厚生労働科学研究費補助金

社会保障国際協力推進研究事業

主にアジアに蔓延するウイルス性肝疾患の制御に資する為の日米合作的肝炎ウイルス基礎研究

平成20年度　総括研究報告書

主任研究者　三代　俊治

平成21年(2009)4月

目次

I. 総括研究報告

厚生労働科学研究費補助金 社会保障国際協力推進研究事業(国際医学協力研究事業)
平成20年度

総括研究報告書

主にアジアに蔓延するウイルス性肝疾患の制御に資する為の日米合作的肝炎ウイルス基礎研究(H20-国医-指定-007)

主任研究者 三代 俊治 東芝病院研究部長

要旨: 本研究は、日米醫學協力研究會(以下"USJCMSP"乃至『日米醫學』と略す)の肝炎専門部會(Hepatitis Panel)の活動の一環として實施された。日米醫學肝炎部會が、亜細亜に広く蔓延する肝炎ウイルスとしてB型とE型(HBV, HEV)を、将來の感染拡大が懸念される肝炎ウイルスとしてC型(HCV)を主要研究標的として定めたことに呼應し、本研究班の今年度の研究活動も此の三種に關するものであった。2008年10月3日に東京で開催した第30回USJCMSP Hepatitis Panel 日米合同會議では、中国の肝炎事情をテーマに日中米で討議した。また、本年度は肝炎部會がUSJCMSPのFive-Year-Reviewの對象部會に選ばれ、従前の活動實績並びに今後の活動方針が厳しく審査された結果、幸いにも高い評価を得ることができた。

A.人的構成

＜主任研究者＞

三代俊治　東芝病院研究部部長(USJCMSP『部會長』)

＜分担研究者＞

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脇田隆字　国立感染症研究所ウイルス第二部部長(USJCMSP『部會員』)

考藤達哉　大阪大学大学院医学系研究科樹状細胞制御治療学准教授

＜研究協力者(USJCMSP『部會員』)＞

林 紀夫　大阪大学大学院医学系研究科消化器内科学教授

＜研究協力者(同上『研究員』)＞ abc順

茶山一彰　広島大学大学院医歯薬学総合研究科分子病態制御内科学教授

榎本信幸　山梨大学医学部第一内科学教室教授

樋野興夫　順天堂大学医学部病理学教授

井廻道夫　昭和大学医学部第二内科学教室教授

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熊田博光　虎の門病院副院長

松浦善治　大阪大学微生物病研究所エマージング感染症研究センター教授

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小俣政男　東京大学大学院医学系研究科消化器内科学教室教授

恩地森一　愛媛大学医学部第三内科学教室教授

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吉澤浩司　広島大学大学院医歯薬学総合研究科疫学・疾病制御学教室教授

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Adrian Di Bisceglie　Saint Louis University School of Medicine

Michael Gale　University of Texas Southwestern

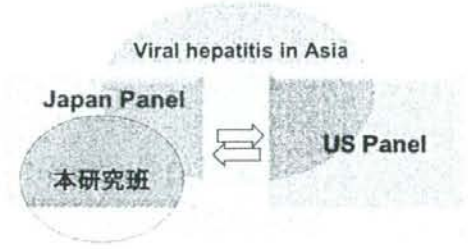
Rajen Koshy	NIAID, NIH
Anna Lok	University of Michigan
Christopher Walker	The Ohio State University

＜研究協力者(班長施設内)＞

SMF Akbar	東芝病院研究部
高橋和明	同上
新井雅裕	東芝病院消化器内科

B. 研究目的

日米の肝炎専門家が協力しアジア諸国の肝炎・肝癌の制御に貢献する(下圖参照)。



C. 研究方法

上記した目的の達成に向けて、班員の夫々が下記 D 及び各論で述べる夫々の方法を用いて研究を實施した。

＜倫理面への配慮＞

行った全ての研究は，個人情報保護を旨とする倫理規定を厳守しつつ行われた。

D. 研究結果及び考察

1. HCV の細胞培養:

CD81 が感染感受性に重要であり、Huh 細胞の HCV 感染感受性は培養条件により変化することが明らかとなった。感染感受性に関わる宿主因子の同定に向けた研究を継続する必要がある(脇田班員)。

2. HBV の分子疫學:

今年度の研究で、2 種類の新たな HBV 組換え遺伝子型(r-HBV)を含む合計 28 種類の r-HBV の存在が明らかとなった。その世界分布には地域特異性が存在した。r-HBV の臨床的意義についてはさらに検討を進める必要がある(溝上班員)。

3. HIV/HCV 共感染の實態把握:

我国に於ける調査から以下の知見を得た。HIV感染症に合併するC型慢性肝炎は、HIV非感染例に比して若年で肝硬変や肝癌へと進行していた。C型肝炎に対するリバビリン併用 PegIFN 療法の治療成績は、HIV 感染例においてHIV 非感染例に比してやや低めであった。副作用はHIV非感染例と同等かそれ以上に強く、特に、HAART 施行中は副作用の発生が多かった。これらの知見は、今後の診療、日米医学協力、アジアの肝炎との比較検討において有用と考えられる(小池班員)。

