Dysfonction chronique post transplantation pulmonaire, enseignements en 2018 de COLT et SysCLAD

CMJ, Grenoble le 05-04-2018

Pr. Christophe Pison, *au nom des consortia SysCLAD et COLT*

Service Hospitalier Universitaire
Pneumologie Physiologie
Pôle Thorax et Vaisseaux
CHU de Grenoble

Inserm1055, Laboratoire de Bioénergétique Fondamentale et Appliquée

Biologie Environnementale et Systémique – BEeSY

UNIVERSITÉ Grenoble Alpes

CHU GRENOBLE ALPES

agence de la biomédecine

SEVENTH FRAMEWORK PROGRAMME

COLT

SysClad

Relations d'intérêts

- **Aides et Objets**
  - **Travels, Meeting, Speakers fees to Pr. Ch. Pison**
  - **Clinical Research to my Hospital**
  - **COPD-Nutrition, Asthma, Pulmonary Hypertension, Lung Transplantation**

- **Pharmas et contrat avec CHU des Alpes**
  - **Actélion**
  - **Astra Zeneca**
  - **Bayer**
  - **Boehringer Ingelheim**
  - **Gilead**
  - **GlaxoSmithKline**
  - **Lilly**
  - **Novartis**
  - **Nutricia-Danone**
  - **Seb**
  - **Pfizer**
  - **Stallergenes**

- **Dispositifs & Soins à domicile**
  - **Therakos, PneumRx, Medwin, PumonX, Holaira AGIR@dom, Vitlalaire, Orkyn, Vitalaire, SOS Oxygène**

Groupe de Transplantation Pulmonaire
1990-2016 > 260 greffes

- **Anesthésistes - Réanimateurs**
  P Albaladejo, C Allègre, D Anglade, D Bedague, O Carle, M Casez-Brasseur, D Colas, G Dessertaine, Y Dubois, M Durand, G Francony, MR Marino, D Protar, S Robin, M Rossi-Blancher

- **Chirurgiens Cardiaques, Thoraciques & Vasculaires**
  D Angelescu, PY Brichon, O Chavanon, G Frey, R Hacini, A Pirvu, P Porcu

- **Pneumologues, Cardiologues, Infectiologues, Psychiatre**
  A Boignard, H Bouvaist, A Briault, B Camara, J Claustre, M Dubuc, S Quétant, P Pavèse, C Pison, C St-Raymond

- **Pharmaciens Cliniciens et Recherche clinique**
  P Bedouch, S Chanoine, C Chérion

- **Imagerie et Pathologie**
  G Ferretti, A Jankowski, E Reymond, O Stephanov,

- **Coordination, Cadres, Système d'information, Psychologues, Assurance Qualité**
  C Fleurence, C Segond, E Tourral, M. Guyot, L Altoukhovitch, F Imburchia

- **Soins de suite, Réhabilitation et Soins à domicile**
  Centre Henri Bazire & AGIR@dom

Nice February 27-28 / March 1, 2018

6TH WORLD SYMPOSIUM ON PULMONARY HYPERTENSION

360, 241 (file active) patients, 2006-2017

- **Pédiatres** : S. Douchin, G. Blaysat
- **Cardiologie, Réhabilitation** : H. Bouvaist, S. Marlière, M. Noirclerc, M. Salvat, C. Saunier, E. Vautrin
- **Imageurs** : G. Ferretti, A. Jankowski, F. Thony, E. Reymond
- **Pneumologues, Interniste** : B. Camara, J. Claustre, S. Quêtant, C. Saint-Raymond, C. Pison, B. Imbert
- **Fonctionnalistes** : B. Aguilaniu, B. Wuyam, S. Doutreleau
- **Pharmaciens cliniciens, recherche clinique**
  P. Bedouch, S. Chanoine, M. Jondot, B. Rey-Robert
- **Soins à domicile** : Agir à Dom

CRCM Adulte et Pédiatrique du CHUGA

Corps médical
- B Camara (responsable médical)
- S Quetant

IDE Coordinatrice
- C Segond

Masseur kinésithérapeute
- JC Benitez

Diététicienne
- C Neveu

Psychologue
- L Altoukovich

Assistante sociale
- Magali Fabre

Secrétariat
- E Julien Binard

Corps médical
- I Pin (responsable médical)
- C LLéréna

IDE Coordinatrice
- C Turblin, M Cheik

Masseur kinésithérapeute
- V Vion

Diététicienne
- Lise Joly

Psychologue
- A Simon Léger

Assistante sociale
- D Cucchi

Secrétariat
- F. Allamanno

Historique de la transplantation pulmonaire

- 1905, 1ère greffe cœur chiot anastomosé au cou d'un chien, Alexis Carrel, Lyon
- 1949, 1ère greffe d'un poumon chez le chien, Pr. Henri Métras, Marseille
- 1952, 1ère greffe rénale donneur vivant, Jean Hamburger

- 1963, 1ère greffe pulmonaire, Pr. J. Hardy, Missippi

- 1981, 1ères greffes cardio-pulmonaires Pr. N. Shumway, San Francisco
- 1982, 1ère greffe cardio-pulmonaire en Europe, Pr. C. Cabrol, Paris
- **1983, mise à disposition Cyclosporine A, laboratoire Sandoz, Novartis**
- **1983, 1ère greffes mono-pulmonaire viables, Pr. J. Cooper, Toronto**
- **1983, 1ère greffe pulmonaire pour mucoviscidose, Pr. M.H. Yacoub, UK**
- 1986, 1ère greffes double pulmonaire en bloc, Pr. J. Cooper, Toronto
- 1989, 1ère greffe double mono-pulmonaire séquentielle sans CEC, Pr. A. Bisson, Foch

- 2011, 1ère série 11 EVLP, Pr. Shaf Keshjavjee, Toronto

- **11 centre de greffes pulmonaires, dont 8 pour la mucoviscidose en France ABM, 1993 à VI-2014, 3 701Tx pulmonaires, 30% soit 1106 pour mucoviscidose**

- ISHLT 1995 àVI-2014, 45 683 Tx pulmonaires, 16,2% soit 7419 pour mucoviscidose

SysCLAD consortium, COLT & STCS

Cohort of lung Transplantation-COLT associating surgeons, anaesthetists - intensivists, physicians, research assistants; ***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. Brimioulle, D. De Backer, J. Créteur, E. Engelman, I. Huybrechts, B. Ickx, T. J. C. Preiser, T. Tuna, L. Van Obberghe, 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:*** D. Angelescu, P.-Y. Brichon, O. Chavanon, G. Frey, R. Hacini, C. Martin, 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, 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, -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, A. Basire, B. Coltey, N. Dufeu, H. Dutau, S. Garcia, J. Y. Gaubert, C. Gomez, S. Laroumagne, A. Nieves, L. C. Picard, M. Reynaud-Gaubert, V. Secq, G. Mouton; ***Nantes:*** O. Baron, C. Brossaud, E. Durand, M. Durand, 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. Reboulleau, P.-J. Royer; ***Le Plessis Robinson, Hôpital Marie Lannelongue:*** D. Fabre, E. Fadel, O. Mercier, S. Mussot, F. Stephan, P. Viard, J. Cerrina, P. Dorfmuller, S. Feuillet, M. Ghigna, Ph. Hervé ; F. Le Roy Ladurie, 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, B. Renaud-Picard, K. Bennedif, S. Vargas; ***Suresnes:*** P. Bonnette, A. Chapelier, P. Puyo, E. Sage, J. Bresson, V. Caille, C. Cerf, J. Devaquet, V. Dumans-Nizard, M. L. Felten, M. Fischler, A. G. 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. Longchampt, F. Mellot, A. Scherrer, L. Temagoult, L. Tricot, M. Vasse, C. Veyrie, L. Zemoura; ***Toulouse:*** J. Berjaud, L. Brouchet, M. Dahan, F. O. Mathe, H. Benahoua, M. DaCosta, I. Serres, V. Merlet-Dupuy, M. Grigoli, A. Didier, M. Murris, L. Crognier, O. Fourcade.

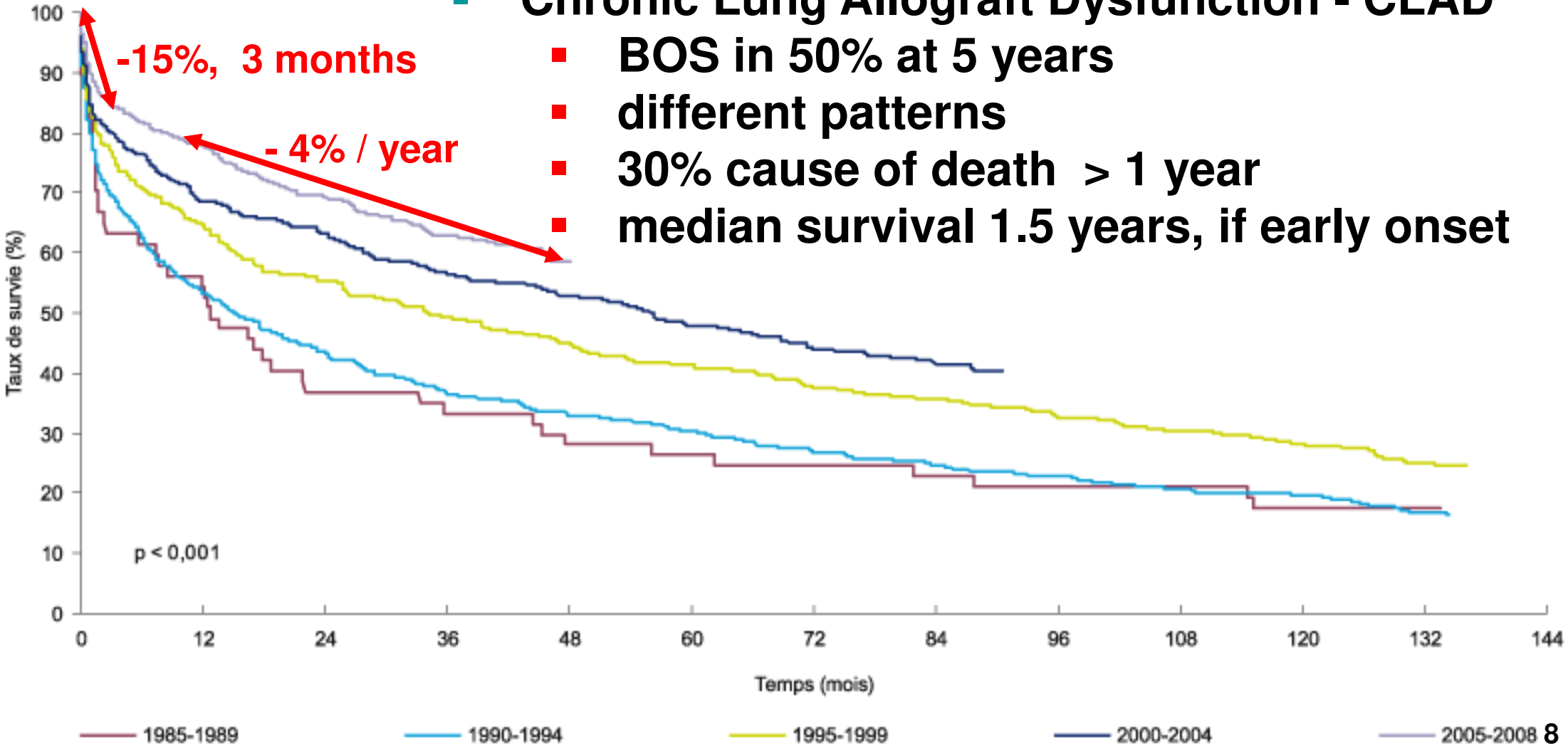
Swiss lung Transplant centers ***Lausanne-Geneva:*** T. Krueger, H. B. Ris, M. Gonzalez, J.-D. Aubert, L. P. Nicod, B. J. Marsland, C. Berutto, T. Rochat, P. Soccal, Ph. Jolliet, A. Koutsokera, C. Marcucci, O. Manuel, E. Bernasconi, M. Chollet, F. Gronchi, C. Courbon; ***Zurich:*** S. Hillinger, I. Inci, P. Kestenholz, W. Weder; R. Schuepbach, M. Zalunardo, C. Benden, U. Buergi, L. C. Huber, B. Isenring, M. M. Schuurmans, A. Gaspert, D. Holzmann, N. Müller, T. Rechsteiner, C. Schmid, B. Vrugt. We would like to thank the following collaborators of the Swiss Lung Transplantation Centers for their contribution in data collection and/or project coordination (alphabetical order): E. Catana, C. Cowaloosur-Noirat, M. F. Derkenne, JL Dreifuss, P. Grendelmeier, J. Hartwig, N. Lourenco, M. Magno, H. Muller- McKenna, E. Perret, and K. Zangger.

Swiss Transplant Cohort Study-STCS: Rita Achermann, Patrizia Amico, John-David Aubert, Philippe Baumann, Guido Beldi, Christian Benden, Christoph Berger, Isabelle Binet, Pierre-Yves Bochud, Elsa Boely, Heiner Bucher, Leo Bühler, Thierry Carell, Emmanuelle Catana, Yves Chalandon, Sabina de Geest, Olivier de Rougemont, Michael Dickenmann, Michel Duchosal, Laure Elkrief, Thomas Fehr, Sylvie Ferrari- Lacraz, Christian Garzoni, Paola Gasche Soccal, Christophe Gaudet, Emiliano Giostra, Déla Golshayan, Karine Hadaya, Jörg Halter, Dominik Heim, Christoph Hess, Sven Hillinger, Hans H. Hirsch, Günther Hofbauer, Uyen Huynh-Do, Franz Immer, Richard Klaghofer, Michael Koller (Head of the data center), Bettina Laesser, Roger Lehmann, Christian Lovis, Oriol Manuel, Hans-Peter Marti, Pierre Yves Martin, Luca Martinolli, Pascal Meylan, (Head, Biological samples management group), Paul Mohacsi, Philippe Morel, Ulrike Mueller, Nicolas J. Mueller (Chairman Scientific Committee), Helen Mueller-McKenna (Head of local data management), Antonia Müller, Thomas Müller, Beat Müllhaupt, David Nadal, Manuel Pascual (Executive office), Jakob Passweg, Juliane Rick, Eddy Roosnek, Anne Rosselet, Silvia Rothlin, Frank Ruschitzka, Urs Schanz, Stefan Schaub, Aurelia Schnyder, Christian Seiler, Susanne Stampf, Jürg Steiger (Head, Executive Office), Guido Stirnimann, Christian Toso, Christian Van Delden (Executive office), Jean-Pierre Venetz, Jean Villard, Madeleine Wick (STCS coordinator), Markus Wilhelm, and Patrick Yerly.

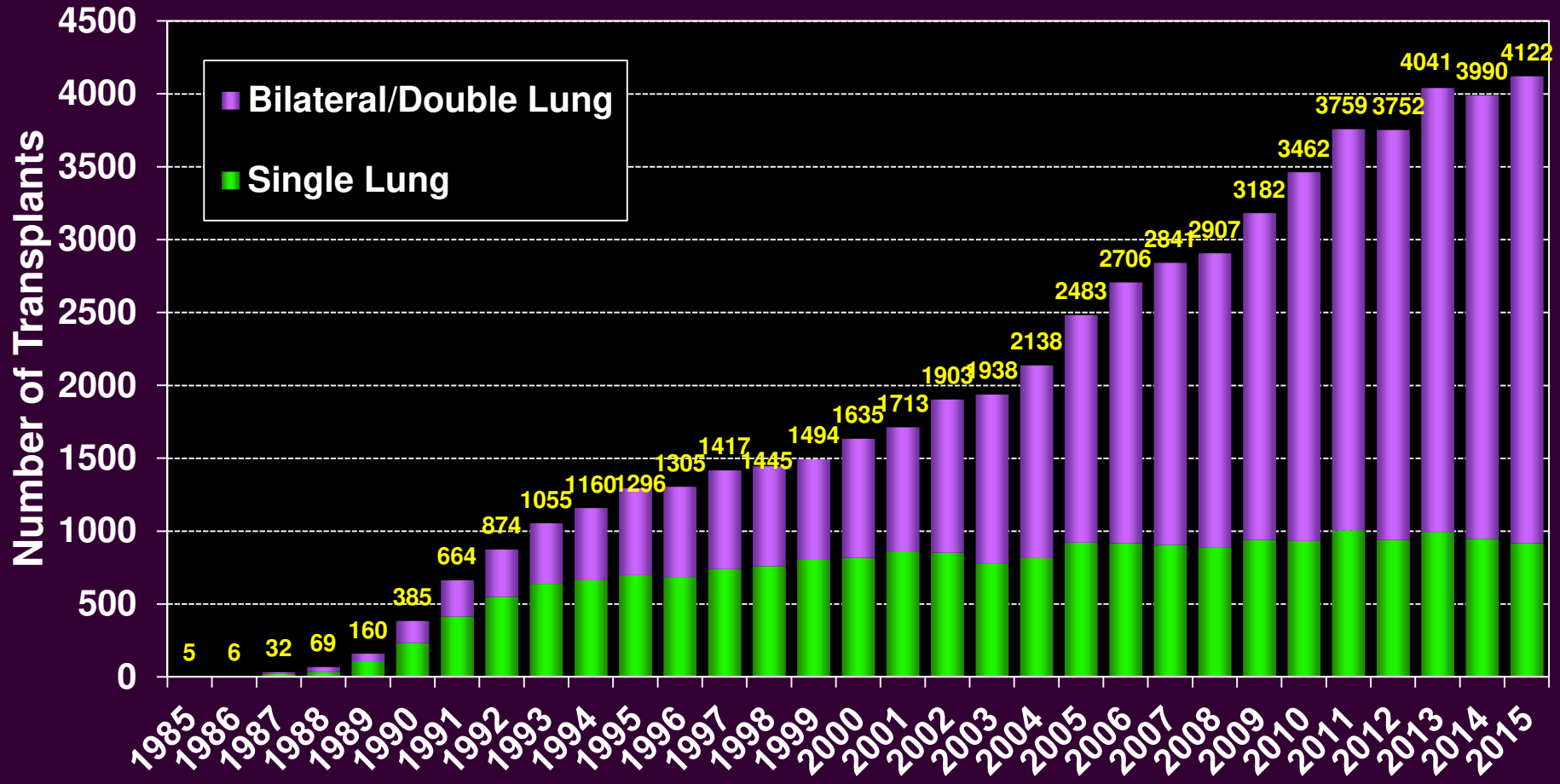
SME and Platforms ***Biomax (Munich, Germany):*** A. Fritz, D. Maier; ***Finovatis (Lyon, France):*** K. Desplanche, D. Koubi; ***GATC*** (***Germany):*** F. Ernst, T. Paprotka, M. Schmitt, B. Wahl; ***Novasdicovery (Lyon, France):*** J.-P. Boissel, G. Olivera-Botello; ***Prométhée Proteomics Platform (Grenoble, France):*** C. Trocmé, B. Toussaint, S. Bourgoin-Voillard, M. Séve; ***Inserm U823, Université GrenobleAlpes (Grenoble, France):*** M. Benmerad, V. Siroux, R. Slama; ***European Institute for Systems Biology & Medicine (Lyon, France):*** C. Auffray, B. de Mulder, Mazein, J. Pellet

Achilles‘ heels in Lung Transplantation

- Shortage of grafts, Primary Graft Dysfunction
- Chronic Lung Allograft Dysfunction - CLAD
  - BOS in 50% at 5 years
  - different patterns
  - 30% cause of death > 1 year
  - median survival 1.5 years, if early onset



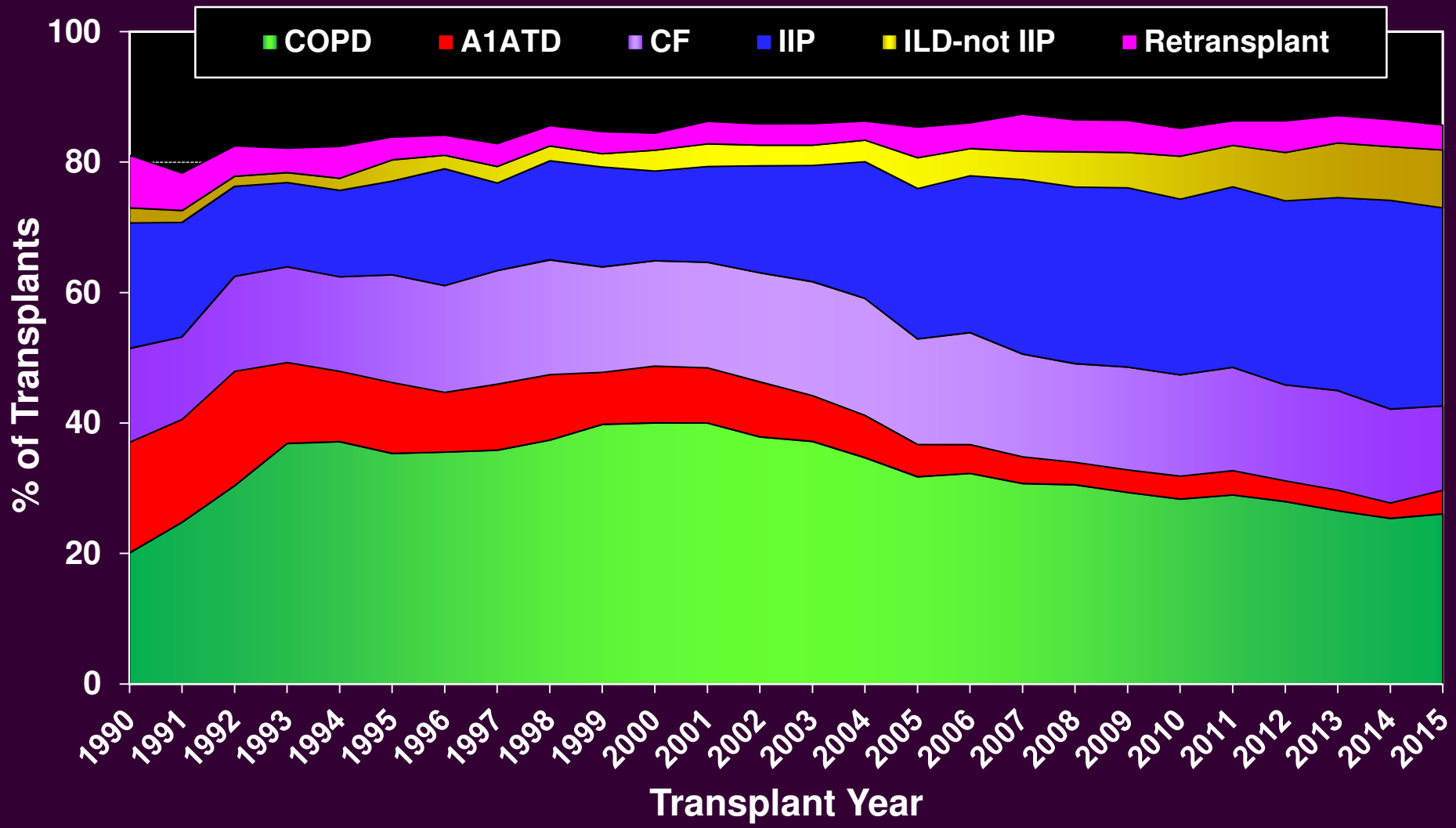
Adult Lung Transplants
Number of Transplants by Year and Procedure Type



NOTE: This figure includes only the adult lung transplants that are reported to the ISHLT Transplant Registry. As such, this should not be construed as representing changes in the number of adult lung transplants performed worldwide.

