SEVENTH FRAMEWORK PROGRAMME

Airway Disease PRedicting Outcomes through Patient Specific Computational Modelling

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Deliverable 10.6

6 month interim report

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Dissemination Level		
PU	Public	**X**
PP	Restricted to other programme participants (including Commission Services)	
RE	Restricted to a group specified by the consortium (including the Commission Services)	
CO	Confidential, only for members of the consortium (including the Commission Services)	

Reporting period: 6 months

1) Number of Work Package: **01**

2) A summary of progress towards objectives and details for each task

Number of deliverable/number of milestone	**Delivery date / due date**	**Describe activities performed to achieve corresponding deliverable/milestone as well as what have been achieved in the reporting period**
MS13 Completion of cross-site validation and baseline CTs and sampling across the cohorts	M 12 / 29/02/12	U-BIOPRED: Due to bureaucratic and legal construct issues many U-BIOPRED sites will only beginning recruiting subjects in September with a goal of completion of baseline visits in July 2012. BTS Severe Asthma: This cohort is on track with Ethics approval expected mid September. EvA: This cohort is on track for recruiting. The only barrier that has been faced is the arrangements of data sharing. Discussions have lead to further understanding and progress is being made toward agreement. Recruiting for the Leicester cohort is ongoing, there are 130 patients recruited for CT. This group of subjects can be used to meet the early requirements for data that can be used the models.
D1.1 Cross sectional Imaging dataset	M 24 / 28/02/13	
MS24 Cross-sectional MRI and lung physiology studies complete	M 24 / 28/02/13	SOPs are currently being collated. The plan is now to amalgamate all the activities into a single Ethics. Aim is to submit Ethics by end of August. There is exisiting Ethics approval for patients to move between the sites the new Ethics will be multi-center. There is existing ethics approval in Leicester for MRI scans. A subset will come to Nottingham for MRI about 10 have come so far. There will be about 50 coming by the end of the year. Forced oscillations will be performed in Leicester. A device has been built in Nottingham and it will be taken to Leicester. This is part of WP 6. Further definition will be obtained regarding the patient cohort being sent from Leicester for the MRI work to be done in Sheffield for WP 6.
D1.2 Proof of concept,	M 48 /	

physiology, and followup dataset	28/02/15	
MS44 Proof-of-concept studies with MRI and lung physiology complete	M 48 / 28/02/15	
MS45 Follow-up CT scans and lung physiology complete	M 48 / 28/02/15	
D1.3 Bronchoscopic sample analysis dataset	M 54 / 31/08/15	
MS50 Acquisition of lung donor and bronchoscopic samples complete	M 54 / 31/08/15	The collection of bronchoscopic tissue in Leicester is ongoing to feed into WP3 in Sheffield. No limitations exist.

3) Highlight clearly significant results

4) If applicable, explain the reasons for deviations from Annex I and their impact on other tasks as well as on available resources and planning

There has been a delay in the recruiting in U-BIOPRED and some challenges for data sharing with other projects. This will mean that milestone MS 13 will not be complete by the end of Feburary 2012. The requirements for data are phased with the large scale data needs come later in the project. Currently with what is available in the Leicester cohort early modeling efforts are proceeding. Consequently the resource expenditure by the clinical centers that re both in AirPROM and U-BIOPRED has been minimal. The mitigation plan for the risk that not enough data is available in the later phases of the project is to focus more on the data that is available in Leicester cohort. While it is most desirable to have pan-European data sets with varying endpoints, the objectives of AirPROM can still be met with the bulk of the data coming from the Leicester cohort.

5) If applicable, explain the reasons for failing to achieve critical objectives and/or not being on schedule and explain the impact on other tasks as well as on available resources and planning

For U-BIOPRED the challenge lies in the construct of a public private partnership. This has lead to the requirement to have complicated legal agreements as there is no one sponsor for the clinical trial. Typically when pharmaceutical companies conduct a trial they are the sponsor. In U-BIOPRED the sponsors are the individual sites, which is complicated by the need to function together under the Grant Agreement. Similarily the ambitions for data gathering are quite high in this project requiring the services of a professional contract research organization which has for similar reasons been difficult to arrange. At the current time these have all been resolved.

For EVA the concern centered around a request to have all partners of both consortia have 2 authors on each manuscript. For the specific modeling papers this is not desirable to those in the modeling field and may indeed limit where the manuscripts can be published. The compromise being reached is that some manuscripts will have many authors while others more modeling focused will have a limited authorship list. This is being arranged for in a supplementary agreement.

Reporting period: 6 months

1) Number of Work Package: **02**

2) A summary of progress towards objectives and details for each task

Number of deliverable/number of milestone	**Delivery date / due date**	**Describe activities performed to achieve corresponding deliverable/milestone as well as what have been achieved in the reporting period**
D2.2.1 Complete omic dataset [existing + new]	M 6 / 31/08/11	SNP genotyping and expression profiling for 250 COPD cases and 250 controls from the EvA cohort is ongoing at the CNG, using the Illumina genotyping and Illumina RNAseq platforms. 30 additional cases will be analysed as part of the Airprom budget. The analysis of the data is being performed by the same group as AirPROM (i.e. CNAG and CNG). The UBIOPRED cohort is currently being recruited (up to 725 subjects) and about 50% of samples are expected to be available in February 2012 (their management board will consider GWAS on all UBIOPRED samples). The means of UBIOPRED sharing of all samples for GWAS as well as combining with AGUSO will be reviewed. Also, Ivo Gut will review the proposal of outsourcing GWAS for UBIOPRED. Discussions harmonizing SOPs and choice of platform have taken place. It will be ideal to have a good comparison between transcriptomics between UBIOPRED and AirPROM. In UBIOPRED the plan is to use xls arrays. There has been discussion about RNAseq as this is the platform of choice of EvA. The first samples will include some test of RNA quality. Within the 12-18 month collection period this will be done for the first batch - if the costs come down in that time frame. If RNAseq is done the comparison issue is less. Currently the samples would be 500 – 600 Euros per array while the cost of RNAseq has just dipped below 700 Euros for 40 million tag-sequences. The data interpretation is on top of this. One could argue that a bigger cost would be comparing two different methods and pulling those together. UBIOPRED would be amenable to

		RNAseq but the budget is an issue. If the arrays are done in 2012 the cost of RNAseq would be the same in cost or maybe lower depending of the evolution of the cost of RNAseq. On the other hand 40 million tag-sequences provide more resolution than arrays. The timing for UBIOPRED could be that it will delay the process. The type of method does not seem to impact the analysis plan for UBIOPRED. Another aspect is using the UBIOPRED SOPs in MedAll for comparison purposes and will be discussed further. The original proposal had planned for the complete omics dataset in 6 month. The genotyping will be done at CNG in 2-3 months, the same for the RNA 100 -200 samples. This is just to produce the data. There will also need to be some work to get the samples to WP 2. Therefore, it is likely the due date will need to be November of December as goal for completion.
MS9 Acquisition of new genome/transcriptome data	M 6 / 31/08/11	BTS Severe Asthma, EvA and U-BIOPRED have provided information on the status of the samples being collected in those consortia via a survey. The information provided is being reviewed.
MS1 Existing genome/transcriptomic/proteome/lipidome datasets integrated in AirPROM knowledge management	M 12 / 29/02/12	Information on each parameter measured within BTS Severe Asthma, EvA and U-BIOPRED has been provided to WP7 via the knowledge management survey.
D2.2.2 Dataset of genome and transcriptomewide analysis	M 24 / 28/02/13	
MS25 Genome analysis complete	M 24 / 28/02/13	
MS26 Transcriptome analysis complete	M 24 / 28/02/13	
MS33 Acquisition of gene sequencing data complete	M 24 / 28/02/13	
MS32 Genetical genomics: genome to expression analysis complete	M 36 / 28/02/14	
D2.2.3 Dataset of combined gene sequencing, genome and transcriptome wide analysis	M 42 / 31/08/14	
MS40 Gene sequencing analysis complete	M 42 / 31/08/14	

3) Highlight clearly significant results

4) If applicable, explain the reasons for deviations from Annex I and their impact on other tasks as well as on available resources and planning

Due to the challenges of sharing samples between consortia, and subject recruitment delays the Deliverable D2.1 Complete omics dataset will not be completed on time. This will not impact the modeling effort as the omics data is planned to input at a later phase, it is more important to understand what types of omics data will be available and this has been achieved. The new projected delivery date of a complete dataset will be September 2012 as U-BIOPRED will not complete recruiting until July 2012. Nonetheless data will be available in 2-3 months time and on a rolling basis for the modeling effort.

5) If applicable, explain the reasons for failing to achieve critical objectives and/or not being on schedule and explain the impact on other tasks as well as on available resources and planning

Reporting period: 6 months

1) Number of Work Package: **03**

2) A summary of progress towards objectives and details for each task

Number of deliverable/number of milestone	**Delivery date / due date**	**Describe activities performed to achieve corresponding deliverable/milestone as well as what have been achieved in the reporting period**
MS6 'black box' model ready for integration	M 4 / 30/06/11	The scale separation diagram is a cartoon description that includes the interactions in the system and what questions need to be to answered.It provides a description that you do not need computational knowledge to understand.'Black box' model constructed and sent on 04 August 2011 to whole consortium for review.
MS8 Micro (WP 3), macro large airway (WP 5), macro small airway (WP 6) models integrated into patient sp	M 6 / 31/08/11	This involves more of the patient side of things for the framework. The link down to genomics level will be more patient specific. Oxford will work from the whole organ level. Amanda and Soder have made contact to work on genotype data. Ongoing discussions have been held between modelers, biologists and clinicians to integrate initial ideas into a patient specific context.
MS14 Integration Individual based models of cells achieved	M 12 / 29/02/12	Primary Cell ex vivo model update: There are two approaches being pursued. 1) Leicester transwell model Consisting of a layer of differentiated epithelial cells (in a transwell) atop a collagen gel embedded with mesenchymal cells (1) Retrieval of ASM cells from collagen gel has been optimised. Time points include 1, 3, 7 & 14 days incubation in gels (3D cell culture). • Previously, only 20% of cells could be retrieved from the collagen gels. • This has now been increased to - 80% for low density gels (those seeded at 62,500cells/ml = 50,000cells/ml) 60% for high density gels (those seeded at 125,000cells/ml = 75,000cells/ml) >> This provides enough cells for analysis by such methods as flow cytometry (2) ASM cells survive culture in collagen gels • Following trypan blue counts, an average of 85% of cells survive following 14 days culture in the collagen gels supplemented with a culture medium that is known to support the growth of epithelial cells. • Cell survival has been confirmed with Annexin V/ PI analysis. >> ASM cells cultured in flasks (2D cell culture) in identical growth medium to those cultured in gels show significant proliferation after 7 days.

		>> As the cells from the gels are still healthy and alive, are cells still being lost upon retrieval – and hence proliferating to a similar degree to those in 2D culture? >> (Further work) ASM cells will be labelled with CFSE and analysed in situ (without digesting the cell) to examine the level of proliferation. (3) ASM Contractile Protein expression is maintained following culture in collagen gels (as previously examined by Heidi Wan) >> (Further work) Time points need to be extended up to 28 days – the amount of time that the mesenchymal cells will be co-cultured with the epithelial cells in order for the epithelial cells to become differentiated. (4) ASM embedded gel contraction with epithelial cells • Non-asthmatic epithelium significantly inhibits the contraction of non-asthmatic ASM cells. • Non-asthmatic epithelium significantly increases the contraction of asthmatic ASM cells. >> Initial analysis suggests that empty transwells do not inhibit the contraction of (600µl sized) ASM-embedded gels. >> (Further work) Unusual contraction patterns are observed when epithelial-seeded transwells are used. Data suggests that the volume of the gel may need to be reduced slightly in order to prevent direct contact (and possible binding of the gel) to the transwells. 2) Nottingham NC3RS Model We are at the early stages of developing an in vitro model of bronchial epithelium with each cell layer (epithelial, fibroblast and immune cells, ASM) cultured on individual scaffold sheets which will then be combined together for co-culture. The co-culture will be carried out within a flow perfusion bioreactor. To date, we have been working on establishing protocols to characterize the ASM, fibroblast and epithelial cells that we will be using so that these are ready to analyse the cells cultured on the scaffolds both in mono and co-culture (protocols are already in place at Nottingham for the immune cells). Initial experiments involving culturing established cell lines of ASM, fibroblast and epithelial origin on the scaffolds have identified scaffold morphologies suitable for the individual cell types and have now to modify scaffold fabrication methodologies slightly to fine tune their characteristics. We will shortly assess primary cell culture on these scaffolds. We have been working closely with Leicester to understand individual cell requirements in terms of culture surface coating (e.g. collagen for epithelial cells) and media composition etc and plan to incorporate their experience into our method development.
MS15 Integration of existing Ex vivo models	M 12 / 29/02/12	
D3.3.1 Validated planar	M 24 /	

epithelial and mesencymal micro-scale model	28/02/13	
MS28 Micro (WP 3), macro large airway (WP 5), macro small airway (WP 6) models integrated into patient sp	M 24 / 28/02/13	
MS34 Integration of multilayered planar model achieved	M 36 / 28/02/14	
MS35 Completion of 3D immunocompetent self-reporting ex-vivo model	M 36 / 28/02/14	
MS39 Multilayed planar model transformed to tubular model	M 40 / 30/06/14	
MS43 Micro (WP 3), macro large airway (WP 5), macro small airway (WP 6) models integrated into patient sp	M 42 / 31/08/14	
D3.3.2 Validated planar multi-layered micro-scale model	M 48 / 28/02/15	
D3.3.3 Validated Tubular micro-scale model	M 52 / 30/06/15	
D3.3.4 Ex vivo models platform	M 54 / 31/08/15	
D3.3.5 Validated integrated micro-scale airway model (shared with WP 8)	M 54 / 31/08/15	

3) Highlight clearly significant results

'Black box' model constructed and sent on 04 August 2011 to whole consortium for review.

4) If applicable, explain the reasons for deviations from Annex I and their impact on other tasks as well as on available resources and planning

5) If applicable, explain the reasons for failing to achieve critical objectives and/or not being on schedule and explain the impact on other tasks as well as on available resources and planning

Reporting period: 6 months

1) Number of Work Package: **04**

2) A summary of progress towards objectives and details for each task

Number of deliverable/number of milestone	**Delivery date / due date**	**Describe activities performed to achieve corresponding deliverable/milestone as well as what have been achieved in the reporting period**
MS2 Standard interfacing description and setup between the software components	M 3 / 31/05/11	A workflow document was composed by Ian Jones from Ansys. This document describes the workflow in WP 4 and will be used as a means of defining the work going forward. Materialise has provided feedback on this document and will undertake efforts to more clearly indicate where information is still missing
MS3 Patients identified from predefined subgroups to generate mesh for 1st cycle CFD	M 3 / 31/05/11	This has been done by Sumit Gupta and sent to Catilin Fetita and Materialise who have created initial meshes. Materialise has provided more detailed meshes which were outputted in a native Fluent format. On the demand of Kelly Burrowes (WP6) , we have provided 3D reconstruction of separate lung lobes. Segmentation of lung lobes will be needed for accurate CFD analysis. Currently this process involves manual interaction which will be further automated. The outlets of the airways were named based the Ikeda nomenclature, allowing to more easily place boundary conditions. A first automated labeling tool was created for this purpose.
D4.4.1 Unified framework integrating the computational tools for rigid large airway modeling	M 6 / 31/08/11	This deliverable will be delayed. This requires frequent integrative interaction and over the summer months that has not been easily achievable. A mitigation plan has been put into place (see below)
MS19 Software optimised for modeling compliant airway walls	M 18 / 31/08/12	
D4.4.2 Integrated framework for compliant large airway wall modelling	M 24 / 28/02/13	
MS31 (WP4) Patients identified from predefined subgroups to generate mesh for 2nd cycle CFD	M 26 / 30/04/13	
MS42 (WP4) Patients identified from predefined subgroups to generate mesh for 3rd cycle CFD	M 38 / 30/04/14	

MS41 Integration of software tools with cloud infrastructure: to facilitate high throughput and automation	M 42 / 31/08/14	This needs to be defined after the files between the models are identified. We are planning to trial run this in a computing cluster - it is a next step project after month 48 or so. There is a need to integrate it with WP 7 and it requires some information from this work package. We do have questions on sizes and types of files for this workflow. It will be interesting to learn the number and size of files. Need to discuss further how data will be actioned - one big file at once or searched via a metafile. This will require a list of the most important questions to be sent out (e.g. input to flow how many and size of DiCOM files). Those questions have been answered by Materialise.
D4.4.3 High throughput semi-automated validated framework for large airway modelling	M 48 / 28/02/15	

3) Highlight clearly significant results

4) If applicable, explain the reasons for deviations from Annex I and their impact on other tasks as well as on available resources and planning

5) If applicable, explain the reasons for failing to achieve critical objectives and/or not being on schedule and explain the impact on other tasks as well as on available resources and planning

The delay in Deliverable 4.1 does have the potential to delay subsequent work as it will serve as a guide to how the various processes will integrate. To date it has been less of an issue. There has been some initial work on the framework, what remains is the answering of some open questions. The mitigation plan is to have frequent teleconferences to facilitate the completion of the framework in a short time frame – 2 months. Thus the planned deliverable date would now be 31/10.

Reporting period: 6 months

1) Number of Work Package: **05**

2) A summary of progress towards objectives and details for each task

Number of deliverable/number of milestone	**Delivery date**	**Describe activities performed to achieve corresponding deliverable/milestone as well as what have been achieved in the reporting period**
MS3 WP5 Pateints identified from predefined subgroups to generate mesh for 1st cycle CFD	M 3 / 31/05/11	This has been done by Sumit Gupta and sent to Catilin Fetita and initial meshes have been generated. There will be a selection of files (10-20 MBs) sent by Leicester and Warwick. They will also be put online.
MS8 Micro (WP 3), macro large airway (WP 5), macro small airway (WP 6) models integrated into patient sp	M 6 / 31/08/11	The 'black box' model was drafted by Rod Smallwood and Kelly Burrowes and was circulated on 04 August 2011 for comment and input from all.
MS23 Compliant walls incorporated	M 24 / 28/02/13	
MS28 Micro (WP 3), macro large airway (WP 5), macro small airway (WP 6) models integrated into patient sp	M 24 / 28/02/13	
D5.5.1 CFD cross sectional dataset using integrated rigid wall model	M 25 / 31/03/13	
MS30 MRI velocitometry data analyzed and ready for validation	M 25 / 31/03/13	
MS31 Patients identified from predefined subgroups to generate mesh for 2nd cycle CFD	M 26 / 30/04/13	
MS36 Experimental rigid wall prototype data analyzed and ready for validation	M 36 / 28/02/14	
MS42 Patients identified from predefined subgroups to generate mesh for 3rd cycle CFD	M 42 / 31/08/14	
MS43 Micro (WP 3), macro large airway (WP 5), macro small airway (WP 6) models integrated	M 42 / 31/08/14	

into patient sp		
D5.2 CFD longitudinal dataset using integrated rigid and compliant wall model	M 48 / 28/02/15	
MS46 Experimental compliant wall prototype data analyzed and ready for validation	M 48 / 28/02/15	
D5.3 Validated large away 'macro-scale' model	M 54 / 31/08/15	

3) Highlight clearly significant results

4) If applicable, explain the reasons for deviations from Annex I and their impact on other tasks as well as on available resources and planning

5) If applicable, explain the reasons for failing to achieve critical objectives and/or not being on schedule and explain the impact on other tasks as well as on available resources and planning

Reporting period: 6 months

1) Number of Work Package: **06**

2) A summary of progress towards objectives and details for each task

Number of deliverable/number of milestone	**Delivery date**	**Describe activities performed to achieve corresponding deliverable/milestone as well as what have been achieved in the reporting period**
MS8 WP6 Micro (WP 3), macro large airway (WP 5), macro small airway (WP 6) models integrated into patient sp	M 6 / 31/08/11	The 'black box' model was drafted by Rod Smallwood and Kelly Burrowes and was circulated on 04 August 2011 for comment and input from all. This involves more of the patient side of things for the framework. The link down to genomics level will be more patient specific. Oxford will work from the whole organ level. Amanda and Soder have made contact to work on genotype data. Salman Siddiqui has supplied information to Kelly Burrowes as to what measurements they will provide and their clinical relevance.
MS16 Cross site validation of Gas washout phantom	M 12 / 29/02/12	Preliminary studies on INNOCOR to take place in 11.2011 in Sweden.
MS10 Gas washout phantom developed	M 21 / 30/11/12	Water phantom developed by Per Gustaffson: Preliminary studies on INNOCOR to take place in 11.2011
D6.1 Dataset using existing 'macro-scale' small airway models of lung impedance, alveolar inflammation, g	M 23 / 31/01/13	Manuscript prepared examining the repeatability and ability to localize the site and nature of small airway disease in asthma/health, of putative small airway biomarkers in WP6: to be circulated to co-authors prior to submission.
MS28 WP6 Micro (WP 3), macro large airway (WP 5), macro small airway (WP 6) models integrated into patient sp	M 24 / 28/02/13	
MS22 MRI and physiology cross sectional dataset analyzed	M 36 / 28/02/14	See M23: Data available and analysed for n=27 asthma, n=15 controls (MBW, IOS, He3-MRI, Static lung volumes/diffusion, FENO)
MS36 Experimental rigid wall prototype data analyzed and ready for validation	M 36 / 28/02/14	
MS43 WP6 Micro (WP 3), macro large airway (WP 5), macro small airway (WP 6) models integrated into patient sp	M 42 / 31/08/14	
D6.2 Dataset using novel small airway 'macro-scale' models	M 48 / 28/02/15	
MS37 Novel small airway integrated models	M 48 / 28/02/15	

developed		
MS46 WP6 Experimental compliant wall prototype data analyzed and ready for validation	M 48 / 28/02/15	
MS47 MRI and physiology proof of concept dataset analyzed	M 48 / 28/02/15	Proof of concept study on 'drug x' in the late stages of contract negotiation. This will be a 3 month placebo controlled trail with AirPROM WP6 data captured at baseline and 3/12: subject to agreement from Jim Wild and drug company.
MS48 Xenon measurements	M 48 / 28/02/15	
MS49 Prototype of platform for gas analysis and low frequency FOT	M 48 / 28/02/15	An FOT device has been built in Nottingham and is ready to be shipped to Leicester for testing. An FOT SOP has been drafted by SS/JOB for AirPROM.
D6.3 Platform for gas analysis and low frequency FOT ready to be commercialized	M 54 / 31/08/15	
D6.4 Report on comparison of He3 with Xenon measurements	M 54 / 31/08/15	
D6.5 Validated small airway 'macro-scale' model	M 54 / 31/08/15	

3) Highlight clearly significant results

(i) Custom FOT device built in Nottingham – this is the first step for completing deliverable 6.6.3
(ii) Manuscript on non-invasive small airway biomarkers prepared and to be submitted to AJRCCM.
(iii) ATS/ERS consensus statement on gas washout developed by Per Gustaffson/Paul Robinson to be presented at the ERS 2011 and subsequently published.

