

Cartographie multi-omique du système immunitaire au cours de la tolérance opérationnelle après allogreffe de cellules souches hématopoïétiques

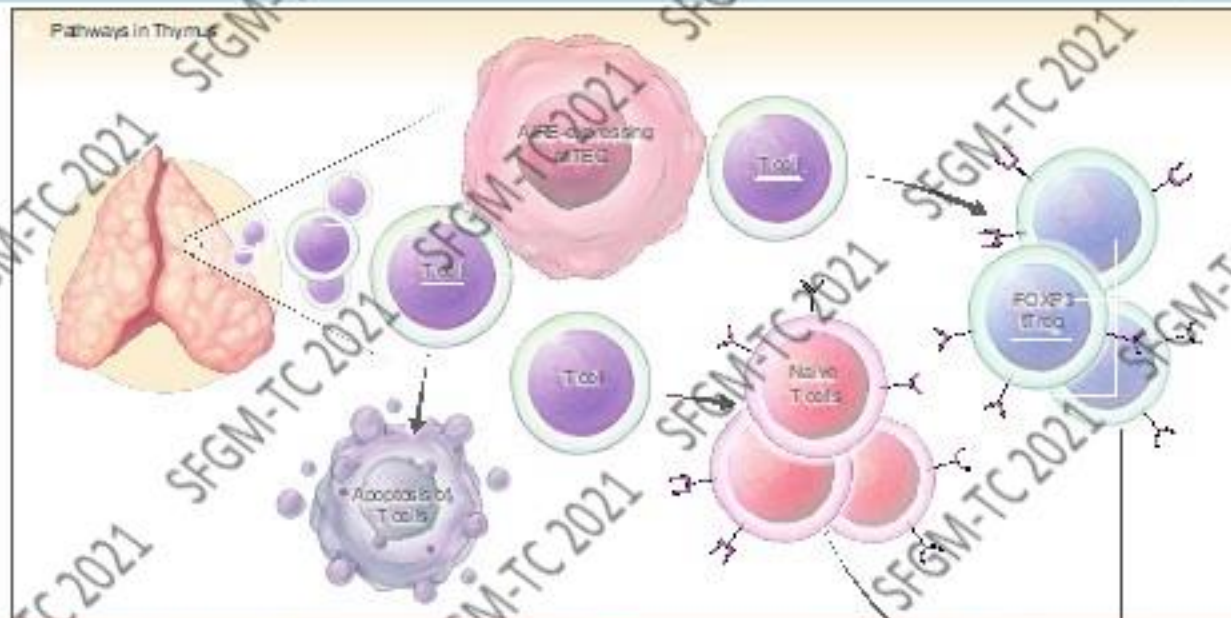
David Michonneau

Service d'hématologie-greffe, hôpital Saint Louis

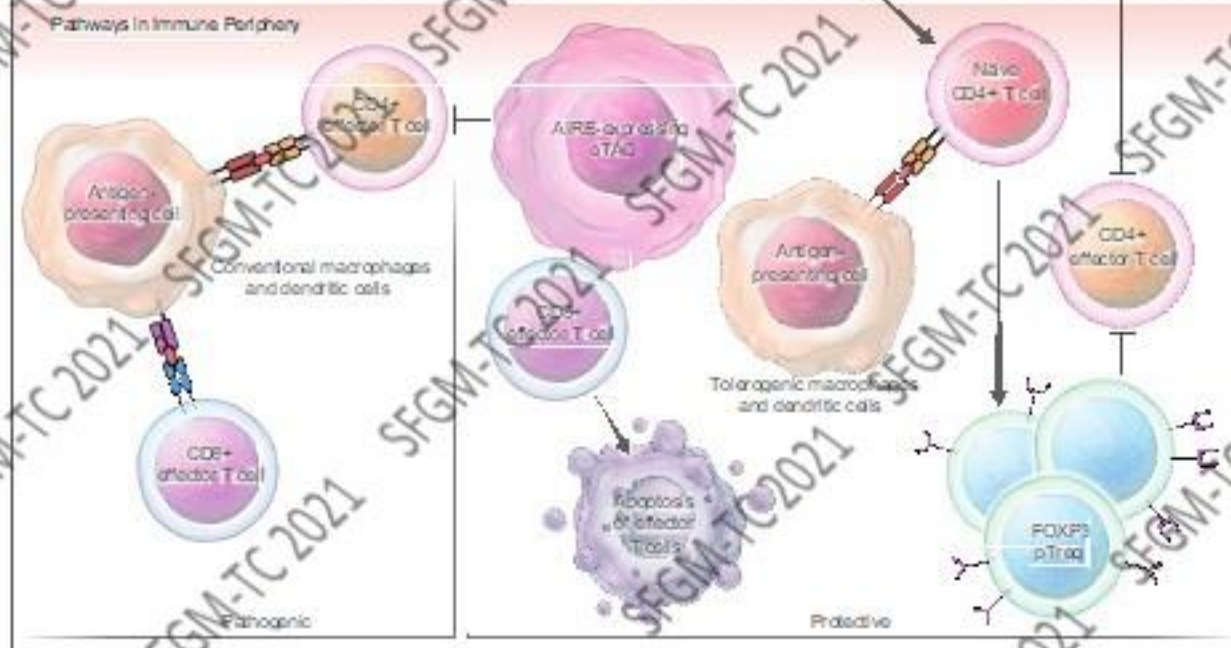
INSERM U976, Human Immunology, Pathophysiology, Immunotherapy, Université de Paris

Tolérance immunitaire

Tolérance centrale



Tolérance périphérique



Tolérance opérationnelle et transplantation

Tolérance opérationnelle après transplantation d'organe solide

HLA-Mismatched Renal Transplantation without Maintenance Immunosuppression

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

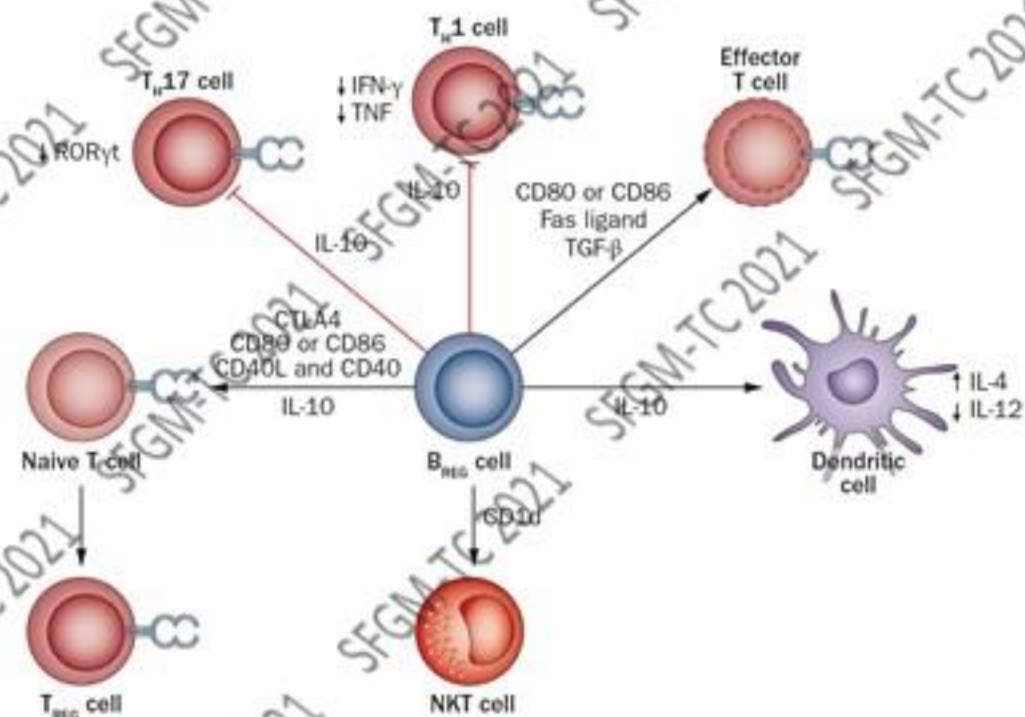
N ENGL J MED 358;4 WWW.NEJM.ORG JANUARY 24, 2008

Rôle des cellules B dans la tolérance opérationnelle en transplantation d'organe solide

