"Current Status of Genetically Engineered Animals"

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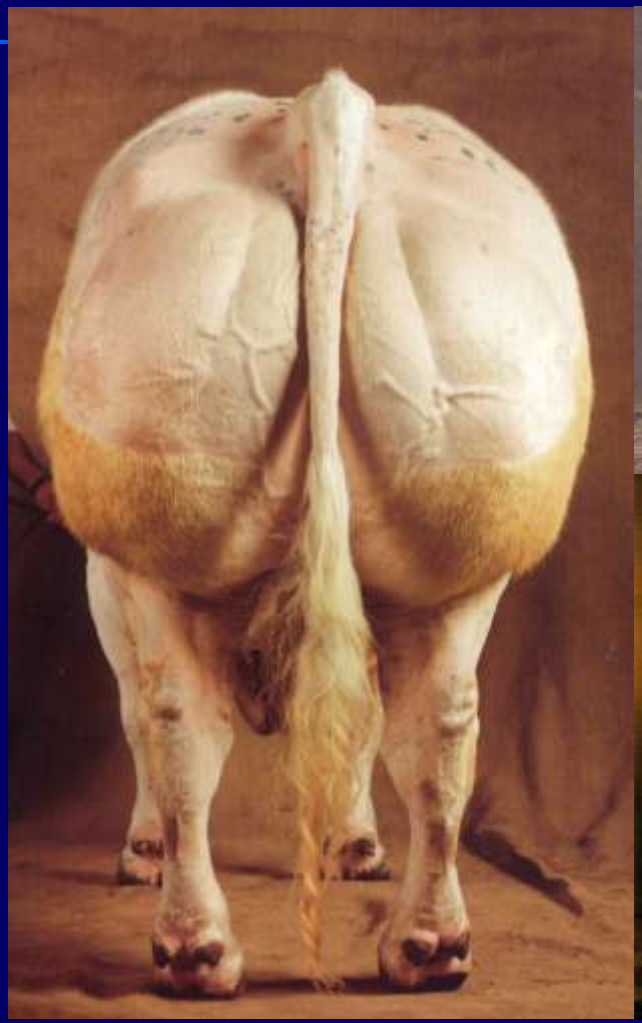
BIO 05/04/10

Animal breeders have been genetically-modifying animals for centuries

I am not going to be talking changes made by animal breeding today…….



But rather changes made by the process of genetic engineering…….

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The Science & Business of BioPharmaceuticals

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August 1, 2006

Production of Recombinant Therapeutic Proteins in the Milk of Transgenic Animals

By Yann Echelard, Carol A. Ziomek, Harry M. Meade

FDA Grants First-Ever U.S. Approval of GE Animal Product

Printer Friendly

For Immediate Release
2/6/2009

Contact:
Contact Karen Batra
202-449-6382

WASHINGTON, D.C. (Friday, February 06, 2009) - Advances in human health care from the genetic engineering of animals are now being realized in the United States. The U.S. Food and Drug Administration (FDA) announced today the first approval of a product derived from a genetically engineered (GE) animal.

ATryn®, a recombinant form of human antithrombin developed by GTC Biotherapeutics, was approved by the FDA for the prevention of peri-operative and peri-partum thromboembolic events in hereditary antithrombin deficient patients. It is not indicated for treatment of thromboembolic events in hereditary antithrombin deficient patients. ATryn® is the first ever transgenically produced therapeutic protein and the first recombinant antithrombin approved in the United States.

Along with the approval of ATryn®, the FDA's Center for Veterinary Medicine also approved GTC's New Animal Drug Application, the first of its kind to regulate GE animals. This is now required for a recombinant technology used to develop transgenic animals, such as the goats that produce recombinant antithrombin. GTC has granted OVATION the right to market ATryn® in the United States and pursue further clinical development.

