

3.5 Inflammatory Diseases

3.5.1 Summary

Chronic inflammatory diseases such as asthma and osteoarthritis affect one in three people in the developed world. There are many unmet medical needs in this field, not least because many medicines give only symptomatic relief rather than treating the underlying medical condition. This section looks at what needs to be done to improve this situation.

- Identify specific biomarkers (molecular and imaging) for inflammatory disease progression and surrogates of treatment outcome and safety. Validation of the target, using genomic programmes to follow certain mechanisms, is important, as this relationship is usually unknown;
- Pharmacogenetic analysis of inflammatory disease groups to subtype responders/non-responders (improved efficacy/safety ratio/predictive adverse effect risk);
- Increased research into disease mechanisms to provide for true disease modifying therapeutic opportunities, as distinct from simple symptomatic treatment;
- Earlier and more frequent interactions between academia, industry and regulators to understand the new sciences and technologies, and development of new and better guidelines;
- Faster and better access to therapeutics with high value outcomes in the EU;
- Develop validated quality-of-life measures that capture drug efficacy beyond primary endpoints used routinely, which could also be used to inform discussions on patient benefits of potential new therapies;
- Develop better *in vivo*, *ex vivo* and *in silico* disease models. This type of modelling should be based on a mechanistic understanding of the disease process as a function of time, and not merely on individual potential target molecules, in other words systems simulation versus target simulation. Consequently, there is a need to characterise disease progression, since this may lead to an overall reduction in the number and duration of clinical trials. To date, only a few attempts have been made to explore mechanistic modelling of inflammatory disease progression.

3.5.2 Introduction

Inflammation is the body's protective response to an injury. If this response goes unchecked, however, it can end up doing more harm than good, which is what happens in a variety of inflammatory disorders. These cover a broad spectrum of conditions, including: rheumatoid and osteoarthritis, asthma, inflammatory bowel disease (Crohn's disease and related conditions), multiple sclerosis, chronic obstructive pulmonary disease (COPD) and allergic rhinitis (hay fever).

Chronic inflammatory diseases represent the greatest collective burden of suffering and economic cost in the developed world:

- One-in-three people are affected;
- Tens of billions of euros in annual healthcare costs.

Rapid progress in inflammation science and medicine has led to many new treatments and reduced suffering for millions, but there is much still to be done. Many of the therapies currently available for inflammatory disorders treat only the symptoms of the disease, and not the underlying cause of inflammation. Although inflammation is the unifying factor among the diseases listed above, the treatment approach required for each type of inflammatory disease may be unique.

3.5.3 Present Status of the Disease Area

- Inflammation represents a wide range of diseases with individual needs;
- Early diagnosis is important for all inflammatory diseases;
- The lack of true disease-modifying treatments is major problem, although examples of disease modification are beginning to emerge in RA and some other inflammatory diseases;
- A greater understanding of pathophysiology is required:
 - The underpinning science is evolving, for example innate immunity and adaptive immunity, but there is a big gap between immuno-inflammatory pathway analysis and a true understanding of disease pathophysiology;
 - Translational inflammation research still nascent;
 - A lack of understanding of the links between pathophysiology, phenotype, genetic and protein markers and clinical outcomes;

- A lack of understanding of how specific inflammation responses or defects lead to different disease outcomes in various organ systems. What are the common themes within inflammation, and what are the differences that ultimately define the phenotypes?;
- Lack of efficacy is still a key issue;
- Safety is also currently an important issue:
 - A lack of understanding of how specific immunomodulation leads to various outcomes in efficacy, host defence, some predictable and unpredictable events;
- A lack of validated biomarkers:
 - Inadequate surrogates of long term benefit;
 - Lack of diagnostic, prognostic and safety markers;
 - Need for complex biomarkers and 'fingerprints' of efficacy and safety;
 - Mechanistic markers for POM;
 - Lack of standardisation.
- A lack of appropriate and predictive pre-clinical models linking human disease to animal models.

How are we Working?

- Multiple relatively small groups and networks:
 - National;
 - Disease-specific.
- The industry–academia interface is sporadic and unco-ordinated;
- Agreed Pan-European Diagnostic/Treatment Disease Definition & Rx standards are not available or not applied for most inflammatory diseases;
- The relationship with regulators could be enhanced;
- Regulatory guidelines require updating to reflect medical need, disease outcomes and appropriate end-points for clinical trials;
- The scientific–clinical interface requires significant improvement, with a focus on translational science, where bridging will be required;
- The interface between both academia and industry with patients at all levels is inadequate;
- There is a need for education, for physicians, scientists, patients and carers;
- Active patient involvement in programme design is needed;
- Active discussion and participation is needed from payers, healthcare providers and governments about the unmet medical need and what they are willing to pay.

Inflammatory Disease Areas where there is both an Unmet Need and an Opportunity

- Arthritis: chronic inflammatory components of osteoarthritis (OA) and rheumatoid arthritis (RA);
- Early diagnosis of RA, reverse, modify RA disease process;
- Early diagnosis of OA, retardation or inhibition of the development of joint destruction and prevention of OA development;
- Severe asthma and chronic obstructive pulmonary disease;
- Allergic rhinitis;
- Inflammatory bowel diseases;
- Chronic pain;
- Multiple sclerosis (already discussed in the section on brain disorders);
- Atherosclerosis;
- Transplantation;
- Eczema and psoriasis;
- Nephritis;
- Septic shock;
- Other less common inflammatory diseases, for example alveolitis, systemic lupus erythematosus and connective tissue diseases. Other inflammatory diseases could also benefit from work on the inflammatory disease areas identified above as high priority.

Arthritis

Arthritis is a chronic inflammatory disease induced when the immune system attacks and begins degrading joints in the body. The disease is present in all ethnic groups and exists in many forms, most commonly osteoarthritis and rheumatoid arthritis.

Osteoarthritis

Osteoarthritis (OA) is a progressive, degenerative joint disease, and is the most common form of arthritis. It can affect people at any age, but occurs most frequently in the middle-aged and the elderly. OA is characterised by the breakdown of the cartilage in the joint, causing the bones to rub against each other. The result is pain and a loss of movement; symptoms can range from mild to severe. Affected joints can also cause swelling, warmth, creaking and stiffness, particularly after periods of inactivity. Osteoarthritis is unlike other forms of autoimmune disease, such as rheumatoid arthritis or systemic lupus, as it does not affect other organs of the body. At present, there are no disease-modifying medicines on the market for OA. Therapy involves the symptomatic treatment of the pain and swelling in the joints.

The most interesting characteristic of the European epidemiology of OA, even compared to the US, is the relative size of the 45–64 year-old population. This demographic is very large in Europe and, as this generation continues to age, OA will clearly become an increasingly large problem and, therefore, an opportunity for the introduction of new disease-modifying medicines. See appendix 8.3 for data on OA.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease that affects the lining of the joints, causing pain, swelling and reduced mobility for the patient. The most common age of onset of RA is between 35 and 55. The disease, therefore, imposes enormous societal costs. RA is not as prevalent as more common musculoskeletal diseases such as OA, but because of its highly debilitating nature, patients bear a heavy disease burden. Work-related disability represents the single largest societal burden associated with RA, surpassing its total treatment costs. Recent prevalence studies and a general ageing of the population in developed countries have increased understanding of the disease burden associated with RA. In addition to causing significant morbidity and economic burdens, an increasing number of patient-based studies have shown that RA leads to premature death, which is associated with both rheumatoid complications and an increase in non-specific causes of death, such as infections. The exact mechanism of RA disease pathogenesis is not yet known, but it is strongly associated with genetic predisposition. RA therapy as a whole is still some way from reaching an efficacy ceiling. See appendix 8.3 for data on RA.

