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# MEETING SPONSORS
Visit our webpage to see all the clinical tests we offer for HLH and other primary immunodeficiencies.

www.cincinnatichildrens.org/DIL
Dear Colleagues,

The Histiocyte Society cordially welcomes you to the 35th Annual Meeting, which will be held in Memphis, TN, on November 3rd, 4th and 5th, 2019 and hosted by the world’s famous St. Jude Children’s Research Hospital.

Founded by the entertainer Danny Thomas and opened in 1962, St. Jude has made a tremendous development over the past six decades. It is a place to go for any pediatric hem/onc where one can learn not only about the most recent developments in the field but also how to perform professional fundraising and how international outreach programs can improve children’s fates and save lives in remote countries.

Memphis itself is not just a city; it is the birthplace and a contemporary witness of the civil rights movement. Downtown Memphis is home to the National Civil Rights Museum at the Lorraine Motel, the site of Dr. Martin Luther King’s assassination. Last year the 50th anniversary of this event has been celebrated and as a result, there are now several new memorials not far from the NCRM. Memphis is also rich in musical history. It is Home of Blues, Soul and Rock ‘n’ Roll. While Graceland is the obvious stop for Elvis fans, there are also a number of live music hot spots for those who like to obtain a personal feeling of the musical flavor of Memphis.

This year our Program Committee was supported by local organizers from the St. Jude staff to prepare an attractive meeting agenda. We have invited Prof. Miriam Merad, a renowned expert on dendritic cell biology to share her new research and its implications for the histiocytic disorders. The traditional Jon Pritchard lecture on Nikolas Symposium this year is dedicated to immune strategies in histiocytosis. The meeting will be rounded up by two thematic symposia on LCH and HLH, as well as by the scientific and meet-the-expert-sessions.

This year the transition of the presidency is due and Michael Jordan from Cincinnati will take over for the next three years.

The social highlights of our meetings are as usual the Welcome Reception and the Annual Banquet. The Welcome Reception will take place in the Skyway Ballroom and open-air rooftop at the historic Peabody Hotel. Enjoy a casual evening of networking and refreshments all while enjoying a special performance by Memphis’ own Stax Music Academy. The Annual Banquet, always a highlight of the meeting, will take place in Elvis’ Car Museum on the grounds of Elvis’ famous Graceland. Tours of the mansion will be provided before making our way to the car museum to enjoy dinner and dancing to the sounds of the St. Jude Band.

As you know, meeting of this format require a lot of time, energy and resources to be properly organized. I would like to specially appreciate our symbiotic partner and key sponsor, the Histiocytosis Association, without whose generous support this meeting would not be possible.

I look forward to seeing you in Memphis!

Welcome to the Histiocyte Society Meeting 2019!

Milen Minkov
President
Histiocyte Society
ABOUT THE HISTIOCYTE SOCIETY

The Histiocyte Society is a professional medical association comprised of more than 200 physicians and scientists from around the world. Members of the organization are considered to be the leaders in understanding and treating histiocytic disorders. The Society is committed to advancing knowledge about histiocytic disorders and improving outcomes for patients through the planning, development, sponsorship and oversight of clinical research.

Building Knowledge

The Histiocyte Society hosts an annual scientific meeting in different locations around the world. Attendance is open to members of the Society as well as other professionals working in the field of histiocytic disorders and related studies. Meetings feature presentations of individual and collective research efforts as well as keynote lectures from guest speakers; special-interest groups convene to discuss and develop new and innovative treatment regimes. This interactive forum allows the best and brightest minds in the histiocytosis community to share the most progressive information and to shape the future of research. Beyond the prolific exchanges that occur during the meeting, presenters work collectively to extend their reach by publishing subsequent articles and manuscripts in scientific journals worldwide.

Advancing Treatment

Through extensive research and collaboration, the Histiocyte Society has made numerous, significant strides in the fight against histiocytic disorders. The Society has established scientific standards for histiocytic disorders that are accepted worldwide; they include: 1) A common language of uniform disease classification, 2) Standardized diagnostic criteria, and 3) Guidelines for patient evaluation and follow-up. The Society remains dedicated to facilitating essential and innovative clinical research – developing critical knowledge and increasingly effective treatments in the pursuit of a cure.

