ON203: A new antibody targeting the oxidized form of macrophage migration inhibitory factor (oxMIF) demonstrates antitumorigenic activity in preclinical models

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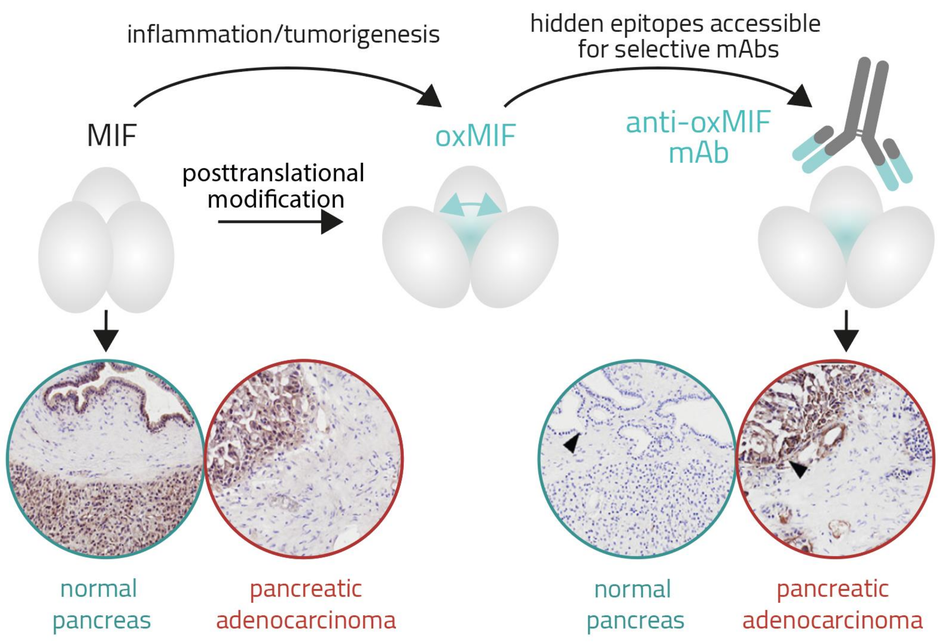
1 Introduction

Macrophage migration inhibitory factor (MIF) is a pleiotropic, pro-inflammatory cytokine which can directly promote tumorigenesis and is able to modulate the tumor microenvironment (TME) to immune evasive and immune tolerant phenotypes. Overexpression of MIF in tumor tissue is associated with poor prognosis. MIF distinguishes from other cytokines and chemokines due to its constitutive expression and high presence in circulation of healthy subjects.[1-12]

MIF is considered undruggable by antibodies and small molecules

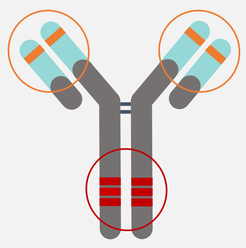
The founders of OncoOne discovered that MIF occurs in two immunologically distinct conformational isoforms, termed reduced MIF (redMIF) and oxidized MIF (oxMIF).[13] The redox-dependent MIF structure modifications affect enzymatic and biological functions[14] - redMIF is the abundantly expressed isoform,[13, 15-16] whereas oxMIF is the disease-related isoform specifically detected in solid tumors.[13, 16] A first generation IgG1 anti-oxMIF antibody, imalumab, was investigated in Phase 1 (NCT01765790) and Phase 2 studies in patients with CRC (NCT02540356) and ovarian cancers (NCT02448810) demonstrating that imalumab was well tolerated and showed signs of efficacy. These studies were terminated prematurely.[17]

oxMIF – the disease-related and druggable isoform of MIF



2 ON203 – optimized targeting of oxMIF

OncoOne's novel and improved anti-oxMIF antibody



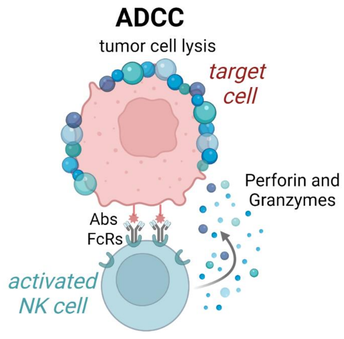
Optimized variable domains
Improved biophysical and pharmacological properties

