

MultiSyn	
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1. Introduction

Despite remarkable progress in the understanding of the molecular pathogenesis of neurodegenerative diseases (NDD), no causative or disease-modifying treatment is currently available. Aggregation of misfolded proteins are thought to play a crucial role in the pathogenesis, but attempts to exploit this knowledge for novel treatments have not been successful. Also, pathogenetically relevant biomarkers of protein aggregation are lacking.

In order to overcome this critical road-block, the MultiSyn project assembled an interdisciplinary consortium, consisting of world-leading experts in structural biology and ligand development, multimodal neuroimaging, animal models and clinical trials to develop a novel imaging system for combined simultaneous molecular and functional imaging (PET-MRI/fMRI) for two rare diseases caused by excessive accumulation of misfolded alpha-synuclein (α SYN), multiple systems atrophy (MSA) and parkinsonism caused by mutations in the alpha-synuclein gene (SNCA), which will serve as proof-of-principle models for the more common and heterogeneous NDD. With this technology we will pioneer the monitoring of protein aggregation as a biomarker for therapeutic effects in the framework of individualized causative treatment. The central aspects of the work-flow including ligand design, software development and drug trials will be driven by three highly specialized SMEs, while translation to animal models and clinical use will be implemented by top academic centers. The groundbreaking progress will include:

1. Establish a multimodal imaging algorithm based on a new PET tracer and embracing structural and functional MRI methods to yield an α SYN specific tool
2. Test this multimodal, molecular neuroimaging algorithm in animal models with regard to its potential for diagnosis, mirroring the natural disease course and response to therapy
3. Translate the algorithm including the therapeutic modality (i.e. immunotherapy with PD01, NCT01568099) to the clinical setting.

In summary, MultiSyn aims to use the most sophisticated Novel PET/MR imaging systems for rodents and humans. The phenotyping of patients, use of biomaterial from patients and control subjects as well as the execution of animal experiments entails ethical issues that all partners involved in the project need to be aware of.

2. Ethical Requirements & Provisions

In the design and ongoing development of the MultiSyn project ethical guidelines from numerous sources will be adhered to. The ASC-Inclusion project will be compliant with the ethical guidelines set out by the Seventh Framework Programme (http://cordis.europa.eu/fp7/ethics_en.html#ethics_cl), as well as the following international codes of practices:

- Helsinki Declaration in its latest version (WMA, October 2008)
- Convention of the Council of Europe on Human Rights and Biomedicine signed in Oviedo on April 4, 1997, and the Additional Protocol on the Prohibition of Cloning Human Beings signed in Paris on 12 January 1998
- UN Convention on the Rights of the Child
- Universal Declaration on the human genome and human rights adopted by UNESCO

Ethical approval for the project will and have be sought in the partner sites as set out below.

Furthermore, MultiSyn partners will conform to relevant EU legislation such as:

- The Charter of Fundamental Rights of the EU
- Directive 95/46/EC of 24 October 1995 on the protection of individuals with regards to processing of personal data and the movement of such data
- Directive 2001/20/EC of 4 April 2001 on clinical good practice
- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use
- Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion
- Detailed guidance for the request for authorisation of a clinical trial to the competent authorities
- Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use and its amendments.
- Regulation (EC) No 1084/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products granted by a competent authority of a Member State
- Regulation (EC) No 1085/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products falling within the scope of Council Regulation (EEC) No 2309/93
- Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions
- Directive 86/609/EEC of 24 Nov. 1986 on the protection of animals
- Directive 2010/63/eu of 22 September 2010 on the protection of animals used for scientific purposes
- Protocol on Protection and welfare of animals (protocol to the Amsterdam Treaty)
- Directive 2009/41/EC of 6 May 2009 on the contained use of genetically modified micro-organisms
- Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC.
- Regulation (EC) No 1946/2003 of the European Parliament and of the Council of 15 July 2003 on transboundary movements of genetically modified organisms (Text with EEA relevance)
- Regulation (EC) No 65/2004 of 14 January 2004 establishing a system for the development and assignment of unique identifiers for genetically modified organisms
- Directive 2000/54/EC of the European Parliament and of the Council of 18 September 2000 on the protection of workers from the risks related to exposure to biological agents at work (7th individual directive within the meaning of Article 16(1) of Directive 89/391/EC)
- Directive 2004/23/EC of the European Parliament and of the Council on Setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells", code number 2002/0128 (COD), Strasbourg, 31 March 2004.

