MEMORANDUM OF UNDERSTANDING

Subject: Memorandum of Understanding for the implementation of a European Concerted Research Action designated as COST Action BM1007: Mast Cells and Basophiles – Targets for Innovative Therapies

Delegations will find attached the Memorandum of Understanding for COST Action BM1007 as approved by the COST Committee of Senior Officials (CSO) at its 180th meeting on 1 December 2010.
MEMORANDUM OF UNDERSTANDING
For the implementation of a European Concerted Research Action designated as
COST Action BM1007
MAST CELLS AND BASOPHILS - TARGETS FOR INNOVATIVE THERAPIES

The Parties to this Memorandum of Understanding, declaring their common intention to participate in the concerted Action referred to above and described in the technical Annex to the Memorandum, have reached the following understanding:

1. The Action will be carried out in accordance with the provisions of document COST 4159/10 “Rules and Procedures for Implementing COST Actions”, or in any new document amending or replacing it, the contents of which the Parties are fully aware of.

2. The main objective of the Action is to identify and characterise novel disease-related cell specific targets that will result in the development of innovative therapeutic strategies for the treatment of chronic inflammatory and autoimmune diseases by focusing on basic, clinical and translational science in mast cell and basophil research across Europe.

3. The economic dimension of the activities carried out under the Action has been estimated, on the basis of information available during the planning of the Action, at EUR 36 million in 2010 prices.

4. The Memorandum of Understanding will take effect on being accepted by at least five Parties.

5. The Memorandum of Understanding will remain in force for a period of 4 years, calculated from the date of the first meeting of the Management Committee, unless the duration of the Action is modified according to the provisions of Chapter V of the document referred to in Point 1 above.
A. ABSTRACT AND KEYWORDS

Mast cells and basophils have long been recognized for their detrimental role in the elicitation of allergic diseases. In recent years, scientific results revealed both cell types as versatile effector cells that exhibit far more complex functions beyond their role in allergy. Mast cells and basophils have been shown to be critically involved in various innate and adaptive immune responses and, thereby, providing beneficial host protecting immunity. In contrast, they also contribute to the development and maintenance of several chronic inflammatory diseases which, even at the present time, lack sufficient treatment options. The diversity of important mast cell and basophil functions places these cell types into promising therapeutic targets. The Action will create a network of European experts to foster a multidisciplinary approach for the identification, characterisation, and development of such targets and their translation into novel therapeutic strategies.

Keywords: mast cell, basophil, inflammatory disease, target, therapy, network

B. BACKGROUND

B.1 General background

Mast cells and basophils were for more than a hundred years primarily regarded to be mere effector cells of allergic and other inflammatory responses. They have long been recognized for their detrimental roles in the elicitation of allergic diseases including allergic rhinitis, asthma, and atopic dermatitis, as well as urticaria and mastocytosis. During the past years, however, a large number of independent studies have revealed several additional important functions of mast cells and basophils beyond their functions in allergy, both in the modulation of diseases and in the promotion of health. These new findings have major implications and suggest that scientists and clinicians must change their approach to dealing with those cells. Mast cells and basophils have been identified to be critical for maintaining health and preventing disease. This has been shown in a number of mouse models for different clinical conditions including sepsis, wound healing, and autoimmune disorders such as Crohn’s disease or multiple sclerosis as well as cardiovascular diseases and cancer. If these ‘good’ functions are also relevant in humans (and there is no reason to believe that they are not),
then the development and clinical use of ‘mast cell and basophil stabilizers’, a major goal of most pharmaceutical industries and countless biotechnology companies, bears tremendous (and avoidable) risks that need to be characterised and circumvented. The good news is that now, for the first time, there is the unique opportunity of being able to develop strategies and drugs that make use of these newly discovered ‘good’ mast cell and basophil functions to prevent and/or control diseases in which mast cells and basophils exert protective effects. During the past years, the use of newly developed and excellent mouse models has shown that mast cells and basophils contribute to both onset and activity in a diverse and large set of common and devastating diseases such as rheumatoid arthritis, multiple sclerosis, atopic dermatitis, and asthma. These ‘bad’ functions largely rely on novel mechanisms of mast cell and basophil activation and effects, both of which are promising targets for the development of better treatment options in these diseases.

To make use of the newly discovered ‘good’ functions and to find ways of controlling the ‘bad’ effects of mast cells and basophils it will be necessary to assess (i) the relevance for the human system, (ii) identify and characterise the pathways and signals of mast cell and basophil activation and their subsequent effects, and (iii) develop ways and tools that target and regulate these pathways and signals. This will require a network of scientists and expert clinicians dealing with mast cell- and basophil-driven diseases led by a joint systematic and cooperative strategy and a comprehensive work programme.

Why COST?

Despite the recent increase in mast cell and basophil research activities, the absence of an interdisciplinary approach frequently leads to limitations in methodological tools, duplication of experimental protocols and controversial findings. By supporting the meetings, conferences, short-term scientific missions and other activities of interdisciplinary oriented researchers, this Action, in contrast to other initiatives that support research itself, offers the best framework to foster the challenge for integration of information not easily accessible to single research groups.

