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　４ 年 １０ 月 ２６ 日現在

機関番号：１４３０１
研究種目：基盤研究(B)（一般）
研究期間：2019～2021
課題番号：１９Ｈ０３３４９

研究課題名（和文）心筋症関連ミトコンドリア・核内遺伝子の協奏的制御を可能にする人工転写因子の開発

研究課題名（英文）Development of Artificial Transcription Factors for Cooperative Regulation of Cardiomyopathy-Related Mitochondrial and Nuclear Genes

研究代表者

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交付決定額（研究期間全体）：（直接経費）　　13,100,000円

研究成果の概要（和文）：本期間においてオンデマンドで核・ミトコンドリア遺伝子を調整するSMART-TFの開発に成功した。特定のDNA配列の認識するSMART-TFを作成し、テロメアダイナミクスの観察を行った。更に、幹細胞の心筋形成促進・脳腫瘍幹細胞転写変化・マウスでの腫瘍転移抑制可能な各SMART-TFの生物学的有効性を実証した。加えてミトコンドリア生合成を標的としたSMART-TFでは、エネルギー代謝を担うAMPK経路の制御やマウスでのPD-1遮断免疫療法についての検証も行っている。他にも生細胞内の変異ミトコンドリアDNAの標的除去を可能とし、ナノ粒子ベースの細胞活性酸素種生成の変化も観察した。

研究成果の学術的意義や社会的意義
現在、核とミトコンドリアが担うエネルギー代謝を特異的に調節する手法は存在していない。 SMART-TFでのAMPKの制御能を実証した本研究は、マスター調節因子が遺伝子転写を変更せずに正確にオンとオフを切り替える「転写療法」と呼ばれる新たな手法開発の可能性を示している。近年、伝染病・非伝染病への核酸ベースの治療法が多々報告されている。従来の治療法は、タンパク質間相互作用を対象とし、多くは患者間で異なる効果をもたらす。我々の核酸ベースの標的治療薬は、患者間で一貫した長期的な効果が期待されるという大きな利点がある。これらは情報学的手法を用いて、精密医療の分野での有用なツールとしての応用が期待される。

研究成果の概要（英文）：The overarching aim of this project to develop biomimetic epigenetic codes that could operate as smart transcription factors (SMART-TFs) and regulate nuclear and mitochondrial genes on demand was successfully achieved. We created a nuclear SMART-TF termed e-PIP-HoGu that recognizes specific DNA sequences with a flexible gap spacing and also decoded telomere dynamics. We demonstrated the bioefficacy of nuclear SMART-TFs to enhance cardiomyogenesis in stem cells, alter transcription in brain cancer stem cells and suppress tumor metastasis in a mouse model. Encouraged with these results, we explored and verified that a SMART-TF termed En-PGC-1 targeting the mitochondrial biogenesis could control AMPK pathway associated with cellular energy metabolism and synergize PD-1 blockade immunotherapy in a mouse model. We developed a mitochondrial SMART-TFs to achieve targeted elimination of mutated mitochondrial DNA in live cells and also demonstrated cellular reactive oxygen species production.

研究分野：薬系化学および創薬科学関連

キーワード：Transcription therapy　Epigenetic codes　Mitochondria　Reactive Oxygen Species　Energy metabolism　Nanoparticle　Immunotherapy　Heteroplasmy

様　式　Ｃ－１９、Ｆ－１９－１、Ｚ－１９（共通）

１．研究開始当初の背景

Reactive oxygen species (ROS) produced from cellular oxidative metabolism in mitochondrial complex I play an essential role in versatile cellular functions, including survival, death, differentiation and signaling. Aberrant ROS production damages the cardiomyocytes that harbor 30% of mitochondria in their cell volume. Modern sequencing technologies have revealed key master regulatory factors involved in cellular energy metabolism and ROS control. One such factor is mitochondrial transcription factor A (TFAM), and it has been reported that ROS production is stopped in cells deficient in TFAM (Proc. Natl. Acad. Sci. U.S.A. 2010, 107, 8788). Although antioxidant drugs have shown great potential, there was a need to target multiple factors. Similarly, AMP-activated kinase (AMPK) play a major role in mitochondrial biogenesis and energy metabolism (J. Physiol. 2006 574, 33). While small molecules targeting the protein-protein interactions associated with the AMPK pathway are known, there was a growing demand to develop tools targeting DNA-protein interactions. Taken together, although there is a collective knowledge about the master regulatory factors in mitochondria and nucleus that regulate cellular energy metabolism, there is no method available to adequately control these multiple targets on demand.

