Nouvelles frontières en Transplantation

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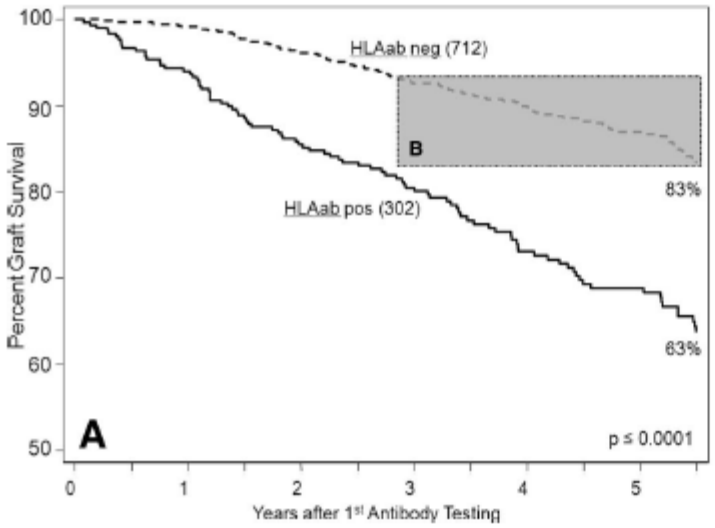
Nouvelles frontières en Transplantation

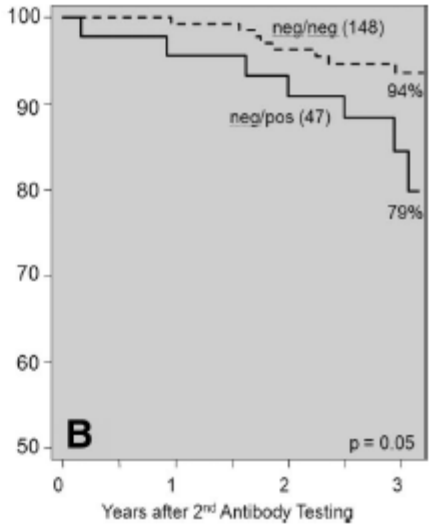
- Greffes contre les barrières immunologiques
  - Hyperimmunisation - Désensibilisation
  - ABO incompatible
  - Tolérance
- Donneurs et organes limites
- Greffes composites
- Xénotransplantation
- Cellules souches et médecine régénérative

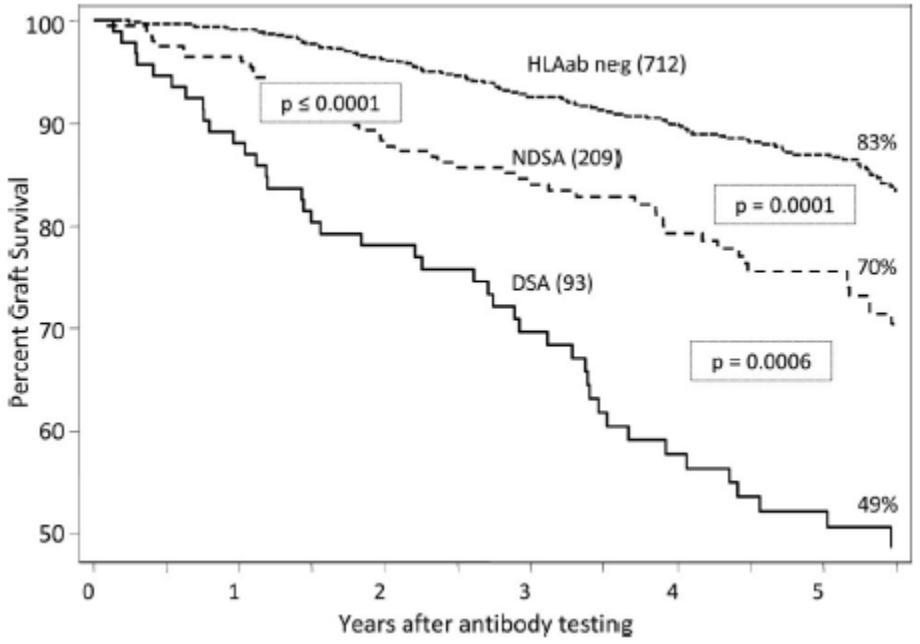
Greffes contre les barrières immunologiques

