Anticorps anti-HLA et Transplantation Rénale

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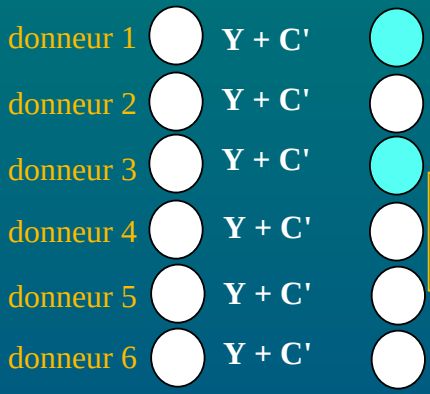
Dépistage

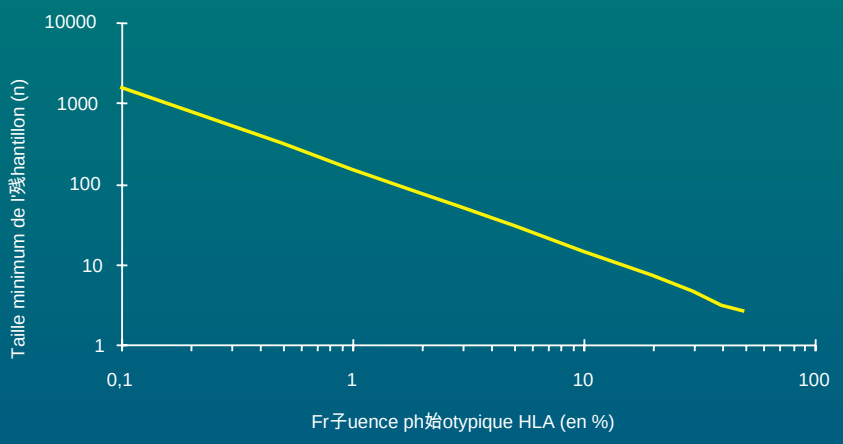
Test de LymphocytoToxicité



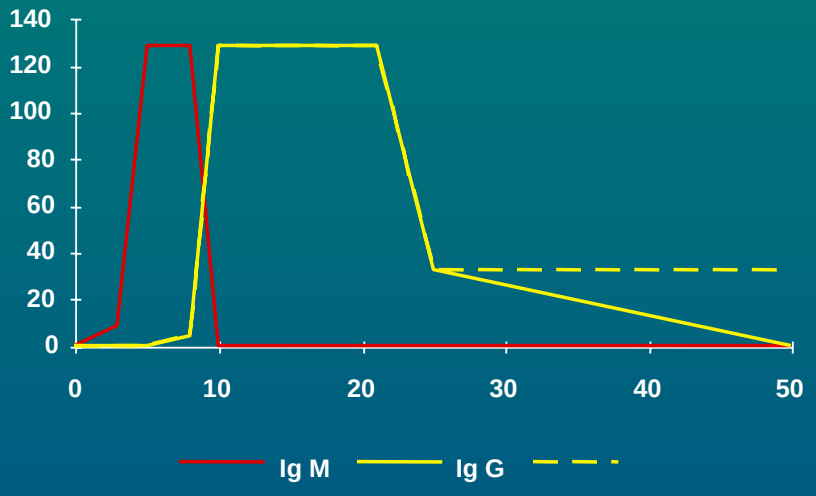
TLT: 2 / 6 33%

DATE	T	B	IgM	IgG	Spec.
1/1/92	12/40	2/10			A2

Une limite technique.....



Cinétique



Paramètres

- Spécificité: auto, classe I, II, non HLA
- Temps: historique, Tx, post-Tx
- Isotype: IgM, IgG, IgA
- Mécanisme d'action: Cytotox, ADCC, activation

soit 108 possibilités..... !!!

Anticorps anti- Classe I

- induits par les TRANSFUSIONS, la TRANSPLANTATION, les GROSSESSES
- responsables de rejets AIGUS

Anticorps anti- Classe II

- essentiellement induits par la TRANSPLANTATION
- entrainent la perte du greffon de maniere retardée, mais aussi responsables de rejets aigus
- tres importants en cas de 2。 transplantation

Autoanticorps

- FREQUENTS: 16% pour Suciu-Foca sur 727 pts
- SANS INFLUENCE SUR LE DEVENIR DE LA GREFFE

Première Stratégie.....

