

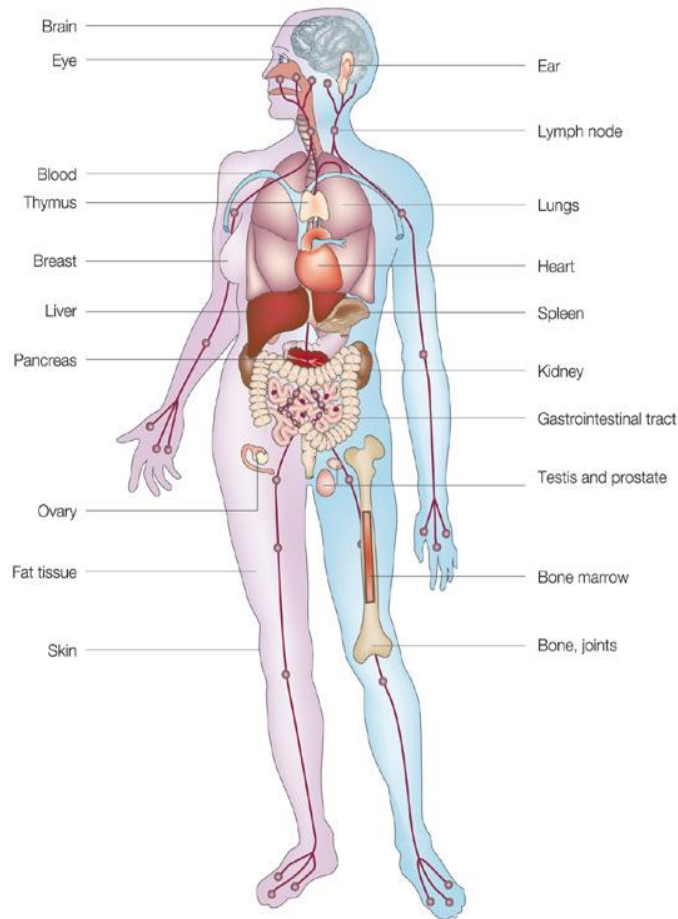
Cortical MIF inhibitor program - the MIF breakthrough

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Non-confidential slide deck

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MIF is a validated clinical target across many disease areas



Nature Reviews | Immunology

Box 2 | MIF in experimental models and human diseases

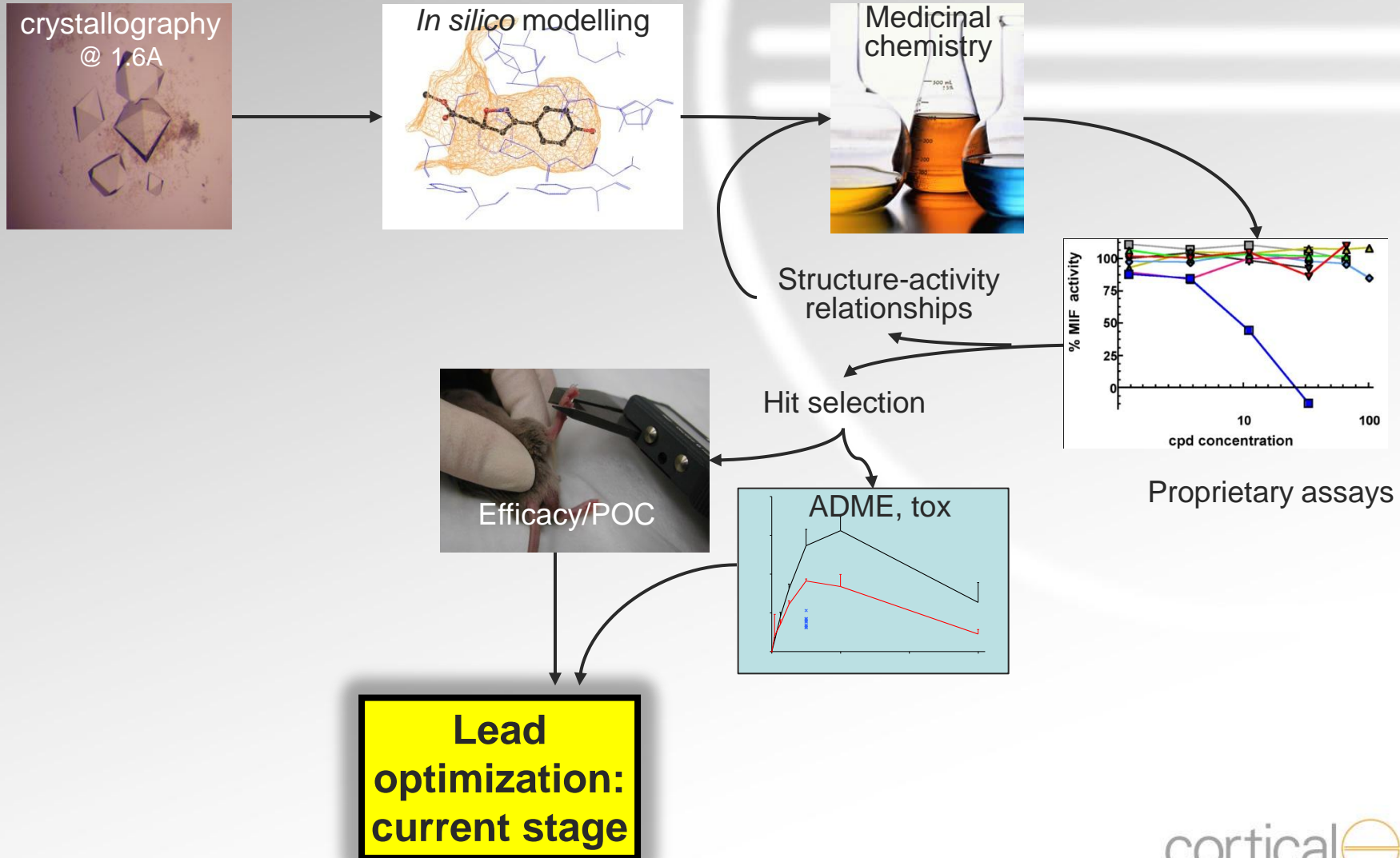
Experimental models in which MIF is an important mediator of pathogenesis

