

## INVITED REVIEW

# Parasitic worm therapy for allergy: Is this incongruous or avant-garde medicine?

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## Clinical & Experimental Allergy

### Abstract

Helminth (worm) therapy has already been used in clinical trials associated with allergy. These were generally small scale, safety orientated trials of short duration, justified by epidemiological and experimental data indicating potentially beneficial immune modulation by some parasites. However, parasites by definition are disadvantageous to their hosts, and helminth infection in particular almost invariably induces an allergic phenotype, rendering this somewhat paradoxical therapeutic approach for allergy open to scrutiny. Is parasitic worm therapy for allergy incongruous medicine, or *avant-garde* medicine? In the present article, we assess the strength of evidence supporting the use of helminth therapy for allergy and critically appraise the trials already completed. Then, should this approach prove successful, we suggest strategies to improve the delivery of helminth therapy, and ways to discover immune response modifiers derived from worms.

**Keywords** allergic rhinitis, clinical trial, helminth, hookworm, immunotherapy, *Necator americanus* (hookworm) RCT (randomized controlled trial), regulatory T cell, T helper 2 (Th2), *Trichuris suis* ova (TSO), worm therapy

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### Introduction

Some epidemiological studies support a causal link between infection with parasitic worms and a reduced incidence of allergic disease, or markers of atopic sensitization (Table 1), although other studies indicate that parasite infection can in fact exacerbate allergic diseases. Nevertheless, further support for a suppressive effect of worm infection on allergy is derived from murine disease models, where superimposed worm infections suppress an allergic phenotype (Table 2). On balance, this background evidence has been used to support the hypothesis that iatrogenic worm infection could be used to treat allergic disease, and a number of clinical trials were initiated. However, it must be pointed out immediately that not all helminth infections can be deemed *therapeutically equal*, with *Ascaris lumbricoides* and filarial parasites associated with Loeffler's syndrome and tropical pulmonary eosinophilia. This makes parasite species selection crucial to the appraisal of this hypothesis. In this respect, the human hookworm *Necator americanus* was chosen as a

candidate infection, because of its relatively benign association with humans at low infection intensity, and the fact that the allergic response seems to have a controlling effect on infection. The hookworm may indeed be exerting a level of control over the allergic phenotype to promote its survival, giving it potential anti-allergic properties (Fig. 1). The second candidate in trial at present is porcine *Trichuris suis*, which represents a zoonotic infection, but is deemed safe because of its perceived inability to develop a full and potentially hazardous life cycle in humans.

However, each parasite has a potential dark side; too many hookworms will cause tissue damage during migration, particularly to the lungs, and will cause excessive blood loss during feeding in the small intestine. These facets of the life cycle led to the dose-ranging safety trials described below. Concerns have also been expressed about the use of a zoonotic infection [*T. suis* ova (TSO)], derived from a porcine species, concerns which will be expanded upon later.

Given the above, and the recent completion and publication of clinical trials [1–3] with hookworms

