60TH ERA CONGRESS
MILAN & VIRTUAL
JUNE 15-18, 2023

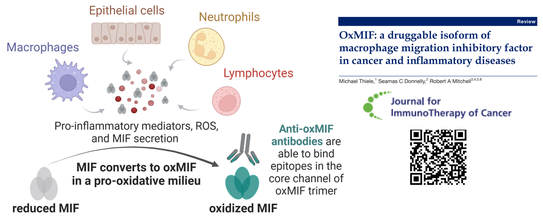
ON104, a novel bioengineered antibody targeting oxidized Macrophage Migration Inhibitory Factor (oxMIF) ameliorates experimental glomerulonephritis

C. Landlinger[1], M.Ferhat[1], Randolf Kerschbaumer[1], Frederick W. K. Tam[2], Maria F. Prendecki[2], Lyndon H. Costa[2], Michael Thiele[1]
[1]OncoOne Research & Development GmbH, 1030 Vienna, Austria
[2]Imperial College London (ICL), Centre for Inflammatory Disease, London W12 0NN, United Kingdom

OncoOne

INTRODUCTION

Macrophage Migration Inhibitory Factor (MIF) is a pleiotropic inflammatory cytokine and a primary counter-regulator of glucocorticoids (GCs) that emerged as a pivotal regulator of immune-mediated disorders including glomerulonephritis (GN). MIF occurs in two immunologically distinct, conformational isoforms: reduced MIF, ubiquitously present in various tissues and the circulation of healthy subjects, and **oxidized MIF (oxMIF),** described as the pathogenic and druggable isoform of MIF[1]. Urinary oxMIF levels in patients with acute lupus nephritis suggests oxMIF contribution to kidney damage[2].



AIM

In this study we evaluated the anti-inflammatory effects of oxMIF neutralization using antibody ON104 in a model of crescentic GN.

METHOD

By advanced antibody engineering we generated the fully human antibody ON104 that is immunosilenced and specific for human oxMIF and its orthologs.

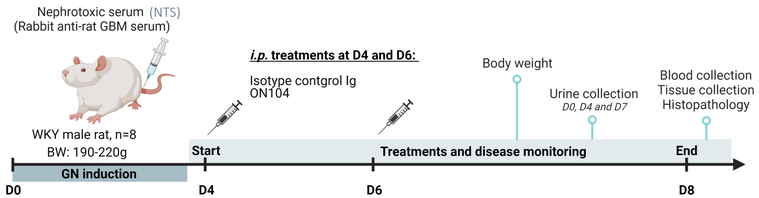
ON104 was tested for its therapeutic potential in a rodent model of GN. Nephritis was induced in male WKY rats by a single intravenous (*i.v.*) injection of rabbit anti-rat GBM (glomerular basement membrane) serum. On day 4 and day 6 after GN induction, ON104 was administrated intraperitoneally (*i.p.*). Body weight, proteinuria, and hematuria were assessed to evaluate GN severity. On day 8, kidneys were harvested for immuno-histological examinations by HE, PAS-staining and IHC staining.

RESULTS

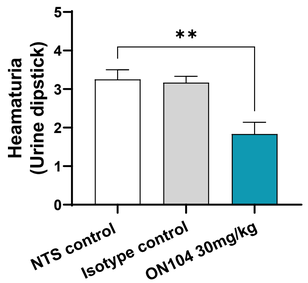
ON104 anti-oxMIF human mAB

1. Neutralization of oxMIF
2. Selective for oxMIF
3. "Immuno-silenced"
4. Beneficial *in vitro* safety profile
5. Combination potential with standard of care therapies

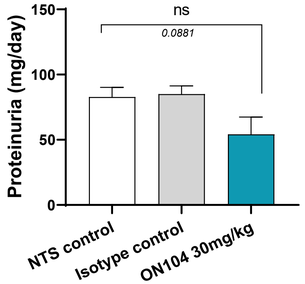
In vivo POC in experimental glomerulonephritis in rats



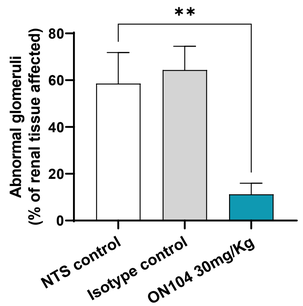
Haematuria

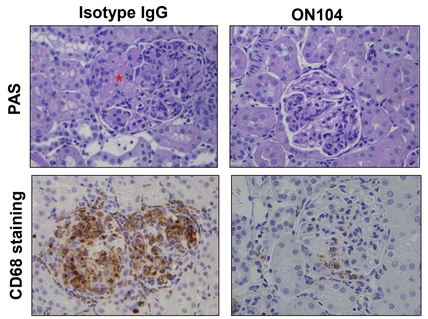


Proteinuria

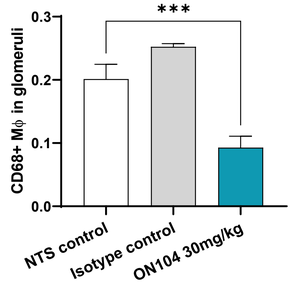


Significantly less crescentic glomeruli and macrophage infiltration





* Necrotic area and fibrocellular crescent formation



All data are expressed as mean ± SEM and analyzed by one-way ANOVA followed Uncorrected Dunnett's test. **p< 0.01: *** p<0.001

ON104 successfully reduces clinical signs of kidney injury and glomerular inflammation

CONCLUSIONS

- Oxidized (ox)MIF is a promising target in GN and chronic inflammatory diseases in general.
- Anti-oxMIF antibody ON104 has a significant impact on the clinical outcome in a rat model of GN.
- Anti-oxMIF antibody ON104 significantly reduces the number of CD68+ macrophages in the glomeruli.
- ON104 represents a promising new treatment option for patients with CIDs, either as monotherapy or in combination with reduced doses of glucocorticoids.

REFERENCES

[1]Thiele M, Donnelly SC, Mitchell RA. OxMIF: a druggable isoform of macrophage migration inhibitory factor in cancer and inflammatory diseases. J Immunother Cancer. 2022;10(9)

[2]Thiele M, Kerschbaumer RJ, Tam FW, et al. Selective Targeting of a Disease-Related Conformational Isoform of Macrophage Migration Inhibitory Factor Ameliorates Inflammatory Conditions. J Immunol. 2015;195(5):2343-2352.

CONTACT INFORMATION

christine.landlinger@oncoone.com
www.oncoone.com