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日中笹川医学奨学金制度

第 45 期＜共同研究コース＞

研　究　報　告　書

2024 年 4 月～2025 年 3 月

公益財団法人　日中医学協会

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日中笹川医学奨学金制度＜共同研究コース＞
日中共同研究に関わる報告書

作成日：2025 年 3 月 31 日

氏 名（漢字）	趙 松吉	氏名（ローマ字）	ZHAO Songji
所属機関・部署・役職	福島県立医科大学ふくしま国際医療科学センター 先端臨床研究センター　教授		
研究テーマ	がん標的アルファ線治療のためのアスタチン-211 標識化学とその薬力学		
中国側共同研究者 氏名と研究者番号	李 飛澤　K4521	中国側共同研究者 所属機関	四川大学原子核科学技術研究所

本共同研究の①研究目的の達成度、②将来性、③今後の展望や予定について述べて下さい。

【達成度】

^{211}At has been regarded as one of the most promising radionuclides for targeted alpha particle therapy. Fukushima Medical University and Sichuan University are two of the institutes that can produce ^{211}At at the medical-use level and have been performing long-term investigations based on radioastatinated compounds. However, both institutions are facing the same issues about ^{211}At-based radiopharmaceuticals as all others are facing worldwide: the low radiolabeling efficiency and unsatisfactory radiochemical stability of corresponding radiolabeled conjugates. Through the collaboration funded by the Japan-China Sasakawa Medical Fellowship, we wanted to develop different strategies to address the above two problems. In this joint research project, we aimed to achieve several goals including (1) the publication of two to three high-impact-factor research papers, (2) the promotion of academic exchanges, including cooperative postdoctoral research projects, and (3) the conduct of at least one clinical trial based on ^{211}At-radiolabeled compounds. To this end, we (1) have published two papers, (2) planning for cooperative postdoctoral research projects, and (3) listed a timeline for clinical trials of ^{211}At-radiolabel PSMA compounds. We have also recently developed radioimmunotherapy for acute myelogenous leukemia using an ^{211}At-radiolabeled CD82 monoclonal antibody targeting CD82 to eradicate leukemia stem cells.

Taken together, we have achieved all our research goals.

【将来性】

We have achieved the goals proposed during this collaborative research period and clarified our future research plans, including joint postdoctoral research projects and clinical trials; therefore, a platform for continued collaborative research has been established. We hope that the launching of this collaborative research platform will help resolve some of the difficulties in the ^{211}At labeling method mentioned above. Our work can provide valuable insights into the ^{211}At radiolabeling of general compounds and may promote the application of ^{211}At-related radiopharmaceuticals.

【今後の展望】

First, we will try to apply for international funding from the Japan Society for the Promotion of Science or the National Natural Science Foundation of China, so that we can maintain our collaboration without monetary constraints. Second, we will keep in touch with each other through Zoom meetings, international academic seminars and self-supported work trips either to Japan or China. Third, we will share our research progress reasonably and timely, so both sides can learn from each other, especially in biological research aspects. Finally, we will seek further possibilities in the following Japan-China Sasakawa Medical Scholarship, either through joint research or postdoctoral programs. Specifically, we will finish preclinical biosafety evaluations of ^{211}At-IPBA-FAPI, ^{211}At-PSMA, or ^{211}At-CD82 in three to five years and identify which among them has the most competitive potential for clinical applications.

We hope that at least one of our designed formulations for cancer-targeted alpha particle therapy will be approved by the Food and Drug Agency of Japan or China in the near future.

日本側共同研究者記名：趙　松吉

日中笹川医学奨学金制度＜共同研究コース＞研究報告書

＊英語または日本語で作成(请用日文或英文书写)

第 45 期　　研究者番号(研究者编号)：K4521　　作成日(书写日期)　：2024 年 12 月16日

氏　名 (姓名)	LI FEIZE 李飞泽	性別 (性别)	Male	生年月日 (出生日期)	1989/12/04

研 究 テーマ (研 究 题 目)	**^{211}At radiolabeling chemistry and pharmacodynamics for cancer-targeted alpha particle therapy**
研究期間(来日～帰国まで) (来日起至回国的研究起止时间)	2024 年 04 月 20 日 ～ 2025 年 01 月 04 日
在日共同研究機関・部署 (在日共同研究单位及部门)	**Advanced Clinical Research Center, Fukushima Global Medical Science Center, Fukushima Medical University**
共同研究者氏名・役職 (共同研究者姓名/职务)	**ZHAO SONGJI 趙松吉** **Professor**
学会参加について (关于在日期间参加学会)	有り(有参加) ☒　　なし(没有参加) ☐ ※参加有の方は下記の欄をご記入下さい。(有参加学会者，请继续填写如下内容) 発表有り(有发表)：学会名称：**Japan-China Sasakawa Medical Scholarship Program Joint Researcher Exchange Meeting** 発表テーマ(发表题目)：**^{211}At radiolabeling chemistry and pharmacodynamics for cancer-targeted alpha particle therapy**
論文発表について (关于在日期间论文发表)	発表有/投稿中(已发表或投稿中)☒　　発表なし(没有发表)☐ ※既にもしくは発表予定有りの方は下記の欄をご記入下さい。 (已发表或有论文投稿中的，请填写如下内容，并另外单独附上全部论文内容的复印件) テーマ(题目)：**Strong Affinity between Astatine and Silver: An Available Approach to Anchoring ^{211}At in Nanocarrier for Locoregional Oncotherapy** 著者名(作者名)：**Ruitong Hou, Tianzhen Ye, Yilin Qin, Long Qiu, Jie Lyu, Fuyuan Tan, Yuanyou Yang, Songji Zhao, Ning Liu, and Feize Li** 雑誌名(期刊名)：**Langmuir** 発行年(发表年度)：**2024** 巻　号(刊卷)：**40** ページ(页数)：**23624-23631** インパクトファクター(影响因子)：**3.7** テーマ(题目)：**^{211}At radiolabeled APBA-FAPI for enhanced targeted-alpha therapy of glioma** 著者名(作者名)：**Tianzhen Ye, Yuying Yu, Guofeng Qu, Huan Ma, Shilong Shi, Jiujian Ji, Jie Lyu, Yuanyou Yang, Ning Liu, and Feize Li** 雑誌名(期刊名)：**European Journal of Medicinal Chemistry** 発行年(发表年度)：**2024** 巻　号(刊卷)：**279** ページ(页数)：**116919** インパクトファクター(影响因子)：**6.0**

日本滞在中の具体的な共同研究内容についての報告
（关于在日期间就研究题目具体开展的共同研究内容的详述）

【研究目的】(研究目的)

^{211}At has been regarded as one of the most promising radionuclides for targeted alpha particle therapy. Fukushima Medical University and Sichuan University are two of these institutes available for producing ^{211}At at medically-used level and have been performing long-term investigations based on radioastatinated compounds. However, both institutions are discouraged by the same issues about ^{211}At based radiopharmaceuticals as all others are facing over the world: the low radiolabeling efficiency and unsatisfactory radiochemical stability of corresponding radiolabeled conjugations. Through the collaboration funded by Japan China Sasakawa Medical Fellowship, we wanted to design different strategies to address above two problems.

【研究経過】(研究经过)

In July 2023, Prof. Zhao visited my group in person in Chengdu, China. We shared each own research progress about ^{211}At radiopharmaceuticals via formal conversation. From each other's presentation, we learned that we both had been working on ^{211}At production and corresponding pharmaceuticals for a long time. We soon concurred to apply for Japan-China Sasakawa Medical Scholarship to form solidified collaboration. Our joint project was approved officially by Japan Medical Association in December 2023, when we decided to perform our research plan separately in Japan and China. On 20/4 2024, I arrived Fukushima Medical University and formally started our research plan where we proposed two strategies to deliver our research goal: During the first approach, we proposed utilizing the strong binding between astatine and silver to achieve highly efficient conjugation between ^{211}At and Ag-based nanoparticles, giving a nanodrug named as ^{211}At@Ag-PEG-FA. During another avenue, a multifunctional binding agent was introduced to simultaneously achieve ^{211}At radiolabeling and tumor retention prolongation of corresponding radiolabeled drug, leading to a radionuclide pharmaceutical ^{211}At-IPBA-FAPI. Besides, we have been working on a newly modified compound ^{211}At-NpG-PSMA towards metastatic castration-resistant prostate cancer with great potential in translation.

【成果】(成果)

^{211}At@Ag-PEG-FA shows an excellent antitumor effect that completely inhibited tumor growth in the first week, effectively prolonging the median survival of mice to 44 days, relative to 16 days in the control group. All the mice exhibits minimal side effects from ^{211}At@Ag-PEG-FA in the experiment, indicating its acceptable biosafety. ^{211}At-IPBA-FAPI presents pronounced tumor inhibition compared to the control group, without noticeable biotoxicity towards main healthy organs/tissues. All these results indicate that introducing a multifunctional binding agent can effectively enhance the utilization of FAPI for ^{211}At conjugation and tumoricidal effect. As for ^{211}At-NpG-PSMA. Our work can provide valuable insights for the ^{211}At radiolabeling of general compounds and may promote the translation of ^{211}At related radiopharmaceuticals.

【今後の論文発表予定】(今后论文发表的计划)

We plan to publish 3 more papers in five years, of which the total impact will be over 15.

【今後の課題】(今后的课题)

Benefiting from this project, I have received further financial support from National Natural Science Foundation of China (Grant No. 12475349), which enable us to continue our collaborative research work more tightly. Prof Zhao and I have decided to do more biosafety evaluations of the prepared radiopharmaceuticals so that we may have a chance to make our drugs move from bench to bed.

本共同研究の①研究目的の達成度、②将来性、③帰国後の展開予定について述べて下さい。
（请就本次合作研究题目的①研究目的的达标情况、②未来的发展可能性、③您回国后今后的合作研究的规划打算作一一论述）

【達成度】(达标情况)

In our application, we proposed to deliver several goals including (1) Publish 2-3 high-IF research papers; (2) Develop academic exchanges including cooperative postdoctoral research projects; (3) Conduct at least one clinical trial based on ^{211}At-radiolabeled compounds. To this end, (1) we have published two papers with impact factors of 3.7 and 6.0 (*side supra* for more details), (2) we are planning for cooperative postdoctoral research projects (3) and we have listed a timeline for clinical trials of ^{211}At radiolabel PSMA compounds. From this sense, we have achieved all research goals.

【将来性】(未来的可能性)

Since we have delivered our basic goals and have clarified future research scheme including cooperative postdoctoral research project and clinical trials, we have great chance to achieve constant international collaborations. We are dedicating ourselves to and we will improve the influence of Asia ¶VUDGKBUPDFHXWLFDOV LQ$1XGLQ radiolabeled compounds.

【帰国後共同研究の展開予定】(回国后的合作规划)

First, we will try to apply for international funding from National Natural Science Foundation of China and any other scientifically financial support, so that we can maintain our collaboration without monetary hesitations. Second, we will keep in touch with each other, through online Zoom meetings, international academic seminars and self-supported work trips either to Japan or China. Third, we will share our research progress reasonably and timely, so both sides can learn from each other, especially in biological research aspects. Finally, we will seek further possibility in following Japan-China Sasakawa Medical Scholarship, either the joint research or postdoctoral programs. Specifically, we will finish preclinical biosafety evaluations of ^{211}At@Ag-PEG-FA, ^{211}At-IPBA-FAPI and ^{211}At-NpG-PSMA in three to five years and work out which has the most competitive potential for clinical practice. We plan to make at least one designed formulation be approved by either Japanese or Chinese food and drug agent for cancer endoradiotherapy in 15 years.

