

平成 22 年度 肝炎等克服緊急対策研究事業 成果概要

研究課題：B 型肝炎の核酸アナログ薬治療における治療中止基準の作成と治療中止を
目指したインターフェロン治療の有用性に関する研究

課題番号：H21-肝炎-一般-001

予定期間：H21 年度から H23 年度まで

研究代表者：田中榮司

所属研究機関：国立大学法人 信州大学

所属部局：医学部

職名：教授

年次別研究費(交付決定額)：1 年目 42,432,000 円 2 年目 36,400,000 円

I. 研究の意義

- (1) B 型肝炎の核酸アナログ薬治療では、治療薬中止後に肝炎の再燃を起こすことが多いが、この再燃を予測する効率的な方法がない。このため、同治療の中止基準がない。
- (2) B 型肝炎の核酸アナログ薬治療には、併用薬などを用いてこれを積極的に中止し、drug free とする方法がない。

II. 研究の目的、期待される成果

- (1) B 型肝炎の核酸アナログ薬治療で、核酸アナログ薬を継続した方が良い症例と中止可能な症例を判断する基準を作成する。
- (2) インターフェロンを併用するなどの方法で、核酸アナログ薬を積極的かつ効率的に中止する方法を開発する。
- (3) 上記(1)と(2)により drug free となる症例が増加し、医療経済にも良い効果が得られる。

III. 2 年間の研究成果

・研究代表者

- (1) 核酸アナログ薬治療中止直後の経過とその後の肝炎再燃との関連を明らかにした。
- (2) 年齢、HBe 抗原・抗体、HBs 抗原量、HB コア関連抗原量、HBV DNA 量などを用いて、核酸アナログ薬中止後の肝炎再燃をより効率的に予測する方法を開発した。この方法を用いて暫定的な中止基準の作成を開始した。
- (3) 核酸アナログ薬治療例(中止例を含む)の前向き観察を全体研究で開始した。

・研究分担者(鈴木義之)

- (1) 核酸アナログ薬治療下で、HB コア関連抗原量が肝細胞中 HBV cccDNA 量と相関すること、および、同薬を中止する場合の指標として有用であることを確認した。
- (2) 核酸アナログ薬中止基準における超高感度 HBV DNA 測定法の意義を検討した。
- (3) 核酸アナログ薬を積極的に中止するための sequential 治療の検討を継続した。

・研究分担者(新海 登)

- (1) 核酸アナログ薬中止基準における超高感度 HBV DNA 測定法の意義を検討し、HB コア関連抗原量、HBs 抗原量、HBV 遺伝子型との関連を検討した。

・研究分担者(平松直樹)

- (1) 核酸アナログ治療薬変更時の耐性出現について検討し、核酸アナログ薬治療を継続すべき場合の薬物の選択について検討した。
- (2) インターフェロン治療と各種 HBV マーカの推移との関連を検討した。
- 研究分担者(狩野吉康)
 - (1) HBs 抗原量、HB コア関連抗原量、HBV DNA 量などについて、核酸アナログ薬治療開始後の変化を多数例で検討し、どの程度の割合で中止可能例が出現するかを検討した。
- 研究分担者(柘植雅貴)
 - (1) HBV RNA+DNA 量の測定法を開発し、HBV DNA 量と比較することにより、中止基準の一つとなりうる可能性を示唆した。
- 研究分担者(今関文夫)
 - (1) 核酸アナログ薬中止後の長期経過をウイルスマーカーとの関連で解析した。
 - (2) HBs 抗原量の自然経過での推移を検討し、中止基準マーカーとしての意義を検討した。
- 研究分担者(髭 修平)
 - (1) 核酸アナログ薬中止の指標として HBV pre-core/ core promoter 変異の意義を検討した。
 - (2) 肝細胞中 HBV cccDNA 量と各種ウイルスマーカーとの関連を検討し、それぞれの意義を検討した。
- 研究分担者(八橋 弘)
 - (1) 核酸アナログ薬中止の基準として、HBe 抗原の陰性化に加え、中止時の HB コア関連抗原量、HBs 抗原量、HBV DNA 量の測定が有用であることを確認した。
- 研究分担者(齋籐正紀)
 - (1) 中止基準のマーカーとなる HB コア関連抗原量は核酸アナログ薬投与期間や HBe 抗原陽性と、また、HBs 抗原量は年齢や肝線維化と関連していることを明らかにした。

IV. 23 年度の課題

- (1) 暫定的な核酸アナログ薬の中止基準を前向き研究で検証する。
- (2) 超高感度 HBV DNA 測定、HBV 遺伝子変異、サイトカインなどの新しいマーカーを検討し、さらに精度の高い中止基準の可能性を検討する。
- (3) 核酸アナログ薬治療例を前向き観察し、中止基準を満たす症例の割合、特徴を検討する。
- (4) 核酸アナログ薬を積極的に中止するための sequential 治療の検討を継続する。

V. 行政施策への貢献の可能性

- (1) 核酸アナログ薬の中止に関するガイドラインを作成
- (2) 核酸アナログ薬治療の効果的な中止方法開発の可能性

VI. 本研究の成果(発表論文・ガイドライン・マニュアル等)

(1) 研究代表者

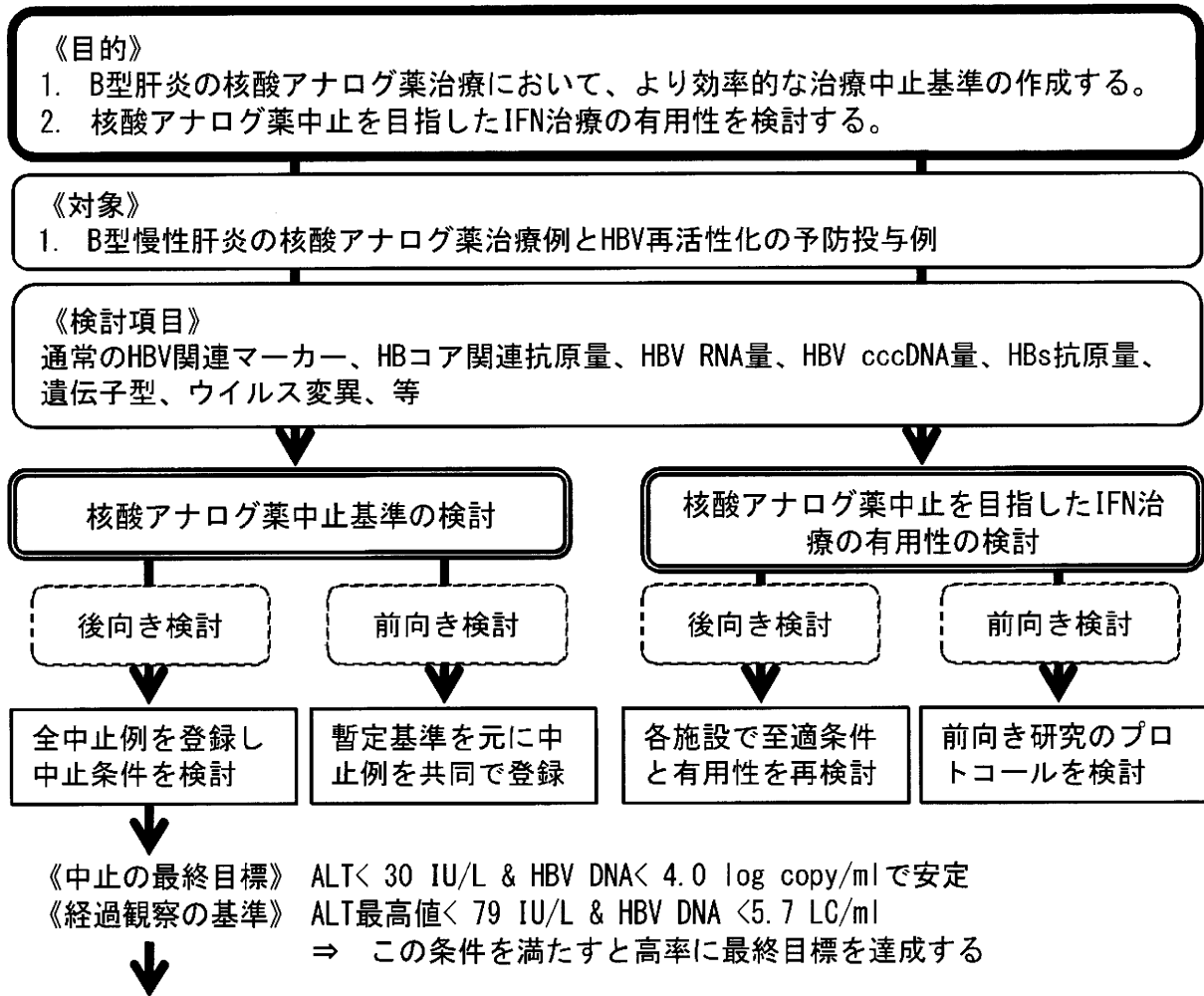
1. Yokosuka O, Kurosaki M, Imazeki F, Arase Y, Tanaka Y, Chayama K, Tanaka E, Kumada H, Izumi N, Mizokami M, Kudo M. Management of hepatitis B: Consensus of the Japan Society of Hepatology 2009. Hepatol Res (in press).
2. Matsumoto A, Maki N, Yoshizawa K, Umemura T, Joshita S, Tanaka E. Comparison of hepatitis B virus DNA, RNA, and core related antigen as predictors of lamivudine resistance in patients with chronic hepatitis B. Shinshu Medical Journal 2010;58(4):153-62.

