

#histologie_comparee

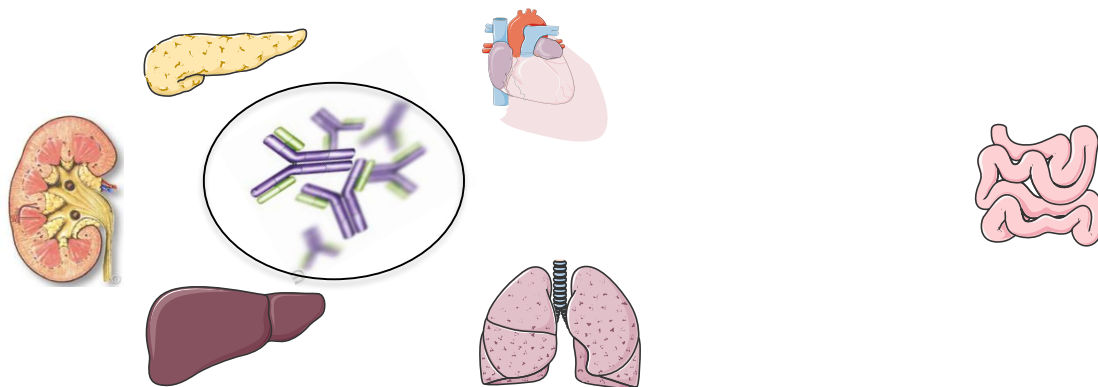
Jean Paul Duong Van Huyen

Service d'Anatomie et Cytologie Pathologiques,
Hôpital Necker-Enfants Malades
Université Paris Descartes Médecine

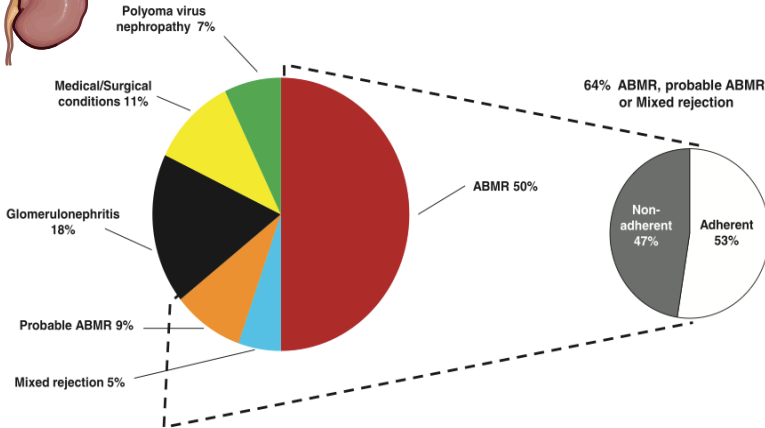
Paris Transplant Group
PARCC HEGP Inserm 970

#histologie_comparée

thématique trans-organe
→ le rejet humoral

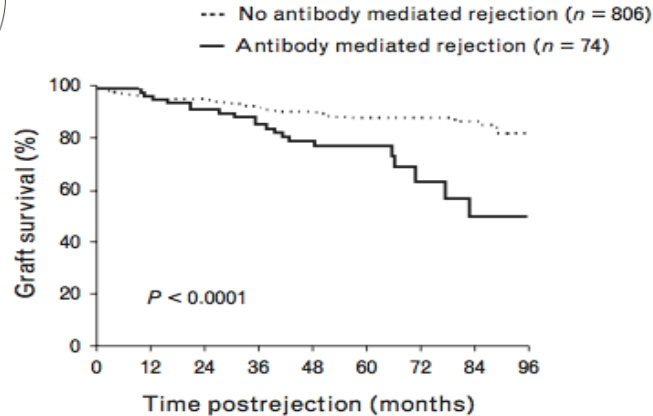


Le rejet humoral en transplantation d'organe solide

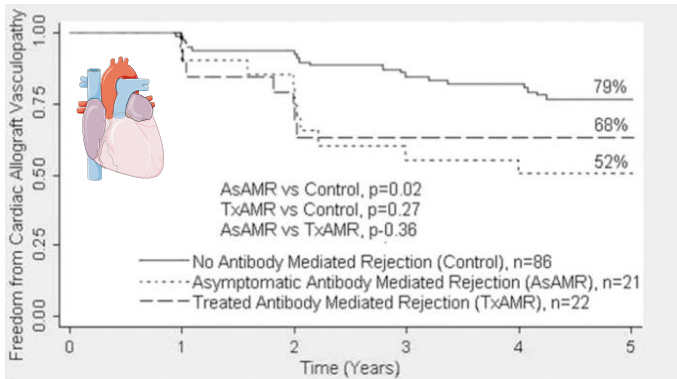


Selleares et al. AJT 2012

Loupy A et al. JASN 2014

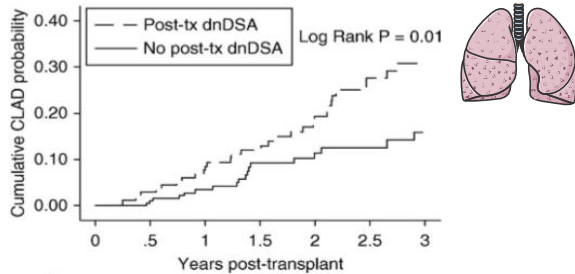


	Number at risk									
	0	12	24	36	48	60	72	84	96	
No ABMR	806	713	679	343	127	92	6			*
ABMR	74	71	67	44	30	6	3			



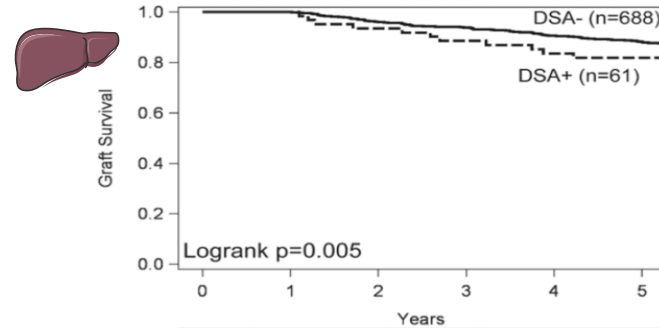
Wu et al. JHLT 2009

Tikkanen et al. Am J Respir Crit Care Med. 2016



Number at risk

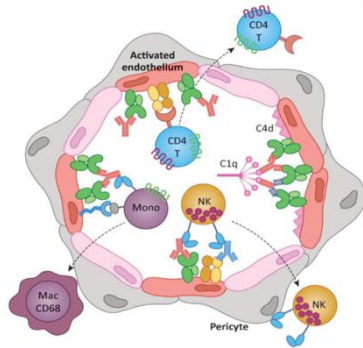
Post-tx dnDSA	0	114	112	95	73	57	36
No post-tx dnDSA	340	196	134	97	75	57	45



