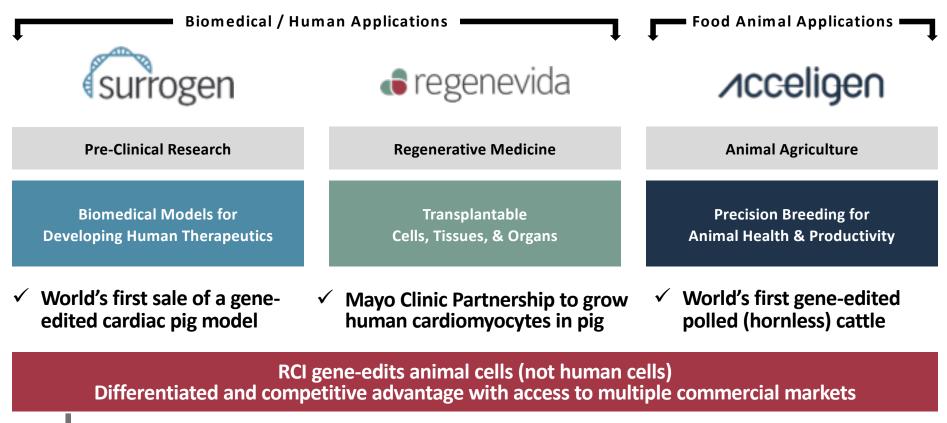
Precision Breeding for Animal Health and Productivity: What does it take to deploy technology in the market place?

> Mitch Abrahamsen, Ph.D. Recombinetics Chief Commercial and Scientific Officer

Acceligen a divisio

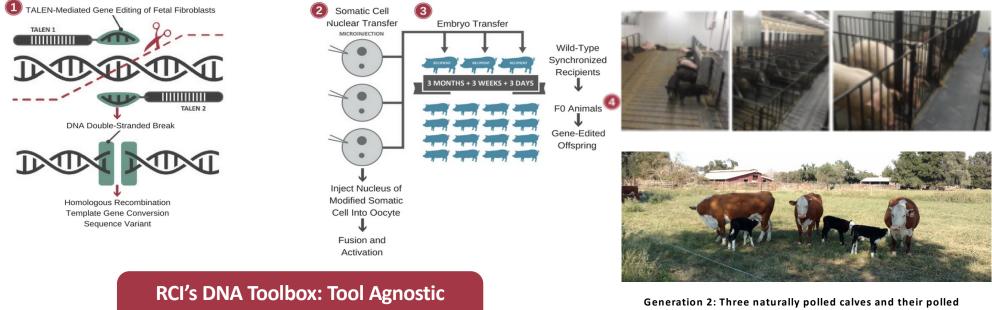
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Recombinetics' Single Gene-editing Platform: 3 Products Lines



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Biomedical Swine Models + Food Animals on the Ground Technology Proven and In Play



TALENs, CRISPR, other Gene-Editing Methods

Generation 2: Three naturally polled calves and their polled mothers 6 new calves born September 2017

RCI's Competitive Advantage: Broad IP in Animal Gene Editing

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>300

Patent applications filed globally for gene-editing methods

- U.S. patent rights for CRISPR gene-editing methods in livestock and aquaculture
- Global rights for TALENs as a principal tool for gene-editing in large animals
- Significant patent issuances by scientifically advanced countries; issuance of broad claims in Europe & China
- Substantial intellectual property in advanced reproductive physiology
- Freedom to operate in many areas allowing path to commercialization
- Allowed claims in Europe broadly directed to allele transfer between livestock animals using TALENs

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Next Generation Breeding Technologies

- To date, all genetic progress is the result of traditional animal breeding programs
 - Mate best animals together
 - Select the best progeny based on data available
 - Repeat
- Most improvement have been focused on collecting better data and improved analysis (mathematical modeling)
 - Genomic Selection programs to better identify best animals
- Clear progress on economic traits robust data sets
- Animal Welfare and Health Traits slow progress
- Data issues relating to expressing phenotypes/variation availability