ISHLT • INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION
2017
JHLT. 2017 Oct; 36(10): 1037-1079

Adult Lung Transplants
Major Indications by Year (%)



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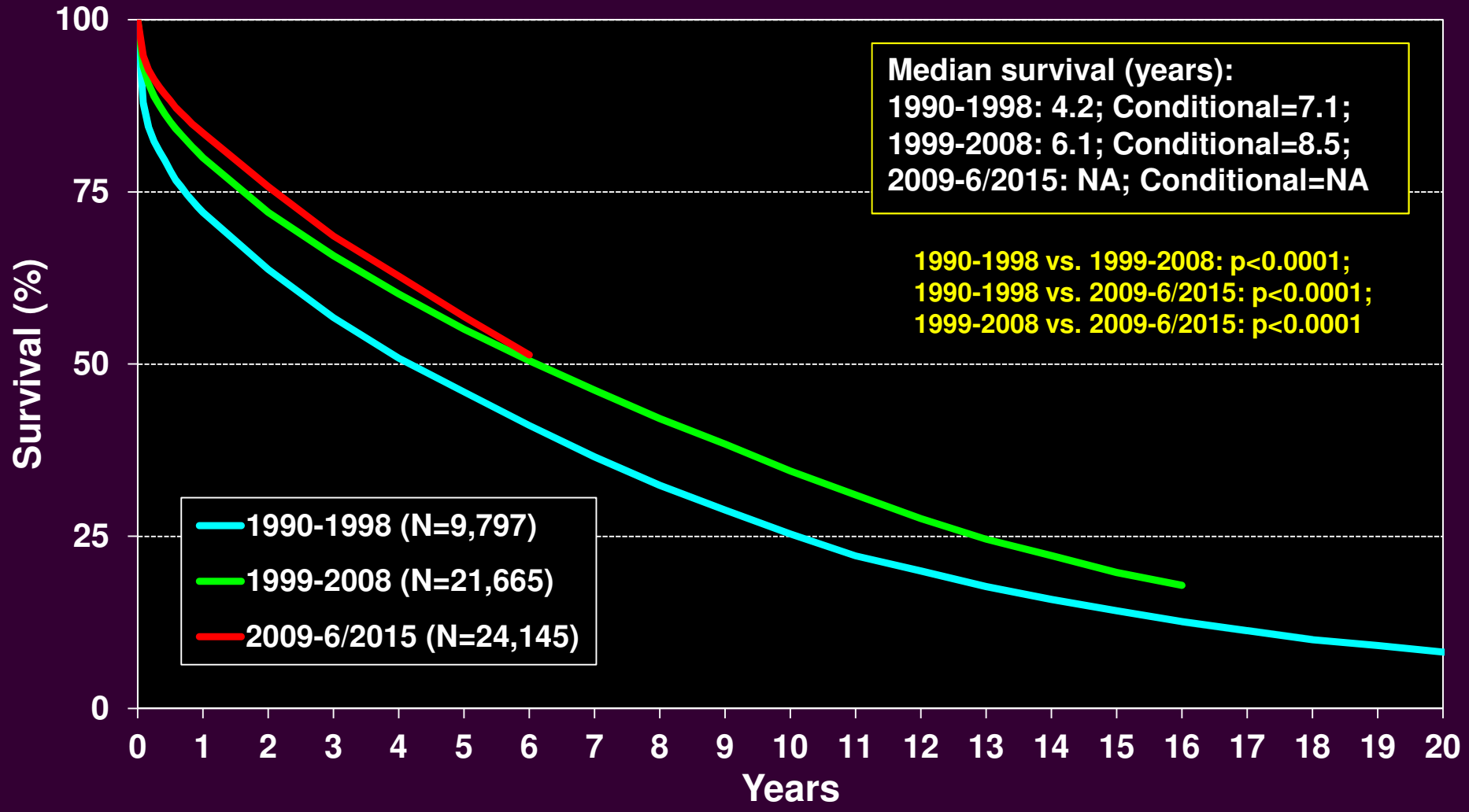
2017
JHLT. 2017 Oct; 36(10): 1037-1079

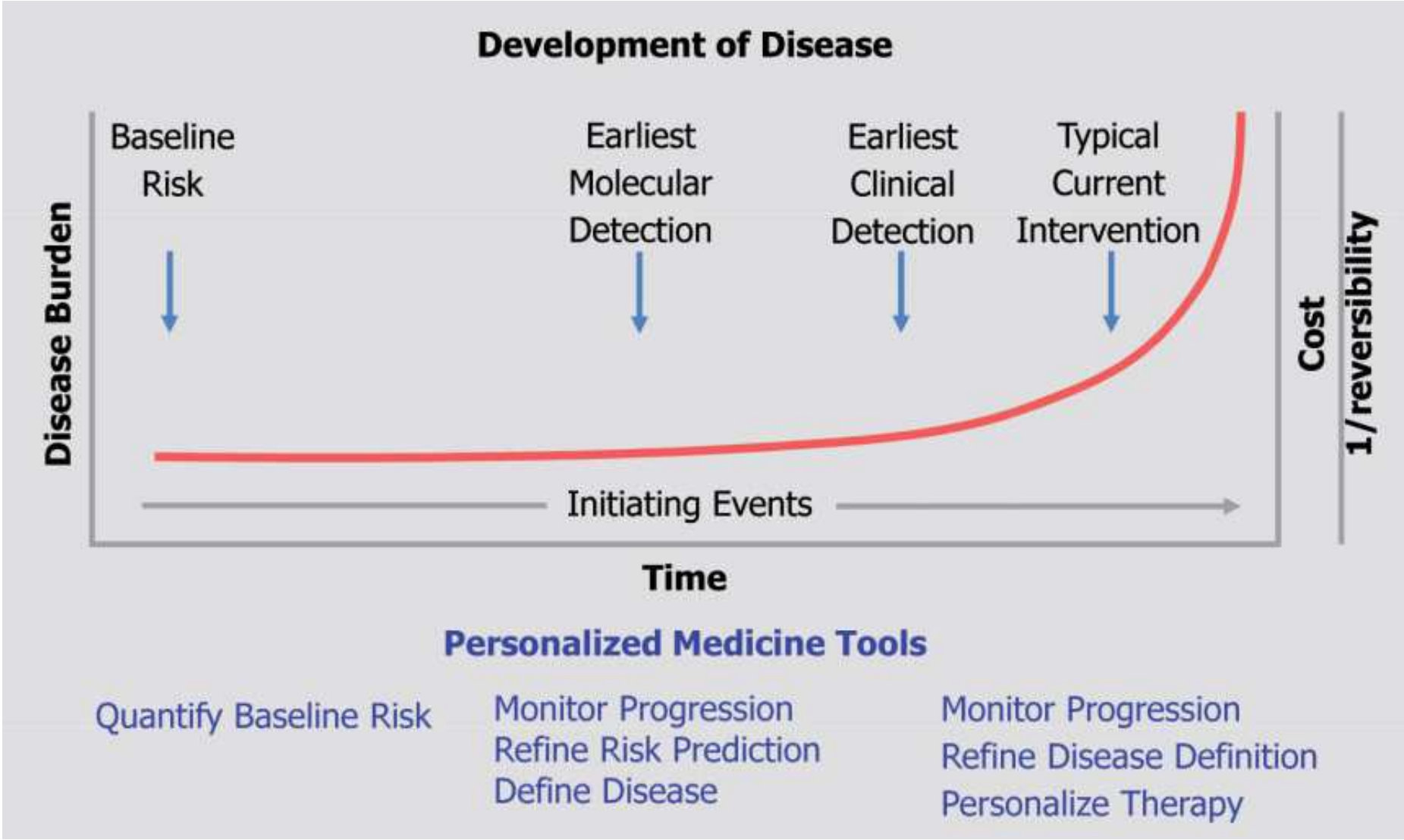
Adult Lung Transplants
Kaplan-Meier Survival by Era
(Transplants: January 1990 – June 2015)



ISHLT • INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION
2017
JHLT. 2017 Oct; 36(10): 1037-1079

Systems Medicine

Systems prediction of Chronic Lung Allograft Dysfunction SysCLAD



Snyderman *et al.* Biotechnol. J. 2012;7:973-9

SEVENTH FRAMEWORK PROGRAMME

SysClad

COLT

STCS SWISS TRANSPLANT COHORT STUDY

FINOVATIS

GATC BIOTECH

biomax

biomax informatics ag

VAINCRE LA MUCOVISCIDOSE

Association Grégory Lemarchal

CHU GRENOBLE

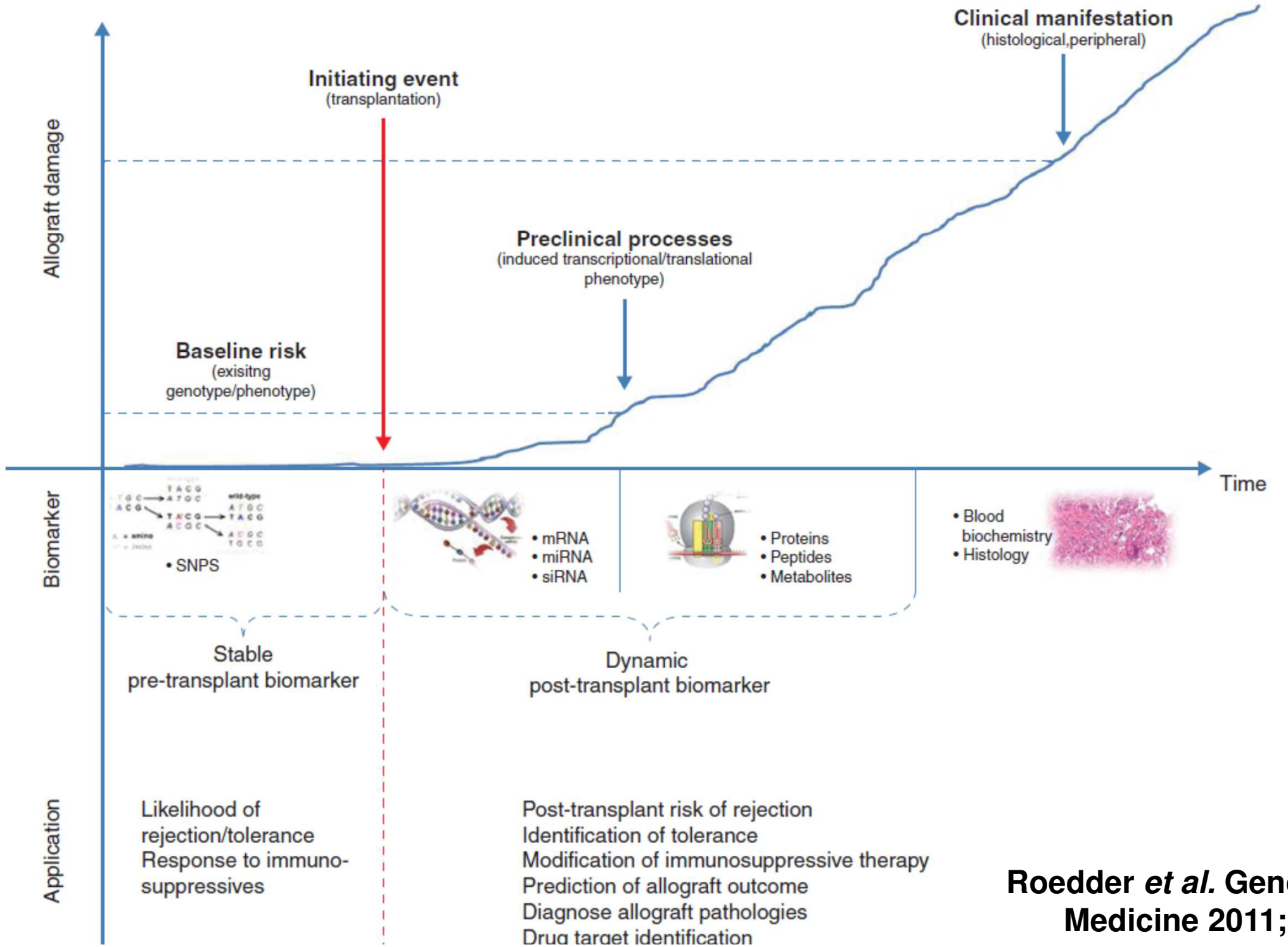
PHRC 2009

RECHERCHE EN SANTÉ RESPIRATOIRE
FONDS DE DOTATION

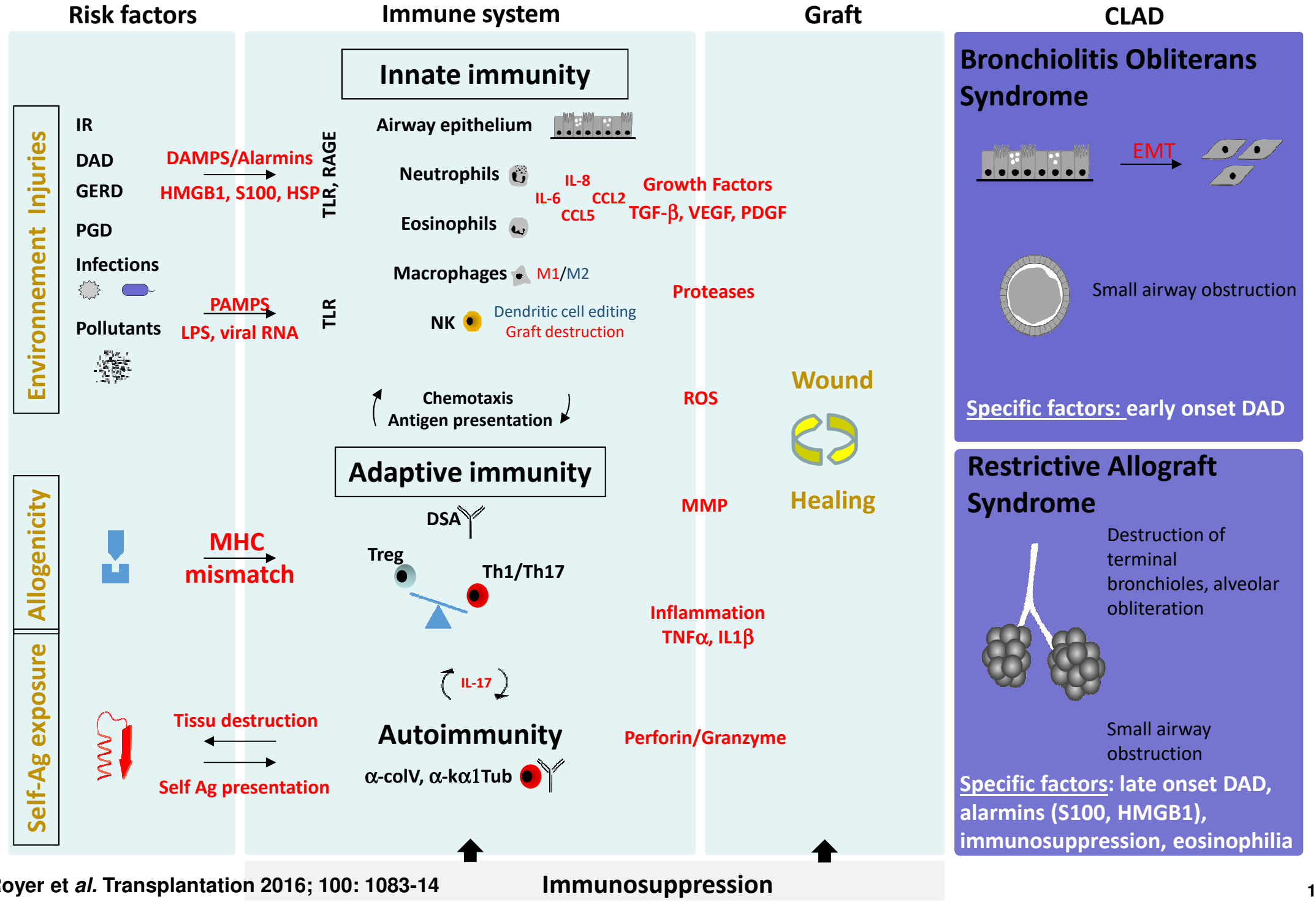
nova discovery
transitioning healthcare

Immunologie, hématologie, pneumologie

Inserm



Roedder *et al.* Genome Medicine 2011;3:37



Royer et *al.* Transplantation 2016; 100: 1083-14

Design, Methods, Objectives

- **COLT French cohort since 09-2009, 11 centres + Bruxelles**
- **Swiss Transplant Cohort Study, STCS since 2008 in Lausanne- Genève, Zurich**

- **I-2018, 1506 transplanted**
  802 reached year-3, or displayed CLAD before year-3, or died before year-3

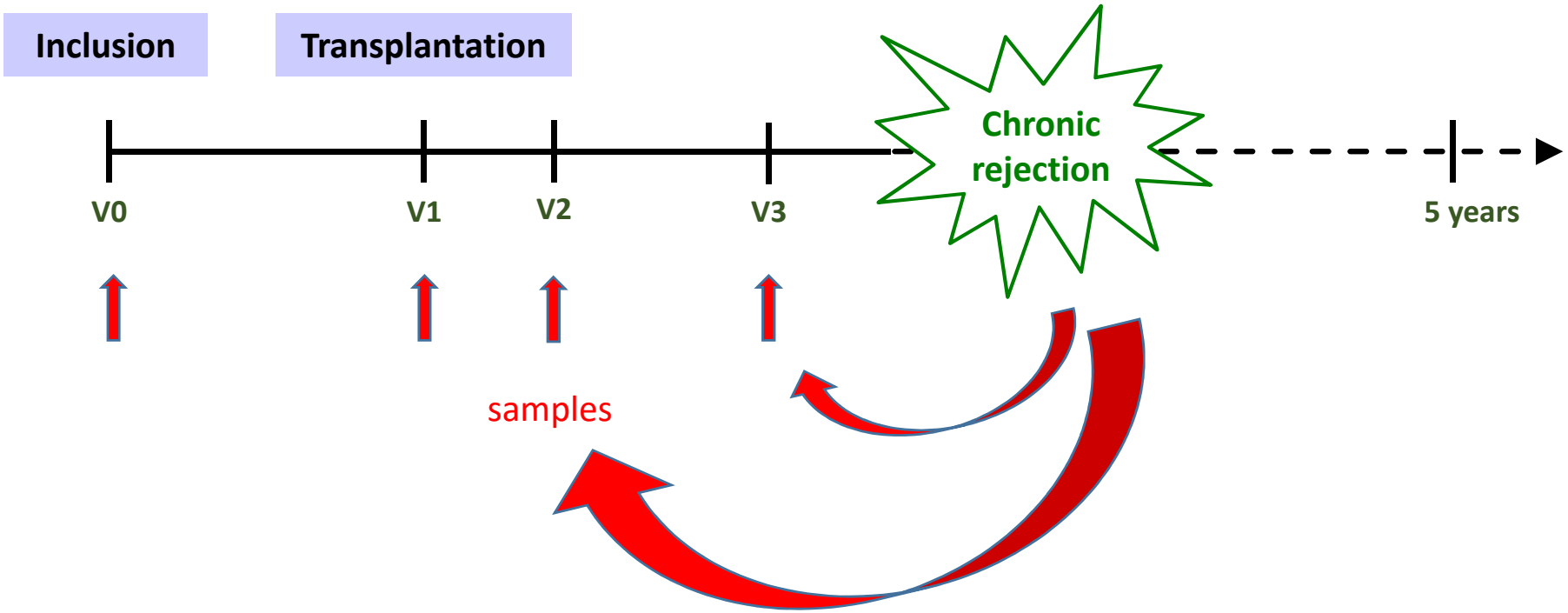
- ***Donors: day 0***
  - **clinics**
  - **HLA**
  - **lung tissue**