研究者自署：李飛澤

日中笹川医学奨学金制度＜共同研究コース＞
日中共同研究に関わる報告書

作成日：2025 年 2 月 20 日

氏 名（漢字）	横堀 將司	氏名（ローマ字）	YOKOBORI Shoji
所属機関・部署・役職	日本医科大学大学院医学研究科救急医学分野教授		
研究テーマ	心停止後症候群患者における集中治療		
中国側共同研究者 氏名と研究者番号	李　昊　K4522	中国側共同研究者 所属機関	西安交通大学第一附属医院重症医学科

本共同研究の①研究目的の達成度、②将来性、③今後の展望や予定について述べて下さい。

【達成度】
李昊医師は、我が国と中国における医療事情や技術の差異を熱心に観察し、特に蘇生後脳症の治療法について深い関心を持ち、熱心に研究に取り組まれました。ディスカッションの中では、中国における高齢化の進行に伴い心停止患者が増加している現状を踏まえ、日本医科大学で学んだ知識と技術を生かし、母国の医療に貢献したいという強い意志をたびたび口にされていました。その熱意をもって積極的に学ばれる姿勢からも、当初の目標を十分に達成されたものと確信しております。

【将来性】
李昊医師は、日本で広く普及している心肺蘇生技術、特に体外式心肺補助装置（ECMO）を用いた治療について、意欲的に学ばれました。お話を伺う限り、中国では ECMO の普及率がまだ十分ではなく、先進的な医療技術と位置づけられているようです。今後、母国に帰国された際には、当施設で習得された知識と技術を同僚の医療者に伝え、医療水準の向上に寄与していただけることを期待しております。また、李医師の経験を通じて、日本の医療に興味を持つ中国の医療者や研究者が、今後も日本医科大学を研鑽の場として選び、研究活動に励んでくださることを心より願っております。

【今後の展望】
医療技術は日進月歩で進化しています。同じアジア圏に位置する隣国であっても、医療技術や知識には依然として大きな違いがあります。しかし、大規模なデータを基盤としたエビデンスレベルの高い研究を推進する中国の研究者と、繊細かつ先進的な集中治療を得意とする我が国の医療者が知識を共有することは、両国の医療発展に大きく寄与すると確信しております。今後も李医師がその架け橋となり、両国の医療連携をさらに深めていかれることを心より期待しています。

日本側共同研究者記名：横堀 將司

日中笹川医学奨学金制度＜共同研究コース＞研究報告書

＊英語または日本語で作成(请用日文或英文书写)

第 45 期　研究者番号(研究者编号)：K4522　作成日(书写日期)：2024 年 9 月　日

氏　名 (姓名)	LI　HAO（李　昊）	性別 (性别)	F	生年月日 (出生日期)	1981. 2. 15

研 究 テーマ （研 究 題 目）	The Protective Effect of Targeted Temperature Management at 33°C Versus 35°C After Out-of-Hospital Cardiac Arrest on post-resuscitation intestinal injury: a Randomized Clinical Trial.
研究期間(来日～帰国まで) (来日起至回国的研究起止时间)	2024 年　5　月　2　日 ～　2024　年　10　月　3　日
在日共同研究機関・部署 (在日共同研究单位及部门)	The Department of Emergency and Critical care Medicine of Nippon Medical School
共同研究者氏名・役職 (共同研究者姓名/职务)	Dr.Shoji Yokobori/Chairman of the department of Emergency and Critical care Medicine of Nippon Medical School
学会参加について (关于在日期间参加学会)	有り(有参加) √　　なし(没有参加) □ ※参加有の方は下記の欄をご記入下さい。(有参加学会者，请继续填写如下内容)

一般参加 (普通参加)	学会名称：The 27th Japan TTM symposium
一般参加 (普通参加)	学会名称：How we got here and where we are going: neuromonitoring 2024-2054
発表有り (有发表)	学会名称：The Japanese society of hypertension International Session　(2024 JSH) 発表テーマ(发表题目)：Perivascular adipose tissue derived-leptin promotes vascular remodelling in high-fat diet induced obestiy rat model　(Poster on site E000055)
発表有り (有发表)	学会名称：Japan-China Sasakawa Medical Scholarship Program 45th Term Joint Researchers Meeting 発表テーマ(发表题目)：Intensive care of Post cardiac arrest patients

論文発表について (关于在日期间论文发表)	発表有/投稿中(已发表或投稿中) □　　発表なし(没有发表) √ ※既にもしくは発表予定有りの方は下記の欄をご記入下さい。 (已发表或有论文投稿中的，请填写如下内容，并另外单独附上全部论文内容的复印件)
	テーマ(题目)：
	著者名(作者名)：
	雑誌名(期刊名)：
	発行年(发表年度)： 巻　号(刊卷)： ページ(页数)： インパクトファクター(影响因子)：

日本滞在中の具体的な共同研究内容についての報告

（关于在日期间就研究题目具体开展的共同研究内容的详述）

【研究目的】（研究目的）

Therapeutic temperature management(TTM), which means to maintain the temperature between 32℃ to 36℃ for at least 24 h, is the standard treatment protocol for unconscious post-resuscitation patients. However, 32℃ to 36℃ is a large range, and clinicians select a targeted temperature depending on their own experience. Furthermore, there is still controversy about the ideal targeted temperature of mild hypothermia therapy. In consideration that studies about protective therapy for post-resuscitation intestinal injury are very limited. Therefore, this study is performed to explore: whether mild hypothermia therapy can exert a protective effect on postresuscitation intestinal injury; the protective effect of different targeted temperatures on post-resuscitation intestinal injury and the ideal targeted temperature.

【研究経過】（研究经过）

This is a randomized, prospective, multiple center study. About 120 out-hospital cardiac arrest patients will be enrolled into our study. After being screened for eligibility, patients are randomly assigned in a 1:1 ratio to targeted temperature management with a target body temperature of either 33°C or 35°C. The intervention period of 48 hours commenced at the time of randomization. Sedation will be mandated in both groups until the end of the intervention period. The goal is to achieve the assigned temperature as rapidly as possible with intravascular or surface temperature management devices. After 48 hours, gradual rewarming to 37° C in hourly increments of 0.5° C is commenced in both groups. The blood inflammatory factors (such as TNF-α, IL-6), and intestinal injury biomarkers (such as iFABP) will be measured and analyzed. After therapeutic target temperature management, all patients will be underwent colonoscopy to observe the intestinal morphology.

【成果】（成果）

1. The clinical study has been registered and was approved by ethics committee
2. The researchers have mastered the techniques of hypothermia therapy
3. The researchers have begun to enroll patients into this clinical trial.

【今後の論文発表予定】（今后论文发表的计划）

1. Published 1-2 papers in famous journal.
2. Apply a foundation for further research.

【今後の課題】（今后的课题）

1. The effect of TTM on intestinal microbiota in post-resuscitation patients.
2. To explore a novel compound for pharmacological hypothermia therapy.

本共同研究の①研究目的の達成度、②将来性、③帰国後の展開予定について述べて下さい。
（请就本次合作研究题目的①研究目的的达标情况、②未来的发展可能性、③您回国后今后的合作研究的规划打算作一论述）

【達成度】（达标情况）

Basically achieved the expected purpose.

【将来性】（未来的可能性）

1. In future , we will send 1-2 research fellows from China to Japan to continue our research.
2. We hope that our results can be cited or included into AHA CPR guideline.

【帰国後共同研究の展開予定】（回国后的合作规划）

3. In future , we will send 1-2 research fellows from China to Japan to continue our research.
4. We plan to organize an international conference in 2025 related to mild hypothermia therapy for further communication, and invite Dr Shoji Yokobori to visit our hospital.
5. We plan to appoint Dr Shoji Yokobori as our honorary professor.

研究者自署：

日中笹川医学奨学金制度＜共同研究コース＞研究報告書

＊英語または日本語で作成(请用日文或英文书写)

第 45 期　　研究者番号(研究者编号)：K4523　　作成日(书写日期)：2024 年 12 月 2 日

氏　名 (姓名)	ZHU KAI 朱凯	性別 (性别)	M	生年月日 (出生日期)	1982/12/27

研 究 テーマ (研 究 题 目)	Analysis of surgical approaches for elderly patients with colorectal cancer liver metastases in Japan and China
研究期間(来日～帰国まで) (来日起至回国的研究起止时间)	2024 年 7 月 1 日 ～2024 年 12 月 31 日
在日共同研究機関・部署 (在日共同研究单位及部门)	Hepato-Biliary-Pancreatic Surgery Division, Artificial Organ and Transplantation Division, Department of Surgery, Graduate School of Medicine, the University of Tokyo
共同研究者氏名・役職 (共同研究者姓名/职务)	Kiyoshi Hasegawa, Professor

学会参加について
(关于在日期间参加学会)

有り(有参加) ☐　　なし(没有参加) ☐

※参加有の方は下記の欄をご記入下さい。(有参加学会者，请继续填写如下内容)

一般参加 (普通参加)	学会名称：
一般参加 (普通参加)	学会名称：
発表有り (有发表)	学会名称： 発表テーマ(发表题目)：
発表有り (有发表)	学会名称： 発表テーマ(发表题目)：

論文発表について
(关于在日期间论文发表)

発表有/投稿中(已发表或投稿中) ☐　　発表なし(没有发表) ☐

※既にもしくは発表予定有りの方は下記の欄をご記入下さい。
(已发表或有论文投稿中的，请填写如下内容，并另外单独附上全部论文内容的复印件)

テーマ(题目)：

著者名(作者名)：

雑誌名(期刊名)：

発行年(发表年度)：
巻　号(刊卷)：
ページ(页数)：
インパクトファクター(影响因子)：

日本滞在中の具体的な共同研究内容についての報告
（关于在日期间就研究题目具体开展的共同研究内容的详述）

【研究目的】（研究目的）

The aim of this project is to compare the impact of treatment protocols on short-term and long-term prognosis and survival rates in very elderly CRLM patients, as well as the correlation between guideline adherence and clinical effectiveness.

【研究経過】（研究经过）

We intend to enroll CRLM patients aged over 80-year-old receiving liver resection from 2011 to 2020 in Hepato-Biliary-Pancreatic Surgery Division, Artificial Organ and Transplantation Division, Graduate School of Medicine, the University of Tokyo and Department of Liver Surgery and Transplantation, Liver Cancer Institute, Zhongshan Hospital, Fudan University. Clinical data such as clinical characteristics, treatment strategy, short and long term prognosis will be collected and analyzed. We will also compare the differences of guidelines in treating CRLM between two countries.

【成果】（成果）

The collecting of data from China has been finished, and the collecting of data from Japan is in progress. Once collecting is finished, immediate collation and analysis of the data from both sides will be proceeded. We are sure that there will be insightful results, which will help us improve the treatment of CRLM patients aged over 80-year-old.

【今後の論文発表予定】（今后论文发表的计划）

Our goal is to complete the research, and get the results published in an academic, peer-reviewed journal.

【今後の課題】（今后的课题）

The research will go on even when I go back to China. Long term surveillance will keep going and we will stay connected with Prof Hasegawa and the colleagues. We can also expand this idea to other tumor types, such as hepatocellular carcinoma, intrahepatic cholangiocarcinoma and perihilar carcinoma

本共同研究の①研究目的の達成度、②将来性、③帰国後の展開予定について述べて下さい。
（请就本次合作研究题目的①研究目的的达标情况、②未来的发展可能性、③您回国后今后的合作研究的规划打算作一论述）

【達成度】（达标情况）
The collecting of data from China has been finished, and the collecting of data from Japan is in progress. Once collecting is finished, immediate collation and analysis of the data from both sides will be proceeded.

【将来性】（未来的可能性）
We are sure that there will be insightful results, which will help us improve the treatment of CRLM patients aged over 80-year-old.

【帰国後共同研究の展開予定】（回国后的合作规划）
The research will go on even when I go back to China. Long term surveillance will keep going and we will stay connected with Prof Hasegawa and the colleagues. We can also expand this idea to other tumor types, such as hepatocellular carcinoma, intrahepatic cholangiocarcinoma and perihilar carcinoma

研究者自署：朱凯

日中笹川医学奨学金制度＜共同研究コース＞
日中共同研究に関わる報告書

作成日：2025 年 2 月 23 日

氏 名（漢字）	水島 昇	氏名（ローマ字）	MIZUSHIMA Noboru
所属機関・部署・役職	東京大学大学院医学系研究科分子細胞生物学専攻 生化学・分子生物学講座　教授		
研究テーマ	新規オートファジー阻害剤の同定		
中国側共同研究者 氏名と研究者番号	蒋 培都　K4524	中国側共同研究者 所属機関	電子科技大学附属医院・四川省人民医院

本共同研究の①研究目的の達成度、②将来性、③今後の展望や予定について述べて下さい。

【達成度】

蒋培都氏が見出したオートファジー制御化合物#524 について、まず当研究室が作成したオートファジーフラックスプローブを用いてオートファジー活性の定量的測定を行ったところ、#524 によってオートファジーが有意に抑制されることが示された。次に、その作用メカニズムについて解析を行った。さまざまなオートファジー因子の局在におよぼす影響を解析した結果、#524 はオートファジーの比較的初期のステップでオートファジーを抑制している可能性が考えられた。また、生化学的解析によって、オートファジーの抑制因子である mTORC1 複合体を活性していることが明らかとなった。よって、#524 はオートファジーの上流に作用している可能性が考えられた。一方で、電子顕微鏡観察ではオートファゴソームの蓄積もみられたことから、#524 はオートファジーの下流も抑制するという複雑な効果を有している可能性も示唆された。これらの実験は当初予定していたものであり、今回の共同研究の目的は十分に達成されたと言える。

【将来性】

オートファジーの制御メカニズムはまだ不明な点も多い。これまでは遺伝学や生化学が主体的であったが、蒋培都氏が行っているような、オートファジー制御化合物の標的を調べるような、いわゆる「ケミカルバイオロジー」的なアプローチも大変有効である。今後、従来の方法では同定されてこなかった、新しいオートファジー制御機構が明らかにされる可能性がある。