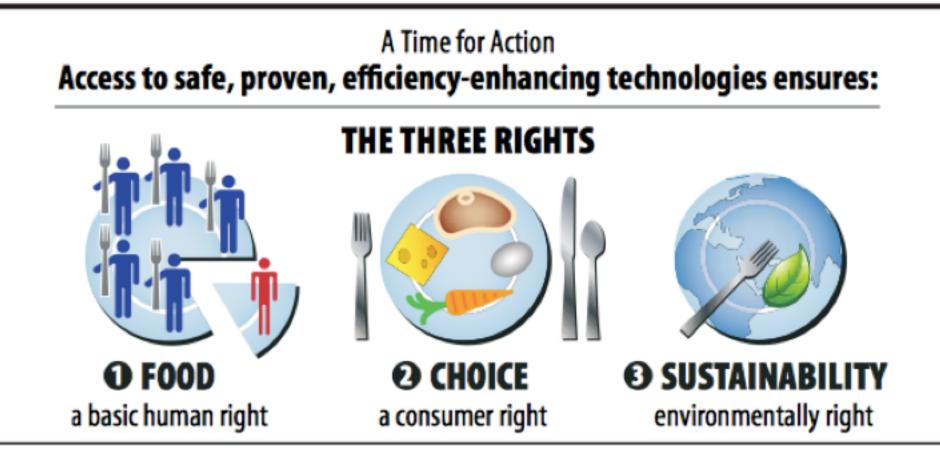
Selective Breeding - Pitfalls

- It is slow and imprecise
- Identifying desirable new genetic variation is a matter of chance
- Selection for specific traits leaves behind favorable variants
- Deleterious mutations may be propagated unintentionally via linkage
- Every round of Reproduction: changes are transmitted
- Gene editing is a complementary tool to use in addition to traditional and genomic selection breeding programs





Drivers for innovation in Animal Agriculture



Drivers for innovation in Animal Agriculture

- Oconsumer expectations developing/developing markets
- Keen interest in how food is produced— developing/developing markets
- OAnimal Welfare issues high visibility emotional
- •New and re-emerging disease challenges
- OEnvironmental impact being quantified/taxed
- Evolving regulations for animal production



Public Perception: Focus on how we treat animals

PRODUCERS

Wanted: More Bulls With No Horns

August 3, 2015 - 4:53 PM ET

ABBIE FENTRESS SWANSON







The rules are changing: How do Breeding companies respond?

Progress Report: Castration of Pigs in the EU

EU - For centuries, surgical castration has been performed on pig farms across Europe. Until recently, the procedure was performed without the use of anaesthesia or analgesia. But now, the EU has proposed an outright ban on surgical castration, effective 1 January, 2018. While some member states have taken great steps in the right direction, progress in other countries has been slow or non-existent, writes Melanie Epp for The Pig Site.

Porcine Health Manag. 2016; 2: 29. Published online 2016 Dec 20. doi: 10.1185/s40813-016-0046-x PMCID: PMC5382460 PMID: 28405455

Go to: 🖂

Pig castration: will the EU manage to ban pig castration by 2018?

Nancy De Briyne,^{E1} Charlotte Berg,² Thomas Blaha,³ and Déborah Temple⁴

Author information
Article notes
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Abstract	Go to: 🖂

Background

In 2010, the 'European Declaration on alternatives to surgical castration of pigs' was agreed. The Declaration stipulates that from January 1, 2012, surgical castration of pigs shall only be performed with prolonged analgesia and/or anaesthesia and from 2018 surgical castration of pigs should be phased out altogether. 9TH JANUARY 2018

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



FOOD FOR THOUGHT

'Environmental Nightmare' After Thousands Of Atlantic Salmon Escape Fish Farm

August 24, 2017 - 10:52 AM ET

COURTNEY FLATT JOHN RYAN

EDON EARTHEIN



Abused the finiting vessel Warathon, Nicholas Gooke (wit) and Nathan Cultee unload 16 familysiaed Atlantic salmon into a container on Tuesday in Bellingham, Wash. Wager Aleman HCMY

Commercial fishing boats are scrambling to catch as many Atlantic salmon as they can after a net pen broke near Washington's Cypress Island. Fishers reported thousands of the non-native fish jumping in the water or washing ashore.

