

Fraud in stem cell research in the case of **Haruko Obokata**

Tanja Berger

Sensation im Labor: Forscher erzeugen Stammzellen mit Zitronensäure

Von *Christina Elmer*

Sie sind die Alleskönner im Körper: Aus Stammzellen kann jede Art von Gewebe entstehen. Bisher ließen sie sich im Labor nur mit komplizierten Verfahren herstellen. Nun haben Forscher eine überraschend einfache Methode entdeckt. Ein kurzes Säurebad überführt Mauszellen in einen einzigartigen Embryonalzustand.

1 Mittwoch, 29.01.2014 - 14:48 Uhr

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Stammzellen - die Multitalente

Embryonale Stammzellen (ES)

Sie gelten als die zellulären Alleskönner: Reift eine befruchtete Eizelle zu einer Blastozyste, einem kleinen Zellklumpen, heran, entsteht in deren Inneren eine Masse aus embryonalen Stammzellen. Die noch nicht differenzierten Stammzellen können sich zu jeder Zellart des menschlichen Körpers entwickeln. Voraussetzung ist, dass sie mit den richtigen Wachstumsfaktoren behandelt werden.

+ Induzierte pluripotente Stammzellen (iPS)

Proteininduzierte pluripotente



Es klingt erstaunlich banal, was japanische Forscher berichten: Statt Körperzellen mit aufwendigen Verfahren zu verjüngen, setzen sie ihr Versuchsmaterial einfach in ein Säurebad. Auf diese Weise erzeugten Haruko Obokata vom Riken-Zentrum für Entwicklungsbiologie im japanischen Kobe und ihre Kollegen aus Mauszellen wahre Alleskönner - und überraschen die Fachwelt nun mit ihren erstaunlichen Resultaten.

Die Wissenschaftler veröffentlichten ihre Ergebnisse in der aktuellen Ausgabe der Fachzeitschrift "Nature": [In einem Artikel](#) beschreiben sie die Entstehung der Stammzellen, [ein weiterer Aufsatz](#) behandelt deren weitere Entwicklung.

Um die [Stammzellen](#) zu erzeugen, behandelten sie viele Körperzellen neugeborener Mäuse mit einer Lösung aus Zitronensäure, deren pH-Wert zwischen 5,4 und 5,8 lag. Eine halbe Stunde dauerte das Säurebad. Von jeweils 15 Zellen überlebten drei die Tortur, von denen eine sich daraufhin radikal verjüngte. Die so gewonnenen Stammzellen bezeichnen die Forscher als STAP-Zellen (stimulus-triggered acquisition of pluripotency).

"Ein Riesenfortschritt"

RETRACTED

ARTICLE

doi:10.1038/nature12968

Stimulus-triggered fate conversion of somatic cells into pluripotency

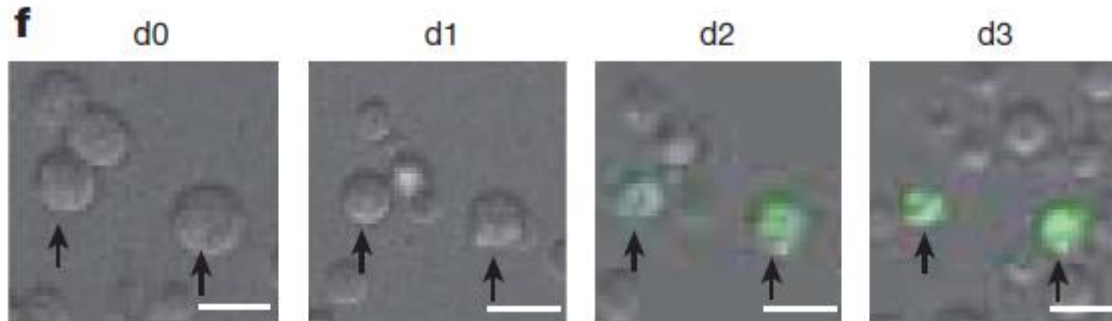
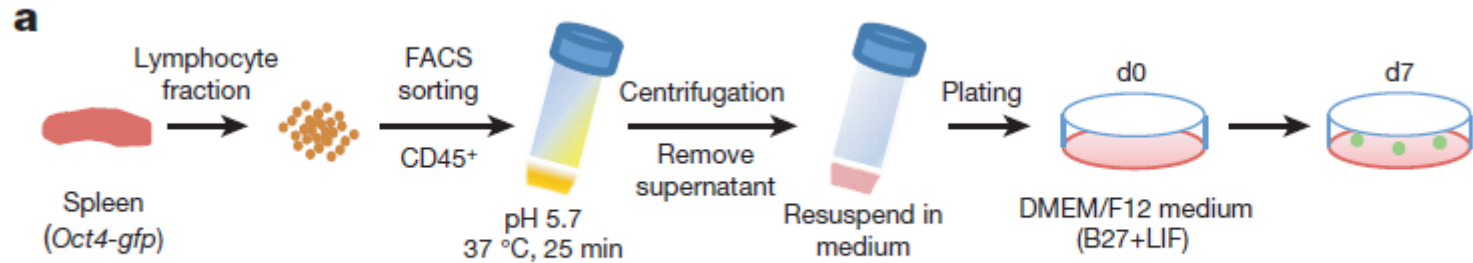
Haruko Obokata^{1,2,3}, Teruhiko Wakayama^{3†}, Yoshiki Sasai⁴, Koji Kojima¹, Martin P. Vacanti^{1,5}, Hitoshi Niwa⁶, Masayuki Yamato⁷ & Charles A. Vacanti¹

