(3) ブタ内臓肉摂取以外の HEV 感染経路の探索(班長、姜班員、鈴木班員、班友多数)。
(4) 興味ある HEV 株(例えばイノシシ由来 genotype 5)の全長配列決定 and/or 感染性クローンの作成(新井班員)
(5) 動物由来 HEV のウイルス様粒子 (VLP) の作製し、VLP を用いた抗体検査法を樹立するとともに、ヒト HEV との抗原性を比較し、動物由来 HEV の血清疫学解析を行う(李班員)。
(6) 北海道地区において献血者の HEV RNA スクリーニング調査と HEV RNA 陽性献血者のフォローアップ調査を継続して実施し、HEV 陽性献血者の感染経路や臨床経過について解明する(日野班員)。

V. 行政施策への貢献の可能性

(1)A 型肝炎について、ワクチン施策の再検討に繋がるデータが提供される。
(2)E 型肝炎について、本邦における E 型肝炎の罹患率、死亡率が減少する。
(3)本研究の推進により、食の安全性、輸血血液の安全性が担保される。

VI. 本研究の成果(発表論文・ガイドライン・マニュアル等)

・研究代表者

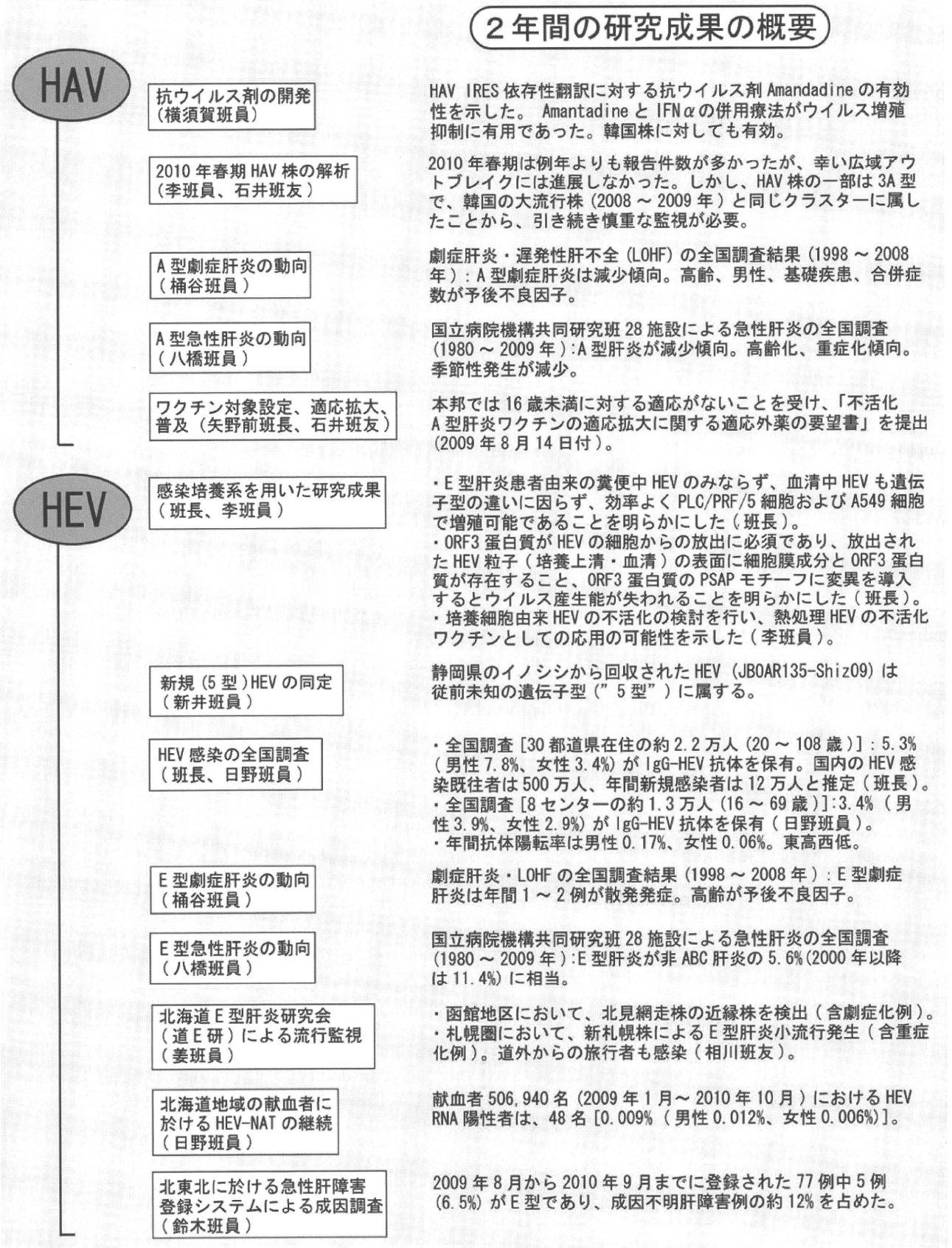
1. Nagashima S, Takahashi M, Jirintai D, Tanaka T, Yamada K, Nishizawa T, Okamoto H. A PSAP motif in the ORF3 protein of hepatitis E virus is necessary for virion release from infected cells. J Gen Virol 2011 (in press).
2. Takahashi M, Tamura K, Hoshino Y, Nagashima S, Yazaki Y, Mizuo H, Iwamoto S, Okayama M, Nakamura Y, Kajii E, Okamoto, H. A nationwide survey of hepatitis E virus infection in the general population of Japan. J Med Virol 82(2): 271-281, 2010.
3. Takahashi M, Tanaka T, Takahashi H, Hoshino Y, Nagashima S, Jirintai, Mizuo H, Yazaki Y, Takagi T, Azuma M, Kusano E, Isoda N, Sugano K, Okamoto H. Hepatitis E Virus (HEV) strains in serum samples can replicate efficiently in cultured cells despite the coexistence of HEV antibodies: characterization of HEV virions in blood circulation. J Clin Microbiol 48(4): 1112-1125, 2010.
4. Ichiyama K, Yamada K, Tanaka T, Nagashima S, Jirintai, Takahashi M, Okamoto H. Determination of the 5'-terminal sequence of subgenomic RNA of hepatitis E virus strains in cultured cells. Arch Virol 154(12): 1945-1951, 2009.
5. Tanaka T, Takahashi M, Takahashi H, Ichiyama K, Hoshino Y, Nagashima S, Mizuo H, Okamoto H. Development and characterization of a genotype 4 hepatitis E virus cell culture system using a HE-JF5/15F strain recovered from a fulminant hepatitis patient. J Clin Microbiol 47(6): 1906-1910, 2009.
6. Yamada K, Takahashi M, Hoshino Y, Takahashi H, Ichiyama K, Nagashima S, Tanaka T, Okamoto H. ORF3 protein of hepatitis E virus is essential for virion release from infected cells. J Gen Virol 90(Pt 8): 1880-1891, 2009.
7. Yamada K, Takahashi M, Hoshino Y, Takahashi H, Ichiyama K, Tanaka T, Okamoto H. Construction of an infectious cDNA clone of hepatitis E virus strain JE03-1760F that can propagate efficiently in cultured cells. J Gen Virol 90(Pt 2): 457-462, 2009.

・研究分担者

(1) Kanda T, Jeong SH, Imazeki F, Fujiwara K, Yokosuka O. Analysis of 5'nontranslated region of hepatitis A viral RNA genotype I from South Korea: comparison with disease severities. PLoS ONE 2010 (in press).
(2) Kanda T, Gauss-Muller V, Cordes S, Tamura R, Okitsu K, Shuang W, Nakamoto S, Fujiwara K, Imazeki F, Yokosuka O. Hepatitis A virus (HAV) protease 3C inhibits HAV IRES-dependent translation and cleaves the polypyrimidine tract-binding protein. J Viral Hepat 17 (9): 618-623, 2010.
(3) Kanda T, Imazeki F, Nakamoto S, Okitsu K, Fujiwara K, Yokosuka O. Internal ribosomal entry-site activities of clinical isolates-derived hepatitis A virus and inhibitory effects of amantadine. Hepatol Res 40 (4): 415-423, 2010.
(4) Yang L, Kiyohara T, Kanda T, Imazeki F, Fujiwara K, Gauss-Muller V, Ishii K, Wakita T, Yokosuka O. Inhibitory effects on HAV IRES-mediated translation and replication by a combination of amantadine and interferon-alpha. Virol J 7: 212, 2010.
(5) Xing L, Wang JC, Li TC, Yasutomi Y, Lara J, Khudyakov Y, Schofield D, Emerson SU, Purcell RH, Takeda N, Miyamura T, Cheng RH. Spatial configuration of hepatitis E virus antigenic domain. J Virol 2010 (in press).
(6) Li TC, Xing L, Mayazaki N, Simon MN, Wall JS, Moore M, Wang CY, Takeda N, Wakita T, Miyamura T, Cheng RH. Structure of hepatitis E virion-sized particle reveals an RNA-dependent viral assembly pathway. J Biol Chem 285(43):33175-33183, 2010.
(7) Yano K, Tamada Y, Yatsuhashi H, Komori A, Abiru S, Ito K, et al. Dynamic epidemiology of acute viral hepatitis in Japan. Intervirology 53(1): 70-75, 2010.
(8) Takeda H, Matsubayashi K, Sakata H, Sato S, Kato T, Hino S, Tadokoro K, Ikeda H. A nationwide survey for prevalence of hepatitis E virus antibody in qualified blood donors in Japan. Vox Sang 99:307-313, 2010.

Ⅶ. Ⅲ(2 年間の研究成果)の概要図等

※ポンチ絵等でわかりやすく簡潔に説明してください。



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1985年1月　自治医科大学助手(予防生態学)
1987年10月 自治医科大学講師(予防生態学)
2000年4月　自治医科大学助教授(予防生態学・分子ウイルス学研究部併任)
2003年4月　自治医科大学教授(感染・免疫学講座ウイルス学部門)、現在に至る。

・主な共同研究者(又は指導を受けた研究者)

指導を受けた研究者

真弓　忠先生、今井光信先生、宮川侑三先生、三代俊治先生

共同研究者

国内外、多数

・主な研究課題

1) A型肝炎ウイルスの塩基配列の解析と遺伝子型分類
2) B型肝炎ウイルスのサブタイプと遺伝子型に関する研究
3) B型肝炎ウイルスの変異と病態に関する研究
4) 新規B型肝炎ウイルス株の同定と遺伝子解析
5) B型肝炎ウイルスの各種測定系の開発
6) C型肝炎ウイルスの塩基配列の解析と遺伝子型分類
7) C型肝炎ウイルスの変異と病態に関する研究
8) C型肝炎ウイルスの各種測定系の開発
9) デルタ肝炎ウイルスの抗体測定系の開発
10) E型肝炎ウイルスの遺伝子配列の解析と分子疫学的研究
11) E型肝炎ウイルスの各種測定系の開発
12) E型肝炎ウイルスの感染培養系の確立とその応用研究
13) E型肝炎ウイルスの増殖機構に関する研究
14) GBV-Cの遺伝子解析と感染疫学に関する研究
15) TTウイルス(アネロウイルス)の同定と分子ウイルス学的研究
16) アジア諸国(インドネシア、ネパール、タイ、ベトナム、中国、モンゴル等)に於ける肝炎ウイルス感染の実態調査と分子疫学的研究
17) 原因不明疾患に関わる未同定ウイルスの探索

・これまでの研究実績

1. ***Nagashima, S., Takahashi, M., Jirintai, D., Tanaka, T., Yamada, K., Nishizawa, T., Okamoto, H., 2011. A PSAP motif in the ORF3 protein of hepatitis E virus is necessary for virion release from infected cells. J Gen Virol. in press***
2. Depamede, S.N., Wahyono, A., Nagashima, S., Takahashi, M., Okamoto, H., 2011. Analysis of the full-length genomes of novel hepatitis B virus subgenotypes C11 and C12 in Papua, Indonesia. J Med Virol 83(1), 54-64.
3. Ishimura, M., Ohga, S., Ichiyama, M., Kusuhara, K., Takada, H., Hara, T., Takahashi, M., Okamoto, H., 2010. Hepatitis-associated aplastic anemia during a primary infection of genotype 1a torque teno virus. Eur J Pediatr 169(7), 899-902.
4. ***Jinshan, Jirintai, Manglai, D., Takahashi, M., Nagashima, S., Okamoto, H., 2010. Molecular and serological survey of hepatitis E virus infection among domestic pigs in Inner Mongolia, China. Arch Virol 155(8), 1217-1226.***
5. Mulyanto, Depamede, S.N., Surayah, K., Tjahyono, A.A., Jirintai, Nagashima, S., Takahashi, M., Okamoto, H., 2010. Identification and characterization of novel hepatitis B virus subgenotype C10 in Nusa Tenggara, Indonesia. Arch Virol 155(5), 705-715.

