（報告様式４）

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## I.　基本情報

事　業　名：（日本語）革新的がん医療実用化研究事業
（英　語）Practical Research for Innovative Cancer Control

研究開発課題名：（日本語）固形がん幹細胞を標的とした革新的治療法の開発に関する研究
（英　語）Research on development of innovative therapeutic methods targeting solid cancer stem cells

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## II. 成果の概要（総括研究報告）

政府が策定した中長期的視野に立った戦略に基づくアクション計画に沿って、平成23年度から開始された10年計画の前期（平成23～25年度）から継続的に新たな知見を創出・医療応用展開し、アンメットメディカルニーズが高い難治性の消化器（膵癌、転移性大腸癌を含む）を対象にした癌幹細胞を標的とした革新的な治療法を開発した。わが国を代表する研究者の多施設共同研究で基盤整備を展開した。平成26～28年度の本計画は、アンメットメディカルニーズが高い難治癌の克服に向けた整備事業として革新シーズの実用化に道筋を付け、治療抵抗性の根源たる癌幹細胞の創薬の加速化を促進した。各領域の最先端に携わるわが国研究者に力を結集した事業内容は、癌幹細胞とリプログラミング（最先端研究の融合）およびアカデミア創薬において内外で卓越した成果を上げつつあり、目標に向けて焦点を絞り更に発展的に事業を展開した。その結果、癌幹細胞の代謝を標的としたCD44vの医師主導型治験、マイクロRNAの人工核酸化による核酸医薬品としての最適化、エクソソームの早期癌への応用、癌幹細胞の生存、維持に関わるベスタチンの構造最適化などの成果を達成することに成功した。また、CD44vに関する医師主導治験、マイクロRNAの人工核酸化による核酸医薬品としての構造最適化、マイクロRNAエクソゾームの早期癌への応用を目指しPOCの取得、ベスタチンの構造最適化及びDDS化を達成した。さらに癌幹細胞の表面分子CD44を標的とする創薬として本年度の研究により、阻害薬としての活性を損なうことなく、水溶性を飛躍的に高めることができるスルファサラジンのPEG修飾体の化学構造を明らかにすることができた。さらに、癌幹細胞を標的とした核酸医薬としてもらう網羅的な遺伝子発現解析からマイクロRNAの標的分子群においてドセタキセル耐性及び造腫瘍性の亢進に関与する分子としてENPP1を同定することに成功した。核酸シーズはPMDAコンサルタントを経て前臨床試験に進んだ。これらを裏付けるPOCとしてリプログラミングをコンセプトとした免疫系制御を含むモデルを作製し、癌の発生段階に促進的に働いて治療標的となることを確認した。以上より難治性消化器癌の癌幹細胞に対する創薬としてドラッグリポジショニングのスルファサラジン及び核酸医薬を創出することができ、臨床応用に向けた実装としてDDS技術を開発することができた。

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In line with the action plan based on the government's 10-year medium to long-term strategy, implemented in 2011, with the charter to continuously produce new knowledge and ideas, in the initial period (between 2011-2013) we have developed an innovative treatment for intractable diseases of the gastrointestinal tracts with unmet medical needs (including pancreatic and metastatic colon cancer) by targeting cancer stem cells. We developed a fundamental infrastructure of multicenter collaborative research through researchers representative of our country. The plan for 2014-2016 involved the promotion of accelerated discovery of treatment resistant stem cancer cells as an avenue for overcoming intractable cancers with high unmet medical needs and the practical application of seed ideas. Through focusing on excellent Japanese researchers in each area, we raised both internal and external standards for cancer stem cells research and reprogramming research (fusion of state-of-the-art research) as well as academic discovery, thereby narrowing the target of research and expanded the project. As a result, we were successful in attaining results regarding, physician-initiated clinical trials of CD44v targeting the metabolism of cancer stem cells, optimization of nucleic acid as a nucleic acid drug by artificial nucleic acids of microRNA, application of exosomes to early cancer, survival and maintenance of cancer stem cells, and the sustainable structural optimization of Bestatin. In the physician initiated-clinical trials, we also achieved structural optimization of the nucleic acid structure of microRNA as a nucleic acid-based drug acquisition of POC with the goal of application of microRNA exosome to early stage cancer and structural optimization of Bestatin and DDS. Additionally, as a result of the current year's drug discovery research, we were able to identify the chemical composition of PEG modified sulfasalazine responsible for the rapid increase in water solubility with no impairment of its inhibitory activity on cancer stem cells CD44 surface antigen. Furthermore, using comprehensive gene expression analysis we succeeded in identifying ENPP1 as a molecule involved in enhancement of docetaxel resistance and tumorigenicity in cancer stem cell targeted nucleic acid therapies. Nucleic acid seeds proceeded to preclinical trials via consultation with the PMDA. As confirmatory POC studies, we developed a model of immune system regulated reprogramming, and confirmed it as a therapeutic target due to its cancer-promoting activity at the stage of cancer development. As a part of the drug repositioning for discovery of anticancer agents and building on the aforementioned results, we were able to create sulfasalazine and nucleic acid therapies for cancer stem cells of intractable gastrointestinal cancer and were able to implement the clinical application of DDS technologies.