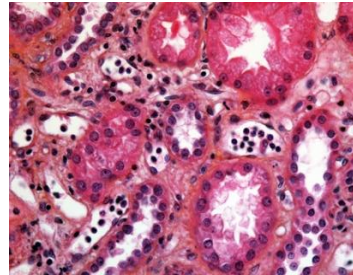
De novo DSA-	688	688	660	645	586	513
De novo DSA+	61	61	57	54	50	42

Kaneku H et al. AJT 2013

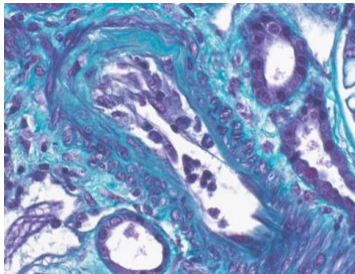
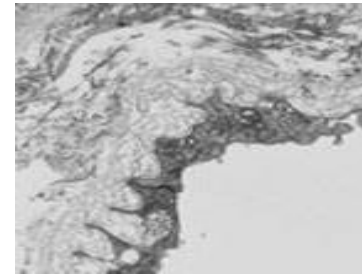
Rejet humoral et tropisme vasculaire



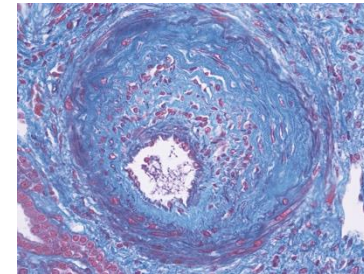
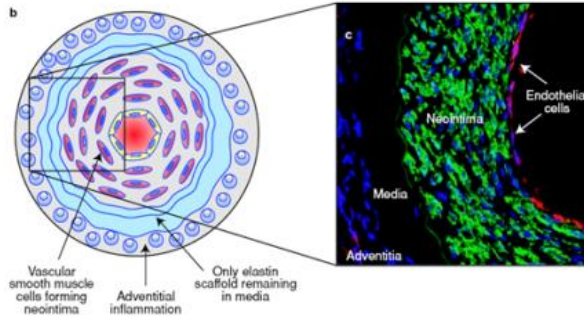
capillarite



multi-lamellation



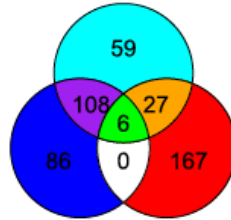
endothélite



artériosclérose

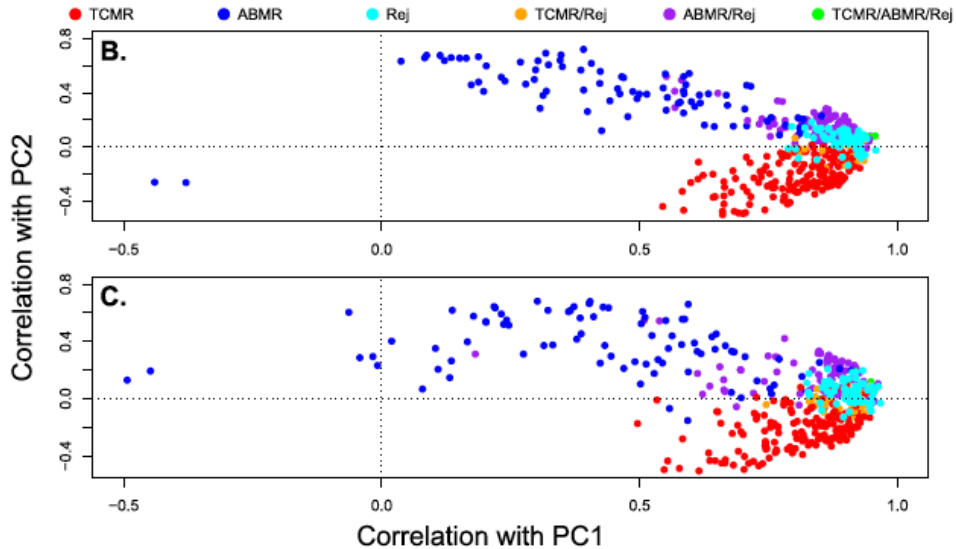
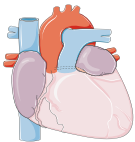


200 Rejection probesets

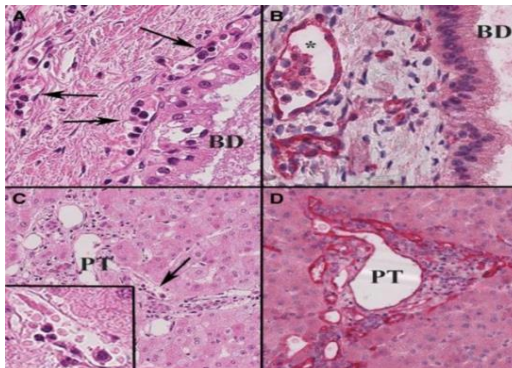
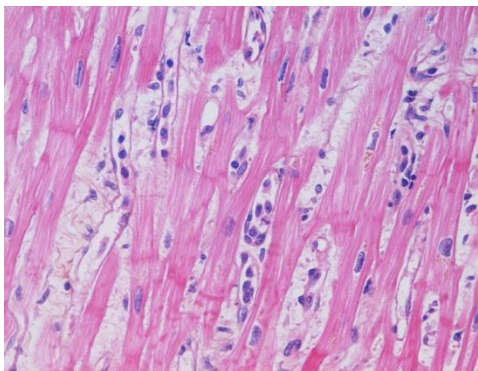
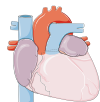
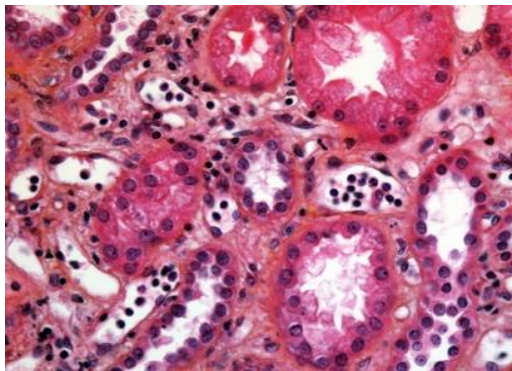
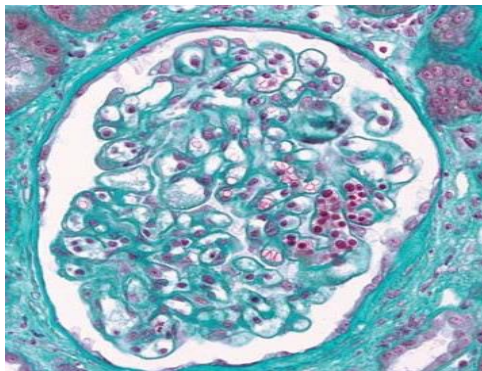