6. Ohto, H., Ishii, T., Kitazawa, J., Sugiyama, S., Ujiie, N., Fujimori, K., Ariga, H., Satoh, T., Nollet, K.E., Okamoto, H., Hoshi, T., 2010. Declining hepatitis C virus (HCV) prevalence in pregnant women: impact of anti-HCV screening of donated blood. Transfusion 50(3), 693-700.
7. ***Takahashi, M., Tamura, K., Hoshino, Y., Nagashima, S., Yazaki, Y., Mizuo, H., Iwamoto, S., Okayama, M., Nakamura, Y., Kajii, E., Okamoto, H., 2010. A nationwide survey of hepatitis E virus infection in the general population of Japan. J Med Virol 82(2), 271-281.***
8. ***Takahashi, M., Tanaka, T., Takahashi, H., Hoshino, Y., Nagashima, S., Jirintai, Mizuo, H., Yazaki, Y., Takagi, T., Azuma, M., Kusano, E., Isoda, N., Sugano, K., Okamoto, H., 2010. Hepatitis E Virus (HEV) strains in serum samples can replicate efficiently in cultured cells despite the coexistence of HEV antibodies: characterization of HEV virions in blood circulation. J Clin Microbiol 48(4), 1112-1125.***
9. ***Davaalkham, D., Enkhoyun, T., Takahashi, M., Nakamura, Y., Okamoto, H., 2009. Hepatitis A and E virus infections among children in Mongolia. Am J Trop Med Hyg 81(2), 248-251.***
10. ***Ichiyama, K., Yamada, K., Tanaka, T., Nagashima, S., Jirintai, Takahashi, M., Okamoto, H., 2009. Determination of the 5'-terminal sequence of subgenomic RNA of hepatitis E virus strains in cultured cells. Arch Virol 154(12), 1945-1951.***
11. ***Inoue, J., Takahashi, M., Mizuo, H., Suzuki, K., Aikawa, T., Shimosegawa, T., Okamoto, H., 2009. Nucleotide substitutions of hepatitis E virus genomes associated with fulminant hepatitis and disease severity. Tohoku J Exp Med 218(4), 279-284.***
12. ***Inoue, J., Ueno, Y., Nagasaki, F., Akahane, T., Fukushima, K., Kogure, T., Kondo, Y., Kakazu, E., Tamai, K., Kido, O., Nakagome, Y., Ninomiya, M., Obara, N., Wakui, Y., Takahashi, M., Okamoto, H., Shimosegawa, T., 2009. Sporadic acute hepatitis E occurred constantly during the last decade in northeast Japan. J Gastroenterol 44(4), 329-337.***
13. Mulyanto, Depamede, S.N., Surayah, K., Tsuda, F., Ichiyama, K., Takahashi, M., Okamoto, H., 2009. A nationwide molecular epidemiological study on hepatitis B virus in Indonesia: identification of two novel subgenotypes, B8 and C7. Arch Virol 154(7), 1047-1059.
14. Ninomiya, M., Takahashi, M., Hoshino, Y., Ichiyama, K., Simmonds, P., Okamoto, H., 2009. Analysis of the entire genomes of torque teno midi virus variants in chimpanzees: infrequent cross-species infection between humans and chimpanzees. J Gen Virol 90(Pt 2), 347-358.
15. Okamoto, H., 2009. History of discoveries and pathogenicity of TT viruses. Curr Top Microbiol Immunol 331, 1-20.
16. Okamoto, H., 2009. TT viruses in animals. Curr Top Microbiol Immunol 331, 35-52.
17. ***Takahashi, K., Okamoto, H., Abe, N., Kawakami, M., Matsuda, H., Mochida, S., Sakugawa, H., Suginoshita, Y., Watanabe, S., Yamamoto, K., Miyakawa, Y., Mishiro, S., 2009. Virulent strain of hepatitis E virus genotype 3, Japan. Emerg Infect Dis 15(5), 704-709.***
18. ***Tanaka, T., Takahashi, M., Takahashi, H., Ichiyama, K., Hoshino, Y., Nagashima, S., Mizuo, H., Okamoto, H., 2009. Development and characterization of a genotype 4 hepatitis E virus cell culture system using a HE-JF5/15F strain recovered from a fulminant hepatitis patient. J Clin Microbiol 47(6), 1906-1910.***
19. Toda, T., Mitsui, T., Tsukamoto, Y., Ebara, T., Hirose, A., Masuko, K., Nagashima, S., Takahashi, M., Okamoto, H., 2009. Molecular analysis of transmission of hepatitis C virus in a nurse who acquired acute hepatitis C after caring for a viremic patient with epistaxis. J Med Virol 81(8), 1363-1370.
20. Toda, T., Mitsui, T., Tsukamoto, Y., Ebara, T., Masuko, K., Takahashi, M., Okamoto, H., 2009. No evidence for patient-to-patient transmission of hepatitis C virus during upper gastrointestinal endoscopy: molecular studies on three acute hepatitis C patients. Dig Endosc 21(3), 147-153.
21. ***Yamada, K., Takahashi, M., Hoshino, Y., Takahashi, H., Ichiyama, K., Nagashima, S., Tanaka, T., Okamoto, H., 2009. ORF3 protein of hepatitis E virus is essential for virion release from infected cells. J Gen Virol 90(Pt 8), 1880-1891.***
22. ***Yamada, K., Takahashi, M., Hoshino, Y., Takahashi, H., Ichiyama, K., Tanaka, T., Okamoto, H., 2009. Construction of an infectious cDNA clone of hepatitis E virus strain JE03-1760F that can propagate efficiently in cultured cells. J Gen Virol 90(Pt 2), 457-462.***
23. Bando, M., Takahashi, M., Ohno, S., Hosono, T., Hironaka, M., Okamoto, H., Sugiyama, Y., 2008. Torque teno virus DNA titre elevated in idiopathic pulmonary fibrosis with primary lung cancer. Respirology 13(2), 263-269.
24. Ennishi, D., Terui, Y., Yokoyama, M., Mishima, Y., Takahashi, S., Takeuchi, K., Okamoto, H., Tanimoto, M., Hatake, K., 2008. Monitoring serum hepatitis C virus (HCV) RNA in patients with HCV-infected CD20-positive B-cell lymphoma undergoing rituximab combination chemotherapy. Am J Hematol 83(1), 59-62.
25. Inoue, J., Ueno, Y., Kogure, T., Nagasaki, F., Kimura, O., Obara, N., Kido, O., Nakagome, Y., Kakazu, E., Matsuda, Y., Fukushima, K., Segawa, H., Nakajima, I., Itoyama, Y., Takahashi, M., Okamoto, H., Shimosegawa, T., 2008. Analysis of the full-length genome of hepatitis B virus in the serum and cerebrospinal fluid of a patient with acute hepatitis B and transverse myelitis. J Clin Virol 41(4), 301-304.

26. Lorenzo, F.R., Tanaka, T., Takahashi, H., Ichiyama, K., Hoshino, Y., Yamada, K., Inoue, J., Takahashi, M., Okamoto, H., 2008. Mutational events during the primary propagation and consecutive passages of hepatitis E virus strain JE03-1760F in cell culture. Virus Res 137(1), 86-96.
27. Ninomiya, M., Takahashi, M., Nishizawa, T., Shimosegawa, T., Okamoto, H., 2008. Development of PCR assays with nested primers specific for differential detection of three human anelloviruses and early acquisition of dual or triple infection during infancy. J Clin Microbiol 46(2), 507-514.
28. Takahashi, M., Hoshino, Y., Tanaka, T., Takahashi, H., Nishizawa, T., Okamoto, H., 2008. Production of monoclonal antibodies against hepatitis E virus capsid protein and evaluation of their neutralizing activity in a cell culture system. Arch Virol 153(4), 657-666.
29. Takahashi, M., Yamada, K., Hoshino, Y., Takahashi, H., Ichiyama, K., Tanaka, T., Okamoto, H., 2008. Monoclonal antibodies raised against the ORF3 protein of hepatitis E virus (HEV) can capture HEV particles in culture supernatant and serum but not those in feces. Arch Virol 153(9), 1703-1713.
30. Davaalkham, D., Ojima, T., Uehara, R., Watanabe, M., Oki, I., Endo, K., Takahashi, M., Okamoto, H., Nakamura, Y., 2007. Analysis of hepatitis B surface antigen mutations in Mongolia: molecular epidemiology and implications for mass vaccination. Arch Virol 152(3), 575-584.
31. Endo, K., Inoue, J., Takahashi, M., Mitsui, T., Masuko, K., Akahane, Y., Okamoto, H., 2007. Analysis of the full-length genome of a subgenotype IIIB hepatitis A virus isolate: primers for broadly reactive PCR and genotypic analysis. J Med Virol 79(1), 8-17.
32. Endo, K., Takahashi, M., Masuko, K., Inoue, K., Akahane, Y., Okamoto, H., 2007. Full-length sequences of subgenotype IIIA and IIIB hepatitis A virus isolates: characterization of genotype III HAV genomes. Virus Res 126(1-2), 116-127.
33. Fukuda, S., Ishikawa, M., Ochiai, N., Suzuki, Y., Sunaga, J., Shinohara, N., Nozawa, K., Tsuda, F., Takahashi, M., Okamoto, H., 2007. Unchanged high prevalence of antibodies to hepatitis E virus (HEV) and HEV RNA among blood donors with an elevated alanine aminotransferase level in Japan during 1991-2006. Arch Virol 152(9), 1623-1635.
34. Gotanda, Y., Iwata, A., Ohnuma, H., Yoshikawa, A., Mizoguchi, H., Endo, K., Takahashi, M., Okamoto, H., 2007. Ongoing subclinical infection of hepatitis E virus among blood donors with an elevated alanine aminotransferase level in Japan. J Med Virol 79(6), 734-742.
35. Kumagai, I., Abe, K., Oikawa, T., Sato, A., Sato, S., Endo, R., Takikawa, Y., Suzuki, K., Masuda, T., Sainokami, S., Endo, K., Takahashi, M., Okamoto, H., 2007. A male patient with severe acute hepatitis who was domestically infected with a genotype H hepatitis B virus in Iwate, Japan. J Gastroenterol 42(2), 168-175.
36. Lorenzo, F.R., Tsatsralt-Od, B., Ganbat, S., Takahashi, M., Okamoto, H., 2007. Analysis of the full-length genome of hepatitis E virus isolates obtained from farm pigs in Mongolia. J Med Virol 79(8), 1128-1137.
37. Lu, L., Li, C., Fu, Y., Gao, F., Pybus, O.G., Abe, K., Okamoto, H., Hagedorn, C.H., Murphy, D., 2007. Complete genomes of hepatitis C virus (HCV) subtypes 6c, 6l, 6o, 6p and 6q: completion of a full panel of genomes for HCV genotype 6. J Gen Virol 88(Pt 5), 1519-1525.
38. Lu, L., Li, C., Fu, Y., Thaikruea, L., Thongswat, S., Maneekarn, N., Apichartpiyakul, C., Hotta, H., Okamoto, H., Netski, D., Pybus, O.G., Murphy, D., Hagedorn, C.H., Nelson, K.E., 2007. Complete genomes for hepatitis C virus subtypes 6f, 6i, 6j and 6m: viral genetic diversity among Thai blood donors and infected spouses. J Gen Virol 88(Pt 5), 1505-1518.
39. Ninomiya, M., Nishizawa, T., Takahashi, M., Lorenzo, F.R., Shimosegawa, T., Okamoto, H., 2007. Identification and genomic characterization of a novel human torque teno virus of 3.2 kb. J Gen Virol 88(Pt 7), 1939-1944.
40. Ninomiya, M., Takahashi, M., Shimosegawa, T., Okamoto, H., 2007. Analysis of the entire genomes of fifteen torque teno midi virus variants classifiable into a third group of genus Anellovirus. Arch Virol 152(11), 1961-1975.
41. Okamoto, H., 2007. Genetic variability and evolution of hepatitis E virus. Virus Res 127(2), 216-228.
42. Sainokami, S., Abe, K., Sato, A., Endo, R., Takikawa, Y., Suzuki, K., Okamoto, H., 2007. Initial load of hepatitis B virus (HBV), its changing profile, and precore/core promoter mutations correlate with the severity and outcome of acute HBV infection. J Gastroenterol 42(3), 241-249.
43. Shrestha, S.M., Shrestha, S., Shrestha, A., Tsuda, F., Endo, K., Takahashi, M., Okamoto, H., 2007. High prevalence of hepatitis B virus infection and inferior vena cava obstruction among patients with liver cirrhosis or hepatocellular carcinoma in Nepal. J Gastroenterol Hepatol 22(11), 1921-1928.
44. Takahashi, M., Tanaka, T., Azuma, M., Kusano, E., Aikawa, T., Shibayama, T., Yazaki, Y., Mizuo, H., Inoue, J., Okamoto, H., 2007. Prolonged fecal shedding of hepatitis E virus (HEV) during sporadic acute hepatitis E: evaluation of infectivity of HEV in fecal specimens in a cell culture system. J Clin Microbiol 45(11), 3671-3679.
45. Takikawa, Y., Yasumi, Y., Sato, A., Endo, R., Suzuki, K., Mori, Y., Akasaka, H., Miura, Y., Sawai, T., Okamoto, H., 2007. A case of acute hepatitis E associated with multidrug hypersensitivity and cytomegalovirus reactivation. Hepatol Res 37(2), 158-165.
46. Tanaka, T., Takahashi, M., Kusano, E., Okamoto, H., 2007. Development and evaluation of an efficient cell-culture

system for Hepatitis E virus. J Gen Virol 88(Pt 3), 903-911.
47. Tsatsralt-Od, B., Takahashi, M., Endo, K., Agiimaa, D., Buyankhuu, O., Ninomiya, M., Lorenzo, F.R., Okamoto, H., 2007. Prevalence of hepatitis B, C, and delta virus infections among children in Mongolia: progress in childhood immunization. J Med Virol 79(8), 1064-1074.
48. Tsatsralt-Od, B., Takahashi, M., Endo, K., Agiimaa, D., Buyankhuu, O., Okamoto, H., 2007. Comparison of hepatitis A and E virus infections among healthy children in Mongolia: evidence for infection with a subgenotype IA HAV in children. J Med Virol 79(1), 18-25.
49. Wibawa, I.D., Suryadarma, I.G., Mulyanto, Tsuda, F., Matsumoto, Y., Ninomiya, M., Takahashi, M., Okamoto, H., 2007. Identification of genotype 4 hepatitis E virus strains from a patient with acute hepatitis E and farm pigs in Bali, Indonesia. J Med Virol 79(8), 1138-1146.
50. Davaalkham, D., Ojima, T., Uehara, R., Watanabe, M., Oki, I., Nymadawa, P., Takahashi, M., Okamoto, H., Nakamura, Y., 2006. Hepatitis delta virus infection in mongolia: analyses of geographic distribution, risk factors, and disease severity. Am J Trop Med Hyg 75(2), 365-369.
51. Inoue, J., Nishizawa, T., Takahashi, M., Aikawa, T., Mizuo, H., Suzuki, K., Shimosegawa, T., Okamoto, H., 2006. Analysis of the full-length genome of genotype 4 hepatitis E virus isolates from patients with fulminant or acute self-limited hepatitis E. J Med Virol 78(4), 476-484.
52. Inoue, J., Takahashi, M., Ito, K., Shimosegawa, T., Okamoto, H., 2006. Analysis of human and swine hepatitis E virus (HEV) isolates of genotype 3 in Japan that are only 81-83 % similar to reported HEV isolates of the same genotype over the entire genome. J Gen Virol 87(Pt 8), 2363-2369.
53. Inoue, J., Takahashi, M., Yazaki, Y., Tsuda, F., Okamoto, H., 2006. Development and validation of an improved RT-PCR assay with nested universal primers for detection of hepatitis E virus strains with significant sequence divergence. J Virol Methods 137(2), 325-333.
54. Inoue, K., Ogawa, O., Yamada, M., Watanabe, T., Okamoto, H., Yoshiba, M., 2006. Possible association of vigorous hepatitis B virus replication with the development of fulminant hepatitis. J Gastroenterol 41(4), 383-387.
55. Kobayashi, K., Ueno, Y., Kobayashi, Y., Akahane, T., Satoh, S., Kikuchi, K., Okamoto, H., Ishii, M., Shimosegawa, T., 2006. Th1 response during ribavirin and interferon-alpha combination therapy in chronic hepatitis C. Hepatol Res 34(2), 104-110.
56. Mitsui, T., Tsukamoto, Y., Hirose, A., Suzuki, S., Yamazaki, C., Masuko, K., Tsuda, F., Endo, K., Takahashi, M., Okamoto, H., 2006. Distinct changing profiles of hepatitis A and E virus infection among patients with acute hepatitis, patients on maintenance hemodialysis and healthy individuals in Japan. J Med Virol 78(8), 1015-1024.
57. Tsatsralt-Od, B., Takahashi, M., Endo, K., Buyankhuu, O., Baatarkhuu, O., Nishizawa, T., Okamoto, H., 2006. Infection with hepatitis A, B, C, and delta viruses among patients with acute hepatitis in Mongolia. J Med Virol 78(5), 542-550.
58. Inoue, J., Takahashi, M., Nishizawa, T., Narantuya, L., Sakuma, M., Kagawa, Y., Shimosegawa, T., Okamoto, H., 2005. High prevalence of hepatitis delta virus infection detectable by enzyme immunoassay among apparently healthy individuals in Mongolia. J Med Virol 76(3), 333-340.
59. Ishii, T., Ohto, H., Takeuchi, C., Ariga, H., Hirai, S., Ujiie, N., Suzuki, H., Okamoto, H., 2005. Evolution in the hypervariable region of the hepatitis C virus in two infants infected by mother-to-infant transmission. Pediatr Int 47(3), 278-285.
60. Mitsui, T., Tsukamoto, Y., Suzuki, S., Yamazaki, C., Masuko, K., Tsuda, F., Takahashi, M., Tsatsralt-Od, B., Nishizawa, T., Okamoto, H., 2005. Serological and molecular studies on subclinical hepatitis E virus infection using periodic serum samples obtained from healthy individuals. J Med Virol 76(4), 526-533.
61. Mizuo, H., Yazaki, Y., Sugawara, K., Tsuda, F., Takahashi, M., Nishizawa, T., Okamoto, H., 2005. Possible risk factors for the transmission of hepatitis E virus and for the severe form of hepatitis E acquired locally in Hokkaido, Japan. J Med Virol 76(3), 341-349.
62. Nagasaki, F., Ueno, Y., Kanno, N., Okamoto, H., Shimosegawa, T., 2005. A case of acute hepatitis with positive autoantibodies who actually had hepatitis E virus infection. Hepatol Res 32(2), 134-137.
63. Nagasaki, F., Ueno, Y., Mano, Y., Igarashi, T., Yahagi, K., Niitsuma, H., Okamoto, H., Shimosegawa, T., 2005. A patient with clinical features of acute hepatitis E viral infection and autoimmune hepatitis. Tohoku J Exp Med 206(2), 173-179.
64. Nakayama, H., Sugai, Y., Ikeya, S., Inoue, J., Nishizawa, T., Okamoto, H., 2005. Molecular investigation of interspousal transmission of hepatitis C virus in two Japanese patients who acquired acute hepatitis C after 40 or 42 years of marriage. J Med Virol 75(2), 258-266.
65. Nishizawa, T., Takahashi, M., Endo, K., Fujiwara, S., Sakuma, N., Kawazuma, F., Sakamoto, H., Sato, Y., Bando, M., Okamoto, H., 2005. Analysis of the full-length genome of hepatitis E virus isolates obtained from wild boars in Japan. J Gen Virol 86(Pt 12), 3321-3326.
66. Ohnuma, H., Yoshikawa, A., Mizoguchi, H., Okamoto, H., 2005. Characterization of genotype H hepatitis B virus

strain identified for the first time from a Japanese blood donor by nucleic acid amplification test. J Gen Virol 86(Pt 3), 595-599.