## III. 成果の外部への発表

（１）学会誌・雑誌等における論文一覧（国際誌 54 件）

1. Mikamori, M., Miyamoto, A., Asaoka, T., Maeda, S., Hama, N., Yamamoto, K., Hirao, M., Ikeda, M., Sekimoto, M., Doki, Y., Mori, M., Nakamori, S. Postoperative Changes in Body Composition After Pancreaticoduodenectomy Using Multifrequency Bioelectrical Impedance Analysis. ***J. Gastrointest. Surg.*** 20(3):611-618, 2016.
2. Yamamoto, H., Oshiro, R., Ohtsuka, M., Uemura, M., Haraguchi, N., Nishimura, J., Takemasa, I., Mizushima, T., Doki, Y., Mori, M. [Corrigendum] Distinct expression of C4.4A in colorectal cancer detected by different antibodies. ***Int. J. Oncol.***, 49(5):2186, 2016.
3. Yamamoto, H., Mori, M. MicroRNAs as Therapeutic Targets and Colorectal Cancer Therapeutics. ***Adv. Exp. Med. Biol.***, 937:239-2347, 2016.
4. Yamamoto, H., Murata, K., Fukunaga, M., Ohnishi, T., Noura, S., Miyake, Y., Kato, T., Ohtsuka, M., Nakamura, Y., Takemasa, I., Mizushima, T., Ikeda, M., Ohue, M., Sekimoto, M., Nezu, R., Matsuura, N., Monden, M., Doki, Y., Mori, M. Micrometastasis Volume in Lymph Nodes Determines Disease Recurrence Rate of Stage II Colorectal Cancer: A Prospective Multicenter Trial. ***Clin. Cancer, Res.***, 22(13):3201-3208, 2016.
5. Wada, H., Eguchi, H., Noda, T., Ogawa, H., Yamada, D., Tomimaru, Y., Tomokuni, A., Asaoka, T., Kawamoto, K., Gotoh, K., Marubashi, S., Umeshita, K., Nagano, H., Doki, Y., Mori, M. Selection criteria for hepatic resection in intermediate-stage (BCLC stage B) multiple hepatocellular carcinoma. ***Surgery.,*** 160(5):1227-1235, 2016.
6. Akita, H., Ritchie, SA., Takemasa, I., Eguchi, H., Pastural, E., Jin, W., Yamazaki, Y., Goodenowe, DB., Nagano, H., Monden, M., Mori, M., Doki, Y. Serum Metabolite Profiling for the Detection of Pancreatic Cancer: Results of a Large Independent Validation Study. ***Pancreas.*** 45(10):1418-1423, 2016.
7. Uemura, M., Kim, HM., Hata, T., Sakata, K., Okuyama, M., Takemoto, H., Fujii, H., Fukuzaki, T., Morita, T., Hata, T., Takemasa, I., Satoh, T., Mizushima, T., Doki, Y., Mori, M. First-line cetuximab-based chemotherapies for patients with advanced or metastatic KRAS wild-type colorectal cancer. ***Mol. Clin. Oncol.***, 5(2):375-379, 2016.
8. Takahashi, H., Suzuki, Y., Nishimura, J., Haraguchi, N., Ohtsuka, M., Miyazaki, S., Uemura, M., Hata, T., Takemasa, I., Mizushima, T., Yamamoto, H., Doki, Y., Mori, M. Characteristics of carbonic anhydrase 9 expressing cells in human intestinal crypt base. ***Int. J. Oncol.***, 48(1):115-122, 2016.
9. Tanaka, K., Miyata, H., Sugimura, K., Kanemura, T., Hamada-Uematsu, M., Mizote, Y., Yamasaki, M., Wada, H., Nakajima, K., Takiguchi, S., Mori, M., Doki, Y., Tahara, H. Negative influence of programmed death-1-ligands on the survival of esophageal cancer patients treated with chemotherapy. ***Cancer, Sci.***, 107(6):726-733, 2016.
10. Osawa, H., Takahashi, H., Nishimura, J., Ohta, K., Haraguchi, N., Hata, T., Yamamoto, H., Mizushima, T., Takemasa, I., Doki, Y., Mori, M. Full-length LGR5-positive cells have chemoresistant characteristics in colorectal cancer. ***Br. J. Cancer,*** 114(11):1251-1260, 2016.

11. Mikami, J., Kurokawa, Y., Takahashi, T., Miyazaki, Y., Yamasaki, M., Miyata, H., Nakajima, K., Takiguchi, S., Mori, M., Doki, Y. Antitumor effect of antiplatelet agents in gastric cancer cells: an in vivo and in vitro study. ***Gastric, Cancer,*** 19(3):817-826, 2016.
12. Ohtsuka, M., Ling, H., Ivan, C., Pichler, M., Matsushita, D., Goblirsch, M., Stiegelbauer, V., Shigeyasu, K., Zhang, X., Chen, M., Vidhu, F., Bartholomeusz, GA., Toiyama, Y., Kusunoki, M., Doki, Y., Mori, M., Song, S., Gunther, JR., Krishnan, S., Slaby, O., Goel, A., Ajani, JA., Radovich, M., Calin, GA. H19 Noncoding RNA, an Independent Prognostic Factor, Regulates Essential Rb-E2F and CDK8-β-Catenin Signaling in Colorectal Cancer. ***EBioMedicine.*** 13:113-124, 2016.
13. Saito, T., Nishikawa, H., Wada, H., Nagano, Y., Sugiyama, D., Atarashi, K., Maeda, Y., Hamaguchi, M., Ohkura, N., Sato, E., Nagase, H., Nishimura, J., Yamamoto, H., Takiguchi, S., Tanoue, T., Suda, W., Morita, H., Hattori, M., Honda, K., Mori, M., Doki, Y., Sakaguchi, S. Two FOXP3(+)CD4(+) T cell subpopulations distinctly control the prognosis of colorectal cancers. ***Nat. Med.***, 22(6):679-684, 2016.
14. Sawada, G., Niida, A., Uchi, R., Hirata, H., Shimamura, T., Suzuki, Y., Shiraishi, Y., Chiba, K., Imoto, S., Takahashi, Y., Iwaya, T., Sudo, T., Hayashi, T., Takai, H., Kawasaki, Y., Matsukawa, T., Eguchi, H., Sugimachi, K., Tanaka, F., Suzuki, H., Yamamoto, K., Ishii, H., Shimizu, M., Yamazaki, H., Yamazaki, M., Tachimori, Y., Kajiyama, Y., Natsugoe, S., Fujita, H., Mafune, K., Tanaka, Y., Kelsell, DP., Scott, CA., Tsuji, S., Yachida, S., Shibata, T., Sugano, S., Doki, Y., Akiyama, T., Aburatani, H., Ogawa, S., Miyano, S., Mori, M., Mimori, K. Genomic Landscape of Esophageal Squamous Cell Carcinoma in a Japanese Population. ***Gastroenterology.***, 150(5):1171-1182, 2016.
15. Mokutani, Y., Uemura, M., Munakata, K., Okuzaki, D., Haraguchi, N., Takahashi, H., Nishimura, J., Hata, T., Murata, K., Takemasa, I., Mizushima, T., Doki, Y., Mori, M., Yamamoto H4,5. Down-Regulation of microRNA-132 is Associated with Poor Prognosis of Colorectal Cancer. ***Ann. Surg. Oncol.,*** 23(Suppl 5):599-608, 2016.
16. Munakata, K., Uemura, M., Tanaka, S., Kawai, K., Kitahara, T., Miyo, M., Kano, Y., Nishikawa, S., Fukusumi, T., Takahashi, Y., Hata, T., Nishimura, J., Takemasa, I., Mizushima, T., Ikenaga, M., Kato, T., Murata, K., Carethers, JM., Yamamoto, H., Doki, Y., Mori, M. Cancer Stem-like Properties in Colorectal Cancer Cells with Low Proteasome Activity. ***Clin. Cancer Res.,*** 22(21):5277-5286, 2016.
17. Hara, H., Takahashi, T., Serada, S., Fujimoto, M., Ohkawara, T., Nakatsuka, R., Harada, E., Nishigaki, T., Takahashi, Y., Nojima, S., Miyazaki, Y., Makino, T., Kurokawa, Y., Yamasaki, M., Miyata, H., Nakajima, K., Takiguchi, S., Morii, E., Mori, M., Doki, Y., Naka, T. Overexpression of glypican-1 implicates poor prognosis and their chemoresistance in oesophageal squamous cell carcinoma. ***Br. J. Cancer.*** 115(1):66-75, 2016.
18. Miyo, M., Konno, M., Nishida, N. Sueda, T., Noguchi, K., Matsui, H., Colvin, H., Kawamoto, K., Koseki, J., Haraguchi, N., Nishimura, J., Hata, T., Gotoh, N., Mastuda, F., Saatoh, T., Mizushima, T., Shimizu, H., Doki, Y., Mori, M., Ishii, H. Metabolic adaptation to nutritional stress in human colorectal cancer. ***Sci. Rep.***, 6:38415, 2016.
19. Nakahara, Y., Yamasaki, M., Sawada, G., Miyazaki, Y., Makino, T., Takahashi, T., Kurokawa, Y., Nakajima, K., Takiguchi, S., Mimori, K., Mori, M., Doki, Y. Downregulation of SIRT4 Expression Is Associated with Poor Prognosis in Esophageal Squamous Cell Carcinoma. ***Oncology.***, 90(6):347-355, 2016.