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Animal Biotechnology and Genomics Education

ARTICLES

nature biotechnology

Production of human monoclonal antibody in eggs of chimeric chickens

Lei Zhu[1], Marie-Cecile van de Lavoir[1], Jenny Albanese[2], David O Beenhouwer[4,5], Pina M Cardarelli[2], Severino Cuison[2], David F Deng[1], Shrikant Deshpande[2], Jennifer H Diamond[1], Lynae Green[2], Edward L Halk[2], Babette S Heyer[1], Robert M Kay[1], Allyn Kerchner[1], Philip A Leighton[1], Christine M Mather[1], Sherie L Morrison[4], Zivko L Nikolov[3], David B Passmore[2], Alicia Pradas-Monne[1], Benjamin T Preston[2], Vangipuram S Rangan[2], Mingxia Shi[1], Mohan Srinivasan[2], Steven G White[3], Peggy Winters-Digiacinto[1], Susan Wong[2], Wen Zhou[1] & Robert J Etches[1]

The tubular gland of the chicken oviduct is an attractive system for protein expression as large quantities of proteins are deposited in the egg, the production of eggs is easily scalable and good manufacturing practices for therapeutics from eggs have been established. Here we examined the ability of upstream and downstream DNA sequences of ovalbumin, a protein produced exclusively in very high quantities in chicken egg white, to drive tissue-specific expression of human mAb in chicken eggs. To accommodate these large regulatory regions, we established and transfected lines of chicken embryonic stem (cES) cells and formed chimeras that express mAb from cES cell–derived tubular gland cells. Eggs from high-grade chimeras contained up to 3 mg of mAb that possesses enhanced antibody-dependent cellular cytotoxicity (ADCC), nonantigenic glycosylation, acceptable half-life, excellent antigen recognition and good rates of internalization.

Origen Therapeutics

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Origen Therapeutics' goal is to develop next generation antibody therapeutics using its proprietary transgenic animal technology to deliver products via chicken's eggs. The company is a leader in developing technology for producing fully human sequence polyclonal antibodies derived from the immune system of chickens.

Vision.
Origen's vision is to become the leading developer of polyclonal antibody therapeutics, a class of immunotherapeutic which shows promise of greatly enhanced efficacy in treating a wide range of diseases including infectious disease, cancer and autoimmune disease.

Mission.
Origen's mission is to apply its proprietary avian transgenesis technology to the development of a platform for the discovery, development and commercialization of fully human sequence polyclonal antibodies. These antibody therapeutics are expected to show the enhanced target destruction found in natural immune responses which are polyclonal in nature.

Origen Therapeutics is a privately held company, founded in 1997. The company is headquartered in Emeryville, California where the company has established laboratories.

www.origentherapeutics.com

Animal Biotechnology and Genomics Education

Cloned transchromosomic calves producing human immunoglobulin

Yoshimi Kuroiwa[1], Poothappillai Kasinathan[2], Yoon J. Choi[3], Rizwan Naeem[4], Kazuma Tomizuka[1], Eddie J. Sullivan[2], Jason G. Knott[2], Anae Duteau[3], Richard A. Goldsby[3], Barbara A. Osborne[5], Isao Ishida[1]*, and James M. Robl[2]*

Published online: 12 August 2002, doi:10.1038/nbt727

Human polyclonal antibodies (hPABs) are useful therapeutics, but because they are available only from human donors, their supply and application is limited. To address this need, we prepared a human artificial chromosome (HAC) vector containing the entire unrearranged sequences of the human immunoglobulin (h*Ig*) heavy-chain (*H*) and lambda (*λ*) light-chain loci. The HAC vector was introduced into bovine primary fetal fibroblasts using a microcell-mediated chromosome transfer (MMCT) approach. Primary selection was carried out, and the cells were used to produce cloned bovine fetuses. Secondary selection was done on the regenerated fetal cell lines, which were then used to produce four healthy transchromosomic (Tc) calves. The HAC was retained at a high rate (78–100% of cells) in calves and the h*Ig* loci underwent rearrangement and expressed diversified transcripts. Human immunoglobulin proteins were detected in the blood of newborn calves. The production of Tc calves is an important step in the development of a system for producing therapeutic hPABs.