The Action will help to establish effective guidelines for beneficial research in this new rapidly expanding topic of biomedical sciences. This Action has a firm foundation for managing research into mast cell and basophil function as well as therapeutic exploitation due to the unique interaction of multidisciplinary scientists involved in the longstanding, internationally respected and non-profit making European mast cell and basophil research network (EMBRN).
Additionally, the Action will establish a multidisciplinary network and coordinate the efforts of the mast cell and basophil laboratories and centres in Europe and build up a platform for the exchange and interaction with biotechnology and major pharmaceutical partners. This interdisciplinary consortium will have the tools, expertise and energy to successfully lead mast cell and basophil research in Europe through the transition from findings in mouse models to better treatment options for patients. It will also internationally strengthen the position of European scientists in this field of research. It will provide for the recruitment and training of excellent junior scientists and promote and facilitate the return of leading European scientists who are presently working outside Europe to secure a strong position of European science in this emerging field of research.

B.2 Current state of knowledge

Previous research in the field of the proposal

Mast cells and basophils are traditionally known for causing or contributing to diseases, especially allergic and inflammatory diseases. They are the most dangerous cells in the organism, as no other cells can bring on such dramatic responses as rapidly and potently as mast cells and basophils in the context of anaphylaxis (anaphylactic shock). Also, there are a number of diseases such as mastocytosis or urticaria that are caused exclusively by mast cells. In addition to these mast cell-driven diseases, mast cells and basophils are thought to contribute to a large number of other pathological. Therapeutically, the means of controlling the contribution of mast cells and basophils to the pathology of diseases are very limited, as it is neither known what activates mast cells and basophils in these settings (besides IgE-mediated mechanisms in allergy), nor what mediators are involved, at least in most cases. Where known, the use of antagonists to single products (e.g. antihistamines) is the best available strategy. Specific antagonists to mast cell and/or basophil activating receptors and negative regulators that shut down selected signalling pathways and downstream responses in these cells are highly desirable. This Action will provide the knowledge that is required to develop them.
Current state of the art of relevant research

Surprisingly and unfortunately, mast cells and basophils in humans have not yet been tested for any of the beneficial effects recently discovered in mice. Therefore, it is not yet known whether or not human mast cells and basophils display the same health promoting and disease preventing functions as their murine counterparts, e.g. protection from bacterial, viral, or parasite infections, promotion of wound healing, UV-induced down-regulation of hypersensitivity responses, protection from UV irradiation as well as from snake venoms and other toxins, etc. Therefore, it will be of great interest, and it will be a major goal of this Action, to show that, and how, mast cells and basophils in humans promote health so that these cell functions as well as their underlying mechanisms can be exploited as pharmaceutical targets for the prevention of disease in humans.

From the Pubmed database, a total of 2241 reports related to mast cell and basophil research during the last ten years have been recorded. Among these, 236 hits relate to review articles, 1135 deal with the biological function of human mast cells and basophils, 45 of which report about clinical trials that directly relate to mast cell or basophil biology.

Altogether, non-European countries, including US, Japan, China, Canada and from South America contributed approximately 53% to the research in this field, whereas European countries contributed to about 47%. Thus, European countries represent approximately half of the world research output in this field. Notably, Europe has the highest concentration of mast cell and basophil researchers in the world and therefore this Action will take advantage of this situation to increase further output and to strengthen the position of European researchers.

Innovation

The reports on the role of mast cells and basophils in physiology and pathophysiology started to appear in the literature only around the late 1980s and, as of today, the available data are variable in quality, yet adequate in quantity to justify a first attempt to integrate and evaluate them in a systematic manner. The focused research interests of single groups on specific scientific questions hamper their cooperation and, most importantly, the direct exchange of information that would be valuable for the advancement of knowledge on mast cell and basophil biology.
The unique training network for early career scientists will exploit the availability within the Action of a wide selection of state-of-the-art equipment and expertise for immunological and molecular modelling, imaging, genomics, proteomics, bioinformatics, cell signalling, and in vitro and in vivo rodent and human model systems. To date, no interdisciplinary integrative approach to mast cell and basophil research has been made by the scientific community, except for a successful preliminary effort to present briefly some related data in a symposium entitled "International mast cell and basophil meeting 2010", organised by the EMBRN (European Mast cell and Basophil Research Network).

Therefore, this Action is innovative in addressing a new integrative interdisciplinary approach for the critical concerted assessment of experimental design and data, by focusing on the current state-of-play pertaining to the basic understanding and the therapeutic potential of important and promising new targets. Furthermore, it aims to address the evaluation and elucidation of critical issues in the field of technical approaches, physiological and pathophysiological importance of mast cells and basophils and on the pharmacological properties of newly discovered targets as well as their therapeutic implementations, thus directing mast cell and basophil research towards a more comprehensive series of end points.

**B.3 Reasons for the Action**

**Main reasons for this Action:**

1. To create an orchestrated and productive network of interdisciplinary oriented researchers with the goal to overcome the current fragmented state of research and to foster a multidisciplinary approach to mast cell and basophil research in order to avoid duplication and confusion, improve the efficacy and increase the chances for successful outcome of these efforts.

2. To build up strong links between the participating research teams and facilitate larger a more ambitious scale collaborations as well as broaden the international contacts of the network with other research teams and with industrial partners.
3. To promote the bench-to-bedside translation of new knowledge in mast cell and basophil biology. Specifically, the Action will establish a novel and very innovative framework that will help basic scientists and clinical experts in working together to transfer scientific progress to clinical medicine.

