

COST

Domain Committee "BMBS"

COST Action BM0806

Start Date 09/04/2009

*Recent advances in histamine receptor H4R
research*

MONITORING PROGRESS REPORT

Reporting Period: from 09.04.2009 to 20.01.2010

This Report is presented to the relevant Domain Committee.
It contains three parts:

- I. Management Report** prepared by the COST Office/Grant Holder
- II. Scientific Report** prepared by the Chair of the Management Committee of the Action
- III. Previous versions of the Scientific Report;** i.e., part II of past reporting periods

The report is a "cumulative" report, i.e. it is updated annually and covers the entire period of the Action.

Confidentiality: the documents will be made available to the public via the COST Action web page except for chapter *II.D. Self evaluation*.

Based on the monitoring results, the COST Office will decide on the following year's budget allocation.

Executive summary (max.250 words):

I. Management Report prepared by the COST Office/Grant Holder



I.A. COST Action Fact Sheet

- **COST Action** BM0806Recent advances in histamine receptor H4R research
- **Domain** BMBS

- **Action details:**

CSO Approval: 24/11/2008
Entry into force: 14/01/2009

End date: 08/04/2013
Extension: NA

- **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.

- **Parties:** *list of countries and date of acceptance*

Parties							
Country	Date	Country	Date	Country	Date	Country	Date
Austria	18/06/2009	Denmark	01/04/2009	Finland	16/04/2009	France	21/04/2009
Germany	14/01/2009	Greece	14/01/2009	Hungary	18/06/2009	Ireland	22/04/2009
Israel	08/09/2009	Italy	27/01/2009	Netherlands	14/01/2009	Poland	14/01/2009
Slovenia	28/10/2009	Spain	20/01/2009	Sweden	25/06/2009	Switzerland	31/07/2009
United Kingdom	14/01/2009						

- Total: 17

Intentions to accept: *list of countries and date*

Intentions to accept the MoU							
Country	Date	Country	Date	Country	Date	Country	Date
Lithuania	N/A						

Total: 1

- **Other participants:**

(Institution Name, Country, Town)

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- **Action Web site:** <http://www.> **Grant Holder Representative**(*name, e-mail*)
 - **Working Groups** (*list of WGs and names and affiliations of participants*)
-



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I.C. Overview activities and expenditure
Action BM0806 - budget 2010

Total Action Budget

90000,00

Remaining Action Commitment

10215,88

Meetings

Meeting Type	Date	Place	Cost	Total
Working Group	6-oct-09	Frankfurt am Main (DE)	5325,54	
Joint Management Committee/Working Group	16-déc-2009	London (UK)	17016,58	
Working Group	29-janv-2010	Florence (IT)	9600	
In conjunction with Workshop/Conference	30-mars-2010	Davos (CH)	4480	
Others	02-avr-2010	Durham (UK)	640	
Management Committee	21-avr-2010	Durham (UK)	25600	
				62662,12

STSM

Beneficiary	Date	From	Cost	Total
Ms Jennifer Stott	05-juil-2009	Belfast BT12 6BN (IE)	420	
Dr Marco Eleopra	01-août-2009	44100, Ferrara (IT)	2500	
Dr Simona Rajtar	24-janv-2010	Ljubljana (SI)	802	
Ms Petra de Kruijf	14-févr-2010	Amsterdam (NL)	1100	
Ms Tünde Simon	01-mars-2010	Budapest (HU)	1800	
Dr Vasily Stegaev	15-mars-2010	Helsinki (FI)	1800	
				8.422

Workshops

Title	Date	Place	Cost	Total
WG4 - Workshop on BioMedChem	6-oct-09	Frankfurt am Main (DE)	2.850	
Symposium -Open Forum	5-nov-09	Athens (GR)	500	
The H4 histamine receptor: new multi-use therapeutic target"	16-déc-2009	London (UK)	2.500	
WG2: Histamine H4 Receptor; Where we are and where we are going	29-janv-2010	Florence (IT)	2.850	
				8.700

79784,12

II. Scientific Report prepared by the Chair of the Management Committee of the Action, describing results achieved during the Action operation in this period, in no more than 3 pages (the report is “cumulative”). All items listed in Sections A, B, and C, below, must be addressed.

Additional documentation such as extended scientific reports, proceedings of workshops, seminars or conferences may be provided separately as an annex to this report, and should be referenced in the report.

II.A. Innovative networking

- *Innovative knowledge resulting from COST networking through the Action. (Specific examples of Results vs. Objectives)*
- *Significant scientific breakthroughs as part of the COST Action. (Specific examples)*
- *Tangible medium term socio-economic impacts achieved or expected. (Specific examples)*
- *Spin off of new EC RTD Framework Programme proposals/projects. (List)*
- *Spin off of new National Programme proposals/projects. (List)*

II.B. Inter-disciplinary networking

- *Additional knowledge obtained from working with other disciplines within the COST framework. (Specific examples)*
- *Evaluation of whether the level of inter-disciplinarity is sufficient to potentially provide scientific impacts. (Specific examples)*
- *Evaluation of whether the level of inter-disciplinarity is sufficient to potentially provide socio-economic impacts. (Specific examples)*

II.C. New networking

- *Additional new members joining the Action during its life.*
- *Total number of individual participants involved in the Action work. (Number of participants. Give % of female and of Early Stage Researcher participants)*
- *Involvement of Early Stage Researchers in the Action, in particular with respect to STSMs, networking activities, and Training Schools. In addition, justification should be provided if less than 4 STSMs were carried out during the year.*
- *Involvement of researchers from outside of COST Countries. (Number of participants from non-COST Countries approved by the CSO. Give % of such participants from countries with reciprocal agreements. Specify their contribution)*
- *Advancement and promotion of scientific knowledge through publications and other outreach activities. (Number of publications and other outreach activities that resulted from COST networking through the Action. Complete list should be given in an annex)*
- *Activities and projects with COST network colleagues.*
- *The capacity of the Action members to raise research funds.*

II.D. Self evaluation

Indicate in no more than 1 page what, in the opinion of the MC, were the main successes, drawbacks (if any) and the key difficulties encountered (if any).

III. Previous scientific report(s)

Part II of past periods' reports are to be found here.

II. Scientific Report

II.A. Innovative networking

- *Innovative knowledge resulting from COST networking through the Action*

In accordance to the aims of the Action, the interdisciplinary networking of experts led to the presentation of novel strategies to improve methodologies for H4R investigation and ligand development as new promising drug candidates. These included innovative methods to discover new H4R ligands through virtual screening and intelligent learning engine technology for the formation of a focused library. The optimization of the affinity of an H4R antagonist based on an active structure increased antagonist affinity by 3400-fold, while work relating mutagenesis and modelling revealed that H4R Q7.42 is a key residue for agonist 4-methyl histamine deep in the binding pocket -rarely seen in G-protein coupled receptors- and D3.32 & E5.46 higher in the binding pocket are crucial for binding of the standard tool, JNJ7777120.

Networking through the Action and close collaborations between academia, research & industry provided supporting data on the complicated JNJ7777120 pharmacology, in accordance to the set objectives, which are valuable for explaining some of the differential effects of H4R-targeting compounds in different tissues and/or cell types. JNJ7777120, as well as acting as an antagonist for the human H4R (hH4R) in terms of G-protein activation, it also can act as a G-protein independent agonist in terms of recruiting β -arrestin, with very similar potencies. Based on the need for more efficient H4R ligands several new compounds have been developed by Action members as indicated by patent applications by e.g. Pfizer (UK), Palau Pharma (ES) and VU University Amsterdam (NL). In a new series of JNJ7777120 analogues, with an N-methylpiperazine amide motif the most promising compound was a 3,5-dichlorobenzo- $[\beta]$ thiophene-2-carboxylic acid derivative. Unexpectedly, the demonstration that N^{ϵ} -acylated imidazolyl-propyl-guanidines developed as H2R agonists are also H3R and H4R (partial) agonists led to the development of the highly potent and selective H4R agonist UR-PI376.

Elucidation of species-differences in H4R properties is one of the objectives of the Action. Along this line of research, species heterogeneity of H4R distribution was demonstrated. Comparative studies on the role of the H4R in gastroprotection showed that the putative H4R agonist, VUF10460 elicited similar gastroprotection to JNJ7777120 in the rat, but not in the mouse. Furthermore, species pharmacology of the novel high affinity selective H4R ligand PF2988403 ($K_i = 9.55\text{nM}$ vs hH4R) showed that the compound profile ranged from neutral antagonist in the hH4R to partial and full agonist for the rat H4R with clear pro-inflammatory effects *in vivo*.