3. 田中榮司. B型肝炎再活性化の病態と対策. 日消誌 2010;107(9):1417-25.

(2)研究分担者

1. Hosaka T, Suzuki F, Kobayashi M, Hirakawa M, Kawamura Y, Yatsuji H, Sezaki H, Akuta N, Suzuki Y, Saitoh S, Arase Y, Ikeda K, Kumada H. HBcrAg is a predictor of post-treatment recurrence of hepatocellular carcinoma during antiviral therapy. *Liver Int* 2010;30(10):1461-70.
2. Huang YW, Chayama K, Tsuge M, Takahashi S, Hatakeyama T, Abe H, Hu JT, Liu CJ, Lai MY, Chen DS, Yang SS, Kao JH. Differential effects of interferon and lamivudine on serum HBV RNA inhibition in patients with chronic hepatitis B. *Antivir Ther.* 2010;15(2):177-84.
3. Noguchi C, Imamura M, Tsuge M, Hiraga N, Mori N, Miki D, Kimura T, Takahashi S, Fujimoto Y, Ochi H, Abe H, Maekawa T, Tateno C, Yoshizato K, Chayama K. G-to-A hypermutation in hepatitis B virus (HBV) and clinical course of patients with chronic HBV infection. *J Infect Dis.* 2009;199(11):1599-607.
4. Fujimoto M, Ichikawa T, Nakao K, Miyaaki H, Shibata H, Eguchi S, Takatsuki M, Nagaoka S, Yatsuhashi H, Kanematsu T, Eguchi K. The significance of enzyme immunoassay for the assessment of hepatitis B virus core-related antigen following liver transplantation. *Intern Med.* 2009;48(18):1577-83.
5. Kurashige N, Ohkawa K, Hiramatsu N, Yakushijin T, Mochizuki K, Oze T, Kiso S, Kanto T, Takehara T, Kasahara A, Doi Y, Yamada A, Fukuda K, Oshita M, Mita E, Fukui H, Nagase T, Yoshihara H, Imai Y, Kato M, Kashihara T, Hayashi N. Lamivudine-to-entecavir switching treatment in type B chronic hepatitis patients without evidence of lamivudine resistance. *J Gastroenterol.* 2009;44(8):864-70.
6. Hige S, Yamamoto Y, Yoshida S, Kobayashi T, Horimoto H, Yamamoto K, Sho T, Natsuizaka M, Nakanishi M, Chuma M, Asaka M. Sensitive assay for the quantification of hepatitis B virus mutants by a minor groove binder probe and peptide nucleic acids. *J Clin Microbiology* 2010;48:4487-94.
7. Karino Y, Toyota J, Kumada H, Katano Y, Izumi N, Kobashi H, Sata M, Moriyama M, Imazeki F, Kage M, Ishikawa H, Masaki N, Seriu T, Omata M. Efficacy and resistance of entecavir following 3 years of treatment of Japanese patients with lamivudine-refractory chronic hepatitis B. *Hepatol Int* 2010;4(1):414-22
8. Wu S, Fukai K, Imazeki F, Arai M, Kanda T, Yonemitsu Y, Yokosuka O. Initial Virological Response and Viral Mutation with Adefovir Dipivoxil Added to Ongoing Lamivudine Therapy in Lamivudine-Resistant Chronic Hepatitis B. *Dig Dis Sci* (in press)
9. Kobayashi M, Suzuki F, Akuta N, Hosaka T, Sezaki H, Yatsuji H, Kobayashi M, Suzuki Y, Arase Y, Ikeda K, Watahiki S, Iwasaki S, Kumada H. Correlation of YMDD mutation and breakthrough hepatitis with hepatitis B virus DNA and serum alanine aminotransferase during lamivudine treatment in hepatitis B. *Hepatology Reserch* 2009;40(2):125-34

Ⅶ. Ⅲ (2年間の研究成果)の概要図等



《核酸アナログ薬中止の暫定基準》

1. 中止時、HBe抗原陰性かつHBV DNA検出感度以下は安全な中止のための必要条件である。
2. さらに、HBs抗原量とコア関連抗原量から、肝炎再燃の危険性別に、以下の3群に分けることが可能であった。また、それぞれの臨床的意義は下記の如くである。
 I群 (HBコア関連抗原 < 3.0 LU/ml & HBs抗原 < 100 IU/ml) 高い確率で中止が可能。
 II群 (IおよびIII群以外) 約60%で中止が可能。今後さらに条件を検討する必要がある群。
 III群 (HBcrAg ≥ 4.0 LU/ml or HBsAg ≥ 1,000 IU/ml) 中止すべきでない群。

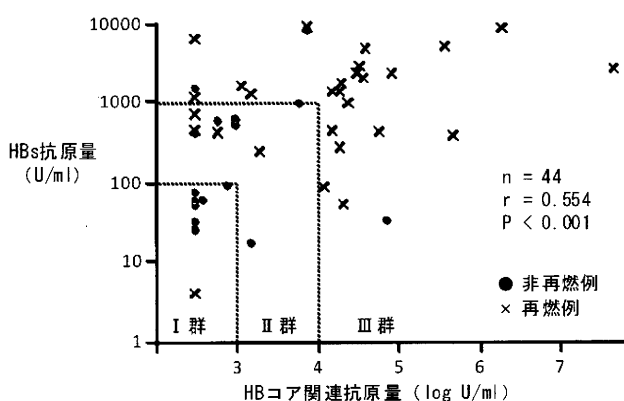


図1：中止時のHBs抗原量とHBコア関連抗原量による群分けと各群での再燃と非再燃症例の分布

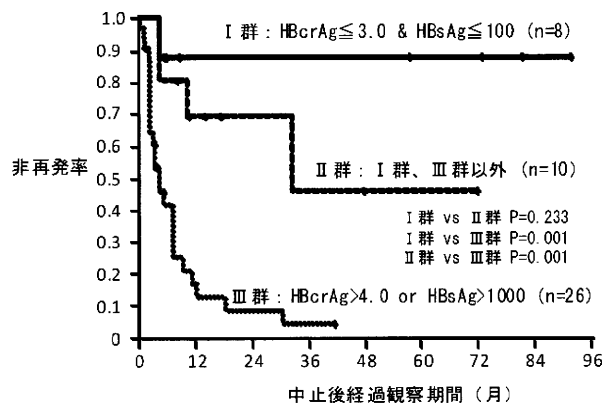


図2：I～III群での非再燃率の推移

●研究代表者の研究歴等

・過去に所属した研究機関の履歴

1. 1987年10月1日～現在 信州大学医学部内科学第二
2. 1999年2月22日～1999年3月15日 Roche診断薬ペンツベルグ研究所
3. 1995年10月1日～1996年3月31日 米国国立衛生研究所 (NIH)
4. 1982年7月1日～1984年12月31日 自治医科大学予防生態
5. 1978年4月1日～1982年6月30日 信州大学大学院医学研究

・主な共同研究者(又は指導を受けた研究者)

1. 清澤研道教授 (信州大学医学部内科学第二)
2. Dr. Georg Hess (Roche診断薬ペンツベルグ研究所、ドイツ)
3. Dr. Harvey J Alter (米国国立衛生研究所、米国)
4. 真弓 忠教授 (自治医科大学予防生態)
5. 古田精市教授 (信州大学大学院医学研究科)

・主な研究課題

1. ウイルス性肝炎における最新の治療法の標準化を目指す研究班 (厚生労働省科学研究費補助金、分担、平成22年度～平成24年度)
2. 肝硬変を含めたウイルス性肝疾患の治療の標準化に関する研究 (厚生労働省科学研究費補助金、分担、平成19年度～平成21年度)
3. B型肝炎ウイルスの抗ウイルス療法における血中RNA遺伝子量測定の意義 (基盤研究C、平成19年度～21年度)
4. リツキシマブ+ステロイド併用悪性リンパ腫治療中のB型肝炎ウイルス再活性化への対策に関する研究 (厚生労働省科学研究費補助金、分担、平成20年度)
5. L3分画および血流中癌細胞テロメラーゼを指標とした肝癌細胞のサベランスの有用性に関する研究 (厚生労働省科学研究費補助金、分担、平成17年度～平成19年度)
6. B型及びC型肝炎ウイルスの新たな感染予防法の確立のための感染病態解明に関する研究 (厚生労働省科学研究費補助金、分担、平成16年度～平成18年度)
7. 非A-E型肝炎の原因ウイルス同定 (基礎研究C2、代表、平成13年度～平成15年度)
8. 肝がんに対する肝移植の有効性とその適応基準の確立に関する研究 (厚生労働省科学研究費補助金、分担、平成13年度～平成15年度)
9. C型およびG型肝炎ウイルスの肝組織内局在と病態 (基盤研究C2、代表、平成9年度～平成11年度)
10. HBs145変異抗原測定系の開発と臨床応用 (ウイルス肝炎財団、日本人研究者の海外派遣、平成10年度)
11. Gene Cutterを用いたC型肝炎ウイルス感染症の遺伝子治療 (基盤研究C、代表、平成6年度～平成8年度)