2019 ANNUAL MEETING MOBILE APP - INVITATION IN YOUR EMAIL

The 2019 Histiocyte Society Annual Meeting has a free mobile event app! The best way to gain access to the app is to click on the invitation that was sent to the email you provided during registration for the Annual Meeting. You can also search for “Histiocyte Society Annual Mtg” in your app store. Only registered attendees have access to the mobile app. See the emailed invitation for detailed instructions for logging into the app. If you accessed last year's mobile app, be sure to download the update for the app to refresh it.

The Annual Meeting app password is “hsmtg2019”.

The app is available in the App Store and Google Play. There is also a desktop/laptop version which you can access at hsmtg2019.zerista.com.

All of the information in the program book is in the app, plus much more! Create your own custom agenda, read all of the abstracts, connect with colleagues, access maps and the poster presentation locations, post pictures, and get the latest news and information right at your fingertips!

For directions on how to download and access the app, look for an invitation in your email. App accounts are linked to the email used to register for the annual meeting.

ANNUAL MEETING PROGRAM

Copyright 2019 by the Histiocyte Society

All programs presented at the 2019 Annual Meeting constitute copyrighted presentations owned by the Histiocyte Society. The copyright of the 2019 Histiocyte Society Annual Meeting Program is owned by the Histiocyte Society. The Histiocyte Society reserves the rights to all recordings and reproductions of presentations at this Annual Meeting and all Histiocyte Society educational and scientific meetings.

Photography Consent

Registration for, attendance at, and participation in the 2019 Histiocyte Society Annual Meeting and other activities constitutes an agreement by the participant to allow the Histiocyte Society to use and distribute (both now and in the future) the registrant’s or attendee’s image and/or voice in photographs, video, electronic reproductions and audio of such events and activities. Please note: St. Jude visitors are not permitted to take photos or videos of patients or families.
The Road to Partnership

Three-month old Bethany Toughill was diagnosed in 1983. Bethany’s dad, Jeff, and her mother, Sally, experienced the same fear that today’s parents feel when learning that their child has this disease. Alone and frustrated, Sally and Jeff were led to find other families affected by histiocytosis so that they could emotionally support each other. In 1986 they founded the Histiocytosis Association, a community comprised of patients, parents, family members and friends.

At about the same time that the Association was founded, a group of physicians formed the Histiocyte Society – an international group of clinicians and scientists committed to improving the lives of patients with histiocytic disorders by conducting clinical and laboratory research into the causes and treatment of this disease. Recognizing that these two groups had the same goal, Histiocytosis Association President Jeffrey Toughill offered the Association’s business resources to help manage the Histiocyte Society. Thus began the partnership that still exists today.

A True Partnership

The Histiocytosis Association and the Histiocyte Society remain separate organizations working toward a common goal, with the Histiocytosis Association serving as the Society’s administrative center (Secretariat) and primary source of funding. The Histiocytosis Association serves the administrative needs of the Histiocyte Society by:

- Organizing and managing the Society’s annual scientific and Executive Board meetings,
- Managing the overall organizational, administrative and financial operations,
- Aiding in the development of organizational guidelines and operating procedures,
- Building, developing and maintaining the organization and annual meeting websites,
- Facilitating communication between Society members and the Executive Board, and
- Building and managing the Society’s membership database.

The Histiocytosis Association Mission

The Histiocytosis Association is dedicated to raising awareness about histiocytic disorders, providing educational and emotional support for patients and families and funding research leading to better treatments and a cure.

The Histiocytosis Association Research Program

At the very heart of the Histiocytosis Association is the steadfast commitment to finding a cure for histiocytic disorders. The Histiocytosis Association is committed and focused on a threefold research plan and philosophy:

- Funding basic science research being conducted worldwide identified through a competitive, peer-review process modeled after that of the National Institutes of Health. The Histiocytosis Association requests research proposals on a yearly basis – usually around May. Once research proposals are received the Histiocyte Society Scientific Committee serves as the first-step review. Scores from this review are then submitted to the Histiocytosis Association’s Medical & Scientific Advisory Committee (MSAC) for a second review. The SAC then makes a recommendation to the Histiocytosis Association’s Board of Trustees concerning grants to be funded.
- Funding clinical studies that result in identifying the best possible treatments for histiocytic disorders.
- Facilitating research by administratively managing the Histiocyte Society.

Since 1992, 189 individual awards have been made to date, representing more than $6.8 million to support critical research around the world. Grant amounts now average $50,000 per project but have been awarded in amounts up to $100,000 in the past. The Histiocytosis Association of Canada (HAC) has provided $265,000 of that funding.