- Patients hyperimmunisés
- Greffes ABO incompatibles

Importance des AlloAc



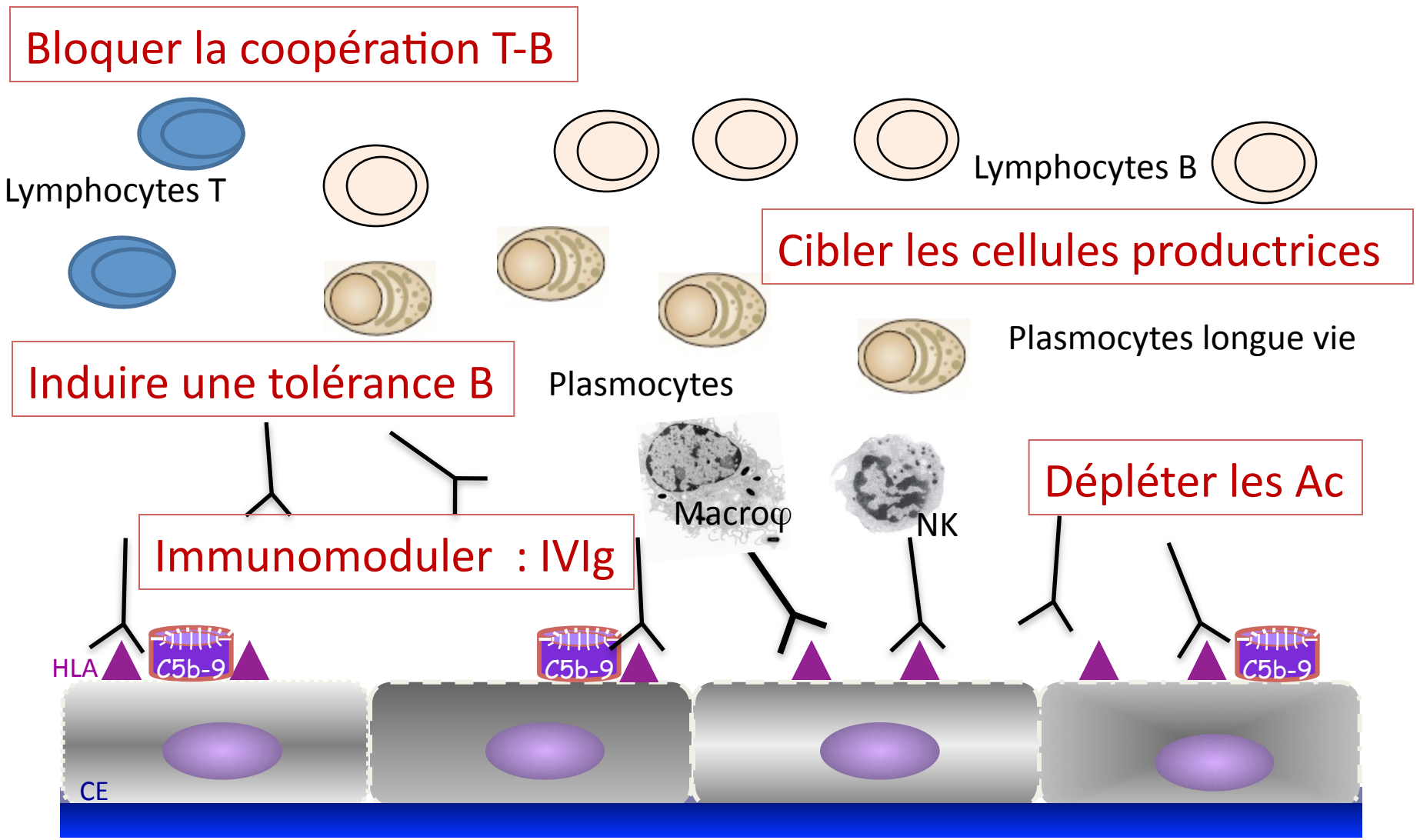




Lachmann et al

Transplantation • Volume 87, Number 10, May 27, 2009

Problématique d'une immunisation humorale

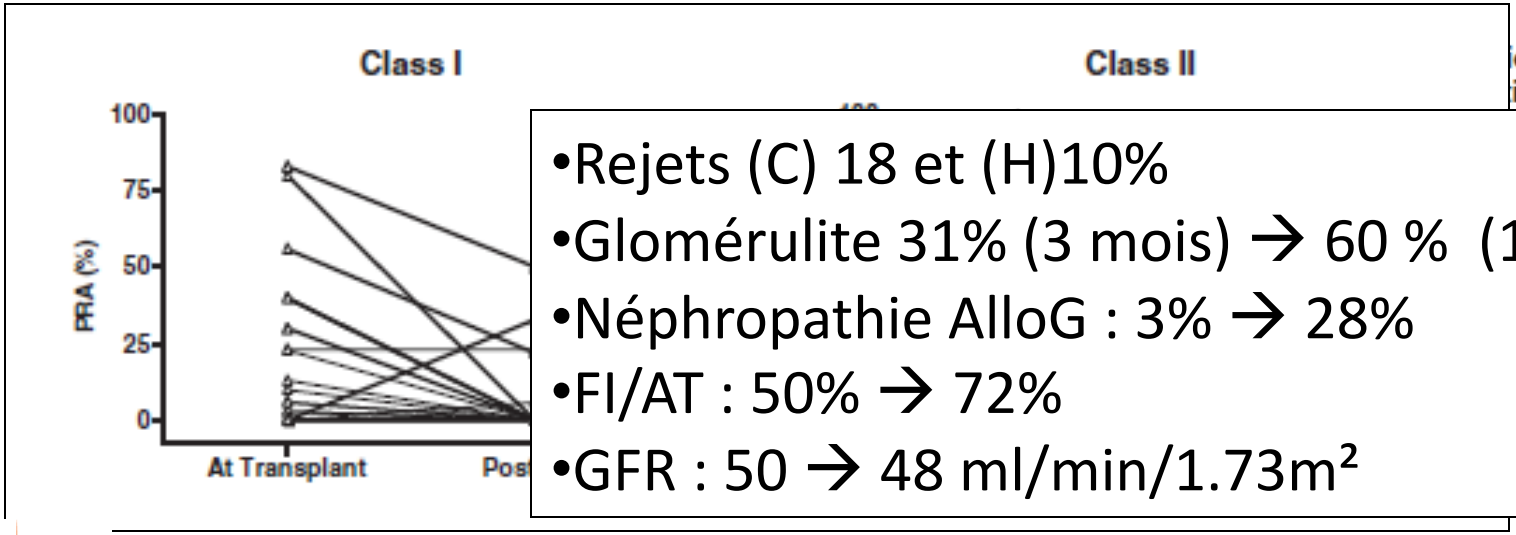


Effets des IVIg sur les Ac anti-HLA

American Journal of Transplantation 2007; 7: 1185–1192
Blackwell Munksgaard

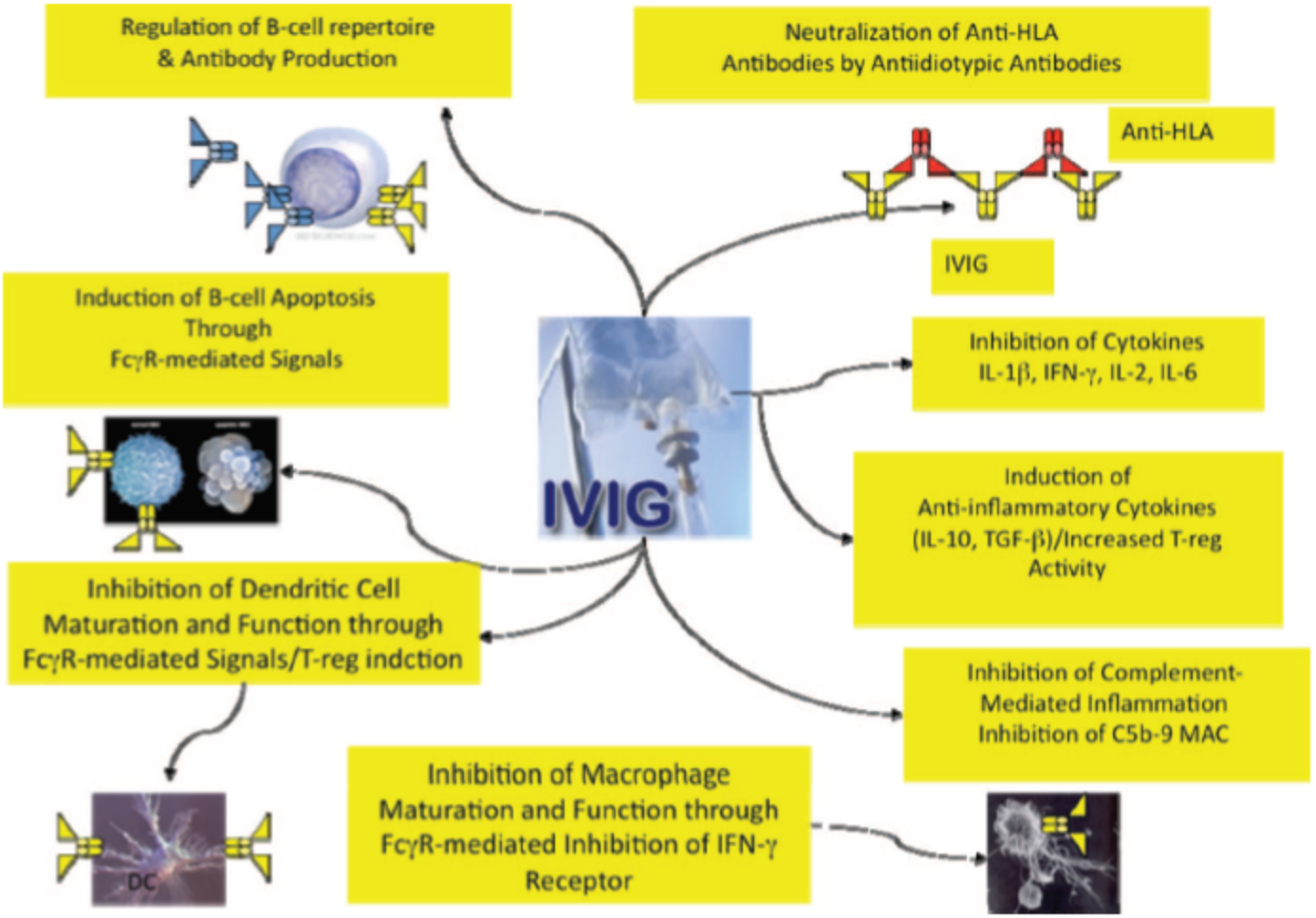
doi: 10.1111/j.1600-6143.2007.01752.x

Posttransplant Prophylactic Intravenous Immunoglobulin in Kidney Transplant Patients at High Immunological Risk: A Pilot Study



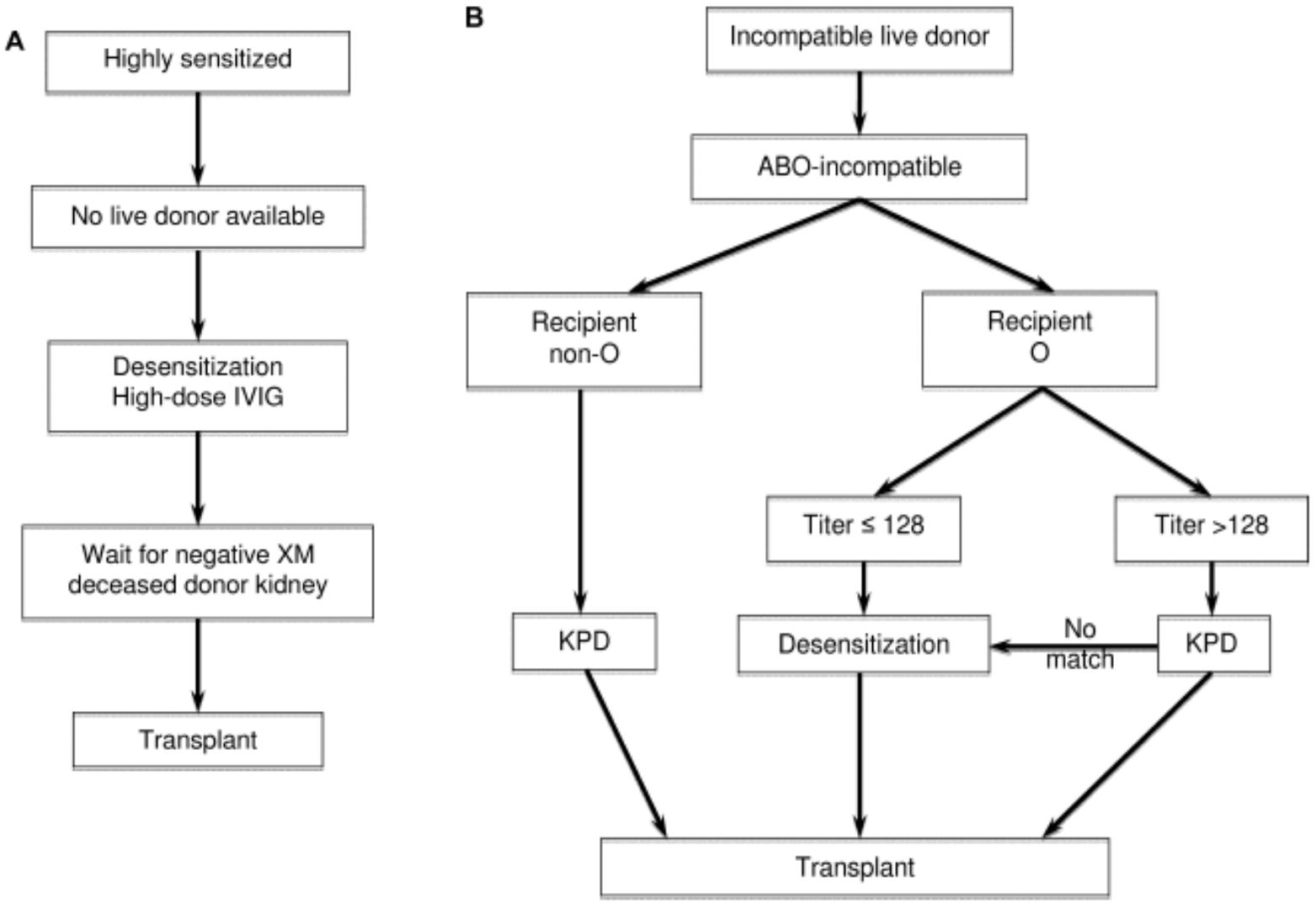
- Rejets (C) 18 et (H)10%
- Glomérulite 31% (3 mois) → 60 % (12 mois)
- Néphropathie AlloG : 3% → 28%
- FI/AT : 50% → 72%
- GFR : 50 → 48 ml/min/1.73m²

IVIg



Jordan et al. *Transplantation* • Volume 88, Number 1, July 15, 2009

Stratégie de désensibilisation



Montgomerry et al. *American Journal of Transplantation* 2010; 10: 449–457

Résultats cliniques en ABO incompatible et XM positif

(A) Graft survival of ABO-incompatible living donor kidney transplantation in large series from Asia, Europe and the United States

Author (ref.)	N	Date transplanted	Graft survival
Takahashi et al. (Am J Transplant. 2004 Jul;4(7):1089–1096)	441	1989–2001	84% [1 year]; 80% [3 year]; 71% [5 year]
Ishida et al. (Am J Transplant. 2007 Apr;7(4):825–831)	117 [1]	2000–2004[1]	94% [1year]; 90% [5 year]
Tyden et al. (Transplantation. 2007 May 15;83(9):1153–1155)	60	2002–2006	97% (17.5 (2–61) months mean follow-up [range])
Montgomery et al. (Transplantation. 2009 Apr 27;87(8):1246–1255)	60	1999–2007	98.3% (1 year); 92.9% (3 year); 88.7% (5 year)[2]

