EUROPEAN SCIENCE FOUNDATION
SETTING SCIENCE AGENDAS FOR EUROPE

Exploratory Workshop Scheme

Standing Committee for the European Medical Research Councils (EMRC)

ESF Exploratory Workshop on

Developmental Origins of Chronic Lung Disease

Feldafing (Germany), 28th April – 1st May 2011

Convened by:

Susanne Krauss-Etschmann, Oliver Eickelberg

SCIENTIFIC REPORT

1. Executive summary

Chronic lung diseases, including chronic obstructive pulmonary disease (COPD), asthma, lung cancer and pulmonary fibrosis are the second leading cause of death in the Western World. Moreover, death rates from chronic lung disease are on the rise, while other leading causes of mortality such as heart disease, some non-pulmonary malignancies or stroke are declining. Despite intensive research efforts, the etiology for the majority of chronic lung diseases remains elusive and only limited therapeutic options are available. In addition, currently available medications give only symptomatic relief, rather than treating the underlying medical condition. However, even with optimized treatment, only established disease will be targeted, while preventive measures - with the exception of never-smoking for some but not all cases of COPD or lung cancer and antenatal steroids for bronchpulmonary dysplasia - are not available. Thus, there is a highly urgent clinical need for the development not only of novel effective therapies but also of preventive strategies.

Several studies suggest that modifications of prenatal and/or early postnatal lung development can have important implications for future lung function and chronic lung disease. Moreover, the risk to develop chronic lung disease may be modified through early exposures during critical developmental windows. This view represents a fundamental change of current pathophysiological concepts and treatment paradigms, and holds the potential to develop novel preventive and/or therapeutic approaches. However, for the successful development of these approaches, key bottlenecks - such as a clear understanding of underlying mechanisms of deviated development as well as the identification and validation of relevant preclinical models to facilitate translational research - need to be overcome.

Accordingly, a three-day Exploratory Workshop was held at the Hotel Kaiserin Elisabeth in Feldafing near Munich, Germany from April 28th – May 1st 2011 with the overall goal to initiate a research consortium, which will collaborate jointly on early developmental determinants of chronic lung disease in the near future. Moreover, the workshop aimed to create the prerequisites for the development of a conceptual scientific framework for further research on the determinants of early pulmonary development associated with later chronic lung disease.

Participation numbered eighteen leading researchers from eight European countries, representing a range of disciplines that covered complementary aspects of developmental origins of chronic lung diseases. These included developmental biology, immunology, cell and molecular biology, genetics, paediatrics, pneumology, and regenerative medicine.
To ensure focused and goal-oriented discussions the participants were asked before the meeting to address the following questions in their talks:

1. What do you consider the most relevant knowledge gaps in your field and with respect to early origins of chronic lung disease?
2. How do you describe your expertise in this context?
3. What additional external expertise do you think should be implemented to close the existing knowledge gaps?

To shorten time to get to know each other, biographic sketches from all participants were circulated prior to the meeting. In addition, the participants met the evening before the program started for an informal get-together.

The program was set up in five sessions: the first two sessions covered basic mechanisms of lung development and genetic factors affecting chronic lung disease, while the remaining session focused on early origins of specific disease entities (COPD, interstitial pulmonary fibrosis and asthma) and early determinants of lung function. The final session addressed tissue-engineering approaches to restore lung tissue. Each session started with a state-of-the-art talk, followed by the single presentations. After each talk, sufficient time was provided for specific questions related to the topic. At the end of each session, participants discussed the most relevant knowledge gaps in the respective fields and the specific requirements to close these gaps. These issues were addressed more comprehensively in single working groups on the second day afternoon.

The general atmosphere was very open and highly interactive. The country surroundings and organized common activities (visit of the Buchheim Museum; guided tour through the monastery of Andechs) further provided ample opportunities for additional informal discussions among participants. All meals were scheduled as part of the program and valuable discussion continued in this setting, too. During the second day, a consensus paper was drafted by two participants and further elaborated during follow-up.