B cells with immune-regulating function in transplantation

Jessica Stolp, Laurence A. Turka and Kathryn J. Wood

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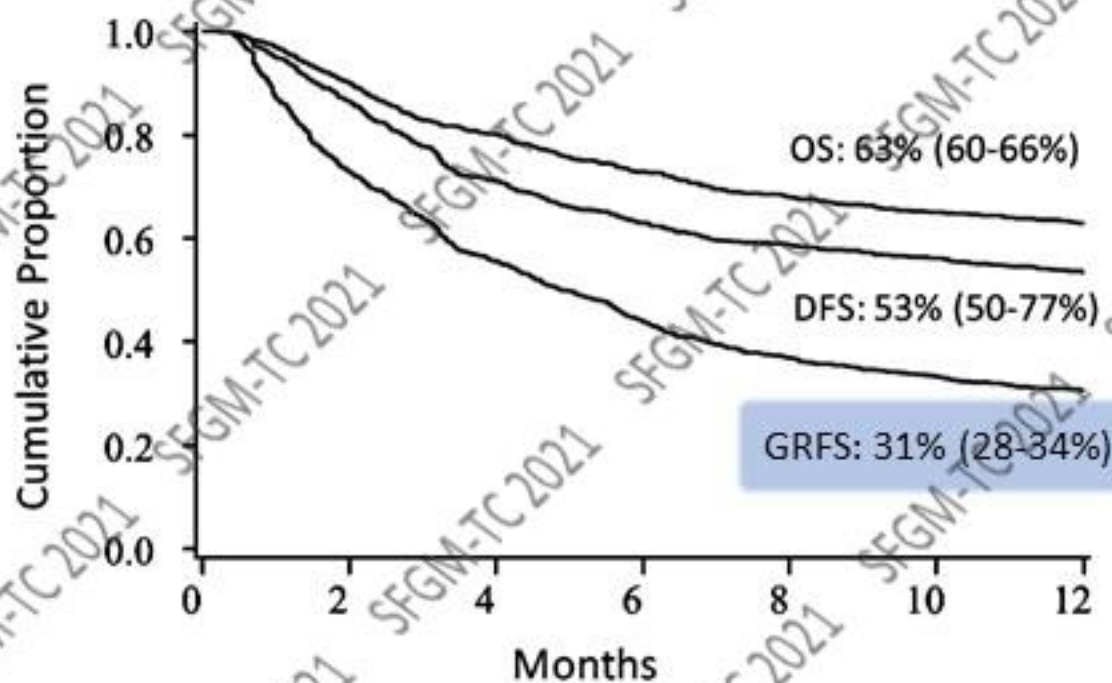


Tolérance immunitaire et allogreffe de CSH

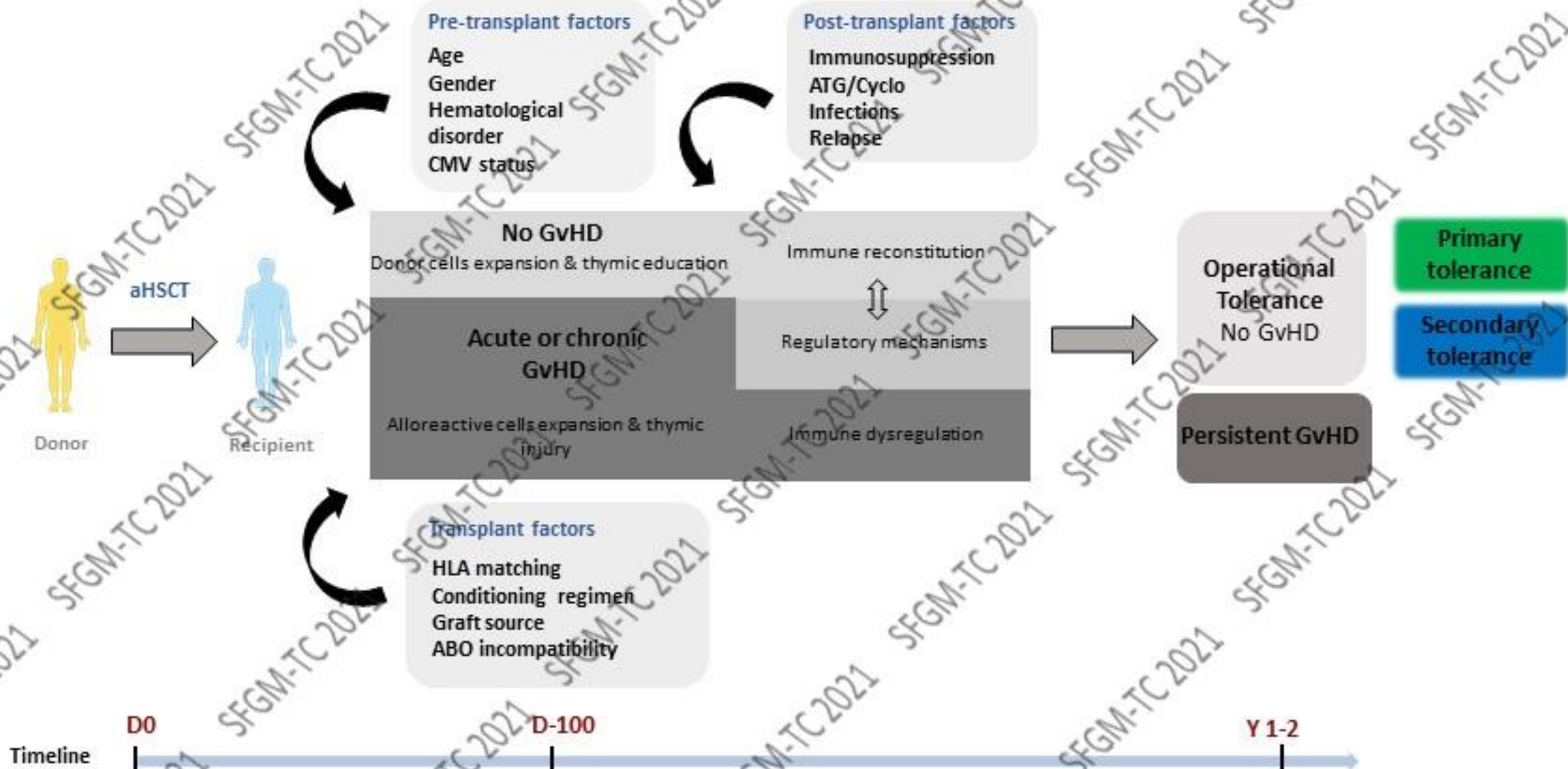
Composite end point of graft-versus-host disease-free, relapse-free survival after allogeneic hematopoietic cell transplantation

Shemar G. Holtan,¹ Todd E. DeFor,² Aleksandr Lazaryan,¹ Nelli Bejanyan,¹ Mukta Arora,¹ Claudio G. Brunstein,¹ Bruce R. Blazar,¹ Margaret L. MacMillan,³ and Daniel J. Weisdorf¹

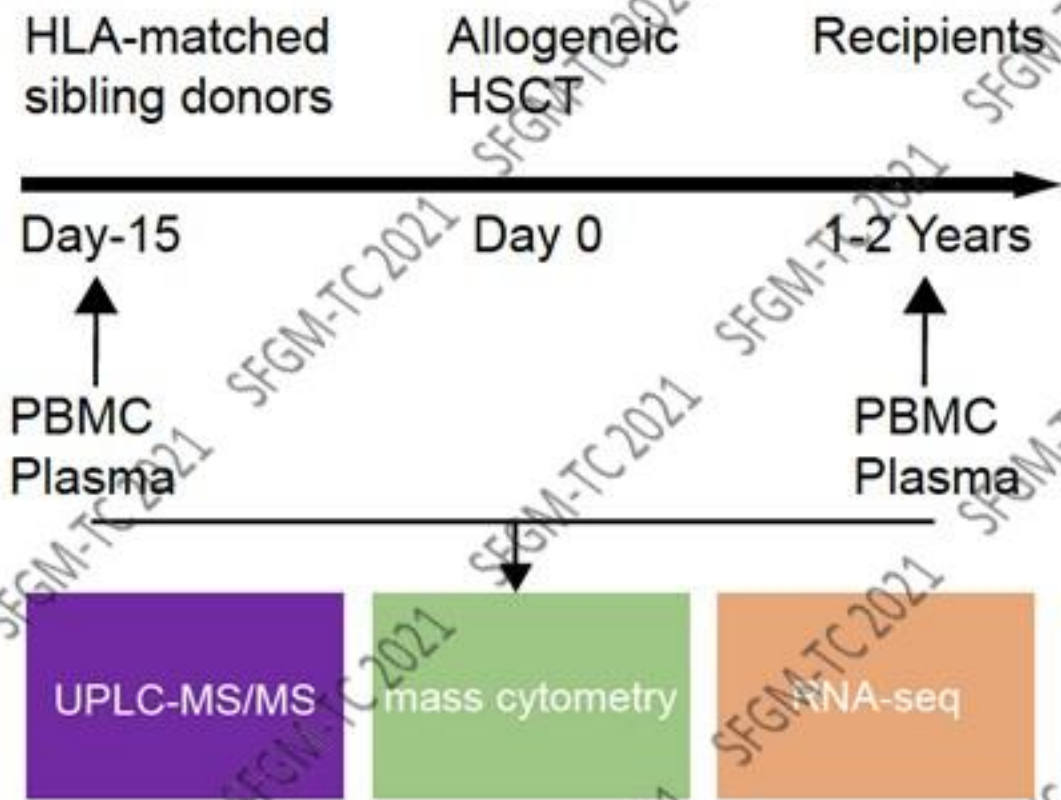
BLOOD, 19 FEBRUARY 2015 • VOLUME 125, NUMBER 8