【今後の展望】

今後、蒋培都氏とは#524 に関する共同研究を継続する予定である。また、オートファゴソームとリソソームの融合に関するより包括的な共同研究も検討中である。日本と中国とでは定期的に合同研究会が開催されており、多くの研究者間で盛んに情報交換や共同研究がなされている。そのような仕組みも利用しながら、蒋培都氏とも密に交流を維持する予定である。2025 年 7 月には、四川を訪問し蒋培都氏とも面会する予定である。

日本側共同研究者記名：水島 昇

日中笹川医学奨学金制度＜共同研究コース＞研究報告書

Supported by 日本財団 THE NIPPON FOUNDATION

＊英語または日本語で作成(请用日文或英文书写)

第 45 期　研究者番号(研究者编号)：K4524　作成日(书写日期)：2024 年 9 月 11 日

氏　名 (姓名)	JIANG PEIDU（蒋 培都）	性別 (性别)	M	生年月日 (出生日期)	1982. 12. 24

研 究 テーマ (研 究 题 目)	Identification of a novel autophagic inhibitor
研究期間(来日～帰国まで) (来日起至回国的研究起止时间)	2024 年 4 月 26 日 ～ 2024 年 9 月 30 日
在日共同研究機関・部署 (在日共同研究单位及部门)	Department of Biochemistry and Molecular Biology Graduate School and Faculty of Medicine The University of Tokyo
共同研究者氏名・役職 (共同研究者姓名/职务)	Noboru MIZUSHIMA・Professor
学会参加について (关于在日期间参加学会)	有り(有参加) ☐　なし(没有参加) ☒ ※参加有の方は下記の欄をご記入下さい。(有参加学会者，请继续填写如下内容)
一般参加 (普通参加)	学会名称：
一般参加 (普通参加)	学会名称：
発表有り (有发表)	学会名称： 発表テーマ(发表题目)：
発表有り (有发表)	学会名称： 発表テーマ(发表题目)：
論文発表について (关于在日期间论文发表)	発表有/投稿中(已发表或投稿中) ☐　発表なし(没有发表) ☒ ※既にもしくは発表予定有りの方は下記の欄をご記入下さい。 (已发表或有论文投稿中的，请填写如下内容，并另外单独附上全部论文内容的复印件)
	テーマ(题目)：
	著者名(作者名)：
	雑誌名(期刊名)：
	発行年(发表年度)： 巻　号(刊卷)： ページ(页数)： インパクトファクター(影响因子)：

日本滞在中の具体的な共同研究内容についての報告
（关于在日期间就研究题目具体开展的共同研究内容的详述）

【研究目的】（研究目的）

The ultimate goal of our collaborative research is to discover and develop novel chemical compounds that can effectively modulate autophagy. These compounds could provide new therapeutic options for diseases characterized by excessive autophagy, such as cancer and autoimmune disorders.

【研究経過】（研究经过）

To achieve this goal, we first utilized GFP-LC3 and GFP-STX17 assays to identify potential autophagy inhibitors. Next, we aim to elucidate the precise mechanisms by which these compounds modulate autophagy. We will then assess their efficacy and safety across various disease models. Finally, we will explore potential synergistic effects when combined with existing therapeutic agents.

【成果】（成果）

Our collaborative research has successfully identified compound #524 as a novel autophagy inhibitor. This compound shows promise as a therapeutic agent for diseases characterized by excessive autophagy.

【今後の論文発表予定】（今后论文发表的计划）

Looking ahead, our publication plans are as follows:

- Conduct a comprehensive analysis of the mechanisms by which compound #524 inhibits autophagy.
- Evaluate the compound across multiple disease models to assess its broader therapeutic potential.
- Investigate the synergistic effects of compound #524 in combination with other therapies.
- Summarize our findings and prepare a manuscript for submission to a leading cell biology journal.
- Address peer review feedback and finalize the manuscript for publication.

【今後の課題】（今后的课题）

Moving forward, our continued collaborative efforts will focus on detailed mechanism studies, preclinical testing, and manuscript preparation for publication.

本共同研究の①研究目的の達成度、②将来性、③帰国後の展開予定について述べて下さい。
（请就本次合作研究题目的①研究目的的达标情况、②未来的发展可能性、③您回国后今后的合作研究的规划打算作一论述）

【達成度】（达标情况）

With the full support of the Japanese research team, we successfully completed the planned research in a relatively short period of time. First, we confirmed that Compound #524 significantly inhibits autophagy activity. We then conducted an in-depth study of the molecular mechanisms underlying this inhibition. Due to the inspection and quarantine regulations for experimental animals, we were unable to transport the conditional gene knockout mice that had already been developed in China to Japan within the required timeframe. Upon my return to China, I will carry out a detailed study on the efficacy and safety of Compound #524 in in vivo experiments.

【将来性】（未来的可能性）

Autophagy is a crucial intracellular degradation pathway, and its dysfunction has been associated with the onset and progression of various diseases. The primary goal of our collaborative research is to identify and develop novel chemical compounds that can effectively modulate autophagy. Such compounds have the potential to offer new therapeutic options for diseases characterized by excessive autophagy, including cancer and autoimmune disorders..

【帰国後共同研究の展開予定】（回国后的合作规划）

We remain dedicated to advancing our collaborative research projects and will continue exploring the therapeutic potential of the compound across various disease models. Additionally, we will examine the synergistic effects of compound #524 in combination with other treatments. Supported by the Japan China Sasakawa Medical Fellowship, we look forward to publishing the results of this cooperative research in leading international academic journals. We are confident that our findings will contribute to the health and well-being of both nations and, ultimately, to the betterment of humanity.

研究者自署： Peidu JIANG

日中笹川医学奨学金制度＜共同研究コース＞
日中共同研究に関わる報告書

Supported by 日本財団 THE NIPPON FOUNDATION

作成日：2025 年 3 月 3/日

氏 名（漢字）	安井 寛	氏名（ローマ字）	YASUI Hiroshi
所属機関・部署・役職	聖マリアンナ医科大学　血液・腫瘍内科学　特任教授		
研究テーマ	リンパ系悪性腫瘍の免疫細胞治療感受性のための免疫オミクスに基づく人工知能モデル		
中国側共同研究者 氏名と研究者番号	王 慧涵、燕 瑋 K4526	中国側共同研究者 所属機関	中国医科大学附属盛京医院

本共同研究の①研究目的の達成度、②将来性、③今後の展望や予定について述べて下さい。

【達成度】
本共同研究期間中、中国側共同研究者である燕副教授が筆頭著者を務めた研究成果「Phosphatidylcholine deactivates cytotoxic CD8+ T cells through UFMylation mediated by exosomal serpinB9 in multiple myeloma」が Nature Communication 誌に受理され、国際的に高く評価される研究成果として結実した。また、日本側研究者と共同で、多発性骨髄腫に対する CAR-T 細胞療法の最新動向と将来展望をまとめた英文総説の執筆にも取り組み、現在は投稿に向けた原稿整備の最終段階にある。さらに、CAR-T 細胞治療後の免疫指標の検討、CAR-T 細胞の機能解析、人工骨モデルを用いた骨病変評価など、多面的な研究活動に取り組み、日中両国の症例データを活用した AI モデル構築にも着手した。半年という限られた期間において、基礎・臨床・データサイエンスを横断する幅広い成果をあげた点で、本共同研究の目的は達成されたと評価できる。

【将来性】
多発性骨髄腫や悪性リンパ腫といった血液腫瘍領域においては、国内症例数の限界が臨床研究推進の障壁となることがしばしば指摘されている。一方、中国医科大学附属盛京医院は年間多数の症例を有し、造血器疾患に関する豊富な臨床データと経験を蓄積している点で、国際共同研究のパートナーとして非常に有望である。とりわけ CAR-T 細胞療法においては、中国国内での臨床試験件数は世界有数であり、実地での知見が豊富であることに加え、日本は薬事承認や製品化における制度的優位性を有しており、両国の強みを補完的に活かす形での協働が可能である。加えて、中国医科大学は日本語教育課程を有する希少な医科大学であり、言語的・文化的障壁が比較的低く、円滑な意思疎通と実務協力、学生や若手研究者間の学術交流などが期待できる。こうした背景から、日中の共同研究には高い発展性と持続可能性があるといえる。

【今後の展望】
今後、免疫オミクスと AI 技術を融合した個別化免疫療法の確立を目指し、以下の取り組みを順次展開する予定である。
・臨床・オミクスデータの統合による大規模データベースの構築：複数の国内外医療機関と連携し、データ共有体制を構築。AI モデル訓練のための多様な症例情報の収集を進める。
・AI 予測モデルの最適化と多施設での臨床実証：既存モデルに改良を加え、予測精度・汎化性能を高めたうえで、実臨床における予測応用を推進する。
・新規免疫細胞治療法の共同開発：CAR-T 細胞に加え、次世代の TCR-T、NK 細胞治療、ワクチン療法なども視野に入れ、日中および他国との多国間連携を模索する。
・他疾患領域への応用拡大：多発性骨髄腫のみならず、悪性リンパ腫など他の造血器腫瘍、AL アミロイドーシスなど他の造血器疾患への展開も視野にいれる。
・医療 AI プラットフォームの開発と人材育成：バイオインフォマティクスと医療現場を結ぶ架け橋となる研究基盤の整備と、次世代研究者育成への貢献。
こうした取り組みを通じて、腫瘍免疫療法の精密化・個別化に寄与し、アジア発の国際的研究成果の創出に向けた継続的な努力が期待される。

日本側共同研究者記名：安井寛

日中笹川医学奨学金制度＜共同研究コース＞研究報告書

＊英語または日本語で作成(请用日文或英文书写)

第 45 期　　研究者番号(研究者编号)：K4526　　作成日(书写日期)：2025 年 1 月 23　日

氏　　名	WANG HUIHAN 王 慧涵	性別	F	生年月日	1979.12.06
所属機関・部署	Department of Hematology, Shengjing hospital, China Medical University				
チームメンバー（成　　員）	YAN WEI 燕 玮				

研 究 テーマ（研 究 题 目）	Establishment of artificial intelligence model of immune cell therapy sensitivity of Lymphocyte malignant tumors based on immunoomics
研究期間(来日～帰国まで)（来日起至回国的研究起止时间）	2024 年 8　月　30　日 ～ 2025　年　2　月　28　日
在日共同研究機関・部署（在日共同研究单位及部门）	St. Mariana Medical University/Department of Hematologic Oncology
共同研究者氏名・役職（共同研究者姓名/职务）	Hiroshi Yasui/Special professor

学会参加について Special professor(关于在日期间参加学会)

有り(有参加)　√□　　なし(没有参加)　□

※参加有の方は下記の欄をご記入下さい。(有参加学会者，请继续填写如下内容)

一般参加（普通参加）	学会名称：
一般参加（普通参加）	学会名称：
発表有り（有发表）	学会名称：The 86th Annual Meeting of the Japanese Society of Hematology 発表テーマ(发表题目)： P1-7-6“Phosphatidylcholine deactivates cytotoxic CD8+ T cells through UFMylation mediated by exosomal serpinB9 in multiple myeloma”
発表有り（有发表）	学会名称： 発表テーマ(发表题目)：

論文発表について（关于在日期间论文发表）

発表有/投稿中(已发表或投稿中) √□　　発表なし(没有发表)□

※既にもしくは発表予定有りの方は下記の欄をご記入下さい。
(已发表或有论文投稿中的，请填写如下内容，并另外单独附上全部论文内容的复印件)

テーマ(题目)：Phosphatidylcholine deactivates cytotoxic CD8+ T cells through UFMylation mediated by exosomal serpinB9 in multiple myeloma

著者名(作者名)：Yan Wei, Shi Xue, Hiroshi Yasui , Wang Huihan

雑誌名(期刊名)：Natural Communication

発行年(发表年度)：

巻　号(刊卷)：

ページ(页数)：

インパクトファクター(影响因子)：

日本滞在中の具体的な共同研究内容についての報告
（关于在日期间就研究题目具体开展的共同研究内容的详述）

【研究目的】（研究目的）

Over the years, the incidence of lymphoid malignancies (such as lymphoma and leukemia) has been increasing year by year, becoming a major category of diseases that seriously threaten human health. Immune cell therapy, especially CAR-T cell therapy, provides new treatment strategies for these diseases. However, the responses of patients to immune cell therapy vary greatly, with some showing significant therapeutic effects while others have limited or even no effect. Therefore, establishing an accurate model for predicting the sensitivity of immune cell therapy is of great significance for improving the success rate of treatment and the quality of life of patients. The purpose of this exchange is to explore international cooperation in CAR-T technology based on immunomics technology and artificial intelligence methods.

【研究経過】（研究经过）

Before deciding to study abroad, I first made a comprehensive investigation on the current research situation in this field at home and abroad. Through reviewing literature, attending academic conferences and communicating with peers, I found that foreign countries have accumulated a lot of experience and data in tumor immunotherapy combined with immunoomics and AI, especially in data processing, algorithm optimization and clinical application. In the process of preparing for the application, I focused on improving my scientific research ability and Japanese language proficiency. I have participated in a number of scientific research projects, accumulated rich experimental data and writing experience, and participated in many international academic conferences, establishing preliminary contacts with foreign scholars. Through unremitting efforts, he finally collaborated with Professor Hiroshi Yasui of St. Mariana Medical University of Japan under the support of Sasakawa Scholarship in Japan.

