The Baboon in Xenotransplant Research

Leonard L. Bailey

1 Introduction

If cross-species transplantation is ever to become a reasonable therapeutic modality for human beings, it will be because the potential for success has been demonstrated in a nonhuman primate model. The imperative has always been to select a primate research subject from a species that is plentiful, is not endangered, readily procreates in a managed environment, and mimics the human response (immunologic homology) to both organ transplantation and potential transfer of infectious disease. Several *Papio* subspecies of baboons, including *Papio hamadryas anubis* (olive baboon), meet these important criteria. These animals remain common in throughout sub-Saharan Africa and have adapted well to the managed environments of major primate centers worldwide. A list of United States-based primate centers housing breeding colonies of baboons can be found in Table 19.1. The Surgical Research Laboratory at Loma Linda University, for instance, has maintained a salutary relationship with the Southwest National Primate Research Center in San Antonio, Texas, for the procurement of juvenile baboon research subjects.

Once relatively inexpensive and portable for use in laboratory research, the commercial value of baboons and the complexities of transferring them from facility to facility have increased significantly during the past two decades. Nevertheless, the olive baboon and its closest relatives remain vital to laboratory investigation of xenotransplantation. Their most important laboratory role may be as recipients of solid organ xenografts, including heart, lung, liver, and kidney. Host immunoregulatory strategies that are efficacious with baboon recipients are, in many instances, directly applicable to the human setting. Maintenance of chronic immunoregulation and graft surveillance is much more difficult in baboons, however, whose nature makes them much less cooperative than human recipients. Baboon recipient mortality and morbidity are reflective of the experience in humans, as are measures of immune response. Baboons are susceptible to most of the same, or similar, infectious agents that threaten human subjects. Hence, they represent an important analogy to the threat of infections facing human recipients. They also represent an excellent model for the potential of infectious disease transfer in clinical trials of

L.L. Bailey *(✉)*
Loma Linda University Medical Center and Children's Hospital, Loma Linda, California 92354

J.L. VandeBerg et al. (eds.), *The Baboon in Biomedical Research*,
DOI 10.1007/978-0-387-75991-3_19,

Table 19.1 U.S. Baboon Research Resources

Center	Affiliation	Address	Web Address
Southwest National Primate Research Center	Southwest Foundation for Biomedical Research	P. O. Box 760549 San Antonio, TX 78245-0549	www.snprc.org
Tulane National Primate Research Center	Tulane University	18703 Three Rivers Road Covington, LA 70433	www.tnprc.tulane.edu
Washington National Primate Research Center	University of Washington	I-421 Health Sciences Box 357330 Seattle, WA 98195-7330	www.wanprc.org/WaNPRC
Division of Animal Resources	University of Oklahoma Health Sciences Center	940 S. L. Young Boulevard BMSB 203 Oklahoma City, OK 73190	w3.ouhsc.edu/Compmed/BaboonResearch Resource.asp

xenotransplantation. Finally, beyond their important role as laboratory recipients, baboons may have substantial potential value as organ and cellular xenodonors.

2 Scope of Experimental Use of Baboons

Baboons have been utilized historically for a number of investigative procedures in which there was direct transfer of organs or blood between animals and humans. Experimental operations involving baboons as donors have included the xenotransplantation of kidneys into human recipients (Starzl et al., 1964), transplantation of a baboon auxiliary heart into a human subject (Barnard et al., 1977), extracorporeal liver perfusion in human subjects with acute fulminating liver failure (Bosman et al., 1968; Hume et al., 1969; Fortner, et al., 1971), orthotopic heart xenotransplantation in a newborn baby (Bailey et al., 1985), orthotopic liver transplantation into human subjects (Starzl et al., 1993), and baboon bone marrow transplantation into a human subject suffering from acquired immunodeficiency syndrome (AIDS) (Exner et al., 1997). While recipient survival was limited in each of these pilot experiments (excepting the bone marrow transplant), a great many scientific and philosophical lessons were learned from each one. Importantly, no public health crisis evolved from any of these experiments.

