COST

Domain Committee "Biomedicine and Molecular Biosciences (BMBS) "

COST Action (*BM1005)*

Start Date (*2011-05-06)*

Gasotransmitters: from basic science to therapeutic applications (ENOG: European Network on Gasotransmitters)

MONITORING PROGRESS REPORT

Reporting Period: *from April 2012-April 2013*

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

I. Management Report *prepared by the Grant Holder*

II. Scientific Report *prepared by the Chair of the Management Committee of the Action*

III. Previous versions of the Scientific Report*; i.e., part II of past reporting periods*

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

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

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

Executive summary (max.250 words):

During the second year of the Action the number of participating investigators increased to 90 and the number of countries involved in the Action has reached 19 (from 11 at submission). This reflects the active recruitment policy the Action followed by contacting additional investigators that work in the field and by having exhibitor booths at 2 international scientific meetings. So far, more than 20 collaborative projects have been initiated among the participating researchers. Also, 7 joint applications for collaborative grants from national sources have been funded. In terms of scientific output during the first two years the Action members published jointly 10 manuscripts as a result of their collaboration through the COST Action. Dissemination activities in the second year include the maintenance and upgrade of the website (www.gasotransmitters.eu), the participation of members of the ENOG network in the Scientific and Organizing Committees of gasotrasnmitter meetings (2nd European Conference on the Biology of H_2S, 3rd International Conference on H_2S Biology and Medicine) and publication of 3 open access papers. Members of the consortium are actively working and making important advancements on gasotransmitter cross-talk, generation of pharmacological inhibitors of H_2S production, design and synthesis of gasotransmitter donor compounds, generation of transgenic animals to study the role of gasotransmitters in health and disease and application of gasotranmitter-based therapeutic approaches in preclinical models of inflammation, cardiovascular and respiratory disease.

I. Management Report prepared by the Grant Holder

I.A. COST Action Fact Sheet

- **COST Action** *BM1005 - Gasotransmitters: from basic science to therapeutic applications (ENOG: European Network on Gasotransmitters)*
- **Domain** *BMBS*

- **Action details:**

CSO Approval: 2 December 2010
Entry into force: 20 January 2011
End date: 5 May 2015
Extension: -

- **Objectives**

The biological and medical importance of the endogenously generated gaseous transmitter nitric oxide was recognized by the 1998 Nobel Prize for Medicine/Physiology. It is now clear that several gasotransmitters; exist and this class of mediators also includes carbon monoxide (CO) and hydrogen sulfide (H_2S). Several of the groups leading this research field are based in the EU, thus, the formation of a European network that collates scattered knowledge, resources and expertise on gaseous mediators will encourage the dissemination of innovation, boost collaborations and increase the European competitiveness in this field. In the longer term, we anticipate this concerted effort will accelerate translational research in inflammation, cardiovascular disease and CNS disorders, areas in which the biology of these three gaseous molecules has been implicated. The benefits from the support of such a network are expected in multiple levels: scientific, innovation/technological and societal.

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

Austria *(31/01/2011)*	Serbia *(25/01/2011)*	
Belgium *(04/04/2011)*	Slovakia *(03/08/2011)*	
Denmark *(08/06/2011)*	*Spain (20/01/2011)*	
France *(10/03/2011)*	*Turkey (25/02/2011)*	
Germany *(20/01/2011)*	*Sweden (18/10/2012)*	
Greece *(20/01/2011)*	*United Kingdom (20/01/2011)*	
Hungary *(17/02/2011)*		
Italy *(20/01/2011)*		
Netherlands *(25/01/2011)*		
Norway *(06/04/2011)*		
Poland *(07/02/2011)*		
Portugal *(25/01/2011)*		

- **Intentions to accept:** Czech Republic (Viktor Kozich). Prof. Kozich's participation has been approved by our MC and we are waiting for the Czech Republic to sigh the MoU.
- **Other participants:**

None

Chair: *Prof. Andreas Papapetropoulos*

University of Patras, Laboratory for Molecular Pharmacology, Department of Pharmacy,Patras, 26504 Greece

Tel/Fax (+30)2610-969337 (office); 2610-969338 (lab)

apapapet@upatras.gr
Science Officer: *Dr Magdalena Radwanska magdalena.radwanska@cost.eu*

DC Rapporteur: *Dr Maija DAMBROVA*

Latvian Institute of Organic Synthesis
Aizkraukles Str. 21
LV1006 Riga
Latvia

Tel. +37167702408
Fax +37167702408
md@biomed.lu.lv

Administrative Officer: *Ms GABRIELA Cristea*
Gabriela.Cristea@cost.eu

- **Action Web site:** *http://www.gasotransmitters.eu/*
- **Grant Holder Representative** *(Dr ANASTASIA PYRIOCHOU, apyriohou@upatras.gr)*

- **Working Groups** *(list of WGs and names and affiliations of participants)*

Working Group 1: Molecular control of gasotransmitter production and signalling
Working Group Leader: Ingrid Fleming (Frankfurt, Germany)

- Ahmed, Asif (Birmingham, UK)
- Asimakopoulou Antonia (Patras, Greece)
- Beck, Charlie (Frankfurt, Germany)
- Behrends, Soenke (Braunschweig, Germany)
- Bouillaud Frédéric (Paris, France)
- Brouckaert, Peter (Gent, Belgium)
- Bucci, Mariarosaria (Naples, Italy)
- Dulak, Jozef (Krakow, Poland)
- Feelisch, Martin (Southampton, UK)
- Fleming, Ingrid (Frankfurt, Germany)
- Francesco Grassi (Bologna, Italy)
- Grassi, Francesco (Bologna, Italy)
- Lamas, Santiago (Madrid, Spain)
- Lauritzen, Martin (Copenhagen, Denmark)
- Mancardi, Daniele (Turin, Italy)
- Martinez Ruiz, Antonio (Madrid, Spain)
- Morbidelli, Lucia (Siena, Italy)
- Motterlini, Roberto (Paris, France)
- Otasevic, Vesna (Belgrade, Serbia)
- Ondrias, Karol (Bratislava, Slovakia)
- Panopoulos, Panagiotis (Patras, Greece)
- Papapetropoulos, Andreas (Patras, Greece)
- Pfeilschifter Josef (Frankfurt, Germany)
- Topouzis, Stavros (Patras, Greece)
- Vieira, Helena (Oeiras, Portugal)
- Yetik, Gunay (Izmir, Turkey)
- Zhou, Zongmin (Athens, Greece)

Working Group 2: Gasotransmitters in disease
Working Group Leader: Matt Whiteman (Exeter, UK)

- Ahmed, Asif (Birmingham, UK)
- Baxter, Gary (Cardiff, UK)
- Beck, Charlie (Frankfurt, Germany)
- Behrends, Soenke (Braunschweig, Germany)
- Dallas, Mark (Reading, UK)
- Djurić, Dragan (Belgrade, Serbia)
- Dulak, Jozef (Krakow, Poland)
- Feelisch, Martin (Southampton, UK)
- Ferdinandy, Peter (Szeged, Hungary)
- Levente, Kiss (Budapest, Hungary)
- Levy, Finn Olav (Oslo, Norway)
- Mancardi, Daniele (Turin, Italy)
- Otasevic, Vesna (Belgrade, Serbia)
- Pechanova, Olga (Bratislava, Slovakia)
- Pfeilschifter Josef (Frankfurt, Germany)
- Sanchez-Ferrer, Carlos-Felix (Madrid, Spain)
- Schinzel, Reinhard (Würzburg, Germany)
- Vieira, Helena (Oeiras, Portugal)
- Wingler, Kirstin (Maastricht, Netherlands)
- Winyard, Paul (Exeter, UK)

- Ytrehus, Kirsti (Tromsø, Norway)

Working Group 3: Chemistry and in vitro pharmacology of gasotransmitter-modifying molecules
Working Group Leader: Giuseppe Cirino (Naples, Italy)

