樹、石川義弘

58. 蛍光色素材料及びその使用方法、2012-518218(2012/8/13)、江口晴樹、石川義弘

59. 薬、薬の誘導装置、体内動態検知器及び薬の設計方法、2012-185940(2012/8/24)、江口晴樹、石川義弘

60. 温熱治療用発熱半導体、PCT/JP2012/072612(2012/9/5)、江口晴樹、石川義弘

61. 自己磁性金属サレン錯体、PCT/JP2012/072794(2012/9/6)、江口晴樹、石川義弘

62. 新規抗がん剤解毒剤、PCT/JP2012/073900(2012/9/19)、江口晴樹、石川義弘

63. ラジカル生成抑制剤、PCT/JP2012/074938(2012/9/27)、江口晴樹、石川義弘

64. 磁性体、及び、磁性体の製造方法、2012-273951(2012/12/14)、江口晴樹、石川義弘

65. 薬、薬の誘導装置、体内動態検知器及び薬の設計方法、2012-246307(2012/12/13)、江口晴樹、石川義弘

66. 磁性薬の適正投与形態提供システム、2012-285824(2012/12/27)、江口晴樹、石川義弘

67. 磁性体、2013-020939(2013/02/05)、江口晴樹、石川義弘

68. 持続性磁性抗がん剤、2013-088559(2013/4/19)、江口晴樹、石川義弘

69. 薬、薬の誘導装置、磁気検出装置及び薬の設計方法、2013-200483(2013/9/26)江口晴樹、石川義弘

70. 鉄サレン錯体　、2014-006299(2014/1/16)、江口晴樹、石川義弘

71. 磁性薬誘導システム、PCT/JP2007/063011(2007/6/28)、江口晴樹、石川義弘、【日本特許登録済】特許 5378792 号

72. 金属サレン錯体化合物、PCT/JP2011/079630(2011/12/21)、江口晴樹、石川義弘

73. 自己磁性金属サレン錯体化合物、PCT/JP2012/051079(2012/1/19)、江口晴樹、石川義弘

74. 自己磁性化合物、PCT/JP2013/083519(2013/12/13)、江口晴樹、石川義弘

75. 自己磁性化合物の治療パターン、PCT/JP2013/084712(2013/12/26)、江口晴樹、石川義弘

76. Drug, Drug Guidance System, magnetic detection system, and drug design method、12/306,706(2012/08/21)、江口晴樹、石川義弘、【米国特許登録】US8,246,975 B2、(有機磁性体によ

る造影剤コンセプト特許)

1. 特許取得

総特許権利取得数１５件、その中日本１１件、米国３件、欧州１件。

日本１１件

① 評価対象化合物の活性度評価方法、江口晴樹、石川義弘、特許 4216277 号

② 抗がん剤、江口晴樹、石川義弘、谷垣勝己、特許 5167481 号

③ 磁性材料、磁性材料の誘導装置及び磁性材料の設計方法、江口晴樹、石川義弘、谷垣勝己、特許 4774536 号

④ MRI システム、江口晴樹、石川義弘、特許 4279335 号

⑤ 磁性を有する薬剤、薬剤の誘導システム、並びに磁気検出装置、江口晴樹、石川義弘、特許 5325427 号

⑥ 磁性体化合物のスクリーニング方法、江口晴樹、石川義弘、特許 5339777 号

⑦ 抗体又は抗原の定量方法、江口晴樹、石川義弘、特許 5408905 号

⑧ 鉄サレン錯体、江口晴樹、石川義弘、特許 4446489 号

⑨ 演算装置及び局所治療薬、江口晴樹、石川義弘、特許 4279330 号

⑩ 磁石および磁石を用いたドラッグデリバリー制御装置、特許登録 5372178 号

⑪ 磁性薬誘導システム江口晴樹、石川義弘、特許 5378792 号

米国２件

① ACTIVITY EVALUATION METHOD FOR EVALUATION TARGET COMPOUND、江口晴樹、石川義弘、US7,337,073B2

②Drug, Drug Guidance System, magnetic detection system, and drug design method、江口晴樹、石川義弘、US8,246,975 B2

欧州１件

① DRUG, DRUG GUIDANCE SYSTEM, MAGNETIC DETECTION SYSTEM, AND DRUG DESIGN METHOD、江口晴樹、石川義弘、EP1920370B1

2. 実用新案登録

該当なし

3.その他

1) Hitoshi Iizuka, Masanari Umemura, Itaru Satou, X, Feng, Haruki Eguchi, Yoshihiro Ishikawa, “Chemotherapeutic and drug delivery system with a novel nano-magnetic particle, EI236”, 第９０回日本生理学会、東京、２０１３年３月

【発表概要】

Chemotherapeutic and drug delivery system with a novel nano-magnetic particle, EI236

Hitoshi Iizuka, Masanari Umemura,Itaru Satou,Fu Senpou,Haruki Eguchi, and Yoshihiro Ishikawa,

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IHI Corporation

Purpose: We have developed a novel magnetic anticancer drug which is designated as EI236. Its ferromagnetic property contributes to new features. 1) Anti-cancer effect 2) drug delivery system (DDS), which is delivered by a magnet to the tumor, resulting in reduced side effects 3) MRI-contrast effect, which is visualized by MRI, evaluating the drug localization and concentration. Thus, the purpose of this study is to examine these features.

Method: The magnetic evaluation of EI236 was confirmed by Electro Spin Resonance (ESR). Anti-tumor effect of EI236 was evaluated by MTT and TUNEL assays in mouse melanoma cells. To examine the anti-cancer effect and magnetic controlled delivery in vivo, we used a mouse model of melanoma grafted on tail. Mice were dived into 3 groups; 1) control group 2) intravenous EI236 injection group 3) intravenous EI236 injection + electromagnet (DDS) group. Furthermore the tumor regression and MRI-contrast effect of EI236 were measured by Magnetic Resonance Imaging (MRI).