20. Sakamoto, T., Kobayashi, S., Yamada, D., Nagano, H., Tomokuni, A., Tomimaru, Y., Noda, T., Gotoh, K., Asaoka, T., Wada, H., Kawamoto, K., Marubashi, S., Eguchi, H., Doki, Y., Mori, M. A Histone Deacetylase Inhibitor Suppresses Epithelial-Mesenchymal Transition and Attenuates Chemoresistance in Biliary Tract Cancer. ***PLoS One.*** 11(1):e0145985, 2016.
21. Ueda, M., Iguchi, T., Masuda, T., Nakahara, Y., Hirata, H., Uchi, R., Niida, A., Momose, K., Sakimura, S., Chiba, K., Eguchi, H., Ito, S., Sugimachi, K., Yamasaki, M., Suzuki, Y., Miyano, S., Doki, Y., Mori, M., Mimori, K. Somatic mutations in plasma cell-free DNA are diagnostic markers for esophageal squamous cell carcinoma recurrence. ***Oncotarget.,*** 7(38):62280-62291, 2016.
22. Wada, N., Kurokawa, Y., Takahashi, T., Hamakawa, T., Hirota, S., Naka, T., Miyazaki, Y., Makino, T., Yamasaki, M., Nakajima, K., Takiguchi, S., Mori, M., Doki, Y. Detecting Secondary C-KIT Mutations in the Peripheral Blood of Patients with Imatinib-Resistant Gastrointestinal Stromal Tumor. ***Oncology.,*** 90(2):112-117, 2016.
23. Komatsu, H., Iguchi, T., Masuda, T., Ueda, M., Kidogami, S., Ogawa, Y., Nambara, S., Sato, K., Hu, Q., Saito, T., Hirata, H., Sakimura, S., Uchi, R., Hayashi, N., Ito, S., Eguchi, H., Sugimachi, K., Eguchi, H., Doki, Y., Mori, M., Mimori, K. HOXB7 Expression is a Novel Biomarker for Long-term Prognosis After Resection of Hepatocellular Carcinoma. ***Anticancer. Res.,*** 36(6):2767-2773, 2016.
24. Komatsu, H., Iguchi, T., Ueda, M., Nambara, S., Saito, T., Hirata, H., Sakimura, S., Takano, Y., Uchi, R., Shinden, Y., Eguchi, H., Masuda, T., Sugimachi, K., Eguchi, H., Doki, Y., Mori, M., Mimori, K. Clinical and biological significance of transcription termination factor, RNA polymerase I in human liver hepatocellular carcinoma. ***Oncol, Rep.,*** 35(4):2073-2080,2016
25. Yamaguchi, T., Sato, H., Kato-Itoh, M., Goto, T., Hara, H., Sanbo, M., Mizuno, N., Kobayashi, T., Yanagida, A., Umino, A., Ota, Y., Hamanaka, S., Masaki, H., Rashid, ST., Hirabayashi, M., Nakauchi, H. Interspecies organogenesis generates autologous functional islets. 542(7640):191-196, ***Nature.***, 2017.
26. Tajima, Y., Ito, K., Umino, A., Wilkinson, AC., Nakauchi, H., Yamazaki, S. Continuous cell supply from Krt7-expressing hematopoietic stem cells during native hematopoiesis revealed by targeted in vivo gene transfer method. ***Sci Rep.,*** 7:40684, 2017.
27. Itakura, G., Kawabata, S., Ando, M., Nishiyama, Y., Sugai, K., Ozaki, M., Iida, T., Ookubo, T., Kojima, K., Kashiwagi, R., Yasutake, K., Nakauchi, H., Miyoshi, H., Nagoshi, N., Kohyama, J., Iwanami, A., Matsumoto, M., Nakamura, M., Okano, H. Fail-Safe System against Potential Tumorigenicity after Transplantation of iPSC Derivatives. 8(3):673-684, ***Stem, Cell, Reports.,*** 2017.
28. Ishida, T., Suzuki, S., Lai, CY., Yamazaki, S., Kakuta, S., Iwakura, Y., Nojima, M., Takeuchi, Y., Higashihara, M., Nakauchi, H., Otsu, M. Pre-Transplantation Blockade of TNF-α-Mediated Oxygen Species Accumulation Protects Hematopoietic Stem Cells. ***Stem, Cells.,*** 35(4):989-1002, 2017.
29. Ieyasu, A., Ishida, R., Kimura, T., Morita, M., Wilkinson, AC., Sudo, K., Nishimura, T., Ohehara, J., Tajima, Y., Lai, CY., Otsu, M., Nakamura, Y., Ema, H., Nakauchi, H., Yamazaki, S. An All-Recombinant Protein-Based Culture System Specifically Identifies Hematopoietic Stem Cell Maintenance Factors. ***Stem, Cell, Reports.,*** 8(3):500-508, 2017.
30. Ando, M., Nakauchi, H. 'Off-the-shelf' immunotherapy with iPSC-derived rejuvenated cytotoxic T lymphocytes. ***Exp, Hematol.,*** 47:2-12, 2017.