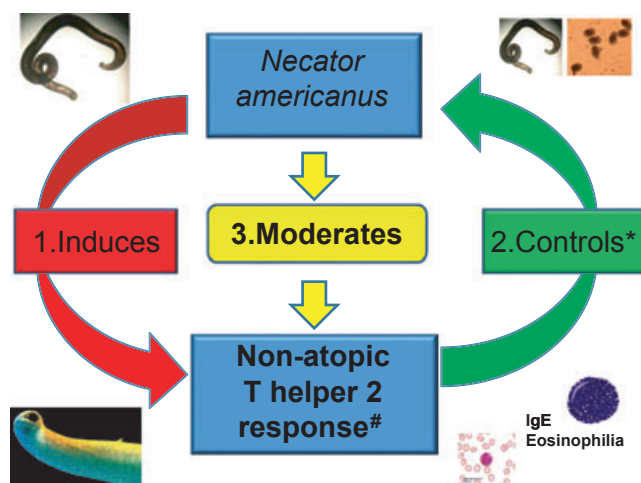


Fig. 1. The relationships between parasites and allergy. Our knowledge of the immunobiology of necatoriasis is used here to illustrate the complexity of the relationship between allergy and parasitic helminths. This is simplified into three interactive and dynamic possibilities. (1) Necatoriasis induces an allergic phenotype, which has been described as 'muted' (Dr J. Croese, personal communication) or non-atopic; (2) the allergic phenotype controls necatoriasis; (3) worms moderate the allergic response. Pathways 1 and 2 are supported scientifically as necatoriasis drives an allergic response (specific IgE, IL-5, IL-13), and eosinophilia and high IgE levels have been correlated with smaller, less fecund parasites [7]. The existence of pathway 3 (illustrative of the therapeutic helminth) remains to be confirmed in humans, although the longevity of infection would support the presence of a worm-driven counter allergic strategy. The figure includes illustrations of an adult female *Necator americanus* in culture (top left), and the cephalic anatomy of an adult worm (bottom left). On the right, illustrations are used to highlight the influence of the allergic phenotype in reducing worm size and fecundity, as reported in the literature [7].

(*N. americanus*) to establish safety during parasite migration through the lungs, and TSO to assess therapeutic benefit in allergic rhinitis (AR), it is considered timely to review the status of this field of investigational medicine by critically appraising worm therapy, and the evidence that has led to the introduction of worms as investigational medicinal products.

The appraisal will:

- review the evidence supporting worm therapy,

- address the apparent failure of some clinical trials to provide evidence for therapeutic benefit,
- suggest ways to improve the design of clinical trials in the future, to promote translation of the evidence supporting worm therapy into patient benefit,
- consider whether therapeutic immune response modifiers can be derived from worms.

However, to begin with, the question as to why clinicians and patients would consider accepting parasites in place of conventional treatments could be of interest.

### Is worm therapy addressing an unmet clinical need? [4–6]

There is widespread recognition that the rising prevalence of allergic diseases represents a major global health problem. Acute exacerbations of asthma or anaphylaxis induced by foods, insect venoms or drugs, may be life threatening. In many conditions, such as severe food allergies, there are no established therapies. Chronic allergic diseases, including AR, asthma, eczema and food allergy, are exceptionally common and represent an enormous socio-economic burden. For example, AR is frequently trivialized, but commonly impacts on quality of life and social functioning. There are an estimated 15 million AR sufferers in the UK, one-third of whom experience moderate-severe symptoms that effect sleep, leisure and work activities. Millions of these individuals likely experience poor symptom control and express high levels of dissatisfaction with conventional treatment. Specific allergen immunotherapy (desensitization) can be effective and disease modifying in such patients. However, use is limited to cases where a single allergen driver is identifiable, and it is not indicated in the majority of patients who are sensitized and simultaneously exposed to numerous allergens. Thus, for AR alone, there is a considerable unmet need for novel effective therapies.

Infection with live worms is proposed by some as a potential treatment for allergic disease. Scientific support is provided by the observation that an allergic phenotype appears to play a positive role in controlling

Table 1. Examples of epidemiological studies supporting helminthic therapy for allergy

| Infection                      | Outcome                                          | Interpretation                                                                  |
|--------------------------------|--------------------------------------------------|---------------------------------------------------------------------------------|
| <i>Ascaris lumbricoides</i>    | Infection moderated atopy                        | Children with immunity to the parasite were more atopic [48]                    |
| <i>Trichuris trichiura</i>     | Infection reduced allergen SPT                   | Infection in childhood protects against atopy [12]                              |
| <i>Schistosoma haematobium</i> | Reduced SPT to dust mite allergen                | Reduced atopy in infected subjects associated with IL-10 [10]                   |
| <i>Mixed helminths</i>         | Risk of wheeze was reduced by hookworm infection | Hookworm infection prevents asthma in atopic individuals [8]                    |
|                                | SPT to dust mite allergen reduced                | Geohelminth infection reduced allergic sensitization in Vietnamese children [9] |
|                                | Worm removal increased allergen SPT              | Helminths suppress allergic skin test reactivity [11]                           |

SPT, skin prick test.

