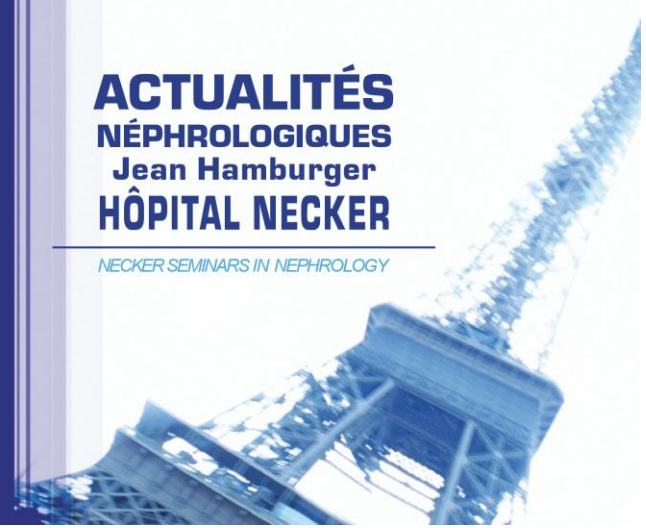


Mardi 13 mai 2025

Nouvelles cibles thérapeutiques en transplantation

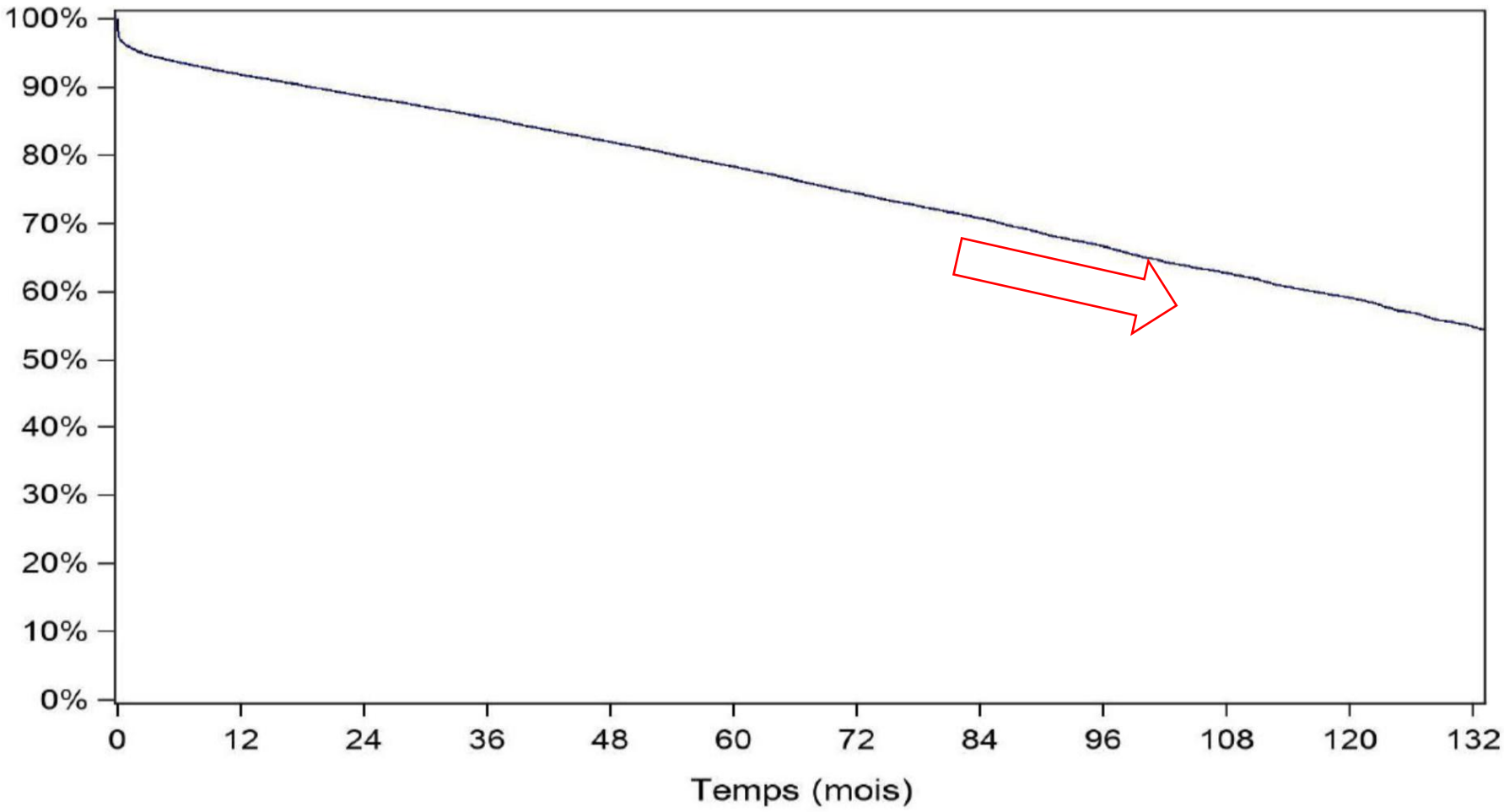
Why and how should we target NK cells ?

@Olivier_Thaunat

Lyon - France

One organ for life: unmet need in renal transplantation

38342 renal transplantations
(France - 2007 to 2018)



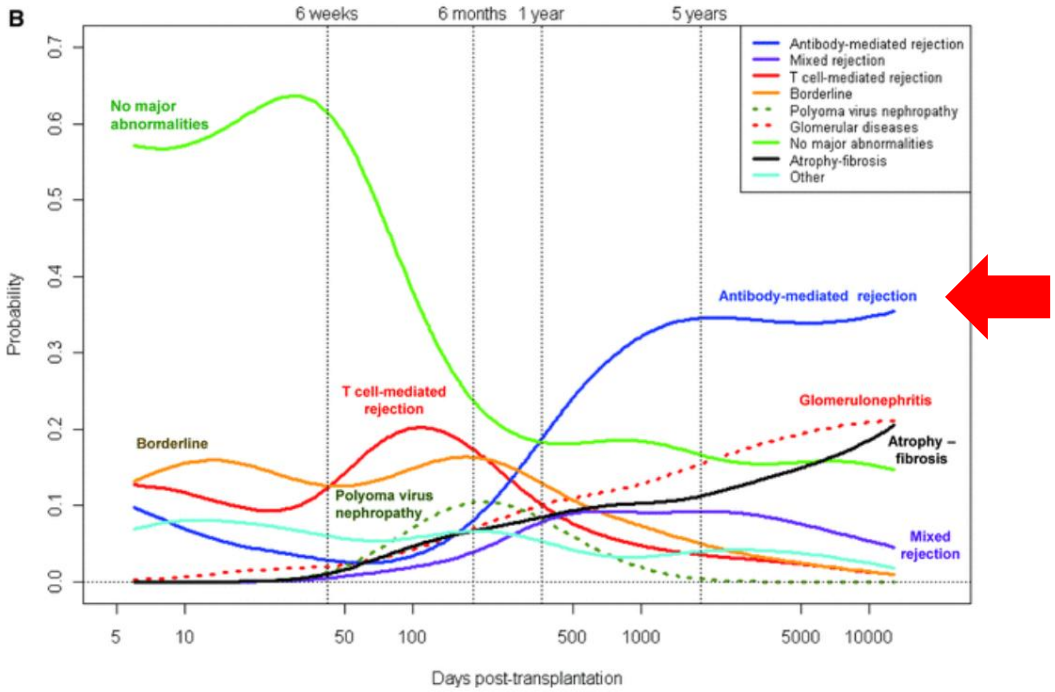
https://www.agence-biomedecine.fr

What is the cause of allograft failure?

American Journal of Transplantation 2012; 12: 388–399
Wiley Periodicals Inc.

Understanding the Causes of Kidney Transplant Failure: The Dominant Role of Antibody-Mediated Rejection and Nonadherence

J. Sellarés[a,b], D. G. de Freitas[a,b], M. Mengel[a,c], J. Reeve[a,c], G. Einecke[d], B. Sis[a,c], L. G. Hidalgo[a,c], K. Famulski[a,c], A. Matas[e] and P. F. Halloran[a,b,*]

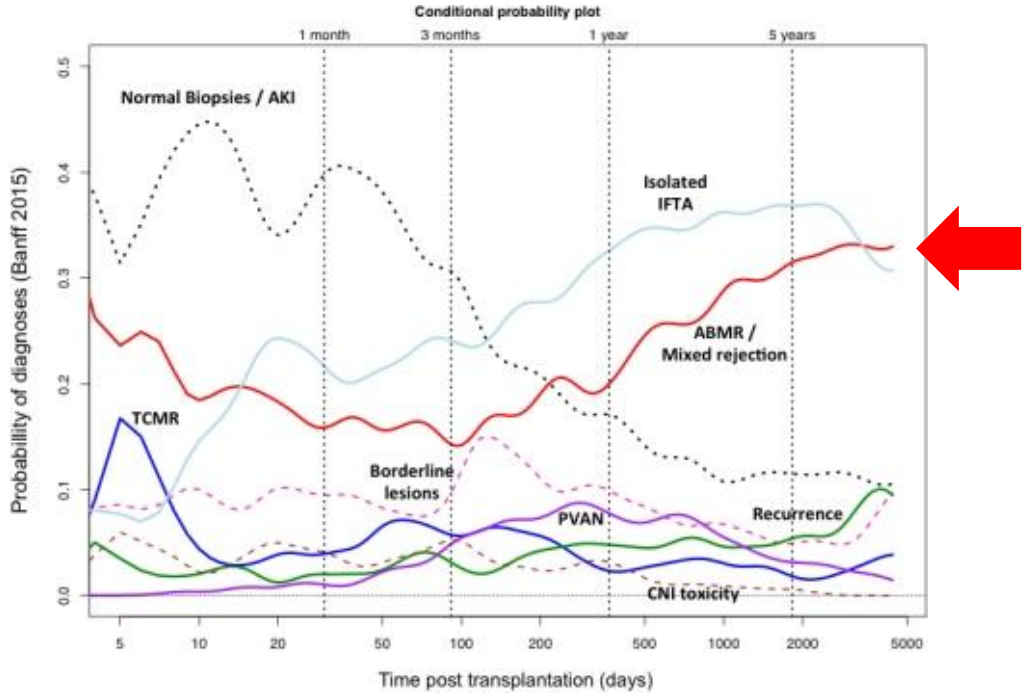


Identifying the Specific Causes of Kidney Allograft Loss: A Population Based Study

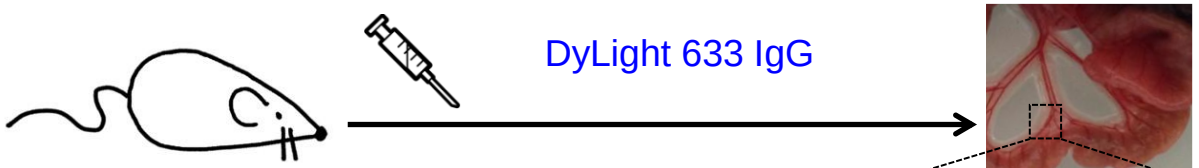
C. Loheac, O. Aubert, D. Viglietti, N. Kamar, M. Delahousse, C. Lefaucheur, A. Loupy.

Paris Translational Research Center for Organ Transplantation, Paris, France.

Meeting: 2018 American Transplant Congress



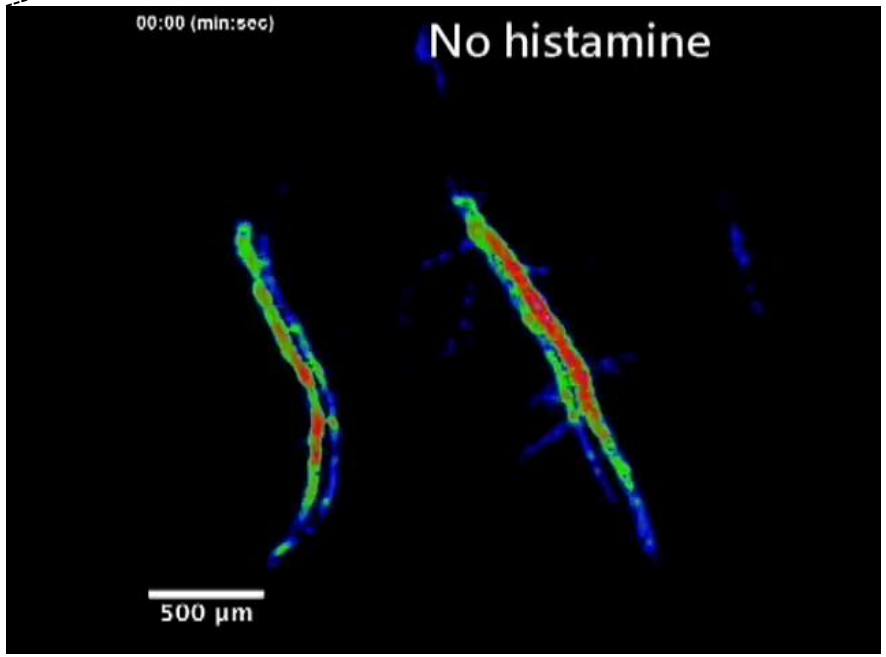
Size matters: DSA are sequestrated in the circulation

