様　式　Ｃ－１９、Ｆ－１９－１、Ｚ－１９　（共通）

科学研究費助成事業　　研究成果報告書

令和　６ 年　 ６ 月 ２５ 日現在

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研究種目：挑戦的研究（萌芽）
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研究課題名（和文）リボソームにおけるRNAタンパク質相互作用をマッピングするための統合的アプローチ

研究課題名（英文）An integrated approach for mapping RNA protein interactions in the ribosome

研究代表者
ナマシヴァヤム　パンディアン（NAMASIVAYAM, Ganesh Pandian）

京都大学・高等研究院・講師

研究者番号：２０６２５４４６

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研究成果の概要（和文）：反応選択的ケミカルプローブを用いた、ナノポアによるディレクトRNAシークエンシングという概念の実証に成功した。その特徴は、IndoCと名付けたインフォマティクス手法により予測精度が改善されたところにある。IndoCによる修飾RNAの検出に関する初期段階での結果に加え、機能性量子ドットのナノバイオ相互作用について論文として報告した。また、コンピュータ支援によって天然物由来の低分子プローブが発見できる可能性について総説にまとめた。現在は戦略を拡張し、狭窄部分などが設計可能な核酸ベースのナノポアを作製することで、RNAの高次構造のほか生体分子全般に利用できるシークエンシング技術の開発を目指している。

研究成果の学術的意義や社会的意義
近年のCovid-19の世界的流行により健康についての信頼性の高い指標として、RNAから細胞内環境に関する正確な情報が得られることが明らかになった。本研究により開発された、ケミカルプローブを用いたディレクトRNAシークエンシング法は、他の研究室でも取り入れることのできる簡便なものである。したがって、感染症であれがんのような非感染性疾患であれ、未知のRNA修飾やその相互作用の場所を特定するマッピング研究への波及効果が期待できる。そうして得られたデータセットの解析は、診断用疾患マーカーあるいは新薬の標的となるようなRNAの新規構造の発見や、不治の希少疾患に対する核酸医薬の創出に役立つ可能性がある。

研究成果の概要（英文）：Using this grant, we have successfully demonstrated the proof-of-concept (POC) studies to verify an integrated approach of harnessing the selective reactivity of chemical probes in the nanopore direct RNA sequencing platform and improving the prediction accuracy using an informatics workflow called Indo-C that can be programmed on demand. Using this methodology, we published initial results on deciphering the inosine and pseudouridine RNA modifications, the nano-bio interaction of the functionalized quantum dot probes as original articles and have summarized the potential of computational-aided discovery of natural product-derived small molecule probes as review articles. Currently, we are extending our strategy to map RNA structural and base modifications and their interaction using programmable nucleic acid-based nanopores in varied sizes, shapes, and constrictions and developing a universally adaptable biomolecular sequencing technology under a JST program.

研究分野：Chemical Biology

キーワード：Transcriptomics　RNA Structures　Nanopore technology　Chemical probes　Informatics　RNA protein interactions　RNA modifications

１．研究開始当初の背景:

RNA plays crucial and diverse roles within the cell. Structural and base modifications in RNA and their interaction with proteins have a wide range of regulatory effects on mRNA, including influencing base pairing, structure, stability, decay, translation, microRNA binding, and codon potential. RNA-protein (RNP) complexes are essential to cellular homeostasis, and their perturbations can lead to cellular dysfunction and diseases like cancer. X-ray crystallography and nuclear magnetic resonance (NMR) spectroscopy offer atomic resolution views, whereas electron cryomicroscopy (cryoEM) plays an increasingly important role in determining the structures of large and vital RNAs at moderate resolution (Nguyen et al. 2016). Although deep insights have been generated from these approaches, they have low throughput and cannot keep pace with the generation of genomic data, which can now be obtained in a matter of days via next-generation sequencing (Shendure et al. 2017). Currently, most techniques use the short-read sequencing (SRS) platform, which provides high accuracy and coverage. However, RNA modifications are not detected by the reverse transcription process used in SRS library preparation. Many protocols use antibodies and modification-specific chemicals to induce adduct formation. These adduct-induced mutation or truncation profiles are then used as a proxy for identifying modifications with single-nucleotide resolution. The main limitations of current methods are: a) laborious sample preparation, b) lower reproducibility across replicates due to multi-step sample preparation, c) difficulty in accurately determining modification stoichiometry due to RNA fragmentation during SRS library preparation, and d) the challenge of simultaneously mapping multiple modifications in a single run. Taken together, there is an increasing demand to develop a new *in vivo* structure probing methodology that can be extended and applied in clinical situations where input RNA is limited and RNA modification-associated enzyme knockouts are not feasible.