Tolérance immunitaire et allogreffe de CSH



Méthodologie



Objectif de l'étude

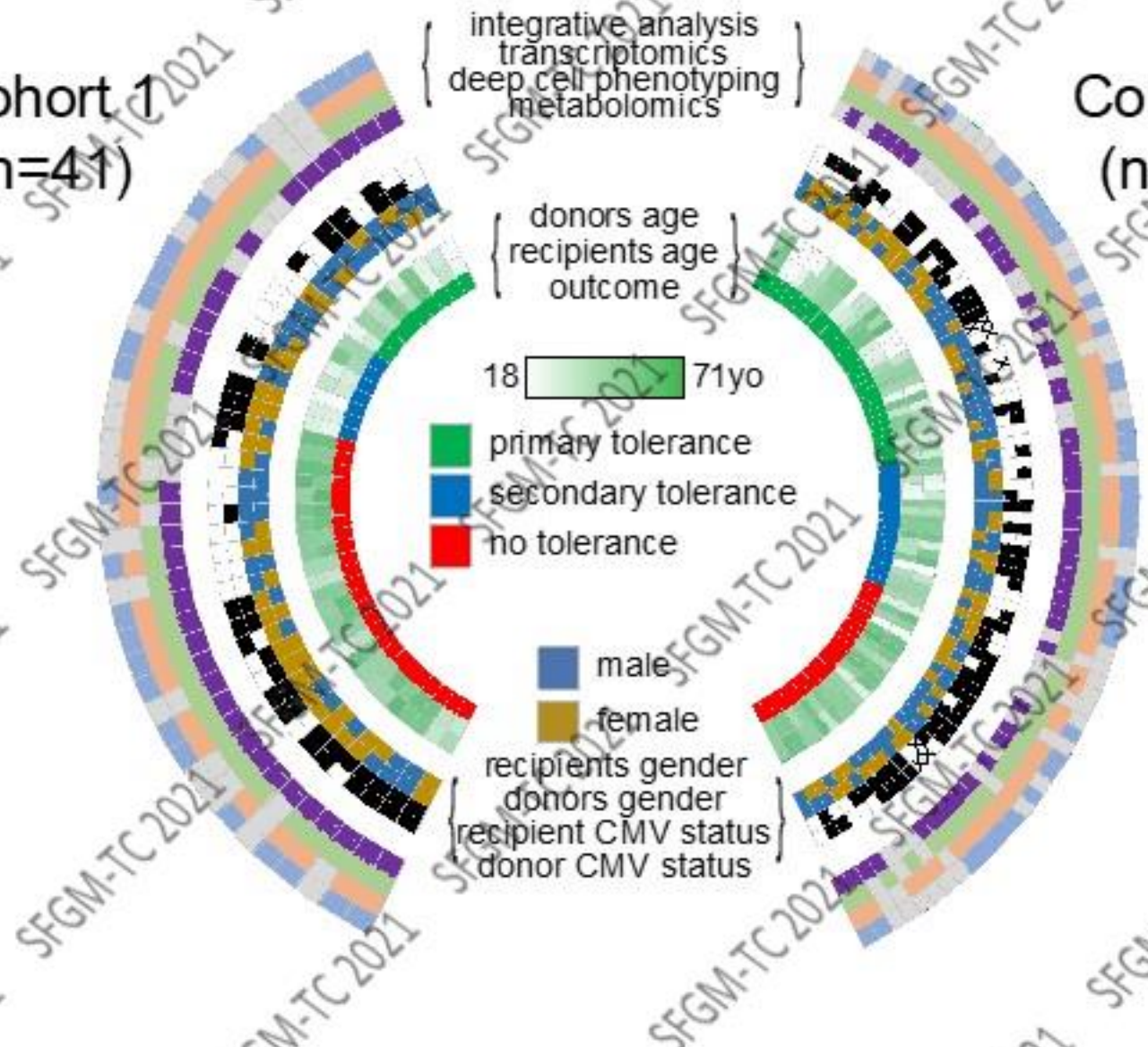
- Quelles sont les modifications du système immunitaire associées à la tolérance opérationnelle après allo-HSCT ?

Description des cohortes



Cohort 1
(n=41)

Cohort 2
(n=69)



integrative analysis
transcriptomics
deep cell phenotyping
metabolomics

donors age
recipients age
outcome

18 71yo

primary tolerance
secondary tolerance
no tolerance

male
female

recipients gender
donors gender
recipient CMV status
donor CMV status

Analyse des données

UPLC-MS/MS

mass cytometry

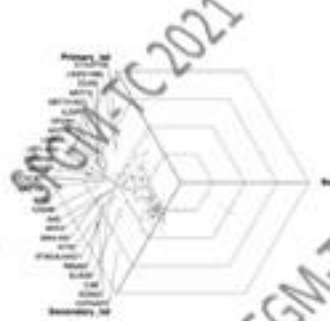
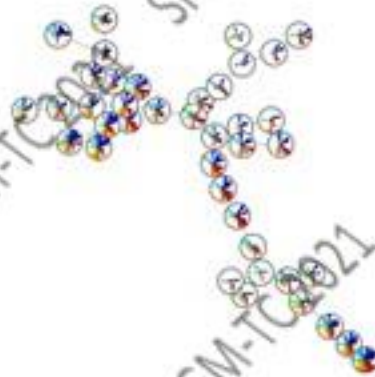
RNA-seq

Data filtration, normalization and transformation

Metabolic pathways

Immune Subset identification

Gene Expression profile



Feature selection using permutation distributions

Tolerance Features

1
1
1
0
0
0

Permutations

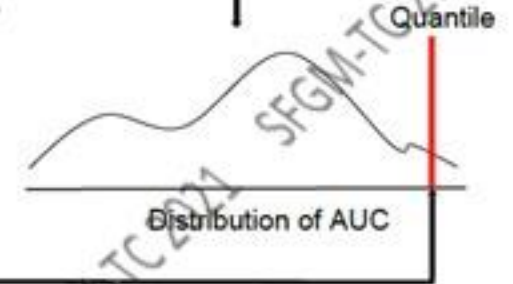
0
1
0
0
0
1

1
1
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0
0

0
0
1
0
0
1

0
0
1
1
0
0

Predict tolerance and compute associated AUC

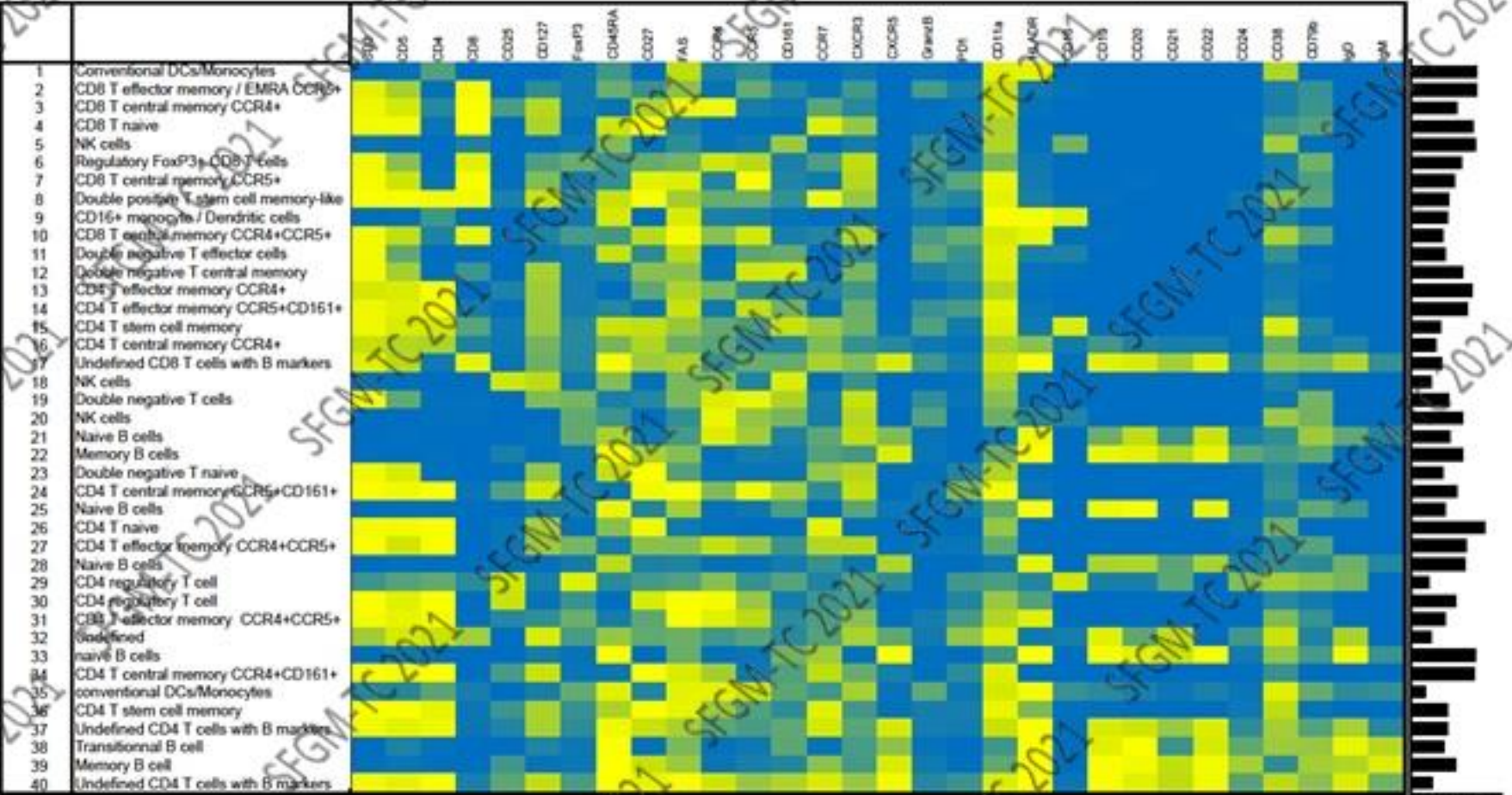
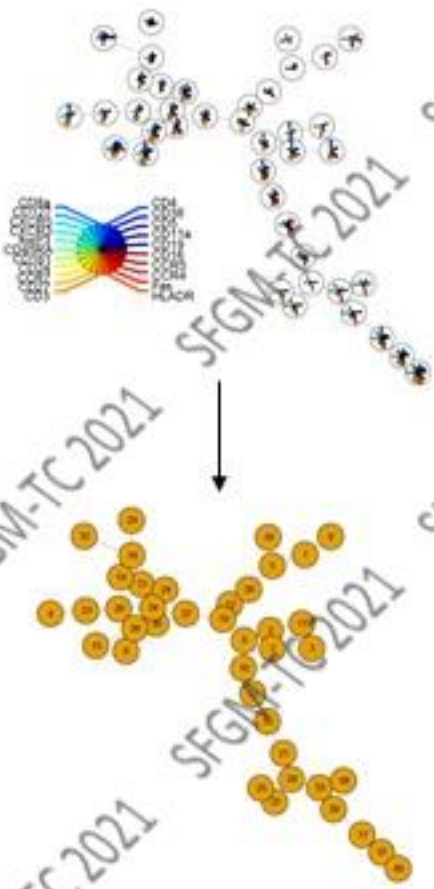