200 ABMR probesets

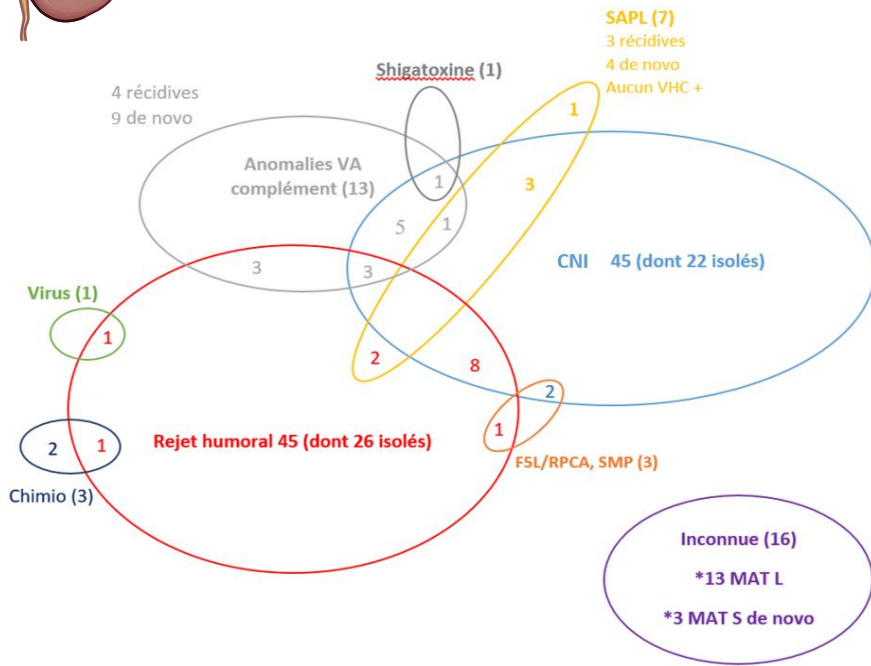
200 TCMR probesets



Inflammation de la microcirculation



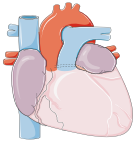
Microangiopathie thrombotique



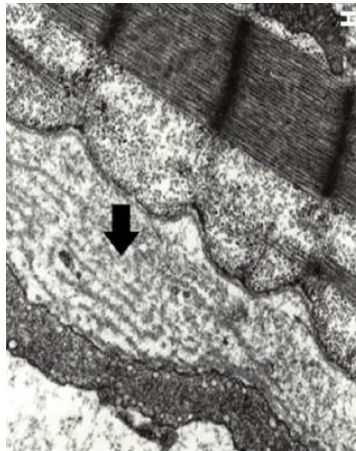
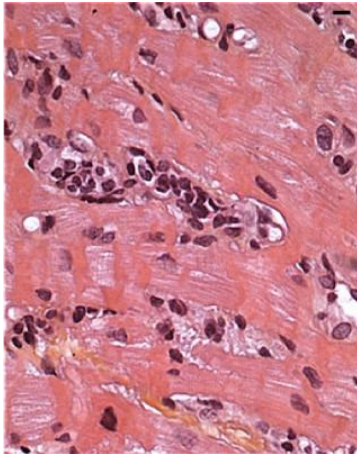
Série de 98 patients
avec MAT post-transplantation
rénale
Necker-Enfants malades

- **MAT de novo:**
n=88/98 (90%)
- **Récidive sur le greffon**
n=10/98 (10%)
- **Etiologies principales**
 - Rejet humoral 47%
 - Toxicité des CNI isolée 25%
- **Etiologie multiples**
dans 37% des cas

Détérioration de la microcirculation

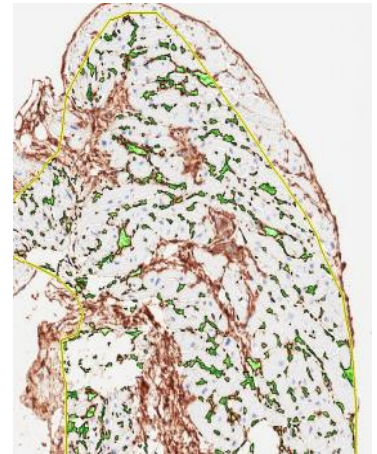


multilamellation



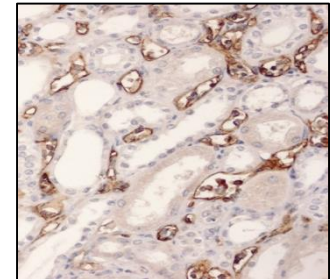
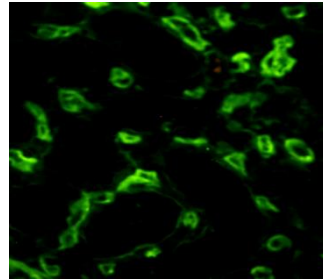
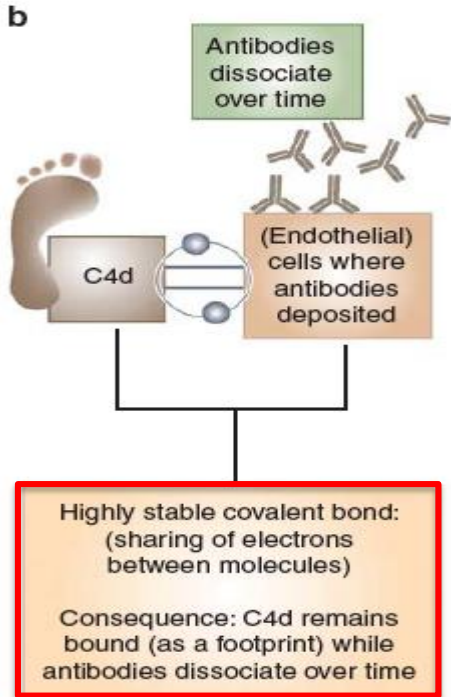
**Bruneval et al.
AJT 2017**