Result: EI236 decreased the cell proliferation and increased apoptosis in MTT and TUNEL assays.EI236 showed the magnetism at room temperature by ESR. We confirmed that application of a magnet enhanced the anti-cancer effect of EI236 in vitro and in vivo. These findings demonstrated that EI236 exhibited anti-cancer effect and DDS.

Conclusion: Our findings suggest that EI236 can serve as a novel magnetic anticancer drug and will assist us in developing a novel and simultaneous treatment strategy of chemotherapeutic and DDS.

2) X. Feng, M. Umemura, H. Fukumura, I. Sato, H. Eguchi and Y. Ishikawa, "New strategy of simultaneous hyperthermo-chemotherapy using a novel nano-magnetic anti-cancer drug", 第９０回日本生理学会、東京、２０１３年３月

【発表概要】

New strategy of simultaneous

hyperthermo-chemotherapy using a novel nano-magnetic anti-cancer drug

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Background: Hyperthermic therapy, which kills cancer cells by increasing the temperature up to 42℃, is attempted in the treatment of advanced or difficult cases. Despite of its effectiveness, it has not been widely used. One reason is that it is technically difficult to increase temperature only in a target cancer site. To address this issue, we have developed a new therapy using a novel nano-magnetic particle, i.e., EI236. EI236 exhibits not only anti-cancer effect, but also magnetism. Because of its magnetism, this drug can generate heat by itself when it is exposed to an alternating current magnetic field (ACMF).

Method: To examine the anti-cancer and hyperthermal effects of EI236 *in vivo*, we used a rabbit model of VX2 cells (rabbit osteosarcoma) grafted on legs. Rabbits were divided into five groups ; 1) no treatment group 2) intra-venous (iv.) EI236 injection group 3) intra-arterial (ia.) EI236 group 4) ia. Methotrexate (MTX) injection group, and 5) ia. EI236+ACMF group. The volume of tumor was measured daily, and then the samples were harvested and evaluated histologically by HE, Ki67, and TUNEL staining.

Results: When EI236 was injected via intra-arterial infusion, the efficacy was similar to that of MTX. When EI236 was injected and the tumor was exposed to ACMF for simultaneous chemotherapeutic and hyperthermal effects, it showed the greatest regression of tumor among all the groups examined. EI236 increased necrosis as determined by HE staining, and further increased it by ACMF. Similarly, EI236 decreased cell proliferation as determined by Ki67, and further decreased it by ACMF. Moreover EI236 increased apoptosis as determined by TUNEL staining, and further increased it by ACMF. These results indicated that the exposure of ACMF greatly enhanced the anti-cancer effect of EI236. Taken together, EI236 exhibited anti-cancer and thyperthermal effects.

Conclusion: These findings suggest that EI236 can assist us in developing a new strategy of simultaneous hyperthermo-chemotherapy in the future.

3) 江口晴樹、平田邦夫、黒谷玲子、福村英信、Singh DJ, 山本雅博、佐藤格、梅村将就、山本雅貴、佐藤衛、石川義弘、「強磁性ナノ粒子化合物を用いたドラッグ・デリバリ・システムと MRI 造影剤の研究」、第８６回日本薬理学会年会、福岡、２０１３年３月

【発表概要】

Controlled drug delivery and magnetic resonance imaging with intrinsic ferromagnetic nano-particle compound

Haruki Eguchi[1, 2 *], Kunio Hirata[3], Reiko Kurotani[4], Hidenobu Fukumura[6], David J. Singh[5], Masahiro Yamamoto[7], Itaru Sato[8], Masanari Umemura[2], Masaki Yamamoto[3], Mamoru Sato[9], and Yoshihiro Ishikawa[2 *,]

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First principles calculations, as the standard method of physics and chemistry to design functional materials, such as semiconductor, solar cell and so on, are applied to identifying the magnetic organic complex. We have found that this magnetic organic complex (EI236) exhibits anti-cancer property and, more important, possesses a magnetic property as it was readily attached to a magnet. EI236 exhibited intrinsic ferromagnetic behaviors from -268 celcius degree to 37 celsius degree and inhibited melanoma expansion in mouse tails when delivered to the melanoma lesion using a commercially available magnet. The local accumulation of the compound, as induced by the magnet, was readily visualized by magnetic resonance imaging (MRI) in mice. (n=4) Thus, EI236 acted as both an anti-cancer drug and an MRI contrast, and had pharmacological effects that could be delivered in a controlled manner. The identification of such compounds can overcome the long-standing problems of controlled drug delivery by magnetic force and may dramatically alter our concept of pharmacotherapy in the future, i.e., drug-targeting using a magnet and drug-dosing using MRI.

4) 江口晴樹、平田邦夫、黒谷玲子、福村英信、SINGH David J、山本雅博、佐藤格、梅村将就、山本雅貴、佐藤衛、石川義弘、「抗がん作用を有する有機強磁性体を用いた化学療法、ドラッグ・デリバリ・システム」、日本薬学会第１３３年会、日本薬学学会、２０１３年３年

【発表概要】

抗がん作用を有する有機強磁性体を用いた化学療法、ドラッグ・デリバリ・システム

Haruki Eguchi[1, 2 *], Kunio Hirata[3], Reiko Kurotani[4], Hidenobu Fukumura[6], David J. Singh[5], Masahiro Yamamoto[7], Itaru Sato[8], Masanari Umemura[2], Masaki Yamamoto[3], Mamoru Sato[9], and Yoshihiro Ishikawa[2,]

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We have found that an organic based magnetic

compound (EI236) exhibits anti-cancer property and, more important, possesses a magnetic property as it was readily attached to a magnet. Identifying such the organic based magnetic compounds are determined by the first principles calculations based on structures obtained by X-ray crystallography analysis. EI236 exhibited intrinsic ferromagnetic behaviors from -268 celcius degree to 37 celsius degree and inhibited melanoma expansion in mouse tails when delivered to the melanoma lesion using a commercially available permanent magnet. The local accumulation of the compound, as induced by the magnet, was readily visualized by magnetic resonance imaging (MRI) in mice. Therefore, EI236 acted as both an anti-cancer drug and an MRI contrast, and had pharmacological effects that could be delivered in a controlled manner. The identification of such compounds can overcome the long-standing problems of controlled drug delivery by magnetic force and may dramatically alter our concept of pharmacotherapy in the future. Thus, target drug delivery, chemotherapy and MRI visual quantitation are no longer separated three therapies. EI236 realizes one therapy through targeted drug delivery, chemotherapy and MRI visual quantitation.