- Andreadou, Ioanna (Athens, Greece)
- Asimakopoulou Antonia (Patras, Greece)
- Bucci, Mariarosaria (Naples, Italy)
- Caliendo, Giuseppe (Naples, Italy)
- Cirino, Giuseppe (Naples, Italy)
- Fleming, Ingrid (Frankfurt, Germany)
- Giannis, Athanassios (Leipzig, Germany)
- Grassi, Francesco (Bologna, Italy)
- Hobbs, Adrian (London, UK)
- Jozkowicz, Alicja (Krakow, Poland)
- Lamas, Santiago (Madrid, Spain)
- Lefebvre, Romain (Gent, Belgium)
- Levente, Kiss (Budapest, Hungary)
- Mayer, Bernd (Gratz, Austria)
- Nagy, Peter, (Budapest, Hungary)
- Motterlini, Roberto (Paris, France)
- Ondrias, Karol (Bratislava, Slovakia)
- Panopoulos, Panagiotis (Patras, Greece)
- Papapetropouos, Andreas (Patras, Greece)
- Perry, Alexis (Exeter, UK)
- Romao, Carlos (Lisbon, Portugal)
- Santagada, incenzo (Naples, Italy)
- Schatzschneider, Ulrich (Würzburg, Germany)
- Schinzel, Reinhard (Würzburg, Germany)
- Spyroulias, George (Patras, Greece)
- Topouzis, Stavros (Patras, Greece)
- Whiteman, Matt (Exeter,UK)
- Wood, Mark (Exeter, UK)
- Zhou, Zongmin (Athens, Greece)

Working Group 4: Evaluation of gasotransmitter-modifying agents in animal models of disease
Working Group Leader: Peter Brouckaert (Gent, Belgium)

- Andreadou Ioanna, (Athens, Greece)
- Baxter, Gary (Cardiff, UK)
- Brouckaert, Peter (Gent, Belgium)
- Cirino, Giuseppe (Naples, Italy)
- Djurić, Dragan (Belgrade, Serbia)
- Ferdinandy, Peter (Szeged, Hungary)
- Glynos Konstantinos (Athens, Greece)
- Hobbs, Adrian (London, UK)
- Jozkowicz, Alicja (Krakow, Poland)
- Lefebvre, Romain (Gent, Belgium)
- Levy, Finn Olav (Oslo, Norway)
- Mayer, Bernd (Gratz, Austria)
- Morbidelli, Lucia (Siena, Italy)
- Pechanova, Olga (Bratislava, Slovakia)
- Sanchez-Ferrer, Carlos-Felix (Madrid, Spain)
- Schatzschneider, Ulrich (Würzburg, Germany)
- Yetik, Gunay (Izmir, Turkey)
- Whiteman, Matt (Exeter,UK)

I.B. Management Committee member list

Name	*Country*	*E-mail*
MC Member		
Prof. Bernhard MAYER	Austria	mayer@uni-graz.at
Prof. Romain LEFEBVRE	Belgium	romain.lefebvre@ugent.be
Prof. Peter BROUCKAERT	Belgium	Peter.Brouckaert@dmbr.Vib-ugent.be
Prof. Martin LAURITZEN	Denmark	marl@glo.regionh.dk
Prof Ulf SIMONSEN	Denmark	us@farm.au.dk
Prof. Roberto MOTTERLINI	France	roberto.motterlini@inserm.fr
Prof. Frédéric BOUILLAUD	France	frederic.bouillaud@inserm.fr
Prof. Ingrid FLEMING	Germany	Fleming@em.uni-frankfurt.de
Prof. Athanasios GIANNIS	Germany	giannis@uni-leipzig.de
Prof. Andreas PAPAPETROPOULOS	Greece	apapapet@upatras.gr
Prof. Stavros TOPOUZIS	Greece	stto@upatras.gr
Prof. Peter FERDINANDY	Hungary	peter.ferdinandy@pharmahungary.com
Dr Peter NAGY	Hungary	peter.nagy@oncol.hu
Prof. Giuseppe CIRINO	Italy	cirino@unina.it
Prof. Salvatore CUZZOCREA	Italy	salvator@unime.it
Prof. Harry van GOOR	Netherlands	h.van.goor@umcg.nl
Prof. Finn Olav LEVY	Norway	f.o.levy@medisin.uio.no
Prof. Kirsti YTREHUS	Norway	kirsti.ytrehus@uit.no
Prof. Jozef DULAK	Poland	jozef.dulak@uj.edu.pl
Prof. Stefan CHLOPICKI	Poland	s.chlopicki@jmrc.org.pl
Prof. Carlos ROMAO	Portugal	carlosromao@mac.com
Dr Helena VIEIRA	Portugal	hvieira@itqb.unl.pt
Prof. Dragan DJURIC	Serbia	drdjuric@eunet.rs
Dr Vesna OTASEVIC	Serbia	vesna@ibiss.bg.ac.rs
Dr Olga PECHANOVA	Slovakia	olga.pechanova@savba.sk
Dr Karol ONDRIAS	Slovakia	karol.ondrias@savba.sk
Prof. Santiago LAMAS	Spain	slamas@cbm.uam.es
Prof. Carlos Felix SANCHEZ-FERRER	Spain	carlosf.sanchezferrer@uam.es
Dr Gunay YETIK ANACAK	Turkey	gunayyetik@gmail.com
Prof Eddie WEITZBERG	Sweden	eddie.weitzberg@ki.se
Prof. Jon LUNDBERG	Sweden	Jon.Lundberg@ki.se
Prof. Adrian HOBBS	United Kingdom	a.j.hobbs@qmul.ac.uk
Prof. Amrita AHLUWALIA	United Kingdom	a.ahluwalia@qmul.ac.uk
MC Substitute		
Dr. Roberta FORESTI	France	roberta.foresti@inserm.fr
Prof. Reinhard SCHINZEL	Germany	schinzel@vasopharm.com
Prof. Sonke BEHRENDS	Germany	s.behrends@tu-braunschweig.de
Dr Konstantinos POULAS	Greece	kpoulas@upatras.gr
Dr Ioanna ANDREADOU	Greece	jandread@pharm.uoa.gr
Prof. Georgios A. SPYROULIAS	Greece	G.A.Spyroulias@upatras.gr
Dr Kirstin WINGLER	Netherlands	k.wingler@maastrichtuniversity.nl
Prof. Alicja JOZKOWICZ	Poland	alicja.jozkowicz@uj.edu.pl
Dr Nuno ARANTES OLIVEIRA	Portugal	nao@alfama.com.pt

Dr. Ines ARAUJO	Portugal	imaraujo@ualg.pt
Dr Vladimir JAKOVLJEVIC	Serbia	drvladakgbg@yahoo.com
Dr Antonio MARTINEZ-RUIZ	Spain	amartinezr.hlpr@salud.madrid.org
Dr Maria MONSALVE PEREZ	Spain	mpmonsalve@iib.uam.es
Dr Mariarosaria BUCCI	Italy	mrbucci@cds.unina.it
Prof. Angela IANARO	Italy	ianaro@unina.it
Dr. Matt Whiteman	United Kingdom	matt.whiteman@pms.ac.uk

I.C. Overview activities and expenditure

(2012-2013) Budget

Total Action Budget: 118,000 Euro
Remaining Action Commitment: 8,355.45 Euro

Meetings

Meeting Type	Date	Place		Cost	Total
ENOG 1st Working group meeting	31/05-01/06 2012	Germany	Travel LOS	14365,65 4896.76	**59,068.60**
2nd Working group meeting	11-12/04/2012	Slovakia	Travel LOS	23440.54 2000.00	

STSM

Beneficiary	Date	Place							Cost	Total
Athanassios Giannis	10-20/4/12	Greece							2000	**10,800.00**
Sofia Bibli	14/05-14/06/2012	UK							2300	
Christoph Nagel	13-26/01/13	UK							1500	
Claudia Pereira	01/04/-31/05/2013	France							2500	
Marian Grman	01/04/-10/05/2013	Hungary							2500	

Workshops

Title	Date		Place	Cost		Total
	From	To				
BM1005 2nd Workshop	18/10/2012	20/10/2012	Hungary	Travel LOS	26478.47 2000.00	**28478.47**

General Support Grants

Beneficiary	Date								Cost	Total
										0

Schools

Title	Date	Place							Cost	Total
										0

Dissemination

Title	Date	Place							Cost	Total
FOLDERS	22/06/2012								996.30	**14,397.48**
Roll-up Posters	08/06/2012								1358.98	
COST booth	28/06/2012								3000.00	
Roll-up Posters	29/06/2012								2551.66	
Website update	10/04/13								1500.00	
Open Access (PloS)									1040.00	
Open Access (John Wiley)									2815.54	
Open Access (BioLife s.a.s)									1135.00	

Others

Action Total : 109,644.55

II. Scientific Report
II.A. Innovative networking

Innovative knowledge resulting from COST networking through the Action.

