CDB

Centre de Diagnòstic Biomèdic

Avenços en histocompatibilitat en el trasplantament d'òrgans sòlids

Eduard Palou
Secció d'Immunologia del Trasplantament
Servei d'Immunologia

CLÍNIC
BARCELONA
Hospital Universitari

Jornada de Recerca i Docència del CDB, 19 de novembre de 2019

CLÍNIC BARCELONA Hospital Universitari

Laboratori d'Histocompatibilitat

Centre de Diagnòstic Biomèdic CDB

Secció d'Immunologia del Trasplantament (Servei d'Immunologia)

Organització Catalana de Trasplantaments (OCATT)

Unitats de Trasplantament Renal infantil:

- Hospital Infantil Vall d'Hebron
- Hospital Sant Joan de Déu

Unitats de Trasplantament Renal en adults:

- Hospital Vall d'Hebron
- Hospital de Bellvitge
- Hospital Clínic
- Fundació Puigvert (Hospital de Sant Pau)
- Hospital del Mar
- Hospital Germans Trias i Pujol

Unitats de Trasplantament Pancreàtic:

- Hospital Clínic
- Hospital Germans Trias i Pujol

Unitats de Trasplantament Hepàtic:

- Hospital Clínic
- Hospital Vall d'Hebron
- Hospital de Bellvitge

Unitats de Trasplantament Cardíac:

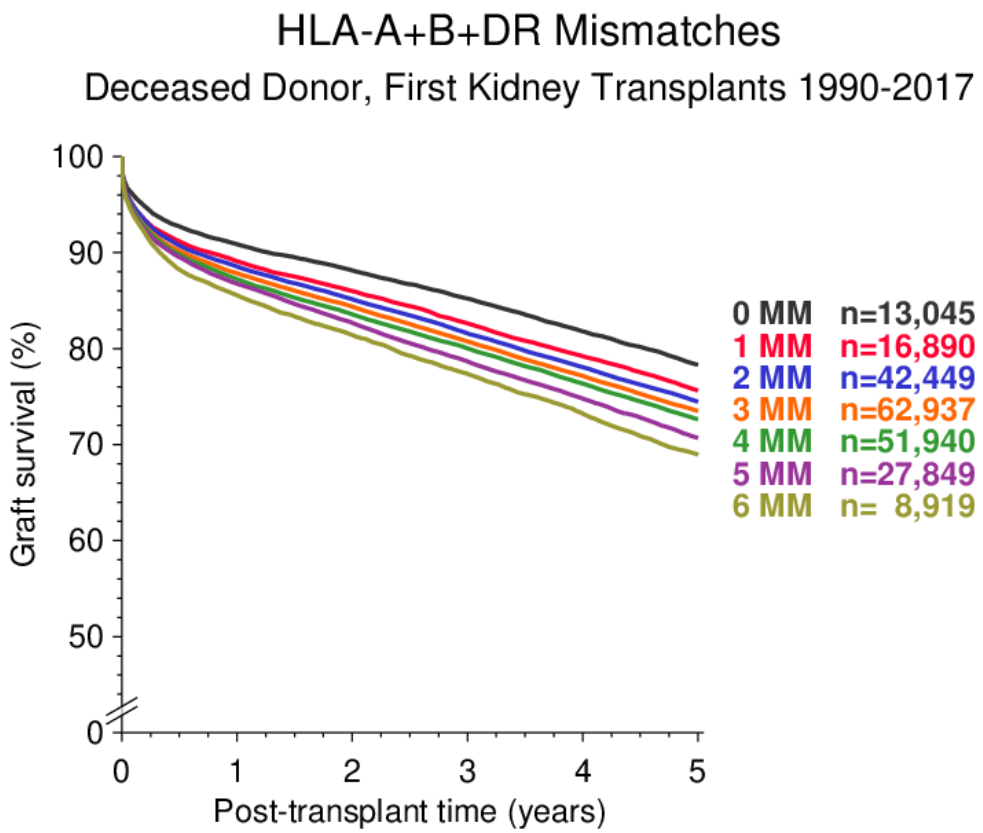
- Hospital Clínic
- Hospital de Sant Pau
- Hospital de Bellvitge

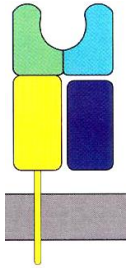
Unitats de Trasplantament Pulmonar:

- Hospital Vall d'Hebron

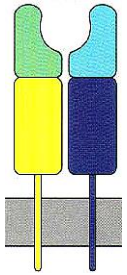
Histocompatibilitat - HLA

HLA: Complexe Major d'Histocompatibilitat (MHC) en humans



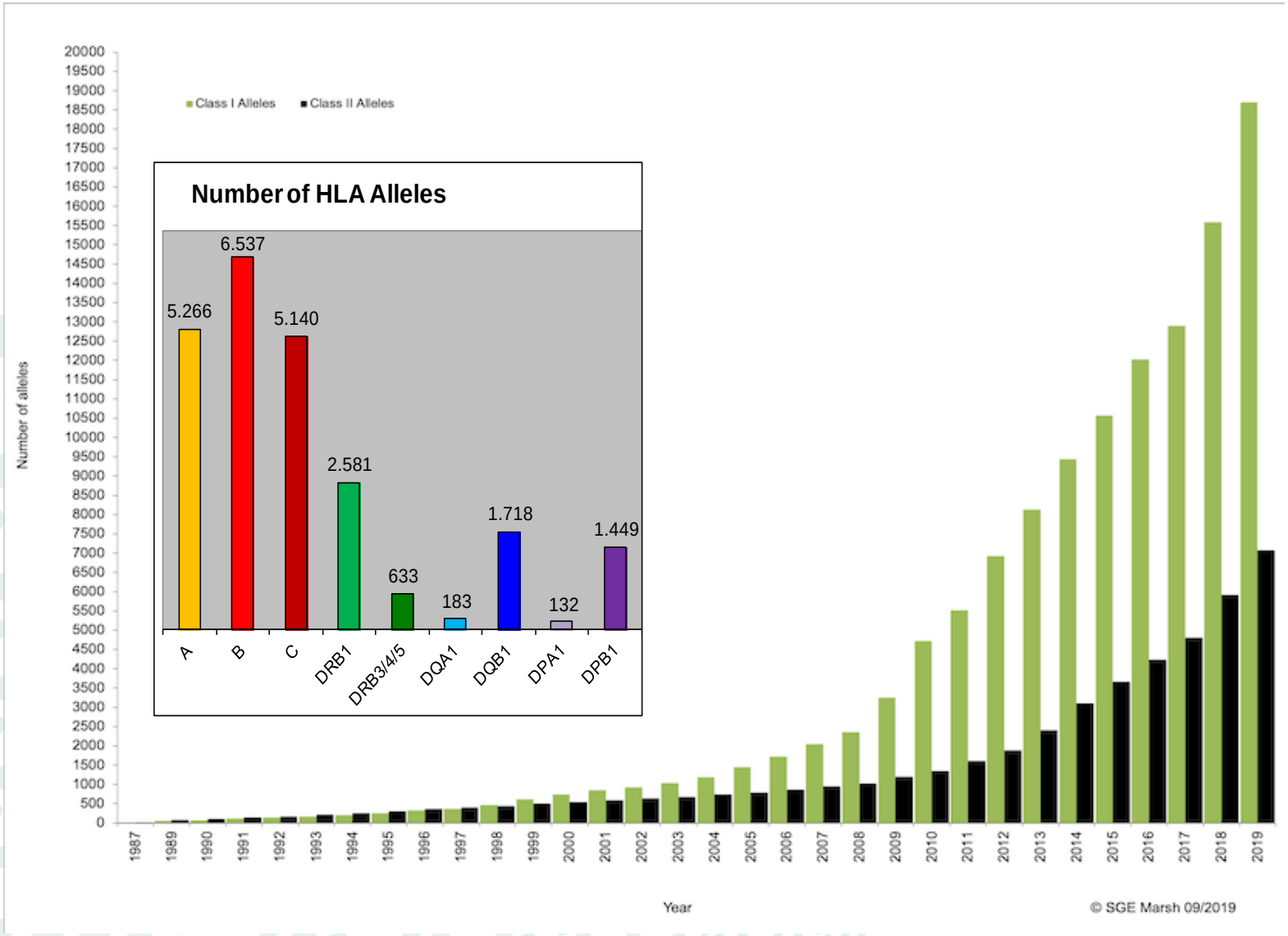


HLA Classe I
(A,B,C)

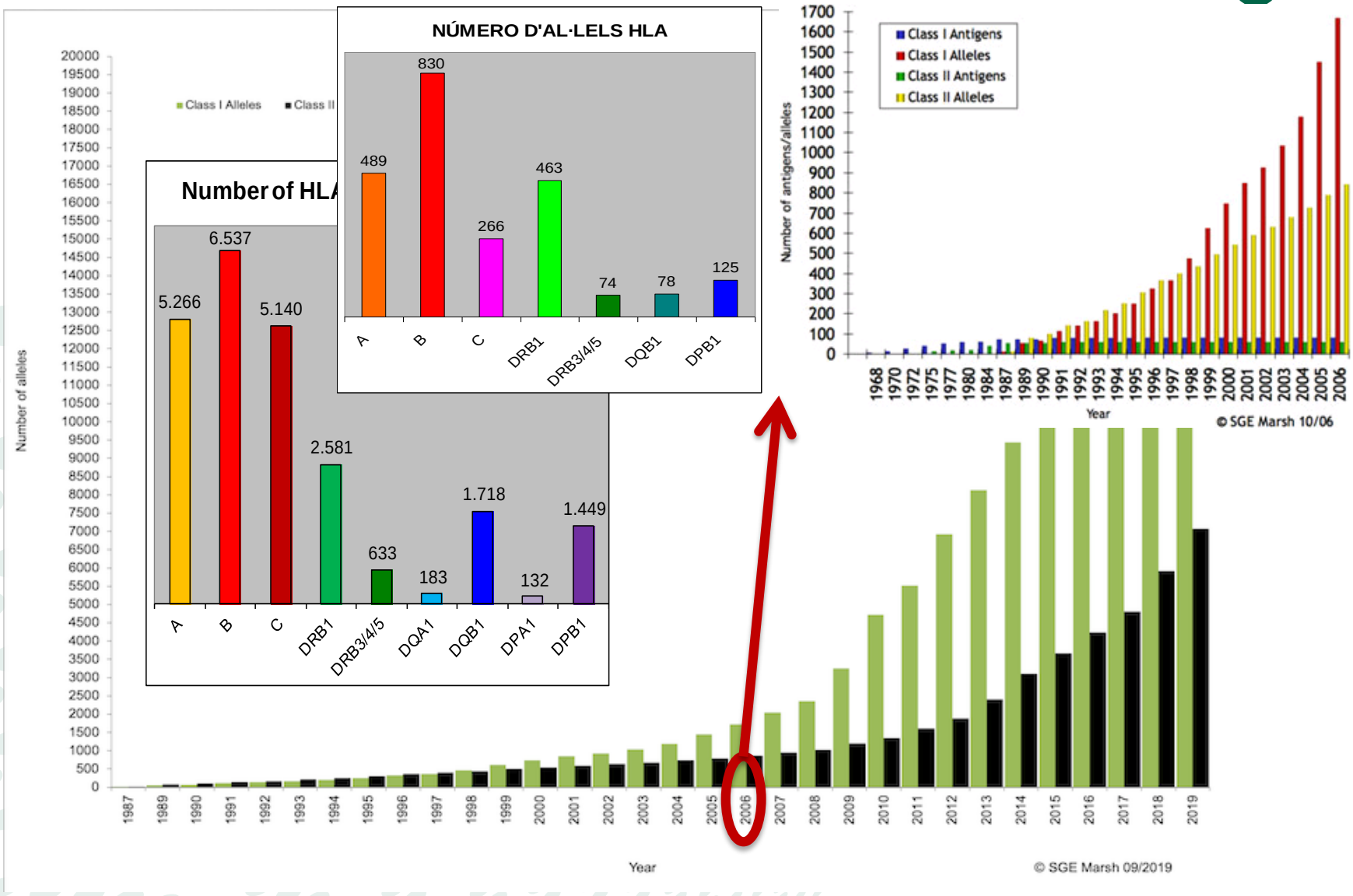


HLA Classe II
(DR,DQ,DP)

Tipificació HLA



Tipificació HLA



Tècniques de tipificació HLA Baixa/Alta Resolució

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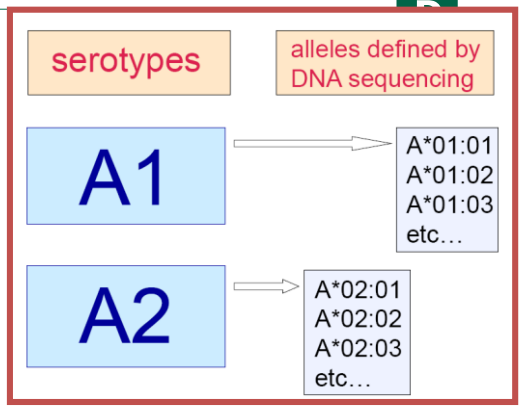
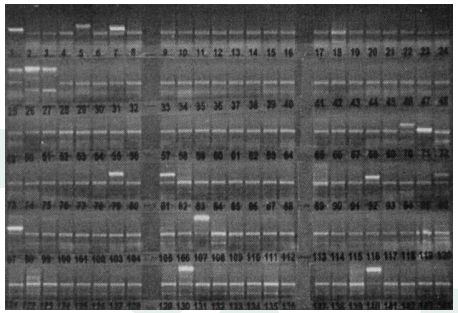
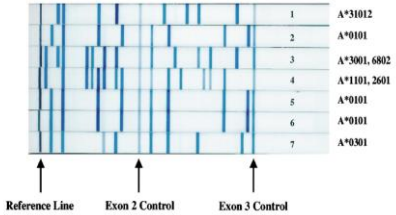


