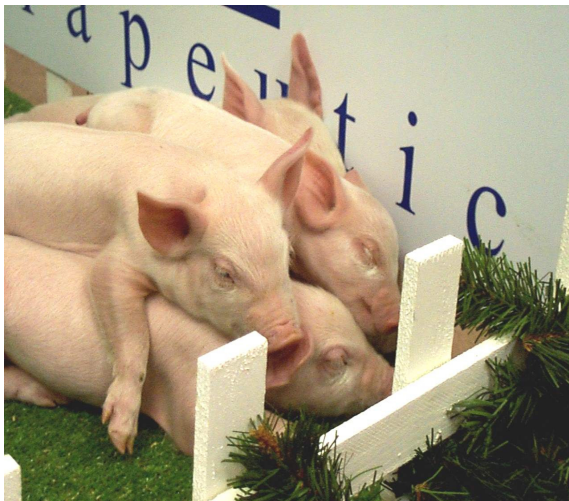# Swine models of Human Conditions

Kevin D. Wells
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Pigs are anatomically, physiologically, and biochemically similar to humans that they soon provide replacement organs for human patients.

nature
biotechnolo gy

VOLUME 20 • NO 3 • MARCH 2002

http://biotech.nature.com

Transplantation-friendly pigs

Carbohydrate arrays

Kinase assays on a solid surface

Engineered T cells target gene therapy

Biomedical Models

Models need to recapitulate the human condition.

Cystic Fibrosis.

Conditions of Ataxia.

Immune function.

Cardiovascular system.

Obesity.

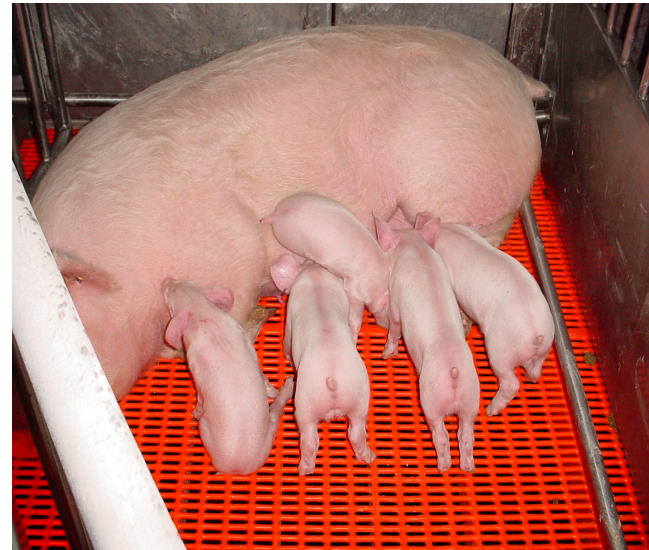# Biomedical Models

Models need to be an appropriate size.

Surgical intervention.

Hardware testing.

Transit time.

Bone load.

Connective tissue damage.

Biomedical Models

Models need to have similar anatomy.

Subcutaneous fat deposition.

Cell ratios (rods vs. cones).

Structure (skin).

Number of cell layers (heart thickness).

Biomedical Models

Models need to have similar behavior.

Diurnal vs. Nocturnal activity.

Pecking order stress.

Food preference.

Biomedical Models

Models need to have similar Physiology.

Vomit Response (pig is the only model).

Fat deposition.

Microbe susceptibility.

Cardiovascular disease.

Biomedical Models

Models need to have similar Chronology.

    In vivo durability of hardware.

    Long-term exposure limits.

    Cellular repopulation.

    Graft/transplant durability.

Genetically modified Pigs

Retinitis Pigmentosa
    Surgical Intervention model.

Cystic Fibrosis
    Full symptomatic recapitulation

Cardiovascular models

Diabetes

Comparative Biology

Human to Pig: biomedical models

Retinitis Pigmentosa

Mutations in Proline 347 produce a dominant phenotype.
Born without symptoms.
By puberty, requires extra light, may have "night blindness.
Over the next 15 years slowly looses all rods, then looses cones.
By 40 years of age, complete blindness.

Transgenic mice reproduce some of the phenotype.
Mice have too few cones.
Too small for surgical intervention.

A better model was needed.