2. Scientific content of the event

The workshop commenced with a presentation of the ESF representative Prof, Richard Imrich who gave a very useful overview about the activities of the ESF and described the various programs offered by the European Science Foundation some of which are supported by other European Commission programs such as Cost Actions. He further pointed out that some programs (e.g. ESF Forward Look) are currently in the progress of re-organization and consequences on further calls have to be awaited.

The following presentations are summarized. For information that is more detailed we would like to refer to the abstracts in the appendix.

The first session covered **basic mechanisms of lung development**. **Christos Samakovlis** gave a state-of-the-art lecture on the development of the drosophila respiratory system. He pointed out that airway maturation of fly embryos occurs through three highly controlled stages: Although several genes are known to be involved in the sequential regulation of these steps, the precise spatial and temporal regulation of epithelial activities during airway maturation remains unknown. 1461 genes, (i.e. 13.4%) were found to be involved in tube maturation, with only 2/3 of them being annotated. Future research is directed at the phenotypic classification of these genes into functional groups related directly to the developmental stages. **Saverio Bellusci** highlighted the essential role of canonical Wnt signaling during lung organogenesis and repair by regulating early progenitor cell fates. He reported differential regulation of central components of the Wnt pathway during embryofetal development and in injury models: while TOPGAL and BATGAL mice demonstrate Wnt signaling in early lung epithelium, BATGAL expression is markedly reduced in more mature lungs but re-induced upon injury. By contrast, Axin2LacZ expression is sustained in embryonic lung and further up-regulated after injury. Moreover, activation of Wnt signaling in parabronchial smooth muscle cells leads to *de novo* expression of Fgf10.

Petra Knaus reported on the molecular mechanism of BMP/TGFß signal transduction and highlighted the multiple levels of fine-tuning this crucial pathway. The mode of receptor activation is regulated by multiple membrane proximal events, as she highlighted by showing a number of biochemical and biophysical approaches. In particular, she presented data on

crosstalk between cGMP and BMP signaling which seems to be aberrant in pulmonary hypertension and under other patho-physiological conditions. Through a comprehensive interactome study, her lab has identified a number of novel disease-related receptor interacting proteins, which might also be relevant for chronic lung disease.

Idiopathic pulmonary fibrosis (IPF) is a fatal disease of unknown etiology and without satisfactory treatment. It is associated with the accumulation of extracellular matrix and fibroblasts in the distal airways. The Hedgehog (HH) pathway is strongly involved in epithelial cells-fibroblasts interaction during fetal lung development. **Arnaud Mailleux** hypothesized that this pathway also plays a key role in epithelium-fibroblast interactions during alveolar repair and lung fibrogenesis. Indeed, his group showed reactivation of the HH pathway in IPF lung tissue. Importantly, a crosstalk between the HH and TGF-β pathways in human lung fibrosis was identified as TGF-β modulated the expression level of key components of the HH pathway in human lung fibrosis. This – together with further data –supports a profibrotic role of the HH pathway in IPF. Moreover, GLI transcription factors were identified as potential therapeutic target for the treatment of IPF.

The second session focused on **heritability of chronic lung diseases.** Estimates from twin studies suggest strong genetic influences where between one and two thirds of the risk of asthma and COPD are attributed to genotype. **Gregory Gibson** made clear that these estimates are strongly confounded by the methods used to control for environmental variables - most notably, smoking. However, the vast majority of the genetic variance remains unexplained, most likely due to the very small attributable risks for each contributing locus. This implies genotype-by-environment (GxE) interactions that themselves are likely to be too modest to be detected in GWAS, yet nevertheless make a substantial contribution to risk. The potential impact of altered growth rates of components of the airways, combined with novel exposures in contemporary urban environments, needs to be considered. A decanalization model for the origins of airway disease was discussed.

Matthias Wjst put forward the question why – despite the multitude of genome-wide disease association - classical genetics do not give the right answers for complex diseases. He suggested that refining phenotype definitions may be more relevant than just increasing sample sizes, and illustrated his thoughts by highlighting several asthma studies. Potential phenotyping approaches include deep sequencing of whole genomes, bisulfite sequencing of various tissues at repeated time points, RNA sequencing from target tissues and novel statistical approaches combining data including GxG, GxE and ExE interaction models to account for the enormous genetic and epigenetic individual variation.

