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研究者評価（指導教官記入欄）

進捗状況	優・良・可・不可から選択してください⇒	優	パーセンテージ⇒	80 %
研究者本人が行った研究の概要	切除不能もしくは進行再発胃癌のバイオマーカーについての情報と治療転帰のデータを電子カルテより収集し、CLDN18.2, PDL1等のバイオマーカーと治療効果についての検討を行った。すでにデータはほぼ収集され、また生存解析等の分析も行い、論文もドラフトは作成している。			
総合評価	【良かった点】 自主的に電子カルテのデータ収集などの調査を行った。			
	【改善すべき点】 特になし。			
	【今後の目標】 論文ドラフトを整えて、投稿すること。			
研究計画書に記載の研究計画の進捗状況	①予想以上に進捗している　②おおむね順調　③やや遅れている　④大幅に遅れている			
進捗が進んでいる内容と遅れている内容及びその理由	1月中に論文投稿が予定されていたが、約1-2か月程度の遅れが想定されるものの、概ね順調である			
現在の進捗状況を踏まえた目標達成見込	達成しうる			
評価者（指導教官記名）	設楽紘平	作成日：	2025年　2　月　17　日	

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研究テーマ(日文)	胃癌における臨床データとバイオマーカー解析					
Research theme	Data analysis of gastric cancer-related clinical information and biomarkers					

1．研究概要（1）
1）目的（Goal）
To evaluate the impact of claudin 18.2 (CLDN18.2) expression on outcomes of first-line immune checkpoint inhibitor (ICI)-containing chemotherapy in patients with human epidermal growth factor receptor 2 (HER2)-negative, proficient mismatch repair (pMMR) and programmed death-ligand 1 (PD-L1)-expressing metastatic or recurrent gastric or gastroesophageal junction cancer (mGC/GEJC).
2）戦略（Approach）
A single-institution and retrospective study was performed.
3）材料と方法（Materials and methods）
Medical records of patients with HER2-negative, pMMR, and PD-L1 CPS ≥1 unresectable/metastatic or recurrent GC/GEJC who received first-line ICI-containing chemotherapy (ICI-chemo) or chemotherapy alone (chemo-alone) between January 2016 and August 2024 were retrospectively analyzed. The impact of CLDN18.2 status on clinical outcomes was evaluated in patients receiving ICI-chemo, with chemo-alone serving as a control to assess the prognostic significance of CLDN18.2 in the absence of ICI.
4）実験結果（Results）
A total of 150 consecutive patients were treated with ICI-chemo, while 313 patients received chemo-alone. CLDN18.2 positivity (≥ 2+ in ≥ 75% tumor cells) was identified in 42 patients (28.0%) in the ICI-chemo group and 94 patients (30.0%) in the chemo-alone group. There were no significant differences in overall response rate (ORR; 68.3% vs. 70.3%, P = 0.842), disease control rate (DCR; 92.7% vs. 94.1%, P = 0.718), progression-free survival (PFS) [hazard ratio (HR) 1.01, P = 0.955], or overall survival (OS) (HR 1.12, P = 0.615) between CLDN18.2-positive and -negative patients in the ICI-chemo group. Similarly, DCR, ORR, PFS and OS outcomes were also comparable between CLDN18.2-positive and -negative patients in the chemo-alone group.
5）考察（Discussion）
The CLDN18.2-positivity rate, defined as ≥ 2+ in ≥ 75% tumor cells with 43-14A (VENTANA Assay), was 28.0% and 30.0% in the ICI-chemo and chemo-alone groups respectively, which were slightly lower to these in SPOTLIGHT and GLOW trials (38.4%).
As for treatment response and survival, focusing on the patients with HER2-negative, pMMR and PD-L1 CPS ≥1 mGC/GEJC, no significant differences in ORRs, DCRs, median PFS and OS were observed between the CLDN18.2-positive and -negative groups in patients who received first-line ICI-chemo treatment.
Due to the lack of head-to-head comparison between zolbetuximab-based chemotherapy and ICI--containing chemotherapy, optimal patient selection also remains a debated issue in clinical practice, particularly in cases with the overlap biomarkers of HER2-negative, pMMR and PD-L1 CPS ≥1 tumors, thus further investigations are warranted to address this issue.
CLDN18.2-positive GC has been demonstrated with complicated immune characteristics.
CLDN18.2 expression exerted no impact on outcomes of first-line ICI-chemo and chemo-alone in patients with HER2-negative, pMMR and PD-L1 CPS ≥1 with mGC/GEJC.
6）当初の研究計画と比し、現在の進捗状況の自己評価　（Self-assessment of the current progress compared to the initial research plan.）
①予想以上に進捗している（Progressing more than expected.）
②おおむね順調　（Mostly on track）
③やや遅れている　（Slightly behind schedule）
④大幅に遅れている（Significantly behind schedule）
7）計画より進んでいる内容と遅れている内容、及びその理由
（Contents that are ahead of schedule and those that are behind schedule, along with the reasons.）
Mostly on track with the initial research plan.

1．研究概要(2)
8)参考文献(References)

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2. 執筆論文 Publication of thesis ※記載した論文を添付してください。Attach all of the papers listed below.

論文名 1 Title	No					
掲載誌名 Published journal						
	年 月	巻(号)	頁 ～ 頁	言語 Language		
第1著者名 First author		第2著者名 Second author		第3著者名 Third author		
その他著者名 Other authors						
論文名 2 Title						
掲載誌名 Published journal						
	年 月	巻(号)	頁 ～ 頁	言語 Language		
第1著者名 First author		第2著者名 Second author		第3著者名 Third author		
その他著者名 Other authors						
論文名 3 Title						
掲載誌名 Published journal						
	年 月	巻(号)	頁 ～ 頁	言語 Language		
第1著者名 First author		第2著者名 Second author		第3著者名 Third author		
その他著者名 Other authors						
論文名 4 Title						
掲載誌名 Published journal						
	年 月	巻(号)	頁 ～ 頁	言語 Language		
第1著者名 First author		第2著者名 Second author		第3著者名 Third author		
その他著者名 Other authors						
論文名 5 Title						
掲載誌名 Published journal						
	年 月	巻(号)	頁 ～ 頁	言語 Language		
第1著者名 First author		第2著者名 Second author		第3著者名 Third author		
その他著者名 Other authors						

3. 学会発表 Conference presentation ※筆頭演者として総会・国際学会を含む主な学会で発表したものを記載してください。

※Describe your presentation as the principal presenter in major academic meetings including general meetings or international meetings.

学会名 Conference	No						
演 題 Topic							
開催日 date	年 月 日	開催地 venue					
形式 method	□ 口頭発表 Oral	□ ポスター発表 Poster	言語 Language	□ 日本語	□ 英語	□ 中国語	
共同演者名 Co-presenter							
学会名 Conference							
演 題 Topic							
開催日 date	年 月 日	開催地 venue					
形式 method	□ 口頭発表 Oral	□ ポスター発表 Poster	言語 Language	□ 日本語	□ 英語	□ 中国語	
共同演者名 Co-presenter							
学会名 Conference							
演 題 Topic							
開催日 date	年 月 日	開催地 venue					
形式 method	□ 口頭発表 Oral	□ ポスター発表 Poster	言語 Language	□ 日本語	□ 英語	□ 中国語	
共同演者名 Co-presenter							
学会名 Conference							
演 題 Topic							
開催日 date	年 月 日	開催地 venue					
形式 method	□ 口頭発表 Oral	□ ポスター発表 Poster	言語 Language	□ 日本語	□ 英語	□ 中国語	
共同演者名 Co-presenter							

4. 受賞（研究業績） Award (Research achievement)

名 称 Award name	No			
	国名 Country		受賞年 Year of award	年 月
名 称 Award name				
	国名 Country		受賞年 Year of award	年 月

5. 本研究テーマに関わる他の研究助成金受給 Other research grants concerned with your resarch theme

受給実績 Receipt record	☐ 有　■ 無
助成機関名称 Funding agency	
助成金名称 Grant name	
受給期間 Supported period	年　月 ～　年　月
受給額 Amount received	円
受給実績 Receipt record	☐ 有　■ 無
助成機関名称 Funding agency	
助成金名称 Grant name	
受給期間 Supported period	年　月 ～　年　月
受給額 Amount received	円

6. 他の奨学金受給 Another awarded scholarship

受給実績 Receipt record	☐ 有　■ 無
助成機関名称 Funding agency	
奨学金名称 Scholarship name	
受給期間 Supported period	年　月 ～　年　月
受給額 Amount received	円

7. 研究活動に関する報道発表 Press release concerned with your research activities

※記載した記事を添付してください。Attach a copy of the article described below

報道発表 Press release	☐ 有　■ 無	発表年月日 Date of release	
発表機関 Released medium			
発表形式 Release method	・新聞　・雑誌　・Web site　・記者発表　・その他（　　）		
発表タイトル Released title			

8. 本研究テーマに関する特許出願予定 Patent application concerned with your research theme

出願予定 Scheduled	☐ 有　■ 無	出願国 Application	
出願内容（概要） Application contents			

9. その他 Others

No.

指導責任者（記名） Kohei Shitara Kohei Shitara

日中笹川医学奨学金制度〈ポストドクターコース〉中間評価書
【指導教官用】

Supported by 日本財団 THE NIPPON FOUNDATION

第45期　　研究者番号：　P4515

氏名	寇 温	KOU WEN	性別	F	生年月日	1986/1/24
中国所属機関（役職）	蘭州大学第一医院薬剤科（主管薬剤師）					
日本研究先機関名・部署	城西国際大学大学院薬学研究科					
指導教官氏名・役職	堀江　俊治　教授、杉山　雄一　特別栄誉教授					
研究テーマ（日本語）	試験管内で薬物輸送/代謝データを用いたPBPKモデリングに基づく 薬物肝クリアランスおよび複雑な薬物相互作用の定量的予測					
研究テーマ（英語）	Quantitative Prediction of the Hepatic Clearance and Complex Drug Interactions using PBPK Modeling with in vitro Transporter/enzyme Data					

研究者評価（指導教官記入欄）

進捗状況	優・良・可・不可から選択してください⇒	優	パーセンテージ⇒	70 %
研究者本人が行った研究の概要	寇温博士（以下、Wendy）は、研究対象の化合物として、直接第Xa因子阻害薬に分類される経口抗凝固薬であるエドキサバン（EDO）を選択した。EDOは、迅速な吸収（Tmax：約1–2時間）と高いバイオアベイラビリティ（約60%）を示し、主に小腸で吸収される。また、P糖蛋白（P–gp）を介した排出を受け、肝代謝は少なく、約50%が未変化体のまま、残りが胆汁・糞便を経由して排泄される。 経口投与時の血中濃度下面積（AUC）は非線形の増加を示すが、これは小腸におけるP–gpの排出が飽和するためと考えられる。また、キニジンやその他のP–gp阻害剤を併用すると、経口クリアランス（CLpo）および腎排泄クリアランスがともに低下する。生理学的薬物速度論（PBPK）モデルに基づく解析では、これらのP–gp阻害剤が小腸、腎臓、肝臓のすべてにおいてP–gpを阻害していることが示唆された。一方、経口投与後の非線形性には、主に消化管吸収過程におけるP–gp排出飽和の寄与が大きいと考えられた。これは、小腸上皮細胞中の薬物濃度が腎臓や肝臓の上皮細胞中の濃度よりも高いことに起因すると推察される。 さらに、類似の治療薬であるアピキサバン（APIX）についても同様の解析を行っており、両薬物の薬物動態特性の違いを明らかにすることを目指している。			
総合評価	【良かった点】 Wendyは熱心に研究に取り組んでおり、その姿勢は高く評価できる。彼女にとってPBPKモデリングは初めての経験であり、さらに未知のアプリケーションであるCGNM法を用いて解析を行ってきた。これらの新しい手法に慣れるために、最初の3～4か月を費やしたが、試行錯誤を重ねながらここまで進めてきたことは、Wendyの忍耐強さと努力の賜物であり、その点を高く評価する。 【改善すべき点】 WendyはPBPKモデリングおよびクリアランスコンセプトを用いた解析に多くの時間をかけている。これらは研究における手法であり、習得することは重要であるが、さらに重要なのは、それを支える基礎理論を深く理解することである。基礎理論を理解しないままでは、自ら応用し発展させることが難しくなる。そのため、単に手法を学ぶだけでなく、理論の理解にも注力することが求められる。 【今後の目標】 当初の計画と比較すると、研究は約3か月遅れている。今後の目標は、臨床データ（血中濃度推移の投与量依存性、他の薬剤との相互作用）を考慮したPBPKモデルを完成させ、論文として投稿することである。さらに、アピキサバン（APIX）についても同様の解析を実施し、両薬物の臨床薬物動態特性の違いを生じさせるメカニズムを解明することが最終的なゴールとなる。			
研究計画書に記載の研究計画の進捗状況	①予想以上に進捗している　②おおむね順調　③やや遅れている　④大幅に遅れている（②に○）			
進捗が進んでいる内容と遅れている内容及びその理由	進捗が遅れている主な課題は、EDOのPBPKモデル解析である。遅れの要因として、基本となる理論の学習と理解に時間を要したことが挙げられる。この課題を克服できるかどうかが、Wendyが優れた研究者へと成長できるかどうかを決定づける要素となる。最も困難な段階ではあるが、粘り強く取り組んでほしい。			
現在の進捗状況を踏まえた目標達成見込	基本となる理論を十分に学び、理解できるようになれば、残りの研究期間は1年以上あるため、目標達成の可能性は十分に高いと考えられる。今後は、より効率的に研究を進められるよう計画を立て、重点的に取り組んでいくことが求められる。			
評価者（指導教官記名）	杉山雄一、堀江俊治	作成日：	2025年　2　月　23　日	

日中笹川医学奨学金制度<ポストドクターコース>中間報告書
【研究者用】

Supported by 日本財団 THE NIPPON FOUNDATION

第45期　　研究者番号：P4515　　作成日：2025年3月10日

氏名	寇 温	KOU WEN	性別	F	生年月日	1986/1/24
中国所属機関(役職)	蘭州大学第一医院薬剤科(副主任薬剤師)					
日本研究先(指導教官)	城西国際大学大学院薬学研究科(堀江　俊治　教授、杉山　雄一　特別栄誉教授)					
研究テーマ(日文)	試験管内で薬物輸送/代謝データを用いたPBPKモデリングに基づく 薬物肝クリアランスおよび複雑な薬物相互作用の定量的予測					
Research theme	Quantitative Prediction of the Hepatic Clearance and Complex Drug Interactions using PBPK Modeling with in vitro Transporter/enzyme Data					

1．研究概要(1)

1)目的(Goal)
To investigate the mechanism of nonlinear pharmacokinetics (PK) of edoxaban.
2)戦略(Approach)
Construct physiologically based pharmacokinetic(PBPK)model to explore the mechanism of nonlinear PK
3)材料と方法(Materials and methods)
Using the Cluster-Gauss Newton method(CGNM) for top-down and middle-out analysis, estimating the in vivo　Km,pgp.
4)実験結果(Results)
The dose normalized AUC showed a good fitting compared with observed data in vivo, However, the CLR(renal clearance) didn't showed good fitting, the only way to improve fitting results is incorporate PSactiveuptake in basolataral side of proximal tuble.
5)考察(Discussion)
From the fitting results, we suspect that there might be uptake transporters involved in edoxaban's elimination, although no reported data showed edoxaban is the subtrates of uptake transporters. Further in vitro experement needed to verify this assumption.
6)当初の研究計画と比し、現在の進捗状況の自己評価　(Self-assessment of the current progress compared to the initial research plan.)
①予想以上に進捗している(Progressing more than expected.)
②おおむね順調　(Mostly on track)
③やや遅れている　(Slightly behind schedule)
④大幅に遅れている(Significantly behind schedule)

7)計画より進んでいる内容と遅れている内容、及びその理由
(Contents that are ahead of schedule and those that are behind schedule, along with the reasons.)
Our experimental results did not turn out as we initially expected. As a result, we need to pause and carefully validate our hypotheses to understand and explain these unusual outcomes. This has slowed down our progress, I think that is precisely the essence of science and also essential for producing meaningful scientific insights.

8)参考文献(References)
1.J Clin Pharmacol 2010;50:743-753.
2.Clin Pharmacokinet (2016) 55:641-655
3.Br J Clin Pharmacol. 2020;1-10.
4.DMD 40:2250-2255, 2012
5.Pharmaceutical Research, Vol.27,No.3,2010
6.Clin. Invest. (2014) 4(7), 619-639
7.Drugs 2011; 71 (12): 1503-1526

1．研究概要(2)

2. 執筆論文 Publication of thesis ※記載した論文を添付してください。Attach all of the papers listed below.

論文名 1 Title						
掲載誌名 Published journal						
	年 月	巻(号)	頁 ～ 頁	言語 Language		
第1著者名 First author		第2著者名 Second author		第3著者名 Third author		
その他著者名 Other authors						
論文名 2 Title						
掲載誌名 Published journal						
	年 月	巻(号)	頁 ～ 頁	言語 Language		
第1著者名 First author		第2著者名 Second author		第3著者名 Third author		
その他著者名 Other authors						
論文名 3 Title						
掲載誌名 Published journal						
	年 月	巻(号)	頁 ～ 頁	言語 Language		
第1著者名 First author		第2著者名 Second author		第3著者名 Third author		
その他著者名 Other authors						
論文名 4 Title						
掲載誌名 Published journal						
	年 月	巻(号)	頁 ～ 頁	言語 Language		
第1著者名 First author		第2著者名 Second author		第3著者名 Third author		
その他著者名 Other authors						
論文名 5 Title						
掲載誌名 Published journal						
	年 月	巻(号)	頁 ～ 頁	言語 Language		
第1著者名 First author		第2著者名 Second author		第3著者名 Third author		
その他著者名 Other authors						

3. 学会発表　Conference presentation ※筆頭演者として総会・国際学会を含む主な学会で発表したものを記載してください。

※Describe your presentation as the principal presenter in major academic meetings including general meetings or international meetings.

