*Forum Minireview***Novel Findings for the Development of Drug Therapy for Various Liver Diseases:
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1-8 Yamadaoka, Suita, Osaka 565-0871, Japan**Received January 5, 2011; Accepted January 6, 2011***Keywords:** hepatitis C virus (HCV), non-alcohol fatty liver disease (NAFLD), non-alcohol steatohepatitis (NASH), liver failure, liver cirrhosis, liver disease

The liver is one of the most important organs associated with digestion, detoxification, production, and storage. Steady progress has been made in the field of hepatology in recent years. More and more clinicians and basic scientists are attracted to this field, resulting in tremendous progress in understanding various aspects of hepatology in recent years. Today "Hepatology" is accepted as an established distinct specialty in the broad discipline of "Gastroenterology". Over the past 2 decades, breakthrough antiviral therapies for chronic hepatitis C virus (HCV) infection and chronic hepatitis B infection have been developed, such as interferon therapy and nucleoside analog reverse transcriptase inhibitor therapy, respectively (Table 1). However, numerous problems still remain to be resolved. Interferon therapy (pegylated interferon α -2a or 2b plus ribavirin) is effective in only 50% of patients with HCV genotype 1 infection, and viral breakthrough is possible due to the emergence of drug resistance in chronic hepatitis B. Furthermore, along with the westernization of lifestyles, the prevalence of a new metabolic-related hepatic disease named non-alcoholic fatty liver disease (NAFLD) has been increasing in recent years around the world. NAFLD can be categorized into non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). NAFL has a relatively benign clinical course, but is not entirely without histological consequences. NASH is

histologically progressive and can lead to cirrhosis or be associated with liver dysfunction. The estimated rate of development of cirrhosis over a period of 10 years is about 20%.

Therefore, the possibility of progression to cirrhosis and liver failure in the present should also be considered. The mechanisms underlying the development of these diseases and the effects of therapy need to be investigated for the development of new effective therapies.

The purpose of the present review is to introduce the latest progress in elucidating the mechanisms of development of these diseases and to discuss the application of the information thus gained to the development of appropriate drug therapies for liver diseases.

HCV was discovered in 1989. Currently, approximately 200 million people around the world are estimated to be chronically infected with HCV. Chronic HCV infection often leads to hepatic cirrhosis and hepatocellular carcinoma, thus posing a worldwide problem, both from the medical and the socioeconomical aspect. In this Forum Minireview series, the first article presented by Sugiyama and colleagues provides clear evidence to suggest that genetic variation of the *IL-28B* gene is associated with the quality of response of the patients to pegylated interferon α plus ribavirin therapy for chronic hepatitis C (1). Until now, the response to interferon therapy has been discussed from the viewpoint of viral factors, such as the virus genotype, viral titers, and the amino acid pattern in the interferon sensitivity-determining region of the viral genome (NS5A, etc.). In recent years, single-nucleotide polymorphisms (SNPs) (ap-

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Table 1. Brief history of hepatitis B, hepatitis C, and non-alcoholic fatty liver disease (NAFLD)

Year	Hepatitis B	Hepatitis C	NAFLD
1960 – 1970's	Hepatitis B virus was discovered in 1963		Chronic liver disease associated with obesity was first reported in the late 1970s
1970 – 1980's		Post-transfusion hepatitis non-A, non-B hepatitis	Ludwig described NASH as a novel liver disease in 1980
1980 – 1990's	Effective vaccines for HBV available since 1982	The hepatitis C virus was discovered in 1989	
1990 – 2000's	i) FDA approved use of <u>interferon-α</u> for treatment in 1992 ii) FDA approved use of <u>lamivudine</u> for treatment in 1998	i) FDA approved use of <u>interferon-α</u> for treatment in 1991 ii) FDA approved use of <u>interferon-α plus ribavirin</u> for treatment in 1998	First National Institute of Health Consensus Conference about “NASH” was held in 1998
2000 – 2010's	i) FDA approved use of <u>adefovir dipivoxil</u> for treatment in 2002 ii) FDA approved use of <u>entecavir</u> for treatment in 2005 iii) FDA approved use of long-acting interferon (peginterferon α -2a) for treatment in 2005 iv) FDA approved use of <u>telbivudine</u> for treatment in 2006	i) FDA approved use of <u>pegylated interferon α-2b</u> for treatment in 2001 ii) <u>Pegylated interferon α-2b plus ribavirin</u> was also approved in 2001 iii) Use of <u>pegylated interferon α-2a</u> for treatment was approved in 2002 iv) Use of <u>pegylated interferon α-2a plus ribavirin</u> for treatment was also approved in 2002	Currently, no specific therapies for NASH exist. Pharmacological trials are as follows: Aim to improve insulin sensitivity and modify underlying metabolic risk factors. i) Insulin-sensitizing agent (metformin, pioglitazone, troglitazone, rosiglitazone) ii) Lipid-lowering medications (statins, fibrates, ezetimibe) iii) Antioxidants (vitamin E, vitamin C) iv) Hepatoprotective agents (betaine, ursodeoxycholic acid, pentoxifylline) v) Angiotensin-converting enzyme inhibitors

