10. Sui S, Kudo A, Suematsu M, Tanaka S, Nakamura N, Ito K, Arii S. Preservation solutions alter Mrp2-dependent bile flow in cold ischemic rat livers. J Surg Res, 2010;159(1):572-81.
11. Uchida Y, Tanaka S, Aihara A, Adikrisna R, Yoshitake K, Matsumura S, Mitsunori Y, Murakata A, Noguchi N, Irie T, Kudo A, Nakamura N, Lai PB, Arii S. Analogy between sphere forming ability and stemness of human hepatoma cells. Oncol Rep. 2010 Nov;24(5):1147-51. PubMed PMID: 20878104.
12. Sugiyama T, Kouyama R, Tani Y, Izumiyama H, Akashi T, Kishimoto S, Arii S, Hirata Y. Giant malignant insulinoma which developed from a non-functioning pancreatic tumor over a long period of time. Intern Med. 2010;49(15):1573-9.
13. Takayasu K, Arii S, Ikai I, Kudo M, Matsuyama Y, Kojiro M, Makuuchi M; Liver Cancer Study Group of Japan. Overall survival after transarterial lipiodol infusion chemotherapy with or without embolization for unresectable hepatocellular carcinoma: propensity score analysis. AJR Am J Roentgenol. 2010;194(3):830-7.
14. Tanaka S, Mogushi K, Yasen M, Noguchi N, Kudo A, Kurokawa T, Nakamura N, InazawaJ, Tanaka H, Arii S. Surgical contribution to recurrence –free survival in patients with macrovascular invasion-negative hepatocellular carcinoma. ***J Am Coll Surg,*** 2009;208:368-374
15. Mahmut Y, Mizushima H, Mogushi K, Obulhasim G, Miyaguchi K, Inoue K, Nakahara I, Ohta T, Aihara A, Tanaka S Arii S, Tanaka H Expression of Aurora B and their alternative variant forms in hepatrocellular carcinoma and the adjacent tissue. ***Cancer Sci,*** 2009;100:472-480
16. Ban D, Kudo A, Sui S, Tanaka S, Nakamura N, Ito K, Suematsu M, Arii S. Decreased Mrp-2 dependent bile flow in the post-warm ischemic rat liver. ***J Surg Res***. 2009;153(2):310-6
17. Gen Y, Yasui K, Zen K, Nakajima T, Tsuji K, Endo M, Mitsuyosi H, Minami M, Itoh Y, Tanaka S, Taniwaki M, Arii S, Okanoue T, Yoshikawa T. A novel amplification target, ARHGAP5, promotes cell spreading and migration by negatively regulating Rho A in Huh-7 hepatocellular carcinoma cells. ***Cancer Lett***, 2009;275:27-34
18. Zen K, Yasui K, Nakajima T, Zen Y, Zen K, Gen Y, Mitsuyosi H, Mimami M, Mitsufuji S, Tanaka S, Itoh Y, Nakanuma Y, Taniwaki M, Arii S, Okanoue T, Yoshikawa T. ERK5 is a target for gene amplification at 17p11 and promotes cell growth in hepatocellular carcinoma by regulating mitotic entry. ***Genes Chromosomes Cancer***, 2009; 48:109-120
19. Tanaka S, Arii S, Yasen M, Mogusi K, Su N-T, Zhao C, Imoto I, Eishi Y, Inazawa J, Miki Y, Tanaka H. Aurora kinase B is a predictive factor for aggressive recurrence of hepatocellular carcinoma after curative hepatectomy ***Br J Surg***, 2008;95:611-619
20. Yasui K, et al CREB3L4, INTS3 and SNAPAP are targets for the 1q21 amplicon frequently detected in hepatocellular carcinoma ***Cancer Genetics and Cytogenetics,*** 2008;180:30-36
21. Nakajima T, Yasui K, Keika Z, Inagaki Y, Fujii H, Minami M, Tanaka S, Taniwaki M, Itoh Y, Arii S, Inazawa J, Okanoue T. Activation of B-Myb by E2F1 in hepatocellular carcinoma ***Hepatology Res,*** 2008; 38:886-895
22. Inagaki Y, Yasui K, Endo M, Nakajima T, Zen K, Tsuji K, Minami M, Tanaka S, Taniwaki M, Itoh Y, Arii S, Okanoue T. CREB3L4, INTS3, and SNAPAP are targets for the 1q21 amplicon frequently detected in hepatocellular carcinoma. ***Cancer Genet Cytogenet,*** 2008;180:30-36
23. Kaneda M, Zhang D, Bhattacharjee R, Nakahama KI, Arii S, Morita I. Vitamin K(2) suppresses malignancy of HuH 7 hepatoma cells via inhibition of conenexin 43 . ***Cancer Lett,*** 2008;8:761-772
24. Eguchi S, Kanematsu T, Arii S, Okazaki M, Okita K, Omata M, Ikai I, Kudo M, Kojiro M, Makuuchi M, Monden M, Matsuyama Y, Nakanuma Y, Takayasu K,; The Liver Cancer Study Group of Japan. Comparison of the outcomes between an anatomical resection and a non-anatomical minor heoatectomy for single hepatocellular carcinomas based on a Japanese nationwide survey. ***Surgery,*** 2008;143:469-475
25. Takamatsu S, Noguchi N, Kudo A, Nakamura N, Kawamura T, Teramoto K, Igari T, Arii S. Influence of risk factors for metabolic syndrome and non-alcoholic fatty liver disease on the progression and prognosis of hepatocellular carcinoma. ***Hepatogastroenterology***, 2008;55:609-614

研究分担者：松井　修

1. Sonoda A, Nitta N, Nitta-Seko A, Ohta S, Takamatsu S, Ikehata Y, Nagano I, Jo J, Tabata Y, Takahashi M, Matsui O, Murata K. Complex comprised of dextran magnetite and conjugated cisplatin exhibiting selective hyperthermic and controlled-release potential. Int J Nanomedicine. 2010 9;5:499-504.
2. Yoneda N, Sato Y, Kitao A, Ikeda H, Sawada-Kitamura S, Miyakoshi M, Harada K, Sasaki M, Matsui O, Nakanuma Y. Epidermal growth factor induces cytokeratin 19 expression accompanied by increased growth abilities in human hepatocellular carcinoma. Lab Invest. 2010;20. [Epub ahead of print]
3. Pugacheva O, Matsui O, Kozaka K, Minami T, Ryu Y, Koda W, Kobayashi S, Gabata T. Detection of small hypervascular hepatocellular carcinomas by EASL criteria: Comparison with double-phase CT during hepatic arteriography. Eur J Radiol. 2010, in press
4. Ozaki K, Matsui O, Kobayashi S, Sanada J, Koda W, Minami T, Kawai K, Gabata T. Selective Atrophy of the Middle Hepatic Venous Drainage Area in Hepatitis C-related Cirrhotic Liver: Morphometric Study by Using Multidetector CT. Radiology. 2010, in press
5. Tsuda N, Matsui O. Cirrhotic rat liver: reference to transporter activity and morphologic changes in bile canaliculi–gadoxetic acid-enhanced MR imaging. Radiology. 2010;256:767-73.
6. Kitao A, Zen Y, Matsui O, Gabata T, Kobayashi S, Koda W, Kozaka K, Yoneda N, Yamashita T, Kaneko S, Nakanuma Y. Hepatocellular carcinoma: signal intensity at gadoxetic acid-enhanced MR Imaging--correlation with molecular transporters and histopathologic features. Radiology. 2010 ;256:817-26.
7. Miyayama S, Yamashiro M, Okuda M, Yoshie Y, Sugimori N, Igarashi S, Nakashima Y, Notsumata K, Toya D, Tanaka N, Mitsui T, Matsui O. Chemoembolization for the treatment of large hepatocellular carcinoma. J Vasc Interv Radiol. 2010;21:1226-34.
8. Miyayama S, Yamashiro M, Okuda M, Yoshie Y, Nakashima Y, Ikeno H, Orito N, Matsui O. Detection of Corona Enhancement of Hypervascular Hepatocellular Carcinoma by C-Arm Dual-Phase Cone-Beam CT During Hepatic Arteriography. Cardiovasc Intervent Radiol. 2010 ;24. [Epub ahead of print]
9. Miyayama S, Yamashiro M, Okuda M, Yoshie Y, Nakashima Y, Ikeno H, Orito N, Notsumata K, Watanabe H, Toya D, Tanaka N, Matsui O. Main Bile Duct Stricture Occurring After Transcatheter Arterial Chemoembolization for Hepatocellular Carcinoma. Cardiovasc Intervent Radiol. 2010; 8. [Epub ahead of print]
10. Mizukoshi E, Nakamoto Y, Arai K, Yamashita T, Mukaida N, Matsushima K, Matsui O, Kaneko S. Enhancement of tumor-specific T cell responses by transcatheter arterial embolization with dendritic cell infusion for hepatocellular carcinoma. *Int J Cancer,* 2010;126(9):2164-74.

11. Kitao A, Zen Y, Matsui O, Gabata T, Nakanuma Y. Hepatocarcinogenesis; multistep changes of drainage vessels at CT during arterial portography and hepatic arteriography--radiologic-pathologic correlation. ***Radiology***, 2009 ;252(2):605-14
12. Ryu Y, Matsui O, Zen Y, Ueda K, Abo H, Nakanuma Y, Gabata T. Multicysticbiliary hamartoma: imaging findings in four cases. ***Abdom Imaging***, in press
13. Miyayama S, Yamashiro M, Okuda M, Aburano H, Shigenari N, Morinaga K, Matsui O. Anastomosis between the hepatic artery and the extrahepatic collateral or between extrahepatic collaterals: observation on angiography. ***J Med Imaging Radiat Oncol***、 2009 ;3(3):271-82.
14. Kobayashi S, Matsui O, Gabata T, Sanada J, Koda W, Minami T, Ryu Y.Radiological and histopathological manifestations of hepatocellular nodular lesions concomitant with various congenital and acquired hepatic hemodynamic abnormalities. ***Jpn J Radiol,*** 2009 ;27(2):53-68
15. Matsui O, Gabata T, Kobayashi S. Optimal imaging of hepatic mass lesions. ***J Gastroenterol Hepatol.***, 2008;23(10):1466-8
16. Miyayama S, Yamashiro M, Okuda M, Yoshie Y, Sugimori N, Igarashi S, Nakashima Y, Matsui O. Usefulness of cone-beam computed tomography during ultraselective transcatheter arterial chemoembolization for small hepatocellular carcinomas that cannot be demonstrated on angiography. ***Cardiovasc Intervent Radiol.,*** 2009 ;32(2):255-64
17. Miyayama S, Mitsui T, Zen Y, Sudo Y, Yamashiro M, Okuda M, Yoshie Y, Sanada T, Notsumata K, Tanaka N, Matsui O. Histopathological findings after ultraselective transcatheter arterial chemoembolization for hepatocellular carcinoma. ***Hepatol Res***, 2009;39(4):374-81
18. Shinmura R, Matsui O, Kadoya M, Kobayashi S, Terayama N, Sanada J, Demachi H, Gabata T. Detection of hypervascular malignant foci in borderline lesions of hepatocellular carcinoma: comparison of dynamic multi-detector row CT, dynamic MR imaging and superparamagnetic iron oxide-enhanced MR imaging. ***Eur Radiol***, 2008; 18(9):1918-24.
19. Kobayashi S, Matsui O, Gabata T, Sanada J, Koda W, Minami T, Kobayashi T. Hemodynamics of small sclerosing hepatocellular carcinoma without fibrous capsule: evaluation with single-level dynamic CT during hepatic arteriography. ***Abdom Imag***, 2008; 33(4):425-7.