Asthma

Asthma is a common chronic disorder of the airways, characterised by airway inflammation, airway hyper-responsiveness and airway narrowing. It is reversible, either with treatment or spontaneously. The annual cost of asthma is estimated to be \$16.1 bn in the US and \$16.3 bn in the EU (NHLBI, 2004; ERS, 2004). See appendix 8.3 for data on asthma.

A survey of asthma severity in Europe (Rabe *et al.*, 2000) found that 18% of asthma patients had severe persistent, 19% moderate persistent, 19% mild persistent and 44% intermittent asthma. Severe asthma is a term that encompasses patients with steroid-resistant, irreversible, refractory, brittle, near fatal and poorly controlled asthma. Although some asthmatics have been severely affected for most of their lives, there appears to be a second group of mainly female, non-atopic adults that develop severe disease in adulthood (ENFUMOSA, 2003).

Asthma is a disease with a moderate-to-high level of unmet need; the high prevalence, extraordinary economic burden to society and significant rate of hospitalisation are balanced somewhat by the availability of effective treatments which, when used properly, are generally successful at controlling the disease. Despite the availability of successful treatments, there is considerable demand for more effective, more convenient medicines. Combined with the high patient population of this chronic disease, the R&D unmet need in asthma creates a significant opportunity for advancing more efficacious treatments.

The greatest need right now is for a disease-modifying drug. We need to be able to down-regulate the inflammatory response, and slow or stop the progression of the disease. This is likely a number of years down the road – Disease opinion leader.

The greatest unmet need is in the moderate-to-severe patient category. We also do not have any drugs that essentially cure the disease, that reverse airway remodelling and that fix airway hyper-reactivity. – Disease opinion leader.

Chronic Obstructive Pulmonary Disease (COPD)

The term chronic obstructive pulmonary disease (COPD) covers a complex group of disorders characterised by a progressive development of airflow limitation. It is set to become the third leading cause of death in the developed world by 2020 (Murray *et al.*, 1997). In 2002, COPD was the fourth most common cause of death in the US, with annual costs estimated to be \$37.2 bn – double that for asthma (NHLBI, 2004). See appendix 8.3 for data on COPD.

Although COPD and asthma are both chronic obstructive diseases of the lung, they differ markedly in the underlying disease process. Consequently, although the majority of medicines used to treat asthma and COPD are the same, they do not provide equivalent benefit in both diseases. Currently, smoking cessation is the only known means of halting the lung destruction associated with COPD, although cessation does not reverse the damage. Meanwhile, only half of moderate and severe COPD patients reach the desired outcome of symptomatic relief and an improved quality of life, largely as a result of the lack of truly efficacious drugs, which is the key factor preventing patients from reaching the desired outcomes.

There are no effective drugs for the loss of airway function. We need a drug that improves the quality of life, or survival. Anything that decreases exacerbations will be welcomed. – Disease opinion leader

I think that the biggest need is to reverse the downhill trend of chronic pulmonary insufficiency. Also, we haven't identified, or haven't had success with, the ability to treat the inflammatory process. – Disease opinion leader

I think the biggest issue in COPD is loss of lung architecture, and most of the anti-inflammatory approaches in COPD don't work very well. So I think there's an unmet need to grow back normal lung, especially alveoli. So, if someone could find appropriate growth factors that could restore lung architecture, then that would be a big breakthrough for that disease. – Disease opinion leader

There are no effective drugs for the loss of airway function. We need a drug that improves the quality of life, or survival. Anything that decreases exacerbations will be welcomed. –Disease opinion leader

Allergic Rhinitis

Allergic rhinitis is by far the most prevalent respiratory condition in the global market, with approximately 146 million sufferers. The close relationship between asthma and allergic rhinitis has led to the 'one airway, one disease' concept, which regards both diseases as a continuum of inflammation involving one common airway, rather than as distinct entities. According to the WHO initiative on allergic rhinitis and asthma, 10–20% of adolescents and 25–33% of adults are affected by allergic rhinitis. However, rates may differ as a result of variations in disease definition, diagnosis criteria and type of population studied. See appendix 8.3 for data on allergic rhinitis.

IBD – Crohn's Disease and Ulcerative Colitis

Crohn's disease (CD) is a chronic inflammation of the intestinal wall, typically affecting its full thickness. Most commonly, it occurs in the lowest portion of the small intestine (ileum) and the large intestine, but it can occur in any part of the digestive tract from the mouth to the anus, and the skin around the anus.

In recent decades, CD has become more common both in Western and developing countries. It occurs roughly equally in both sexes, and is more common among Jewish people. Most cases begin before the age of 30; the majority start between the ages of 14 and 24. The causes of CD are unknown.

Ulcerative colitis (UC) is a chronic disease in which the large intestine becomes inflamed and ulcerated, leading to episodes of bloody diarrhoea, abdominal cramps and fever. The disease can start at any age, but usually begins between the ages of 15 and 30. About 10% of patients who appear to have UC only suffer a single attack. However, a proportion of such patients may actually be suffering from an undetected infection rather than true UC. For most patients, UC is a chronic disease that waxes and wanes over time. The causes of UC remain unknown. See appendix 8.3 for epidemiology of the IBD population.

Physicians have ranked the lack of therapies for severe disease as an important unmet need in IBD, and drug R&D is still some way from reaching an efficacy ceiling.

Chronic Pain

In general, the management of inflammatory and neuropathic pain is still unsatisfactory with currently available medicines, and many people obtain only partial and temporary relief while experiencing problems with side-effects. The pathophysiology of chronic pain is poorly understood. It may be a result of persistent inflammation at the level of the first-order nociceptive neuron; plastic changes at the level of the dorsal horn neuron, thalamus, cortex or subcortical structures; or a combination of persistence inflammation and plastic changes. Although much research has been done to develop a better understanding of the pathophysiology of pain, neuronal mechanisms and pain pathways serving pain, much is still unknown. The promise of genomics and proteomics and other related technologies to enhance our understanding of the molecular-genetic basis of nociception, inflammation and plasticity in the nervous system will likely lead to new targets for analgesia in chronic inflammatory diseases such as RA and OA, and new chemical entities entering the drug development pipeline. The scientific challenge is to use existing and emerging expertise and technologies to:

- Identify which signals initiate plasticity and develop markers for these;
- Discover the participation of novel genes in plasticity that are relevant to pain mechanisms;
- Use imaging techniques to identify pain-activated areas in humans that may provide opportunities to follow effectiveness of new therapeutic approaches;
- Utilise this information to improve the diagnosis and initiate novel treatment strategies for pain.

