Brussels, 13 November 2018

COST 114/18

**DECISION**

Subject: **Memorandum of Understanding for the implementation of the COST Action "European Research Network on Signal Transduction" (ERNEST) CA18133**

The COST Member Countries and/or the COST Cooperating State will find attached the Memorandum of Understanding for the COST Action European Research Network on Signal Transduction approved by the Committee of Senior Officials through written procedure on 13 November 2018.

**MEMORANDUM OF UNDERSTANDING**

For the implementation of a COST Action designated as

**COST Action CA18133**
**EUROPEAN RESEARCH NETWORK ON SIGNAL TRANSDUCTION (ERNEST)**

The COST Member Countries and/or the COST Cooperating State, accepting the present Memorandum of Understanding (MoU) wish to undertake joint activities of mutual interest and declare their common intention to participate in the COST Action (the Action), referred to above and described in the Technical Annex of this MoU.

The Action will be carried out in accordance with the set of COST Implementation Rules approved by the Committee of Senior Officials (CSO), or any new document amending or replacing them:

a. “Rules for Participation in and Implementation of COST Activities” (COST 132/14 REV2);
b. “COST Action Proposal Submission, Evaluation, Selection and Approval” (COST 133/14 REV);
c. “COST Action Management, Monitoring and Final Assessment” (COST 134/14 REV2);
d. “COST International Cooperation and Specific Organisations Participation” (COST 135/14 REV).

The main aim and objective of the Action is to bring together scientists from diverse disciplines to synergistically develop a common, comprehensive and holistic map of signal transduction that will advance development of pathway-specific chemical modulators. This will be achieved through the specific objectives detailed in the Technical Annex.

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 48 million in 2018.

The MoU will enter into force once at least seven (7) COST Member Countries and/or COST Cooperating State have accepted it, and the corresponding Management Committee Members have been appointed, as described in the CSO Decision COST 134/14 REV2.

The COST Action will start from the date of the first Management Committee meeting and shall be implemented for a period of four (4) years, unless an extension is approved by the CSO following the procedure described in the CSO Decision COST 134/14 REV2.

**TECHNICAL ANNEX**

## OVERVIEW

**Summary**

All cells face the vital challenge of sensing their environments and responding in appropriate ways. This process is accomplished by transmembrane signal transduction, which is present in every species and governs every aspect of how an organism functions. In regard to human health, there is a huge drive to understand how transmembrane signal transduction networks function on the molecular, cellular and physiological level so that drugs can be designed to modulate different aspects of the signal transduction cascade in highly specific ways. Despite significant progress in understanding the individual components, signal transduction as a whole is not fully understood. Fundamental questions remain regarding how different signalling pathways are activated and modulated in precise and reproducible ways. Filling this gap in knowledge is absolutely necessary to advance the next generation of drugs that will achieve therapeutic efficacy while minimizing side effects. A prime example of this research challenge is the large family of G protein-coupled receptors (GPCRs), which are the target of more than a third of all marketed drugs. The COST Action ERNEST (European Research Network on Signal Transduction) will tackle this challenge by uniting scientists from different disciplines spanning the molecular, cellular, physiological, and clinical perspectives. This network of diverse investigators will be uniquely able to synergistically develop an unprecedented comprehensive understanding of signal transduction that will advance drug design efforts in Europe, for the benefit of societies and human health worldwide.

| **Areas of Expertise Relevant for the Action** | **Keywords** |
|---|---|
| ● Biological sciences: Signal transduction<br>● Biological sciences: Biochemistry of signal transduction<br>● Biological sciences: Cell signalling and cellular interactions<br>● Biological sciences: Computational biology<br>● Biological sciences: Biological systems analysis, modelling and simulation | ● Signal transduction<br>● GPCR<br>● molecular mechanisms<br>● drug design<br>● database resources |

**Specific Objectives**

To achieve the main objective described in this MoU, the following specific objectives shall be accomplished:

Research Coordination

● Develop a multidimensional signalling map with molecular, spatial and temporal information detailing how different signal transduction pathways give rise to distinct cellular responses, and how aberration in signal transduction gives rise to disease.
● Utilize the signalling map to create new pathway-specific chemical modulators of signal transduction.
● Establish community-accepted best practice principles in measuring and reporting ligand bias and pathway selectivity.
● Promote new methods and technologies for experimental investigation of signal transduction.
● Develop specialized public resources (e.g. databases and web-based analysis tools) for the integration, sharing and utilization of information and data pertaining to modulation of signal transduction (e.g. ligand bias and functional selectivity).

Capacity Building

● Promote communication, knowledge exchange and cooperation between investigators from different disciplines, institutions, and countries to cultivate a comprehensive picture of transmembrane signal transduction that spans the molecular, cellular, physiological and clinical perspectives.
● Strengthen the European scientific community by: a) expanding the scientific, transferable and collaborative skills of Early Career Investigators (ECIs) through training, educating and mentoring; b) promoting gender balance in the field; c) enhancing research, collaboration and leadership opportunities for

investigators from less research-intensive countries.

# 1. S&T EXCELLENCE

## 1.1. CHALLENGE

### 1.1.1. DESCRIPTION OF THE CHALLENGE (MAIN AIM)

All cells face the common challenge of sensing the external environment, transducing this information into the cytoplasm, and then responding in a timely and appropriate way. These basic tenets of transmembrane signal transduction are found in multiple systems from all species. Signal transduction networks govern every aspect of how an organism functions, and aberrations in these systems lead to disease. In regard to human health, there is a huge drive to understand how signalling networks function on the molecular, cellular and physiological level so that drugs can be designed to modulate different aspects of the signal transduction cascade. A prime example of this research challenge is the large family of G protein-coupled receptors (GPCRs). Currently, more than one-third of all marketed drugs target a GPCR, to treat conditions such as asthma, diabetes, schizophrenia, hypertension, viral infection, and cancer. Despite significant progress in understanding the individual components, signal transduction as a whole is not fully understood. Fundamental questions remain regarding how different signalling pathways are activated and precisely modulated. Filling this gap in knowledge is absolutely necessary to advance the next generation of drugs that will achieve therapeutic efficacy while minimizing side effects. The COST Action **ERNEST** (**E**uropean **R**esearch **Ne**twork on **S**ignal **T**ransduction) will tackle this challenge by uniting scientists from different disciplines spanning the molecular, cellular, physiological, and clinical perspectives. This network of diverse investigators will be uniquely able to synergistically develop an unprecedented comprehensive understanding of signal transduction that will advance drug design efforts in Europe, for the benefit of societies and human health worldwide.