２．研究の目的

A closer look at the gene regulation system suggests that some naturally occurring transcription factors (TFs)utilize protein modifications called "epigenetic codes" to precisely control multiple factors at the right place and time. *N*-Methylpyrrole-*N*-Methylimidazole polyamide (PIP) is a well-known small molecule that selectively recognizes four Watson-Crick base pairs in DNA and can be pre-programmed to mimic the DNA binding domain of the natural TFs. The overarching aim of this project is to develop them as biomimetic epigenetic codes with higher functionality called smart transcription factors (SMART-TFs) by assembling various functional compounds in a chemical and/or nanoparticle platform. SMART-TFs are expected to control ROS levels and intracellular energy metabolism and provide an innovative strategy called transcription therapy that overcomes the existing bottlenecks in treating diseases like cardiomyopathy. Based on the initial results, we extended the scope to decode and recode the epigenome for immunotherapy and precision medicine.

３．研究の方法

We sequentially developed SMART-TFs and demonstrated their incremental bioefficacy in various cell lines. PIPs were synthesized using solid-phase peptide synthesizer [PSSM-8(Shimadzu)] and were characterized using HPLC (PU-2089, JASCO) and MALDI-TOF/MS.

(1) Design and synthesis of ligands and nanoparticles with higher functionality:In mammals, 50-70% of transcription factors (TFs) operate in pairs to orchestrate accurate spatiotemporal gene expression. Therefore, we designed an epigenetically active cucurbit[7]uril-assisted DNA-binding Host-Guest system, termed **ePIP-HoGu**, that mimics the cooperative function of a TF pair and is capable of recruiting epigenetic modifiers to the target DNA sites (**Fig.1A, Chem.Commun.,2020,56, 2296**). We enhanced nuclear

accumulation of a 12-ring PIP by incorporating a tri-arginine moiety (**Fig.1B,Chem.Commun.,2020,56,12371**) and conjugated them with a bromodomain inhibitor to create the biomimetic epigenetic code for mitochondrial biogenesis.

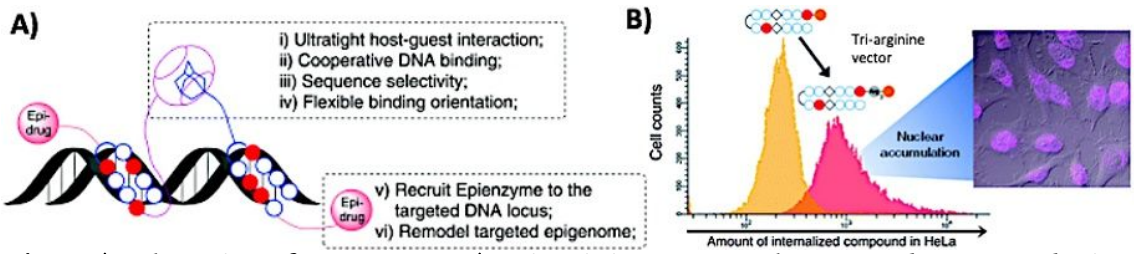

***Fig.1.A)** Schematics of e-PIP-HoGu, **B)** Triarginine vector enhances nuclear accumulation.*

SPR experiments were performed on a Biacore X instrument (GE Healthcare). Most endogenous ROS produce a link between mitochondrial function, DNA integrity and telomere dynamics. We developed a near-infrared fluorogenic pyrrole-imidazole polyamide probe (SiR-TTet59B) to visualize telomeres by conjugating a silicon-rhodamine (SiR) fluorophore with a tandem tetramer pyrrole-imidazole polyamide targeting 24 bp in the telomeric double-stranded (ds) DNA. A multifunctional conjugate targeting mitochondria was designed using PIPs, mitochondrial penetrating peptide (MPP) and DNA alkylating agent (chlorambucil) for sequence-selective adenine alkylation. Nanoparticle-based smart transcription factors for mitochondria was synthesized using Glutathione (GSH)-functionalized gold nanoclusters and conjugation of designer PIP and MPP ligands was performed through 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC)/ N-hydroxysuccinimide (NHS, Thermo Fisher Scientific) coupling and purified by an Amicon filter membrane. TEM imaging was performed on a Philips CM12 model coupled with AMT digital camera (model: XR111). Hydrodynamic sizes and zeta potentials of nanoparticles were measured using a ZS Nano Zetasizer dynamic light scattering instrument from Malvern Instruments (Malvern, UK). The UV-Vis absorption and fluorescence spectrum of nanoparticles were measured in a quartz cuvette by Varian Cary 50 spectrophotometer, and Cary Eclipse Fluorescence Spectrometer from Agilent, respectively.

