The pan-PPAR agonist IVA337 has anti-fibrotic effects in multiple *in vitro* and *in vivo* fibrosis models

50 rue de Dijon, 21121 Daix, France
(www.inventivapharma.com)

Irena Konstantinova, Jean-Michel Luccarini, Evelyne Defrêne, Céline Estivalet, Ingrid Jantzen, Julien Tessier, Elodie Vasseur, Jeanne-Marie Germain, Francine Kupkowski, Claude Robert, Patrick Faye, Pascale Tuyaa Boustugue, Alain Philippot, Vincent Virely, Xavier Gawronski, Guillaume Wettstein, Claudia Fromond, Pierre Broqua, Jean-Louis Junien

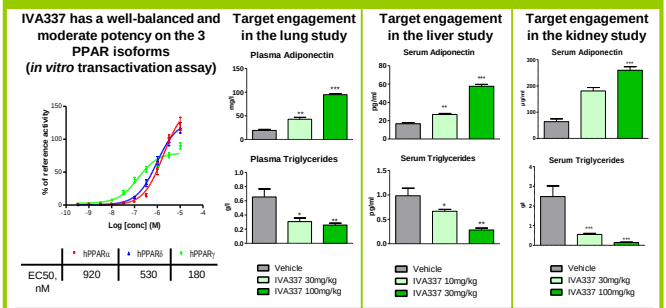
1-INTRODUCTION

Background: Numerous evidences point to a fundamental role of peroxisome proliferator-activated receptors (PPARs) in the control of fibrogenesis. Anti-fibrotic effects have been observed following treatment with PPARγ, PPARα or PPARδ agonists in several fibrosis models affecting specific aspects of fibrogenesis in different organs. This suggest that a pan-PPAR agonist might represent an attractive anti-fibrotic therapeutic approach.

Objective: To investigate the anti-fibrotic effects *in vitro* and *in vivo* of IVA337, a well-balanced pan-PPAR agonist (EC50: PPARγ 0.2 µM, PPARα 0.9 µM, PPARδ 0.5 µM).

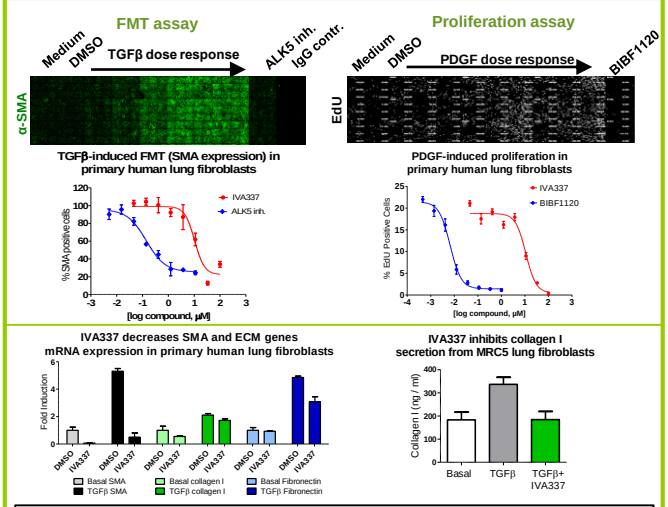
Methods: The effects of IVA337 were investigated in primary human lung fibroblasts and pulmonary artery smooth muscle cells *in vitro* and in lung, liver and kidney fibrosis models *in vivo*.

2- IVA337 PHARMACOLOGY PROFILE AND TARGET ENGAGEMENT



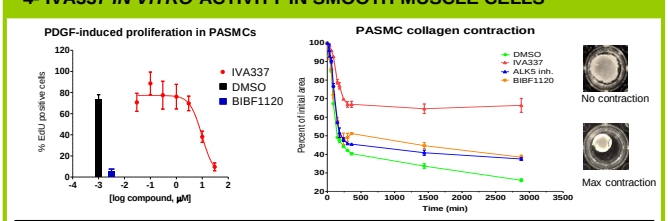
IVA337 is a moderate and well-balanced pan-PPAR agonist. *In vivo*, activation of PPARγ and PPARα by IVA337 is demonstrated by a dose-dependent increase of circulating adiponectin and a decrease of circulating triglycerides, respectively.

3- IVA337 *IN VITRO* ACTIVITY IN HUMAN FIBROBLASTS



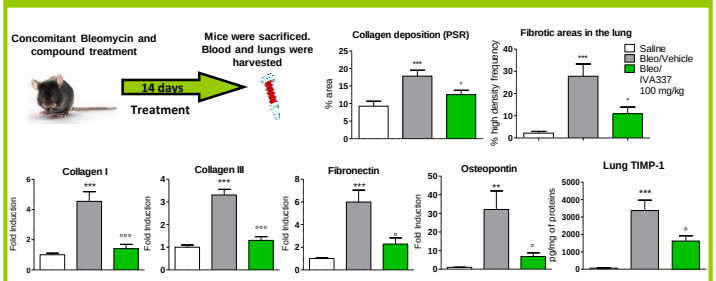
IVA337 inhibits TGFβ-induced fibroblast to myofibroblast transition (FMT) and PDGF-induced proliferation in primary human lung fibroblasts. In addition, IVA337 decreases SMA and extracellular matrix (ECM) genes expression and inhibits collagen secretion. Similar data on FMT and proliferation were obtained in primary human skin fibroblasts (not shown).