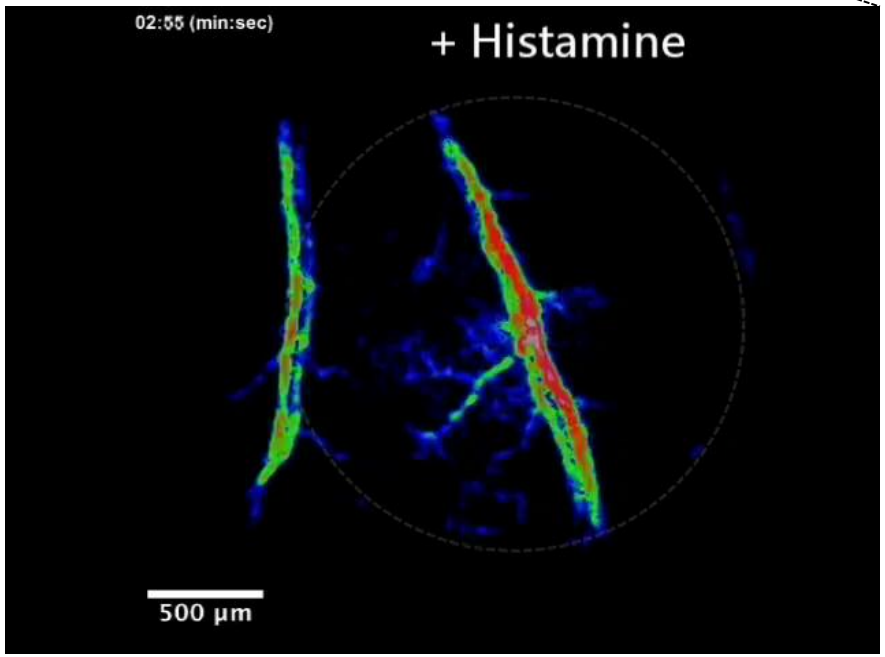


DyLight 633 IgG

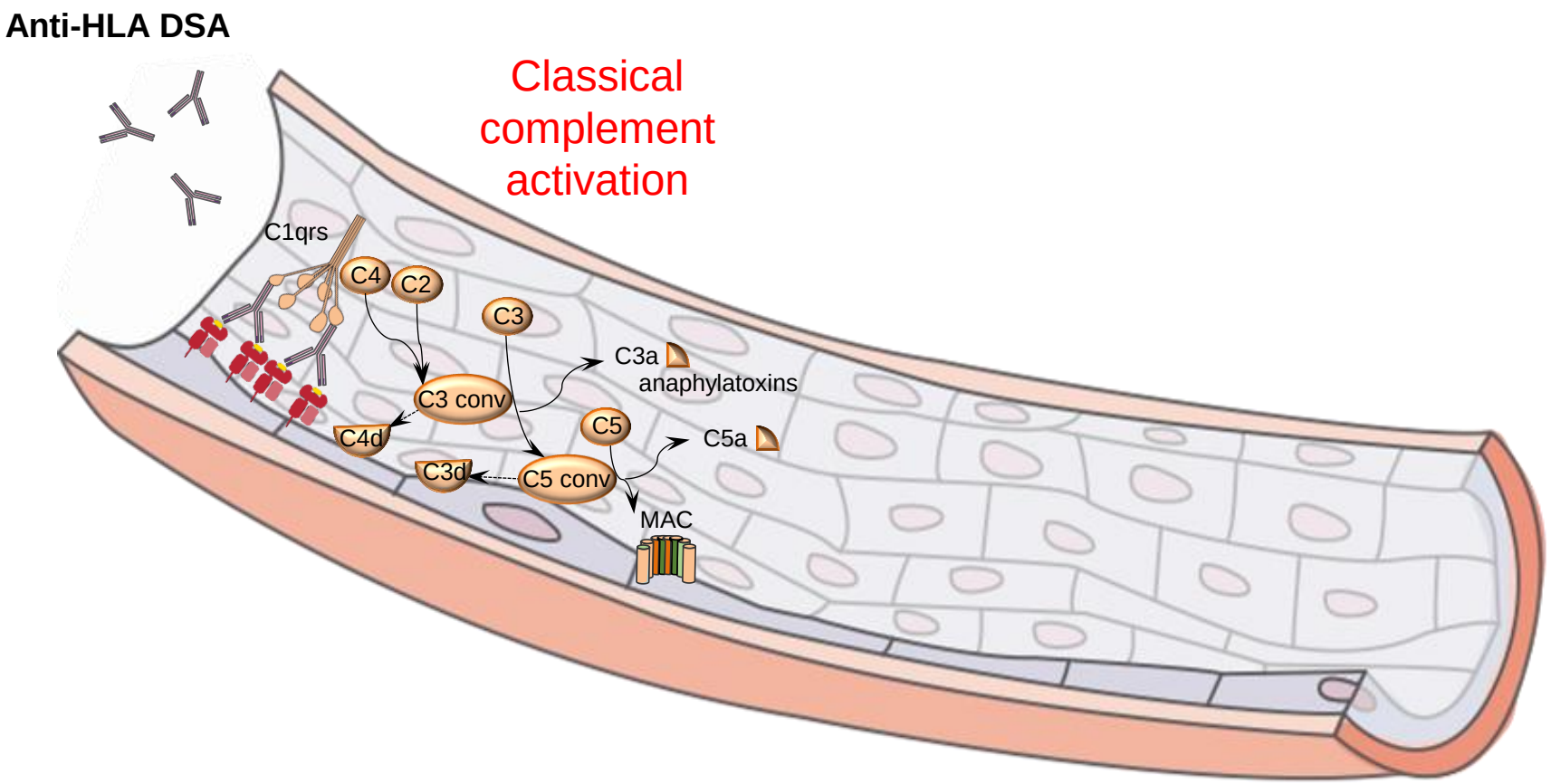
Intravital microscopy

Chen, J Clin Invest, 2018



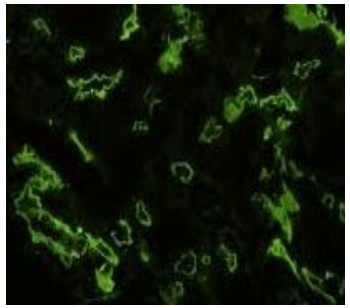


Immunopathology of AMR

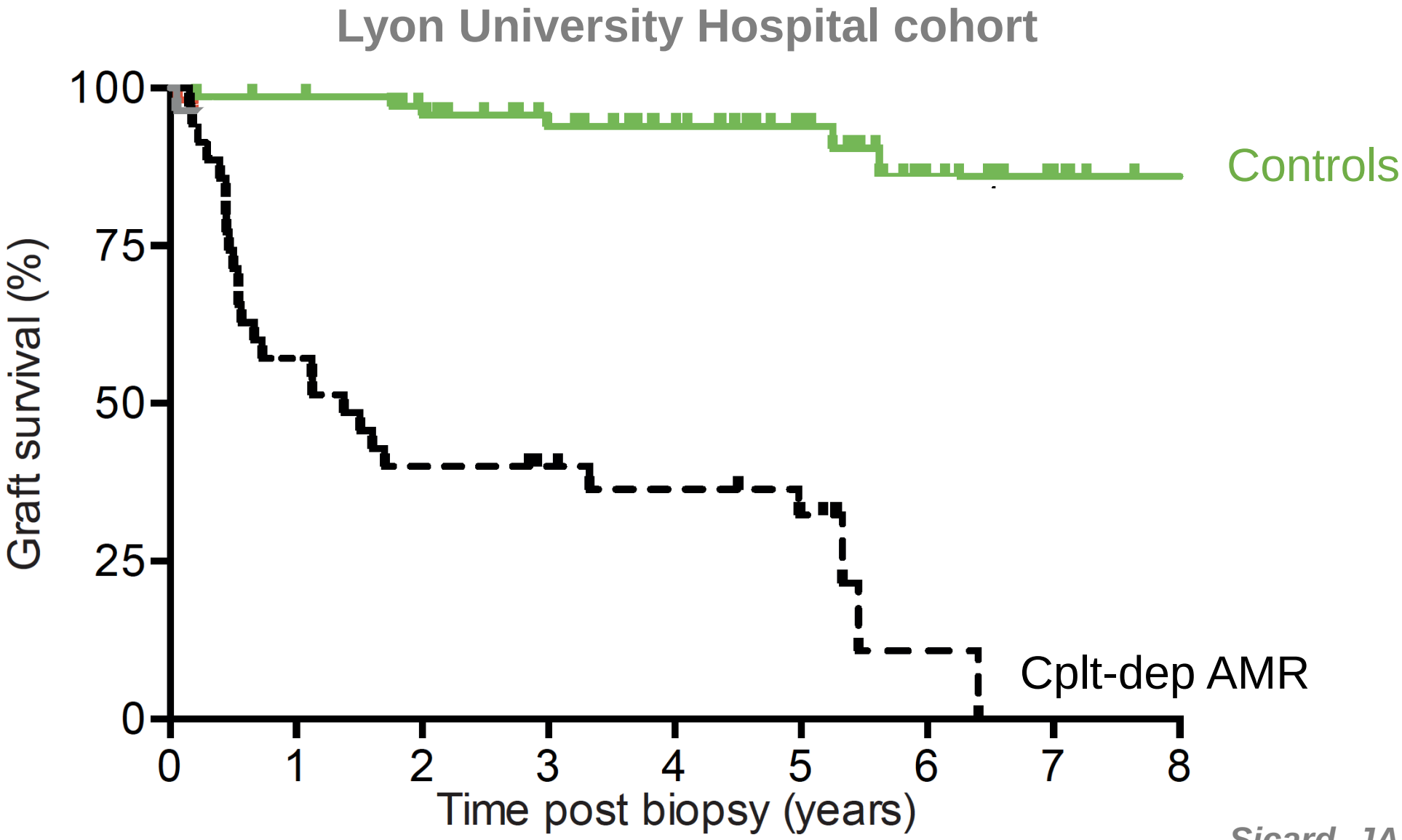


Histological features in the biopsy

C4d

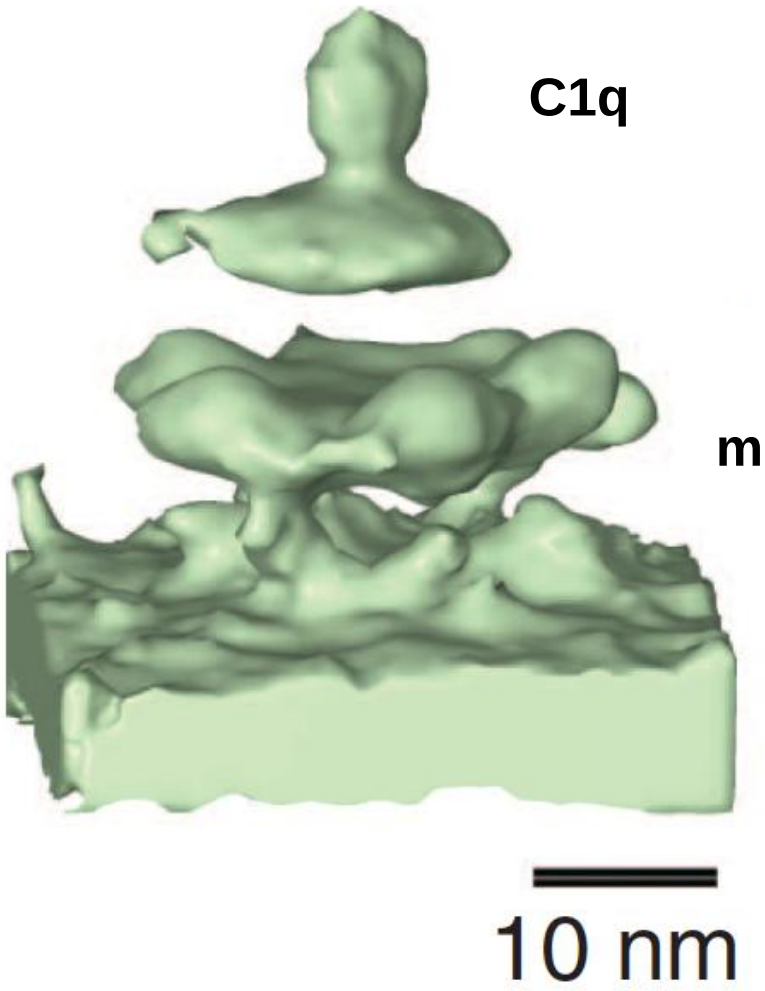


"Complement-dependent AMR" and renal graft survival

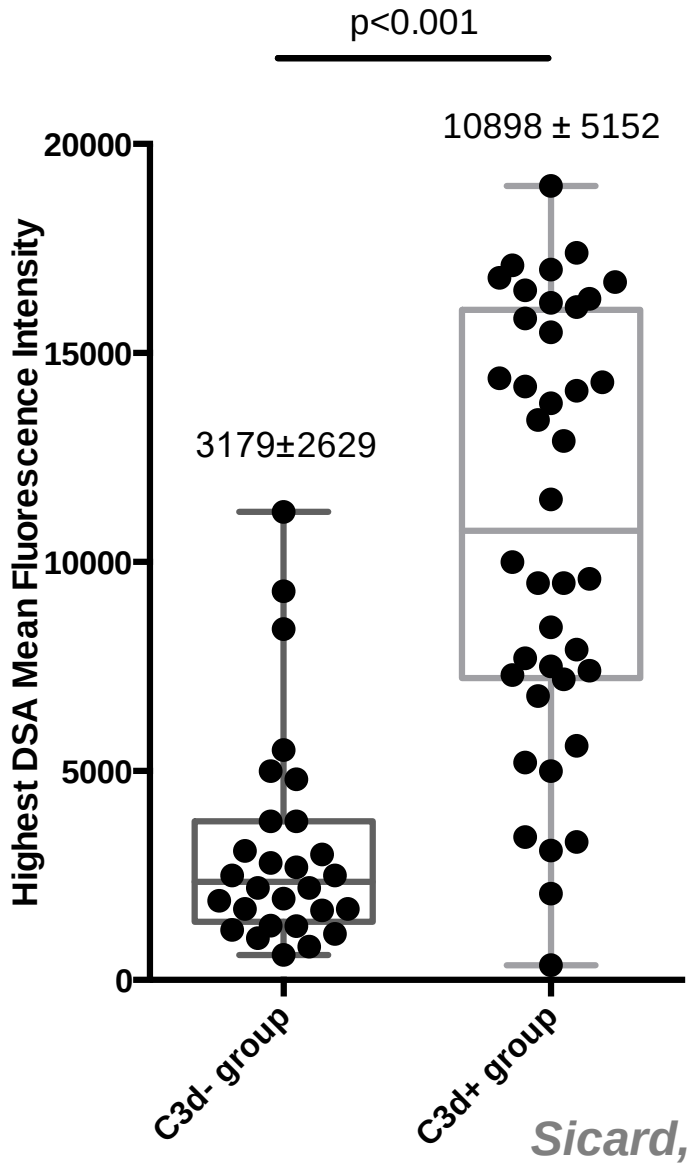


Sicard, JASN, 2015

DSA-mediated complement activation

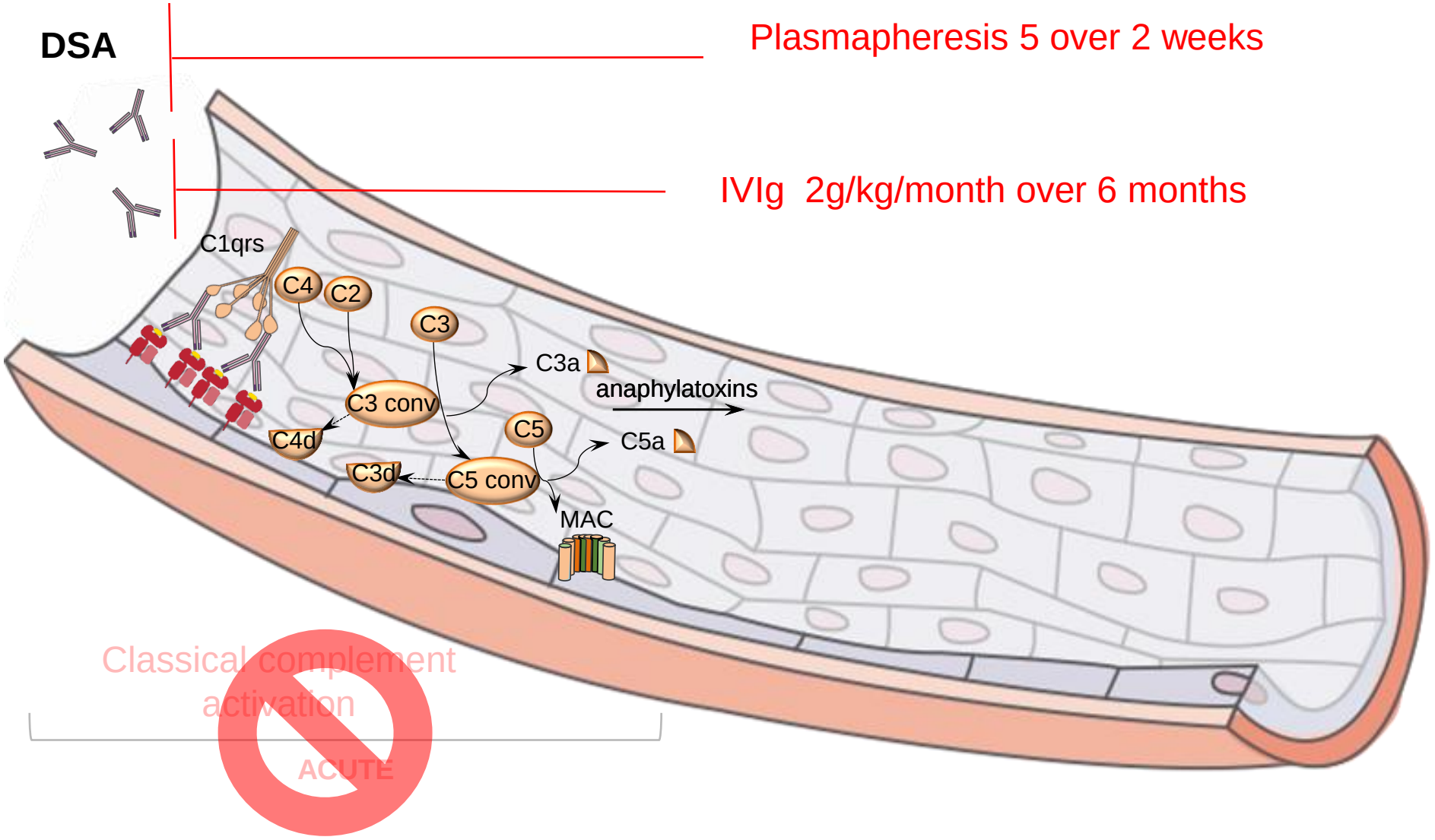


Diebolder, Science, 2014

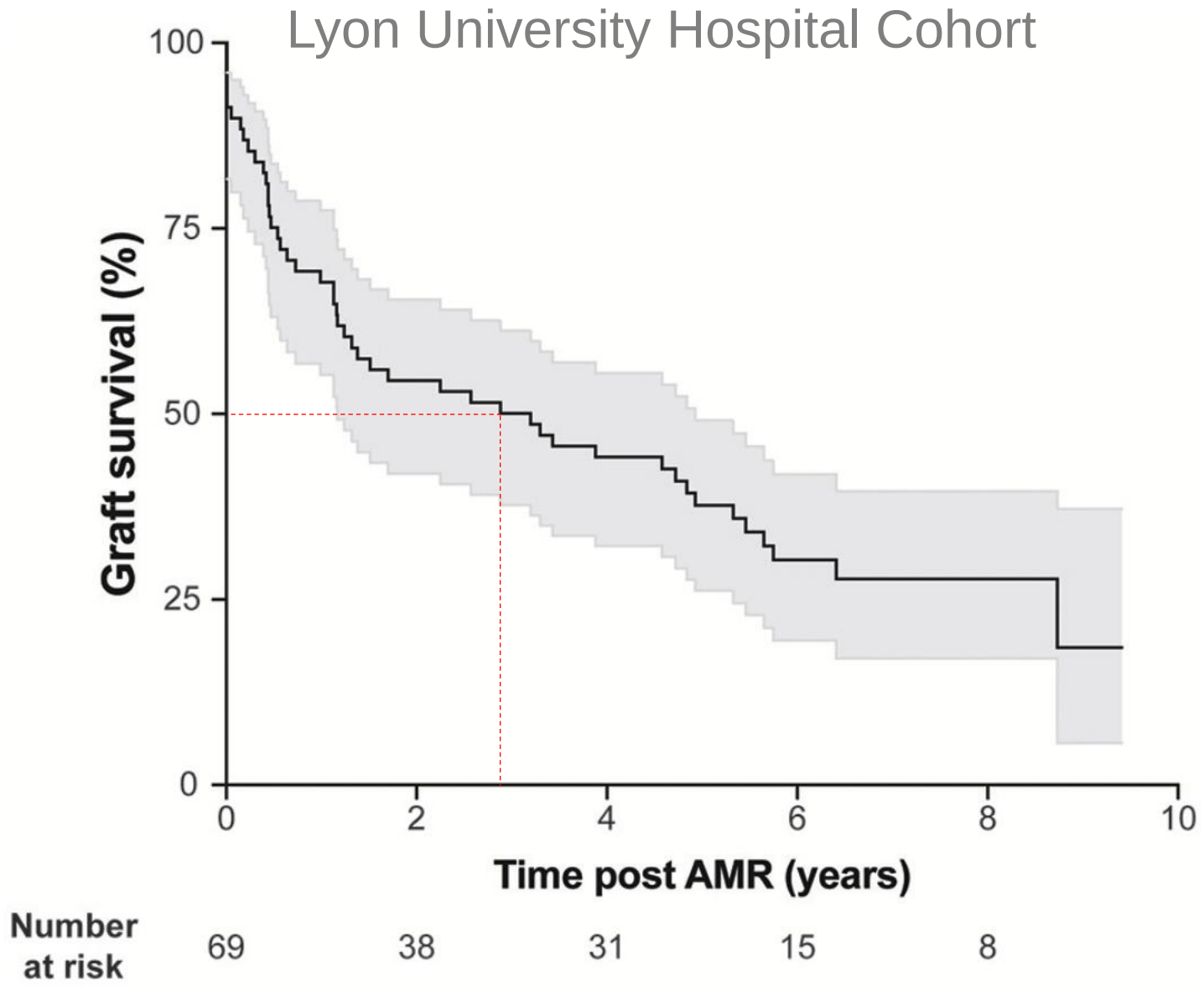


Sicard, JASN, 2015

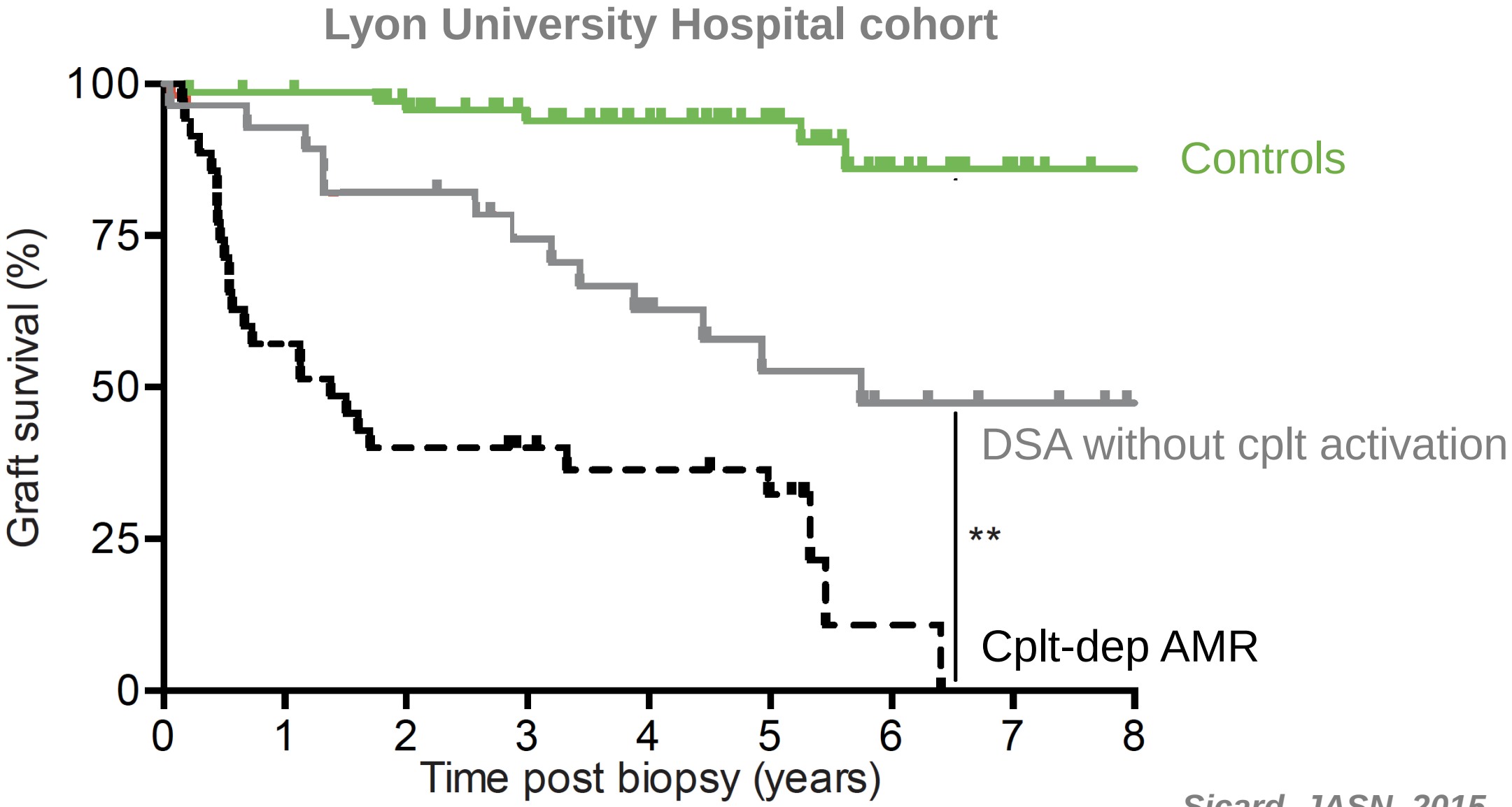
Treatment of AMR



Therapeutic outcomes in AMR



