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Overview

Incidence of Neoplasia in Pigs and Its Relevance to Clinical Organ Xenotransplantation

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As clinical pig organ xenotransplantation draws closer, more attention is being paid to diseases that affect pigs and those that provide a potential risk to human recipients of pig organs. Neoplasia arising from the pig organ graft is one such concern. Various tumors and other neoplastic diseases are well known to show increased incidence in organ allotransplant recipients receiving immunosuppressive therapy. Whether this effect will prove to be the case after xenotransplantation has not yet been established. Malignant tumors in young pigs are rare, with lymphosarcoma, nephroblastoma, and melanoma being the most common. The combination of noninvasive techniques and intraoperative examination of the pig organ likely will readily confirm that a pig organ graft is tumor-free before xenotransplantation. Posttransplantion lymphoproliferative disorder (PTLD) is a concern after allotransplantation, but the incidence after solid organ allotransplantation is low when compared with hematopoietic cell allotransplantation (for example, bone marrow transplantation), unless immunosuppressive therapy is particularly intensive. Organ-source pigs used for clinical xenotransplantation will be bred and housed under designated pathogen-free conditions and will be free of the γ-herpesvirus that is a key factor in the development of PTLD in pigs. Therefore if a recipient of a pig xenograft develops PTLD, it will almost certainly be of recipient origin. The increasing availability of organs from pigs genetically-engineered to protect them from the human immune response likely will diminish the need for intensive immunosuppressive therapy. Considering the low incidence of malignant disease in young pigs, donor-derived malignancy is likely to be rare in patients who receive pig organ grafts. However, if the graft remains viable for many years, the incidence of graft malignancy may increase.

Abbreviations: PERV, porcine endogenous retrovirus; PTLD, posttransplantation lymphoproliferative disorder;

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Given the many anatomic and physiologic similarities between humans and pigs,[20] genetically-engineered pigs are being developed as sources of organs and cells for clinical transplantation into human patients with end-stage organ failure.[23] The survival of pig kidney and heart grafts in immunosuppressed NHP now extends to many months and even years in occasional cases.[49,55,57,76,77] The function of these organs appears to be good, with relatively minor abnormalities.[58] This progress has been associated with (1) the availability of increasingly sophisticated genetically-engineered pigs;[15,21] (2) the introduction of novel immunosuppressive agents, particularly those that block the second T-cell signal (costimulation blockade);[96] (3) improved understanding of the inflammatory response to a pig xenograft; and (4) increasing experience in the management of NHP with pig organ or cell grafts. Pigs are now available with as many as 9 genetic manipulations that include (1) deletion of the 3 known pig xenoantigens against which humans have natural (preformed) xenoreactive antibodies; (2) transgenic expression of one or more human complement-regulatory and coagulation-regulatory proteins; and (3) transgenic expression of other human genes that protect the graft from human immune or inflammatory responses.

Nevertheless, exogenous immunosuppressive therapy is still required to suppress the adaptive immune response, but the optimal immunosuppressive regimen for use after xenotransplantation remains to be determined, and whether this optimal regimen will be more intense than that required after allotransplantation is uncertain. Regimens targeted to blockade of the CD40–CD154 costimulation pathway (with agents that are not yet approved by the United States FDA) have proved most successful to date,[96] with combinations of FDA-approved (conventional) immunosuppressive agents being less effective.[115] Although most genetic engineering of pigs has been directed toward protecting the graft from the innate immune response, genetic manipulations that can protect against the adaptive immune response are available, if necessary.[43,56,62,85,90]

One aspect of xenotransplantation that has not been fully investigated is the potential risk of the development of a malignant condition in the transplanted pig organ. We have therefore reviewed the available literature to assess whether this risk is clinically significant. In human organ recipients, de novo malignancy in kidney, liver, and heart allografts is relatively rare.[24,95,117] Among the most common malignancies in immunosuppressed patients after organ allotransplantation are nonmelanoma skin and lip tumors, nonHodgkin lymphoma, and colorectal, lung, breast, and prostate cancers.[12,18] The incidence of most of these