Table 2. Examples of murine models supporting helminthic therapy for allergy

| Infection                                                     | Outcome                                                                           | Mechanism                                                                                                                                                                                                                  |
|---------------------------------------------------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Heligmosomoides polygyrus</i>                              | Reduced airway inflammation<br>Suppression of allergic response to peanut extract | CD4 <sup>+</sup> CD25 <sup>+</sup> Foxp3 <sup>+</sup> regulatory T cells [13]<br>Reduced allergen specific IgE production.<br>IL-10 dependent [16]                                                                         |
| <i>Litomosoides sigmodontis</i><br><i>Schistosoma mansoni</i> | Reduced lung hyper-reactivity<br>Suppression of airway inflammation               | Regulatory T cells and TGF- $\beta$ [15]<br>IL-10 from CD4 <sup>+</sup> T cells and CD19 <sup>+</sup> B-cells. [14]<br>CD4 <sup>+</sup> CD25 <sup>+</sup> Foxp3 <sup>+</sup> regulatory T cells.<br>IL-10 independent [17] |

worm infections in humans [7]. Worms in turn may have developed mechanisms for suppressing Th2 immune responses to survive, leading to the working model presented in Fig. 1, for hookworm parasites. Hookworms also possess the possible advantage of imparting therapeutic longevity in the allergic host, precluding the need for repeated treatment. This is because *N. americanus* survives in the human gut for a number of years. However, given the unconventional nature of this approach, the evidence supporting live worm therapy should be rigorously reviewed at this juncture.

### Worm therapy: reviewing the supporting evidence

Some epidemiological studies show a negative correlation between infection with parasitic helminths and indicators of atopy (Table 1). In particular, a study of urban and rural populations in Ethiopia found that the risk of respiratory wheeze associated with house dust sensitization was reduced in the presence of hookworm infection [8]. Other studies have shown reduced skin prick test (SPT) reactivity to common allergens in children infected with intestinal nematodes [9] and schistosomes [10]. Furthermore, in some studies, parasite removal increased SPT reactivity [11]. Moreover, it appears that infection with helminths may afford long term protection from atopy as it has been demonstrated that children infected with *Trichuris trichiura* in early life exhibited reduced skin test reactivity towards allergens, independent of their infection status at the time of skin test [12]. However, it is important that caution is exercised when considering the outcomes of epidemiological studies, particularly those where SPT is used as a primary outcome, as reductions in SPT reactivity may not necessarily coincide with clinical benefit. Accordingly, scientists have used murine models of allergic disease to support the epidemiological evidence for the immune modulatory capacity of worm infection (Table 2). For example, allergic airway inflammation was suppressed in the presence of *Heligmosomoides polygyrus* [13], *Schistosoma mansoni* [14] or *Litomosoides*

*sigmodontis* [15]. Similarly, peanut sensitization was reduced by *H. polygyrus* [16].

An important factor in interpreting animal models of worm therapy must be the recognition of the unnatural dose regimens used to induce immune modulatory effects. Infection is rarely acquired by humans, or mice, as a high dose single exposure; trickle infection is the norm. Furthermore, the presence of such a large bolus of worms at sites immunologically removed from the diseased organ could have a significant effect on the ability of the immune system to divert its response from the site of infection to the site of disease. Nevertheless, one could argue that animal models have been extremely useful in pointing immunologists towards the cellular mechanisms by which worms may suppress immune responses associated with disease, with regulatory lymphocytes currently in prime position as the mediators of the beneficial effects recorded [13–15, 17]. Furthermore, animal models provide a platform in which to test immune modulatory molecules isolated from parasites.

