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Invited Review

Prerequisites for the pharmaceutical industry to develop and commercialise helminths and helminth-derived product therapy

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ABSTRACT

During the past 10 years, immunologists, epidemiologists and parasitologists have made many new exciting discoveries in the field of helminth-mediated immune regulation. In addition, many animal experiments have shown that certain helminths or products derived from helminths can protect mice from developing allergic or autoimmune disease. Some clinical trials utilising *Trichuris suis* or *Necator americanus* for the treatment of allergic disorders and inflammatory bowel disease have been conducted. The outcomes of these trials suggest that they may be used to treat these disorders. However, to date no helminth therapy is routinely being applied to patients and no helminth-derived product therapy has been developed. In order to bring new drugs to the market and shoulder the enormous costs involved in developing such therapies, pharmaceutical companies need to be involved. However, currently the resources from the pharmaceutical industry devoted to this concept are relatively small and there are good reasons why the industry may have been reluctant to invest in developing these types of therapies. In this review article, the hurdles that must be overcome before the pharmaceutical industry might invest in these novel therapies are outlined.

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1. Introduction

During the past 10 years, there has been fruitful inter-disciplinary cooperation between parasitologists, immunologists and epidemiologists, leading to many exciting and important findings with respect to identifying host-parasite immune regulatory networks. In particular, the inverse relationship between helminth infections and allergy and autoimmunity is intriguing. Numerous epidemiological studies that have found such a relationship and validation of this concept in animal models have supported the hypothesis that helminth infections protect against the development of both autoimmunity and atopic disorders (Kamradt et al., 2005).

Epidemiological studies from Ecuador, Vietnam, Brazil, Africa and Germany show a negative correlation between infection with helminths and atopy. Often mentioned are hookworm infections with *Ancylostoma duodenale* and *Necator americanus*, schistosomiasis, or infections with *Ascaris lumbricoides* and *Trichuris trichiura* (Flohr et al., 2009; Elliott and Weinstock, 2012). Positive effects on skin-prick-test (SPT) have been shown for *A. lumbricoides*, *T. trichiura, Schistosoma* and hookworm. Positive effects on eczema for *A. lumbricoides* and on asthma for hookworm and *Schistosoma mansoni* infections were observed.

An effective impact on Crohns disease in 80% of patients was achieved in a trial with *Trichuris suis* infection (Summers et al., 2005; Zaccone et al., 2006; Reddy and Fried, 2009). Other helminths successfully used to control immunological disease are *T. trichiura*, *Oxyuris* spp., *Schistosoma haematobium* and *Enterobius vermicularis* (Erb, 2009; Elliott and Weinstock, 2012).

Furthermore, this negative correlation has been observed in animal models. Mice infected with the hookworm, *Nippostrongylus brasiliensis*, in a murine asthma model 8 or 4 weeks before Ovalbumin (OVA) challenge showed reduced eosinophilic inflammation in the lungs, lower Eotaxin levels and reduced OVA-specific IgG_1 and IgE serum levels (Wohlleben et al., 2004). The same effect was achieved by infection with the gastrointestinal nematode, *Heligmosomoides polygyrus*, in a similar asthma model (Wilson et al., 2005; Hartmann et al., 2009). *Schistosoma mansoni*, *H. polygyrus*, *Trichinella spiralis* and *Hymenolepis diminuta* were successfully used in colitis mouse models (Ruyssers et al., 2008). Other helminths effectively used in animal experiments of type 1 diabetes, autoimmune encephalomyelitis, multiple sclerosis (MS) and other diseases are *S. mansoni*, *T. suis*, *T. spiralis*, *Litomosoides sigmodontis*, *Strongyloides stercoralis* and *Strongyloides venezuelensis* (Zaccone

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et al., 2006; Erb, 2009; Elliott and Weinstock, 2012; Kuijk et al., 2012).

Not surprisingly, products derived from different helminths have also been found to have immunomodulatory properties. For example, ES62, a filarial-derived product shows anti-inflammatory effects in many different models and *Ascaris suum* extracts (ASC) suppress OVA-specific IgE antibodies in murine models of asthma (Lima et al., 2002). Suppression of the T helper (Th)2 response and airway hyperreactivity (AHR) in mice were also achieved by application of the suppressive protein of *A. suum* (PAS-1) or *N. brasiliensis* excretory-secretory protein (NES) (Trujillo-Vargas et al., 2007; Erb, 2009). Many additional examples exist in published literature and the reader is referred to the other articles and excellent reviews in this issue dealing in detail with the new scientific findings. Multiple scientific examples of host-parasite immune regulatory networks that can be targeted from the disease standpoint have been identified. So what is needed to gain support from the pharmaceutical industry for helminth therapy (HT) and helminth-derived product therapy (HDPT) for the treatment of human diseases?