67. Shibayama, T., Masuda, G., Ajisawa, A., Hiruma, K., Tsuda, F., Nishizawa, T., Takahashi, M., Okamoto, H., 2005. Characterization of seven genotypes (A to E, G and H) of hepatitis B virus recovered from Japanese patients infected with human immunodeficiency virus type 1. J Med Virol 76(1), 24-32.
68. Simmonds, P., Bukh, J., Combet, C., Deleage, G., Enomoto, N., Feinstone, S., Halfon, P., Inchauspe, G., Kuiken, C., Maertens, G., Mizokami, M., Murphy, D.G., Okamoto, H., Pawlotsky, J.M., Penin, F., Sablon, E., Shin, I.T., Stuyver, L.J., Thiel, H.J., Viazov, S., Weiner, A.J., Widell, A., 2005. Consensus proposals for a unified system of nomenclature of hepatitis C virus genotypes. Hepatology 42(4), 962-973.
69. Takahashi, M., Kusakai, S., Mizuo, H., Suzuki, K., Fujimura, K., Masuko, K., Sugai, Y., Aikawa, T., Nishizawa, T., Okamoto, H., 2005. Simultaneous detection of immunoglobulin A (IgA) and IgM antibodies against hepatitis E virus (HEV) Is highly specific for diagnosis of acute HEV infection. J Clin Microbiol 43(1), 49-56.
70. Takahashi, M., Nishizawa, T., Tanaka, T., Tsatsralt-Od, B., Inoue, J., Okamoto, H., 2005. Correlation between positivity for immunoglobulin A antibodies and viraemia of swine hepatitis E virus observed among farm pigs in Japan. J Gen Virol 86(Pt 6), 1807-1813.
71. Tokita, H., Fukui, H., Tanaka, A., Kamitsukasa, H., Yagura, M., Harada, H., Okamoto, H., 2005. Risk factors for the development of hepatocellular carcinoma among patients with chronic hepatitis C who achieved a sustained virological response to interferon therapy. J Gastroenterol Hepatol 20(5), 752-758.
72. Tsatsralt-Od, B., Takahashi, M., Nishizawa, T., Endo, K., Inoue, J., Okamoto, H., 2005. High prevalence of dual or triple infection of hepatitis B, C, and delta viruses among patients with chronic liver disease in Mongolia. J Med Virol 77(4), 491-499.
73. Tsatsralt-Od, B., Takahashi, M., Nishizawa, T., Inoue, J., Ulaankhuu, D., Okamoto, H., 2005. High prevalence of hepatitis B, C and delta virus infections among blood donors in Mongolia. Arch Virol 150(12), 2513-2528.
74. Fukuda, S., Sunaga, J., Saito, N., Fujimura, K., Itoh, Y., Sasaki, M., Tsuda, F., Takahashi, M., Nishizawa, T., Okamoto, H., 2004. Prevalence of antibodies to hepatitis E virus among Japanese blood donors: identification of three blood donors infected with a genotype 3 hepatitis E virus. J Med Virol 73(4), 554-561.
75. Koizumi, Y., Isoda, N., Sato, Y., Iwaki, T., Ono, K., Ido, K., Sugano, K., Takahashi, M., Nishizawa, T., Okamoto, H., 2004. Infection of a Japanese patient by genotype 4 hepatitis e virus while traveling in Vietnam. J Clin Microbiol 42(8), 3883-3885.
76. Mitsui, T., Tsukamoto, Y., Yamazaki, C., Masuko, K., Tsuda, F., Takahashi, M., Nishizawa, T., Okamoto, H., 2004. Prevalence of hepatitis E virus infection among hemodialysis patients in Japan: evidence for infection with a genotype 3 HEV by blood transfusion. J Med Virol 74(4), 563-572.
77. Okamoto, H., Takahashi, M., Nishizawa, T., Usui, R., Kobayashi, E., 2004. Presence of antibodies to hepatitis E virus in Japanese pet cats. Infection 32(1), 57-58.
78. Sainokami, S., Abe, K., Kumagai, I., Miyasaka, A., Endo, R., Takikawa, Y., Suzuki, K., Mizuo, H., Sugai, Y., Akahane, Y., Koizumi, Y., Yajima, Y., Okamoto, H., 2004. Epidemiological and clinical study of sporadic acute hepatitis E caused by indigenous strains of hepatitis E virus in Japan compared with acute hepatitis A. J Gastroenterol 39(7), 640-648.
79. Shrestha, S.M., Shrestha, S., Tsuda, F., Nishizawa, T., Takahashi, M., Gotanda, Y., Okamoto, H., 2004. Genetic changes in hepatitis E virus of subtype 1a in patients with sporadic acute hepatitis E in Kathmandu, Nepal, from 1997 to 2002. J Gen Virol 85(Pt 1), 97-104.
80. Sonoda, H., Abe, M., Sugimoto, T., Sato, Y., Bando, M., Fukui, E., Mizuo, H., Takahashi, M., Nishizawa, T., Okamoto, H., 2004. Prevalence of hepatitis E virus (HEV) Infection in wild boars and deer and genetic identification of a genotype 3 HEV from a boar in Japan. J Clin Microbiol 42(11), 5371-5374.
81. Takahashi, M., Nishizawa, T., Gotanda, Y., Tsuda, F., Komatsu, F., Kawabata, T., Hasegawa, K., Altankhuu, M., Chimedregzen, U., Narantuya, L., Hoshino, H., Hino, K., Kagawa, Y., Okamoto, H., 2004. High prevalence of antibodies to hepatitis A and E viruses and viremia of hepatitis B, C, and D viruses among apparently healthy populations in Mongolia. Clin Diagn Lab Immunol 11(2), 392-398.
82. Tanaka, H., Yoshino, H., Kobayashi, E., Takahashi, M., Okamoto, H., 2004. Molecular investigation of hepatitis E virus infection in domestic and miniature pigs used for medical experiments. Xenotransplantation 11(6), 503-510.
83. Wibawa, I.D., Muljono, D.H., Mulyanto, Suryadarma, I.G., Tsuda, F., Takahashi, M., Nishizawa, T., Okamoto, H., 2004. Prevalence of antibodies to hepatitis E virus among apparently healthy humans and pigs in Bali, Indonesia: Identification of a pig infected with a genotype 4 hepatitis E virus. J Med Virol 73(1), 38-44.
84. Yamamoto, T., Suzuki, H., Toyota, T., Takahashi, M., Okamoto, H., 2004. Three male patients with sporadic acute hepatitis E in Sendai, Japan, who were domestically infected with hepatitis E virus of genotype III or IV. J Gastroenterol 39(3), 292-298.
85. Kato, S., Okamoto, H., Nishino, Y., Oyake, Y., Nakazato, Y., Okuda, M., Fujisawa, T., Iinuma, K., Blaser, M.J., 2003.

Helicobacter pylori and TT virus prevalence in Japanese children. J Gastroenterol 38(12), 1126-1130.
86. Kuno, A., Ido, K., Isoda, N., Satoh, Y., Ono, K., Satoh, S., Inamori, H., Sugano, K., Kanai, N., Nishizawa, T., Okamoto, H., 2003. Sporadic acute hepatitis E of a 47-year-old man whose pet cat was positive for antibody to hepatitis E virus. Hepatol Res 26(3), 237-242.
87. Nakamura, M., Wang, J., Murakami, T., Ajiki, T., Hakamata, Y., Kaneko, T., Takahashi, M., Okamoto, H., Mayumi, M., Kobayashi, E., 2003. DNA immunization of the grafted liver by particle-mediated gene gun. Transplantation 76(9), 1369-1375.
88. Nishizawa, T., Takahashi, M., Mizuo, H., Miyajima, H., Gotanda, Y., Okamoto, H., 2003. Characterization of Japanese swine and human hepatitis E virus isolates of genotype IV with 99 % identity over the entire genome. J Gen Virol 84(Pt 5), 1245-1251.
89. Okamoto, H., Takahashi, M., Nishizawa, T., 2003. Features of hepatitis E virus infection in Japan. Intern Med 42(11), 1065-1071.
90. Okamoto, H., Yasui, K., Zhao, C., Arii, S., Inazawa, J., 2003. PTK2 and EIF3S3 genes may be amplification targets at 8q23-q24 and are associated with large hepatocellular carcinomas. Hepatology 38(5), 1242-1249.
91. Shrestha, S.M., Shrestha, S., Tsuda, F., Nishizawa, T., Gotanda, Y., Takeda, N., Okamoto, H., 2003. Molecular investigation of hepatitis E virus infection in patients with acute hepatitis in Kathmandu, Nepal. J Med Virol 69(2), 207-214.
92. Takahashi, M., Nishizawa, T., Miyajima, H., Gotanda, Y., Iita, T., Tsuda, F., Okamoto, H., 2003. Swine hepatitis E virus strains in Japan form four phylogenetic clusters comparable with those of Japanese isolates of human hepatitis E virus. J Gen Virol 84(Pt 4), 851-862.
93. Takahashi, M., Nishizawa, T., Okamoto, H., 2003. Identification of a genotype III swine hepatitis E virus that was isolated from a Japanese pig born in 1990 and that is most closely related to Japanese isolates of human hepatitis E virus. J Clin Microbiol 41(3), 1342-1343.
94. Tokita, H., Fukui, H., Tanaka, A., Kamitsukasa, H., Yagura, M., Harada, H., Hebisawa, A., Kurashima, A., Okamoto, H., 2003. Circulating KL-6 level at baseline is a predictive indicator for the occurrence of interstitial pneumonia during interferon treatment for chronic hepatitis C. Hepatol Res 26(2), 91-97.
95. Tokita, H., Harada, H., Gotanda, Y., Takahashi, M., Nishizawa, T., Okamoto, H., 2003. Molecular and serological characterization of sporadic acute hepatitis E in a Japanese patient infected with a genotype III hepatitis E virus in 1993. J Gen Virol 84(Pt 2), 421-427.
96. Yazaki, Y., Mizuo, H., Takahashi, M., Nishizawa, T., Sasaki, N., Gotanda, Y., Okamoto, H., 2003. Sporadic acute or fulminant hepatitis E in Hokkaido, Japan, may be food-borne, as suggested by the presence of hepatitis E virus in pig liver as food. J Gen Virol 84(Pt 9), 2351-2357.
97. Aikawa, T., Kojima, M., Takahashi, M., Nishizawa, T., Okamoto, H., 2002. Identification of indigenous hepatitis E virus from a Japanese patient who contracted sporadic acute hepatitis in 1982. J Infect Dis 186(10), 1535-1536; author reply 1536-1537.
98. Akahane, Y., Okada, S., Sakamoto, M., Wakamiya, M., Kitamura, T., Tawara, A., Naitoh, S., Tsuda, F., Okamoto, H., 2002. Persistence of hepatitis B viremia after recovery from acute hepatitis B: correlation between anti-HBc titer and HBV DNA in serum. Hepatol Res 24(1), 8.
99. Al-Knawy, B., Okamoto, H., Ahmed El-Mekki, A., Elbagir Khalafalla, M., Al Wabel, A., Qazi, F., Khan, A., Shatoor, A., 2002. Distribution of hepatitis C genotype and co-infection rate with hepatitis G in Saudi Arabia. Hepatol Res 24(2), 95.
100. Hiroishi, K., Eguchi, J., Ishii, S., Okamoto, H., Mitamura, K., Imawari, M., 2002. Differential effect of cytotoxic T lymphocyte variant epitopes on generation and cytotoxicity in chronic hepatitis C virus infection. Hepatol Res 24(2), 91.
101. Mizuo, H., Suzuki, K., Takikawa, Y., Sugai, Y., Tokita, H., Akahane, Y., Itoh, K., Gotanda, Y., Takahashi, M., Nishizawa, T., Okamoto, H., 2002. Polyphyletic strains of hepatitis E virus are responsible for sporadic cases of acute hepatitis in Japan. J Clin Microbiol 40(9), 3209-3218.
102. Ohto, H., Ujiie, N., Takeuchi, C., Sato, A., Hayashi, A., Ishiko, H., Nishizawa, T., Okamoto, H., 2002. TT virus infection during childhood. Transfusion 42(7), 892-898.
103. Okamoto, H., Takahashi, M., Nishizawa, T., Tawara, A., Fukai, K., Muramatsu, U., Naito, Y., Yoshikawa, A., 2002. Genomic characterization of TT viruses (TTVs) in pigs, cats and dogs and their relatedness with species-specific TTVs in primates and tupaias. J Gen Virol 83(Pt 6), 1291-1297.
104. Peng, Y.H., Nishizawa, T., Takahashi, M., Ishikawa, T., Yoshikawa, A., Okamoto, H., 2002. Analysis of the entire genomes of thirteen TT virus variants classifiable into the fourth and fifth genetic groups, isolated from viremic infants. Arch Virol 147(1), 21-41.
105. Shrestha, S.M., Takeda, N., Tsuda, F., Okamoto, H., Shrestha, S., Shrestha, V.M., 2002. High prevalence of hepatitis B virus infection amongst Tibetans in Nepal. Trop Gastroenterol 23(2), 63-65.