RESEARCH

Genetically engineered large animal model for studying cone photoreceptor survival and degeneration in retinitis pigmentosa

Robert M. Petters, Curtis A. Alexander, Kevin D. Wells, E. Bruce Collins, Jeffrey R. Sommer, Maria R. Blanton, Guadalupe Rojas, Ying Hao[1], William L. Flowers, Eyal Banin[3], Artur V. Cideciyan[3], Samuel G. Jacobson[3], and Fulton Wong[1,2*]

*Department of Animal Science, North Carolina State University, Raleigh, NC. [1]Department of Ophthalmology and [2]Departments of Neurobiology and Pathology, Duke University School of Medicine, Durham, NC. [3]Department of Ophthalmology, Scheie Eye Institute, University of Pennsylvania, Philadelphia, PA. *Corresponding author: (e-mail: fulton.wong@duke.edu).*

Patients with retinitis pigmentosa (RP) typically develop night blindness early in life due to loss of rod photoreceptors. The remaining cone photoreceptors are the mainstay of their vision; however, over years or decades, these cones slowly degenerate, leading to blindness. We created transgenic pigs that express a mutated rhodopsin gene (Pro347Leu). Like RP patients with the same mutation, these pigs have early and severe rod loss; initially their cones are relatively spared, but these surviving cones slowly degenerate. By age 20 months, there is only a single layer of morphologically abnormal cones and the cone electroretinogram is markedly reduced. Given the strong similarities in phenotype to that of RP patients, these transgenic pigs will provide a large animal model for study of the protracted phase of cone degeneration found in RP and for preclinical treatment trials.

Genetically engineered large animal model for studying cone photoreceptor survival and degeneration in retinitis pigmentosa

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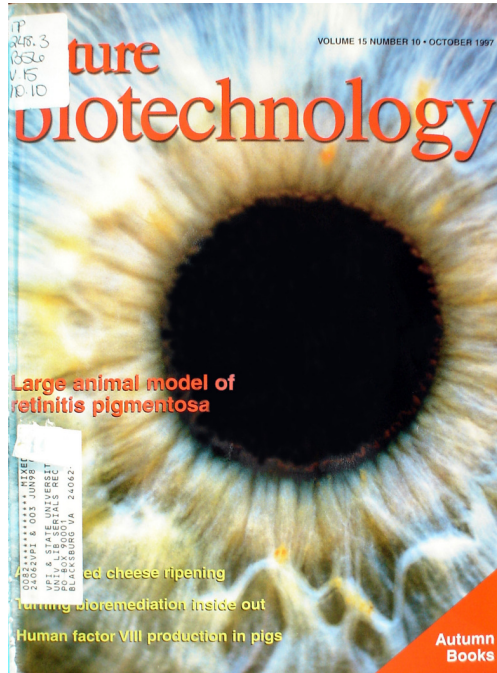
Transgenic RP Pigs remain a great model!

Symptoms begin at 5-6 months

Disease progression is complete by 20 months.

Histology is very similar at all stages.

Altered light responses of single rod photoreceptors in transgenic pigs expressing P347L or P347S rhodopsin

Timothy W. Kraft,[1,2] Derron E. Allen,[1] Robert M. Petters,[3] Ying Hao,[4] You-Wei Peng,[4] Fulton Wong[4,5]

Departments of [1]Physiological Optics and [2]Neurobiology, School of Optometry, University of Alabama, Birmingham, AL; [3]Department of Animal Science, North Carolina State University, Raleigh, NC; Departments of [4]Ophthalmology and [5]Neurobiology Duke University Medical Center, Durham, NC

Purpose: Numerous mutations of rhodopsin lead to rod cell death and ultimately to complete blindness, yet little is known about the alterations in the physiology of the light sensors containing the aberrant protein, the rod photoreceptors.
Methods: Suction pipettes were used to record the light responses from single rod photoreceptors isolated from the retinas of transgenic pigs of various ages and at progressive stages of retinal degeneration.
Results: We have observed changes in the photoresponse of transgenic porcine rods containing both wild type and mutant rhodospin. Our findings are consistent with the idea that substitutions at position proline 347 of rhodopsin interfere with the inactivation of R*. In addition the level of photoreceptor degeneration is positively correlated with an acceleration and desensitization of the photoresponse to dim flashes.
Conclusions: It appears that the phototransduction cascade, even when initiated by wild type rhodopsin molecules is altered in a way that is progressive with the level of retinal degeneration. A model consistent with our observations introduces the idea of a binding site for the carboxy terminus of rhodopsin on rhodopsin kinase.

Cystic Fibrosis: ten mouse models

Partial recapitulation of the intestinal phenotype.

Airway epithelium

   Partial recapitulation of upper airway phenotype.