- ***Recipients: before Tx, day-0 Tx, M6-M12 post LTx***
  - **Clinics - e.CRF**
  - **Pollution by geolocalization**
  - **Blood: HLA, transcriptomics x 2, proteomics x 2, miRNA x 1, lymphocytes subpopulations, exome sequencing**
  - **BAL: microbiote & macrophages polarization, proteomics x 2**

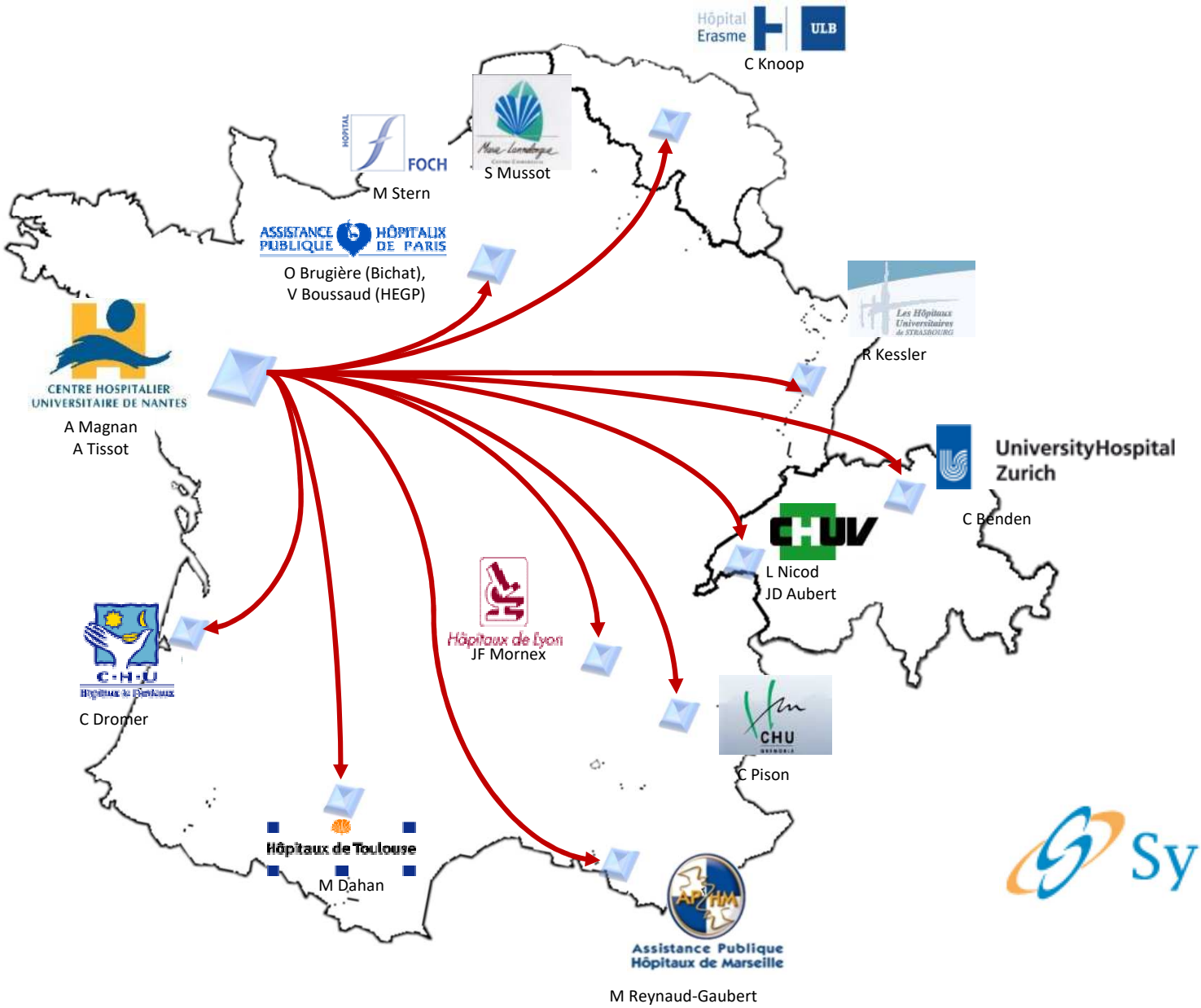
- **<u>Objective: to predict CLAD @ year-3, as soon as year-1</u>**

COLT

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



COLT



SysClad

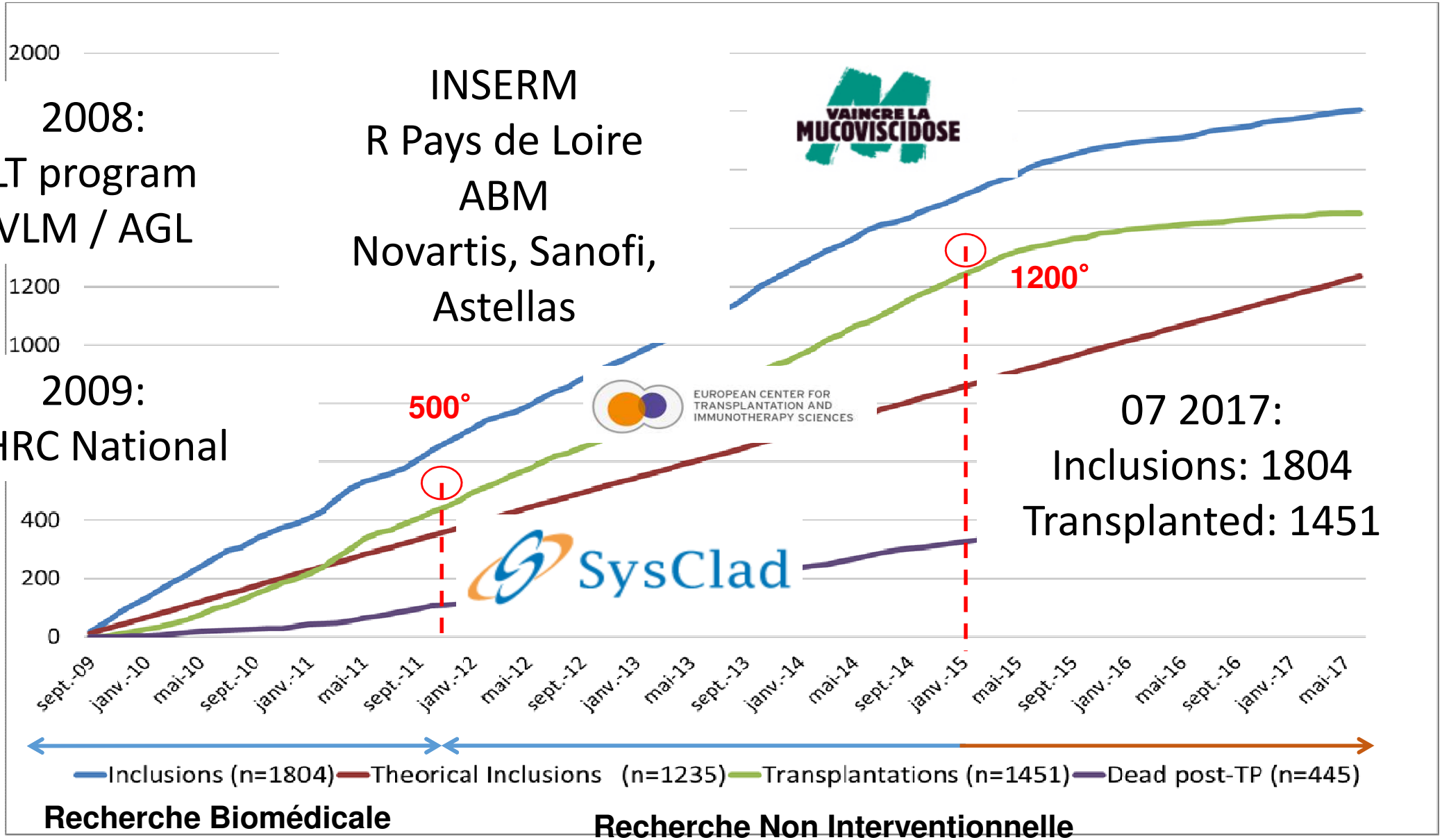
Patients STCS 2008-2014

COLT / SysCLAD Story

2008:
LT program
VLM / AGL

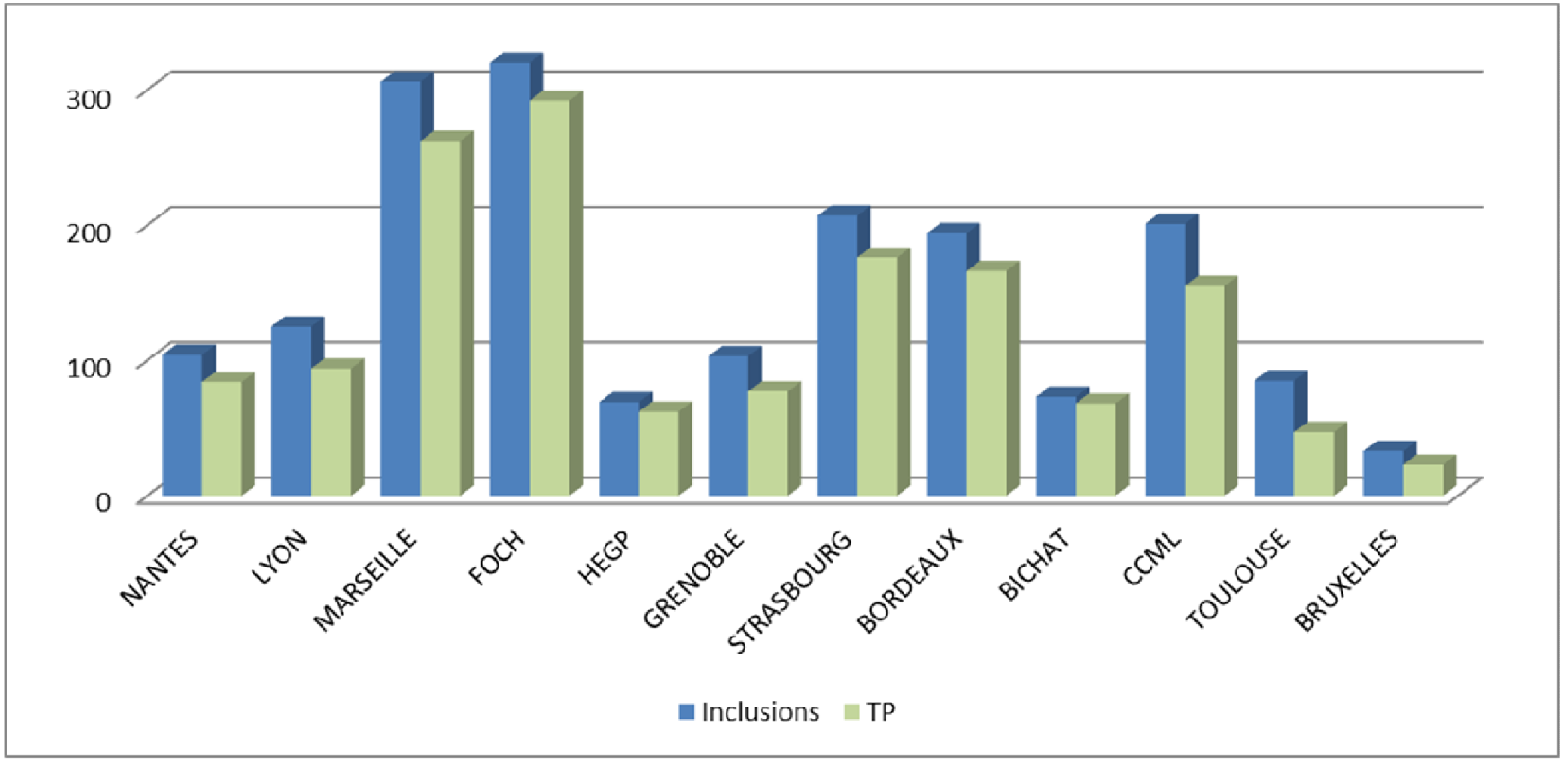
2009:
PHRC National

INSERM
R Pays de Loire
ABM
Novartis, Sanofi,
Astellas

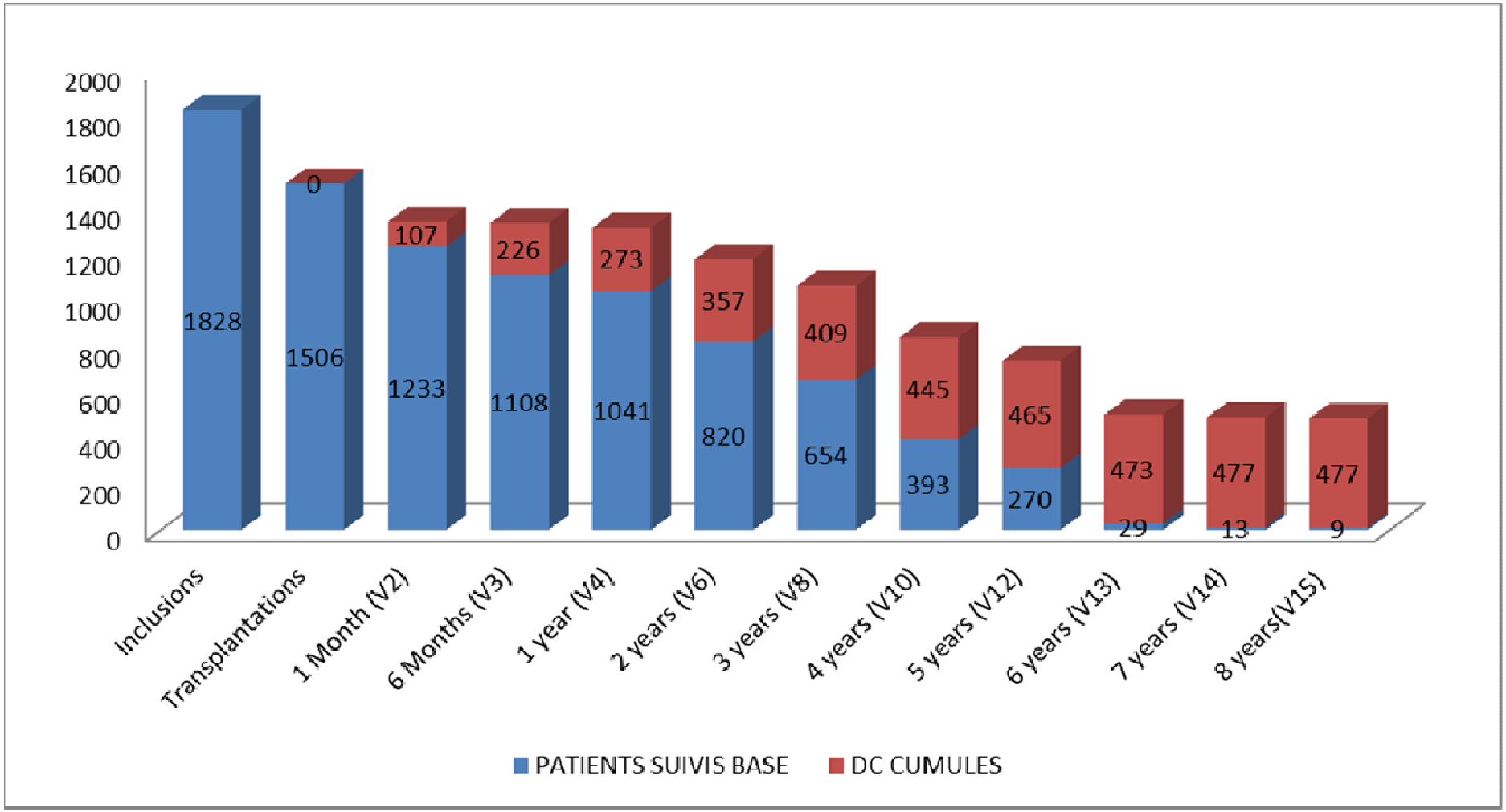


07 2017:
Inclusions: 1804
Transplanted: 1451

Avancement de la cohorte / centre



Cohort progression



- 654 patients with 3 years of follow-up post transplant
- 270 patients with 5 years of follow-up
- 477 patients deceased including 273 <1 year post-transplant

Current Classification of
Chronic Lung Allograft Dysfunction

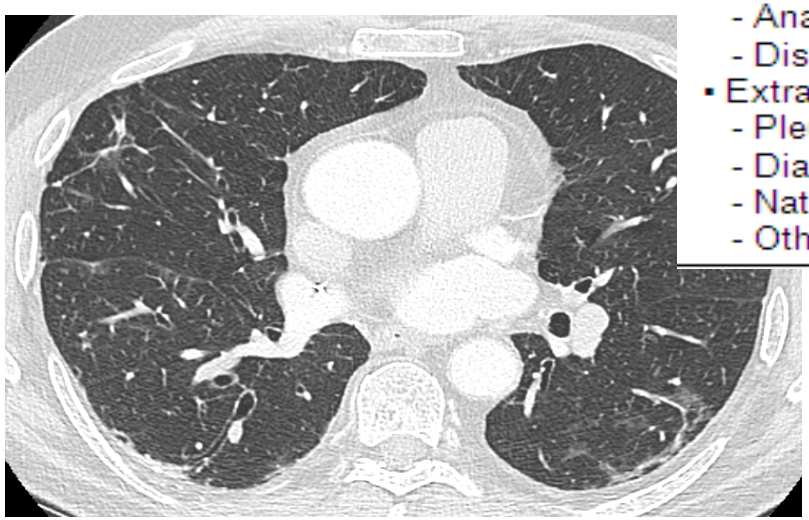
CLAD

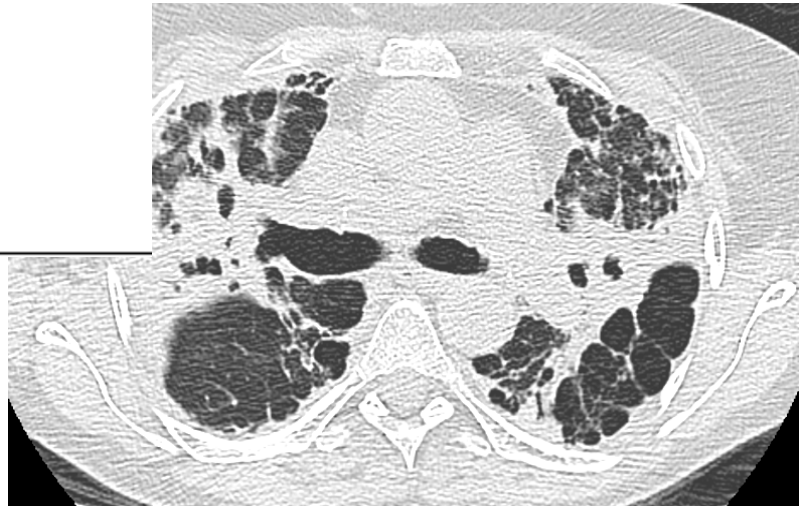
BOS

RAS

Confounding factors

- Allograft
  - Persistent acute rejection
  - ARAD
  - Infection
  - Anastomotic stricture
  - Disease recurrence
- Extra-allograft
  - Pleural disease
  - Diaphragm dysfunction
  - Native lung hyperinflation
  - Other

