FARM FOUNDATION® FORUM

INNOVATION IN GENE EDITING AND PLANT BREEDING: A LOOK AT SCIENTIFIC ADVANCEMENT AND CONSUMER PERSPECTIVES IN FOOD AND AGRICULTURE

NOVEMBER 7, 2023

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Farm Foundation

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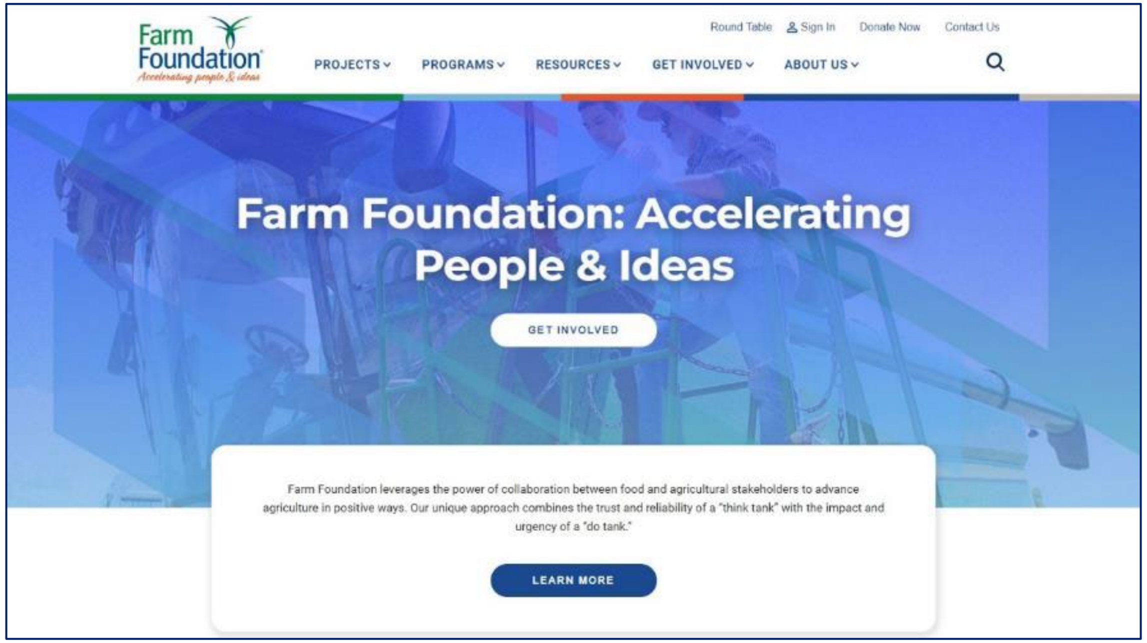

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IMPORTANT NOTES

- Submit questions by clicking on the **Q&A Button** at the bottom of your screen.
- Please **include your name and company** so questions may be contextually understood.
- Due to **time limits**, we may not be able to ask all questions submitted.
- This Forum is being recorded and will be posted on our website at **farmfoundation.org** as well as the Farm Foundation **YouTube** channel.
- Please take the **short survey** at the conclusion of the Forum.

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JAYSON LUSK, PH. D., MODERATOR

Vice President and Dean,
Division of Agricultural Sciences & Natural Resources,
Oklahoma State University

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ALLEN VAN DEYNZE, PH. D.

Director, Seed Biotechnology Center,
Associate Director, Plant Breeding Center,
University of California, Davis

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Gene Editing: An Opportunity to Play?

Allen Van Deynze,
avandeynze@ucdavis.edu

Innovations in Plant Breeding

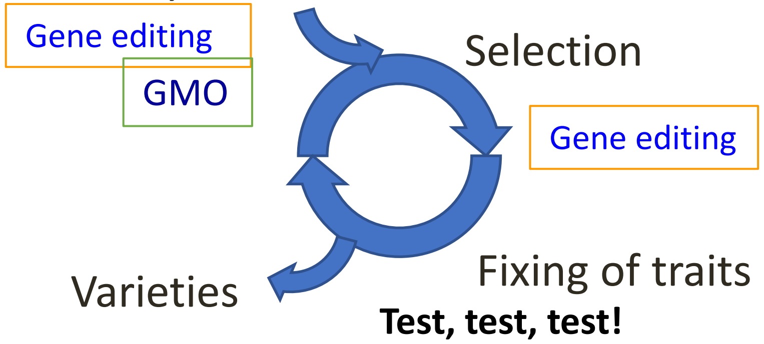
- Understanding genetic principles (Mendel, Hardy and Weiberg; 1865-1910)
- Statistics and Experimental Design (Fisher; Snedecor; Pearson; 1920-30s, Melchinger 2005)
- Hybridization and Heterosis (Shull 1908, East 1936, Gardner 1963)
- **Biotechnology**: tissue culture, mutation breeding, **transgenics**, **gene editing, genome editing,** synthetic biology (1950s+)
- Speed to market technologies: doubled haploids, counter seasonal nurseries
- Genomics and bioinformatics/**machine learning** (1990s+)
- **High Throughput Phenotyping** and **Artificial Intelligence** (2010s+)
- Intellectual Property and Regulation
- A Well-Educated Workforce

Plant Breeding

a product-oriented discipline of sciences rooted in selection theory, quantitative genetics and statistics for crop improvement that encompasses an increasing number of support technologies to sustain society

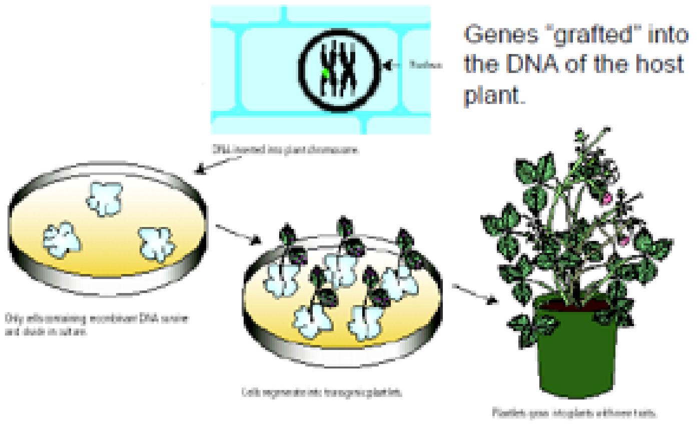
Components:

Generate diversity-controlled crosses



Traditional Gene Modifications Technologies

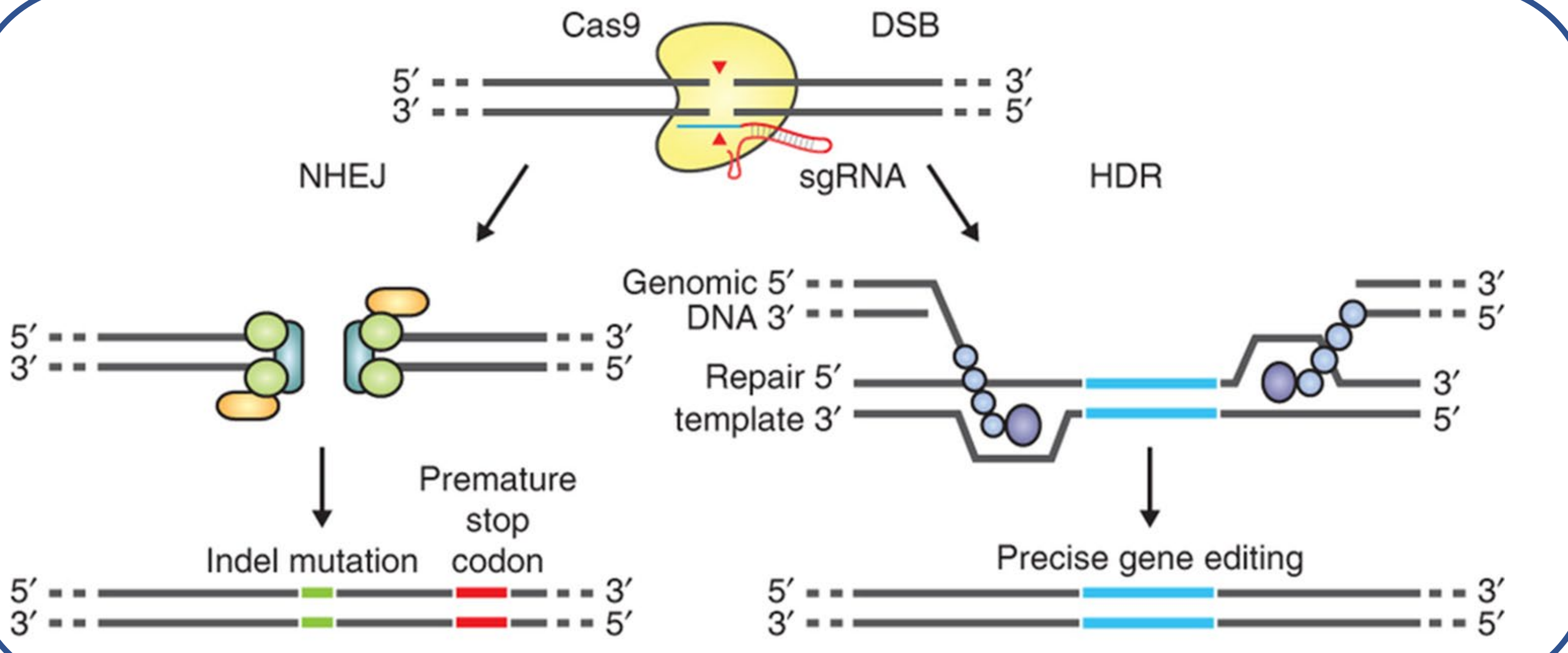
- Agrobacterium Transformation
  - Chromosome integration
  - Limited hosts and genotypes
  - Requires plant regeneration
- Biolistics (gene gun)
  - Chromosome integration
  - More hosts/genotypes?
  - Requires plant regeneration
  - Multiple insertions
  - Gene fragments



Gene Gun

Gene Editing Strategies

- Chromosome integration optional
- Expand hosts and genotypes
- May be more acceptable for regulatory and consumers



Cell

Chromosome

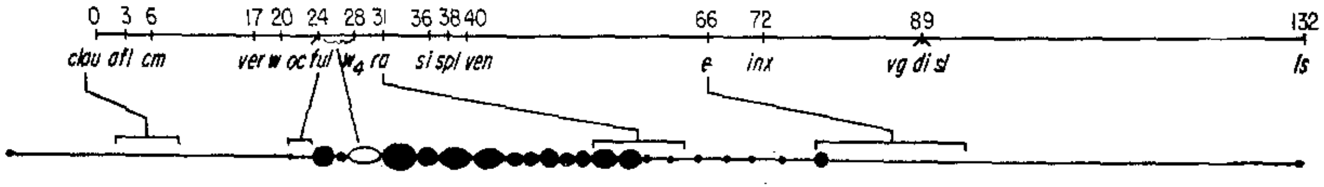
UCDAVIS Plant Breeding Academy

Many New Gene Editing Technologies

- Alternative PAM sites—example CF1 (Cas12)
- Base editing
- Enhancer
- Repressor
- Epigenetic
- Gene stacking

What Are Gene Stacks?

- Simply the combination of genes in plants
- Most plants have >25,000 genes that confer unique combination of traits
- Plant Breeders and farmers have been “stacking” genes for 100s of years.

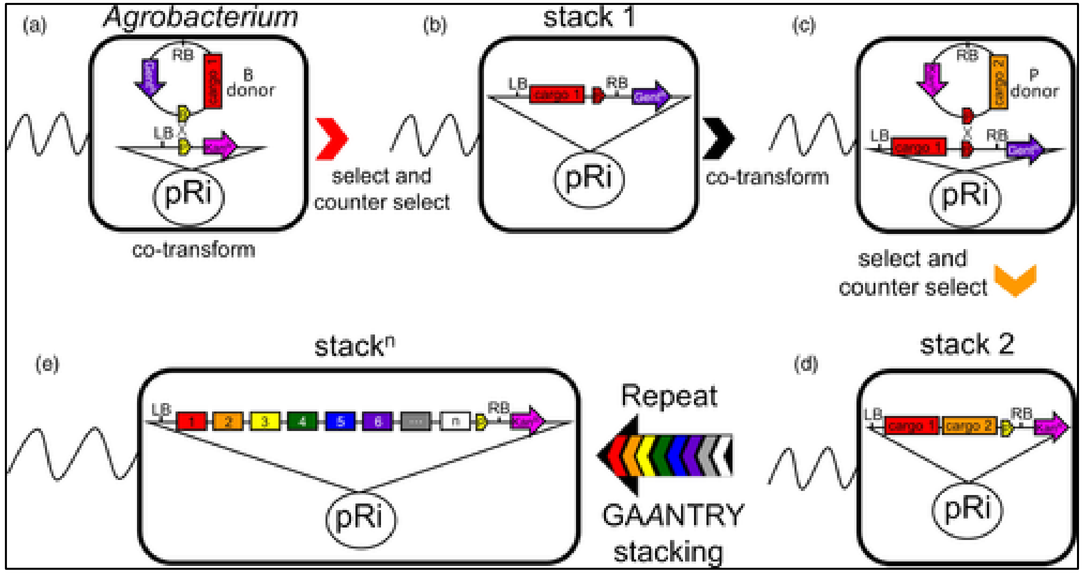


I. *a/l (albi/olium).* Seedlings very slow growing; cotyledons white
II. *clau (clausa).* Leaves more highly divided with acute serrations
III. *cm (curly mottled).* Strong virus-like mottling and distortion

Gurdev S. Khush and Charles M. Rick

Department of Vegetable Crops, University of California, Davis

(Received April 25, 1967)



Collier et al. The Plant Journal, Volume: 95, Issue: 4, Pages: 573-583, First published: 14 June 2018, DOI: (10.1111/tpj.13992)

Breeding Goals (some) for the Next 20 Years

Sustainable production of food, feed and fiber: customer driven

- Increase yields to feed an increasing population
- Increase yields per acre as acres of arable land decline
- Increase water and temperature tolerances due to climate change
- Increase disease and pest resistance as we move away from chemical controls to genetic controls.
- Improve nitrogen use efficiency and nitrogen fixation in all crops
- Enhance attributes of quality, flavor, nutrition, quality

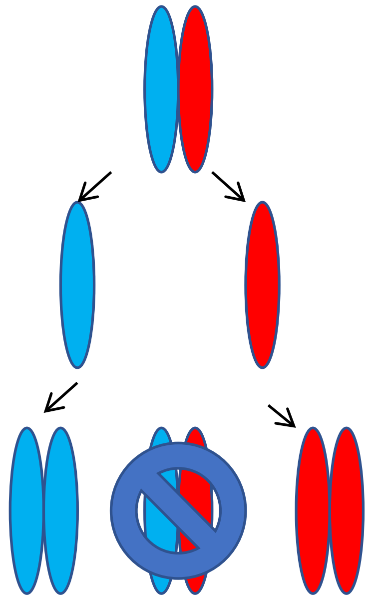
We need all of the tools!