Public Perception: How do Breeding companies respond?

Grieg Seafood says 21,700 salmon escaped in Loch Snizort

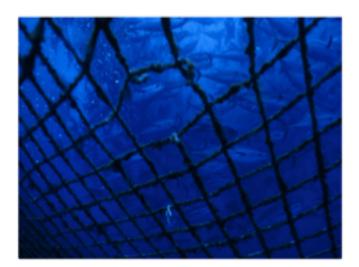
③ 20 February 2018

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Grieg Seafoods said it believed about 21,700 fish had escaped after damage to a cage

A salmon farming company has admitted a major escape from one of its cages anchored in Loch Snizort, near the Isle of Skye.



Keeping Wild Stocks Wild

When fish or shrimp are kept in pens or ponds that are connected to natural waterbodies, some can escape. This isn't as harmless as you might think. In some cases, escapees can impact wild populations by competing with them for food, habitat and spawning partners.

Environmental Concerns

Deliberate sex reversal of farmed fish is common

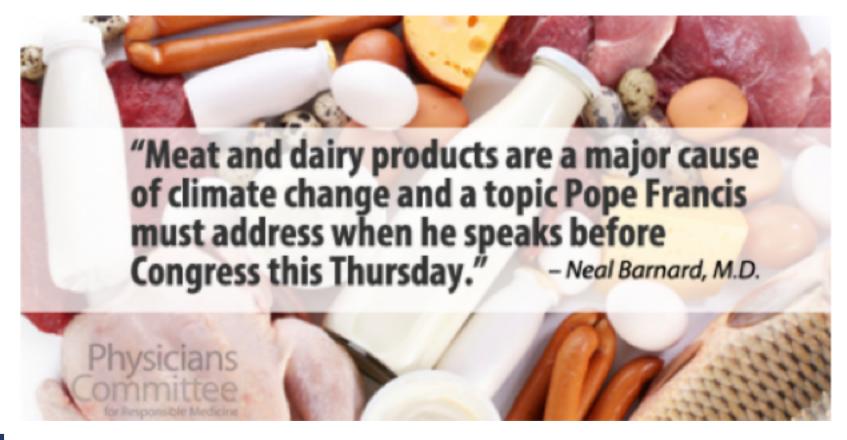
Deliberate sex reversal is a common practice in aquaculture of some popular fish such as tilapia and <u>halibut</u>. The primary purpose is produce fish of the sex that is larger at maturity or otherwise has more desirable commercial characteristics. Sex change is accomplished using a combination of testosterone and other androgens, estrogens, and <u>aromatase inhibitors</u> such as <u>Femara</u> at various life stages of the fish. Efforts are made to keep the hormones to a low enough level to avoid obvious deformities in the fish or compromise their survival. Although use of such hormones does not necessarily mean that the fish themselves have high hormone levels when slaughtered, the safety of this practice has not been established.



