National Cancer Center, Japan

Center for Promotion of Translational Research (CPOT)

CPOT Research Seeds Catalogue

国立がん研究センター 橋渡し研究推進センター
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国立がん研究センター 橋渡し研究推進センター
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Investigation of non-clinical study items for an antigen-presenting cell platform for cancer therapy

Yasushi UEMURA, DDS. Ph.D.
Lab Head, Cancer Immunotherapy/EPOC/NCC

CPOT #21-PreF-02

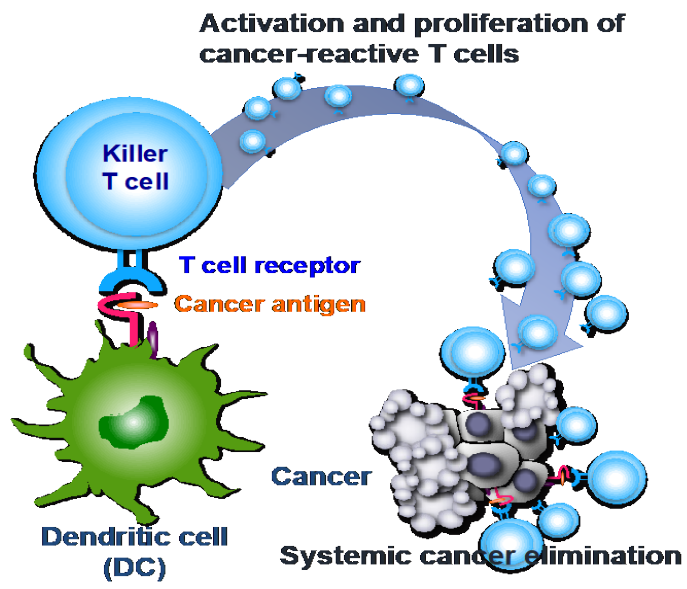
Summary

Key Words: #iPS cells, #Immune response, #Immune checkpoint inhibitor resistance, #Dendritic cells, #Universal-type cell preparation, #Standardization, #Mass-production, #cost reduction

【Background】

Dendritic cells (DCs) are the antigen-presenting cells with the most potent T-cell stimulating activity.

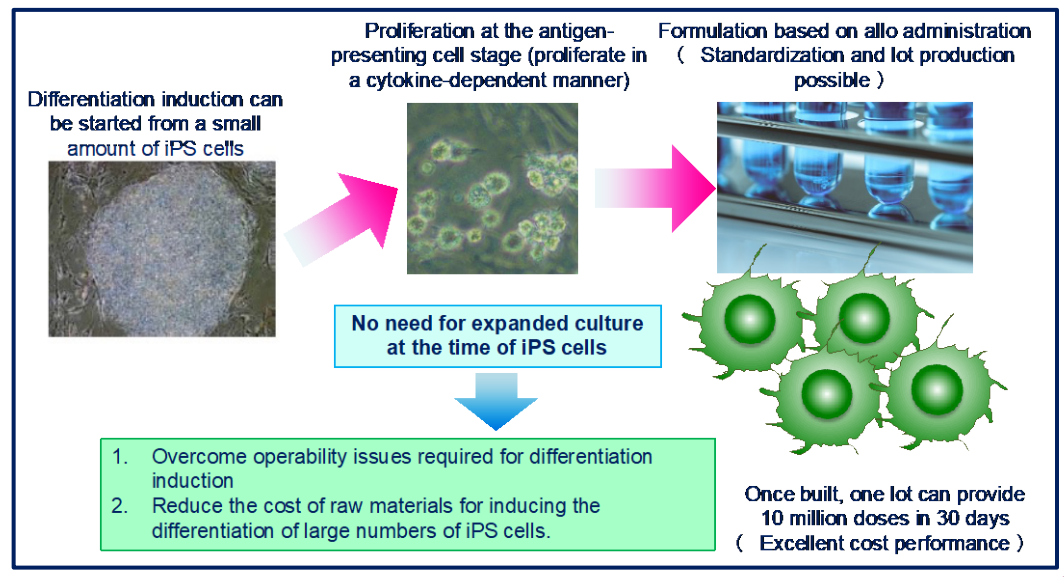
Cellular therapy, in which DCs are loaded with cancer antigens and administered, is considered one of the most effective treatments. However, due to the inability to obtain a sufficient amount of DC progenitor cells from patient and unstable quality, stable efficacy has not yet been achieved, and the development of new cell preparations to replace autologous DC is expected.



【Research & Development】

We have constructed DC-like antigen-presenting cells that can be grown in a cytokine-dependent manner from allogenic iPS cells and that exhibit better clinical efficacy than autologous DCs. This system has the following advantages.

1. non-self-directed iPS cells (Quality Stability)
2. Versatility through universalization (Destruction of unnecessary HLA)
3. Enables mass production (can be multiplied in the final product))
4. Lower cost (lot production possible)
5. Improved efficacy through genetic modification



Innovation

1. By introducing three genes into myeloid lineage cells differentiated from iPS cells, we constructed DC-like antigen-presenting cells whose proliferation can be controlled by cytokines.
2. The ability to provide large quantities of functionally stable DC-like antigen-presenting cells without the need for complex manipulations such as DC differentiation and maturation processes.
3. The HLA gene, which is not involved in cancer antigen presentation, is disrupted by genome editing, making it highly versatile.

Expected Utility

- Widely applicable to the treatment of cancers for which chimeric antigen receptor (CAR)-T cell therapy is not indicated.
- Can be applied to the treatment of cancer resistant to immune checkpoint inhibitors.
- It is possible to formulate antigen-presenting cells loaded with target cancer antigens proposed by pharmaceutical companies.

IP Information

Application numbers: 2020-084821 (2020.5.13), 2020-149486 (2020.9.4), PCT/JP2021/18121 (2021.5.13), 2022-087065 (2022.5.27)

Partnering

- Pharmaceuticals

Reference

- Zhang R, et al. (2015) Cancer Immunol Res 3(6): 668-677.
- Tsuchiya N, et al. (2019) Cell Rep 29(1): 162-175.
- Mashima H, et al. (2020) Oncoimmunol 9(1): 1814620.
- Mashima H, et al. (2021) Mol Ther Methods Clin Dev 21: 171-179
- Zhang R, et al. (2021) J Immunol Regen Med 12: 100042.

National Cancer Center (NCC) Japan / CPOT seeds

Drug discovery of chromosomal instability inducers to convert "Cold to Hot tumor"

Akihiro OHASHI, Ph.D.
Lab Head, Translational Genomics/EPOC/NCC

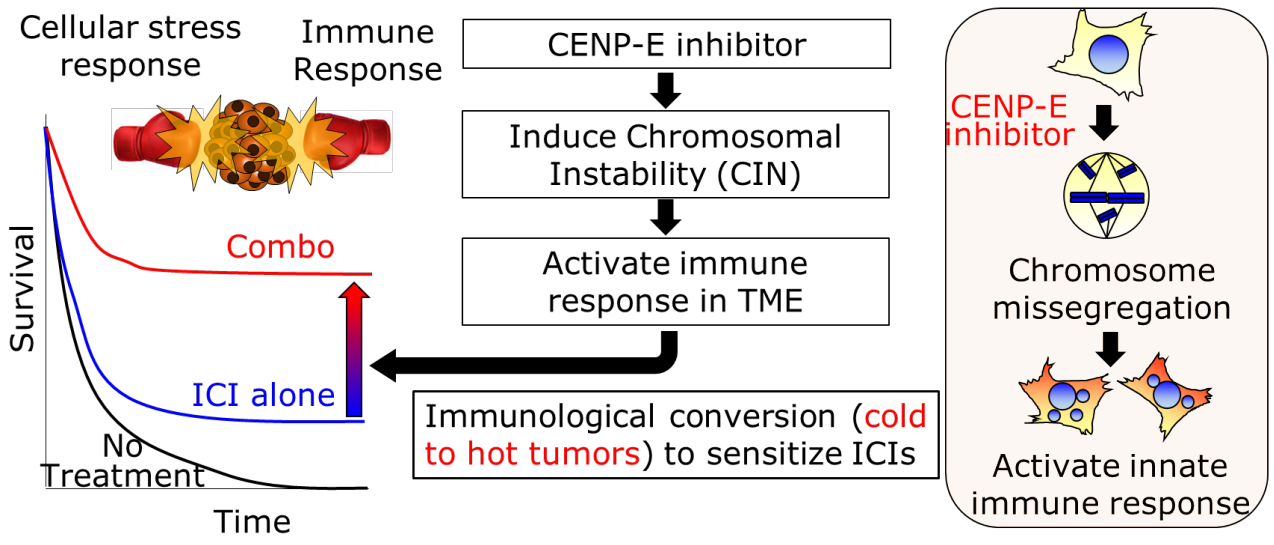
CPOT #21-A-02

Summary

Key Words: #small molecules, #immune reaction, #macnine learning, #drug screening

【Objective】

Develop novel CENP-E inhibitors to enhance antitumor activity of immune checkpoint inhibitors (ICIs).



