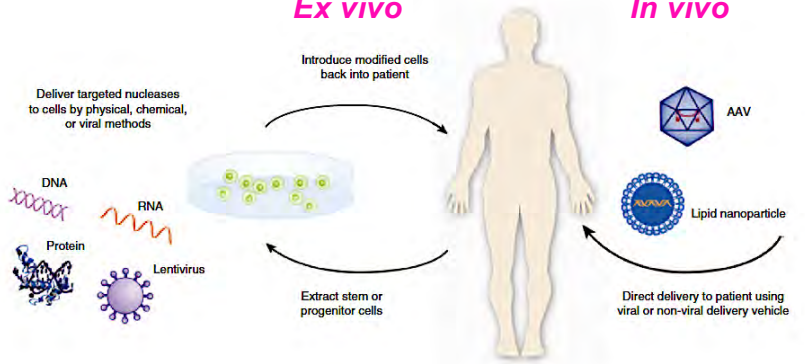
PMDA 第29回科学委員会

話題提供：

ゲノム編集技術の臨床応用の現状

小 澤　敬 也

自治医科大学 名誉教授、客員教授
免疫遺伝子細胞治療学（タカラバイオ）講座



臨床応用

- ❖ HIV感染症
- ❖ ユニバーサルCAR-T療法
- ❖ 遺伝子改変T細胞療法の強化（PD-1遺伝子の破壊）

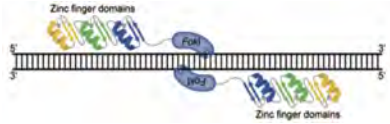
＜予定＞
- ❖ 鎌状赤血球症
- ❖ サラセミア

- ❖ ハンター症候群

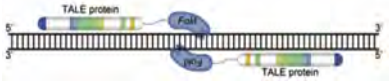
＜予定＞
- ❖ ハーラー症候群
- ❖ 血友病

ゲノム編集技術の遺伝子治療への応用

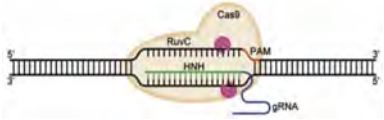
ZFN (Zinc finger nuclease)　Sangamo BioSciences



Talen (Transcription Activator-Like Effector Nuclease)



CRISPR/Cas9
(Clustered Regularly Interspaced Short Palindromic Repeats)

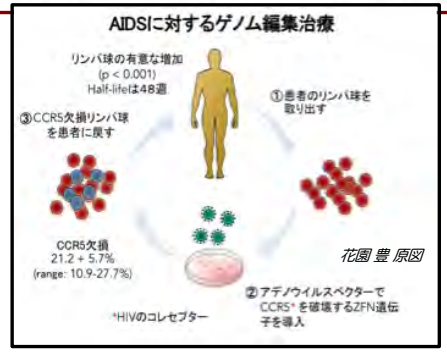


HIV感染症に対するゲノム編集治療

N Engl J Med 370: 901-910, 2014

Gene Editing of *CCR5* in Autologous CD4 T Cells of Persons Infected with HIV

Pablo Tebas, M.D., David Stein, M.D., Winson W. Tang, M.D., Ian Frank, M.D., Shelley Q. Wang, M.D., Gary Lee, Ph.D., S. Kaye Spratt, Ph.D., Richard T. Surosky, Ph.D., Martin A. Giedlin, Ph.D., Geoff Nichol, M.D., Michael C. Holmes, Ph.D., Philip D. Gregory, Ph.D., Dale G. Ando, M.D., Michael Kalos, Ph.D., Ronald G. Collman, M.D., Gwendolyn Binder-Scholl, Ph.D., Gabriela Plesa, M.D., Ph.D., Wei-Ting Hwang, Ph.D., Bruce L. Levine, Ph.D., and Carl H. June, M.D.



