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研究課題名（和文）Potential role of club cell secretory protein (CC16) in development of obese asthma: findings from a birth cohort and animal studies

研究課題名（英文）Potential role of club cell secretory protein (CC16) in development of obese asthma: findings from a birth cohort and animal studies

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研究成果の概要（和文）：1)成人喘息コホート：循環CC16レベルは、BMIが低い群と比較して高い群で有意に低下した。BMIが気道過敏性、喘息重症度、吸入ステロイド量に及ぼす影響を、CC16が介在することを明らかにした。血清CC16は喀痰好酸球比率および血中ペリオスチンレベルと逆相関していた。重症喘息患者では、循環CC16が低い場合にFEV1の急速な低下を認めた。2) 北海道出生コホート：血漿CC16は喘息有病率およびT2バイオマーカーと逆相関していた。3)実験研究：肥満のマウスおよびヒトの末梢気道におけるCC16発現細胞の割合が減少していた。

研究成果の学術的意義や社会的意義
We showed the effects of reduced human CC16 in development of obese asthma and Th2 inflammation in children and adults for first time. CC16 levels is useful for risk stratification for prevention of progressive airway inflammation, and optimization of asthma treatment especially obese individuals.

研究成果の概要（英文）：1) Adult asthma cohort: BMI was significantly and monotonously associated with reduced circulating CC16 levels in adults. Mediation analysis revealed that CC16 mediates effects of BMI on airway hyperresponsiveness, asthma severity, and required dose of inhaled corticosteroid. Also, serum CC16 was inversely associated with sputum eosinophils and blood periostin as T2 biomarkers. Patients with the lowest tertile of serum CC16 levels at baseline had a -14.3 mL decline in FEV1 than those with the highest tertile over 5 years of follow-up. 2) Hokkaido Birth cohort: Plasma CC16 was inversely associated with asthma prevalence, and T2 biomarkers(FeNO and blood eosinophils). 3) Experimental studies: The percentage of CC16-expressing cells was reduced in the small airways of both mice and humans with obesity. Obesity reduced circulating CC16 levels but not surfactant protein SP-A and SP-D levels in the mice.

研究分野：Pulmonary Medicine, epidemiology

キーワード：Asthma　Obesity　Birth cohort　General population　Adult asthma　circulatory CC16　Experimental studies　CC16 polymorphism

１．研究開始当初の背景

Two billion people are currently overweight or obese in the world (WHO 2016). Asthma and obesity are among the most common chronic childhood disorders with a recent parallel dramatic increase in prevalence (Eder et al. NEJM 2006). However, the underlying mechanism and key molecules in obese asthma and its relation to airway inflammation are not well addressed. Club cell secretory protein (CC16) is a major anti-inflammatory pneumoprotein, produced by club cells in distal airways. CC16 in amniotic fluid serve as a marker of bronchial epithelium growth and low levels of this lung-specific protein in cord blood in preterm births independently predicts the development of bronchopulmonary dysplasia (Schrama et al. EJP 2008). Mice deficient in CC16 expression exhibit higher levels of eosinophilic airway inflammation through augmented T-helper cell type 2 (Th2) responses and reconstitution of CC16 in CC16-/- mice can reverse this altered phenotype (Hung et al. JACI 2004). Although, previous studies reported the association of asthma and obesity, the key molecule(s) and underlying mechanisms of the association are not well understood. In our adult asthma cohort with cross-sectional design, we observed that obesity and asthma independently are associated with reduced serum CC16 (Goudarzi et al. JSA 2017). We recently found that obesity reduces CC16 levels in non-allergic mice models (non-published data). Therefore, we hypothesized that CC16 might be involved in the pathogenesis of airways disease in obese individuals with asthma or other allergic diseases.

２．研究の目的

In this study, we aimed to:

i) Investigate the effects of blood CC16 levels on development of obese asthma (and other allergic phenotypes) and Th2 inflammation in children and adults.

ii) Demonstrate underlying mechanisms of the effects of CC16 on obese asthma and orchestration of Th2 and eosinophilic airway inflammation using experimental studies.

