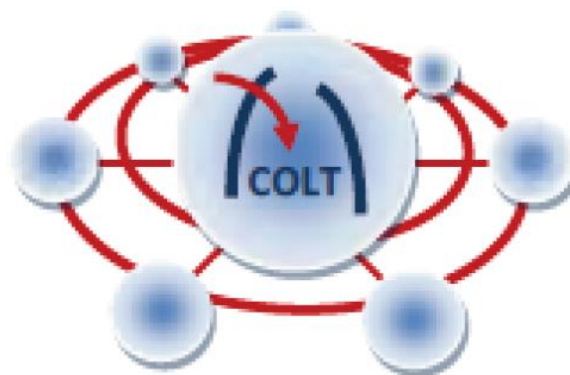


# Comarqueurs et rejet chronique pulmonaire

Résultats de l'Initiative de la Cohorte  
de Greffe Pulmonaire (COLT)

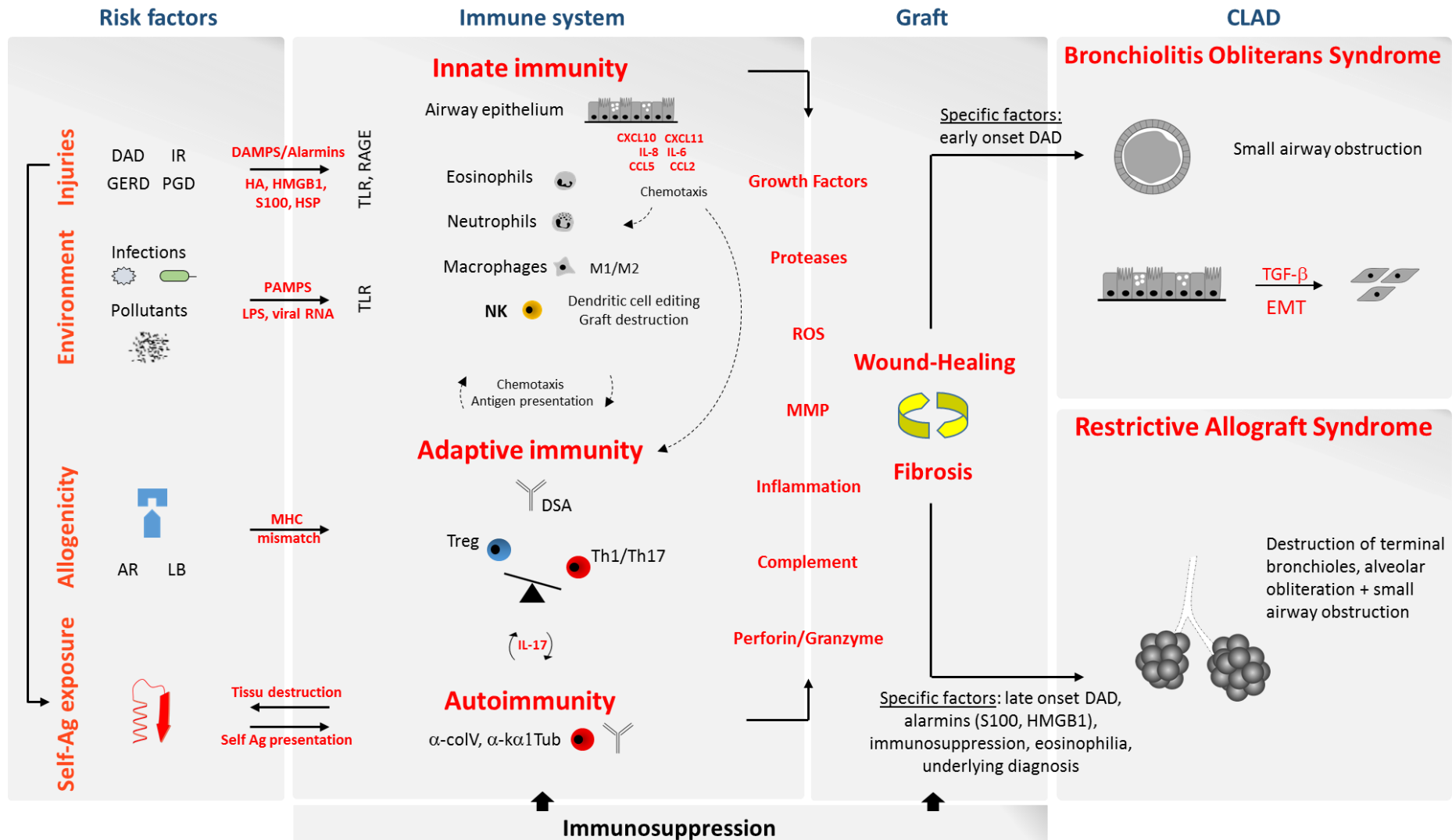


Antoine Magnan, Adrien Tissot, Aurore Foureau,  
Maxim Durand, Carole Brosseau, Pierre-Joseph Royer,  
Eugénie Durand, Richard Danger, Sophie Brouard

Université de Nantes, CHU de Nantes, l'institut du thorax,  
Service de pneumologie,

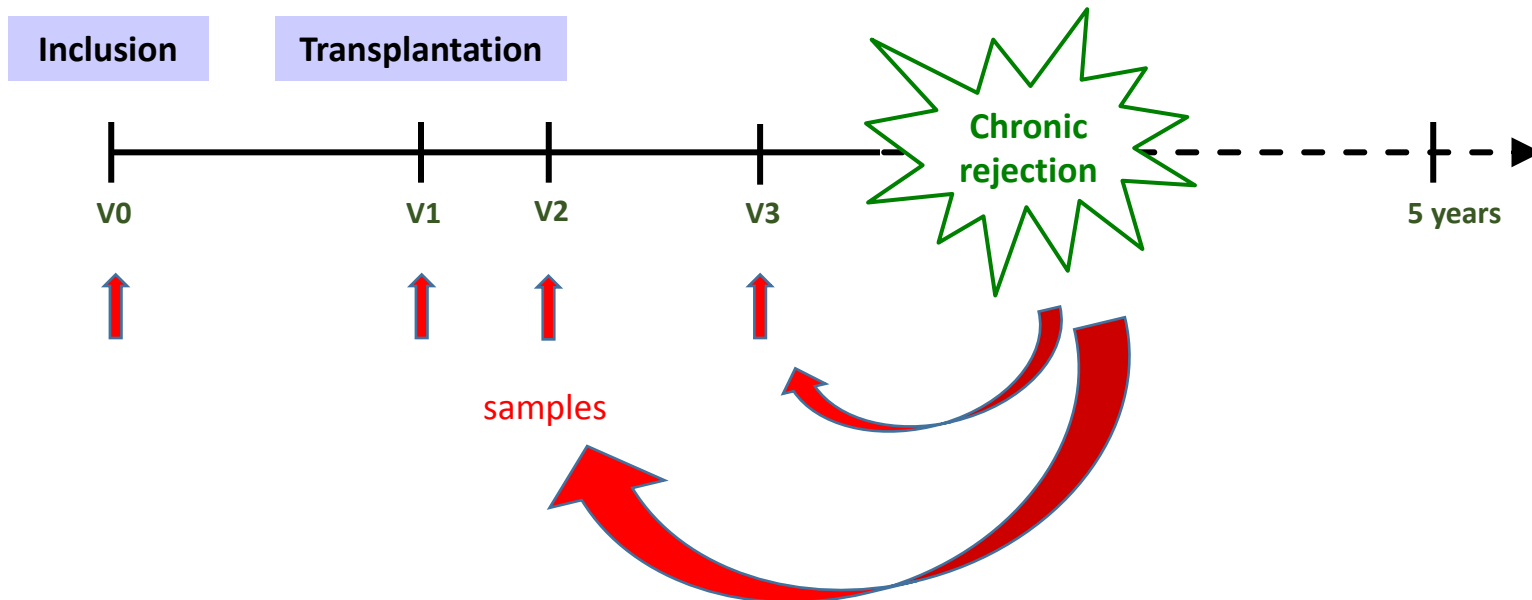
INSERM 1087 / CNRS 6291, INSERM UMR 1064