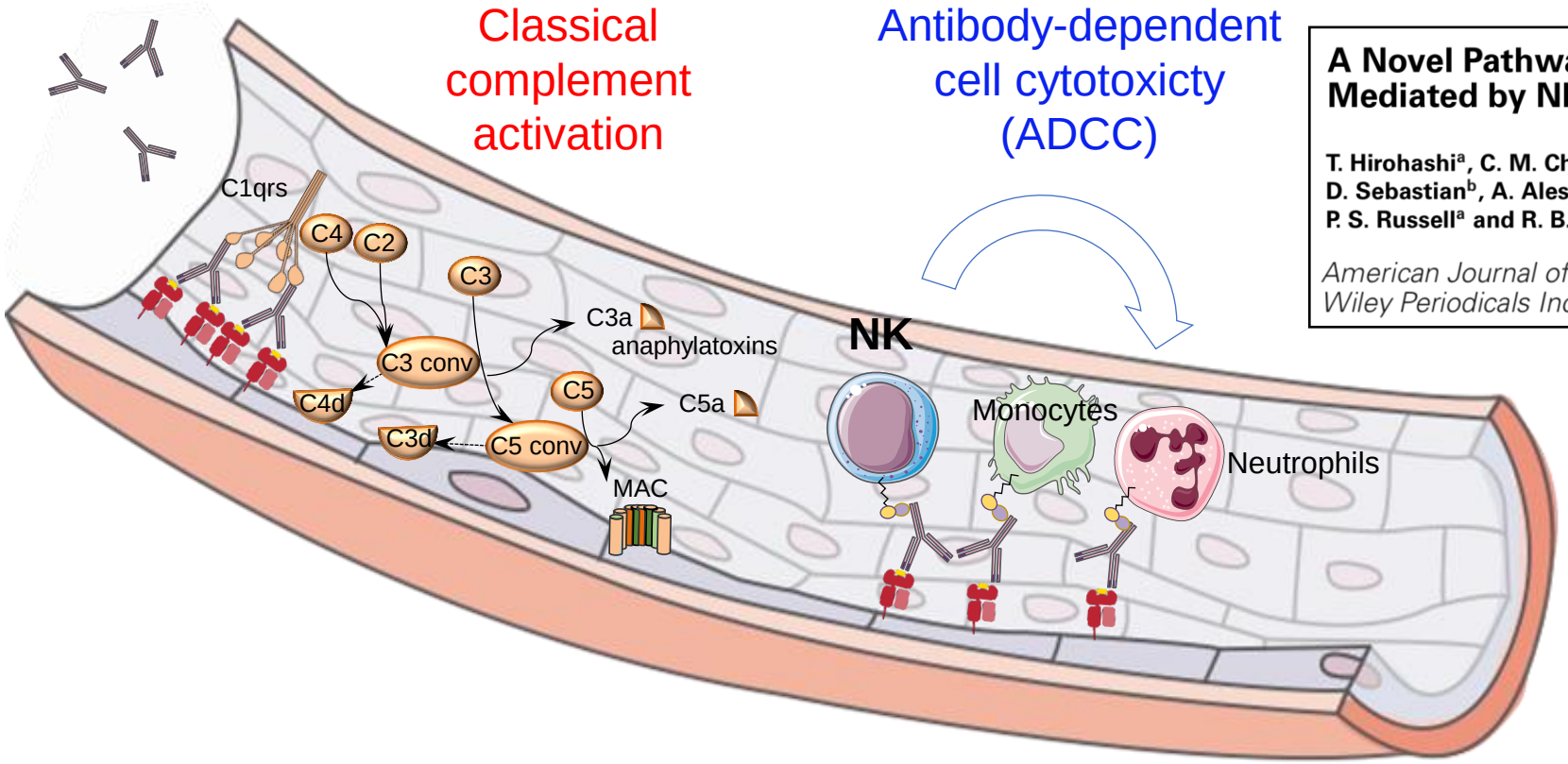
"Complement-dependent AMR" and renal graft survival



Sicard, JASN, 2015

Immunopathology of AMR

Anti-HLA DSA



A Novel Pathway of Chronic Allograft Rejection Mediated by NK Cells and Alloantibody

T. Hirohashi[a], C. M. Chase[a], P. Della Pelle[b], D. Sebastian[b], A. Alessandrini[a], J. C. Madsen[a], P. S. Russell[a] and R. B. Colvin[b,*]

American Journal of Transplantation 2012; 12: 313–321
Wiley Periodicals Inc.

Histological features in the biopsy

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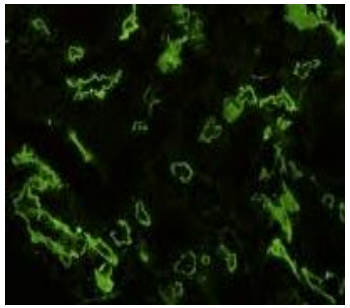
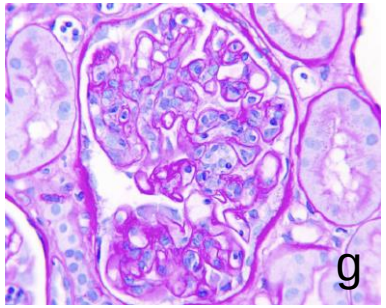
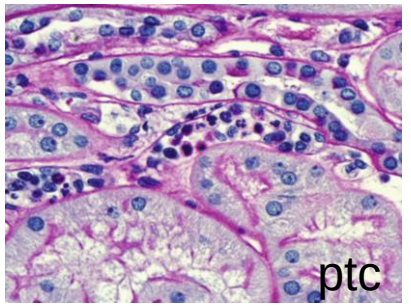


MVI





Why and how should we target NK cells ?

