

# Euro-Histio-Net Meeting, Genoa

Held on March 11, 2011, 1.30 p.m. – 7.30 p.m. and March 12, 2011, 9 a.m. to 1 p.m.

at Hotel NH Marina, Porto Antico, Genova, Italy

## Present:

- I. Astigarraga, Hospital de Cruces, Barakaldo, Spain (BIOEF)
- B. Boshoeven, Histiocytosehilfe e.V., Germany
- L. Debar, Association Histiocytose France, France
- J. Donadieu, Hôpital Trousseau, Paris, France (AP HP), Coordinator
- M. Girschikofsky, Austrian Working Group for Histiocytic Diseases in Adults, Austria
- R. Haupt, Istituto Giannina Gaslini, Genova, Italy (IGG)
- C. Khayat, Hospital St Joseph Peter Noun, Beirut, Lebanon
- I. Malinowska, Medical University of Warsaw, Poland
- M. Minkov, St. Anna Children's Cancer Research Institute, Vienna, Austria (CCRI)
- J. Miron, Association Histiocytose France, France
- D. Miron, Association Histiocytose France, France
- V. Nanduri, The Histiocytosis Research Trust, Sutton Coldfield, UK (HRT)
- R. Price, The Histiocytosis Research Trust, Sutton Coldfield, UK (HRT)
- M. J. Stefaniak, Pediatric University Hospital Lublin, Poland
- J. Visser, The Histiocytosis Research Trust, Sutton Coldfield, UK (HRT)
- E. Schaefer, Hôpital Trousseau, Paris, France (AP HP), Project Manager

## 1. Opening of the meeting, welcome and introduction (R. Haupt and J. Donadieu)

Riccardo Haupt welcomed all attendees. A folder was distributed containing the agenda, two contact forms, and the English version of the Euro Histio Net Guidelines for Diagnosis, Clinical Work-up and Treatment during Childhood. Jean Donadieu, Chair, opened the meeting on March 11 at 1.30 pm.

## 2. Adoption of the agenda

The attendees adopted the meeting agenda without any changes.

### 3. Final approval of web pages:

#### a. Guidelines for diagnosis, clinical work-up and treatment of LCH during childhood (only concerning web presentation) (R. Haupt and E. Schaefer).

- **Text parts:**  
The attendees approved that the text parts should be published on the web as presented. The author group will only be listed on the welcome page of the guidelines part. All other pages will display “Euro-Histio-Net work group for childhood LCH guidelines” as author.
- **Tables.**  
The attendees approved the following decision: E. Schaefer will check, if the technical system of the web portal allows for presenting the tables of the guidelines document as digital tables, for which the translation functionality will be available. If this is not possible or would cause extra costs, all tables shall be added as illustrations (jpg or png files).
- **Chapters.**  
The attendees approved that the web version of the guidelines will be displayed without the chapter numbers of the original version. This will require some modifications in the contents, where references to other chapters are made. These chapters should be linked directly.
- **Algorithms.**  
The attendees approved that the chapter numbers should be replaced in the web version and that all pages should be linked directly.
- **Therapy.**  
The attendees approved that no login for the chapter therapy will be required in order not to restrict access. In return, the importance of patients being included into clinical trials must be pointed out and a webportal page listing currently ongoing studies will be linked. In addition, each therapy page must contain the instruction that the document refers to childhood LCH.
- **Printing.**  
There was general agreement that a pdf file as printing version containing all guidelines contents should be available.
- **Publishing.**  
The pediatric LCH guidelines should be published in *Pediatric Blood and Cancer* (PBC) as peer reviewed medical journal. Jean Donadieu will contact Bob Arceci to ask for the preconditions.
- **Guidelines in tissue banking.**  
A first version of guidelines in tissue banking was drafted. It was suggested that Riccardo Haupt contacts Peter Beverley and asks for his experiences in this matter.