p http://www.nature.com/naturebiotechnology

www.hematech.com

Xenotransplantation 2010: 17: 48–60
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doi: 10.1111/j.1399-3089.2009.00564.x

XENOTRANSPLANTATION

Structural characterization of α1,3-galactosyltransferase knockout pig heart and kidney glycolipids and their reactivity with human and baboon antibodies

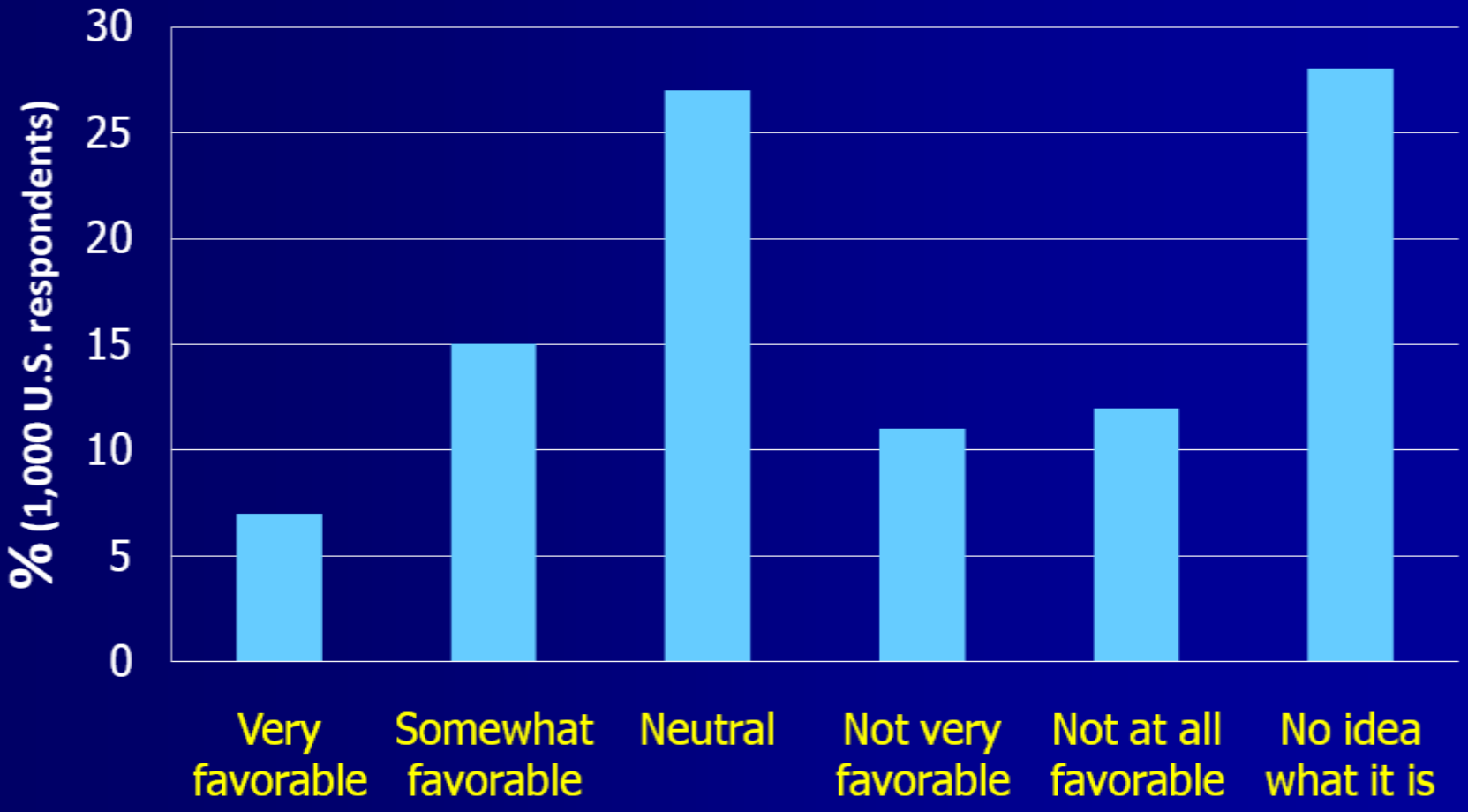
Diswall M, Ångström J, Karlsson H, Phelps CJ, Ayares D, Teneberg S, Breimer ME. Structural characterization of α1,3-galactosyltransferase knockout pig heart and kidney glycolipids and their reactivity with human and baboon antibodies.
Xenotransplantation 2010; 17: 48–60. © 2010 John Wiley & Sons A/S.