After arriving in Japan on August 30, 2024, I will settle down and go through the relevant procedures. In the face of the challenges of language and cultural differences, I will quickly adjust my mind and devote myself to my study and work. On September 4, 2024, he participated in the 45th Joint Research researcher Exchange meeting held at the Japan Foundation in Tokyo, where he made a research plan and reported the current research results of the project "Establishment of artificial intelligence model of immune cell therapy sensitivity of Lymphocyte malignant tumors based on immunoomics". Research work: 1. Peripheral blood of patients before and after receiving CAR-T therapy was collected. Relevant clinical data were collected, including cancer type, age, previous treatment regimen, efficacy, staging, stratification, CAR-T treatment efficacy, side effects, etc. 2. Flow cytometry was used to detect immune indicators (TNF/IL/INF) in peripheral blood. 3. Use immunoomics information to establish artificial intelligence models to predict the efficacy and safety of CAR-T therapy. 4. Validated the model with Chinese and Japanese patient data. 5. Apply the constructed artificial intelligence model before clinical treatment to improve the clinical therapeutic effect of CAR-T. In the previous research, we have applied the routine laboratory indicators of multiple myeloma patients to establish an early diagnosis AI model, and have mastered and mastered the artificial intelligence model construction method. At present, CAR-T therapy for myeloma has been carried out, and 4 patients have received treatment. Professor Yasui of St. Mariana Medical University used MI-FCM to quantitatively assess the percentage of CAR cells concentrated and the number of enrichment points to detect the immune function of CAR cells.

During the exchange, I followed Professor Yasui to visit the artificial bone Model Laboratory of the Science and Technology Department of Meiji University, Japan, reported on myeloma osteopathy, carried out scientific research cooperation on the related role of myeloma cells and bone, and jointly built myeloma artificial bone model. Related cell cultures were performed, including myeloma cells, osteoblasts, osteoclasts, myeloma cells combined with HA, HA with osteoblasts, HA with osteoclasts. Read a lot of articles related to CAR T-cell therapy for multiple myeloma, and co-authored the review "CAR T-cell therapy for multiple myeloma: current status and future perspectives" with Professor Yasui. Cd19-car-t cell related studies were carried out. Eight CAR-T cells from healthy volunteers were cloned and tested for cytotoxicity after being stimulated by CD19 antigen. CAR-T cell depletion related indexes (PD-1/LAG-3/TIGIT) were detected.

During the exchange, I followed Professor Yasui to visit the outpatient and ward of hematology Department of St. Mariana Medical University, and carried out related clinical practice. Japan has rich experience in the treatment of hematologic malignancies, the world's leading transplantation technology, and the perfect national medical insurance system, which promotes the application of many new drugs and new technologies. CAR-T technology, as a hot spot in the treatment of hematologic malignancies, is also widely carried out in Japan. Professor Yasui has rich experience in clinical and scientific research. An appointment system is implemented in the outpatient department, and five patients are booked in each outpatient department. Although the number of patients is small, the doctor explains the condition, treatment plan, related risks, and prognosis in detail, and fully communicates with the patients, and suitable patients are admitted to the ward for hospitalization. The wards set up transplantation wards, CAR-T treatment wards and intensive care wards, and

carry out relevant treatment and nursing for patients according to different treatment schemes. Under the guidance of Professor Yasui, I systematically learned the acquisition, processing and analysis methods of immunoomics data, and deeply understood the application of various machine learning algorithms and deep learning models in tumor immunotherapy. I have participated in several research projects related to immune cell therapy for lymphocytic malignancies, from sample collection, data processing to model building, striving for excellence in every step. Through continuous practice, I not only improved my experimental skills, but also gradually mastered the construction and optimization methods of AI models. In order to verify the accuracy and reliability of the AI model, I collected a large amount of clinical data, including patients' immunoomics data, treatment response data and survival data. In the process of data processing and analysis, I encountered many challenges. For example, immunoomics data is characterized by high dimensionality, sparsity and loud noise, which brings great difficulties to model training. In order to solve this problem, I tried a variety of feature selection and data dimensionality reduction methods, optimized the model parameters, and finally established a stable AI model with good predictive effect. In the experimental validation phase, I worked closely with the Japanese clinical team to apply the model to actual patient samples, evaluating its ability to predict sensitivity to immune cell therapy. The results show that the model can accurately predict the treatment response of patients, which provides strong support for the formulation of individualized treatment plan.

【成果】（成果）

Read a lot of articles related to CAR T-cell therapy for multiple myeloma, and co-authored the review "CAR T-cell therapy for multiple myeloma: current status and future perspectives" with Professor Yasui. Cd19-car-t cell related studies were carried out. Eight CAR-T cells from healthy volunteers were cloned and tested for cytotoxicity after being stimulated by CD19 antigen. CAR-T cell depletion related indexes (PD-1/LAG-3/TIGIT) were detected.

As poster P1-7-6 "Phosphatidylcholine deactivates cytotoxic CD8+ T cells through UFMylation mediated by exosomal serpinB9 in. "multiple myeloma" co-investigators participated in the Japan Hematology Congress held in Kyoto on October 11, 2024, to exchange ideas with scholars from all over the world and broaden their horizons. These experiences not only enriched my body of knowledge, but also made me deeply realize the importance of teamwork and interdisciplinary communication.

Co-wrote the article with the title of "Phosphatidylcholine deactivates cytotoxic CD8+ T cells through UFMylation mediated by exosomal serpinB9 in. "multiple myeloma", and is in the process of reviewing the manuscript of Natural Communication.

【今後の論文発表予定】（今后论文发表的计划）

After returning to China, I plan to first establish my own research team in a well-known university or scientific research institution in China, continue to deepen the research on the artificial intelligence model of immune cell therapy sensitivity of lymphocyte malignant tumors based on immunoomics, and publish relevant papers. Specifically, I will start from the following aspects:

Data integration and sharing: Establish cooperative relations with a number of medical institutions and scientific research institutions at home and abroad, integrate more clinical data and immunoomics data, form a shared database, and provide sufficient data support for model training and verification.

Model optimization and validation: On the basis of the existing model, further optimize the algorithm and parameters to improve the accuracy and generalization ability of the model. At the same time, a large-scale clinical validation study was carried out to evaluate the effect of the model in practical application.

Results translation and application: Work closely with clinical teams to translate research results into clinical applications and provide personalized immune cell therapy for patients. At the same time, we actively seek cooperation with biomedical enterprises to promote the industrialization and commercialization of the results.

【今後の課題】（今后的课题）

On the basis of the short-term plan, I will further expand the research direction and explore other influencing factors of immune cell therapy sensitivity, such as genetic background and environmental factors. Design and writing topics:

Multi-omics data fusion: Integrate multi-omics data such as genome, transcriptome, proteome and metabolome to build a more comprehensive bioinformatics model and reveal the molecular mechanism of immune cell therapy sensitivity.

Novel biomarker screening: Using AI algorithms to screen biomarkers related to immune cell therapy sensitivity, providing new targets for clinical diagnosis and treatment.

Clinical application expansion: The research results will be extended to other types of tumors and immune system diseases to explore the broad application prospects of immune cell therapy.

本共同研究の①研究目的の達成度、②将来性、③帰国後の展開予定について述べて下さい。
（请就本次合作研究题目的①研究目的的达标情况、②未来的发展可能性、③您回国后今后的合作研究的规划打算作一论述）

【達成度】（达标情况）
Complete the research objectives as planned during the study in Japan.

【将来性】（未来的可能性）
The experience of studying abroad has benefited me a lot. I not only improved my scientific research ability and academic level, but also cultivated my ability to think independently and solve problems. These experiences make me more confident to face the challenges ahead. After returning to China, I will continue to devote myself to the research of the artificial intelligence model of immune cell therapy sensitivity of lymphocyte malignant tumors based on immunoomics, and contribute my strength to promoting the individualized, precise and intelligent development of tumor immunotherapy. I believe that in the near future, our research results will bring benefits to the vast number of patients.

【帰国後共同研究の展開予定】（回国后的合作规划）
In the long-term plan, I will be committed to promoting the individualized, precise and intelligent development of tumor immunotherapy. Specifically, I will start from the following aspects:
Intelligent medical platform construction: Integrate medical resources, bioinformatics data and AI algorithms to build an intelligent tumor immunotherapy platform to provide patients with a full range of personalized diagnosis and treatment services.
International cooperation and exchange: Strengthen cooperation and exchange with well-known universities, scientific research institutions and medical institutions at home and abroad, and jointly promote scientific and technological progress and clinical application in the field of tumor immunotherapy.
Talent training and team building: Cultivate a group of young scholars and researchers with innovative spirit and practical ability, and build a high-level tumor immunotherapy research team.

研究者自署：王慧涵

日中笹川医学奨学金制度＜共同研究コース＞
日中共同研究に関わる報告書

Supported by 日本財団 THE NIPPON FOUNDATION

作成日：2025 年 5 月 20 日

氏 名（漢字）	ニヨンサバ フランソワ	氏名（ローマ字）	François NIYONSABA
所属機関・部署・役職	順天堂大学大学院医学研究科アトピー疾患研究センター　副センター長、教授		
研究テーマ	アトピー性皮膚炎におけるスルフォラファンの緩和効果に関する研究		
中国側共同研究者 氏名と研究者番号	王　珊　K4527	中国側共同研究者 所属機関	首都医科大学附属北京児童医院

本共同研究の①研究目的の達成度、②将来性、③今後の展望や予定について述べて下さい。

【達成度】

王　珊氏は、順天堂大学アトピー疾患研究センターでの共同研究期間中、アトピー性皮膚炎におけるスルフォラファンの作用機序解明に真摯に取り組まれ、着実に成果を上げられました。分子生物学的手法や動物モデルを用いた実験を積極的に習得され、当研究室のプロジェクトに大きく貢献されました。これらの成果は現在、論文としてまとめられており、近い将来の学術誌への投稿が期待されます。また、国際学会での発表準備も進められ、研究成果の発信にも尽力されています。

【将来性】

本研究で得られた知見は、アトピー性皮膚炎に対する新規治療法開発に向けた重要な一歩となります。スルフォラファンという天然化合物を用いたアプローチは、副作用の少ない治療オプションとして大きな可能性を秘めています。今後は、より詳細な分子メカニズムの解明と、臨床応用に向けた前臨床試験の実施が期待されます。また、日中共同研究の枠組みを活かし、より大規模なデータ収集と解析を進めることで、この分野のさらなる発展に寄与できると確信しております。

【今後の展望】

王　珊氏の帰国後も、現在進行中の研究プロジェクトを円滑に完了させるため、データの最終解析と論文執筆を引き続き共同で進めて参ります。特に、スルフォラファンの長期的な治療効果および安全性の検討は、今後の重要な研究課題となるでしょう。さらに、順天堂大学と北京児童病院との共同研究を一層発展させるべく、共同論文の執筆や国際共同研究資金の申請、研究者交流プログラムの推進、学術セミナーの共催などを通じて、両機関の連携をより強化して参ります。また、本研究で確立した手法や知見を基盤として、新たな臨床応用研究へと発展させることで、日中両国の医療発展に大きく貢献できるものと確信しております。

日本側共同研究者記名：ニヨンサバ フランソワ

日中笹川医学奨学金制度<共同研究コース>研究報告書

Supported by 日本財団 THE NIPPON FOUNDATION

＊英語または日本語で作成(请用日文或英文书写)

第45期　研究者番号(研究者编号)：K4527　作成日(书写日期)：2025年5月20日

氏名 (姓名)	Wang Shan 王珊	性別 (性别)	F	生年月日 (出生日期)	1988/01/29

研究テーマ (研究题目)	Exploration of mechanistic insights into the potential alleviating effects of sulforaphane in atopic dermatitis
研究期間(来日～帰国まで) (来日起至回国的研究起止时间)	2024年5月3日 ～ 2025年6月30日
在日共同研究機関・部署 (在日共同研究单位及部门)	Atopy (Allergy) Research Center, Juntendo University Graduate School of Medicine
共同研究者氏名・役職 (共同研究者姓名/职务)	François NIYONSABA, Professor

学会参加について (关于在日期间参加学会)

有り(有参加) ✓　　なし(没有参加) □

※参加有の方は下記の欄をご記入下さい。(有参加学会者，请继续填写如下内容)