106. Suzuki, K., Aikawa, T., Okamoto, H., 2002. Fulminant hepatitis E in Japan. N Engl J Med 347(18), 1456.
107. Takahashi, M., Asabe, S., Gotanda, Y., Kishimoto, J., Tsuda, F., Okamoto, H., 2002. TT virus is distributed in various leukocyte subpopulations at distinct levels, with the highest viral load in granulocytes. Biochem Biophys Res Commun 290(1), 242-248.
108. Takahashi, M., Nishizawa, T., Yoshikawa, A., Sato, S., Isoda, N., Ido, K., Sugano, K., Okamoto, H., 2002. Identification of two distinct genotypes of hepatitis E virus in a Japanese patient with acute hepatitis who had not travelled abroad. J Gen Virol 83(Pt 8), 1931-1940.
109. Tokita, H., Murai, S., Kamitsukasa, H., Yagura, M., Harada, H., Takahashi, M., Okamoto, H., 2002. High TT virus load as an independent factor associated with the occurrence of hepatocellular carcinoma among patients with hepatitis C virus-related chronic liver disease. J Med Virol 67(4), 501-509.
110. Tokita, H., Murai, S., Kamitsukasa, H., Yagura, M., Harada, H., Takahashi, M., Okamoto, H., 2002. TT virus of certain genotypes may reduce the platelet count in patients who achieve a sustained virologic response to interferon treatment for chronic hepatitis C. Hepatol Res 23(2), 105-114.
111. Yokoyama, H., Yasuda, J., Okamoto, H., Iwakura, Y., 2002. Pathological changes of renal epithelial cells in mice transgenic for the TT virus ORF1 gene. J Gen Virol 83(Pt 1), 141-150.
112. Asabe, S., Nishizawa, T., Iwanari, H., Okamoto, H., 2001. Phosphorylation of serine-rich protein encoded by open reading frame 3 of the TT virus genome. Biochem Biophys Res Commun 286(2), 298-304.
113. Bando, M., Ohno, S., Oshikawa, K., Takahashi, M., Okamoto, H., Sugiyama, Y., 2001. Infection of TT virus in patients with idiopathic pulmonary fibrosis. Respir Med 95(12), 935-942.
114. Muljono, D.H., Nishizawa, T., Tsuda, F., Takahashi, M., Okamoto, H., 2001. Molecular epidemiology of TT virus (TTV) and characterization of two novel TTV genotypes in Indonesia. Arch Virol 146(7), 1249-1266.
115. Okamoto, H., Mayumi, M., 2001. TT virus: virological and genomic characteristics and disease associations. J Gastroenterol 36(8), 519-529.
116. Okamoto, H., Nishizawa, T., Takahashi, M., Asabe, S., Tsuda, F., Yoshikawa, A., 2001. Heterogeneous distribution of TT virus of distinct genotypes in multiple tissues from infected humans. Virology 288(2), 358-368.
117. Okamoto, H., Nishizawa, T., Takahashi, M., Tawara, A., Peng, Y., Kishimoto, J., Wang, Y., 2001. Genomic and evolutionary characterization of TT virus (TTV) in tupaias and comparison with species-specific TTVs in humans and non-human primates. J Gen Virol 82(Pt 9), 2041-2050.
118. Okamoto, H., Takahashi, M., Nishizawa, T., Fukai, K., Muramatsu, U., Yoshikawa, A., 2001. Analysis of the complete genome of indigenous swine hepatitis E virus isolated in Japan. Biochem Biophys Res Commun 289(5), 929-936.
119. Shibayama, T., Masuda, G., Ajisawa, A., Takahashi, M., Nishizawa, T., Tsuda, F., Okamoto, H., 2001. Inverse relationship between the titre of TT virus DNA and the CD4 cell count in patients infected with HIV. AIDS 15(5), 563-570.
120. Tokita, H., Murai, S., Kamitsukasa, H., Yagura, M., Harada, H., Hebisawa, A., Takahashi, M., Okamoto, H., 2001. Influence of TT virus on the histopathological features of nonalcoholic fatty liver disease. Hepatol Res 19(3), 197-211.
121. Tokita, H., Murai, S., Kamitsukasa, H., Yagura, M., Harada, H., Takahashi, M., Okamoto, H., 2001. Influence of TT virus infection on the thrombocytopenia of patients with chronic liver disease. Hepatol Res 20(3), 288-300.
122. Tokita, H., Murai, S., Kamitsukasa, H., Yagura, M., Harada, H., Tawara, A., Takahashi, M., Okamoto, H., 2001. Influence of TT virus on the clinical course of alcoholic liver disease. Hepatol Res 19(2), 180-193.
123. Tsuda, F., Takahashi, M., Nishizawa, T., Akahane, Y., Konishi, K., Yoshizawa, H., Okamoto, H., 2001. IgM-class antibodies to TT virus (TTV) in patients with acute TTV infection. Hepatol Res 19(1), 1-11.
124. Yusufu, Y., Mochida, S., Matsui, A., Okamoto, H., Fujiwara, K., 2001. TT virus infection in cases of fulminant hepatic failure-evaluation by clonality based on amino acid sequence of hypervariable regions. Hepatol Res 21(1), 85-96.
125. Itoh, Y., Takahashi, M., Fukuda, M., Shibayama, T., Ishikawa, T., Tsuda, F., Tanaka, T., Nishizawa, T., Okamoto, H., 2000. Visualization of TT virus particles recovered from the sera and feces of infected humans. Biochem Biophys Res Commun 279(2), 718-724.
126. Ohto, H., Ujiie, N., Sato, A., Okamoto, H., Mayumi, M., 2000. Mother-to-infant transmission of GB virus type C/HGV. Transfusion 40(6), 725-730.
127. Okamoto, H., Fukuda, M., Tawara, A., Nishizawa, T., Itoh, Y., Hayasaka, I., Tsuda, F., Tanaka, T., Miyakawa, Y., Mayumi, M., 2000. Species-specific TT viruses and cross-species infection in nonhuman primates. J Virol 74(3), 1132-1139.
128. Okamoto, H., Nishizawa, T., Tawara, A., Peng, Y., Takahashi, M., Kishimoto, J., Tanaka, T., Miyakawa, Y., Mayumi, M., 2000. Species-specific TT viruses in humans and nonhuman primates and their phylogenetic relatedness. Virology 277(2), 368-378.
129. Okamoto, H., Nishizawa, T., Tawara, A., Takahashi, M., Kishimoto, J., Sai, T., Sugai, Y., 2000. TT virus mRNAs detected in the bone marrow cells from an infected individual. Biochem Biophys Res Commun 279(2), 700-707.
130. Okamoto, H., Takahashi, M., Kato, N., Fukuda, M., Tawara, A., Fukuda, S., Tanaka, T., Miyakawa, Y., Mayumi, M.,

2000. Sequestration of TT virus of restricted genotypes in peripheral blood mononuclear cells. J Virol 74(21), 10236-10239.
131. Okamoto, H., Takahashi, M., Nishizawa, T., Tawara, A., Sugai, Y., Sai, T., Tanaka, T., Tsuda, F., 2000. Replicative forms of TT virus DNA in bone marrow cells. Biochem Biophys Res Commun 270(2), 657-662.
132. Okamoto, H., Ukita, M., Nishizawa, T., Kishimoto, J., Hoshi, Y., Mizuo, H., Tanaka, T., Miyakawa, Y., Mayumi, M., 2000. Circular double-stranded forms of TT virus DNA in the liver. J Virol 74(11), 5161-5167.
133. Tawara, A., Akahane, Y., Takahashi, M., Nishizawa, T., Ishikawa, T., Okamoto, H., 2000. Transmission of human TT virus of genotype 1a to chimpanzees with fecal supernatant or serum from patients with acute TTV infection. Biochem Biophys Res Commun 278(2), 470-476.
134. Ukita, M., Okamoto, H., Nishizawa, T., Tawara, A., Takahashi, M., Iizuka, H., Miyakawa, Y., Mayumi, M., 2000. The entire nucleotide sequences of two distinct TT virus (TTV) isolates (TJN01 and TJN02) remotely related to the original TTV isolates. Arch Virol 145(8), 1543-1559.
135. Usuda, S., Okamoto, H., Tanaka, T., Kidd-Ljunggren, K., Holland, P.V., Miyakawa, Y., Mayumi, M., 2000. Differentiation of hepatitis B virus genotypes D and E by ELISA using monoclonal antibodies to epitopes on the preS2-region product. J Virol Methods 87(1-2), 81-89.
136. Akahane, Y., Sakamoto, M., Miyazaki, Y., Okada, S., Inoue, T., Ukita, M., Okamoto, H., Miyakawa, Y., Mayumi, M., 1999. Effect of interferon on a nonenveloped DNA virus (TT virus) associated with acute and chronic hepatitis of unknown etiology. J Med Virol 58(3), 196-200.
137. Ikeda, H., Takasu, M., Inoue, K., Okamoto, H., Miyakawa, Y., Mayumi, M., 1999. Infection with an unenveloped DNA virus (TTV) in patients with acute or chronic liver disease of unknown etiology and in those positive for hepatitis C virus RNA. J Hepatol 30(2), 205-212.
138. Itoh, K., Hirakawa, K., Okamoto, H., Ukita, M., Tanaka, H., Sawada, N., Tsuda, F., Miyakawa, Y., Mayumi, M., 1999. Infection by an unenveloped DNA virus associated with non-A to -G hepatitis in Japanese blood donors with or without elevated ALT levels. Transfusion 39(5), 522-526.
139. Koike, K., Shimotouno, K., Okada, S., Okamoto, H., Hayashi, N., Ueda, K., Kaneko, S., Yokosuka, O., Chiba, T., Marusawa, H., Hino, O., Utida, T., Omata, M., Juji, T., Nojiri, N., Takada, K., Miyamura, T., Osuga, T., Ito, Y., 1999. Survey of hepatitis B virus co-infection in hepatitis C virus-infected patients suffering from chronic hepatitis and hepatocellular carcinoma in Japan. Jpn J Cancer Res 90(11), 1270-1272.
140. Nishizawa, T., Okamoto, H., Tsuda, F., Aikawa, T., Sugai, Y., Konishi, K., Akahane, Y., Ukita, M., Tanaka, T., Miyakawa, Y., Mayumi, M., 1999. Quasispecies of TT virus (TTV) with sequence divergence in hypervariable regions of the capsid protein in chronic TTV infection. J Virol 73(11), 9604-9608.
141. Okamoto, H., Kato, N., Iizuka, H., Tsuda, F., Miyakawa, Y., Mayumi, M., 1999. Distinct genotypes of a nonenveloped DNA virus associated with posttransfusion non-A to G hepatitis (TT virus) in plasma and peripheral blood mononuclear cells. J Med Virol 57(3), 252-258.
142. Okamoto, H., Nishizawa, T., Ukita, M., 1999. A novel unenveloped DNA virus (TT virus) associated with acute and chronic non-A to G hepatitis. Intervirology 42(2-3), 196-204.
143. Okamoto, H., Nishizawa, T., Ukita, M., Takahashi, M., Fukuda, M., Iizuka, H., Miyakawa, Y., Mayumi, M., 1999. The entire nucleotide sequence of a TT virus isolate from the United States (TUS01): comparison with reported isolates and phylogenetic analysis. Virology 259(2), 437-448.
144. Okamoto, H., Takahashi, M., Nishizawa, T., Ukita, M., Fukuda, M., Tsuda, F., Miyakawa, Y., Mayumi, M., 1999. Marked genomic heterogeneity and frequent mixed infection of TT virus demonstrated by PCR with primers from coding and noncoding regions. Virology 259(2), 428-436.
145. Tsuda, F., Okamoto, H., Ukita, M., Tanaka, T., Akahane, Y., Konishi, K., Yoshizawa, H., Miyakawa, Y., Mayumi, M., 1999. Determination of antibodies to TT virus (TTV) and application to blood donors and patients with post-transfusion non-A to G hepatitis in Japan. J Virol Methods 77(2), 199-206.
146. Ukita, M., Okamoto, H., Kato, N., Miyakawa, Y., Mayumi, M., 1999. Excretion into bile of a novel unenveloped DNA virus (TT virus) associated with acute and chronic non-A-G hepatitis. J Infect Dis 179(5), 1245-1248.
147. Usuda, S., Okamoto, H., Iwanari, H., Baba, K., Tsuda, F., Miyakawa, Y., Mayumi, M., 1999. Serological detection of hepatitis B virus genotypes by ELISA with monoclonal antibodies to type-specific epitopes in the preS2-region product. J Virol Methods 80(1), 97-112.
148. Horiike, N., Michitaka, K., Okamoto, H., Masumoto, T., Ohno, N., Nadano, S., Yamashita, Y., Hino, T., Kanaoka, M., Onji, M., 1998. GB virus C/hepatitis G virus infection in autoimmune liver diseases. J Gastroenterol 33(3), 463-464.
149. Inoue, K., Yoshiba, M., Sekiyama, K., Okamoto, H., Mayumi, M., 1998. Clinical and molecular virological differences between fulminant hepatic failures following acute and chronic infection with hepatitis B virus. J Med Virol 55(1), 35-41.
150. Kanai, K., Kako, M., Kumada, T., Tsubouchi, H., Aikawa, T., Kojima, M., Harada, H., Kawasaki, T., Nakashima, M., Okamoto, H., Mishiro, S., 1998. High-dose (9 MU) long-term (60 weeks) alfa-interferon therapy for chronic hepatitis