# CLAD : mécanismes

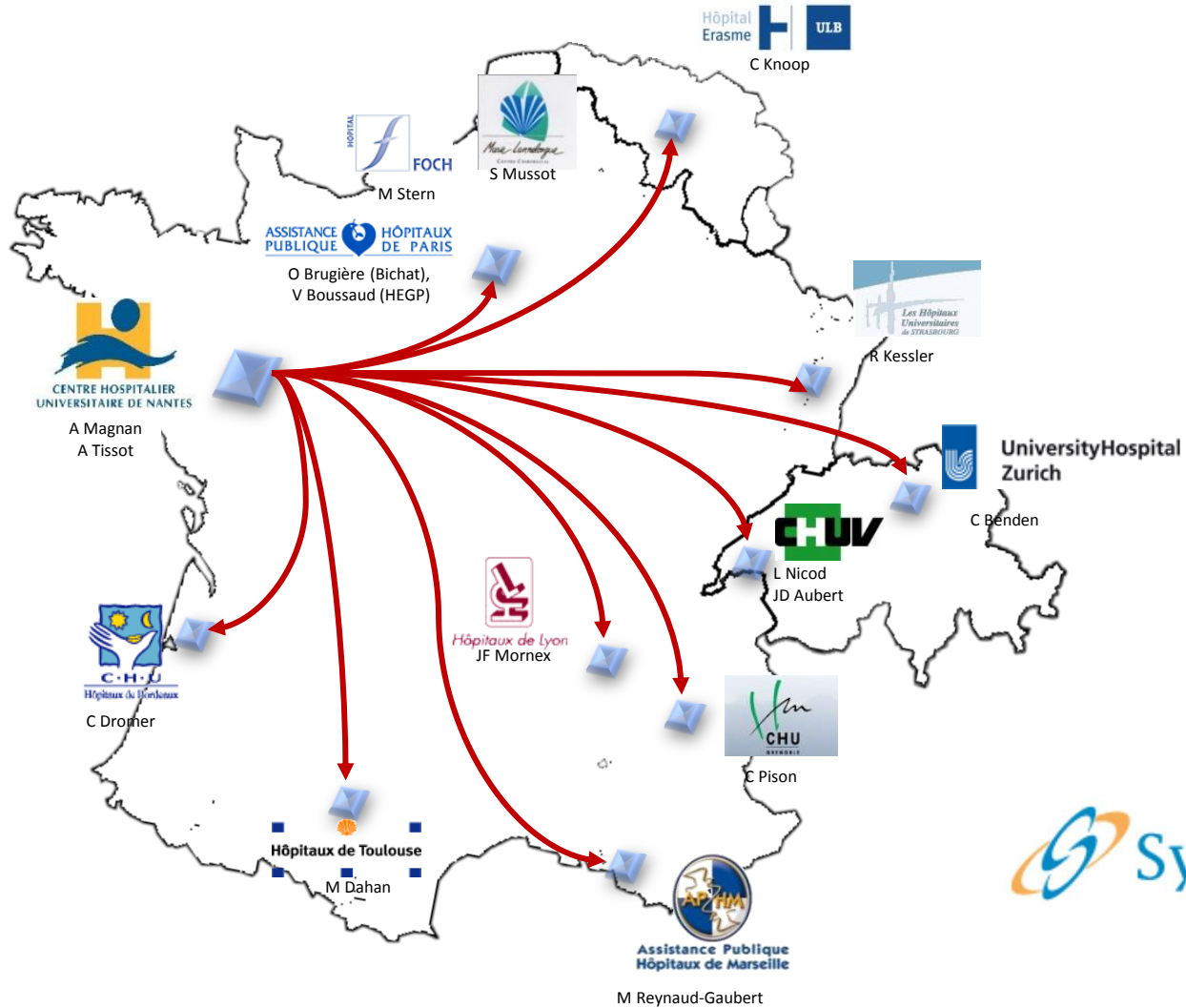


# COLT

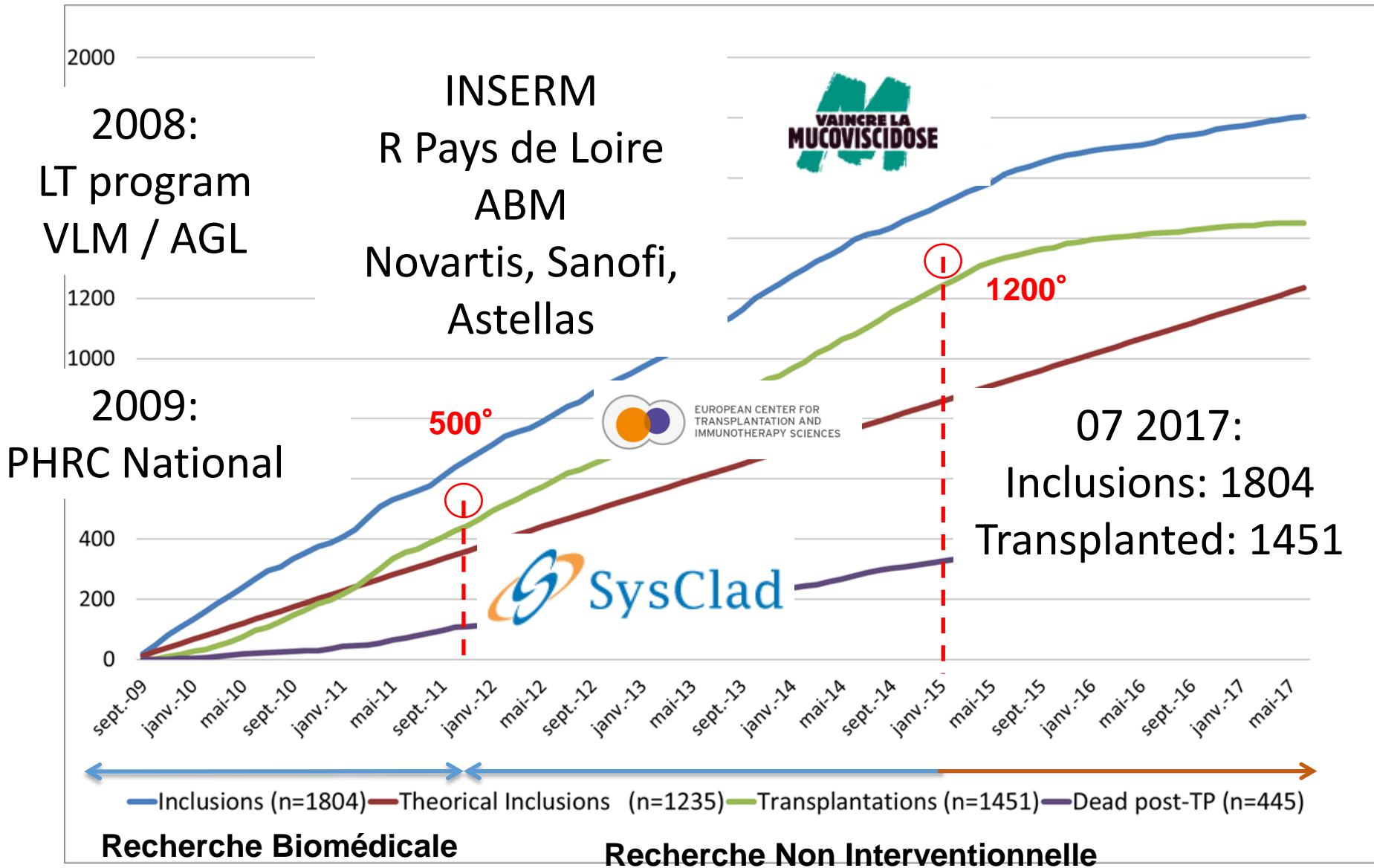
Research of early predictive factors of CLAD  
Towards 4P medicine ?



# COLT



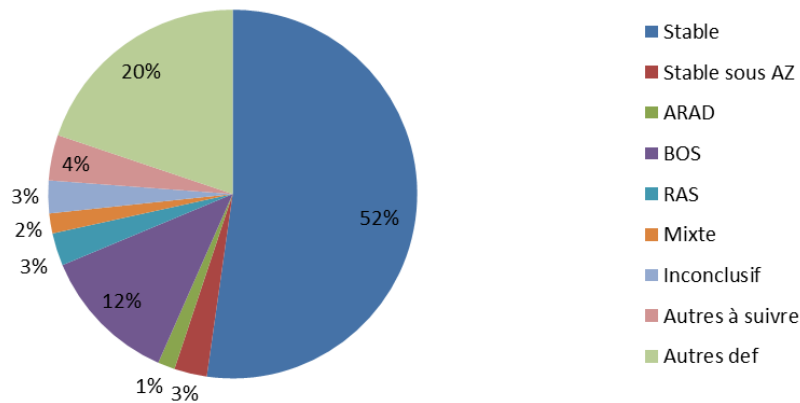
# COLT / SysCLAD Story



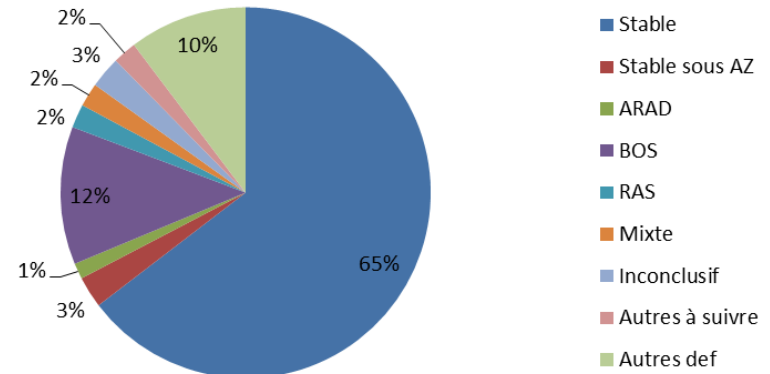
# Dysfonction Chronique du Greffon:

## Classification of adjudicated patients after 3 years post transplant

Répartition des patients par Catégorie  
(n=802)