The most important area of research that developed and matured during the second year of the Action relates to the role of soluble guanylyl cyclase (sGC) in chronic obstructive pulmonary disease. To study the role for this NO receptor in COPD we used two different models: a model of smoking mice and the tracheal banding (TB) model. Pulmonary expression of sGC, both at mRNA and protein level, was decreased in mice exposed to cigarette smoke Similarly, sGCα1 -/- mice exposed to cigarette smoke exhibited bronchial hyperresponsiveness (BHR). Activation of sGC by BAY58-2667 restored the sGC signaling and attenuated BHR. Similar in mice subjected to TB, exhibited a significant increase in BALF cellularity and protein content, consistent with the presence of acute inflammation. TB resulted in an increase in tissue elasticity and airway resistance and in a downward shift of the pressure-volume curve. TB reduced the expression of both α1 and β1 subunits of sGC, at mRNA and protein level in the lung. Pharmacological activation of sGC, using BAY 58-2667, both before and after TB, reversed disease severity. These studies have involved three laboratories from the COST Action: Papapetropoulos (EL), Brouckaert (BE), and Giannis (DE). These observations indicate that sGC activation protects mice in models of COPD by reducing inflammation and improving lung mechanics and raise the possibility that sGC could potentially be used to ameliorate lung function in COPD patients. This is especially important as a new sGC activating agent (riociguat) is expected to receive approval by the FDA and EMA in 2013 for pulmonary hypertension. Our results form the scientific basis for evaluation of this drug in COPD patients.

Significant scientific breakthroughs as part of the COST Action.

A significant finding that resulted from the interaction of 4 researchers of the Action Giannis (DE), Cirino (IT), Papapetropoulos (EL), Spyroulias (EL) regards the selectivity of H_2S synthesis inhibitors. In a paper published in the British Journal of Pharmacology these authors reported that β-cyanoalanine (BCA), a CSE inhibitor, was more potent in inhibiting CSE than propargylglycine (PAG). Similarly to PAG, L-aminoethoxyvinylglycine only inhibited CSE, but did so at much lower concentrations. On the other hand, aminooxyacetic acid (AOAA), a frequently used CBS inhibitor, was more potent in inhibiting CSE compared to BCA and PAG (IC50 1.1+0.1μM); the IC50 for AOAA for inhibiting CBS was 8.5+0.7 μM. Trifluoroalanine and hydroxylamine, two compounds that have also been used to block H2S biosynthesis, both blocked the activity of CBS and CSE. Trifluoroalanine had a four-fold lower IC_{50} for CBS vs CSE, while hydroxylamine was 60-fold more selective against CSE. We concluded that, although PAG, AVG and BCA exhibit selectivity in inhibiting CSE vs. CBS, no selective pharmacological CBS inhibitor is currently available. This represents a key finding for this field of research, since these pharmacological tools are used widely to probe the physiological and pathological importance of H_2S, and a systemic evaluation of potency and selectivity has been lacking.

Another interesting finding on the mechanism of vasorelaxation triggered by H_2S resulted from the interaction of 3 researchers of the Action Bucci (IT), Cirino (IT) and Papapetropoulos (EL). Pretreatment of aortic rings with sildenafil attenuated NaHS-induced relaxation, confirming previous findings that H_2S is a phosphodiesterase inhibitor. In addition, vascular tissue levels of cGMP in cystathionine gamma lyase knockouts were lower than those in wild-type control mice. Treatment of aortic rings with NaHS, a fast releasing H_2S donor, enhanced phosphorylation of vasodilator-stimulated phosphoprotein in a time-dependent manner, suggesting that cGMP-dependent protein kinase (PKG) is activated after exposure to H_2S. Incubation of aortic rings with a PKG-I inhibitor (DT-2) attenuated NaHS-stimulated relaxation. Interestingly, vasodilator responses to a slowly releasing H_2S donor (GYY 4137) were unaffected by DT-2, suggesting that this donor dilates mouse aorta through PKG-independent pathways. Dilatory responses to NaHS and L-cysteine (a substrate for H_2S production) were reduced in vessels of PKG-I knockout mice (PKG-I-/-). Moreover, glibenclamide inhibited NaHS-induced vasorelaxation in vessels from wild-type animals, but not PKG-I-/- mice, suggesting that there is a cross-talk between K_{ATP} channels and PKG. Our

results confirm the role of cGMP in the vascular responses to NaHS and demonstrate that genetic deletion of PKG-I attenuates NaHS and L-cysteine-stimulated vasodilation.

As stated in last year's review, the team of Prof. Giannis had synthesized a number of sGC activators. In collaboration with Prof. Papapetropoulos their activity has been evaluated; one of the compounds is more potent that any currently available sGC activator. The lead compound (derivative 20) activated sGC 4.8-fold more than the parent compound BAY 58-2667. Co-crystalization of 20 with the Ns H-NOX domain revealed that the increased conformational distortion at the C-terminal region of αF helix containing 110-114 residues contributes to the higher activation triggered by 20. This manuscript has been submitted for publication.

Also members of the network (Cirino, Papapetropoulos) have completed work on zofenopril. The main finding is that H_2S is released by this clinically used ACE inhibitor and contributes to its vasoprotective actions. This manuscript has been submitted for publication.

Tangible medium term socio-economic impacts achieved or expected.

Through the collaboration of chemists and pharmacologists it is likely that within the next few years selective H_2S synthesis inhibitors, better CO-releasing molecules and better H_2S donors will become available. Development of novel gasotransmitter-based therapies offers significant opportunities for European Pharma and Biotech companies. Thus, benefits for both Industry and Academia are expected, as well as general multiplier effect for the European Union economy and society. The impact and potential benefits to EU economy and society may be categorized as medium- and long-term. Medium-term benefits include the training and incorporation into the scientific community of new scientists, thus reducing unemployment of skilled personnel. Long-term benefits might result from the discovery of lead molecules, promising chemical structures and targetable mechanisms that participate in human disease and the translation of basic science findings into therapeutic tools with obvious impacts on public health and quality of life.

Spin off of new EC RTD Framework Programme proposals/projects:

- Last year Prof. Harald Schmidt along with 4 more participants of this Action applied for a new COST Action, EU-ROS (BM1203), that was funded this year. Substantial synergies are expected between our Action and EU-ROS.