In the field of H4R downstream signalling and elucidation of its role in (patho)physiology, data provided by academic research and industry, supported the importance of H4R in allergic inflammation and asthma. The novel H4R linkage with the chemokine US28 receptor to tether both receptors within the cell, yet increase G-protein-mediated signalling via NK κ B, offers new potential for manipulating inflammatory processes. An *in vitro* test model for H4R with the co-expression of different G-proteins was described complemented with an acute murine asthma model where the synergistic role of H1R and H4R as potential benefit in asthma therapy was shown. A H4R knockout mice model was used to establish the wide ranging role of the H4R in immune responses showing positive JNJ7777120 effects in both the sensitization and challenge phase in airway inflammation and the modulation of dendritic T cell cytokine production and T_H2 polarization by H4R. In the field of skin diseases, new data demonstrated the functional expression of the H4R on keratinocytes, with higher levels in deeper vs outer layers of the skin and higher keratinocyte H4R expression in atopic dermatitis (AD), but not psoriasis or lupus patients. H4R are also expressed in antigen-presenting cells and are up-regulated in both AD and psoriasis while human *ex vivo* Langerhans cells (LC) express H4Rs, which upon activation modulate cytokine and chemokine levels and promote LC migration into deeper areas.

Innovative knowledge was obtained in the area of H4R localisation. H4R expression on endocrine cells and functional expression on central nervous system (CNS) neurons indicate an extensive biological role in addition to its significant role in immune and inflammatory processes. It is suggested that neuronal H4R is implicated in itch phenomena in mice, while H4R was shown to be present in murine salivary gland. Furthermore, H4Rs are expressed in human submandibular glandular intercalated duct and acinar cells, in a testosterone-dependent manner, implicating H4R dysregulation in the pathology of Sjögren's syndrome and providing insights into the sexual dimorphism in autoimmune diseases.

- *Significant scientific breakthroughs as part of the COST Action*

A novel H4R antagonist developed for the treatment of allergic rhinitis and asthma entered Phase I clinical trials (Palau Pharma Barcelona, ES). Numerous novel patent applications have been filed covering the new developments in this field.

- *Tangible medium term socio-economic impacts achieved or expected*

The outcome the novel H4R antagonist brought to a Phase I clinical trial is expected to provide a more effective approach for the treatment of allergic rhinitis and asthma. Knowledge transfer and the potential for increased collaboration between academia and industry result from the contacts established during the WG meetings. Groups from the pharmaceutical industry representing start-up SME and big companies are involved in the Action: Palau Pharma Barcelona (ES), EtnaLead (University of Catania spin off, IT), Pfizer Global Research & Development, Griffin Discoveries (VU University Amsterdam, NL). Finally, numerous bilateral projects between Action members and Research & Development departments of various pharmaceutical companies, such as Johnson & Johnson, USA have been established.

- *Spin off of new EC RTD Framework Programme proposals/projects*

VU University Amsterdam (NL) contacts with Palau Pharma Barcelona (ES) and Pfizer (UK)

- *Spin off of new National Programme proposals/projects.*

Dr Chazot received a nationally competitive grant where the COST Action was commented on very favourably by the reviewers. Since this is the 1st year of the Action, most members pursue research funded by projects approved before the start of the Action.

II.B. Inter-disciplinary networking

- *Additional knowledge obtained from working with other disciplines*

Cloning of alternatively spliced H4R isoforms by molecular biologists and geneticists facilitated the development and validation of species-specific and selective molecular and cellular probes, such as antibodies against the H4R that are used by molecular biologists, biochemists and pharmacologists for the reliable identification of species- and tissue- differences in H4R properties. Related multidisciplinary studies revealed that the first potent and selective non-imidazole H4R antagonist JNJ7777120 might act as an agonist in some animal models of disease. Moreover, the identification of the H4R in the brain guides pharmacological studies towards the exploration of potential side effects of H4R ligands from the CNS and to the consequences of their ability to permeate the blood brain barrier. Following collaboration of basic scientists with clinical doctors within the COST framework the potential implication of H4R dysregulation in the pathology of Sjögren's syndrome and a link between histamine and sex steroids was reported for the first time. Finally, experts in bioinformatics provided pharmaceutical chemistry with additional tools for more effective H4R-targeting molecule design in the future, while transfer of clinical experience by medical doctors is expected to have an impact on the defragmentation of preclinical pharmacology research leading to less time- and money-consuming experimental protocols (for detailed description see II.A.).

- *Evaluation of whether the level of inter-disciplinarity is sufficient to potentially provide scientific impacts*

During the first 9 months of the Action, inter-disciplinarity provided the means for the integration of information not easily accessible to distinct disciplines that shed light on the causes of some controversial and misleading reports on both H4R function and ligand properties and avoided duplication of experimental protocols directing H4R research towards more comprehensive end points. Knowledge transfer in a new research field has potential impacts on innovative projects, grant proposals and increasing networking. To this end a new database of H4R compound pharmacodynamic and pharmacokinetic information is being developed by WG3 and WG4, which will be the basis for a comprehensive review co-authored by many groups in the Action.

- *Evaluation of whether the level of inter-disciplinarity is sufficient to potentially provide socio-economic impacts*

Close co-operation with the pharmaceutical industry has already been established and developed significantly with many collaborative studies initiated and/or published (see Annex 1). However, there is a need to invite medicines policy makers and scientific authorities to join the

activities of the Action in order to improve the interdisciplinary knowledge, experiences and skills and to bring new ideas and cooperation into the Action.

II.C. New networking

- *Additional new members joining the Action during its life*

17 parties (+ 1 Intention) have joined the Action. In total 39 members (28 + 11 substitutes) constitute the Management Committee (male 59% : female 41%)

- *Total number of individual participants involved in the Action work.*

More than 70 individual participants are involved in the Action's work. About 35% are Early Stage Researchers and 40% are female

- *Involvement of Early Stage Researchers in the Action*

Two Early Stage Researchers are coordinating the Short-Term Scientific Mission program under the direction of the MC. Concerning STSMs, 7 applications (57% female) have been sent through the COST office and approved by the MC to be carried out until April 2010. Two STSMs have already been completed. There is extensive correspondence between young researchers and STSM Coordinators, mostly concerning financial support issues (STSM report in Annex 2).

- *Involvement of researchers from outside of COST Countries*

The network has been reinforced by the participation of 2 scientists from non-COST countries (50% non-COST country with reciprocal agreement) approved by JAF: Prof. George Lees (University of Otago, New Zealand) and Prof. Elena Rivera (University of Buenos Aires, Argentina). The MC agreed Ivan Sammut to replace G. Lees who leaves Otago University. Prof Rivera has reported exciting new data to support the role of the H4R in tumourgenesis. Her group's expertise on the H4R role in cancer supports the Action in this very important field of research that is inadequately explored by European research teams. Prof W Abdou (National Research Centre, Cairo, Egypt) and Professor K Ueno (Pharmaceutical Sciences, Chiba University, Japan) have both recently expressed interest on affiliation to the Action. A number of joint projects between Action members and scientists from non-COST countries are in progress.

- *Advancement and promotion of scientific knowledge through publications and other outreach activities*

The results of the Action have been presented in 42 publications in peer-review scientific journals and in 35 presentations (poster, oral, plenary lectures) in international and national meetings. Three presentations by ESRs involved in the Action received the 1st, 2nd prize and a special commendation in the 'Arthur A. Hancock Young Investigator Award' contest, sponsored by Abbott Laboratories, USA (38th EHRS meeting, Fulda, Germany, 2009). A special volume of the international scientific journal 'Frontiers in Bioscience' entitled 'Histamine revisited: the H₄ receptor in health and disease' edited by the Chair and containing scientific contributions from Action members is scheduled for September 2010. Additionally, Action members (including ERSs) published 6 reports in international and national journals and gave 2 lectures and 3 open public lectures in international and national meetings to promote the aims of COST and of the Action BM0806. Other outreach activities include patent applications, the close collaboration with scientific societies and the organisation of an Open Forum (see complete list in Annex 1).

- *Activities and projects with COST network colleagues*

Following the kick-off MC meeting (9/4/2009, Brussels, BE), a Joint Extended Steering Committee and 38th EHRS meeting, the 2nd MC meeting and an Open Forum were organised. One workshop and 1 symposium were held jointly with the meetings of WGs 1, 3 and 4. WG2 meeting & workshop are scheduled for 29-30 January 2010. A Joint WG conference with the 39th EHRS meeting will be held on 21-25 April 2010. A number of Action members are involved in already approved or submitted joint research projects (see complete list in Annex 3).

