Biotechnology Innovation Organization

The State of Innovation

Opportunities and Challenges
Bringing Animal Biotech Products to Market

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BIO Food and Agriculture

Opportunities

- Challenges of plant and animal breeding
  - Limited to traits that exist in breeding populations
  - Selection for desirable traits can introduce negative ones
  - Slooooow!

- The promise of new genome editing tools
  - Flexible, faster, relatively inexpensive
  - Wider array of species
    - Fruits, vegetables, trees, grasses, animals
  - Diversity of traits
    - Climate change adaptation, drought tolerance, pest resistance
    - Consumer traits: longer shelf life, improved nutritional profiles
    - Animal health and welfare
  - Accessible to a broader range of developers

Genome Editing in Animals

Increased meat production	Cattle, sheep, goat, pig
Hornlessness (polled)	Cattle
Removed boar taint	Pig
Sterility	Pig, chicken, fish
Gender selection	Chicken
PRRSV resistance	Pig
ASFV resilience	Pig
Bovine tuberculosis resilience	Cattle
Enhanced omega-3 content	Fish

Derived from Tait-Burkard et al 2018

Genome Editing in Animals

Acceligen
A RECOMBINETICS COMPANY

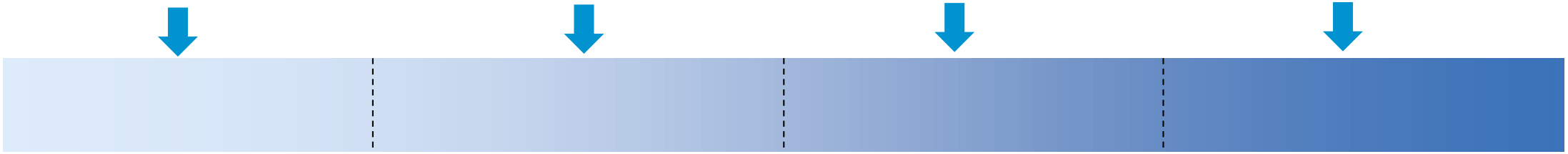
Heat Tolerant Cattle

Genus

PRRSv Resistant Pigs

Genome Editing Continuum

Targeted Deletion Mutation	Targeted Gene Editing	Targeted Gene Insertion	Targeted Gene Insertion
Allele silencing through small deletions or additions	Recreate an allele from a wild relative	"Cisgenic" Insert gene from same gene pool	"Transgenic" Insert gene from any source



Similar to:	Natural and induced mutations	Conventional breeding	GMO?	GMO

Policy Implications

- Fewer genetic changes than breeding and mutagenesis
  - Unintended changes less frequent than background genetic variability
- Products difficult to distinguish from those created by other techniques
  - Genetic changes may look identical to changes created via other means
- Broader application
  - More developers, more organisms, more traits
- Success of technology will depend on expense of regulatory systems

Consequences

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PERSPECTIVE OPEN

Proposed U.S. regulation of gene-edited food animals is not fit for purpose

Alison L. Van Eenennaam[1], Kevin D. Wells[2] and James D. Murray[1,3]

Dietary DNA is generally regarded as safe to consume, and is a routine ingredient of food obtained from any living organism. Millions of naturally-occurring DNA variations are observed when comparing the genomic sequence of any two healthy individuals of a given species. Breeders routinely select desired traits resulting from this DNA variation to develop new cultivars and varieties of food plants and animals. Regulatory agencies do not evaluate these new varieties prior to commercial release. Gene editing tools now allow plant and animal breeders to precisely introduce useful genetic variation into agricultural breeding programs. The U.S. Department of Agriculture (USDA) announced that it has no plans to place additional regulations on gene-edited plants that could otherwise have been developed through traditional breeding prior to commercialization. However, the U.S. Food and Drug Administration (FDA) has proposed mandatory premarket new animal drug regulatory evaluation for all food animals whose genomes have been intentionally altered using modern molecular technologies including gene editing technologies. This runs counter to U.S. biotechnology policy that regulatory oversight should be triggered by unreasonable risk, and not by the fact that an organism has been modified by a particular process or technique. Breeder intention is not associated with product risk. Harmonizing the regulations associated with gene editing in food species is imperative to allow both plant and animal breeders access to gene editing tools to introduce useful sustainability traits like disease resistance, climate adaptability, and food quality attributes into U.S. agricultural breeding programs.

