COST

Domain Committee BMBS

Start date:05/06/2007

End date:04/06/2011

COST Action BM 0604

Myelin Orphan Diseases in Health
MYELINET

FINAL REPORT

MYELIN ORPHAN DISEASES
IN HEALTH – COST BM 0604

Summary :
The objective of the Action was to better understand and fight orphan diseases affecting the CNS nerve-insulating myelin such as inherited leukodystrophies for further applications to myelin repair in more common myelin diseases (premature, multiple sclerosis). The diversity of causative genes and the rarity of each individual disease led to establish a coordinated and multidisciplinary approach. The 84 individual participants from 20 European or associated countries involved in the Action include representatives of affected patients and their families, experts in medical ethics, clinicians, neuroscientists and SME in information system and biotherapy. For this purpose, the Action supported yearly patients-researchers meetings, various working groups workshop as well as two European or international open research meetings including 36% Early Stage Researchers or medical doctors. The main innovative knowledge and scientific breakthroughs were defining (a) the organisation of an European database devoted to leukodystrophies, (b) the animal models for preclinical trials (b) the omics strategies for disease biomarkers, (c) the common pathological pathways involved in the neurodegenerative process observed in all leukodystrophies, (d) the viral vectors and cells suitable for gene and cell therapy, (e) ethical issues in research for rare diseases at an European level. Actions with the Neurinfnet COST Action allowed interfaces for multiple sclerosis. Collaborative recommendations or results were included in 68 joints publications. The dynamic and multidisciplinary expertise of Action participants allowed to obtain, a FP7 medium scale support on the call HEALTH-2009-2 *Rare neurological diseases,* named “Therapeutic challenge in leukodystrophies: translational and ethical research towards clinical trials” (LEUKOTREAT).

I. Management Report

I.A. COST Action Fact Sheet

COST Action *BM0604- Myelin orphan diseases in health*
- **Domain: BMBS**

- **Action details:**

CSO Approval: 20/11/2006 **End date:** 04/06/2011
Entry into force: 07/02/2007

- **Objectives**

The main objective of the Action is to promote a scientific and medical interactive European effort in the multidisciplinary field of myelin-related pathologies in order to develop new therapeutic strategies for the largest number of patients**.**

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

Country	Date	Status
Austria	07/02/2007	Confirmed
Belgium	08/06/2007	Confirmed
Cyprus	27/02/2007	Confirmed
Denmark	07/02/2007	Confirmed
France	06/02/2007	Confirmed
Germany	07/02/2007	Confirmed
Israel	07/02/2007	Confirmed
Italy	22/05/2007	Confirmed
Norway	12/06/2007	Confirmed
Poland	26/02/2007	Confirmed
Spain	07/02/2007	Confirmed
Switzerland	17/12/2007	Confirmed
United Kingdom	07/02/2007	Confirmed

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Action Web site: http://www.myelinet.fr/

Working Groups

WG1: Characterizing white matter diseases for therapies

WG2: Biomarkers for leukodystrophies treatment

WG3: Innovative gene and cell therapies in leukodystrophies

WG4: Ethical impacts of therapeutic challenges in leukodystrophies

And Pharmacological strategies to treat leukodystrophies" (WP1 and 3)

I.B. Management Committee member list

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I.C. Overview activities and expenditure

2008

Meeting Type	**Date**	**Place**	**Cost**	**Total**
Management Committee	05-juin-2007	Brussels (BE)	8454,22	
Management Committee	28-mars-2008	Paris (FR)	4185	
				12639,22

Schools

Type	Date	Place	Cost	Total
SCHOOL_LECTURERS	19-nov-07	Alicante (ES)	1046	
SCHOOL_ORGANISER	19-nov-07	Alicante (ES)	800	
SCHOOL_STUDENTS	19-nov-07	Alicante (ES)	600	
				2446

2009
Meetings

Meeting Type	**Date**	**Place**	**Cost**	**Total**
MC/WG	06-juin-2008	C.Ferrand(FR)	34362,47	
Working Group	25-sept-08	Paris (FR)	5147,77	
In conjunction with Conference	28-mars-2009	Paris (FR)	9466,57	
				48976,81

Workshop support

Title	Date	Place	Cost	Total
First Myelinet Workshop	06-juin-2008	Clermont-Ferrand (FR)	3.000	
MC Myelinet and Family Research	28-mars-2009	Sevres (FR)	3.000	
				6.000

General Support Grants

Title	Date		Cost	Total
General	22-sept-08		2.000	
				2.000

Meetings

Meeting Type	**Date**	**Place**	**Cost**	**Total**
In conjunction with Conference	25-juin-2009	Luxembourg (LU)	39142,22	
Working Group	07-sept-09	Paris (FR)	3103,81	
In conjunction with Conference	08-sept-09	Paris (FR)	40143,64	
Management Committee	18-mars-2010	Paris (FR)	22971,06	
				105360,7

STSM

Beneficiary	Date	From	Cost	Total
Dr Vanja Tepavcevic	04-juil-2009	Paris (FR)	908	
Ms Christina Fenger	16-mai-2010	Odense (DK)	689	
				1.597

Workshop support

Title	Date	Place	Cost	Total
Joint event with euroglia 2009	08-sept-09	Paris (FR)	3.000	
Leukotreat	18-mars-2010	Paris (FR)	2.190	
				5.190

2011
Meetings

Meeting Type	**Date**	**Place**	**Cost**	**Total**
Working Group	27-sept-10	Paris (FR)	8134,06	
Workshop	09-nov-10	Burgos (ES)	13484,52	
Final Conference	23-mai-2011	Paris (FR)	21610,22	
				43228,8

STSM

Beneficiary	Date	From	Cost	Total
Dr Mélina BEGOU	04-janv-2011	Clermont-Ferrand (FR)	1460	
				1.460

Workshop support

Title	Date	Place	Cost	Total
Final Conference	23-mai-2011	Paris (FR)	1.800	
				1.800

Total: 230698,6

II. Final Scientific Report

II.A. Innovative networking

The objective of the Myelinet networking was to develop actions in order to understand and fight orphan diseases affecting CNS nerve insulating myelin (leukodystrophies, LDs) for further applications to myelin repair in more common myelin diseases (premature, multiple sclerosis) by (1) Identifing the cause and explore the pathological pathways (WG1), (2) Discover novel biomarkers to act as diagnostic/prognostic tools or drug targets (WG2), (3) Promote drug development and innovative therapeutic strategies (WG3), (4) Debate ethical and societal implications and concerns of results and assure their scientific dissemination (WG4)

1. Innovative knowledge and scientific breakthroughs

The specificity and success of the COST Actions was to stimulate interactions at the European level: (1) from patients to fundamental researchers through annual meetings between patients and researchers, (2) from ethical to therapeutic issues for LDs through WG and larger meetings between members of the ethical committee, clinicians, molecular, cellular as well as biochemical neuroscientists, (3) from orphan genetic to non genetic myelin diseases through European or international open meetings.

The main innovative knowledge and scientific breakthroughs for each WG were very productive

<u>WG1</u>

- defining at the European level the establishment and organisation of a common database (DB). Three WG1 meetings were specifically organized for this purpose. Meetings related to the implementation of the European LeukoDB in term of ethical issues, sharing clinical data, biological samples, and information systems as well are definition of common dataset.
- defining the actions for the main objectives of the DB (i) better knowing the natural history of each group of leukodystrophies, (ii) analysing phenotype-genotype correlation, (iii) establishing a biobank.
- defining common physiopathological mechanisms which lead to brain dysfunctions in LDs. The role of oxidative stress has been demonstrated for adrenoleukodystrophy (ALD) (publication) and is now investigate for two other groups of LDs with success through the COST actions
- optimizing innovative researches on glutamate receptors on glial cells (publication) for the physiopathology of LDs
- cooperating for the LDs with an undetermined cause allowed to identify new phenotypes, new genes (see publications)

<u>WG2</u>

- defining biomarkers for two groups of LDs (PLP1 and EIF2B related diseases) for investigation in a larger group of patients through the biobank created
- optimizing metabolomic analysis in order to screen markers of redox proteomics and lipidomic.