A very simple genetic “variation” is being male or female. Sex differences exist with respect to prevalence, severity and mortality of asthma and COPD. **Dirkje S. Postma** emphasized that environmental exposures may synergise with genetic differences, due to different types of activities, and playing times spent outside between boys and girls. The underpinnings of gender differences may already start *in utero*, where there is significantly different in timing of lung maturation, branching morphogenesis, and production of e.g. surfactants, between both sexes. The small airways in the lung form the largest part of the lung breathing area, and thus contribute very significantly to airway obstruction. Today there is an unmet need to better diagnose and assess the severity of small airway disease and investigate whether these small airways can be specifically targeted with small particle size treatment. It is needed to better assess gender differences in origins of lung development, involvement of the small airways and their interrelationship. The speaker emphasized that we need collaboration between clinicians for childhood and adult respiratory care, biologists,

immunologists, geneticists, studies in animal models and *in vitro* systems to achieve this goal.

A growing body of evidence implicates regulation of gene expressions via microRNAs both in complex human diseases and during development. Since single microRNAs can address key components of complex signaling pathways, they were suggested as attractive therapeutic targets for several clinical conditions. However, insights into specific miRNA functions remain limited. To unravel tissue-specific miRNA functions **Jo Vandesompele** presented an integrative approach, which is based on a multi-level integration of corresponding miRNA and mRNA gene expressions, miRNA target prediction, transcription factor target prediction and mechanistic models of gene network regulation. The predicted miRNA functions are accessible in an interactive online compendium and mining tool of high-dimensional newly generated and published miRNA expression profiles. This "microRNA bodymap" project provides users with a single one-stop data-mining solution and has great potential to become a community resource also for the present consortium.

The Workshop program proceeded with sessions on **specific lung diseases** starting with COPD. **Andrew Bush** stated that cohort studies have established that lung function either tracks or deteriorates, but never improves, after the preschool years. For normal lifelong lung function, the pre-requisites are (a) normal lung function at birth; (b) normal growth in lung function until the adult plateau; and (c) no accelerated deterioration from the plateau. Among several harmful antenatal factors, maternal smoking is the most important factor as it causes structural effects on the developing lung, and alters the fetal immune system, thereby priming the child for a greater susceptibility to viral infections.

An important risk group for future COPD may be preterm infants, who are becoming more frequent with continuously improving survival rates. The speaker highlighted that presence of any of five problems in childhood (maternal or paternal asthma, childhood asthma, maternal smoking and childhood respiratory infections) predicts worse adult lung function, a faster rate of lung function decline, and a greater prevalence of COPD. The speaker emphasized that the time has come to launch an interventional studies. In this respect, he suggested to ask the mother three simple questions:

1. Do you have asthma?
2. Do you smoke?
3. Does the baby's father have asthma?

If the answer to all three is in the affirmative, then the baby is at high risk of COPD. Suggested interventions included 1) Minimising ETS exposure (cotinine measurements) and/or exposure to pollution 2) monitoring weight gain in the first year of life 3) preventing obesity and 4) ensuring optimal Vitamin D status.

The group agreed that - in view of the long observation periods required for COPD - it is mandatory to establish long-term research programs to carry on results from early observations into adulthood.

Although many observations suggest that disease risks for asthma and COPD are established *in utero*, there is a lack of translational models to study the underlying mechanisms. In this respect, **Machteld N. Hylkema** shared exciting news by showing that newborn mice from dams exposed to cigarette smoke during pregnancy have a lower expression of genes, related to the Wnt signaling pathway. Moreover, more airway

remodeling occurred in adult non-smoking offspring from these smoke exposed dams. Preliminary data by a collaborating group (L. Kobzik, Boston, USA), showed altered methylation in the promoter regions of certain genes which are relevant to airway remodelling in human fetal lung samples from smoking as opposed to fetal samples form non-smoking mothers. These data indicate that early life effects, such as maternal smoking, may permanently alter fetal gene expressions through epigenetic modifications, setting the threshold for higher susceptibility to develop asthma and COPD.