#### b. FAQ about LCH for patients (I. Astigarraga and E. Schaefer).

- **Categories:**  
The presented categories were approved by the attendees. I. Astigarraga announced, that following a review of the web question list of the Italian patient association AIRI (based on 6 years of experience), she will add some questions and answers concerning the categories *inheritance* and *contagiousness*. In addition, it was suggested to check for the use of the categories *relation to cancer*, *prognosis* and *side effects of therapy*.
- **Questions and Answers.**  
The contents of all presented questions and answers were approved by the attendees. V. Nanduri has agreed to make some necessary language modifications.
- **“New” and “revised” annotations.**  
The attendees approved that after the initial launch of the FAQ web page, each newly added question should be annotated as “new” and each modification should be marked as “revised”.
- **Key word administration.**  
It was generally agreed to ask SNTL to realise a technical tool for a keyword administration.

- **Feedback of patient associations.**

It was suggested that before translations to the other languages will start, R. Price should ask the members of the UK patient association, if the answers are appropriate and comprehensible for patients. Any modifications needed should be made before starting the translation process.

c. Maps of Experts for Europe (I. Astigarraga and E. Schaefer).

There was general agreement to provide the following different categories of maps:

- Histio Net coordinators – List of associated partners and collaborating partners is available.
  - National coordinators for LCH IV – List will be requested from the Histiocyte Society once the LCH IV study is opened.
  - National coordinators for HLH – List will be requested from the Histiocyte Society.
  - National experts for childhood LCH
  - National experts for adult LCH
  - International experts for other histiocytoses and associated syndromes
- In all cases, personal data will only be published if the persons agree.

The following responsibilities have been defined after approval of the concerned person (marked with “\*”); for all countries of which no representative attended the meeting, it has been suggested to ask the following persons to accept to be responsible (marked with “?”):

- **List of national experts for childhood LCH**

- |                                 |                                      |
|---------------------------------|--------------------------------------|
| – Austria: Milen Minkov *       | – Italy: Riccardo Haupt *            |
| – Belgium: Stefaan Van Gool ?   | – Lebanon: Claudia Khayat *          |
| – Bulgaria: Milen Minkov ?      | – Norway: Marit Hellebostad ?        |
| – Czech Rep.: Hubert Mottl ?    | – Poland: Maria J. Stefaniak *       |
| – Denmark: Karsten Nysom ?      | – Serbia: Dragan Micic ?             |
| – France: Jean Donadieu *       | – Spain: Itziar Astigarraga *        |
| – Germany: Thomas Lehrnbecher ? | – Sweden: Jan-Inge Henter ?          |
| – Greece: Dora Moustaka ?       | – The Netherlands: Cor van den Bos ? |
| – Ireland: Corrina McMahon ?    | – UK: Johann Visser *                |

- **List of national experts for adult LCH**

- |                                    |                              |
|------------------------------------|------------------------------|
| – Austria: Michael Girschikofsky * | – Greece: Polyzois Makras ?  |
| – Czech Rep.: Z. Adam ?            | – Spain: Diego M. Castillo ? |
| – France: Abdellatif Tazi ?        | – UK: Matthew Collin ?       |
| – Germany: Joachim Fichter ?       |                              |

- **List of international experts for other histiocytoses and associated syndromes**

- HLH: Ask Gritta Janka, Germany, if she can compile a list or recommend somebody who could be responsible for compiling it.
- ECD: Ask Kathy Brewer, ECD Global Alliance, if she can compile a list or recommend somebody who could be responsible for compiling it.
- JXG and SHML (RDD): Ask Oussama Abla, Canada, if he can compile a list or recommend somebody who could be responsible for compiling it.

**There was general agreement to leave the following decisions to the responsible (inter)national experts (see lists above):**

1. Which word to use for “experts” (considering the fact that “centre of reference” has to be used according to the definition of the European Union Committee of Experts on Rare Diseases EUCERD, former Rare Diseases Task Force RDTF).
2. What persons to include into the lists, depending on existing (inter)national networks or on personal knowledge, if no network is available yet.

Nevertheless, Euro-Histio-Net has to make sure that a certain expertise is guaranteed. Therefore, the following definitions have been approved by the attendees:

- **An expert for LCH has to fulfil at least one of the following criteria**
  - Minimum number of LCH patients seen: 5 in the last 2 years or
  - Participation in at least 1 formal study for LCH or
  - Minimum number of peer reviewed publications about LCH: 3 or
  - Being a member of the Histiocyte Society or of a national working group for LCH
- **An expert for any other histiocytosis or any associated syndrome has to fulfil at least one of the following criteria:**
  - Multiple patients treated/seen or
  - Minimum number of peer reviewed publications: 1

#### d. Contact forms for patients and for professionals (E. Schaefer).

Following the Boston meeting, no suggestions for modifications of the contact forms for patients and for professionals were made. Therefore, these contact forms were presented for final approval in order to have them programmed for the web portal.