4. To advance and support joint research/study initiatives with pharmaceutical and biotechnological companies. To this end, the Action will establish relationships with partners in the pharmaceutical industry that currently run programmes for the development of mast cells and basophils stabilizers or antagonists of their products for the treatment of related diseases and/or are interested in the development of treatment strategies that make use of newly discovered protective functions of mast cells and basophils. This will further increase the visibility of the research field in Europe. It will also allow participants of the Action with promising results from investigator initiated proof-of-concept and phase I studies to promote the translation of their new therapeutic strategies generated within the framework of the Action by developing and performing clinical trials together with industry partners.

5. To initiate a pan-European Framework Programme 7 funded consortium of leading mast cell and basophil labs. The participating labs will put together a task force that will organise a European network of excellence and submit an application for its European funding, which will further strengthen the standing of European mast cell and basophil labs in the international scientific community and which will provide for the continuation of the projects and activities initiated by this Action.

**Expected results**

1. The high degree of knowledge dissemination regarding the basic understanding and the outstanding therapeutic potential of mast cell and basophil targeting for new drug development, the free exchange of innovative concepts and the expansion of knowledge to a broader basic and clinical research community will diminish the interdisciplinary barrier, increase the interest of other academic and industrial researchers in the importance of this field, encourage joint major European grant applications, and ensure the scientific advances targeted by the Action.
2. Training and mobility of young European scientists in the field and introduction of updated information to the education process.

3. The social benefits will be the growth of the leadership of Europe in this area of research and the increased awareness of the European general public about the importance of the Action to improve health and quality of life.

**Means needed to achieve the objectives**

1. Working Group (WG) meetings, workshops, training schools and Short-Term Scientific Missions (STSMs) and annual conferences will permit experts to be invited to maintain advanced information on the focused research and to improve the cooperation with researchers in academia, research institutes, industry and health services to ensure interaction between the various research areas, assess key advances and foster important new directions.

2. Establishment of a website fully dedicated to the activities of this Action to provide information and offer other services that participants may request as well as opportunities for further groups to enrich the Action.

3. Open forum to promote understanding of the importance of the Action to the general public.

**B.4 Complementarity with other research programmes**

No directly related European Union funded projects are available in the European programmes databases. The Action will be complementary with the European mast cell and basophil research network (EMBRN), which was recently founded as a European platform for mast cell and basophil research. The Action will seek cooperation with any related project that may arise during the duration of the Action and participants will be encouraged to submit joint European proposals in the future.
C. OBJECTIVES AND BENEFITS

C.1 Main/primary objectives

The main objective of the Action is the identification and characterisation of novel disease-related cell specific targets that will result in the development of innovative therapeutic strategies for the treatment of chronic inflammatory and autoimmune diseases by focusing on basic, clinical and translational science in mast cell and basophil research across Europe.

C.2 Secondary objectives

- Identification of current knowledge and significant gaps in mast cell and basophil biology.
- Establishing and strengthening interdisciplinary research in mast cell and basophil biology across Europe.
- Development of a comprehensive strategy and specific action plan for converting results from basic science into novel therapeutic strategies.
- Gain knowledge and broaden the training and mobility of young European scientists.

C.3 How will the objectives be achieved?

The objectives will be achieved by:

- The annual conference, meetings and STSMs that promote accumulation and exchange of specific knowledge, ensure interaction between the various research areas and foster important new directions in this field of biomedical research.
- Inviting clinical physicians, the medicines policy makers and the scientific authorities from industry, research and academia working in the field to meetings, workshops, training schools and conferences in order to improve the interdisciplinary knowledge, experiences and skills and bring new ideas and cooperation into the Action.
• Intensive introduction of young researchers from immunology, chemistry, biomedical sciences, preclinical and clinical pharmacology into this Action, serving as the strong basis for the progress of their research.

• Advertising the meetings, objectives and outcomes of the Action in scientific societies, the institutional press of the participants and, where possible, in the local, national, and/or European mass media.

• Creating and regularly updating a high quality specific webpage dedicated to this Action in order to provide information to participants, to disseminate the scientific knowledge, to bring the Action closer to other researchers, the pharmaceutical industry and the public, and to provide the template for best practice and the compendium “Handbook of current Models, Methods, and Techniques in Mast cell and Basophil Research” to inform European consortia on how best to address scientific issues in mast cell and basophil research.

• Action publishing high-impact and quality co-authored papers in international journals, special issues in international scientific journals and/or specialist books to spread recent results as well as the current status, lacks, and goals of important scientific topics in the field and to disseminate the interdisciplinary knowledge of this topic in the scientific community.

• Defining mid-to-long-term key aspects for future scientific goals in mast cell and basophil research and publication of a joint White Paper.