   No phenotype in lower airway.

Hepatobiliary sytem

   No Phenotype in liver.

   Partial recapitulation in Gall Bladder.

Partial recapitulation in pancreas.

Normal male fertility and unexpected reduced female fertility.

Poor recapitulation in Salivary Gland.

Similar phenotype in tooth enamel.

Production of *CFTR*-null and *CFTR*-ΔF508 heterozygous pigs by adeno-associated virus–mediated gene targeting and somatic cell nuclear transfer

Christopher S. Rogers,[1] Yanhong Hao,[2] Tatiana Rokhlina,[1] Melissa Samuel,[2] David A. Stoltz,[1] Yuhong Li,[1] Elena Petroff,[1] Daniel W. Vermeer,[1] Amanda C. Kabel,[1] Ziying Yan,[3] Lee Spate,[2] David Wax,[2] Clifton N. Murphy,[2] August Rieke,[2] Kristin Whitworth,[2] Michael L. Linville,[2] Scott W. Korte,[2] John F. Engelhardt,[3] Michael J. Welsh,[1,4,5] and Randall S. Prather[2]

[1]Department of Internal Medicine, University of Iowa Carver College of Medicine, Iowa City, Iowa, USA. [2]Division of Animal Sciences, Office of Animal Resources, University of Missouri, Columbia, Missouri, USA. [3]Department of Anatomy and Cell Biology, University of Iowa Carver College of Medicine, Iowa City, Iowa, USA. [4]Howard Hughes Medical Institute, Iowa City, Iowa, USA. [5]Department of Molecular Physiology, University of Iowa Carver College of Medicine, Iowa City, Iowa, USA.

Progress toward understanding the pathogenesis of cystic fibrosis (CF) and developing effective therapies has been hampered by lack of a relevant animal model. CF mice fail to develop the lung and pancreatic disease that cause most of the morbidity and mortality in patients with CF. Pigs may be better animals than mice in which to model human genetic diseases because their anatomy, biochemistry, physiology, size, and genetics are more similar to those of humans. However, to date, gene-targeted mammalian models of human genetic disease have not been reported for any species other than mice. Here we describe the first steps toward the generation of a pig model of CF. We used recombinant adeno-associated virus (rAAV) vectors to deliver genetic constructs targeting the CF transmembrane conductance receptor (*CFTR*) gene to pig fetal fibroblasts. We generated cells with the *CFTR* gene either disrupted or containing the most common CF-associated mutation (ΔF508). These cells were used as nuclear donors for somatic cell nuclear transfer to porcine oocytes. We thereby generated heterozygote male piglets with each mutation. These pigs should be of value in producing new models of CF. In addition, because gene-modified mice often fail to replicate human diseases, this approach could be used to generate models of other human genetic diseases in species other than mice.

Disruption of the *CFTR* Gene Produces a Model of Cystic Fibrosis in Newborn Pigs

Christopher S. Rogers,[1*] David A. Stoltz,[1*] David K. Meyerholz,[2*] Lynda S. Ostedgaard,[1] Tatiana Rokhlina,[1] Peter J. Taft,[1] Mark P. Rogan,[1] Alejandro A. Pezzulo,[1] Philip H. Karp,[1,3] Omar A. Itani,[1] Amanda C. Kabel,[1] Christine L. Wohlford-Lenane,[4] Greg J. Davis,[1] Robert A. Hanfland,[5] Tony L. Smith,[5] Melissa Samuel,[6] David Wax,[6] Clifton N. Murphy,[6] August Rieke,[6] Kristin Whitworth,[6] Aliye Uc,[4] Timothy D. Starner,[4] Kim A. Brogden,[7] Joel Shilyansky,[5] Paul B. McCray Jr.,[4] Joseph Zabner,[1] Randall S. Prather,[6] Michael J. Welsh[1,3,8†]

Almost two decades after *CFTR* was identified as the gene responsible for cystic fibrosis (CF), we still lack answers to many questions about the pathogenesis of the disease, and it remains incurable. Mice with a disrupted *CFTR* gene have greatly facilitated CF studies, but the mutant mice do not develop the characteristic manifestations of human CF, including abnormalities of the pancreas, lung, intestine, liver, and other organs. Because pigs share many anatomical and physiological features with humans, we generated pigs with a targeted disruption of both *CFTR* alleles. Newborn pigs lacking CFTR exhibited defective chloride transport and developed meconium ileus, exocrine pancreatic destruction, and focal biliary cirrhosis, replicating abnormalities seen in newborn humans with CF. The pig model may provide opportunities to address persistent questions about CF pathogenesis and accelerate discovery of strategies for prevention and treatment.

