15th World Congress on Inflammation

OncoOne

ON104, a next-generation antibody targeting oxidized macrophage migration inhibitory factor (oxMIF), in experimental models of glomerulonephritis and rheumatoid arthritis

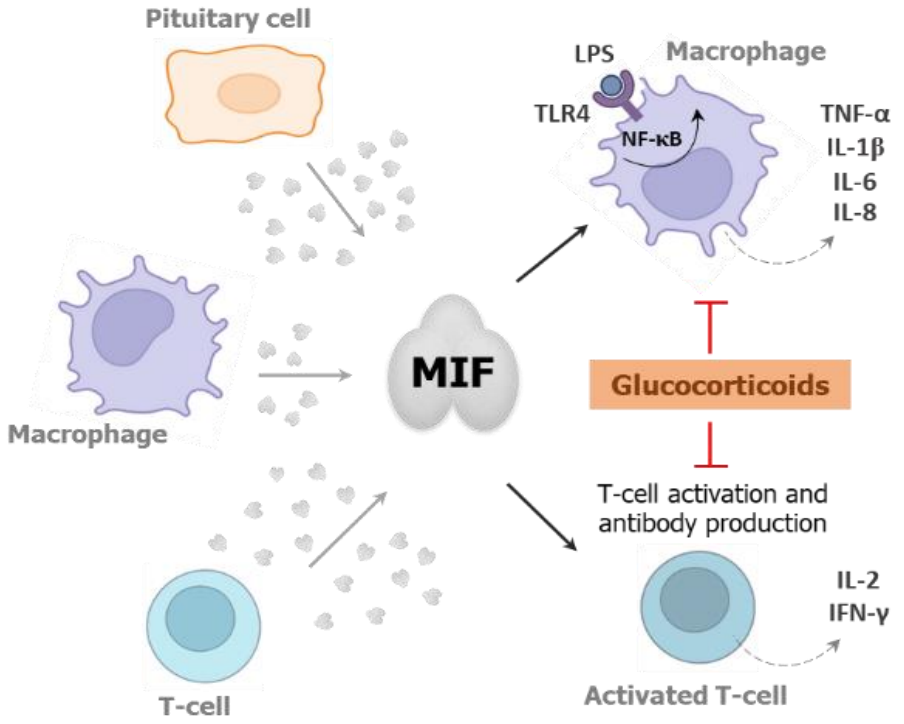
Presented by Christine Landlinger

OncoOne R&D

MIF: key driver of inflammation

Macrophage migration inhibitory factor (MIF) is implicated in autoimmune and inflammatory disorders, e.g. RA, IBD, SLE, asthma, COPD, atherosclerosis, oncogenesis, and metabolic disorders.

- Promotes pro-inflammatory **monocyte/macrophage activation**
- Promotes the release of **proinflammatory mediators**
- **Overrides** anti-inflammatory effects of **glucocorticoids** (GCs)
- **Inhibits** immune **cell apoptosis**
- MIF **genetic polymorphisms** associated with disease severities



Adapted from Riedemann et al., Nature Medicine 2003

MIF has been proven undruggable by antibodies and small molecules:

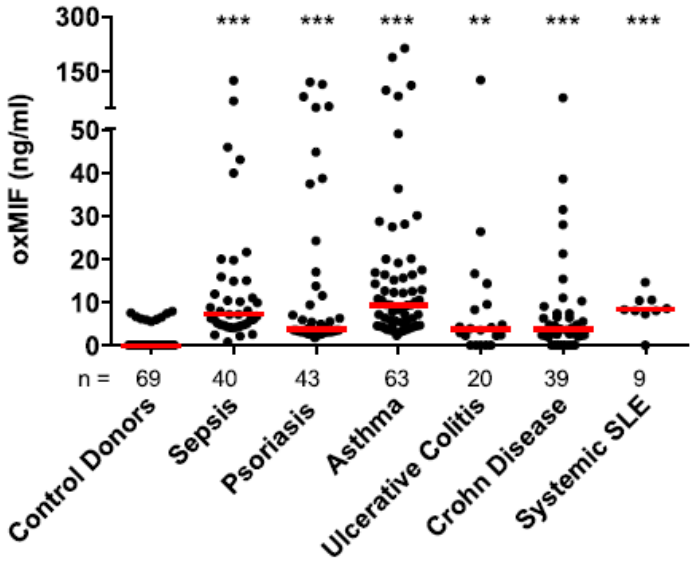
→ Present in surplus in tissue and plasma (2-6nM) also in healthy subjects