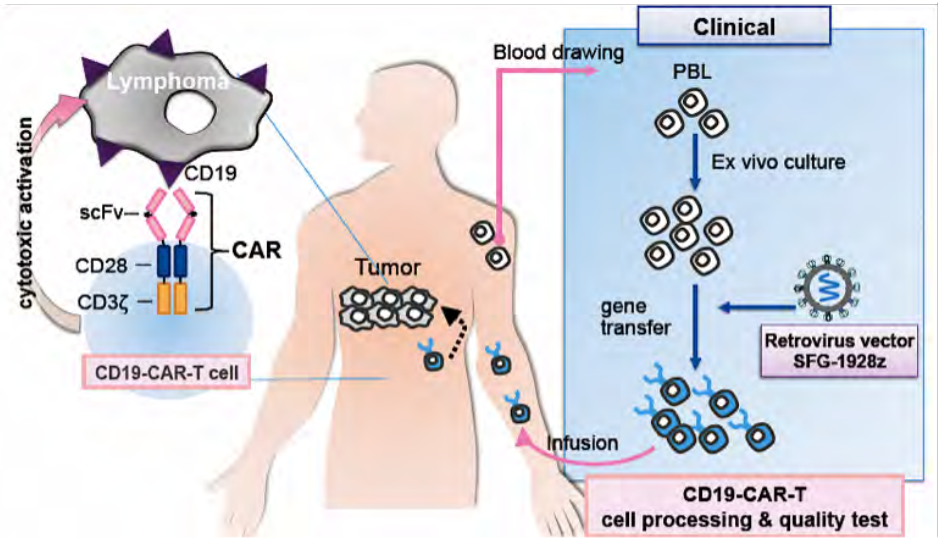
U.S. National Library of Medicine
ClinicalTrials.gov

NCT02500849

Safety Study of Zinc Finger Nuclease CCR5-modified Hematopoietic Stem/Progenitor Cells in HIV-1 Infected Patients

Official Title ICMJE	A Pilot Study to Evaluate the Feasibility, Safety and Engraftment of Zinc Finger Nuclease (ZFN) CCR5 Modified CD34+ Hematopoietic Stem/Progenitor Cells (SB-728mR-HSPC) in HIV-1 (R5) Infected Patients
Brief Summary	The purpose of the study is to evaluate the safety and feasibility of administering SB-728mR-HSPC after conditioning with busulfan.
Detailed Description	The objective of the study is to evaluate the safety and feasibility of giving autologous SB-728mR-HSPC to HIV-1 (R5) infected patients who are being treated with cART and have undetectable virus but suboptimal CD4+ cell levels. To strengthen the possibility that CCR5-disrupted HSPCs engraft, patients will receive either a two- or three-day (Cohort 1 or Cohort 2) course of busulfan (dose targeting AUC of 4000 [illegible]) before being infused with the genetically modified cells. At 9-12 mon[illegible]
Study Start Date ICMJE	July 2015
Estimated Primary Completion Date	July 2018
Study Sponsor ICMJE	City of Hope Medical Center
Collaborators ICMJE	Sangamo Therapeutics
Investigators ICMJE	Principal Investigator: Amrita Y. Krishnan, MD, City of Hope Medical Center

CD19-CAR-T細胞による B細胞性腫瘍に対する養子免疫遺伝子療法



cellectis
EDITING LIFE

Next-Generation CAR T-Cells to Cure Cancer

Gene Edited Off-the-shelf Immunotherapies:
A Future-defining Shift in Simplicity, Availability, and Cost-effectiveness

Universal CAR-T Cells Produced Using Genome Editing Technology

CANCER IMMUNOTHERAPY

Baby's leukemia recedes after novel cell therapy

Gene editing used to create "off-the-shelf" T cells

Science 13 November 2015: Vol. 350 no. 6262 p. 731

The 11-month-old girl had already run through every treatment. Her immune system was barely functioning, and oncologists couldn't collect T cells from her for personalized therapy.

