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EDITORIAL

All about NASH: disease biology, targets, and opportunities on the road to NASH drugs

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When it comes to unmet medical needs, nonalcoholic steatohepatitis (NASH), a progressive form of the nonalcoholic fatty liver disease (NAFLD), is definitely on the top of the list, affecting 1.5%–6.45% population and at least 100 million people worldwide. Over the past two decades, pharmaceutical and biotech companies around the globe have devoted extensive resources to the discovery and development of NASH drugs. Unfortunately, no NASH drug has been approved by FDA, EMA, or any other leading regulatory agencies as of today. The future for NASH drug discovery and development has faced tremendous uncertainty with capital investment into this field experiencing a "cold winter" since 2019. What are the biological basis and valid drug targets of NASH? What are the key regulatory issues? How to overcome the obstacles ahead on the road to the first NASH drug? In order to answer these questions, we invite ten experts and their colleagues to share their visions and insights into the challenges and opportunities of NASH drug discovery and development, from disease mechanism and origins, to therapeutic targets and diagnosis, and to treatment development and regulatory perspectives.

NASH is a complex disease but fundamentally a disorder from metabolic homeostasis that displays dysregulation of glucose, lipid, and bile acid metabolism. With the respects of lipid metabolism, the roles of bile acids have been long overlooked but started to attract more attention from researchers, because bile acids are the essential mediators for absorption of water-insoluble fats and cholesterols into liver and blood circulations. FXR, a bile acid nuclear receptor, is the master regulator of bile acid synthesis, excretion, and absorption. As such FXR has been a hot drug target for developing treatments for NASH, with many drug candidates into clinical trials. The first two articles by Xie and coworkers [1] and by Li and coworkers [2] will provide comprehensive review on bile acid biology, FXR structures, and drug discovery of NASH. In human body, our metabolism is subjected to cyclic control of circadian rhythm, for example, bile acid excretion adapts to daily cycles of up and down-regulation in response to food intakes. Breaking the metabolic cycles that follow the circadian rhythm could also result in metabolic disorders that lead to NASH. REV-ERB is an orphan nuclear receptor that plays key roles in controlling the metabolic rhythm in liver and its dysregulation could lead to NASH, which will be the subject reviewed by Burris and colleagues [3].

NASH is also characterized as excess of nutrition and energy, which exhibits exacerbated accumulation of fats in the liver and other peripheral tissues. Mitochondria is the power generator of cells and its homeostasis is key to the health of liver. The biology of mitochondria homeostasis and its role in liver steatosis to NASH will be reviewed by Li and colleagues [4]. Glucose is the preferred carbon source for all living organisms and glucose imbalance has caused many diseases, including diabetes and NASH. In human, glucose metabolism is tightly regulated by metabolic hormones, including insulin, glucagon, and glucagon-like peptide 1 (GLP-1). GLP-1 and its mimetics have been used successfully to treat diabetes and are in clinical trials for NASH, which will be reviewed by Wang and colleagues [5]. Besides the traditional protein targets for NASH, microRNAs are emerging to play key roles in regulating metabolism and NASH disease progression, in addition to serving as NASH biomarkers. Numerous microRNAs have been shown to promote NAFLD pathogenesis and progression through increasing lipid accumulation, oxidative stress, mitochondrial damage, and inflammation. The miR-23-27-24 clusters, composed of miR-23a-27a-24- 2 and miR-23b-27b-24-1, have been implicated in various biological processes as well as many diseases. Niu and colleagues review the current knowledge on miR-27, miR-24, and miR-23 in NAFLD/NASH pathogenesis and discuss their potential significance in NAFLD/NASH diagnosis and therapy [6].

Since many unsuccessful attempts for NASH drugs have been made over the past years, the current pipeline will be both valuable and informative to companies and professionals in this field. Wu and colleagues review the recent advancements in the development of NASH drugs, focusing on efficacy and safety profiles of therapeutic candidates currently in phase II and III trials. They anticipate that with the improved understanding of NASH pathogenesis and critical endpoints, effective therapeutics with an acceptable safety profile will be available for the treatment of NASH in the foreseeable future [7].

In patients with NASH, the fibrosis stage is the most predictive factor of long-term events. Although some novel drugs have shown promise in preclinical studies and led to improvement in terms of hepatic fat content and steatohepatitis, a considerable proportion of them have failed to achieve histological endpoints of fibrosis improvement. In this review, Fan and colleagues discuss current definitions for the evaluation of treatment efficacy in fibrosis improvement for NASH patients, and summarize novel agents in the pipeline with different mechanisms [8]. The challenges in the development of novel agents for fibrotic NASH and NASH cirrhosis are also summarized.

In order to study disease progression and effectiveness of an investigational drug, we need to have a pair of "eyes" to examine patients. Although non-invasive diagnosis methods are ideal and under intensive studies, it is expected that liver biopsy will remain as the key standard of NASH diagnosis in the coming years. Currently liver biopsy is used as the main inclusion criteria and the primary therapeutic endpoint in NASH clinical trials. FDA and EMA guidance indicates that for clinical approval of new drugs in the treatment of NASH, trials should include patients who have liver biopsy-proven NASH with stage 2 fibrosis or higher. Although liver biopsy is of great value, it is facing unprecedented challenges for patient enrollment and safety. You and colleagues review the value and challenges of liver biopsy in the development of new NASH drugs [9].

Despite official agency guidance, the regulatory pathway to ultimate product approval remains unclear due to both the extrahepatic factors that contribute to NASH as well as the organizational structure of FDA, with its traditional separation of

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therapeutic indications within discrete review divisions. Harvey reviews regulatory considerations for clinical development and criteria for FDA approval of NASH drugs [10]. He indicates that the regulatory process will continue to evolve around clinical trial endpoints to support NASH treatment approval, which includes both liver-based and traditional metabolic measurements.

Tremendous challenges remain for understanding the disease mechanisms and for developing treatments for NASH. Despite these challenges, we have witnessed great technological breakthroughs in gene editing, genomic sequencing, proteomics, large-scale chemical synthesis, and RNA-based drugs in recent years. With the focus on the unmet medical needs of NASH and additional investments into this field, we expect that the field of NASH is positioned to launch into a rapid advancement phase with respects to basic science and therapeutic development. We hope that this special issue, with collection of 10 reviews dedicated to NASH, will provide valuable insights into NASH biology, drug targets, diagnosis and regulatory issues that would ultimately lead to FDA-approved drugs for NASH.

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