4. HBV・HCV 感染の免疫:

C 型肝炎、B 型肝炎患者のミエロイド DC (MDC)を HCV NS3/4A 阻害剤や抗 HBV 核酸アナログで処理するとサイトカイン産生能が回復した。ウイルス肝炎患者 MDC における TLR/RIG-I の機能低下は、DC が病原体感染を十分に感知できず、効果的に免疫系を活性化できない可能性を示唆しているが、選択的抗ウイルス剤は MDC 機能の回復効果も期待できることが示された(考藤班員)。

5. 亜細亜に於ける HBV/HCV/HEV/HIV の疫學:

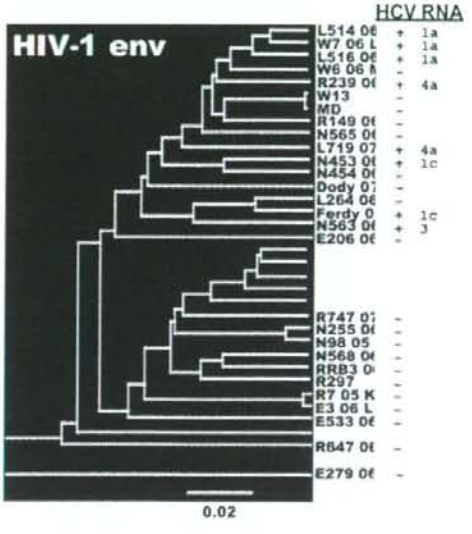
(1) バングラデシュ

首都ダッカの Bangabandhu Sheikh Mujib 醫大の Mamun Al-mahtab 醫師と共同研究を實施した。海外への出稼ぎ労働者の出國前檢診や献血の際のスクリーニング等により偶然發見された「無症状の HBV carrier」総計 310 名について、HBV viral load, HBeAg, Serum ALT を測定し、且つ全例に腹部超音波檢査と肝生檢を施行したところ、有意の necro-inflammation 所見が HBeAg 陽性者の 90.7%、HBeAg 陰性者の 45.3%に認められ、要治療患者が夛數潜在していることが示唆された。適切なガイドラインに従った治療を受けられるのは一部富裕層に限られる一方で、市中の藥局で誰でも処方箋なしに Lamivudine 等の抗ウイルス剤を購入し得るという同國の現状に鑑み、今後の問題として、不適切治療による病状の悪化や drug-resistant HBV mutants のスプレッドが危惧される。発展

途上國用の特別の「治療ガイドライン」を作成すべきかもしれない(三代班長)

(2) インドネシア

ロンボク島(バリ島の東)は夙に HBV 高侵淫地域として知られていたが、近年 HCV が HIV と共に同島に上陸し、以後急速にスプレッドしつつある。首都マタラムの HIV/AIDS Clinic の Wenny 室長との共同研究により HIV と HCV の遺伝子解析を試みたところ、HIV/HCV 共感染群と HIV 單獨感染群の間に HIV の遺伝子型の明らかな相違がみられた(下圖參照)。この相違が疫學的要因(感染経路等)によるのかウイルス學的要因(相互干渉等)によるのか今後の追求が必要である(三代班長)。



E. 日米合同會議

第30回USJCMSP Hepatitis Panel日米合同會議を、2008年10月3日、JDDW2008・日本肝臓學會・ウイルス肝炎研究財団等との共催で、東京都港区のグランドプリンスホテル高輪・新高輪で開催した。日米両國の部會員は一名(Anna Lok)を除き全員參集した。

同日午前に行なわれた business meeting では、(i) 肝炎部會にとって本年度の最大の關心事の一つであったFive-Year-Reviewが無事に終了したこと(其のreviewに供された文書を本稿の後續頁に「付録」として示す)、

(ii) 次年度の日米合同肝炎部會會議をAIDS部會と合同で9月にPortlandで開催すること、

(iii) 其のテーマはHIVとHBV/HCVのco-infectionの疫學・病理病態・治療に絞ること、

等が話し合われた。

午後に行なったscientific meetingでは、「中国病毒性肝炎和關連肝疾患的實態和對策(Reality and countermeasures for viral hepatitis and related liver disease in China)」と題するシンポジウムを組み、中国から招待した9名の研究者(陶其敏、遲寶榮、程留芳、王福生、劉玉蘭、霍繼榮、胡和平、劉杰、孟祥偉)と、北京に拠點を設けて日中合作的肝炎・エイズ研究を推進しつつある東大醫科研の岩本愛吉教授から、研究の現況を發表して貰い討議を行なった(下圖參照)。中国には凡そ1億人のHBV感染者が存在すると推定されている故、今後も經續して(より緊密な)日中米間の研究協力が必要であることが參加者により再確認された。


第10会場 (グランドプリンスホテル新高輪 平安)

14:00~17:00 肝臓学会特別企画 (肝臓学会)

USJCMSP Hepatitis Panel, VHPJ, MMRFとの共同開催 中国病毒性肝炎和関連肝疾患的実態和対策 (Reality and countermeasures for viral hepatitis and related liver disease in China)

司会 北京大 劉 玉蘭
司会 USJCMSP R. Koshy

肝特企2-1. Re-Opening Remarks for China-Japan Collaboration on Viral Hepatitis
BeiJing University People's Hospital, BeiJing, China Q. M. Tao

