Precision Breeding for improved Animal Health and Welfare

Mitch Abrahamsen, PhD. Chief Commercial and Scientific Officer

Acceligen a division of recombinetics

Recombinetics' Proprietary Gene-editing Platform: 3 Product Lines

Biomedical / Human Applications

Food Animal Applications

surrogen	regenevida	acceligen
Pre-Clinical Research	**Regenerative Medicine**	**Animal Agriculture**
Biomedical Models for Developing Human Therapeutics	**Transplantable Cells, Tissues, & Organs**	**Precision Breeding for Animal Health & Productivity**

RCI gene-edits animal cells (not human cells)
Differentiated and competitive advantage with access to multiple commercial markets

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Editing to cure disease – Somatic cell editing (gene therapy)
Editing for genetic improvement – Germline editing

August 2018:
Closed $34 million
Series A Round
Recombinetics

2019:
Direct Funding
Acceligen

Business Overview

Acceligen
Food Animal Applications

Animal Agriculture

Precision Breeding for Animal Health, Welfare & Productivity

Gene-Editing to Select Natural-Occurring Animal Traits

Acceligen partners with key global animal genetics companies based on industry and consumer pull

- ✓ Societal demand for improved animal welfare
- ✓ Proactive response to animal health challenges and food safety concerns
- ✓ Growing population and limited production resources require improved efficiency
- ✓ Climate change and environmental pressures require improved genetics for sustainable production

Animal Welfare

Focus on consumer and regulatory acceptance; traits difficult to achieve by conventional breeding

1. Naturally-hornless (polled) cattle
2. Naturally-cool (SLICK/Thermotolerant)
3. Naturally Castration-Free Swine

Animal Health & Productivity

Focus on key targets for the animal breeding companies; proprietary deployment in genetics company germplasm

1. Limitations within current germplasm (disease resistant)
2. Key factors for production improvement (litter size; growth rate, yield)

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Food Animal Applications

Animal Agriculture

Precision Breeding for
Animal Health, Welfare & Productivity

Accelerating genetic improvement to address critical issues in global farming

Animal Health Overview

Partnerships with global animal genetics companies to meet industry, retailer and consumer demand for:

Technology looking for a problem

vs.

Problem in need of a technology

Who Benefits?

In Europe, These Little Piggies Can't Get to Market.

Precision Breeding Can Provide a Humane Solution for Pork Producers

9TH JANUARY 2018

PIG WELFARE CRISIS CONTINUES: EUROPEAN DECLARATION ON ALTERNATIVES TO PAINFUL SURGICAL CASTRATION FAILS TO DELIVER

European Union Bans Mechanical Castration of Male Pigs Jan. 2018

Precision Breeding Solutions for Cattle Health & Welfare

Second Generation of Recombinetics' Gene-Edited Naturally Hornless (Polled) Cattle

Six new healthy precision-bred calves were born in September 2017 including the world's first precision-bred heifer

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Global Livestock Sector & Cattle in the Tropics

- **Elite genetics are not adapted**
- **Breed development takes time**
- **Can gene editing help solve this problem?**

30% of the land	$1.4 Trillion Global Market	1.3 billion employed Long Value Chains	53% GDP in IN	33% Ag GDP in EE

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Genselle: First Generation Naturally Cool Calf in the News (SLICK/Heat Tolerant) Born in Brazil July 2018

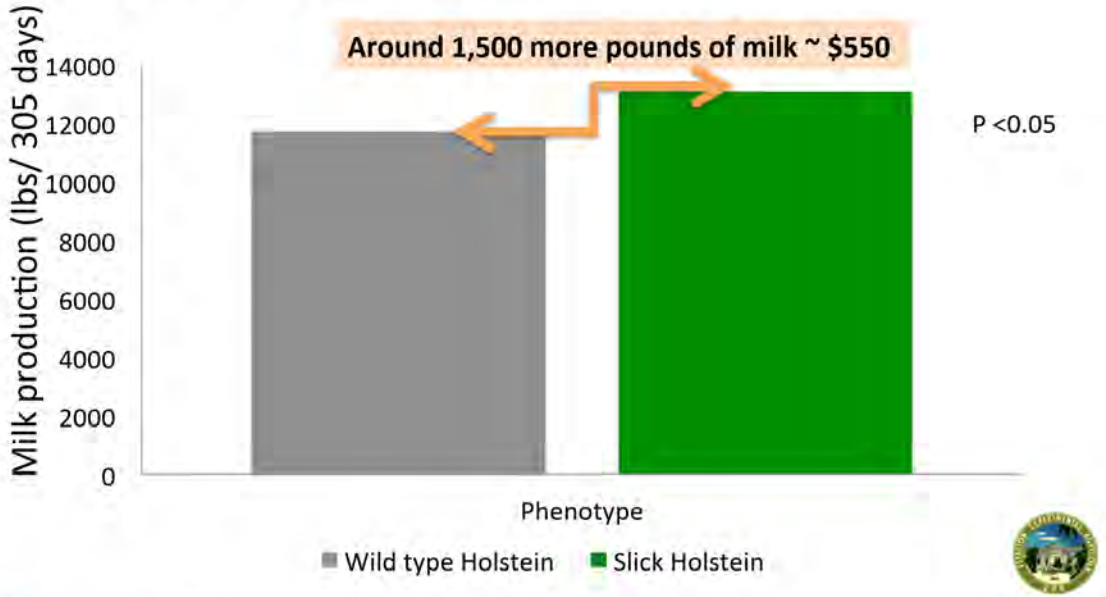
VIDEO THE WALL STREET JOURNAL.