【Research organization】

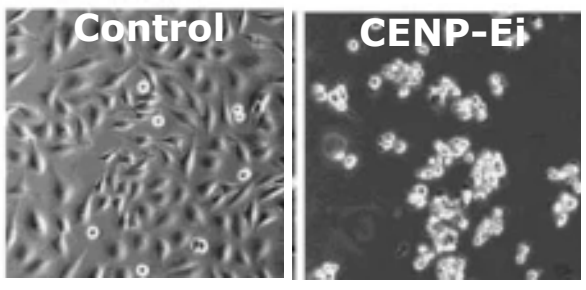
Integration of drug discovery and AI screening
-Research collaboration between NCC-EPOC and FNL-

Preclinical PoC
Pharmacological studies

AI-based screening
In silico drug design

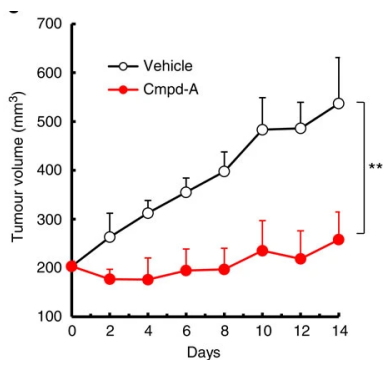
【Examples of pharmacological studies】

***In vitro* growth assay**

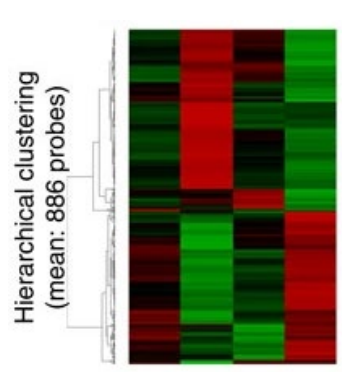


Ohashi A., et al. Nature Commun. (2015)

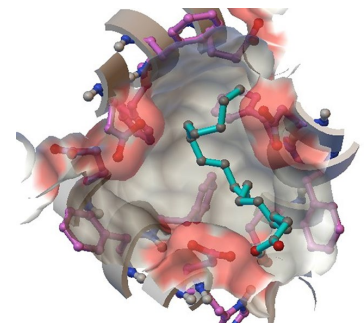
***In vivo* efficacy**



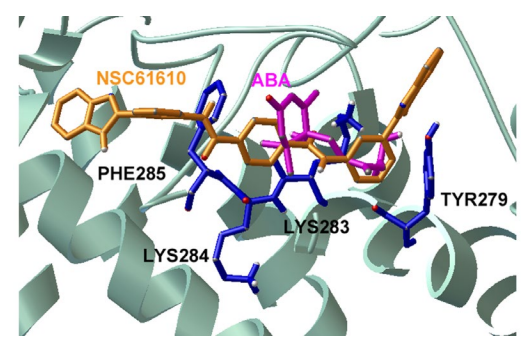
Gene expression



【Examples of *in silico* docking models】



Lu P., et al. Plos ONE (2015)



Lu P., et al. Plos ONE (2012)

Innovation

In collaboration with Frederick National Laboratory for Cancer Research (FNL), we are developing novel centromere-associated protein-E (CENP-E) inhibitors utilizing AI-based *in silico* drug design technologies. We are also conducting mechanistic analyses with reference compounds to determine the novel aspects of CENP-E inhibitors on immune oncology, especially focusing on the combinational effects of CENP-E inhibitors with ICIs. The novel CENP-E inhibitors have potential to be the first-in-class drug and are expected to be differentiated form other class of therapeutics (e.g., STING agonists or other chemotherapeutics) in selectivity, efficacy, and toxicity.

Expected Utility

While ICIs have achieved great advances in cancer therapies for immunologically activated tumors (hot tumors) across multiple cancer types, a large proportion of cancers as non-inflamed tumors (cold tumors) are still refractory or poorly responsive. Here, we would like to propose that combination therapies with CENP-E inhibitors would be a promising strategy to clinically improve ICI therapies.

IP Information

Ohashi A. : Therapeutic agent for cancer, WO 2012/008507

Partnering

- Pharmaceuticals
- Biotech/Drug Discovery Service
- Venture capitals

Reference

- Ohashi A, et al. (2015) Nature Commun. 6(1): 1-16.
- Ohashi A, et al. (2015) Plos ONE 10(12): e0155675
- Ohashi A, et al. (2016) Oncotarget 9(26): 18480-93
- Hirayama T, et al. (2015) J. Med. Chem 58(20):8036-53
- Hirayama T, et al. (2016) Bio Med Chem Lett 26(17):4294-4300

Identification of novel receptors for desacyl ghrelin that improves cardiotoxicity induced by anticancer drugs, and development of drugs to prevent and cure cardiotoxicity

CPOT #21-A-06

Yasuhito UEZONO, Ph.D.
Project Leader, Supportive Care/EPOC/NCC

Summary

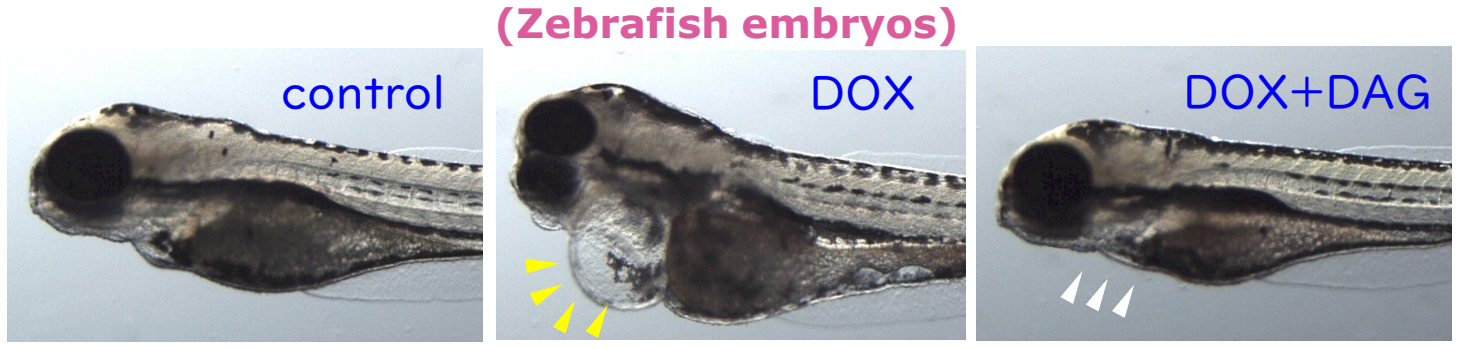
Key Words: #Small molecule, #Biomarker, #Signal analysis, #Drug development, #Supportive care

Even molecular-targeted drug have been put into practical use, conventional chemotherapy in combination with several anti-cancer drugs is still recognized as a standard treatment for many neoplasm. Doxorubicin (DOX) is an anthracycline anti-cancer drug as the basis of chemotherapy. DOX is effective to a wide range malignant tumors such as malignant lymphoma, lung cancer, breast cancer, various gastrointestinal cancers, however, it causes irreversible drug-induced cardiac dysfunction.

