Langerhans Cell Histiocytosis: An Overview

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Children‘s Cancer Research Institute
St. Anna Children‘s Hospital
Vienna, Austria
LCH a very long story…

- Hand-Schüller-Christian Syndrome
- Letterer-Siwe disease
- Eosinophilic granuloma
- Histioctysis X
- Langerhans Cell Histiocytosis

Achievements:
- Case description (Hand, 1893)
- Unifying concept (Lichtenstein, 1953)
- Origin arguments (Nezelof, 1973)
- Clonality (Willman, 1994)
- BRAF Mutation (Badalian-Very, 2010)
- Myeloid neoplasia (Beres, 2013)

St. Anna Children’s Hospital
International LCH Study Reference Center
LCH-IV Study since 2012
What was Known About LCH until recently?

- Abnormal proliferation and dissemination of clonal dendritic cells, which carry much of the surface antigen profile of normal Langerhans cells
- Any organ (bone, skin, liver, lungs, spleen, lymph node, brain, etc.) can be involved
- Wide spectrum of clinical presentation with variable course
- Granuloma formation (various proportions of T-lymphocytes, granulocytes, monocytes and eosinophils) and abundance of cytokines evidence inflammatory reaction
The Mononuclear Phagocyte System

Berres ML et al., Adv Immunol, 2013, 120: 127-161
Are the LCH cells really LCs?

Cell-Specific Gene Expression in Langerhans Cell Histiocytosis Lesions Reveals a Distinct Profile Compared with Epidermal Langerhans Cells

Carl E. Allen, Liunan Li, Tricia L. Peters, Hon-chiu Eastwood Leung, Alexander Yu, Tsz-Kwong Man, Sivashankarappa Gurusiddappa, Michelle T. Phillips, M. John Hicks, Amos Gaikwad, Miriam Merad and Kenneth L. McClain

*J Immunol* 2010; 184:4557-4567; Prepublished online 10 March 2010;
doi: 10.4049/jimmunol.0902336
http://www.jimmunol.org/content/184/8/4557

Are the LCH cells really LCs?

Table 1. Comparison of real-time PCR and microarray results: LCH CD207 versus control skin CD207

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Real-Time PCR</th>
<th>Array</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPP1</td>
<td>162.6</td>
<td>22.5–37.0</td>
</tr>
<tr>
<td>CEACAM6</td>
<td>76.7</td>
<td>10.1</td>
</tr>
<tr>
<td>CDK2NA</td>
<td>73.9</td>
<td>2.1–4.9</td>
</tr>
<tr>
<td>JAK3</td>
<td>46.1</td>
<td>1.9–7.1</td>
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<tr>
<td>VNN1</td>
<td>44.0</td>
<td>5.2–7.7</td>
</tr>
<tr>
<td>SMYD3</td>
<td>34.8</td>
<td>9.3–12.4</td>
</tr>
<tr>
<td>AFF3</td>
<td>24.7</td>
<td>3.1–11.3</td>
</tr>
<tr>
<td>HOXB7</td>
<td>20.7</td>
<td>6.6–6.8</td>
</tr>
<tr>
<td>DUSP4</td>
<td>15.7</td>
<td>3.4–10.3</td>
</tr>
<tr>
<td>MMP9</td>
<td>15.5</td>
<td>7.6</td>
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<tr>
<td>MMP1</td>
<td>11.5</td>
<td>7.2</td>
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<tr>
<td>CCR1</td>
<td>8.6</td>
<td>4.5–5.7</td>
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<tr>
<td>CCL5</td>
<td>8.6</td>
<td>4.6</td>
</tr>
<tr>
<td>NRP1</td>
<td>4.8</td>
<td>4.5–9.5</td>
</tr>
<tr>
<td>TNFRSF9</td>
<td>4.6</td>
<td>5.8–6.4</td>
</tr>
<tr>
<td>DCAL1</td>
<td>3.2</td>
<td>5.1–6.6</td>
</tr>
<tr>
<td>CD36</td>
<td>−28.1</td>
<td>(1.4–14.4)</td>
</tr>
<tr>
<td>S100A8</td>
<td>−60.2</td>
<td>(22.5–26.2)</td>
</tr>
<tr>
<td>EpCAM</td>
<td>−204.4</td>
<td>−38.1</td>
</tr>
<tr>
<td>CDH1</td>
<td>−269.6</td>
<td>(32.2–123.6)</td>
</tr>
<tr>
<td>PERP</td>
<td>−1,172</td>
<td>(3.9–227.5)</td>
</tr>
<tr>
<td>S100A7</td>
<td>−14,201</td>
<td>(1.7–74)</td>
</tr>
<tr>
<td>IL-2</td>
<td>NA</td>
<td>1.0</td>
</tr>
<tr>
<td>IL-17</td>
<td>NA</td>
<td>1.1</td>
</tr>
</tbody>
</table>