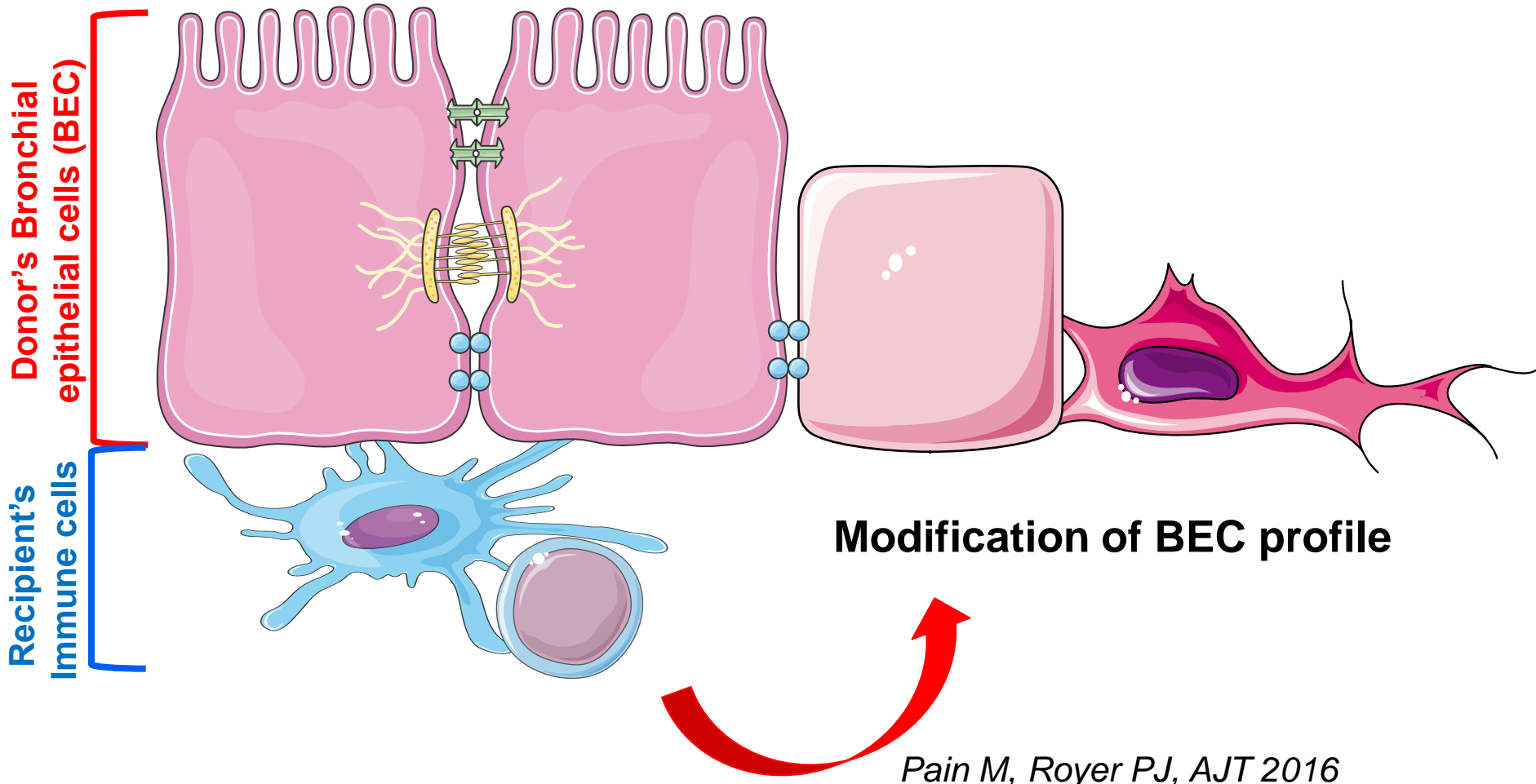
Répartition des patients atteint de mucoviscidose par catégorie (n=291)



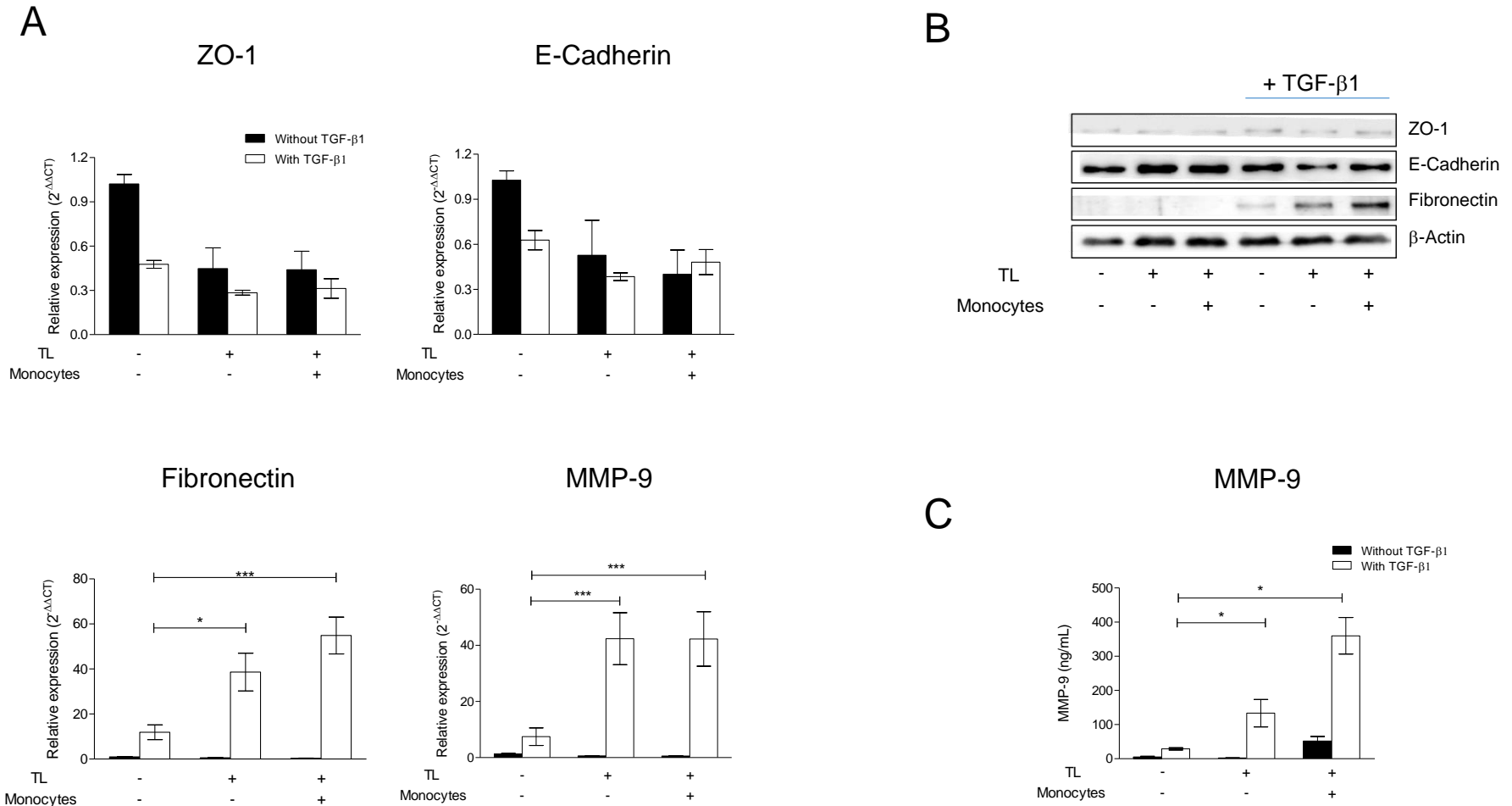
- **Nov 2017: 1<sup>st</sup> adjudications at 5 years: 250 patients « stable » at 3 years**

# MMP9 Story

Airway epithelial cells exposed to allogeneic T cells produce MMP9 through a CCL2/CCR2 pathway: implications for chronic lung allograft dysfunction.



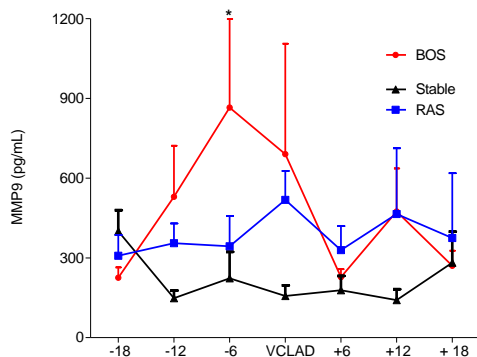
# Airway epithelial cells exposed to allogeneic T cells produce MMP9 through a CCL2/CCR2 pathway: implications for chronic lung allograft dysfunction.



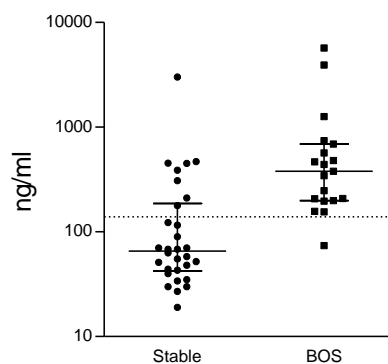


# Airway epithelial cells exposed to allogeneic T cells produce MMP9 through a CCL2/CCR2 pathway: implications for chronic lung allograft dysfunction.