Breeding Tools: Doubled Haploids

- Homozygosity in a single generation
- Reduced population sizes
- More accurate phenotypes

Methods

- CenH3: Engineered centromere-mediated haploids (UC Davis)
- Anther culture
- Microspore culture



Plant Biotechnology Journal Open Access

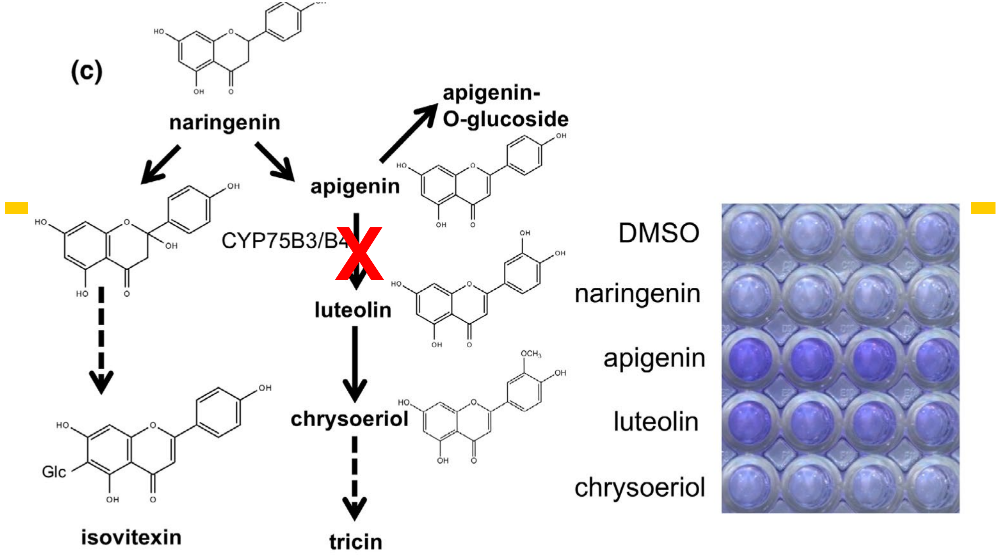
Plant Biotechnology Journal (2022) **20**, pp. 2135–2148

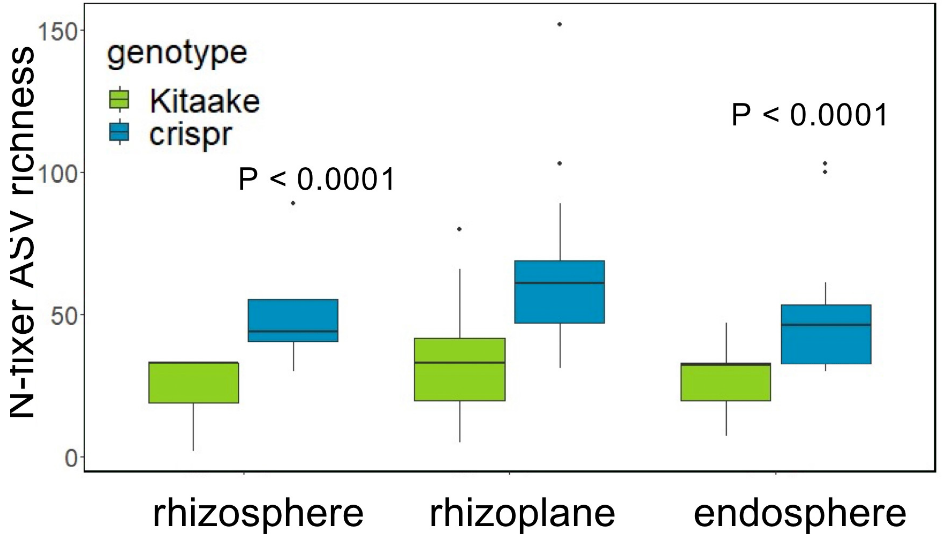
doi: 10.1111/pbi.13894

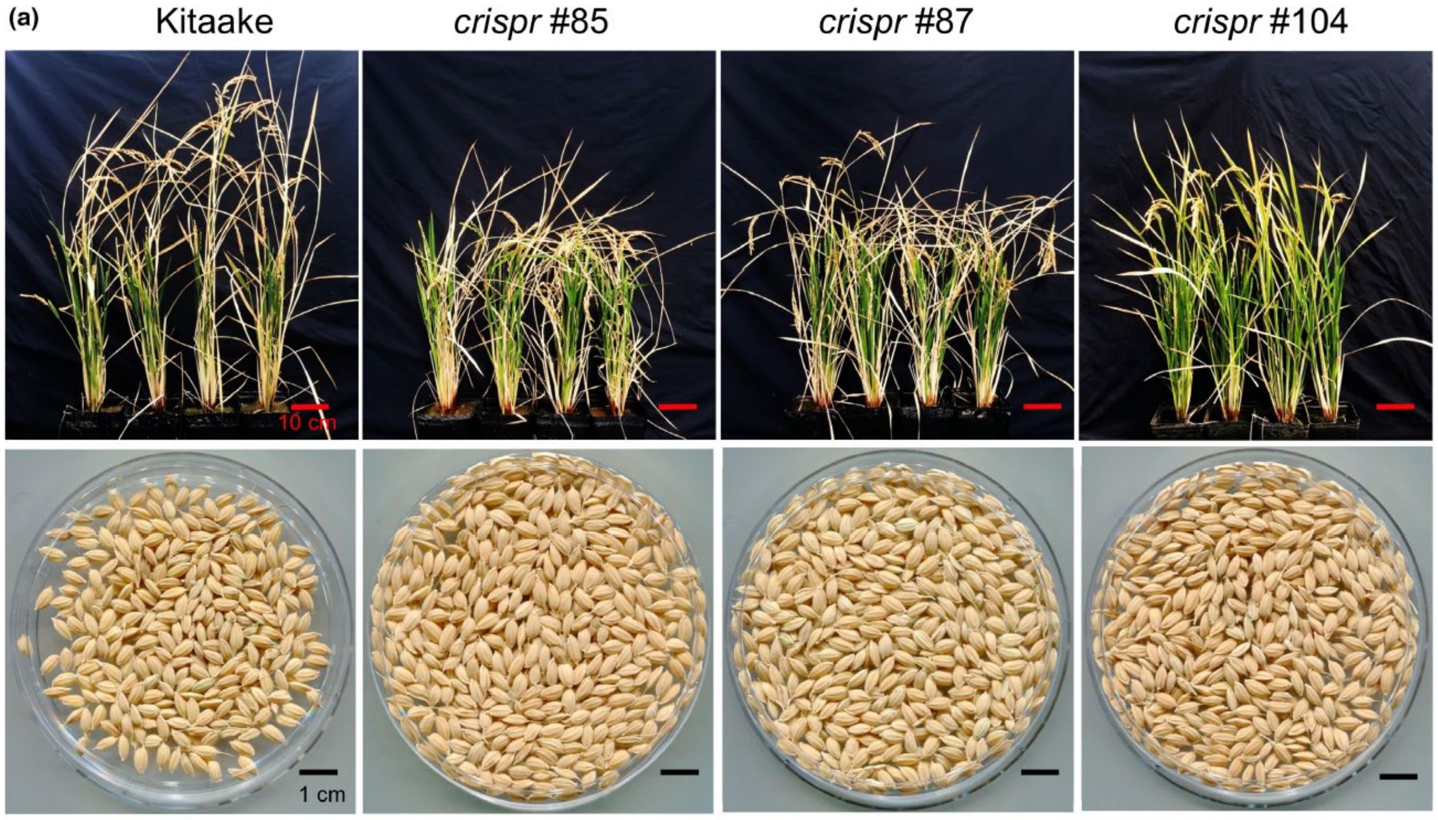
Genetic modification of flavone biosynthesis in rice enhances biofilm formation of soil diazotrophic bacteria and biological nitrogen fixation

Dawei Yan[1], Hiromi Tajima[1], Lauren C. Cline[2], Reedmond Y. Fong[3], Javier I. Ottaviani[3,4], Howard-Yana Shapiro[1] and Eduardo Blumwald[1,*]

[1]*Department of Plant Sciences, University of California, Davis, California, USA*
[2]*Bayer Crop Science, St. Louis, Missouri, USA*
[3]*Department of Nutrition, University of California, Davis, California, USA*
[4]*Mars Inc., McLean, Virginia, USA*



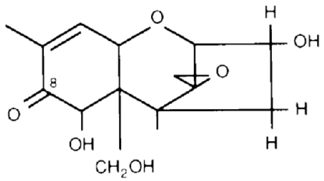




Food Safety Concerns in Crops

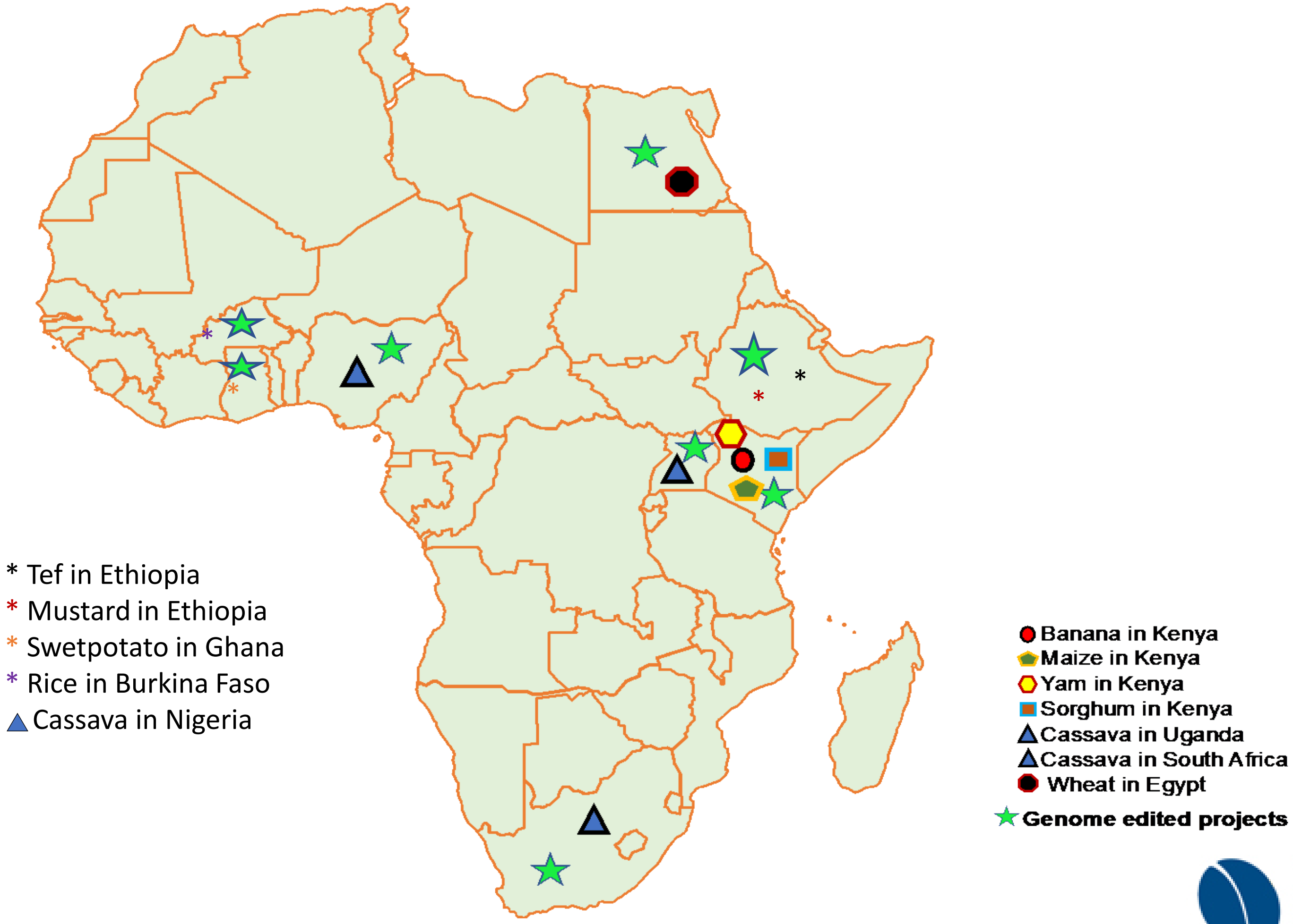
(Low probability, High Consequence)

- Mycotoxins
- Salmonella
- Pathogenic E. coli
- Listeria, etc.
- Heavy metals
- Nitrates,
- Allergens



Gene Editing in Africa

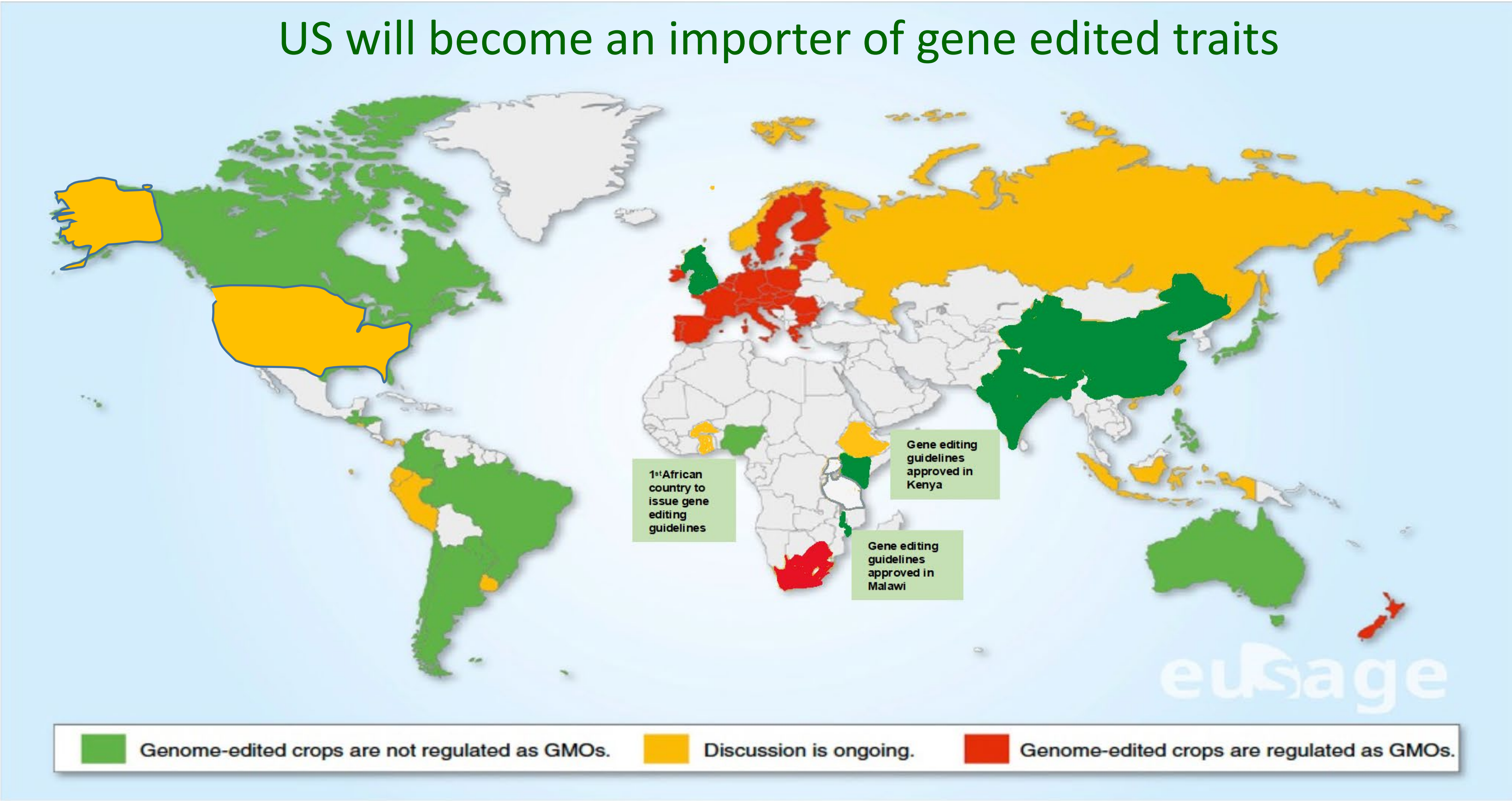
- Many researchers are exploring the potential of gene editing in developing crop varieties for a better and more sustainable African Agriculture.



Tripathi et al. 2022 Frontiers in Genome Editing

UCDAVIS Seed Biotechnology Center

Global Overview of Legislation for Genome Editing



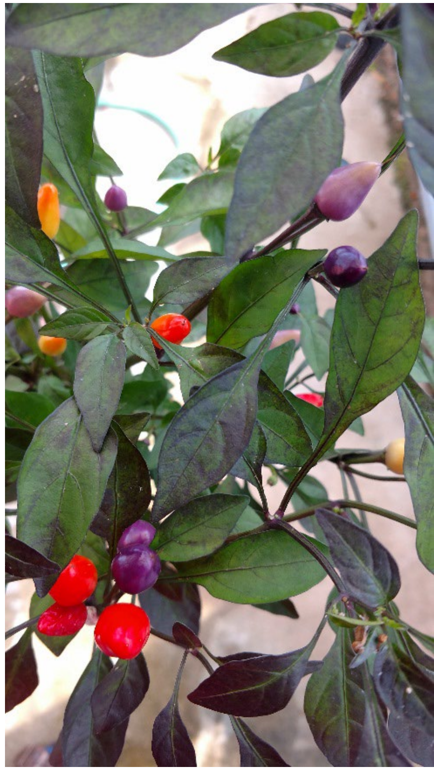
Policy Should Enable Innovation Across All Private and Public Sectors

- Policy must address all crops, not just big 5.
- Most major crops are polyploid, i.e. have duplicated genes
- Gene editing is not only knock-outs
- Breeders have stacked (pyramid) genes for a >100 years in all crops
- The biology of crops is well-documented
- Plant Breeding has 100 years of delivering safe food and products
- Policy should enable innovation across borders
- The agricultural industry is well regulated based on product

We need all of the tools!

UCDAVIS
Seed Biotechnology Center

QUESTIONS??



Allen Van Deynze, UC Davis, avandeynze@ucdavis.edu

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RICHARD LAWRENCE, PH.D.