Perte en capillaires



**Revelo et al.
Cardiovasc Pathol 2012**

Le C4d en transplantation rénale

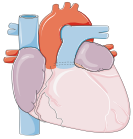


Score du C4d: en fonction du pourcentage de capillaires positifs:

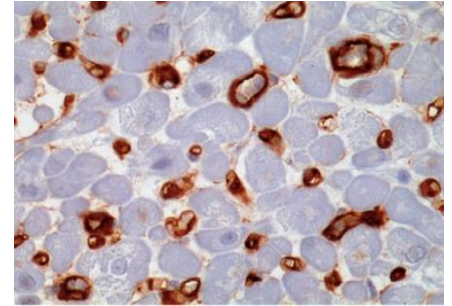
- C4d1: <10%
- C4d2: 10-50%
- C4d3: >50%



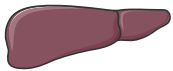
Le C4d dans les autres transplantations



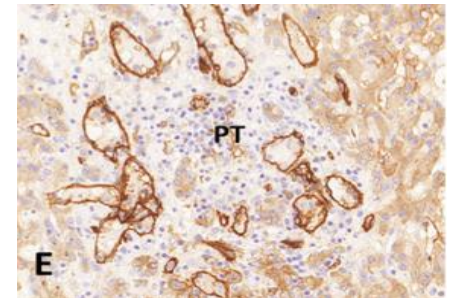
- positif si C4d diffus (>50% des capillaires)



Berry et al. JHLT 2013

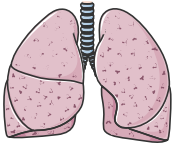


- (0) Pas de C4d sur les microvaisseaux portaux (capillaires et veines portes)
- (1) Minimal C4d (<10% des microvx portaux sur > de 50% circonférence)
- (2) Focal C4d (10-50%)
- (3) Diffuse C4d (>50%) avec souvent extension aux sinusoides/veinules périportaux

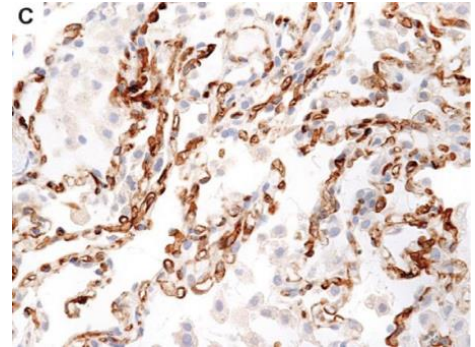


Demetris et al. Am J Transplant 2016

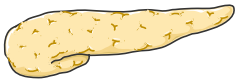
Le C4d dans les autres transplantations



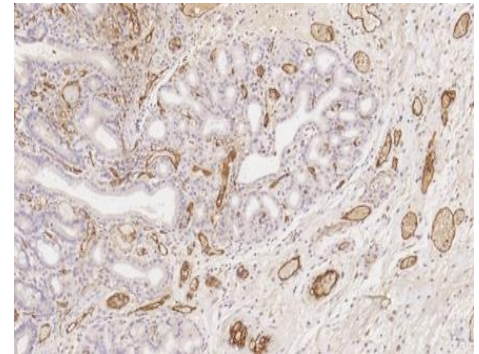
- positif si C4d diffus (>50%)



Aguilar et al., AJT 2017



- positif $\geq 1\%$ des capillaires interacinaires



De Kort et al. AJT 2014

Atteinte vasculaire du rejet humoral

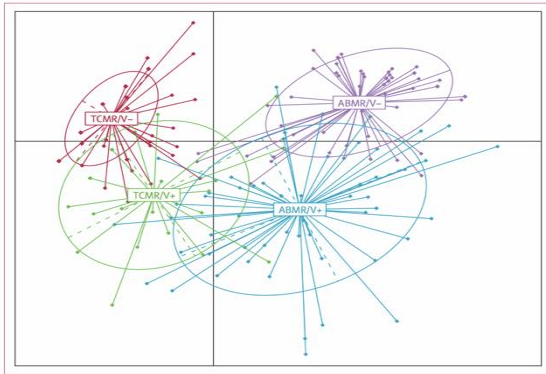
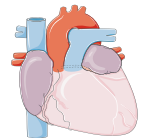
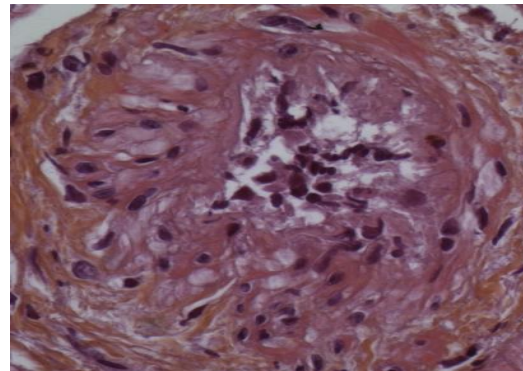
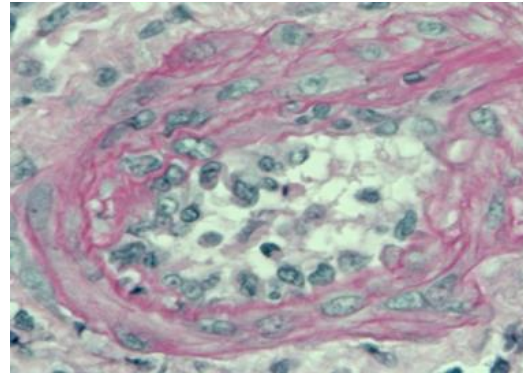


