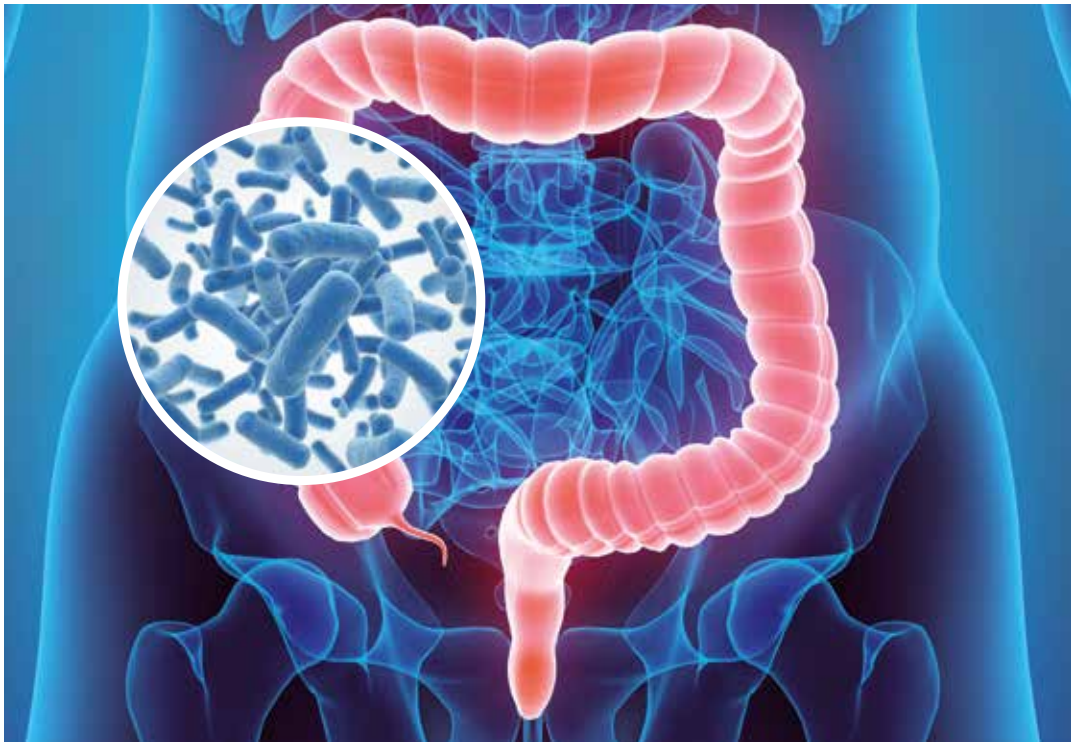
TNO I-SCREEN

INTESTINAL MICROBIOTA SCREENING PLATFORM FOR DETERMINING METABOLISM OF DRUGS



TNO innovation for life

TNO's intestinal screening model (TNO i-screen) helps to quickly identify pharmacological compounds that are metabolized by intestinal microbiota. For pharmaceutical companies, searching for novel pharmaceuticals is a complex and time-consuming process. When a novel drug has been selected, extensive in vitro and clinical studies are required to demonstrate its metabolism, safety and efficacy prior to releasing it to the market. Increasing evidence has shown that gut microbiota are involved in the metabolic transformation of many drugs, influencing drug pharmacokinetics and thus, efficacy and safety profiles.

THE TECHNOLOGY EXPLAINED

TNO developed the i-screen platform for in vitro evaluation of drug metabolism through intestinal microbiota. Human gut microbiota are cultured anaerobically in a multi-well system to mimic the human intestinal in vivo metabolism. This allows for determining the potential of intestinal microbiota to metabolize drug candidates. The starting population of microbiota in the TNO i-screen can be a standardized ex-vivo intestinal microbiota pool collected from either healthy volunteers, or for example obese, or lean adults or even children. This would confer the inherent differences found in each individual's specific gut microflora.

BENEFITS

TNO i-screen enables rapid identification of drugs that are susceptible to metabolism by intestinal microbiota. Additionally, it can be used to identify unknown metabolites transformed by intestinal microbiota. Normally, human metabolite profiling and identification data are generated during Phase II and/or III of clinical trials. Human metabolites can thus be identified in preclinical stages, thereby de-risking and accelerating the drug development process. Each i-screen can be simultaneously exposed to a large number of different conditions, allowing for cost effective screening of interesting candidate drugs. Experiments in TNO's i-screen are also not subject to lengthy regulatory processes and allow testing of drug candidates early on in the evaluation.