Here we report a unique cellular reprogramming phenomenon, called stimulus-triggered acquisition of pluripotency (STAP), which requires neither nuclear transfer nor the introduction of transcription factors. In STAP, strong external stimuli such as a transient low-pH stressor reprogrammed mammalian somatic cells, resulting in the generation of pluripotent cells. Through real-time imaging of STAP cells derived from purified lymphocytes, as well as gene rearrangement analysis, we found that committed somatic cells give rise to STAP cells by reprogramming rather than selection. STAP cells showed a substantial decrease in DNA methylation in the regulatory regions of pluripotency marker genes. Blastocyst injection showed that STAP cells efficiently contribute to chimaeric embryos and to offspring via germline transmission. We also demonstrate the derivation of robustly expandable pluripotent cell lines from STAP cells. Thus, our findings indicate that epigenetic fate determination of mammalian cells can be markedly converted in a context-dependent manner by strong environmental cues.

→Haruko Obokata, a young biochemist, at the RIKEN Center for Developmental Biology in Kobe, Japan

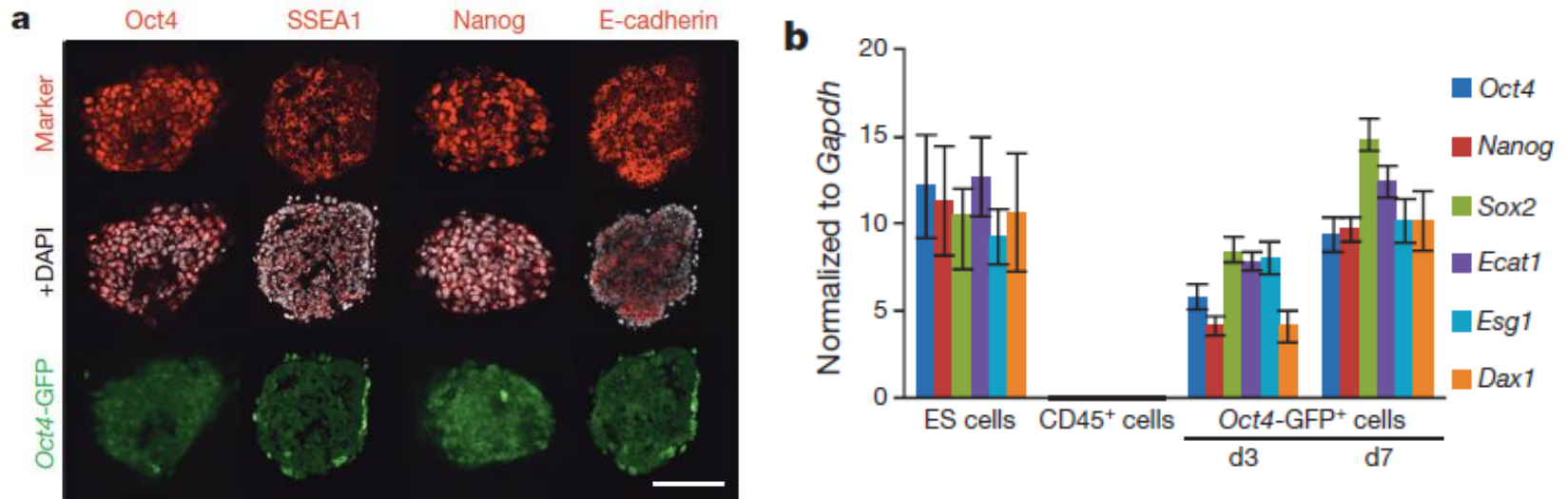
Obokata, H. *et al.* Stimulus-triggered fate conversion of somatic cells into pluripotency. Nature 505, 641–647 (2014).