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The pig model fully
recapitulates Cystic Fibrosis

ORIGINAL PAPER

Production of endothelial nitric oxide synthase (eNOS) over-expressing piglets

Y. H. Hao · H. Y. Yong · C. N. Murphy · D. Wax · M. Samuel · A. Rieke ·
L. Lai · Z. Liu · D. C. Durtschi · V. R. Welbern · E. M. Price ·
R. M. McAllister · J. R. Turk · M. H. Laughlin · R. S. Prather · E. B. Rucker

Abstract Vascular function, vascular structure, and homeostasis are thought to be regulated in part by nitric oxide (NO) released by endothelial cell nitric oxide synthase (eNOS), and NO released by eNOS plays an important role in modulating metabolism of skeletal and cardiac muscle in health and disease. The pig is an optimal model for human diseases because of the large number of important similarities between the genomic, metabolic and cardiovascular systems of pigs and humans. To gain a better understanding of cardiovascular regulation by eNOS we produced pigs carrying an endogenous eNOS gene driven by a Tie-2 promoter and tagged with a V5 His tag. Nuclear transfer was conducted to create these animals and the effects of two different oocyte activation treatments and two different culture systems were examined. Donor cells were electrically fused to the recipient oocytes. Electrical fusion/activation (1 mM calcium in mannitol: Treatment 1) and electrical fusion (0.1 mM calcium in mannitol)/chemical activation (200 μM Thimerosal for 10 min followed by 8 mM DTT for 30 min: Treatment 2) were used. Embryos were surgically transferred to the oviducts of gilts that exhibited estrus on the day of fusion or the day of transfer. Two cloned transgenic piglets were born from Treatment 1 and low oxygen, and another two from Treatment 2 and normal oxygen. PCR, RT-PCR, Western blotting and immunohistochemistry confirmed that the pigs were transgenic, made message, made the fusion protein and that the fusion protein localized to the endothelial cells of placental vasculature from the conceptuses as did the endogenous eNOS. Thus both activation conditions and culture systems are compatible with development to term. These pigs will serve as the founders for a

Monday, 20 July 2009; 3:00 pm - 4:30 pm
Platform Session 10

Production of Cloned Pigs Carrying an Endothelial-Specific Transgene Designed to Overexpress Human Catalase to Study the Vasodilatory Effects of Hydrogen Peroxide (H$_2$O$_2$).

Jeffrey J. Whyte [1], **Emily Mahan** [2], **Melissa Samuel** [2], **Kristin M. Whitworth** [2], **Yanhong Hao** [2], **Clifton Murphy** [2], **Randall S. Prather** [2], and **M. Harold Laughlin** [2] [1] *University of Missouri, Columbia, MO, USA;* [2]

ABSTRACT 92

Hydrogen peroxide (H$_2$O$_2$) is an oxidant with a long half-life, capable of diffusing across cellular membranes and acting as a signaling molecule in vascular endothelial cells. The association between H$_2$O$_2$ and vasodilators such as nitric oxide (NO) is becoming increasingly important to our understanding to the regulation of vascular tone. Previous studies suggest that these vasodilators may play a critical role in disease states such as atherosclerosis and preeclampsia. The objective of the current study is to determine how NO, produced by endothelial nitric oxide synthase (eNOS),is influenced by H$_2$O$_2$ in the swine vasculature. We have developed cloned transgenic Yucatan minipigs carrying a transgene designed to overexpress human catalase (hCat) in an endothelial-specific manner, subsequently metabolizing endogenous H$_2$O$_2$. Yucatan minipig fetal fibroblasts stably transfected with an hCat overexpression construct were isolated into single-cell populations by fluorescence automated cell sorting (FACS) based on fluorescence of a co-transfected eGFP plasmid. Cells sorted into 96-well plates yielded viable colonies in 30% of the wells. Presence of the hCat transgene in fibroblasts was determined by PCR genotyping. Transgenic fibroblasts were used for nuclear transfer into enucleated oocytes by electrofusion. A minimum of 140 cloned embryos were used for embryo transfer into four surrogates. These embryo transfers yielded pregnancies in all four sows. Cloned piglets from three sows near parturition were delivered by cesarean section. A total of six cloned male Yucatan mini piglets from two of the litters were positive for the tie2-catalase transgene as determined by PCR genotyping. These piglets will be used to compare the endothelial response in transgenic versus wild-type pigs. The similarities between swine and human cardiovascular anatomy and physiology suggest that this pig model will provide critical information on the regulation of eNOS by H$_2$O$_2$ and the mechanism sunderlying human vascular health in response to exercise and in specific disease states. This work is funded by a grant from the NIH (R24 RR018276-05) to MHL.