Spin off of new National Programme proposals/projects:
Funded:

- Dr Topouzis (IT) and Ondrias (SK) were awarded a bilateral Greece-Slovakia grant titled "Study of the molecular mechanisms of action and functions of the novel endogenous gasotransmitter, hydrogen sulfide (H2S) in arterial cells"
- Hobbs (UK) –Levy (NO): Funding from the Norwegian Government in tandem with a Norwegian biotech company (Serodus) to look at an existing licensed medicine in resistant hypertension. Title: Innovation Project for the Industrial Sector
- Vieira (PT)- Motterlini (FR): "Translational and mechanistic approaches on carbon monoxide as a modulator of neuroinflammation and neuroprotection in glial cells", International Grant from the Agence National de la Recherche in France and the Fundação para a Ciência e a Tecnologia (FCT) in Portugal.
- Morbidelli (IT)-Papapetropoulos (GR) PRIN call of the Ministero dell'Università, dell'Istruzione e della Ricerca (Italy). "Metal complexes for the control of the metastatic process (COMETA)"
- Araujo (PT)-Martinez-Ruiz (ES): "Metal Carbonyls for CO-based Therapies: challenges and successes" funded by Accion Integrada Portugal-Espana

Applied for:

- Papapetropoulos (GR)-Yetik (TR) "Does cigarette smoking alter the cardioprotective effect of postconditioning and regulate vascular tone?"
- Wood (UK), Winayrd (UK) and Whiteman (UK). "Do novel slow release hydrogen sulfide donors have therapeutic potential for the treatment o diabetic microvascular angiopathy?"

- Roberta Foresti (F), Roberto Motterlini (F), Ulrich Schatzschneider (DE). ANR-DFG Programme Blanc (joint French-German call): "Carbon-monoxide releasing molecules (CO-RMs) as therapeutic agents to promote wound healing"

II.B. Inter-disciplinary networking

During the second year of the Action there has been intense collaboration between the chemists and biologists. In our WG meeting in Frankfurt the MC had decided to recruit more chemists, so we felt that more expertise in this discipline was needed. Ten more chemists from different countries (UK, Italy, Hungary, Portugal, Germany, Greece) were recruited by the Action and are working to generate H_2S and CO donors and to design and synthesize inhibitors of gasotransmitter synthesis to make them available to ENOG members that would like to use these agents in their models. ENOG has also added a new group with expertise in transgenic animal technology (Prof. Pfeilschifter and Beck) that are generating conditional knockout of cystathionine-gamma-lyase [CTH]. The floxed mice are available and are being distributed among the members to generate species-specific knockouts. Initially, Prof. Fleming will generate the endothelial-specific KO, Prof. Cirino the smooth-muscle specific KO and Prof. Papapetropoulos the cardiomyocyte-specific KO. We believe that the close collaboration between chemists, pharmacologists and experts in transgenic technologies will yield significant results in the coming years, particular with regard to the development of novel therapeutics.

II.C. New networking

When the Action was approved we had 20 participating researchers from 11 counties. The total number of participants exceeds 90 and we now have a total of 19 countries represented on the MC. Almost all countries have at least 2 MC members and many have MC substitutes, too. During submission we only had 1 female MC member, while the total number of females on the MC is now 14 (including MC substitutes). The total number of female participants is now over 40%, as we actively promoted gender balance among new recruits to the Action. The total number of early stage researchers (post graduate students, postdoctoral fellows up to 4 years after their PhD) who participated in the Actions activities is 10; we are working on further increasing ESR participation in the Action.

So far, four STSM have been approved and we have received another 2 at the time the report is being written. The results from the completed STSM have been presented in our recent working group meeting in Slovakia. This is substantially better than the 2 STSM completed in our first year, but still falls short from our goal that was 8 STSM for the second year. We believe that with the number of collaborations increasing between the Action participants, this number will increase next year. As a way to further promote STSM, we have decided to highlight their results in our WG meetings.

So far we have no researchers from non-COST Countries, but the Action has invited 4 speakers from non-COST countries to our events this second year. We continue to welcome participants from these countries who would like to join the Action.

During this second year members of the Action have published jointly 7 manuscripts as a result of their collaboration through the COST Action. A detailed list of these publications can be found on the Action's website.

As a result of the interactions within the COST network several participants have started working together. A partial list of these projects is given below. Levy (NO)-Hobbs (UK): Role of CNP in the heart; Sanchez-Ferrer (SP)-Hobbs (UK): characterization of EDHF in human vessels; Topouzis (EL) - Hobbs (UK): CNP-H2S functional interaction in endothelial biology; Sanchez-Ferrer (SP)-Lamas (SP): micro RNA-155 and endothelium-dependent relaxation; Gaxter-Whiteman: novel H_2S donor molecules in myocardial ischemia-reperfusion injury ex vivo and in vivo; Papapetropoulos-Giannis: generation of H_2S synthesis inhibitors, Fleming (GE) - Mayer (AT): Uncoupling of endothelial NO synthase; Cirino-Bucci-Papapetropoulos: pharmacological characterization of H_2S donors in the vascular system, Brouckaert-Lefebvre: role of sGC in gastro-intestinal motility;

Brouckaert-Papapetropoulos: role of sGC in COPD; Brouckaert-Cirino: role of H_2S in vascular biology in knockout mice; Motterlini-Lefebvre anti-oxidative and anti-inflammatory effects of the heme oxygenase-1/biliverdin reductase pathway in the gastrointestinal tract; Motterlini-Mayer mechanism underlying sGC activation by CORMS in tissues. Andreadou-Papapetropoulos: protective role of H_2S in acute myocardial infarction; Papapetropoulos-Beck: generation of cardiac-specific CSE knockouts; Pfeilschifter-Fleming: generation of endothelium-specific CSE knockouts; Beck-Cirino: generation of smooth muscle-specific CSE knockouts; Cirino-Yetik: The role of H_2S in the urogenital system; Yetik (TR)-Fleming (DE): technology transfer to set-up gene silencing and adenovirus infections of vascular cells; Nagy (HU)-Ondrias (SK): H2S-NO interaction in aqueous solutions studied by stopped-flow spectrophotometry; Motterlini (FR)-Vieira (PT): protective role of CO in astrocytes; Romao (PT)-Papapetropoulos (EL): effects of CORMs on H_2S production; Lefebvre (BE) – Motterlini (FR): Effect of CO-releasing molecules against oxidative stress and apoptosis in intestinal epithelial cells.

The capacity of the Action members to raise research funds. During the second year of the Action several members have received funding for new grants from their respective national agencies. Some of the current funding is listed below. Prof. Papapetropoulos and Topouzis received a grant to study H_2S and angiogenesis by the Greek Secretariat of Research and Technology and Prof. Papapetropoulos received an Excellence award from the same agency to work on the role of H_2S in the cardiovascular system. Prof. Motterlini receive two grants one from Fonds National de la Recherche Luxembourg and one Interdisciplinary Project Grant funded by University Paris Est Creteil. Prof. Mayer received a grant on endothelial dysfunction by the Austrian Science Fund (FWF). Prof. Hobbs was awarded three different gasotransmitter-related grants from the British Heart Foundation, one grant from the NIH (USA) and one from the California State University Program for Education & Research in Biotechnology. Prof. Bouillaud received a grant from Sorbonne Paris Cité. Prof. Levy has been awarded two grants: one from The Research Council of Norway and the other from the South-Eastern Norway Regional Health Authority. Dr. Nagy has received a Curie International Reintegration Grant on H_2S. Prof. Weitzberg's research is funded by the Swedish Research Council, the Swedish Heart and Lung Foundation, the Stockholm City Council (ALF), the Torsten Söderbergs Foundation, the Karolinska Insitutet and an EU project "Flaviola". Prof. Mayer was awarded a grant from the Austrian National Funding Organization. Prof. Cirino was awarded a grant by the Ministry for University and Research of Italy. Prof. Ondrias received a grant from the Slovak Research and Development Agency. Dr. Eck and Prof. Pfeilschifter's research is funded through the Deutsche Forschungsgemeinschaft. Prof. Dulak has received 5 grants from the National Science Center and the Ministry of Science and Higher Education of Poland.

