Work And Budget Plan

BM1206 Grant Agreement Period 3

01/06/2015 to 31/05/2016

Section I: Action Profile

Action General Information

Action Code	BM1206	MC Chair	Dr Sergi Castellvi-Bel
Action Title	BM1206 - Cooperation Studies on Inherited Susceptibility to Colorectal Cancer		
MOU	BM1206-MoU	Draft MOU	oc-2012-1-11711
CSO Approval Date	2012-11-21		
Action Start Date	2013-04-30	Action End Date	2017-04-29
Science Officer	Dr INGA DADESHIDZE	Administrative Officer	Ms Jeannette Nchung

Participating COST Member Countries and Cooperating State:

	ITC		Non-ITC		Total
Cost Countries having accepted the MOU	Number	9	Number	13	22
	% of all ITCs	40.91%	% of all non-ITCs	59.09%	
Number of MC Members	14		18		32

Country and Acceptance Date		
AT 07/01/2013	IE 13/01/2014	RS 28/02/2014
HR 06/03/2014	IL 29/05/2013	ES 28/11/2012
CY 17/06/2013	IT 14/02/2013	SE 07/02/2013
CZ 06/06/2013	MT 12/03/2013	TR 07/05/2013
FI 17/12/2012	NL 21/01/2013	UK 28/11/2012
FR 14/06/2013	NO 22/10/2013	MK 27/02/2013
DE 17/01/2013	PT 11/01/2013	
EL 10/04/2014	RO 07/06/2013	

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International cooperation

	NNC	IPC	Specific Organisation	Total
Number of entities formally approved to join Action	0	1	0	1
Number of countries	0	1	0	1

Working Groups

	WG Title	WG Leader	Number of Members
WG1	Genetic Association Studies	Prof Ian Tomlinson	112
WG2	Functional Genomics	Dr JOSE LUIS GOMEZ-SKARMETA	50
WG3	Next Generation Sequencing	Dr Tom van Wezel	98
WG4	Statistical Modelling	Dr Albert Tenesa	115

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Section II: MoU objectives and Grant Agreement Period Goals and Activities

Action Objectives from MoU

Aim/primary Objective	The main objective of the Action is to comprehensively understand the impact of inheritedsusceptibility in CRC for profiling individual disease risk and performing early screening andtreatment monitoring. By doing so, new molecular biomarkers will be implemented andvalidated for personalized CRC medicine.
Secondary objectives	• Identification of new CRC susceptibility variants: A polygenic model of inherited susceptibility to CRC implies the co-inheritance of multiple risk variants. So far, 20 common, low-penetrance genetic variants for CRC susceptibility have been identified by GWAS. This Action will permit to boost sample size and statistical power (participating cohorts sum up more than 50,000 cases and 50,000 controls) and, therefore, it is very likely that additional genetic variants linked to CRC will be identified. Large-scale meta-analyses of existing and newly generated GWAS data will be performed and replication of initial GWAS findings in additional cohorts will be used to robustly confirm those genetic variants that participate in CRC susceptibility. • Functional links for CRC susceptibility variants: Most GWAS variants are unlikely to alter protein function and fine mapping and functional studies will be used to identify a correlated functional variant. The identification of the functional variation that causes increased CRC risk may lead to the development of new means of preventing the disease. However, the journey from the associated polymorphism to functional variant is not simple and will require additional work. In order to perform an initial search for readily identifiable functional variants, fine mapping in the regions close to each disease-associated single nucleotide polymorphism (SNP) or copy number variant (CNV) should be undertaken, enriching for variants in strong linkage disequilibrium (LD) with that SNP/CNV and with possible functional effects. Basic functional work should also be performed, such as assessing the levels of mRNAs and proteins in each region in patients of known genotypes, as well as more complex studies such as chromatin mapping, gene reporter and allele-specific expression experiments. • Genetic variants involved in CRC survival and treatment toxicity: CRC genetic susceptibility variants could also act as biomarkers for CRC survival and treatment response. For instance, inherited genetic variants can modulate the pharmacokinetics/pharmacodynamics of drugs used in CRC treatment by substantially affecting individual response and toxicity to chemotherapy. Therefore, GWAS data will be analyzed regarding CRC survival and treatment toxicity in order to identify genetic variants linked to differential prognosis and adverse drug reactions. • Genetic variants enriched in CRC subgroups: The impact of CRC susceptibility genetic variation will not be universally generic and some of the risk variants will impact preferentially on CRC subtypes, such as early-onset or microsatellite-unstable CRC