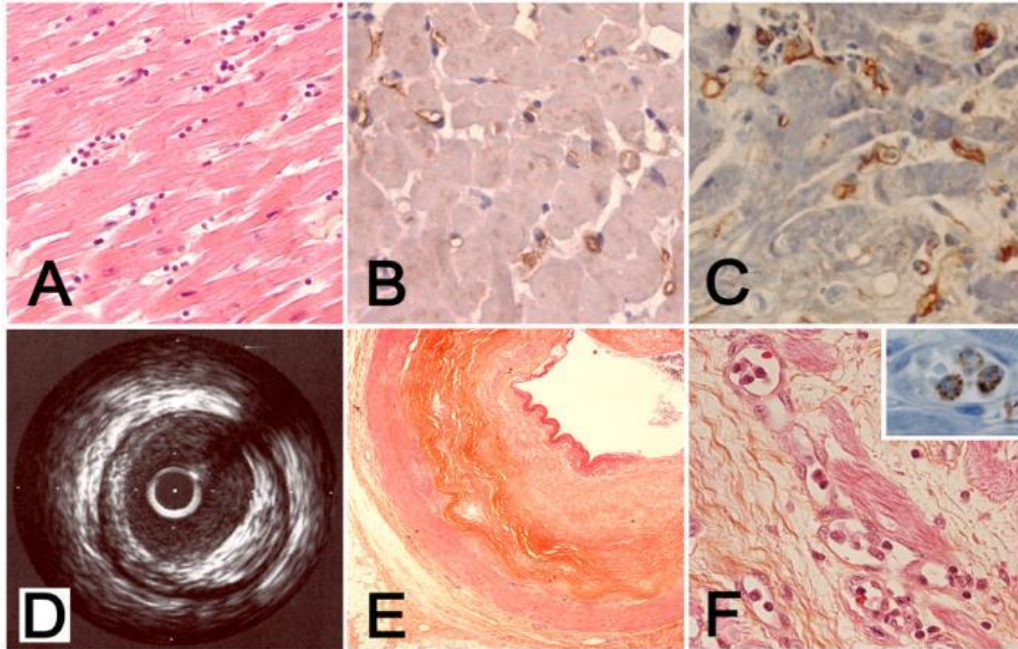
Figure 1: Identification of four distinct rejection patterns according to clinical, histological, and immunological variables

Lefaucheur et al. Lancet 2013



Lésion chroniques vasculaires

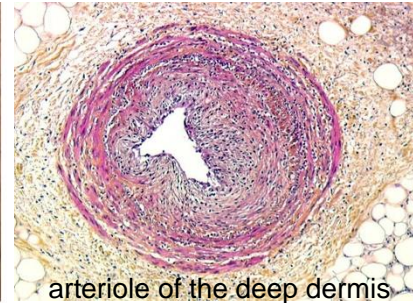
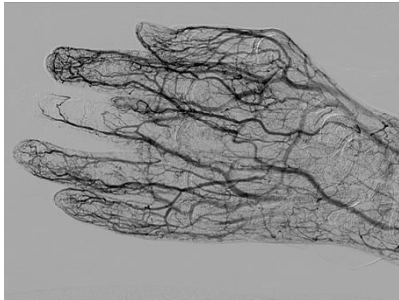
A, B et C : 8 ans post-TX



D : 10 ans post-TX

E et F : 12 ans post-TX

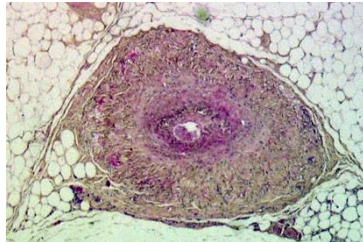
Allograft vasculopathy in VCA is related to ABMR



Finger amputation Arterial necrosis 11 years after bilateral hand transplantation



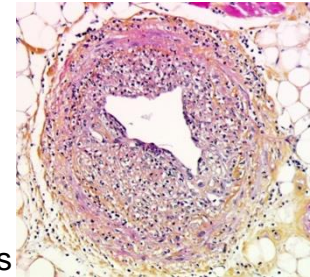
Sentinel skin graft
Necrosis
9 years post TR



Flap nutrient artery



Partial face graft necrosis
10 years post TR



Necrotic skin

Face transplantation : Chronic humoral rejection 9 years post TR

ABMR du greffon rénal: diagnostic



➤ **Pathologie** (au moins 1)

Acute/actif ABMR

- Inflammation de la microcirculation (g > 0 et/ou cpt > 0)
- Lésion d'artérite intimale (v > 0)
- MAT, en l'absence d'autres causes
- NTA

➤ **Interaction entre les anticorps et l'endothelium** (au moins 1)

- C4d + (C4d2 / C4d3 en IF, ou C4d > 0 en IHC sur coupes paraffines).
- MI+ : [g + ptc] ≥ 2
- Marqueurs moléculaires: ENDATS.

➤ **DSA +** (anti-HLA ou autres).

Chronic/actif ABMR

- Transplant glomerulopathy (cg > 0)
- PTC multilayering (EM++)
- Intimal thickening/fibrosis

The Banff 2015 Kidney Meeting Report: Current Challenges in Rejection Classification and Prospects for Adopting Molecular Pathology

Loupy A et al. AJT 2017

ABMR greffon hépatique: diagnostic



➤ Pathologie

- Turgescence endothéliale des microvaisseaux espaces porte
- Dilatation des capillaires portaux et veinules
- Capillarite (monocytes, éosinophiles, neutrophiles)
- Œdème porte
- Réaction ductulaire
- +/-cholestase
- artérite

➤ C4d+ diffus microvasculaire (=3)

➤ DSA + (anti-HLA ou autres).

➤ Exclusion des autres causes

2016 Comprehensive Update of the Banff Working Group on Liver Allograft Pathology: Introduction of Antibody-Mediated Rejection

Demetris et al. AJT 2016

ABMR greffon pulmonaire: diagnostic

Table 1 Definition and Diagnostic Certainty of Clinical Pulmonary Antibody-mediated Rejection

	Allograft dysfunction	Other causes excluded	Lung histology	Lung biopsy C4d	DSA
Definite	+	+	+	+	+
Probable ^a	+	+	+	-	+
Probable	+	+	+	+	-
Probable	+	+	-	+	+
Probable	+	-	+	+	+
Possible	+	+	+	-	-
Possible	+	+	-	-	+
Possible	+	+	-	+	-
Possible	+	-	+	+	-
Possible	+	-	+	-	+
Possible	+	-	-	+	+

