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

Brussels, 21 November 2012

CM1207

MEMORANDUM OF UNDERSTANDING

Subject :	Memorandum of Understanding for the implementation of a European Concerted Research Action designated as COST Action CM1207: GLISTEN: GPCR-Ligand Interactions, Structures, and Transmembrane Signalling: a European Research Network

Delegations will find attached the Memorandum of Understanding for COST Action as approved by the COST Committee of Senior Officials (CSO) at its 186th meeting on 20 - 21 November 2012.

MEMORANDUM OF UNDERSTANDING
For the implementation of a European Concerted Research Action designated as

COST Action CM1207
GLISTEN: GPCR-LIGAND INTERACTIONS, STRUCTURES, AND TRANSMEMBRANE SIGNALLING: A EUROPEAN RESEARCH NETWORK

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 4154/11 "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 create a pan-European multidisciplinary network of researchers investigating G protein-coupled receptor signalling to gain in-depth understanding of GPCR mechanisms and to use this knowledge to design chemical modulators of GPCRs.

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 56 million in 2012 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

G protein-coupled receptors (GPCRs) are the largest family of proteins involved in signal transduction across membranes and one of the most important pharmaceutical drug target classes. In the past five years, an unprecedented number of X-ray structures of GPCRs have been solved, providing first peeks at the molecular details of their function. Based on these and forthcoming structures, this COST Action will bring together experts in a wide range of complementary methods to unravel details of the activation mechanism, ligand binding, and the effect of the membrane and other interaction partners on GPCRs. The information exchange that will be made possible by the COST Action will lead to innovative insights into mechanistic details of GPCR function. This will in turn give rise to novel effector molecules to be used as lead structures for drug development, offering valuable new opportunities for European pharmaceutical research and industry.
Keywords: G protein-coupled receptor, biased signalling, activation mechanism, drug discovery, GPCR-membrane interactions

B. BACKGROUND

B.1 General background

G protein-coupled receptors (GPCRs) are the largest group of integral membrane proteins transducing signals in humans. They act as receptors for a multitude of endogenous ligands and represent one of the most important types of therapeutic targets. Almost every physiological function, from sight, smell and emotion, to heart rate, immune cell and neural communication entails a GPCR. Conversely, GPCR malfunction can lead to or promote severe diseases such as Parkinson's, Alzheimer's, cancer, schizophrenia, autoimmune diseases or metabolic syndrome. Not surprisingly then, GPCRs are the targets of over 30% of currently marketed drugs. Most of these drugs have been identified through classical pharmacology and medicinal chemistry without an atomistic understanding of the structural and functional facets of drug-receptor interaction.

For *rational* drug design in the true sense of the word, it is imperative, however, to understand how these receptors function at a molecular level and how their activity is modulated. In-depth and detailed understanding of GPCR dynamics and interactions will seamlessly be translatable to more effective and more specific medications with fewer side effects.

Despite the spectacular advances in GPCR structure determination of the past five years, only about 1% of all human GPCRs have been crystallised. Moreover, the structures are only static snapshots

of the receptors in select discrete conformations and the time-resolved mechanism is unclear. The mechanism of activation, the nature of ligand-dependent signalling, and the role of oligomerisation are still poorly understood. While the GPCR structures disclose the binding locations of potent ligands, this information has yet to be harvested for the design of novel drugs. What is direly needed, but currently lacking, is the transformation of the present “stamp collection” of single structures to a fundamental and exploitable understanding of how GPCRs work and can be therapeutically influenced. Such a comprehensive interdisciplinary view of the interplay of structural, functional and interaction parameters in mechanistic detail is necessary to efficiently design ligands, i.e. potential drugs. In addition, it is likely that the many yet uninvestigated interactions of GPCRs offer fundamentally novel opportunities to modulate GPCR signalling. Numerous publications about individual aspects of GPCR signalling have appeared in the past decades, but only the recently determined (and upcoming) X-ray structures allow all these dots to be connected. This COST Action has the aim but also the scientific acumen to form a complete picture of GPCR mechanisms, complete with a dynamic view. This view will be achieved by connecting and exchanging information between a wide panel of experimental and theoretical researchers with expertise in complementary approaches, each of which will contribute a different detail. The Action will also create and communicate blueprints and best practices for investigating GPCRs and finding GPCR modulators. Both will lead to an increase in scientific knowledge in Europe and worldwide, and will open the door for the creation of new, improved and highly targeted drugs against diseases with a high societal burden such as cancer or metabolic syndrome. A particular focus of this Action will be on Class A GPCRs, including those that are difficult to crystallise and address with ligands, and Class B and C GPCRs, for which at present no structures of the transmembrane domain exist. Determining such structures, investigating them and finding ligands for them will represent a big step forward as it will inform the field about the commonalities and differences between different classes of GPCRs.

