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To the Editor,

We thank Drs. Panda and Das for their interest and comments on our recent paper published in Arthritis and Rheumatism (1). The idea that parasitic worms can protect humans against the development of allergic and autoimmune inflammatory conditions has received recent acceptance by many researchers (2, 3) and this has triggered the race to find the individual worm components, which provide protection against disease development. In spite of the increased incidence of diseases such as inflammatory bowel disease, type 1 diabetes, multiple sclerosis and asthma in areas of the world where worms have effectively been eliminated as a public health problem, the strongest support for a protective role of worms and their products is arguably derived from studies using mouse models. As an example of this, our recent paper extends our previous work (4, 5) on the ability of ES-62, a phosphorylcholine (PC)-containing molecule secreted by the rodent filarial nematode *Acanthocheilonema viteae*, to protect against the development of collagen-induced arthritis (CIA) in mice. CIA is widely used as a model for human autoimmune rheumatoid arthritis (RA) and perhaps consistent with this, ES-62 has also been shown to be active in preventing pro-inflammatory cytokine secretion from synovial cells derived from RA patients (4, 5). Nevertheless, the relationship between RA and the presence of parasitic worm infection is less well reported than the inverse correlations described for many of the inflammatory disorders referred to above. We were therefore very interested to see the impressive data provided by Drs. Panda and Das in their letter, which clearly indicated absence of filarial infection in RA patients from an area endemic for filariasis.

Drs. Panda and Das conducted their study in the transmission area of Odisha, India, which is highly endemic for the filarial nematode *Wuchereria bancrofti*, the most common cause of human lymphatic filariasis. The presence of infection was determined using the well-established Og4C3 ELISA for circulating parasite antigen. Of the RA-free control group, 40% scored positive via this diagnostic assay and 8% were also found to have microfilariae (parasite larval forms) in their bloodstreams. Consistent with the idea that parasites promote their survival by secreting immunomodulators, the presence of such circulating antigen and/or antigen-secreting microfilariae would be expected to be associated with immunoregulation that may protect against development of RA. Conversely, none of the RA patients were found to have *W. bancrofti* antigen in their bloodstream. Such a clear distinction between the two groups is striking and can certainly be viewed as evidence for *W. bancrofti* infection protecting against development of RA. Further studies in other areas of filarial nematode transmission should indicate whether this is a general phenomenon being observed but of note, this paper follows on from a recent study (also in India) showing decreased incidence of infection with *W. bancrofti* in individuals with type I diabetes (6).

Given the potential importance of the data provided by Drs. Panda and Das it would also be interesting to explore whether the RA patients were ever infected by *W. bancrofti,* given that they will have been continuously exposed to the parasite via the bite of infected mosquitoes (the vector) from birth. Towards this, information relating to (parasite-specific) isotype-specific antibody reactivity and/or documentation on the presence of pathological features of filariasis for the RA patients may be available to the authors. It may also be prudent to analyse the treatment history of the RA patients to consider whether they have received any drugs, which could possibly impact on nematode development or viability or alternatively, whether they have received anthelmintics for previous infection.

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Returning to ES-62, we agree with the opinion of the authors and Prof Finkelman (2) that this particular worm product has limitations as a therapeutic and indeed we would go further and say that such a large immunogenic protein, whose active moiety (PC) is a nematode-specific post-translational modification, is simply unsuitable for this purpose. It is for this reason, that we have turned our attention to developing drug-like small molecule analogues of the PC moiety of ES-62, which appears to be its active immunomodulatory moiety, as when chemically conjugated to "inert" proteins, we have previously shown it to be effective in CIA and on peripheral blood and synovial membrane cells from RA patients (5). Indeed, we have recently been successful in synthesizing such a novel compound that mimics ES-62 in protecting against CIA, and by the same mechanism of action (manuscript in preparation).

Finally, the combination of our data and that provided by Drs. Panda and Das may also reinforce the use of CIA as a model for testing worms and their products as possible preventive agents or therapies with respect to RA. Although the authors refer to the CIA model as being imperfect due to its acute nature, it is the most commonly employed model for human RA (7), sharing several pathological features with the human condition. Furthermore relapsing versions of the model are available and it is also amenable to both manipulation of immunological phenotype and drug target validation. Indeed, to date, it has played a crucial role both in identifying potential pathogenic mechanisms of autoimmune disease and in the development of new biologically based therapeutics for RA.

William Harnett, PhD, University of Strathclyde and Margaret M. Harnett, PhD, University of Glasgow

1. Pineda MA, McGrath MA, Smith PC, Al-Riyami L, Rzepecka J, Gracie JA, et al. The parasitic helminth product ES-62 suppresses pathogenesis in CIA by targeting of the IL-17-producing cellular network at multiple sites. Arthritis Rheum. 2012;64:3168-78.
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