２．研究の目的:

The pocket-sized Oxford nanopore sequencing technology (ONT) facilitates rapid RNA profiling by generating ultra-long direct RNA sequencing (dRNA-Seq) reads without reverse transcriptase. The Nanopore sequencing platform operates by ratcheting RNA into a protein pore where the migration triggers a distinct change in the stable current maintained across the pore. Subsequently, the resulting current pattern is converted to sequence information with machine learning algorithms. Since the base-calling (current to nucleotide sequence conversion) algorithms are trained on conventional bases such as A, G, C and T, any modified bases present in RNA may deviate from the standard model. The resulting difference between modified and unmodified nucleotides may be base quality, mismatch, deletion, current intensity, or dwell time. This can detect RNA base and structural modifications or their interaction with proteins with single nucleotides and single molecule information. This project aims to harness the selective reactivity of chemical probes to overcome the existing bottlenecks in detecting RNA modifications and their interactions with proteins and enhance their detection accuracy at the single nucleotide resolution with the following advantages (***Figure 1***). Our group has been making steadfast progress in screening and identifying optimal chemical probes that are compatible with protein nanopores and based on the initial results, we planned to complement the approach with modified algorithms.

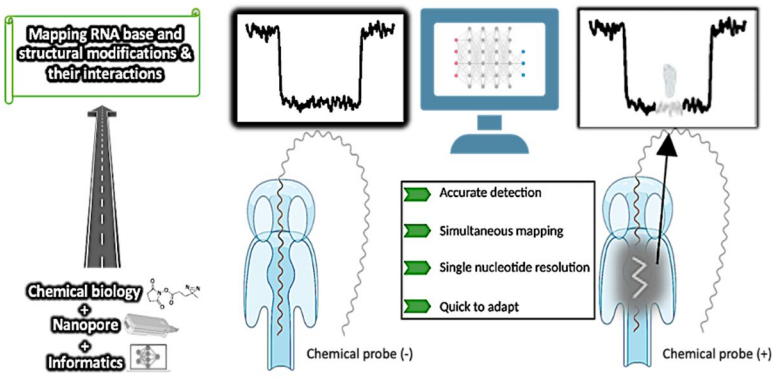

Figure 1. *Schematic illustration of using an integrated chemical biology and informatics approach to fast-track the mapping of RNA modifications and interactions using Oxford Nanopore sequencing Technology (ONT). The expected merits of this strategy are listed in the inset box.*

３．研究の方法:

Sample and library preparation: The In vitro Transcription (IVT) templates were purchased from IDT for short IVT RNA synthesis with a polyA tail sequence. The TRIPLEscript plasmid template was transcribed using T7 polymerase. The PolyA tailing of long IVT RNA was done using the Poly(A) Tailing Kit. The MEGA script™ T7 Transcription Kit was used for all IVT reactions. Pseudouridine-5'-triphosphate and Inosine-5'-triphosphate were used in place of uridine and guanosine. Inosine IVT RNA was synthesized as 100% and 50% Inosine-modified variants using different dNTPs. Acrylonitrile cyanoethylation reaction was carried out with and without acrylonitrile. The RNA was then subjected to cDNA synthesis and primer amplification using the SuperScript III One-Step RT-PCR System with Platinum Taq DNA polymerase. 500 ng of RNA was used for direct RNA-Seq library (SQK-RNA002) preparation following the ONT protocol version - DRS_9080_v2_revK_14Aug2019. The RNA was ligated to the ONT RT Adapter, reverse transcribed, and purified using Agencourt RNAClean XP beads. The RNA:cDNA hybrid was then ligated with an RNA Adapter (RMX) and purified again before loading onto a primed R9.4.1 flow cell for sequencing on a MinION sequencer with MinKNOW acquisition software version v1.14.1.