· EVITER L'IMMUNISATION !.....

IMMUNISATION DANS LE SYSTEME HLA

PRE-SENSIBILISATION

ANTICORPS	Nbe Pts	TR ant.	Sexe (M/F)	Multipares	P.R.A.
Transitoires	14	1	8/6	75%	44%
Persistent	40	40	20/20	30%	85%
Persistent	19	0	**1/18**	**89%**	77%

Scornik Transpl. 1984;37:249-253

IMMUNISATION DANS LE SYSTEME HLA

PRE-SENSIBILISATION

30 patients avec Rejet Irreversible

25 (83%) P.R.A. -

5 (17%) P.R.A. +

7 sans BT

18 BT

0 P.R.A. +

13 (72%) P.R.A. +

Scornik Transpl. 1984;38:594-598

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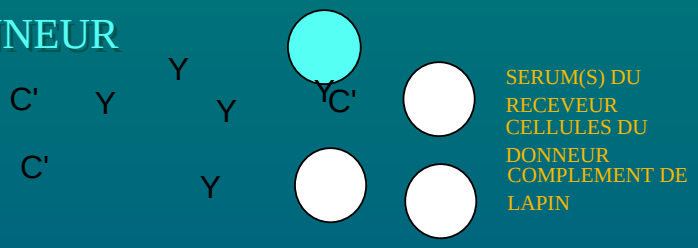
IMMUNISATION DANS LE SYSTEME HLA

PRE-SENSIBILISATION

ANTICORPS après BT	Nbe Pts	FACS pre-BT
Transitoires	9	1 (11%)
Absents	12	1 (8%)
Persistant	14	9 (64%)

Le Cross-Match

RECHERCHE D'Ac DIRIGES CONTRE LE DONNEUR



-SUR CELLULES T (ganglion) : RECHERCHE D'ANTI-CLASSE I

-SUR CELLULES B (rate) : RECHERCHE D'ANTI-CLASSE II

-"CHAUD" ou "FROID"