Head of Genome Editing, Yield, Disease, and Quality Research, Bayer Crop Science

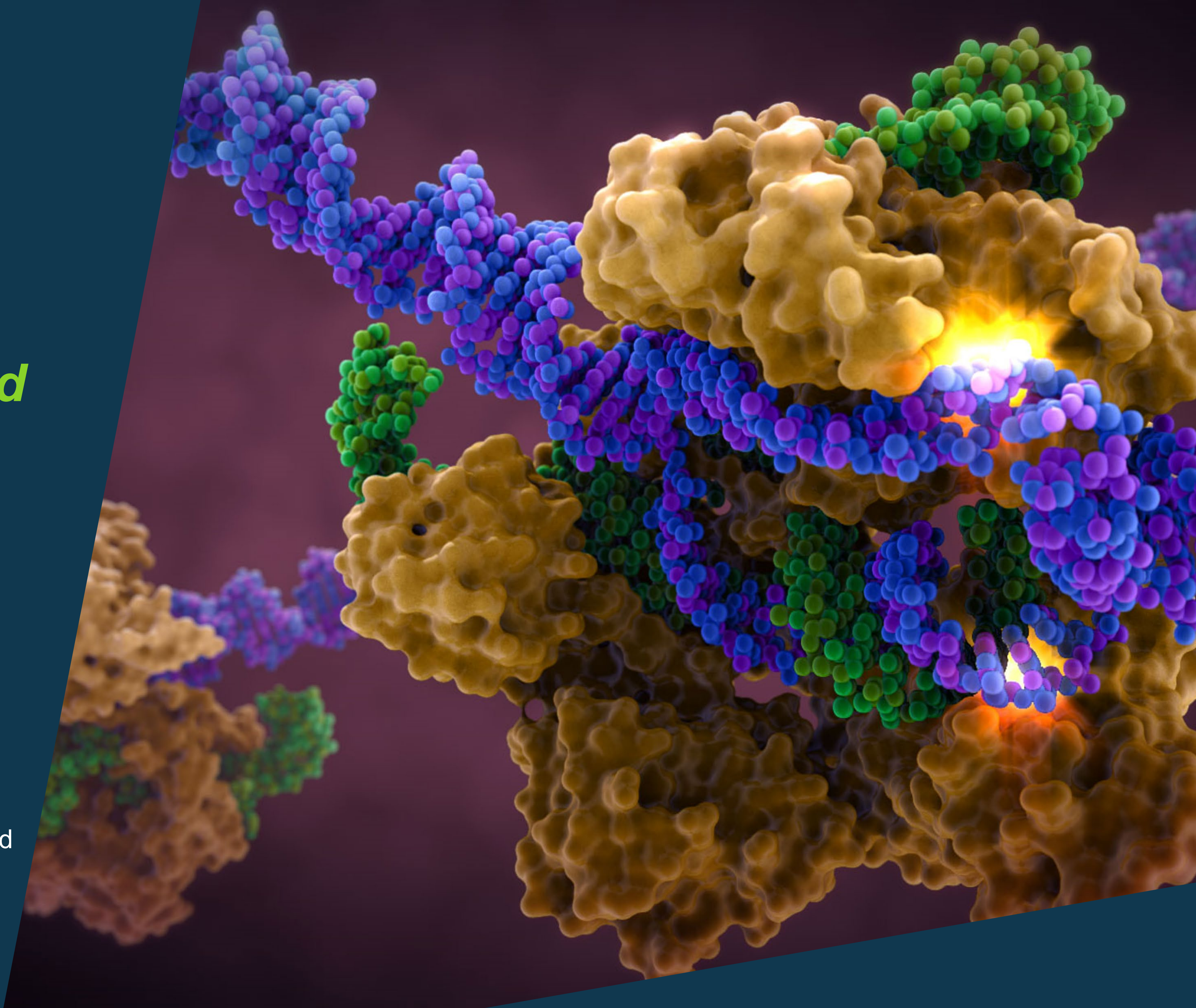
Genome editing as a tool to create targeted variation in plants –

Rick Lawrence

Bayer Crop Science

Head of Genome Editing, Yield, Disease, and Quality Research

Oct 24, 2023

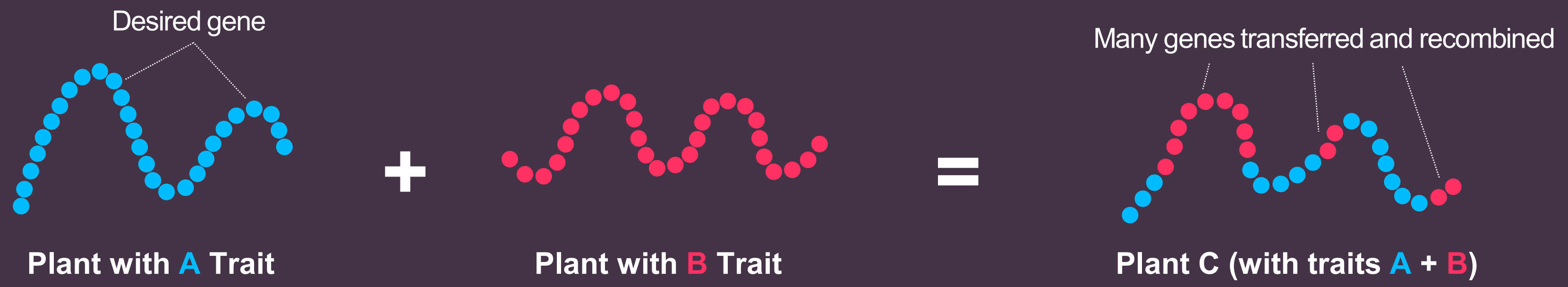


Plant science is constantly evolving

The efficiency and accuracy with which plant traits can be improved is increasing

Beginning in 10,000 BC:

Plant Breeding



Beginning in the 1990s:

Gene Editing

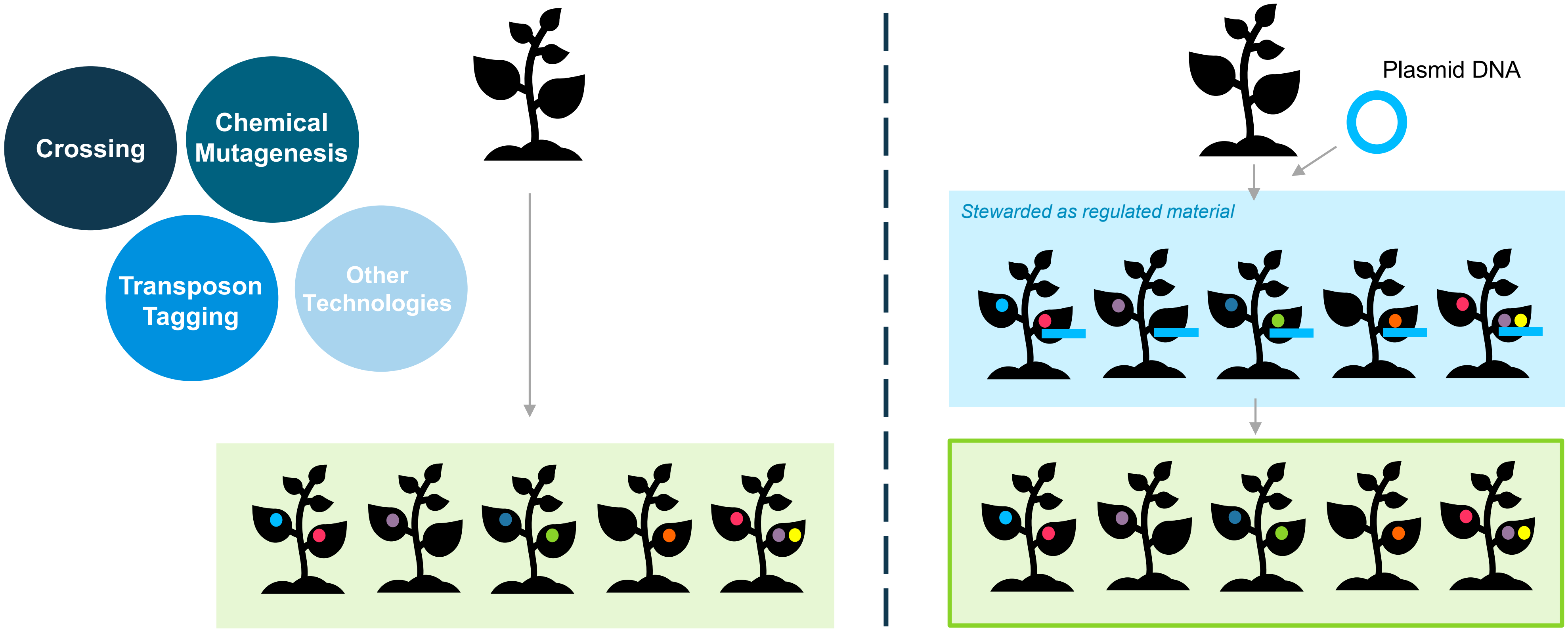
Beginning in the 1970s:

GMOs

Genome editing is one of many tools to create variation, and should be regulated like tools that provide similar outcomes

Desired State: Plants without transgene/editing components are out of scope of GM regulation and treated like conventional breeding

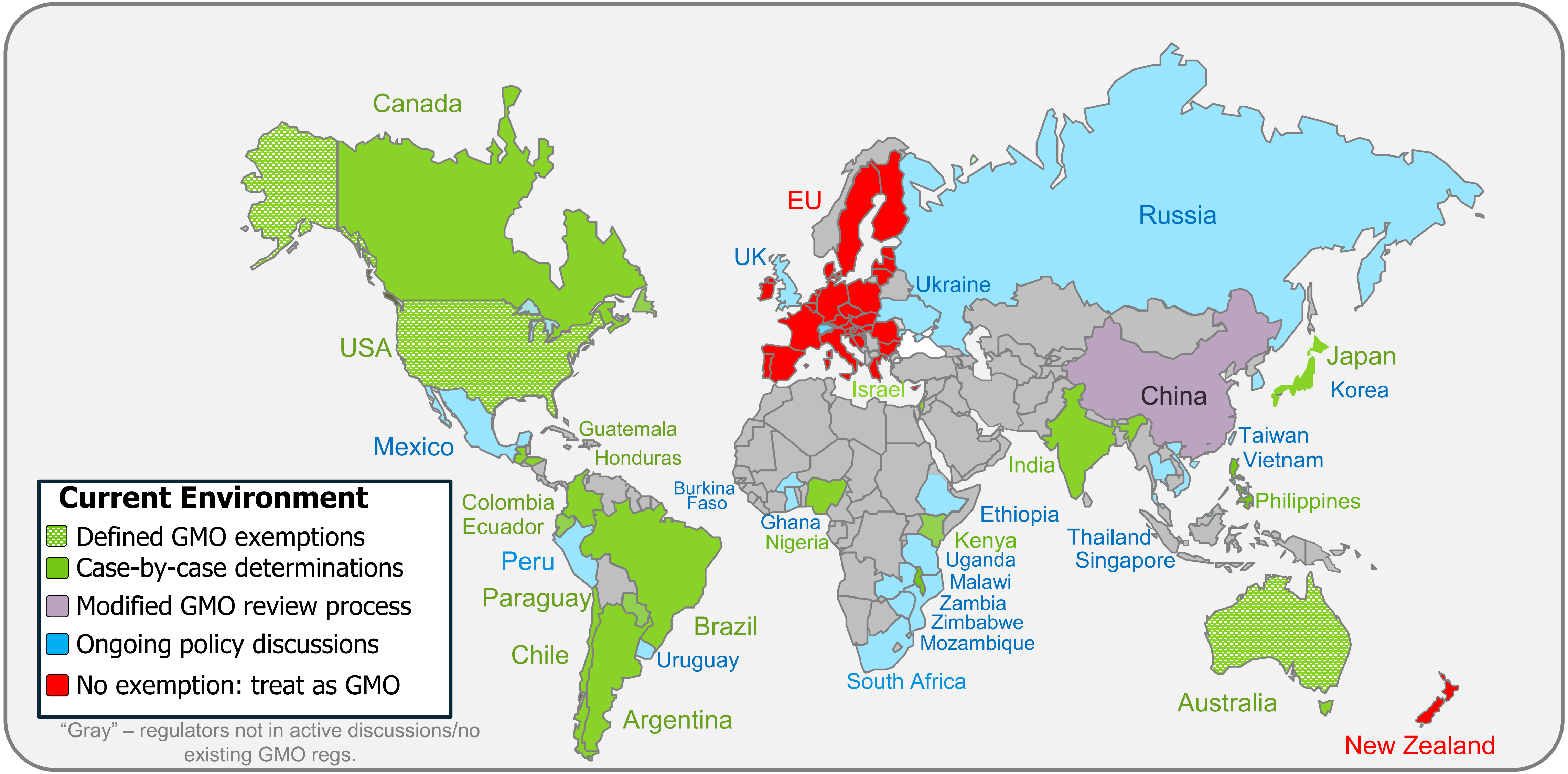
Conventional Breeding | Genome Editing



Conventional breeding

Final products do not contain foreign DNA therefore should not be regulated as GMO, but rather treated like conventional breeding

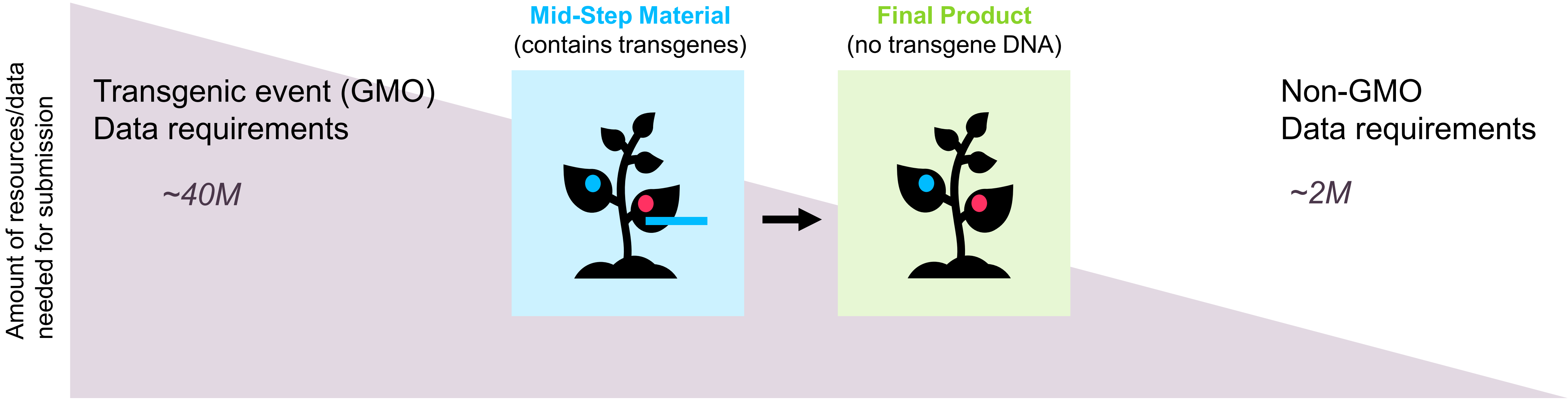
The current genome editing policy landscape is diverse and complex

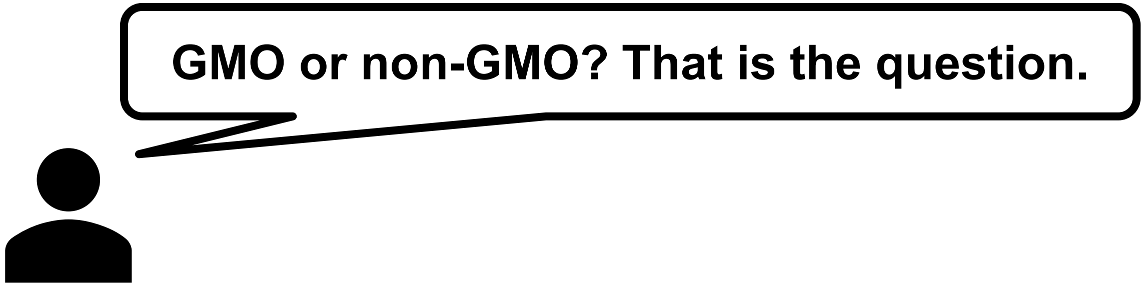


"Gray" – regulators not in active discussions/no existing GMO regs.

v.08.16.23

The main challenge in the genome editing regulatory landscape is the unpredictable nature of timeline and requirements



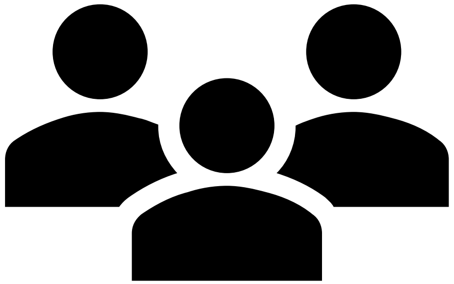


Lassoued et al 2019
AgBio Investor Report 2022

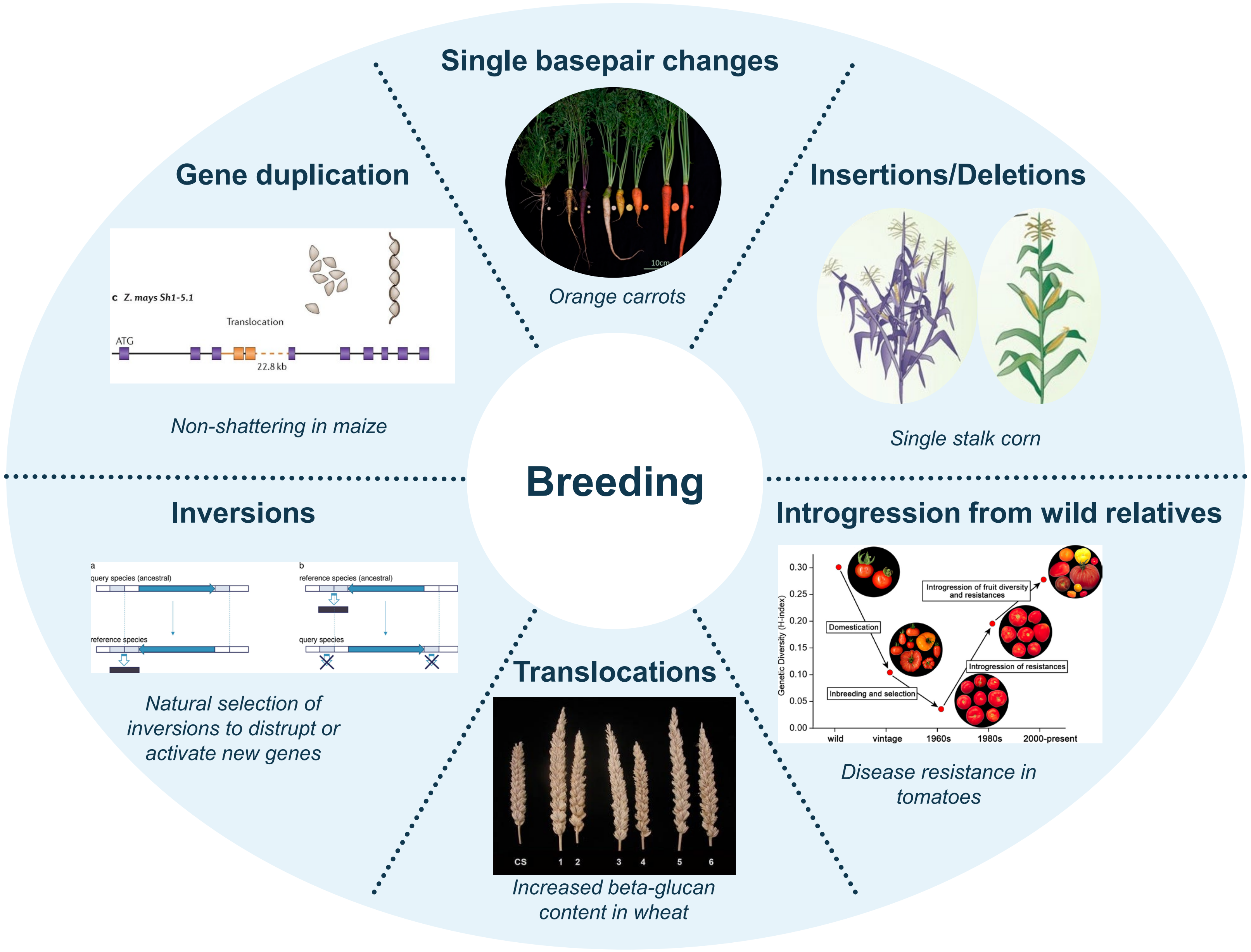
Common theme across regulatory policies around the globe