5) Haruki Eguchi, Kunio Hirata, Reiko Kurotani, Hidenobu Fukumura, David J. Singh, Masahiro Yamamoto, Itaru Sato, Masanori Umemura, Masaki Yamamoto, Yoji Nagashima, Yoshihiro Ishikawa, "Targeted drug delivery system and magnetic resonance imaging with intrinsic ferromagnetic nano-particle compound", American Association for Cancer Research Annual Meeting 2013, Washington DC, U.S.A., April 2013

【発表概要】

Targeted drug delivery system and magnetic resonance imaging with intrinsic ferromagnetic nano-particle compound

Haruki Eguchi[1, 2 *], Kunio Hirata[3], Reiko Kurotani[4], Hidenobu Fukumura[6], David J. Singh[5], Masahiro Yamamoto[7], Itaru Sato[8], Masanari Umemura[2], Masaki Yamamoto[3], Mamoru Sato[9], and Yoshihiro Ishikawa[2]

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First principles calculations based on structures obtained by X-ray crystallography analysis are applied to identifying the intrinsic ferromagnetic nano-particle compound. We have found that this organic based nano-particle compound (EI236) exhibits anti-cancer property and, more important, possesses a magnetic property as it was readily attached to a magnet. EI236 exhibited intrinsic ferromagnetic behaviors from -268 celcius degree to 37 celsius degree and inhibited melanoma expansion in mouse tails when delivered to the melanoma lesion using a commercially available magnet. The local accumulation of the compound, as induced by the magnet, was readily visualized by magnetic resonance imaging (MRI) in mice. (n=4) Thus, EI236 acted as both an anti-cancer drug and an MRI contrast, and had pharmacological effects that could be delivered in a controlled manner. The identification of such compounds can overcome the long-standing problems of controlled drug delivery by magnetic force and may dramatically alter our concept of pharmacotherapy in the future, i.e., drug-targeting using a magnet and drug-dosing using MRI.

6) Umemura M, Fukumura H, Sato I, Feng X, Hitoshi Izuka, Eguchi H, Ishikawa Y, "Application of a novel nano-manetic anti-cancer drug to hyperthermia", American Association for Cancer Research Annual Meeting 2013, Washington DC, U.S.A., April 2013

【発表概要】

Application of a novel nano-magnetic anti-cancer drug to hyperthermia

Umemura M[1], Fukumura H[1], Sato I[1], Feng X[1], Hitoshi Izuka[1], Eguchi H[2],Ishikawa Y[1]

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Background: Hyperthermic therapy is a type of cancer treatment in which body tissue is exposed to high temperature (up to 113° F). Despite its effectiveness, it has not been widely used. One reason is that it is technically difficult to increase high temperature only in a target cancer site. To address this issue, we have developed a novel nano-magnetic particle, i.e., EI236. EI236 exhibits not only anti-cancer effect, but also ferromagnetic property. Because of its magnetism, this drug can generate heat by itself when it is exposed to an alternating current magnetic field (ACMF).

Method: We established a rabbit model of VX2 cells (rabbit osteosarcoma) grafted on legs to examine the anti-cancer and hyperthermal effects of EI236 *in vivo.* Rabbits (n=4 for each group) were divided into five groups ; 1) no treatment group 2) intra-venous (iv.) EI236 injection group 3) intra-arterial (ia.) EI236 group 4) ia. Methotrexate (MTX) injection group, and 5) ia. EI236+ACMF group. The volume of tumor was measured daily, and then the samples were harvested and evaluated histologically by HE, Ki67, and TUNEL staining.

Results: The effect of EI236 was similar to that of MTX when EI236 was injected via intra-arterial infusion. Via intra-arterial infusion was more effective than iva intra-venous infusion. When EI236 was injected and the tumor was exposed to ACMF for simultaneous chemotherapeutic and hyperthermal effects, it showed the greatest regression of tumor among all the groups examined. EI236 significantly increased necrosis as determined by HE staining, and further increased it by ACMF. Similarly, EI236 decreased cell proliferation as determined by Ki67, and further decreased it by ACMF. Moreover EI236 increased apoptosis as determined by TUNEL staining, and further increased it by ACMF. These results demonstrated that the exposure of ACMF greatly enhanced the anti-cancer effect of EI236. Taken together, EI236 exhibited simultaneous effects of anti-cancer and thyperthermia.

Conclusion: These results demonstrate that EI236 can provide us in developing a new strategy of simultaneous hyperthermo-chemotherapy in the future.

7) Itaru Sato, Kenji Mitsudo, Masanori Umemura, Xianfeng Feng, Jun-ichi Baba, Hideyuki Nakashima, Mitomu Kioi, Haruki Eguchi, Yoshihiro Ishikawa and Iwai Tohnai, "Novel thermo-chemotherapy using a new magnetic anti-cancer drug", American Association for Cancer Research Annual Meeting 2013, Washington DC, U.S.A.,

April 2013

【発表概要】

Novel thermo-chemotherapy using a new magnetic anti-cancer drug

Itaru Sato[1], Kenji Mitsudo[1], Masanari Umemura[2],Xianfeng Feng[2],Jun-ichi Baba[1], Hideyuki Nakashima[1], Mitomu Kioi[1], Haruki Eguchi[3],Yoshihiro Ishikawa[2] and Iwai Tohnai[1]

[1] Department of Oral and Maxillofacial surgery , Yokohama City University-School of Medicine

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[3]IHI corporation

Background

Radical surgery for patients with head and neck cancer can cause dysfunctions such as dysphagia, dysarthria, and mastication disorder as well as decrease quality of life. Here, a new magnetic anticancer drug (EI236) was developed giving an anti-cancer effect.