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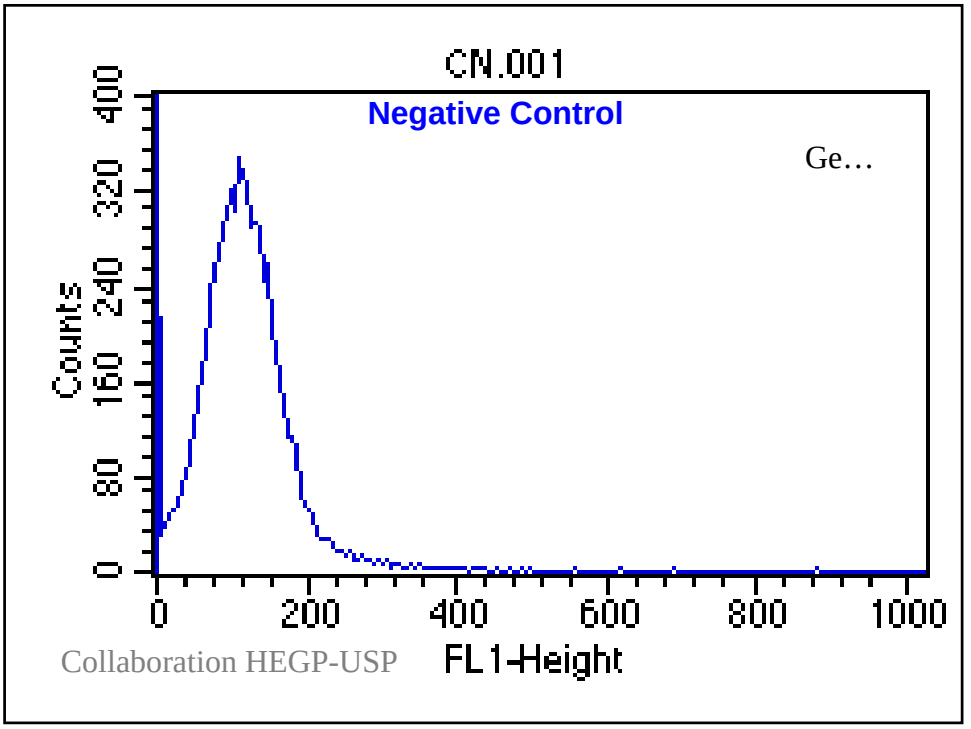
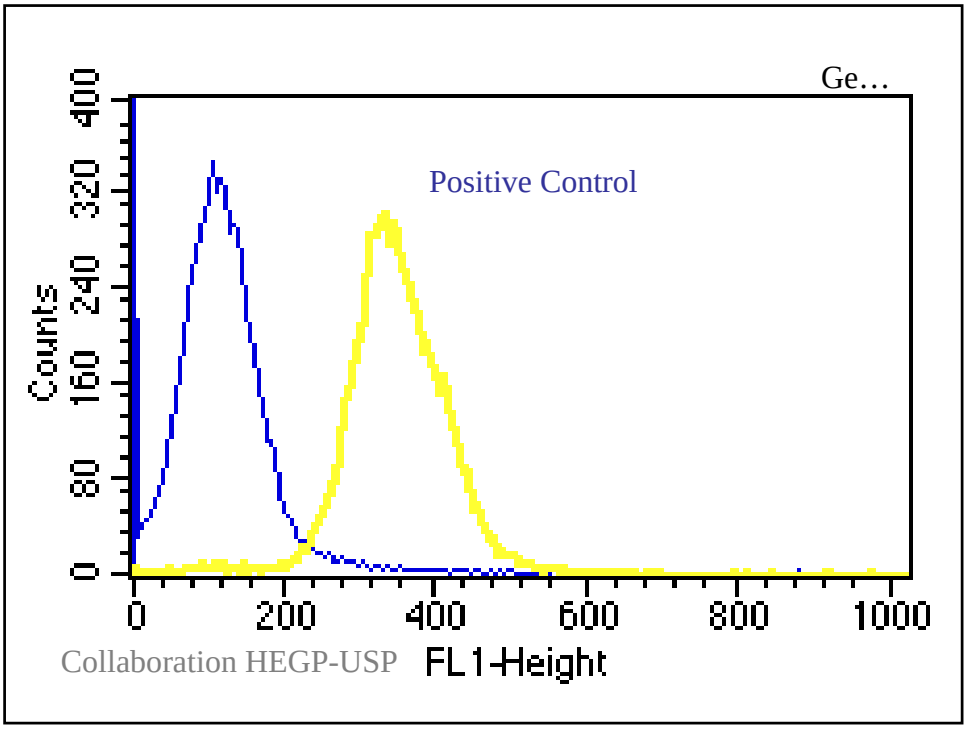
Les Cross-matches....

- Cytotoxique "classique" CDC
- Cytotoxique "sensibilisé" AHG
- Par Cytométrie de Flux


CN.001
Negative Control
Ge…
Counts
0
80
160
240
320
400
0
200
400
600
800
1000
Collaboration HEGP-USP
FL1-Height