### Worms on trial

The evidence cited above provides a rationale for testing worm therapy. However, parasitic helminths are pathogenic and the pathology caused by the parasite has to be negligible if iatrogenic infection is to be considered as a safe potential therapeutic approach. In addition, parasitic helminths can exacerbate inflammatory conditions in humans [18] and in experimental animals [19], highlighting the need for considered care when advancing into infection involving human volunteers. Accordingly, early clinical trials using hookworm (*N. americanus*) [20] and TSO [21] were relatively small, designed to initially identify safe and tolerated doses, particularly in view of the reservations expressed about using a parasite with a systemic migratory phase to its lifecycle (*N. americanus*), the use of a zoonotic infection (TSO) in humans [22] and the potential of *Trichuris muris* to induce a phenotype similar to human inflammatory bowel disease (IBD) in mice [23].

*Trichuris suis*: This is a natural parasite of pigs, hence it is classed as a zoonotic infection of humans. The parasite is reputed to be non-invasive in humans, remaining in the gut. This justifies the repeated, large dosage regimes used for TSO. However, some have reservations about this assumed restriction of residence.

*Necator americanus*: An exquisitely anthropomorphic parasite, adult parasites live as separate sexes in the duodenum, producing fertile eggs following mating. These eggs are deposited on the ground in the fecal mass, and then hatch into larvae. Over a period of approximately 10 days at 28°C, and following larval moult, the third stage or L3 larva is ready to penetrate human skin. Penetration results in itching, hence the use of histamine as a placebo in RCTs. From the skin, the larva enter the circulation, then the lungs, and migrate via the trachea and oesophagus to the gut, where they may reside for years. The duration of migration from skin to gut is in the region of 3–4 weeks (coinciding with the period of lung function monitoring in recent safety trials [1, 2]). Over infection causes tissue damage in the lungs, and blood loss and accompanying iron-deficiency anaemia as the adults feed on intestinal tissue [24].

## Completed trials

### *Trichuris suis ova*

Although TSO therapy appears to impart clinical benefit in IBD patients [25], it was not possible to translate the apparently beneficial anti-allergic effects of worms seen in field studies to allergic patients undergoing iatrogenic infection. The absence of a demonstrable effect in clinical studies to date may be multi-factorial, applicable to all 'therapeutic' worm species and involving parameters such as:

- the site of infection, and the induction of organ-specific immune suppression;
- the timing of infection, for example in relation to the pollen season;
- the lack of heterogeneity of infection, with possible cross-boosting by different worm species [26];
- the frequency and longevity of infection, replicating the natural life-cycle.

Natural low dose trickle infection may afford the parasite an opportunity to engage and boost relevant immune regulatory networks, immunological events which have yet to be monitored closely in any clinical trial. Indeed, the use of repeated low dose inocula of

*T. muris* in mice has been shown to be sufficient to engage immune regulatory networks without stimulating protective immunity [27]. Recently, published comments [28, 29] on the trial of TSO in AR by Bager *et al.* [3] offer further explanations for the apparent failure of TSO to provide therapeutic benefit. These include the use of too few doses together with the relatively late administration of TSO treatment in respect to the onset of the pollen season. Furthermore, the greater severity of pre-trial baseline symptoms in the active vs. placebo-treated group and subsequent reduced use of medication in the TSO group were suggested as being indicative of hidden therapeutic benefit [28]. Finally, it was proposed that the treatment of disorders in which the target organ (nose, lung) is remote from the site of direct contact with parasite material (i.e. the gut) should involve use of higher or multiple doses to allow for systemic effects. Given the experiences of Bancroft *et al.* [27], an alternative to high dose single bolus infection would be to explore the potential of exposure to low dose 'trickle' infection to induce immune regulatory networks.

### *Necator americanus*

The three hookworm trials completed to date [1, 2, 20] were safety orientated, short-term (12 weeks) studies designed to verify the safety of larval passage through the lungs. The safety of infection, in terms of lung function, was confirmed and worm infection did not potentiate existing anti-allergen IgE responses [30, 31]. However, these studies were neither designed nor empowered to demonstrate therapeutic benefit. Low level infection was shown to be immunogenic, a supposed pre-requisite for the activation of regulatory networks, although circulating levels of phenotypic regulatory T cells (Tregs) were not increased following infection [32]. However, in AR, infection was largely superimposed upon the grass pollen season. This contrasts with immunotherapy – an established and effective treatment thought to work by inducing Tregs – which is initiated at least several months before natural pollen exposure. In summary, a platform has been established for progression, although experience to date suggests that improved trial strategies should be tabled at this juncture.