Stimulus-triggered conversion of lymphocytes into Oct4-GFP1 cells.



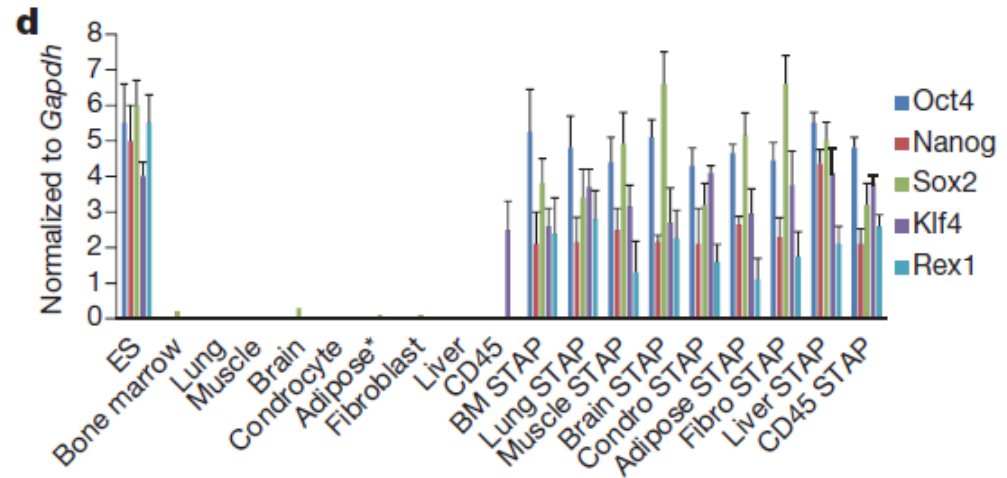
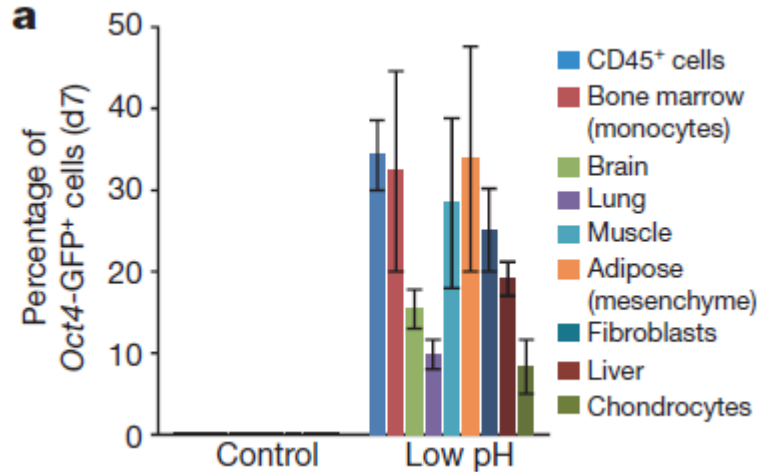
Obokata, H. *et al.* Stimulus-triggered fate conversion of somatic cells into pluripotency. *Nature* 505, 641–647 (2014).

Low-pH-induced Oct4-GFP1 cells represent pluripotent cells.



Obokata, H. *et al.* Stimulus-triggered fate conversion of somatic cells into pluripotency. *Nature* 505, 641–647 (2014).

STAP cell conversion from a variety of cells by low-pH treatment.



Obokata, H. *et al.* Stimulus-triggered fate conversion of somatic cells into pluripotency. *Nature* 505, 641–647 (2014).