<u>WG3</u>

- defining the pharmacological strategies as well as the innovative cell and gene therapies to be develop in order to be applied for the largest number of LDS
- optimizing knowledge on the biology of myelinating cells for cell therapy in inborn error of myelin formation
- optimizing vectors able to target myelinating cells: success story for ALD gene therapy in human, preclinical trials established for MLD, new promising”oligodendrocyte target vector”

<u>WG4</u>

- establishing an ethical comity helping to define the LeukoDB charter for users as well as a common consent form for clinical as well as biological data as the result of two specific meetings

- defining a research program in ethic for LDs in order to determine the impact of the emerging innovative therapies on patients expectations and the development of the patient as actor of its own research

2. Socio economic and projects impacts

- increasing the number of European families having access to a genetic counsel in LDs
- improving the severe handicap related to LDS by preventive (as demonstrate with ALD) or curative therapeutic approaches
- involving patients and their families in the disease knowledge and as actor of the research
- ethical debate at the European level on common patient consent, database users chart, impact of innovative therapy.

3. Spin off of new EC RTD FP and/or National Programme proposals

- The dynamic and multidisciplinary expertise of COST participants allowed to obtain a FP7 medium scale support on the call HEALTH-2009-2.4.4-1 *Rare neurological diseases,* named "Therapeutic challenge in leukodystrophies: translational and ethical research towards clinical trials" (LEUKOTREAT). This three years project support researches of the COST participants who developed in vitro or in vivo models of known forms of lLDs. In this project, the COST support the meetings keeping a central role for the development and diffusion of the European leuko databases (LDB), scientific interactions, dissemination of knowledge and interactions with patients and families organization. The Leukotreat contract start in March 2010 according to the five directions (Work package, WP) defined in 2008 and 2009 by the COST working groups : "Characterizing white matter diseases for therapies" (WP1), "Biomarkers for leukodystrophies treatment"(WP2) , "Pharmacological strategies to treat leukodystrophies" (WP3), "Innovative gene and cell therapies in leukodystrophies".(WP3), "Ethical impacts of therapeutic challenges in leukodystrophies"(WP4)
- Proposal for the E Rare 2011 call for proposals have been submitted including 3 COST partners
- The cooperation for LDs with an undetermined cause allowed to develop a "push project" of the ELA foundation involving 8 COST Partners (in Italy (2) France(3),Lebanon(1) and Tunisia(2))
- The expertise acquired in the field of database for research in orphan disease stimulated interactions for new FP7 call for proposition in the field of rare diseases
- Cost partners reinforced their national actions on rare diseases through their involvement in Myelinet particularly in France (national label of reference centre for rare disease for 2 cooperating partners), in Germany (renewal of the financial support for Leukonet), in Italy (cooperative network) and in Spain (support of family and medical doctors national actions)

II.B. Inter-disciplinary networking

The COST Myelinet Action is by definition an interdisciplinary networking from fundamental research to patients. The COST project has initiate for the first time a coordinated action toward a large heterogeneous group of orphan neurodegenerative disorders involving the brain white matter

The originality of the Myelinet COST actions were to create an interface not only between clinicians in charge of LD patients and researchers in the field of molecular, cellular and biochemical approaches but also between clinicians / researchers and patients and their family.
This multidisciplinary within the same WG and within the different WG was very fruitful as shown in the example done in II.A particularly
- creating an information system able to register and interface data coming from different sources
- accelerating and optimizing the test of innovative therapeutic strategies by choosing "a model of LDs" and multiplying the approaches
- organizing patients and families-Myelinet researchers meetings allow to stimulate ethical debates and the creation of an ethical comity and specific research projects in ethics

This inter-disciplinary networking stimulate Cost partners to participate to
- the Neurinfnet COST program (Myelinet vice chair). The Neurinfnet and Myelinet actions organize and support different symposia and one training school at the Euroglia Paris meeting in September

2009 (Myelinet vice chair was the president of the organizing committee)
- the European Union Committee of Experts on Rare Disease (EUCERD) Workshop , 8th -9th December 2010, Luxemburg (chair)

II.C. New networking

1. Additional new participants join our Action during the whole action time. A new SME (Trophos) have been included due to the potential remyelination of their molecules (French ANR project on multiple sclerosis perform in collaboration with COST institutional lab)

2. Total number of individual participants involved in the Action work was 84 including 48% of female and 30 Early Stage Researcher or Medical Doctors participants.

3. Early Stage Researchers represent 36% of the participants involved in the Action. All are responsible of specific research programs of the COST.
Due to the multidisciplinary approach of our actions we support two types of training schools
- Fundamental knowledge of white matter and myelin organized each year by S Martinez (Spain) for mice models and during the Euroglia meeting.
- Practical knowledge to recognize and treat LDs *organized as an experimental initiative with ELA Spain.* The four training sessions *"MRI recognition pattern of leukodystrophies*" were particularly appreciated. Identical initiative through Europe will be encouraged.
The action supports less than four STSMs per year due to the difficulties related to the COST rules (number of days, no payment in advances). The actions supported were mainly to learn lab technics.

4. Myelinet involved 8 researchers from outside of COST Countries (4 from Tunisia, 3 from Turkey, one from Lebanon) representing 10 % of participants from countries with reciprocal agreements. Their contribution is important for the clinical (4 researchers) and molecular (5 researchers) aspects of LD. Identification of new genes involved in LDs have been accelerated by a collaborative work with Lebanon in LD with Hypodontia and Tunisia (whole genome analysis of 32 consanguineous families). Collaboration with Chili by the Chair have been pursue in November 2010. Collaboration with Egypt has been initiated through a specific support from the French/Egypt Foreign ministries. Large collaborations with Japan, USA and Australia have been pursue

5. During the actions, the Myelinet participants has published in the field of the COST action a total of 293 original publications and 68 reviews/books including collaborative recommendations. 66 were joints publications.

6 The capacity of the Action members to raise research funds is particularly fruitful at national and European levels. In rare disease as LDs projects at European level are particularly encouraged

II.D. Self evaluation

Myelinet was a challenging COST action due its field in a heterogenous group of orphan diseases with the rarity of each individual disease and the multidisciplinary of partners including patients and families association. The main success was to perform coordinated actions despite the diversity of disease cause and partners. The action provides to Europe a better visibility in the field of orphan myelin diseases for researchers, medical doctors and families associations with national and international outcomes. The dynamic created through the COST action allowed finalizing a specific FP7 Heath call proposals for rare neurological disorders with the objective to develop therapeutical trials for LDs of known cause (LEUKOTREAT). The organisation of two open meetings, one specifically devoted to white matter diseases (Myelinet – ELA Workshop, Luxemburg) and the second associated with the European meeting devoted to glial cells (Euroglia, Paris), stimulated the Action toward more common white matter diseases and fundamental research on the biology of glial cells. However, the impact of these broader actions remains difficult to evaluate and was particularly difficult to organize due to the COST rules without planned budget

each year. We discover during the last trimester 2010 that the budget allocated for the final meeting was too short for an open meeting. Supports of the COST for STSM exchanges within partners remain not currently used by partners despite large information done by the Myelinet Chair and scientific officer due to the COST rules (particularly restrictions concerning the minimal and maximum number of days, no payment in advance). For budget reasons, training schools were organized as associated actions with a limited number of days. The last organized with the ELA-Spain family association was limited to almost 2 very active full days in order to limit the budget. Actions of dissemination toward website were also very restricted. Again the budget allocated for support was difficult to obtain and very small. During the last two years, we focused our Action toward coordination of the therapeutic challenges included in the LEUKOTREAT project. This issue has reinforced the innovative knowledge and scientific breakthroughs of our Action toward for therapeutic trials for LDs of known cause but decreased the participation of Myelinet members outside the FP7 project for broader open actions. Plan of actions was particularly difficult to manage in absence of defined budget and with the changes in COST management during the last year.