Informatics workflow: Base-calling and mapping of dRNA-Seq reads were performed using MinKnow-GUPPY (V 3.4.5), enabling accurate base calling. The reads were mapped to the reference sequence using minimap2 (version- 2.17-r941) with specific settings. The mapped reads were filtered and sorted, and the mapping workflow was adapted from a specific source. Mouse brain reads were mapped to gencode vM24 transcript reference and reference genome Grcm38.p6. Nanopore parameters such as mismatch error, trace, and signal intensity were extracted using scripts associated with the nanoRMS package. All plots were generated using R (4.0.2). Support Vector Machine learning was utilized to analyze K-mer-related features such as mismatch, insertion, deletion, and base quality. TOMBO analysis was performed using TOMBO (v1.5.1), and compatible files were extracted for the IGV genome browser.

In vivo Probing: Three-month-old ICR mice were purchased from Shimizu, Japan, and their forebrain was dissected and homogenized. RNA purification was performed, and the integrity and concentration of the RNA were checked. The recovered mouse brain RNA was used for dRNA-Seq library preparation for our new approach called Nano ICE-Seq; we used Mouse Brain Poly A+ RNA (cat:636207, Clontech, TAKARA) and performed Cyanoethylation treatment. We used Kcna1, Gria2, Nduaf12, Itf22, and Wipi2 primers for amplicon generation, which were then purified using QIAquick PCR Purification Kit. The purified amplicons were used for nanopore library preparation with the Ligation Sequencing Kit SQK-LSK109 standard protocol. Data analysis involved base-calling FAST5 files using MinKnow-GUPPY (V 3.4.5), mapping to a reference sequence using minimap2, and filtering mapped reads based on quality.

４．研究成果

4.1. Chemical Probe-Based dRNA-Seq Assessment of Inosine modifications: As a proof-of-concept, we evaluated the impact of **A-I** modification by creating a workflow using RNA transcripts with inosine modifications at the pre-determined sites, as mentioned in the methods above. The dRNA-Seq results showed consistent mismatch errors on **I**-modified sites compared to unmodified (UM)sites. We examined four key parameters (base quality, mismatch, insertion, and deletion) for all possible 5-mers to identify the differentiation between UM and **I**-modified transcripts. We used 5-mer-related parameters for downstream analysis. The results of our study show that using mismatch error as a parameter can predict **A-I** modification with high accuracy. We also compared the signal intensity parameter using TOMBO packages. While it shows differences between UM and **I**-modified transcripts, it is not as reliable for **A-I** site identification as the mismatch errors (***Figure 2A***). To verify if inosine-modification-associated mismatch error can be validated through chemical adducts, we explored if we can adapt the acrylonitrile selective reactivity toward **I**-modification in the dRNA-Seq platform. Chemical probe-treated (CEI) transcripts were generated by treating the **I**-modified transcripts with acrylonitrile. Our results showed that the dRNA-Seq approach is more suitable for recovering the heavy or moderate **A-I** editing sites. The TOMBO comparative analysis focuses solely on the signal difference. Our designer workflow further validated that CEI adducts could significantly disrupt the signal and trace value of dRNA-Seq reads as inosine modification (***Figure 2B***). The reactivity of acrylonitrile towards

pseudouridine (Ψ) modification is partial under our reaction conditions, so we have not further explored Ψ modification in our work. Acrylonitrile shows mild cross-reactivity with modifications other than **I** and Ψ, but those modifications are less abundant and are not explored in this study. We tested our chemical probe-based dRNA-Seq method on mouse brain poly-A enriched mRNA. Cyanoethylation coupled with Sanger sequencing confirmed the acrylonitrile reactivity on the mouse transcriptome. All samples were sequenced using independent flow cells. The gene count shows a good correlation within biological replicates and an independently published mouse brain dRNA-Seq transcriptome. N50 revealed moderate fragmentation of input RNA due to the high temperature in acrylonitrile treatment. We evaluated the previously reported **A-I** and Ψ sites and chose a read count cutoff (>5 reads) yielded 13 and 27 bonafide **A-I** and Ψ sites with mismatch errors. The *in vivo* **A-I** editing sites captured using dRNA-Seq showed **I**-associated mismatch errors. We performed cyanoethylation-based Sanger validation of four **A-I** editing sites. The Sanger validation revealed that the dRNA-Seq mismatch error inferred as the **I** in the Tox4 site harbored SNV. The "quick to adapt" Nano ICE-Seq with 30 h of runtime (experiment to analysis) could efficiently probe clinically relevant differential **A-I** sites as diagnostic or prognostic markers (***Figure 2C***). The above results were published (*ACS Chem. Biol.* 2022, 17, 2704-2709).