研究分担者：佐田　通夫

1. Kawaguchi T, Yamagishi S, Itou M, Okuda K, Sumie S, Kuromatsu R, Sakata M, Abe M, Taniguchi E, Koga H, Harada M, Ueno T, Sata M. Pigment epithelium-derived factor inhibits lysosomal degradation of Bcl-xL and apoptosis in HepG2 cells. Am J Pathol 2010; 176: 168-176.
2. Kawaguchi T, Yamagishi SI, Sata M. Structure-function relationships of PEDF. Curr Mol Med 2010; 10: 302-311.
3. Kawaguchi T, Taniguchi E, Morita Y, Shirachi M, Tateishi I, Nagata E, Sata M. Association of exogenous insulin or sulphonylurea treatment with an increased incidence of hepatoma in patients with hepatitis C virus infection. Liver Int 2010; 30: 479-486.
4. Nakamura A, Ueno T, Yagi Y, Okuda K, Ogata T, Nakamura T, Torimura T, Iwamoto H, Sivakuma R, Sata M, Tsutsumi V, Yasuda K, Tomiyasu Y, Obayashi K, Tashiro K, Kuhara S. Human primary cultured hepatic stellate cells can be cryopreserved. Med Mol Morphol 2010; 43: 107-115.
5. Kumamoto M, Toyonaga A, Inoue H, Miyakoda K, Morita Y, Emori K, Sakamoto Y, Oho K, Sata M. Long-term results of balloon-occluded retrograde transvenous obliteration for gastric fundal varices: hepatic deterioration links to portosystemic shunt syndrome. J Gastroenterol Hepatol 2010; 25: 1129-1135.
6. Takata A, Kuromatsu R, Ando E, Iwamoto H, Fukushima N, Sumie S, Torimura T, Sata M. HCC develops even in the early stage of chronic liver disease in elderly patients with HCV infection. Int J Mol Med 2010; 26: 249-256.
7. Fukushima N, Kuromatsu R, Arinaga-Hino T, Ando E, Takata A, Sumie S, Nakano M, Kawaguchi T, Ide T, Torimura T, Sata M. Adipocytokine involvement in hepatocellular carcinoma after sustained response to interferon for chronic hepatitis C. Hepatol Res 2010; 40: 911-922.
8. Sivakumar R, Koga H, Selvendiran K, Maeyama M, Ueno T, Sata M. Autocrine loop for IGF-1 receptor signaling in SLUG-mediated epithelial-mesenchymal transition. ***International Journal of Oncology*** 2009;34:329-338.
9. Ishida Y, Nagamatsu H, Koga H, Yoshida H, Kojiro M, Sata M. Hepatocellular carcinoma with a "nodule-in-nodule" appearance reflecting an unusual dilated pseudoglandular structure. ***Intern Med***, 2008; 47(13):1215-8.
10. Maeyama M, Koga H, Selvendiran K, Yanagimoto C, Hanada S, Taniguchi E, Kawaguchi T, Harada M, Ueno T, Sata M. Switching in discoid domain receptor expressions in SLUG-induced epithelial-mesenchymal transition. ***Cancer*** 2008;113: 2823-2831.
11. Sumie S, Kuromatsu R, Okuda K, Ando E, Takata A, Fukushima N, Watanabe Y, Kojiro M, Sata M. Microvascular invasion in patients with hepatocellular carcinoma and its predictable clinicopathological factors. ***Annals of Surgical Oncology*** 2008;15:1375-1382

研究分担者：青柳　豊

1. Takamura M, Yamagiwa S, Wakai T, Tamura Y, Kamimura H, Kato T, Tsuchiya A, Matsuda Y, Shirai Y, Ichida T, Ajioka Y, Aoyagi Y. Loss of liver-intestine cadherin in human intrahepatic cholangiocarcinoma promotes angiogenesis by up-regulating metal-responsive transcription factor-1 and placental growth factor. Int J Oncol. 2010;36(1):245-54.
2. Korita P, Wakai T, Shirai Y,Matsuda Y, Sakata J, Takamura M, Yano M, Sanpei A, Aoyagi Y, Hatakeyama K, Ajioka Y. Multidrug resistance–associated protein 2 determines the efficacy of cisplatin in patients with hepatocellular carcinoma. Oncology Reports, in press.
3. Kobayashi M, Narisawa R, Sato Y, Takeuchi M, Aoyagi Y Self-limiting risk of metachronous gastric cancers after endoscopic resection. Dig Endosc. 2010;22(3):169-73.
4. Osaki A, Kubota T, Suda T, Igarashi M, Nagasaki K, Tsuchiya A, Yano M, Tamura Y, Takamura M, Kawai H, Yamagiwa S, Kikuchi T, Nomoto M, Aoyagi Y. Shear wave velocity is a useful marker for managing nonalcoholic steatohepatitis. World J Gastroenterol. 2010 Jun 21;16(23):2918-25.
5. Tamura Y, Igarashi M, Kawai H, Suda T, Satomura S, Aoyagi Y. Clinical Advantage of Highly Sensitive On-Chip Immunoassay for Fucosylated Fraction of Alpha-Fetoprotein in Patients with Hepatocellular Carcinoma. Dig Dis Sci. 2010, in press
6. Yamamoto T, Morita S, Go R, Obata M, Katsuragi Y, Fujita Y, Maeda Y, Yokoyama M, Aoyagi Y, Ichikawa H, Mishima Y, Kominami R. Clonally expanding thymocytes having lineage capability in gamma-ray-induced mouse atrophic thymus. Int J Radiat Oncol Biol Phys. 2010;77(1):235-43.
7. Kurita S, Ohkoshi S, Yano M, Yamazaki K, Suzuki K, Aoki YH, Matsuda Y, Wakai T, Shirai Y, Ichida T, Aoyagi Y. Progression of hypermethylation of the p16 (ink4a) gene from normal liver to nontumorous liver and hepatocellular carcinoma: An evaluation using quantitative PCR analysis. ***Dig Dis Sci***, 2009; 54(1):80-8.
8. Tamura Y, Yamagiwa S, Aoki Y, Kurita S, Suda T, Ohkoshi S, Nomoto M, Aoyagi Y. Serum alpha-fetoprotein levels during and after interferon therapy and the development of hepatocellular carcinoma in patients with chronic hepatitis C. ***Dig Dis Sci***, 2009;54(11)2530-7

研究分担者：田中博　研究代表者の項参照

研究分担者：森安　史典

1. Liu GJ, Moriyasu F, Hirokawa T, Rexiati M, Yamada M, Imai Y. Expression of heat shock protein 70 in rabbit liver after contrast-enhanced ultrasound and radiofrequency ablation. Ultrasound Med Biol 36(1): 78-85, 2010

2. Liu GJ, Wang W, Xie XY, Xu HX, Xu ZF, Zheng YL, Liang JY, Moriyasu F, Lu MD. Real-time contrast-enhanced ultrasound imaging of focal liver lesions in fatty liver. Clin Imaging 34(3):211-221, 2010
3. Liu GJ, Xu HX, Xie XY, Xu ZF, Zheng YL, Liang JY, Lu MD, Moriyasu F. Does the echogenicity of focal liver lesions on baseline gray-scale ultrasound interfere with the diagnostic performance of contrast-enhanced ultrasound? Eur Radiol 2009;19(5):1214-1222,
4. Sugimoto K, Shiraishi J, Moriyasu F, Doi K. Computer-aided diagnosis of focal liver lesions by use of physicians' subjective classification of echogenic patterns in baseline and contrast-enhanced ultrasonography. ***Acad Radiol***, 2009;16(4): 401-411,
5. Moriyasu F, Itoh K. Efficacy of perflubutane microbubble-enhanced ultrasound in the characterization and detection of focal liver lesions: phase 3 multicenter clinical trial. ***AJR Am J Roentgenol***, 2009;193(1): 86-95.
6. Sugimoto K, Shiraishi J, Moriyasu F, Saito K, Doi K. Improved detection of hepatic metastases with contrast-enhanced low mechanical-index pulse inversion ultrasonography during the liver-specific phase of sonazoid: observer performance study with JAFROC analysis. ***Acad Radiol***, 2009;16(7): 798-809.
7. Saito K, Sugimoto K, Nishio R, Araki Y, Moriyasu F, Kakizaki D, Tokuuye K. Perfusion study of liver lesions with superparamagnetic iron oxide: distinguishing hepatocellular carcinoma from focal nodular hyperplasia. ***Clin Imaging***, 2009;33(6): 447-53.
8. Liu GJ, Moriyasu F, Hirokawa T, Rexiati M, Yamada M, Imai Y. Optical microscopic findings of the behavior of perflubutane microbubbles outsideand inside Kupffer cells during diagnostic ultrasound examination. ***Invest Radiol***, 2008;43:829-36
9. Shiraishi J, Sugimoto K, Moriyasu F, Kamiyama N, Doi K. Computer-aided diagnosis for the classification of focal liver lesions by use of contrast-enhanced ultrasonography. ***Med Phys***, 2008;35:1734-46.
10. Sugimoto K, Moriyasu F, Kamiyama N, Metoki R, Yamada M, Imai Y, Iijima H. Analysis of morphological vascular changes of hepatocellular carcinoma by microflow imaging using contrast-enhanced sonography. ***Hepatol Res***, 2008;37:790-9.

研究分担者：川崎　誠治

1. Ishizaki Y, Sugo H, Yoshimoto J, Imamura H, Kawasaki S. Pancreatoduodenectomywith or without early ligation of the inferior pancreatoduodenalartery: Comparison of intraoperative blood loss and short-term outcome. World J Surg 2010;34:2939-2944.
2. Sugiyama Y, Ishizaki Y, Imamura H, Sugo H, Yoshimoto J, Kawasaki S. Effects of intermittent Pringle's manoeuvre on cirrhotic compared with normal liver. Br J Surg 2010;97:1062-9.
3. Tsukada A, Ishizaki Y, Nobukawa B, Kawasaki S. Embryonal sarcoma of the liver in an adult mimicking complicated hepatic cyst: MRI findings. J Magn Reson Imaging. 2010;31:1477-80.
4. Omori S, Ishizaki Y, Sugo H, Yoshimoto J, Imamura H, Yamataka A, Kawasaki S. Direct measurement of hepatic blood flow during living donor liver transplantation in children. J PediatrSurg 2010;45:545-8.
5. Nomura R, Ishizaki Y, Sugo H, Yoshimoto J, Imamura H, Kawasaki S. Late-onset venous outflow obstruction treated by placement of a Foley balloon catheter in living donor liver transplantation using a left lobe. Clin Transplant in press.
6. Shibata N, Shimazaki H, Sano N, Kawasaki S, Arai H. Psychiatric and psychological outcomes of Japanese living donors following liver transplantation. Psychiatry ***Clin Neurosci.*** 2009 ;63(4): 583-5.
7. Makino Y, Shimanuki Y, Fujiwara N, Morio Y, Sato K, Yoshimoto J, Gunji Y, Suzuki T, Sasaki S, Iwase A, Kawasaki S, Takahashi K, Seyama K. Peritoneovenous shunting for intractable chylous ascites complicated with lymphangioleiomyomatosis. ***Intern Med***, 2008, 47: 281-285.
8. Konishi N, Ishizaki Y, Sugo H, Yoshimoto J, Miwa K, Kawasaki S Impact of a left lobe graft without modulation of portal flow in adult-to-adult living donor liver transplantation. ***Am J Transpl.*** 2008, Jan 8(1):170-174.
9. Ishizaki Y, Kawasaki S. The evolution of liver transplantation for hepatocellular carcinoma (past, present, and future). ***J Gastroenterol.*** 2008, 43(1):18-26.

研究分担者：角谷眞澄

1. Fujinaga Y, Kadoya M, Ueda K, Kurozumi M, Matsushita T, Ohya A, Kitou Y, Ueda U: Hepatic venous phase of the liver is already affected by hepatobiliary uptake of Gd-EOB-DTPA: comparison between Gd-EOB-DTPA and Gd-DTPA in dynamic MRI on 3.0-T apparatus. Eur Radiol20 supplement 1: S52, 2010
2. Hatta T, Fujinaga Y, Kadoya M, Ueda H, Murayama H, Kurozumi M, Ueda K, Komatsu M, Nagaya T, Joshita S, Kodama R, 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, 2010, in press
3. Naito K, Ichiyama T, Kawakami S, Kadoya M, Tabata T, Matsuda M, Ikeda S: AL amyloidosis with spontaneous hepatic rupture: successful treatment by transcatheter hepatic artery embolization. Amyloid 15: 137-139, 2008

研究分担者：泉　並木

1. Izumi N. Diagnosis and treatment algorithm of the Japanese society of Hepatology: a consensus-based practice guideline. Oncology 2010;78:78-86.
2. Asahina Y, Tsuchiya K, Tamaki N, Hirayama I, Tanaka T, Sato M, Yasui Y, Hosokawa T, Ueda, Kuzuya T, Nakanishi H, Itakura J, Takahashi Y, Kurosaki M, Enomoto N, Izumi N. Effect of aging on risk for hepatocellular carcinoma in chronic hepatitis C virus infection. Hepatology 2010;52:518-27.
3. Izumi N. Recent advances in radiofrequency ablation for early hepatocellular carcinoma. J Gastroemterol Hepatol 2010 in press.
4. Kurosaki M, Hosokawa T, Matsunaga K, Hirayama I, Tanaka T, Sato M, Yasui Y, Tamaki N, Ueda K, Tsuchiya K, Kuzuya T, Nakanishi H, Itakura J, Takahashi Y, Asahina Y, Enomoto N, Izumi N. Hepatic steatosis in chronic hepatitis C is a significant risk factor for developing hepatocellular carcinoma independent of age, sex, obesity, fibrosis stage and response to interferon therapy. Hepatol Res 2010;40:870-7.
5. Kudo M, Han KH, Kokudo N, Cheng AL, Choi BI, Furuse J, Izumi N, Park JW, Poon RT, Sakamoto M. Liver cancer working group report. Jpn J Clin Oncol 2010;40:i19-27.
6. Asahina Y, Izumi N, Hirayama I, Tanaka T, Sato M Yasui Y, Komatsu N, Umeda N, Hosokawa T, Ueda K, Tsuchiya K, Nakanishi H, Itakura J, Enomoto N, Tasaka M, Sakamoto N, Miyake S. Potential relevance of cytoplasmic viral sensors and related regulatos involving innate immunity in antiviral response. ***Gastroenterology***, 2008;134(5):1396-405.
7. Kurosaki M, Matsunaga K, Hirayama I, Tanaka T, Sato M, Umeda N, Hosokawa T, Ueda K, Tsuchiya K, Nakanishi H, Itakura J, Asahina Y, Miyake S, Enomoto

N, Izumi N. The presence of steatosis and elevation of alanine aminotransferase levels are associated with fibrosis progression in chronic hepatitis C with non-response to interferon therapy. ***J Hepatol***, 2008; 48(5):736-42.