LCH cells are a distinct entity

starting material: fresh biopsy samples (few mm³)

Hutter et al. Blood 2012;120:5199-5208
Langerhans cell histiocytosis (LCH) has a broad spectrum of clinical behaviors; some cases are self-limited, whereas others involve multiple organs and cause significant mortality. Although Langerhans cells in LCH are clonal, their benign morphology and their lack (to date) of reported recurrent genomic abnormalities have suggested that LCH may not be a neoplasm. Here, using 2 orthogonal technologies for detecting cancer-associated mutations in formalin-fixed, paraffin-embedded material, we identified the oncogenic BRAF V600E mutation in 35 of 61 archived specimens (57%). TP53 and MET mutations were also observed in one sample each. BRAF V600E tended to appear in younger patients but was not associated with disease site or stage.

Langerhans cells stained for phospho-mitogen–activated protein kinase kinase (phospho-MEK) and phospho-extracellular signal-regulated kinase (phospho-ERK) regardless of mutation status. High prevalence, recurrent BRAF mutations in LCH indicate that it is a neoplastic disease that may respond to RAF pathway inhibitors. (Blood. 2010;116(11):1919-1923)
And even more genes and mutations...

Figure 1. Somatic MAP2K1 mutations in LCH. (A) The frequency of mutually exclusive BRAF and MAP2K1 mutations in LCH is shown. (B) A portion of the MAP2K1 gene including exons 2 and 3 is depicted at the bottom, and regions of the MEK1 protein encoded by exons 2 and 3 are depicted above. Somatic mutations in LCH involve the N-terminal negative regulatory region encoded by exon 2 and the catalytic core encoded by exon 3.

## Mutations in LCH: Summary

<table>
<thead>
<tr>
<th>Genes</th>
<th>Mutations</th>
<th>Pathway</th>
<th>Frequency</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRAF</strong></td>
<td><strong>V600E</strong></td>
<td>MAPK</td>
<td>35/61 (57%)&lt;br&gt;64/100 (64%)&lt;br&gt;22/42 (52%)&lt;br&gt;9/16 (56%)&lt;br&gt;2/16 (12%)&lt;br&gt;1/16 (6%)&lt;br&gt;Case report</td>
<td>Badalian-Very G. et al., 2010&lt;br&gt;Berres ML et al., 2014&lt;br&gt;Bubolz AM et al., 2014&lt;br&gt;Satoh T et al., 2012</td>
</tr>
<tr>
<td><strong>ARAF</strong></td>
<td>F351L / Q347_A348del&lt;br&gt;T70M / BRAF V600E</td>
<td>MAPK</td>
<td>1/41 (2%)</td>
<td>Nelson DS et al., 2014&lt;br&gt;Chakraborty R et al., 2014</td>
</tr>
<tr>
<td><strong>MAP2KI</strong></td>
<td>R47Q&lt;br&gt;F53_Q58delInsL&lt;br&gt;K57_G61 del&lt;br&gt;R49C / A106T&lt;br&gt;E102_I103del&lt;br&gt;H100_I103delInsPL&lt;br&gt;I99_K104del&lt;br&gt;C121S / G128V&lt;br&gt;E102_I103del&lt;br&gt;Q58_E62del&lt;br&gt;F53_Q58delInsL&lt;br&gt;Q56P&lt;br&gt;C121S / G128D&lt;br&gt;Q56_G61del&gt;R&lt;br&gt;C121S</td>
<td>MAPK</td>
<td>11/40 (28%) of all&lt;br&gt;11/22 (50%) of BRAF&lt;sup&gt;wt&lt;/sup&gt;&lt;br&gt;7/41 (17%) of all&lt;br&gt;7/21 (33%) of BRAF&lt;sup&gt;wt&lt;/sup&gt;&lt;br&gt;3/30 (10%) of all&lt;br&gt;3/20 (15%) of BRAF&lt;sup&gt;wt&lt;/sup&gt;</td>
<td>Brown NA et al., 2014&lt;br&gt;Chakraborty R et al., 2014&lt;br&gt;Nelson DS et al, 2015</td>
</tr>
<tr>
<td><strong>MAP3KI</strong></td>
<td>T799fs&lt;br&gt;L148fs&lt;br&gt;E1286V</td>
<td></td>
<td>3/30 (10%) of all&lt;br&gt;3/20 (15%) of BRAF&lt;sup&gt;wt&lt;/sup&gt;</td>
<td>Nelson DS et al., 2015</td>
</tr>
<tr>
<td><strong>PIK3CA</strong></td>
<td>E542K</td>
<td>PI3K/AKT MAPK</td>
<td>1/86 (1.2%)</td>
<td>Heritier S et al., 2015</td>
</tr>
</tbody>
</table>
Activated pathways