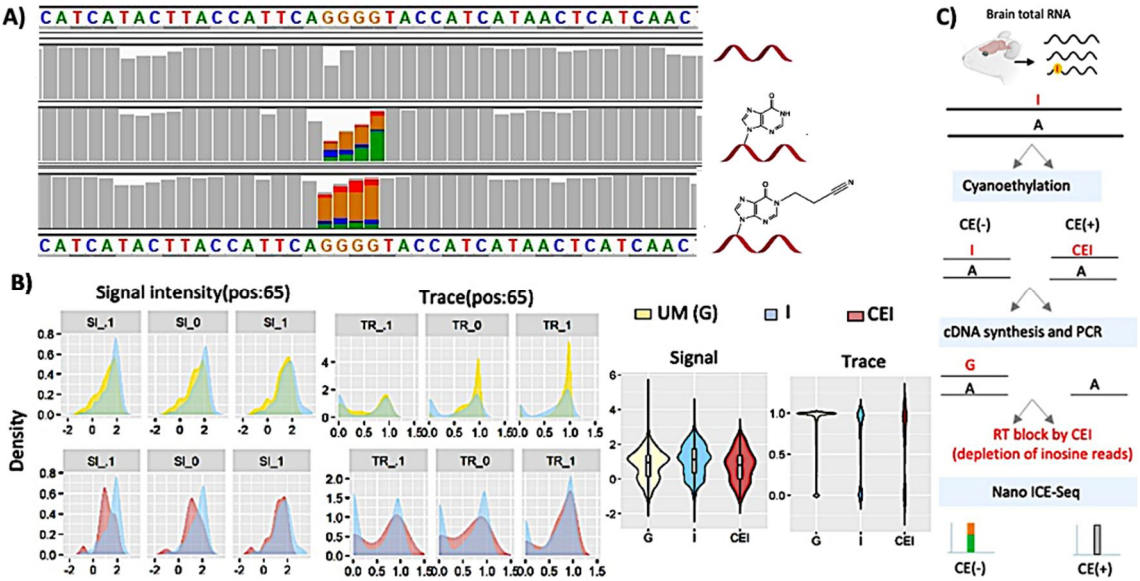

Figure 2. A) *IGV snapshot of unmodified (UM), Inosine (**I**) and cyanoethyl inosine (**CEI**) transcripts showing mismatch. Mismatch frequency > 0.2% is represented in colors. Green(adenosine), orange (guanosine), blue (cytosine) and red (thymine).* ***B)*** *Density plot showing the distribution of signal intensity (SI) and trace (TR) among unmodified-G, modified-**I**, and CEI conditions. The distributions are shown for position 65 in the synthetic RNA (position "0" in the figure) and its upstream and downstream positions as −1 and +1.* ***C)*** *Schematic overview showing mouse brain samples subjected to nanopore sequencing and depicting Nano ICE-Seq workflow our lab developed for in vivo probing.*

4.2. Informatics approach to distinguish RNA modifications: When sequenced on the ONT platform, it has been shown that Ψ -modified sites are often called U/C mismatches. The base-calling program Guppy generates 'meta-information' on the raw signal, including "Trace," which has been used to measure the stoichiometry of Ψ modifications in ribosomal RNA. Lower trace values indicate lesser confidence in base calling, potentially as an indicator of Ψ. A synthetic IVT SNP model was generated to differentiate between Ψ modifications and single nucleotide variations, showing similar U/C mismatch patterns. Using nanoRMS and the Kolmogorov-Smirnov statistic, the difference between trace value distributions for the SNP model and Ψ containing RNA was quantified, revealing significant differences. We explored the use of trace value distributions in distinguishing between Ψ modifications and single nucleotide variations in RNA from biological samples. Obtaining matched controls for dRNA-seq data is challenging, so we attempted an internal comparison strategy called `Indo-C` (***Figure 3A***). We conjectured that comparing base-calling parameters of a given position to other positions within the dataset could reveal differences between Ψ and unmodified nucleotides. We conducted dRNA-seq for yeast total RNA for this investigation and mapped it to the yeast rRNA transcriptome. We identified Ψ sites using the IndoC

method and used nanoRMS to extract features. Representative distribution plots (***Figures 3B and 3C***) were calculated using various statistics using trace value and signal intensity. We performed principal component analysis and binary classification, obtaining a reasonable ROC-AUC of 0.83 for yeast and 0.77 for human rRNA data. Part of these results were published (*Genomics 2022,114(3),110372*).