Ankersmit
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January 2014



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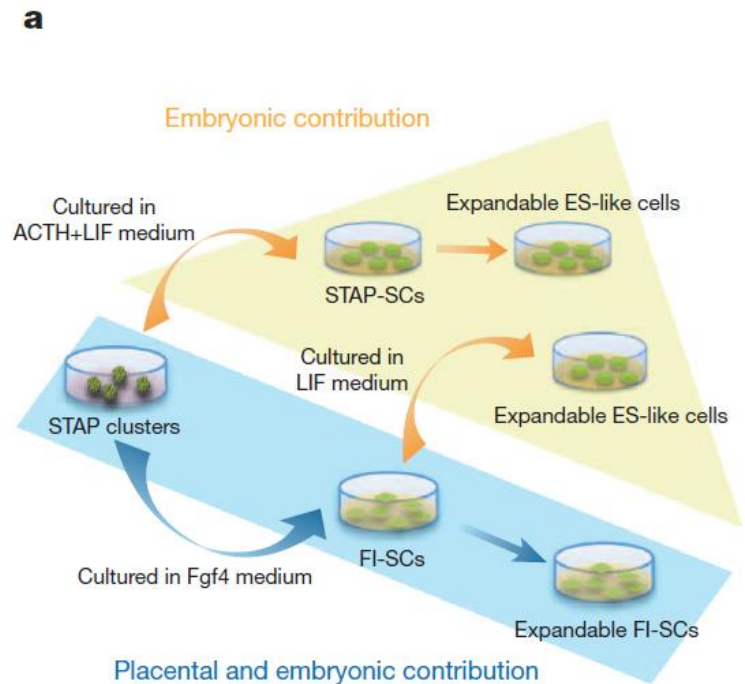
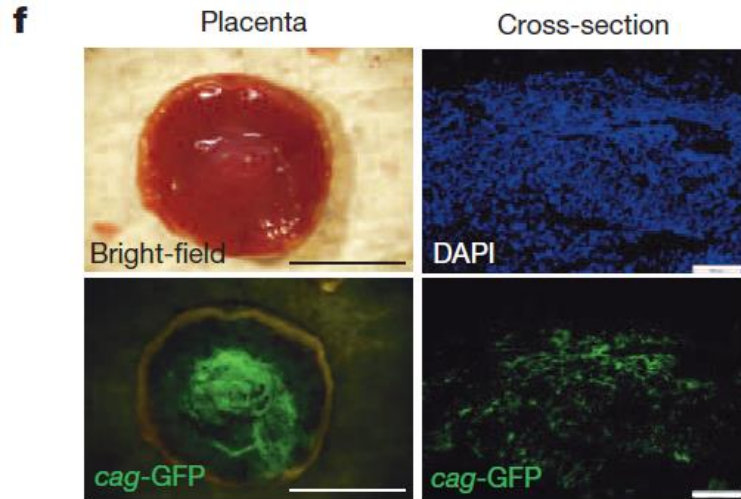
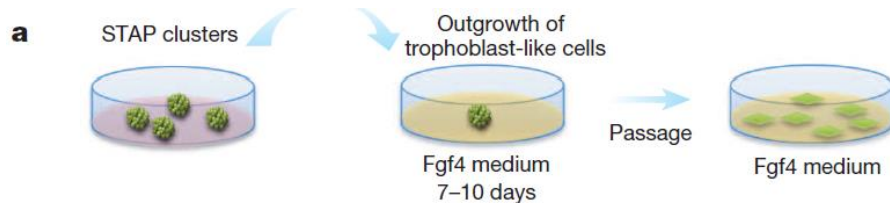
doi:10.1038/nature12969

Bidirectional developmental potential in reprogrammed cells with acquired pluripotency

Haruko Obokata^{1,2,3}, Yoshiki Sasai⁴, Hitoshi Niwa⁵, Mitsutaka Kadota⁶, Munazah Andrabi⁶, Nozomu Takata⁴, Mikiko Tokoro², Yukari Terashita^{1,2}, Shigenobu Yonemura⁷, Charles A. Vacanti³ & Teruhiko Wakayama^{2,8}

Obokata, H. *et al.* Bidirectional developmental potential in reprogrammed cells with acquired pluripotency. *Nature* 505, 676–680 (2014).

Fgf4 treatment induces some trophoblast-lineage character in STAP cells.



Obokata, H. *et al.* Bidirectional developmental potential in reprogrammed cells with acquired pluripotency. *Nature* 505, 676–680 (2014).

The screenshot shows the Spiegel Online website interface. At the top, it says 'SPIEGEL ONLINE WISSENSCHAFT'. Below that is a navigation bar with categories like Politik, Wirtschaft, Panorama, Sport, Kultur, Netzwerk, Wissenschaft, Gesundheit, einestages, Karriere, Uni, Reise, Auto, and Stil. A search bar is on the right. The main headline reads 'Japanische Stammzellstudie: Zweifel an den Ergebnissen verdichten sich' by Kristin Hüttmann. Below the headline is a photograph of a mouse embryo glowing with green fluorescence. The caption below the photo says 'Fortschritt oder Fälschung: Ein Mäuseembryo, erzeugt aus Stammzellen' and credits Haruko Obokata. A short paragraph follows: 'Stammzellen mit einem einfachen Säurebad erzeugen - die Ergebnisse japanischer Forscher klangen fast zu schön, um wahr zu sein. Jetzt verhärten sich tatsächlich die Vorwürfe, dass die Forscher geschummelt haben.'