31. Tarusawa, E., Sanbo, M., Okayama, A., Miyashita, T., Kitsukawa, T., Hirayama, T., Hirabayashi, T., Hasegawa, S., Kaneko, R., Toyoda, S., Kobayashi, T., Kato-Itoh, M., Nakauchi, H., Hirabayashi, M., Yagi, T., Yoshimura, Y. Establishment of high reciprocal connectivity between clonal cortical neurons is regulated by the Dnmt3b DNA methyltransferase and clustered protocadherins. ***BMC Biol.*** 14(1):103, 2016.
32. Koide, S., Oshima, M., Takubo, K., Yamazaki, S., Nitta, E., Saraya, A., Aoyama, K., Kato, Y., Miyagi, S., Nakajima-Takagi, Y., Chiba, T., Matsui, H., Arai, F., Suzuki, Y., Kimura, H., Nakauchi, H., Suda, T., Shinkai, Y., Iwama, A. Setdb1 maintains hematopoietic stem and progenitor cells by restricting the ectopic activation of nonhematopoietic genes. ***Blood.,*** 128(5):638-649, 2016.
33. Kaneko, S., Kakinuma, S., Asahina, Y., Kamiya, A., Miyoshi, M., Tsunoda, T., Nitta, S., Asano, Y., Nagata, H., Otani, S., Kawai-Kitahata, F., Murakawa, M., Itsui, Y., Nakagawa, M., Azuma, S., Nakauchi, H., Nishitsuji, H., Ujino, S., Shimotohno, K., Iwamoto, M., Watashi, K., Wakita, T., Watanabe, M. Human induced pluripotent stem cell-derived hepatic cell lines as a new model for host interaction with hepatitis B virus. ***Sci Rep.,***6:29358, 2016.
34. Chen, JY., Miyanishi, M., Wang, SK., Yamazaki, S., Sinha, R., Kao, KS., Seita, J., Sahoo, D., Nakauchi, H., Weissman, IL. Hoxb5 marks long-term haematopoietic stem cells and reveals a homogenous perivascular niche. ***Nature.***, 530(7589):223-227, 2016.
35. Taya, Y., Ota, Y., Wilkinson, AC., Kanazawa, A., Watarai, H., Kasai, M., Nakauchi, H., Yamazaki, S. Depleting dietary valine permits nonmyeloablative mouse hematopoietic stem cell transplantation. ***Science.,*** 354(6316):1152-1155, 2016.
36. Naito, M., Azuma, R., Takemoto, H., Hori, M., Yoshinaga, N., Osawa, S., Kamegawa, R., Kim, H. -J., Ishii, T., Nishiyama, N., Miyata, K., Kataoka, K. Multilayered polyion complexes with dissolvable silica layer covered by controlling densities of cRGD-conjugated PEG chains for cancer-targeted siRNA delivery. ***J. Biomater. Sci. Polym. Ed.*** 2017. (in press)
37. Yi, Y., Kim, H. -J., Mi, P., Zheng, M., Takemoto, H., Toh, K., Kim, B. -S., Hayashi, K., Naito, M., Matsumoto, Y., Miyata, K., Kataoka, K. Targeted systemic delivery of siRNA to cervical cancer model using cyclic RGD-installed unimer polyion complex-assembled gold nanoparticles. ***J. Control. Release,*** 244 PartB: 247-256, 2016.
38. Chen, Q., Osada, K., Ge, Z., Uchida, S., Tockary, T. A., Dirisala, A., Matsui, A., Toh, K., Takeda, K. M., Liu, X., Nomoto, T., Ishii, T., Oba, M., Matsumoto, Y., Kataoka, K., Polyplex micelle installing intracellular self-processing functionalities without free catiomers for safe and efficient systemic gene therapy through tumor vasculature targeting, ***Biomaterials***, 113: 253-265, 2016.
39. Kinoh, H., Miura, Y., Chida, T., Liu, X., Mizuno, K., Fukushima, S., Morodomi, Y., Nishiyama, N., Cabral, H., Kataoka, K., Nanomedicines eradicating cancer stem-like cells in vivo by pH-triggered intracellular cooperative action of loaded drugs. ***ACS Nano,*** 10 (6): 5643-5655, 2016.
40. Wang, M., Miura, Y., Tsuchihashi, K., Miyano, K., Nagano, O., Yoshikawa, M., Tanabe, A., Makino, J., Mochida, Y., Nishiyama N., Saya, H., Cabral, H., Kataoka, K., Eradication of CD44-variant positive population in head and neck tumors through controlled intracellular navigation of cisplatin-loaded nanomedicines. ***J. Control. Release.,*** 230: 26-33, 2016.
41. Nishiyama, N., Matsumura, Y., Kataoka, K., Development of polymeric micelles for targeting intractable cancers. ***Cancer Sci.,*** 107 (7): 867-874, 2016.

