus bakeri* infection mice can prevent disease. This is the IBD model in which disease develops because the mouse displays a deficiency in Treg cells.

Foxp3+ T cells that make IL10 are critically important for protection from colitis. Mice bearing a conditional deletion of the IL10 allele limited to Foxp3 expressing T cells develop spontaneous colitis (Rubtsov et al., 2008), further attesting to the importance of these cells. Infection with *H. polygyrus bakeri* aids the *a*ccumulation of Foxp3+/IL10+ T cells in the colon, small bowel and MLNs.

A small proportion of Treg cells express CD8+. These cells also may have a role in helminthic control of IBD. They can inhibit T lymphocyte proliferation through cell contact

and Class I Major Histocompatability Complex (MHC) interactions. They do not require IL10 or TGFβ to exert their effect (Metwali et al., 2006).

It is not fully appreciated how the various regulatory type T cells work to control IBD. One potential mechanism is through the production of regulatory cytokines such as IL10 or TGFβ that impede effector cytokine production. Helminths such as *S. mansoni* and *H. polygyrus bakeri* protect mice from TNBS colitis by reducing IFNγ production from Th1 type effector T cells and by limiting IL12 p40 release (Elliott et al., 2003), which are properties associated with IL10 and at times TGFβ.

Th17 cells that make IL17 have a role in driving colitis. *Heligmosomoides polygyrus bakeri* infection inhibits IL17 secretion from a Th17 T cell partly through promoting IL4 and IL10 production (Elliott et al., 2008). Helminth exposure is unable to reverse colitis and regulate IL17 production in the Rag/CD25- CD4+ transfer colitis model if the transferred T cells lack the capacity to respond to IL4, suggesting that IL4 is important for the regulation of IL17 (D. Elliott, unpublished observation).

TGFβ is a centrally important immune modulatory cytokine in inflammation. Transgenic mice with T cells that cannot respond to TGFβ spontaneously develop colitis. In this transgenic mouse, infection with *H. polygyrus bakeri* cannot prevent colitis or dampen mucosal Th1 responsiveness. This shows that *H. polygyrus bakeri* may require TGFβ signaling through mucosal T cells to prevent IBD (Ince et al., 2009).

Although Treg cells and IL10 are sufficient to control IBD in murine models of this disease, it was evident that helminths retained the capacity to prevent and suppress colitis in mice totally lacking IL10 or just functional IL10-producing Treg cells (Elliott et al., 2004; Hang et al., 2010). This suggested that helminths activated at least one other immune regulatory circuit that could function independently of IL10 and Tregs to control disease.

This led to the discovery that *H. polygyrus bakeri* infection alters the function of the dendritic cell (DC) in the gut and MLN of Rag mice, rendering these cells highly regulatory (Blum et al., 2012; Hang et al., 2010). They by themselves are sufficient to prevent IBD. These cells function to block antigen-specific T cell responses in the gut using a presently unknown mechanism that does not require IL10, TGFβ or Tregs. The regulatory DC must physically contact other cellular components in the gut mucosa to control the response.

Helminths also may offer protection from IBD through macrophage-dependent pathways. Macrophages are plentiful in the intestines. Helminthic infections stimulate the host to make IL10 and Th2 cytokines such as IL4 and IL5. These cytokines “alternatively” activate macrophages, rendering them strong producers of TGFβ, IL10 and other immune modulatory factors.

There are several reports supporting the role of macrophages in the control of IBD. Adult *S. mansoni* worms protect mice from DSS-induced enteritis through activation of macrophages. This protection does not require IL10, TGFβ or Treg cells (Smith et al., 2007). Moreover, cystatin, a secreted cysteine protease inhibitor of several filarial species, protects mice from DSS colitis (Schnoeller et al., 2008). This effect of cystatin on macrophages is the reported mechanism of action (Klotz et al., 2011). *Heligmosomoides polygyrus bakeri* infection also induces regulatory macrophages that can limit disease in the Rag/IL10KO T cell transfer model of colitis. In DNBS-induced IBD, infection with the intestinal tapeworm *H. diminuta* protects mice from colitis through a macrophage-dependent mechanism (Johnston et al., 2010).

