European Cooperation in the field of Scientific and Technical Research - COST -

Secretariat

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COST 250/08

MEMORENDUM OF UNDERSTANDING

Subject :	Memorandum of Understanding for the implementation of a European Concerted Research Action designated as COST Action BM0806: Recent advances in histamine receptor H4R research

Delegations will find attached the Memorandum of Understanding for COST Action BM0806 as approved by the COST Committee of Senior Officials (CSO) at its 172nd meeting on 24-25 November 2008.

MEMORANDUM OF UNDERSTANDING

For the implementation of a European Concerted Research Action designated as

COST Action BM0806

RECENT ADVANCES IN HISTAMINE RECEPTOR H4R RESEARCH

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 270/07 "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 foster a multidisciplinary approach to H4R research, and to focus on the current state of play pertaining to the basic understanding and the huge therapeutic potential of this important new drug target.

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 2008 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

The recently identified histamine H4 receptor (H4R) has attracted much interest because of its function and potential therapeutic exploitation. Principally expressed on haematopoietic cells, it plays a significant role in immune responses and inflammatory processes. The Action will create a network of European experts to foster a multidisciplinary approach to H4R research, and to enhance basic understanding and the therapeutic potential of this new drug target. Sub objectives are a) evaluation and elucidation of critical issues pertaining to H4R function, pharmacological profile and therapeutic implementation of its ligands, b) promotion of the deployment of new instrumentation and reliable experimental models, c) development of a forum for free exchange of new concepts and training of young European scientists. The Action will originally include scientists with competences ranging from chemical synthesis to clinical pharmacology. More than 20 teams will constitute 4 interdisciplinary Working Groups: methodological approaches; basic research on physiological and pathophysiological importance; structure-activity and preclinical investigations on properties of new selective ligands; therapeutic potential of H4R and new compounds. The dissemination plan includes a dedicated website, meetings, workshops, Short-Term Scientific Missions, an open forum and a best practice template.

Keywords: histamine H4 receptor, interdisciplinary research, physiology and pharmacology, training, translational research

B. BACKGROUND

B.1 General background

The histaminergic system has proved to be a rich source of useful drugs over the last five decades with a number reaching blockbuster status. In addition to the well-established roles of histamine in the treatment of allergic conditions and gastric ulcers, it is now accepted that the biogenic amine plays a role in neurotransmission and immune cell chemotaxis.

Shortly after the cloning of the histamine H3 receptor (H3R), the identification of the H4R in 2000/2001 by several groups independently initiated a major effort to characterize the role of this new receptor in the modulation of immune system processes, while growing attention is now directed towards its therapeutic exploitation in autoimmune disorders and cancer.

The structural similarities between the H3R and H4R and the overlap as well as species differences between their pharmacological profiles are recognised as causes of many controversial reports that have misled evaluation of H4R function in both physiology and pathophysiology. The identification of selective compounds for these receptors, based on differences in the structure-activity relationships (SAR), has only partially facilitated this situation. Moreover, the advances in genomics, proteomics and bioinformatics have added a new dimension to the area. The potential exploitation of these technologies in histaminergic systems is currently under investigation. H4R antagonists are in preclinical assessment for a range of inflammatory disorders and cancers; some showing promise for potential entry into clinical trials.

However, the reported data are currently inadequate to provide exploitable conclusions on the cellular and molecular mechanisms underlying the actions of the H4R and on its cross-talk with endogenous molecules. Despite the recent increase in H4R 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 exchanges 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.

Additionally, it 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 H4R function as well as therapeutic exploitation due to the unique interaction of chemists, molecular biologists, biochemists, pharmacologists and clinical researchers involved in the long-standing, internationally respected and non-profit making European Histamine Research Society (EHRS).

B.2 Current state of knowledge

Previous research in the field of the proposal

The physiological functions of histamine have been recognized for more than 100 years, yet new roles are still being discovered. The crucial regulatory character of histamine in many cellular events is exerted via four types of histamine receptors: H1R, H2R, H3R, and H4R. H1R (antihistamines) and H2R antagonists are widely used in the treatment of allergy and gastrointestinal disorders, respectively, while H3R antagonists may have therapeutic value in dementias, psychotic and sleep disorders as well as obesity. Most importantly, the newly discovered H4R has helped refine our understanding of histamine.

The H4R is a pertussis-toxin sensitive G protein coupled receptor (GPCR) and in spite of the high sequence homology with the H3R, the markedly different expression pattern indicates distinct functions. The H4R is mainly expressed on cells of the haemopoietic lineage, such as the eosinophils, dendritic cells, T lymphocytes, basophils and mast cells and its expression can be induced or altered in response to inflammatory stimuli. Interestingly, H4R activation mediates even the migration of the histamine-releasing mast cells. Histamine binding to the H4R leads to leukocyte and mast cell chemotaxis to sites of inflammation via inhibition of cAMP formation, Ca2+ mobilization and protein kinase cascades. The H4R appears to have higher affinity for histamine compared with the H1R, while the role of the H4R in the modulation of cytokine production by immunoregulatory cells implies its importance in inflammation and in infectious and autoimmune diseases.