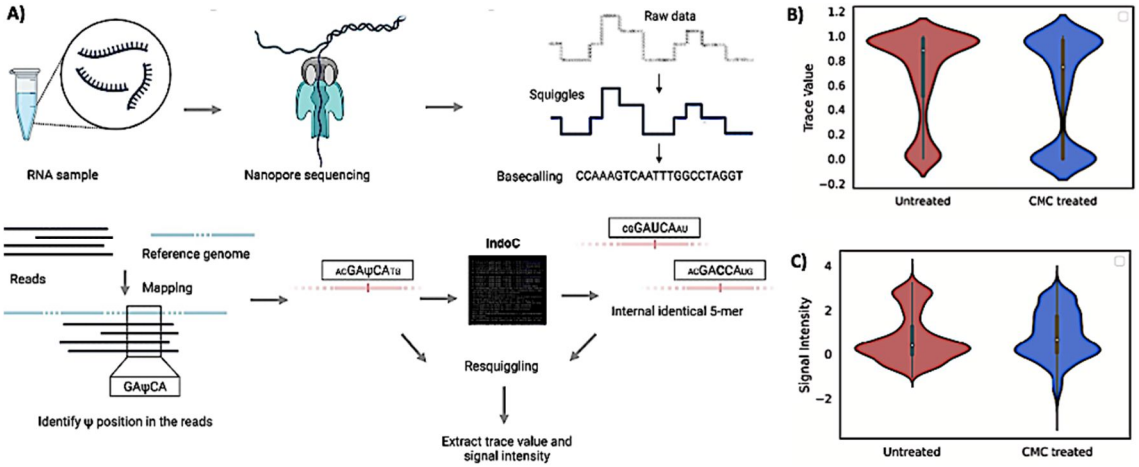

Figure 3. *A) Schematic representation of IndoC workflow. Violin plots for trace* ***B)*** *and signal intensity* ***C)*** *for all the bonafide Ψ sites in yeast rRNA comparing CMC-treated and untreated conditions.*

4.3. Deciphering RNA protein interactions: Encouraged by the platform set by the previous workflow, we moved on to the leading objective of our research, which is to develop an integrated approach to map RNA structural and base modifications and their interaction with proteins. We have successfully designed, synthesized, and identified the novel bifunctional probe that interacts with specific components of RNA structural modifications and their interaction with the peptide sequences of ribosomal proteins. We have also advanced the Indo-C as an informatic software to distinguish characteristic current signal trace changes due to resulting covalent adducts from the original pattern during nanopore sequencing and achieved a single nucleotide prediction accuracy of 79% using RNA-targeted CRISPR-CAS13a system. Furthermore, we also extended our strategy to map 8-oxo-7,8-dihydroguanine at single-nucleotide resolution in synthesized DNA strands. We encountered a bottleneck of a size limitation of the chemical probe, and there needs to be a trade-off between the size and selective reactivity and small molecule probes need to be of optimal size to enter the one nm-sized bacterial nanopore. To overcome this issue, we devised an approach to create a new protocol and device by ourselves. Because modifying the bacterial pores is laborious and not precise, we perform a one-pot synthesis to create nucleic acid-based programmable nanopores of varied sizes (5 - 8 nm) and shapes (two or three constrictions). We have optimized our strategy in an *in vitro* CRISPR system and are now evaluating its efficacy in an *in vitro* cancer cell line to study tumor ribosomes. As an extension, we also use human dermal fibroblasts to probe inflammatory skin disorders and mesenchymal stem cells to probe osteoarthritis.

We also review articles including a summary about how machine-learning tools could aid the discovery of natural product-derived small molecules that can serve as targeted therapeutics and probes. Furthermore, the nano-bio interaction and related biophysical studies of the functionalized quantum dots, which is expected to harbor the bi-functional probe to decipher RNA-protein interaction, was tested using the *in vitro* and *in vivo* models. These results form an ideal platform for the integrated approach to mapping RNA dynamics.

