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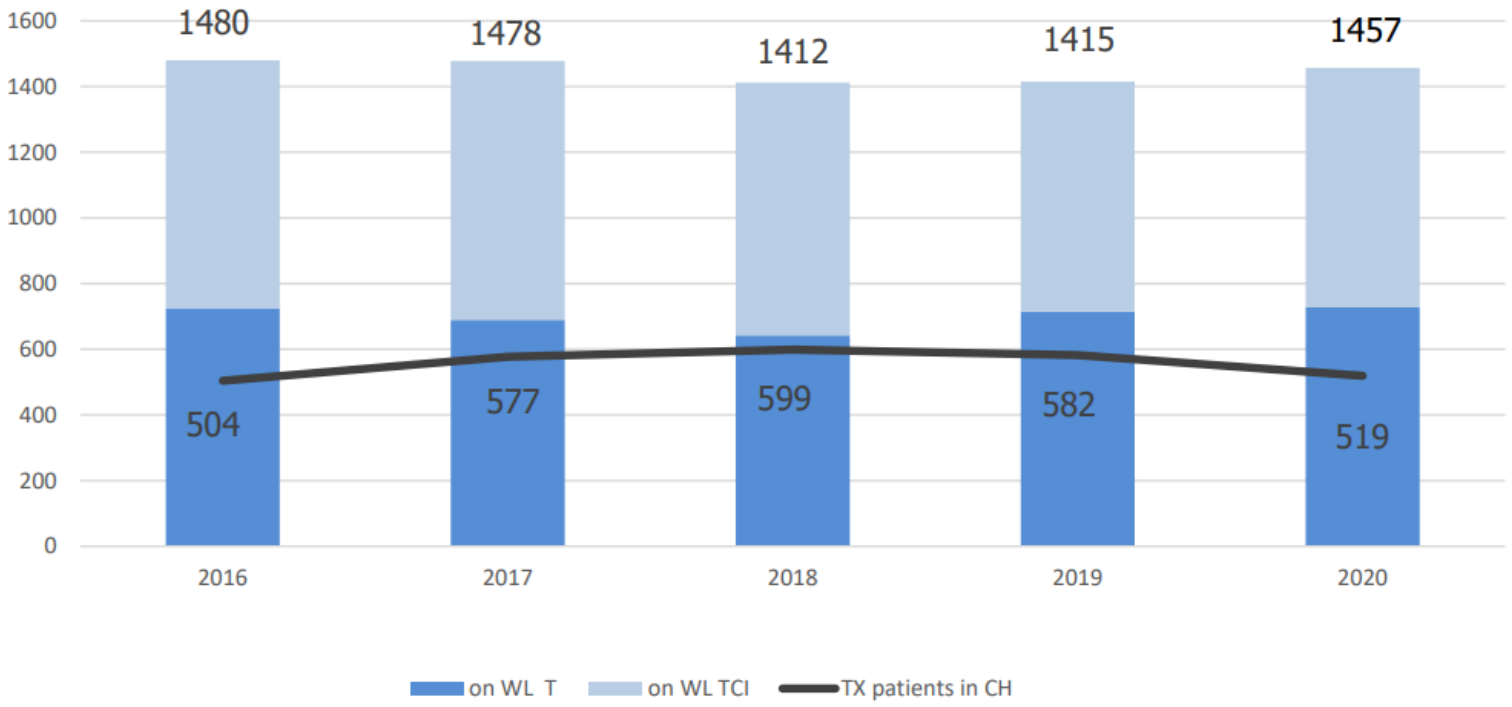
Xenotransplantation, a possible solution for the shortage of human organ donors ?

Leo Bühler

Need for Xenotransplantation ?

WAITING LIST AND TRANSPLANTATIONS 2016-2020



Alternatives to Allotransplantation ?

- **Mechanical Assist Devices / Artificial Organs**
  - Dialysis
  - Left ventricular assist-device (LVAD)
    Biventricular assist-device (BVAD)
  - Total artificial heart (TAH)?
  - Artificial liver?
  - Artificial lung?
- Tissue engineering ?
- Stem cells ?
- **Xenotransplantation**

Advantages of Xenotransplantation

- **Unlimited source of organs**
- **Elective surgery**
- **Earlier timing of transplantation**
- **Increased indications for transplantation**

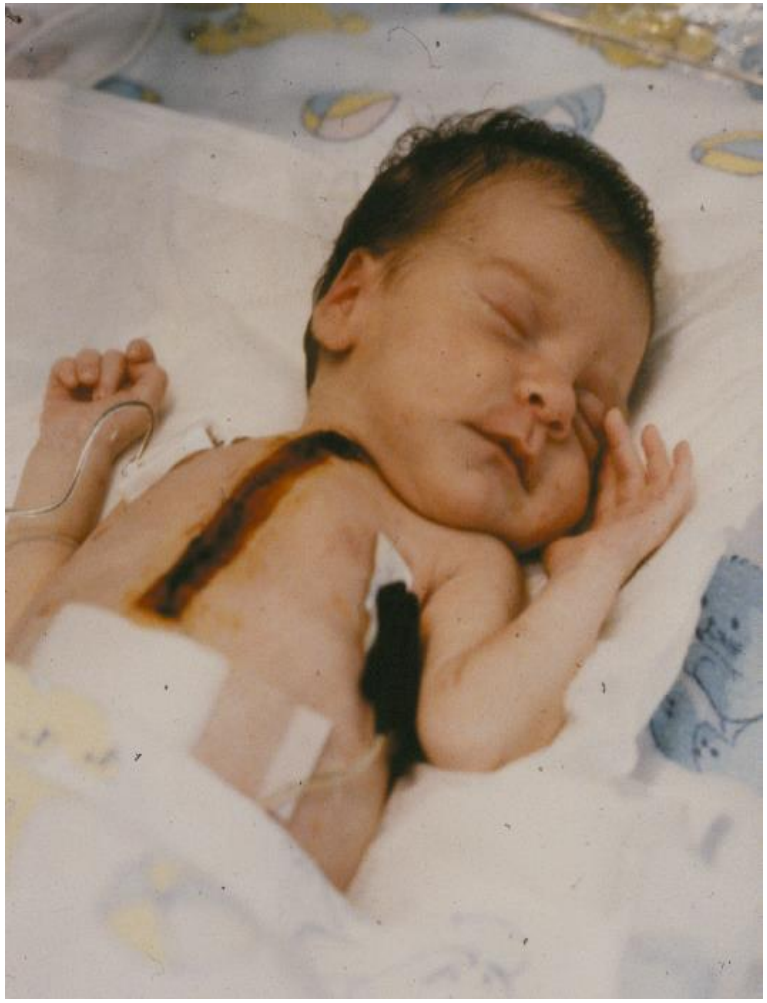
First attempts to perform organ (xeno)transplants


Alexis Carrel, M.D.