### 1.1.2. RELEVANCE AND TIMELINESS

Signal transduction networks are composed of different proteins that interact with one another, and small molecules that suppress or stimulate these interactions can modulate cellular responses and physiology. Naturally occurring modulators of signal transduction (i.e. drugs) have been used by people for thousands of years. In the last decades, pharmaceutical companies have generated large libraries of synthetic compounds and tested them systematically for effects on living cells or animals, in the hope of identifying useful therapeutic agents. In an alternative strategy, molecules are designed to fit into the molecular structure of a protein, thereby affecting the function of that protein. This approach has led to many notable successes, including new types of opioids that treat pain with reduced side effects and highly specific antipsychotics. However, using static protein structures for ligand design has its limitations, since the dynamics, kinetics and other intricacies of the protein interactions that compose signal transduction networks are not taken into account. For example, transmembrane receptors and intracellular signalling proteins do not exist in singular “off” and “on” states, but instead adopt a whole ensemble of conformationally distinct states with preferences for distinct signalling pathways. Different ligands stabilize different receptor conformational states, allowing for ***bias*** with respect to which signalling pathway is activated. Moreover, the subcellular location and timing of intracellular protein interactions has a major influence on the cellular response. While most drug-design efforts have thus far been focused on the transmembrane receptor itself, researchers are now targeting downstream signalling components for specific modulation of signal transduction. Recently developed technologies are enabling researchers to delve deeper into the mechanisms of signal transduction at the molecular, cellular and systems level. The last few years have also seen proliferation and advancement of data mining tools that allow massive amounts of information to be shared and collectively understood within the research community. Despite these advances, the field lacks a common, comprehensive and holistic

view of signal transduction. Only by the concerted action of a network of scientists from different fields in physics, chemistry and biology can a detailed map of signal transduction from molecule to cell and organism be developed. This map is ultimately required to address the Challenge.

## 1.2. OBJECTIVES

### 1.2.1. RESEARCH COORDINATION OBJECTIVES

The main objective of the Action is to develop a common, comprehensive and holistic map of signal transduction that will advance development of pathway-specific chemical modulators. This unique and innovative goal will be realised by networking of a diverse group of researchers in the field through frequent Working Group meetings, Training Schools (TS), Short-Term Scientific Missions (STSM) and sharing of knowledge through a commonly developed database. Specific research coordination objectives are:

1. ***Develop a multidimensional signalling map with molecular, spatial and temporal information detailing how different signal transduction pathways give rise to distinct cellular responses, and how aberration in signal transduction gives rise to disease.*** This objective represents the **specific** task of integrating diverse knowledge and knowhow from research groups scattered across Europe into a single detailed map. Given their prevalence in the human body and medical relevance, mapping efforts will primarily focus on (but not be limited to) GPCR-mediated signal transduction networks. This objective is **measurable**, since a tangible output will result that will be widely used and cited in the field. It is **achievable**, since the required knowledge and expertise is already present in Europe. It is **relevant**, since the map will benefit signal transduction researchers across all disciplines. It is **timely**, since the field currently lacks a map that accurately reflects the complexities of signal transduction.

***2. Utilize the signalling map to create new pathway-specific chemical modulators of signal transduction.*** This objective represents the **specific** task of developing a new generation of compounds that modulate activity of a single targeted signalling pathway. It is **measureable**, since the developed compounds will be tested for their specificity and effectiveness, and some will be applied as molecular tools to dissect mechanisms. It is **achievable**, since world-renowned experts are already working on this in Europe, and their efforts will be boosted by the signalling map developed and the additional collaboration possibilities offered by the Action. It is **relevant**, considering the potential innovation in treating a wide range of human diseases. It is **timely**, since the required knowledge and technology are present and ready to be applied within the context of the comprehensive signalling map.

***3. Establish community-accepted best practice principles in measuring and reporting ligand bias and pathway selectivity.*** This objective represents the **specific** task of standardizing a fundamental concept in signal transduction. It is **measureable**, since tangible publications in the form of whitepapers or journal articles will result, which will be heavily cited in the future. It is **achievable**, since the required expertise will be present in the Action network, and new methods promoted by the Action will further support the realisation of this goal. It is **relevant**, since the signal transduction field sorely lacks a commonly accepted, well-defined concept of ligand bias and pathway selectivity. This objective is **timely**, since recent findings underscore the importance of bias and selectivity in how unique and specific cell responses result from different stimuli, despite the limited cellular machinery.

***4. Promote new methods and technologies for experimental investigation of signal transduction.*** This objective is **specific**, since it will enable researchers to push the field forward and enrich the comprehensive signal transduction map. It will be **measureable** by the number of publications, grant applications, and public resources. It is **achievable**, since Europe is a leader in technological advancement in biomedical research. It is **relevant**, since scientific breakthroughs and discoveries are triggered by new powerful technologies. It is **timely**, since insights into the molecular and spatiotemporal complexities of signal transduction require advanced methods and technologies.

***5. Develop specialized public resources (e.g. databases and web-based analysis tools) for the integration, sharing and utilization of information and data pertaining to modulation of signal transduction (e.g. ligand bias and functional selectivity).*** This objective represents the **specific** task of developing an open-access knowledge platform. It is **measurable**, since a database will result as output, the success of which will be reflected in numbers of data entries, users and citations. It is **achievable**, since a critical mass of knowledge exists, and more will be generated through the course

of the Action. The database will be constructed by experienced Action members supported by national funding schemes. It is **relevant**, since the signal transduction field lacks a database focused on bias and selectivity. It is **timely**, as currently there is significant interest in Europe and worldwide.

### 1.2.2. CAPACITY-BUILDING OBJECTIVES

The Action aims to create a diverse multidisciplinary network of researchers. Diversity will be manifest not only in core expertise, but also career level, gender, country of residence, and type of institution (e.g. academia or industry). Excellent research groups are present in every corner of Europe, and the Action will bring these groups together in cooperation. Specific capacity-building objectives are:

***1. Promote communication, knowledge exchange and cooperation between investigators from different disciplines, institutions, and countries to cultivate a comprehensive picture of transmembrane signal transduction that spans the molecular, cellular, physiological and clinical perspectives.*** This objective is **specific**, since it involves bringing together scientists through the Action network, who otherwise would not have the opportunity to connect and work together. It is **measureable**, since the establishment of collaborations will lead to a number of grant applications and publications. It is **achievable**, since a significant number of signal transduction groups are present in Europe and will participate in the Action. It is **relevant**, since developing a comprehensive, multidimensional map of signal transduction requires scientists with different expertise and perspectives to be brought together. It is **timely**, as interest in this topic is high, and every European country supports signal transduction research through their national funding schemes.

***2. Strengthen the European scientific community by: a) expanding the scientific, transferable and collaborative skills of Early Career Investigators (ECIs) through training, educating and mentoring; b) promoting gender balance in the field; c) enhancing research, collaboration and leadership opportunities for investigators from less research-intensive countries.*** This multifaceted objective is **specific**, as it addresses an important aspect of the Action network composition. It will be **measureable** by the number of individuals from target groups participating in the Action, and the number of activities aimed at promoting these target groups. It is **achievable**, since the Action will have networking tools available to promote diversity and inclusion. It is **relevant**, since inclusion of target groups will naturally enhance cooperation opportunities and scientific advancement in the Action, and the promotion of ECIs will ensure a strong European research community in the future. This objective is **timely**, since the target groups represent a significant portion of those doing excellent signal transduction research in Europe.

