The future of HLH treatment: translating fundamental insights into clinical realities

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How do we improve the outcomes for children with HLH?

What are the problems?

1. The disease is rare and the diagnosis is problematic
   > Raise awareness (we can all help with this)
   > Improve diagnostic criteria (based on new understanding)

2. There is ample ‘room for improvement’ of initial therapies
   > The disease is poorly understood
     >> Make a laboratory model and use it to:
     Understand how HLH develops
     Understand how current therapy works (drugs, BMT)
     Find new therapies
     >>>> Test new therapeutic discoveries in patients
     Conduct clinical trials

3. There is ample room for improvement of BMT for patients with HLH
   > Try new approaches in transplantation
   > Use laboratory models to develop alternatives (gene therapy)
## Diagnostic Criteria (per HLH2004 study):  
Genetic mutation(s) associated with HLH, or at least 5 of 8:  
1. Fever  
2. Splenomegaly  
3. Cytopenias (affecting at least 2 cell lineages)  
4. Hypertriglyceridemia or hypofibrinogenemia  
5. Elevated ferritin (>500 ng/ml)  
6. Elevated sCD25 (sIL2r)  
7. Low or absent NK cell function  
8. Hemophagocytosis evident on biopsy (in bone marrow, spleen, liver, or lymph node)
A pathophysiologic view of HLH patterns

(what does our increasing understanding of HLH tell us about how we may recognize it in the future?)

<table>
<thead>
<tr>
<th>Category 1: Predisposing Immunodeficiency</th>
<th>Category 2: Significant Immune Activation</th>
<th>Category 3: Abnormal Immunopathology</th>
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</thead>
<tbody>
<tr>
<td>Low or absent NK cell function</td>
<td>Fever</td>
<td>Cytopenias</td>
</tr>
<tr>
<td>Genetic defect of cytotoxicity</td>
<td>Splenomegaly/Hepatomegaly</td>
<td>Decreased fibrinogen or increased triglycerides</td>
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<tr>
<td>Family history of HLH</td>
<td>Elevated Ferritin (&gt;3000 ng/ml)</td>
<td>Hemophagocytosis</td>
</tr>
<tr>
<td>Prior episode(s) of HLH or unexplained cytopenias</td>
<td>Elevated sCD25</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Markers of impaired cytotoxicity: Decreased expression of perforin, SAP, XIAP, or mobilization of CD107a</td>
<td>Elevated sCD163&lt;sup&gt;93&lt;/sup&gt;</td>
<td>CNS involvement</td>
</tr>
</tbody>
</table>

(The HLH-2004 diagnostic criteria are listed in bold.)

How do we understand what is going on in patients with HLH?
Mouse Model of HLH:

Infect with LCMV

prf1-/-

Prolonged fever/excessive splenomegaly
Pancytopenia
Hypofibrinogenemia/hypertriglyceridemia
Elevated sIL2R, ferritin
Hemophagocytosis
Absent NK function
Hypercytokinemia
Tissue infiltration with MΦ’s/ T cells
Fatal immunopathology in liver, CNS, etc.

Jordan et al, Blood, 2004
Figure 1. LCMV-infected pfp-/− mice display clinical and laboratory features of HLH
Figure 4. Both CD8+ T cells and IFNγ are necessary for the development of an HLH-like disorder in LCMV-infected pfp-/- mice

3 steps to HLH...

Normal individual:

Pathogens

(+) → Dendritic cells

(+) → (CD8⁺) T cells

(−) → Cytokines

→ Cytotoxic killing

→ ‘Immunity’

HLH-prone individual:

Pathogens

(+) → Dendritic cells

(+++) → (CD8⁺) T cells

‘HyperImmunity’

(+++) → IFN-γ

→ Macrophages

→ HLH
Rational Targets for treating HLH

Treat infection

\[ \xrightarrow{(+)} \] Dendritic cells/ APC’s

\[ \xrightarrow{ (+++)} \] ATG/ CAMPATH

\[ \xrightarrow{ (+++)} \] Etoposide

\[ \xrightarrow{ (+++)} \] ‘HyperImmunity’

\[ \xrightarrow{ (+++)} \] IFN-\( \gamma \)

\[ \xrightarrow{ \text{Targets for future therapies} } \]

\[ \xrightarrow{ \text{Macrophages} } \]

\[ \xrightarrow{ \text{HLH} } \]

Ongoing research efforts:
1. Can we combine ATG and etoposide for better effects? (the HIT-HLH trial)
2. Can we develop therapies (using the mouse model) to specifically target the dendritic cells and T cells which are driving HLH?
Hybrid ImmunoTherapy for Hemophagocytic LymphoHistiocytosis

WWW.ClinicalTrials.gov Identifier: NCT01104025
HIT-HLH

• Trial incorporates initial ATG, followed by weekly etoposide. After the first week, dexamethasone dosing is similar to HLH94/2004
• Rationale: Clinical and biologic studies suggest that a useful synergy between ATG and Etoposide may be observed
• Eligible patients: have active HLH and have not been treated in recent months with etoposide (some steroids OK)
• Trial is open for enrollment in Cincinnati and at 10 other collaborating centers in the US and Canada
• Primary outcomes:
  – Survival and complete response rates at 8 weeks
• Secondary outcomes:
  – Survival and response rates until time of HCT, or up to six months after enrollment (if no HCT)
  – Define response/relapse kinetics
Newer strategies for BMT are associated with higher survival in patients with HLH

Kaplan-Meier 3-year survival curves for the MAC and RIC groups.

GENE THERAPY FOR HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH)

FIXING A CRITICAL ‘CIRCUIT BREAKER’ IN THE IMMUNE SYSTEM

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Perforin deficiency appears highly suitable for gene therapy

• Monogenic disorder
  – All disease-associated mutations are ‘loss of function’ (No ‘dominant negatives’)

• Correction in only a small portion of cells is sufficient for disease protection

• Current therapies carry significant risks
Gene therapy for murine HLH

Marrow LSK’s

prf-/-

Transduce with prf1 lentivirus

prf-/-

16 weeks

IFN-γ Cytopenias etc.

LCMV
Acknowledgements

**Jordan Lab**
Catherine Terrell
Scott Millen

Prior members:
Supriya Pokkali
Erin Zoller
Ted Johnson
Rob Thacker

**Collaborators:**

**Gene therapy project:**
Punam Malik
Kim Risma
Bobby Gaspar (UCL/London)

**Novel therapeutics:**
Dave Hildeman
Jonathan Katz

**HIT-HLH trial:**
Lisa Filipovich
The HIT-HLH Network (10+ PI’s)

**CCHMC clinical care/research:**
Lisa Filipovich
Rebecca Marsh
Other colleagues

**Funding:**
NIH/NHLBI
The Histiocytosis Association
Liam’s Lighthouse Foundation

The Center for Immunologic Research