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neoplasms is at least twice that in the general population, with skin cancers being much more common.[12,18]

It is important to remember that, in immunosuppressed patients with any type of organ allograft or xenograft, any tumor that does arise is much more likely to be of recipient origin rather than donor origin, and this propensity should be borne in mind throughout the posttransplantation period of follow-up. In this regard, we are unaware of any tumors that have arisen in immunosuppressed NHP with pig solid organ grafts, though this may in part be related to the relatively short period of follow-up (days or weeks rather than months or years) in the majority of cases.

The average lifespan of most domestic pigs is 15 to 27 y,[37,60,112] but most pigs are slaughtered before the age of 6 mo as sources of food. Therefore, relatively little is known about malignancies that occur in older pigs.[72] So that their organs will be appropriate in size for transplantation into even the largest of human recipients, pigs will likely be used for clinical xenotransplantation when they are younger than 6 mo; therefore it is particularly important to review the data on malignancies that develop in young pigs. In addition, because the pig organ will continue to age after transplantation (with a probable increase in the risk of malignancy), some knowledge of the incidence of neoplasia in older pigs would be valuable. However, a large study in old pigs would be time-consuming and expensive and may not prove worthwhile.

Tumor Incidence in Pigs

Cancer in pigs is rare, with fewer than 40 cases per 1 million slaughtered pigs (Table 1), although the incidence might be higher due to underreporting.[3] Lymphosarcoma, which includes leukemia and lymphoma, is the most common malignancy in pigs, followed by nephroblastoma, melanoma, and primary and secondary liver malignancies.[1,3,7,9,26,34] Some studies suggest that the most common tumor in pigs is nephroblastoma,[2,14,45] but general agreement is that lymphosarcoma is most common.[10,25,26,28,34] During 1991 through 2003, the Animal Health Laboratory (Ontario, Canada) received specimens from 28 cases of lymphosarcoma but only 4 of nephroblastoma and 6 of melanoma.[1] Another study reported a higher incidence of nephroblastoma compared with lymphosarcoma, but the incidence of nephroblastoma was only 0.007%.[45] Another author reported an equal incidence.[14]

In the context of xenotransplantation, other relevant (although rare) malignancies include cardiac rhabdomyoma, rhabdomyosarcoma, and secondary pulmonary tumors.

Lymphosarcoma

The classification of lymphosarcoma has been modified over time. During the 1960s, these neoplasms were generally classified as multicentric or thymic[3] or as lymphoblastic, lymphocytic, histiocytic, or mixed.[72] However, the term 'multicentric' is misleading, and 'disseminated lymphoma of unknown primary' is more appropriate. Subsequently, lymphosarcomas were classified as Burkitt, immunoblastic, medium-sized, and mixed-cell types.[46] More recently, lymphosarcomas in pigs (Table 2) have been classified according to the World Health Organization scheme for human lymphomas.[53,82]

The incidence of lymphosarcoma has been stable over the past several decades and is similar throughout the world, varying between 3 and 25 cases per 1 million pigs.[1,3,46,72] In the United States, the incidence during 1957 through 1967 varied between 13 to 21 per million.[72] One author reported that most cases (58%) occurred in pigs younger than 6 mo,[3] whereas another noted that 66% occurred in pigs younger than 12 mo. One study observed 2 peaks of incidence, with 60% of cases occurring by 6 mo and 20% occurring by 21 mo of age.[89]