研究分担者：髙山　忠利

1. Mamiya T, Yamazaki K, Masugi Y, Mori T, Effendi K, Du W, Hibi T, Tanabe M, Ueda M, Takayama T, Sakamoto M. Reduced transforming growth factor-beta receptor II expression in hepatocellular carcinoma correlates with intrahepatic metastasis. Lab Invest. 2010 Sep;90(9):1339-45.
2. Wang X, Nagase H, Watanabe T, Nobusue H, Suzuki T, Asami Y, Shinojima Y, Kawashima H, Takagi K, Mishra R, Igarashi J, Kimura M, Takayama T, Fukuda N, Sugiyama H. Inhibition of MMP-9 transcription and suppression of tumor metastasis by pyrrole-imidazole polyamide. Cancer Sci. 2010 Mar;101(3):759-66.
3. Yamazaki S, Takayama T, Makuuchi M. The technical advance and impact of caudate lobe venous reconstruction in left liver: additional safety for living-related donor liver transplantation. Transpl Int. 2010 Apr 1;23(4):345-9.
4. Kochi M, Fujii M, Kanamori N, Kaiga T, Okubo R, Hagiwara K, Funada T, Tamegai H, Takayama T. Irinotecan plus S-1 for liver metastases of gastric cancer. Hepatogastroenterology. 2009 Nov-Dec;56(96):1755-9.
5. Yamamoto J, Kosuge T, Saiura A, Sakamoto Y, Shimada K, Sano T, Takayama T, Sugawara Y, Yamaguchi T, Kokudo N, Makuuchi M. Effectiveness of hepatic resection for early-stage.hepatocellular carcinoma in cirrhotic patients: subgroup analysis according to Milan criteria. ***Japanese Journal of Clinical Oncology,*** 2008; 37: 287-295.
6. Yamazaki S, Takayama T. Surgical treatment of hepatocellular carcinoma: Evidence-based outcomes. ***World Journal of Gastroenterology,***, 2008; 14: 685-692.
7. Takayama T, Makuuchi M, Kojiro M, Lauwers GY, Adams RB, Wilson SR, Jang HJ, Charnsangavej C, Taouli B. Early hepatocellular carcinoma: pathology, imaging, and therapy. ***Annals of Surgical Oncology***, 2008; 15: 972-978.
8. Suzuki, K Mazaki T, Mannmoto J, Ishii Y, Hideki, AMasuda Hennmi and Takayama T. Hepatic Angiomyolipoma Mimicking Malignancy: A Case Report. ***The Nihon University Journal of Medicine***, 2008; 67: 238-241.
9. Sugitani M, Aramaki O, Kikuchi K, Sheikh A, Oinuma T, Mamiya T, Takayama T, Nemoto N. Two cases of Primary Malignant Fibrous Histiocytoma of the Liver: Immunohistochemical Expression of Ezrin and its Relationship with Prognosis. ***Acta Histochemica et Cytochemica,*** 2008; 43: 83-88
10. Yamazaki S, Takayama T, Watanabe Y, Oikawa T, Hayashi Y, Kochi M, Moriguchi M, Higaki T, Inoue K. Imaging modality of three-dimensional CT in caudate cholangioma: assessment for respectability. ***Hepato-Gastroenterology.*** 2007; 54: 397-399.

研究分担者：國土　典宏

1. Takamoto, T., T. Hashimoto, K. Sano, Y. Maruyama, K. Inoue, S. Ogata, T. Takemura, Kokudo N and M. Makuuchi, Recovery of liver function after the cessation of preoperative chemotherapy for colorectal liver metastasis. Ann Surg Oncol, 2010. 17(10): p. 2747-55.
2. Shindoh, J., Y. Mise, S. Satou, Y. Sugawara, and Kokudo N, The intersegmental plane of the liver is not always flat--tricks for anatomical liver resection. Ann Surg, 2010. 251(5): p. 917-22.
3. Mise, Y., H. Imamura, T. Hashimoto, Y. Seyama, T. Aoki, K. Hasegawa, Y. Beck, Y. Sugawara, M. Makuuchi, J. Nakajima, and Kokudo N, Cohort study of the survival benefit of resection for recurrent hepatic and/or pulmonary metastases after primary hepatectomy for colorectal metastases. Ann Surg, 2010. 251(5): p. 902-9.
4. Kudo, M., K.H. Han, Kokudo N, A.L. Cheng, B.I. Choi, J. Furuse, N. Izumi, J.W. Park, R.T. Poon, and M. Sakamoto, Liver Cancer Working Group report. Jpn J Clin Oncol, 2010. 40 Suppl 1: p. i19-27.
5. Kokudo N., and J. Arita, Staging for intrahepatic cholangiocarcinoma. Liver Int, 2010. 30(7): p. 931-3.
6. Kishi, Y., H. Imamura, Y. Sugawara, K. Sano, J. Kaneko, Kokudo N., and M. Makuuchi, Evaluation of donor vasculobiliary anatomic variations in liver graft procurements. Surgery, 2010. 147(1): p. 30-9.
7. Ishizawa, T., Y. Bandai, M. Ijichi, J. Kaneko, K. Hasegawa, and Kokudo N. Fluorescent cholangiography illuminating the biliary tree during laparoscopic cholecystectomy. Br J Surg, 2010. 97(9): p. 1369-77.
8. Inoue, Y., M. Takahashi, J. Arita, T. Aoki, K. Hasegawa, Y. Beck, M. Makuuchi, and Kokudo N., Intra-operative freehand real-time elastography for small focal liver lesions: "visual palpation" for non-palpable tumors. Surgery, 2010. 148(5): p. 1000-11.
9. Harada, N., T. Ishizawa, A. Muraoka, M. Ijichi, K. Kusaka, M. Shibasaki, K. Yamamoto, K. Hasegawa, Y. Bandai, and Kokudo N. Fluorescence navigation hepatectomy by visualization of localized cholestasis from bile duct tumor infiltration. J Am Coll Surg, 2010. 210(6): p. e2-6.
10. Deng, Y.B., G. Nagae, Y. Midorikawa, K. Yagi, S. Tsutsumi, S. Yamamoto, K. Hasegawa, Kokudo N, H. Aburatani, and A. Kaneda, Identification of genes preferentially methylated in hepatitis C virus-related hepatocellular carcinoma. Cancer Sci, 2010. 101(6): p. 1501-10.
11. Akai, H., S. Kiryu, I. Matsuda, J. Satou, H. Takao, T. Tajima, Y. Watanabe, H. Imamura, Kokudo N., M. Akahane, and K. Ohtomo, Detection of hepatocellular carcinoma by Gd-EOB-DTPA-enhanced liver MRI: Comparison with triple phase 64 detector row helical CT. Eur J Radiol, 2010.
12. Inoue Y, Hasegawa K, Ishizawa T, Aoki T, Sano K, Beck Y, Imamura H, Sugawara Y, Kokudo N , Makuuchi M. Is there any difference in survival according to the portal tumor thrombectomy method in patients with hepatocellular carcinoma? Surgery, 2009; 145(1):9-19.
11. Ishizawa T, Fukushima N, Shibahara J, Masuda K, Tamura S, Aoki T, Hasegawa K, Beck Y, Fukayama M, Kokudo N. Real-time identification of liver cancers by using indocyanine green fluorescent imaging. Cancer, 2009; 115(11):2491-504.
12. Ishizawa T, Tamura S, Masuda K, Aoki T, Hasegawa K, Imamura H, Beck Y, Kokudo N. Intraoperative fluorescent cholangiography using indocyanine green: a biliary road map for safe surgery. J Am Coll Surg, 2009; 208(1):e1-4.
13. Kokudo N, Makuuchi M. Evidence-based clinical practice guidelines for hepatocellular carcinoma in Japan: the J-HCC guidelines. J Gastroenterol, 2009; 44 Suppl 19:119-21.
14. Yamamoto K, Imamura H, Matsuyama Y, Hasegawa K, Beck Y, Sugawara Y, Makuuchi M, Kokudo N. Significance of alpha-fetoprotein and des-gamma-carboxy prothrombin in patients with hepatocellular carcinoma undergoing hepatectomy. Ann Surg Oncol, 2009; 16(10):2795-804
15. Gao FJ, Cui SX, Chen MH, Cheng YN, Sun LR, Ward SG, Kokudo N, Tang W, Qu XJ. Des-gamma-carboxy prothrombin increases the expression of angiogenic factors in human hepatocellular carcinoma cells. Life Sci, 2008; 83(23-24):815-20.

16. Xiang CH, Zhang W, Inagaki Y, Zhang KM, Nakano Y, Kokudo N, Sugawara Y, Dong JH, Nakata M, Tang W. Measurement of serum and tissue des-gamma-carboxyprothrombin in resectable hepatocellular carcinoma. Anticancer Res 2008; 28(4B):2219-24.
17. Hasegawa K, Imamura H, Ijichi M, Matsuyama Y, Sano K, Sugawara Y, Kokudo N, Makuuchi M. Inclusion of tumor markers improves the correlation of the Milan criteria with vascular invasion and tumor cell differentiation in patients with hepatocellular carcinoma undergoing liver resection (#JGSU-D-07-00462). J Gastrointest Surg, 2008;12(5):858-66.
18. Makuuchi M, Kokudo N, Arii S, Futagawa S, Kaneko S, Kawasaki S, Matsuyama Y, Okazaki M, Okita K, Omata M, Saida Y, Takayama T, Yamaoka Y. Development of evidence-based clinical guidelines for the diagnosis and treatment of hepatocellular carcinoma in Japan. Hepatol Res, 2008; 38(1):37-51.
19. Hasegawa K, Kokudo N, Makuuchi M. Surgery or ablation for hepatocellular carcinoma? Ann Surg 2008; 247(3):557-8.
20. Hasegawa K, Makuuchi M, Takayama T, Kokudo N, Arii S, Okazaki M, Okita K, Omata M, Kudo M, Kojiro M, Nakanuma Y, Takayasu K, Monden M, Matsuyama Y, Ikai I. Surgical resection vs. percutaneous ablation for hepatocellular carcinoma: a preliminary report of the Japanese nationwide survey. J Hepatol 2008; 49(4):589-94

研究分担者：稲澤　譲治

1. Furuta M, Kozaki KI, Tanaka S, Arii S, Imoto I, Inazawa J. miR-124 and miR-203 are epigenetically silenced tumor-suppressive microRNAs in hepatocellular carcinoma. ***Carcinogenesis***, 2010;31(5):766-76.
2. Arai E, Ushijima S, Gotoh M, Ojima H, Kosuge T, Hosoda F, Shibata T, Kondo T, Yokoi S, Imoto I, Inazawa J, Hirohashi S, Kanai Y. Genome-wide DNA methylation profiles in liver tissue at the precancerous stage and in hepatocellular carcinoma. ***Int J Cancer***, 2009; 125:2854-62
3. Tanaka S, Arii S, Yasen M, Mogusi K, Su N-T, Zhao C, Imoto I, Eishi Y, Inazawa J, Miki Y, Tanaka H. Aurora kinase B is a predictive factor for aggressive recurrence of hepatocellular carcinoma after curative hepatectomy ***Br J Surg***, 2008;95:611-619

研究分担者：山本　雅一

1. Matsuda A, Kuno A, Kawamoto T, Matsuzaki H, Irimura T, Ikehara Y, Zen Y, Nakanuma Y, Yamamoto M, Ohkohchi N, Shoda J, Hirabayashi J, Narimatsu H. Wisteria floribunda agglutinin-positive mucin 1 is a sensitive biliary marker for human cholangiocarcinoma. Hepatology. 2010 Jul;52(1):174-82.
2. Uchiyama K, Yamamoto M, Yamaue H, Ariizumi S, Aoki T, Kokudo K, Ebata T, Nagino M, Ohtsuka M, Miyazaki M, Eiichi Tanaka E, Kondo S, Uenishi T, Kubo S, Yoshida H, Unno M, Imura S, Shimada M, Ueno M, Takada T. Impact of Nodal Involvement on Surgical Outcomes of Intrahepatic Cholangiocarcinoma —The Survey of the Study Group for Hepatic Surgery of the Japanese Society of Hepato-biliary-Pancreatic Surgery. J Hepatobiliary Pancreat Science (in press).
3. Shimizu K, Kotera Y, Aruga A, Takeshita N, Takasaki K, Yamamoto M. Postoperative Adjuvant Dendritic Cell Vaccine plus Activated T Cell Transfer in Patients with Cholangiocarcinoma. International Journal of Cancer (in press).
4. Ariizumi S, Kotera Y, Katagiri S, Yamamoto M. Favorable long-term surgical outcomes of hepatocellular carcinoma in patients with hepatitis B envelope antibody. J Surg Oncol. 2010 May 1;101(6):471-5.
5. Higuchi R, Ota T, Araida T, Kobayashi M, Furukawa T, Yamamoto M. Prognostic relevance of ductal margins in operative resection of bile duct cancer Surgery. 2010 Jul;148(1):7-14. Epub 2010 Feb 8.
6. Seimiya M, Tomonaga T, Matsushita K, Sunaga M, Oh-Ishi M, Kodera Y, Maeda T, Takano S, Togawa A, Yoshitomi H, Otsuka M, Yamamoto M, Nakano M, Miyazaki M, Nomura F. Identification of novel immunohistochemical tumor markers for primary hepatocellular carcinoma; clathrin heavy chain and formiminotransferase cyclodeaminase. Hepatology, 2008; 48(2):519-30.
7. Yamamoto M, Ariizumi S, Katagiri S, Kotera Y, Takahashi Y .The value of anatomical liver sectionectomy for patients with a solitary hepatocellular carcinoma from 2 to 5 cm in greatest diameter. J Surg Oncol., 2009; 100 (7): 585-588.
8. Ariizumi S, Yamamoto M, Takasaki K. Right hepatectomy for hepatocellular carcinoma in patients with an indocyanine green retention rate at 15 minutes of 10% or higher. Dig Surg, 2009;26(2)135-142