42. Takahashi, RU., Prieto-Vila, M., Hironaka, A., Ochiya, T. The role of extracellularvesicle microRNAs in cancer biology. ***Clin. Chem. Lab. Med***., 55(5):648-656, 2017. (in press)
43. Yokoi, A., Yoshioka, Y., Yamamoto, Y., Ishikawa, M., Ikeda, SI., Kato, T., Kiyono, T., Takeshita, F., Kajiyama, H., Kikkawa, F., Ochiya, T. Malignant extracellular vesicles carrying MMP1 mRNA facilitate peritoneal dissemination in ovarian cancer. ***Nat. Commun.***, 8:14470, 2017.
44. Kosaka, N., Yoshioka, Y., Fujita, Y., Ochiya, T. Versatile roles of extracellular vesicles in cancer. ***J. Clin. Invest.,*** 126(4):1163-1172, 2016.
45. Sawada, G., Niida, A., Uchi, R., Hirata, H., Shimamura, T., Suzuki, Y., Shiraishi, Y., Chiba, K., Imoto, S., Takahashi, Y., Iwaya, T., Sudo, T., Hayashi, T., Takai, H., Kawasaki, Y., Matsukawa, T., Eguchi, H., Sugimachi, K., Tanaka, F., Suzuki, H., Yamamoto, K., Ishii, H., Shimizu, M., Yamazaki, H., Yamazaki, M., Tachimori, Y., Kajiyama, Y., Natsugoe, S., Fujita, H., Mafune, K., Tanaka, Y., Kelsell, DP., Scott, CA., Tsuji, S., Yachida, S., Shibata, T., Sugano, S., Doki, Y., Akiyama, T., Aburatani, H., Ogawa, S., Miyano, S., Mori, M., Mimori, K. Genomic landscape of esophageal squamous cell carcinoma in a japanese population. ***Gastroenterology***, 150(5):1171-11782, 2016.
46. Ogawa, H., Konno, M., Kawamoto, K., Nishida, N., Koseki, J., Mizushima, T., Satoh, T., Eguchi, H., Doki, Y., Mori, M., Ishii, H. Fetal hepatocyte derived culture medium elicits adipocyte differentiation to bile duct cell lineages in mouse. ***Biomedical, Reports***, 2016. (in Press)
47. Noguchi, K., Konno, M., Eguchi, H., Kawamoto, K., Mukai, R., Nishida, N., Koseki, J., Wada, H., Akita, H., Satoh, T., Marubashi, S., Nagano, H., Doki, Y., Mori, M., Ishii, H. c-Met affects gemcitabine resistance over carcinogenesis in a mouse model of pancreatic cancer. ***Oncol. Lett.***, 2016. (in Press)
48. Baek, SJ., Sato, K., Nishida, N., Koseki, J., Azuma, R., Kawamoto, K., Konno, M., Hayashi, K., Satoh, T., Doki, Y., Mori, M., Ishii, H., Ogawa, K. MicroRNA miR-374, a potential radiosensitizer for carbon ion beam radiotherapy. ***Oncol. Rep.***, 36(5):2946-2950, 2016.
49. Colvin, S. H., Nishida, N., Konno, M., Haraguchi, N., Takahashi, H., Nishimura, J., Hata, T., Kawamoto, K. Asai, A., Tsunekuni, K., Koseki, J., Mizushima, T., Satoh, T., Doki, Y., Mori, M., Ishii, H. Oncometabolite D-2-hydroxyglurate directly induces epithelial-mesenchymal transition and is associated with distant metastasis in colorectal cancer. ***Sci. Rep.***, 6:36289,2016.
50. Miyo, M., Konno, M., Nishida, N. Sueda, T., Noguchi, K., Matsui, H., Colvin, H., Kawamoto, K., Koseki, J., Haraguchi, N., Nishimura, J., Hata, T., Gotoh, N., Mastuda, F., Saatoh, T., Mizushima, T., Shimizu, H., Doki, Y., Mori, M., Ishii, H. Metabolic adaptation to nutritional stress in human colorectal cancer. ***Sci. Rep.***, 6:38415, 2016.
51. Yokobori, T., Suzuki, S., Miyazaki, T., Sohda, M., Sakai, M., Tanaka, N., Ozawa, D., Hara, K., Honjo, H., Altan, B., Fukuchi, M., Ishii, H., Iwatsuki, M., Sugimachi, K., Sudo, T., Iwaya, T., Nishida, N., Mimori, K., Kuwano, H., Mori, M. Intestinal epithelial culture under an air-liquid interface: a tool for studying human and mouse esophagi. ***Dis. Esophagus.,*** 29(7):843-847, 2016.
52. Hashimoto, K., *Yamada, Y., Semi, K., Yagi, M., Tanaka, A., Itakura, F., Aoki, H., Kunisada, T., Woltjen, K., Haga, H., Sakai, Y., Yamamoto, T., Yamada, Y. Cellular context-dependent consequences of Apc mutations on gene regulation and cellular behavior. ***Proc. Natl. Acad. Sci. U. S. A.,*** 114(4):758-763, 2017.
53. Taguchi, J., *Yamada, Y. Unveiling the Role of Senescence-Induced Cellular Plasticity. ***Cell Stem Cell.***, 20(3):293-294, 2017.

54. Komura, S., Semi, K., Itakura, F., Shibata, H., Ohno, T., Hotta, A., Woltjen, K., Yamamoto, T., Akiyama, H., *Yamada, Y. An EWS-FLI1-Induced Osteosarcoma Model Unveiled a Crucial Role of Impaired Osteogenic Differentiation on Osteosarcoma Development. ***Stem Cell Reports.,*** 12;6(4):592-606, 2016.

（2）学会・シンポジウム等における口頭・ポスター発表

1. 未来へつなぐ消化器病学―消化器外科の立場から―, 特別発言, 森正樹, 京王プラザホテル, 第102回日本消化器病学会総会, 2016/4/21～23, 国内.
2. JSGS-SSO International Symposium2016, 司会, Mori M, Seto Y, あわぎんホール, 第71回日本消化器外科学会総会, 2016/7/14～16, 国内.
3. 消化器癌領域における指針の医療研究開発, 座長, 森正樹、石岡千加史, パシフィコ横浜, 第75回日本癌学会学術総会, 2016/10/6～8, 国内.
4. リキッドバイオプシー　最近の動向, モーニングレクチャー, 森正樹, パシフィコ横浜, 第75回日本癌学会学術総会, 2016/10/6～8, 国内.
5. Novel cancer immunotherapy utilizing iPS cell technology,口頭, Nakauchi, H., Siebel Stem Cell Symposium, Stanford, CA. 2016/1/20, 国外.
6. From Stem Cells to Organs: Exploiting the organ niche for interspecific organogenesis,口頭, Nakauchi, H., “Advances in Organogenesis and Tissue Engineering Symposia” at John Hopkins University, Baltimore, Maryland. 2016/5/25, 国外.
7. Induced pluripotent stem cell-derived rejuvenated T-cell therapy with suicide gene-based safeguard system, ポスター, Ando, M., Nishimura, T., Yamazaki, S, Yamaguchi, Tomoyuki, Brenner, Malcolm and Nakauchi, H., International Society for Stem Cell Research (ISSCR), San Francisco, CA. 2016/6/22～25, 国外.
8. Use of iPSC technology for personalized medicine, 口頭, Nakauchi, H, EMBL-Stanford Conference: Personalized Health, Stanford, CA. 2016/11/2, 国外.
9. Stem Cell Niche for Cells and Organs, 口頭, Nakauchi, H, BMS Seminar Series UCSF, San Francisco, CA, 2016/11/9, 国外.
10. Inter-species Organogenesis: Generation of Mouse Islets in Rats for Long-term, Immunosuppression-free Glycemic Control in Diabetic Mice, 口頭, Nakauchi H, Olympic Valley, CA, Keystone Symposia, 2017/1/12, 国外.
11. Inhibition of lymph node metastasis and effective treatment of head and neck squamous cell carcinoma via cyclic-RGD mediated delivery of cisplatin-loaded micelles, ポスター, 宮野一樹、三浦裕、松本有、岩田要、佐谷秀行、宮園浩平、西山伸宏、H. Cabral、山岨達也、片岡一則, 東京大学駒場キャンパス、目黒区、東京, 第16回東京大学生命科学シンポジウム, 2016/4/23, 国内.
12. PEG 及びリガンド密度を制御可能な多層型 siRNA デリバリーキャリアの開発, ポスター, 内藤瑞、東亮太、武元宏泰、堀真緒、大澤重仁、H. -J. Kim、石井武彦、西山伸宏、宮田完二郎、片岡一則, 川崎生命科学・環境研究センター、川崎市、神奈川県, 遺伝子・デリバリー研究会第16回シンポジウム, 2016/5/16, 国内.