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(MSI+ CRC). If some of the CRC genetic susceptibility variants appear to be associated with some clinical and familial features, it could have potential important implications for screening and surveillance strategies for this disease.

- New predisposition genes for CRC in families with unknown genetic basis: Next generation sequencing will be useful to identify new CRC predisposition genes in selected high-risk and early-onset families with unknown genetic basis from the participating cohorts.
- Interactions between CRC susceptibility variants and environment: CRC risk is undoubtedly determined by complex interactions between genetic and lifestyle/dietary risk factors. Epidemiological studies have established several dietary risk factors for colorectal neoplasia; these include low vegetable and high red meat consumption and micronutrient deficiency and excessive alcohol intake. CRC genetic susceptibility variants are thus likely to interact with these environmental lifestyle risk factors to modify risk and they should be incorporated into models of predisposition.
- High risk CRC profile of inherited variants by statistical modelling: Besides gene-environment interactions, it is also entirely conceivable that epistatic interactions between CRC genetic susceptibility variants may exist. A high-risk CRC profile using mentioned parameters could be developed using data from all participating cohorts and be very useful as a molecular tool for personalized CRC medicine.

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Grant Agreement Period

Grant Agreement Period Start Date	01/06/2015	Grant Agreement Period End Date	31/05/2016

Grant Agreement Period Goals

Number	Grant Agreement Period Goal	MoU Objective(s) it relates to
GAPG 1	Identification of new CRC genetic susceptibility variants	Aim/Primary objective Secondary objective 1
GAPG 2	Identification of new adenoma genetic susceptibility variants	Aim/Primary objective Secondary objective 1
GAPG 3	Meta-analysis of CRC genome-wide association studies (GWAS)	Aim/Primary objective Secondary objective 1
GAPG 4	Fine-mapping of CRC genetic susceptibility variants	Aim/Primary objective Secondary objective 2
GAPG 5	Fine-mapping of adenoma genetic susceptibility variants	Aim/Primary objective Secondary objective 2
GAPG 6	Functional links for CRC genetic susceptibility variants	Aim/Primary objective Secondary objective 2
GAPG 7	Functional links for adenoma genetic susceptibility variants	Aim/Primary objective Secondary objective 2
GAPG 8	Genotype-phenotype correlation of CRC genetic susceptibility variants with patient survival and treatment response	Aim/Primary objective Secondary objective 3
GAPG 9	Genotype-phenotype correlation of CRC genetic susceptibility variants with CRC subgroups	Aim/Primary objective Secondary objective 4
GAPG 10	Identification of new predisposition genes for familial CRC	Aim/Primary objective Secondary objective 5
GAPG 11	Identification of new predisposition genes for serrated polyposis syndrome	Aim/Primary objective Secondary objective 5
GAPG 12	Functional characterization of new candidate predisposition genes for CRC	Aim/Primary objective Secondary objective 2 Secondary objective 5
GAPG 13	Meta-analysis of next generation sequencing data	Aim/Primary objective Secondary objective 5
GAPG 14	Consortium database compiling clinical, tumoral, molecular, genotyping and sequencing data	Aim/Primary objective Secondary objective 1 Secondary objective 2

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		Secondary objective 3 Secondary objective 4 Secondary objective 5 Secondary objective 6 Secondary objective 7
GAPG 15	Epistatic interaction between CRC/adenoma genetic susceptibility variants	Aim/Primary objective Secondary objective 6 Secondary objective 7
GAPG 16	Gene-environment interaction for CRC/adenoma genetic susceptibility variants	Aim/Primary objective Secondary objective 6 Secondary objective 7