This Gene-Edited Calf Could Transform the Beef Industry

Is Geneselle Naturally Cool™ in a Brazilian way?

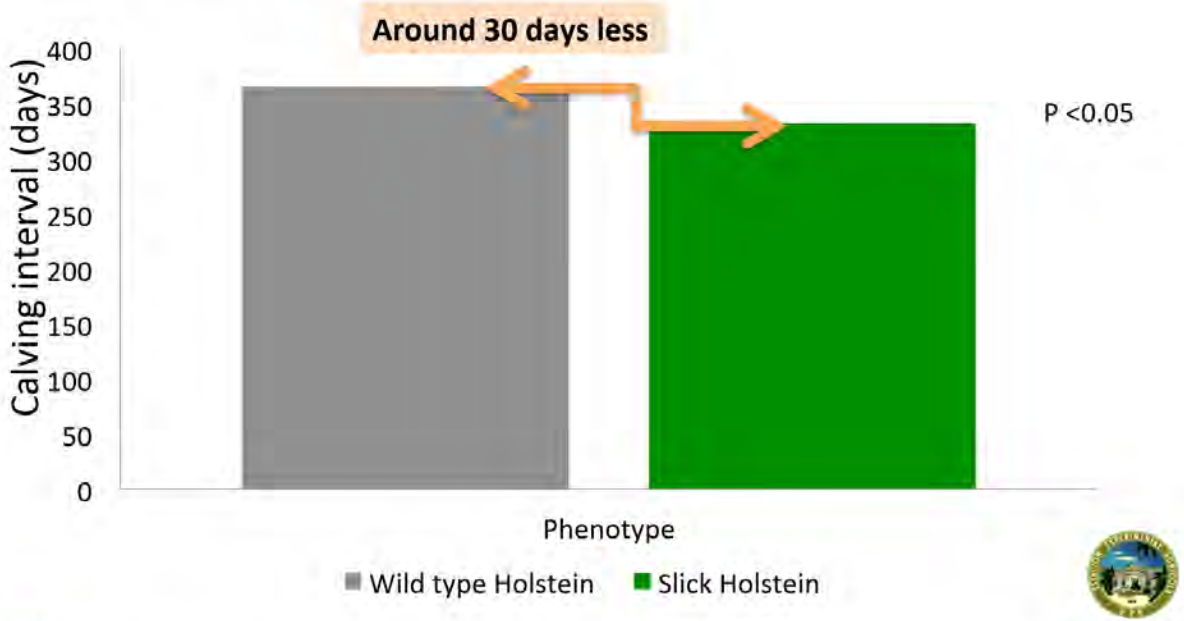
How much is SLICK worth for dairy?

Figure 3. Milk production of Puerto Rican Holstein cows with different hair coat



USDA United States Department of Agriculture National Institute of Food and Agriculture This work is supported by the USDA National Institute of Food and Agriculture, Hatch projects H-444 (AN:100450), H-452 (AN: 1003628), and H-453 (AN: 1003564)

Figure 4. Calving interval of Puerto Rican Holstein cows with different hair coat



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Initial Go-To-Market Strategy

Leverage Strategic Partnerships to Deploy Key Welfare and Economic Traits

Partnerships with leading global genetic companies allow for efficient deployment of key welfare and economic traits with minimal capital constraints and maximized revenue capture.

- Advantages: ***No need to own production systems; leverage developed distribution networks; and access to established customer bases and relationships***

Bovine – Beef and Dairy

- **Naturally Hornless (Polled)**
- **Heat Tolerant (SLICK)**
- **TB Disease Resistance**

Swine

- **Castration-Free Swine**
- **PRRSV Resistance**
- **FMDV Resistance**

Aquaculture

- **Male Sterility**
- **Mono-sexing**
- **Disease Resistance**

Contracted Partners

SEMEX Genetics for Life®

Boviteq™

Benchmark Holdings plc

DNA GENETICS Greater gains. Improved performance.