一般参加 (普通参加)	学会名称：The 123rd Annual Meeting of the Japanese Dermatological Association. Kyoto, Japan
一般参加 (普通参加)	学会名称：
発表有り (有发表)	学会名称：14th Georg RAJKA International Society of Atopic Dermatitis (ISAD), Doha, Qatar 発表テーマ(发表题目)： SERPINB7 mutations in hereditary palmoplantar keratosis and atopic dermatitis
発表有り (有发表)	学会名称：The 49th Annual Meeting of the Japanese Society for Investigative Dermatology. Nagoya, Japan 発表テーマ(发表题目)：Potential alleviating effect of sulforaphane on atopic dermatitis
発表有り (有发表)	学会名称：The 124th Annual Meeting of the Japanese Dermatological Association. Yokohama, Japan 発表テーマ(发表题目)：Potential alleviating effect of microbial metabolite hypoxanthine on atopic dermatitis

論文発表について (关于在日期间论文发表)

発表有/投稿中(已发表或投稿中) ✓　　発表なし(没有发表) □

※既にもしくは発表予定有りの方は下記の欄をご記入下さい。
(已发表或有论文投稿中的，请填写如下内容，并另外单独附上全部论文内容的复印件)

テーマ(题目)：The interaction between the skin microbiome and antimicrobial peptides within the epidermal immune microenvironment: Bridging insights into atopic dermatitis

著者名(作者名)：Shan Wang, Ge Peng, Alafate Abudouwanli, Mengyao Yang, Quan Sun, Wanchen Zhao, Arisa Ikeda, Yi Tan, Lin Ma, Hideoki Ogawa, Ko Okumura, François Niyonsaba

	雑誌名(期刊名)：Allergology International
	発行年(发表年度)：Under revision 巻　号(刊卷)：－ ページ(页数)：－ インパクトファクター(影响因子)：6.2
	テーマ(题目)：Improvement of atopic dermatitis-like symptoms in a murine model via the chromogranin A-derived peptide catestatin
	著者名(作者名)：Ge Peng, Wanchen Zhao, Alafate Abudouwanli, Quan Sun, Mengyao Yang, Shan Wang, Yi Tan, Arisa Ikeda, Shigaku Ikeda, Hideoki Ogawa, Ko Okumura, François Niyonsaba
	雑誌名(期刊名)：Allergology International
	発行年(发表年度)：2025 巻　号(刊卷)：Feb 21 ページ(页数)：9 インパクトファクター(影响因子)：6.2
	テーマ(题目)：AMP-IBP5: a multifunctional antimicrobial peptide for advanced wound healing and inflammatory skin disorders
	著者名(作者名)：Alafate Abudouwanli, Ge Peng, Mengyao Yang, Wanchen Zhao, Quan Sun, Shan Wang, Yi Tan, Arisa Ikeda, Hideoki Ogawa, Ko Okumura, François Niyonsaba
	雑誌名(期刊名)：Journal of Functional Biomaterials
	発行年(发表年度)：2025 巻　号(刊卷)：16(5) ページ(页数)：14 インパクトファクター(影响因子)：5.0

日本滞在中の具体的な共同研究内容についての報告
（关于在日期间就研究题目具体开展的共同研究内容的详述）

【研究目的】（研究目的）

Research Background and Significance

Atopic dermatitis (AD) is a chronic inflammatory skin disorder marked by impaired skin barrier function, dysregulated immune responses, and microbial dysbiosis. Conventional therapies primarily aim to alleviate symptoms; however, effective and sustainable treatment options remain limited. Recent research underscores the potential of natural bioactive compounds and microbiome-based interventions in modulating AD pathogenesis. Sulforaphane (SFN), a bioactive compound derived from cruciferous vegetables, has demonstrated notable antioxidative and anti-inflammatory properties. Nevertheless, its effects on inflammatory skin conditions such as AD have not been fully elucidated.

Research Objectives

This study aims to investigate the potential therapeutic effects and underlying mechanisms of SFN in the context of AD.

【研究経過】（研究经过）

Using bioinformatics databases including Swiss Target Prediction, DisGeNET, GeneCards, and STRING, we identified overlapping molecular targets associated with both SFN and AD. These targets include NOS2, NOS3, EGFR, DUSP1, MAPK1, MAPK14, JAK1, JAK2, and TYK2. Pathway analysis conducted via Metascape and KEGG enrichment highlighted several key signaling pathways, notably the AGE/RAGE/MAPK pathway. In our *in vitro* experiments, SFN was found to downregulate the mRNA expression of pro-inflammatory cytokines IL6 and IL33, as well as antimicrobial peptides, including human b-defensin-2(hBD2), in normal human epidermal keratinocytes stimulated with IL-4, IL-13, LPS, or poly I:C. Simultaneously, SFN upregulated the expression of *TJP1*, a gene associated with skin barrier integrity.

These findings suggest that SFN may exert anti-inflammatory and barrier-supportive effects by modulating key cytokines and signaling pathways involved in AD pathogenesis, potentially through regulation of the AGE/RAGE/MAPK signaling axis.

【成果】（成果）

1. Theoretical contributions: Our findings suggest that SFN may alleviate the clinical manifestations of AD and exert anti-inflammatory effects by modulating the expression of key cytokines involved in AD pathogenesis. This mechanism is potentially mediated through the regulation of the AGE/RAGE/MAPK signaling pathway.
2. Scholarly publications: I have completed a review article, which is currently under revision based on reviewers' feedback.
3. Research collaboration: I have co-authored two articles published in peer-reviewed academic journals.
4. Academic Presentations:I delivered an oral presentation at an international academic conference. In addition, I presented research in poster format at two academic conferences held in Japan.

【今後の論文発表予定】（今后论文发表的计划）

1. I submitted a review article, which is currently under revision based on reviewers' comments.
2. I am in the process of preparing a research article for submission.

【今後の課題】（今后的课题）

In the near future, I plan to apply for Sino-Japanese collaborative research grants focusing on a novel skin barrier-related gene and its role in the pathogenesis of AD. Preliminary experiments for this project have already been conducted.

本共同研究の①研究目的の達成度、②将来性、③帰国後の展開予定について述べて下さい。
（请就本次合作研究题目的①研究目的的达标情况、②未来的发展可能性、③您回国后今后的合作研究的规划打算作一论述）

【達成度】（达标情况）

During my research exchange at Juntendo University, I successfully completed most of the planned experimental procedures. The remaining work will be continued collaboratively in both Japan and China after my return. During this period, I completed a review article (currently under review) and made significant progress on a collaborative study investigating the effects of SFN on AD (manuscript in preparation).
I actively engaged in academic exchanges, including delivering oral presentations at international conferences and participating in regular laboratory meetings. Throughout this period, I also gained extensive hands-on experience in a range of molecular and cellular techniques.

【将来性】（未来的可能性）

This collaboration has paved the way for further research into microbiome-based therapies for AD. The preliminary data and established research networks provide a strong foundation for future joint publications and grant applications, particularly in the context of Sino-Japanese collaborative projects. Moreover, the findings hold significant potential for clinical translation, especially in pediatric dermatology.

【帰国後共同研究の展開予定】（回国后的合作规划）

Upon returning to China, I will continue working with Juntendo University to finalize ongoing studies and initiate new collaborative projects. I intend to integrate the knowledge and skills acquired during my research exchange into clinical research initiatives. Additionally, I aim to promote sustained academic exchange through joint seminars, collaborative workshops, and researcher exchange programs, thereby strengthening long-term bilateral collaboration in dermatological innovation.

研究者自署：Shan Wang

日中笹川医学奨学金制度＜共同研究コース＞
日中共同研究に関わる報告書

Supported by 日本財団 THE NIPPON FOUNDATION

作成日：2025 年 5 月 14 日

氏 名（漢字）	鈴木 祐介	氏名（ローマ字）	Suzuki Yusuke
所属機関・部署・役職	順天堂大学大学院医学研究科腎臓内科学　教授		
研究テーマ	IgA 腎症における標的メサンギウム抗原の探索		
中国側共同研究者 氏名と研究者番号	李　鑫　K4528	中国側共同研究者 所属機関	中国医科大学附属第四医院

本共同研究の①研究目的の達成度、②将来性、③今後の展望や予定について述べて下さい。

【達成度】
近年我々は、腎糸球体メサンギウム細胞に対する IgA 型自己抗体が、IgA 腎症患者の血清に存在し、この抗体が、腎炎発症・進展の 1st hit を形成することを発見した（Y. Nihei, et al. Sci. Adv, 2023）。自己抗原として、β2 スペクトリンと CBX3 を同定し、抗 β2 スペクトリン IgA 抗体および抗 CBX3IgA 抗体が、IgA 腎症患者の血清に特異的に検出されることを報告した（Koizumi, et al. Kidney Int Rep, 2025）。一方、高い特異度(94%)と比較して、感度が比較的低かった(両自己抗体の陽性率は約 50%)ことから、我々は、IgA 腎症には、β2 スペクトリンと CBX3 以外の標的自己抗原が存在する可能性を考え、本共同研究にて検証した。
複数の IgA 腎症患者の腎生検切片から、レーザーマイクロダイセクション法を用いて糸球体成分を収集した。収集糸球体成分から、Jacalin ビーズを用いて、IgA 腎症患者の糸球体に沈着している IgA 抗体を抽出した。当初精製 IgA 抗体に認識されるメサンギウム抗原を、質量分析法にて明らかにすることを計画していたが、約 5000 個の糸球体を用いても、認識メサンギウム抗原を免疫沈降するために十分な量の IgA 抗体が精製できなかった。したがって、今後は他の手法を用いて抗原同定を行う必要があると考えられた。

【将来性】
IgA 腎症における新たな自己抗原を同定することを目標とする本共同研究は、IgA 腎症病態解明に向けて重要な意義を持つ。中国側共同研究者である李鑫は、深い探求心と研究課題達成に向けた粘り強さを持ち合わせており、将来的に新たな自己抗原が同定できる可能性は高い。

【今後の展望】
他の手法を検討し、新たな標的抗原を同定する。得られた知見を国際学会で発表し、論文報告を行う。

日本側共同研究者記名：鈴木祐介

日中笹川医学奨学金制度＜共同研究コース＞研究報告書

＊英語または日本語で作成(请用日文或英文书写)

第 45 期　　研究者番号(研究者编号)：K4528　　作成日(书写日期)：2024 年 12 月 2 日

氏　名 (姓名)	LI XIN 李　鑫	性別 (性别)	F	生年月日 (出生日期)	1993/10/26

研 究 テーマ (研 究 题 目)	Identification of Novel IgA type autoantibodies against mesangial autoantigen in patients with IgA nephropathy
研究期間(来日～帰国まで) (来日起至回国的研究起止时间)	2024 年 6 月 30 日 ～2024 年 12 月 31 日
在日共同研究機関・部署 (在日共同研究单位及部门)	Juntendo University; Nephrology department
共同研究者氏名・役職 (共同研究者姓名/职务)	Suzuki Yusuke; Professor

学会参加について
(关于在日期间参加学会)

有り(有参加) ☒　　なし(没有参加) ☐

※参加有の方は下記の欄をご記入下さい。(有参加学会者，请继续填写如下内容)

一般参加 (普通参加)	学会名称：第 25 回東京国際 IgA 腎症セミナー
一般参加 (普通参加)	学会名称：
発表有り (有发表)	学会名称： 発表テーマ(发表题目)：
発表有り (有发表)	学会名称： 発表テーマ(发表题目)：

論文発表について
(关于在日期间论文发表)

発表有/投稿中(已发表或投稿中) ☐　　発表なし(没有发表) √☒

※既にもしくは発表予定有りの方は下記の欄をご記入下さい。
(已发表或有论文投稿中的，请填写如下内容，并另外单独附上全部论文内容的复印件)

テーマ(题目)：

著者名(作者名)：

雑誌名(期刊名)：

発行年(发表年度)：
巻　号(刊卷)：
ページ(页数)：
インパクトファクター(影响因子)：

日本滞在中の具体的な共同研究内容についての報告
（关于在日期间就研究题目具体开展的共同研究内容的详述）

【研究目的】（研究目的）
IgA nephropathy (IgAN) is the most common primary form of glomerular disease worldwide with a complex pathogenesis involving abnormal immune responses and carries a high lifetime risk of kidney failure. Recently, we have reported novel IgA-type autoantibodies against mesangial cell autoantigens, βII-spectrin and CBX3, in the serum of IgAN patients (Science Advances, 2023. Life Sci. Alliance 2024). About half of IgAN patients were positive for serum anti-βII-spectrin and/or anti-CBX3 IgA, suggesting the existence of other undiscovered autoantigens. The aim of this study is to systematically screen and identify novel autoantigens in IgAN to further elucidate the immunopathological mechanisms of IgAN and provide new targets for clinical diagnosis and treatment

【研究経過】（研究经过）
Collect kidney samples from patients diagnosed with βII-spectrin-negative and CBX3-negative IgAN and control subjects and isolate glomerular mesangial cells from the kidney samples by engineering techniques or laser microdissection. Use high-throughput proteomic techniques (e.g., LC-MS/MS) combing with bioinformatics analysis to analyze the mesangial cells protein expression profiles of patients and control groups to identify proteins that are significantly expressed or modified in IgAN patients. Validate the candidate proteins by Western blotting, immunofluorescence, immunohistochemistry and ELISA. Use immunoprecipitation to verify the binding of candidate proteins to IgA antibodies from patients. In clinical experiments, we will assess the correlation between IgA autoantibodies against the newly identified autoantigens and clinical parameters of IgAN (e.g., proteinuria, serum creatinine levels, renal function) and analyze the expression and antibody response differences in various subtypes of IgAN.