Understanding analgesic mechanisms provides an opportunity to move forward to a new way of assessing analgesics, based on an understanding of the mechanisms involved rather than the empirical way in which analgesic development has been driven in the past. The way to move forward clinically is to measure multiple signs and symptoms, not just global measures, to evaluate the natural history, to validate mechanistic hypotheses, and to gain an insight into the mechanisms that operate in individual patients. It must be recognised that laboratory pain models should not only be disease models but also mechanism models, and that these models can be used to screen for novel targets and validate mechanisms using drugs and functional genomic approaches. One of the big challenges is to understand the mechanisms that convert short-term pain into a pain that persists and becomes intractable, rather than returning to baseline. How can treatments that prevent the development of long-lasting pain be effectively evaluated? Can patients be targeted more effectively by not treating the disease, but the actual mechanism that produces the pain?

The extrapolation from pre-clinical promise to validation of new therapeutic strategies in humans, however, is costly, time-consuming, and uncertain, representing significant challenges to analgesic drug development and regulatory oversight for safety and efficacy. Therefore, data that can be generated in disease models to help elucidate the mechanism of action for an unprecedented analgesic can supplement required clinical efficacy studies to increase confidence in rationale in the regulatory submissions. There is a critical need to combine pre-clinical pain models with information generated by anatomy and histochemistry to investigate the contribution of a receptor or channel on the animal's behaviour. These animal models allow the mechanism of novel drugs to be predicted in a pain state. However, they do not necessarily predict the response of a human to a particular drug. If a single model is insufficient, observing similar relative activity across several models provides convergent validation of the pharmacology of that drug's effect. If a drug does not show similar outcomes across models, it suggests that tissue injury models have their own distinct pharmacology. One model may be an effective screening tool that detects the activity of many drugs, while other models in which the same agonist does not work may represent models of hyperpathia. Convergent validity suggests that a prediction may play out over a variety of mechanisms.

Building on past research, there is a critical need to:

- Integrate the wealth of knowledge around various precedent mechanisms of action of analgesics;
- Understand the effects of NCEs on locally-released mediators of inflammation using *in vivo* microdialysis;
- Understand the effects of NCEs on first order nociceptive neurons (IAdelta and C-fibres) using evoked potentials;
- Understand the pharmacodynamics of BOLD fMRI signals in key brain regions known to subserve pain signalling in response to induced pain;

- Understand pharmacodynamic changes in putative nociceptive neuromodulators using magnetic resonance spectroscopy (MRS) and LC-MS of appropriate biofluids;
- Integrate all of the data to provide a reasonable mechanism of action should facilitate registration of unprecedented NCEs.

There is a major need for mechanism and outcome pain biomarkers to:

- Provide objective measurements of pain;
- Probe mechanisms of pain in man;
- Translate from animal to human biomarkers, and back-translate from patients to man to animals;
- Provide objective data to allow early go or no-go decisions on NCEs, particularly for unprecedented approaches;
- Provide information to help dose-set in Phase II studies.

Pain biomarkers need to be reproducible, robust and sensitive to clinical pain (disease effects) and to drug (pharmacological) effects, and to behave in a manner that is well enough understood to allow confident predictions to be made when they are employed in drug development studies.

3.5.4 Bottlenecks

The main issues considered by the working group were the following:

- Active patient involvement – a must-have in programme design;
- Early diagnosis is important for all inflammatory diseases;
- Some of the diseases are increasing in incidence and prevalence, and some like COPD are becoming the fastest growing common causes of death, morbidity and healthcare burden to society;
- Some common pathways understanding of the biology, for example from smoking, could help the understanding of the pathophysiology of COPD, lung cancer, atherosclerosis, Alzheimer's and so on;
- Other inflammatory diseases could also benefit from work on the identified high-priority inflammatory disease areas;
- Few disease modifying treatments are available in these indications – a critical gap;
- The underpinning science is evolving (for example macrophages, B cells, T cells, target tissues, genetics and, proteomics) but there is a big gap between inflammatory pathway analysis and true understanding of disease pathophysiology.

Patients

Given that the EU has judged it is important that the patient groups should be involved in the planning and operation of the research, it is an advantage that many inflammatory diseases influence quality-of-life and mortality, but still leave the subjects with significant morbidity and an enormous healthcare burden in an ageing population.

Professional Groups

The work proposal is itself multidisciplinary, and the overall proposal involves a unique combination of professionals (academics, clinicians), established industries (pharmaceuticals, diagnostics, scanning) and SMEs (biotechnology, diagnostics, special support services). Furthermore, each of those groups also includes a diverse array of talents. Thus, each project which is funded by the EU must involve a team, the individual members of which will have to teach their skills to the other members.

Industrial Growth

The established industries and the SMEs already have a substantial potential for growth, based on existing knowledge. However, the opportunities for the development of new areas are enormous, especially for SMEs.

These include, among many others:

- Biomarkers;
- Diagnostics;
- Therapeutics;
- Population screening;
- Education;
- Nanotechnology;

- Imaging hardware optimised for measurements;
- Software for image quantification.

The Rank Order of Importance of the Bottlenecks is:

- Patient recruitment;
- Identification and validation of biomarkers;
- Predictive pharmacology;
- Risk assessment.

3.5.4.1 Patient Recruitment (European Asset): Dedicated Contact Networks (Patients, Clinicians, Academia, Industry)

- Patient recruitment is often the time-limiting factor for clinical trials;
- A pan-European database of patients with inflammatory diseases with defined uniform diagnostic and patient history data, including prior drug exposure, HLA background, whether they are responders or non-responders, disease progression and effects of intervention;
- A pan-European IT infrastructure for clinical trial data management is technically within reach. If standards are established and adopted, this could eventually lead to large reductions in overhead costs for industry, and wider possibilities for academics to study healthcare intervention in pan-European collaborations. This would improve the competitive position of Europe versus the US and Japan considerably;
- A pan-European database will further aid research into inflammatory disease sub-groups, helping disease profiling;
- Identify and leverage evidence-based treatment benefits across different inflammatory diseases, and ensure rapid deployment across Europe of such therapies;
- A pan-European information campaign should inform the public about the safety of trials and the importance of participating for the benefit of healthcare;
- Identifying academic research centres would enable translational research activities, allowing a greater understanding of disease sub-groups, heterogeneity, and disease progression;
- Creation of Pan-European Research Hubs in different inflammatory disease areas that capture basic research, biomarker, clinical investigation techniques collectively building on national initiatives that already exist, such as the one for MS in Denmark;
- There is a need for an education and training component for clinicians, with protected time for research and trial work.

3.5.4.2 Identification and Validation of Biomarkers

Increasingly, information derived from clinical studies in the field of biomarkers and pharmacogenetics is being used in early development. The usage of both this information and data generated in early discovery will provide enhanced predictive capability of compounds' likely behaviour in man. This enables weak compounds to be dropped earlier in the development process, thereby reducing the resource burden associated with high rates of late-stage attrition and freeing pipeline resources. Importantly, the usage of clinical information in discovery will promote increased dialogue and collaboration between clinical and academic scientists, and those at the laboratory bench. Consequently, the industry can expect the new drug discovery paradigm to be based on the integration of fields such as genomics and proteomics, structural biology, chemistry, physiology, pharmacology and population biology, alongside the integration of the clinic and the laboratory.

