Minipig Translational Research Models
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Introduction

Miniature swine have been utilized as translational research models with outcomes in high concordance with humans in a variety of systems. Much of the data justifying the minipig models has been published in books and review manuscripts.\(^1\)\(^-\)\(^16\) Summary publications of some of the major models have also been published online (http://www.sinclairresearch.com/Literature/Literature.aspx). Major systems utilized in these types of studies are: cardiovascular, dermal, digestive, urogenital, neurologic, ophthalmic, and musculoskeletal. This manuscript will discuss areas where swine have been demonstrated to be translational models with direct application to humans.

Cardiovascular

The growth of the cardiovascular system has been more refined as a comparison to humans than most other tissues or systems. The growth and maturity of the heart and great vessels in swine from fetal to sexual maturity is roughly equivalent to the development of the same structures in humans from birth to early sexual maturity. Thus the effects of treatments performed in immature swine can provide an insight into their effect on humans from infancy until the teenage years in a time frame of 4-5 months.\(^1\), \(^17\)-\(^18\)

Medical device implantation is a common preclinical use of porcine surgical models. In particular the implantation of devices in the heart and blood vessels is a favored translational model. Other common preclinical surgical cardiovascular models are vascular graft implants and creation of aneurysms in the aorta and neck. When implanting intravascular devices the growth of the blood vessels needs to be considered for chronic protocols. Implantation of a device into the aorta of an immature farm pig may be inappropriate for these studies because the diameter of the vessel can be expected to grow 35-40% and the length 25-30% over a period of 6 months. The growth of the blood vessels in miniature breeds is substantially less and thus they are used for chronic implantation studies. The size of the heart and great vessels in sexually mature Hanford minipigs is more similar in size to those of humans than other miniature breeds. The Yucatan minipigs has a slightly larger heart: body weight ratio than the other breeds but since it is smaller than the Hanford the heart tends to never reach the size of the human. In general most cardiovascular device studies require minipigs >40 kg unless the study is pediatric in nature.\(^1\), \(^10\)

Intravascular interventional catheter techniques are widely used in swine as well.\(^1\)-\(^4\), \(^11\) In particular the implantation of intravascular stents was developed as a translational model due to the ability of the pig to develop restenosis in the same manner as humans. Development of drug eluding stents was primarily due to studies in miniature swine. Other intravascular stents would include the development of medicated stents for ablation of aneurysms.

Atherosclerosis may be induced in normal swine by a variety of methodologies and swine develop the complex lesions in the same manner as humans. Any of the methods requires that the pigs be fed an atherogenic diet. There is not any consensus on the percentage of the ingredients of a diet that will produce lesions in swine. In fact, part of the goals of a study may be to modify the amounts and types of atherogenic substances in the diet. The levels of cholesterol vary between 0.5-4.0% in the literature. It is likely that 2% is adequate to produce lesions in most studies. Fat levels also vary widely in the diets and have been used up to 50% of the composition. Induction of atherosclerosis by diet alone usually takes 6-12 months to develop. The development of lesions may be accelerated and specific areas targeted by employing techniques that damage the endothelium. The endothelium is denuded by inflation of angioplasty balloons in the artery of interest and pulling back on them. Goodrich\(^20\) developed a unique model of menopause and atherosclerosis in Yucatan minipigs. Sexually mature Yucatan micropigs were ovariectomized and fed a 4% cholesterol diet free of plant phytoestrogens with 40% of the calories from fat for 6 months. Some authors have concluded that the Yucatan mini- and micropig is superior to other miniature breeds for these studies.\(^1\), \(^19\)-\(^22\)