In a presentation given on behalf of Janet Stocks and Samatha Sonnappa, who were unable to attend the meeting for personal reasons, **Andrew Bush** emphasized the necessity to distinguish effects of pulmonary disease from those of lung growth and development. However, structural assessments of lung and airway dimensions do not necessarily reflect functional changes in lung growth and development, or vice versa. The choice of lung function testing technique is determined by the region of complex airway structure branching which is being interrogated. In this respect, advantages and disadvantages of the available lung function techniques (spirometry, lung clearace index, DCLO, hyperpolarized helium) were discussed. Notwithstanding, techniques to measure lung function from birth to old age have now been developed which are suitable tools to monitor lung growth during intervention studies.

The following presentation of **Melanie Königshoff** focused on the Wnt/beta-catenin signalling pathway and discussed the involvement of this pathway in lung development and disease. The Wnt/beta-catenin signalling is altered in chronic lung disease, such as idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease. Data presented depicted an important role of Wnt/beta-catenin signalling in epithelial cell repair mechanisms and highlighted that modulation of Wnt/beta-catenin signalling may be a suitable future target for therapy.

Histopathological hallmarks of idiopathic pulmonary fibrosis are alveolar epithelial cell injury and hyperplasia, (myo-)fibroblast activation, increased deposition of extracellular matrix and fibroblasts foci in close proximity with sites of alveolar injury/hyperplasia. So far, the origin of activated (myo-)fibroblasts in IPF is not clear and may involve epithelial-mesenchymal transition (EMT), circulating progenitor cells, local fibroblast pool or a combination thereof.

Oliver Eickelberg discussed basic mechanisms and developmental aspects of pulmonary fibrosis. For example, molecular mediators such as TGF-beta/BMP, Notch and Wnt, all of which are involved pulmonary fibrosis, also play a role in development. In addition, one WNT target gene, WNT-inducible signalling protein-1 (WISP1), is associated with proliferation, cytoprotection, as well as extracellular matrix production. Moreover, blockade of WISP1 improved survival in the bleomycin model of pulmonary fibrosis and might therefore, represent a novel therapeutic target. The speaker proposed that epithelial-mesenchymal transition is not a uniform response to different insults, but may instead entail different mechanisms and outcomes if started in different compartments or by different primary injuries. This view has fundamental consequences on the development of therapeutic strategies. However, a number of questions remain open: thus, it is unclear if complete EMT is required to cause disease and how complete EMT should be defined. Moreover, the precise functional contribution of EMT-derived cells to disease pathogenesis remains to be elucidated.

Guy Brusselle raised the question if genes/genetic loci that have been implicated in lung function in healthy population-based GWAs are also important for the disease COPD and if

so, during which period of life i.e. during lung development and/or growth (foetal life, childhood, adolescence) and/or during adulthood?

In this respect, data from a large collaborative study (CHARGE consortium; ~21.000 individuals) were presented, showing an association of eight loci with reduced FEV1/FVC. As an example, Hedgehog interacting protein was identified, which is important for lung development is also associated with risk for COPD. So far, accelerated decline in lung function has been considered the main event in COPD. This concept has now been challenged since impaired lung growth is also an important contributor to the pathogenesis of COPD. Another layer of gene regulation involves microRNAs: a correlation between sputum microRNAs and FEV1 was observed in COPD patients. Moreover, target genes of the down-modulated microRNA let-7c were enriched in sputa from patients with severe COPD. The concentration of one predicted target, tumor necrosis factor type II, correlated inversely with sputum levels of let-7c. Thus, dysregulation of micro-RNAs in induced sputum and lungs of smokers and patients with COPD may be a central mediator of persistent airway inflammation and remodeling.