patients infected with HCV genotype 1b. Arch Virol 143(8), 1545-1554.
151. Kayaba, K., Igarashi, M., Okamoto, H., Tsuda, F., 1998. Prevalence of anti-hepatitis C antibodies in a rural community without high mortality from liver disease in Niigata prefecture. J Epidemiol 8(4), 250-255.
152. Okamoto, H., Akahane, Y., Ukita, M., Fukuda, M., Tsuda, F., Miyakawa, Y., Mayumi, M., 1998. Fecal excretion of a nonenveloped DNA virus (TTV) associated with posttransfusion non-A-G hepatitis. J Med Virol 56(2), 128-132.
153. Shrestha, S.M., Subedi, N.B., Shrestha, S., Maharjan, K.G., Tsuda, F., Okamoto, H., 1998. Epidemiology of hepatitis C virus infection in Nepal. Trop Gastroenterol 19(3), 102-104.
154. Tanaka, H., Okamoto, H., Luengrojanakul, P., Chainuvati, T., Tsuda, F., Tanaka, T., Miyakawa, Y., Mayumi, M., 1998. Infection with an unenveloped DNA virus (TTV) associated with posttransfusion non-A to G hepatitis in hepatitis patients and healthy blood donors in Thailand. J Med Virol 56(3), 234-238.
155. Tokita, H., Okamoto, H., Iizuka, H., Kishimoto, J., Tsuda, F., Miyakawa, Y., Mayumi, M., 1998. The entire nucleotide sequences of three hepatitis C virus isolates in genetic groups 7-9 and comparison with those in the other eight genetic groups. J Gen Virol 79 (Pt 8), 1847-1857.
156. Toyoda, H., Fukuda, Y., Hayakawa, T., Takamatsu, J., Saito, H., Okamoto, H., 1998. GB virus C/hepatitis G virus isolates in Japanese haemophiliacs and their origins. Thromb Haemost 80(2), 242-245.
157. Usuda, S., Okamoto, H., Tsuda, F., Tanaka, T., Miyakawa, Y., Mayumi, M., 1998. An enzyme-linked immunosorbent assay with monoclonal antibodies for the determination of phosphorylated hepatitis B core protein (p21c) in serum. J Virol Methods 72(1), 95-103.
158. Akiyama, H., Nakamura, N., Tanikawa, S., Sakamaki, H., Onozawa, Y., Shibayama, T., Tanaka, S., Tsuda, F., Okamoto, H., Miyakawa, Y., Mayumi, M., 1998. Incidence and influence of GB virus C and hepatitis C virus infection in patients undergoing bone marrow transplantation. Bone Marrow Transplant 21(11), 1131-1135.
159. Fujiwara, T., Iwata, A., Iizuka, H., Tanaka, T., Okamoto, H., 1998. Transfusion transmitted virus. Lancet 352(9136), 1310-1311.
160. Graeme Woodfield, D., Gane, E., Okamoto, H., 1998. Hepatitis TT virus is present in New Zealand. N Z Med J 111(1066), 195-196.
161. Chiyoda, S., Inoue, J., Okamoto, H., 1997. Co-infection with GB virus C in an area of high endemicity for human T-lymphotropic virus type I in Japan. Infection 25(2), 129-130.
162. Hiroishi, K., Kita, H., Kojima, M., Okamoto, H., Moriyama, T., Kaneko, T., Ishikawa, T., Ohnishi, S., Aikawa, T., Tanaka, N., Yazaki, Y., Mitamura, K., Imawari, M., 1997. Cytotoxic T lymphocyte response and viral load in hepatitis C virus infection. Hepatology 25(3), 705-712.
163. Inoue, T., Sakamoto, M., Akahane, Y., Okamoto, H., Miyakawa, Y., Mayumi, M., 1997. Response to interferon of GB virus C and hepatitis C virus in patients with chronic hepatitis. Am J Gastroenterol 92(11), 1981-1985.
164. Izumi, T., Sasaki, R., Tsunoda, S., Akutsu, M., Okamoto, H., Miura, Y., 1997. B cell malignancy and hepatitis C virus infection. Leukemia 11 Suppl 3, 516-518.
165. Kako, M., Kanai, K., Aikawa, T., Iwabuchi, S., Takehira, Y., Kawasaki, T., Tsubouchi, H., Hino, K., Tsuda, F., Okamoto, H., Miyakawa, Y., Mayumi, M., 1997. Response to interferon-alpha 2a in patients with e antigen-negative chronic hepatitis B. J Clin Gastroenterol 25(2), 440-445.
166. Kaneko, T., Moriyama, T., Udaka, K., Hiroishi, K., Kita, H., Okamoto, H., Yagita, H., Okumura, K., Imawari, M., 1997. Impaired induction of cytotoxic T lymphocytes by antagonism of a weak agonist borne by a variant hepatitis C virus epitope. Eur J Immunol 27(7), 1782-1787.
167. Kinoshita, T., Miyake, K., Nakao, H., Tanaka, T., Tsuda, F., Okamoto, H., Miyakawa, Y., Mayumi, M., 1997. Molecular investigation of GB virus C infection in hemophiliacs in Japan. J Infect Dis 175(2), 454-457.
168. Kondo, M., Horie, Y., Okano, J., Kitamura, A., Maeda, N., Kawasaki, H., Mishiro, S., Yamamoto, S., Itou, T., Saeki, S., Tanaka, S., Okamoto, H., 1997. High prevalence of hepatitis C virus infection in Japanese patients with porphyria cutanea tarda. Hepatology 26(1), 246.
169. Koyama, T., Tsuda, F., Ishikawa, K., Oishi, H., Tazawa, M., Yoshizawa, H., Sato, S., Okamoto, H., 1997. Antibodies to hepatitis C virus and elevated transaminase levels in a town of hyperendemicity in Iwate, Japan. J Gastroenterol Hepatol 12(1), 67-72.
170. Miyakawa, Y., Okamoto, H., Mayumi, M., 1997. The molecular basis of hepatitis B e antigen (HBeAg)-negative infections. J Viral Hepat 4(1), 1-8.
171. Nagayama, R., Miyake, K., Okamoto, H., 1997. Effect of interferon on GB virus C and hepatitis C virus in hepatitis patients with the co-infection. J Med Virol 52(2), 156-160.
172. Nakao, H., Okamoto, H., Fukuda, M., Tsuda, F., Mitsui, T., Masuko, K., Iizuka, H., Miyakawa, Y., Mayumi, M., 1997. Mutation rate of GB virus C/hepatitis G virus over the entire genome and in subgenomic regions. Virology 233(1), 43-50.
173. Nishizawa, T., Okamoto, H., Konishi, K., Yoshizawa, H., Miyakawa, Y., Mayumi, M., 1997. A novel DNA virus (TTV) associated with elevated transaminase levels in posttransfusion hepatitis of unknown etiology. Biochem Biophys

Res Commun 241(1), 92-97.
174. Okamoto, H., Nakao, H., Inoue, T., Fukuda, M., Kishimoto, J., Iizuka, H., Tsuda, F., Miyakawa, Y., Mayumi, M., 1997. The entire nucleotide sequences of two GB virus C/hepatitis G virus isolates of distinct genotypes from Japan. J Gen Virol 78 (Pt 4), 737-745.
175. Sasaki, N., Matsui, A., Momoi, M., Tsuda, F., Okamoto, H., 1997. Loss of circulating hepatitis C virus in children who developed a persistent carrier state after mother-to-baby transmission. Pediatr Res 42(3), 263-267.
176. Shibayama, T., Tanaka, S., Ajisawa, A., Masuda, G., Okamoto, H., 1997. Coinfection of GB virus C with HIV-1 in Japan. J Acquir Immune Defic Syndr Hum Retrovirol 15(4), 319-320.
177. Shimizu, M., Osada, K., Okamoto, H., 1997. Transmission of GB virus C by blood transfusions during heart surgery. Vox Sang 72(2), 76-78.
178. Shrestha, S.M., Shrestha, S., Tsuda, F., Sawada, N., Tanaka, T., Okamoto, H., Miyakawa, Y., Mayumi, M., 1997. Infection with GB virus C and hepatitis C virus in drug addicts, patients on maintenance hemodialysis, or with chronic liver disease in Nepal. J Med Virol 53(2), 157-161.
179. Sugai, Y., Nakayama, H., Fukuda, M., Sawada, N., Tanaka, T., Tsuda, F., Okamoto, H., Miyakawa, Y., Mayumi, M., 1997. Infection with GB virus C in patients with chronic liver disease. J Med Virol 51(3), 175-181.
180. Usuda, S., Okamoto, H., Ohnuma, H., Tanaka, T., Machida, A., Miyakawa, Y., Mayumi, M., 1997. A monoclonal antibody against a hepatitis B e antigen epitope borne by six amino acids encoded by the precore region. J Virol Methods 68(2), 207-215.
181. Wang, Y., Chen, H.S., Fan, M.H., Liu, H.L., An, P., Sawada, N., Tanaka, T., Tsuda, F., Okamoto, H., 1997. Infection with GB virus C and hepatitis C virus in hemodialysis patients and blood donors in Beijing. J Med Virol 52(1), 26-30.
182. Watanabe, T., Ishiguro, M., Kametani, M., Sugai, Y., Takakuwa, K., Akahane, Y., Masuko, K., Shimizu, M., Kojima, M., Fujita, K., Tsuda, F., Okamoto, H., 1997. GB virus C and hepatitis C virus infections in hemodialysis patients in eight Japanese centers. Nephron 76(2), 171-175.
183. Yoshikawa, A., Fukuda, S., Itoh, K., Kosaki, N., Suzuki, T., Hirakawa, K., Nakao, H., Inoue, T., Fukuda, M., Okamoto, H., 1997. Infection with hepatitis G virus and its strain variant, the GB agent (GBV-C), among blood donors in Japan. Transfusion 37(6), 657-663.
184. Aikawa, T., Kojima, M., Onishi, H., Tamura, R., Fukuda, S., Suzuki, T., Tsuda, F., Okamoto, H., Miyakawa, Y., Mayumi, M., 1996. HLA DRB1 and DQB1 alleles and haplotypes influencing the progression of hepatitis C. J Med Virol 49(4), 274-278.
185. Aikawa, T., Sugai, Y., Okamoto, H., 1996. Hepatitis G infection in drug abusers with chronic hepatitis C. N Engl J Med 334(3), 195-196.
186. Akahane, Y., Miyazaki, Y., Naitoh, S., Takeda, K., Tsuda, F., Okamoto, H., Itoh, K., Miyakawa, Y., Mayumi, M., 1996. Cold activation of complement for monitoring the response to interferon in patients with chronic hepatitis C. Am J Gastroenterol 91(2), 319-327.
187. Egawa, K., Yukawa, T., Arakawa, S., Nakao, H., Inoue, T., Tanaka, T., Tsuda, F., Okamoto, H., Miyakawa, Y., Mayumi, M., 1996. Infection with GB virus C in leprous patients in Japan. J Med Virol 49(2), 110-114.
188. Egawa, K., Yukawa, T., Arakawa, S., Tanaka, T., Tsuda, F., Okamoto, H., Miyakawa, Y., Mayumi, M., 1996. Hepatitis C virus antibody, viral RNA and genotypes in leprous patients in Japan. J Hepatol 24(4), 397-402.
189. Fujimura, Y., Ishimoto, S., Shimoyama, T., Narita, N., Kuze, Y., Yoshioka, A., Fukui, H., Tanaka, T., Tsuda, F., Okamoto, H., Miyakawa, Y., Mayumi, M., 1996. Genotypes and multiple infections with hepatitis C virus in patients with haemophilia A in Japan. J Viral Hepat 3(2), 79-84.
190. Holland, P.V., Barrera, J.M., Ercilla, M.G., Yoshida, C.F., Wang, Y., de Olim, G.A., Betlach, B., Kuramoto, K., Okamoto, H., 1996. Genotyping hepatitis C virus isolates from Spain, Brazil, China, and Macau by a simplified PCR method. J Clin Microbiol 34(10), 2372-2378.
191. Izumi, T., Sasaki, R., Miura, Y., Okamoto, H., 1996. B cell malignancy and hepatitis C virus infection. Leuk Res 20(5), 445.
192. Izumi, T., Sasaki, R., Miura, Y., Okamoto, H., 1996. Primary hepatosplenic lymphoma: association with hepatitis C virus infection. Blood 87(12), 5380-5381.
193. Izumi, T., Sasaki, R., Shimizu, R., Miyazato, A., Hoshino, Y., Miura, Y., Okamoto, H., 1996. Hepatitis C virus infection in Waldenstrom's macroglobulinemia. Am J Hematol 52(3), 238-239.
194. Kanai, K., Kako, M., Aikawa, T., Hino, K., Tsubouchi, H., Takehira, Y., Iwabuchi, S., Kawasaki, T., Tsuda, F., Okamoto, H., Miyakawa, Y., Mayumi, M., 1996. Core promoter mutations of hepatitis B virus for the response to interferon in e antigen-positive chronic hepatitis B. Am J Gastroenterol 91(10), 2150-2156.
195. Kanazawa, K., Aikawa, T., Tsuda, F., Okamoto, H., 1996. Hepatitis C virus infection in patients with psoriasis. Arch Dermatol 132(11), 1391-1392.
196. Kanazawa, K., Yaoita, H., Tsuda, F., Okamoto, H., 1996. Hepatitis C virus infection in patients with urticaria. J Am Acad Dermatol 35(2 Pt 1), 195-198.

197. Kohno, H., Inoue, T., Tsuda, F., Okamoto, H., Akahane, Y., 1996. Mutations in the envelope gene of hepatitis B virus variants co-occurring with antibody to surface antigen in sera from patients with chronic hepatitis B. J Gen Virol 77 (Pt 8), 1825-1831.
198. Lvov, D.K., Samokhvalov, E.I., Tsuda, F., Selivanov, N.A., Okamoto, H., Stakhanova, V.M., Stakhgildyan, I.V., Doroshenko, N.V., Yashina, T.L., Kuzin, S.N., Suetina, I.A., Deryabin, P.G., Ruzaeva, L.A., Bezgodov, V.N., Firsova, L.A., Sorinson, S.N., Mishiro, S., 1996. Prevalence of hepatitis C virus and distribution of its genotypes in Northern Eurasia. Arch Virol 141(9), 1613-1622.
199. Masuko, K., Mitsui, T., Iwano, K., Yamazaki, C., Okuda, K., Meguro, T., Murayama, N., Inoue, T., Tsuda, F., Okamoto, H., Miyakawa, Y., Mayumi, M., 1996. Infection with hepatitis GB virus C in patients on maintenance hemodialysis. N Engl J Med 334(23), 1485-1490.
200. Moriyama, K., Okamoto, H., Tsuda, F., Mayumi, M., 1996. Reduced precore transcription and enhanced core-pregenome transcription of hepatitis B virus DNA after replacement of the precore-core promoter with sequences associated with e antigen-seronegative persistent infections. Virology 226(2), 269-280.
201. Mulyanto, Suwignyo, S., Tsauri, S., Itoh, K., Mizui, M., Tsuda, F., Okamoto, H., Yoshizawa, H., Mishiro, S., 1996. An easy dipstick assay for anti-core antibodies to screen blood donors for hepatitis C virus viremia. Vox Sang 70(4), 229-231.
202. Nakao, H., Okamoto, H., Tokita, H., Inoue, T., Iizuka, H., Pozzato, G., Mishiro, S., 1996. Full-length genomic sequence of a hepatitis C virus genotype 2c isolate (BEBE1) and the 2c-specific PCR primers. Arch Virol 141(3-4), 701-704.
203. Nishiyama, Y., Nakashima, H., Hino, K., Mori, K., Ishikawa, M., Okamoto, H., 1996. Infection with hepatitis GB virus among Japanese hemophiliacs. Transfusion 36(7), 669.
204. Okamoto, H., Kobata, S., Tokita, H., Inoue, T., Woodfield, G.D., Holland, P.V., Al-Knawy, B.A., Uzunalimoglu, O., Miyakawa, Y., Mayumi, M., 1996. A second-generation method of genotyping hepatitis C virus by the polymerase chain reaction with sense and antisense primers deduced from the core gene. J Virol Methods 57(1), 31-45.
205. Sato, K., Tanaka, T., Okamoto, H., Miyakawa, Y., Mayumi, M., 1996. Association of circulating hepatitis G virus with lipoproteins for a lack of binding with antibodies. Biochem Biophys Res Commun 229(3), 719-725.
206. Shimizu, M., Osada, K., Okamoto, H., 1996. Transfusion-transmitted hepatitis G virus following open heart surgery. Transfusion 36(10), 937.
207. Shrestha, S.M., Shrestha, D.M., Gafney, T.E., Maharjan, K.G., Tsuda, F., Okamoto, H., 1996. Hepatitis B and C infection among drug abusers in Nepal. Trop Gastroenterol 17(4), 212-213.
208. Tameda, Y., Kosaka, Y., Tagawa, S., Takase, K., Sawada, N., Nakao, H., Tsuda, F., Tanaka, T., Okamoto, H., Miyakawa, Y., Mayumi, M., 1996. Infection with GB virus C (GBV-C) in patients with fulminant hepatitis. J Hepatol 25(6), 842-847.
209. Tokita, H., Okamoto, H., Iizuka, H., Kishimoto, J., Tsuda, F., Lesmana, L.A., Miyakawa, Y., Mayumi, M., 1996. Hepatitis C virus variants from Jakarta, Indonesia classifiable into novel genotypes in the second (2e and 2f), tenth (10a) and eleventh (11a) genetic groups. J Gen Virol 77 (Pt 2), 293-301.
210. Tsuda, F., Hadiwandowo, S., Sawada, N., Fukuda, M., Tanaka, T., Okamoto, H., Miyakawa, Y., Mayumi, M., 1996. Infection with GB virus C (GBV-C) in patients with chronic liver disease or on maintenance hemodialysis in Indonesia. J Med Virol 49(3), 248-252.
211. Yui, K., Ishiguro, T., Okamoto, H., 1996. Infection with GB virus C in female prisoners who were drug abusers in Japan. Infection 24(5), 392.
212. Aikawa, T., Kanai, K., Kako, M., Kawasaki, T., Hino, K., Iwabuchi, S., Tsubouchi, H., Takehira, Y., Tsuda, F., Okamoto, H., et al., 1995. Interferon-alpha 2a for chronic hepatitis B with e antigen or antibody:comparable antiviral effects on wild-type virus and precore mutant. J Viral Hepat 2(5), 243-250.
213. Feray, C., Gigou, M., Samuel, D., Paradis, V., Mishiro, S., Maertens, G., Reynes, M., Okamoto, H., Bismuth, H., Brechot, C., 1995. Influence of the genotypes of hepatitis C virus on the severity of recurrent liver disease after liver transplantation. Gastroenterology 108(4), 1088-1096.
214. Itoh, K., Tanaka, H., Shiga, J.I., Hirakawa, K., Tanaka, T., Akahane, Y., Tsuda, F., Okamoto, H., Miyakawa, Y., Mayumi, M., 1995. Cold activation of complement as a marker of hepatitis C viremia in sera from blood donors. Transfus Sci 16(3), 283-289.
215. Kanazawa, K., Yaoita, H., Tsuda, F., Murata, K., Okamoto, H., 1995. Association of prurigo with hepatitis C virus infection. Arch Dermatol 131(7), 852-853.
216. Kita, H., Hiroishi, K., Moriyama, T., Okamoto, H., Kaneko, T., Ohnishi, S., Yazaki, Y., Imawari, M., 1995. A minimal and optimal cytotoxic T cell epitope within hepatitis C virus nucleoprotein. J Gen Virol 76 (Pt 12), 3189-3193.
217. Kita, H., Moriyama, T., Kaneko, T., Okamoto, H., Hiroishi, K., Ohnishi, S., Imawari, M., 1995. HLA B44-restricted cytotoxic T lymphocyte responses to the peptides of HCV nucleoprotein residues 81-100 in patients with chronic hepatitis C. J Gastroenterol 30(6), 809-812.
218. Miyakawa, Y., Okamoto, H., Mayumi, M., 1995. Classifying hepatitis C virus genotypes. Mol Med Today 1(1), 20-25.