12. 新しくクローニングされた G 型肝炎ウイルスの研究 (ウイルス肝炎財団、日本人研究者の海外派遣、平成 7 年度)

・これまでの研究実績

《特許権等知的財産権》

1. 特願 2003-83283 : HBV-RNA を含む HBV 粒子 (2003/3/25)
2. 特願 2004-558464 : B 型肝炎ウイルスの薬物抵抗性を識別する方法 (2003/12/10)
3. 特願平 8-167497 : C 型慢性肝炎の治療効果を事前に予測するためのキット (1996/6/27)
4. 特願平 6-71701 : 競合 PCR 法による核酸の簡易定量法 (1994/3/15)

《政策提言》

1. B型慢性肝炎の治療ガイドライン (2008~2010年)
2. C型慢性肝炎の治療ガイドライン (2008~2010年)
3. ウイルス性肝硬変に対する包括的治療のガイドライン (2008~2010年)
4. 免疫抑制・化学療法により発症するB型肝炎の診療ガイドライン (2009年)
5. 肝疾患における肝炎ウイルスマーカーの選択基準 (4版、2006年)
6. 肝機能検査法の選択基準 (7版、2006年)

《発表論文》

1. Yoneda S, Umemura T, Katsuyama Y, Kamijo A, Joshita S, Komatsu M, Ichijo T, Matsumoto A, Yoshizawa K, Ota M, Tanaka E. Association of serum cytokine levels with treatment response to pegylated interferon and ribavirin therapy in genotype 1 chronic hepatitis C patients. J Infect Dis (in press).
2. **Yokosuka O, Kurosaki M, Imazeki F, Arase Y, Tanaka Y, Chayama K, Tanaka E, Kumada H, Izumi N, Mizokami M, Kudo M. Management of hepatitis B: Consensus of the Japan Society of Hepatology 2009. Hepatol Res (in press)**
3. Hatta T, Fujinaga Y, Kadoya M, Ueda H, Murayama H, Kurozumi M, Ueda K, Komatsu M, Nagaya T, Joshita S, Kodama R, Tanaka E, Uehara T, Sano K, Tanaka N. Accurate and simple method for quantification of hepatic fat content using magnetic resonance imaging: a prospective study in biopsy-proven nonalcoholic fatty liver disease. J Gastroenterol (in press).
4. Umemura T, Zen Y, Hamano H, Joshita S, Ichijo T, Yoshizawa K, Kiyosawa K, Ota M, Kawa S, Nakanuma Y, Tanaka E. Clinical significance of immunoglobulin G4-associated autoimmune hepatitis. J Gastroenterol (in press).
5. **Matsumoto A, Maki N, Yoshizawa K, Umemura T, Joshita S, Tanaka E. Comparison of hepatitis B virus DNA, RNA, and core related antigen as predictors of lamivudine resistance in patients with chronic hepatitis B. Shinshu Medical Journal 58(4):153-62, 2010.**
6. **Kumada H, Okanoue T, Onji M, Moriwaki H, Izumi N, Tanaka E, Chayama K, Sakisaka S,**

- Takehara T, Oketani M, Suzuki F, Toyota J, Nomura H, Yoshioka K, Seike M, Yotsuyanagi H, Ueno Y. Guidelines for the treatment of chronic hepatitis and cirrhosis induced by hepatitis B virus infection for the fiscal year 2008 in Japan. *Hepatology* 40: 1-7, 2010.**
7. Kumada H, Okanoue T, Onji M, Moriwaki H, Izumi N, Tanaka E, Cyayama K, Sakisaka S, Takehara T, Oketani M, Suzuki F, Toyota J, Nomura H, Yoshioka K, Seike M, Yotsuyanagi H, Ueno Y. Guidelines for the treatment of chronic hepatitis and cirrhosis induced by hepatitis B virus infection for the fiscal year 2008 in Japan. *Hepatology* 40: 8-13, 2010.
 8. Tanaka N, Zhang X, Sugiyama E, Kono H, Horiuchi A, Nakajima T, Kanbe H, Tanaka E, Gonzalez FJ, Aoyama T. Eicosapentaenoic acid improves hepatic steatosis independent of PPARalpha activation through inhibition of SREBP-1 maturation in mice. *Biochem Pharmacol* 80(10):1601-12, 2010.
 9. Tamura Y, Igarashi M, Suda T, Wakai T, Shirai Y, Umemura T, Tanaka E, Kakizaki S, Takagi H, Hiasa Y, Onji M, Aoyagi Y. Fucosylated fraction of alpha-fetoprotein as a predictor of prognosis in patients with hepatocellular carcinoma after curative treatment. *Dig Dis Sci* 55(7):2095-101, 2010.
 10. Nagaya T, Tanaka N, Suzuki T, Sano K, Horiuchi A, Komatsu M, Nakajima T, Nishizawa T, Joshita S, Umemura T, Ichijo T, Matsumoto A, Yoshizawa K, Nakayama J, Tanaka E, Aoyama T. Down-regulation of SREBP-1c is associated with the development of burned-out NASH. *J Hepatology* 53(4):724-31, 2010.
 11. Tsuruta G, Tanaka N, Hongo M, Komatsu M, Horiuchi A, Hamamoto K, Iguchi C, Nakayama Y, Umemura T, Ichijo T, Matsumoto A, Yoshizawa K, Aoyama T, Tanaka E. Nonalcoholic fatty liver disease in Japanese junior high school students: its prevalence and relationship to lifestyle habits. *J Gastroenterol* 45(6):666-72, 2010.
 12. Tsutsui M, Tanaka N, Kawakubo M, Sheena Y, Horiuchi A, Komatsu M, Nagaya T, Joshita S, Umemura T, Ichijo T, Matsumoto A, Yoshizawa K, Aoyama T, Tanaka E, Sano K. Serum fragmented cytokeratin 18 levels reflect the histologic activity score of nonalcoholic fatty liver disease more accurately than serum alanine aminotransferase levels. *J Clin Gastroenterol* 44(6):440-7, 2010.
 13. Uehara T, Hamano H, Kawa S, Sano K, Oki K, Kobayashi Y, Nagaya T, Akamatsu T, Kurozumi M, Fujinaga Y, Tanaka E, Honda T, Ota H. Chronic gastritis in the setting of autoimmune pancreatitis. *Am J Surg Pathol* 34(9):1241-9, 2010.
 14. Joshita S, Umemura T, Yoshizawa K, Katsuyama Y, Tanaka E, Ota M. A2BP1 as a novel susceptible gene for primary biliary cirrhosis in Japanese patients. *Hum Immunol* 71(5):520-4, 2010.
 15. Joshita S, Umemura T, Yoshizawa K, Katsuyama Y, Tanaka E, Nakamura M, Ishibashi H, Ota M. Association analysis of cytotoxic T-lymphocyte antigen 4 gene polymorphisms with primary biliary cirrhosis in Japanese patients. *J Hepatology* 53(3):537-41, 2010.
 16. 田中榮司. B型肝炎再活性化の病態と対策. *日消誌* 107(9):1417-25, 2010.

17. **Kusakabe A, Tanaka Y, Mochida S, Nakayama N, Inoue K, Sata M, Isoda N, Kang J H, Sumino Y, Yatsushashi H, Takikawa Y, Kaneko S, Yamada G, Karino Y, Tanaka E, Kato J, Sakaida I, Izumi N, Sugauchi F, Nojiri S, Joh T, Miyakawa Y, Mizokami M. Case-control study for the identification of virological factors associated with fulminant hepatitis B. *Hepatol Res* 39(7): 648-656, 2009.**
18. Matsumoto A, Tanaka E. Pretreatment prediction of virological response to peginterferon plus ribavirin therapy in patients with chronic hepatitis C, using viral and host factors: some concerns (reply). *Hepatology* 49(6): 2125; author reply 2125-2126, 2009.
19. **Matsuura K, Tanaka Y, Hige S, Yamada G, Murawaki Y, Komatsu M, Kuramitsu T, Kawata S, Tanaka E, Izumi N, Okuse C, Kakumu S, Okanoue T, Hino K, Hiasa Y, Sata M, Maeshiro T, Sugauchi F, Nojiri S, Joh T, Miyakawa Y, Mizokami M. Distribution of hepatitis B virus genotypes among patients with chronic infection in Japan shifting toward an increase of genotype A. *J Clin Microbiol* 47(5): 1476-1483, 2009.**
20. Okanoue T, Itoh Y, Hashimoto H, Yasui K, Minami M, Takehara T, Tanaka E, Onji M, Toyota J, Chayama K, Yoshioka K, Izumi N, Akuta N., Kumada H. Predictive values of amino acid sequences of the core and NS5A regions in antiviral therapy for hepatitis C: a Japanese multi-center study. *J Gastroenterol* 44(9): 952-963, 2009.
21. Tanaka N, Horiuchi A, Yamaura T, Komatsu M, Yokoyama T, Okaniwa S, Nagaya T, Yoshizawa K, Kiyosawa K, Aoyama T, Tanaka E. Efficacy and safety of addition of minor bloodletting (petit phlebotomy) in hepatitis C virus-infected patients receiving regular glycyrrhizin injections. *J Gastroenterol* 44(6): 577-582, 2009.
22. Tanaka Y, Nishida N, Sugiyama M, Kurosaki M, Matsuura K, Sakamoto N, Nakagawa M, Korenaga M, Hino K, Hige S, Ito Y, Mita E, Tanaka E, Mochida S, Murawaki Y, Honda M, Sakai A, Hiasa Y, Nishiguchi S, Koike A, Sakaida I, Imamura M, Ito K, Yano K, Masaki N, Sugauchi F, Izumi N, Tokunaga K, Mizokami M. Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. *Nat Genet* 41(10): 1105-1109, 2009.
23. Umemura T, Katsuyama Y, Hamano H, Kitahara K, Takayama M, Arakura N, Kawa S, Tanaka E, Ota M. Association analysis of Toll-like receptor 4 polymorphisms with autoimmune pancreatitis. *Hum Immunol* 70(9):742-6, 2009.
24. Umemura T, Ichijo T, Yoshizawa K, Tanaka E, Kiyosawa K. Epidemiology of hepatocellular carcinoma in Japan. *J Gastroenterol* 44 (Suppl 19): 102-107, 2009.
25. Fujiwara K, Kojima H, Yonemitsu Y, Yasui S, Imazeki F, Miki M, Suzuki K, Sakaida I, Okita K, Tanaka E, Omata M, Yokosuka O. Phylogenetic analysis of hepatitis A virus in sera from patients with hepatitis A of various severities. *Liver Int* 29(6): 838-845, 2009.
26. Okiyama W, Tanaka N, Nakajima T, Tanaka E, Kiyosawa K, Gonzalez FJ, Aoyama T. Polyene phosphatidylcholine prevents alcoholic liver disease in PPARalpha-null mice through attenuation of increases in oxidative stress. *J Hepatol* 50(6): 1236-1246, 2009.