→ Risks of interference with physiological functions of MIF

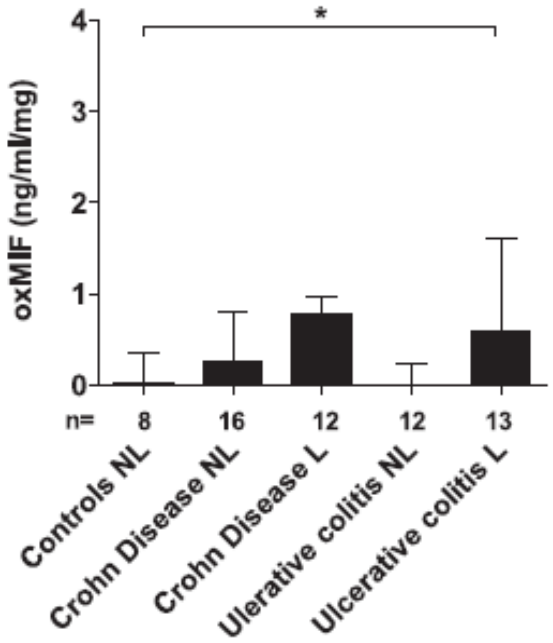
OxMIF a novel target for inflammatory diseases

- OxMIF is the oxidized and supposedly disease-related isoform of MIF
- OxMIF is specifically present in the circulation and inflamed tissue of patients with CID

oxMIF is present in circulation of patients with CID



SN from whole tissue cultures from biopsies from UC and Crohn Disease patients



Thiele et al, J Immunol, 2015

ON104: Optimized anti-oxMIF human mAB

Starting point for engineering

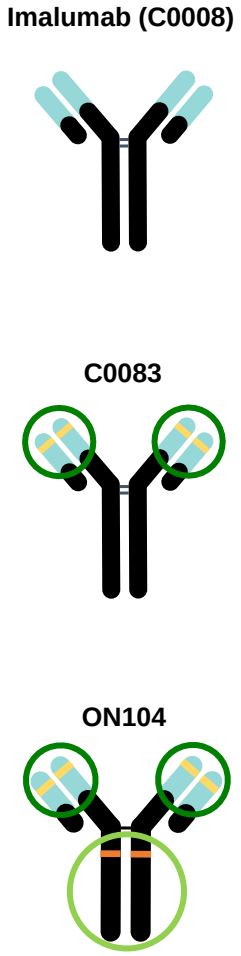
- Human IgG1 **anti-oxMIF antibody imalumab**
- In house production without the N-terminal lysine was used as a **benchmark control** (C0008)

Optimization of variable region (V_H & V_L)

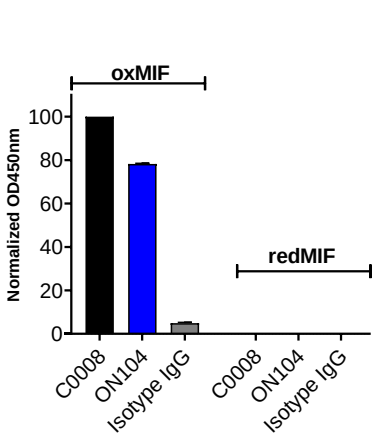
- Improved manufacturability and stability (decreased hydrophobicity and aggregation)
- Retained biological properties (binding, specificity)
- Improved bioavailability and pharmacokinetic