HENDRIX GENETICS

Naturally Hornless (Polled) Commercial Partnership with Semex

Premier North American Dairy Genetics Company (5/29/18)

NUTRITION & HEALTH

Feedstuffs

Recombinetics, Semex form alliance to improve cattle well-being

SEMEX®
Genetics for Life®

real agriculture

Gene editing allows for polled dairy genetics without the production drag

Good News

AGDAILY

LIVESTOCK NEWS TECHNOLOGY

Precision breeding partnership will eliminate need to dehorn dairy cows

By AGDAILY Reporters • Published: May 29, 2018

■October 1

This Genetics Company Is Editing Horns Off Milk Cows

● Recombinetics says its genetically edited Holsteins are ready to milk, but FDA rules are in flux.

By Adam Piore

Bloomberg Businessweek

Castration-Free Swine Partnership with Hendrix and DNA Genetics

FFAR Awards $500,000 Grant to Improve Swine Health and Well-Being

Researchers at Recombinetics Will Use Advanced Breeding Techniques to Eliminate Need for Surgical Castration

NEWS

Recombinetics, DNA Genetics form alliance to end surgical castration of swine

Alliance aims to improve swine health and well-being by developing precision breeding technology.

National Hog Farmer

Recombinetics and DNA Genetics form alliance to end surgical castrations of swine

Jan 03, 2018

"Precision breeding includes a range of technologies that will have a strong impact on genetic improvement programs. This specific project is an innovative use of precision breeding techniques that have the potential of improving both animal health and efficiency. We are pleased to be a part of making this technology available to the pork industry," Tom Rathje, Chief Technical Officer, DNA Genetics.

NEWS

Hendrix Genetics joins alliance to end surgical castration of swine

Precision breeding technologies will provide solution for pork producers.

HENDRIX GENETICS

FFAR

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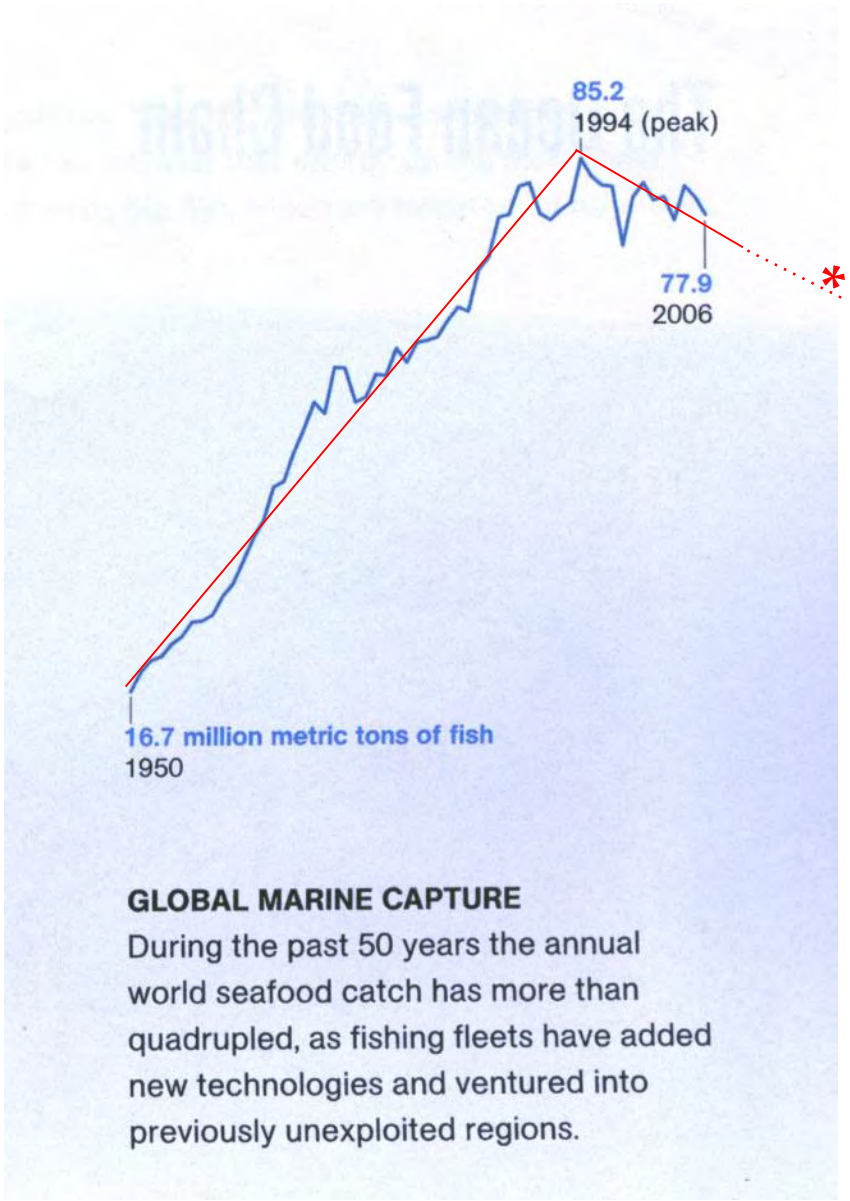
NATIONAL PORK PRODUCERS COUNCIL