The characterisation of the H4R as the immune system histamine receptor is evidenced by findings from diverse in vivo and in vitro studies using experimental animals or human biological samples. H4R antagonists have been reported to be effective candidates in treating diseases associated with chronic pruritus and asthma, where the H1R antihistamines are not optimally effective. In rheumatoid arthritic synovial cell cultures, the H4R was shown to be expressed in fibroblast- and macrophage-like cells. H4R antagonism caused significant inhibition of polymorphonuclear cell influx into the peritoneum or pleural cavity in neutrophilia models, while in experimental colitis, it effectively reduced colonic injury, neutrophil infiltration and cytokine production.

In a rat model of carrageenan-induced acute inflammation, it influenced both paw edema and thermal hyperalgesia. Furthermore, experimental evidence links the H4R to additional pathological conditions. Using compounds with mixed selectivity for the H4R, it was shown that the receptor may be involved in the modulation of liver ischemia/reperfusion injury and in the histaminergic control of hormone release in the rat neurohypophysis. The latest reports argue for decreased H4R levels and altered distribution of histamine receptors in human colon cancer as well as for the involvement of the H4R in the histamine-mediated proproliferative and proangiogenic effects in cancer cell lines. The H4R-modulated cell cycle arrest and cyclin expression in haematopoietic progenitors links the receptor with the regulation of haematopoiesis and implies the therapeutic exploitation of the cell cycle arrest as a means of protecting haematopoietic progenitors from chemotherapy myelotoxicity.

Yet, a major problem that is frequently overlooked is the differences in H4R localisation and pharmacological properties that may arise from the species variability of the H4R isoforms. The cloning of the first two alternatively spliced H4R isoforms from CD34+ cord blood cell derived eosinophils and mast cells, was reported this year. A comparative study on the H4R, in various species commonly used in research, revealed substantial pharmacological variation, while some sporadic related information can be obtained indirectly from studies in tissues like the eye and the cartilage. Moreover, H4R expression in the central nervous system was controversial until 2007, when the first immunohistochemical evidence (supported by functional evidence reported this year) on its expression on neurons in both the central and autonomic nervous system was presented, thus indicating that the H4R may serve multiple distinct roles, in addition to the direct control of inflammation. Thus, despite the existence of the H4R in lower species, its tissue distribution and pharmacological characterization in various species remains largely elusive, limiting the elucidation of its role in vivo. Additional complexity arises from the overlap of the H3R and H4R pharmacological profiles. This has been partially circumvented by the identification of selective compounds based on the SAR differences of histamine derivatives. However, many studies have employed non-selective compounds, like the H3/H4 antagonist thioperamide and the H2/H4 agonist dimaprit and therefore the derived data need to be re-evaluated carefully before reaching solid conclusions.

Given the aptitude of the H4R to modulate primarily the function of inflammatory cells, it appears to be a promising target for drug design, especially because a limited number of selective H4R ligands have been discovered so far. Interestingly, in a large validated structure-based virtual screening (SBVS), a compound database comprising more than 8.7 million entries screened against the human H4R (hH4R) homology yielded 16 compounds with significant H4R affinity that can serve as starting points in the development of selective H4R ligands in future.

Current state of the art of relevant research

From the Pubmed database, a total of 97 papers related to H4R research were recorded since 2000. Of these, 87 hits deal with the biological function and pharmacology of the H4R and another 10 with drug design and synthesis of H4R ligands. Taken together, non-European countries (US, Japan, Australia, Canada and China together) contributed circa 54% to the research in this field, while EU countries contributed circa 46%. Thus, EU countries represent approximately half of the world research output in this field. Notably, Europe has the highest concentration of histamine researchers in the world and therefore this Action wishes to take advantage of this unique position to increase further the output to compete with the non-EU. The main research is carried out in molecular pharmacology and drug assessment focused on the elucidation of the molecular mechanisms of H4R action, the development of reliable methodology for these investigations and synthesis and evaluation of new selective H4R ligands.

Innovation

The reports on the role of the H4R in mammalian physiology and pathophysiology started to appear in the literature only at the beginning of the new millennium and, after 8 years, 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 complicate their cooperation and, most importantly, the direct exchange of information that would be valuable for the advancement of knowledge on the H4R role and exploitation.

