NRS Roadmap Cystic Fibrosis

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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

Search terms:
The inventory was based on the following search terms in the period 2008-may 2013:
http://apps.webofknowledge.com/.
Topic= Cystic Fibrosis
Address= Netherlands
Title = Cystic Fibrosis

In total this review revealed 172 papers. From these 172 all papers with one or more authors as 1st or 2nd or last or 2nd last author from a Dutch centre were selected, after which 131 papers remained.

Summary:

Papers on CF last 5 years

	Dutch initiatives	Dutch collaborators	Total
Groningen	12	1	13
Amsterdam	9	6	15
Utrecht	47	12	59
Rotterdam	37	13	50
Maastricht	4	1	5
Nijmegen	6	3	9
Den Haag	12	2	14
Heerlen	3	1	4
Others	1	2	3
Total	131	41	172

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

Areas with good visibility	Areas with less visibility
- Imaging	- Gene therapy
- Organoids	- Biological mechanisms
- Animal Models	- Development and aging
- Clinical studies	- Gastrointestinal disease
- Epidemiology of infectious agents	- Diabetes in CF
- Diagnostis	- Non-medical therapy
	- Pharmacodynamics
	- Screening

3. Research needs

Facts and Figures:

Patient numbers 2011			
	Children	Adults	Total
Groningen	63	80	143
Amsterdam	90	83	173
Utrecht	221	165	386
Rotterdam	137	131	268
Maastricht	28	36	64
Nijmegen	41	47	88
Den Haag	49	203	252
Total	629	745	1374

In The Netherlands, 53.5% of CF patients are male, 46.5% are female, mean age of the population 19.2 years[1]. Neonatal birth screening for CF was started in May 2011. 54.8% of the patients have a homozygous mutation for F508del, 7.3% has a non-F508del mutation on both alleles. In children, mean value of FEV1 was 90.5% predicted. 18% was positive for P. aeruginosa, median Weight for Height z-score was +0.03. In adults the mean FEV1 was 59.9% predicted. 52% was positive for P. aeruginosa, median BMI was 21.6.

Euro costs[2]

- Total estimated health care costs are estimated as k€ 25 per patient per year, resulting in an estimated health care cost of about M€ 35 for the CF population in The Netherlands per year.

Unmet needs:(extracted from: LAN verkenning 2010[3])

Cystic Fibrosis is the most common inherited disease in The Netherlands, until now only symptomatic therapy is available. Despite aggressive nutritional support, antibiotic treatment of severe and sustained respiratory infections mean life expectancy is still limited to 35-40 years. The disease requires a multidisciplinary approach asking for highly centralized care. With improving prognosis the disease has become increasingly complicated (CF-related

diabetes, CF-related liver disease, multidrug antimicrobial resistance, osteoporosis, etc), requiring intensive follow up and treatment of patients. Recent scientific developments highly focus on individualized curative treatment using CFTR-modifying small molecules and improvement of antimicrobial treatment using inhaled antibiotics. These developments ask for highly specialized care, high patient numbers and a strong infrastructure of CF-centers to enable participation in clinical trials into new treatment regimen. Besides this the multidisciplinary and lifelong treatment ask for an adequate financing structure, which does not hamper transmural and multifaceted care.

Reference:

[1]Annual report of Dutch Cystic Fibrosis Foundation 2011 (covering over 95% of all patients) http://www.cfonderzoek.nl/cf-registratie/

[2] Maatschappelijke kosten voor astma, COPD en respiratoire allergie. RIVM Rapport 260544001/2012

[3] Feiten en Cijfers chronische Longziekten 2010

4. Summary SWOT analysis

Results of the web-based SWOT

Strengths 1. Infection and inflammation 2. Imaging 3. Basic mechanisms, including patient derived (organoids) and animal (mice) models	*Weaknesses* 1. Some centres too small for adequate expertise/research 2. Psychosocial aspects and lifestyle *3.* Transition paediatric-adult care
Opportunities 1. Collaborative efforts on treatment of basic defect 2. Central clinical database 3. Biobanking	*Threats* 1. National competition vs collaboration 2. Limited research funding 3. Lack of quality control systems

Relevance of research judged by 3 international experts (order of importance):
See table Relevance of research judged by international experts in appendix

	Mean
Phenotyping and Severity	3.75
Biological mechanisms	3.00
Environment and lifestyle	2.66
Development and ageing	2.33
Prevention	1.00
Diagnosis monitoring	3.66
Therapy medical	3.33
Therapy non-medical	2.25
Biobanking	1.00
Data management clinical studies	3.25
Implementation and care	2.00

5. Description of the interface of CF with other Roadmap areas

Both with regard to the model of care and to basic research on the origin and treatment of the basic defect, CF is a model disease for many other respiratory diseases. For example:

- Development of small molecules, CFTR activators/potentiators: CFTR plays a role as modifier gene in e.g. asthma and COPD
- Anti-inflammatory drugs: obvious parallel to chronic diseases like Asthma, COPD and IPF
- Microbiome of the airways: course of colonization, disease specificity, effects of antibiotic treatment: also important for other respiratory infections
- Stem cells, regenerative medicine and biobanking: broadly applicable.