The following session focused on **developmental origins of asthma** beginning with a state-of-the art lecture on “Cellular Interactions in Asthma” by **Sven-Erik Dahlén.** The necessity to develop biomarkers for asthma a) to monitor treatment response and b) to determine disease susceptibility was emphasized. Chitinases were discussed as potential biomarkers for severe asthma, but any biomarker is dependent on phenotype stability. An example for a novel pathway that may be exploited for therapeutic purposes are bitter taste receptors, which are not only found on the tongue but are also on airway smooth muscle cells. Agonists such as saccharin, chloroquine and denatonium evoked increased intracellular calcium in ASM in a Gβγ-, phospholipase Cβ and inositol trisphosphate receptor-dependent manner. This would be expected to evoke contraction but unexpectedly caused relaxation of isolated ASM (Deshpande et al, Nature Medicine 2010).

Oxylipins such as eicosanoids are endogenous signaling molecules that are formed from fatty acids by oxygenation. These lipid mediators have been extensively studied for their role in inflammation for many respiratory diseases. The speaker emphasized that profiling of oxylipins will greatly increase our ability to examine cross-talk between biological pathways as well as specific compartments in the body. In turn, this will increase our insight into disease processes and has great potential to identify new biomarkers for disease diagnosis as well as novel therapeutic targets.

Epidemiologic studies e.g. comparing infants delivered by cesarean section with infants born by natural delivery have indicated that early commensal colonization influences the incidence of allergic diseases. However, mechanistic insight how commensal bacteria could affect immune responses is lacking. **Benjamin Marsland** shared exciting new data by showing that hallmark features of allergic airway disease, airway eosinophilia, IgE production and Th2 cytokines are elevated in germ-free (GF) mice after experimental induction of asthma as compared to control specific pathogen–free (SPF) mice. This phenotype was reversible when GF mice were colonized with the commensal flora from SPF mice. Mechanistic insight was given by assessing regulatory immune cells: while numbers of Treg remained unaltered, frequencies of lung alveolar macrophages and plasmocytoid dendritic cells were reduced in GF mice compared to SPF mice after experimental asthma induction. Thus, commensal bacteria attenuate allergic airway inflammation, and this is associated with alterations in the populations and maturation status of lung immune cells.

Little is known about whether patterns of early growth are associated with altered respiratory and immune development. **Graham Roberts** reported new data relating prenatal and infant growth patterns to wheeze and atopy at age 3 years in a large cohort of 1548 children. A rapid growth trajectory during 11 to 19 weeks gestation followed by late gestation growth faltering was shown to be associated with atopy. This suggests that influences affecting fetal growth may also alter immune development. A lower early fetal growth trajectory is associated with non-atopic wheeze, possibly reflecting an association with smaller airways. An association between postnatal adiposity gain and wheeze may partly reflect prenatal influences that cause fetal growth to falter but are then followed by postnatal adiposity gain.

John Holloway discussed a range of evidence that showed that asthma susceptibility was determined by gene-environment interactions *in utero*. For example, genes identified to be asthma susceptibility genes such as ADAM33 are expressed in the developing lung and associated with lung function in early childhood before the onset of clinical asthma. The importance of *in utero* development to asthma was highlighted by studies that show lung function at birth can predict later onset of disease and that maternal environmental exposure during pregnancy is associated with disease incidence in childhood. For example, data showing that maternal acetaminophen (paracetamol) exposure during pregnancy interacts with both maternal and child genetic variation to increase risk of asthma. However, while human genetic and environmental epidemiological studies can identify potential causes of disease, these will require the use of animal models to provide supporting evidence and to investigate biological mechanisms and effectiveness of potential preventative strategies. Novel data was presented showing that in a rat model of developmental programming, altered maternal nutrition lead to a bronchial hyperresponsiveness phenotype in offspring.