The big areas for research are:

- Diagnostic & prognostic markers for inflammation and tissue damage;
- Surrogate markers for drug efficacy and safety;
- Markers of host-defence, risk-benefit evaluation and so on;
- Markers for functional recovery or disease modification;
- Predictive genotyping, although the societal implications of this must be considered;
- Population screening not only, through genetics but also using other technologies that can provide a high degree of specificity and sensitivity;
- **Pharmacogenetic markers** of inflammatory disease groups to subtype responders and non-responders, which should result in improved efficacy and safety ratios, and be predictive of adverse event risks;
- **Pharmacogenetics** (patients, ex: allotype responses to antibodies) – five years:
- Polyomics:

- Some of the emerging omics technologies will be useful in the area of identifying common pathways between apparently different diseases although, in this case, it will be important to establish primary aetiological changes from secondary effector mechanisms. A further use for both genetics and other omics will be the evaluation of the comparability of the animal models to human disease. They may, additionally, be useful in explaining the variation in response that is sometimes observed when compounds are tested against multiple animal models.
- **Pharmacogenomics** (diseases) – 20 years:
 - Increased target confidence in mechanisms for inflammation indications with positive human association;
 - The identification of common factors that increase risk or protect against multiple diseases suggests some common physiology, for example the Delta-32 CCR5 mutation confers protection against both rheumatoid arthritis and ischaemic heart disease. One of the key advantages of using genetics to identify these links is that a temporal relationship between the factor under study and the indication is established as germ-line genetic variation is essentially fixed at conception.
- **Imaging:** In monitoring disease progression by techniques such as MRI, the big areas for research are:
 - Bioimaging Centres of Excellence for Inflammatory Disease Groups will support the drug discovery and development process using whole body *in vivo* imaging techniques such as MRI, microPET, microCT and high resolution ultrasound. In addition to *in vivo* imaging capabilities, the COE can provide the PET radiotracer development and image analysis and processing solutions that are necessary for image quantification;
 - Linkage of imaging to monitoring disease activity and progression;
 - Standardisation of bioimaging modalities;
 - Building on Cambridge CoE for OA.

Validation of Biomarkers and Standardisation of Biomarker Assays

The big areas for research are:

- Establishing European standards for the validation of markers;
- Co-ordination of national networks, tissue banks, clinical expertise, SMEs' discovery and pharma;
- Regulatory standards and dialogue for the acceptance of validation.

3.5.4.3 Predictive Pharmacology

The big areas for research are:

- Development of *in vivo* and *in vitro* models that translate to human pathology, and are predictive of clinical efficacy and safety and host defence;
- Tools for functional pharmacology in humans;
- Access to appropriate diagnostic imaging and technology, plus technologists;
- Training of clinical and basic pharmacologists;
- Proof-of-concept networks in the academic sector;
- Systems approach to understanding disease processes;
- Modelling and simulation in inflammatory drug development:
 - *In silico* modelling and simulation can be applied at every stage of the drug development process, from the virtual modelling of cellular function, such as the whole network of molecular interactions involved in cell biology, to modelling virtual populations. These methods are considered the most likely source of the power and tools required for the much-needed re-organisation of drug development, providing the following can be achieved:
 - A framework for the continuous integration of drug development knowledge through a European web-based network;
 - Improved study designs and more informative studies;
 - Easier answers to regulatory questions, possibly eliminating the need for more clinical studies and ensuring an improved cost-benefit ratio.

- For this to happen, it will be necessary to:
 - Encourage the development and application of modelling and simulation;
 - Enhance the confidence of various partners in using models and their outcome;
 - Create models that are as mechanistically-based as possible:
 - Use recent advances in molecular modelling, high-performance computing technology, structural chemistry and PK/PD and disease modelling to develop new maps predicting molecular events to individual clinical and population outcomes;
 - Develop new technology platforms such as nanotechnology as systems integrators to study disease and develop new treatments with high value outcomes.
- The following partners are equally important in achieving this goal:
 - Academics: to develop the theoretical and conceptual basis for the model and perform quality assessment and control of components;
 - Big pharmaceutical companies: to conduct retrospective and prospective analyses of the application;
 - SMEs: to provide specific information, for example in the fields of IT and genomics;
 - Regulators: to conduct retrospective analyses of the application and establish good practice by providing anonymous data for the validation of models by academia and industry, and promoting confidence in modelling.

Systems Modelling – Disease Classification to Aid Clinical Disease Profile and Indications Discovery

Co-morbidities, although expressing different symptomatic phenotypes, are likely to provide evidence for uniting molecular pathologies, such as the recognition of obesity, diabetes and hypertension as symptoms of metabolic syndrome. For example, for 50 years it has been known that patients with rheumatoid arthritis are far more likely to develop cardiovascular problems as a result of arterial disease, yet only in the past couple of years have we begun to investigate and identify the common mechanisms that underlie the two conditions. Mathematical and textual meta-analyses of the existing (published and proprietary) data can be employed uncover co-morbidities. A second phase of dedicated investments in collaborative research work with academic epidemiologists could also be considered.

3.5.4.4 Risk Activity and Outcome Assessment with Authorities

The big areas for research are:

- Adaptive and innovative trial designs for Phase I, II and III;
- Bayesian methodology and other statistical techniques (e.g. N of 1 trials) to get an early read-out on efficacy and safety;
- Multidimensional scaling techniques;
- Developing, amending and applying validated quality-of-life and disease activity and severity measures that capture drug efficacy beyond primary end-points used routinely, and which could also predict the patient benefits of potential new therapies;
- Establishing good working practices with authorities early in the process;
- Electronic patient records and electronic data capture technologies.

3.5.5 Resources

Costs for many (but not all) of the individual inflammation efficacy enablers have been estimated, and are summarized in appendix 8.4. Most of the research topics proposed would last between five and seven years. The total cost of undertaking the enablers listed will exceed €300 mn over a period of five years. As many of these proposals are in outline format, the costs represent a best guess by the participant group. These figures will be updated as the proposals are developed and approved.