C.4 Benefits of the Action

The Action will constitute an important element in a multi-disciplinary coordination of basic and clinical science in mast cell and basophil research in Europe. The comprehensive strategy of the Action will facilitate the coordination of research and create an interactive platform for sharing resources, knowledge, reagents, technology and methodology in mast cell and basophil biology. In consequence, this will help to extend the scientific knowledge and accelerate the translation from basic research into novel therapeutic strategies. In particular, the Action will lead to the following benefits:
For the scientific community

- Improvement of the dialogue, interaction, coordination and cooperation within the European mast cell and basophil research community.
- Harmonisation of existing technologies and deployment of the optimal state-of-the-art methodology in mast cell and basophil biology.
- Generation of innovative technologies for the development of mast cell and basophil targeting therapies.
- Dissemination of information to scientific societies, medicines policy makers and health officials.
- Enhancement of education, training and mobility of young European scientists.
- Basis for joint major effective European grant funding applications.

For the public society and economy

- Improvement of therapeutic approaches for patients suffering from mast cell and/or basophil mediated diseases.
- Development of novel therapeutic strategies to improve treatment options for chronic inflammatory diseases in which these cell types or their mediators are involved.
- Cooperation with biotechnology and pharmaceutical companies in the translation and pre-commercial development of potential marketable innovative targets.
- Increased awareness of the European general public.

C.5 Target groups/end users

The end users of the expected results are:

- Pharmacology, medicinal chemistry, molecular biology, genomics, proteomics, immunology and clinically oriented researchers and young investigators working or wishing to work in the field of mast cell and basophil, allergy, inflammation and immunology research and drug development.
• Graduate and Ph.D. students of pharmacology, medicine, chemistry, pharmacy, molecular biology, genomics, proteomics, immunology and biomedical sciences.
• Researchers from the pharmaceutical industry.
• The European research community, through scientific societies such as the EMBRN, the International Union of Basic and Clinical Pharmacology (IUPHAR) and the Federation of European Biochemical Societies (FEBS).
• The European Medicines Agency (EMA), national medicines policy makers and health officials.
• The whole European and world society, clinical physicians with an interest in allergic, inflammatory and other mast cell and basophil mediated disorders.
• Patients suffering from mast cell and basophil mediated diseases and their relatives.

D. SCIENTIFIC PROGRAMME
D.1 Scientific focus

The Action fosters a multidisciplinary approach to mast cell and basophil research in order to increase understanding and to translate this knowledge into the development of potentially beneficial end points. This goal will be achieved through collaborations and interactions organized into groups associated with the respective objectives (see sections C.1, C.2). An extensive contribution of young scientists and female researchers will be encouraged. The partners have the necessary scientific and clinical expertise and technical means to perform the experimental parts, while this Action will benefit greatly from the primary participants being active and enthusiastic members of the EMBRN. Each area identified below broadly represents the responsibility of participants to set the standards and to facilitate data integration within the Action:
1. One area will be dedicated to the collection of current knowledge in mast cell and basophil biology, their physiological and pathophysiological importance in health and disease and the identification of significant gaps. The majority of symptoms related to chronic allergic and inflammatory diseases are maintained by mast cell and basophil mediator release. As of today, no selective cell targeting treatment strategies for mast cells and/or basophils are available that would be able to inhibit cell activation or survival. Therefore, the Action focuses on the identification and characterisation of novel mast cell and basophil functions, activating receptors, signs of activation and regulatory pathways. Isolated targets, such as the death receptors TRAIL-R1 or TRAIL-R2, the inhibitory receptors CD300a or Siglec-8 and several forms of VEGFs and their receptors expressed by human mast cells have been described to be involved in cell homeostasis as well as inflammatory and neoplastic (lymph-)angiogenesis, but did not reach the state for pharmacological implication so far. To identify such potential targets, define and outline such important future research topics and to make such targets available for further investigation in a multidisciplinary setting for their development into therapeutic targets is a major goal of the Action.

2. The second area will concentrate on the methodology used for the investigation of mast cell and basophil biology. This includes in vivo, in vitro, in situ models, genomic and proteomic. A dedicated scientific consortium will collect, standardise, and approve current protocols and techniques. Finally, a “Handbook of current Models, Methods, and Techniques in Mast cell and Basophil Research” as a compilation of standard operating procedures will be developed and released to be available to all scientists active in mast cell and basophil research. This Action takes advantage of the recent innovations in genomics, proteomics and bioinformatics to encourage participants to develop and implement the relevant scientific and technical means to initiate studies on the identification of novel cell related therapeutic targets and compounds that may interfere with mast cell and basophil functions.
3. The information obtained from basic research and preclinical investigations is imperative for the identification of biological and pharmaceutical mast cell and basophil related targets. Specific targets that can be delivered selectively to those cell types include: (i) Biological agents that specifically modulate mast cell/basophil function and activity. (ii) Mimic or prevent the action of specific mast cell/basophil mediators and their biological activity. (iii) Control mast cell and basophil trafficking to primary and/or secondary target organs in relevant diseases. In order to reach the objectives of the Action, immunologists, pharmacologists and biomedical scientists will contribute to a better understanding of pharmacological properties of mast cell and basophil targets and the use as selective agents in various preclinical investigations. Newly discovered targets with additional properties will be tested as pharmacological tools and disseminated to the members for novel experiments. The experimental means to achieve the objectives range from cell cultures, *in vitro* and *ex vivo* preparations to *in vivo* experiments in models of disease, where the biological significance of mast cells and basophils is a key tool to reveal the function of innovative targets in their health promoting or disease preventing properties.