(B) Summary of reported graft survival in positive crossmatch transplantation

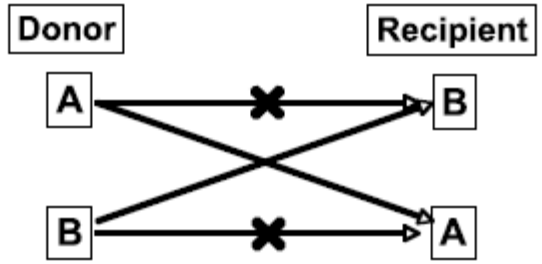
Author (ref.)	N	Date transplanted	XM technique	Desensitiziaton method	Donor type	Analysis time	Graft survival
Stegall et al. (Am J Transplant. 2006 Feb;6(2):346–351)	61	2000–2005	T AHG XM	Plasmapheresis or IVIG	Living	1 year	82%
Higgins et al. (Transplantation. 2007 Oct 15;84(7):876–884)	24	–	CDC; FCXM; microbead	Plasmapheresis	Both	3 months	87.5%
West-Thielke et al. (Am J Transplant. 2008 Feb;8(2):348–354)	22 AA; 28 non-AA	2001–2007	FCXM	Plasmapheresis	Living	1 year	82.6% AA; 94.1% non-AA
Higgins et al. (Lancet. 1996 Nov 2;348(9036):1208–1211)	13	–	CDC; FCXM	Immunoadsorption	Deceased	26 months (median)	53.8%
Jordan et al. (Transplantation. 2003 Aug 27;76(4):631–636)	42[3]	–	CDC	IVIG	Both	2 years	89.1%
Vo et al. (Am J Transplant. 2008 Jan;8(1):144–149)	54	2005–2007	CDC; FCXM	IVIG	Both	1 year	96%
Vo et al. (N Engl J Med. 2008 Jul 17;359(3):242–251)	16	2005–2007	CDC; FCXM	IVIG	Both	1 year	94%
Lorenz et al. (Transplantation. 2005 Mar 27;79(6):696–701)	9[4]	1999–2003	CDC	Immunoadsorption	Deceased	3 year	78%
Haririan et al. (Am J Transplant. 2009 Mar;9(3):536–542)	41	1999–2006	FCXM	Plasmapheresis	Living	5 year	69.4%
Vo et el. (Am J Transplant. 2006 Oct;6(10):2384–2390)	97	1999–2005	CDC	IVIG	Both	2 years	84% Group 1; 90%

Montgomerry et al. *American Journal of Transplantation* 2010; 10: 449–457

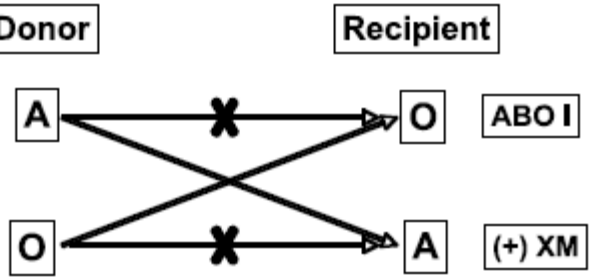
Don croisé

Montgomery

Conventional- only ABOi pairs A/B or B/A
(<3% of donor/recipient pairs eligible)



Unconventional
(all ABOI and + XM donor/recipient pairs eligible)



Discuté en France dans le cadre de la révision en cours de la loi Bioéthique

Tolérance immune

Acceptation prolongée du greffon même après interruption de l'immunosuppression

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Tolerance and Chimerism after Renal and Hematopoietic-Cell Transplantation

John D. Scandling, M.D., Stephan Busque, M.D., Sussan Dejbakhsh-Jones, M.S., Claudia Benike, B.S., Maria T. Millan, M.D., Judith A. Shizuru, M.D., Ph.D., Richard T. Hoppe, M.D., Robert Lowsky, M.D., Edgar G. Engleman, M.D., and Samuel Strober, M.D.

SUMMARY

We describe a recipient of combined kidney and hematopoietic-cell transplants from an HLA-matched donor. A post-transplantation conditioning regimen of total lymphoid irradiation and antithymocyte globulin allowed engraftment of the donor's hematopoietic cells. The patient had persistent mixed chimerism, and the function of the kidney allograft has been normal for more than 28 months since discontinuation of all immunosuppressive drugs. Adverse events requiring hospitalization were limited to a 2-day episode of fever with neutropenia. The patient has had neither rejection episodes nor clinical manifestations of graft-versus-host disease.

N Eng J Med 2008

BRIEF REPORT

HLA-Mismatched Renal Transplantation without Maintenance Immunosuppression

Tatsuo Kawai, M.D., A. Benedict Cosimi, M.D., Thomas R. Spitzer, M.D., Nina Tolkoff-Rubin, M.D., Manikkam Suthanthiran, M.D., Susan L. Saidman, Ph.D., Juanita Shaffer, B.S., Frederic I. Preffer, Ph.D., Ruchuang Ding, M.D., Vijay Sharma, Ph.D., Jay A. Fishman, M.D., Bimalangshu Dey, M.D., Dicken S.C. Ko, M.D., Martin Hertl, M.D., Nelson B. Goes, M.D., Waichi Wong, M.D., Winfred W. Williams, Jr., M.D., Robert B. Colvin, M.D., Megan Sykes, M.D., and David H. Sachs, M.D.

SUMMARY

Five patients with end-stage renal disease received combined bone marrow and kidney transplants from HLA single-haplotype mismatched living related donors, with the use of a nonmyeloablative preparative regimen. Transient chimerism and reversible capillary leak syndrome developed in all recipients. Irreversible humoral rejection occurred in one patient. In the other four recipients, it was possible to discontinue all immunosuppressive therapy 9 to 14 months after the transplantation, and renal function has remained stable for 2.0 to 5.3 years since transplantation. The T cells from these four recipients, tested in vitro, showed donor-specific unresponsiveness and in specimens from allograft biopsies, obtained after withdrawal of immunosuppressive therapy, there were high levels of P3 (FOXP3) messenger RNA (mRNA) but not granzyme B mRNA.

N Eng J Med 2008

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Chimerism and Tolerance in a Recipient of a Deceased-Donor Liver Transplant

Stephen I. Alexander, M.B., B.S., Neil Smith, M.B., B.S., Min Hu, M.D., M.Med., Deborah Verran, M.B., Ch.B., Albert Shun, M.B., B.S., Stuart Dorney, M.B., B.S., Arabella Smith, M.B., B.S., Boyd Webster, M.B., Ch.B., Peter John Shaw, M.B., B.S., Ahti Lammi, M.B., B.S., and Michael O. Stormon, M.B., B.S.

SUMMARY

Complete hematopoietic chimerism and tolerance of a liver allograft from a deceased male donor developed in a 9-year-old girl, with no evidence of graft-versus-host disease 17 months after transplantation. The tolerance was preceded by a period of severe hemolysis, reflecting partial chimerism that was refractory to standard therapies. The hemolysis resolved after the gradual withdrawal of all immunosuppressive therapy.

N Eng J Med 2008

Long-Term Follow-Up of Recipients of Combined Human Leukocyte Antigen-Matched Bone Marrow and Kidney Transplantation for Multiple Myeloma With End-Stage Renal Disease

Thomas R. Spitzer,[1,6] Megan Sykes,[2] Nina Tolkoff-Rubin,[3] Tatsuo Kawai,[4] Steven L. McAfee,[1] Bimalangshu R. Dey,[1] Karen Ballen,[1] Francis Delmonico,[4] Susan Saidman,[5] David H. Sachs,[2] and A. Benedict Cosimi[4]

Background. Specific tolerance after combined kidney and bone marrow transplantation for multiple myeloma with end-stage renal disease through mixed lymphohematopoietic chimerism has been achieved, as evidenced by prolonged normal renal function without ongoing immunosuppression.

Methods. To achieve potent antimyeloma responses and induce tolerance for the renal allograft, seven patients (median age: 48 years [range: 34–55 years]) with multiple myeloma and end-stage renal disease underwent a combined human leukocyte antigen-matched kidney and bone marrow transplant with lead follow-up time of more than 12 years. Preparative therapy for the transplant consisted of high-dose cyclophosphamide, equine antithymocyte globulin and pretransplant thymic irradiation. Cyclosporine as the sole posttransplant immunosuppressive therapy was tapered and discontinued as early as day 73 posttransplant.

Results. All seven patients achieved mixed chimerism. One patient developed acute graft-versus-host disease and two chronic graft-versus-host disease. Five of seven patients are alive, four with no evidence of myeloma from 4 to 12.1 years posttransplant. Three patients have normal or near-normal renal function without needing systemic immunosuppression. Two patients with normal renal function off immunosuppression were returned to immunosuppressive therapy without evidence of rejection because of the occurrence of chronic graft-versus-host disease.

Conclusions. These long-term follow-up data show that sustained renal allograft tolerance and prolonged antimyeloma responses are achievable after human leukocyte antigen-matched kidney and bone marrow transplantation and the induction of mixed lymphohematopoietic chimerism.

Donneurs et organes limites

Machines de perfusion extra-corporelle

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 1, 2009 VOL. 360 NO. 1

Machine Perfusion or Cold Storage
r Kidney Transplantation

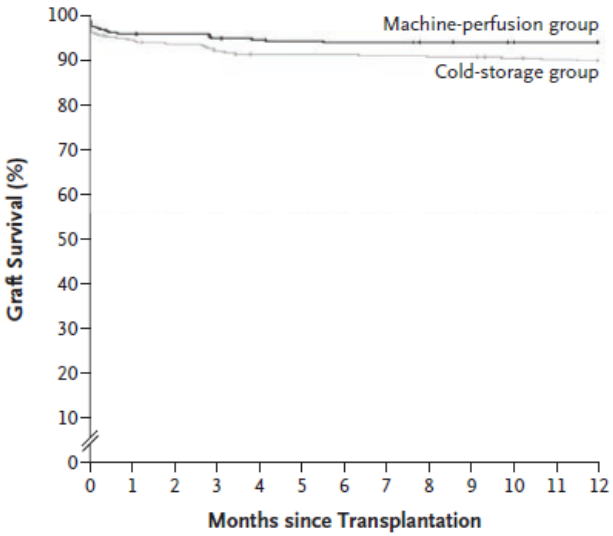


Figure 3. Graft Survival after Transplantation.

The rate of graft survival at 1 year in the machine-perfusion group was significantly higher than the rate in the cold-storage group (94% vs. 90%, P=0.04). Data on graft survival were censored at the time of death in patients who died with a functioning allograft.

- Moins de retard de démarrage (p=0.01)
- Meilleure récupération de fonction rénale
- Meilleure créatinine pendant les 2 premières semaines et moindre risque d'échec de greffe (p= 0.03)
- Meilleure survie à un an

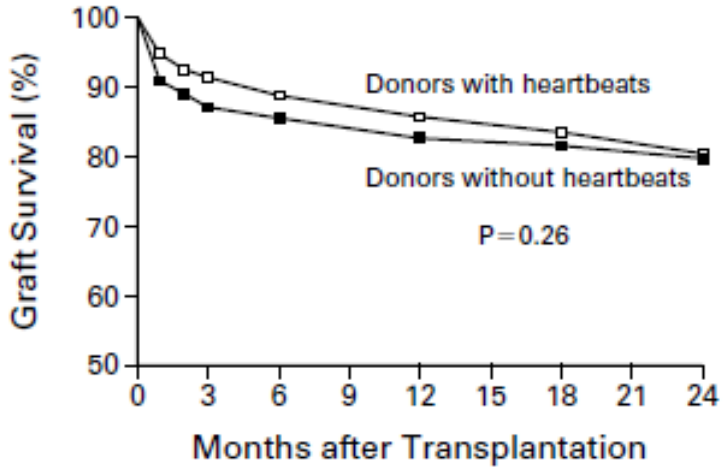
the primary end point was de-
eek after transplantation). Sec-
unction, delayed graft function
tinine level, primary nonfunc-
jection, toxicity of the calcineu-
ft and patient survival.