4) If applicable, explain the reasons for deviations from Annex I and their impact on other tasks as well as on available resources and planning

5) If applicable, explain the reasons for failing to achieve critical objectives and/or not being on schedule and explain the impact on other tasks as well as on available resources and planning

Reporting period: 6 months

1) Number of Work Package: **07**

2) A summary of progress towards objectives and details for each task

Number of deliverable/number of milestone	**Delivery date**	**Describe activities performed to achieve corresponding deliverable/milestone as well as what have been achieved in the reporting period**
D7.1 Specification document	M 6 / 31/08/11	This deliverable is 80% complete but still needs the collection of some specific inputs from various work packages to be finalized. It is projected to be complete by the end of September.
MS11 Initial database infrastructure	M 6 / 31/08/11	A prototype to semantically describe connections between different models as well as experimental data for input and as output data has been provided. There will be a continual process of feedback on the interface.
MS17 Framework populated with high priority legacy data and public resources	M 12 / 29/02/12	This involves technical integration of federated sources, while the other resources are technical databases. This work is underway with a provision of text mining references. Integration of legacy CT scans is currently being planned.The issues are: what resources are available; data analysis; the models; and defining how they need to integrate. In terms of data flow: need support from WP 4 and 5 when working on CT scans (there is software provided by Fluidda and Ansys as well as PSNC). Biomax can define the requirements. Also, there will need to be some data flow between WP 1 to modelers.
D7.2 Semantic data model with mapped resources and initial data flow	M 18 / 31/08/12	
MS20 DataSHaPER rules and mappings	M 18 / 31/08/12	
MS27 Cloud based computation support	M 24 / 28/02/13	
D7.3 Algorithm integration for automatic data flows	M 30 / 31/08/13	
D7.4 Semantic mapping of developed models	M 38 / 30/04/14	
D7.5 Final knowledge base	M 60 / 29/02/16	

3) Highlight clearly significant results

A detailed knowledge management survey was conducted to obtain details of what data inputs and outputs are needed in the process of building models. This both provided the necessary information and built up the understanding of what is needed and how it will all integrate moving forward.

4) If applicable, explain the reasons for deviations from Annex I and their impact on other tasks as well as on available resources and planning

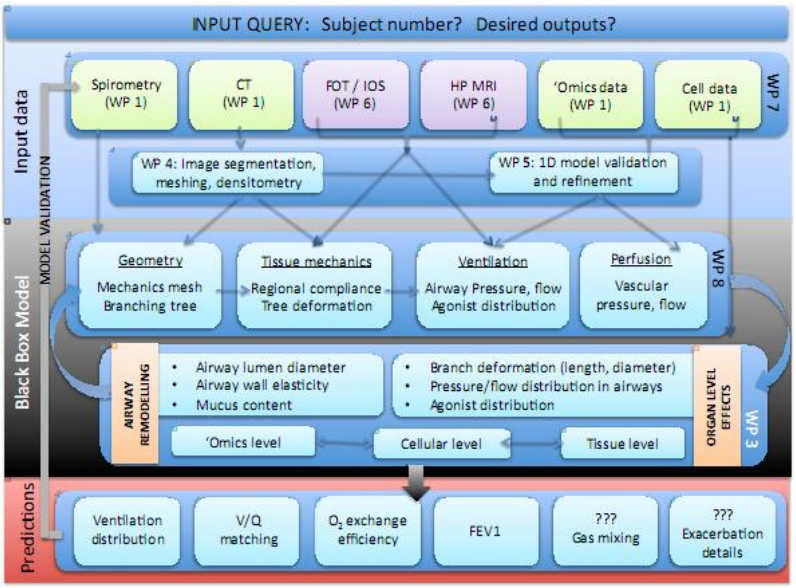
5) If applicable, explain the reasons for failing to achieve critical objectives and/or not being on schedule and explain the impact on other tasks as well as on available resources and planning

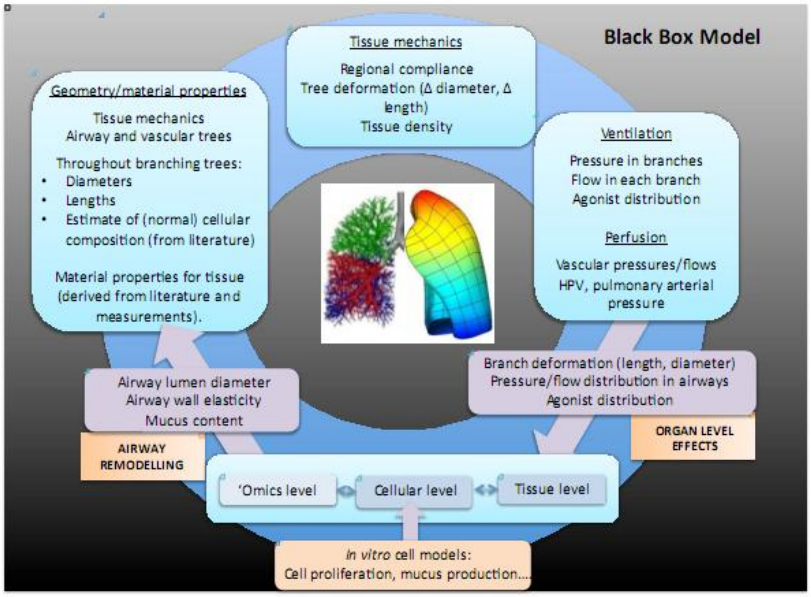
D 7.1 will be delayed by one month. This is largely due to the difficulty in getting final input during the summer months. This will have no impact on other tasks as its main purpose is to provide information for use in developing the database model which is already in progress. It will also serve to highlight areas of integration moving forward and a one month delay is not of consequence.

Reporting period: 6 months

1) Number of Work Package: **08**

2) A summary of progress towards objectives and details for each task

Number of deliverable/number of milestone	**Delivery date / due date**	**Describe activities performed to achieve corresponding deliverable/milestone as well as what has been achieved in the reporting period**
MS6 'black box' model ready for integration	M 4 / 30/06/11	'Black box' model constructed and sent on 04 August 2011 to whole consortium for review.
MS8 WP8 Micro (WP 3), macro large airway (WP 5), macro small airway (WP 6) models integrated into patient specific model	M 6 / 31/08/11	The 'black box' model was drafted by Rod Smallwood and Kelly Burrowes and was circulated on 04 August 2011 for comment and input from all. This is a starting point for model integration but will develop over time. We have put together a schematic of how we see the models fitting together - as the first, simplest step. It consists of 2 diagrams - the first one showing what input information we hope to parameterise the models with (to start with) and some of the suggested output variables. 

		 **The computational framework…?** • As the simplest first start we (UOXF) can provide (to Bindi/Rod's group) a file (or files) that contains information about the conducting airway tree: – Node file containing: x, y, z coordinates. – Element file containing nodal connectivity. – Field file containing: • Radius (unstrained or initial radius solution or both?); • Initial solutions of airway pressure and flow rates (at which part of the breathing cycle? Or provide mean +/- SD?) • Parenchymal loads – Bindi what values exactly do you want? i.e. length, diameter deformation? Stresses exerted on airway? At which part of the breathing cycle or use mean? • Etc - this will evolve over time.... Or depending on run times, model complexity etc– could we call Bindi/Rod's code remotely? Or plan for this in future? • Cell-tissue level computations done on selected airways and the following information sent back to Oxford: – Airway radius, airway wall elasticity etc (this will evolve).... • Whole organ model to resolve for ventilation and tissue deformation. If solutions change by xx amount, send new files for further computations at cell/tissue level.
MS21 First iterative cycle model integration workshop held	M 18 / 31/08/12	A preliminary F2F meeting took place in Nottingham on 7th June 2011 to discuss models and clinical outcomes. This will provide the basis for the integration workshop in a year's time.
D8. 5 Report on model integration workshop	M 19 / 30/09/12	
MS28 WP8 Micro (WP 3), macro large airway (WP 5), macro small airway (WP 6) models integrated into patient specific model	M 24 / 28/02/13	
MS29 Cross sectional statistical modelling at	M 24 / 28/02/13	

individual scales in parallel with WP 2 completed		
D8. 1 Dataset multi-scale statistical modelling of cross-sectional data	M 36 / 28/02/14	
MS38 Longitudinal statistical modelling at individual scales in parallel with WP 2 completed	M 36 / 28/02/14	
MS43 WP8 Micro (WP 3), macro large airway (WP 5), macro small airway (WP 6) models integrated into patient specific model	M 42 / 31/08/14	
D8. 2 Dataset statistical modelling of longitudinal data	M 48 / 28/02/15	
D8.8.3 'Macro-scale' computational airway model: validated patient specific image functional models	M 48 / 28/02/15	
D8. 4 'Multi-scale' patient specific airway model: validated and integrated 'macro' and 'micro' model	M 58 / 31/12/15	

3) Highlight clearly significant results

'Black box' model consisting of a series of diagrams highlighting inputs and outputs of the various models and how they interact was constructed and sent on 04 August 2011 to whole consortium for review. This will provide the basis for further integration discussions.

Mesh of a single lung has been created and normal tissue deformation predicted using the Oxford Chaste software. A new model of ventilation is being developed and preliminary solutions will soon be available from this model.

4) If applicable, explain the reasons for deviations from Annex I and their impact on other tasks as well as on available resources and planning

5) If applicable, explain the reasons for failing to achieve critical objectives and/or not being on schedule and explain the impact on other tasks as well as on available resources and planning

Reporting period: 6 months

1) Number of Work Package: **09**

2) A summary of progress towards objectives and details for each task

Number of deliverable/number of milestone	**Delivery date**	**Describe activities performed to achieve corresponding deliverable/milestone as well as what have been achieved in the reporting period**
D9.9.1 Video describing consortium approach	M 6 / 31/08/11	Anne-MarieWish circulated the animatic for the video as well as the image stills. On track to have video ready live on the website in the first week of September. A file of the storyboard and of the video still is attached. The video is a two minute overview of the project that takes the viewer through the current situation of severe asthma treatment, and the aims and approach of the project.
MS7 External facing website	M 6 / 31/08/11	Anne-Marie Wish collating the written sections which will then be put on-line. The website has been created and information is being uploaded. An offline version of the website has been site via a secure site to all WP members, you can view this via the link and login details below. The Website will go live in the first week of September. http://www.airprom.european-lung-foundation.org/ Login = airprom Password = 383zH
MS12 Position paper describing approach submitted	M 9 / 30/11/11	
D9.9.4 White papers on approach	M 12 / 29/02/12	
MS18 First living lab workshop	M 12 / 29/02/12	The first workshop is secured as a post graduate course in the ERS Congress 2012, with topics and speakers confirmed.
D9.9.2 Report on foundation living lab workshops	M 14 / 30/04/12	
D9.9.6 Interim Prospectus plan	M 30 / 31/08/13	
D9.9.3 Report on patient specific model living lab workshops	M 42 / 31/08/14	
MS51 Exploitation meeting	M 54 / 31/08/15	Exploitation Committee established and held first meeting on 02 August 2011 via TC. Aim to hold quarterly meetings at first and BioSci Consulting will Chair. Next TC will be held in November 2011 would be the next TC. An exploitation committee Charter has been drafted and adopted. An informal face to face meeting will also take place during the ERS conference.
D9.9.5 White paper on patient specific model	M 60 / 29/02/16	
D9.9.7 Prospectus/exploitation	M 60 / 29/02/16	

plan		

3) Highlight clearly significant results

Video describing the consortium's approach and the external facing website have been 95% produced (see deliverable report, and attached description of the website)

Exploitation Committee established and held first meeting on 02 August 2011 and Charter was adopted. (see attached Charter)

4) If applicable, explain the reasons for deviations from Annex I and their impact on other tasks as well as on available resources and planning

5) If applicable, explain the reasons for failing to achieve critical objectives and/or not being on schedule and explain the impact on other tasks as well as on available resources and planning

Reporting period: 6 months

1) Number of Work Package: **10**

2) A summary of progress towards objectives and details for each task

Number of deliverable/number of milestone	**Delivery date**	**Describe activities performed to achieve corresponding deliverable/milestone as well as what have been achieved in the reporting period**
D10.2 Reports on advances in the field	M 1 / 31/03/11	This has been completed and includes sections on modeling, statistical modeling and sequencing and genotyping technologies.
MS4 Collaboration Platform established	M 3 / 31/05/11	AirPROM on-line platform set-up by BioSci Consulting and holds contact details for all consortium members, minutes from TCs and F2F meetings, and documents (e.g. SOPs, presentations), which are all searchable.
D10.11 Next generation online collaboration platform	M 4 / 30/06/11	The Collaboration Platform has been established and is in use by the consortium for holding files, tracking actions, and registering minutes in a structured fashion.
MS5 Organizational meeting convened	M 4 / 30/06/11	Kick-off meeting held in Leicester on 07 and 08 April 2011 with good attendance from all WPs.
D10.6 month interim report	M 6 / 31/08/11	Reports complied from all WPs in August 2011.
D10.7 18 month interim report	M 18 / 31/08/12	
D10.8 30 month interim report	M 30 / 31/08/13	
D10.9 42 month interim report	M 42 / 31/08/14	
D10.10 54 month interim report	M 54 / 31/08/15	
D10.1 Reports on yearly meeting	M 60 / 29/02/16	
D10.3 Reports on strategic advisory board input	M 60 / 29/02/16	
D10.4 Reports on Ethics and safety board meetings	M 60 / 29/02/16	

3) Highlight clearly significant results

Advances in the field report completed and online collaboration platform established. In addition each work package is having monthly teleconferences separately or in conjunction with a closely allied work package and a monthly Scientific Board teleconference has been established.

4) If applicable, explain the reasons for deviations from Annex I and their impact on other tasks as well as on available resources and planning

5) If applicable, explain the reasons for failing to achieve critical objectives and/or not being on schedule and explain the impact on other tasks as well as on available resources and planning

Appendix I - report of organizational meeting

Attendees

David Laszlo Tarnoki MD	SE - Semmelsweis University
Adam Domonkos Tarnoki MD	SE - Semmelsweis University
Susanna Palkonen	E.F.A. - European Federation of Asthma Associations
Dr Ekaterina Mirgorodskaya	SU-DART - Vastra Gotalands Lans Landsting
Louise Wain	ULEIC - University of Leicester
Wim Vos	FLUID - FluiDA nv
Igor Chernyavsky	UNOTT - University of Nottingham
Vimal Raj	
Anthony Rowe	Imperial - Imperial College London
Andrew Leishman	BC - BioSci Consulting
Liam Heaney	QUB - The Queen's University of Belfast
Dr David Parr	UHCW - University Hospitals Coventry and Warwickshire
Neil Fitch	BC - BioSci Consulting
Nisha Rana	ULEIC - University of Leicester
Mitesh Pancholi	ULEIC - University of Leicester
Ian Jones	AUL - ANSYS UK, Ltd.
Christopher Newby	ULEIC - University of Leicester
Peter Sterk	AMC - University of Amsterdam
Dhananjay Desai	ULEIC - University of Leicester
Sherif Gonem	ULEIC - University of Leicester
Beverley Hargadon	ULEIC - University of Leicester
Amisha Singapuri	ULEIC - University of Leicester
SHAILENDRA SINGH	ULEIC - University of Leicester
Carolina Walker	ULEIC - University of Leicester
Ruth Saunders	ULEIC - University of Leicester
Selina Finney	ULEIC - University of Leicester
Chris Brightling	ULEIC - University of Leicester
Riccardo Polosa	UNICT - University of Catania, Italy
Imre Barta	OKTPI - National Koranyi Institute
Andrew Leishman	BC - BioSci Consulting
Afsaneh Maleki-Dizaji	USFD - University of Sheffield
Dieter Maier	BIOMAX - Biomax Informatics AG
Anne-Marie Wish	ELF - European Lung Foundation
Pippa Powell	ELF - European Lung Foundation
Richard Clayton	USFD - University of Sheffield
Andreas Fritz	BIOMAX - Biomax Informatics AG
Rod Smallwood	USFD - University of Sheffield
Bindi Brook	UNOTT - University of Nottingham
Sumit Gupta	ULEIC - University of Leicester
John Owers-Bradley	UNOTT - University of Nottingham
Charles Auffray	ULEIC - University of Leicester
Juan Parra-Robles	USFD - University of Sheffield
Jim Wild	USFD - University of Sheffield
Justin Penrose	AUL - ANSYS UK, Ltd.
Kelly Burrowes	UOXF.BL - University of Oxford
Per Gustafsson	SU-DART - Vastra Gotalands Lans Landsting

Mònica Bayés	FPPCB - Fundacio Privada Parc Cientific de Barcelona
Loems Ziegler-Heitbrock	HMGU - Helmholtz Zentrum München German Research Center for Environmental Health
Yongmann Chung	UOW - University of Warwick
Catalin FETITA	Institut Telecom - GET/ Institute National des Telecommunications, Department ARTEMIS
Dr Gregory J Gibbons	UOW - University of Warwick
Salman Siddiqui	ULEIC - University of Leicester
Ariel Oleksiak	PSNC - Instytut Chemi Bioorganicznej Pan
Marcin Adamski	PSNC - Instytut Chemi Bioorganicznej Pan
Bart Veeckmans	MATE - Materialise N.V.
Roelinde Middelveld	KI -Karolinska Inst,Sweden
Roel Wirix-Speetjens	MATE - Materialise N.V.
Scott Wagers	BC - BioSci Consulting
Oliver Jensen	**UNOTT - University of Nottingham**
Felicity Rose	**UNOTT - University of Nottingham**

Agenda

Day 1 April 7th University of Leicester - Charles Wilson Building 2nd Floor

930 Registration & Tea/Coffee

1000 Introduction - plan for the meeting and overview WP leads 5 mins

1100 Organization and progress monitoring

1130 Financial reporting aspects - review of budgets what they and what they are for

1230 Lunch - 4th floor

1330-1500 Work Packages meet - tasks and details first 6 months

- 1st Floor Park Lounge
- 2nd Floor Belvoiur City Annex
- 2nd Floor Belvoir City Lounge
- 2nd Floor Belvior Park Annex
- 2nd Floor Belvior Park Lounge
- WP 3 and 8
- WP 4 and 5
- WP 1 and 2
- WP 7 data management
- WP 6
- WP 9

1500 Tea & Coffee Break

1530 Work Groups report - tasks and details first 6 months decisions taken

1700 Overview of progress - plan for next day

1800 adjourn

1930 Dinner at The Belmont Hotel - Rowan Room Ground Floor

Work Package Breakouts

- Review 6 month milestone deliverables
- Review 6 month tasks
- Add tasks as needed
- Identify barriers
- Face to face meetings
- Review presentation to group

Provide a slide for Day 2 discussions for:

- Intellectual Property Plan
- Model integration across consortium
- Quality plan - SOPs etc
- Data management

Day 2 April 8th The Belmont Hotel- Rose Room

745 Tea & Coffee on arrival

800 Intellectual Property Plan

900 Model integration across consortium - lead by WP 8

1000 Tea & Coffee Break

1030 Continue Model integration across consortium

1200 Quality plan - SOPs etc

1230 Lunch

1330-1500 Data management - lead by WP 7

1500 General Assembly

agree in principle of data sharing

newly identified changes to plan

linking with MRC COPD consortium

1600 adjourn

Tea & Coffee served

Notes from AirPROM annual meeting 2011

Elements listed from synrgy platform match project tasks, milestones and deliverables from final proposal.