The scientific impact is likely substantial: not only are GPCRs involved in numerous signalling cascades and diseases, but comparatively little is understood about membrane proteins in general. New findings in the context of this Action will thus have ramifications outside of the GPCR field.

Why COST? A COST Action offers the best possibilities to investigate GPCRs in a fundamentally interdisciplinary way. This undertaking involves a plethora of custom-made reagents, assays, techniques and software. Such tailored solutions are best developed by bringing experts together to collaboratively develop them. Communication between the individual, nationally funded, research teams is ideally coordinated through the activities enabled by a COST Action. The tools offered to educate and train early-stage researchers (ESRs) will create a generation of highly interdisciplinary

individuals. Furthermore, several young investigators who have been intimately involved overseas in the breakthrough discoveries of the past five years have recently returned to Europe and are eager to contribute to the European research community. This COST Action will be an attractive vehicle to (re)integrate GPCR researchers and ensure that experience acquired abroad is assimilated within the European research area, for example through Short-Term Scientific Missions (STSMs).

B.2 Current state of knowledge

GPCRs signal via conformational changes. GPCRs are in fact the ultimate versatile switches of cell function. Upon activation by an agonist, GPCRs undergo conformational changes and interact with G proteins or G protein interacting proteins, which in turn directly and/or indirectly modulate the function of kinases that phosphorylate downstream signalling proteins. These GPCR-driven protein interaction networks modulate, among others, the activities of a variety of transcription factors, regulate gene expression or activate proteins involved in e.g. cytoskeletal rearrangement.
What is missing? Most of the GPCR X-ray structures available to date are complexes with ligands that act as antagonists or inverse agonists. These structures thus represent energetically stable inactive-state conformations. The paths from this state to the active ones and the rates at which conformational change happens are unclear, however. The few agonist- and G protein-bound GPCR X-ray structures only provide limited explanations, as they show only subtle changes within the binding pocket.
This COST Action will investigate the structural changes during the activation process using a mix of X-ray crystallography, Nuclear Magnetic Resonance (NMR) and Molecular Dynamics (MD) simulations. Moreover, it will develop specific agents to stabilise individual receptor conformations (cf. D.2 Working Group WG1).
GPCR ligands can display pathway bias. Different ligands can stabilise (or block) multiple conformational states of the same receptor. Each state may be linked to a different pathway and a different functional outcome. GPCRs thus do not only turn ON or OFF a *single* signalling pathway, but can modulate several pathways in parallel. This phenomenon is called *pathway bias* of a ligand. Furthermore, many GPCRs have allosteric sites and ligands binding there can alter orthosteric ligand affinity and/or efficacy.
What is missing? The structural determinants, i.e. receptor regions, conformations, and ligand binding sites of GPCRs that dictate biased signalling are completely unknown. Binding to allosteric sites is equally poorly investigated. Allosteric ligands are highly attractive, however, as they are associated with increased receptor subtype selectivity and the potential to “fine tune” normal

physiological signalling.

This COST Action will investigate pathway bias by setting up specialised screens to identify ligands with biases that will allow the separate investigation of different pathways. Additionally, a focus will be on the identification and exploitation of allosteric binding sites (cf. D.2 WG2).