Neutrophil margination, neutrophil capillaritis and arteritis,

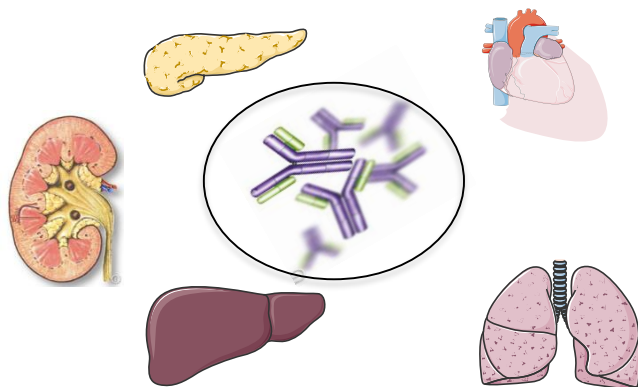
Levine et al. JHLT. 2016

Diagnostic du rejet humoral en transplantation d'organe solide

	Rein	Coeur	Foie	Pancréas	Poumon
Histologie	+	+	+	+	+
C4d	+/-	+/-	+	+	+
DSA	+/-	-	+	+	+
Moléculaire	+/-	-	-	-	-

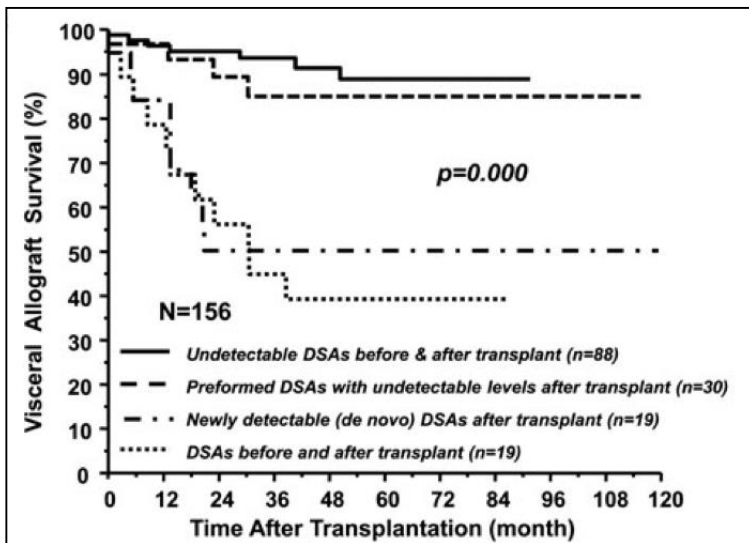
#histologie_comparée

thématique trans-organe
→ le rejet humoral



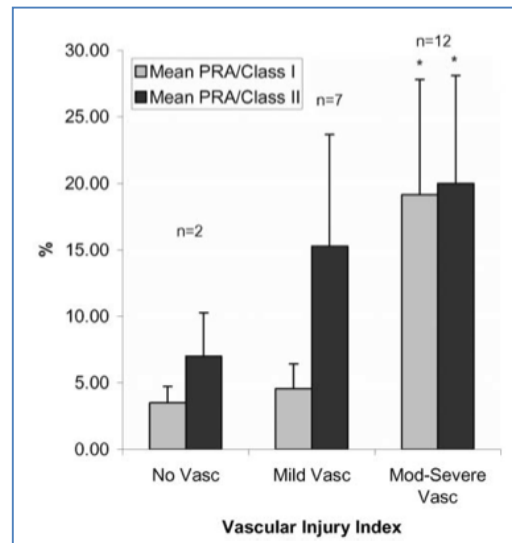
Le rejet humoral en transplantation intestinale

DSA associés à la perte du greffon



Abu-Elmagd et al AJT 2012

Lésions vasculaires :
dilatation, congestion,
suffusions hémorragiques, œdème



Ruiz et al. AJT 2003

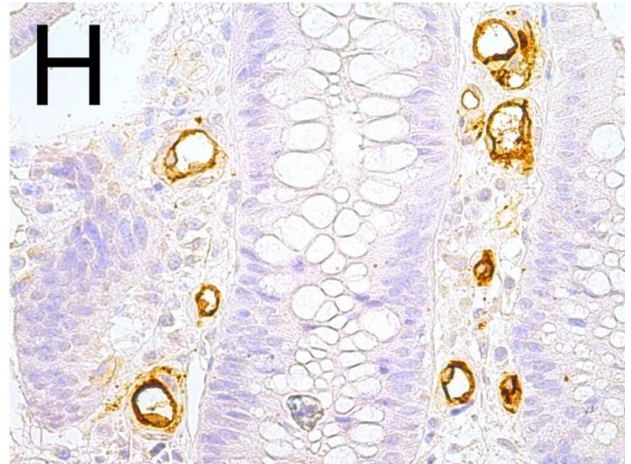
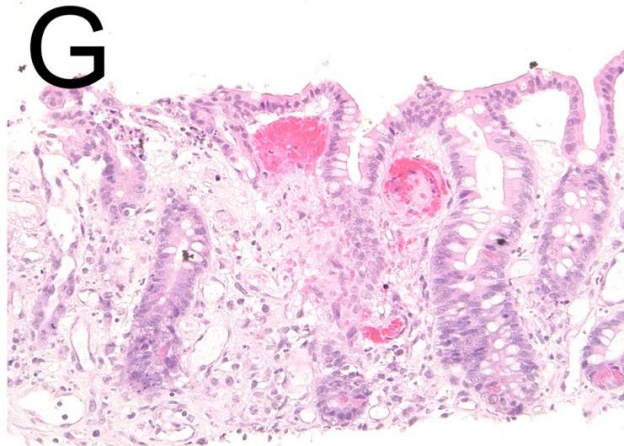
Un seul type de rejet reconnu

Type of rejection	Grade of rejection	Histological changes
<i>No evidence</i> of acute rejection	Grade 0	<ul style="list-style-type: none"> Unremarkable histological changes
<i>Indeterminate</i> for acute rejection	Grade ind	<ul style="list-style-type: none"> < 6 apoptotic bodies per 10 crypt cross section Focal inflammatory infiltrate No superficial epithelium injury Intact mucosa
Acute cellular rejection, <i>mild</i>	Grade 1	<ul style="list-style-type: none"> Crypt injury and destruction ≥ 6 apoptotic bodies per 10 crypt cross section Mild to moderate inflammatory infiltrate Edema and vascular congestion possible
Acute cellular rejection, <i>moderate</i>	Grade 2	<ul style="list-style-type: none"> Crypt injury and destruction distributed more diffusely ≥ 6 apoptotic bodies per 10 crypt cross section Confluent apoptosis Focal crypt loss Focal superficial erosions possible Moderate to severe inflammatory infiltrate Edema, vascular congestion villus blunting frequent
Acute cellular rejection, <i>severe</i>	Grade 3	<ul style="list-style-type: none"> Diffuse mucosal erosion and/or ulceration Marked degree of crypt damage and destruction Marked diffuse inflammatory infiltrate Granulation tissue and/or fibropurulent (pseudomembranous) exsudate possible (exfoliative rejection) Arteritis possible