4. The therapeutic potential of newly discovered compounds constitutes another important goal of the Action. This area will concentrate on the development and generation of strategies to promote the rapid translation of recent findings in mast cell and basophil biology from animal studies into the human situation. As of today, mast cells are difficult to study in the human system and have been shown to be heterogeneous and exhibit differences in phenotype and function in different tissues, and even within the same tissue. This mast cell heterogeneity needs to be better characterised, especially in the translational process from the murine to the human situation. The generation of strategies for a rapid and solid translation of scientific results from the murine to the human system is a fundamental step for the development of novel and innovative mast cell or basophil targeting therapeutic options in humans.
D.2 Scientific work plan methods and means

Mast cells and basophils are considered as promising targets for the treatment of chronic allergic and inflammatory as well as autoimmune diseases, such as urticaria, asthma, allergic rhinitis, atopic dermatitis, psoriasis, inflammatory bowel disease and rheumatoid arthritis. Along this line of evidence, the Action addresses issues concerning the therapeutic potential of novel targets for the treatment of major pathologies, sets the standards for better strategies and considers the economic consequences of any novel therapeutic intervention in comparison to existing treatment approaches. The tools are the preclinical, clinical and epidemiological aspects related, initially, to chronic allergic and inflammatory disorders, together with the pharmacological properties of cell related targets. This process will unite basic and clinical researchers (partners or new candidates) to set clear and valid standards, to develop a template for best practice and to increase awareness of the general public, while the Action will benefit from a uniquely strong association with the major international (including many European) pharmaceutical companies. Many of the Action members are pioneers in the investigation of mast cell and basophil functions and their implications in health and disease. This unique expertise will be invaluable to the success in the translational components of this Action.

The scientific programme is based on four initial, mutually interlocking Working Groups (WGs), defined by the Management Committee (MC), that favour the rapid dissemination of results and the productive exchange of ideas between the various expert teams and stimulate this interdisciplinary Action. Modifications of any existing WG (addition of members with new expertise) may take place during the course of the Action, upon approval by the MC. The flexibility of the framework facilitates the integration of new European groups that may have interests with the major objectives of this Action. The interactions encourage, promote and offer the means for solving emerging problems and limitations, since the expertise, experiences and experimental capabilities of the members are accessible to all participants. This Action will give particular emphasis to the ethical aspects of research (both pre-clinical and clinical).
In all WGs, the work will be equally and fairly divided among members and it will be carried out in three phases. In phase 1, all available data will be collated, presented and evaluated during the initial meetings, the workshops and seminars organised by each WG. For young researchers to acquire highly specialised techniques covering various disciplines, the Action will make use of STSMs and training schools. WG leaders will be in charge of all WG tasks, upon approval by the MC. In phase 2, the outcome of phase 1 from all WGs will be discussed and evaluated during the annual MC conference, where firm conclusions/memorandum will be achieved. Phase 3 is dedicated to achieve consensus conclusions and recommendations for ongoing and future research topics in the field and to report the overall activities of the Action in the final publication.

The annual conference will focus on the integration of available information for the evaluation and elucidation of critical issues in the field of technical approaches, physiological and pathophysiological importance of mast cells and basophils and on the pharmacological properties of newly discovered targets as well as their therapeutic implementations. The aim will be to present and discuss new achievements, give an overview to the participants, ensure interaction between the various research fields, determine new important directions, and eventually invite new participants to the Action. Sessions during the workshops and/or annual meetings will be dedicated to present special lectures open to the general public to promote understanding of the importance of the Action.

The total duration of the Action is four years. The first period of one year will be devoted to building the WGs in line with the relevant topics. At the later stages, this Action will set the standards in all aspects of mast cell and basophil, a template for best practice will be made available and emphasis will be given to the increased awareness of the general public to the importance of the Action. The last year will be devoted to the synthesis of the results achieved, development of conclusions and recommendations for unmet needs and further research activities in the field and the final report.
The following aspects will be considered at any time of the Action's duration.

**WG 1: Physiological and pathophysiological importance of mast cells and basophils in health and disease**

- Collection of current knowledge in mast cell and basophil biology and identification of significant gaps in mast cell and basophil physiology and pathology.
- Integration and critical evaluation of data, derived from basic research, on the complex interaction between mast cell and basophils in immunological models.
- Summaries the state-of-the-art biological significance of mast cells and basophils in health and disease
- Identification of new mast cell and basophil functions, mechanisms of activation and regulation, molecular mechanisms of pathways, specifically identification and characterisation of: (i) signals that are critical for the activation of mast cells and basophils, (ii) key mast cell and basophil mediators, (iii) regulatory pathways of mast cell and basophil activation and effector functions.
- Identification and characterisation of novel mast cell and basophil functions in detail by using established mouse models of disease including mast cell-deficient mice and by creating new animal models. Among these studies are investigations on infectious diseases, autoimmune and allergic disorders, malignant tumours, neurological and neurodegenerative conditions, and cardiovascular disorders.
- Definition of important future research topics and publication of a joint White Paper.