“The future of organ transplantation depends on the feasibility to perform heterotransplantation”

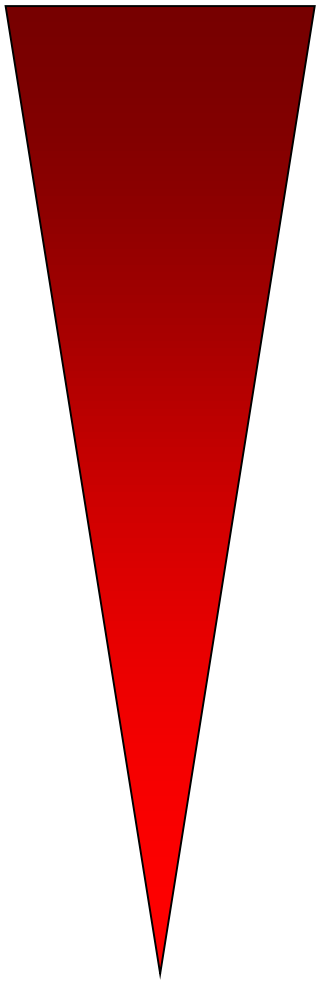
Alexis Carrel 1907

Clinical Experience in Xenotransplantation



- 1984 »Baby Fae«
- Diagnosis: Hypoplastic left ventricle
- Survival of 20 days with baboon heart
- Histology: acute humoral rejection

Xenograft rejection: Pathogenesis



- Antibody
- Complement
- Monocytes, macrophages, NK
- T cells
- Coagulation

New developments ?

- Manipulation of recipient
- Manipulation of donor

Manipulation of Donor

Transgenic animals, expressing human complement regulatory proteins:

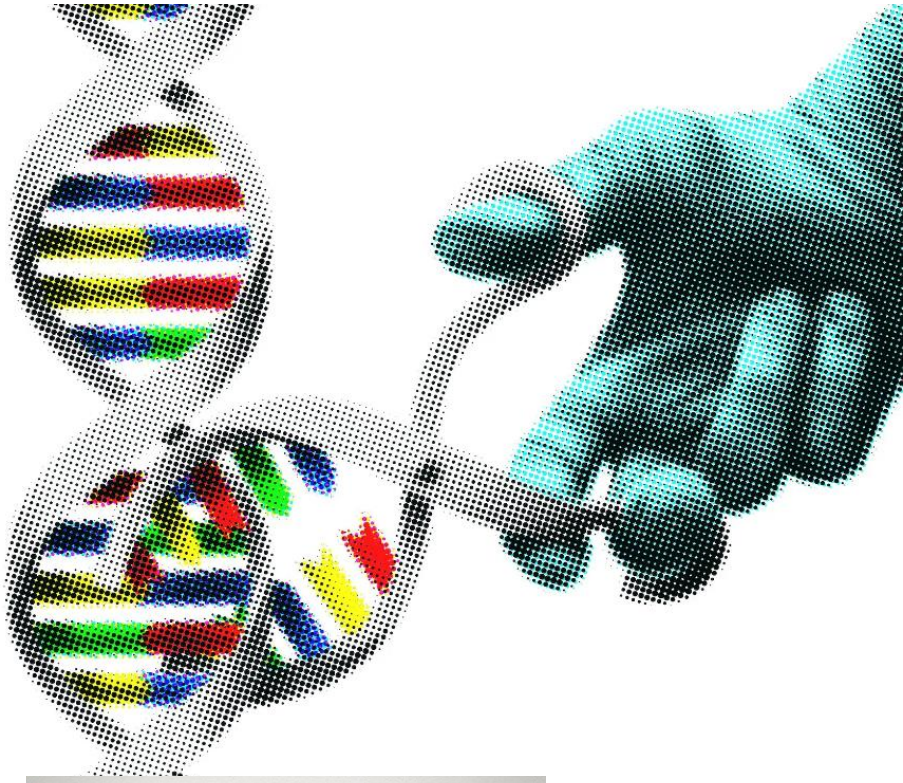
- **CD55 human decay accelerating factor (hDAF)**
- **CD46 membrane cofactor protein (MCP)**
- **CD59 membrane inhibitor of reactive lysis**

GT-KO Miniature Swine, born 2002

The New York Times

CRISPR, 10 Years On: Learning to Rewrite the Code of Life

The gene-editing technology has led to innovations in medicine, evolution and agriculture — and raised profound ethical questions about altering human DNA.



New genetically modified pigs

GTKO/CD46/CD55/CIITA-knockdown pigs
GTKO/CD55/CD59/CD39 pigs
GTKO/CD46/TMICAM
GTKO/CD46 expressing TFPI/CD39/CTLA4-Ig only in the islets
GTKO/CD46/TM
GTKO/CD47
…

nature COMMUNICATIONS

ARTICLE

Received 20 Jan 2016 | Accepted 23 Feb 2016 | Published 5 Apr 2016

DOI: 10.1038/ncomms11138 OPEN

Chimeric 2C10R4 anti-CD40 antibody therapy is critical for long-term survival of *GTKO.hCD46.hTBM* pig-to-primate cardiac xenograft

Muhammad M. Mohiuddin[1], Avneesh K. Singh[1], Philip C. Corcoran[1], Marvin L. Thomas III[2], Tannia Clark[3], Billeta G. Lewis[2], Robert F. Hoyt[4], Michael Eckhaus[2], Richard N. Pierson III[5], Aaron J. Belli[6], Eckhard Wolf[7], Nikolai Klymiuk[7], Carol Phelps[8], Keith A. Reimann[6], David Ayares[8] & Keith A. Horvath[1]

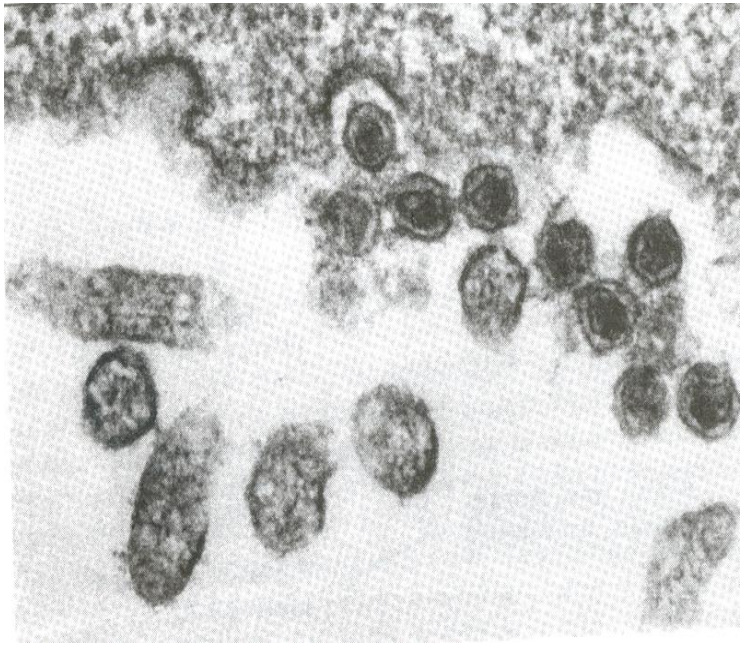
Donor pig: Alpha Gal Knockout, transgenic for human CD46 and hTBM

Recipient: Baboons

Immunosuppression: Thymoglobulin, Rituximab, Mycophenolate Mofetil , anti-CD 40 mAb