Several points can be concluded from the above discussion. Helminths do not control intestinal inflammation through induction of just one particular cytokine or regulatory circuit. Instead, they activate several distinct mechanisms to control gut inflammation. At least several of these regulatory pathways are initiated through activation of cells associated with innate immunity. Also, it seems likely that not all helminth species use precisely the same mechanisms to accomplish this task (Table 2).

5. How do helminths communicate with the host?

Helminths must interact through direct contact with host cells or by the release of soluble molecules to alter susceptibility to enteritis. The presence of worm-derived factors that can control disease is supported by the observation that extracts from *H. diminuta* adult worms (Johnston et al., 2010) or administration of dead schistosome ova protect mice from IBD (Elliott et al., 2003). *Heligmosomoides polygyrus bakeri* and other helminths secrete proteins that can induce T cells to express Foxp3 (Grainger et al., 2010), which has implications for IBD control. Helminths produce a number of products with potential immune modulatory properties. This is an area of growing research interest reviewed elsewhere by other authors within this issue.

Intestinal helminths also must overcome the gut epithelial barrier to affect host immunity. Intestinal helminths go through several larval stages before maturing into adults. These larvae live within the epithelial layer of the intestine, closely associated with host intestinal leukocytes. Thus, in some cases, it is possible the larvae, rather than the adult forms of these organisms, interact with the host immune system to control IBD. While some intestinal helminths live free in the intestinal lumen, others attach to the epithelium allowing yet another potential port of communication. Luminal helminths release substances that modulate the function of DCs (Segura et al., 2007; Hewitson et al., 2009; Taylor et al., 2009). In the gut, DC dendrites cross the epithelial barrier, allowing sampling of intestinal contents. Interaction of intestinal helminths with these exposed dendrites could provide an important means of communication. The intestinal epithelial lining can release substances that affect mucosal immune function. Communication between helminths and the nearby host epithelium may also prove important. Such an interaction has been shown in *Trichuris muris* infection. In this infection, *T. muris* stimulates intestinal epithelial cells to make thymic stromal lymphopoietin, which in turn affects DC function promoting the intestinal Th2 response to the worm (Taylor et al., 2009). Intestinal helminths live within an ocean of stool containing billions of bacteria. The composition of intestinal flora has implications for health and disease. As demonstrated using *H. polygyrus bakeri* (Walk et al., 2010), intestinal helminth infections may alter the makeup of intestinal flora, which could impact host immunity.

There are a variety of helminthic species that have evolved to live in different regions of the gut. Some helminths attach to the intestinal wall while others move freely without anchoring to the intestinal lining. Still others can reach beneath the epithelial lining. It seems likely that at least some of the various helminthic species have evolved to employ distinctly unique approaches to access and signal to the host's immune system.

6. Safety considerations

Using helminths to treat human disease has raised some safety concerns. Natural exposure to *T. suis* has no known pathogenic potential. Safety trials in patients with IBD have revealed no side-effects. Some patients with either multiple sclerosis or seasonal allergy have received the agent and reported brief episodes of loose stool that rapidly clear (Bager et al., 2010; Fleming et al., 2011). Concern has been voiced that *T. suis* may migrate aberrantly to organs distant from the gut in immune compromised hosts with inflamed intestines,

particularly when they receive prednisone, azathioprine, anti-TNF therapy and other such treatments. However, this has not occurred in the clinical trials conducted to date. Hookworm does have pathogenic potential in humans, although low-level infection is extremely well tolerated. Public health records suggest that most children who carry hookworm have silent infections. Because the larvae travel through the lungs before entering the GI tract, acute infection can cause pulmonary inflammation. Hookworm also can trigger abdominal cramping and diarrhea, particularly during the acute stage of the infection. Long-term infections are associated with iron deficiency anemia, especially in malnourished children of less developed countries.