The Cellectis cells had been genetically engineered to avoid two major pitfalls. Scientists used a gene-editing technique called transcription activator-like effector nucleases (TALENs) to cut out the T cell receptor gene. Without it, the cells can't recognize the recipient's body as foreign. The cells were also designed to survive the intense therapy: an antibody called Campath, intended to protect the donor T cells from attack by wiping out the child's own immune system. Campath targets an immune-cell marker called CD52, so the company used TALENs to remove CD52 from its donor cells—ensuring that Campath wouldn't attack them, too. Finally, just as doctors have done with a patient's own T cells, the researchers made DNA modifications to the foreign cells so they would home in on leukemia.

Sci. Transl. Med. **9**, eaaj2013 (2017) 25 January 2017

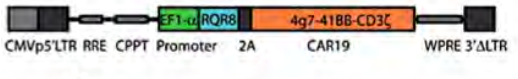
SCIENCE TRANSLATIONAL MEDICINE | REPORT

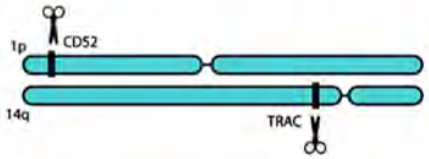
CANCER

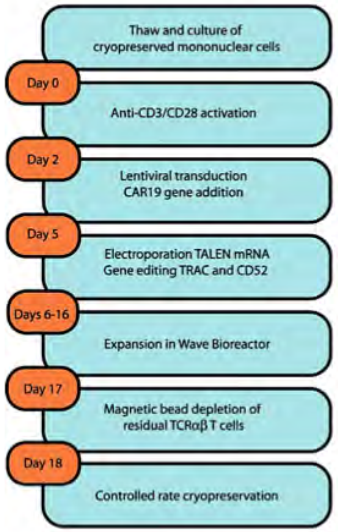
Molecular remission of infant B-ALL after infusion of universal TALEN gene-edited CAR T cells

Waseem Qasim,[1,2]* Hong Zhan,[1] Sujith Samarasinghe,[2] Stuart Adams,[2] Persis Amrolia,[1,2] Sian Stafford,[1] Katie Butler,[1] Christine Rivat,[1] Gary Wright,[2] Kathy Somana,[2] Sara Ghorashian,[1] Danielle Pinner,[2] Gul Ahsan,[2] Kimberly Gilmour,[2] Giovanna Lucchini,[2] Sarah Inglott,[2] William Mifsud,[2] Robert Chiesa,[2] Karl S. Peggs,[3] Lucas Chan,[4] Farzin Farzaneh,[4] Adrian J. Thrasher,[1] Ajay Vora,[5] Martin Pule,[3] Paul Veys[1]

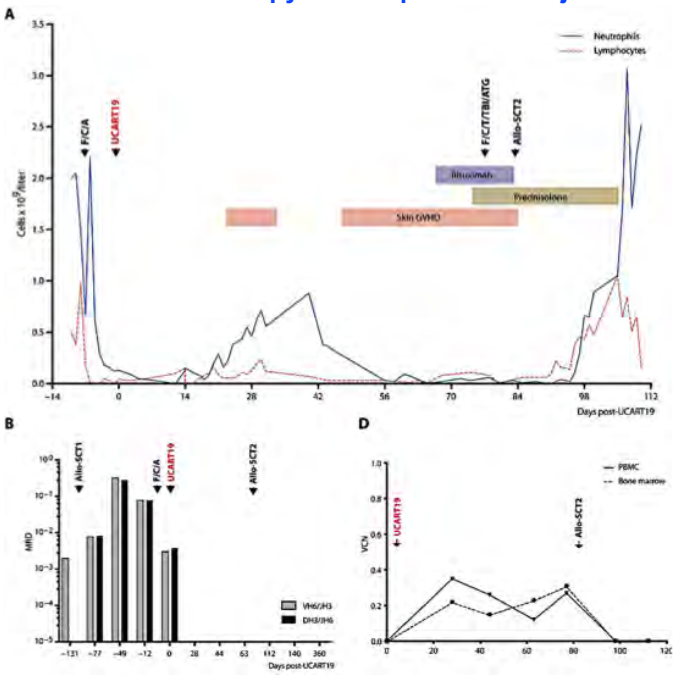
Autologous T cells engineered to express chimeric antigen receptor against the B cell antigen CD19 (CAR19) are achieving marked leukemic remissions in early-phase trials but can be difficult to manufacture, especially in infants or heavily treated patients. We generated universal CAR19 (UCART19) T cells by lentiviral transduction of non–human leukocyte antigen–matched donor cells and simultaneous transcription activator-like effector nuclease (TALEN)–mediated gene editing of T cell receptor α chain and CD52 gene loci. Two infants with relapsed refractory CD19⁺ B cell acute lymphoblastic leukemia received lymphodepleting chemotherapy and anti-CD52 serotherapy, followed by a single-dose infusion of UCART19 cells. Molecular remissions were achieved within 28 days in both infants, and UCART19 cells persisted until conditioning ahead of successful allogeneic stem cell transplantation. This bridge-to-transplantation strategy demonstrates the therapeutic potential of gene-editing technology.