**WG 2: Methodological approaches for the investigation of the mast cell and basophil biology**

- Harmonisation and distribution of standardised state-of-the-art models, methods, tools, and techniques in mast cell and basophil research.
- Implementation of genomic/proteomic/bioinformatics-based scientific and technical tools
- Establishment of a dedicated scientific consortium to collect, standardise, and approve current protocols and techniques.
• Creation of standard operating procedures and dissemination to all scientists active in mast cell and basophil research.
• Development and publication of a Compendium “Handbook of current Models, Methods, and Techniques in Mast cell and Basophil Research”

WG 3: Identification of biological and pharmaceutical mast cell/basophil related targets

• Specific considerations on selective target delivery to those cell types include: 1) Biological agents that specifically modulate mast cell/basophil function and activity. 2) Mimic or prevent the action of specific mast cell/basophil mediators and their biological activity. 3) Control mast cell and basophil trafficking to primary and secondary target organs in relevant diseases.
• Analysis of novel findings on mast cell and basophil biology for their relevance in humans by using primary human mast cells, collections of tissue samples and cohorts of patients.
• Evaluation of pharmacological properties of newly discovered targets and preclinical investigations.

WG 4: Therapeutic potential of mast cell and basophil targeting strategies

• Generation of strategies to promote the rapid translation of recent findings in mast cell and basophil biology from animal studies into the human situation.
• Characterisation of mast cell heterogeneity, especially in the translational process from the murine to the human system.
• Set the standards for better strategies on the potential pharmacological interventions in mast cell and basophil biology for the treatment of allergy and chronic inflammatory diseases and comparison with current treatment approaches.
• Evaluation of existing clinical trials and potential of new targets to enter clinical trials.
• Translation of upcoming novel results into preclinical studies, transfer to the clinic by performing proof of concept-studies with available compounds or initiation of drug development with partners in the pharmaceutical industry.
• Evaluation of the economic consequences of any novel therapeutic intervention.
E. ORGANISATION

E.1 Coordination and organisation

The Management Committee (MC; with elected Chair and Vice-Chair and up to two representatives from each signatory country), will oversee all planning, implementation and coordination during the Action in line with Rules and Procedures for implementing COST Actions. To assure a more rapid, efficient and flexible coordination, a highly collaborative Core Group (CG) of the MC will be formed by the Chair, vice-Chair and up to four selected experts. The CG will be responsible for the preparation of various documents, emerging matters and information for the MC and WG meetings. Four Working Groups (WG; with leaders selected by WG participants) will be formed by distributing the partners according to their expertise (some may fall under multiple WGs). The participating teams will perform their research using financial support from national sources. The WGs will promote inclusion of young/early career investigators and will nominate one researcher less than 35 years who will be responsible for coordinating the younger scientists in order to voice their opinions, ideas and specific needs to the MC. Each WG will hold an annual meeting, preferably in conjunction with related non-Action activities in order to attract a wide audience (100-200 participants) and two to four STSM, workshops, and seminars in four years, where new results and technologies will be presented and discussed in depth and collaborations between the research teams will be encouraged.

STSMs will allow researchers to work with other participating teams, thus developing fruitful collaborations to overcome research fragmentation and fostering joint publications and grant applications. The workshops and seminars will be devoted to the education of selected young European scientists working in mast cell and basophil research and will introduce advanced knowledge and expertise by lectures, workshops and discussions and by invitation of other European and non-European experts not involved in the Action. The selection of participating young scientists and invited experts will be made by the MC, in collaboration with the leaders of the appropriate WGs.
The MC will organise at least two workshops/training schools (3-5 days) in four years, aimed at disseminating the proceedings, expertise and techniques developed within the Action through intensive training in advanced aspects of immunology, molecular biology, biochemistry, preclinical and clinical science. Continuously emerging concerns on the role of mast cells and basophils in inflammatory diseases, the identification of useful targets and their therapeutic implementation of will be the main topics. Optimally, training schools are arranged as summer schools and targeted for 10-30 researchers. An annual conference will be organised by the MC, involving the scientists of the Action. This conference will coincide with the annual MC meeting and will ensure interaction between the various research areas, assess key advances and foster important new directions. Additional separate meetings can be decided by the MC depending on special needs. The closing MC meeting and the final report will summarise and evaluate the results and support their future impact. In order to reduce expenses, MC meetings to monitor the Action will be scheduled around other Action events. During all activities ethical rules and gender balance will be strictly applied.

A dedicated website will be established in accordance with COST Office requirements to provide information for participants and to offer other services that participants may request. The MC will appoint a competent member to as webmaster and oversee the website update. This website will give organisation, full contact and CV details, announce events (workshops, conferences, etc) and information on the results of the Action (minutes, publications, special journal issues, etc), provide a listing of publications of the participants (updated at least once per year), will have links to educational and industrial establishments, funding bodies, charities and related societies, and it will offer opportunities for further groups to enrich the Action. A special section in the website will be dedicated to young researchers.
E.2 Working Groups

The Action will consist of four initial WGs defined by the MC. Additional WGs or modifications of any existing WG (additional member(s) or national team(s) with new competences) may take place during the Action. This flexible framework facilitates the integration of new European researchers having overlapping interests with the major objectives of this Action. Thus, it maximises the integration of data and the elucidation of continuously emerging issues and helps European researchers to maintain the leadership in mast cell and basophil research. Close cooperation and relationships between the WGs favours the rapid and efficient dialogue and the dissemination of new achievements and results to participants (see section D).

These interactions stimulate this interdisciplinary Action to determine successful directions to be followed on mast cell and basophil research and future application(s).