Two Organizations, One Goal

The Histiocytosis Association and the Histiocyte Society have been committed partners for nearly 35 years. Though separate organizations, they share a common goal that binds their continued partnership - to find better treatments and, ultimately, a cure leading to a world free of histiocytic disorders.

To learn more about the Histiocytosis Association visit www.histio.org.
ACKNOWLEDGEMENTS AND RECOGNITIONS

HISTIOCYTE SOCIETY EXECUTIVE BOARD
President ......................................................... Milen Minkov 2016-2019
President-Elect ............................................. Michael Jordan 2017-2019
Treasurer ....................................................... Karin Beutel 2016-2018
Secretary ....................................................... Kim Nichols 2017-2018
Member-at-Large ........................................... Carl Allen 2017-2020
Member-at-Large ........................................... Scott Baker 2017-2020

HISTIOCYTE SOCIETY EDUCATION COMMITTEE
Patrick Campbell, Chairperson 2017-2019
Itziar Astigarraga 2018-2020
Gleb Bronin 2017-2019
Barbara Degar 2017-2019
Michael Henry 2017-2019
Elena Sieni 2017-2019
Julie Talano 2018-2020

HISTIOCYTE SOCIETY SCIENTIFIC COMMITTEE
Rebecca Marsh, Chairperson 2017-2019
Ed Behrens 2018-2020
Rikhia Chakraborty 2018-2020
Julien Haroche 2017-2019
Jennifer Picarsic 2017-2019
Astrid van Halteren 2018-2020

HISTIOCYTE SOCIETY STUDY GROUP CHAIRPERSONS
Adult Histiocytosis ......................................... Michael Girschikofsky
Epidemiology/Late Effects .............................. Riccardo Haupt /Vasanta Nanduri
HLH ............................................................ Jan-Inge Henter
LCH-IV ......................................................... Milen Minkov/Carlos Rodriguez-Galindo
Rare Histiocytic Disorders ......................... Oussama Abla

HLH STEERING COMMITTEE
Michael Jordan, Interim Co-Chairperson 2017-2021
Kim Nichols, Interim Co-Chairperson 2015-2019
Itziar Astigarraga 2016-2020
Scott Baker 2018-2022
Stephan EhI 2016-2020
Jan-Inge Henter 2014-2018
AnnaCarin Home 2015-2019
Gritta Janka 2016-2020
Kai Lehmbert 2017-2021
Elena Sieni 2015-2019
Zhao Wang 2015-2019

LCH STEERING COMMITTEE
Carl Allen, Interim Co-Chairperson 2016-2020
Karin Beutel, Interim Co-Chairperson 2017-2021
Patrick Campbell 2018-2022
Michael Girschikofsky 2015-2019
Michelle Hermiston 2017-2021
Rima Jubaran 2017-2021
Stephan Ladisch 2015-2019
Milen Minkov 2018-2022
Vasanta Nanduri 2016-2020
Barrett Rollins 2017-2021
Kimo Stine 2018-2022
Cor van den Bos 2015-2019
Johannes Visser 2015-2019

RARE HISTIOCYTIC DISORDERS STEERING COMMITTEE
Oussama Abla, Chairperson 2016-2020
Jorge Braier 2016-2020
Eli Diamond 2015-2019
Benjamin Durham 2017-2021
Jean-Francois Emile 2017-2021
Michael Girschikofsky 2017-2021
Julien Haroche 2018-2022
Eric Jacobsen 2015-2019
Ron Jaffe 2015-2019
Zdenka Krenova 2019-2022
Akira Morimoto 2017-2021
Jennifer Picarsic 2015-2019
Sheila Weitzman 2016-2020

HISTIOCYTE SOCIETY PAST PRESIDENTS
Carlos Rodriguez-Galindo 2013-2016
Jim Whitlock 2010-2013
Alexandra Filipovich 2007-2010
Jan-Inge Henter 2004-2007
R. Maarten Egeler 2001-2004
Kenneth McClain 1998-2001
Göran Elinder 1996-1998
Helmut Gadner 1992-1996
Stephan Ladisch 1989-1992
Blaise Favara 1987-1989
Christian Nezelof 1985-1987