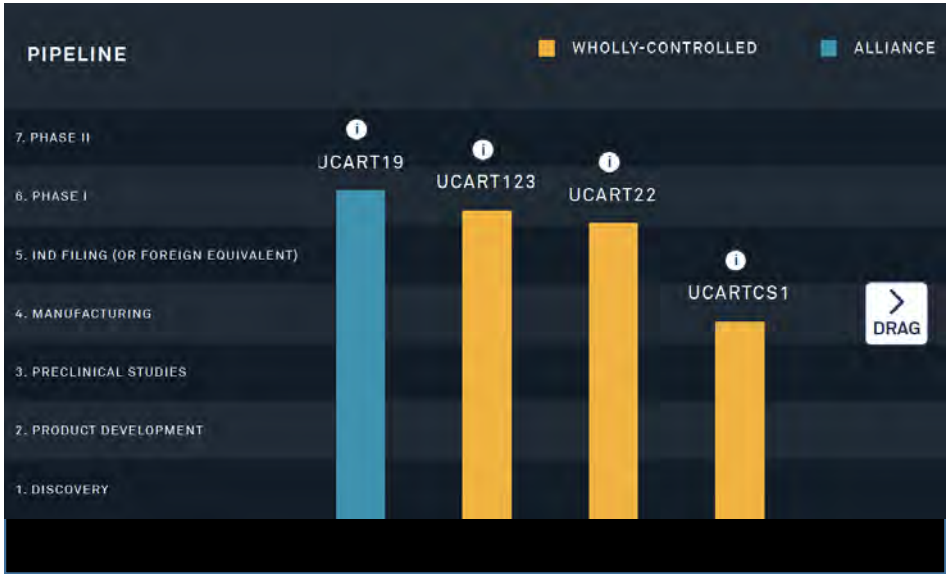


UCART19 therapy and response in subject 1

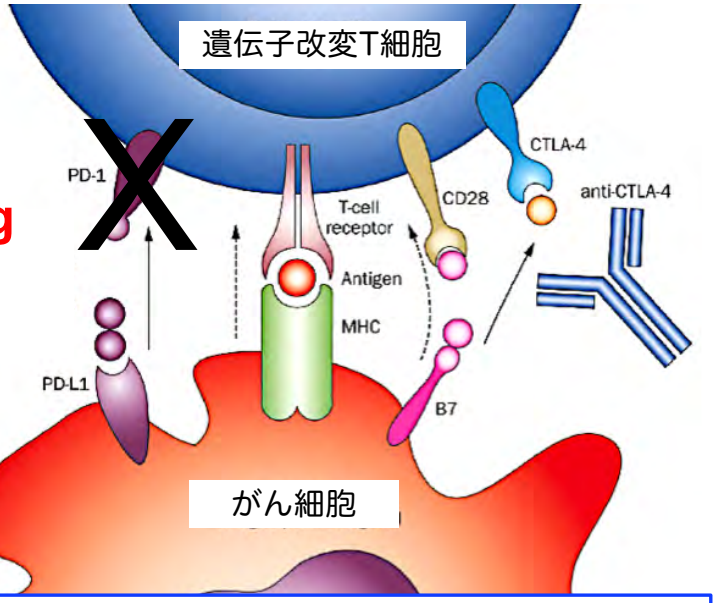


cellectis
EDITING LIFE

Development of a product candidate takes place in several stages



Gene editing



Immune checkpoint blockade

The genome-editing method CRISPR may soon be tested in a clinical trial for the first time.

First proposed human test of CRISPR passes initial safety review

Science

By **Jocelyn Kaiser** | Jun. 21, 2016 , 5:15 PM

The proposed clinical trial, in which researchers would use CRISPR to engineer immune cells to fight cancer, won approval from the Recombinant DNA Advisory Committee (RAC) at the U.S. National Institutes of Health.
For the CRISPR trial, a UPenn-led team wants to remove T cells from patients and use a harmless virus to give the cells a receptor for NY-ESO-1, a protein that is often present on certain tumors but not on most healthy cells.
To boost the staying power of the engineered T cells, the UPenn group wants to use CRISPR to disrupt the gene for a protein called PD-1.

BIOTECHNOLOGY

CRISPR gene editing tested in a person

Trial could spark biomedical duel between China and US.

24 NOVEMBER 2016 | VOL 539 | NATURE | 479

On 28 October, a team led by oncologist Lu You at Sichuan University in Chengdu delivered the modified cells into a patient with aggressive lung cancer as part of a clinical trial at the West China Hospital, also in Chengdu.