WG1: Physiological and pathophysiological importance of mast cells and basophils in health and disease

- Integration and evaluation of the functional significance of mast cells and basophils in chronic inflammatory and autoimmune diseases (with WG3).
- Characterisation of potential therapeutic targets (with WG2).

WG2: Methodological approaches for the investigation of mast cell and basophil biology

- Assessment and validation of existing and novel methodologies targeting the detection of potential therapeutic targets in mast cell and basophil biology (with WG1, WG4).
- Harmonisation, standardisation, and distribution of state-of-the art models and techniques (with WG1, WG3, WG4).
**WG3: Identification of biological and pharmaceutical mast cell and basophil related targets**

- Development of selective cell related targets and cell delivery systems (WG1, WG2)
- Evaluation of pharmaceutical properties of newly discovered targets and preclinical investigations (WG1, WG4).

**WG4: Therapeutic potential of mast cell and basophil targeting strategies**

- Standards for better strategies on the potential pharmaceutical interventions in mast cell and basophil biology (WG1, WG2, WG3)
- Strategies to promote rapid translation of recent findings into clinical applications (WG2, WG4).
- Evaluation of existing clinical trials and potential of new targets to enter clinical trials (with WG1, WG3).
- Economic consequences of any novel therapeutic intervention (with WG3).

**E.3 Liaison and interaction with other research programmes**

Individual members of this Action have successfully obtained national funding streams, some have already prepared and submitted joint European research proposals and participate in close productive collaborations yielding high-impact multidisciplinary outputs. However, since no directly related European funded projects are currently available this Action facilitates a large number of joint proposal applications in the future through the organised events, particularly seminars, workshops, meetings and the website.
E.4 Gender balance and involvement of early-stage researchers

The Action builds up strong European interdisciplinary links among immunology, molecular and cellular biology, genetics, preclinical and clinical research and pharmaceutical industries through enhancement of communication between several groups from a minimum of 9 COST countries. An important objective of the Action is to facilitate and broaden the training and mobility of young European scientists within these disciplines. Emerging researchers will be housed in the WGs. The Action will nominate an early stage/young researcher to be in charge of coordinating the younger scientists and a special section in the website will be dedicated to the interests of young researchers. The Action will extensively involve women in the networking where gender balance will be strictly applied. Currently, the proportion of women having team-leading responsibilities in this Action is 40%. An extensive contribution of female scientists will be encouraged to develop the activities of the Action, paying attention to an appropriate gender balance in the nomination of the Chair and Vice-Chair of the MC and the heading of the WGs, in the examination of proposals and in invited experts and new participants. The MC will place gender balance and early-stage researcher involvement as a standard item on all its agendas and encourage invitation of emerging scientists and women to present communications in WG meetings.

F. TIMETABLE

The duration of the Action is four years. The timescale is presented in Table 1.

Table 1. Timescale of the events organised by the Action.
At the Inaugural Meeting of the Action the MC (national experts appointed by the signatory
countries) selects the MC Chair, Vice Chair, the Grant Holder and announces the selected WG
Leaders. A Core Group of the MC will be formed by the Chair, Vice-Chair and up to four selected
experts. The work plan and budget for the first year is drafted to enable an efficient start of the
Action through the use of the financial instruments.

As the COST Office provides significant scientific and administrative support, and the Grant Holder
has an important part in the financial arrangements and reporting, continual coordination and
efficient transfer of information will be ensured by the MC for all events organised by the Action.
Reporting will be integrated in a way to aid the MC and Grant Holder in preparing scientific and
financial reports in a timely fashion.
The first MC meeting will mark the beginning of the Action and will be followed by the first annual conference and the first meeting of each WG. The last MC meeting will coincide with a forum open to the general public and will mark the end of the Action. The MC will discuss and organise in advance all Action future activities scheduled within the following months and the possibilities to enlarge the participation of other research groups. Throughout the course of the Action, each WG will hold an annual meeting, which will coincide with the MC conference. The Core Group of the MC shall meet when deemed necessary to discuss emerging matters regarding the events organised by the MC and the WGs and the needs of young researchers.

G. ECONOMIC DIMENSION

The following 9 COST countries have actively participated in the preparation of the Action or otherwise indicated their interest: CZ, DE, ES, FI, FR, IL, IT, SE, UK.

On the basis of national estimates, the economic dimension of the activities to be carried out under the Action has been estimated at 36 Million € for the total duration of the Action. This estimate is valid under the assumption that all the countries mentioned above but no other countries will participate in the Action. Any departure from this will change the total cost accordingly.

A large number of European and non-European Pharmaceutical companies have expressed significant interest in and support for this Action.

Based on discussions with key Action contributors and the COST guidance, the expected total manpower expressed in person-years dedicated to the activities of the Action for years 1 to 4 will be 10 per year and participating country.

The participants of the Action will contribute to the economic dimension of the Action by adding valuable internal resources.
H. DISSEMINATION PLAN

H.1 Who?