27. Okanoue T, Itoh Y, Minami M, Hashimoto H, Yasui K, Yotsuyanagi H, Takehara T, Kumada T, Tanaka E, Nishiguchi S, Izumi N, Sata M, Onji M, Yamada G, Okita K, Kumada H. Guidelines for the antiviral therapy of hepatitis C virus carriers with normal serum aminotransferase based on platelet counts. *Hepatol Res* 38(1): 27-36, 2008.
28. Shirakawa H, Matsumoto A, Joshita S, Komatsu M, Tanaka N, Umemura T, Ichijo T, Yoshizawa K, Kiyosawa K, Tanaka E. Pretreatment prediction of virological response to peginterferon plus ribavirin therapy in chronic hepatitis C patients using viral and host factors. *Hepatology* 48(6): 1753-1760, 2008.
29. Tanaka E, Matsumoto A, Yoshizawa K, Maki N. Hepatitis B core-related antigen assay is useful for monitoring the antiviral effects of nucleoside analogue therapy. *Intervirology* 51 Suppl 1: 3-6, 2008.
30. Tanaka E, Umemura T. History and prevention of de novo hepatitis B virus-related hepatitis in Japan and the world. *Clinical Journal of Gastroenterology* 1(3): 83-86, 2008.
31. Tanaka N, Nagaya T, Komatsu M, Horiuchi A, Tsuruta G, Shirakawa H, Umemura T, Ichijo T, Matsumoto A, Yoshizawa K, Aoyama T, Kiyosawa K, Tanaka E. Insulin resistance and hepatitis C virus: a case-control study of non-obese, non-alcoholic and non-steatotic hepatitis virus carriers with persistently normal serum aminotransferase. *Liver Int* 28(8): 1104-1111, 2008.
32. Umemura T, Tanaka E, Kiyosawa K, Kumada H. Mortality secondary to fulminant hepatic failure in patients with prior resolution of hepatitis B virus infection in Japan. *Clin Infect Dis* 47(5): e52-56, 2008.
33. Tanaka N, Nagaya T, Komatsu M, Horiuchi A, Tsuruta G, Shirakawa H, Umemura T, Ichijo T, Matsumoto A, Yoshizawa K, Aoyama T, Kiyosawa K, Tanaka E. Insulin resistance and hepatitis C virus: a case-control study of non-obese, non-alcoholic and non-steatotic hepatitis virus carriers with persistently normal serum aminotransferase. *Liver Int* 28(8): 1104-1111, 2008.
34. Tanaka N, Sano K, Horiuchi A, Tanaka E, Kiyosawa K, Aoyama T. Highly purified eicosapentaenoic acid treatment improves nonalcoholic steatohepatitis. *J Clin Gastroenterol* 42(4): 413-418, 2008.
35. Umemura T, Ota M, Yoshizawa K, Katsuyama Y, Ichijo T, Tanaka E, Kiyosawa K. Association of cytotoxic T-lymphocyte antigen 4 gene polymorphisms with type 1 autoimmune hepatitis in Japanese. *Hepatol Res* 38(7): 689-695, 2008.
36. Umemura T, Muto H, Tanaka E, Matsumoto A, Ichijo T, Yoshizawa K, Akamatsu T, Kiyosawa K, and the Nagano Interferon Treatment Research Group. Anti-Helicobacter seropositivity: influence on severity and treatment response in patients with chronic hepatitis C. *J Viral Hepatitis* 14: 48-54, 2007
37. Yokosawa S, Yoshizawa K, Ota M, Katsuyama Y, Kawa S, Ichijo T, Umemura T, Tanaka E, Kiyosawa K. A genomewide DNA microsatellite association study of Japanese patients with autoimmune hepatitis type 1. *Hepatology* 45: 384-390, 2007
38. Umemura T, Ota M, Yoshizawa K, Katsuyama Y, Ichijo T, Tanaka E, Kawa S, Kiyosawa K.

- Lack of association between FCRL3 and FcγRII polymorphisms in Japanese type 1 autoimmune hepatitis. *Clin Immunol* 122: 338-342, 2007
39. Tanaka N, Horiuchi A, Yamaura T, Komatsu M, Tanaka E, Kiyosawa K. Efficacy and safety of 6-month iron reduction therapy in patients with hepatitis C virus-related cirrhosis: a pilot study. *J Gastroenterol* 42: 49-55, 2007
 40. Matsumoto A, Tanaka E, Minami M, TOkanoue T, Yatsushashi H, Nagaoka S, Suzuki F, Kobayashi M, Chayama K, Imamura M, Yotsuyanagi H, Nakaoka S, Maki N, Kawata S, Kumada H, Iino S, Kiyosawa K: Low serum level of hepatitis B core-related antigen indicates unlikely reactivation of hepatitis after cessation of lamivudine therapy. *Hepatol Res* 37: 661-666, 2007
 41. Fujiwara K, Yokosuka O, Imazeki F, Miki M, Suzuki K, Okita K, Tanaka E, Omat M: Genetic analysis of hepatitis A virus protein 2C in sera from patients with fulminant and self-limited hepatitis A. *Hepato-Gastroenterology* 54: 871-877, 2007
 42. Fujiwara K, Yokosuka O, Imazeki F, Miki M, Suzuki K, Okita K, Tanaka E, Omat M: Analysis of hepatitis A virus protein 2B in sera of hepatitis A of various severities. *J Gastroenterol* 42: 560-6, 2007
 43. Tanaka E, Matsumoto A, Suzuki F, Kobayashi M, Mizokami M, Tanaka Y, Okanoue T, Minami M, Chayama K, Imamura M, Yatsushashi H, Nagaoka S, Yotsuyanagi H, Kawata S, Kimura T, Maki N, Iino S, Kiyosawa K, and HBV Core-Related Antigen Study Group. Measurement of hepatitis B virus core-related antigen is valuable for identifying patients who are at low risk of lamivudine resistance. *Liver Int* 26:90-96, 2006
 44. Tanaka N, Ichijo T, Okiyama W, Mutou H, Misawa N, Matsumoto A, Yoshizawa K, Tanaka E, Kiyosawa K. Laparoscopic findings in patients with nonalcoholic steatohepatitis. *Liver Int* 2:32-38, 2006
 45. Misawa N, Matsumoto A, Tanaka E, Rokuhara A, Yoshizawa K, Umemura T, Maki N, Kimura T, Kiyosawa K. Patients with and without loss of hepatitis B virus DNA after hepatitis B e antigen seroconversion have different virological characteristics. *J Med Virol* 78:68-73, 2006
 46. Ogata K, Ide T, Kumashiro R, Kumada H, Yotsuyanagi H, Okita K, Akahane Y, Kaneko S, Tsubouchi H, Tanaka E, Moriwaki H, Nishiguchi S, Kakumu S, Mizokami M, Iino S, Sata M. Timing of interferon therapy and sources of infection in patients with acute hepatitis C. *Hepatology Research* 34:35-40, 2006
 47. Tanaka N, Tanaka E, Sheena Y, Komatsu M, Okiyama W, Misawa N, Muto H, Umemura T, Ichijo T, Matsumoto A, Yoshizawa K, Horiuchi A, Kiyosawa K. Useful parameters for distinguishing nonalcoholic steatohepatitis with mild steatosis from cryptogenic chronic hepatitis in the Japanese population. *Liver Int* 26:956-963, 2006
 48. Rokuhara A, Matsumoto A, Tanaka E, Umemura T, Yoshizawa K, Kimura T, Maki N, Kiyosawa K. Hepatitis B virus RNA is measurable in serum and can be a new marker for monitoring lamivudine therapy. *J Gastroenterol* 41: 785-790, 2006