肝特企2-2. Prominence of Hepatitis B in Chinese Population
Jilin University, Chanechun, China B. R. Chi

肝特企2-3. Hepatitis B virus genotypes in Chanechun, China
Jilin University Chanechun, China X. W. Meng

肝特企2-4. Analysis of current epidemic situation of viral hepatitis in Hunan Province of China
Department of Gastroenterology, the 2nd XiangYa Hospital, Central South University, Changsha, China J. R. Huo, J. Zh. Ren

肝特企2-5. Correlation between HBV-DNA level and progression to cirrhosis in patients with chronic hepatitis B
Zhong Shan Hospital, Fudan University, Shanghai, China J. Wang

肝特企2-6. Grb7β knockdown inhibits invasion/metastasis of human HCC by interference with FAK phosphorylation, extracellular matrix remodeling in SMMC7721 cells
General Hospital of Chinese Liberation Army, BeiJing, China L. F. Cheng, Z. Li
Liaoning Medical College, Jinzhou, China R. J. Su

肝特企2-7. Molecular Features of Hepatocellular Carcinoma (HCC)
Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai H. P. Hu

肝特企2-8. Cloning and functional study of novel genes and their predicting value for HCC
Dept. of Digestive Diseases and State Key Laboratory for Cancer Biology, XiJing Hospital, The Fourth Military Medical University, Xi'an, China J. Liu

肝特企2-9. Immune modulators regulate HBV-specific CD8 T-cell function, affecting outcome of hepatitis B BeiJing 第2 Hospital, BeiJing, China F. S. Wang

肝特企2-10. China-Japan Joint laboratories for hepatitis virus research: a challenging project
Research Center for Asian Infectious Diseases, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan A. Iwamoto

10月3日

F. 米国側部會との共同プロジェクト

2年前の日米合同會議で議決された「藥剤耐性HBV変異株データベースの構築」という日米パネル共同プロジェクト(責任者=米国側 Anna Lok/日

本側溝上雅史)は、一回の telephone conference (日本からは班長研究協力者 SMF Akbar が参加)と一回の對面會議(香港での APASL 開催時にLok／溝上が會談)により實現可能性を模索したが、主として米国NIHからの資金援助が得られないという理由により、一頓挫の状態にある。

G. 日米肝炎の今後の方向性

學問の深化(眞實の追求)を怠ってはならない。しかし、それだけが本研究班の存在意義ではない。2006 年に日米間で合議した「肝炎部會五カ年計画 "Hepatitis Panel Guidelines (2006-2010)"」から再末尾のパラグラフを引用する。

Establish a collaborative research network in Asia and the Pacific Rim. A goal is to foster scientific exchange and forge collaborations with other Asia/Pacific Rim researchers, particularly with regard to the molecular epidemiology and pathogenesis of hepatitis B and E viruses that are major causes of liver disease in this region. Patterns of HBV drug resistance in Asian countries, and causes underlying increased drug resistance rates in some regions, is one focus of this effort. Small informal meetings will be used to launch and sustain multi-national research collaborations.

本研究班に參画する研究者は皆「その道のエクスパート」だから、黙っていても學問研究は進歩するだろう。しかし上記引用中で述べられているゴールは純粋學問的通常努力では達成され得ず、ラボワークを超えた特別の努力と良きチームワークを必要とする類いのゴールである。そもそも「亜細亜の為に」が USJCMSP のレゾンデートルである故、今後も本研究班が USJCMSP 肝炎部會を represent する存在であり續けるのであれば、上記の方向性を決して見失っては不可い。繰り返すが、本研究班は特別なミッションを背負った研究班であって、學術本位の研究班ではない。亜細亜の人々を肝疾患から解放する為に、今後も一層の奮闘努力が必要である(＝去り行く老兵からの遺言と御解釈頂き度い)。

H. 研究発表(此處には班長分あるいは班長研究協力者分のみ示す;班員分は研究成果一覧を參照)

Al-Mahtab Mamun, Rahman Salimur, Sheikh Mohammad Fazle Akbar et al. High HBV DNA load, HBeAg positivity and considerable hepatic necro inflammation in patients with incidentally detected, asymptomatic chronic HBV-infected individuals from Bangladesh. Hepatology 2008; 48(4): 690A (AASLD Abstract)

Al-Mahtab Mamun, Rahman Salimur, Sheikh Mohammad Fazle Akbar et al. Lack of correlation between viral load and extent of liver damages in patients with chronic HBV infection at Bangladesh. Hepatology 2008; 48(4): 690A (AASLD Abstract)

Kazuaki Takahashi, Hiroaki Okamoto, Natsumi Abe, Manri Kawakami, Hiroyuki Matsuda, Satoshi Mochida, Hiroshi Sakugawa, Yoshiki Suginoshita, Seishiro Watanabe, Kazuhide Yamamoto, Yuzo Miyakawa, Shunji Mishiro. A Virulent Strain (JIO) of Hepatitis E Virus Genotype 3 in Japan: Analysis of Complete or Near-Complete Sequences of Human and Swine Isolates. Emerging Infectious Diseases 2009 (in press)