WP10
D10.2 add in the advance mentioned by Rod Smallwood
10.2.1.a Version 1.0 of platform established
Platform presented at annual (kick off) meeting
Other: Review of progress – Planning face to face meetings

WP1
1.1 Barriers identified; CT harmonization, Ethics approval, Quality, IP and data sharing
1.1.1 Action – follow up UBIOPRED CT scans
1.1.1 Identify new regular time for WP1 TC's
1.1.3 Action – Clarify data legal ownership between AirPROM, EVA and UBIOPRED

WP2
D2.1 Omic dataset will not be completed in 6 months, however there could be a improvement in the data analysis
2.1 Barriers identified: Harmonisation of RNA extraction and storage protocol; Alveolar NO measurments; Necessity for four baseline scans from EVA for normal controls (all scans types will be needed to see if CFD can be done.
2.3.1 Eva data: Blood; Variants 3024972non dbSNP variants 158840 Deleterious 1028BR Epithel Variants 994394non dbSNP variants 161754 Deleterious 1028BR Epithel mpileup Variants 116non dbSNP variants

WP3 – see WP2

WP4
M2: Word document to be made with tables describing standard interfacing between the software components each step described by respective partner with final integration of document by WP 4 lead

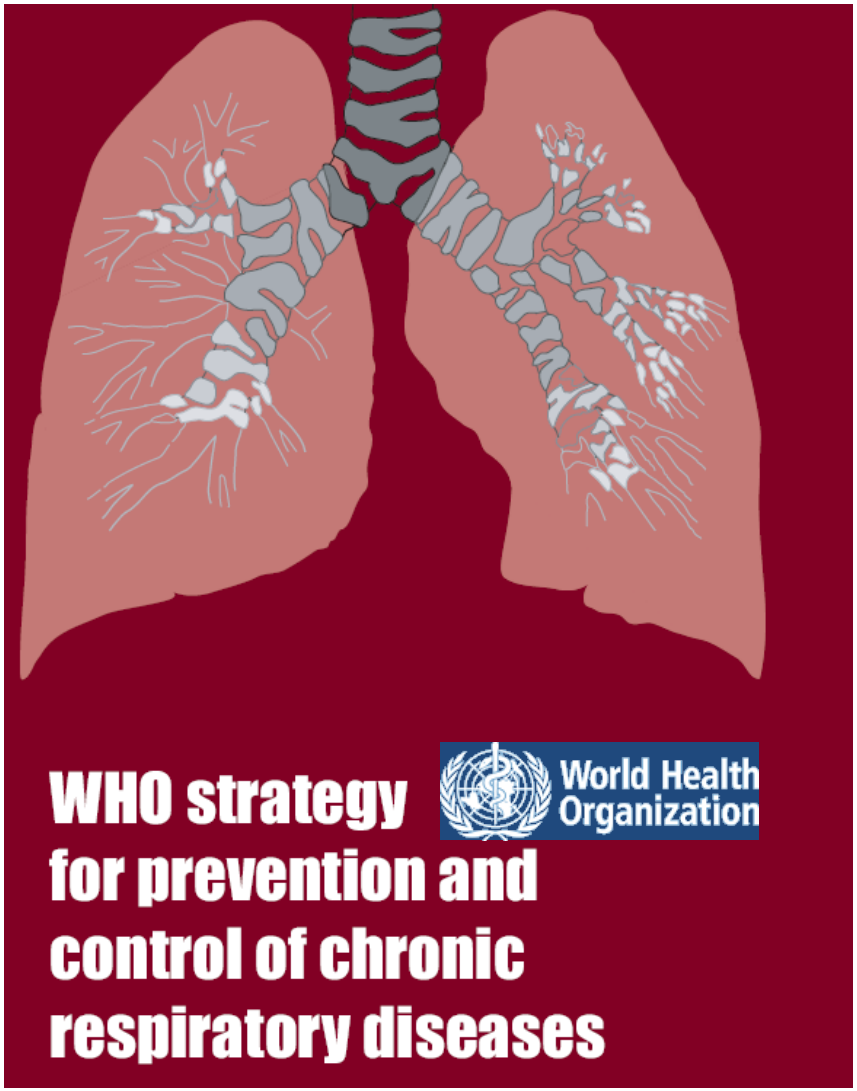
WP7
7.3.4 Link up with Anthony Rowe regarding the process in UBIOPRED for direct data integration (Dieter Maier)
7.5 Barriers identified: Data that is entered into the analysis needs to be clarified; process of input of model parameter information into the system needs to be established.

WP8
8.1 Barrier identified: software exploitation regarding repository for models
M6 Black box model starts with just epithelium
8.4 Barriers identified: Definition of a model; Ability to integrate software as well as the models; Need to produce descriptions of the models that allow automatic connections; defining clinically important parameters for a model; models should not be open because it is then not guaranteed that they are backwards compatible; communication between different groups of people

WP9
9.1 Action: Make contact with Idiko regarding PG course
9.2.1 Action: Add living labs course structure to organ meeting agenda (S.Wagers)
Action: Follow up on creation of logo (S.Wagers)
9.2.2 Action: Identify video illustrator (N.Fitch)
9.2.4 Action: Contact ELF press officer for draft press release/circulate
9.4 Barrier: Timely sign off of addendum and CA

Slides to be here as PDF

Airway Disease PRedicting Outcomes through Patient Specific Computational Modelling

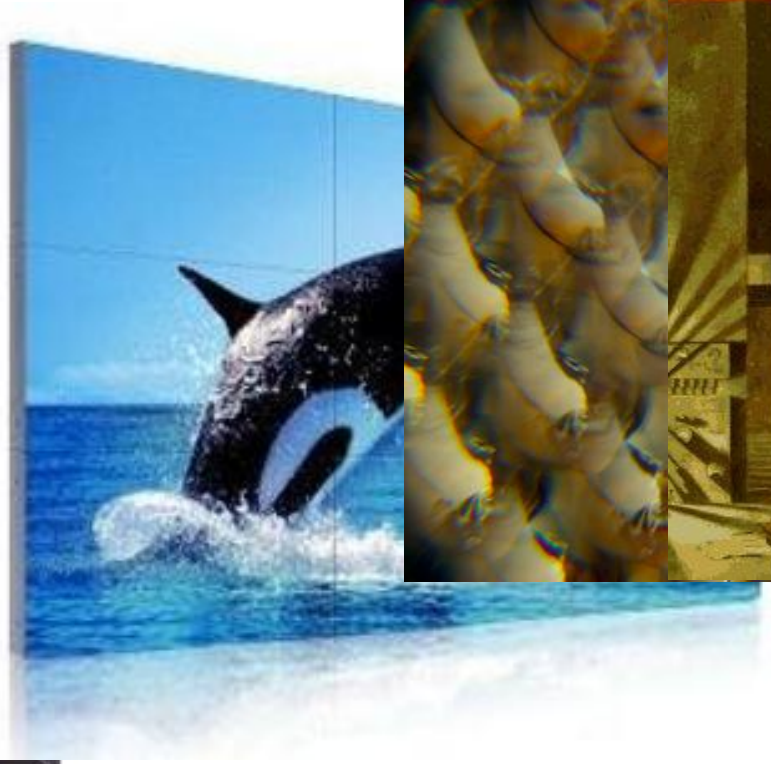


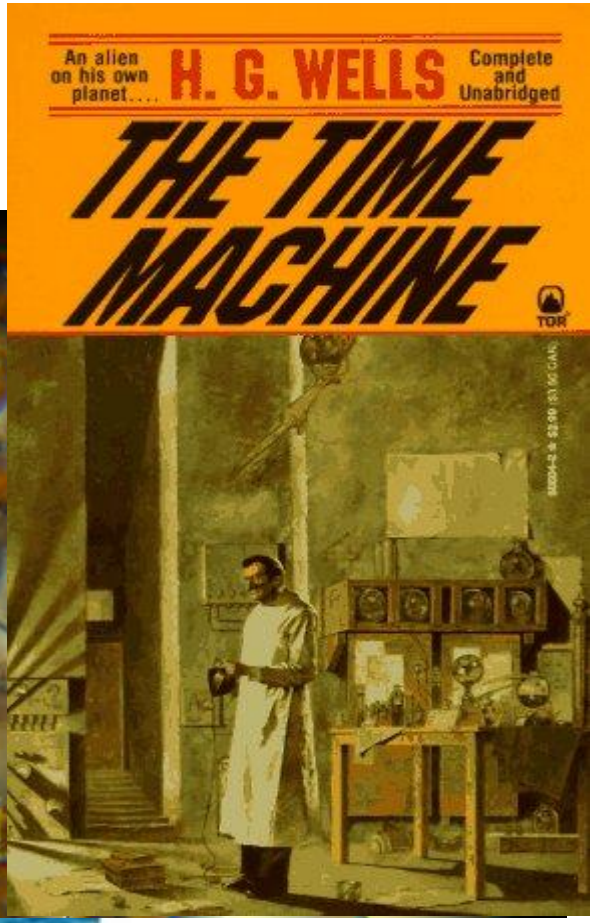
AirPROM

- Validated models to predict airways disease progression and response to treatment
- Platform to translate patient-specific tools
- Personalised management of airways disease.

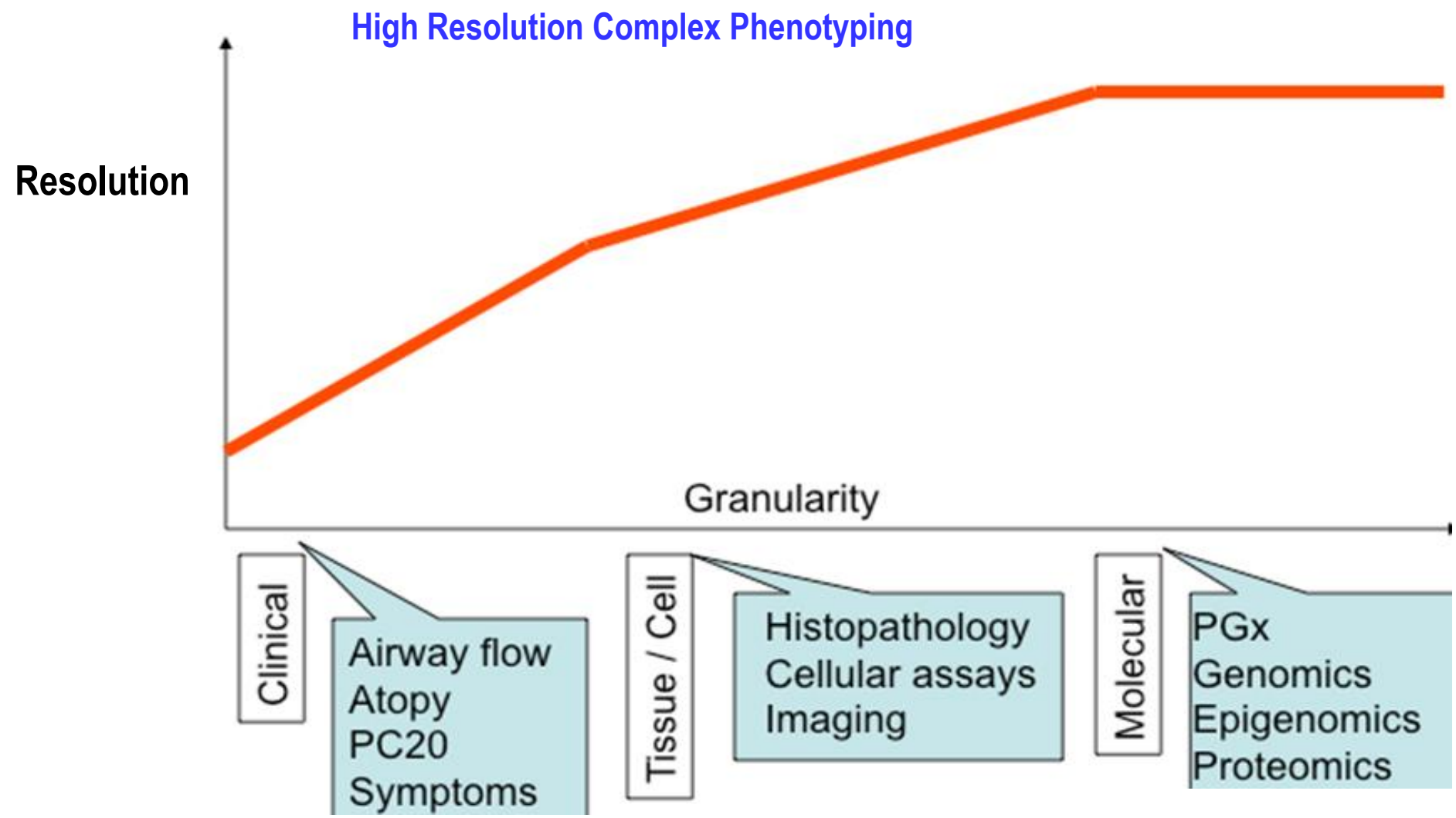
Unravelling Complexity

“If you can not *measure* it, you can not improve it”.
Lord Kelvin

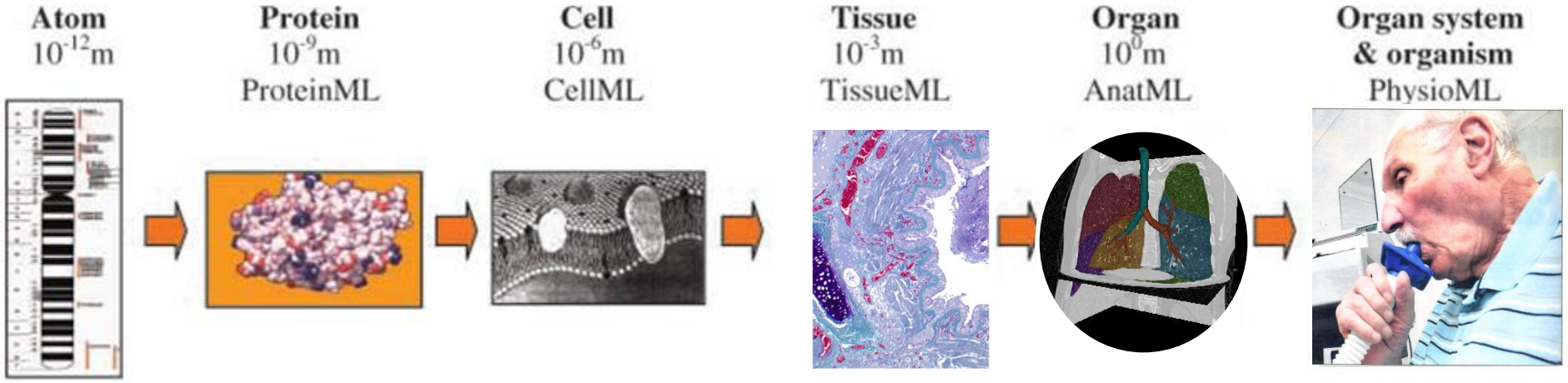




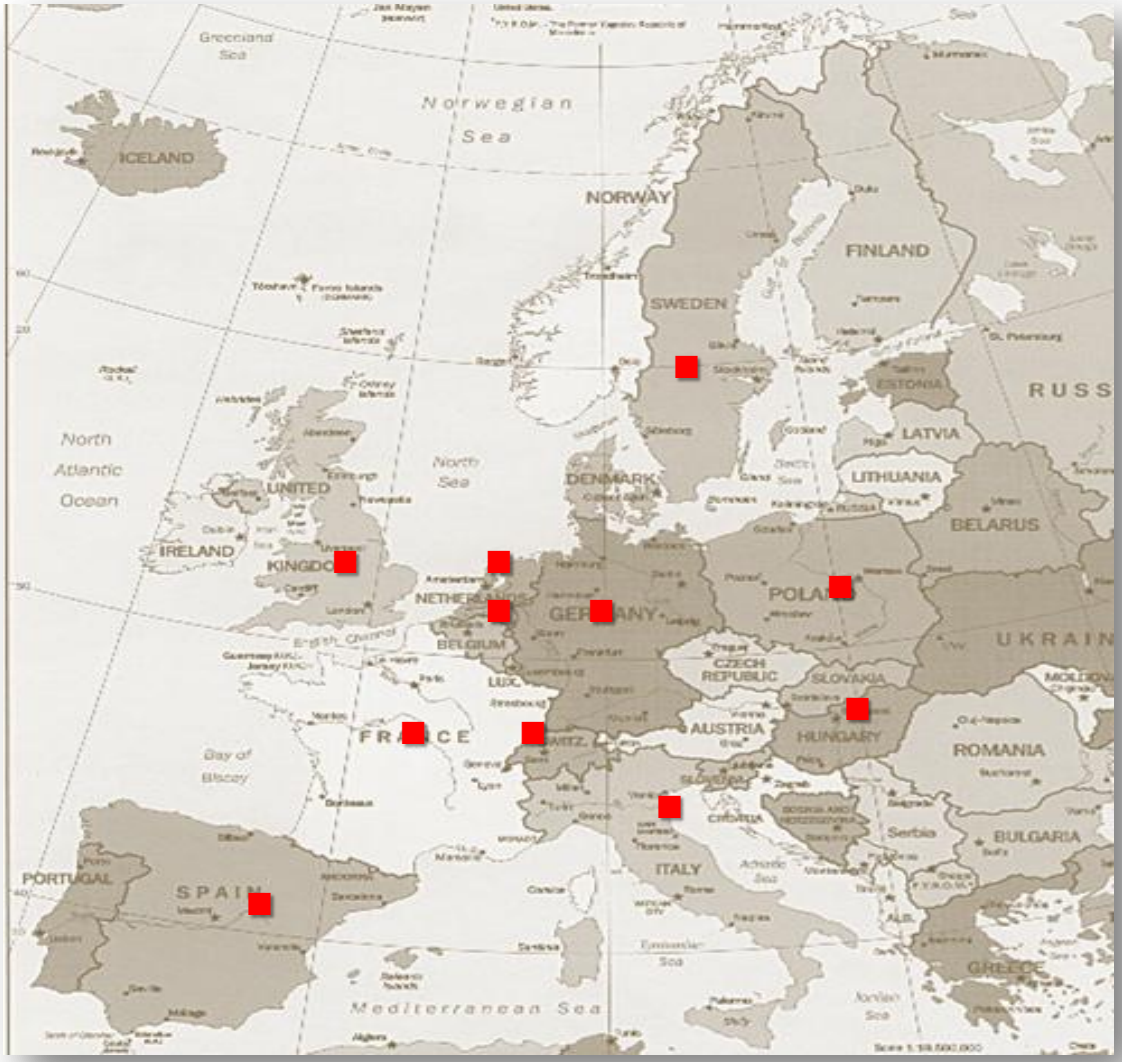
Unravelling Complexity



AirPROM- Airway Disease Predicting Outcomes Through Patient Specific Computational Modelling



Consortium as a Whole



Consortium Membership

- 11 EU countries

- 25 Academic partners
- 3 SMEs
- 3 Large industry partners
- European Respiratory Society
- 2 patient organisations ELF, EFA

- WP Leads from 6 EU Countries

European Approach Essential

- Breadth of expertise
- Clinical validation (14 clinical centres)
- Exploitation

AirPROM

Consortium as a Whole

Consortium as a Whole

Academic (12)

Leicester (ULEIC)
Amsterdam (AMC)
Oxford (UOXF)
Paris (INST TELECOM)
Barcelona (FPPPCB)
Nottingham (UNOTT)
Munich (HMGU)
Belfast (QUB)
Sheffield (USFD)
Warwick (UOW)
Paris CEA)
Poznan (PSNC)

Industry (6)

Materialise (MATE)
Ansys (AUL)
FluiDA (FLUID)
BIOMAX (BIOMAX)
BioSci Consulting (BC)
Objet Geometries (OBJ)

Patient Groups & Professional Society (3)

European Respiratory Society (ERS)
European Federation of Asthma Associations (EFA)
European Lung Foundation (ELF)

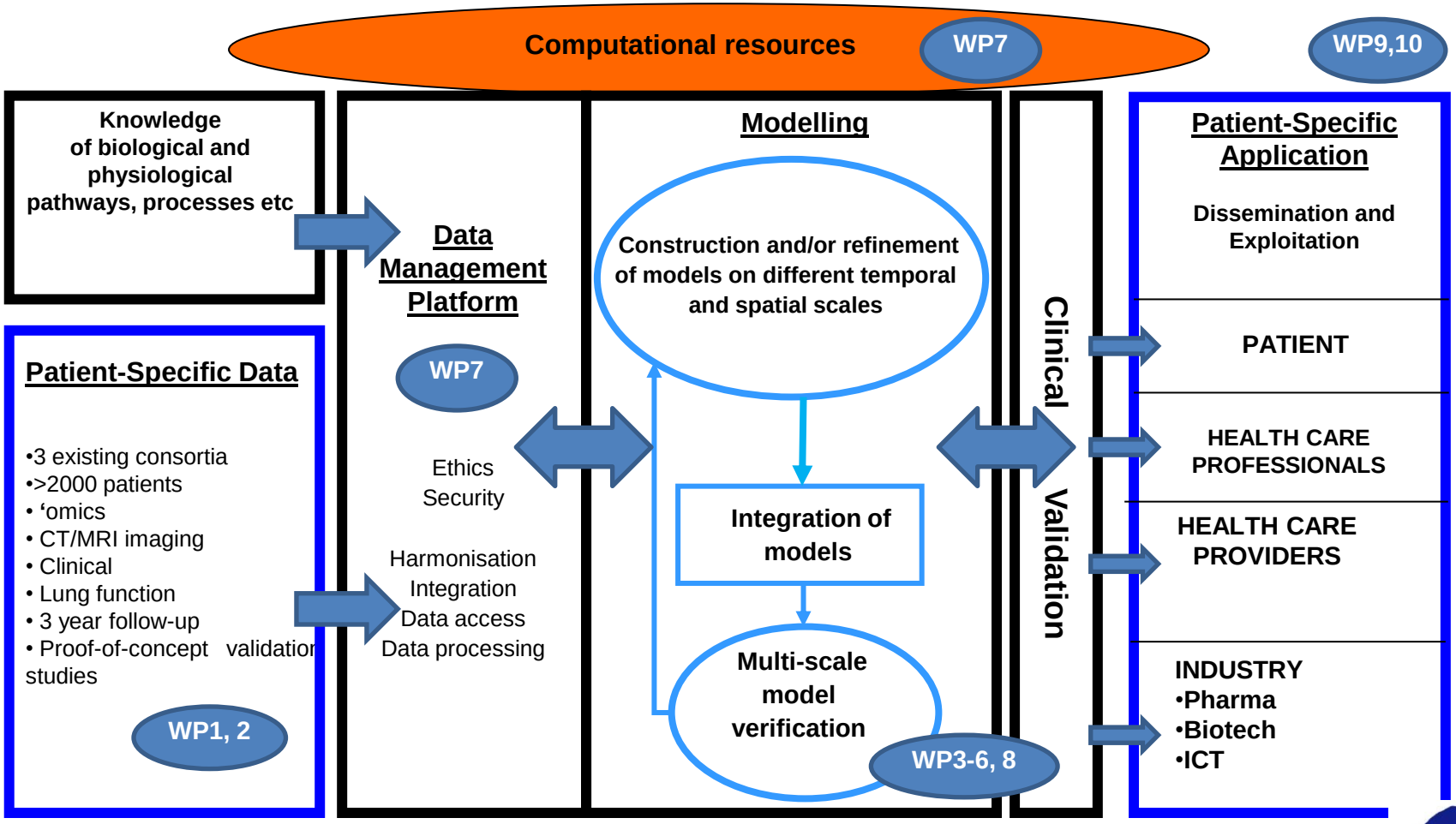
Clinical Partners (13)

Imperial (IMP)
Southampton (SOTON)
Catania (UNICT)
Budapest (OKTPI)
Manchester (MANC)
Umea (UMEA)
Marseilles (ULMDI)
Karolinska (KI)
Ferrara (UNIFE)
Warsaw (IGICHP)
Gothenburg (UGOT)
Budapest (SE)
Coventry (UHCW)