35 YEARS HISTIOCYTE SOCIETY
2019 | MEMPHIS, TN USA
## ACKNOWLEDGEMENTS AND RECOGNITIONS

### NEZELOF PRIZE IN CLINICAL SCIENCE Awardees

<table>
<thead>
<tr>
<th>Name</th>
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<tbody>
<tr>
<td>Jennifer Picarsic</td>
<td>2018</td>
</tr>
<tr>
<td>Elena Sieni</td>
<td>2017</td>
</tr>
<tr>
<td>Francesca Minoia</td>
<td>2016</td>
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<tr>
<td>Alexandra Löfsted</td>
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<td>Vasanta Nanduri</td>
<td>2014</td>
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<td>Carl Allen</td>
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<tr>
<td>Stephen Simko</td>
<td>2012</td>
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<td>Thomas Lehrnbecher</td>
<td>2011</td>
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<td>Rebecca Marsh</td>
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<tr>
<td>Rebecca Marsh</td>
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<tr>
<td>Jorge Braier</td>
<td>2008</td>
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<tr>
<td>Kenneth McClain</td>
<td>2007</td>
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<tr>
<td>Loretta Lau</td>
<td>2006</td>
</tr>
<tr>
<td>AnnaCarin Horne</td>
<td>2005</td>
</tr>
<tr>
<td>Marie Ouachée-Chardin</td>
<td>2004</td>
</tr>
<tr>
<td>Manuel Steiner</td>
<td>2003</td>
</tr>
<tr>
<td>Jorge Braier</td>
<td>2002</td>
</tr>
<tr>
<td>Wolfgang Holter</td>
<td>2001</td>
</tr>
<tr>
<td>Kazuhiro Kogawa</td>
<td>2000</td>
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</table>

### NEZELOF PRIZE IN BASIC SCIENCE Awardees

<table>
<thead>
<tr>
<th>Name</th>
<th>Year</th>
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<tbody>
<tr>
<td>Lauren Meyer</td>
<td>2018</td>
</tr>
<tr>
<td>Hirofumi Shibata</td>
<td>2017</td>
</tr>
<tr>
<td>Edward Behrens</td>
<td>2016</td>
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<tr>
<td>Benjamin Durham</td>
<td>2015</td>
</tr>
<tr>
<td>Samuel Chiang Cern Cher</td>
<td>2014</td>
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<tr>
<td>Gayane Badalan-Very/Kim Nichols</td>
<td>2013</td>
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<tr>
<td>Edward Behrens</td>
<td>2012</td>
</tr>
<tr>
<td>Edward Behrens</td>
<td>2011</td>
</tr>
<tr>
<td>Michelle Hermiston</td>
<td>2010</td>
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<tr>
<td>Michael Jordan</td>
<td>2009</td>
</tr>
<tr>
<td>Matthew Collin</td>
<td>2008</td>
</tr>
<tr>
<td>Kejian Zhang</td>
<td>2007</td>
</tr>
<tr>
<td>Alessandra Santoro</td>
<td>2006</td>
</tr>
<tr>
<td>Udo zur Stadt</td>
<td>2005</td>
</tr>
<tr>
<td>Cristina Costa/Kimberly Risma</td>
<td>2004</td>
</tr>
<tr>
<td>Michael B, Jordan</td>
<td>2003</td>
</tr>
<tr>
<td>Susan Lee/Joyce Villanueva</td>
<td>2002</td>
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<tr>
<td>Maurizio Aricó</td>
<td>2001</td>
</tr>
<tr>
<td>Pieter Leenen</td>
<td>2000</td>
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### ROBERT J. ARCECI AWARD FOR BEST POSTER

<table>
<thead>
<tr>
<th>Name</th>
<th>Year</th>
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<tbody>
<tr>
<td>Amel Sengal</td>
<td>2018</td>
</tr>
<tr>
<td>Caroline Hutter</td>
<td>2017</td>
</tr>
<tr>
<td>Sandra Ammann</td>
<td>2016</td>
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### HISTIOCYTE SOCIETY GOLDEN PIN RECIPIENTS