No specific pig breed is more susceptible to lymphosarcoma than others, and the occurrence of lymphosarcoma in pigs is sporadic.[3] Frequently (in approximately 90% of cases), when diagnosed, lymphosarcomas are already widely disseminated (so-called multicentric),[3,45,72] with liver, kidney, lymph nodes, and spleen being the organs most commonly involved.[3] Similar to the presentation in humans, gastrointestinal tract lymphomas originate in Peyer patches, and metastasize to local mesenteric lymph nodes; in later stages, metastasis to abdominal organs is seen.[46,61,63,65,79,106] Metastasis to the heart is rare.[72]

The etiology of lymphosarcoma is unknown, but one author suggested that it can be related to the porcine lymphoma C-type virus,[6] which is an oncornavirus related to the feline leukemia virus. McTaggart reported the autosomal recessive nature of lymphosarcoma in a herd of large white pigs in Scotland.[70] Since the affected animals died before sexual maturity, the recessive mode of inheritance was not confirmed.[47,70,75] Presently, it is uncertain whether lymphosarcomas are genetically-linked, chemically-induced, or caused by a virus.[1]

Hodgkin-like lymphoma is rare in pigs, but can present with massive splenomegaly. The affected animal can be anemic and icteric.[72] The dermal form of lymphosarcoma is the common variant of mast-cell leukemia, with involvement of the entire body surface. The systemic form is a less-common variant.[8,72] Granulocytic lymphoma (chloroma) can (and does) occur in pigs, with characteristic lesions in the skull, vertebrae, femur, and ribs. Characteristic green-colored lesions can be seen in the liver.[13,65]

Thymic B-cell lymphoma, intestinal large B-cell lymphoma, thymic γδ T-cell lymphoma, and γδ T-cell lymphoma are malignant lymphomas that occur only in pigs.[82] Thymomas are well-encapsulated and rarely metastasize, even when large (for example, 8 to 15 cm).[72]

Renal Tumors

The most common renal tumors in pigs are nephroblastomas (Table 3), whereas adenocarcinomas are rare, although renal adenomas and hemangiomas can occur; clear cell renal carcinomas are not found in pigs. Secondary renal tumors are more common than primary tumors, with the most common secondary tumor being lymphosarcoma.[26,97,103]

Porcine nephroblastoma commonly develops between 5 to 24 mo of age and may be clinically insidious.[45,73] It is considered to be more common in males, but some studies have reported equal sex distribution.[97] In contrast to the disease in humans, pig nephroblastoma rarely contains metaplastic tissue. Metastasis is comparatively rare in pig nephroblastomas, and although the pigs are slaughtered at a young age, even very large tumors appear to be relatively benign.[45,73] The human counterpart of porcine nephroblastoma—Wilms tumor—is often associated with systemic anomalies or is part of a syndrome; however, there is no evidence of associated anomalies or specific chromosomal abnormality in swine.[75]

Other sarcomas (for example, fibrosarcoma) can arise from the capsule of the kidney.[97] Renal adenoma formation in humans can occur as a progressive transformation of epithelium of the renal tubules and cysts of the kidneys damaged by arteriosclerosis and cystic change; human renal adenoma is considered to be a preneoplastic condition. These changes are rare in pigs.[97]

Melanoma

Genetically-modified pigs potentially are a good source of skin for use as a wound dressing in humans or as a permanent graft for patients with burns.[114] Melanoma is rare in pigs (Table 4),

Table 1. Incidence of malignancies in pigs, as reported in the literature

Author, year	Reference	Country	No. of pigs examined	No. of malignancies per 1 million pigs
Moulton 1963	78	United States	64,209,639	31
Reisinger 1963	88	United States	NR	34
Misdorp 1967	74	Netherlands	NR	40
Anderson 1968	4	United Kingdom	3,700,000	38
Migaki 1969	72	United States	NR	20
Hayashi 1988	46	Japan	1,672,136	20