研究分担者：飯島　尋子

1. Yoshikawa S, Iijima H, Saito M, Tanaka H, Imanishi H, Yoshimoto N, Yoshimoto T, Futatsugi-Yumikura S, Nakanishi K, Tsujimura T, Nishigami T, Kudo A, Arii S, Nishiguchi S. Crucial role of impaired Kupffer cell phagocytosis on the decreased Sonazoid-enhanced echogenicity in a liver of a nonalchoholic steatohepatitis rat model. Hepatol Res. 2010;14. [Epub ahead of print]
2. Yamamoto, T., Nakamura, H., Liu, W., Cao, K., Yoshikawa, S., Enomoto, H., Iwata, Y., Koh, N., Saito, M., Imanishi, H., Shimomura, S., Iijima H., Hada, T. and Nishiguchi, S. Involvement hepatoma-derived growth factor in the growth inhibition of hepatocellular carcinoma cells by vitamin K_2. ***J Gastroenterol***, 2009;44:228-235.
3. Sasaki, S, Iijima H, Moriyasu, F., Waki, H. Definition of Contrast Enhancement Phases of the Liver Using a Perfluoro-Based Microbubble Agent, Perflubutane Microbubbles. ***Ultrasound Med Biol***. 2009 ; 35:1819-1827
4. Wilson SR, Jang HJ, Kim TK, Iijima H, Kamiyama N, Burns PN. Real-time temporal maximum-intensity-projection imaging of hepatic lesions with
5. Kudo M, Zheng RQ, Kim SR, Okabe Y, Osaki Y, Iijima H, Itani T, Kasugai H, Kanematsu M, Ito K, Usuki N, Shimamatsu K, Kage M, Kojiro M. Diagnostic accuracy of imaging for liver cirrhosis compared to histologically proven liver cirrhosis. ***Intervirology***, 2008; 51 Suppl 1:17-26.
6. Wilson SR, Kim TK, Iijima H, Kimiyama N, Jang HJ, Burns NP. Real time temporal maximum intensity projection (MIP) imaging of liver lesions using contrast ultrasound. ***Am J Roentgenol***, 2008;190(3):691-5

研究分担者：佐賀恒夫

1. Saga T, Koizumi M, Furukawa T, Yoshikawa K, Fujibayashi Y. Molecular imaging of cancer-evaluating characters of individual cancer by PET/SPECT imaging. ***Cancer Sci,*** 2009; 100:375-381

研究分担者：坂元亨宇

1. Sakamoto M, Effendi K, Masugi Y. Molecular diagnosis of multistage hepatocarcinogenesis. Jpn J Clin Oncol 2010;40(9): 891-6. (Review)Mamiya T, Yamazaki K, Masugi Y, Mori T, Effendi K, Du W, Hibi T, Tanabe M, Ueda M, Takayama T, Sakamoto M. Reduced transforming growth factor-beta receptor II expression in hepatocellular carcinoma correlates with intrahepatic metastasis. Lab Invest 2010;90(9): 1339-45.
2. Effendi K, Mori T, Komuta M, Masugi Y, Du W, Sakamoto M. Bmi-1 gene is upregulated in early-stage hepatocellular carcinoma and correlates with ATP-binding cassette transporter B1 (ABCB1) expression. Cancer Sci 2010;101: 666-672.

3. Sakamoto M. Early HCC: diagnosis and molecular markers. J Gastroenterol. 2009;44 Suppl 19:108-11. (Review)
4. Yamazaki K, Takamura M, Masugi Y, Mori T, Du W, Hibi T, Hiraoka N, Ohta T, Ohki M, Hirohashi S, Sakamoto M. Adenylate cyclase-associated protein 1 overexpressed in pancreatic cancers is involved in cancer cell motility. Lab Invest 2009;89(4):425-32.
5. International Consensus Group for Hepatocellular Neoplasia. Pathologic diagnosis of early hepatocellular carcinoma: a report of the international consensus group for hepatocellular neoplasia. Hepatology 2009;49(2):658-64.
6. Ojima H, Kanai Y, Iwasaki M, Hiraoka N, Shimada K, Sano T, Sakamoto Y, Esaki M, Kosuge T, Sakamoto M, Hirohashi S. Intraductal carcinoma component as a favorable prognostic factor in biliary tract carcinoma. Cancer Sci 2009;100(1):62-70.
7. Sakamoto M, Mori T, Masugi Y, Effendi K, Rie I, Du W. Candidate molecular markers for histological diagnosis of early hepatocellular carcinoma. Intervirology 2008;51 Suppl 1:42-5. (Review)
8. Sakamoto M. Early HCC: diagnosis and molecular markers. J Gastroenterol. 2009;44 Suppl 19:108-11. Yamazaki K, Takamura M, Masugi Y, Mori T, Du W, Hibi T, Hiraoka N, Ohta T, Ohki M, Hirohashi S, Sakamoto M. Adenylate cyclase-associated protein 1 overexpressed in pancreatic cancers is involved in cancer cell motility. ***Lab Invest,*** 2009;89(4):425-32.
9. International Consensus Group for Hepatocellular Neoplasia. Pathologic diagnosis of early hepatocellular carcinoma: a report of the international consensus group for hepatocellular neoplasia. ***Hepatology.***2009;49(2):658-64.
10. Sakamoto M, Mori T, Masugi Y, Effendi K, Rie I, Du W. Candidate molecular markers for histological diagnosis of early hepatocellular carcinoma. ***Intervirology.*** 2008;51 Suppl 1:42-5. Review.

研究分担者：井本逸勢 研究代表者の項参照

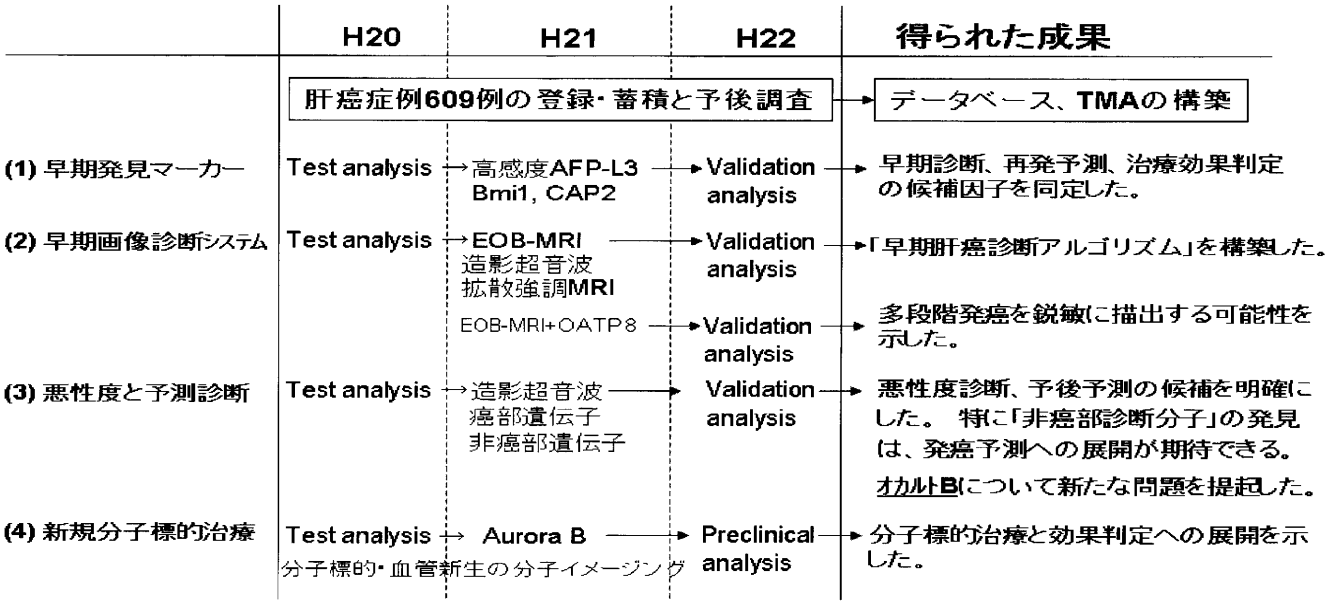
研究分担者：田中　真二　研究代表者の項参照

研究課題の実施を通じた政策提言（寄与した指針又はガイドライン等）：科学的根拠に基づく肝癌診療ガイドライン 2009年版（有井滋樹・川崎誠治・高山忠利・國土典宏・田中真二　他）

特許：稲澤　譲治、井本　逸勢、有井　滋樹、他2名。ﾏｲｸﾛRNAの発現量の変化を指標とする肝細胞癌の検出方法および癌抑制剤/整理番号P09-034/平成21年11月2日

特許: 坂元亨宇、他２名。血中の CAP2 の測定方法、肝臓疾患の検出方法及び血中 CAP2 測定用検出キット.特願 2009-060966、2009

Ⅶ. Ⅲ(3年間の研究成果)の概要図等



●研究代表者の研究歴等

・過去に所属した研究機関の履歴

昭和 48 年　　京都大学医学部卒業　同第１外科入局
昭和 57 年 8 月　京都大学医学部第１外科　助手
昭和 59 年 8 月　米国ニューヨーク州立ローゼルパークメモリアル研究所留学
昭和 60 年 12 月　京都大学医学部第１外科　助手
平成　5 年 5 月　京都大学医学部第１外科　講師
平成 10 年 7 月　京都大学医学部第１外科 助教授
平成 12 年 4 月　東京医科歯科大学大学院　分子外科治療学分野　肝胆膵外科　教授
平成 16 年 4 月　分野の名称が分子外科治療学分野から肝胆膵・総合外科に変更，輸血部長併任

・主な共同研究者(又は指導を受けた研究者)

特になし。

・主な研究課題

肝胆膵外科　・癌の分子生物学的研究　・肝類洞壁細胞研究

・これまでの研究実績

発表業績

1. Arii S, Tanaka S, Mitsunori Y, Nakamura N, Kudo A, Noguchi N, Irie T. Surgical strategies for hepatocellular carcinoma with special reference to anatomical hepatic resection and intraoperative contrast-enhanced ultrasonography. ***Oncology.*** , 2010;78 Suppl 1:125-30.
2. Arii S, Sata M, Sakamoto M, Shimada M, Kumada T, Shiina S, Yamashita T, Kokudo N, Tanaka M, Takayama T, Kudo M. Management of hepatocellular carcinoma: Report of Consensus Meeting in the 45th Annual Meeting of the Japan Society of Hepatology (2009). ***Hepatol Res***, 2010;40(7):667-85.
3. Arii S. Molecularly targeted therapy for hepatocellular carcinoma from the basic and clinical aspects. ***Int J Clin Oncol.*** , 2010;15(3):234.
4. Tanaka S, Arii S. Current status of molecularly targeted therapy for hepatocellular carcinoma: basic science. ***Int J Clin Oncol,*** 2010;15(3):235-41.
5. Tanaka S, Mogushi K, Yasen M, Noguchi N, Kudo A, Nakamura N, Ito K, Miki Y, Inazawa J, Tanaka H, Arii S. Gene-expression phenotypes for vascular invasiveness of hepatocellular carcinomas. ***Surgery,*** 2010 Mar;147(3):405-14.
6. Tanaka S, Arii S. Medical treatments: in association or alone, their role and their future perspectives: novel molecular-targeted therapy for hepatocellular carcinoma. ***J Hepatobiliary Pancreat Sci***, 2010 Jul;17(4):413-9.
7. Aihara A, Tanaka S, Yasen M, Matsumura S, Mitsunori Y, Murakata A, Noguchi N, Kudo A, Nakamura N, Ito K, Arii S. The selective Aurora B kinase inhibitor AZD1152 as a novel treatment for hepatocellular carcinoma. ***J Hepatol***, 2010;52(1):63-71.
8. Murakata A, Tanaka S, Mogushi K, Yasen M, Noguchi N, Irie T, Kudo A, Nakamura N, Tanaka H, Arii S. Gene expression signature of the gross morphology in hepatocellular carcinoma. ***Ann Surg***. (in press)
9. Furuta M, Kozaki KI, Tanaka S, Arii S, Imoto I, Inazawa J. miR-124 and miR-203 are epigenetically silenced tumor-suppressive microRNAs in hepatocellular carcinoma. ***Carcinogenesis***, 2010;31(5):766-76.
10. Sui S, Kudo A, Suematsu M, Tanaka S, Nakamura N, Ito K, Arii S. Preservation solutions alter Mrp2-dependent bile flow in cold ischemic rat livers. ***J Surg Res,*** 2010;159(1):572-81.
11. Uchida Y, Tanaka S, Aihara A, Adikrisna R, Yoshitake K, Matsumura S, Mitsunori Y, Murakata A, Noguchi N, Irie T, Kudo A, Nakamura N, Lai PB, Arii S. Analogy between sphere forming ability and stemness of human hepatoma cells. ***Oncol Rep***. 2010 Nov;24(5):1147-51. PubMed PMID: 20878104.
12. Sugiyama T, Kouyama R, Tani Y, Izumiyama H, Akashi T, Kishimoto S, Arii S, Hirata Y. Giant malignant insulinoma which developed from a non-functioning pancreatic tumor over a long period of time. ***Intern Med***. 2010;49(15):1573-9.
13. Takayasu K, Arii S, Ikai I, Kudo M, Matsuyama Y, Kojiro M, Makuuchi M; Liver Cancer Study Group of Japan. Overall survival after transarterial lipiodol infusion chemotherapy with or without embolization for unresectable hepatocellular carcinoma: propensity score analysis. ***AJR Am J Roentgenol.*** 2010;194(3):830-7.
14. Tanaka S, Mogushi K, Yasen M, Noguchi N, Kudo A, Kurokawa T, Nakamura N, InazawaJ, Tanaka H, Arii S. Surgical contribution to recurrence –free survival in patients with macrovascular invasion-negative hepatocellular carcinoma. ***J Am Coll Surg***, 2009;208:368-374
15. Mahmut Y, Mizushima H, Mogushi K, Obulhasim G, Miyaguchi K, Inoue K, Nakahara I, Ohta T, Aihara A, Tanaka S Arii S, Tanaka H Expression of Aurora B and their alternative variant forms in hepatrocellular carcinoma and the adjacent tissue. ***Cancer Sci,*** 2009;100:472-480
16. Gen Y, Yasui K, Zen K, Nakajima T, Tsuji K, Endo M, Mitsuyosi H, Minami M, Itoh Y, Tanaka S, Taniwaki M, Arii S, Okanoue T, Yoshikawa T. A novel amplification target, ARHGAP5, promotes cell spreading and migration by negatively regulating Rho A in Huh-7 hepatocellular carcinoma cells. ***Cancer Lett,*** 2009;275:27-34
17. Zen K, Yasui K, Nakajima T, Zen Y, Zen K, Gen Y, Mitsuyosi H, Mimami M, Mitsufuji S, Tanaka S, Itoh Y, Nakanuma Y, Taniwaki M, Arii S, Okanoue T, Yoshikawa T. ERK5 is a target for gene amplification at 17p11 and promotes cell growth in hepatocellular carcinoma by regulating mitotic entry. ***Genes Chromosomes Cancer,*** 2009; 48:109-120