Consortium as a Whole

Strengths of the consortium
•Experience in modelling
•Clinical expertise
•Connections to pharmaceutical industry
•Expertise in technology development
•Scientists of stature
•Professional project management
•European-wide dissemination

Airway Disease PRedicting Outcomes through Patient Specific Computational Modelling

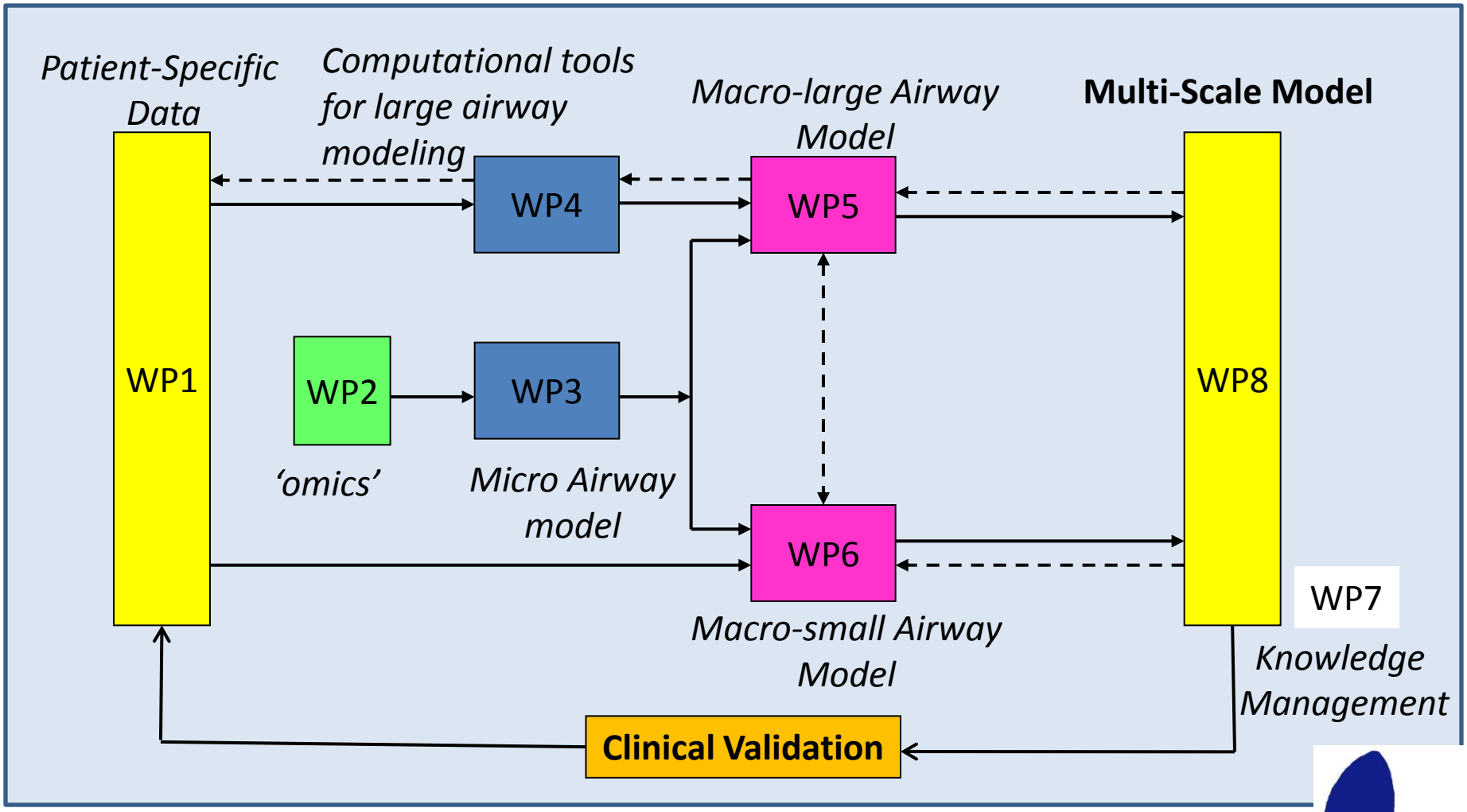


Airway Disease PRedicting Outcomes through Patient Specific Computational Modelling

	Work Package Title	Work Package Committee
WP1	Imaging acquisition, validation of centres, analysis of geometry and densitometry	**Peter Sterk, Loems Ziegler-Heitbrock, Liam Heaney, Chris Brightling**
WP2	Omic platforms-GWAS, transcriptome, and proteome	**Ivo Gut, Martin Tobin, *Jörg Hager***
WP3	Micro-airway model	**Rod Smallwood, Bindi Brook, Chris Brightling**
WP4	Integration of computational tools for large airway high-throughput modelling	**Roel WirixSpeetjens, CatalinFetita, Ian Sayers, Ariel Oleksiak**
WP5	Macro-large airway model	**Jan de Backer, Greg Gibbons, Justin Penrose, Sumit Gupta**
WP6	Macro-small airway model	**John Owers-Bradley, Jim Wild, Salman Siddiqui, Per Gustaffsen**
WP7	Knowledge management & security	**Dieter Maier, Paul Burton, Ariel Oleksiak**
WP8	Patient-specific modelling: multi-scale integration	**Kelly Burrowes, Rod Smallwood, Paul Burton & Dieter Maier**
WP9	Exploitation, training & dissemination	**Scott Wagers, Ian Sayers, Ann Marie Audley, Susanna Palkonen**
WP10	Scientific coordination & project management	**Chris Brightling, Scott Wagers and all other WP Leads**

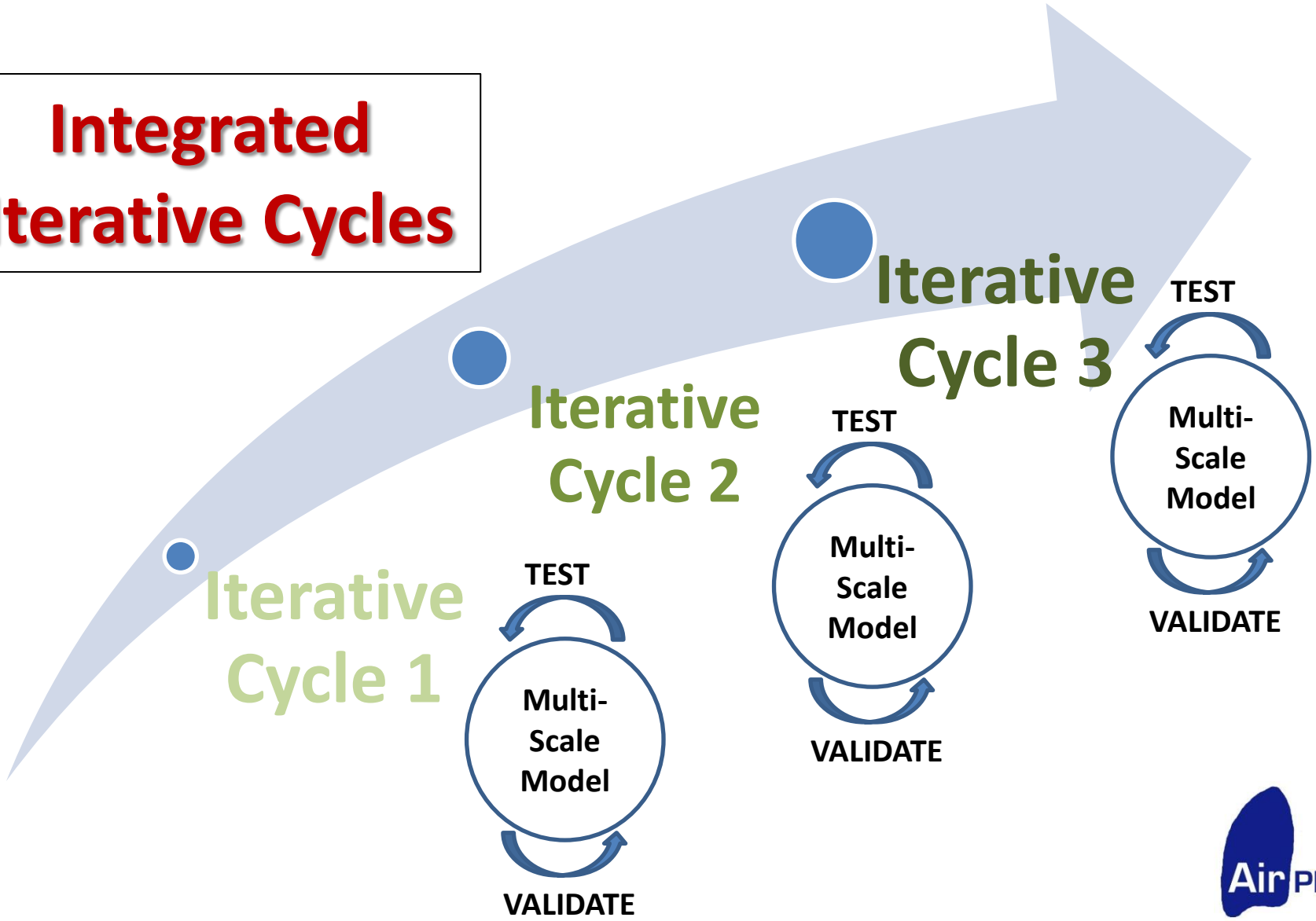
AirPROM

Work Package Integration



Work Package Integration

Integrated Iterative Cycles

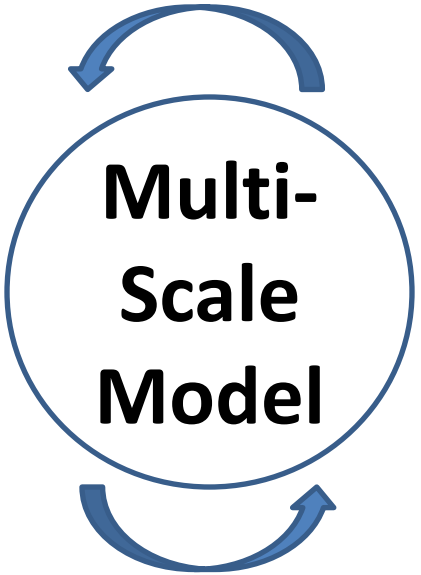


Clinical Validation

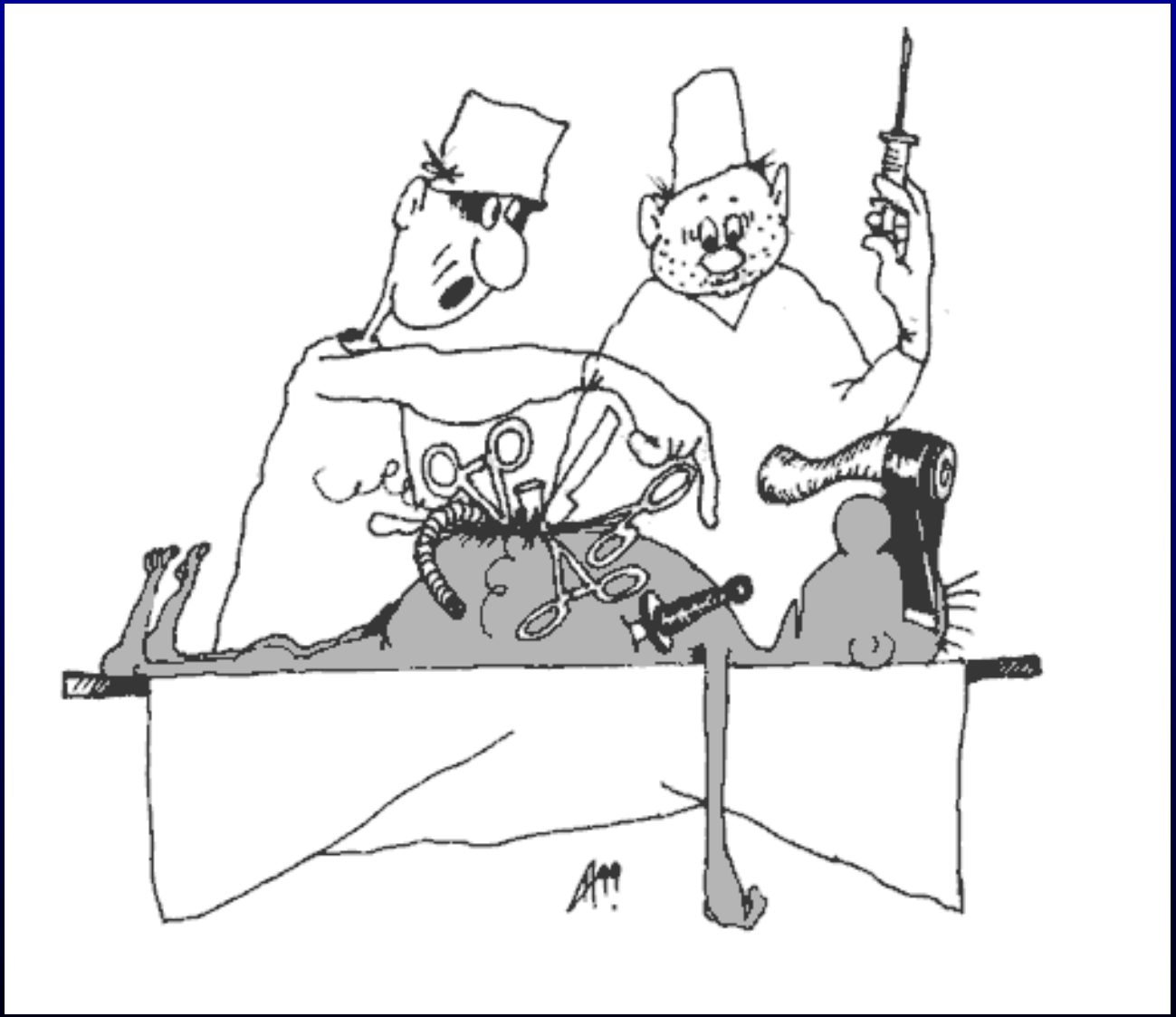
Multi-scale Data

Cross-sectional, Longitudinal

Intervention Studies



Personalised Healthcare / Target Identification



WP1 Imaging acquisition, validation of centres, analysis of geometry and densitometry

WP1 Committee: Peter Sterk (Lead), Loems Ziegler-Heitbrock, Liam Heaney, Chris Brightling

Aim - to complete and align data between the three cohorts U-BIOPRED, EvA and BTS Severe Asthma

Objectives

1. Completion and alignment of clinical data capture across existing cohorts
2. Hyperpolarised noble gas magnetic resonance imaging and advanced physiology in selected populations
3. Collection of bronchoscopic airway samples and lung tissue
4. Curation of data into data knowledge platform

WP1 The three cohorts; what they provide

Unbiased Biomarkers for the Prediction of Respiratory Disease

U-BIOPRED

Asthma, 575, COPD 100, Healthy 100, lung function, blood
Lung samples: lavage, brush, biopsy, transcriptome, proteome
Time points 0,6,30 months Start 05/2010

Emphysema versus Airway Disease

EvA

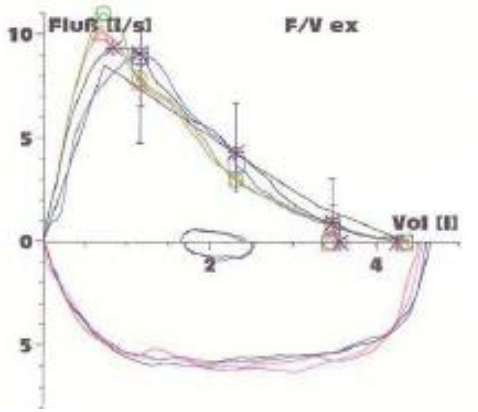
COPD 900 (300 more detailed), Healthy 300, lung function, blood
CT for airway dimensions baseline in COPD
Lung samples: lavage, brush, transcriptome, proteome, GWAS
Time points 0 months Start 10/2008
On 04 / 2011 CT 340 Bronchoscopy 230 cases 230 controls

BTS Severe Asthma Cohort

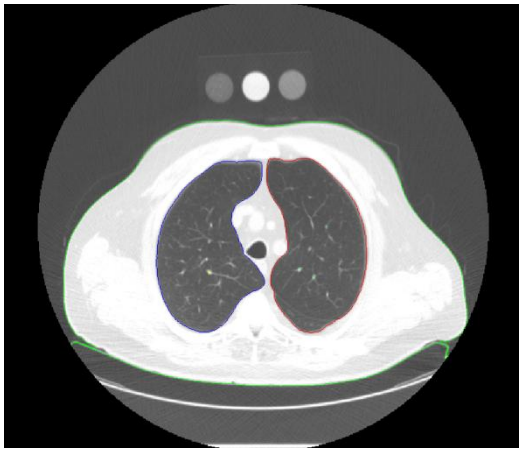
Asthma, severe 700 (100 more detailed), lung function, blood
CT for airway dimensions baseline in asthma, GWAS
Time points 0 months, after therapy Start 01/2009

AirPROM

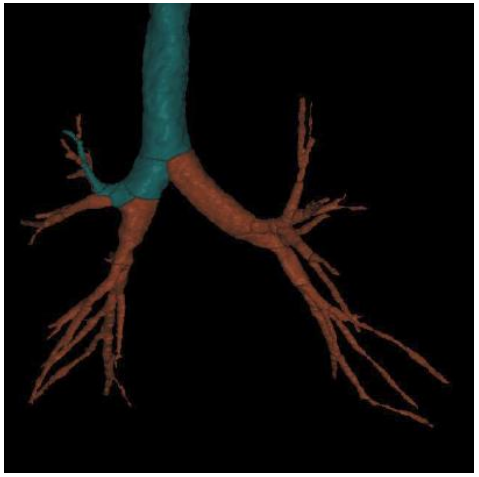
WP1 illustration of outputs from the work package



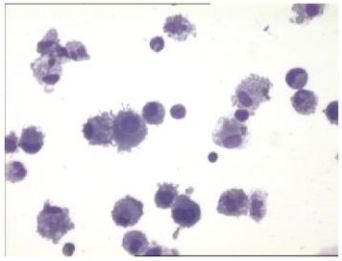
Flow data show airway disease



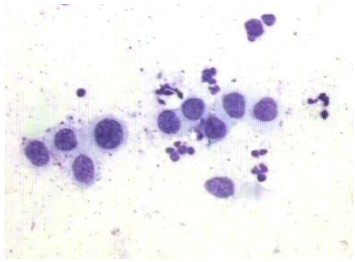
Standardized CT image



Airway modelling using Vida



Broncho-alveolar leukocytes



Airway epithelia

are analyzed for gene expression

These and other data on the bronchial system are integrated into multiscale modelling of the human airways.

WP1 The three cohorts; completion and alignment

U-BIOPRED

CT scans for airway dimensions at baseline and year 3, GWAS

EvA

Genetic analysis of mixed phenotype cases
CT scans for airway dimensions and detailed physiology at year 3

Baseline CT scans - full inspiratory and expiratory scans
CT scans for airway dimensions and detailed physiology at year 3

align SOPs for clinical data, lung physiology, CT normalization, phantoms
complete genetic analysis
complete CT scans, perform standardized CT analysis

AirPROM

WP1 advanced studies

Small airway physiology

Multiple breath sulphur hexafluoride gas washouts
Forced oscillation techniques and impulse oscillometry
Exhaled breath analysis
Hyperpolarised noble gas magnetic resonance imaging

Impact of therapies

Oral steroids for 2 weeks
Macrolides for 6 months
Anti-IL5 for 12 months
Lung volume reduction surgery

Validation on resected lung tissue

Assess biomechanical properties
Test flow model

WP1 Deliverables and Milestones

Deliverables WP1		**Month**
D1.1	Cross sectional Imaging dataset	24
D1.2	Proof of concept, physiology, and followup dataset	48
D1.3	Bronchoscopic sample analysis dataset	54
Milestones		
M13	Completion of cross-site validation and baseline CTs and sampling across the cohorts	12
M24	Cross-sectional MRI and lung physiology studies complete	24
M44	Proof-of-concept studies with MRI and lung physiology complete	48
M45	Follow-up CT scans and lung physiology complete	48
M50	Acquisition of lung donor and bronchoscopic samples complete	54

AirProm WP2

Start: month 1

End: month 45

Total *person-months:* 91

Partners contributing to WP2

CEA = Centre National de Génotypage (CNG)

ULEIC = University of Leicester

FPPCB = Centro Nacional de Análisis Genómico (CNAG)

AirProm WP2

Task 1. Complete the genomic and transcriptomic datasets

1.1 Genomic data (CEA):

WG-Genotyping of 800 samples (Human660W-Quad BeadChip)

1.2 Transcriptomic data (CEA, FPPCB):

Expression profiling of 200 individuals (HT-12 v3 Expression BeadChip)

AirProm WP2

Task 2. Genomic analysis (ULEIC)

2.1 Imputation of common SNPs (MAF ≥5%) from European ancestry HapMap

2.2 Genome Wide Association Study (GWAS)

Additive genetic model; alternative genetic models

Meta-analysis of GWAS data from allied consortia (BTS severe asthma AUGOSA, EvA, SPIROMETER and GABRIEL FP6)

2.3 Imputation of SNPs of intermediate frequency (MAF 1-5%) using HapMap and 1000 genomes project data.

2.4 Validation of associated variants using Sequenom iPlex technology in additional asthma and COPD samples (AUGOSA,GABRIEL, SPIROMETER and EvA projects)

Task 3. Transcriptomic analysis and linking to genomic data (FPPCB, CEA, ULEIC)

3.1 **Data transferred to knowledge management platform**

The data will be combined with the data from 600 samples in EvA and from the ‘omic’ data in U-BIOPRED.

Clustering, differential expression analysis.