## Optimizing the immunological strategy

With safety trials now complete, the experience with hookworm suggests that infection regimens may need to be modified to induce an immune regulatory phenotype conducive to therapeutic benefit. For example, by analogy to grass pollen immunotherapy, it may be preferable to repeatedly prime/boost the immune regulatory environment before the pollen season with a divided

low dose worm inoculum, as a prelude to in season allergen exposure. The effect of priming/boosting on the appearance of Tregs, as seen in murine models, should be monitored in parallel. In addition, allowing parasites, like hookworm, an extended period of residence in the gut may also be therapeutically beneficial. Animal models suggest that gut-resident nematode parasites can drive Treg responses that subsequently exert bystander effects at sites of inflammation distal from the gut. In the case of *H. polygyrus*, it is possible to envisage an immunological scenario where the gut resident bolus infection establishes a 'Treg pool' (TRP)<sup>1</sup> as infection is associated with the development of a splenic 'suppressor cell' population [33]. Cells recruited from within this TRP could then migrate to sites of allergic inflammation in the skin, lung and gut (Fig. 2). According to this hypothesis, suppression of host Th2 responses by the parasite-induced TRP serves to promote the parasite life-cycle in the case of hookworms, as they migrate from the skin to the gut via the lungs, and to render moderate infections asymptomatic. This apparent moderation of inflammatory responses may be more efficient in fully adapted host-parasite relationships, given the severity of eosinophilic enteritis seen following *Ancylostoma caninum* (dog hookworm) infections in humans. 'In Northern Australia, the dog hookworm was proven the cause of a minor epidemic of eosinophilic enteropathy.....patent (*N. americanus*) hookworm infections are usually not associated with a clinical enteropathy' (Dr John Croese, personal communication). In summary, the anti-allergic effects of the well-adapted parasite may be an unintended bystander manifestation of its survival strategy.

In a trial planned in multiple sclerosis patients based at the Nottingham Queen's Medical Centre, 25 hookworms will be allowed to remain in residence for a full 9 months. We speculate that this period of residence will result in an increased opportunity to establish and maintain a TRP of sufficient magnitude to translate into an anti-inflammatory effect and therefore therapeutic benefit. It is reasonable to suggest that this is already happening in the field, where life-long trickle infections may be establishing a TRP of sufficient immunomodulatory power to result in systemic anti-allergic effects, whereas supporting the longevity of infection.

### Future directions for worm research in allergy

If the potential value of worm therapy is accepted, then new clinical strategies become essential. For example, it

<sup>1</sup>The term TRP is used for simplicity, with the explicit understanding that alternative populations of regulatory cells exist (RLPs; regulatory leucocyte populations), which could contribute to the anti-allergic effect of worms, either alone or in conjunction with a TRP.