Susanne Krauss-Etschmann addressed the potential role of microRNAs in developmental origins of asthma. When studying developmental origins of disease, microRNAs are of particular interest, as single microRNAs can target few key components of distinct gene regulatory pathways in a cell or tissue specific manner and thereby coordinate the temporal and spatial expressions of 100s of genes. Pilot data from a mouse model of maternal genetic asthma predisposition, showed de-regulation of 31 of 641 miRNAs in wildtype offspring asthma prone dams compared to offspring of dams without asthma predisposition. These microRNAs highly targeted the Wnt pathway. This indicates that maternal genetic asthma predisposition is sufficient to alter neonatal miRNA expession during development and might thereby influence lung development.

Clare M. Lloyd explained that although airway remodelling has been associated with chronic asthma, it remains unclear whether it develops as a result of chronic cycles of inflammation in response to allergen or in parallel with allergic lung inflammation. To solve this question, a model of neonatal allergic airway disease was developed by the speakers group, which allows assessing changes in structure and functioning in the context of normal postnatal lung growth & development as well as the maturing immune system. Neonatal mice exposed to allergen soon after birth show AHR and remodelling occurring with Th2 type inflammation, and unlike in a similar adult model of disease, the remodelling and inflammation develop in parallel, rather than sequentially. The speaker pointed out that the route of allergen exposure is highly critical when assessing the contribution of single mediators and underscored the importance of developing mouse models that are relevant to clinical disease phenotypes. The speaker emphasized that disease models need to reflect not only genetic influences, but also environmental influences such as age, diet, infection history and allergen exposure when investigating interactions between resident pulmonary cells and infiltrating immune cells.

In the last session on **tissue engineering** **Paolo Macchiarini** described two tracheal replacement approaches. The first approach is based on a decellularized donor scaffold to be seeded with cells from the recipient in a bioreactor. Here the importance to maintain the basal membrane while avoiding DNA contamination was emphasized. The second approach relies on *in vivo* regeneration where a scaffold is placed at the site of the defect and populated by recipient cells. The latter approach may require application of growth factors to promote migration and differentiation of stem cells in the scaffold.

Summary of scientific discussions

The participants agreed that a major advantage of this Exploratory Workshop was to bring scientists from diverse disciplines together that usually would not meet at scientific conferences. It became clear that each discipline could contribute different tools and knowledge, which opens a number of unique opportunities to understand developmental origins of respiratory diseases. For example it was suggested, to test effects of specific exposures in simple organisms and transfer the results to higher organisms focusing on evolutionary conserved developmental pathways (”smoking flies”). On the other hand, relevant exposures first need to be identified in epidemiological studies. Here, the importance of correct phenotyping was stressed in order to make sure that the right populations and outcomes are being studied.

However, it became also clear during the discussions that not only for establishing collaboration between basic and clinical sciences but also among the different disciplines bridging systems are lacking.

The participants identified a number of important tools that are already available and range from different animal models in different species, genetics in its broadest sense including epigenetics etc. However, there is a lack of tools e.g. for lineage tracing of airway cells to track origin of pathological cell types in disease and beneficial cell types in wound repair. In addition, animal models that allow the study of transgenerational transmission of disease risks are only limitedly available.

At several occasions it was underlined that after years of intense research the time has come to move on from observational cohort studies, the time has come to launch an interventional study.

3. Assessment of the results, contribution to the future direction of the field, outcome

The consortium prioritized the following key areas for future research:

1. The identification of risk factors for adverse lung development

Clinicians and epidemiologists identify early risk factors associated with CLD in later life. These can be tested in models systems to provide the basis for mechanistic studies. A census of existing birth cohorts will help to assess the interaction of genetic and environmental determinants for CLD.

2. The identification of critical developmental windows

Model systems (e.g. drosophila, rodents) allow identifying key developmental windows for modification of disease risks Moreover they allow to test interventions. However, transgenerational models facilitating translational research need to be developed and validated.