49. Ozasa A, Tanaka Y, Orito E, Sugiyama M, Kang JH, Hige S, Kuramitsu T, Suzuki K, Tanaka E, Okada S, Tokita H, Asahina Y, Inoue K, Kakumu S, Okanoue T, Murawaki Y, Hino K, Onji M, Yatsushashi H, Sakugawa H, Miyakawa Y, Ueda R, Mizokami M. Influence of genotypes and precore mutations on fulminant or chronic outcome of acute hepatitis B virus infection. *Hepatology* 44: 326-334, 2006
50. Yoshizawa K, Ota M, Katsuyama Y, Ichijo T, Matsumoto A, Tanaka E, Kendo K. Genetic analysis of the HLA region of Japanese patients with type 1 autoimmune hepatitis. *J Hepatol* 42:578-584, 2005
51. Sun XH, Rokuhara A, Tanaka E, Gad A, Mutou H, Matsumoto A, Yoshizawa K, Kiyosawa K. Nucleotide mutations associated with hepatitis B e antigen negativity. *J Med Virol* 76:170-175, 2005
52. Tanaka E, Matsumoto A, Takeda N, Li T-C, Umemura T, Yoshizawa K, Miyakawa Y, Miyamura T, Kiyosawa K. Age-specific Antibody to Hepatitis E Virus Stays Constant during the Past 20 Years in Japan. *J Viral Hepatitis* 12:439-442, 2005
53. Matsumoto A, Tanaka E, Rokuhara A, Kiyosawa K, Kumada H, Omata M, Okita K, Hayashi N, Okanoue T, Iino S, Tanikawa K, and the Inuyama Hepatitis Study Group. Efficacy of lamivudine for preventing hepatocellular carcinoma in chronic hepatitis B: A multicenter retrospective study of 2,795 patients. *Hepatology Research* 32:173-184, 2005
54. Kimura T, Ohno N, Terada N, Rokuhara A, Matsumoto A, Yagi S, Tanaka E, Kiyosawa K, Ohno S, Maki N. Hepatitis B virus DNA-negative Dane particles lack core protein but contain a 22-kDa precore protein without C-terminal arginine-rich domain. *J Biol Chem* 280:21713-21719, 2005
55. Rokuhara A, Sun X, Tanaka E, Kimura T, Matsumoto A, Yao D, Yin L, Wang N, Maki N, Kiyosawa K. Hepatitis B virus core and core-related antigen quantitation in Chinese patients with chronic genotype B and C hepatitis B virus infection. *J Gastroenterol Hepatol* 20: 1726-1730, 2005
56. Yagi S, Mori K, Tanaka E, Matsumoto A, Sunaga F, Kiyosawa K, Yamaguchi K. Identification of novel HCV subgenome replicating persistently in chronic active hepatitis C patients. *J Med Virol* 77:399-413, 2005
57. Gad A, Tanaka E, Matsumoto A, Wahab MA, Serwah AH, Attia F, Ali K, Hassouba H, El-Deeb AE, Ichijyo T, Umemura T, Muto H, Yoshizawa K, Kiyosawa K. Assessment of KL-6 as a tumor marker in patients with hepatocellular carcinoma. *World J Gastroenterol* 11(42): 6607-6612, 2005
58. Gad A, Tanaka E, Matsumoto A, Serwah AE, Attia F, Hassan A, Sanny A, Ali K, Abbas A, El-Deeb AE, Sun XH, Umemura T, Ichijo T, Ehara T, Yoshizawa K, Kiyosawa K. Ethnicity affects the diagnostic validity of alpha-fetoprotein in hepatocellular carcinoma. *Asia-Pacific Journal of Clinical Oncology* 1: 64-70, 2005
59. Higashi K, Tsukiyama-Kohara K, Tanaka T, Tanaka E, Kiyosawa K, Kohara M.

- Characterization of hypervariable region in hepatitis C virus envelope protein during acute and chronic infection. *Arch Virol* 150: 883-898, 2005
60. Muto H, Tanaka E, Matsumoto A, Yoshizawa K, Kiyosawa K, Nagano Interferon Treatment Research Group. Type of human leukocyte antigen and changes in HCV core antigen concentration for predicting efficacy of Interferon- α treatment in patients with chronic hepatitis C: Analysis by a prospective study. *J Gastroenterol* 39: 674-680, 2004
 61. Ksahara A, Tanaka H, Okanou T, Imai Y, Tsubouchi H, Yoshioka K, Kawata S, Tanaka E, Hino K, Hayashi K, Tamura S, Itho Y, Kiyosawa K, Kakumu S, Okita K, Hayashi N. Interferon treatment improves survival in chronic hepatitis C patients showing biochemical as well as virological responses by preventing liver-related death. *J Viral Hepatitis* 11:148-156, 2004
 62. Kato N, Sugauchi F, Ozasa A, Kato T, Tanaka Y, Sakugawa H, Sata M, Hino K, Onji M, Okanou T, Tanaka E, Kawata S, Suzuki K, Hige S, Ohno T, Orito E, Ueda R, Mizokami M. Hepatitis B virus genotype G is an extremely rare genotype in Japan. *Hepatol Res* 30:199-203,2004
 63. Imai Y, Kasahara A, Tanaka H, Okanou T, Hiramatsu N, Tsubouchi H, Yoshioka K, Kawata S, Tanaka E, Hino K, Hayashi K, Tamura S, Itho Y, Sasaki Y, Kiyosawa K, Kakumu S, Okita K, Hayashi N. Interferon therapy for aged patients with chronic hepatitis C: improved survival in patients exhibiting a biochemical response. *J Gastroenterol* 39:1069-1077, 2004
 64. Nakajima T, Kamijo Y, Tanaka N, Sugiyama E, Tanaka E, Kiyosawa K, Fukushima Y, Peters JM, Gonzalez FJ, Aoyama T. Peroxisome proliferator-activated receptor α protects against alcohol-induced liver damage. *Hepatology* 40:972-980, 2004
 65. Kiyosawa K, Umemura T, Ichijo T, Matsumoto A, Yoshizawa K, Gad A, Tanaka E. Hepatocellular carcinoma: recent trends in Japan. *Gastroenterology* 127:S17-S26, 2004
 66. Imamura H, Matsuyama Y, Tanaka E, Ohkubo T, Hasegawa K, Miyagawa S, Sugawara Y, Minagawa M, Takayama T, Kawasaki S, Makuuchi, M: Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. *J Hepatol* 38: 200-207, 2003
 67. Yoshizawa K, Ota M, Saito S, Maruyama A, Yamaura T, Rokuhara A, Orii K, Ichijo T, Matsumoto A, Tanaka E, Kiyosawa K: Long-term follow-up of hepatitis C virus infection: HLA class II loci influences the natural history of the disease. *Tissue Antigens* 61: 159-165, 2003
 68. Kobayashi N, Tanaka E, Umemura T, Matsumoto A, Iijima T, Higuchi M, Hora K, Kiyosawa K. Clinical significance of SEN virus infection in patients on maintenance hemodialysis. *Nephrol Dial Transpl* 18: 348-352, 2003
 69. Kimura T, Rokuhara A, Matsumoto A, Yagi S, Tanaka E, Kiyosawa K, Maki N. New enzyme immunoassay for detection of hepatitis B virus core antigen (HBcAg) and relation between levels of HBcAg and HBV DNA. *J Clin Microbiol* 41: 1901-1906, 2003
 70. Yamaura T, Tanaka E, Matsumoto A, Rokuhara A, Orii K, Yoshizawa K, Miyakawa Y, Kiyosawa K. A case-control study for early prediction of hepatitis B e antigen seroconversion by hepatitis

