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Meeting report of the COST action BM0806 'Recent advances in histamine receptor H_4R research'

E. Tiligada

The meeting of the COST Action BM0806 '*Recent advances in histamine receptor H_4R research*' took place as an integral part of the 39th Annual EHRS meeting held in University of Durham, UK. The main objective of the COST Action BM0806 is to foster a multidisciplinary approach to histamine H_4 receptor (H_4R) research and to focus on the current state of play pertaining to the basic understanding and the huge therapeutic potential of this new drug target. The Action builds up strong European interdisciplinary links through enhancement of communication among more than 120 senior and young scientists from at least 40 European groups based on 19 COST and 2 non-COST countries, who actively participate in the 4 mutually interlocking working Groups (WG) of the Action.

H_4R is the most recently discovered histamine receptor subtype which is linked to a variety of immune and inflammatory disorders. Selective H_4R antagonists are reported to be entering the clinic, thus materialising the "bench to bedside" concept. COST Action BM0806 has a firm foundation for managing research into the H_4R function and therapeutic exploitation due to the unique interaction of biochemists, molecular and cellular biologists, geneticists, chemists, pharmacologists and clinical researchers involved in the EHRS. During the joint meeting, Action members built up strong interdisciplinary links with 'histaminologists' through enhancement of communication, rapid result dissemination and productive exchange of ideas that will enable the expert teams to work jointly towards more beneficial end-points associated with this potential new drug target. Broadening the training of Early Stage Researchers (ESRs) in all aspects of H_4R research and stimulation of their potential mobility, by using the Short-Term Scientific Mission (STSM) COST tool, were additional constructive outcomes of this joint activity. The Programme abstracts will be available on the Action website (http://www.histamineresearch.com) later in 2010.

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The COST conference attracted more than 50 Action members and comprised a 5 hour WG1 methods Workshop for ESRs, a Public Lecture, a Plenary Lecture, 3 Oral Sessions, 12 peer-reviewed posters, a Management Committee meeting and WG2, 3 & 4 meetings. All sessions were co-chaired by a senior scientist and an ESR, thus offering experience to young investigators in these important roles. A major output from the breakout groups that occurred during the conference was a unique agreement from many of the Pharmaceutical Industry members to support an information resource of key H_4R compounds which will be made freely available to the Action members and form the basis of a comprehensive compendium for promotion of H_4R basic and translational research.

The COST WG1 workshop highlighted the range of expertise and state-of-the-art facilities and model systems available within the Action and attracted approximately 40 ESRs and senior scientists from the Action and the host University. The 5 speakers covered a wide range of topics that encouraged, promoted and offered the means for solving emerging problems and limitations in H_4R research: Professor Rob Leurs (VU University Amsterdam, NL)—Medicinal Chemistry & receptor modelling; Professor Andras Falus (Semmelweis University, HU)—Genomics & bioinformatics; Dr Abdel Ennaceur (University of Sunderland, UK)—In vivo preclinical studies; Dr Paul L Chazot (University of Durham, UK)—Antibody production & validation; Professor Emmanuela Masini (University of Florence, IT)—Inflammation models.

The COST Action Public Lecture, delivered by Professor Jean-Charles Schwartz (Bioprojet, FR), was dedicated to the memory of the Nobel Laureate Professor Sir James Black, friend & colleague to many within the EHRS and the COST Action. This impressive talk related the story of the discovery of histamine in the brain and the subsequent path to the present day and was filmed and recorded for Public online dissemination *gratis* as both expert and public versions. Dr Steve Liu (Pfizer, UK) delivered the COST Plenary Lecture relating to the therapeutic opportunities offered through targeting of the H_3R and H_4R in treating airway and inflammatory diseases and presented a large body of supporting preclinical evidence.

The following highlights of the 15 oral and 12 poster COST Action BM0806 presentations show the advancements on H_4R research reported by ESRs. S. Nijmeijer (VU University Amsterdam, NL) offered new insights into H_4R regulation and histamine–chemokine cross-talk by elegantly illustrating the formation of H_4R surface dimers which recruit β-arrestin and internalise upon activation as well as the H_4R heterodimerisation with chemokine receptors CXCR4. S. Tünde (Semmelweis University, HU) provided further information on H_4R function by reporting reduction of H_2R and H_4R expression and elevated migration by prolonged histamine treatment during dendritic cell (DC) differentiation, and elevated antigen presenting capacity of $H_4R^{-/-}$ DCs compared to their wild type counterparts. In a STSM report, J. Stott (Queens University Belfast, UK) showed the detection of H_3R and H_4R in cell lines and primary human nasal epithelial cells from controls and patients with cystic fibrosis and suggested an important route to activating chloride transport in cystic fibrosis epithelial cells. S. Mommert (Hannover Medical School, DE) demonstrated H_4R functional expression on human memory Th17, and A.K. Kumawat (Örebro University, SE) reported reduced H_4R and H_2R expression in precolitic compared to wild type mice and H_4R increases with colitis progression in a mouse model of Crohn's disease. Regarding H_4R involvment in cancer, N. Massari (University of Buenos Aires, AR) showed the presence of H_4R in metastatic human melanoma cells and its association with histamine-mediated cell proliferation, senescence and differentiation. Additions to the panel of available selective H_4R ligands were presented by B. Savall (J&J, USA) who reported the new high affinity oxime agonist JNJ28610244 and the development of a 2-aryl benzimidazole series, where changes of diamine led from an agonist to an antagonist. Finally, exciting new clinical data were reported by Dr J. Alfon (Palau Pharma, ES) on UR-63325 which has entered into Phase I clinical trials for asthma and allergic rhinitis and showed no adverse, including CNS-associated, side-effects.

In addition to the organiser Vice-Chair of the Action Dr. P.L. Chazot (University of Durham, UK), active contributors of the meeting were the Chair of the Action Dr. E. Tiligada (University of Athens Medical School, GR) and 21 Management Committee members including the WG1-4 leaders and co-leaders Professor A. Falus (Semmelweis University, HU), Professor H. Schwelberger (Medical University Innsbruck, AT), Professor E. Masini (University of Florence, IT), Dr. E. Schneider (Université René Descartes, FR), Professor R. Leurs (VU University Amsterdam, NL), Professor G. Coruzzi (University of Parma, IT), Professor H. Stark (Johann Wolfgang Goethe University, DE) and Professor M. Ennis (Queen's University Belfast, UK). The meeting was attended in part by the COST officials Dr. M. Radwanska (Science Officer), Professor P. Andjus (Rapporteur) and Ms A. Van der Snickt (Administrative Officer). Overall, this joint EHRS/COST Action BM0806 conference attracted all the major players in international academic research and pharmaceutical industry who have interest in H_4R-related research and drug development, and pooled the scientific resources and expertise in order to meet the major challenges in understanding the functional pharmacology and therapeutic potential of the H_4R. Yet, as Dr Liu summarised eloquently the state-of-play for H_4R research in his last slide: "A big challenge remains on establishing preclinical rationale with existing tools and the significant cross species pharmacology differences".