Helminthic infection could carry additional risks. During the early phase of helminthic colonization, exposure to an enteric bacterial pathogen may intensify the subsequent inflammatory response to the bacterial infection (Chen et al., 2006; Weng et al., 2007). This mostly has been shown in the settling of helminth/bacterial co-infection experiments in which rodents are simultaneously acutely infected with both organisms. Also raised is the question of whether helminthic infections promote AIDS progression in patients bearing HIV (Da'Dara and Harn, 2010) and impede therapy (Walson et al., 2008). They also may impair responses to HIV vaccines under development and other vaccines (Sabin et al., 1996). The capacity of some helminths to suppress or deviate immune responses to antigens unrelated to the helminth (Jarrett, 1972; Kullberg et al., 1992; Pearlman et al., 1993; Liu et al., 2002; Sacco et al., 2002; Hartmann et al., 2011), possibly through their promotion of IL10 release raises the question whether the therapeutic use of helminths will predispose patients to bacterial, protozoan (Kolbaum et al., 2012) or viral infections. However, the risk from therapeutic helminthic exposure seems modest compared with the dangers of modern day therapies for IBD including corticosteroid, immune modulator and anti-cytokine agents, which are well known to promote and worsen infections with viral, bacterial and fungal pathogens.

Patients with IBD and other serious immune-related diseases face a life-long struggle with these conditions. Most of the currently available therapies expose patients to substantial risk, while in many cases they provide limited efficacy. Administration of an immune modulatory vaccine such as *T. suis*, which stimulates immune regulatory circuits to limit disease activity, offers a new approach to the treatment of IBD with the likelihood of little risk for serious complications.

Acknowledgments

This work was supported by DK058755, DK091987, VAHC, and bequests from the Schneider Family, Friedman Family, Gilman Family. (Funding source is from these families who have personal foundations. They all live in the US.)

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- Hygiene and loss of helminthic infections contributed to the spread of inflammatory bowel diseases
- Helminths have therapeutic potential for the treatment of inflammatory bowel disease
- They work through activation of regulatory T cells and modulation of dendritic cell function
- They likely will prove safe in therapeutic applications

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[b]	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
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 phases (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.

Table 2

Helminths in murine models of colitis.