13. Smart targeted therapy by self-assembled supramolecular nanosystems, 基調講演, Kataoka, K., Montreal Convention Center, Montréal, Canada, 10th World Biomaterials Congress, 2016/05/19, 国外.
14. Polymeric micelles: From a rational design to clinical development, 総会講演, Kataoka, K., Centro de Investigacion Principe Felipe, Valencia, Spain, 11th International Symposium on Polymer Therapeutics (ISPT): From Laboratory to Clinical Practice, 2016/5/23, 国外.
15. リガンド導入 PEG 化金ナノ粒子のリガンド認識能向上を目指した表面設計, ポスター, 内藤瑞、石井武彦、宮田完二郎、安楽泰孝、Y. Yi、神保琢夫、高江誓詞、福里優、堀真緒、長田健介、片岡一則, 神戸国際会議場・展示場、神戸市、兵庫県, 第 65 回高分子学会年次大会, 2016/5/25, 国内.
16. 環状 RGD ペプチドを修飾した白金制がん剤内包ミセルのがん幹細胞治療への応用, ポスター, 持田祐希、M. Wang、H. Cabral、三浦裕、西山伸宏、片岡一則, 神戸国際会議場・展示場、神戸市、兵庫県, 第 65 回高分子学会年次大会, 2016/5/25, 国内.
17. リガンド密度を制御可能な有機･無機ハイブリッド多層型 siRNA デリバリーキャリアの開発, 口頭, 内藤瑞、東亮太、武元宏泰、堀真緒、大澤重仁、H. -J. Kim、石井武彦、西山伸宏、宮田完二郎、片岡一則, グランシップ(静岡県コンベンションアーツセンター)、静岡市、静岡県, 第 32 回 DDS 学会学術大会, 2016/6/30, 国内.
18. 難治性頭頸部扁平上皮癌に対するリガンド搭載シスプラチンミセルによる治療戦略, ポスター, 宮野一樹、三浦裕、松本有、岩田要、佐谷秀行、宮園浩平、西山伸宏、H. Cabral、山岨達也、片岡一則, グランシップ(静岡県コンベンションアーツセンター)、静岡市、静岡県, 第 32 回 DDS 学会学術大会, 2016/6/30, 国内.
19. Self-assembled supramolecular nanosystems for smart targeted therapy of intractable diseases, 総会講演, Kataoka, K., Harbin Engineering University, Harbin, China, International Symposium on Polymer and Related Materials, 2016/7/10, 国外.
20. Self-assembled supramolecular nanosystems for smart targeted therapy of intractable diseases, 総会講演, Kataoka, K., Sungkyunkwan University, Seoul, Korea, BICS Opening Symposium, 2016/8/31, 国外.
21. Drug and gene delivery by self-assembled supramolecular nanosystems, 特別講演, Kataoka, K., Fullon Hotel Tamsui Fishermen's Wharf, New Taipei City, Taiwan, 2016 Tissue Engineering and Regenerative Medicine International Society- Asia Pacific Meeting (TERMIS-AP 2016), 2016/9/05, 国外.
22. PEG 及びリガンド密度のコントロールが可能な有機無機ハイブリッドナノ粒子の機能評価, ポスター, 内藤瑞、武元宏泰、H. -J. Kim、堀真緒、大澤重仁、西山伸宏、宮田完二郎、片岡一則, 神奈川大学横浜キャンパス、横浜市、神奈川県, 第 65 回高分子討論会, 2016/9/15, 国内.
23. 環状 RGD ペプチドを修飾した白金制がん剤内包高分子ミセルを用いたリンパ節転移／治療抵抗性がんの治療, 口頭, 持田祐希、H. Cabral、牧野惇、三浦裕、M. Wang、西山伸宏、片岡一則, 神奈川大学横浜キャンパス、横浜市、神奈川県, 第 65 回高分子討論会, 2016/9/16, 国内.
24. Self-assembled supramolecular nanosystems for smart targeted therapy of intractable diseases, 総会講演, Kataoka, K., Hana Square, Korea University, Seoul, Korea, The First International Society for Nanomedicine Congress (1st ISNM), 2016/9/29, 国外.
25. 夢を形に：ナノテクノロジーで創る体内病院～あらゆる微小空間で生体機能をコントロールする革新技術の創製～, 招待講演, 片岡一則, 日本工業倶楽部、千代田区、東京都, 公益財団法人服部報公会 第 86 回設立記念会, 2016/10/07, 国内.

