

Development of screening cascade in inflammation disease

CASE STUDY

Oncodesign Services has over 25 years of experience in pharmacology services, initially in oncology but then extended to inflammatory diseases. A large range of *in vivo* models are readily available or can be developed for specific request.

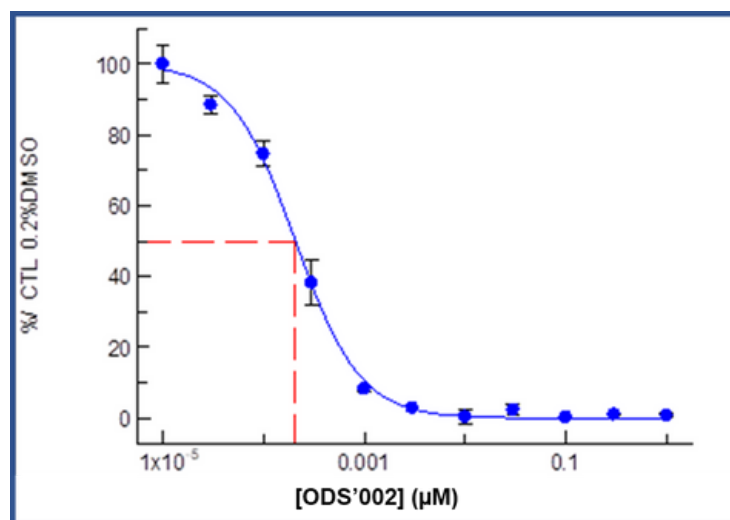
In this case study, our client wanted to develop a **new kinase inhibitor** used in the treatment of Inflammatory Bowel Disease. Oncodesign services established a screening cascade which allowed to deliver **preclinical candidates** with:

- Cellular assay
- *Ex-vivo* whole blood assay
- Early ADME
- PK/PD
- *In vivo* validation

Here, we show the data of one of the selected candidate **ODS'002**, which was prepared and tested via multiple step.

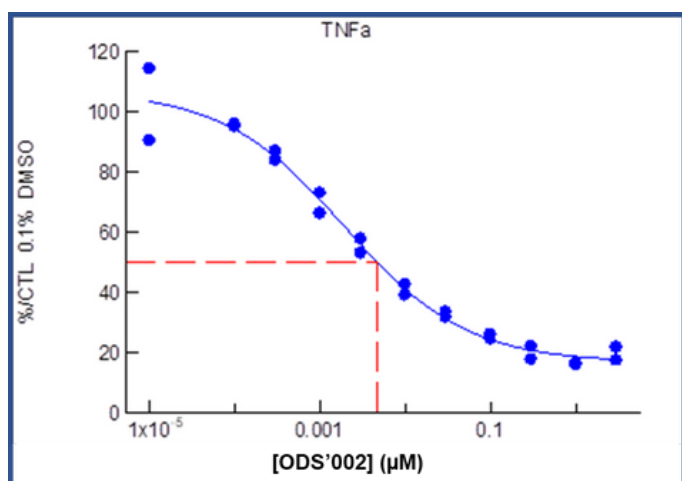
1 In vitro screening

Binding inhibition alphaLISA assay was performed to validate ODS'002 activity towards the desired target.

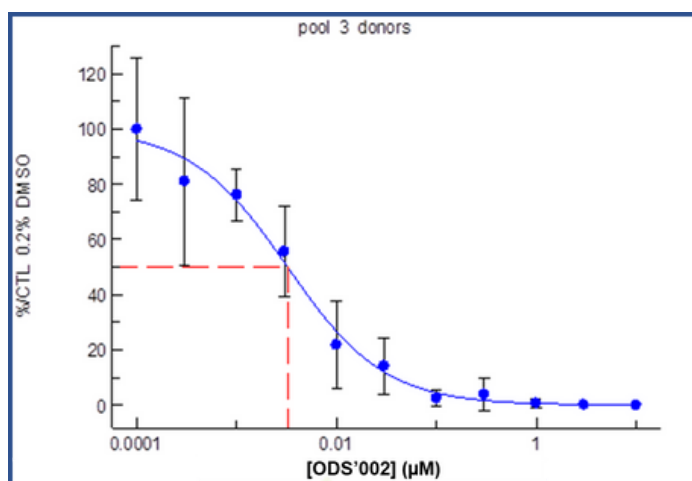


Human recombinant kinase target inhibition – binding assay in alphaLISA – IC50 = 0.2nM

Subsequently, cellular assay permitted to evaluate the capacity of ODS'002 to inhibit L18-MDP-induced TNFa expression. The assay was validated on mouse, rat and human PBMCs.