- *The capacity of the Action members to raise research funds.*

The joint publications (Annex 1) and the good reputation of the network provide an excellent capacity for research fund raising. During the first 9 months of the Action members have submitted national, European and international research proposals, most being under evaluation.

III. Previous scientific report(s)

N/A

Annex 1: Publications and other outreach activities (9.4.2009 to 20.1.2010)

- *COST Publications in peer-review journals*
 1. Abrighach H, Fajardo I, Sánchez-Jiménez F, Urdiales JL Exploring polyamine regulation by nascent histamine in a human transfected cell model. *Amino Acids*, 2009, [Epub ahead of print].
 2. Alfón J, Ardanaz N, Gil-Torregrosa B, Fernández A, Balsa D, Carceller E, Gómez L, Merlos M, Cortijo J, Morcillo E. Bartrolí X. UR-60427, a Novel H₄ Receptor-Inverse Agonist that Shows Good Efficacy in a Rat Asthma Model. *Inflammation Research*, *in press*
 3. Ángeles A, Morreale A, Negri A, Sánchez-Jiménez F, Moya-García AA Substrate uptake and protein stability relationship in mammalian histidine decarboxylase. *Proteins* 2009; 78(1):154-161
 4. Chazot PL, Tiligada E. The European Histamine Research Society (EHRS) symposium for EPHAR 2008. *Inflamm Res* 2008; 57:S05–S06
 5. Chazot PL. Advances in histamine pharmacology reveal new drug targets. *Br J Pharmacol*. 2009;157(1):1-3
 6. Connelly WM, Shenton FC, Lethbridge N, Leurs R, Waldvogel HJ, Faull RL, Lees G, Chazot PL. The histamine H₄ receptor is functionally expressed on neurons in the mammalian CNS. *Br J Pharmacol*. 2009;157(1):55-63.
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 3. Sander K*, Zivkovic A, Stark H. Internationaler COST-Aktion-Workshop. *Pharmazeutische Zeitung* 2009, 44, 4177-4178.
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 5. Tiligada E, Chazot PL. Aims and perspectives of the COST Action BM0806: Recent advances in histamine receptor H₄R research. Proceedings of the 38th Meeting of the European Histamine Research Society, 2009:62:O38 – *Oral presentation*
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4. Chazot P. H₄R and sex steroids in salivary glands and Sjögren's syndrome, British Soc for Pharmacology, 17.12.2009, London, UK
5. Chazot PL. COST Workshop Speaker "BioMed Chem on histamine H₄ receptors: New compounds for translational step" Frankfurt, Germany October 2009
6. Chazot PL. Emerging Concepts in brain histamine – H₃ and H₄ histamine receptors in the CNS. Symposium Speaker SFN Conference Satellite Chicago, USA October 2009
7. Chazot PL. The CNS Histamine H₃ and H₄ receptors: molecular pharmacology, clinical applications and COST Action, July 2009, Speaker, Otago University School of Medical Sciences, NZ
8. Chazot PL. The Histamine H₃ and H₄ receptors: molecular pharmacology and clinical applications. July 2009, Speaker, Pfizer, Sandwich, UK
9. Clarke N, Brown C, Lane C, Mowbray C, Lim H, Leurs R, Schenck E, Perros-Huguet C, Yeadon M. Translation of species differences in histamine H₄ pharmacology with PF-2988403 BPS winter meeting 2009, London, UK
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14. Kottke T*, Schneider E, Seifert R, Stark H. Functional Characterization of (1*H*-imidazol-4-yl)alkyl Derivatives at Histamine H₄ Receptor. 38th Annual Meeting of the European Histamine Research Society (EHRS), Fulda/Germany (May 13 -16, 2009), Abstract book P20 (p. 82).
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COMMENDATION

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18. Moya-García A, Rodríguez C, Morillas I, Pino-Ángeles A, Fajardo I, García-Ranea JA, Sánchez-Jiménez F. Systemic approach to histamine receptor 4 activation. BPS winter meeting 2009, London, UK
19. Proschak E* *et al.* H₄R Pseudoreceptor for homology model refinement and virtual screening. Meeting of WG4, Frankfurt, Germany, 2009, SL4.
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21. Rayan A. The utility of Intelligent Learning Engine in Drug Discovery Informatics. BPS winter meeting 2009, London, UK
22. Rivera ES. The H₄ receptor and cancer pharmacology. BPS winter meeting 2009, London, UK
23. Roßbach K*, Stark H, Sander K, Kietzmann M, Bäumer W. Histamine H₃ Receptor Antagonist-Induced Pruritus can be Inhibited by Blockade of Histamine H₁ and H₄ Receptors. 38th Annual Meeting of the European Histamine Research Society (EHRS), Fulda/Germany (May 2009), Abstract book P24 (p. 86).
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ARTHUR A. HANCOCK YOUNG INVESTIGATOR AWARD 2ND PRIZE
26. Sander K*, Kottke T, Tanrikulu Y, Proschak E, Schneider EH, Seifert R, Schneider G, Stark H. Functional Characterization of Diaminopyrimidines as Histamine H₄ Receptor Ligands. *Frontiers in Medicinal Chemistry*, Barcelona/Spain (October 4-6, 2009). *Drugs Fut.* 2009, 34 (Suppl. A), 198 (PC.142).
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28. Sasse A, Eleopra M, Stark H. Recent Advances in Histamine H₄ Receptor Research. XVIIIth European Conference of GPA2 "Groupement des Pharmacochimistes de l'Arc Atlantique" (GP2A), Group of Medicinal Chemists of the Atlantic Arc, Trinity College Dublin/Ireland (September 3-4, 2009).
29. Stark H. Histamine Receptor Antagonists – From Bench to Bedside. 9th International Symposium on Pharmaceutical Sciences (ISOPS-9), Ankara/Turkey (June 23-26, 2009).
30. Stark H. Novel Histamine Receptor Ligands – From Bench to Bedside. Trinity College, Dublin/Ireland (September 18, 2009).
31. Stegaev V*, Chazot PL, Konttinen Y. H₄R in murine and human salivary glands: effect of DHEA pro-hormone, Joint meeting of the Danish Stem Cell and Finnish Musculoskeleta PhD Graduate Schools, Odense, Denmark, 11.12.2009
32. Tiligada E Pharmacology and therapeutic perspective of the histamine H₄ receptor: state-of-the-art, International COST Action BM0806 Workshop on

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* ESR first author presenters

- *Special Issues in peer-review journals*

1. Histamine revisited: the H₄ receptor in health and disease. Ed E. Tiligada, *Frontiers in Bioscience*, Sep 2010 (*Action members will be primary contributors*)
2. The clinical potential of targeting H₄ histamine receptors. Ed PL Chazot, *Current Anaesthesia and Critical Care*, Jan 2011 (*ESRs will be primary contributors*)

- *COST Open Public Lectures*

1. Kostelidou K. COST - a fast and flexible mechanism to fund scientific networking in Europe and beyond. INVITED LECTURE - COST Athens Open Forum "Scientific networking in the service of biomedicine and society", Athens, Greece, 6.11.2009
2. Kyriakidis D. Materialisation of European research policy - Difficulties in Greek research. COST Athens Open Forum "Scientific networking in the service of biomedicine and society", Athens, Greece, 6.11.2009
3. Schwartz JC. scheduled for the Joint WG1-4 conference and 39th EHRS meeting, Durham University, UK, 21-25 April 2010
4. Tiligada E. New drug targets in inflammatory disorders: from bench to bedside. The COST BM0806 paradigm. COST Athens Open Forum "Scientific networking in the service of biomedicine and society", Athens, Greece, 6.11.2009

- *Patents*

WO 2007031529

WO 2009056551

WO 2009068512

WO 2009077608

WO 2009080721

WO 2009115496

1 patent applied for by R. Leurs (June 2009)

- *Other outreach activities*

1. *Close collaboration with the European Histamine Research Society (EHRS) in numerous scientific issues related to histamine research*

A symposium on "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 Congress in 2008 as a preliminary effort to present briefly some H₄R-related. This symposium yielded a special themed issue

of the British Journal of Pharmacology based on reviews and original articles from Action members on the current state-of-play in H4R research (BrJ Pharmacol Volume 157(1) May 2009, edited by Vice Chair Paul L Chazot, Durham University, UK)

Organisation of the Joint WG1-4 conference and 39th Annual EHRS meeting held on 21-25 April 2010 in Durham, UK (host: Vice-Chair Paul L Chazot, Durham University, UK). The conference is important since it will bring BM0806 members in contact with participants of the main international scientific society dedicated to the study of histamine and it will make possible for the first time for all participating members to meet and discuss collaboration opportunities (details on www.dur.ac.uk/conference.booking/details/?id=40). Notably, 40% of the abstracts submitted to this EHRS conference focus on H4R research.