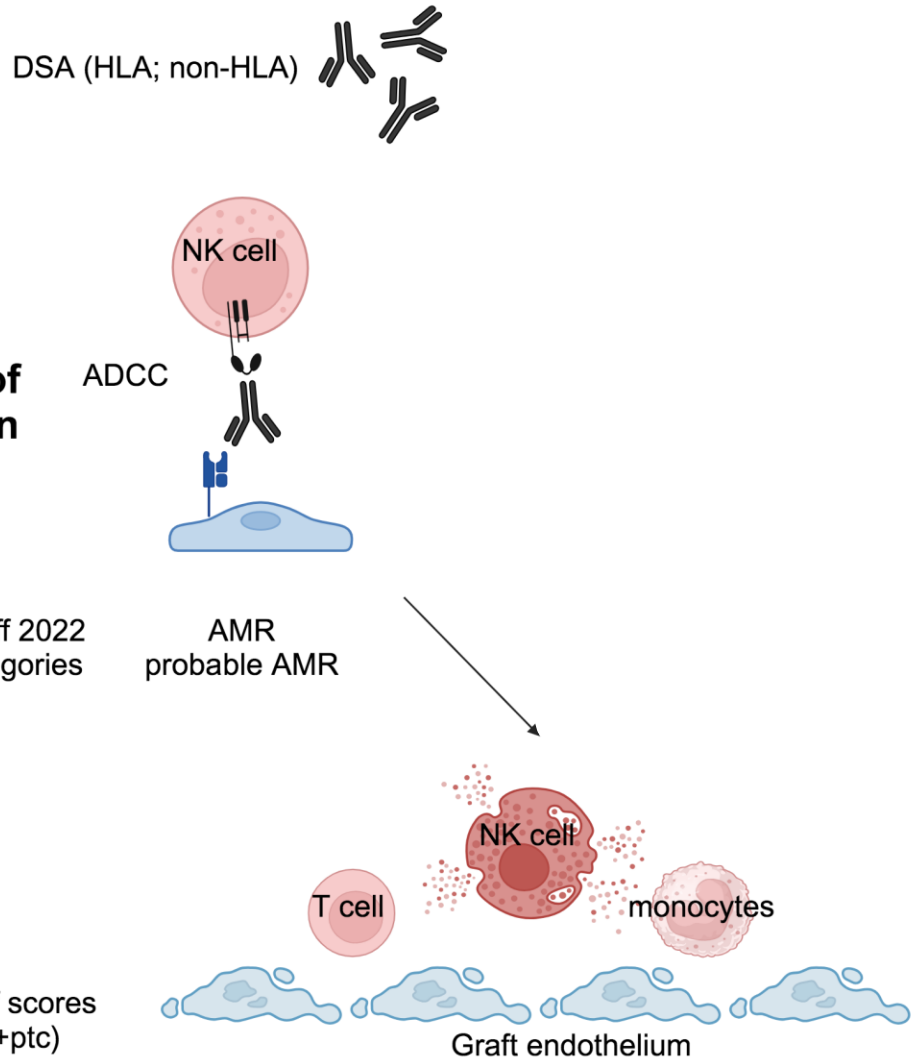
ADCC-dep (chronic) AMR: major cause of graft failure
=> Targeting NK cells seems a promising approach…

Innate cells are dowstream effectors in rejection

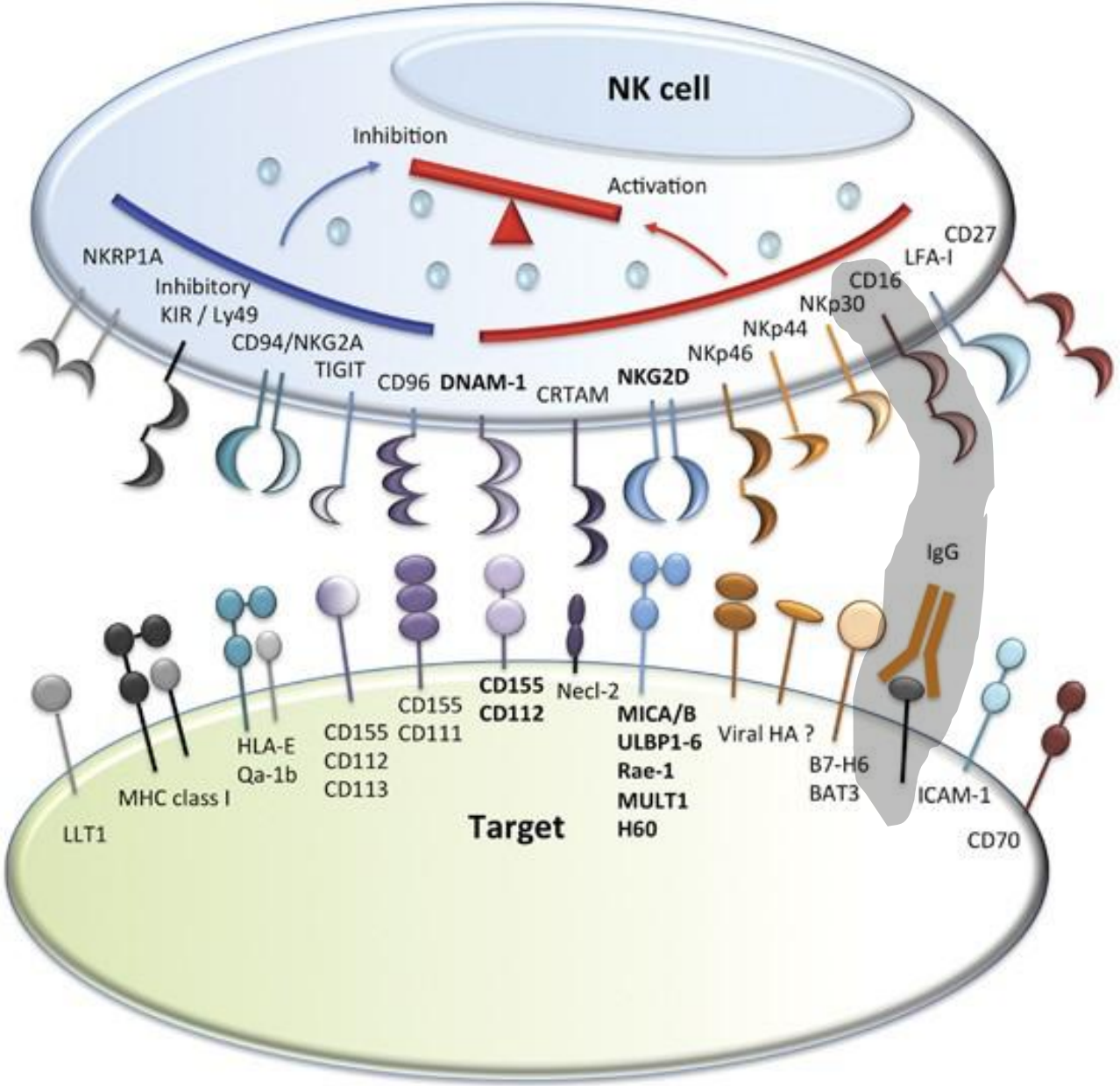
e.g. role of NK in AMR

Adaptive immunity
(allorecognition)

Innate immunity
(damages)



NK cell receptors

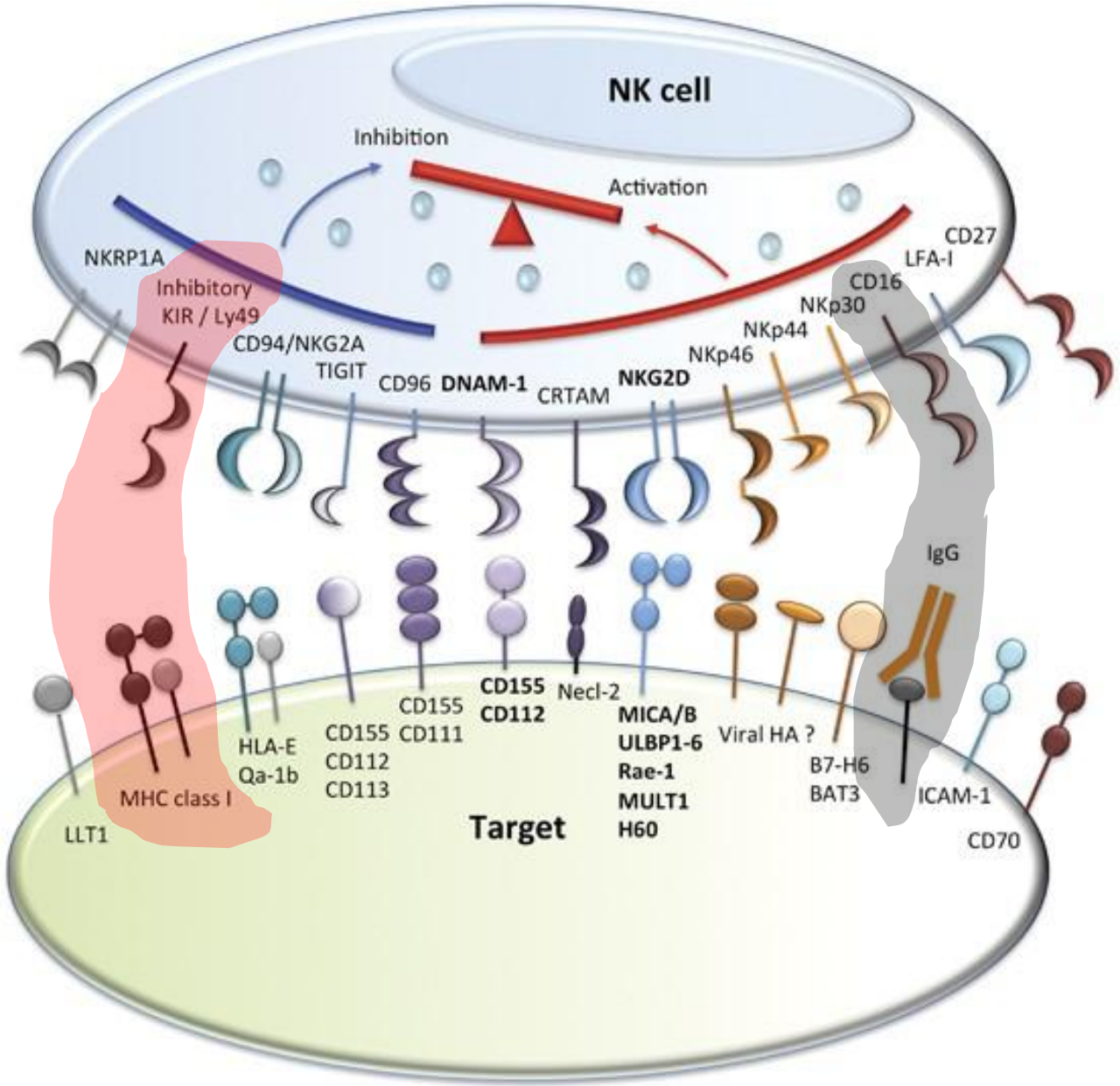


"AMR"

Antibody-dependent cell cytotoxicity

NK cell receptors

Missing self ??

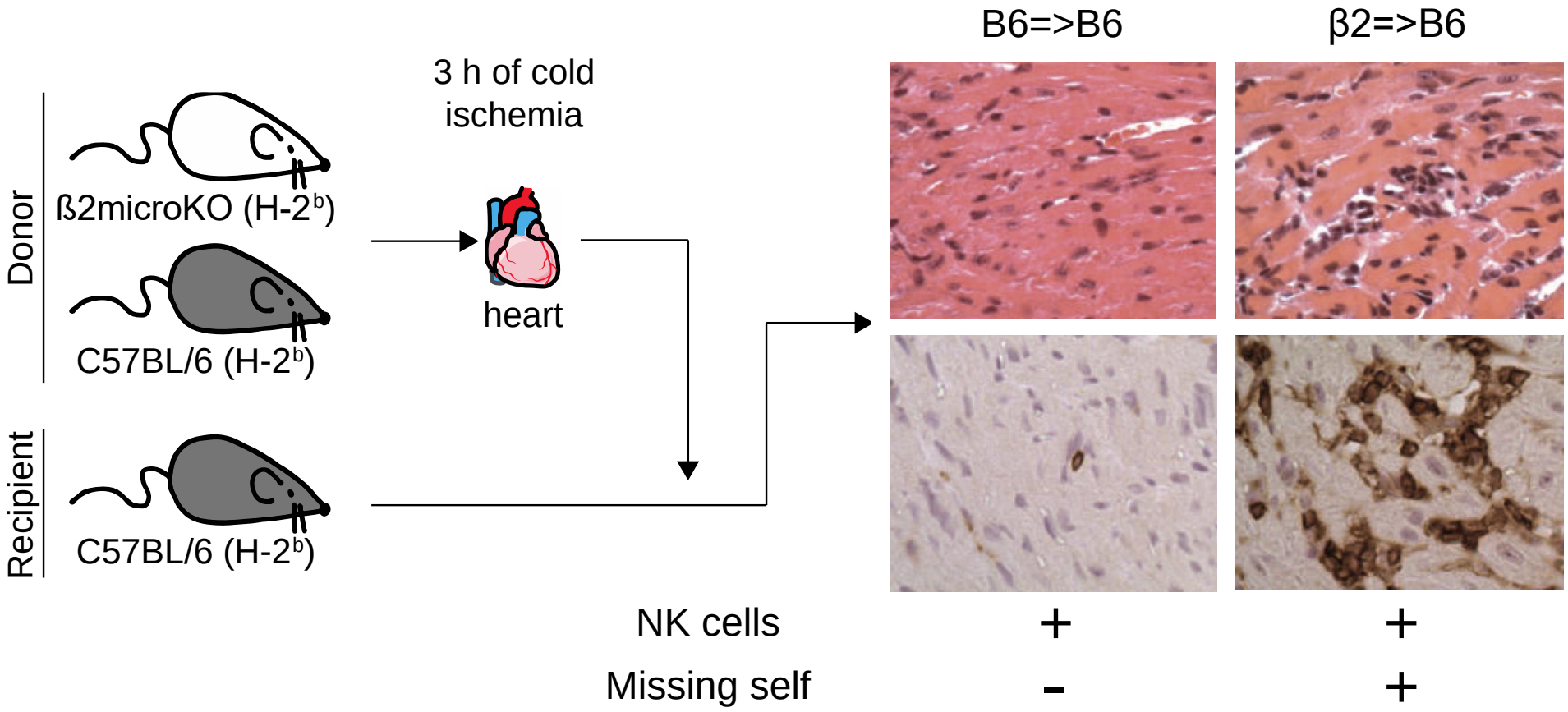


"AMR"

Antibody-dependent cell cytotoxicity

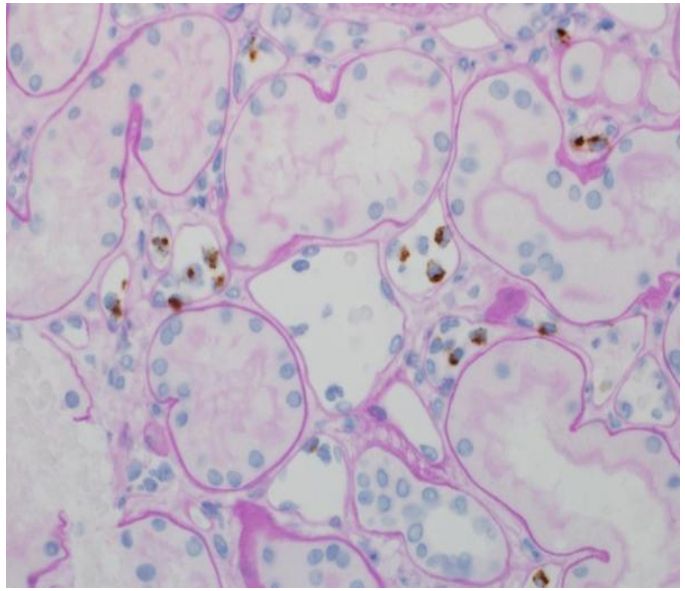
In vivo model

Nat Comms, 2019



Antibody-independent MVI

Clinical validation



Microvascular inflammation (MVI+)

in 129 patients on 938 patients screened

→ MVI-DSA-
75 patients
Ctl group

↓

Donor specific antibodies

(anti-HLA and non-HLA)