Despite these limited, but notable clinical outcomes, baboons have not been utilized extensively as organ and cell donors in laboratory and clinical research. The

more important current role of baboons in the laboratory investigation of cross-species transplantation involves the investigation of their immune response capability, their native and acquired infectious disease profile, and their surrogate role as primate recipients of porcine xenografting. The literature is replete with this type of experimentation using baboon subjects.

For example, baboons have been used to study naturally occurring antibodies that are directed toward native porcine antigenic targets, such as Gal oligosaccharides and *N*-glycolylneuraminic acid (the Hanganutziu-Deicher antigen) (Lin et al., 1997; Dehoux et al., 2002; Holmes et al., 2002; Teranishi et al., 2002). Naturally occurring recipient antibody may be removed temporarily by: (1) using extracorporeal adsorption on a carbohydrate or immunoadsorption column (Taniguchi et al., 1996; Alwayn et al., 1999; Brenner et al., 2000), (2) pre-treating the primate host with norfloxacin to remove bowel aerobic Gram-negative bacteria (Mañez et al., 2001), or (3) neutralizing them by repeated infusions of anti-idiotypic antibody preparations (McMorrow et al., 2002). Interestingly, anti-idiotypic antibody generated against human Galα1,3Gal antibodies is highly cross-reactive with baboon sera, suggesting that the baboon immune composition is a reasonable facsimile of that observed in human hosts.

Baboons have also been used to study the xenogeneic cellular immune response to pigs. The roles of several immunocytes, including natural killer cells, activated T and B cells, macrophages, monocytes, and granulocytes, are under investigation (Dehoux et al., 2001). While hyperacute rejection relates largely to pre-existing antibody and the triggering of intravascular coagulation, delayed acute rejection is produced, in part, by a profound, and as yet, poorly characterized innate cellular immune response that is both antibody-dependent and independent. The baboon response, both ex vivo and in vivo, appears to mirror that expected of human hosts.

The study of cellular xenotransplantation, such as porcine islet cell transplantation (Maki et al., 1996; Cozzi et al., 2000; Adams et al., 2001; Bühler et al., 2002; Cantarovich et al., 2002), has been conducted using the baboon model. And, because they are readily available and because their immune response and adaptation to immunoregulation and antimicrobial therapy mimics that observed in humans, baboons have become a highly desirable model for the study of solid organ xenotransplantation. Baboons have been used as hosts for orthotopic and heterotopic heart, lung, liver, and kidney xenotransplantation. The vast majority of recent investigations involve baboon recipient survival and the characterization and manipulation of the primate immune response to organ transplants derived from commercially produced transgenic pigs. Thus far, baboon host and pig graft survivals have been measured in days or weeks. Most recent graft survival in a modified pig-to-primate model is about 60 days. These outcomes represent a technical, if not a clinically practical, victory.

Pig grafts, which are modified to express a human complement-regulatory molecule, are not hyperacutely rejected by primate hosts. However, delayed acute rejection has been a major impediment to graft and/or host survival. This so-called vascular rejection is clearly multifactorial and is the subject of much ongoing research. It is a powerful and lethal response against which chemical or genetic

blockade has not yet been successful. Use of Gal knock-out porcine donors may further extend graft survival among primate recipients. Transplantation between highly divergent species, such as pig to primate, is clearly a tall mountain to climb in immunoregulatory terms.

Perhaps less Himalayan and more Appalachian in metaphorical nature are the xenotransplants between species that are more similar, such as macaque to baboon, or baboon to human (as in the 1984 Loma Linda heart and the 1992 Pittsburgh liver clinical trials). Outcomes between rhesus monkey donors and immature baboon hosts will be summarized later in this chapter. These outcomes have been far more durable, and hence more clinically relevant, than those observed to date among baboon recipients of porcine xenografts.