Therefore, we assessed the potential role of club cell protein-16 (CC16) as main anti-inflammatory airway protein in obese asthma patients in independent cohorts in children and adults. In addition, we explored the mechanisms how obesity affects CC16 protein and asthma outcomes in experimental studies.

３．研究の方法

1) Adult asthma cohort

Our adult asthma cohort is a multicenter, observational study involving patients with severe asthma (Konno et al. Ann Am Thorac Soc. 2018; Goudarzi et al. JACI Practice

2019). This study was approved by the ethics committees of Hokkaido University Hospital and its 29 affiliated hospitals/pulmonary clinics. Briefly, we enrolled 206bpatients diagnosed with asthma by pulmonologists between February 2010 and September 2012 at the Hokkaido University Hospital and its 29 affiliated hospitals/pulmonary clinics. The diagnosis of severe asthma was based on the American Thoracic Society criteria for refractory asthma in 2000, with minor modifications (Konno et al. Ann Am Thorac Soc. 2018). The study included 79 non-severe and 127 patients with severe asthma who underwent procedural evaluations during their 2-day stay at the Hokkaido University Hospital. Several clinical parameters were evaluated in all participants upon hospitalization.

2) Hokkaido Birth cohort

It is an ongoing population-based prospective birth cohort study that began in 2002 (n = 20,926 mother-child pairs). For allergic condition assessment, follow-up questionnaires were distributed to children aged 1, 2, 4, 7 and 10 years old, which included questions pertaining to wheeze, rhinitis and eczema from the “International Study of Asthma and Allergies in Childhood” (ISAAC) questionnaires. Also, information on anthropometric measures, doctor-diagnosis of asthma, and confounders will be extracted from the same questionnaires. Serum CC16 protein was measured 10 years of age (n=428) by ELISA (Bio Vendor Laboratory Medicine). We have collected blood samples of children at age 10. We measured three T2 biomarkers in children including blood eosinophils, FeNO and total serum IgE. In addition, we examined specific IgE for 13 types of common inhaled and food allergens. Using 200 microliter of buffy coats, we will extract DNA for further analysis. The *CC16* A38G polymorphism (rs3741240) will be identified using the TaqMan system (Applied Biosystems, Foster City, CA, USA). Because of influence of CC16 genotype on circulatory protein levels, *CC16* A38G polymorphism was included in the adjusted models for data analysis.

3) Experimental studies

C57BL/6 Wild-type mice randomly were divided into two subgroups given normal chow or a high-fat diet. Blood CC16 levels and other products of club cells (SP-A and SP-D) in control mice vs. high-fat diet mice. After ruling out asthma, COPD, or other chronic respiratory diseases by spirometry and HRCT, we collected cancer-free human lung samples among never smokers.

４．研究成果

1) Adult asthma cohort

a) We first examined whether obesity reduces airway/circulatory CC16 levels using

three independent epidemiological studies. Then, we explored the mediatory role of CC16 in the relationship of overweight/obesity with clinical asthma measures. Circulating CC16 levels were assessed by ELISA in three independent human populations, including two groups of healthy and general populations and asthma patients. A causal mediation analysis was conducted to determine whether circulatory CC16 acted as a mediator between overweight/obesity and clinical asthma measures. BMI was significantly and monotonously associated with reduced circulating CC16 levels in all three populations. Finally, mediation analysis revealed significant contributions of circulatory CC16 in the association between BMI and clinical asthma measures; 21.8% of its total effect in BMI's association with airway hyperresponsiveness of healthy subjects ($p = 0.09$), 26.4% with asthma severity ($p = 0.030$), and 23% with the required dose of inhaled corticosteroid ($p = 0.042$). In logistic regression analysis, 1-SD decrease in serum CC16 levels of asthma patients was associated with 87% increased odds for high dose ICS requirement ($p < 0.001$). As conclusion, we demonstrated that airway/circulating CC16, which is inversely associated with BMI, may mediate development and severity in overweight/obese asthma (Goudarzi et al. *Respiratory Research*, 2022).