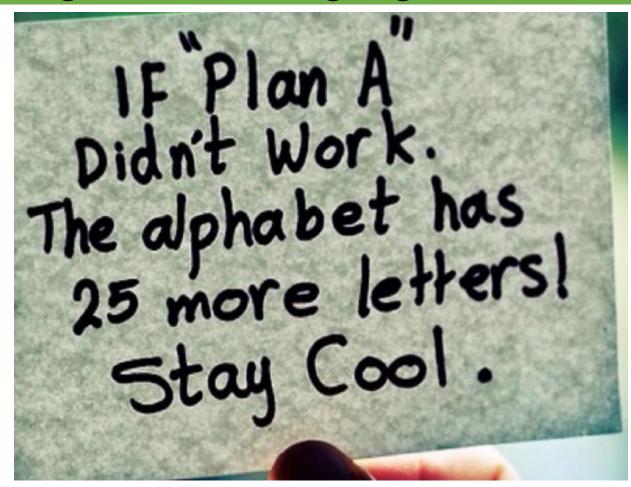
THE PROS AND CONS OF FISH FARMING



Breeding for a Changing World

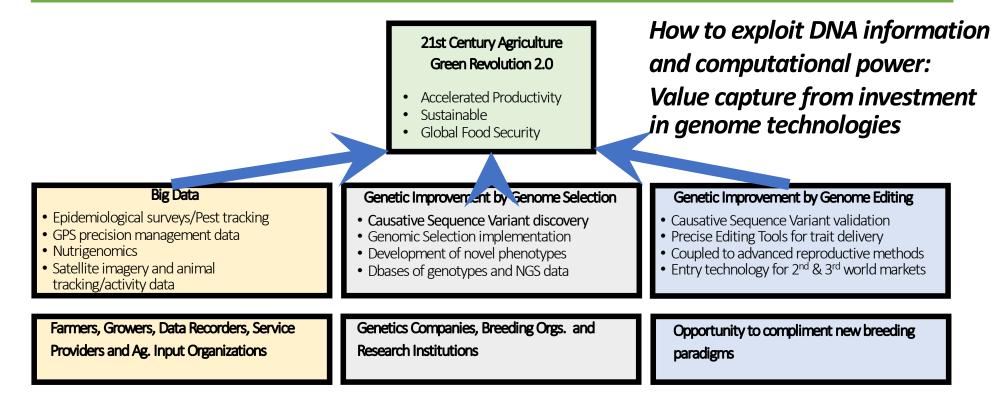


Breeding for a Changing World





Green Revolution 2.0 in Animal Agriculture:



In the era of cheap genotypes; phenotypes are King!

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Acceligen Food Animal Applications

Animal Agriculture

Precision Breeding for Animal Health, Welfare & Productivity



Strategic Overview

Development and Commercialization of Elite Animal Health and Welfare Traits

- Work based on intimate knowledge of public and proprietary genome databases and association study for key animal welfare and productivity traits
- 2. Focus on partnerships with key global genetics and animal breeding companies based on industry and consumer pull
 - ✓ Societal pressure on animal welfare
 - ✓ Growing population
 - ✓ Climate change
 - ✓ Health challenges and food safety concerns

First-to-Market: Animal Welfare Traits

....Consumer and regulatory acceptance; difficult to achieve by conventional breeding

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

Next Up: Animal Productivity Traits

Focus on traits that are key targets for the animal breeding companies to address; proprietary deployment in genetics company's germplasm

- Limitations within current germplasm (disease resistant)
- Key factors for production improvement (litter size; growth rate, vield)
 16



The Challenge: Mechanical Dehorning is Difficult for Animals and Producers



Animal Welfare Problem: Painful Dehorning of Dairy and Beef Cattle

- **1. Population problem:** High Merit dairy animals generally have horns, which must be removed.
- 2. Procedure: ~15 million calves polled each year in US
- **3.** Animal welfare imperative: Dehorning is proven painful, increases risk of infection and death; unpleasant for producers and animals
- Cost: Minimum cost to mechanically poll ~ \$5-\$20 per animal; increased risk of health and wellness. Eg.~\$US138M mortality loss from polling in Australia
- 5. Growing consumer and retailer pressure to address animal welfare in modern supply chains.





