NRS Roadmap Lung Transplantation

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1. Inventory of Dutch research efforts in this field over the past five years(2008-2013) by ISI web of knowledge

The team has made an inventory of Dutch lung transplant research over the last 5 years Search terms:
Topic: Lung Transplantation
Publication year: 2008-2013
Address: Netherlands

This resulted in 238 hits. 92 of these hits addressed lung transplantation. From this search, papers describing original research were selected, resulting in 61 original articles. 14, being considered as basic research and 47 as clinical research. No reviews were found.

Summary:

Institute	**Article number**
Erasmus Medical Center	8
Revalidation Centre Horn	1
Leiden University Medical Center– LUMC /Eurotransplant	4
Maastricht University Medical Center	1
Radboud University Medical Centre	1
University Medical Center Groningen – UMCG	24
University Medical Center Utrecht/ Nieuwegein	22
Total	61

2. Visibility Dutch research judged by international experts (see also Appendix)

Areas with good visibility	Areas with less visibility
Donation after circulatory death (NHB)	Allograft dysfunction
HSV after LTX	Translational research
CMV / EBV driven PTLD	BOS mechanisms
Clinical outcomes after LTX	Risk factors
Cost evaluation	Phenotyping
Genetic studies with BOS	Treatment
Biomarkers with BOS	

3. Research needs

Facts and Figures[1]
At an annual base approximately 40 lung transplantation take place in the Netherlands.

Euro costs[2]
- Lung transplantation unit cost
  € 214,875:

Lung transplantation:
COPD is the most important indication for lung transplantation, followed by Cystic Fibrosis. The number of lung transplantations as a result of COPD has increased in recent years. In 2007 there were 66 lung transplantations from which 15 lung transplantations due to COPD.
The total incremental costs for a transplanted patient were estimated on € 210,000[2]

Unmet needs (extracted from: LAN rapport 2010[3])
When the usual therapy does not have sufficient effect, then in some cases can be applied for a lung transplantation. Most important restriction: factor is the supply of donorlungs[1]

References
[1] Feiten en cijfers 2013 Chronische Longziekten, LAN 2013
[2] Enckevort et al. Life time costs of lung transplantation. Health economics 1997;6:479
[3] Feiten en Cijfers chronische Longziekten 2010

4. Summary SWOT analysis

Results of the web-based SWOT

Strengths	*Weaknesses*
1. Regular meetings between the centers 2. Prevalent diseases: importance for population 3. Large samples (biobanking)	1. Low number of transplantations and mostly single center studies 2. Diversity of LTX indications 3. Donor shortage
Opportunities	*Threats*
1. Collaboration in research also by harmonization of clinical protocols 2. Post-LTX complications determining morbidity en mortality (DM, renal failure etc) in common with other solid organ transplant programs (heart/kidney/liver) 3. National and international collaboration with companies and/or other centres: EVLP, diagnostic biomarkers	1. Differences in interpretation of protocols between centers (acceptance of donor lungs, inclusion criteria?) 2. Competition and lack of trust between centers 3. Lack of grant opportunities

Relevance of research judged by international experts (order of importance):
See Table *Relevance of research judged by international experts* in appendix

	Mean
Phenotyping and Severity	3.00
Biological mechanisms	3.00
Environment and lifestyle	1.50
Development and ageing	1.00
Prevention	2.50
Diagnosis monitoring	3.75
Therapy medical	2.25
Therapy non-medical	2.25
Biobanking	1.25
Data management clinical studies	2.50
Implementation and care	3.00

5. Description of the interface of lung transplantation with other Roadmap areas

The web based SWOT analysis does not lead to a clear conclusion. But from the discussion within the group some conclusions can be drawn. There are many opportunities but research in the field of lung transplant is difficult due to low numbers. Collaboration offers chances to increase these numbers and to focus research questions.
Overlap with other disciplines can be seen in:

- Medical therapy: last resort: LTX
- Biobanking: Cancer, COPD, LTX, PH, CF
- Data management clinical studies: all
- Lifestyle: cancer

6. Priorities for Dutch research in the area for 2014-2019

- Decrease of donor shortage
- Prevention and treatment of long term co-morbidities

7. What is needed to let the research priorities listed be successful?

- collaboration To improve the quality of research in The Netherlands, more collaboration of the Transplant research centres is needed. This will have impact on quality and quantity of research.
- registry, systematic biobanking, EVLP program,
  This will allow better basic research towards unravelling the origins of BOS, by increasing numbers of samples. Collaboration between centers and delineation of research question is needed to this aim. Moreover, this will also have impact on the research priority above to prevent and treat long-term co-morbidities after LTX.
- To develop better interventions, international collaboration, probably world-wide, is needed. At this moment some international trials are up and running in which Dutch groups participate. Lung transplantation is less suited to study many topics, like environmental life style risk factors and development and aging, mainly due to low numbers but collaboration (internationally) offers also opportunities in this area.