５．主な発表論文等

〔雑誌論文〕　計11件（うち査読付論文　11件／うち国際共著　11件／うちオープンアクセス　11件）

１．著者名 Karthikeyan Subramani、Thirunarayanan Ayyavu、Shano Leon Bernet、Hemamalini Arasappan、Sundaramoorthy Anandh、Mangaiyarkarasi Rajendiran、Abu Norhidayah、Ganesan Singaravelu、Chinnathambi Shanmugavel、Pandian Ganesh N.	４．巻 14
２．論文標題 Chalcone derivatives' interaction with human serum albumin and cyclooxygenase-2	５．発行年 2024年
３．雑誌名 RSC Advances	６．最初と最後の頁 2835～2849
掲載論文のDOI（デジタルオブジェクト識別子） 10.1039/D3RA07438B	査読の有無 有
オープンアクセス オープンアクセスとしている（また、その予定である）	国際共著 該当する

１．著者名 Anjila P.K Fathima、Tharani G.R.、Sundaramoorthy Anand、Kumar Shanmugam Venkat、Subramani Karthikeyan、Chinnathambi Shanmugavel、Pandian Ganesh N.、Raghavan Vimala、Grace Andrews Nirmala、Ganesan Singaravelu、Rajendiran Mangaiyarkarasi	４．巻 196
２．論文標題 An ultra-sensitive detection of Melamine in milk using Rare-earth doped Graphene Quantum Dots-Synthesis and Optical Spectroscopic approach	５．発行年 2024年
３．雑誌名 Microchemical Journal	６．最初と最後の頁 109670～109670
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１．著者名 Vaijayanthi Thangavel、Pandian Ganesh N.、Sugiyama Hiroshi	４．巻 6
２．論文標題 Pyrrole Imidazole Polyamides A Frontrunner in Nucleic Acid‐Based Small Molecule Drugs	５．発行年 2023年
３．雑誌名 Advanced Therapeutics	６．最初と最後の頁 2300022
掲載論文のDOI（デジタルオブジェクト識別子） 10.1002/adtp.202300022	査読の有無 有
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２．論文標題 Surface charge-dependent cytokine production using near-infrared emitting silicon quantum dots	５．発行年 2024年
３．雑誌名 Scientific Reports	６．最初と最後の頁 9618
掲載論文のDOI（デジタルオブジェクト識別子） 10.1038/s41598-024-60536-2	査読の有無 有
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1．著者名 Lathakumari Saranya、Seenipandian Sumitha、Balakrishnan Subburathinam、Raj Audre Preena Maria Sundar、Sugiyama Hiroshi、Pandian Ganesh N、Sivasubramaniam Sudhakar	4．巻 31
2．論文標題 Identification of genes responsible for the social skill in the earthworm, Eudrilus eugeniae	5．発行年 2023年
3．雑誌名 Gene Reports	6．最初と最後の頁 101774～101774
掲載論文のDOI（デジタルオブジェクト識別子） 10.1016/j.genrep.2023.101774	査読の有無 有
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1．著者名 Dhivahar J.、Parthasarathy Anutthaman、Krishnan Kathiravan、Kovi Basavaraj S.、Pandian Ganesh N.	4．巻 9
2．論文標題 Bat-associated microbes: Opportunities and perils, an overview	5．発行年 2023年
3．雑誌名 Heliyon	6．最初と最後の頁 e22351～e22351
掲載論文のDOI（デジタルオブジェクト識別子） 10.1016/j.heliyon.2023.e22351	査読の有無 有
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2．論文標題 Nucleic acid‐based small molecules as targeted transcription therapeutics for immunoregulation	5．発行年 2023年
3．雑誌名 Allergy	6．最初と最後の頁 843～860
掲載論文のDOI（デジタルオブジェクト識別子） 10.1111/all.15959	査読の有無 有
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1．著者名 Chinnathambi Shanmugavel、Shirahata Naoto、Kumar Mahima、Karthikeyan Subramani、Abe Katsuhiko、Thangavel Vaijayanthi、Pandian Ganesh N.	4．巻 13
2．論文標題 Nano bio interaction between human immunoglobulin G and nontoxic, near-infrared emitting water-borne silicon quantum dot micelles	5．発行年 2023年
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掲載論文のDOI（デジタルオブジェクト識別子） 10.1039/D3RA00552F	査読の有無 有
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１．著者名 Sahayasheela Vinodh J.、Lankadasari Manendra B.、Dan Vipin Mohan、Dastager Syed G.、Pandian Ganesh N.、Sugiyama Hiroshi	４．巻 39
２．論文標題 Artificial intelligence in microbial natural product drug discovery: current and emerging role	５．発行年 2022年
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掲載論文のDOI（デジタルオブジェクト識別子） 10.1039/D2NP00035K	査読の有無 有
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１．著者名 Ramasamy Soundhar、Sahayasheela Vinodh J.、Sharma Surbhi、Yu Zutao、Hidaka Takuya、Cai Li、Thangavel Vaijayanthi、Sugiyama Hiroshi、Pandian Ganesh N.	４．巻 17
２．論文標題 Chemical Probe-Based Nanopore Sequencing to Selectively Assess the RNA Modifications	５．発行年 2022年
３．雑誌名 ACS Chemical Biology	６．最初と最後の頁 2704～2709
掲載論文のDOI（デジタルオブジェクト識別子） 10.1021/acschembio.2c00221	査読の有無 有
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１．著者名 Vaijayanthi Thangavel、Pandian Ganesh N.、Sugiyama Hiroshi	４．巻 -
２．論文標題 Pyrrole Imidazole Polyamides A Frontrunner in Nucleic Acid‐Based Small Molecule Drugs	５．発行年 2023年
３．雑誌名 Advanced Therapeutics	６．最初と最後の頁 -
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オープンアクセス オープンアクセスとしている（また、その予定である）	国際共著 該当する