→ **anonymous observers** (“Blogger auf der Plattform Pubpeer“) began noting mistakes in the papers: including evidence of image manipulation, duplications and plagiarism

→ **could not reproduce the method**

RIKEN research centre in Japan:

→ Investigative Committee was established on February 17



Sensationsstudie: Forscher will eigene Stammzell-Entdeckung zurückziehen

- Co-author Wakayama said that it is advisable to withdraw the paper and to submit it later again when the data are correct and verified
- But another co-author Vacanti contradicted

RIKEN research centre in Japan:

- organized an inquiry
- found inadequacies in data management, record-keeping and oversight
- image manipulation (spliced together gel lanes from different experiments to appear as one)
- Plagiarism (method have been copied from another paper)
- image of cells in a teratoma that had also appeared in her PhD dissertation

March 31, 2014

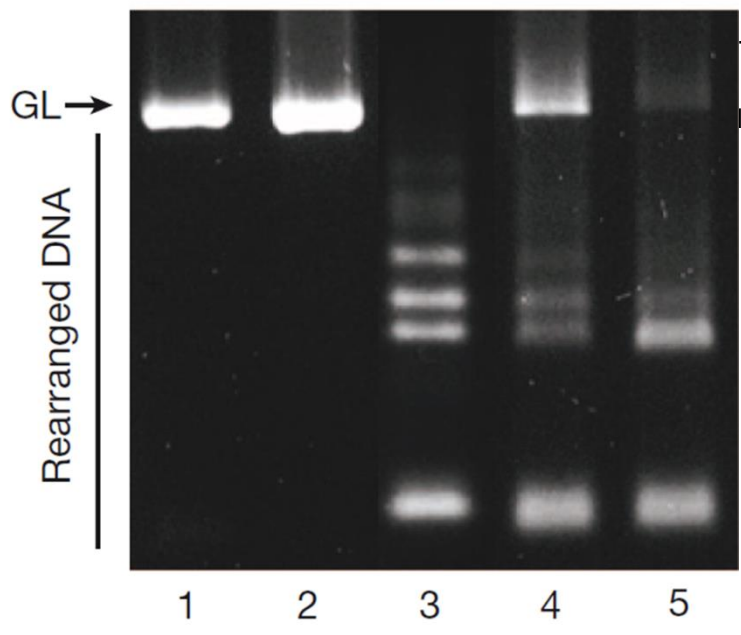
To: Ryoji Noyori, RIKEN President

Report on STAP Cell Research Paper Investigation

Research Paper Investigative Committee
Shunsuke Ishii, Chair
Atsushi Iwama
Haruhiko Koseki
Yoichi Shinkai
Tetsuya Taga
Jun Watanabe



i
ES cells
Fibroblasts
Sorted Lymphocytes
Sorted Oct4-GFP 1
Sorted Oct4-GFP 2



Obokata, H. *et al.* Nature 505, 641–647 (2014).