- Apoptoses
- Inflammation du chorion
- Nécrose glandulaire
- Déficits glandulaires
- Érosions, ulcérations
- Bourgeon charnu

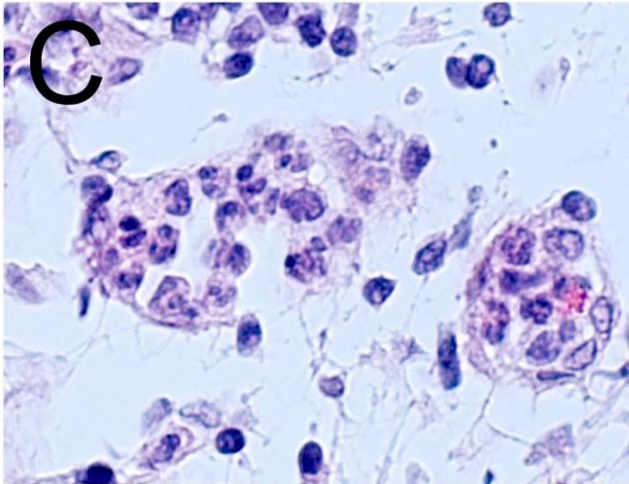
Ulcération & μthrombose

C4d positif

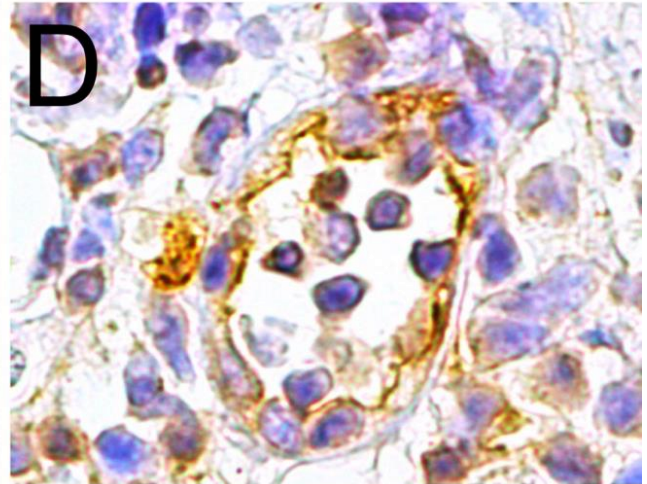


Rabant, Racape et al. AJT 2018

Capillarite intestinale



C4d positif



Rabant, Racape et al. AJT 2018

Définir les signes histologique du rejet humoral intestinal



Les signes histologiques associés à la positivité du C4d ?

Reprendre toutes les Biopsies intestinales (n=345)
de 23 enfants greffés à Necker –Enfants malades (2009-14)



Grille de lecture histopathologique intégrant capillarite, etc..
C4d systématique
Evaluation séquentielle des DSA
C1q binding
Outcome



Histopathologie du rejet humoral
Facteurs pronostics : C4d? DSA?

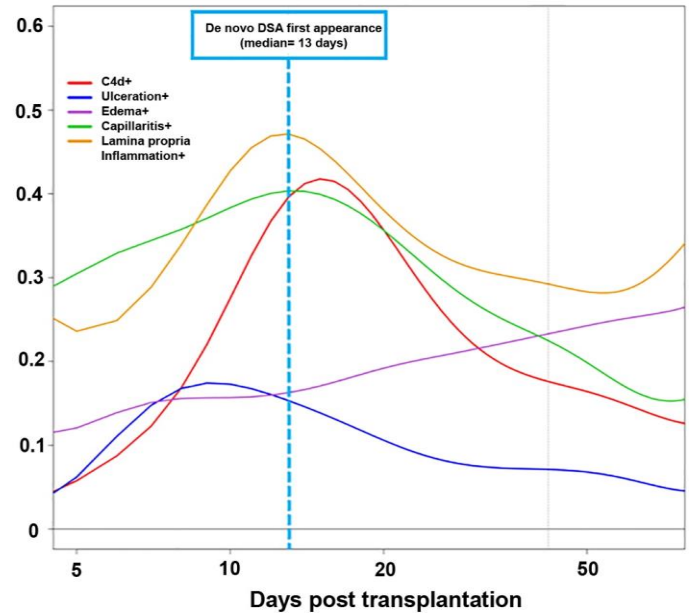
DSA > 1000 MFI

- absent : 5/23
- préformés : 6/23
- de novo : 12/23

DSA C1q : 9/18

C4d+ : 75/345 BI

Conditional probability plots



Histological and immunological characteristics according to the C4d status (<2 vs ≥2)