【成果】（成果）
At present, we have successfully purified IgA antibodies and extracted 5,000 glomeruli, and follow-up experiments are in progress.

【今後の論文発表予定】（今后论文发表的计划）
After all the experiments were completed, the data were sorted out and the paper was published.

【今後の課題】（今后的课题）
We extended the HLA typing sequencing of the currently known IgA novel antigens(βII-spectrin and CBX3), expecting to find the correlation between the two and clinical indexes.

本共同研究の①研究目的の達成度、②将来性、③帰国後の展開予定について述べて下さい。
（请就本次合作研究题目的①研究目的的达标情况、②未来的发展可能性、③您回国后今后的合作研究的规划打算作一论述）

【達成度】（达标情况）
At present, the experiment is progressing smoothly, two-thirds of the experiment has been completed, the remaining part will be continued in Japan, and the unfinished part will be continued after returning China.

【将来性】（未来的可能性）
This study aims to systematically screen and identify novel autoantigens in the serum of IgAN patients, thereby revealing further insights into the immunopathological mechanisms of IgAN. The results are expected to provide new targets for early diagnosis, prognosis evaluation, and personalized treatment of IgAN.

【帰国後共同研究の展開予定】（回国后的合作规划）
We will conduct follow-up communication through online meetings and other means to ensure the smooth progress of the project.

研究者自署： 李鑫

日中笹川医学奨学金制度＜共同研究コース＞
日中共同研究に関わる報告書

作成日：2025 年 3 月 31 日

氏 名（漢字）	本田 賢也	氏名（ローマ字）	HONDA Kenya
所属機関・部署・役職	慶應義塾大学医学部微生物学・免疫学教室		
研究テーマ	膀胱癌における間質成分の進化ががん細胞の浸潤と転移に与える影響の研究		
中国側共同研究者 氏名と研究者番号	劉 碧天　K4529	中国側共同研究者 所属機関	中国医科大学附属盛京医院

本共同研究の①研究目的の達成度、②将来性、③今後の展望や予定について述べて下さい。

【達成度】

One of the major obstacles in bladder cancer treatment is the infiltration of cancer cells into the fibroblast-rich stroma, which significantly alters therapeutic strategies and patient prognosis. The complex tumor-stroma interactions contribute to immune evasion, drug resistance, and tumor progression, posing substantial challenges for effective treatment.

Bitian conducted a multi-omics analysis on tissue from a representative patient with muscle-invasive bladder cancer (MIBC). Spatial transcriptomics and spatial metabolomics provided a comprehensive view of the heterogeneity between cancer cells and stromal cells. Notably, spatial metabolomics captured unique metabolic signatures associated with the invasion of cancer cells into the stromal layer. These stromal cells, exhibiting distinct metabolic characteristics, are likely to play a crucial role in facilitating the transition of cancer cells from the epithelial layer to deeper stromal regions.

Furthermore, single-cell sequencing identified genetic convergence between cancer cells and a subset of fibroblasts, highlighting specific genes implicated in cancer-stroma interactions. Further classification of fibroblasts exhibiting these unique signatures—potentially associated with transcription factors and inflammatory mediators—led to the identification of cancer-associated fibroblast (CAF) subpopulations. These distinct CAF subpopulations are hypothesized to facilitate cancer cell invasion by remodeling the stromal barrier, thereby enabling tumor penetration into muscle tissues.

【将来性】

By integrating spatial multi-omics data with single-cell sequencing, this study provides key insights into the molecular and metabolic mechanisms underlying cancer cell infiltration and stromal remodeling, offering potential targets for therapeutic intervention in muscle-invasive bladder cancer.

【今後の展望】

Based on current findings, this collaborative research will continue revealing in dept the role of fibroblast subtypes and metabolism in promoting cancer progression. We will explore (1) the interactions between immune cells, such as mast cells and CAFs. (2) the potential role of gut bacteria and their metabolism in the progression of bladder cancer.

日本側共同研究者記名：本田賢也

日中笹川医学奨学金制度<共同研究コース>研究報告書

Supported by 日本財団 THE NIPPON FOUNDATION

＊英語または日本語で作成(请用日文或英文书写)

第45期　研究者番号(研究者编号)：K4529　作成日(书写日期)：2024年9月24日

氏名 (姓名)	LIU BITIAN（刘 碧天）	性別 (性别)	M	生年月日 (出生日期)	1988.12.8

研究テーマ (研究题目)	Evolution of the Stromal Component in Bladder Cancer Leading to Cancer Cell Infiltration and Metastasis
研究期間(来日～帰国まで) (来日起至回国的研究起止时间)	2024年5月1日 ～ 2024年11月28日
在日共同研究機関・部署 (在日共同研究单位及部门)	Keio University School of Medicine, Dept. of Microbiology and Immunology
共同研究者氏名・役職 (共同研究者姓名/职务)	Kenya Honda Professor

学会参加について (关于在日期间参加学会)

有り(有参加) ☐　　なし(没有参加) ☑

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論文発表について (关于在日期间论文发表)

発表有/投稿中(已发表或投稿中)☐　　発表なし(没有发表)☑

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テーマ(题目)：
著者名(作者名)：
雑誌名(期刊名)：
発行年(发表年度)： 巻　号(刊卷)： ページ(页数)： インパクトファクター(影响因子)：

日本滞在中の具体的な共同研究内容についての報告
（关于在日期间就研究题目具体开展的共同研究内容的详述）

【研究目的】（研究目的）

The breakthrough of the submucosal or stromal layer in bladder cancer can significantly alter treatment approaches and prognosis. The infiltration of cancer cells into the fibroblast-rich stroma remains poorly understood.

【研究経過】（研究经过）

We conducted multi-omics analysis on tissue from a patient with muscle-invasive bladder cancer. Spatial transcriptomics revealed heterogeneity between cancer cells and stromal cells, while spatial metabolomics captured tissue images depicting cancer cells breaking through the stromal layer to invade muscle tissues. Spatially-aware nearest shrunken centroids clustering in metabolomics further distinguished cancer and stromal cells based on differential metabolism. Metabolite differentiation analysis across different clusters revealed metabolic disparities both between cancer cells and within the stromal matrices themselves. Single-cell sequencing identified subsets of cancer cells and stromal cells, highlighting differentiated cells where some exhibited convergent cellular characteristics. This finding aligns with spatial metabolomic observations, indicating distinct metabolic profiles among differentiated cells. Single-cell sequencing also pinpointed specific genes in cancer cells and fibroblasts responsible for mutual homogenization. Differential metabolites derived from these genes likely mediate this process. Our integrated approach combining spatial multi-omics analysis and single-cell sequencing provides insights into key differentiating genes and metabolites crucial for understanding cancer cell infiltration and proliferation within the stroma.

【成果】（成果）

Through integrating multi-omics analysis of bladder cancer, we identified the fibroblast subtype within the stroma that is most susceptible to infiltration by cancer cells. This subtype, in coordination with mast cells, differentiates into cancer-associated fibroblasts that play a key role in promoting cancer progression.

【今後の論文発表予定】（今后论文发表的计划）

This collaborative study still requires extensive work for validation and will be completed over the next few years. Ultimately, we aim to publish a paper in an international journal, revealing the key stromal transformations and collaborating immune cells involved in the progression of bladder cancer.

【今後の課題】（今后的课题）

Basing on this research, we will explore the potential role of bacteria in the progression of bladder cancer.

本共同研究の①研究目的の達成度、②将来性、③帰国後の展開予定について述べて下さい。
（请就本次合作研究题目的①研究目的的达标情况、②未来的发展可能性、③您回国后今后的合作研究的规划打算作一论述）

【達成度】（达标情况）

We identified fibroblast subtypes through single-cell sequencing data and utilized metabolic enrichment analysis to select key cancer-associated fibroblast subpopulations.

【将来性】（未来的可能性）

We speculate that the combined actions of cancer cells, mast cells, and bacteria induce the deterioration of the stroma.

【帰国後共同研究の展開予定】（回国后的合作规划）

We will continue our collaborative research to explore the relationships between bladder cancer, bacteria, and the immune system, with the hope that our findings will contribute to future diagnosis and treatment of bladder cancer. Additionally, we will further investigate therapeutic approaches targeting the immune system and microbiota to improve the prognosis of bladder cancer.

研究者自署： Liu Bitian

日中笹川医学奨学金制度＜共同研究コース＞
日中共同研究に関わる報告書

作成日：2025 年 3 月 26 日

氏 名（漢字）	光武 範吏	氏名（ローマ字）	MITSUTAKE Norisato
所属機関・部署・役職	長崎大学原爆後障害医療研究所　放射線災害医療学研究分野　教授		
研究テーマ	甲状腺癌における癌関連線維芽細胞が治療抵抗性に及ぼす影響とその分子機構の解明		
中国側共同研究者 氏名と研究者番号	孟 召偉、孫 丹陽 K4530	中国側共同研究者 所属機関	天津医科大学総医院

本共同研究の①研究目的の達成度、②将来性、③今後の展望や予定について述べて下さい。

【達成度】

これまでのところ、予定されていた研修期間におけるすべての実験は、ほぼ予定通り実施されており、かつ再現性にも注意を払って行われています。

まず、正常な線維芽細胞に対して適切なサイトカイン刺激を与えることにより、腫瘍関連線維芽細胞（cancer-associated fibroblasts: CAFs）様細胞への形質転換を誘導することに成功しました。特に、最近注目されている myofibroblastic CAF（myCAF）および inflammatory CAF（iCAF）様細胞に選択的な誘導を行っています。

さらに、活性化された CAF と甲状腺がん細胞との共培養系を確立し、腫瘍細胞と微小環境の構成細胞との相互作用を模倣した条件下での培養を行いました。

次の段階では、CAF の存在が甲状腺がん細胞の放射線感受性に及ぼす影響について、*in vitro* および *in vivo* の両実験系を用いて検討する予定です。この評価により、CAF が放射線治療に対して与える修飾的効果の有無や、その分子機構に関する知見が得られることが期待されます。

【将来性】

本研究は、臨床現場における実際の課題を出発点とし、それらの問題に対して科学的手法に基づくアプローチを通じて解決を図ることを目的としています。特に、甲状腺がんにおける治療抵抗性と腫瘍随伴線維芽細胞（CAF）との関連性を明らかにすることを目指しており、本研究が成功すれば、CAF の関与するメカニズムを通じて治療抵抗性の本質的理解が得られると期待されます。

さらに、CAF が甲状腺がん細胞の脱分化過程に関与している可能性があることから、その機構を解明することにより、脱分化の進行を抑制、あるいは可逆的に制御できる可能性も示唆されます。これにより、脱分化により I-131 の取り込み能を失った甲状腺がん細胞に対して、その取り込み能を回復させる新たな治療戦略の開発が可能となるかもしれません。

このような成果は、放射性ヨウ素不応性甲状腺がん（RAI-refractory thyroid cancer）や未分化甲状腺がん（anaplastic thyroid cancer）に対する新たな治療標的を提供し、これまで有効な治療選択肢が限られていた症例における予後の改善に寄与する可能性があります。

【今後の展望】

中国側で、臨床検体を用いた同様の実験を継続し、さらに *in vivo* 実験を追加することにより、論文作成を目指します。

日本側共同研究者記名：光武　範吏

日中笹川医学奨学金制度＜共同研究コース＞研究報告書

＊英語または日本語で作成(请用日文或英文书写)

第 45 期　研究者番号(研究者编号)：K4530　作成日(书写日期)：2025 年 2 月　11 日

氏　名	MENG ZHAOWEI 孟 召伟	性別	M	生年月日	1977.11.02
所属機関・部署	Tianjin Medical University General Hospital・Department of Nuclear Medicine				
チームメンバー（成　員）	SUN DANYANG 孙丹阳				

研 究 テーマ（研 究 题 目）	Molecular mechanisms by which cancer-associated fibroblasts affect treatment resistance in thyroid cancer
研究期間(来日～帰国まで)（来日起至回国的研究起止时间）	2024 年 9 月 2 日 ～2025 年 3 月 7 日
在日共同研究機関・部署（在日共同研究单位及部门）	Atomic Bomb Disease Institute, Nagasaki University・Department of Radiation Medical Sciences
共同研究者氏名・役職（共同研究者姓名/职务）	Norisato Mitsutake, MD PhD・Professor and Chairman

学会参加について（关于在日期间参加学会）

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論文発表について（关于在日期间论文发表）

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テーマ(题目)：

著者名(作者名)：

雑誌名(期刊名)：

発行年(发表年度)：
巻　号(刊卷)：
ページ(页数)：
インパクトファクター(影响因子)：

日本滞在中の具体的な共同研究内容についての報告
（关于在日期间就研究题目具体开展的共同研究内容的详述）

【研究目的】（研究目的）

This research aims to serve as a starting point for understanding the relationship between treatment resistance and cancer-associated fibroblasts (CAFs) in thyroid cancer. By elucidating the molecular mechanisms involved, we hope to identify potential targets for enhancing the effectiveness of existing treatments and improving patient outcomes.

