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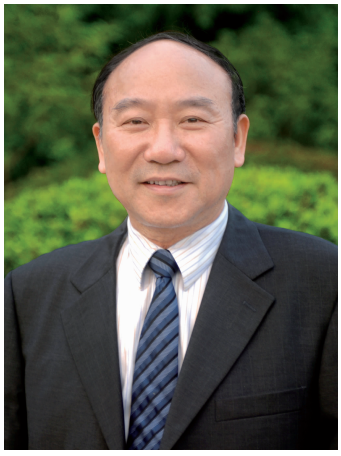
Monograph



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Editor's note：*Translational medicine helps with predicting，preventing，diagnosing，and treating of diseases. Here the author has addressed the clinical needs in diagnosing，drug developing，artificial liver and liver transplantation，cell transplantation and tissue engineering for hepatitis B virus（HBV）-related liver diseases（including carcinoma and hepatic failure）. Furthermore，the author argues that the integration of basic，clinical and translational researches will facilitate effective translation of basic findings into clinical applications in predicting，preventing，diagnosing，and personalized therapeutics of hepatic diseases，which is a lofty challenge in this field.*

# Translational research on the treatment of HBV related end stage liver disease in China

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The morbidity and mortality rates of various chronic diseases including malignancy remain high，despite great progress has been achieved in preclinical basic research by widely application of "-omics" technologies such as genomics，proteomics and metabonomics over the past 30 years. Therefore，in order to timely employ achievement of basic research into public health service development，translational medicine has emerged to be the bridge connecting basic research and daily clinical practice. The fundamental purpose of medical research is to lower mortality rates and reduce incidences of diseases which improve people's health and life quality，to fulfill this idea，translational medicine which sits in the intersection of "bench to bedside" aims to break the barriers between basic research and clinical practice，promote the two-way rapid transformation，ultimately improve general public's healthcare. With the encouraging perspective that benefit patients，the major tasks of translational research shall focus on investigating crucial problems of key diseases including HBV related end stage liver disease which will assist physicians to diagnosis and treat patients better in the near future.

Since 2003，developed countries like United States，member states of European Union and Japan have started to establish translational medical centers. Among them，over 60 centers have been set up so far across U. S. A with annual support of $ 500 million in translational research. Meanwhile，"National Outline of Medium-and Long-Term Program

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for Science and Technology Development (2006 to 2020)" which published by the Chinese State Council pointed out the ultimate goals of national science and technology development in the field of Population and Health are "noticeably enhancing the level of major diseases prevention and control, curbing the spread of major diseases, including HIV/AIDS, hepatitis and other major diseases, striving for breakthroughs in new drugs and key medical equipment, and developing a technological capability for industrialization." For this purpose, the major scientific projects of "Prevention and control of major infectious diseases such as AIDS and viral hepatitis" and "Significant new drugs development" were specifically set up by state to support research in these key fields during "the 11th National Five Year Plan", which in turn has greatly drew active participation of translational medicine researchers. Although China's translational medicine research just started within recent 2 years, more and more translational medicine research centers has been established in various medical facilities. Combining with their own disciplinary academic advantages respectively, all these centers are striving to seek for ground-breaking progress in translational medicine research. Until now, many promising novel ideas, innovative methods and technologies have been under development, we hope these products generated by translational medicine centers one day could be used in clinical practice prolonging survival time and improving life quality of patients. With these firmly ground work, we are looking forward to a fruitful future of Chinese translational medicine research.

## 1 The diagnosis and treatment of HBVrelated liver diseases and translational medicine research

Hepatitis B is one of the common chronic infectious diseases in China. It is estimated that there are about 100 million HBV carriers and roughly 30 million hepatitis B patients, among which 5 to 8 million patients will end up with severe liver cirrhosis and liver cancer, while the prevalence of HBV is relatively limited in Western countries. Translational medicine research on "the Diagnosis and Treatment HBV-related Liver Diseases" is an important component of the China's state key program "prevention and control of major infectious diseases such as AIDS and viral hepatitis" and is also a major area gets long term support from our country's multiple basic and clinical research grants. In order to reduce the morbidity and mortality of HBV-related liver diseases in China effectively, how to make the timely translation of the achievements of basic research to clinical application remains the primary task of this key program in the next 5 years known as Chinese central government's "the 12th Five Years Plan" period.