In March 2017, a group at Peking University in Beijing hopes to start three clinical trials using CRISPR against bladder, prostate and renal-cell cancers.
The disabled gene codes for the protein PD-1, which normally puts the brakes on a cell's immune response: cancers take advantage of that function to proliferate.

Sangamo THERAPEUTICS

Sangamo Announces Treatment of First Patient in Landmark Phase 1/2 Clinical Trial Evaluating In Vivo Genome Editing for MPS II

RICHMOND, Calif., Nov. 15, 2017 /PRNewswire/ – Sangamo Therapeutics, Inc. (Nasdaq: SGMO) today announced treatment of the first patient in the Phase 1/2 clinical trial ("the CHAMPIONS study") evaluating SB-913, an investigational *in vivo* genome editing therapy for people with mucopolysaccharidosis type II (MPS II), also known as Hunter syndrome.

GENE THERAPY

In vivo genome editing of the albumin locus as a platform for protein replacement therapy

Rajiv Sharma,[1,*] Xavier M. Anguela,[1,2,*] Yannick Doyon,[3,*] Thomas Wechsler,[3] Russell C. DeKe
David E. Paschon,[3] Jeffrey C. Miller,[3] Robert J. Davidson,[1] David Shivak,[3] Shangzhen Zhou,[1] Ju
Philip D. Gregory,[3] Michael C. Holmes,[3] Edward J. Rebar,[3] and Katherine A. High[1,2]

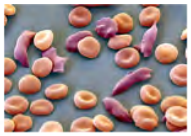
Blood 126: 1777-1784, 2015

Key Points

- AAV- and ZFN-mediated targeting of the albumin locus corrects disease phenotype in mouse models of hemophilia A and B.
- Robust expression from the albumin locus provides a versatile platform for liver-directed protein replacement therapy.