## 1.3. PROGRESS BEYOND THE STATE-OF-THE-ART AND INNOVATION POTENTIAL

### 1.3.1. DESCRIPTION OF THE STATE-OF-THE-ART

In order to survive and reproduce, all living cells must be able to sense their environments and respond in an appropriate way. Nature accomplishes this task by signal transduction, the process of passing external stimuli into and through the cell in order to induce cellular responses. Every signalling pathway essentially consists of a series of macromolecular interactions, and the signal is carried through the chain of interactions by biochemical events (e.g. changes in protein structure, association or dissociation of small molecules, or chemical modification of proteins). Most signalling pathways consist of a transmembrane ***receptor*** protein that binds an extracellular ***ligand*** (e.g. small molecule, peptide, or ion). This event triggers binding of intracellular ***effector*** proteins that then produce ***second messengers***, usually small molecules or protein modifications, which activate the next level of effector proteins. Each molecular interaction along a pathway can be considered a ***node***, at which the signal can be modulated and amplified, and different signalling cascades can consist of any number of nodes.

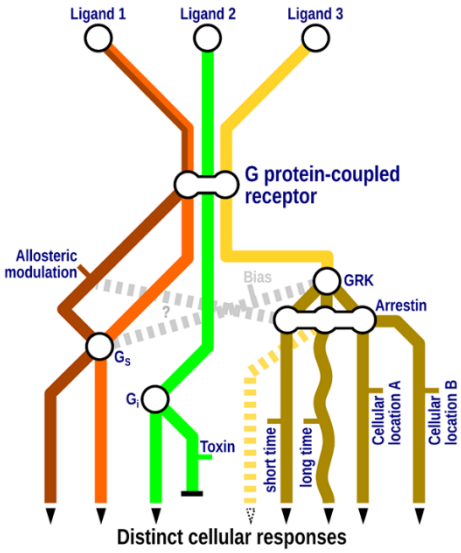



**Figure 1.** *Simplified map showing how diversity in cellular responses arises from a limited number of nodes in a GPCR signal transduction network. The dashed lines indicate possible crosstalk between nodes, or pathways that have yet to be discovered.*

The spectrum of stimuli encountered by cells is both sizable and diverse, as is the number and type of cellular responses elicited by these stimuli. Yet, remarkably, signal transduction systems use a relatively limited repertoire of intracellular signalling components. This fact indicates that the cellular signalling apparatus is flexible and versatile. Versatility is achieved by modulation - at the molecular, spatial and temporal level - of the macromolecular interactions at each node in the pathway. In effect, a limited number of nodes, each with several alternative downstream pathways, can give rise to a vast number of distinct signalling pathways (**Fig. 1**). At the same time, the biological role of signal transduction demands specificity and precision in signalling. This is, in part, achieved through a large number of receptors, each of which binds only one or a few endogenous ligands (e.g. >800 GPCRs, 59 receptor tyrosine kinases, 24 integrins). The molecular and spatiotemporal mechanisms by which all these different receptors elicit unique and reproducible cellular responses is the major focus of this Action.

On the atomic scale, the receptor is a dynamic structure that exists in different conformations (i.e. states). The binding of a ligand enhances the presence of some receptor states over others. States can be described as either active or inactive, depending on whether they can couple to effectors or not. Moreover, ligands can selectively stabilize receptor states that preferentially interact with certain primary effectors over others, a concept called ***biased agonism***. Put another way, different ligands can stimulate different signalling pathways with different efficacy. Recent experimental evidence suggests that receptor conformations bound to different biased agonists are subtly different, and it is not understood how these small differences are communicated to intracellular effectors.

Signal transduction plays a ubiquitous and critical role in normal physiology, and aberrations in signalling leads to disease. Aberration is normally defined as too much or too little signalling and can occur at any level within the signalling cascade. The most common causes of inappropriate signalling are mutations or overexpression of the protein components of the signalling pathway, over- or under-production of endogenous ligands, or exposure to exogenous compounds that stimulate or suppress normal signal transduction (e.g. toxins). Currently many research groups are unravelling signalling pathways that contribute to different disease states. However, given the combinatorial complexity arising from the branching of signal transduction nodes, and the interconnected nature of different signalling pathways, the design of ***functionally selective*** drugs is complicated. A small molecule designed to specifically bind a certain receptor will not elicit the desired biological activity if it is not known how binding of that ligand will affect receptor-effector and downstream interactions. Hence, a comprehensive and multidimensional map of signal transduction is required.

Over the last 10 years, research on signal transduction has been propelled forward by new methods and technologies spanning many disciplines. These include advancements in structural biology (nanobodies for stabilization of proteins and protein complexes and free electron laser for small, poorly diffracting crystals), computational biology (longer time-scale molecular dynamics simulations of complex systems), cell biology (visualization of cellular structures and proteins, including super-resolution microscopy, biosensors and single molecule fluorescence) and systems biology (genome, proteome, interactome, etc.). Given the usefulness of chemical modulators of signal transduction and the drive to develop new therapeutics, online databases for sharing and analysis of structural, computational and pharmacological data have been developed. Europe is notably at the forefront in this movement and home to the well-known IUPHAR/BPS Guide to pharmacology, ChEMBL, and GPCRdb. Despite these successes, most researchers see the need for more comprehensive interdisciplinary databases that link different types of data so that signal transduction can be understood as a whole.

### 1.3.2. PROGRESS BEYOND THE STATE-OF-THE-ART

In order to progress beyond the current state-of-the-art and understand how nature achieves selectivity

and versatility in signal transduction, the field must deepen and expand knowledge of how interactions within pathway nodes are modulated. In particular:

*Protein structural dynamics* – Different ligands signal through the same receptor protein to stimulate different pathways. What structural signals are imposed by biased agonists on receptors, and how are these signals recognized by effector proteins? How do effector proteins selectively engage some binding partners over others? In order to answer these and other questions, deeper insight of the molecular interactions between ligands, receptors and interactions partners, as well as downstream signalling molecular interactions, is required. This view must not be limited to static pictures of protein complexes but also contain dynamic information that takes into account conformational equilibria, protein flexibility and disorder, binding/unbinding events, and local environmental factors.

*Modulation of signalling networks* – How do different receptors use the same intracellular signalling machinery to bring about distinct and complex physiological outcomes? Intracellular localization and/or compartmentalization likely play a key role, as well as the timing of interactions within the signalling cascade. In order to understand the complex cellular and physiological outcomes of signal transduction, macromolecular interactions in the cell must be mapped in both *space* and *time*. These additional dimensions are necessary to create an accurate and realistic signalling map.

*Chemical modulators of signal transduction* – Functionally selective agonists have only recently been developed for a handful of GPCRs, and there is great potential to target a much wider variety of receptors. These efforts will build upon new knowledge acquired about how different ligands tune the macromolecular interactions that compose signal transduction networks, and how ligand-binding signals are propagated through different signalling pathways. Besides drug development, the field requires chemical tools to study signal transduction, i.e. specific inhibitors to determine which pathways receptors signal through, or how different signalling networks are interconnected. Such chemical tools will make mapping signal transduction pathways possible.

*Modelling of signal transduction pathways* – Computational modelling of signal transduction networks will be a key facet of the Action and its holistic signalling map. All experimental data describing macromolecular interactions at the nodes of the signalling network (e.g. binding affinity and rate constants) will be integrated into a quantitative model of the whole system, which will be a powerful tool to study how different ligands distinctly modulate signalling networks.