MYELOID NEOPLASIA

Mutually exclusive recurrent somatic mutations in MAP2K1 and BRAF support a central role for ERK activation in LCH pathogenesis

Rikhia Chakraborty,1 Oliver A. Hampton,2,3 Xiaoyun Shen,1 Stephen J. Simko,1,4 Albert Shih,1 Harshal Abhyankar,1 Karen Phaik Har Lim,1,5 Kyle R. Covington,2,3 Lisa Trevino,2,3 Niyad Dewal,2,3 Donna M. Muzny,3 Harshavardhan Doddapaneni,3 Jianhong Hu,3 Linghua Wang,2,3 Philip J. Lupo,1,4 M. John Hicks,1,4,6 Diana L. Bonilla,7 Karen C. Dwyer,7 Marie-Luise Berres,8-10 Poulikos I. Poulikakos,8,9,11 Miriam Merad,8-10 Kenneth L. McClain,1,4 David A. Wheeler,2,3 Carl E. Allen,1,4,5 and D. Williams Parsons1-5

1Texas Children’s Cancer Center, Texas Children’s Hospital, Houston, TX; 2Department of Molecular and Human Genetics, 3Human Genome Sequencing Center, 4Division of Pediatric Hematology-Oncology, Department of Pediatrics, 5Program in Translational Biology and Molecular Medicine, and 6Department of Pathology and Immunology, Baylor College of Medicine, Houston, TX; 7Stem Cell Transplantation and Cellular Therapy, University of Texas MD Anderson Cancer Center, Houston, TX; and 8Department of Oncological Sciences, 9Tisch Cancer Institute, 10Immunology Institute, and 11Department of Dermatology, Icahn School of Medicine, New York, NY

Legend:
ERBB3 gene codes for Receptor tyrosine-protein kinase erbB-3, also known as HER3 (human epidermal growth factor receptor 3), a membrane bound protein

Ref.: Chakraborty R et al., Blood, 2014, 124: 3007-3015
Mutations and Maturation Stage

MYELOID NEOPLASIA

e-Blood

BRAFV600E mutant protein is expressed in cells of variable maturation in Langerhans cell histiocytosis

Felix Sahm,1,2 David Capper,1,2 Matthias Preusser,3 Jochen Meyer,2 Albrecht Stenzinger,4 Felix Lasitschka,4 Anna-Sophie Berghoff,5 Antje Habel,1 Marion Schneider,6 Andreas Kulozik,7 Ioannis Anagnostopoulos,8 Leonhard Müllauer,9 Gunhild Mechtensheimer,4 and Andreas von Deimling1,2

1Department of Neuropathology, Institute of Pathology, Ruprecht-Karls-Universität Heidelberg, Heidelberg, Germany; 2Clinical Cooperation Unit Neuropathology, German Cancer Research Center (DKFZ), Heidelberg, Germany; 3Department of Medicine I and Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria; 4Department of General Pathology, Institute of Pathology, Ruprecht-Karls-Universität Heidelberg, Heidelberg, Germany; 5Institute of Neurology and Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria; 6Experimental Anaesthesiology, University Hospital Ulm, Ulm, Germany; 7Department of Pediatric Oncology, Hematology and Immunology, University Children's Hospital of Heidelberg, Heidelberg, Germany; 8Institute of Pathology, Charité-University Medicine Berlin, Berlin, Germany; and 9Institute of Pathology, Medical University Vienna, Vienna, Austria