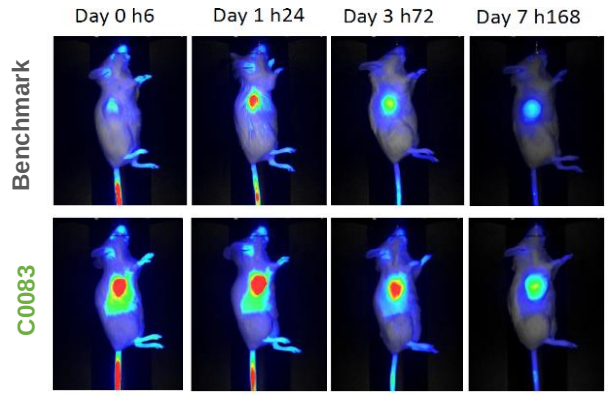
Optimization of Fc-Region

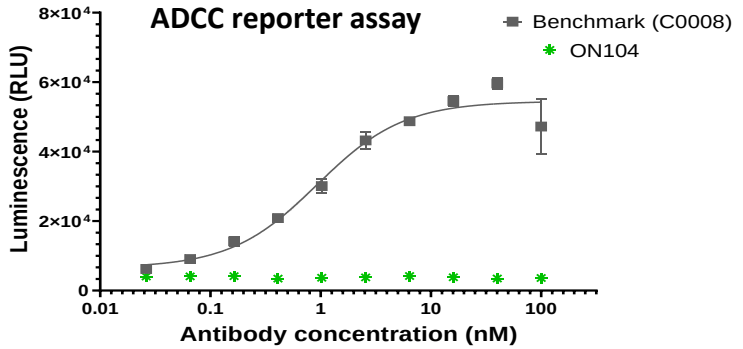
- LALA mutations in the Fc regions
- Devoid of Fcɣ receptor binding



- **Well tolerated** in patients with CRC, NSCL, and ovarian cancer (NCT02540356)
- **Stable disease** (SD) **≥4 months in 13 out of 39 patients** (Mahaligham et al, 2019)
- Phase 2 trials **prematurely terminated** (NCT02540356, NCT02448810)