Miyuki Taniguchi, Soo Ryang Kim, Shunji Mishiro, Kazuaki Takahashi, Myung Hee Shin, Haesun Yun, Man Suk Park, Li, Zhongmin, Kim Mi kyung, Fang Jinnv, Yoshitake Hayashi. Epidemiology of hepatitis E in Northeastern China, South Korea and Japan. Journal of Infection 2009 (in press)

Matsubayashi K, Kang JH, Sakata H, Takahashi K, Shindo M, Kato M, Sato S, Kato T, Nishimori H, Tsuji K, Maguchi H, Yoshida J, Maekubo H, Mishiro S, Ikeda H. A case of transfusion-transmitted hepatitis E caused by blood from a donor infected with hepatitis E virus via zoonotic food-borne route. Transfusion 2008 Jul; 48(7): 1368-75

Toyoda H, Honda T, Hayashi K, Katano Y, Goto H, Kumada T, Takahashi K, Abe N, Mishiro S, Takamatsu J. Prevalence of hepatitis E virus IgG antibody in Japanese patients with hemophilia. Intervirology 2008; 51(1): 21-5

I. 知的財産権の出願・登録状況

1. 特許:なし.
2. 実用新案登録:なし.
3. その他:なし.

＜付記＞

2009 年 2 月 24 日に配信された BBC news によれば、インドで大規模な HBV 集団感染が發生した(下圖參照)。2 週間の間に 43 人もの死者が出たという報道が眞實であるなら、このアウトブレイクに關與したウイルス株の高病原性が示唆される。誰かの手によって HBV genome analysis が實行されねばならないが、斯様な事例こそ『日米肝炎』の最大の關心事の一つであるから、「日米-亜細亜の肝炎研究ネットワーク」の構築が急がれる。

Page last updated at 06:42 GMT, Tuesday, 24 February 2009

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Gujarat starts mass vaccination

A mass vaccination of some 60,000 people has begun in India's western Gujarat state to ward off an outbreak of hepatitis B, officials say.

In the past fortnight, 43 people have died of the disease in Sabarkantha district, officials said.

Police are looking for a doctor who allegedly gave injections to many of the patients without changing syringes.

The hepatitis B virus is transmitted through contact with the bodily fluids of an infected person.

The virus can be transmitted via unprotected sex or sharing of contaminated needles. Pregnant mothers also tend to pass it on to their babies.

The police is looking for a doctor in connection with the outbreak

Absconding

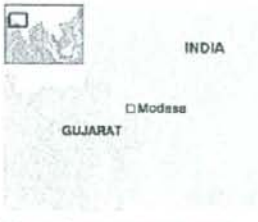
Sabarkantha district official M Thennarasan told the BBC another 80 people had been admitted to a local hospital with symptoms of hepatitis B.

He said that nearly 56,000 people in Modasa town, where people have been infected with the virus, had been vaccinated by government doctors on Monday.

The remaining 4,000 people in the town would be vaccinated on Tuesday, he said.

Federal and state health authorities are investigating the cause of the outbreak.

Early investigations had revealed that some of the patients had received injections from a local doctor who ran a clinic in the town a few months ago, Mr Thennarasan said.



"Some patients have said that the doctor had not changed syringes or used disposable ones during the injections."

Police are looking for the absconding doctor and his clinic had been sealed.

United States-Japan Cooperative Medical Science Program
5 Year Review of the Hepatitis Panels (2003-2008)

Membership

Current American and Japanese Members of the Hepatitis Panel are listed below. There has only been one recent change in membership. Professor Kunitada Shimotohno has resigned from the Panel because of retirement. Dr. Takaji Wakita of National Institute of Infectious Diseases has replaced Dr. Shimotohno. Dr. Wakita is a pre-eminent virologist who developed the most robust cell culture model available for studying replication of hepatitis C virus (HCV), which has been a longstanding major Research Objective 0f the Panel. He has international collaborations with others, including many American scientists, to unravel how HCV interacts with host cells. The Panel is fortunate to have a scientist with his expertise and international reputation in virology to replace Prof. Shimotohno.

Panel Members

United States

Chair

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(Chair 2004- ; Member 2004-)
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Japan

Chair

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Hepatitis Panel Guidelines (2006-2010)

Viral hepatitis remains a serious public health problem in Asia and the United States. Persistent infections with the viruses responsible for hepatitis B (HBV) and hepatitis C (HCV) are still a significant cause of morbidity and mortality with very limited treatment options. HBV replication is effectively suppressed by nucleoside analogues like lamivudine but the development of drug resistance on therapy is common and highly problematic. Whether resistant HBV variants emerge more frequently in some regions of Asia than others, perhaps due to inconsistencies in drug treatment regimens, is largely unexplored but could represent a substantial risk to public health. With regard to chronic hepatitis C, the only approved therapy (pegylated interferon and ribavirin) is toxic, expensive, and provides a sustained virologic response in less than 50% of infected individuals. How HCV resists interferon and other innate immune responses is only

partially understood. Recently developed cell culture models of HCV replication have the potential to reveal new viral evasion strategies and insights into treatment approaches. The link between subversion of innate immunity and ineffective adaptive immune responses in persistent hepatitis virus infections is also unclear, and at least for HCV this gap in our knowledge could represent a significant barrier to development of an effective vaccine. Chronic HBV and HCV infections also increase the risk of liver cancer but by molecular mechanisms of hepatocarcinogenesis that remain obscure.