IMPAIRED INCRETIN EFFECT IN TRANSGENIC PIGS EXPRESSING A DOMINANT NEGATIVE RECEPTOR FOR GLUCOSE-DEPENDENT INSULINOTROPIC POLYPEPTIDE IN THE PANCREATIC ISLETS

S. Renner, B. Keßler, N. Herbach, D. C. von Waldthausen, R. Wanke, A. Hofmann, A. Pfeifer and E. Wolf

Abstract

Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) are secreted by specific cell types in the intestine and are responsible for the so-called incretin effect, the phenomenon that an oral glucose load elicits a higher insulin response than does an intravenous glucose load. In patients with type 2 diabetes mellitus the overall incretin effect is reduced. This fact is mostly attributed to a lowered insulinotropic effect of GIP, while the effect of GLP-1 is preserved. In order to better understand the consequences of impaired function of GIP, knockout mice lacking a functional GIP receptor (GIPR$^{-/-}$) as well as transgenic mice expressing a dominant negative GIPR (GIPR^{dn}) were established. While GIPR$^{-/-}$ mice show only relatively mild changes in glucose homeostasis, GIPR^{dn} mice display a distinct diabetic phenotype due to disturbed development of the endocrine pancreas (Herbach *et al*. 2005 Regul. Pept. **125**, 103–117). To further clarify the underlying mechanisms, we used a novel, highly efficient gene transfer technology based on lentiviral vectors (Hofmann *et al*. 2003 EMBO Rep. **4**, 1054–1060; Hofmann *et al*. 2006 Mol. Ther. **13**, 59–66) to generate transgenic pigs expressing a GIPR^{dn} under the control of the rat *Ins2* promoter (RIP). RIP-GIPR^{dn} transgenic pigs develop normally and do not display diabetes mellitus up to at least one year of age. Weekly measured fasting blood glucose levels in transgenic animals did not show a significant difference compared to control pigs. The same was true for monthly determined fructosamine levels. However, RIP-GIPR^{dn} transgenic pigs exhibited reduced insulin release and higher glucose levels than non-transgenic littermate controls in an oral glucose tolerance test. The area under the curve (AUC) for insulin was 49% smaller ($P < 0.01$) and the AUC for glucose 26% larger ($P < 0.05$) in RIP-GIPR^{dn} transgenic pigs ($n = 5$) than in their non-transgenic littermate controls ($n = 5$). These findings demonstrate that expression of a GIPR^{dn}, which was shown by RT-PCR in isolated pancreatic islets, disturbs the function of GIP in transgenic pigs. Thus we have created a novel, clinically relevant animal model for studying the roles of the GIP/GIPR system. Quantitative morphological studies of the pancreas are being performed to clarify whether GIPR function is essential for pancreatic islet development and maintenance.

Glucose intolerance and reduced proliferation of pancreatic b-cells in transgenic pigs with impaired GIP function

Simone Renner1, Christiane Fehlings1,*, Nadja Herbach2,*, Andreas Hofmann3, Dagmar C. von Waldthausen1, Barbara Keßler1, Karin Ulrichs5, Irina Chodnevskaja5, Vasiliy Moskalenko5, Werner Amselgruber6, Burkhard Göke7, Alexander Pfeifer3,4, Rüdiger Wanke2, Eckhard Wolf1

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ORIGINAL PAPER

Dominant-negative mutant hepatocyte nuclear factor 1α induces diabetes in transgenic-cloned pigs

Kazuhiro Umeyama · Masahito Watanabe ·
Hitoshi Saito · Mayuko Kurome · Sadaaki Tohi ·
Hitomi Matsunari · Keizaburo Miki · Hiroshi Nagashima

Abstract Pigs have been recognized as an excellent biomedical model for investigating a variety of human health issues. We developed genetically modified pigs that exhibit the apparent symptoms of diabetes. Transgenic cloned pigs carrying a mutant human hepatocyte nuclear factor 1α gene, which is known to cause the type 3 form of maturity-onset diabetes of the young, were produced using a combined technology of intracytoplasmic sperm injection-mediated gene transfer and somatic cell nuclear transfer. Although most of the 22 cloned offspring obtained died before weaning, four pigs that lived for 20–196 days were diagnosed as diabetes mellitus with nonfasting blood glucose levels greater than 200 mg/dl. Oral glucose tolerance test on a cloned pig also revealed a significant increase of blood glucose level after glucose loading. Histochemical analysis of pancreas tissue from the cloned pigs showed small and irregularly formed Langerhans Islets, in which poor insulin secretion was detected.