3. Independent Ethics Board

An Independent Ethics Board has been established with the kick-off meeting of MultiSyn. Members of this board are at present Prof. Max Lillefort (Lund University) and Nickie Roberts (MSA Trust, UK).

As Nickie Roberts will be leaving the MSA Trust with end of May 2015 MultiSyn will seek to find a competent person who will replace Nickie Roberts favourably with a patient organisation background.

4. Summary of work done in reporting period 1 (October 2013-March 2015)

Broken down to aims, the work performed and results achieved can be summarised as follows:

Aim 1. Establish a multimodal imaging workflow based on specific PET tracers and embracing structural and functional MRI methods to yield a tool that sensitively and specifically detects α SYN pathology and associated changes (WP1):

Development of labelling strategies for novel PET tracer

- Successful radiochemical synthesis of ^{18}F -sery363b, ^{11}C -sery392b and ^{11}C -sery512a under conditions easily adoptable to GMP compliant manufacture for in vivo PET imaging of alpha-synuclein aggregates
- Compounds showed good blood brain barrier penetration, but specific binding does not reach the required significance level in the brain yet (observed in autoradiography and PET experiments).
- Optimization of the synthesis of anle253b as a PET tracer
- Successful synthesis and biophysical analysis of further undisclosed potential PET compounds by partner MODAG
- Tritiation of five most promising compounds to speed-up tracer development
- The first two tritiated compounds (^3H -anle138b, ^3H -anle2F4CP) did not reach specific binding levels in human brain slices of MSA and LBD yet but gave a cortical staining pattern in AD patients. Tritiated anle138b labels protein aggregates in tissue sections from animal models and human patients. However, it binds to Abeta in Alzheimer tissue so is not selective enough to be a marker for α SYN. It is possible that it is also detecting tau in frontal areas of PSP and DLB patients. Immunostaining is required to clarify the nature of the frontal binding.

Characterization of binding affinity and specificity of PET compounds in vitro

- Preparation and provision of fibrils from recombinant α syn
- Development of a dot blot assay for competition studies
- Fibril binding assay for ^{11}C -PIB was set up but requires further optimization

Set-up of dedicated PET/fMRI scan protocols in rodents

- Dedicated PET/fMRI scan protocols were being set up with ^{11}C -raclopride PET experiments and with BOLD fMRI imaging protocols at resting state with a simultaneous dynamic PET acquisition for 60 min using the tracer ^{18}F FDG for mice and rat models

Development of a dedicated software module enabling the handling and quantitative voxelwise evaluation of simultaneously acquired PET-MRI data

- Inclusion of parametric mapping into PNEURO for synergistic PET/MR analysis of structural and functional data.
- Extension of PNEURO from human to animal brains.
- Addition of a perfusion mapping plug-in for ASL MRI data and diffusion mapping and tensor calculation plug-in for DTI MRI data.
- Implementation of a palette of fiber tracking algorithms based on tensor results.
- 3D visualization of fibers together with planar images.
- R scripts for the statistical analysis of multiparametric outcome data in longitudinal studies.
- Implementation of a non-invasive kinetic model for D2 Receptor PET Scans with ^{11}C -Raclopride.

Aim 2. Test this multimodal, molecular neuroimaging methodology in animal models with regard to its potential for diagnosis, monitoring the natural disease course and response to therapy, as well as guide and optimize therapeutic interventions(WP2).

Specific characterisation of mouse, rat and pig models

- Triton insoluble human asyn as well as ProteinK resistant aggregates of asyn were found in the striatum of rats injected with rAAV vectors into the substantia nigra which makes this rat model suitable for testing a novel asyn PET tracer.
- We successfully expressed for the first time human asyn and GFP in the pig substantia nigra.
- Aged (10-15 month old) PLP-ASYN mice have an overall increased ASYN load which includes oligomeric species and insoluble forms.
- Increased α SYN could be confirmed in whole brain lysates of the PLP- α SYN mouse model of MSA by Western blot analysis.
- Total ASYN levels in CSF of 8-9 month old PLP-ASYN mice were higher than WT controls.
- Initiation of preparations for immunotherapy experiments in the AAV-a-syn rat model

PET imaging of rat and pig models

- In the AAV- α SYN overexpression rat model, we found a positive correlation between ^{11}C -PiB binding and α SYN load as well as dopaminergic cell loss, measured with ^{11}C -methylphenidate and postsynaptic D2 receptor expression changes, measured with ^{11}C -raclopride.
- We used PET imaging to validate a novel AAV-aSYN pig model of PD. We found decreased striatal VMAT2 binding on the side of aSYN injection 12 weeks after inoculation along with increased microglial activation compared to GFP animals. ^{11}C Sery512A and B PET showed no significant aSYN binding.
- In an initial study, the ^{11}C Sery392 tracer showed increased uptake in the striatum and ventral midbrain of pig models on the side of injection of AAV-aSYN.

