

CARDIOVASCULAR SAFETY



TNO innovation
for life

Cardiovascular (CV) safety assessment is becoming increasingly important in the development of new drugs. Especially in the field of oncology, where innovative medication has led to a prolonged life expectancy of patients, there is an increased interest not only in managing, but also in the early prediction and better understanding of the cardiovascular risk in early drug development.

WHAT DO WE OFFER?

Based on our translational and predictive mouse models (>200 studies performed), in depth knowledge of this therapeutic domain and (mechanistic) toxicology, we offer various solutions to assess cardiovascular safety:

- › Applying our metabolic preclinical models for safety testing of drugs that are suspected to have side effects in the cardiovascular or metabolic spectrum (for examples see below);
- › In both the preclinical as well as the clinical phase, TNO can measure and interpret subtle changes in lipid modulation (including HDL, LDL, apolipoproteins and PCSK9);
- › Consultancy to advise on cardiovascular safety de-risking experiments and strategies.

These approaches are especially applicable to compounds inhibiting kinases (e.g. JAK inhibitors), anti-inflammatory compounds and other compounds in the field of chronic inflammation and oncology.

EXAMPLES OF STUDIES PERFORMED IN CARDIOVASCULAR SAFETY

Our models turned out to be sensitive for assessing side effects for various classes of drugs. A selection of the compounds tested:

Torcetrapib (CETP-inhibitor)¹

- › Clinical observation: increased CV-related mortality and morbidity
- › TNO models show a pro-inflammatory lesion phenotype, more vulnerable plaque phenotype potentially explaining the increased event rate, most probably caused by increased aldosterone levels in mice as seen in patients



› This was followed up by studies with others CETP-inhibitors²

Bexarotene (Targretin, RXR-agonist)³

- › Targretin is a chemotherapeutic drug against cutaneous T-cell lymphoma and differentiated thyroid carcinoma
- › Clinically it induces dyslipidemia in patients (increased total cholesterol (TC) and triglyceride (TG))
- › This was also observed in a TNO model, with an underlying mechanism of increased VLDL production and increased CETP activity leading to decreased HDL
- › Application of E3L.CETP as a test model for mechanistic understanding of dyslipidemia caused by drugs

FXR and LXR agonists^{4,5}

- › Compounds in development as novel treatment strategies for cardiovascular and metabolic disease
- › In E3L.(CETP) FXR and LXR agonists caused dyslipidemia by increasing CETP expression in the liver (CETP is a target gene). LXR agonists also increase lipogenesis and liver fattening, therefore a potential risk for liver-specific LXR- and FXR-agonists. In E3L mice LXR agonists had anti-atherosclerotic effects

HIV protease inhibitors⁶

- › Compounds against AIDS (infectious disease)
- › Clinical: induces dyslipidemia in patients (increased TC and TG) and lipodystrophy

- › Findings in the clinic for ritonavir (effect) and atazanavir (no effect) were confirmed in the TNO models. For amprenavir, effects found in mouse but not in men
- › Decreased LPL-mediated clearance of post-prandial lipoproteins and VLDL particles
- › Further application: use of E3L.CETP a test model model for studies on mechanistic background of dyslipidemia caused by drugs

JAK-inhibitors

- › Tyrosine kinase inhibitors for rheumatoid arthritis (RA)
- › Clinical: RA increases IL-6. IL-6 stimulates the JAK-STAT pathway and decreases TC and HDL-cholesterol (increase (V)LDLR and endothelial lipase) in humans and non-human primates. JAK-inhibitors reverse this effect, thereby increasing LDL and HDL in patients
- › TNO model: in E3L.CETP IL-6 treatment for 4 weeks led to a significant decrease in plasma cholesterol and HDL-cholesterol as in patients. In E3L.CETP with no/low grade inflammation JAK-inhibition had beneficial effects: the compound did not have adverse effects on plasma lipids after 4 weeks of treatment. In fact, beneficial effects were observed as reflected by a significant decrease in plasma cholesterol, contained in the apoB-containing lipoproteins, and an increase in HDL-cholesterol

REFERENCES

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TNO HEALTHY LIVING

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