Clinical data relation to selected features (age, gender...)

Multi-omics integrative analysis (PCA)

Identification des populations immunitaires: FlowSOM

40 métaclusters (27 marqueurs phénotypiques)

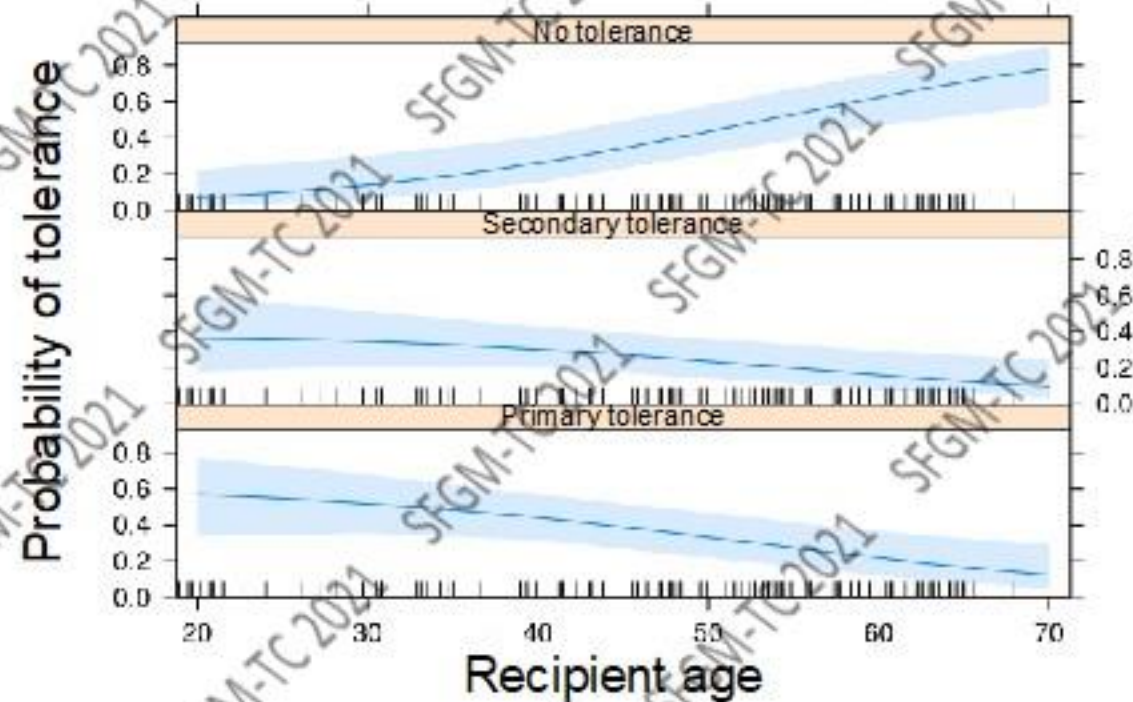


x 11 marqueurs fonctionnels → 440 populations

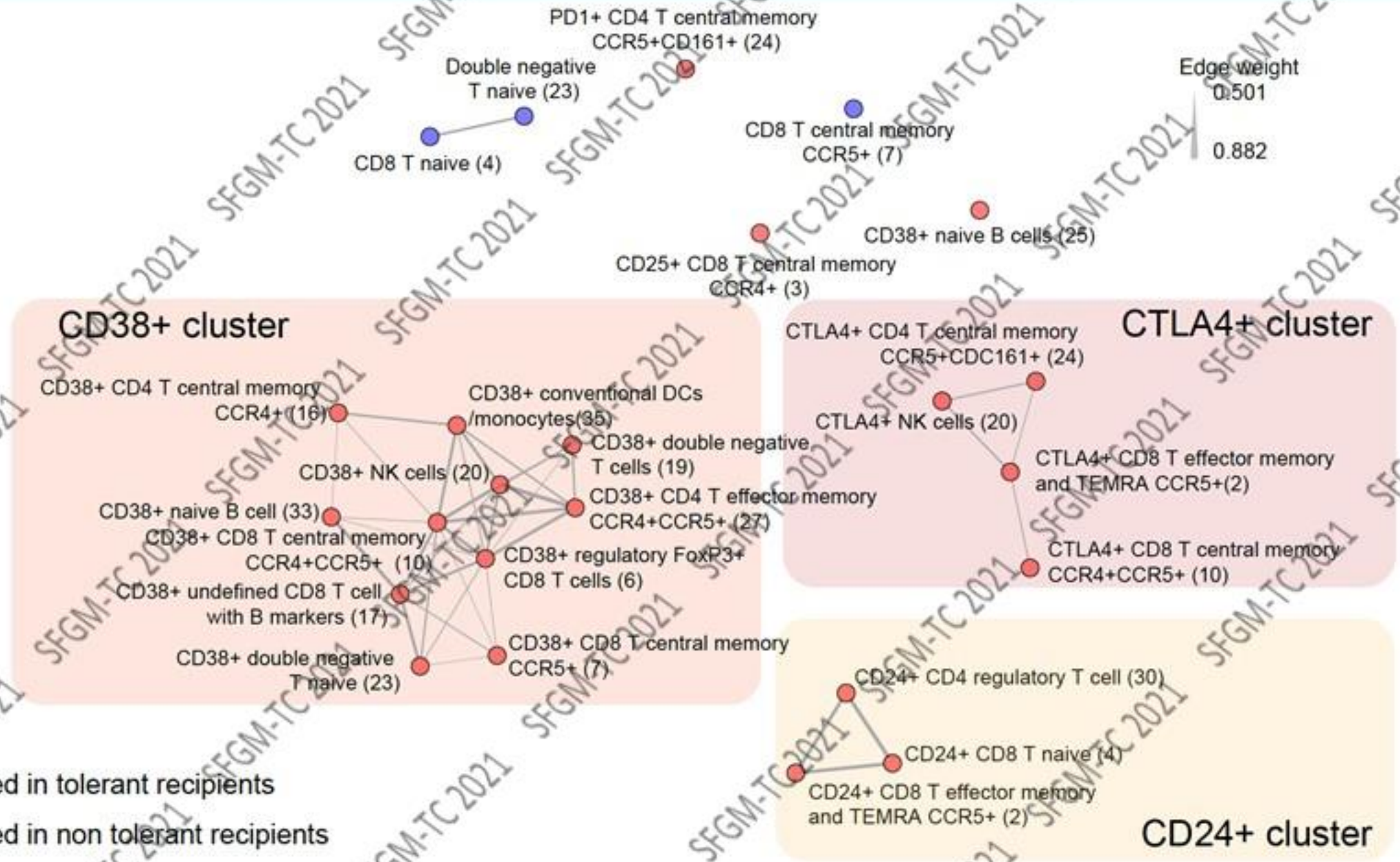
0.01 0.1 1 10 100
log (% of CD45+)