Introduction

Advances in transgenic technologies have enabled the production of animals showing disease progression similar to that seen in humans (Prather et al. 2003). These animals provide models for etiological and pathogenetic research and are also useful tools for the development of new drugs (Larsen and Rolin 2004; Lunney 2007; Prather et al. 2003).

Hemizygous minipigs produced by random gene insertion and handmade cloning express the Alzheimer's disease-causing dominant mutation APPsw

Peter M. Kragh · Anders Lade Nielsen · Juan Li · Yutao Du · Lin Lin ·
Mette Schmidt · Ingrid Brück Bøgh · Ida E. Holm · Jannik E. Jakobsen ·
Marianne G. Johansen · Stig Purup · Lars Bolund · Gábor Vajta ·
Arne Lund Jørgensen

Abstract In an effort to develop a porcine model of Alzheimer's disease we used handmade cloning to produce seven transgenic Göttingen minipigs. The donor fibroblasts had been stably transfected with a plasmid cassette containing, as transgene, the cDNA of the neuronal variant of the human amyloid precursor protein gene with the Swedish mutation preceded by beta-globin sequences to induce splicing and a human PDGFbeta promoter fragment to drive transcription. Transgene insertion had occurred only at the *GLIS3* locus where a single complete copy of the transgene was identified in intronic sequences in opposite direction. Similar and robust levels of the transgene transcript were detected in skin biopsies from all piglets and the sequence of full-length transcript was verified. Consistent with PDGFbeta promoter function, high levels of transgene expression, including high level of the corresponding protein, was observed in brain tissue and not in heart or liver tissues. A rough estimate predicts that accumulation of the Aβ peptide in the brain may develop at the age of 1–2 years.

ORIGINAL PAPER

Varying phenotypes in swine versus murine transgenic models constitutively expressing the same human Sonic hedgehog transcriptional activator, *K5-HGLI2ΔN*

Amy C. McCalla-Martin · Xiaoxin Chen ·
Keith E. Linder · Jose L. Estrada ·
Jorge A. Piedrahita

Abstract This study was undertaken to characterize the effects of constitutive expression of the hedgehog transcriptional activator, Gli2, in porcine skin. The keratinocyte-specific human transgene, *K5-hGli2ΔN*, was used to produce transgenic porcine lines via somatic cell nuclear transfer techniques. In mice, *K5-hGli2ΔN* induces epithelial downgrowths resembling basal cell carcinomas. Our porcine model also developed these basal cell carcinoma-like lesions, however gross tumor development was not appreciated. In contrast to the murine model, diffuse epidermal changes as well as susceptibility to cutaneous infections were seen in the swine model. Histologic analysis of transgenic piglets revealed generalized epidermal changes including: epidermal hyperplasia (acanthosis), elongated rete ridges, parakeratotic hyperkeratosis, epidermal neutrophilic infiltration, capillary loop dilation and hypogranulosis. By 2 weeks of age, the transgenic piglets developed erythematic and edematous lesions at high contact epidermal areas and extensor surfaces of distal limb joints. Despite antibiotic treatment, these lesions progressed to a deep bacterial pyoderma and pigs died or were euthanized within weeks of birth. Non-transgenic littermates were phenotypically normal by gross and histological analysis. In summary, constitutive expression of the human *hGli2ΔN* in keratinocytes, results in cutaneous changes that have not been reported in the *K5-hGli2ΔN* murine model. These findings indicate a need for a multiple species animal model approach in order to better understand the role of Gli2 in mammalian skin.

A. C. McCalla-Martin · K. E. Linder ·

Swine Biomedical Models

Any manipulation that can be done in mice, can also be accomplished in pigs.

Gene knockouts
Gene replacement
Gene modification
Gene addition
Modified expression

Swine Biomedical Models

Any manipulation that can be done in mice, can also be accomplished in pigs.

    Gene knockouts
    Gene replacement
    Gene modification
    Gene addition
    Modified expression

When the pig is the appropriate model, technology is not an obstacle.