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 chemical synthesis/analysis, 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 H4R research has been made by the scientific community, except for a successful preliminary effort to present briefly some related data in a symposium entitled "The Histamine H3 and H4 receptors: drug targets for the anti-histamines of the 21st century", organised by the EHRS during The Federation of European Pharmacological Societies (EPHAR) Congress in 2008. This symposium will yield, later in the year, a focused volume of the British Journal of Pharmacology based on reviews and original articles from group members on the current state-of-play in H4R research.

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 this important new drug target. Furthermore, it aims to address the urgent elucidation of critical issues that have arisen and continue to arise in the field of the (patho)physiological importance of the H4R and on the pharmacological profile and therapeutic implementation of its ligands, thus directing H4R research towards a more comprehensive series of end points.

B.3 Reasons for the Action

Main reasons for this Action:

1) Creation of 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 H4R 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 and more ambitious scale collaborations as well as broaden the international contacts of the network with other research teams and with industrial partners.

Expected results:

1) The high degree of knowledge dissemination regarding the basic understanding and the huge therapeutic potential of this new drug target, the free exchange of innovative concepts and the expansion of knowledge to a broader chemistry, pharmacology, biomedical 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) Integration of research perspectives and technologies, as well as deployment of new instrumentation and reliable models that will advance the technological strategies employed in this field of research.
3) Training and mobility of young European histamine scientists and introduction of updated information into the education process at the universities.
4) 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 improving health and quality of life.

Means required to achieve the objectives:

1) Working Group (WG) meetings, workshops, training schools and Short-Term Scientific Missions (STSMs) 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. The WGs will be devoted to the education of selected young European scientists. They will introduce and disseminate the in vivo, in vitro, in situ, in silico methodological approaches, the data on the (patho)physiological importance of the H4R systems, as well as the pharmacological properties of new selective compounds and the therapeutic potential of the H4R ligands.
2) The annual conference will ensure cross-fertilisation between the various research areas, assess key advances and foster important new directions.
3) 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.

4) Promotion of high-impact and quality co-authored papers in international journals and conferences, special issues in scientific journals and/or specialist books.
5) Open fora to promote understanding of the importance of the Action to the general public.
6) A template for best practice to inform other European consortia on how best to address further critical issues in biomedical research.

B.4 Complementarity with other research programmes

No directly related EU funded projects are available in the EU programmes databases. This 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 EU proposals in the future.

C. OBJECTIVES AND BENEFITS

C.1 Main/primary objectives

The main objective of this Action is to foster a multidisciplinary approach to H4R research, and to focus on the current state of play pertaining to the basic understanding and the huge therapeutic potential of this important new drug target.

C.2 Secondary objectives

The secondary objectives are to:

– Enhance the communication and to build up strong links between the participating research teams though the website and the WGs annual meetings and workshops, where all groups will participate at least twice in four years.
– Facilitate larger and more ambitious scale collaborations by encouraging at least 3 joint major European grant applications per year.
– Gain knowledge and broaden the training and mobility of young European scientists within the participating research groups though the website and at least one annual meeting, workshop, seminar, training school or STSM per WG.

– Set the standards in methodological approaches and develop a forum for free exchange of ideas and data leading to a template for best practice to be made available through the website and societies at the end of the Action.
– Increase the awareness of the general public via at least one open forum per year.

C.3 How will the objectives be achieved?

The objectives will be achieved by:

– 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 make available the template for best practice to inform European consortia on how best to address critical issues in H4R research.
– Action publishing at least 15 (per year) high-impact and quality co-authored papers in international journals, special issues in international scientific journals and/or specialist books that will help to disseminate the interdisciplinary knowledge of this topic in the scientific community.
– 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 chemistry, biomedical sciences and preclinical and clinical pharmacology into this Action, serving as the strong basis for the advancement 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.
– The annual conference, meetings and STSMs that promote accumulation and exchange of specific knowledge, ensure cross-fertilisation between the various research areas and foster important new directions in this field of biomedical research.

C.4 Benefits of the Action

This Action will promote, between present and new Action members, a free-exchange of new ideas and training opportunities in state-of-the-art technologies. A multidisciplinary approach and a close allegiance to the pharmaceutical industry, built over the last several years through the EHRS, maximise the potential of this new therapeutic target. This Action will maintain the leadership of Europe in this important area of research and promotes European general public understanding of the Action for improving health and quality of life.

The outcomes that will be achieved by the Action are:

- Attenuation of the interdisciplinary barrier in scientific research to avoid duplication and confusion as well as to inspire new fruitful cooperation on novel H4R topics.
- Deployment of the optimal state-of-the-art methodology.
- Basis for joint major effective European grant funding applications.
- Enhancement of training and mobility of young European scientists.
- Dissemination of information to scientific societies, medicines policy makers and health officials.
- 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 and clinically oriented researchers and young investigators working or wishing to work in the field of histamine, inflammation and cancer research and drug design.
- Graduate and Ph.D. students of pharmacology, medicine, chemistry, pharmacy, molecular biology, genomics, proteomics and biomedical sciences.
- Researchers from the pharmaceutical industry.
- The European research community, through scientific societies such as the EHRS, the International Union of Basic and Clinical Pharmacology (IUPHAR) and the Federation of European Biochemical Societies (FEBS).