	n	All biopsies (n=345)	n	C4d negative (<2) (n= 267)	n	C4d positive (≥ 2) (n= 78)	p
Time since transplantation (days), mean (SD), y	345	45.9 (60.8)	267	51.1 (66.6)	78	28.2 (28.2)	0.0136
Mucosal erosion/ulceration , No. of positive biopsies (%)	345	40 (11.6)	267	20 (7.5)	78	20 (25.6)	<0.0001
Lamina propria inflammation , No. of positive biopsies (%)	Grade 1	93 (27.5)	264	67 (25.4)	74	26 (35.1)	<0.0001
	Grade 2/3	30 (8.9)		16 (6.1)		14 (18.9)	
Chorion edema , No. of positive biopsies (%)	341	63 (18.5)	265	45 (17)	76	18 (23.7)	0.184
Apoptosis , No. of positive biopsies (%)	337	64 (19)	264	42 (15.9)	73	22 (30.1)	0.011
Gland necrosis , No. of positive biopsies (%)	337	55 (16.3)	263	33 (12.5)	74	22 (29.7)	0.001
Fibrosis , No. of positive biopsies (%)	345	19 (5.5)	267	14 (5.2)	78	5 (6.4)	0.778
Thrombosis , No. of positive biopsies (%)	345	25 (7.2)	267	13 (4.9)	78	12 (15.4)	0.005
Capillary dilatation and congestion hemorrhage , No. of positive biopsies (%)	345	175 (50.7)	267	132 (49.4)	78	43 (55.1)	0.440
Capillaritis , No. of positive biopsies (%)	Grade 1	166 (50.9)		134 (53.2)		32 (43.2)	<0.0001
	Grade 2	22 (6.7)	252	15 (5.9)	74	7 (9.5)	
	Grade 3	75 (23)		45 (17.9)		30 (40.5)	
Mitosis , No. of positive biopsies (%)	337	61 (18.1)	264	49 (18.6)	73	12 (16.4)	0.734
Acute cellular rejection* , No. of positive biopsies (%)	No rejection	192 (55.8)		159 (59.8)		33 (42.3)	<0.0001
	Undetermined	76 (22.1)		61 (22.9)		15 (19.2)	
	Mild rejection	33 (9.6)	266	26 (9.8)	78	7 (9)	
	Moderate rejection	21 (6.1)		11 (4.1)		10 (12.8)	
	Severe rejection	22 (6.4)		9 (3.4)		13 (16.7)	

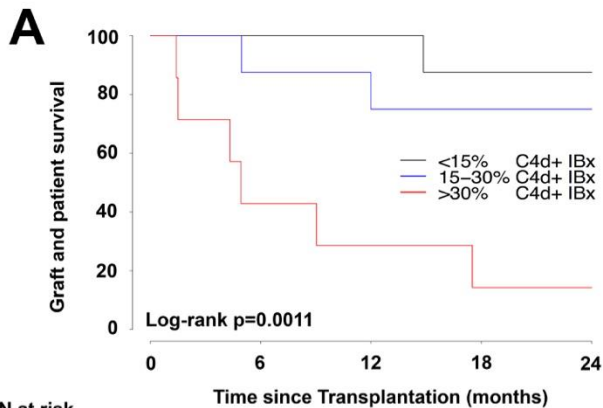
UNIVARIATE ANALYSIS

			OR	95% CI	P
Histology	Log(Delay Bx-Tx)	No	1	-	
		Yes	0.476	(0.250 to 0.902)	0.023
	Ulceration	No	1	-	
		Yes	4.259	(2.152 to 8.428)	<0.0001
	Lamina propria inflammation	No	1	-	
		Grade 1	2.066	(1.154 to 3.699)	0.015
		Grade 2	4.658	(2.082 to 10.423)	0.000
	Chorion Oedema	No	1	-	
		Yes	1.517	(0.817 to 2.816)	0.186
	Apoptosis	No	1	-	
		Yes	2.280	(1.253 to 4.150)	0.007
	Gland necrosis	No	1	-	
		Yes	2.949	(1.590 to 5.469)	0.001
	Fibrosis	No	1	-	
		Yes	1.238	(0.431 to 3.550)	0.692
	Thrombosis	No	1	-	
		Yes	3.552	(1.549 to 8.147)	0.003
	Capillary dilatation & Congestion haemorrhage	No	1	-	
		Yes	1.256	(0.757 to 2.085)	0.377
	Capillaritis (composite)	No	1	-	
		Grade 1	2.770	(1.028 to 7.464)	0.044
		Grade 2	5.413	(1.504 to 19.477)	0.010
		Grade 3	7.733	(2.778 to 21.525)	0.000
Mitosis	No	1	-		
	Yes	0.863	(0.432 to 1.725)	0.677	
Clinical	Number of Transplantation	No	1	-	
		Yes	1.48	(0.799 to 2.742)	0.213
	Liver Transplantation	No	1	-	
		Yes	0.599	(0.360 to 0.997)	0.049

MULTIVARIATE ANALYSIS

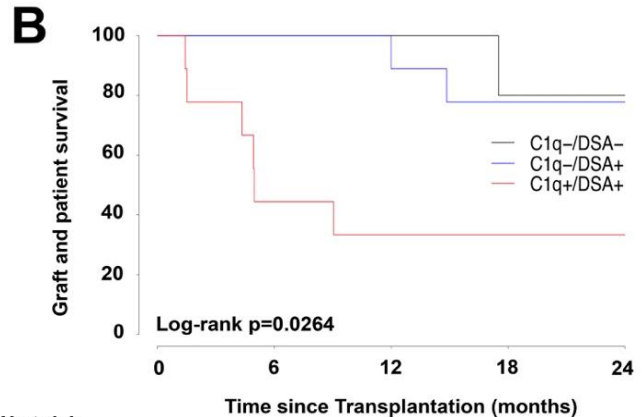
			OR	95% CI	P
Histology	LP Inflammation	No	1	-	
		Grade 1	1.954	(1.021 to 3.741)	0.043
		Grade 2	3.095	(1.239 to 7.736)	0.016
	Ulceration	No	1	-	
		Yes	2.796	(1.185 to 6.597)	0.019
	Chorion Edema	No	1	-	
		Yes	2.160	(1.089 to 4.283)	0.028
	Capillaritis	No	1	-	
		Grade 1	2.004	(0.717 to 5.602)	0.185
		Grade 2	4.016	(1.019 to 15.829)	0.047
Grade 3		5.169	(1.781 to 15.002)	0.003	
Clinical	Liver Transplantation	No	1	-	
		Yes	0.556	(0.308 to 1.003)	0.051

Outcome : Persistence du C4d et C1q binding



N at risk

	0	6	12	18	24
<15% C4d+	8	8	8	7	7
15-30% C4d+	8	7	6	5	5
>30% C4d+	7	3	2	1	1



N at risk

	0	6	12	18	24
C1q-/DSA-	5	5	5	4	4
C1q-/DSA+	9	9	8	6	6
C1q+/DSA+	9	4	3	3	3

#histologie_comparee

- Comme attendu, “marche” plutôt pas mal dans une pathologie comme le rejet humoral (histologie comme reflet de la physiopathologie)
- permet d'étendre les connaissances à de nouvelles SOT
- Attention tout de même aux spécificités d'organes : contact avec le milieu extérieur & modulation par l'infectieux, organe « immun »
- Garder aussi en tête que on se place « dans la maladie » et que l'histopathologie comparée ne dit répond pas vraiment à la place respective du rejet humoral dans les différentes SOT

Merci !