(2) Characterization and biological evaluation studies: Gene expression analysis were carried out by extracting total RNA with a RNeasy Mini Kit (Qiagen). RNA integrity was assessed using a Bioanalyzer 2100 (Agilent Technologies). After reverse transcription using ReverTraAce qPCR RTMasterMix with gDNA Remover (Toyobo), the reaction was performed in a LightCycler 480 (Roche Diagnostics GmbH). Statistical analysis was performed using Prism 7. Flow cytometry analysis and immunostaining studies were performed with FACS ARIA II (BD Biosciences) and FV1200 Laser Scanning Microscope (Olympus). RNA sequencing (Illumina platform), chromatin immunoprecipitation sequencing, Chem-Seq, Bind-n-seq analysis (Ion torrent PGM) and nanopore sequencing (oxford nanopore technology) and ingenuity pathway analysis (IPA-Qiagen) were harnessed for genome and epigenome analysis. Electrophoretic mobility shift assay (EMSA), thermal shift (T_m) and the *in vitro* histone acetyl transferase-ChIP-qPCR assay were used to characterize binding efficacy. Mitochondrial activation parameters e.g., potential, mass, and ROS generation were assessed using vital dyes MitoTracker Deep Red,

MitoTracker Green, MitoSOX Red/CellROX (Life Technologies). FAO was assessed using ‘Fatty Acid Oxidation Detection Reagent’ (FAOBlue) (Funakoshi). The mtDNA copy numbers are measured using mtDNA-encoded NADH dehydrogenase 1 (ND1) and was normalized to the signal for nuclear hexokinase 2 (HK2) gene. Oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) were measured using an XFe96 Extracellular Flux analyzer (Seahorse Biosciences). For the ROS assay, 10 μM dichloro-dihydro-fluorescein diacetate (DCFH-DA) was used. and ROS levels were quantified by measuring intracellular fluorescent intensities using Nikon Element Air software.

4．研究成果

(1) Targeted epigenetic modulation enhanced cardiomyogenesis in stem cells and synergized PD-1 blockade immunotherapy in mouse model: The epigenome has an essential role in orchestrating transcriptional activation. We first created a designer TF-mimic termed **ePIP-HoGu** capable of partaking the co-operative binding capacity of TF pairs. The *in vitro* histone acetyl transferase-ChIP-qPCR assay using four kinds of nucleosomes showed synergistic recruitment of an epigenetic modifier to the target DNA repeat locus with flexible gap spacings. We then incorporated the tri-arginine moiety to enhance nuclear accumulation of a 12-ring PIP without compromising sequence selectivity and achieved efficient repression of SOX2-downstream genes and HER2 transcription in HeLa cells. Simultaneously, we performed screening studies using the α-myosin heavy chain promoter-driven reporter and identified a designer ligand **G** that could epigenetically activate cardiac-related genes. Intracellular Ca^{2+} studies in mouse embryonic stem cells verified that **G** enhances the generation of spontaneous beating cells **(Fig.2, J. Cell. Physiol.2021, 236, 3946).**

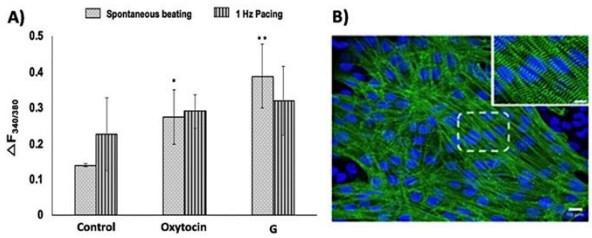

***Fig.2A)** Signal amplitudes of calcium transients from cells obtained upon pacing at a frequency of 1 Hz. **B)** Immunostaining (cTnT)of G treated stem cells on Day 11.*