II.D. Self evaluation

Successes/Positive outcomes. The MC feels that the Action is making significant progress. We were very happy that the Action received a number of additional new applications and is still growing in size, increasing the number of countries represented from 11 to 19 and the researchers from 20 to over 90. Through this recruitment we were able to improve the gender-balance in the Action, as we have appointed several female colleagues as MC members and MC substitutes. A number of applications for new members were received through dissemination activities at meetings. Members of the ENOG network participate in the Scientific and Organizing Committees of the 2nd European Conference on the Biology of H_2S Biology, the 3rd International Conference on H_2S Biology and Medicine; the existence of ENOG is highlighted/promoted in all of these events. Many of our new applications have come through our website; this is important as it proves the website is highly visible. Substantial effort to raise awareness of the scientific community about the existence of the Action led us to design an attractive, informative and easily navigable web page. The web page includes many features not related exclusively to the Action (for example upcoming meetings in the field, hot papers of the month, etc). Our website has received 13,000 visits since it was first open to the public in September 2011 and ranks 2nd if one looks up "gasotransmitters" in Google. In terms of *scientific achievements* we are pleased that in this second year, members of our network have co-authored 7 publications proving that Action members have been working intensively together to accomplish the goals set by the Action. The common publications of the Action are listed on the website and include manuscripts published in

PLoS One, Br. J. Pharmacol., Free Radic Biol Med, Antioxid Redox Signal. etc). We should also emphasize that the Action has been invited to put together a themed issue for the British Journal of Pharmacology on gasotransmitters and a Perspectives in Pharmacological Sciences for the Journal of Pharmacology and Experimental Therapeutics. There is also a lot of interest in setting up collaborative projects; more than 30 different collaborations are already in place (a partial list of those can be found in part IIC of the annual report). Also, this past year COST participants have been awarded 5 joint applications for collaborative grants from national sources that we submitted during the first year of the Action. The initiative to create a database of reagents and tools (antibodies, mice, plasmids, chemicals, adenoviruses etc) that are not commercially available, to share between ENOG members and the rest of the scientific community, is in absolute alignment with the collaborative spirit of COST. This list is under construction and constantly updated and will be publicly accessible through the webpage. A lot of the Action activities in the first year involved the Action Chair; this is now no longer the case as many different collaborations have been set up between Action members that do not involve the Chair.

Drawbacks. The main shortcoming of the Action still remains the relatively small number of ESR presently involved in the Action, although this has increased compared to the first year. To improve this we have instated an ESR lecture in every meeting to give emphasis to the ESR participation in our events. Also, the MC decided in its last meeting to advise senior participants and group leaders to invite one ESR from their group in every meeting, provided that the budget permits their reimbursement. This year the Action has approved 4 STSMs and we have received 2 more at the time this report in being written. Thus, our STSM record is improving (2 in the first year), but still we would like to have 10 STSM per grant period.

Difficulties. Our main difficulty this year related to the organization of the training school we had planned. We wanted to have a hands-on training school so there was need to pay for reagents and use of equipment. The financing system used by COST was so rigid and complex that at the end we had to cancel this event. Although, this was not the sole reason for cancelling the event, it contributed substantially to our decision. The organization of a training school was postponed for next year (March 2014 in Italy) and will consist of lectures only, as we have dropped the hands-on idea. In addition, it was agreed by the MC that training in specific *in vivo* models (that was the role of the training school) would be better facilitated by individually- tailored STSMs.

III. Previous scientific report(s)

COST

Domain Committee "Biomedicine and Molecular Biosciences (BMBS) "

COST Action (*BM1005)*

Start Date (*2011-05-06)*

Gasotransmitters: from basic science to therapeutic applications (ENOG: European Network on Gasotransmitters)

MONITORING PROGRESS REPORT

Reporting Period: *from (April 2011-April 2012)*

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

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

The report is a "cumulative" report, i.e. it is updated annually and covers the entire period of the Action.
Confidentiality: the documents will be made available to the public via the COST Action web page except for chapter *II.D. Self evaluation*.
Based on the monitoring results, the COST Office will decide on the following year's budget allocation.

Executive summary (max.250 words):
During the first year of the Action the number of participating investigators increased from 18 to 40 and the number of countries that have joined the Action have reached 17 (from 11 at submission). After a successful first scientific meeting in Madrid in January 2012, more than 15 collaborative projects have been initiated among the participating researchers. Also, 7 joint applications for collaborative grants from national sources have been submitted from members of the network. In terms of scientific output during the first year members of the Action published jointly 3 manuscripts as a result of their collaboration through the COST Action. Dissemination activities of the first year include the creation of a website (www.gasotransmitters.eu) , the organization of a gasotransmitter symposium during the 2011 Winter meeting of the British Pharmacological Society and participation of members of the ENOG network in the Scientific and Organizing Committees gasotrasnmitter meetings (1st European Conference on the Biology of H_2S Biology, 2nd International Conference on H_2S Biology and Medicine, 7th International Congress of Heme oxygenases). Members of the consortium are actively working and making important advancements on gasotransmitter cross-talk, generation of pharmacological inhibitors of H_2S production, design and synthesis of gasotransmitter donor compounds, generation of transgenic animals to study the role of gasotransmitters in health and disease and application of gasotranmitter-based therapeutic approaches in preclinical models of inflammation, cardiovascular and respiratory disease.

I. Management Report prepared by the Grant Holder

I.A. COST Action Fact Sheet

- **COST Action** *BM1005 - Gasotransmitters: from basic science to therapeutic applications (ENOG: European Network on Gasotransmitters)*
- **Domain** *name*

- **Action details:**

CSO Approval: 2 December 2010
Entry into force: 20 January 2011
End date: 5 May 2015
Extension: -

- **Objectives**

The biological and medical importance of the endogenously generated gaseous transmitter nitric oxide was recognized by the 1998 Nobel Prize for Medicine/Physiology. It is now clear that several gasotransmitters; exist and this class of mediators also includes carbon monoxide (CO) and hydrogen sulfide (H_2S). Several of the groups leading this research field are based in the EU, thus, the formation of a European network that collates scattered knowledge, resources and expertise on gaseous mediators will encourage the dissemination of innovation, boost collaborations and increase the European competitiveness in this field. In the longer term, we anticipate this concerted effort will accelerate translational research in inflammation, cardiovascular disease and CNS disorders, areas in which the biology of these three gaseous molecules has been implicated. The benefits from the support of such a network are expected in multiple levels: scientific, innovation/technological and societal.

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

Austria *(31/01/2011)*	Serbia *(25/01/2011)*	
Belgium *(04/04/2011)*	Slovakia *(03/08/2011)*	
Denmark *(08/06/2011)*	Spain *(20/01/2011)*	
France *(10/03/2011)*	Turkey *(25/02/2011)*	
Germany *(20/01/2011)*	United Kingdom *(20/01/2011)*	
Greece *(20/01/2011)*		
Hungary *(17/02/2011)*		
Italy *(20/01/2011)*		
Netherlands *(25/01/2011)*		
Norway *(06/04/2011)*		
Poland *(07/02/2011)*		
Portugal *(25/01/2011)*		

- **Intentions to accept:** Sweden (Jon Lundberg, Eddie Weitzberg), Malta (Giuseppe Di Giovanni). We have been contacted by the above investigators in these countries but we are unsure of the current status of MoU acceptance*)*

- **Other participants:**
None

Chair: *Prof. Andreas Papapetropoulos*

University of Patras, Laboratory for Molecular Pharmacology, Department of Pharmacy,Patras, 26504 Greece

Tel/Fax (+30)2610-969337 (office); 2610-969338 (lab)

apapapet@upatras.gr

DC Rapporteur: *Dr Maija DAMBROVA*

Latvian Institute of Organic Synthesis
Aizkraukles Str. 21
LV1006 Riga
Latvia

Tel. +37167702408
Fax +37167702408
md@biomed.lu.lv

Science Officer: *Dr Magdalena Radwanska*

Administrative Officer: *Ms GABRIELA*

magdalena.radwanska@cost.eu *Cristea*
Gabriela.Cristea@cost.eu

- **Action Web site:** *http://www.gasotransmitters.eu/*
- **Grant Holder Representative** *(Dr ANASTASIA PYRIOCHOU, apyriohou@upatras.gr)*