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Section IV: Work and Budget Plan for the Grant Agreement Period

Work and Budget Plan Summary

A. COST Networking Tools	EUR
(1)Meetings	88,889.00
(2)Training Schools	0.00
(3)STSMs	20,000.00
(4)Dissemination	7,400.00
(5)Other Expenses Related to Scientific Activities	200.00
B. Total Science Expenditure(sum of(1) to (5))	116,489.00
C. FSAC(max. of 15% of B)	17,473.35
D. Total Expenditure(B+C)	133,962.35

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Meetings

Overview

Meeting Title	Meeting Type	Dates	Location	ITC	Total Cost(EUR)
September 2015 meeting	Management Committee Meeting, Working Group Meeting, Workshops/Conferences	17/09/2015 - 18/09/2015	Istanbul (Turkey)	Yes	49,500.00
March 2016 meeting	Management Committee Meeting, Working Group Meeting, Workshops/Conferences	17/03/2016 - 18/03/2016	Prague (Czech Republic)	Yes	39,389.00
				Total	88,889.00

Details

Meeting Type	Management Committee Meeting,Working Group Meeting,Workshops/Conferences		
Title of the Meeting	September 2015 meeting		
Grant Period Goal(s) it will address	Identification of new CRC genetic susceptibility variants,Identification of new adenoma genetic susceptibility variants,Meta-analysis of CRC genome-wide association studies (GWAS),Genotype-phenotype correlation of CRC genetic susceptibility variants with patient survival and treatment response,Genotype-phenotype correlation of CRC genetic susceptibility variants with CRC subgroups,Consortium database compiling clinical, tumoral, molecular, genotyping and sequencing data,Epistatic interaction between CRC/adenoma genetic susceptibility variants,Gene-environment interaction for CRC/adenoma genetic susceptibility variants		
Description	Co-located workshop, MC meeting and WG meeting in September 2015 focusing on WG1 and WG4		
Output(s)	Workshop dedicated to WG1 and WG4. Presentations of participants regarding efforts in WG1 and WG4. Sharing agreements regarding WG1 and WG4 data.		
Location	Istanbul (Turkey)	ITC	Yes
Start Date	2015-09-17 13:00:00	End Date	2015-09-18 16:00:00
Duration	2 days		
Number of expected total participants	60	Number of participants to be reimbursed from COST funds	50
Average reimbursement(per participant)(EUR)	790.00	Total Reimbursement costs (EUR)	39,500.00
Local Organiser Support (EUR)	10,000.00		

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Total cost of the meeting (EUR)	49,500.00

Meeting Type	Management Committee Meeting,Working Group Meeting,Workshops/Conferences		
Title of the Meeting	March 2016 meeting		
Grant Period Goal(s) it will address	Fine-mapping of CRC genetic susceptibility variants,Fine-mapping of adenoma genetic susceptibility variants,Functional links for CRC genetic susceptibility variants,Functional links for adenoma genetic susceptibility variants,Identification of new predisposition genes for familial CRC,Identification of new predisposition genes for serrated polyposis syndrome,Functional characterization of new candidate predisposition genes for CRC,Meta-analysis of next generation sequencing data		
Description	Co-located workshop, MC meeting and WG meeting in September 2015 focusing on WG2 and WG3		
Output(s)	Workshop dedicated to WG2 and WG3. Presentations of participants regarding efforts in WG2 and WG3. Sharing agreements regarding WG2 and WG3 data.		
Location	Prague (Czech Republic)	ITC	Yes
Start Date	2016-03-17 13:00:00	End Date	2016-03-18 16:00:00
Duration	2 days		
Number of expected total participants	58	Number of participants to be reimbursed from COST funds	47
Average reimbursement(per participant)(EUR)	787.00	Total Reimbursement costs (EUR)	36,989.00
Local Organiser Support (EUR)	2,400.00		
Total cost of the meeting (EUR)	39,389.00		