学会名 Conference					
演　題 Topic					
開催日 date	年　月　日	開催地 venue			
形式　method	□ 口頭発表　Oral　□ ポスター発表　Poster	言語　Language	□ 日本語	□ 英語	□ 中国語
共同演者名 Co-presenter					
学会名 Conference					
演　題 Topic					
開催日 date	年　月　日	開催地 venue			
形式　method	□ 口頭発表　Oral　□ ポスター発表　Poster	言語　Language	□ 日本語	□ 英語	□ 中国語
共同演者名 Co-presenter					
学会名 Conference					
演　題 Topic					
開催日 date	年　月　日	開催地 venue			
形式　method	□ 口頭発表　Oral　□ ポスター発表　Poster	言語　Language	□ 日本語	□ 英語	□ 中国語
共同演者名 Co-presenter					
学会名 Conference					
演　題 Topic					
開催日 date	年　月　日	開催地 venue			
形式　method	□ 口頭発表　Oral　□ ポスター発表　Poster	言語　Language	□ 日本語	□ 英語	□ 中国語
共同演者名 Co-presenter					

4. 受賞(研究業績) Award (Research achievement)

名　称 Award name				
	国名 Country		受賞年 Year of	年　月
名　称 Award name				
	国名 Country		受賞年 Year of	年　月

5. 本研究テーマに関わる他の研究助成金受給 Other research grants concerned with your resarch theme

受給実績 Receipt record	☐ 有　☐ 無
助成機関名称 Funding agency	
助成金名称 Grant name	
受給期間 Supported period	年　月 ～　年　月
受給額 Amount received	円
受給実績 Receipt record	☐ 有　☐ 無
助成機関名称 Funding agency	
助成金名称 Grant name	
受給期間 Supported period	年　月 ～　年　月
受給額 Amount received	円

6. 他の奨学金受給 Another awarded scholarship

受給実績 Receipt record	☐ 有　☐ 無
助成機関名称 Funding agency	
奨学金名称 Scholarship name	
受給期間 Supported period	年　月 ～　年　月
受給額 Amount received	円

7. 研究活動に関する報道発表 Press release concerned with your research activities

※記載した記事を添付してください。Attach a copy of the article described below

報道発表 Press release	☐ 有　☐ 無	発表年月日 Date of release	
発表機関 Released medium			
発表形式 Release method	・新聞　・雑誌　・Web site　・記者発表　・その他(　　)		
発表タイトル Released title			

8. 本研究テーマに関する特許出願予定 Patent application concerned with your research theme

出願予定 Scheduled	☐ 有　☐ 無	出願国 Application	
出願内容(概要) Application contents			

9. その他 Others

指導責任者(記名)　Yuichi Sugiyama

日中笹川医学奨学金制度<ポストドクターコース>中間評価書
【指導教官用】

第45期　　研究者番号：　P4516

氏名	賀 渝淼	HE YUMIAO	性別	F	生年月日	1992/12/30
中国所属機関（役職）	中国医学科学院北京協和医院麻酔科（医師）					
日本研究先機関名・部署	東京工業大学生命理工学研究科丸山研究室					
指導教官氏名・役職	丸山　厚　教授					
研究テーマ（日本語）	インテリジェントドラッグデリバリーシステムの開発					
研究テーマ（英語）	Development of Polymer-based Intelligent Extended-release Drug Delivery System for Analgesics					

研究者評価（指導教官記入欄）

進捗状況	優・良・可・不可から選択してください⇒	優	パーセンテージ⇒	80 %
研究者本人が行った研究の概要	1，文献調査を念入りに行い、ヒアルロン酸分解物の免疫活性に関する情報を得た。 2．ヒアルロン酸分解物の調製法に関して再現実験を行った。 3．ヒアルロン酸分解物をGPCおよび質量分析により詳細にキャラクタリゼーションした。 4．細胞培養の立ち上げを含め、免疫活性測定法のセットアップを行った。			
総合評価	良かった点 専門と異なった分野であり、特に化学反応や化学的分析に関しては、全く経験が無かったが、勤勉に勉強し順調に慣れつつある。			
	【改善すべき点】 化学とりわけ合成化学に経験が無いため、その分野でのコミュニケーションでは苦労している。			
	【今後の目標】 目的であるヒアルロン酸コンジュゲート体の調製を円滑に推進し、その免疫活性を明らかにしてい			
研究計画書に記載の研究計画の進捗状況	②おおむね順調			
進捗が進んでいる内容と遅れている内容及びその理由	ヒアルロン酸分解物の解析は、質量分析を自ら取り入れ、良好に進捗している。 一方、コンジュゲート体合成は、やや遅れているが、研究室の移動もあり、やむを得ないところもある。			
現在の進捗状況を踏まえた目標達成見込	コンジュゲート体の合成が順調に進めば、目標の達成見込みは高い。			
評価者（指導教官記名）	丸山厚	作成日：	2025年　2　月　10　日	

日中笹川医学奨学金制度<ポストドクターコース>中間報告書
【研究者用】

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研究テーマ(日文)	インテリジェントドラッグデリバリーシステムの開発					
Research theme	Development of Polymer-based Intelligent Extended-release Drug Delivery System for Analgesics					

１．研究概要（1）

1）目的（Goal）

This study aims to systematically investigate the anti-inflammatory mechanisms of enzymatically digested hyaluronic acid oligosaccharides mediated by Toll-like receptor 4 (TLR4) antagonism. And based on their molecular characteristics, design and construct a hyaluronic acid oligosaccharide comb-like copolymer. By optimizing the molecular structure of the copolymer, we seek to enhance its stability, TLR4 receptor affinity, and anti-inflammatory and analgesic functions, thereby providing a theoretical foundation and technical solution for the development of highly effective and long-lasting novel anti-inflammatory and analgesic drugs.

2）戦略（Approach）

(1) Preparation and Evaluation of Enzymatically Digested Hyaluronic Acid Oligosaccharide

Low-molecular-weight hyaluronic acid polysaccharides were enzymatically degraded using hyaluronidase derived from bovine testes and Streptococcus to obtain mixtures of saturated and unsaturated hyaluronic acid oligosaccharides. The composition of the enzymatic degradation products will be controlled by adjusting the digestion time and enzyme/substrate ratio. The oligosaccharide mixtures were characterized using gel permeation chromatography (GPC), proton nuclear magnetic resonance (H1NMR), and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS). The anti-inflammatory effects of the oligosaccharide mixtures were evaluated by measuring the secretion of inflammatory factors from LPS-activated THP-1 cells co-cultured with the oligosaccharide mixtures.

(2) Synthesis and Characterization of Comb-like Copolymers

Using positively charged poly-l-lysine as the backbone, hyaluronic acid oligosaccharides were chemically grafted onto the backbone through controlled reaction conditions to form the comb-like copolymer. GPC is used to determine the molecular weight distribution and polymerization degree. H1NMR is used to analyze the chemical structure and grafting ratio. Surface plasmon resonance (SPR) is used to assess the affinity of comb-like polymer for the TLR4 receptor. In vivo fluorescence imaging is used to evaluating the metabolic activity of comb-like copolymers.

(3) Evaluation of Anti-inflammatory and Analgesic Functions of Comb-like Copolymers

The comb-like copolymers are co-cultured with LPS and THP-1 cells. The secretion levels of TNF-α, IL-1β, and IL-6 are measured using ELISA to validate the ability to inhibit TLR4-mediated inflammatory responses. Furthermore, the pain behavior assessment in a rat chronic constriction injury (CCI) model and the degree of spinal glial cell activation are used to verify the effectiveness of the selected comb-like copolymers in alleviating neuropathic pain and inhibiting the transition to chronic pain.

3）材料と方法（Materials and methods）

(1) Materials:

1 Hyaluronidase from bovine testes 1g, H3506
2 MP Biomedicals Hyaluronidase from Streptomyces Hyalurolyticus, ~2000 U/mg, 151270
3 Potassium Hyaluronate from Bacteria 1g, H1808
4 Lipopolysaccharides from Escherichia coli O55:B5 10mg, L2880
5 Human TNF-α ELISA Kit 96回用, 639-42331
6 Human IL-1 beta Instant ELISA Kit, BMS224INST
7 IL-6 Human ELISA Kit 96 tests, BMS213-2
8 THP-1 cell line
9 Others: RPMI Medium, FBS, P/S, MTT, PLL…

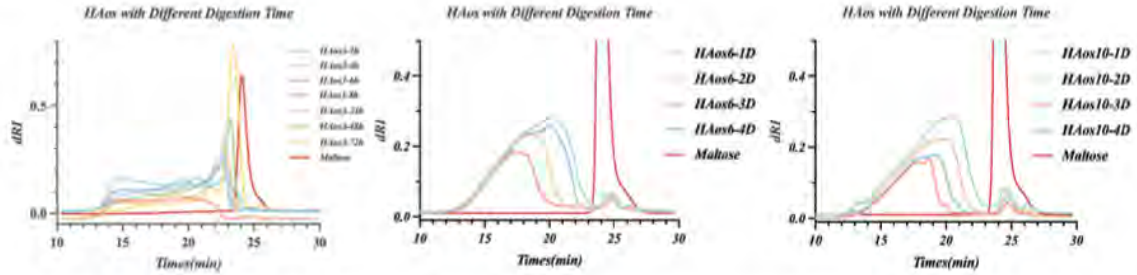
(2) Methods:

The methods employed in the project include: enzymatic digestion, cell culture, GPC (Gel Permeation Chromatography), H1NMR (Proton Nuclear Magnetic Resonance), MALDI-TOF-MS (Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry), ELISA (Enzyme-Linked Immunosorbent Assay), in vivo fluorescence imaging, SPR (Surface Plasmon Resonance), CCI model (Chronic Constriction Injury model), pain behavioral tests, and immunofluorescent staining.

4）実験結果（Results）

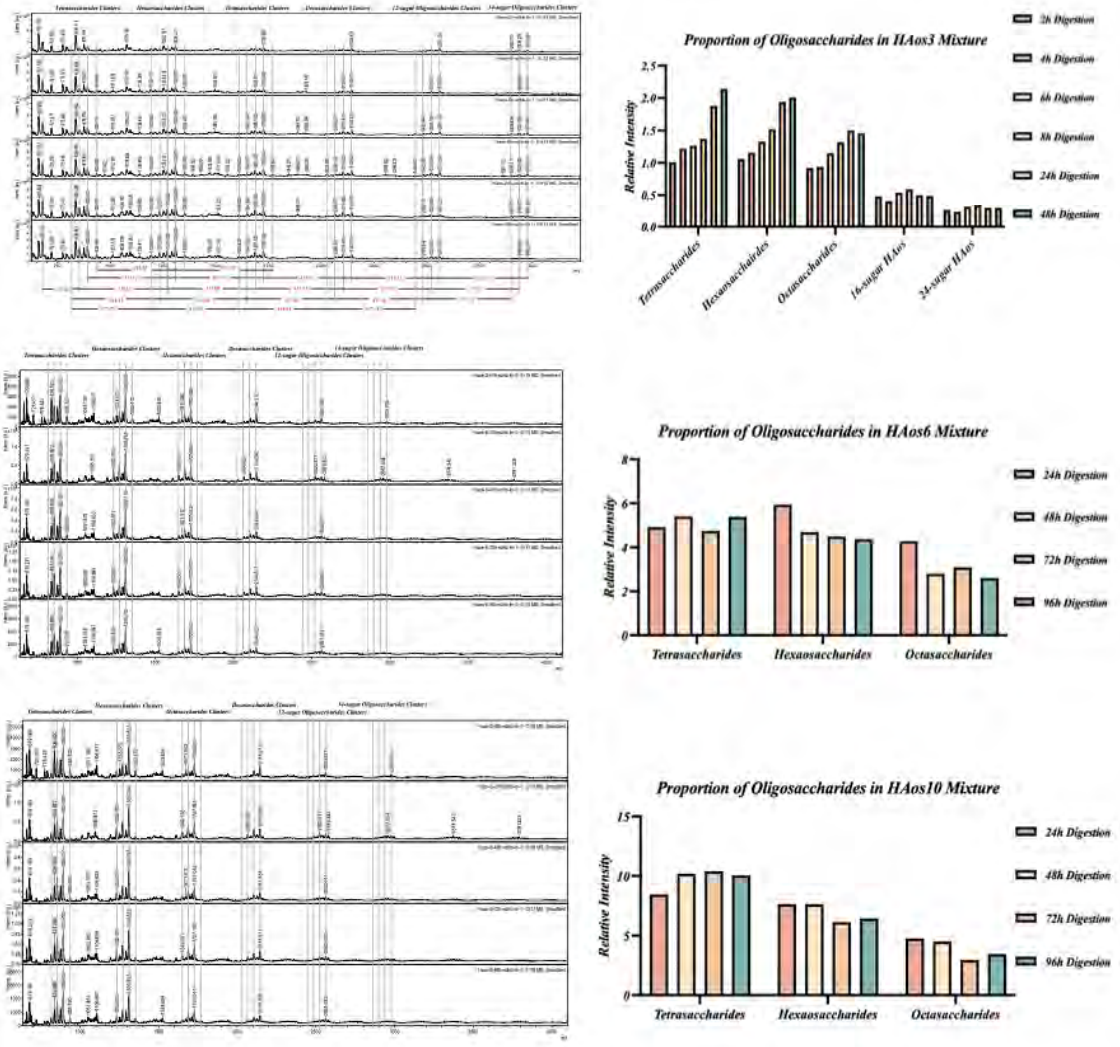
(1) Characterization of Digested HA Oligosaccharides by Hyaluronidase from bovine testes

a. GPC chromatograms of HAos with different hyaluronidase concentration and digestion time

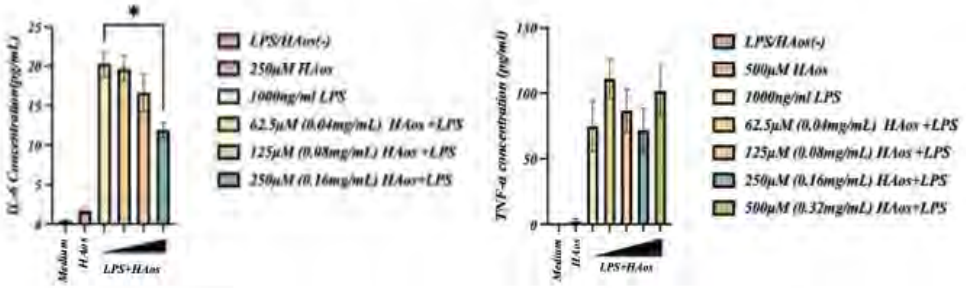


Abbreviations: HAos3, the weight ratio of hyaluronidase to HA is 3:25; HAos6, the ratio is 625; HAos10, the ratio is 10:25.

b. MALDI-TOF-MS Spectrums and Composition Ecaluation of HAos3, HAos6 and HAos10



(2) Anti-inflammatory Effect of HAos3-72h



5）考察（Discussion）

By regulating the enzymatic digestion time and the enzyme-to-substrate ratio of the hyaluronic acid oligosaccharide mixture, the composition of the mixture can be effectively modulated. This enzymatically digested HAos mixture significantly inhibits the secretion of inflammatory factors in LPS-activated THP-1 cells, with its anti-inflammatory effects demonstrating a dose-dependent manner.

6）当初の研究計画と比し、現在の進捗状況の自己評価　（Self-assessment of the current progress compared to the initial research plan）

①予想以上に進捗している（Progressing more than expected）

②おおむね順調　（Mostly on track）

③やや遅れている　（Slightly behind schedule）

④大幅に遅れている（Significantly behind schedule）

7）計画より進んでいる内容と遅れている内容、及びその理由

（Contents that are ahead of schedule and those that are behind schedule, along with the reasons）

At present, the anti-inflammatory properties of hyaluronic acid oligosaccharides have not been systematically evaluated, and the synthesis and characterization of the copolymers have not been completed as originally planned. In the early stages of the research, a significant amount of time was allocated to the familiarization and optimization of experimental techniques. In the later stages, we will expedite the completion of the planned experimental tasks as soon as possible.

8）参考文献（References）

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2. 執筆論文 Publication of thesis ※記載した論文を添付してください。Attach all of the papers listed below.

論文名 1 Title	Trends and Hotspots in Nanomedicine Applications for Pain: A Bibliometric Analysis from 1999 to 2024					
掲載誌名 Published journal	ACS OMEGA					
	2025 年 2 月	xx 巻（号）	xx 頁 ～ xx 頁	言語 Language	English	
第 1 著者名 First author	Shuailei Wang	第 2 著者名 Second author	Yumiao He	第 3 著者名 Third author	Yuguang Huang	
その他著者名 Other authors	no					
論文名 2 Title						
掲載誌名 Published journal						
	年 月	巻（号）	頁 ～ 頁	言語 Language		
第 1 著者名 First author		第 2 著者名 Second author		第 3 著者名 Third author		
その他著者名 Other authors						
論文名 3 Title						
掲載誌名 Published journal						
	年 月	巻（号）	頁 ～ 頁	言語 Language		
第 1 著者名 First author		第 2 著者名 Second author		第 3 著者名 Third author		
その他著者名 Other authors						
論文名 4 Title						
掲載誌名 Published journal						
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その他著者名 Other authors						
論文名 5 Title						
掲載誌名 Published journal						
	年 月	巻（号）	頁 ～ 頁	言語 Language		
第 1 著者名 First author		第 2 著者名 Second author		第 3 著者名 Third author		
その他著者名 Other authors						

3. 学会発表 Conference presentation ※筆頭演者として総会・国際学会を含む主な学会で発表したものを記載してください。

※Describe your presentation as the principal presenter in major academic meetings including general meetings or international meetings.

学会名 Conference	2024 Beijing Medical Association Anesthesiology Branch Annual Academic Conference				
演　題 Topic	Extended-Release Analgesics Based on Polymer Materials				
開催日 date	2024　年　7　月　12　日	開催地 venue	Beijing China		
形式　method	☑　口頭発表　Oral　☑　ポスター発表　Poste	言語　Language	☐　日本語　☐　英語　☑　中国語		
共同演者名 Co-presenter	no				
学会名 Conference	2024 PUMCH Anesthesia Tribune				
演　題 Topic	How the Integration of Medicine and Engineering Can Be Applied to the Field of Extended-Release Analgesics				
開催日 date	2024　年　12　月　8　日	開催地 venue			
形式　method	☑　口頭発表　Oral　☐　ポスター発表　Poste	言語　Language	☐　日本語　☐　英語　☑　中国語		
共同演者名 Co-presenter	no				

4. 受賞（研究業績 Award (Research achievement)

名　称 Award name				
	国名 Country name		受賞年 Year of	年　月
名　称 Award name				
	国名 Country name		受賞年 Year of	年　月

５．本研究テーマに関わる他の研究助成金受給 Other research grants concerned with your resarch theme

受給実績 Receipt record	□ 有　■ 無
助成機関名称 Funding agency	
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受給期間 Supported period	年　月 ～　年　月
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受給額 Amount received	円

６．他の奨学金受給 Another awarded scholarship

受給実績 Receipt record	■ 有　□ 無
助成機関名称 Funding agency	China International Medical Foundation
奨学金名称 Scholarship name	China International Medical Foundation & Chinese Society of Anesthesiology Overseas Study Funding Program
受給期間 Supported period	2025 年 4 月 ～ 2026 年 3 月
受給額 Amount received	2,000,000 円

７．研究活動に関する報道発表 Press release concerned with your research activities

※記載した記事を添付してください。 Attach a copy of the article described below

報道発表 Press release	□ 有　■ 無	発表年月日 Date of release	
発表機関 Released medium			
発表形式 Release method	・新聞　・雑誌　・Web site　・記者発表　・その他（　）		
発表タイトル Released title			

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出願予定 Scheduled application	□ 有　□ 無	出願国 Application country	
出願内容（概要） Application contents			

９．その他 Others

指導責任者（記名）　丸山　厚

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Article

Trends and Hotspots in Nanomedicine Applications for Pain: A Bibliometric Analysis from 1999 to 2024

Shuailei Wang, Yumiao He, and Yuguang Huang*

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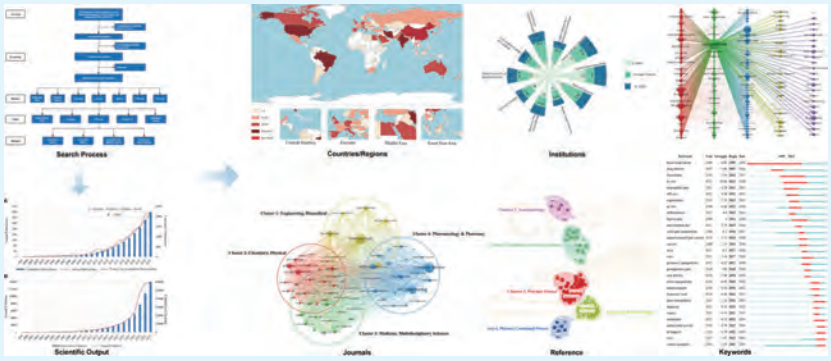

ABSTRACT: **Background:** Pain, especially chronic pain, is a leading cause of individuals seeking medical attention and presents a significant public health challenge due to its widespread prevalence and associated healthcare costs. Nanomedicine has shown considerable potential in pain management research. However, there is a lack of comprehensive bibliometric and trend analyses that explore the current status, research hotspots, and future directions of nanomedicine applications in pain. **Methods:** To fill this gap, we analyzed English language publications related to nanomedicine and pain from the Web of Science Core Collection, spanning the period from January 1, 1999, to May 24, 2024. The analysis focused on publication trends, contributions by countries/regions, institutions, journals, research categories, prominent authors, key references, and keywords. **Results:** A total of 2370 papers were included. China leads in the number of published papers (785, 33.12%) and hosts numerous high-output institutions and funding agencies, followed by the USA. The International Journal of Pharmaceutics emerged as the leading journal in terms of publication volume. A clear interdisciplinary platform has been established between nanomedicine and the field of pain. "Nanoparticles" and "drug delivery" were identified as high-frequency keywords. The drug delivery systems for pain treatment were considered the main research hotspots, particularly for chronic pain. The keyword citation bursts indicate that the pain of biomarker monitoring is a future trend. **Conclusions:** The application of nanomedicine in pain has advanced rapidly. Increased funding and international collaboration are necessary with future potential to expand from pain treatment to monitoring and diagnosis.