U.S. REGULATORY SUPPORT

"NPPC urges the Trump administration to move regulatory oversight of gene editing in animals from the FDA to the USDA's Animal and Plant Health Inspection Service. "

Innovation

- ✓ The challenge - provide genetic improvement of food animals to meet human demands → without compromising animal well-being and the environment
  - What do we want?
    - Closing the yield gap
  - How do we get it?
    - New technologies
  - How do commercialize?
    - Regulatory Environment
      - Domestic
      - International



NBT's are Scientifically-Sound Breeding Methods: We have been safely eating polled cattle for thousands of years

- Hornless (polled) genetics >5000 years old
  - ancient (*celtic*) allele has been found in an Icelandic bovine skull dating back to 1000 AD
- The *celtic* allele found in polled British beef breeds (i.e. Angus) can be safely bred into all dairy breeds
- RCI has proven capability to introduce polled into a horned genetic line of dairy cattle

Who Supports?

- Holstein USA. Buri (father of our 6 new polled calves) is in registry and qualifies for export status
- Humane Society USA supports gene-editing for animal welfare
- National Pork Producers Council
- Semex Alliance

Spotigy & Buri pictured at 1 month,

Regulation by FDA – tied to the pre-DNA past

A drug is something that changes the form or function of an animal

Federal Food, Drug, and Cosmetic Act

Acronym	FFDCA, "FD&C Act"
Enacted by the	75th United States Congress
Citations	
Public Law	75-717
Stat.	52 US Stat. 1040
Codification	
U.S.C. sections created	21 U.S.C. § 301 et seq
Legislative history	

- Signed into law by President Franklin D. Roosevelt on June 25, 1938

The Francis Crick Papers

The Discovery of the Double Helix, 1951-1953

- Biographical Information
- The Discovery of the Double Helix, 1951-1953
- Defining the Genetic Coding Problem, 1954-1957
- Deciphering the Genetic Code, 1958-1966
- Embryology and the Organization of DNA in Higher Organisms, 1966-1976
- From Molecular Biology to Neurobiology, 1976-2004
- Further Readings
- Glossary

Documents Visuals

The discovery in 1953 of the double helix, the twisted-ladder structure of deoxyribonucleic acid (DNA), by James Watson and Francis Crick marked a milestone in the history of science and gave rise to modern molecular biology, which is largely concerned with understanding how genes control the chemical processes within cells. In short order, their discovery yielded ground-breaking insights into the genetic code and protein synthesis. During the 1970s and 1980s, it helped to produce new and powerful scientific techniques, specifically recombinant DNA research, genetic engineering, rapid gene sequencing, and monoclonal antibodies, techniques on which today's multi-billion dollar biotechnology industry is founded. Major current advances in science, namely genetic fingerprinting and modern forensics, the mapping of the human genome, and the promise, yet unfulfilled, of gene therapy, all have their origins in Watson and Crick's inspired work. The double helix has not only

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NATIONAL PORK PRODUCERS COUNCIL

U.S. REGULATORY SUPPORT

"NPPC urges the Trump administration to move regulatory oversight of gene editing in animals from the FDA to the USDA's Animal and Plant Health Inspection Service. "

Possible Pathways to Regulatory Approval

1. White House Executive Order: FDA to USDA reassignment
2. Congressional Farm Bill
3. FDA process – revision; strategic plan
4. Support from Barnyard and other Allies
   - ✓Holstein USA (Buri is registered)
   - ✓Humane Society US supports gene-editing for animal welfare
   - ✓National Pork Producers Council
   - ✓Semex Alliance

Leadership on BIO's Board of Directors Food and Ag Section Governing Board and the Gene Editing Board Advisory Group.

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THE HUMANE SOCIETY OF THE UNITED STATES

NATIONAL PORK PRODUCERS COUNCIL

Bio Biotechnology Industry Organization

A Global Plan of to Bring Desired Products to Market

The U.S. Might Not be a First Mover Here – That is Okay

- ✓ While the U.S. represents a tremendous opportunity for Acceligen, the Company is focusing its resources on markets that already accept the technology.
- ✓ ***Brazil, Canada, Argentina and Australia*** all have favorable impressions of non-transgenic gene editing and have a defined pathway of 6 to 24 months to allow regulatory approval and commercialization of Acceligen's food animal products.
- ✓ ***Japan*** recommends <u>not regulating</u> non-transgenic gene-edited products. Opposite – European Court of Justice ruled all gene-editing is GMO.