– The European Medicines Agency (EMEA), national medicines policy makers and health officials.
– The whole EU and world society, clinical physicians with an interest in inflammatory disorders and cancers, and patients suffering from inflammatory diseases and cancer.

D. SCIENTIFIC PROGRAMME

D.1 Scientific focus

The Action fosters a multidisciplinary approach to H4R 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 EHRS. 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 concentrate on the methodology used for the investigation of the H4R systems. This includes in vivo, in vitro, in situ and in silico models, as well as genomic, proteomic, transcriptomic studies and molecular and cellular probes. To date, major problems in evaluating research findings have arisen due to the frequently overlooked species-differences in H4R localisation and pharmacological properties, the high homology shared with the H3R and the limited information on H4R isoforms.

    (a) Molecular biologists and geneticists will assess and validate the methodologies employed for the identification, localisation, expression and distribution of the H4R, largely using validated selective immunological tools. Participants of the Action have developed the first probes for the hH4R and have contributed significantly in the characterisation of the H4R as the immune system histamine receptor, using experimental animals, cell cultures and ex vivo preparations.

To date most studies target a range of inflammatory disorders, although H4R association with ischemia/reperfusion injury, endocrine and neuronal processes and cancer has not been ignored. Aided by clinical and epidemiological data, scientists will develop assays to identify the qualitative and quantitative modifications in H4R expression and distribution in disease states in order to identify the aetiological, symptomatic and/or prognostic value of the findings. Following data integration and evaluation by the interdisciplinary team, the molecular and cellular probes will be applied to suitable cell lines, animal models of disease, knock-in and knock-out animals and patient samples.

(b) Biochemists and medicinal chemists together with preclinical pharmacologists will determine the optimal experimental conditions for the investigation of the signalling pathways associated with H4R function in a range of cells and tissues and under various conditions. An important research task to be coordinated by the Action is the use of appropriate cell types and animal species or even strains for the investigation of the mechanisms underlying the role of the H4R in order to avoid controversial and inconclusive findings.

(c) This Action takes advantage of the recent advances in genomics, proteomics and bioinformatics to encourage participants to develop and implement the relevant scientific and technical means to initiate studies on H4R interaction with the myriad of genes and proteins that may define physiology and pathology.

2. The second area will deal with the physiological and pathophysiological importance of the H4R systems integrating and critically evaluating data derived mainly from basic research. The barriers to successful classification of H4R-mediated signals in various cell types and conditions will be identified by the Action through the understanding and characterisation of the complexity and integration of upstream and downstream signalling pathways, their cross-talk with other endogenous pathways and their connection to particular cell types, using modern techniques and new specific markers and ligands.

(a) Aiming to merge all fragmented data into exploitable conclusions, biochemists, molecular scientists and pharmacologists contribute to the characterization and elucidation of the molecular structure and functional role of the H4R, a major effort initiated by several groups independently. The H4R is a 390 amino acid, seven-transmembrane GPCR and in spite of the high sequence homology with the H3R, its greatly distinct expression pattern indicates different functions. Most related research is performed by traditional pharmacology, while genomics-based approaches revealed that the hH4R gene is mapped on chromosome 18q11.2, spanning more than 21 kbp and containing three exons and two large introns. The identification and pharmacological characterization of two hH4R splice variants from CD34+ cord blood derived eosinophils was reported only very recently by two of the Action's groups. In view of the great interest in the H4R as a pharmacological target and the large diversity of isoforms for the related H3R, molecular scientists and biochemists will focus on the identification of H4R isoforms which is of utmost importance for validation strategies.