26. Self-assembled supramolecular nanosystems for smart targeted therapy of intractable diseases, 総会講演, Kataoka, K., CaixaForum de Tarragona, Tarragona, Spain, ICREA Conference on Functional Nanocontainers, 2016/10/18, 国外.
27. Self-assembled supramolecular nanosystems for targeting therapy of intractable diseases, 総会講演, Kataoka, K., Melbourne Convention Centre, Melbourne, Australia, 17th International Biotechnology Symposium and Exhibition(IBS 2016), 2016/10/27, 国外.
28. ナノテクノロジーが拓く未来医療 -体内病院の実現を目指して-, 招待講演, 西山伸宏, 一橋講堂 学術総合センター, 第 11 回 四大学連合文化講演会, 2016/10/30, 国内
29. リガンド密度をコントロール可能な有機・無機ハイブリッド多層型ナノ粒子の設計と機能評価, ポスター, 内藤瑞、武元宏泰、H. -J. Kim、堀真緒、大澤重仁、西山伸宏、宮田完二郎、片岡一則, 東京理科大学葛飾キャンパス、葛飾区、東京都, 日本核酸医薬学会第 2 回年会, 2016/11/16, 国内.
30. リガンド密度をコントロール可能な有機・無機ハイブリッド型 siRNA 内包ナノ粒子の設計と機能評価, ポスター, 内藤瑞、武元宏泰、H. -J. Kim、堀真緒、大澤重仁、西山伸宏、宮田完二郎、片岡一則, 福岡国際会議場、福岡市、福岡県, 日本バイオマテリアル学会 シンポジウム 2016(第 38 回), 2016/11/22, 国内.
31. Novel glutamine-based polymeric ligand for transporter-mediated tumor targeting, Yamada, N., Honda Y., Takemoto, H., Nomoto, T., Matsui, M., Tomoda, K., Nishiyama, N., Ito International Center, The University of Tokyo, 3rd International Conference on Biomaterials Science in Tokyo (ICBS2016), 2016/11/28, 国内
32. pH-Activatable targeted nanomedicine eradicates orthotopic mesothelioma bearing recalcitrant cancer stem cell sub-population, ポスター, Kinoh, H., Miura, Y., Fukushima, S., Cabral, H., Kataoka, K., Ito Hall located at The University of Tokyo, Tokyo, Japan, 3rd Internatioal Conference on Biomaterials Science in Tokyo(ICBS2016), 2016/11/28, 国外.
33. Effective treatment of locally advanced head and neck squamous cell carcinoma bearing cancer stem-like cells by cRGD peptide-installed cisplatin-loaded micelles, ポスター, Miyano, K., Cabral, H., Miura, Y., Matsumoto, Y., Kinoh, H., Nishiyama, N., Yamasoba, T., Kataoka, K., Ito Hall located at The University of Tokyo, Tokyo, Japan, 3rd Internatioal Conference on Biomaterials Science in Tokyo(ICBS2016), 2016/11/28, 国外.
34. Supramolecular nanosystems for smart diagnosis and therapy of intractable diseases, 総会基調講演, Kataoka, K., Ito Hall located at The University of Tokyo, Tokyo, Japan, 3rd Internatioal Conference on Biomaterials Science in Tokyo(ICBS2016), 2016/11/30, 国外.
35. Nanomedicine strategies for enhancing efficacy against head and neck squamous cell carcinoma bearing cancer stem-like cells, ポスター, Cabral, H., Miyano, K., Wang, M., Miura, Y., Matsumoto, Y., Kinoh, H., Nishiyama, N., Yamasoba, T., Kataoka, K., Swiss Federal Institute of Technology(EPFL), Lausanne, Switzerland, Frontiers2016 - Joint Symposium of the EPFL and the University of Tokyo, 2016/12/06, 国外.
36. Development of supramolecular nanodevices for cancer diagnostics and therapy, 招待講演, Nishiyama, N., KIST, Korea, The Korean Academy of Science and Technology (KAST) Symposium for Young Scientists in Drug Delivery: Redirecting the Research Field, 2016/12/08, 国外.

37. Development of staurosporine/epirubicin-loaded polymeric micelles as a robust in vivo therapy against differentiated cells and cancer stem-like cells, ポスター, Zhang, J., Kinoh, H., Chida, T., Liu, X., Miura, Y., Cabral, H., Kataoka, K., Fukuoka International Confress Center, Fukuoka, The 11th SPSJ International Polymer Conference (IPC2016), 2016/12/14, 国外.
38. ユニットPIC/金ナノ粒子ハイブリッドナノキャリアによるがん標的siRNAデリバリー / Targeted hybrid nanocarriers fabricated from unit polyion complexes and gold nanoparticle for systemic siRNA delivery to solid tumors, 口頭, 宮田完二郎、内藤瑞、Y. Yi, H. -J. Kim, 片岡一則, 横浜市開港記念会館、横浜市、神奈川県, 第 26 回日本 MRS 年次大会, 2016/12/19, 国内.
39. PEG およびリガンド密度をコントロールした多層型ナノ粒子の設計と機能評価 / Multi-layered polyion complexes with controlled densities of PEG and ligands for siRNA delivery, ポスター, 内藤瑞、武元宏泰、H. -J. Kim、堀真緒、大澤重仁、西山伸宏、宮田完二郎、片岡一則, 横浜市開港記念会館、横浜市、神奈川県, 第 26 回日本 MRS 年次大会, 2016/12/20, 国内.
40. Development of staurosporine/epirubicin-loaded micelles for cooperative synergistic treatment against cancer cells and cancer stem-like cells, ポスター, Zhang, J., Liu, X., Kinoh, H., Cabral, H., Kataoka, K., Kawasaki City Industrial Promotion Hall, Kawasaki, Kanagawa, 11th Annual Symposium on Nanobiotechnology 2017, 2017/2/27, 国外.
41. Supramolecular nanosystems for smart diagnosis and therapy of intractable diseases, 総会講演, K. Kataoka, Nihon University Tsudanuma Campus, Chiba, Japan, 11th International Gel Symposium, Japan (GelSympo2017), 2017/3/08, 国外.
42. Nishimori, T., Yamada, N., Takemoto, H., Suina K., Yamasaki, J., Nomoto, T., Matsui, M., Tomoda, K., Nagano, O., Saya, H., Nishiyama, N., Development of intravenously injectable sulfasalazine derivatives to treat stem-like cancer cells, Kyoto Research Park, Buzz Hall, International Symposium on Drug Delivery and Pharmaceutical Sciences: Beyond the History (ISDDPS), 2017/3/9, 国内
43. A new paradigm in cancer pathogenesis, diagnosis and therapy, 座長, 落谷孝広、稲澤譲治, パシフィコ横浜, 第 75 回日本癌学会学術総会, 2016/10/6, 国内.
44. がん進展におけるエクソソームの役割, 演者, 落谷孝広, パシフィコ横浜, 第 75 回日本癌学会学術総会, 2016/10/6, 国内.
45. 大腸癌の飢餓ストレスに適応した代謝変化, Japanese Oral Sessions, 今野雅允、三代雅明、西田尚弘、川本弘一、小関準、土岐祐一郎、森正樹、石井秀始. パシフィコ横浜, 第 75 回日本癌学会学術総会, 2016/10/8, 国内.
46. NEW STRATEGY FOR OVERCOMING MULTIFACETED THERAPY-RESISTANT CANCER STEM CELLS, スピーカー, Ishii, H., パレスホテル東京, 第 47 回高松宮妃癌研究基金国際シンポジウム, 2016/11/9, 国内.
47. Overcoming therapy-resistant cancer stem cells, 口演, Ishii, H., DoubleTree By Hilton Hotel Orlando Airport, 15th World Congress on CANCER THERAPY, BIOMARKER ＆CLINCAL RESEARCH, 2016/12/5, 国外.
48. 多能性幹細胞の種差に関わる内在性因子, シンポジウム, 石井秀始、今野雅允, 仙台国際センター, 第 16 回日本再生医療学会総会, 2017/3/9, 国内.
49. DISSECTING CANCER BIOLOGY WITH iPSC TECHNOLOGY, Yamada, Y., The 41st NAITO Conference, 2016/7/7, 国内.

