# Precision Medicine for Infectious Diseases at the MIF Locus

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## Abstract

Human 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.

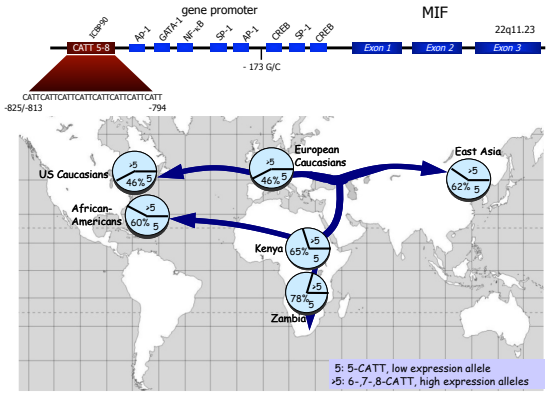



**Figure 1.** ***Top***: The *MIF* locus with its three exons and the -794 $CATT_{5-8}$ functional microsatellite. ***Bottom***: Global population stratification of *MIF* alleles, showing the highest prevalence of the low-expression *MIF* 5-CATT allele in sub-Saharan Africa.

## Recent Publications

1. Das, R., et al. (2013) Macrophage Migration Inhibitory Factor (MIF) is a critical mediator of the innate immune response to *Mycobacterium tuberculosis*. *Proc Natl Acad Sci USA* **110** E2997-E3006

2. Savva, A., et al.. (2016) Functional polymorphisms of macrophage migration inhibitory factor as predictors of morbidity and mortality of pneumococcal meningitis. *Proc Natl Acad Sci USA*. **113**, 3597-3602

3. Yende, S., et al. (2009) The influence of *MIF* polymorphisms on outcome from community-acquired pneumonia. *FASEB J* **23**, 2403-2411

4. Jorgensen, W. L., et al. (2010) Receptor agonists of macrophage migration inhibitory factor. *Bioorg & Med Chem Letts* **20**, 7033-7036

5. McDevitt, M. A., et al. (2006) A critical role for the host mediator macrophage migration inhibitory factor in the pathogenesis of malarial anemia. *J Exp Med* **203**, 1185-1196



## Biography

Rick Bucala obtained his undergraduate degree from Yale College and completed a combined MD/PhD at Rockefeller University. After a fellowship at the Pasteur Institute, he trained in internal medicine at the Brigham and Women's Hospital and Harvard Medical School. The Bucala group cloned the cytokine MIF (macrophage migration inhibitory factor) and its receptor, and identified functional polymorphisms in the MIF gene. The laboratory has developed rapid biochips to determine MIF polymorphisms in field settings, which facilitate clinical investigations of MIF genetic polymorphisms in malaria, tuberculosis, and other diseases. Anti-MIF developed by the group has completed phase II clinical testing and small molecule approaches to modulating MIF action are under development. Laboratory investigations also have expanded to encompass investigation of the orthologous MIF proteins produced by parasites, their role in immune evasion, and their potential for vaccine approaches.

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**Notes/Comments:**