Dutch basic scientists have developed extensive experience, expertise and facilities, which can be used for other respiratory diseases. Examples are: genetics, biomarkers, imaging (HRCT), mouse models, tissue engineering.

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

- The origins of CF and treatment of the basis defect
- Diagnosis and treatment of infection
- Inflammation and antimicrobial defense

Provide the reasons for these choices

These themes cover the areas which are of high interest in the international developments on CF and are fully in line with research priorities in the patient domain (see pt 8). During last 5 years about 50% of the papers from Dutch groups fitted in one of these priorities. Recently a collaborative network between the centres of Utrecht, Rotterdam and The Hague was raised, focusing on the top of these priorities. In this network close collaboration between basic scientists (in both Rotterdam and Utrecht) a clinical scientists was installed to perform cutting edge transmural research. This collaborative scientific focus was adopted by the Dutch Cystic Fibrosis Society and the Society is committed to raise funds for these topics during the next coming 5 years.

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

The collaborative scientific focus in the 3 CF centres has been adopted by the Dutch Cystic Fibrosis Society and the Society is committed to raise funds for these topics during the next coming 5 years To be successful the topics should be focus of both outstanding basic scientists and of clinical caregivers in a strong collaborative network. Currently basic scientist groups working in this field are:

- The Utrecht CF lab (Beekman, Clevers) focusing on regenerative medicine and the molecular basis of CFTR. This group recently published some high impact papers in this area.
  The Rotterdam cell biology and MDL labs (Scholte, de Jonge) which have longstanding experience with both research into mode of action of CFTR repairing drugs and into inflammatory mechanisms in CF. These groups developed unique CF mouse models
- The Utrecht Cellular chemistry group (Braakman), focusing on protein folding especially CFTR. This group is the only European member of the American CFTR folding consortium
- Several microbiology labs (Utrecht, Rotterdam, The Hague, Nijmegen) have focused on different infectious aspects with regard to CF an are internationally renown.

The clinical groups which have highly driven the scientific output during last 5 years are concentrated in The Hague, Rotterdam and Utrecht (Heijerman, Tiddens, Van der Ent). Together these clinical groups care for two thirds of all patients in The Netherlands. The groups share protocols, data and have longstanding experience in longitudinal data-acquisition in extensive groups of patients.
To be successful in the research priorities it will be of utmost importance that these basic and clinical scientists collaborate in sharing knowledge (low threshold meetings), patient materials (biobanking) and patient data. A recent collaborative study initiative of these groups (HIT-CF) has a high potential of creating breakthroughs in diagnosis and treatment of CF. Proper infra-structure and finances of this initiative will be critical factors for success.

8. What do patients want?

In 2012 the Dutch Cystic Fibrosis Foundation performed an intensive survey of research priorities amongst patients with CF. The top 5 of these priorities was (with number of related scientific papers in last 4 years (out of 118) between brackets):

- The origin of CF and treatment of the basis defect (9)
- Diagnosis and treatment of infections (32)
- Inflammation and antimicrobial defense (6)
- Tiredness and fitness (8)
- Psychological and social functioning (3)

During last 5 years the Dutch CF Foundation has become one of the major sponsors of CF research in the Netherlands.

Table 1 . Top 10 most cited basic research initiated by a Dutch group

Theme	Article	Citations	
		Total	Mean/yr
Inert gas washout	Gustafsson, P. M, De Jong, P. A, Tiddens, H. A. W. M, Lindblad, A. Multiple-breath inert gas washout and spirometry versus structural lung disease in cystic fibrosis.	17	12.0
Inhaled treatment	Heijerman, H, Westerman, E, Conway, S, Touw, D, Doring, G. Inhaled medication and inhalation devices for lung disease in patients with cystic fibrosis: A European consensus.	22	8.5
Best practice guidelines	Castellani, C, Southern, K. W, Vernooij, A, Elborn, S..European best practice guidelines for cystic fibrosis neonatal screening.	16	7.7
Intestinal Cl-secretion	Bijvelds, M. J. C, Bot, A.G. M, Escher, J.C, de Jonge, H.R. Activation of Intestinal Cl- Secretion by Lubiprostone Requires the Cystic Fibrosis Transmembrane Conductance Regulator	9	6.5
Small airways	Tiddens, H. A. W. M, Donaldson, S.H, Rosenfeld, M, Pare, P. D. Cystic Fibrosis Lung Disease Starts in the Small Airways: Can We Treat It More Effectively?	16	5.3
Viral infections	van Ewijk, B. E, van der Zalm, M. M, Wilbrink, B, van der Ent, C. K. Prevalence and Impact of Respiratory Viral Infections in Young Children With Cystic Fibrosis: Prospective Cohort Study.	8	4.5
Mouse models	Wilke, M, Buijs-Offerman, de Jonge, Hugo R, Scholte, Bob J. Mouse models of cystic fibrosis: Phenotypic analysis and research applications.	12	3.7
CT Scans	Loeve, M, Lequin, M. H, Tiddens, H. A. W. M. Cystic Fibrosis: Are Volumetric Ultra-Low-Dose Expiratory CT Scans Sufficient for Monitoring Related Lung Disease?	10	3.0
Pseudomonas aeruginosa	Wainwright, C. E, Vidmar, S, Colin F, Tiddens, H.A. Effect of Bronchoalveolar Lavage-Directed Therapy on Pseudomonas aeruginosa Infection and Structural Lung Injury etc.	16	2.7
A fumigates colonization	de Vrankrijker, A. M. M.; van der Ent, C. K.; …. Bonten, M. J. M.; Wolfs, T. F. W. Aspergillus fumigatus colonization in cystic fibrosis: implications for lung function?	9	2.3