Ghrelin is an orexigenic peptide hormone identified by Kojima and Kangawa in 1999 (Kojima M, 1999). **We found that DesAcyl Ghrelin (DAG,** deacylated form of ghrelin) inhibited the cardiotoxicity by DOX to the H9C2 rat cardiomyocytes, zebrafish embryos (see below) and mouse DOX-induced cardiac dysfunction. DAG has been thought to act through unidentified receptors (Baldanzi G, 2002; Yanagi, 2018).

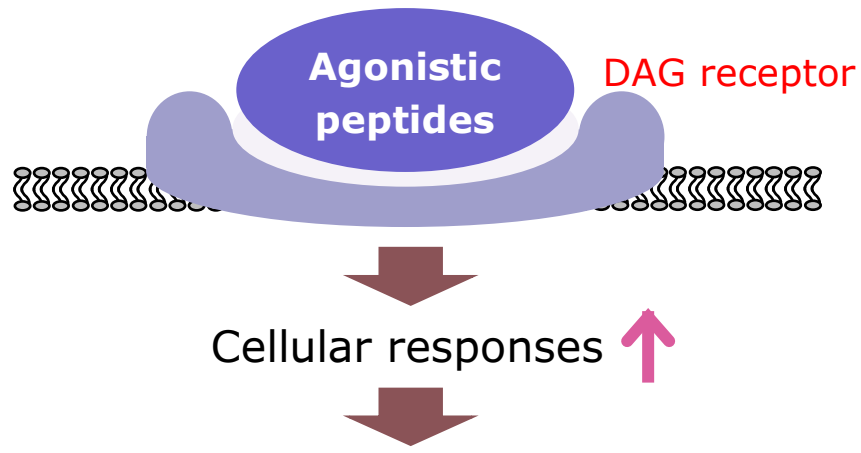
We have identified a novel receptor for DAG and found approximately 40 unique peptides with a high affinity to the DAG receptor which might be able to act as potential agonists. We are developing novel pharmaceutical peptides to prevent DOX-induced cardiac dysfunction.

DAG suppressed DOX-induced expansion of pericardium (Zebrafish embryos)



Emergence of DOX-induced cardiotoxicity

Suppression of cardiotoxicity by DAG



Suppression of DOX-induced cardiac dysfunction

Innovation

Many approaches to reduce DOX-induced cardiac dysfunction have been developed like by DDS improvement.

Beside these approaches, we'd like to commit to optimize DOX treatment with another innovative approaches.

We have already completed the in vitro screening with 6 million different peptide sequences to identify candidates of high-affinity peptide to the DAG receptor. We are currently evaluating their suppressive effects on doxorubicin-induced cardiac dysfunction in animal models.

Expected Utility

We will innovate and develop a novel therapy supporting patients to receive full-dose anti-cancer chemotherapy safely without DOX-induced cardiac dysfunction by using our novel peptides which bind to a novel DAG receptor.

We hope to make this approach utilized for improving any cardiac dysfunction induced by other than DOX as well, by identifying signal pathways of DAG receptor.

IP Information

N/A

Partnering

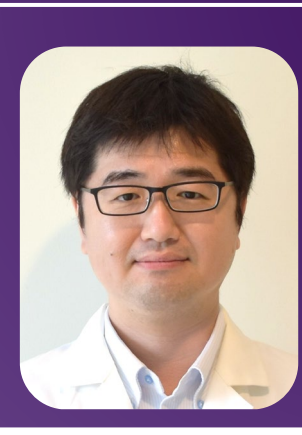
- Pharmaceuticals
- Chemical/Fibers
- Biotech/Drug Discovery Service
- Venture capitals

Reference

- Kojima M, et al. (1999) Nature 402: 656-660.
- Baldanzi G, et al. (2002) J Cell Biol 159: 1029-1037.
- Yanagi S, et al. (2018) Cell Metab 27: 786-804.

National Cancer Center (NCC) Japan / CPOT seeds

Development of homogenous radioactive antibodies using Fc glycan engineering technology



Hiroki TAKASHIMA, M.D., Ph.D.
Lab Head, Developmental Therapeutics/EPOC/NCC

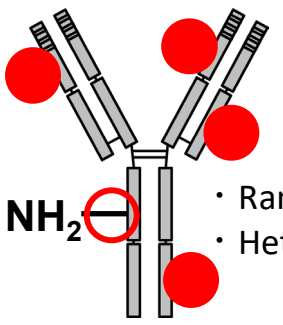
CPOT #21-A-13

Summary

Key Words: #Antibody engineering/labeling, #Imaging

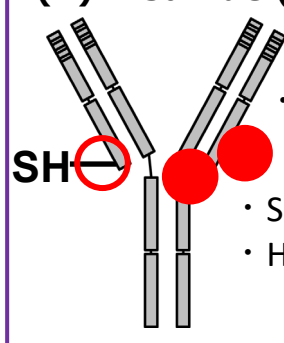
Conventional modification

(A) Lysine (Lys) conjugation



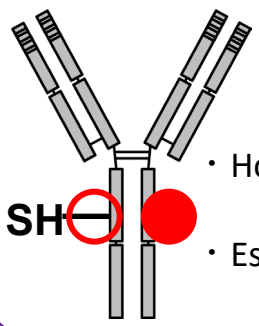
- Random modification
- Heterogeneous immunoconjugate

(B) Disulfide (SS) bond cleavage



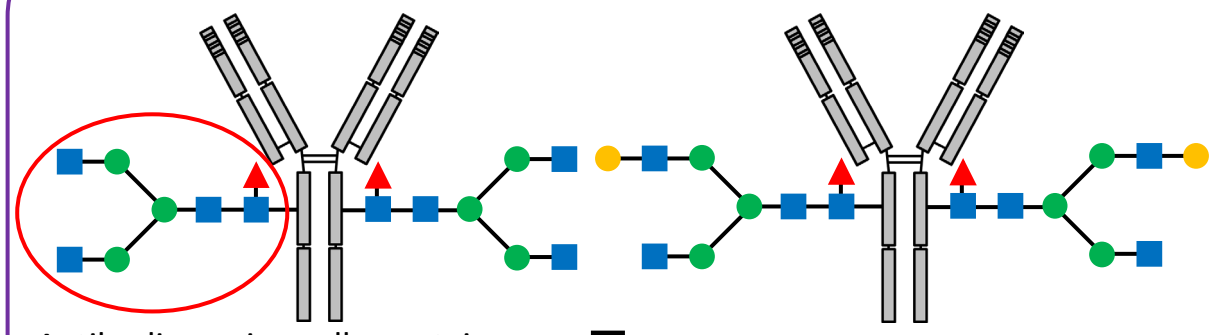
- Attachment to thiol groups
- SS bond cleavage
- Heterogeneous immunoconjugate

(C) Amino acid substitution



- Site-specific modification
- Homogeneous immunoconjugate
- Essential to establish engineered mAbs