Optimized Fc
Engineered Fc to enhance Fc-mediated effector functions

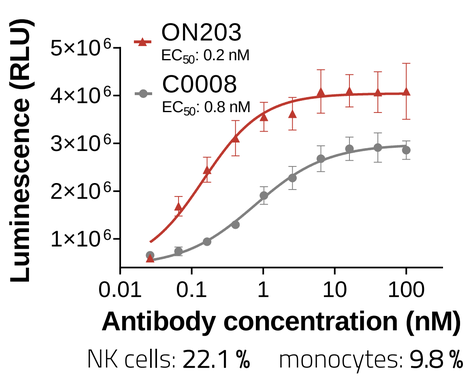
The bioengineered second-generation anti-oxMIF antibody ON203 is less hydrophobic and demonstrated reduced aggregation, while retaining the low nM affinity of imalumab. The IgG1/2 hybrid constant heavy chain region was modified to enhance its effector functions.

3 Improved *in vitro* tumor cell killing by ON203

a) PBMC-mediated cell killing assay for antibody-dependent cellular cytotoxicity (ADCC)

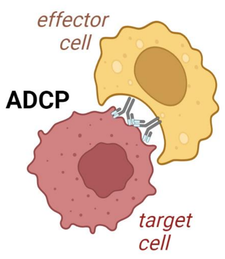


HCT116 colon cancer cells expressing HiBiT and pMIF were incubated with human PBMCs (E:T ratio 40:1) in the presence of different concentrations of ON203 or C0008 (imalumab) for 24h.

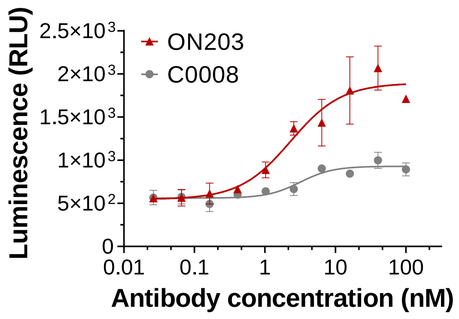


NK cells: **22.1 %** monocytes: **9.8 %**

b) Antibody-dependent cellular phagocytosis (ADCP)



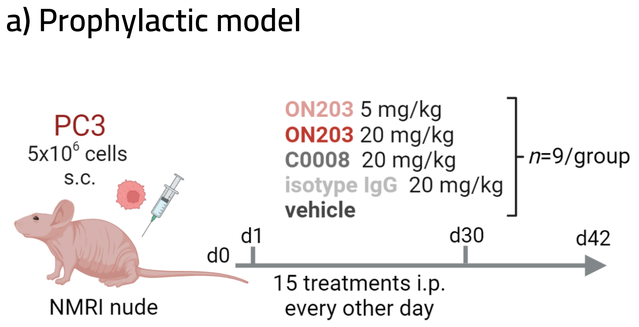
Engineered effector cells (huFcγRIIA-H Jurkat reporter cells) were incubated with ON203 or C0008 (imalumab) in the presence of HCT116 pMIF target cells.

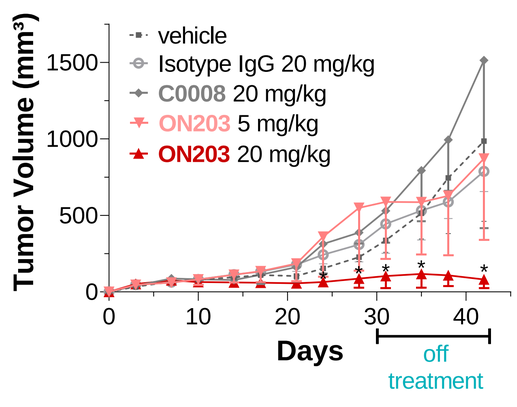


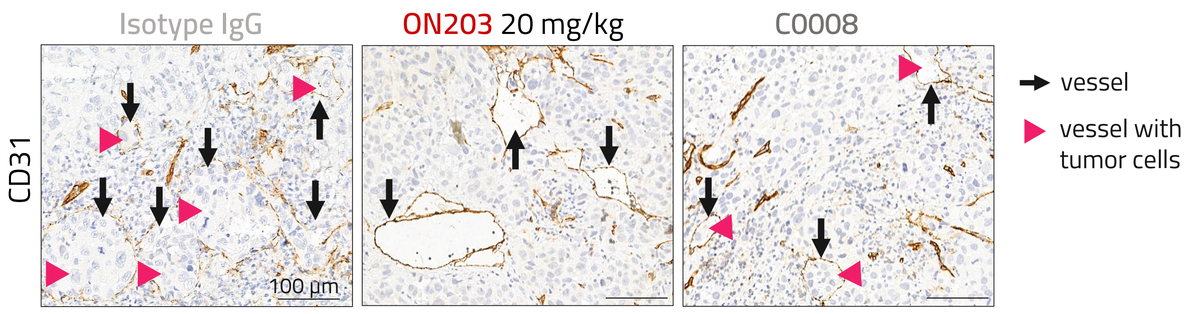
ON203 has improved ADCC and ADCP activity