Edits are considered exempt/excluded/as-safe-as conventional if the edit

"Can be generated through conventional breeding"



Many types of molecular changes occur naturally to enable trait differences and breeding advancements



Danilova et al. Theoretical and Applied Genetics. (2017)
Meyer and Purugganan. Nature Reviews Genetics (2013)
Tsiantis, M. Nature Genetics 43, 1048–1050 (2011).
Schouten et al. Frontiers in Plant Science Volume 10 (2019).
Hirabayashi and Owens. Evolution. 77:4, 1117-1130. (2023).
Ellison et al. Genetics. 210:1497-1508. (2018)

Naturally occurring genetic changes are commonly introduced during domestication and breeding

These modifications happened without knowledge of the underlying genetic changes

Genetic underpinnings were all discovered posthoc

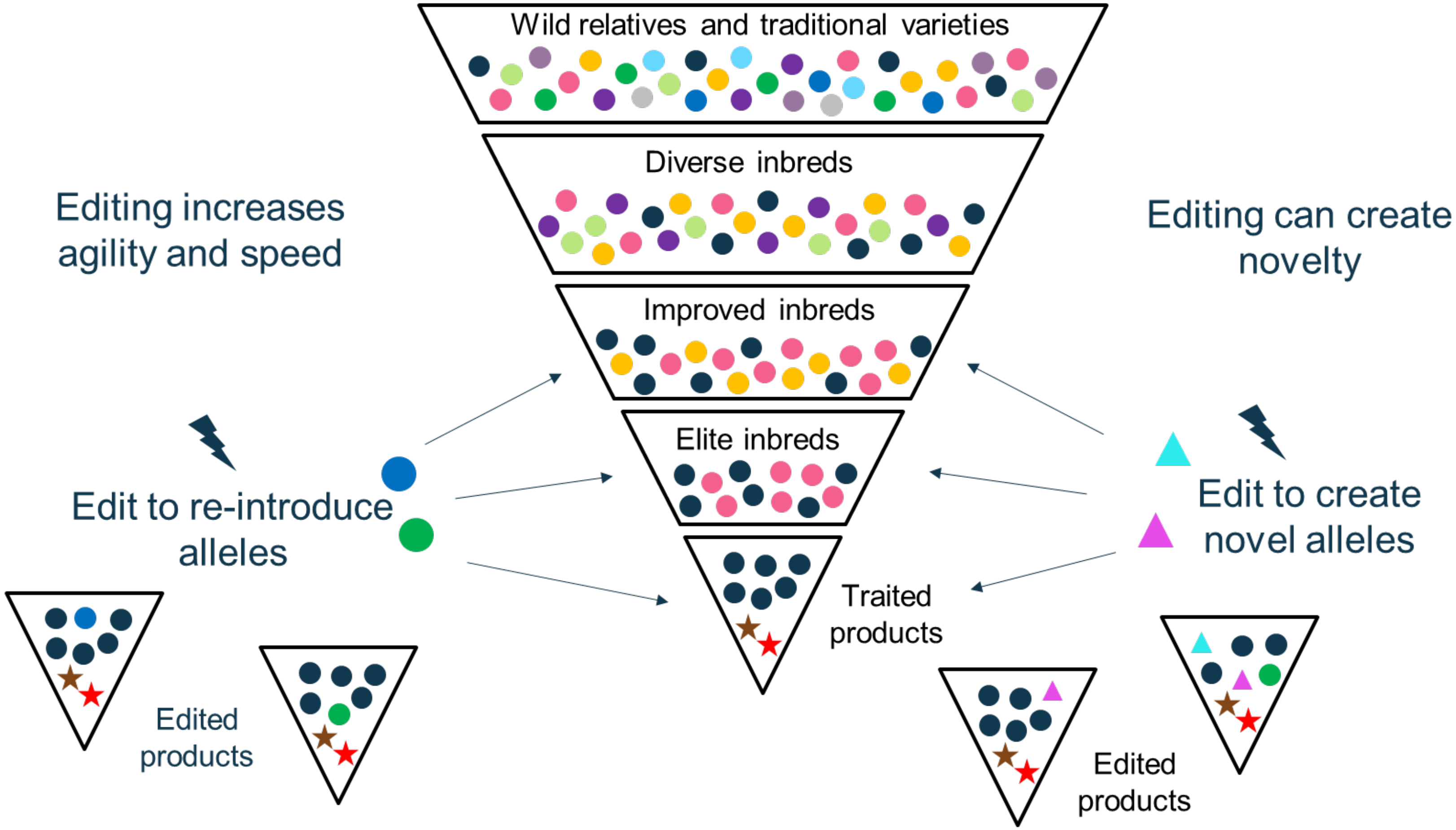
Table 1. Examples of naturally occurring genetic changes common in plants and the resulting characteristic.

Genetic change	Genotypic or phenotypic example	Reference
Transposable elements (transposons)	White grapes, blood oranges	Lisch (2013)
	>25,000 unique insertions detected across 31 varieties of soybean	Tian et al. (2012)
	Yellow maize	Palaisa et al. (2003)
	>50 new inserts of a transposon per rice plant per generation	Naito et al. (2006)
	Elongated tomato fruit	Xiao et al. (2008)
	Round or wrinkled peas (Mendel)	Ellis et al. (2011)
	2 million transposons exchanged between higher plants	El Baidouri et al. (2014)
Organellar DNA in nuclear DNA	Gain and loss of mitochondrial DNA common to maize inbred lines	Lough et al. (2008)
	Gain and loss of chloroplast DNA common to maize inbred lines	Roark et al. (2010)
Bacterial genes	Expression of several bacterial genes in sweet potatoes	Kyndt et al. (2015)
Crossing with wild relatives	>60 wild relatives have been used for >100 characteristics (80% involve pest or disease resistance) in 13 crops	Hajjar and Hodgkin (2007)
	Dozens of alien genes used in wheat breeding	Jones et al. (1995)
Pararetroviruses	Stable viral DNA in rice genome	Liu et al. (2012)
	Stable viral DNA in tomato (previously also seen in potato)	Staginnus et al. (2007)
Florendoviruses	Stable integrations in all plants	Geering et al. (2014)
Insertions and deletions	Submergence-tolerant rice	Xu et al. (2006)
	Dwarf sorghum	Multani et al. (2003)
	Yellow soybean seeds	Tuteja et al. (2004)
Single-nucleotide polymorphisms (SNPs)	Maize proteins (300–400 amino acids long) from 2 alleles differ by 3–4 amino acids	Tenaillon et al. (2001)
	Maize genome has 55 million SNPs	Gore et al. (2009)
	Green Revolution gene has 2 SNPs for dwarf wheat	Peng et al. (1999)
	One SNP caused loss of shattering in domestic rice	Konishi et al. (2006)
	Tall or short pea plants (Mendel)	Ellis et al. (2011)
	7 new SNPs created per meiosis per billion base pairs	Ossowski et al. (2010)
Presence, absence, or copy number of genes	856 wild-type soybean genes absent in cultivated varieties (and >186,000 DNA insertions or deletions)	Lam et al. (2010)
	>10^6 SNPs, 30,000 insertion or deletions, and a few large chromosomal deletions (>18 genes) in 6 elite maize varieties	Lai et al. (2010)
	Copy number variation relates to soybean cyst nematode resistance	Cook et al. (2012)
	Pinot Noir, Corvina, and Tannat wine grapes have 1873 genes not found in other wine grapes	Da Silva et al. (2013)
	Only 81% of *Brassica* genes are always present in the same number	Golicz et al. (2016)
	2500 genes found only in either B73 or PH207	Hirsch et al. (2016)
	G. soja genotypes can vary by 1000 to 3000 gene families from each other	Li et al. (2014)

Glenn et al 2017. Crop Science

"Editing to Breed" is where genome editing can make the highest impact to drive innovation and advance agriculture

Fully incorporating editing in various aspects of the breeding pipeline



Concept demonstrated in Lorenzo et al, BREEDIT: a multiplex genome editing strategy to improve complex quantitative traits in maize, The Plant Cell, Volume 35, Issue 1, January 2023, Pages 218–238,


Thank
you

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Senior Vice President, Scientific Affairs and Policy,
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INNOVATION IN GENE EDITING AND PLANT BREEDING

Farm Foundation Forum

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www.betterseed.org

American Seed Trade Association (ASTA)

Founded in 1883. Represent all sectors of the seed industry

- A-Z (Alfalfa to zucchini)
- Fruits, Vegetables, Row Crops, Field Crops, Ornamentals
- Conventional, organic, biotech

Nearly 700 members, including:

- Integrated seed companies
- Seed distributors
- Breeding and Licensing companies (genetics)
- Seed treatments
- Machinery
- Testing facilities
- Universities

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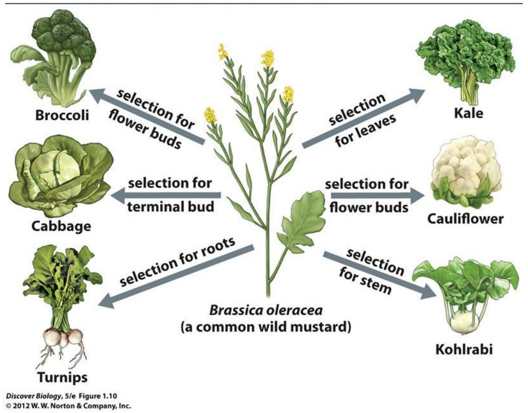
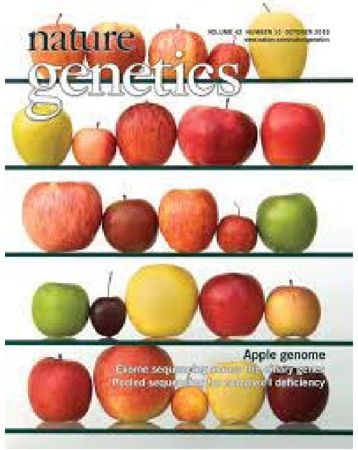
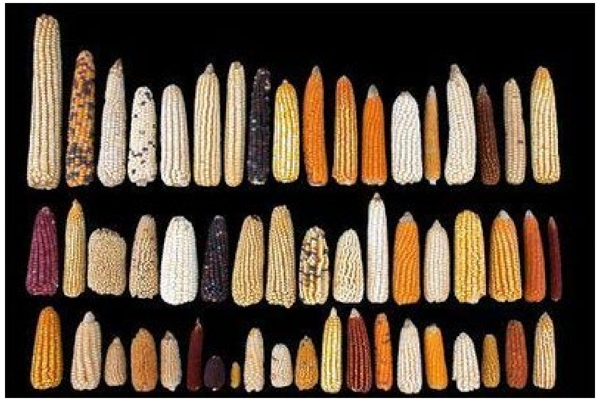
Expressions of genetic variability

PHIL SIMON, UW–MADISON, USDA-ARS

CHANNA PRAKASH







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JIANGSHUO SU HORTICULTURE RESEARCH 1OCT2019

DALIA TAHER FRONTIERS PLANT SCIENCE 25AUG201

USDA-ARS

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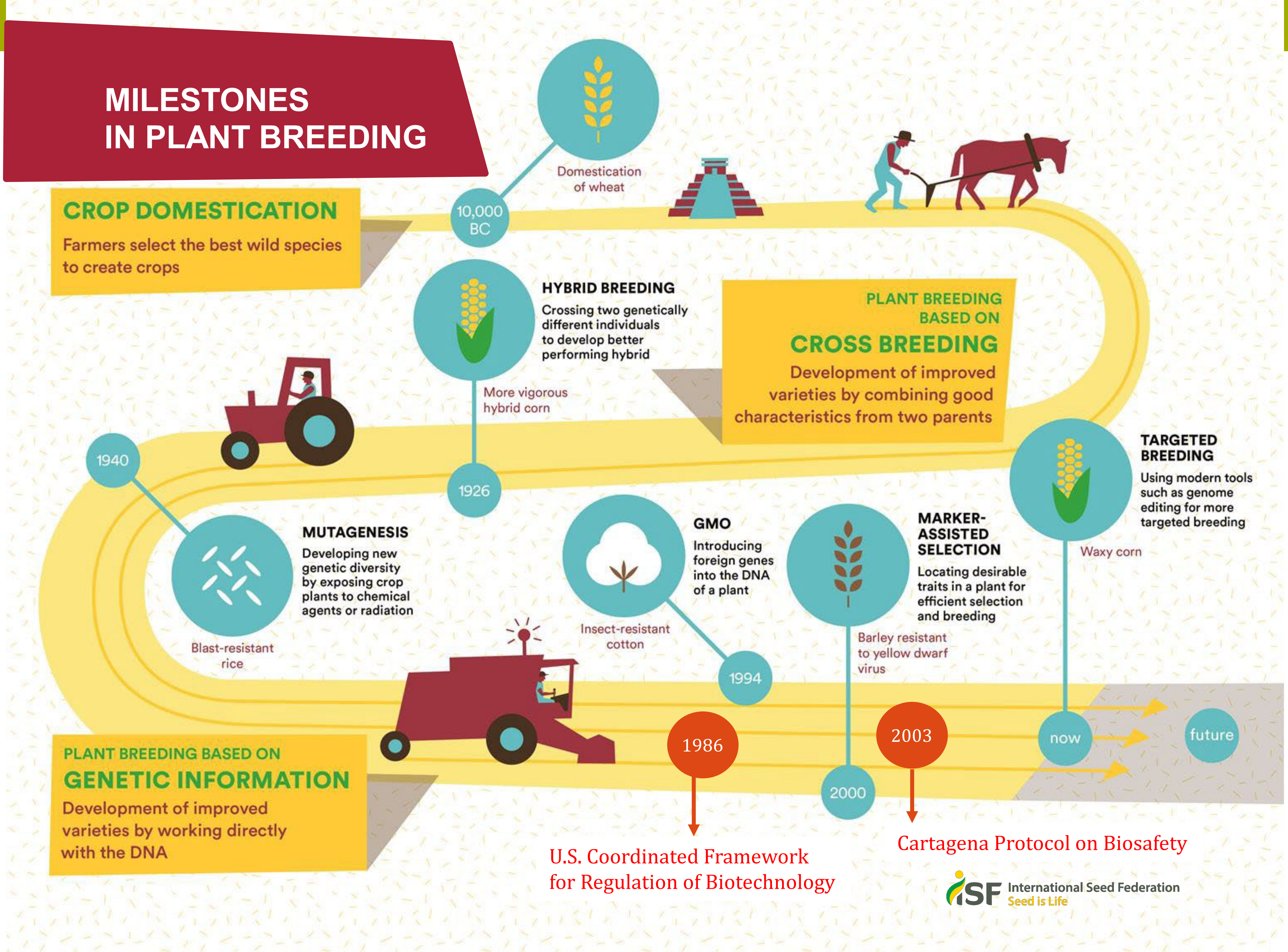
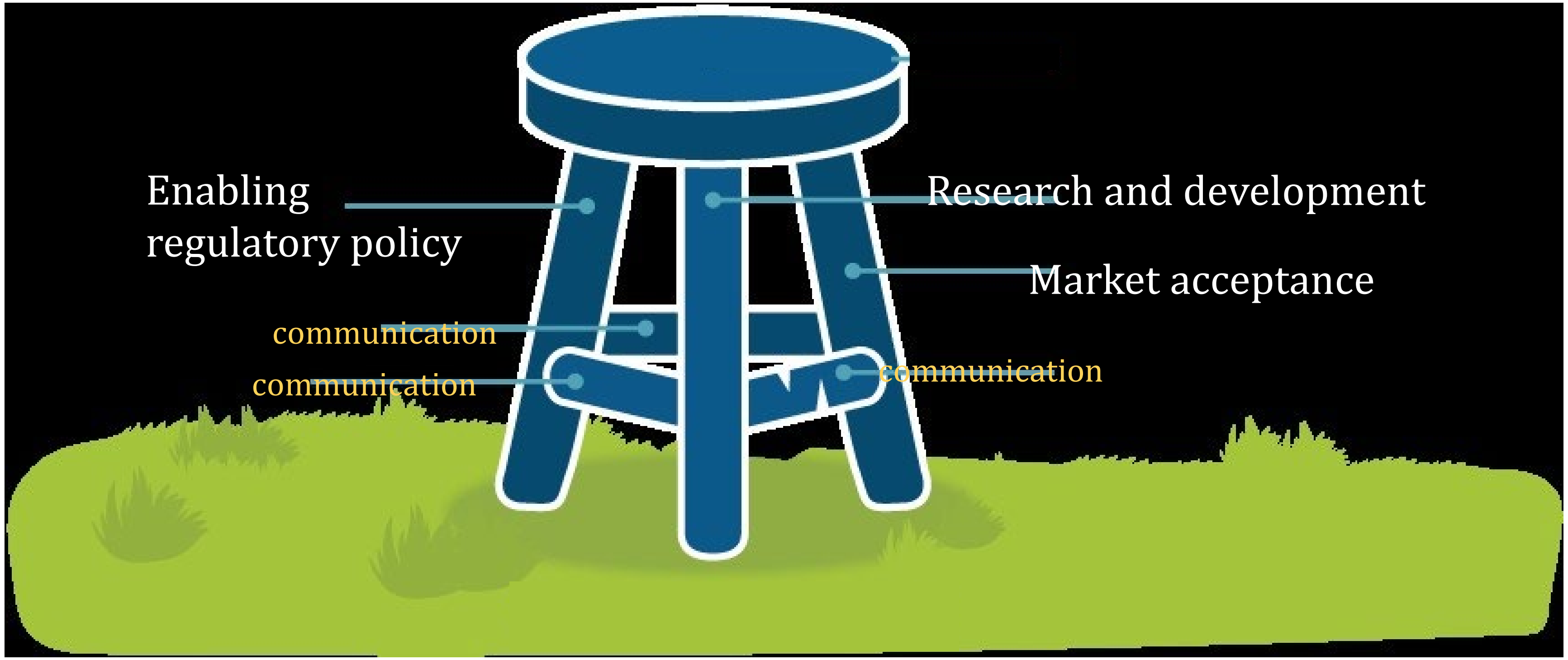
MILESTONES IN PLANT BREEDING