## 2 Research and development of novel medications for Hepatitis B

Currently antiviral therapy is the most effective treatment for HBV infection among immune therapy, anti-fibrosis therapy, gene therapy and psychological therapy. The ideal termination point for antiviral treatment is undetectable HBsAg with or without anti-HBs positive; sustained HBeAg seroconversion is the satisfied termination point; basic termination point of therapy is sustained negative HBV-DNA. The current primary medications used to treat HBV are interferon-α (α-IFN) and nucleoside analogues. Interferon including normal interferon (e. g. Interferon alfa-2b Injection, Roferon) and pegylated interferon (e. g. Pegintron, Pegasys) exhibits immune-mediated anti-HBV effects. It is characterized by its limited course of treatment, no drug resistance and high seroconversion rate of HBeAg and HBsAg, however, it, the other side, shows average performance in inhibiting HBV replication and poor patient compliance due to its administration method of subcutaneous injection. Nucleotide analogues can be divided into three types: L-nucleotides (e. g. Lamivudine, Telbivudine, Emtricitabine, and Clevudine), acyclic phosphate compound classes (e. g. Adefovir Dipivoxil, Tenofovir) and cyclopentane/vinyl (Entecavir). The main profile of nucleotide analogues treatment is strong efficacy in suppressing of HBV replication and good patient compliance and tolerance with oral administration, but its application is limited by shortcomings consisting of high rate of drug resistance mutations, low rate of HBeAg and HBsAg seroconversion, incapability to reach the satisfied termination point of treatment, and unpredictable course of treatment. Global pharmaceutical companies have always been being dedicated into intensive development of these two categories of medications producing various products mentioned above, especially PEG-interferon. In China, a number of class 1 novel medications with independent intellectual property have been being tested in clinical trials during "the 11th Five-Year Plan" period, such as "Y-PEG-recombinant human interferon α2b" and "recombinant human serum albumin-interferon α2b fusion protein injection". In addition, immunomodulatory therapy discovery like HBV vaccine is also a long-term research emphasis for Chinese scientists, such as currently undergoing clinical trials of PEG thymosin α1 and therapeutic (synthetic peptide) hepatitis B vaccine. Both clinical trials designed for novel targeted medications on distinctions of patient gene polymorphisms, epigenetics, HBV genotype, and

progression of diseases, and establishment of personalized therapy guideline are historic missions for translational medicine researchers who devoted in HBV-related liver disease.

## 3 The diagnosis and treatment of liver cancer and translational medical research

China has the highest incidence as well as mortality worldwide. In 2010, there were 418 000 new cases and 380 000 liver cancer related deaths, which made it the second cause of cancer death and become a major national healthy problem in China. Liver cancer can cause a chronic illness with an insidious onset and then a rapid progress, accompanied with post-hepatic cirrhosis in over 85% patients. As a result, most cases were not detected until advanced stage, among which only close to 20% could be treated by surgery. However, the recurrence rate in 5 years after surgery is up to 50% to 70%, while the 5-year survival rate is close to 5%. During the last decade, a lot of novel achievements have been made in fundamental research of liver cancer, such as the impact of liver stem cells and the specific micro-environment on tumor genesis and the determination of whether the primary liver cancer and the recurrent hepatocellular carcinoma has the same origin or not through molecular cloning. All these will have a major positive impact on prevention and early diagnosis of liver cancer, and how to apply these to the clinical will remain the emphasis in translational medical research on HBV-related liver cancer. At the present, although the surgery-oriented multidisciplinary treatment of liver cancer (including surgical resection, radiological interventions like TACE and RF ablation, systemic chemotherapy, molecular targeted therapy, radiation therapy, integrated Chinese-Western therapy and so on) has become the primary approaches to better outcomes, it should be taken into account that the current guidelines or consensus for liver cancer treatment are mostly established on clinical experience, retrospective studies of clinical data, and foreign achievements. There are few clinical evidence that can support these guidelines or consensus, and the exact effects of each therapy are still contentious. So far, as no standards on the liver cancer management are available in China, it's necessary to coordinate and conduct the researches on the combination of different therapies, and to develop scientific strategies for liver cancer prevention and control. A standard on liver cancer management proceeding from China's reality will then be established to comprehensively utilize current therapies, improve the overall survival rate of liver cancer patients, and reduce the recurrence after surgery.