There have been a number of investigations of infectious disease transfer between porcine donors and baboon recipients (Martin et al., 1998, 1999; Blusch et al., 2000, 2002). All species appear to have experienced a wide range of microbial infections. Of these, viruses and even prions (since barnyard animals have become potential donors) are of significant concern in xenotransplantation and public health circles. Most viruses and prions are thought to be species-specific in their origins. They may or may not produce disease in their natural host, but several examples (e.g., Ebola, SARS, influenza, spongiform encephalopathy, monkey pox, and possibly HIV) have produced illness and death among inadvertently exposed human beings. Some of these and other viruses are (or may be) capable, through horizontal transmission, of producing profound global public health consequences. A recent article in the lay press alludes to this concern (Boyce, 2003).

Fear of producing a new or adaptive viral illness in the human species through the "unnatural" mechanism of xenotransplantation seems to be based on several factors: (1) incomplete understanding of "known" viruses, (2) potential evolution of some, as yet "unknown" virus, (3) ability of viruses to mutate, transform, or activate in an unnatural or surrogate environment, and (4) lack of adequate antiviral therapy. There is particular concern about endogenous virus particles that seem to exist as an important piece of the genetic code of a species (e.g., PERV, or porcine endogenous retrovirus). Experimentation in baboons should help define the true importance of each fear. Baboon recipient models will undoubtedly play a role in determining each specific donor animal's potential for producing or transmitting conventional or novel viral illnesses to human patients.

3 Technical Considerations

Baboons are an extremely important and valuable asset in xenotransplantation research. For practical reasons, younger, smaller female baboons are the most valuable. While size is important for short-term and terminal experiments, it is an even more vital factor when long-term support, maintenance, and surveillance are at stake. Juvenile baboons are easier for the transplant research team to manage and are generally less hazardous to their surroundings and their caregivers than are their

adult counterparts. They require less transfusion volume during major operations, particularly those using cardiopulmonary bypass. They are easier to sedate and anesthetize. One or two full-size adult baboons, utilized as blood donors, will usually suffice for a vigorous xenotransplantation research laboratory.

Baboons, like other primates, usually require injection of a dissociative agent, such as ketamine, for regular graft surveillance. Anesthesia for operative procedures in baboons is administered much as that for human infants and children in the hospital setting. While protocols vary from laboratory to laboratory, all teams use some form of dissociation (ketamine) and sedation (Zolasepam and Tiletamine) prior to endotracheal intubation. Anesthesia is then maintained with inhalation agents, including N_2O_2 and isofluorane. Depth and control of anesthesia is monitored by using indwelling groin arterial and venous catheters and electrocardiography. An arterial blood gas is useful for making initial ventilator adjustments, but blood sampling and blood wasting must be kept to a minimum in juvenile baboons, which possess small blood volumes. Additional venous infusion catheters are inserted into the dorsal arm veins.

It is extremely difficult to keep venous and arterial sampling and infusion catheters, drainage catheters, and endotracheal tubes in place in post-operative baboons without severely restricting the animal. Invasive devices, therefore, are completely withdrawn as the animal emerges from anesthesia. Orthotopic heart transplantation, for example, is accomplished with excellent operative outcomes using this less restrictive approach. Other specific surgical research protocols may require more contained or invasive perioperative management. Most animals will not require post-operative intravenous fluids and intense monitoring to assure their operative survival. Close observation is important, however, particularly for assessment of the animal's discomfort. Pain is controlled using regular injections of a narcotic during the initial 12–24 h, and, on occasion, thereafter depending upon an individual animal's needs. Baboons are quite intuitive about the timing of post-operative oral intake of water and food, hence both may be made available to them during the early perioperative period. Baboons are usually capable of being returned to maintenance quarters within 24 h of an operation, where treats such as favorite fruits are provided.