Extensive discussions of the technical possibilities and their consequences revealed the need for modifications in the contact form for professionals. It was adapted accordingly and approved by the attendees (see attachment 2):

- There will be different contact forms for the different diseases and syndromes.
- Fields marked with \* will be mandatory.
- The list of countries must be editable and should appear as a drop-down list. Only countries where experts have agreed to receive the emails will be listed. "Other" will be sent to the web portal administrator.
- Entry in the fields child/adult and country will define to whom the request will be sent. Processing the contact email will not require intervention but will be done automatically.

For the contact forms for patients, several aspects arose and were discussed:

- It is almost impossible to estimate the work load, if the contact form for patients is sent automatically to histiocytosis experts. It is even not predictable, how many undiagnosed patients will use the contact form fearing they might have one kind of histiocytic disease.
- Several web pages within the Euro Histio Net web portal will provide contact information in order to enable patients to find specialists.
- Main task of the contact form for patients will be to provide immediate help. Therefore, there should be a functionality which provides links within the web portal.
- In addition, there should be an automatic transfer of a request to a patient association in case that the patient wishes to get in touch with other patients.

#### **4. Appointment of responsible persons and instructions for work**

##### a. Translators or coordinators of the translation teams:

Responsibility for translations will be divided in "technical" contents needed for the installation of the web portal, guidelines for childhood LCH, guidelines for adult LCH, contents for professionals and contents for patients. The responsible persons will be reviewers of the translated contents and have to build their translation teams on their own in order to reduce the work load. Responsibilities are marked as shown in attachment 1.

## Instructions for work for the translations:

- The **“technical” translations** must be added to the right column of the word file “Core\_translations\_form”. They will be copied and pasted by a web administrator in order to build the language version of the web portal.
- The printing version of the **guidelines documents** should be translated using the word document “Guidelines\_translation\_form”: replace all English words, leave all references, use the lists on pages 11 and 12 for translating the contents of the algorithms. It was suggested to replace the English translations in the list of the authors’ institutions on page 1 by the original national names and to translate only the countries.
- All **web portal contents** can be translated in one of the following ways:
  - Using the “translate” functionality provided by the content management system of the web portal.
  - Editing the contents “inside” of a language in the content management system.
  - Copying the whole page to the left column of a word document formatted in landscape format with two columns. Adding the translations in the right column while keeping the correspondance of the contents of the two columns (add line breaks where necessary).

E. Schaefer will write a user manual and send it to the translators.

### b. Final approval before publication (one person for each language).

The persons responsible for the translations will decide about their “own” translators or teams of translators. As far as they were present, they agreed to be responsible for the final approval before publication.

### c. Compilation and final approval of national maps of experts (one person for each country)

The persons responsible for the compilation of the lists will decide for their own countries, based on the criteria provided by the Euro Histio Net group. As far as they attended the meeting, they agreed to be responsible for the final approval before publication.

## 5. Division of tasks and instructions for work

### a. Authors for additional information on special aspects of LCH (e. g. genetics).

Concerning the guidelines for tissue banking, Riccardo Haupt will contact Peter Beverly. He may be able to give an important input to the draft. Further contents for the webportal and possible authors or contributors will be discussed and defined by email.

### b. Authors for information about other histiocytic diseases.

Will be discussed and defined by email.

### c. Translations.

Translations of these additional contents will be discussed as and when required.

d. Dissemination of information about the web portal (one responsible patient representative and one responsible doctor for each country, if possible)

The following persons will be responsible for disseminating information about the webportal within the national pediatric medical societies:

- Austria: Milen Minkov
- Belgium: Stefaan Van Gool
- Bulgaria: Milen Minkov
- France: Jean Donadiou
- Germany: T. Lehrnbecher
- Greece: Dora Moustaka
- Italy: Riccardo Haupt
- Spain: Itziar Astigarraga
- UK: Johann Visser
- Netherlands: Cor van den Bos
- Sweden: Jan-Inge Henter
- Norway: Marit Hellebostad
- Ireland: Corrina McMahon
- Denmark: Karsten Nysom
- Poland: Maria Jolanta Stefaniak
- Czech R.: Hubert Mottl
- Serbia: Dragan Micic
- Lebanon: Claudia Khajat

As far as they were present, they have agreed to be responsible. All the others will be asked if they want to be responsible.