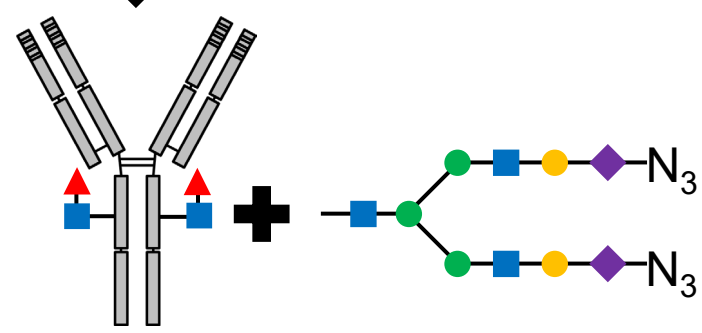
Modification via Fc glycan engineering



Antibodies universally contain Fc glycans

→ **High versatility**

1: Glycan cleavage

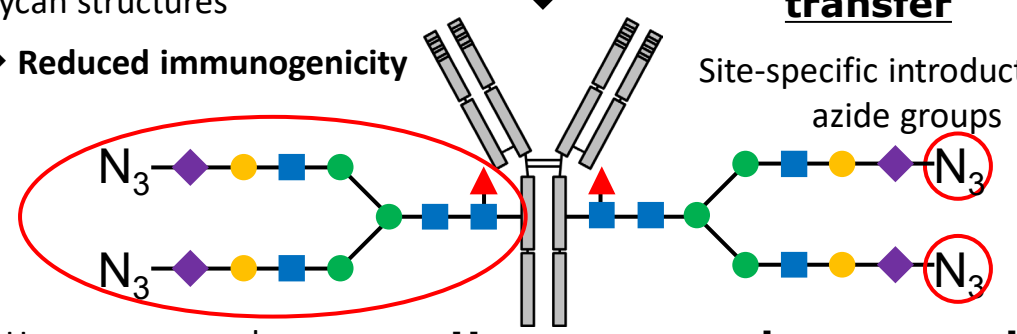


Removal of nonhuman type glycan structures

→ **Reduced immunogenicity**

2: Azide-carrying glycan transfer

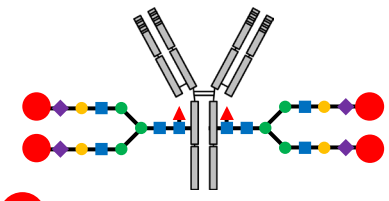
Site-specific introduction of azide groups



Homogeneous glycan

Homogeneous immunoconjugate

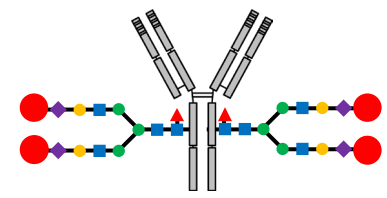
ADC



: Anticancer drug

- Controlled DAR
- Long circulation time

Radioactive mAb



: Chelating agent

- Controlled modification site
- Controlled labeling efficiency
- Optimized biodistribution

Innovation

Antibody modification	Structure	Site selectivity	SS bond	Versatility
Lys conjugation (A)	Heterogenous	-	Non-cleavage	++ (not available to mAbs with Lys in CDR)
SS bond cleavage (B)	Heterogenous	+	Cleavage	+++ (universally available to mAbs)
Amino acid substitution (C)	Homogenous	+++ (Specific)	Non-cleavage	+ (essential to establish engineered mAbs)
Fc glycan engineering	Homogenous	+++ (Specific)	Non-cleavage	+++ (universally available to mAbs)

Expected Utility

1. Focusing on the development of homogenous radioactive mAbs using Fc glycan engineering technology, then our antibody modification platform can contribute to improving reproducibility in RI labeling.
2. The modification platform can be used for preparing other armed antibodies as well as radioactive mAbs, and universally available to pre-established mAbs.

IP Information

N/A

Partnering

- ➢ Pharmaceuticals
- ➢ Biotech/Drug Discovery Service
- ➢ CMO/CDMO/CRO/SMO
- ➢ Medical/Diagnosis/Research Devices

Reference

- Manabe S, et al. (2019) Bioconjug Chem 30: 1343-1355.
- Takashima H, et al. (2021) Cancer Sci 112:1975-1986.

National Cancer Center (NCC) Japan / CPOT seeds

Non-clinical seeds targeting tumor suppressors

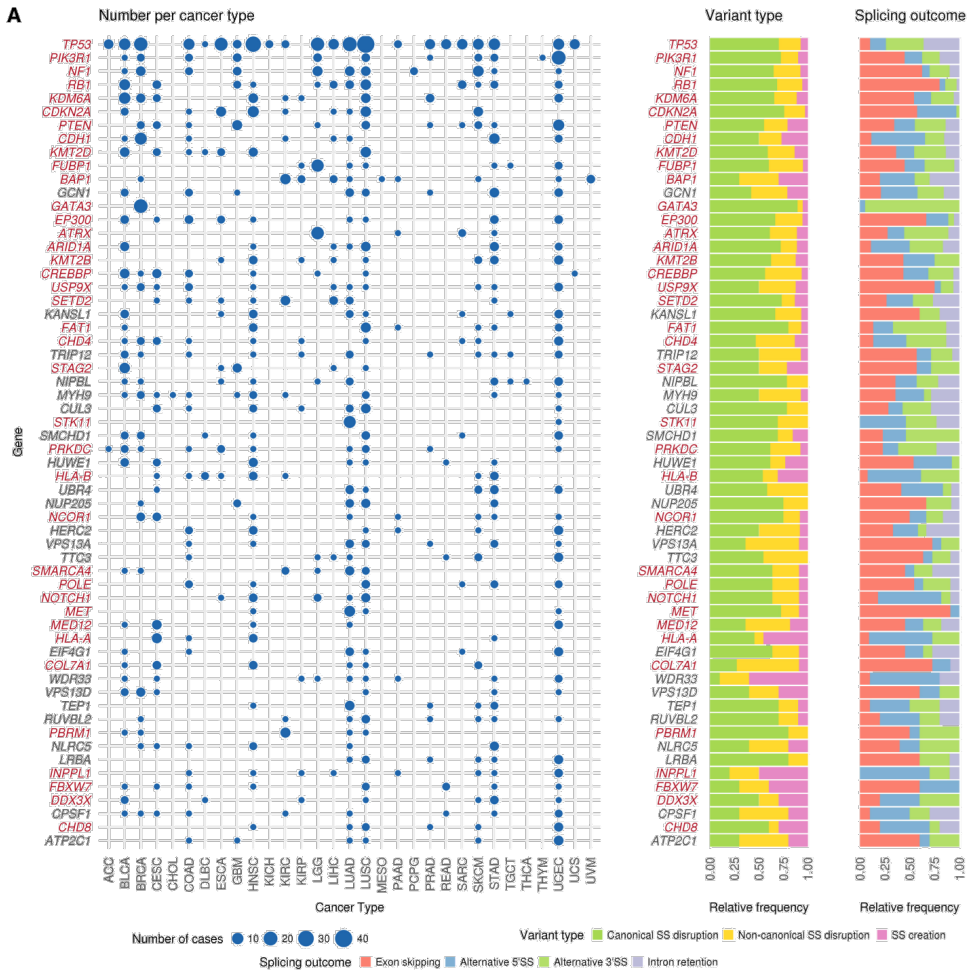
Akihide YOSHIMI, M.D., Ph.D.
Division Chief,
Cancer RNA Research/Research Institute/NCC

CPOT #21-A-22

Summary

Key Words: #Cancer, #ASO, #Nucleid acid therapeutics, #RNA, #Splicing, #Gene mutation, #CRISPR/Cas9

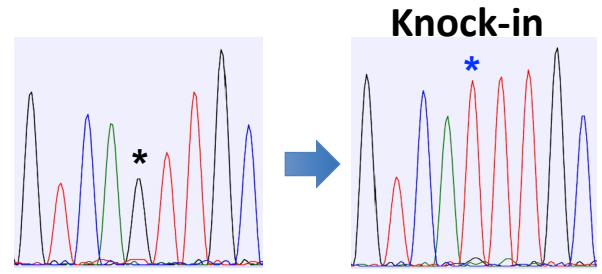
(1) Detection of SAV (Splicing-associated variant) by analyzing >230,000 NGS data



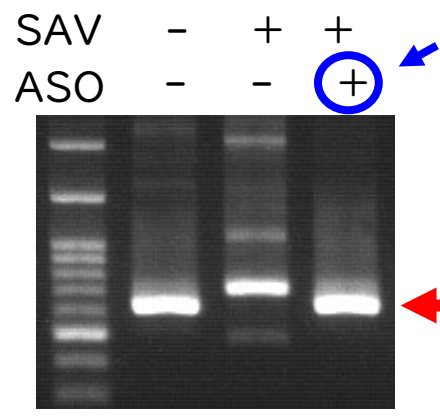
Shiraishi Y, et al. *Nat Commun* accepted.
Shiraishi Y, et al. *Genome Res* 2018.