*Standardizing ligand bias* – The field requires community-wide accepted methods to assess and report ligand bias in GPCR signalling. Inconsistencies in reported data have hampered comparison and generated confusion within the field. This problem will be addressed by constructive discussions within the Action, which will help shape a public database of biased agonists and relevant experimental data. The motivation for the Action to develop such a resource is based on current high interest, the fast rate of new publications on the topic, and feasibility within a 4-year timeframe. This database will not only catalogue all known ligands with observed bias but will also connect these compounds to published structural and functional data. The envisioned database will fulfil an important need within the community and will support standardization in measuring and reporting ligand bias.

### 1.3.3. INNOVATION IN TACKLING THE CHALLENGE

Given the current level of expertise in Europe, the Action can realistically generate several high-impact innovations. Firstly, the Action will promote and coordinate the development of new technologies in structural, computational, and cell biology, which will be applicable not only for the study of signal transduction but in many fields of biomedical research. Secondly, the Action will develop a common definition of ligand bias with respect to measuring techniques and reporting. This innovation will be a key facet of a new database focused on biased ligands that will benefit GPCR research and drug design worldwide. Thirdly, the Action will develop a detailed map of signal transduction pathways that describes not only the proteins, chemical messengers and their interactions, but also contains space and time dimensions to account for dynamics, cellular location, and timing of interactions. The goal of the map is to envision how biased ligands bring about different cellular responses. Such a detailed, multidimensional map of signal transduction has thus far not been attempted for biased agonism at GPCRs. Finally, the Action will coordinate and boost the development of new pathway-targeted chemical modulators of signal transduction, to be used as tools for the study of signal transduction and for future development as therapeutic agents. The potential of this last innovation to improve human health worldwide is significant and cannot be overstated.

## 1.4. ADDED VALUE OF NETWORKING

### 1.4.1. IN RELATION TO THE CHALLENGE

In order to meet the Challenge, a holistic view of the signalling process is required, as well as the practical knowhow to design, synthesize and bring chemical modulators of signal transduction to market. The Action will meet these requirements by integrating different viewpoints offered by different experimental approaches, methodologies and expertise. In practical terms, the scientific network will link physiologists and clinicians to cell biologists who can elucidate the signalling pathways and molecular mechanisms underlying physiology and pathophysiology (i.e. disease). Cell biologists will be linked to structural biologists for atomistic insights into their systems of interest, which will be harnessed by computational chemists/biologists to design chemical modulators of signal transduction. Drug designers will be linked to organic and medicinal chemists for compound synthesis and cell biologists and pharmacologists for biological testing of these compounds. Academic researchers in all these diverse fields will connect to pharmaceutical companies to develop chemical modulators discovered within the Action to lead compounds. A major advantage of ERNEST over most current efforts at drug design in academia and industry, which focus on individual receptors, is an increase in targeting possibilities that will be offered by the comprehensive signalling map, both in terms of diverse biomolecular targets within the signalling pathways and spatiotemporal information for the design of chemical modulators that act more precisely. A further advantage gained by networking will be to set standards within the field, in order to avoid confusion and duplication of efforts, and to avoid contradicting results that are simply due to differing measurement methods.

### 1.4.2. IN RELATION TO EXISTING EFFORTS AT EUROPEAN AND/OR INTERNATIONAL LEVEL

**1) CM1207 - GLISTEN**
*GPCR-Ligand Interactions, Structures, and Transmembrane Signalling - a European Research Networ*k (COST Action, expired May 2017)
**2) FP7-KBBE-613879 - SynSignal**
*Synthetic Signaling Circuits* (Framework 7-Specific Programme “Cooperation”: Food, Agriculture and Biotechnology, expired October 2017)
**3) FP7-115366 – K4DD**
*Kinetics for Drug Development* (Framework 7 Innovative Medicines Initiative Joint Undertaking (IMI JU), expired October 2017)
**4) CA15135 - MuTaLig**
*Multi-target paradigm for innovative ligand identification in the drug discovery process* (COST Action, due to expire April 2020)
**5) CA15205 - GREEKC**
*Gene Regulation Ensemble Effort for the Knowledge Commons* (COST Action, due to expire September 2020)
**6) H2020-MSCA-ITN-2015 - ONCORNET**
*Oncogenic GPCR Network of Excellence and Training* (Innovative Training Network funded by Horizon 2020, due to expire December 2018)
**7) H2020-MSCA-ITN-2015 CaSR Biomedicine**
*Calcium-Sensing Receptor (CaSR): Therapeutics for Non-Communicable Diseases* (Innovative Training Network funded by Horizon 2020, due to expire February 2020)
**8) H2020-MSCA-ITN-2016 SAFER**
*Selective Agonists For Serotonin Receptors* (Innovative Training Network funded by Horizon 2020, due to expire August 2021)

There are eight recent EU-funded cooperation and networking grants that are complementary to ERNEST. Among these, ERNEST is unique in its breadth of scope and aim to develop a comprehensive signalling map that integrates all knowledge, including output from these other networks. **1)** The COST Action GLISTEN (CM1207) was focused on the GPCR as main signalling unit. ERNEST will vastly expand this view with a holistic approach that will offer novel opportunities for discovery, as more targets besides the receptors and their interplay are considered. Specifically, the complexities of biased agonism, pathway selectivity, physiology and pathophysiology can only be understood within the context of the entire signal transduction system. The added value of ERNEST lies in the establishment of exchanges with scientists working on the many other components in the signalling network. **2)** The collaborative project grant SynSignal (FP7-KBBE-613879) was focused on the application of synthetic biology to study and modulate signalling systems for pharmaceutical, industrial and commercial uses. ERNEST will incorporate the output of SynSignal in its broader and more comprehensive understanding

signal transduction in biological systems. **3)** The collaborative industry-academia project network K4DD (FP7-115366) was focused on integrating drug-target binding kinetics in the drug discovery decision-making process, thereby bringing about more efficacious drugs. Output from this network will be incorporated into ERNEST, especially ligand on/off rates to target receptors and the influence of ligand binding kinetics on downstream signalling. **4)** The COST Action MuTaLig (CA15135) is focused on the development of compounds that target more than one macromolecule to synergistically bring about a specific therapeutic effect. This network is primarily rooted in medical chemistry, and close cooperation with ERNEST is expected. **5)** The COST Action GREEKC (CA15205) focuses on building an "integrated knowledge management framework" for the field of gene regulation. Although the biological focus of this Action differs from that of ERNEST, the two networks share an interest in creating comprehensive knowledge and data platforms for communication and coordination of European researchers. In this regard ERNEST would seek out collaboration with GREEKC for achieving this research coordination objective. **6, 7, 8)** There are three GPCR-related innovative training networks (ITN), focused on training of doctoral students within a network of established academic labs and industry. Each ITN is focused only on one or two receptor types and does not have the breadth of ERNEST. However, the signal transduction-focus and multidisciplinary approaches of these ITNs are highly compatible with ERNEST, and close cooperation will benefit the ITNs and the Action.