b) We assessed whether serum CC16 is associated with eosinophilic inflammation in patients with severe asthma. We also examined the effect of this protein on the annual decline in forced expiratory volume in the first second (FEV_1) and the risk of exacerbation using a longitudinal approach. We recruited 127 patients with severe asthma from 30 hospitals/pulmonary clinics in Hokkaido, Japan. The least square means and standard error were calculated for T-helper 2 (Th2) biomarkers and pulmonary function test across CC16 tertiles at baseline. We did the same for asthma exacerbation and annual decline in FEV_1 with 3 and 5 years' follow-up, respectively. We found that serum CC16 was inversely associated with sputum eosinophils and blood periostin, Th2 biomarkers, in a dose-response manner. Baseline CC16 and FEV_1/forced vital capacity ratio were positively associated in adjusted models (p for trend = 0.008). Patients with the lowest tertile of serum CC16 levels at baseline had a -14.3 mL decline in FEV_1 than those with the highest tertile over 5 years of follow-up (p for trend = 0.031, fully adjusted model). We did not find any association of CC16 with exacerbation risk. As conclusion, Patients with severe asthma with lower circulatory CC16 had enhanced eosinophilic inflammation with rapid FEV_1 decline over time (Goudarzi et al. *Respiratory Medicine*, 2023).

2) Hokkaido Birth cohort

a) We examined the pre- and postnatal factors associated with Th2 biomarkers using multivariable logistic regression analysis (n = 428) and extended the results to the original cohort (n = 17,009) using inverse probability weighting. We also measured typical Th2 biomarker distribution in all examined children and healthy participants

without allergic diseases (n = 180). At age 9-11, wheeze (odds ratio (OR) 7.63), rhinitis (OR 3.14), and eczema (OR 2.46) were significantly associated with increased blood eosinophils. All three allergic conditions were associated with FeNO and total serum IgE, but the ORs were smaller than those for blood eosinophils. Secondhand smoking was inversely associated with the blood eosinophils (OR, 0.38). Similar results were found in the original cohort. Male sex and prenatal factors (maternal smoking and parental history of allergies) were not independent predictors of high Th2 levels. We concluded that in addition to wheezing and rhinitis, eczema and secondhand smoke exposure are independent factors for Th2 biomarker interpretation in children. Furthermore, the typical values and cutoff values of blood eosinophils and FeNO in adults are lower than those in children, and such thresholds are not applicable to children (Goudarzi et al. *Allergology International*, 2023).

b) We assessed association of BMI with CC16 and found that there is inverse association between obesity and plasma CC16 levels which was in line with our results from adults. On the other hand, children with wheeze had significantly lower plasma CC16 (median 5.2, IQR 3.8-6.1) compared to children without wheeze (median 5.6, IQR 4.3-7.1). Plasma CC16 was inversely associated with wheeze and asthma prevalence, with a 1 ng/mL increase in CC16 decreasing the risk of wheeze by 20% (adjusted odds ratio: 0.80, 95% CI: 0.66-0.99). CC16 was inversely associated with T2 phenotypes, including blood eosinophils and FeNO in crude and adjusted models. In addition, we further adjusted the associations with *CC16* polymorphism and the results did not change. Therefore, the association of CC16 with obesity, asthma outcomes, and T2 biomarkers were, at least partially, independent of *CC16* polymorphism. We are preparing a manuscript to publish these data in a high impact international journal.

3) Experimental studies

The percentage of cells expressing club markers in obese vs. non-obese mice and human airways was determined by immunohistochemistry. The percentage of CC16-expressing cells was reduced in the small airways of both mice and humans with obesity. Obesity reduced circulating CC16 levels but not surfactant protein SP-A and SP-D levels in the mice, indicating specific effects of obesity on club cells in the airways (Goudarzi et al. *Respiratory Research*, 2022).