Extract targetable SAVs by ASO (Antisense Oligonucleotide)

(2) Knock-in SAVs using the CRISPR/Cas9 gene editing and Designing ASO targeting aberrant splicing



Knock-in of a SAV



Aberrant splicing by SAV and Correction of aberrant splicing by designed ASO

Successful correction of Aberrant splicing

Innovation

- Identification of targetable genetic mutations across cancers based on analysis of >230,000 NGS data.
- Already confirmed favorable effects of our ASOs.
- Efficient In-house CRISPR-Knockin technology (>90% success rate).
- Abundant achievement in this field (see the References below): Pan-cancer splicing analysis, Development of RNA therapeutics, Novel PDX models, preclinical trial, Access to samples from cancer patients (>460,000) etc.

Expected Utility

"Target the Untargetable, Treat the Untreatable"

✓ We aim to develop RNA therapeutics (ASOs) targeting ~3.0% of cancer patients.

SAV frequency of Gene A we've interested.

Partnering

- Pharmaceuticals
- Biotech/Drug Discovery Service
- Venture capitals

IP Information

Lab Twitter: @YoshimiLab

Lab Website →

Reference

- Yoshimi A, et al. (2019) ***Nature*** 574: 273-277.
- De Munck S, et al. (2021) ***Nature*** 600:143-147.
- Liu Z, Yoshimi A, et al. (2020) ***Cancer Discov.*** 10: 806-821.
- Seiler M, Yoshimi A, et al. (2018) ***Nat Med.*** 24: 497-504.
- Yoshimi A, et al. (2017) ***Blood*** 130:397-407.

National Cancer Center (NCC) Japan / CPOT seeds

Safe genome editing therapy for HPV-associated lesions by all-in-one adenovirus vectors expressing multicopy guide RNAs and Cas9 nickase

CPOT #21-A-27

Tohru KIYONO, M.D.,D.M.Sc.
Project Lead, Prevention of HPV-related cancer/EPOC/NCC

Summary

Key Words: #CRISPR/Cas9, #Cancer prevention, #HPV, #Cancer therapy, #Adenovirus vector

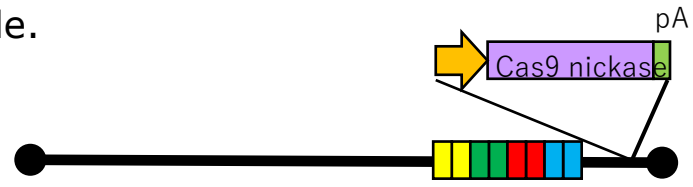
Aim:

To develop non-invasive therapies to cure HPV-associated cancers

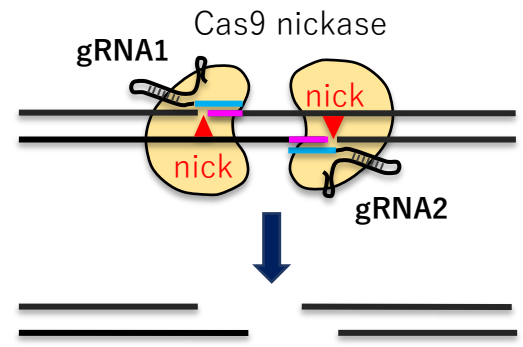
Background:

- Oncogenic HPV infection is responsible for almost 5% of all cancer worldwide.
- About 500,000 women were diagnosed with cervical cancer and about 300,000 women died from the disease (In Japan, over 10,000 women are diagnosed and about 2,700 women die from the disease).
- About 100,000 adults (40% are HPV positive) are diagnosed with oropharyngeal cancer every year with 50,000 estimated deaths（In Japan, 2,900 estimated cases and 1,300 estimated deaths).
- The current standard treatments of these cancers can often cause significant reduction of QOL such as loss of or reduced fertility and long lasting dyslalia and/or dysphagia.
- Therefore, it is necessary to develop non-invasive therapies which can maintain QOL after the treatment.
- Since proliferation of HPV-associated cancer cells depend on the expression of HPV oncogenes, disruption of the HPV oncogenes by genome editing could cure these cancers.
- Although WHO aims 40% reduction of cervical cancer incidence by 2050, reduction of cervical cancer cases are estimated to be only 20% even in the best scenario (Lancet Oncol 2019; 20: 394–407).

Adenovirus vector for the therapy



Eight gRNA expression units



Double-stranded break by double nicking

Innovation

- As most HPV-associated cancers are caused by either HPV16 or HPV18, the same therapeutic vectors can be applied to almost all the patients worldwide.
- Double nicking with Cas9 nickase and multiple gRNAs can enhance specificity with negligible off-target effects.
- We have succeeded to develop an all-in-one adenovirus vector expressing Cas9 nickase and 8 gRNAs.
- As the all-in-one vector can express Cas9 nickase and 8 gRNAs in the same cells, it can completely disrupt the HPV oncogenes E6 and E7.

Expected Utility

A major obstacle for clinical application of CRISPR/Cas9 gene editing technology has been its off-target effects. A double-nicking technology can reduce off-target effects to a negligible level. This technology-based adenovirus vector with 8 gRNAs can completely disrupt the HPV oncogenes. Imagine that the injection of candidate drug can cure the cancers which can be treated only by surgery now.

IP Information

PCT/JP2019/037255 、 priority to JP2019-121668, JP2018-17927 application filed by Institute of Microbial Chemistry、Sept 24, 2019, Novel virus vector and methods for producing and using same （Invector Tomoko Nakanishi, Izumu Saito）; Worldwide application WO EP US JP

Partnering

- Pharmaceuticals
- Medical institute
- Biotech/Drug Discovery Service

Reference

- Kato Y, et al. (2021) Int J Mol Sci. 22(19)10570.
- Nakanishi T, et al. (2021) Sci Rep.11(1)3961.
- Nakanishi T, et al. (2019) J. Gene Med. 21(11): e3115.

National Cancer Center (NCC) Japan / CPOT seeds

Development of technology for detection and evaluation of mutation rates and sites by cellular endogenous base editing

Masayuki SAKURAI, Ph.D.
Associate Professor, Research Institute for Biomedical Sciences,
Tokyo University of Science

CPOT #21-A-38

Summary

Key Words: #Small molecule, #Diagnostics/Lab test, #DNA, #RNA #A-to-I DNA editing