18. Tanaka S, Arii S, Yasen M, Mogusi K, Su N-T, Zhao C, Imoto I, Eishi Y, Inazawa J, Miki Y, Tanaka H. Aurora kinase B is a predictive factor for aggressive recurrence of hepatocellular carcinoma after curative hepatectomy. ***Br J Surg***, 2008;95:611-619
19. Yasui K, et al CREB3L4, INTS3 and SNAPAP are targets for the 1q21 amplicon frequently detected in hepatocellular carcinoma Cancer Genetics and ***Cytogenetics***, 2008;180:30-36
20. Nakajima T, Yasui K, Keika Z, Inagaki Y, Fujii H, Minami M, Tanaka S, Taniwaki M, Itoh Y, Arii S, Inazawa J, Okanoue T. Activation of B-Myb by E2F1 in hepatocellular carcinoma ***Hepatology Res***, 2008; 38:886-895
21. Inagaki Y, Yasui K, Endo M, Nakajima T, Zen K, Tsuji K, Minami M, Tanaka S, Taniwaki M, Itoh Y, Arii S, Okanoue T. CREB3L4, INTS3, and SNAPAP are targets for the 1q21 amplicon frequently detected in hepatocellular carcinoma. ***Cancer Genet Cytogenet***, 2008;180:30-36
22. Kaneda M, Zhang D, Bhattacharjee R, Nakahama KI, Arii S, Morita I. Vitamin K(2) suppresses malignancy of HuH 7 hepatoma cells via inhibition of conenexin 43 . ***Cancer Lett***, 2008;8:761-772
23. Eguchi S, Kanematsu T, Arii S, Okazaki M, Okita K, Omata M, Ikai I, Kudo M, Kojiro M, Makuuchi M, Monden M, Matsuyama Y, Nakanuma Y, Takayasu K, ;The Liver Cancer Study Group of Japan Comparison of the outcomes between an anatomical resection and a non-anatomical minor heoatectomy for single hepatocellular carcinomas based on a Japanese nationwide survey. ***Surgery***, 2008;143:469-475
24. Takamatsu S, Noguchi N, Kudo A, Nakamura N, Kawamura T, Teramoto K, Igari T, Arii S. Influence of risk factors for metabolic syndrome and non-alcoholic fatty liver disease on the progression and prognosis of hepatocellular carcinoma. ***Hepatogastroenterology***, 2008;55:609-614
25. Makuuchi M, Kokudo N, Arii S, Futagawa S, Kaneko S, Kawasaki S, Matsuyama Y, Okazaki M, Okita K, Omata M, Saida Y, Takayama T, Yamaoka Y Development of evidence-based clinical guidelines for the diagnosis and treatment of hepatocellular carcinoma in ***Japan Hepatology Res***, 2008; 38:37-51
26. Hasegawa K, Makuuchi M, Takayama T, Kokudo N, Arii S, Okazaki M, Okita K, Omata M, Kudo M, Kojiro M, Nakanuma Y, Takayasu K, Monden M, Matsuyama Y, Ikai I, for the Liver Cancer Study Group of Japan Surgical resection vs percutaneous ablation for hepatocellular carcinoma: A preliminary report of the Japanese nationwide survey ***J Hepatology***, 2008; 49:589-594
27. Ito K, Ozasa H, Noda Y, Koike Y, Arii S, Horikawa S Effect of non-essential amino acid glycine administration on the liver regeneration of partially hepatectomized rats with hepatric ischemia/reperfusion injury. ***Clin Nutr***, 2008;27:773-780
28. Ban D, Kudo A, Sui S, Tanaka S, Nakamura N, Ito K, Suematsu M, Arii S. Decreased Mrp-2 dependent bile flow in the post-warm ischemic rat liver. ***J Surg Res***. 2009;153(2):310-6
29. Minamimura K, Sato K, Yagita H, Tanaka T, Arii S, Maki T. Strategies to induce marked prolongation of secondary skin allograft survival in alloantigen-primed mice. ***Am J Transplant*** 2008;8(4):761-72
30. Liu HY, Teramoto K, Kawamura K. Oda K, Ishiwata K, Arii S. Evaluation of tumor growth in vivo in a rat model of liver metastasis, using a newly devised index obtained by positron emission tomography with [18F]FDG.***J Heaptobiliary Pancreas Surg*** 2007;14:276-282
31. Tanaka S, Noguchi N, Ochiai T, Kudo A, Nakamura N, Ito K, Kawamura T, Teramoto K, Arii S. Outcome and recurrence of initially respectable hepatocellular carcinoma meeting Milan Criteria: Rationale for partial hepatectomy as first strategy ***J Am Coll Surg***, 2007; 204:1-6
32. Ito K, Ozasa H, Noda Y, Koike Y, Arii S, Horimawa S Splenic artery ligation improves remnant liver function in partially hepatectomized rats with ischemia/reperfusin injury. ***Liver International***, 2007;27:400-407
33. Zhang D, Kaneda M, Nakahama KI, Arii S, Morita I. Connexin 43 expression promotes malignancy of HuH 7 hepatocellular carcinoma cells via the inhibition of cell-cell communication. ***Cancer Letter***, 2007;252: 208-215
34. Ikai I, Arii S, okazaki M, Okita K, Omata M, Kojiro M, Takayasu K, Nakanuma Y, Makuuchi M, Matsuyama Y, Monden M, Kudo M Reports of the 17th Natiojnwide Follow-up survey of primary liver cancer in Japan. ***Hepatol Res***. 37:676-691, 2007
35. Irie T Asahina K, Teramoto K, Arii S, Teraoka H Hepatic progenitor cells in the mouse extrahepatic bile du8ct after a bile duct ligation ***Stem Cells and Development***, 2007;16:979-987
36. Satoh E, Li XK, Hara Y, Ogata K, Guo L, Kitazawa Y, Funeshima-Fujii N, Satoh T, Miyagi T, Teramoto K, Arii S, Kimura H. Sensitization to enhanced green fluorescence protein minor histocompatibility antigen by gene transduced cells and peritoneal exudate macrophages. ***Transpl Immnunol***, 2007; 18:73-84
37. Tanaka S, Wands JR, Arii S. Induction of angiopoietin-2 gene expression by Cox-2. A novel role for Cox-2 inhibitors during hepatocarcinogenesis. ***J Hepatology***, 2006; 44(1):233-5
38. Tanaka S, Pero SC, Taguchi K, Shimada M, Mori M, Krag DN, Arii S. A specific peptide ligand for Grb7 signal transduction protein inhibits invasion and metastasis of pancreatic cancer. ***J Natl Cancer Inst***, 2006;98:491-498

知的財産権の取得及び申請状況

国際出願
発明の名称：臓器機能維持改善液　　出願番号 PCT/JP2006/304269
出願日：平成 18 年 3 月 6 日
出願人：国立大学法人　東京医科歯科大学、株式会社　ミノファーゲン製薬
発明者：工藤　篤、有井　滋樹、和氣健二郎、阪野　功

特許
発明の名称：マイクロ RNA の発現量の変化を指標とする肝細胞癌の検出方法および癌抑制剤

整理番号：P09-034
出願日：平成21年11月2日
出願人：国立大学法人　東京医科歯科大学
発明者：稲澤　譲治、小崎　健一、井本　逸勢、古田　繭子、有井　滋樹

研究課題の実施を通じた政策提言（寄与した指針又はガイドライン等）

科学的根拠に基づく肝癌診療ガイドライン　2005年版
科学的根拠に基づく肝癌診療ガイドライン作成に関する研究班/編
金原出版株式会社、　ISBN 4-307-20200-7

科学的根拠に基づく肝癌診療ガイドライン　2009年版
日本肝臓学会/編、金原出版株式会社、　ISBN 978-4-307-20273-2

平成23年度肝炎等克服緊急対策研究事業への新規研究課題の応募状況

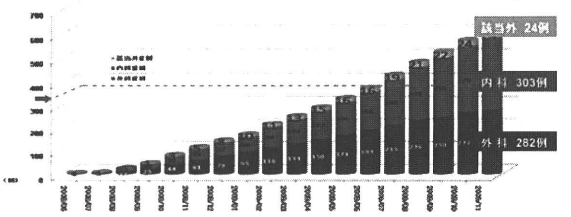
特になし

肝癌早期発見を目的とした分子マーカーおよび画像診断システムの開発
(H20 - 肝炎 - 一般 - 001)

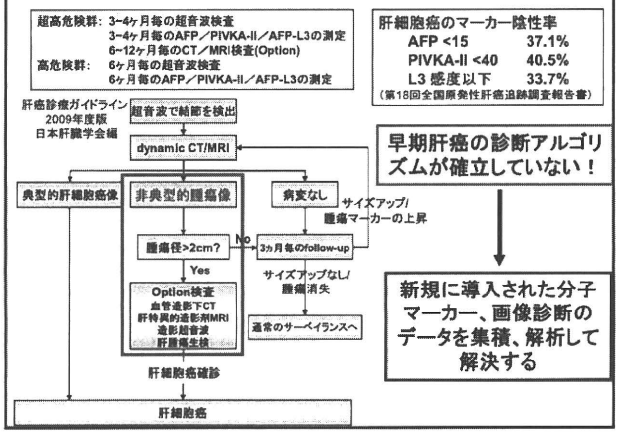
1. 早期発見に関わる分子マーカーを開発する。
2. 早期診断のための画像診断システムを開発する。

症例登録数推移

全体登録数 609例



「肝癌診療ガイドライン」サーベイランス・診断アルゴリズム



新たな分子マーカーの同定

[癌部におけるTransporter OATP8の意義]

多段階発癌との深い関連性

[非癌部における
酸化ストレスと関連するCYP1A2]

発癌因子、再発因子の可能性

診断アルゴリズムの再構築

EOB-MRI、造影超音波が開発され、保険適応となった。
これらの新規画像診断法により

1) 早期肝癌の診断
2) 早期肝癌と異型結節との鑑別
3) 微小結節の発見
4) 悪性度判定

などが期待され、とくに現行の診断アルゴリズムで未完成の非多血性肝細胞の診断に貢献することが考えられる。

本研究班では各種画像診断で非多血性結節と診断され組織学的(生検)診断の確定した病変を集積し、肝癌診断アルゴリズムの再構築を試みた。

成果

肝癌早期発見を目的とした分子マーカーおよび画像診断システムの開発
(H20 - 肝炎 - 一般 - 001)

分子マーカー	画像診断システム
AFP高感度L3分画 早期診断、治療後の効果判定	非定型的肝腫瘍 従来の診断アルゴリズムでは未解決
OATP8 早期診断マーカー	・EOB-MRI画像 ・造影超音波画像
CYP1A2 発癌・再発マーカー	↓ 肝癌診断アルゴリズムの提唱

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：癌胎児性抗原を利用した肝がんの超早期診断法と発症予防ワクチンの開発
課題番号　：H20-肝炎--一般-002
予定期間　：H20 年度から H22 年度まで
研究代表者　：中面哲也
所属研究機関：国立がん研究センター東病院 臨床開発センター
所属部局　：がん治療開発部
職名　：機能再生室長
年次別研究費(交付決定額)：
1 年目 24,696,000 円　2 年目 24,696,000 円　3 年目 22,226,000 円　計 71,618,000 円