【研究経過】（研究经过）

1. Approaches to Activating Normal Fibroblasts into myCAF and/or iCAF

The classification of CAFs mainly includes the following two major subtypes: one population expressing inflammatory markers such as interleukin 6 (IL-6) and leukemia inhibitory factor (LIF), which was therefore named "inflammatory CAFs" (iCAFs), and another population expressing myofibroblast markers, such as αSMA, which was therefore named "myofibroblastic CAFs" (myCAFs) .By reviewing the literature, we induced the conversion of normal fibroblast (BJ/HE49 cells) into myCAFs through TGFβ stimulation and into iCAFs through TNFα.

The activation of these fibroblasts was confirmed by qPCR to assess the expression of different markers, including myCAFs markers such as α-SMA(ACTA) and POSTN, and iCAFs markers such as IL-6 and IL-1β.

2. Preparation of the conditioned medium

BJ cells and HE49 cells were cultured in RPMI-1640 medium supplemented with 5% FBS at 37°C with 5% CO_2 for 24 hours. The medium was then replaced with fresh medium containing TNFα or TGFβ for stimulation. After 48 hours of incubation, the supernatant was collected and centrifuged at 3000 g for 30 minutes to remove cell debris.

3. Inducing myCAF and/or iCAF by co-culturing thyroid cancer cells with activated fibroblasts.

Thyroid cancer cells (TPC-1 and FRO) were cultured in RPMI-1640 medium supplemented with 5% FBS at 37°C with 5% CO_2 for 24 hours. Then the medium was replaced with the conditioned medium, and the cells were cultured for additional 24 hours. Following this, cells were collected, and total RNA was extracted. The KOD SYBR qPCR Mix kit was used for detection on an CFX Opus 96 machine, with TBP as the internal control. Three replicate wells were set up for each sample, and the results were analyzed using the bundled software. The expression of the target gene mRNA was quantified using the ΔΔCt method.

4. Investigating the differences in cell growth, migration, and radiation sensitivity of the thyroid cancer cells induced by these co-culture combinations.

Thyroid cancer cells (TC cells) were cultured in a 96-well cell culture plate and treated with different conditioned media for 24 and 48 hours. Cell proliferation was assessed using the cell counting kit-8 (CCK-8) according to the manufacturer's instructions.

To study cell migration, TC cells were seeded at a density of 5×10^5 cells per well in a 6-well culture plate. When the cell density reached 90–100%, a sterile plastic pipette tip was used to create a scratch in the cell monolayer. The cells were then washed twice with serum-free medium (or phosphate-buffered saline, PBS) to remove cell debris, and conditioned medium (CM) was added for 24 hours of culture. Scratch images were observed and photographed under a phase-contrast microscope (Nikon, Japan) at 4 × magnification. The scratch repair area rate was calculated using the Image J software (National Institutes of Health, MD, USA).

【成果】（成果）

1. Characterization of normal fibroblasts after stimulation with TGF-β and TNF-α

After 72 hours of TNFα stimulation, BJ cells exhibited a more elongated, needle-like shape, while after 72 hours of TGFβ stimulation, they acquired a more spindle-shaped morphology. In contrast, HE49 cells showed little morphological change under both stimuli.

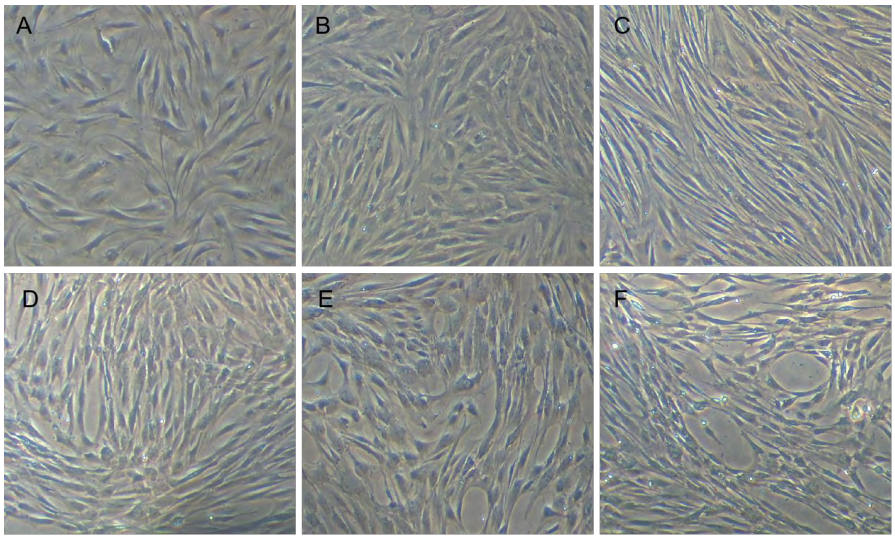


Figure1. The morphology of normal fibroblasts under different stimulations.

A. BJ-Control; B. BJ-TGFβ; C. BJ-TNFα; D. HE49-Control; E. HE49-TGFβ; F. HE49-TNFα

2. TNFα can promote the formation of iCAFs.

We co-cultured the TC cells with TNFα-conditioned medium, and the levels of iCAF markers, such as IL-6 and IL-1β, were increased compared with the control group.

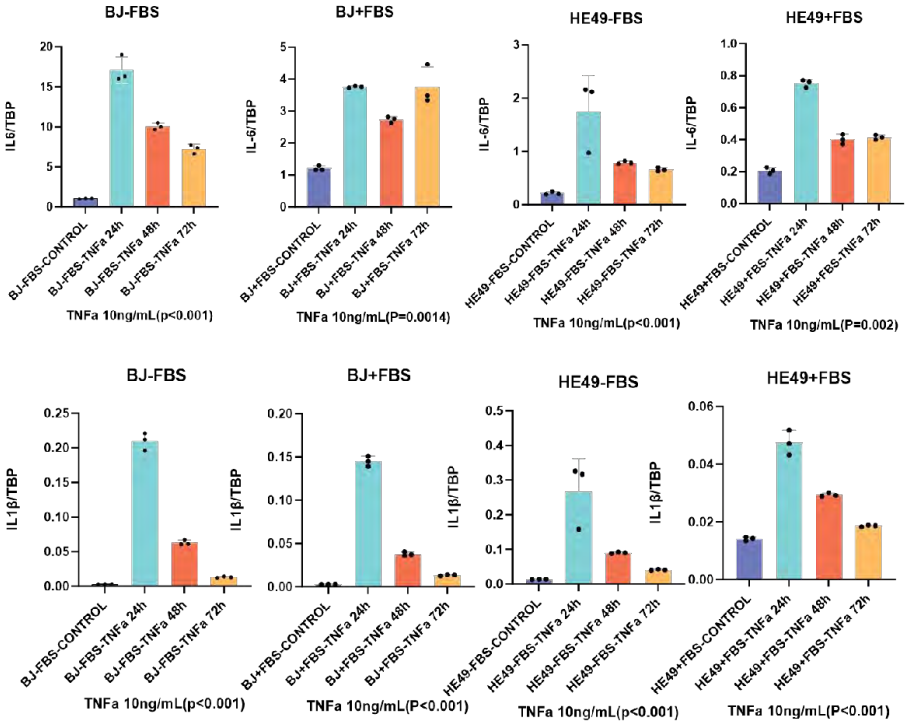


Figure2. Comparative qPCR analysis of iCAF (IL6 and IL1β) markers in normal fibroblasts with or without TNFα stimulation.

3. TGFβ can promote the formation of myCAFs.

We co-cultured the TC cells with TGFβ-conditioned medium, and the levels of myCAF markers, such as α-SMA (ACTA) and POSTN, were increased compared with the control group.

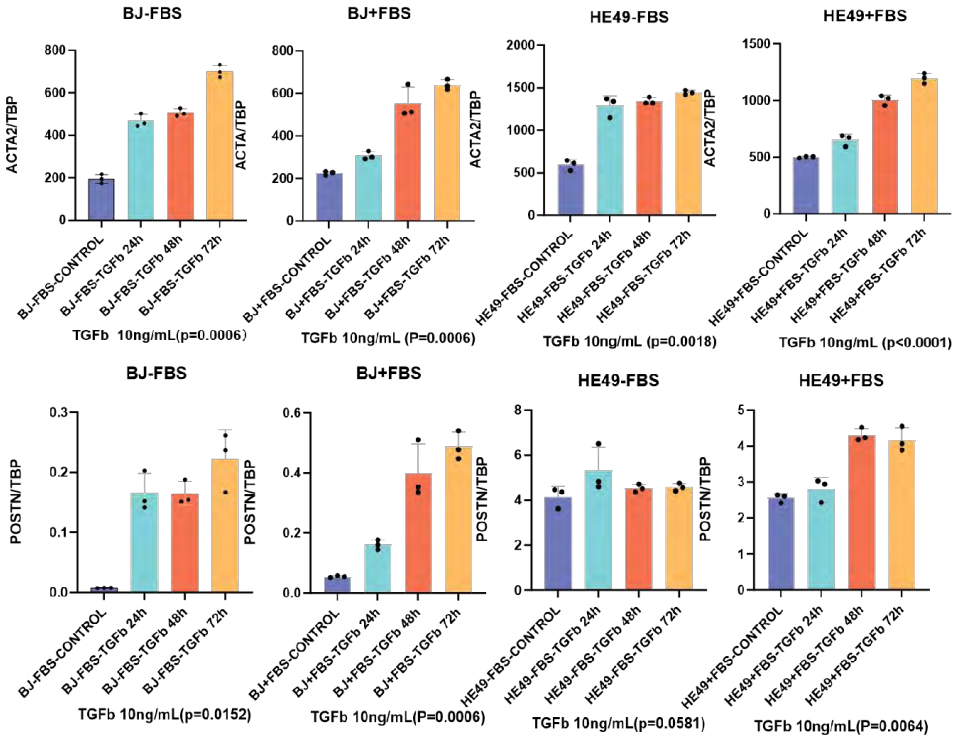


Figure3. Comparative qPCR analysis of myCAF (ACTA and POSTN) markers in normal fibroblasts with or without TGFβ stimulation.