Ge…
Positive Control
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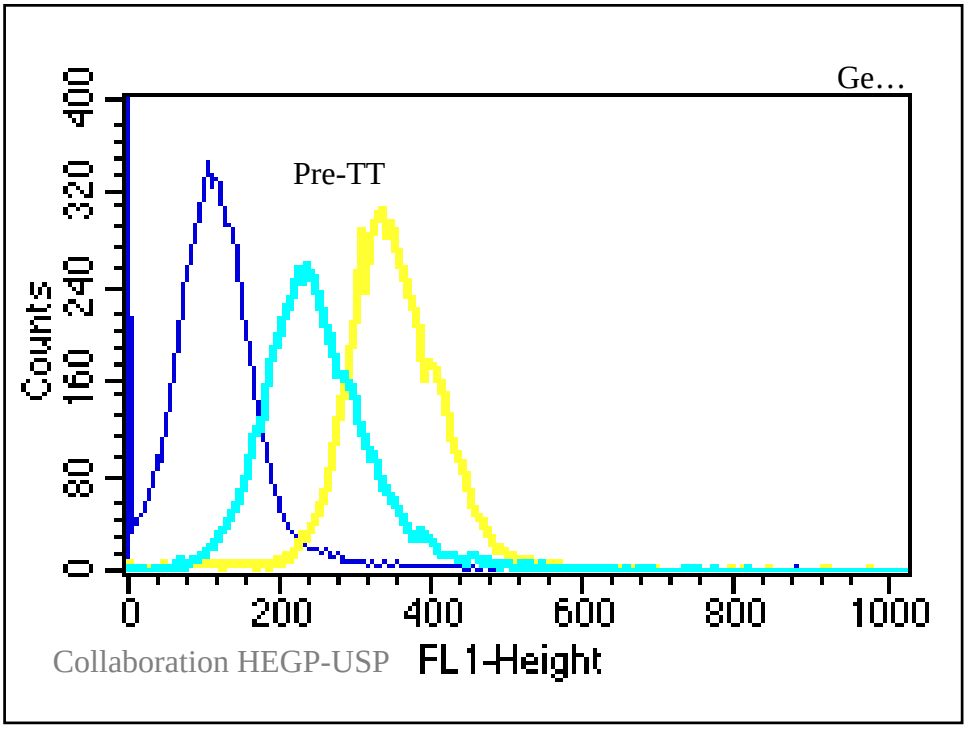
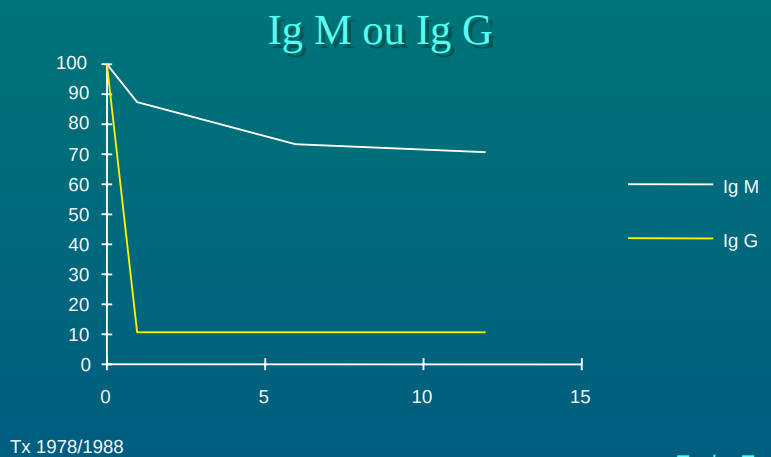
Collaboration HEGP-USP
FL1-Height



Isotype

- M: sans importance.....
- G: pathogénes
- A: protecteurs.....

Cross-match CDC anti T (classe I)



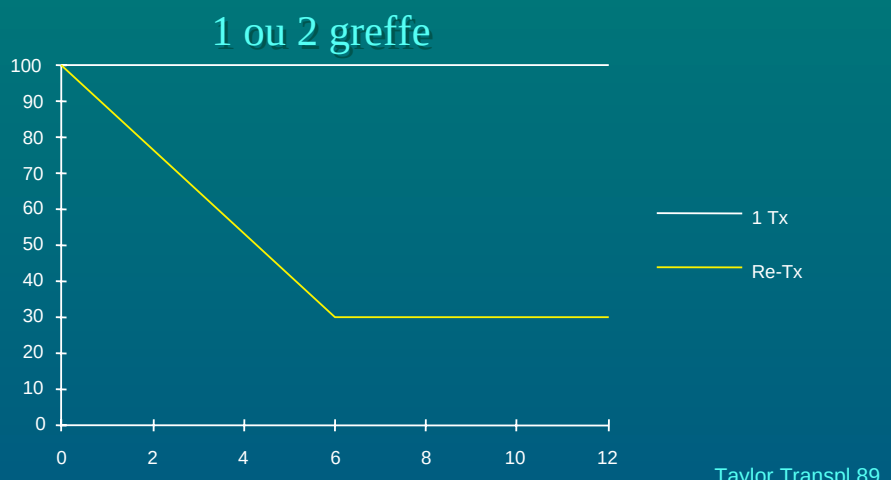
Tx 1978/1988

Taylor Transpl 89

Cross-match CDC anti B (classe II)