- **Working Groups** *(list of WGs and names and affiliations of participants)*

Working Group 1: Molecular control of gasotransmitter production and signalling
Working Group Leader: Ingrid Fleming (Frankfurt, Germany)

- Behrends, Soenke (Braunschweig, Germany)
- Brouckaert, Peter (Gent, Belgium)
- Bucci, Mariarosaria (Naples, Italy)
- Dulak, Jozef (Krakow, Poland)
- Fleming, Ingrid (Frankfurt, Germany)
- Lamas, Santiago (Madrid, Spain)
- Lauritzen, Martin (Copenhagen, Denmark)
- Morbidelli, Lucia (Siena, Italy)
- Motterlini, Roberto (Paris, France)
- Otasevic, Vesna (Belgrade, Serbia)
- Papapetropoulos, Andreas (Patras, Greece)
- Topouzis, Stavros (Patras, Greece)
- Vieira, Helena (Oeiras, Portugal)
- Yetik, Gunay (Izmir, Turkey)

Working Group 2: Gasotransmitters in disease
Working Group Leader: Harald Schmidt (Maastricht, Netherlands)

- Baxter, Gary (Cardiff, UK)
- Behrends, Soenke (Braunschweig, Germany)
- Djurić, Dragan (Belgrade, Serbia)
- Dulak, Jozef (Krakow, Poland)
- Ferdinandy, Peter (Szeged, Hungary)
- Levy, Finn Olav (Oslo, Norway)
- Otasevic, Vesna (Belgrade, Serbia)
- Sanchez-Ferrer, Carlos-Felix (Madrid, Spain)
- Schinzel, Reinhard (Würzburg, Germany)
- Schmidt, Harald (Maastricht, Netherlands)
- Vieira, Helena (Oeiras, Portugal)
- Wingler, Kirstin (Maastricht, Netherlands)
- Ytrehus, Kirsti (Tromsø, Norway)

Working Group 3: Chemistry and in vitro pharmacology of gasotransmitter-modifying molecules
Working Group Leader: Giuseppe Cirino (Naples, Italy)

- Andreadou, Ioanna (Athens, Greece)
- Bucci, Mariarosaria (Naples, Italy)
- Cirino, Giuseppe (Naples, Italy)
- Fleming, Ingrid (Frankfurt, Germany)
- Giannis, Athanassios (Leipzig, Germany)
- Hobbs, Adrian (London, UK)
- Jozkowicz, Alicja (Krakow, Poland)
- Lamas, Santiago (Madrid, Spain)
- Lefebvre, Romain (Gent, Belgium)
- Mayer, Bernd (Gratz, Austria)
- Motterlini, Roberto (Paris, France)
- Ondrias, Karol (Bratislava, Slovakia)
- Papapetropouos, Andreas (Patras, Greece)
- Schatzschneider, Ulrich (Würzburg, Germany)
- Schinzel, Reinhard (Würzburg, Germany)
- Spyroulias, George (Patras, Greece)

- Topouzis, Stavros (Patras, Greece)

Working Group 4: Evaluation of gasotransmitter-modifying agents in animal models of disease
Working Group Leader: Peter Brouckaert (Gent, Belgium)

- Andreadou Ioanna, (Athens, Greece)
- Baxter, Gary (Cardiff, UK)
- Brouckaert, Peter (Gent, Belgium)
- Cirino, Giuseppe (Naples, Italy)
- Djurić, Dragan (Belgrade, Serbia)
- Ferdinandy, Peter (Szeged, Hungary)
- Hobbs, Adrian (London, UK)
- Jozkowicz, Alicja (Krakow, Poland)
- Lefebvre, Romain (Gent, Belgium)
- Levy, Finn Olav (Oslo, Norway)
- Mayer, Bernd (Gratz, Austria)
- Morbidelli, Lucia (Siena, Italy)
- Sanchez-Ferrer, Carlos-Felix (Madrid, Spain)
- Schatzschneider, Ulrich (Würzburg, Germany)
- Schmidt, Harald (Maastricht, Netherlands)
- Yetik, Gunay (Izmir, Turkey)

I.B. Management Committee member list

Name	*Country*	*E-mail*
MC Member		
Prof. Bernhard MAYER	Austria	mayer@uni-graz.at
Prof. Romain LEFEBVRE	Belgium	romain.lefebvre@ugent.be
Prof. Peter BROUCKAERT	Belgium	Peter.Brouckaert@dmbr.Vib-ugent.be
Prof. Martin LAURITZEN	Denmark	marl@glo.regionh.dk
Prof. Roberto MOTTERLINI	France	roberto.motterlini@inserm.fr
Prof. Ingrid FLEMING	Germany	Fleming@em.uni-frankfurt.de
Prof. Athanasios GIANNIS	Germany	giannis@uni-leipzig.de
Prof. Andreas PAPAPETROPOULOS	Greece	apapapet@upatras.gr
Prof. Stavros TOPOUZIS	Greece	stto@upatras.gr
Prof. Peter FERDINANDY	Hungary	peter.ferdinandy@pharmahungary.com
■ Dr Tamas CSONT	Hungary	tamas.csont@pharmahungary.com PENDING
Prof. Giuseppe CIRINO	Italy	cirino@unina.it
Prof. Harald SCHMIDT	Netherlands	h.schmidt@maastrichtuniversity.nl
Prof. Finn Olav LEVY	Norway	f.o.levy@medisin.uio.no
Prof. Kirsti YTREHUS	Norway	kirsti.ytrehus@uit.no
Prof. Jozef DULAK	Poland	jozef.dulak@uj.edu.pl
Dr Nuno ARANTES OLIVEIRA	Portugal	nao@alfama.com.pt
Dr Helena VIEIRA	Portugal	hvieira@itqb.unl.pt
Prof. Dragan DJURIC	Serbia	drdjuric@eunet.rs
Dr Vesna OTASEVIC	Serbia	vesna@ibiss.bg.ac.rs
Dr Olga PECHANOVA	Slovakia	olga.pechanova@savba.sk
Dr Karol ONDRIAS	Slovakia	karol.ondrias@savba.sk
Prof. Santiago LAMAS	Spain	slamas@cbm.uam.es
Prof. Carlos Felix SANCHEZ-FERRER	Spain	carlosf.sanchezferrer@uam.es
Dr Gunay YETIK ANACAK	Turkey	gunayyetik@gmail.com
Prof. Adrian HOBBS	United Kingdom	a.j.hobbs@qmul.ac.uk
Prof. Gary BAXTER	United Kingdom	baxtergf@cardiff.ac.uk
MC Substitute		
Prof. Reinhard SCHINZEL	Germany	schinzel@vasopharm.com
Prof. Sonke BEHRENDS	Germany	s.behrends@tu-braunschweig.de
Dr Konstantinos POULAS	Greece	kpoulas@upatras.gr
Dr Ioanna ANDREADOU	Greece	jandread@pharm.uoa.gr
■ Prof. Georgios A. SPYROULIAS	Greece	G.A.Spyroulias@upatras.gr PENDING
Dr Kirstin WINGLER	Netherlands	k.wingler@maastrichtuniversity.nl
Prof. Alicja JOZKOWICZ	Poland	alicja.jozkowicz@uj.edu.pl
■ Dr Vladimir JAKOVLJEVIC	Serbia	drvladakgbg@yahoo.com PENDING
Dr Antonio MARTINEZ-RUIZ	Spain	amartinezr.hlpr@salud.madrid.org
■ Dr Maria MONSALVE PEREZ	Spain	mpmonsalve@iib.uam.es PENDING
■ Prof. Amrita AHLUWALIA	United Kingdom	a.ahluwalia@qmul.ac.uk

