Targeting the Oxidized Macrophage Migration Inhibitory Factor (oxMIF) – a Novel Treatment Approach for Rheumatoid Arthritis

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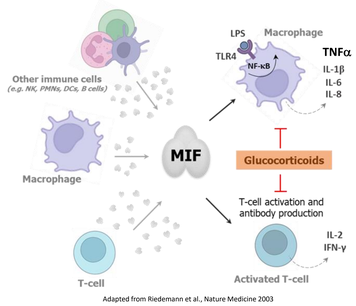
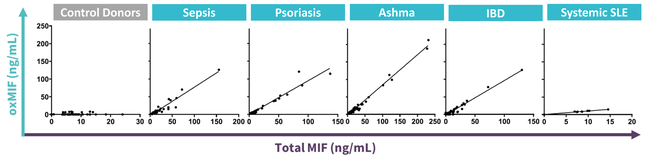
1 MIF as a Therapeutic Target in Inflammatory Diseases

Macrophage migration inhibitory factor (MIF) is a primary mediator of adaptive and innate immune responses, as well as the primary counter-regulator of glucocorticoids (GCs), and therefore a pivotal regulator in rheumatoid arthritis (RA)[1-5]. MIF occurs in two immunologically distinct conformational isoforms, reduced MIF (redMIF) which is ubiquitously present in various tissues and the circulation of healthy subjects, and the disease-related and druggable isoform oxidized MIF (oxMIF)[6-7]. Thus, targeting oxMIF represents a new and promising treatment option for patients with autoimmune disorders such as RA[8].

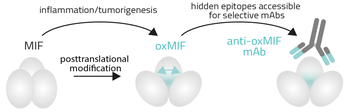


Adapted from Riedemann et al., Nature Medicine 2003

oxMIF – is present in patients with CID



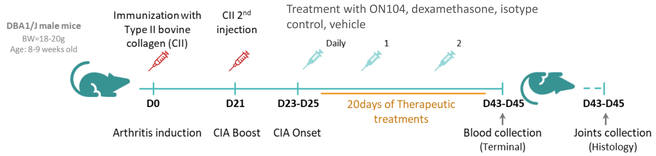
Plasma levels of oxMIF in samples from healthy controls and patients with acute or chronic inflammatory diseases. Plasma levels of total MIF and oxMIF were determined in all individual samples and correlated to each other[9].



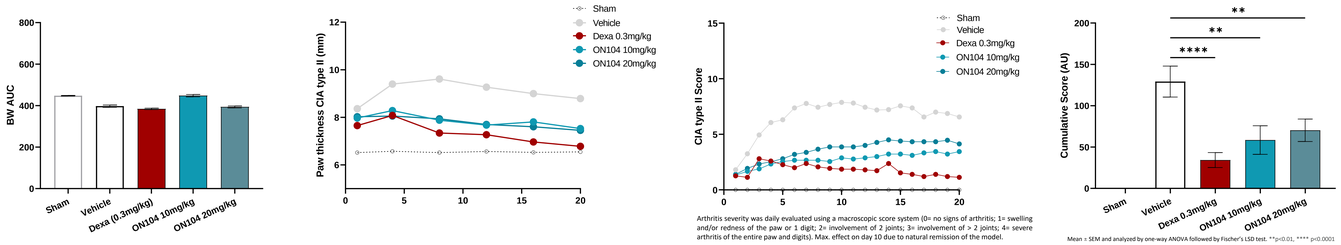
⇨ oxMIF is the disease related and antibody druggable isoform of MIF[8]

3 Method: Collagen-Induced Arthritis in DBA/1J Mice

- DBA/1J mice were immunized with bovine type II collagen, followed by a boost at D21, to induce joint inflammation and tissue damage.
- At disease onset, mice were treated twice weekly for 20 days with ON104 (10 and 20 mg/kg) and dexamethasone as a positive control (n=8/9 per group).
- Disease severity in CIA mice was assessed by paw swelling and clinical scoring and histological examination of joints is planned.



4 ON104 Ameliorates Symptoms in a Mouse Model of RA



Arthritis severity was daily evaluated using a macroscopic score system (0= no signs of arthritis; 1= swelling and/or redness of the paw or 1 digit; 2= involvement of 2 joints; 3= involvement of > 2 joints; 4= severe arthritis of the entire paw and digits). Max. effect on day 10 due to natural remission of the model.