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The reason some cattle grow horns whereas others do not (Fig. 1), and a Granny Smith looks different from a Red Delicious apple is due to selection by breeders on naturally-occurring variations in genomic DNA sequences. Technically, these variations are known as alleles and result from changes, or variations, in the DNA sequence caused by mutations. There are literally millions of naturally-occurring DNA variations between any two healthy individuals of a given species. These variations are the reason genetic tests like "23andMe™" can identify family members and lineages; we share more unique alleles, or mutations, with our close relatives than we do with unrelated individuals.

To put this in perspective, one study of whole genome sequence data from 2703 individual cattle in the 1000 Bull Genomes Project revealed more than 86.5 million differences (variants) between different breeds of cattle. These variants included 2.5 million insertions and deletions of one, or more, base pairs of DNA, and 84 million single nucleotide variants, where one of the four nucleotides making up DNA (A, C, G, T) had been changed to a different one.[1] A small fraction of these mutations have been selected by breeders owing to their beneficial effects on characteristics of agronomic importance. None of these naturally-occurring variants are known to produce ill effects on the consumers of milk or beef products. In fact, every meal we have ever consumed is genetically distinct from every other meal in terms of genomic DNA sequences. Genetic variation per se does not pose a unique hazard as it relates to food safety. All non-processed foods harbor DNA as a natural component and that DNA is different in every individual of every food species (both plants and animals).

Variations in the DNA between individuals result in differences in appearance, known as phenotypes. The observable characteristics of each selection candidate (individual that may be selected for breeding), resulting from the interaction of its genotype with the environment, are recorded during routine phenotypic evaluations. So-called "off-types" that deviate from the desired characteristics are identified and not used for breeding purposes. Breeders select only the most viable, productive, and healthy individuals to be parents of the next generation. In the words of one animal geneticist,[2] "For millennia, animal breeders have performed what amounts to a mega-scale, phenotype-driven mutagenesis screen."

Although plants and animals produced from conventional breeding methods are routinely evaluated for changes in productivity, reproductive efficiency, reactions to disease, and quality characteristics, they are not routinely evaluated for unintended effects at the molecular level.[3] Regulatory agencies do not evaluate new conventionally-bred varieties for health and environmental safety prior to commercial release. Selection for more productive and resilient plant and animal varieties has been an incredibly important component of improving yield while resulting in a decreased environmental footprint per unit of food production. Since 1960, global livestock productivity has increased 20–30%,[4] due in large part to genetic improvements resulting from selection.[5,6]

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National Hog Farmer

vchal/iStock/GettyImages

Argentina, Brazil and Canada outpacing U.S. in gene editing

Andrew Bailey, NPPC's lead counsel for Science and Technology, says it's important to point out that no other country has approached regulation of GE technologies the same way as FDA is proposing.

Ann Hess | Jun 25, 2019

U.S. pork producers will fall behind global competitors if the U.S. Food and Drug Administration continues to move forward with plans to regulate livestock gene editing as a drug. That was the message the National Pork Producers Council

NEWS IN FOCUS

The firm that developed this transgenic salmon has tried for years to bring it to market in the United States.

BIOTECHNOLOGY

Creators of gene-edited animals bypass US market

Regulatory confusion has prompted some US researchers to seek product approval abroad.

BY HEIDI LEDFORD

In a few weeks, reproductive biologist Charles Long will travel from Texas to São Paulo, Brazil, in search of collaborators willing to take on his studies of gene-edited "I'm going to move the entire damn project down there."

US researchers who develop genetically engineered livestock have long dealt with a dearth of research funding and an uncertain path to market. Many had hoped that the advent of to contain DNA from other species.

But in 2017, the FDA released draft guidance that suggested it will regulate gene-edited animals, too, as 'animal drugs'. The only animal that the FDA has approved by that pathway is a fast-growing genetically engineered salmon,

Fostering Innovation

In order to foster innovation, regulatory systems must:

- Ensure animal health and welfare, food safety, environmental health
- Be science-based, risk proportionate
- Have clear, transparent processes and evaluation criteria with predictable timelines
- Allow animals to be treated as normal animals
- Globally aligned

Social License

Even with appropriate regulatory systems, *what else* might be necessary to support successful commercialization?

- Consumer trust
- Communication
- Product stewardship
- Supply-chain awareness
- Consumer disclosure/labeling?

Thank you!

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