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An effective MASH drug is good, but biotech can make it better

Understanding this complex disease requires better model systems and large-scale data.

The US Food and Drug Administration recently approved Madrigal Pharmaceuticals' Rezdiffra (resmetirom) for the treatment of metabolic dysfunction-associated steatohepatitis (MASH) in adults. The new drug is a groundbreaking win for a disease with no previous therapy. MASH, previously known as noncirrhotic non-alcoholic steatohepatitis (NASH), occurs when excess fat cells build up in the liver, leading to inflammation, scarring and possible liver failure. It affects 1.5–6.45% of the worldwide population.

MASH has sorely tested biopharma's tenacity and ingenuity. Over the past two decades, pharma and biotech companies globally have attempted — and failed — to develop drugs. The search for an effective drug has frustrated companies, investors and patients. Novo Nordisk, Eli Lilly, Pfizer and AstraZeneca have all tried their own MASH drugs against different pathways; some are still in phase 2 and 3 trials[1], but many have been pulled in recent years when not enough positive effect was seen compared with placebo. Big pharma also has the new glucagon-like peptide-1 (GLP-1) agonists, which are being trialed to see whether they can be used against MASH. Results so far are promising, which is expected, as weight loss is the primary treatment suggested for reducing MASH progression. Considering the many failed attempts, the approval of Resmetirom is noteworthy. But as a drug, it is far from ideal: only 25–30% of patients with MASH benefit from treatment.

The main problem is that we have yet to understand the molecular mechanisms underpinning the disease. MASH is complex, and there is much to still learn about the pathways involved[2]. We know that it is a metabolic disorder characterized by dysregulation of glucose, lipid and bile acid metabolism. Fats accumulate in the liver and other peripheral tissues, eventually leading to liver fibrosis. However, MASH varies in its progression between individuals, and there are several layers of metabolic, genetic and epigenetic pathway changes. As a result, drugs have been developed against intermediate targets in lipid metabolism, inflammatory responses or fibrotic progression. Phase 3 clinical trial endpoints are either reduction of fatty acid accumulation or reversal in progression of fibrosis. These mitigate the end pathologies but do not necessarily to tackle disease initiation or early-stage progression.

We also lack validated biomarkers for easy or early MASH screening. Resmetirom is a thyroid hormone receptor-β (THRβ) agonist that reduces liver fibrosis, perhaps by boosting the ability of hepatocytes to burn lipids[3], but we do not even know for sure how it works.

Most MASH studies are in mice, in which MASH is induced by high-fat, high carbohydrate 'Western' diets. Researchers cannot use cell lines or organoids because MASH development depends on the microenvironment of the liver and the metabolic response of an individual. However, the type of diet and amount of fat is critical for modeling disease progression. Diets high in different sugars, for instance, lead to varied disease phenotypes. Genetics can play a part, too, as some mouse models, such as the *Foz/Foz* mutant strain, develop MASH after 4–8 weeks of a Western diet rather than 16 weeks in wild type[4].

Humanized mouse models, containing both human and mouse liver cells, may be better placed to tell us something about the early stages of the disease. In these chimeras, the human liver cells develop a metabolic state consistent with human fatty liver disease whereas the mouse liver cells remain normal[5]. The limitation here is that these mice also lack immune systems, so the inflammatory response associated with MASH in humans is missing.

While these models have been scientifically informative, they have proven impractical when screening for drug responses. Researchers usually have to repeat their experiments in multiple mouse models to show that the results are independent of any specific model[6]. In addition, in humans, MASH develops over years, not weeks.

In this age of big 'omics data, can we do better? First, we need a solid understanding of the biology that underlies the development of the disease. We need a global picture of the transcriptomic, proteomic and metabolic changes that occur at each stage of the disease. This disease progression in mice is often heterogeneous — but it is that way in humans too. Instead of trying to make a 'one size fits all' mouse model, why not capitalize on this heterogeneity and find ways to target populations at different stages, with different manifestations of MASH? Companies need practical solutions to screen for drugs that will affect the disease at each of these stages.

Some biotech companies are already thinking about this. One approach is from Gordian Biotechnology, which is looking at MASH and other complex diseases related to aging. Gordian's mosaic screening combines gene therapy with single-cell sequencing and enables multiple drugs to be investigated in a single animal (for MASH, typically mouse or primate, but they use horse or primate models for other aging conditions). Multiple drugs can be barcoded and delivered to an organ and localized responses to each drug analyzed. Looking across a variety of animals could provide information on which drugs work best, in what phenotypes. Machine learning will also be helpful here.

Other companies are looking to move past the 'one target, one drug' approach and use more human-based models. Ochre Bio is developing RNA therapies targeted to the liver, using deep phenotyping of human-centric translational models. Cellarity has realized that a complex disease will likely need multiple protein targets and is using single-cell transcriptomics data combined with large perturbation datasets from human samples to find small molecules that could influence disease pathways.

The industry also needs to be more aware of patients and their disease stage during clinical trials. Often, people with MASH have comorbidities that can compromise trial results and lead to response heterogeneity. We know that obesity and type 2 diabetes are risk factors for MASH, but we do not know the exact interplay between the conditions.

There need to be enough participants and the trials must be long enough to show an effect in this slow-evolving disease. Looking at endpoints, it takes over a year to see fibrosis disappear. Furthermore, liver biopsies are the only way to measure progression without clear biomarkers, and biopsies are invasive.

While it is possible that GLP-1 agonists may help MASH at early stages, there are still uncertainties around their long-term use, and MASH is a long-term disease. Biopharma has failed in its attempt to find a 'one size fits all' solution, but companies can do better if they stop trying to cure the symptoms and instead try to understand the underlying pathology.

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