Visceral, and Transplantation Surgery, University Hospital Essen, Essen (J.T., B.P.N., A.P.); and Deutsche Stiftung Organtransplantation, Frankfurt (G.R.K.) — both in Germany; and the Department of Abdominal Transplant Surgery — Transplant Coordination, University Hospital Leuven, Leuven (F.G., J.P.); and the De-

Donneurs à cœur non battant

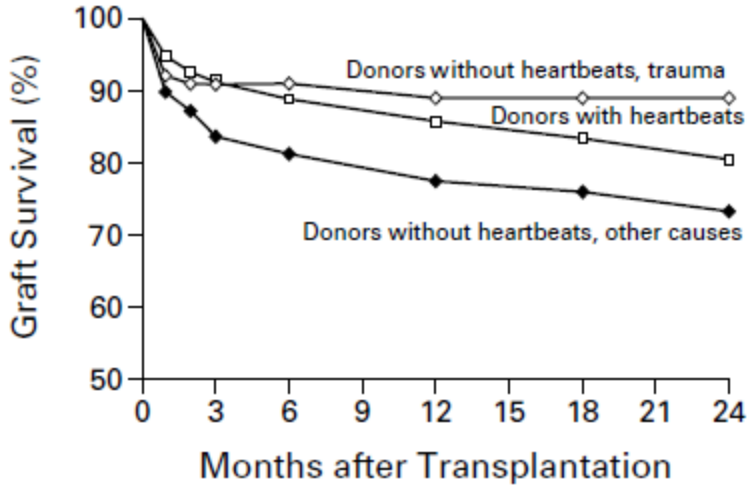
TRANSPLANTATION OF KIDNEYS FROM DONORS WHOSE HEARTS HAVE STOPPED BEATING

YONG W. CHO, PH.D., PAUL I. TERASAKI, PH.D., J. MICHAEL CECKA, PH.D., AND DAVID W. GJERTSON, PH.D.



NO. OF GRAFTS

Donors with heartbeats	8718	7136	6368	3983	2308	1169
Donors without heartbeats	229	178	153	97	61	40



NO. OF GRAFTS FROM DONORS WITHOUT HEARTBEATS

Death from trauma	106	82	74	41	24	18
Death from other causes	123	96	79	56	37	22

beats. as compared with 86 percent for grafts from

N Engl J Med 1998;338:221-5.

Classification de Maastricht

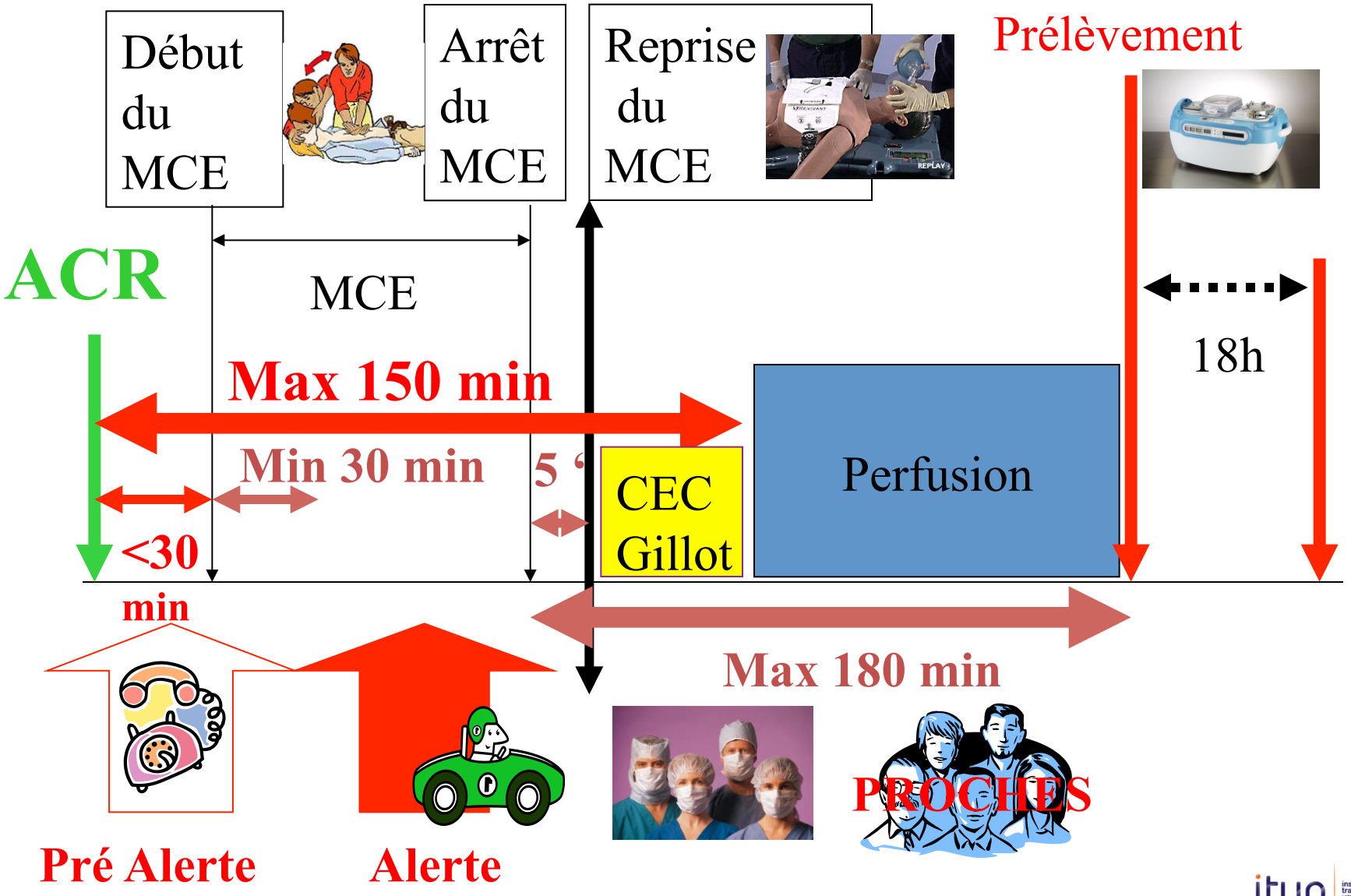
Classe 1 « Dead on arrival »

Classe 2 « Unsuccessful Rescuscitation »

Classe 3 « Awaiting Cardiac Arrest »

Classe 4 « Cardiac Arrest in a Brain Dead Donor»

Limites de temps ALERTE

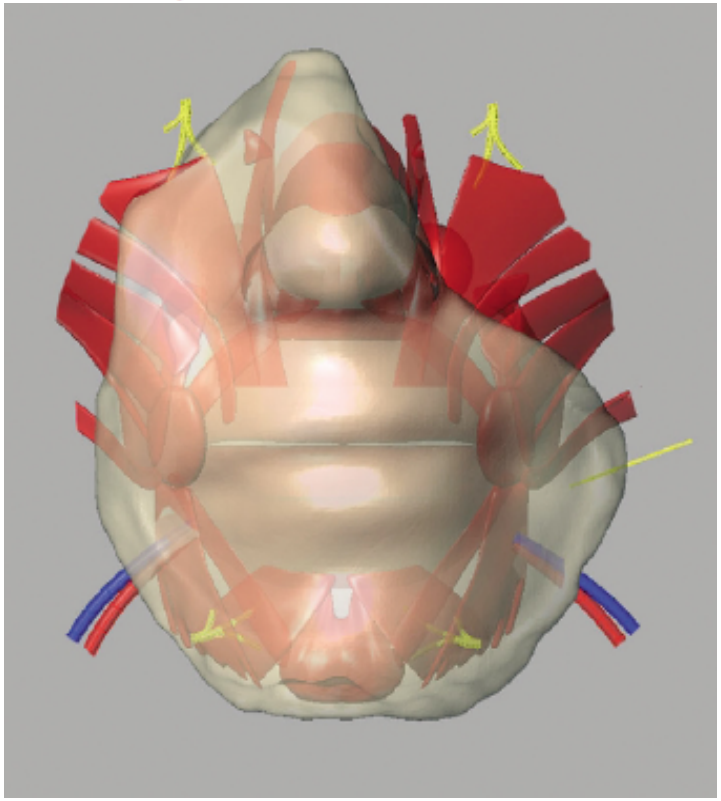


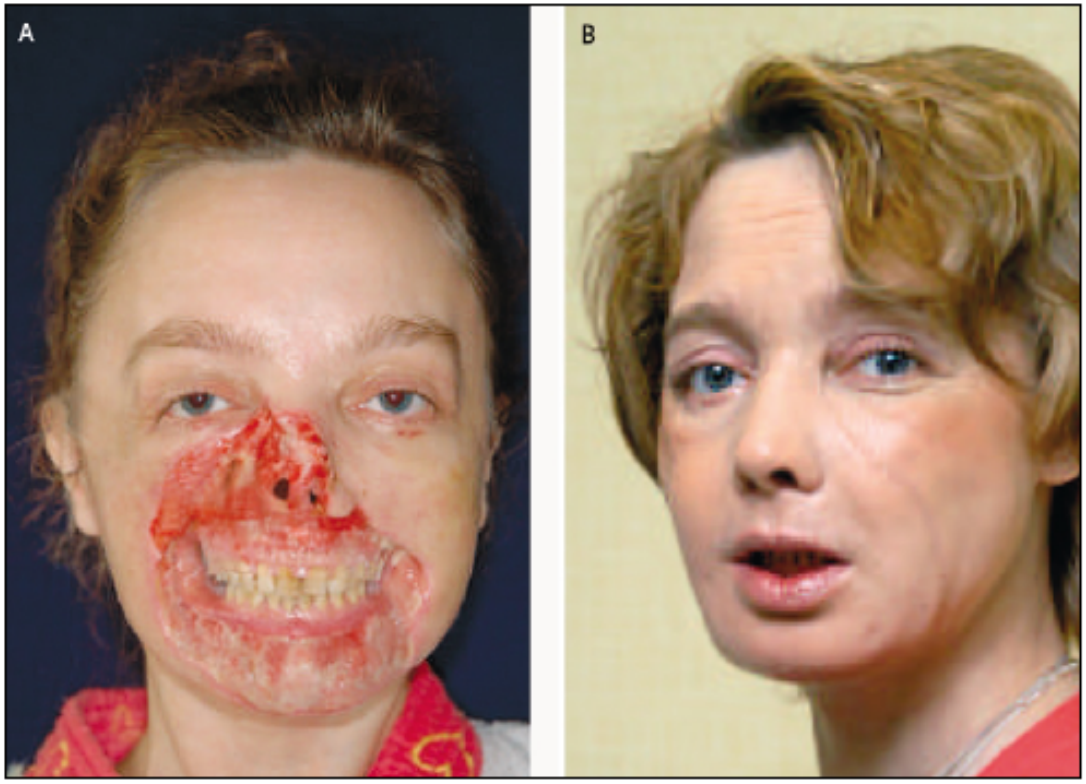
Les greffes composites

First human face allograft: early report

Bernard Devauchelle, Lionel Badet, Benoit Lengelé, Emmanuel Morelon, Sylvie Testelin, Mauricette Michallet, Cédric D'Hauthuille, Jean-Michel Dubernard