- PCR-SSP: Primers específics de seqüència

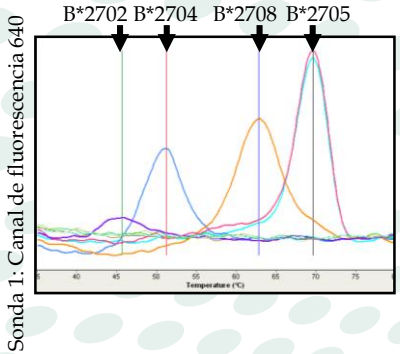


- PCR-SSO: Oligonucleòtids (sondes) específiques de seqüència

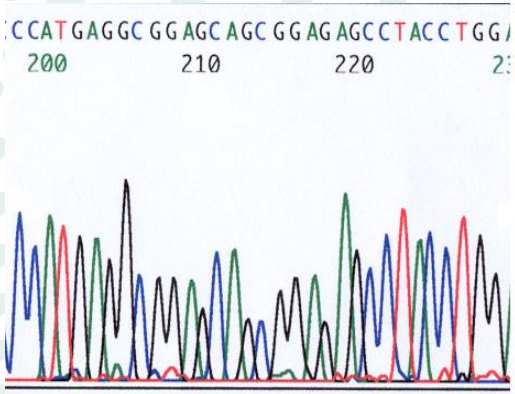


Luminex

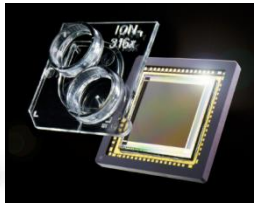
- PCR a temps real



- PCR-SBT: Seqüenciació directa



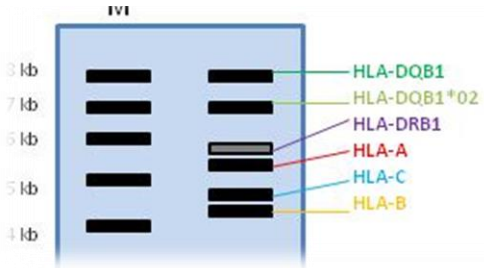
- NGS: Seqüenciació de nova generació

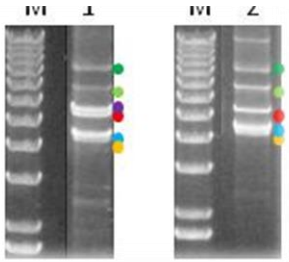


Tipificació HLA

- NGS: Tipificació HLA d'alta resolució

  Receptors en llista d'espera i donants vius

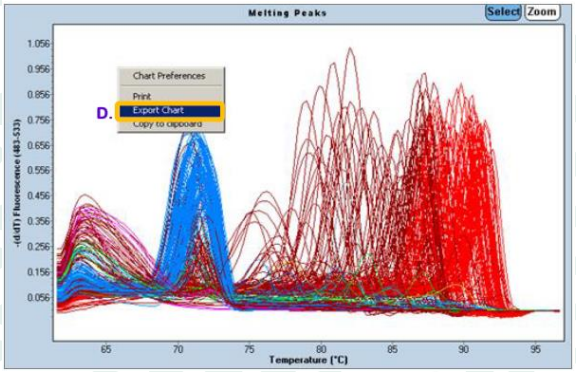


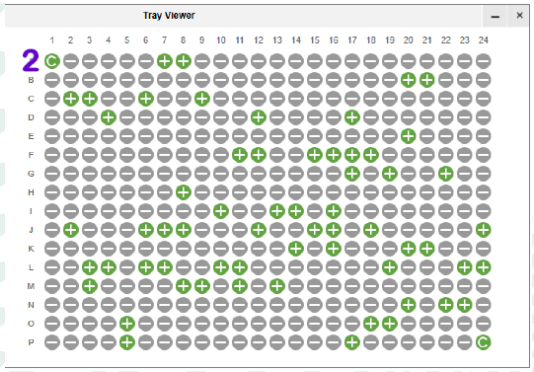


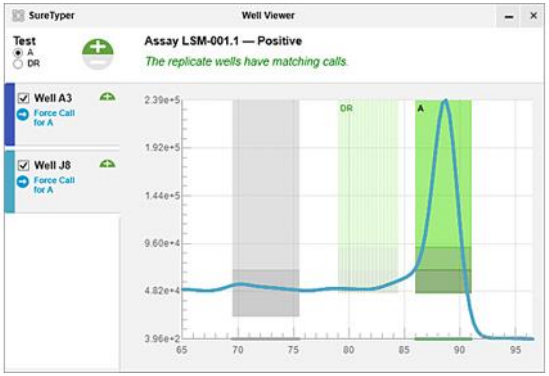
BANC DE SANG I TEIXITS

- PCR a temps real: Tipificació HLA-A,B,C,DRB1,DRB3/4/5,DQA1,DQB1,DPA1,DPB1

  Donants cadàver

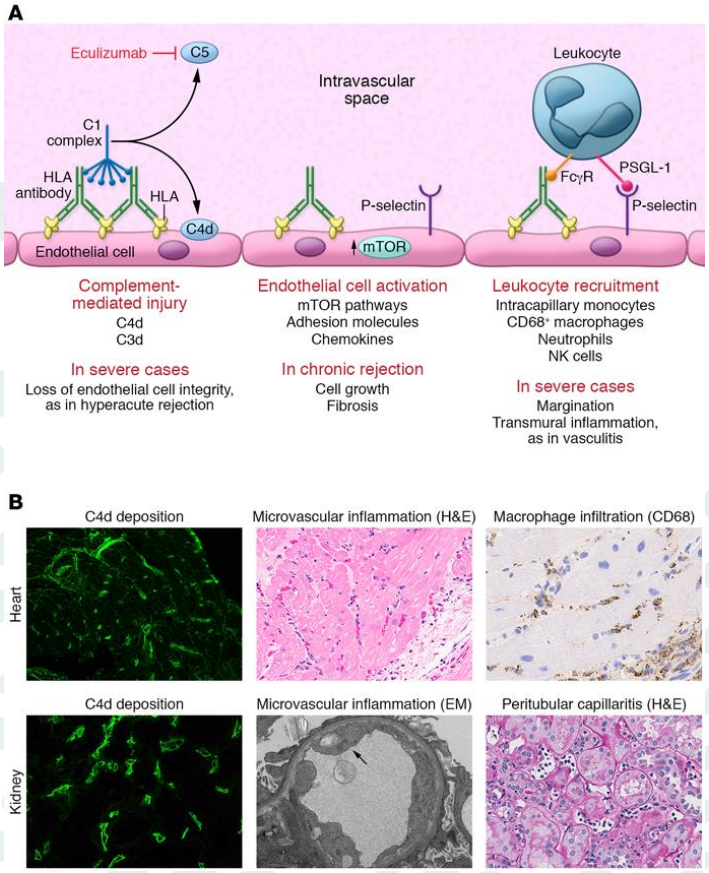




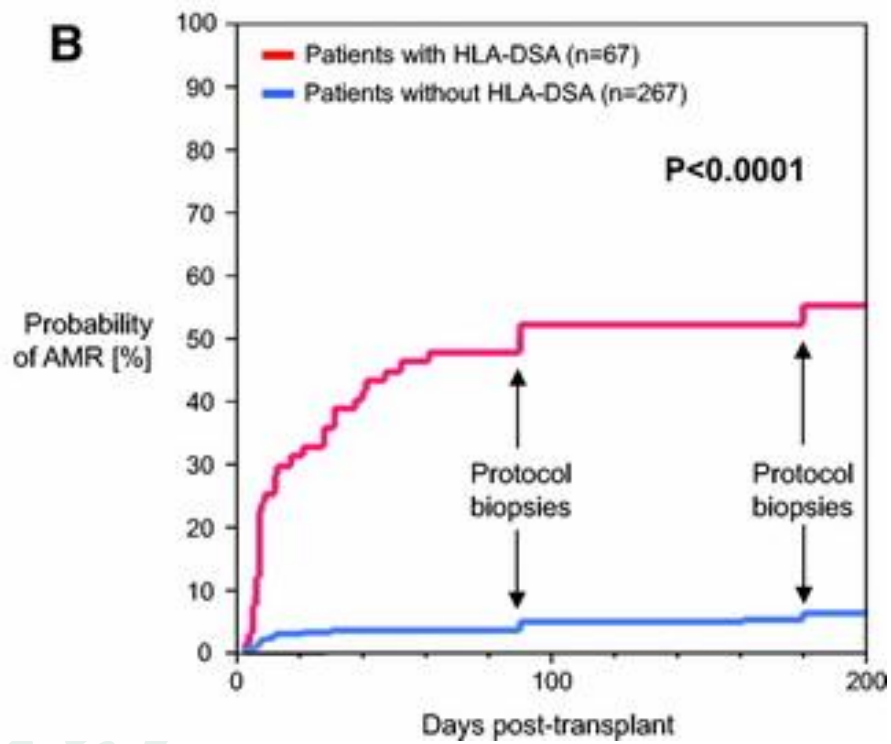


Anticossos anti-HLA

Rebuig mediat per anticossos (AMR)



Valenzuela, Reed. J Clin Invest 2017



Clinical relevance of pretransplant donor-specific HLA antibodies detected by single-antigen flow-beads.

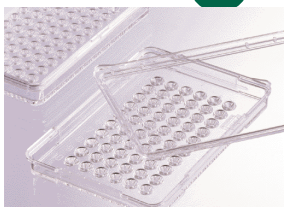
Amico et al. Transplantation 2009

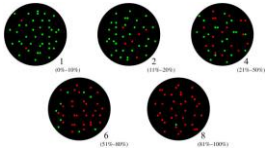
Determinació d'anticossos anti-HLA

- Cribratge:

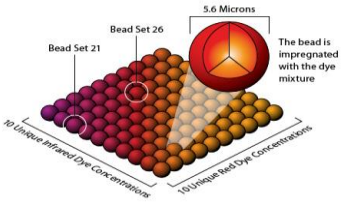
  - Citotoxicitat CDC-PRA (Panel Reacting Antibodies):

    Millor predictor del risc de XM-CDC Positiu





  - **Fase Sòlida (Luminex)**: Més sensible

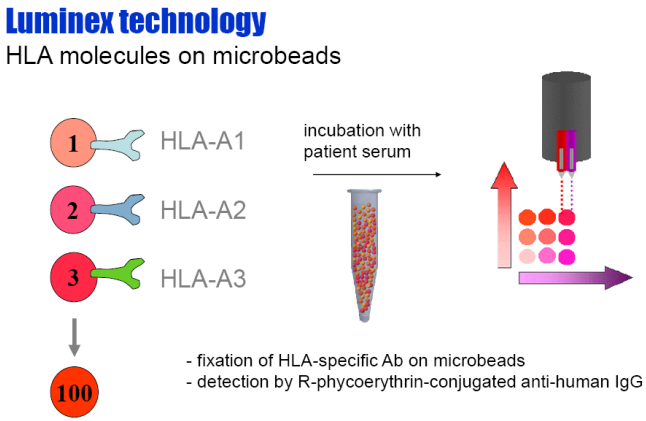


- Assignació de l'especificitat:

  - Citotoxicitat (CDC-PRA)

  - **Antigen Aïllat** (Single Antigen):

    Predictor XM CDC i FC Negatiu,
    inclús en pacients hipersensibilitzats



cPRA: % de positivitat en front un panell de donants

Determinació d'anticossos anti-HLA

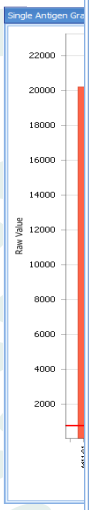
- Citotoxicitat (CDC-PRA):

Sera Screening Report By TRAY ID 2019.11.12

Traylot	Trayloc	Seraid	Name Specificity	Aveg	Sample Date Tpos	ABO Fneg	M/C	#Rxn Fpos	#Pos Tneg	# 8 Rxn Incl	%Pos Strg	Rval	Chsq
C3822	08C				. .		C	32	1	0	3.1		
			Overall	6.000	1	1		0	30	50.0	0.000	0.696	15.5
			B45	6.000	1	1		0	30	50.0	0.000	0.696	15.5
C3822	08B				. .		C	32	0	0	0.0		
C3822	08A						C	32	0	0	0.0		

Single Antigen Analysis

Bead Count	Antigen ID	Cut-off	Raw Value	MFI/LRA	Assignment	BG Adjusted	AD-MFI	AD-BG Adjusted	A	B	C	Bw	A Serology	B Serology	C Serology	Raw Value Graph	RAD	Epitopes