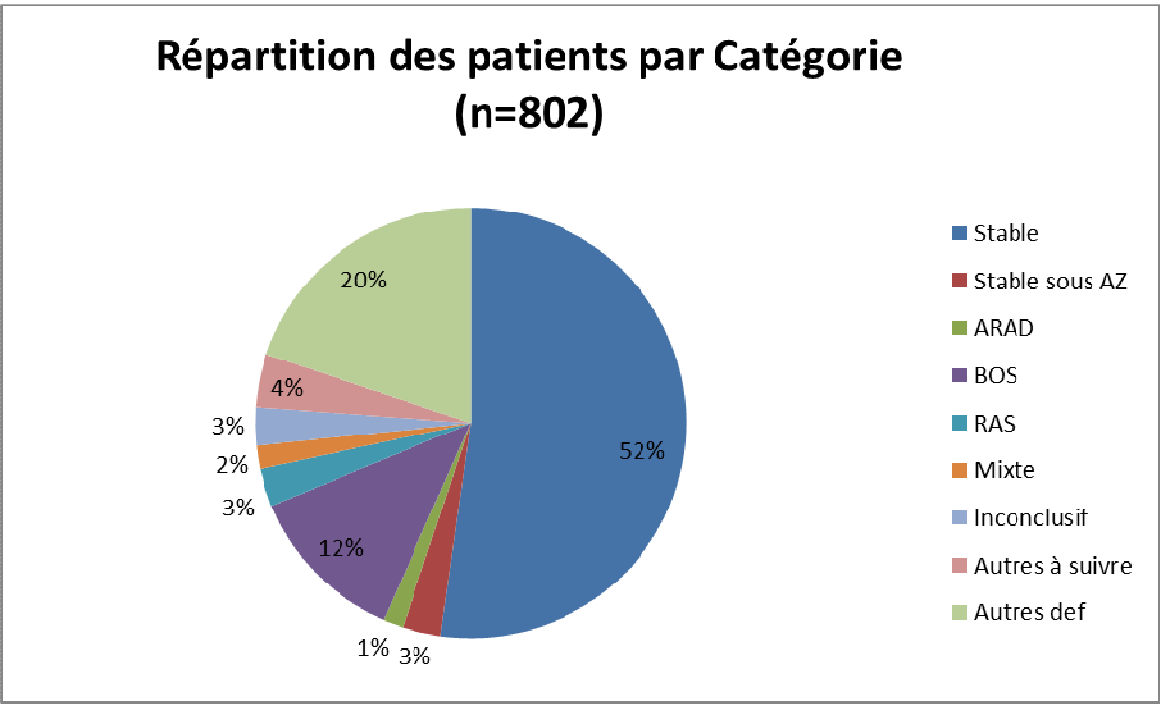


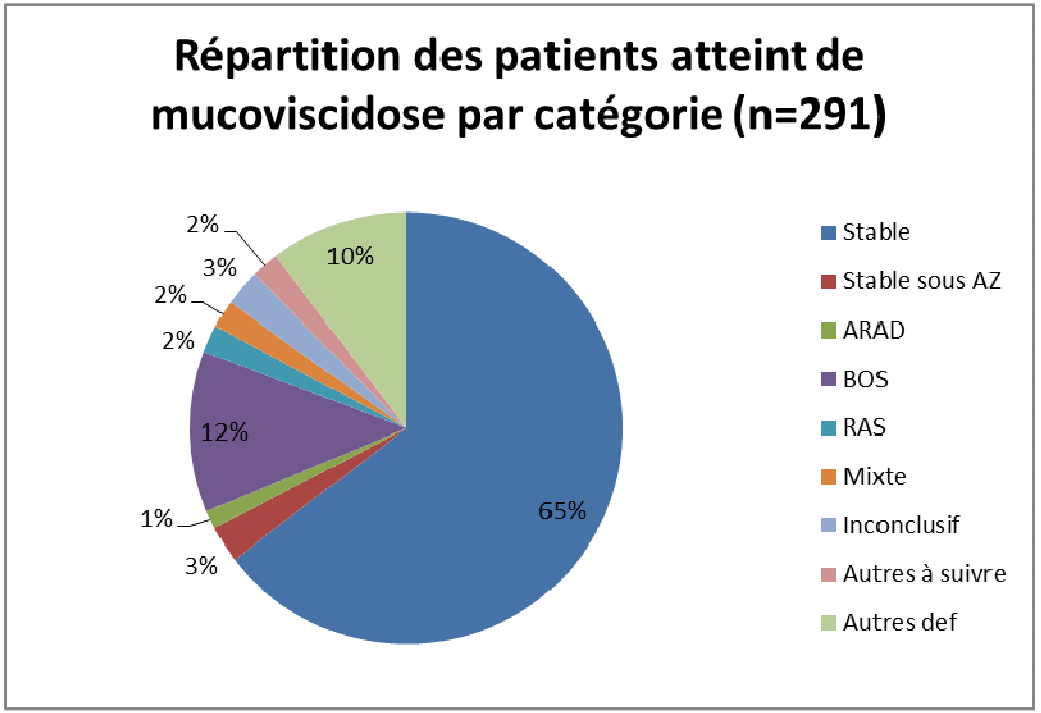


12 adjudication meetings with 7 experts

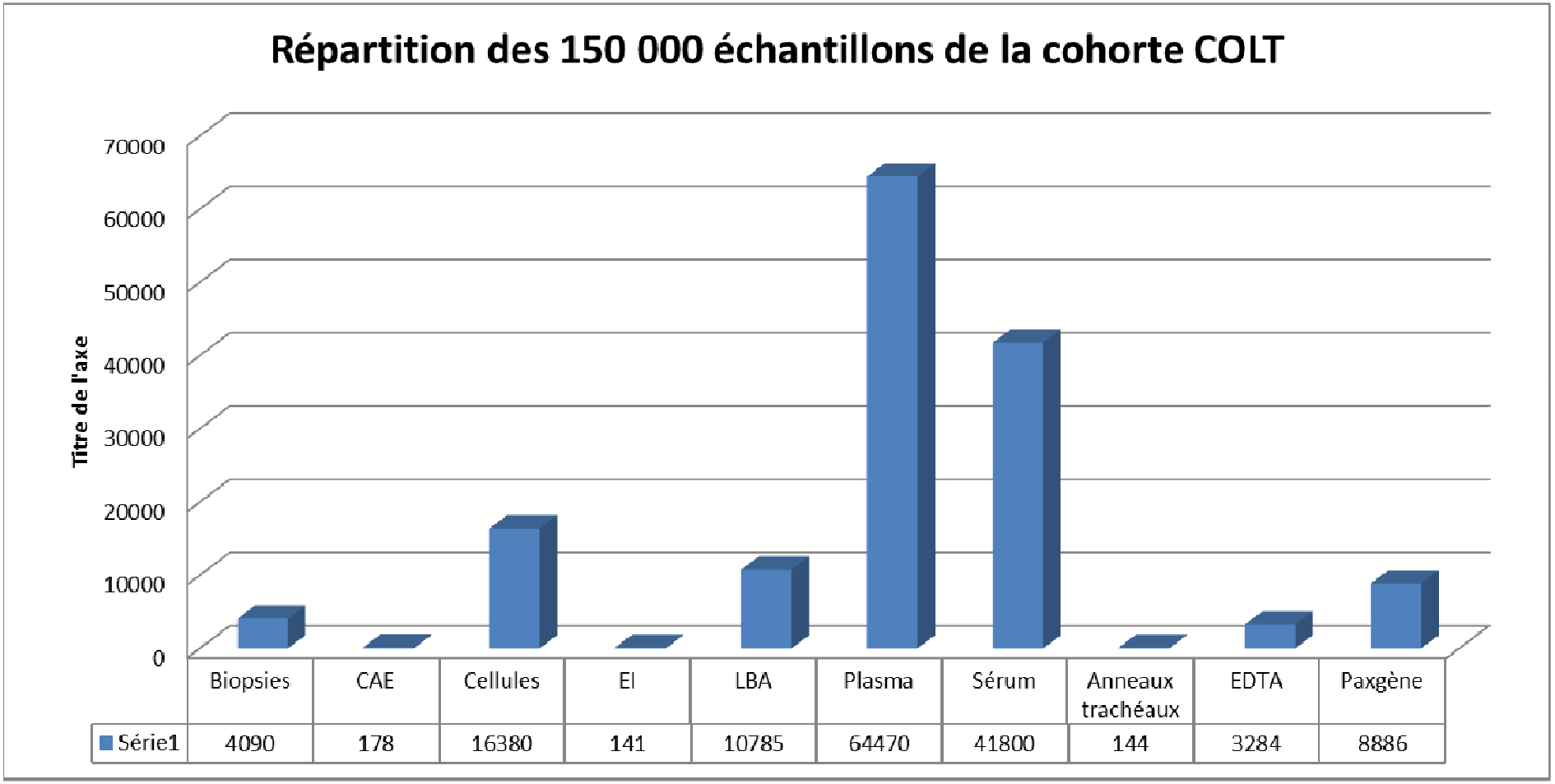
Dysfonction Chronique du Greffon

Classification of adjudicated patients after 3 years post transplant





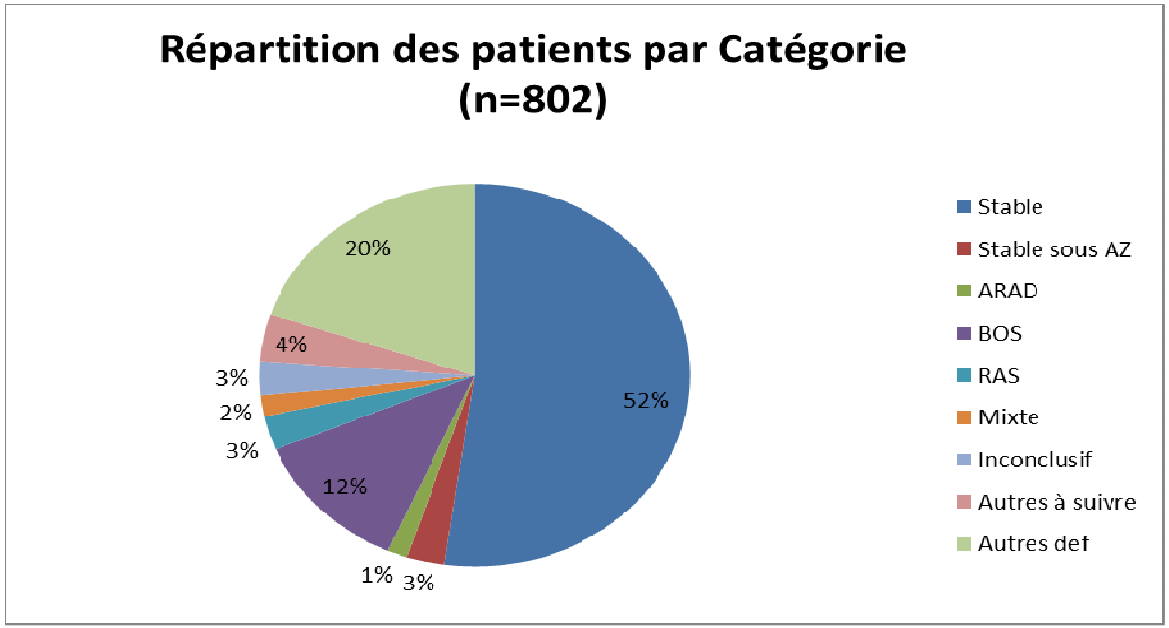
Biocollection

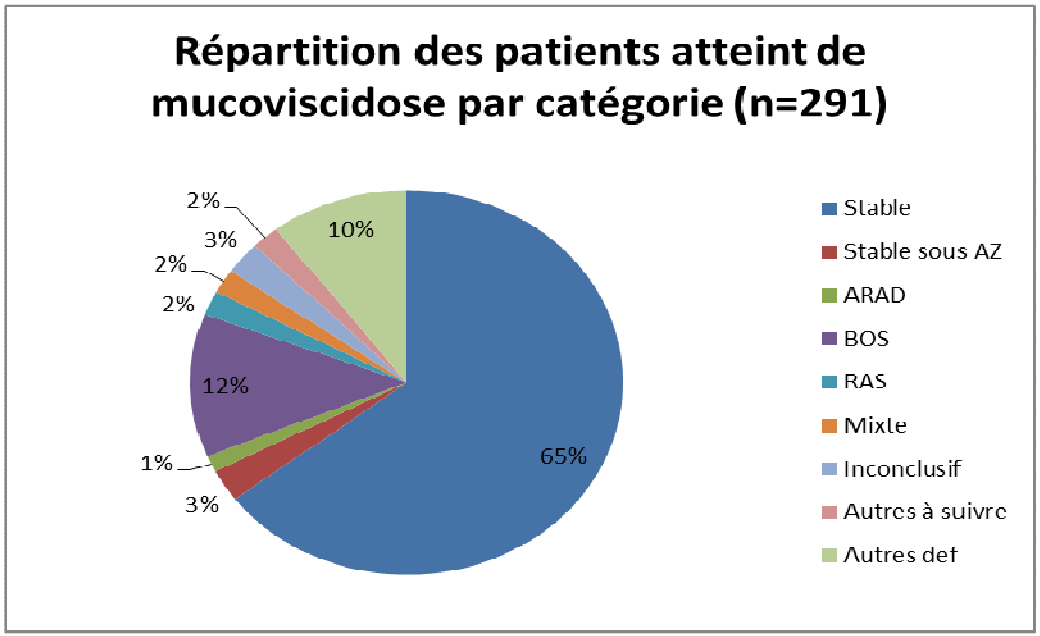


- Number of samples: 150 000
- > 90 % in Nantes « CRB » (certified since 24th July 2014, NF S96-900 de l'Afnor

Dysfonction Chronique du Greffon

Classification of adjudicated patients after 3 years post transplant

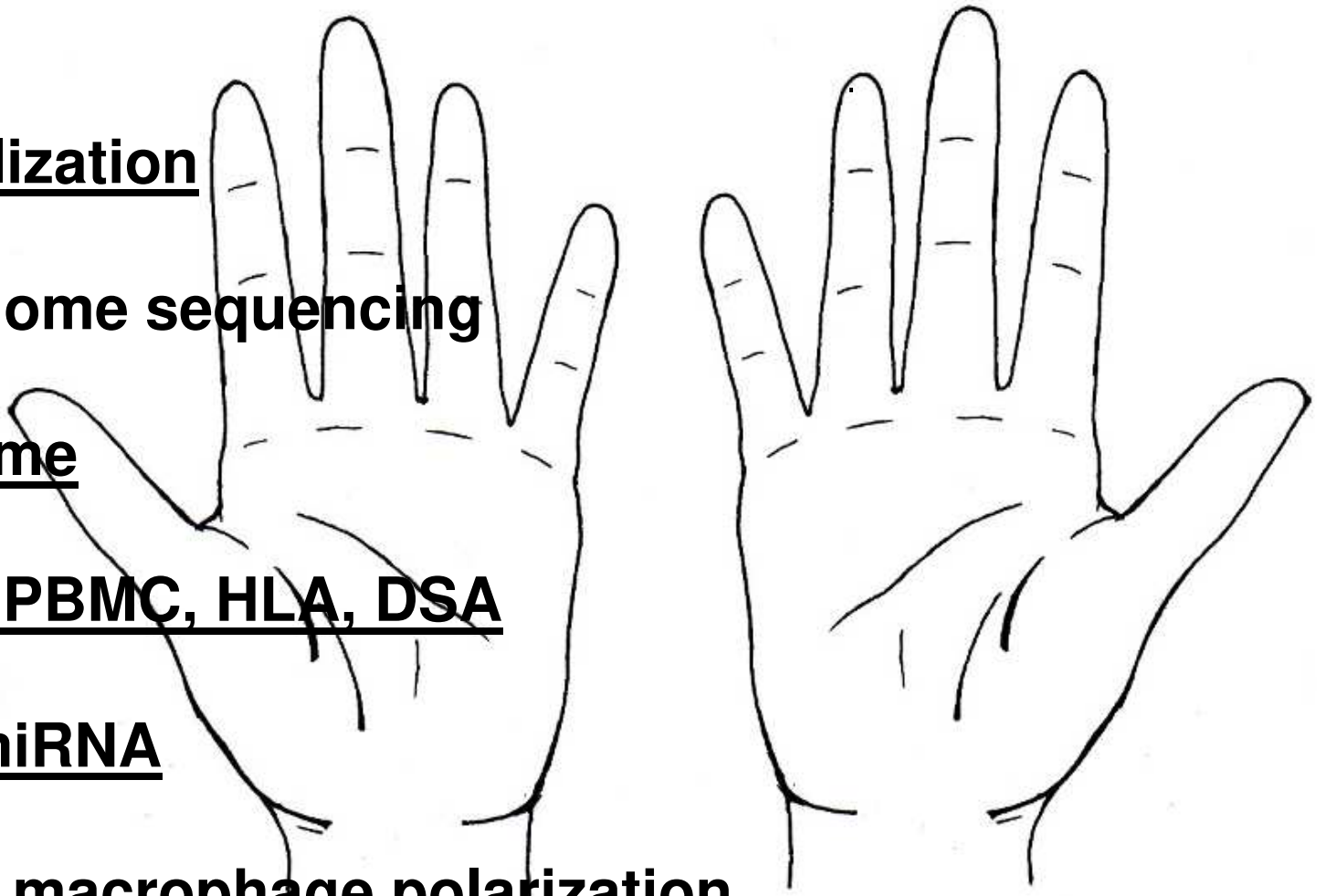




- **Nov 2017: 1st adjudications at 5 years: 250 patients « stable » at 3 years**

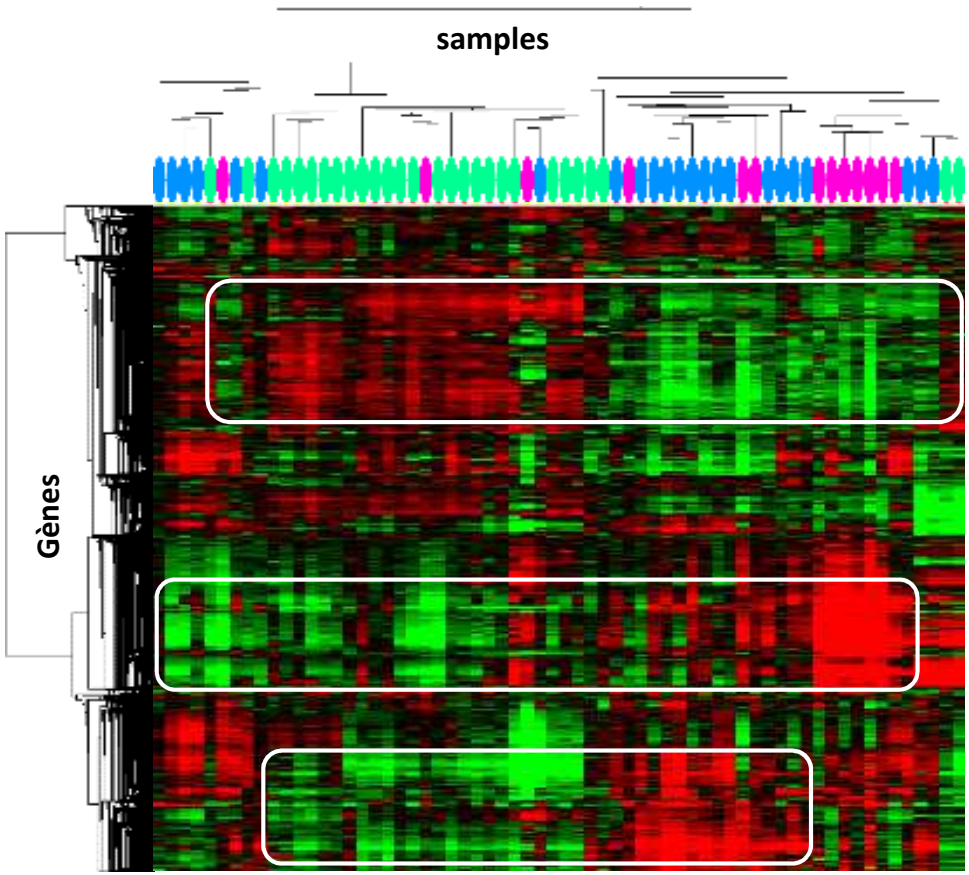
Fingers & Hand prints to predict CLAD

1. Clinicome 1st year
2. Pollution by geolocalization
3. Recipient exome genome sequencing
4. BAL / Plasma proteome
5. Immuno-monitoring, PBMC, HLA, DSA
6. Transcriptome and miRNA
7. Lung microbiote and macrophage polarization



Complex biomarkers: transcriptome in patients waiting for lung transplant

Hierarchical cluster



Helthy volunteers (HV)
Cystic fibrosis
Pulmonary Hypertension

Signature of respiratory failure

Signature **PAH**

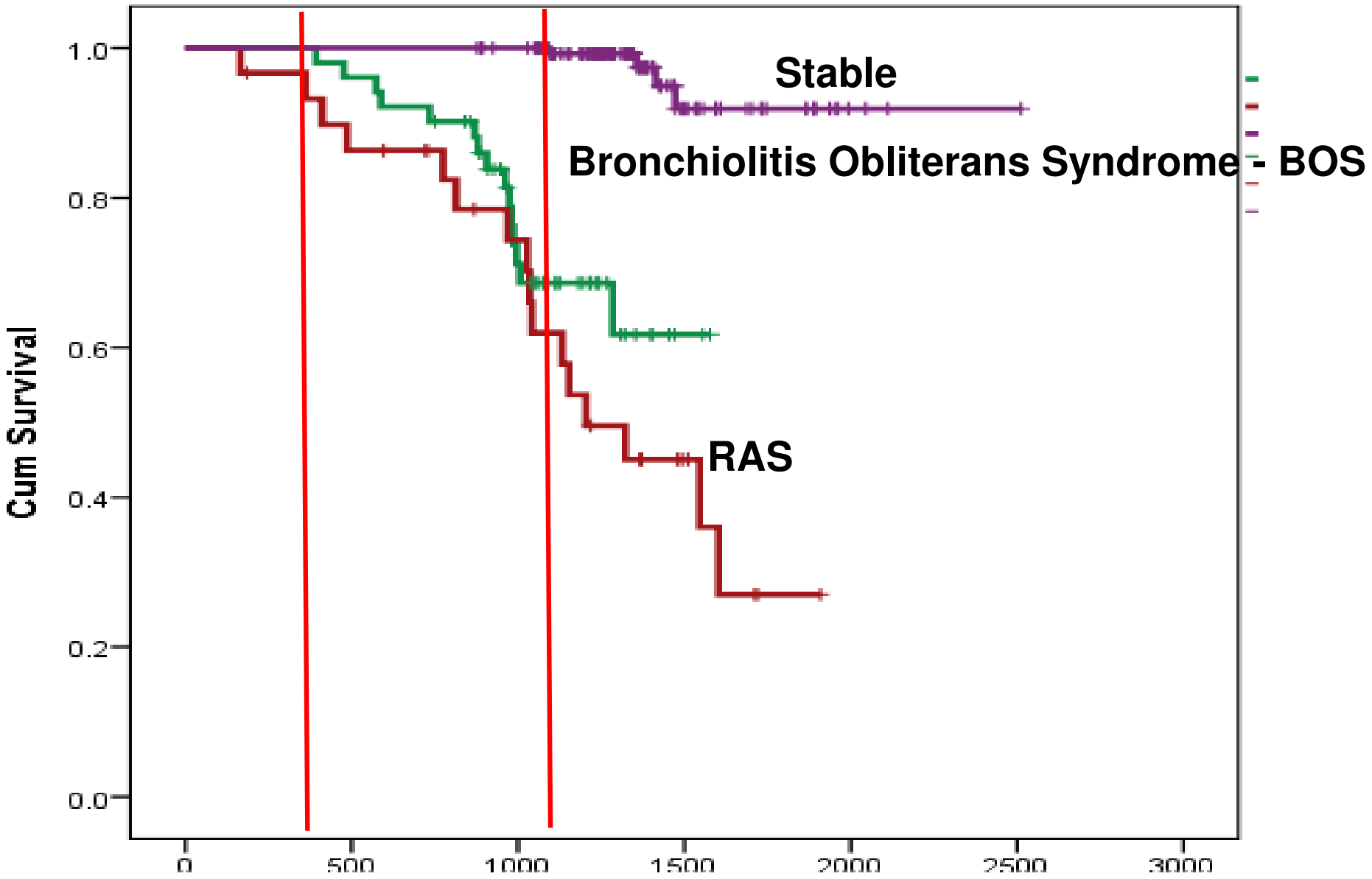
Signature **Cystic Fibrosis**

Over expressed genes

Under expressed genes

J Chesné, Plos One 2014

Clinicome, outcomes at year-3



Koutsokera *et al.* 2016, *in revision*

Clinicome, prediction at 3 years

frontiers in Medicine

ORIGINAL RESEARCH
published: 17 July 2017
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Check for updates