50. Dissecting the cancer biology with iPS cell technology, Yamada, Y., The 9th Guangzhou International Conference on Stem Cell and Regenerative Medicine, Guangzhou, 2016/12/21, 国外.

（3）「国民との科学・技術対話社会」に対する取り組み

1. キングスカイフロント夏の科学イベントにおける小中学生を対象とした体験学習の提供（イベント名 : ナノマシーンを体験しよう！）, 片岡一則, ナノ医療イノベーションセンター, 2016/8/4, 国内.
2. 川崎市立川崎高等学校付属中学校の生徒に対する体験学習, 片岡一則, ナノ医療イノベーションセンター, 2017/3/9, 国内.
3. iPS 細胞作製技術を用いたがんエピゲノム研究, 山田泰広, 名古屋市立大学オープンカレッジ, 2016/11/18, 国内.
4. iPS 細胞を使ってがんを知る, 山田泰広, 日本がん分子標的治療学会学術集会 20 回記念 特別企画 市民公開講座, 2016/6/1, 国内.

（4）特許出願

東京大学

1. 特願 2016-22720 号

（報告様式４）

【課題管理番号 16ck0106022h0103】

平成　29　年　4　月　28　日

# 平 成 28 年 度　委 託 研 究 開 発 成 果 報 告 書

## I.　基本情報

事　業　名：（日本語）革新的がん医療実用化研究事業
（英　語）Practical Research for Innovative Cancer Control

研究開発課題名：（日本語）固形がん幹細胞を標的とした革新的治療法の開発に関する研究
（英　語）Research on development of innovative therapeutic methods targeting solid cancer stem cells

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実 施 期 間：平成　28　年　4　月　1　日　～　平成　29　年　3　月　1　日

分担研究開発課題名：（日本語）難治性消化器癌幹細胞のCD44v経路等を標的とした治療戦略の開発
（英　語）Development of a therapeutic strategy targeting CD44v pathway in refractory gastrointestinal cancer stem cells

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## II. 成果の概要（総括研究報告）

研究開発代表者：国立大学法人大阪大学・大学院医学系研究科・森正樹の総括研究報告を参照。

## III. 成果の外部への発表

（１）学会誌・雑誌等における論文一覧（国内誌　　0　件、国際誌　6　件）

1. Sosulski A, Horn H, Zhang L, Coletti C, Vathipadiekal V, Castro CM, Birrer MJ, Nagano O, Saya H, Lage K, Donahoe PK, Pépin D. CD44 Splice Variant v8-10 as a Marker of Serous Ovarian Cancer Prognosis. *PLoS One.2016, 11:e0156595.*
2. Shitara K, Doi T, Nagano O, Imamura CK, Ozeki T, Ishii Y, Tsuchihashi K, Takahashi S, Nakajima TE, Hironaka S, Fukutani M, Hasegawa H, Nomura S, Sato A, Einaga Y, Kuwata T, Saya H, Ohtsu A. Dose-escalation study for the targeting of CD44v+ cancer stem cells by sulfasalazine in patients with advanced gastric cancer (EPOC1205). *Gastric Cancer,* 2017, 20:341-349.
3. Takayama T, Kubo T, Morikawa A, Morita T, Nagano O, Saya H. Potential of sulfasalazine as a therapeutic sensitizer for CD44 splice variant 9-positive urogenital cancer. *Med Oncol.* 2016, 33, 45.
4. Wang M, Miura Y, Tsuchihashi K, Miyano K, Nagano O, Yoshikawa M, Tanabe A, Makino J, Mochida Y, Nishiyama N, Saya H, Cabral H, Kataoka K. Eradication of CD44-variant positive population in head and neck tumors through controlled intracellular navigation of cisplatin-loaded nanomedicines. *J Control Release.* 2016, 31:26-33.
5. Tsuchihashi K, Okazaki S, Ohmura M, Ishikawa M, Sampetrean O, Onishi N, Wakimoto H, Yoshikawa M, Seishima R, Iwasaki Y, Morikawa T, Abe S, Takao A, Shimizu M, Masuko T, Nagane M, Furnari FB, Akiyama T, Suematsu M, Baba E, Akashi K, Saya H, Nagano O. The EGF Receptor Promotes the Malignant Potential of Glioma by Regulating Amino Acid Transport System xc(-).Cancer Res. 2016, 76, 2954-63.
6. Seishima R, Okabayashi K, Nagano O, Hasegawa H, Tsuruta M, Shimoda M, Kameyama K, Saya H, Kitagawa Y. Sulfasalazine, a therapeutic agent for ulcerative colitis, inhibits the growth of CD44v9+ cancer stem cells in ulcerative colitis-related cancer. *Clin Res Hepatol Gastroenterol.* 2016, pii: S2210-7401(15)00288-0.

（２）学会・シンポジウム等における口頭・ポスター発表

1. Cancer therapy targeted to CD44v-xCT-mediated antioxidant system, 口頭, 永野修, 第 14 回日本臨床腫瘍学会学術総会, 2016/7/29, 国内.
2. Cancer treatment strategy targeting antioxidant system potentiated by CD44v-xCT in stem-like cancer cells, 口頭, 永野修, ALBERTA-JAPAN AGENCY FOR MEDICAL RESEARCH AND DEVELOPMENT (AMED) WORKSHOP FOR MEDICAL INNOVATION, 2017/2/24, 国外

（３）「国民との科学・技術対話社会」に対する取り組み

無し

（４）特許出願

【　該当：　有　・　(無)　】