PET/MRI methodology

- Bolus plus constant infusion experiments with ^{11}C -raclopride were established to measure DA release in rats and mice and future experiments will be performed using simultaneous ^{11}C -raclopride PET/BOLD fMRI
- Simultaneous BOLD fMRI/ ^{18}F -FDG PET experiments were successfully established

Aim 3. Translate the workflow including the therapeutic modality (i.e. immunotherapy with PD01A, NCT01568099) to the clinical setting (WP3):

- Multimodal imaging algorithms combining PET-imaging and fMRI have been developed and implemented
- Statistical tools and data management pipelines for the analysis of multimodal imaging have been established.
- Approval to use ^{11}C -methylphenidate, ^{11}C -raclopride and ^{11}C -PiB in human patients has been obtained.
- PiB-PET imaging in MSA and PDGBA patients has been performed and data analysis is currently ongoing.
- Principle discussions on clinical trial design
- Preliminary planning of the statistical analysis plan (SAP)

5. Ethical issues relevant for reporting period 1 (October 2013-March 2015)

5.1 Human studies

No human study as planned in the MultiSyn work programme has been started or undergone ethical review to date. This is partly due to the fact that the clinical studies are planned for later stages of MultiSyn, however, also due to the delay in identifying a novel PET tracer that specifically binds to alpha synuclein.

However, preclinical experiments done in MultiSyn showed promising results for the clinically approved PET tracer ¹¹C-PiB. Therefore, the feasibility of PiB-imaging as an alternative means to image protein aggregates in neurodegenerative alpha-synucleinopathies has been explored. As ¹¹C-PiB is approved as a PET-tracer in the differential diagnosis of dementing disorders in a clinical setting, imaging has been performed in selected patients in whom this investigation was justified, based on the judgement of their treating physician, in order to rule out additional Aβ-pathology. Thus, examinations were performed with an approved compound based on clinical judgement.

5.2 Use of human material

The approval of the local ethic committee for the usage of human brain samples is given to "Neurobiobank München" at the Center for Neuropathology and Prion Research, Munich (Armin Giese).

5.3 Use and protection of animals

The details regarding numbers, uses and treatment of mice respectively rats are detailed per partner below.

General remark: The MultiSyn projects involving the use of animal models are written according to the European Council Directive 2010/63/EU of 22 September 2010 on the protection of animals used for scientific purposes. In addition the projects have taken/will take all national regulations for the use of animals in research into account and will seek approval through local Ethics Review Committees.

All experiments have been supervised by trained and competent staff. All animal experimentation protocols in MultiSyn have been reviewed by the Institutional Ethical or Animal Care and Use Committees, established in all the Institutions involved in the project and will adhere to national and EU standards for animal research. Principles of the three R's - reduction, refinement, and replacement – have been applied to all listed projects. More precisely, MultiSyn partners will take initiatives to:

- **reduce** animal experimentation. This may be possible by coordinating animal experimentation at consortium level in order to reduce the number of experiments and improve knowledge communication. Additionally, imaging procedures allow repetitive use of the same animals and thus, reduce significantly the animal number
- **refine** animal experimentation by using best practices, which alleviate or minimise potential pain, suffering and distress and enhance animal well being, also, since imaging allows the repetitive use of the same animals during disease progression, the statistical accuracy improves. We see that we can achieve with small animal PET a reproducibility of better 5% in brain imaging,
- **replace** animal experimentation, when possible, with methods that do not require experimentation or other scientific procedures on animals.

Justification of species chosen: The choice of species to be used in animal experiments is based on scientific relevance and ethical considerations. In the MultiSyn project we will make use of mice, rats and minipigs as vertebrate models. The rationale for use of the respective species is given below.

Rodents: Transgenic mice and rats allow studying the pathophysiological aspects of diseases and unravelling new molecular mechanisms involved in disease. Most importantly, they allow identifying and validating biomarkers that are of relevance for the MultiSyn project (proof of concept), studies which can only be performed in animal models. Their homogeneous 'clinical' characteristics allow the use of limited numbers of animals in any given experiment. The principle of diversity is respected, as the genetically modified animals are restricted to experimental studies and are not spread outside experimental laboratories.