- 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 polychondritis^{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

Cortical's MIF Inhibitor Program



Cortical Breakthrough: Proprietary cellular assays

- MIF is a unique protein with unique mechanisms of action
 - Cellular assays for screening & lead optimisation have eluded the field
- Cortical has developed proprietary cellular assays enabling fast compound ranking, SAR, screening
- **This enabling technology removes a chronic roadblock in the field**

Cortical's MIF Program

1. MIF is a validated target in multiple disease areas
2. Cortical has developed enabling technology that remove a longstanding roadblock in the field
3. Cortical's small molecule MIF inhibitor program has
 - POC compounds: efficacy in animal models, nonGLP tox
 - X-ray compound-protein co-crystallography
 - Proprietary assays
 - Extensive compound library (patents for 3 scaffolds, in various levels of examination)
 - A clear pathway in lead optimisation

Cortical is actively seeking partnering opportunities

MIF Target Validation

Indication	Human disease overexpression	Association with MIF promoter SNPs	Inhibited disease models in MIF ^{-/-}	Data with compounds (*Cortical)
RA	√	√	√	√*
SLE	√	√	√	√*
Asthma	√	n.d	√	√
MS	√	n.d	√	√
Colitis	√	√	√	√
Atherosclerosis	√	√	√	√*

MIF is a validated target across many disease areas – multiple clear clinical strategies

Indication subset		Broad/Common	Niche
Inflammation	Chronic	RA	SLE
		Asthma	MS
		Atherosclerosis	
	Acute	Colitis	
		Asthma flare	ARDS
Colitis flare	MS flare		
Metabolic/ Cardiovascular	Chronic	Insulin resistance/ Type II diabetes	
		Obesity	
		Atherosclerosis	
	Acute	Myocardial infarction	
Oncology		Colon	Many examples
		Lung	
		Stomach	

MIF biology supports therapeutic targeting

Activity	Effect of MIF	Effect of MIF depletion or inhibition
Leukocyte recruitment	↑ increased	decreased ↓
MAP kinase activation	↑ increased	decreased ↓
Cytokine expression	↑ increased	decreased ↓
Angiogenesis	↑ increased	decreased ↓
Apoptosis (eg macrophage, synoviocyte)	decreased ↓	↑ increased
Glucocorticoid sensitivity	decreased ↓	↑ increased
Insulin sensitivity	decreased ↓	↑ increased

Targeting MIF opens new broad indications

Example - steroid sparing

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Rheumatology 2006; 1 of 7

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Review

Macrophage migration inhibitory factor and glucocorticoid sensitivity

D. Aeberli, M. Leech and E. F. Morand

Glucocorticoids (GCs) are widely used in the treatment of inflammatory diseases including rheumatoid arthritis (RA). Treatment with GC is associated with significant dose-dependent side-effects. The pro-inflammatory cytokine macrophage migration inhibitory factor (MIF) has emerged in recent years as a candidate factor which could regulate GC sensitivity. MIF is induced by GC, and is able to override anti-inflammatory actions of GCs. In this review, we summarize the pro-inflammatory actions of MIF with respect to RA, describe the interactions between MIF and GC and examine ~~new~~ evidence, which identifies MIF as a specific target for steroid sparing.

KEY WORDS: MIF, Glucocorticoids, Steroid sparing, Rheumatoid arthritis.

...evidence which identifies MIF as a specific target for steroid sparing

Targeting MIF opens new niche indications

Example - accelerated atherosclerosis in RA, SLE

Nature Reviews Drug Discovery | AOP, published online 13 April 2006; doi:10.1038/nrd2029

REVIEWS

MIF: a new cytokine link between rheumatoid arthritis and atherosclerosis

*Eric F. Morand**, *Michelle Leech** and *Jürgen Bernhagen*¹

Abstract | Macrophage migration inhibitory factor (MIF) is well established as a key cytokine in immuno-inflammatory diseases such as rheumatoid arthritis. Inflammation is now also recognized as having a crucial role in atherosclerosis, and recent evidence indicates that MIF could also be important in this disease. Here, we review the role of MIF in rheumatoid arthritis and atherosclerosis, discuss the ways in which MIF and its relationship with glucocorticoids could link these diseases, and consider the potential of MIF as a new therapeutic target for small-molecule and antibody-based anti-cytokine drugs.

Morand*, Nature Reviews Drug Discovery, 2006
*Cortical Founder

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