５．主な発表論文等

〔雑誌論文〕　計15件（うち査読付論文　15件／うち国際共著　15件／うちオープンアクセス　14件）

１．著者名 Goudarzi Houman、Kimura Hirokazu、Kimura Hiroki、Makita Hironi、Takimoto-Sato Michiko、Abe Yuki、Oguma Akira、Matsumoto Munehiro、Takei Nozomu、Matsumoto-Sasaki Machiko、Shimizu Kaoruko、Suzuki Masaru、Shijubo Noriharu、Huang Shau-ku、Hizawa Nobuyuki、Nishimura Masaharu、Konno Satoshi	４．巻 206
２．論文標題 Association of serum CC16 levels with eosinophilic inflammation and respiratory dysfunction in severe asthma	５．発行年 2023年
３．雑誌名 Respiratory Medicine	６．最初と最後の頁 107089～107089
掲載論文のDOI（デジタルオブジェクト識別子） 10.1016/j.rmed.2022.107089	査読の有無 有
オープンアクセス オープンアクセスとしている（また、その予定である）	国際共著 該当する

１．著者名 Goudarzi Houman、Ikeda-Araki Atsuko、Bamai Yu Ait、Ito Sachiko、Inao Tasuku、Yokota Isao、Miyashita Chihiro、Kishi Reiko、Konno Satoshi	４．巻 72
２．論文標題 Potential determinants of T helper 2 markers and their distribution in school-aged children	５．発行年 2023年
３．雑誌名 Allergology International	６．最初と最後の頁 100～106
掲載論文のDOI（デジタルオブジェクト識別子） 10.1016/j.alit.2022.07.009	査読の有無 有
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１．著者名 Goudarzi Houman、Kimura Hirokazu、Kimura Hiroki、Makita Hironi、Ito Yoichi M.、Nishimura Masaharu、Konno Satoshi	４．巻 23
２．論文標題 Effects of obesity on CC16 and their potential role in overweight/obese asthma	５．発行年 2022年
３．雑誌名 Respiratory Research	６．最初と最後の頁 174
掲載論文のDOI（デジタルオブジェクト識別子） 10.1186/s12931-022-02038-1	査読の有無 有
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１．著者名 Kimura Hirokazu、Shimizu Kaoruko、Tanabe Naoya、Makita Hironi、Goudarzi Houman、Sato Susumu、Ono Junya、Izuhara Kenji、Hirai Toyohiro、Nishimura Masaharu、Konno Satoshi	４．巻 128
２．論文標題 Further evidence for association of YKL-40 with severe asthma airway remodeling	５．発行年 2022年
３．雑誌名 Annals of Allergy, Asthma and Immunology	６．最初と最後の頁 682～688.e5
掲載論文のDOI（デジタルオブジェクト識別子） 10.1016/j.anai.2022.03.016	査読の有無 有
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1．著者名 Goudarzi Houman、Onozawa Masahiro、Takahashi Makoto	4．巻 24
2．論文標題 Future career plans of medical students and the COVID‐19 pandemic: Time to recover?	5．発行年 2022年
3．雑誌名 Journal of General and Family Medicine	6．最初と最後の頁 139～140
掲載論文のDOI（デジタルオブジェクト識別子） 10.1002/jgf2.591	査読の有無 有
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1．著者名 Oguma Akira、Shimizu Kaoruko、Kimura Hirokazu、Tanabe Naoya、Sato Susumu、Yokota Isao、Takimoto-Sato Michiko、Matsumoto-Sasaki Machiko、Abe Yuki、Takei Nozomu、Goudarzi Houman、Suzuki Masaru、Makita Hironi、Hirai Toyohiro、Nishimura Masaharu、Konno Satoshi	4．巻 72
2．論文標題 Differential role of mucus plugs in asthma: Effects of smoking and association with airway inflammation	5．発行年 2023年
3．雑誌名 Allergology International	6．最初と最後の頁 262～270
掲載論文のDOI（デジタルオブジェクト識別子） 10.1016/j.alit.2022.10.007	査読の有無 有
オープンアクセス オープンアクセスとしている（また、その予定である）	国際共著 該当する

1．著者名 Abe Yuki、Suzuki Masaru、Kimura Hirokazu、Shimizu Kaoruko、Takei Nozomu、Oguma Akira、Matsumoto-Sasaki Machiko、Goudarzi Houman、Makita Hironi、Nishimura Masaharu、Konno Satoshi	4．巻 22
2．論文標題 Blood eosinophil count variability in chronic obstructive pulmonary disease and severe asthma	5．発行年 2022年
3．雑誌名 Allergology International	6．最初と最後の頁 00139-3
掲載論文のDOI（デジタルオブジェクト識別子） 10.1016/j.alit.2022.11.012	査読の有無 有
オープンアクセス オープンアクセスとしている（また、その予定である）	国際共著 該当する