Minipigs: Crucial prerequisites for the development of safe preclinical protocols in biomedical research are suitable animal models that would allow for human-related validation of valuable research information gathered from experimentation with lower mammals. In this sense, the miniature pig, sharing many physiological similarities with humans, offers several breeding and handling advantages (when compared to non-human primates), making it an optimal species for preclinical experimentation.

Level of suffering of animals:

Animal discomfort/suffering must clearly be minimized for ethical and experimental reasons. Daily evaluation has been carried out by trained personnel (including for competent pre- and postoperative care) and under the supervision of an attending veterinarian. The animals are acclimated to the experimental conditions prior to the experimental start and care has been taken to minimize pain, fear and illness. Both short and long-term stress and pain have been avoided by using refined experimental conditions including appropriate anaesthesia: state-of-the-art surgical facilities and techniques.

Partner 1 EBERHARD KARLS UNIVERSITY TUEBINGEN (GE): EKUT has used healthy rats and mice to establish the required imaging protocols and workflows as laid-out in WP 1. In addition, EKUT gets animal models from the partner institutions. All experimental procedures have been approved by the local official (Regierungspräsidium) prior the start of the project. The Department of Preclinical Imaging and Radiopharmacy has approved animal holding facilities within the animal imaging area so that we can maintain a high hygiene level during longitudinal studies. We have specialized people and veterinarians who ensure the well being of the animals. All animals have been housed in IVC cages, in air conditioned rooms and get food and water ad libitum.

Partner 2 LUNDS UNIVERSITET (SE): At ULUND the experimental research activities will be requiring about 200 female young adult Sprague Dawley rats to be housed and used during the project period. The models that will be implemented at ULUND are based on the use of adeno-associated viral vectors encoding for human wild type of mutated forms of α SYN gene and either rodent variants of α SYN or the GFP marker protein as the control vectors. The animals are housed under controlled light, heat and humidity conditions and provided with food and water ad libitum.

All experimental work has received ethics approval by the Lund Malmö region ethics board. Applications are approved and renewed on 3-yearly intervals.

Swedish authorities have very recently adopted EU legislation for work involving animals, which has come into effect from January 1, 2013.

Partner 3 IMU (AT): IMU has bred, housed and used about 700 mice for project by date. All experiments involving animals have received approval by the local committee for animal experiments. The following mouse models are being used:

PLP-h α SYN mice, overexpressing human α -Synuclein in oligodendroglia and representing a model of MSA. Genetic background-, sex- and age-matched wild type controls will be C57Bl/6 mice.

The animal work will include validation of PET markers (wt 50 : tg 50); correlation of wet and imaging markers in different age groups (wt 100 : tg 100); analysis of disease progression by PET imaging (wt 100: tg 100) and finally, PET imaging in an interventional pre-clinical study lowering α -Synuclein levels (wt 100 : tg 100).

Partner 4 BRFAA (GR): BRFAA has performed analysis of tissues and biological fluids of rats that have undergone viral injections and euthanasia in Lund and of mice (transgenic and non-transgenic) from Innsbruck.

All animal facilities of BRFAA are accredited and registered by the appropriate veterinary services under European Directive 86/609/EEC. All animals are housed in accordance to the European Legal framework for the Protection of animals used for scientific purposes (European Convention 123/Council of Europe and Directive 86/609/EEC), the current Guidelines of International Organizations such as the Association for the Assessment and Accreditation of Laboratory Animal Care International-AAALAC Int., and the Federation of European Laboratory Animal Science Associations-FELASA). The Animal Facilities implement a complete veterinary medical care program which includes preventive medicine, surveillance, diagnosis, treatment and control of diseases as well as veterinary care of the animals used in experimental protocols. A health monitoring program is also in force, in accordance to the Guidelines issued by the FELASA. All animal research protocols including viral injections and in vivo microdialysis, as well as analysis of animal (mouse and rat) body fluids and tissues, are also licensed by the appropriate ethical committees and veterinary services.

Codes regarding animal work are described in the above section, and represent applications of EC directives.

Partner 5 Aarhus Universitet (DK): It is estimated that 80 rats and 22 Goettingen minipigs will be housed and used for the whole project. All experiments involving animals must be approved, monitored and regulated by The Danish Animal Experimentation Inspectorate.

