

Source: Okayama University (JAPAN), Public Relations Division

For immediate release: 23 June 2021

Okayama University research: Meeting high demand: Increasing the efficiency of antiviral drug production in bacteria.

(Okayama, 23 June) **In a study published in the journal *Bioscience, Biotechnology, and Biochemistry*, researchers from Okayama University induce mutations in a bacterial strain to increase the production of an antiviral chemical it secretes.**

The COVID-19 pandemic has shed light on the need for antiviral drugs which are effective in suppressing viruses. Sinefungin is one such antibiotic produced by the bacteria *Streptomyces incarnatus* NRRL8089 (*S. incarnatus*) and has shown efficacy against multiple viruses including the SARS coronavirus. However, to understand its full potential in clinical studies large quantities of the compound are required. Now, Professor TAMURA Takashi and his Okayama University research team have found a way to increase to triple the production efficiency of sinefungin by inducing multiple mutations in *S. incarnatus*.

Molecular biologists have shown that antibiotic synthesis in certain bacteria can be increased by mutating an enzyme called RNA polymerase (RNAP). RNAP plays a role in running the genetic machinery inside a cell. Thus, to start off their study the researchers picked a segment of RNAP that is typically mutated for this purpose. Using biostatistical modeling, they then identified four potential sites of mutation. Subsequently, six mutant strains with varying combinations of mutations were created. Changes in sinefungin synthesis were then investigated.

While the production efficiency of sinefungin was higher in three mutants, a strain termed 'dsRC' showed three times the usual sinefungin release after 8 days. What's more, the total bacterial mass remained similar in all the strains, suggesting that antibiotic production alone (and not cell growth) was altered.

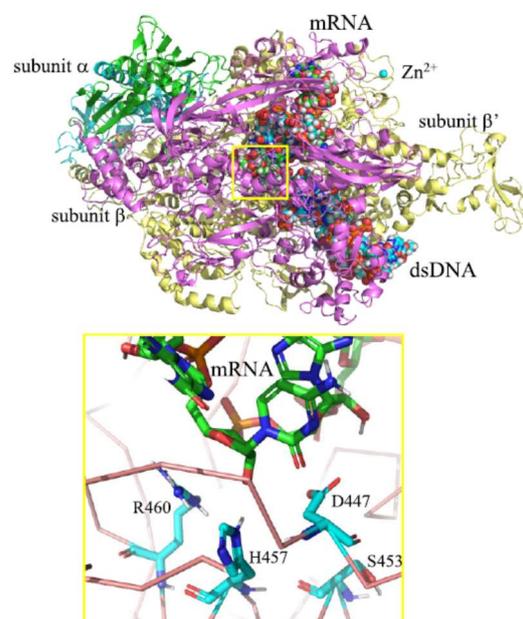
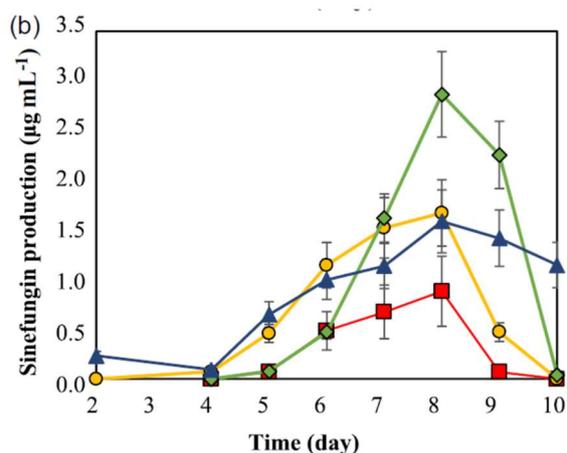
The structure of biochemical molecules always determines changes in their functionality. Therefore, the team used computational modeling to better depict the structure of RNAP—particularly the spatial arrangement of the mutation sites. RNAP is responsible synthesizing RNA strands from DNA (a process that goes on to form the basis for all biological functions). When the spatial configuration of RNAP and its associated DNA/RNA complex was examined, the four sites on RNAP were found to be in close proximity to the newly growing RNA strand. Three of these sites also seemed to be interacting with the RNA. The mutations could likely be involved with RNA synthesis thereby impacting the production of sinefungin. In an unexpected observation, four additional sites on RNAP intercalated with the RNA strand were found. The effects of mutations at these sites, however, remain to be understood.