Integumentary

There are many similarities between pig and human skin including a sparse hair coat, relative thick epidermis, epidermal turnover kinetics, lipid composition, carbohydrate biochemistry, enzyme histochemistry, lipid biophysical properties and arrangement of dermal collagen and elastic fibers. Swine are used as one of the primary translational models in dermal toxicology, phototoxicology, transdermal absorption and contact dermal allergy.\(^11\), \(^12\), \(^13\), \(^14\), \(^23\), \(^24\)
The pig has been identified as a primary translational model in wound healing studies with approximately 78% concordance with humans in wound treatments.\textsuperscript{1, 11, 25} Because pigs have fixed skin their gross healing characteristics quantify as being similar to humans including having similar elastic properties. Primary models include incisional wounds, excisional wounds, skin flaps and skin grafts. The wounds that have been studied have been both superficial and full thickness in nature. Surgical wounds heal by a combination of epithelization and dermal repair. Within hours epithelial cells at the margin of a wound begin to migrate and proliferation starts occurring within 24 hours. Differentiation follows as cells migrate from the basal epithelial layer. The dermal layer heals by the formation of clots and inflammation by leukocytes and macrophages which signal fibroblasts to synthesize collagen. Full thickness excisional wounds undergo wound contraction which can be grossly quantified as a phase of wound repair.\textsuperscript{1-8} Aspects of epidermal regeneration that have been studied in swine include migration, proliferation and differentiation. Wound closure, tensile strength and bioassays of specific components, such as collagen, have been performed in pigs and compare favorably to humans. Because of their size multiple wounds can be placed on the same animal, thus allowing the animal to serve as its own control. Most studies place the wounds bilaterally on the flanks. Miniature pigs have been used for chronic wound healing models because they more accurately simulate adult human healing rates as compared to farm pigs whose exaggerated growth rate may skew the study.

**Digestive**

The liver, pancreas and gastrointestinal tract have similarities in function to that of the human, even though there are obvious anatomic differences, especially in the gastrointestinal tract. The stomach contains a muscular outpouching (torus pyloricus), the majority of the large intestinal tract is coiled into a series of centripetal and centrifugal coils (spiral colon) and the small intestine has a unique pattern of bifurcation of the mesenteric vessels in the subserosa. In spite of these anatomic differences the physiology of digestion is very analogous to humans since it is a true omnivore. Swine have been used in studies involving nutritional supplements and total parenteral nutrition because of the digestive physiology.\textsuperscript{1, 11}

The liver has been utilized in numerous surgical studies involving transplantation and repair. Portal vein catheterization has been utilized in drug metabolism studies and the cytochrome P-450 system has been extensively studied in drug testing and toxicology. Like all animals there are both differences and similarities in the isozymes when comparing swine and humans.\textsuperscript{8, 12-14} Swine are increasingly used in drug development and toxicology, however, the differences in the P 450 system must be considered when evaluating whether the particular test substance should be studied in swine.

The pancreas has many similarities to humans as exemplified by the fact that pork insulin was the primary treatment for diabetes for much of the 20th century before other forms of insulin were developed. The pig is utilized as a model of chemically and surgically produced diabetes and as a model for the cardiometabolic syndrome.\textsuperscript{1, 8, 11, 26} Porcine islet cells are also a primary source of insulin being studied for xenotransplantation.

**Urogenital**

Pig and human kidneys are more anatomically similar to each other than other commonly used large animals. The kidneys are characterized by multilobular structure with an internal kidney anatomy which is a true multireniculate, multipapillate organ with a true calyceal system like humans.\textsuperscript{1, 27, 28} The anatomic similarities, in particular the internal renal anatomy, have made swine a primary model for the study of renal diseases and surgery. The pig is the only lab animal which can develop intrarenal reflux and associated pyelonephritis both as a spontaneous and an induced model.\textsuperscript{27} Renal hypertension can be induced in a two kidney model by reduction of renal blood flow.\textsuperscript{28}