1. INTRODUCTION

Pain, which is recognized as the fifth vital sign, is characterized as an unpleasant sensory and emotional experience related to or similar to the sensation associated with actual or potential tissue damage.[1] Chronic pain, in particular, is a major reason why people seek medical care, which is a significant public health issue due to its high prevalence and substantial healthcare costs.[2] Despite the availability of various drugs and treatments for pain management, such as nonsteroidal anti-inflammatory drugs, opioids, and physical therapy, these methods often carry side effects, risk of drug dependence, and limited efficacy.[3] However, these conventional methods are often insufficient, particularly for chronic and complex pain, underscoring the need for more effective and targeted treatments such as those offered by nanomedicine.

"Nanomedicine" appeared in scientific publications in 2000 first.[4,5] Nanomedicine centers on the healthcare applications of nanotechnology and has demonstrated significant potential in pain research.[6] For pain management, encapsulating analgesic drugs in nanocarriers with controlled size and surface properties can extend the drug's retention time in the body, thus achieving long-lasting pain relief.[7−9] Since approval by the Food and Drug Administration (FDA) in 2011, liposomal bupivacaine (Exparel) can provide up to 72 h of sustained analgesia and has been adopted for postoperative pain management.[10−12] Nanoparticles can transport analgesic

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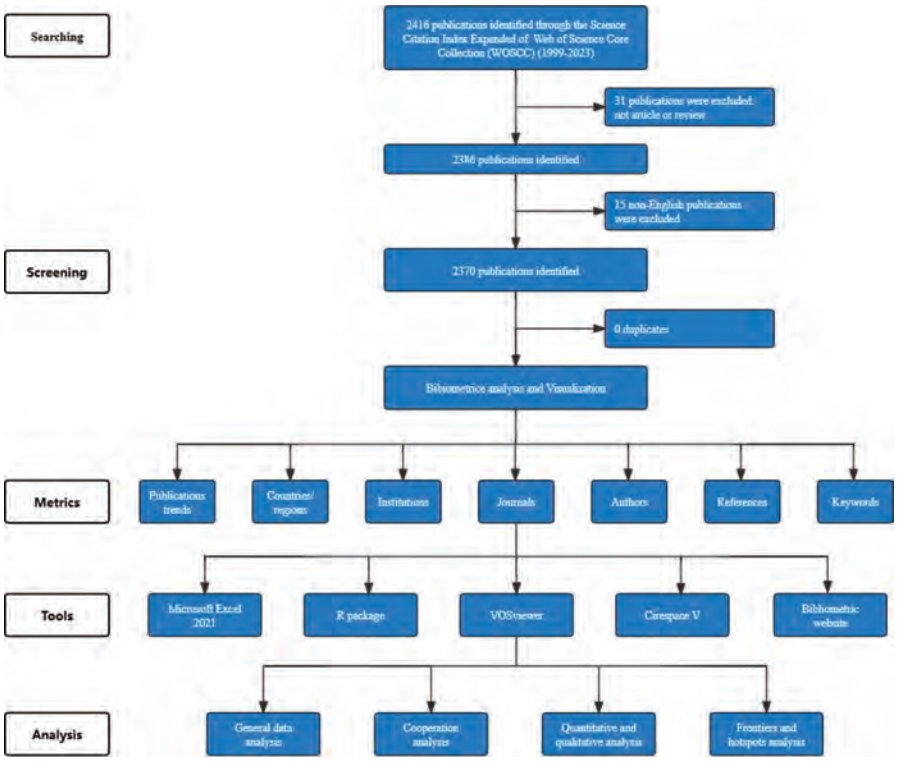

Figure 1. Flowchart of the search process.

drugs, enabling specific recognition and accumulation at pain sites through surface modification and functionalization, thereby enhancing local drug concentration and minimizing systemic side effects.[13] Moreover, nanotechnology can be combined with photothermal and magnetic hyperthermia therapies to enhance analgesic effects, thereby providing more comprehensive and personalized pain management solutions.[14] In addition to treatment, nanomedicine also holds promise for the detection of pain biomarkers, which can provide real-time monitoring of pain and its progression.[15] These characteristics make nanomedicine highly promising for postoperative pain, chronic pain, and cancer-related pain management, where long-term and precise management is required for pain control. However, only a small fraction of the research in this field ultimately benefits patients, and many nanomedicine-related products may never advance beyond clinical trials. In this case, an analysis of the overall trend and hotspots in this field is needed in order to gain a better understanding for future development.

However, there remains a lack of systematic and comprehensive analysis of the evolution and hotspots of nanomedicine's applications in pain management, resulting in fragmented and inconsistent interpretations of research trends.[16] First, for the treatment of pain, existing nanomedicine-related reviews only focus on postoperative pain[17] and neuropathic pain,[18] lacking coverage of other chronic pain types. For example, the review of nanomedicine for cancer pain dates back to 2005.[19] In addition, most related reviews were published before 2022, which might not capture the latest developments. Furthermore, we noticed that newly evolved applications of nanomedicine now extend beyond pain treatment to include pain monitoring with biomarkers.[15,20] Moreover, in addition to pain-related diseases, pain conditions such as injection pain could also be addressed by advanced nanotechnology or nanomaterials, which would be instrumental in overall pain management and inspire future trends. The trends highlight the need for a more systematic and comprehensive evaluation of nanomedicine's role in pain management.

Bibliometric analysis provides a valuable solution to these limitations. Bibliometric methods have been widely used in medical research to analyze the impact of publications, collaboration networks, and emerging topics.[21,22] Unlike traditional narrative reviews, bibliometric analysis allows for the identification of key contributors, influential publications, and shifts in research priorities over time. By analyzing citation networks, collaboration patterns, and emerging topics, bibliometric methods allow for an in-depth understanding of the connections between key research areas, offering insights into the scientific impact and collaboration dynamics. Therefore, it provides an objective, data-driven approach to assess research trends, identify hotspots, and predict the evolution of a field. In this study, bibliometric methods were used to determine the evolution of research topics, highlight emerging trends, and propose future directions for the applications of nanomedicine in pain management.

2. METHODS

2.1. Data Source and Search Strategy. The Web of Science Core Collection (WoSCC) data set is among the most extensive and impactful databases spanning various interdisciplinary domains, and it is widely utilized as a primary data source for bibliometric research.[23] All publications were obtained and downloaded from the WoSCC database on May 25, 2024. The search strategy was presented as follows:

TS = (nanotechn* or nanoparticle* or nanomaterial* or nanosheet* or nanocomposit* or nanotube* or nanowire* or nanorod* or nanofiber* or nanocrystal* or nanodot* or

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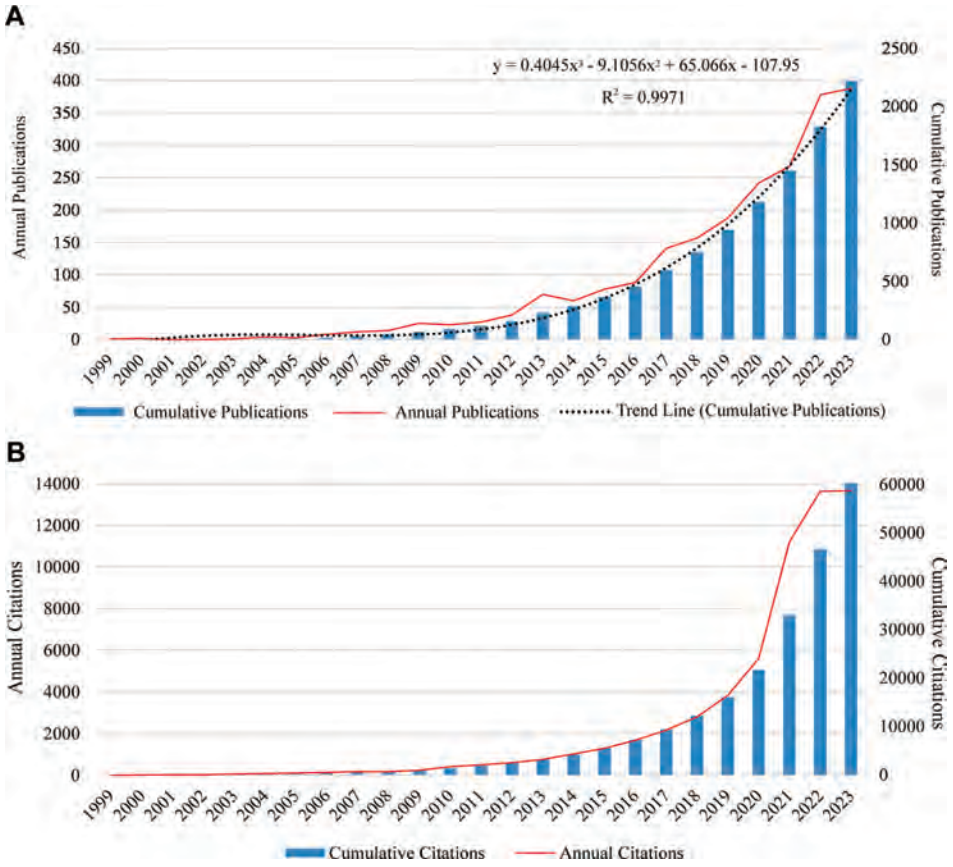

Figure 2. Annual and cumulative publications (A) and citation (B) on nanotechnology applications for pain research worldwide from 1999 to 2023.

"quantum dot*" or nanosphere* or nanodevice* or nanocluster* or nanocarrier* or nanoliposome* or nanoemulsion* or nanogels* or nanoconjugate* or nanodiamond*) and TS = (pain*).[24−27]

2.2. Data Extraction. Publications included from WoSCC were analyzed in various file formats. "Full records and cited references" were selected as the content of the records. "Plain text file" format was used for data analyzed by VOSviewer and CiteSpace and the "tab-delimited file" format for the online Web site (https://bibliometric.com/). Additionally, total citations, average citations, and H-index were obtained from Citation Report of WoSCC.

2.3. Data Visualization and Analysis. This study utilized VOSviewer (Version 1.6.20), CiteSpace V (Version 6.3 R2), Microsoft Excel (2021), RStudio (2023), and an online bibliometric tool (http://bibliometric.org) for bibliometric analysis and visualization (Figure 1). VOSviewer, a widely used bibliometric analysis tool, was used for coauthorship analysis of countries/regions, institutions, and authors, as well as cocitation analysis of journals and references, and keyword co-occurrence analysis.[28,29] The choices and configurations of VOSviewer are shown in Table S1. CiteSpace was used for cocitation analysis of institutions and references, dual-map overlay of journals, and burst analysis of keywords and references.[30] Merging keywords mainly involves synonyms, aliases, and singular/plural forms to maintain the research quality.[31] Microsoft Excel is primarily used to generate bar and line charts of publication and citation counts. RStudio is employed to generate geographic distribution maps of countries/regions and bar charts for institutions, authors, and keywords. The Online bibliometric tool is used to generate the stacked bar chart and chord diagram for visualization of countries/regions.

The key indicators utilized in the bibliometric analysis of this study are listed below. Total link strength (TLS) reflects the overall strength of connections between a node and other nodes and represents the overall level of collaboration.[32] A higher TLS value indicates more connections for the node in the network, indicating a greater influence and significance. In addition, betweenness centrality (BC) measures the frequency with which a node (such as an institution) appears on the shortest paths between other nodes.[33] Nodes with a BC value exceeding 0.1 are generally considered key and central in the network.[34] Additionally, the modularity Q score, ranging from 0 to 1, is used to evaluate the network structure. A Q score above 0.3 suggests a well-organized network structure.[35] The weighted mean silhouette S score, ranging from −1 to 1, is used to evaluate the network reliability. An S score above 0.7 signifies a highly reliable network.[36]

3. RESULTS

3.1. Study Selection and Scientific Output. Figure 1 illustrates the search process flowchart. The keyword search in the WoSCC database yielded 2416 publications associated with pain and nanomedicine. Among these, 31 publications of nonarticle and review types were excluded, and 15 publications were excluded due to language restrictions. Additionally, no

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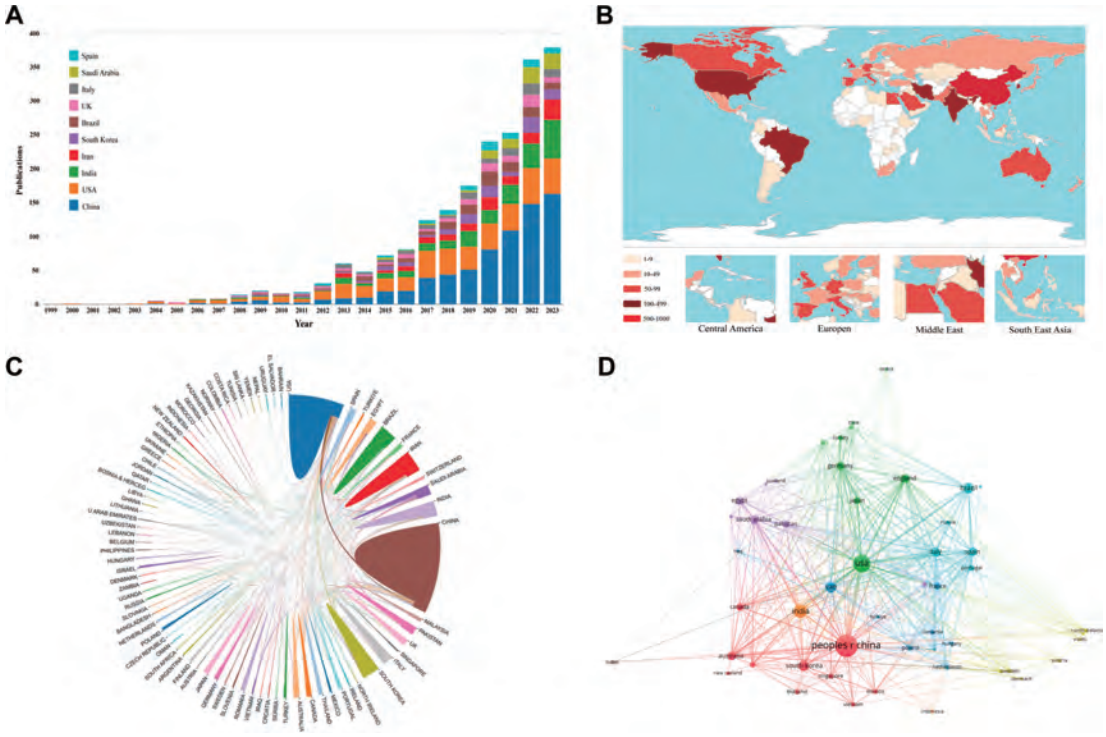

Figure 3. (A) Changing trend of the annual publication quantity in the top 10 countries/regions from 1999 to 2023. (B) Geographic distribution map based on the total publications. (C) Cross-country/region collaboration visualization map. (D) Countries/regions citation overlay visualization map.

duplicates were discovered by CiteSpace. Finally, 2370 publications were included.

The global trend of 2370 publications and total citations on nanomedicine in pain research over the past 25 years is shown in Figure 2. The compound annual growth rate (CAGR) of publications was found to be 41.0%.[37] From 1999 to 2023, the cumulative number of publications followed a third-degree polynomial distribution ($y = 0.4045x^3 - 9.1056x^2 + 65.066x - 107.95$, $R^2 = 0.9971$, Figure 2A). It is observed that before 2006, the number of published articles was minimal. However, between 2007 and 2017, there was a marked increase in publications, and post-2017, the publication rate surged dramatically, with 377 and 388 papers published in 2022 and 2023, respectively. The CAGR of the citations was 36.9% (Figure 2B). By the search date, the total number of citations for all the literature amounted to 64,999, averaging 27.4 citations per paper, with an H-index of 96.

3.2. Countries/Regions. Research on nanomedicine for pain has seen contributions from 88 countries/regions. Figure 3A shows the publication trends of the top 10 countries from 1999 to 2024. China leads with 785 papers (33.12%), demonstrating significant productivity. The United States follows with 442 papers (18.65%) but stands out in total citations (24,755) and average citations per paper (56.0), indicating high research impact. England, with 82 papers (3.46%), achieves an exceptional average citation count of 142.4, highlighting its significant academic influence (Table 1). The geographic distribution map (Figure 3B) shows that most publications originate from East Asia and America. Besides China and the United States, other countries with over 100 publications include India, Iran, South Korea, and Brazil.

The cross-country/region collaboration chord diagram (Figure 3C) shows close cooperation among the most productive countries. China, depicted in dark brown, has extensive connections, signifying its central role in international research collaborations. The United States, represented in blue, also shows significant collaborative links, particularly with China mutually, the United Kingdom, and Canada. This visualization highlights the intricate and widespread nature of international research cooperation, with key nations serving as pivotal nodes in the global scientific community. A citation overlay visualization map of 52 countries and regions by VOSviewer is shown in Figure 3D. Germany was the first country to start pain research-based nanomedicine in 1999. Since then, many countries (shown in red) have increased participation, especially between 2020 and 2022, indicating growing global interest in nanomedicine and pain research.

Table 1. Top 10 Productive Countries/Regions' Nanotechnology Applications for Pain Research

rank	country	counts	percentage	total citations	average citation	H-index
1	China	785	33.12%	15,831	20.2	59
2	USA	442	18.65%	24,755	56.0	60
3	India	239	10.08%	6364	26.6	37
4	Iran	142	5.99%	2747	19.3	32
5	South Korea	123	5.19%	2698	21.9	29
6	Brazil	122	5.15%	11,135	91.3	29
7	Italy	94	3.97%	2862	30.4	26
8	Saudi Arabia	93	3.92%	1069	11.5	19
9	UK	82	3.46%	11,673	142.4	30
10	Australia	78	3.29%	2927	37.5	28

3.3. Institutions and Funding. Over 3100 institutions have published research on nanomedicine applications for

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Table 2. Top 10 Productive Institutions on Nanotechnology Applications for Pain Research

rank	institution	country	counts	percentage	total citations	average citation	H-index
1	Egyptian Knowledge Bank	Egypt	69	2.91%	1207	17.5	23
2	Chinese Academy of Sciences	China	57	2.41%	1477	25.9	20
3	Shanghai Jiao Tong University	China	43	1.81%	801	18.6	17
4	Sichuan University	China	40	1.69%	821	20.5	12
5	Tehran University of Medical Sciences	Iran	38	1.6%	946	24.9	19
6	Harvard University	USA	32	1.35%	1275	39.8	17
7	University of California System	USA	32	1.27%	1231	38.5	18
8	Universidade Estadual de Campinas	Brazil	31	1.31%	699	22.6	14
9	Centre National de la Recherche Scientifique	France	30	1.27%	764	25.5	12
10	Islamic Azad University	Iran	29	1.22%	562	19.4	11

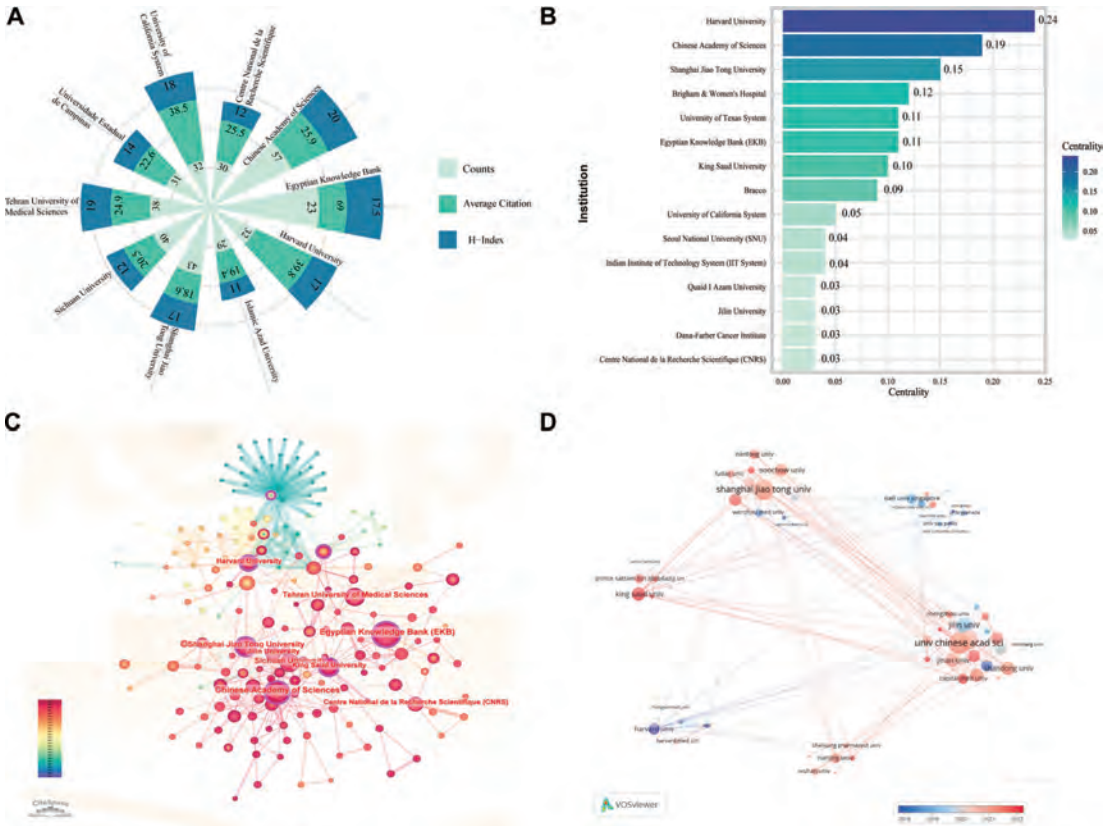

Figure 4. (A) Polar bar chart of counts, average citations, and H-index of the top productive 10 institutions. (B) Institutions with top 15 betweenness centrality. (C) Visualization map of institutions analysis. (D) Institutions overlay a visualization map.

pain. As shown in Table 2, these institutions are globally diverse. The polar bar chart summarizes publication counts, average citations, and the H-Index of the top 10 most productive institutions (Figure 4A). The Egyptian Knowledge Bank (EKB) ranks first with 69 papers, contributing 2.91% of total publications, and has 1207 citations, averaging 17.5 citations per paper. Following EKB are the Chinese Academy of Sciences, Shanghai Jiao Tong University, and Sichuan University. EKB has the highest H-Index at 23, while Harvard University has the highest average citation count at 39.8. Figure 4C shows a visualization map of institutional analysis by CiteSpace. Harvard University and the Chinese Academy of Sciences occupy central positions with betweenness centrality (BC) scores of 0.24 and 0.19, respectively (Figure 4B), indicating significant research output and influence. Many institutions such as Harvard University, MIT, and Islamic Azad University entered the field earlier, whereas nearly all Chinese institutions joined after 2020, as indicated by reddish nodes in Figure 4D.

