

PARTNERING OPPORTUNITY:

MIF Small Molecule Inhibitor Program



Cortical is a discovery-phase, Australian biotechnology company founded to pursue the development of small-molecule inhibitors of MIF for the treatment of inflammation and other diseases.

PLATFORM

- Small-molecule inhibitors of macrophage migration inhibitory factor (MIF)
 - 3 compound scaffolds in lead optimization
 - Technology from Monash University, lead by Professor Eric Morand

OPPORTUNITY

- Inflammation market: unmet need for targeted small-molecule approaches
- Small-molecule MIF inhibition offers:
 - a. a biologically distinct target, uncrowded space
 - b. breadth of inflammatory indications
 - blockbuster (e.g. RA) and niche indications (e.g. SLE)
 - c. oral administration: competitive advantage compared with biologicals
 - d. mechanism-based application to steroid sparing
 - e. additional roles of MIF in atherosclerosis, metabolic disease and cancer
- Potential first-in-class line of therapeutics
 - No small-molecule targeted therapies currently approved in inflammation
 - No known clinical-stage MIF antagonist programs worldwide
- Cortical's program provides a **platform** for MIF inhibitor development
 1. Robust Composition of Matter and Use claims over independent scaffolds
 2. Library of >1000 compounds, SAR driven program
 3. Proprietary assay methodology – unique in MIF space
 4. X-ray crystallography (Cortical compound-MIF co-crystals)
 5. Mechanistically driven clinical strategy
 6. Lead optimisation underway

COMPANY DETAILS:

Cortical Pty Ltd
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www.cortical.com.au

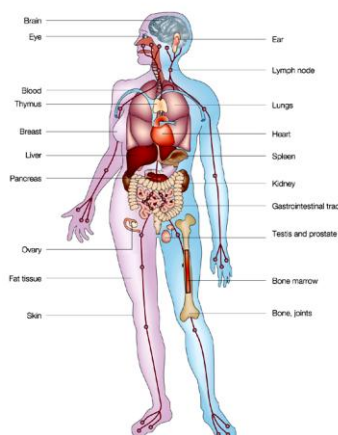
FURTHER INFORMATION

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TARGET

Macrophage migration inhibitory factor (MIF) - a differentiated target

- Unique pro-inflammatory protein
- MIF^{-/-} mouse: normal phenotype except in disease models
- Pivotal in immune-inflammatory diseases, atherosclerosis, metabolic disease and cancer



Nature Reviews | Immunology

Experimental models in which MIF is an important mediator of pathogenesis

- Sepsis and toxic-shock syndrome^{7, 8, 60, 66, 72}, delayed-type hypersensitivity⁸⁸, adjuvant- and antigen-induced arthritis^{89, 90}, glomerulonephritis⁹¹⁻⁹⁴, acute lung injury⁷⁵, allograft rejection⁹⁵, inflammatory bowel disease (colitis)^{96, 97}, gastritis⁹⁸, pancreatitis⁹⁹, atherogenesis¹⁰⁰, encephalomyelitis¹⁰¹ and uveoretinitis¹⁰²

Human pathologies associated with increased MIF expression by organs or systems

- Immune system: sepsis, septic shock and allograft rejection^{60, 79, 83, 84, 103, 104}
- Lung: adult respiratory distress syndrome, asthma, tuberculosis and Wegener's granulomatosis^{4, 85-87, 105}
- Kidney: glomerulonephritis^{106, 107}
- Bones and joints: rheumatoid arthritis, systemic-onset juvenile idiopathic arthritis and polycondritis^{6, 81, 108-110}
- Gastrointestinal tract: colitis and Crohn's disease^{96, 111}
- Skin: atopic dermatitis, psoriasis and systemic sclerosis¹¹²⁻¹¹⁴
- Endocrine system: type-2 diabetes and pancreatitis^{99, 115}
- Brain: multiple sclerosis and neuro-Behcet's disease¹¹⁶
- Eye: uveitis and iridocyclitis^{117, 118}
- Heart and vasculature: atherosclerosis¹¹⁹
- Ear: otitis¹²⁰

Validation of target in inflammatory diseases

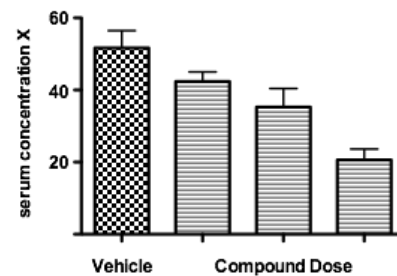
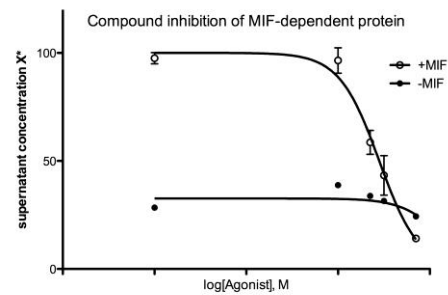
- Models of RA, SLE, colitis, multiple sclerosis, asthma abrogated in MIF $-/-$ mice
- MIF is overexpressed in serum/tissues of patients
- *MIF* gene polymorphisms are associated with risk or severity of inflammatory diseases

Steroid Sparing

- Unique characteristic of target: MIF directly regulates glucocorticoid sensitivity
- Mechanism dependent on regulation of key MAP kinase inhibitory phosphatase, MKP-1
- MIF inhibition potentially offers specific mechanism-based steroid-sparing activity

TECHNOLOGY

Proprietary cell-based assays	Proprietary, scalable, cell-based assays that yield SAR and selectivity information. Overcomes major road-block in the field.
X-ray co-crystallography	Proprietary compound-protein X-ray co-crystallography data-sets at 1.6 Å, further strengthening the foundation of SAR.
Proof of concept	Oral efficacy demonstrated in models of RA and atherosclerosis.
	Good pharmaceutical properties (low MW, negative off-target screens, negative Ames tests and hERG binding, short synthetic routes).
	Clean <i>in vivo</i> toxicity (non-GLP 5-day repeat dose studies).
IP	Composition of Matter and Use claims over independent scaffolds and proprietary assay methodology. Patents are granted in several jurisdictions and pending examination elsewhere.



Cortical's proprietary *in vitro* assays determine compound activity and selectivity via inhibition of cellular expression of a MIF-dependent pro-inflammatory protein (upper panel).

The same compound *in vivo* dose-dependently inhibits LPS-induced serum concentrations of the same protein (lower panel).

MARKET

- The inflammatory disease market is over \$60 BN annually with strong recent growth expected to continue¹. Future growth in this sector may be driven by a new wave of targeted therapies based on orally available small molecules.
- Cortical is developing small molecule inhibitors of the pro-inflammatory molecule MIF. MIF is a unique molecule which has been validated as a therapeutic target in a wide range of **inflammatory diseases (such as OA, RA, asthma/COPD, lupus, MS, colitis, atherosclerosis), metabolic diseases and cancers.**

¹ <http://www.news-medical.net/news/20100105/Report-on-the-lucrative-immuneinflammatory-disease-marketplace.aspx>