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"Developmentofaneuronalmicroscopeforcellcharacterization andmanipulation"

(NeuronalmicRoscopyforcellbehaviorViouralExaminationandmanipulation)

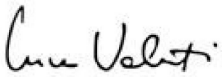
Acronym:REVEAL

ProtocolversionnumberSee1.0Date:09December2020

Promoter:IRCCSCa'GrandaFoundationMaggiorePoliclinicoHospital,ViaSforza 28,20122Milan,Italy

Coordinatingcenter:UOC Transfusion Center IRCCSCa'GrandaFoundationOspedaleMaggiorePoliclinico,ViaSforza35,20122Milan,Italy

PrincipalInvestigator: Prof.Luca VittorioValenti



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FLOWCHART

	Screening	Intervention
Period	(-t1)	(t1)
Enlistment		
informedconsent	-	
inclusion/exclusioncriteria	-	
Administrationoftheintervention		
Biologicalsamplecollection		-

LISTOFABBREVIATIONS

ALS: Automated Lab Solutions GmbH

THEREIS: EthicsCommittee

CEA: Commissariatàl'énergieatomiqueetauxénergiesalternatives

CI:InformedConsent

CRF: CaseReportForm,datacollectionform**EC:**

EuropeanCommunity

ENS: EcoleNormaleSupérieuredeLyon**GCP:**GoodClinicalPractic

e, good clinical practice **HCC:**HepatocellularCarcinoma,

hepatocellularcarcinoma**LMU:**LudwigMaximilian University

of Munich **WUT:**PolitechnikaWarszawska

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10. PRACTICEMANAGEMENT

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1. INTRODUCTION

1.1 Backgroundandrationale

Hepatocellularcarcinoma(HCC)isthemostcommontypeofprimarylivercancerandisaleadingcause of cancer-related death worldwide. The prognosis of HCC remains poor, with a 5-yearsurvivalrateof18%(1).RiskfactorsforHCCincludeviralinfection,autoimmunehepatitis,chronicalcohol use or metabolic fatty liver disease, obesity, and diabetes mellitus (2). Furthermore,alterationsandchronicinflammationofthemicroenvironmentcanfacilitatethetransformationofnormalliverstemcellsintoprecanceroustumorstemcells(3).Alltheseunderlyingpathogenicstimulicaninduceaspectrumofgeneticandepigeneticmodifications,whichareinvolvedinthecellcycle,cellgrowthandregulationofadhesion.Therefore,heterogeneityandtumorprimingpotentialarisefromacombinationofbothendogenousandexogenousfactors(4).Inparticular,hepatocellularcarcinomaisanextraordinarilyheterogeneousdiseaseduetothemorphologicalandhistologicaldiversityofliverceltypes,andsuchintratumoralheterogeneityrepresentsamajorchallengefortumorcharacterizationandtherapeuticmanagementofpatientswithHCC.

Currentinvitromodels,basedonconventionalhepatomaandhepatocarcinomacelllines,failtorecapitulatekeycharacteristicsoftumortissuesuchasthree-dimensionaltissuearchitecture,cellular heterogeneity, and cell-cell interactions. Organoids, which are 3D cellular structuresgeneratedfrombothinducedpluripotentstemcellsandadulttissue-residentstemcells,haverecently been exploited to overcome the limitations of 2D cell culture systems, emerging aspowerful tools for studying human diseases (5, 6). This is possible as they are able to stablypreservethegeneticinformationoftheautologoustissueandmimicthepathologicalstateofthetissueitself.
These structures will be the basis for developing a new and promisingmethodology of microscopy, called "neuronal", which is strongly based on neural networks capable of perception, interpretation, inference, prediction, decision, and action.