3.2 **Component analyses for multi-dimensional analysis to establish predictive models**

AirProm WP2

Task 4. Genome and transcriptome sequencing (FPPCB)

4.1 **Gene and transcriptome (RNA-Seq) sequencing of sub-phenotypes**

(familial cough without airway hyper-responsiveness, Cough and senory peripheral neuropathy, airway inflammation without airway hyper-responsiveness, and frequent exacerbations and inflammation without airflow obstruction)

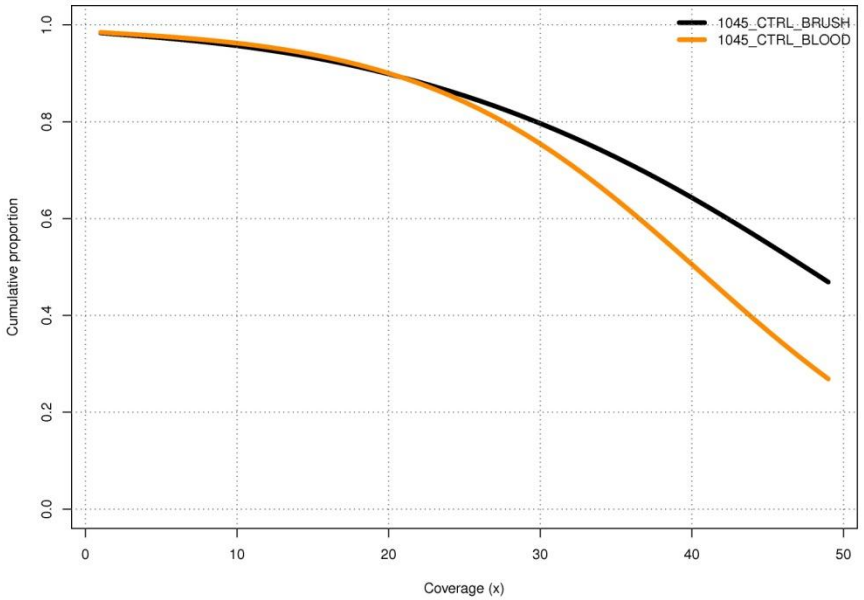
4.2 **WG-Seq and RNA-Seq of 10 samples selected from GWAS and Expression array studies**.

Delive-rable Number [61]	Deliverable Title	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D2.2.1	Complete omic dataset [existing + new]	11	29.40	O	PP	6
D2.2.2	Dataset of genome and transcriptome wide analysis	32	49.30	O	PP	24
D2.2.3	Dataset of combined gene sequencing, genome and transcriptome wide analysis	11	12.30	O	PU	42

Milestone number [59]	Milestone name	Lead benefi-ciary number	Delivery date from Annex I [60]	Comments
MS1	Existing genome/transcriptomic/proteome/lipidome datasets integrated in AirPROM knowledge management	11	12	
MS9	Acquisition of new genome/transcriptome data	11	6	
MS25	Genome analysis complete	1	24	
MS26	Transcriptome analysis complete	32	24	
MS32	Genetical genomics: genome to expression analysis complete	11	36	
MS33	Acquisition of gene sequencing data complete	11	24	
MS40	Gene sequencing analysis complete	11	42	

EvA

WG-Seq
DNA from blood lymphocytes
DNA from bronchial epithelial cells



Strand bias Filter

1045_CTRL		BLOOD	BR Epithel	BR Epithel mpileup (Somatic)
	Variants	3024972	2994394	116
	non dbSNP variants	158840	161754	68
	Deleterious *	1028	967	0

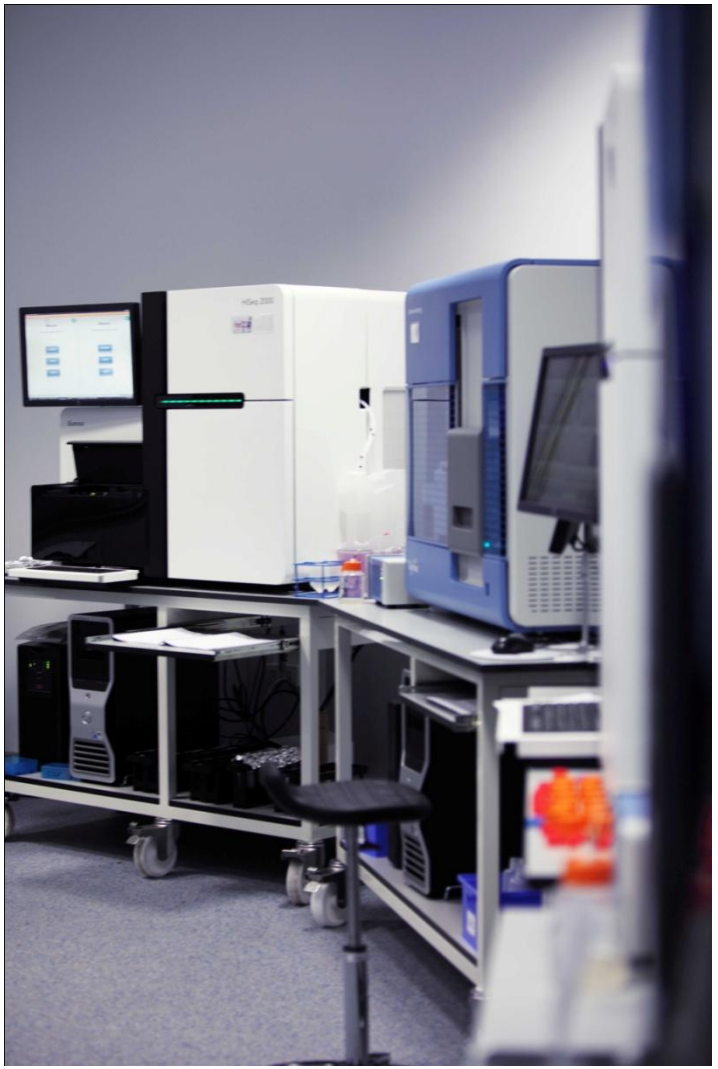
Sequencing Instruments

6 Illumina Genome Analyzer IIx
8 Illumina HiSeq2000
4 Illumina cBots

Sequencing capacity
200 Gbases per day

Anticipated Specifications with TruSeq v3 Reagent Kits

	HiSeq 2000	HiSeq 1000
Output	540–600 Gb	270–300 Gb
Reads per Run	Up to 6 billion paired-end reads	Up to 3 billion paired-end reads
Performance	> 80% about Q30 at 2 x 100 bp	> 80% about Q30 at 2 x 100 bp



Informatics

10 x 10 Gb/s

Barcelona Super Computer 10,240 cores

850 core cluster supercomputer
1.2 petabyte hardiscs

Other projects at CNAG

Revolutionary Approaches and Devices for Nucleic Acid analysis **(READNA)**

Finding biomarkers of anti-microbial drug resistance via a systems biology analysis of fungal pathogen interactions with the human immune system (**SYBARIS**)

European Sequencing and Genotyping Infrastructure (**ESGI**)

Sharing capacity across Europe in high-throughput sequencing technology to explore genetic variation in health and disease (**GEUVADIS**)

Airway Disease PRedicting Outcomes through Patient Specific Computational Modelling (**AirPROM**)

Markers of emphysema and airway disease in COPD (**EVA**)

Unveiling the Iberian lynx genome

Genetic susceptibility factors in attention-deficit/ hiperactivity disorder

cnag

centre nacional d'anàlisi genòmica
centro nacional de análisis genómico

Marta Gut
Anna Carreras
Julie Blanc
Marta Lopez
Silvia Carbonell
Gloria Plaja
Rahnehild Birkenkamp
Isabelle Brun-Heath
Lidia Agueda
Katja Khalem

Simon Heath
Francesc Castro
Jordi Camps
Paolo Ribeca
Tyler Alioto
Matt Ingham
Andre Corvelo
Emanuele Raineri
Leonor Frias
Jean-Remi Trotta
Micha Sammeth
Santiago Marco
Olga Fernando

Ivo Gut
Mònica Bayés
David Badia
Diego Ravenda
Anna Borrell

WP3 Micro-airway Model

WP3 Committee: Rod Smallwood (Lead), Bindi Brook, Chris Brightling
Partners: ULEIC, UNOTT, USFD

Hypothesis- Abnormalities of the bronchial epithelium as a result of gene-environment interactions lead to remodelling of the large and small airways and a consequent change in lumen size and the mechanical properties of the airway wall.

Aims- To develop a validated 'micro-scale' computational airway model integrated with the 'macro-scale' airway model in the later work packages.

To extend existing computational models (e.g. Epitheliome, Coast, Cardiome projects) to include the composition and mechanical properties of the airway wall validated using ex vivo 3-dimensional models.

A multi-scale model of the response of the bronchial wall to insult (chemical, cellular, physical) incorporating both individual-based and continuum models, will update the airway dimensions and physical properties in longer length-scale models of the lung.

WP 3 'Micro-airway Model' Objectives

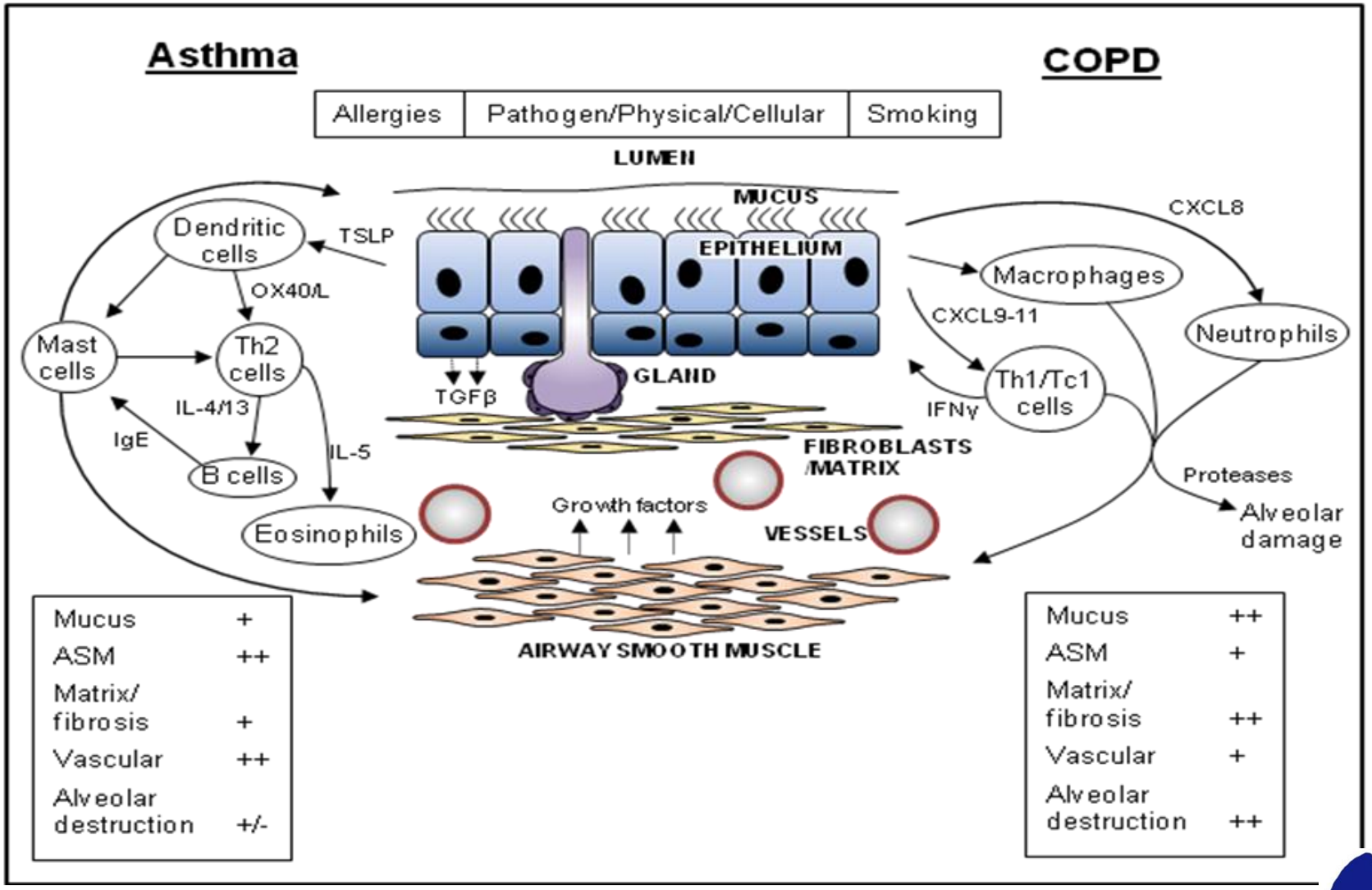
1. **Planar model-** Modify, extend and link existing models to provide a predictive computational model for comparison with the *ex vivo* model of the bronchial wall (USFD, UNOTT).

2. **Validate-** the planar model against the response (to agonists and mechanical stimuli) of the *ex vivo* model (ULEIC, UNOTT).

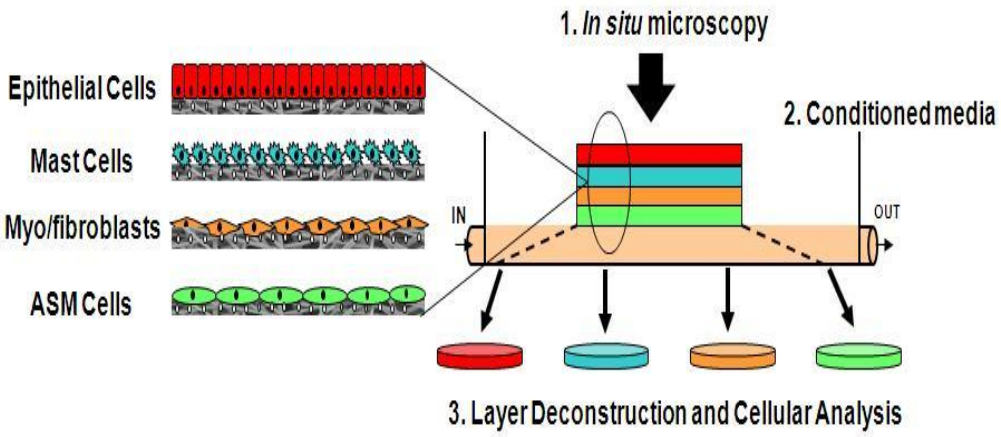
3. **Cylindrical model-** Modify, extend and link existing models as for objective (1) to provide a predictive computational model of a full-thickness section of the bronchial wall for incorporation into the systems model of the lung (UNOTT, USFD).

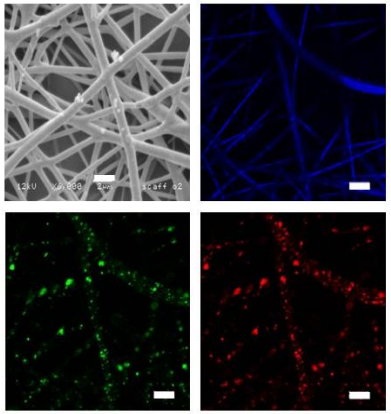
4. **Application-** of the cylindrical model to predict changes in bronchial dimensions, physical properties, resulting from insult, and use these to inform higher level models of airways and lung (USFD, UNOTT).

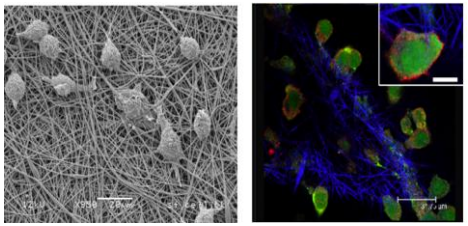
WP 3 Modelling Immunopathology

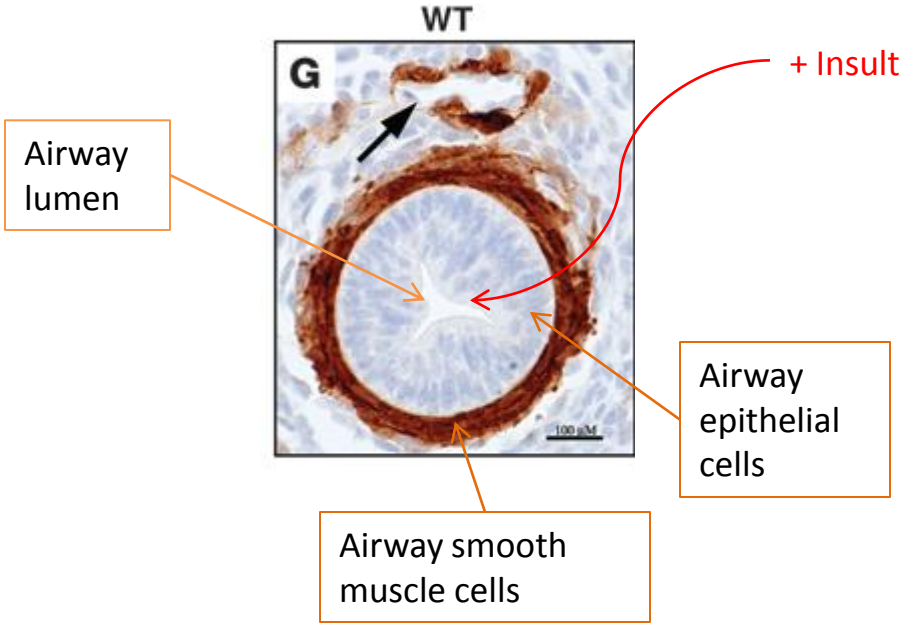


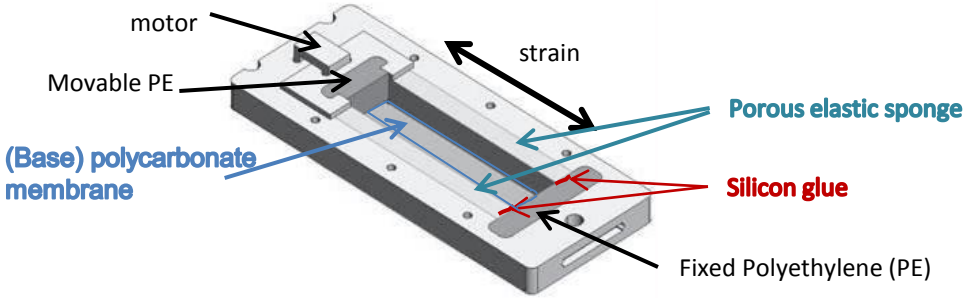
WP 3 Ex Vivo models











WP3 Deliverables & Milestones

Deliverables WP3		Month
D3.1	Validated planar epithelial and mesencymal micro-scale model	23
D3.2	Validated planar multi-layered micro-scale model	48
D3.3	Validated Tubular micro-scale model	52
D3.4	Ex vivo models platform	54
D3.5	Validated integrated micro-scale airway model (shared with WP 8)	54
Milestones		
M6	'black box' model ready for integration [shared with WP8)	4 (framework)
M8	Micro (WP 3), macro large airway (WP 5), macro small airway (WP 6) models integrated into patient specific model framework (black box).	6
M14	Integration Individual based models of cells achieved	12 (cycle 1)
M15	Integration of existing Ex vivo models	12
M28	Micro (WP 3), macro large airway (WP 5), macro small airway (WP 6) models integrated into patient specific cycle #1	24
M34	Integration of multilayered planar model achieved	36 (cycle 2)
M35	Completion of 3D immunocompetent self-reporting ex-vivo model	36
M39	Multilayed planar model transformed to tubular model	40 (cycle 3)
M43	Micro (WP 3), macro large airway (WP 5), macro small airway (WP 6) models integrated into patient specific cycle #2	42

WP4: Computational Tools for Large Airway High-Throughput Modelling

WP4 Committee: Roel Wirix-Speetjens (Lead), Catalin Fetita, Ian Sayers, Ariel Oleksiak

Scope - provide the morphological properties of large airways computed from patient CT data to derive the functional behaviour via a computational workflow.

The work package will integrate existing tools dealing with the target actions and will develop the missing functionalities leading to process automation and high throughput modelling.

In addition, as the tools are to be used in an automated manner, it is important to address the issues of robustness, efficiency and accuracy of all the processes, so as to have a workflow which can be used reliably and easily by non-experts.

WP 4 ‘Computational Tools’ Objectives

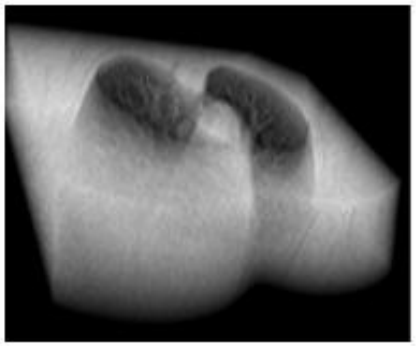
1. **Segmentation** of airway lumen and lung lobes from CT images and computation of airway calibre and centreline (inlet/outlet definition and link to small airways).

2. **Meshing:** Generation of a *surface* mesh model from the airway lumen segmentation and *volume* mesh.

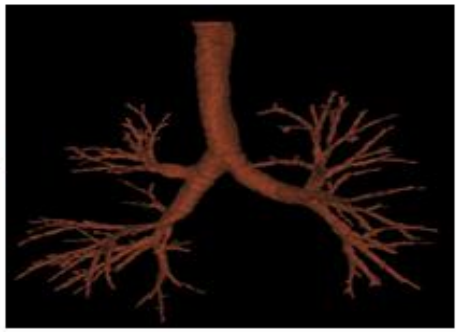
3. **Optimisation of CFD modelling tools:** Improve existing turbulence models, incorporate deformable walls, optimise overall CFD process.

4. **High-throughput semi-automated framework:** *Optimise* segmentation process for minimal user-interaction, boundary definition and process runtime (parallelization and GPU). *Automate* execution of (part of) the analysis and integrate with management framework (WP7).