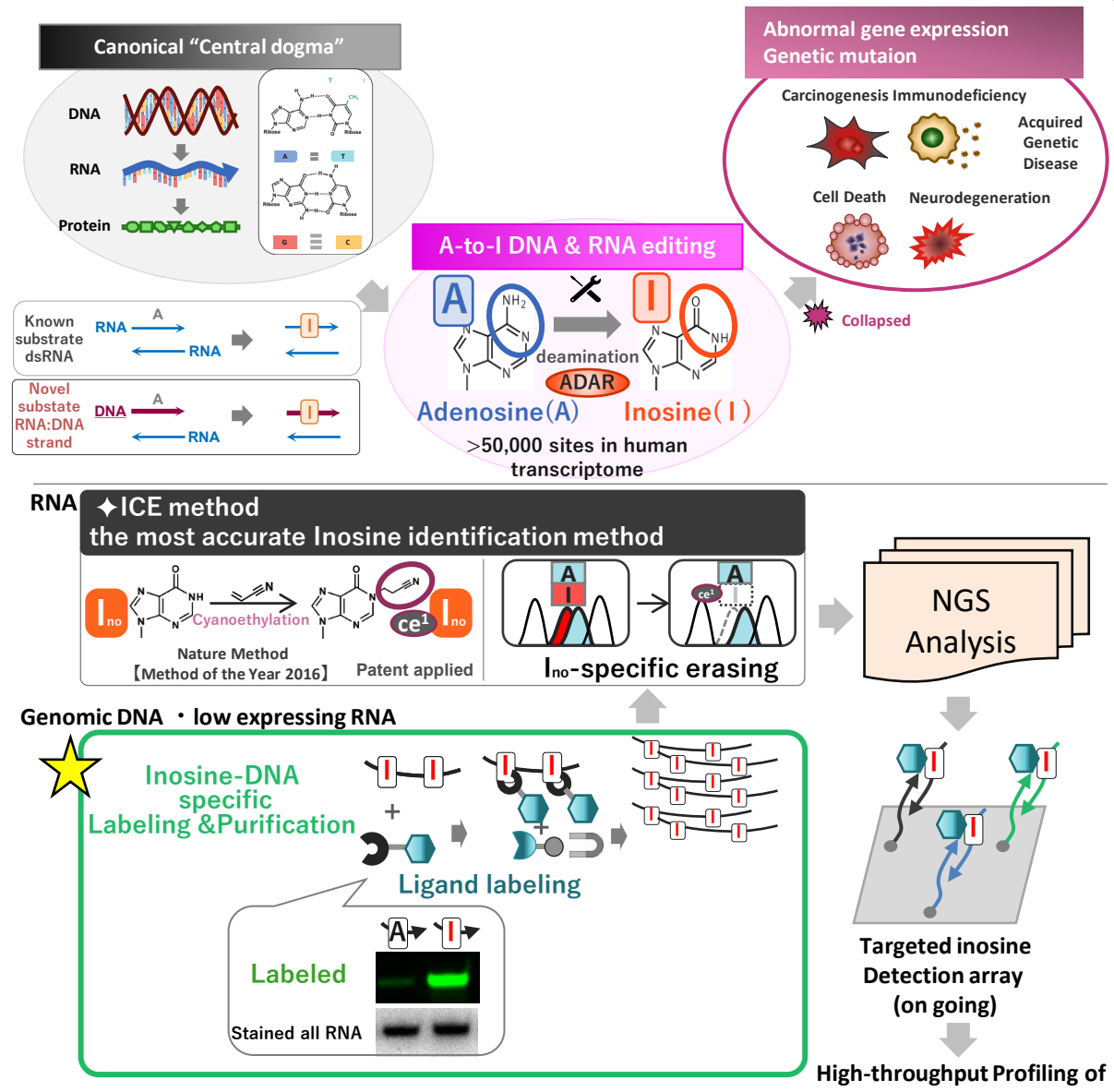
<Summary>

We have developed a new technology to identify inosine bases in DNA utilizing inosine-specific labeling & purification. The technology brings us new finding of A-to-I editing sites in DNA and RNA relating to cancer, genetic disease, and individual differences. (see the figure)

<Background>

Our cells have mechanism modifying the base structure of DNA and RNA. In this study, we focused on the inosine (I) produced by the adenosine (A) deamination by the ADAR enzyme. It is called as A-to-I editing. In human brain transcriptomes, more than 50,000 sites of A-to-I RNA editing have been reported. Since A-to-I editing has a similar effect of A-to-G alteration, it modulates DNA/RNA information and structure, resulting in various biological phenomena. The ADAR had been thought to edit only double-stranded RNAs. However, recently we found that even DNA:RNA hybrid double strand can be a substrate, and even A in DNA is edited to I. The fact indicates our cell have an innate genome DNA editing system regulated by guide RNA. We assume that certain DNA mutations causing carcinogenesis and genetic disease would be because of abnormal A-to-I DNA editing.

Thus, we here developed a new technology with high sensitivity and accuracy to systemically identify overlooked inosines in DNA to clarify those functions.



Innovation

The only existing technology to discriminate and demonstrate I and G for A-to-I editing sites is the ICE method described above. Especially in DNA editing, the number of molecules per cell is tiny, so high sensitivity is required. Therefore, we developed inosine-specific chemical labeling and enrichment/purification(patent application in preparation), followed by next-generation sequencing analysis. The technology made it possible to analyze inosines in low expressed mRNA, lincRNA, microRNA, etc., which are usually undetectable because of contamination by other non-edited RNAs. Furthermore, once any A-to-I DNA/RNA editing site is proven, it is possible to efficiently profile the presence/absence and percentage of editing by microarray after inosine-specific fluorescent labeling or enrichment and purification.

Expected Utility

Product ・Detection kit, Editing profiling array.

Target ・Cancer, Genetic Mutations.
・Diseases caused by abnormal A-to-I editing in RNA/DNA.
・DNA/RNA editing determining individual differences.

Usage: Profiling of A-to-I editing in DNA, mRNA, lincRNA, microRNA using a slight amount tissue/cell specimen, blood, urine, etc.

Early diagnosis for carcinogenesis and gene mutations.

IP Information

- Paten in JP: Applied 2005-229335 Opened 2008-259425
- Patent: WO2007018169A1(Aug 2006/8/7)
- Tested: Nat Chem Biol 2010, Genome Res.2014, on going
- Award: NATURE METHODS METHOD OF THE YEAR 2016

Partnering

- Pharmaceuticals
- Medical/Diagnosis/Research Devices

Reference

- Sakurai M, et al. (2021) Nat. Commun. 12:1654.
- Li X, et al. (2017) Nature Methods 14: 23-31.
- Sakurai M, et al. (2014) Genome Res. 24: 522-534.
- Sakurai M, et al. (2010) Nat. Chem. Biol. 6: 733-740.

Regenerative therapy for anal dysfunction using adipose tissue-derived stem cells

- multiple transplantation and scaffold tissue -

CPOT #22-S-04

Yuji NISHIZAWA M.D., Ph.D.
Colorectal Surgery Dept. & Quality Management/
East Hospital/NCC

Summary

Key Words: #Somatic stem cells, #Anal dysfunction, #Rectal cancer, #ASCs

【 Postoperative anal dysfunction in rectal cancer 】

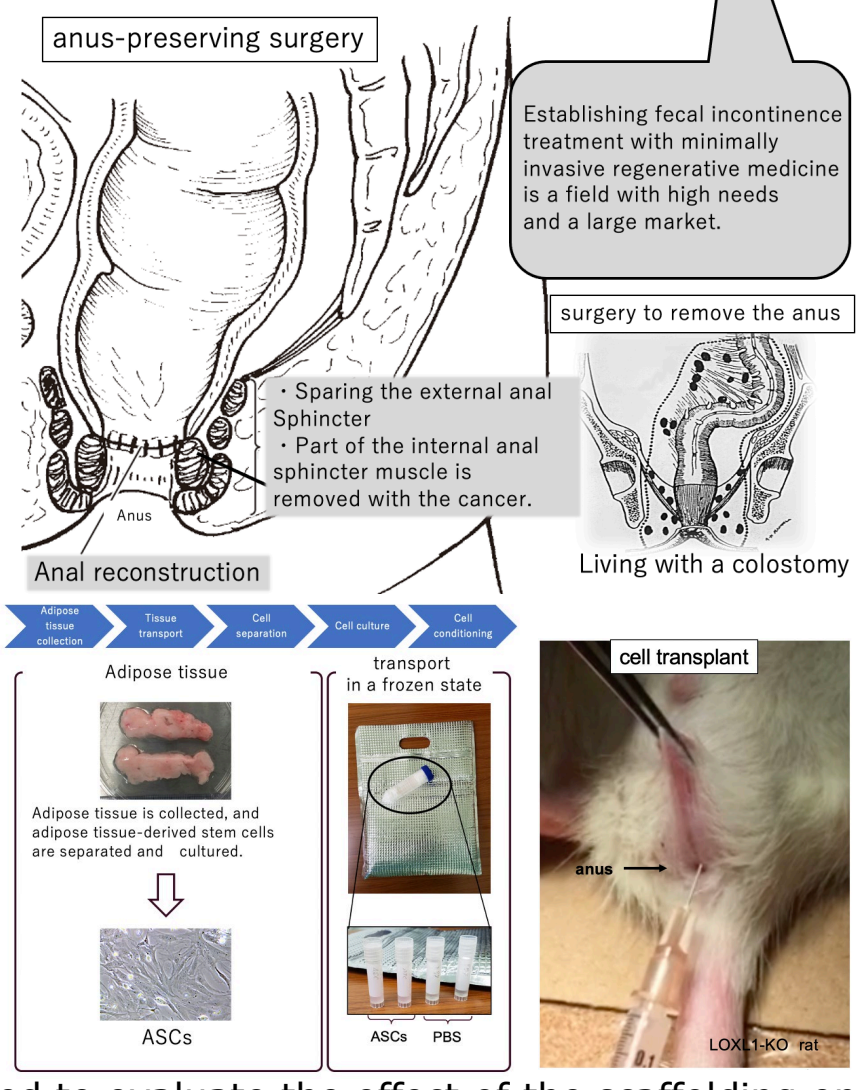
Colorectal cancer is the most prevalent disease. The 5-year survival rate for rectal cancer exceeds 70%. Anus-preserving surgery for rectal cancer has become popular, but the rate of postoperative anal dysfunction is as high as 80-90%, and patients are increasing year by year. There are potentially many patients with anal dysfunction, and the market for treatment of it is large. It is expected that minimally invasive regenerative medicine will be established as a treatment for fecal incontinence.