<table>
<thead>
<tr>
<th>Name</th>
<th>Year</th>
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<tbody>
<tr>
<td>Jorge Braier</td>
<td>2017</td>
</tr>
<tr>
<td>Lisa Filipovich</td>
<td>2017</td>
</tr>
<tr>
<td>Gritta Janka</td>
<td>2016</td>
</tr>
<tr>
<td>Stephan Ladisch</td>
<td>2016</td>
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<tr>
<td>R. Maarten Egeler</td>
<td>2015</td>
</tr>
<tr>
<td>Sheila Weitzman</td>
<td>2014</td>
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<tr>
<td>Shinsaku Imashuku</td>
<td>2010</td>
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<tr>
<td>Helmut Gadner</td>
<td>2008</td>
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<tr>
<td>Jon Pritchard</td>
<td>2006</td>
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<tr>
<td>Giulio D'Angio</td>
<td>2002</td>
</tr>
<tr>
<td>Sally Kivilis</td>
<td>2001</td>
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<tr>
<td>Elizabeth Kontoyannis</td>
<td>2000</td>
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<tr>
<td>Paul Kontoyannis</td>
<td>2000</td>
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<tr>
<td>Jeffrey M. Toughill</td>
<td>1998</td>
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### HISTIOCYTE SOCIETY HONORED MEMBERS

<table>
<thead>
<tr>
<th>Name</th>
<th>Year</th>
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</thead>
<tbody>
<tr>
<td>Helmut Gadner</td>
<td>2008</td>
</tr>
<tr>
<td>Shinsaku Imashuku</td>
<td>2007</td>
</tr>
<tr>
<td>Gritta Janka</td>
<td>2007</td>
</tr>
<tr>
<td>Valerie Broadbent</td>
<td>2000</td>
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<tr>
<td>Blaise Favara</td>
<td>1998</td>
</tr>
<tr>
<td>Mark Nesbit</td>
<td>1998</td>
</tr>
<tr>
<td>Christian Nezelof</td>
<td>1998</td>
</tr>
</tbody>
</table>

---

2019 | MEMPHIS, TN USA
Congratulations to the Histiocyte Society’s 2019 Travel Scholarship recipients:

Mayada Abu Shanap
for the abstract titled,
OUTCOME OF CHILDREN WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH) TREATED AT KING HUSSEIN CANCER CENTER
This abstract will be presented during the Poster Presentation Session on Monday, November 4, 2019.

Guido Felizzia
for the abstract titled,
CONGENITAL HIGH RISK LANGERHANS CELLS HISTIOCYTOSIS. HIGHER RESPONSE WITH EMPIRICAL USE OF VEMURAFENIB. CASE REPORT
This abstract will be presented during the Poster Presentation Session on Monday, November 4, 2019.

Muhammad Rafie Raza
for the abstract titled,
OUTCOME OF LANGERHANS CELL HISTIOCYTOSIS (LCH) - A SIXTEEN YEARS STUDY
This abstract will be presented during the Poster Presentation Session on Monday, November 4, 2019.

Each year the Histiocyte Society awards at least one scholarship based on the applicant’s demonstration of need for financial assistance in order to attend the Annual Meeting. Scholarships are awarded in the amount of $1,000 US and are based on the availability of funds.

A special thank you to Sobi for sponsoring one of the Travel Scholarships this year.
## AT-A-GLANCE AGENDA

### SATURDAY • NOVEMBER 2, 2019

<table>
<thead>
<tr>
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<th>Event</th>
<th>Location</th>
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<tbody>
<tr>
<td>0830</td>
<td>Buses Start Running</td>
<td>Peabody/Hu/St. Jude</td>
</tr>
<tr>
<td>1000</td>
<td>Executive Board Meeting*</td>
<td>Meeting Room 1</td>
</tr>
<tr>
<td>1300</td>
<td>HS Board/ECD Global Alliance Joint Lunch*</td>
<td>Meeting Room 3</td>
</tr>
<tr>
<td>1600</td>
<td>Coffee Break</td>
<td>Atrium</td>
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<tr>
<td>1730</td>
<td>LCH Steering Committee Meeting*</td>
<td>Meeting Room 2</td>
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<tr>
<td>1830</td>
<td>Rare Histiocytic Disorders Steering Committee Meeting*</td>
<td>Meeting Room 1</td>
</tr>
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<td>2030</td>
<td>Last Bus Leaves St. Jude</td>
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### SUNDAY • NOVEMBER 3, 2019