↓ YES
MVI+DSA+
75 patients

↓ NO
MVI+DSA-
54 patients

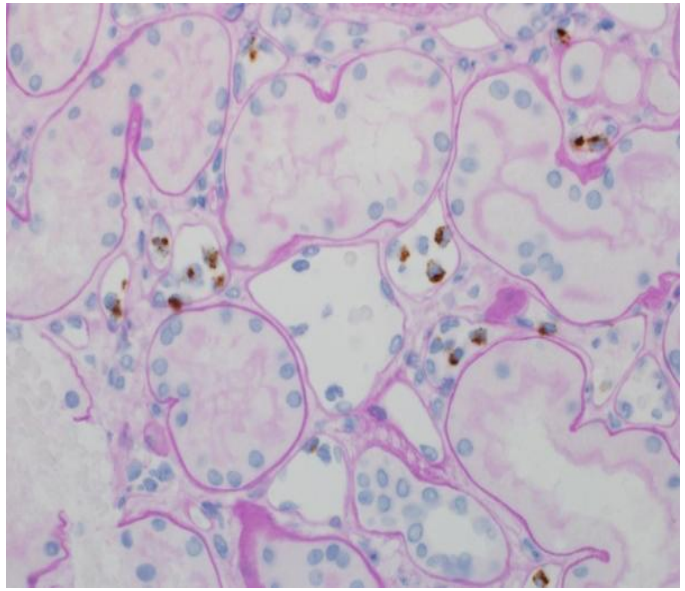
C3d binding assay

\+ → MVI+DSA+C3d+
40 patients

\- → MVI+DSA+C3d-
25 patients

Nat Comms, 2019

Clinical validation



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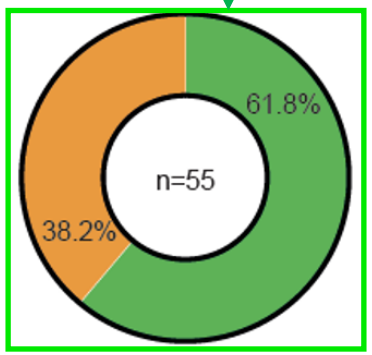

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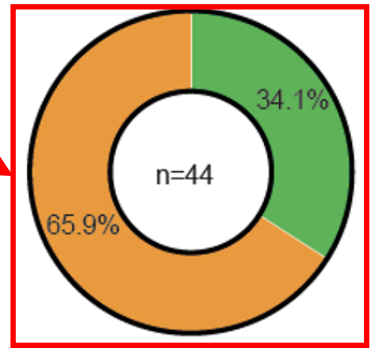
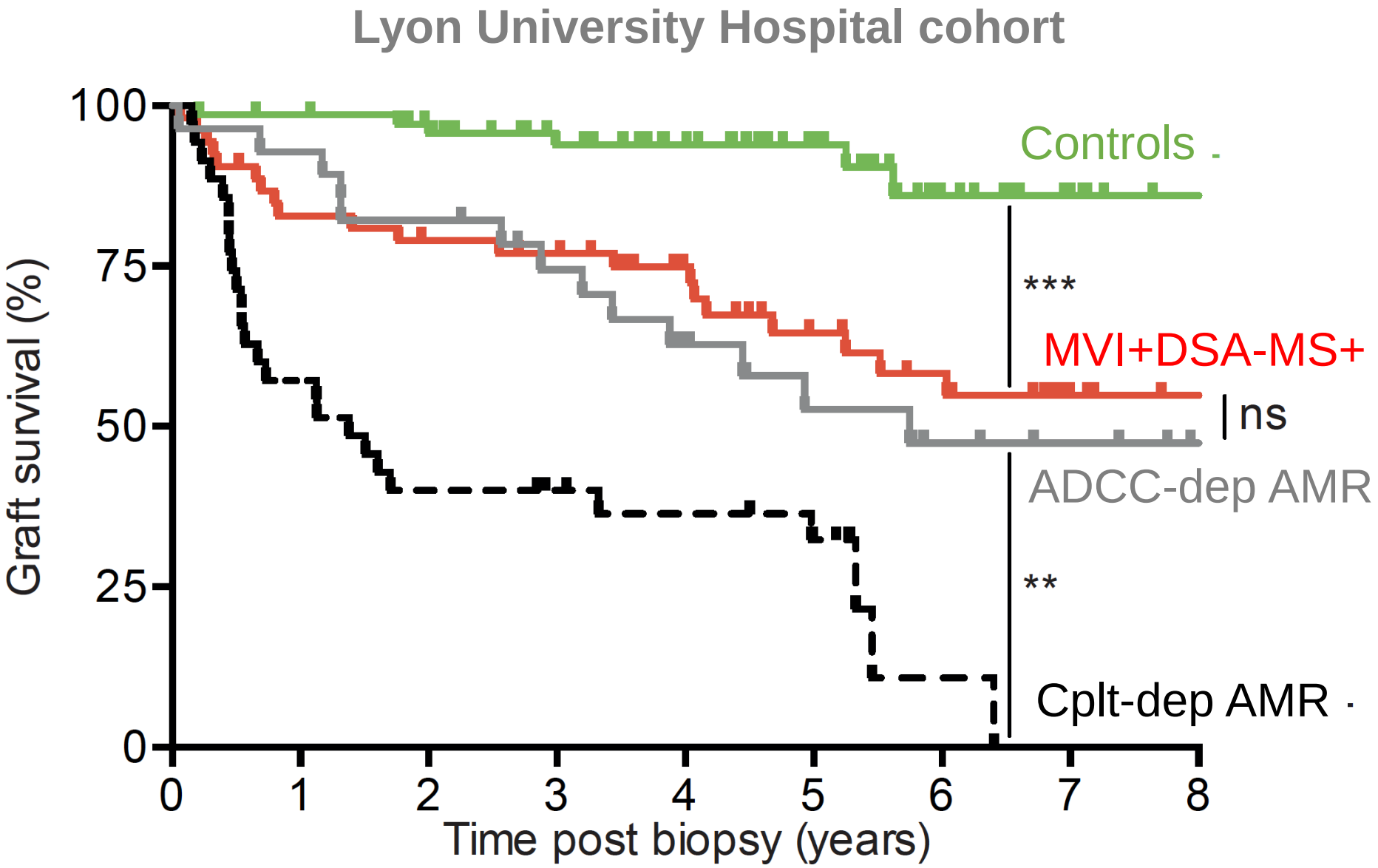


Missing self
No missing self

Nat Comms, 2019

Clinical validation

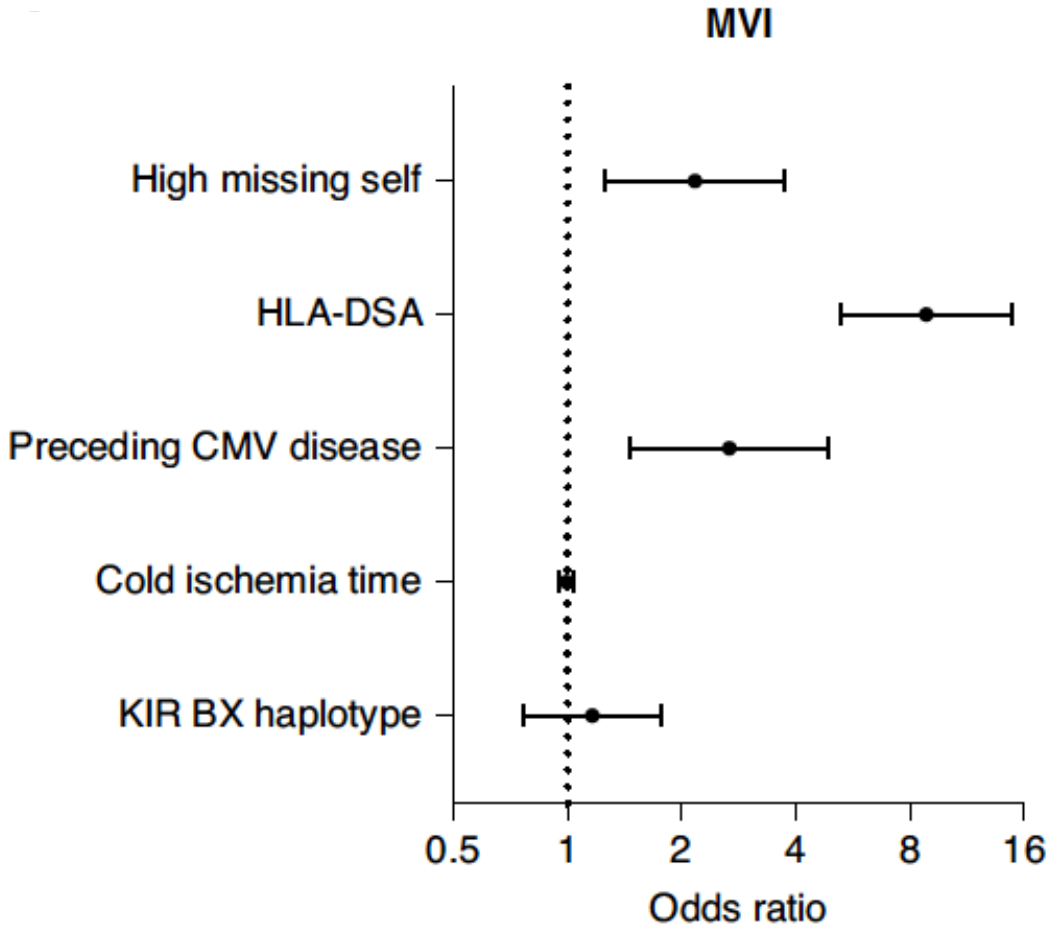


Nat Comms, 2019

External validation

Population-based study of 924 consecutive kidney transplantations

Collaboration with M. Naesens & J. Calleymen



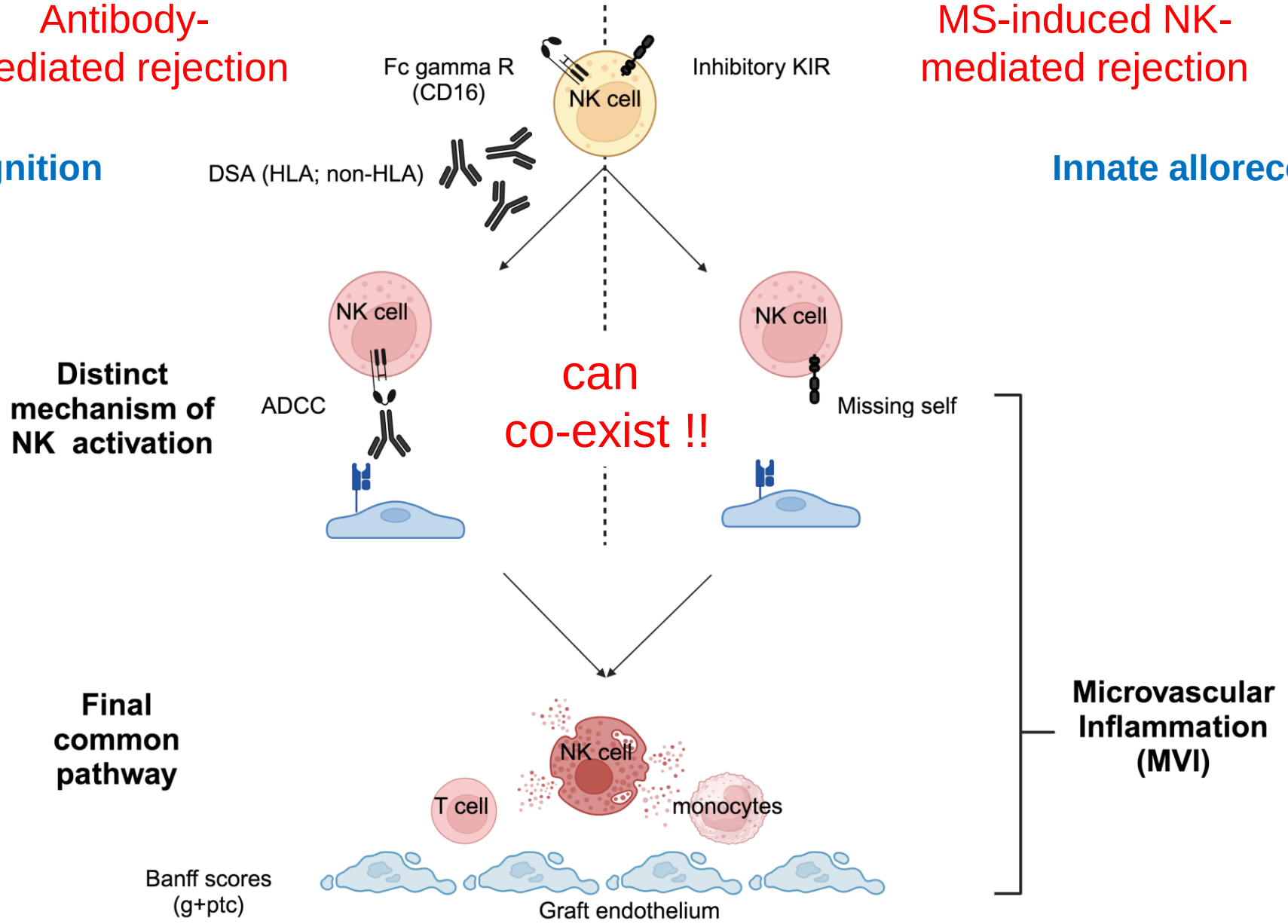
MVI = final common pathway of distinct rejection endotypes

Antibody-mediated rejection

MS-induced NK-mediated rejection

Adaptive allorecognition

Innate allorecognition



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ADCC-dep (chronic) AMR = major cause of graft failure
=> Targeting NK cells seems a promising approach…

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Why and how should we target NK cells ?

ADCC-dep (chronic) AMR = major cause of graft failure
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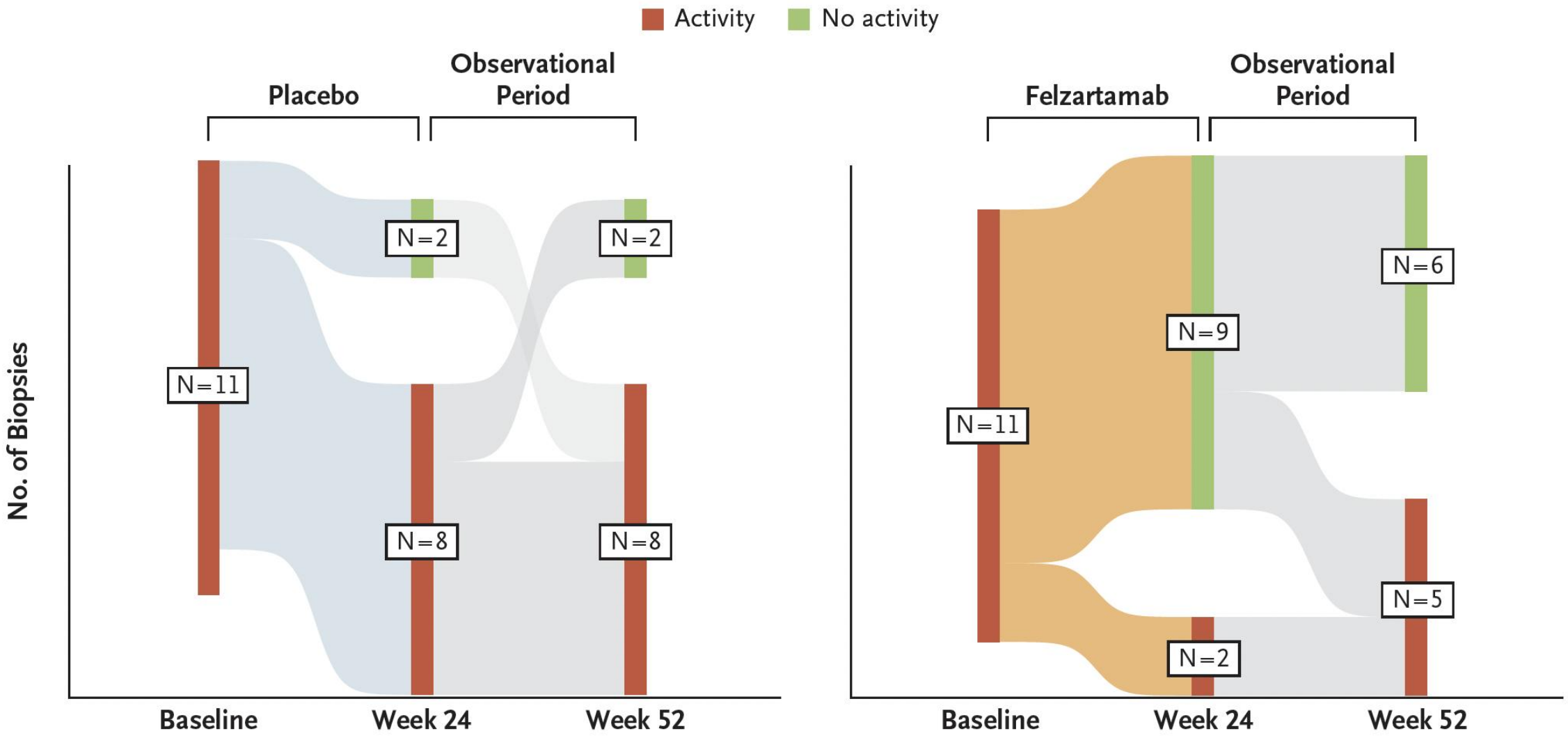
MS-induced NK cell-mediated rejection
=> Targeting NK cells seems a promising approach…

How should we do it?