I.C. Overview activities and expenditure

(2011-2012) Budget

Total Action Budget: 87,000 Euro
Remaining Action Commitment: 48,000 Euro

Meetings

Meeting Type	Date	Place		Cost	Total
2nd MC meeting	19-20/12/2012	Madrid	Travel LOS	20947,28 2000	0 (held together with Workshop)

STSM

Beneficiary	Date	Place							Cost	Total
Athanassios Giannis	10-20/4/12	Patras, Greece							2500	**2500**

Workshops

Title	Date		Place	Cost		Total
	From	To				
COST BM1005 Workshop: Gasotransmitters in health and disease	19/01/2012	20/01/2012	Madrid	Travel LOS	20947,28 2000	22,947.28

General Support Grants

Beneficiary	Date								Cost	Total
										0

Schools

Title	Date	Place							Cost	Total
										0

Dissemination

Title	Date	Place							Cost	Total
Website construction and maintenance									2500	**2500**

Others

Action Total : 27 947,28

II. Scientific Report

II.A. Innovative networking

Innovative knowledge resulting from COST networking through the Action.

Perhaps the most important idea that developed at the time we were writing the COST proposal, is the complementary action of NO and H_2S on cGMP-regulated pathways and the observation that H_2S is an endogenous phosphodiesterase (PDE) inhibitor. This idea developed from collaborative studies between the laboratories of Prof. Cirino and Prof. Papapetropoulos and has lead already to one publication, the submission of another manuscript currently under peer-review and a manuscript that is accepted for publication in the Proc. Natl Acad Sci USA (at the time this report is being written the manuscript does not show on Pubmed). The observations that H_2S i) is an endogenous PDE inhibitor and ii) synergizes with the prototype gasotransmitter NO have opened up new avenues for H_2S research, both in basic science and the possible applications that this finding might have for drug design.

Significant scientific breakthroughs as part of the COST Action.

A significant finding that resulted from the interaction of 3 researchers of the Action (Bucci, Cirino, Papapetropoulos) is the detrimental effect of current CO-releasing molecules is NO-induced vasorelaxation, as we observed that all of the CORMs tested produced reactive oxygen species. Thus, we proposed that design of improved, "second-generation" CORMs devoid of unwanted properties (ROS generation, NO scavenging) is needed for this class of compounds to be used in establishing the therapeutic utility of CO in preclinical and clinical models.

Another significant finding that resulted from the interaction of 5 researchers of the Action (Bucci, Cirino, Topouzis, Papapetropoulos and Giannis) is the generation and *in vitro* and *in vivo* testing of two novel H_2S donors. Thioglycine and L-thiovaline were found to be slowly releasing H_2S donors that are more potent and efficacious than NaHS, Na_2S and GYY4137 (the most widely used H_2S donors). In addition, we demonstrated that thioglycine releases H_2S and increases plasma levels of this gasotransmitter when administered *in vivo*. Thioglycine, could thus, be used when supplementation of H_2S at a slow rate is desired (to mimic endogenous H_2S production), in order to restore physiological levels of this gasotransmitter that are reduced due to disease/pathological processes.

In a manuscript accepted for publication by Cardiovas. Res. COST participants (Andreadou and Papapetropoulos) reported that short-term pravastatin treatment reduces infarction in cholesterol fed rabbits independently of lipid lowering, through eNOS activation. This observation is clinically relevant as it might be applicable to hypercholestrolemic patients following myocardial infarction.

The team of Prof. Giannis has synthesized a number of soluble guanylyl cyclase activators. In collaboration with Prof. Papapetropoulos their activity has been tested; one of the compounds is more potent that any currently available sGC activator. The lead compound has been co-crystallized with a sGC homologous protein and further experiments are underway to characterize the molecular mechanism of action of this compound. This work is still unpublished, but expected to be sent out for peer-review in the summer of 2012.

Members of the network (Cirino, Topouzis, Papapetropoulos) are working on the role of H_2S released by clinically used drugs which could contribute to their mechanism of action. We believe that these observations are quite important as the mechanism of action of these drugs might be revised to include H_2S release.

Tangible medium term socio-economic impacts achieved or expected.

Through the collaboration of chemists and pharmacologists it is likely that within the next few years selective H_2S synthesis inhibitors, better CO-releasing molecules and better H_2S donors will become available. Development of novel gasotransmitter-based therapies offers significant opportunities for European Pharma and Biotech companies. Thus, benefits for both Industry and Academia might be are expected, as well as general multiplier effect for the European Union economy and society. The impact and potential benefits to EU economy and society may be categorized as medium- and long-term. Medium-term benefits include the training and incorporation into the scientific community of new scientists, thus reducing

unemployment of skilled personnel. Long-term benefits might result from the discovery of lead molecules, promising chemical structures and targetable mechanisms that participate in human disease and the translation of basic science findings into therapeutic tools with obvious impacts on public health and quality of life.

Spin off of new EC RTD Framework Programme proposals/projects:

- Drs Papapetropoulos, Topouzis and Spyroulias were among the participants of a funded REGPOT EU FP7 grant entitled "Establishment of a Centre of Excellence for structure-based drug target characterization: strengthening the research capacity of South-Eastern Europe (SEE-DRUG)"
- Prof. Harald Schmidt along with 4 more participants of this Action, have applied for a new COST Action, EU-ROS that has been short-listed for funding in the oc-2011-2 call.
- Spin off of new National Programme proposals/projects:

  Funded: Andreadou (GR)- Papapetropoulos (GR) "H_2S: a new endogenous signaling molecule with protective actions in the cardiovascular system", Greek Society for Cardiology, 2011-12.

  Applied for:
- Hobbs (UK) –Levy (NO): Applied for funding to the Norwegian Government in tandem with a Norwegian biotech company (Erodus) to look at an existing licensed medicine in resistant hypertension. Title: Innovation Project for the Industrial Sector
- Cirino (IT), Bucci (IT), Papapetropoulos(GR). Applied for a grant through the PRIN call of the Ministero dell'Università e della Ricerca (Italy). "Role of the L-cysteine/hydrogen sulphide pathway in inflammatory based diseases: development of a new therapeutic target"
- Vieira (PT)- Motterlini (FR): Applied for an International Grant to the Agence National de la Recherche in France and the Fundação para a Ciência e a Tecnologia (FCT) in Portugal.
- Andreadou (GR)- Papapetropoulos (GR) "H_2S-based therapies for cardiovascular disease, Greek Secretariat of Research and Technology, Greece-China cooperation grants.
- Morbidelli (IT)- Papapetropoulos (GR) Applied for an grant through the PRIN call of the Ministero dell'Università, dell'Istruzione e della Ricerca (Italy). "Metal complexes for the control of the metastatic process (COMETA)"
- Whiteman (UK)-Winyard (UK) "Hydrogen sulfide: a novel mediator of inflammation in human macrophages" Medical Research Council, UK

II.B. Inter-disciplinary networking

During the first year of the Action we have formed a strong network between chemists and biologists that will possibly lead to the generation of pharmacological tools and agents that target gasotransmitter pathways. Chemists in the Action (Giannis, Schatzschneider) are working to generate H_2S and CO donors and to design and synthesize inhibitors of gasotransmitter synthesis to make them available to ENOG members that would like to use these agents in their models. Also, Dr. Whiteman (a new member of the Action) has made available to the ENOG participants a variety of H_2S donors and has encouraged chemists in his institute to join the Action (pending). Similarly chemists working with Prof. Cirino have generated a series of compounds that are being tested for their ability to inhibit H_2S synthesis. ENOG members with expertise in transgenic animal technology (Prof. Brouckaert) are working on generating animals (cystathionine-gamma-lyase [CTH] conditional knockouts, H105F sGC β1 knock-in) that will be useful to other members of the network to answer questions related to role of gasotransmitters in physiology and disease. The cost of developing the CTH conditional mice will be split among 3-4 ENOG investigators as discussed in our Madrid conference. We believe that the close collaboration between chemists, pharmacologists and experts in transgenic technologies will yield significant results in the coming years, particular with regard to the development of novel therapeutics.