Langerhans cell histiocytosis (LCH) is a clinically and histologically heterogeneous disorder. Its classification as either reactive inflammatory or neoplastic has been a matter of debate. However, the recent finding of frequent BRAFV600E mutations in LCH argues for the latter. The exact cell type that harbors the mutation and is responsible for proliferation remains to be identified. We here apply a BRAFV600E mutation-specific antibody to detect the BRAF mutant cells in lesions from 89 patients with LCH. We found BRAFV600E mutations in 34 of 89 (38%) lesions. In lesions with the BRAFV600E mutation, the majority of cells coexpressing S-100 and CD1a harbored mutant BRAFV600E protein. These cells also expressed CD14 and CD36, whereas various fractions exhibited CD207. On the other hand, CD80 and CD86 expression was also present on BRAFV600E-positive cells. Thus, cells of variable maturation, exhibiting an immunohistochemical profile compatible either with myeloid cell or with dedifferentiated Langerhans cell antigens, carry the BRAFV600E mutation. In conclusion, we identify and characterize the neoplastic cells in LCH with BRAFV600E mutations by applying a mutation-specific marker and demonstrate feasibility for routine screening. (Blood. 2012;120(12):e28-e34)

Ref.: Sahm F et al., Blood, 2012, 120: e28-e34
BRAF-V600E expression in precursor versus differentiated dendritic cells defines clinically distinct LCH risk groups

Marie-Luise Berres,1,2,3 Karen Phaik Har Lim,4 Tricia Peters,5 Jeremy Price,1,2,3 Hitoshi Takizawa,7 Hélène Salmon,1,2,3 Juliana Idoyaga,8,9,10 Albert Ruzo,8 Philip J. Lupo,4,6 M. John Hicks,5 Albert Shih,4 Stephen J. Simko,4,6 Harshal Abhyankar,4,6 Rikhia Chakraborty,4,6 Marylene Leboeuf,1,2,3 Monique Beltrão,3 Sérgio A. Lira,3 Kenneth M. Heym,11 Venetia Bigley,12 Matthew Collin,12 Markus G. Manz,7 Kenneth McClain,4,6 Miriam Merad,1,2,3 and Carl E. Allen4,6

Langerhans cell histiocytosis (LCH) is a clonal disorder with elusive etiology, characterized by the accumulation of CD207+ dendritic cells (DCs) in inflammatory lesions. Recurrent BRAF-V600E mutations have been reported in LCH. In this study, lesions from 100 patients were genotyped, and 64% carried the BRAF-V600E mutation within infiltrating CD207+ DCs. BRAF-V600E expression in tissue DCs did not define specific clinical risk groups but was associated with increased risk of recurrence. Strikingly, we found that patients with active, high-risk LCH also carried BRAF-V600E in circulating CD11c+ and CD14+ fractions and in bone marrow (BM) CD34+ hematopoietic cell progenitors, whereas the mutation was restricted to lesional CD207+ DC in low-risk LCH patients. Importantly, BRAF-V600E expression in DCs was sufficient to drive LCH-like disease in mice. Consistent with our findings in humans, expression of BRAF-V600E in BM DC progenitors recapitulated many features of the human high-risk LCH, whereas BRAF-V600E expression in differentiated DCs more closely resembled low-risk LCH. We therefore propose classification of LCH as a myeloid neoplasia and hypothesize that high-risk LCH arises from somatic mutation of a hematopoietic progenitor, whereas low-risk disease arises from somatic mutation of tissue-restricted precursor DCs.

Putative Model on LCH Pathobiology

(A) High-Risk LCH Multisystem
- Circulating precursor
- Tissue-restricted precursor
- Tissue-restricted DC
- LCH DC precursor
- CD34+

(B) Low-Risk LCH Multifocal
- Altered Differentiation
- Increased Proliferation
- Increased Migration

(C) Low-Risk LCH Single Lesion

(D) LCH Lesion
- CD207
- CD1a
- Lymphocytes
- Macrophages
- Eosinophils

Ref.: Berres ML et al., BJH, 2014, 120: 127-161
Current View on LCH Pathogenesis

- Myeloid dendritic precursors
- Myeloid neoplastic clone with inflammatory properties
  - Cytokine/chemokine production
  - Lymphocyte/macrophage recruitment and activation
  - Granuloma formation ± systemic inflammation
    - Tissue damage (e.g. osteolysis)
    - Fever, cytopenia, organ dysfunction

Somatic mutations: BRAF, MAP2K1, ARAF, other

(Modified from Arceci RJ, „Atypical cellular disorders“, Hematology 2002, 297 ff)
Implications of the New Knowledge