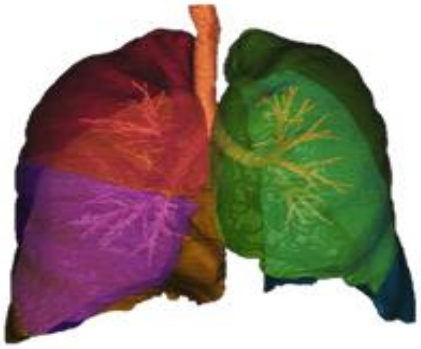
WP4 Image Analysis en Processing



Volumetric CT data

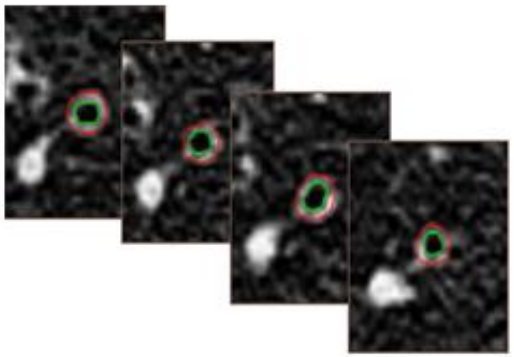


Segmented airway tree

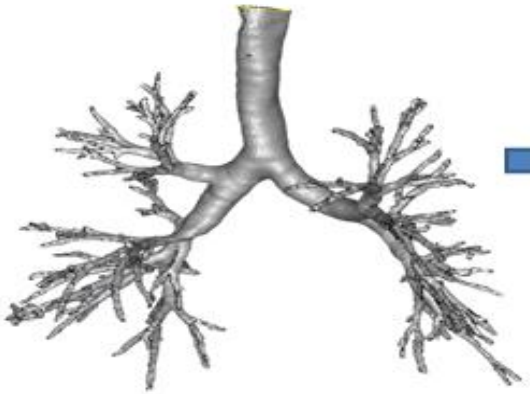


Lobe Segmentation

Boundary conditions



Quantitative analysis



Mesh modelling

CFD Simulation

WP4 Deliverables & Milestones

Deliverables WP4		Month
D4.1	Unified framework integrating the computational tools for rigid large airway modelling	6
D4.2	Integrated framework for compliant large airway wall modelling	24
D4.3	High throughput semi-automated validated framework for large airway modelling	54
Milestones		
M2	Standard interfacing description and setup between the software components	3
M3	Patients identified from predefined subgroups to generate mesh for 1st cycle CFD [shared with WP 5]	3
M19	Software optimised for modelling compliant airway walls	18
M31	Patients identified from predefined subgroups to generate mesh for 2nd cycle CFD [shared with WP 5]	26
M41	Integration of software tools with cloud infrastructure: to facilitate high throughput and automation	42
M42	Patients identified from predefined subgroups to generate mesh for 3rd cycle CFD [shared with WP 5]	42

WP5 Macro- Large airway Model

WP5 Committee:Jan De Backer, Greg Gibbons, Justin Penrose, Sumit Gupta

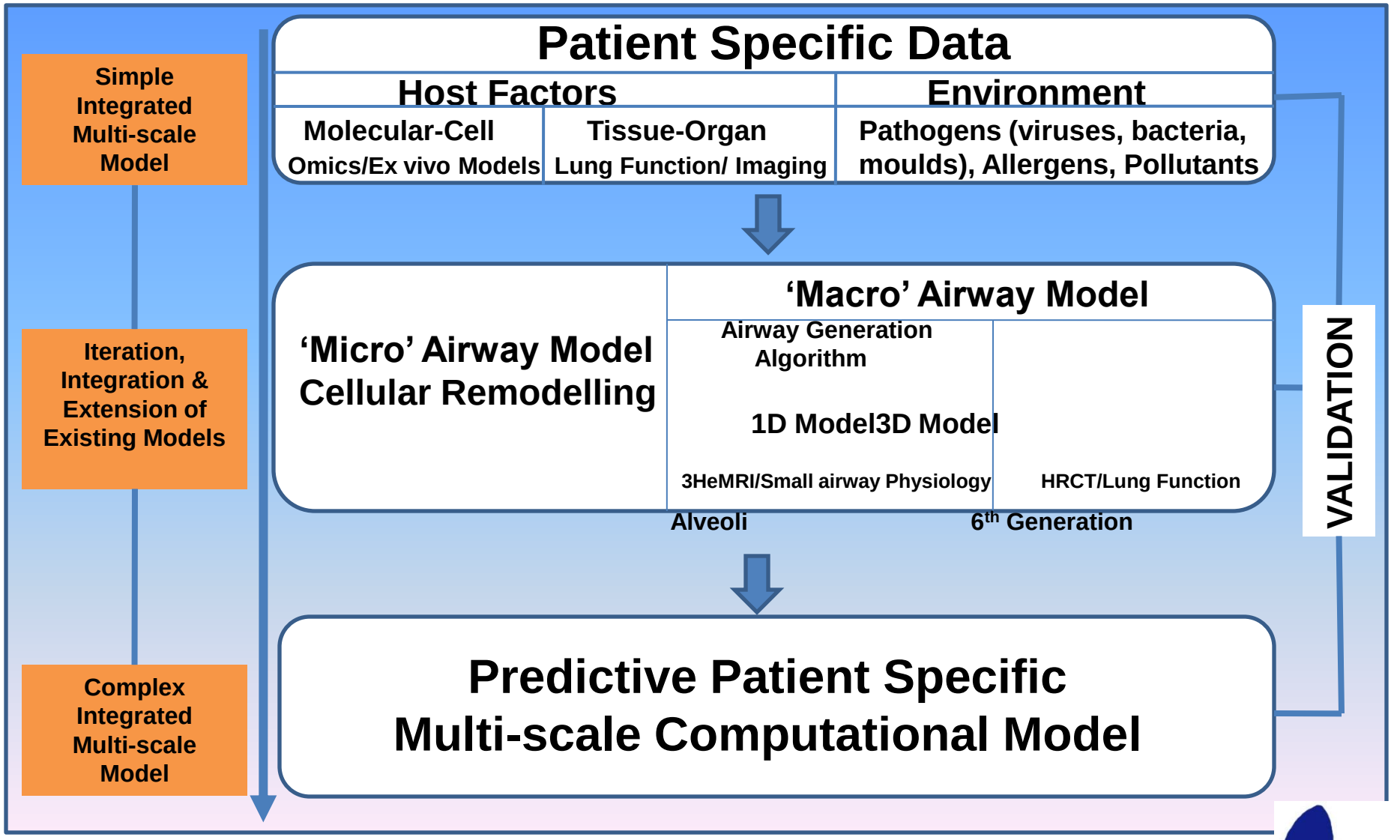
Hypothesis- abnormalities of the bronchial epithelium as a result of gene-environment interactions lead to remodelling of the large and small airways and a consequent change in lumen size and the mechanical properties of the airway wall.

Aims- To develop a validated 'macro-scale' computational airway model integrated with the 'micro-scale' airway model in the later work packages.

To extend existing computational models with advanced properties of the airway wall validated using ex vivo 3-dimensional models.

A multi-scale model of the response of the bronchial wall to insult (chemical, cellular, physical) incorporating both individual-based and continuum models, will update the airway dimensions and physical properties in longer length-scale models of the lung.

WP 5 Multi-Scale Modelling

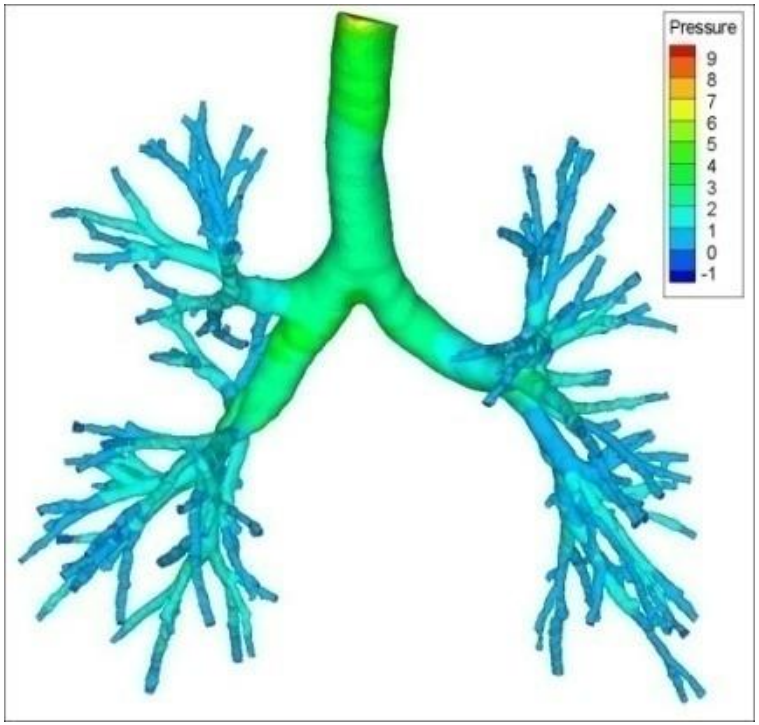


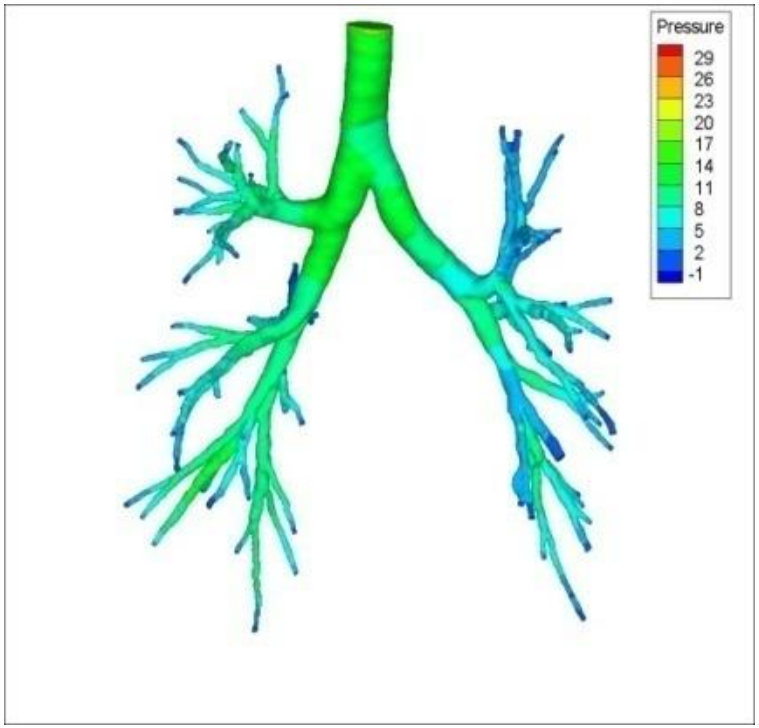
WP 5 ‘Macro large-airway Model’ Objectives

1. CFD models using CT data from WP 1 &4
2. Experimental *in silico* validation
3. Experimental MRI *in vivo* validation

WP 5 Multi-Scale Modelling

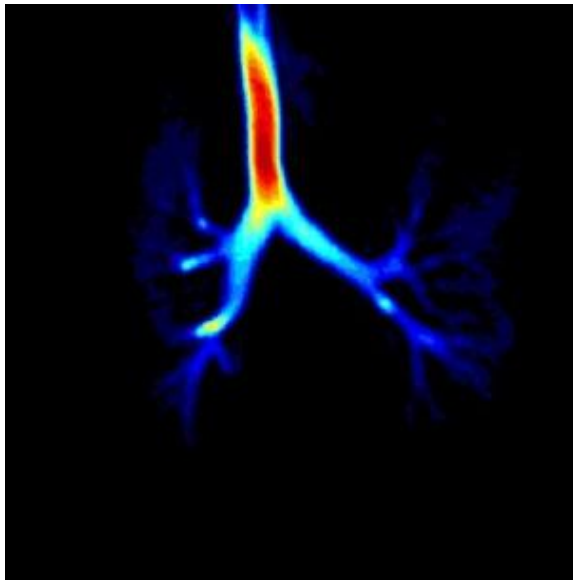
1. CFD models using CT data from WP 1 &4
   - Patient models from existing database WP1
   - Segmentation and meshing from WP4
   - Patient specific flow properties throughout the large airway model





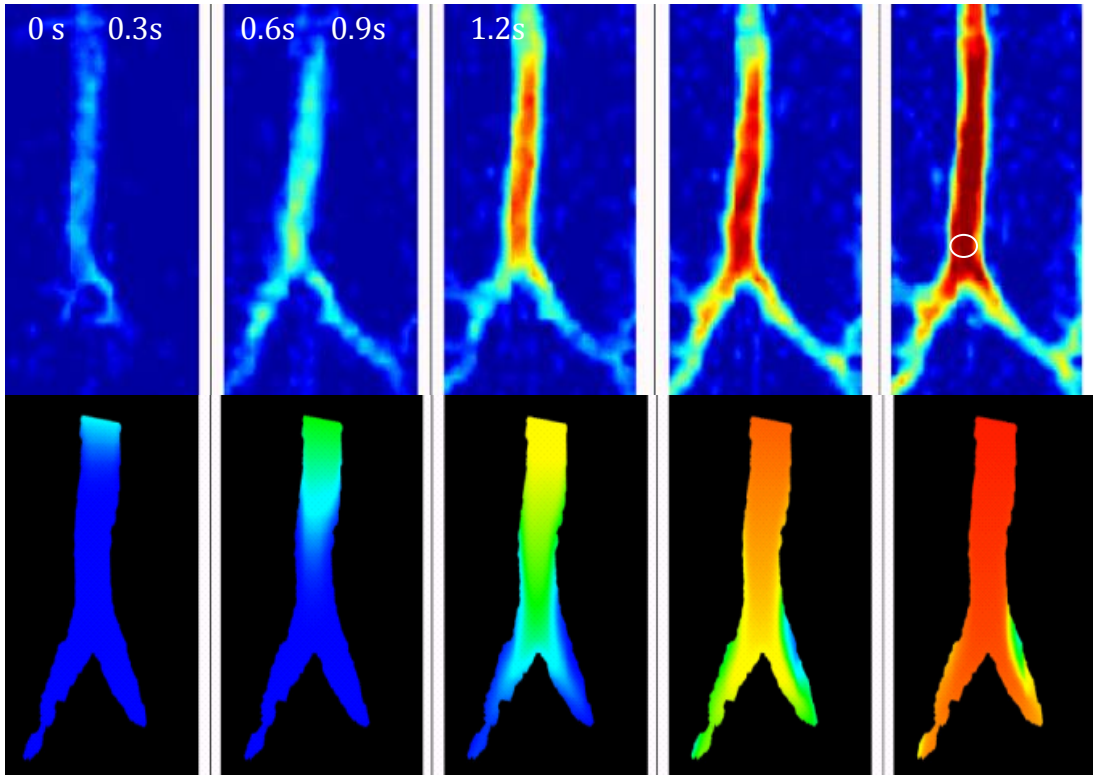
WP 5 ‘Macro large-airway Model’ Objectives

2. Experimental validation
   - Rapid prototyping of patient specific models
   - Experimental flow assessment through models
   - Comparison with CFD simulations



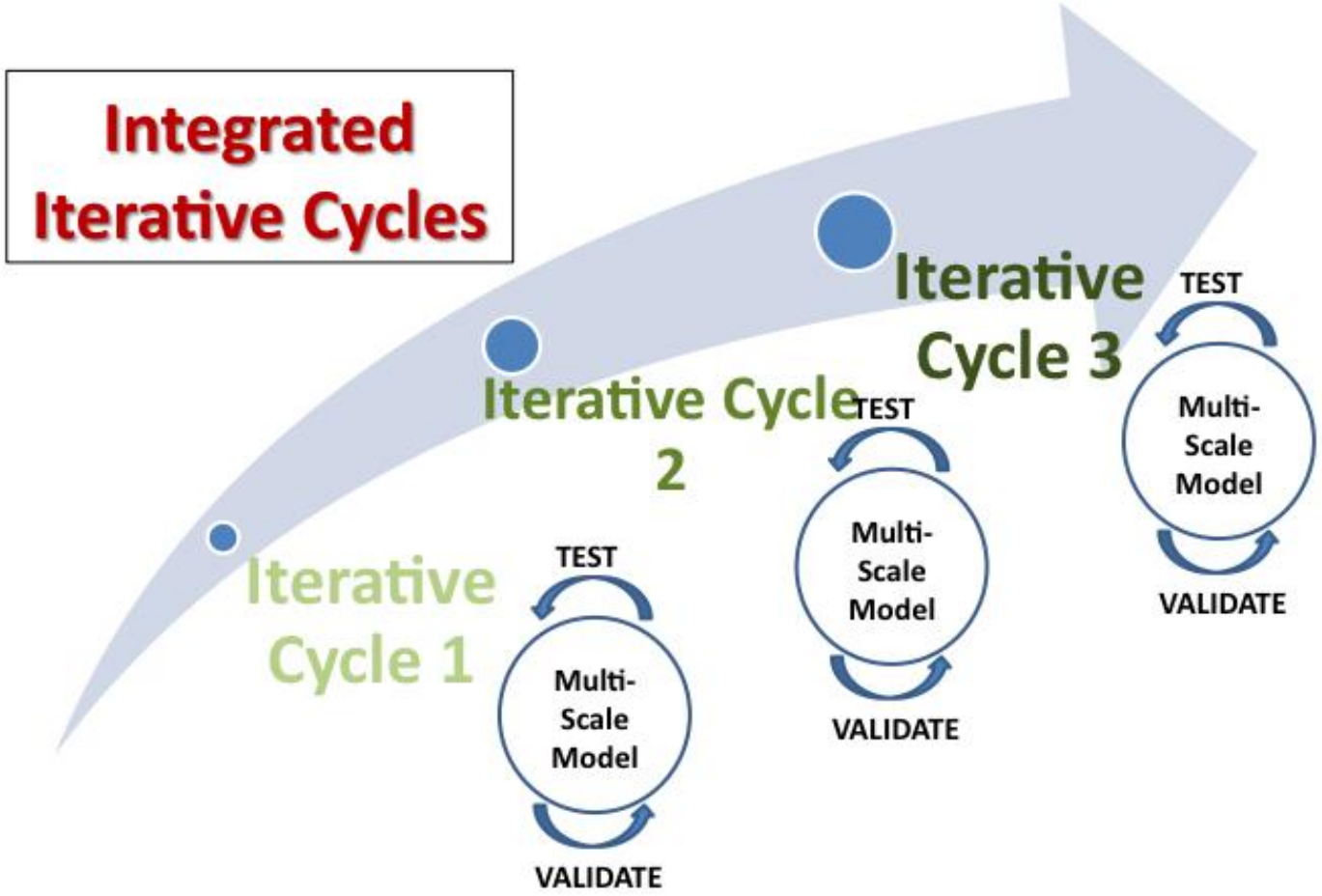
WP 5 ‘Macro large-airway Model’ Objectives

3. Experimental MRI *in vivo*validation
   - MRI method in selected patients
   - Provides in-vivo flow patient specific flow properties
   - Comparison with CFD simualtions



WP 5 Macro large-airway Model

- Iterative integration in multi-scale model to ensure an accurate and clincially relevant but workable methodology



WP5 Deliverables & Milestones

Deliverables WP5		Month
D5.1	CFD cross sectional dataset using integrated rigid wall model	24
D5.2	CFD longitudinal dataset using integrated rigid and compliant wall model	48
D5.3	Validated large away 'macro-scale' model	54
Milestones		
M3	Patients identified from predefined subgroups to generate mesh for 1st cycle CFD [shared with WP 4]	3
M8	Micro (WP 3), macro large airway (WP 5), macro small airway (WP 6) models integrated into patient specific model framework (black box). [shared with WP 3,6,8]	6
M31	Patients identified from predefined subgroups to generate mesh for 2nd cycle CFD [shared with WP 4]	26
M23	Compliant walls incorporated	23
M30	MRI velocitometry data analyzed and ready for validation	25
M28	Micro (WP 3), macro large airway (WP 5), macro small airway (WP 6) models integrated into patient specific cycle #1 [shared with WP 3,6,8]	24
M36	Experimental rigid wall prototype data analyzed and ready for validation [shared with WP 6]	36
M42	Patients identified from predefined subgroups to generate mesh for 3rd cycle CFD [shared with WP 4]	42
M43	Micro (WP 3), macro large airway (WP 5), macro small airway (WP 6) models integrated into patient specific model cycle #2 [shared with WP 3,6,8]	42
M46	Experimental compliant wall prototype data analyzed and ready for validation [shared with WP 6]	48

AirPROM- WP6

Salman Siddiqui: University of Leicester
John Owers-Bradley: University of Nottingham
Jim Wild: University of Sheffield
Per Gustafsson: University of Gothenburg

Aims

(i) Phenotype the small airways of patients with asthma and COPD using composite measures of applied physiology, imaging and exhaled breath.

(ii) Provide measurements using existing models of the small airways for WP8.

(iii) Extend and develop existing models.

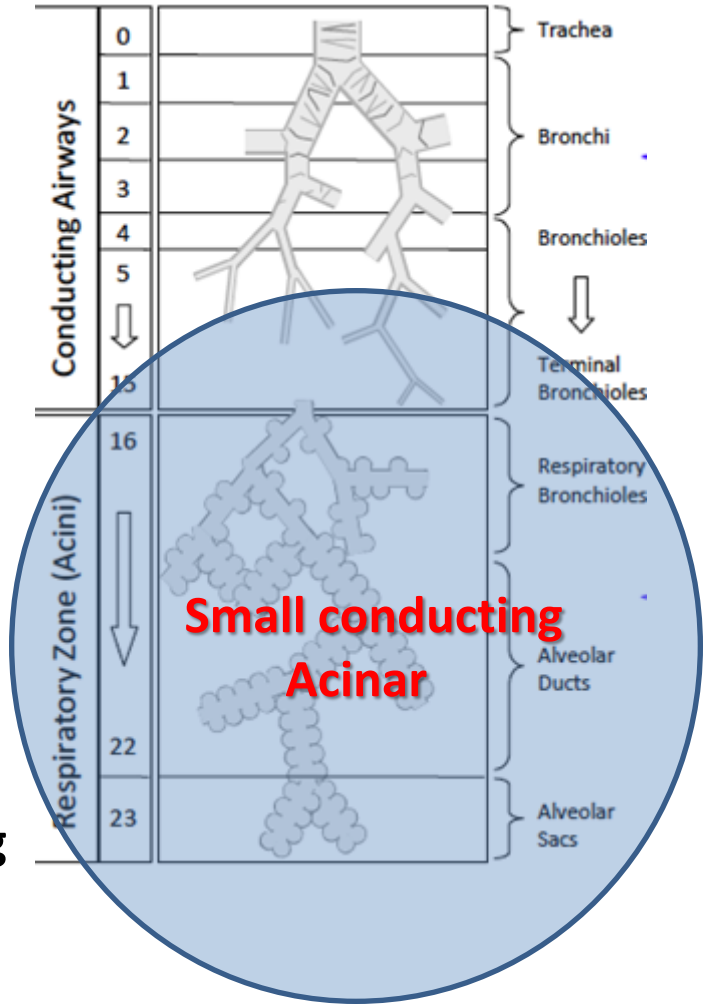
Which Patients, Which Airways?