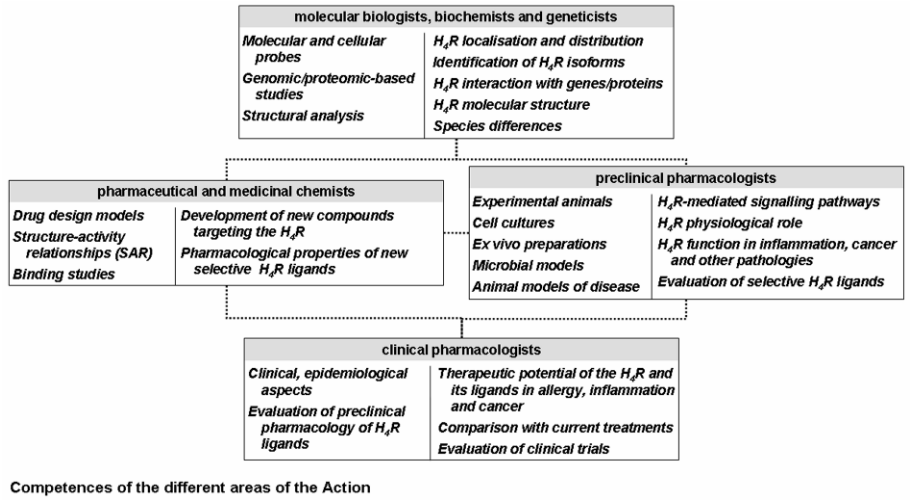
(b) A major research task of the Action is the interdisciplinary coordination of approaches employing biochemical, pharmacological, molecular and genomics/proteomics-based techniques in experimental animals, cell cultures, ex vivo preparations and microbial models, for understanding the signalling pathways underlying H4R function in a range of cells and tissues and under various conditions. The interplay between H4R-expressing cells is a key issue. One direction to be considered is the H4R contribution to inflammatory processes and allergy. The H4R appears to modulate allergic responses via its influence on T cell activation, on the balance of T helper lymphocyte 1 (Th1) and 2 (Th2) and on Th17/Tregulatory (Treg) cell interaction. It mediates eosinophil migration from the bloodstream into the sites of inflammation via rearrangements of the actin cytoskeleton. Interestingly, H4R activation mediates even the migration of mast cells, which themselves are a major source of histamine in mammals, leading to chronic inflammation. Another direction is the involvement of the H4R in cancer biology and the differences in H4R-mediated biological responses between normal and cancer cells.

Using immunological and biochemical tools, reports relate H4R expression to breast and colon cancer, while histamine exerts both proproliferative and proangiogenic effects via H2R/H4R activation and cross-talk with other pathways, such as prostaglandin production. A third direction will encourage research and integrate data regarding H4R-mediated mechanisms in ischemia/reperfusion injury, hormone release, central and peripheral neuronal function, cell stress response or any further processes which may become apparent over the duration of the Action.

3. The information obtained from basic research and preclinical investigations is imperative for the evaluation of the pharmacological properties of new selective compounds targeting the H4R. Without disregarding the deployment of modern tools for drug design, such as SBVS and fragment based design approaches, this research task takes advantage of traditional pharmacological tools, mainly SAR and dose-response relationships to disclose the properties of the receptor, against which pharmaceutical chemists design or screen compounds for activity. Albeit limited by the available GPCR structural information, a research task of particular importance is the interdisciplinary evaluation of the pharmacological properties of the hitherto relatively small number of selective H4R agonists and antagonists. First evidence on the existence of the H4R was postulated by pharmacological studies in eosinophils, where blockade of the histamine-mediated calcium influx by the known H3R antagonist thioperamide was observed, whereas only weak activation of the calcium response was obtained with the potent H3R agonist (R)-a-methylhistamine. Indeed, thioperamide is now considered as an H3R/H4R antagonist and its use in a number of studies justifies the re-evaluation of the reported findings. One direction in this area addresses issues regarding the properties of synthetic imidazole- and non-imidazole-containing compounds. Many of the imidazole-based ligands exhibit binding affinity for both H4R and H3R. The first potent and selective non-imidazole H4R antagonists were reported in 2001, while in 2004 evidence was provided for the in vivo anti-inflammatory activity of JNJ7777120, the 1-[(5-chloro-1H-indol-2-yl)carbonyl]-4-methylpiperazine with Ki 4.5nM vs the hH4R. Despite its pharmacokinetic limitations, this compound is still useful in pharmacological and preclinical investigations, together with the tricyclic clozapine analogue VUF6884 and an increasing series of new H4R agonists and antagonists.

In order to reach the objectives of the Action, pharmaceutical and medicinal chemists, biochemists, pharmacologists and biomedical scientists will contribute to a better understanding of pharmacological properties of the H4R and its ligands by using selective agents in various preclinical investigations. Newly designed H4R ligands with additional properties will be designed as pharmacological tools and disseminated to the members for novel experiments. The experimental means to achieve the objectives range from cell cultures, microbial models and ex vivo preparations to in vivo experiments in physiological animals and models of disease, where the use of H4R antagonists is a key tool to reveal the role of the H4R in many circumstances.