4 Xenotransplantation Survival Patterns

The abbreviated survival of porcine xenografts in baboon hosts has been discussed earlier in this chapter. With further genetic and immunochemical modification of both donors and recipients, the survival of widely divergent porcine xenografts within the primate host environment should increase, and eventually become clinically relevant. This process will require extensive characterization of the recipient immune response, and will involve prolonged labor-intensive effort before the immunological mysteries are decoded. Simultaneously, the challenges of documenting the level of infectious disease risks associated with xenotransplantation, irrespective of the donor species, must be evaluated.

In contrast to the relatively short survival of porcine xenografts, clinically relevant survival of baboon recipients of orthotopically transplanted rhesus monkey hearts has been documented (Matsumiya et al., 1996a; Bailey and Gundry, 1997; Asano et al., 2003). Using immunoregulatory strategies readily adaptable to a clinical protocol for additional baboon-to-human infant xenotransplants, laboratory host survival has consistently exceeded a year, and in some cases has extended beyond 2 years. Growth of both the baboon hosts and their xenografts has been documented (Matsumiya et al., 1996b). Despite the complexities of a chronic immunosuppression and surveillance protocol in the baboon model, the animals have experienced a vigorous existence while entirely dependent upon their xenohearts. Death from xenograft rejection has been uncommon. Prevention and/or treatment of disseminated cytomegalovirus, however, has been problematic and cytomegalovirus infection led directly or indirectly to a number of the late deaths.

These xenotransplantation studies between different, but similar, primate species (concordant xenotransplants) provide a benchmark for survival in clinically relevant laboratory experimentation. Infectious disease transfer among long-term survivors has not yet been studied. However, microbial analysis of specimens from long-term laboratory primate survivors of concordant xenotransplantation, coupled with an array of donor-recipient specimens from the 1984 clinical trial (Baby Fae), should provide vital data on the potential for viral and other infectious disease transfer.

5 Baboons as Potential Organ Donors

Baboons are an excellent potential source of solid organs, tissue, and cells for use in xenotransplantation into humans. The immunology and, hence, the potential for durable outcomes, parallels clinical allografting. Control of the recipient immune response, utilizing a rational, clinically applicable protocol of immunoregulation, has been demonstrated. Histo-blood group O baboons, although uncommon, have been identified, and the molecular genetics of their ABO locus has been investigated (Diamond et al., 1997). Propagation of a colony of “universal” baboon donors for pediatric recipients is feasible, although industrial-strength support, such as that applied to the development of pigs as organ donors, will be required.

6 Ethics Applied to Use of Baboons in Xenotransplantation Research

The ethics of animal use for purposes of transplantation should be consistent across species and between captive and wild-caught animals. Moral responsibility assumes the target species is not endangered in the wild or is readily bred in captivity, and is treated with compassion and respect. Organ transplantation does not, and will never, represent an excuse for wholesale slaughter of any animal species. However,

preservation and enhancement of the human species is the legitimate aim of xenotransplantation. That alone justifies utilization of baboons as surrogate participants in the research process. The individual life and welfare of a human should, ethically speaking, always trump concerns for the individual life of an animal, be it nonhuman primate or otherwise.

The concern for the broader issues of health and welfare of the human species is also a vital part of the quest for xenotransplantation. That quest goes beyond individual recipients and their families and caregivers. It has the potential to involve all of mankind if, indeed, novel infections of animal origin are introduced into the global population. Investigators need to determine if the cross-species transplantation risk to public health is real or if it is simply a perception of risk. Based on anecdotal history and laboratory and clinical studies, a "real" risk has yet to be demonstrated. Copious laboratory virology, however, suggests that caution is appropriate.

