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Indole Propionic Acid: a Small Molecule Links between Gut Microbiota and Tuberculosis

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Gut bacteria produce numerous metabolites that can circulate systemically and influence host physiology (1). Indole-3-propionic acid (IPA) is the first microbiome-derived metabolite with the potential to impact tuberculosis, now the single leading infectious cause of death in adults, surpassing HIV (2). IPA is found in human serum, has been shown to inhibit β-amyloid fibril formation, and can act as a neuroprotectant against a variety of oxidotoxins (3). It is in early clinical development to treat patients with Friedreich's ataxia (ClinicalTrials.gov identifier NCT01898884). In the human host, IPA is produced by *Clostridium sporogenes* and other gut symbionts from the aromatic amino acid tryptophan, revealing a clear association between circulating IPA and the presence of the producing species in mouse gut (4). Importantly, IPA was shown to impact the intestinal barrier and systemic host immunity in mice (4). The recent findings of Negatu et al., linking IPA and tuberculosis (5), thus constitute exciting new developments in the role of the microbiome in infectious diseases.

In a whole-cell screen of a fragment library designed to identify novel antituberculosis compounds, Negatu et al. discovered that IPA exerts antitubercular activity *in vitro*. Efficacy studies in *M. tuberculosis*-infected mice showed that the compound is also active *in vivo* (5). This suggests for the first time a functional link between gut microbiota and tuberculosis. Whether the effect of IPA is due to direct antibacterial activity, indirect immunomodulatory functions, or a combination of both remains to be determined.

While there is increasing interest in associations between gut microbiome species and disease state, the finding that a metabolite produced by the gut microbiota shows antituberculosis activity *in vitro* and *in vivo* is the first tangible indication for an impact of the microbiome on tuberculosis. This discovery opens up a whole series of questions. Is there a role for IPA in tuberculosis susceptibility or progression to and severity of disease? Does the metabolite support latent tuberculosis infection? Could IPA be useful as an add-on to current antituberculosis drug regimens to accelerate cure? Which bacterial and host factors are involved in the mechanism of action of IPA? Can medicinal chemists design a new antituberculous agent using IPA as a lead compound?

Negatu's results highlight the promise of IPA as a potential "low-hanging fruit" to treat tuberculosis, since it is in clinical development for another disease indication and has thus met stringent tolerability criteria in preclinical studies. Not only could IPA be investigated as an add-on to current antituberculous drug regimens, it also constitutes—owing to its small size and attractive physicochemical properties—an ideal starting point for target-based drug optimization.

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