Building a three legged-stool



american
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association

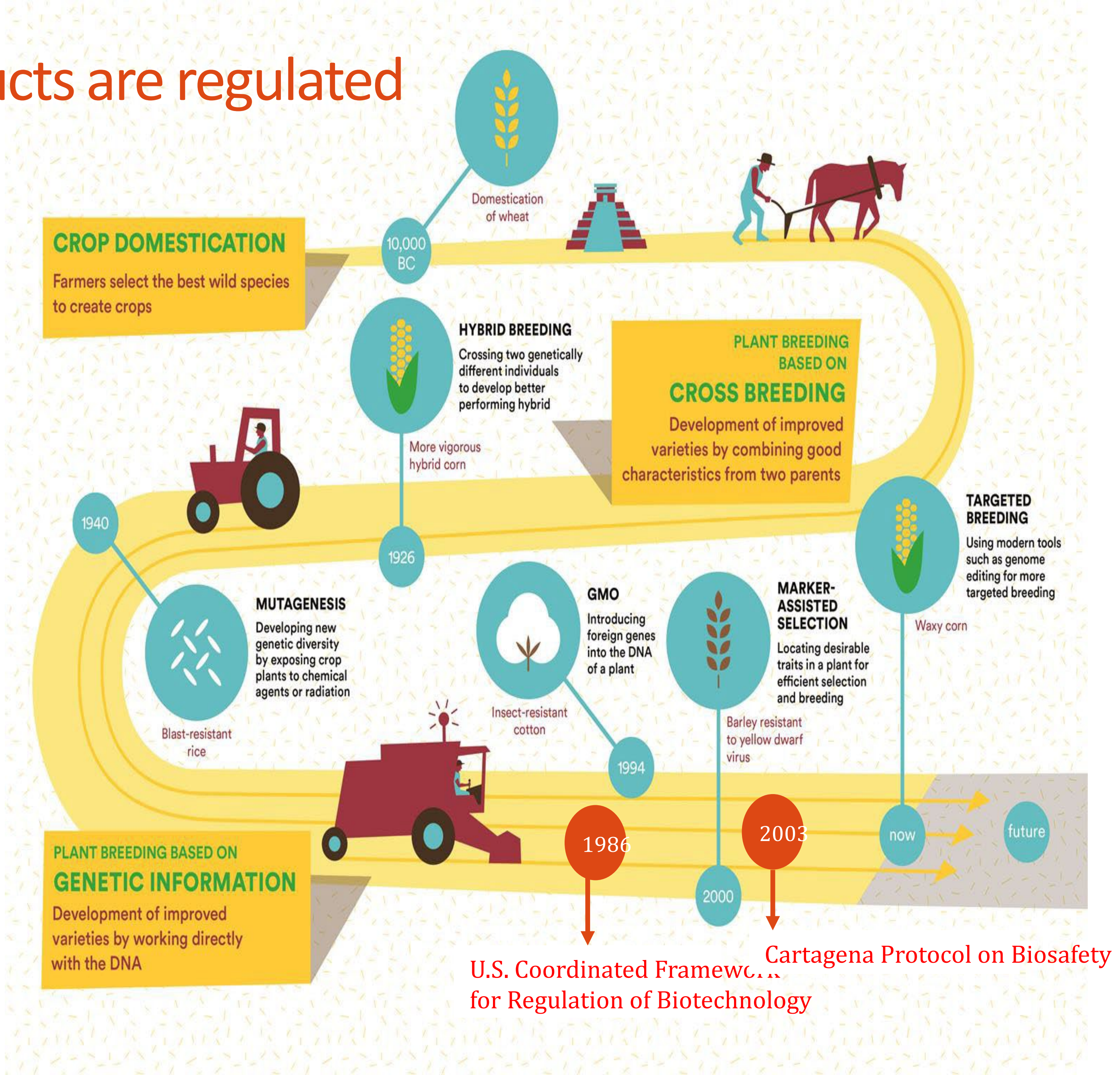
All new plant varieties & their products are regulated

Breeding method neutral

- Variety registration
- Seed laws and regulations
- Phytosanitary regulations
- General environmental safety/liability laws & regulations
- Food/feed laws and regulations

Breeding technology specific

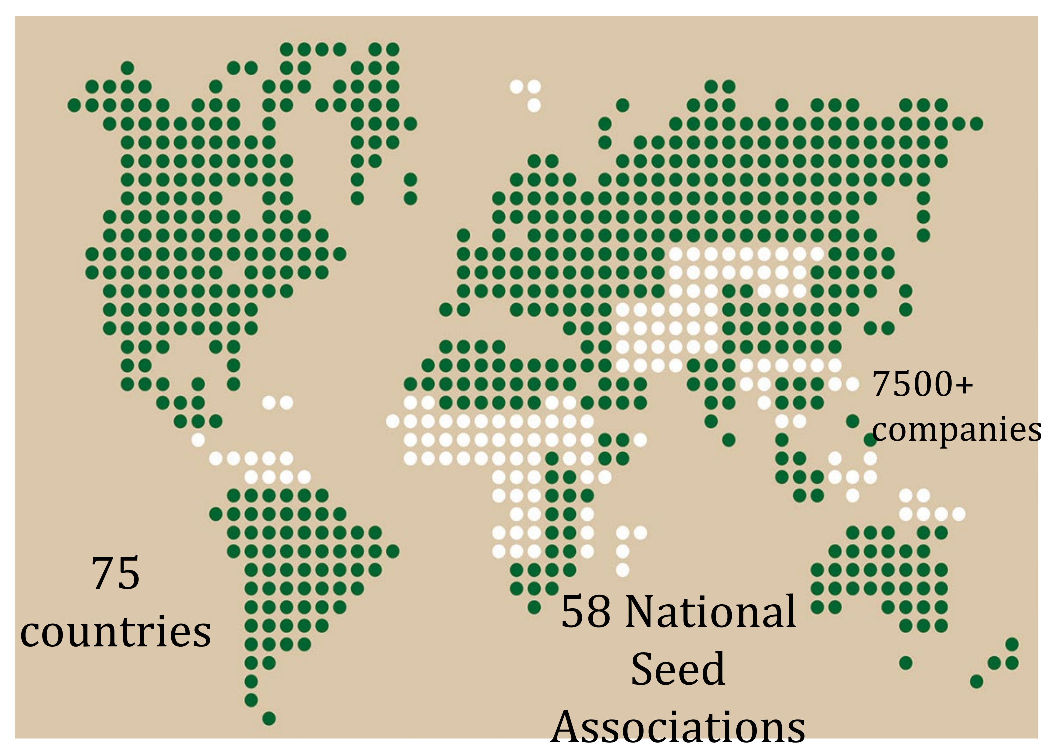
- *GMO regulations*



Should genome edited varieties be regulated as GMOs?

Underlying Principle

"Plant varieties developed through the latest breeding methods ***should not be differentially regulated*** *if they are similar or indistinguishable from varieties that could have been produced through earlier breeding methods or can be found in nature.*



ISF International Seed Federation
Seed is Life

Enabling Regulatory Policy

International Seed Federation
Seed is Life

ENGLAND
Case-by-case approach excluding certain gene edited products- secondary legislation expected

EUROPE
Policy proposal suggesting 2 categories : Conventional-like and GMO-light

ISRAEL
Case-by-case guidance that excludes certain gene edited products

RUSSIA
Decree for R&D program clarifying that gene editing products are “conventional-like”

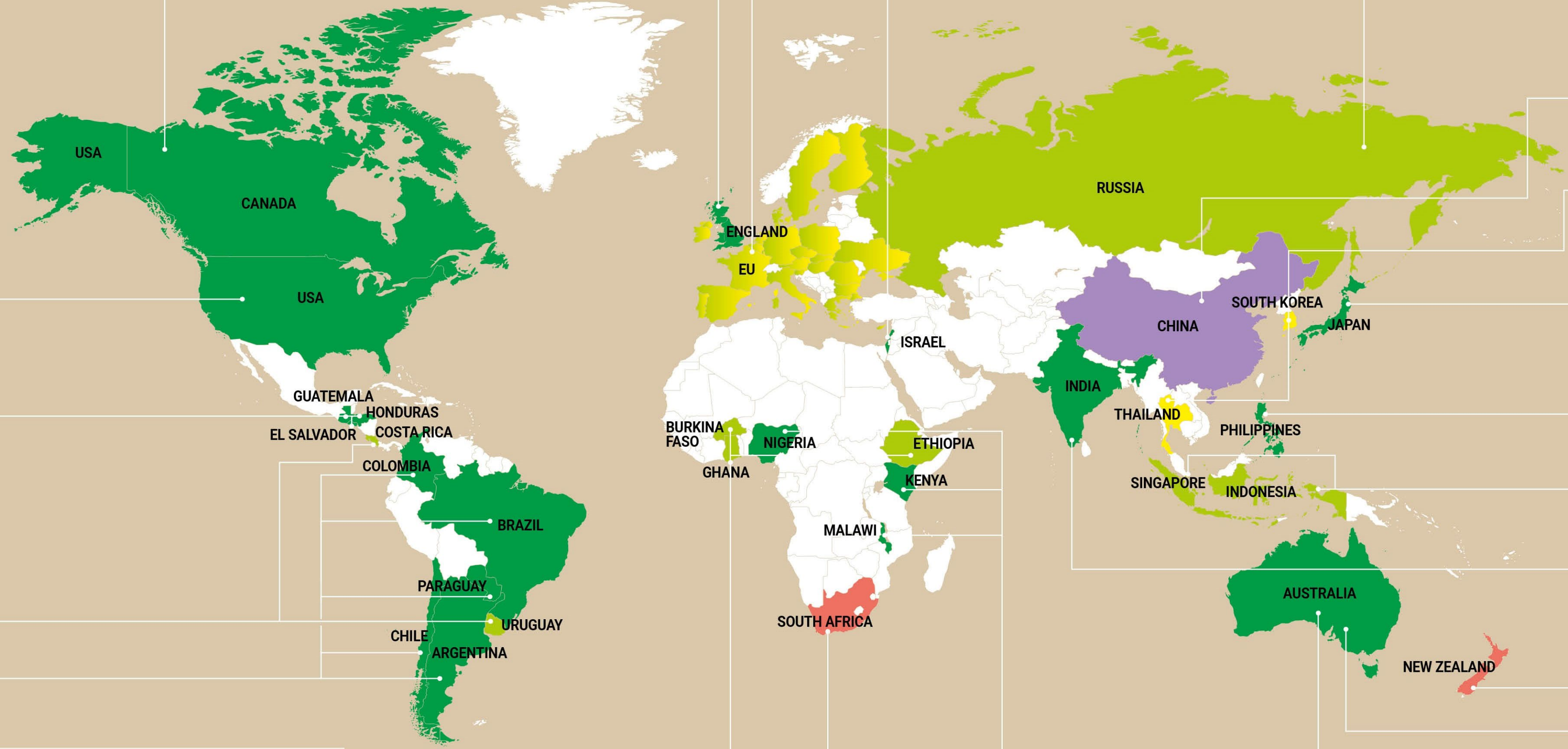
CANADA
Product based approach; Health Canada and CFIA guidance for food finalized excluding plants without foreign DNA, CFIA guidance on feed tbd

USA
USDA excludes certain products: others case-by-case; EPA: exempts certain products; FDA: tbd

GUATEMALA, HONDURAS, EL SALVADOR
Case-by-case approach, excluding certain gene edited products without novel combinations of DNA

COSTA RICA, URUGUAY
Draft case-by-case approach, excluding certain gene edited products without novel combinations of DNA

ARGENTINA, CHILE, BRAZIL, COLOMBIA, PARAGUAY
Case-by-case approach, excluding certain gene edited products without novel combinations of DNA



CHINA
Provisional “GMO-light” guidance

SOUTH KOREA, THAILAND
Proposed revised LMO act (GMO-light)

JAPAN
Case-by-case approach excluding certain gene edited products

PHILIPPINES
Case-by-case approach excluding gene edited products without foreign DNA

INDONESIA, SINGAPORE
Draft proposal to exempt certain gene edited products

INDIA
Exclusion of SDN1/2, case-by-case approach

AU-NZ-FSANZ
Proposal for updated framework for food/feed expected

- Differentiation from GMO regulations (at least by one agency/authority)
- Draft proposal to differentiate from GMO regulations (at least by one agency/authority)
- Draft proposal where products considered GMO’s but with simplified assessment procedure/requirements
- Products considered GMO’s but with simplified assessment procedure/requirements

ETHIOPIA, BURKINA FASO, GHANA
Draft guidance excluding certain gene edited PBI products

SOUTH AFRICA
Government notice that NBTs are GMOs, ongoing appeal procedure

NIGERIA, MALAWI, KENYA
Case-by-case approach excluding certain gene edited products

AUSTRALIA - OGTR
Revised gene tech regulation excludes SDN-1 gene editing applications, new legislation is expected

NEW ZEALAND
High Court decision that specific techniques are GMOs

International Policy: General Observations

- Growing alignment in recognizing that not all gene edited plants should be treated as GMOs (e.g., no foreign DNA in final product)
- Case-by-case consultation process
- Many countries allow for consultation at early-stage development (at product conception stage)
- Regional harmonization are underway (e.g., Central and South America)

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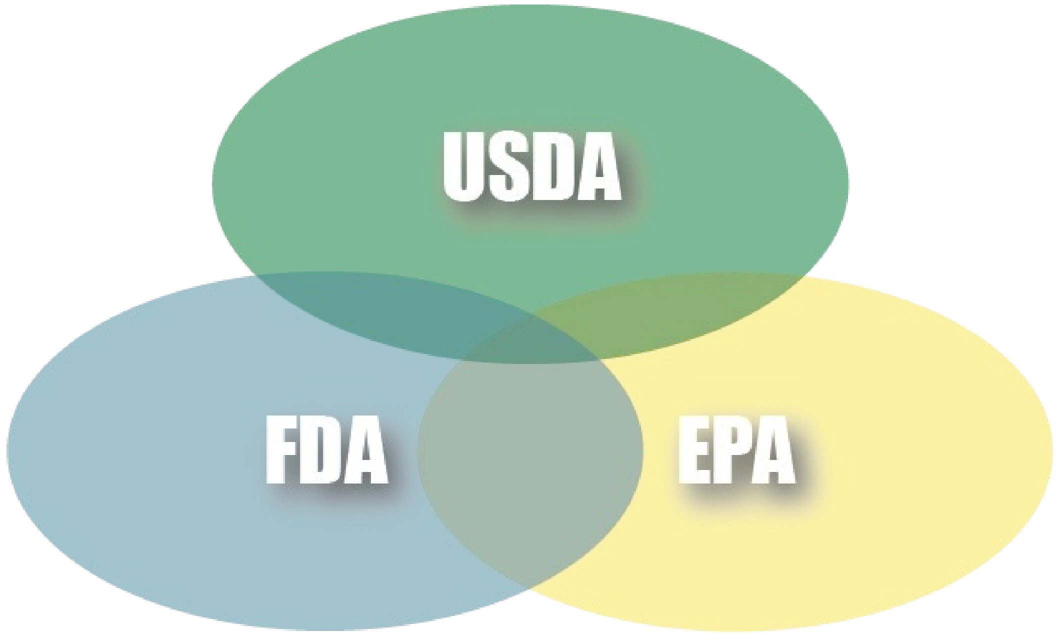
US Coordinated Framework

- USDA: Importation, interstate movement, environmental release
- EPA: Plant incorporated protectant
- FDA: Foods derived from new plant varieties



Products of Biotechnology (plants), regulated based on the intended use.