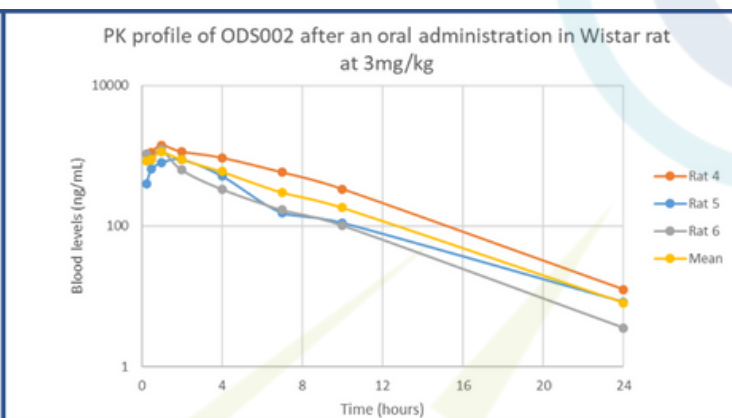
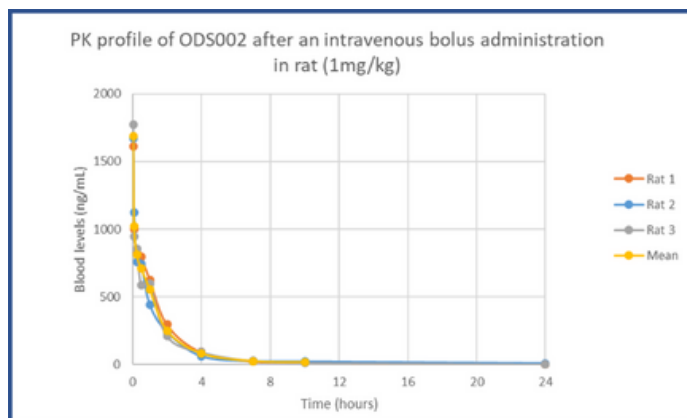
L18-MDP-induced TNFa inhibition – Mouse macrophages cell assay. IC50 = 5nM



L18-MDP-induced TNFa inhibition – Ex-vivo target engagement - Human whole blood assay IC50 = 3nM

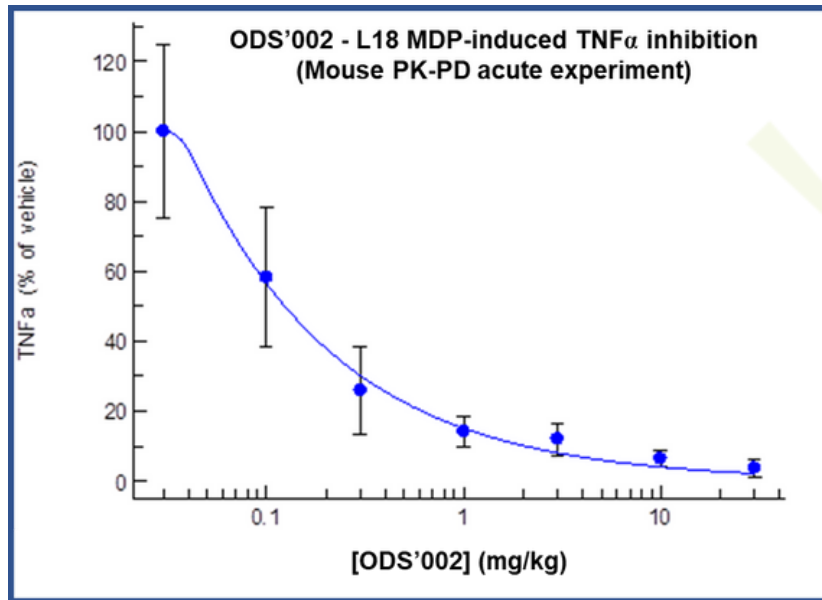
2 Early ADME evaluation

After the initial in vitro ADME is validated, the pharmacokinetic profile was assessed. Here is the profile of ODS'002 in rats allowing to calculate its bioavailability.



Rat pharmacokinetics (IV clearance and PO biodistribution, with a Tmax of around 2h) – Bioavailability = 85% (ratio oral DNAUC / IV DNAUC). DNAUC: dose-normalized area under the curve

To complement the profile, PK/PD relationship in mice was determined. The ODS'002 test compound was delivered PO[ND1] [NL2], followed by L18-MDP induction of TNFa expression (IV at T+1h). The quantification of TNFa expression is performed at T+2h (PO Tmax).



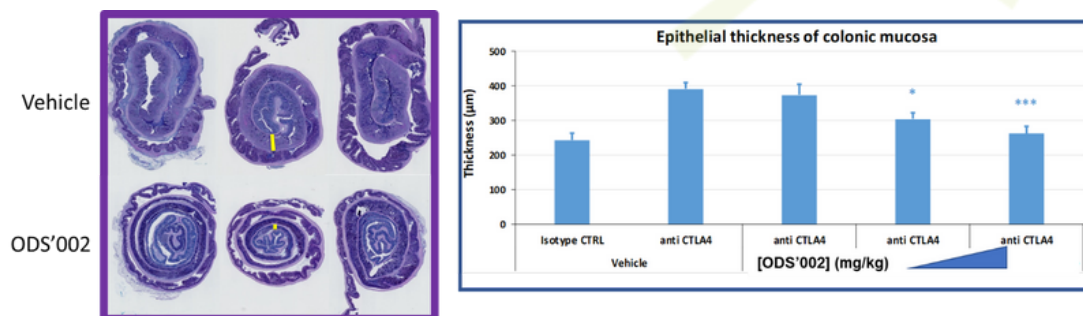
Mouse pharmacokinetics/pharmacodynamics relationship – Acute administration
In-vivo target engagement IC₅₀ ~0.1 mg/kg

3

In vivo validation

Anti-CTLA4 and DSS-induced chronic colitis model in mouse

Several readouts are used to demonstrate the therapeutic effect of test compounds (mouse weight monitoring; colonic target gene expression; histology for disease scoring; goblet cells & mucus quantification; epithelial thickness of colonic mucosa).



Colitis model /combination of anti-CTLA-4 and DSS (Dextran Sodium Sulfate), a chemical irritant. ODS'002 protects the colon from inflammation-driven epithelial thickening.

Who is Oncodesign Services?

Oncodesign Services is a Contract research organization (CRO) specializing in **drug discovery** and **preclinical services**. From target identification to IND filing, the company contributes to the development of innovative therapies in oncology, inflammation and infectious diseases.

Oncodesign Services has 230 employees in France, Canada and the United States.



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