69	149	3.88	8673	299.07	Positive	8516	8596	8440		B*27:05		Bw4		B27			1.0090	76ED
94	148	3.82	8580	295.86	Positive	8417	8371	8212		B*27:03		Bw4		B27			1.0250	76ED
112	164	3.98	4255	146.71	Positive	4087	4350	4178		B*47:01		Bw4		B47			0.9780	76ED
91	153	3.74	2586	89.17	Positive	2435	2781	2618		B*37:01		Bw4		B37			0.9300	76ED
104	160	3.77	2511	86.59	Positive	2355	2521	2364		B*44:02		Bw4		B44(12)			0.9960	199V
77	161	4.10	2406	82.97	Positive	2229	2389	2214		B*44:03		Bw4		B44(12)			1.0070	199V
74	177	3.55	1167	40.24	Positive	1037	1035	919		B*67:01		Bw6		B67			1.1280	
90	172	4.07	841	28.98	Positive	661	967	760		B*55:01		Bw6		B55(22)			0.8690	
95	159	4.19	750	25.86	Negative	559	804	599		B*42:01		Bw6		B42			0.9330	
87	118	3.96	628	23.70	Negative	452	672	483	A*29:02				A29(19)				0.9350	
87	136	3.84	614	21.17	Negative	457	612	456		B*08:01		Bw6		B8			1.0030	
93	155	3.68	540	18.62	Negative	396	530	389		B*39:01		Bw6		B3901			1.0180	
97	154	3.66	525	18.10	Negative	381	520	377		B*38:01		Bw4		B38(16)			1.0100	
86	117	3.99	457	17.23	Negative	280	545	334	A*29:01				A29(19)				0.8380	
101	171	3.93	362	12.48	Negative	196	393	213		B*54:01		Bw6		B54(22)			0.9210	
92	158	3.78	293	10.09	Negative	141	312	150		B*41:01		Bw6		B41			0.9390	
104	176	3.74	252	8.69	Negative	99	256	100		B*59:01		Bw4		B59			0.9860	
112	162	3.93	204	7.03	Negative	40	222	44		B*45:01		Bw6		B45(12)			0.9190	
78	122	3.90	197	7.42	Negative	33	214	35	A*33:01				A33(19)				0.9200	
73	143	3.89	194	6.69	Negative	40	178	37		B*15:12		Bw6		B76(15)			1.0910	
85	139	4.63	184	6.34	Negative	-47	202	-52		B*14:02		Bw6		B65(14)			0.9120	
79	181	3.97	177	6.10	Negative	9	200	10		B*82:02		Bw6					0.8870	
72	109	3.73	167	6.28	Negative	11	172	11	A*03:01				A3				0.9670	
80	147	3.81	161	5.55	Negative	1	163	1		B*18:01		Bw6		B18			0.9860	
103	123	3.89	146	5.51	Negative	-21	180	-26	A*33:03				A33(19)				0.8120	
83	120	4.30	144	5.43	Negative	-51	179	-63	A*31:01				A31(19)				0.8050	
81	138	3.90	131	4.52	Negative	-44	143	-48		B*14:01		Bw6		B64(14)			0.9130	
70	194	3.51	128	2.17	Negative	-97	164	-125			C*12:02						0.7790	
99	119	4.27	126	4.75	Negative	-69	151	-83	A*30:01				A30(19)				0.8360	
101	124	3.69	123	4.64	Negative	-29	148	-35	A*34:02				A34(10)				0.8330	
108	186	4.00	122	2.07	Negative	-172	352	-496			C*04:01				Cw4		0.3470	
74	134	4.06	118	4.07	Negative	-65	129	-71		B*07:02		Bw6		B7			0.9140	