2. *Open Forum 'Scientific networking in the service of biomedicine and society'*, Athens, Greece, 06/11/2009 (hosts: Prof. Dimitrios Kyriakidis, National Hellenic Research Foundation & Aristotle University of Thessaloniki and Dr. Ekaterini Tiligada, University of Athens Medical School, GR). This very stimulating presentation of the COST programme by Action members and the Senior Science Officer Dr. Kaliopi Kostelidou was attended by about 100 students, scientists, researchers, media representatives and the general public. It was followed by discussion on a number of issues raised by the audience (the scientific report of the meeting appears in Annex 4)
3. The Action has established close links with various EU Societies including BPS, FENS, EPHAR and EAACI
4. Establishment of a website dedicated to the activities of the Action (www.histamineresearch.com)

Annex 2: Short Term Scientific Missions - Report

STSM Report from 09.4.2009 to 20.01.2010

Seven STSM applications have been submitted to the COST Office and another 2 are scheduled (no online application yet) until April 2010 (43% male, 57% female). Additionally, Prof. G. Coruzzi offered to host another one. All 7 STSMs have been approved by the MC. Three STSMs have already been approved by the COST Office, 2 of which are completed.

Most of the correspondence concerned financial support issues. It was made clear to applicants that according to the rules (COST Vademecum (§3.4-3.6, 20/11/2008), the Action budget of 13000€ for 10-13 STSMs (minutes of ESC meeting, Fulda DE, 13.5.2009) and common practice, the criteria concerning the budget are: short stay (e.g. 5-10 working days) budget is based on daily allowance figures and travel costs. For 1m, 2m & 3m visits the grant is normally 1100 €, 1800 € & 2500 €, respectively. Exceptional cases are assessed individually depending on the justification provided by the applicant. STSMs where home & host institutes are in the same country are not reimbursed. Blanket email was sent to all WG members with information on the www and on the "administrative procedure" that is uploaded on the www (an updated version created by Dr Zampeli and some minor corrections were forwarded to the webmaster through the Action Chair for uploading).

The scientific content of all applications was in agreement with the scope of the Action. Four out of 7 applications were approved for the budget requested; the other 3 were approved for a budget lower than that requested by the applicant. Ms Kristine Rossbach performed a STSM from Hannover (DE) to Giessen (DE) without been reimbursed since she never sent an online application (NB: the home & host institutes are in the same country anyway).

Cassia Azevedo Zezzi has been appointed as the new Administrative Officer responsible for the STSMs of our Action. Unfortunately, there is no direct information from the COST Office regarding completion of the reimbursement procedure. The STSM Coordinator asks the applicants to report on the completion of the reimbursement procedure.

There is an urgent need to advertise STSMs in the website. The STSM Coordinators suggested a link to be created for STSM advertisement (eg G. Coruzzi's suggestion). Dr Zampeli requested from MC members the names & emails of young scientists working in each lab in order to have a list of Young/ES researchers, yet only 3 MC members responded. The STSM Coordinators are asking the co-operation of all MC members regarding this matter.

Dr Evangelia Zampeli
Dr Aurelio Moya-Garcia
STSM Coordinators

STSMs													
N	STSM	Name of Applicant	Home Institution	Host Institution	STSM duration	STSM title	Online Application	Budget requested	Budget approved	MC Approval	MC VOTES	Final Scientific report	Reimbursement
1	BM0806 STSM 4627	Stott Jennifer Jstott01@qub.ac.uk	The Queen's University of Belfast, UK	Paul CHAZOT School of Biological & Biomedical Sciences Durham University, Durham UK	5-10/7/09 5 days		28/4/09	420 €	420 €	24/6/09	100% (YES)	4/8/09	19/10/09
2	BM0806 STSM 4853	Marco Eleopra marcoeleopra@gmail.com	Department of Pharmaceutical Sciences, University of Ferrara, IT	Astrid SASSE School of Pharmacy & Pharmaceutical Sciences, Trinity College University of Dublin, IR	1/8/09-31/10/09 3 months	Design & synthesis of novel histamine H4R agonists	17/6/09	2.500 €	2.500 €	24/6/09	93,5% (YES) 1 comment	4/11/09	23/11/09
3	BM0806 STSM 4903	Vasily Stegaev vasily.stegaev@helsinki.fi	University of Helsinki, FI	Andras FALUS Semmelweis University Budapest, HU	15/3/10-15/5/10 2 months	H4R in salivary glands	25/7/09	3.300 €	1.800 €	27/7/09	93,5% (YES)	N/A	N/A
4	BM0806 STSM 5519	Simon Tünde	Semmelweis University Department of Genetics, Cell & Immunobiology Budapest, HU	Liam O'MAHONY Swiss institute for allergy and asthma research Davos, CH	1/3/10-30/4/10 2 months	Dendritic cell activation through H4R in response to microbial ligands following stimulation	17/11/09	3.500 €	1.800 €	28/11/09	87,5% (YES)	N/A	N/A
5	BM0806 STSM 5545	Petra de Kruijf p.de.kruijf@gmail.com	VU University of Amsterdam, Faculty of Science Amsterdam, NL	Paul CHAZOT School of Biological & Biomedical Sciences Durham University Durham, UK	14/2/10-13/3/10 1 month	Probing the role of the H4 histamine receptor in the human & murine IBD & COPD	24/11/09	1.100 €	1.100 €	28/11/09	87,5% (YES)	N/A	N/A
6	BM0806 STSM 5668	Simona Rajtar simona.rajtar@mf.uni-lj.si	University of Ljubljana, Faculty of Medicine, Dept. of Pharmacology & Experimental Toxicology, Ljubljana, SI	Katherine Tiligada Department of Pharmacology Medical School University of Athens, Athens GR	24-29/1/10 5days	Effect Of The H4 Receptor Antagonist On The Cartilaginous, Vascular And Esophageal Histamine Content	14/12/09	802 €	802 €	17/12/09	75% (YES)	N/A	N/A
7		Konstantinos Papamichael kpapamdoc@yahoo.gr	Department of Pharmacology Medical School University of Athens, Athens GR	Paul CHAZOT School of Biological & Biomedical Sciences Durham University Durham, UK	21-30/4/10 10days	Expression of the H4 histamine receptor in the intestine of inflammatory bowel disease patients.	12/1/10	1200 €	pending	13/1/10	77,77% (YES)	N/A	N/A

Future STSMs

N	STSM	Name of Applicant	Home Institution	Host Institution	STSM duration	STSM title	Online Application	Budget requested	Budget approved	MC Approval	MC VOTES	Final Scientific report	Reimbursement
8		Marek Staszewski marek.staszewski@umed.lodz.pl	Department of Synthesis & Technology of Drugs Medical University of Łódź, Łódź, PL	Rob LEURS VU University Amsterdam, Faculty of Science Amsterdam, NL									
9		Ashok Kumawat ashok.kumawat@oru.se	School of Health and Medical Sciences Örebro University, Örebro, SE	Paul CHAZOT School of Biological & Biomedical Sciences Durham University Durham, UK	April 2010								

STSM proposals

N	STSM	Name of Applicant	Home Institution	Host Institution	STSM duration	STSM title	Online Application	Budget requested	Budget approved	MC Approval	MC VOTES	Final Scientific report	Reimbursement
				Gabriella Coruzzi Dept. Human Anatomy, Pharmacology and Forensic Medicine, Section of Pharmacology, Parma, IT	3 months: April-June 2010 OR September - December 2010	In vivo pharmacology of H4R ligands: focus on inflammation and gastrointestinal tract							

Annex 3: Activities & projects with COST network colleagues (9.4.09-20.1.10)