## 4 Artificial liver therapy for liver failure and translational medical research

The liver failure caused by HBV-related severe hepatitis is common in China. The mortality would be as high as 50% ~80% when the artificial liver supporting system cannot be used immediately to maintain the electrolyte balance and excrete toxins. Non-biological artificial liver supporting system can balance the internal environment by exchanging plasma and adsorbing bilirubin and hemodialysis. And it has been sufficiently developed and widespread in China at present. Otherwise, the immortalized human hepatocyte-derived bio-reactor presents the basic functions of normal liver cells, such as synthesis of albumin and blood coagulation factors, gluconeogenesis, and metabolism of toxins. Excitingly, the self-developed bio-artificial liver supporting technology has been developing rapidly, and will enter clinical trials in China soon. More early predictive parameters and novel prognostic indicators for liver failure will be uncovered to facilitate the clinical application of this bio-artificial liver supporting system. As basic research has been mostly finished, the clinical applications of these achievements in clinic come to the focus of the future translational medical research on HBV-related liver diseases.

## 5 The translational medical research on liver transplantation

At the current stage, liver transplantation is the only effective therapy for HBV-related end-stage liver diseases, and the recipients may promise a long-term survival with high life quality. Although the liver transplantation technology in China has been well-developed and applied broadly, there are still many problems remain to be resolved, such as the immunologic rejection, the shortage of donors, the recurrence of original diseases after transplantation as well as chronic graft failure. In recent two decades, lots of basic and clinical researches sponsored by the national "863 Program", "973 Plan" and the "11$^{th}$ Five-Year Key Program" have been carried out, and some important achievements have been made, such as individual immunosuppressive regimen, the prevention of HBV recurrence after transplantation by HBIG combined with lamivudine, the recruiting criteria of liver transplantation for liver cancer patients according to tumor biological markers, living donor liver transplantation, split liver transplantation, and legislation of brain death. However, more achievements like new immunosuppressive agents and immunosuppressive regimen, marginal graft, heterotransplantation, immune tolerance after transplantation, and prevention of chronic graft failure, are still de-

manding for perfection, and further translational medical research will be needed to promote their clinical application. Liver transplantation, as the leading age technology in modern medicine and representing for the large organ transplantations, suggests that biomedical researches and clinical practice are complement each other, which is the main trend in two-way translational medical research in China at present.

## 6 Cells and tissue regeneration medicine

Regenerative medicine restores or establishes normal function by replacing or regenerating human cells, tissues or organs and is considered as a potential therapy in future. For those patients with end-stage liver disease, an effective approach with a combination of cell transplantation and artificial liver support will be needed to established. Importantly, based on cell transplantation, regenerative medicine has the potential to solve the problem of the shortage of organs available for donation, as well as solves the problem of organ transplant rejection. A recent study from H Salama *et al.* showed that 48 patients with end-stage liver disease who received autologous hematopoietic stem cell transplantation had long-term survival benefit with better liver function. Although administration of high does G-CSF might attribute to such improvement by bone marrow mobilization during treatment. Compared with other graft types, autologous hematopoietic stem cell transplantation has avoided the potential immunogenic or tumorigenic risks. First we should evaluate the benefit and disadvantage, and then make a personal optimal therapeutic regimen. How to convert this technology into clinical application is a question needed to be solved as soon as possible for the translational medical research in China.

## 7 Sample collection and storage system construction

China with the largest population in the world has high incidence of many diseases. For example, there are nearly 100 million HBV carriers in China and it's a big burden for Chinese health care system. It also constitutes the biggest "clinical sample bank", facilitating the development of translational medical research. Over the past decade, many large medical institutions in China have established scientific specimen banks and follow-up databases, which are the important foundations for translational medicine. To establish a standard therapeutic approach of HBV-related diseases, based on environment, lifestyle and genetic factors, needs extensive verification in multi-area with a large sample size, by using of high-throughput and ultra high-throughput detection technology, analyzing mass data , founding multi-center study with a large sample size and basic validation, developing new medications or new methods, making multi-center pre-clinical and early phase clinical trials, and applying new achievements. With the help of translational medicine, researchers will find more effective ways to solve the healthy problems of Chinese people.

## 8 Summary

Previously the key point of treatment chronic diseases, such as HBV-related liver disease, is prevention and early detection. And now translational medicine integrates research from the basic science, clinical trials and experience from Chinese traditional medicine with the aim of optimising patient care and preventive measures which may extend beyond healthcare service. For HBV-related liver disease, improved detection may translate into better survival and individualized treatments establishment may lead more efficacious and safe therapy. Translational research thus informs guidelines about needs, acceptability, effectiveness, and cost efficiency in ecological settings and policies to promote uptake for optimal management and resource use.

It is a tough history of struggling with diseases. The translational medicine starts its first step in China as a new concept. It will integrate research from the basic sciences, social sciences and political sciences in the future and will aim to improve the health of the Chinese populations. Opportunities come along with challenges and nothing is impossible.