2. OBJECTIVE/HYPOTHESISOFTHEEXPERIMENT

Theaimoftheproject,withinwhichthisclinicalstudyispart,istovalidatetheabilityofa"neuronal"microscopetodecipherthemolecular
mechanismsattheoriginofcancer,especiallybyaddressingtheproblemofbiologicalheterogeneity.
Molecular characterization of tumor cell subtypes at the single-cell level has the potential toresolvethetemporalorderofeventsgoverningthedevelopmentaltrajectoriesoflivercancer.Thankstotheneuronalmicroscopeable
toselectindividualcells,weintendtoidentifyandisolatecellsatdifferentpointsofthetrajectoriesthatleadfr

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omthenormalstatetothe

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tumor("past,presentandfuture").
Morespecifically,thescientificprojectaimstodevelopa"cell-harvestingneuronalmicroscope"thatwillallowincombinationwithbiologicalanalyses(proteomics,genetics,etc.)tocharacterizethecellularheterogeneityknowntocauselivercancer.Thechallengeistodevelopthisnewmolecularimagingtechniquewhichcanpotentiallyrevealnewcellularmechanismsattheoriginofadisease.
Todemonstratethat,thisneuronal microscopy canleadtounderstandingthecellularoriginofadisease,itwillbeusedtodecipher,identifyandpredictthestateofcellsoriginatingfromlivertumorsderivedfrompatientsandmousemodelsofthisdisease.

2.1 Primaryobjective

TheprimaryobjectiveofthestudyconductedattheFondazione IRCCS Ca' Granda Ospedale Maggiore Policlinicoistogenerateandcharacterizethree-dimensionalcell culture models,calledorganoids,ofthemainlivercellpopulations,inordertoimitatetheearlystages of human carcinogenesisand then analyze the onsetof HCC, to identifythe specific mechanismsinvolvedinhepatocellularcarcinoma.

2.2 Secondaryobjectives

1. Liverorganoids(normal,pre-tumorortumor) are used to"train"theneuronalmicroscope in order todistinguishvariouscellsubtypeswithinheterogeneouscultures and recognizepre-neoplastic cellsable to initiatethe transition froma normalstatetoatumorstate.

2. On thisbasis, a"singlecell sampling"system willbedeveloped thatwillallow usto detectandcollectdifferentsubtypesoflivercellsthatareexpectedtobecomecancerousandtoanalyzethem beforethetumormanifestsitself.

3. STUDYDESIGN

3.1 Studydesign

Interventional,withthecollectionofbiological,non-pharmacological,monocentricmaterial.

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RESPONSIBILITY(roleofthepromoterandcollaborators)

Operationalunit	*Participantname*	*Roleandfunctionsinthefirm*
Department of TransfusionMedicineandHematology, Fondazione IRCCSCa' Granda Ospedale MaggiorePoliclinico	Dr.DanielePrati Prof.LucaValenti(principalinvestigator)	Samplerecruitmentandcharacterization; Isolation and generation oforganoids,spheroidsandtissues;Characterizationoforganoidsbygeneand proteinexpression Dataanalysis

Internalcollaborations:

Operationalunit	*Participantname*	*Roleandfunctionsinthefirm*
UOCGeneralSurgeryandLiverTransplants, Fondazione IRCCS Ca' Granda OspedaleMaggiorePoliclinico	Prof.GiorgioRossi	Reportingofeligiblepatientsandsamplecharacterization
UOCScientificDirectionFondazione IRCCSCa' Granda OspedaleMaggiorePoliclinico	Dr.StefanoGatti	Reporting of eligible patients,sample characterization andsupportincell isolationprotocols

Externalcollaborations:

Collaboratingbody	*Roleandfunctionsintheproject*
Commissariatàl'énergieatomiqueetauxénergiesalternatives,France(CEA)	Development of the 2D neuronal scanning lens-free microscopeandprototypingofthe3Dneuronalmicroscope;validationofthemicroscopeprototypesthroughtheuseofhumanandmurinesamplesgeneratedrespectivelyattheFoundationandENSLyon
Iprasense,France	Technicaldevelopmentandimplementationofthelens-free neuronalmicroscope
EcoleNormaleSupérieuredeLyon,France(ENS)	Generation of mouse models of liver disease;processingandisolationofsamplesgeneratedattheFoundation;sequencingandtranscriptomicanalysisofsinglecellstogeneratecelltrajectories