Encouraged with the achievement of this milestone ahead of our schedule, we explored the new direction to identify small-molecule modulators of immune cells capable of augmenting the effect of programmed cell death protein 1 (PD-1) blockade, leading to better cancer treatment. We created **EnPGC-1** that can trigger the targeted induction of the peroxisome proliferator-activated receptor-gamma coactivator 1 alpha/beta (PGC-1a/b), a regulator of mitochondrial biogenesis. **EnPGC-1** enhanced mitochondrial activation, energy metabolism, proliferation of CD8+ T cells in vitro, and, in particular, enhanced oxidative phosphorylation, a feature of long-lived memory T cells. Genome-wide gene analysis suggests that **EnPGC-1** can regulate T cell activation as a major biological process. **EnPGC-1** also synergizes with PD-1 blockade to enhance antitumor immunity and improved host survival **(Fig.3, Cell Chem. Biol.2022,29,463).**

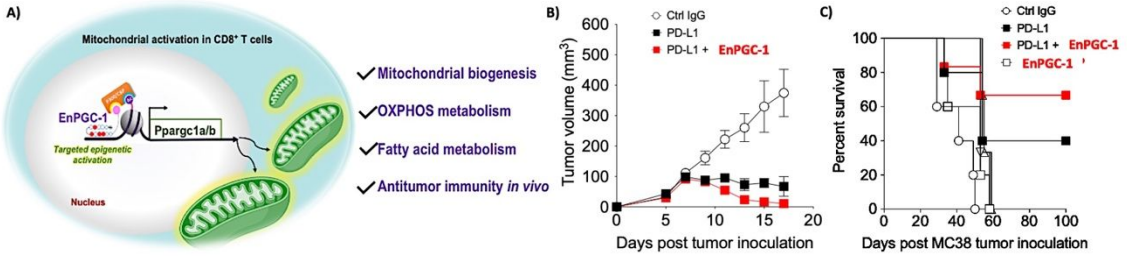

***Fig.3** A) Schematics of EnPGC1-mediated epigenetic induction of mitochondrial biogenesis, **B)** Tumor graphs and C) survival curve in a mouse model were plotted.*

(2) Targeted modulation of mitochondrial function and ROS production: Although eliminating mutated mitochondrial DNA (mtDNA) has potential to cure mitochondrial diseases, no chemical-based drugs in clinical trials are capable of selective modulation of mtDNA mutations. We constructed a multi-functional conjugate that allowed chlorambucil to alkylate mutant adenine more efficiently than other sites in mtDNA. *In vitro* DNA alkylation assay showed that our compound **8950A-Chb(Cl/OH)** targeting a nonpathogenic point mutation in HeLa S3 cells (m.8950G>A) could reduce the mtDNA possessing the target mutation in cultured HeLa S3 cells **(Fig.4A, Cell Chem. Biol.2022,29, 690).** We developed a nanoparticle-based mitochondrial transcription regulator (**MitoScript**) through a biomimetic approach by conjugating PIP, MPP onto ultrasmall fluorescent nanoparticles. **MitoScript** demonstrated high colloidal stability, outstanding biocompatibility, efficient cell uptake, selective mitochondria targeting, and can be monitored in live cells using near-infrared (IR) fluorescence. Most importantly, **MitoScript** effectively and selectively manipulated mtDNA transcription in a human model cell line. Specifically, **MitoScript** targeting the light strand promoter (LSP) and not the heavy strand promoter (HSP) region of mtDNA resulted in downregulation of ND6 gene suppression that eventually altered the redox status of cells (Submitted manuscript)**(Fig.4B)**.