4. The therapeutic potential of the H4R and the new histaminergic compounds constitute another important goal of the Action. The H4R is considered as a promising target for the treatment of chronic diseases with an inflammatory component, such as asthma, inflammatory bowel disease and rheumatoid arthritis. Quite recently, its role has also been postulated in the proliferation of colon carcinoma cells, in the modulation of angiogenesis, and in mediating pruritis. H4R antagonists are in preclinical assessment for a range of inflammatory disorders and cancers and with some promising potential to enter clinical trials. Along this line of evidence, the Action addresses issues concerning the therapeutic potential of this novel drug target for the treatment of major acute and chronic pathologies, sets the standards for better strategies and considers the economic consequences of any novel therapeutic intervention vs existing treatment approaches. The tools are the preclinical, clinical and epidemiological aspects related, initially, to inflammatory disorders and cancer, together with the pharmacological properties of the H4R and its new specific ligands. 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 (through long-term EHRS membership and participation) with the major international (including many European) pharmaceutical companies currently developing H4R therapeutics (including Abbott, Johnson & Johnson, GSK, UCB CellTech, Servier, Pfizer, Bayer, Cellzome etc). Many of the Action members are pioneers in the development of novel H4R compounds, with a number of these pharmacophores currently under development and patent protection. This unique expertise will be invaluable to the success in the translational components of this Action.



Competences of the different areas of the Action

D.2 Scientific work plan – methods and means

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 oriented 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 two phases. In phase 1, all available data will be collated, presented and evaluated during the initial meetings and the workshop/seminar 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 reached.

The annual conference will focus on the integration of available information for the evaluation and urgent elucidation of critical issues that have arisen and continue to arise in the field of methodological approaches, (patho)physiological importance of the H4R and on the pharmacological profile and therapeutic implementation of its ligands. The aim is to present and discuss new achievements, give an overview to the participants, ensure cross-fertilisation 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 six months 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 H4R research, 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 six months will be devoted to the synthesis of the results achieved and the final report.

The scheme described below identifies the responsibilities, objectives and achievements of each WG and the communication amongst them and with the MC, which will coordinate all initiatives for the final objectives through a Core Group. The following aspects will be considered at any time of the Action's duration, but the activities will be highlighted in the order mentioned below.

WG1, Methodological approaches for the investigation of the H4R systems:

– Assessment and validation of existing and novel methodologies (in vivo, in vitro, in situ, in silico models; genomic/proteomic/transcriptomic studies; molecular and cellular probes) targeting H4R distribution and characterisation.
– Development of assays to identify the qualitative and quantitative modifications in H4R expression and distribution in disease states.
– Determination of the optimal experimental conditions for the biochemical and pharmacological investigation of the mechanisms associated with H4R function in a range of cells and tissues under various environments that define physiology and pathophysiology.

– Development and implementation of genomic/proteomic/bioinformatics-based scientific and technical tools to initiate the study of the interaction of the H4R with other cellular components.

WG2, Physiological and pathophysiological importance of the H4R systems:

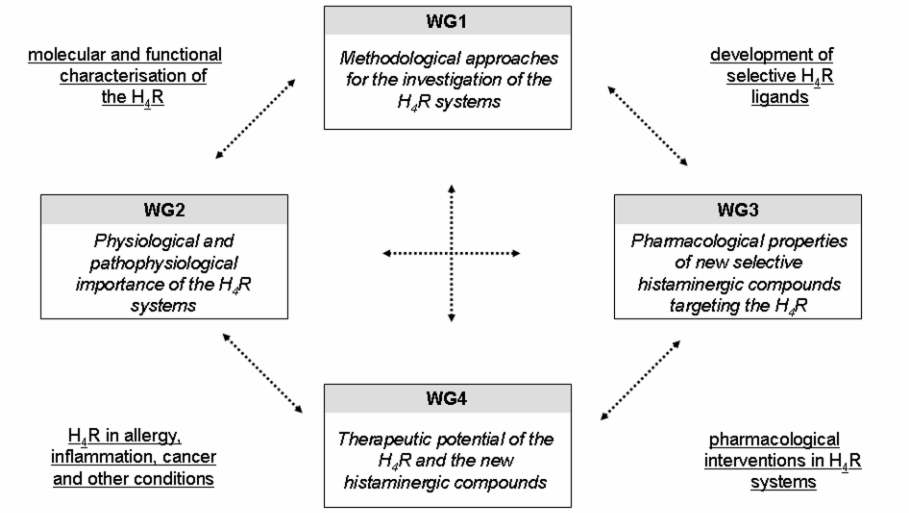
– Identification of H4R isoforms and elucidation of H4R molecular structure.
– Integration and critical evaluation of data, derived mainly from basic research, on the complex H4R-mediated signals in various cell types and conditions.
– Elucidation of the role of H4R in allergy, inflammation, cancer and other conditions.

WG3, Pharmacological properties of new histaminergic compounds targeting the H4R:

– Evaluation of the pharmacological and physicochemical properties of new selective H4R ligands using data derived from SAR and dose-response relationships and preclinical investigations.
– Consideration of modern tools such as SBVS and fragment based design for drug development.
– Consideration at the early stage absorption, distribution, metabolism, excretion and toxicity (ADMET) properties of the new compounds, drug-likeness and drug ability.
– Design of novel H4R ligands with additional properties concerning imaging (e.g. PET/SPECT ligands, fluorescence ligands) or pharmacological profiling (e.g. COX inhibition, immune modulation).