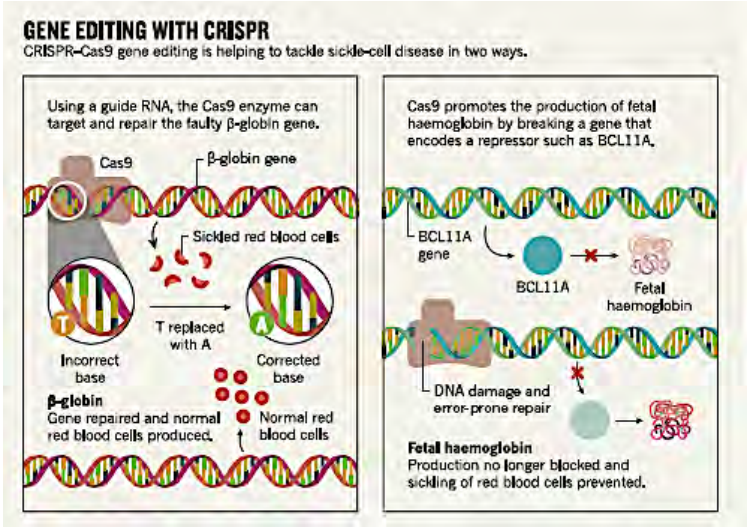
GENE THERAPY

Erasing sickle-cell disease



Clinical trials may soon test whether gene editing can cure a group of debilitating haemoglobin disorders.

28 SEPTEMBER 2017 | VOL 549 | NATURE | S29



CRISPR Beta-Thalassemia Treatment Approved for Clinical Trial in Europe

First genome-editing trial in Europe gets go-ahead

16 April 2018
By Shaoni Bhattacharya (Appeared in BioNews 945)

Europe's first clinical trial to use genome editing in humans has received approval to start later this year.

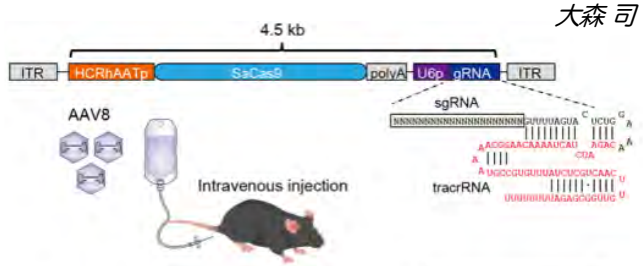
CRISPR Therapeutics, headquartered in Zug, Switzerland, has got the regulatory go-ahead to test its therapy in patients with the inherited blood disorder, beta-thalassemia.

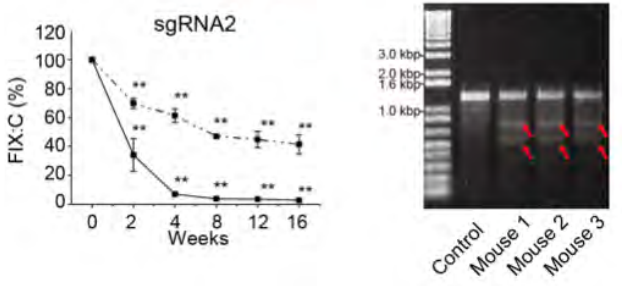
The therapy, developed by CRISPR Therapeutics in collaboration with Vertex Pharmaceuticals, works by extracting a patient's blood stem cells and then using genome editing to make them produce high levels of fetal haemoglobin in red blood cells. The cells are then transfused back into the same patient. By elevating the levels of this type of haemoglobin in a patient's blood, researchers hope to alleviate the need for blood transfusions in beta-thalassemia patients and avoid sickle cell crises in sickle cell patients.

The approved trial aims to test the safety and efficacy of the therapy in adult beta-thalassemia patients in Europe.