4- IVA337 *IN VITRO* ACTIVITY IN SMOOTH MUSCLE CELLS



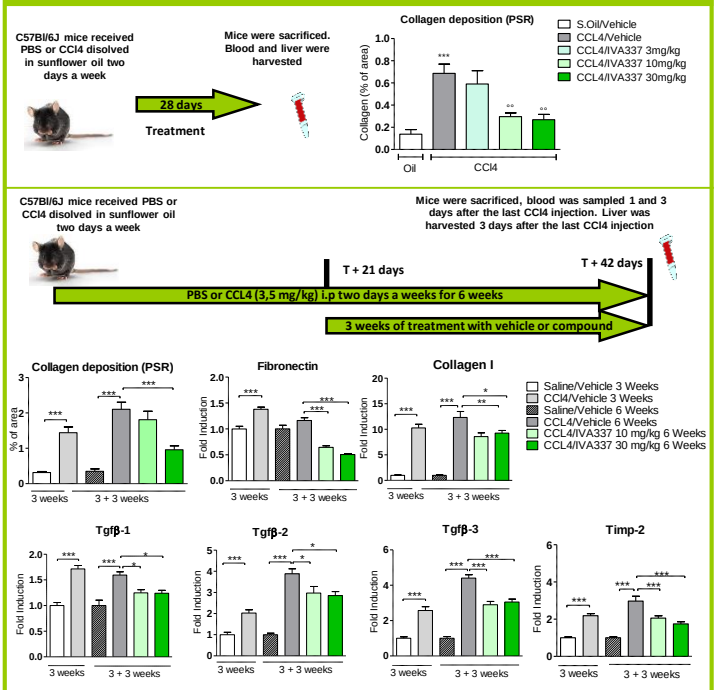
IVA337 inhibits PDGF-induced proliferation in primary human artery smooth muscle cells (PASMC). In addition, IVA337 inhibits contractility in 3D collagen gel contraction assay. Thus, IVA337 could inhibit aspects of vascular remodelling during fibrogenesis.

5- IVA337 ACTIVITY IN BLEOMYCIN LUNG FIBROSIS MODEL



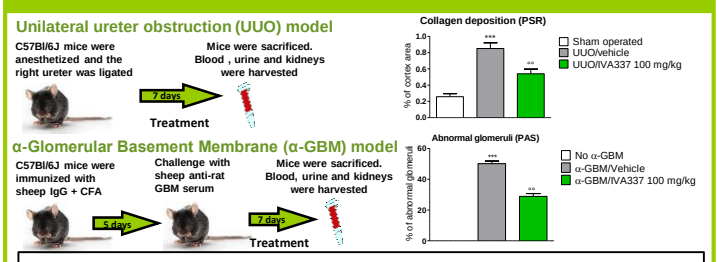
IVA337 blocks fibrogenesis in a prophylactic Bleomycin lung fibrosis model. 14 days treatment inhibits collagen accumulation as well as the expression of a set of fibrotic and inflammatory genes and proteins.

6- IVA337 ASSESSMENT IN CCL4 LIVER FIBROSIS MODEL



IVA337 inhibits fibrogenesis and reverses established fibrosis induced by CCL4 in the liver, as demonstrated by decreased collagen accumulation and inhibition of expression of fibrotic and inflammatory markers.

7 - IVA337 ACTIVITY IN KIDNEY FIBROSIS / INJURY MODELS



IVA337 prevents kidney inflammation and fibrosis in the UUO and α-GBM glomerulonephritis models as demonstrated by decreased collagen accumulation and inflammatory markers.

8 - CONCLUSIONS

Our findings confirm that PPARs play an important role in fibrogenesis and demonstrate that simultaneous activation of all PPAR isoforms by IVA337 exerts potent anti-fibrotic, anti-vascular remodelling and anti-inflammatory effects. These findings support the potential therapeutic effect of IVA337 for the treatment of SSc and other fibrotic conditions including IPF, NASH and DN. IVA337 is currently under investigation in dcSSc patients (FASST clinical trial).

Additional data on skin fibrosis will be presented on **19 Feb, Session 6 at 17.40 by Prof. Yannick Allanore**
PAN PPAR AGONIST IVA337 IS EFFECTIVE IN PREVENTION AND TREATMENT OF EXPERIMENTAL SKIN FIBROSIS