USDA regulation 7CFR340 (May 2020)

Exemptions

(voluntary confirmation process)

A plant that contains a *single* modification of a type in *one* of the following three categories is exempt from regulation:

1. A change resulting from cellular repair of a targeted DNA break in the absence of an externally provided repair template; or

2. A targeted single base pair substitution; or

3. Introduction of a gene known to occur in the plant's gene pool, or a change in a targeted sequence to correspond to a known allele of such a gene or to a known structural variation present in the gene pool.

Opportunity to petition to add new exemptions

Plant-trait-mode of action

(PTMoa)

already reviewed and determined not subject to the regulations.

Regulatory Status Review

EPA oversight of plant incorporated protectant (PIP) (July 2023)

Exemptions

- PIPs created through conventional breeding
- Loss of function PIPs
  - Mandatory notification
  - 5 years record keeping
- Certain PIPs created through genetic engineering from a sexually compatible plant
  - Mandatory notification and confirmation
  - 5 years record keeping

No limit on # of PIP per plant

Registration

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Challenges in the US system – inconsistent exemption scope, process

USDA APHIS BRS (May 2020)

- Voluntary confirmation of exemptions
- Single modification on one pair of chromosome
- Doesn't apply to multiplexing of modifications
- Can add new exemption categories

EPA (July 2023)

- Mandatory confirmation for some exemptions; mandatory notification for others
- Limited to "identical substance", matching regulatory regions, "matching sequence to native allele"
- Can apply to multiplexing of modifications
- No easy way to add exemption categories.

FDA: applies to all foods

- Food must be safe
- Labeling must be truthful and not misleading

Endogenous Substances

Added Substances

Generally Regarded as Safe (GRAS)

- Legal without premarket approval
- Safe (reasonable certainty of no harm
- Safety information publicly available
- Safety information widely accepted by experts

Food Additives

- Requires premarket review and approval
- Safe (reasonable certainty of no harm
- Safety information not yet publicly available
- Safety information not yet widely accepted by experts

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FDA: Foods derived from new plant varieties

- 1992 Statement of Policy for Foods Derived from New Plant Varieties
  - *applied to all foods derived from all new plant varieties, regardless of the methods used to develop the varieties*
  - *Foods from new plant varieties must be as safe as comparable foods*
- Guidance on Consultation Procedures Foods Derived From New Plant Varieties

  a set of procedures for voluntary premarket food safety consultations
- In 2017, the FDA published Request for Information "Genome Editing in New Plant Varieties Used for Foods"

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Take home messages – Regulatory landscape

- Regulatory trend internationally – differentiation genome edited products from GMO
- Path to market – visible but with challenges
  - Regulatory scheme in major markets still TBD (China, Europe)
  - Difference in implementation
  - Difference in timeline for decision making
- Regulatory leadership not the same
  - South America
  - Japan
  - Canada

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Thank you!

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ALISON VAN EENENNAAM, PH.D.

Professor of Cooperative Extension,
Animal Biotechnology and Genomics,
Department of Animal Science,
University of California, Davis

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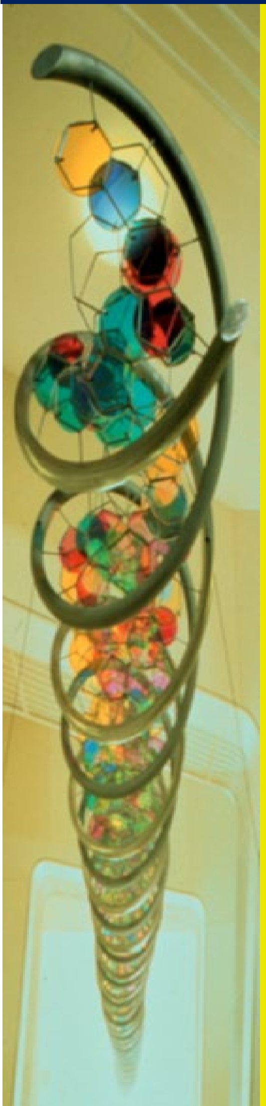
Global Status of Gene Edited Food Animals and their Products



Alba Ledesma (Post-doc)

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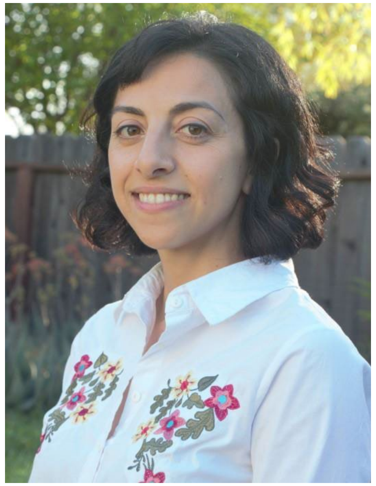
WEBSITE: https://animalbiotech.ucdavis.edu



A recent literature review found 195 English-language category peer-reviewed publications producing gene edited food animals for agriculture – the purpose breakdown is below

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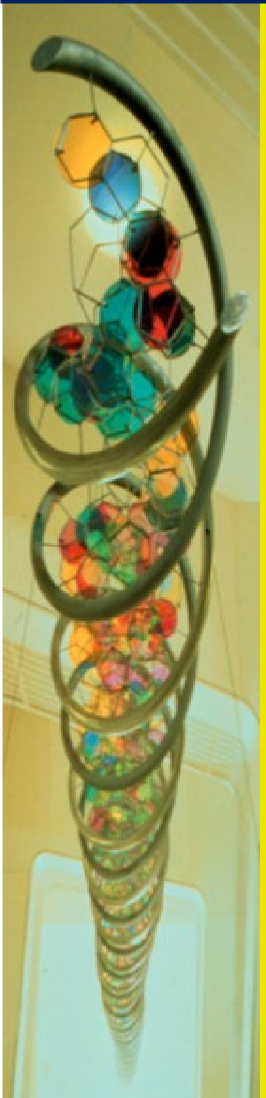
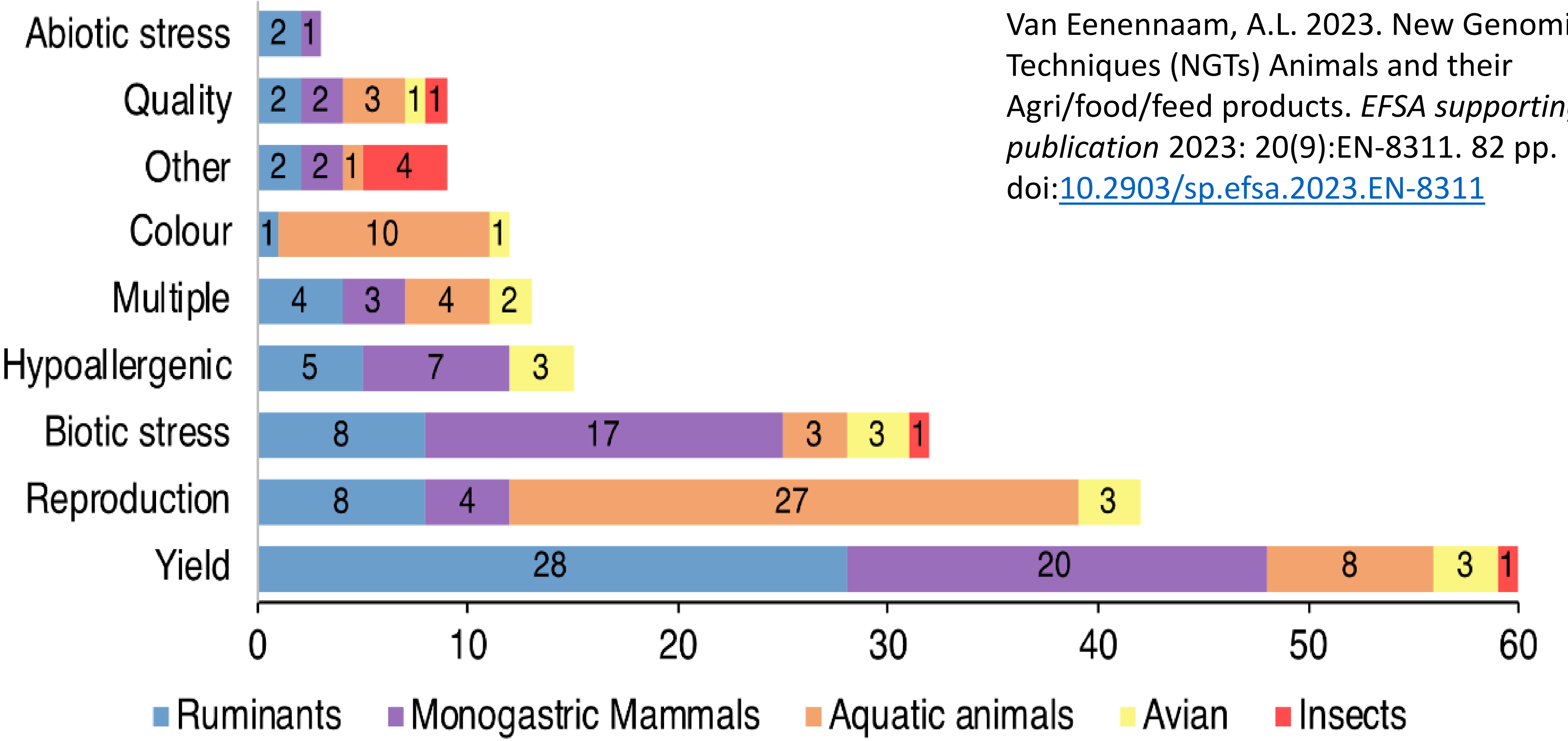
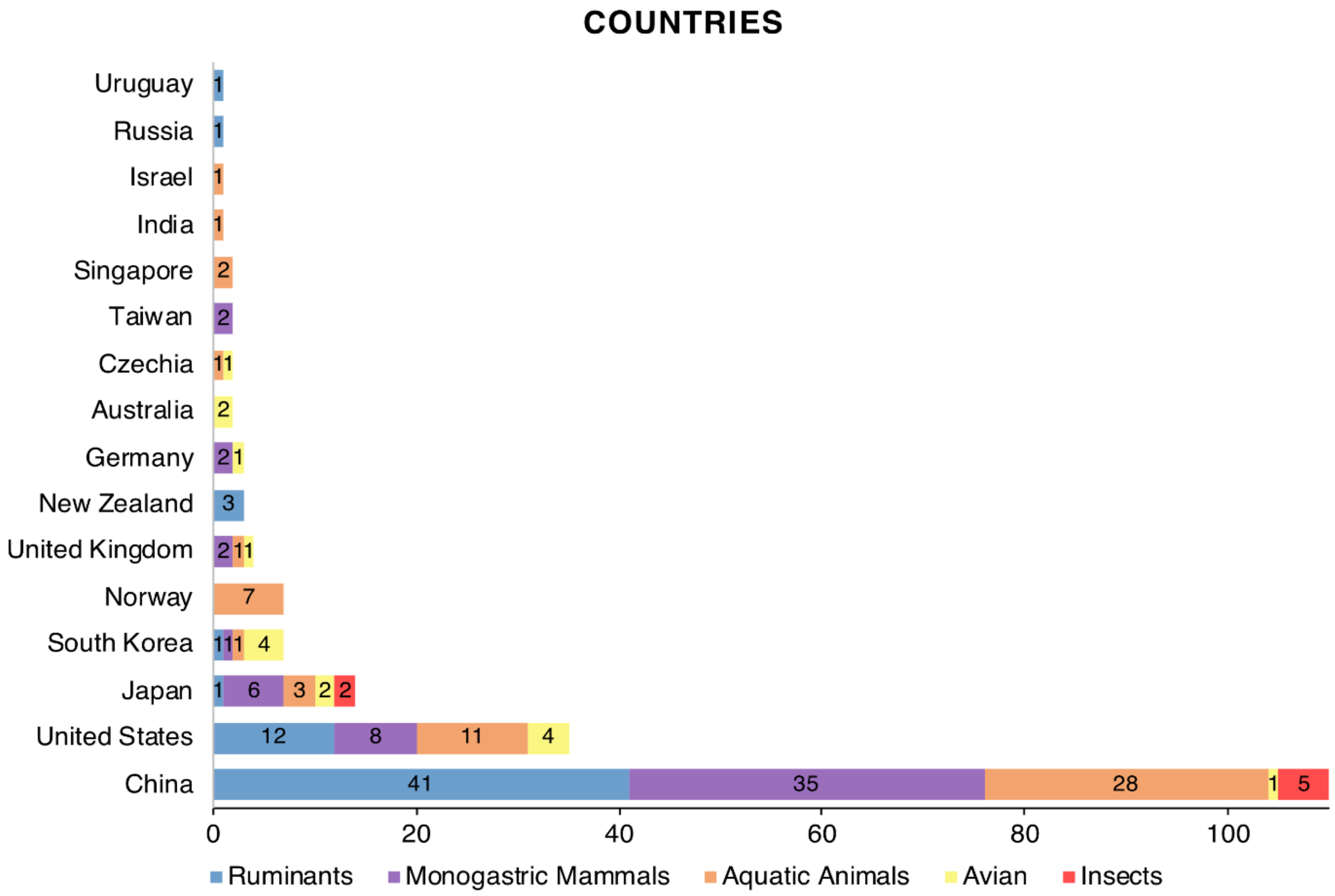




Van Eenennaam, A.L. 2023. New Genomic Techniques (NGTs) Animals and their Agri/food/feed products. *EFSA supporting publication* 2023: 20(9):EN-8311. 82 pp. doi:10.2903/sp.efsa.2023.EN-8311

Animal category breakdown X country of peer-reviewed publications producing gene edited food animals for agriculture



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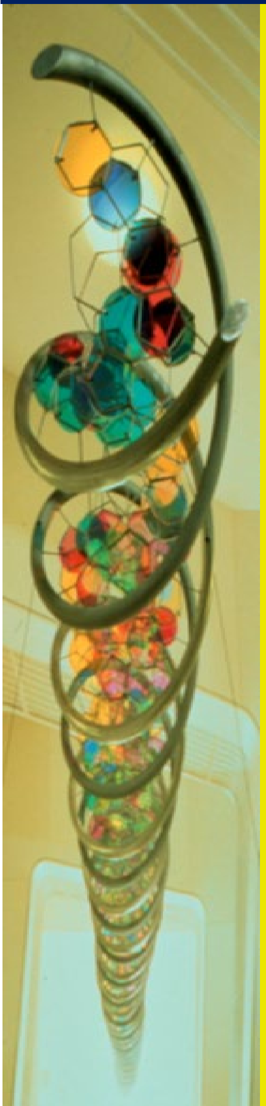
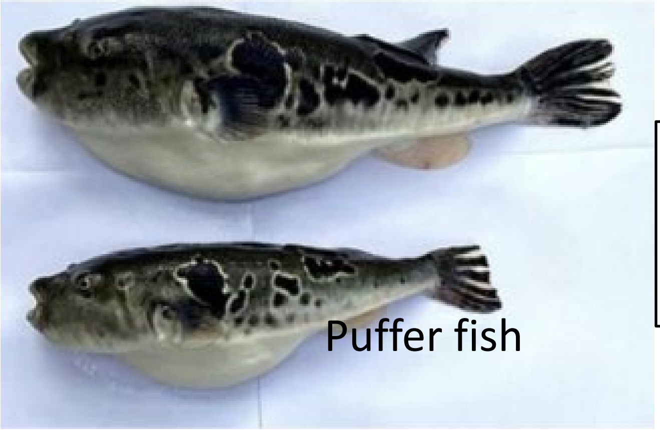
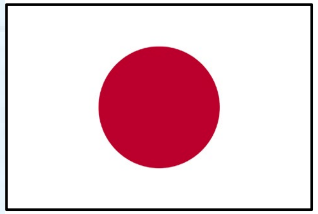