EI236 is a novel magnetic nanoparticle.EI236 has three characters; 1) anti-cancer effect, 2)Drug Delivery System (DDS) and 3) hypothermic effect in an alternating current magnetic field (ACMF). EI236 will be a new contrast agent in magenetic resonance imaging (MRI). We evaluated the treatment efficacy of the anti-cancer effects of EI236 using rabbit's oral cancer cells in vitro and in vivo.

Methods

The anti-cancer effect of the EI236 was measured by MTT assay using VX2 cells were employed as a transplantable tumor in rabbits. We established rabbit's VX2 tongue cancer model. Rabbits were divided into 4 groups: control group, intravenous EI236 injection (5mg/kg×7days) (i.v. group), intravenous EI236 + electromagnet (i.v. + DDS group), intravenous EI236 + electromagnet + alternating magnetic field (i.v. + DDS + HT group). The size of tumors was measured daily for 7 days. Rabbits were sacrificed after the completion of the experiment, and histopathological effects on the tongue tumor were evaluated.

Results

IC50 of VX2 cells treated with CDDP was about 7.5μM, and that of VX2 cells treated with EI236 was also about 7.5μM, indicating that EI236 had an antitumor effect equal to that of CDDP. i.v. + DDS group and the i.v. + DDS + HT group showed significant decrease in tumor volume compared with control group in rabbit VX2 tongue tumor model. HE staining analysis demonstrated significant

difference in the size of necrotic area among the 4 groups. In the control group, it was 15%. In the i.v. group, it was 28.8%. In the i.v.＋DDS group, it was 50%. Further, in the i.v. + DDS + HT group, the size of necrosis was greatest and was 63.8%. In particular, iv + DDS + HT group showed disappearance of the tumor cell nucleus in almost all fields.

Ki67 positive cells were also counted in 3,000 cells for each group, and positive cell ratio was determined. The median ratio of Ki67 index was 45.8% in the control group, 25.4% in the i.v. group, 18.8% in the i.v.＋DDS group, and 4.5% in the i.v. + DDS + HT group. These differences were statistically significant among four groups

Conclusion

The results in this study confirmed the effect of the novel nanoparticles, which was founded engineered approaches, as anti-cancer treatment. In particular, EI236 had anti-cancer effect with heat induction in alternating magnetic fluid. We demonstrated that EI236 is useful in a novel cancer therapy. We are optimizing to use EI236 clinically.

8) 梅村将就、江口晴樹、石川義弘、A novel nano-magnetic particle with cytotoxic and a novel technology of designing intrinsic ferromagnetism compound, 第７２回日本癌学会学術総会、横浜、2013年10月

【発表概要】

We previously reported a novel nano-magnetic particle with anti-cancer effect, EI236. Because of its ferromagnetism, it can be delivered by a magnet and visualized by magnetic resonance imaging (MRI). It also generates heat when exposed to an alternation current magnetic field (ACMF). We found the key structure which contributes this particle to ferromagnetism by X-ray crystallographic analysis. Thus, we succeeded in synthesizing the conventional anti-cancer drug with ferromagnetism, HHPS133. We evaluated its magnetism and anticancer effect. We measured its magnetism by a superconducting quantum interference device system. Proliferation was measured by the MTT assay. Apoptosis and cell cycle were measured by fluorescence activated cell sorting. T2-wighted images were recorded by MRI. We confirmed that it had ferromagnetic property. It suppressed proliferation and promoted apoptosis of breast cancer cells. It also accumulated G2/M phase. We visualized it by MRI. These results suggested that we

succeeded in synthesizing the conventional drug with ferromagnetic property. This new technology could make it possible to synthesize various commercial available drugs with ferromagnetic.

9) 岩井麻樹、梅村将就、佐藤格、永迫茜、FENG Xianfeng、星野雄二郎、井上誠一、青木伊知男、江口晴樹、石川義弘、A conventional anti-cancer drug designed artificially with ferromagnetic, EI2573M、第７２回日本癌学会学術総会、横浜、2013年10月

【発表概要】

We previously reported a novel nano-magnetic particle with anti-cancer effect, EI236. Because of its ferromagnetism, it can be delivered by a magnet and visualized by magnetic resonance imaging (MRI). It also generates heat when exposed to an alternation current magnetic field (ACMF). We found the key structure which contributes this particle to ferromagnetism by X-ray crystallographic analysis. Thus, we succeeded in synthesizing the conventional anti-cancer drug with ferromagnetism, EI2573M. We evaluated its magnetism and anticancer effect. We measured its magnetism by a superconducting quantum interference device system. Proliferation was measured by the MTT Assay. Cell Cycle was measured by fluorescence activated cell sorting. T2-weighted images were recorded by MRI. We confirmed that it had ferromagnetic property. It suppressed proliferation of breast c ancer cells and accumulated G2/M phase. We visualized it by MRI. These results suggested that we succeeded in converting the conventional drug to ferromagnetic property. This new technology could make it possible to convert various commercially available drugs to ferromagnetic.