Funding agencies are crucial for research. The bar chart in Figure S1 shows the top 10 funding agencies. The Natural Science Foundation of China (NSFC) leads with 370 funded articles, showcasing China's commitment to scientific research. The United States Department of Health and Human Services and the National Institutes of Health funded 172 articles, indicating substantial US support. These funding agencies drive research outputs and scientific progress globally.

3.4. Journals. Currently, publications on nanomedicine applications for pain research span 776 journals (Figure 5A). The *International Journal of Pharmaceutics* leads with the highest number of publications, totaling 61 articles and 1631 citations (Table 3). Notably, *Biomaterials*, with 28 publications, achieved the highest average citation per article, 50.4, and the highest impact factor (IF) of 14.0. All top 10 journals are

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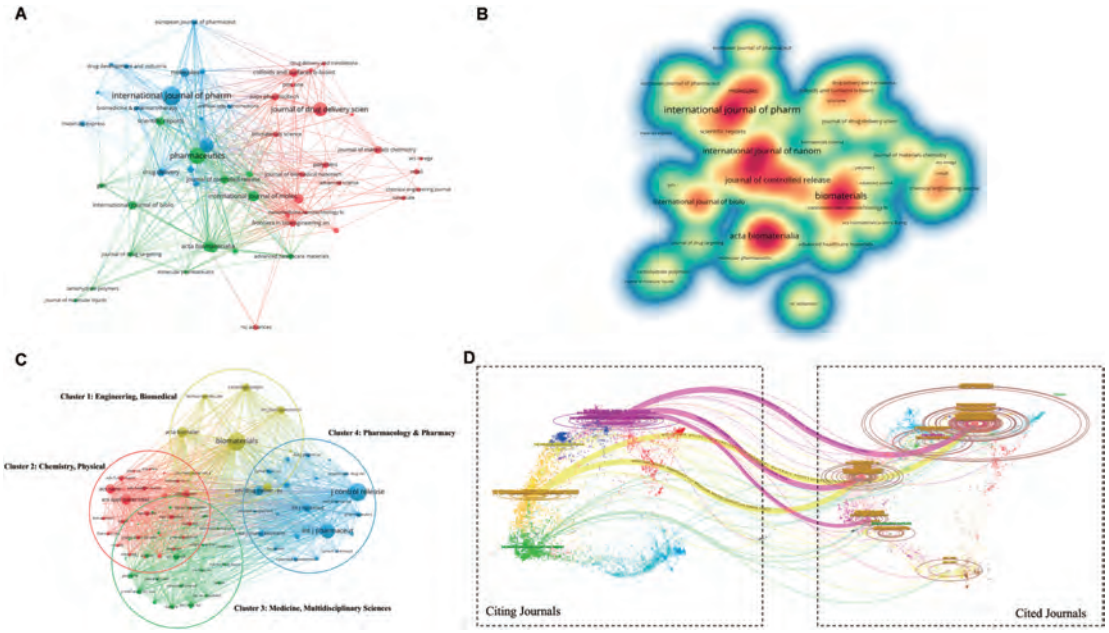

Figure 5. Network (A) and density (B) visualization map of journals analysis. (C) Network visualization map of Journal cocited analysis. (D) Dual-map overlap of journals on nanotechnology applications for pain research.

Table 3. Top 10 Most Productive Journals

rank	journal	country	counts	citations	average citation	IF(2022)	JCR(2022)	H-index
1	International Journal of Pharmaceutics	Netherlands	61	1631	26.7	5.8	Q1	23
2	Pharmaceutics	Switzerland	53	803	15.2	5.4	Q1	16
3	International Journal of Nanomedicine	New Zealand	45	1207	26.8	8.0	Q2	20
4	Journal of Drug Delivery Science and Technology	France	44	484	11.0	5.0	Q1	13
5	International Journal of Molecular Sciences	Switzerland	33	557	16.9	5.6	Q1	14
6	Acta Biomaterialia	UK	32	1213	37.9	9.7	Q1	17
7	Biomaterials	Netherlands	28	1410	50.4	14.0	Q1	20
8	Molecules	Switzerland	27	656	24.3	4.6	Q2	9
9	ACS Applied Materials & Interfaces	USA	26	1154	44.4	9.5	Q1	12
10	International Journal of Biological Macromolecules	Netherlands	25	880	35.2	8.2	Q1	16

classified in Q1 according to the 2022 Journal Citation Report (JCR), indicating high ranking and impact. Significant journals include the *International Journal of Pharmaceutics* (H-Index of 23) and *Biomaterials* (H-Index of 22), underscoring their influence. The VOSviewer-generated visualization (Figure 5B) highlights the central role and high impact of these journals.

Co-citation analysis reveals 82 journals cocited over 300 times, forming four clusters: Engineering, Biomedical; Chemistry, Physical; Medicine, Multidisciplinary Sciences; and Pharmacology and Pharmacy, indicating multidisciplinary collaboration (Figure 5C). *Advanced Materials* and *Proceedings of the National Academy of Sciences of the United States of America* have the highest BC values (0.12), followed by the *Journal of Control Release* (0.1) (Figure S2). A dual-map (Figure 5D) shows that literature from Physics/Materials/Chemistry and Molecular/Biology/Immunology journals often cites works from Chemistry/Materials/Physics (f = 9064, 4665) and Molecular/Biology/Genetics (f = 6713, 5817).

3.5. Authors. A total of 13,406 authors have contributed to the publication of papers on nanomedicine applications for pain research. Table 4 highlights the top 10 most prolific authors, with six hailing from Brazil, emphasizing the country's strong presence in this field. The leading author, Eneida de Paula from the State University of Campinas (Unicamp) in Brazil, boasts the most publications (22), citations (584), and an H-Index of 13. Following her are Shih-Jung, Liu from Chang Gung University in China and Ribeiro, Ligia Nunes de Morais from the State University of Campinas (Unicamp) in Brazil. Despite being tenth in the number of publications (8 papers), Donnelly, Ryan F. from Queen's University Belfast in

Table 4. Top 10 Most Productive Authors

rank	author	country	counts	citations	average citation	H-index
1	Eneida de Paula	Brazil	22	584	26.5	13
2	Liu, Shih-Jung	China	13	164	12.6	8
3	Ribeiro, Ligia Nunes de Morais	Brazil	12	293	24.4	8
4	Janjic, Jelena M.	USA	12	185	15.4	8
5	Shin, Hyo Jung	South Korea	10	94	9.4	7
6	Breitkreitz, Marcia Cristina	Brazil	10	196	19.6	7
7	De Araujo, Daniele Ribeiro	Brazil	9	302	33.56	8
8	Rodrigues Da Silva, Gustavo Henrique	Brazil	9	131	14.6	6
9	Fraceto, Leonardo	Brazil	8	273	34.1	7
10	Donnelly, Ryan F.	UK	8	424	53	6

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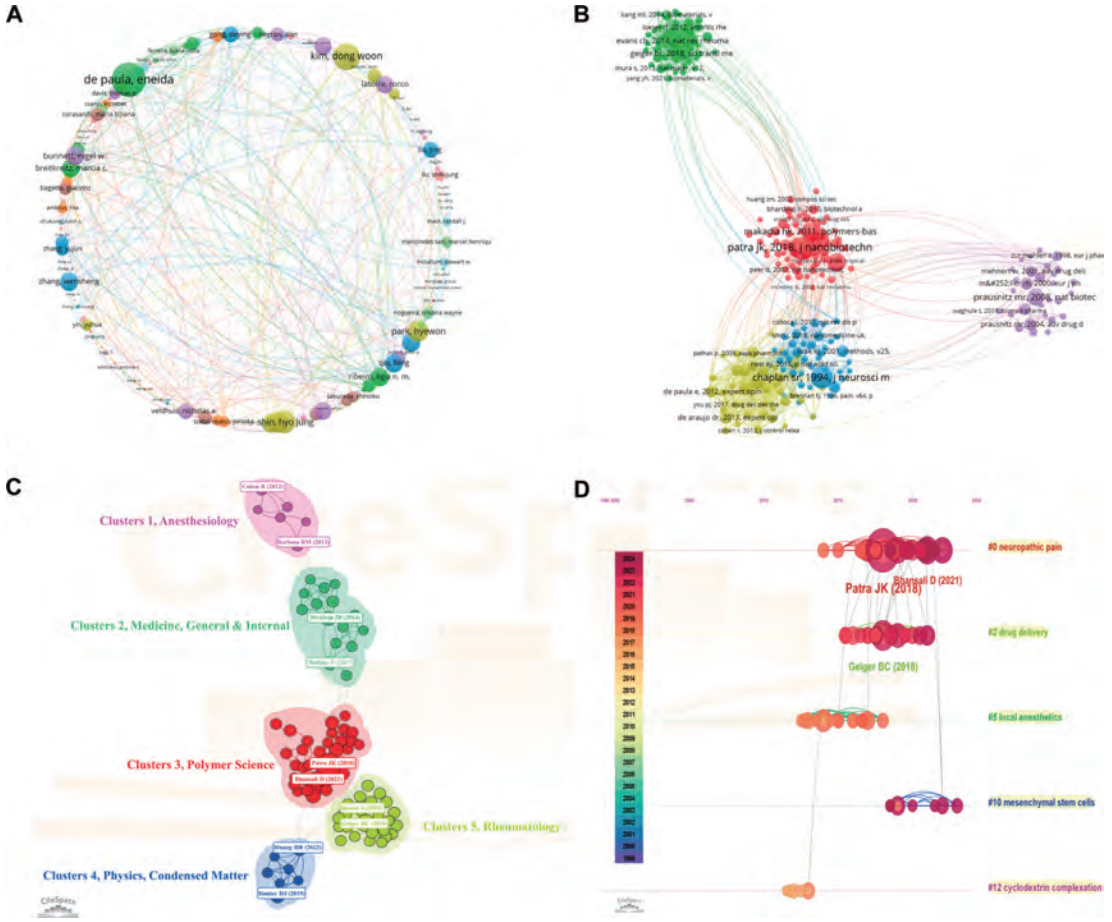

Figure 6. (A) Network visualization map of authors coauthorship analysis. (B) Network visualization map of references cocitation analysis. Visualization of cluster view (C) and timeline view (D).

Table 5. Top 10 Original Articles Concerning Nanotechnology and Pain Research

rank	title	journal	years	first author	citations
1	Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine	New England Journal of Medicine	2020	Polack, FP	9211
2	What controls the optical properties of DNA-linked gold nanoparticle assemblies?	Journal of the American Chemical Society	2000	Storhoff, JJ	1116
3	Microneedles for transdermal drug delivery	Advanced Drug Delivery Reviews	2004	Prausnitz, MR	1049
4	Biological activities of curcumin and its analogues (Congeners) made by man and Mother Nature	Biochemical Pharmacology	2008	Anand, P	916
5	Properties of Zinc Oxide Nanoparticles and Their Activity Against Microbes	Nanoscale Research Letters	2018	Siddiqi, KS	593
6	Diagnostics for SARS-CoV-2 infections	Nature Materials	2021	Kevadiya, BD	472
7	Photodynamic Therapy: Past, Present and Future	Chemical Record	2017	Chilakamarthi, U	355
8	On-Demand Dissolvable Self-Healing Hydrogel Based on Carboxymethyl Chitosan and Cellulose Nanocrystal for Deep Partial Thickness Burn Wound Healing	Acs Applied Materials and Interfaces	2018	Huang, WJ	334
9	Silver Coordination Polymers for Prevention of Implant Infection: Thiol Interaction, Impact on Respiratory Chain Enzymes, and Hydroxyl Radical Induction	Antimicrobial Agents and Chemotherapy	2010	Gordon, O	326
10	Emerging microand nanotechnology based synthetic approaches for insulin delivery	Chemical Society Reviews	2014	Mo, R	325

the United Kingdom, has the highest average citations of 53 citation per paper with a total citation count of 424, indicating a strong impact of his work. The network visualization map shows closely collaborating author clusters centered around researchers like Eneida de Paula and Kim Dong Woon, indicating their significant influence and active collaborative relationships (Figure 6A).

3.6. References. This study included 2370 publications, of which 88 were cited over 100 times. Table 5 details the top 10 cited papers, with the highest citation count belonging to Polack FP's 2020 article in the *New England Journal of Medicine*, cited 9211 times.[38] This clinical trial, titled "Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine", demonstrated that the BNT162b2 successfully provided 95% protection against COVID-19. However, the safety included

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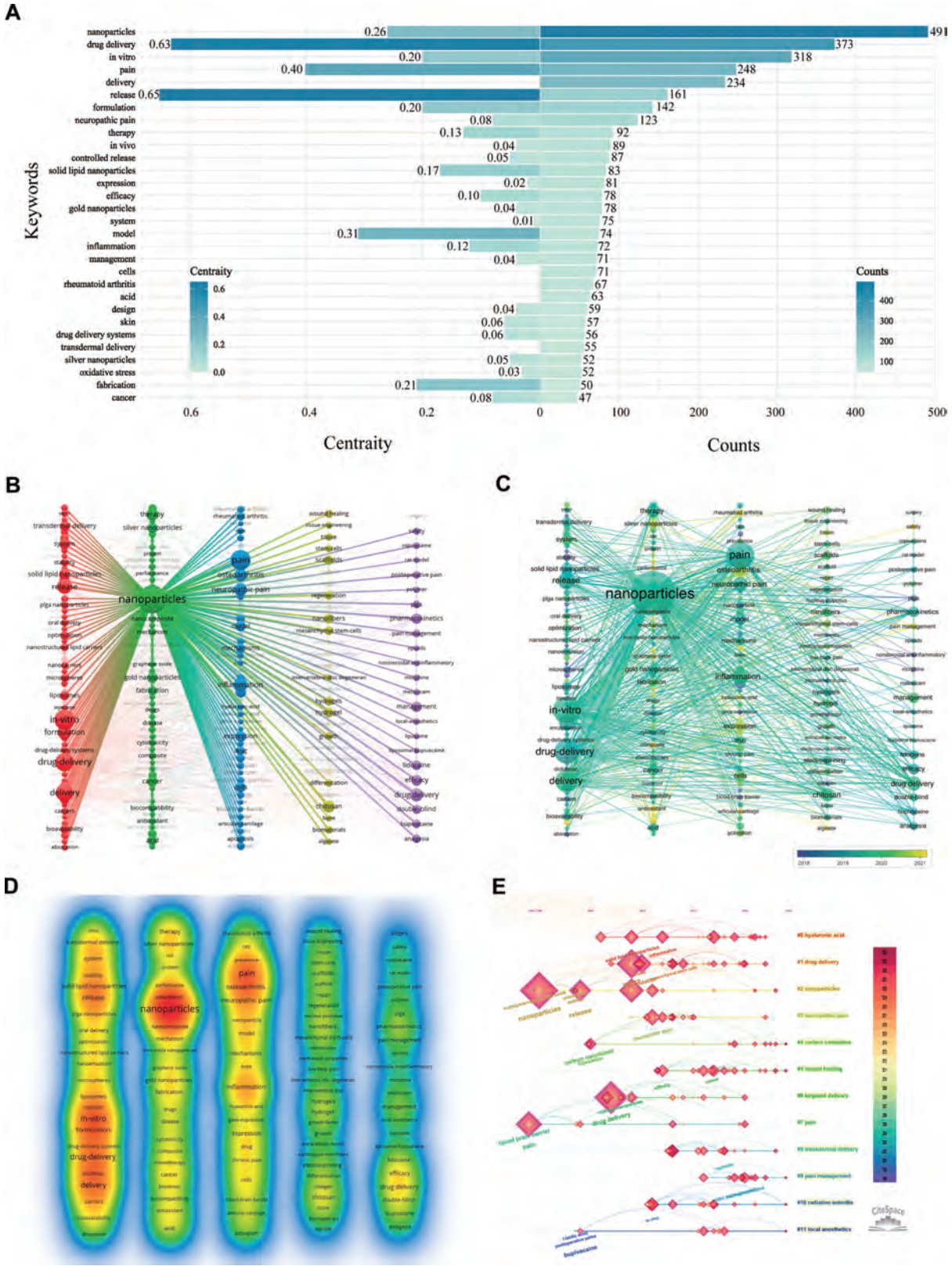

Figure 7. (A) Top 30 cocitation keywords with the highest frequency. Network (B), overlay (C), and density (D) visualization map of keywords co-occurrence analysis. (E) Visualization map of the timeline view.

short-term mild to moderate pain at the injection site and a headache. Following closely are articles by Storhoff, JJ from Northwestern University[39] and Prausnitz, MR from Georgia Institute of Technology (2004) in USA,[40] with 1116 and 1049 citations, respectively. The network visualization map of references cocitation analysis (Figure 6B) shows that Patra

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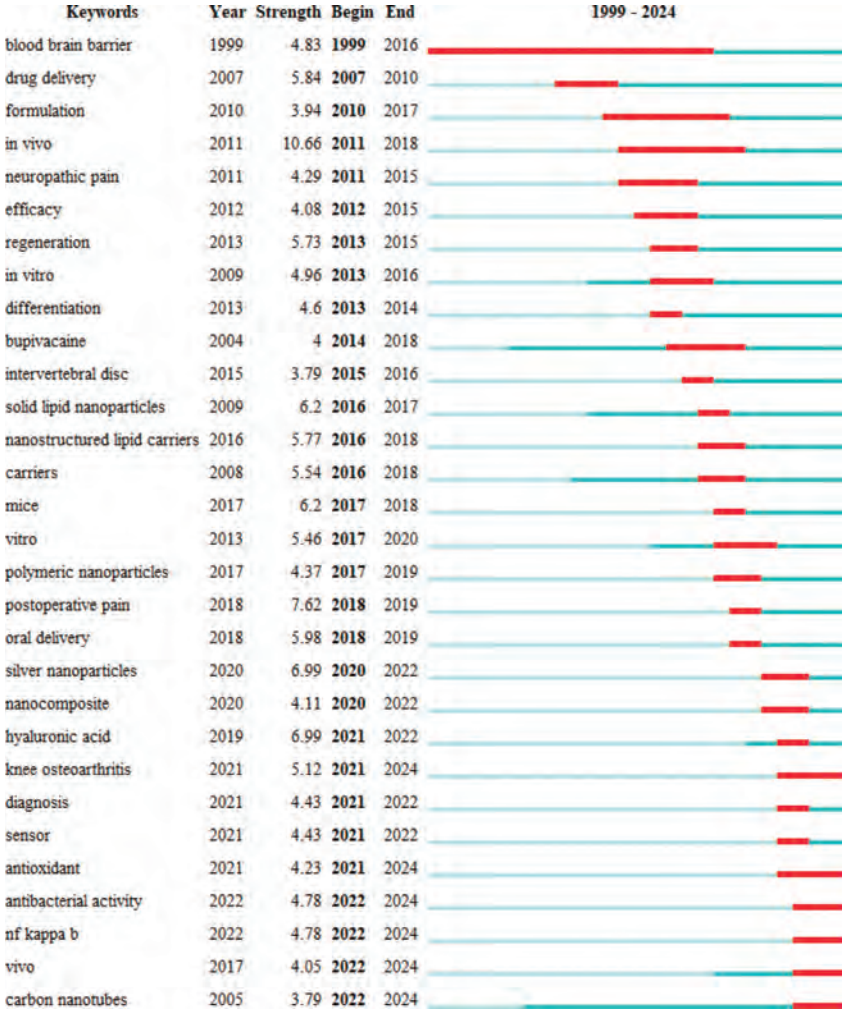

Figure 8. Top 30 keywords with the strongest citation bursts.