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STSM

Number	8
Average cost per STSM(EUR)	2,500.00
Total cost(EUR)	20,000.00

How will the STSMs contribute to the achievement of the Grant Period Goals?
Identification of new CRC genetic susceptibility variants,Identification of new adenoma genetic susceptibility variants,Meta-analysis of CRC genome-wide association studies (GWAS),Fine-mapping of CRC genetic susceptibility variants,Fine-mapping of adenoma genetic susceptibility variants,Functional links for CRC genetic susceptibility variants,Functional links for adenoma genetic susceptibility variants,Genotype-phenotype correlation of CRC genetic susceptibility variants with patient survival and treatment response,Genotype-phenotype correlation of CRC genetic susceptibility variants with CRC subgroups,Identification of new predisposition genes for familial CRC,Identification of new predisposition genes for serrated polyposis syndrome,Functional characterization of new candidate predisposition genes for CRC,Meta-analysis of next generation sequencing data,Consortium database compiling clinical, tumoral, molecular, genotyping and sequencing data,Epistatic interaction between CRC/adenoma genetic susceptibility variants,Gene-environment interaction for CRC/adenoma genetic susceptibility variants These Exchange Visits are aimed at strengthening the existing networks by allowing scientists to go to an institution or laboratory in another COST Country to foster collaboration, to learn a new technique or to take measurements using instruments and/or methods not available in their own institution/laboratory. They are particularly intended for young scientists. STSM will generally contribute to all GP goals and outputs will include those specific to the related goal.

Disseminations

Title	Type	Publisher/provider	Expected date of Release	Cost(EUR)
Website maintenance	Action Website	Antaviana, S.L.	01/06/2015	1,200.00

How will this Dissemination contribute to the achievement of the Grant Period Goals?
Identification of new CRC genetic susceptibility variants,Identification of new adenoma genetic susceptibility variants,Meta-analysis of CRC genome-wide association studies (GWAS),Fine-mapping of CRC genetic susceptibility variants,Fine-mapping of adenoma genetic susceptibility variants,Functional links for CRC genetic susceptibility variants,Functional links for adenoma genetic susceptibility variants,Genotype-phenotype correlation of CRC genetic susceptibility variants with patient survival and treatment response,Genotype-phenotype correlation of CRC genetic susceptibility variants with CRC subgroups,Identification of new predisposition genes for familial CRC,Identification of new predisposition genes for serrated polyposis syndrome,Functional characterization of new candidate predisposition genes for CRC,Meta-analysis of next generation sequencing data,Consortium database compiling clinical, tumoral, molecular, genotyping and sequencing data,Epistatic interaction between CRC/adenoma genetic susceptibility variants,Gene-environment interaction for CRC/adenoma genetic susceptibility variants

Title	Type	Publisher/provider	Expected date of Release	Cost(EUR)
Open access	Printed publication	Open access	01/10/2015	6,200.00

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publications		publishers		

How will this Dissemination contribute to the achievement of the Grant Period Goals?	
Identification of new CRC genetic susceptibility variants,Identification of new adenoma genetic susceptibility variants,Meta-analysis of CRC genome-wide association studies (GWAS),Fine-mapping of CRC genetic susceptibility variants,Fine-mapping of adenoma genetic susceptibility variants,Functional links for CRC genetic susceptibility variants,Functional links for adenoma genetic susceptibility variants,Genotype-phenotype correlation of CRC genetic susceptibility variants with patient survival and treatment response,Genotype-phenotype correlation of CRC genetic susceptibility variants with CRC subgroups,Identification of new predisposition genes for familial CRC,Identification of new predisposition genes for serrated polyposis syndrome,Functional characterization of new candidate predisposition genes for CRC,Meta-analysis of next generation sequencing data,Consortium database compiling clinical, tumoral, molecular, genotyping and sequencing data,Epistatic interaction between CRC/adenoma genetic susceptibility variants,Gene-environment interaction for CRC/adenoma genetic susceptibility variants	
Total Disseminations	7,400.00

OERSA

Item	Cost(EUR)
Bank fees	200.00

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