Coordination of early adopters will drive global regulatory alignment/harmonization among "like minded" countries

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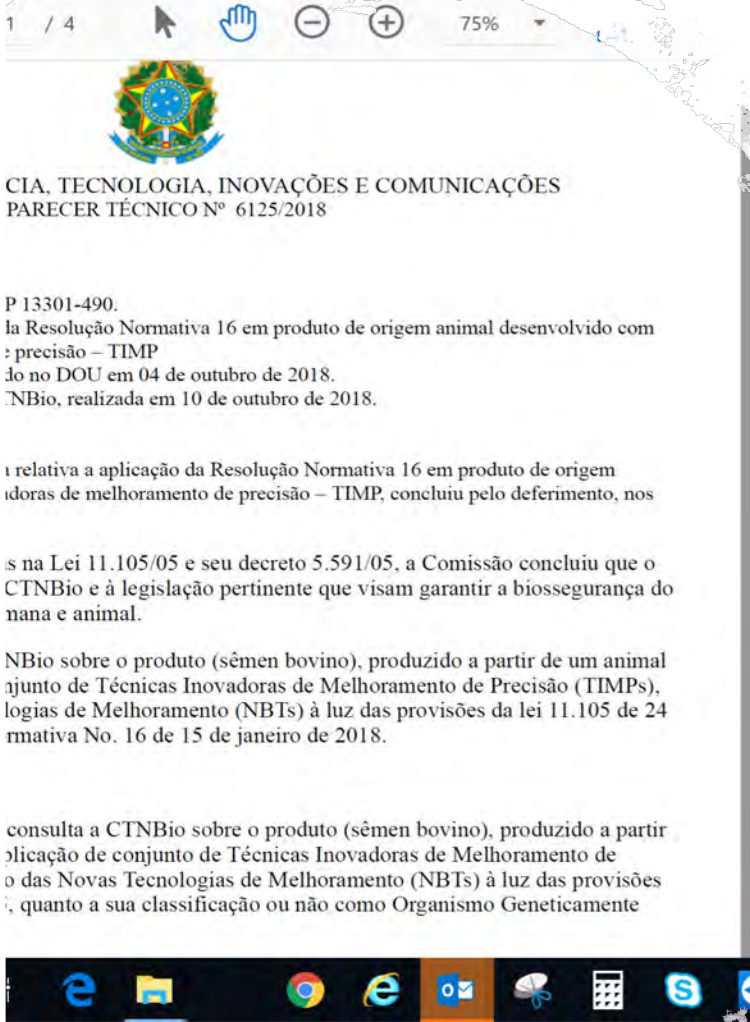


CIA, TECNOLOGIA, INOVAÇÕES E COMUNICAÇÕES
PARECER TÉCNICO Nº 6125/2018

P 13301-490.
la Resolução Normativa 16 em produto de origem animal desenvolvido com
precisão – TIMP
do no DOU em 04 de outubro de 2018.
NBio, realizada em 10 de outubro de 2018.

relativa a aplicação da Resolução Normativa 16 em produto de origem
doras de melhoramento de precisão – TIMP, concluiu pelo deferimento, nos

s na Lei 11.105/05 e seu decreto 5.591/05, a Comissão concluiu que o
CTNBio e à legislação pertinente que visam garantir a biossegurança do
nana e animal.

NBio sobre o produto (sêmen bovino), produzido a partir de um animal
njunto de Técnicas Inovadoras de Melhoramento de Precisão (TIMPs),
logias de Melhoramento (NBTs) à luz das provisões da lei 11.105 de 24
rmativa No. 16 de 15 de janeiro de 2018.

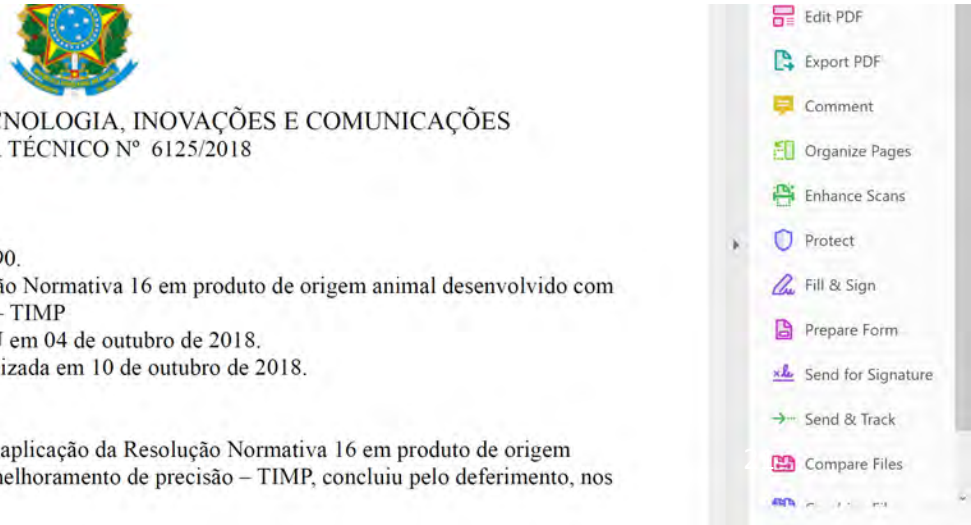
consulta a CTNBio sobre o produto (sêmen bovino), produzido a partir
plicação de conjunto de Técnicas Inovadoras de Melhoramento de
o das Novas Tecnologias de Melhoramento (NBTs) à luz das provisões
, quanto a sua classificação ou não como Organismo Geneticamente