JK from Dongguk University, South Korea,[41] and Chaplan SR from the University of California, USA,[42] are major citation hotspots, highlighting important research themes in the field.

The cluster analysis generated by CiteSpace clearly identifies five main research clusters: Cluster 1: Anesthesiology, Cluster 2: Medicine, General and Internal, Cluster 3: Polymer Science, Cluster 4: Physics, Condensed Matter, and Cluster 5: Rheumatology (Figure 6C). A *Q* value of 0.9486 and an *S* value of 0.9184 reflect effective clustering and network homogeneity. The different clusters reflect the diverse research directions within the field, ranging from biomaterials to nanomedicine and from medicine to physics, indicating the multidisciplinary nature of the research. The timeline view of cocitation references visually depicts the temporal characteristics of research hotspots (Figure 6D). Neuropathic pain, drug delivery, and mesenchymal stem cells appear to be prominent research hotspots with significant activity in recent years. Other notable clusters include drug delivery and local anesthetics, reflecting ongoing research interest in these areas. Figure S3 provides a summary of the top 25 references with the most significant citation bursts. This study observed the start of citation bursts in 2017, spearheaded by McAlvin JB's 2014 publication on biomaterials.[11] The latest citation bursts were detected in 2024, indicating an ongoing research interest in the field. Among these references, Patra JK's 2018 paper on nanobiotechnology had the strongest burst strength, indicating its significant impact on recent research.[41]

3.7. Keywords. The study analyzed 11,088 keywords. Figure 7A highlights the top 30 keywords that appear most frequently. The most frequently occurring keywords were "nanoparticles", "drug delivery", and "in vitro". Additionally, "pain", "neuropathic pain", and "rheumatoid arthritis" were the three most researched diseases in this area. Table S2 also lists the 15 most frequently studied diseases.

The keyword co-occurrence analysis showed the clustering of different keywords, forming five thematic clusters (Figure 7B). The red cluster shows the application of nanotechnology in drug delivery systems, such as "nanoparticles", "drug delivery", "in vitro", and "release". The green cluster focuses on the development of new nanomaterials and cancer treatment, such as "nanocomposite", "gold nanoparticles", "biocompatibility", "antioxidant", and "cancer". The blue cluster mainly studies the application of nanotechnology in pain management and inflammation treatment, such as "osteoarthritis", "neuropathic pain", and "inflammation". The yellow cluster mainly researches the application of nanotechnology in tissue engineering and regenerative medicine, such as wound healing, tissue engineering, stem cells, and "scaffolds". The purple cluster focuses on pharmaceutical research, such as "pharmacokinetics", "efficacy", and "local

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anesthetics". Overlay (Figure 7C) and density (Figure 7D) visualization map of keywords co-occurrence analysis showed that hot topics such as "nanoparticles" and "drug delivery" began to significantly increase around the year 2020.

The timeline view shows the research trends and clustering of different keywords over time (Figure 7E). From 1999 to 2005, research mainly focused on the basic study of nanoparticles and their potential in drug delivery. From 2005 to 2015, the application of nanotechnology began to expand into multiple fields including carbon nanotubes, targeted delivery, neuropathic pain, and wound healing. From 2015 to 2024, hyaluronic acid, transdermal delivery, and integrated pain management became new research hotspots with increasing studies on radiation enteritis and local anesthetics.

Keyword citation bursts indicate significant research interest within specific time frames (Figure 8). Notably silver nanoparticles (2020 strength 6.99) in antibacterial and material science nanocomposites (2020 strength 4.11), hyaluronic acid (2021 strength 6.9) in skincare and antiaging knee osteoarthritis treatment (2021 strength 5.12), diagnostic technology (2021 strength 4.43), new sensors (2021 strength 4.43), antioxidants (2021 strength 4.23), and high-efficiency antibacterial materials (2022 strength 4.78) highlight these fields' future research importance.

4. DISCUSSION

In this study, the 2370 papers used in this study were written by 13,406 authors from 3103 institutions in 87 countries, published in 776 journals, and cited 132,517 references from 15,354 journals. This study analyzes the publication trends and geographical distribution of nanomedicine in the field of pain research over the past 26 years. It also provides an overview of the knowledge map and research hotspots and anticipates emerging research areas.

4.1. Analysis of the Geographical Distribution of Publications. Overall, the total number of publications between 1999 and 2017 was less than 500. After 2017, the number of publications on nanomedicine in pain research surged globally. The number of papers published after 2017 (1762 papers) is 3.88 times that of those published before 2017 (454 papers). Numerous factors contributed to this prosperity. First, the integration of nanomedicine with other disciplines such as biotechnology and chemistry has promoted advancements in the synthesis and characterization of nanomaterials.[43] Cluster analysis suggests that publications include top journals in the fields of chemistry and materials such as *Advanced Materials*, *Journal of the American Chemical Society*, and *Angewandte Chemie-International Edition*, indicating that frontier technologies in chemistry and material science are being actively applied in pain treatment. Incorporation with updated clinical ideology further boosts the development of nanomedicine. Nanomedicine designing responsive drug delivery systems aligns perfectly with the Enhanced Recovery After Surgery (ERAS) principles and the need for precise and personalized medicine. For instance, two-dimensional silicene mesoporous nanomaterials designed by S. Yin et al. achieved spatial and temporal controlled release of ropivacaine under near-infrared triggering.[44] This integration has promoted the application of nanomaterials in biomedicine, such as targeted drug delivery, which improves efficacy and reduces side effects furthermore.[45]

Funding support is a critical factor in advancing nanomedicine research for pain management. The financial investments made by different countries directly affect the quantity and quality of the research output. Sufficient funding can drive technological innovation and facilitate the advancement of the field.[46−48] Research by Wang et al. has demonstrated that funded studies tend to perform better in terms of journal impact factors and citation counts.[49] In addition, based on Price's law, we identified 176 highly influential researchers who have published more than four papers, collectively contributing 892 papers, which accounts for approximately 38% of the total publications.[50,51] This indicates that the field is developing in a more concentrated manner. Behind this phenomenon lies robust funding support and the accumulation of resources in high-GDP countries and research institutions. As a high-GDP country, the United States has leveraged funding from government agencies such as the US Department of Health Human Services and National Institutes of Health (NIH) to propel early research and ongoing development of nanomedicine in pain management.[46,52] The United States was among the first countries to apply nanomedicine to pain research, with leading institutions like Harvard University and the University of California system contributing 18.65% of total publications (Figure 3A). Furthermore, according to data from the European Commission's Joint Research Centre, the United States holds the largest share (53%) of nanomedicine patent applications.[53,54] The substantial economic resources of the United States have allowed it not only to fund basic research but also to directly support the conduct of clinical trials, thereby facilitating the integration of nanomedicine into patient care. The most classic example in this field is the successful translation of multivesicular liposomes to EXPAREL. In 2017, EXPAREL received FDA approval for new indications that expanded its previous use in wound infiltration to interscalene brachial plexus nerve block for the postsurgical regional analgesia in shoulder surgeries, such as total shoulder arthroplasty and rotator cuff repair.[55] This approval was based on clinical trials demonstrating its efficacy and safety in providing pain relief for up to 72 h after surgery.

China's funding investment has also been rapidly increasing.[48] Since 2018, the number of annual publications in China has reached its highest levels, with particularly rapid growth in recent years—publishing 144 papers in 2022 and 159 papers in 2023.[56] This growth is attributed to significant government funding, with the National Natural Science Foundation of China providing only 370 grants. Despite these advancements, China's research output still lags behind that of countries like the United States and the United Kingdom in terms of international impact and citation counts, which may be attributed to the relatively shorter research accumulation period in China and lower patents.[53,54] There is no innovative long-lasting analgesia based on a drug delivery system approved in China. In the future, increasing publication quality instead of quantity and enhancing technology translation success rates may be key areas of focus for China.

From the perspective of globalization, international collaboration has become a crucial driver of progress in nanomedicine research. The United States and China have the most extensive cooperation, both with each other and with other countries (Figure 3C). Cross-border collaboration provides both financial and resource support. By partnering with high-income countries like the United States, China has accelerated research in pain management and drug delivery systems.[57] The United States's financial and technological advantages have

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expedited the translation of Chinese research. Meanwhile, China's large population provides a natural advantage in conducting clinical trials, particularly in areas such as patient recruitment and clinical data diversity. For instance, we found that only Chinese scholars have published 43 clinical studies on bupivacaine liposomes for pain management through searching the PubMed database by December 23, 2024. The publications involved multiple clinical disciplines such as orthopedics, thoracic surgery, and obstetrics, covering research on postsurgical incision infiltration, nerve blocks, and joint cavity injections. Furthermore, international collaboration has allowed low-income countries to access the latest technological platforms and research methods, promoting the localization of technology. For example, Hengrui Medicine's bupivacaine liposome injection was approved by the FDA in July 2024. It becomes China's first extended-release local anesthetic, using proprietary DepoFoam technology to encapsulate bupivacaine in multivesicular liposomes for sustained release.[58]

In summary, to advance the application of nanomedicine in pain management and improve global health outcomes, governments and research institutions worldwide should increase research funding and enhance international collaboration for the production of higher-impact research and the successful translation of products.

4.2. Analysis of Research Categories. Recognizing key journals and conducting citation analysis offer researchers reliable references, aiding in the selection of appropriate journals for a literature review or article submission. Nanomedicine's significant characteristics in pain research include its multiresearch categories and interdisciplinary nature, spanning chemistry, physics, engineering, biomedicine, pharmacology, pharmacy, and multidisciplinary sciences.

In chemistry and physics, representative journals include *the Journal of the American Chemical Society* and *Advanced Materials*. As scientists in this field focus on developing nanomaterials with specific properties for targeted drug delivery and pain management, the most influential publication (1116 citations) in nanomedicine is "What Controls the Optical Properties of DNA-Linked Gold Nanoparticle Assemblies?" which is published in *the Journal of the American Chemical Society*.[39] This research highlights the importance of aggregate dimensions in determining the optical properties of DNA-linked nanoparticle clusters, crucial for advancing nanoparticle-based colorimetric detection techniques. In pharmacology and pharmacy, key journals include *Advanced Drug Delivery Reviews* and *the Journal of Controlled Release*. Research in this field focuses more on nanoparticle-based drug delivery systems to enhance the efficacy and safety of pain medications. The most influential publication (1049 citations) is "Microneedles for transdermal drug delivery", demonstrating the promise of microneedles in painlessly delivering drugs through the skin, published by *Advanced Drug Delivery Reviews*.[40] In engineering and biomedicine, representative journals are *Biomaterials* and *Acta Biomaterialia*, where the development of novel biomaterials for medical applications, including drug delivery systems and tissue engineering solutions, is a key point. The most influential publication (916 citations) is "Biological activities of curcumin and its analogues (Congeners) made by man and Mother Nature" from *Biochemical Pharmacology*, highlighting curcumin's anti-inflammatory, antioxidant, and analgesic properties.[59] In summary, with the advancement of nanotechnology and interdisciplinary collaboration, experts from various fields are working together to translate nanotechnology applications from the technical design to clinical application in multi-dimensional aspects.[60]

4.3. Overview of Knowledge Maps. Keyword burst detection is used to capture a sharp increase in citations or keyword popularity over a certain period of time and can act as an effective approach to pinpoint hotspots or themes. From 1999 to 2024, the research focus at different stages has continuously evolved.

During 2000−2005, research in nanomedicine for pain was in its infancy with only 11 publications. Researchers have begun exploring drug delivery systems for the treatment of postoperative pain. The PLA microsphere system loaded with lidocaine through the oil/water solvent evaporation technology[61] and lipid nanocarriers as drug delivery systems for intravenous ibuprofen[62] has been developed, which are pivotal explorations of nanomedicine in the treatment of postoperative pain. At this time, the initial connection between nanomedicine and postoperative pain treatment began to appear.

During 2006−2010, research focused on the design of novel nanostructured drug carriers and their applications in drug delivery. Carbon nanotubes[63] and chitosan nanoparticles[64] became key research areas in nanomaterials, focusing on their preparation, functionalization, and applications in drug delivery and biomedicine. Indications of pain treatment in this field extended to cancer pain beyond postoperative pain,[65] with abundant analgesics loaded besides local anesthetics and nonsteroidal anti-inflammatory drugs, and opioid delivery systems emerging.[66] These studies reflected the rapid development and widespread application of nanotechnology in the biomedical field at that time.

From 2011 to 2015, nanomedicine rapidly developed in the field of pain, combined with its application in regenerative medicine.[67] While chronic pain[68] began to draw increasing attention, more research focused on understanding its mechanisms and developing new treatments. The advancement of nanomedicine technology, shifting from in vitro to in vivo experiments, improved the efficacy of conventional analgesics and provided potential pain treatments.[69] In 2013, research on regenerative medicine emerged, which involves the tissue and organ regeneration after trauma, and therefore is also correlated with pain initiation and persistency.[70] The technologies in regenerative medicine, including stem cell therapy and regenerative medicine materials,[71] can be utilized in pain medicine as well. Furthermore, the research achievements of this period significantly enhanced the understanding and treatment of chronic pain and advanced regenerative medicine.

From 2016 to 2020, nanomedicine experienced explosive growth in the field of pain, particularly in the development of more fascinating nanomaterials and drug carriers. Solid lipid nanoparticles (SLNs) composed of natural or synthetic lipids possess high biocompatibility and are gradually being applied to enhance the bioavailability of poorly soluble drugs by encapsulating drugs.[72] In 2016, Basha et al. systematically developed and evaluated an SLN carrier system for the local anesthetic benzocaine and found that SLNs are good candidates for encapsulating poorly soluble benzocaine.[73] Additionally, biodegradable polymer nanoparticles are also being developed for the sustained release of opioid drugs.[74,75] Postoperative pain became a major research focus again in 2018, with an emphasis on developing new analgesics, and research on oral drug delivery systems also emerged. In 2020,

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research on silver nanoparticles and nanocomposites[76] focused on their preparation and applications in antimicrobial and biomedical fields. These studies not only advanced the application of nanomedicine in pain management but also laid the foundation for developing more effective treatments in the future.

From 2021 to 2024, nanomedicine continued to grow and innovate in the field of pain. The application of hyaluronic acid[77] in tissue repair and drug delivery became an important direction, and the pathological mechanisms and treatment methods for knee osteoarthritis also received widespread attention.[78] Additionally, new diagnostic tools, nanobiosensors for biomedical applications,[79] the development of antioxidants,[80] and their use in preventing oxidative stress-related diseases were also research hotspots. Significant progress was also made in developing antibacterial materials and drugs and in studying the mechanisms and therapeutic potential of NF-kappa B in inflammation and immune responses.[81] Research during this period reflected the continuous innovation and widespread application of nanotechnology in the biomedical field.

4.4. Analysis of Research Hotspots. The drug delivery systems in nanomedicine applications for pain are considered the main research hotspot, which involves applications in neuropathic pain, arthritis-related pain, and cancer pain. Currently, in clinical settings, the drugs used for managing chronic pain are generally nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids. However, these drugs often lack adequate efficacy in their pharmacological activity and biological distribution, particularly in terms of the ligands and molecular targets involved in pain signal transduction within the nervous system, which result in unwanted side effects.[14] Nanomedicines for pain treatment are expected to overcome these drawbacks, offering new hope for the effective treatment of chronic pain and the development of novel therapeutics.

From the perspective of modulating analgesic function, nanomedicine can regulate pain-related cell membrane receptors, eliminate harmful pain stimuli, and help develop novel local anesthetics. G protein-coupled receptors (GPCRs) play a crucial role in the transmission and regulation of pain, particularly opioid receptors[82,83] and neurokinin-1 receptors (NK1R)[84] on the cell membrane. Nanomedicine delivery systems can precisely target GPCRs within endosomes, overcoming the unspecificity-related side effects of traditional drugs, especially in chronic pain treatment.[85] Furthermore, the major function of NSAIDs is reducing the production of inflammatory mediators such as prostaglandins by inhibiting cyclooxygenase (COX).[86] However, other proinflammatory molecules such as reactive oxygen species (ROS), histamine, ATP, and glutamate cannot be targeted by current analgesics. Functional drug delivery carriers can encapsulate the eliminator of these proinflammatory molecules, enabling precise targeting, thus achieving the goal of pain relief. For instance, Ling et al. developed an antioxidant cascade nanoenzyme that delivers superoxide dismutase (SOD), thereby eliminating ROS, reducing oxidative stress and effectively alleviating inflammatory pain.[87] Lastly, current local anesthetics used in clinical pain management suffer from short durations of action and toxicity. However, modified local anesthetics, including encapsulated in drug delivery systems solely or combining with adjuncts, can significantly extend the duration of action while reducing toxic reactions.[88] Therefore, nanomedicine can be used flexibly in modulating the function of current analgesics.

From the perspective of designing drug delivery systems, the research hotspots mainly include the development of stimulus-responsive, targeted therapy, and intelligent and multifunctional drug delivery systems. First, the development of nanoparticles that respond to external stimuli (such as pH, temperature, and light) can increase drug concentration specifically at the pain site and reduce systemic side effects. Zhang et al. developed a PLEL-based thermosensitive hydrogel system loaded with bupivacaine (LB), in which the soluble charged cation form enables rapid release, while the poorly soluble base form allows pH-responsive release. In rat models, the system provided pain relief lasting about 7 times longer than traditional LB HCl for postoperative pain management.[89] Second, nanomedicines can be designed with specific surface modifications, allowing them to specifically target pain-related cells or receptors, thereby reducing the impact on normal cells. In 2020, the DOPR agonist DADLE was conjugated to a liposome shell targeting DOPR-positive nociceptors and incorporated into a mesoporous silica core, effectively inducing long-term suppression of neuronal activity to alleviate inflammatory pain.[85] Additionally, since 2020, keywords such as "silver nanoparticles", "hyaluronic acid", "carbon nanotubes", "antioxidant", and "antibacterial activity" have surged, making the design of multifunctional nanodrug carriers, instead of delivering drugs simply, a research hotspot. For example, Chen et al. designed an injectable electrospun fiber-hydrogel composite drug system that sequentially releases clonidine and ropivacaine, achieving long-lasting pain relief (>20 h) and sensorimotor segregation effect. This system holds great promise for providing regional long-term walking analgesia.[90] Moreover, Chen et al. developed an NIR-activated multifunctional Pt@MPDA/QX314@Fibrin material, achieving local analgesia, swift hemostasis, anti-inflammatory, antioxidant, and antibacterial benefits for the treatment of diabetic chronic ulcers.[91] In addition, Zuo at al. developed a smart delivery system that consists of amphiphilic copolymers responsive to reactive oxygen species and an encapsulated neurotransmitter-conjugated KCC2 agonist. The system can exert dual effects of neuroprotection and neuromodulation by scavenging accumulated reactive oxygen species and efficiently and specifically targeting particular neurons, therefore promoting the recovery of spinal cord injury.[92] These trends indicate that drug delivery systems will focus more on the design and application of drug delivery systems with combined and comprehensive functions and on the treatment of refractory diseases and pain, such as neuropathic pain and chronic pain, to enhance drug effectiveness, minimize adverse effects, and facilitate personalized medicine.