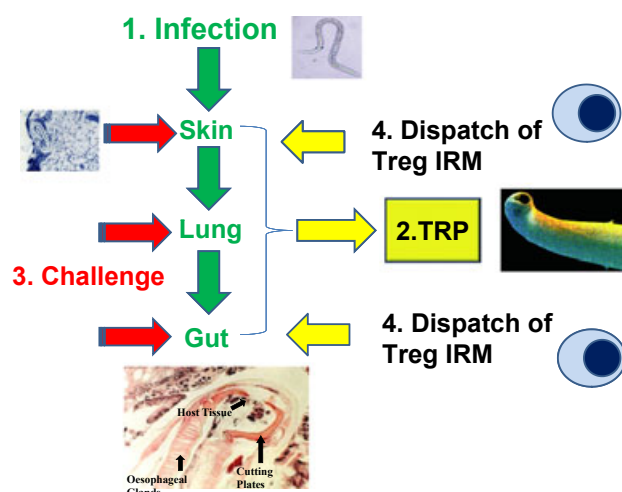


Fig. 2. The Treg pool hypothesis. *Necator americanus*, which infects percutaneously, then migrates to the gut via the lungs, (1) establishes a Treg pool (TRP) (2) in lymphoid tissue. This TRP is mobilized on reinfection or allergen challenge (3), resulting in the dispatch and recruitment of Tregs (4) to sites of inflammation. The local anti-inflammatory effects of these cells are geared to promote parasite infection and survival. In this context, it is likely that the immediate allergic response to larval penetration of the skin (called 'ground itch') is designed to begin to trap and kill larvae on entry. Larvae could be further targeted by the late-phase response, which begins soon after the initiation of the immediate response, and involves the recruitment of CD4 T cells, macrophages, neutrophils and eosinophils, under the influence of IL-16 and MIP 1 $\alpha$ . In allergic disease, migration of these Tregs to sites of allergen exposure may similarly counter local inflammatory responses. Hypothetically, the TRP would be over-populated, possibly through parasite-induced polyclonal expansion, as opposed to having just sufficient Treg to moderate immune activity against the parasites themselves. Surplus Treg would then act in a bystander manner to moderate immunological disease. The surplus Treg pool would ideally contain Treg of a phenotype capable of suppressing allergic inflammation, possibly CD45RA<sup>-</sup> Foxp3 in CD4 T cells [43]. The figure includes illustrations of the infective skin-penetrating L3 larva of *Necator americanus*, and a section of the adult stage, attached to the gut and feeding on intestinal tissue.

is almost certainly unrealistic to expect 10 larvae of *N. americanus* resident for only 12 weeks, as occurred in initial safety trials, to reverse established pro-allergic memory immune responses. Therefore, future trial planning may incorporate the following considerations:

- 1 It may be necessary to introduce an infection regime of sufficient and appropriate stimulatory power to establish a therapeutic TRP. Treg recruitment to the respiratory mucosa and skin from this TRP would take place during subsequent natural allergen exposure, resulting in bystander regulation of allergen-specific Th2 responses.
- 2 It may be appropriate in future trials to initially test effects of worm infection regimens on physiological and immunological biomarkers rather than true clinical end-points, for which early 'proof of concept'

### Immunotherapy/Worm infection/Worm IRMs

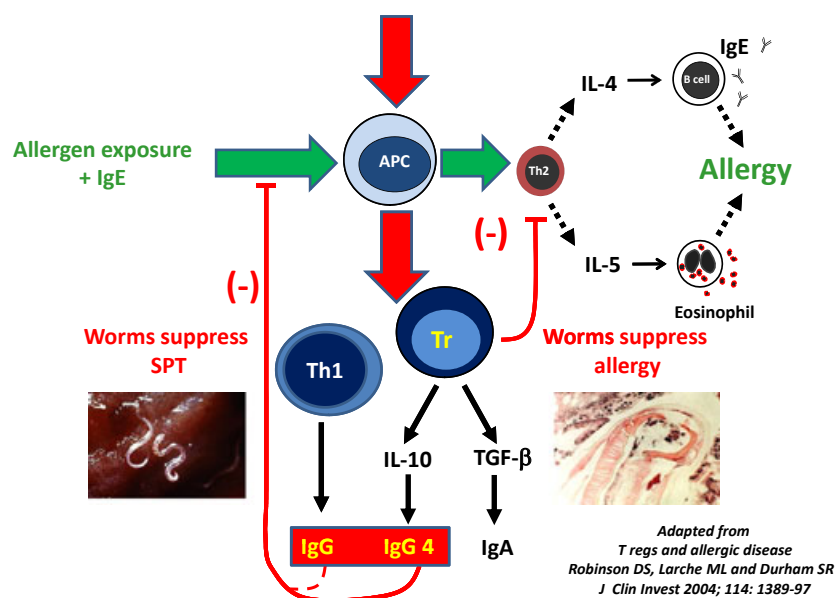


Fig. 3. The cellular and molecular bases for the success of immuno and worm therapy in moderating allergy. A depiction of the cellular and molecular mechanisms by which immunotherapy, worms and their products, immune response modifiers (IRMS), may act to reduce allergic responses in patients. It is hypothesized that worms and immunotherapy may share mechanisms of immune modulation, to reduce allergic responses in the skin and other vital organs. Adapted from Robinson DS, Larche ML and Durham SR. *J Clin Invest* 2004; 114: 1389–97.