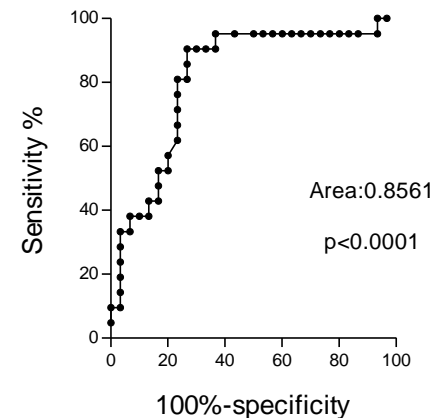
A



B



C



A cut-off value of 139 ng/ml of MMP-9 allowed the prediction of BOS at 6 months with 94% sensitivity and 73% specificity

# Regulatory T cells in transplantation

- Regulation of inflammation : asthma, autoimmune diseases, ...
- Growing interest in studying T regs in organ transplantation : operational tolerance, acute rejection, clinical trials.

The number of FoxP3+ cells in transbronchial lung allograft biopsies does not predict bronchiolitis obliterans syndrome within the first five years after transplantation

Dorrit Krustrup<sup>a</sup>, Martin Iversen<sup>b</sup>, Torben Martinussen<sup>c</sup>, Hans Henrik L. Schultz<sup>b</sup> and Claus B. Andersen<sup>a</sup>

## Dynamics of Human Regulatory T Cells in Lung Lavages of Lung Transplant Recipients

David C. Neujahr,<sup>1,5</sup> Adriana C. Cardona,<sup>2</sup> Onome Ulukpo,<sup>2</sup> Mark Rigby,<sup>2</sup> Andres Pelaez,<sup>1</sup> Allan Ramirez,<sup>1</sup> Anthony A. Gal,<sup>3</sup> Seth D. Force,<sup>4</sup> E. Clinton Lawrence,<sup>1</sup> Allan D. Kirk,<sup>2</sup> and Christian P. Larsen<sup>2</sup>

## REGULATORY CD4+CD25+ T CELLS IN THE PERIPHERAL BLOOD OF LUNG TRANSPLANT RECIPIENTS: CORRELATION WITH TRANSPLANT OUTCOME

FEDERICA MELONI,<sup>1,5</sup> PATRIZIO VITULO,<sup>1</sup> ALESSIA MARONE BIANCO,<sup>1</sup> ENRICA PASCHETTO,<sup>1</sup> MONICA MOROSINI,<sup>1</sup> ALESSANDRO CASCINA,<sup>1</sup> IOLANDA MAZZUCHELLI,<sup>2</sup> LAURA CIARDELLI,<sup>3</sup> TIBERIO OGGIONI,<sup>1</sup> ANNA MARIA FIETTA,<sup>1</sup> ERNESTO POZZI,<sup>1</sup> AND MARIO VIGANÒ<sup>4</sup>

## Lung function early after lung transplantation is correlated with the frequency of regulatory T cells

Tomoyuki Nakagiri · Gregor Warnecke · Murat Avsar · Stefanie Thissen · Bianca Kruse · Christian Kühn · Petra Ziehme · Ann-Kathrin Knöfel · Nodir Madrahimov · Meinoshin Okumura · Yoshiki Sawa · Jens Gottlieb · André R. Simon · Axel Haverich · Martin Strüber

## Decreased Percentage of CD4<sup>+</sup>FoxP3<sup>+</sup> Cells in Bronchoalveolar Lavage From Lung Transplant Recipients Correlates With Development of Bronchiolitis Obliterans Syndrome

Sangeeta M. Bhorade,<sup>1,5</sup> Hong Chen,<sup>1</sup> Luciana Molinero,<sup>2</sup> Chuanhong Liao,<sup>3</sup> Edward R. Garrity,<sup>1</sup> Wickii T. Vigneswaran,<sup>4</sup> Rebecca Shilling,<sup>1</sup> Anne Sperling,<sup>1</sup> Anita Chong,<sup>4</sup> and Maria-Luisa Alegre<sup>2</sup>

IMMUNOBIOLOGY AND GENOMICS

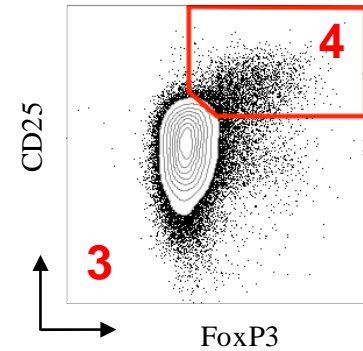
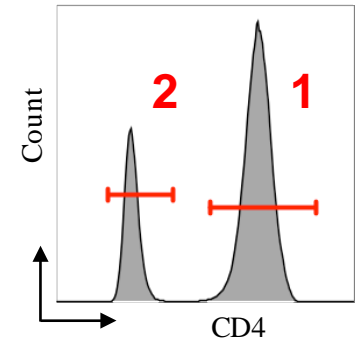
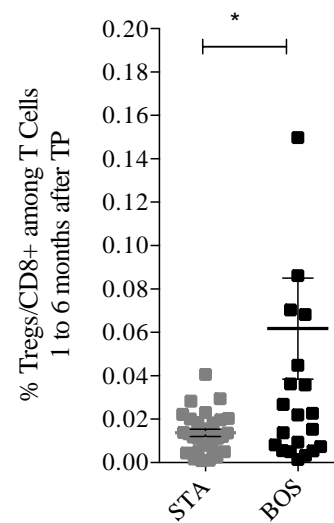
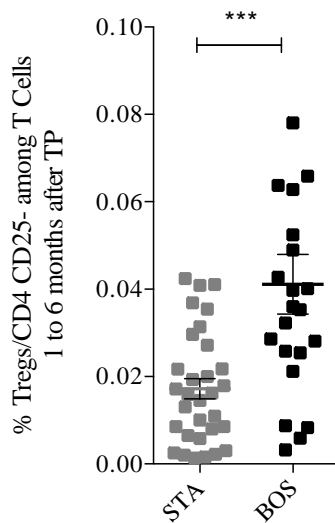
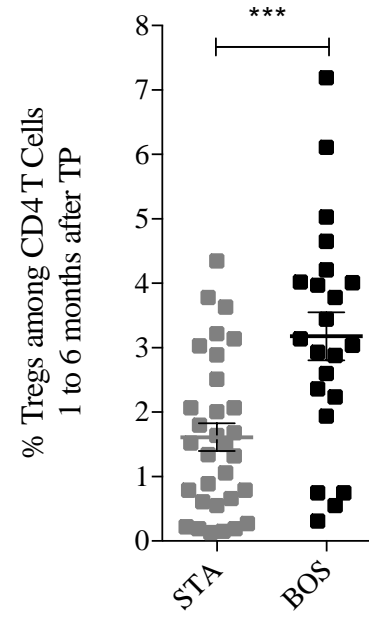
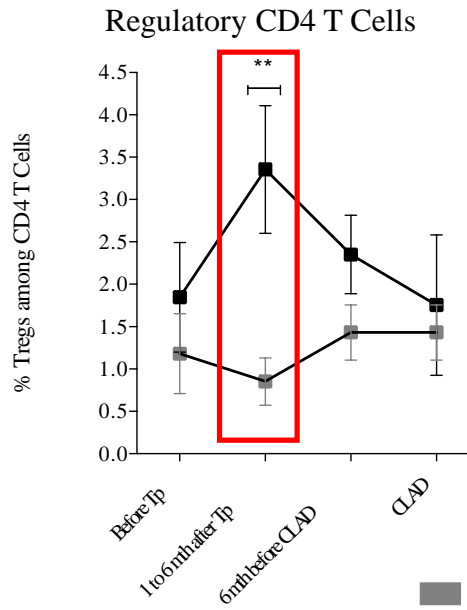
## T Regulatory Cells in Stable Posttransplant Bronchiolitis Obliterans Syndrome

Emilie Mamessier,<sup>1</sup> Anne-Marie Lorec,<sup>2</sup> Pascal Thomas,<sup>3</sup> Monique Badier,<sup>3</sup> Antoine Magnan,<sup>1,4</sup> and Martine Reynaud-Gaubert<sup>1</sup>