Previous Scientific Reports

II. Scientific Report

II.A. Innovative networking achieved in 2010

During this year, the aim of our Myelinet network was to coordinate the development of therapeutic trials in the inherited forms of white matter disorders and the identification of new molecular diagnostic markers.

II.A.1.Therapeutic approaches of known forms of leukodystrophies: "Leukotreat"

The dynamic and multidisciplinary expertise of COST participants allowed us to obtain a FP7 medium scale support on the call HEALTH-2009-2.4.4-1 *Rare neurological diseases,* named "Therapeutic challenge in leukodystrophies: translational and ethical research towards clinical trials" (LEUKOTREAT). This three year project support researches of the COST participants who developed in vitro or in vivo models of known forms of leukodystrophies. In this project, the COST support the meetings keeping a central role for the development and diffusion of the European leuko databases (LDB), scientific interactions, dissemination of knowledge and interactions with patients and families organization (see Annex I)

The Leukotreat contract start in March 2011 according to the **five directions** defined in 2008 and 2009 by the COST working groups
"Characterizing white matter diseases for therapies" (WP1)
"Biomarkers for leukodystrophies treatment"(WP2)
"Pharmacological strategies to treat leukodystrophies" (WP1 and 3)
"Innovative gene and cell therapies in leukodystrophies".(WP3)
"Ethical impacts of therapeutic challenges in leukodystrophies"(WP4)

The Kick off meeting (Paris, March 18-19 2010) supported by the COST established three important tasks for the year 2010

- *Task 1: Scientific interactions between COST partners of the different work package*. The proof of concept of innovative therapeutic strategies is tested by one of the partners in one type of LDs and applied eventually to other LDs through the network. For example, the proof of concept of a human gene therapy in neurodegenerative disease published by a COST partner for adrenoleukodystrophy (Science 2009) will be tested for other LDs by 3 COST partners.
- *Task 2: Establishment of European Leukodystrophies database (EU-LDB*) according to the COST specifications: (a) creation of three leuko reference centres (LeucoRC) with a specific area of expertise (France for clinical research and molecular biology, Italy for Neuroimaging and bioinformatics, Germany for epidemiology and biochemistry), (b) nomination of coordinators for each large group of leukodystrophies (Peroxisomes-

lysomes; hypomyelinating leukodystrophies, cavitating leukodystrophies) and each gene involved in leukodystrophies, (c) inclusion of a common core of specifications for leukodystrophies and their genes
- *Task 3: Creation of an ethical committee* in order to establish (a) the LDB chart at European level, (b) a common patients consent, (c) specific researches in ethical issues

A specific meeting between the ethical committee and COST partners of EU-LDB has been held in Paris the 27-28 September 2010 with the COST support. The LDB chart (see annex II) has been validated by all partners.

A complementary meeting restricted to the COST partners of EU-LDB has been held in Burgos November the 11th 2010 after the medical training school organized with ELA-Espagna and the COST support (November 10th and 11th). The common core of specifications have been finalized (see annex III)

II.A.2.Identification of new forms of leukodystrophies

This innovative networking was stimulated in 2010 by three different actions involving 2009 new Myelinet participants

- Specifications of the EU-LDB for undetermined leukodystrophies (Burgos November 11th 2010)
- Cooperation in the field of adult forms of autosomique dominant leukodystrophies linked to the 5q region coordinated by Alfredo Brusco (Dept. of Genetics Biology and Biochemistry University of Turin Torino, Italy) and Pierre Labauge (coordinator of the LeukoFrance for adult LDs, Dept of Neurology, Montpellier-Nimes University, France) (see publications annex IV)
- Cooperation in the field of hypomyelinating LDs associated with hypodontia initiated with André Megarbane (Unité de Génétique Médicale , Faculté de médecine, Université Saint Joseph, Beirut, Lebanon) allowed to identify the chromosomal localisation (see publications annex IV) and the gene involved (under publication)
- Cooperation in the field of innovative strategies to identify new genes involved in leukodystrophies through a “push project” of the ELA foundation involving 8 COST Partners (in Italy (2) France(3) , Lebanon(1) and Tunisia(2)

II.B. Inter-disciplinary networking

The COST Myelinet Action is already a very interdisciplinary networking. In 2010, COST participants organized:

- Patients and families-Myelinet researchers meeting: Paris-Sevres: March 29th 2010 www.ela-asso.com (summary in ELA infos suppl june 10)
- Myelinet medical training for leukodystrophies: , “*Diagnostic and Therapeutic approaches in Leukodystrophies*”, Burgos , November 9-10-11th 2010 (www.ela-espana.com, program and report enclosed). The meeting have been host in the Centro de Referencia Estatal de Atención a Personas con Enfermedades Raras y sus Familias (Creer) (www.creenfermedadesraras.es)

and participated to
- the Neurinfnet COST program meetings (vice chair)
- the European Union Committee of Experts on Rare Disease (EUCERD) Workshop , 8th -9th December 2010, Luxemburg (chair)

II.C. New networking

1. A new UK member intend to join our Action in August 2010
Christopher Proud,School of Biological Sciences, Life Sciences Building, University of Southampton, Southampton, UK

2. Total number of individual participants involved in the Action work is now 84 including 48% of female and 30 Early Stage Researcher or Medical Doctors participants.

3. Early Stage Researchers represent 36% of the participant involved in the Action. All are responsible of specific research programs of the COST..
- *A two days training school* have been organized for young medical doctors and post doc in Burgos with the COST support in order to stimulate knowledge to recognize and treat LDs. This initiative was also supported by ELA-Espana in order to stimulate cooperation of Spanish MD with European expert in the field. The four training sessions *"MRI recognition pattern of leukodystrophies*" were particularly appreciated. Identical initiative through Europe must be encouraged.
- *Two STSMs supported by the COST were carried out during the year.*

° the STSM Application of Chritina FENGER, Neurobiology Research Institute of Molecular Medicine, University of Southern Denmark (DK) has been supported by the COST action in order to learn the technique "combined *in situ* hybridization (ISH) and immunohistochemistry on paraffin tissue" in May *2010.*The host institute was Prof. Tanja KUHLMANN, Institut für Neuropathologie, Universitätsklinikum Münster, Münster (Germany)

°The STSM application of Dr Melina BEGOU, Inserm UMR 931, Clermont-Ferrand France on analyses of mouse models of the leukodystrophy Pelizaeus-Merzbacher Disease (PMD) have been accepted for a COST support in January 2010 The Host Institute will be the Max Planck Institute Gottingen (K Nave). The project allows comparing existing and novel transgenic PMD models in order to determine which is the most relevant for which type of PMD for therapeutic trials.

4. Myelinet involved 8 researchers from outside of COST Countries (4 from Tunisia, 3 from Turkey, one from Lebanon) representing 10 % of participants from countries with reciprocal agreements. Their contribution is important for the clinical (4 researchers) and molecular (5 researchers) aspects of LD. Identification of new genes involved in LDs have been accelerated by a collaborative work with Lebanon in LD with Hypodontia and Tunisia (whole genome analysis of 32 consanguineous families). Collaboration with Chili by the Chair have been pursue in November 2010. Collaboration with Egypt has been initiated through a specific call. Large collaborations with Japan and USA have been pursue

5. During 2010, the Myelinet participants has published a total of 140 original publications and 39 reviews/books including collaborative recommandations. Twenty three are signed by at least 2 COST participants (see publications annex IV).

