Low-Dose Aspirin and Ibuprofen’s Sterilizing Effects on Mycobacterium tuberculosis Suggest Safe New Adjuvant Therapies for Tuberculosis

To the Editor—The report on the intrinsic antimycobacterial activity of ibuprofen and low-dose aspirin in a novel murine tuberculosis model is fascinating
and of relevance in the field [1]. The paired advances of reporting new drug targets and further describing a readily reproducible model using commercially available C3HeB/FeJ mice is exciting. The authors have chosen not to describe further work on mechanisms of the non-steroidal anti-inflammatory drug (NSAID) effects in their preliminary report, but the accompanying editorial [2] considers the anti-inflammatory role of these cyclooxygenase inhibitors, revolving around prostaglandin (particularly PGE2) inhibition and consequent immune mediator cellular effects.

Mention is also made in the editorial [2] of potential contributions of lipoxins in tuberculosis pathogenesis. Previous animal model data (using mouse strains differing from those used by Vilaplana et al [1]) showed that the level of lipoxin A4 (LXA4) was increased after *Mycobacterium tuberculosis* infection, negatively impacting anti- *M. tuberculosis* immune responses and increasing the likelihood of dying from the infection [3].

Importantly, and paradoxically, the opposite effect of the same lipoxin pathway is likely to be indicated by these new animal model data. Low doses of aspirin reduced the mycobacterial burden in the necrotizing pulmonary granulomas and protected mice from death due to tuberculosis [1]. Although the dose of aspirin is specified in the article only as being “low,” it is improbable that it is exerting a direct anti-inflammatory effect, which requires high doses. It is more likely low-dose aspirin will be acting by the mechanism of aspirin-triggered lipoxins (ATLs) [4]. These ATLs are the 15-epimeric forms of LXA4 and reproduce its actions in all regards. However, because the anti-inflammatory actions of ATLs, including proresolutive effects on established inflammation, are mediated solely by aspirin and not by other NSAIDs [4], it is clear that additional effects must be present to account for the action of ibuprofen.

Another important putative mechanism, which is not considered in the editorial by Ivanyi and Zumla [2], by which NSAIDs may reduce *M. tuberculosis* growth in a live animal is through inhibition of tumor necrosis factor α (TNF-α) via nuclear factor κ-light-chain enhancer of activated B cells (NF-κB) stabilization. This has been shown to occur with NSAIDs in vitro [5]. Indeed, ibuprofen is among the weaker suppressors of this crucial inflammatory pathway, compared with other NSAIDs and related agents [6].

While administration of TNF-α blockers to humans latently infected with *M. tuberculosis* increases the likelihood of reactivation of infection [7], this does not necessarily indicate that opposing TNF-α is deleterious at all stages of tuberculosis. An animal model shows that TNF-α blockade via etanercept, used concurrently with standard tuberculosis therapy, reduces the number of viable *M. tuberculosis* in early infection, as well as the rate of relapse of tuberculosis [8]. Earlier, a human study of etanercept, combined with tuberculosis chemotherapy in human immunodeficiency virus–infected patients with tuberculosis, showed reduced time to sputum conversion in etanercept-treated participants [9]. There was also a trend toward improved resolution of lung infiltrates and cavities with etanercept use, despite the numbers in the phase I trial being small. These results have led to suggestions regarding the value of TNF-α blockade, particularly with infliximab, to efficiently block granuloma formation and increase clearance of *M. tuberculosis* in combination with effective tuberculosis chemotherapy [10].

Mice used in this model [1] are readily available and, in contrast to the recently described humanized bone marrow, liver, and thymus (BLT)–transplantation mouse model, which requires surgical implantation of human fetal lymphoid tissue under the kidney capsule [11], required no additional manipulation to be a competent host for *M. tuberculosis*. It is interesting to note that Vilaplana et al also observed necrotic pulmonary lesions in the C3HeB/FeJ mice after intravenous infection [1], whereas an earlier study of experimental tuberculosis in this species [12] used aerosol infection, which is more relevant as a model for natural infection.

Our interest in this area is heightened by our current human trials, in which we are measuring the effects of low doses of aspirin (100 mg and 300 mg daily) on ATL and NF-κB levels during sepsis (Australian New Zealand Clinical Trials Registry no. 12611000649910; available at: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12611000649910). If we are able to show that treatment of sepsis with low-dose aspirin inhibits NF-κB activation (and consequently reduces TNF-α expression), this may be the safest approach for adjuvant use of salicylates for tuberculosis therapy. We await further reports on the mechanisms of the observed effects of ibuprofen and low-dose aspirin on *M. tuberculosis* growth and mortality in this convenient mouse model [1] with great anticipation.

### References

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