4.5. Analysis of Trends. In addition to drug delivery, nanomedicine has demonstrated significant advantages in pain of biomarker monitoring of pain. Pain monitoring faces several challenges, primarily due to its high subjectivity and individual variability, which make traditional assessment methods (such as the numeric rating scale) inadequate for accurately reflecting the intensity of pain. Additionally, the complex physiological mechanisms underlying pain involve the interaction of multiple systems, including nervous, immune, and endocrine systems. Existing monitoring techniques face challenges to comprehensively capture the dynamic changes in pain, particularly for the continuous and real-time monitoring of chronic pain, highlighting significant limitations.

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With continual advances in nanotechnology and nanomaterials, nanomedicine provides a potential solution for the precise detection of pain biomarkers, similar to the monitoring of cancer biomarkers.[93,94] Biomarkers are indicators of a disease's physiological state, including proteins, DNA/RNA, or chemicals produced by abnormal cells.[95] Gold nanoparticles, with their high surface area and surface plasmon resonance (SPR) effect, enable efficient detection of low concentrations of pain-related biomarkers.[96] By functionalizing gold nanomaterials to bind with specific biomolecules, we can significantly enhance the sensitivity of pain monitoring, offering strong technical support for real-time monitoring. Osteoarthritis is a common chronic inflammatory disease currently lacking a fundamental drug treatment. The insufficient understanding of its early symptoms and diagnostic methods has made it a global health issue.[97,98] Researchers have designed MoS2-AuNR composite materials by combining gold nanorods with molybdenum disulfide (MoS2) nanosheets to achieve precise localization and monitoring of osteoarthritis pain.[99] The gold nanorods enhance the optical signal via the SPR effect, while the MoS2 coating improves both the photoacoustic and photothermal performance, thereby increasing the sensitivity of bioimaging and treatment. By conjugating with antibodies, functionalized gold nanorods can specifically target nerve growth factor (NGF), a biomarker associated with osteoarthritis pain.[100,101] In mouse models, this nanoprobe successfully targets and accumulates at the pain site, with the signal intensity enabling precise pain monitoring and localization. Additionally, the photothermal effect release by the probes can be used to alleviate pain, providing an effective solution for precise treatment.

With the development of wearable devices and smart sensors, pain monitoring is expected to become more intelligent, enabling real-time tracking of pain changes.[102] By assembling conductive MXene nanosheets and silver nanowires (AgNWs) on an electrospun elastic substrate, researchers have developed a flexible, breathable skin sensor for ultrasensitive sensing and photothermal therapy in patients with tenosynovitis.[103] Therefore, localization, monitoring, and treatment of pain will be three key points considered and integrated in nanomaterials designing.

During injection procedures in clinical nursing, it is crucial to employ the appropriate techniques and safety measures to avoid drug-related complications. Particularly, local anesthetics can lead to severe consequences when they inadvertently cause vascular injection or nerve damage. Additionally, obtaining patient consent is equally important due to pain. Research has shown that needle thickness significantly affects pain perception. The finer needles effectively reduce pain and thereby improve patients' satisfaction.[104] In recent years, microneedles have been widely utilized for drug delivery, and microneedle arrays offer higher patient satisfaction and more efficient transdermal drug delivery. As an improved version of microneedles, nanoneedles have a smaller size and enhanced penetration ability. Nanoneedles can deliver drugs to the skin's microcirculation without stimulating skin nerves, thereby enabling painless treatment.[40,105] For pain treatment, Zhang et al. developed a microneedle patch loaded with ropivacaine and $NaHCO_3$, the MN patch intelligently modulates drug release based on the pH value of the surgical incision microenvironment.[106] The patch successfully extends the local anesthesia duration to over 72 h and addresses the limitations of existing invasive treatments in postoperative pain management. In additions, for local anesthesia, Yang et al. developed a lidocaine/hyaluronic acid bubble microneedle patch (Lido/HA bMNP).[107] This patch can rapidly release lidocaine for pain relief (>1 h) and has the potential to replace injection-based local anesthesia in medical aesthetics.

Despite significant advancements, nanomedicine in the field of pain still faces numerous challenges. First of all, the primary limitation of nanomaterials is the reliable evaluation of long-term biocompatibility, which is particularly crucial in the treatment of chronic pain as patients often require prolonged medication use.[108] Moreover, the targeted delivery and controlled release of nanomedicines in vivo remain technical bottlenecks; precise delivery of drugs to pain sites without affecting other tissues requires further research.[109] Furthermore, the complexity and high cost of preparing and producing nanomedicines are also obstacles to their widespread application.[110] At last, the regulatory and approval processes for nanomedicine are relatively complex and lengthy, adding to the difficulty of translating research products into clinical applications.[111] Addressing these challenges is crucial for enhancing the potential of nanomedicines in pain treatment.

4.6. Limitations. This study has two limitations. First, relying on the WoSCC database may result in partial literature searching. However, the journals within the WoSCC database follow Bradford's Law,[112] ensuring that the most significant publications are accurately identified and obtained. Second, we excluded 15 non-English publications, which may lead to research bias.

5. CONCLUSIONS

This research is a comprehensive bibliometric analysis of publications on nanomedicine applications in pain research from 1999 to 2024. This research highlights the characteristics of publication trends from the scopes of countries/regions, institutions, journals, categories, authors, references, and keywords. According to this report, nanomedicine in the field of pain is rapidly developing, with the United States and China leading in the volume of publications and hosting numerous high-output institutions with the support of abundant funding. A clear interdisciplinary platform has been established between nanomedicine and the field of pain, with "nanoparticles" and "drug delivery" being high-frequency keywords. Therefore, funding support and international cooperation are crucial for the development. Beyond delivering drugs simply, functional materials have been designed to make pain in the management process more precise and intelligent. Among these, the pain of biomarker monitoring and painless nanotechnology, such as nanoneedles, are future trends.

■ ASSOCIATED CONTENT

Data Availability Statement

All the data are available from the web of science (https://webofscience.clarivate.cn/wos/woscc/basic-search).

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c10893.

Options and settings of VOSviewer for nanotechnology applications for pain research, top 15 commonly investigated diseases in nanotechnology applications for pain research based on the frequency of author keywords co-occurrence, top 10 active funding agencies on nanomedicine applications for pain research, journals

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with top 10 betweenness centrality, and top 25 references with the strongest citation bursts (PDF)

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Notes

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ABBREVIATIONS

IASP	International Association for the Study of Pain
FDA	Food and Drug Administration
WoSCC	Web of Science Core Collection
IF	impact factor
TLS	total citation scores
BC	betweenness centrality
CAGR	compound annual growth rate
EKB	Egyptian Knowledge Bank
NSFC	Natural Science Foundation of China
JCR	Journal Citation Report
ERAS	enhanced recovery after surgery
JRC	Joint Research Centre
EXPAREL	bupivacaine liposome injectable suspension
SLNs	Solid lipid nanoparticles.

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研究テーマ（英語）	Elucidation of the pathogenetic mechanism of nephrotic syndrome					

研究者評価（指導教官記入欄）

進捗状況	優・良・可・不可から選択してください⇒	良	パーセンテージ⇒	80 %
研究者本人が行った研究の概要	本研究者が、当教室の最も重要な研究テーマである「蛋白尿の発症機序の解明、有効な新規治療法の開発」に沿って、教室の先行研究論文、Pubmed上に掲載されている蛋白尿発症メカニズムに関する文献を勉強し、国内外の本分野と関連分野の研究動向を把握した。研究プロジェクトを実施するため、実験材料の作製法、タンパク質発現と遺伝子発現の解析法、細胞培養法などの実験基本手技を習得した。 実験基本手技を確認しながら、ネフローゼ症候群（蛋白尿）モデルで発現が低下している分子として同定した1価陽イオンチャネルTRPM4 に焦点を当てた教室の研究プロジェクトに参加し、予備実験を行った。予備実験のあと、各臓器、腎臓の各分画、ヒト培養ポドサイトにおけるTRPM4とその関連分子Ca^{2+}チャネルTRPC6の発現、ならびに糸球体、ポドサイトにおけるTRPM4の詳細な局在、TRPM4とTRPC6の局在関係を解析した。TRPM4の病態形成における役割を検討するために、微小変化型ネフローゼ症候群のラットモデルにおけるTRPM4の発現解析を行った。			
総合評価	【良かった点】 教室の先行研究とプロジェクトの研究背景を把握したうえでプロジェクトに真剣に取り組み、実験がうまくいかなかった時も諦めず、周りの先生方に相談しながら、繰り返し実験を行ったことが良かった点である。 【改善すべき点】 検討項目の優先順位、実験のスケジュールを十分に検討した上で、研究計画に沿って時間をより有効利用することが望まれる。 【今後の目標】 培養細胞と動物の病態モデルでの検討を継続し、ポドサイト傷害におけるTRPM4の役割を明らかにする。			
研究計画書に記載の研究計画の進捗状況	①予想以上に進捗している　②おおむね順調　③やや遅れている　④大幅に遅れている			
進捗が進んでいる内容と遅れている内容及びその理由				
現在の進捗状況を踏まえた目標達成見込	現在の進捗状況を踏まえると、目標達成の見込みは良好であると考えている。			
評価者（指導教官記名）	河内 裕 ・ 内許玉楓	作成日：	2025年　3　月　10　日	

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【研究者用】

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研究テーマ(日文)	ネフローゼ症候群の病因、病態の解明					
Research theme	Elucidation of the pathogenetic mechanism of nephrotic syndrome					

1．研究概要（1）

1）目的（Goal）

Podocytes play a crucial role in maintaining the glomerular filtration barrier. Dysfunction or injury of podocytes is a key contributor to proteinuria and the progression of kidney diseases such as diabetic nephropathy and focal segmental glomerulosclerosis (FSGS) [1]. The slit diaphragm bridging the neighbouring foot processes of podocytes functions as the final barrier of the glomerular capillary wall for preventing the leak of plasma proteins into primary urine [2]. By cDNA subtraction assay, transient receptor potential melastatin 4 (TRPM4) was identified as a molecule downregulated in the initiation phase of puromycin aminonucleoside (PAN) nephropathy, a mimic of human nephrotic syndrome with podocyte injury [3-4]. TRPM4 is a monovalent cation channel, and functions to facilitate Na+ influx and consequently suppress Ca2+ influx [5]. TRPC6 is expressed at podocyte slit diaphragm and binds to nephrin, a key functional molecule of the slit diaphragm [6-7]. It is accepted that TRPC6 plays a central role in the regulation of Ca2+ influx at the slit diaphragm, and that a gain-of-function of TRPC6 and increase in Ca2+ influx are involved in familial FSGS [8] and in acquired proteinuric kidney diseases such as minimal change nephrotic syndrome and membranous nephropathy [7]. As previous reported, TRPM4 as a monovalent cation channel, can facilitate Na+ influx and consequently suppress Ca2+ influx [9]. We hypothesized that TRPM4 regulates Ca2+ influx at the slit diaphragm by modulating TRPC6 function and that the downregulation of TRPM4 increases Ca2+ influx and is involved in podocyte (slit diaphragm) injury. The aim of the present resesarch was to investigate the localization and funciton of TRPM4 in podocytes, as well as the association between TRPM4 and TRPC6, pathological role of TRPM4 in podocytes injury.

2）戦略（Approach）

①Analysis of the expression of TRPM4, and its localization in glomeruli with rat renal tissue.
②Analysis of the association between TRPM4 and TRPC6.
③Analysis of the pathogenic role of TRPM4 in podocyte injury with animal models of human nephrotic syndrome.

3）材料と方法（Materials and methods）

①RT-PCR
Total RNA was extracted from each organ,and cultured podocytes using TRIzol™ Reagent (Thermo Fisher Scientific, CA, USA). cDNA synthesis was carried out using the Applied Biosystems™ High-Capacity cDNA Reverse Transcription Kit. The mRNA expression levels of TRPM4, TRPC6, and Nephrin in each organ, tissue, and cultured podocytes were analyzed by RT-PCR. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as an internal control.
②Immunofluorescence staining
Frozen blocks of rat renal cortex were sectioned at 3 μm using a cryostat and fixed in acetone for 1 minute. Cultured podocytes on coverslips were fixed in PLP fixative at room temperature for 1 minute. The primary antibodies used were as follows: goat anti-TRPM4 antibody (Santa Cruz, #SC-27540) and rabbit anti-TRPC6 antibody (NSJ Bioreagents, #R30847). The secondary antibodies used were FITC-conjugated donkey anti-goat antibody (Protos Immunoresearch, Burlingame, CA) and FITC-conjugated swine anti-rabbit IgG antibody (DAKO, Glostrup, Denmark). The stained specimens were examined under a fluorescence microscope (BX-50; Olympus, Tokyo, Japan).To evaluate changes in TRPM4 staining in the glomeruli of disease model rats, staining intensity was quantified using scoring system: staining in ≥75% of the glomerular tuft was scored as 4, 50-75% as 3, 25-50% as 2, and 0-25% as 1. At least 30 glomeruli per rat were evaluated, and the mean scores of the disease model (n = 3) and normal control groups (n = 5) were statistically analyzed using an unpaired t-test with GraphPad Prism 5.0 software version 5.04 (GraphPad Software, San Diego, CA, USA).
③Cell culture of human podocytes
The cultured podocytes were maintained in RPMI 1640 medium (Nissui Pharmaceutical, Tokyo, Japan) supplemented with 10% fetal bovine serum (FBS) (Life Technologies, Grand Island, NY). Undifferentiated podocytes were maintained at 33℃ and induced to differentiate by culturing at 37℃ for two weeks. Following differentiation, the expression of the podocyte functional molecule Nephrin was confirmed, and the cells were collected for further analyses, including RT-PCR, immunofluorescence staining.

4）実験結果（Results）

①Physiological condition
a. mRNA Expression of TRPM4 and TRPC6 in various organs and cultured podocyte.
TRPM4 was expressed in various organs, as well as TRPC6.The expression of both TRPM4 and TRPC6 were detected in all fractions of kidney samples, and predominantly in glomeruli. Both molecules were detected in differentiated podocytes.

1．研究概要(2)

b. TRPM4 is mainly localized at the slit diaphragm of podocyte.
Immunostaining of TRPM4 in renal cortex was restricted to glomeruli. Localization of TRPM4 in glomeruli depicted that TRPM4 expression was along the capillary loop. Dual-labeling immunofluorescence (IF) with glomerular-cell markers showed that TRPM4 staining was apart from Thy1.1 (a mesangial cell marker) and RECA1 (an endothelial cell marker). As to the IF with podocytes markers, TRPM4 staining did not overlap with synaptopodin (a marker for the cytoplasm of foot process) and integrin $\alpha 3$ (a marker for apical memebrane of foot process). TRPM4 was highly costained with nephrin (a marker for slit diaphragm). By Immuno-electron microscopic method, TRPM4 was found mainly localized at slit diaphragm.
c.TRPM4 is colocalized with TRPC6 in podocyte.
The staining of TRPM4 was highly colocalized with TRPC6 in glomeruli. TRPC6 was colocalized with nephrin.
②Pathological condition
In PAN nephropathy (1 hour after disease induction), the intensity of immunostaining of TRPM4 was significantly decreased ($p<0.05$).

5)考察(Discussion)
Our findings demonstrate that TRPM4 is restrictedly expressed in podocytes in glomeruli. TRPM4 localizes at the slit diaphragm where it co-localizes with nephrin, a key protein of the slit diaphragm [6-7]. This observation supports previous study [4] highlighting the significance of TRPM4 in podocyte function regulation. Furthermore, we observed a strong co-localization of TRPM4 with TRPC6 in the glomeruli, indicating a potential functional relationship between the two channels. TRPC6 is involved in calcium signaling, a crucial process for maintaining podocyte structural integrity and function [10-11]. The co-localization of TRPM4 with TRPC6 suggests that TRPM4 may regulate TRPC6 function by potentially influencing calcium influx across the podocyte membrane. Given the critical role of calcium in podocyte function [12], our results indicate that TRPM4 may serve as a modulator of TRPC6, and any disruption in this regulatory balance could lead to calcium imbalance induced podocyte damage and contribute to the progression of glomerular diseases. Additionally, the absence of overlap between TRPM4 and markers for mesangial and endothelial cells further supports the idea that TRPM4 is specifically involved in podocyte function, emphasizing its potential role in podocyte injury and repair processes. In pathological conditions, the finding of the decreased expression of TRPM4 at 1 hour after disease induction indicated that downregulation of TRPM4 serves as an initiation event of podocyte injury. In conclusion, our study highlights the interaction between TRPM4 and TRPC6 in podocytes and offers valuable insights into how their dysregulation could play a role in the development of kidney diseases.
The reearch plan of next year will be focused on the investigation on the functional interaction of TRPM4 with TRPC6 both in physiological and pathological conditions. Additional research is needed to fully understand the molecular mechanisms governing this interaction and to evaluate its potential as a therapeutic target for glomerular disorders.

6)当初の研究計画と比し、現在の進捗状況の自己評価 (Self-assessment of the current progress compared to the initial research plan.)
①予想以上に進捗している(Progressing more than expected.)
②おおむね順調 (Mostly on track)
③やや遅れている (Slightly behind schedule)
④大幅に遅れている(Significantly behind schedule)

7)計画より進んでいる内容と遅れている内容、及びその理由
(Contents that are ahead of schedule and those that are behind schedule, along with the reasons.)

8)参考文献(References)
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2. 執筆論文 Publication of thesis ※記載した論文を添付してください。Attach all of the papers listed below.

論文名 1 Title	None					
掲載誌名 Published journal						
	年 月	巻(号)	頁 ～ 頁	言語 Language		
第1著者名 First author		第2著者名 Second author		第3著者名 Third author		
その他著者名 Other authors						
論文名 2 Title						
掲載誌名 Published journal						
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論文名 4 Title						
掲載誌名 Published journal						
	年 月	巻(号)	頁 ～ 頁	言語 Language		
第1著者名 First author		第2著者名 Second author		第3著者名 Third author		
その他著者名 Other authors						
論文名 5 Title						
掲載誌名 Published journal						
	年 月	巻(号)	頁 ～ 頁	言語 Language		
第1著者名 First author		第2著者名 Second author		第3著者名 Third author		
その他著者名 Other authors						

3. 学会発表 Conference presentation ※筆頭演者として総会・国際学会を含む主な学会で発表したものを記載してください。

※Describe your presentation as the principal presenter in major academic meetings including general meetings or international meetings.