Impact des variables cliniques

	Secondary tolerance			No tolerance		
	odds ratio	95% confidence interval	p value	odds ratio	95% confidence interval	p value
recipient age	1.003	(0.965; 1.043)	0.864	1.082	(1.034; 1.133)	0.0006
antithymocyte globulin	0.141	(0.041; 0.478)	0.001	0.096	(0.028; 0.329)	0.0001
graft source	0.458	(0.127; 1.653)	0.233	0.108	(0.022; 0.521)	0.005
donor CMV status	1.293	(0.423; 3.956)	0.651	3.644	(1.207; 10.995)	0.021
Intercept	1.494	(0.207; 10.775)	0.690	0.064	(0.005; 0.690)	0.023

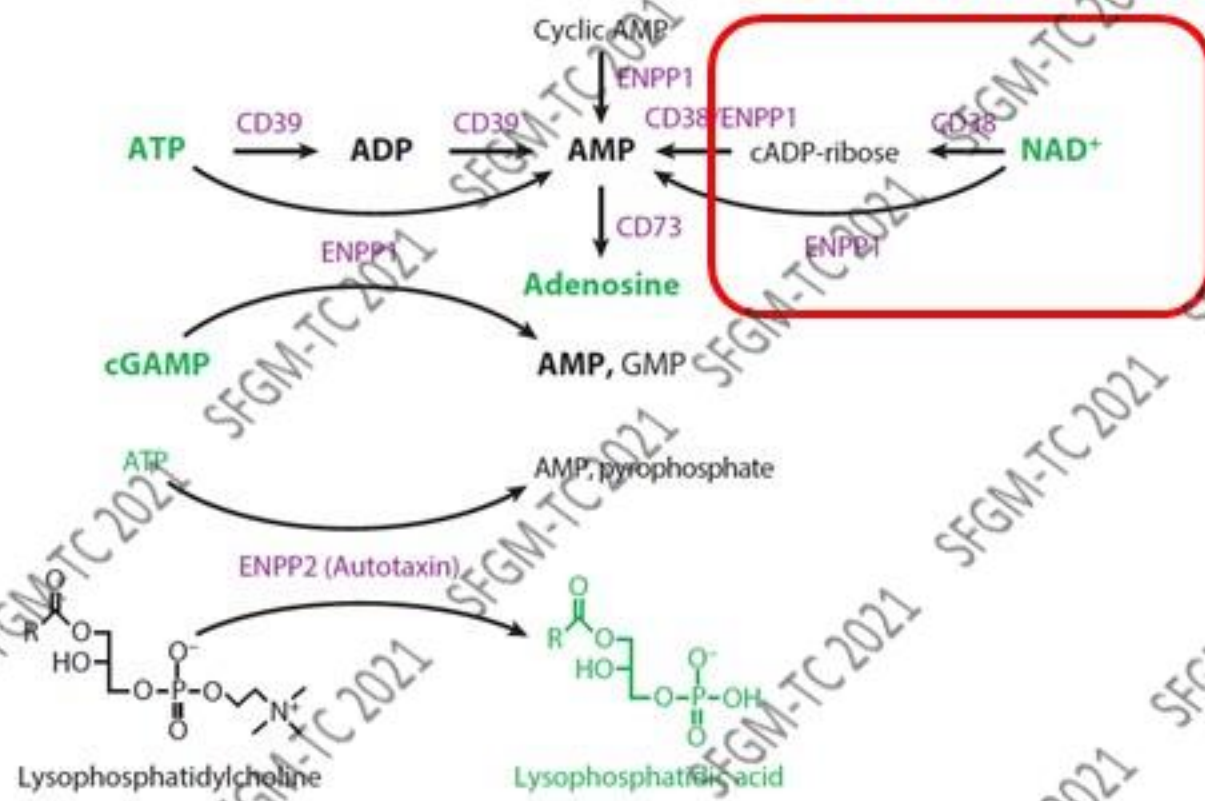


Phénotype des cellules immunitaires des receveurs tolérants et non tolérants



Métabolisme des purines et régulation de la réponse immunitaire

Non tolérant



CD38 ecto-enzyme in immune cells is induced during aging and regulates NAD⁺ and NMN levels

Claudia C. S. Chini¹, Thais R. Peclat¹, Gina M. Warner¹, Sonu Kashyap¹,
 Jair Machado Espindola-Netto¹, Guilherme C. de Oliveira¹, Lilian S. Gomez¹, Kelly A. Hogan¹,
 Mariana G. Tarfagó¹, Amrutesh S. Puranik^{1,4}, Guillermo Agorrodoy¹, Katie L. Thompson¹,
 Kevin Dang², Starlynn Clarke², Bennett G. Childs³, Karina S. Kanamori¹, Micaela A. Witte¹,
 Paola Vidal¹, Anna L. Kirkland¹, Marco De Cecco^{4,9}, Karthikeyani Chellappa³,
 Melanie R. McReynolds⁴, Connor Jankowski⁴, Tamara Tchkonina⁷, James L. Kirkland⁷,
 John M. Sedivy⁴, Jan M. van Deursen³, Darren J. Baker³, Wim van Schooten³, Joshua D. Rabinowitz⁴,
 Joseph A. Baur³ and Eduardo N. Chini^{1,10}

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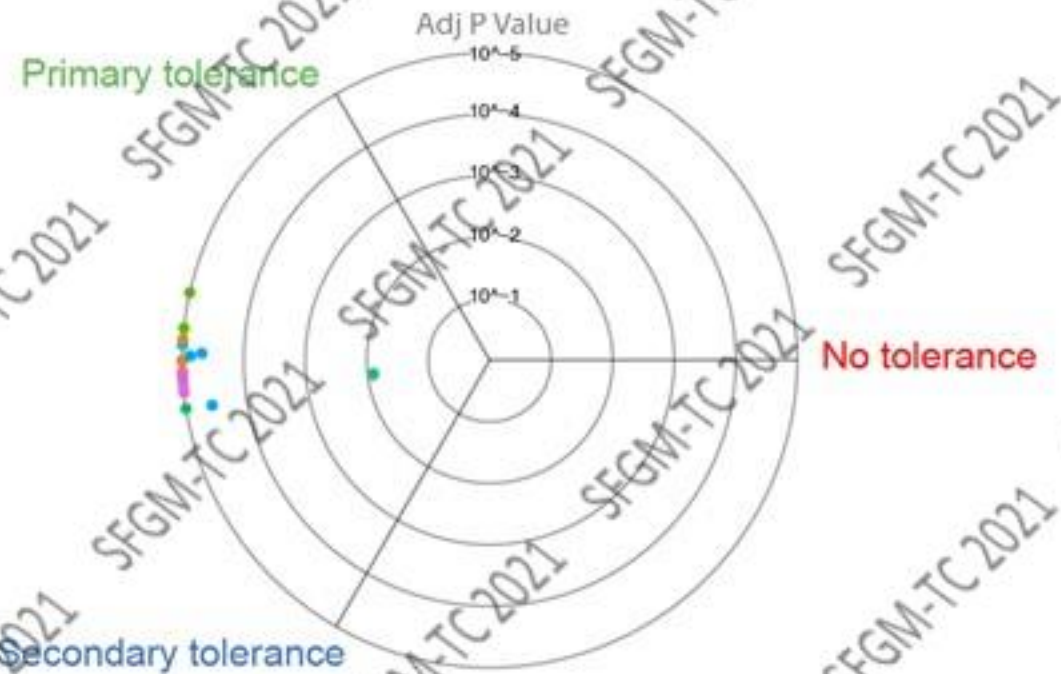
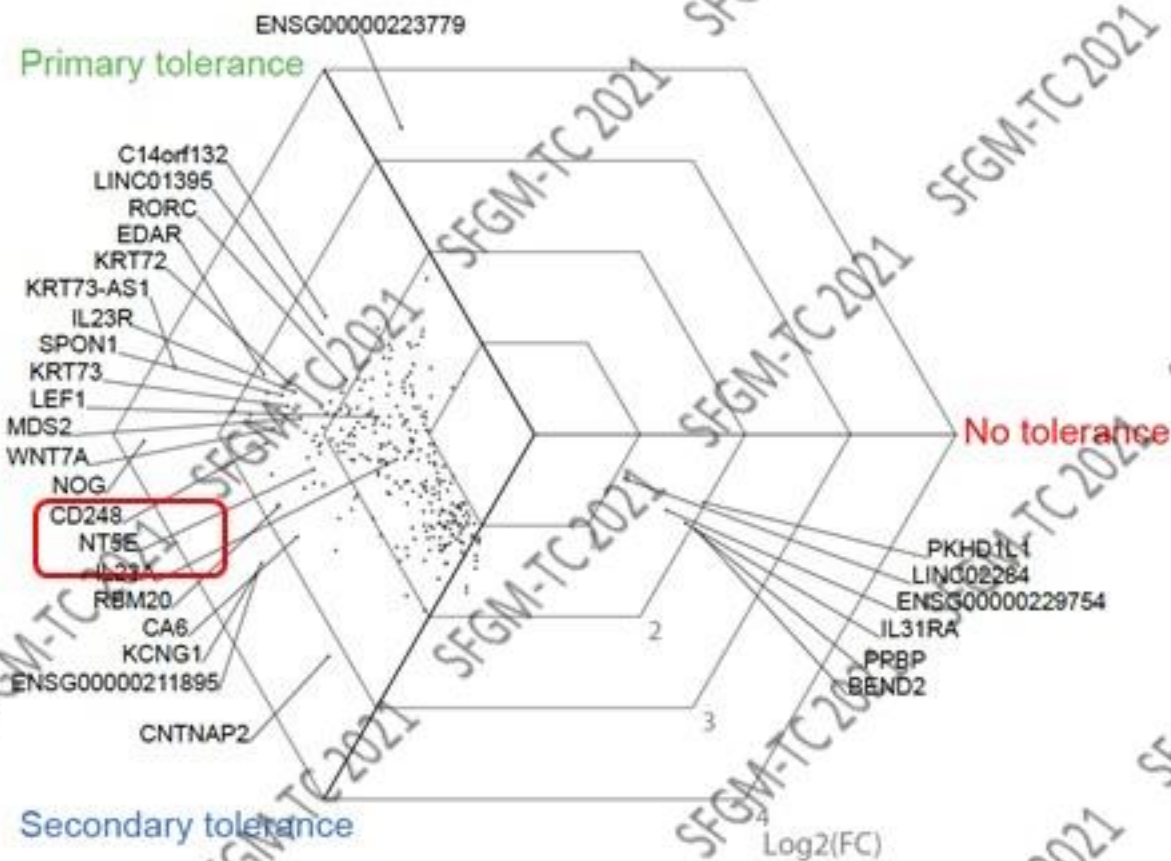
Senescent cells promote tissue NAD⁺ decline during ageing via the activation of CD38⁺ macrophages

