A potential role of oxidized Macrophage Migration Inhibitory Factor (oxMIF) in NLRP3 inflammasome activation

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1 OncoOne at a glance

Over 60 years of collective experience developing oxMIF therapies

Founded
June 7th, 2018
US office founded
Sept 13th, 2021

17 employees
Highly motivated and skilled experts
~50% PhD´s

Worldwide network of research collaborations
Imperial College London; Brown University; University of Catania (IT), Med. Univ Graz (AT), …

Head office
3400 Klosterneuburg, Austria
Labs & Offices
Karl-Farkas-Gasse 22, 1030 Vienna
US Headquarter
Boston, MA, est. 2021

Our mission

Unlocked the macrophage migration inhibitory factor **(MIF), a critical driver in innate and adaptive immunity** in cancers and immunology	Harnessing the **disease-related and druggable isoform of MIF**: the oxidized macrophage migration inhibitory factor (**oxMIF**)	**Two lead antibody drug candidates** optimized for the treatment of **solid tumors (ON203)** and **autoimmune disorders (ON104)**, respectively

Project Timelines and Pipeline Progress

		2018-2020	2021	2022	2023	2024	2025	2026	2027	2028
Oncology	ON203	Research	Preclinical			Phase I	Phase II		Phase III	
Immunology	ON104		Research		Preclinical	Phase I	Phase II		Phase III	

2 OncoOne's lead candidate ON104

ON104: anti-oxMIF mAb optimized for the treatment of inflammatory diseases

- **Anti-oxMIF Fab**: Bioengineered, 2nd-generation anti-oxMIF **Fab** with Improved biophysical and pharmacological properties with low nM affinity to oxMIF compared to the 1st generation anti-oxMIF antibody "imalumab".
- **Anti-oxMIF Fc:** Silenced 2nd-generation anti-oxMIF **Fc** with abolished FcγR binding and further effector functions.

ON104

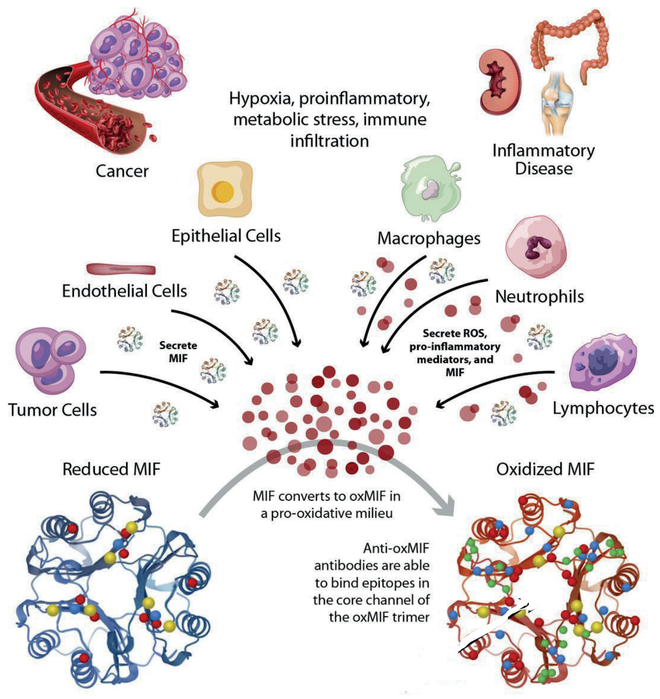
OxMIF-binding Fab
with optimized variable domains

Optimized Fc
To abolish FcγR binding and effector function

- **Hydrophobicity ↓**
- **Aggregation ↓**
- **Pharmacokinetics ↑**
- **Biodistribution ↑**

3 Macrophage migration inhibitory factor

MIF is a primary mediator of adaptive and innate immune responses, primary counter-regulator of glucocorticoids (GCs), and required for inflammasome activation[6]. Therefore, MIF is a pivotal regulator in chronic inflammation including rheumatoid arthritis, lupus nephritis, inflammatory bowel diseases and more[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)[7-8]. Thus, targeting oxMIF represents a new and promising treatment option for patients with chronic inflammation and autoimmune disorders [9].



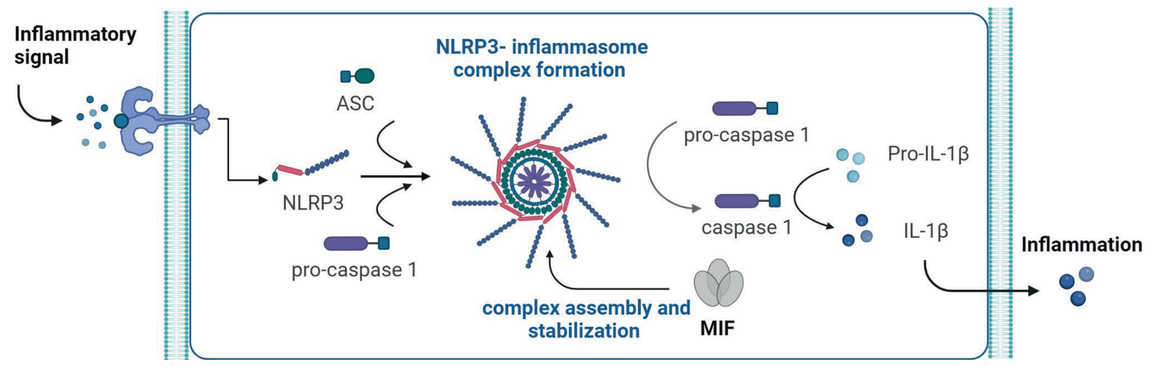
oxMIF generation during inflammation [10]. Under inflammatory conditions, MIF produced by a variety of tissue-resident cells is converted by the pro-oxidative and pro-inflammatory milieu into an oxidized isoform "oxMIF "

- that overrides GC activity,
- increases immune cell recruitment
- and promotes inflammation.