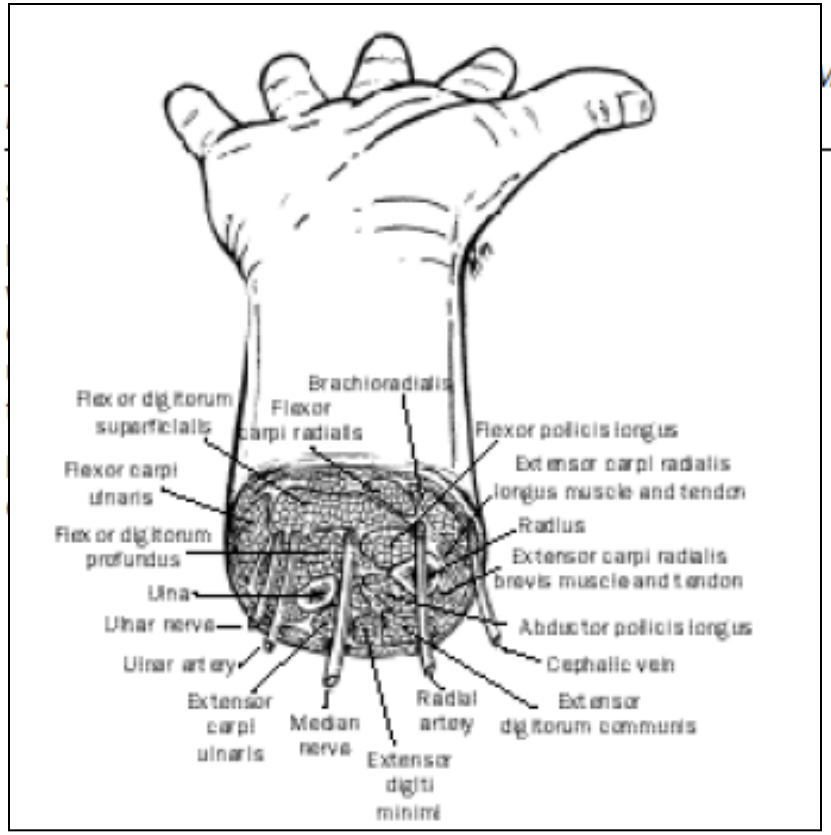
Summary





Early reports

Human hand allograft: report on first 6 months



Marco Lanzetta, Xavier Martin, Hari Kapila,

Interpretation Hand allotransplantation is technically feasible. Currently available immunosuppression seems to prevent acute rejection. If no further episode of rejection occurs, the functional prognosis of this graft should be similar to if not better than that reported in large series of autoreconstruction.

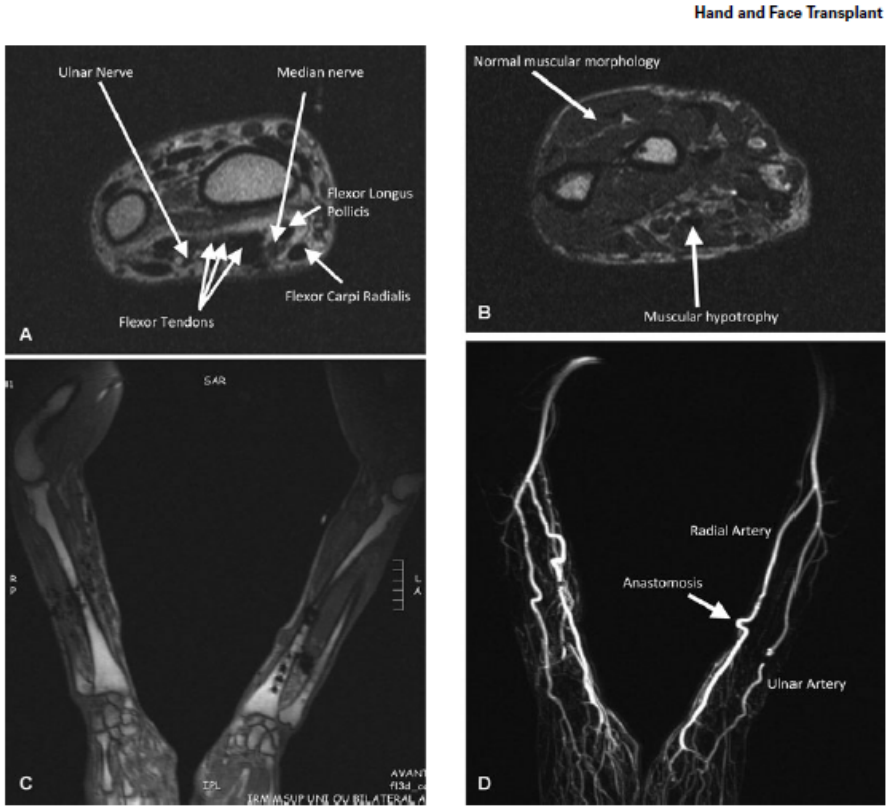
Lancet 1999; **353:** 1315–20
See Commentary page 1286

American Journal of Transplantation 2011; 11: 808–816
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2011.03469.x

Long-Term Follow-Up in Composite Tissue Allotransplantation: In-Depth Study of Five (Hand and Face) Recipients

Composite tissue allotransplantations (CTAs) have clinically shown little, if any, evidence of chronic rejection. Consequently, the effect of chronic rejection on bones, joints, nerves, muscles, tendons and vessels may still have undescribed implications. We thoroughly assessed all allograft structures by histology, magnetic resonance imaging, ultrasonography and high resolution peripheral quantitative computed tomography scan in four bilateral hand-grafted patients (10, 7, 3 and 2 years of follow-up, respectively) and in one facial allotransplantation (5 years of follow-up). All the recipients presented normal skin structure without dermal fibrosis. Vessels were patent, without thrombosis, stenosis or intimal hyperplasia. Tendons and nerves were also normal; muscles showed some changes, such as a variable degree of muscular hypotrophy, particularly of intrinsic muscles, accompanied by fatty degeneration that might be related to denervation. In the majority of hand-grafted patients graft radius and recipient tibia showed a decrease in trabecular density, although in the graft radius the alterations also involved the cortices. No deterioration of graft function was noted. In these cases of CTA no



Xénotransplantation

Les raisons du regain d'intérêt récent pour la xénotransplantation

- La pénurie d'organes
- L'émergence de nouvelles technologies : transgénèse, clonage, thérapie génique

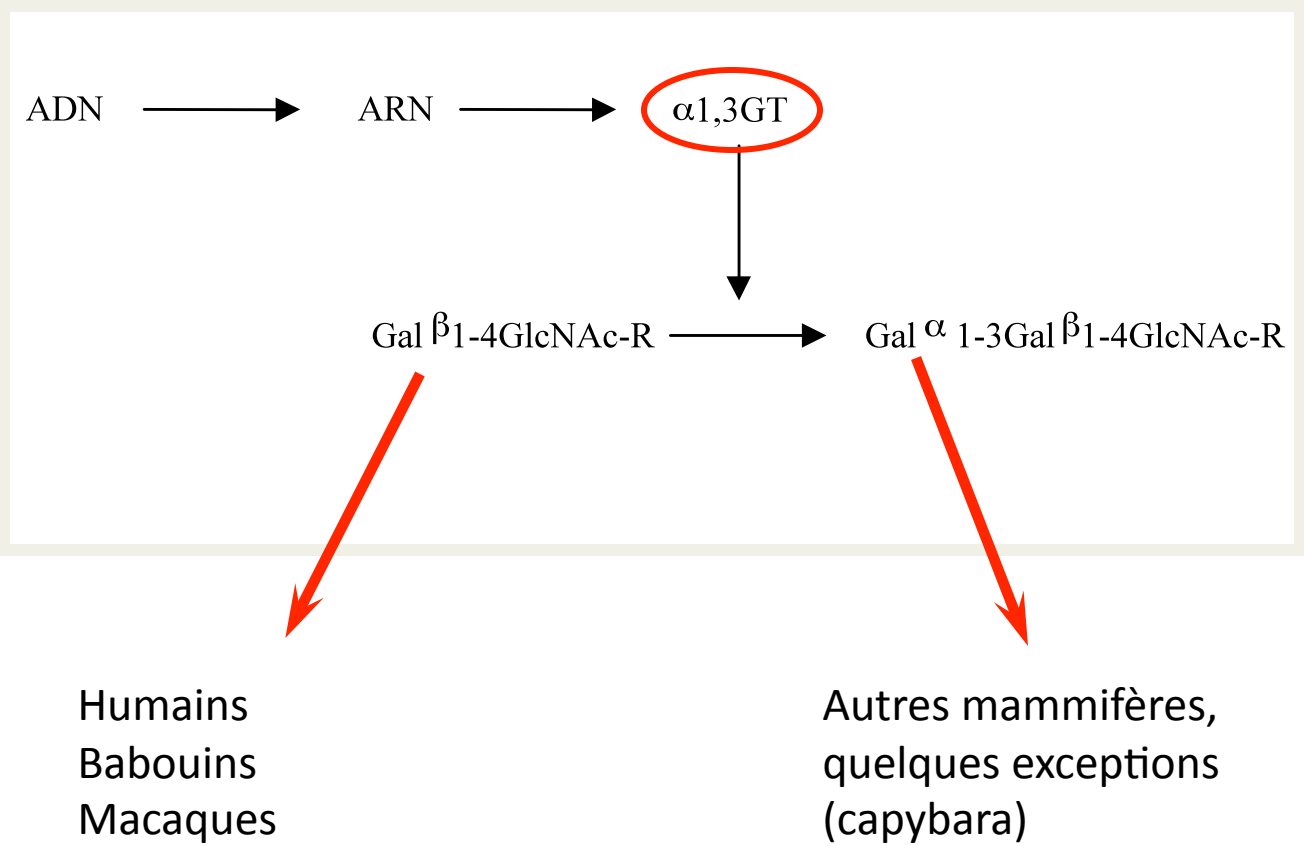
Historique de la Xénotransplantation

DONNEUR	ORGANE	SURVIE	ANNEE	AUTEURS
Chimpanzé	REIN	9 mois	1964	Reemtsma
Monkey	REIN	10 jours	1964	Reemtsma
Babouin	REIN	4 jours	1964	Hitchcock
Babouin	REIN	2 mois	1964	Starzl
Chimpanzé	COEUR	Insuffisance cardiaque	1964	Hardy
Chimpanzé	FOIE	14 jours	1969-1974	Starzl
Babouin	COEUR	Rejet suraigu	1977	Barnard
Chimpanzé	COEUR	4 jours	1977	Barnard
Babouin	COEUR	4 semaines	1985	Bailey
Babouin	FOIE	70 jours	1992	Starzl