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LudwigMaximilianUniversityofMunich,Germany(LMU)	Proteomicandmulti-omicanalyzesofcellandorganoidclusters
AutomatedLabSolutionsGmbH,Germany(ALS)	Developmentandvalidationofthelens-freeneuronalmicroscope;creationoftheprototypefortheisolationofsinglecells
PolitechnikaWarszawska,Poland(WUT)	Metrological evaluation and validation of the developed 2Dand 3D microscopes, through the design and production ofcalibrationsamplesusing3Dprintingtechnology

3.2 Inclusioncriteria

Adultpatientsundergoingsurgicalcholecystectomy,liverresectionforhepatocellularcarcinomaor whole liver explants, who have given consent to participate in the study, will be included.

3.3 Exclusioncriteria

Patientswhoarepositiveforchronicviralhepatitis(HCV-RNAandHBsAg)willbeexcluded.

4. PROCEDURESRELATINGTOTHESTUDY

4.1Intervention

IncollaborationwiththeLiverTransplantUnit of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico,wastetissuesampleswillbecollectedfrompatientsundergoingcholecystectomy,liverresection forhepatocellularcarcinoma(bothintra-tumoralandextra-tumoraltissues)ortakenfromexplantedwholelivers.
Thiswillallowustoisolatecellsandgenerateorganoidsstartingfromthethreeconditionsofinteresttous:

1) normallivertissues(cholecystectomy);
2) diseasedliver(extra-tumoralparenchymaandliverexplants);
3) hepatocellularcarcinoma.

Weaimtocollectupto10independentsamplespertissuetype.

To validate the heterogeneity obtained in vitro using organoids, mono- and multi-lineage liverspheroidswillbegeneratedbyexploitingpreviouslyestablishedhepatomacelllines(11),namely:phenotypically differenthepatomacelllines (HepG2andSNU398cells)

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andprimarycelllinesrepresentativeoftumorheterogeneity(HCC-1,HCC-2,HCC-3,generatedwithin thestudy"ImpactoftheI148MvariantofthePNPLA3geneontheregulationofretinolmetabolismand activation of human hepatic stellate cells", Opinion No. 29_2016 and 29_2016bis, proceedings300/2016),culturedin96-wellplates.
Tostudytheroleofspecificgeneticpathwaysinregulatingtumorheterogeneity,wewillknockdowngenesof interestforHepG2hepatomacells.Toregulatetheexpressionofspecificproteinsincellularmodels,wewillu sespecificantisenseoligonucleotides(morpholinos:MPO,GeneTools)thatblockproteintranslation,orMP Othatdoesnotrecognizeanym RNAsequenceasacontrol.