CLÍNIC BARCELONA Hospital Universitari

Proves encreuades (cross-match)

Centre de Diagnòstic Biomèdic CDB

Cross-match virtual (AriCat)

ARiADNA | Receptores | Donantes | Pruebas | Listados | Maestros | REDMO | Emails | Documentos | español

Número Paciente
D43260

ABO
A

Tipaje Resumen

A	B	C	DRB1	DRB345	DQB1	DQA1	DPB1	DPA1	MICA
A*01, A*33	B*14, B*57	C*07, C*08	DRB1*01, DRB1*07	DRB4*01:03	DQB1*03:03, DQB1*05	DQA1*01, DQA1*02	DPB1*04:01, DPB1*17:01		

#	Receptor	UTR	Edad	ABO	A	B	DRB1	DQB1	PRA-CDC	Antígeno Aislado	F.Búsqueda	ÚLT.
1	30595	1	24	A+	A*02 A*03	B*18 B*50	DRB1*03 DRB1*07		12 Negativo. 1 Negatiu	DRB1*01:01+ DRB1*01:02+ DRB1*01:03+ DQB1*03:01=4+/4 DQB1*03:02=3+/3 DQB1*03:03=3+/3 DQB1*05:01=2+/2 DQB1*05:02=1+/1 DQB1*05:03=1+/1 DQA1*01:01=1+/1 DQA1*01:02=4+/4 DQA1*01:03=2+/2 DQA1*01:04=2+/2 DQA1*02:01=3+/5 DPB1*04:01=3+/5 DPB1*17:01=1+/1 A*01:01- A*33:01- A*33:03- B*14:01- B*14:02- B*57:01- C*07:01- C*07:02- C*08:01- C*08:02- C*17:01- DRB1*07:01- DRB4*01:01- DPB1*04:02=0+/2	29/10/2019	92
2	28978	1	48	A-	A*02 A*23	B*15 B*44	DRB1*07 DRB1*11		6 Negatiu 4 Negativo.	DQB1*03:02=2+/3 DQB1*05:01=2+/2 DQA1*01:01=1+/1 DQA1*01:02=3+/4 DQA1*02:01=1+/5 A*01:01- A*33:01- A*33:03- B*14:01- B*14:02- B*57:01- C*07:01- C*07:02- C*08:01- C*08:02- C*17:01- DRB1*01:01- DRB1*01:02- DRB1*01:03- DRB1*07:01- DRB4*01:01- DQB1*03:01=0+/4 DQB1*03:03=0+/3 DQB1*05:02=0+/1 DQB1*05:03=0+/1 DQA1*01:03=0+/2 DQA1*01:04=0+/2 DPB1*04:01=0+/5 DPB1*04:02=0+/2 DPB1*17:01=0+/1	05/09/2019	76
3	29343	1	39	A+	A*03 A*24	B*07	DRB1*07 DRB1*15		6 Negatiu 6 Negativo.	A*01:01- A*33:01- A*33:03- B*14:01- B*14:02- B*57:01- C*07:01- C*07:02- C*08:01- C*08:02- C*17:01- DRB1*01:01- DRB1*01:02- DRB1*01:03- DRB1*07:01- DRB4*01:01- DQB1*03:01=0+/4 DQB1*03:02=0+/3 DQB1*03:03=0+/3 DQB1*05:01=0+/2 DQB1*05:02=0+/1 DQB1*05:03=0+/1 DQA1*01:01=0+/1 DQA1*01:02=0+/4 DQA1*01:03=0+/2 DQA1*01:04=0+/2 DQA1*02:01=0+/5 DPB1*04:01=0+/5 DPB1*04:02=0+/2 DPB1*17:01=0+/1	19/07/2019	0
4	38457	1	40	A+	A*02 A*-	B*44 B*55	DRB1*07 DRB1*-	DQB1*02:02 DQB1*-	3 Negativo.	A*01:01- A*33:01- A*33:03- B*14:01- B*14:02- B*57:01- C*07:01- C*07:02- C*08:01- C*08:02- C*17:01- DRB1*01:01- DRB1*01:02- DRB1*01:03- DRB1*07:01- DRB4*01:01- DQB1*03:01=0+/4 DQB1*03:02=0+/3 DQB1*03:03=0+/3 DQB1*05:01=0+/2 DQB1*05:02=0+/1 DQB1*05:03=0+/1 DQA1*01:01=0+/1 DQA1*01:02=0+/4 DQA1*01:03=0+/2 DQA1*01:04=0+/2 DQA1*02:01=0+/5 DPB1*04:01=0+/5 DPB1*04:02=0+/2 DPB1*17:01=0+/1	14/06/2019	0
5	5391	1	42	A1+	A*02 A*25	B*13 B*51	DRB1*07 DRB1*13		3 A29 3 Negativo. 1 INESP	DQB1*03:01=4+/4 DQB1*03:02=2+/3 DQB1*03:03=3+/3 DPB1*04:01=2+/5 DPB1*04:02=2+/2 A*01:01- A*33:01- A*33:03- B*14:01- B*14:02- B*57:01- C*07:01- C*07:02- C*08:01- C*08:02- C*17:01- DRB1*01:01- DRB1*01:02- DRB1*01:03- DRB1*07:01- DRB4*01:01- DQB1*05:01=0+/2 DQB1*05:02=0+/1 DQB1*05:03=0+/1 DQA1*01:01=0+/1 DQA1*01:02=0+/4 DQA1*01:03=0+/2 DQA1*01:04=0+/2 DQA1*02:01=0+/5 DPB1*17:01=0+/1	14/06/2019	74
6	26904	1	36	A+	A*03 A*69	B*07 B*44	DRB1*03 DRB1*07	DQB1*02:01 DQB1*02:02	4 A1 17 Negativo. 5 Negatiu 1 - 1 A2 1 A24 1 A29 1 No Aplica	A*01:01+ C*07:01+ C*07:02+ C*08:01+ C*08:02+ DRB1*01:01+ DRB1*01:02+ DRB1*01:03+ DQB1*03:01=4+/4 DQB1*03:02=3+/3 DQB1*03:03=3+/3 DQB1*05:01=2+/2 DQB1*05:02=1+/1 DQB1*05:03=1+/1 DQA1*01:01=1+/1 DQA1*01:02=4+/4 DQA1*01:03=2+/2 DQA1*01:04=2+/2 DQA1*02:01=3+/5 DPB1*17:01=1+/1 A*33:01- A*33:03- B*14:01- B*14:02- B*57:01- C*17:01- DRB1*07:01- DRB4*01:01-	07/03/2019	99

