Genetically Modified (GM) Animals: Developments in Research and Policy Framework

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The Global Challenge: Feeding the World Sustainably by 2050

- Increase Food Production Without Expanding Agricultural Land
- Reduce Growth In Demand for Food and Other Agricultural Products
- Reduce Greenhouse Gas Emissions from Agricultural Production

Source: Dr. Mingala’s PPT APEC 2023
Impact of Climate Change on Food Systems

- Decreased arability
- Fisheries
- Hunger food security & nutrition
- Reduced yields
- Planting and harvesting changes
- Emerging food risks
- Increased irrigation

Source: Dr. Mingala’s PPT APEC 2023
Source: https://www.sciencedirect.com/science/article/pii/S0963996920302817
Meat is an important source of nutrition for many people around the world.

Global demand for meat is growing: over the past 50 years, meat production has more than tripled.

Challenge: produce and consume meat, dairy and other protein products in a way that reduces its environmental impacts.
Livestock Industry challenges

- Adverse environmental condition
- Lack of new breeding animals
- High cost of farm inputs
- Transboundary animal diseases

Biotechnology is the use of biology to develop new products, methods and organisms intended to improve human health and society.

Source: https://www.techtarget.com/whatis/definition/biotechnology#:~:text=Biotechnology%20is%20the%20use%20of,discovery%20of%20fermentation.
ANIMAL / LIVESTOCK BIOTECHNOLOGY

Has a long history, beginning as far as 8,000 years ago

Domestication and Artificial Selection

Modern Animal Biotechnology began only following discovery of genetic code
ANIMAL / LIVESTOCK BIOTECHNOLOGY

- Increased Income for Livestock Food Producers
- Doubling Food Production to meet the supply for demand
- Climate Change and Disease Resilient or Resistant Animals
- Proper Animal management
- Rapid Diagnosis and Modern Disease Surveillance

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The Cartagena Protocol on Biosafety to the Convention on Biological Diversity is an international treaty governing the movements of living modified organisms (LMOs) resulting from modern biotechnology from one country to another. It was adopted on 29 January 2000 as a supplementary agreement to the Convention on Biological Diversity and entered into force on 11 September 2003.

(Cartagena, Colombia to Montreal, Canada)
CARTAGENA PROTOCOL

Article 3 – Use of Terms

(g) "Living modified organism" means any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology;

(h) "Living organism" means any biological entity capable of transferring or replicating genetic material, including sterile organisms, viruses and viroids;

(i) "Modern biotechnology" means the application of:
   a. In vitro nucleic acid techniques, including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles, or
   b. Fusion of cells beyond the taxonomic family, that overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection;
Introduction of Genetically Modified (GM) Animals

- **GM Animal** - involves altering its genetic material by adding, changing or removing certain DNA sequences in a way that does not occur naturally. It aims to modify specific characteristics of an animal or introduce a new trait, such as disease resistance or enhanced growth (EFSA).

- Two Methods:
  - Transgenesis / Cisgenesis (transfer of genes) in animals
  - Deletion of genetic information
Nutrition
Breeding
Trait Loci
Marker Assisted Breeding
Copy Number Variation
Genome-Wide Associated Study
Genomics
Proteomics
Metabolomics
Nuclear Transfer / Cloning
Microinjection
Phenotype Assay
Proper Management

Disease Models / Resistance
Xenotransplantation
• Cells
• Tissues
• Organs
• Bio Pharmacology
• Drugs
• Devices
• Biologicals
• High Value Products

Milk and meat quality
Milk and meat composition
Productivity increased
Conformation
Robustness
Fecundity
Environmental Resilience
Environmental Footprint
Use of New Breeding Innovation as a *Driver for Change in Livestock*

Cell Mediated Genomic Editing

**Cell Source**
- Zygote
- Fibroblasts

**Gene Editing**
- CRISPR/Cas9
  - Knockout
- CRISPR/Cas9-PCV
  - Base editor
  - Prime editor
  - Knock-in
  - Point-mutation

**Cell Manipulation**
- Electroporation
- Microinjection
- Micromanipulation of zygote
- Nuclear transfer
- Enucleation
- Cloned embryo
- Fusion and activation

**Embryo Transfer**
- Sheep
- Goat
- Pig
- Cow

**Applications**
- Fiber production
- Reproduction traits
- Meat production
- Milk quality
- Animal welfare
- Disease resistance
- Agricultural
- Xenotransplantation
- Animal models
- Gene therapy
- Pharmacological protein
- Biomedical

*Perisse et al., 2021*
The Philippine Carabao Center has adopted the **SOMATIC CELL NUCLEAR TRANSFER** technology to complement other existing reproductive tools for buffaloes. The present work was conducted to develop/optimize a system for cloning through somatic cell nuclear transfer in water buffalo. Buffalo clone embryos had been successfully produced in-vitro.

Selokar et al., 2022
Gene Editing

DNA editing

A DNA editing technique, called CRISPR/Cas9, works like a biological version of a word-processing programme’s “find and replace” function.