Le choix de l'animal donneur

- Les primates : NON
  - **les rétrovirus (proximité d'espèce)**
  - **problèmes éthiques**
- Le porc : OUI
  - **culture et facilité d'élevage**
  - **taille et physiologie compatibles**
  - **accès à la transgénèse et clonage**
  - **risque viral demeure**

Spécificité des humains et des primates de l'ancien monde



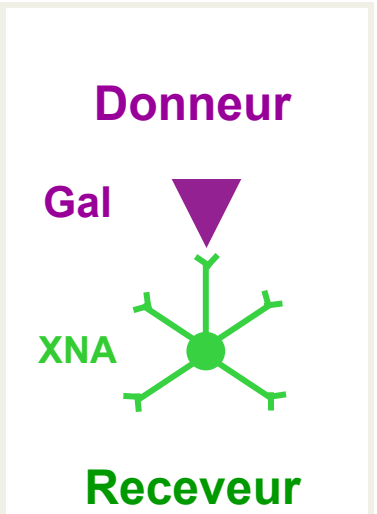
Galα1-3Gal : Ag xénogénique

Porc

Galα1-3Galβ1-4GlcNAc (Gal)

Homme/Primate de l'ancien monde

Fucα1-2Galβ1-4GlcNAc (H) ⋯→ Groupe sanguin A ou B



Xénotransplantation

- **Combinaison discordante : porc sur homme/primate**

Ac préformés → **Rejet hyperaigu** → **Rejet vasculaire aigu**

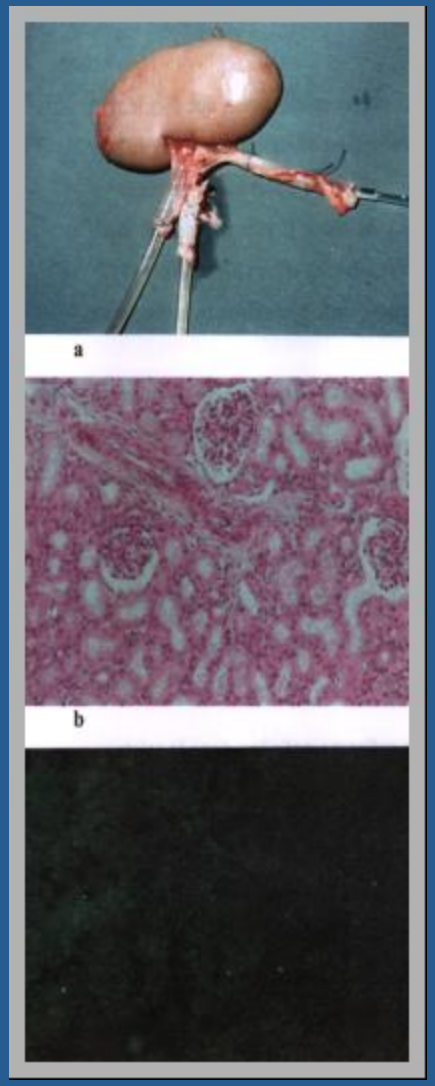
- **Combinaison concordante : hamster sur rat**

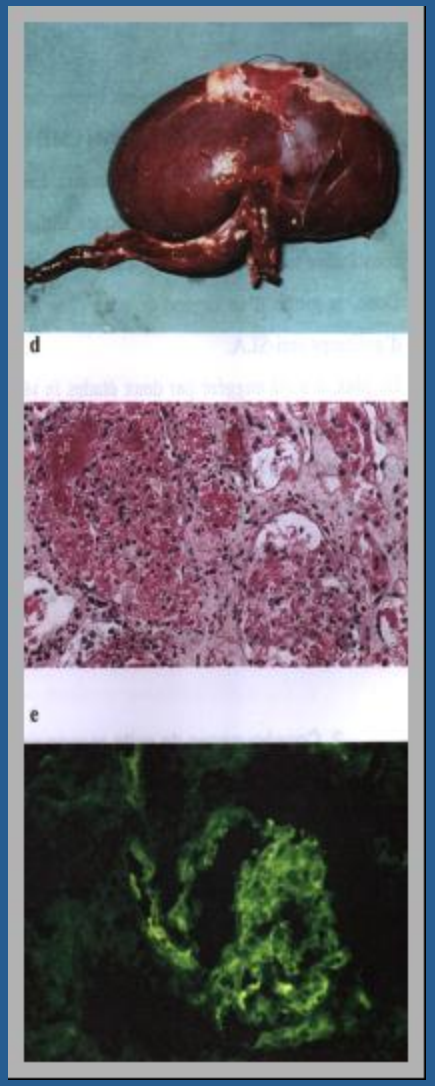
Pas Ac préformés → **Rejet vasculaire aigu**