<table>
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<tr>
<td>0730</td>
<td>Buses Start Running</td>
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<td>0800</td>
<td>Meeting Registration and Check-In</td>
<td>Atrium</td>
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<tr>
<td>0830</td>
<td>LCH-IV Study Management Group Session*</td>
<td>Closed Session</td>
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<td>0830</td>
<td>Adult LCH Disease Discussion Session</td>
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<td>Coffee Break</td>
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<td>1000</td>
<td>LCH Disease Discussion Session</td>
<td>Lecture Hall</td>
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<td>1230</td>
<td>Lunch</td>
<td>Domino’s Event Center</td>
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<td>Rare Histiocytic Disorders Discussion Session</td>
<td>Lecture Hall</td>
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<td>1330</td>
<td>HLH Education Session*</td>
<td>Board Room</td>
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<td>1330</td>
<td>HLH Steering Committee Meeting*</td>
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<td>LCH Education Session</td>
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<td>HLH/MAS Disease Discussion Session</td>
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<td>1700</td>
<td>Rare Histiocytoses Education Session</td>
<td>Board Room</td>
</tr>
<tr>
<td>1830</td>
<td>Welcome Reception</td>
<td>Peabody Hotel—Skyway and Rooftop</td>
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<tr>
<td>1845</td>
<td>Last Bus Leaves St. Jude</td>
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</tbody>
</table>

Buses will start at The Peabody, then stop at The Hu before proceeding to St. Jude Children’s Research Hospital. Transportation will continue looping all day until the final pickup time listed. Travel time from the pickup at The Peabody to St. Jude Children’s Research Hospital is approximately 15 minutes.

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**WWW.HISTIOCYTESOCIETY.ORG/MEMBERSHIP**

* Indicates closed session
* Indicates that advance registration was required
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<tr>
<th>Time</th>
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<tr>
<td>0730</td>
<td>Buses Start Running</td>
<td>Peabody/Hu/St. Jude</td>
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<tr>
<td>0800</td>
<td>Meeting Registration and Check-In</td>
<td>Peabody/Hu/St. Jude</td>
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<tr>
<td>0800</td>
<td>Poster Presentation Setup</td>
<td>Board Room</td>
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<tr>
<td>0800</td>
<td>Education Committee Meeting*</td>
<td>Meeting Room 7</td>
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<tr>
<td>0800</td>
<td>Scientific Committee Meeting*</td>
<td>Meeting Room 1</td>
</tr>
<tr>
<td>0900</td>
<td>Opening Ceremonies</td>
<td>Atrium</td>
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<tr>
<td>0915</td>
<td>Guest Speaker Presentation</td>
<td>Auditorium</td>
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<tr>
<td>1000</td>
<td>Coffee Break</td>
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<tr>
<td>1030</td>
<td>HLH Symposium: HLH Intersection with the Inflammasome</td>
<td>Auditorium</td>
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<tr>
<td>1230</td>
<td>Lunch</td>
<td>Domino’s Event Center</td>
</tr>
<tr>
<td>1230</td>
<td>Young Investigator’s Luncheon*</td>
<td>Lecture Hall</td>
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<tr>
<td>1330</td>
<td>Scientific Session I: Oral Presentations</td>
<td>Auditorium</td>
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<tr>
<td>1500</td>
<td>Coffee Break</td>
<td>Atrium</td>
</tr>
<tr>
<td>1530</td>
<td>Scientific Session II: Presidential Symposium</td>
<td>Auditorium</td>
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<tr>
<td>1700</td>
<td>Poster Presentation Session</td>
<td>Meeting Room 5/Board Room</td>
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**MONDAY • NOVEMBER 4, 2019**

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<tr>
<td>0830</td>
<td>Clinical Studies and Registries Update</td>
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<tr>
<td>0915</td>
<td>Jon Pritchard Lecture on the Nikolas Symposium</td>
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<tr>
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<tr>
<td>1030</td>
<td>LCH Symposium: Exploring Mechanisms of LCH Pathogenesis Beyond BRAF</td>
<td>Auditorium</td>
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<tr>
<td>1230</td>
<td>Lunch</td>
<td>Domino’s Event Center</td>
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<tr>
<td>1230</td>
<td>AME Histi Working Group Meeting</td>
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<tr>
<td>1230</td>
<td>HLH Meet the Expert Lunch Session*</td>
<td>Meeting Room 2</td>
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<tr>
<td>1230</td>
<td>LCH Meet the Expert Lunch Session*</td>
<td>Meeting Room 5</td>
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<tr>
<td>1230</td>
<td>Rare Histiocytes Meet the Expert Lunch Session*</td>
<td>Meeting Room 3</td>
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<tr>
<td>1330</td>
<td>Scientific Session III: Oral Presentations</td>
<td>Auditorium</td>
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<tr>
<td>1500</td>
<td>Presentation of Late Breaking Abstracts</td>
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</tr>
<tr>
<td>1530</td>
<td>General Assembly Business Meeting*</td>
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<tr>
<td>1630</td>
<td>Executive Board Meeting*</td>
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<tr>
<td>1630</td>
<td>Education Committee Meeting*</td>
<td>Auditorium</td>
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<tr>
<td>1630</td>
<td>Scientific Committee Meeting*</td>
<td>Auditorium</td>
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<tr>
<td>1715</td>
<td>Staggered Group Transportation to Histiocyte Society Annual Banquet</td>
<td>Peabody Lobby</td>
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<tr>
<td>2000</td>
<td>Histiocyte Society Annual Banquet, Closing Ceremonies &amp; Awards*</td>
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**TUESDAY • NOVEMBER 5, 2019**