The following experimentally-induced synucleinopathy animal model will be used in rat:

Sprague-Dawley rats will be injected with adeno-associated viral vectors containing human wild type α SYN or green fluorescent protein (GFP). We will use two models, one where α SYN expression is restricted to nigrostriatal dopaminergic cells and a second where the expression will be widespread affecting the cortical areas, thus representing a more severe form of synucleinopathy.

Approximately 40 rats will be injected with adeno-associated viral vectors containing α SYN and 40 rats will be injected with adeno-associated viral vectors containing green fluorescent protein. In 20 rats per group, the nigrostriatal dopaminergic areas will be targeted, and in 20 rats per group, rats will be injected in cortical regions for more severe and widespread effects. All rats will be imaged in a high field 9.4 Telsa Bruker microMRI to assess disease states. Following the MRI scans, microPET scans will be conducted in all rats using novel ^{11}C and ^{18}F tracers at selected timepoints (6-24 weeks) to validate new PET tracers that target α SYN deposits in the brain and study the longitudinal effects and potential reversal of neuronal damage induced by novel α SYN lowering drugs. From previous studies, we expect that including 10 rats per group is sufficient to detect statistically significant differences by microPET, therefore we will use 10 rats in each group for each of the two timepoints (assuming that same rats can be PET + MRI scanned). In all rats, the non-lesioned side of the brain will be used as an internal control.

The Aarhus PET Center has extensive experience in modeling Parkinson's disease in minipig (MPTP and proteasome inhibition). In order to establish a novel α SYN overexpression model in minipig, the following experimentally-induced synucleinopathy animal model will be used:

Adeno-associated viral vectors containing human wild type α SYN or green fluorescent protein will be injected into the right substantia nigra of Göttingen minipigs. The initial pilot study using 6 minipigs (4 α SYN and 2 GFP) will focus on the viral delivery parameters for optimal expression of the transgene in the target dopamine neurons. After 4-6 weeks, minipigs will be perfused with 4% paraformaldehyde and the brain quickly removed for histology in order to test the injection coordinates and whether the transduction in the target area was successful. Further longitudinal behavioural and brain imaging studies using PET and MRI techniques will be performed in an additional 16 minipigs (8 α SYN and 8 GFP) in order to assess disease progression and response to α SYN lowering drugs. We previously have found that a sample size of 8 minipigs per group was sufficient to detect significant differences between groups. PET and MRI studies will be performed as described above for rat, but using a Siemens PET/CT for PET scans and a Bruker 3.0 Tesla scanner for MRI studies. The non-lesioned side of the brain will be used as an internal control. Once the unilateral substantia nigra α SYN overexpression model is established and validated in minipig, additional animals may be required to perform studies in which α SYN is injected into the striatum, cortical areas, or bilaterally into both sides of the substantia nigra in order to induce different pathology.

The virus surgeries will be done in a Class II facility available at the Aarhus University Farm (Påskehøjgård Centeret). The surgical tools and waste will be autoclaved. All surfaces in the surgery table will be cleaned with 2x virkon solution. The animals may shed viral particles for up to 48 hours after surgery and thus the bedding will also be autoclaved before disposal. After surgery, minipigs and rats will be housed in an appropriate facility for genetically modified animals.

All experiments will first be approved and then monitored and regulated by The Danish Animal Experimentation Inspectorate. Animals will be monitored daily by an animal technician and a veterinarian will provide weekly assessments of the animals. Rats and minipigs will be deeply anesthetized during all surgical and scanning procedures and will receive antibiotics or analgesics as needed after surgery. Whenever possible, animals will be used as their own controls in order to reduce the number of animals used in this study. Humane endpoints include weight loss of over 10% body weight, bleeding complications or signs of hypoxia under anesthesia.

Rat and pig experiments will be performed in accordance with the Danish Animal Experimentation Act and EU legislation.

Partner 7 MODAG (GER): It was estimated that an amount of about 200 mice will be housed and used for the whole project.

The following mouse models will be used: A30P- α SYN transgenic mice (Thy1-promotor, Kahle et al., Am J Pathol 2001, 159: 2215-25)

Experiments involving animals have been approved by the local committee for animal experiments. Approvals for similar types of experiments have already been obtained (AZ 209.1/211-2531-66/04, 55.2-1-54-2531-32-08, AZ 33.42502-056/06)

6. Conclusions

As outlined in this report a number of ethical issues have identified in the current research project. Each of these issues has been addressed by the project teams to ensure the maximum ethical compliance.