Anthony J. Covarrubias^{1,2}, Abhijit Kale^{1,4}, Rosalba Perrone^{1,4}, Jose Alberto Lopez-Dominguez¹,
 Angela Oliveira Pisco³, Herbert G. Kasler³, Mark S. Schmidt⁴, Indra Heckenbach^{1,5}, Ryan Kwok¹,
 Christopher D. Wiley³, Hoi-Shan Wong³, Eddy Gibbs³, Shankar S. Iyer⁴, Nathani Basisty¹,
 Qiuxia Wu¹, Ik-Jung Kim³, Elena Silva¹, Kaitlyn Vitangcol¹, Kyong-Oh Shin^{1,2}, Yong-Moon Lee⁷,
 Rebecah Riley¹, Issam Ben-Sahra⁴, Melanie Ott⁹, Birgit Schilling¹, Morten Scheibye-Knudsen⁴,
 Katsuhiko Ishihara¹⁰, Stephen R. Quake¹¹, John Newman^{1,2}, Charles Brenner^{4,10}, Judith Campisi¹
 and Eric Verdin^{1,2}

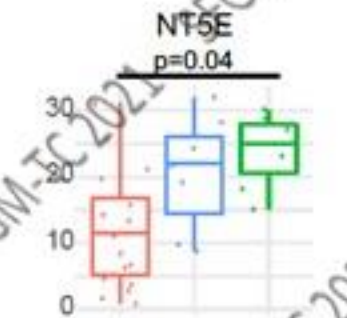
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L'ecto-enzyme CD38 déplete les cellules en NAD et produit de l'ADP-ribose cyclique qui induit la signalisation calcique intracellulaire

Profil transcriptomique des patients tolérants et non tolérants

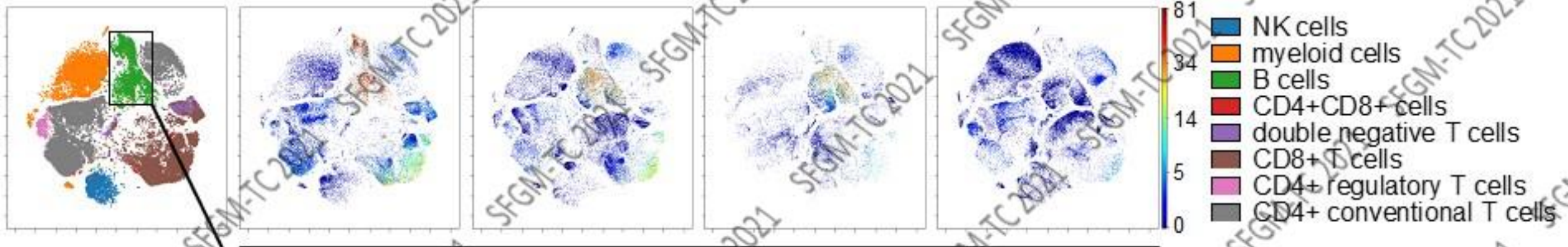


- Adaptative immune response
- Cell activation
- Inflammatory response
- Leukocyte Migration
- Lymphocyte differentiation
- Regulation of defense response
- Regulation of immune response
- Cytokine signaling
- GTPase Signaling
- Wnt Signaling
- Nucleobase-containing compound metabolic process