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**GUEST SPEAKER HIGHLIGHTS**

**Carl Allen** is currently Co-Chair of the Lymphoma and Histiocytosis Programs at the Texas Children’s Cancer and Hematology Centers (TXCH), where he directs translational research efforts. His research focus is on understanding mechanisms of aberrant immune function in human disease, including histiocytic disorders, lymphoproliferative disorders and lymphomas. His team has a history of productive collaborations (Miriam Merad (Mount Sinai), Matthew Collin (Newcastle), Florent Ginhoux (Singapore) and Markus Manz (Zurich)) to use complementary experimental models and approaches to understand pathogenesis of Langerhans cell histiocytosis. Their work to date has contributed to re-defining the cell of origin as an immature myeloid precursor (Allen et al., JI 2010), determined that state of differentiation of cell of origin determines clinical manifestations of disease (Berres et al., JEM 2014), created the first mouse models of LCH (Berres et al., JEM 2014), and identified functionally active recurrent mutations in MAP2K1 and BRAF in LCH (Chakraborty et al., 2014; Chakraborty et al., 2016). Together with Carlos Rodriguez-Galindo, they were awarded a grant to establish the North American Consortium for Histiocytosis Research, now including more than 30 institutions, which has launched 2 clinical trials and a LCH correlative biology study.

**Scott Canna** is an Assistant Professor of Pediatrics and of Immunology, a practicing Pediatric Rheumatologist, and an RK Mellon Institute Scholar at the University of Pittsburgh Children’s Hospital. He has been actively pursuing the mechanisms of auto- and hyperinflammatory diseases since 2005. This began with training in human translational autoinflammation at the NIH, where he contributed to the seminal discovery that IL-1 blockade abolished systemic inflammation in patients with NLRP3 inflammasome hyperactivity. In fellowship and early post-doctoral work under Dr. Edward Behrens, he helped characterize a novel murine model Macrophage Activation Syndrome (MAS) that examined the balance of Interferon-g with IL-10. Back at the NIH as a Metzger Scholar, Dr. Canna led a that identified NLRC4 inflammasome hyperactivity as a driver of both elevated IL-18 and life-threatening MAS. His group also demonstrated that IL-18 blockade may be a rational and feasible treatment strategy for MAS, supporting development of an orphan clinical trial in monogenic MAS. Dr. Canna’s training and approach have been consistently translational, beginning with (particularly genetic) observations in human inflammatory diseases, and then leveraging *in vivo* murine models and cellular immunology to better understand mechanisms of human auto- and hyperinflammation. Since beginning his independent, NIH-funded laboratory in 2016, his group has begun to connect the dots between NLRC4, IL-18, and MAS.

**Matthew Collin** is Professor of Haematology at Newcastle University and Newcastle upon Tyne Hospitals NHS Foundation Trust. He received a PhD from Oxford University in 1992, supervised by Siamon Gordon and graduated with an MD in 1995. After a year at the South Island Bone Marrow Transplant Unit in Christchurch with Derek Hart, he moved to Newcastle in complete training in haematology. He received a Leukaemia Research Fund UK Bennett Senior Fellow in Experimental Haematology in 2006 and spent one year in the lab of Miriam Merad. Back in Newcastle he set up the Human DC Lab (http://www.hudendritic.org) where he continues as Co-PI with Venetia Bigley. His work has focussed on analysing human DC in vivo, from defining the subsets of interstitial DC and mapping their correspondence with murine DC, to identifying genes controlling human DC development, and the contribution of DC deficiency to primary immunodeficiency. He has also made contributions to the field of histiocytosis and is currently interested in the influence of somatic mutation on immunity.