Image from http://www.fwi.co.uk/livestock/buyers-guide-calfdisbudders-on-test.htm



Benefits for Animals, Producers and Consumers: Naturally Hornless Calves

- ✓ Benefit to her: no painful, dehorning process
- Benefit to the farmer: avoids unpleasant dehorning process; farmer could spend additional \$5-\$20 on polled semen and break even on the cost of dehorning
- ✓ Benefit to consumers and retailers: Naturally Hornless animal welfare trait provides "guilt free" milk and meat



Commercial Partners (Global Genetics Companies) On Board

U.S. Regulatory Framework Lags Science



Acceligen's NBT Advantage: Unique Development Capability



Regional adaptations



Value added





Disease resilience



- Genetic Improvement
 Animal breeders are king
 - DNA chips and NGS
 - Outputs Dairy production comparisons
 - USA 9.61 tons milk/cow
 - Germany 7.08 tons milk/cow
 - New Zealand 4.62 tons milk/cow

The Yield Gap in Dairy

- Brazil 1.38 tons milk/cow
- □ India produces 1.15 tons milk/cow
- Africa has 3 top ten cow number countries – none in top 20 for production

Gene editing provides

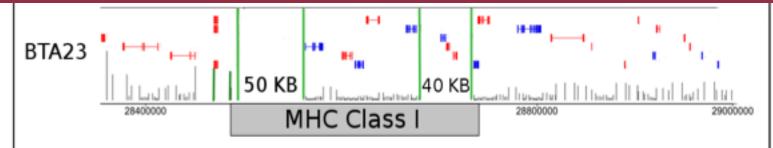
Gene editing provides a rapid and robust approach for adapting elite genetic populations for deployment in tropical regions. 20

Three intuitive ways to close the yield gap for advanced breeding

Adapt elite breeds for intensive production in the tropics

Accelerate production from indigenous, adapted breeds

Disease resistance – when there is no host resistance





Go to market strategy: MESSAGING and POSITIONING

Absolutely critical for success: Science vs Passion



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







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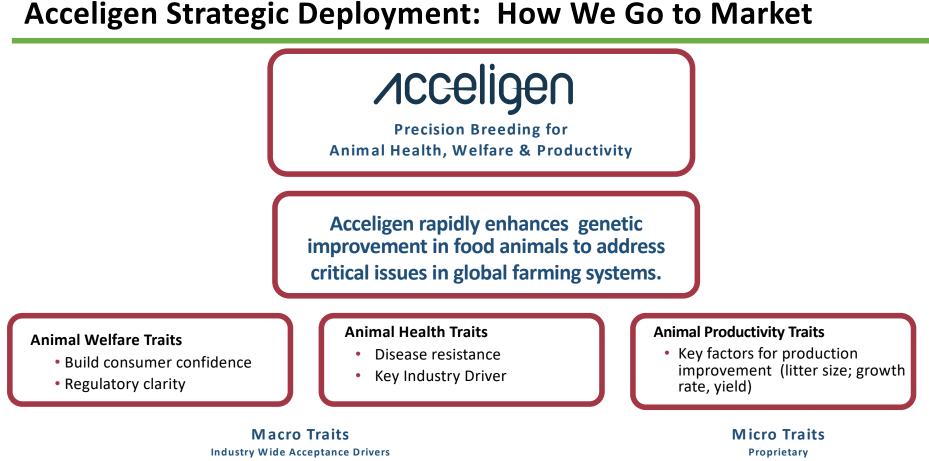
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First Movers Preferences Dominant Traits Impacting all Genetic Stocks

25

Competitive Advantage

Unique to Specific Genetic Stocks

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Acceligen's Elite Traits will be Commercialized with Partners



- Bovine Beef and Dairy
- Naturally Hornless (Polled)
 - ✓ Two global genetics

companies as commercial partners North America and European based

- Heat Tolerant (SLICK)
 - ✓ Animals to be born Q2 2018
- TB Disease Resistance
 - ✓ \$1.3 M development grant received Q1 2018; funding

from 3 countries for isolation of disease resistance genesMeat Yield (Double Muscle)





Swine

• Castration-Free Pigs ✓ Commercialization

> development grant received; Agreements with two major swine genetics companies focused on animal

development

- PRRSV
 - ✓ Development and commercial partner identified
- FMDV
 - Proof of concept animal developed; semen collection in progress to develop production



Aquaculture

- Male Sterility and Monosexing
 - ✓ Development and commercial partner identified; LOI signed

Partnerships with leading global genetic companies

allow for efficient deployment of key welfare and economic traits with minimal capital constraints and maximized revenue

- capture.
- No need to "own" genetic stocks; access to established elite and commercially relevant genetics
- No need to own production systems
- Exploit developed distribution networks
- Exploit established customer bases and relationships

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Consumer/Producer Acceptance

A Changing Consumer Acceptance Trend?

