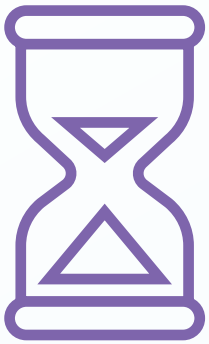
BIOMARKER-DRIVEN
DRUG DEVELOPMENT

Metabolon

Five Translational Insights Key to a **Successful First-in-Human (FIH) Study**

METABOLITE-BASED BIOMARKER DISCOVERY AND VALIDATION

Metabolon



Closer to the Phenotype, Faster

The use of animal models in early phase drug development is essential for the translation of drug findings from bench to bedside. While there have been many advances in developing more effective animal models, such as fit-for-purpose knock-out models and humanized mouse models, translational success rates from pre-clinical animal studies to human clinical trials remain frustratingly low.

Translational work can help the clinical team understand the underlying biology of their drug through late-stage mouse studies, non-human primate studies or first-in-human studies. But many questions can linger, such as whether the methodology to induce an ailment has influenced the results, or whether it was even a valid comparison in the first place. This human-animal model divide is significant enough that one recent paper referred to it as "the valley of death."[1]

Unfortunately, this is not the only problem development teams face in pre-clinical. By the time you get to Phase I, you should have clear biomarkers of response, safety, dosing and timing. Yet because the mechanism of action isn't always explicit, there can be real uncertainty about how a human subject will respond. Multiomics-based strategies based on mechanistic data can't provide sufficient clarity to resolve these issues. But there is an approach that can: metabolomics.

Metabolomics can help uncover the important characteristics of a targeted disease state based on actual phenotypical, per-patient response.[2]

1 Seyhan AA. "Lost in translation: The valley of death across preclinical and clinical divide – identification of problems and overcoming obstacles," *Translational Medicine Communications* 4, 18 (2019). https://doi.org/10.1186/s41231-019-0050-7

2 And the second one should read, Needham, Brittany D., Adame, Mark D., et al. "Plasma and Fecal Metabolite Profiles in Autism Spectrum Disorder," *Biological Psychiatry* 89, 5 (2020). https://doi.org/10.1016/j.biopsych.2020.09.025

Metabolon

It can also help confirm whether those characteristics are conserved in pre-clinical models, which is a particularly powerful component of metabolism given the extremely high level of translation of primary and secondary metabolism across mammalian biology. This rich, high-dimensional data can augment other 'omics information and help bridge potential gaps that keep you from understanding the underlying mechanism of the disease. This, in turn, helps control costs in other investigational areas and allows you to reach your research endpoint faster and more efficiently. In fact, metabolomics can provide five critical translation insights you need as you approach first-in-human.

1. Efficacy – make a go/no-go decision easier

Every investigation needs to determine how effectively the drug candidate engages the target and alters the pathway of interest. Only metabolomics measures the system's small molecule output, identifying metabolites that are directly related to your pharmacological target of interest. This more holistic and comprehensive view of how the metabolic pathways report on target engagement delivers a greater level of confidence in your drug's efficacy. And depending on your end-goal target, metabolomics can also help you identify off-target effects and help clarify which obstacles you must overcome with your molecule's particular chemistry.

This more holistic and comprehensive view of how the metabolic pathways report on target engagement delivers a greater level of confidence in your drug's efficacy.

2. Safety – get an early view of potential unintended impact

Poor safety profiles that weren't predicted in animal studies can derail your clinical trial program – but sometimes they don't reveal themselves until late into clinical phases. Metabolomics is uniquely suited to uncover whether your drug is creating a safety concern in pre-clinical and early phase clinical trials, helping you identify potential issues before precious time or financial resources are lost.

Another way metabolomics adds value is by identifying underlying metabolic differences that may be responsible for divergent patient responses to your drug. This can help you identify simple strategies to keep more patients in your trials.

3. Mechanism – generate the supporting evidence needed for your Investigational New Drug (IND) application

The thrill of discovering that your drug performs as anticipated may be tempered by the fact that you lack validated data that demonstrate how it works in order for your IND application to be approved. This requires moving beyond educated guesses about what could be happening and determining what is actually going on – and ultimately being able to predict a response.

It can be easy to overlook the fact that just because a transcript is generated, it doesn't necessarily mean that it is translated into a protein. Or even if a protein is generated, that protein may not be functional and impacting the system. **Metabolomics lets you achieve a more granular level of understanding of what is actually happening *in vivo* – whether your drug is in fact acting in the manner you want it to. Metabolomics can also uncover differing patient outcomes to the treatment – for both responders and non-responders.**

The functional *in vivo* data from metabolomics allow you to correlate back to the transcriptomics and genomics data you already have and pinpoint differences that may account for the results. Additionally, with an appropriate study design of longitudinal samples, metabolomics can help you measure the underlying kinetics and activity happening in an entire system versus that of a fixed micro-environment to see the changes over time. If there is a difference, metabolomics can help you determine how meaningful it is.

4. Dosing – find the line between not enough and too much

Metabolomics can help determine the optimal dosing strategy to achieve your desired effects, without triggering off-target or toxic events. It does so by delivering the pharmacokinetic and pharmacodynamic biomarkers you need to track the movement of your drug through the body: absorption, distribution, bioavailability, metabolism and excretion. These biomarkers provide critical data about how the body responds to different dose sizes and can help minimize any potential unintended consequences from larger doses. Moreover, if the drug is a small molecule, it can be multiplexed onto a metabolomics platform and yield reports on levels of the specific drug and catabolic derivatives (e.g., sulfation, glucuronidation) to assist with ADME properties.

Create a deeper understanding

Why do certain carriers of a germline mutation develop diseases such as cancer, while others do not? Metabolomics can illuminate the biological cascade and begin to inform answers.

Metabolomics can make your translational models stronger, since many pathways and metabolites are conserved across species. When going from mouse to human, glycolysis remains the same, while mouse versions of genomic mutations may not.

By querying the phenotype and tracking when peak response to your molecule occurs, dose timing answers can be made clearer.

Metabolon

5. Timing – define the dosing schedule

The same data that can help you pinpoint dose size can also help clarify what the proper redosing strategy should be to maintain an efficacious level of drug within the system. Armed with information such as how quickly your drug works, you can determine other critical factors, such as whether you're sampling at the right time to measure the effect correctly. Metabolomics data can also suggest what kind of dosing regimen is called for: should you do a one-hour, three-hour or 24-hour dose? These answers can be made clear by querying the phenotype and tracking when peak response to your molecule occurs.

Conclusion

As you move forward toward early clinical trials, having clear translational insight can be enormously important. As a methodology, metabolomics is uniquely qualified to help you bridge between the theoretical and practical, between the function and actual activity of your drug molecule. Finally, collaborating with a proven metabolomics expert like Metabolon can complement and extend the work of your in-house teams, and make their efforts more efficient in your overall program.

Discover more ways metabolomics can add unique value to your drug development efforts at metabolon.com

+1 (919) 572-1711
info@metabolon.com
www.metabolon.com
617 Davis Drive, Suite 100, Morrisville, NC, 27560
© 2021 Metabolon, Inc. All rights reserved.
MP.CLP.201221