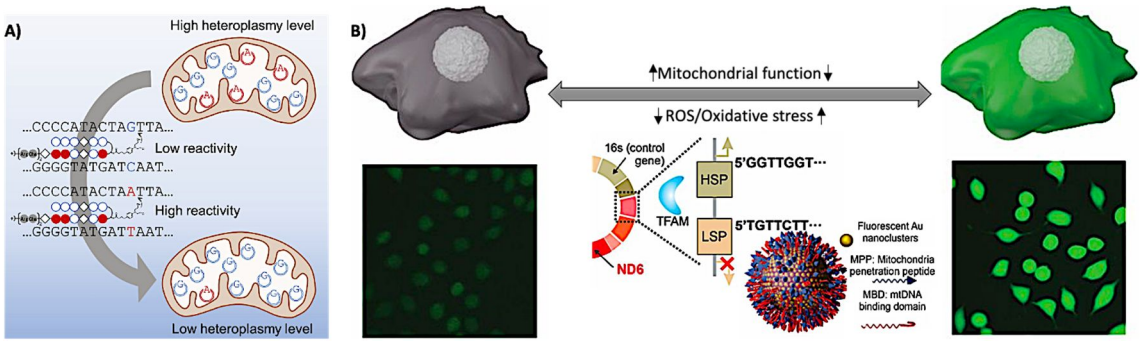

***Fig.4**A) Schematics of multi-functional conjugate reducing heteroplasmy levels in mitochondria **B)** A proof-of-concept design of a MitoScript targeting ND6 gene in mitochondria genome to regulate ROS levels and mitochondrial function.*

(3) Nano-sized smart biomaterials for extended application in precision medicine: We also developed chemical and informatics-based nanopore sequencing approach to decode RNA epigenetics (**Genomics 2022, 114: 110372**) and developed structural colored microfluidics as nano biosensors (**Nat.commun.2022,13,2282**). We also decoded telomere length and dynamics in cancer cells and harnessed artificial intelligence for medical image analysis (**J. Am. Chem. Soc. 2020, 142,17356**).

５．主な発表論文等

〔雑誌論文〕　計13件（うち査読付論文　12件／うち国際共著　7件／うちオープンアクセス　6件）

１．著者名 Qin Detao、Gibbons Andrew H.、Ito Masateru M.、Parimalam Sangamithirai Subramanian、Jiang Handong、Enis Karahan H.、Ghalei Behnam、Yamaguchi Daisuke、Pandian Ganesh N.、Sivaniah Easan	４．巻 13
２．論文標題 Structural colour enhanced microfluidics	５．発行年 2022年
３．雑誌名 Nature Communications	６．最初と最後の頁 2281
掲載論文のDOI（デジタルオブジェクト識別子） 10.1038/s41467-022-29956-4	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 －