For adults, it will be necessary to disseminate the information to many different medical societies: Orthopedics, Dermatologists, Endocrinologists, Neurologists, Internal, Neurosurgeons, Pulmonologists, Maxillofacial Surgeons, ENT, Hemat/Oncologists. The national experts for LCH in adults (see page 3) will be asked, if they agree to disseminate.

e. Compilation of link collections (one responsible patient representative for each country)

This will be discussed and defined by email or in a telephone conference.

## **6. Data base.**

a. Decision for IT company:

The associated partners discussed in a meeting on the morning of March 11 that the negotiations with AIT have not been successful. Therefore, they decided unanimously that Jean Donadiou will ask the French IT company which provides the French LCH database, if they can provide a copy of this database in English language.

b. Future or alternative plans.

Unfortunately, there will be two databases for the future of LCH. One will be the LCH IV database of the Histiocyte Society which is mainly dedicated to children and provides some additional registry options. The second one will be the Euro Histio Net database which will cover the important aspects for adult LCH and for the rarer associated syndromes.

It is probable, that different people will use these databases due to the fact, that in LCH, pediatricians don't treat adult patients and most of the specialists for the associated syndromes aren't specialists for LCH. The Euro Histio Net database will provide a tool for all those patients who are currently not registered at all while the LCH IV database will provide a tool for all those kinds of patients who have been enrolled in the clinical trials of the last years.

It was suggested that the mandatory data of both data bases should be matched in order to have a common registry.

## 7. “Real life”.

### a. How can national and international expert teams benefit on the functionalities of expert sessions?

The proceeding for expert sessions could be the following:

- Register members of the respective group
- Choose target group (e.g. French Study Group)
- Subscribe for invitation
- Meeting organiser announces session to an EHN administrator
- Administrator will provide „Expert session form“
- Organiser completes and edits the form
- Organiser processes the invitation
- Members view and comment
- Session takes place at the scheduled time

This proceeding will have the following advantages:

- Central administration of group members
- Automatic email invitation to all group members
- Upload of files by means of a secure connection on a secure server (https://)
- Access to files: secure connection
- No data transfer via email
- Very cheap solution

It will also have some disadvantages:

- A meeting must be announced to an administrator.
- No screen sharing → the organiser has to describe which page, which paragraphe.
- The telephone conference must be organised separately

A suggestion for an expert session form was made and discussed in detail. Several suggestions were made and several modifications implemented. Finally, the form was unanimously agreed as shown in attachment 3. In addition, there should be a case number for every case and the session should be stored. It would be helpful to have a “chatting” possibility and a field to draw a summary of the discussions. Each case should be classified and cases related, if necessary (e.g. patient record).

### b. How can patient associations benefit on the web portal functionalities and strengthen international cooperations?

Patient associations will benefit from up-to-date information which is scientifically approved. They will perhaps be able to generate members via the webportal links.

They can share existing contents. Examples for existing contents:

- France: Imaginary dialogue with a child.
- Germany: Kid’s brochure, adult brochure about pediatric LCH, HLH Information
- Italy: Frequently asked questions list
- Spain: Experience with a web forum for patients
- United Kingdom: Comprehensive parent’s guide

Finally, the patient associations can divide work for producing what is missing and share new documents.

### c. How will patients and doctors benefit on the Euro-Histio-Net web portal?

- Up-to-date information.
- Online availability, at any time of the day
- Availability in countries without existing networks
- Produce and share what is missing

d. How will experts for rare aspects of LCH and for associated syndromes benefit on the web portal?

- Information will be available in many European languages spoken worldwide and some additional languages like Arabic and Russian.
  - The percentages of people using the internet on a regular basis in their private life are constantly increasing in all countries.
- => Information will be spread, asking doctors can be referred to web portal contents and work load for the specialists can be reduced by dividing tasks.