4. Thyroid cancer cells co-cultured with activated fibroblasts.

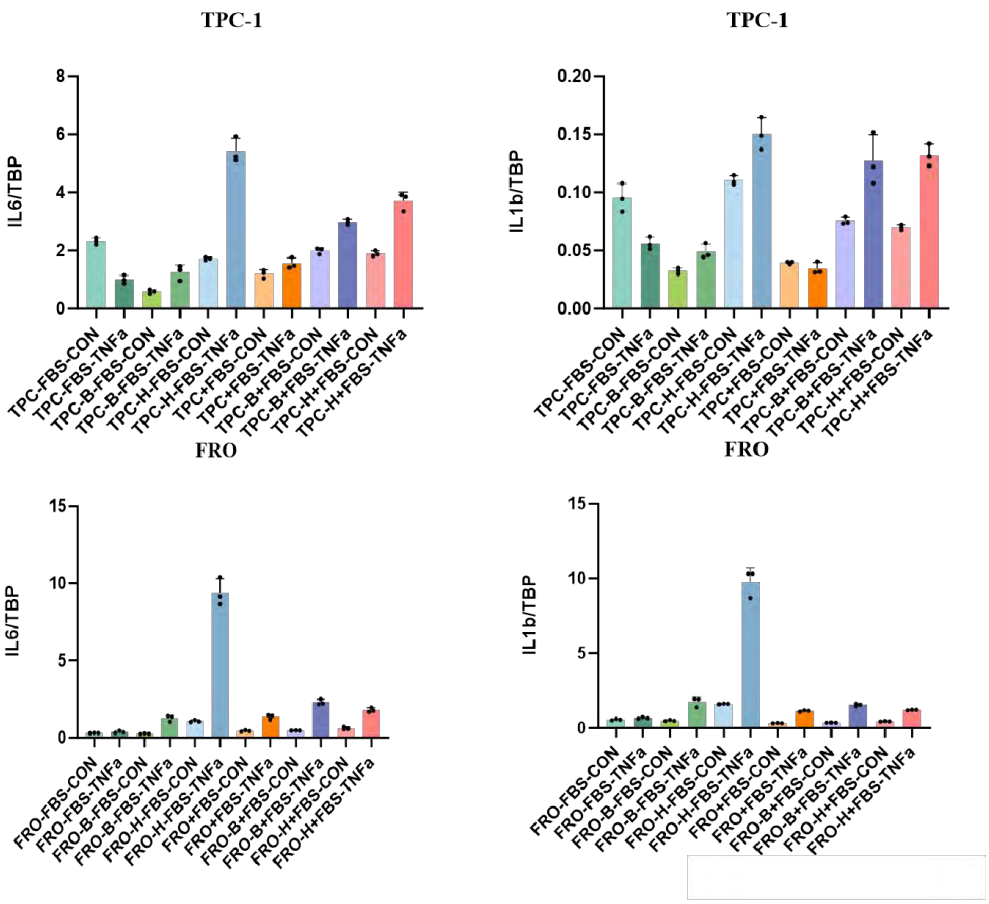
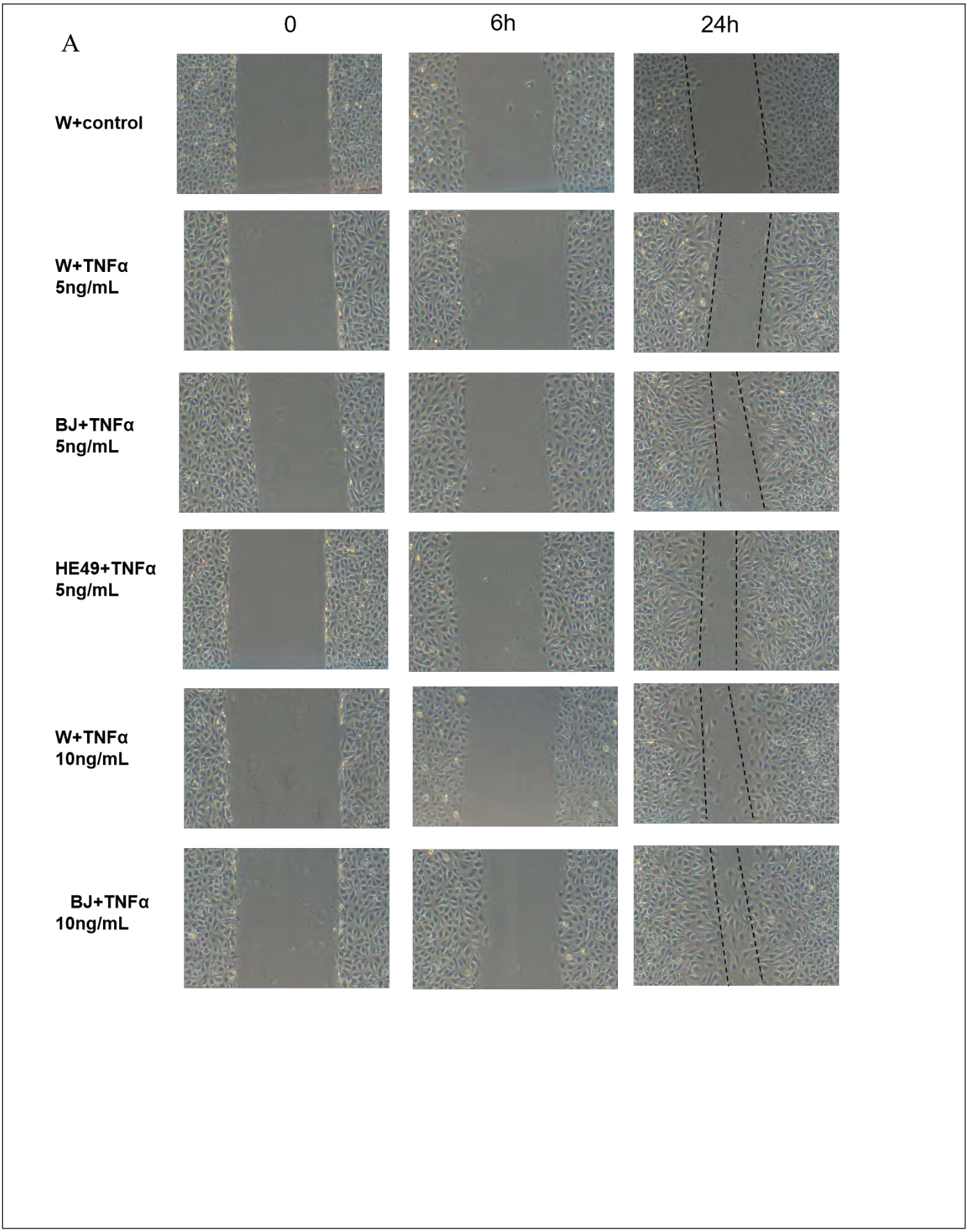


Figure 4. Comparative qPCR analysis of iCAF markers (IL-6 and IL-1β) treated with the conditioned medium and complete medium.

5. Cancer-associated fibroblast-conditioned medium enhances the migration abilities of TC cells


A
0
6h
24h
W+control
W+TNFα
5ng/mL
BJ+TNFα
5ng/mL
HE49+TNFα
5ng/mL
W+TNFα
10ng/mL
BJ+TNFα
10ng/mL

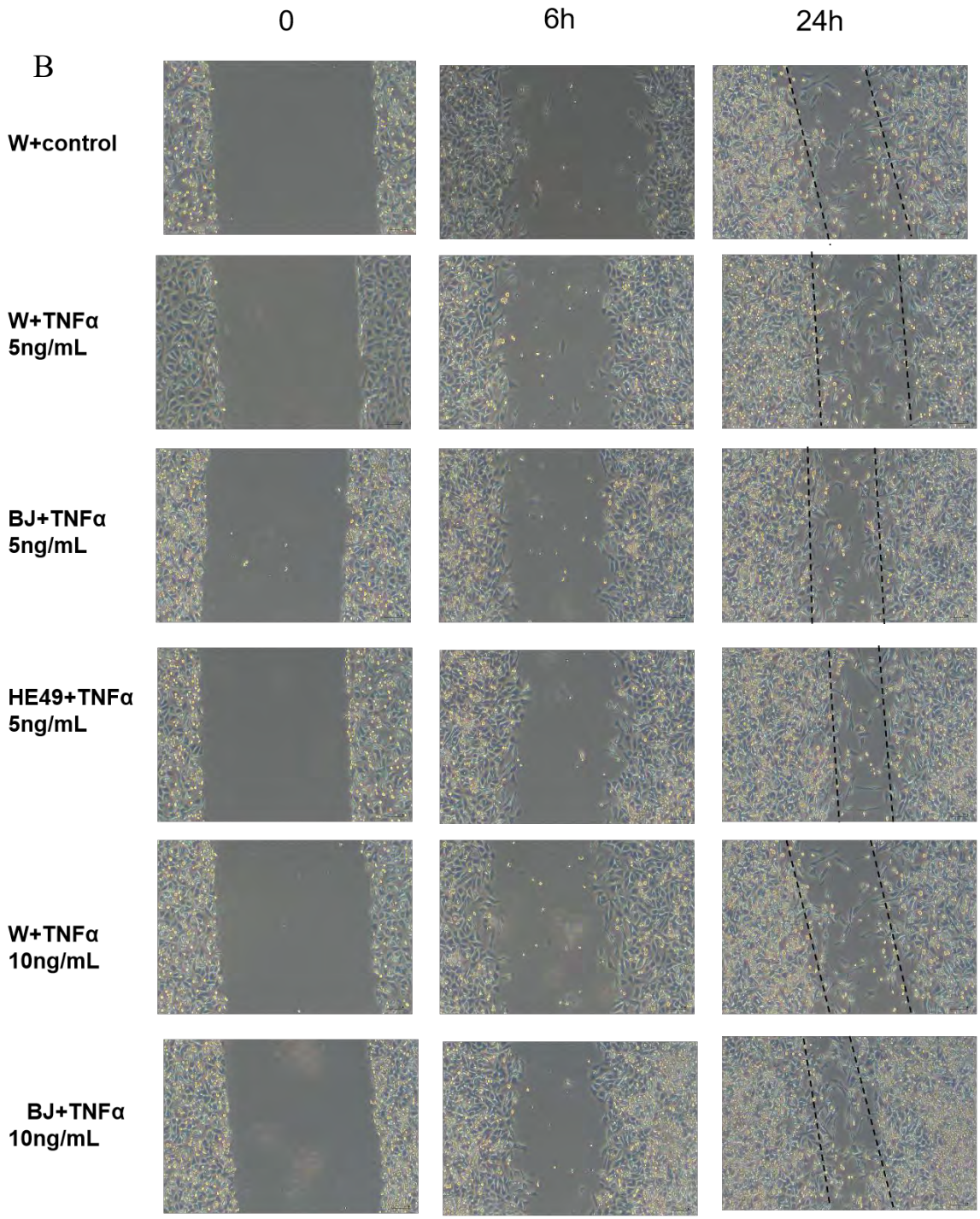


Figure 5. Effect of conditioned medium on TC cell migration.

TPC-1 (A) and FRO (B) cells were co-cultured with activated fibroblasts (BJ+TNFα, HE49+TNFα) at concentrations of 5 or 10 ng/mL. The control group included W+control (complete medium without cells) and W+TNFα (TNFα without cells) at concentrations of 5 or 10 ng/mL. Images were taken at 0, 6, and 24 hours after wound formation.

【今後の論文発表予定】（今后论文发表的计划）

The study aims to explore the relationship between treatment resistance and cancer-associated fibroblasts (CAFs) in thyroid cancer. Currently, the experiments are in progress, and we have successfully induced the transformation of normal

fibroblasts into myCAF and/or iCAF. Additionally, we have co-cultured thyroid cancer cells with these activated fibroblasts. Moving forward, our next steps will focus on evaluating the impact of CAFs on the radiation sensitivity of thyroid cancer cells, both in vitro and in vivo.

After completing the experiments, statistical analyses will be performed to interpret the results and validate the significance of the findings. Once the data are finalized, we plan to draft a manuscript and submit it to a prestigious international academic journal. We hope this research will help identify potential therapeutic targets to enhance the efficacy of existing treatments and improve patient outcomes.

【今後の課題】（今后的课题）

Differentiated thyroid cancer (DTC) dedifferentiation, the emergence of radioactive iodine-refractory differentiated thyroid cancer (RAIR-DTC), and the loss of ^{131}I uptake in tumor lesions represent significant clinical challenges in thyroid cancer treatment. Building on our research into the interaction between cancer-associated fibroblasts (CAFs) and thyroid cancer cells, future studies will focus on addressing key questions in the field, particularly whether CAFs contribute to ^{131}I treatment resistance and cellular dedifferentiation.

The next phase of our research will further investigate whether CAF activation or inhibition modulates the ^{131}I uptake capacity of DTC cells, and whether CAF inhibition can reverse DTC cell dedifferentiation while enhancing the therapeutic efficacy of ^{131}I. By studying the tumor-stroma interaction, we aim to clarify the role of CAFs in thyroid cancer progression and identify novel therapeutic targets and strategies to overcome ^{131}I treatment resistance.

本共同研究の①研究目的の達成度、②将来性、③帰国後の展開予定について述べて下さい。
（请就本次合作研究题目的①研究目的的达标情况、②未来的发展可能性、③您回国后今后的合作研究的规划打算作一论述）

【達成度】（达标情况）

So far, all experimental steps have been executed as planned. We have successfully induced the transformation of normal fibroblasts into myCAF and/or iCAF. Additionally, we have co-cultured thyroid cancer cells with these activated fibroblasts. Throughout the process, we have ensured the quality and accuracy of the experiments, adhering strictly to all standards and requirements. The next phase will focus on evaluating the impact of CAFs on the radiation sensitivity of thyroid cancer cells, both in vitro and in vivo.

【将来性】（未来的可能性）

Our research is based on clinical issues and aims to address them through scientific investigation. If successful, we can understand the relationship between treatment resistance and CAFs in thyroid cancer. This may the potential to inhibit or even reverse the progression of thyroid cancer cell dedifferentiation and restore their ability to uptake ^{131}I. This could provide a new therapeutic target for iodine-refractory thyroid cancer and undifferentiated thyroid cancer, improving patient prognosis.

【帰国後共同研究の展開予定】（回国后的合作规划）

After returning to China, I plan to continue collaborating with both domestic and international research teams to further develop and expand on the current research. The collaboration will focus on whether CAF-regulated pathways can affect ^{131}I uptake in TC, and whether the interaction between CAFs and TC has a significant impact on ^{131}I therapy resistance.

We will obtain fresh cancer tissues and adjacent normal thyroid tissues from DTC patients who have undergone total thyroidectomy in thyroid surgery. From these tissues, we will isolate and culture paired CAFs and NFs primary cells. Then, we will further verify whether NFs can be activated into myCAFs/iCAFs through different methods. Additionally, by intervening in CAF-related metabolic pathways, we will determine their impact on thyroid cancer invasiveness, metastasis, apoptosis, and iodine resistance. Through these collaborative efforts, we expect to identify potential targets for enhancing the effectiveness of existing treatments and improving thyroid cancer patient outcomes.

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