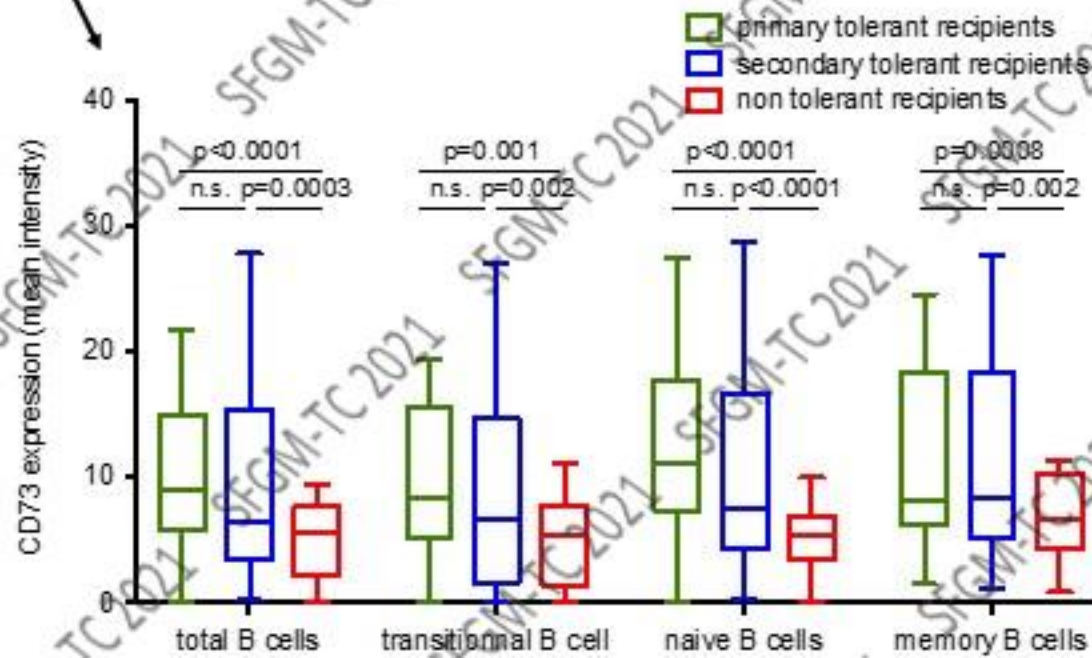


NT5E/CD73 expression in tolerant and non tolerant patients

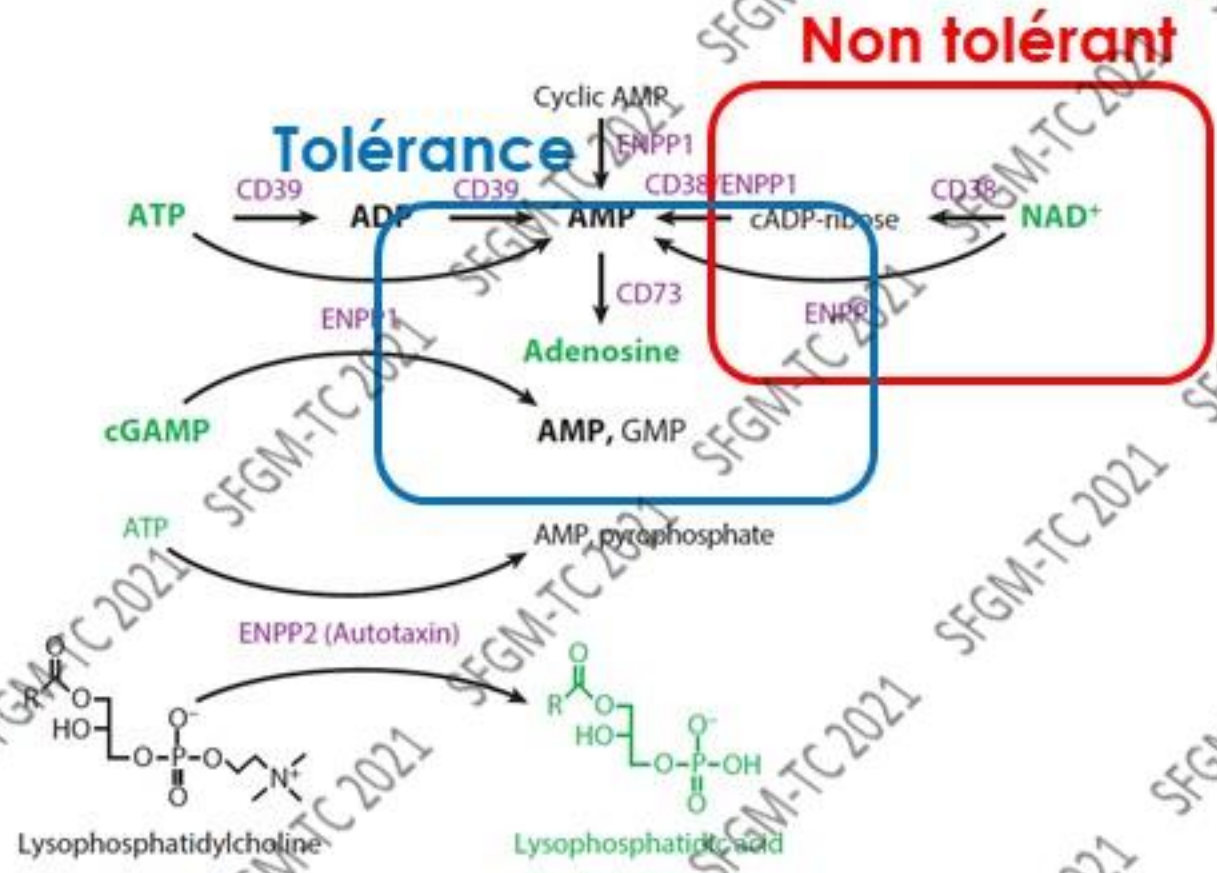
Healthy donor Primary tolerant recipient Secondary tolerant recipient Non tolerant recipient



CD73 expression

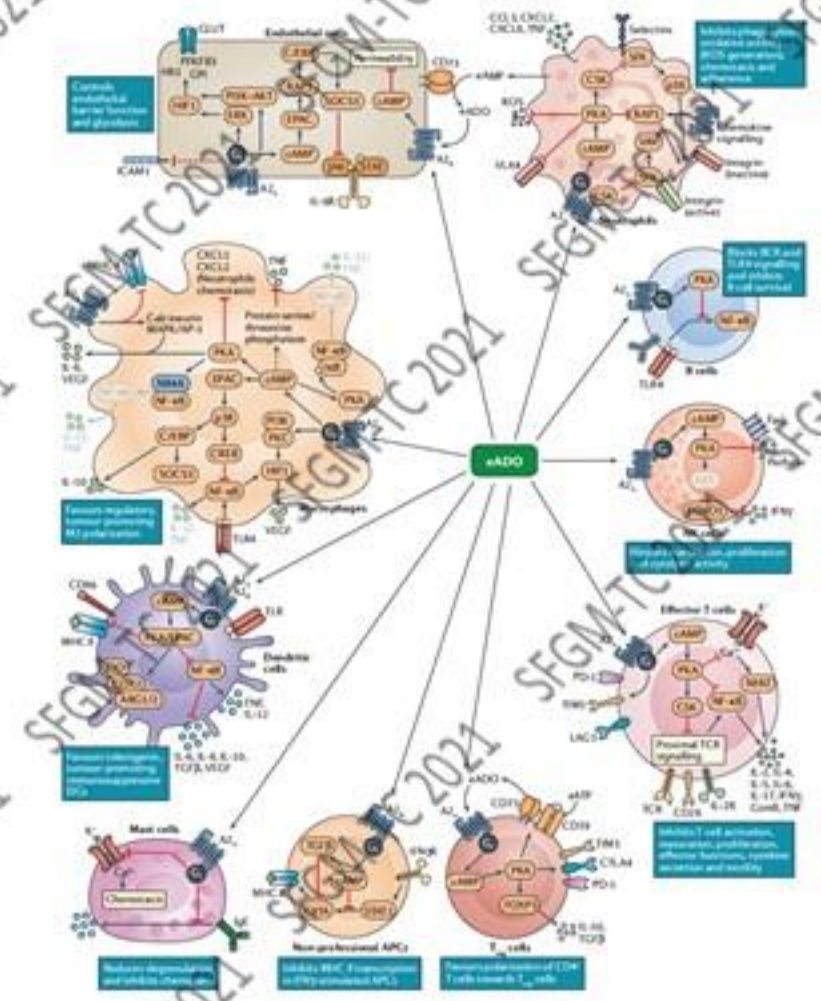


Métabolisme des purines et régulation de la réponse immunitaire

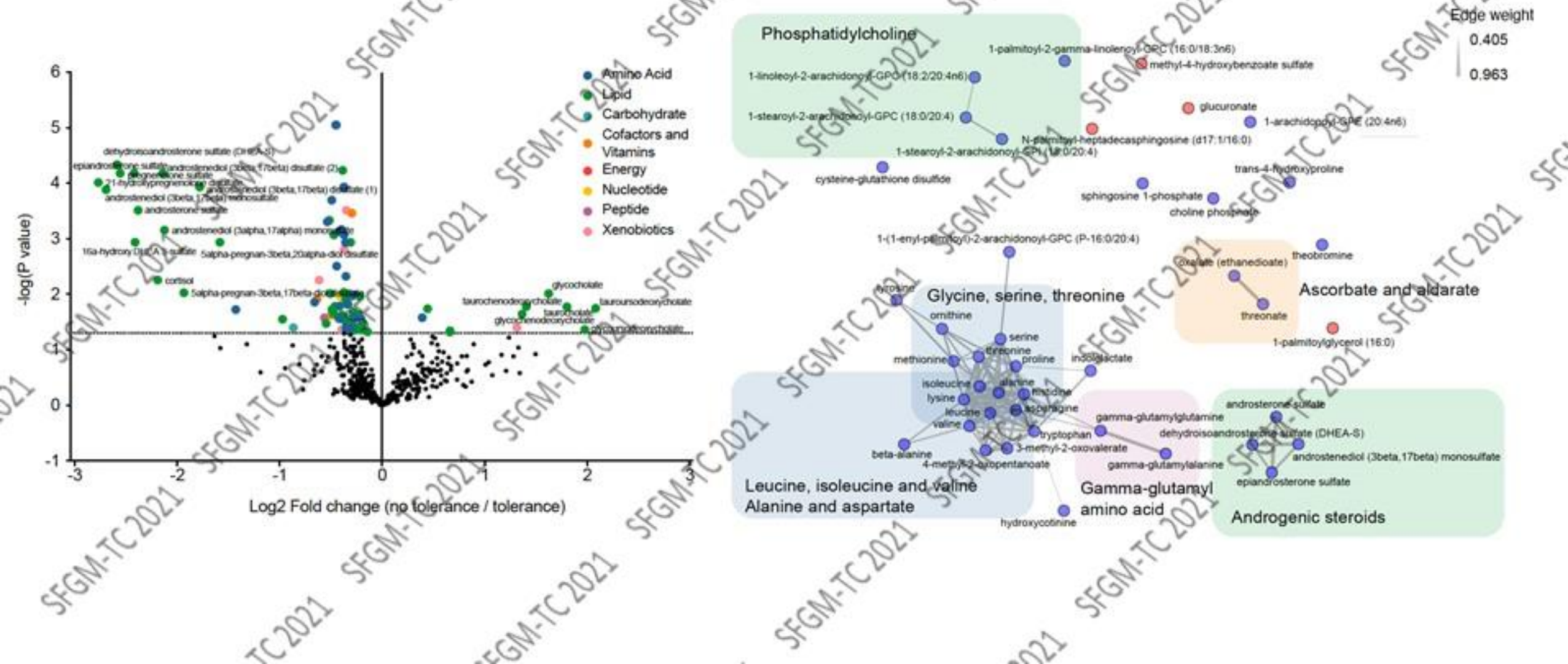


The adenosine pathway in immuno-oncology

Bertrand Allard^{1,2}, David Allard^{1,2}, Laurence Buisseret^{3,5} and John Stagg^{1,2,5}



Métabolome des receveurs tolérants et non tolérants



Intégration des données cliniques et biologiques

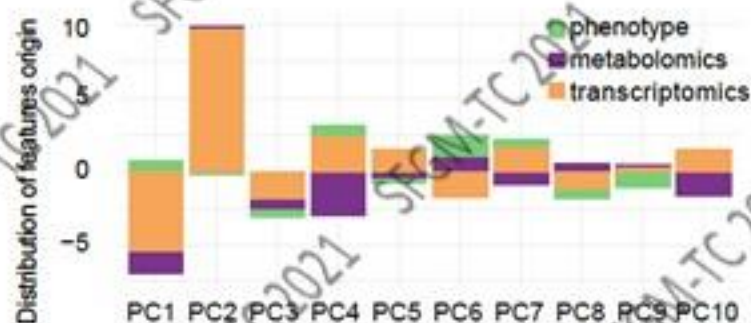
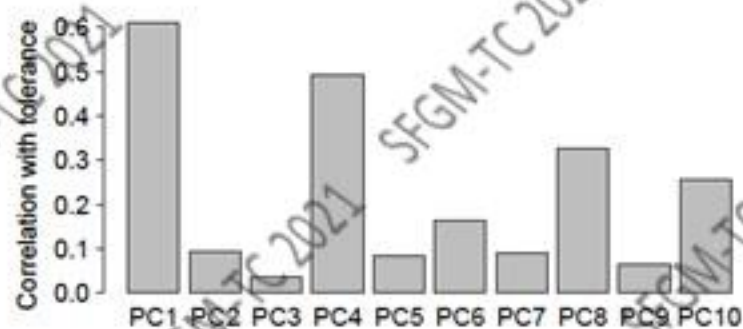
Mass cytometry
n=24