Development of a Multivariate Prediction Model for Early-Onset Bronchiolitis Obliterans Syndrome and Restrictive Allograft Syndrome in Lung Transplantation

OPEN ACCESS

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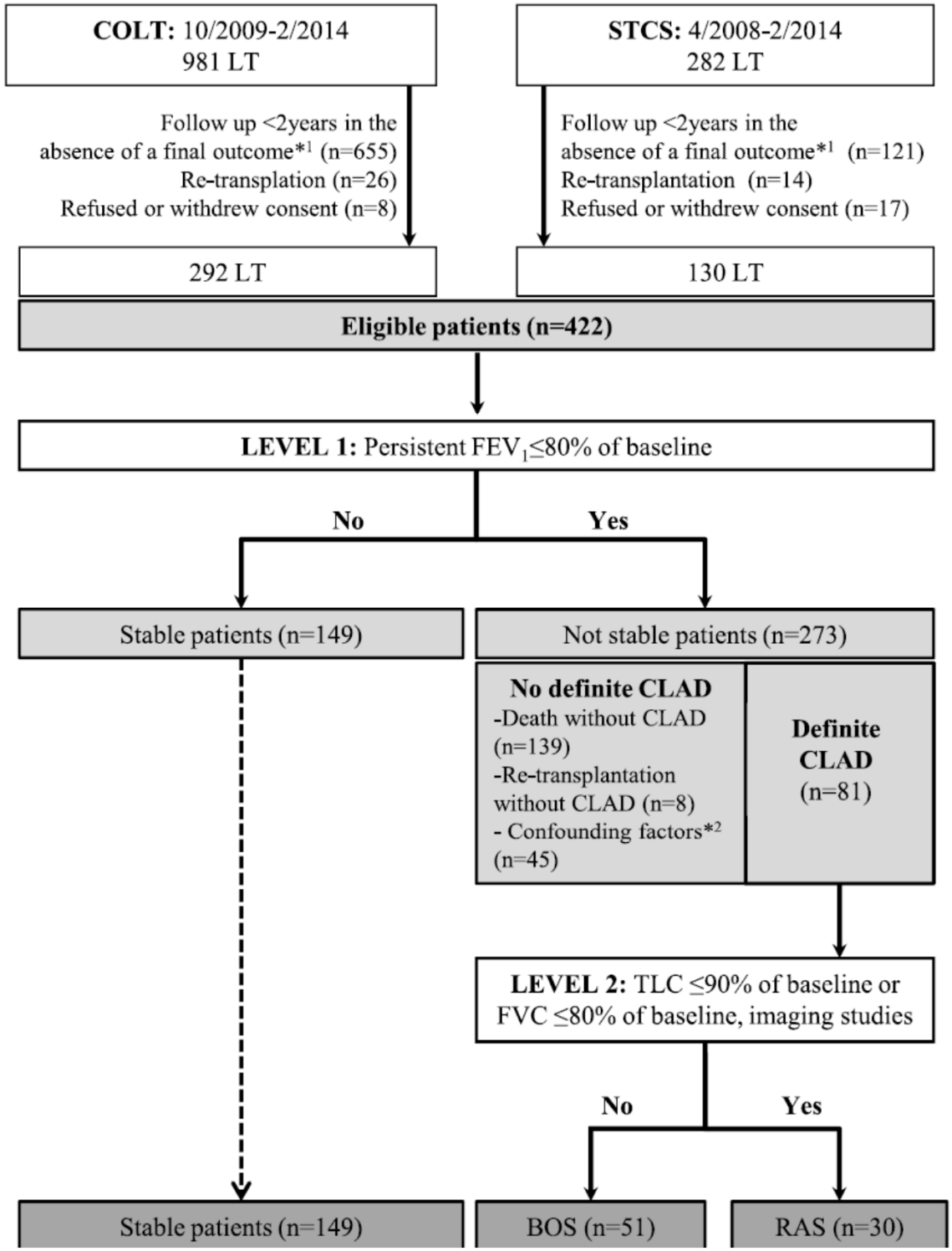

COLT: 10/2009-2/2014
981 LT
STCS: 4/2008-2/2014
282 LT
Follow up <2years in the absence of a final outcome*1 (n=655)
Re-transplation (n=26)
Refused or withdrew consent (n=8)
Follow up <2years in the absence of a final outcome*1 (n=121)
Re-transplantation (n=14)
Refused or withdrew consent (n=17)
292 LT
130 LT
Eligible patients (n=422)
LEVEL 1: Persistent FEV1≤80% of baseline
No
Yes
Stable patients (n=149)
Not stable patients (n=273)
No definite CLAD
-Death without CLAD (n=139)
-Re-transplantation without CLAD (n=8)
- Confounding factors*2 (n=45)
Definite CLAD (n=81)
LEVEL 2: TLC ≤90% of baseline or FVC ≤80% of baseline, imaging studies
No
Yes
Stable patients (n=149)
BOS (n=51)
RAS (n=30)

Clinicome, prediction at 3 years

TABLE 2 | Risk factors for the development of CLAD (multivariate analysis adjusted for center effect) by 3 years post-LT.

Variable		Univariate analysis		Multivariate analysis	
		OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Recipient age		1.002 (0.998, 1.006)	0.2288	0.971 (0.938, 1.006)	0.102
Donor age		1.002 (0.998, 1.006)	0.3172		
Difference of R/D age		1.000 (0.997, 1.004)	0.9041		
Recipient smoking	Yes	1.128 (0.996, 1.277)	0.0598		
Recipient BMI		1.012 (0.998, 1.025)	0.0924		
Underlying diagnosis	CF	Baseline		Baseline	
	COPD	1.167 (1.002, 1.361)	**0.049**	5.158 (1.444, 18.426)	**0.012**
	ILD/IPF	1.345 (1.133, 1.596)	**<0.001**	9.429 (2.291, 38.807)	**0.002**
	Others	1.109 (0.928, 1.326)	0.2573	2.435 (0.783, 7.569)	0.124
Sum of HLA mismatches		1.011 (0.948, 1.077)	0.7396		
Max cold ischemia time		1.000 (0.999, 1.001)	0.6245		
Induction treatment	Basiliximab	Baseline		Baseline	
	None	1.134 (0.981, 1.310)	0.0914	1.382 (0.451, 4.236)	0.572
	rATG	1.261 (1.084, 1.467)	**0.0029**	3.519 (0.946, 13.085)	0.060
PGD stage 3	Yes	0.928 (0.646, 1.333)	0.6853		
Immunosuppression	Cyclosporin	Baseline			
	Tacrolimus	0.914 (0.805, 1.037)	0.1635		
Y1 t-AR		1.003 (0.938, 1.072)	0.9392		
Y1 t-infections		1.003 (0.970, 1.036)	0.8784		
Y1 t-CMV		1.019 (0.899, 1.155)	0.764		
DSA before LT	Yes	1.240 (1.056, 1.455)	**0.0092**		
Y1 DSAs (I or II)	Yes	1.316 (1.135, 1.526)	**0.0004**		
Y1 DSAs I	Yes	1.240 (1.014, 1.515)	**0.0370**		
Y1 DSAs II	Yes	1.357 (1.162, 1.585)	**0.0001**	4.221 (1.784, 9.991)	**0.001**

Clinicome, prediction at 3 years

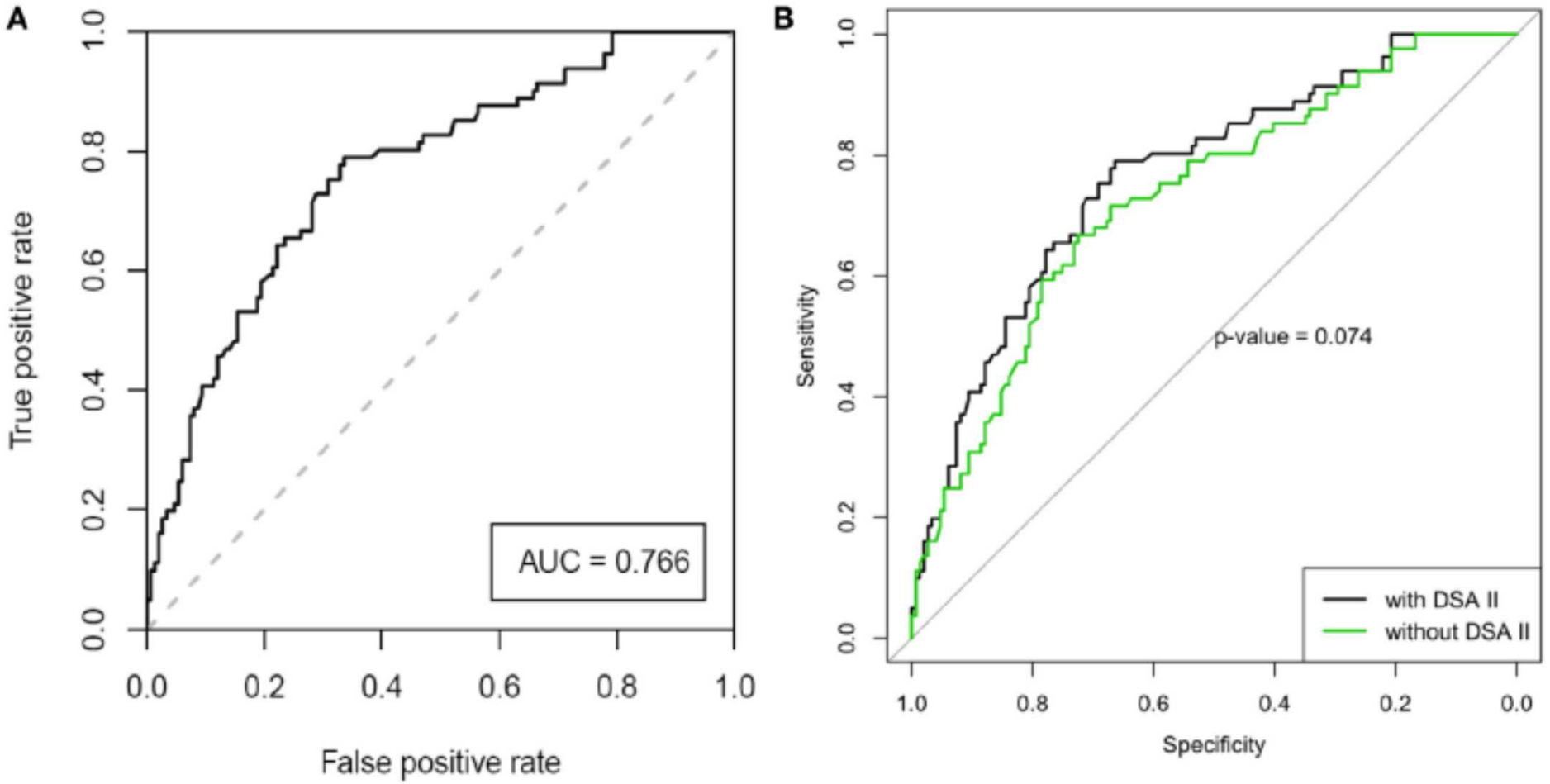
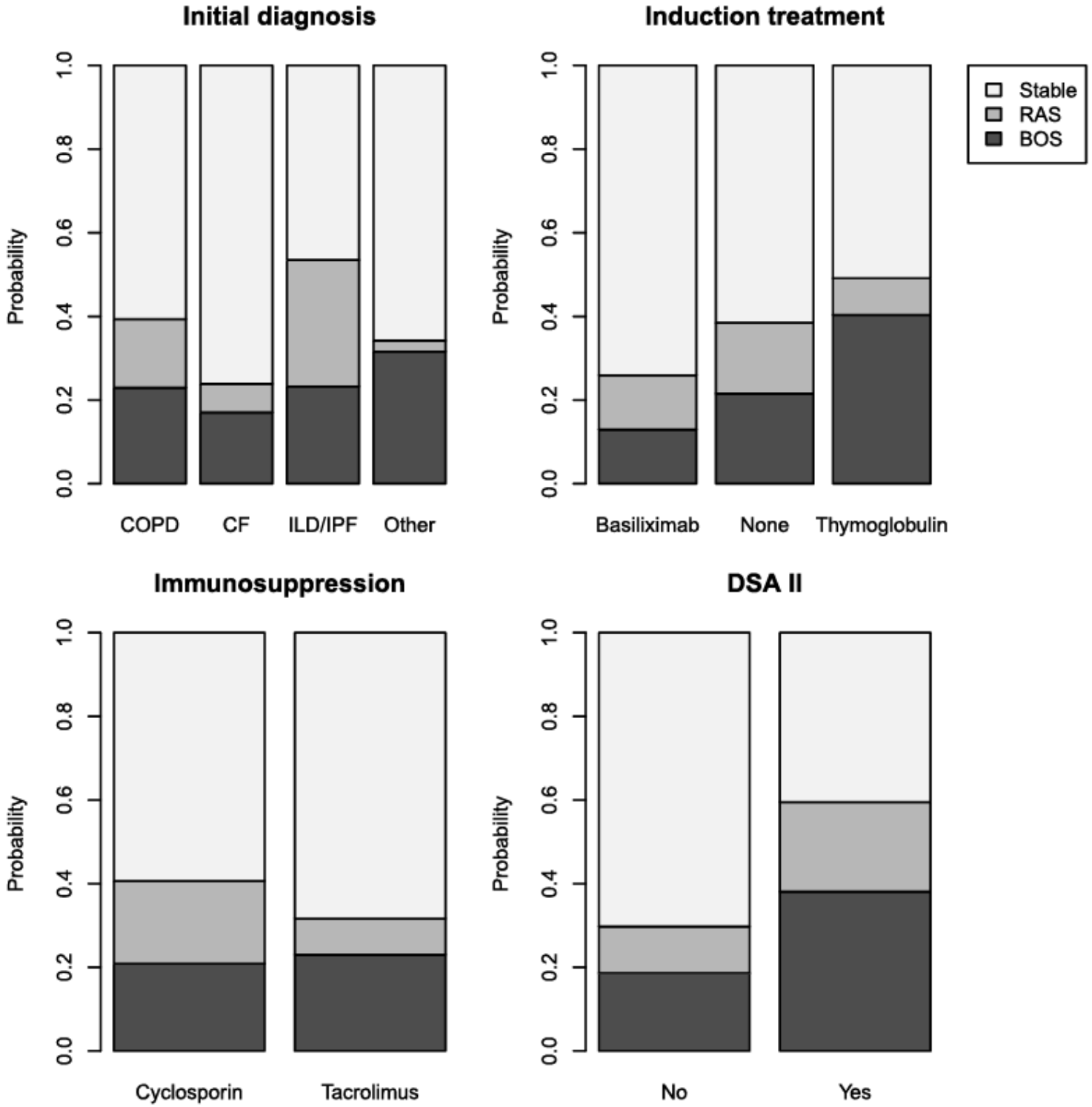


FIGURE 2 | **(A)** Receiver operating characteristic (ROC) analysis of the best performing model for the prediction of early-onset chronic lung allograft dysfunction after adjusting for center effect [area under the curve (AUC) = 0.766, SE = 0.0325, 95% CI 0.703–0.830]. **(B)** ROC curve of the model, with and without the parameter of "Y1 class II DSA" (AUC 0.766 vs. 0.730, respectively, $p = 0.074$).

Clinicome, prediction at 3 years

TABLE 4 | Risk factors for BOS and RAS by 3 years post-LT as compared to stable recipients (multivariate multinomial analysis).

Variable		BOS		RAS	
		OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Underlying diagnosis	CF	Baseline		Baseline	
	COPD	1.606 (0.559, 4.610)	0.379	3.857 (1.041, 14.289)	**0.043**
	ILD/IPF	2.436 (0.738, 8.036)	0.144	5.467 (1.482, 20.170)	**0.011**
	Other	2.589 (0.848, 7.905)	0.095	0.230 (0.022, 2.398)	0.219
Immunosuppression	Cyclosporin	Baseline		Baseline	
	Tacrolimus	3.179 (0.704, 14.357)	0.133	0.670 (0.080, 5.590)	0.711
Induction treatment	Basiliximab	Baseline		Baseline	
	None	0.541 (0.117, 2.505)	0.432	4.528 (0.888, 23.076)	0.069
	rATG	3.101 (0.681, 14.123)	0.144	2.393 (0.307, 18.674)	0.405
Y1 DSAs II	Yes	3.827 (1.459, 10.040)	**0.006**	6.965 (1.839, 26.376)	**0.004**


Initial diagnosis
Probability
0.0
0.2
0.4
0.6
0.8
1.0
COPD
CF
ILD/IPF
Other
Induction treatment
Probability
0.0
0.2
0.4
0.6
0.8
1.0
Basiliximab
None
Thymoglobulin
Stable
RAS
BOS
Immunosuppression
Probability
0.0
0.2
0.4
0.6
0.8
1.0
Cyclosporin
Tacrolimus
DSA II
Probability
0.0
0.2
0.4
0.6
0.8
1.0
No
Yes

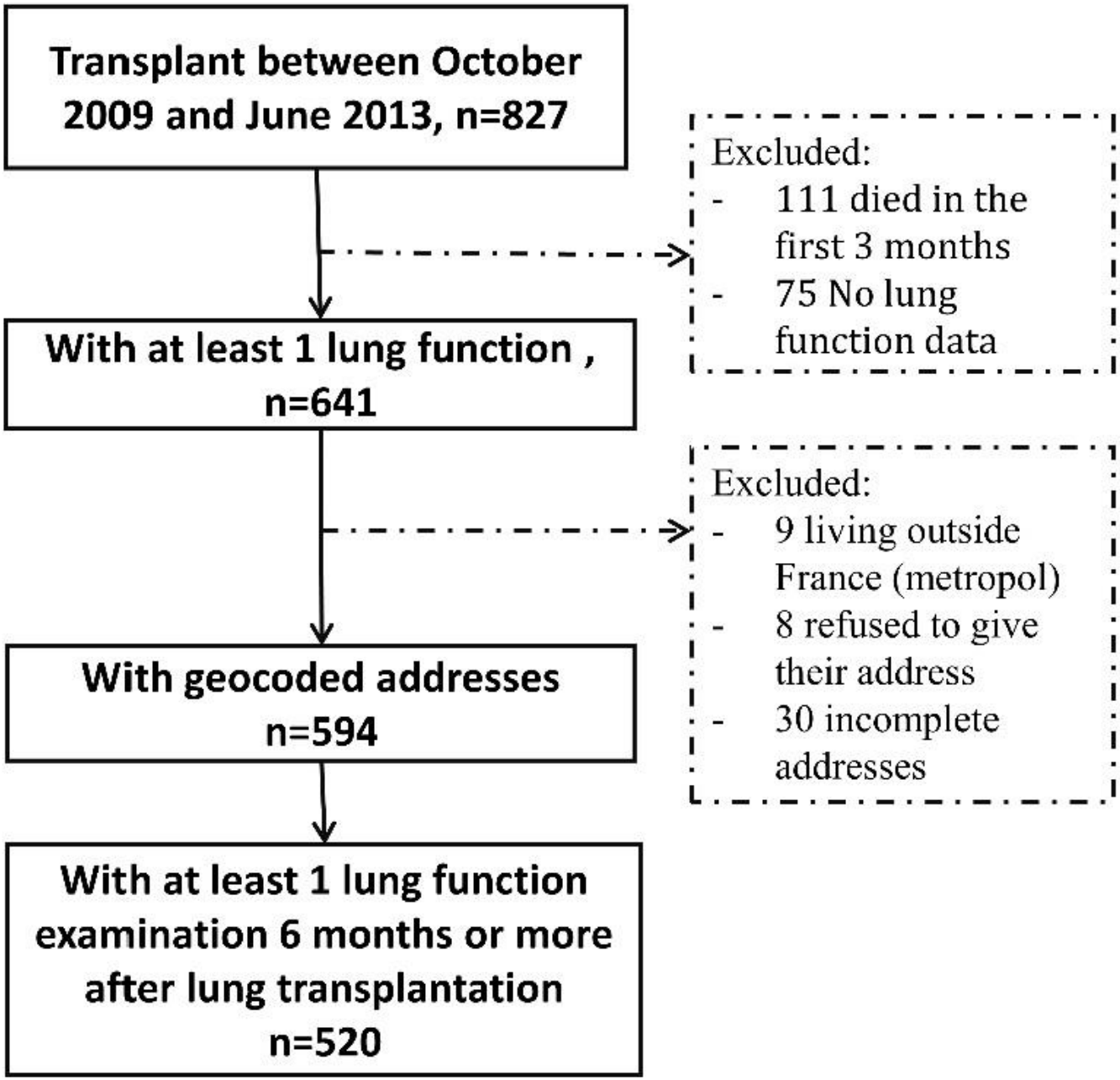
Chronic Effects of Air Pollution

Chronic effects of air pollution on lung function after lung transplantation in the Systems prediction of Chronic Lung Allograft Dysfunction (SysCLAD) study