10) 江口晴樹、石川義弘、抗がん作用を有する有機磁性体の開発、日本ハイパーサーミア学会　第３０回大会、横浜、2013年8月

【発表概要】

演題名:

抗がん作用を有する有機磁性体の開発

演題名英文表記:

Development of organic based magnetic compound with anti-cancer properties

○江口晴樹(株式会社IHI)、石川義弘（横浜市立大学）

演題本文:

【目的】

磁性体は従来、酸化鉄に代表される無機化

合物に限られていたが、最近では有機化合物の中にも存在することが発見された。そこで、有機化合物の一種である医薬品の磁性体化の可能性をコンピュータ解析で検討した。

【方法】IHI 独自の解析方法である量子論を用いた物質設計手法（第一原理計算）により、従来は知られていなかった磁性をもつ可能性の高い薬剤（EI236）を横浜市大医学部循環制御医学のもつ薬剤化合物ライブラリから見出すことに成功した。その後、EI236 の磁気特性を調べた結果、人間の体温を想定した 37℃においても磁性体特有の「磁場―磁化曲線」が得られ、磁性体であることを初めて発見し、同時に解析結果の正当性を裏付けた。また、通常の有機化合物の一部を改変し、有機磁性体となるような物質設計にも成功した。

【結果】

マウスに発生させた皮膚がんに対して、投与したEI236が磁場によって誘導できるかどうかの検討を行った。その結果、治療なしと比較して、抗がん剤投与では明らかながん組織の縮小が見られ、さらにがん組織において磁石で誘導をかけた群では、がんは大幅に縮小した。これは、磁場によりEI236 を患部に誘導できた、つまり、ドラッグ・デリバリ・システムとして機能したことを示す。

さらに、MRI 造影剤としても機能するかどうかを検討した。マウス尾静脈より EI236 を全身投与し、尻尾に永久磁石による磁場をかけてEI236を誘導し、MRIによる撮影を行ったところ、磁場誘導部位においてＥＩ236 の集積が確認できた。このことはEI236 が MRI 造影剤としても機能することを示す。

【結語】

有機磁性体 EI236 は、室温で強磁性の性質を保有し、かつ化合物自身が抗がん活性を有する。今後は、今後は様々なところで応用が始まっている三位一体型の抗がん剤（磁場誘導 DDS、MRI 診断薬、温熱治療）を用いて新しい抗がん治療を提案したい。

11）梅村将就、江口晴樹、佐藤格、FENG Xianfeng、岩井麻樹、來生　知、光藤健司、藤内祝、石川義弘、有機磁性体有機化合物を用いた画期的化学・温熱同時療法の新たなる展開、日本ハイパーサーミア学会　第３０回大会、横浜、2013 年 8 月

【発表概要】

新規磁性体有機化合物を用いた画期的化学・温熱同時療法の新たなる展開

梅村将就[1]，江口晴樹[2]，佐藤格[3]，馮 先鋒[1]，岩井麻樹[1]，來生　知[3]，光藤健司[3]，藤内祝[3]，石川義弘 1

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【目的】本学が行っている医工連携にて，

江戸時代の造船での起業を原点とする(株)IHI の持つ磁性体設計技術を医療転用し，抗がん作用を持つ新規磁性有機化合物を同定した。我々の目的はこの薬剤の持つ特徴を最大限に生かした新しい抗癌治療の開発である。一般に抗がん剤などの医薬品化合物は，有機化合物であるため磁性を持たないとされる。本薬剤は抗がん作用だけでなく，マグネタイトに匹敵する強磁性を有する。従来，様々な方法で薬剤の磁性化が試みられてきたが，体内での安定性の問題などにより，大きな展開には至っていない。一方，本薬剤はそれ自体に強磁性を有するため，生体内でも極めて高い安定性を示す。我々はこの磁性特性を医薬品化合物へ応用した。先行研究にて本薬剤は，磁性特性により磁場誘導，交流磁場印加による発熱効果，及びMRIにおける造影効果が得られることがわかっている。【方法】ヒト悪性中皮腫を中心に，様々ながん細胞を対象に本薬剤の効果を検討する。また，独自に開発した交流磁場発生装置を用いてがん細胞に対する温熱効果を評価した。【結果】悪性中皮腫において，本薬剤は強い抗がん効果を持つことがわかった。また，体外からの磁石による磁場誘導にて胸腔内で任意に本薬剤を集積できた。すなわち，磁石にて局所に薬剤濃度を高めることができ，副作用の軽減が期待できる。また，ヒト悪性中皮腫培養細胞にて，交流磁場印可による本薬剤の温熱効果により，薬剤単独投与よりも高い腫瘍殺傷効果持つことがわかった。【結語】磁場により薬剤を局所に集積したうえで，交流磁場を印可することで従来の温熱療法の課題であった局所選択的な加温が可能である。本薬剤の構造解析にて磁性に寄与する化学構造の詳細も明らかになり，臨床の場で広く使用されているある市販抗がん剤を磁性化することにも成功した。今後は抗がん剤だけでなく，臨床で使用されている様々な薬剤を磁性化し，ドラッグデリバリーや温熱効果などを同時に行う画期的な治療を開発していく。

12) 佐藤格、光藤健司、梅村将就、來生　知、中島英行、江口晴樹、石川義弘、藤内祝、抗がん作用を有する新規磁性微粒子を用いたハイパーサーミアへの応用、日本ハイパーサーミア学会　第３０回大会、横浜、2013年８月

【発表概要】

Development of new Thermochemotherapy with controlled drug delivery using a novel magnetic anti-cancer drug

抗がん作用を有する新規磁性微粒子を用いたハイパーサーミアへの応用

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【目的】口腔癌に対するハイパーサー ミアの一つとして磁性体を用いた組織内加温法の開発を行っている。IHI(株)がもつ金属材料技術及び磁性制御技術を医療転用し，抗がん作用を持つ新規磁性有機化合物(EI236)の同定に成功した。EI236は、永久磁石を用いることによって腫瘍への集積を可能とし、Drug Delivery System(DDS)による治療効果を実証した。さらに，磁性体であることから高周波磁場下において発熱作用を有しハイパーサーミアの効果も得られることがわかっている。今回われわれは家兎VX2細胞に対するEI236の抗腫瘍効果についての検討を行った。