Organism	Common name	Species name	Number (N=195)	Yield	Reproduction	Biotic Stress/ Abiotic Stress	Hypoallergenic/ Quality	Multiple Traits	Other
Mammals (59%)	Pigs	*Sus scrofa*	52	16	4	18	9	3	2
	Cattle	*Bos taurus taurus* *Bos taurus indicus*	23	4	4	10	4		1
	Sheep	*Ovis aries*	20	13	2		2	2	1
	Goats	*Capra hircus*	17	11	2		1	2	1
	Rabbits	*Oryctolagus cuniculus*	4	4					
Avian (8%)	Chickens	*Gallus gallus*	13	2	3	3	4	1	
	Japanese Quail	*Coturnix japonica*	2	1					1
	Duck	*Anas platyrhyncos*	1					1	
Aquatic Animals (29%)	Nile tilapia	*Oreochromis niloticus*	18		16			1	1
	Atlantic salmon	*Salmo salar*	7		3		2		2
	Common carp	*Cyprinus carpio*	4					2	2
	Farmed carp	*Labeo rohita*	1			1			
	White crucian carp	*Carassius auratus*	1						1
	Mozambique Tilapia	*Oreochromis mossambicus*	1						1
	Gibel carp	*Carassius gibelio*	2		2				
	Olive flounder	*Paralichthys olivaceus*	2	2					
	Loach	*Paramisgurnus dabryanus*	1						1
	Channel catfish	*Ictalurus punctatus*	7	2	1	2	1	1	
	Southern catfish	*Silurus meridionali*	1	1					
	Yellow catfish	*Pelteobagrus fulvidraco*	2	1	1				
	Sterlet	*Acipenser ruthenus*	2	1					1
	Tiger pufferfish	*Takifugu rubripes*	1	1					
	Red sea bream	*Pagrus major*	1	1					
	Blunt snout sea bream	*Megalobrama amblycephala*	1	1					
	Rainbow Trout	*Oncorhynchus mykiss*	1		1				
	Redhead cichlid	*Vieja melanura*	1						1
	Royal farlowella	*Sturisoma panamense*	1						1
	Oyster	*Crassostrea gigas*	1	1					
Insects (4%)	Silk worm	*Bombyx mori*	3	1		1	1		
	Honeybee	*Apis mellifera*	4						4
TOTAL			195	32%	20%	18%	12%	7%	11%

Gene editing myostatin to obtain myostatin (Tilapia, Bream) and leptin receptor (Puffer) KO fish



Puffer fish



Red Sea Bream

Fish (Tilapia)

Nile tilapia with increased fillet yield

- Fish embryos injected with CRISPR/Cas9 mRNA to t
- Deletions of nucleotides to knockout the gene
- Increased growth rate and feed conversion
- Product considered non-GMO in 2019

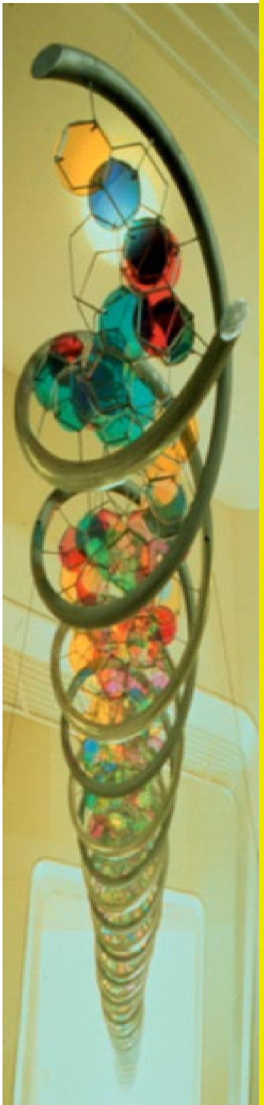
Brazil

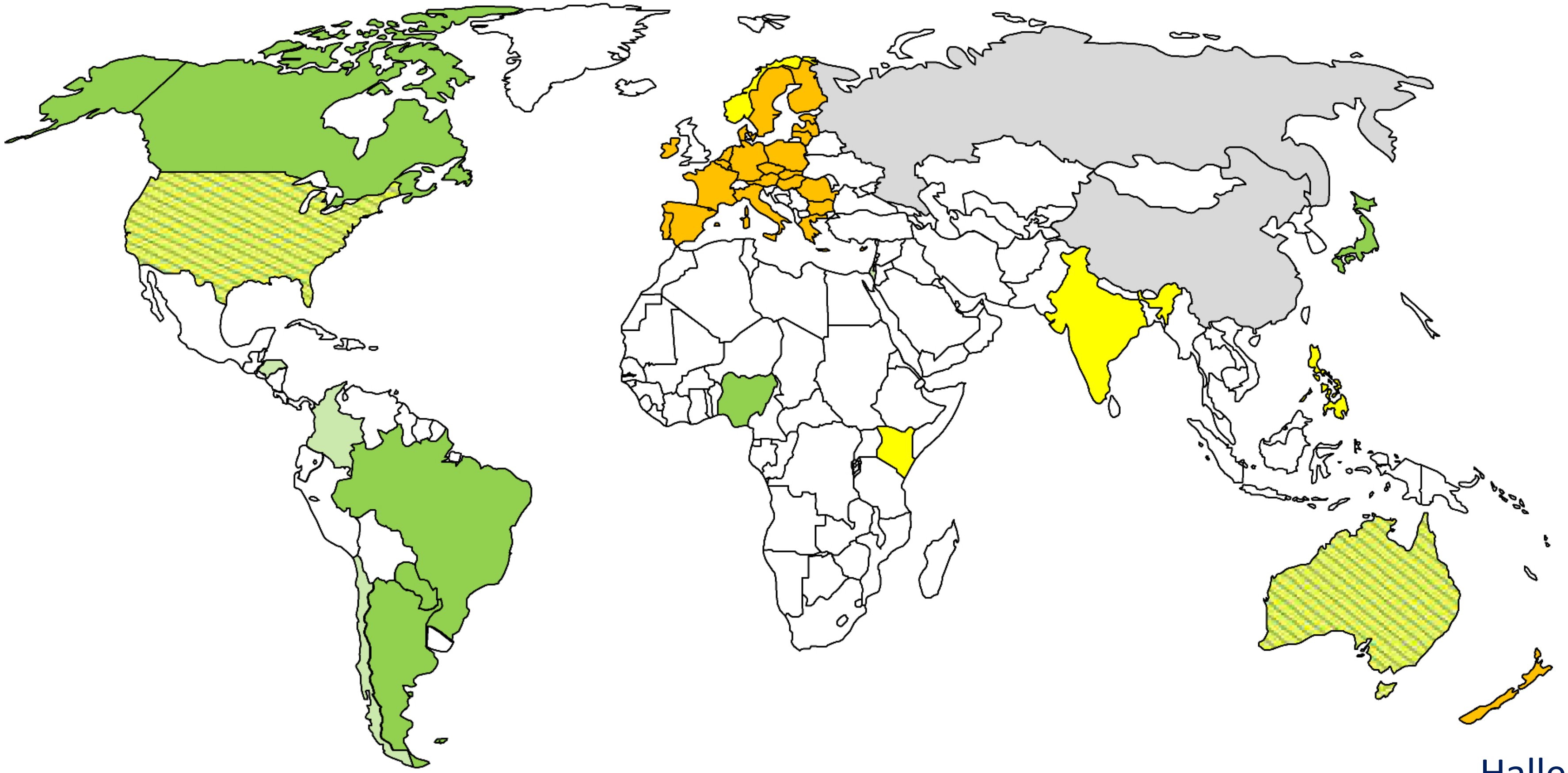
Argentina

https://sites.google.com/a/vt.edu/animalbiotechresources/2020-4th-intl-workshop

As of **2 January 2021**

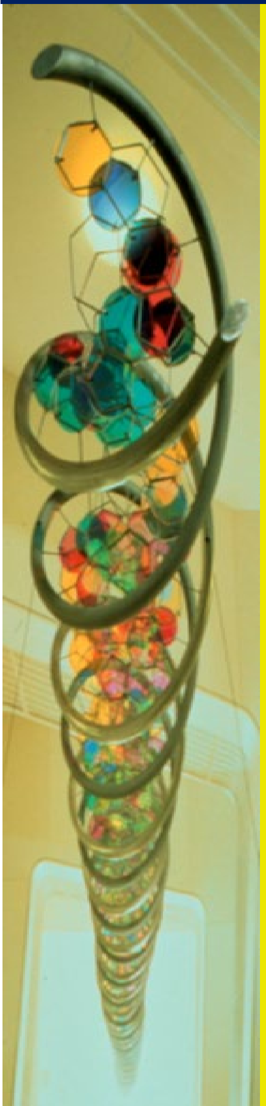
Overview of national or supranational regulatory regimes for GM or GnEd animals





- Countries with regulatory policy with exclusions
- Countries with regulatory policy with exclusions (plants only)
- Countries with pending policies, regulations, or legal rulings
- Countries with GMO only policy with no exclusions

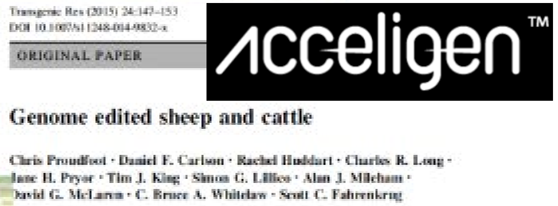
Hallerman *et al.* 2022. Towards progressive regulatory approaches for agricultural applications of animal biotechnology *Transgenic Res* **31**, 167–199



Cattle with simple modifications were determined to be "non-GMO" in Brazil in 2021

Cattle

- Semen from a bull (Nelore) with double muscle
  - TALENs injection into the cytoplasm of IVF zygotes
  - Indels to knockout the myostatin gene
- Male and female with slick hair
  - CRISPR/Cas9 injection into the cytoplasm of IVF zygotes;
  - Mutations inserted in the prolactin receptor
- Both considered non-GMO in 2021


Transgenic Res (2015) 24:147–153
DOI 10.1007/s11248-014-9832-x

ORIGINAL PAPER

Genome edited sheep and cattle

Chris Proudfoot · Daniel F. Carlson · Rachel Huddart · Charles R. Long · Jane H. Pryor · Tim J. King · Simon G. Lillico · Alan J. Mileham · David G. McLaren · C. Bruce A. Whitelaw · Scott C. Fahrenkrug

https://sites.google.com/a/vt.edu/animalbiotechresources/2020-4th-intl-workshop

Cattle with simple modifications were determined to be “non-GMO” in Argentina 2020

- *SLICK* edited Red Angus
- Double edited Celtic Pc polled/*SLICK* Holstein

In partnership with Kheiron S.A.

Previous Consultation Instance: product under development

- Produced using TALENs
- 1) Celtic allele: hornless trait. Naturally present in Angus, Simmental, Limousin, Charolais and Galloway
- 2) SLICK allele: improved heat-tolerance trait. Naturally present in Senepol, Carora,Limonero and Romosinuano.

June 2020 – no foreign DNA sequence and as such “no new combination of genetic material” And so considered “non-GMO”

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https://sites.google.com/a/vt.edu/animalbiotechresources/2020-4th-intl-workshop

FDA gives enforcement discretion to *SLICK* cattle submission by Acceligen (Recombinetics)

FDA Makes Low-Risk Determination for Marketing of Products from Genome-Edited Beef Cattle After Safety Review

Decision Regarding Slick-Haired Cattle is Agency's First Enforcement Discretion Decision for an Intentional Genomic Alteration in an Animal for Food Use

March 7, 2022

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Share

https://www.fda.gov/news-events/press-announcements/fda-makes-low-risk-determination-marketing-products-genome-edited-beef-cattle-after-safety-review

Content current as of:

03/07/2022

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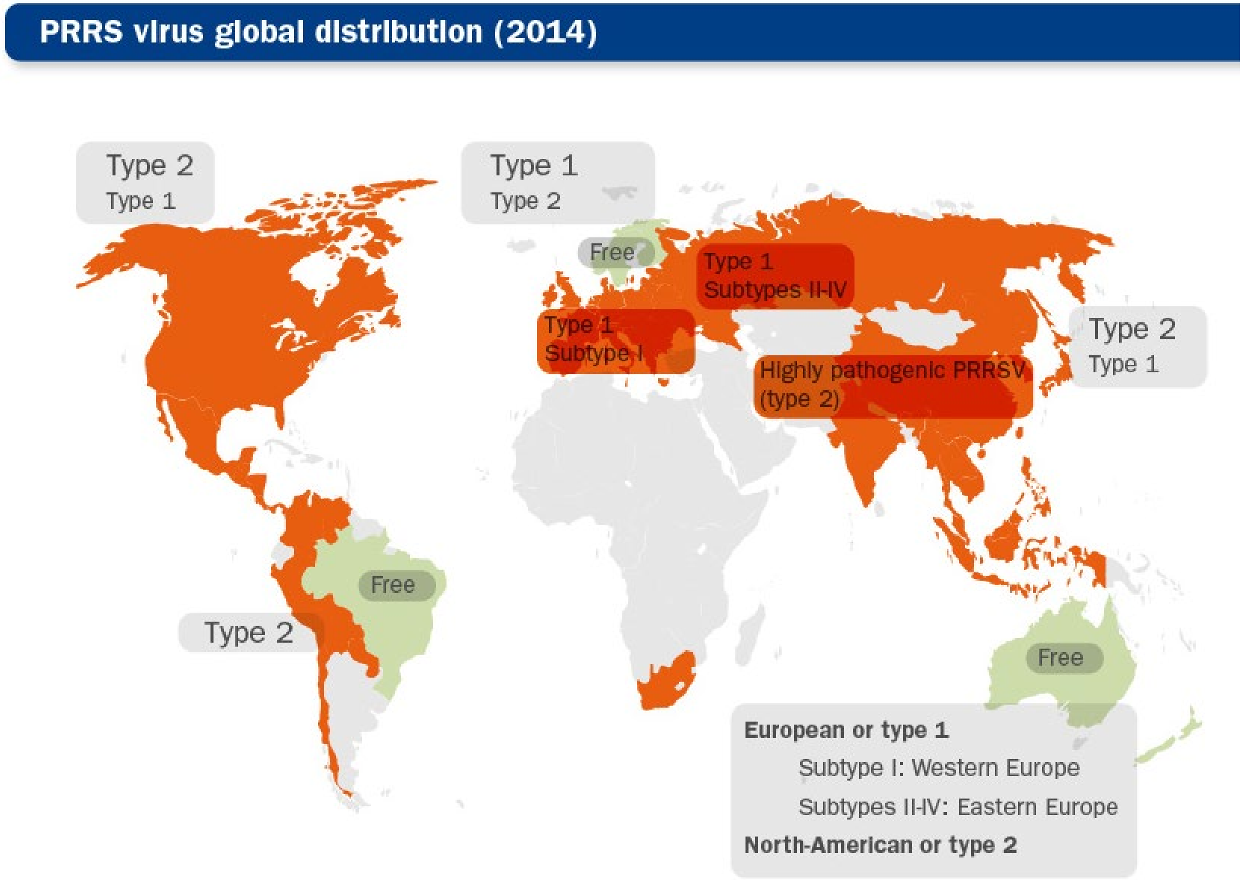
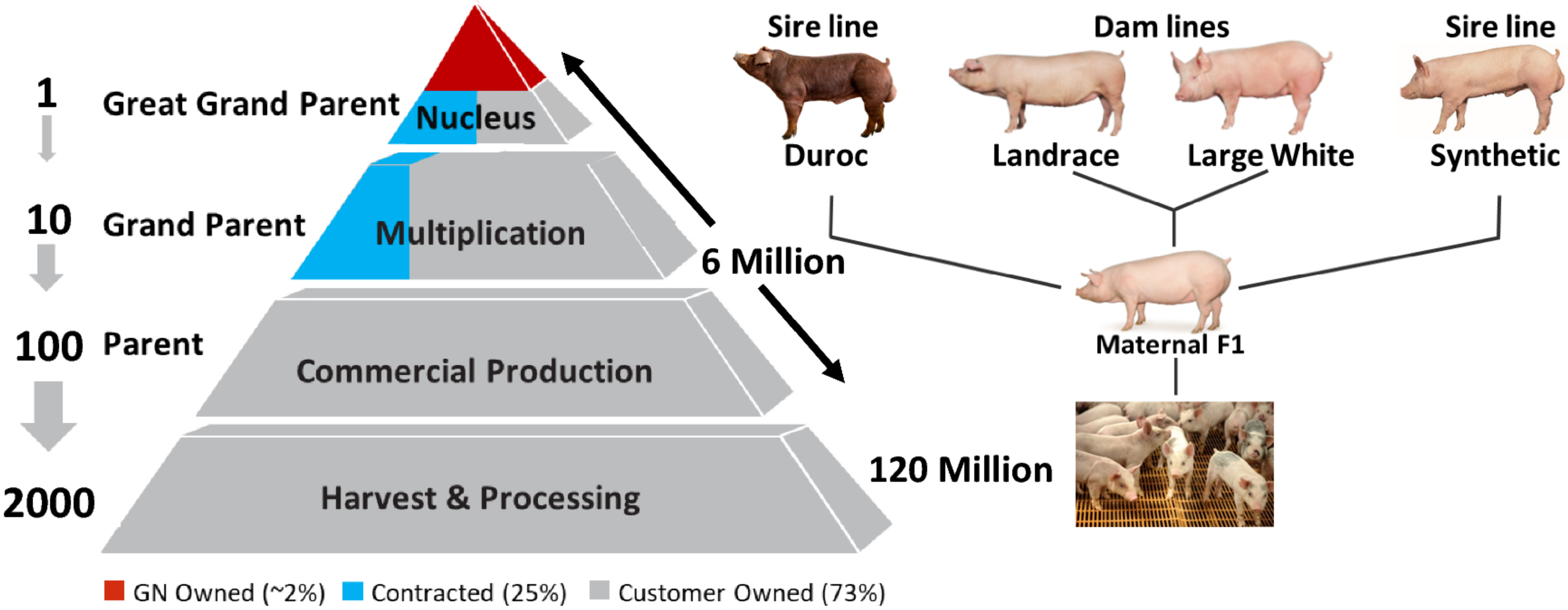
Gene editing to produce Porcine Reproductive & Respiratory Syndrome (PRRS) virus resistant pigs