II.C. New networking

When the Action was approved we had 20 participating researchers from 11 counties. Up to now, 18 new members from a total of 17 countries (6 new countries) have joined the Action. The total female participants during submission was 18% and is now 34%, as we actively promoted gender balance among new recruits to the Action. The total number of early stage researchers (post graduate students, postdoctoral fellows up to 4 years after their PhD) who participated in the recent

workshop in Madrid or who are actively involved with the Action is 9; we are working on further increasing ESR participation in the Action.

So far, one STSM has been approved and is ongoing at the time the report is being written and one more STSM application has been received. The second STSM is from a female ESR who has requested to go to a foreign lab to learn new techniques. The Chair of the Action has also been informally notified that one more ESR will be applying for a STSM. However, it seems highly likely that during this first year less than 4 STSM in total will be carried out. This is disappointing, and we have made it a high priority for next year to increase the number of STSM by planning them well in advance. We believe that the fact that many of the participants did not know each other before the Action started has contributed to a slow start with the STSM. The Chair has been informed of multiple developing collaborations that would involve ESR and will potentially make use of STSM, but these will happen mostly starting year 2 of the Action. As a way to promote STSM we have placed an announcement and instructions on how to apply for STSM on the main page of out Action in a prominent spot. We also plan to advertise the STSM in various meetings and events and encourage young investigators to participate in these exchanges.

So far we have no researchers from non-COST Countries, but we welcome any particpants from these countries who would like to join the Action. In addition, members of the Action will be participating in World Congresses related to the topic of our Action and will promote the Action to non-EU audiences. Our Aim is to recruit participants from at least 10 countries from the US, Canada, South America, Asia and Australia. It was agreed at the Madrid meeting that many researchers interested in the gasotransmitter field may have been overlooked, or were not aware of, this COST Action. Thus, it was agreed that a proactive recruitment process (e.g. personal emails, suggestions to the Management Committee, advertising at pertinent conferences) would be followed.

During this first year members of the Action have published jointly 3 manuscripts as a result of their collaboration through the COST Action. A detailed list of these publications can be found in the Annex. There are also two manuscripts that have been submitted and two abstracts in international meetings.

As a result of the interactions within the COST network several participants have started working together. A partial list of these projects is given below. Gaxter-Whiteman: novel H_2S donor molecules in myocardial ischemia-reperfusion injury ex vivo and in vivo; Papapetropoulos-Giannis: generation of H_2S synthesis inhibitors, Mayer-Fleming: effect of PYK2 and eNOS phosphorylation; Cirino-Bucci-Papapetropoulos: pharmacological characterization of H_2S donors in the vascular system, Schmidt- Altenhoefer-Papapetropoulos: novel endogenous activators of soluble guanylyl cyclase; Brouckaert-Lefebvre: role of sGC in gastro-intestinal motility; Brouckaert-Papapetropoulos: role of sGC in COPD and generation of conditional cth lox/lox mice; Brouckaert-Cirino: role of H_2S in vascular biology in knockout mice; Brouckaert-Schmidt: exchange of research materials (tissues from sGC transgenic mice) and role of NOX in shock; Motterlini-Lefebvre anti-oxidative and anti-inflammatory effects of the heme oxygenase-1/biliverdin reductase pathway in the gastrointestinal tract; Motterlini-Mayer mechanism underlying sGC activation by CORMS in tissues. Andreadou-Papapetropoulos: protective role of H_2S in acute myocardial infarction; Giannis-Schmidt: synthesis of NOX inhibitors.

The capacity of the Action members to raise research funds. During this year several Action members received new grants. Prof. Harald Schmidt was awarded a European Research Council Established Investigator grant. Prof. Papapetropoulos and Topouzis received a grant to study H_2S and angiogenesis by the Greek Secretariat of Research and Technology and Prof. Papapetropoulos received an Excellence award from the same agency to work on the role of H_2S in the cardiovascular system. Prof. Mayer received a grant on endothelial dysfunction by the Austrian Science Fund (FWF). Prof. Hobbs was awarded three different gasotransmitter-related grants from the British Heart Foundation, one grant from the NIH (USA) and one from the California State University Program for Education & Research in Biotechnology.

II.D. Self evaluation

Successes/Positive outcomes. The MC feels that the progress made during the first year was satisfactory. We were very happy that the Action received a large number of new applications resulting in almost a doubling of the original size of the network, increasing the number of countries represented from 11 to 17 and the researchers from 20 to 38. Through this recruitment we were able to improve the gender-balance in the Action (now 34% female). A number of applications for new members were received through dissemination activities at meetings. For example the Chair and Vice-Chair organized a gasotransmitter symposium during the 2011 Winter Meeting of the British Pharmacological Society. Members of the ENOG network participated in the Scientific and Organizing Committees of the 1st European Conference on the Biology of H_2S Biology, the 2nd International Conference on H_2S Biology and Medicine, the 7th International Congress of Heme oxygenases; the existence of ENOG was highlighted/promoted in all of these events. The majority of the new applications, though, came through our website; this is important as it proves the website is highly visible. Substantial effort to raise awareness of the scientific community about the existence of the Action led us to design an attractive, informative and easily navigable web page. The web page includes many features not related exclusively to the Action (for example upcoming meetings in the field, hot papers of the month, etc). Our website has received 3500 visits since it was first open to the public in September 2011 (an average of 500 hits per month) and ranks in the top 4 choices if one looks up "gasotransmitters" in Google. In terms of *scientific achievements* we are pleased that already in the first year and in spite of the fact that most of the participants did not know each other, members of our network have started working together and co-authoring publications; 3 manuscripts have been published in high impact peer-reviewed journals (Arterioscler Thromb Vasc Biol, Cardiovasc. Res,, Bioorg. Med. Chem). There is also a lot of interest in setting up collaborative projects; more than 15 different collaborations are already in place (a partial list of those can be found in part IIC of the annual report). Also, this past year COST participants have submitted 7 joint applications for collaborative grants from national sources. The initiative to create a database of reagents and tools (antibodies, mice, plasmids, chemicals, adenoviruses etc) that are not commercially available, to share between ENOG members and the rest of the scientific community, is in absolute alignment with the collaborative spirit of COST. This list will be publicly accessible through the webpage.

Drawbacks. The main shortcomings relate to the relatively small number of ESR presently involved in the Action and the low number of STSM carried out this first year. We are fully aware of both shortcomings and are intensively working on improving the Action performance in this area. Also, we are working on further developing the Action network especially by involving researchers from non-represented COST countries and non-COST nations. Engaging researchers from North and South America, Asia and Australia is important in providing global reach, as extensive gasotransmitter expertise resides outside the EU. As CO-related research is somewhat underrepresented, we plan to actively engage additional researchers that work on this topic. A lot of the activities (manuscripts, grants, collaborations) involve the Action Chair. This is something that to some extent is justified as the Action is in its first year and most participants know the Chair, but not all participants know each other well. The participation of the Chair in scientific collaborations is expected to decrease percentage-wise as more participants engage in common projects over time; this will be a measure of success of networking within the Action (this last sentence is a personal statement of the Action Chair).

Difficulties. Many members are not familiar with COST rules and procedures, as this is the first time many participants have taken part in a EU-funded project. We are working on improving this, especially among MC members. Also, the reimbursement for the first meeting we had has been slow, but we hope to improve that as the procedure is now in place in the Grant Holder institution.

III. Previous scientific report(s)

This is our first year. No previous reports exist