Perspective:
Another dimension for drug discovery

'Deep phenotyping' of human cohorts, including the collection of microbiome data, could transform therapy development, says Eran Segal.

Last year, drug company Novartis began charging US$2.1 million per patient for its new spinal muscular atrophy treatment – breaking the record for the world's most expensive drug. With so many compounds failing to reach the clinic, and the cost of turning a molecular entity into a therapy reaching billions, it's no wonder that drugs have become so expensive. But we can do better.

One way to reduce costs is to use genetic data to inform drug design. Genetic information helps researchers to demonstrate that drug targets are relevant to the disease from the start, and drugs with this evidence are twice as likely to be approved as those without (M. R. Nelson *et al. Nature Genetics* **47**, 856–860; 2015). But we can further optimize drug discovery. If we start with a 'deep' molecular profile that includes data about the microbiome and genome, as well as information about metabolites and proteins (the metabolome and proteome), coupled with physiological measurements, we might be able, in some cases, to skip animal testing and move straight to human trials.

The ability to start drug discovery with this in-depth information is particularly useful for finding microbiome-related therapies. Rather than focus on microbial targets with therapeutic value in animal models that might turn out to be rare in the human microbiome, or that act through different mechanisms in people, we can start with microbes associated with human disease. Interventions to modify bacteria can also start directly in people. The idea is to collect dietary and microbiome data from many individuals, derive models of how diet affects composition of the microbiome, and then validate the models with controlled dietary interventions. With more than 5 million bacterial genes, the microbiome represents a prolific reservoir of modifiable targets with potentially therapeutic effects.

The gut microbiome has been implicated in numerous conditions, including autoinflammatory disease, autism, cardiovascular disease and cancer. Growing evidence from animal and human studies suggests that it has causal effects in disease, such as by regulating host gene expression or by producing metabolites that circulate in the blood. And because the microbiome is predominantly shaped not by genetics but by modifiable environmental factors such as diet, this presents an opportunity to intervene.

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For example, dietary interventions are being targeted towards gut bacteria that synthesize the metabolite trimethylamine N-oxide (TMAO). It has been suggested that elevated plasma levels of TMAO cause cardiovascular disease; reducing TMAO production could, therefore, help to lower disease risk. And in neurological diseases, microbiome-derived metabolites that reach intestinal neurons could provide a means of getting metabolites through the barrier that separates the brain from circulating blood.

The microbiome can also affect the efficacy of pharmaceutical drugs. Bacterial enzymes, for example, can metabolize the Parkinson's disease drug L-DOPA, and gut bacteria can affect a person's response to cancer immunotherapy. Dietary changes targeting bacteria that interfere with drug metabolism could, therefore, be effective supplements to existing treatments. The regulatory path for approving such microbiome-nutrition interventions is much easier than for conventional pharmaceutical products.

The development of microbiome-related therapeutics faces many challenges, including the need to establish causal mechanisms. However, even if these are unknown, we might still be able to use human microbiome data to devise therapies. For example, our team has targeted post-meal blood glucose levels, which are important in obesity and diabetes. We tracked blood glucose levels in 900 people, and collected data about their microbiome, genetics, metabolomics, diet and lifestyle (D. Zeevi *et al. Cell* **163**, 1079–1094; 2015). We found that people respond differently to the same meal, and devised a machine-learning algorithm that accurately predicted these personalized responses from clinical and microbiome data. In short-term and 12-month randomized controlled trials, we showed that personalized dietary interventions based on the algorithm successfully balanced glucose levels in people with higher than normal blood sugar – outperforming the standard-of-care diet.

We need new approaches to drug development. Cohorts made up of rich molecular and physiological profiles from many volunteers offer one way to prioritize human-relevant targets for development. These cohorts must be constructed carefully – the type and depth of the data collected should be relevant to the disease being studied. Having multiple types of data on the same people can be powerful for defining more exact targets and for discovering novel disease biomarkers and drug targets. Deep profiling also allows the disease state or treatment response to be modelled as a continuum, avoiding the need for arbitrary thresholds that categorize people as responders or non-responders, for example. This might lead to better estimates of disease risk and better prioritization of people to treatments and randomized controlled trials.

Longitudinal measurements of the same people are also crucial. Such studies bypass confounding factors of interpersonal variability because the volunteers serve as their own control. Finally, because resources are always limited, cohort size is an important consideration. A study of thousands or tens of thousands of participants still allows longitudinal, deep molecular profiling, but keeps costs realistic. Now is the time to use deep cohorts to end the era of laborious, costly, risky and time-consuming drug discovery. We can't afford another world record.