6 The capacity of the Action members to raise research funds is particularly fruitful at national and European levels. Four European new networking have been supported or initiated for support through the COST program

- "Innovative strategies to identify new genes involved in leukodystrophies", call 2010 foundation ELA, international level. Four Cost participants supported (Tunisia, Lebanon, France, Italy)
- "Classification of LD with an adult onset" (LeukoFrance) coordinated by Pierre Labauge, Montpellier-Nimes University involving the different reference centres for Multiple Sclerosis, adult neurogentic and inherited vascular diseases in France. The COST network allowed stimulating collaborative research with Italy (Torino) and training (Burgos training school participants).
- "Thyroid hormones transport by oligodendrocytes", call 2010, Jerome Lejeune Foundation. Two Cost participants supported (France and Netherlands)
- "Physiopathology of EIF2B related disorders", call 2010, E Rare. Four Cost participants (France, Italy, Germany, England)

II.C. Self evaluation

Main successes are the very active, multidisciplinary interactions existing within the Myelinet COST participants including patients organizations. Myelinet actions provide to Europe a strong

position in the field of inherited White Matter diseases and allow obtaining a FP7 support with the objective to develop therapeutical trials. During this year, we focused our actions toward coordination of Myelinet participants to these therapeutic challenges. Meetings related to the implementation of the European LeukoDB in term of ethical issues, sharing clinical data, biological samples, and information systems as well are training of medical doctors in Europe were our priority and allowed to obtain the consensus needed.

The final COST meeting will be mainly devoted to the main results obtained in developing therapeutical challenges in inherited White Matter diseases and their dissemination.

II. Scientific Report

II.A. Innovative networking achieved in 2009

We focus our attention on the individually rare forms of white matter disorders, the leucodystrophies (LDs) in order to stimulate the development of therapeutic trials in coordination with the patients associations at the European level.

For this purpose, transversal actions based on the multidisciplinary expertise of COST participants have been made by the working groups through four important workshops and meetings organized by the Myelinet COST participants according to the five directions defined last year

"Characterizing white matter diseases for therapies" (WP1)
"Biomarkers for leukodystrophies treatment" (WP2)
"Pharmacological strategies to treat leukodystrophies" (WP1 and 3)
"Innovative gene and cell therapies in leukodystrophies".(WP3)
"Ethical impacts of therapeutic challenges in leukodystrophies"(WP4)

"Characterizing white matter diseases" (WP1, coordination Enrico Bertini, Italy)
During a one day meeting the 7th of September we have established a working plan to establish the European Leukodystrophies database. In a first approach the existing databases in France, Germany, Italy (clinical databases, biobank and mutation database) will be connected in coordination with the Information Systems of the SME Soluscience involved in the Myelinet network. Each of this three leuco reference centre (LeucoRC) will have a specific area of expertise (France for clinical research and molecular biology, Italy for Neuroimaging and bioinformatics, Germany for epidemiology and biochemistry). In a second approach, the others countries will be connected through these 3 LeucoRC according to their geographical localization. A coordinator for each large group of leukodystrophies (Peroxisomes-lysomes; hypomyelinating leukodystrophies, cavitating leukodystrophies) have been defined. Specifications corresponding to each group of leukodystrophies and to each gene involved in leukodystrophies will be established by each partner for a meeting expected in March 2010
DNAs have been exchanged through partners (Italy, Germany, and France) in order to define new genes involved in leukodystrophies. Different candidate genes have been defined after discussions concerning gene functions, transgenic mice phenotype during the March and July meeting. After the march meeting, two new partners have been included, one in Italy and one in Lebanon

"Biomarkers for leukodystrophies treatment"(WP2, coordination Aurora Pujol, Spain)
Two types of actions have been done
- Defining the specificity and significance of biomarkers already identified.
We focus our work on the eIF2B GEF activity for the eiF2B related leukodystrophies and NAAG in hypomyelinating leukodystrophies. Further samples have been obtained through the COST partners to confirm the interest of this marker. For the eIF2 GEF activity, collaboration through the COST (UK partner) will allow the innovative synthesis of a synthetic eIF2 substrate in yeast instead of those extracts from the rat liver not suitable for routine lab purpose.
Through the COST collaboration we will also test the role of NAAG in inherited disorders of leukodystrophies using patients' biological fluids. Two UK COST partners are testing the role of this molecule on oligodendrocytes function (Luxembourg ELA meeting)
- identifying new biomarkers: new approaches using lipidomic (LL partners) and glycome (France partner) in LD have been discussed and established due to the role of glycoproteins in cell

interactions within the white matter and of lipids in myelin production and stability.

"Pharmacological strategies to treat leukodystrophies" (WP1 and 3, coordination Hawke Werner, Germany)
The improved understanding of the pathophysiological pathways causing LDs that has been gained in the past few years by the different COST partners offers new entry points to design rational pharmacological treatment attempts. Several partners are closely interconnected by existing collaborations, as demonstrated by previous joint publications. Technical expertise will be collaboratively shared in evaluating therapy efficacy, and successful approaches will be applied to other LDs with related pathophysiology.
Different collaborative actions have been settled in order to test pharmacological therapies *in vitro* and *in vivo* models of prototypic LDs
- Cholesterol-derivatives for remyelination and neuroprotection in LD (COST partner Trophos)
- Anti-oxidative and anti-inflammatory dietary supplement
- Release of misfolded proteins
- Enhancement of translation
- Modulation of specific gene expression or enzyme replacement

"Innovative gene and cell therapies in leukodystrophies".(WP3, coordination Patrck Aubourg, France)
COST partners participated to the effort to demonstrate the potential of cell and gene therapy in LDs. Phase I/II clinical trials based on the combination of gene and cell therapy, using hematopoietic stem cells (HSC) and lentiviral vectors (LV) in ALD and MLD have been initiated. First results of this gene therapy in three ALD affected patients seem very promising. During the COST Luxembourg meeting, our objectives have been to intensify this effort in order to:
- Pursue and interpret the on-going clinical trials using HSC and LV for ALD and MLD in a coordinated way, for further application to other LDs;
- Unravel the mechanisms of disease correction of the LD brain by studying microglia reconstitution after transplantation;
- Test the feasibility and therapeutic potential of a) direct gene delivery to the brain by using intracerebral injection and novel viral vectors with glial tropism; b) gene silencing approaches specifically targeting OLs; c) Neural Steam Cells- or microglia precursor-based approaches to treat LDs.

"Ethical impacts of therapeutic challenges in leukodystrophies"(WP4, coordination Gregoire Moutel, France)
Research in medical ethics aims, at the international level, at better understanding patients' needs and health care professionals' duties related to the progress made in biomedical research, technology and information systems. The Laboratory of Medical Ethics and Forensic Medicine (Gregoire Moutel, Paris V) involved in the COST project have defined two objectives:
1) To identify patients' expectations towards the research project and to establish appropriate answers which can be brought to them concerning their participation and communication during the research project.
2) To study how patients may produce a useful knowledge for scientific purpose.
These issues have been settled during the two meetings organized in collaboration with the European Leukodystrophy family association (ELA) in Paris (March 2009) and Luxembourg (July 2009). Exchanges have been initiated with other family associations devoted to LDs in Europe (UK, Italy, Germany) during the Luxembourg meeting

Dissemination of knowledge have been particularly active during this year through the different meetings organized with the COST support
- In March 2009 (Paris) for information of patients and their families affected by LDs
- In July 2009 (Luxembourg) for medical doctors and researchers involved or interested to be involved in LDs
- In September 2009 (Paris) for researchers more generally interested in glial cells and their disorders

The medium scale proposal presented by the Myelinet COST partners to answer to the European

Commission Call for proposals HEALTH-2009-2.4.4-1 *Rare neurological diseases,* in December 2008, named "Therapeutic challenge in leukodystrophies: translational and ethical research towards clinical trials" (LEUKOTREAT) have been accepted. This success demonstrates the dynamic of the COST Myelinet project to elaborate collaborative studies. In this project, the COST network will keep a central role for the development and diffusion of the European leuko databases, dissemination of knowledge, interactions with patients and families organization.