Ethical approval for the work being done in MultiSyn has been received by all partners.

The project teams will continually refer to the ethics guidelines and recommendations set out in the DoW of MultiSyn.

Appendix 1: Confirmation by all relevant MultiSyn partners to comply with ethical regulations

Confirmation of receipt of favourable opinions of the relevant ethics committee and the regulatory approval of the respective competent national or local authority in case such opinions or approvals are required

Herewith I confirm that the research work planned in the MultiSyn project (602646) – funded under the 7th FP of the EU – in work package 1, 2 and 3

has received favourable opinions of the relevant ethics committee and the regulatory approval of the respective competent national or local authority in case such opinions or approvals are required.

Copies of the ethical approvals will be provided to the MultiSyn coordinator for submission to the European Commission.



Signature

Date 1. Oktober 2013

Signatory name: Thomas Gasser

Partner name: EKUT

Confirmation of receipt of favourable opinions of the relevant ethics committee and the regulatory approval of the respective competent national or local authority in case such opinions or approvals are required

Herewith I confirm that the research work planned in the MultiSyn project (602646) – funded under the 7th FP of the EU – in work package 2

has received favourable opinions of the relevant ethics committee and the regulatory approval of the respective competent national or local authority in case such opinions or approvals are required.

Copies of the ethical approvals will be provided to the MultiSyn coordinator for submission to the European Commission.



LUNDS UNIVERSITET

Signature and Stamp

Dec 2, 2013

Date

Deniz Kirik

Signatory name:

Partner name:

ULUND

Confirmation of receipt of favourable opinions of the relevant ethics committee and the regulatory approval of the respective competent national or local authority in case such opinions or approvals are required

Herewith I confirm that the research work planned in the MultiSyn project (602646) – funded under the 7th FP of the EU – in work package 2

has received favourable opinions of the relevant ethics committee and the regulatory approval of the respective competent national or local authority in case such opinions or approvals are required.

Copies of the ethical approvals will be provided to the MultiSyn coordinator for submission to the European Commission.

Signature and Stamp



Date 25/03/14 Signatory name: PROF. GREGOR K. WENNING

Partner name: INNSBRUCK MEDICAL UNIVERSITY

UNIVERSITÄTSKLINIK für NEUROLOGIE
Vorstand: Univ.-Prof. Dr. Werner Poewe
Neurologische Ambulanz
A-6020 Innsbruck, Anichstr. 35
Tel.: 0512/504-24239, Fax: 0512/504-23880

Confirmation of receipt of favourable opinions of the relevant ethics committee and the regulatory approval of the respective competent national or local authority in case such opinions or approvals are required

Herewith I confirm that the research work planned in the MultISyn project (602646) – funded under the 7th FP of the EU – in work package 2 and 3

has received favourable opinions of the relevant ethics committee and the regulatory approval of the respective competent national or local authority in case such opinions or approvals are required.

Copies of the ethical approvals will be provided to the MultISyn coordinator for submission to the European Commission.

A handwritten signature in black ink, appearing to read 'L. Stefanis', is written over a horizontal line. The signature is stylized and cursive.

Signature and Stamp

Date 1. Oktober 2013

Signatory name: Leonidas Stefanis

Partner name: BRFAA

Confirmation of receipt of favourable opinions of the relevant ethics committee and the regulatory approval of the respective competent national or local authority in case such opinions or approvals are required

Herewith I confirm that the research work planned in the MultISyn project (602646) – funded under the 7th FP of the EU – in work package 2

has received favourable opinions of the relevant ethics committee and the regulatory approval of the respective competent national or local authority in case such opinions or approvals are required.

Copies of the ethical approvals will be provided to the MultISyn coordinator for submission to the European Commission.



Signature and Stamp

Date November 8th Signatory name: Anne Landau

Partner name: Aarhus (David Brooks)

Confirmation of receipt of favourable opinions of the relevant ethics committee and the regulatory approval of the respective competent national or local authority in case such opinions or approvals are required

Herewith I confirm that the research work planned in the MultISyn project (602646) – funded under the 7th FP of the EU – in work package 2

has received favourable opinions of the relevant ethics committee and the regulatory approval of the respective competent national or local authority in case such opinions or approvals are required.

Copies of the ethical approvals will be provided to the MultISyn coordinator for submission to the European Commission.



Signature and Stamp

Date 2.10.13 Signatory name: Armin Giese

Partner name: MODAG GmbH