3. Identification of vulnerable cell populations and disease causing pathways

Their identification will lead to testable hypotheses and treatment targets for translational studies and generate biomarker signatures for disease risks

4. Correction of aberrant development

Development and evaluation of delivery systems and strategies for targeting of aberrant pathways

During the discussions, it became evident that a number of European clinical and research institutions currently study developmental origins of CLD with adequate national resources for research. However, current efforts are fragmented and lack a comprehensive platform for synergistic collaboration, for sharing common goals and concepts.
In this respect, the following key issues were emphasized:

1. The necessity of a multidisciplinary approach to understand developmental origins of chronic lung diseases.
2. The importance of a stable continuous platform, offering the best chance for future joint collaboration
3. The necessity to create a structured multidisciplinary Research Agenda on early origins of CLD
4. The essential need to develop effective bridging systems between basic and clinical science to ensure that research results are translated in foreseeable time into measurable benefits for the patients

Among several strategies discussed, application for a COST (European Cooperation in Science and Technology) Action was prioritized, as it allows creating a coordinated and highly synergistic translational research program by sharing ideas, resources, protocols and results from experimental and clinical research. This will in turn lead to enhanced scientific and translational output. Moreover, current EU programs do not offer pertinent topics. Accordingly, an application for a COST Action was prepared after the Exploratory Workshop and submitted to the EU (30.9.2011)

On the second day of the meeting, the participants agreed to prepare a consensus paper that was further elaborated during the meeting and is currently in preparation. As an immediate result of the Workshop, an opinion statement paper on the usefulness of spirometry to diagnose of COPD was published (Postma et al “I have taken my umbrella , so of course it does not rain” Thorax 2011 doi:0.1136/thoraxjnl-2011-200758), which highlights that current diagnostic modalities ignore the potential influence of early life in determining adult lung function.

In summary, this Exploratory Workshop provided an outstanding opportunity for sharing results from experimental and clinical research including unpublished data and allowed the formation of a preliminary, highly cross-disciplinary network for future collaboration.

4. Final program

Thursday 28 April 2011,

Afternoon	*Arrival*
18.00 – 20.00	Get together and Buffet dinner, Hotel Kaiserin Elisabeth

Friday 29 April 2011

08.30-08.40	**Welcome by Convenor** **Susanne Krauss-Etschmann** (CPC, Munich, DE)
08.40-09.00	**Presentation of the European Science Foundation (ESF)** **Richard Imrich** (ESF Standing Committee for the European Medical Research Councils - EMRC)
09.00-11.15	**Session 1: Mechanisms of lung development** **Chair: Christos Samakovlis**
09.00-9.45	"**Mechanisms of epithelial morphogenesis" (state-of-the-art)** **Christos Samakovlis** (The Wenner-Gren Institute, Stockholm, Sweden)
09.45-10.15	**"Wnt signalling in the developing lung"** **Saverio Bellusci** (Justus-Liebig-Universität, Gießen, Germany)
10.15 -10.45	*Coffee / Tea Break*
10.45-11.15	**"BMP signaling under physiological and patho-physiological conditions"** **Petra Knaus** (Freie Universität Berlin, Berlin, Germany)
11.15-11.45	**"Sonic hedgehog pathways in interstitial pulmonary fibrosis"** **Arnaud Mailleux** (Université Denis Diderot, Paris, France)
12.15-12.45	**Discussion**
12.45-14.15	*Lunch*
14.15-18.30	**Session 2: Heritability of chronic lung diseases** **Chair: Gregory Gibson**
14.15-14.45	**"Heritability of complex diseases and the lessons from GWAS" " (state-of-the-art)** **Gregory Gibson** (Center for Integrative Genomics, Basel, Switzerland)
14.45-15.15	**"Why classical genetics do not give the answers"** **Matthias Wjst** (Comprehensive Pneumology Center, Munich, Germany)
15.15-15.45	*Coffee / tea break*
15.45-16.15	**"Can we explain sex differences in chronic lung disease"** **Dirkje S. Postma** (University of Groningen, Groningen, Netherlands)
16.15-16.45	**"MicroRNA body map: dissecting miRNA function through integrative genomics"** **Jo Vandesompele** (Gent University Hospital, Ghent, Belgium)

16.45-18.00 **Discussion**

19.00 *Guided Tour at the "Monastery of Andechs" with Dinner*

Saturday 30 April 2011

08.30-12.30 **Session 1: Developmental origins of COPD and fibrosis**
Chair: Andrew Bush