Ⅰ．研究の意義

(1) 予後不良の肝がんの治療成績向上のためには、肝がんの超早期診断マーカーの開発や新規治療法さらには予防法の開発が必要である。

Ⅱ．研究の目的、期待される成果

(1) 本研究は肝細胞がんの超早期診断法と発症予防ワクチンの開発を主な目的とする。
(2) 肝細胞がんの新規免疫細胞療法の開発も目指す。
(3) 本研究の成果により、我が国に 350 万人存在するともいわれている肝炎ウイルスキャリアの肝細胞がんの発症抑制、肝がんの治療成績の向上等が期待される。

Ⅲ．3 年間の研究成果

研究代表者（中面哲也）
研究分担者（木下 平、古瀬純司、池田公史、千住 覚、河島光彦、野村和弘、小井戸薫雄、藤山重俊、本間 定、豊田秀徳、西村泰治）

(1) 肝細胞がんの超早期診断法の開発では、一部の慢性肝炎・肝硬変患者の末梢血中に検出される CTL や様々な血清マーカーが、CT で検出されない超早期のがんを診断している可能性を示し、多くの肝硬変患者をもつ 4 施設と超早期診断法の有効性を検証する大規模な臨床疫学研究を開始した。本研究期間内には既存のマーカーと我々が同定したマーカーの超早期診断における有用性を証明するには至らなかったが、プロトアレイを用いた網羅的解析では期待できる抗体が多数見出されており、多くの肝細胞がん患者の末梢血に存在する血中循環がん細胞(CTC)をも証明できたことから、これらの方法には今後期待が持てる。(中面、野村、小井戸、藤山、本間、豊田)
(2) 肝細胞がんのワクチンの開発では、進行肝細胞がん患者を対象に GPC3 ペプチドワクチンの臨床第 I 相試験を実施して、安全性とほぼ全例でのペプチド特異的キラーT 細胞(CTL)の誘導効果を確認した。60%の症例に最低 2 ヶ月間は腫瘍を増悪させない効果が、80%には腫瘍マーカー

の低下が認められた。また 20%の症例では、腫瘍の縮小、消失、壊死などの臨床的な効果も認められ、30mg、3 回投与の 1 例では著明な腫瘍縮小効果が出現した。総合的に判断して推奨投与量は 3.0mg に決定した。(中面、木下、古瀬、池田)

(3) CTL 療法の開発では、GPC3 ペプチドワクチン投与患者 PBMC から HLA-$A2^+$, $GPC3^+$癌細胞株を傷害し得る GPC3 ペプチド特異的 CTL クローンを複数樹立した。現在、TCR 遺伝子のクローニングを進めており、TCR 遺伝子導入細胞移入療法へ向けた検討を行っている。GPC3 ペプチドワクチン投与患者の少量の PBMC (2×10^6個) から、新規 CTL 培養法を用いて、GPC3 ペプチド特異的 CTL が大量に誘導可能であることが確認された。(中面)

(4) ES-DC ワクチン及び細胞療法の開発では、ヒト iPS 細胞の作製および iPS 細胞からの樹状細胞への分化誘導技術を確立できた。(千住)

(5) 肝細胞がんに対する陽子線治療の有効性と安全性のデータを検証し、ペプチドワクチンとの併用の臨床試験を計画した。(河島、中面)

Ⅳ. 今後考えられる新たな課題

(1) 肝細胞がんの超早期診断法の開発では、今後も検体を集め、網羅的解析で有望であった新規マーカーや既存のマーカーの有用性を引き続き検証する。また、肝硬変患者を対象とした CTC の検出の研究を実施する。

(2) 肝細胞がんのワクチンの開発では、臨床試験で引き続き再発予防効果の検証、進行がんへの有効性の検証を行い、さらには、陽子線との併用や予防ワクチンの開発を念頭に置いたペプチド溶液のみのワクチンの臨床試験も実施する。

(3) CTL 療法の開発では、新規ペプチド特異的 CTL 培養法を用いた臨床試験を展開するとともに、TCR 遺伝子導入細胞移入療法の開発も引き続き実施する。

(4) ES-DC ワクチン及び細胞療法の開発では、患者個別の iPS 細胞の樹立を行う場合は、やはりコストが大きな問題となる、安全性が確立されていないなど、まだまだ課題は多い。

Ⅴ. 行政施策への貢献の可能性

(1) 肝細胞がんの超早期診断マーカー、新規治療法・予防法の開発による肝細胞がんの治療成績の向上と医療費の削減

(2) 肝炎ウィルスキャリアの肝細胞がんの発症抑制

(3) iPS 細胞の有用性の認知

Ⅵ. 本研究の成果(発表論文・ガイドライン・マニュアル等)

(中面哲也、木下 平、西村泰治、野村和弘、河島光彦、池田公史)

(1) Nobuoka D, Kato Y, Gotohda N, Takahashi S, Nakagohri T, Konishi M, Kinoshita T, Nakatsura T. Postoperative serum alpha-fetoprotein level is a useful predictor of recurrence after hepatectomy for hepatocellular carcinoma. ***Oncol Rep.*** 24(2):521-528, 2010.

(2) Shirakawa H, Suzuki H, Shimomura M, Kojima M, Gotohda N, Takahashi S, Nakagohri T, Konishi M, Kobayashi N, Kinoshita T, Nakatsura T. Glypican-3 expression is correlated with poor prognosis in hepatocellular carcinoma. ***Cancer Sci.*** 100(8):1403-1407, 2009.

(3) Shirakawa H, Kuronuma T, Nishimura Y, Hasebe T, Nakano M, Gotohda N, Takahashi S, Nakagohri T, Konishi M, Kobayashi N, Kinoshita T, Nakatsura T. Glypican-3 is a useful diagnostic marker for a component of hepatocellular carcinoma in human liver cancer. ***Int. J. Oncol***. 34:649-656, 2009.

(4) Motomura Y, Ikuta Y, Kuronuma T, Komori H, Ito M, Tsuchihara M, Tsunoda Y, Shirakawa H, Baba H, Nishimura Y, Kinoshita T, Nakatsura T. HLA-A2 and -A24- restricted Glypican-3-derived peptide vaccine induce Specific CTLs: Preclinical study using mice. ***Int. J. Oncol.*** 32(5):985-990, 2008.

(5) Saito Y, Oba N, Nishinakagawa S, Mizuguchi Y, Kojima T, Nomura K, Nakatsura T. Identification of β2-microgloblin as a candidate for early diagnosis of imaging invisible hepatocellular carcinoma in patient with liver cirrhosis. ***Oncol. Rep.*** 23(5):1325-1330, 2010.

(6) Hayashi E, Motomura Y, Shirakawa H, Yoshikawa T, Oba N, Nishinakagawa S, Mizuguchi Y, Kojima T, Nomura K, Nakatsura T. Detection of glypican-3-specific CTLs in chronic hepatitis and liver cirrhosis. ***Oncol. Rep.*** 22:149-54, 2009.

(7) Kawashima M, Kohno R, Nakachi K, Nishio T, Mitsunaga S, Ikeda M, Konishi M, Takahashi S, Gotohda N, Arahira S, Zenda S, Ogino T, Kinoshita T. Dose-volume histogram analysis of the safety of proton beam therapy for unresectable hepatocellular carcinoma. ***Int J Radiat Oncol Biol Phys.*** In Press, 2010.

(8) 中面哲也, ペプチドワクチン　国内で臨床試験の行われているペプチドワクチン療法　GPC3 (特集：がん免疫療法の進歩と問題点－ペプチドワクチン療法、抗体療法、細胞療法－), 月刊 Mebio 2010 年 12 月号 (vol. 27 No. 12), メジカルビュー社, 49-55, 2010

(9) 中面哲也, 標準化へ向けた glypican-3 ペプチドワクチンの臨床試験, Biotherapy, 23(2):192-197, 2009

(10) 中面哲也, 臨床編 5. 肝細胞がん－新規腫瘍抗原 (glypican-3<GPC3>) を利用したワクチン療法, がんペプチドワクチン療法 (中村祐輔編), 中山書店, 76-83, 2009

(11) 中面哲也, 肝細胞癌に対する Glypican-3(GPC3)ペプチドワクチンの臨床第 I 相試験, リンパ学, 31(2):66-70, 2008

(12) 中面哲也, Glypican-3(GPC3)ペプチドワクチンによる肝細胞癌の予防・治療法, G. I. Research, 16(1):17-23, 2008

(西村泰治、千住　覚)

(13) Senju S, Haruta M, Matsumura K, Matsunaga Y, Fukushima S, Ikeda T, Takamatsu K, Irie A, Nishimura Y. Generation of dendritic cells and macrophages from human induced pluripotent stem cells aiming at cell therapy. ***Gene Therapy***, in press.

(14) Senju S, Matsunaga Y, Fukushima S, Hirata S, Matsuyoshi H, Nishimura Y. Pluripotent stem cells-derived dendritic cells for immunotherapy. ***Front Biosci.*** 2: 1520-1527, 2010.

(15) Senju S, Hirata S, Motomura Y, Fukuma D, Matsunaga Y, Fukushima S, Matsuyoshi H, Nishimura Y. Pluripotent stem cells as source of dendritic cells for immune therapy. ***Int. J. Hematol.*** 91(3): 392-400, 2010.

(16) Senju S, Haruta M, Matsunaga Y, Fukushima S, Ikeda T, Takahashi K, Okita K, Yamanaka S, Nishimura Y. Characterization of dendritic cells and macrophages generated by directed differentiation from mouse induced pluripotent stem cells. ***Stem Cells.*** 27(5):1021-1031, 2009.

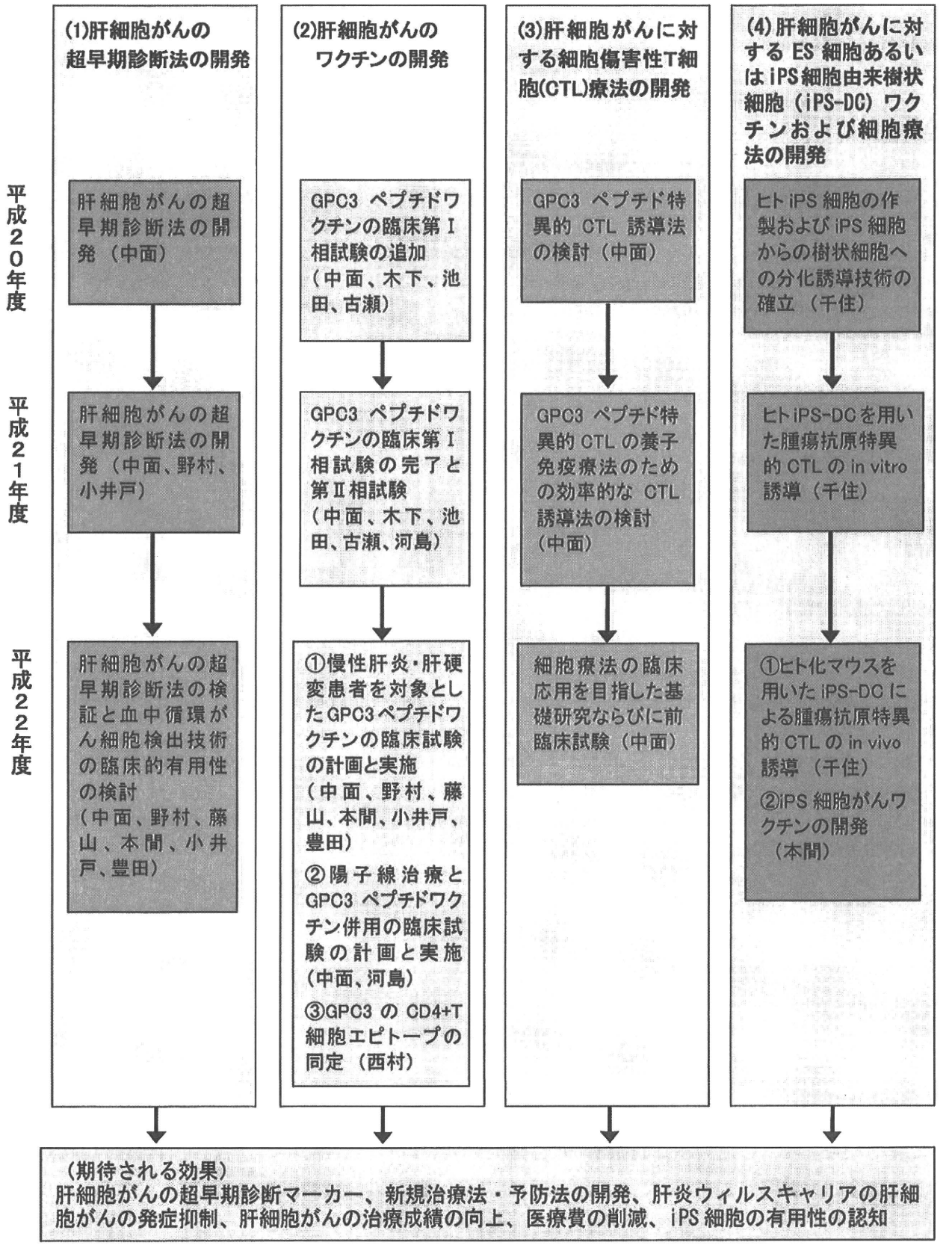
(17) Matsunaga Y, Fukuma D, Hirata H, Fukushima S, Haruta M, Ikeda T, Negishi I, Nishimura Y, Senju S. Activation of antigen-specific cytotoxic T lymphocytes by β2-microglobulin or TAP1 gene disruption and the introduction of recipient-matched MHC class I gene in allogeneic ES cell-derived dendritic cells. ***J. Immunol.*** 181(9):6635-6643, 2008.