1．著者名 Kimura Hirokazu、Makita Hironi、Taniguchi Natsuko、Takei Nozomu、Matsumoto Munehiro、Kimura Hiroki、Goudarzi Houman、Shimizu Kaoruko、Suzuki Masaru、Nishimura Masaharu、Konno Satoshi	4．巻 70
2．論文標題 Determination of the cutoff values of Th2 markers for the prediction of future exacerbation in severe asthma: An analysis from the Hokkaido Severe Asthma Cohort Study	5．発行年 2021年
3．雑誌名 Allergology International	6．最初と最後の頁 68～73
掲載論文のDOI（デジタルオブジェクト識別子） 10.1016/j.alit.2020.09.001	査読の有無 有
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1．著者名 Kishi Reiko、Ikeda-Araki Atsuko、Miyashita Chihiro、Itoh Sachiko、Kobayashi Sumitaka、Ait Bamai Yu、Yamazaki Keiko、Tamura Naomi、Minatoya Machiko、Ketema Rahel Mesfin、Poudel Kritika、Miura Ryu、Masuda Hideyuki、Itoh Mariko、Yamaguchi Takeshi、Fukunaga Hisanori、Ito Kumiko、Goudarzi Houman	4．巻 26
2．論文標題 Hokkaido birth cohort study on environment and children’s health: cohort profile 2021	5．発行年 2021年
3．雑誌名 Environmental Health and Preventive Medicine	6．最初と最後の頁 59
掲載論文のDOI（デジタルオブジェクト識別子） 10.1186/s12199-021-00980-y	査読の有無 有
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2．論文標題 Association of abdominal visceral adiposity with sputum IL-5 levels in asthma	5．発行年 2022年
3．雑誌名 Allergology International	6．最初と最後の頁 137～139
掲載論文のDOI（デジタルオブジェクト識別子） 10.1016/j.alit.2021.08.003	査読の有無 有
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1．著者名 Goudarzi Houman、Onozawa Masahiro、Takahashi Makoto	4．巻 24
2．論文標題 Impact of the Covid-19 pandemic and ensuing online teaching on pre-clinical medical education	5．発行年 2024年
3．雑誌名 BMC Medical Education	6．最初と最後の頁 66
掲載論文のDOI（デジタルオブジェクト識別子） 10.1186/s12909-023-04967-x	査読の有無 有
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1．著者名 Yang Yichi、Kimura Hirokazu、Yokota Isao、Makita Hironi、Takimoto-Sato Michiko、Matsumoto-Sasaki Machiko、Matsumoto Munehiro、Oguma Akira、Abe Yuki、Takei Nozomu、Goudarzi Houman、Shimizu Kaoruko、Suzuki Masaru、Nishimura Masaharu、Konno Satoshi、Isada Akira	4．巻 132
2．論文標題 Applicable predictive factors extracted from peak flow trajectory for the prediction of asthma exacerbation	5．発行年 2023年
3．雑誌名 Annals of Allergy, Asthma & Immunology	6．最初と最後の頁 469～476
掲載論文のDOI（デジタルオブジェクト識別子） 10.1016/j.anai.2023.11.015	査読の有無 有
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1．著者名 Zeng Yi、Goudarzi Houman、Ait Bamai Yu、Ketema Rahel Mesfin、Roggeman Maarten、den Ouden Fatima、Gys Celine、Miyashita Chihiro、Ito Sachiko、Konno Satoshi、Covaci Adrian、Kishi Reiko、Ikeda-Araki Atsuko	4．巻 181
2．論文標題 Exposure to organophosphate flame retardants and plasticizers is positively associated with wheeze and FeNO and eosinophil levels among school-aged children: The Hokkaido study	5．発行年 2023年
3．雑誌名 Environment International	6．最初と最後の頁 108278～108278
掲載論文のDOI（デジタルオブジェクト識別子） 10.1016/j.envint.2023.108278	査読の有無 有
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1．著者名 Wu Dongze、Jin Yingzhao、Xing Yuhan、Abate Melsew Dagne、..., Houman Goudarzi, ...	4．巻 64
2．論文標題 Global, regional, and national incidence of six major immune-mediated inflammatory diseases: findings from the global burden of disease study 2019	5．発行年 2023年
3．雑誌名 eClinicalMedicine	6．最初と最後の頁 102193～102193
掲載論文のDOI（デジタルオブジェクト識別子） 10.1016/j.eclinm.2023.102193	査読の有無 有
オープンアクセス オープンアクセスではない、又はオープンアクセスが困難	国際共著 該当する