NR, not reported

Table 2. Lymphosarcoma in pigs

Author, year	Reference	Classification (*n*)	Comment
Anderson 1968	3	Multicentric (57)	Half of the pigs were 3-6 mo old; the remainder were older than 6 mo
		Thymic (35)	
Migaki 1969	72	Lymphomas (200)	Metastases were common to liver and kidneys; less common to lung and gastrointestinal tract; and rare to heart
		Chronic granulomatous (35)	Presentation of the chronic granulomatous disease was similar to Hodgkin disease in humans
		Thymoma (5)	Size of thymoma was between 8 and 15 cm and had distinct a capsule without any evidence of metastasis
		Mastocytoma (5)	Mastocytoma was in the dermis, 0.5 to 2.5 cm in size, and involved the entire body
		Granulocytic disease (2)	
Stevenson 1973	101	Not classified	Located near the pancreas, with metastases in abdominal organs
Fisher 1978	34	Multicentric (1)	High percentage of tumors present without clinical signs
		Visceral (4)	
		Peripheral (2)	
		Thymic (1)	
Bastianello 1983	7	Not classified	Lymph node involvement only in 8 cases; in the remainder, metastases were present in lymph node, liver, and kidney
Marcato 1987	65	Multicentric (34)	
		Gastrointestinal (4)	Gastrointestinal lymphomas metastasized to mesenteric lymph nodes
		Thymic (4)	
		Eosinophilic myeloid (1)	
		Panmyelosis (1)	
		Chloroma (1)	Osteoperiosteal lesions of the skull, vertebrae, femur, ribs present
		Plasma cell (1)	All lymph nodes, including tonsils, were enlarged with plasma cell lymphosarcoma
		Erythremic myelosis (1)	
		Hodgkin type (1)	
Skavlen 1986	100	Hypodiploid lymphoblasts	
Kadota 1986	59	Lymphoplasmacytic (2)	
		Immunoblastic (1)	
Hayashi 1988	46	Burkitt type (16)	66% cases were in pigs younger than 1 y; remaining cases occurred at 1–4 y of age
		Immunoblastic (2)	
		Medium sized (3)	
		Mixed cell (15)	
Nakajima 1989	79	Abdominal (7)	Most were a follicular variant of lymphoma
		General (7)	

Table 2. Continued.

Author, year	Reference	Classification (*n*)	Comment
Bean 1989	8	Not classified	Disseminated visceral (intrathoracic) and peripheral lymph node involvement
Kashima 1990	61	Gastrointestinal tract lymphosarcomas	Peyer patches were replaced with tumor cells Serosal surface involvement of other abdominal organs was present; follicular variety in 2 cases
Tanimato 1994	106	Diffuse large cell type (10)	Solitary intramural nodules in the terminal ileum, 3 to 25 cm in size; histologically, all masses were in Peyer patches
		Small cell (1)	Involvement of liver, spleen, and kidney
Vo 2004	110	Not classified	T-cell lymphoma originating from large intestine
Alsop 2005	1	Not classified	All cases were in pigs <6 mo of age
Hejari 2005	48	Not classified	Enlarged hepatic lymph nodes
Yang 2007	116	T-cell lymphoma	Coalescing mass at greater curvature of stomach
Rocha 2011	92	Large B cell lymphoma	20 × 10 × 8 cm in mesenteric lymph nodes Metastasis to the liver, orbit, and adjacent brain
Brum 2012	13	Granulocytic lymphoma	5-y-old pig; green-colored masses in vertebrae, sternum, pelvis, long bones, and spleen
Ogihara 2012	82	Thymic γδ T cell (7) Intestinal large B cell (4) Precursor B lymphoblastic (3) Thymic B cell (1) Follicular (1) Diffuse centroblastic (1)	Author concluded that classification system used for human lymphoma is not sufficient for classification of swine lymphosarcoma

Numbers in parentheses indicate the number of cases of the specific type of lymphoma