October 4, 2018: Brazilian Government Declares Buri's Polled Progeny Non-GMO

Brazil is Bullish on Gene-Editing: Non-GMO

Regulatory movements - Naturally Polled™

- **Brazil – polled is non-GMO according to law – open for commercialization**
- CAN – introgression of the polled allele is likely not a novel food; testing the system
- AUS – pregnancies established from Buri – due in March – test OGTR's system
- USA – FDA has given relief on recips and polled calves of founder animals being allowed into food chain – but is a DNA sequence variant really a drug?
- EU – gene editing = GMO; so this July 2018 decision completely block gene editing innovations in food animals



.ÉRIO DA CIÊNCIA, TECNOLOGIA, INOVAÇÕES E COMUNICAÇÕES
PARECER TÉCNICO Nº 6125/2018

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nsulta relativa a aplicação da Resolução Normativa 16 em produto de origem animal desenvolvido com
vadoras de melhoramento de precisão – TIMP
évio nº: 6193/2018 , publicado no DOU em 04 de outubro de 2018.
. 216ª Reunião Ordinária da CTNBio, realizada em 10 de outubro de 2018.
: DEFERIDO

NBio, após apreciação da Consulta relativa a aplicação da Resolução Normativa 16 em produto de origem
nal desenvolvido com técnicas inovadoras de melhoramento de precisão – TIMP, concluiu pelo deferimento, nos
mos deste Parecer Técnico.

Innovation Consortium Announced @WTO

- Argentina*
- Australia
- Brazil
- Canada
- Colombia
- the Dominican Republic
- Guatemala
- Honduras
- Jordan
- Paraguay
- the United States
- Uruguay
- Vietnam
- The Secretariat of the Economic Community of West African States.

surrogen

'TO Members Support Policy Approaches to Enable Innovation in Agriculture

SDA Office of Communications sent this bulletin at 11/02/2018 12:02 PM EDT

View as a webpage

Press Release

WTO Members Support Policy Approaches to Enable Innovation in Agriculture

WASHINGTON, Nov. 2, 2018 – U.S. Secretary of Agriculture Sonny Perdue today announced that the United States has joined with 12 other nations to support policies that enable agricultural innovation, including genome editing. The International Statement on Agricultural Applications of Precision Biotechnology was released in Geneva at the World Trade Organization (WTO) Committee on the Application of Sanitary and Phytosanitary Measures.

"Precision biotechnologies such as genome editing hold great promise for both farmers and consumers around the world. These tools can play a critical role in helping farmers address many of the production challenges they face while improving the quality and nutritional value of foods available to consumers worldwide," said Perdue.

"Unfortunately, such technologies too often face regulatory roadblocks that are based on misinformation and political posturing. Therefore, it's gratifying to see Argentina and other allies come together under the WTO umbrella to publicly embrace science-based regulatory systems that will allow us to unlock the huge potential of these new

Bad experiments -> bad papers -> bad publicity

Correspondence

Unexpected mutations after CRISPR–Cas9 editing *in vivo*

Kellie A Schaefer, Wen-Hsuan Wu, Diana F Colgan, Stephen H Tsang, Alexander G Bassuk ✉ & Vinit B Mahajan ✉

No unexpected CRISPR-Cas9 off-target activity revealed

by trio sequencing of gene-edited mice

Authors

Vivek Iyer *
Katharina Boroviak
Mark Thomas
Brendan Doe
Edward Ryder
David Adams

Nature journal retracts controversial CRISPR paper after authors admit results may be wrong

Nature Methods has retracted a 2017 paper suggesting a common gene editing technique may cause widespread collateral damage to the genome.