Mean ± SEM and analyzed by one-way ANOVA followed by Fischer's LSD test. **p<0.01, **** p<0.0001

⇨ Significant reduction of clinical signs of RA after the treatment with 10 and 20 mg/kg ON104.

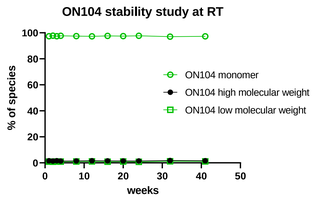
2 ON104: Anti-oxMIF mAb Optimized for the Treatment of Inflammatory Diseases

ON104

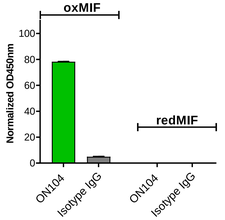
Optimized variable domains
Improved biophysical and pharmacological properties compared to the 1st generation anti-oxMIF antibody imalumab

Optimized Fc
Engineered Fc to abolish effector functions

- ✓ Neutralization of oxMIF
- ✓ Abolished effector functions
- ✓ Optimized physiochemical properties
- ✓ Optimal pharmacological properties



Differential binding ELISA

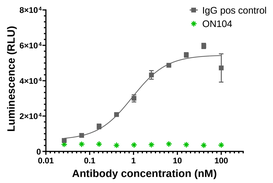


SPR affinity measurement

Affinity to oxMIF orthologs was assessed by Surface Plasmon Resonance (SPR) using oxMIF as analyte and ON104 as ligand.

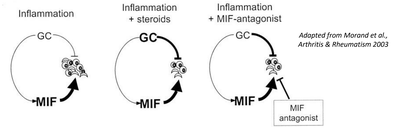
ON104 K_D, nM (SD)	
Human oxMIF	5.13 (0.94)
Mouse oxMIF	27.7 (1.59)
Rat oxMIF	20.0 (4.29)

ADCC reporter assay with target cells



Antibody dependent cellular cytotoxicity (ADCC) mediated by human PBMCs
HCT116 colon cancer cells expressing HiBiT and pMIF were incubated with human PBMCs from different donors (effector to target ratio 40:1) in the presence of different concentrations of ON203 for 24h. Cytotoxicity was measured by luminescence.

5 Add-on Effect of Sub-Therapeutic Doses of Dexamethasone and ON104

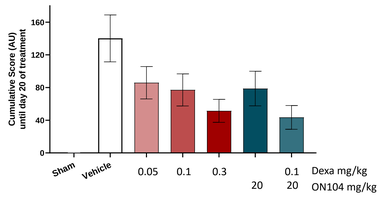


Adapted from Morand et al., Arthritis & Rheumatism 2003

- Exogenous GCs suppress inflammation in concentrations high enough to counterbalance the effects of MIF.
- The addition of (ox)MIF antagonists could allow the control of inflammation with lower dosages of GCs.

ON104 acts on top of Dexamethasone in CIA

DBA/J mice CIA mice were treated twice weekly for 20 days with ON104 and dexa and a combination thereof (n=8/9 per group).



- ✓ MIF is the primary counter-regulator of endogenous and exogenous GCs.
- ✓ Combining ON104 and dexamethasone treatment increases the treatment effect in CIA.
- ✓ ON104 has the potential as a GC sparing therapy for chronic inflammatory diseases.

6 Summary & Conclusion

- ➢ oxMIF is a pivotal regulator of innate and adaptive immunity and highly elevated in the circulation and tissue patients with inflammatory diseases
- ➢ ON104 is an anti-oxMIF monoclonal antibody optimized for the use in chronic inflammatory diseases.
- ➢ The treatment of ON104 ameliorates symptoms in a mouse model of RA. Histological examinations of the joins are still ongoing.
- ➢ ON104 is effective in combination with dexamethasone.
- ➢ ON104 has the potential to become a well-tolerated non-steroidal anti-inflammatory drug for patients with RA.
- ➢ ON104 has the potential as a GC sparing therapy.

ON104 is on track to enter **clinical phase I** by Q4 2023

References
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