- HLA, non HLA
- Ig G, Ig M
- 1 ou 2 greffe

Cross-match anti classe II



Taylor Transpl 89

Ac anti-HLA pre-TX et perte du greffon

	ELISA			CDC		
	<10%	10-50%	>50%	<10%	10-50%	>50%
Perte de Greffon	12	3	5	13	5	2
Pas de perte	88	13	3	73	28	3

p<0,0009

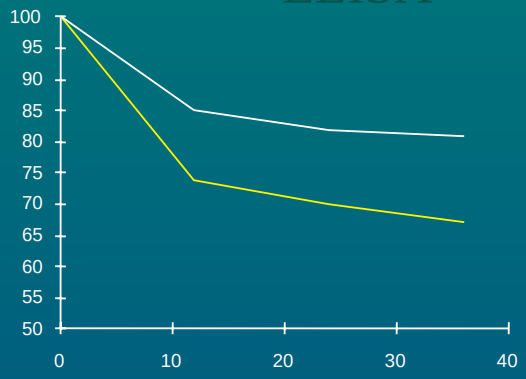
p=0,2

124 Tx 1991-1994

Monteiro Transpl. 97

Survie du greffon: Ac avant TR

ELISA

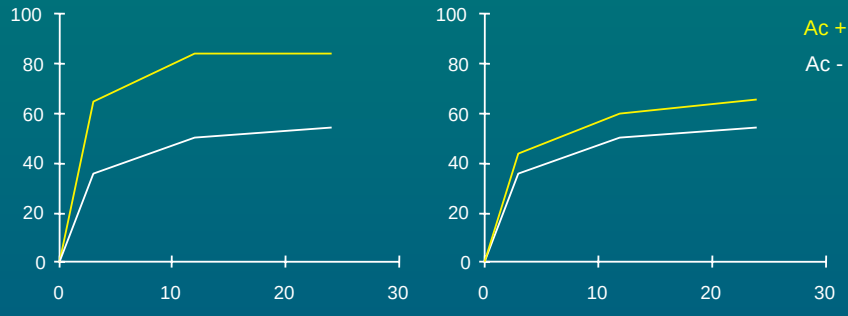


n= 181
Ac +
Ac -
n=312
p < 0,001

Kerman Transpl 96

Anticorps et fréquence des rejets

ELISA/CDC serum pre-Tx



ELISA (P < 0,05)

CDC (ns)

136 premières greffes pédiatriques

Dalla Vecchia Transpl 97

LA STRATEGIE

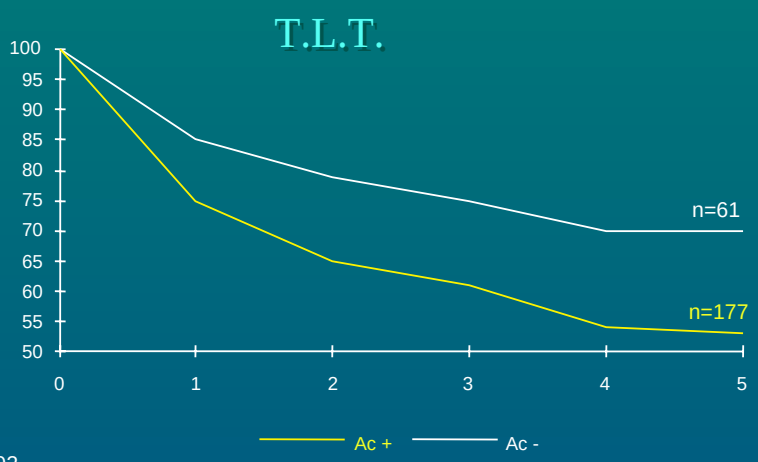
EVITER L'IMMUNISATION !