ARiADNA 0.8 | Ayuda

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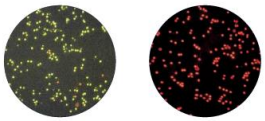
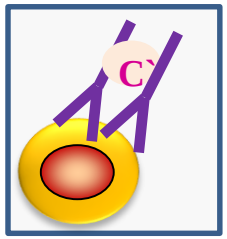
Proves encreuades (cross-match)

- Citotoxicitat (CDC):

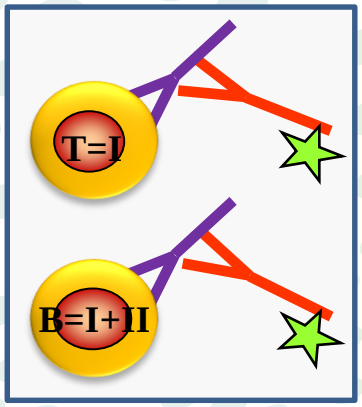
  Predictor del risc de Rebuig Hiper-Agut.

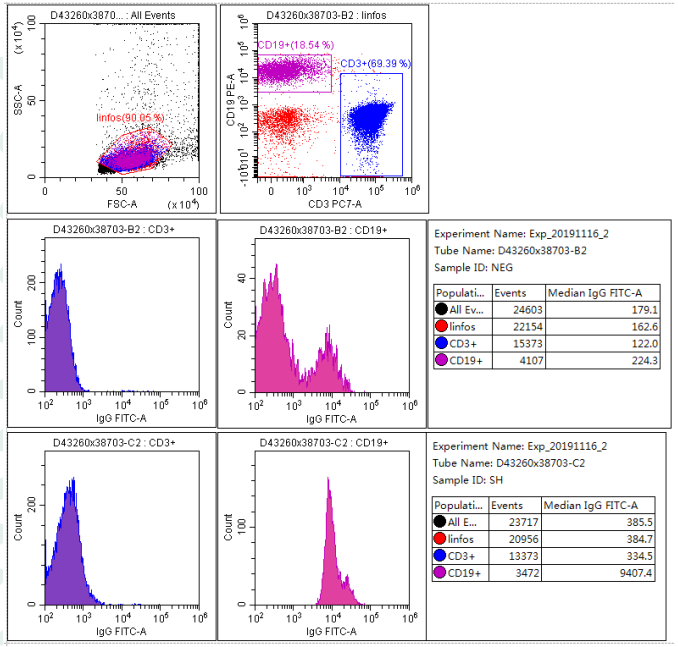


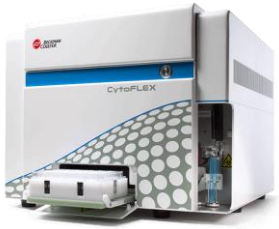


- **Citometria de Flux** (FC): Més Sensible

  Predictor del risc de la pèrdua d'empelt, sobretot en re-trasplantament.







Avaluació del Risc immunològic

Tx Renal (Selecció donant-receptor):

No Acceptable:

- **CDC-XM Positiu** 20% superviv. 48h
- **Re-Tx: FC-XM Positiu, CDC-XM Neg**

Risc de pèrdua empelt 1any: augment 7% (Gebel 2003)

Acceptable:

- **1er Tx: FC-XM Positiu, CDC-XM Neg**

Risc de pèrdua empelt: augment 10% (Gebel 2003)

- **XM Virtual Positiu, FC i CDC-XM Neg**

55% Risc AMR, 68% superviv. 5 anys (*Amico 2009)*

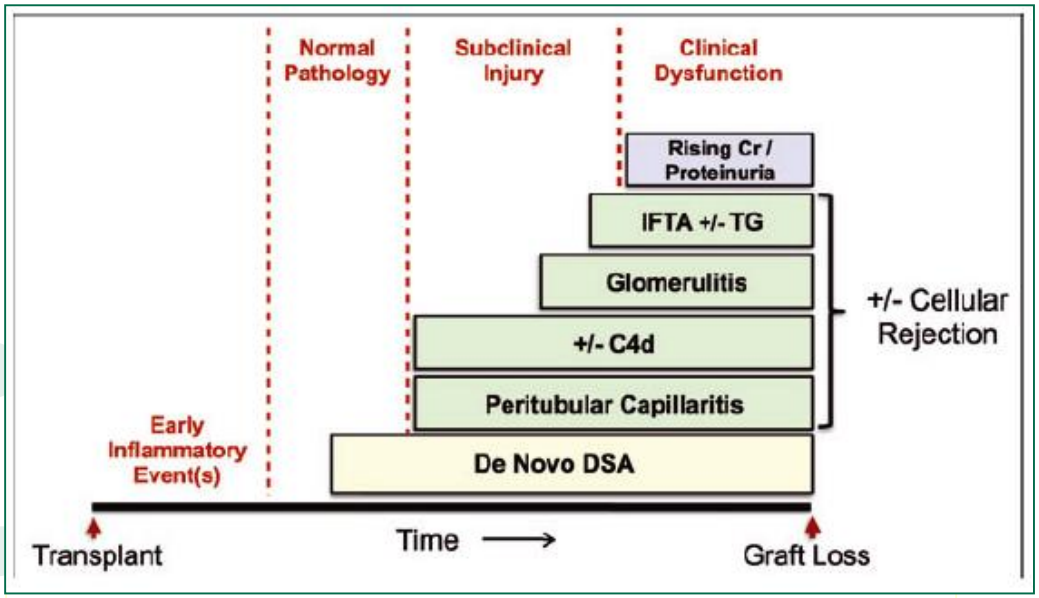
Òptim:

- **XM Virtual Negatiu**

5% Risc AMR, 89% superviv. 5 anys (*Amico 2009)*

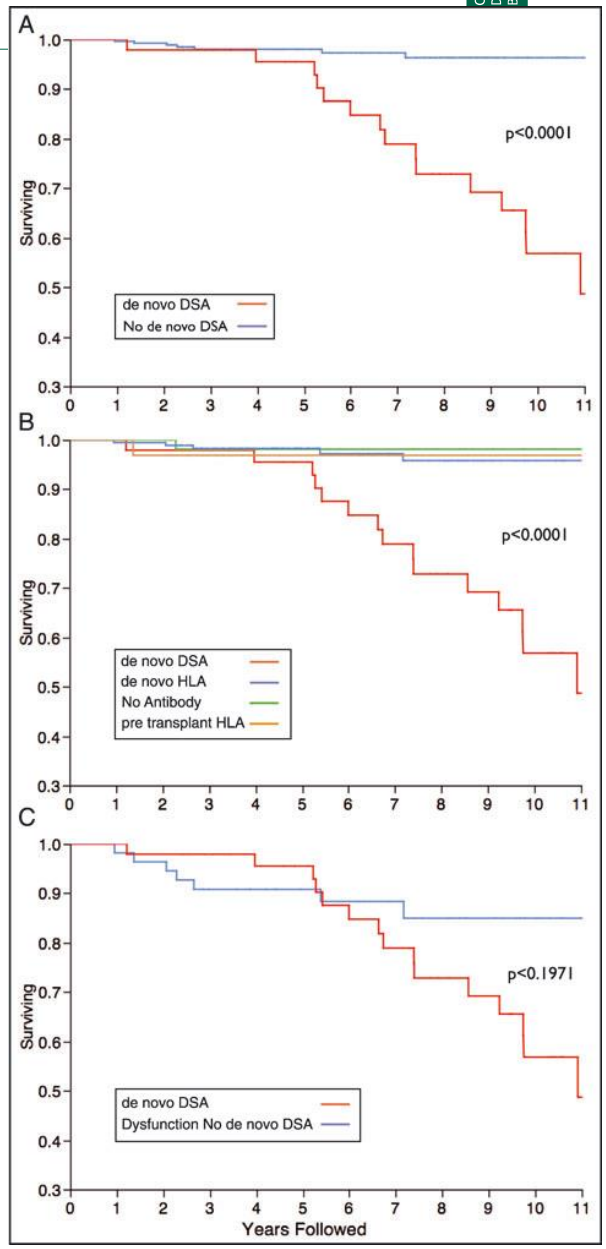
Quina és la probabilitat de trobar un millor donant per aquest receptor? cPRA (PRA calculat)