GPCR transmembrane signalling is a complex process. In the last decade, it has become clear that many GPCRs may function as homo- or heterodimers or even higher order oligomers. Moreover, GPCRs entertain interactions with a myriad of other proteins, such as beta-arrestin and PDZ domains. All these interactions have implications for trafficking, signalling, receptor internalisation, and pharmacology and thus for our general understanding of GPCR signalling and druggability, yet they are only poorly understood.

What is missing? Little is known how different membrane parameters, such as the saturation degree of the constituent phospholipids and the cholesterol content, affect membrane proteins (including GPCRs). Unspecific effects on the conformational states and receptor oligomerisation can be driven by bulk properties of the membrane, e.g. thickness and curvature, but also this is not understood well.

This COST Action will shed light on the role of the membrane for receptor activation and oligomerisation by employing techniques such as peptide mapping, Protein Lipid Overlay, and MD simulations (cf. D.2 WG3).

From GPCR structures to the discovery of modulators. The different crystal structures show various ligand binding modes that provide starting points for the design of GPCR-regulating bioactive compounds. In fact, stabilising the receptor with potent ligands has been key for X-ray structure determination, and some ligands have been custom-made for this purpose. All of these new X-ray structures have also immediately been used for *in silico* discovery of (fragment-like) ligands.

What is missing? The structure-based *optimisation* of virtual screening hits and the *rational* design of molecules with a particular efficacy or allosteric binding mode still remain difficult tasks in which experimental data is of utmost importance to guide the calculations. In fact, recent blind predictions of the three-dimensional structures of GPCR-ligand complexes have highlighted not only the possibilities, but also the challenges of computer-aided prediction of GPCR-ligand interactions. Moreover, future X-ray structures will also need novel molecules for stabilisation. This COST Action will, synthetically and computationally, identify GPCR ligands and characterise them in terms of binding kinetics and thermodynamics, efficacy, and pathway bias (cf. D.2 WG4).

In GPCR research, Europe has lost ground compared to the US and Japan. One manifestation of this fact is the gap in terms of solved X-ray structures which has widened since 2007. There are many reasons for this acceleration of GPCR research outside of Europe, one of the most important ones

being that researchers in the US are very well connected through an NIH-funded GPCR network within the PSI:Biology initiative, giving member labs an advantage because of early access to data and sharing of expertise and techniques. Research groups in the US use experimental approaches such as X-ray structure determination, classical pharmacological ligand identification, or investigation of individual pathways, and they have also contributed to theoretical investigations with docking, homology modelling and MD simulations.

B.3 Reasons for the Action

Although the recent three-dimensional structures of GPCRs have increased our understanding of functional, computational and biophysical studies, still only the surface has been scratched. Given the scientific relevance of GPCRs and their high potential in life sciences and technology, there is a considerable scientific need to fully understand GPCR signalling. Only with a complete understanding of GPCR function will rational and efficient design and prediction of the activity and efficacy of modulators be possible. The possibilities for novel drugs are vast: only about 50 (out of an estimated 800) GPCRs from eleven subfamilies have been targeted with drugs so far and laying the scientific foundation for the discovery of more drugs will give European pharmaceutical research a competitive edge. Gaining such deep understanding is only possible within a closely knit network of experts in different experimental and computational methods, because each method will contribute a different piece of the puzzle. This COST Action will integrate all structural, functional, computational, biophysical, biochemical, medicinal chemistry and translational expertise on GPCRs available from the European experts in each field. This will lead to an increased intensity of collaborations, resulting in a boost in scientific knowledge, streamlined grant applications and the emergence of a generation of young researchers with interdisciplinary training and the potential to become leaders in the GPCR field. Moreover, close collaborations between academia and industry participants are an integral part of this Action. The collaborations will facilitate further application of Action results and will also provide attractive future perspectives for young scientists who wish to pursue their career in the pharmaceutical industry. The implementation of intensive communication across the boundaries of various disciplines through the coordination by the COST Action will help each research group overcome obstacles of their particular approach.
Obtained insights with respect to structure, function and pharmacology will help ensure the competitiveness and excellence of European GPCR research. Given the success of the many GPCR drugs targeting only few GPCRs nowadays, one can only imagine how many more viable drug targets there could be. With GPCRs involved in all kinds of maladies from cancer to Alzheimer's

there is also a considerable societal need for new drugs to improve and maintain health. The results coming out of this Action will help discover novel ways to influence the receptors and design drugs that alleviate severe diseases constituting substantial societal burdens.