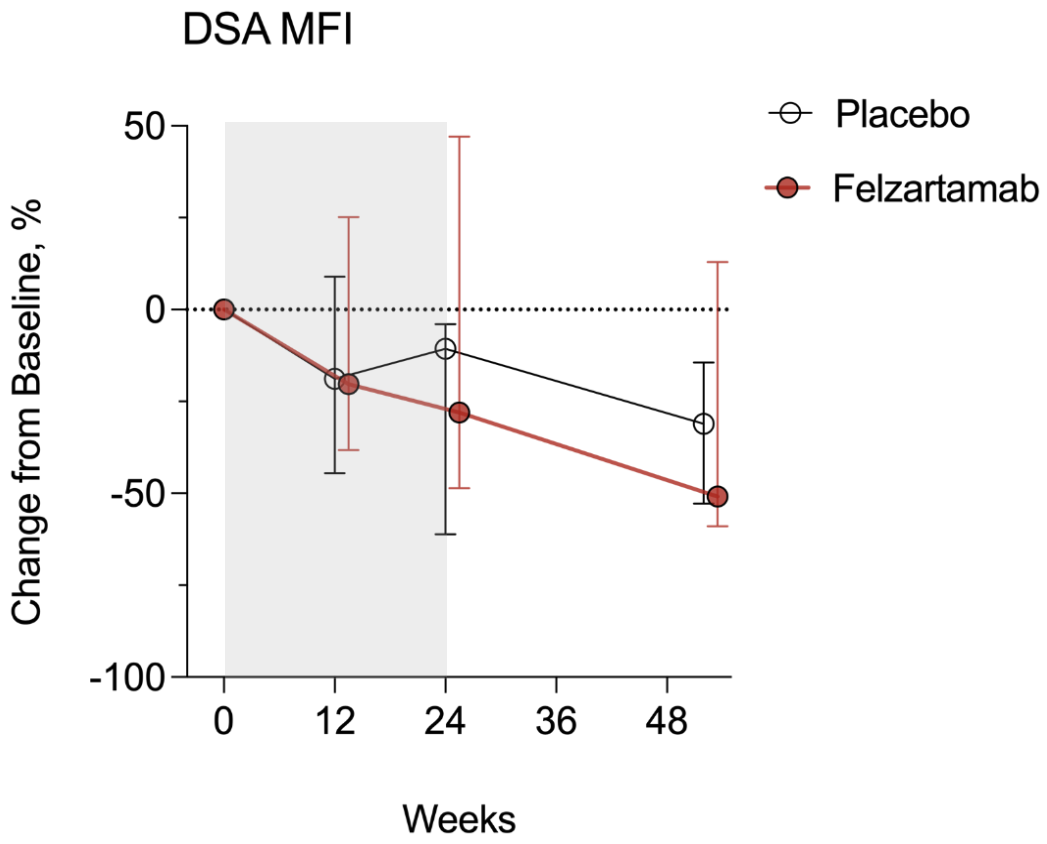
Felzartamab (transiently) reverses DSA-induced MVI



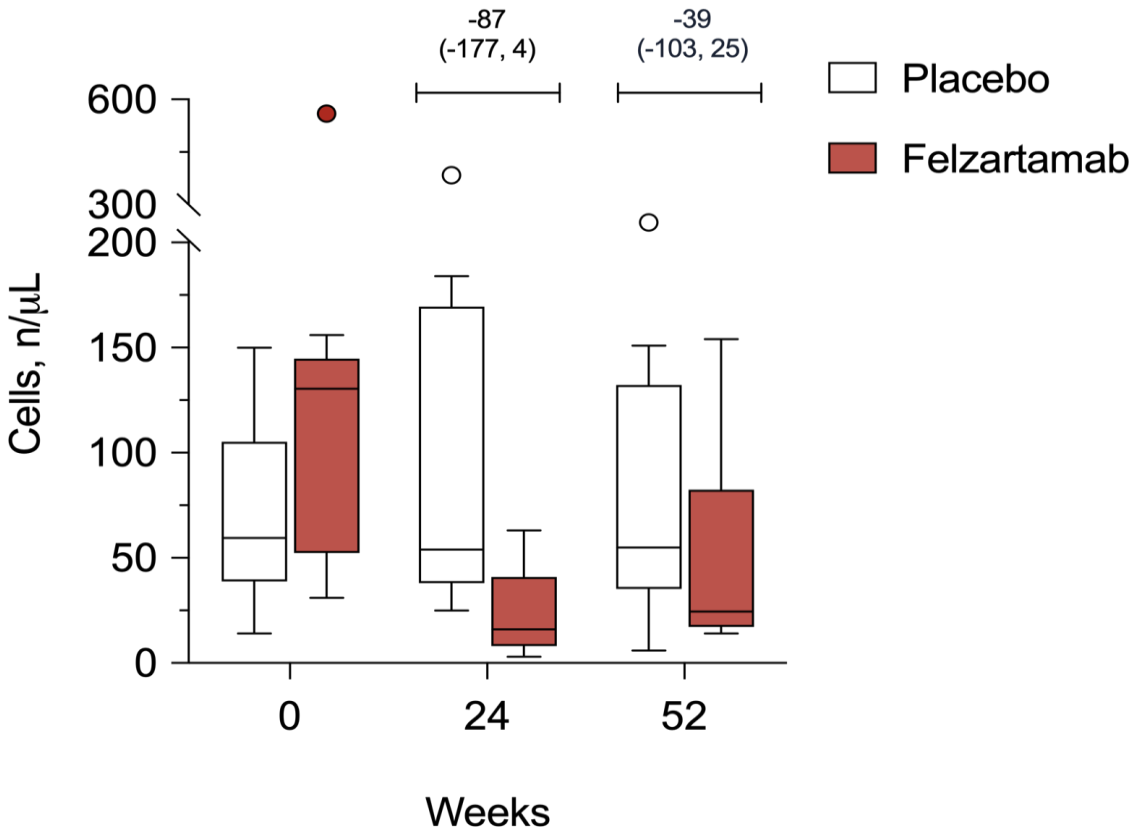
Mayer, NEJM, 2024

Felzartamab (anti-CD38)

Not through its action on PC…



By depleting NK!



Mayer, NEJM, 2024

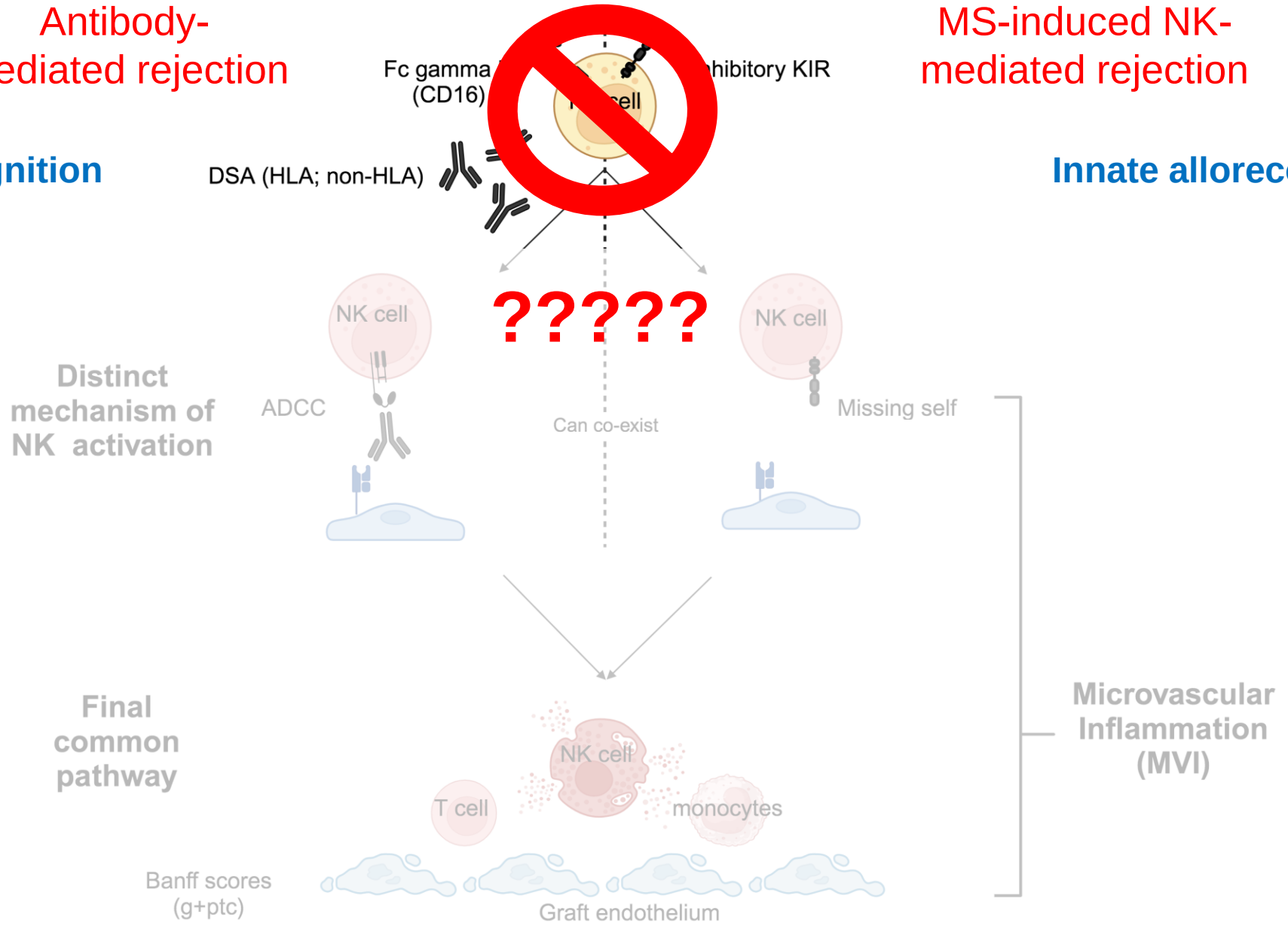
Can NK depletion cure both AMR and MS-induced MVI ?