4 Superior *in vivo* efficacy in prostate cancer xenografts

a) Prophylactic model

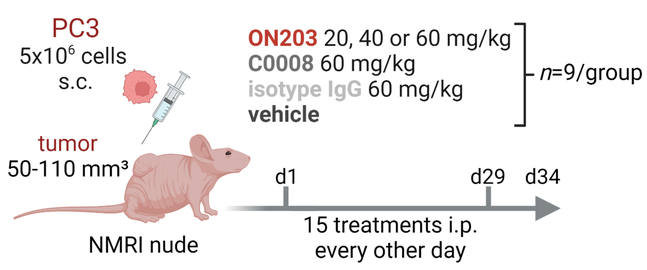


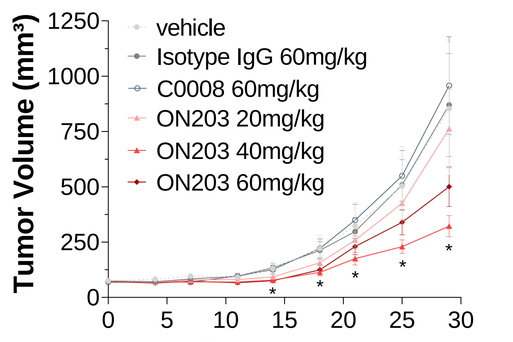


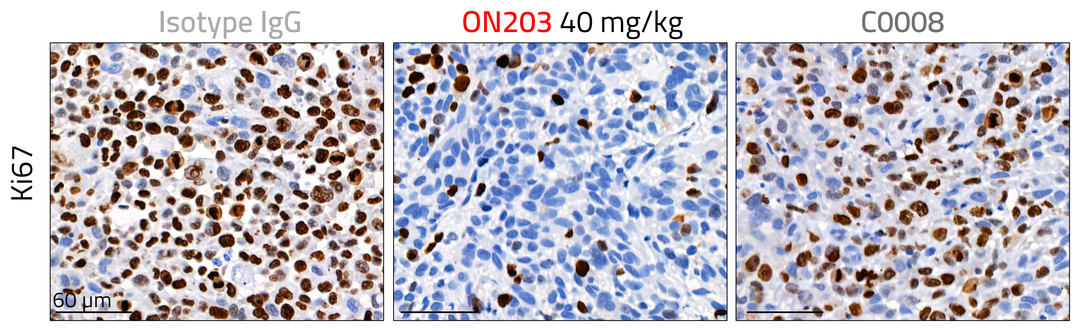


- Treatment of PC3 prostate cancer xenografts with ON203 reduced increase in tumor volumes compared to C0008 (imalumab). Even 12 days post treatment with ON203 tumor volumes remained stable.
- Reduced tumor vessel density (CD31) and intravasation upon treatment with ON203.

b) Therapeutic model







- Treatment of established PC3 prostate cancer xenograft tumors models with ON203 reduced increase in tumor volumes compared to C0008 (imalumab) also exemplified by decreased proliferation markers (Ki67).

Treatment with ON203
- ➤ reduced tumor volumes
- ➤ reduced neoangiogenesis, tumor cell intravasation and proliferation

5 Conclusions & Outlook

- ➤ MIF is a pivotal regulator of innate and adaptive immunity with a wide range of therapeutic applications in **oncology**
- ➤ Drugging the disease-related isoform oxMIF is the key for drugging MIF

Re-engineering of the first generation anti-oxMIF mAb imalumab led to ON203
- \+ improved physicochemical properties (hydrophobicity ↓, aggregation ↓)
- \+ *in vitro* efficacy (ADCC & ADCP)
- \+ improved efficacy in *in vivo* cancer models

- ➤ ON203 has a high potential for combinations with angiogenesis- and immune checkpoint-inhibitors

Lead candidate **ON203** is on track to enter **clinical phase I** by Q1 2023

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