3.5.6 List of Contributors

Improved Predictivity of Efficacy Evaluation: Inflammatory Diseases			
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Patient Organisations	Johnstone	Robert	People with Arthritis/ Rheumatism in Europe
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8.3 Epidemiology Data on Inflammatory Diseases

Osteoarthritis current and future estimated prevalence by country, 2003 and 2010			
	2003	2010	CAGR (%)
US (000s) 1,3	26,060	29,466	1.8
US (% of population)	9.2	9.9	
Japan (000s) 1,2	15,935	17,924	1.7
Japan (% of population)	12.5	14.1	
France (000s) 1	5,804	6,356	1.3
France (% of population)	9.7	10.5	
Germany (000s) 1	8,596	9,600	1.6
Germany (% of population)	10.4	11.7	
Italy (000s) 1	6,248	6,808	1.2
Italy (% of population)	11	12.2	
Spain (000s) 4	4,780	5,270	1.4
Spain (% of population)	12.1	13.1	
UK (000s) 5	5,810	6,303	1.2
UK (% of population)	9.8	10.6	
Total	73,233	81,727	1.6
<p>1. Lawrence RC <i>et al.</i> (1998), Felson DT <i>et al.</i> (1987 and 1995) Lanes SF <i>et al.</i> (1997), Bolen J <i>et al.</i> (2002). 2. Yoshida S <i>et al.</i> (2002) 3. Hochberg <i>et al.</i> (1995) and RCGP 1991 Morbidity stats from General Practice and applied to US data. 4. Carmona L <i>et al.</i> (2001) 5. Felson <i>et al.</i> (1998) Stakeholder Insight: Osteoarthritis Survey (Q1.5) used to extrapolate total OA prevalence from studies on a single joint.</p>			

Rheumatoid Arthritis population, main five Europe, by age and sex, 2003					
	RA population by age (000s)				
	15–44	45–59	60–74	75+	Total
France male	1.3	17.7	21.4	18.4	58.8
France female	8.4	57.9	62.3	50.9	179.6
France total	9.7	75.5	83.7	69.4	238.4
Germany male	3.5	47.7	73.0	42.0	166.2
Germany female	19.8	134.5	184.3	126.6	465.2
Germany total	23.3	182.2	257.3	168.6	631.4
Italy male	1.0	13.8	20.5	16.3	51.6
Italy female	6.1	42.7	56.6	41.4	146.8
Italy total	7.1	56.5	77.1	57.7	198.4
Spain male	0.7	8.5	12.0	10.2	31.4
Spain female	7.0	42.0	52.7	39.7	141.3
Spain total	7.7	50.4	64.7	49.9	172.7
UK male	2.4	33.7	44.1	36.8	117.0
UK female	14.2	97.7	108.2	86.4	306.5
Main 5 EU male	9.0	121.3	171.0	123.7	424.9
Main 5 EU female	55.5	374.8	464.0	345.1	1,239.4
Main 5 EU total	64.5	496.1	635.0	468.7	1,664.3
Main 5 EU male	9.0	121.3	171.0	123.7	424.9
Source: Symmons et al, 2002 (UK); Saraux et al, 1999 (France); Cimmino et al, 1998 (Italy); Carmona et al, 2001 (Spain), UN Population Database, 2003					

TRA prevalence, main five Europe, 2003						
	France	Germany	Italy	Spain	UK	Total
% of population, 15+	0.49%	0.90%	0.40%	0.51%	0.88%	0.67%
Source: Symmons et al, 2002 (UK); Saraux et al, 1999 (France); Cimmino et al, 1998 (Italy); Carmona et al, 2001 (Spain), UN Population Database, 2003;						

Asthma prevalence and diagnosed population by country and age, 2005								
	US	Japan	France	Germany	Italy	Spain	UK	Average
Prevalence (%)								
Children (0–14)	7.9	5.7	6.1	7.1	6.0	4.8	13.7	7.3
Adults (15–64)	7.2	3.6	4.6	4.4	3.6	4.0	7.9	5.0
Elderly (65+)	8.7	5.1	6.1	5.9	5.1	5.5	9.4	6.5
Average	7.9	4.8	5.6	5.8	4.9	4.8	10.3	6.3
Population (m)*	US	Japan	France	Germany	Italy	Spain	UK	Total
Children (0–14)	63.6	17.9	11.2	11.9	8.0	5.8	10.7	129.1
Adults (15–64)	199.6	84.9	39.6	55.3	38.1	28.3	39.4	485.2
Elderly (65+)	36.9	25.2	9.9	15.4	11.2	7.1	9.5	115.2
Total	300	127.9	60.7	82.6	57.3	41.2	59.6	729.3
Asthma population (m)	US	Japan	France	Germany	Italy	Spain	UK	Total
Children (0–14)	5.0	1.0	0.7	0.8	0.5	0.3	1.5	9.5
Adults (15–64)	14.4	3.1	1.8	2.4	1.4	1.1	3.1	24.5
Elderly (65+)	3.2	1.3	0.6	0.9	0.6	0.4	0.9	7.5
Total	22.6	5.4	3.1	4.2	2.4	1.8	5.5	41.5
Diagnosed population (m)	US	Japan	France	Germany	Italy	Spain	UK	Total
Children (0–14)	3.4	0.7	0.5	0.6	0.3	0.2	1.0	6.7
Adults (15–64)	12.1	2.6	1.5	2.0	1.2	1.0	2.6	22.9
Elderly (65+)	1.6	0.6	0.3	0.5	0.3	0.2	0.4	3.9
Total	17.1	3.9	2.3	3.1	1.8	1.3	4.1	33.5
<i>* UN database figures</i>								
Source: DMHC2046								

COPD prevalence and diagnosed population by country and disease severity, 2005								
	US	France	Germany	Italy	Spain	UK	Japan	Total
Population* (m)	300.0	60.7	82.6	57.3	41.2	59.6	127.0	728.4
Prevalence (%)	4.1	4.4	4.6	4.6	4.4	4.3	4.4	
Segment size (m)	12.3	2.7	3.8	2.6	1.8	2.6	5.6	31.4
Mild (31%)	3.8	0.8	1.2	0.8	0.6	0.8	1.7	9.7
Moderate (35%)	4.3	0.9	1.3	0.9	0.6	0.9	2.0	11.0
Severe (34%)	4.2	0.9	1.3	0.9	0.6	0.9	1.9	10.7
Diagnosed population (m)								
Moderate (~0%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Moderate (~50%)	2.2	0.5	0.7	0.5	0.3	0.5	1.0	5.5
Severe (~90%)	3.8	0.8	1.2	0.8	0.6	0.8	1.7	9.6
Total diagnosed population (m)	5.9	1.3	1.8	1.3	0.9	1.3	2.7	15.1
* UN database figures								
Source: DMHC1615								

Allergic rhinitis prevalence and population by country, 2005								
	US	France	Germany	Italy	Spain	UK	Japan	Total
Population (m)	300.0	60.7	82.6	57.3	41.2	59.6	127.0	728.4
Prevalence (%)	19.8	24.6	18.2	17.1	14	26.5	19.6	n/a
Allergic rhinitis population (m)	59.4	14.9	15	9.8	5.8	15.8	25.1	145.8
* UN database figures								
Source: DMHC1936								

Prevalence and incidence of CD by country							
Country	Population, 000s	Prevalence per 100,000	Prevalence	Annual incidence 100,000	inci-per	Annual incidence	inci-
US	293,028	144.1	422,253	5.8		16,996	
Japan	127,333	5.85	7,449	0.51		649	
France	60,424	30.7	18,550	9.2		5,559	
Germany	82,425	30.7	25,304	4.4		3,627	
Italy	58,057	40.0	23,223	2.5-4.4		2,555	
Spain	40,281	19.8	7,976	5.1-5.2		2,095	
UK	60,271	75.8	45,685	3.8		2,290	
Totals	721,819	N/a	550,441	N/a		33,770	