Results: Median Survival Time = 298 days, **longest survival 945 days**

Porcine endogenous Retrovirus (PERV)



PERV are present in the porcine genome

In vitro: infection of human cells possible (Patience et al. Nat Medicine, 1997)

In vivo: No infection detected in patients recipient of a porcine xenograft (Paradis et al. Science, 1999)

Science

REPORT

Cite as: D. Niu *et al.*, *Scienc*
10.1126/science.aan4187 (2017)

Inactivation of porcine endogenous retrovirus in pigs using CRISPR-Cas9

Dong Niu,[1,2*] Hong-Jiang Wei,[3,4*] Lin Lin,[5*] Haydy George,[1*] Tao Wang,[1*] I-Hsiu Lee,[1*] Hong-Ye Zhao,[3] Yong Wang,[6] Yinan Kan,[1] Ellen Shrock,[7] Emal Lesha,[1] Gang Wang,[1] Yonglun Luo,[5] Yubo Qing,[3,4] Deling Jiao,[3,4] Heng Zhao,[3,4] Xiaoyang Zhou,[6] Shouqi Wang,[8] Hong Wei,[6] Marc Güell,[1†] George M. Church,[1,7,9†] Luhan Yang[1†‡]

[1]eGenesis, Inc., Cambridge, MA 02139, USA. [2]College of Animal Sciences, Zhejiang University, Hangzhou 310058, China. [3]State Key Laboratory for Conservation and Utilization of Bio-Resources in Yunnan, Yunnan Agricultural University, Kunming 650201, China. [4]College of Animal Science and Technology, Yunnan Agricultural University, Kunming, 650201, China. [5]Department of Biomedicine, Aarhus University, 8000 Aarhus C, Denmark. [6]Department of Laboratory Animal Science, College of Basic Medical Sciences, Third Military Medical University, Chongqing, 400038, P. R. China. [7]Department of Genetics, Harvard Medical School, Boston, MA 02115, USA. [8]Research Institute of Shenzhen Jinxinnong Technology CO., LTD., Shenzhen 518106, China. [9]Wyss Institute for Biologically Inspired Engineering, Harvard University, Cambridge, MA 02138, USA.

*These authors contributed equally to this work.

†These authors contributed equally to this work.

‡Corresponding author. Email: luhan.yang@egenesisbio.com

Xenotransplantation is a promising strategy to alleviate the shortage
transplantation. In addition to the concern on pig-to-human immunol
cross-species transmission of porcine endogenous retroviruses (PER
application of this approach. Earlier, we demonstrated the feasibility
immortalized pig cell line. Here, we confirmed that PERVs infect hum
transfer of PERVs among human cells. Using CRISPR-Cas9, we inacti
primary cell line and generated PERV-inactivated pigs via somatic ce
highlighted the value of PERV inactivation to prevent cross-species v
the successful production of PERV-inactivated animals to address th
xenotransplantation.

World Health Organization

Human Organ and Tissue Transplantation

From the Eighth Plenary Meeting of the Fifty-Seventh World Health Assembly in Geneva

The Fifty-Seventh World Health Assembly,

Recalling resolutions WHA40.13, WHA42.5 and WHA44.25 on organ procurement and transplantation;
Having considered the report on human organ and tissue transplantation;
Noting the global increase in allogeneic transplantation of cells, tissues and organs;
Concerned by the growing insufficiency of available human material for transplantation to meet patient needs;
Aware of ethical and safety risks arising in the transplantation of allogeneic cells, tissues and organs, and the need for special attention to the risks of organ trafficking;
Recognizing that living xenogeneic cells, tissues or organs, and human bodily fluids, cells, tissues or organs that have had *ex vivo* contact with these living xenogeneic materials, have the potential to be used in human beings when suitable human material is not available;
Mindful of the risk associated with xenogeneic transplantation of the transmission of known or as yet unrecognized xenogeneic infectious agents from animals to human beings and from recipients of xenogeneic transplants to their contacts and the public at large;
Recognizing that transplantation encompasses not only medical but also legal and ethical aspects, and involves economic and psychological issues,

Allogeneic Transplantation

1. URGES Member States:
   (1) to implement effective national oversight of procurement, processing and transplantation of human cells, tissues and organs, including ensuring accountability for human material for transplantation and its traceability;
   (2) to cooperate in the formulation of recommendations and guidelines to harmonize global practices in the procurement, processing and transplantation of human cells, tissues and organs, including development of minimum criteria for suitability of donors of tissues and cells;
   (3) to consider setting up ethics commissions to ensure the ethics of cell, tissue and organ transplantation;
   (4) to extend the use of living kidney donations when possible, in addition to donations from deceased donors;
   (5) to take measures to protect the poorest and vulnerable groups from "transplant tourism" and the sale of tissues and organs, including attention to the wider problem of international trafficking in human tissues and organs;
2. REQUESTS the Director-General:
   (1) to continue examining and collecting global data on the practices, safety, quality, efficacy and epidemiology of allogeneic transplantation and on ethical issues, including living donation, in order to update the Guiding Principles on Human Organ Transplantation (*1*);
   (2) to promote international cooperation so as to increase the access of citizens to these therapeutic procedures;
   (3) to provide, in response to requests from Member States, technical support for developing suitable transplantation of cells, tissues or organs, in particular by facilitating international cooperation;
   (4) to provide support for Member States in their endeavours to prevent organ trafficking, including drawing up guidelines to protect the poorest and most vulnerable groups from being victims of organ trafficking;

Xenogeneic Transplantation

1. URGES Member States:
   (1) to allow xenogeneic transplantation only when effective national regulatory control and surveillance mechanisms overseen by national health authorities are in place;
   (2) to cooperate in the formulation of recommendations and guidelines to harmonize global practices, including protective measures in accordance with internationally accepted scientific standards to prevent the risk of potential secondary transmission of any xenogeneic infectious agent that could have infected recipients of xenogeneic transplants or contacts of recipients, especially across national borders;
   (3) to support international collaboration and coordination for the prevention and surveillance of infections resulting from xenogeneic transplantation;
2. REQUESTS the Director-General:
   (1) to facilitate communication and international collaboration among health authorities in Member States on issues relating to xenogeneic transplantation;
   (2) to collect data globally for the evaluation of practices in xenogeneic transplantation;
   (3) to inform proactively Member States of infectious events of xenogeneic origin arising from xenogeneic transplantation;
   (4) to provide, in response to requests from Member States, technical support in strengthening capacity and expertise in the field of xenogeneic transplantation, including policy-making and oversight by national regulatory authorities;
   (5) to report at an appropriate time to the Health Assembly, through the Executive Board, on implementation of this resolution.

From the Eighth Plenary Meeting of the World Health Assembly, 22 May 2004, A57/VR/8. WHA57.18, agenda item 12.14.
Address correspondence to: Luc Noel, M.D., World Health Organization. E-mail: noell@who.int.