This study shows a relatively simple and fast method of increasing the production of sinefungin in bacterial cells. “Our genome editing technique altering rif cluster residues arbitrarily now allows any point mutation at the target residues D447, S453, H457, and R460, or at new target candidates F445, R619, R495, and I503,” conclude the researchers. With the issue of large scale production partially solved, procuring sinefungin for testing in animal and human studies should be relatively easy.

Background

RNA polymerase and transcription: All cells undergo a set process to execute biological functions. The DNA within cells contains a set of instructions which are first transcribed onto an RNA strand by a process called transcription. The RNA then goes on to create protein molecules which are the primary facilitators of cellular functions. RNA polymerase is an enzyme that helps synthesize the RNA strand during transcription. The orientation of the mutation sites suggested their interference with the transcription process. Perhaps proteins related to sinefungin production were subsequently impacted.

Mutations: A mutation is a change caused in the sequence of the DNA. Thus, a specific set of instructions within the DNA strand are altered which lead to a change in the chemical structure of the end product: the protein. In this case, mutations at the four sites on the RNA polymerase protein facilitated its close interaction with the nascent RNA strand.



Caption

Left. Production of sinefungin was the highest in the dsRC strain (green), followed by the GsRf (yellow) and GLhC (blue) strains.

Right. Computational models showing the close interactions between the four sites of mutation (R460, H457, D447, and S453) and the RNA strand.

Reference

Saori Ogawa, Hitomi Shimidzu, Koji Fukuda, Naoki Tsunekawa¹, Toshiyuki Hirano, Fumitoshi Sato, Kei Yura, Tomohisa Hasunuma, Kozo Ochi, Michio Yamamoto, Wataru Sakamoto, Kentaro Hashimoto, Hiroyuki Ogata, Tadayoshi Kanao, Michiko Nemoto, Kenji Inagaki, and Takashi Tamura. Multiple mutations in RNA polymerase β -subunit gene (*rpoB*) in *Streptomyces incarnatus* NRRL8089 enhance production of antiviral antibiotic sinefungin: modeling rif cluster region by density functional theory. *Bioscience, Biotechnology & Biochemistry*, 2021, Vol. 85, No. 5, 1275-1282.

DOI: <https://doi.org/10.1093/bbb/zbab011>

Reference (Okayama Univ. e-Bulletin): Professor TAMURA's team

OU-MRU Vol.65 : [Game changer: How do bacteria play Tag?](#)

Correspondence to

Professor TAMURA Takashi, Ph.D.
Department of Bioresources Chemistry,
Okayama University Graduate School of Environmental
and Life Science, 1-1-1, Tsushima-naka, Kita-ku, Okayama
700-8530, Japan.
E-mail: tkamura@okayama-u.ac.jp



Professor TAMURA Takashi

Further information

Okayama University
1-1-1 Tsushima-naka, Kita-ku, Okayama 700-8530, Japan
Public Relations Division

E-mail: www-adm@adm.okayama-u.ac.jp

Website: http://www.okayama-u.ac.jp/index_e.html

Okayama Univ. e-Bulletin: <http://www.okayama-u.ac.jp/user/kouhou/ebulletin/>

We love OKAYAMA UNIVERSITY:

<https://www.youtube.com/watch?v=7cXlTtQIk3E>

Okayama University Image Movie (2020):

<https://www.youtube.com/watch?v=vQxeL0ztSLA>

Okayama University supports the Sustainable Development Goals: <https://sdgs.okayama-u.ac.jp/en/>



Okayama University Medical Research Updates (OU-MRU)

 The whole volume : [OU-MRU \(1- \)](#)