【Our research】

LOXL1-KO (Lysyl oxidase like-1 knockout) rats were used as a fecal incontinence model. ASCs established from inguinal adipose tissue were transplanted into the anus at the 3, 6, 9 and 12 o'clock positions. Using SDrats as the control group, the anal leak point pressure under electrical anal stimulation was significantly higher in the transplanted group than in the control group 4 weeks after transplantation. Local transplantation of ASCs was found to enhance the effect of anal function.

【 This study and development 】

A cultured ASCs group and an ASCs + adipose tissue group will be compared to evaluate the effect of the scaffolding on the anal function. In addition, by transplanting ASCs and ASCs + adipose tissue twice each, we will compare the effect of anal function between the single-transplantation group and the multiple-transplantation group. Based on the scaffold and the number of times of transplantation, we will establish a new highly effective treatment method.



Innovation

Regenerative medicine using cultured adipose stem cells, which can utilize a large number of adipose stem cells by collecting a small amount of autologous fat in a minimally invasive manner, is novel as a safe and highly effective treatment method. The aim is to research and develop more effective treatment methods using multiple transplantation, which are considered to be the great merits of treatments using cultured adipose stem cells, and adipose tissue as a scaffold. It will lead to the establishment of a treatment method that is superior in cost-effectiveness.

Expected Utility

In order to switch the cell source from non-cultured to cultured, establishing this POC will be an opportunity to build a new business model, and it may be a new regenerative medicine using ASCs. In particular, there is no established treatment for this fecal incontinence treatment. Clinical derivation as a therapeutic package including biofeedback is the key to practical application.

IP Information

- Patent application: No. 2019-199791
- Title of Invention: Probe for Electromyography, Packaged Probe, Connector for External Device for Probe, Biofeedback Device
- Applicant: National Cancer Center

Partnering

- Medical institute
- Biotech/Drug Discovery Service
- Medical/Diagnosis/Research Devices
- Venture capitals

Reference

- Nishizawa Y, et al. (2021) Colorectal Dis. 23:3196-3204.
- Nishizawa Y, et al. (2021) Ann Surg. 275:e636-e644.
- Kondo A, Nishizawa Y, et al. (2021) Colorectal Dis. 23:1745-1754
- Fecal Incontinence Clinical Guidelines (The Japan Society of Coloproctology)

Innovation of Supplements Inducing Genome Stability Maintenance for Cancer Prevention

CPOT # 22-S-05

Ken-ichi YOSHIOKA, Ph.D.
Lab Chief, Genome Stability Maintenance,
Research Institute/NCC

Summary

Key Words: #Cancer prevention, #Small molecule, #Genome stability maintenance, #Supplement

Objective

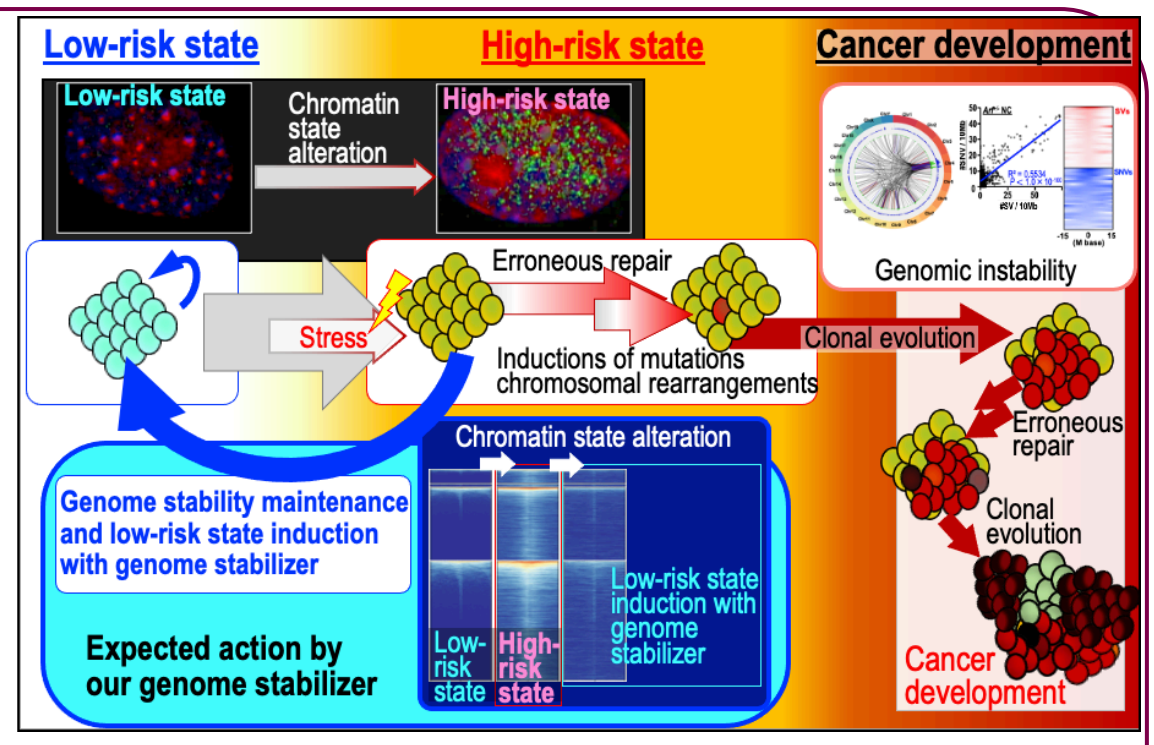
The overall aim of this project is innovation of a cancer prevention supplement (and/or drug) that inhibits clonal evolution with inducing the effect of genome stability maintenance. Given that most cancer is developed with genomic instability, majority must be the potential target of this cancer prevention strategy.

Background

Cancer development steps progress through multiple rounds of clonal evolution. We have recently shown that such clonal evolution can be induced with genomic instability, i.e., triggered by replication stress-associated DNA damages and the resulting erroneous repairs. In fact, the most cancers develop with genomic instability. This importantly suggests that most of those are theoretically preventable with genome stability maintenance.

Fundamentals and preparations

We have been studying mechanistic aspects of genomic instability, especially (1) induction pathways of chromosomal rearrangements and mutations and (2) chromatin state risking genome stability and that regulation. Based on those knowledge, we screened compounds that induce the effect to maintain genome stability and constructed a genome stabilizer. Currently, we are studying the cancer prevention effect by the genome stabilizer and the action mechanism.