US: Loftus EV Jr <i>et al.</i> , Crohn's disease in Olmsted County, Minnesota, 1940-1993: incidence, prevalence, and survival. <i>Gastroenterology</i> . 1998 Jun; 114 (6): 1161-1168. Erratum in: Loftus EV Jr, Reply. <i>Gastroenterology</i> . 1999 Jun; 116 (6): 1507.					
Japan: Morita N <i>et al.</i> , Incidence and prevalence of inflammatory bowel disease in Japan: nationwide epidemiological survey during the year 1991. <i>Journal of Gastroenterology</i> . 1995 Nov; 30 Suppl 8: 1-4.					
France: prevalence: German prevalence applied to French population; incidence: Shivananda S <i>et al.</i> , Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). <i>Gut</i> . 1996 Nov; 39 (5): 690-697.					
Germany: prevalence: Gastro-Pro; incidence: Shivananda S <i>et al.</i> , Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). <i>Gut</i> . 1996 Nov; 39 (5): 690-697.					
Italy: prevalence: Trallori G <i>et al.</i> , A population-based study of inflammatory bowel disease in Florence over 15 years (1978-92). <i>Scandinavian Journal of Gastroenterology</i> . 1996 Sep; 31 (9): 892-899; incidence: Shivananda S <i>et al.</i> , Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). <i>Gut</i> . 1996 Nov; 39 (5): 690-697.					
Spain: prevalence: Gastro-Pro; incidence: Shivananda S <i>et al.</i> , Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). <i>Gut</i> . 1996 Nov; 39 (5): 690-697.					
UK: prevalence: Gastro-Pro; incidence: Shivananda S <i>et al.</i> , Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). <i>Gut</i> . 1996 Nov; 39 (5): 690-697.					
Where range is given for incidence, higher estimate is used to calculate patient numbers					
Totals may not tally due to rounding					
na: not applicable					
Prevalence and incidence of UC by country					
Country	Population, 1000s	Prevalence per 100,000	Prevalence	Annual incidence per 100,000	Annual incidence
US	293,028	229	671,034	7.6	22,270
Japan	127,333	18.12	23,073	1.95	2,483
France	60,424	27.3	16,496	6.7	4,048
Germany	82,425	27.3	22,502	4.1	3,379
Italy	58,057	121.0	70,249	8.6-9.1	5,283
Spain	40,281	109.96	44,293	7.4-9.8	3,948
UK	60,271	30-122	73,531	10	6,027
Totals	721,819	N/a	921,177	N/a	47,439
US: Loftus EV Jr <i>et al.</i> , Ulcerative colitis in Olmsted County, Minnesota, 1940-1993: incidence, prevalence, and survival. <i>Gut</i> . 2000 Mar; 46 (3): 336-343.					
Japan: Morita N <i>et al.</i> , Incidence and prevalence of inflammatory bowel disease in Japan: nationwide epidemiological survey during the year 1991. <i>Journal of Gastroenterology</i> . 1995 Nov; 30 Suppl 8: 1-4.					
France: prevalence: German prevalence applied to French population; incidence: Shivananda S <i>et al.</i> , Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). <i>Gut</i> . 1996 Nov; 39 (5): 690-697.					
Germany: prevalence: Dirks E <i>et al.</i> , [Prospective study of the incidence and prevalence of ulcerative colitis in a large urban population in Germany (western Ruhr area)]. <i>Zeitschrift für Gastroenterologie</i> . 1994 Jun; 32 (6): 332-337; incidence: Shivananda S <i>et al.</i> , Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). <i>Gut</i> . 1996 Nov; 39 (5): 690-697.					
Italy: prevalence: Trallori G <i>et al.</i> , A population-based study of inflammatory bowel disease in Florence over 15 years (1978-92). <i>Scandinavian Journal of Gastroenterology</i> . 1996 Sep; 31 (9): 892-899; incidence: Shivananda S <i>et al.</i> , Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). <i>Gut</i> . 1996 Nov; 39 (5): 690-697.					
Spain: prevalence: Saro Gismera C <i>et al.</i> , [Incidence and prevalence of inflammatory bowel disease. Asturian study in 5 areas (EIICEA). Spain]. <i>Anales de Medicina Interna</i> . 2003 Jan; 20 (1): 3-9; incidence: Shivananda S <i>et al.</i> , Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). <i>Gut</i> . 1996 Nov; 39 (5): 690-697.					
UK: prevalence: Gastro-Pro; incidence: Shivananda S <i>et al.</i> , Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). <i>Gut</i> . 1996 Nov; 39 (5): 690-697.					

8.4 Inflammatory Diseases Detailed Analysis

8.4.1 Osteoarthritis

Priority Research Area	Enabler Description ¹	Rationale ²	Enabler Scope ³	Technical Feasibility	Key players, networks and org.'s	Who will do it	Total Estimated External Investment Cost (€€)	Metrics of Success	Comments
Develop validated QoL measures that capture drug efficacy beyond primary endpoints used routinely, which could also predict pharmacoeconomic benefits of potential new therapies.	Biomechanical property evaluation tools.	The availability of biochemical evaluation tools and their relation to quality of life markers would enable to predict the impact of deterioration or improvement on the patients and better assessment of therapies.	specific	Under Validation	European orthopaedic research society, EULAR, Patient groups	Academia = industry > patients > Clinicians		Validated Accepted	
Develop better disease models (especially in vivo), which are more predictive for drug efficacy.	Develop Clinical OA subtype specific animal models.	Development of subtype specific animal models of OA will allow to develop subtype specific therapies to be subsequently tested in clinical trials.	specific	Under Validation	EULAR; European Orthopaedic Research Society; Industry	Industry = Academia > Clinicians = Patients	8M€ over 5 year	Validated Accepted	No NIH initiatives

¹ (Outline of the scientific approach)

² (How does the efficacy enabler address the bottlenecks?)

³ (Consideration of managing generic issues eg biomarkers centres for more than one disease area)

Priority Research Area	Enabler Description ¹	Rationale ²	Enabler Scope ³	Technical Feasibility	Key players, networks and org.'s	Who will do it	Total Estimated External Investment Cost (€€)	Metrics of Success	Comments
Increased research into disease mechanisms to provide for true-disease modifying therapeutic opportunities as distinct from simple symptomatic treatment.	Genomic diagnostic, prognostic, outcome biomarkers.	Biochemical and Genomic biomarkers would identify the patient characteristics associated with early OA as well as those associated with more rapid progression of OA for the selection of patient populations for POM/POC trials.	specific	Under Validation	EULAR; European Orthopaedic Research Society; Institute of Biochemistry, Lund	Clinicians = Patients = Academia > Industry	2000 pts; 20M€ over 5 year	Validated Accepted	US NIH Program (OAI) already initiated - read out 2005-2010 [This is not a program that will provide much information on disease mechanisms. Rather it will provide information on how a variety of indicators change over the 5 year period.
Develop validated QoL measures that capture drug efficacy beyond primary endpoints used routinely, which could also predict pharmacoeconomic benefits of potential new therapies.	Joint function assessment tools.	Validated Joint function assessment tools would allow to determine quality of life and changes in quality of life within short term after initiation of therapy and improve the evaluation of response to therapy.	specific	Under Validation	EULAR; European Orthopaedic Research Society; Institute of Biochemistry, Lund	Academia = Patients = Clinicians > Industry	Subsets of patients needed; total 5000 over 5 years; 6M€ over 5 years		
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome.	Imaging biomarkers	A more sensitive and precise imaging biomarker could identify a compound early in development that significantly alters the rate of progression of OA through reduction of joint (e.g., cartilage) destruction.	OA & RA	Mature	EULAR; European Orthopaedic Research Society; Institute of Biochemistry, Lund	Clinicians = Patients = Academia > Industry			US NIH OAI Project. The project does not contain any intervention.
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome.	Biochemical outcome, mechanism, diagnostic, prognostic biomarkers.	Biochemical and Genomic biomarkers that can identify early in development a compound capable of significantly altering the progression of OA would allow pursuit of a product concept that is cost-prohibitive with the available technology.	specific		EULAR; European Orthopaedic Research Society; Institute of Biochemistry, Lund;	Clinicians = Patients = Academia > Industry	2000 pts; 25M€ over 7 year		