1．著者名 Haakenstad Annie、Irvine Caleb Mackay Salpeter、Knight Megan、..., Houman Goudarzi, ...	4．巻 399
2．論文標題 Measuring the availability of human resources for health and its relationship to universal health coverage for 204 countries and territories from 1990 to 2019: a systematic analysis for the Global Burden of Disease Study 2019	5．発行年 2022年
3．雑誌名 The Lancet	6．最初と最後の頁 2129～2154
掲載論文のDOI（デジタルオブジェクト識別子） 10.1016/S0140-6736(22)00532-3	査読の有無 有
オープンアクセス オープンアクセスとしている（また、その予定である）	国際共著 該当する

〔学会発表〕　計8件（うち招待講演　1件／うち国際学会　8件）

1．発表者名 Houman Goudarzi, Hirokazu Kimura, Hironi Makita, Mune Matsumoto, Nozomu Takei, Kaoruko Shimizu, Taku Watanabe, Masaharu Nishimura, Satoshi Konno
2．発表標題 Effects of obesity on CC16 and their potential role in obese asthma
3．学会等名 Japan Society for Allergology 71st Annual Meeting（国際学会）
4．発表年 2022年

１．発表者名
Houman Goudarzi, Masahiro Onozawa, Makoto Takahashi

２．発表標題
Career plans and academic performance of medical students before, during, and beyond COVID-19 pandemic: Time to recover?

３．学会等名
The 54th Annual meeting of the Japan Society for Medical Education（国際学会）

４．発表年
2022年

１．発表者名
Yu Ait Bamai, Celine Guys, Michiel Bastiaensen, Atsuko Ikeda-Araki, Rahel Mesfin Ketema, Houman Goudarzi, Chihito Miyashita, Satoshi Konno, Reiko Kishi

２．発表標題
Mixture exposure to plastic-related short half-life chemicals and associations with childhood asthma and allergies: The Hokkaido Study

３．学会等名
The 34th Annual ISEE conference（国際学会）

４．発表年
2022年

１．発表者名
Houman Goudarzi, Atsuko Araki, Chihiro Miyashita, Yu Ait Bamai, Sachiko Ito, Reiko Kishi, Masaharu Nishimura, Satoshi Konno

２．発表標題
Prevalence and time trends of allergic disease among Japanese children: Interpretation of T helper 2 biomarker levels for clinical applications

３．学会等名
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４．発表年
2020年

１．発表者名
Satoshi Konno, Houman Goudarzi, Hirokazu Kimura, Masaru Suzuki, Kaoruko Shimizu, Hiroki Kimura, Noriharu Shijubo, Shau-ku Huang, Masaharu Nishimura

２．発表標題
Association of circulatory CC16 with type 2 inflammation and pulmonary dysfunction: Potential role of CC16 in obese asthma

３．学会等名
65th Annual Meeting of Thomas L. Petty Aspen Lung Conference（招待講演）（国際学会）

４．発表年
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〔図書〕　計0件

〔産業財産権〕

〔その他〕
https://www.cehs.hokudai.ac.jp/en
Website of Hokkaido Study
https://www.cehs.hokudai.ac.jp/hokkaidostudy/

6．研究組織

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〔国際研究集会〕　計0件

8．本研究に関連して実施した国際共同研究の実施状況

共同研究相手国	相手方研究機関			
米国	Icahn School of Medicine at Mount Sinai	New York		
米国	Johns Hopkins University	Baltimore		