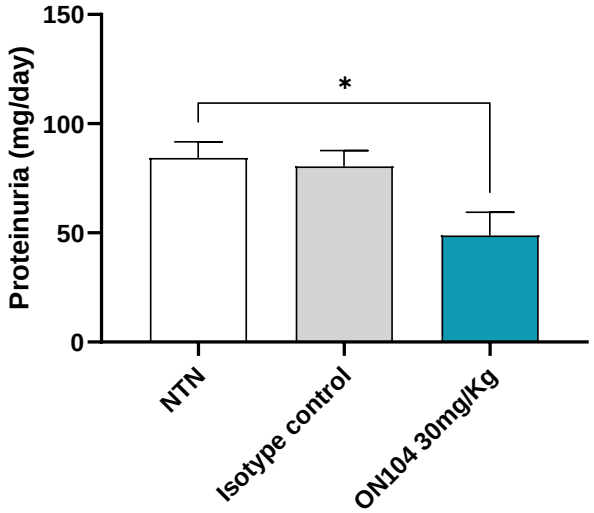


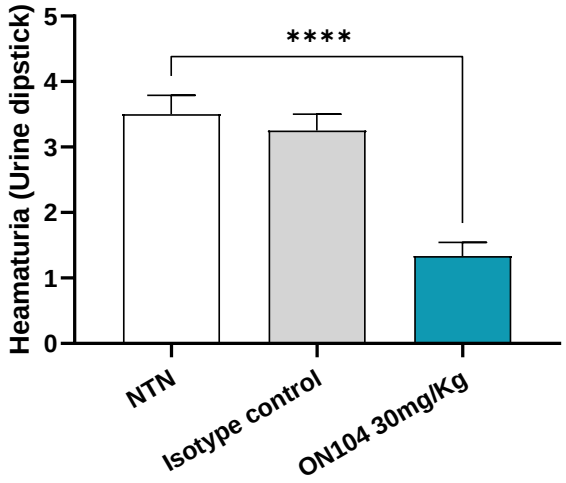


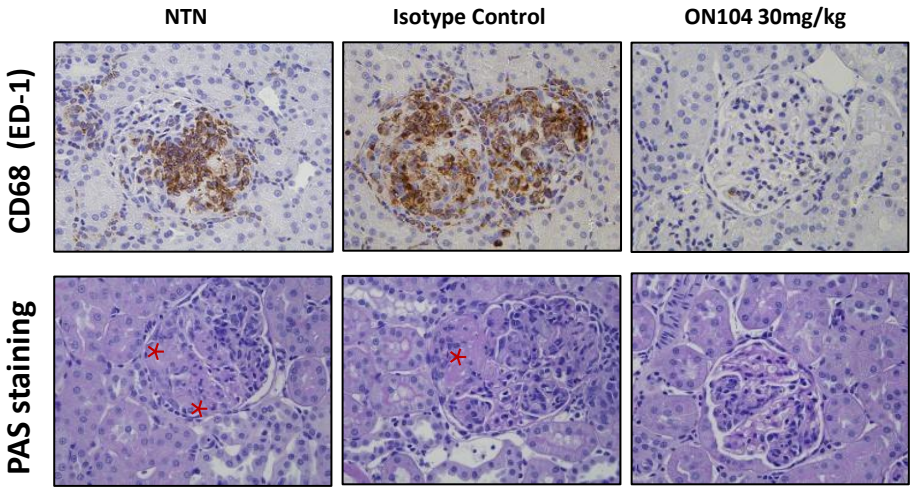


In vivo POC: ON104 ameliorates glomerulonephritis (GN) in rats

- WKY rats were injected with rabbit anti-glomerula nephrotoxic serum to induce nephrotoxic nephritis (NTN).
- Rats were **treated twice** with mABs on day 4 and day 6 (n=6-8 per group).
- Rats were sacrificed on day 8 for urine, blood, and tissue analysis.







Staining of glomeruli

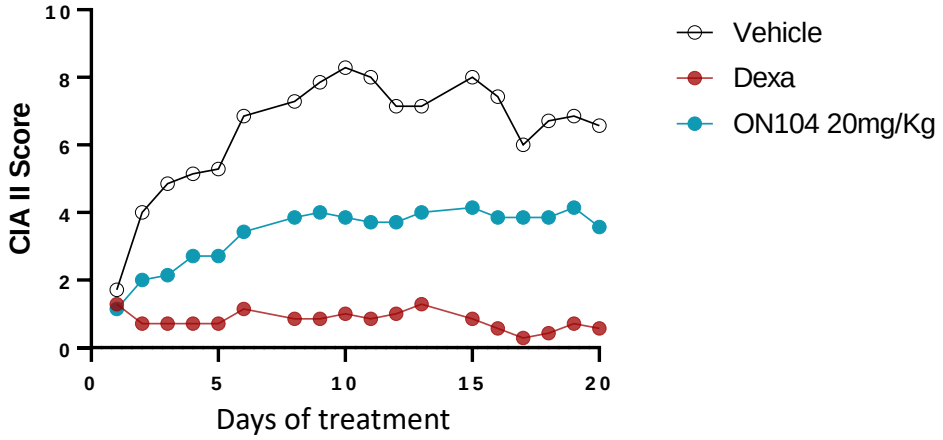
Data are presented as mean ± SEM and analyzed by one-way ANOVA followed by Dunnett's test (compared to NTN group), *p<0.05,**** p<0.0001

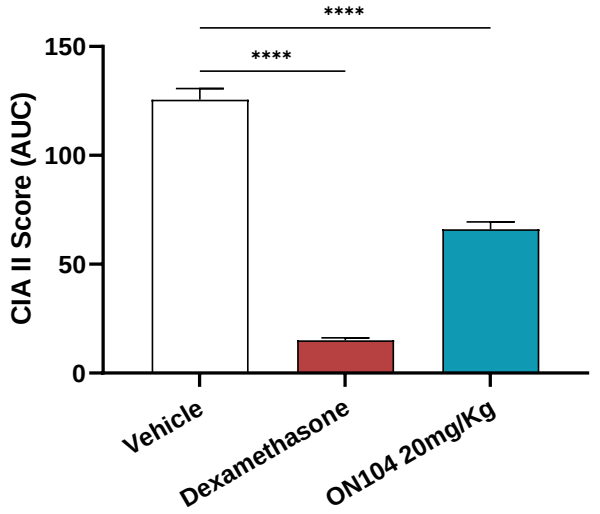
Treatment with anti-oxMIF mAb ON104 reduces proteinuria, haematuria, and macrophage infiltration, all together main signs of kidney damage and dysfunction

ON104 ameliorates symptoms in a mouse model of RA

Mouse model of Rheumatoid Arthritis: collagen II induced arthritis (CIA II)

- DBA/J mice were immunized with bovine type II collagen, followed by a boost at D21, to induce joint inflammation and tissue damage.
- After onset of arthritis mice were **treated twice weekly for 20 days** with ON104 20mg/kg, dexamethasone 0.3 mg/kg and controls (n=7 per group).
- Max effect on day 10 due to natural remission of the model.