- *COST network meetings*

1. 09/04/2009: **1st MC meeting**, Brussels, Belgium (organised by the COST office)
2. 13-16/05/2009: Joint **Extended Steering Committee meeting** and 38th Annual Meeting of the European Histamine Research Society (EHRS), Fulda, Germany (host: Prof. Friedhelm Diel, University of Applied Sciences HS, Fulda, DE). Action members made numerous contacts with representatives from the pharmaceutical industry and histaminologists from all over the world during the meeting, where the presentations on the histamine H4R exceeded 30% of the total scientific contributions (the scientific report appears in Annex 5).
3. 5-6/10/2009: **WG4 meeting & Workshop on 'BioMedChem on Histamine H₄ Receptor: New Compounds for Translational Steps'**, Frankfurt, Germany (Host: Prof. Holger Stark, Johann Wolfgang Goethe-Universitaet, DE). This inspiring event was an excellent starting point for histamine H4R-related co-operations. The meeting was attended by 72 participants, including numerous doctoral and post-doctoral fellows, from 11 countries, reflecting the high level of the 8 lectures, 4 selected short presentations and the discussion on this topic. The workshop was mainly focused on the evaluation and the therapeutic potential of H4R ligands in allergy and asthma (the full program and the scientific report of the meeting appear in Annex 6).
4. 06/11/2009: **Open Forum 'Scientific networking in the service of biomedicine and society'**, Athens, Greece (hosts: Prof. Dimitrios Kyriakidis, National Hellenic Research Foundation & Aristotle University of Thessaloniki and Dr. Ekaterini Tiligada, University of Athens Medical School, GR). This very stimulating presentation of the COST programme by Action members and the Senior Science Officer Dr. Kaliopi Kostelidou was attended by about 100 students, scientists, researchers, media representatives and the general public. It was followed by discussion on a number of issues raised by the audience (the scientific report of the meeting appears in Annex 4)
5. 17/12/2009: **2nd MC meeting** and Joint **WG1 & WG3 meeting & Symposium of the British Pharmacological Society on 'The histamine H₄ receptor: new multi-use therapeutic target'** London, United Kingdom (host: Dr Paul Chazot, Durham University, UK). At this first joint WG1 & WG3 workshop a total of 5 plenary and 6 short lectures were presented. The speakers within the symposium were either active Action members or affiliates of this Action, from Europe, North and South America. Affiliated BPS peer-reviewed oral communications were also presented. Pfizer disclosed for the first time a structure of one of their lead series, whereas Novartis showed new pharmacology of JNJ7777120. Furthermore, preclinical evidence for a role of H4R drugs in itch, allergic airway conditions and cancer was presented. Key therapeutic arenas in which H4R is expected to impact were discussed in this symposium, including chronic inflammatory disorders, itch, ulcers, neuropathic pain and cancers (the program and the scientific report of the meeting appears in Annex 7)
6. 29-30/1/2010: **1st WG2 meeting & workshop on 'Histamine H₄ Receptor: Where we are and where we are going...'** Florence, Italy (host: Prof. Emanuela Masini, University of Florence, IT). The program of the meeting appears in Annex 8.
7. 21-25/4/2010: **Joint Working Groups Conference and EHRS Annual meeting** Durham, UK (host: Dr Paul L Chazot, Durham University, UK). The meeting will offer oral presentations and posters, while a Training Workshop on H4R dedicated to ESRs will give the opportunity to young researchers to present and discuss their work on the H4R. It will make possible for the first time for all participating members to meet and discuss collaboration opportunities. A Core Group meeting will also be organized on this occasion (see announcement in Annex 9)

- *Projects with COST colleagues*

1. *Role of the H₄ histamine receptor in pain transmission and chronic pain states*, BJA/Royal College of Anaesthesia Prize studentship (George Lees, University of Otago, NZ & Paul Chazot, Durham University, UK) - Approved
2. *Consequences of histamine receptor H₄ inhibition in a murine model of the autoimmune CNS inflammatory disease multiple sclerosis (MS): experimental allergic encephalomyelitis (EAE)*, Abbott Laboratories (B. Passani & P. Chazot) - Submitted
3. *The H₄ histamine receptor: potential in acute and chronic pain*, BBSRC/CASE Pfizer studentship (P. Chazot & S. Liu) - Submitted
4. *H4R in intercalated duct progenitor cells and acinar secretory cells in healthy mice and human compared to NOD Sjögren model and Sjögren syndrome patients* (Y. Konttinen, A. Falus, E. Buzas, V. Timasi, H. Stark, P. Chazot & P. Panula)
5. *Preclinical evaluation of histamine H₃ and H₄ receptor ligands on the levels of inflammatory mediators in experimental arthritis*, Bilateral exchange program DAAD IKYDA 2010 Germany-Greece (E. Tiligada & H. Stark) – Submitted
6. *Investigation of the immunomodulatory role of histamine H₄ receptor in experimental arthritis* Bilateral exchange program Plato 2010 Greece-France (E. Tiligada & E. Schneider) – Submitted
7. *H4Rs in a female-dominant and common autoimmune disease, Sjögren's syndrome* (Y. Konttinen) Academy of Finland - To be submitted 29.01.2010
8. *Identification of novel H₄ antagonists*, (A. Rayan & S. Guccione) - To be submitted

Annex 4: Open Forum – Athens, GR - 06.11.2009 - Report

Athens, 11.11.2009

Scientific Report

Athens Open Forum: *Scientific networking in the service of biomedicine and society* National Hellenic Research Foundation (NHRF), Athens (GR) – 06.11.2009

Reference: COST-Workshop-BM0806-02333

About 100 students, scientists, researchers, media representatives and the general public attended this Open Forum. The STSM/YR Coordinator of the Action BM0806 Dr. E. Zampeli also attended the meeting. The event was advertised through the websites of the NHRF (www.eie.gr/news-en.html) and the University of Athens (www.uoa.gr/uoagr/uoaindex.htm) and it was broadcasted live (<rtsp://vod.ekt.gr/broadcast/eiecost.rm>). COST promotional material and reprints of joint publications of BM0806 members were available to all participants. A warm welcome was addressed by Prof. D. Kyriakidis (Director of the National Hellenic Research Foundation & BM0806 MC member) and by Prof. Z. Papadopoulou-Daifoti (Head of the Department of Pharmacology, Medical School, University of Athens).

In the introductory talk on 'MATERIALISATION OF EUROPEAN RESEARCH POLICY–DIFFICULTIES IN GREEK RESEARCH', Prof. D. Kyriakidis focused on the Science, Technology and Competitiveness key figures report 2008/2009 (EUR 23608). He emphasized that EU will meet the needs and the challenges for competitive research, science and technology, within and beyond the European Research Area, by relying on inter-governmental networking structures such as COST.

The Senior Science Officer Dr. K. Kostelidou gave an excellent and attractive description of 'COST-A FAST AND FLEXIBLE MECHANISM TO FUND SCIENTIFIC NETWORKING IN EUROPE AND BEYOND'. This was complemented by a comprehensive presentation of BM0806 by the Action Chair Dr. E. Tiligada in her talk on 'NEW DRUG TARGETS IN INFLAMMATORY DISORDERS: FROM BED TO BEDSIDE. THE COST BM0806 PARADIGM'. The lectures introduced the importance of scientific networking in the defragmentation of research and the clear contribution of COST to translational research that may lead to beneficial end points for the society.

The meeting ended with discussion on a number of issues raised by the audience. These included mostly queries on COST-related procedures. The participation of the Science Officer was vital for the dissemination of information on the COST programme, while the brief update on the scientific content of BM0806 by the Chair of the Action motivated scientists and the general public towards the appreciation of the therapeutic and socio-economic potential of new drug targets. The numerous favorable responses from the audience demonstrated that this has been a very stimulating and successful event.

Dr. Ekaterini Tiligada (Chair of BM0806) & Prof. Dimitrios Kyriakidis (MC member, GR)
Organizers of the Athens Open Forum

The poster is for the Athens Open Forum, part of the COST Action BM0806 (2008-2013) titled 'Recent Advances in Histamine Receptor H4R Research'. It lists participating countries (AT, CH, DE, DK, ES, FR, GR, HU, IL, IT, NL, PL, SE, SI, UK) and identifies the Chair of the Action as Ekaterini Tiligada and the COST Science Officer as Kalliope Kostelidou. The event is scheduled for Friday, 6 November 2009, at the National Hellenic Research Foundation Amphitheatre 'Leonidas Zervas', starting at 11:00 am. Key speakers listed are D. Kyriakidis (Director of the NHRF), K. Kostelidou (Senior Science Officer, COST Office, Brussels), and E. Tiligada (Associate Professor of Pharmacology, Medical School UoA). The poster also includes logos for COST and the NHRF, and states 'FREE ENTRANCE'.