〔学会発表〕　計7件（うち招待講演　7件／うち国際学会　2件）

１．発表者名 Ganesh Pandian NAMASIVAYAM
２．発表標題 Harnessing Informatics for Personalized Medicine
３．学会等名 MacDiarmid Institute-Kyoto University Workshop（招待講演）
４．発表年 2023年

１．発表者名
Ganesh Pandian NAMASIVAYAM

２．発表標題
Programmable small molecules to regulate genetic information inside live cells on demand

３．学会等名
MacDiarmid Institute-iCeMS symposium（招待講演）

４．発表年
2023年

１．発表者名
Ganesh Pandian Namasivayam

２．発表標題
Chemical Biology approach for precision medicine

３．学会等名
Next Generation Healthcare - Interdisciplinary Approaches（招待講演）

４．発表年
2023年

１．発表者名
Ganesh Pandian NAMASIVAYAM

２．発表標題
Scripting an Eco-system for Precision Medicine: Navigating the Journey to Bridge Boundaries for Synergistic Integration?"

３．学会等名
Kyoto winter school-2024, `Quantifying Dynamics of Life`（招待講演）

４．発表年
2024年

１．発表者名
NAMASIVAYAM Ganesh Pandian

２．発表標題
DNA-based targeted transcription therapeutics for precision medicine

３．学会等名
Functional nucleic acids: Recent landscapes and therapeutic applications - EMBO Lecture Series（招待講演）（国際学会）

４．発表年
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１．発表者名
NAMASIVAYAM Ganesh Pandian

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Targeted transcription therapeutics for skin cell reprogramming

３．学会等名
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４．発表年
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Nucleic acid-based small molecule therapeutics

３．学会等名
Swiss Institute of Allergy and Asthma Research - University of Zurich Lecture Series（招待講演）

４．発表年
2023年

〔図書〕　計0件

〔産業財産権〕

〔その他〕

Reading RNA modifications more precisely
https://www.asiaresearchnews.com/content/reading-rna-modifications-more-precisely
Oxford nanopore social media site
https://twitter.com/nanopore/status/1562411398881505284?lang=bg

６．研究組織

	氏名 （ローマ字氏名） （研究者番号）	所属研究機関・部局・職 （機関番号）	備考
研究分担者	Ｐａｃｋｗｏｏｄ　Ｄａｎｉｅｌ (Packwood Daniel) (40640884)	京都大学・高等研究院・准教授 (14301)	

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８．本研究に関連して実施した国際共同研究の実施状況

共同研究相手国	相手方研究機関