B.4 Complementarity with other research programmes

Despite the importance of GPCRs, only three projects related to them are funded at the EU level:

- BM0806 “Recent advances in histamine receptor H4R research” (COST Action; due to expire in April 2013).
- CM1103 “Structure-based drug design for diagnosis and treatment of neurological diseases: dissecting and modulating complex function in the monoaminergic systems of the brain” (COST Action; due to expire in November 2015).
- FP7-PEOPLE-2007-1-1-ITN “Structural Biology of Membrane Proteins” (Initial Training Network funded by FP7; due to expire in August 2012).

The histamine receptor Action (BM0806) focuses on a single Class A GPCR, and the Action on the treatment of neurological diseases (CM1103) is limited to the modulation of GPCRs involved in neuropsychiatric disorders. While the foci of these Actions compared to the one presented here are substantially different and far less inclusive, both would make excellent partners for specific subprojects. The Training Network was mainly concerned with the education of researchers in the first five years of their career, but will have expired by the time that this Action is launched. Its emphasis was markedly different and covered membrane proteins in general. Nonetheless, several researchers who have been involved in the ITN have already expressed their desire to be part of GLISTEN.

C. OBJECTIVES AND BENEFITS

C.1 Aim

The aim of the Action is to create a pan-European multidisciplinary network of researchers investigating all aspects of G protein-coupled receptor signalling with the goal to gain in-depth and general understanding of GPCR mechanisms and to use this knowledge to identify and design

chemical modulators of GPCR-mediated signalling. The individual research groups will contribute biophysical, chemical, computational and pharmacological methods and focus on four areas, namely GPCR dynamics, biased signalling, GPCR-lipid/protein interactions, and the discovery and design of GPCR ligands.

C.2 Objectives

The main objective of elucidating the GPCR signalling mechanism in all its breadth can be subdivided in scientific and organisational objectives.
Scientific objectives the Action Members will focus on are:

- Integrating knowledge to create a dynamic picture of GPCR function from ligand binding to G protein activation.
- Gaining new fundamental understanding how different signalling pathways can be elicited by different ligands on the same receptor.
- Investigating the roles of lipids and protein interaction partners during GPCR activation.
- Advancing ligand discovery and design for GPCR modulation and chemical biology.

Organisational objectives facilitated by COST Action instruments include:

- Creating and maintaining a pan-European close-knit network of GPCR experts using a wide range of complementary techniques.
- Facilitating communication and the exchange of information between different research groups, thus fostering collaborations and joint grant applications.
- Promoting information exchange and collaboration between academia and research-based industry participants.
- Educating ESRs so that they become interdisciplinary leaders in GPCR research.
- Supporting the mobility of ESRs between partner institutions to build interdisciplinary research capacity in Europe.

Examples of quantitative measures of the success of this COST Action are:

- Number of publications in peer-reviewed journals authored by Action Members.
- Number of STSMs supported by the Action.

- Number of Workshops and Training Schools (TSs) held.
- Number of X-ray structures and new chemical entities emerging from member labs of the Action.

C.3 How networking within the Action will yield the objectives?

The objectives will be achieved by establishing cooperation and improving the exchange of scientific knowledge and technology via the creation of a network of Europe's leading GPCR experts. This Action aims to build up and deepen cooperation between GPCR researchers in Europe by holding regular meetings, contributing to international conferences and collaborating with industry partners. More specifically, the Action will:

- Foster collaborations and multidisciplinary approaches which are instrumental in GPCR research.
- Bring together researchers at the annual WG meetings in order to learn about the existence, the potential, but also the limitations of complementary methods.
- Help researchers learn each other's' scientific language, supported through Workshops, TSs and STSMs, in order to identify interdisciplinary solutions and efficiently coordinate collaborations.
- Educate ESRs, as they will be the ones carrying out most of the research and thus have to be familiar with their collaborators' methods.
- Transfer skills and knowledge among institutions through STSMs.
- Foster interactions between academic labs and industrial end users, the latter potentially exploiting the novel chemical matter identified within this Action as lead compounds.