HOW GENE EDITING WILL CHANGE AGRICULTURE

By Betsy Freese 11/22/2016

For thousands of years, farmers have been choosing which traits their crops and livestock carry by using selective breeding. The first genetically modified crops were commercialized in the 1990s. In 2012, a huge scientific breakthrough changed what is possible yet again.

Gene editing, led by the discovery of CRISPR-Cas, promises widespread, accelerated, and targeted discoveries. Areas of the genome linked to specific traits can now be precisely edited. Cut and paste, so to speak. Gene editing could eventually provide a catalog of options for farmers to

order exactly what they need. Think of it like customizing a tractor. Don't need a frontend loader? Remove it. Need dual rear wheels? Add them.

NOT YOUR OLD GMOS

Gene editing allows scientists to genetically engineer organisms without inserting foreign (transgenic) DNA. This makes it different from GMOs and means it may not be regulated the same. In fact, the USDA has already ruled that certain uses of CRISPR-Cas technology, such as keeping mushrooms from turning brown, will not be regulated as GMOs. (CRISPR is the guide that controls the precise gene editing. Cas represents the molecular scissors that do the cutting.)

When GMO crops first came into widespread use in agriculture in the 1990s, the initial information from companies using the technology was vague, assuming the public would both understand and accept the technology. Today, those companies realize they need strategic plans to educate both farmers and consumers about the benefits of this technology. While few people question the use of GMOs to produce medicine (insulin-producing bacteria, for example), someone whose life depends on regular insulin injections might reject GMO crops.





Enhancing animal welfare via genetic modification

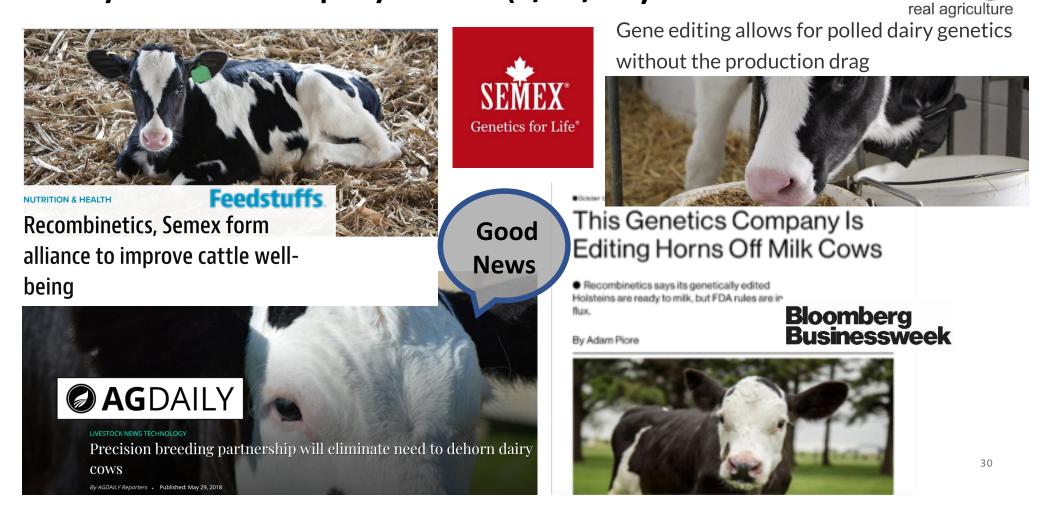
8. Share 👩 4 👽 Tweet 🖗 0 in 0 🕰 0



Dehorning cattle is going to become one of the primary issues facing the dairy and beef industry in the near future, Dr. Jen Burton, veterinarian for Organic Valley CROPP Cooperative, predicted last year.