Antibody-mediated rejection

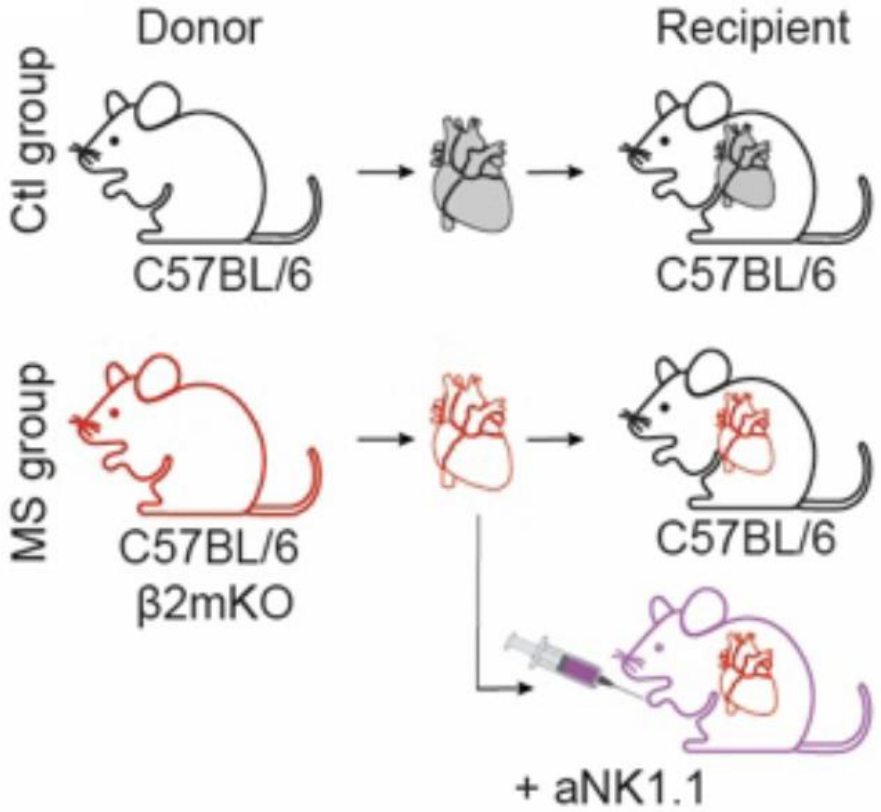
MS-induced NK-mediated rejection

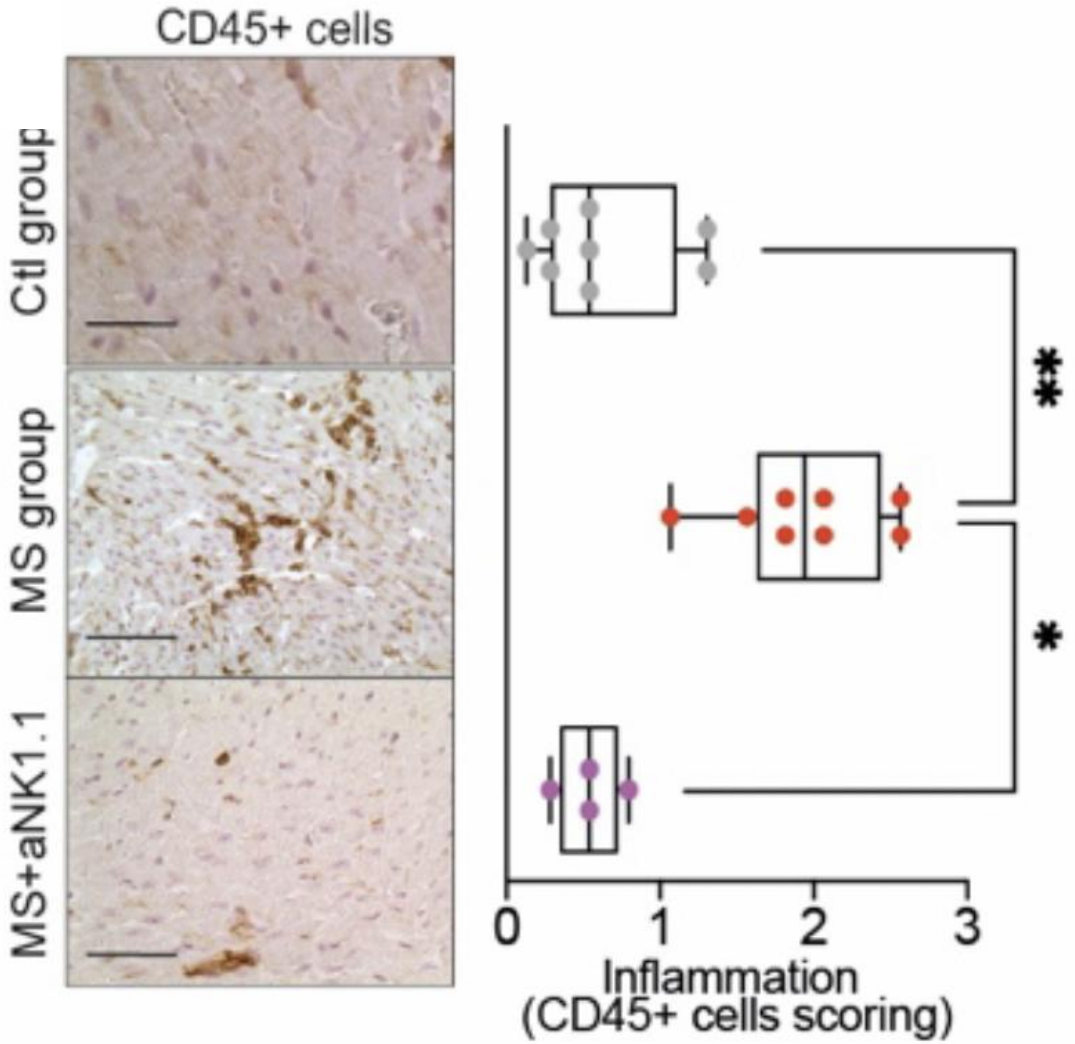
Adaptive allorecognition

Innate allorecognition



In vivo model





Conclusion

Recognition of allogeneic non-self is NOT a prerogative of adaptive immunity => innate allorecognition !

Distinct allorecognition mechanisms converge toward a final common pathway => MVI lesions => chronic vascular rejection

The entering point in this final common pathway is NK cell activation

Conclusion

Sensing of allogeneic non-self is NOT a prerogative of adaptive immunity => innate allorecognition !

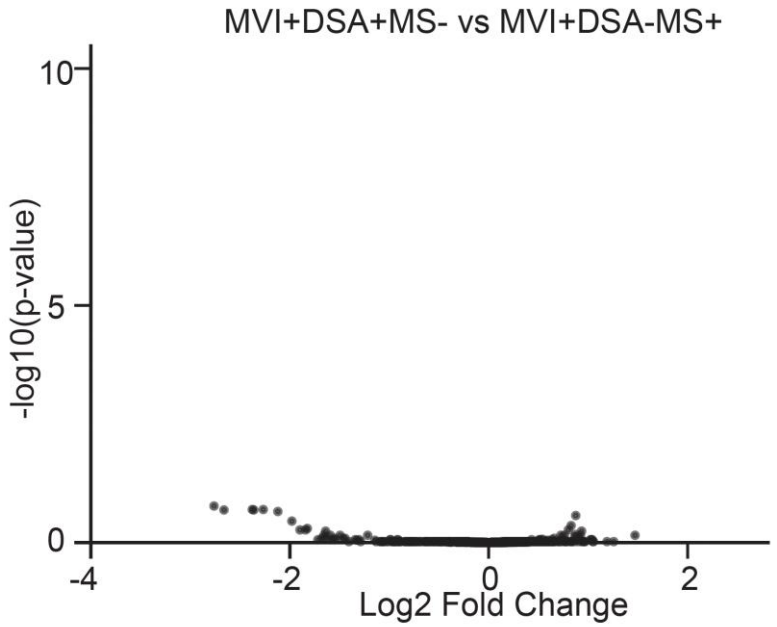
Distinct allorecognition mechanisms converge toward a final common pathway => MVI lesions => chronic vascular rejection

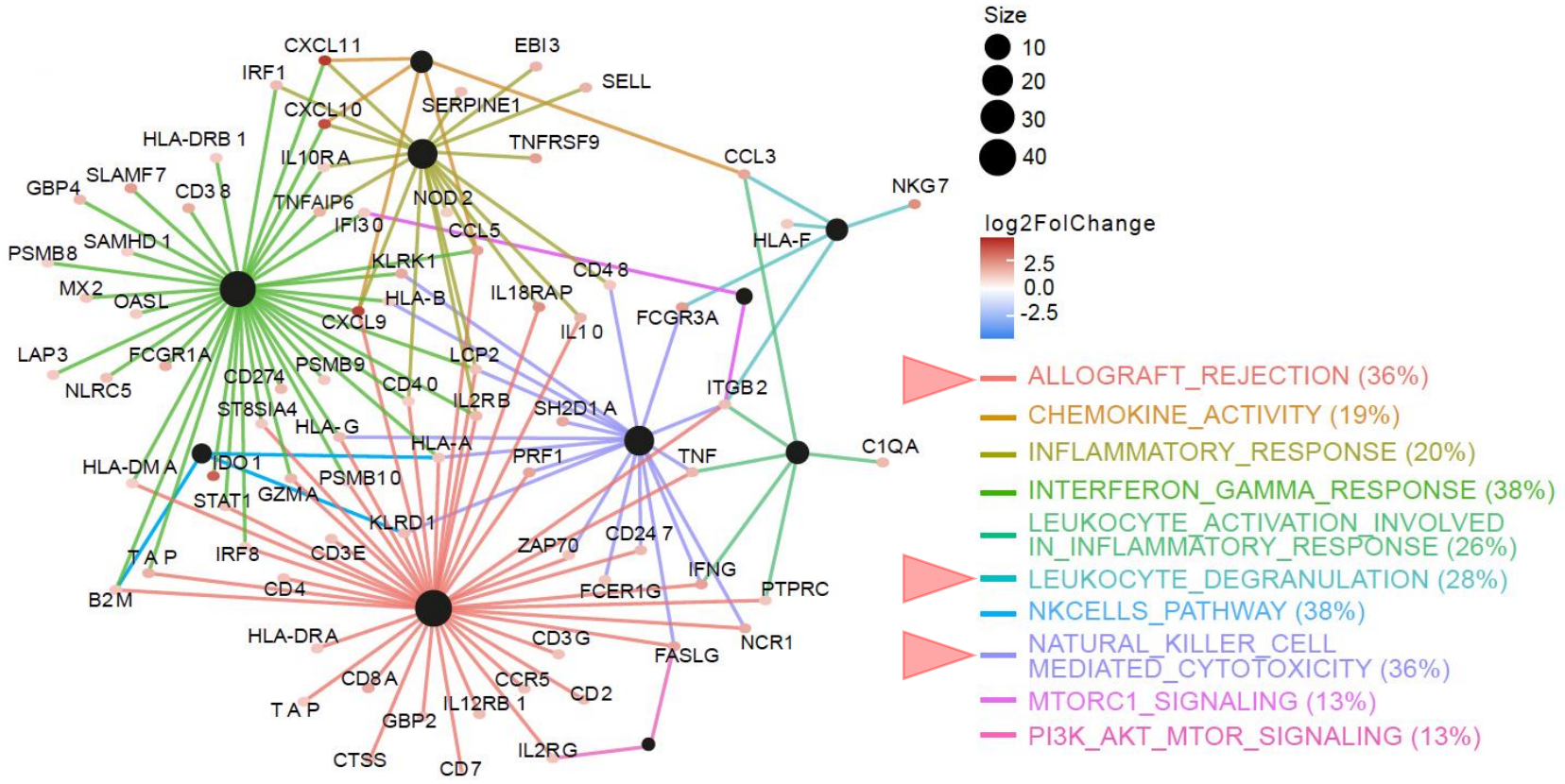
The entering point in this final common pathway is NK cell activation

The depletion of NK cells with anti-CD38 seems a promising (but transient) approach (TBC)