【方法】VX2細胞株を用いて、EI236単独に比べ高周波磁場下にて発熱させ、温熱効果を加えることで抗腫瘍効果の増強を比較検討した。抗腫瘍効果は、FACSでアポトーシスを検出し判定を行った。また，動物実験（家兎VX2舌癌モデル）では、① コントロール群、② EI236単独連日静脈投与群（5mg/kg）③ EI236連日投与(5mg/kg)＋電磁石によるDDS④ EI236連日投与(5mg/kg)＋電磁石（DDS）＋ハイパーサーミア（HT）群の4群である。治療は7日間を1クールとし腫瘍径を連日測定し、腫瘍体積率と病理組織学的に抗腫瘍効果を判定した。

【結果】細胞実験より、EI236単独に比べ高周波磁場下でのEI236は、半分の濃度で同等以上の抗腫瘍効果を認めた。動物実験では、コントロール群と比較してEI236投与＋DDS群およびEI236投与＋DDS＋HT群では明らかな腫瘍縮小効果を認め、特にEI236投与＋DDS＋HT群では腫瘍の著明な抗腫瘍効果を認めた。病理組織学的所見においても、コントロール群と比較して有意に壊死率の増大を認めた。

【結語】EI236は抗腫瘍効果を有するだけでなくDDSおよびハイパーサーミアの併用が可能な新しい癌治療となることが示唆された。

13) 石川義弘、江口晴樹、温熱治療における新規磁性抗がん剤の役割日本ハイパーサーミア学会　第３０回大会、横浜、2013年8月

【発表概要】

第30回　日本ハイパーサーミア学会

石川義弘　　江口晴樹

抄録

温熱治療における新規磁性抗がん剤の役割

がん治療における温熱療法は半世紀以上の歴史を持ち、その有効性と安全性から幅広く世界で支持されてきた。近年ではマグネタイト粒子に様々な活性物質をリンクさせたミセル粒子も開発され、単なる温熱治療だけでなく、温熱を利用した薬剤の放出や画像診断など、これまでにない用途において活用されている。その多くは現段階では動物実験に留まるが、最近では、欧州において新規なる温熱療法が実用化され、大きな注目を集めている。既存のマグネタイト粒子に特殊コーテイングを施し、発熱特性を高めた粒子をがん局所に注入し、大型交流磁場発生装置で高熱を発生させ、がん組織の死滅を可能にする装置である。EU27カ国において脳腫瘍を対象として認可され、様々な医療機関での使用実績をもつ。現在米国を中心に、肝がん等に対する適応拡大を目的とした臨床試験が進んでいる。これらの技術は、マグネタイト粒子の磁性特性

を、どのように活用するかにおいて先進的であると考えられる。しかるに近年、産学連携および医工連携プログラムを通じて、(株)IHI 基盤技術研究所における材料設計技術の医療転用が行われ、これにより医薬品に磁性を付加する技術が開発された。これまで船舶やジェットエンジンの材料開発に使用されてきた手法である。本技術を用いることにより、これまでマグネタイト粒子に依存してきた磁性物質に新たな広がりが加わった。この広がりの一つが、新規磁性抗がん剤であり、強磁性を持つが、マグネタイト粒子の存在を必要としない。あるいは抗がん剤の分子自体が磁性を持つ。このため、マグネタイト粒子に起因した様々な問題を解決することが出来るため、温熱療法と抗がん治療の新しい治療法が可能となった。さらに抗がん剤自体が磁性を持つため、MRI での定量が可能である。このことは局所で発熱するだけでなく、がん組織への集積量を、画像によって定量できることを意味する。このような異分野技術を用いることにより、様々な新規磁性体物質が開発されており、今後の可能性について検証する。

14) 江口晴樹、黒谷玲子、福村英信、佐藤格、梅村将就、石川義弘、有機自己磁性化合物を用いた磁場誘導ドラッグ・デリバリ・システム、分子デリバリー研究会：物理と薬学のコラボレーション、東京、2013年10月

【発表概要】

有機自己磁性化合物を用いた磁場誘導ドラッグ・デリバリ・システム

江口晴樹[*1]、黒谷玲子[*2]、福村英信[*3]、佐藤格[*3]、梅村将就[*3]、石川義弘[*3]

Magnetic targeted drug delivery using an intrinsic organic based magnetic compound

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Abstract: We found an intrinsic organic based magnetic compound (EI236) that exhibits anti-cancer property and possesses a magnetic property as it was readily attached to a conventional permanent magnet. First principles calculations, such as the standard method of physics and chemistry to design functional materials, are applied to identifying the EI236 exhibited ferromagnetic behaviors at 37 ℃ and inhibited melanoma expansion in mouse tails when delivered to the melanoma lesion using a commercially available permanent magnet. The local accumulation of the compound, as induced by the magnet, was readily visualized by magnetic resonance imaging (MRI) in mice. Thus, this acted as both an anti-cancer drug and an MRI contrast, and had pharmacological effects that could be delivered in a controlled manner. The identification of such compounds may overcome the long-standing problems of controlled drug delivery by magnetic force and may dramatically alter our concept of pharmacotherapy in the future, i.e., drug-targeting using a magnet and drug-dosing using MRI.

Key Words : intrinsic organic based magnetic compound , first principles calculations, magnetic targeted drug

delivery, magnetic resonance imaging (MRI).