Motivated by the contributions from industry participants, an intellectual property (IP) strategy has been included in the planning of this Action, detailed in subsection H.3 of the Dissemination Plan. A careful planning of IP issues will make the translation of basic research to industrial applications easier.

C.4 Potential impact of the Action

The Action primarily aims at scientific and technological progress. Novel insights into GPCR signalling mechanisms will lead to:

- A concerted push in the investigation of GPCRs, in particular their activation mechanism and different ways to modulate their activity.
- Novel approaches for membrane protein research.
- Tool compounds created to aid functional and structural studies which are potentially directly translatable to pharmaceutically active compounds. This transfer will be facilitated by the inclusion of biotech and pharmaceutical companies in the Action.
- A thorough understanding of biased signalling which will be exploitable for novel ways to modulate GPCR activity.
- Closely coordinated collaborative research projects.
- Young investigators who will have been trained in multiple complementary techniques within the Action and will become competitive investigators to help keep Europe at the peak of GPCR basic and therapeutic research.
- The establishment of a stable, highly multi-disciplinary network of researchers from academia and industry across Europe.

C.5 Target groups/end users

There are three main groups who will benefit from the results of this Action.

- Academics, who will have access to a substantially increased body of knowledge and novel tools and methods for GPCR research.
- Biotech and pharmaceutical companies, who will benefit from the chemical matter identified and developed for the various approaches investigated by the member groups of the Action. These molecules will provide leads and new starting points for efficient pharmaceutical research. In fact, the inclusion of biotech and pharmaceutical companies is one of the hallmarks of this Action.
- Patients, who will gain access to novel targeted medications in higher numbers.

D. SCIENTIFIC PROGRAMME

D.1 Scientific focus

GPCRs, despite their small size, are sophisticated allosteric machines with multiple signalling outputs. They signal through different G protein isoforms or G protein-independent effectors upon ligand binding, suggesting the existence of multiple ligand-specific active states. Characterising these functionally distinct structures is challenging, but essential for understanding the mechanism of physiological signalling and for developing more effective drugs. Most active-state conformations are unstable in the absence of specific cytosolic signalling partners representing major challenges for structural biology and drug design. This Action will focus on the generation and distribution of tools, assays and computational methods to study these transient functional conformations, leading to a better understanding of receptor dynamics, biased signalling, and the ways these receptors interact with ligands, downstream signalling proteins and lipids. All of the WGs will keep in close contact, as there are significant overlaps in methods and investigated subjects.

D.2 Scientific work plan – methods and means

WG1: Dynamics

Most of the available GPCR structures represent energetically stable inactive-state conformations. How and at which rates receptors shift between inactive and active states is still unclear. WG1 will fill in the gaps between the static X-ray snapshots using techniques that explicitly take into account dynamics, such as NMR, Fourier-transform infrared spectroscopy (FTIR), MD simulations and Förster Resonance Energy Transfer (FRET). In particular, WG1 will:

- Identify X-ray structures of different functional GPCR conformations and measure their exchange kinetics to understand the dynamical equilibria.
- Develop nanobodies as conformation selective tools.
- Investigate the number of conformational states during activation and their degree of conservation among GPCRs.
- Detail the dynamic processes of ligand-induced activation of specific molecular switches and biased signalling pathways. (cf. WG2)
- Study the process of ligand entry/exit and evaluate its potential relation to affinity, efficacy, and selectivity.

- Integrate the available structural information of active and intermediate states using steered-MD simulations to sample receptor conformational space while moving between these states.
- Design new experiments (e.g. optimal positions for labelling with fluorescent probes) based on computational predictions to obtain higher-resolution information on structural changes upon receptor activation.