proximately 1/500 – 1/1000 base pairs and more than 1% of the population) have been intensively investigated in many diseases. Identification of disease-associated SNPs and their detection through genome-wide association study (GWAS) (useful for detecting from 300,000 to 900,000 SNPs simultaneously) are thought to be useful tools for exploring genetic factors involved in the development of diseases and the response to therapies. In this study, GWAS identified host genomic factors (*IL-28B*) that might affect the response to interferon therapy. The detection of SNP of *IL-28B* could improve the rate of prediction of spontaneous clearance and the response to interferon therapy in patients with viral hepatitis C. Furthermore, *IL-28B* belongs to the interferon- λ family, and interferon- λ has been reported to inhibit HCV replication to the same degree as interferon- α at low concentrations. This novel finding could lead to the development of a novel therapeutic strategy for this infection. In addition, the development of a new protease inhibitor and vaccine are expected for the treatment/prevention of hepatitis C.

In 1980, Ludwig et al. described NASH, the most serious form of NAFLD, as a novel liver disease. In recent years, the number of obese patients has been steadily increasing, and obesity has become a major cause of morbidity and mortality in the US since the 1990s. Also,

obesity has come to be recognized as one of the most important risk factors for NAFLD. Therefore, the report by Ludwig et al. has had a great impact on the management of patients with NAFLD since the late 1990s. The estimated number of patients with NAFLD has reached 80 – 100 million in the U.S., and 10 million NAFLD patients are estimated to exist even in Japan. Furthermore, effective drug therapy for NASH has not been established yet. Since it is unclear what pathways might be involved in the pathogenesis and progression of NASH in its common form, identifying the mechanisms responsible for the progression of NASH would be helpful for devising effective therapeutic strategies for this disease. In the second article, Fujita and colleagues investigated the role of hepatic mitochondrial triglyceride transfer protein (MTTP), a key factor for triglyceride (TG) transport, in the development of NASH (2). They showed that the hepatic expression of MTTP mRNA was impaired in NASH patients as compared with that in NAFL patients. Furthermore, because both genetic and environmental factors have been revealed to be important for the development of NAFLD, Fujita also reported that NASH patients tend to have a much higher incidence of SNP of MTTP. Therefore, induction of hepatic MTTP expression could be a potential drug target in NASH. However, since the pathogenesis of NASH is thought to be hetero-

geneous, it is necessary to continue to explore the causes of NASH other than that MTPP SNP. Moreover, NASH is a part of the metabolic syndrome, and it is necessary to pay attention to the disease in a holistic manner. Currently, no specific therapies for NASH exist. The most important recommendations given to persons with this disease at present are to reduce their body weight (if obese or overweight), follow a balanced and healthy diet, increase their daily physical activity level, avoid alcohol, and avoid unnecessary medications. These are standard recommendations, but they can make a difference. They are also helpful for other conditions, such as heart disease, diabetes, and high serum cholesterol. People with NASH often have other medical conditions, such as diabetes, high blood pressure, and elevated serum cholesterol. These conditions should also be treated with medications and adequately controlled; the presence of NASH or elevated liver enzymes should not lead to avoidance of treatment of these other conditions. Actually, NAFLD has been reported to be associated with an elevated risk of cardiovascular events among type 2 diabetic patients. According to one theory, the cause of death among patients with NASH is more often cardiovascular disease or non-liver malignancy than cirrhosis.