ISSN 0041-1337/04/7804-493
DOI: 10.1097/01.TP.0000137052.23326.E6

REFERENCE

1. World Health Assembly. Document WHA44/1991/REC/1, Annex 6.

Xenogeneic Transplantation

1. URGES Member States:
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IXA and HUG Hôpitaux Universitaires de Genève in collaboration with World Health Organization

Buhler L. et al. Transplantation 2010, 2021

View data

Specific search

No	Tissue/Animal/Country	Consult
1	- Kidney cells | Hamster | Switzerland	
2	- Adult cells | Sheep | Germany	
3	- Chromaffin cells | Calf | Switzerland	
4	- Fetal cells | unknown | Switzerland	
5	- Fetal ventral mesencephalic cell | Pig | USA	
6	- stem cells | rabbit, pig, | Nigeria	
7	Embryonic stem cells - | blue shark | Mexico	
8	Embryonic stem cells - - fetal cells, adult cells | rabbits, cattle, sheep | Mexico	
9	Embryonic stem cells - - fetal cells, adult cells | cattle, sheep,rabbits | Germany	
10	Fetal islet like cell clusters - | Pig | Sweden	
11	Hepatocytes - | Pig | France	
12	Islets of Langerhans - | Pig | Russia	
13	Islets of Langerhans - | Rabbit | Russia	
14	Islets of Langerhans - | Pig | New zealand	
15	Islets of Langerhans - | Pig | China	
16	Islets of Langerhans - - Sertoli cells | Pig | Mexico	

Specific search

Loi fédérale sur la transplantation d'organes, de tissus et de cellules (Loi sur la transplantation)

du 8 octobre 2004 (Etat le 1er juillet 2007)

L'Assemblée fédérale de la Confédération suisse,

vu l'art. 119*a*, al. 1 et 2, de la Constitution[1],
vu le message du Conseil fédéral du 12 septembre 2001[2],

arrête:

Chapitre 3 Organes, tissus et cellules d'origine animale

Art. 43 Régime de l'autorisation

[1] Quiconque entend transplanter sur l'être humain des organes, des tissus ou des cellules d'origine animale ou des transplants standardisés issus de ceux-ci doit préalablement obtenir une autorisation de l'office.

ORIGINAL ARTICLE FREE PREVIEW

Results of Two Cases of Pig-to-Human Kidney Xenotransplantation

Robert A. Montgomery, M.D., D.Phil., Jeffrey M. Stern, M.D., Bonnie E. Lonze, M.D., Ph.D., Vasishta S. Tatapudi, M.D., Massimo Mangiola, Ph.D., Ming Wu, M.D., Elaina Weldon, M.S.N., A.C.N.P.-B.C., Nikki Lawson, R.N., Cecilia Deterville, M.S., Rebecca A. Dieter, Pharm.D., B.C.P.S., Brigitte Sullivan, M.B.A., Gabriella Boulton, B.A., et al.

May 19, 2022
N Engl J Med 2022; 386:1889-1898
DOI: 10.1056/NEJMoa2120238

Abstract

BACKGROUND Xenografts from genetically modified pigs have become one of the most promising solutions to the dearth of human organs available for transplantation. The challenge in this model has been hyperacute rejection. To avoid this, pigs have been bred with a knockout of the alpha-1,3-galactosyltransferase gene and with subcapsular autologous thymic tissue.

Related Articles

PERSPECTIVE MAY 19, 2022

Performed in 2021 at 2 centers:

- Follow-up of maximum 3 days
- Testing for technical logistics
- Public perception

Clinical pig-to-human heart xenotransplant Baltimore January 7th 2022

BRIEF REPORT

Genetically Modified Porcine-to-Human Cardiac Xenotransplantation

Bartley P. Griffith, M.D., Corbin E. Goerlich, M.D., Ph.D., Avneesh K. Singh, Ph.D., Martine Rothblatt, Ph.D., Christine L. Lau, M.D., Aakash Shah, M.D., Marc Lorber, M.D., Alison Grazioli, M.D., Kapil K. Saharia, M.D., Susie N. Hong, M.D., Susan M. Joseph, M.D., David Ayares, Ph.D., and Muhammad M. Mohiuddin, M.D.

SUMMARY

A 57-year-old man with nonischemic cardiomyopathy who was dependent on venoarterial extracorporeal membrane oxygenation (ECMO) and was not a candidate for standard therapeutics, including a traditional allograft, received a heart from a genetically modified pig source animal that had 10 individual gene edits. Immunosuppression was based on CD40 blockade. The patient was weaned from ECMO, and the xenograft functioned normally without apparent rejection. Sudden diastolic thickening and failure of the xenograft occurred on day 49 after transplantation, and life support was withdrawn on day 60. On autopsy, the xenograft was found to be edematous, having nearly doubled in weight. Histologic examination revealed scattered myocyte necrosis, interstitial edema, and red-cell extravasation, without evidence of microvascular thrombosis — findings that were not consistent with typical rejection. Studies are under way to identify the mechanisms responsible for these changes. (Funded by the University of Maryland Medical Center and School of Medicine.)

A 57-YEAR-OLD MAN WITH CHRONIC MILD THROMBOCYTOPENIA, HYPERtension, nonischemic cardiomyopathy, and previous mitral valve repair was hospitalized for severe heart failure with a left ventricular ejection fraction (LVEF) of 10%. His care was escalated to include multiple intravenous inotropic agents, and the placement of an intraaortic balloon pump was added on hospital day 11. Despite these measures, he had multiple ventricular arrythmias with arrests leading to resuscitation and began to receive peripheral venoarterial extracorporeal membrane oxygenation (ECMO) on hospital day 23.

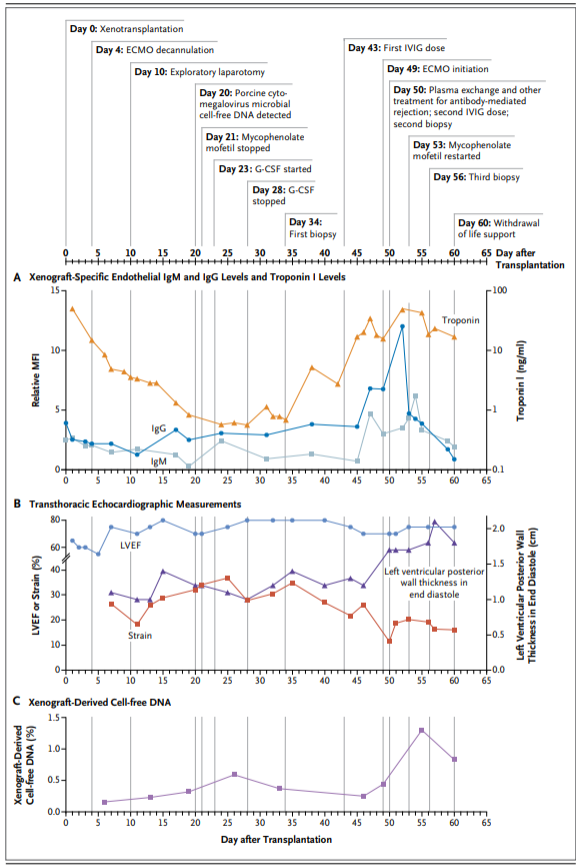
The patient was deemed to have poor adherence to treatment, which is an exclusion criterion for allotransplantation and mechanical circulatory support. At the time that his condition was assessed by our hospital selection committee for advanced circulatory support, he had a 3-week history of nonambulatory status. His case was reviewed by two regional and two prominent national heart-transplantation programs, and the request for a transplant was denied by all four programs. Our selection committee agreed to consider experimental xenotransplantation. To offset the patient's history of poor adherence to treatment, enhanced postprocedure oversight was planned by the transplantation team. Although the patient favored a heart transplant from a human donor, he was informed of his options and agreed to undergo xenotransplantation.