# 2. IMPACT

## 2.1. EXPECTED IMPACT

### 2.1.1. SHORT-TERM AND LONG-TERM SCIENTIFIC, TECHNOLOGICAL, AND/OR SOCIOECONOMIC IMPACTS

In the short-term the Action will stimulate collaborations between academic groups of quite disparate fields, which will be brought together because of the unprecedented holistic view of the signalling process undertaken by ERNEST. In addition, collaborations between academia and industry will be pushed by the new targeting possibilities offered by the Action's signalling map. Collaborations with Inclusiveness Target Countries (ITC) will be encouraged. In the mid-term, these newly established collaborations will generate high profile, interdisciplinary publications and stimulate research activity by acquisition of grant money from EU, European and local funding bodies. During the course of the Action, exchange of knowledge and technical knowhow will be supported through STSMs, which will result in strengthening of ties, more publications, grant applications, and promotion of ECIs. The Action will additionally stimulate mobility and exchange in Europe by personal networking at the meetings and advertising of open positions on the Action website. These activities will break down barriers between fields and advance interdisciplinary cooperation.

In the long-term, the Action will advance a holistic view of signal transduction and establish new paradigms for modulation of signalling pathways. The detailed multidimensional map and database tools that will be developed through the course of the Action will be valuable resources for the research community for many years to come. In addition, new chemical modulators developed through the Action will be invaluable for future research and as starting points for drug development. Economic activity in Europe will be stimulated from these resources, as pharmaceutical companies will act on the insights obtained within the Action and will push to bring drugs to market. These therapeutic agents will have a significant and positive socioeconomic impact by improving human health in Europe and worldwide.

The Action will have further long-term impact through the cross-disciplinary training of ECIs, as these investigators will drive the field of signal transduction research into the future. In particular, STSMs will open up career perspectives and opportunities for ECIs. Furthermore, the Action will promote diversity in the leadership ranks of European research by promoting target groups, especially women and those from less research-intensive countries.

## 2.2. MEASURES TO MAXIMISE IMPACT

### 2.2.1. PLAN FOR INVOLVING THE MOST RELEVANT STAKEHOLDERS

The Action's core stakeholders are researchers from the fields of physics, chemistry and biology in academia, both established group leaders and ECIs, medical professionals and clinicians, and biotechnology and pharmaceutical companies. Other stakeholders are funding agencies, government agencies and politicians who are involved in human-health-related issues, as well as the general citizenry awaiting better medicines. In order to involve all these stakeholders, the Action will:

- Organize scientific meetings for information exchange and sharing of findings; Regular meetings (>half in ITCs) planned well in advance will foster a reliable network of collaborations
- Develop directed networking and collaboration platforms in order to stimulate interaction between investigators coming from diverse fields (e.g. clinical, basic science and industry)
- Send up to two MC members as emissaries to key conferences in one of the fields covered in ERNEST in order to attract established researchers and companies
- Organize training schools and courses aimed at educating Action members with established and novel methodologies and technologies
- Establish information exchange with intersecting COST Actions and other networks
- Transfer knowledge and skills between research groups through STSMs
- Address funding agencies by publishing whitepapers detailing suggestions for incentives to intensify research in key areas of ERNEST. Inform governmental and regulatory authorities about potentially paradigm-changing discoveries that might call for adaptation of regulatory processes
- Share key results with the general public through press releases and online dissemination channels (see next section)

### 2.2.2. DISSEMINATION AND/OR EXPLOITATION PLAN

The Action will disseminate its discoveries primarily through publications, in the form of whitepapers and articles in peer-reviewed journals, and scientific presentations. Whitepapers will be shared directly with non-scientific stakeholders from governmental and research funding bodies where appropriate. Financial support will be allocated for open access publications resulting from collaborations within the Action, in particular for participants from countries with limited funding opportunities. Action members will also advertise results at other international meetings they attend with their own funding, which will recruit new members and cooperation partners to the Action. In general, the scientific output of the Action will be continuously exploited to stimulate collaboration between different research groups, both within academia and between academia and industry. STSMs will play an essential role in cross-disciplinary and cross-domain (academic/industry) exchange and dissemination of scientific knowledge.

Given the potential of the Action to generate new tool compounds, chemical modulators and other technologies that can be exploited commercially, participants will be made aware of potentially exploitable results and educated on patentability and protection of intellectual property. The Action will recruit experts from academia (e.g. university technology transfer offices) and industry (e.g. financial and technology officers) to inform participants, for example at workshops at the bi-annual meetings and through information and links posted on the Action website.

The Action will reach the general public and non-expert stakeholders through the internet and social media platforms (e.g. LinkedIn, Twitter, Facebook). Country-specific popular science forums and press releases will be used communicate the research focus and key findings of the Action to the lay public in their native language. The Action will additionally work with patient forums, for example the European Patients' Academy (EUPATI), to assist in the education of patients on drug discovery and development and disseminate ERNEST results and activities. Action members (in particular ECIs) will perform entertaining skits in non-technical language for the general public at the bi-annual meetings (i.e. Science-slam), and Action members will be encouraged to participate in community outreach activities (e.g. university "open House" days, science fairs and vocational orientation days at schools). Finally, the Action will organize workshops to familiarize non-experts on different methodologies and disciplines. Video recordings of these skits and tutorials, posted in the Action website and other popular online forums (e.g. YouTube), will widely disseminate the collective knowledge of the network and provide materials for Action members who serve as advisors to governments and public interest groups.

The **Action website** will be a hub for all dissemination channels. Key features will be: List of all Action members (including affiliation, link to homepage, discipline and methodological expertise), which aims to catalyse collaborations; Comprehensive list of all publications emanating from the Action; List of upcoming events (e.g. annual meetings, training schools, community outreach activities); Summary of each meeting organized by the Action; Advertising of open positions in research groups and companies of Action members, to stimulate mobility and exchange; Links to all databases and tools developed in the Action; Video recordings of educational materials, including skits and workshops.

## 2.3. POTENTIAL FOR INNOVATION VERSUS RISK LEVEL

### 2.3.1. POTENTIAL FOR SCIENTIFIC, TECHNOLOGICAL AND/OR SOCIOECONOMIC INNOVATION BREAKTHROUGHS

Firstly, the Action holds potential for scientific breakthroughs by advancing the understanding of signal transduction on the molecular, spatial and temporal level and using this knowledge to build an unprecedented multidimensional map of signalling. This venture is likely to succeed, as Europe has renowned experts and strong productive research groups whose perspectives span the molecular, cellular and whole organism-level. A foreseen difficulty is that a comprehensive map of signalling will become too large and complex to be useful. In order to avoid this risk, the Action will focus on underexplored pathways that are intensively studied by its participants. The Action will foster the building of interdisciplinary collaborations that will allow these pathways to be fully elaborated with molecular, cellular and physiological details. These elaborated pathways will then form the basis of the signalling map, which will be expanded to connect pathways to indicate their cross-talk and interrelatedness.

Secondly, the Action holds potential for technological innovation by pushing the development of new methods to study signal transduction, and by standardizing existing methods to improve usefulness and data comparison. Although challenging, this goal is also likely to succeed due to the highly qualified pool of scientists, researchers and engineers available in Europe. One specific goal of the Action is to standardize the measurement and reporting of biased agonism at GPCRs. This goal entails some risk, as different investigators will have different opinions on how this should be done, and new methods may need to be developed. Despite this risk, the standardization of biased agonism assays is necessary to support the development of biased and pathway-selective ligands. The Action will be uniquely suited to achieve this goal due to its wide base of experts from academia and industry, and by recruiting additional experts (also from non-COST countries) to fill any knowledge gaps. At least one Action meeting will be dedicated to methodological standardization.