219. Sato, S., Suzuki, K., Akahane, Y., Akamatsu, K., Akiyama, K., Yunomura, K., Tsuda, F., Tanaka, T., Okamoto, H., Miyakawa, Y., Mayumi, M., 1995. Hepatitis B virus strains with mutations in the core promoter in patients with fulminant hepatitis. Ann Intern Med 122(4), 241-248.
220. Tanaka, S., Yoshiba, M., Iino, S., Fukuda, M., Nakao, H., Tsuda, F., Okamoto, H., Miyakawa, Y., Mayumi, M., 1995. A common-source outbreak of fulminant hepatitis B in hemodialysis patients induced by precore mutant. Kidney Int 48(6), 1972-1978.
221. Tokita, H., Okamoto, H., Luengrojanakul, P., Vareesangthip, K., Chainuvati, T., Iizuka, H., Tsuda, F., Miyakawa, Y., Mayumi, M., 1995. Hepatitis C virus variants from Thailand classifiable into five novel genotypes in the sixth (6b), seventh (7c, 7d) and ninth (9b, 9c) major genetic groups. J Gen Virol 76 (Pt 9), 2329-2335.
222. Yoshiba, M., Okamoto, H., Mishiro, S., 1995. Detection of the GBV-C hepatitis virus genome in serum from patients with fulminant hepatitis of unknown aetiology. Lancet 346(8983), 1131-1132.
223. Akahane, Y., Kojima, M., Sugai, Y., Sakamoto, M., Miyazaki, Y., Tanaka, T., Tsuda, F., Mishiro, S., Okamoto, H., Miyakawa, Y., Mayumi, M., 1994. Hepatitis C virus infection in spouses of patients with type C chronic liver disease. Ann Intern Med 120(9), 748-752.
224. Hadiwandowo, S., Tsuda, F., Okamoto, H., Tokita, H., Wang, Y., Tanaka, T., Miyakawa, Y., Mayumi, M., 1994. Hepatitis B virus subtypes and hepatitis C virus genotypes in patients with chronic liver disease or on maintenance hemodialysis in Indonesia. J Med Virol 43(2), 182-186.
225. Hino, K., Sainokami, S., Shimoda, K., Iino, S., Wang, Y., Okamoto, H., Miyakawa, Y., Mayumi, M., 1994. Genotypes and titers of hepatitis C virus for predicting response to interferon in patients with chronic hepatitis C. J Med Virol 42(3), 299-305.
226. Horikita, M., Itoh, S., Yamamoto, K., Shibayama, T., Tsuda, F., Okamoto, H., 1994. Differences in the entire nucleotide sequence between hepatitis B virus genomes from carriers positive for antibody to hepatitis B e antigen with and without active disease. J Med Virol 44(1), 96-103.
227. Itoh, K., Tanaka, H., Shiga, J., Hirakawa, K., Akahane, Y., Tsuda, F., Okamoto, H., Miyakawa, Y., Mayumi, M., 1994. Hypocomplementemia associated with hepatitis C viremia in sera from voluntary blood donors. Am J Gastroenterol 89(11), 2019-2024.
228. Kojima, M., Osuga, T., Tsuda, F., Tanaka, T., Okamoto, H., 1994. Influence of antibodies to the hypervariable region of E2/NS1 glycoprotein on the selective replication of hepatitis C virus in chimpanzees. Virology 204(2), 665-672.
229. Luengrojanakul, P., Vareesangthip, K., Chainuvati, T., Murata, K., Tsuda, F., Tokita, H., Okamoto, H., Miyakawa, Y., Mayumi, M., 1994. Hepatitis C virus infection in patients with chronic liver disease or chronic renal failure and blood donors in Thailand. J Med Virol 44(3), 287-292.
230. Masuko, K., Okuda, K., Meguro, T., Murayama, N., Mitsui, T., Ohmori, T., Murata, K., Tsuda, F., Okamoto, H., 1994. Hepatitis C virus antibodies, viral RNA and genotypes in sera from patients on maintenance haemodialysis. J Viral Hepat 1(1), 65-71.
231. Nagayama, R., Miyake, K., Tsuda, F., Okamoto, H., 1994. IgM antibody to a hepatitis C virus core peptide (CP14) for monitoring activity of liver disease in patients with acute or chronic hepatitis C. J Med Virol 42(3), 311-317.
232. Nakata, S., Song, P., Duc, D.D., Nguyen, X.Q., Murata, K., Tsuda, F., Okamoto, H., 1994. Hepatitis C and B virus infections in populations at low or high risk in Ho Chi Minh and Hanoi, Vietnam. J Gastroenterol Hepatol 9(4), 416-419.
233. Okamoto, H., Kojima, M., Sakamoto, M., Iizuka, H., Hadiwandowo, S., Suwignyo, S., Miyakawa, Y., Mayumi, M., 1994. The entire nucleotide sequence and classification of a hepatitis C virus isolate of a novel genotype from an Indonesian patient with chronic liver disease. J Gen Virol 75 (Pt 3), 629-635.
234. Okamoto, H., Mishiro, S., 1994. Genetic heterogeneity of hepatitis C virus. Intervirology 37(2), 68-76.
235. Okamoto, H., Mishiro, S., Tokita, H., Tsuda, F., Miyakawa, Y., Mayumi, M., 1994. Superinfection of chimpanzees carrying hepatitis C virus of genotype II/1b with that of genotype III/2a or I/1a. Hepatology 20(5), 1131-1136.
236. Okamoto, H., Tsuda, F., Akahane, Y., Sugai, Y., Yoshiba, M., Moriyama, K., Tanaka, T., Miyakawa, Y., Mayumi, M., 1994. Hepatitis B virus with mutations in the core promoter for an e antigen-negative phenotype in carriers with antibody to e antigen. J Virol 68(12), 8102-8110.
237. Saitoh, H., Naitoh, S., Okamoto, H., Akahane, Y., 1994. Prompt decrease of circulating hepatitis C virus in patients with chronic hepatitis C after treatment with interferon. J Interferon Res 14(5), 239-244.
238. Sakamoto, M., Akahane, Y., Tsuda, F., Tanaka, T., Woodfield, D.G., Okamoto, H., 1994. Entire nucleotide sequence and characterization of a hepatitis C virus of genotype V/3a. J Gen Virol 75 (Pt 7), 1761-1768.
239. Shrestha, S.M., Tsuda, F., Okamoto, H., Tokita, H., Horikita, M., Tanaka, T., Miyakawa, Y., Mayumi, M., 1994. Hepatitis B virus subtypes and hepatitis C virus genotypes in patients with chronic liver disease in Nepal. Hepatology 19(4), 805-809.
240. Song, P., Duc, D.D., Hien, B., Nakata, S., Chosa, T., Watanabe, J., Tsuda, F., Murata, K., Okamoto, H., 1994. Markers of hepatitis C and B virus infections among blood donors in Ho Chi Minh City and Hanoi, Vietnam. Clin Diagn Lab

Immunol 1(4), 413-418.
241. Suzuki, H., Iino, S., Shiraki, K., Akahane, Y., Okamoto, H., Domoto, K., Mishiro, S., 1994. Safety and efficacy of a recombinant yeast-derived pre-S2 + S-containing hepatitis B vaccine (TGP-943): phase 1, 2 and 3 clinical testing. Vaccine 12(12), 1090-1096.
242. Takahashi, M., Yamada, G., Doi, T., Takatani, M., Kishi, F., Miyamoto, R., Yoshizawa, H., Okamoto, H., Tsuji, T., 1994. Intrafamilial clustering of genotypes of hepatitis C virus RNA. Acta Med Okayama 48(6), 293-297.
243. Tokita, H., Okamoto, H., Tsuda, F., Song, P., Nakata, S., Chosa, T., Iizuka, H., Mishiro, S., Miyakawa, Y., Mayumi, M., 1994. Hepatitis C virus variants from Vietnam are classifiable into the seventh, eighth, and ninth major genetic groups. Proc Natl Acad Sci U S A 91(23), 11022-11026.
244. Tokita, H., Shrestha, S.M., Okamoto, H., Sakamoto, M., Horikita, M., Iizuka, H., Shrestha, S., Miyakawa, Y., Mayumi, M., 1994. Hepatitis C virus variants from Nepal with novel genotypes and their classification into the third major group. J Gen Virol 75 (Pt 4), 931-936.
245. Wang, Y., Tao, Q.M., Zhao, H.Y., Tsuda, F., Nagayama, R., Yamamoto, K., Tanaka, T., Tokita, H., Okamoto, H., Miyakawa, Y., et al., 1994. Hepatitis C virus RNA and antibodies among blood donors in Beijing. J Hepatol 21(4), 634-640.
246. Woodfield, D.G., Harness, M., Rix-Trott, K., Tsuda, F., Okamoto, H., Mayumi, M., 1994. Identification and genotyping of hepatitis C virus in injectable and oral drug users in New Zealand. Aust N Z J Med 24(1), 47-50.
247. Yamada, G., Takahashi, M., Miyamoto, R., Tsuji, T., Yoshizawa, H., Okamoto, H., 1994. Prediction of interferon effect in chronic hepatitis C by both quantification and genotyping of HCV-RNA. Dig Dis Sci 39(2), 441.
248. Yamamoto, K., Horikita, M., Tsuda, F., Itoh, K., Akahane, Y., Yotsumoto, S., Okamoto, H., Miyakawa, Y., Mayumi, M., 1994. Naturally occurring escape mutants of hepatitis B virus with various mutations in the S gene in carriers seropositive for antibody to hepatitis B surface antigen. J Virol 68(4), 2671-2676.
249. Yoshiba, M., Dehara, K., Inoue, K., Okamoto, H., Mayumi, M., 1994. Contribution of hepatitis C virus to non-A, non-B fulminant hepatitis in Japan. Hepatology 19(4), 829-835.
250. Yoshiba, M., Sekiyama, K., Inoue, K., Sugata, F., Okamoto, H., 1994. Genotype of hepatitis C virus in fulminant hepatitis C. Dig Dis Sci 39(1), 220-221.
251. Kinoshita, T., Miyake, K., Okamoto, H., Mishiro, S., 1993. Imported hepatitis C virus genotypes in Japanese hemophiliacs. J Infect Dis 168(1), 249-250.
252. Kondo, Y., Tsukada, K., Takeuchi, T., Mitsui, T., Iwano, K., Masuko, K., Itoh, T., Tokita, H., Okamoto, H., Tsuda, F., et al., 1993. High carrier rate after hepatitis B virus infection in the elderly. Hepatology 18(4), 768-774.
253. Nagayama, R., Tsuda, F., Okamoto, H., Wang, Y., Mitsui, T., Tanaka, T., Miyakawa, Y., Mayumi, M., 1993. Genotype dependence of hepatitis C virus antibodies detectable by the first-generation enzyme-linked immunosorbent assay with C100-3 protein. J Clin Invest 92(3), 1529-1533.
254. Ohnuma, H., Machida, A., Okamoto, H., Tsuda, F., Sakamoto, M., Tanaka, T., Miyakawa, Y., Mayumi, M., 1993. Allelic subtypic determinants of hepatitis B surface antigen (i and t) that are distinct from d/y or w/r. J Virol 67(2), 927-932.
255. Okamoto, H., Tokita, H., Sakamoto, M., Horikita, M., Kojima, M., Iizuka, H., Mishiro, S., 1993. Characterization of the genomic sequence of type V (or 3a) hepatitis C virus isolates and PCR primers for specific detection. J Gen Virol 74 (Pt 11), 2385-2390.
256. Okamoto, H., Wang, Y., Tanaka, T., Machida, A., Miyakawa, Y., Mayumi, M., 1993. Trans-complementation among naturally occurring deletion mutants of hepatitis B virus and integrated viral DNA for the production of viral particles with mutant genomes in hepatoma cell lines. J Gen Virol 74 (Pt 3), 407-414.
257. Sato, K., Okamoto, H., Aihara, S., Hoshi, Y., Tanaka, T., Mishiro, S., 1993. Demonstration of sugar moiety on the surface of hepatitis C virions recovered from the circulation of infected humans. Virology 196(1), 354-357.
258. Takahashi, K., Kishimoto, S., Ohori, K., Yoshizawa, H., Okamoto, H., Miyakawa, Y., Mayumi, M., 1993. SDS-PAGE after micro-affinity adsorption for analysis of heterogeneous antigen polypeptides in individual sera. J Immunol Methods 157(1-2), 217-223.
259. Taniguchi, S., Okamoto, H., Sakamoto, M., Kojima, M., Tsuda, F., Tanaka, T., Munekata, E., Muchmore, E.E., Peterson, D.A., Mishiro, S., 1993. A structurally flexible and antigenically variable N-terminal domain of the hepatitis C virus E2/NS1 protein: implication for an escape from antibody. Virology 195(1), 297-301.
260. Wang, Y., Okamoto, H., Tsuda, F., Nagayama, R., Tao, Q.M., Mishiro, S., 1993. Prevalence, genotypes, and an isolate (HC-C2) of hepatitis C virus in Chinese patients with liver disease. J Med Virol 40(3), 254-260.
261. Watanabe, J., Matsumoto, C., Fujimura, K., Shimada, T., Yoshizawa, H., Okamoto, H., Iizuka, H., Tango, T., Ikeda, H., Endo, N., et al., 1993. Predictive value of screening tests for persistent hepatitis C virus infection evidenced by viraemia. Japanese experience. Vox Sang 65(3), 199-203.
262. Yoshiba, M., Sekiyama, K., Iwabuchi, S., Takatori, M., Tanaka, Y., Uchikoshi, T., Okamoto, H., Inoue, K., Sugata, F., 1993. Recurrent fulminant hepatic failure in an HB carrier after intensive chemotherapy. Dig Dis Sci 38(9), 1751-1755.