Annex 5: ESC – Fulda, DE - 13.05.2009 - Report

Fulda, 18 May 2009

REFERENCE: COST-Workshop-BM0806-02100 - **SCIENTIFIC REPORT**
Local Organiser: Prof. Friedhelm Diel, University of Applied Sciences HS Fulda
Date: 13/05/2009
Place: Fulda (DE)

Dear Dr Radwanska,

I am pleased to inform you that the Extended Steering Committee meeting of the COST Action BM0806: **Recent advances in histamine receptor H₄R research** was held in Pavillon Maritim Hotel Am Schlossgarten, Fulda, Germany on 13 May 2009, at 17.45-19.45 according to schedule. Twelve members of the MC attended the Extended Steering Committee meeting, as it is evident from the attached participants' list that has been signed by each one of them. Upon completion of the ESC meeting, 11 MC members remained in Fulda in order to participate in the 38th Annual Meeting of the European Histamine Research Society (EHRS) that was held during the subsequent days in Maritim Hotel, Fulda, Germany (www.ehrs-2009.de/index.php?page=welcomed-fulda&PHPSESSID=a66cae7c129fc1b95045e8a8acea7afb).

During the annual EHRS meeting, the presentations on the histamine H₄ receptors exceeded 30% of the total scientific contributions, indicating the topicality of this area of research. On Saturday May 16th at 15.00, the Chair of the Action Dr Ekaterini Tiligada presented the Action BM0806 to the EHRS members in a very informative formal talk entitled "*Aims and Perspectives of the COST Action BM0806: Recent advances in histamine receptor H₄R research*". In addition, the MC members had the chance to inform the EHRS participants about the Action during many informal discussions.

Considering that the participants of the EHRS meeting focus their research interest in histamine, it was certainly a very timely topic to discuss with histaminologists that came from all over the world. Many participants expressed interest in histamine H₄ receptor research, in initiating collaborations and in joining the Action. Moreover, a number of representatives from the pharmaceutical industry that participated in the EHRS meeting expressed interest in the Action that could be beneficial for future collaborations concerning translational research.

Overall, the ESC meeting was a great success both from the organisational point of view and in terms of dissemination of scientific information. It attracted the interest of a number of scientists that will hopefully lead to future interdisciplinary interactions and collaborations in the field of H₄ receptor research and potential therapeutic applications.

Yours sincerely,

Professor Friedhelm Diel
Local Organizer

Annex 6: WG4 – Frankfurt am Main, DE – 06-07.10.2009 – Report

COST ACTION BM0806: RECENT ADVANCES IN HISTAMINE RECEPTOR H4R RESEARCH

Scientific Report – Workshop of Working Group 4

BioMEDCHEM on Histamine H4 Receptor - New Compounds for Translational Steps

JOHANN WOLFGANG GOETHE-UNIVERSITY FRANKFURT AM MAIN, GERMANY

TUESDAY OCTOBER 6 2009

A total of 72 participants, including numerous doctoral and post-doctoral fellows, from 11 different countries attended this inaugural meeting of Working Group 4 (WG4) of the COST Action BM0806. After welcome from Prof Tiligada (COST chair); Prof Schubert-Zsilavecz (Vice-President of the Goethe University) and Prof Stark (Chairman of WG4), the meeting consisting of 8 plenary and 4 selected presentations began.

Prof Tiligada gave an excellent introduction to the field and in particular the role of histamine in inflammation and immunomodulation. Prof Ennis described the presence of H4R on several cell types involved in inflammation and presented data indicating that H4R antagonists may prove useful in the treatment of allergy and asthma – at least in murine models. Dr Kiss described innovative methods to discover new H4R ligands through the use of virtual screening. Prof Buschauer elegantly demonstrated his findings that several of the compounds developed as H2R agonists were also (partial) agonists at the H3R and H4R. This led to the development of a highly selective H4R agonist. Dr Rayan also described a method of data mining – Intelligent Learning Engine Technology – the use of which has led to the development of a focused library for development of H4R antagonists. Dr Smits described the research procedure to optimize the affinity of an H4R antagonist based on an active structure. This approach increased the affinity by 3400 fold. Dr de Graaf utilized *in silico* guided site directed mutagenesis together with quantitative structure-activity relationships to examine the ligand-binding pocket of the H4 receptor. Dr Alfon described an H4R antagonist, developed at his company, which was active in two murine asthma models and has entered Phase I clinical trials. Prof Seifert nicely explained his *in vitro* test model for H4 receptors with the co-expression of different G proteins and the synergistic roles of H1 and H4 receptors as potential benefit in asthma therapy. Prof Radeke gave a look into related immunomodulatory roles of sphingolipids and their influence on dendritic cells. With the last lecture of this workshop the vice-chair Prof Chazot showed the species heterogeneity of H4 receptor distribution in different brain regions and their potential impact on the translational research from animal models to human trials.

Taking all together this has been a very stimulating and successful workshop lecturing topical state-of-the-art H4 receptor research with the meeting of different European co-operation partners and the making of new co-operation.

M. Ennis, H. Stark (WG 4)



International COST Action Workshop – BM0806 – WG 4

BioMedChem on Histamine H₄ Receptor
New Compounds for Translational Steps



Program and Schedule

Monday, October 5, 2009			
18:00	WG 4 assembly – general meeting		
Tuesday, October 6, 2009 – Workshop			
9:00	Greetings roses COST chair (E. Tiligada), Vice president of the Goethe-University (M. Schubert-Zsilavecz) Workshop chair (H. Stark)		
9:15	Char. H. Stark Elaeniri Tiligada PL-1 PHARMACOLOGY AND THERAPEUTIC PERSPECTIVE OF THE HISTAMINE H ₄ RECEPTOR: STATE-OF-THE-ART	University of Athens, GR	
9:45	Madeline Ennis PL-2 H ₄ RECEPTORS AND LUNG DISEASE	Queen's University of Belfast, UK	
10:15 – 10:45	Coffee		
10:45	Char. R. Leurs Robert Kiss PL-3 CHEMICAL SPACE OF H ₄ LIGANDS EXPLORED BY MOLECULAR MODELING	Heriot-Watt University, UK	
11:15	Armin Buschauer PL-4 CHANGING HISTAMINE RECEPTOR SELECTIVITY BY BIOSYNERGIC REPLACEMENTS: IMIDAZOLYLALKYLIMIDAZOLINONES AND RELATED COMPOUNDS AS POTENT AND SELECTIVE H ₄ R AGONISTS	University of Regensburg, D	
11:45	Anwar Rayan SL-1 THE UTILITY OF INTELLIGENT-LEARNING ENGINE FOR DISCOVERING NOVEL H ₄ ANTAGONISTS	Al-Qassemi Academic College, IL	
12:00	Rogier A. Smits SL-2 LIGAND BASED DESIGN OF NOVEL HISTAMINE H ₄ RECEPTOR ANTAGONISTS: OPTIMIZATION OF AN ISOQUINOLINE FRAGMENT	VU University Amsterdam, NL	
12:15 – 13:00	Lunch time		
13:00	Char. E. Tiligada Chris de Graaf SL-3 MUSCUS MORPHUEUS, PROMETHUEUS, PHARMACON: HISTAMINE RECEPTOR SELECTIVITY SWITCHES	VU University Amsterdam, NL	
13:15	Ewgenii Proschak SL-4 H ₄ R PSEUDORECEPTOR FOR HOMOLOGY MODEL REFINEMENT AND VIRTUAL SCREENING	Goethe-University Frankfurt, D	
13:30	Jose Alfin PL-5 UR-10427: FIRST H ₄ RECEPTOR ANTAGONIST IN PRECLINICAL DEVELOPMENT AT PALAU PHARMA	Palau Pharma Barcelona, ES	
14:00	Roland Seifert PL-6 MOLECULAR ANALYSIS OF THE HISTAMINE H ₄ -RECEPTOR AND ITS PATHOPHYSIOLOGICAL ROLE IN BRONCHIAL ASTHMA	Hannover Medical School, D	
14:30 – 15:00	Coffee		
15:00	Chair: R. Gutzmer Heinried H. Radeke PL-7 IMMUNE MODULATION OF DENDRITIC CELLS EMPLOYING SPHINGOLIPID ENZYMES AND GPCR LIGANDS	Goethe-University Frankfurt, D	
15:30	Paul L Chazot PL-8 FURTHER EVIDENCE OF DISTINCT ROLES AND THERAPEUTIC POTENTIAL FOR THE H ₂ AND H ₄ HISTAMINE RECEPTORS IN THE CNS	Durham University, UK	
16:00	Closing remarks		