Despite his biventricular heart failure, the patient had preserved renal function

From the Department of Surgery (B.P.G., C.E.G., A.K.S., C.L.L., A.S., M.M.M.), the Program in Trauma, R. Adams Cowley Shock Trauma Center, Department of Medicine (A.G.), the Institute of Human Virology, Division of Infectious Diseases (K.K.S.), and the Department of Medicine, Division of Cardiology (S.N.H., S.M.J.), University of Maryland School of Medicine, Baltimore, and United Therapeutics, Silver Spring (M.R., M.L.) — both in Maryland; and Revivicor, Blacksburg, VA (D.A.). Dr. Griffith can be contacted at bgriffith@som.umaryland.edu or at the Department of Surgery, University of Maryland School of Medicine, 110 S. Paca St., 7th Floor, Baltimore, MD 21201. Dr. Mohiuddin can be contacted at mmohiuddin@som.umaryland.edu or at the Department of Surgery, University of Maryland School of Medicine, 10 S. Pine St., MSTF 434B, Baltimore, MD 21201.

This article was published on June 22, 2022, at NEJM.org.

DOI: 10.1056/NEJMoa2201422


Day 0: Xenotransplantation
Day 4: ECMO decannulation
Day 10: Exploratory laparotomy
Day 20: Porcine cytomegalovirus microbial cell-free DNA detected
Day 21: Mycophenolate mofetil stopped
Day 23: G-CSF started
Day 28: G-CSF stopped
Day 34: First biopsy
Day 43: First IVIG dose
Day 49: ECMO initiation
Day 50: Plasma exchange and other treatment for antibody-mediated rejection; second IVIG dose; second biopsy
Day 53: Mycophenolate mofetil restarted
Day 56: Third biopsy
Day 60: Withdrawal of life support
Day after Transplantation
A Xenograft-Specific Endothelial IgM and IgG Levels and Troponin I Levels
Relative MFI
Troponin I (ng/ml)
Troponin
IgG
IgM
B Transthoracic Echocardiographic Measurements
LVEF or Strain (%)
Left Ventricular Posterior Wall Thickness in End Diastole (cm)
LVEF
Strain
Left ventricular posterior wall thickness in end diastole
C Xenograft-Derived Cell-free DNA
Xenograft-Derived Cell-free DNA (%)
Day after Transplantation

JOURNAL OF VIROLOGY, May 2002, p. 4734–4740 Vol. 76, No. 10
0022-538X/02/$04.00+0 DOI: 10.1128/JVI.76.10.4734–4740.2002

Activation of Cytomegalovirus in Pig-to-Primate Organ Xenotransplantation

Nicolas J. Mueller,[1] Rolf N. Barth,[2] Shin Yamamoto,[2] Hiroshi Kitamura,[2] Clive Patience,[3] Kazuhiko Yamada,[2] David K. C. Cooper,[2] David H. Sachs,[2] Amitinder Kaur,[4] and Jay A. Fishman[1]*

Infectious Diseases Division, Massachusetts General Hospital and Harvard Medical School,[1] and Transplantation Biology Research Center, Massachusetts General Hospital,[2] Boston, Immerge BioTherapeutics Inc., Charlestown,[3] and Division of Immunology, New England Regional Primate Research Center, Harvard Medical School, Southborough,[4] Massachusetts

Received 3 December 2001/Accepted 19 February 2002

Xenotransplantation of porcine organs carries the risk of reactivation of latent virus in donor and recipient tissues as well as transmission of viruses between species. We have investigated the activation of baboon cytomegalovirus (BCMV) and porcine CMV (PCMV) in a pig-to-primate model of xenotransplantation. Tissues originating from a series of six swine-to-baboon composite thymokidney xenotransplants were investigated. Four immunosuppressed baboons died (survival range, 7 to 27 days) with the graft in situ. Increases in BCMV DNA copy numbers occurred in three (75%) of these baboons and was thought to be responsible for pneumonitis and the death of one animal. In two baboons, disseminated intravascular coagulation was successfully treated by graftectomy and discontinuation of immunosuppression. PCMV was upregulated in five of six xenografts (83%). PCMV infection was associated with ureteric necrosis in one xenograft. Although significantly increased in native tissues, low levels of BCMV and PCMV were also detected in tissues other than that of the native viral host species. The cross-species presence of CMV did not appear to cause clinical or histological signs of invasive disease. Thus, viral infections with clinical disease were restricted to tissues of the native species of each virus. Intensive immune suppression currently required for xenotransplantation results in a significant risk of reactivation of latent infections by BCMV and PCMV. It is not yet known whether viral DNA detected across species lines represents cellular microchimerism, ongoing viral infection, or uptake of free virus. The observation of graft injury by PCMV demonstrates that CMV will be an important pathogen in immunosuppressed xenograft recipients. Strategies must be developed to exclude CMV from porcine organ donors.

Infection is a major problem in transplantation (7). In particular, cytomegalovirus (CMV) is the most significant post-transplant infection in human allotransplantation. CMV is activated from latency by the allo-immune response and by the immune suppression needed to maintain graft function (7, 17–19). CMV is a betaherpesvirus that causes invasive disease and lifelong latent infection in many mammalian species. Xenotransplantation of swine tissues has been proposed to alleviate the shortage of human organs available for allotransplantation. Swine are considered the organ donors of choice for xenotransplantation for reasons of physiological compatibility, breeding characteristics, and ethical considerations (13).

We have investigated the induction of xenograft tolerance in a pig-to-baboon model based on a previously described pig-to-mouse model involving thymectomy, T-cell depletion, and the transplantation of donor thymic tissue (14, 24). Allotransplant studies of miniature swine have demonstrated that composite thymic tissue-renal allografts with a limited course of immune suppression, thymectomy, and T-cell depletion can induce tolerance across class I and fully-mismatched barriers (23). However, xenotransplantation in the pig-to-baboon model requires intensive immune suppression. This suppression enhances the risk of reactivation of latent CMV in the baboon recipient as well as in the transplanted porcine organ. Consequently, there may be an enhanced risk of transmission of these viruses between donor and recipient (5–7, 16). Techniques which readily distinguish active infection from passive acquisition of virus in vivo are not yet available.

We have developed quantitative molecular assays specific for baboon CMV (BCMV) and porcine CMV (PCMV) to assess the potential for activation of CMV replication and to investigate the potential for interspecies transmission of CMV in this pig-to-baboon model.