THE INNOVATIVE MEDICINES INITIATIVE

THE INNOVATIVE MEDICINES INITIATIVE

Priority Research Area	Enabler Description ¹	Rationale ²	Enabler Scope ³	Technical Feasibility	Key players, networks and org.'s	Who will do it	Total Estimated External Investment Cost (€€)	Metrics of Success	Comments
Develop validated QoL measures that capture drug efficacy beyond primary endpoints used routinely, which could also predict pharmacoeconomic benefits of potential new therapies.	Outcome research questionnaires. Specific outcome studies demonstrating reduction in time to joint replacement would be valuable.	QoL measures validated for OA would allow to identify patients with the highest need of therapeutic intervention and to assess response to therapy; they would also allow to discern the best Bio-Imaging markers to be used as surrogates.	OA	Under Validation	EULAR; European Orthopaedic Research Society	Clinicians = Patients > Academia > Industry	3000 pts; 6M€ over 5 year		Competition in Canada; Australia; US
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome.	Develop biochemical marker kits for in office physician use with following attributes (1) Easy access (2) Implementable in clinic, lab or home (3) Results can be interpreted by PCPs, rheumatologists & orthopaedic specialists to monitor efficacy.	This would allow early diagnosis and introduction of disease modifying intervention before major tissue damage has occurred.	OA	Under Validation	EULAR; Nordic Bioscience	Industry = SMEs > Academia > Clinicians = Patients	5000 pts; 15M€ over 5 year		

8.4.2 Rheumatoid Arthritis

Priority Research Area	Enabler Description ¹	Rationale ²	Enabler Scope ³	Technical Feasibility	Key players, networks and org.'s	Who will do it	Total Estimated External Investment Cost (€€)	Metrics of Success	Consideration of interaction with KM, E&T and Safety	Comments
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome.	Imaging/Biochemical Diagnostic Biomarkers. To select patients with early disease.	This would allow initiation of early treatment to appropriate patients which could lead to prevention and delay of joint damage & disability and improvement in remission. Could also potentially identify novel targets.	RA	Under Validation	EULAR	Academia = Industry = SMEs > Clinicians = Patients	2000 pts; 30M€ over 5 year			Europe Leading Edge
Develop better disease models (especially in-vivo), which are more predictive for drug efficacy.	Need models that reflect clinical chronicity & exacerbation pattern of RA.	Would allow for better drug targeting & validation. Models need to be validated through genomic comparison of key pathways in models and patients.	specific	Under Validation	EULAR; IP Autocure	Industry = Academia > Clinicians = Patients	12M€ over 5 year	Validated Accepted		
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome.	Imaging/Biochemical Prognostic Biomarkers. To identify patients at risk for rapid progression to shorten clinical trials.	This would allow initiation of early treatment to appropriate patients which could lead to prevention and delay of joint damage & disability and improvement in remission. Could also potentially identify novel targets.	RA	Under Validation	EULAR	Academia = Industry = SMEs > Clinicians = Patients	2000 pts; 40M€ over 7 year			Europe Leading Edge
Increased research into disease mechanisms to provide for true-disease modifying therapeutic opportunities as distinct from simple symptomatic treatment.	Epidemiological studies to identify at risk populations; to select patients with early disease and to identify patients at risk for rapid progression to shorten clinical trials.	Better knowledge on disease mechanisms would allow the development of better targeted therapies; knowledge on subsets of disease would allow specific-tailored therapies to be developed and tested, including improved assessment of benefit: risk ratios	RA	Under Validation	National databases & EULAR	Clinicians = = Industry = Patients > Academia	30,000 pts; 20M€ over 7 year		Knowledge Management	Europe Leading Edge

Priority Research Area	Enabler Description ¹	Rationale ²	Enabler Scope ³	Technical Feasibility	Key players, networks and org.'s	Who will do it	Total Estimated External Investment Cost (€€)	Metrics of Success	Consideration of interaction with KM, E&T and Safety	Comments
Develop validated QoL measures that capture drug efficacy beyond primary endpoints used routinely, which could also predict pharmaco-economic benefits of potential new therapies.	Prognostic Disability & Activity Scores.	New and better tools to address novel endpoints such as remission or to distinguish better between effects of different therapies would allow to better address the efficacy of novel targeted therapies and reduce trial sizes.	RA	Under Validation	EULAR	Clinicians = Industry = Patients > Academia	10,000 pts; 8M€ over 5 year		Knowledge Management	
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome.	Develop biochemical marker kits for in office physician use.	Important for early disease detection, prognostication and early therapy.								
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome.	Imaging Outcome Biomarker Joint ultrasonography. Sensitive for measuring synovial inflammation via detection of synovial thickening and synovial vascularity. Inexpensive. Prone to operator and reader bias, potential issues with reproducibility renders.	Use of novel biomarkers of disease progression would allow earlier recognition of treatment effects or failures and to reduce the length and the size of trials.	RA	Under Validation	EULAR	Academia = Patients > Clinicians > Industry	2000 patients; 20M€ over 5 years			
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome.	RA biomarker that correlates with clinical outcomes.	Availability of prognostic biomarkers would allow to subset patients for clinical trials and improve long-term outcome of disease by directing intensive therapies to such populations; this would also improve the benefit: risk ratio	RA	Under Validation	EULAR	Academia = Patients > Industry > Clinicians	4000 patients; 8M€ over 5 years			

Priority Research Area	Enabler Description ¹	Rationale ²	Enabler Scope ³	Technical Feasibility	Key players, networks and org.'s	Who will do it	Total Estimated External Investment Cost (€)	Metrics of Success	Consideration of interaction with KM, E&T and Safety	Comments
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome.	Safety biomarker for immunosuppressive side-effects. This is a necessity in RA where physicians are uneasy with broad immunosuppressives.	Availability of biomarkers to predict safety of therapies would decrease adverse events and increase benefit: risk ratio	All diseases	Under Validation	All major European Societies	Industry > Academia = Patients > Clinicians				
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome.	Prednisone Methods Study in humans: Identify inflammation and side-effects biomarkers that are differentially modulated by prednisone.	Such biomarkers would allow to design 'safe' glucocorticoids which are badly needed given their excellent therapeutic effects but having a significant adverse event profile.	All diseases	Under Validation		Industry > Academia = Patients > Clinicians				