AAVによる肝臓のゲノム編集

大森 司（自治医科大学）

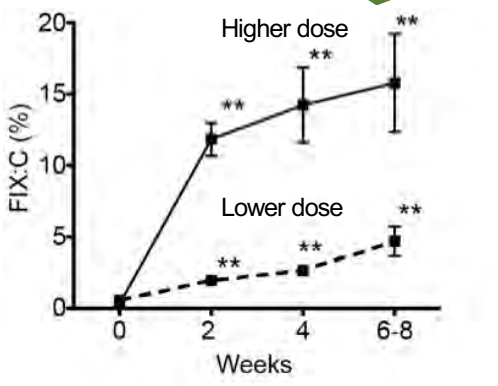




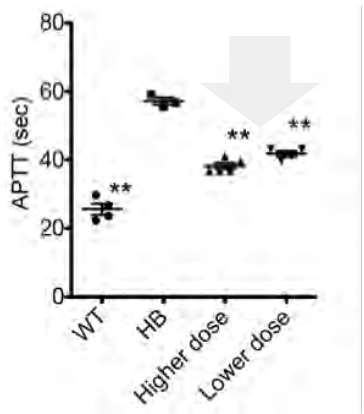
Ohmori et al., Scientific Reports 2017;7:4159

ゲノム編集による血友病Bマウスの治療

凝固因子の上昇



凝固時間改善



NHK、読売新聞、毎日新聞、日経バイオ、科学新聞など多くのメディアに取り上げられた。

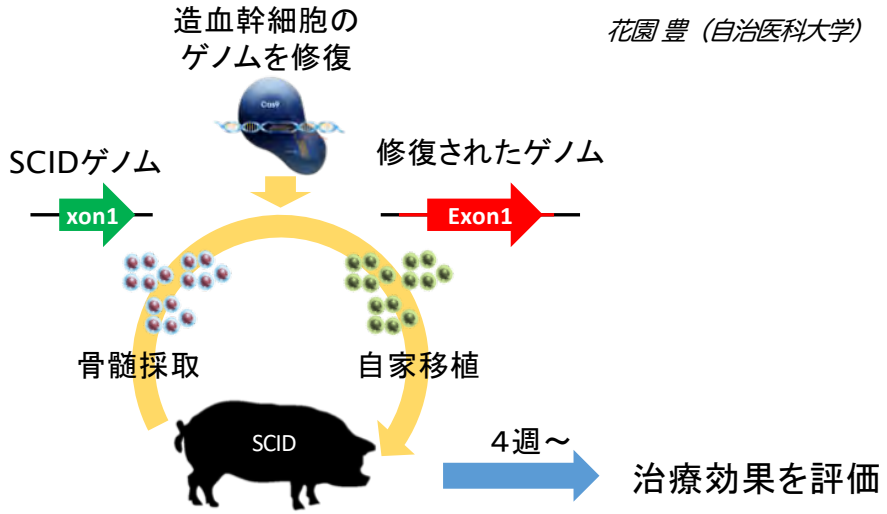
特願2017−004198

Ohmori et al., Scientific Reports 2017;7:4159

SCIDピッグを使ったゲノム編集治療の前臨床研究を開始！

世界初！

花園 豊（自治医科大学）



10 MARCH 2016 | VOL 531 | NATURE | 167

Learn from DIY biologists

The citizen-science community has a responsible, proactive attitude that is well suited to gene-editing, argues **Todd Kuiken**.

INDEPENDENT

How DIY gene editing could lead to a global catastrophe

After a virus was created from mail-order DNA, scientists are sounding the alarm about the genetic tinkering carried out in garages and living rooms

朝日新聞 DIGITAL

ＤＩＹバイオ増殖、個人が自宅でゲノム編集　規制後追い

大学や企業の研究室に属さず、自宅で バイオテクノロジー の実験を繰り返す「バイオハッキング」や「DIYバイオ」と呼ばれる活動が、米国で話題になっている。遺伝子 を改変するゲノム編集を手軽にできるようになったことなどが背景にある。だが、自分の体を実験台にする「過激」なケ ースも登場。規制は後追いになっている。

ＮＡＳＡの研究者をへて、「バイオハッカー」になったジョサイア・ザイナーさん。自宅でゲノム編集実験ができるキットを販売するーカリフォルニア州オークランド、香取啓介撮影

Jichi Medical University