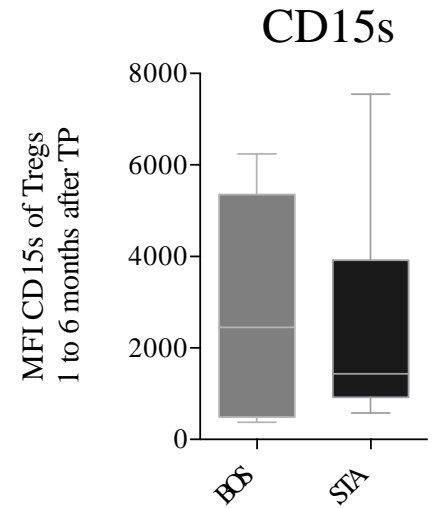
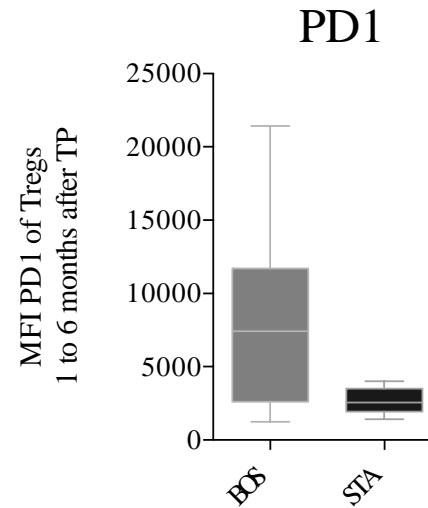
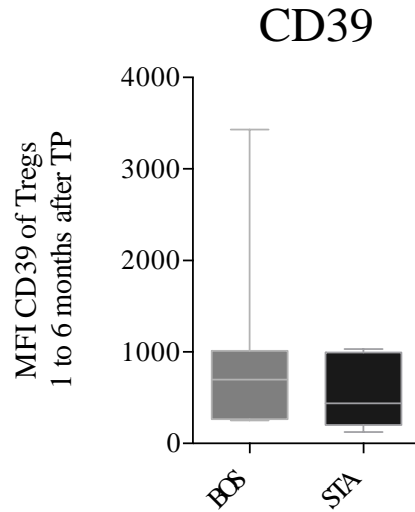
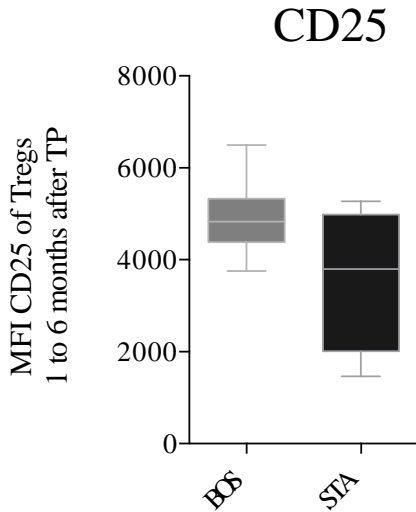
- No consensus about the link between Tregs and BOS occurrence.

# Regulatory T cells profile

4



# Regulatory T cells profile

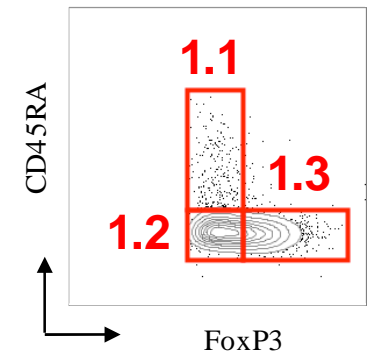
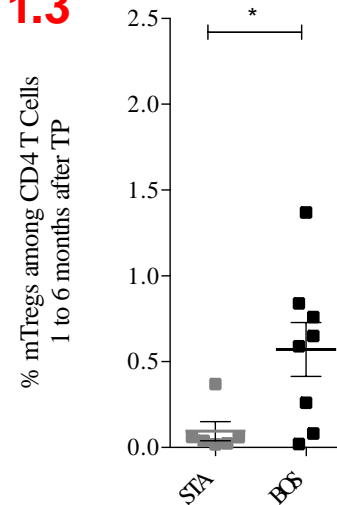


## Immunity

### Functional Delineation and Differentiation Dynamics of Human CD4<sup>+</sup> T Cells Expressing the FoxP3 Transcription Factor

Makoto Miyara,<sup>1,10</sup> Yumiko Yoshioka,<sup>1,9</sup> Akihiko Kitoh,<sup>1,9</sup> Tomoko Shima,<sup>1,9</sup> Kajsa Wing,<sup>1</sup> Akira Niwa,<sup>2</sup> Christophe Parizot,<sup>3</sup> Cécile Tafin,<sup>3</sup> Toshio Heike,<sup>2</sup> Dominique Valeyre,<sup>4</sup> Alexis Mathian,<sup>3</sup> Tatsutoshi Nakahata,<sup>2</sup> Tomoyuki Yamaguchi,<sup>1</sup> Takashi Nomura,<sup>1</sup> Masahiro Ono,<sup>1</sup> Zahir Amoura,<sup>5,6</sup> Guy Gorochoy,<sup>3,6</sup> and Shimon Sakaguchi<sup>1,7,8,\*</sup>

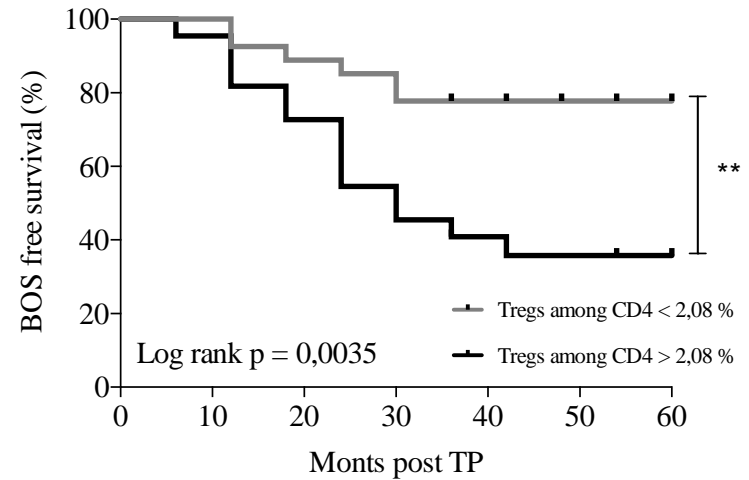
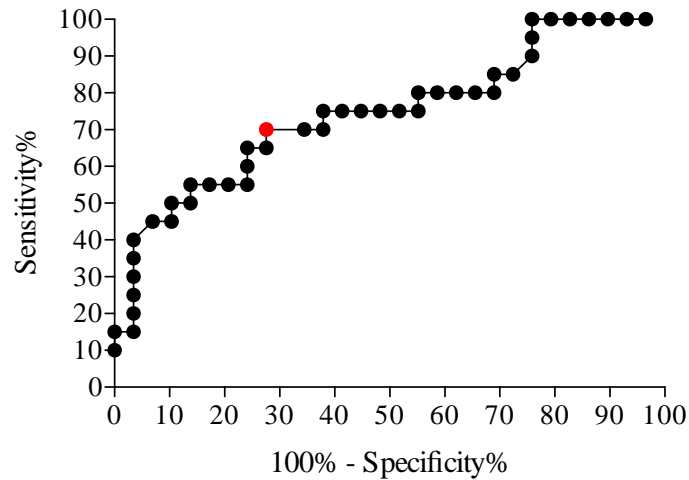
**1.3**



- 1. FoxP3 CD4<sup>+</sup> Tregs
- 1.1 nTregs FoxP3<sup>low</sup> CD45RA<sup>+</sup>
- 1.2 nonTregs FoxP3<sup>low</sup> CD45RA<sup>-</sup>
- 1.3 mTregs FoxP3<sup>hi</sup> CD45RA<sup>-</sup>

# Conclusion

- Increase of Tregs proportion with a memory phenotype early after TP for patients who will declare a BOS in the five years.

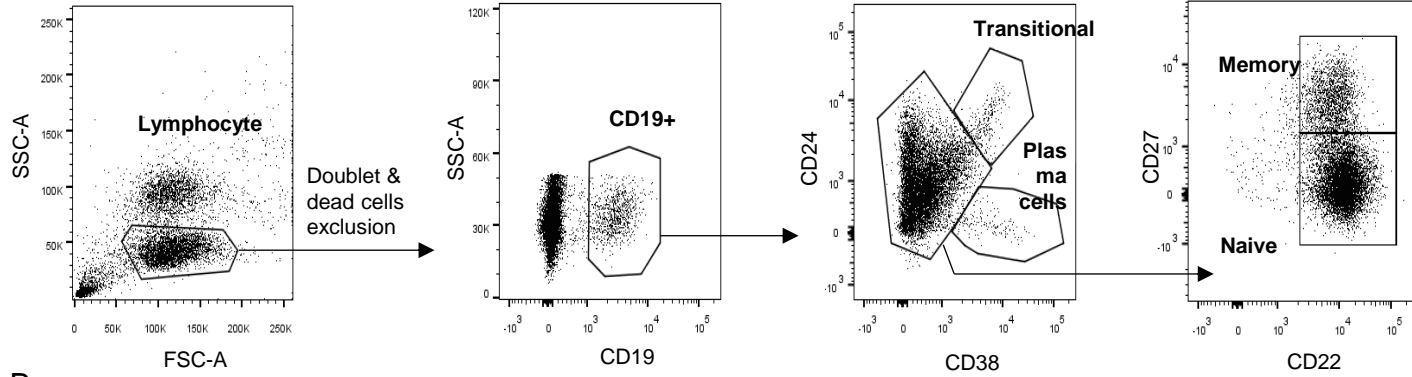


- New potential biomarker of the BOS occurrence, which could help to manage CLAD after lung transplantation in the next decades.