Anticossos Anti-HLA Donant-Específics De Novo



Wiebe, C. Am J Transplantation 2012

Evolution and Clinical Pathologic Correlations of **De Novo Donor-Specific HLA Antibody** Post Kidney Transplant



Diagnòstic diferencial del rebuig:

- Cel·lular (DSA Neg)
- Humoral (DSA Pos)

Pronòstic de l'empelt:

- Bo (DSA Neg): >95%
- No tan bo (DSA Pos): ~70%

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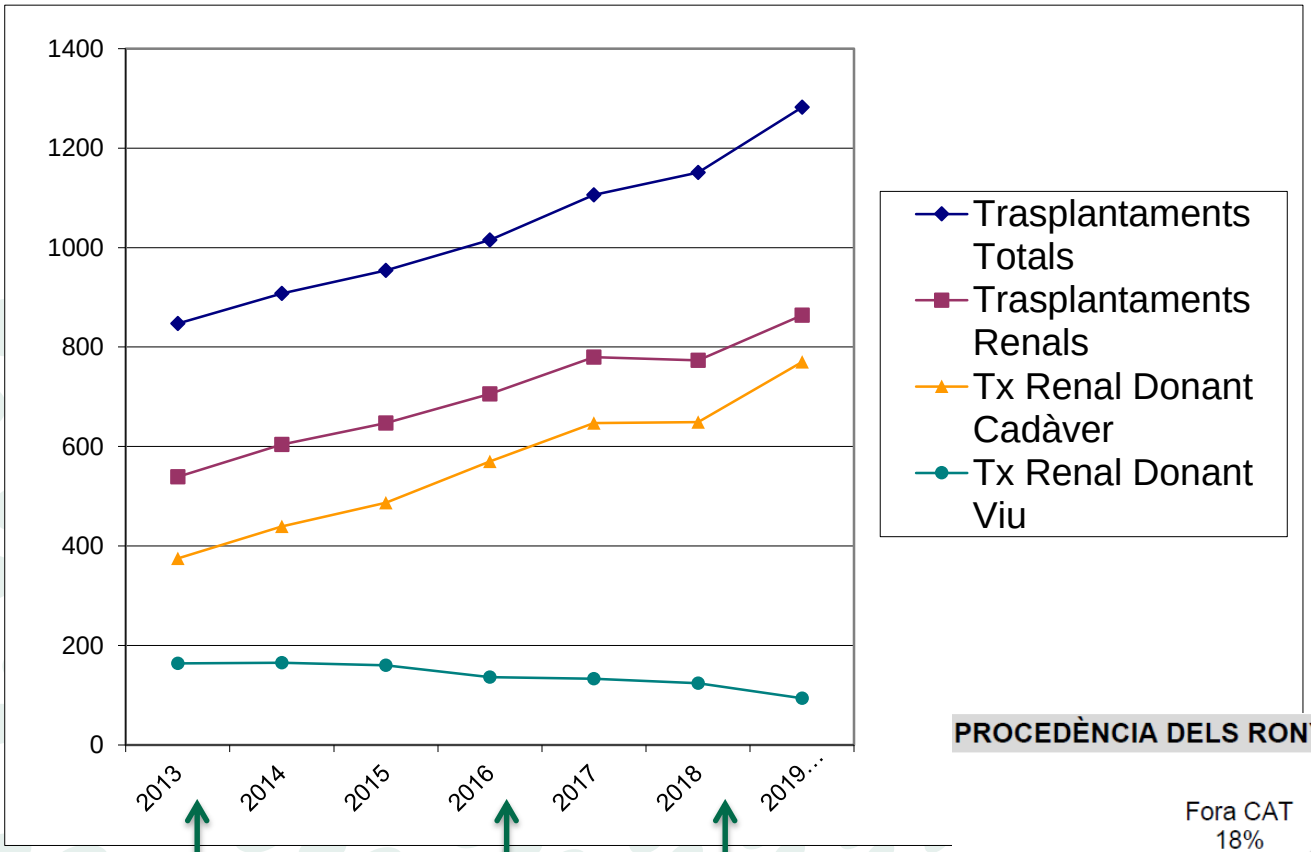
Guia d'estudis immunològics en el Trasplantament Renal 2018

Document aprovat pel Grup de Treball d'Immunologia de la Comissió Assessora de Trasplantament Renal i Pancreàtic (**OCATT**) en la reunió del dia 20 de juny de 2018.

Aprovat per la Comissió Assessora de Trasplantament Renal i Pancreàtic del dia 24 d'octubre de 2018.

Aquest document pretén ser una guia per a la sol·licitud i interpretació del **Catàleg de prestacions del Laboratori d'Histocompatibilitat de Catalunya (LHC)** tant per facilitar el trasplantament d'òrgans com per contribuir al diagnòstic diferencial del rebuig mediat por al·loanticossos i per a avaluar el risc de pèrdua de l'empelt en el posttransplantament.