- Vol.1 : [Innovative non-invasive 'liquid biopsy' method to capture circulating tumor cells from blood samples for genetic testing](#)
- Vol.2 : [Ensuring a cool recovery from cardiac arrest](#)
- Vol.3 : [Organ regeneration research leaps forward](#)
- Vol.4 : [Cardiac mechanosensitive integrator](#)
- Vol.5 : [Cell injections get to the heart of congenital defects](#)
- Vol.6 : [Fourth key molecule identified in bone development](#)
- Vol.7 : [Anticancer virus solution provides an alternative to surgery](#)
- Vol.8 : [Light-responsive dye stimulates sight in genetically blind patients](#)
- Vol.9 : [Diabetes drug helps towards immunity against cancer](#)
- Vol.10 : [Enzyme-inhibitors treat drug-resistant epilepsy](#)
- Vol.11 : [Compound-protein combination shows promise for arthritis treatment](#)
- Vol.12 : [Molecular features of the circadian clock system in fruit flies](#)
- Vol.13 : [Peptide directs artificial tissue growth](#)
- Vol.14 : [Simplified boron compound may treat brain tumours](#)
- Vol.15 : [Metamaterial absorbers for infrared inspection technologies](#)
- Vol.16 : [Epigenetics research traces how crickets restore lost limbs](#)
- Vol.17 : [Cell research shows pathway for suppressing hepatitis B virus](#)
- Vol.18 : [Therapeutic protein targets liver disease](#)
- Vol.19 : [Study links signalling protein to osteoarthritis](#)
- Vol.20 : [Lack of enzyme promotes fatty liver disease in thin patients](#)
- Vol.21 : [Combined gene transduction and light therapy targets gastric cancer](#)
- Vol.22 : [Medical supportive device for hemodialysis catheter puncture](#)
- Vol.23 : [Development of low cost oral inactivated vaccines for dysentery](#)
- Vol.24 : [Sticky molecules to tackle obesity and diabetes](#)
- Vol.25 : [Self-administered aroma foot massage may reduce symptoms of anxiety](#)
- Vol.26 : [Protein for preventing heart failure](#)
- Vol.27 : [Keeping cells in shape to fight sepsis](#)
- Vol.28 : [Viral-based therapy for bone cancer](#)
- Vol.29 : [Photoreactive compound allows protein synthesis control with light](#)
- Vol.30 : [Cancer stem cells' role in tumor growth revealed](#)
- Vol.31 : [Prevention of RNA virus replication](#)
- Vol.32 : [Enzyme target for slowing bladder cancer invasion](#)
- Vol.33 : [Attacking tumors from the inside](#)
- Vol.34 : [Novel mouse model for studying pancreatic cancer](#)
- Vol.35 : [Potential cause of Lafora disease revealed](#)
- Vol.36 : [Overloading of protein localization triggers cellular defects](#)
- Vol.37 : [Protein dosage compensation mechanism unravelled](#)
- Vol.38 : [Bioengineered tooth restoration in a large mammal](#)
- Vol.39 : [Successful test of retinal prosthesis implanted in rats](#)
- Vol.40 : [Antibodies prolong seizure latency in epileptic mice](#)
- Vol.41 : [Inorganic biomaterials for soft-tissue adhesion](#)

- Vol.42 : [Potential drug for treating chronic pain with few side effects](#)
- Vol.43 : [Potential origin of cancer-associated cells revealed](#)
- Vol.44 : [Protection from plant extracts](#)
- Vol.45 : [Link between biological-clock disturbance and brain dysfunction uncovered](#)
- Vol.46 : [New method for suppressing lung cancer oncogene](#)
- Vol.47 : [Candidate genes for eye misalignment identified](#)
- Vol.48 : [Nanotechnology-based approach to cancer virotherapy](#)
- Vol.49 : [Cell membrane as material for bone formation](#)
- Vol.50 : [Iron removal as a potential cancer therapy](#)
- Vol.51 : [Potential of 3D nanoenvironments for experimental cancer](#)
- Vol.52 : [A protein found on the surface of cells plays an integral role in tumor growth and sustenance](#)
- Vol.53 : [Successful implantation and testing of retinal prosthesis in monkey eyes with retinal degeneration](#)
- Vol.54 : [Measuring ion concentration in solutions for clinical and environmental research](#)
- Vol.55 : [Diabetic kidney disease: new biomarkers improve the prediction of the renal prognosis](#)
- Vol.56 : [New device for assisting accurate hemodialysis catheter placement](#)
- Vol.57 : [Possible link between excess chewing muscle activity and dental disease](#)
- Vol.58 : [Insights into mechanisms governing the resistance to the anti-cancer medication cetuximab](#)
- Vol.59 : [Role of commensal flora in periodontal immune response investigated](#)
- Vol.60 : [Role of commensal microbiota in bone remodeling](#)
- Vol.61 : [Mechanical stress affects normal bone development](#)
- Vol.62 : [3D tissue model offers insights into treating pancreatic cancer](#)
- Vol.63 : [Promising biomarker for vascular disease relapse revealed](#)
- Vol.64 : [Inflammation in the brain enhances the side-effects of hypnotic medication](#)
- Vol.65 : [Game changer: How do bacteria play Tag?](#)
- Vol.66 : [Is too much protein a bad thing?](#)
- Vol.67 : [Technology to rapidly detect cancer markers for cancer diagnosis](#)
- Vol.68 : [Improving the diagnosis of pancreatic cancer](#)
- Vol.69 : [Early gastric cancer endoscopic diagnosis system using artificial intelligence](#)
- Vol.70 : [Prosthetics for Retinal Stimulation](#)
- Vol.71 : [The nervous system can contribute to breast cancer progression](#)
- Vol.72 : [Synthetic compound provides fast screening for potential drugs](#)
- Vol.73 : [Primary intraocular lymphoma does not always spread to the central nervous system](#)
- Vol.74 : [Rising from the ashes—dead brain cells can be regenerated after traumatic injury](#)
- Vol.75 : [More than just daily supplements — herbal medicines can treat stomach disorders](#)
- Vol.76 : [The molecular pathogenesis of muscular dystrophy-associated cardiomyopathy](#)
- Vol.77 : [Green leafy vegetables contain a compound which can fight cancer cells](#)
- Vol.78 : [Disrupting blood supply to tumors as a new strategy to treat oral cancer](#)
- Vol.79 : [Novel blood-based markers to detect Alzheimer's disease](#)