WG2: Biased Signalling

Intriguingly, different ligands that bind to the same GPCR protein are able to induce different downstream signalling protein pathways, resulting in *pathway bias.* This offers new venues for drug discovery and will minimise the risk of adverse side effects. Members of WG2 will develop and apply bias screening methodologies and assays to identify and further develop novel *biased* GPCR modulators. Biophysical approaches and molecular modelling studies using the novel ligands as functional probes will provide crucial insight into the structural determinants (receptor regions, conformations) of GPCRs that dictate biased signalling, which will tie in with the goals of WG1. Specific tasks are to:

- Develop bias (multiplex) screening methodologies (G protein [in]dependent readouts) to identify biased ligands.
- Develop novel biased orthosteric and allosteric ligands with high selectivity for single signalling pathways.
- Develop a series of structurally related compounds with different signalling bias, to determine a structure-bias activity-relationship and correlate it with conformational changes.
- Determine X-ray structures of receptors in complex with different ligands or downstream signalling proteins.

The conformational changes induced by the ligands developed in the first three tasks will be studied using X-ray crystallography, FTIR, NMR , Bioluminescence Resonance Energy Transfer (BRET) , environment sensitive fluorescent probes , and MD simulations of ligand binding. This will be particularly effective when combined with mutational studies.

WG3: GPCR Lipid/Protein Interactions

Researchers in WG3 will investigate the interactions between GPCRs and partners that are *not*

small molecules. This includes interactions with the various components of receptor-embedding membranes, which are known to influence GPCR function as well as receptor oligomerisation. WG3 will also study GPCR-protein interactions with, for example, other GPCR monomers, G proteins, and PDZ domains. Another focus will be posttranslational lipid modifications of GPCRs and G proteins that affect membrane binding, trafficking and signalling. WG3 members will use and further develop a wide range of techniques specific for protein-protein and protein-lipid interactions. Tasks and methods will include to:

- Investigate membranes as inducers of oligomerisation.
- Evaluate lipids and cholesterol as GPCR ligands.
- Study the influence of cholesterol content on GPCR function and dynamics. (cf. WG1)
- Elucidate the role of palmitoylation and other posttranslational modifications on GPCR structure, dynamics and function.
- Use peptide mapping, computational surface mapping, genomic direct-coupling analysis, and SCAM (substituted cysteine accessibility method) to investigate GPCR-protein interactions.
- Develop peptides and peptidomimetics (this WG) and small molecules (WG4) to inhibit or enhance GPCR-partner interactions.

WG4: Discovery & Design of GPCR Ligands

WG4 will focus on the discovery, design and optimisation of small molecules that interact with GPCRs. This will provide new tracks in biomedical research and aid the other researchers in the Action in carrying out their tasks.

Members of WG4 will seek and identify novel GPCR ligands for applications in medicinal chemistry (e.g. identification of new chemical series for GPCRs of high therapeutic interest; prediction of selectivity of GPCR ligands), chemical biology (e.g. chemical probes for investigating function and signalling of GPCRs; cf. WG2 and WG3), and structural biology (e.g. design of ligands to stabilise a particular GPCR conformation; cf. WG1).

These research topics will be carried out through a combination of complementary experimental and computational methods. In detail, WG4 will:

- Set up efficient virtual and experimental screening strategies.
- Develop methods and tools to computationally predict ligand binding properties.
- Adapt methods and tools to identify fragment-sized binders.

- Synthesise ligands, libraries, and chemical probes.
- Characterise the kinetics and thermodynamics of protein-ligand binding.
- Profile the mechanism of action (binding site, functional activity, signalling) of ligands.

E. ORGANISATION

E.1 Coordination and organisation

The Management Committee (MC; with and up to two representatives from each signatory country will appoint a Chair and a Vice-Chair from among its members), will oversee all planning, implementation and coordination during the Action according to document COST 4154/11 “Rules and Procedures for implementing COST Actions”. To ensure 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 five selected experts (e.g. the WG Leaders). The CG will be responsible for the preparation of documents, emerging matters and information for the MC and WG meetings. One member of the CG will be designated as Dissemination Officer, in charge of the website and coordinating and encouraging publication and dissemination of results. The MC will furthermore appoint an Equality Officer in order to ensure that the ambitious goals to include female and early-stage researchers will be reached. Lastly, an STSM Manager will be elected, who will oversee the appropriate allotment of STSMs to all COST countries, WGs, and subpopulations based on gender, age and scientific experience.
The MC will:

- Appoint all officers, and establish a meeting schedule.
- Plan the budget and allocate funds.
- Organise two TSs for education of ESRs and dissemination of results.
- (Co)Organise a scientific conference in year 4 to disseminate the results of the Action to the scientific community.
- Hold regular Skype or Video teleconferences to update stakeholders within and outside of the Action.
- Set up and maintain a website for the Action and encourage the deposition of content from Action Members at regular intervals.
- Document and monitor milestones defined by each WG.
- Encourage and supervise the active mentoring of female and early-stage researchers by senior investigators.

- Coordinate dissemination of results with an eye towards the preservation of IP.

General milestones for the Action:

- Year 1: Constitution of the WGs, establishment of the procedures, planning of the meeting schedule, setup of the website.
- Year 2: WG meetings, WG work plan definitions finalised, STSMs, joint grant applications of Action participants, TS.
- Year 3: WG meetings, STSMs, joint grant applications, publications in peer-reviewed journals.
- Year 4: TS, Scientific Conference, publications in peer-reviewed journals.

E.2 Working Groups

Four Working Groups, as described in section D.2, with Leaders elected by the MC, will be formed by distributing the participating groups according to their expertise (a few may fall under multiple WGs). The participating teams will perform their research using financial support from national sources. The WGs will promote inclusion of female and early-stage researchers and will nominate one of each as responsible for coordinating and promoting female and early-stage researchers, respectively, in order to voice their opinions, ideas and specific needs to the MC. Each WG will:

- Organise at least four meetings in four years, where new results and methods will be presented, discussed in depth and collaborations encouraged and coordinated.
- (Co)organise one TS to educate select young European scientists and bring in expertise from outside the Action.
- Manage and hold Workshops to foster interdisciplinary training of researchers.
- Encourage and coordinate joint publications and grant applications.
- Set WG-specific milestones and communicate them and the progress made towards achieving them to the MC.
- Interact with other WGs to evaluate joint projects and avoid duplication of efforts.

E.3 Liaison and interaction with other research programmes

This Action will explore opportunities for synergy in select subaims with COST Actions BM0806, which focuses on the Histamine H4 receptor, and CM1103, which deals with monoaminergic receptors in the brain. None of these Actions has the broad scope and the focus on the signalling mechanism characteristic of this Action, but they would make excellent collaboration partners for their particular protein target classes (CM1103) or as external speakers in TSs (BM0806). Another initiative that might be an interesting partner for larger-scale exploitation of findings of this Action is EU-OPENSCREEN, the European Infrastructure of Open Screening Platforms for Chemical Biology. In particular, assays of WG2 or leads from WG4 might make valuable starting points for larger screens.

E.4 Gender balance and involvement of early-stage researchers

This COST Action will respect an appropriate gender balance in all its activities and the Management Committee will place this as a standard item on all its MC agendas. The Action will also be committed to considerably involve early-stage researchers. This item will also be placed as a standard item on all MC agendas.
The Action will strive to involve female and early-stage researchers on all levels of the organisation. As target percentage for female and early-stage researchers, respectively, 40% are defined. WG Leaders will be asked to proactively identify and invite candidate participants of each target group. Moreover, each WG will nominate representatives for the female and early-stage participants, so that their specific needs can be voiced.
In parallel, senior participants will be actively encouraged to mentor ESRs and female scientists to decrease the barriers for participation. For the participation in Workshops, TSs and STSMs, priority will be given to ESRs.

F. TIMETABLE

The duration of the Action is four years. It will commence with the kick-off meeting at which the WGs will be established, the procedures drafted and a schedule for the following meetings drawn up. Whenever feasible, the MC meetings will be held in conjunction with WG meetings or Workshops to make efficient use of time and resources. One meeting will be held per WG and year, with the option for a second one (denoted by 'o' in the table) in case of significant scientific

developments.