- Liquid biopsies?
- Assessment of disease burden (staging)?
- Response evaluation (MRD)?
- Rational (targeted) therapy
EPIDEMIOLOGY

- any age group
- incidence 0.1-1/100,000 children/year
  (1/20,000 children by age 15)
- incidence in adults?
- male:female 1:1 to 2:1
AGE DISTRIBUTION OF LCH

- Bone - unifocal
- Bone - multifocal
- Skin
- MS

% vs. age (in years)
SIGNS AND SYMPTOMS OF LCH

- PAIN, LOCAL SWELLING, MOTION DEFICIT
- SKIN RASH
- NEUROLOGICAL SYMPTOMS
- AURAL DISCHARGE
- POLYURIA, POLYDIPSIA
- ENDOCRINOPATHIES
- FEVER
- COUGH, DYSPNEA
- DIARRHEA; FAILURE TO THRIVE
- TEETH LOSS
ORGAN INVOLVEMENT IN LCH
n=275

- Bone: 79%
- Skin: 25%
- Liver: 11%
- Spleen: 9%
- Ears: 8%
- Lungs: 6%
- DI: 6%
- GI: 5%
- Endocr.: 3%
- Eyes: 2%
HISTOPATHOLOGICAL DIAGNOSIS OF LCH

Light microscopy

Immunohistochemistry

Electron microscopy

DEFINITIVE DIAGNOSIS

CD1a +
Birbeck granules
CD207 + (Langerin)
# OBLIGATORY CLINICAL AND LABORATORY EVALUATION

<table>
<thead>
<tr>
<th>Physical examination</th>
<th>Complete examination, special attention to: skin and mucosal lesions, floating teeth, proptosis, chronic otitis, aural discharge, cough, dyspnea, enlarged liver, spleen, or LN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory tests</td>
<td>CBC, ALT, AST, γ-GT, ALP, bilirubin, total protein, albumin, coagulation (aPTT, TT, fibrinogen), urine specific gravity and osmolality</td>
</tr>
<tr>
<td>Imaging</td>
<td>Skeletal survey, chest x-ray, abdominal ultrasound</td>
</tr>
<tr>
<td>Test</td>
<td>Indication</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>HLA-typing and donor search</td>
<td>Involvement of risk organs</td>
</tr>
<tr>
<td>Bone marrow tap and trephine biopsy</td>
<td>Anemia, leukopenia, thrombocytopenia</td>
</tr>
<tr>
<td>Respiratory function test, HRCT</td>
<td>Dyspnea, changes on thorax x-ray</td>
</tr>
<tr>
<td>Lung biopsy (if BAL negative)</td>
<td>Dyspnea, changes on thorax x-ray (Cave opportunistic infections)</td>
</tr>
<tr>
<td>Gut endoscopy (biopsy?)</td>
<td>chronic, diarrhea, malabsorption, weight loss</td>
</tr>
<tr>
<td>Liver biopsy</td>
<td>Liver dysfunction (discrimination between active disease and cirrhosis)</td>
</tr>
<tr>
<td>Panoramic x-ray of the jaw</td>
<td>Floating teeth, lumps or mucosal lesions</td>
</tr>
<tr>
<td>Skull CT</td>
<td>Suspected orbital, temporal or other skull base lesion</td>
</tr>
<tr>
<td>MRI of the brain</td>
<td>Neurological or endocrine abnormalities</td>
</tr>
<tr>
<td>Consult endocrinologist</td>
<td>DI, growth failure, other endocrine abnormalities</td>
</tr>
<tr>
<td>Consult neurologist/psychologist</td>
<td>DI, neurological signs and symptoms, abnormal MRI</td>
</tr>
<tr>
<td>Consultation ENT specialist, audiogram</td>
<td>Chronic otitis, otorrhea, hearing loss</td>
</tr>
<tr>
<td>Consult ophthalmologist</td>
<td>Proptosis, orbital lesions</td>
</tr>
</tbody>
</table>
CLINICAL CLASSIFICATION

SINGLE SYSTEM DISEASE
Single or Multiple Site
Bone
Skin
Lymph node
(CNS, Lungs, Thyroid)

MULTI SYSTEM DISEASE
> 2 organs involved
± risk organ involvement
TREATMENT OF SINGLE SYSTEM LCH
## DATA OF THE DAL-HX STUDIES on single-system LCH