1. 緒　　言

電気を通す有機材料や水素のみを通過させる分離膜材料などの特殊な機能を持った材料の開発では、通常、構造予測と合成そして機能確認試験を繰り返すため、多大な時間と費用が必要になる。IHI ではこのような機能性材料の探索や改良を効率的に行うため、コンピュータを用いた計算を材料設計に応用する技術に取り組んできた。本報告では横浜市立大学と共同で、本技術を適用した磁性を有する有機化合化合物を材料の探索に適用した。見出した抗がん剤は、室温でも強磁性である有機自己磁性化合物である。マウスを用いた薬理実験の結果、磁場により薬剤を患部に集中させる「ドラッグ・デリバリ・システム」、さらにはＭＲＩの画像診断に有効な「造影剤」としても適用可能であることがわかった。

磁性体は従来、酸化鉄に代表される無機化合物に限られていたが、最近では有機化合物の中にも存在することが発見された（図１）。そこで、有機化合物の一種である医薬品の磁性体化の可能性をコンピュータ解析で検討した。

2. 方　　法

磁性体は従来、酸化鉄に代表される無機化合物に限られていたが、最近では有機化合物の中にも存在することが発見された。そこで、有機化合物の一種である医薬品の磁性体化の可能性をコンピュータ解析で検討した。本研究では、量子論を用いた物質設計手法（第一原理計算）により、従来は知られていなかった磁性をもつ可能性のある有機磁性体を横浜市立大学医学部循環制御医学のもつ薬剤化合物ライブラリを用いてスクリーニングをおこなった。

3. 結果および考察

3・1 解析と磁性の評価

計算を用いた材料の機能評価法では、物質を構成している複数個の原子について、その内部電子の回転挙動を詳しく解析する。磁性特性評価のアルゴリズムには独自の解析方法を考案して機能確認を行い、短期間で磁性を持つ可能性の高い薬剤を数個にまで絞り込んだ。次に絞り込んだ数個について磁気特性を調べた。その結果、その中の一つの化合物に磁性材料に特有の「磁場-磁化特性曲線」を保有することが明らかになり、それは有機自己磁性化合物であることを確認した。以下見出した本化合物を EI236 と呼称する。

3・2 有効性確認試験

これら薬剤の中の一つについて、医療応用に対する磁性の有効性を調べた。マウスの尻尾に発生させた皮膚がんに対して、投与した EI236 が磁場によって誘導できるかどうかの検討を行った。その結果、治療なしと比較して、抗がん剤投与では明らかながん組織の縮小が見られ、さらにがん組織において磁石で誘導をかけた群では、がんは大幅に縮小した。これは、磁場により EI236 を患部に誘導できた、つまり、ドラッグ・デリバリ・システムとして機能したことを示す。

さらに、MRI 造影剤としても機能するかどうかを検討した。マウス尾静脈より EI236 を全身投与し、尻尾に永久磁石による磁場をかけて EI236 を誘導し、MRI による撮影を行ったところ、磁場誘導部位において EI236 の集積が確認できた。このことは EI236 が MRI 造影剤としても機能することを示す。

4. 結　　論

有機自己磁性化合物 EI236 は、室温で強磁性の性質を保有し、かつ化合物自身が抗がん活性を有する。今後は、今後は様々なところで応用が広まるよう有機自己磁性化合物を用いた新しい抗がん治療を提案したい。

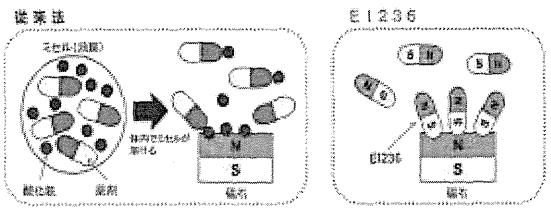

図１　従来法の磁性薬（左図）と本方法（EI236）の違い。

15) Feng Xiangfeng, Umemura Masanari, Sato Itaru, Miyajima Akiyoshi, Ohtake Makoto, Makino Ayako, Eguchi Haruki and Ishikawa Yoshihiro, Development of a new cancer-therapeutic method using a nano-magnetic particle for malignan t pleural mesothelioma、第 91 回日本生理学会大会、鹿児島、2014 年 3 月

【発表概要】

Development of a new cancer-therapeutic method for malignant pleural mesothelioma

Feng Xianfeng[1], Umemura Masanari[1], Sato Itaru[1], Ito Kayoko[1], Miyajima Akiyoshi[1], Ohtake Makoto[1], Makino Ayako[1],Eguchi Haruki[2],Ishikawa Yoshihiro[1]

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Background: Malignant pleural mesothelioma (MPM) is one of the worst poor-prognosis tumors of serosal surface, such as the pleura and the peritoneum. Depending on the condition of patient, age, time of diagnosis, and other factors, the survival time is from 4 to 12 months from onset of symptoms. However this tumor is rare once, its incidence is increasing in the world, as result of widespread exposure to asbesto. It is very difficult to diagnosis to this disease, if can, it is also difficult to cure because of lack of the established regimen for malignant mesothelioma. Therefore, we have developed a new hyperthermia therapy using a namo-magnetic particle, EI236, which we identified. EI236 exhibits not only anti-cancer effect but also ferromagnetism, which could generate heat power in an alternating current magnetic field (AMF).

Method and Results: We have experienced with use of EI236 for treating MPM cells. EI236 promoted reactive oxygen species (ROS) of MPM cells in a dose-dependent manner. We performed the electrophoresis of supercoiled plasmid

DNA in the presence of various concentrations of EI236 or cisplatin. The result showed that EI236 induced DNA nicking, which was similar to that of cisplatin. EI236 exhibited potent anti-cancer effect on several MPM cells in a dose-dependent manner by MTT assay. The anti-cancer effect of EI236 was greater than that of cisplatin. EI236 promoted apoptosis of various MPM cells, and further by exposed to AMF.

Conclusion: Our study show EI236 acts simultaneously as anti-cancer drug and hyperthermic effect in MPM cells, suggesting that EI236 can assist us in developing a new treatment method for malignant pleural mesothelioma in the future.

16) Masanari Umemura, Ayako Makino, Itaru Sato, Xianfeng Feng, Maki Iwai, Kayoko Ito, Akiyoshi Miyajima, Makoto Otake, Akane Nagasako, Kousuke Matsuo, Haruki Eguchi and Yoshihiro Ishikawa, A novel treatment for triple-negative breast cancer using intrinsic magnetized paclitaxel, AACR Annual Meeting 2014, San Diego, USA, April 2014

【発表概要】

A novel treatment for triple-negative breast cancer using intrinsic magnetized paclitaxel

Masanari Umemura[1], Ayako Makino[1], Itaru Sato[1], Xianfeng Feng[1], Maki Iwai[1], Kayoko Ito[1], Akiyoshi Miyajima[1], Makoto Otake[1], Akane Nagasako[1], Kosuke Matsuo[1], Haruki Eguchi[2], and Yoshihiro Ishikawa[1].