08.30-09.15 **"Is COPD a developmental disease?" (state-of-the-art)**
Andrew Bush (Imperial College London, London, UK)

9.15 – 9.45 **"Maternal smoking and risk of asthma & COPD in offspring"**
Machteld N. Hylkema (University of Groningen, Groningen, Netherlands)

09.45-10.15 **Early life determinants of lung function in health and disease"**
Andrew Bush (Imperial College London, London, UK)

10.15-10.45 *Coffee / Tea Break*

10.45-11.15 **"WNT signaling in COPD and interstitial pulmonary fibrosis"**
Melanie Königshoff (Comprehensive Pneumology Center, Munich, Germany)

11.15-11.45 **"Pulmonary fibrosis: Basic mechanisms and developmental aspects"**
Oliver Eickelberg (Comprehensive Pneumology Center, Munich, Germany)

11.45-12.15 **"Genetic susceptibility in COPD"**
Guy Brusselle (Gent University Hospital, Ghent, Belgium

12.15-12.45 **Discussion**

12.45 -14.15 *Lunch*

14.00-18.00 **Working Groups**

14.00-15.30 **Working Groups 1 -3**

15.30-16.15 *Coffee / Tea Break*

16.15-18.00 **Discussion of results from working groups and on follow-up activities (Moderation Oliver Eickelberg)**

19.00 *Visit of Buchheim Museum and Dinner*

Sunday 1 May 2011

08.30-12.30 **Session 1: Developmental origins of asthma**
Chair: Sven-Erik Dahlén

08.30-09.15 **"Cellular interactions in asthma" (state-of-the-art)**
Sven-Erik Dahlén (Karolinska Institute, Stockholm, Sweden)

09.15-09.45 **"Early immune responses to the environment"**
Benjamin Marsland (Institute of Integrative Biology, Lausanne, Switzerland)

09.45-10.15 **"Determinants of fetal and infant growth on respiratory symptoms"**
Graham Roberts (University of Southampton School of Medicine, Southhampton, UK)

10.15-10.00	*Coffee / Tea Break*
10.00 -10.30	**"Early determinants of asthma pathogenesis"** **John W. Holloway** (University of Southampton School of Medicine, Southhampton, UK)
10.30-11.00	**"Potential role of microRNAs in developmental origins of asthma"** **Susanne Krauss-Etschmann** (Comprehensive Pneumology Center, Munich, Germany)
11.00-11.30	**"Developmental pathways in asthmatic airway remodelling"** **Clare M. Lloyd** (Imperial College London, London, UK)
11.30-12.30	**Discussion**
12.30-14.00	*Lunch*
	Session 2: Tissue engeneering
14.00 -14.30	**"Reprogramming cells for regenerative medicine"** **Paolo Macchiarini** (University Hospital Careggi, Florence, Italy)
14.30-15.00	*Coffee / Tea Break*
15.00-17.00	**Discussion and Summary** (Specification of follow-up acitivities; Preparation of a draft consensus paper)
17.15	*Departure*

5. Final list of participants

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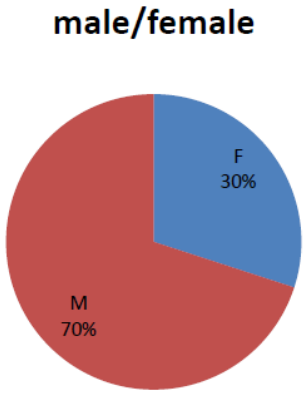
6. Statistical information on participants

The age range of the participants was from 35 years to senior scientists.

Two female participants had to cancel their participation for personal reason shortly before the workshop, resulting in a higher proportion of male participants (Table 1).

Table 1. Gender distribution

	(n)	(%)
F	6	30
M	14	70



The participants came from eight European countries, one participant had meanwhile moved to the USA (Table 2).

Table 2. Geographical distribution

Country	Number of participants
Belgium	2
France	1
Germany	6
Italy	1
Netherlands	2
Switzerland	1
UK	4
USA	1
Sweden	2