Thebiopsyfragmentsorfragmentsobtainedfromsurgicalresectionswillbetransportedin Celsiorperfusio nsolutionat4°Candwillbeprocessedatthe TranslationalMedicinelaboratoryintheshortestpossibletimet oisolateliverorganoids.Thetissueswillbemechanicallyfragmentedintosmallpieces,avoidingreducingth emtosinglecells;thiswillincreasetheformationefficiencyoftheorganoids.Thenthefragmentswillbefurth ersubjectedtoenzymaticdigestionwithasolutioncontaining CollagenaseandDNaseat37°C.Thecellclust ersobtainedfromenzymaticdigestionwillbeincludedinreducedgrowthfactorMatrigel.OncetheMatrigel haspolymerized,thecompleteculturemediumto
growliverorganoidswillbeadded.Isolationsobtainedfromnormaltissueswillbeculturedinmediumcontai ning:AdvancedDMEM/F12supplementedwith1%N2and1%B27(bothfromGIBCO),1.25mMN-Acetylcysteine(Sigma),10nMLeu-Gastrin(Sigma),50ng/mlEGF(Peprotech),1μg/mlRSPO1(Peprotech),100ng/mlFGF10(Peprotech),25 ng/ml HGF (Peprotech), 10 mM Nicotinamide (Sigma), 5 μM A83.01 (Peprotech), and 10 μM Forskolin(Peprotech).Inordertoincreasetheisolationefficiencyoftheorganoidsforthefirstfewdays,25ng /ml Noggin (Peprotech), 100 ng/ml Wnt3a (peprotech) and 10 μM Rock inhibitor Y27632 (Peprotech) willbeaddedtothemedium.Isolationsobtainedfromtumortissueswillbedivided and culturedinclassicalmediumor
intumoroidmediumcontaining:AdvancedDMEM/F12supplementedwith1%N2and1%B27(both from GIBCO), 1.25 mM N-Acetylcysteine(Sigma), 10 nM Leu-Gastrin (Sigma), 50 ng/ml EGF(Peprotech),100ng/mlFGF10(Peprotech),25ng/mlHGF(Peprotech),10mMNicotinamide (Sigma), 5 μM A83.01(Peprotech), 10 μM Forskolin (Peprotech),and 3 nM dexamethasone(Sigma)(8).

The samples isolated at the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico will be sent to the ENS in Lyon, that incollaborationwithCEA will developthetranscriptomicanalysisonbothwholehumanorganoidsandisolatedcells, using theneuronalmicroscope.
CEA,throughtheuseofhumanandmurinecellsamplesisolatedattheFondazione IRCCS Ca' Granda Ospedale Maggiore PoliclinicoandENSLyonrespectively,willdevelopthe2Dand3Dimagingplatforms. LMUincollaborationwithCEAwilldevelopproteomicanalysisbothonwholehumanorganoidsandonisolat edcellsusingtheneuronalmicroscope.

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5. ENDPOINTS

5.1 PrimaryEndpoint

Isolation of epithelial cells in order to generate models of major hepatocellular carcinoma cellpopulations in a three-dimensional culture, called liver organoids, and their molecularcharacterizationofthegeneratedmodels.

5.2SecondaryEndpoints

· Knowledgeofthebehavioralandmorphologicaldifferencesbetweenphysiologicalandtumorhepatocytes;

· Knowledgeofthemolecularmechanismsunderlyingcellularlevelobservationsexploiting“omics”technologiesandCRISPR-Cas9geneticengineering.

6. DURATION / TIMELINE OF THE STUDY

Month and year of study start: 01/2021

Monthand year of enrollment closure: 01/2024

Month and yearofstudyend:01/2025

The study will have a duration of 48 months. In the first three years we expect to enroll approximately 30 subjects inaccordancewiththeinclusioncriteria.

PROJECTGANTT

Intervention	Period(months)			
	1-12	13-24	25-36	37-48
Enlistment	-	-	--	
Informedconsent	-	-	-	
Inclusion/exclusion criteria	-	-	-	
Generationoforganoids	-	-	-	

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Evaluationofgeneexpressioninliverorganoids	--	--	--	

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Evaluationofspecificliver proteinsinliverorganoids	--	--	--	
Datacorrelationanalysis		-	-	-

7. STATISTICANALYSIS

7.1 Samplesizeanddataanalysis

Previouslypublishedworks(7,8,9,10)havehighlightedthatthegenerationefficiencyofliver

organoidsis approximately 90%starting from surgicalresections and 33%from biopsies (7,8). Consideringtheseestimates,inordertoisolateatleast6independentorganoidculturesofeachtypeof conditionof interestinour study,itis estimatedto recruitatleast 30donors(10 foreachconditionstudied).Theintentistoobtainreplicatesforanalyseswithasufficientrepresentationofthedif ferentstagesofliverdamage(normalliver,inflammation/fibrosisandhepatocarcinoma)andtobeabletomapth eimpactofthemostcommonhereditarygeneticvariants(presentinatleast20%ofindividuals)inthepopulation.