The perception of risk to the public health has occasionally stimulated intense, almost evangelical debate in public forums, in news media, and in the world of science fiction literature and motion pictures. The shading of objectivity on this issue has been distressingly counterproductive to the development of xenotransplantation. Clearly, if the discussion about the risk to public health is not laced with reason and solid, clinically applicable science, then the xenotransplant enterprise will not go forward, and will not succeed. Guidelines and safeguards for this type of research should be established, and investigators should thoroughly examine the potential for infectious disease transfer from animal donor to human recipient and beyond. Progress in xenotransplantation and future clinical trials cannot be aborted on the basis of a general fear of potential risk to public health. Intensive research is needed to minimize the public health concerns associated with what may be a critical life-saving approach in the future.

It is reassuring to note that man's considerable medically controlled exposure to a variety of animals has yet to produce a significant infectious disease consequence extending beyond the patient. Such exposure has, historically, included monkey and dog lung oxygenators for open heart surgery; extracorporeal liver perfusion using baboons and pigs; human transplants using baboon corneas; and kidney, liver, and heart transplantation using baboon, chimpanzee, sheep, and pig organs. One of the chimpanzee kidney recipients circulated in the public domain for nine and a half months, and a number of other individuals with intense medical exposure to live animal organs have experienced long-term survival. No issue affecting the public health has surfaced from these real, if anecdotal, experiences.

7 Summary

Baboons fit the important criteria to be major players in the quest for safe and effective xenotransplantation. They are unendangered as a species, are readily available from captive breeding colonies, and can be produced in large numbers if required. Their infectious disease profiles and immune responses may be documented using

currently available and developing laboratory technologies. Although they may have significant potential as organ donors, baboons are presently being employed primarily in the laboratory investigation of pig to primate xenotransplantation. They have contributed significantly to the scientific understanding and the advancement of both concordant and discordant xenotransplantation.

References

Adams, D. H., Kadner, A., Chen, R. H., and Farivar, R. S. (2001). Human membrane cofactor protein (MCP, CD 46) protects transgenic pig hearts from hyperacute rejection in primates. *Xenotransplantation* 8:36–40.

Alwayn, I. P., Basker, M., Buhler, L., and Cooper, D. K. (1999). The problem of anti-pig antibodies in pig-to-primate xenografting: Current and novel methods of depletion and/or suppression of production of anti-pig antibodies. *Xenotransplantation* 6:157–168.

Asano, M., Gundry, S. R., Izutani, H., Cannarella, S. N., Fagoaga, O., Bailey, L. L. (2003). Baboons undergoing orthotopic concordant cardiac xenotransplantation surviving more than 300 days: Effect of immunosuppressive regimen. *J. Thorac. Cardiovasc. Surg.* 125:60–70.

Bailey, L. L., and Gundry, S. R. (1997). Survival following orthotopic cardiac xenotransplantaton between juvenile baboon recipients and concordant and discordant donor species: Foundation for clinical trials. *World J. Surg.* 21:943–950.

Bailey, L. L., Nehlsen-Cannarella, S. L., Concepcion, W., Jolley, W. B. (1985). Baboon-to-human cardiac xenotransplantation in a neonate. *JAMA* 254:3321–3329.

Barnard, C. N., Wolpowitz, A., and Losman, J. G. (1977). Heterotopic cardiac transplantation with a xenograft for assistance of the left heart in cardiogenic shock after cardiopulmonary bypass. *S. Afr. Med. J.* 52:1035–1038.

Blusch, J. H., Patience, C., Takeuchi, Y., Templin, C., Roos, C., Von Der Helm, K., Steinhoff, G., and Martin, U. (2000). Infection of nonhuman primate cells by pig endogenous retrovirus. *J. Virol.* 74:7687–7690.

Blusch, J. H., Patience, C., and Martin, U. (2002). Pig endogenous retroviruses and xenotransplantation. *Xenotransplantation* 9:242–251.

Bosman, S. C., Terblanche, J., Saunders, S. J., Harrison, G. G., and Barnard, C. N. (1968). Cross-circulation between man and baboon. *Lancet* 2:583–585.

Boyce N. (2003). Down on the organ farm. New hope that animals could one day shorten the wait for a transplant. *U.S. News World Rep.* 134(21):47–48.