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i

GL →

Rearranged DNA

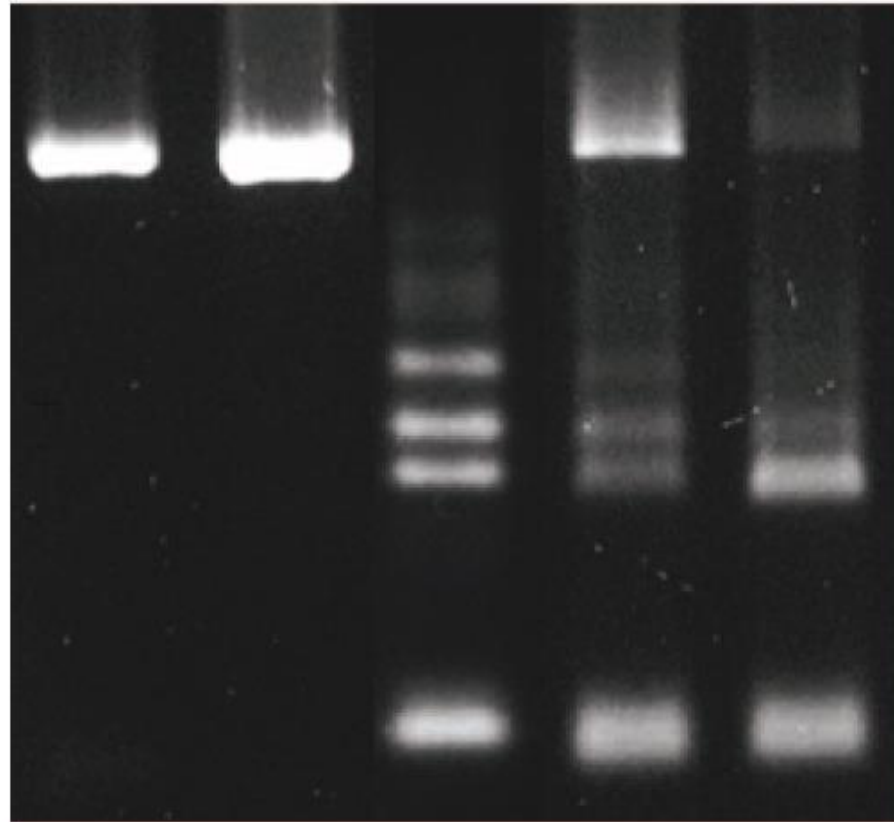
ES cells

Fibroblasts

Lymphocytes

Sorted Oct4-GFP 1

Sorted Oct4-GFP 2



1

2

3

4

5



Umstrittene Stammzellstudie: Manipuliert und gefälscht?



Haruko Obokata: Laut Studie hat ihr Team Zellen mit Säure in den Embryonalzustand zurückversetzt

REUTERS/ Kyodo

Die Kritik an einer umstrittenen Stammzellstudie verschärft sich. Nach einer internen Untersuchung kommt das beteiligte Forschungszentrum zu dem Schluss: Die Leiterin der Studie hat manipuliert und gefälscht.

→1 April 2014: RIKEN Investigative Committee concluded that

Obokata had committed scientific misconduct

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Nachrichten > Wissenschaft > Medizin > Stammzellforschung > Stammzellen: Ergebnis umstrittener Studie von Forscherin verteidigt

Umstrittene Stammzellstudie: Studienleiterin verteidigt Ergebnis der Arbeit



Haruko Obokata: Kopiert, um die Präsentation eingängiger aussehen zu lassen

DPA

Die Debatte um die umstrittene Studie zur Verjüngung von Stammzellen geht in die nächste Runde. Jetzt verteidigt die Autorin die Arbeit: Das Ergebnis sei korrekt. Zuvor war sie der Manipulation beschuldigt worden.

Stammzellen: Forscherin widerruft Studie zur Zellverjüngung

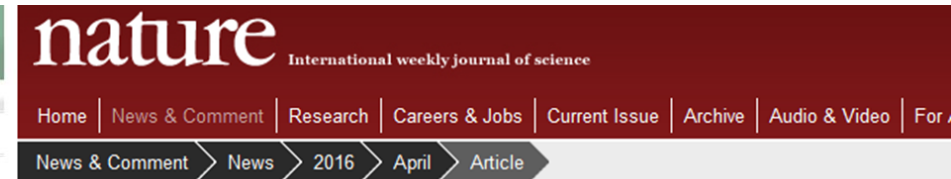


Zweifel bleiben: Haruko Obokata bei der Präsentation ihrer Arbeit am 28. Januar in Tokio

REUTERS/ Kyodo

Ende einer Sensation? Im Januar erregt eine Studie weltweit Aufsehen: Ein kurzes Säurebad überführte Mauszellen angeblich in eine Art Embryonalzustand. Jetzt widerruft die Forscherin offenbar ihre Arbeit.

- *Nature* retracts articles only when all co-authors agree
- Obokata relented and **agreed** to retract both papers



Stammzellforschung: Wissenschaftsmagazin zieht Skandalstudie zurück



Haruko Obokata bei einer Pressekonferenz: Die Studien werden zurückgezogen

DPA/ Nature

"Forscher erzeugen Stammzellen mit Zitronensäure" - die Meldung machte weltweit Schlagzeilen. Nun hat die renommierte Zeitschrift "Nature" die Studien offiziell zurückgezogen.

NATURE | NEWS



Papers on 'stress-induced' stem cells are retracted

High-profile reports claiming an easy way to create pluripotent cells were flawed, *Nature* announces.