II.B. Inter-disciplinary networking

The COST Myelinet Action is already a very interdisciplinary networking. The meetings organized were very interactive and multidisciplinary in the field of myelin diseases as well as biology of glial cells and exchanges with patients – families associations
This interdisciplinary approach has been particularly reinforced this year in two fields
- Neuroinflammation of the white matter. Cooperative actions with the Neurinfnet COST program allowed organizing the Euroglia meeting held in Paris in September 2009 with the COST support of both the MYELINET and NEURINFNET. Three Myelinet members participated to the international translational program devoted to treatment of multiple sclerosis "Cellular and Molecular therapies for Myelin Repair and Axonal Loss in MS" included
- Ethic and social impacts of LDs. A specific research program on the impact of innovative treatments in LDs has been elaborated with the COST partners and different research groups in the field of medical ethic and law. Two Myelinet COST meetings have involved European family associations devoted to LDs. Cooperation between the Belgian, German and French associations have been particularly active.

II.C. New networking

1. Additional new members have joined the Action this year through the different meeting organized allowing the development of new scientific program
   - *Dept. of Genetics Biology and Biochemistry University of Turin Torino, Italy (Alfredo Brusco) in the field of the molecular biology of LDs*
   - *Gaslini Institute, Genova, Italy (Mirella Filocoma, Roberta Bianchiri, Federico Zara) in the field of the molecular biology of LDs*
   - *Adolf-Butenandt-Institut, University of Munich, Germany(Christian Brösamle) in the field of animal models of LDs (Zebra Fish)*
   - *Unité de Génétique Médicale , Faculté de médecine, Université Saint Joseph, Beirut, Lebanon (André Megarbane) in the field of the molecular biology of LDs*
   - *Children's Hospital - Developmental Pediatrics and Child Neurology Eberhard Karls Universitat Tuebingen, Tubingen, Germany (Prof. Dr. I. Krägeloh-Mann,) in the field of the clinical aspects of LDs*
   - *Dept. of Physiological Chemistry University Medical Centre Johannes Gutenberg University Mainz, Mainz Germany (Matthias Klugmann) in the field of gene therapy **
   - *Department of Internal Medicine , Erasmus MC, Rotterdam, The Netherlands (Theo J Visser) in the field of thyroid hormones transport by oligodendrocytes*

2. Total number of individual participants involved in the Action work is now 83 including 48% of female and 30 Early Stage Researcher participants. In addition, 16 PhD students and 9 post doc participate to the Luxemburg ELA meeting and 19 PhD students and 14 post doc to the Paris Euroglia meeting

3. Early Stage Researchers represent 36% of the participant involved in the Action. All are responsible of specific research programs of the COST. All presented poster or oral presentation to the different research meeting and 10 of them to the family research meeting.
   - A four days training school have been organized for Doc and Post doc during the Euroglia meeting in Paris. Twenty four doc and post doc have been supported by the Myelinet action to participate to this training school entitled "glial biology and diseases*"* All participate to lectures, poster discussions and symposia presented by Cost members or invited speakers)
   - *Four STSMs were carried out during the year.*

°Collaborative work between the Max Planck Institute Gottingen (K Nave) and the GReD, INSERM (O Boespflug-Tanguy) allowed the development of a PLP mutated humanized mice mutant particularly useful for pharmacological approaches. Melina Begou (France) spent one week in the German lab. In March 2009 (supported by the max Planck Insitute)

°The STSM carried by Yline CAPRI (PhD student, France) during 3 weeks in May 2009 in Rotterdam (Pr Visser lab) allowed analysing the capacity of oligodendrocytes and fibroblasts of dysmyelinating mutated patients to transport the thyroid hormone T3 (supported by the Auvergne University grant)

°A STSM was carried out by Imen Dorboz from the Pasteur Institute of Tunis from June to December 2009 in the French leukonetwork (INSERM GReD) in order to identify genes involved in undetermined leukodystrophies (supported by ELA and the INSERM-DGRST collaborative program)

° the STSM Application of Dr Vanja Tepavcevic,INSERM U975,Paris(FR) has been supported by the COST action in order to perform "Ultrastructural analysis of the subventricular zone during inflammatory demyelination in July 2009. The host institute, was the Jose Manuel Garcia Verdugo,Unidad de Neurobiología Comparada Instituto Cavanilles de Biodiversidad y Biología Evolutiva, Paterna in Valencia (Spain)

4. Myelinet involved 8 researchers from outside of COST Countries (4 from Tunisa, 3 from Turkey, one from Lebanon) representing 10 % of participants from countries with reciprocal agreements. Their contribution is important for the clinical (4 researchers) and molecular (5 researchers) aspects of LD. The high rate of consanguinity observed in these countries accelerates the identification of new genes involved in LDs (homozygozity mapping). Contacts have been done with Chili by the Chair in November 2009. Large collaborations exist with Japan and USA (10 collaborative projects)

5. During 2009, the Myelinet participants has published a total of 73 original publications including 4 in the top10 journals and 13 reviews. (list enclosed)
In addition, the COST participants publish the reports on the 2008-2009 outbreaks of the research in LDs for the patients and their families (March Paris meeting) through the ELA family association journal (ELA info) translate in French, German, Italian, Spanish and English
The COST Myelinet participants have organized very successful Workshop and meeting

- Patients and families-Myelinet researchers meeting: Paris-Sevres: March 29th 2009 www.ela-asso.com (summary in ELA infos suppl june 09 (www.ela-asso.com/?q=node/6305, summary and program enclosed)
- Myelinet – ELA Workshop, "Therapeutic Challenges in white matter diseases", Luxemburg , June 26-27th 2009 (www.ela-asso.com, program and report enclosed). The meeting have been host in the Luxembourg European commission building by Ernst Moutschen, EC representative in Luxemburg
- The Vice chair of the COST Myelinet action was the scientific organizer of the 9th European Meeting on Glial cells held in Paris in 8-12 September 2009 (www.glialcells2009paris.com, publication in Glia, Volume 57, Issue S13). X symposium chaired or organized by COST MYELINET participants have been supported by the COST (program and report enclosed)

6. Collaborative activities and projects exist with the Neurinfnet COST network colleagues. Seven Myelinet participants are involved in both actions. Euroglia meeting organised by both actions

7. The capacity of the Action members to raise research funds is particularly fruitful at national and European levels.

-All participants are leaders in their field and Principal investigator of at least one national grant in the field of LDs, glial cells biology or innovative therapy.