263. Yoshikawa, A., Tanaka, T., Hoshi, Y., Kato, N., Tachibana, K., Iizuka, H., Machida, A., Okamoto, H., Yamasaki, M., Miyakawa, Y., et al., 1993. Chimeric hepatitis B virus core particles with parts or copies of the hepatitis C virus core protein. J Virol 67(10), 6064-6070.
264. Akahane, Y., Aikawa, T., Sugai, Y., Tsuda, F., Okamoto, H., Mishiro, S., 1992. Transmission of HCV between spouses. Lancet 339(8800), 1059-1060.
265. Iizuka, H., Ohmura, K., Ishijima, A., Satoh, K., Tanaka, T., Tsuda, F., Okamoto, H., Miyakawa, Y., Mayumi, M., 1992. Correlation between anti-HBc titers and HBV DNA in blood units without detectable HBsAg. Vox Sang 63(2), 107-111.
266. Kanagawa, H., Takai, E., Tsuda, F., Machida, A., Kojima, M., Ishijima, A., Tanaka, T., Okamoto, H., Miyakawa, Y., Mayumi, M., 1992. Hepatitis B surface antigen particles of subtypes adw and adr, and compound subtype (adwr) in symptom-free carriers in Japan. J Med Virol 37(4), 288-293.
267. Kanai, K., Kako, M., Okamoto, H., 1992. HCV genotypes in chronic hepatitis C and response to interferon. Lancet 339(8808), 1543.
268. Machida, A., Ohnuma, H., Tsuda, F., Munekata, E., Tanaka, T., Akahane, Y., Okamoto, H., Mishiro, S., 1992. Two distinct subtypes of hepatitis C virus defined by antibodies directed to the putative core protein. Hepatology 16(4), 886-891.
269. Mitsui, T., Iwano, K., Masuko, K., Yamazaki, C., Okamoto, H., Tsuda, F., Tanaka, T., Mishiro, S., 1992. Hepatitis C virus infection in medical personnel after needlestick accident. Hepatology 16(5), 1109-1114.
270. Miyamoto, H., Okamoto, H., Sato, K., Tanaka, T., Mishiro, S., 1992. Extraordinarily low density of hepatitis C virus estimated by sucrose density gradient centrifugation and the polymerase chain reaction. J Gen Virol 73 (Pt 3), 715-718.
271. Okada, S., Akahane, Y., Suzuki, H., Okamoto, H., Mishiro, S., 1992. The degree of variability in the amino terminal region of the E2/NS1 protein of hepatitis C virus correlates with responsiveness to interferon therapy in viremic patients. Hepatology 16(3), 619-624.
272. Okamoto, H., Kanai, N., Mishiro, S., 1992. Full-length nucleotide sequence of a Japanese hepatitis C virus isolate (HC-J1) with high homology to USA isolates. Nucleic Acids Res 20(23), 6410.
273. Okamoto, H., Kojima, M., Okada, S., Yoshizawa, H., Iizuka, H., Tanaka, T., Muchmore, E.E., Peterson, D.A., Ito, Y., Mishiro, S., 1992. Genetic drift of hepatitis C virus during an 8.2-year infection in a chimpanzee: variability and stability. Virology 190(2), 894-899.
274. Okamoto, H., Kurai, K., Okada, S., Yamamoto, K., Lizuka, H., Tanaka, T., Fukuda, S., Tsuda, F., Mishiro, S., 1992. Full-length sequence of a hepatitis C virus genome having poor homology to reported isolates: comparative study of four distinct genotypes. Virology 188(1), 331-341.
275. Okamoto, H., Sugiyama, Y., Okada, S., Kurai, K., Akahane, Y., Sugai, Y., Tanaka, T., Sato, K., Tsuda, F., Miyakawa, Y., et al., 1992. Typing hepatitis C virus by polymerase chain reaction with type-specific primers: application to clinical surveys and tracing infectious sources. J Gen Virol 73 (Pt 3), 673-679.
276. Okamoto, H., Tsuda, F., Machida, A., Munekata, E., Akahane, Y., Sugai, Y., Mashiko, K., Mitsui, T., Tanaka, T., Miyakawa, Y., et al., 1992. Antibodies against synthetic oligopeptides deduced from the putative core gene for the diagnosis of hepatitis virus infection. Hepatology 15(2), 180-186.
277. Okamoto, H., Yano, K., Nozaki, Y., Matsui, A., Miyazaki, H., Yamamoto, K., Tsuda, F., Machida, A., Mishiro, S., 1992. Mutations within the S gene of hepatitis B virus transmitted from mothers to babies immunized with hepatitis B immune globulin and vaccine. Pediatr Res 32(3), 264-268.
278. Takahashi, K., Kishimoto, S., Yoshizawa, H., Okamoto, H., Yoshikawa, A., Mishiro, S., 1992. p26 protein and 33-nm particle associated with nucleocapsid of hepatitis C virus recovered from the circulation of infected hosts. Virology 191(1), 431-434.
279. Takahashi, K., Okamoto, H., Kishimoto, S., Munekata, E., Tachibana, K., Akahane, Y., Yoshizawa, H., Mishiro, S., 1992. Demonstration of a hepatitis C virus-specific antigen predicted from the putative core gene in the circulation of infected hosts. J Gen Virol 73 (Pt 3), 667-672.
280. Wang, Y., Okamoto, H., Mishiro, S., 1992. HCV genotypes in China. Lancet 339(8802), 1168.
281. Yamada, G., Takahashi, M., Tsuji, T., Yoshizawa, H., Okamoto, H., 1992. Quantitative HCV RNA and effect of interferon therapy in chronic hepatitis C. Dig Dis Sci 37(12), 1926-1927.
282. Yoshiba, M., Sekiyama, K., Sugata, F., Kanamori, H., Kodama, F., Okamoto, H., 1992. Activation of hepatitis C virus following immunosuppressive treatment. Dig Dis Sci 37(3), 478.
283. Yoshiba, M., Sekiyama, K., Sugata, F., Okamoto, H., Yamamoto, K., Yotsumoto, S., 1992. Reactivation of precore mutant hepatitis B virus leading to fulminant hepatic failure following cytotoxic treatment. Dig Dis Sci 37(8), 1253-1259.
284. Yoshikawa, A., Takahashi, K., Kishimoto, S., Tsuda, F., Akahane, Y., Naito, S., Tanaka, T., Yoshizawa, H., Yamasaki, M., Okamoto, H., et al., 1992. Serodiagnosis of hepatitis C virus infection by ELISA for antibodies against the putative core protein (p20c) expressed in Escherichia coli. J Immunol Methods 148(1-2), 143-150.

285. Yotsumoto, S., Kojima, M., Shoji, I., Yamamoto, K., Okamoto, H., Mishiro, S., 1992. Fulminant hepatitis related to transmission of hepatitis B variants with precore mutations between spouses. Hepatology 16(1), 31-35.
286. Kojima, M., Shimizu, M., Tsuchimochi, T., Koyasu, M., Tanaka, S., Iizuka, H., Tanaka, T., Okamoto, H., Tsuda, F., Miyakawa, Y., et al., 1991. Posttransfusion fulminant hepatitis B associated with precore-defective HBV mutants. Vox Sang 60(1), 34-39.
287. Kosaka, Y., Takase, K., Kojima, M., Shimizu, M., Inoue, K., Yoshiba, M., Tanaka, S., Akahane, Y., Okamoto, H., Tsuda, F., et al., 1991. Fulminant hepatitis B: induction by hepatitis B virus mutants defective in the precore region and incapable of encoding e antigen. Gastroenterology 100(4), 1087-1094.
288. Miyakawa, H., Kako, M., Nagai, K., Hino, K., Iwabuchi, S., Miyachi, K., Okamoto, H., Mayumi, M., 1991. HCV-RNA in type 2 autoimmune hepatitis. Am J Gastroenterol 86(11), 1688-1689.
289. Okamoto, H., Okada, S., Sugiyama, Y., Kurai, K., Iizuka, H., Machida, A., Miyakawa, Y., Mayumi, M., 1991. Nucleotide sequence of the genomic RNA of hepatitis C virus isolated from a human carrier: comparison with reported isolates for conserved and divergent regions. J Gen Virol 72 (Pt 11), 2697-2704.
290. Sastrosoewignjo, R.I., Sandjaja, B., Okamoto, H., 1991. Molecular epidemiology of hepatitis B virus in Indonesia. J Gastroenterol Hepatol 6(5), 491-498.
291. Terazawa, S., Kojima, M., Yamanaka, T., Yotsumoto, S., Okamoto, H., Tsuda, F., Miyakawa, Y., Mayumi, M., 1991. Hepatitis B virus mutants with precore-region defects in two babies with fulminant hepatitis and their mothers positive for antibody to hepatitis B e antigen. Pediatr Res 29(1), 5-9.
292. Yoshiba, M., Sekiyama, K., Sugata, F., Okamoto, H., 1991. Diagnosis of type C fulminant hepatitis by the detection of antibodies to the putative core proteins of hepatitis C virus. Gastroenterol Jpn 26(2), 234.
293. Yoshiba, M., Sekiyama, K., Sugata, F., Okamoto, H., Mayumi, M., 1991. Persistence of HCV replication in non-A, non-B fulminant viral hepatitis. Gastroenterol Jpn 26(2), 235.
294. Akahane, Y., Yamanaka, T., Suzuki, H., Sugai, Y., Tsuda, F., Yotsumoto, S., Omi, S., Okamoto, H., Miyakawa, Y., Mayumi, M., 1990. Chronic active hepatitis with hepatitis B virus DNA and antibody against e antigen in the serum. Disturbed synthesis and secretion of e antigen from hepatocytes due to a point mutation in the precore region. Gastroenterology 99(4), 1113-1119.
295. Kanai, K., Iwata, K., Nakao, K., Kako, M., Okamoto, H., 1990. Suppression of hepatitis C virus RNA by interferon-alpha. Lancet 336(8709), 245.
296. Luengrojanakul, P., Ohnuma, H., Tachibana, K., Usuda, S., Okamoto, H., Tanaka, T., Tsuda, F., Machida, A., Mayumi, M., 1990. Common and subtypic determinants of hepatitis B surface antigen particles: susceptibility to reduction and/or alkylation evaluated with monoclonal antibodies. Jpn J Exp Med 60(5), 253-261.
297. Mishiro, S., Hoshi, Y., Takeda, K., Yoshikawa, A., Gotanda, T., Takahashi, K., Akahane, Y., Yoshizawa, H., Okamoto, H., Tsuda, F., et al., 1990. Non-A, non-B hepatitis specific antibodies directed at host-derived epitope: implication for an autoimmune process. Lancet 336(8728), 1400-1403.
298. Ohnuma, H., Takai, E., Machida, A., Tsuda, F., Okamoto, H., Tanaka, T., Naito, M., Munekata, E., Miki, K., Miyakawa, Y., et al., 1990. Synthetic oligopeptides bearing a common or subtypic determinant of hepatitis B surface antigen. J Immunol 145(7), 2265-2271.
299. Okamoto, H., Munekata, E., Tsuda, F., Takahashi, K., Yotsumoto, S., Tanaka, T., Tachibana, K., Akahane, Y., Sugai, Y., Miyakawa, Y., et al., 1990. Enzyme-linked immunosorbent assay for antibodies against the capsid protein of hepatitis C virus with a synthetic oligopeptide. Jpn J Exp Med 60(4), 223-233.
300. Okamoto, H., Okada, S., Sugiyama, Y., Tanaka, T., Sugai, Y., Akahane, Y., Machida, A., Mishiro, S., Yoshizawa, H., Miyakawa, Y., et al., 1990. Detection of hepatitis C virus RNA by a two-stage polymerase chain reaction with two pairs of primers deduced from the 5'-noncoding region. Jpn J Exp Med 60(4), 215-222.
301. Okamoto, H., Okada, S., Sugiyama, Y., Yotsumoto, S., Tanaka, T., Yoshizawa, H., Tsuda, F., Miyakawa, Y., Mayumi, M., 1990. The 5'-terminal sequence of the hepatitis C virus genome. Jpn J Exp Med 60(3), 167-177.
302. Okamoto, H., Omi, S., Wang, Y., Imai, M., Mayumi, M., 1990. Trans-complementation of the C gene of human and the P gene of woodchuck hepadnaviruses. J Gen Virol 71 (Pt 4), 959-963.
303. Okamoto, H., Yotsumoto, S., Akahane, Y., Yamanaka, T., Miyazaki, Y., Sugai, Y., Tsuda, F., Tanaka, T., Miyakawa, Y., Mayumi, M., 1990. Hepatitis B viruses with precore region defects prevail in persistently infected hosts along with seroconversion to the antibody against e antigen. J Virol 64(3), 1298-1303.
304. Omi, S., Okamoto, H., Tsuda, F., Mayumi, M., 1990. Defects in the precore region of hepatitis B virus DNA in a plasma pool from carriers seropositive for antibody against e antigen and with infectivity in chimpanzees. J Gastroenterol Hepatol 5(6), 646-652.
305. Takeda, K., Akahane, Y., Suzuki, H., Okamoto, H., Tsuda, F., Miyakawa, Y., Mayumi, M., 1990. Defects in the precore region of the HBV genome in patients with chronic hepatitis B after sustained seroconversion from HBeAg to anti-HBe induced spontaneously or with interferon therapy. Hepatology 12(6), 1284-1289.
306. Yamanaka, T., Akahane, Y., Suzuki, H., Okamoto, H., Tsuda, F., Miyakawa, Y., Mayumi, M., 1990. Hepatitis B