EXAMPLES OF THE I-SCREEN AT WORK

Example 1: Intestinal microbiota driven metabolism of sulfasalazine

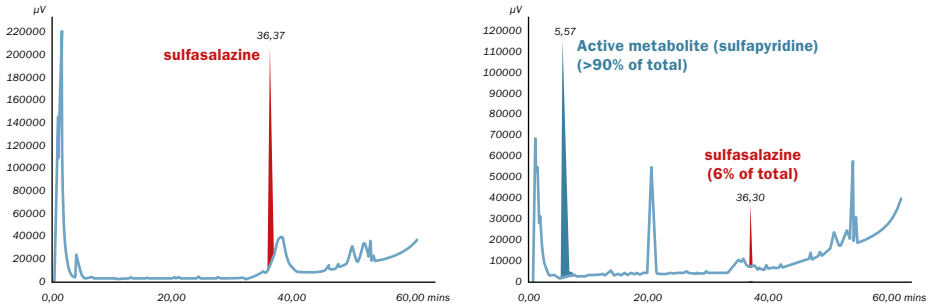
TNO has successfully applied the i-screen to demonstrate that sulfasalazine in the i-screen system is metabolized as has been shown in vivo. Sulfasalazine is designed specifically to be metabolized by human intestinal microbiota to the 5-aminosalicylic acid that has therapeutic effect [2]. However, clinical studies demonstrated that sulfasalazine is mainly metabolized to sulfapyridine by the intestinal bacteria, which give rise to side-effects. In this example, microbiota from healthy adults were exposed to 100 µM sulfasalazine. Samples were taken after 0 and 24 hrs. and were analyzed by HPLC.

Example 2: Intestinal microbiota driven metabolism of nizatidine, in collaboration with Pfizer Inc.

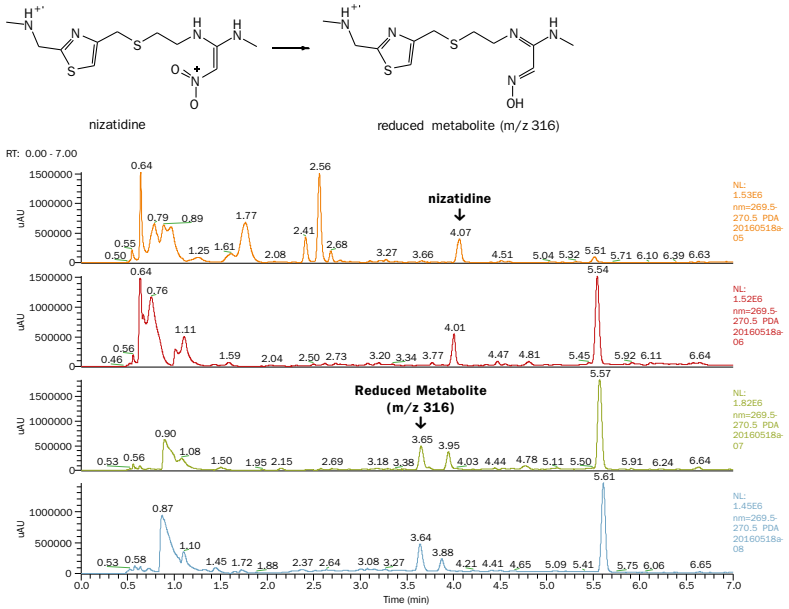
In a second example, TNO has successfully applied the i-screen in the investigation of nizatidine, a pharmaceutical compound that is known to be metabolized by human intestinal microbiota [3]. After the incubation period, the analysis of the samples was performed by Pfizer Inc. using high resolution mass spectrometry. The microbiota from healthy adults were exposed to 50 µM nizatidine and samples taken after 0, 6, 24 and 48 hrs, clearly demonstrated the metabolic capacity of gut microbiota.

ADDITIONAL APPLICATIONS

- Screening of pro-drugs that are transformed to active drugs by intestinal microbial metabolism
- Diversity by Next Generation Sequencing using the MiSeq platform (16S/ITS2 amplicon sequencing)
- (Metagenomic) microbial expression profiling using the NextSeq platform
- Metabolic shifts by SCFA analysis (acetate, proprionate, butyrate), BCFA (iso-butyrate, iso-valerate), or numerous other metabolites for clinical and infant nutrition



Sulfasalazine is metabolized in TNO's i-screen to sulfapyridine



Pfizer Inc. nizatidine is metabolized in TNO's i-screen to a reduced metabolite

CONTRACTING

This service is performed as contract research at TNO. We are always looking for collaborative partners in the next pharmaceutical or biotech project.

REFERENCES

1. Sara JT et al. 1983. Science. 220(4594):325-7.
2. Peppercorn MA. 1984. Ann Intern Med. 101(3): 377-86.
3. Kandler MP et al. 1986. Drug Metab Dispos. 14(2): 175-82.

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