Table 3. Nephroblastoma in pigs

Author, year	Reference	*n*	Comment
Feldman 1928	33	11	In 2 cases, tumors were in the sublumbar region (extranephric embryonal nephroma), possibly from a mesonephros remnant
Cotchin 1960	26	6	Bilateral tumor in 1 case
Misdorp 1967	74	12	
Sandison 1968	97	16	Equal sex distribution; largest tumor weighed 20 kg; metastases reported in only 2 cases
Migaki 1971	73	205	Age reported in 161 cases, of which 93% were <1 y old; size ranged from 1–40 cm; heaviest tumor was 34.1 kg; 1 case of hepatic metastases; 2 cases of pulmonary metastases
Fisher 1978	34	2	
Hayashi 1986	45	74	Metastases in 2 cases; nephroblastoma classified as nephroblastic, epithelial, mesenchymal, or miscellaneous
Brum 2015	14	11	

but some breeds (for example, Duroc) are particularly prone to its development.[107] Miniature swine have an increased prevalence of cutaneous melanoma.[40] In some species of miniature swine (for example, Sinclair, Hormell, Munich troll, MeLiM), melanoma is inherited and passed from one generation to the next.[38,51,64] Melanoma usually affects adult pigs, but presentation can be congenital. There is no sex predilection.[50,64]

The majority of melanomas in Sinclair miniature swine are malignant (but regress spontaneously), in contrast to only a few being malignant in Duroc swine.[27,29,52,84] The first locus related to inheritance of malignant melanoma is in the swine MHC complex, but the second locus is independent of the complex. The second locus is inherited in a heterozygous pattern and requires somatic mutation of the normal allele for tumorgenesis.[108,109] Melanocytic lesions can develop from precursor lesions.[51]

In contrast to its presentation in humans, melanoma is extremely rare in the unpigmented skin of white swine (for example, Large White), and its development is not related to UV rays. Spontaneous complete regression of primary melanomas can occur in pigs, resulting from a cellular lymphocytic response,

Table 4. Melanoma in pigs

Author, year	Reference	Breed	*n*	Comments
Pickens 1918	86	Duroc	1	Multiple lesions throughout the body
Caylor 1926	17	Duroc	3	
Case 1964	16	Crossbreed	1	Present at birth
Hjerpe 1964	50	Duroc	2	Both gilts were from same litter
Strafuss 1968	102	Hormel miniature pig	11	Melanocytic lesions (melanomas and deeply pigmented melanin spots) in 21% pigs in the herd; no predilection for any specific anatomic region
Flatt 1972	36	NR	NR	Several melanotic lesions over the internal organs
Greene 1973	39	NR	NR	Extracutaneous melanoma in the spine
Manning 1974	64	Miniature pig	3	Two cases had lesions at birth
Thirloway 1977	107	Duroc	1	Recurrence seen after primary excision, with distant metastasis
Fisher 1978	34	5 Duroc, 2 crossbreeds	7	Small cutaneous lesions to nodules, large mass present, one case had paralysis at birth due to metastasis to spine

NR, not reported

and even disseminated lesions may regress,[52,64] Vitiligo follows the regression of a melanoma,[91] but melanin can remain in the lymph nodes and visceral organs and can be mistaken for metastases.[75] Squamous cell carcinomas of skin are rare in pigs.[71]

Primary Liver Tumors

Primary liver malignancy is rare in young pigs.[4,74] One group did not identify any hepatic tumors in 1 million slaughtered pigs.[2] However, primary liver malignancies have been reported in Vietnamese pot-bellied pigs at an average age of 16 y; the average lifespan of this breed is 20 to 25 y (thus providing a good opportunity to study the pathology of liver tumors in aging pigs).[41,80] The reported tumors were primarily hepatocellular carcinomas of trabecular or solid-pattern histopathology, with a single case of hemangioendothelioma.[4,41,80]