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

Theme	Article	Citations	
		Total	Mean/Yr
CFTR assay	Dekkers JF, Wiegerinck CL, De Jonge HR, van der Ent CK, Middendorp S, Beekman JM. A functional CFTR assay using primary cystic fibrosis intestinal organoids.	22.5	
Genetica	Okiyoneda T, Veit G, Dekkers JF, Beekman JM, Lukacs GL. Mechanism-based corrector combination restores AF 508-CF TR folding and function.	14.7	
Treatment PPARy	Dekkers JF, van der Ent CK, Kalkhoven E, Beekman JM. PPARy as a therapeutic target in cystic fibrosis	10.0	

APPENDIX

Opinions of international key opinion leaders

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

Expert 1
- Imaging – Rotterdam
- Organoids – Utrecht
- Animal models – Rotterdam
- Clinical (eg exercise, pharmacology) - various

Expert 2
3 groups are very visible.
- The group of Kors van der Ent.
- The group of Harry Heijermann.
- The group of Harms Tiddens. Level: 4-5

These groups are doing very good studies in the field of the lung disease in cystic fibrosis patients bioth children and adult patients. The have published excellent papers on animal experiments, in vitro studies and clinical studies. Especially studies omn high resolution CT scan evaluation of the CF lung pathology has been leading internationally, but also epidemiological studies of spread of the P. Aeruginosa lung infection and characterization of the bacteria are very good. They have also made very good contributio to the improve the use of inhaled and systemic antibiotic based on pharmacokinetic/pharmacodynamic calculations and measurements.
The research group of Bob Scholte is also prominent in the field of basic research, level 3-4.

Expert 3
- Organoids; basic research, drug testing, diagnostic Utrecht team; top of the bill 5
- Lung imaging: Rotterdam H Tiddens team 5
- ICM diagnostic tool, drug testing Rotterdam H Dejonge team 4
- Treatment of CF lung disease The Hague H Heijerman, 3

Expert 4
My expertise in CF is confined to basic science. In my view, the most visible Dutch CF researchers are H. de Jonge (mainly intestinal studies), J. Beekman (nasal CFTR and intestinal organoids), B. Scholte (CF mouse model, airway injury and RNA interference in airway cells) and I. Braakman (molecular biology of CFTR folding). I know there are also excellent physician researchers who focus on clinical aspects and airway infection (Tiddens and van der Ent come to mind) but I do not follow those areas closely.

Expert 5
- Bob Scholte (Mouse models and lung regeneration)
- Jeffrey Beekman (assays in organoids)
- Harm Tiddens (scoring of CT scans)

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

Expert 1

Expert 2

- Gene therapy
- Biological mechanisms
- Development and ageing
- The gastrointestinal area
- Diabetes in CF
- Therapy non-medical

Expert 3

- Pharmacodynamics in CF The Hague 3
- Newborn screening Jeannette Dankert-Roelse 3

Expert 4
Translational research towards CF drug therapies, physiological studies of ion transport by airways, mucobiology.

Expert 5
- Protein biochemistry
- CFTR physiology (very good in the past with Jan Bijman and Henk Veeze)

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

Research performed in the Netherlands in the field of **Cystic Fibrosis**

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

	1	2	3	4*	5	Mean
Phenotyping and Severity	4	4	5		2	3.75
Biological mechanisms	4	2	3		3	3.00
Environment and lifestyle	2	4	2			2.66
Development and ageing	2	2	3			2.33
Prevention	1	1	1			1.00
Diagnosis monitoring	2	4	5			3.66
Therapy medical	3	4	3			3.33
Therapy non-medical	1	2	2		4	2.25
Biobanking	1	1	1		0	1.00
Data management clinical studies	2	4	3		4	3.25
Implementation and care	2					2.00

*** give no relevance**