Mette Diswall,[1] Jonas Ångström,[1] Hasse Karlsson,[2] Carol J. Phelps,[3] David Ayares,[3] Susann Teneberg,[2] and Michael E. Breimer,[1]

[1]Department of Surgery, Institute of Clinical

www.revivicor.com

What is your overall impression of using biotechnology with animals that produce food products such as meat, milk, and eggs?



IFIC (2008) http://www.ific.org/research/biotechres.cfm

Proportional increase in world head of livestock 1961-2004; data from FAO (2005)

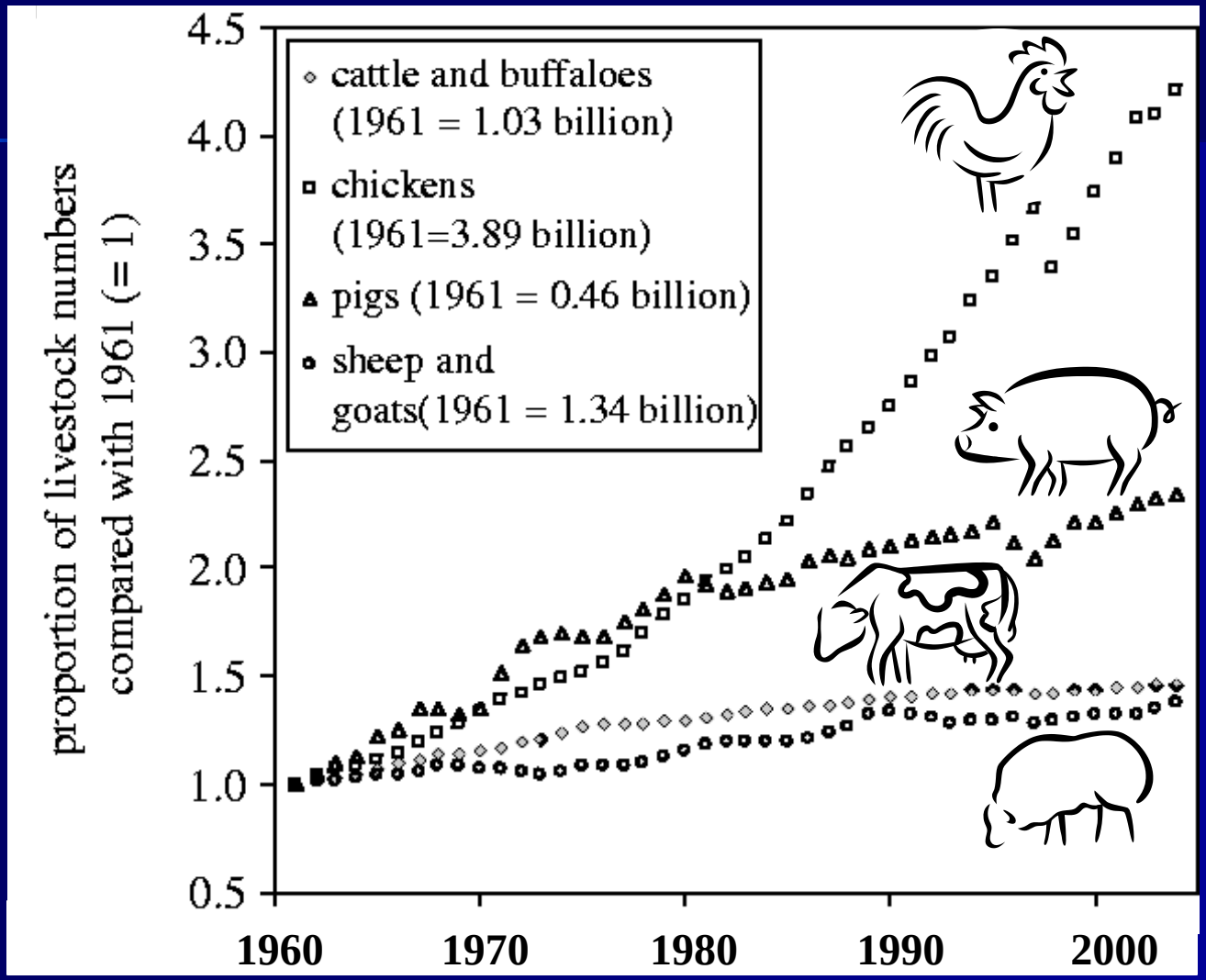


Figure based on Pretty, J. (2008) Agricultural sustainability: concepts, principles and evidence. Philosophical Transactions of the Royal Society B-Biological Sciences 363:447-465.