(豊田秀徳)

(18) Yasuda E, Kumada T, Toyoda H, Kaneoka Y, Maeda A, Okuda S, Yoshimi N, Kozawa O. Evaluation of clinical utility of Glypican-3 (GPC3), measured by a commercially available ELISA kit with GPC3 antibody, as a serological and histological marker for hepatocellular carcinoma. ***Hepatol Res.*** 2010; 40: 477-485.

Ⅶ. Ⅲ(3 年間の研究成果)の概要図等

癌胎児性抗原を利用した肝がんの超早期診断法と発症予防ワクチンの開発



●研究代表者の研究歴等

・過去に所属した研究機関の履歴

平成 4 年－5 年；熊本大学医学部外科学第 2 講座（小川道雄先生）
平成 5 年－6 年；三井大牟田病院外科
平成 6－9 年；国立がんセンター東病院肝胆膵外科レジデント、がん診療の傍ら、研究所支所病理部及びがん治療開発部（江角浩安先生）にも所属し研究に従事、日本外科学会認定医取得
平成 9－17 年；熊本大学大学院医学薬学研究部免疫識別学分野（西村泰治先生）、うち 1 年半は久留米大学医学部免疫学講座（伊東恭悟先生）に国内留学
平成 12 年；日本学術振興会特別研究員 DC2 採用
平成 13 年；熊本大学大学院医学研究科外科系修了、医学博士、日本学術振興会特別研究員 PD 採用、同研究科助手に就任
平成 17 年 10 月；国立がんセンター東病院臨床開発センターがん治療開発部機能再生室長（現職）

・主な共同研究者（又は指導を受けた研究者）

小川道雄　市立貝塚病院・総長
江角浩安　国立がん研究センター東病院
西村泰治　熊本大学大学院生命科学研究部免疫識別学分野・教授
木下　平　国立がん研究センター東病院・院長代理兼副院長
古瀬純司　杏林大学腫瘍内科・教授
井本　滋　杏林大学乳腺外科・教授
中村祐輔　東京大学医科学研究所・ヒトゲノム解析センター長、
　　国立がん研究センター・研究所長

・主な研究課題

肝細胞がんの超早期診断法と予防・治療ワクチンの開発
迅速な創薬化を目指したがんペプチドワクチン療法の開発
がん抗原特異的細胞傷害性 T 細胞（CTL）治療の臨床導入を目指した研究
科学的根拠に基づくがん免疫療法の開発

・これまでの研究実績

1. Tanaka, Y., Nakasone, H., Yamazaki, R., Sato, K., Sato, M., Terasako, K., Kimura, S., Okuda, S., Kako, S., Oshima, K., Tanihara, A., Nishida, J., Yoshikawa, T., Nakatsura, T., Sugiyama, H., Kanda, Y. Single-cell analysis of T-cell receptor repertoire of HTLV-1 Tax-specific cytotoxic T cells in allogeneic transplant recipients with adult T-cell leukemia/lymphoma. Cancer Res. 70(15):6181-92, 2010.
2. ***Nobuoka, D., Kato, Y., Gotohda, N., Takahashi, S., Nakagohri, T., Konishi, M., Kinoshita, T., Nakatsura, T. Postoperative serum alpha-fetoprotein level is a useful predictor of recurrence after hepatectomy for hepatocellular carcinoma. Oncol Rep. 24(2):521-528, 2010.***
3. ***Saito, Y., Oba, N., Nishinakagawa, S., Mizuguchi, Y., Kojima, T., Nomura, K., and Nakatsura, T. Identification of β2-microgloblin as a candidate for early diagnosis of imaging invisible hepatocellular carcinoma in patient with liver cirrhosis. Oncol. Rep. 23(5):1325-1330, 2010.***
4. Yokomine, K., Senju, S., Nakatsura, T., Irie, A., Hayashida, Y., Ikuta, Y., Harao, M., Imai, K., Baba, H., Iwase, H., Nomori, H., Takahashi, K., Daigo, Y., Tsunoda, T., Nakamura, Y., Sasaki, Y., and Nishimura, Y. The forkhead box M1 transcription factor as a candidate of target for anti-cancer immunotherapy. Int J Cancer. 126(9);2153-63, 2010.
5. Horie, K., Tsuchihara, M., Nakatsura, T. Silencing of secreted protein acidic and rich in cysteine inhibits the growth of human melanoma cells with G_1 arrest induction. Cancer Sci. 101(4):913-919, 2010.

6. Mukohara, T., Shimada, H., Ogasawara, N., Wanikawa, R., Shimomura, M., Nakatsura, T., Ishii, G., Park, J.O., Jänne, P.A., Saijo, N., and Minami, H. Sensitivity of breast cancer cell lines to the novel insulin-like growth factor-1 receptor (IGF-1R) inhibitor NVP-AEW541 is dependent on the level of IRS-1 expression. Cancer Lett. 282(1):14-24, 2009.
7. ***Shirakawa, H., Suzuki, H., Shimomura, M., Kojima, M., Gotohda, N., Takahashi, S., Nakagohri, T., Konishi, M., Kobayashi, N., Kinoshita, T., and Nakatsura, T. Glypican-3 expression is correlated with poor prognosis in hepatocellular carcinoma. Cancer Sci. 100(8):1403-1407, 2009.***
8. ***Hayashi, E., Motomura, Y., Shirakawa, H., Yoshikawa, T., Oba, N., Nishinakagawa, S., Mizuguchi, Y., Kojima, T., Nomura, K., and Nakatsura, T. Detection of glypican-3-specific CTLs in chronic hepatitis and liver cirrhosis. Oncol. Rep. 22:149-54, 2009.***
9. ***Shirakawa, H., Kuronuma, T., Nishimura, Y., Hasebe, T., Nakano, M., Gotohda, N., Takahashi, S., Nakagohri, T., Konishi, M., Kobayashi, N., Kinoshita, T., and Nakatsura, T. Glypican-3 is a useful diagnostic marker for a component of hepatocellular carcinoma in human liver cancer. Int. J. Oncol. 34:649-656, 2009.***
10. Ikuta, Y.*, Hayashida, Y.*, Hirata, S., Irie, A., Senju, S., Kubo, T., Nakatsura, T., Monji, M., Sasaki, Y., Baba, H., and Nishimura, Y. (*These two authors contributed equally.) Identification of the H2-K^d-restricted cytotoxic T lymphocyte epitopes of a tumor-associated antigen, SPARC, which can stimulate antitumor immunity without causing autoimmune disease in mice. Cancer Sci.100(1):132-137, 2009.
11. Harao, M., Hirata, S., Irie, A., Senju, S., Nakatsura, T., Komori, H., Ikuta, Y., Yokomine, K., Imai, K., Inoue, M., Harada, K., Mori, T., Tsunoda, T., Nakatsuru, S., Daigo, Y., Nomori, H., Nakamura, Y., Baba, H., and Nishimura, Y. HLA-A2-restricted CTL epitopes of a novel lung cancer-associated cancer testis antigen, cell division cycle associated 1, can induce tumor-reactive CTL. Int J Cancer. 123(11):2616-25, 2008.
12. Muchemwa, F.C., Nakatsura, T., Fukushima, S., Nishimura, Y., Kageshita, T., and Ihn, H. Differential Expression of Heat Shock Protein 105 in melanoma and melanocytic naevi. Melanoma Res. 18(3):166-171, 2008.
13. ***Motomura, Y., Ikuta, Y., Kuronuma, T., Komori, H., Ito, M., Tsuchihara, M., Tsunoda, Y., Shirakawa, H., Baba, H., Nishimura, Y., Kinoshita, T., and Nakatsura, T. HLA-A2 and -A24- restricted Glypican-3-derived peptide vaccine induce Specific CTLs: Preclinical study using mice. Int. J. Oncol. 32(5):985-990, 2008.***
14. Yokomine, K., Nakatsura, T., Senju, S., Nakagata, N., Minohara, M., Kira, JI., Motomura, Y., Kubo, T., Sasaki, Y., and Nishimura, Y. Regression of intestinal adenomas by vaccination with heat shock protein 105-pulsed bone marrow-derived dendritic cells in $Apc^{Min/+}$ mice. Cancer Sci. 98(12):1930-1935, 2007.
15. Muchemwa, F.C., Nakatsura, T., Ihn, H., and Kageshita, T. Heat shock protein 105 is overexpressed in squamous cell carcinoma and extramammary Paget disease but not in basal cell carcinoma. Br. J. Dermatol. 155: 582-585, 2006.
16. Komori, H., Nakatsura, T., Senju, S., Yoshitake, Y., Motomura, Y., Ikuta, Y., Fukuma, D., Yokomine, K., Harao, M., Beppu, T., Matsui, M., Torigoe, T., Sato, N., Baba, H., and Nishimura, Y. Identification of HLA-A2- or HLA–A24-restricted CTL epitopes possibly useful for glypican-3-specific immunotherapy of hepatocellular carcinoma. Clin. Cancer Res. 12(9): 2689-2697, 2006.
17. Hosaka, S., Nakatsura, T., Tsukamoto, H., Hatayama, T., Baba, H., and Nishimura, Y. Synthetic small interfering RNA targeting heat shock protein 105 induces apoptosis of various cancer cells both in vitro and in vivo. Cancer Sci. 97: 623-632, 2006.
18. Yokomine, K., Nakatsura, T., Minohara, M., Kira, JI., Kubo, T., Sasaki, Y., Nishimura, Y. Immunization with heat shock protein 105-pulsed dendritic cells leads to tumor rejection in mice. Biochem. Biophys. Res. Comm. 343:269-278, 2006.
19. Motomura, Y., Senju, S., Nakatsura, T., Matsuyoshi, H., Hirata, S., Monji, M., Komori, H., Fukuma, D., Baba, H., and Nishimura, Y. Embryonic stem cell-derived dendritic cells expressing glypican-3, a recently identified oncofetal antigen, induce protective immunity against highly metastatic mouse melanoma, B16-F10. Cancer Res. 66(4): 2414-2422, 2006.
20. Ikuta, Y., Nakatsura, T., Kageshita, T., Fukushima, S., Ito, S., Wakamatsu, K., Baba, H., and Nishimura, Y. Highly sensitive detection of melanoma at an early stage based on the increased serum SPARC and Glypican-3 levels. Clin. Cancer Res. 11(22): 8079-8088, 2005.