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Background: We previously reported the identification of a novel nano-organic compound, EI236, an anti-cancer agent with intrinsic magnetic property. In addition to anti-cancer effect, its ferromagnetic property contributes to unique features. 1) It can be attracted by a magnet. 2) It can be visualized by magnetic resonance imaging (MRI). Hereby, we have identified the key mechanism that contributes to magnetism by X-ray crystallographic analysis, and succeeded in generating a novel paclitaxel with intrinsic magnetism; this is a single paclitaxel compound, and is *not* a paclitaxel encapsulated in micelle with magnetic particles. Our aim is to examine its effect on triple negative-breast cancer (TNBC) cells. Method: The magnetization of the magnetized paclitaxel was measured with a superconducting quantum

interference device (SQUID) (Quantum Design MPMS7 system). Breast cancer cells, MDA-MB-453 (TNBC) and MCF7 (Non-TNBC), were obtained from RIKEN Bioresource center. Cell proliferation assay was performed using a commercially available kit, XTT Cell Proliferation Assay Kit. Apoptotic cells were stained with APC Annexin V and 7-AAD, and measured by fluorescence activated cell sorting (FACS), to evaluate early and late apoptosis. Cell cycle analysis was performed using The Cycletest™ Plus DNA Reagent Kit and assessed using FACS. **Results**: Plots of magnetization versus magnetic field revealed that the magnetized paclitaxel exhibits spontaneous magnetization in SQID. Magnetized paclitaxel was easily attracted by a commercial bar magnet. Magnetized paclitaxel exhibits greater anti-cancer effect than original paclitaxel in TNBC and Non-TNBC cells in a dose-dependent manner. Magnetized paclitaxel induced apoptosis and G2/M arrest in cell cycle analysis in a dose-dependent manner, suggesting that magnetized paclitaxel retained the original anti-cancer property. In MRI T2 -weighted imaging, signal intensity was changed in a concentration-dependent manner with magnetized paclitaxel, but not with commercial available paclitaxel. **Conclusion**: These results suggested that various conventional anti-cancer drugs might be similarly magnetized, leading to novel drug development in future cancer chemotherapy.

17) Itaru Sato, Masanari Umemura, Kenji Mitsudo, Xianfeng Feng, Hideyuki Nakashima, Mitomu Kioi, Haruki Eguchi, Iwai Tohnai and Yoshihiro Ishikawa, Development of thermochemothrapy using cisplatin and ferucarbotran (Resovist) in head and neck cancer, AACR Annual Meeting 2014, San Diego, USA, April 2014

【発表概要】

Development of thermochemotherapy using cisplatin and ferucarbotran (Resovist®) in head and neck cancer

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Background: Radical surgery for patients with advanced head and neck cancer causes dysfunctions as well as decreases quality of life. To overcome this issue, we developed a new combination therapy of cisplatin and inductive hyperthermia using ferucarbotran (Resovist®). Ferucarbotran, which is made of superparamagnetic iron oxide, generates heat when exposed to an

alternating magnetic fields (AMF). Herein, we explored whether ferucarbotran could be used as a heat source for hyperthermia upon exposure to AMF in the presence of cisplatin . Our aim is to evaluate the simultaneous therapeutic efficacy of chemotherapy and inductive hyperthermia for head and neck cancer.

Materials and Methods: OSC-19 and HSC-3, human oral cancer cell lines, were used in this study. Cell proliferation was assessed by methyl thiazolyl tetrazorium (MTT) assay. The intracellular level of reactive oxygen species (ROS) was measured using fluorescent dye 2', 7'-dichlorodihydrofluorescein diacetate. Apoptotic cells were stained with Annexin V, allophycocyanin conjugate and 7-amino-actinomycin D, and measured by fluorescence activated cell sorting (FACS), to evaluate early and late apoptosis. . Thermal images and temperature were obtained by thermograpy and thermometer. Alternating magnetic fields were generated by a transistor-driven vertical coil at a frequency of 308 KHz and electric current (EC) 250 A.

Results: Ferucarbotran generated heat in a dose- and time-dependent manner when exposed to an AMF, suggesting that ferucarbotran could be used as a heat source for hyperthermia. As we expected, Cisplatin suppressed proliferation of OSC-19 and HSC-3 cells in a dose-dependent manner, not only furucarbtran. First, we performed MTT assay and ROS generation assay to evaluate whether hyperthermia effect enhanced anti-cancer effect in the presence of cisplatin. Simply incubation at 42 ° C for one hour enhanced the anti-cancer effect and ROS generation in the presence of cisplatin. Cisplatin induced apoptosis of OSC-19 and HSC-3 cells in a dose-dependent manner. Ferucarbotran further promoted cisplatin-induced apoptosis compared to cisplatin alone, when exposed to an AMF for an hour. Thus, the combination of cisplatin with ferucarbotran /AMF was more effective than cisplatin alone, suggesting that we could reduce the amount of cisplatin in clinical usage.

Conclusion: Our findings suggest that combination therapy of cisplatin and ferucarbotran in an AMF may be used to develop a new combination therapy for head and neck cancer.

18) 松尾光祐、福村英信、梅村将就、佐藤格、FENG Xianfeng、江口晴樹、石川義弘、齋藤知行、抗がん活性を持つ新規磁性体有機化合物を用いた温熱・化学同時療法、第４１回日本生体電気・物理刺激研究会、横浜、2014 年 4 月

【発表概要】

抗がん活性を持つ新規磁性体有機化合物を用いた温熱・化学同時療法

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【目的】

我々は，磁気的特性と抗がん活性を併せ持つ有機化合物(EI236)を同定した。この有