Thirdly, the Action holds market potential and potential for positive socio-economic impact, in the form of new chemical modulators that can be translated into more and better treatments for patients worldwide. The Action will actively pursue the translational potential of all results with the expectation that this long-term goal will be realised. Indeed, the first functionally selective drugs have already been developed. The Action will further this goal by equipping drug designers with vital information and networking them with medicinal chemists and pharmaceutical companies. Drug discovery and design always carries high risk due to the complexities of the biological targets, yet the potential for valuable return is significant.

# 3. IMPLEMENTATION

## 3.1. DESCRIPTION OF THE WORK PLAN

### 3.1.1. DESCRIPTION OF WORKING GROUPS

The Action will be built of five Working Groups (WGs), which are thematically interrelated. The WGs will work closely together in achieving their individual objectives. This cooperation is why this Action network is necessary, since the Challenge of understanding signal transduction as a whole and of developing functionally selective therapeutics cannot be achieved without bringing the different perspectives and expertise of the WGs together.

***WG1: Macromolecular interactions in signalling pathways***

Signal transduction is mediated by macromolecular interactions. The protein players in signal transduction cascades are molecular machines whose conformations and movements are modulated by interactions with small molecules and other biological macromolecules, to give rise to different signalling states. While structural information has increased dramatically in recent years, most structures represent a single protein in an isolated and inactive state. The main ***objective*** of WG1 is elucidation of the atomic-level structural dynamics and molecular interactions that give rise to signal transduction, with emphasis on how modulation of interactions generates specificity in transmembrane receptor-mediated signal transduction. Specifically, WG1 will contribute molecular-level detail to the holistic map of signal transduction developed by the Action. The ***task*** of WG1 is to coordinate research on:

1. The structural basis for molecular interactions among signalling proteins using high-resolution methods (e.g. X-ray crystallography, NMR, cryo-electron microscopy)
2. Dynamic interactions among signalling proteins using time-resolved methods (e.g. NMR, EPR, single molecule FRET, super-resolution microscopy and computational approaches)
3. Common features in protein structure and dynamics that are shared among signalling proteins
4. The influence of kinetics in receptor-ligand and protein-protein interactions on signalling
5. The interplay between subcellular localization and protein-protein interactions, such as the dynamic localization of arrestin and G proteins, interaction with the cytoskeleton, etc., and how they affect signalling outcomes (cf. WG2)
6. Molecular mechanisms of signal propagation and modulation through the entire cascade, and how this gives rise to longer-term cell responses (e.g. gene expression) (cf. WG2)
7. The influence of Single Nucleotide Polymorphisms (SNPs) on how clinically-used drugs interact with receptors and other signalling proteins, for the advancement of personalized medicine

WG1 will accomplish these tasks by the following ***activities***: promotion and coordination of research on molecular structure and dynamic analyses of signalling proteins at bi-annual WG meetings; organization of a training school(s) focused on structural dynamics of biological macromolecules; coordination of STSMs to promote knowledge sharing and cooperation.

***Milestones***: Progress will be monitored at WG meetings by the Action MC.

***Deliverables:*** Integration framework(s) for cataloguing, sharing and understanding data generated by Action members to be used in developing a multidimensional signalling map; Scientific publications reporting structural dynamics of signalling proteins.

***WG2: Biological roles of signal transduction***

The biological importance of macromolecular interactions can only be understood within the context of the living cell. The main ***objective*** of WG2 is to connect the molecular interactions and their subcellular localization to the cellular response and physiological state. Signalling pathways must be defined and characterized for different cell types and systems, involving experts in different physiological systems (e.g. neurobiology, cardiovascular, cancer, and immunity) within the Action network. This activity has the benefit that new model biological systems can be developed, and new therapeutic targets can be identified. Signalling pathways must also be defined in order to understand how disease results from imbalances in signal transduction. The ***task*** of WG2 is to coordinate research on:

1. Different signal transduction networks in different physiological systems, with respect to receptor type, which cytosolic effectors are involved, and which downstream signalling pathways are affected
2. New protein targets for structure/function analysis (cf. WG1)
3. Characterization of chemical modulators of signal transduction within the cellular context; determining which signalling pathways in model systems are modulated by compounds developed by WG3
4. Efficacy of ligands designed by WG3 in cell-based assays and animal models, with the goal of bringing these compounds towards clinical trials (translational medicine)
5. The spatiotemporal aspects of signalling, i.e. how the location and timing of macromolecular interactions affects the signalling outcome (cf. WG1), using high-resolution and time-resolved cell imaging methods
6. Computational modelling of signalling networks incorporating experimental data that quantitatively describes ligand-dependent modulation of signalling; identification of novel signalling hubs that could be potential therapeutic targets

WG2 will accomplish these tasks by the following ***activities***: promotion and coordination of research on biological roles of signal transduction at bi-annual WG meetings; organization of a training school(s),

e.g. about high-resolution cell imaging for investigating spatiotemporal control of signalling; coordination of STSMs to promote knowledge sharing and cooperation.
***Milestones***: Progress will be monitored at WG meetings by the Action MC.
***Deliverables:*** Integration framework(s) for cataloguing, sharing and understanding data generated by Action members to be used in developing a multidimensional signalling map; Scientific publications reporting the biological roles of signal transduction.

***WG3: Molecular modulators of signal transduction***
WG3 will harness the chemical space for modulation of protein interactions and signalling. The core ***objective*** is the design and optimization of molecules that interact with components of the signal transduction cascade. The design of functionally-selective therapeutics will be possible through information about relevant receptor conformations or residues provided by WG1 and WG2. WG3 will also work closely with WG4 (advanced technologies and methods) and industry partners to develop chemical probes to be used to investigate cell signalling mechanisms (cf. WG1 and WG2) and to stabilize GPCR complexes with binding partners for high-resolution structural analysis (cf. WG1). The ***task*** of WG3 is to coordinate research on:

1. Design and synthesis of molecular modulators, including small molecules, peptides and peptidomimetics, that target specific proteins, protein conformations or signalling pathways; also to be used as tools in studying structure, dynamics and kinetics (cf. WG1)
2. Characterization of molecular probes that target multiple proteins and/or multiple signalling pathways (polypharmacological activity)
3. Design and chemical optimization of selective inhibitors of intracellular signalling proteins, to be used for dissecting signalling pathways (cf. WG2)
4. Identification and synthesis of allosteric modulators and bitopic ligands and characterization of their impact on signalling pathways (cf. WG2)

WG3 will accomplish these tasks by the following ***activities***: promotion and coordination of research to identify tailored molecular modulators at bi-annual WG meetings; organization of a training school(s), e.g. about computational and *in vitro* screens for novel chemical matter; coordination of STSMs, in particular between academia and industry to foster knowledge exchange, expertise transfer, and joint projects.
***Milestones***: Progress will be monitored at WG meetings by the Action MC.
***Deliverables:*** Chemical modulators of signal transduction, especially those with novel mode of action and well-defined selectivity or polypharmacology; Scientific publications the development and synthesis of new molecular modulators.