- The medium scale FP7 Heath project LEUKOTREAT has been totally elaborate through the Myelinet COST actions. All participants are members of the MYELINET.(enclosed the project)

II.C. Self evaluation

Main successes are the very active, multidisciplinary interactions existing within the Myelinet COST actions including patients and families organizations through Europe.
Myelinet actions provide to Europe a strong position in the field of White Matter diseases, Myelinet group leaders being international recognized expert in their field
Financial supports asked to the COST office this year has allowed major actions towards patients and their families (ethical issues, European collaboration within the European associations) and the young researchers/ Doc and Post Doc (active participation to the Euroglia meeting).
Supports of the COST for STSM exchanges within partners remain not currently used by partners despite information done by the Myelinet Chair and scientific officer. The main reasons are the restrictions concerning the minimal and maximum number of days,
The support of the FP7 Heath program LEUKOTREAT which will start in March 2010 for 3 years will be an important acceleration for the collaborative actions elaborated by the different Myelinet participants.
Myelinet COST support will include workshop, meetings, STSM organisations which will allow a larger participations of non supported Leukotreat partners involved in the COST action particularly in the field of glial cell biology and development and to increase the Leukodatabase participants through Europe.
Different meetings are already scheduled in 2010

- March 18 and 19th in Paris for Leukotreat partners
- June one day WP1 partner meeting for the Leukotreat database
- September, COST and Leukotreat partners

II. Scientific Report

II.A. Results achieved in 2008

The white matter (WM) of the brain is damaged in a number of clinically important pathological disorders affecting newborns, children and adults from genetic (leukodystrophies) or acquired (multiple sclerosis, white matter disorders of the premature) origin. A common motif related to the severity of this heterogeneous group of disorders is the axonal dysfunction due to myelin deficiency or destruction. Development of therapeutic approaches for myelin repair and neuroprotection is the aim of our COST action.

During this year transversal actions based on the multidisciplinary expertise of COST participants have been made. Due to the complexity of the factors involved in acquired WM diseases we focus our attention on inherited forms (leucodystrophies, LDs) in order to define prototypic pathologies for future therapeutic trials. For this purpose, different questions have been raised by the working groups through workshops and meetings:
-Which pathologies can be used for therapies to tackle myelin formation/destruction issues as well as glial cells dysfunctions in neurodegeneration? (WP1)
-Which biomarkers for myelin destruction and axonopathy exist and/or must be developed (WP2)
-Which pathophysiological pathways common to different WM diseases can provide new targets for pharmacological strategies? (WP1 and WP3)
-Which diseases are the best candidates for innovative gene and cell therapies? (WP3)
-What are the family expectations and the ethical issues raised by innovative therapies? (WP4)

"Characterizing white matter diseases for therapies" (WP1)
Classification based on disease cell targets has been proposed. Expertise of different partners and recommendations for database management systems and information technology support for biobanks made by "e rare" has help to define informations need for future therapeutic trials: epidemiology, natural history, genotype/phenotype correlation for a sufficient number of patients. Strategies have been proposed to connect, enlarge and improve at a European level through the COST network the existing databases (clinical databases, biobank and mutation database) in coordination with the Information Systems SME Soluscience involved in the Myelinet network. For this purpose five news COST participants have been also included.

"**Biomarkers for leukodystrophies treatment**"(WP2)
The specificity and significance of biomarkers already identified in individual groups of LDs have

been established. Experiences using transcriptomic and/or proteomic analysis (biological fluids, lymphoblasts, fibroblasts, myelin extracts) have been exchanged. The need for innovative lipidomics screening of affected samples due to the main role of lipid metabolism in myelin production and maintenance has been underlined. Two Cost participants have been more particularly involved in this aspect

"**Pharmacological strategies to treat leukodystrophies**" (WP1 and 3)
Pathophysiological pathways common to different LDs have been defined in order to offer new entry points to design pharmacological treatments applicable for the largest number of patients. Molecules: with a neuroprotective effect, anti-oxidant or anti-stress activities or able to eliminate misfolded proteins have been discussed as well as the best cellular and animal models to be used. Solutions to improve brain delivery must be encouraged.

"**Innovative gene and cell therapies in leukodystrophies**".(WP3)
The combined expertise in cellular and animal models of LDs and in gene and cell therapies for the brain from COST Myelinet participants has help (i) to evaluate the strategy used for on going human trials combining gene and cell therapy using hematopoietic stem cells "corrected" *via* lentiviral vectors for "therapeutic" gene delivery to the WM, (ii) to discuss strategies allowing direct delivery of the therapeutic gene to the brain for rapidly progressing and fatal infantile forms of LDs. For this purpose the San Raffaele Telethon Institute for Gene Therapy (HSR-TIGET) in Italy has been included as Myelinet COST participant. Development of viral or non viral vectors targeting predominantly glial cells has been defined as a key step for efficacy and a new COST participant from Germany (University of Mainz) has been included to increase this expertise. LDs appeared especially attractive to test cell-based therapeutic strategies in the brain due to the homing, dividing and migrating capacities of glial cells. The type of cells (neuronal stem cells, oligodendrocytes or microglial precursors…) and the prototypic models to be used have been discussed.

"**Ethical impacts of therapeutic challenges in leukodystrophies**"(WP4)
In LDs as in other neurodegenerative disorders in which a severe cognitive and motor deterioration is observed without curative therapies, perspectives of new therapeutic issues through research programs represent hopes and fears. However, in LDs because the most severe forms affect children, these expectations are mainly expressed by the parents. The genetic origin of LDs in which family recurrence can exist including one mildly affect parent as in X-linked forms, rise additional problems. Therefore specific research in medical ethics appeared important in order (i) to better understand patients' needs and health care professionals' duties related to the progress made in biomedical research, technology and information systems, (ii) to promote best practices during the process of research in order to optimize the development of therapeutic trial for the largest number of patients. For this purpose, a well-experienced research team strongly skilled in medical ethics (Pr HERVE and Dr MOUTEL, Laboratory of Medical Ethics and Forensic Medicine, Faculty of Medicine of the University of Paris Descartes) has been solicited.

The multidisciplinary, scientific and medical interactive European effort developed through the Myelinet action allowed COST members to elaborate a medium scale proposal to answer to the European Commission Call for proposals HEALTH-2009-2.4.4-1 *Rare neurological diseases,* in December 2008, named "Therapeutic challenge in leukodystrophies: translational and ethical research towards clinical trials" (LEUKOTREAT). The COST network has a central role for the development and diffusion of European databases, dissemination of knowledge, interactions with patients and families organization.
Specific programs to answer to the "E rare" call for proposal 2009 have been also elaborated

To increase the networking activities of the COST Myelinet toward knowledge on white matter diseases, new COST countries have been included: Poland, Sweden, Denmark, Cyprus , Greece, Slovenia, Serbia and, in addition to one research group in Germany (Mainz) and two in Italy (Milano, Geneva). Tunisia (2 research teams in Sfax and Tunis) has been included as non COST country. Two participants in USA, one in Japan and one in Chile are in the process of inclusion.

Synergistic activities have been pursued with
- Neurifnet of the BM COST program. 7 Members of Myelinet including the Vice chair participate to

both meeting and symposia in order to maintain the links need in the field of neuroinflammation of the white matter. Both COST networks have actively participated to the open Euroglia meeting that will be held in Paris in September 2009 with the COST support. Annick Baron Van Evercooreen, vice chair of the Myelinet is one of the principal organizator.
- European multidisciplinary approaches devoted to specific groups of LDs coordinated by COST partners and supported by (i) EC grants [X-ALD, LSHM-CT2004-502987; Refsum disease, QLG3-CT-2002-00696; Peroxisome disorders, LSHG-CT-2004-512018], (ii) European Leukodystrophies Association (ELA) Foundation grants (EIF2B related disorders; therapeutic strategies in PLP related disorders; in ALD or MLD; undetermined leukodystrophies) or (iii) specific programs (Franco-Tunisia INSERM cooperative program). Five STSMs have been supported preferentially through these specific research grants due to the administrative limitations of the COST organisation in term of day, support and delays
- the international translational program devoted to treatment of multiple sclerosis "Cellular and Molecular therapies for Myelin Repair and Axonal Loss in MS" included 3 Myelinet members R Franjlin, A Baron, C French Constant

The partner ELA has reinforced interactions between scientists and families affected by inherited WM diseases. Strategies to connect, enlarge and improve European families network have been initiated.