Themainanalyseswillbeconductedfromcellculturesisolatedfromasingleindividual.Giventhedescriptive natureofmappingcellularphenotypesandgeneexpression,andthelargenumberoforganoids($>10^3$)andc ells($>10^9$)fromasingleindividual,wewillhavesufficientstatisticalpower($>80\%$)toidentifyandanalyzespe cificcellularsubsetsrepresenting$>1\%$ofthepopulationoverall.

8. ADVERSEEVENTS

Theprojectdoesnotinvolvetheadministrationofdrugsorothersubstancesoradhocinvasiveintervention soutsideofnormalclinicalpractices.Therefore,noadverseeventsareexpected.

9. RISK/BENEFITASSESSMENT

The study does not predict an immediate benefit for the donors,buttheresultsofthistrialwillhavethepotentialtoleadtoadecodingofthemechanismsattheoriginof tumordevelopment,resolvethetemporalorderoftheeventsthatregulatetheevolutionarytrajectory,under standtheprogression,characterizationandimprovethetherapeuticmanagementofpatients.

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10. PRACTICEMANAGEMENT

10.1 Datacollectionandmanagement

For each participant will be assigned a unique code upon enrollment. The file associating theparticipant'scodewiththerelevantidentificationdatawillbestoredseparatelyonacomputer protected with a password.Thestudydatabasewillbeprotectedwith a different passwordandaccessibleonlytostaff designatedbytheprincipalinvestigator.Theunique code will be used to prevent that unauthorized individual will be able to discover the identity of the enrolled patient.Only designed investigators will be able to know the identity of the enrolled subjects.

Regardingdatastorage:datathat can be made publicly accessible,to all partnerswillberequiredtouseanopenaccessrepository,linkedtothetoolsproposedbytheEuropeanCommunity(e.g.OpenAIRE)toensureaccesstopublicationsandabibliographicmetadataarchiveinastandardformat,includingtheinformationrequiredbytheEC.

10.2 Regulatoryaspectsandethicalconsiderations

10.2.1 ApprovaloftheCompetentAuthority

Inaccordancewithcurrentregulations,theprincipalinvestigatormustobtainapprovalfromtheappropriateCompetentAuthoritybeforestartingtheclinicalstudy.
ThisstudywillbeconductedinaccordancewiththerulesoftheICH/GCP(InternationalConferenceofHarmonization/GoodClinicalPractice)andallapplicablelaws,includingtheDeclarationofHelsinkiofJune1964,asamendedbythelatestWorldMedicalAssociationGeneralAssemblyinSeoul,2008.

10.2.2 ApprovaloftheEthicsCommittee

Theinvestigatormustensurethattheprotocolhasbeenseenandapprovedbythelocalindependent Ethics Committee (EC) beforestartingthestudy.
TheEC
mustalsoreviewandapprovetheinformedconsent(IC)formandallwritteninformationreceivedfromthepatientpriortoenrollmentinthestudy.
Ifitisnecessarytomodifytheprotocoland/ortheICduringthestudy,theinvestigatorwillbetheguarantorandthereforethepersoninchargeofensuringthereviewandapprovalofthismodifieddocumentaccordingtotheEC'srequest.

Thecontentofthesechangeswillbeimplementedonlyaftertheechasapprovedthem.Untilthattime,itwillbenecessarytorefertothepreviousversionofthealreadyapproveddocument.