The notice has a long backstory: After the paper was published, it immediately drew an outcry from critics (including representatives from companies who sell the tool, whose stock fell after publication)

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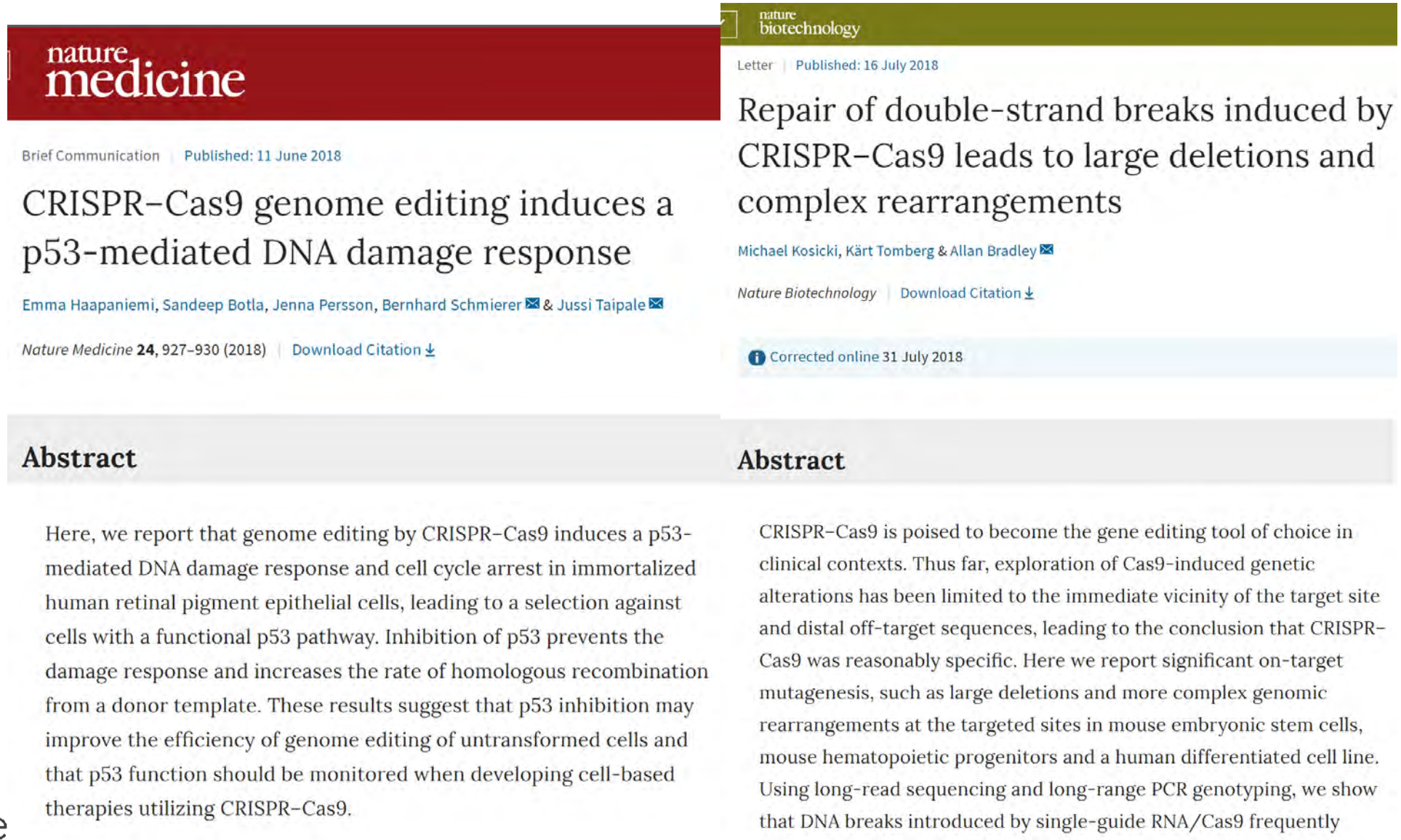
Not relevant outside the laboratory…



nature medicine

Brief Communication | Published: 11 June 2018

CRISPR–Cas9 genome editing induces a p53-mediated DNA damage response

Emma Haapaniemi, Sandeep Botla, Jenna Persson, Bernhard Schmierer & Jussi Taipale

Nature Medicine **24**, 927–930 (2018) | Download Citation

Abstract

Here, we report that genome editing by CRISPR–Cas9 induces a p53-mediated DNA damage response and cell cycle arrest in immortalized human retinal pigment epithelial cells, leading to a selection against cells with a functional p53 pathway. Inhibition of p53 prevents the damage response and increases the rate of homologous recombination from a donor template. These results suggest that p53 inhibition may improve the efficiency of genome editing of untransformed cells and that p53 function should be monitored when developing cell-based therapies utilizing CRISPR–Cas9.

nature biotechnology

Letter | Published: 16 July 2018

Repair of double-strand breaks induced by CRISPR–Cas9 leads to large deletions and complex rearrangements