Originality and Status of Similar Studies Worldwide

- There is still some debate about how cancer develops. The conventional view is that cancer is a consequence of biological “bad luck”, because mutations are randomly induced as replication errors. Therefore, the current worldwide recommendation is “regular medical checks” to assist early detection and thus avoid cancer-associated death.
- Our recent findings shed light on the possibility of cancer prevention. Strategy of cancer prevention through genome stability maintenance is completely original.

Innovation

It has been broadly recognized that cancer is a consequence of biological bad luck and hence unavoidable. However, our recent results suggested a possibility of cancer prevention through genome stability maintenance. Importantly, given that most cancers are developed with genomic instability, many of those must be the potential targets of cancer prevention through genome stability maintenance. In this project, we will challenge for the innovation of cancer prevention supplements (and/or drugs), namely genome stabilizer. To our knowledge, this is the first project that aims to enhance genome stability maintenance to prevent cancer.

Expected Utility

Many cancer patients die after several years of treatment and subsequent recurrence. Since cancer is a disease associated with aging, this cancer journey is a significant problem for the quality of life in elderly people, which is now a social problem due to social aging.

The future prospect of this project is the development of a novel cancer-prevention supplement (and/or drug). Given that most human cancers develop with genomic instability, many of those are likely the target of this cancer prevention strategy. In addition, since genome stability further contributes to the homeostasis, association of multiple health benefit effects are expected.

IP Information

N/A

Partnering

- Pharmaceuticals
- Biotech/Drug Discovery Service
- Food/Beverages

Reference

- Matsuno Y, et al. (2021) iScience 124: 102313.
- Yoshioka K, et al. (2021) Cancer Science 112: 515-522.
- Matsuno Y, et al. (2020) Scientific Rep. 110: 5388.
- Matsuno Y, et al. (2019) Nature Com. 110: 3925.
- Atsumi Y, et al. (2015) Cell Rep. 113: 2728-2740.

National Cancer Center (NCC) Japan / CPOT seeds

Development of an antibody to evaluate DNA replication stress for ATR inhibitor biomarker

Bunsyo SHIOTANI, Ph.D.
Lab Chief, Genome Stress Signaling,
NCC Research Institute

CPOT # 22-S-06

Summary

Key Words: #antibodies, #biomarkers, #ATR inhibitors, #DNA replication stress

-Purpose-

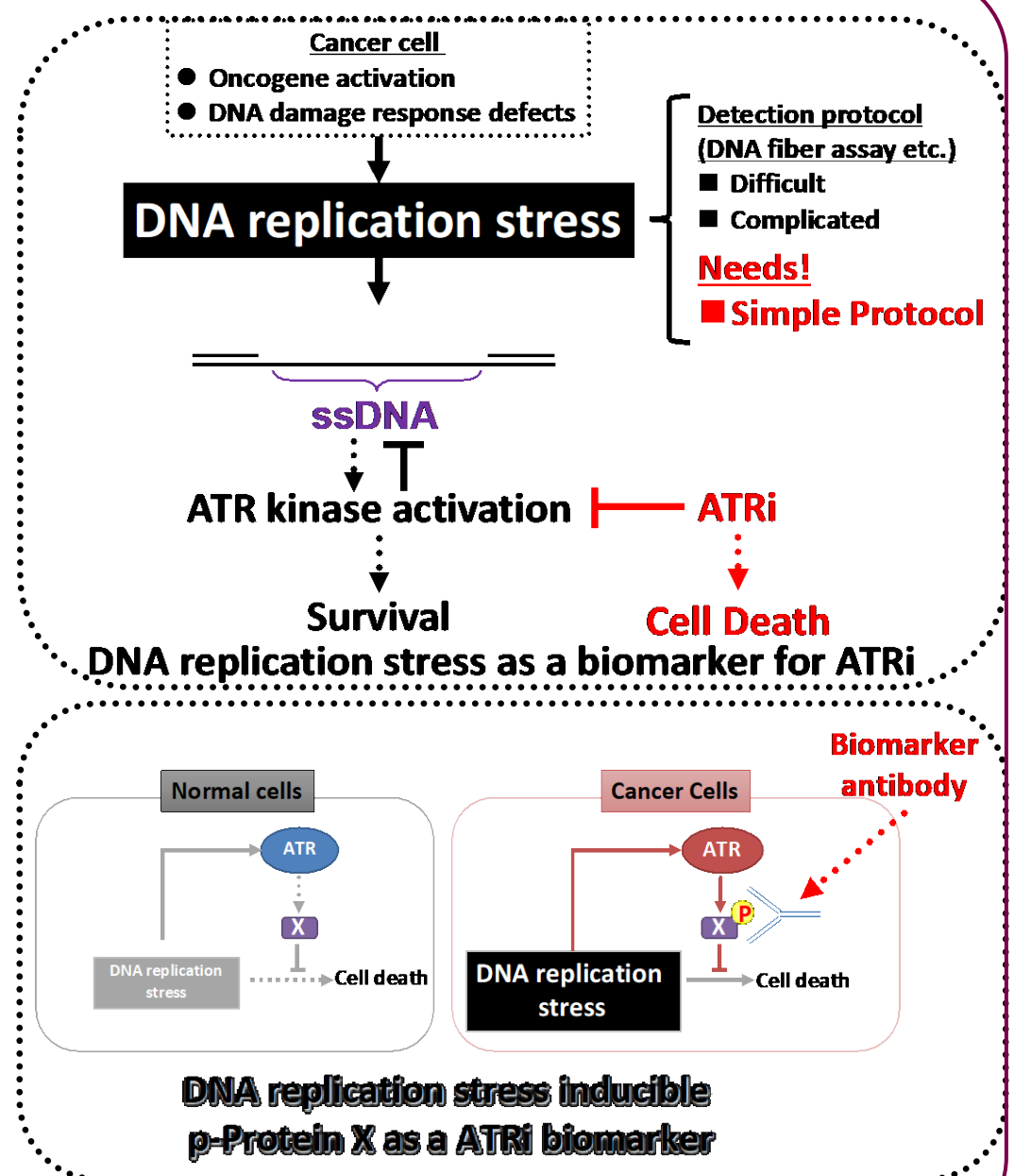
To develop phospho-specific antibodies of ATR-dependent substrates that respond to DNA replication stress and apply them as DNA replication stress and ATR inhibitor biomarkers.

-Background-

- Activation of oncogenes and abnormalities in DNA damage response factors induce DNA replication stress in cancer cells.
- ATR kinase responds to DNA replication stress and contributes to cancer cell survival.
- ATR inhibitors are effective against tumors with high DNA replication stress.
- DNA replication stress level is a potential biomarker for ATR inhibitors.
- Development of a simple and rapid evaluation method for DNA replication stress level is an urgent issue.

-Solution-

DNA replication stress-induced phosphorylation substrate (protein X) specific antibodies are used as biomarkers for ATR inhibitors.



Innovation

Based on phosphoproteome analysis, we have found that Protein X is phosphorylated in the presence of oncogene activation-induced DNA replication stress and that Protein X phosphorylation is required for ATR-dependent DNA replication stress tolerance. We have already started to generate a rabbit monoclonal antibody against phosphorylated-Protein X.

Our findings are completely novel, as Protein X has never been reported as a DNA replication stress biomarker.

Expected Utility

1. Protein X phospho-antibody will be utilized as a biomarker for ATR inhibitors (Phase I/II), which are attracting attention as novel anticancer agents.
2. Target cancer types
   Lung cancer, pancreatic cancer, colorectal cancer, etc.

Partnering

- Pharmaceuticals
- Medical institute
- Medical/Diagnosis/Research Devices

IP Information

N/A

Reference

- Kurashima K, et al. (2020) NAR Cancer 2(2):zcaa005

国立がん研究センター 橋渡し研究推進センター
National Cancer Center
Center for Promotion of Translational Research