MATERIALS AND METHODS

Pig-to-baboon xenotransplantation. Landrace pigs ($n = 5$; approximate weight on date of transplantation, 40 kg) transgenic for human decay-accelerating factor were provided by Novartis Pharmaceuticals, Inc. (East Hanover, N.J.). One animal served as the donor for two xenografts. Sera of two pig donors (for baboons 69-144 and 69-222) were available for PCMV serologic testing by an immune fluorescence assay, and they demonstrated titers of 1:1,024 and 1:64 (Animal Disease Diagnostic Laboratory, Purdue University, West Lafayette, Ind.). A composite thymokidney graft was created by the autologous transplantation of porcine thymic tissue from the native thymus under the renal capsule (22). After a period of 1 to 2 months, the thymic tissue developed a new blood supply from renal vessels with normal thymic architecture. These thymokidneys were used for xenotransplantation studies of baboons. Baboons (*Papio anubis*; $n = 6$) weighing between 8 and 20 kg were purchased from Biological Resources Foundation (Houston, Tex.). At the time of thymokidney transplantation, all the baboons had additional porcine thymic tissue transplanted into the omentum. In each recipient, one native kidney remained in situ. All baboons used in these studies were BCMV seropositive (Esoterix Inc., San Antonio, Tex.).

* Corresponding author. Mailing address: Transplantation Infectious Disease, Massachusetts General Hospital, 55 Fruit St., GRJ 504, Boston, MA 02114. Phone: (617) 726-5777. Fax: (617) 726-5411. E-mail: jfishman@partners.org.

National Kidney Foundation

Enhancing Kidney Transplantation:
The Role of Xenografts

A Scientific Workshop Sponsored by the National Kidney Foundation

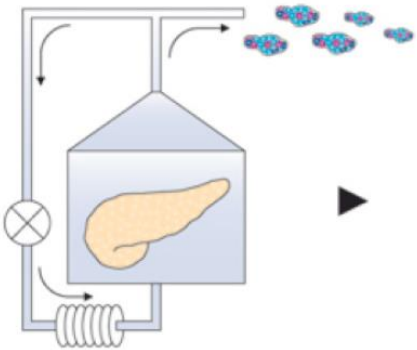
April 11-12, 2022
Location: Washington, DC

New clinical trials for xenotransplantation:

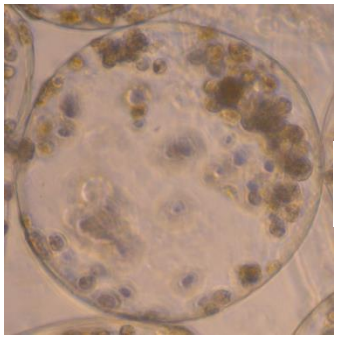
1) Pre-clinical model with 6 months survival
2) Donor pig genetically modified with xenoantigens deletion and addition of transgenes
3) Patient selection based on age, allo-sensitization
4) Immunosuppression includes CD40 pathway mAb
5) Infectious disease surveillance requires screening of donor animals, long-term follow-up recipient her/his close contacts

Cell Xenotransplantation

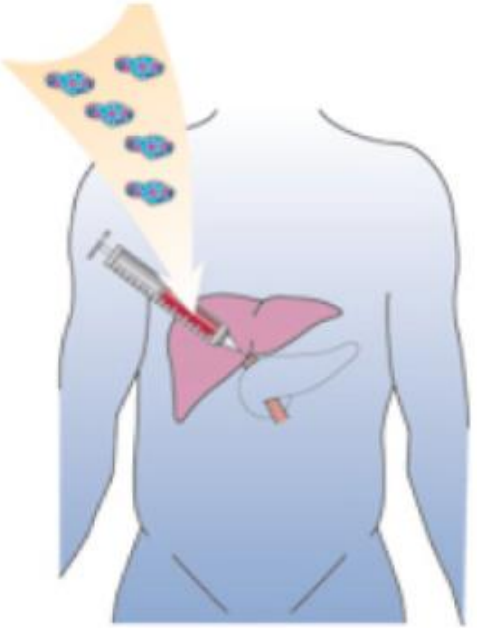
Porcine organ donor (pancreas or liver)



Cell isolation



Encapsulation (size of capsules 400 microns)