- RECHERCHE SIMPLE PAR TLT
- RECHERCHE D'ANTI-CLASSE II
- ELIMINATION DES Ig M ET AUTOANTICORPS
- DETERMINATION DES SPECIFICITES
- RECHERCHE REGULIERE POST-Tx

Immunological risk assessment	Risk categories		
CM donor-reactive, HLA-specific, IgG	*High risk*	*Intermediate risk*	*Low risk*
Current positive direct CDC	**x**		
Current positive AGH-CDC	**x**		
Current positive flow-CM only	**x**		
Historic positive direct CDC		**x**	
Historic positive AGH-CDC		**x**	
Historic positive flow-CM only		**x**	
Current and historic negative CDC			**x**
Current and historic neg AGH-CDC			**x**
Current and historic negative flow-CM			**x**

Gebel HM, AJT 2003.

Survie du greffon: Ac apres TR



87/92

Barr, Transpl. Proc. 93

Survie du greffon: Ac après TR

Cross-match

64 patients 1987/1989

	13 avec Ac	51 sans Ac	
p < 0,0005	100%	41%	Rejet
p < 0,005	80%	32%	Rejet Sévére
p < 0,002	38%	4%	Perte de G.

Halloran Transpl. 92

Anticorps et sévérité du rejet

206 patients 1990/1993

82 avec rejet — 124 sans rejet

63 rejets Ac - — 19 rejets Ac +

9% — 79% — Perte du greffon 1 an

Lobo Transpl. 95

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Anticorps et sévérité du rejet

64 patients 1987/1989

	13 avec Ac	51 sans Ac	
p < 0,0005	100%	41%	Rejet
p < 0,005	80%	32%	Rejet Sévére
p < 0,002	38%	4%	Perte de G.

Halloran Transpl. 92

Théorie Humorale

Toute perte de greffon est précédée de l'apparition d'anticorps anti-HLA anti classe I ou classe II

Terazaki, A.J.T. 2003

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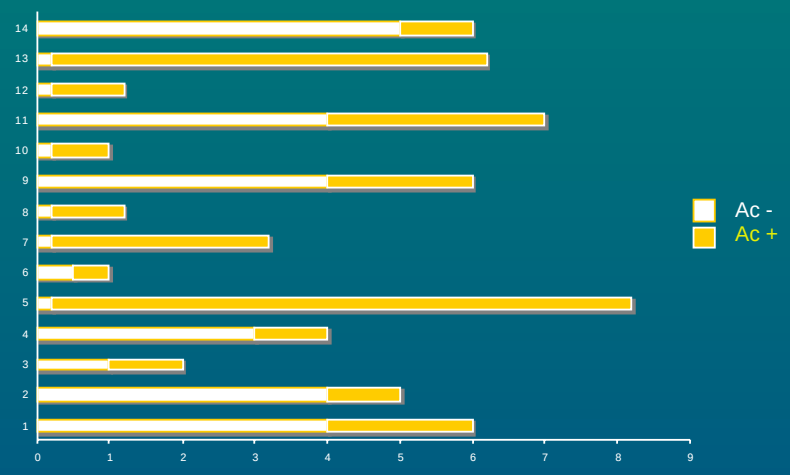
Théorie Humorale



