# Targeting oxidized Macrophage Migration Inhibitory Factor (oxMIF) with antibody ON104: a promising therapeutic approach for rheumatoid arthritis

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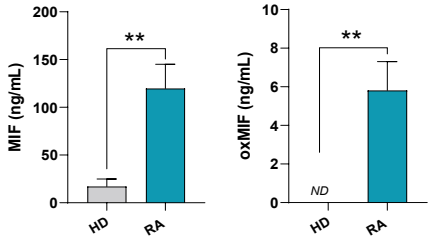
## 1 Oxidized Macrophage Migration Inhibitory Factor (oxMIF)

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)[1-6]. MIF occurs in two immunologically distinct conformational isoforms, reduced MIF (MIF) which is ubiquitously present in various tissues and the circulation of healthy subjects, and the disease-related and druggable isoform oxidized MIF (oxMIF)[7-10]. Thus, targeting oxMIF represents a new and promising treatment option for patients with autoimmune disorders such as RA[11].

## 2 Circulating oxMIF levels in patients with RA







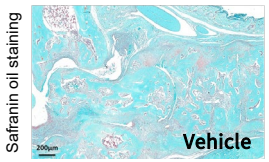
Plasma from Healthy Donors (HD) (n=9) and from patients with Rheumatoid Arthritis (RA) (n=15) were analyzed by ELISA for the presence of MIF and oxMIF.

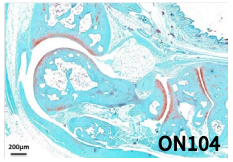
Data are expressed as mean ± SEM. Statistical significance was determined using Mann-Whitney test. ** p <0.01.

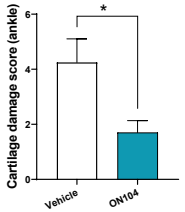
oxMIF is present in the circulation of patients with rheumatoid arthritis (RA) but not detectable in healthy donors (HD).

## 3 ON104 reduces cartilage damage in a RA mouse model

Mice with collagen-induced arthritis were treated twice weekly for 20 days with ON104 ( 20mg/kg), and vehicle control.



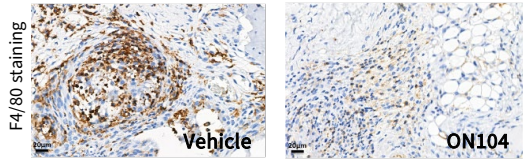




Data are expressed as mean ± SEM. Statistical significance was determined using Mann-Whitney test. * p <0.05.

Intact bone and cartilage (red) in the ON104 group.
Joint injury was significantly reduced after 20 mg/kg ON104 treatment.

## 4 ON104 reduces immune cell infiltration in the joints in the RA model

Joints of mice were isolated at the end of the study and analyzed for macrophage infiltration.

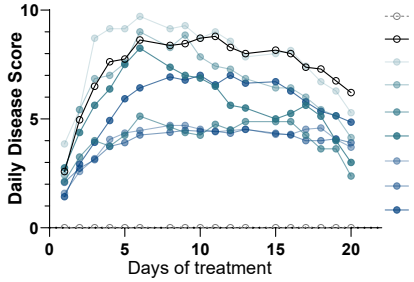


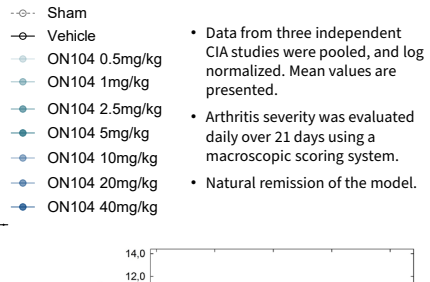

Data are expressed as mean ± SEM. Statistical significance was determined using Mann-Whitney test. **** p <0.0001.

Infiltration of F4/80-positive macrophages into joints was significantly reduced after 20 mg/kg ON104 treatment.

## 5 ON104 ameliorates clinical RA symptoms in a dose dependent way

### Cumulative Disease Scoring

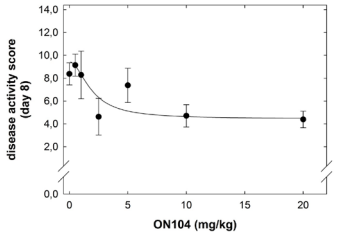



- Data from three independent CIA studies were pooled, and log normalized. Mean values are presented.
- Arthritis severity was evaluated daily over 21 days using a macroscopic scoring system.
- Natural remission of the model.

### Dose-Response Evaluation

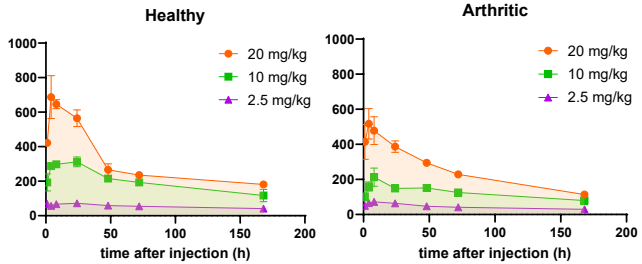
4-parameter logistic equations manually implemented; iterative curve fitting/ minimizing of least square deviation with a Marquart-Levenberg algorithm. In collaboration with Prof. Freissmuth from the Institute of Pharmacology at the Medical University in Vienna.




Pharmacological active dose of ON104 covers 2.5 up to 20 mg/kg.
$EC_{50}$ of ON104 ~ 1-2 mg/kg in mice; $ED_{90}$ of ON104 is ~4-5 mg/kg.
5-fold higher affinity of ON104 to human oxMIF.

## 6 PK of ON104 in arthritic *versus* healthy mice

Plasma concentration (µg/ml) of ON104 after a single *i.p.* injection.




| ON104 | AUC (µg/ml*h) (mean±SD) | |
|---|---|---|
| DBA/1J mice | **Arthritic** | **Healthy** |
| **2.5 mg/kg** | 7324 ± 403 | 9063 ± 454 |
| **10 mg/kg** | 20478 ± 962 | 32902 ± 3227 |
| **20 mg/kg** | 41207 ± 2266 | 50005 ± 2628 |

Arthritic mice show lower ON104 plasma conc. than healthy mice.
Excellent dose linearity of ON104 AUC for arthritic and healthy mice.

## Conclusion

- oxMIF is elevated in the plasma of RA patients.
- ON104 has a significant treatment effect in an experimental mouse model of RA:
  - Reduced clinical symptoms (e.g. paw thickness)
  - Reduced immune cell infiltration in the joints
- Dose-linear plasma exposure of ON104 in mice with lower concentrations in arthritic mice.
- $EC_{50}$ of ON104 in mice is 1-2 mg/kg.

**References:**

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