Leicester Physiology
100 GINA 3-5 Asthma
80-100 COPD

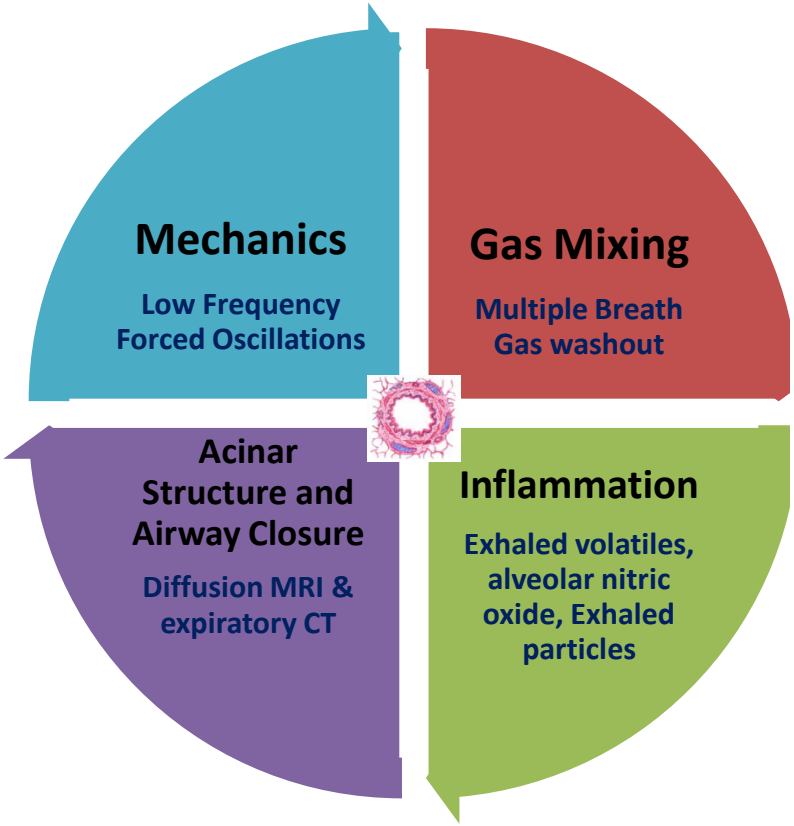
Swedish Physiology
100 GINA 2-5 Asthma

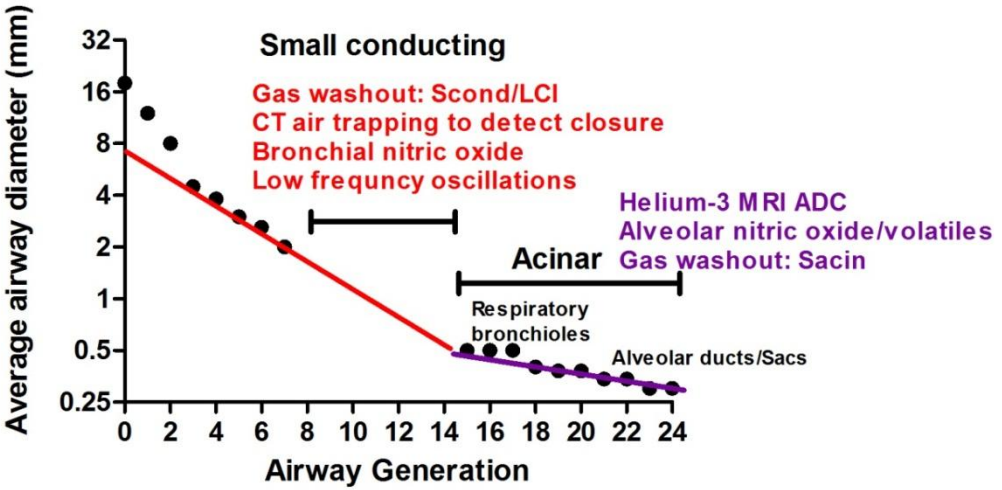
Lei-Nott-Sheffield
Diffusion MRI cohort
60 (20A/20 COPD/20 C)

Allied Consortia : EvA/UBIOPRED/BTS
CT imaging of emphysema/air trapping



What Techniques?





Existing Models?

Technique	Model
Forced Oscillation Technique	Constant Phase Model/ RIC models
Multiple Breath Gas Washout	Paiva and Engel Model (Scond/Sacin)
Alveolar Nitric Oxide	Tsoukias & George two compartment model ± correction
Hyperpolarised Helium-3 MRI	Yablonskiy multi b-value spectroscopy Outer airway radius/alveolar sleeve depth

WP6 - Small Airways - Deliverables

Deliverables WP6		Month
D6.1	Dataset using existing 'macro-scale' small airway models of lung impedence, alveolar inflammation, gas mixing and alveolar diffusion	23
D6.2	Dataset using novel small airway 'macro-scale' models	48
D6.3	Platform for gas analysis and low frequency FOT ready to be commercialized	54
D6.4	Report on comparison of He3 with Xenon measurements	54
D6.5	Validated small airway 'macro-scale' model	54
Milestones		
M8	Micro (WP 3), macro large airway (WP 5), macro small airway (WP 6) models integrated into patient specific model framework (black box). [shared with WP 3,5,8]	6
M10	Gas washout phantom developed	6
M16	Cross site validation of Gas washout phantom	12
M22	MRI and physiology cross sectional dataset analyzed	21
M28	Micro (WP 3), macro large airway (WP 5), macro small airway (WP 6) models integrated into patient specific model cycle #1[shared with WP 3,5,8]	24
M37	Novel small airway integrated models developed	36
M43	Micro (WP 3), macro large airway (WP 5), macro small airway (WP 6) models integrated into patient specific model cycle #2. [shared with WP 3,5,8]	42
M47	MRI and physiology proof of concept dataset analyzed	48
M48	Xenon measurements	48
M49	Prototype of platform for gas analysis and low frequency FOT	48
M46	Experimental compliant wall prototype data analyzed and ready for validation [shared with WP 5]	48

WP7 Knowledge management and security

WP 7 Committee: Dieter Maier (Lead), Paul Burton & Ariel Oleksiak

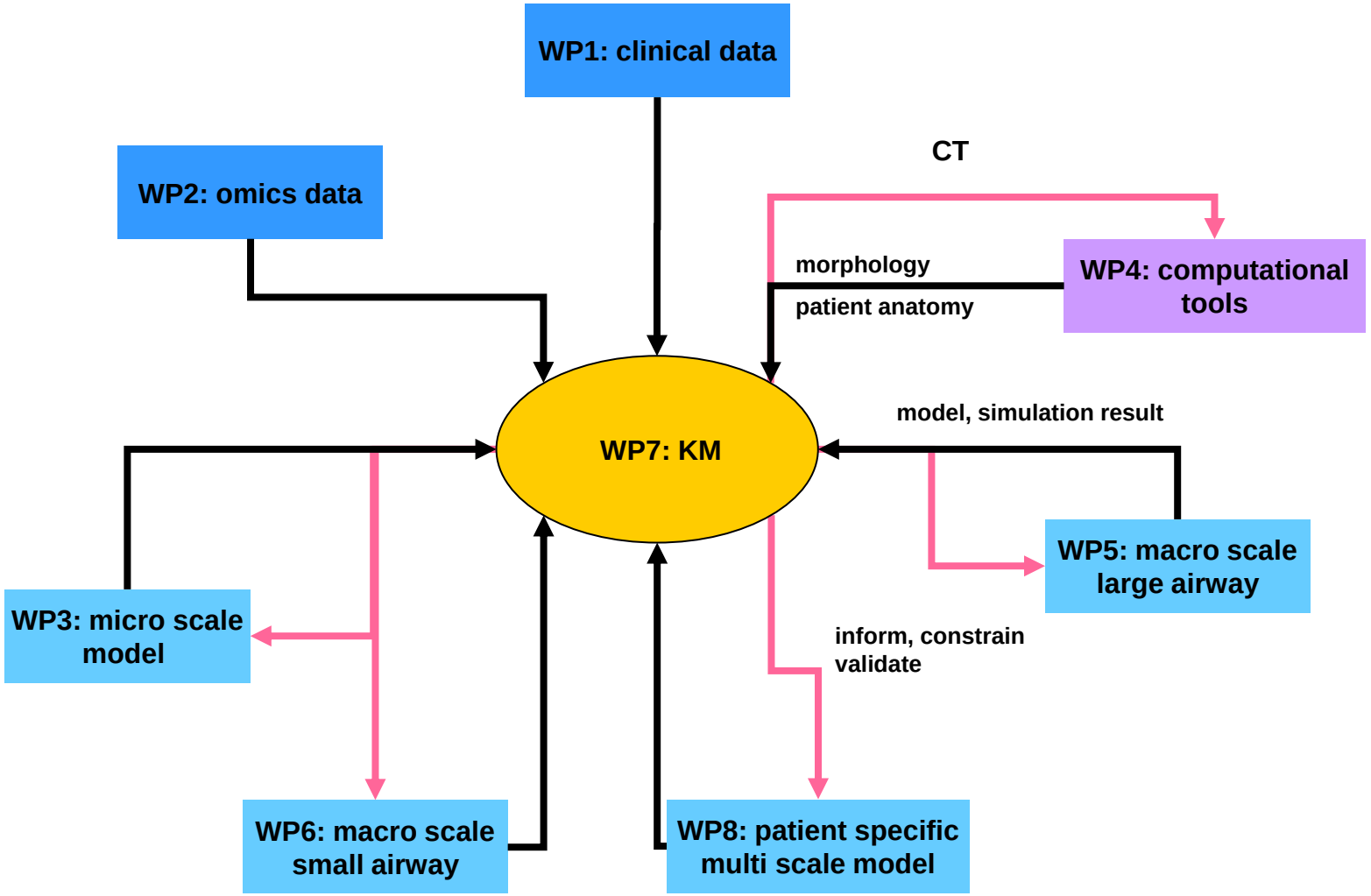
Hypothesis- complex disease processes can be understood and ultimately manipulated by systematic observation of multiple parameters and iterative multi-scale model and simulation generation and validation. To enable the modelling process large scale data of diverse types and security levels needs to be semantically integrated and made available to seed, inform, constrain and validate the models.

Aims- Provide a secure federated data retrieval, exchange, processing and warehousing knowledge management infrastructure.
Semantically integrate the clinical, biobanking physiological, genetic, experimental and imaging data made available or produced within WP1-6, and 8 with existing biological and medical information and knowledge from allied consortia (U-BIOPRED, EvA and BTS) and public databases (e.g. PubMed and OMIM at NCBI, Reactome at EBI).
Make the resulting resource available for analysis and modelling (WP3-6, and 8 i.e. model generation, parameterisation, constraining, integration and validation) and sharing, collaboration and publication within the AirPROM consortium and beyond.

WP 7 Objectives

1. **Analysis and specification** of detailed technical requirements for the AirPROM data workflow with focus on semantic mapping, data formats and security.
2. Agile prototyping of the **integrative semantic data model** and interface
3. **Technical integration** with federated data resources, harmonisation, analysis and modelling applications.
4. Supporting the interactive and automatic AirPROM **data flows**

WP1-7 Data flows



WP7 Deliverables & Milestones

Deliverables WP7		Month
D7.1	Specification document	6
D7.2	Semantic data model with mapped resources and initial data flow	18
D7.3	Algorithm integration for automatic data flows	30
D7.4	Semantic mapping of developed models	38
D7.5	Final knowledge base	60
Milestones		
M11	Initial database infrastructure	6
M17	Framework populated with high priority legacy data and public resources	12
M20	DataSHaPER rules and mappings	18
M27	Cloud based computation support	24

WP8 Patient-Specific Modelling:

Multi-Scale Integration

WP 8 Committee: Kelly Burrowes (Lead), Rod Smallwood, Paul Burton & Dieter Maier
Partners: ULEIC, UOXF.BL, UNOTT, USFD, ANSYS, BIOMAX

Hypothesis- Disordered airway physiology and frequent exacerbations observed in asthma and COPD are a consequence of gene-environment interactions that result in airway remodelling at the molecular-tissue 'micro' scale and consequent changes in the airway structure and function at an organ 'macro' scale.

Aims- This work package will integrate the computational models derived from WP 3-6 and extend the statistical modelling undertaken in WP 2 with the aim to develop a patient-specific multi-scale predictive computational airway model.

The models will increase in complexity through a series of iterations as the data from each scale becomes more complex and the scales are integrated, but will become more efficient and semi-automated.

WP 8 Objectives

1. **Integration and extension** of the statistical data analyses across the scales to identify groups with future risk of disease progression and response to therapy (ULEIC, BIOMAX → WPs 1, 2).

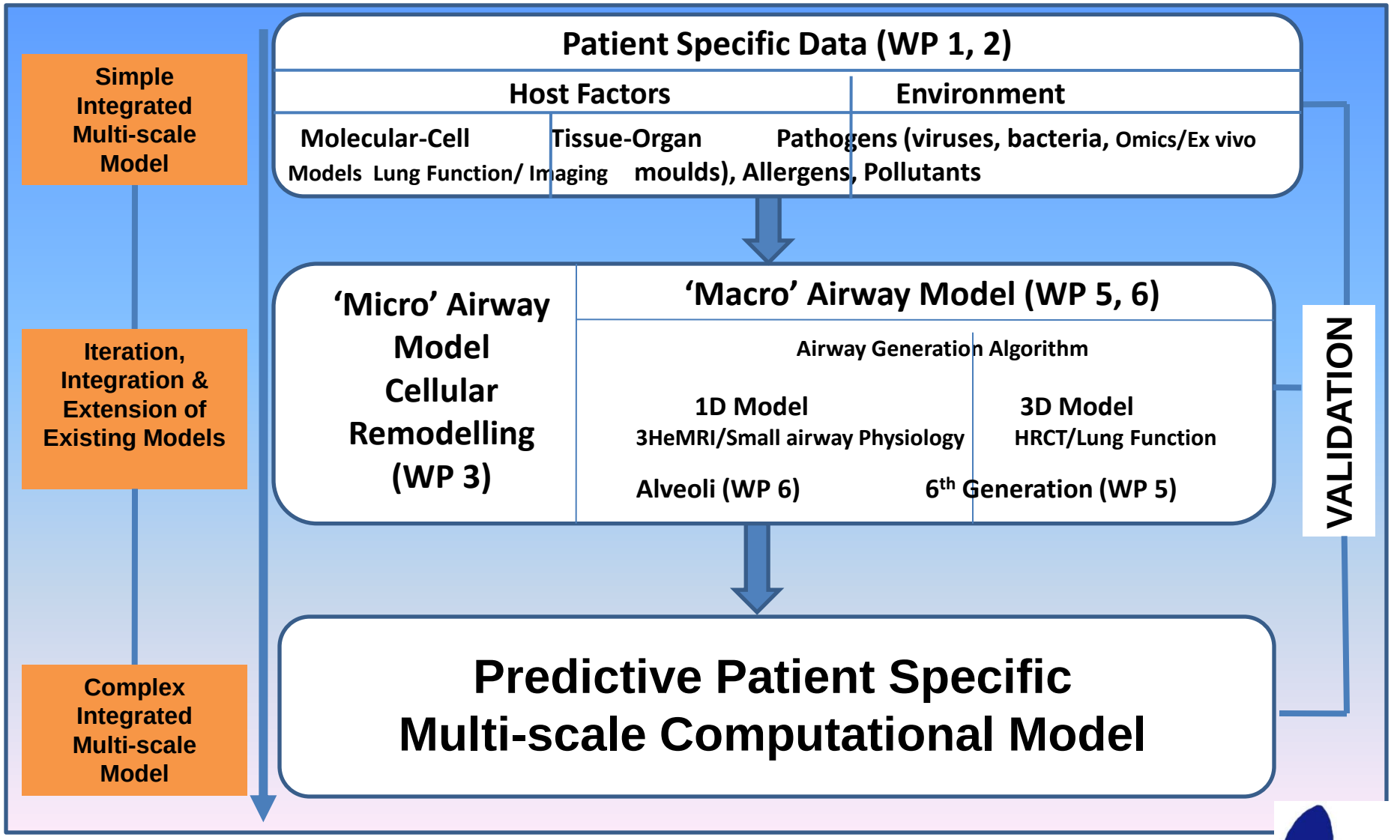
2. **Modify, extend and link existing models** of large and small airways to provide an integrated patient-specific predictive 'macro airway' model (UOXF.BL, USFD, UNOTT → WPs 4, 5, 6).

3. **Validate** the predictive capability of the 'macro airway' model using in vivo clinical studies (UOXF.BL, ULEIC).

4. **Multi-scale patient-specific computational airway model** integrated from the 'macro' and 'micro' models (UOXF.BL, USFD, UNOTT → WPs 3-6S).

5. **Validate** the predictive capability of the airway model using in vivo clinical studies (UOXF.BL, USFD, UNOTT, ANSYS, ULEIC).

Multi-Scale Integrative Model



WP3 & 8 Work Package Integration

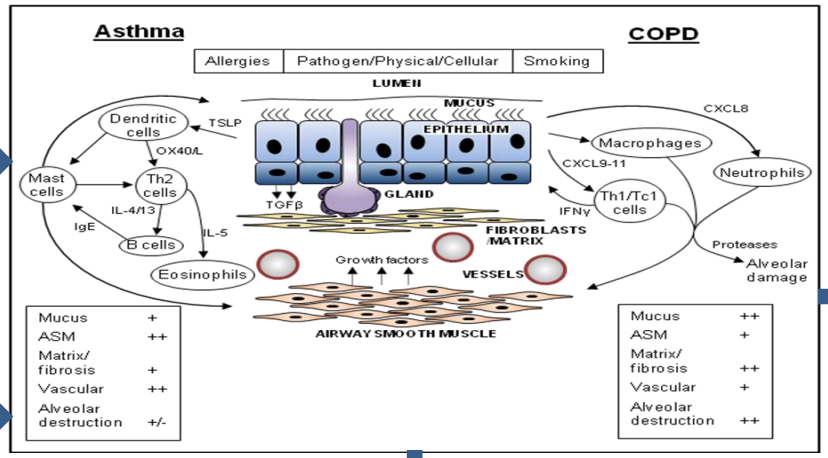
Challenges:
- TSLP
- Cytokines
- Pathogens

VENTILATION
Airway Model
Large (WP5) Small (WP6)

Macro small airways model constrained by image segmentation and properties from micro model (WP6)

CONTROL
Runtime:
- Initialisation to steady state
- Challenge
- Run to new steady state

INPUTS
Initialisation:
- Cell phenotype
- Active signalling
- pathways

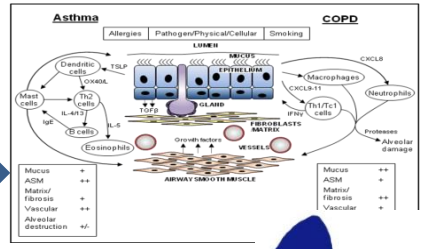


Data Repository (WP7)

INTERROGATE

Starting Conditions Determined from Multi-Scale Data (WP1,2)

Compare Time Series Data from model to clinical progression



WP8 Deliverables & Milestones

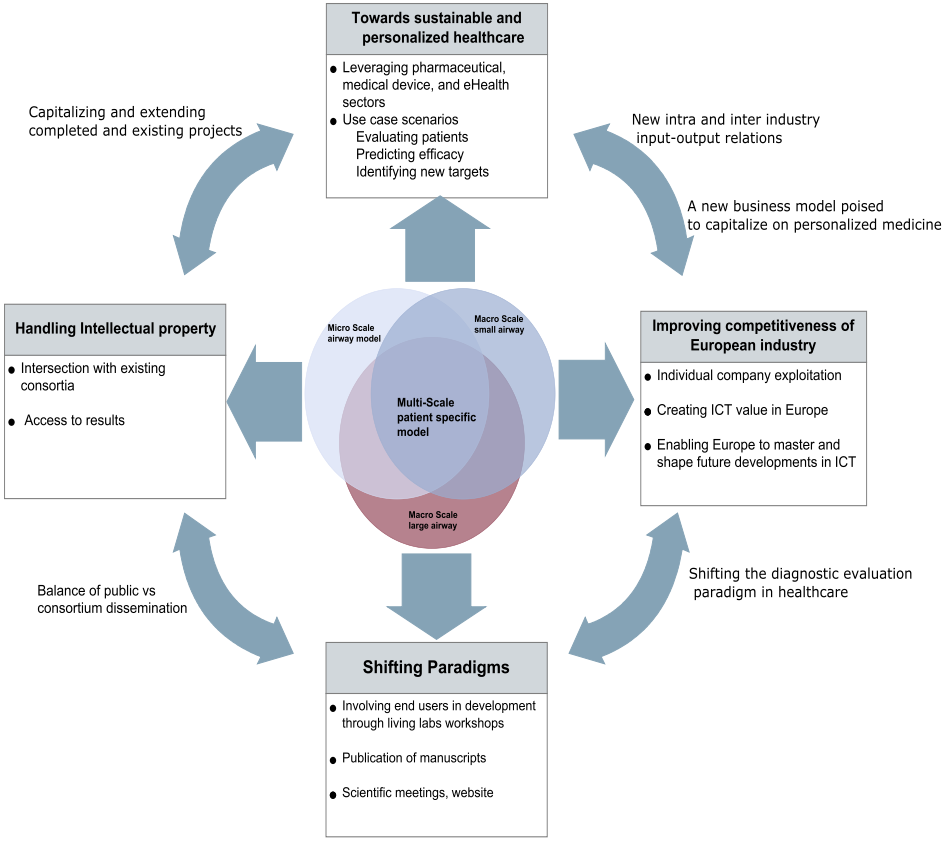
Deliverables WP8		Month
D8.1	Dataset multi-scale statistical modelling of cross-sectional data	36
D8.2	Dataset statistical modelling of longitudinal data	48
D8.3	'Macro-scale' computational airway model: validated patient specific image functional models	48
D8.4	'Multi-scale' patient specific airway model: validated and integrated 'macro' and 'micro' model (cycle #3)	58
Milestones		
M6	'black box' model ready for integration [shared with WP 3]	4
M29	Cross sectional statistical modelling at individual scales in parallel with WP 2 completed	24
M38	Longitudinal statistical modelling at individual scales in parallel with WP 2 completed	36
M8	Micro (WP 3), macro large airway (WP 5), macro small airway (WP 6) models integrated into patient specific model framework (black box).	6
M28	Micro (WP 3), macro large airway (WP 5), macro small airway (WP 6) models integrated into patient specific cycle #1	24
M43	Micro (WP 3), macro large airway (WP 5), macro small airway (WP 6) models integrated into patient specific cycle #2	42

WP9 Exploitation, training, dissemination

WP 9 Lead: Scott Wagers

Committee: Scott Wagers, Ian Sayers, Ann-Marie Audley, Susanna Palkonen

Scope- this work package will provide the framework to deliver the dissemination and exploitation of the technologies and platforms derived from AirPROM in order to translate the patient-specific computational predictive airway models into practice.