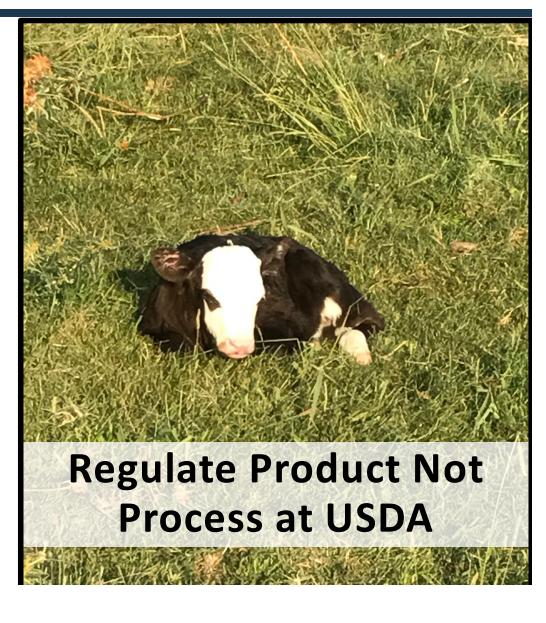
Gene editing could be one way to save livestock from painful procedures such as dehorning. This type of genomic alteration is called subgenic, and doesn't involve genes from other species, but is simply a manipulation of the animal's genetic material working within the available genetic material from the same species.

Naturally Hornless (Polled) Commercial Partnership with American Dairy Genetics Company Semex (5/29/18)



Acceligen's Regulatory Position

- 1. Non-transgenic food animals should be regulated by USDA, not FDA.
 - Acceligen's gene-edited animals have native traits and are not GMO. Naturally-occurring genes are not drugs.
- 2. Our gene-editing technology and process is precise and safe, with no off-target effects.
 - Naturally-occurring alleles from the same species selected to make hornless cattle. We've been safely eating hornless cows for millennia.
- Traditional breeding methods are not subject to regulation; Gene-editing just accelerates desired traits
 - Traditional breeding requires ~20 generation backcross from horned to polled to return to high value milk productivity and quality
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Pathway to Regulatory Approval

- 1. Working with White House, USDA and Congress to get regulatory purview for Gene-Edited animals moved from FDA to USDA
 - Coordination with White House and USDA Interagency Task Force on Agriculture and Rural Prosperity
 - ✓ 2018 Farm Bill
- Concurrently, seek regulatory approval in a country outside the U.S. for our gene-edited bovine and swine where the pathway is defined or deregulated.
 - US government will need to address trade disparities. Focus countries: Brazil; Australia; New Zealand; Argentina; Canada; Ireland. China TBD with commercial partner.
- 3. Round Up the Barnyard and other Allies
 - Holstein USA. Buri (father of our 6 new polled calves) is in registry and qualifies for export status
 - Humane Society US supports gene-editing for animal welfare
 - ✓ National Pork Producers Council
 - ✓ Semex Alliance









Farm Bill 2018:

Policy, Politics, and Potential

and the Gene Editing Board Advisory Group.



Castration-Free Swine Partnership: 2 International Genetics Companies and Recombinetics Plus NPPC Advocacy

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

M POSTED ON DECEMBER 14, 2017 🛛 CATEGORIES: GRANT, NEWS 🔍 NO COMMENTS YET

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



NEW

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.







Hendrix Genetics joins alliance to end surgical castration of swine

Precision breeding technologies will provide solution for pork producers.



We need to think differently!

NO ONE EVER ACHIEVED SUCCESS BY DOING THE SAME OL', SAME OL'.

.....After all, electricity and the light bulb were not invented by incremental improvements to the candle





a division of recombinetics



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