- B virus DNA levels and mutations in the precore region and core promoter. *J Med Virol* 70: 545-552, 2003
71. Gad A, Tanaka E, Matsumoto A, el-Hamid Serwah A, Ali K, Makledy F, el-Gohary A, Orii K, Iijima A, Rokuhara A, Yoshizawa K, Nooman Z, Kiyosawa K. Factors predisposing to the occurrence of cryoglobulinemia in two cohorts of Egyptian and Japanese patients with chronic hepatitis C infection: ethnic and genotypic influence. *J Med Virol* 70: 594-599, 2003
 72. Rokuhara A, Tanaka E, Matsumoto T, Kimura T, Yamaura T, Orii K, Sun X, Yagi S, Maki N, Kiyosawa K. Clinical evaluation of a new enzyme immunoassay for hepatitis B virus core-related antigen: a marker distinct from viral DNA for monitoring lamivudine treatment. *J Viral Hepatitis* 10: 324-330, 2003
 73. Malaty HM, Tanaka E, Kumagai T, Ota H, Kiyosawa K, Graham DY, Katsuyama T. Seroepidemiology of helicobacter pylori and hepatitis A virus and the mode of transmission of infection: a 9-year cohort study in rural Japan. *Clin Infect Dis* 37: 1067-1072, 2003
 74. Umemura T, Tanaka E, Ostapowicz G, Brown KE, Heringlake S, Tassopoulos NC, Wang RYH, Yeo AE, Shih JWK, Orii K, Young NS, Hatzakis A, Manns MP, Lee WM, Kiyosawa K, Alter HJ. Investigation of SEN virus infection in patients with cryptogenic acute liver failure, hepatitis-associated aplastic anemia, or acute and chronic non-A-E hepatitis. *J Infect Dis* 188: 1545-1552, 2003
 75. Gad A, Tanaka E, Orii K, Rokuhara A, Nooman Z, Serwah AEH, El-Sherif A, El-Essawy M, Yoshizawa K, Kiyosawa K. Clinical significance of TT virus infection in maintenance hemodialysis patients of an endemic area for hepatitis C infection. *Hepato Res* 22: 13-19, 2002
 76. Kimura T, Rokuhara A, Sakamoto Y, Yagi S, Tanaka E, Kiyosawa K, Maki N. Sensitive enzyme immunoassay for hepatitis B virus core-related antigens and their correlation to virus load. *J Clin Microbiol* 40: 439-445, 2002
 77. Kakegawa T, Ise H, Sugihara N, Nikaido T, Negishi N, Akaike T, Tanaka E. Soluble asialoglycoprotein receptors reflect the apoptosis of hepatocytes. *Cell Transplantation* 11: 407-415, 2002
 78. Umemura T, Alter HJ, Tanaka E, Orii K, Yeo AET, Shih JWK, Matsumoto A, Yoshizawa K, Kiyosawa K. SEN virus: response to interferon alfa and influence on the severity and treatment response of coexistent hepatitis C. *Hepatology* 35: 953-959, 2002
 79. Yoshizawa K, Cioca DP, Kawa S, Tanaka E, Kiyosawa K.: Peroxisome proliferator-activated receptor γ ligand troglitazone induces cell cycle arrest and apoptosis of hepatocellular carcinoma cell lines. *Cancer* 95: 2243-2251, 2002
 80. Higuchi M, Tanaka E, Kiyosawa K: Epidemiology and clinical aspects on hepatitis C. *Jpn J Infect Dis* 55: 69-77, 2002
 81. Kiyosawa K, Tanaka E: Characteristics of hepatocellular carcinoma in Japan. *Oncology* 62 (suppl 1): 5-7, 2002
 82. Kiyosawa K, Tanaka E: Hepatitis C virus in the etiology of hepatocellular carcinoma. In: Tabor

- E (ed), *Virus and Liver Cancer*. pp31-42, ELSEVIER, New York, 2002
83. Kiyosawa K, Tanaka E: Hepatocellular carcinoma and hepatitis C. In: Sarin SK, Okuda K (eds), *Hepatitis B and C carrier to cancer*. pp315-329, ELSEVIER INDIA, Harcourt, 2002
 84. Aoyagi K, Iida K, Ohue C, Matsunaga Y, Tanaka E, Kiyosawa K, Yagi S: Performance of a conventional enzyme immunoassay for hepatitis C virus core antigen in the early phases of hepatitis C infection. *Clin Lab* 47: 119-127, 2001
 85. Gad A, Tanaka E, Orii K, Rokuhara A, Nooman Z, Serwah AH, Shoair M, Yoshizawa K, Kiyosawa K: Relationship between hepatitis C virus infection and schistosomal liver disease: not simply an additive effect. *J Gastroenterol* 36: 753-758, 2001
 86. Hosaka S, Kawa S, Aoki Y, Tanaka E, Yoshizawa K, Karasawa Y, Hosaka N, Kiyosawa K: Hepatocarcinogenesis inhibition by caffeine in ACl rats treated with 2-acetylaminofluorene. *Food Chem Toxicol* 39: 557-561, 2001
 87. Orito E, Ichida T, Sakugawa H, Sata M, Horiike N, Hino K, Okita K, Okanoue T, Iino S, Tanaka E, Suzuki K, Watanabe H, Hige S, Mizokami M: Geographic distribution of hepatitis B virus (HBV) genotype in patients with chronic HBV infection in Japan. *Hepatology* 34: 590-594, 2001
 88. Orito E, Mizokami M, Sakugawa H, Kojiro M, Ishikawa K, Ichida T, Okanoue T, Yotsuyanagi H, Iino S, Japan HBV genotype research group: A case-control study for clinical and molecular biological differences between hepatitis B viruses of genotype B and C. *Hepatology* 33: 218-223, 2001
 89. Tanaka E, Takeda N, Li TC, Orii K, Ichijo T, Matsumoto A, Yoshizawa K, Iijima T, Takayama T, Miyamura T, Kiyosawa K: Seroepidemiological study of hepatitis E virus infection in Japan using a newly developed antibody assay. *J Gastroenterol* 36: 317-321, 2001
 90. Umemura T, Alter HJ, Tanaka E, Yeo AE, Shih JW, Orii K, Matsumoto A, Yoshizawa K, Kiyosawa K: Association between SEN virus infection and hepatitis C in Japan. *J Infect Dis* 184: 1246-1251, 2001
 91. Kiyosawa K, Tanaka E: Strategy for lamivudine-resistant YMDD mutant-associated chronic hepatitis B. *J Gastroenterol* 36: 139-141, 2001
 92. Iijima A, Tanaka E, Kobayashi M, Yagi S, Mizokami M, Kiyosawa K: Relationship between histological prognosis of chronic hepatitis C and amount of hepatitis C virus core protein in serum. *J Gastroen Hepatol* 15: 311-319, 2000
 93. Gad A, Tanaka E, Orii K, Todoriki K, Serwah A EH, El-Sherif A, Nooman Z, Kiyosawa K: Clinical significance of TT virus infection in patients with chronic liver disease and volunteer blood donors in Egypt. *J Med Virol* 60: 177-181, 2000
 94. Malaty HM, Kumagai T, Tanaka E, Ota H, Kiyosawa K, Graham DY, Katsuyama T: Evidence from nine-year birth cohort study in Japan of transmission pathways of *Helicobacter pylori* infection. *J Clin Microbiol* 38: 1971-1973, 2000
 95. Inada H, Yoshizawa Y, Ota M, Katsuyama Y, Ichijo T, Umemura T, Tanaka E, Kiyosawa K: T cell repertoire in the liver of patients with primary biliary cirrhosis. *Hum Immunol* 61: 675-683,

2000

96. Tanaka E, Ohue C, Aoyagi K, Yamaguchi K, Yagi S, Kiyosawa K, Alter HJ: Evaluation of a new enzyme immunoassay for hepatitis C virus (HCV) core antigen with clinical sensitivity approximating that of genomic amplification of HCV RNA. *Hepatology* 32: 388-393, 2000
97. Umemura T, Yoshizawa K, Ota M, Katsuyama Y, Inada H, Tanaka E, Kiyosawa K: Analysis of T cell repertoire in the liver of patients with chronic hepatitis C. *Clin Exp Immunol* 121: 120-126, 2000
98. Muramatsu T, Hora K, Ako S, Tachibana N, Hora K, Tanaka E: The role of hepatitis C virus infection in glomerulopathy. *Hepatology* 18: 190-202, 2000
99. Orii K, Tanaka E, Rokuhara A, Maruyama A, Ichijo T, Yoshizawa K, Kendo K: Persistent infection mechanism of GB virus C/hepatitis G virus differs from that of hepatitis C virus. *Intervirology* 43: 139-145, 2000
100. Nishizawa Y, Tanaka E, Orii K, Rokuhara A, Ichijo T, Yoshizawa K, Kiyosawa K: Clinical impact of genotype 1 TT virus infection in patients with chronic hepatitis C and response of TT virus to alpha-interferon. *J Gastroenterol Hepatol* 15: 1292-1297, 2000
101. Rokuhara A, Tanaka E, Yagi S, Mizokami M, Hashikura Y, Kawasaki S, Kiyosawa K: De novo infection of hepatitis B virus in patients with orthotopic liver transplantation: analysis by determining complete sequence of the genome. *J Med Virol* 62: 471-478, 2000
102. Tanaka E, Kiyosawa K: Natural history of acute hepatitis C. *J Gastroenterol Hepatol* 15 (suppl): E97-E104, 2000
103. Kiyosawa K, Tanaka E: A new era of interferon treatment for chronic hepatitis C is coming. *J Gastroenterol* 5: 652-654, 2000
104. Desmond P, Yano M, Kaldor J, Kao JH, Tanaka E, Amarapurkar D, Yatsunami H, Zeniya M: Asia-pacific consensus on diagnosis and treatment of chronic hepatitis B and C. In: Liaw YF, McCaughan G, Farrell G, Yano M (eds), Draft working party reports from the Asia-Pacific consensus on prevention and management of chronic hepatitis B and C, pp3i-3iv, Blackwell Science Asia Pty Ltd., Sydney, 2000
105. Aoyagi K, Ohue C, Iida K, Kimura T, Tanaka E, Kiyosawa K, Yagi S: Development of a simple and highly sensitive enzyme immunoassay for hepatitis C virus core antigen. *J Clin Microbiol* 37: 1802-1808, 1999
106. Kobayashi M, Tanaka E, Nakayama J, Furuwatari C, Katsuyama T, Kawasaki S, Kiyosawa K: Detection of GB virus-C/hepatitis G virus genome in peripheral blood mononuclear cells and liver tissue. *J Med Virol* 58: 114-121, 1999
107. Matsumoto A, Yeo AET, Shih JWK, Tanaka E, Kiyosawa K, Alter HJ. Transfusion-associated TT virus infection and its relation to liver disease. *Hepatology* 30: 283-288, 1999
108. Oguchi T, Tanaka E, Orii K, Kobayashi M, Hora K, Kiyosawa K: Transmission of and liver injury by TT virus in patients on maintenance hemodialysis. *J Gastroenterol* 34: 234-240, 1999