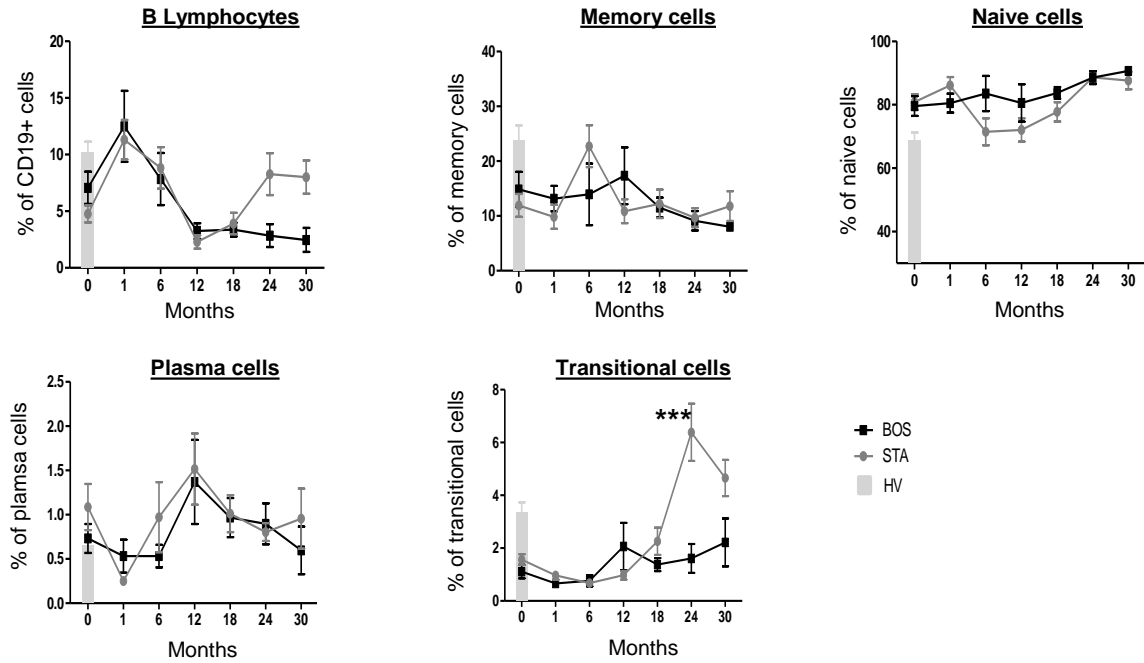
## **Circulating CD9+ B cells: biomarker of long-term BOS-free survival after Lung Transplantation (94/100)**

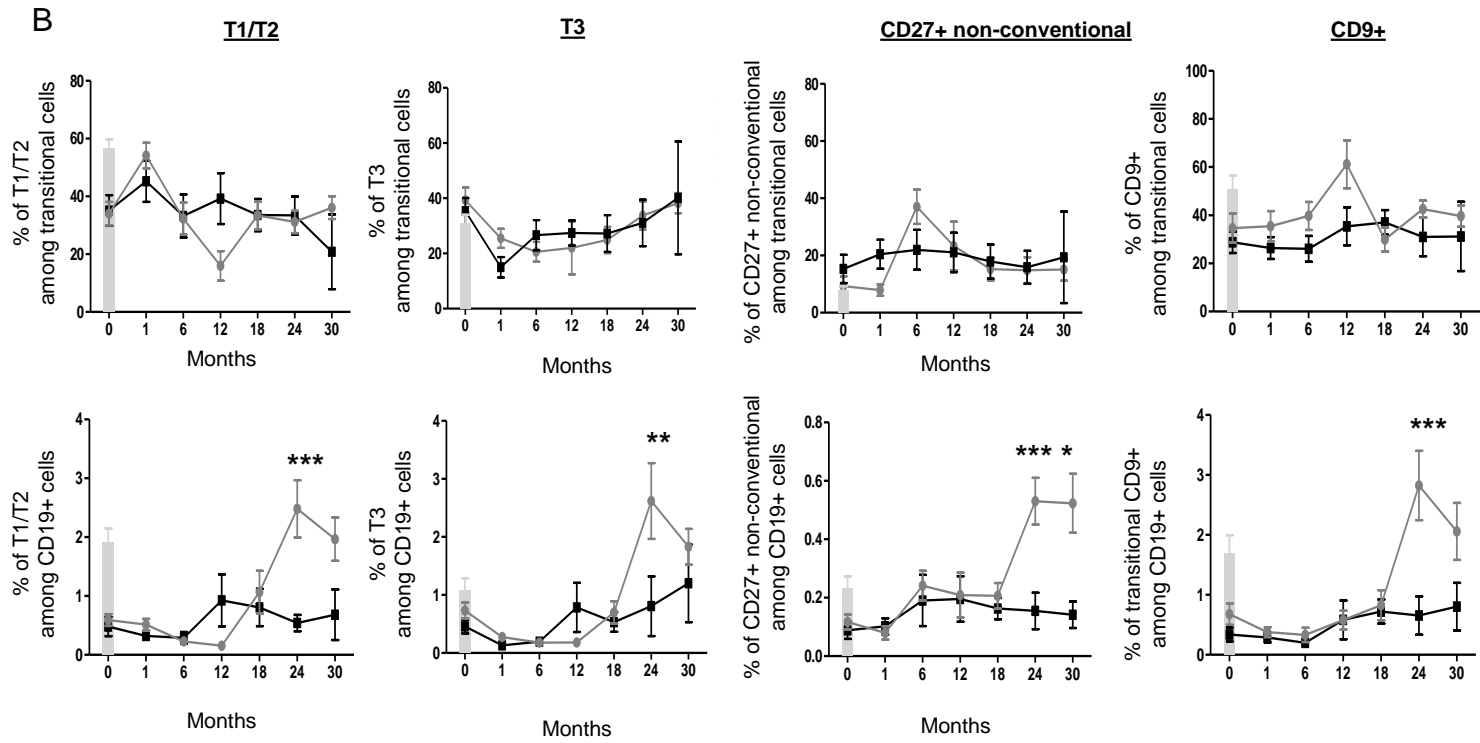
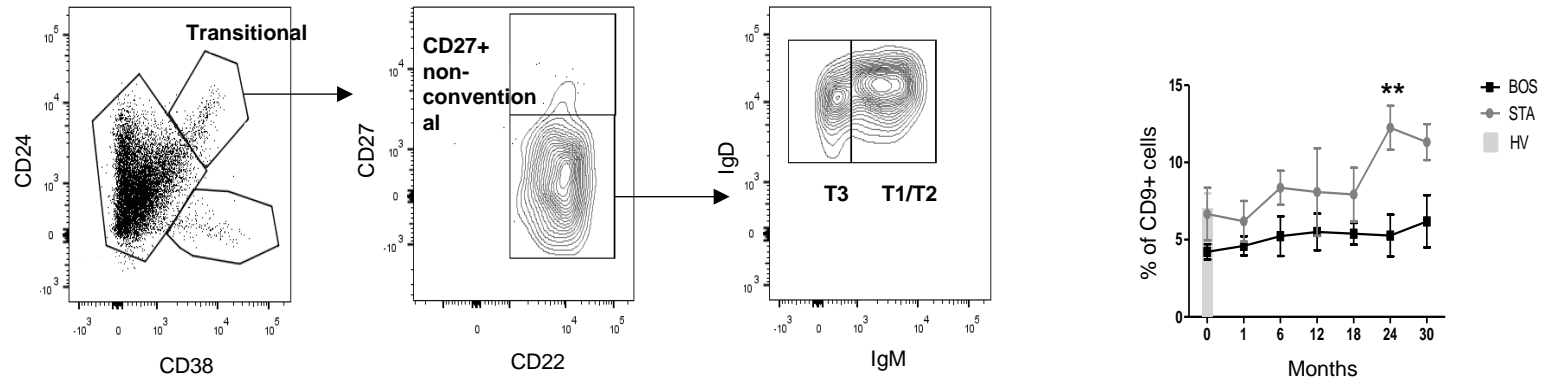
Carole Brosseau <sup>1,2,5,6+</sup>, Maxim Durand <sup>1,2,3+</sup>, Eugénie Durand <sup>1,2</sup>, Richard Danger <sup>1,2</sup>, Jennifer Loy <sup>5,6</sup>, Aurore Foureau <sup>5,6</sup>, Mélanie Chesneau <sup>1,2</sup>, Philippe Lacoste <sup>5,6</sup>, Pierre-Joseph Royer <sup>5,6</sup>, Adrien Tissot<sup>1,2,3,5,6</sup>, Antoine Roux<sup>5</sup>, Martine Reynaud-Gaubert<sup>6</sup>, Romain Kessler<sup>7</sup>, Sacha Mussot<sup>8</sup>, Claire Dromer<sup>9</sup>, Olivier Brugière<sup>10</sup>, Jean François Mornex<sup>11</sup>, Romain Guillemain<sup>12</sup>, Marcel Dahan<sup>13</sup>, Christiane Knoop<sup>14</sup>, Christophe Pison<sup>15</sup>, Laurent Nicod<sup>16</sup>, Antoine Magnan <sup>5,6\$</sup>, Sophie Brouard <sup>1,2,4\$</sup> & COLT and SysCLAD consortia\*.