Perspective

Transcriptomic analysis

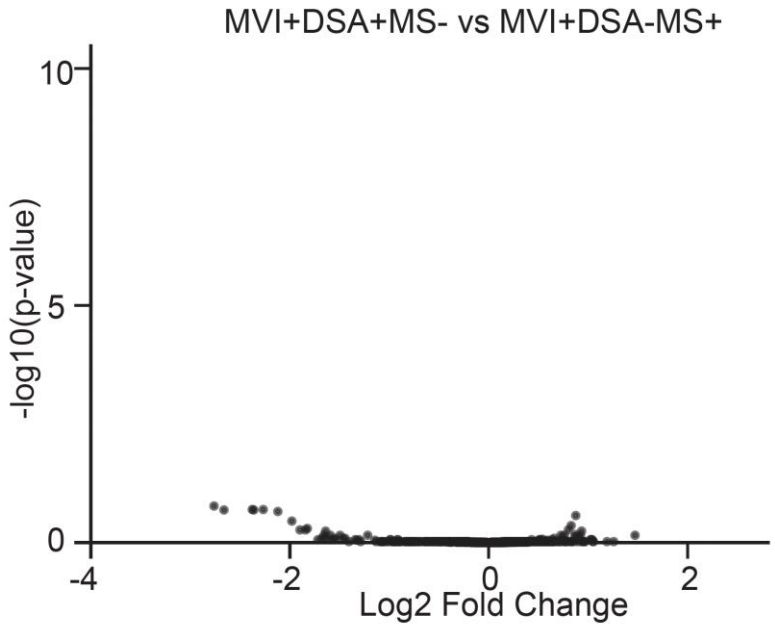


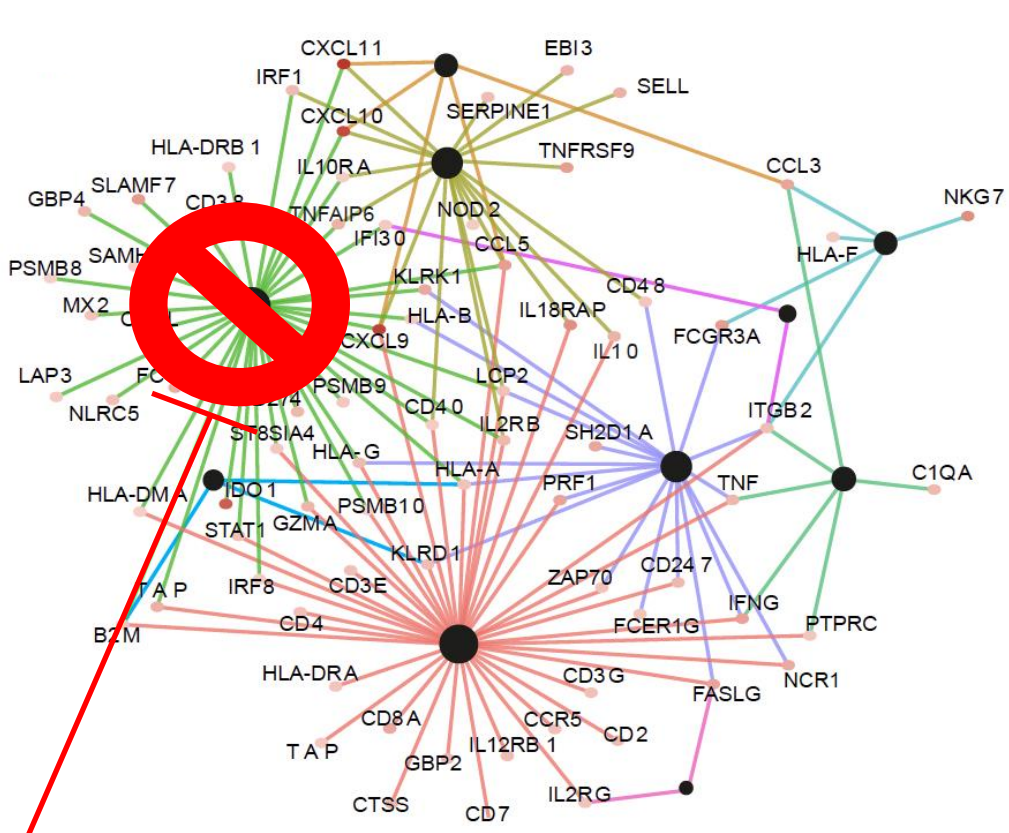


Collaboration with C. Roufosse & J. Beadle

Perspective

Transcriptomic analysis

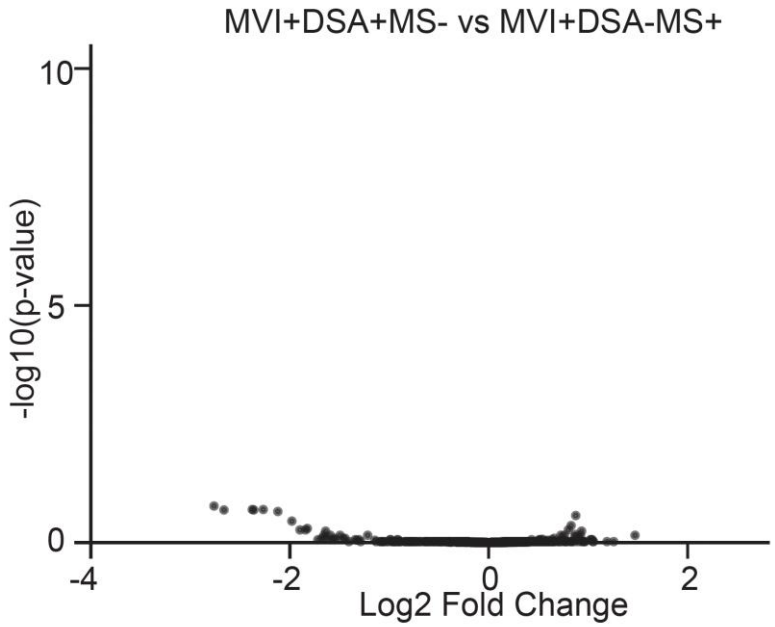


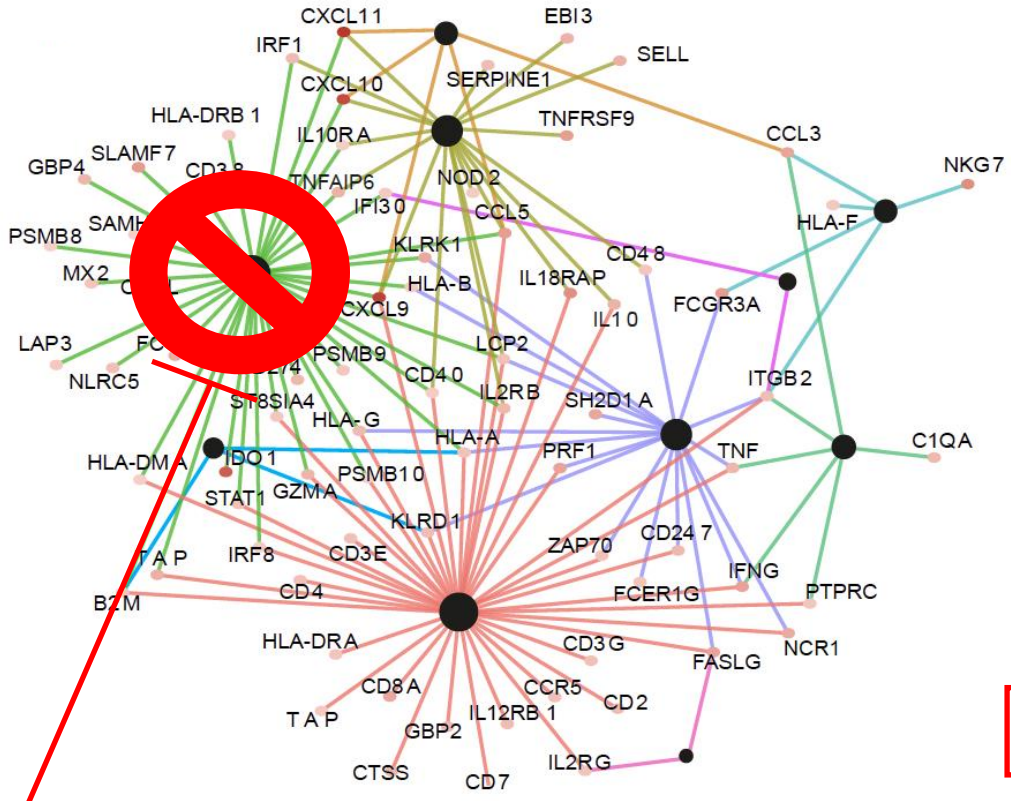


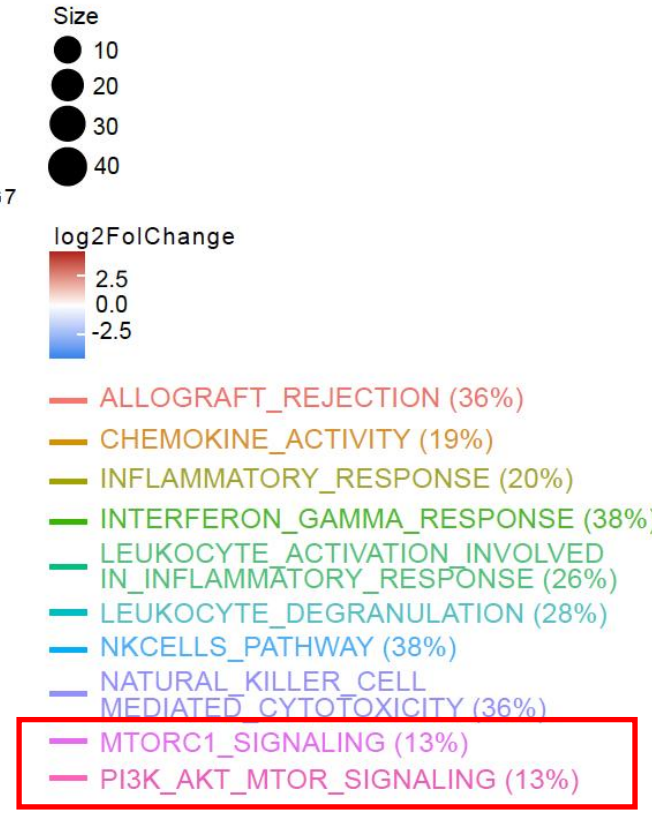
Emapalumab ?
JAKinibs ?

Perspective

Transcriptomic analysis



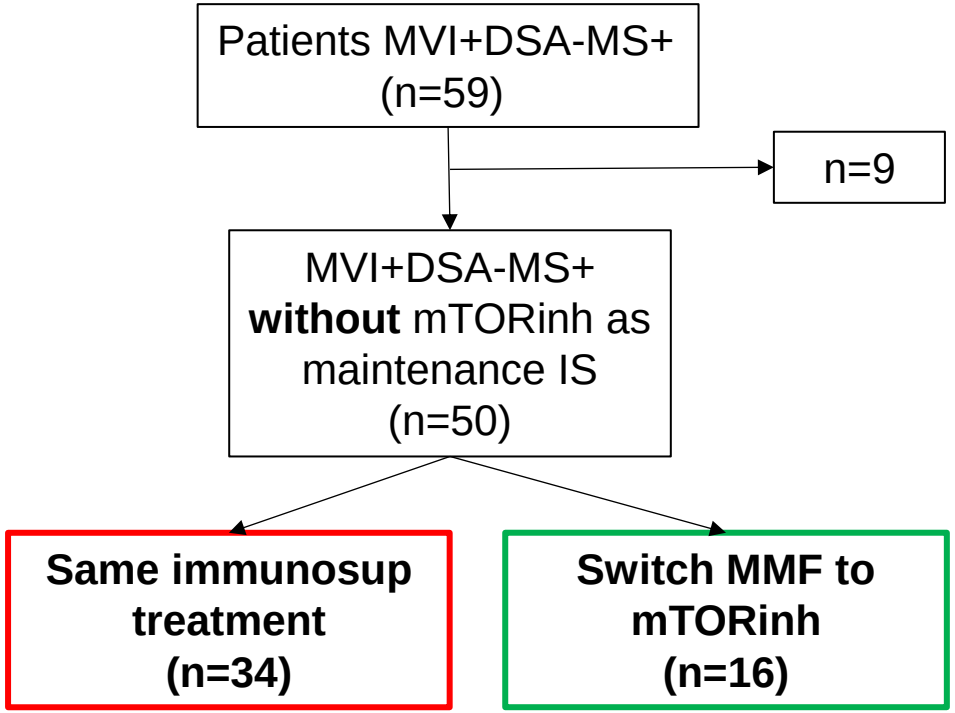




Emapalumab ?
JAKinibs ?

mTOR inhibitors ?

Pilot clinical study



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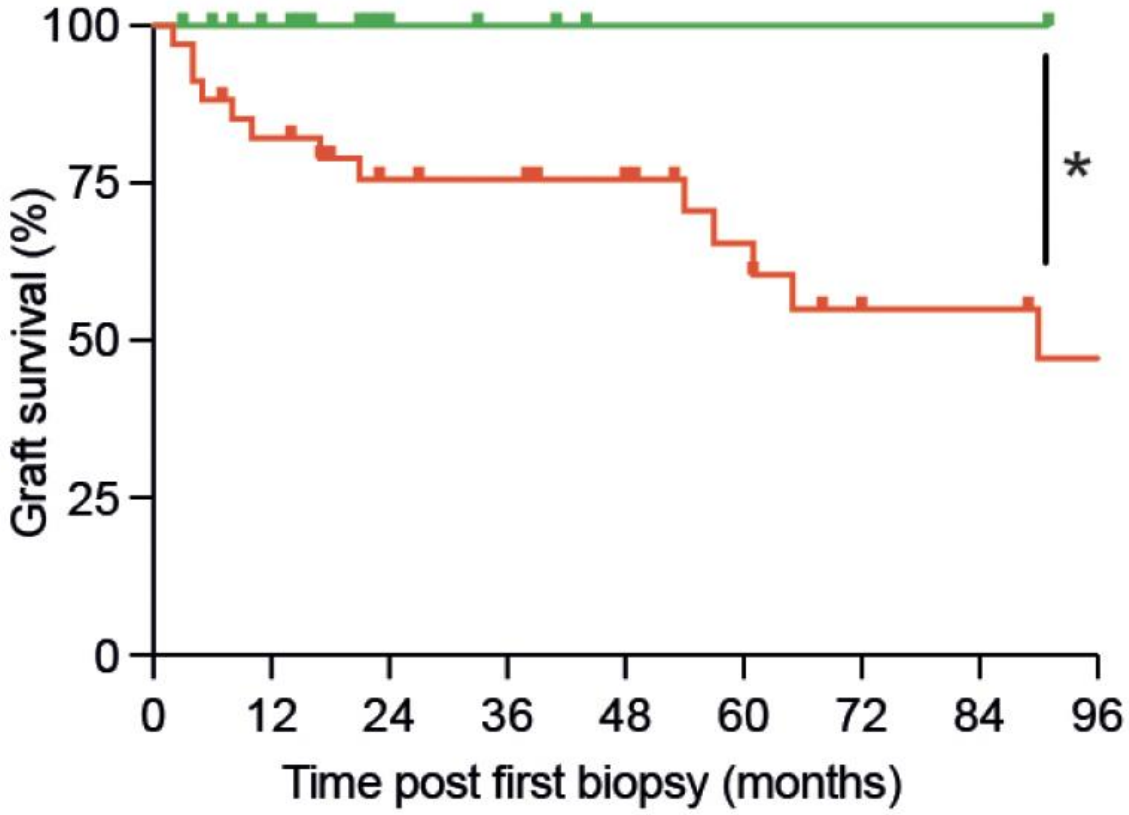
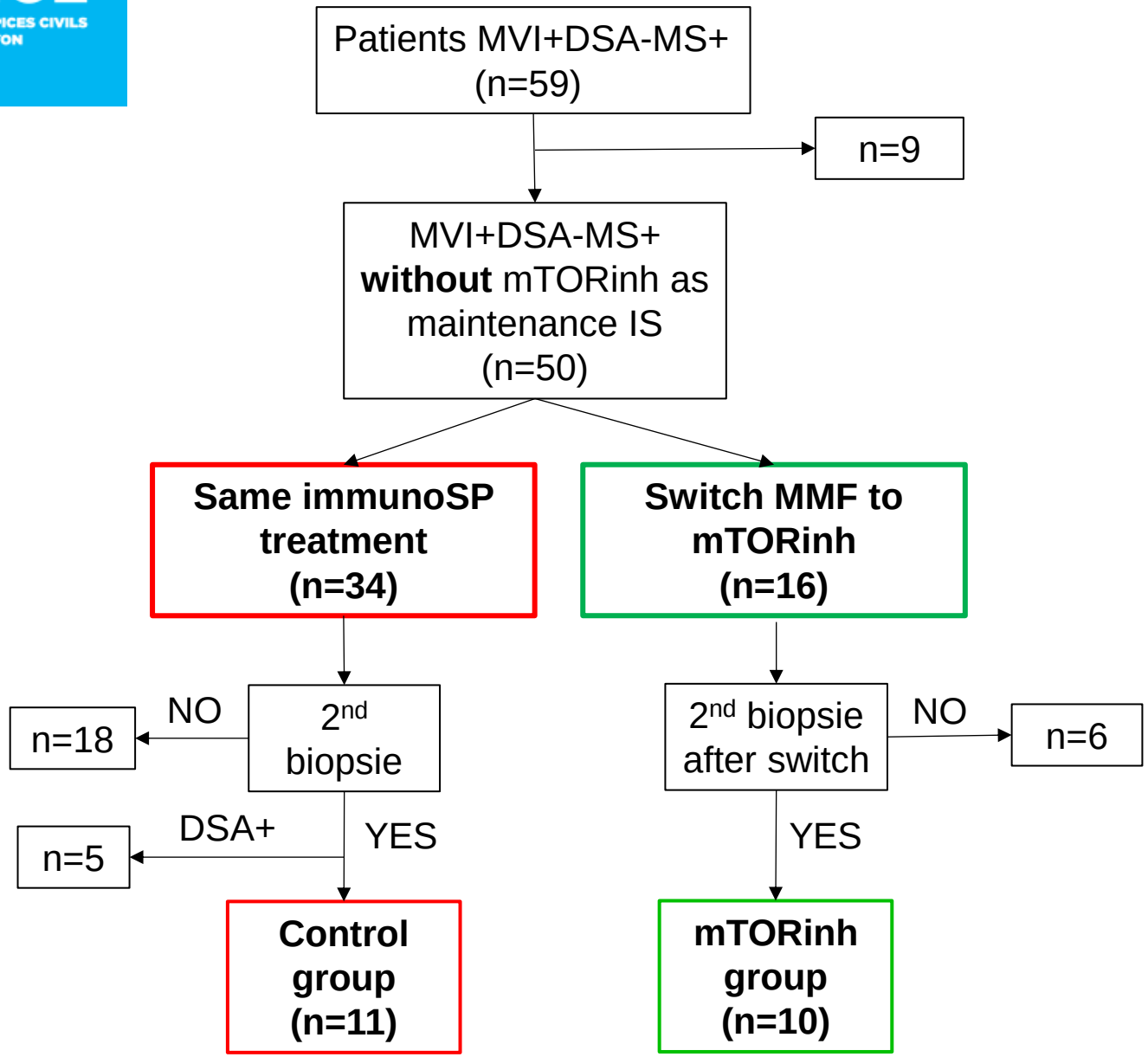


No. at risk									
Ctl	34	28	22	21	18	14	9	9	7
CNI+mTOR	16	12	5	4	2	2	2	2	0

Pilot clinical study



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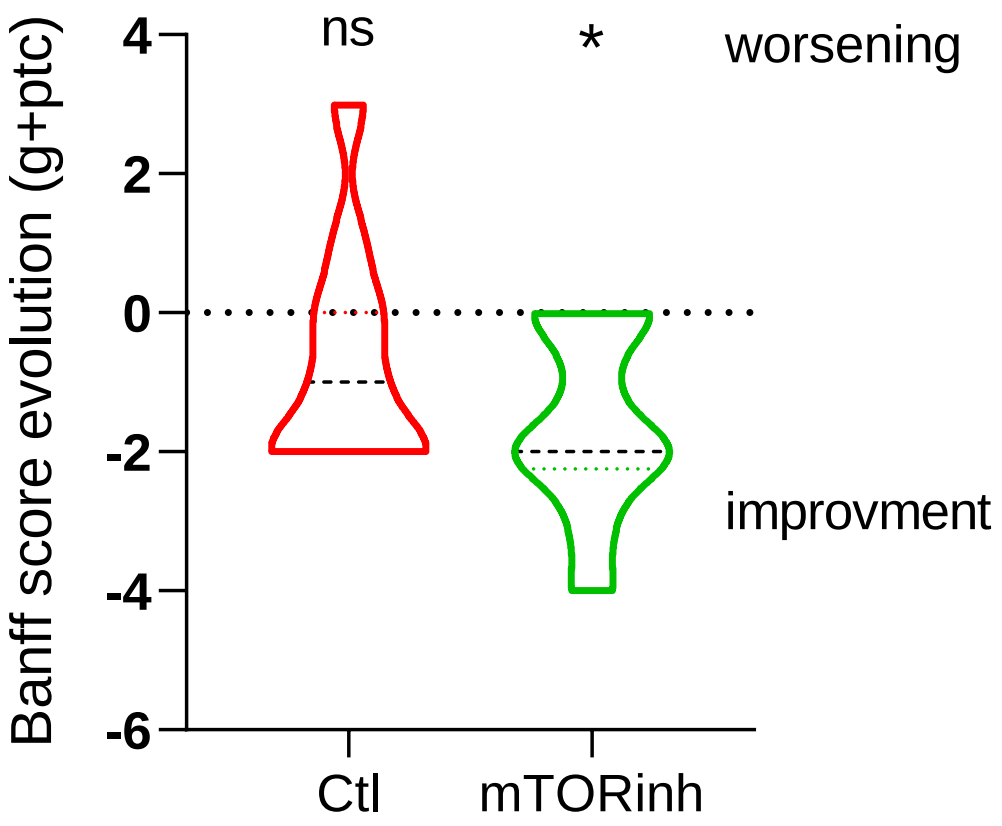

Acknowledgments

Centre International de Recherche en Infectiologie

T. Barba
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Pathology Lab
M. Rabeyrin

EFS ÉTABLISSEMENT FRANÇAIS DU SANG

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