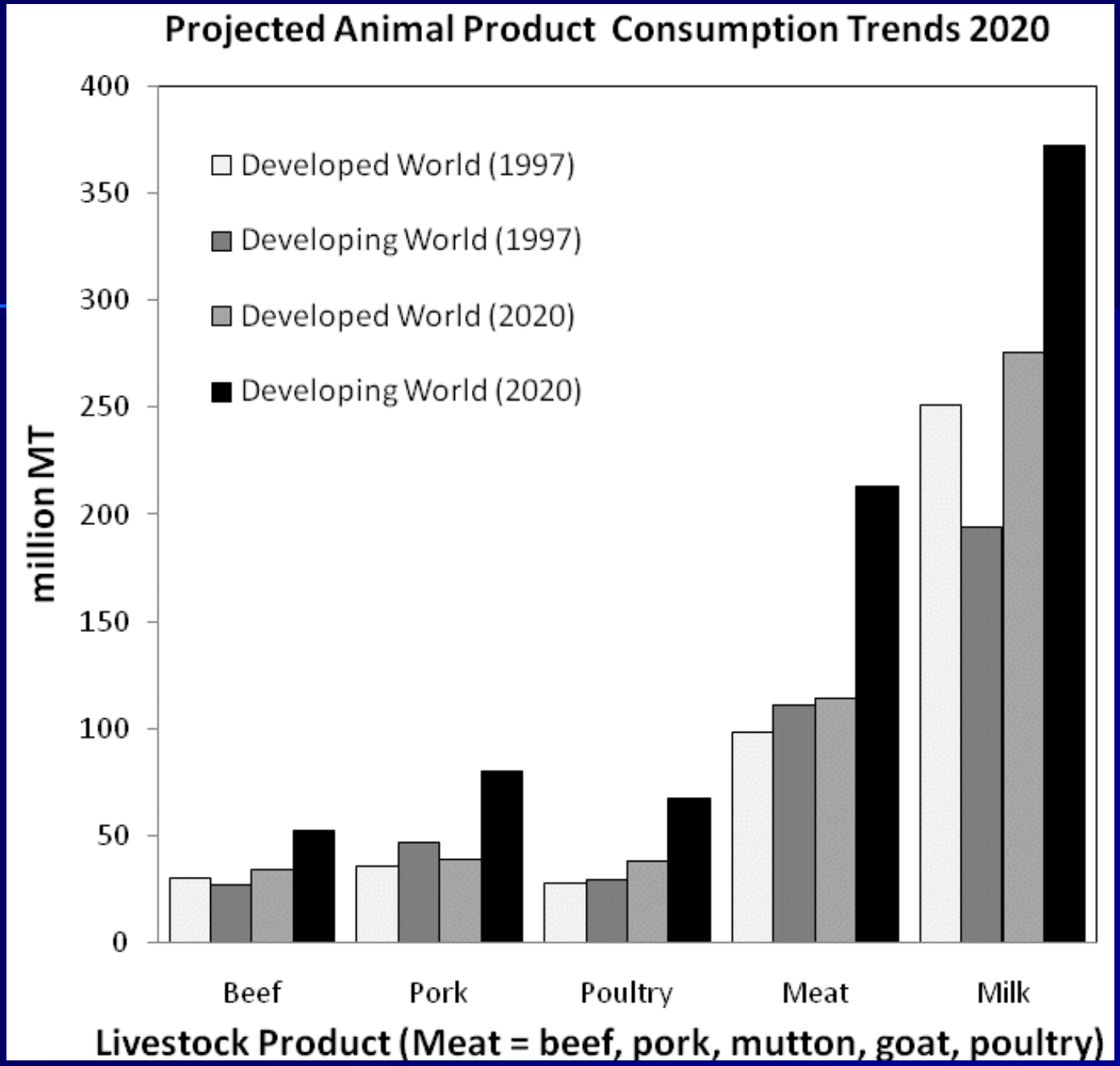


Figure from Delgado, C. L. 2003. Rising consumption of meat and milk in developing countries has created a new food revolution. Journal of Nutrition 133:3907S-3910S.

Extant GE livestock applications

ENVIRONMENTAL	Species	Gene	Approach
Decreased P in manure	Swine	Phytase	Transgene overexpression
DISEASE RESISTANCE			
Mastitis resistance	Cattle	Lysostaphin	Transgene expression
BSE resistance	Goat, Cattle	Prion	RNAi transgene; knockout
Visna virus resistance	Sheep	Visna virus envelope gene	Transgene expression
Mastitis resistance	Goats	Lysozyme	Transgene expression
GCH virus resistance	Grass Carp	Lactoferrin	Transgene expression
Bacterial resistance	Channel Catfish	Cecropin B gene	Transgene expression
PRODUCT QUALITY			
Increased ω-3 fatty acids in meat	Swine	n-3 fatty acid desaturase	Clone/Transgene expression
Increase cheese yield from milk	Cattle	β-casein, κ-casein	Clone/Transgene expression
PRODUCTIVITY			
Enhanced growth rate	Many fish species	Growth Hormone	Transgene expression
Enhanced milk production	Swine	α-lactalbumin	Transgene expression
Enhanced growth rate	Swine	Growth hormone	Transgene expression
Enhanced growth rate	Swine	Insulin-like-growth factor	Transgene expression

Fahrenkrug et al. 2010. Precision Genetics for Complex Objectives in Animal Agriculture. J. Anim Sci. In press. doi:10.2527/jas.2010-2847

Enviropig™ (Low-phosphorus manure)

RESEARCH ARTICLE

Nature Biotechnology 2001

Pigs expressing salivary phytase produce low-phosphorus manure

Serguei P. Golovan[1,2], Roy G. Meidinger[2], Ayodele Ajakaiye[3], Michael Cottrill[1], Miles Z. Wiederkehr[4], David J. Barney[4], Claire Plante[5], John W. Pollard[5], Ming Z. Fan[3], M. Anthony Hayes[6], Jesper Laursen[7,8], J. Peter Hjorth[7], Roger R. Hacker[3], John P. Phillips[2,*], and Cecil W. Forsberg[1,*]