**A**

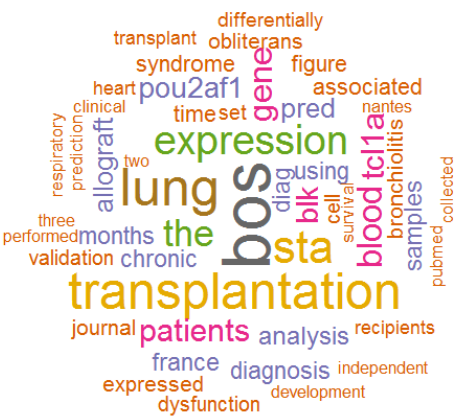


**B**









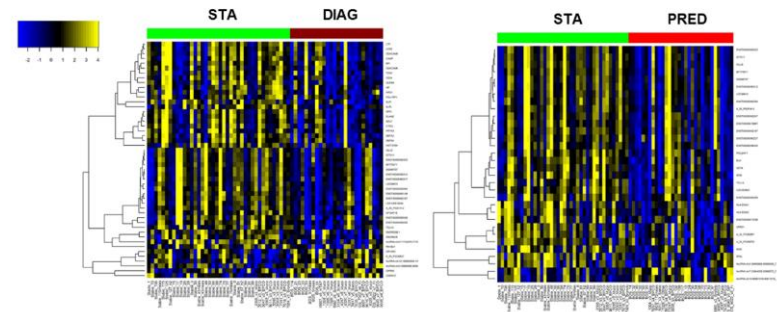
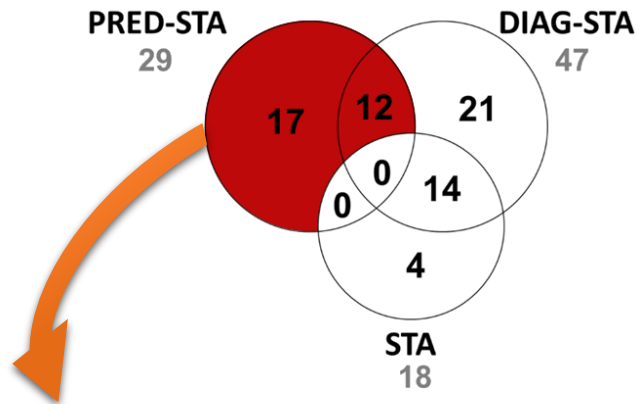
# Blood Gene Expression Predicts Bronchiolitis Obliterans Syndrome Appearance After Lung Transplantation

Richard Danger\*, Pierre-Joseph Royer\*,  
Damien Reboulleau, Eugénie Durand, Jennifer Loy, Adrien Tissot, Philippe Lacoste, Antoine Roux,  
Martine Reynaud-Gaubert, Carine Gomez, Romain Kessler, Sacha Mussot, Claire Dromer, Olivier  
Brugière, Jean-François Mornex, Romain Guillemain, Marcel Dahan, Christiane Knoop, Karine  
Botturi, Christophe Pison, Angela Koutsokera, Laurent P. Nicod,  
Sophie Brouard\*, Antoine Magnan\*  
and the COLT and SysCLAD Consortia



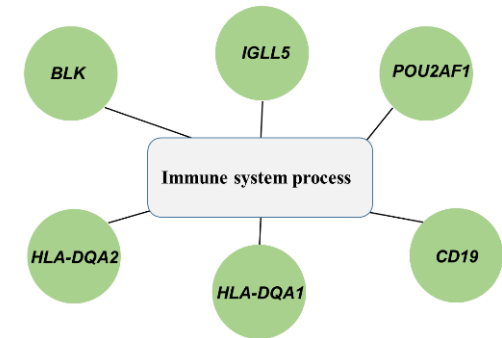
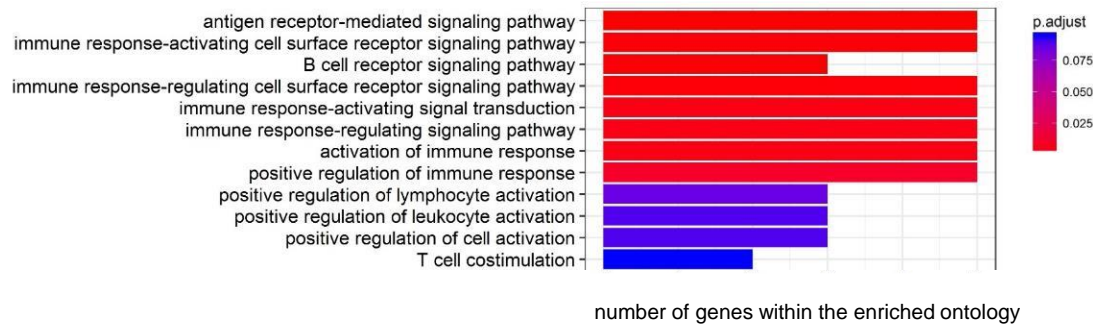
# Blood gene expression associated with BOS

- Identification of differential genes (t-statistic from R *limma* package; p.value <5% and fold change >1.5)



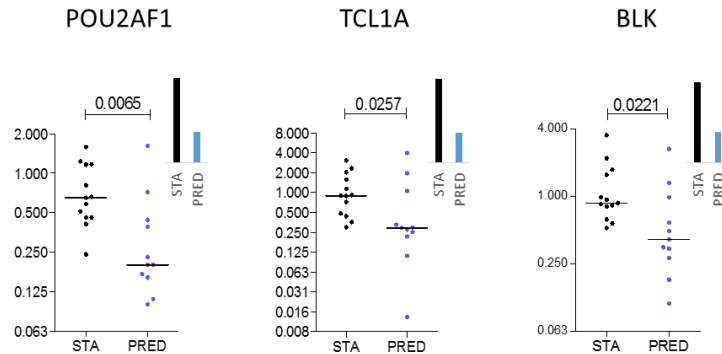
- Enrichment of down-regulated and immune-related genes in PRED versus STA comparison

Gene ontology analysis:

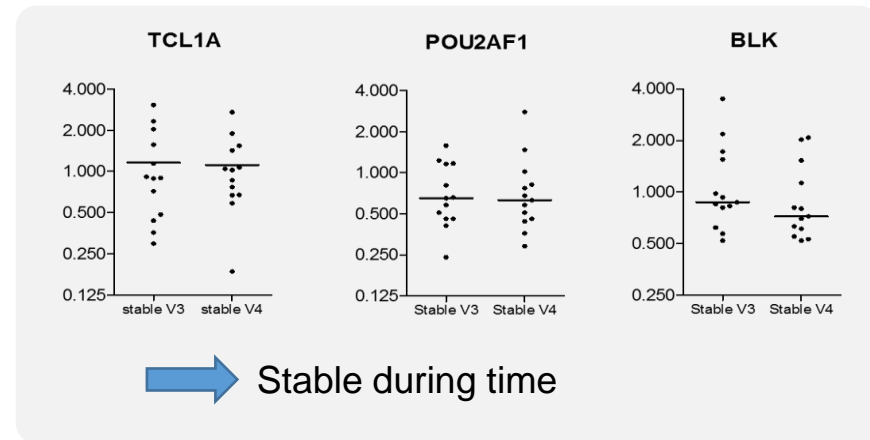
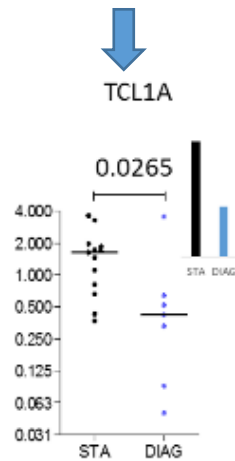


# Prediction of BOS: independent validation

- Validation of genes associated with BOS appearance



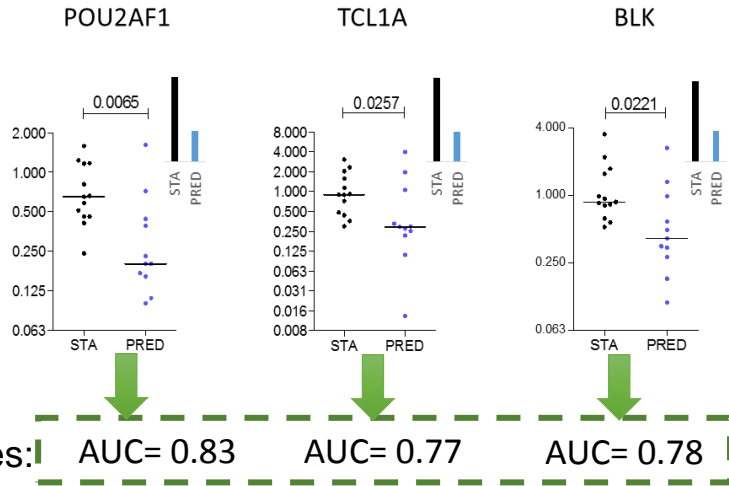
-individual qPCR  
-samples from new patients:  
n= 13 STA & 11 PRED  
→ independent validation