Brenner, P., Reichenspurner, H., Schmoeckel, M., Wimmer, C., Rucker, A., Eder, V., Meiser, B., Hinz, M., Felbinger, T., Muller-Hocker, J., Hammer, C., and Reichart, B. (2000). IG-therasorb immunoapheresis in orthotopic xenotransplantation of baboons with landrace pig hearts. *Transplantation* 69:208–214.

Bühler, L., Deng, S., O'Neil, J., Kitamura, H., Koulmanda, M., Baldi, A., Rahier, J., Alwayn, I.P.J., Appel, J.Z., Awwad, M., Sachs, D.H., Weir, G., Squifflet, J.P., Cooper, D.K.C., and Morel, P.H. (2002). Adult porcine islet transplantation in baboons treated with conventional immunosuppression or a non-myeloablative regimen and CD154 blockade. *Xenotransplantation* 9:3–13.

Cantarovich, D., Blancho, G., Potiron, N., Jugeau, N., Fiche, M., Chagneau, C., Letessier, E., Boeffard, F., Loth, P., Karam, G., Soulillou, J.P., and Le Mauff, B. (2002). Rapid failure of pig islet transplantation in non human primates. *Xenotransplantation* 9:25–35.

Cozzi, E., Bhatti, F., Schmoeckel, M., Chavez, G., Smith, K.G., Zaidi, A., Bradley, J. R., Thiru, S., Goddard, M., Vial, C., Ostlie, D., Wallwork, J., White, D. J., and Friend, P. J. (2000). Long-term survival of nonhuman primates receiving life-supporting transgenic porcine kidney xenografts. *Transplantation* 70:15–21.

Dehoux, J. P., de la Parra, B., Latinne, D., Bazin, H., and Gianello, P. (2001). Effect in vitro and *in vivo* of a rat anti-CD2 monoclonal antibody (LO-CD2b) on pig-to-baboon xenogeneic cellular (T and natural killer cells) immune response. *Xenotransplantation* 8: 193–201.

Dehoux, J. P., de la Parra, B., Latinne, D., Bazin, H., and Gianello, P. (2002). Characterization of baboon anti-porcine IgG antibodies during acute vascular rejection of porcine kidney xenograft. *Xenotransplantation* 9:338–349.

Diamond, D. C., Fagoaga, O. R., Nehlsen-Cannarella, S. L., Bailey L. L., and Szalay, A. A. (1997). Sequence comparison of baboon ABO histo-blood group alleles: Lesions found in O alleles differ between human and baboon. *Blood Cells Mol. Dis.* 23:242–251.

Exner, B. G., Neipp, M., and Ildstad, S. T. (1997). Baboon bone marrow transplantation in humans: Application of cross-species disease resistance. *World J. Surg.* 21:962–967.

Fortner, J. G., Beattie, E. J., Jr., Shiu, M. H., Howland, W. S., Sherlock, P., Moor-Jankowski, J., and Wiener, A. S. (1971). The treatment of hepatic coma in man by cross-circulation with baboon. In: Goldsmith, E. I., and Moor-Jandowski, J. (eds.), *Medical Primatology 1970*. Karger, Basel, pp. 62–68.

Holmes, B. J., Richards, A. C., Awwad, M., Copeman, L. S., Mclaughlin, M. L., Cozzi, E., Schuurman, H.-J., and Davies, H. F. S. (2002). Anti-pig antibody levels in naïve baboons and cynomolgus monkeys. *Xenotransplantation* 9:135–147.

Hume, D. M., Gayle, W. E., Jr., and Williams, G. M. (1969). Cross circulation of patients in hepatic coma with baboon partners having human blood. *Surg. Gynecol. Obstet.* 128:495–517.