**8. Euro-Histio-Net after 2011.**

a. Funding for a project manager in 2012

Some associations have already agreed to provide a funding for the project management in 2012. On the afternoon of March 12, there will be a meeting of the patient associations representatives in order to discuss the possibilities of raising additional funds.

b. Prospects (Jean Donadieu)

For the immediate future, it is planned to ask for a prolongation of the project (3 months). After the end of the EU funded project, there are three options:

- To stop the project
- To try to renew a DG sancó grant to have more time (a new 3–year term)
- To apply to a new EU grant, e.g. DG research FP7 grants.

Preparing a call will take at least one year during which a key issue will be to keep a project manager.

**DG Sanco:**

There is usually only a single grant possible with a limited amount of money versus the administrative tasks and there will be no support for needs like data managing.

**FP7 grants:**

These grants fund translational research / basic science and they are extremely competitive. They provide much more money (3 to 6 m€ with the same administrative burden. Rare diseases are in the new call.

**GENE HISTIO – A proposal**

Two FP7 possibilities:

- a) 2012-2.1.1-1: Clinical utility of –omics for better diagnosis and treatment of rare diseases.
- b) 2012-2.4.4-1: Preclinical and/or clinical development of substances with a clear potential as orphan drugs.

*Background:* B raf mutations in Langerhans cell histiocytosis, first published by Badalian-Verly et al., Boston. Since August, B raf mutations were found in a batch of 20 French patients and a germline mutation regulating B raf pathways in one patient. B raf inhibitors are a therapy class which is already available and companies have been contacted. In France, a study called GENE HISTIO was launched.

*Short term aims of the French GENE HISTIO:*

- To determine at large scale the clinical profile of patients with B raf mutations
- To determine new somatic mutations of the B raf - MEK – ERK pathways
- To seek for LCH biomarkers
- To seek for a genetic profile of LCH

*Long term aims:*

1. Targeted drugs
  - 4 B raf inhibitors in development (ex: melanoma)
  - Rank Ligand inhibitors – amgen (denosumab)
2. Medical needs
  - Refractory hematological LCH – a less toxic approach
  - Long term sequelae – lung, liver, CNS, pituitary
  - Chronic LCH
3. Preliminary works to propose B raf inhibitors
  - To define the clinical and biological profile
  - Pre clinical study

*Operational organisation in 2 cohorts:*

1. Prevalent cases of which the medical history is known, parafin or frozen samples are available and the patient / family volunteer.
2. New cases of which the medical history is not known, parafin or frozen samples are taken and the patient family is available.

*Starting point:*

1500 registered French patients from the national network, review of 494 blood samples, frozen tumours and parafin blocks is already organised.

*Associated teams:*

A pathologic laboratory in Paris will study 'standard mutations' and the King's college laboratory will perform research of new mutations and pre-clinical study. (Geissmann & Collins have applied for an H R Trust grant.) A central bio bank will be organised in France and the coordination will be done by the French registry.

*Proposition:*

The French concept involves already 2 EU member states. It could be extended to other countries or institutions. In addition to the biological projects, an epidemiological survey could be added as well as dissemination and communication activities (e.g. by means of the Euro Histio Net webportal). An FP7 grant would provide enough money to support the organisation of teams in different countries or regions (e.g. epidemiological survey for children and adults, realisation of standard B raf mutations at national level, organisation of a biobank). If chosen as an FP7 project, there would be a budget of 3-6 m€, provided there will be an agreement between research laboratories in additional countries.

The doctors among the attendees of the meeting appreciated this suggestion and supported that further negotiations will take place.

## **9. Questions and Remarks / Any other Business.**

No further questions and remarks were raised, no other matters discussed.

Jean Donadieu closed the meeting on March 12 at 1 p.m.

These minutes arise from the project *Euro-Histio-Net 2008 - A reference network for Langerhans cell histiocytosis and associated syndromes in EU* which has received funding from the European Union, in the framework of the Public Health Programme. Sole responsibility for the content of this document lies with the authors. The Executive Agency is not responsible for any use that may be made of the information contained therein.



