

The key to personalized therapies

How to cross the translation barrier with metabolomics in pharmaceutical R&D

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Translatable



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quantitative



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multifunctional

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Smooth translation from mouse to man

Fit for purpose technology across the pharmaceutical R&D workflow

High attrition rates remain a reality of pharmaceutical R&D. By providing a wealth of valuable information not offered by other technologies, metabolomics (Mx) can help improve results. The versatility of metabolomics makes it a valuable tool for your biomarker strategy from discovery to approval.

Cell lines

- ▶ Mode of action studies
- ▶ Compound prioritization

Animal models

- ▶ Response biomarker
- ▶ Dose selection
- ▶ Mol. toxicology

Patients

- ▶ Dose verification
- ▶ Safety biomarker
- ▶ Stratification biomarker

Discovery

Preclinical
research

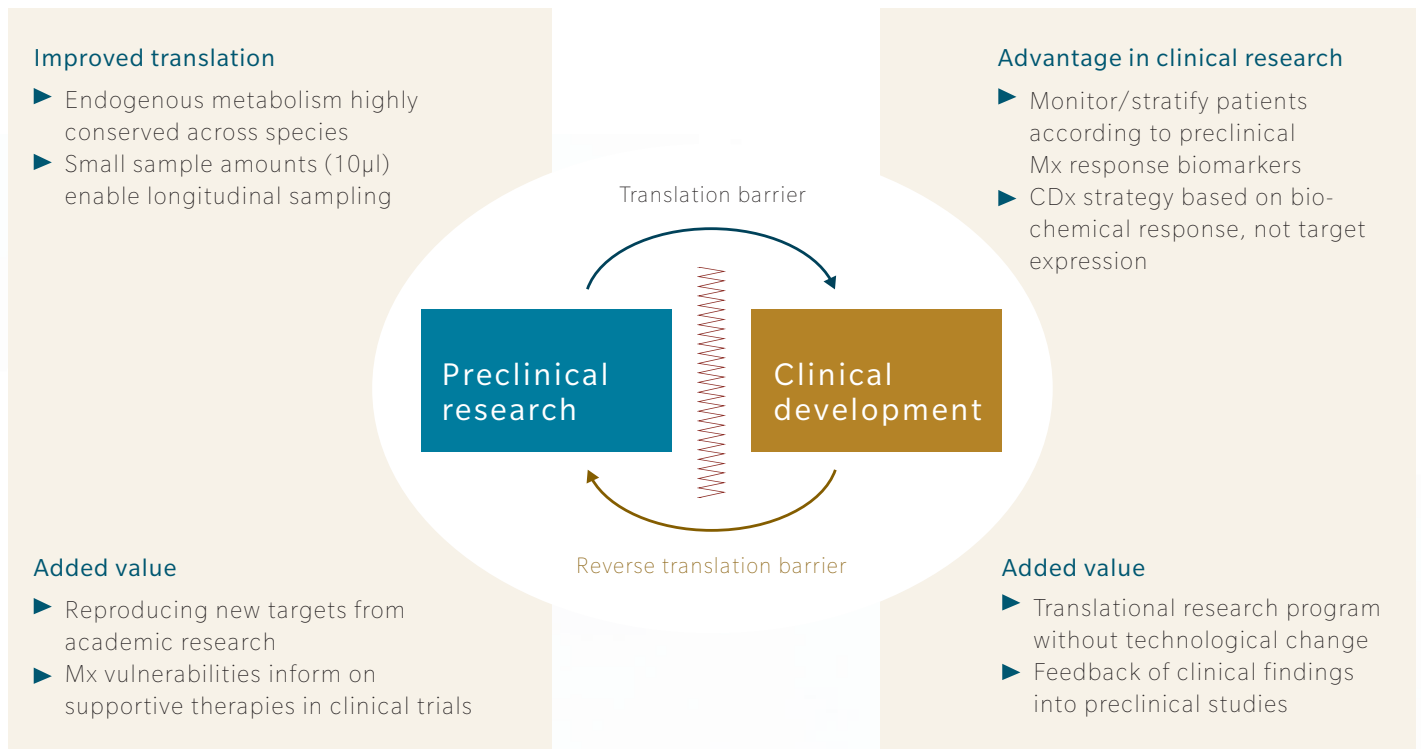
Clinical
development

Approval/
Market



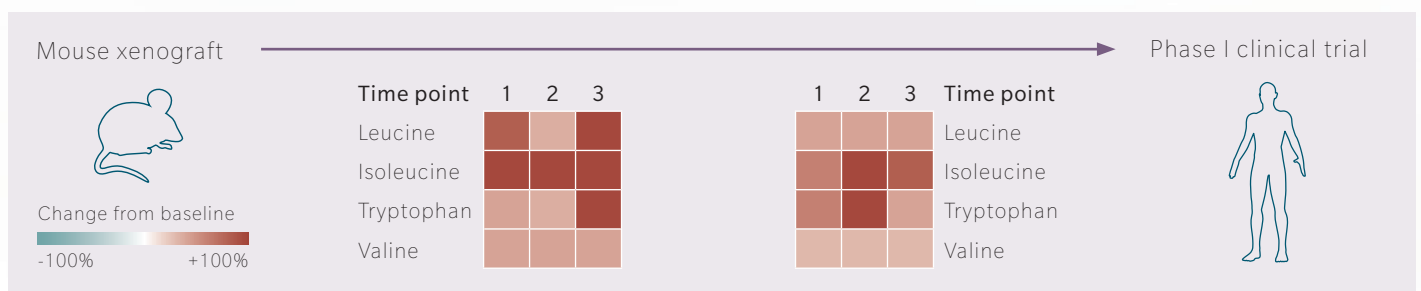
Crossing the translation barrier

Metabolomics as an ideal tool to support preclinical and clinical research



Ideally, the pharmaceutical R&D cycle flows smoothly from discovery to market approval. In reality, the development of a novel therapeutic faces immense challenges in transitioning from phase to phase. Consequently, only a fraction of compounds evaluated in the clinical stages of development eventually reach the market. Metabolomics can be a key technology in addressing those challenges.

Case study PI3K inhibition — Translation of Mx-based pharmacodynamic biomarkers



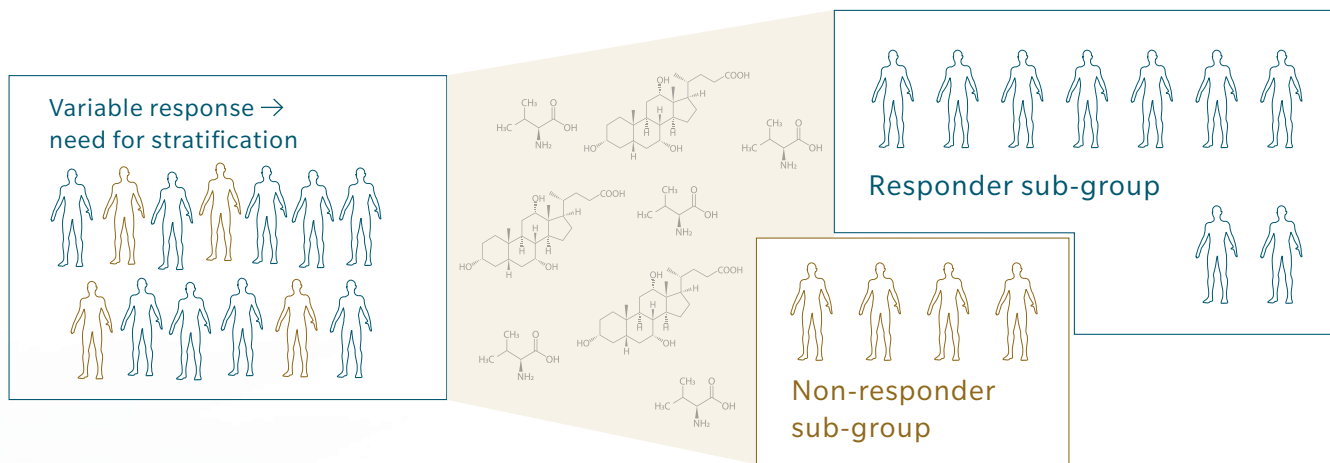
Metabolomics allows for a better functional understanding of effects and toxicities of pharmaceutical compounds. Plasma metabolomics can serve as a liquid biopsy for translational pharmacodynamic biomarker studies, as shown here for an investigational PI3K inhibitor*:

- 26 metabolites with dose-dependent response to PI3K inhibition
- 22 of which successfully replicated in a Phase I clinical trial
- Altered levels of branched-chain amino acids (BCAAs) in line with dose-limiting hyperglycemia

*published in Ang et al., Mol Cancer Ther 2016

Metabolomics as performance CDx for patient stratification

Identifying response determinants, enabling patient management

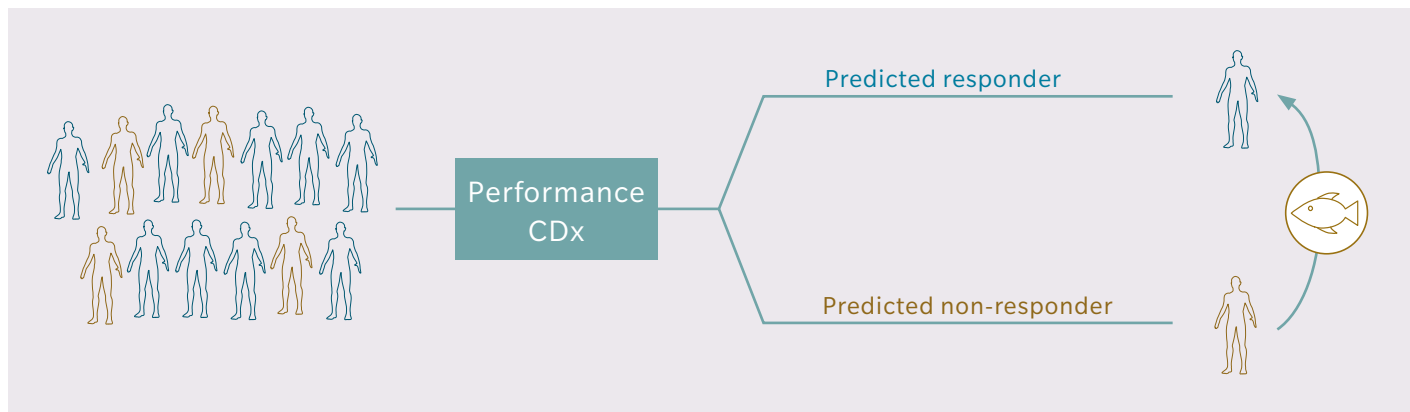


Metabolomics can improve our understanding of treatment response factors, improve success rates of development programs and have a positive impact on patient outcomes in multiple ways:

- Identification of likely responders at baseline with an approach independent of target expression
- Discovery of novel approaches to enhance response
- Early assessment of sustained response, relapse and/or disease progression
- Sensitive molecular toxicology approach

Knowledge about the determinants and prerequisites for therapeutic response can help move development programs forward, improve therapy compliance, and has health economic benefits.

Case study — Response prediction in immune checkpoint inhibitor therapy



Mock et al.* have shown the potential of metabolomics-based biomarker signatures as Performance CDx. They have confirmed that response to immune checkpoint inhibitors is not defined by expression of immune checkpoints alone.

The study in patients with urological cancers treated with immune checkpoint inhibitors found that

- Age together with a certain group of lipid metabolites helps assign patients to responder or non-responder group at baseline (ROC 0.935)
- Lipids that contain very-long-chain fatty acids (VLCFA, with 22 or more C atoms) drive this effect
- Probable mechanistic explanations are enhanced peroxisomal function and anti-tumor immunity

As VLCFA are contained in nutritional sources such as fish or fish oil, there might be an easy nutritional approach that could improve response to immunotherapeutics.

*Mock et al., Cancer Immunol Immunother, 2019

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