- *Dissemination*

Conferences, Workshops and Training Schools (list and programme)
- Patients and families-Myelinet researchers meeting: Paris-Sevres: March 29th 2008 (summary in ELA infos suppl june 08 and program on www.myelinet.fr)

- Myelinet Workshop, "News and perspectives in Leukodystrophies", Clermont-Ferrand SuperBesse , June 6-8th 2008 (program and report on www.myelinet.fr)

-FP7 Heath Leukotreat project workshop, Paris, September 29th 2008 (program and report on www.myelinet.fr; proposal on the intranet Myelinet Cost web site)

-Gordon conference MYELIN, May 4-9, 2008, Il Ciocco Hotel and Resort, Lucca (Barga), Italy: 10 Myelinet participants including 9 speakers and 4 symposium organized and chaired by COST members (Gordon Research Conferences - 2008 Program (Myelin) http://www.grc.org/programs.aspx?year=2008&program=myelin

White matter diseases: lessons for MS? Charles ffrench-Constant (Edinburgh, UK)
Repair and regeneration in vivo Anne Baron-Van Evercooren (Paris, France)
Extracellular signaling and myelination in CNS and PNS Klaus-Armin Nave (Göttingen,Germany)
Glial cell death and axonal pathology David Attwell (London, UK)

- training school*:* "DEVELOPMENTAL ANATOMY OF THE MOUSE EMPRYO II" Alicante, November 2008 (Salvador Martinez).

- *Web site (description)*

available on www.myelinet.fr

- *Scientific and Technical Cooperation*

Cooperation within Myelinet participants

Clinical research: 10 countries involved (16 institutions)
Animal models development and analysis: 5 countries (Gottingen and Clermont-Ferrand; Paris, -Strasbourg; Paris-Clermont-Ferrand-Tel Aviv-Manchester; Gottingen- Genova)
Oxidation stress in leukodystrophies: 3 countries (Clermont Ferrand, Paris, Bonn, Barcelona)
Gene therapy in leukodystrophies 3 countries (Paris, Milano, Bonn, Mainz)
Cell therapy in leukodystrophies and MS: 4 countries (Cambridge, Paris, Clermont-Ferrand, Milano) Bonn)
Physiopathology of EIF2B related disorders: 4 countries (Paris, Clermont Ferrand, Tel Aviv, Manchester, Geneva)
Physiopathology of MLC1 related disorders: 4 countries (Roma, Paris, Clermont-Ferrand, Barcelonna, Ankara)

Physiopathology of hypomyelinating disorders 4 countries (Cyprus, Genova, Gottingen, Clermont-Ferrand)
Physiopathology and treatment in ALD 4 countries (Paris, Vienna, Amsterdam, Barcelonna, Gottingen)
Physiopathology and treatment in MLD: 3 countries (Paris, Bonn, Hamburg, Milano)

Cooperations with other institutions

INSERM/DGRST Franco-Tunisian cooperation
International translational program "Cellular and Molecular therapies for Myelin Repair and Axonal Loss in MS"

- *Transfer of results*

Two SME are included in the COST Myelinet (Atheris, Soluscience). An information system devoted to leukodystrophies has been elaborated by O Boespflug-tanguy lab and Soluscience (PRAI e nnovergne lifegrid EC project)

A new SME (Trophos) have been included due to the potential remyelination of their molecules (ANR project collaboration with COST institutional lab)

- *Contacts in the ERA*

EC grants : X-ALD, LSHM-CT2004-502987; Refsum disease, QLG3-CT-2002-00696; Peroxisome disorders, LSHG-CT-2004-512018
FP7 Health program, proposal sent by the Myelinet Action in December 2008

III. Evaluation Report *prepared by the "ad hoc" Evaluation Panel established by the Domain Committee and the COST Office.*

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The evaluation panel participated to the Final conference and MC meeting in Paris in May 2011. Participation to final meeting provided an outlook on the performance and scientific results of the Action.

The evaluation panel has received the MoU, Annual reports and the Final report from COST Office and obtained information on the Action in BMBS committee meetings.

Evaluation: Dr Anu Jalanko (Rapporteur)

1. *Results versus objectives*

The Action had a very slow start and the network was mainly activated during the second year of operation. The scientific objectives were reformulated during 2008-2009 to focus more into those pathophysiological pathways providing new biomarkers and promoting innovative therapeutic strategies. The evaluation of how the results match the objectives is not straightforward since the reformulated objectives are not completely opened in the annual reports. From 2008 and onwards the Action was actively involved in setting up an FP 7 project Leukotreat (started in 2010) and the COST action essentially seems to follow the Leukotreat general objectives and has been organised through Work Packages:

WP1(WG1): Characterizing white matter diseases for therapies

According to the Myelinet reports 2008 and 2009, the main redefined objectives of this WP were to define the establishment and organization of the European Leukodystrophies database and characterization of new genes involved in leukodystrophies. The project has organized the database, now elaborated under FP7/Leukotreat and novel leukodystrophy (LD) genes have been characterized. The characterization of pathological mechanisms was the original goal of this WP and the participants have been extensively involved in this goal and produced novel information about animal models and common pathological mechanisms underlying LDs. This WP contains most of the joint activities between Myelinet participants and has resulted in excellent scientific publication record.

WP2(WG2): Biomarkers for leukodystrophies treatment

Here the partners have worked towards two goals, i.e. defining the specificity and significance of biomarkers already identified and identifying new biomarkers. According to the original plan, this WP has utilized proteomic and metabolomic analysis for biomarker screening and identified markers for two types of LDs.

WP1&WP3: Pharmacological strategies to treat leukodystrophies

In 2009, The Action settled collaborative actions to test pharmacological therapies in vitro and in vivo models of LDs. Here, also a SME was involved. As a result, animal models for preclinical trials have been defined and solutions to improve brain delivery have been discussed.

WP3(WG3): Innovative gene and cell therapies in leukodystrophies

According to plans, wide spectrum of applications have been and continue to be tested; neural stem cells, progenitors, iPS cells, ES-cells; spectrum of lentiviral and AAV-vectors. The approaches have largely been the same that are used in a variety of rare neurological diseases. Gene therapy was shown to be beneficial in preclinical trials of ALD. Applications targeting myelinated cells include most novelty and potential to treat LDs.

WP4(WG4): Ethical impacts of therapeutic challenges in leukodystrophies

The goals of the Ethical WP defined in 2008-2009 have been to identify patient's expectations towards the research project and promoting the best practices of research to optimize therapeutic trials. This WP has established an ethical committee to define the ethical issues related to the database etc. Dissemination has been active and

ethical issues have been discussed widely in the workshops. Good relationships to patient organizations have been a special strength of this Action.

The extent of collaborations within and between the WPs is not quite clear. Besides scientific goals, this Action was involved in organsing conferences, although the visibility of COST was not clear. The action involved young scientists as members of the consortium, but it remained unclear if they really benefited from this action. STSMs were not utilized satisfactorily.

2. *Innovative networking*

The scientific outcome of the action has been excellent, the best year being 2010 with 140 publications in very good journals. The best scientific results lie in gaining better understanding of the pathophysiology (WP1) and in this area the networking has been most active. As a significant outcome of networking, WP1 has initiated the European database project. The most significant scientific breakthroughs include identification of novel genes (and phenotypes) of LDs, defining the role of oxidative stress in ALD, the role of glutamate receptors on glial cells, successful preclinical gene therapy of ALD and applications to target myelinating cells for therapy.