QR code that gives you direct access to our recently published review article about oxMIF biology

An anti-oxMIF therapy will improve immune cell function, promote tissue repair and disease regression

4 MIF and NLRP3-inflammasome activation [6]



MIF specifically participates to assembly of NLRP3 inflammasome complex. This complex formation can promote chronic inflammation by increased release of IL-1β

Systemic lupus erythematosus
- Lupus snRNP immune complex stimulates MIF production and subsequent NLRP3 activation and IL-1β production by human monocytes[11]

Joint inflammation
- Increased MIF and IL-1β levels in synovial fluid from patients and mice with gout. Crystals formation triggers NLRP3 inflammasome activation and IL-1β release during acute gout in mice[12]

Neuro-inflammation
- Patients with Parkinson have elevated MIF levels and pharmacological inhibition of NLRP3 decreases MIF expression and neuro-inflammation[13]

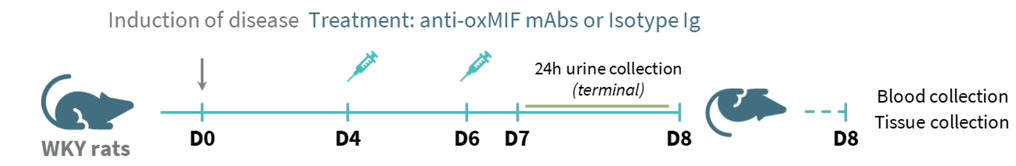
Kidney inflammation
- Pharmacological inhibition of MIF reduces NLRP3, ASC, caspase-1, and IL-1 β renal expression and attenuates acute kidney injury (AKI)[14]
- MIF up-regulation during AKI promotes NLRP3 inflammasome mediated cell pyroptosis and renal damage. MIF genetic deficiency prevents these damage[15]

Sepsis
- Pharmacological inhibition or genetic deficiency of MIF inhibits NLRP3 activation and IL-1 release during LPS-induced endotoxemia[6]

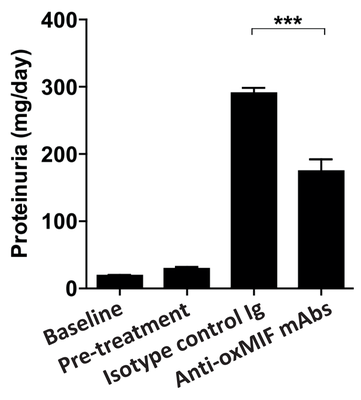
MIF is linked to many inflammatory diseases and auto-immune disorders with involvement of the NLRP3 inflammasomes

5 Decreased IL-1 β levels after oxMIF inhibition *in vivo* [9]

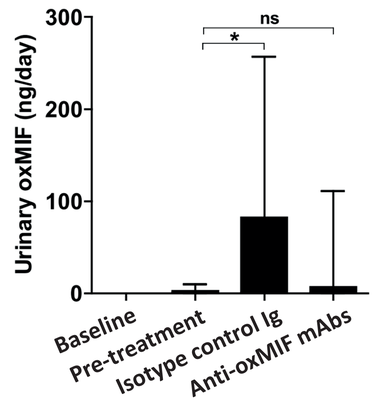
Efficacy of anti-oxMIF antibody was evaluated in a rat model of Glomerulonephritis



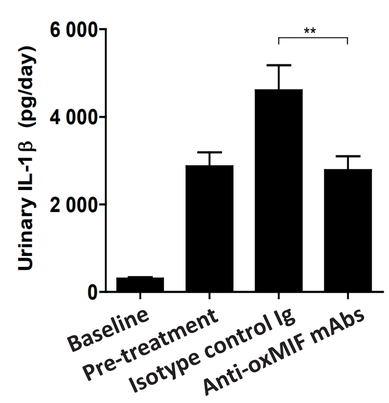
Urinary protein levels
Kidney injury marker



Urinary oxMIF



Urinary IL1b
NLRP3 inflammasome-dependent cytokine



Data are expressed as mean and SEM from two independent experiments (n=16). One-way ANOVA followed by Dunnett's Multiple Comparison test (*vs.* control IgG group) for statistical analyses. * p<0.05, ** p<0.001, and *** p<0.0001

Successful reduction of kidney injury, local inflammation and inflammasome-related cytokine production during rat Glomerular Nephritis (GN)

6 Summary & conclusions

- **oxMIF** is responsible for the pathological activities of MIF
- OncoOne's is developing **the anti-oxMIF mAb ON104**
- **Anti-oxMIF antibody** significantly decreases local release of IL-1b, a cytokine related to NLRP3 inflammasome activation
- **oxMIF neutralization** significantly improves renal function in an inflammatory glomerulonephritis model

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