Other Tumors

Cardiac rhabdomyoma has been seen in stillborn pigs and in pigs that died from other causes. Although cardiac rhabdomyomas may simply be an incidental finding, these tumors can be life-threatening[11] and may be associated with sudden death in piglets, probably related to disturbances in cardiac conduction.[67] Some authors have considered them to be hamartomas,[42] but others consider them to be true neoplasms because of evidence of nuclear division.[99] Cardiac rhabdomyomas in pigs can vary in size from less than a millimeter to several centimeters.[67]

Rhabdomyosarcomas originate from the heart muscle, urinary bladder, or appendicular skeleton and are occasionally seen in pigs younger than 6 mo. These tumors are associated with deletion of the long arm of the X chromosome.[111]

Pot-bellied pigs have an increased propensity for genital tract tumors, especially tumors of the uterus. Leiomyoma and leiomyosarcoma have been reported (at 11 to 14 y of age). These tumors more often infiltrate locally than metastasize distantly.[80]

Endocrine tumors are rare in pigs.[66,98] Primary pulmonary malignancies are rare, but secondary lymphosarcoma occurs infrequently in the lung.[5]

Posttransplantation Lymphoproliferative Disorder (PTLD)

PTLD is a potentially fatal complication of immunosuppressive therapy in clinical allotransplantation[104] and comprises abnormal proliferation of B cells in various presentations ranging from polymorphic expansion to malignant monoclonal lymphoma.[69,83,113] Host-type and donor-type PTLD can occur after organ and bone marrow allogeneic transplants,[54,68,118] with hematopoietic stem cell transplantation being associated with an increased incidence.

The intensity of immunosuppression, degree of MHC mismatch, and infection by Epstein–Barr virus are some of the important risk factors associated with PTLD after bone marrow allotransplantation in humans.[19,93,113] Similar factors—but with porcine lymphotropic herpesvirus 1 (a γ-herpesvirus) playing a role instead of Epstein–Barr virus—may be associated with PTLD in miniature swine undergoing a mixed hematopoietic cell chimerism protocol.[19,32] The virus responsible for the 'respiratory and reproductive syndrome' has been associated with PTLD in pigs that underwent liver allotransplantation.[105] Cytokine alterations and decreased antitumor surveillance may be factors in the development of PTLD.[19]

In clinical transplantation, PTLD either coincides with or follows an increase in the viral load of Epstein–Barr virus.[94] T-cell depletion at the time of transplantation is associated with an increased incidence of PTLD. The incidence of PTLD in cynomolgus monkeys with allografts or xenografts was reported to be 10 of 245 (that is, 4.1%) and 9 of 231 (that is, 3.9%), respectively. There was no obvious association between the immunosuppressive regimen and the development of PTLD.[68]

The induction of tolerance to pig xenografts through hematopoietic stem cell transplantation is still in the future and—in our opinion—is not likely to occur until the transplantation of pig organs is associated with good function and safety in conventionally immunosuppressed patients. However, if attempts are made to induce tolerance to a pig organ (for example, by hematopoietic stem cell xenotransplantation), then pretransplantation induction therapy may have to be intensive and include whole-body or thymus irradiation. Nevertheless, through designated pathogen-free breeding and housing, the pigs that will be used for clinical xenotransplantation should be free of all major pathogenic viruses, including the γ-herpesvirus that is the key factor in PTLD in pigs, and so, if PTLD develops, it will almost certainly be of recipient origin.

Whatever the origin, if PTLD develops, reduced immunosuppressive therapy and the administration of virally-primed T cells can decrease viral activation.[113]

Discussion

Although some breeds are susceptible to specific malignancies, young pigs of most breeds only rarely develop malignant tumors (Tables 2 through 4). Miniature swine, in which the incidence of melanoma is rather higher than in some other breeds,

have been used for many studies related to the induction of tolerance to allografts, but the risk of melanoma developing in a young miniature swine organ graft is small.