RNA-seq
n=278

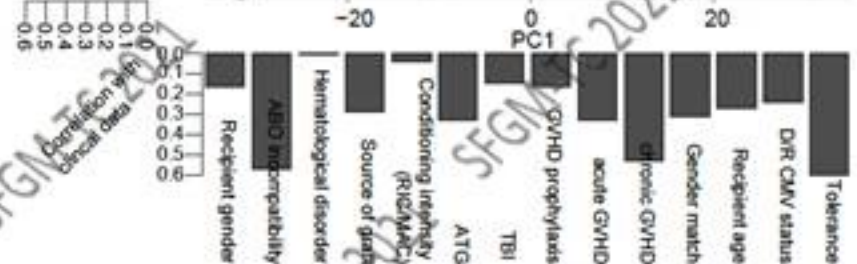
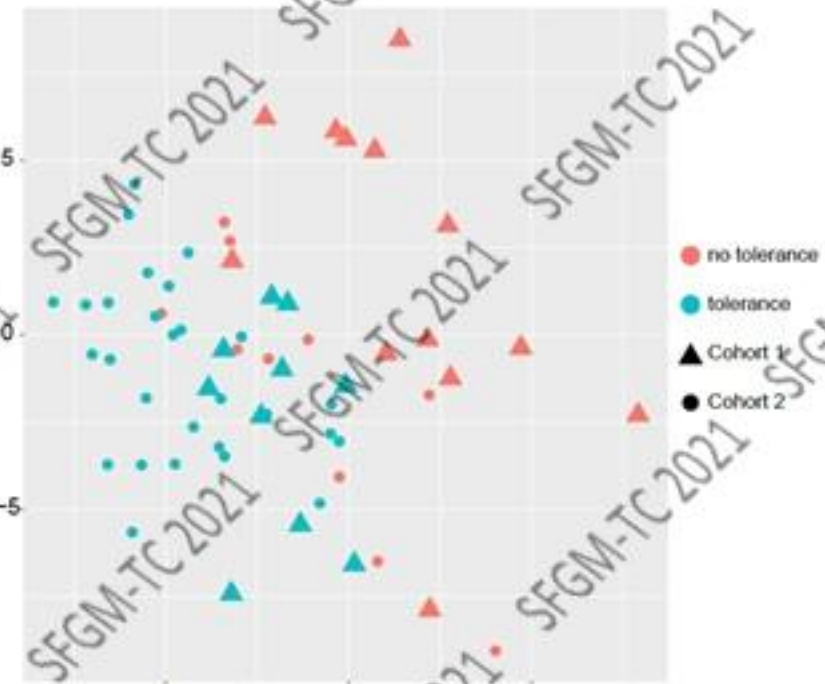
Metabolomics
n=42

Clinical data relation to selected features
(age, gender...)

Multi-omics integrative analysis (PCA)

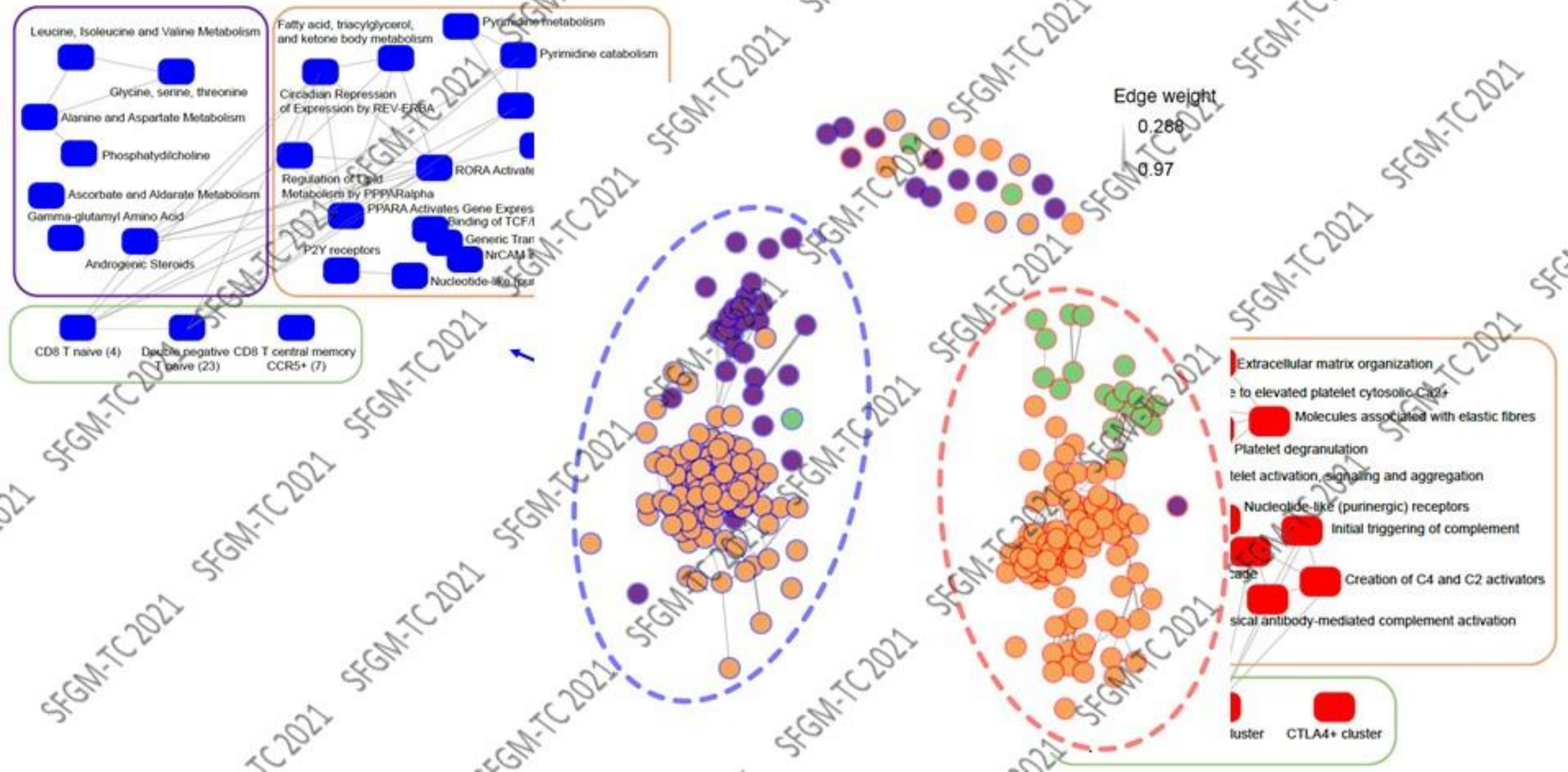


Recipient gender
ABO incompatibility
Hematological disorders
Source of Graft
Conditioning intensity (RIC/MAC)
ATG
TBI
GVHD prophylaxis
acute GVHD
chronic GVHD
Gender match
Recipient age
D/R CMV status
Tolerance



	Tolerance ~ PCs			Tolerance ~ PCs + clinical variables		
	Odds Ratio	95% CI	p value	Odds Ratio	95%	p value
PC1	0.82	[0.73, 0.90]	<0.001	0.86	[0.75, 0.95]	0.012
PC4	0.67	[0.49, 0.85]	0.004	0.70	[0.49, 0.93]	0.028
Recipients' Age				0.97	[0.90, 1.05]	0.461
Graft Source				9.50	[1.08, 139.01]	0.059
ATG				16.31	[2.31, 195.43]	0.011
CMV Donor				0.35	[0.05, 2.00]	0.252

Intégration des données : tolérance ou non tolérance



Conclusion

Tolérance



- Androgen steroids were correlated with :
- ✓ naive CD8+ and double negative T cells,
 - ✓ pyrimidine and purine catabolism (CD73/NT5E)
 - ✓ Stemness-associated genes (TCF1/LEF1)

Androgen
steroids

Allo-réactivité persistante



- CD38-expressing cluster was correlated with:
- ✓ complement activation (C1QA, B, C)
 - ✓ P2Y purinergic receptor signaling (P2RY1)
 - ✓ and platelets activation (SERPING1)

Recipient aging



Remerciements



@HIPI_Inserm



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l'association qui lutte contre les leucémies

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