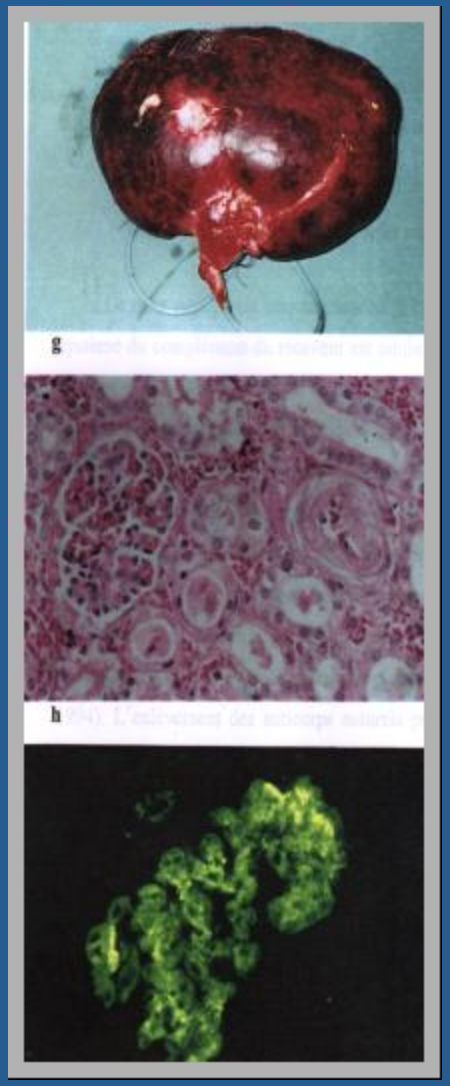
Rein normal

Rejet hyperaigu

Rejet vasculaire aigu







macroscopie

histologie

IgM

Le rejet hyperaigu

Recrutement leucocytaire

Ac xénoréactifs Complément

C3a/C5a

Défenses cellules endothéliales au repos: ADPase, Thrombomoduline, TFPI

Médiateurs d'inflammation C3a/C5a, histamine, LT4

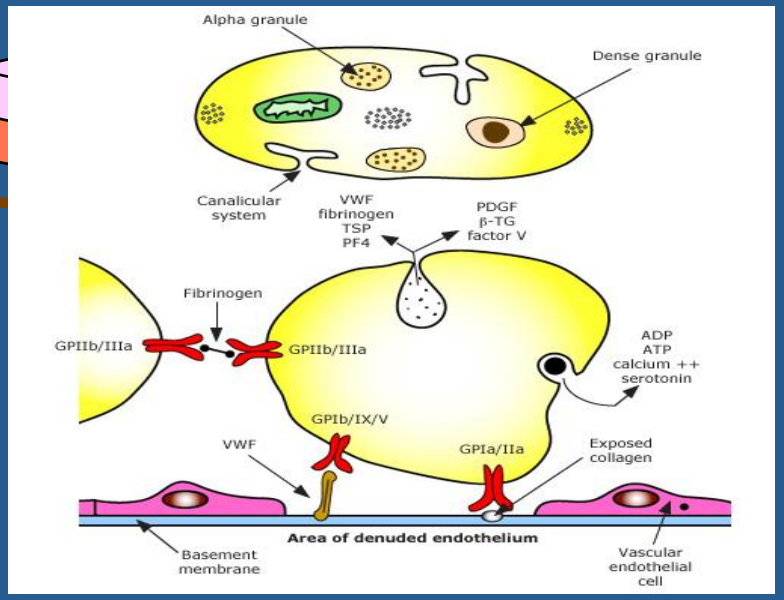
PAF

P-sélectine

galα1-3gal

gpIb

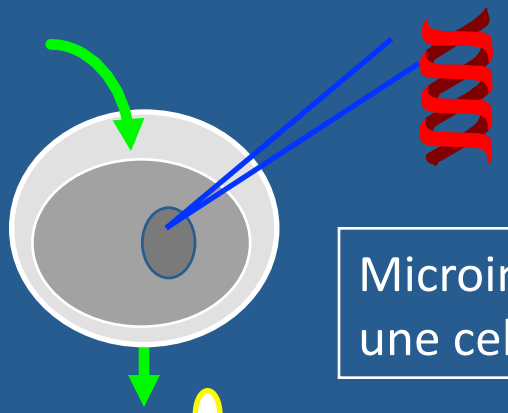
vWF



Activation endothéliale de type I:
rétraction endothéliale, P-sélectine

Transgénèse

Superovulation et fécondation



Construct ADN

Microinjection embryon stade une cellule

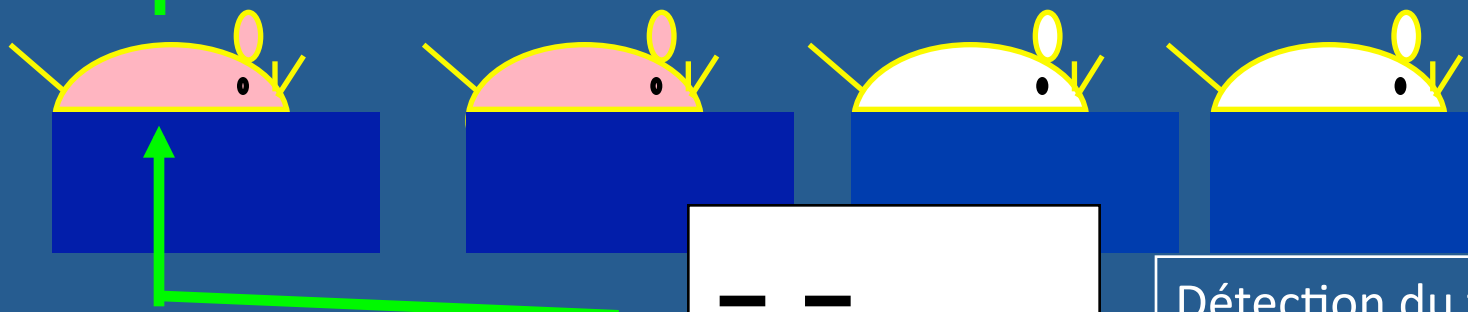
Femelle pseudogestante

3 semaines

3 semaines

8-12 semaines

Cryopréservation
Reproduction
F1 hémizygote
F2 homozygote
Analyse expression Tg



Fondateur, F0

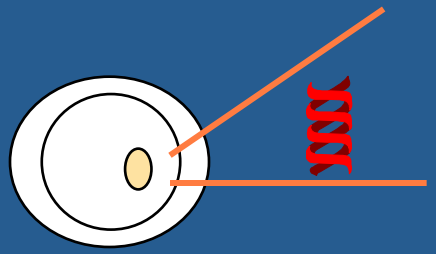
Détection du transgène

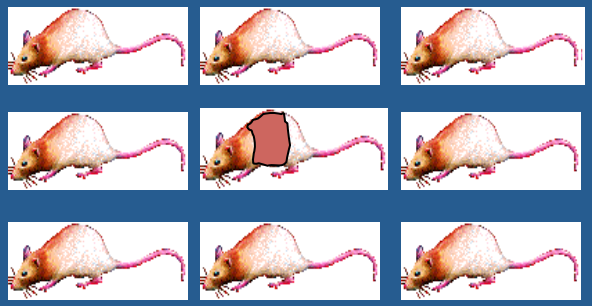
Protocoles utilisant des organes de porcs transgéniques

Author/Year	Recipient	Porcine graft	Treatment	Graft survival
McCurry/1995	Baboon	Heart	hDAF+hCD59+SPx+CyP+ AZA+CS+IA	4-30h
Norin/1996	Baboon	Lung	hCD59	<12h
White/1995	Cynomolgus	Heart	HDAF	5 days
Cozzi/1995/1997	Cynomolgus	Heart	hDAF+CsA+CyP+CS	6-62 days
Kroshus/1997	Baboon	Heart	hCD59+IA+SPx+CsA+ CS+MTX	<10 days
Lin/1997	Baboon	Heart	hCD59/hDAF+IA+CsA +CyP+CS	<29 days
Daggett/1998	Baboon	Lung	hDAF/hCD59 hDAF/hCD59+IA	<4h <24h
Zaidi/1998	Cynomolgus	Kidney	hDAF+CsA+CyP+CS	6-35 days
Waterworth/1998	Baboon	Heart	HDAF	2-21 days
Yeatman/1998	Baboons	Lung	hDAF+hCD59	<3h
Bhatti/1997 /1999	Baboon	Heart	hDAF+CsA+CyP+CS hDAF+CsA+CyP+CS+ SPx	3 months
Vial/2000	Baboon	Lung	hDAF+CsA+CyP+CS	39 days
Cowan/2000	Baboon	Kidney	CD55/HT CD55/CD59/HT	30h 5 days

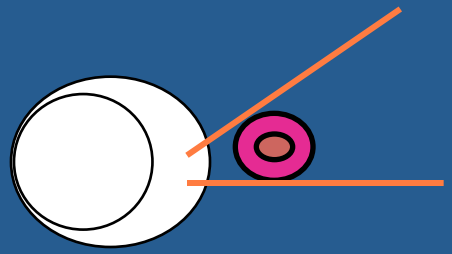
McGregor 2003	Baboon	Heart	**CD46 +FK Rapa/αCD20/NEX1285**	4.5 months

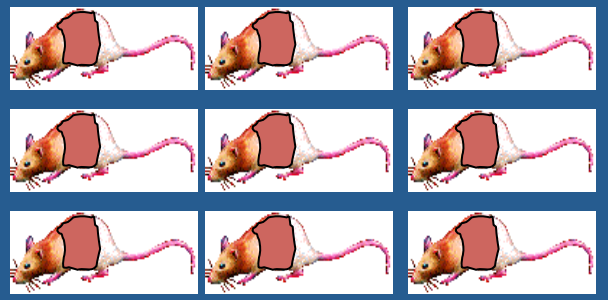
Microinjection ADN





Transfert nucléaire





Temps	plus long	plus court
Integration du gène	non-contrôlée	contrôlée
Nouveau gène	surexpression	surexpression
	knock-down:	knock-out

antisense, intrabodies, intrakines, toxines ou genes suicide
competition enzymatique, mutants dominant negatifs

Les porcs Gal KO

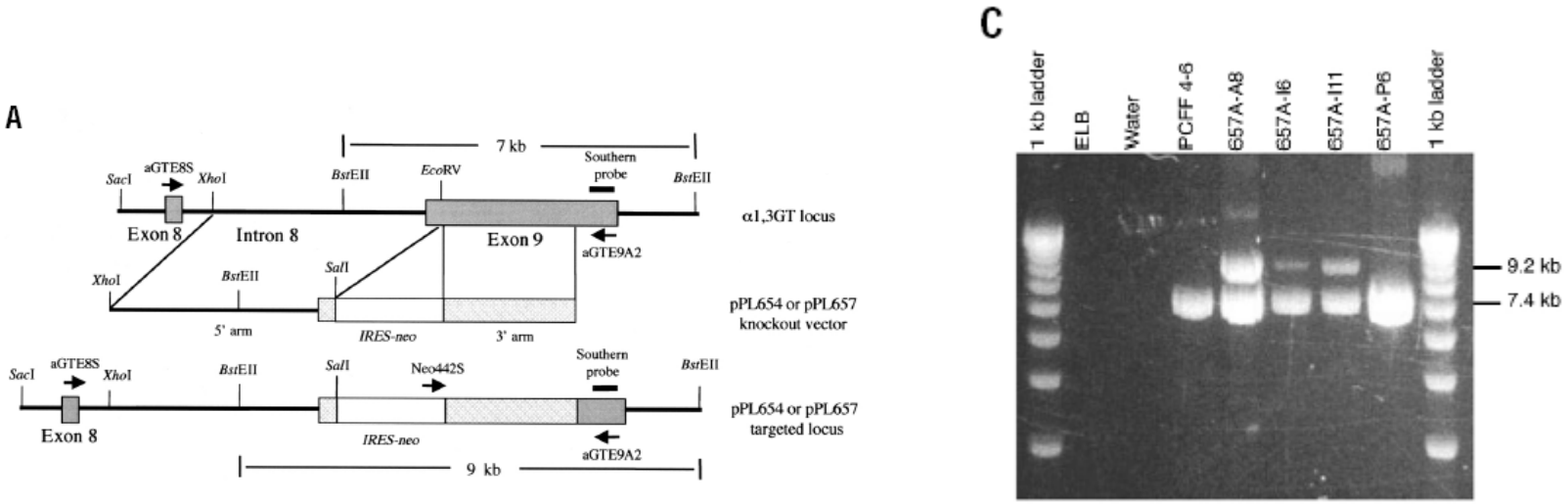


Figure 3. Five α1,3GT gene knockout piglets at 2 weeks of age.

αGT KO hétézygote

KO , 2eme allèle

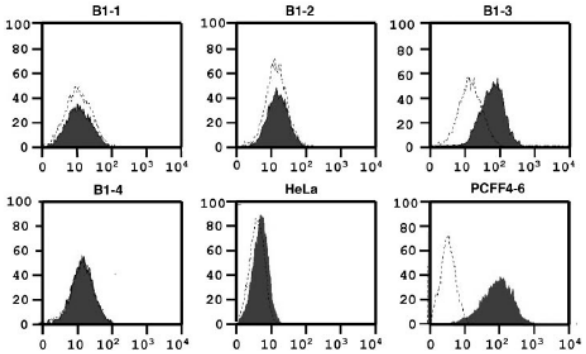


Fig. 1. Flow cytometry analysis of 680B1-1 to B1-4 cells with GS-IB4 lectin staining. Horizontal and

αGT KO homozygote

Dai Y, Nature Biotechnology, 20, March 2002

Phelps, Science January 2003

Heart transplantation in baboons using α1,3-galactosyltransferase gene-knockout pigs as donors: initial experience

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Hearts from α1,3-galactosyltransferase knockout pigs (GalT-KO, *n* = 8) were transplanted heterotopically into baboons using an anti-CD154 monoclonal antibody–based regimen. The elimination of the galactose-α1,3-galactose epitope prevented hyperacute rejection and extended survival of pig hearts in baboons for 2–6 months (median, 78 d); the predominant lesion associated with graft failure was a thrombotic microangiopathy, with resulting ischemic injury. There were no infectious complications directly related to the immunosuppressive regimen. The transplantation of hearts from GalT-KO pigs increased graf survival over previous studies.

on flow cytometry and a low level of cytotoxicity (>20% at 1:2–1:16) to GalT-KO peripheral blood mononuclear cells (PBMC). Pre- and immediate post-transplantation treatment reduced the T cell count to <500 cells/mm^3, but no considerable reduction of B cells (CD20$^+$) was observed.

Both GalT-low pig hearts were rejected within 20 min and showed histopathological features consistent with hyperacute rejection, with diffuse moderate-to-severe IgM deposition, and focal IgG and C4d deposition.