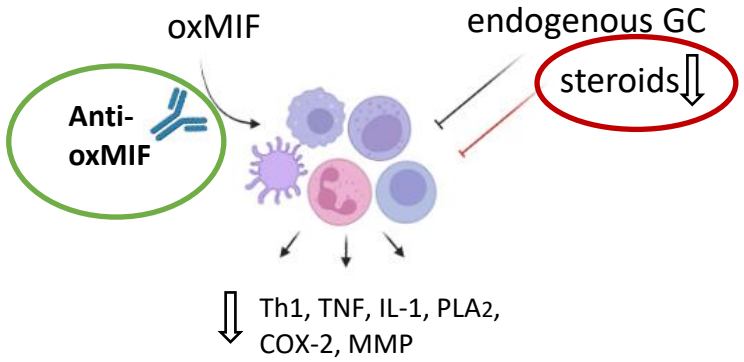


Data are presented as mean ± SEM and analyzed by one-way ANOVA followed by Fisher's test. **** p<0.0001

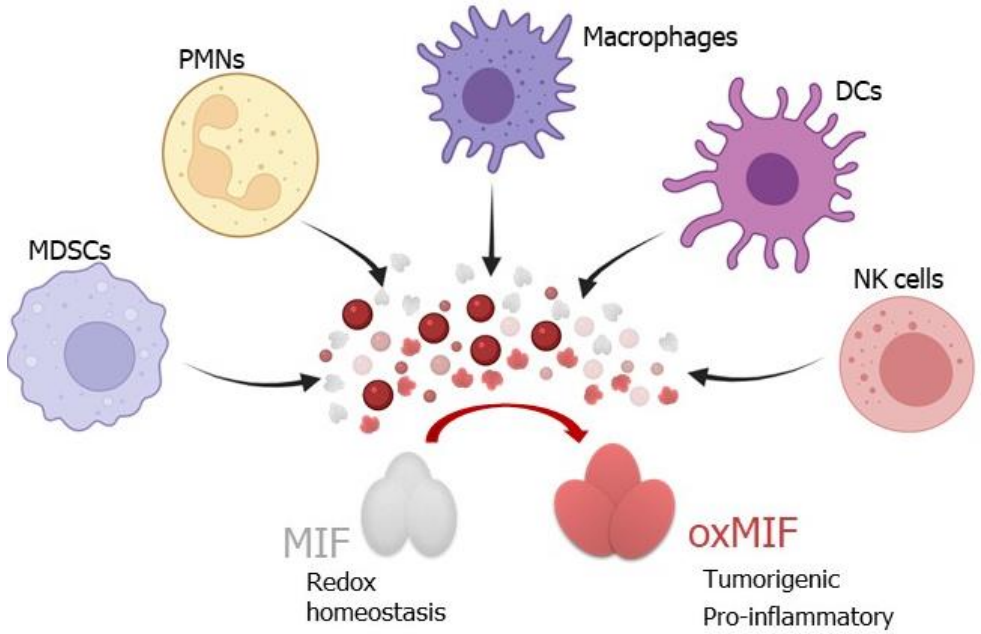
ON104 significantly reduces disease severity (clinical score and paw thickness) in a mouse model of type II CIA

Summary

- Antibody engineering improved stability, biodistribution and PK compared to first generation anti-oxMIF antibody imalumab
- ON104 was highly effective in model of GN model in rats (decreased proteinuria and glomerular crescents)
- ON104 ameliorates CIA in mice
- GC sparing will be tested in follow-up studies



Hypothesis**: immune cell activation within inflamed tissue leads to **MIF to oxMIF conversion** and **inflammatory response exacerbation



Acknowledgments

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