Meriem Benmerad[1,2,3], Rémy Slama[1,2,3], Karine Botturi[4], Johanna Claustre[5,6], Antoine Roux[7], Edouard Sage[7], Martine Reynaud-Gaubert[8], Carine Gomez[8], Romain Kessler[9], Olivier Brugière[10], Jean-François Mornex[11], Sacha Mussot[12], Marcel Dahan[13], Véronique Boussaud[14], Isabelle Danner-Boucher[15], Claire Dromer[16], Christiane Knoop[17], Annick Auffray[18], Johanna Lepeule[1,2,3], Laure Malherbe[19], Frederik Meleux[19], Laurent Nicod[20], Antoine Magnan[4], Christophe Pison[5,6] and Valérie Siroux[1,2,3] on behalf of the SysCLAD consortium[21]

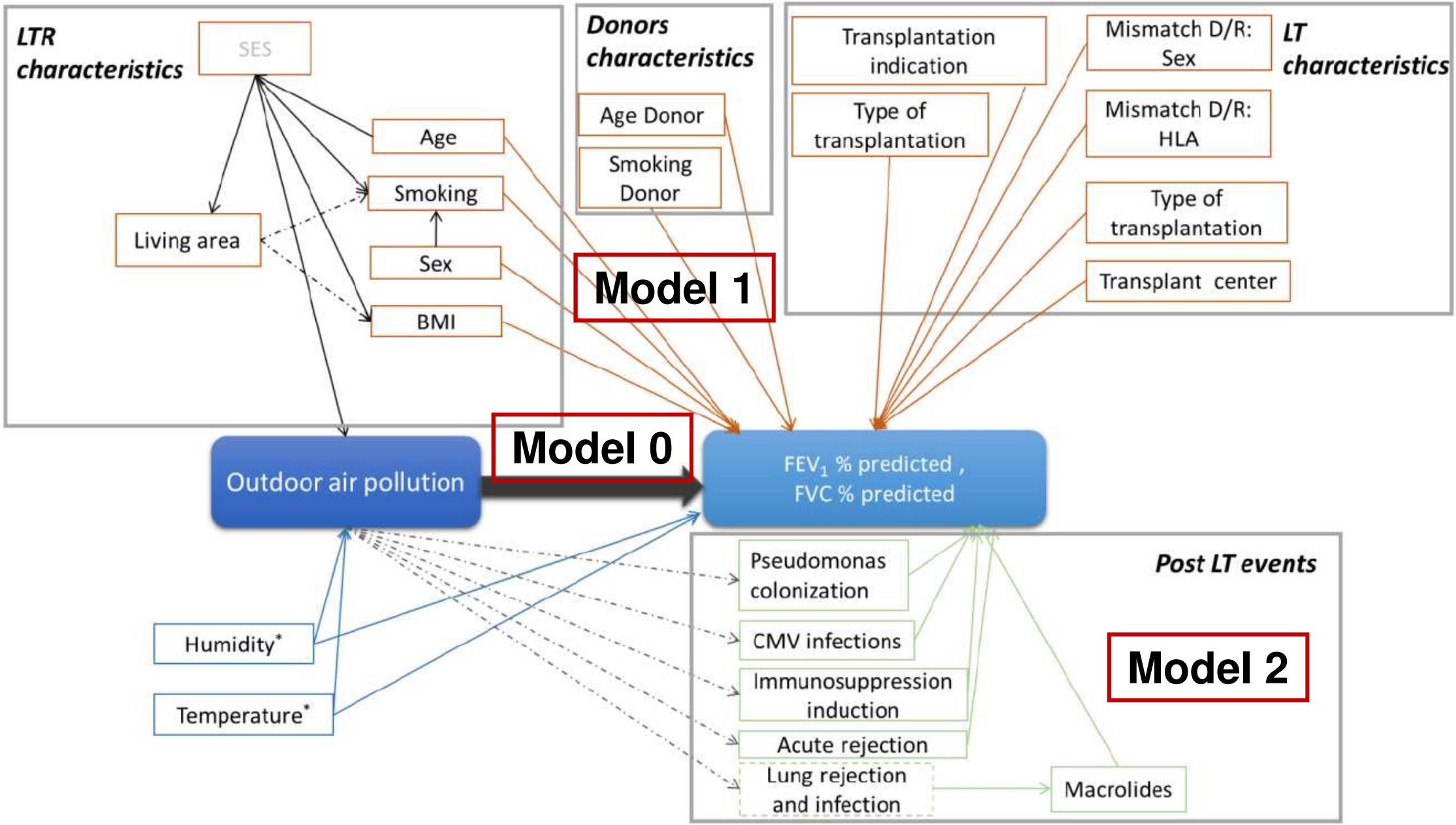
Benmerad *et al. ERJ* 2017; 49: 1-12

Chronic Effects of Air Pollution



Benmerad *et al. ERJ* 2017; 49: 1-12

Chronic Effects of Air Pollution



Benmerad *et al. ERJ* 2017; 49: 1-12

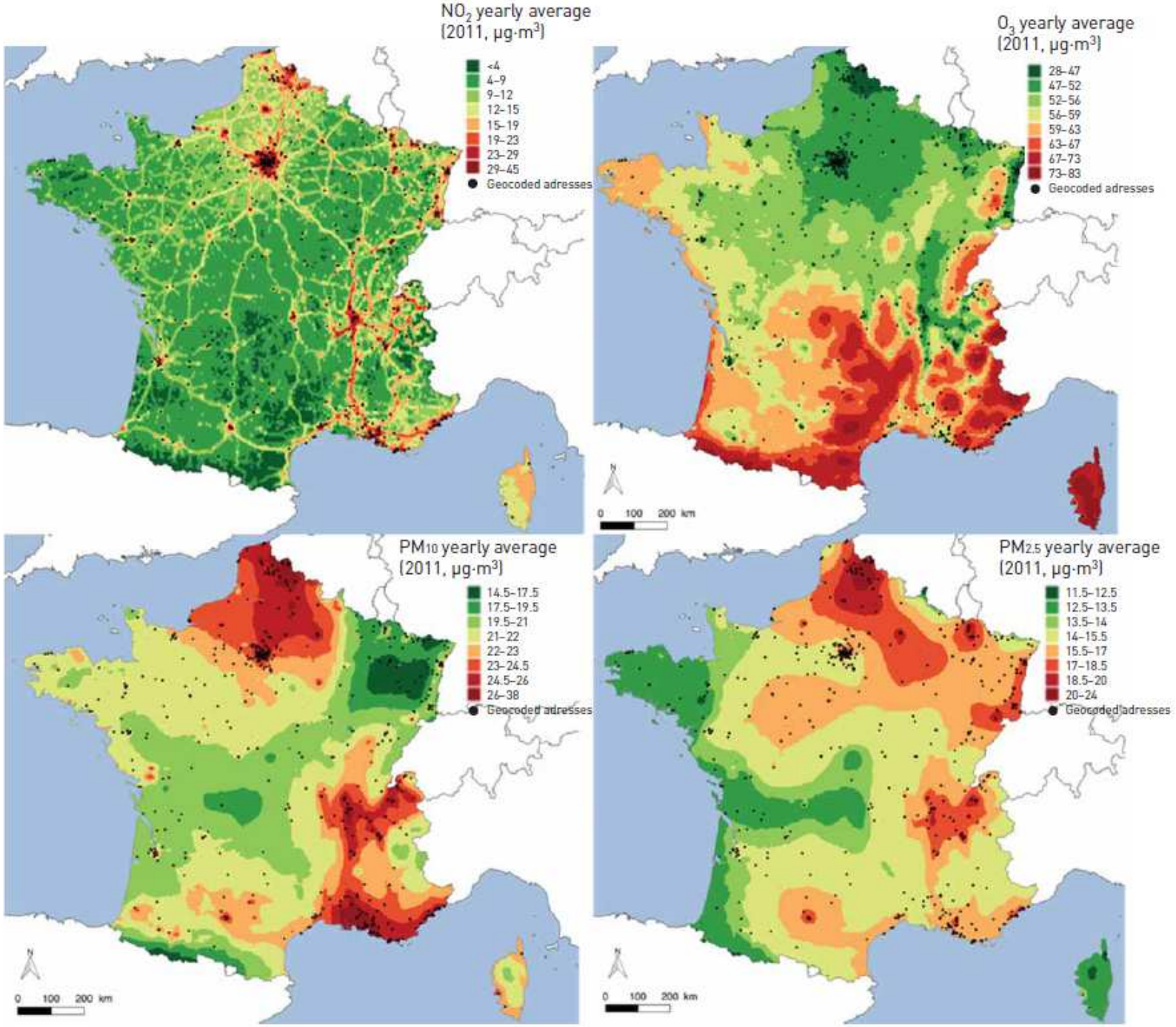


FIGURE 2 Averaged 12-month concentration of particulate matter with an aerodynamic cut-off of 2.5 µm ($PM_{2.5}$) and 10 µm (PM_{10}), NO_2 and O_3 across France in 2011.

Chronic Effects of Air Pollution

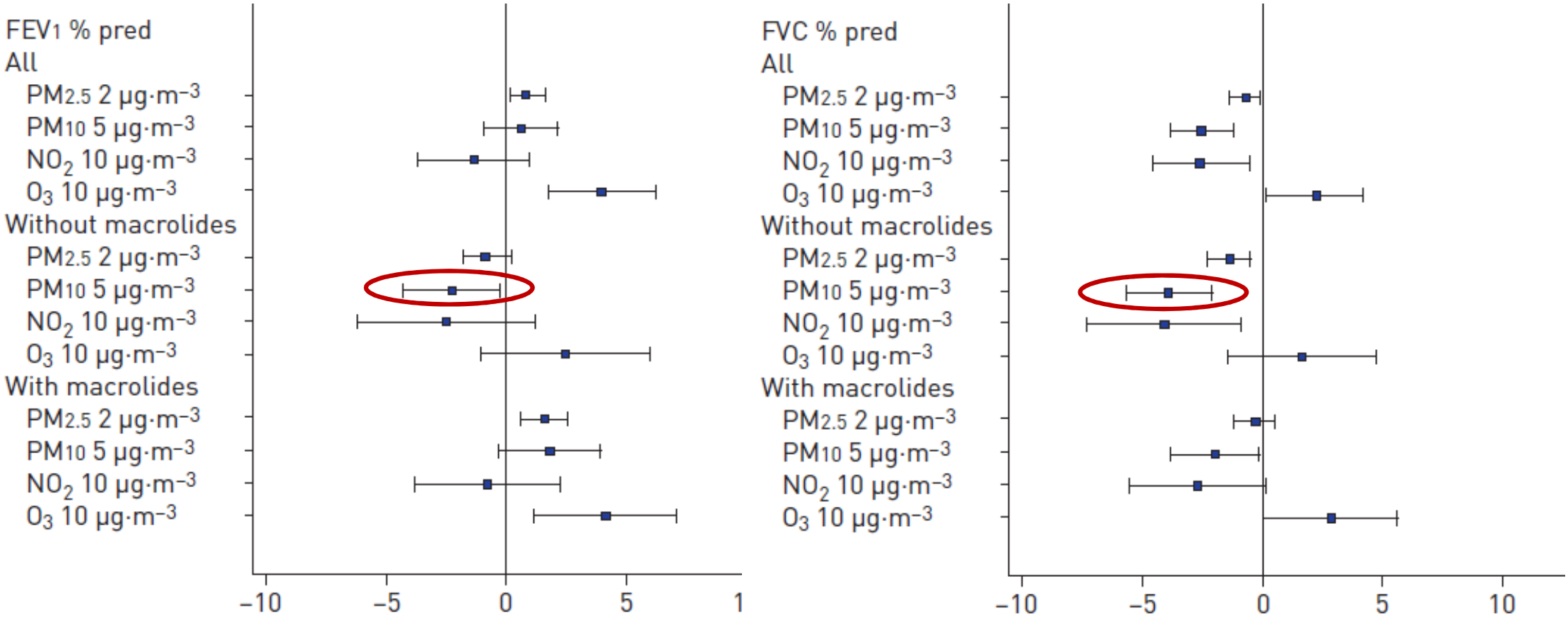
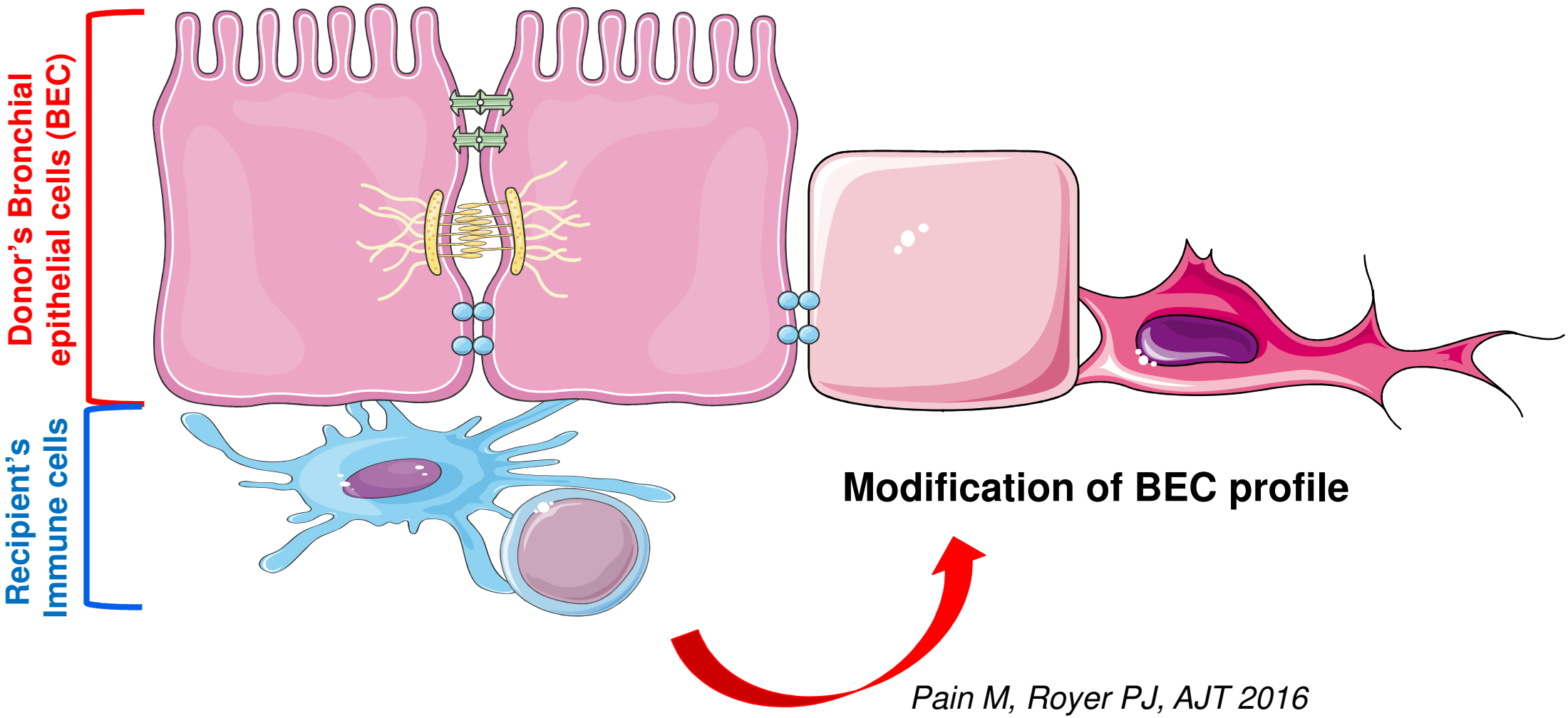


FIGURE 3 Adjusted associations between air pollutants exposure and level of (a) FEV_1 % predicted and (b) FVC % predicted in the whole population and according to the use of macrolides. PM_x: particulate matter with an aerodynamic cross section of x µm.

Benmerad *et al. ERJ* 2017; 49: 1-12

MMP9 Story

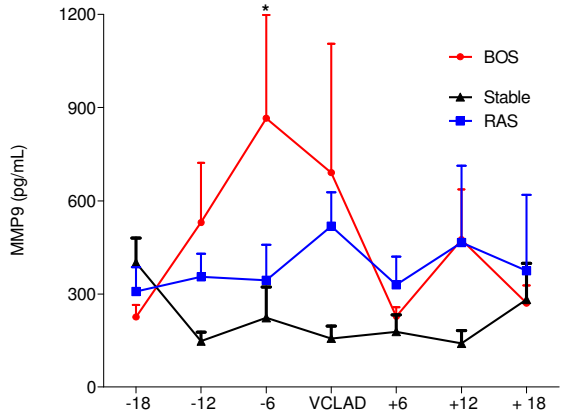
Airway epithelial cells exposed to allogeneic T cells produce MMP9 through a CCL2/CCR2 pathway: implications for chronic lung allograft dysfunction.



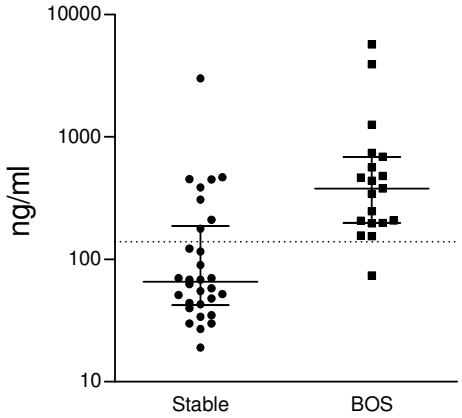
Pain M, Royer PJ, AJT 2016

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

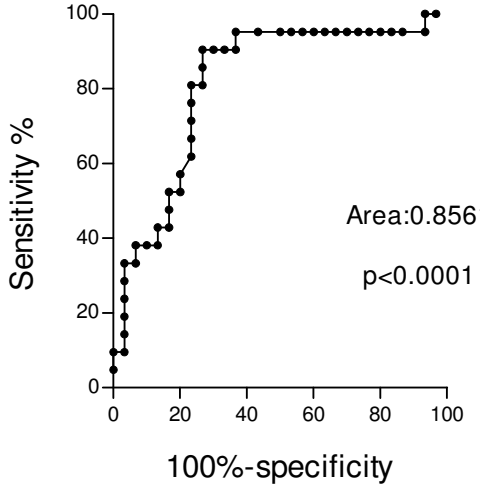
A



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

Pain M, Royer PJ, AJT

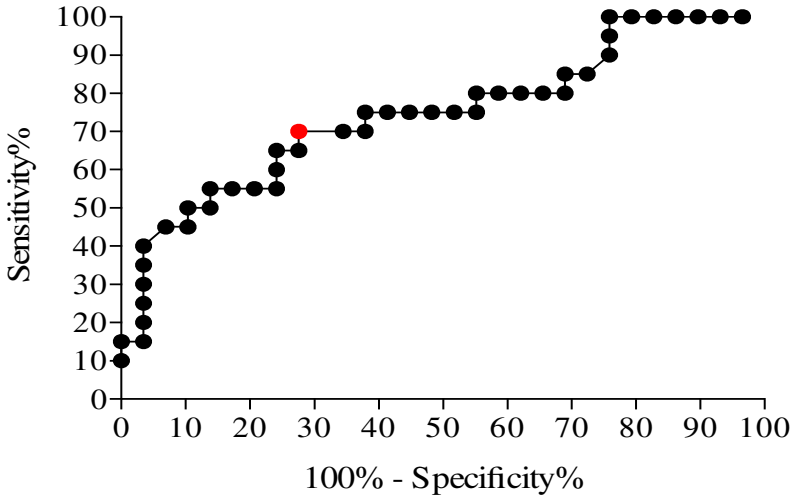
Regulatory T lymphocytes profile as a possible predictive biomarker of the Bronchiolitis Obliterans Syndrome after lung transplantation

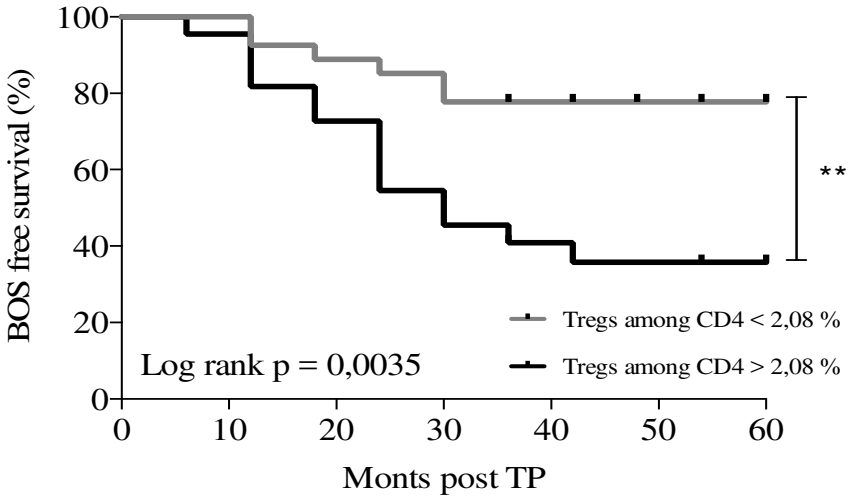
Maxim Durand[1,2,3*], Philippe Lacoste[2,3*], Carole Brosseau[1,2], Eugénie Durand[2], Jennifer Loy[2], Pierre Joseph Royer[2], Antoine Magnan[2], Sophie Brouard[1] & COLT Consortium

[1] Center for Research in Transplantation and Immunology, INSERM U1064, Nantes, France
[2] l'institut du thorax, INSERM U1087/CNRS U6291, Nantes, France
[3] Université de Nantes, Nantes, France

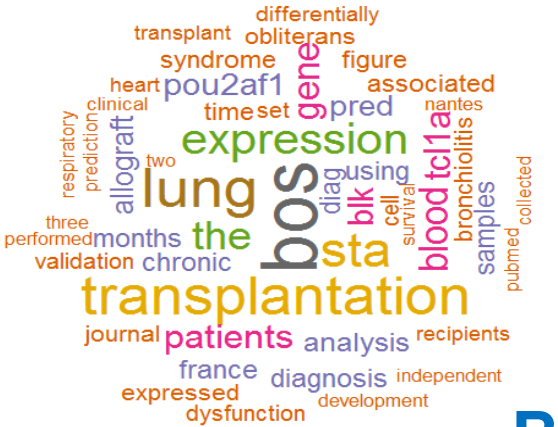
Conclusion

- 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.