21. Matsuyoshi, H., Hirata, S., Yoshitake, Y., Motomura, Y., Fukuma, D., Kurisaki, A., Nakatsura, T., Nishimura, Y., and Senju, S. Therapeutic effect of α-galactosylceramide-loaded dendritic cells genetically engineered to express SLC/CCL21 along with tumor antigen against peritoneally disseminated tumor cells. Cancer Sci. 96(10): 889-896, 2005.
22. Miyazaki, M.*, Nakatsura, T.*(*Equal contribution), Yokomine, K., Senju, S., Monji, M., Hosaka, S., Komori, H., Yoshitake, Y., Motomura, Y., Minohara, M., Kubo, T., Ishihara, K., Hatayama, T., Ogawa, M., and Nishimura, Y. DNA vaccination of HSP105 leads to tumor rejection of colorectal cancer and melanoma in mice through activation of both CD4+ and CD8+ T cells. Cancer Sci. 96: 695-705, 2005.
23. Nakatsura, T., Nishimura, Y. Usefulness of a novel oncofetal antigen Glypican-3 for diagnosis of hepatocellular carcinoma and melanoma. (review) BioDrugs 19:71-77, 2005.
24. Nakatsura, T., Komori, H., Kubo, T., Yoshitake, Y., Senju, S., Katagiri, T., Furukawa, Y., Oagawa, M., Nakamura, Y., and Nishimura, Y. Mouse homologue of a novel human oncofetal antigen, Glypican-3, evokes T cell-mediated tumor rejection without autoimmune reactions in mice. Clin. Cancer Res. 10: 8630-8640, 2004.
25. Nakatsura, T., Kageshita, T., Ito, S., Wakamatsu, K., Monji, M., Ikuta, Y., Senju, S., Ono, T. and Nishimura, Y. Identification of glypican-3 as a novel tumor marker for melanoma. Clin. Cancer Res. 10: 6612-6621, 2004.
26. Monji, M., Nakatsura, T., Senju, S., Yoshitake, Y., Sawatsubashi, M., Shinohara, M., Kageshita, T., Ono, T., Inokuchi, A. and Nishimura, Y. Identification of a novel human cancer/testis antigen, KM-HN-1, recognized by cellular and humoral immune responses. Clin. Cancer Res. 10: 6047-6057, 2004.
27. Yoshitake, Y., Nakatsura, T., Monji, M., Senju, S., Matsuyoshi, H., Tsukamoto, H., Hosaka, S., Komori, H., Fukuma, D., Ikuta, Y., Katagiri, T., Furukawa, Y., Ito, H., Shinohara, M., Nakamura, Y., and Nishimura, Y.: Proliferation potential-related protein, an ideal esophageal cancer antigen for immnotherapy, identified using complementary DNA microarray analysis. Clin. Cancer Res. 10: 6437-6448, 2004.
28. Kai, M., Nakatsura, T., Egami, H., Senju, S., Nishimura, Y., and Ogawa, M. Heat shock protein 105 is overexpressed in a variety of human tumors. Oncology Reports 10: 1777-1782, 2003.
29. Nakatsura, T., Monji, M., Senju, S., Yamada, K., Ogawa, M., and Nishimura, Y. Identification of cancer antigens by SEREX. International Congress Series 1255: 343-349, 2003.
30. Nakatsura, T., Yoshitake, Y., Senju, S., Monji, M., Komori, H., Motomura, Y., Hosaka, S., Beppu, T., Ishiko, T., Kamohara, H., Ashihara, H., Katagiri, T., Furukawa, Y., Fujiyama, S., Ogawa, M., Nakamura, Y., and Nishimura, Y. Glypican-3, overexpressed specifically in human hepatocellular carcinoma, is a novel tumor marker. Biochem. Biophys. Res. Comm. 306: 16-25, 2003.
31. Azuma, K., Shichijo, S., Maeda, Y., Nakatsura, T., Nonaka, Y., Fujii, T., Koike, K., and Itoh, K. Mutated p53 Gene Encodes a Non-Mutated Epitope Recognized by HLA-B*4601-restricted and Tumor-reactive CTLs at Tumor Site. Cancer Res. 63: 854-858, 2003.
32. Monji, M., Senju, S., Nakatsura, T., Yamada, K., Sawatsubashi, M., Inokuchi, A., and Nishimura, Y. Head and Neck Cancer Antigens Recognized by the Humoral Immune System. Biochem. Biophys. Res. Comm. 294: 734-741, 2002.
33. Maeda, Y., Ito, M., Harashima, N., Nakatsura, T., Hida, N., Imai, N., Sato, Y., Shichijo, S., Todo, S., and Itoh, K. Cleavage and polyadenylation specificity factor (CPSF)-derived peptides can induce HLA-A2-restricted and tumor-specific CTLs in the majority of gastrointestinal cancer patients. Int. J. Cancer 99: 409-417, 2002.
34. Nakatsura, T., Senju, S., Ito, M., Nishimura, Y., Itoh, K. Cellular and Humoral Immune Responses to A Human Pancreatic Cancer Antigen, CLP, Originally Defined by the SEREX Method. Eur. J. Immunol. 32: 826-836, 2002.
35. Yamada, K., Senju, S., Shinohara, T., Nakatsura, T., Murata, Y., Ishihara, M., Nakamura, S., Ohno, S., Negi, A., and Nishimura, Y. Lens epitherial derived growth factor as an autoantigen in Vogt-Koyanagi-Harada disease. Immunol. Lts. 78: 161-168, 2001.
36. Nakatsura, T., Senju, S., Yamada, K., Jyotsuka, T., Ogawa, M., and Nishimura, Y. Gene cloning of immunogenic antigens over-expressed in pancreatic cancer. Biochem. Biophys. Res. Comm. 281: 936-944, 2001.

37. Yamada, K., Senju, S., Nakatsura, T., Murata, Y., Ishihara, M., Nakamura, S., Ohno, S., Negi, A., Nishimura, Y. Identification of a novel autoantigen UACA in patients with panuveitis. Biochem.Biophys.Res.Comm.280:1169-76, 2001.
38. Haga, Y., Nakatsura, T., Shibata, Y., Sameshima, H., Nakamura, Y., Tanimura, M., and Ogawa, M. Human gastric carcinoid detected during long-term antiulcer therapy of H2 receptor antagonist and proton pump inhibitor. Dig Dis Sci. 43: 253-257, 1998.
39. Nakatsura, T., Hasebe, T., Tsubono, Y., Ryu, M., Kinoshita, T., Kawano, N., Konishi, M., Kosuge, T., Kanai, Y., and Mukai, K. Histological prognostic parameters for adenocarcinoma of the pancreatic head. Proposal for a scoring system for prediction of outcome. J. Hepatobiliary Pancreat. Surg. 4:441-448, 1997.
40. Tanizaki, H., Ryu, M., Kinoshita, T., Kawano, N., Konishi, M., Cho, A., Nakatsura, T., Natsume, T., Takahashi, S., Sugita, M., Izuishi, K., Yoshino, M., Furuse, J., Iwasaki, M., and Tsubono, Y. Comparison of clinical features and survival in patients with hepatitis B and C virus-related hepatocellular carcinoma. Jpn. J. Clin. Oncol. 27: 67-70, 1997.
41. 中面哲也, 第 5 章がんワクチン がん抗原の同定法と種類、それを用いた免疫療法, 次世代ワクチンの産業応用技術 (神谷齊監修), シーエムシー出版, 213-218, 2010
42. ***中面哲也, ペプチドワクチン 国内で臨床試験の行われているペプチドワクチン療法 GPC3 (特集：がん免疫療法の進歩と問題点－ペプチドワクチン療法、抗体療法、細胞療法－), 月刊 Mebio 2010 年 12 月号 (vol. 27 No. 12), メジカルビュー社, 49-55, 2010***
43. 中面哲也, 免疫療法(特集:がん治療の最前線), 理大科学フォーラム 2010 年 11 月号, 東京理科大学, 32-35, 2010
44. ***中面哲也, 標準化へ向けた glypican-3 ペプチドワクチンの臨床試験, Biotherapy, 23(2):192-197, 2009***
45. 中面哲也, 木下平, 古瀬純司, 進行肝細胞がん患者を対象とした HLA-A24 および-A2 結合性 Glypican-3(GPC3)由来ペプチドワクチンの臨床第 I 相試験, 臨床薬理の進歩, 財団法人臨床薬理研究振興財団, 30:160-166, 2009
46. 中面哲也, 第 2 部 がんと免疫の最前線 file-3 がんと免疫の専門医が語る, 免疫細胞治療(武藤徹一郎監修), 幻冬舎, 100-109, 2009
47. ***中面哲也, 臨床編 5. 肝細胞がん－新規腫瘍抗原 (glypican-3〈GPC3〉) を利用したワクチン療法, がんペプチドワクチン療法 (中村祐輔編), 中山書店, 76-83, 2009***
48. 中津川宗秀, 中面哲也, 第 2 章 がん化学療法の標的 12. がん免疫療法, がん化学療法・分子標的治療 update (西條長宏、西尾和人編), 中外医学社, 86－91, 2009
49. ***中面哲也, 肝細胞癌に対する Glypican-3(GPC3)ペプチドワクチンの臨床第 I 相試験, リンパ学, 31(2):66-70, 2008***
50. ***中面哲也, Glypican-3(GPC3)ペプチドワクチンによる肝細胞癌の予防・治療法, G. I. Research, 16(1):17-23, 2008***
51. 西村泰治, 中面哲也, 千住覚, 新規癌胎児性抗原 Glypican-3 の肝細胞癌の診断と免疫療法への応用、日本臨床免疫学会会誌、31(5):383-91, 2008
52. 中面哲也, 癌免疫療法, 腫瘍内科, 1(5):449-453, 2007
53. 小森宏之, 中面哲也, 本村裕, 別府透, 西村泰治, 馬場秀夫, 癌胎児性抗原 Glypican-3 を標的とした癌ワクチン療法, Biotherapy, 21(1):62-68, 2007
54. 小森宏之, 中面哲也, 本村裕, 別府透, 石河隆敏, 馬場秀夫, 西村泰治, 新規癌胎児性抗原 Glypican-3 を標的とした肝細胞癌の免疫療法, 分子細胞治療, 6(2):57-61, 2007
55. 影下登志郎, 福島聡, 尹浩信, 西村泰治, 中面哲也, 悪性黒色腫の新しい血清マーカーGlypican-3 と SPARC, 臨床皮膚科, 60(5)増刊号:169-172, 2006
56. 小森宏之, 中面哲也, 別府透, 西村泰治, 馬場秀夫, Glypican-3(GPC3)を標的とした免疫療法の有用性の検討, 癌と化学療法, 33(12):1742-1744, 2006
57. 吉武義泰, 中面哲也, 西村泰治, 癌免疫療法の新展開, 日本臨床, 63(4) (増刊:『臨床免疫学 (上) -基礎研究の進歩と最新の臨床-』) :46-55, 2005

58. 中面哲也, 西村泰治, 腫瘍抗原ペプチドを駆使した癌免疫療法の新展開, 実験医学, 第 22 巻 5 号 (増刊 ; 免疫研究のフロンティア) ,215-220,2004
59. 中面哲也, 西村泰治, cDNA マイクロアレイ解析による腫瘍特異抗原の探索, 臨床免疫, 41(4):369-378,2004
60. 中面哲也, 西村泰治, cDNA マイクロアレイ解析による腫瘍特異抗原の探索「肝細胞癌の腫瘍マーカーおよび腫瘍特異抗原としての Glypican-3(GPC3)の同定 ; その臨床応用への可能性,医学をゲノムする (第 27 回阿蘇シンポジウム記録 2003) ,115-127,2004
61. 中面哲也, 西村泰治, 癌と HLA-癌細胞の排除における HLA の役割, 医学のあゆみ, 207(8):543-548,2003
62. 中面哲也, 門司幹男, 西村泰治, SEREX Surgery Frontier, 9(3):244-247,2002
63. 江上寛, 甲斐幹男, 中面哲也, 小川道雄, Heat shock protein 救急・集中治療, 14(9): 969-974,2002
64. 小田竜也, 竜崇正, 中面哲也, 向井清, 長谷部孝裕, 膵臓癌の分子生物学的, 病理学的予後予測指標肝胆膵, 34(3):319-323,1997
65. 竜崇正, 木下平, 小西大, 井上和人, 中面哲也, 夏目俊之, Grisson 鞘一括肝中央 2 区域切除外科, 59(4):425-430,1997

特許の取得及び申請状況 ;

国内 : 特許取得 2 件、出願中 8 件　海外 : 特許取得 2 件、出願中 8 件

1. 国際特許出願番号 : PCT/JP2006/315631, (国内 : 2005-230702),
   発明者 : 西村泰治、中面哲也、小森宏之,
   発明の名称 : HLA-A2 陽性者用 Glypican-3(GPC3)由来癌拒絶抗原ペプチド及びこれを含む医薬,
   出願人 : 西村泰治、中面哲也、小森宏之, (国内 : 国立大学法人熊本大学),
   出願日 : 2006 年 8 月 8 日 (国内 : 2005 年 8 月 9 日)
2. 国際特許出願番号 : PCT/JP2006/315630, (国内 : 2005-230671),
   発明者 : 西村泰治、中面哲也、小森宏之,
   発明の名称 : HLA-A2 陽性者用 HSP105 由来癌拒絶抗原ペプチド及びこれを含む医薬,
   出願人 : 西村泰治、中面哲也、小森宏之, (国内 : 国立大学法人熊本大学),
   出願日 : 2006 年 8 月 8 日 (国内 : 2005 年 8 月 9 日)
3. 国際特許出願番号 : PCT/JP2005/14567, (国内 : 2004-303688),
   発明者 : 西村泰治、中面哲也、生田義明,
   発明の名称 : 悪性黒色腫の新規な診断剤,
   出願人 : 西村泰治、中面哲也、生田義明, (国内 : 国立大学法人熊本大学),
   出願日 : 2005 年 8 月 9 日 (国内 : 2004 年 10 月 19 日)
4. 国際特許出願番号 : PCT/JP2005/14566, (国内 : 2004-235087),
   発明者 : 西村泰治、中面哲也、保坂征司,
   発明の名称 : RNAi を利用した抗腫瘍剤,
   出願人 : 西村泰治、中面哲也、保坂征司, (国内 : 国立大学法人熊本大学),
   出願日 : 2005 年 8 月 9 日 (国内 : 2004 年 8 月 12 日)
5. 国際特許出願番号 : PCT/JP2004/016374, (国内 : 2003-368725),
   発明者 : 西村泰治、中面哲也,
   発明の名称 : 悪性黒色腫 (メラノーマ) の診断剤,
   出願人 : くまもとテクノ産業財団,
   出願日 : 2004 年 10 月 28 日 (国内 : 2003 年 10 月 29 日)

6. 国際特許出願番号：PCT/JP2004/011736,（国内：2003-291073),
発明者：中面哲也、吉武義泰、中村祐輔、西村泰治,
発明の名称：食道癌の抗原およびその利用,
出願人：くまもとテクノ産業財団,
出願日：2004 年 8 月 10 日（国内：2003 年 8 月 11 日）
7. 国際特許出願番号：PCT/JP03/11049,（国内：2002-255668）
発明者：中面哲也、西村泰治,
発明の名称：癌抗原及びその利用,
出願人：くまもとテクノ産業財団,
出願日：2003 年 8 月 29 日,（国内：2002 年 8 月 30 日）
8. 国際特許出願番号：PCT/JP03/10459,（国内：2002-245831),
発明者：西村泰治、中面哲也、中村祐輔,
発明の名称：「ペプチド及びこれを含む医薬」,
出願人：キリンビール株式会社,
出願日：2003 年 8 月 26 日,（国内：2002 年 8 月 19 日）

・平成 23 年度肝炎等克服緊急対策研究事業への新規研究課題の応募状況

申請なし