Michael Kosicki, Kärt Tomberg & Allan Bradley

Nature Biotechnology | Download Citation

Corrected online 31 July 2018

Abstract

CRISPR–Cas9 is poised to become the gene editing tool of choice in clinical contexts. Thus far, exploration of Cas9-induced genetic alterations has been limited to the immediate vicinity of the target site and distal off-target sequences, leading to the conclusion that CRISPR–Cas9 was reasonably specific. Here we report significant on-target mutagenesis, such as large deletions and more complex genomic rearrangements at the targeted sites in mouse embryonic stem cells, mouse hematopoietic progenitors and a human differentiated cell line. Using long-read sequencing and long-range PCR genotyping, we show that DNA breaks introduced by single-guide RNA/Cas9 frequently

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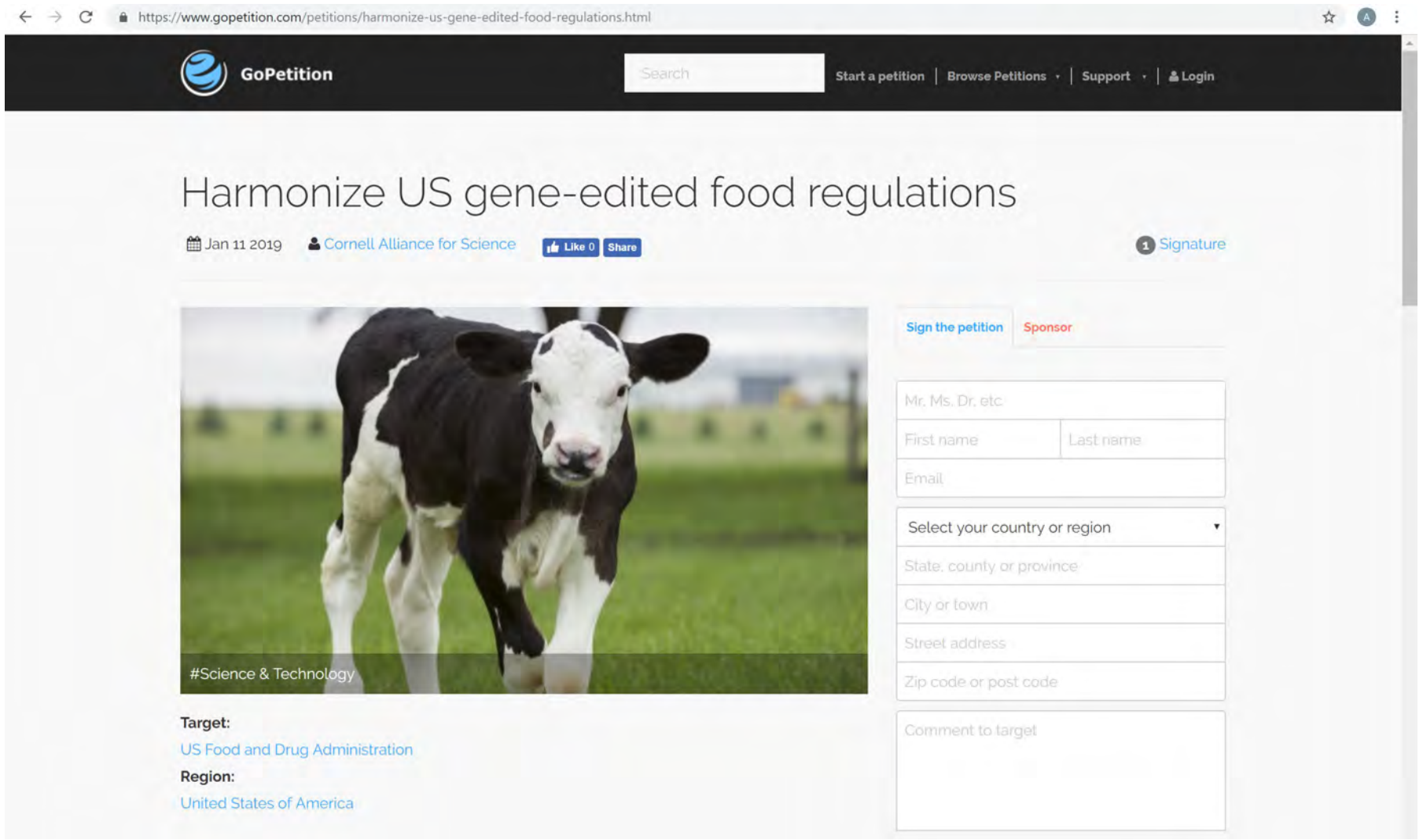
ANIMAL SCIENCE

https://www.gopetition.com/petitions/harmonize-us-gene-edited-food-regulations.html

https://tinyurl.com/DNAisNOTaDRUG



New Breeding Techniques for Naturally-Occurring Traits; Bringing Precision-Bred Food Animals to Market

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