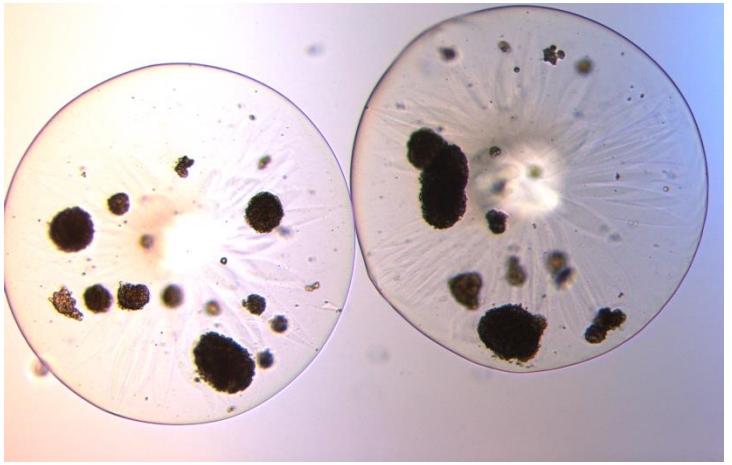
Transplantation to human

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

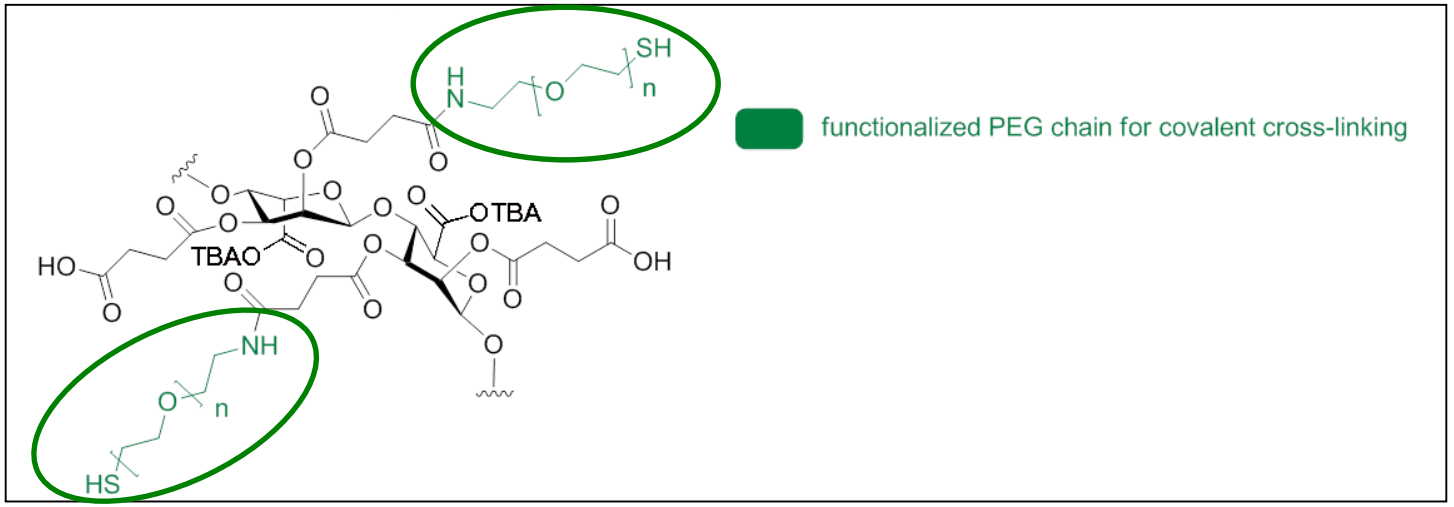
Pr Sandrine Gerber

Immunoprotection of encapsulated cells

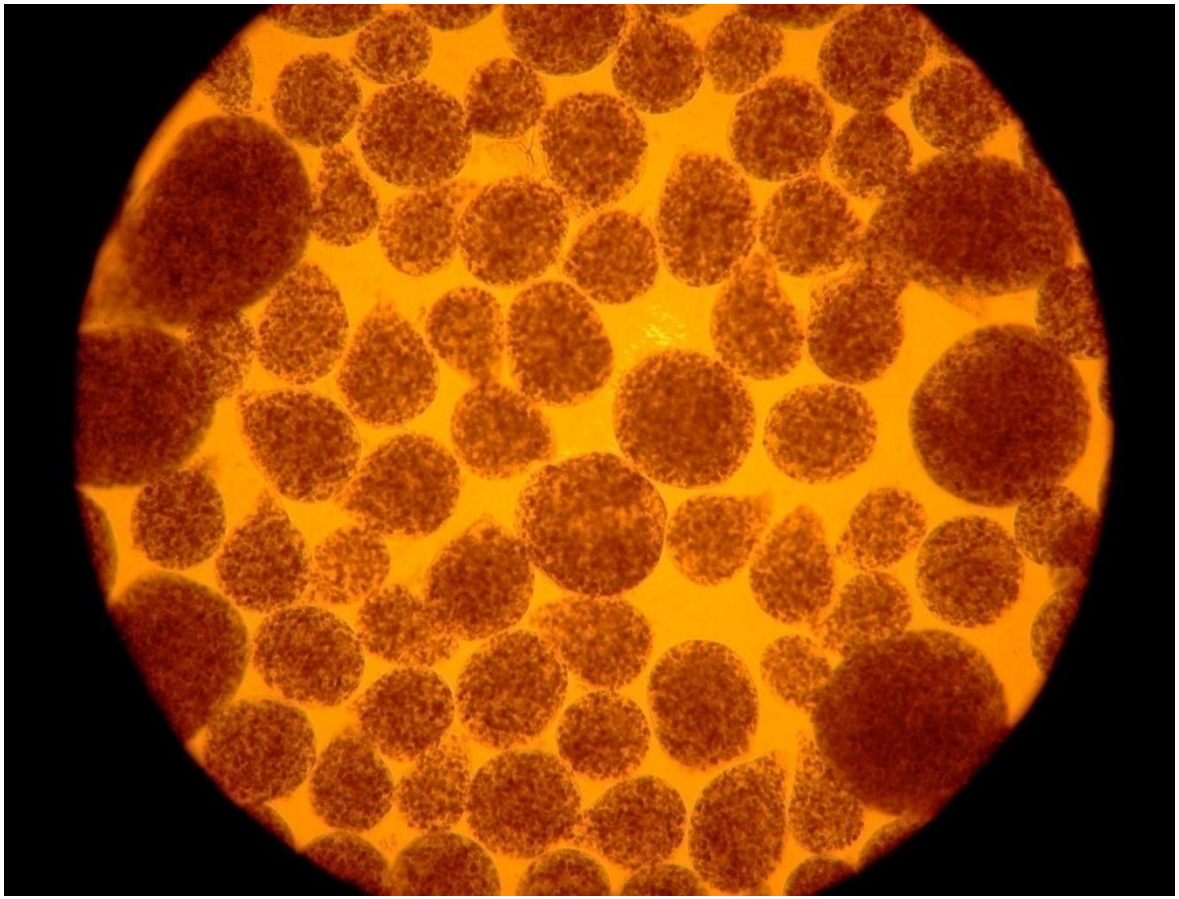
Calcium Alginate
Poly-Ethylene Glycol (PEG)



Microsphere (600um diameter)