***WG4: Advanced methodologies and technologies***
The main ***objective*** of WG4 is to promote advanced methodologies and technologies within the Action, and to coordinate sharing through collaboration. Included are novel approaches that can help achieve the aims of the Action, as well as re-purposing of existing methods and technologies from other fields of biomedical research. This WG will also establish best practice principles for the application of commonly used methodologies across groups within and beyond the Action. These advancements in experimental approach and technology will support WG1, WG2, and WG3 in achieving their goals. Specific ***tasks*** coordinated by WG4 are:

1. Promotion of innovative structural biology tools (cf. WG1), including novel computational tools for designing protein constructs for crystallisation
2. Promotion and implementation of cutting-edge computational biology tools, rooted in big data analysis, deep learning and advanced simulation algorithms (cf. WG1 and WG3)
3. Promotion of advanced methods for visualization of macromolecular interactions in living cells (cf. WG1 and WG2), e.g. in-cell fluorescence labelling, single molecule FRET and BRET-based biosensors, single molecule methods to monitor ligand-effector protein binding (FCS, TIRF)
4. Sharing of established experimental approaches within the network, including biophysical (super-resolution microscopy), physiological (real-time single cell subcellular monitoring of second messengers, photopharmacology), genetic manipulations (optogenetics, CRISPR-Cas9), and systems analysis (proteomics, native mass-spec of membrane proteins and complexes) (cf. WG2)
5. Promotion of methodological approaches to synthesise ad-hoc molecular probes required by WG1, WG2, WG3 (e.g. fluorescent ligands, bivalent ligands and bitopic ligands), and of new preparative methods to obtain and optimize allosteric modulators and biased ligands

6. Coordinate the development of cell-based and *in vitro* assays for testing compounds for functionally selectivity (cf. WG2 and WG3); develop community-wide accepted best practice principles for determining ligand bias at GPCRs, e.g. cellular localization and activation assays

WG4 will accomplish these tasks by the following ***activities***: promotion of cutting-edge methods and technologies at bi-annual WG meetings; organization of a training school(s) to train and inform Action participants about advanced methods and technologies; coordination of STSMs to promote sharing of methods and technologies between groups.
***Milestones***: Progress will be monitored at WG meetings by the Action MC.
***Deliverables:*** Publicly available catalogue of methodologies and technologies available within the network to promote cooperation, including "best practice guidelines" and "standard methods" for the benefit of non-experts; Scientific publications reporting new methods and technologies developed within the Action.

***WG 5: Public web resources***

The key ***objective*** of WG5 is to structure, integrate and make accessible all types of different experimental data emanating from the Action. Online databases have greatly benefited the signal transduction research community in the past five years. WG5 will contribute key public online resources in this area for reference data and analysis tools. This represents a ***deliverable*** of this WG and of the Action. Experts from all WGs will design and use this resource and thus increase the dissemination of their scientific results. The ***task*** of WG5 is to coordinate:

1. Establish a reference probe database based on annotation of published biased receptor agonists and signal protein inhibitors with biological activity data (e.g. affinity/potency)
2. Community-driven development of a reference protein database for sequence alignments, structures, functional data and simulations for GPCRs, G proteins, arrestins, and others
3. Creation of an atlas of GPCR signalling pathways in biological function, drug therapies and adverse effects
4. Development of data analysis and visualization tools for comparing druggable binding pockets across a target protein family to infer probes or to increase selectivity
5. Development of data-driven tools to design new experiments, including mutations to elucidate molecular mechanisms and maps of ligand binding site hotspots for biased agonist design
6. Storage of data generated within the Action to facilitate collaborations, dissemination in the wider signalling community, and long-term sustainability
7. Cross-linking of these resources with existing major databases, such as UniProt, ChEMBL, PDB and GuideToPharmacology, to further increase the usability and dissemination

WG5 will accomplish these tasks by the following ***activities***: tight coordination of database structure and input at bi-annual WG meetings; organization of a training school(s), e.g. about efficient uses of databases and correct data entry; coordination of STSMs to implement novel features.
***Milestones***: Progress will be monitored at WG meetings by the Action MC.
***Deliverables:*** Community-driven database(s) for probes, proteins, and signalling pathways (with special emphasis on functional selectivity), including data visualization tools, tools for experiment design, and a sharing framework to facilitate collaborations and dissemination; Scientific publications documenting the development of said databases and tools.

In addition, all five Working Groups will be involved in generating the following **key deliverables** of the Action:

1. A holistic map of signal transduction, documenting one or more signal transduction pathways with high-resolution structural, spatiotemporal and physiological details.

2. Dissemination of an Action-authored publication documenting the development and realisation of the multidimensional signalling map.

3. Community-accepted definitions of functional selectivity, including standardized measurement and reporting methods, to be published as whitepaper or journal article.

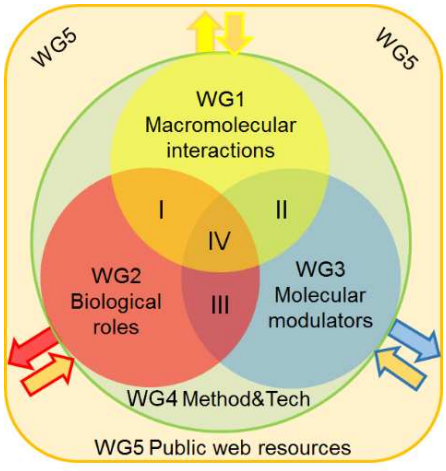
4. Action website containing appropriate content, including links to data integration frameworks, databases, tools, and educational materials.

### 3.1.2. GANTT DIAGRAM

The Action will commence with the first Management Committee (MC) meeting, at which the WGs and future meeting schedule will be established. Over four years the Action will hold seven bi-annual WG meetings, each of which will cover topics from every WG. At these meetings, each WG will monitor and evaluate the current state of the signalling map in order to coordinate strategies to fill potential gaps. For cost- and time-efficiency, MC and CG meetings will take place in conjunction with WG meetings, as will thematically distinct workshops. Training schools will each be organized by one or more WGs and held separately.

| Activity | Year 1 | | | | Year 2 | | | | Year 3 | | | | Year 4 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| First MC meeting | | | | | | | | | | | | | | | | |
| WG meeting | | | | | | | | | | | | | | | | |
| MC meeting | | | | | | | | | | | | | | | | |
| CG meeting | | | | | | | | | | | | | | | | |
| Workshops | | | | | | | | | | | | | | | | |
| Training schools | | | | | | | | | | | | | | | | |
| Website setup/update | | | | | | | | | | | | | | | | |
| Publications | | | | | | | | | | | | | | | | |
| Publications on method standardization | | | | | | | | | | | | | | | | |
| Internal version of database online | | | | | | | | | | | | | | | | |
| Public release of database | | | | | | | | | | | | | | | | |
| Update integration WG information platforms | | | | | | | | | | | | | | | | |
| Input and update to signalling map | | | | | | | | | | | | | | | | |
| Publication of signalling map | | | | | | | | | | | | | | | | |

### 3.1.3. PERT CHART (OPTIONAL)




In lieu of a typical PERT chart, here is illustrated the thematic synergism between the WGs. WGs 1, 2, and 3 form the core of scientific knowledge of the Action. Their overlap represents ways that they will support one another in achieving their respective tasks, e.g.:
I. WG2 will provide targets for structural analysis by WG1
II. WG1 will prove high resolution structures of protein targets for design of molecular probes
III. WG3 will provide molecular probes to be characterized in biological systems by WG2
IV. WG1, 2 and 3 will work together in developing chemical modulators to be tested in biological systems.
WG4 will support the three core Working Groups with new methods and technologies and also establish best practice standards for the application of these methodologies. Output from the three core Working Groups (arrows out) will be incorporated by WG5 into database resources for public dissemination, and WG5 will generate database tools that will feedback into the three core WGs (arrows in).