Annex 7: WG1&3 – London, UK – 17.12.2009 – Report

Scientific Report

**BPS Winter Conference 17th December 2009 Queen Elizabeth II Conference Centre, London
COST Action BM0806 Symposium: The histamine H₄ receptor: new multi-use therapeutic target**

Introduction

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. However, more recently, it has been shown also to be expressed on endocrine cells, and to be functionally expressed in the CNS on neurons, indicating an extensive biological role. Key therapeutic arenas in which this receptor is expected to impact were discussed in this symposium, including chronic inflammatory disorders, itch, ulcers, neuropathic pain and cancers. This symposium was a follow-up to the successful EP_{HAR} histamine symposium in 2008 (which formed the basis for a themed edition of the British Journal of Pharmacology published in March 2009, and was sponsored and promoted as part of the ESF COST Action BM0806 entitled “Recent advances in histamine H₄ receptor research (HARR4-EuCOST)” (<http://www.histamineresearch.com>). The main objective of this Action is to support a network of European experts to foster a multidisciplinary approach to H₄R research, and enhance basic understanding and the therapeutic potential of this exciting new drug target. The symposium was chaired by the Paul L Chazot (Vice Chair of the Action) and Dr Katarina Tiligada (Chair of the Action). The speakers within the symposium were either active Action members or affiliates of this Action, from Europe, North and South America. Affiliated BPS peer-reviewed oral communications are also reviewed herein.

Symposia

Professor Rob Leurs (Leiden/Amsterdam Centre for Drug Discovery (LACDR), The Netherlands) introduced the topic by discussing many of the key molecular pharmacological aspects of the receptor. Two new main themes were discussed, one based on recent work relating to mutagenesis and modelling the agonist and antagonist binding sites within the H₄R. H₄R Q7.42 is a key residue for agonist 4-methyl histamine (4-MeHis) deep in the binding pocket, while D3.32 and E5.46 higher in the binding pocket are crucial for JNJ7777120 inverse agonist/antagonist binding. Notably, it is rare to have a large polar residue in the agonist binding site for the GPCR family. The second theme focussed on very new unpublished data which demonstrated that the H₄R interacts directly with the chemokine US28 receptor to tether both receptors within the cell, yet increase signalling via NKκB in a G-protein-mediated mechanism. This novel linkage offers new potential for manipulating inflammatory processes.

Dr Lars Karlsson (Johnson & Johnson Pharmaceutical Research & Development, San Diego, USA) focussed on the role of the H₄R in chronic inflammation in the lung and itch, using JNJ7777120 which is the prototype selective H₄R inverse agonist/antagonist developed by Johnson & Johnson. This compound, despite not being taken forward into the clinic mainly due to its short half-life, has proved to be an invaluable experiment tool for studying the role of the H₄R. The H₄R knockout (KO) mice, produced by the same company, have also proved to be a valuable model system. In these H₄R KO mice, significant reductions in macrophages, eosinophils, lymphocytes as well as changes in cytokine production profile (IL-4, -5, -6, -13 and -17 levels) have been observed compared to wild type mice, establishing the wide ranging role of the H₄R in immune responses. Using an ovalbumin/Alum airway inflammation mouse model, clear positive effects were seen with JNJ7777120 in both the sensitization and challenge phase, with reduction in eosinophils in both. Improved lung function was also seen. Dendritic T cells were suggested as major players in both phases; H₄R activation modulates DC cytokine production, as evidenced using H₄R KO mice and pharmacological manipulations. Furthermore, H₄R activation potentiates Th2 T cell polarization (changes in IL-4, -6 and -17). In terms of itch, histamine induces bouts of scratching which are greatly reduced in the H₄R KO mouse; furthermore, JNJ7777120 (3-100mg/kg po) also significantly reduces bouts of itch in wild-type mice. This strongly implicates the

H₄R in the itch phenomena. Sedating H₁R antagonists have small positive effects, but non-sedating antagonists have no significant effect in this model. Interestingly, combining a sedating H₁R antagonist with JNJ7777120, completely ablates the histamine-induced scratching bouts. This was not achievable using non-sedating H₁R antagonists. A similar picture was seen with IgE-induced itch. Importantly, haematopoietic cells do not seem to be involved, as only centrally active H₄R antagonists work; non-CNS permeating compounds have no effect on itch, strongly supporting the idea that these effects are via neuronal H₄R_s, consistent with recent work from the Abbott group (USA) and Paul Chazot (UK).

Professor Ralf Gutzmer (Hannover Medical School, Germany) discussed the role of the H₄R in atopic dermatitis (AD) and psoriasis. H₄R are expressed on antigen-presenting cells (APC) cells (dendritic cells) and are upregulated in both AD and psoriasis versus controls. Human *ex vivo* Langerhans cells (LC) express the H₄R, and upon activation inhibit CLC-12, increase TNF α and IL-12 levels and promote migration of LCs into deeper areas. These effects were blocked by H₄R antagonists. New data was presented demonstrating the expression of the H₄ receptor on keratinocytes, with higher levels in deeper layers versus outer layers of the skin. Keratinocyte H₄R expression was higher in AD, but not psoriasis or lupus patients. H₄R activation elicited increased keratinocyte proliferation and skin thickening; whether this involves effects upon differentiation and/or apoptosis is as yet unknown.

Sjögren's syndrome (SS) is an autoimmune disease with unknown etiology and unclear pathogenesis. Salivary and lacrimal glands are affected and there is a strong female dominance in this autoimmune disease. It is hypothesised that SS is associated with low androgen levels. Dr Paul Chazot (Durham University, UK) in collaboration with the group of Professor Yrjö Konttinen (Helsinki University, Finland) reported for the first time the presence of H₄R_s in murine salivary gland samples, with specific staining identified in the both intercalated ducts and in the acini. No expression was seen in the HDC KO mice tissue, where testosterone levels are known to be depleted. Furthermore, H₄R_s were expressed in both Human Submandibular Glandular (HSG) intercalated duct cells and HSGm acinar cells, in a testosterone-dependent manner. This implicates the dysregulation of H₄R_s in the pathology of Sjögren's syndrome.

Professor Elena Rivera (Universidad de Buenos Aires, Argentina) reported exciting new data to support the role of the H₄R in tumourigenesis. Histamine via the H₄R appears to increase apoptosis, while clobenpropit (H₄R partial agonist) and VUF8430 (H₄R agonist) decrease proliferation and increase senescence in a range of tumour cell lines. JNJ7777120 reduces lung metastases (by 80%) in MDA-MB-231 xenograph tumour-bearing mice. JNJ7777120 reduced H₄R in histidine decarboxylase (HDC)-positive cells. Both the H₃ and H₄ receptors are expressed in benign and malignant carcinomas. Higher level of expression of the H₄R was detected in malignant versus benign breast carcinomas. Whether an agonist or an antagonist is the ideal strategy is yet to be determined; both may lead to reduced levels of H₄R activities, via a different time-course.

Professor Gabriella Coruzzi (University of Parma, Italy) discussed recent data relating to the role of the H₄R in gastroprotection. We have recently reported the presence of H₄R_s in the rat gastric mucosa, specifically located on ghrelin-producing cells, in contrast to the H₃R which are expressed on the HDC-positive enterochromaffin-like (ECL) cells. Two ulcer models of differential severity were utilized to determine the role of the H₄R in the stomach. JNJ7777120 (at anti-inflammatory doses of 10-30mg/kg sc) significantly reduced the mild gastric mucosal damage induced by indomethacin (20mg/kg sc.) or indomethacin (30mg/kg sc) plus bethanechol (5mg/kg ip) in both the rat and mouse, respectively. Interestingly, the putative H₄R agonist, VUF10460 (3,10,30 mg/kg) elicited similar gastroprotection to JNJ7777120 in the rat, but not the mouse model. Neither antagonist nor agonist ligands were effective in severe gastric lesion 0.6N HCl model. The species pharmacology of the ligands described in this and the previous study, and the levels of local histamine, may also be of relevance to these apparently paradoxical results. The species differences require further investigation, but the results suggest the potential for H₄R antagonists as gastroprotective anti-inflammatory agents.