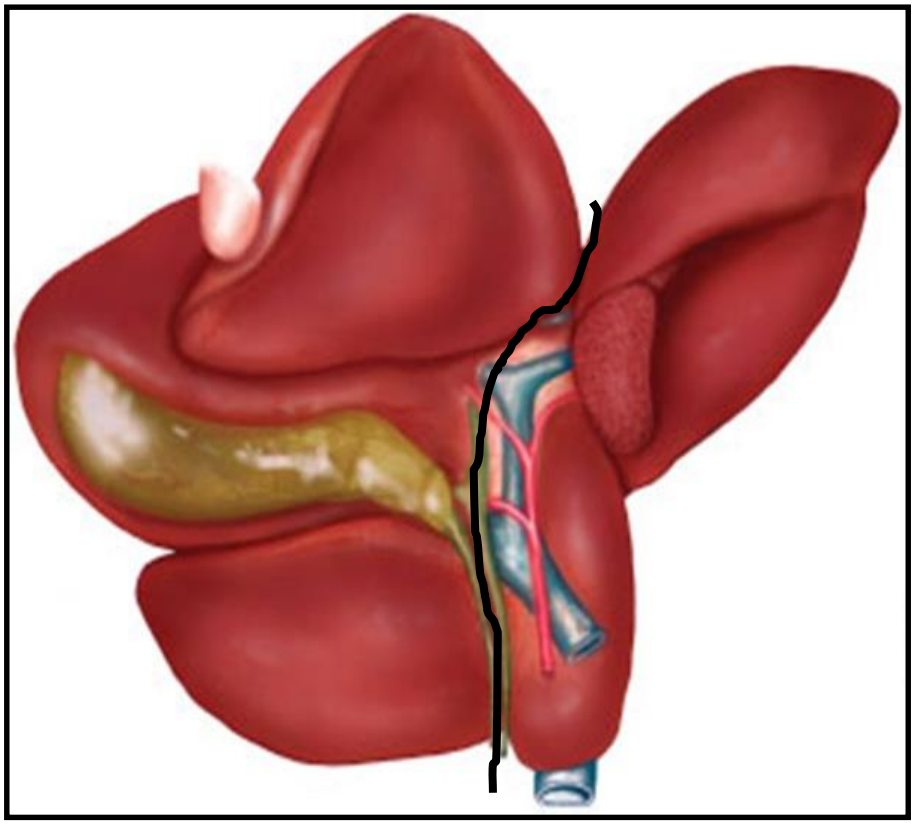
Encapsulated Porcine Hepatocytes

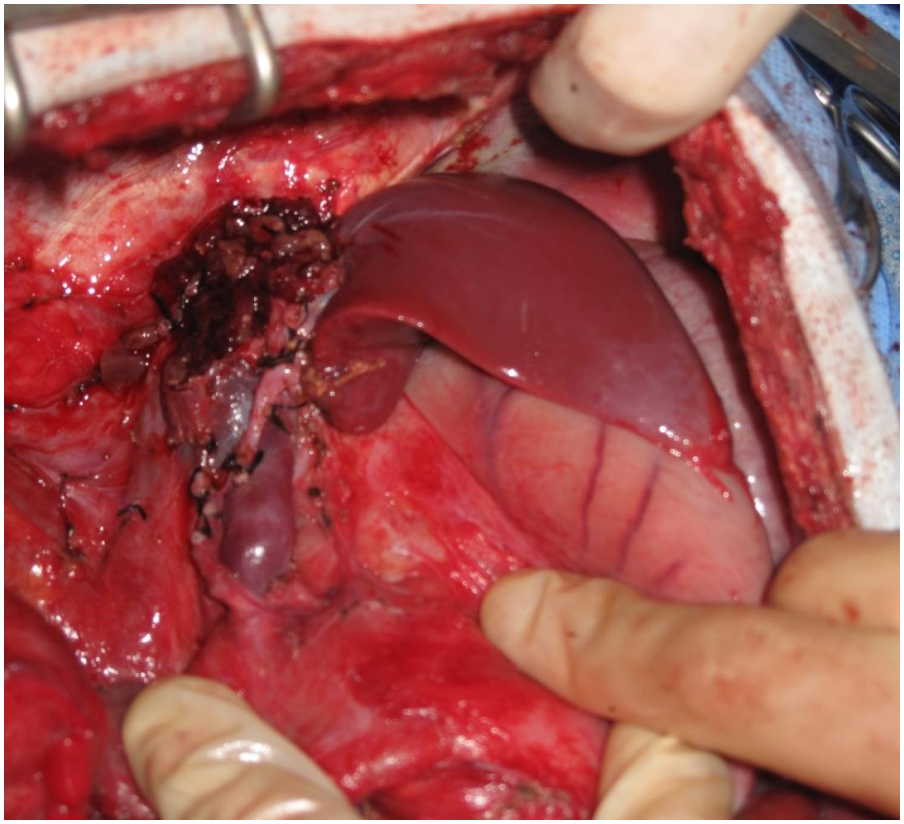


At day 1 in culture (10x)

Mai G. et al. Xenotransplantation 2005
Mei J. et al. Cell Transplant 2009
Sgroi A. et al. Cell Transplant 2011

Establishment of Acute Liver Failure Model in Baboons

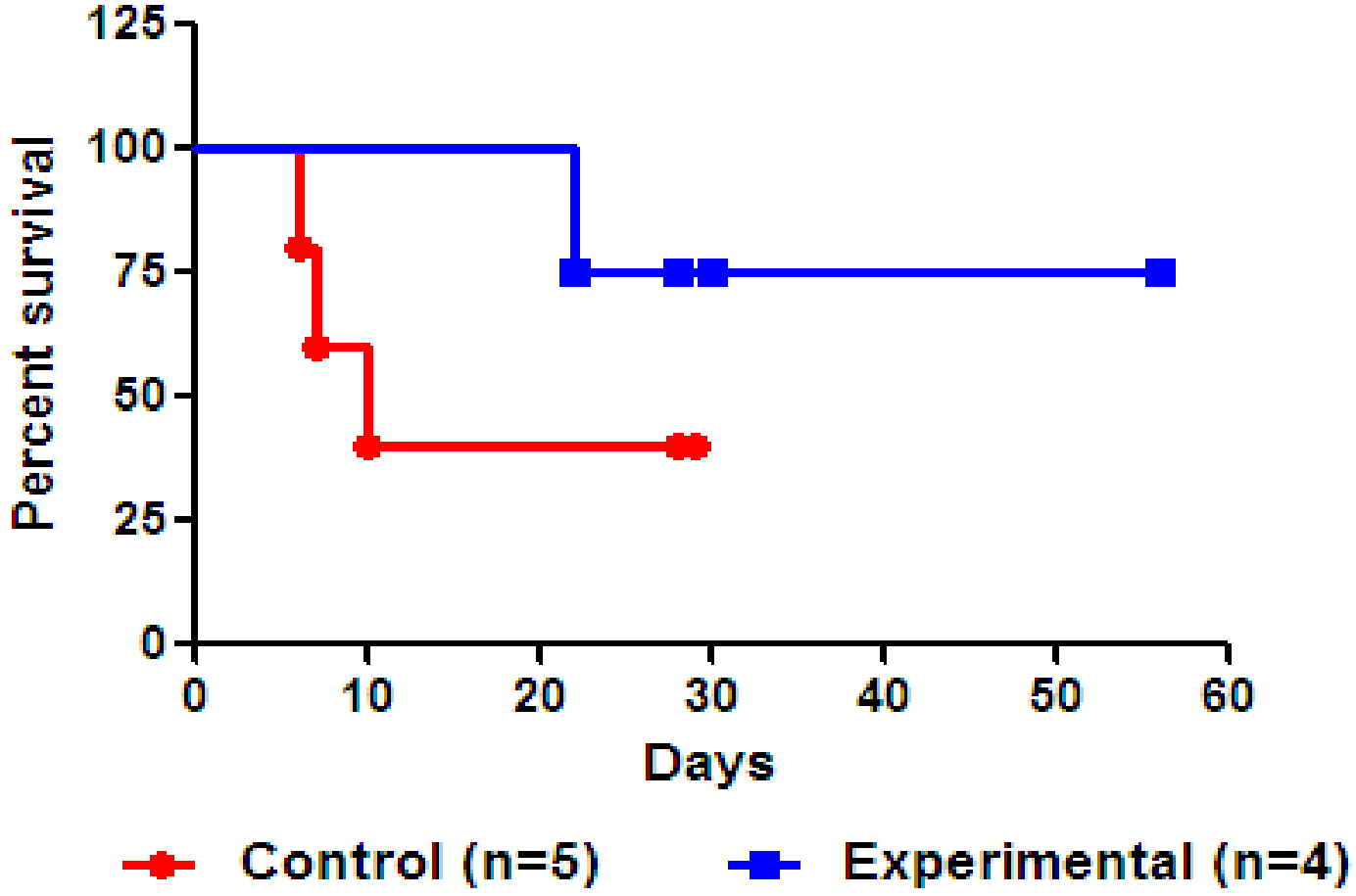




75% Hepatectomy +/- Warm ischemia

Machaidze Z. et al, Xenotransplantation 2017

Encapsulated porcine hepatocytes rescue acute liver failure in baboons



Machaidze Z. et al, Xenotransplantation 2017

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

swissmedic

Phase 1-2 safety-efficacy, single center trials

- **Encapsulated porcine hepatocytes**
  for acute liver failure without offer of standard liver transplantation

- **Encapsulated porcine islets**
  for type 1 diabetes patients sensitized, overweight

Road Map to clinical application

Conclusions

- **Protocols for organ and cell xenotransplantation are in preparation for clinical application**

- **Selected patients will be considered**

  - **Kidney failure**
  - **Heart failure**
  - **acute liver failure**
  - **type I diabetes**

- **Safety will be monitored in collaboration with Swissmedic, IXA, WHO**

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