Although rare, lymphosarcoma is the most common tumor in pigs. Considering its propensity to widespread dissemination, it will be important to exclude its presence in organ-source pigs for clinical xenotransplantation. The leukemic form can be excluded through hematologic screening, but the most common presentation is lymphomatous rather than leukemic.[46,61,65,79,106] The exact origin is often unknown but is probably lymphatic tissues (for example, lymph nodes, Peyer patches). Examination of abdominal and thoracic organs is therefore important. Inspection and palpation are necessary to confirm that the lymph nodes surrounding the potential xenograft organ are free of tumor. Because the pigs that are used as sources of organs will always be young and thus the incidence of tumors will be very low, we suggest that careful visual inspection and palpation is sufficient to exclude tumors. Although noninvasive modalities (for example, ultrasonography, CT, MRI) or invasive methods (for example, fine-needle aspiration for cytology or open biopsy for histology) could be performed to exclude tumors, we suggest that when any doubt arises, a different pig should be selected.

Gastrointestinal lymphosarcoma is not the only neoplasia that metastasizes to the liver; the liver is a common site for metastases of other malignancies, for example, melanoma. Radiologic investigation (for example, CT) could be useful for screening for any occult, suspicious lesions or enlarged lymph nodes. Regarding malignant melanoma, given that these tumors are rare in nonpigmented (white) pigs,[75] the use of nonpigmented pigs and clinical examination should be sufficient to exclude tumors from the organs and skin. Echocardiography and MRI can be used to screen for small rhabdomyomas. Once again, however, whenever there is any doubt regarding whether a primary tumor or metastasis is present, a different pig should be selected.

Screening for malignant disease in pigs may be difficult, but regular euthanasia and necropsy of sentinel animals in the herd likely will alert us to the presence of any developing pathology.

Panels of viruses that need to be excluded from the organ-source pigs have been compiled.[35,44] These lists can be modified if additional viruses are identified or when regional variations in virus populations occur. The viruses included in most panels are those that (1) are endemic to the pig population in the United States; (2) cause seasonal outbreaks, and (iii) are associated with less common localized outbreaks. Less prevalent viruses, those lacking pathogenicity, and those not found in the United States have been excluded. The screening panels include viruses such as porcine lymphotropic herpesvirus and thus should reduce the risk of virus-related neoplasia and infection in organ-source pigs.

The founder pigs of the organ-source herd will be bred by Cesarean section to avoid any microbiologic contamination from sows, but subsequent generations will be born naturally. If the source pigs are bred and housed under biosecure isolation conditions, all (or most) pathogenic microorganisms can be eradicated from the herd.[35] Nevertheless, concern has been raised that porcine endogenous retroviruses (PERV), which are present within the nucleus of every pig cell, may be pathogenic in human recipients. There is little or no evidence that PERV are detrimental to pigs; for example, PERV do not appear to be associated with any known infectious or neoplastic condition. Furthermore, humans have equivalent retroviruses (that is, HERV) in every cell nucleus; these viruses similarly have not been judged to be factors in any human disease process. Nevertheless, concern has been raised that PERV may be pathogenic in humans or may recombine with HERV to form new viruses that possibly induce malignant change.

Although PERV have been demonstrated to infect human cells in vitro, this outcome has been achieved only under stringent specific laboratory conditions, and there has been no evidence of PERV infection of humans after various clinical xenotransplantation procedures (for example, transplantation of pig skin or spleen). Although genetic engineering techniques could be used to prevent PERV activation[30,31,87]or to knock out PERV,[81] it is generally considered that the risk of PERV infection is insufficient to make these procedures necessary when organ xenotransplantation enters clinical trials. However, the final decision will be made by the national regulatory authorities (for example, the FDA in the United States).[22]

In conclusion, we suggest that the risk of malignant tumors developing in young pigs that are to be used as the source of an organ for clinical xenotransplantation is small. Careful examination of each pig and its organs during the 'donor' operation should be sufficient to exclude any malignant condition. Although several noninvasive tests can confirm the absence of tumors, when there is any doubt, it probably is most prudent to select another pig.

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