HOW THE TECHNIQUE WORKS

- A cell is transfected with an enzyme complex containing:
  - Guide molecule
  - Healthy DNA copy
  - DNA-cutting enzyme

- A specially designed synthetic guide molecule finds the target DNA strand.

- An enzyme cuts off the target DNA strand.

- The defective DNA strand is replaced with a healthy copy.

Sources: Reuters; Nature; Massachusetts Institute of Technology
Figure 1
An abbreviated schematic history of 35 years of genetically engineered livestock featuring some of the well-known celebrities of the field. Abbreviations: CRISPR/Cas9, clustered regularly interspaced short palindromic repeat targeted by Cas 9 nuclease; SCNT, somatic cell nuclear transfer; TALEN, transcription activator-like effector nuclease; ZFN, zinc-finger nuclease.

Gene Edited Animals in the Pipeline

• Intentional Genomic Alteration
• Slick hair coat – to better regulate their internal body temperature with an increased capacity of sweating

Source: Goetz Laible, 2022

Littlejohn et al., Nature Communications 5:5861 (2014)

• Color diluted dairy cattle
• Lightening the coat color can reduce the radiative heat gain from exposure to the sun

Source: ISAAA Inc., 2021

PMEL -/-  PMEL +/-
Gene Edited Animals in the Pipeline

- A typical horned dairy cow (right) and a genome-edited cow without horns that contains a DNA sequence found in hornless cattle (Photo courtesy of Alison L. Van Eenennaam, Dept. of Animal Science, University of California-Davis)

- GalSafe Pigs
- GM pig to prevent allergies

Source: ISAAA Inc., 2021

Source: Goetz Laible, 2022
Gene Edited Animals in the Pipeline

- Red Angus
- Red Angus females have excellent milk production and have a strong maternal instinct
- This breed produces a highly desired carcass with the meat being of excellent quality, this is due to the intra muscular marbling

Source: Goetz Laible, 2022
Gene Edited Animals in the Pipeline

- Porcine Reproductive and Respiratory Syndrome -resistant pigs
- Bird flu resistant chicken
  - contain an extra gene that interrupts the transmission of bird flu

Source:

Source:
https://www.ed.ac.uk/roslin/facilities-resources/larif/case-studies/industry-partners
Gene Edited Animals in the Pipeline

- Rosita Isa – was born that expressed milk containing proteins present in human milk but lacking in cow milk.

Source: https://www.theguardian.com/environment/2018/jun/24/genetically-engineered-animals-the-five-controversial-science

- A genetically modified male mosquitoes that carry a “self-limiting gene”; the offspring do not reach adulthood, reducing the spread of mosquito-borne diseases (Oxitec)
Applications and uses of GM / GE Animals

DISEASE

Nonhuman primate models for AIDS

Macaca mulatta (rhesus)
Macaca nemestrina (pigtailed)
Macaca fascicularis (crab-eating)

• HIV-1: only replicates in chimpanzees—disease in 10 years
• SIV: simian immunodeficiency virus; transferred from African to Asian macaques in captivity and caused disease like AIDS
• SHIV: chimera that has the HIV Envelope and the backbone of SIV; these viruses cause disease after passage in macaques

TEST SYSTEM DEVELOPMENT

Transgenic mice have been invaluable tools:

An example:
Normal mice cannot be infected with polio virus. They lack the cell-surface molecule that, in humans, serves as the receptor for the virus. So normal mice cannot serve as an inexpensive, easily-manipulated model for studying the disease. However, transgenic mice expressing the human gene for the polio virus receptor can be infected by polio virus and even develop paralysis and other pathological changes characteristic of the disease in humans.

• Work is in progress to develop new models by altering the susceptibility of mice to pathogens of humans.
Applications and uses of GM / GE Animals

GENE THERAPY

Gene Therapy

functioning gene

cell with non-functioning gene

cell functioning normally

GENE THERAPY FOR CYSTIC FIBROSIS

AAV vector

CFTR

Organoids

CF mouse model
Larger species, such as pigs and baboons, are preferred for development as donors because of the similarity of their organ size to that of humans.
GM Animals Regulatory Policy

DOST-DA-DENR-DOH-DILG
Joint Department Circular
No. ___, Series of 2022


STATUS: Under series of Stakeholder Consultation within the country
GM Animals Regulatory Policy

Applicability

- genetically-modified fisheries and other aquatic resources
- domesticated animals and biological products used for animal husbandry or veterinary purposes
- biological agents used for biocontrol derived from the use of modern biotechnology and containing novel combinations of genetic materials

Products of gene editing that do not contain novel combinations of genetic materials are not covered by this Circular.
Ways Forward

To ensure an enabling environment for biotechnology undertakings:

1. Implementation of a clear, predictable, science-based, and risk-proportionate regulations

2. Establishment of an adaptive and responsive policies that can adapt to rapid advancements and emerging technologies

3. Foster international cooperation and harmonization of regulatory standards to streamline global biotech development and facilitate cross-border research and trade

4. Adequate/sufficient funding for biotech, research, and innovation

5. Education and Public Awareness
Thank you!
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