WP 9 Objectives

1) Assure exploitation

2) Support training efforts

3) Facilitate Dissemination

WP 9 Dissemination

Dissemination to:

1) Clinician/Scientists
   - Living labs

2) Public and policy makers
   - Website
   - Video
   - Dissemination kits
   - Press releases

WP Training

1) Establish post doc exchange
   - Living labs

2) Supporting PhD students with Knowledge Management
   - Use of knowledge management platform

WP 9 Exploitation

1) Living labs
   - Clinicians
   - Industry

2) Groundwork for exploiting Foreground
   - White papers
   - Exploitation committee
   - Market analysis

WP 9 Deliverables & Milestones

Deliverables WP9		Month
D9.1	Video describing consortium approach	6
D9.2	Report on foundation living lab workshops	14
D9.3	Report on patient specific model living lab workshops	42
D9.4	White papers on approach	12
D9.5	White paper on patient specific model	60
D9.6	Prospectus/exploitation plan	60
Milestones		
M7	External facing website	6
M12	Position paper describing approach submitted	9
M18	First living lab workshop	12
M51	Exploitation meeting	54

WP10 Scientific Coordination and Project Management

WP10 Committee: Chris Brightling, Scott Wagers and all other WP Leads

Scope- This work package will provides the framework to deliver the scientific coordination and project management to underpin the success of AirPROM.

Objectives

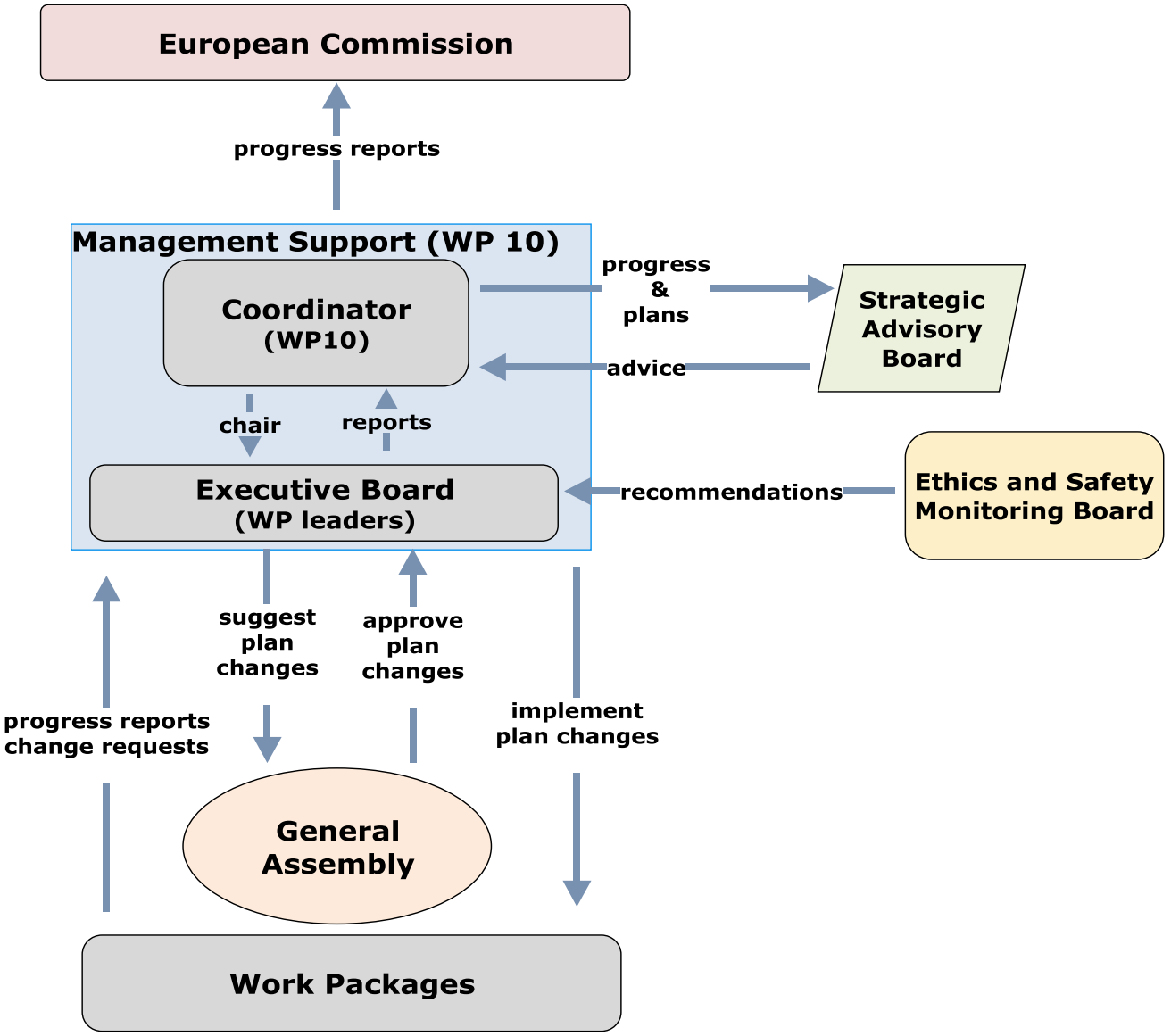
1. Ensure scientific coordination and integration

2. Provide collaboration infrastructure for facilitating interaction and monitoring progress

3. Monitor and assist in management of risks of non-delivery

4. Manage consortium finances

WP10 Management Structure



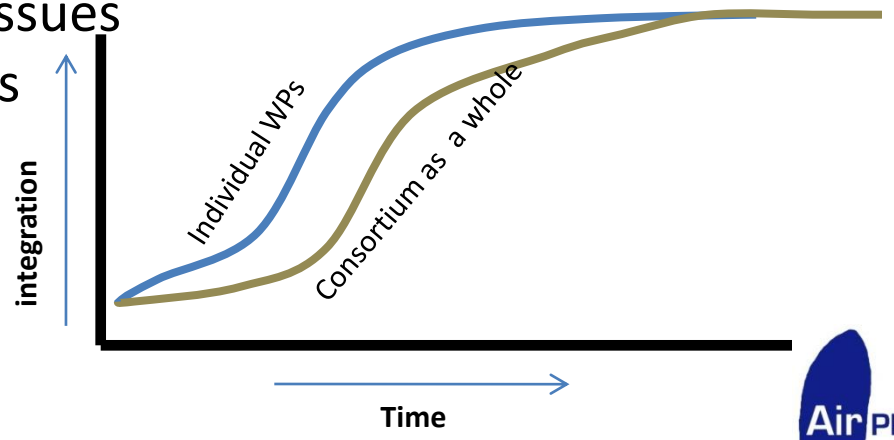
WP10 Risk Management

Barriers to integration:

1. Logistical issues
2. Lack of consortium wide interaction
3. Progress delays
4. Scientific – not yet feasible "focus on high risk ICT collaborative research"

Mitigation processes:

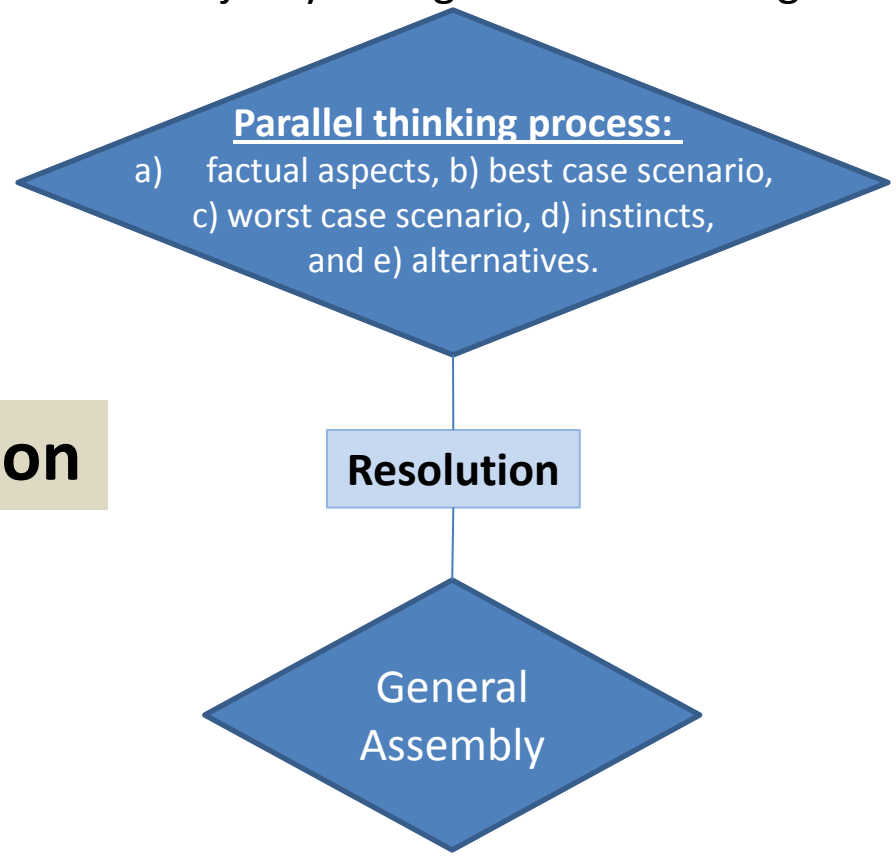
1. Proactive planning
2. Increasing integrative interactions
3. Heightened focus on inter WP issues
4. Raising awareness of milestones



WP10 Decision Making

- Decisions can only be made when 2/3 of a Consortium body members have had the opportunity to discuss the issue in a meeting/teleconference
- Meetings with <2/3 members present will carry all new decisions until next meeting
- Strive for consensus, otherwise majority voting with chair having casting vote

Conflict Resolution



WP10 Ethics

•**Ethical Principles-** The research proposed will be conducted in full compliance with the Helsinki Declaration and FP7 article 6 as well as any national laws or regulations in the countries where the research will be conducted. http://www.ccmo-online.nl/hipe/uploads/downloads/EU-2001-20_ENG.pdf.

•**Informed consent-** We will follow the European recommendations regarding informed consent: ftp://ftp.cordis.europa.eu/pub/fp7/docs/informed.consent.doc.

•**Anonymisation-** Encrypted databases for storage of coded patient data will be generated and coded patient data from existing databases will be used.

•**Management of ethical issues within AirPROM-**

- •**First level:** Overall co-ordination of the project
- •**Second level:** Ethics and Safety Board (ESB)

WP10 Ethics

Multi-scale Data

Cross-sectional, Longitudinal

Intervention Studies

AirPROM

WP10 Ethics

Procedure /Test	Risks involved	Risk Management
1) **Blood sampling**	Local pain, bleeding or infection	Appropriate treatment
1) **Induced sputum**	bronchoconstriction	Treatment with inhaled bronchodilators
1) **Bronchoscopy**	Minor damage to airways and vocal chords, bleeding, infection, pneumothorax	Procedure performed by experience bronchoscopist with ICU back-up. Monitoring of oxygen saturations and blood pressure before, during and after the procedure.
1) **Hyperpolarised ^{3}He / ^{129} Xe**	Exposure to non-ionising radiation, side effects due to helium or xenon inhalation	Subject screening to rule out contraindications for MRI, strict adherence to EU and local guidelines, investigation performed in presence of trained medical personnel with vital sign monitoring
1) **Computed Tomography scanning**	Exposure to ionising radiation, detection of clinically important pathology or malignancy	Audit scanner consoles to ensure effective radiation exposure is below 5 mSv during the course of the study, All scans reported by clinical radiologist to exclude clinically important pathology
1) **Genetic testing**	Confidentiality issues	All genetic data will be anonymised and coded. No personal information identifying the subject to the sample will be available to the researchers.

WP10 Deliverables & Milestones

Deliverables WP 10		
D10.1	Reports on yearly meeting	12
D10.2	Reports on advances in the field	24
D10.3	Reports on strategic advisory board input	12, 24, 36, 48
D10.4	Reports on Ethics and safety board meetings	12, 24, 36, 48
D10.5	Reports on model integration workshops	3, 18, 36, 54
D10.6	Yearly reports	12,24,36,48,60
D10.7	Next generation online collaboration platform	4
Milestones		
M4	Collaboration Platform established	3
M5	Organizational meeting convened	4
M21	First iterative cycle model integration workshop held	18

Appendix II – report of model integration meeting

AirPROM WP3 & WP8 Meeting Minutes

Nottingham June 7th 2011

Attendees:

Bindi Brook, Oliver Jensen, Igor Chernyavsky, Felicity Rose, Gavin Morris, Rod Smallwood, Asfaneh, Mark Burkitt, Kelly Burrowes, Rafael Bordas, Minsuok Kim, Lucy Peel/Woodman, Ruth Saunders, Chris Newby, Salman Siddiqui, Chris Brightling, Youngman Chung, Sherif Gonem, Andrew Leishman

1. Input / output / role summary

ACTION(S): BioSci Consulting to confirm timings of future TCs, try rotating chair of meetings, and send out agenda items + reminder prior to TC.

a. Experimental models (Lucy Woodman)

Inputs: IL-13, IL-18, IL-33 and TSLP, etc for Asthma and RAGE, etc for COPD

Outputs: Biomechanics and airway closure

Input models:

i) Primary cell ex vivo model (output: mesenchymal cell contraction and epithelial ciliary function, synthetic function for all cells).
ii) Self-reporting lung tissue model (output: initial examination of cell response to the PGLA fibre scaffolds – cell morphology, viability; progressing to examination of the role of individual cell types and impact of cell-cell interaction / cell interdependency through using nanosensors and cell tracker dyes).
iii) Precision cut lung slice model (viability can be 2 – 9 weeks) (output: airway contraction, cell migration and differentiation).

Models will consist of a broad range of cells from the airway (epithelial myo/fibroblasts, smooth muscle, mast cells) and will be developed in a collaboration between Nottingham and Leicester.

These studies address 3NCRs aims. Will also collaborate with MedImmune to test biological therapeutics (e.g. Ph II anti-IL-13, and IL-33).

b. Cellular models (Rod Smallwood)

Models based on what they have done with epithelial models. Agent based. Including different cell types represented as specific agents.

Setting up an SVN server in Sheffield – code repository, and test data sets stored there.

Need to discuss flow of data between sites.

Omics data to cell level model: Gene regulatory networks + signaling models. Need to establish what is necessary and feasible, where data held, etc. Large amounts of data will be generated.

Cell level model to/from cylindrical biochemical model: parameter values, loosely coupled, small amount of data.

Cylindrical biomechanical model to airway model: parameter values, loosely coupled, small amount of data.

Need to firm up populations of patients (including controls) that want to compare.

ACTION(S): Felicity Rose and modellers to discuss what signaling pathways, etc are most important to focus on and how to link these models together. Decide what is the simplest thing that can be made to get this started (e.g. start passing data that's already available). Needs to be driven by what biologists want. **Biologists and modellers** to arrange small F2F meetings to help facilitate increased understanding of each other's needs and to identify and agree on pieces of work.

Rod to make a 'shopping list' to send to Felicity so they know what parameters are required to construct the model with.

c. Tissue level models (Bindi Brook)

Cylindrical model. Stresses in thick muscle layer. Starting point will be stress in lung slices in response to agonists. Use lung slices to validate mathematical model.

Focus on airway wall (epithelium, fibroblast, ECM and ASM imposing axi-symetry). Plus parenchyma.

Inputs/Outputs: cell and organ models (elastic growth model, mechanical stress / strain distribution, etc).

Bindi – takes inputs from organ and cell level models

Inputs from cell models: Degradation, proliferation rates, etc

Input from organ level models: Parenchymal loads

Outputs to cell level – population densities, how these change within the cylindrical models.

Outputs to organ level: Vessel wall properties, thickness, layer stiffness

Note: this is just a model of smooth muscle contraction and does not consider air-flow, surfactants, or mucus.

ACTION(S): Modellers to discuss how best to homogenise data outputs from each model and identify which interactions are needed.

d. Statistical modeling (Chris Newby)

Typical respiratory outcomes (FEV1, FVC, Eos count, neutrophil count, etc).

Inputs: all quantitative measured variables (e.g. from CT scans).

Outputs: factor analysis / latent variable model.

Links: sputum cell counts to tissue level models, spirometry measurements and other demographics to whole organ.

Latent variable in asthmatics (e.g. atopy, lung volume, etc) - can potentially look at latent variables over time.

Can also test relationships between variables and latent variables.

Aim to identify correlations to determine specific pathways and pathologies (e.g. airway obstruction + eosinophilia link, etc). Can also add in new variables.

Implementation – will use R language with SEM packages.

Factor and pathway analysis – causality between factors.

e. Whole organ modeling (Kelly Burrowes)

WP8 aims to bring all the models together to a whole organ model.

WP1 + WP2 links to WP3, WP5 + WP6 which feed into WP8.

Input WP4, Outputs flows to WP3.

Areas to work on in WP8: Airway remodeling, Tissue deformation, Ventilation, Clinical outcomes and validation (need to discuss what is the most clinically useful (e.g. FEV1)).

CTs for asthma will be inhaled and exhaled. However, unlikely to have both CTs for COPD as normally just get one measurement.

WP6 will image small airways and can pass that information to WP8.

f. Desirable clinical outcomes (Salman Siddiqui)

Clinical study projects that will feed into AirPROM are: EVA (CT/GWAS readout driven), U-BIOPRED (integrated omics based handprints), and Asthma UK (UK based asthma longitudinal consortium).

AirPROM WP4 & WP5 will look at large airways CT, density, etc, small airways ventilation, etc, tissue biopsies, brushings, and Omics.

Outcomes should be Exacerbations (predict, prevent, prognosticate) + Stratify (patients).

Knowledge gaps that could be bridged in AirPROM: why do airways in respiratory patients close/narrow, and sometimes result in catastrophic closure.

Aim to link information to better select predictive intervention studies (c.f. IL-5 mAb intervention in eosinophilic asthmatics).

AirPROM Golden 60 (deep phenotyping of 20 asthma, 20 COPD, and 20 controls).

Desirable for AirPROM to create a unique identity (i.e. novel approach to stratify medicine).

Note that will also get environmental analysis data (i.e. characterise bacterial, viral and allergen load).

ACTION(S): All presenters to e-mail copies of slides to Bio Sci Consulting to log on AirPROM collaboration tool for everyone to see.

2. Discussion and allocation of tasks and deliverables

WP3 ‘Micro-airway model’ tasks –

Planar model: **Rod and Felicity**,

Model validation: **Lucy and Rod**,

Cylindrical airway model: **Bindi and Oliver**,

Embedding the micro-scale airway (cylindrical) model in the systems model (i.e. Application): **Bindi and Rod**

Note: First batch of CT scans have gone from Leicester to Paris, etc.

WP8 'Patient specific modeling: multi-scale integration' tasks –

Integration and extension of the statistical data analyses across the scales to identify groups with future risk of disease progression and response to therapy: **Chris N**,

Modify, extend and link existing models of large and small airways to provide an integrated patient specific predictive 'macro airway' model: **Kelly and Salman**,

Validate the predictive capability of 'macro' airway model using in vivo clinical studies: **Sumit and Kelly**,

Multi-scale patient-specific computational airway model integrated from the 'macro' and 'micro' models: **Kelly and Rod**,

Validate the predictive capability of airway model using in vivo clinical studies: **Sherif and Kelly**,

Project quality and assessment: **Chris B**

3. 12 month work plan. Informal discussion on the following topics:

    a. WP3 already discussed in meeting (see above)

    b. WP8 already discussed in meeting (see above)

    c. WP3 & WP8 integration already discussed in meeting (see above)

    d. Software – how will we integrate models? Version control server will be set-up at Sheffield and proposal to use a similar system for AirPROM. Server will force multiple users to reconcile a particular document. Could possibly link from Zoho project to server. However, problem might be the ability to track changes. **ACTION(S): Rod** to make recommendations to group.

e. SOPs – MIASE **ACTION(S): Everyone** to familiarize themselves with this new process to ensure SOPs can easily be followed by a third party.

f. Biomax – knowledge management survey **ACTION(S): Everyone** needs to complete using Zoho Creator. **BioSci Consulting** to resend instructions for logging in. **Rod** to e-mail Dieter about need for modeling to input already and then will e-mail other modelers on outcome.

g. Identify barriers/risks Main one is for Biologists and Modellers to start having smaller F2F meetings to understand each other's needs and capabilities and to identify pieces of work to get started with (in line with project aims). If these interactions don't start to happen quickly then there is a sizeable risk of not meeting timelines. Other challenges raised by Rod – Interface between biology and models? How do we coupled across the scales? What do we do about long time scales?

4. Summary & any other business

Plan to do a state of the art review and Chris B has already started to discuss options with journal editors.

Several people across AirPROM have been allocated to do 2-page reports. In effect, these will be filed and kept by EU (not published, just something we need to do). However, these 2-page reports could be used to start a formal publication submission to a journal, which provides added incentive to complete these reports. **ACTION(S): Kelly and Chris N** will complete 2-page reports for WP3 and WP8.