The target audiences for the dissemination of results are mainly:

- Researchers in academia and pharmaceutical industry involved in immunological, biological, pharmacological and medical projects, as well as basic scientists and clinical researchers, clinicians and health officials involved in the diagnosis and treatment of allergy and inflammatory diseases.
- Young scientists and university teachers to introduce quality research opportunities and updated information on the role of mast cells and basophils in health and disease into the education process.
- The European general public will be introduced to the general character and widespread incidence of allergy and chronic inflammatory diseases with the importance of the Action for improving health and quality of life.
- The pharmaceutical industry and biotechnology (Small to Medium Enterprises and major pharmaceutical companies) to develop new compounds selectively targeting the activation and mediator release by mast cells and basophils. Therefore, the Action is expected to yield significant new intellectual property and the dissemination of this information to industrial partners will be actively sought in order to attract interest in the exploitation of the results.
- European and national government policy makers, because they will provide clear information on a novel therapeutic approach for common diseases with socio-economic impact, including allergy, asthma, chronic inflammatory and autoimmune disorders which profoundly compromise public health and the welfare of the society.
- European Medicines Agency (EMEA), the national medicines policy makers and health officials who will be the ultimate targets of the results since the Action endeavours to create an environment for the therapeutic exploitation of the newly discovered compounds and for the assessment of their potential to enter clinical trials for a range of inflammatory disorders by the.
H.2 What?

Dissemination methods will target either all types of target audience or selected target groups. The progress of the Action and the results of its evaluation will be taken into consideration in the dissemination plan during the course of the Action. On all occasions appropriate advertising and publicity will be attempted.

Website

- The creation of a regularly updated website is of primary importance for the dissemination of information about the Action. The MC will consider the website to be the main method to highlight and promote the activities and results of the Action. It will be established in accordance with COST Office requirements and it will give information about the members and the activities of the Action (members’ contact details, future meetings, training schools, workshops, conferences and other events), create the means for researchers involved in the Action to spread their results, present the topic and maintain the visibility of the Action to other scientists so as to encourage collaborations with interested research teams and collect information on the worldwide progress in the field of mast cell and basophil research. The website will contain scientific knowledge, listing of publications from participants (updated every at least once a year by the responsible person), the template for best practice and the results of the Action.

- A special section will be dedicated to young scientists (information on job, post-doctoral positions, etc). At the regular access level, information and conclusions will be disseminated to both, expert and non-expert audiences, while part of the website will be secured and shared internally among the members of the Action. Conferences, workshops, and publications
• Members of the Action will publish research articles in international peer-reviewed journals and present their findings at national and international scientific meetings, where they will interact with the related scientific and industrial community. The efficient dissemination of the interdisciplinary results obtained by this Action in the scientific community will also be achieved by publication of high-impact and quality co-authored papers in international journals, special issues and/or specialist books.

• The contents of selected conferences, workshops, seminars, and training schools could be the subject of specific books, journal volumes or electronic material (CD/DVD) to be disseminated to different audiences.

Key aspects for future scientific goals

• The definition of mid-to-long-term key aspects for future scientific goals in mast cell and basophil research as a final outcome of the Action will be published as a joint White Paper as well as the development, publication and dissemination of the Compendium “Handbook of current Models, Methods, and Techniques in Mast cell and Basophil Research”.

Non-technical meetings and publications

• A forum open to the general public annually and at the final stage of the Action, regular recorded Blogs and open lectures for educational purposes and articles directed to a general audience and published in non-specialised journals and the institutional press of the participants will be used to expand the public knowledge of this Action.

Contacts with industry

• Researchers from the pharmaceutical industry (many already productively involved with Action members) will be invited to participate in meetings in order to exchange experiences and ideas on mast cell and basophil research and application perspectives and to initiate novel co-operations.
Contacts with the educational staff

- The members of this Action will be encouraged to introduce this topic in the educational plans of their institutions. This Action will be given as an example of best practice in research methods to undergraduates and postgraduates.

Contacts with other networks

- An important aspect for the improvement of the Action is the interaction with other networks that are directly or indirectly connected with mast cell and basophil and immunological research (all research fields with therapeutic relationships). This includes respective local and national charities and Lay Societies.

H.3 How?

- The Action internal website will be used for the documentation of the Action activities and will be accessible to the Action members and the COST Office. Announcements on the website will include the minutes of the MC meetings, summaries and brief reports of the WG meetings, STSMs, training schools and other events of the Action, as well as lists of participants.
- A technical section will be established on the website to focus on methodological approaches in order to support methodology transfer and to establish effective guidelines for beneficial research in this new rapidly expanding field of biomedical sciences.
- Aiming to maintain the leadership of Europe in mast cell and basophil research, the MC and WG meetings and conferences will be structured so as to provide effective and equal dissemination of the scientific progress within the Action, to arrange the communication of breakthroughs or areas with particularly interesting extensions for the Action by outside experts, to encourage the active participation and quality training of young investigators and early career scientists and to ensure gender balance on all occasions.
• The multidisciplinary nature of the Action and the combination of experts in a number of fields provide an exceptional opportunity to satisfy the demand for publication of innovative approaches and high-impact and quality results in prestigious international journals.

• The potential commercial exploitation of the basic understanding of this important new drug target will be actively sought within the Action as well as through facilitation of contacts and larger and more ambitious scale collaborations with appropriate pharmaceutical companies.

• The Action will be committed to extend public awareness of novel therapeutic approaches in allergy, asthma, inflammation and autoimmunity through an open forum, local and national Lay Society groups (patient societies) and controlled communication through the media.

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