Pre-Tx suppression of Anti-HLA antibodies

- Drugs
- IVIg
- IVIg/PP
- IVIg/Cyclophosphamide
- Rituximab

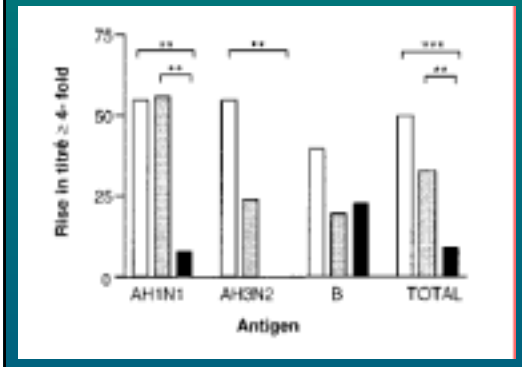
Cellcept

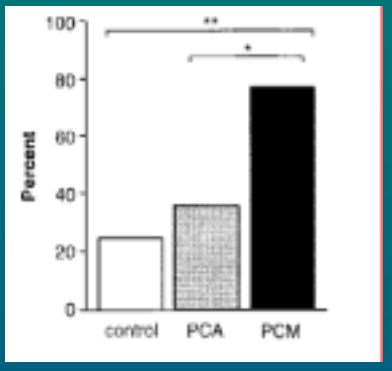
Vaccination under Cellcept therapy

- 38 pts, 25 cyA-P-Aza, 13 cyA-P-Cellcept
- 20 controls
- Ab response to Influenza vaccine

Smith, N.D.T. 1998

Cellcept





Smith, N.D.T. 1998

IVIg: IntraVenous Immunoglobulins

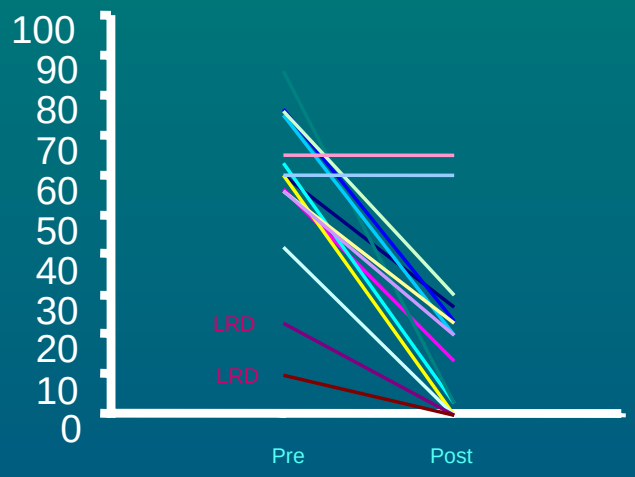
- High dose
- with Plasmapheresis: IVIg/PP
- with cyclophosphamide: Cy/IVIg

Glotz et al

Jordan et al

Ratner et al

Desimmunization results



IVIg coupled to Plasmapheresis

John Hopkins

- 18 patients
- 8 cytotoxic XM +, 10 flow XM + (class I or II)
- 5 re-Transplants
- Combination of PP and IVIg
- 5 acute rejections, C4d positive

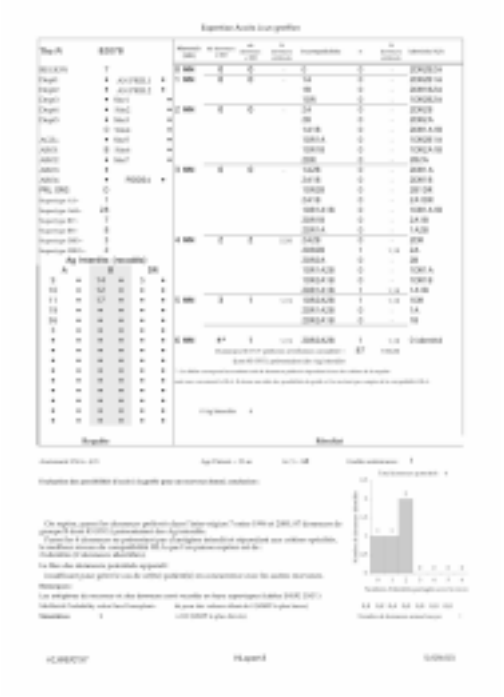
Montgomery, Trans Proc 2002

Rituximab and anti-HLA Abs

work in progress...

- 9 pts with 3 dose regimens (50-150-375mg/m2)
- 1 success: 87 to 51% PRA
- 1 decrease in titer
- some modifications....