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10.2.3 InformedConsent(IC)

Theinvestigatororotherstaffdesignedbythe investigatorshouldinformpeopleaboutallaspectsandproceduresofthestudy. Theprocessforobtaininginformedconsentmustcomplywithcurrentregulatoryprocedures.Theinvestigator(ordesignatedcollaborator)andthesubjectmustdateandsigntheinformedconsentformbeforethat thepatientinitiatesanystudy-relatedprocedures.Thesubjectwillreceiveacopy of the CI dated and signed by both parties; the original copy will be kept in the archivesdesignatedforstudy.Neithertheinvestigatornordesignatedpersonnelshouldinanywayexertany coercion or influence on a subject to participate or continue to participate in the study. Asubject'sdecisiontoparticipateinthestudymustbecompletelyvoluntary.Theinvestigatoranddesignated personnelshouldemphasizetothesubjectthathemaywithdrawconsentatanytimewithoutpenaltyorlossofanybenefitstowhichhemaybeentitled.

Writtenororalinformationrelatingtothestudy,includingthewrittenconsentform,mustnotcontainanylinguisticexpressionthatforcesthesubjectto(evenapparently)waivehisorherlegalrights,orthatwouldexoneratetheinvestigator,theinstitutionorthesponsorfromliabilityfornegligence.

10.3 Dutiesoftheexperimenter

Inaccordancewithapplicablelocalregulations,theinvestigatormustsendperiodicreportsregardingtheprogressofthestudyinhiscentertotheECandnotifytheECoftheclosureofthe study. Periodic reporting and closure notification are part of the investigator'sresponsibilities.

10.4 Studymonitoring

In accordance with applicable regulations and good clinical practice (GCP), the clinical monitor must visit or contactthe center periodically. The duration, nature and frequency of such visits/contacts depend on the frequencyof recruitment,the qualityof thedocuments heldby thecenter andtheir adherenceto theprotocol.

Throughthesecontacts,themonitormust:

· monitorandevaluatetheprogressofthestudy

· examinethedatacollected

· conductverificationofthesourcedocument

· identifyeachproblemanditssolutions

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Thepurposesofthemonitoringactivityaretoverifythat:

- the rights and welfare of the subject are respected
- The study data are accurate, complete, and can be verified from the original documents
- thestudyisconductedinaccordancewiththeprotocolandanyapprovedamendments,GCPandapplicableregulations

Theinvestigatormust:

- giveto the clinical monitordirectaccesstoallrelevantdocumentation
- dedicatepartofhisandhisstaff'stimetotheclinical monitortodiscussthemonitoringresultsandanyotherpossibleaspects.

Theclinical monitorshouldalsocontactthecenterpriortothestartofthestudytodiscusstheprotocolanddatacollectionprocedureswiththestaff.

10.5 Qualityassuranceofthestudy

AsPromoter,FondazioneIRCCSCa'Granda,OspedaleMaggiorePoliclinicocancarryoutaqualitycontrolcheckonthestudyatitsdiscretion.Inthiscase,theinvestigatormustallowtheclinical monitordirectaccesstoallrelevantdocumentationanddedicatesomeofhisorhertimeandstafftothereviewertodiscussthemonitoringresultsandanyotheraspectsofthestudy.

Furthermore,RegulatoryAuthoritiescancarryoutinspections.Inthiscase,theinvestigatormustgrantthinspectordirectaccesstoallrelevantdocumentation,anddedicatepartofhistimeandstafftotheinspectortodiscussthemonitoringresultsandanyotheraspectsofthestudy.

10.6 Closureofthestudy

Atthetimeofstudyclosure,themonitorandtheinvestigatormustactivateaseriesofprocedures:

- reviewallstudydocumentation
- reconcilestudydata
- reconcileallclarificationreports.

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10.7 Archivingofdocuments

Inaccordancewithcurrentnationalregulations,theinvestigatormustkeepacopyofalldocumentationandstoreitinadryandsafeplaceafterthestudyisclosed.

10.8 Disclosureofinformationregardingscientificdiscovery

10.8.1 Confidentiality

Theinvestigatorandotherpersonnelinvolvedinthestudymustprocessallinformationrelatingtothestudy(including theprotocol,dataobtainedandalldocumentationproducedduringthestudy)andmustnot use suchinformation, dataor reportsfor purposesother than thosedescribed inthe protocol.