学会名 Conference	None				
演 題 Topic					
開催日 date	年 月 日	開催地 venue			
形式 method	□ 口頭発表 Oral □ ポスター発表 Poster	言語 Language	□ 日本語 □ 英語 □ 中国語		
共同演者名 Co-presenter					
学会名 Conference					
演 題 Topic					
開催日 date	年 月 日	開催地 venue			
形式 method	□ 口頭発表 Oral □ ポスター発表 Poster	言語 Language	□ 日本語 □ 英語 □ 中国語		
共同演者名 Co-presenter					
学会名 Conference					
演 題 Topic					
開催日 date	年 月 日	開催地 venue			
形式 method	□ 口頭発表 Oral □ ポスター発表 Poster	言語 Language	□ 日本語 □ 英語 □ 中国語		
共同演者名 Co-presenter					
学会名 Conference					
演 題 Topic					
開催日 date	年 月 日	開催地 venue			
形式 method	□ 口頭発表 Oral □ ポスター発表 Poster	言語 Language	□ 日本語 □ 英語 □ 中国語		
共同演者名 Co-presenter					

4. 受賞（研究業績） Award (Research achievement)

名 称 Award name				
	国名 Country		受賞年 Year of award	年 月
名 称 Award name				
	国名 Country		受賞年 Year of award	年 月

5. 本研究テーマに関わる他の研究助成金受給 Other research grants concerned with your resarch theme

受給実績 Receipt record	□ 有　■ 無
助成機関名称 Funding agency	
助成金名称 Grant name	
受給期間 Supported period	年　月 ～　年　月
受給額 Amount received	円
受給実績 Receipt record	□ 有　□ 無
助成機関名称 Funding agency	
助成金名称 Grant name	
受給期間 Supported period	年　月 ～　年　月
受給額 Amount received	円

6. 他の奨学金受給 Another awarded scholarship

受給実績 Receipt record	□ 有　■ 無
助成機関名称 Funding agency	
奨学金名称 Scholarship name	
受給期間 Supported period	年　月 ～　年　月
受給額 Amount received	円

7. 研究活動に関する報道発表 Press release concerned with your research activities

※記載した記事を添付してください。Attach a copy of the article described below

報道発表 Press release	□ 有　□ 無	発表年月日 Date of release	
発表機関 Released medium			
発表形式 Release method	・新聞　・雑誌　・Web site　・記者発表　・その他（　　）		
発表タイトル Released title			

8. 本研究テーマに関する特許出願予定 Patent application concerned with your research theme

出願予定 Scheduled	□ 有　□ 無	出願国 Application	
出願内容（概要） Application contents			

9. その他 Others

指導責任者（記名） 河内裕、内許玉楓

日中笹川医学奨学金制度〈ポストドクターコース〉中間評価書
【指導教官用】

第45期　　研究者番号：　P4518

氏名	周 英	ZHOU YING	性別	F	生年月日	1983/11/10
所属機関（役職）	金沢大学医薬保健研究域保健学系（研究協力員）					
日本研究先機関名・部署	金沢大学医薬保健研究域保健学系					
指導教官氏名・役職	田中 浩二・教授					
研究テーマ（日本語）	日本における精神科医療通訳の実態と心理的体験					
研究テーマ（英語）	actual situation and psychological experiences of psychiatric interpreters in japan					

研究者評価（指導教官記入欄）

進捗状況	優・良・可・不可から選択してください⇒	良	パーセンテージ⇒	75 %
研究者本人が行った研究の概要	本研究は、日本における精神科医療通訳者の現状を明らかにし、彼らが抱える心理的負担や職業的課題を調査し、必要な支援策を検討することを目的としている。精神科の通訳は、単なる言語の通訳ではなく、患者の感情や文化的背景を理解しながら適切に対応する必要がある。しかし、資格制度が整備されておらず、雇用や報酬の不安定さが課題となっている。 本研究では、精神科での通訳経験が3年以上の通訳者15名にインタビューを実施し、彼らの経験や課題を詳しく分析している。質的研究の手法を用い、共通する問題点や必要な支援策を抽出し、今後の改善策を提案することを目指している。精神科通訳者に特化した研究はこれまで十分に行われておらず、本研究の意義は大きいといえる。			
総合評価	【良かった点】 精神科医療通訳者の経験に着目し、具体的な課題を明らかにしている点が優れている。インタビューを活用した質的研究を適切に進めており、データの収集と分析が計画通り行われている。研究成果を国際雑誌に投稿し、学術的発信に積極的に取り組んでいることも評価できる。 【改善すべき点】 研究の背景や意義を、既存の研究と比較してより明確に示すことで、より研究の独自性を強調できる。インタビュー結果の分析をさらに深め、支援策の提案をより具体的にすることが望ましい。 【今後の目標】 今後の課題として、研究の理論的背景をより強化し、研究の意義を明確にすることがあげられる。さらに、分析結果を深め、具体的な支援策をより具体的に提案できるよう取り組んでいく必要がある。国際雑誌の査読プロセスが長期化しているため、査読結果に迅速に対応しつつ、他の発信手段も積極的に活用し、研究成果の公表を進めることが望ましい。			
研究計画書に記載の研究計画の進捗状況	①予想以上に進捗している　(②おおむね順調)　③やや遅れている　④大幅に遅れている			
進捗が進んでいる内容と遅れている内容及びその理由	研究は、計画通り順調に進んでいる。さらに、本研究と並行して、プライマリヘルスワーカーによる地域における自殺リスク者支援の実態と困難、人工知能時代における会議通訳者の心境とストレス、能登半島地震が及ぼした健康や生活への影響と回復に関する被災者の経験といった、複数の関連する研究にも積極的に取り組んでいる。これらのテーマは、いずれも社会的に重要であり、医療・福祉・言語サービスといった多様な分野と関連している。			
現在の進捗状況を踏まえた目標達成見込	精神科医療通訳者の実態と心理的体験については、現在査読中であり、研究の主要な成果を発信することが十分可能である。また、本研究の枠を超えて、医療・福祉・言語サービスなど多岐にわたる研究活動を進めている。このように、多角的な視点をもって研究に取り組んでおり、目標達成の見込みは高いと評価する。			
評価者（指導教官記名）	田中浩二	作成日：	2025年　3　月　10　日	

日中笹川医学奨学金制度<ポストドクターコース>中間報告書
【研究者用】

第45期　　研究者番号：P4518　　作成日：2025年3月10日

氏名	周 英	ZHOU YING	性別	F	生年月日	1983/11/10
所属機関(役職)	金沢大学医薬保健研究域保健学系（研究協力員）					
日本研究先（指導教官）	金沢大学医薬保健研究域保健学系（田中 浩二　教授）					
研究テーマ(日文)	日本における精神科医療通訳の実態と心理的体験					
Research theme	actual situation and psychological experiences of psychiatric interpreters in japan					

1．研究概要（1）

1）目的（Goal）

本研究は、日本における精神科医療通訳者の現状を明らかにし、彼らが直面する心理的負担や職業的課題について調査し、必要な支援策を検討することを目的としている。精神科医療の現場では、通訳者は単なる言語の仲介者ではなく、患者の感情や文化的背景を理解し、適切なコミュニケーションを図る必要がある。しかし、精神科領域を含む医療通訳者は国家資格制度が確立されておらず、報酬や雇用の安定性が欠如している。この上で、現場でのトラウマ体験も加わり、通訳者の心理的負担が増大し、バーンアウトや感情的消耗のリスクが高まる。本研究では、精神科通訳者の経験を詳細に分析し、今後の支援策や制度改善の方向性を示唆する。

2）戦略（Approach）

本研究は質的研究手法を採用し、精神科領域における医療通訳者の経験を深く掘り下げることを目的とする。具体的には、精神科での医療通訳経験を3年以上もつ15名の通訳者を対象に、半構造化インタビューを実施した。インタビューでは、通訳者が直面する困難や感情的負担、職務遂行における工夫や適応戦略、そして今後の支援の必要性について詳しく取得した。得られたデータはNvivoを用いて分析し、共通するテーマやパターンを抽出した。

3）材料と方法（Materials and methods）

本研究は質的研究デザインを採用し、通訳者の主観的経験を詳細に分析した。対象は精神科医療通訳経験が3年以上ある15名の通訳者である。半年かけてオンラインインタビューを実施し、通訳者の職務経験、心理的影響、職務上の課題、支援の必要性などを中心に聴取した。収集したデータはすべて文字起こしを行い、質的分析を通じて統一的なテーマを抽出した。

4）実験結果（Results）

本研究の結果、精神科医療通訳者が直面する問題点や支援の必要性に関する四つの主要なテーマが浮かび上がった。
第一に、社会的認知の不足、制度的な制約、過酷な労働環境、精神的ストレスといった抑制要因が存在する。医療通訳者は公的に認められておらず、正式な資格制度がないため、社会的な支援が不足している。また、ボランティアとして活動する場合が多く、収入が不安定であることが指摘された。さらに、精神科の患者との接触により、通訳者自身が感情的負担を抱えるケースも多い。
第二に、促進要因として、医療機関や派遣機関からの支援、患者や医療従事者からの感謝、仕事を通じた自己成長などがあげられる。特に、患者や医療スタッフからの感謝の言葉は、通訳者のモチベーション向上につながっている。
第三に、医療通訳者の特性として、奉仕の精神や適応能力、ストレス対処能力が求められることが明らかになった。精神科領域では特に、通訳者が柔軟な対応力を持ち、患者に寄り添いながらも冷静さを保つことが重要である。
最後に、専門的基盤の確立の必要性が強調された。研修制度の整備や資格制度の導入が求められており、通訳者自身も制度改革への意欲を持っていることが分かった。

5）考察（Discussion）

日本における精神科医療通訳者の活動は、主にボランティアに依存しており、社会的な認知が不足している。正式な資格制度が存在しないため、通訳者は不安定な立場では働かざるを得ない。また、精神科の患者と向き合うことで、感情的負担が増し、心理的ストレスが蓄積する。一方で、患者や医療従事者からの感謝が通訳者のモチベーションを高める重要な要素となっている。通訳者は高い倫理観を持ち、言語スキルだけでなく精神的な強さも求められる職業である。そのため、適切な研修制度やメンタルヘルスサポートを導入することが必要不可欠である。
今後の展望として、医療通訳を専門職として確立するためには、資格制度の導入や研修プログラムの整備が不可欠である。さらに、通訳者の待遇改善に向けた政策提言が求められる。

1．研究概要(2)

6)当初の研究計画と比し、現在の進捗状況の自己評価 （Self-assessment of the current progress compared to the initial research plan.）
おおむね順調です。

7)計画より進んでいる内容と遅れている内容、及びその理由
（Contents that are ahead of schedule and those that are behind schedule, along with the reasons.）
本研究の成果をもとに作成した英文論文を国際雑誌に昨年10月に投稿したが、現在も査読中の状態にあり、発表までに時間がかかっている。査読プロセスが長引いているため、論文発表が遅れている点が課題となっている。今後は、査読結果を踏まえた修正作業を迅速に行い、できる限り早期に発表できるよう努める。

8)参考文献（References）
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- Butler, C. (2008). *Speaking the unspeakable: Female interpreters' response to working with women who have been raped in war*. *Clinical Psychology Forum, 192*, 22–26.

2. 執筆論文 Publication of thesis ※記載した論文を添付してください。Attach all of the papers listed below.

論文名 1 Title	精神科医療通訳の「患者擁護」について				
掲載誌名 Published journal	日中医学				
	2022 年 11 月	Vol.37 No.3 巻(号)	29/59 頁 ～ 33/62 頁	言語 Language	日本語・中国語
第1著者名 First author	周英	第2著者名 Second author	堤敦朗	第3著者名 Third author	
その他著者名 Other authors					
論文名 2 Title					
掲載誌名 Published journal					
	年 月	巻(号)	頁 ～ 頁	言語 Language	
第1著者名 First author		第2著者名 Second author		第3著者名 Third author	
その他著者名 Other authors					
論文名 3 Title					
掲載誌名 Published journal					
	年 月	巻(号)	頁 ～ 頁	言語 Language	
第1著者名 First author		第2著者名 Second author		第3著者名 Third author	
その他著者名 Other authors					
論文名 4 Title					
掲載誌名 Published journal					
	年 月	巻(号)	頁 ～ 頁	言語 Language	
第1著者名 First author		第2著者名 Second author		第3著者名 Third author	
その他著者名 Other authors					
論文名 5 Title					
掲載誌名 Published journal					
	年 月	巻(号)	頁 ～ 頁	言語 Language	
第1著者名 First author		第2著者名 Second author		第3著者名 Third author	
その他著者名 Other authors					

3. 学会発表 Conference presentation ※筆頭演者として総会・国際学会を含む主な学会で発表したものを記載してください。

※Describe your presentation as the principal presenter in major academic meetings including general meetings or international meetings.

学会名 Conference	第31回多文化間精神医学会学術総会		
演 題 Topic	日本における精神科医療通訳者の実態と心理的体験		
開催日 date	2024 年 11 月 23、24 日	開催地 venue	国際医療福祉大学成田キャンパス
形式 method	☑ 口頭発表 Oral ☐ ポスター発表 Poster	言語 Language	☑ 日本語 ☐ 英語 ☐ 中国語
共同演者名 Co-presenter			
学会名 Conference			
演 題 Topic			
開催日 date	年 月 日	開催地 venue	
形式 method	☐ 口頭発表 Oral ☐ ポスター発表 Poster	言語 Language	☐ 日本語 ☐ 英語 ☐ 中国語
共同演者名 Co-presenter			
学会名 Conference			
演 題 Topic			
開催日 date	年 月 日	開催地 venue	
形式 method	☐ 口頭発表 Oral ☐ ポスター発表 Poster	言語 Language	☐ 日本語 ☐ 英語 ☐ 中国語
共同演者名 Co-presenter			
学会名 Conference			
演 題 Topic			
開催日 date	年 月 日	開催地 venue	
形式 method	☐ 口頭発表 Oral ☐ ポスター発表 Poster	言語 Language	☐ 日本語 ☐ 英語 ☐ 中国語
共同演者名 Co-presenter			

4. 受賞（研究業績） Award (Research achievement)

名 称 Award name				
	国名 Country		受賞年 Year of award	年 月
名 称 Award name				
	国名 Country		受賞年 Year of award	年 月

5. 本研究テーマに関わる他の研究助成金受給 Other research grants concerned with your resarch theme

受給実績 Receipt record	□ 有　■ 無
助成機関名称 Funding agency	
助成金名称 Grant name	
受給期間 Supported period	年　月 ～　年　月
受給額 Amount received	円
受給実績 Receipt record	□ 有　■ 無
助成機関名称 Funding agency	
助成金名称 Grant name	
受給期間 Supported period	年　月 ～　年　月
受給額 Amount received	円

6. 他の奨学金受給 Another awarded scholarship

受給実績 Receipt record	□ 有　■ 無
助成機関名称 Funding agency	
奨学金名称 Scholarship name	
受給期間 Supported period	年　月 ～　年　月
受給額 Amount received	円

7. 研究活動に関する報道発表 Press release concerned with your research activities

※記載した記事を添付してください。Attach a copy of the article described below

報道発表 Press release	□ 有　■ 無	発表年月日 Date of release	
発表機関 Released medium			
発表形式 Release method	・新聞　・雑誌　・Web site　・記者発表　・その他（　　）		
発表タイトル Released title			

8. 本研究テーマに関する特許出願予定 Patent application concerned with your research theme

出願予定 Scheduled	□ 有　■ 無	出願国 Application	
出願内容（概要） Application contents			

9. その他 Others

指導責任者（記名） 田中 浩二

日中笹川医学奨学金制度<ポストドクターコース>中間評価書
【指導教官用】

Supported by 日本財団 THE NIPPON FOUNDATION

第45期　　研究者番号：　P4519

氏名	王 婷梅	WANG TINGMEI	性別	F	生年月日	1989/3/5
中国所属機関（役職）	華中科技大学同済医学院附属同済医院皮膚科（主治医師）					
日本研究先機関名・部署	大阪公立大学大学院医学研究科色素異常症治療開発共同研究部門					
指導教官氏名・役職	片山　一朗　特任教授					
研究テーマ（日本語）	尋常性白斑の発症機序究明と治療開発					
研究テーマ（英語）	Elucidation of the Pathogenesis of Vitiligo and Development of Treatments					

研究者評価（指導教官記入欄）

進捗状況	優・良・可・不可から選択してください⇒	良	パーセンテージ⇒	60 %
研究者本人が行った総合評価	【研究概要】			
	【良かった点】 ・独自の視点で白斑の病態に関する仮説を構築し、実験計画も緻密に立てられている点が大変評価できる。 ・RT-PCR、ウェスタンブロッティング、ELISA等を用いた多角的な手法により、角化細胞と線維芽細胞間の相互作用の新たな知見を得たことは、今後の応用展開に大いに寄与するでしょう。			
	【改善すべき点】 ・統計解析や誤差管理に関する記述がやや不十分なため、実験結果の再現性を担保するための詳細な手法の補強が望まれる。 ・また、最新文献との比較検討をさらに深め、研究背景の説得力を高める必要がある。			
	【今後の目標】 ・現段階の成果を踏まえ、さらなる検証実験を実施し、悪循環仮説の確証に努めていく。 ・臨床応用を見据え、分子標的治療への展開も視野に入れ、国内外学会での成果発表を積極的に進める。 ・最後に、実験手法の改善と新技術の導入により、より精緻なデータ解析を行い、研究の信頼性を高めることを目指す。			
研究計画書に記載の研究計画の進捗状況	①予想以上に進捗している　(②)おおむね順調　③やや遅れている　④大幅に遅れている			
進捗が進んでいる内容と遅れている内容及びその理由	実験データの蓄積および初期の仮説支持に関する結果は順調に進んでおり、実験環境や装置の運用も安定している。			
現在の進捗状況を踏まえた目標達成見込	現在、実験データは着実に蓄積され、初期仮説を支持する結果が得られているため、当初設定した目標の達成は十分に見込まれる。			
評価者（指導教官記名）	片山一朗	作成日：	2025年　3　月　10　日	

日中笹川医学奨学金制度<ポストドクターコース>中間報告書
【研究者用】

Supported by 日本財団 THE NIPPON FOUNDATION

第45期　　研究者番号：P4519　　作成日：2025年3月10日

氏名	王 婷梅	WANG TINGMEI	性別	F	生年月日	1989/3/5
中国所属機関(役職)	華中科技大学同済医学院附属同済医院皮膚科(主治医師)					
日本研究先(指導教官)	大阪公立大学大学院医学研究科色素異常症治療開発共同研究部門(片山　一朗　特任教授)					
研究テーマ(日文)	尋常性白斑の発症機序究明と治療開発					
Research theme	Elucidation of the Pathogenesis of Vitiligo and Development of Treatments					

1．研究概要（1）

1）目的（**Goal**）In our previous research, we found increased matrix metalloproteinase 2 (MMP2) from human fibroblasts is a key factor responsible for basement membrane (BM) disruption and melanocyte disappearance in vitiligo[1]. Damage to the epidermal BM alters interactions between epidermal keratinocytes and the extracellular matrix[2]. Epidermal keratinocytes interaction with extracellular matrix components could affect epidermal homeostasis and keratinocyte phenotypes[2]. There is emerging evidence that keratinocytes in lesional vitiliginous skin are distinct from keratinocytes in normal skin. In our previous study, we also found the disruption of BM altered the adhesion pattern between the BM and keratinocytes: there was a reduction in integrin-laminin interactions in basal keratinocytes while collagen XVII -collagen IV interactions were increased[1]. Under pathological conditions, extensive BM destruction results in enhanced release of cytokines in the epidermis[2]. MMP2 expression could be regulated by paracrine signaling and numerous cytokines including TGF-β, TNF-α, IL-1β, IL-6 and IFN-γ could stimulate MMP2 expression[3-6]. In our previous study, we also found TGF-β, TNF-α, IL-1β, IL-6 and IFN-γ were highly expressed in the epidermis of vitiliginous skin[1]. Therefore, we put forward a hypothesis that there may be a vicious cycle in which MMP2 destroys basement membrane; the consequent disruption of the BM alters the phenotype of keratinocytes, resulting in cytokine production, which in turn upregulates MMP2 expression in fibroblasts. Overall, the purpose of the present study is to investigate the relationship between cytokines from keratinocytes and MMP2 expression in fibroblasts in vitiligo.

2）戦略（**Approach**）Cultured human dermal normal fibroblasts were stimulated with various cytokines to detect MMP2 expression and secretion; subsequently, the signaling pathways of these cytokines responsible for triggering MMP2 production and secretion in fibroblasts were examined. We also examined whether altering the adhesion mode of keratinocytes affects their production and secretion of cytokines that induce MMP2 expression.

3）材料と方法（**Materials and methods**）MMP2 production and secretion were analyzed by RT-PCR, Western blotting and Elias following TGF-β, TNF-α, IL-1β, IL-6 and IFN-γ stimulation of cultured human dermal fibroblasts. Concentration gradients of cytokines capable of inducing both production and secretion of MMP2 in fibroblasts were established, and the effects of varying cytokine concentrations on MMP2 production and secretion were analyzed by RT-PCR, Western blotting and Elisa. The potential signaling pathways involved in cytokine-mediated MMP2 production in fibroblasts were examined using Western blotting. By either knocking down the ITGA3, ITGA6 or ITGB1 expression in keratinocytes using siRNA technology or modifying the coating substrates form laminin to collagen of culture dishes, we examined whether alterations in keratinocyte adhesion could modulate their production and secretion of cytokines.

4）実験結果（**Results**）We found TNF-α, IL-1β could induce MMP2 production and secretion in cultured human normal dermal fibroblast. And this induction is associated with P38 signaling activation. Inhibition of ITGB1 in keratinocytes or using the collagen IV as the coating substrate could increase the secretion of TNF-αand IL-1β from keratinocytes.