109. Orii K, Tanaka E, Umemura T, Rokuhara A, Iijima A, Yoshizawa K, Imai H, Kiyosawa K: Prevalence and disease association of TT virus infection in Japanese patients with viral hepatitis. *Hepatol Res* 14: 161-170, 1999
110. Rumin S, Berthillon P, Tanaka E, Kiyosawa K, Traubad MA, Bizollon T, Guillat C, Gripon P, Guguen-Guillouzu C, Inchauspe G, Trepo C: Dynamic analysis of hepatitis C virus replication and quasispecies selection in long-term cultures of adult human hepatocytes infected in vitro. *J Gen Virol* 80: 3007-3018, 1999
111. Umemura T, Tanaka E, Ota M, Orii K, Yoshizawa K, Imai H, Sodeyama T, Kiyosawa K: TT virus infection in an area of high-endemicity for hepatitis C. *Hepatol Res* 13: 212-220, 1999
112. Vidalin O, Tanaka E, Spengler U, Trepo C, Inchauspe G: Targeting of hepatitis C virus core protein for MHC I or MHC II presentation does not enhance induction of immune responses to DNA vaccination. *DNA Cell Biol* 18: 611-621, 1999
113. Yoshizawa K, Ota M, Katsuyama Y, Ichijo T, Inada H, Umemura T, Tanaka E, Kiyosawa K: T cell repertoire in the liver of patients with autoimmune hepatitis. *Hum Immunol* 60: 806-815, 1999
114. Kiyosawa K, Tanaka E: GB virus C/hepatitis G virus. *Intervirology* 42: 185-195, 1999
115. Tanaka E. Does GBV-C/HGV replicate in the liver? *J Gastroenterol* 34: 721-723, 1999
116. Kobayashi M, Tanaka E, Oguchi H, Hora K, Kiyosawa K: Prospective follow-up study of hepatitis C virus infection in patients undergoing maintenance haemodialysis: comparison among haemodialysis units. *J Gastroen Hepatol* 13: 604-609, 1998
117. Kobayashi M, Tanaka E, Matsumoto A, Yoshizawa K, Imai H, Sodeyama T, Kiyosawa K: Clinical application of hepatitis C virus core protein in early diagnosis of acute hepatitis C. *J Gastroenterol* 33: 508-511, 1998
118. Kumagai T, Malaty HM, Graham DY, Hosogaya S, Misawa K, Furihata K, Ota H, Sei C, Tanaka E, Akamatsu T, Shimizu T, Kiyosawa K, Katsuyama T: Acquisition versus loss of helicobacter pylori infection in Japan: results from an 8-year birth cohort study. *J Infect Dis* 178: 717-721, 1998
119. Tanaka E, Tacke M, Kobayashi M, Nakatsuji Y, Kiyosawa K, Schmolke S, Engel AM, Hess G, Alter HJ: Past and present hepatitis G virus infections in area where hepatitis C is highly endemic and those where it is not endemic. *J Clin Microbiol* 36: 110-114, 1998
120. Tanaka E, Kiyosawa K, Shimoda K, Hino K, Tacke M, Schmolke S, Engel AM, Hess G: Evolution of hepatitis G virus infection and antibody response to envelope protein with transfusion-associated non-A, non-B hepatitis. *J Viral Hepatitis* 5: 153-159, 1998
121. Kiyosawa K, Tanaka E, Sodeyama T: Hepatitis C virus and hepatocellular carcinoma, In: Reesink HW (ed), *Hepatitis C Virus*, no. 62, pp161-180, *Curr Stud Hematol Blood Transf*, Basel, 1998
122. Kiyosawa K, Ichijo T, Kobayashi M, Tanaka E, Sodeyama T: Hepatitis C: diagnosis, quantification and genotyping. In: Sarin SK and Hess G (eds), *Transfusion Associated*

- Hepatitis: Diagnosis, Treatment and Prevention, pp186-195, CBS PUBLISHERS & DISTRIBUTORS, New Delhi, 1998
123. Ichijo T, Nakatsuji Y, Tanaka E, Alter HJ, Yoshizawa K, Imai H, Sodeyama T, Kiyosawa K: Autoimmune hepatitis type 1 without evidence of hepatitis G virus infection. *Int Hepatol Commun* 6: 219-224, 1997
 124. Kobayashi M, Tanaka E, Matsumoto A, Ichijo T, Kiyosawa K: Antibody response to E2/NS1 hepatitis C virus protein in patients with acute hepatitis C. *J Gastroen Hepatol* 12: 73-76, 1997
 125. Tanaka E, Yamaguchi K, Uemura K, Kobayashi M, Iijima A, Kiyosawa K, Yagi S, Hasegawa A: Hepatitis G virus/GB virus C infection in patients with chronic non-B, non-C hepatitis. *Int Hepatol Commun* 6: 137-143, 1997
 126. Tanaka E, Nakatsuji Y, Kobayashi M, Iijima A, Ichijo T, Imai H, Yoshizawa K, Sodeyama T, Kiyosawa K: Hepatitis G virus/GB virus C infection in an area of high endemic hepatitis C virus infection. *Hepatol Res* 7: 130-135, 1997
 127. Ideura T, Tanaka E, Nakatsuji Y, Kobayashi M, Kanno Y, Oguchi H, Hora K: Clinical significance of hepatitis G virus infection in patients on long-term haemodialysis. *J Gastroen Hepatol* 12: 762-765, 1997
 128. Ichijo T, Matsumoto A, Kobayashi M, Furihata K, Tanaka E. Quantative measurement of HCV RNA in the serum: A comparison of three assays based on different principles. *J Gastroen Hepatol* 12: 500-506, 1997
 129. Tacke M, Schmolke S, Schlueter V, Sauleda S, Esteban JI, Tanaka E, Kiyosawa K, Alter HJ, Schmitt U, Hess G, Ofenloch-Haehnle B, Engel AM: Humoral immune response to the E2 protein of hepatitis G virus is associated with long-term recovery from infection and reveals a high frequency of hepatitis G virus exposure among healthy blood donors. *Hepatology* 26: 1626-1633, 1997
 130. Alter HJ, Nakatsuji Y, Tanaka E, Melpolder J, Kim J, Shih JWK, Kiyosawa K: The role of the hepatitis G virus in the causation of transfusion associated hepatitis and cryptogenic liver disease and the impact of HGV on coexistent HCV infection. In: Rizzetto M, et al. (eds.), *Viral Hepatitis and Liver Disease*. pp358-362, Edizioni Minerva Medica S.p.A., Torino, 1997
 131. Mori H, Yabu K, Yoshizawa K, Tanaka E, Kiyosawa K: Lymphocyte proliferative responses to recombinant hepatitis C virus antigens in patients with chronic hepatitis C. *J Gastroen Hepatol* 11: 697-704, 1996
 132. Shimodaira S, Ishida F, Ichikawa N, Tahara T, Kato T, Kodaira H, Ito T, Tanaka E, Sodeyama T, Kiyosawa K, Kitano K: Serum thrombopoietin (c-Mpl ligand) levels in patients with liver cirrhosis. *Thromb and Haematosi*s 76: 545-548, 1996
 133. Tanaka E, Kiyosawa K, Matsumoto A, Kashiwakuma T, Hasegawa A, Mori H, Yanagihara O, Ohta Y: Serum levels of hepatitis C virus core protein in patients with chronic hepatitis C treated with interferon Alfa. *Hepatology* 23: 1330-1333, 1996
 134. Kobayashi M, Tanaka E, Sodeyama T, Urushihara A, Matsumoto A, Kiyosawa K: The