*POU2AF1*: POU class 2 associating factor 1  
*BLK*: B lymphoid tyrosine kinase  
*TCL1A*: T-cell leukaemia/lymphoma 1A

# Prediction of BOS: independent validation

- Validation of genes associated with BOS appearance



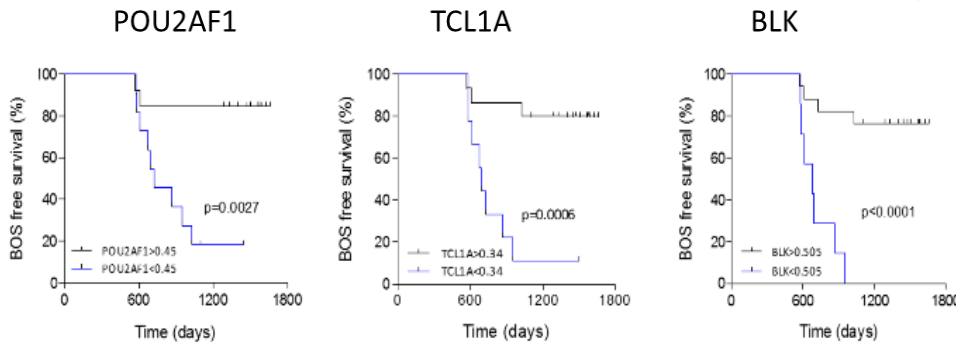
-individual qPCR  
 -samples from new patients:  
 n= 13 STA & 11 PRED

➔ independent validation

➔ Excellent discriminative ability

- Prediction of BOS appearance

➔ 3 genes to predict BOS



*POU2AF1*: POU class 2 associating factor 1  
*BLK*: B lymphoid tyrosine kinase  
*TCL1A*: T-cell leukaemia/lymphoma 1A

# Blood Gene Expression Predicts Bronchiolitis Obliterans Syndrome Appearance After Lung Transplantation

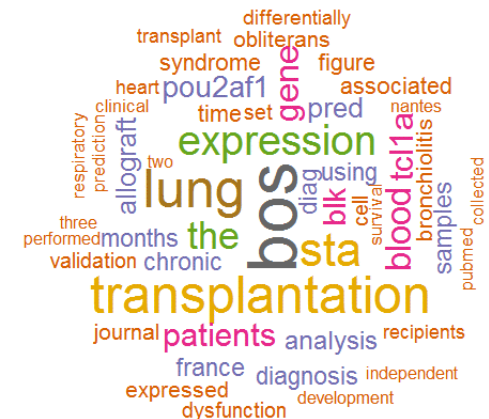
## Conclusion

- Identification of 3 genes as predictive biomarkers of BOS
- Whole blood and qPCR: non-invasive and compatible with clinical settings
- Suggests a role of B cells in BOS mechanisms

patent: [EP16306125.2](#)  
work submitted



Validation of these 3 genes in a large prospective cohort



# Conclusions: Biomarqueurs issus de COLT et SysCLAD

- MMP9
- Treg
- B transitionnels CD9 +
- Pou2AF1, BLK, TCL1A



A valider en pratique clinique

Score composite à construire

# SysCLAD consortium

**Cohort Of Lung Transplantation-COLT** (associating surgeons; anaesthetists-intensivists; physicians, research staff) **Bordeaux:** J. Jougon, J.-F. Velly; H. Rozé; E. Blanchard, C. Dromer; **Bruxelles:** M. Antoine, M. Cappello, M. Ruiz, Y. Sokolow, F. Vanden Eynden, G. Van Nooten; L. Barvais, J. Berré, S. Brimiouille, D. De Backer, J. Créteur, E. Engelman, I. Huybrechts, B. Ickx, T. J.C. Preiser, T. Tuna, L. Van Obberghé, N. Vancutsem, J.-L. Vincent; P. De Vuyst, I. Etienne, F. Féry, F. Jacobs, C. Knoop, J.L. Vachiéry, P. Van den Borne, I. Wellemans ; G. Amand, L. Collignon, M. Giroux; **Grenoble** E. Arnaud-Crozat, V. Bach, P.-Y. Brichon, P. Chaffanjon, O. Chavanon, A. de Lambert, J.-P. Fleury, S. Guigard, R. Hacini, K. Hireche, A. Pirvu, P. Porcu; P. Albaladejo, C. Allègre, A. Bataillard, D. Bedague, E. Briot, M. Casez-Brasseur, D. Colas, G. Dessertaine, M. Durand, G. Francony, A. Hebrard, M.R. Marino, B. Oummahan, D. Protar, D. Rehm, S. Robin, M. Rossi-Blancher; C. Augier, P. Bedouch, A. Boignard, H. Bouvaist, E. Brambilla, A. Briault, B. Camara, J. Claustre, S. Chanoine, M. Dubuc, S. Quétant, J. Maurizi, P. Pavèse, C. Pison, C. Saint-Raymond, N. Wion; C. Chérion; **Lyon** R. Grima, O. Jegaden, J.-M. Maury, F. Tronc; C. Flamens, S. Paulus; J.-F. Mornex, F. Philit, A. Senechal, J.-C. Glérant, S. Turquier; D. Gamondes; L. Chalabresse, F. Thivolet-Bejui; C. Barnel, C. Dubois, A. Tiberghien; **Paris, Hôpital Européen Georges Pompidou** F. Le Pimpec-Barthes, A. Bel, P. Mordant, P. Achouh; V. Boussaud; R. Guillemain, D. Méléard, M.O. Bricourt, B. Cholley ; V. Pezella; **Marseille:** G. Brioude, X.B. D'Journo , C. Doddoli. P. Thomas, D. Trousse ; S. Dizier, M. Leone, L. Papazian; F. Bregeon, B. Coltey, N. Dufeu, H. Dutau, S. Garcia, JY. Gaubert, C. Gomez, S. Laroumagne, A. Nieves, L. C. Picard, F. Rey, M. Reynaud-Gaubert, JM. Rolain, E. Sampol, V. Secq; I. Bouvin ; **Nantes** O. Baron, P. Lacoste, C. Perigaud, J.C. Roussel; I. Danner, A Haloun A. Magnan, A Tissot; T. Lepoivre, M. Treilhaud; K. Botturi-Cavaillès, S. Brouard, R. Danger, J. Loy, M. Morisset, M. Pain, S. Pares, D. Rebouilleau, P.-J. Royer ; **Le Plessis Robinson, Hôpital Marie Lannelongue** Ph. Darteville, D. Fabre, E. Fadel, O. Mercier, S. Mussot; F. Stephan, P. Viard; J. Cerrina, P. Dorfmueller, S. Feuillet M. Ghigna, Ph. Hervén F. Le Roy Ladurie, J. Le Pavec, V. Thomas de Montpreville; L. Lamrani; **Paris, Hôpital Bichat** Y. Castier, P. Mordant, P. Cerceau, P. Augustin, S. Jean-Baptiste, S. Boudinet, P. Montravers ; O. Brugière, G. Dauriat, G. Jébrak, H. Mal, A. Marceau, A.-C. Métivier, G. Thabut, E. Lhuillier, C. Dupin, V. Bunel; **Strasbourg** P. Falcoz, G. Massard, N. Santelmo; G. Ajob, O. Collange O. Helms, J. Hentz, A. Roche; B. Bakouboula, T. Degot, A. Dory, S. Hirschi, S. Ohlmann-Caillard, L. Kessler , R. Kessler, A. Schuller; K. Bennedif, S. Vargas; **Suresnes** P. Bonnette, A. Chapelier, P. Puyo, E. Sage; J. Bresson, V. Caille, C. Cerf, J. Devaquet, V. Dumans-Nizard, ML. Felten, M. Fischler, AG. Si Larbi, M. Leguen, L. Ley, N. Liu, G. Trebbia; S. De Miranda, B. Douvry, F. Gonin, D. Grenet, A.M. Hamid, H. Neveu, F. Parquin, C. Picard, A. Roux, M. Stern; F. Bouillioud, P. Cahen, M. Colombat, C. Dautricourt, M. Delahousse, B. D'Urso, J. Gravisse, A. Guth, S. Hillaire, P. Honderlick, M. Lequintrec, E. Longchamp, F. Mellot, A. Scherrer, L. Temagoult, L. Tricot; M. Vasse, C. Veyrie, L. Zemoura; **Toulouse** J. Berjaud, L. Brouchet, M. Dahan; F. Le Balle, O. Mathe ; H. Benahoua, A. Didier, A.L. Goin, M. Murriss; L. Crognier, O. Fourcade.

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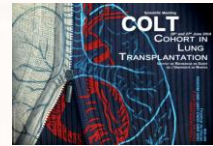
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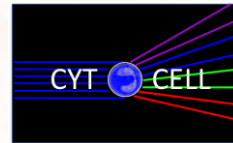


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# Remerciements

PHRC 2009