Hepatitis E virus (HEV) is an enterically transmitted cause of sporadic acute hepatitis in Japan and large epidemics elsewhere in Asia. HEV is also present within the U.S. and is prevalent in commercial swine and poultry stock. However, its importance as a potential threat to agricultural interests is not well defined. There is strong evidence for occasional zoonotic spread in Asia. Recent studies by Panel members have demonstrated that HEV is harbored by a variety of wild and domesticated animal species, particularly swine, that are a potential source of zoonotic transmission to humans. A vaccine to prevent this infection is still not available. The virus is unique and has a number of novel molecular features concerning its structure and interactions with the host cell that remain poorly understood. Development and deployment of an effective preventive vaccine will ultimately require a better understanding of the molecular virology and immunology of hepatitis E, as well as the epidemiology and pathogenesis of HEV infection.

Hepatitis A virus (HAV) is also enterically transmitted, and remains an important, vaccine-preventable cause of acute hepatitis. The epidemiology of hepatitis A has undergone significant change in many Asian/Pacific Rim countries during the past two decades, with many shifting from high-moderate to moderate-low endemicity. This has been associated with a corresponding increase in the age of infection, from early childhood to early adult years. Importantly, HAV infections are significantly more severe when acquired after early childhood, suggesting that the region may see an increase in hepatitis A-related morbidity and more frequent disease outbreaks

The Joint Hepatitis Panels have expertise and interests in four broad research areas focused on these medically important hepatitis viruses, particularly HBV, HCV and HEV. The goals are to:

- Identify molecular mechanisms of hepatocellular injury and carcinogenesis in HBV and HCV infections that are likely to form the basis for more effective strategies to prevent and treat virus-associated liver disease including cancers that are a major public health problem in Asia. A related and very practical goal is to provide an explanation for the apparently higher rates of HCV-associated liver cancer in Japan versus North America.
- Develop an understanding of how persistent hepatitis viruses are controlled by, and subvert, *innate* immune responses to facilitate development of effective antiviral therapies and vaccines. This goal builds on expertise of the Panels in cellular and molecular innate immunity to HCV. Studies of intrahepatic natural killer (NK) cell activity and type I interferon responses in the HCV infected liver have the potential to provide a comprehensive picture of innate immunity and

why it fails in persistent hepatitis C. Observations in HCV infection will be contrasted with those in HBV infection through periodic joint meetings with experts in innate immunity to HBV.

- Develop an understanding of how persistent hepatitis viruses are controlled by, and subvert, *adaptive* immune responses. Why these responses fail, and how they might be restored by therapeutic intervention, is unknown. Mechanisms of viral evasion from T lymphocyte and antibody responses will be explored with a focus on HCV. Related is the goal of defining how disruption of innate immunity might alter or impair adaptive immune responses to facilitate HCV persistence.
- Establish a collaborative research network in Asia and the Pacific Rim. A goal is to foster scientific exchange and forge collaborations with other Asia/Pacific Rim researchers, particularly with regard to the molecular epidemiology and pathogenesis of hepatitis B and E viruses that are major causes of liver disease in this region. Patterns of HBV drug resistance in Asian countries, and causes underlying increased drug resistance rates in some regions, is one focus of this effort. Small informal meetings will be used to launch and sustain multi-national research collaborations.

Hepatitis Panels Research Objectives (2006-2010)

The USJCMSP Hepatitis Panel Research Objectives that were revised at the 27th Annual Joint Panels meeting in Kona, Hawaii, USA, in December, 2005. The Research Objectives are the guiding principles for organization of panel activities.

1. ***Develop cell culture and animal model systems to study replication and pathogenesis of multiple HCV genotypes.*** This is an essential goal to understand virus-host cell interactions precipitating hepatic inflammation and hepatocellular carcinoma, viral evasion of cellular defense mechanisms, as well as to improve and develop antiviral therapies.

2. ***Gain insight into innate and adaptive immunological responses in HBV and HCV infections that resolve or persist, and consequences of co-infection with HIV.*** Emphasis is placed on understanding how these two arms of the immune response are linked in successful and failed host responses. Our ultimate objective is to develop immuno-therapeutic approaches for treatment of these infections, either alone or in combination with existing therapies.

3. ***Unravel molecular mechanisms of hepatocellular cancer caused by HCV and HBV.*** A focus is to understand higher rates of HCV-associated hepatocellular carcinoma in Japan versus the United States. Because this probably cannot be entirely explained by differences in diagnostic criteria, alternate hypotheses including earlier spread of HCV in the Japanese population, or more common co-infection with HBV and HCV in Japan, will be developed and tested.

4. ***Define the epidemiology of HBV, HCV, and HEV-associated liver disease in Asia/Pacific regions.*** Yearly panel meetings will be used to establish collaborations with other Asian and Pacific Rim scientists for the study of pathogenesis of these infections. Molecular epidemiology of HEV infection in Asia/Pacific regions is an important related goal, since it is highly likely that as yet unknown strains of HEV would be found in humans and animal reservoirs.