surface antigen particles with all four subtypic determinants: point mutations of hepatitis B virus DNA inducing phenotypic changes or double infection with viruses of different subtypes. Mol Immunol 27(5), 443-449.
307. Yotsumoto, S., Okamoto, H., Tsuda, F., Miyakawa, Y., Mayumi, M., 1990. Subtyping hepatitis B virus DNA in free or integrated forms by amplification of the S-gene sequences by the polymerase chain reaction and single-track sequencing for adenine. J Virol Methods 28(2), 107-116.
308. Okamoto, H., Omi, S., Wang, Y., Itoh, Y., Tsuda, F., Tanaka, T., Akahane, Y., Miyakawa, Y., Mayumi, M., 1989. The loss of subtypic determinants in alleles, d/y or w/r, on hepatitis B surface antigen. Mol Immunol 26(2), 197-205.
309. Okamoto, H., Yotsumoto, S., Tsuda, F., Machida, A., Mayumi, M., 1989. Quantitative and qualitative differences in serum HBV DNA between HBeAg positive carriers and those positive for anti-HBe. Jpn J Exp Med 59(6), 259-262.
310. Sugai, Y., Okamoto, H., 1989. State of hepatitis B virus DNA in peripheral blood mononuclear cells from persistently infected individuals: correlation with e antigen and viral DNA in the serum as well as with the activity of liver disease. Tohoku J Exp Med 158(1), 73-84.
311. Tachibana, K., Tanaka, T., Usuda, S., Okamoto, H., Tsuda, F., Akahane, Y., Miyakawa, Y., Mayumi, M., 1989. Hepatitis B surface antigen with an excess or deficiency in subtypic determinants in sera from asymptomatic carriers in Japan. Viral Immunol 2(1), 25-29.
312. Okamoto, H., Tsuda, F., Sakugawa, H., Sastrosoewignjo, R.I., Imai, M., Miyakawa, Y., Mayumi, M., 1988. Typing hepatitis B virus by homology in nucleotide sequence: comparison of surface antigen subtypes. J Gen Virol 69 (Pt 10), 2575-2583.
313. Imai, M., Hoshi, Y., Okamoto, H., Matsui, T., Tsurimoto, T., Matsubara, K., Miyakawa, Y., Mayumi, M., 1987. Free and integrated forms of hepatitis B virus DNA in human hepatocellular carcinoma cells (PLC/342) propagated in nude mice. J Virol 61(11), 3555-3560.
314. Okamoto, H., Imai, M., Kametani, M., Nakamura, T., Mayumi, M., 1987. Genomic heterogeneity of hepatitis B virus in a 54-year-old woman who contracted the infection through materno-fetal transmission. Jpn J Exp Med 57(4), 231-236.
315. Okamoto, H., Imai, M., Miyakawa, Y., Mayumi, M., 1987. Site-directed mutagenesis of hepatitis B surface antigen sequence at codon 160 from arginine to lysine for conversion of subtypic determinant from r to w. Biochem Biophys Res Commun 148(1), 500-504.
316. Okamoto, H., Imai, M., Tsuda, F., Tanaka, T., Miyakawa, Y., Mayumi, M., 1987. Point mutation in the S gene of hepatitis B virus for a d/y or w/r subtypic change in two blood donors carrying a surface antigen of compound subtype adyr or adwr. J Virol 61(10), 3030-3034.
317. Okamoto, H., Tsuda, F., Mayumi, M., 1987. Defective mutants of hepatitis B virus in the circulation of symptom-free carriers. Jpn J Exp Med 57(4), 217-221.
318. Matsui, T., Takano, M., Miyamoto, K., Itoh, Y., Yoshizawa, H., Koike, M., Mochizuki, T., Tanaka, E., Okamoto, H., Imai, M., et al., 1986. Nude mice bearing human primary hepatocellular carcinoma that produces hepatitis B surface, core, and e antigens, as well as deoxyribonucleic acid polymerase. Gastroenterology 90(1), 135-142.
319. Okamoto, H., Imai, M., Shimozaki, M., Hoshi, Y., Iizuka, H., Gotanda, T., Tsuda, F., Miyakawa, Y., Mayumi, M., 1986. Nucleotide sequence of a cloned hepatitis B virus genome, subtype ayr: comparison with genomes of the other three subtypes. J Gen Virol 67 (Pt 11), 2305-2314.
320. Okamoto, H., Usuda, S., Imai, M., Tachibana, K., Tanaka, E., Kumakura, T., Itabashi, M., Takai, E., Tsuda, F., Nakamura, T., et al., 1986. Antibody to the receptor for polymerized human serum albumin in acute and persistent infection with hepatitis B virus. Hepatology 6(3), 354-359.
321. Usuda, S., Tsuda, F., Gotanda, T., Tachibana, K., Nomura, M., Okamoto, H., Imai, M., Nakamura, T., Miyakawa, Y., Mayumi, M., 1986. A solid-phase enzyme immunoassay for the common and subtypic determinants of hepatitis B surface antigen with monoclonal antibodies. J Immunol Methods 87(2), 203-210.
322. Okamoto, H., Imai, M., Usuda, S., Tanaka, E., Tachibana, K., Mishiro, S., Machida, A., Nakamura, T., Miyakawa, Y., Mayumi, M., 1985. Hemagglutination assay of polypeptide coded by the pre-S region of hepatitis B virus DNA with monoclonal antibody: correlation of pre-S polypeptide with the receptor for polymerized human serum albumin in serums containing hepatitis B antigens. J Immunol 134(2), 1212-1216.

経口肝炎班の背景

·平成15年-17年
本邦におけるE型肝炎の診断・予防・疫学に関する研究（第1次E型班）

·平成18年-20年
E型肝炎の感染経路・宿主域・遺伝的多様性・感染防止・診断・治療に関する研究
（第2次E型班）

第3次E型班
A型班
→ 平成21年-23年 経口肝炎班

経口感染する肝炎ウイルス(A型、E型)の感染防止、遺伝的多様性、および治療に関する研究

2年間の研究成果の概要(その2)

HEV

- E型急性肝炎の動向（八橋班員）：国立病院機構共同研究班 28 施設による急性肝炎の全国調査（1980 ～ 2009 年）：E 型肝炎が非 ABC 肝炎の 5.6%(2000 年以降は 11.4%) に相当。
- E型劇症肝炎の動向（橘谷班員）：劇症肝炎・LOHF の全国調査結果（1998 ～ 2008 年）：E 型劇症肝炎は年間 1 ～ 2 例が散発発生。高齢が予後不良因子。
- 北海道E型肝炎研究会（道E研）による流行監視（姜班員）：・函館地区において、北見網走株の近縁株を検出（含劇症化例）。・札幌圏において、新札幌株によるE型肝炎小流行発生（含重症化例）。道外からの旅行者も感染（福川班友）。
- 北海道地域の献血者に於けるHEV-NATの継続（日野班員）：献血者 506,940 名（2009 年 1 月～ 2010 年 10 月）における HEV RNA 陽性者は、48 名 [0.009%（男性 0.012%、女性 0.006%)]。
- 北東北に於ける急性肝障害登録システムによる成因調査（鈴木班員）：2009 年 8 月から 2010 年 9 月までに登録された 77 例中 5 例 (6.5%) が E 型であり、成因不明肝障害例の約 12% を占めた。

主な研究課題

A型肝炎について：

- 近年、低浸淫国における流行が報告され、本邦でも流行の可能性がある。発生状況のモニタリングを実施し、重症・劇症化の機序を解明する。
- 抗ウイルス剤の開発に向けた基礎研究
- ワクチンで予防可能な疾患でありながら、本邦では接種対象が明確ではなく、普及していないという現状を踏まえ、ワクチンの接種対象をより明確なものとし、普及・啓発を行う。

E型肝炎について：

- 国内感染E型肝炎の過半数が感染源不明のままであり、更なる実態解明を推進し、感染防止に役立てる。
- 臨床像および起因ウイルスの詳細な検討、治療法の確立により重症化、劇症化の阻止を目指す。
- 細胞培養系を用いて、これまでに不明な点が多いHEV増殖機構の解明、また培養細胞由来HEVの不活化ワクチンとしての応用の検討を行う。

2年間の研究成果の概要(その3)

HEV

- HEV感染の全国調査（班長、日野班員）：・全国調査 [30 都道県在住の約 2.2 万人 (20 ～ 108 歳)]：5.3%（男性 7.8%、女性 3.4%）が IgG-HEV 抗体を保有。国内の HEV 感染既往者は 500 万人、年間新規感染者は 12 万人と推定（班長）。・全国調査 [8 センターの約 1.3 万人 (16 ～ 69 歳)]：3.4%（男性 3.9%、女性 2.9%）が IgG-HEV 抗体を保有（日野班員）。・年間抗体陽転率は男性 0.17%、女性 0.06%。東高西低。
- 新規（5型、6型）HEVの同定（班長、新井班員）：静岡県のイノシシから分離された HEV（JBOAR135-Shiz09）、また、岡山県のイノシシから分離された HEV（wbJOY_06）は従前未知の遺伝子型（それぞれ"5型"と"6型"）に属する。
- 感染培養系を用いた研究成果（班長、李班員）：・E型肝炎患者由来の糞便中 HEV のみならず、血清中 HEV も遺伝子型の違いに因らず、効率よく PLC/PRF/5 細胞および A549 細胞で増殖可能であることを明らかにした（班長）。・ORF3 蛋白質が HEV の細胞からの放出に必須であり、放出された HEV 粒子（培養上清・血清）の表面に細胞膜成分と ORF3 蛋白質が存在すること、ORF3 蛋白質の PSAP モチーフに変異を導入するとウイルス産生能が失われることを明らかにした（班長）。・培養細胞由来 HEV の不活化の検討を行い、熱処理 HEV の不活化ワクチンとしての応用の可能性を示した（李班員）。

2年間の研究成果の概要(その1)

HAV

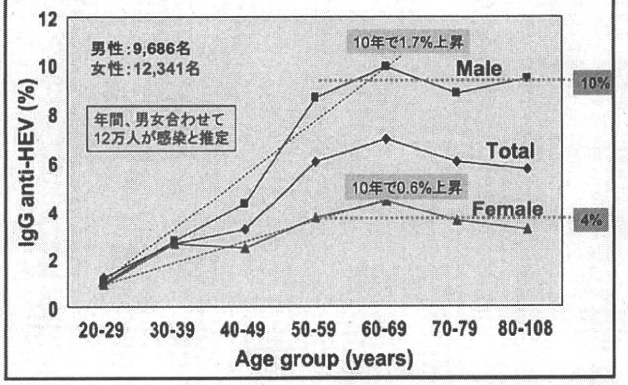
- A型急性肝炎の動向（八橋班員）：国立病院機構共同研究班 28 施設による急性肝炎の全国調査（1980 ～ 2009 年）：A 型肝炎が減少傾向。高齢化、重症化傾向。季節性発生が減少。
- 2010年春期HAV株の解析（李班員、石井班友）：2010 年春期は例年よりも報告件数が多かったが、幸い広域アウトブレイクには進展しなかった。しかし、HAV 株の一部は IIIA 型で、韓国の大流行株（2008 年～）と同じクラスターに属したことから、引き続き慎重な監視が必要。
- A型劇症肝炎の動向（橘谷班員）：劇症肝炎・遅発性肝不全（LOHF）の全国調査結果（1998 ～ 2008 年）：A 型劇症肝炎は減少傾向。高齢、男性、基礎疾患、合併症数が予後不良因子。
- 抗ウイルス剤の開発（横須賀班員）：HAV IRES 依存性翻訳に対する抗ウイルス剤 Amandadine の有効性を示した。Amantadine と IFNα の併用療法がウイルス増殖抑制に有用であった。韓国株に対しても有効。
- ワクチン対象設定、適応拡大、普及（矢野前班長、石井班友）：本邦では 16 歳未満に対する適応がないことを受け、「不活化 A 型肝炎ワクチンの適応拡大に関する適応外薬の要望書」を提出（2009 年 8 月 14 日付）。

一般健常人におけるHEV感染の全国調査

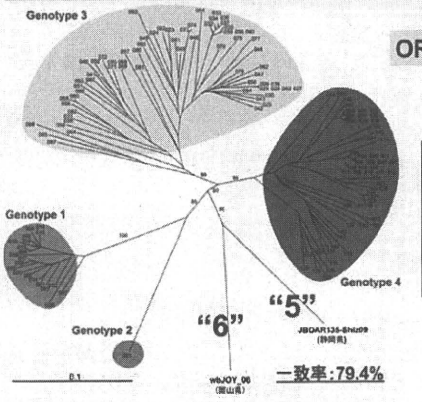
30都道県からの22,027例の健康診断検体
男性：9,686例
女性：12,341例
年齢：56.8 ± 16.7 歳
（20～108 歳）
2002年 1月～2007年 12月

J Med Virol 82:271-281, 2010

性別、年代別のIgGクラスHEV抗体陽性率



野生イノシシ由来の2種類の新規HEV株を発見



新たな遺伝子型に分類されうる、更なる未同定のHEV株の存在が示唆され、HEV遺伝子の多様性についての継続的な調査・解析が必要。

一致率:79.4%

哺乳動物から分離されるHEVの遺伝子型

- Genotype 1
  humans
- Genotype 2
  humans

ヒトのみ

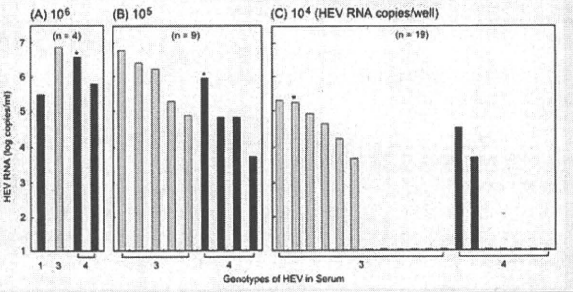
人獣共通

- Genotype 3
  humans, swine, wild boars, deer, *mongoose*, *rabbits*
- Genotype 4
  humans, swine, wild boars
- (Genotype 5?) 暫定的
  wild boar (JBOAR135-Shiz09、静岡県)
- (Genotype 6?) 暫定的
  wild boar (wbJOY_06、岡山県)

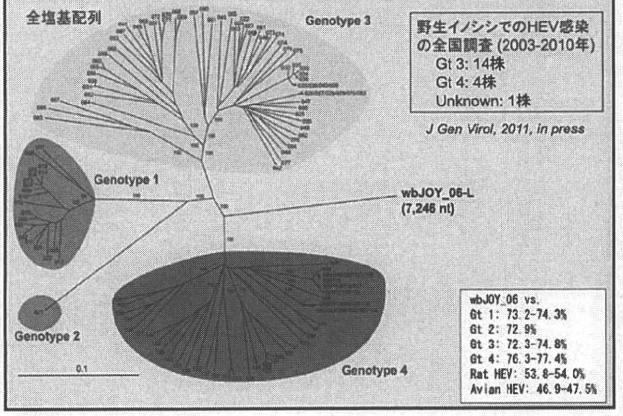
HEVの培養系

PLC/PRF/5細胞やA549細胞を用いた細胞培養系において、E型肝炎患者の糞便由来HEVのみならず、血清中HEVも増殖可能であることを明らかにした。

J Clin Microbiol 48:1112-1125, 2010



新しい遺伝子型に分類されうるHEV株の発見



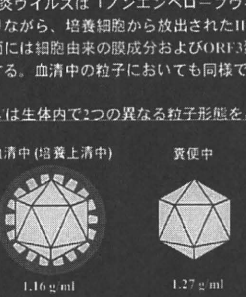
野生イノシシでのHEV感染の全国調査(2003-2010年)
Gt 3: 14株
Gt 4: 4株
Unknown: 1株

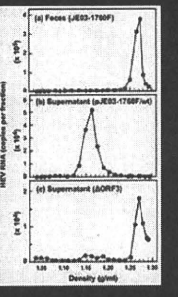
J Gen Virol, 2011, in press

ORF3欠失変異体(ΔORF3)を用いた解析

E型肝炎ウイルスは「ノンエンベロープウイルス」でありながら、培養細胞から放出されたHEV粒子の表面には細胞由来の膜成分およびORF3蛋白質が存在する。血清中の粒子においても同様である。

HEVは生体内で2つの異なる粒子形態をとる。





- ORF3蛋白質は感染細胞からのウイルス粒子の放出に重要である。
- HEV粒子表面の修飾形成はORF3蛋白質の発現に依存している。

J Gen Virol 90:1880-1891, 2009