8.4.3 COPD

Priority Research Area	Enabler Description ¹	Rationale ²	Enabler Scope ³	Technical Feasibility	Key players, networks and org.'s	Existing infrastructure and infrastructure needs ⁴	Who will do it	Total Estimated External Investment Cost (€€)	Metrics of Success	Comments
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome.	Biomarkers of lower airway inflammation.	Inflammation of the lower airways is a recognized as an important component of the pathophysiology of both severe asthma and COPD. Currently accepted measures of the effects of inflammation, such as lung function tests, are all indirect and not sufficient.	Specific	Under Validation	ERS	ATS-ERS Joint Task Force on COPD Biomarkers	Clinicians = Patients = Academia > Industry	2000 pts; 10M€ over 5 year	Validation Accepted	ERS-ATS workshop on biomarkers in COPD; SMEs.
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome.	Biomarker of disease progression.	The inflammation in the airways changes during COPD stages of disease. Current accepted measures do not reflect this.	specific	Under Validation	ERS		Clinicians = Patients = Academia > Industry	2000 pts; 5M€ over 5 year	Validation Accepted	
Develop better disease models (especially in-vivo), which are more predictive for drug efficacy.	Model of lung destruction & physiology.	Further our knowledge of the pathways driving tissue inflammation & tissue destruction.	specific	Under Validation	Industry; SMEs; Academia		Industry = SMEs > Academia > Clinicians = Patients	10M€ over 5 year	Validation Accepted	US; Canada; Australia

¹ (Outline of the scientific approach)

² (How does the efficacy enabler address the bottlenecks?)

³ (Consideration of managing generic issues eg biomarkers centres for more than one disease area)

⁴ (eg hubs, imaging centers of excellence, patient DBs)

Priority Research Area	Enabler Description ¹	Rationale ²	Enabler Scope ³	Technical Feasibility	Key players, networks and org.'s	Existing infrastructure and infrastructure needs ⁴	Who will do it	Total Estimated External Investment Cost (€€)	Metrics of Success	Comments
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome.	Airway Challenges/PFT	A model of neutrophilia that could allow for POM studies which targeted therapies.	specific	Under Validation	Academia; Clinicians		Clinicians = Patients = Academia > Industry	200 pts; 3M€ over 2 year	Validation Accepted	

8.4.4 COPD/Severe Asthma

Priority Research Area	Enabler Description ¹	Rationale ²	Enabler Scope ³	Technical Feasibility	Key players, networks and org.'s	Existing infrastructure and infrastructure needs ⁴	Who will do it	Total Estimated External Investment Cost (€€)	Metrics of Success	Comments
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome.	Biomarkers in Exhaled Breath Condensate/sputum.	Non-invasive means of measuring airway inflammation & control. The HbA1C of asthma!!	specific	Under Validation	ERS; SMEs; Industry	EU Collaboration on Severe Asthma (BIOAire) & ATS-ERS Joint Task Force on COPD Biomarkers	Industry = SME = Academia > patient = Clinician	1000 pts; 2M€ over 2 year	Validation Accepted	ERS-ATS workshop on biomarkers in COPD; Nth American Investigators in collaboration with Industry.

¹ (Outline of the scientific approach)

² (How does the efficacy enabler address the bottlenecks?)

³ (Consideration of managing generic issues eg biomarkers centres for more than one disease area)

⁴ (eg hubs, imaging centers of excellence, patient DBs)

Priority Research Area	Enabler Description ¹	Rationale ²	Enabler Scope ³	Technical Feasibility	Key players, networks and org.'s	Existing infrastructure and infrastructure needs ⁴	Who will do it	Total Estimated External Investment Cost (€€)	Metrics of Success	Comments
Increased research into disease mechanisms to provide for true-disease modifying therapeutic opportunities as distinct from simple symptomatic treatment.	Genomic diagnostic, prognostic, outcome biomarkers.	Biochemical and Genomic biomarkers would identify the patient characteristics associated with early COPD and Severe Asthma as well as those associated with more rapid progression of disease for the selection of patient populations for clinical trials.	specific	Under Validation	ERS		Clinicians = Patients = Academia > Industry	2000 pts; 20M€ over 5 year	Validation Accepted	
Develop better disease models (especially in vivo), which are more predictive for drug efficacy.	Model of exacerbations in controlled conditions.	Further our knowledge of the pathways driving exacerbations thus directing better therapies.	specific	Under Validation	ERS; SMEs; Industry; Academia		Industry = SMEs > Academia > Clinicians = Patients	7M€ over 5 year	Validation Accepted	
Develop validated QoL measures that capture drug efficacy beyond primary endpoints used routinely, which could also predict pharmacoeconomic benefits of potential new therapies.	Better outcomes measure.	Current accepted measures of lung function in patients with moderate to severe airways disease are not sensitive to intervention and do not adequately reflect the well-being of patients. QoL measurement may be a more precise tool to monitor clinical outcome.	specific	Under Validation	ERS; BTS		Clinicians = Patients = Academia > Industry	2000 pts; 5M€ over 5 year	Validation Accepted	ATS
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome.	Biomarkers for lung damage and repair.	Damage & repair to the lung is recognized as an important component of the pathophysiology of both severe asthma and COPD. Currently accepted measures of the effects of inflammation, such as lung function tests, are all indirect and not sufficiently specific.	specific	Under Validation	ERS	ATS-ERS Joint Task Force on COPD Biomarkers	Clinicians = Patients = Academia > Industry	2000 pts; 10M€ over 5 year	Validation Accepted	ERS-ATS workshop on biomarkers in COPD; Nth American Investigators in collaboration with Industry.

8.4.5 Severe Asthma

Priority Research Area	Enabler Description ¹	Rationale ²	Enabler Scope ³	Technical Feasibility	Key players, networks and org.'s	Existing infrastructure and infrastructure needs ⁴	Who will do it	Total Estimated External Investment Cost (€€)	Metrics of Success	Comments
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome.	Airway Challenges/PFT.	A functional measure that can diagnose sub-clinical disease; provide early POC.	specific	Under Validation	Academia; Clinicians		Clinicians = Patients = Academia > Industry	200 pts; 3M€ over 2 year	Validation Accepted	
Identify Specific Biomarkers (molecular & imaging) of Inflammatory Disease progression and surrogates of treatment outcome.	Biomarker of lower airway inflammation in Asthma.	Inflammation of the lower airways is a recognized as an important component of the pathophysiology of both asthma and COPD. Currently accepted measures of the effects of inflammation, such as lung function tests, are all indirect and not sufficiently specific.	specific	Under Validation	Academia; Clinicians; Industry; SMEs		Clinicians = Patients = Academia > Industry	2000 pts; 10M€ over 5 year	Validation Accepted	EU collaboration on severe asthma (BIOAire).

¹ (Outline of the scientific approach)

² (How does the efficacy enabler address the bottlenecks?)

³ (Consideration of managing generic issues eg biomarkers centres for more than one disease area)

⁴ (eg hubs, imaging centres of excellence, patient DBs)