Despite the benefits accruing from therapy for various liver diseases, treatment does not always succeed in all the people. Due to its large blood supply, the liver has some remarkable regenerative properties. The liver can compensate for a significant amount of damage, but eventually a threshold is reached and liver functions decline markedly, resulting in liver decompensation. The common signs of liver decompensation are as follows: abnormal clearance of proteins absorbed through the intestinal tract, resulting in ammonia retention and hepatic encephalopathy, and abnormal excretory function of the liver leads to accumulation of bilirubin in the blood, producing jaundice. In addition, increased sinusoidal pressure, such as with severe inflammation or scarring of the liver, leads to fluid accumulation in the abdomen (ascites) that becomes more difficult to control with progressive liver decompensation. In the end, scarred liver tissue acts as a barrier to blood flow and causes increased portal blood pressure (portal hypertension). A major consequence is the rupture of esophageal varices, causing massive and potentially fatal bleeding. The manifestations of liver decompensation, such as hepatic encephalopathy, ascites, variceal bleeding, and elevation of the serum bilirubin can seriously affect the patients' quality of life (QOL). In patients who are unsuitable candidates for liver transplantation (advanced age, non-availability of donor, other organ failure, etc.), not much can be done but to treat the symptoms as they appear.

The third article presented by Takami and colleagues

shows the epoch-making study that revealed the possibility of liver regeneration by administration of autologous bone marrow infusion (ABMi) (3). Takami and colleagues has been conducting a clinical study since 2003, based on the data from an abundance of basic studies. Without adverse effects, the clinical features of decompensated liver cirrhosis, such as reduced serum albumin levels, reduced total protein levels, and elevated Child-Pugh Scores, have improved significantly in many patients participating in this study. Now, since liver transplantation is recognized as the only curative therapy for decompensated liver disease, more and more progress of this liver regenerative study is required to improve the possibility of treatment of decompensated liver disease. ABMi is pioneering research in the field of regenerative medicine and offers the promise of fruitful use of induced pluripotent stem cells (iPS cell) and embryonic stem cells (ES cell) in the future.

Apart from the diseases covered in this forum mini review, a number of other diseases, such as alcoholic hepatic disease, autoimmune liver disease, and hepatocellular carcinoma still remain to be discussed. Especially, the development of new molecular-target drugs for hepatocellular carcinoma is desired.

Furthermore, various liver diseases can influence the functioning of other internal organs, including the kidney (hepatorenal syndrome), lungs (hepatopulmonary syndrome), heart, and brain (hepatic encephalopathy). Furthermore, recent epidemiological studies have suggested that HCV infection is associated with an increased risk of development of type 2 diabetes mellitus (DM), irrespective of the presence of hepatic cirrhosis. In addition, type 2 diabetes and higher BMI have been reported to be associated with an increased risk of hepatocellular carcinoma. It is important to clarify the relation between diabetes, hyperlipidemia, and various liver diseases (including malignancy) because this might facilitate the development of appropriate drug therapies and new medications for the liver diseases. Therefore, a cohort study focused on holistic involvement of the body is also necessary.

This forum minireview is based on the symposium on "Novel Findings for the Development of Drug Therapy for Various Liver Disease" held at the 83rd Annual Meeting of The Japanese Pharmacological Society held in Osaka on March 14, 2010. The authors hope that this forum minireview series will help the readers gain a better understanding of various liver diseases and promote the application of this knowledge for the development of appropriate drug therapies for these diseases.

References

- 1 Sugiyama M, Tanaka Y, Nakanishi M, Mizokami M. Novel findings for the development of drug therapy for various liver diseases: Genetic variation in *IL-28B* is associated with response to the therapy for chronic hepatitis C. *J Pharmacol Sci.* 2011;115:263–269.
- 2 Fujita K, Imajo K, Shinohara Y, Nozaki Y, Wada K, Yoneda M, et al. Novel findings for the development of drug therapy for various liver diseases: Liver microsomal triglyceride transfer protein activator may be a possible therapeutic agent in non-alcoholic steatohepatitis. *J Pharmacol Sci.* 2011;115:270–273.
- 3 Takami T, Terai S, Sakaida I. Novel findings for the development of drug therapy for various liver diseases: Current state and future prospects for our liver regeneration therapy using autologous bone marrow cells for decompensated liver cirrhosis patients. *J Pharmacol Sci.* 2011;115:274–278.