Theserestrictionsdonotapplyto:

1) informationthatbecomespubliclyavailable,notduetonegligenceonthepartoftheinvestigatororhisstaff;

2) informationrequiringconfidentialdisclosuretoCEforthesolepurposeofevaluatingthestudy;

3) informationthatmustbedisclosedinordertoobtainappropriatemedicalcareforastudysubject.

10.8.2 Publications

TheIRCCSCa'GrandaFoundation,OspedaleMaggiorePoliclinicoisthesoleownerofthedata.Awebsitededicated totheprojectwillbebuiltwithprivatesectionsthatwillservetheprojectpartnersas update and exchange channels, as well as to build a data archive to be used in the post-projectexploitation phase. The public section will contain the project description (e.g. objectives, partners,fundingsource,etc.),publishedarticlesandongoingwork.Thescientificdirectorofthestudywillwritea final report and make the results public at the end of the study. The data will be made publicanonymouslyandpresentedasrequiredinaggregatemode.InaccordancewiththeprovisionsoftheGrant Agreement,thedisseminationoftheresultswilltakeplaceassoonaspossible,byappropriatemeans,includingscientificpublications.

10.9 Intellectualpropertyrightsonthestudyresults

Most data will be associated with results that may have commercial or industrial protectionpotential and therefore cannot be made accessible for verification and re-use generally duetointellectualpropertyprotectionmeasures.
However, relevant data necessary for verifying results published in scientific journals can be madeaccessibleonacase-by-casebasis.

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AConsortiumAgreementwillbenegotiatedandsignedbyallpartiesinordertospecify,amongotherthings,thetermsandconditionsrelatingtoownership,accessrights,exploitationofthebackgroundandresultsaswellasthedisseminationoftheresults,inaccordancewiththegrantagreementandRegulationn°1290/2013of11December2013.
TheconsortiumagreementwillbebasedontheDESCAHorizon2020ModelConsortiumAgreementwiththenecessaryadaptationsconsideringthespecificcontextandpartiesinvolvedintheprojectand
willbebasedonthefollowingprinciples:

· Thepartieswillidentifytheknowledge,information,data(ofanyformornature),know-how,technical material and/or assets protected by industrial and/or intellectual property rights orsusceptibletoprotection,(Background)heldand/ordevelopedinanycapacityindependentlybyeachof the Parties at a time prior to the start of the Project which they will make available for theimplementationoftheprojectandwillevaluatetheiravailabilityforaccessrightswithregardtotherightsofpotentialthirdpartiesonsuchbackgroundtotheextentthatthisinformationisknowntotherespectivepartyattheti meoftheassessment;
· Ownershipofresults,includingjointresultsgeneratedbytwoormoreparties,willgotothepartyorpartiesthat generatedsuchresults;
· Theproprietarypartieswilltakeallappropriatemeasurestoprotecttheresultssusceptibletocommercialorindustrialexploitation,inparticularthroughintellectualpropertyrights,whereappropriate;
· Thepartieswillusereasonableeffortstoexploitanddisseminatetheresults,directlyorindirectly,forexamplebylicensingsuchresults;
· Each party will grant the other parties access rights (through licenses) to its Background and the resultsgenerated during the Project, only if strictly necessary for the implementation of the project itself and/orfortheexploitationoftheresultsofsuchotherparties(onfairandreasonableterms).

11. INDEMNITYANDCOMPENSATIONINCASEOFDAMAGES

In the event of unwanted events or any damage that may arise from participation inresearch,ourInstitute'sInsurancePolicyisalsoextendedtocoverindividualsparticipatinginresearchprojects.

12. FINANCIALAGREEMENTS

ThecostsofstudyproceduresexceedingnormalclinicalpracticewillbeentirelycoveredbythefundsderivingfromtheHorizon2020-EuropeEUfinancing.

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13. DISCLOSURESONCONFLICTSOFINTEREST

Theinvestigatorsdeclarenoconflictsofinterest.

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