Colitis Model/Strain	Helminth	Result	Mechanisms of Action	Reference
TNBS Colitis				
BALB/c	*Schistosoma mansoni* egg antigen	Prevention of colitis	Inhibition of Th1 response Augmentation of Th2 and T regulatory (IL10) responses Requires Stat6 circuits	Elliott et al. (2003)
BALB/c	*Heligmosomoides polygyrus bakeri*	Prevention of colitis	Inhibition of Th1 response Augmentation of mast cell response	Sutton et al. (2008)
Swiss OF1	*S. mansoni* proteins	Prevention of colitis	Inhibition of Th1 and Th17 responses Augmentation of IL10 and TGFb	Ruyssers et al. (2009)
BALB/c	*Schistotoma japonicum* eggs	Prevention of colitis	Inhibition of IFNγ and augmentation of IL10 response.	Zhao et al. (2009)
BALB/c	*S. japonicum* eggs	Prevention of colitis	Maintenance of epithelial barrier function	Xia et al. (2011)
BALB/c	*Trichinella spiralis* 53KDa protein	Prevention of colitis	Reduced serum IFNγ, TNFα and increased serum IL4, and IL13. Reduced colonic IL6, TNFα	Du et al. (2011)
DNBS Colitis				
C57BL/6	*T. spirialis*	Prevention of colitis	Induction of Th2 response Inhibition of Th1 response	Khan et al. (2002)
BALB/c	*Hymenolepis diminuta*	Prevention of colitis	Inhibition of Th1 response Induction of IL4 and IL10 Protection requires IL10	Hunter et al. (2005)
BALB/c	*H. diminuta* extract	Prevention of colitis	Reduced TNFα production Augmented IL4 and IL10 response	Johnston et al. (2010)
C57BL/6	*T. spiralis* antigen	Prevention of colitis	Suppression of IL1b response Augmented TGFb and IL13 response	Motomura et al. (2009)
DSS Colitis				
BALB/c	*H. diminuta*	Improved ion transport but no change in histology	Presumed Th2 augmentation	Reardon et al. (2001)
BALB/c	*S. mansoni*	Prevention of colitis	Mediated by induction of F4/80+ macrophages	Smith et al. (2007)
NMRI	*S. mansoni*	Protection from colitis but requires actual infection	Reduced TNFα production Augmented IL4 and IL10	Bodammer et al. (2011)
BALB/c	*Ancylostoma ceylanicum* proteins	Prevention of colitis	Inhibited Th1 and Th17 responses	Cancado et al. (2011)
C57BL/6	*Acanthocheilonema viteae* cystatin	Prevention of colitis	Induction of alternatively activated macrophages	Schnoeller et al.(2008)
C57BL/6	*Anisakis simplex* MIF-like protein	Protection from colitis	Inhibition of Th1, *T*NFα, and IL13 responses Augmentation of TGFβ, IL10 and Treg (Foxp3+) response	Cho et al. (2011)
IL10$^{-/-}$ Colitis				
C57BL/6	*H. polygyrus bakeri*	Protection from developing colitis	Not determined	Elliott et al. (2000)
C57BL/6	*H. polygyrus bakeri*	Treatment (reversal) of established colitis	Inhibition of IL12p40 and Th1 circuits Induction of FoxP3+ T regulatory cells	Elliott et al. (2004)
C57BL/6	*H. polygyrus bakeri*	Treatment (reversal) of established colitis	Inhibition of Th17 circuits through induction of IL4 and IL10	Elliott et al. (2008)

Colitis Model/Strain	Helminth	Result	Mechanisms of Action	Reference
C57BL/6	Transient *Trichuris muris*	Protection from developing colitis	Not determined	Elliott et al. (2000)
C57BL/6	Persistent *T. muris*	Exacerbation of colitis	Induction of IL13R antagonist blocking IL13 signaling	Wilson et al. (2011)
TGFβRIIDN colitis				
C57BL/6	*H. polygyrus bakeri*	No effect on colitis	Induction of IL10 and control of colitis requires TGFβ signaling	Ince et al. (2009)
Transfer Colitis				
C57BL6	*H. polygyrus bakeri*	Treatment (reversal) of established colitis	Induction of a CD8+ regulatory T cell	Metwali et al. (2006)
C57BL/6	*H. polygyrus bakeri*	Protection from colitis	Induction of alternative tolerogenic dendritic cells	Hang et al. (2010) Blum et al. (2012)
C57BL/6 , $IL10^{-/-}$ OT2	*H. polygyrus bakeri*	Protection from antigen-driven colitis	Inhibition of Th17 and Th1 responses Augmentation of IL10 and Foxp3	Leung et al. (2012)
Oxazolone colitis				
BALB/C	*H. diminuta*	Exacerbation of colitis	Induction of Th2 circuits	Hunter et al. (2007)
BALB/c	*H. diminuta*	Exacerbation of colitis	Induction of IL5 and eosinophil trafficking	Wang et al. (2010)
Infectious colitis				
- Citrobacter rodentium				
BALB/c	*H. polygyrus bakeri*	Exacerbation of *Citrobacter* infection	Augmentation of Th2 circuitry Requires intact Stat6 signaling	Chen et al. (2005)
BALB/c	*H. polygyrus bakeri*	Exacerbation of *Citrobacter* infection	Alternatively activated macrophages and IL10 production	Chen et al. (2006)

TNBS, trinitrobenzene sulfonic acid; DNBS, dinitrobenzene sulfonic acid; DSS, dextran sodium sulfate; Treg, regulatory T cells.