5. ***Evaluate the prevalence of HBV and HCV mutants that are resistant to new and established antiviral therapies in regions of Asia.*** A primary objective is to facilitate monitoring of HBV and HCV antiviral escape variants as they emerge in Asia and the United States. A key related goal is to develop an open access data base to compile mutations that lead to drug resistance.

Discussion of Recent Activities Related to Research Objectives

Japanese and American Hepatitis Panel members have contributed significantly to a number of important research developments that are relevant to the Research Objectives of the Panels, as highlighted by the following list of selected major research accomplishments.

(A). HBV and HCV pathogenesis/antiviral therapy and resistance. Database activities.

(i) Documented the impact of antiviral therapy on the outcome of HCV and HBV infection after liver transplantation.

(ii) Defined growing problem of antiviral drug resistance for treatment of HBV.

(iii) Refined antiviral regimens for effective treatment of HCV and HBV infections and defined factors predictive of outcome.

(iv) Development and public release of a comprehensive hepatitis virus database.

(v) Initiated an international collaboration to establish a standard nomenclature for HBV resistance mutations and develop a framework for establishing a database to catalogue these mutations.

(B). HCV virology, immunology and cell culture models.

(i) Identified an isolate of HCV that replicates authentically in a cell culture model. Established and refined HCV replicon models for understanding the function of viral proteins.

(ii) Provided evidence that cyclophilins serve as essential cellular factors for HCV RNA replication, and their function in HCV replication can be modulated with inhibitors like cyclosporine.

(iii) Defined molecular mechanisms leading to dysregulation of innate immune signaling by viral proteins. The pathways disrupted involved host proteins like IPS-1/MAVS, TLR3, SOCS, and viral proteins like the NS3/4A protease and NS5A RNA-dependent RNA polymerase.

(iv) Identified defects in dendritic cell function due to failure to activate NK cells and skewed function of NKT cells.

(v) Documented defects in myeloid and plasmacytoid dendritic cell function in chronic hepatitis C.

(vi) Provided evidence for an essential role of T lymphocytes in control of HCV replication.

(vii) Investigated the prevalence of HCV/HIV co-infection in Japan.

(viii) Demonstrated the involvement of specific HCV proteins such as core in the pathogenesis of liver disease associated with HCV infection, including steatosis and hepatocellular carcinoma, and provided evidence for the importance of oxidative stress in HCV-related disease.

(C). Molecular epidemiology of HBV/HCV infection and hepatocellular carcinoma in Asia.

(i) Characterized epidemiological features of hepatitis virus transmission in Japan, India, and China, and importantly in under-studied regions of Asia like Indonesia, Tajikistan, Uzbekistan, Mongolia, and the Solomon Islands.

(ii) Furthered understanding of the relationship between HBV genotype distribution and hepatocellular cancer.

(iii) Defined virological and clinical implications of genetic variation in the HBV precore/core promoter regions.

(D). Zoonotic transmission of HEV

(i) Provided detailed analysis of the molecular epidemiology of HEV strains indigenous to Japan, and the relationship to zoonotic transmission.

(ii) Identified risk factors leading to HEV infection associated with consumption of uncooked meat from game and domesticated species.

Review and Evaluation of the Hepatitis Panels Program

Membership. The Japanese and American panels have undergone an almost complete turnover in membership since 2004, including the leadership of both. This has provided the Panels with a fresh perspective on major research objectives and vigorous new leadership. One recent addition to the Japanese panel, Dr. Takaji Wakita, is an exceptionally strong addition. He has truly helped to transform many areas of HCV research with his isolation of JFH1 virus and the development of a cell culture model for HCV infection that has become a laboratory standard globally. Dr. Wakita lends to the Panels unique expertise and a brings a robust research program that further integrates the research interests of its members. Moreover, the Japanese Panel members have developed strong ties with investigators in Asian countries where the molecular epidemiology of hepatitis virus infection is still poorly understood. Outreach to these countries by Panel members is strong and improving, and will be important to improved control of hepatitis infections in the region.

Research Objectives. The five Research Objectives are focused on major problems of virally-caused liver diseases in Asia, including the epidemiology and pathogenesis of chronic hepatitis, cirrhosis and liver cancer. Some Objectives do not have easily measurable benchmarks, as they are focused on exploratory or basic immunology and virology of liver diseases necessary to development of vaccines and therapies. Nonetheless, they are important. Progress can be readily assessed by a number of important discoveries, such as recognition of the role of cyclophilins in HCV replication in Prof. Shimotohno's laboratory that has led to the development of novel small molecule antiviral compounds now in Phase II clinical trials. Other objectives are more practical in nature, focused on emerging problems with current therapies, and provide opportunities for the Panels to educate or otherwise promote changes in clinical practice to improve outcomes. The balance between Research Objectives that are exploratory (and thus difficult to benchmark) versus practical (with specific achievable goals) is excellent, providing overall a good framework for translational research.