	Year 1				Year 2				Year 3				Year 4			
Kick-off meeting	X															
Website set up		X														
Website update				X		X		X		X		X		X		X
MC meeting	X				X				X				X			
CG meeting		X		X		X		X		X		X		X		X
WG meetings			X		o		X		o		X		o		X	
Training School							X								X	
Workshop					X				X				X			
Scientific conference														X		

G. ECONOMIC DIMENSION

The following COST countries have actively participated in the preparation of the Action or otherwise indicated their interest: BE, CH, DE, DK, ES, FI, FR, HU, IL, IT, NL, PL, SE, UK. On the basis of national estimates, the economic dimension of the activities to be carried out under the Action has been estimated at 56 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.

H. DISSEMINATION PLAN

H.1 Who?

Dissemination of the aims and achievements of GLISTEN will be focused on:

1. Academic researchers working in the GPCR field and industrial researchers in companies developing cures for diseases connected with GPCR malfunction. These groups will directly benefit from the output, especially the novel chemical matter, generated by the research coordinated by this Action (Target Group 1 [TG1]).
2. Policy makers on a European or Member State level who develop and fund research programmes, so that they might issue calls that build on the findings of this Action. The importance of GPCRs in different diseases makes this an especially rewarding objective for improving health and quality of life [TG2].
3. The general public, facilitated by educational staff, in order to heighten awareness of the benefits of interdisciplinary, translational research. Including the fundamentals of GPCR function in university curricula will help ensure that future researchers can build upon the results of this Action [TG3].

H.2 What?

This Action will need tools for careful dissemination and exploitation of results that ensure efficient scientific progress in this highly multidisciplinary environment. Thus, the Action will use a range of tools, including:

1. Publications in peer-reviewed scientific journals (including special issues for Action participants). [TG1,2]
2. A centrally managed web site with internal and public areas. [TG1]
3. Organisation of WG meetings, also together with relevant WGs of related Actions. [TG1]
4. Organisation and support of Workshops and TSs (e.g. molecular modelling, structural biology, molecular pharmacology, or biophysics to study GPCRs). [TG1]
5. (Co)organisation of an international conferences focussed on key research themes as defined by the Action's WGs. [TG1]
6. Press releases to disseminate important scientific results of GLISTEN participants. [TG3]Lectures and teaching events at educational institutions in the respective Member States. [TG2,3]

7. Social networks and open-source information sites (e.g. Linkedin/ResearchGate Groups or Wikipedia). [TG1,2,3]
8. Patents. [TG1,2]

H.3 How?

Dissemination will be a prime focus of the Action in order to maximise the impact of the protocols and molecules developed during the funding period. Wherever possible, COST funding will be acknowledged and the Action Members will be encouraged to use COST logos and links to the Action's internet presence on their own websites.

Website, Social & Professional Networks. The website will contain proceedings of meetings and conferences as well as TS tutorials and teaching materials. It will further catalogue the guidelines and best practices for GPCR research protocols. This will be combined with information about the respective experts for a particular technique to facilitate exchange of knowledge and materials. Professional Networks will be used as open discussion fora.

Workshops, Lectures & Teaching. Materials developed within the Action will increase the reach of the efforts and achievements and enable the training of a new generation of scientists that can work in multidisciplinary research teams in order to address challenging scientific problems in GPCR research.

Publications. The results emerging from this Action will be published in high-impact journals and thus reach a diverse scientific community. Moreover, they will be the bases for presentations at international conferences and within the pharmaceutical industry.

Action Tools & Conferences. WG meetings will be held at regular intervals to ensure that milestones are reached. STSMs will help to propagate techniques and results inside and outside the Action. The public conference in year 4 will be a forum to interact with scientists worldwide. The conference also will put the results in a greater scientific context.

Patents. Protecting IP without slowing scientific progress will be possible by the close collaborations between academia and industry coordinated by the Action. The Dissemination Officer will be the primary coordinator of the publication of scientific results without losing patent protection. On the other hand, patent-worthy molecules and approaches will still be available for research purposes for Action Member labs. Patents themselves will be handled by the individual researchers and their home institutions. IP considerations will be placed as a standard item on all MC agendas.