To address the problem of manure-based environmental pollution in the pork industry, we have developed the phytase transgenic pig. The saliva of these pigs contains the enzyme phytase, which allows the pigs to digest the phosphorus in phytate, the most abundant source of phosphorus in the pig diet. Without this enzyme, phytate phosphorus passes undigested into manure to become the single most important manure pollutant of pork production. We show here that salivary phytase provides essentially complete digestion of dietary phytate phosphorus, relieves the requirement for inorganic phosphate supplements, and reduces fecal phosphorus output by up to 75%. These pigs offer a unique biological approach to the management of phosphorus nutrition and environmental pollution in the pork industry.

"reduces fecal phosphorus output by up to 75%"

www.uoguelph.ca/enviropig

Mastitis-resistant cows
(inflammation of mammary gland)

nature biotechnology

ARTICLES

Nature Biotechnology 23:445-451. 2005

Genetically enhanced cows resist intramammary *Staphylococcus aureus* infection

Robert J Wall[1], Anne M Powell[1], Max J Paape[2], David E Kerr[3], Douglas D Bannerman[2], Vernon G Pursel[1], Kevin D Wells[4], Neil Talbot[1] & Harold W Hawk[1]

Mastitis, the most consequential disease in dairy cattle, costs the US dairy industry billions of dollars annually. To test the feasibility of protecting animals through genetic engineering, transgenic cows secreting lysostaphin at concentrations ranging from 0.9 to 14 mg/ml in their milk were produced. *In vitro* assays demonstrated the milk's ability to kill *Staphylococcus aureus*. Intramammary infusions of *S. aureus* were administered to three transgenic and ten nontransgenic cows. Increases in milk somatic cells, elevated body temperatures and induced acute phase proteins, each indicative of infection, were observed in all of the nontransgenic cows but in none of the transgenic animals. Protection against *S. aureus* mastitis appears to be achievable with as little as 3 mg/ml of lysostaphin in milk. Our results indicate that genetic engineering can provide a viable tool for enhancing resistance to disease and improve the well-being of livestock.

http://www.nature.com/naturebiotechnology

"Mad cow"-resistant cows
(bovine spongiform encephalopathy (BSE))

nature biotechnology

Nature Biotechnology 2007

Production of cattle lacking prion protein

Jürgen A Richt[1,6], Poothappillai Kasinathan[2], Amir N Hamir[1], Joaquin Castilla[3], Thillai Sathiyaseelan[2], Francisco Vargas[1], Janaki Sathiyaseelan[2], Hua Wu[2], Hiroaki Matsushita[2], Julie Koster[2], Shinichiro Kato[4,5], Isao Ishida[4], Claudio Soto[3], James M Robl[2] & Yoshimi Kuroiwa[4–6]

Prion diseases are caused by propagation of misfolded forms of the normal cellular prion protein PrP^{C}, such as PrP^{BSE} in bovine spongiform encephalopathy (BSE) in cattle and PrP^{CJD} in Creutzfeldt-Jakob disease (CJD) in humans[1]. Disruption of

PrP-specific western blot analyses on fibroblasts (**Fig. 1d**), peripheral blood lymphocytes (**Fig. 1e**) and brain stem (**Fig. 1f**) from wild-type and *PRNP*$^{-/-}$ calves using the mouse anti-bovine PrP monoclonal antibody F89. We detected PrP-specific bands in the wild-type calves.

nature.com/naturebiotechnology

PNAS

Suppression of prion protein in livestock by RNA interference

PNAS 2006

Michael C. Golding*, Charles R. Long†, Michelle A. Carmell*, Gregory J. Hannon*‡, and Mark E. Westhusin†§

*Watson School of Biological Sciences, Cold Spring Harbor Laboratory, Howard Hughes Medical Institute, 1 Bungtown Road, Cold Spring Harbor, NY 11724; and †Department of Veterinary Physiology, College of Veterinary Medicine, Texas A&M University, College Station, TX 77843