WG4, Therapeutic potential of the H4R and the new compounds:

– Set the standards for better strategies on the potential pharmacological interventions in H4R systems.
– The H4R as a target for the treatment of chronic inflammatory diseases, allergy and cancer. Comparison with current treatment approaches.
– Evaluation of existing clinical trials and potential of H4R ligands to enter clinical trials.
– Economic consequences of any novel therapeutic intervention.



Strategy of the Action illustrated by the interactions (arrows) between the Working Groups (WG) and the major predicted outcomes (underlined text).

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.

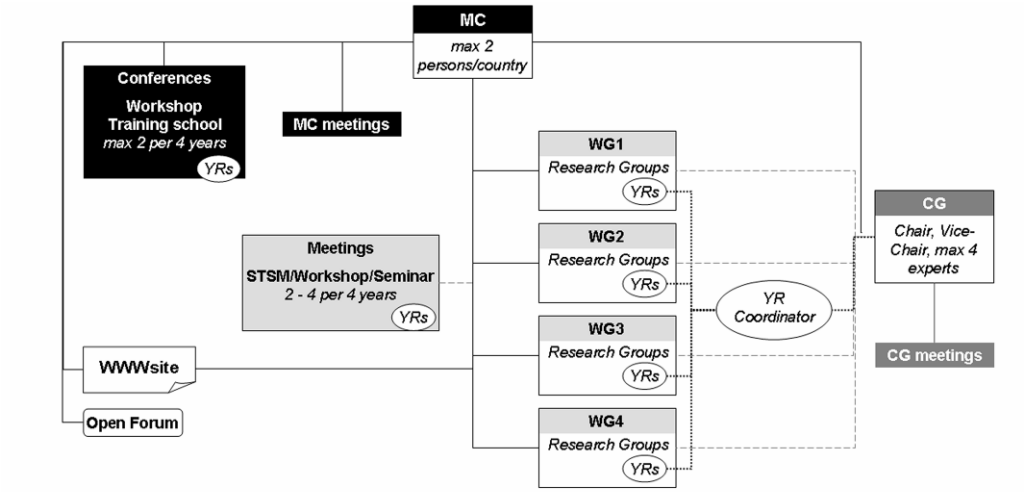
Four Working Groups (WG; with leaders selected by the MC) will be formed by distributing the partners according to their expertise (some may fall under multiple WGs). The participating teams will perform their research using financial support from national sources. The WGs will promote inclusion of young/early 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 of STSM/workshops/seminars in four years, where new results and methods 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/seminars will be devoted to the education of selected young European scientists working on histamine 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 leader 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 molecular biology, biochemistry, pharmaceutical/medicinal chemistry, preclinical and clinical pharmacology. Continuously emerging concerns on the H4R role, primarily in inflammation and cancer and on the pharmacology and therapeutic implementation of its ligands 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 it will help participants to keep up with all the research, ensure cross-fertilisation 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 first annual conference will coincide with the kick-off meeting. 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), 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. The previously successful EHRS website will be used as a template (www.ehrs.org).



Schematic organisation of the Action . CG: Core Group, MC: Management Committee, STSM: Short-Term Scientific Mission, WG: Working Group, YR: Young Researcher

E.2 Working Groups

The MC will define 4 initial WGs. Additional WGs or modifications of any existing WG (addition of 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 histamine biomedical research. Close cooperation between the WGs favours the rapid and efficient dialogue and the dissemination of new achievements and results to participants.

These interactions stimulate this interdisciplinary Action to determine successful directions to be followed on H4R research and future application(s). The scheme presented below identifies the essential responsibilities of each WG and the relationships between them (see section D).

WG1, Methodological approaches for the investigation of the H4R systems:

– Assessment and validation of existing and novel methodologies targeting H4R distribution, characterisation and interaction with other cellular components (with WG2).
– Development of assays to identify modifications in H4R expression, protein modification and distribution in disease states (with WG2, WG4).
– Determination of the optimal experimental conditions for the investigation of the functional role of the H4R in physiology and pathophysiology (with WG2, WG3, WG4).

WG2, Physiological and pathophysiological importance of the H4R systems:

– Identification and characterisation of H4R isoforms and molecular structure (with WG1, WG3).
– Integration of the H4R-mediated signals in various cell types and conditions (with WG1, WG3, WG4).

WG3, Pharmacological properties of new selective compounds targeting the H4R:

– Pharmacological properties of selective H4R ligands using structure-activity (SAR) and dose-response relationships and preclinical investigations (with WG1, WG2).
– Consideration of modern tools such as structure-based virtual screening and fragment based design for drug development (with WG1, WG2).
– Preclinical evaluation of promising H4R drug candidates (with WG2, WG4).