- natural course of chronic hepatitis C: a comparison between patients with genotypes 1 and 2 hepatitis C viruses. *Hepatology* 23: 695-699, 1996
135. Nakatsuji Y, Shih JWK, Tanaka E, Kiyosawa K, Wages Jr J, Kim JP and Alter HJ: Prevalence and disease association of hepatitis G virus infection in Japan. *J Viral Hepatitis* 3: 307-316, 1996
136. Kashiwakuma T, Hasegawa A, Kajita T, Takata A, Mori H, Ohta Y, Tanaka E, Kiyosawa K, Tanaka T, Tanaka S, Hattori N, Kohara M: Detection of hepatitis C virus specific core protein in serum of patients by a sensitive fluorescence enzyme immunoassay (FEIA). *J Immunol Methods* 190: 79-89, 1996
137. Tanaka E, Alter HJ, Nakatsuji Y, Shih JWK, Kim JP, Matsumoto A, Kobayashi M, Kiyosawa K: Effect of hepatitis G virus infection on chronic hepatitis C. *Ann Intern Med* 125: 740-743, 1996
138. Suzuki T, Tanaka E, Matsumoto A, Urushihara A, Sodeyama T, Kiyosawa K: Usefulness of simple assays for serum concentration of hepatitis C virus (HCV) RNA and HCV genotype in predicting response of patients with chronic hepatitis C to interferon alpha2a therapy. *J Med Virol* 46: 162-168, 1995
139. Tanaka E, Kiyosawa K, Matsushima T, Ishikawa K, Hino K, Tanaka S, Nose H, Kumada H, Iino S, Kamimura T, Unoura M, Mizokami M, Okanoue T, Kuroki T, Yamada G, Miura T, Yano M, Tsubouchi H, Kohara M, Sato S, Hattori N. Genotyping ELISA Study Group: Epidemiology of genotypes of hepatitis C virus in Japanese patients with type C chronic liver diseases: a multi-institute analysis. *J Gastroen Hepatol* 10: 538-545, 1995
140. Tanaka T, Lau JYN, Mizokami M, Orito E, Tanaka E, Kiyosawa K, Yasui K, Ohta Y, Hasegawa A, Tanaka S, Kohara M: Simple fluorescent enzyme immunoassay for detection and quantification of hepatitis C viremia. *J Hepatol* 23: 742-745, 1995
141. Kiyosawa K, Tanaka E, Sodeyama T, Yoshizawa K, Yabu K, Furuta K, Imai H, Nakano Y, Usuda S, Uemura K, Furuta S, Watanabe Y, Watanabe J, Fukuda Y, Takayama T, South Kiso Hepatitis Study Group: Transmission of hepatitis C in an isolated area in Japan: community-acquired infection. *Gastroenterology* 106: 1596-1602, 1994
142. Matsumoto A, Tanaka E, Suzuki T, Ogata H, Kiyosawa K: Viral and host factors that contribute to efficacy of interferon- α 2a therapy in patients with chronic hepatitis C. *Digest Dis Sci* 39: 1273-1280, 1994
143. Tanaka E, Kiyosawa K, Matsumoto A, Sodeyama T, Urushihara A, Suzuki T, Kobayashi M, Furuta S: Prevalence of hepatitis C virus with different genotypes determined by a group-specific antibody assay in Japanese patients with chronic liver disease due to hepatitis C virus infection. *Jpn J Med Sci Biol* 47: 47-57, 1994
144. Uchida T, Shikata T, Tanaka E, Kiyosawa K: Immunoperoxidase staining of hepatitis C virus in formalin-fixed, paraffin-embedded needle liver biopsies. *Virchows Archiv* 424: 465-469, 1994

145. Urushihara A, Sodeyama T, Matsumoto A, Tanaka E: Change in antibody titers to hepatitis C virus following interferon therapy for chronic infection. *J Med Virol* 42: 348-356, 1994
146. Urushihara A, Suzuki T, Matsumoto A, Tanaka E, Sodeyama T, Kiyosawa K, Furuta S: Quantitative assay for anti-HCV-core antibody in healthy individuals found anti-HCV positive during a mass screening. *Int Hepatol Commun* 2: 47-51, 1994
147. Yabu K, Kiyosawa K, Ako S, Usuda S, Yoshizawa K, Tanaka E, Sodeyama T, Furuta S. Type C chronic hepatitis associated with thrombocytopenia in two patients. *J Gastroenterol Hepatol* 9: 99-104, 1994
148. Yabu K, Kiyosawa K, Mori H, Matsumoto A, Yoshizawa K, Tanaka E, Furuta S: Serum collagen type IV for the assessment of fibrosis and resistance to interferon therapy in chronic hepatitis C. *Scand J Gastroenterol* 29: 474-479, 1994
149. Yamaguchi K, Tanaka E, Higashi K, Kiyosawa K, Matsumoto A, Furuta S, Hasegawa A, Tanaka S, Kohara M: Adaptation of hepatitis C virus for persistent infection in patients with acute hepatitis. *Gastroenterology* 106: 1344-1348, 1994
150. Kiyosawa K, Tanaka E, Sodeyama T, Furuta S: Natural history of hepatitis C. *Intervirol* 37: 101-107, 1994
151. Furuta K, Kiyosawa K, Sone H, Matsumoto A, Tanaka E, Sodeyama T, Imai H, Furuta S: Chronological changes of hepatitis B and C virus markers in Japanese patients with hepatocellular carcinoma. In: Nishioka K, et al. (eds.), *Viral Hepatitis and Liver Disease*, pp690-693, Springer-Verlag, Tokyo, 1994
152. Kiyosawa K, Sodeyama T, Tanaka E, Furuta S: Hepatitis C virus infection in health care workers. In: Nishioka K, et al. (eds), *Viral Hepatitis and Liver Disease*, pp479-482, Springer-Verlag, Tokyo, 1994
153. Mori H, Yabu K, Yoshizawa K, Usuda S, Tanaka E, Kiyosawa K, Hasegawa A, Kohara M, Furuta S: In vitro immune responses specific for NS3 regional peptide (C7) and core regional peptide (C11) of HCV in chronic hepatitis C. In: Nishioka K, et al. (eds.), *Viral Hepatitis and Liver Disease*, pp 182-185, Springer-Verlag, Tokyo, 1994
154. Sodeyama T, Kiyosawa K, Urushihara A, Matsumoto A, Tanaka E, Furuta S, Mizokami M, Akahane Y: Transmission of hepatitis C virus through needlestick accidents in health care workers. In: Nishioka K, et al. (eds.), *Viral Hepatitis and Liver Disease*, pp 459-462, Springer-Verlag, Tokyo, 1994
155. Khan M, Husain M, Yano M, Hashizume K, Yousuf M, Tanaka E, Matsumoto A, Furuta S, Kiyosawa K: Comparison of seroepidemiology of hepatitis C in blood donors between Bangladesh and Japan. *Gastroenterologia Jpn* 28 (suppl 5): 28-31, 1993
156. Kiyosawa K, Seki T, Tanaka E, Sodeyama T, Furuta K, Furuta S, Hino K, Ota M, Inoko H: Comparison of the clinical and immunogenetic features between patients with autoimmune hepatitis and patients with type C chronic active hepatitis. *Gastroenterologia Jpn* 28 (suppl 4): 63-68, 1993

157. Kiyosawa K, Sodeyama T, Tanaka E: Progress of asymptomatic hepatitis B surface antigen carriers. *Ann Intern Med* 119: 535, 1993
158. Nakamura T, Hayama M, Sakai T, Hotchi M, Tanaka E: Proliferative activity of hepatocytes in chronic viral hepatitis as revealed by immunohistochemistry for proliferating cell nuclear antigen. *Hum Pathol* 24: 750-753, 1993
159. Nakano Y, Kiyosawa K, Sodeyama T, Tanaka E, Yoshizawa K, Furuta K, Nakatsuji Y, Urushihara A, Furuta S: Anti-c100 antibodies to hepatitis C virus in patients with chronic hepatitis C virus infection treated with interferon. *Scand J Gastroenterol* 28: 335-342, 1993
160. Seki T, Kiyosawa K, Ota M, Furuta S, Fukushima H, Tanaka E, Yoshizawa K, Kumagai T, Mizuki N, Ando A, Inoko H: Association of primary biliary cirrhosis with leukocyte antigen DPB1*0501 in Japanese patients. *Hepatology* 18: 73-78, 1993
161. Sodeyama T, Kiyosawa K, Urushihara A, Matsumoto A, Tanaka E, Furuta S, Akahane Y: Detection of hepatitis C virus markers and hepatitis C virus genomic-RNA after needlestick accidents. *Arch Intern Med* 153: 1565-1572, 1993
162. Tanaka E, Kiyosawa K, Nakatsuji Y, Inoue Y, Miyamura T, Chiba J, Furuta S: Clinical significance of antibodies to nonstructural and core protein of hepatitis C virus in posttransfusion hepatitis patients during long-term follow-up. *J Med Virol* 39: 318-324, 1993
163. Tanaka E, Kiyosawa K, Seki T, Matsumoto A, Sodeyama t, Furuta S, Kumagai T, Kohara M: Low prevalence of hepatitis C virus infection in patients with auto-immune hepatitis type 1. *J Gastroenterol Hepatol* 8: 442-447, 1993
164. Oguchi H, Miyasaka M, Tokunaga S, Hora K, Ichikawa S, Ochi T, Yamada K, Nagasawa M, Kanno Y, Aizawa T, Watanabe H, Yoshizawa S, Sato K, Terashima M, Yoshie T, Oguchi S, Tanaka E, Kiyosawa K, Furuta S: Hepatitis virus infection (HBV and HCV) in eleven Japanese hemodialysis units. *Clin Nephrol* 38: 36-43, 1992
165. Yoshizawa K, Kiyosawa K, Usuda S, Yabu K, Nakatsuji Y, Yamada S, Furuta K, Tanaka E, Sodeyama T, Furuta S, Kaneko S, Nakane PK: New hepatocellular carcinoma cell line SUHC-1 established from a patient with hepatitis C virus RNA in serum. *Jpn J Cancer Res* 83: 871-877, 1992
166. Nakatsuji Y, Matsumoto A, Tanaka E, Ogata H, Kiyosawa K: Detection of chronic hepatitis C virus infection by four diagnostic systems: First-generation and second-generation Enzyme-linked immunosorbent assay, second-generation recombinant immunoblot assay and nested polymerase chain reaction analysis. *Hepatology* 16: 300-305, 1992
167. Yousuf M, Nakano Y, Tanaka E, Sodeyama T, Kiyosawa K: Persistence of viremia in patients with type C chronic hepatitis during long-term follow-up. *Scand J Gastroenterol* 27: 812-816, 1992
168. Shimizu S, Kiyosawa K, Sodeyama T, Tanaka E, Nakano M: High prevalence of antibody to hepatitis C viruses in heavy drinkers with chronic liver diseases in Japan. *J Gastroenterol Hepatol* 7: 30-35, 1992