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## Precision medicine for infectious diseases at the MIF locus

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**H**uman genetic studies together with data from mouse models indicate that variations in the expression of Macrophage Migration Inhibitory Factor (MIF) affect the severity of different infections. MIF is expressed by the innate response to promote pathways necessary for pathogen clearance. Functional polymorphisms in the MIF gene (MIF) occur commonly, with the lowest expression promoter variants present in 45-78% of studied populations. In community-acquired pneumonia, high genotypic MIF expressers show a 50% increased survival benefit when compared to low genotypic MIF expressers. There is population stratification at the MIF locus and evidence for allelic selection in regions endemic for malaria, where low genotypic MIF expression appears to protect from the lethal inflammatory sequelae of infection. Evidence of MIF's role in protection from Mycobacterium infection has prompted examination of the potential contribution of MIF alleles to the high prevalence of TB in Africa. In an HIV+ cohort, genetic low expressers of MIF were 2.4 times more frequently

identified among patients with Mycobacterium bacteremia than those without. A higher prevalence of low expression alleles among TB cases than controls without active TB also was observed. As South Africans show the highest global prevalence of low expression MIF alleles, this finding suggests a contribution of functional MIF polymorphisms to the high prevalence of TB in this population. Insights into the structure-function relationship between MIF and its receptor have enabled the design of first-in-class small molecule MIF agonists that enhance MIF binding and signal transduction. One MIF agonist (MIF20) shows beneficial action in mouse models of Mycobacterium and *S. pneumoniae* infection. Pharmacologic augmentation of MIF, which is in pre-clinical development, may be a useful strategy in low genotypic MIF expressers. Such an approach may be especially beneficial as adjunctive therapy in resistant or difficult to treat infections as in MDR and XDR TB.

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