Lin, S. S., Kooyman, D. L., Daniels, L. J., Daggett, C. W., Parker, W., Lawson, J. H., Hoopes, C. W., Gullotto, C., Li, L., Birch, P., Davis, R. D., Diamond, L. E., Logan, J. S., and Platt, J. L. (1997). The role of natural anti-Gal alpha 1-3Gal antibodies in hyperacute rejection of pig-to-baboon cardiac xenotransplants. *Transplant. Immunol.* 5:212–218.

Maki, T., O'Neil, J. J., Porter, J., Mullon, C. J., Solomon, B. A., and Monaco, A. P. (1996). Porcine islets for xenotransplantation. *Transplantation* 62:136–138.

Mañez, R., Blanco, F. J., Díaz, I., Centeno, A., Lopez-Pelaez, E., Hermida, M., Davies, H. F. S., and Katopodis, A. (2001). Removal of bowel aerobic gram-negative bacteria is more effective than immunosuppression with cyclophosphamide and steroids to decrease natural α-Galactosyl IgG antibodies. *Xenotransplantation* 8:15–23.

Martin, U., Steinhoff, G., Kiessig, V., Chikobava, M., Anssar, M., Morschheuser, T., Lapin, B., and Haverich, A. (1998). Porcine endogenous retrovirus (PERV) was not transmitted from transplanted porcine endothelial cells to baboons in vivo. *Transpl. Int.* 11:247–251.

Martin, U., Steinhoff, G., Kiessig, V., Chikobava, M., Anssar, M., Morschheuser, T., Lapin, B., and Haverich, A. (1999). Porcine endogenous retrovirus is transmitted neither *in vivo* nor *in vitro* from porcine endothelial cells to baboons. *Transpl. Proc.* 31:913–914.

Matsumiya, G., Gundry, S. R., Fukushima, N., Kawauchi, M., Zuppan, C. W., and Bailey, L. L. (1996a). Pediatric cardiac xenograft growth in a rhesus monkey-to-baboon transplantation model. *Xenotransplantation* 3:76–80.

Matsumiya, G., Gundry, S. R., Nehlsen-Cannarella, S., Fagoaga, O., Morimoto, T., Arai, S., Folz, J., and Bailey, L. L. (1996b). Successful long-term concordant xenografts in primates: Alteration of the immune response with methotrexate. *Transplant. Proc.* 28: 751–753.

McMorrow, I. M., Buhler, L., Treter, S., Neethling, F. A., Alwayn, I. P. J., Comrack, C. A., Kitamura, H., Awwad, M., DerSimonian, H., Cooper, D.K.C., Sachs, D. H., and LeGuern, C. (2002). Modulation of the *in vivo* primate anti-Gal response through administration of anti-idiotypic antibodies. *Xenotransplantation* 9:106–114.

Starzl, T. E., Marchioro, T. L., Peters, G. N., Kirkpatrick, C. H., Wilson, W. E. C., Porter, K. A., Rifkind, D., Ogden, D. A., Hitchcock, C. R., and Waddell, W.R. (1964). Renal heterotransplantation from baboon to man: Experience with 6 cases. *Transplantation* 2:752–776.

Starzl, T. E., Fung, J., Tzakis, A., Todo, S., Demetris, A. J., Marino, I. R., Doyle, H., Zeevi, A., Warty, V., and Michaels, M. (1993). Baboon-to-human liver transplantation. *Lancet* 341:65–71.

Taniguchi, S., Neethling, F. A., Korchagina, E. Y., Bovin, N., Ye, Y., Kobayashi, T., Niekrasz, M., Li, S., Koren, E., Oriol, R., and Cooper, D. K. (1996). *In vivo* immunoadsorption of antipig antibodies in baboons using a specific Gal(alpha)1-3Gal column. *Transplantation* 62: 1379–1384.

Teranishi, K., Manez, R., Awwad, M., and Cooper, D. K. C. (2002). Anti-Galα1-3Gal IgM and IgG antibody levels in sera of humans and old world non-human primates. *Xenotransplantation* 9:148–154.