The reproductive tract of the female is typical of that of a bicornuate species that produces litters the pig has a diffuse epitheliochorial placenta with drug transport and metabolic mechanisms similar to humans.\textsuperscript{2, 4, 7} This type of placenta does not invade the endometrium. Maternal layers retained are the endometrial epithelium, the connective tissue and the uterine endothelium. The placental membranes include the yolk sac, amnion, allantois and chorion and the latter two membranes fuse at an early stage to form a chorioallantoic type of placenta. The chorioallantois is responsible for transplacental transport of
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nutrients from the sow. There is essentially no transplacental transport of immunoglobulins to the fetus and the newborn pig acquires its passive immunity from colostrum. Human placenta is discoidal hemochorial and passage of immunoglobulins does occur. The pig has been used as a fetal surgical model to study the effects of wound healing in the fetus and the effects of drug delivery systems to the fetus. 1, 29

**Neurologic**

The use of porcine neurologic models, especially ones involving trauma, has significantly increased in recent years. Swine are used because they have a similar gross anatomy of the brain including a large gyrencephalic brain with a predominance of white matter. The porcine brain exhibits a growth spurt just before and following gestation in a similar manner to humans. The major increases in cerebral weight, total protein, cell number, DNA content and myelination occur approximately 2 weeks before gestation and 2 weeks after gestation. They are born with sensory systems almost fully functional. In comparing brain development to humans the pig from birth to 26 weeks of age compares favorably with the period of birth to 18 years in humans.30-32 Behavioral testing in swine is also being rapidly developed to evaluate the effects of treatment post trauma. It is likely that porcine neurologic models with continue to be developed.

**Ophthalmic**

Porcine eyes have been developed as models in a variety of disease conditions and have been demonstrated to provide a favorable comparison to humans.31-40 The retina is the most common structure that is reported in the literature and has provided models for study of retinitis pigmentosa in a transgenic pig, retinal detachment, and retinal deterioration due to induced glaucoma. Porcine vitreous humor has a composition more similar to humans than other common laboratory animals and has been used in studies to develop artificial vitreous humor to be used as a replacement for humans. Corneal repair following trauma has also been a porcine model used for preclinical studies.

**Musculoskeletal**

The musculoskeletal system has bones and muscles much more massive than those of the human and that system is only utilized for a few specific procedures. The closure of all of the epiphyses of the long bones of the various breeds are as follows: domestic breeds 3.5-4 years, Hanford 2.5-4 years, Yucatan 2-3 years, Yucatan micropig 1.5-2 years, Sinclair 1.5-2 years. By comparison the epiphyses of humans are generally all closed at 17-25 years of age. Bone remodeling occurs throughout life in all of these species.

A detailed study of the temperomandibular joint indicated that the pig favorably compared to humans.42 The pig has a reciprocally fitting meniscotemporal joint and a condylomeniscal joint of the condylar type. The size of the articular structures, the shape of the meniscus, and the omnivorous chewing characteristics of swine provided additional justification for the use of this model over that of rodents, rabbits, carnivores, and herbivores that were examined.

A comprehensive review of bone healing models in craniofacial surgery has recently been performed.43 It makes a detailed comparison of reported studies using multiple species and swine are frequently sited. Most of the studies in swine involved implants and grafts to regenerate healing in critical sized defects. The point is made that the size of a critical defect in swine is going to vary depending upon the location, breed and age of the animal.

Healing of cartilage defects in the stifle joint is another area where swine have been shown to compare favorably withhumans, when compared with other large animal species.44, 45 This area of cartilage metabolism and wound healing is justified as a preclinical model based upon the thickness of the cartilage and the metabolic properties of that tissue in swine.

**General Surgical Models**

Swine have become the default general surgical model worldwide, whereas most of the models prior to the 1990’s used dogs as the primary general surgical model. The trend of using swine as a preclinical translational research model is likely to continue to increase. Miniature swine as compared to farm pigs should be the definitive models for the chronic studies necessary to gain regulatory approval for these studies. The exponential growth factors of farm pigs change the characteristics of many of the studies and they should only be
used for short term studies for pilot data for studies which require long term groups such as the 3, 6, 12 month group studies.

**Selected References**