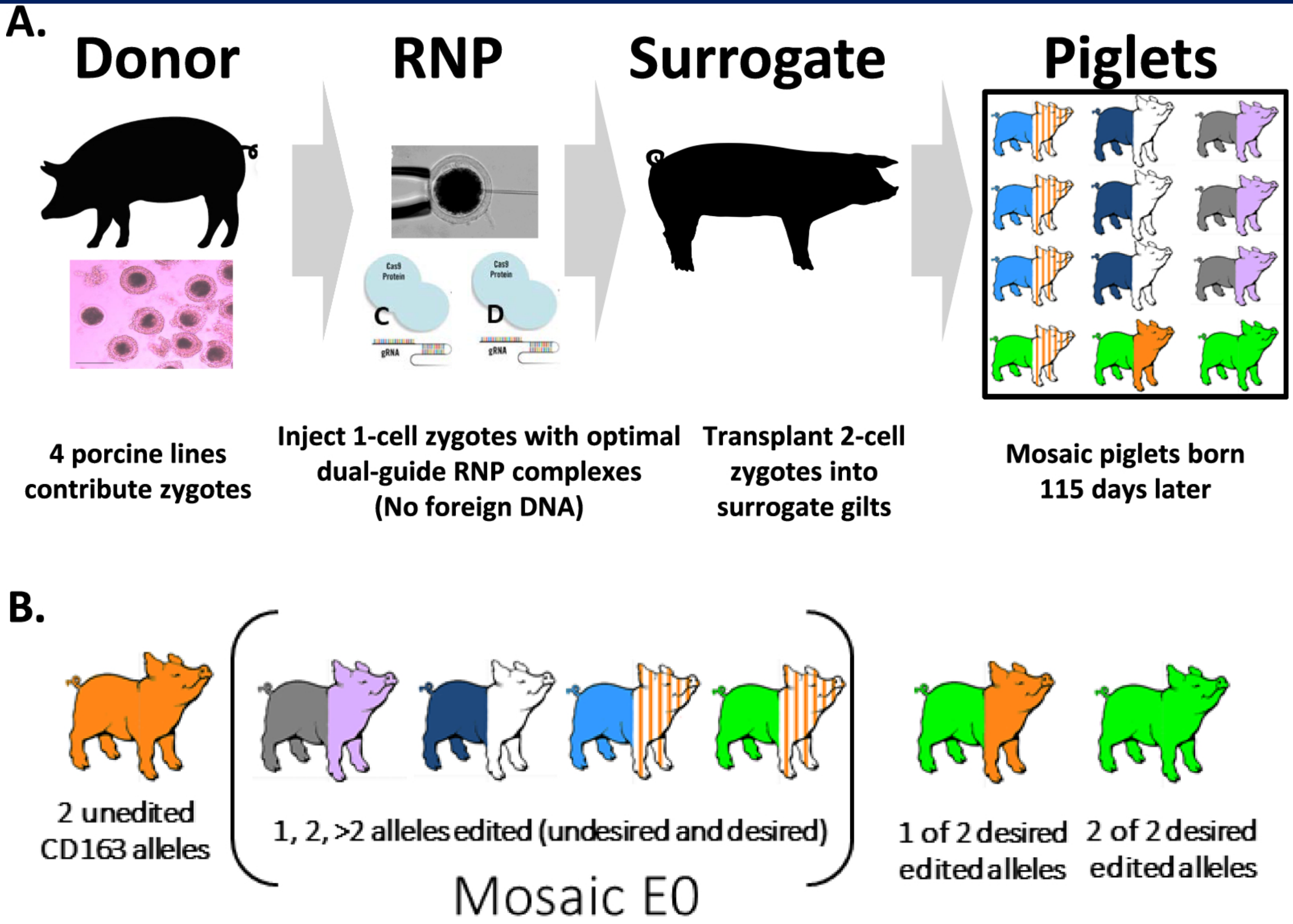
Whitworth et al. 2016. **Gene-edited pigs are protected from porcine reproductive and respiratory syndrome virus (PRRSV).** Nature Biotechnology 34:20-22.

Technical considerations towards commercialization of respiratory and reproductive syndrome (PRRS) virus resistant pigs

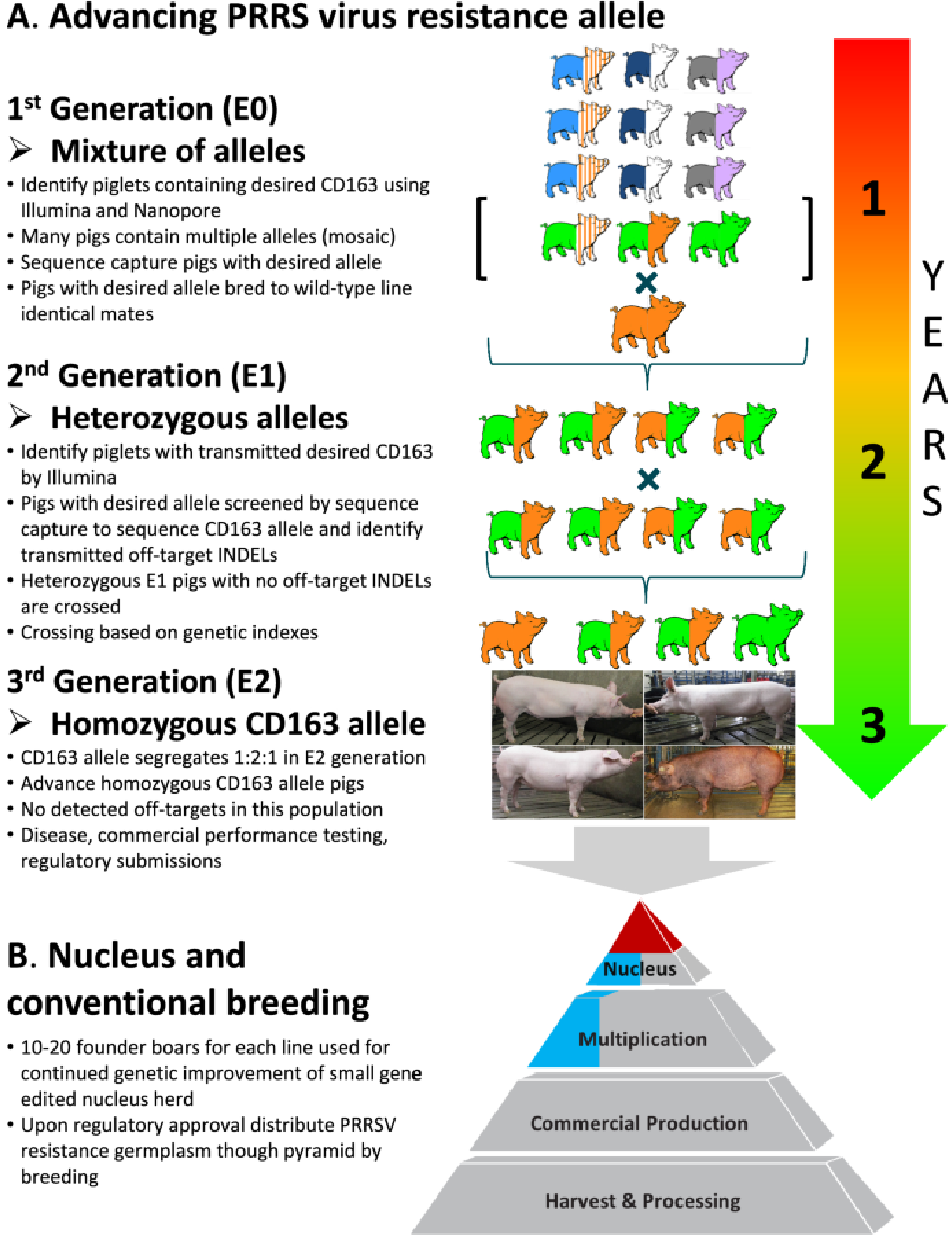


Mark Cigan, A., Knap, P.W. 2022. **Technical considerations towards commercialization of porcine respiratory and reproductive syndrome (PRRS) virus resistant pigs**. *CABI Agric Biosci* **3**, 34

Scaled production of pigs containing modified allele of CD163.



Mark Cigan, A., Knap, P.W. 2022. *CABI Agric Biosci* **3**, 34

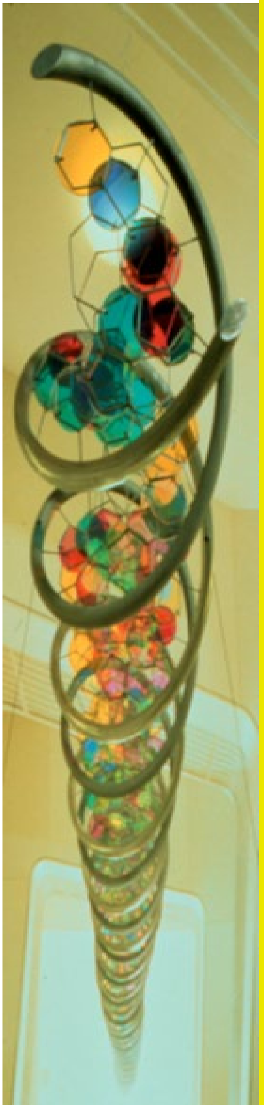


Scaled breeding steps for 1st, 2nd & 3rd generation of pigs to generate gene edited nucleus herd.

"Approximately 10–20 high genetic merit CD163$^{m/m}$ boars across 2 maternal and 2 paternal lines are used to maintain a small nucleus population for multiplication and genetic improvement. ***Upon approval****, these founders would be multiplied and distributed to producers for commercial production and sale using conventional breeding practices."*

Mark Cigan, A., Knap, P.W. 2022. *CABI Agric Biosci* **3**, 34

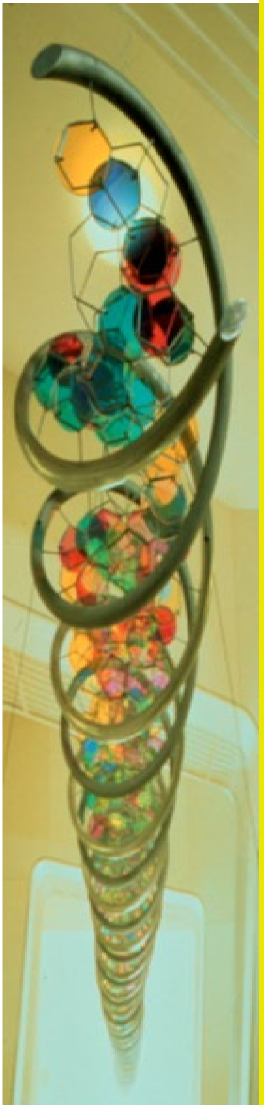
Would a gene-edited knock-out food animal be subject to additional regulations in this country?



Country	Additional Regulations?	Basis of trigger/regulation?
Argentina	No	Novel DNA sequence/transgene
Australia	No	Use of nucleic acid repair template
Brazil	No	Novel DNA sequence/transgene
Canada	No (?)	Trait novelty (i.e. novel product risk)
European Union	Yes	Is a GMO if used a mutagenesis technique not in existence before 2001
Japan	No	No exogenous genes
New Zealand	Yes	Using of in vitro technique that modifies the genes/genetic material
United States	Yes	New Animal Drug

Van Eenennaam FFF 2023

Would a gene-edited knock-in of endogenous allele in food animal be subject to additional regulations?



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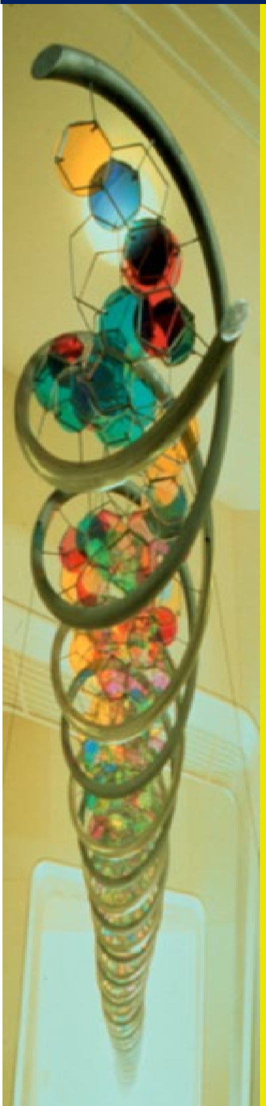
United States	Yes	New Animal Drug

Van Eenennaam FFF 2023

Editing as a Cherry on Top of the Breeding Sundae

It will be able to introduce useful alleles without linkage drag, and potentially bring in useful novel genetic variation from other breeds



Genome Editing

Somatic cell nuclear transfer cloning

Genomic Selection

Embryo Transfer

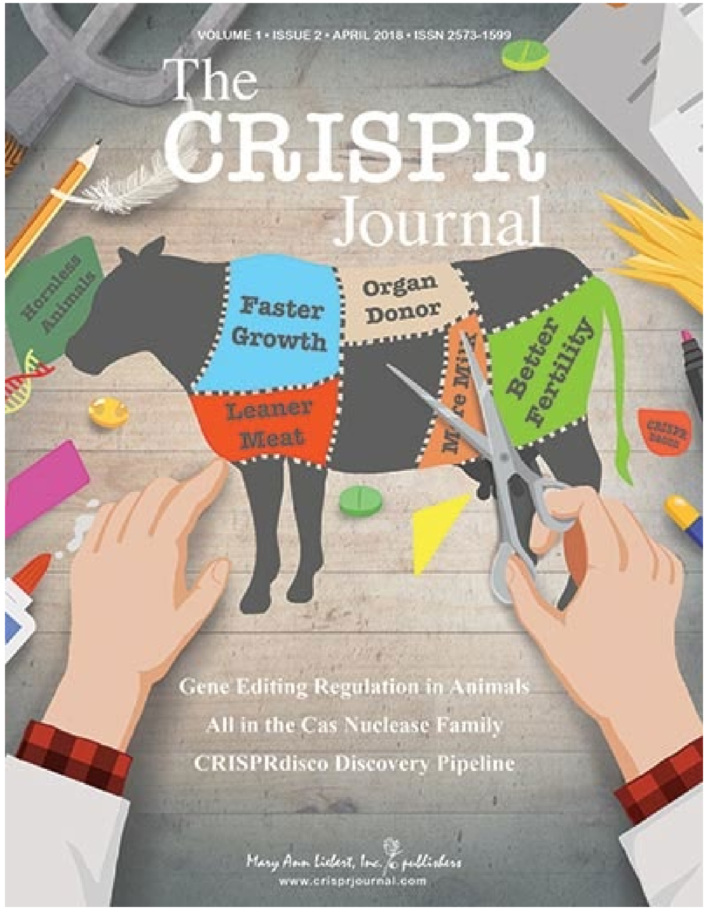
Artificial insemination

Progeny testing

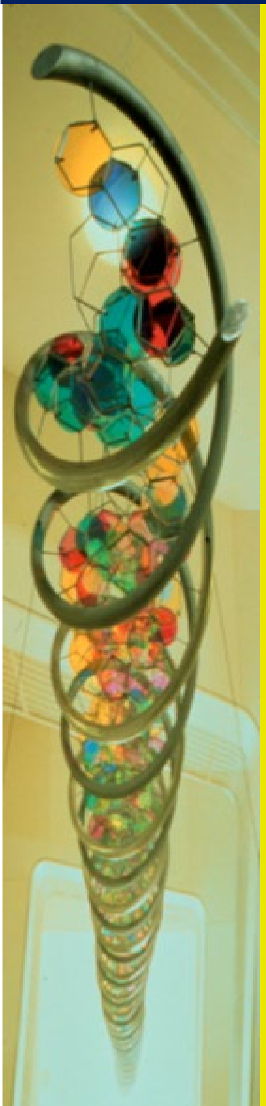
Performance recording

Development of breeding goals

Association of like minded breeders



Van Eenennaam, A. L. 2018. The Importance of a Novel Product Risk-Based Trigger for Gene-Editing Regulation in Food Animal Species. 1 (2): 101-106. https://doi.org/10.1089/crispr.2017.0023



Summary

- Genome editing offers an approach to introduce useful genetic variation and alleles without the linkage drag typically associated with cross-breeding.
- Scaling useful edits to commercial livestock breeding programs will be technically complicated and expensive
- Regulators in many countries consider simple edits (e.g. knockouts, moving allele from one breed to another) with no “foreign DNA” to be “non-GMO”
- The fate of genome editing in livestock will depend upon developing a risk-based regulatory framework

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UC DAVIS ANIMAL SCIENCE

- Dr. Josephine Trott
- Dr. Joey Owen
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- Dr. Elizabeth Maga
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- Dr. Tamer A. Mansour
- Dr. Xiang (Crystal) Yang
- Amy Young
- Barbara Nitta
- Ross lab members

- Dr. John Cole, URUS Group LP
- Dr. Pablo Ross, ST genetics
- Dr. Tad Sonstegard, Acceligen
- Dr. Bo Harstine, Select Sires Inc.

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FFAR
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SELECT SIRES INC.

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2017-33522-27097, 2017-38420-26790, 2018-67030-28360, 2020-67015-31536, 2020-70410-32899

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Tue, December 12, 2023

9:00 AM CST

on Zoom

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