Affiliated Oral Communications

Dr Jadwiga Handzlik (Jagiellonian University, Cracow, Poland) describe the design and synthesis of a new series of JNJ7777120 analogues, with an N-methylpiperazine amide motif. The most promising compound was a 3,5-dichlorobenzo[b]thiophene-2-carboxylic acid derivative with a

moderate affinity for the H₄R. The reduction in affinity compared to the parent compound related to the lack of –NH– in the heterocyclic element within the new compound series.

Dr Elisabeth Rosethorne (Novartis Institute for Biomedical Research, Horsham, UK) described a pharmacological complication of using JNJ J7777120. As well as acting as an antagonist for the hH₄R in terms of G-protein activation (GTPγS assay), JNJ J7777120 also can act as an agonist in terms of recruiting beta-arrestin, with very similar potencies, but the latter independent of G protein activation. This may have implications in explaining differential effects of this (and other H₄R) compounds in different tissues and/or cell types.

Further to the species issue eluded to previously, Dr Nick Clark (Pfizer Global R & D, Sandwich, UK) reported the detailed species pharmacology of a novel high affinity (K_i = 9.55nM v hH₄R) selective H₄R ligand, PF-2988403. The profile differed dependent on test species with a full spectrum displayed, ranging from neutral antagonist (hH₄R), to partial and full agonist for the rH₄R. Interestingly, the *in vivo* effects of this compound in the rat reflected this agonist pharmacology, with clear pro-inflammatory effects.

Summary

Overall, the information reported in this conference provided further validation for the development of H₄R inverse agonists/antagonists as novel therapeutic agents for a range of clinical arenas. Interpretation of preclinical testing remains problematical due to significant inter-species pharmacological differences. However, a number of international pharmaceutical companies are taking their H₄R drug candidates into the clinic for a growing list of indications.

Dr Paul L Chazot (Organiser)

School of Biological & Biomedical Sciences, Durham University, UK

BPS

THURSDAY 17 DECEMBER 2009

SYMPOSIA

Westminster Suite

Targeting the endocannabinoid system for gastrointestinal diseases

Organizers:

Professor Roger Pertwee (*University of Aberdeen*)
Professor Keith Sharkey (*University of Calgary*)
Dr Karen Wright (*Lancaster University*)

Chairs:

Professor Roger Pertwee (*University of Aberdeen*) and
Dr Karen Wright (*Lancaster University*)

- 09:00 Introduction
Professor Roger Pertwee
(*University of Aberdeen*)
- 09:15 Therapeutic needs and strategies for GI diseases
Professor Brendan Whittle
(*William Harvey Research Institute*)
- 09:45 Potential therapeutic application of cannabinoid drugs in irritable bowel syndrome
Dr Angelo Izzo
(*University of Naples, Italy*)
- 10:15 Coffee Break
- 10:45 Impact of cannabinoids on the maintenance of intestinal barrier integrity
Dr Karen Wright
(*Lancaster University*)
- 11:15 Issues in drug development in GI disorders
Dr Alyson Fox
(*Novartis*)
- 11:45 Panel discussion (all speakers)

St James' Suite

The histamine H₄ receptor: new multi-use therapeutic target (COST Action BM0806)

Organizer:

Dr Paul L Chazot (*University of Durham*)

Chairs:

Dr Paul L Chazot (*Durham University*)
Dr Katherine Tiligada (*University of Athens, Greece*)

- 09:00 Recent advances in the molecular pharmacology of the H₄ histamine receptor
Professor Rob Leurs
(*Leiden/Amsterdam Center for Drug Research (LACDR), The Netherlands*)
- 09:30 Drug development for targeting the H₄ histamine receptor
Dr Lars Karlsson
(*Johnson & Johnson Pharmaceutical Research and Development, USA*)
- 10:00 Selected short talk 1
- 10:15 Coffee Break
- 10:45 The H₄ receptor and cancer pharmacology
Professor Elena S Rivera
(*Universidad de Buenos Aires, Argentina*)
- 11:15 The role of the histamine H₄ receptor in chronic inflammatory skin disorders
Professor Ralf Gutzmer
(*Hannover Medical School, Germany*)
- 11:45 Selected short talk 2
Selected short talks are from submitted abstracts

Annex 8: WG2 – Florence, IT – 29-30.1.2010 – Programme

COST WORKSHOP Histamine H₄ Receptor Where we are and where we are going... January 29th - 30th 2010

**Military Department of Forensic Medicine, Caserma Redi, Via Venezia 5 - 50129, Florence,
Italy**

January 29th, 2010

- 13:00-15:00 Registration of participants and formalities for the European Community
- 14:45-15:00 Gian Franco Gensini (Dean of Florence Medical School) and Emanuela Masini
Welcome to the participants
- 15:00-17:00 *Receptor and drug discovery***
- Chairmen: Paul Chazot (UK) and Gabriella Coruzzi (IT)**
Speakers 30 min. each (25 min. presentation plus 5 min. discussion)
- 15:00 Rob Leurs *"From fragments to new histamine H₄R antagonists"*
- 15:30 Kerstin Sander *"New insights in histamine H₄Receptors ligands"*
- 16:00 Elke Schneider *"H₄ histamine receptors mediate cell cycle arrest in growth factor-induced murine and human hematopoietic progenitor cells"*
- 16:30-17:00 Free presentations (15 min. each)**
- 16:30 Hubert Schwelberger *"Histamine signaling and metabolism associated with ischemia/reperfusion during solid organ transplantation"*
- 16:45 Agnieszka Fogel *"Regional blood flow regulation in rat model of ulcerative colitis; histamine receptors involved"*
- 17:00-17:15 Coffee break**
- 17:00-18:30 COST Member Meeting and WG2 Meeting**
- 20:30 Dinner at Villa Viviani**

January 30th, 2010

- 9:00-10:30 *From receptors to function***
- Chairmen: Patrizio Blandina (IT) and Katherine Tiligada (GR)**
Speakers: 30 min. each (25 min. presentation plus 5 min. discussion)
- 9:00 Paul L Chazot: *"Expansion of the physiological roles subserved by the histamine H₄ receptor and their potential therapeutic exploitation: anatomical and functional evidence"*
- 9:30 Pertti Panula: *"Histaminergic regulation of brain endothelial cells"*
- 10:00 Beatrice Passani: *"Histamine and neuroprotection"*
- 10:30-11:00 Coffee break**
- 11.00- 13.15 *Role of H₄ agonists and antagonists in inflammatory diseases***
- Chairmen: Madeleine Ennis (UK) Pertti Panula (FR)**
- 11:00 Madeleine Ennis *"H₄ receptors and lung disease"*
- 11:30 Katherine Tiligada *"The H₄ receptor in arthritic disorders"*
- 12:00 Bernhard Gibbs: *"Therapeutic approaches for targeting basophils in allergy"*
- 12:30 Gabriella Coruzzi: *"Histamine And The Stomach: Damage Or Protection?"*
- 13:00 Alfredo Vannacci & Alessandra Pugi: *"Pharmacovigilance issues in anti-histamines research"*
- 13.15-13.30 Closure of the workshop Patrizio Blandina and Emanuela Masini:**
- 13.30-14.30 Lunch**

Annex 9: WG1-4 – Durham, UK – 21-25.4.2010 – Announcement



**EHRS 2010 Durham
Hatfield College
21st-25th April**



Science Programme:

Invited Plenary speakers:

Professor J-C Schwartz (Bioprojet, France)
Professor P Blandina (Florence, IT)
Dr T Lovenberg (J&J, US)
Dr T Esbenshade (Abbott, US)
Dr Steve Liu (Pfizer, UK)



Symposia (short oral) & Poster sessions:

Potential Topics:

Technologies – molecular – cellular – systems - Medicinal chemistry - In vitro pharmacology & physiology - In vivo pharmacology & physiology - Translational aspects – Clinical

Inflammation – neuroscience – cancers – allergies and more.....

Conference partially funded by COST Action BM0806: HARR4-Eu with MC and WG1-4 meetings & **Training Workshops: Early Career Histaminologists**

Social programme:

Elizabethan Feast – Lumley Castle (1388) - Prospective Tours - York City (The White Rose) Durham City (The Prince Bishops) - International Glass Centre, Sunderland - Invited Chancellor of University of Durham, Bill Bryson, Internationally renowned Writer - Talk on the wonders of Durham; history & culture

Travel:

Flight: International Airports - Newcastle (30min from Durham by coach)
Durham-Tees Valley (30min from Durham by coach)

Train: 3h direct from London King's Cross Station (East Coast Main line)

Host: Dr Paul L Chazot

paul.chazot@dur.ac.uk