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

CRTI UMR 1064 Centre de Recherche en Transplantation et Immunologie

UNIVERSITÉ DE NANTES

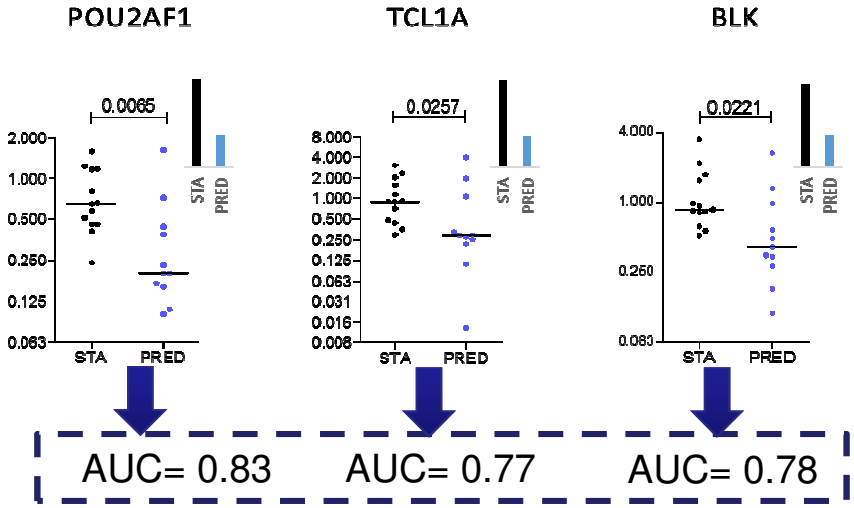
Inserm

itun institut transplantation urologie néphrologie INSERM - UMR 643

CENTRE HOSPITALIER UNIVERSITAIRE DE NANTES

Prediction of BOS: independent validation

- Validation of genes associated with BOS appearance



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

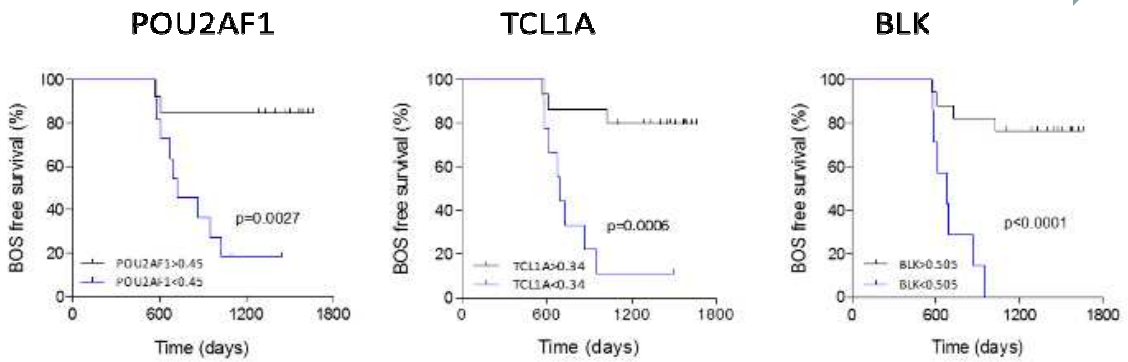
➡ independent validation

ROC curves: AUC= 0.83 AUC= 0.77 AUC= 0.78

➡ Excellent discriminative ability

- Prediction of BOS appearance

➡ 3 genes to predict BOS



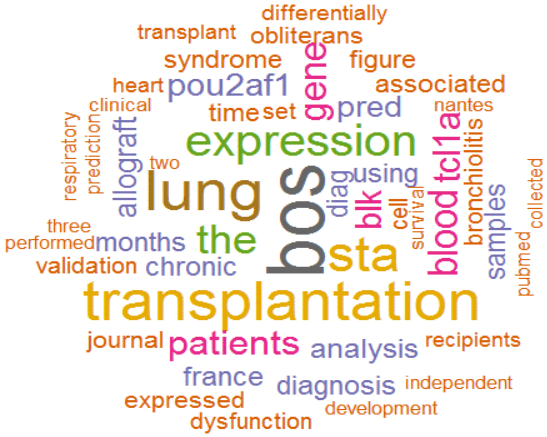
POU2AF1: POU class 2 associating factor 1
BLK: B lymphoid tyrosine kinase
TCL1A: T-cell leukaemia/lymphoma 1A

Blood Gene Expression Predicts Bronchiolitis Obliterans Syndrome Appearance After Lung Transplantation

- 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

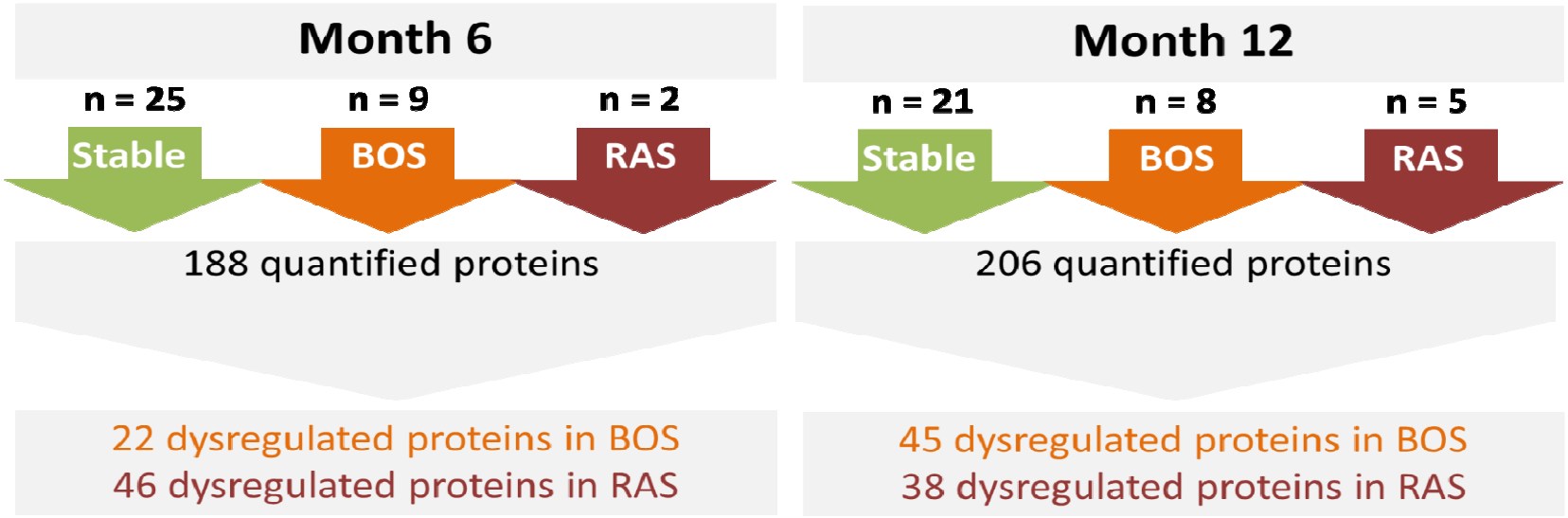
patent: EP16306125.2
work submitted

Validation of these 3 genes in a large prospective cohort

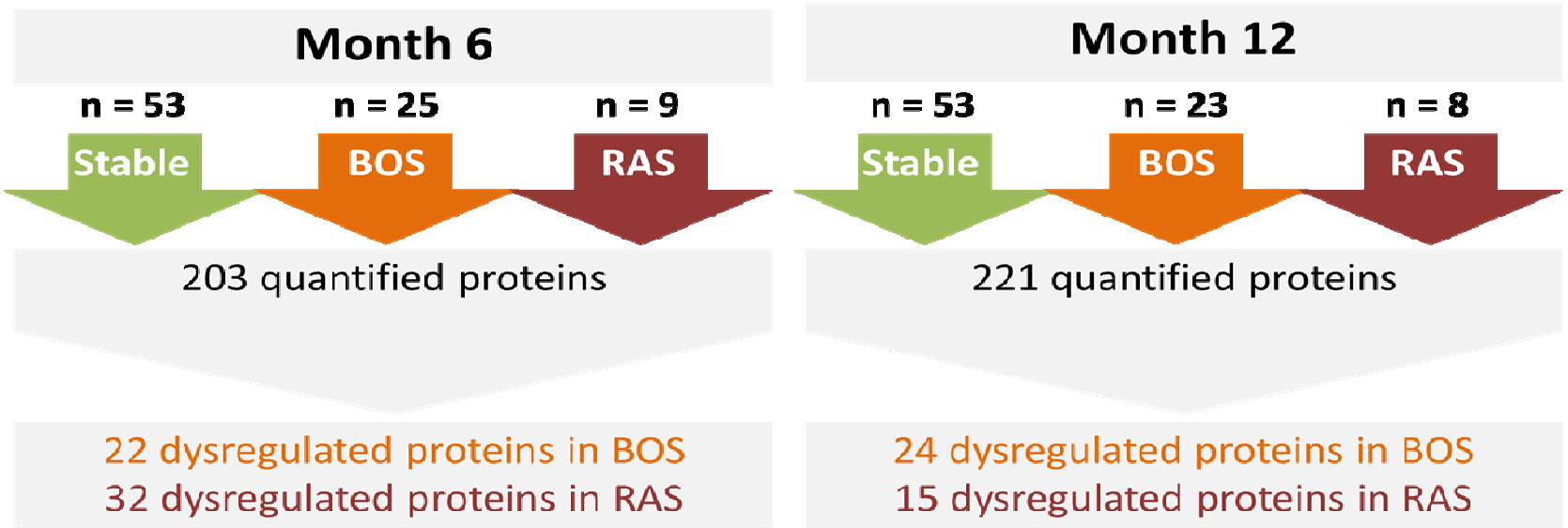


Proteomics

BAL samples in iTRAQ experiments



Plasma samples in iTRAQ experiments

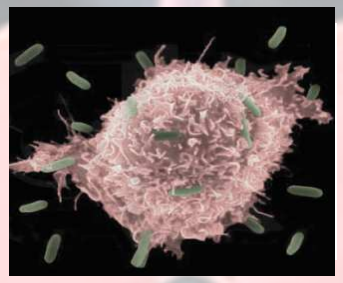


Claustre *et al.* In *preparation*

Lung Microbiote & BAL Macrophage polarization

BAL cells
(CHUV standards)

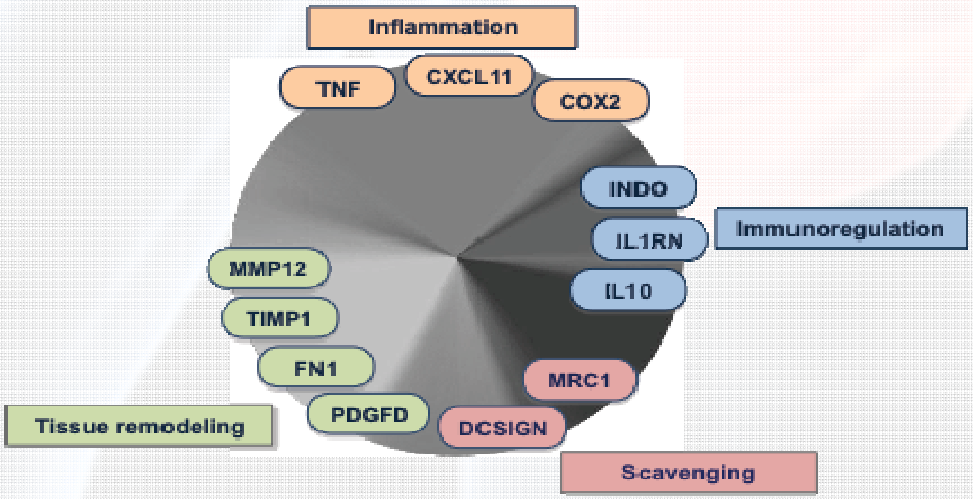
Macrophages	> 85%
Neutrophils	< 3%
Eosinophils	< 0.5%
Lymphocytes	< 12%
Bronchial cells	< 10%



Lung microbiota
(Data from Hilty M et al. PLoS ONE 2010)

Bacteroidetes	42.0%
Firmicutes	32.5%
Proteobacteria	12.3%
Fusobacteria	10.2%
Actinobacteria	2.6%

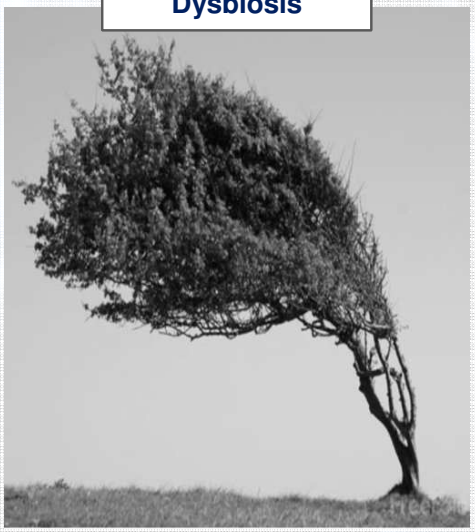
RNA isolation ↓ **Real-time PCR-based quantification**



DNA isolation ↓ **Real-time PCR-based quantification**

Balanced microbiota

Dysbiosis



Bernasconi *et al.* AJRCCM 2016; 194: 1252-63

Airway Microbiota Determines Innate Cell Inflammatory or Tissue Remodeling Profiles in Lung Transplantation

Eric Bernasconi[1], Céline Pattaroni[1], Angela Koutsokera[1], Christophe Pison[2,3,4], Romain Kessler[5], Christian Benden[6], Paola M. Soccal[7], Antoine Magnan[8], John-David Aubert[1], Benjamin J. Marsland[1*], and Laurent P. Nicod[1*]; on behalf of the SysCLAD Consortium[‡]

[1]Service de Pneumologie, Centre Hospitalier Universitaire Vaudois and Swiss Transplant Cohort Study, Lausanne, Switzerland; [2]Clinique Universitaire de Pneumologie, Centre Hospitalier Universitaire (CHU), Grenoble, France; [3]Université Grenoble Alpes, Grenoble, France; [4]Inserm1055, Saint Martin d'Hères, France; [5]Service de Pneumologie, Nouvel Hôpital Civil, CHU, Strasbourg, France; [6]Division of Pulmonary Medicine, University Hospital Zurich, Zurich, Switzerland; [7]Division of Pulmonary Medicine, Geneva University Hospitals, Geneva, Switzerland; and [8]L'institut du thorax, Service de Pneumologie, CHU, Nantes, France

Abstract

Rationale: In lung transplant recipients, long-term graft survival relies on the control of inflammation and tissue remodeling to maintain graft functionality and avoid chronic lung allograft dysfunction. Although advances in clinical practice have improved transplant success, the mechanisms by which the balance between inflammation and remodeling is maintained are largely unknown.

Objectives: To assess whether host–microbe interactions in the transplanted lung determine the immunologic tone of the airways, and consequently could impact graft survival.

Methods: Microbiota DNA and host total RNA were isolated from 203 bronchoalveolar lavages obtained from 112 patients post-lung transplantation. Microbiota composition was determined using 16S ribosomal RNA analysis, and expression of a set of genes involved in prototypic macrophage functions was quantified using real-time quantitative polymerase chain reaction.

Measurements and Main Results: We show that the characteristics of the pulmonary microbiota aligned with distinct innate cell gene expression profiles. Although a nonpolarized activation was associated with bacterial communities consisting of a balance between proinflammatory (e.g., *Staphylococcus* and *Pseudomonas*) and low stimulatory (e.g., *Prevotella* and *Streptococcus*) bacteria, "inflammatory" and "remodeling" profiles were linked to bacterial dysbiosis. Mechanistic assays provided direct evidence that bacterial dysbiosis could lead to inflammatory or remodeling profiles in macrophages, whereas a balanced microbial community maintained homeostasis.

Conclusions: The crosstalk between bacterial communities and innate immune cells potentially determines the function of the transplanted lung offering novel pathways for intervention strategies.

Keywords: microbiome; macrophages; airway remodeling

Airway microbiota signals anabolic and catabolic remodeling in the transplanted lung

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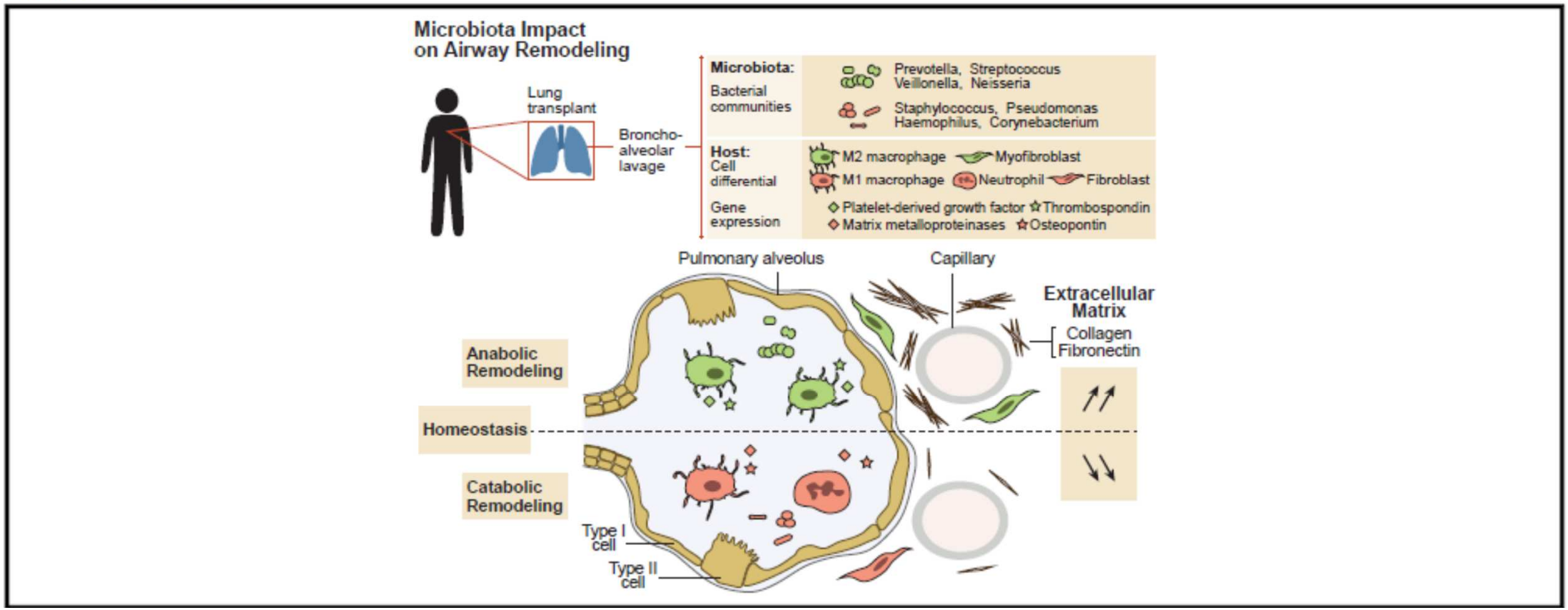
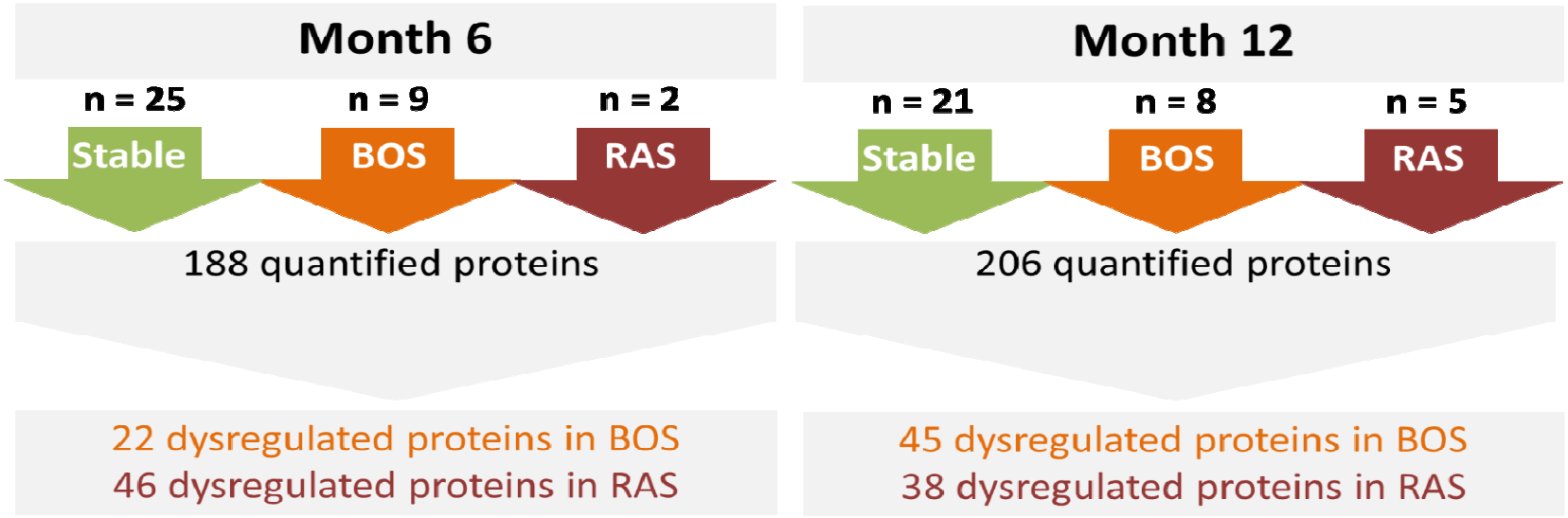
Lausanne, Zurich, and Geneva, Switzerland; and Grenoble, Saint Martin d'Hères, Nantes, and Strasbourg, France