Interaction with other organizations including USJCMSP Panels and Board. The Hepatitis Panels have excelled in this goal. They have made an effort to leverage their activities by jointly sponsoring meeting workshops and sessions with organizations like Asian Pacific Association for the Study of the Liver (APASL) and the American Association for the Study of Liver Diseases (AASLD). Most importantly, they have carried out joint meetings with other USJCMSP Panels and Boards in ways that have significantly furthered Panel Objectives. This reflects the forward thinking, collaborative leadership of the Hepatitis Panels on both sides. In 2004, the Hepatitis Panels held a successful joint meeting with the Environmental Genomics and Carcinogenesis Panel in Kyoto, and in early 2008 a very successful major meeting with the Immunology Board held in Galveston. Plans to meet in the future with the HIV/AIDS Panel should be encouraged given the common challenges both groups face in developing vaccines and antivirals for highly mutable RNA viruses like HIV and HCV, as well as the difficult medical problem of co-infection. Finally, the Panels have established and expanded

extensive collaborative networks in most countries of Asia to further Panel Goals, as highlighted by a successful symposium held jointly with APASL in 2007 that featured speakers from many Asian countries like Pakistan and Mongolia. The Panels also attempt to provide educational opportunities for young trainees in Asian countries. An example of this has been the use of Opportunity Pool Funds to sponsor travel of trainees to the joint meeting of the Hepatitis Panels and Immunology Board in Galveston in early 2008.

1. Relevance of the research to the objectives of the U.S.-Japan Cooperative Medical Science Program.

Research in liver diseases is highly relevant to the objectives of the U.S.-Japan Cooperative Medical Science Program. Viral hepatitis (HBV, HCV, HEV) remains a substantial public health problem in Asia. For at least two of these viruses (HBV, HCV) liver cancer is an outcome of chronic infection that places a large burden on developing and developed economies of the region. Most importantly, approaches to prevent and treat infection with this viruses face challenges. For HBV, a highly effective and safe vaccine is available but it has yet to be widely deployed in all regions of Asia Moreover, for the substantial population of individuals with chronic HBV infection, antiviral therapies are not yet widely available and the emergence of drug-resistant virus strains is a threat. No vaccine exists to prevent or treat HCV infection and current antiviral therapies are not highly effective. Newer antiviral therapies are on the horizon but the emergence of drug resistant variants is likely to pose a significant challenge. The Research Objectives of the Hepatitis Panels have been designed to address these public health needs by fostering collaboration on the epidemiology and molecular pathogenesis of liver diseases including cancer, and the immunology and virology of hepatitis virus infections. There are tangible examples of close collaboration between the scientists of the U.S. and Japan who are members of the Panel, as well as other affiliate members from Asian countries outside of Japan.

2. Fulfillment of the Panel's research guidelines and its basic and practical objectives.

The Panels closely follow the Research Objectives established in 2005 as part of the five year review/planning initiative for the USJCMSP. Research guidelines and objectives are clear and many have specific and measurable outcomes. The objective to understand the virology and immunology of chronic hepatitis C is essential to develop new strategies to prevent and treat infection. Japanese and American Panel Members have provided leadership in these areas. As an example significant progress has been made in understanding the relationship between innate and adaptive immune responses and how HCV subverts host immunity (Hayashi, Koike, Gale, Walker). Progress towards the very practical goal of establishing a tractable cell culture model for HCV was achieved by Panel member Wakita. His generosity in the sharing the model with laboratories around the world has been widely recognized and has had a significant impact of our understanding of virus-host cell relationship. Molecular epidemiology of HEV infection in Asia (Mishiro) remains a critical question given that the virus is endemic in many countries, animal reservoirs are incompletely understood, and a newly developed effective vaccine is not likely to be deployed in the foreseeable future. Objectives related

to HBV research have been clinically driven, and focus especially on the emergence of drug resistance mutations. Panel members (Mizokami, Lok, DiBisceglie) and the Panel Secretary (Koshy) have convened a series of meetings with internationally recognized experts in this field that led to published recommendations for resistance mutation nomenclature and highlighted the need for database to catalogue these HBV variants. Efforts to gain from this activity a broader understanding of how antiviral drugs are used in Asian countries and what it might mean for emergence of resistant HBV variants are ongoing.

3. Appropriateness of the stated objectives in the light of current knowledge, needs and opportunities.

The emphasis of the Panel's research on a better understanding of the molecular virology of HCV and the immunologic basis of the longterm persistence of HCV is highly appropriate, as knowledge gained in these activities will be central to the development of effective virus-specific therapies which may ultimately be capable of replacing interferon as the standard of care, or vaccines for both prevention and potentially therapy of this infection. The focus on improved clinical utilization of available antiviral therapies for HBV infection is also clearly appropriate. These viruses together are major contributors to morbidity and mortality in Asia and the Americas as they are frequent causes of liver-specific mortality, and liver cancer. Molecular technology is advancing rapidly and a continuation of the regular exchange of information and trainees between Japanese and American laboratories will assure that this knowledge is used appropriately and in a timely fashion. Zoonotic infections with HEV have also been recognized in Japan and are another appropriate focus for the panels. Currently lacking within the Panel objectives, however, is any focus on HAV, and the panels should be encouraged to monitor the incidence of acute hepatitis A in Asian-Pacific Rim nations given the changing nature of HAV epidemiology in the region, as well as the utilization of inactivated HAV vaccines within the region.