WG4, Therapeutic potential of the H4R and the new compounds

– Strategies on the pharmacological interventions in H4R systems (with WG1, WG2, WG3).
– Comparison of the H4R as a novel drug target with current treatment approaches in inflammatory diseases, allergy and cancer (with WG2, WG3).

– Evaluation of existing clinical trials and potential of H4R ligands to enter clinical trials (with WG2, 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 EU research proposals and participate in close productive collaborations yielding high-impact multidisciplinary outputs. However, since no directly related EU 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 biochemistry, molecular and cellular biology, genetics, preclinical and clinical pharmacology and pharmaceutical and medicinal chemistry through enhancement of communication between at least 25 groups from a minimum of 9 COST and 2 non-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%. In addition to the proposer, an extensive contribution of women 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 researchers 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.

Event	1st Year		2nd Year		3rd Year		4th Year	
MC kick-off meeting	X							
WG meetings (1 per WG)	X		X		X		X	
STSM/workshop/seminar (2-4/WG/4 years)		X		X		X		X
MC meeting	X	X	X	X	X	X	X	X
MC conference	X		X		X		X	
Core Group meeting		X		X		X		X
MC training school				X		X		
Open forum		X		X		X		X
Closing MC meeting - Final report								X

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 the WG Leaders. A Core Group of the MC will be formed by the Chair, Vice-Chair and up to four selected experts. The workplan and budget for the first year is drafted to enable an efficient start to Action through 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 it will coincide with 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 WGs will hold an annual meeting, which will coincide with the MC conference, and two of Short-Term Scientific Missions (STSMs) or workshops or seminars in four years. 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 COST countries have actively participated in the preparation of the Action or otherwise indicated their interest: France:FR; Germany:DE; Greece:GR; Hungary:HU; Italy:IT; Netherlands:NL; Poland:PL; Spain: ES; United Kingdom: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.

In addition, two major universities in South America and New Zealand have participated in the preparation of this action. 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 90/year.

H. DISSEMINATION PLAN

H.1 Who?

The target audiences for the dissemination of results are mainly researchers in Academia and pharmaceutical industry involved in chemical, biochemical, biological, pharmacological and medical projects, as well as clinical researchers, clinicians and health officials involved in the diagnosis and treatment of allergy, inflammatory diseases and cancer. In addition, the dissemination of the results to young researchers and university teachers will introduce quality research opportunities and updated information on the histaminergic systems into the education process.

The general character and widespread incidence of allergy, inflammation and cancer make this an attractive and justifiable object to familiarise the European general public with the importance of the Action for improving health and quality of life.

The results on the evaluation of cellular and molecular probes for the investigation of the H4R are expected to attract the attention of industry involved in the development, manufacturing and provision of diagnostic tools and markers.
This highly integrative and interdisciplinary Action, with dedicated teams with varied and unique skills, provides new knowledge, and innovative and state-of-the-art methodology that challenges a broad audience in biomedical sciences and preclinical research to consider the recently identified H4R as a novel mechanism underlying immune system responses that may facilitate the development of more effective strategies against allergy, inflammatory disorders and cancer.

Consequently, opportunities and challenges will emerge to stimulate pharmaceutical industry (Small to Medium Enterprises and major pharmaceutical companies) to develop new selective compounds targeting the H4R. 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.

The results obtained in this Action will be also very important for 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, autoimmune disorders and cancer which profoundly compromise public health and the welfare of society. In particular, the Action endeavours to create an environment for the therapeutic exploitation of the new compounds and for the assessment of their potential to enter clinical trials for a range of inflammatory disorders and cancers by the European Medicines Agency (EMEA), the national medicines policy makers and health officials who will be the ultimate targets of the results.

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 H4R research. The website will contain scientific knowledge, listing of publications from MC members (updated every 3 months 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 in specialised journals: 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 and training schools could be the subject of specific books, journal volumes or electronic material (CD/DVD), and will form the basis for updating the histamine section of the IUPHAR database of G protein-coupled receptors (GPCRs) and ion channels (currently edited by an Action member) to be disseminated to different audiences. 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: H4R 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 H4R research and application perspectives and to initiate novel cooperations.

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 cross-fertilisation with other networks that are directly or indirectly connected with histamine research, immunological fields, cancer research and inflammation/pain (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 officials. 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. This will provide information on the progress of the Action and facilitate the follow-up and the monitoring of the duties. 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 histamine 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.

Moreover, 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.

Finally, the Action will be committed to extend public awareness of novel therapeutic approaches in allergy, asthma, inflammation and cancer through an open forum, local and national Lay Society groups and controlled communication through the media.