Communicated by James E. Womack, Texas A&M University, College Station, TX, February 2, 2006 (received for review November 21, 2005)

Given the difficulty of applying gene knockout technology to species other than mice, we decided to explore the utility of RNA interfering RNAs enables induction of silencing by "classical" DNA expression vectors and has thus become adaptable to cell

Envisioned GE livestock applications

ENVISIONED APPICATIONS	Species	Proposed Approach
Suppressing infectious pathogens (e.g. foot-and-mouth disease resistance)	Various	RNAi (Lentivirus)
Avian flu resistance	Poultry	RNAi (Lentivirus)
Coronavirus-resistance	Swine	RNAi /Knockout
Low lactose milk	Cattle	Transgene expression
Low lactose milk	Cattle	RNAi /Knockout
Increased ovulation rate	Sheep	RNAi /Knockout
High omega-3 fatty acid milk	Cattle	Transgene expression
Resistance to Brucellosis	Cattle	Transgene expression
Decreased P in manure	Poultry	Transgene expression
Increased lean-muscle growth	Cattle	RNAi /Knockout
Increased post-natal growth	Various	RNAi /Knockout
Enhanced mammary gland development	Various	RNAi /Knockout

Fahrenkrug et al. 2010. Precision Genetics for Complex Objectives in Animal Agriculture. J. Anim Sci. In press. doi:10.2527/jas.2010-2847

Disease-resistant genetically modified animals

Rev. sci. tech. Off. int. Epiz., 2005, **24** (1), 275-283

***Rev. sci. tech. Off. int Epiz.* 2005**

Disease-resistant genetically modified animals

C.B.A. Whitelaw & H.M. Sang

Roslin Institute, Department of Gene Function and Development, Roslin, Midlothian, EH25 9PS, Scotland, United Kingdom

Summary

Infectious disease adversely affects livestock production and animal welfare, and has impacts upon both human health and public perception of livestock production. The authors argue that the combination of new methodology that enables the efficient production of genetically-modified (GM) animals with exciting new tools to alter gene activity makes the applications of transgenic animals for the benefit of animal (and human health) increasingly likely. This is illustrated through descriptions of specific examples. This technology is likely to have specific application where genetic variation does not exist in a given population or species and where novel genetic improvements can be engineered. These engineered animals would provide valuable models with which to investigate disease progression and evaluate this approach to controlling the disease. The authors propose that the use of GM animals will complement the more traditional tactics to combat disease, and will provide novel intervention strategies that are not possible through the established approaches.

Keywords

Disease – Gene expression – Genetic modification – Infection – Livestock – Virus.

"Would there be general acceptance of transgenic technology if it could be applied to engineering resistance to influenza in poultry and therefore lessen the risk of an influenza epidemic, such as the one in 1918 that killed more than 20 million people?"

Clark,J. & Whitelaw,B. 2003. A future for transgenic livestock. Nature Reviews Genetics 4, 825-833

2001 foot-and-mouth outbreak in UK

$ 3.5 to $6 billion lost, Numerous producer suicides
Millions of animals slaughtered from 10,000 farms

Is it possible that "playing it safe" by not pursuing research and development in genetically engineered animals might deny us a technique or products which could prevent an environmental or public health disaster in fifty years time, or could prove invaluable in the treatment of some livestock disease?

"...genetic engineering is a key technology, which will be vital for meeting the world's future food needs. While animal genetics alone will not solve the world's future food problems, to fail to apply the best available technologies to the solution of contemporary and future food shortages would be morally reprehensible."

Fahrenkrug et al. 2010. Precision Genetics for Complex Objectives in Animal Agriculture. J. Anim Sci. In press. doi:10.2527/jas.2010-2847


B
Red
Orange
Yellow
Green
Wild Type


GMO'S
TREATOR
TRICK?


HUMAN GROWTH HORMONE GENE
MT
PROMOTER
pBR