The Action has been very active in networking with patients and patient organizations. This collaboration has resulted in very good impacts. Genetic counselling is now available to larger number of families, the dissemination processes have been very active to involve the families into training and this has resulted in increasing the public's knowledge about LDs. Ethical issues have been considered prominently. The ethical debate about the database, including consents, has increased the awareness about the possibilities of disease databases and biobanks to promote health.

The Action is involved in new FP7 initiatives, most significantly in the FP7 Leukotreat project. The Myelinet project is very strongly integrated with Leukotreat.
The Action members were also involved in the E Rare 2011 call and COST partners have reinforced national actions on rare diseases.

3. *Inter-disciplinary networking*

BM0604 is a multi-disciplinary network and joins researchers from several disciplines, however mostly within the biomedical sciences. The action has been very active in interacting with patient organisations and this may result in socio-economic impacts. BM0604 was interacting actively with the COST Action NEURINFNET and this interaction brought up visions from common mechanisms underlying demyelinating diseases. It is very early to evaluate whether the level of inter-disciplinarity was sufficient to provide scientific impacts. Rather, the biomedical expertise and innovation within the action can very well result in scientific and health care impacts in the area of rare diseases.

4. *New networking*

84 individual participants from14 European and 3 non-European countries were involved in BM0604. During its duration, the Action has attracted some new groups to join Myelinet, but their contribution/participation is unclear. Data on the yearly evolution of members is lacking. Two of the new members were SMEs and their participation has been prominent.

Early stage researchers constitute 36 % of participants. They were perhaps not involved optimally and STSMs were not utilized efficiently. Young researchers were invited to two major open meetings during the action.

Female researchers constituted 48 % of the members and 8 researchers from the 3 non-COST countries were involved.

Promotion and dissemination of scientific knowledge was excellent. The Myelinet participants published a total of 293 original publications and 68 reviews/books. 66 were joint publications. It is not known in which portion of the publications COST is acknowledged.

The Action participated in organization of two major European conferences. The visibility of COST was not evident.

5. *Coordination and management*

The coordination and management of BM0604 Action was not very good. The information exchange between the Chair and the COST office (and rapporteur) was suboptimal.

The MC had 8 meetings. The participation of MC members to these meetings may not have been good (at least in the final meeting). The management was structured through 4/5 WPs and their programmes were essentially the same as in the FP7 Leukotreat project. The integration of Myelinet and Leukotreat was the major basis of this Action. The scientific outcome of the consortium is excellent but it is not clear if COST brought any added value. Yearly progress reports are generally satisfactory, although many of them were delivered very late and this caused difficulties for the COST office and the rapporteur to perform the yearly follow-up. The final report is confusing at some parts. Better exchange of information between the MC Chair and COST office could also have helped to better coordinate and manage the Action. The financial management seems not very professional and this was clearly evident from the self evaluation part of the final report.

6. *Strengths and weaknesses*

Strengths:

Excellent combination of experts in oligodendrocyte biology, relevant rare diseases, gene therapy, infrastructures (to collect epidemiological, natural history, etc data) and construction of databases.

The scientific activity of the network is excellent with 293 original publications, including relevant scientific breakthroughs.

Weaknesses:

Although the Action was scientifically very active, the translation of the pathophysiological knowledge to patient care is challenging and outcomes of the therapeutic approaches can only be evaluated after several years. More novel & innovative approaches could have been used in the therapy section.

The management and coordination was not very good, the action had a very slow start and was not able to utilize the COST instrument efficiently.

Evaluation: Prof Roland Pochet

7. *Results versus objectives*

The objective of the Action was to better understand and fight orphan diseases affecting the CNS

nerve-insulating myelin such as inherited leukodystrophies for further applications to myelin repair in more common myelin diseases (premature, multiple sclerosis). The diversity of causative genes and the rarity of each individual disease led to try to establish a coordinated and multidisciplinary approach. The 84 individual participants from 20 European or associated countries involved in the Action include representatives of affected patients and their families, experts in medical ethics, clinicians, neuroscientists and SME in information system and biotherapy.
The main failure is that the objective « To develop **information systems** for the research partners of this program, for families, and physicians » was not at all achieved neither the claim (cf MoU) the install the innovative activity of a European MYELINET DATABASE with a website access. A fortiori, the aim of the Action « not to create only individual databases in each field but to build integrative system able to connect the data coming from the different bases in order to optimize development of original correlation between phenotype/ genotype/NMR/ transcriptomic/proteomic analysis » was not achieved.

Furthermore the claim that « MYELINET website will provide a semi-automatic reporting system to facilitate reports for all types of actions or meetings in order to organize workshops and to stimulate new interactions with neighbour research fields, patients and families and to develop and maintain an interactive website dedicated to the Action for public disseminations and internal secured exchanges of information (http://www.myelinet.eu) was not fulfilled.

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- To efficiently distribute information for affected families. Action supported patients-researchers meeting as well as two European or international open research meetings.

8. *Innovative networking*

- innovative knowledge which resulted from COST networking through the Action
  - Cooperating for the Leukodystrophiess with an undetermined cause allowed to identify new phenotypes, new genes
- significant scientific breakthroughs as part of the COST Action,
  - not yet visible
- tangible and important socio-economic impacts,
  - Extend information exchange to patients and families for disease information, disease follow up and clinical protocols
- spin off of new EC RTD FP and/or National Programme proposals.
  - Participants of the Action succeeded in obtaining a FP7 medium scale support on the call HEALTH-2009-2 *Rare neurological diseases,* named “Therapeutic challenge in leukodystrophies: translational and ethical research towards clinical trials” (LEUKOTREAT).
- Describe the level of inter-disciplinarity, its benefits and impacts
  - involving patients and their families in the disease knowledge and as actor of the research
- evaluation of whether the level of inter-disciplinarity was sufficient to potentially provide scientific and/or socio-economic impacts.
  - increasing the number of European families having access to a genetic counsel in Leukodystrophias

- ethical debate at the European level on common patient consent, database users chart, impact of innovative therapy.

9. New networking

- evolution of members joining the Action,
  - This inter-disciplinary networking stimulate Cost partners to participate to the Neurinfnet COST action BM0603 « Neurinfnet ». The Neurinfnet and Myelinet actions co-organized and supported symposia and one training school during the Euroglia Paris meeting in September 2009 (Myelinet vice chair was the president of the organizing committee)
- total number of individual participants involved in the Action work,
  - 84
- involvement and contribution of Early Stage Researchers (ESR), female researchers, and researchers from outside of COST Countries,
  - 30 ESR
  - 40 female
- advancement, promotion, and dissemination of scientific knowledge through publications (by Action members that resulted from COST networking through the Action) and other outreach activities,
  - The list of publications provided by the chair did not allow to evaluate how many publications where indeed made by at least 2 authors from 2 participants of the Action but from different countries.
- activities and projects with COST colleagues, including from other Actions,
  - The Neurinfnet and Myelinet actions organize and support different symposia
- capacity of the Action members to raise research funds.

10. Coordination and management

Describe the effectiveness of coordination and management.

The management capacity was very weak with low commitment of the chair (see budget spending) and failure in reaching objectives (Database) described in the MoU

Strengths and weaknesses

Strengths

- Coordination of actions within diversity of disease causes and partners.
- Effort in the diffusion of knowledge in orphan myelin diseases for researchers, medical doctors and families associations with national and international outcomes.
- This COST action allowed finalizing a specific FP7 Heath call proposals for rare neurological disorders with the objective to develop therapeutical trials for leukodystrophias of known cause (LEUKOTREAT).

Weaknesses

- Management of the action
- Budget use
- STSM not much used
- No Database
- Website

IV. DC General Assessment prepared by the Domain Committee

DC comments on the quality of the Action in no more than one page. It should illustrate the

“success story” (if applicable) of the Action, with concrete examples and names of persons who can be contacted for further details.