### 3.1.4. RISK AND CONTINGENCY PLANS

**Networking and Management Risks**
1. The risk of **not attaining and maintaining a critical mass of excellent academic researchers** is

low. Signal transduction research in Europe is strong, diverse and geared for collaborative efforts To mitigate the risk of waning interest and declining participation, the MC will proactively recruit participants by announcing ERNEST at European and international meetings and sending targeted emails to principal investigators of the most recent and significant publications in the field. Initial interest and enthusiasm will be maintained during the lifetime of the Action by having a detailed and well-planned meeting schedule that benefits all participants with learning and networking opportunities.

2. The risk of **not attracting industry and pharmaceutical company involvement** is low. Europe hosts many well-established companies as well as smaller start-up ventures that are keen to collaborate with academic scientists. Representatives from six pharmaceutical or biotech companies have already expressed interest in participating in the Action. Other EU-funded networks with a focus on drug-design (e.g. GLISTEN and ONCORNET) have established successful cooperation between academia and industry, and ERNEST will do the same. Any eventual lack of representation of industry will be mitigated by proactive recruitment, as described above.

3. The risk of an **unstable management** is considered medium. Key Action participants (Chair, Vice Chair, etc) might get appointments outside of COST countries and can thus not serve in their respective capacities any longer. This risk will be mitigated by maintaining a diverse and fully involved Core Group (CG), so that substitutions can be readily made without harming Action progress. In addition, there will be expertise-overlap in WG leaderships, so that the burden of management can be shared if necessary.

**Research risks**
1. The risk that **key results corresponding to Action deliverables are published by competitors outside the network** is considerable, considering the number of signal transduction-labs throughout the world. However, this possibility does not undermine the overall goal of the Action. Findings published from outside the network will be incorporated into the Action's knowledge base for building the comprehensive map of signal transduction and harnessed to develop better chemical modulators. The risk that **the central concept of ERNEST is published elsewhere** is low, as it would require resources that are not commonly available to individual research groups.

2. The risk of failing to **deliver a comprehensive multi-dimensional map of signal transduction** is low. Expertise for input at all levels will be present, and WG Leaders will ensure that information is integrated in a useful way. The Action will ensure that all major signalling pathways are covered from the beginning with more than one target so that the failure to proceed with an individual target will have only a minor influence on the overall objective of the Action. Any inconsistencies in quantitative information will be resolved collectively by experts within the Action. The development and documentation of the signalling map will be managed by a *systems integration group* made up of members from each WG. This group will also mitigate any lack of progress by identifying the causes undermining the project and taking appropriate actions.

3. The risk of failing to **develop chemical modulators of signal transduction** is low, and the chances of **pushing some of these compounds to pharmaceutical applications** are fair. The Action will contain the academic and industrial expertise needed to design chemical modulators (WG3), with the information and support provided by the other WGs. The Action will mitigate this risk of delay in developing lead compounds – a common scenario in drug design – by involving experts from industry, especially at the early stages to avoid common pitfalls and push progress.

4. The risk that **necessary technologies and techniques are not available** within the Action is low. The importance of advanced methodologies and technologies in pushing research forward is why ERNEST has a WG devoted to this topic. WG4 will promote cutting-edge technologies available within the Action network and thereby spur internal collaborations that will mitigate lack of progress due to technical limitations of individual partners. WG4 will also identify methodological deficiencies in the network and mitigate this problem by recruiting academic/industry experts from COST-countries as well as non-COST countries who may follow different strategies.

## 3.2. MANAGEMENT STRUCTURES AND PROCEDURES

The Management Committee (MC) will be composed of up two representatives from each participating country, appointed by the COST National Coordinator (CNC), and will oversee all planning, implementation and coordination during the Action as outlined in COST 132/14 REV 3 "Rules for

Participation in and Implementation of COST Activities" and COST 134/14 REV 3 "COST Action Management, Monitoring and Final Assessment". The MC will elect the Chair, Vice-Chair, Grant Holder, WG leaders, Dissemination, Exploitation and Equality Officers. The Dissemination Officer will be in charge of the Action website and supporting publication and dissemination of results. The Exploitation Officer will support Action participants in the handling and development of exploitable results. The Equality Officer will monitor balanced participation of female researchers, ECIs and investigators from ITCs and support their inclusion by reporting to the MC and coordinating events aimed at recruiting these target groups. The MC will additionally appoint one or more ECI Representatives to coordinate Action activities aimed at mentoring, training and promotion of ECIs. A Core Group (CG) consisting of Chair, Vice-Chair, WG leaders, Dissemination and Equality officers, and ECI Representative(s) will be formed for efficient coordination of activities. The CG will also be responsible for reporting to the MC regarding WG progress and milestone achievement. Finally, the MC will appoint an STSM Manager, who will ensure fair distribution of STSMs with regard to COST country, WGs, gender, age, and scientific experience in close coordination with the Equality Officer. The MC will:

- Coordinate, implement and manage the Action; supervise appropriate allocation of COST funding
- Prepare progress reports, financial assessment, and MC meeting minutes to be submitted to the COST Association
- Decide on WG meeting locations and date, and appoint local organizers. More than half of meetings shall be held in ITC countries
- Decide which Action participants are eligible for reimbursement
- Monitor overall progress of the Action and achievement of deliverables; recommend steps to remedy lack of progress or failure to achieve deliverables
- Monitor effectiveness of dissemination activities
- Ensure gender balance, inclusiveness of ECIs and investigators from ITCs

## 3.3. NETWORK AS A WHOLE

Europe is strong in signal transduction research, and the European biomedical community has a long track record of collaborative research. The fundamental importance of signal transduction to life, and the potential benefit of functionally selective drug design, has motivated every European country to support research on this topic with high priority. Representation from 30 or more European countries is expected in the Action, and recruitment from Near Neighbour Countries (NNC) and International Partner Countries (IPC) will be sought by advertising the network. It is expected that each area of expertise is represented by multiple European investigators, ensuring that every facet of the Action will be adequately addressed. The Action will strive to be as inclusive as possible, since the more researchers in a particular field that participate, the higher the throughput (e.g. number of systems that can be investigated) and benefit. The Action MC will monitor the spectrum of expertise present during the WG meetings, and if gaps are present, the Action will recruit the needed expertise with advice from the WG Leaders.

Considering the numbers of European speakers and participants at relevant international conferences in the past few years, there's also no doubt that the critical mass for the Action is available in Europe. Importantly, this strong European presence extends to poster presentations at these events, which reflects a large community of ECIs who will carry on the research and ensure that the legacy of ERNEST will extend a long way into the future.