studies are likely to be underpowered. An example of a suitable physiological biomarker could be the late phase skin response to intradermal allergen provocation, which is inhibited by specific allergen immunotherapy in parallel with the appearance of Treg responses [34]. Similar to these observations in immunotherapy, the cutaneous late response could potentially provide a useful indication of worm-induced immune modulation (Figs 2 and 3).

A complementary approach adopted by some is to investigate worms for secretion of low molecular weight immunomodulatory factors, for use either as drugs or adjuvants for immunotherapy vaccines. Helminth infections are undoubtedly pro-allergic, a fact long recognized by the pharmaceutical industry, where models using worm infection to induce allergy have been used (the ON switch) as a valuable component of anti-allergic drug discovery programmes [35, 36]. Indeed, some of the molecules responsible for driving the Th2 response to worms are beginning to be recognized [37–40] (Fig. 4). With regard to the anti-allergic effects of worms (the OFF switch), it has been hypothesized that in addition to using enzymes to destroy pro-allergic chemokines [41], host-adapted hookworms secrete non-immunogenic immune suppressive molecules to promote their life cycle in humans. According to this hypothesis, these products could also suppress allergen-induced IgE and eosino-

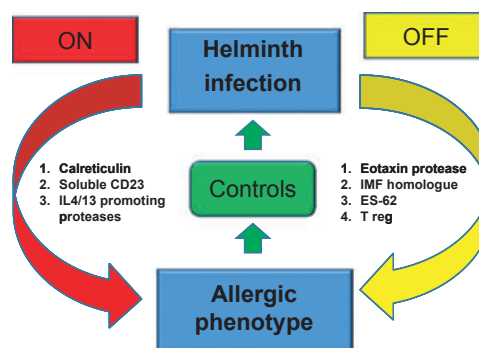


Fig. 4. The worms' allergy on/off switch. The factors which worms use to drive the allergic phenotype (the ON switch) are beginning to be recognized, and include secreted calreticulin [37–39], proteases which innately induce IL-4/13 production by basophils [39], and, possibly, release of soluble CD23 [44]. As examples of molecular counter-measures (the OFF switch), worms secrete enzymes which neutralize eotaxin [41] and immune-suppressive molecules which target T cells [45]. In addition, worms expand regulatory lymphocyte populations. These molecular counter-measures, particularly those falling into the low molecular weight non-immunogenic category, could be exploited to treat allergy and other immunological diseases [46, 47].

phil responses, immunological parameters that are also associated with a partial host protective response to worm infection. If secretion of immune modulators is confirmed, anti-allergic molecules secreted by hookworms could be discovered using refined separation

technology and screened against clinically relevant immune assays.

## Conclusion

Although the effectiveness of worm therapy in humans remains to be proven, it may be important to encourage the scientific and clinical community to address the issue of therapeutic helminth infection critically, in the absence of viable therapeutic alternatives, particularly for severe allergic and autoimmune diseases.

To date, considerable resources have been invested in animal models with the aim of developing an understanding of the immunological events initiated by parasites to support their survival, and to moderate disease in the process. These data provide a strong rationale for supporting and perhaps prioritizing translational studies in humans, in an attempt to treat disease with controlled worm infection or worm-derived immune modulators.

The successful application of worm therapy to allergic diseases will be dependent on a strategy which har-

nesses the combined immunological knowledge gleaned from epidemiological investigation, safety trials and murine model systems. This strategy will aim to engage immune regulatory networks in a safe and beneficial manner that results in neither excessive immune suppression nor unacceptable levels of pathology directly arising from worm infection [42].

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