## Attachment 1: Responsibilities for Translations

done      \* agreed      ? to ask

- **Technical contents (Reviewer / Translator):**

- Arabic: Claudia Khayat\* /
- Bulgarian: Milen Minkov\* /
- Dutch: Maarten Egeler\* /
- French: Jean Donadieu\* /
- German: Eva Schaefer / Frank Hoffmann
- Greek: Helen Papadaki? /
- Italian: Riccardo Haupt / Anna Capurro
- Polish: Maria Jolanta Stefaniak\* /
- Portuguese: Mariana Bohns Michalowski\* /
- Russian: Milen Minkov\* /
- Serbian: Dragan Micic\* /
- Spanish: Itziar Astigarraga / Susana García Obregón
- Swedish:

- **LCH guidelines for childhood (Reviewer / Translator):**

- Arabic: not needed, because doctors usually speak either English or French
- Bulgarian: Milen Minkov\* /
- Dutch: Maarten Egeler\* /
- French: Jean Donadieu\* /
- German: Gritta Janka ? /
- Greek: Helen Papadaki? /
- Italian: Riccardo Haupt / Anna Capurro
- Polish: not needed, because doctors usually speak either English or Russian
- Portuguese: Mariana Bohns Michalowski\* /
- Russian: Milen Minkov\* /
- Serbian: Dragan Micic\* /
- Spanish: Itziar Astigarraga\* /
- Swedish: still needed due to the description in the grant agreement

- **LCH guidelines for adults (Reviewer / Translator):**

- Arabic: not needed, because doctors usually speak either English or French
- Bulgarian: Milen Minkov? /
- Dutch: Maarten Egeler? /
- French: Abdellatif Tazi? /
- German: Michael Girschikofsky\* /
- Greek: Polyzois Makras\* /
- Italian: Maurizio Arico ? /
- Polish: not needed, because doctors usually speak either English or Russian
- Portuguese:
- Russian: Milen Minkov? /
- Serbian: Dragan Micic? /
- Spanish: Itziar Astigarraga\* /
- Swedish: Finn Wesenberg? /

- **Contents for Professionals (also very important for the information of patient associations):**
  - Arabic: Claudia Khayat\*
  - Bulgarian: Milen Minkov\*
  - Dutch:
  - French: Jean Donadieu\*
  - German: Gritta Janka?
  - Greek:
  - Italian:
  - Polish: Maria Jolanta Stefaniak\* and Iwona Malinowska\*
  - Portuguese:
  - Russian: Milen Minkov\*
  - Serbian:
  - Spanish: Itziar Astigarraga\* and Carlos Rodriguez-Galindo\*
  - Swedish:
  
- **Contents for Patients:**
  - Arabic:
  - Bulgarian:
  - Dutch: Karel Hahlen?
  - French: Lydia Debar?
  - German: Eva Schaefer\*
  - Greek: Dora Moustaka?
  - Italian: Franco Sponchiado?
  - Polish:
  - Portuguese:
  - Russian:
  - Serbian:
  - Spanish: Raúl Suarez?
  - Swedish: Urban Beinö\*

Attachment 2:

# Contact Form Professionals

\*Full name incl. titles

\*Correct email address

\*Institution

\*City

\* Your Country:

- Austria
- Belgium
- Canada
- France
- Germany
- Greece
- Italy
- Ireland
- Lebanon
- Morocco
- Poland
- Spain
- Sweden
- The Netherlands
- United Kingdom
- United States of America
- Other: \_\_\_\_\_

\*Age of the patient:

Child  Adult \_\_\_\_\_years

Date of diagnosis

Organs/Systems involved

Treatment

Response to treatment  Yes  No

Serious side effects  Yes  No

Relevant Comorbidities  Yes  No

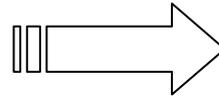
Current Concern

\*  I agree that my email is sent automatically to different experts.

# Attachment 3: Expert Session Form

Please select group you want to invite ▾

- Please select group you want to invite
- Association Histiocytose France
- ECD Group
- French study group
- Histiozytosehilfe e.V.
- UK national group



## Memberlist:

- Member 1
- Member 2
- Member 3
- Member 4
- Member 5
- Member 6
- Member 7
- Member 8

- 
- 
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- Upload agenda
- Upload pdf-file
- Upload jpg
- Upload ppt-pres.

Case report

Title of the meeting

02-04-2011, 14:00

Date, time incl. time zone

Want to present a  
difficult case of  
nail involvement.

Invitation text

0033-1-55-809090

Telephone Number

\*123456#

Login Code for Telco

[www.link.net/exact\\_link](http://www.link.net/exact_link)

Invite