<table>
<thead>
<tr>
<th>Overall survival:</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event-free survival:</td>
<td>82%</td>
</tr>
<tr>
<td>Reactivations</td>
<td>18%</td>
</tr>
<tr>
<td>Permanent consequences:</td>
<td>25%*</td>
</tr>
</tbody>
</table>

* 50% of the PC present at diagnosis

CURRENT RECOMMENDATIONS

SS-LCH

95% Skeleton
- unifocal: Local Therapy, «wait & see»
- multifocal: Systemic Therapy

5% Skin
- unifocal: Local or systemic Therapy

<1% Lymph nodes
- unifocal: Resection
- multifocal: Systemic Therapy
TREATMENT OF MULTISYSTEM LCH
PROSPECTIVE CLINICAL TRIALS
OF THE HISTIOCYTE SOCIETY

• LCH I Study 1991-1995
• LCH II Study 1996-2000
• LCH III Study 2001-2008

STUDY CENTER
ST. ANNA CHILDREN ‘S HOSPITAL
VIENNA, AUSTRIA
GENERAL THERAPEUTIC APPROACH

• INITIAL THERAPY
  • intensive, duration 6-12 weeks

• CONTINUATION THERAPY
  • non-intensive, duration at least 12 months
STANDARD INITIAL THERAPY

**VBL** 6 mg/m² i.v. bolus

**PRED** 40 mg/m²/day orally; weekly; reduction after week 4

Week:

1. VBL 6 mg/m² i.v. bolus
2. PRED 40 mg/m²/day orally; weekly; reduction after week 4

**VBL** 6 mg/m² i.v. bolus

**PRED** 40 mg/m²/day orally; weekly for 3 days
STANDARD CONTINUATION THERAPY

PRED/VBL Pulses

± mercaptopurine

VBL 6 mg/m² i.v. bolus

PRED 40 mg/m²/day
day 1-5 q 3 week

6MP 50 mg/m²/day
orally;daily
CURRENT LCH PROBLEMS

MORTALITY
- all MS-LCH: 10%
- RO+MS-LCH: 20%

MORBIDITY
- Reactivations (~40%)
- Permanent Consequences:
  - Liver/Lung fibrosis: 20%
  - Diabetes insipidus: 20%
  - Anterior pituitary dysfunction: 10%
  - Neurodegeneration: 10% of MS
LCH-IV
International Collaborative Treatment Protocol for Children and Adolescents with LANGERHANS CELL HISTIOCYTOSIS

EudraCT Nr.: 2011-001699-20
International Sponsor: St. Anna Kinderkrebsforschung
(Children's Cancer Research Institute)
Vienna, Austria

Protocol Version 1.0, April 13th, 2011
(corrected version, November 25th, 2012)

Protocol Code Number: 042011

Disclaimer:
This protocol is a research document, and is intended for research purposes only. It is not to be copied, redistributed or used for any other purpose without the prior written permission of the Histiocyte Society. The treatments in this protocol are intended only for use by clinical investigators; they may not prove to be more effective than standard treatment, and should not be used to direct the practice of medicine by any person or to provide individualized medical care, treatment, or advice to any patient who has not provided written informed consent for participation in this study. Treating physicians who are seeking guidance for the standard treatment of a histiocytic disorder should contact the Histiocyte Society.
(http://www.histiocytesociety.org)

Start of the Study: December 1st, 2012
**LCH IV Registry & Stratification**

- **STRATUM I**: n=1200 (800 rand.) 1\textsuperscript{st}-line Therapy (Group 1 & 2)
  - Lack of response, Progression, in risk organs

- **STRATUM II**: n=400 2\textsuperscript{nd}-line Therapy for Non-risk LCH
  - Progression, Reactivation, in non-risk organs

- **STRATUM III**: n=30 Salvage Therapy for Risk LCH
  - Lack of response, Progression, in risk organs

- **STRATUM IV**: n=25 LCH-HSCT

- **STRATUM V**: n=50 Monitoring & Treatment of CNS-LCH

- **STRATUM VI**: n=450 Natural history and Management of “other” SS-LCH
  - Progression, Reactivation

- **STRATUM VII**: Long-term Follow up

- **STRATUM VII**: Multisystem, multifocal bone, and special single system LCH

- **STRATUM VII**: Isolated tumorous LCH of the brain

- **STRATUM VII**: Other single system LCH
LCH-IV: Teilnehmende Länder