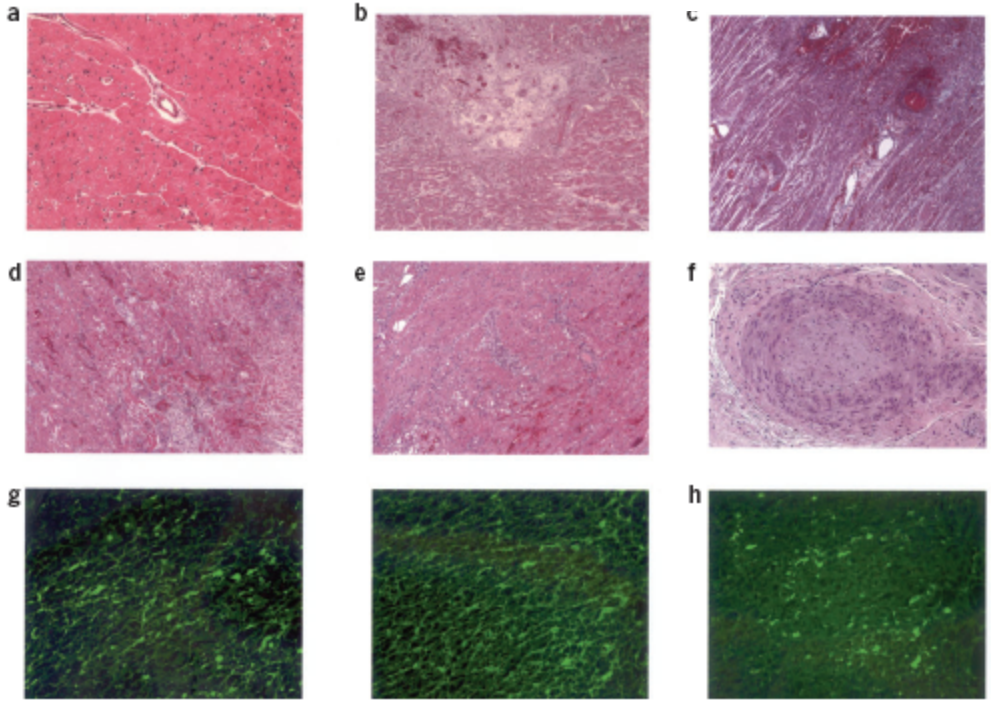
No GalT-KO heart underwent hyperacute rejection, and there were no major complications directly related to the immunosuppressive regimen. Of >100 blood cultures drawn over the course of the experiments, only three were positive; no case was associated with clinical infection. Three baboons died when donor heart contractions remained good, one on day 56 from bleeding and two by euthanasia on days 23 (anemia) and 16 (ischemic limb) (Table 1b). In five baboons, pig heart contractions ceased on days 59, 67, 78, 110 and 179, respectively (median 78 d; mean 99 d); we excised the hearts and continued to monitor the baboons. Graft survival of 179 d is the longest

Group 1: GalT-KO pig donors (*n* = 8)

B214	14	+	–	–	59	TM, focal AHXR, alive
B216	14	+	–	–	>56	Died, heart beating, TM
B218	–	+	–	–	67	TM, focal AHXR, alive
B223	–	+	1–12	(late)	110	MI, TM, AHXR, ACR, vasculopathy, alive
B225	–	+	1–12	–	>23	MI, euthanized, heart beating, mild TM
B226	4	+	–	+	>16	Euthanized, heart beating, minimal TM
B228	4	–	–	+	179	TM, focal AHXR, alive
B229	4	+	1–12	+	78	MI, TM, focal AHXR, alive

Group 2: GalT-low pig donors (*n* = 2)

B220	–	+	–	–	<1	Hyperacute rejection
B222	–	+	–	–	<1	Hyperacute rejection



Aspects sécuritaires

- Le risque viral: les rétrovirus du porc (PERV)
  - risque individuel
  - risque collectif
- Les PERV sont capables in vitro d'infecter des cellules humaines
- Autres virus : NIPAH ou virus H5N1, responsable de la grippe aviaire, décelée dans des échantillons prélevés sur des porcs en 2001 et 2003

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Long-Term Controlled Normoglycemia in Diabetic Non-Human Primates After Transplantation with hCD46 Transgenic Porcine Islets

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Xenotransplantation of porcine islets into diabetic non-human primates is characterized by (i) an initial massive graft loss possibly due to the instant blood-mediated inflammatory reaction and (ii) the requirement of intensive, clinically unfriendly immunosuppressive therapy. We investigated whether the transgenic expression of a human complement-regulatory protein (hCD46) on porcine islets would improve the outcome of islet xenotransplantation in streptozotocin-induced diabetic Cynomolgus monkeys. Immunosuppression consisted of thymoglobulin, anti-CD154 mAb for costimulation blockade, and mycophenolate mofetil. Following the transplantation of islets from wild-type pigs (n = 2) or from 1,3-galactosyltransferase gene-knockout pigs (n = 2), islets survived for a maximum of only 46 days, as evidenced by return to hyperglycemia and the need for exogenous insulin therapy. The transplantation of islets from hCD46 pigs resulted in graft survival and insulin-independent normoglycemia in four of five monkeys for the 3 months follow-up of the experiment. One normalized recipient, selected at random, was followed for >12 months. Inhibition of complement activation by the expression of hCD46 on the pig islets did not substantially reduce the initial loss of islet mass, rather was effective in limiting antibody-mediated rejection. This resulted in a reduced need for immunosuppression to preserve a sufficient islet mass to maintain normoglycemia long-term.

Key words: Complement regulation, diabetes mellitus, islet xenotransplantation, non-human primate, transgenic pigs

Abbreviations: ACR, acute C-peptide response; alloTx, allotransplantation; AST, arginine stimulation test; ATG, antithymocyte globulin; Gal, galactose α1,3-galactose; CRP, complement-regulatory protein; GT-KO, α 1,3-galactosyltransferase gene-knockout; HBSS, Hank's balanced salt solution; hCD46, human CD46 transgenic; IBMIR, instant blood-mediated inflammatory reaction; IEQ, islet equivalent; IVGTT, intravenous glucose tolerance test; LMW-DS, low molecular weight dextran sulfate; MMF, mycophenolate mofetil; NHP, non-human primate; PERV, porcine endogenous retrovirus; RIA, radio immuno assay; SI, stimulation index; STZ, streptozotocin; Tg, transgenic; Tx, transplantation; WT, wild-type; xenoTx, xenotransplantation.

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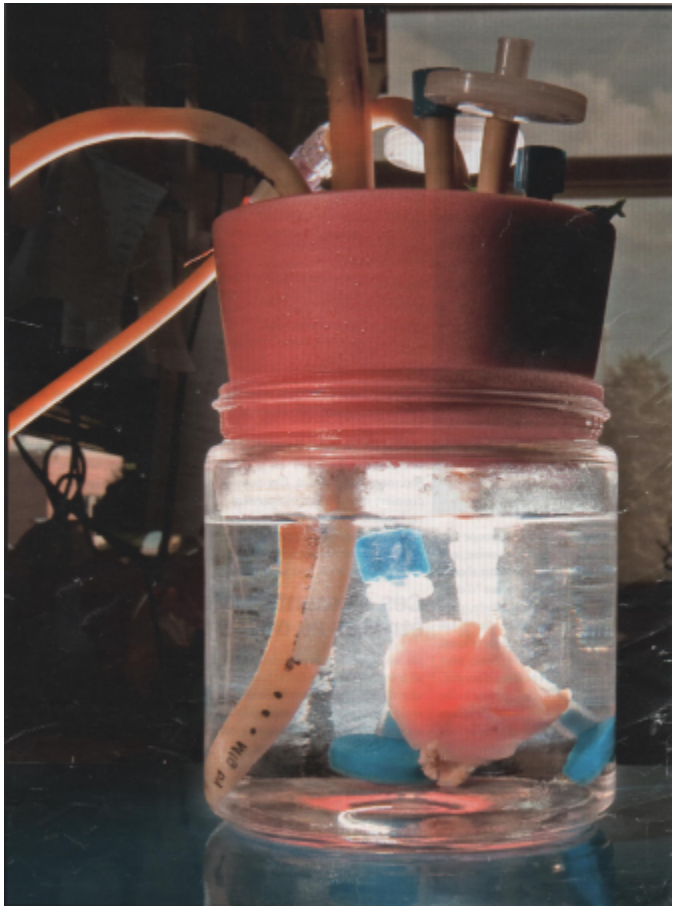
Introduction

Excellent short-term results with islet allotransplantation (alloTx) have been achieved (1). However, the shortage of donor islets, poor long-term outcomes (2) and the risk of allosensitization (3), jeopardizing future kidney transplantation (Tx) in type 1 diabetic patients, have led to active discussions about future directions of this field (4–7). The need for data indicating the efficacy of alternative islet sources in non-human primate (NHP) models has been highlighted (4). Successful xenotransplantation (xenoTx) of porcine insulin-producing cells into diabetic patients could restore physiologic islet function, without the risk of allosensitization (8). Pig insulin has been successfully used for years in treating diabetic patients. Long-term pig islet survival under a limited immunosuppressive protocol would significantly expand the clinical applicability of β-cell replacement therapy for diabetes.

Previously, two groups demonstrated the feasibility of pig islet Tx in NHP (9,10). One group achieved function of adult

Cellules souches et médecine régénérative

Cellules souches et médecine régénérative



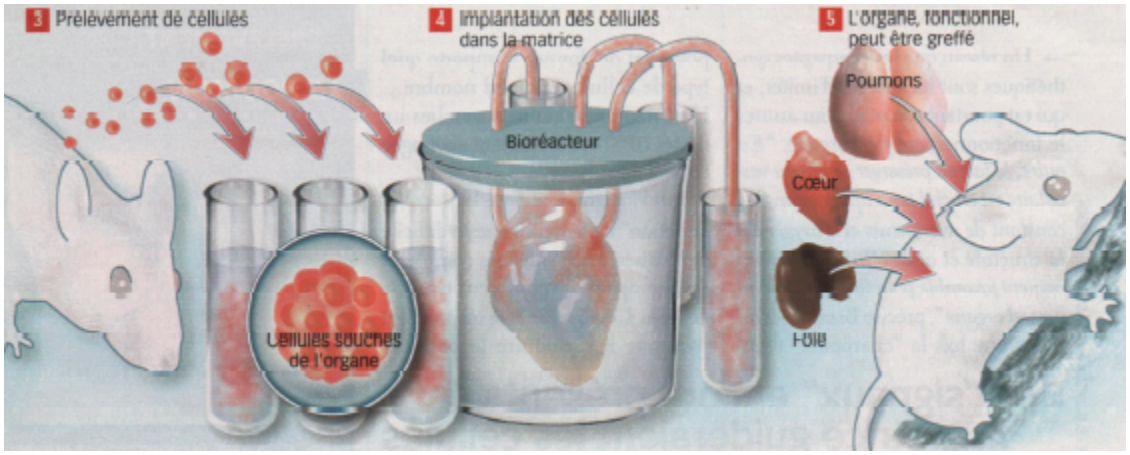
Cellules souches

Cellules souches embryonnaires : cultivées à partir de cellules issues d'embryons à un stade très précoce

Cellules souches adultes : présentes dans divers tissus (moelle +++, tissu adipeux , peau, muscle …)

iPS : induced pluripotent stem cells :cellules de la peau reprogrammées en cellules souches

Régénération d'organes ?



Recoloniser une matrice d'organe par des cellules souches du receveur ? -→ Greffe

Merci
et
Vive la recherche !

Merci
et
Vive la recherche !