David Cyranoski

02 July 2014

- both papers were **retracted** on **2 July 2014**
- "the editors and referees could not have detected the fatal faults in this work"
- Obokata has been hospitalized

CELL-INDUCED STRESS

As a much-hailed breakthrough in stem-cell science unravelled this year, many have been asking: **'Where were the safeguards?'**

- some scientists said they accepted it based only on the **reputation** of Obokata's co-authors
- no one has yet been able to repeat the experiment
- Obokata claimed that they were mistakes and has denied wrongdoing
- ***The EMBO Journal***: it takes about one-third of her working week to check all accepted manuscripts for the four journals published by *EMBO Press*
- ***Nature***: random spot-checking of images during the production process (limitations in resources) → **the STAP papers were not checked**

CELL-INDUCED STRESS

As a much-hailed breakthrough in stem-cell science unravelled this year, many have been asking: **‘Where were the safeguards?’**

- Co-authors **Sasai** and **Wakayama** (not involved in the misconduct) carried **“heavy responsibility”**
- Wakayama takes the blame for not making more effort to check Obokata’s work

**“There has to be control, but also trust in science,
otherwise the system breaks down completely,”**

says Maria Leptin, a molecular biologist and director of *EMBO*



NATURE | NEWS



Stem-cell scientists mourn loss of brain engineer

A famous name in regenerative medicine, Yoshiki Sasai was found dead on 5 August.

David Cyranoski

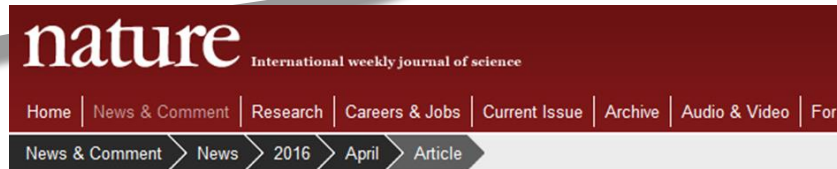
05 August 2014

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Yoshiki Sasai (1962–2014)

- Sasai committed suicide
- deputy director of the RIKEN Center for Developmental Biology (CDB) in Kobe, Japan
- Sasai was a co-author of the two nature papers (STAP)
- reason for Sasai`s apparent suicide still not clear



NATURE | NEWS



Stem-cell pioneer blamed media 'bashing' in suicide note

Lawyer for Yoshiaki Sasai's family reveals motive of Japanese researcher's act following STAP controversy.

David Cyranoski

13 August 2014 | Clarified: 15 August 2014

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Yoshiaki Sasai (1962–2014)

- Sasai was “worn out by the unjust bashing in the mass media and the responsibility he felt towards RIKEN and his laboratory”
- Sasai was hammered in the Japanese media
- Kishi report and media attacks were factors in explaining Sasai's suicide



Skandal um Studie: Stammzell-Sensation entpuppt sich als Pleite



Skandal-Studie: Ups, da waren embryonale Stammzellen drin

Independent investigation:

- STAP cells were contaminated with **three** distinct **embryonic stem cell lines** and presumable also with **trophoblasts** (type of cell that can form the placenta)
- open questions: how the contamination occurred or whether it was accidental?
- other labs could not reproduce the method
- **Obokata had failed to repeat her experiments → Obokata resigned with blame**



NATURE | NEWS



Questions linger over stress-induced stem cells

Investigation confirms STAP cells were contaminated, but mystery still surrounds original results.

Heidi Ledford

31 December 2014

nature

International weekly journal of science

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News & Comment > News > 2016 > April > Article

NATURE | NEWS



President of Japan's RIKEN research labs resigns

Ryoji Noyori's 12-year tenure saw the discovery of an element and a stem-cell scandal.

David Cyranoski

24 March 2015

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L: The Asahi Shimbun via Getty/R. Kyodo via Newscom

RIKEN president Ryoji Noyori (left) at his resignation press conference. He will be replaced by Hiroshi Matsumoto (right, pictured at a Kyoto University press conference in 2011).

→ **Ryoji Noyori**, long-time president of Japan's RIKEN network of basic-research laboratories has resigned

Institute:

→ not press charges against the lead author of the fraudulent research, Haruko Obokata (was found guilty of misconduct)
→ it will ask her to return the ¥600,000 that she used to publish the papers

April 2015

COLLATERAL DAMAGE

*How a case of misconduct brought a leading
Japanese biology institute to its knees.*

RIKEN Center for Developmental Biology

SCIENTIST'S PARADISE (before the misconduct):

- enjoyed generous salaries and research funds → they did not depend on grants
- 163 papers that its researchers published in 2013, one-third were in leading international journals including *Nature*, *Science* and *Cell*

April 2015

COLLATERAL DAMAGE

*How a case of misconduct brought a leading
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RIKEN Center for Developmental Biology

Effects after the misconduct:

- half of its labs have been closed, merged or assigned to other organizations
- its leadership has been replaced → Hiroshi Hamada took over as director
- News teams camped in the lobby, trailed Obokata, Sasai and many other CDB researchers and administrators
- blame to the CDB and RIKEN as a whole
- 40% cut to the centre's budget
- researchers have been scrambling to supplement their finances with grants

The screenshot shows the top portion of a news article on the Nature website. The header includes the 'nature' logo and navigation links. The article title is 'Failed replications put STAP stem-cell claims to rest' by David Cyranoski, dated 23 September 2015. The sub-headline reads: 'Multiple labs conclude that the seemingly miraculous results originated from contamination with ordinary stem cells.'

nature International weekly journal of science

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News & Comment > News > 2016 > April > Article

NATURE | NEWS

Failed replications put STAP stem-cell claims to rest

Multiple labs conclude that the seemingly miraculous results originated from contamination with ordinary stem cells.

David Cyranoski

23 September 2015

- seven teams in four countries tried to replicate the procedure under various conditions
- teams' work amounted to 133 attempts to produce STAP cells, all of which failed
- both Oct4-GFP and wild-type cells emitted low level broad spectrum fluorescence detectable within both green and red filters, indicating **autofluorescence**

January 2016

The Japan Times

HARUKO OBOKATA



NATIONAL

JAN 27, 2016

Obokata breaks silence, suggests colleague bears blame for STAP debacle

BY TOMOKO OTAKE

A former star scientist with the Riken research institute who was accused of fraud in 2014 tells her side of the story.

Obokata is ready to tell her side of the story: **The book is titled “Ano Hi” (“That Day”)**



January 2016

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NATIONAL

JAN 27, 2016

Obokata breaks silence, suggests colleague bears blame for STAP debacle

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A former star scientist with the Riken research institute who was accused of fraud in 2014 tells her side of the story.

Obokata is ready to tell her side of the story: **The book is titled “Ano Hi” (“That Day”)**

- Obokata insists she was at least partially successful in creating cells that have the potential to turn into any kind of body tissue
- Obokata claims that she was “framed” as the individual who mixed in ES cells
- **crucial parts** of the STAP experiments were handled only by **Wakayama** (works at Yamanashi University)
- Obokata received the cells used in the experiments from Wakayama, and directs suspicions at him instead
- Obokata received a disciplinary discharge by Riken in February 2015

February 2016

The Japan Times

HARUKO OBOKATA



CRIME & LEGAL

FEB 18, 2016

Obokata questioned over alleged theft of Riken stem cell samples

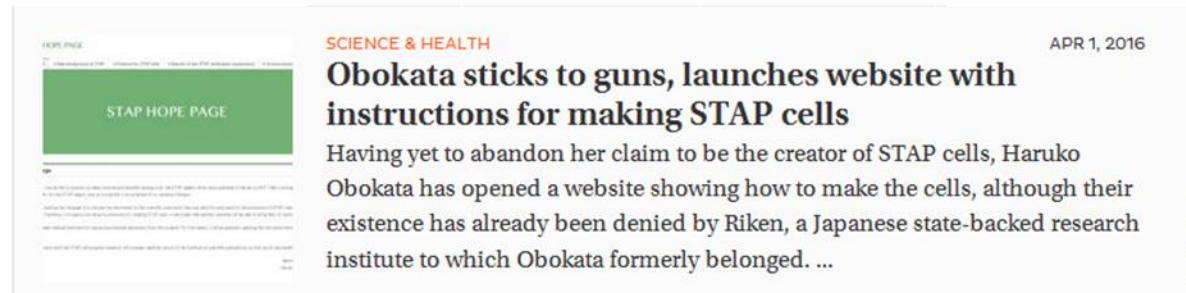
The academic scandal over a debunked stem cell discovery has taken a criminal turn, with police questioning the scientist at the center of the storm. Disgraced researcher Haruko Obokata recently underwent voluntary questioning in connection with the alleged theft of stem cell samples from ...

- voluntary questioning in connection with the alleged theft of stem cell samples from her former employer
- Riken itself has not reported any crime
- A container labeled “ES cells” was found in Obokata’s laboratory during the investigation, but Obokata denied mixing them

March-April 2016

The Japan Times

HARUKO OBOKATA



→ Haruko Obokata has **opened a website** showing how to make the cells (**Protocol for STAP cells**), although their existence has already been denied by Riken

→ English-language website **STAP Hope Page**:

“My goal in starting this webpage is to provide the information to the scientific community that may allow for solid proof of the production of STAP cells to be achieved,” she writes

→ Obokata is under medical treatment for mental and physical depression from this incident

Thank you for your attention!