Viera, Transpl. 2004



Post-Tx suppression of anti-HLA antibodies

- IVIg
- IVIg/PP
- Rituximab
- Tacro-Cellcept

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Post-Tx suppression of anti-HLA antibodies

High Dose IVIg

- 17 patients
- 13 rejections CR, 4 AbR
- Patient survival 18 months: 94%
- Graft survival 18 months : 71%

Luke, Transpl 2001

Post-Tx suppression of anti-HLA antibodies

IVIg/PP

- 16 patients
- 100% StR, 50% AbR
- Graft survival at 1 year: 81% (84%)

Rocha, Transpl 2003

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Post-Tx suppression of anti-HLA antibodies

Rituximab

- 17 pts with AHR
- Failure of IVIg/PP or histology
- 2 losses
- Creat from 4.1 to 2.8 at month 2

Montgomery, ATC 2004

We can learn to live with them...

ABO mismatch

		IgG			IgM		
Pt	A.H.R.	Baseline	Tx	1 year	Baseline	Tx	1 year
1		64	1	64	16	<1	4
2		64	1	2	4	<1	1
3		64	2	2	32	1	4
4		32	<1	4	16	<1	2
5		16	<1	2	4	<1	4
6		128	8	16	32	4	16
7	+	512	8	8	16	<1	2
8	+	128	8	2	8	1	1

Gloor, Transpl 2003

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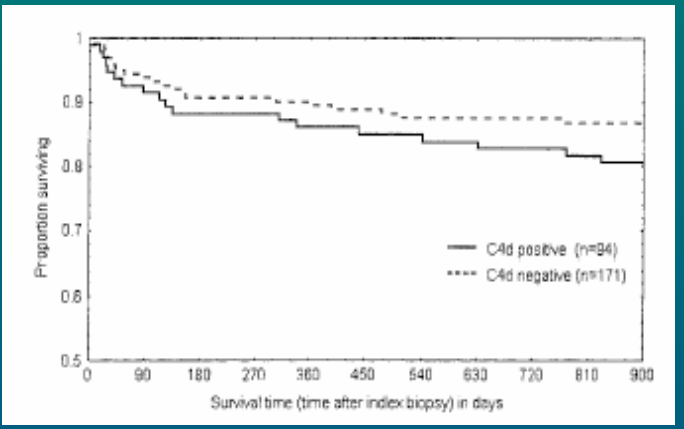
We can learn to live with them...

HLA mismatch

- Low titer at transplant
- C4d positive subclinical rejections
- Accommodation ?

We can learn to live with them...



Nickeleit, J.A.S.N. 2002

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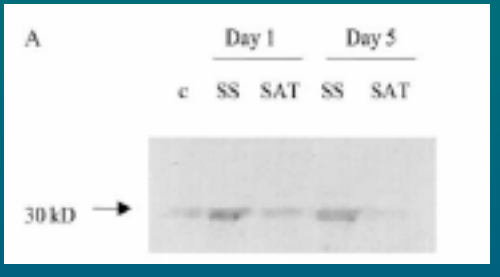
We can learn to live with them...

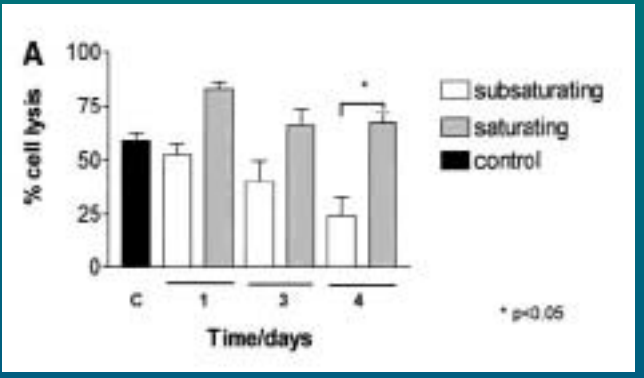
Protective gene Up-regulation



Salama, A.J.T. 2001

We can learn to live with them...

Acquired resistance to C-mediated lysis



Salama, A.J.T. 2001

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The challenge ahead....

is a change of paradigm !

- More and more sensitive testings....
- More and more sensitized patients....
- More and more anti-donor antibodies....

The existence of anti-donor antibodies may not be an absolute contra-indication to transplantation !