In order to understand why pharmaceutical companies appear not to be too interested in these types of therapy, it is important to understand what old and new challenges the pharmaceutical industry is facing. First of all, the attrition rate in the clinic for novel concepts is increasing, although there is often excellent proof of concept (PoC) in animal models (van der Worp et al., 2010; Arrowsmith, 2011). Secondly, the efficacy achieved by the novel concept compared with the 'gold standard' or other drugs already on the market (including generic drugs) is often not sufficient to gain approval from the authorities or secure the appropriate price, reimbursement and market access. Pharmaceutical companies now face more pressure than in the past to ensure that a new drug concept has a significantly high chance of being successful in the clinic. In short, the new drug needs to be highly efficacious – clinically significantly better than standard of care, patent protected and have the potential to create sufficient revenue to help sustain ongoing research and development. Many new drug concepts unfortunately are not able to show evidence that they might clear these hurdles in order to be supported for further development. In our opinion, new drug concepts need to be backed by compelling human disease-relevant science focusing on humans (and not solely on animal models) and on diseases with the greatest unmet medical need. Nevertheless we also believe that in the long term, excellent science will prevail – leading to novel drugs that meaningfully help patients.

2. Is there a case to be made for HT or the use of HDPT?

Helminths can infect and live in humans for a very long time. In order to survive the parasites need to evade the immune response of the host. This is achieved by the helminths modulating the human immune response directed against them by activating immune regulatory networks, in particular regulatory T (Treg) cells (many different phenotypes), regulatory B (Breg) cells, regulatory macrophages (alternatively activated) and regulatory dendritic cells (DCs) (Cooper, 2009; Erb, 2009; Flohr et al., 2009). Treg cells are possibly the most important cell type because during a first or chronic infection a Treg cell pool is established in the lymphoid tissue. Treg cells are mobilized out of this pool on reinfection or continuously activated, resulting in the recruitment of Treg cells to the site of inflammation, where they promote the parasite infection through anti-inflammatory effects (Maizels et al., 2009; Pritchard et al., 2012). These cells either directly by cell/cell interaction or by the production of anti-inflammatory cytokines e.g. IL-10 and or transforming growth factor (TGF)-β, mediate their anti-inflammatory/regulatory effects. It is not absolutely clear whether the host has any direct benefit from this. Epidemiological studies show that helminth infections indirectly or directly correlate with decreased atopy or autoimmunity, suggesting that helminths suppress the development of these diseases in humans. Numerous animal experiments support this hypothesis and it appears that helminths produce molecules which are immunomodulatory (see above). However, looking at the evidence carefully a more diverse picture evolves. Firstly, not all helminth infections in humans are associated with a reduction in atopy and autoimmunity. *Ascaris lumbricoides*, *N. americanus* and filarial parasites are associated with Loeffler's syndrome (tropical pulmonary eosinophilia) sometimes followed by Loeffler's endocarditis (an eosinophilic myocarditis with a tendency toward endomyocardial fibrosis and clinical manifestations of thromboembolism which can result in acute heart failure) (Pritchard et al., 2012).

Secondly, for many other helminth infections different data, supportive and non-supportive, have been published. Cohort studies from different countries showed a high variance in the study outcomes for the same helminth: ranging from no significant effect to a negative or a positive correlation (*T. trichiura* or *A. lumbricoides* in asthma) (Erb, 2009). The beneficial effect of worm infections seen in field studies has not always been reproducible in clinical trials (Pritchard et al., 2012).

Thirdly, even in published reports where there is a general association between helminth infestation and lower atopy or autoimmunity rates, many patients with helminth infections still develop atopy or autoimmunity. Nevertheless, taking into account all of the recent publications, considerable evidence has demonstrated that some helminths can, in some patients, reduce the development of atopy and autoimmunity. However, it is not clear which type of helminths will protect which patient from developing atopy or autoimmunity. It is unknown which exact mechanism is used to induce the protection. Another problem is that the most convincing evidence is based largely on preventative situations e.g. helminths or helminth-derived products (HDPs) are present before a putative atopic or autoimmune response develops. Treatment of serious atopic or autoimmune disease with helminths or HDPs is an entirely different matter and may be much more difficult because established immune responses are intrinsically more difficult to address than inhibition of their development. Since the major mechanism postulated to inhibit atopy or autoimmunity is the induction of regulatory mechanisms or cells, it is worthwhile to examine other therapies aimed at utilising this mechanism. Since the resurgence of interest in Treg cells, many academic groups and pharmaceutical companies have tried to develop novel therapies directly enhancing Treg cell function in humans to combat autoimmunity and atopy. In short, the understanding of how immune regulation works has increased tremendously but not a single therapy has made it into humans, with the exception of better specific immunotherapy for atopic diseases using an allergen in combination with adjuvant aimed at increasing Treg cell numbers (Mohapatra et al., 2010; Zuberbier et al., 2010; Casale and Stokes, 2011). The major reason is that immune regulation is a transient process and needs to be induced permanently. In particular, this is the case during parasitic infections, where the immunosuppressive effects end once the parasite has been eliminated. Trying to induce immune regulation in the absence of parasites is extremely difficult. Therefore efforts are ongoing to directly expand CD4+ Treg cells from the patient in vitro. By transferring these optimally immune suppressive cells back into the patient it is hoped that these cells will inhibit the aberrant immune response causing the immunopathlogy. Successful interventions using this approach will also support the use of HT or HDPT to achieve similar effects. It can be argued that the specific immune therapy for atopy using allergens has achieved this. Since there are many companies

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