8. What do patients want?

More transplantations
Shorter waiting time (personal communication)

Table 1 . Top 10 most cited <u>basic research</u> initiated by a Dutch group:

Theme	Article	Citations	
		Total	Mean/ yr
1	Kastelijn, E.A, van Moorsel, C.H.M, Rijkers, G.T, Ruven, H.J.T, Karthaus, V, Kwakkel-van Erp, J.M, van de Graaf, E.A, Zanen, P, van Kessel, D.A, Grutters, J.C, van den Bosch, J.M.M. Polymorphisms in innate immunity genes associated with development of bronchiolitis obliterans after lung transplantation. J Heart Lung Transplant. 2010; 29(6):665-71.	11	5.5
2	Paantjens, A.W. M, Erp, J.M. Kwakkel-van, van Ginkel, W.G.J, van Kessel, D.A, van den Bosch, J.M.M, van de Graaf, E.A, Otten, H.G. Serum thymus and activation regulated chemokine levels post-lung transplantation as a predictor for the bronchiolitis obliterans syndrome. Clin Exp Immunol. 2008; 154(2):202-8.	4	1.0
3	Paantjens, A.W.M, van de Graaf, E.A, Heerkens, H.D, Kwakkel-van Erp, J.M, Hoefnagel, T, van Kessel, D.A, van den Bosch, J.M.M, Otten, H.G. Chimerism of dendritic cell subsets in peripheral blood after lung transplantation. J Heart Lung Transplant. 2011; 30(6):691-7.	3	3.0
4	Kastelijn, E.A, van Moorsel, C.H, Ruven, H.J, Karthaus, V, Kwakkel-van Erp, J.M, van de Graaf, E. A, Zanen, P, van Kessel, D.A, Grutters, J.C, van den Bosch, J.M. Genetic polymorphisms in MMP7 and reduced serum levels associate with the development of bronchiolitis obliterans syndrome after lung transplantation. J Heart Lung Transplant. 2010; 29(6):680-6.	3	1.5
5	van der Kaaij, N.P, Kluin, J, Haitsma, J.J, den Bakker, M.A, Lambrecht, B.N, Lachmann, Burkhard; de Bruin, R.W.F, Bogers, A.J.J.C. Surfactant pretreatment decreases long-term damage after ischemia-reperfusion injury of the lung. Eur J Cardiothorac Surg. 2009; 35(2):304-12.	3	1.0

Table 2. Top 10 most cited clinical research initiated by a Dutch group:

Theme	Article	Citations	
		Total	Mean/ yr
1	Erasmus, M.E, Verschuuren, E.A. M, Nijkamp, D. M, Vermeyden, J.W; van der Bij, W. Lung Transplantation from Nonheparinized Category III Non-Heart-Beating Donors. A Single-Centre Report Transplantation. 2010; 27;89(4):452-7.	26	13.0
2	den Hengst, W.A, Gielis, J.F, Lin, J.Y, Van Schil, P. E, De Windt, L.J, Moens, A.L. Lung ischemia-reperfusion injury: a molecular and clinical view on a complex pathophysiological process. Am J Physiol Heart Circ Physiol. 2010; 299(5):H1283-99.	19	9.5
3	Bakker, N.A, Verschuuren, E. A, Veeger, N.J, van der Bij, W, van Imhoff, G.W, Kallenberg, C.G, Hepkema, B.G. Quantification of Epstein-Barr virus-DNA load in lung transplant recipients: A comparison of plasma versus whole blood. J Heart Lung Transplant. 2008; 27(1):7-10.	16	4.0
4	Anderson, R. L, Hiemstra, P. S, Ward, C, Forrest, I. A, Murphy, D, Proud, D, Lordan, J, Corris, P. A, Fisher, A. J. Antimicrobial peptides in lung transplant recipients with bronchiolitis obliterans syndrome. Eur Respir J. 2008; 32(3):670-7.	15	3.8
5	Vermeijden, J. W; Zijlstra, Jan G, Erasmus, Michiel E, van der Bij, Wim, Verschuuren, Erik A. Lung Transplantation for Ventilator-Dependent Respiratory Failure. J Heart Lung Transplant. 2009; 28(4):347-51.	10	3.3

APPENDIX

Opinions of international key opinion leaders

Question 1
Which research topics and groups in Lung Transplantation research are visible and have impact on pulmonary physicians and researchers outside the Netherland?

Expert 1
Only group visible internationally are
- Verschuuren
- Erasmus
- van der Bij et al Groningen

Topics which this group have an international reputation is:
- Donation after Circulatory Death
- Herpes Virus infections after lung transplant
- EBV driven post transplant lymphoproliferative disease
- Clinical outcomes after lung transplantation

Expert 2
Groningen has some research on CMV infections, EBV and the relation with PTLD. Erik Verschuuren is an active member of the infection council of the ISHLT. Previously they performed good research on cost evaluation of lung transplantation, but this is a long time ago.
- Good research with excellent data on NHB donors
- Rotterdam has no obvious research in lung transplantation.
- Utrecht/Niewegein has an interest in genetic studies in lung transplantation with BOS and death as outcome variable and also in biomarkers for BOS.

Expert 3

Expert 4
Research in immunosuppression related viral infection and management of immunosuppression has international top level and impact. Use of immunological methods in patient management has international impact

Question 2
Which research topics in Lung Transplantation research are less visible to physicians and researchers outside the Netherland?

Expert 1
Although the Groningen group have collaborated in across European research efforts in lung transplantation including international multicentre clinical trials of immunosuppression. The other groups in the Netherlands have little exposure on the international stage.
There is little to no work going on in basic science of allograft dysfunction including animal modeling or translational research studies into disease mechanisms.

Expert 2
BOS mechanisms, risk factors, phenotyping, treatment

Expert 3

Expert 4
Basic research is less visible**.**

Relevance of research judged by international experts (order of importance)

Research performed in the Netherlands in the field of **Lung Transplantation**

0 = no relevant research
5 = excellent research international top level

	1	2	3	4	mean
Phenotyping and Severity	3	2	4	3	3.00
Biological mechanisms	3	3	3	3	3.00
Environment and lifestyle	0	1	3	2	1.50
Development and ageing	0	1	1	2	1.00
Prevention	0	3	3	4	2.50
Diagnosis monitoring	4	3	3	5	3.75
Therapy medical	0	1	4	4	2.25
Therapy non-medical	0	1	5	3	2.25
Biobanking	0	1	0	4	1.25
Data management clinical studies	3	1	2	4	2.50
Implementation and care	3	2	4	3	3.00