- Vol.80 : [A novel 3D cell culture model sheds light on the mechanisms driving fibrosis in pancreatic cancer](#)
- Vol.81 : [Innovative method for determining carcinogenicity of chemicals using iPS cells](#)
- Vol.82 : [Making memories — the workings of a neuron revealed](#)
- Vol.83 : [Skipping a beat — a novel method to study heart attacks](#)
- Vol.84 : [Friend to Foe—When Harmless Bacteria Turn Toxic](#)
- Vol.85 : [Promising imaging method for the early detection of dental caries](#)
- Vol.86 : [Plates and belts — a toolkit to prevent accidental falls during invasive vascular procedures](#)
- Vol.87 : [Therapeutic potential of stem cells for treating neurodegenerative disease](#)
- Vol.88 : [Nanotechnology for making cancer drugs more accessible to the brain](#)
- Vol.89 : [Studying Parkinson’s disease with face-recognition software](#)
- Vol.90 : [High levels of television exposure affect visual acuity in children](#)



「Pergola」 Kazuyo Sejima + Ryue Nishizawa / SANAA
 Okayama University (Tsushima Campus, Okayama City)
http://www.okayama-u.ac.jp/eng/access_maps/Tsushima_Campus.html



Okayama University supports the Sustainable Development Goals

◆ About Okayama University

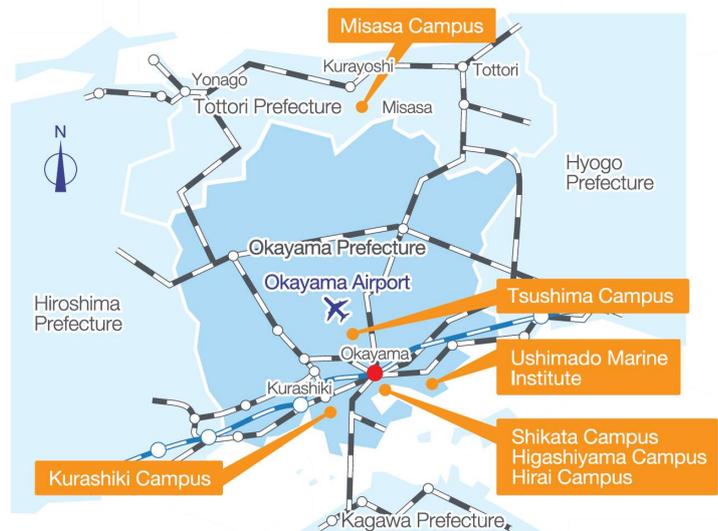
Okayama University is one of the largest comprehensive universities in Japan with roots going back to the Medical Training Place sponsored by the Lord of Okayama and established in 1870. Now with 1,300 faculty and 13,000 students, the University offers courses in specialties ranging from medicine and pharmacy to humanities and physical sciences.

Okayama University is located in the heart of Japan approximately 3 hours west of Tokyo by Shinkansen.

Website: http://www.okayama-u.ac.jp/index_e.html



Japan (日本)



Hirofumi Makino, M.D., Ph.D.
President, Okayama University



Japan.
Committed to SDGs



岡山大学
OKAYAMA UNIVERSITY



“Okayama University supports the Sustainable Development Goals”

Okayama University Integrated Report => [click](#)

An integrated report is intended to explain how an organization creates value over time through an organic integration of the vision and the combination of financial information and other information. Through this report we hope to promote greater interest in Okayama University among readers everywhere. In order to help us make improvements in future editions, we encourage you to contact us with any comments and suggestions you may have.