GRAPHICAL ABSTRACT

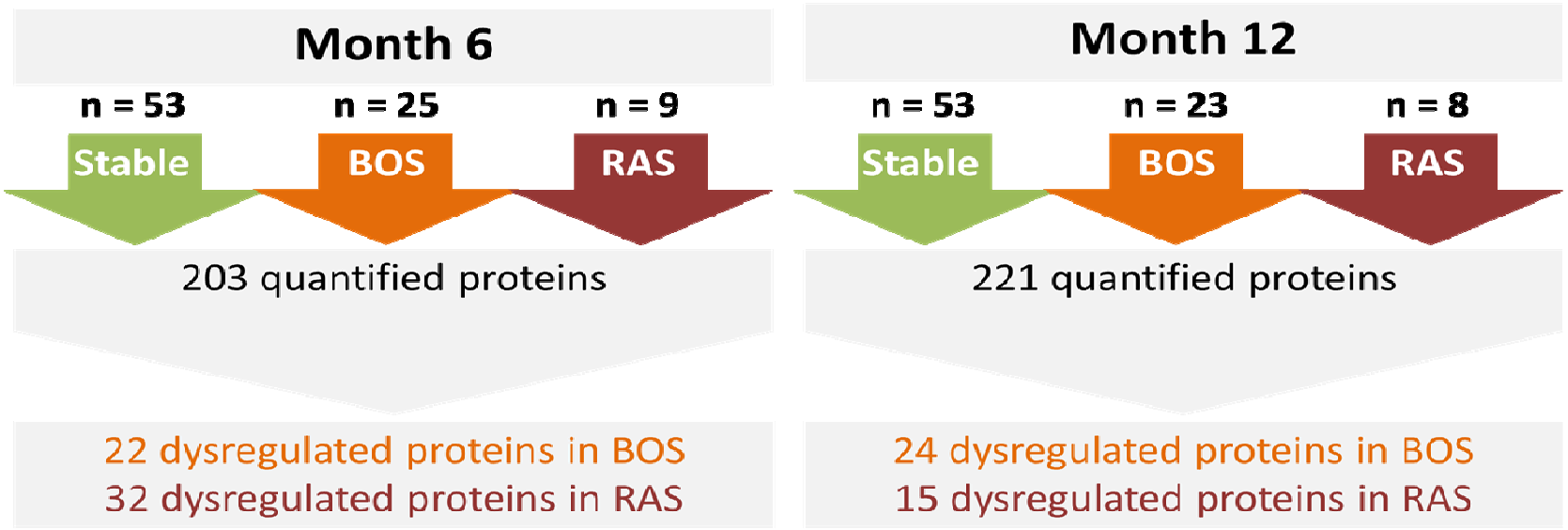


Proteomics

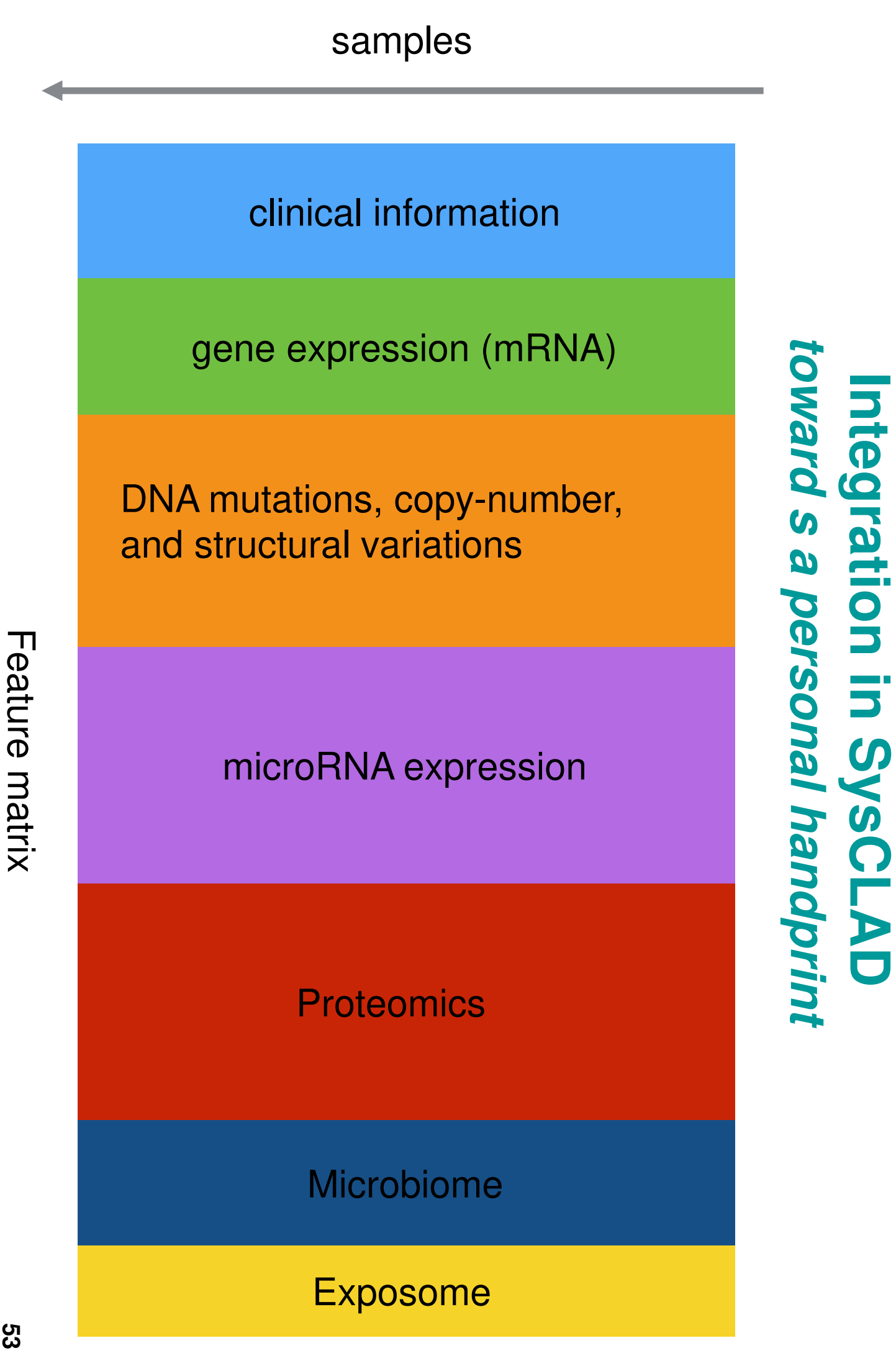
BAL samples in iTRAQ experiments



Plasma samples in iTRAQ experiments



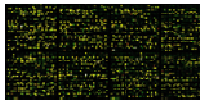
Claustre *et al.* 2016, ***submitted***


samples
clinical information
gene expression (mRNA)
DNA mutations, copy-number,
and structural variations
microRNA expression
Proteomics
Microbiome
Exposome
Feature matrix
Integration in SysCLAD
toward s a personal handprint

Identification of early biomarkers of CLAD

Blood (Paxgene)

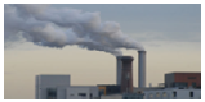
Transcriptome



Microbiome

BAL

Environment

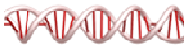


Geolocalisation

SysCLAD model

DNA

Genotyping

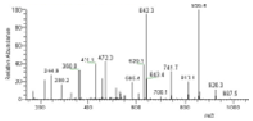


Biomarkers
Prediction
Mechanisms

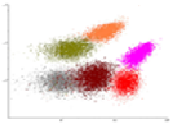
Clinicome

Clinical data

Proteome



Immunomonitoring

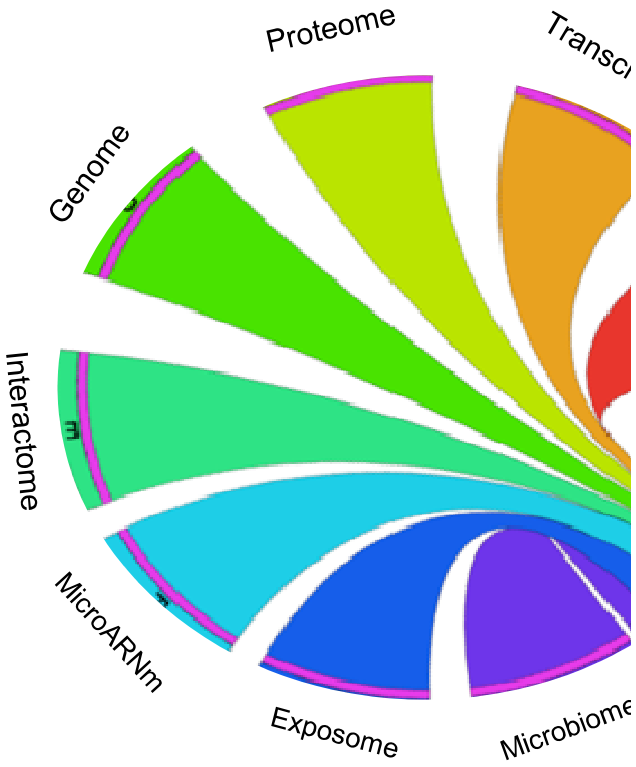


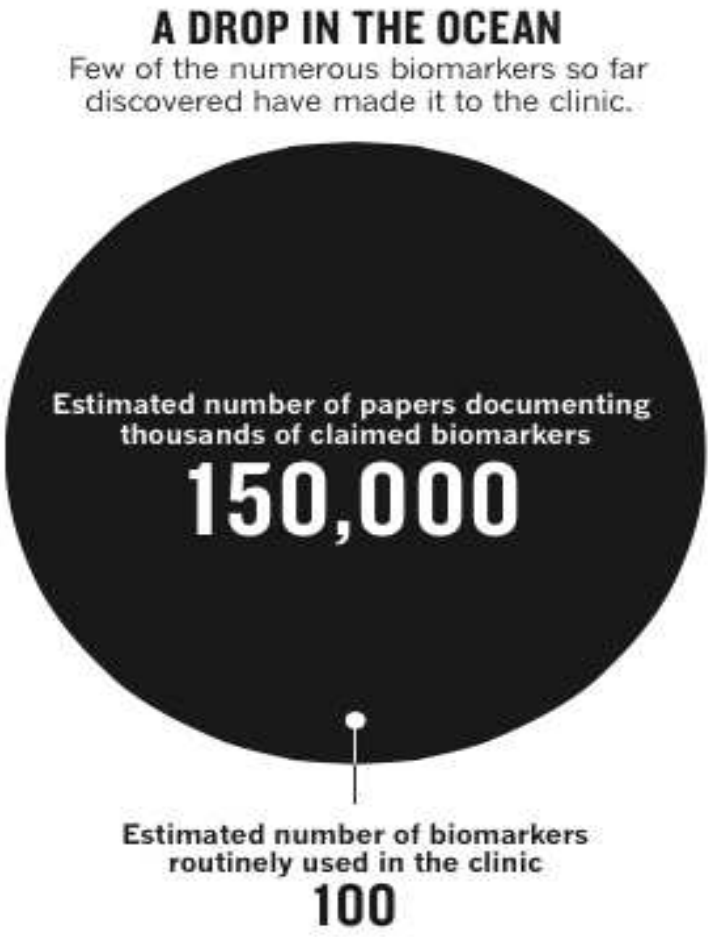
Plasma/BAL

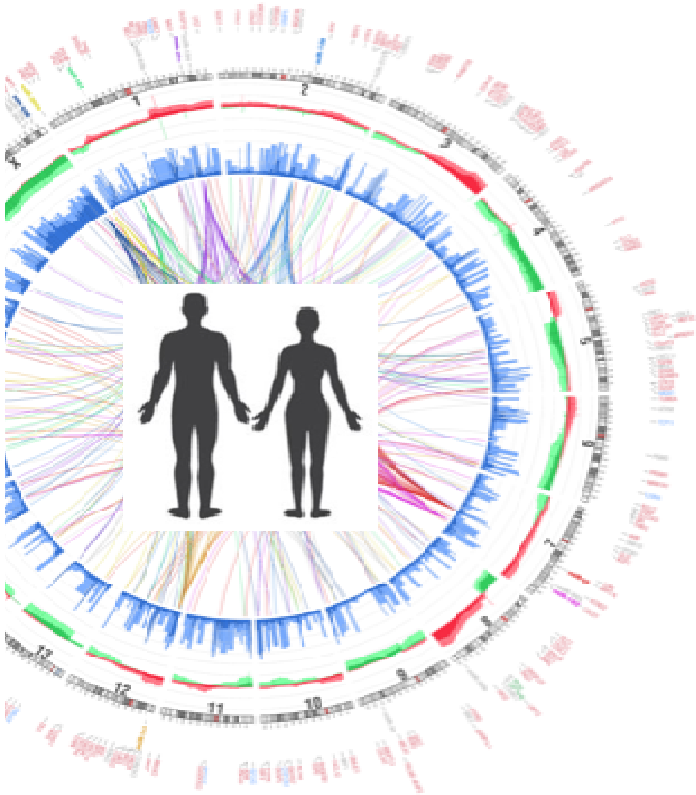
PBMC

Integration in SysCLAD

towards a personal handprint or limits of single biomarker





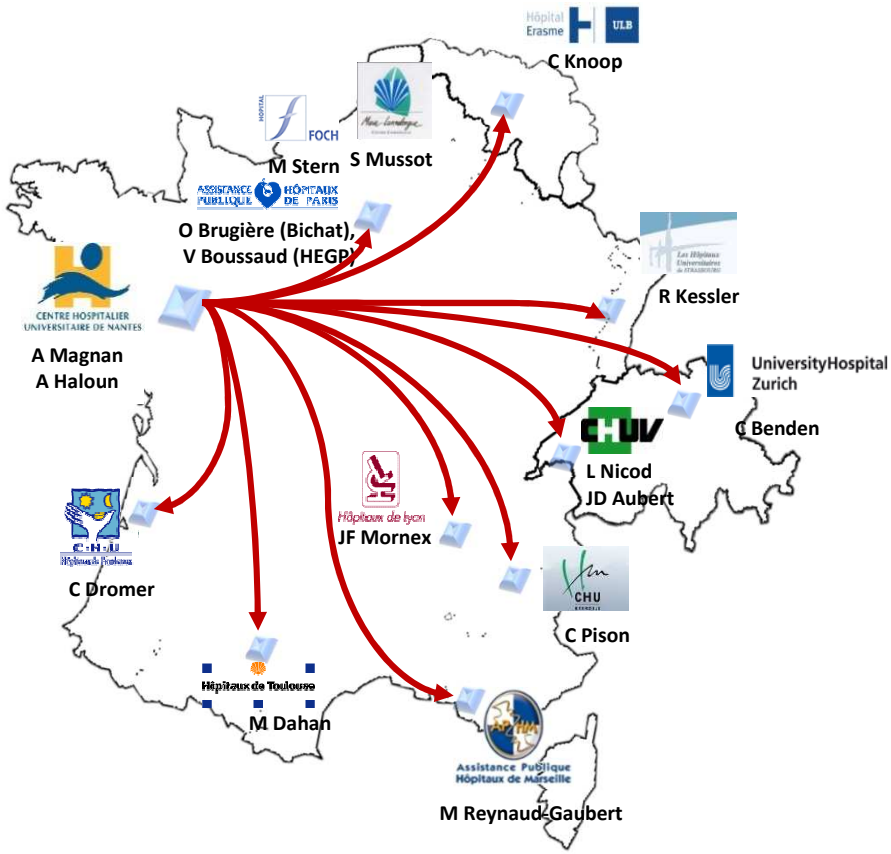


Nature 469, 156–157 (13 January 2011)

Only one to monitor acute rejection after cardiac transplantation -AlloMap®

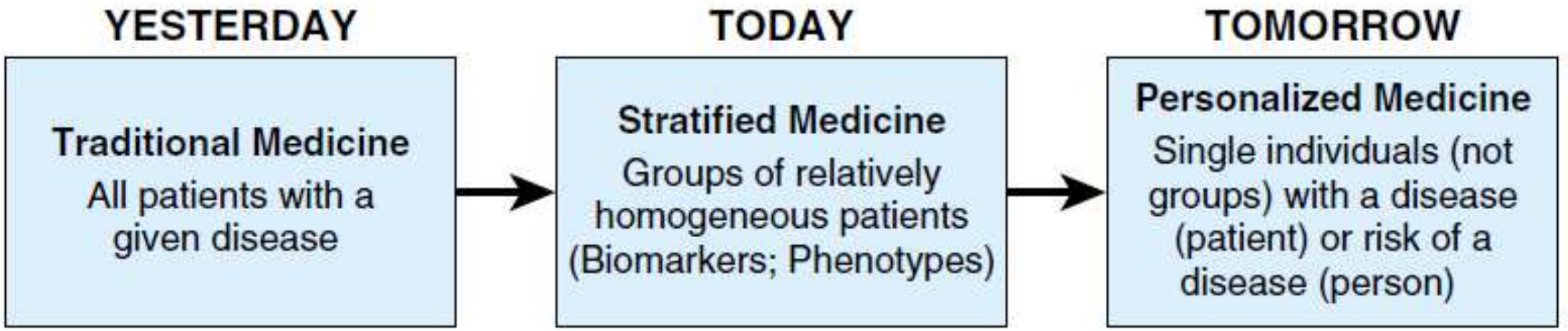
Side effects

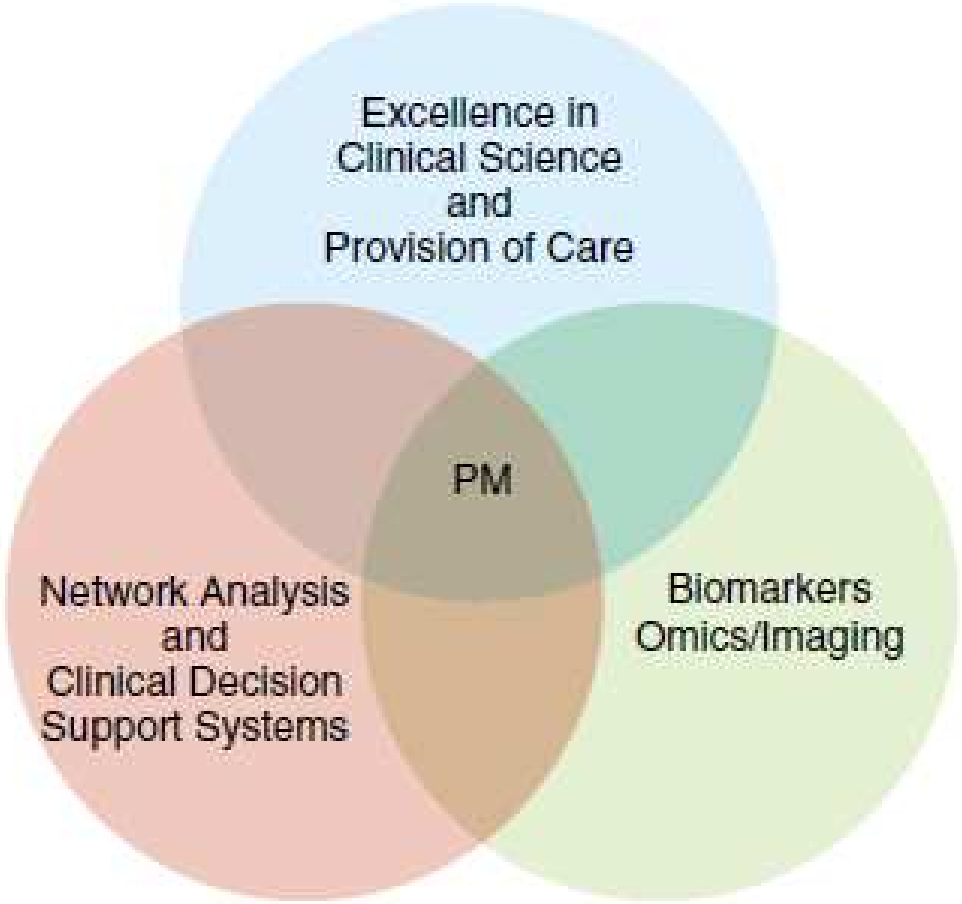
- Positive chemistry
- Network of surgeons, pulmonologists, researchers.
- New labs driven to Lung Tx (S Brouard, V Siroux…)
- Gift to youngers



COLT demain

- Optimization:
  - Simplified CRF
  - Data clinic
- Validation of biomarkers
- Complex signatures (handprints), score prédictif du CLAD
- Biomarkers at 5 years of follow-up
- Pre-transplant biomarkers
- COLT opened for other teams / Laboratories (valorization of the biocoll)
- Personalized medicine in LT through system approach





Agusti A *et al.*
AJRCCM 2015

Remerciements

PHRC 2009

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