4. Can the Panels' objectives be achieved through the approaches currently being utilized?

Panel members are well-positioned to advance Research Objectives for two reasons. They are as a group highly collaborative, and they wisely leverage international meetings to foster interactions with investigators in other Asian countries, including some like Pakistan, Mongolia, Indonesia, and Vietman where more information on the epidemiology of liver cancer and hepatitis virus infections is greatly needed. The Panel members conduct cutting edge research in the molecular virology and immunology of these viruses, and the organization of the Panel activities positions the program to effectively disseminate these technologies to others working on liver diseases in Asian countries where the need for them is obvious and growing. This is highlighted by the meeting now being planned on functional genomics of hepatitis virus infections (and possibly HIV co-infection) which will be held in 2009 and will feature scientists from Asia.

5. Time frame for accomplishing the Panels' objectives.

Given the scope and magnitude of virally-related liver disease in Asia-Pacific Rim countries, the time frame for prevention and control of the cancer and viral diseases of the liver within the Panels' purview is likely to be indefinite. An effective vaccine for prevention of HEV infection has been recently developed, but the vaccine has yet to be produced commercially and the disease is likely to remain endemic in some Asian countries for years. There is thus an important need to continue research into the epidemiology of this infection, as well as the basic molecular virology of HEV. As noted above, the development of vaccines and next generation antiviral therapies for HCV has been slow and is likely to be complex because of the high rate of viral mutations and the poorly understood nature of hepatitis C pathogenesis. Likewise, HBV infection remains a very substantial public health problem will persist for many years despite the availability of an effective vaccine. Emergence of drug-resistant variants of HBV is inevitable given the large burden of disease in some Asian countries and is likely to present new threats and challenges. The Panels' multidisciplinary members will continue to define new research objectives in this changing world environment.

6. ***Interactions with other panels and boards.***

The Hepatitis Panels have shown exceptional leadership in organizing multiple, effective interactions with other USJCMSP panels and boards that have productively crossed conventional disciplinary boundaries. During the 2004 Kyoto meeting of the Delegations and the Panels, the Hepatitis and Environmental Genomics and Carcinogenesis Panels jointly sponsored a meeting focused on the epidemiology and pathogenesis of liver cancer in Asia. This was a very successful meeting that involved leading scientists from several Asian countries. To further the Research Objective of better understanding the immunology of liver diseases, the Hepatitis Panels and Immunology Board met jointly in Galveston in January 2008. Together they shaped the agenda of a 2.5 day meeting on Hepatic Inflammation and Immunity that was attended by about 200 participants, with over 40 invited speakers, from around the globe, including many from China, Taiwan, and India. This was a highly successful meeting that was uniquely multidisciplinary. Many speakers provided insights into the latest concepts in the regulation and function of the immune system with a focus on relevance to the liver. Others spoke to the unique immunological environment of the liver. The meeting sessions and related events provided opportunities to establish scientific collaborations in this area that will be important to the future activities of the Hepatitis Panels. Importantly, plans to meet jointly with other Panels are ongoing. Given the similar problems faced in developing drugs and vaccines for HCV and HIV, and serious medical problem caused by co-infection with these viruses, the Hepatitis Panels have approached the HIV/AIDS Panel to arrange a joint meeting. As outlined in the Panels 2007 application of Opportunity Funds, this will probably occur in conjunction with the meeting on Functional Genomics planned for 2009.

Should the current panel guidelines be modified?

The guidelines were reviewed as recently as December 2005 in during the 27th annual Hepatitis Panels meeting in Hawaii. Part of the rationale for Guideline review at that time was to make the Research Objectives as practical as possible so that outcomes could be specific and measurable. This is difficult given that many of the Objectives are focused on basic questions of liver pathogenesis caused by infection and cancer, where clear endpoints are difficult to identify. The Panels thus did not rewrite guidelines to set finite benchmarks. Instead they chose to place priority on those existing Research Objectives that had practical goals. The approach was to emphasize those Objectives with measurable outcomes that could be achieved with a modest allocation of resources. For instance the practical goal of providing guidance and education related to HBV drug resistance mutations n Asia is being achieved through unique programs like the Opportunity Funds and by partnering with international liver meetings like AASLD and APASL to convene recognized experts to achieve consensus opinions on mutation nomenclature.

7. New guidelines

No new guidelines beyond those reviewed in December 2005 are planned.

Joint meetings.

The Hepatitis Panels have made outstanding progress toward their goals set in 2005 to meet jointly with key USJCMSP panels and boards to further Research Objectives. Specifically they have:

1. Consulted and collaborated with the Environmental Genomics and Carcinogenesis Panel to develop a better understanding of molecular tumorigenesis and co-factors contributing to liver cancer in Asian countries.
2. Established collaborations with the Immunology Board to develop testable hypotheses for failure of immunity in persistent HBV and HCV infections. The Joint Annual Meeting held in Galveston (January 2008) was a significant step forward toward this goal.
3. Contact with the HIV/AIDS panel was made in 2007 with the goal of planning a joint meeting to address common issues of concern around vaccine development, antiviral therapy and co-infection with HIV and hepatitis viruses, particularly HCV. With a successful application for Opportunities Funds, plans for this meeting are now developing.

Submitted by:

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II. 分担研究報告