5）考察（**Discussion**）The change of adhesion of keratinocytes from integrin-laminin to collagen XVII-collagen IV could induce the TNF-αand IL-1β secretion from keratinocytes. And the increased secretion of TNF-αand IL-1β could further induce the MMP2 production and secretion in fibroblasts by activation of P38 signaling pathway. There is a vicious cycle between keratinocytes-fibroblasts.

6)当初の研究計画と比し、現在の進捗状況の自己評価 （Self-assessment of the current progress compared to the initial research plan.）

①予想以上に進捗している（Progressing more than expected.）

②おおむね順調 （Mostly on track）

③やや遅れている （Slightly behind schedule）

④大幅に遅れている（Significantly behind schedule）7）計画より進んでいる内容と遅れている内容、及びその理由

（Contents that are ahead of schedule and those that are behind schedule, along with the reasons.）

7)計画より進んでいる内容と遅れている内容、及びその理由

（Contents that are ahead of schedule and those that are behind schedule, along with the reasons.）

8)参考文献（Reference）

[1]Yang F, Yang L, et al. Disorganisation of basement membrane zone architecture impairs melanocyte residence in vitiligo. J Pathol 2024; 264: 30-41.

[2]Yazlovitskaya EM, Plosa E, Bock F, et al. The laminin-binding integrins regulate nuclear factor κB-dependent epithelial cell polarity and inflammation. J Cell Sci 2021;134: jcs259161.

[3]Philips N, Keller T, Gonzalez S. TGF beta-like regulation of matrix metalloproteinases by anti-transforming growth factor-beta, and anti-transforming growth factor-beta 1 antibodies in dermal broblasts: implications for wound healing. Wound Repair Regen 2004; 12: 53-59.

[4]Choi JY, Piao MS, Lee JB, et al. Propionibacterium acnes stimulates pro-matrix metalloproteinase-2 expression through tumor necrosis factor-alpha in human dermal broblasts. J Invest Dermatol 2008; 128: 846-854.

[5]Siwik DA, Chang DL, Colucci WS. Interleukin-1beta and tumor necrosis factor-alpha decrease collagen synthesis and increase matrix metalloproteinase activity in cardiac broblasts in vitro. Circ Res 2000; 86: 1259-1265.

[6]Kusano K, Miyaura C, Inada M, et al. Regulation of matrix metalloproteinases (MMP-2, -3, -9, and -13) by interleukin-1 and interleukin-6 in mouse calvaria: association of MMP induction with bone resorption. Endocrinology 1998; 139: 1338-1345.

2. 執筆論文 Publication of thesis ※記載した論文を添付してください。Attach all of the papers listed below.

論文名 1 Title						
掲載誌名 Published journal						
	年 月	巻(号)	頁 ～ 頁	言語 Language		
第1著者名 First author		第2著者名 Second author		第3著者名 Third author		
その他著者名 Other authors						
論文名 2 Title						
掲載誌名 Published journal						
	年 月	巻(号)	頁 ～ 頁	言語 Language		
第1著者名 First author		第2著者名 Second author		第3著者名 Third author		
その他著者名 Other authors						
論文名 3 Title						
掲載誌名 Published journal						
	年 月	巻(号)	頁 ～ 頁	言語 Language		
第1著者名 First author		第2著者名 Second author		第3著者名 Third author		
その他著者名 Other authors						
論文名 4 Title						
掲載誌名 Published journal						
	年 月	巻(号)	頁 ～ 頁	言語 Language		
第1著者名 First author		第2著者名 Second author		第3著者名 Third author		
その他著者名 Other authors						
論文名 5 Title						
掲載誌名 Published journal						
	年 月	巻(号)	頁 ～ 頁	言語 Language		
第1著者名 First author		第2著者名 Second author		第3著者名 Third author		
その他著者名 Other authors						

3. 学会発表 Conference presentation ※筆頭演者として総会・国際学会を含む主な学会で発表したものを記載してください。

※Describe your presentation as the principal presenter in major academic meetings including general meetings or international meetings.

学会名 Conference	Regional conference of dermatology (RCD2024)								
演 題 Topic	Clinicopathological Characteristics of SASH1-Related Dyschromatosis								
開催日 date	2024 年	10 月	2 日	開催地 venue	kuala lumpur, Malaysia				
形式 method	□ 口頭発表 Oral	☑ ポスター発表 Poster		言語 Language	□ 日本語	☑ 英語	□ 中国語		
共同演者名 Co-presenter	Lingli Yang, Sylvia Lail, Yunhua Deng, Ichiro Katayamal								
学会名 Conference									
演 題 Topic									
開催日 date	年	月	日	開催地 venue					
形式 method	□ 口頭発表 Oral	□ ポスター発表 Poster		言語 Language	□ 日本語	□ 英語	□ 中国語		
共同演者名 Co-presenter									
学会名 Conference									
演 題 Topic									
開催日 date	年	月	日	開催地 venue					
形式 method	□ 口頭発表 Oral	□ ポスター発表 Poster		言語 Language	□ 日本語	□ 英語	□ 中国語		
共同演者名 Co-presenter									
学会名 Conference									
演 題 Topic									
開催日 date	年	月	日	開催地 venue					
形式 method	□ 口頭発表 Oral	□ ポスター発表 Poster		言語 Language	□ 日本語	□ 英語	□ 中国語		
共同演者名 Co-presenter									

4. 受賞(研究業績) Award (Research achievement)

名 称 Award name				
	国名 Country		受賞年 Year of	年 月
名 称 Award name				
	国名 Country		受賞年 Year of	年 月

5. 本研究テーマに関わる他の研究助成金受給 Other research grants concerned with your resarch theme

受給実績 Receipt record	☐ 有 ☐ 無
助成機関名称 Funding agency	
助成金名称 Grant name	
受給期間 Supported period	年 月 ～ 年 月
受給額 Amount received	円
受給実績 Receipt record	☐ 有 ☐ 無
助成機関名称 Funding agency	
助成金名称 Grant name	
受給期間 Supported period	年 月 ～ 年 月
受給額 Amount received	円

6. 他の奨学金受給 Another awarded scholarship

受給実績 Receipt record	☐ 有 ☐ 無
助成機関名称 Funding agency	
奨学金名称 Scholarship name	
受給期間 Supported period	年 月 ～ 年 月
受給額 Amount received	円

7. 研究活動に関する報道発表 Press release concerned with your research activities

※記載した記事を添付してください。Attach a copy of the article described below

報道発表 Press release	☐ 有 ☐ 無	発表年月日 Date of release	
発表機関 Released medium			
発表形式 Release method	・新聞 ・雑誌 ・Web site ・記者発表 ・その他( )		
発表タイトル Released title			

8. 本研究テーマに関する特許出願予定 Patent application concerned with your research theme

出願予定 Scheduled	☐ 有 ☐ 無	出願国 Application	
出願内容(概要) Application contents			

9. その他 Others

指導責任者(記名) 片山一朗

日中笹川医学奨学金制度〈ポストドクターコース〉中間評価書
【指導教官用】

Supported by 日本財団 THE NIPPON FOUNDATION

第45期　　研究者番号：　P4520

氏名	汪 沙	WANG　SHA	性別	F	生年月日	1984/4/20
中国所属機関（役職）	首都医科大学附属北京婦産医院婦科微創センター（助理研究員）					
日本研究先機関名・部署	鳥取大学					
指導教官氏名・役職	原田 省　副学長					
研究テーマ（日本語）	子宮内膜症と子宮腺筋症の病因に関する研究					
研究テーマ（英語）	Novel approach to pathogenesis of endometriosis and adenomyosis					

研究者評価（指導教官記入欄）

進捗状況	優・良・可・不可から選択してください⇒	可	パーセンテージ⇒	40　%
研究者本人が行った研究の概要	これまで、当教室では子宮内膜症マウスモデルを作成して、病巣発生へのメカニズムや各種薬剤の効果　を評価した知見を報告してきた。今回、本研究者は、① 子宮内膜組織の移植による子宮内膜症を模した　マウスモデルと、② 子宮内膜組織への細径針による穿刺による子宮腺筋症を模したマウスモデルを融合　したハイブリッド動物モデルの作成を行った。本マウスモデルは、重症の子宮内膜症患者にみられる病態　を模することから、これまでに類を見ない疾患モデルから得られるデータは意義深い。子宮内膜症と子宮　腺筋症を合併する患者は、不良な妊娠予後をきたし、周産期合併症の発生率が高くなることが知られている。少子晩婚化により、罹患率上昇が危惧される両疾患の動物モデルの安定した実験系を構築するとともに、投与する卵巣ホルモンの至適量や実験条件を検討した。			
総合評価	【良かった点】 新規動物モデルの作成に成功した。本学医学部 統合生理学との共同研究としている。			
	【改善すべき点】 さらに安定した実験手技を確立する。			
	【今後の目標】 安定した実験結果を得ること。両疾患に特有な疼痛メカニズムの解明と妊孕性低下について検討する。			
研究計画書に記載の研究計画の進捗状況	①予想以上に進捗している　②おおむね順調　(③)やや遅れている　④大幅に遅れている			
進捗が進んでいる内容と遅れている内容及びその理由	モデルの標準化ならびに投与するホルモン量の調整に時間を要した。実験手技の取得に時間を要した。			
現在の進捗状況を踏まえた目標達成見込	十分期待できる。			
評価者（指導教官記名）	谷口 文紀	作成日：	2025年　2　月　19　日	

日中笹川医学奨学金制度<ポストドクターコース>中間報告書
【研究者用】

第45期　　研究者番号：P4520　　作成日：2025年3月10日

氏名	汪 沙	WANG SHA	性別	F	生年月日	1984/4/20
中国所属機関(役職)	首都医科大学附属北京婦産医院婦科微創センター（助理研究員）					
日本研究先（指導教官）	鳥取大学（原田 省　副学長）					
研究テーマ(日文)	子宮内膜症と子宮腺筋症の病因に関する研究					
Research theme	Novel approach to pathogenesis of endometriosis and adenomyosis					

1．研究概要(1)

1）目的（Goal）Endometriosis and adenomyosis are sister entities with similar molecular mechanisms. Both tissues originate from the eutopically located intracavitary endometrium. The purpose of this study was to establish a novel mouse model that combined endometriosis and adenomyosis.

2）戦略（Approach）Animal models are useful in the study of endometriosis and adenomyosis to elucidate its pathogenesis and to develop therapies. We attempted to mimic the mechanical damage of the endometrium, which is generally considered a main cause of adenomyosis in the mouse uterus. Experimental endometriosis in mice was surgically induced and to determine the cardinal features of endometriosis.

3）材料と方法（Materials and methods）3.1 Induction of adenomyosis by mechanical stimulation of the mouse uterus; All adult female mice (8-16 weeks old) underwent ovariectomy 2 weeks before the uterine puncture procedure to eliminate the influence of estrous cycle. Ovariectomized mice were anesthetized by isoflurane and laparotomized with median abdominal incision. One of the 2 uterine horns in each mouse was punctured 100 times per 1 cm using a 30 G needle throughout the myometrium and endo metrium. The needle penetrated the uterus, and the needle puncture was performed 100 times per horn in each mouse. The mice were then sacrificed in specific postoperative periods, and both horns were collected from each mouse for histological analysis.3.2 Experimental endometriosis Experimental endometriosis in mice was surgically induced. Briefly, all mice were ovariectomized then injected subcutaneously with estradiol (0.5μg/mouse). After 1 week, donor uteri were removed en bloc after euthanasia. The removed uteri were slit longitudinally with a linear incision and minced into pieces approximately 0.5 mm in diameter using dissection scissors and a surgical scalpel. To create experimental endometriosis, recipient mice were anesthetized using a mixture of medetomidine, midazolam and butorphanol (0.3, 4.0, and 5.0 mg/kg, respectively). Laparotomy was performed through a 0.5-cm sub abdominal midline incision. The incised peritoneum was then closed by suturing. Sham surgeries performed in control mice comprised only opening and closing of the abdomen. 3.3 Tissue preparation for hematoxylin and eosin staining (H&Estaining) and Immunohistochemistry； Uterine tissues and cysts were sectioned, fixed in 10% formalin, dehydrated gradually in ethanol, and embedded in paraffin at 60℃. For hematoxylin and eosin staining (H&E staining), sections were cut horizontally at a thickness of 6μm and mounted on slides for analysis. Furthermore, antibodies to CK8 and αSMA were used.

4）実験結果（Results）4.1 Establishment of the mechanical induced adenomyosis mouse model; For all mice, one horn was punctured, defined as the adenomyosis horn (ADS horn), while the other was left intact, defined as the control horn. We compared the data from14days and 28days- sampling after puncture. Adenomyotic lesions were completed 14 days after uterine injury. Unpunctured control horn showed endometrial glands and stroma surrounded by well-defined, concentric layers of smooth muscle cells. H&E staining of ADS horn showed endometrial basement membrane collapse and endometrial cell invagination into the myometrium. And on postoperative day 28, adenomyotic lesions became more pronounced. Adenomyotic lesions with glandular components surrounded by stromal layer were developed within the myometrium.H&E staining and immunohistochemistry on day 28 revealed that the myometrium contained CK8-positive columnar epithelial cells with a CK8- and αSMA-negative stromal layer. There is significant difference in horn length between control horn and ADS horn on postoperative day 28.

4.2 Confirm the optimal dosage of E2 administration on adenomyosis model;Adenomyosis is an estrogen-dependent disease. Long-term exposure to either estrogen or progesterone without the presence of the opposing other hormone increases the risk of the development of adenomyosis. We intended to test the effect of different concentrations (0.001、0.01、0.5、1μg/mouse、natural cycle) of E2 on the adenomyotic lesion formation. We investigated the extent of the adenomyosis lesions after the administration of different concentrations of E2 by H&E staining. With the increasement of estrogen concentration, the adenomyotic lesions that had glandular tubular structures consisting of epithelium and stroma within the myometrium became much more pronounced. As the concentration of E2 increases, the adhesion between the uterus and surrounding tissues becomes increasingly severe.Under the natural cycle,the inflammatory response and degree of adhesion in the uterine cavity are the lowest.Even if for the adenomyosis patients, long-term exposure to estrogen and progesterone are both important for the disease formation.We still need further evidence to make clarify if the natural cycle is the is the optimal choice;4.3 Establishment of the endometriosis and adenomyosis hybrid model;As we are the first group to conduct this hybrid model. The first trial of endometriosis and adenomyosis hybrid model, we planned to clarify some details contributing the endometriosis model and adenomyosis model. We set up two groups to detect if puncture would affect the cyst of endometriosis model. One group conducted transplantation and puncture at the same time. The other group conducted transplantation firstly, 2 weeks later conducted puncture.In both two groups, most of the lesions were observed around the abdominal incision, the intestinal membrane and the renal capsule. From the perspective of reducing secondary damage, conducted the transplantation and puncture at the same time is the most ideal.In group two, conducted transplantation firstly then 2 weeks later conducted puncture, the number and weight of the cyst has significantly increased compared with group1. The procedure of puncture was a stimulating factor for the growth of cyst.Our preliminary research results indicated that conducted puncture and transplantation at the same time and after four week to detect the formation of two disease was much more reasonable.However, we need extra data to clarify the result.

1．研究概要(2)

5)考察(Discussion)Uterine adenomyosis and endometriosis often coexist and their features are similar. We successfully set up the hybrid model that combined the feature of adenomyosis and endometriosis. This hybrid model can help us to shed light on the pathogenesis of adenomyosis and endometriosis. Our mouse model mimics the internal adenomyosis and peritoneal endometriosis even with its limitation, should be considered as a breakthrough for the investigation of adenomyosis and endometriosis

6)当初の研究計画と比し、現在の進捗状況の自己評価 (Self-assessment of the current progress compared to the initial research plan.)
①予想以上に進捗している(Progressing more than expected.)
②おおむね順調 (Mostly on track)
③やや遅れている (Slightly behind schedule)
④大幅に遅れている(Significantly behind schedule)

7)計画より進んでいる内容と遅れている内容、及びその理由
(Contents that are ahead of schedule and those that are behind schedule, along with the reasons.)

8)参考文献(References)
[1] Taniguchi F, Wibisono H, Mon Khine Y, Harada T. Animal models for research on endometriosis[J]. Frontiers in Bioscience-Elite, 2021, 13(1): 37-53.
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2. 執筆論文 Publication of thesis ※記載した論文を添付してください。Attach all of the papers listed below.

論文名 1 Title						
掲載誌名 Published journal						
	年 月	巻(号)	頁 ～ 頁	言語 Language		
第1著者名 First author		第2著者名 Second author		第3著者名 Third author		
その他著者名 Other authors						
論文名 2 Title						
掲載誌名 Published journal						
	年 月	巻(号)	頁 ～ 頁	言語 Language		
第1著者名 First author		第2著者名 Second author		第3著者名 Third author		
その他著者名 Other authors						
論文名 3 Title						
掲載誌名 Published journal						
	年 月	巻(号)	頁 ～ 頁	言語 Language		
第1著者名 First author		第2著者名 Second author		第3著者名 Third author		
その他著者名 Other authors						
論文名 4 Title						
掲載誌名 Published journal						
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第1著者名 First author		第2著者名 Second author		第3著者名 Third author		
その他著者名 Other authors						
論文名 5 Title						
掲載誌名 Published journal						
	年 月	巻(号)	頁 ～ 頁	言語 Language		
第1著者名 First author		第2著者名 Second author		第3著者名 Third author		
その他著者名 Other authors						

3. 学会発表 Conference presentation ※筆頭演者として総会・国際学会を含む主な学会で発表したものを記載してください。

※Describe your presentation as the principal presenter in major academic meetings including general meetings or international meetings.

学会名 Conference							
演 題 Topic							
開催日 date	年 月 日		開催地 venue				
形式 method	□ 口頭発表 Oral	□ ポスター発表 Poster	言語 Language	□ 日本語	□ 英語	□ 中国語	
共同演者名 Co-presenter							
学会名 Conference							
演 題 Topic							
開催日 date	年 月 日		開催地 venue				
形式 method	□ 口頭発表 Oral	□ ポスター発表 Poster	言語 Language	□ 日本語	□ 英語	□ 中国語	
共同演者名 Co-presenter							
学会名 Conference							
演 題 Topic							
開催日 date	年 月 日		開催地 venue				
形式 method	□ 口頭発表 Oral	□ ポスター発表 Poster	言語 Language	□ 日本語	□ 英語	□ 中国語	
共同演者名 Co-presenter							
学会名 Conference							
演 題 Topic							
開催日 date	年 月 日		開催地 venue				
形式 method	□ 口頭発表 Oral	□ ポスター発表 Poster	言語 Language	□ 日本語	□ 英語	□ 中国語	
共同演者名 Co-presenter							

4. 受賞(研究業績) Award (Research achievement)

名 称 Award name				
	国名 Country		受賞年 Year of	年 月
名 称 Award name				
	国名 Country		受賞年 Year of	年 月

5. 本研究テーマに関わる他の研究助成金受給 Other research grants concerned with your resarch theme

受給実績 Receipt record	□ 有　□ 無
助成機関名称 Funding agency	
助成金名称 Grant name	
受給期間 Supported period	年　月 ～　年　月
受給額 Amount received	円
受給実績 Receipt record	□ 有　□ 無
助成機関名称 Funding agency	
助成金名称 Grant name	
受給期間 Supported period	年　月 ～　年　月
受給額 Amount received	円

6. 他の奨学金受給 Another awarded scholarship

受給実績 Receipt record	□ 有　□ 無
助成機関名称 Funding agency	
奨学金名称 Scholarship name	
受給期間 Supported period	年　月 ～　年　月
受給額 Amount received	円

7. 研究活動に関する報道発表 Press release concerned with your research activities

※記載した記事を添付してください。Attach a copy of the article described below

報道発表 Press release	□ 有　□ 無	発表年月日 Date of release	
発表機関 Released medium			
発表形式 Release method	・新聞　・雑誌　・Web site　・記者発表　・その他(　　)		
発表タイトル Released title			

8. 本研究テーマに関する特許出願予定 Patent application concerned with your research theme

出願予定 Scheduled	□ 有　□ 無	出願国 Application	
出願内容(概要) Application contents			

9. その他 Others

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