１．著者名 Ramasamy Soundhar、Mishra Shubham、Sharma Surbhi、Parimalam Sangamithirai Subramanian、Vaijayanthi Thangavel、Fujita Yoto、Kovi Basavaraj、Sugiyama Hiroshi、Pandian Ganesh N.	４．巻 114
２．論文標題 An informatics approach to distinguish RNA modifications in nanopore direct RNA sequencing	５．発行年 2022年
３．雑誌名 Genomics	６．最初と最後の頁 110372～110372
掲載論文のDOI（デジタルオブジェクト識別子） 10.1016/j.ygeno.2022.110372	査読の有無 有
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１．著者名 Sahayasheela Vinodh J.、Yu Zutao、Hirose Yuki、Pandian Ganesh N.、Bando Toshikazu、Sugiyama Hiroshi	４．巻 95
２．論文標題 Inhibition of GLI-Mediated Transcription by Cyclic Pyrrole-Imidazole Polyamide in Cancer Stem Cells	５．発行年 2022年
３．雑誌名 Bulletin of the Chemical Society of Japan	６．最初と最後の頁 693～699
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１．著者名 Malinee Madhu、Pandian Ganesh Namasivayam、Sugiyama Hiroshi	４．巻 29
２．論文標題 Targeted epigenetic induction of mitochondrial biogenesis enhances antitumor immunity in mouse model	５．発行年 2022年
３．雑誌名 Cell Chemical Biology	６．最初と最後の頁 463～475.e6
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1．著者名 Hidaka Takuya、Hashiya Kaori、Bando Toshikazu、Pandian Ganesh N.、Sugiyama Hiroshi	4．巻 29
2．論文標題 Targeted elimination of mutated mitochondrial DNA by a multi-functional conjugate capable of sequence-specific adenine alkylation	5．発行年 2022年
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3．雑誌名 SSRN Electronic Journal	6．最初と最後の頁 -
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2．論文標題 Designing Biomimicking Synthetic Transcription Factors for Therapeutic Gene Modulation	5．発行年 2021年
3．雑誌名 Cell-Inspired Materials and Engineering. Fundamental Biomedical Technologies. Springer, Cham.	6．最初と最後の頁 135～161
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1．著者名 Tsubono Yutaro、Kawamoto Yusuke、Hidaka Takuya、Pandian Ganesh N.、Hashiya Kaori、Bando Toshikazu、Sugiyama Hiroshi	4．巻 142
2．論文標題 A Near-Infrared Fluorogenic Pyrrole Imidazole Polyamide Probe for Live-Cell Imaging of Telomeres	5．発行年 2020年
3．雑誌名 Journal of the American Chemical Society	6．最初と最後の頁 17356～17363
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1．著者名 Lee Jin‐A、An Jieun、Taniguchi Junichi、Kashiwazaki Gengo、Pandian Ganesh N.、Parveen Nazia、Kang Tong Mook、Sugiyama Hiroshi、De Debojyoti、Kim Kyeong Kyu	4．巻 236
2．論文標題 Targeted epigenetic modulation using a DNA‐based histone deacetylase inhibitor enhances cardiomyogenesis in mouse embryonic stem cells	5．発行年 2020年
3．雑誌名 Journal of Cellular Physiology	6．最初と最後の頁 3946～3962
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2．論文標題 Enhanced nuclear accumulation of pyrrole imidazole polyamides by incorporation of the tri-arginine vector	5．発行年 2020年
3．雑誌名 Chemical Communications	6．最初と最後の頁 12371～12374
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2．論文標題 A synthetic transcription factor pair mimic for precise recruitment of an epigenetic modifier to the targeted DNA locus	5．発行年 2020年
3．雑誌名 Chemical Communications	6．最初と最後の頁 2296～2299
掲載論文のDOI（デジタルオブジェクト識別子） 10.1039/C9CC09608F	査読の有無 有
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1．著者名 Malinee Madhu、Kumar Alok、Hidaka Takuya、Horie Masanobu、Hasegawa Kouichi、Pandian Ganesh N.、Sugiyama Hiroshi	4．巻 28
2．論文標題 Targeted suppression of metastasis regulatory transcription factor SOX2 in various cancer cell lines using a sequence-specific designer pyrrole?imidazole polyamide	5．発行年 2020年
3．雑誌名 Bioorganic & Medicinal Chemistry	6．最初と最後の頁 115248～115248
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1．発表者名 NAMASIVAYAM Ganesh Pandian
2．発表標題 Programmable synthetic gene switches for mitochondrial gene modulation
3．学会等名 World Mitochondria Society Congress- Targeting Mitochondria 2021（招待講演）（国際学会）
4．発表年 2021年～2022年

1．発表者名 NAMASIVAYAM Ganesh Pandian
2．発表標題 Big data for Precision Medicine
3．学会等名 UK-Japan Young Scientist Workshop（招待講演）（国際学会）
4．発表年 2021年～2022年

1．発表者名 NAMASIVAYAM Ganesh Pandian
2．発表標題 DNA-based genetic switches: Impact on our health
3．学会等名 Department of Biotechnology-India - National DNA day（招待講演）
4．発表年 2021年～2022年

１．発表者名
NAMASIVAYAM Ganesh Pandian

２．発表標題
Smart biomaterials for precision medicine

３．学会等名
SMART BIOMATERIALS: From Diagnostics to Therapeutics（招待講演）

４．発表年
2021年～2022年

１．発表者名
NAMASIVAYAM Ganesh Pandian

２．発表標題
Genetic switches for precision medicine

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〔図書〕　計0件

〔産業財産権〕

〔その他〕
PD-1阻害剤によるがん免疫治療法の効果を高めるミトコンドリア活性化剤 https://www.icems.kyoto-u.ac.jp/news/4468/ ミトコンドリアの変異DNAを減らす化合物の開発 https://www.icems.kyoto-u.ac.jp/news/4421/
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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
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７．科研費を使用して開催した国際研究集会

〔国際研究集会〕　計0件

８．本研究に関連して実施した国際共同研究の実施状況

共同研究相手国	相手方研究機関			
米国	Rutgers University			
スイス	AO Research Institute	University of Zurich		
インド	Indian Institute of Technology - Roorkee			
マレーシア	University of Cyberjaya			