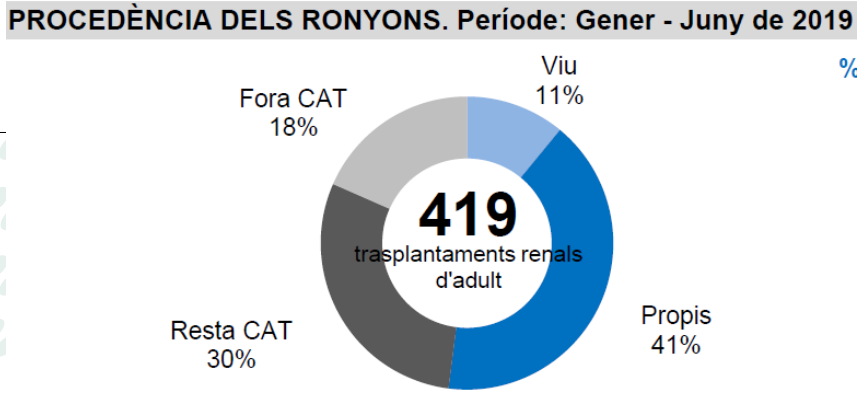
Trasplantaments a Catalunya



Aprovació Guia 2013

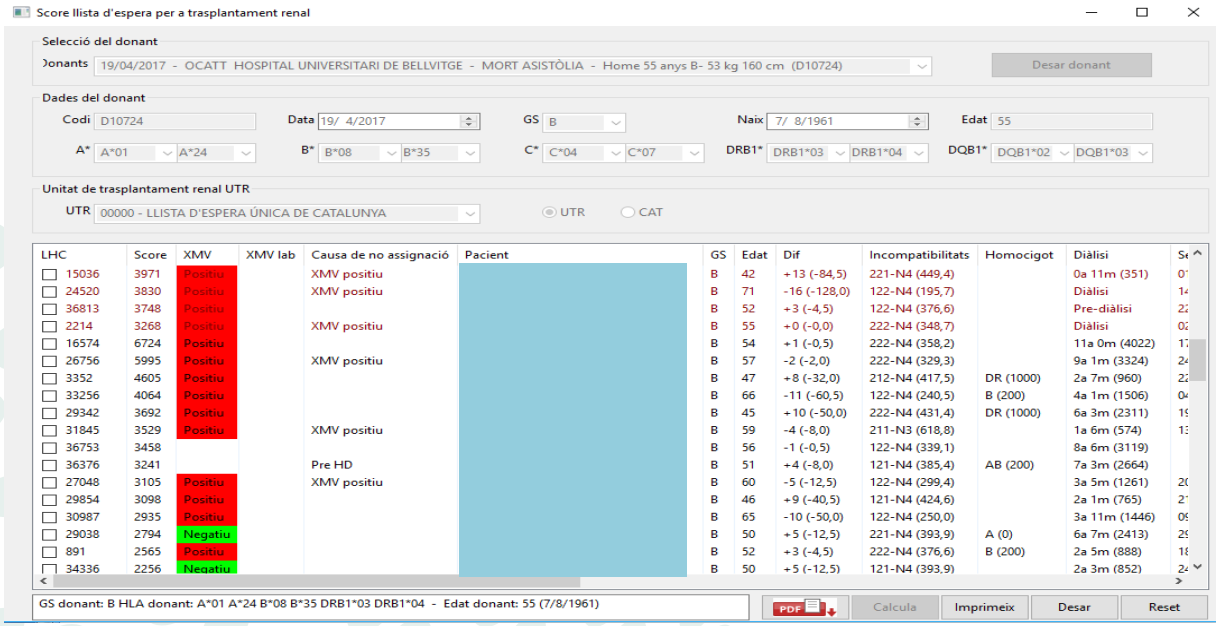
Inici implementació Guia 2013

Revisió Guia 2018

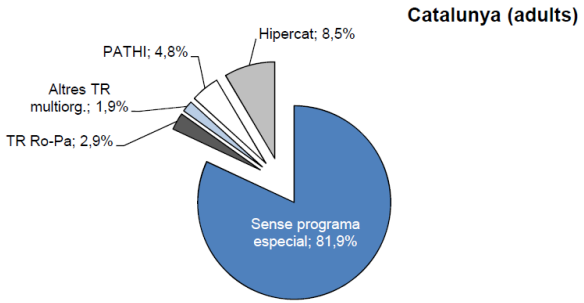


Selecció de receptors (Tx renal)

- Eina d'assignació de donants en receptors renals: Score (DTX-OCATT)

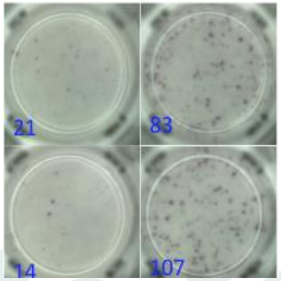


- Programes priorització Pacients Hipersensibilitzats:
  - PATHI a Espanya (ONT): cPRA>98%
  - HiperCat (Catalunya-OCATT): cPRA>90%

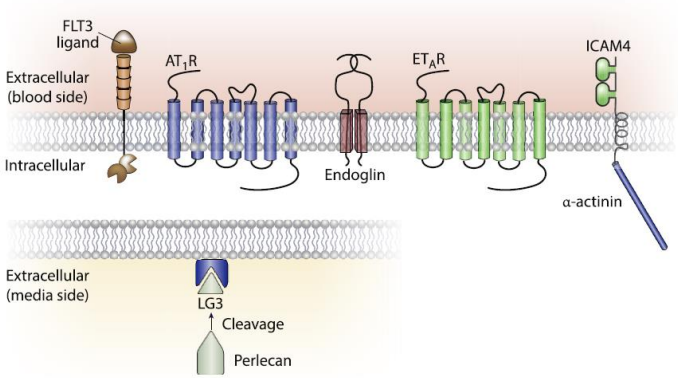


Histocompatibilitat: més enllà de l'HLA

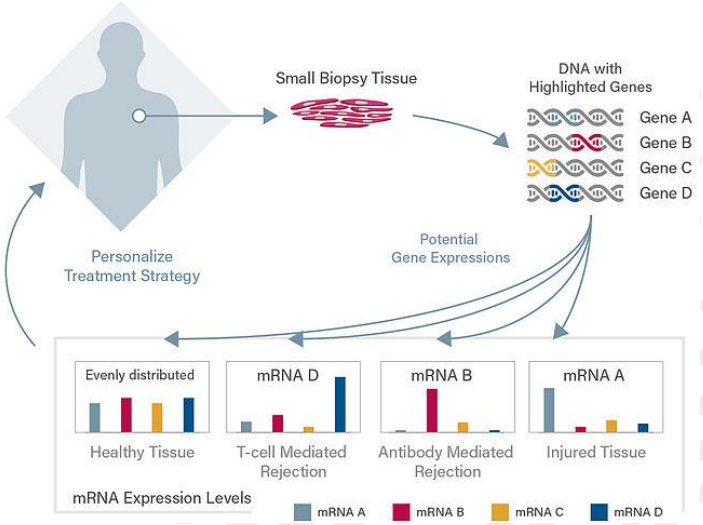
Monitorització dels **limfòcits T / limfòcits B memòria** al·loreactius específics de donant



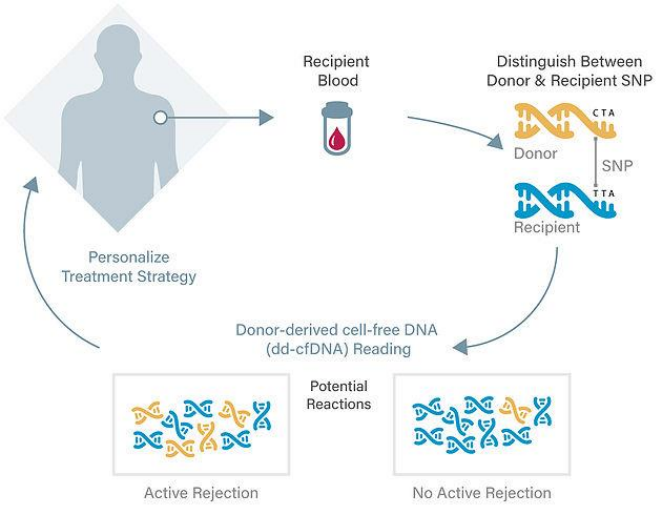
Altres **anticossos no-HLA**



Perfils d'**expressió proteica/gènica**



DNA circulant derivat del donant



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Moltes gràcies per la vostra atenció!