**Christopher Glass** received M.D. and Ph.D. degrees from UC San Diego and performed internship and residency training in Internal Medicine at Brigham and Women’s Hospital. He returned to UC San Diego for fellowship training in Endocrinology and Metabolism and then joined the UC San Diego faculty. He is currently Professor of Cellular and Molecular Medicine and Professor of Medicine at UC San Diego. Dr. Glass has had a long-standing interest in elucidating the molecular mechanisms by which sequence specific transcription factors, co-activators and co-repressors regulate the development and function of macrophages in health and disease. His current studies use a combination of genetics and genomics to define molecular mechanisms specifying transcriptional regulatory elements that establish macrophage identity and cell-specific responses to environmental signals. Dr. Glass’ laboratory is currently applying these approaches to understand pathological programs of macrophage gene expression that promote the development of atherosclerosis, diabetes, cancer and neurodegenerative diseases.
GUEST SPEAKER HIGHLIGHTS

Raphaëla Goldbach-Mansky is the Chief of the Translational Autoinflammatory Diseases Section (TADS) in the Laboratory of Clinical Immunology and Microbiology (LCIM) at NIAID at the NIH. Dr. Goldbach-Mansky’s translational research program focuses on clinical and translational studies in children with early-onset autoinflammatory diseases. Her research applies an integrative approach to characterize the genetic and molecular causes of autoinflammatory diseases and to design targeted treatment studies to investigate the role of specific inflammatory pathways in the pathogenesis of autoinflammatory diseases with the ultimate goal to improve disease outcomes. Her studies in patients with NOMID and DIRA established targeted treatments with IL-1 inhibitors as standard of care and led to FDA approval of anakinra for NOMID in 2012. Her recent translational and interventional studies in CANDLE and SAVI focus on understanding the pathogenic role for Type I Interferons in the disease pathogenesis and the role of IL-18 in autoinflammatory diseases that present with macrophage activation syndrome.

Thirumala-Devi Kanneganti is the Vice Chair of Immunology and the Rose Marie Thomas Endowed Chair at St. Jude Children’s Research Hospital in Memphis, Tennessee. The field of innate immunity and inflammasome has emerged as a central focus in biomedical research in recent years, and Dr. Kanneganti’s contributions are at an outstanding level and at the forefront of this research area. She is listed by Thompson Reuters/Clarivates in the top 1% of immunologists in the world (2017, 2018), based on citations per paper. Her first major contribution, amongst many others, to the field of innate immunity was the initial discovery of the role of the NLRP3 inflammasome in caspase-1 activation by microbial components (Nature 2006 Mar 9;440(7081):233-6). Her research identified the activation mechanisms of inflammasomes during infections and autoinflammatory diseases and the crosstalk between several cell death pathways, namely pyroptosis, apoptosis and necroptosis. Using novel genetic mouse models and in-depth molecular and biochemical analyses, her lab has discovered distinct and previously unrecognized functions of the cytokines IL-1α, IL-1β and IL-33 and their signaling pathways in inflammatory diseases and cancer. Her lab has recently identified ZBP1/DAI as an innate sensor of influenza virus that triggers the NLRP3 inflammasome and programmed cell death pathways. Additionally, research from her lab discovered roles for NLRC3 in regulating PI3K signaling and for the cGAS-STING-IRF-GBP-IRGB10 pathway in liberating ligands that are eventually sensed by the AIM2 and NLRP3 inflammasomes. Dr. Kanneganti has authored approximately 230 original peer-reviewed publications, with many of them appearing in top-ranking journals. Her studies have contributed significantly to shaping our current understanding of the NLRs, inflammasomes, interferons, cell death and cytokines of the IL-1 family in all areas of immunology and infectious disease research.

Miriam Merad, M.D.; Ph.D. is the Mount Sinai Chair professor in Cancer Immunology and the Director of the Precision Immunology Institute at Mount Sinai School of Medicine in New York. Dr. Merad also co-Directs, the Cancer Immunology program at The Mount Sinai Tisch Cancer Institute and is the Director of the Mount Sinai Human Immune Monitoring Center (HIMC). Dr. Merad’s research over the past 20 years has focused on understanding the mechanisms that control the development and functional identity of tissue resident dendritic cells and macrophages during homeostasis, and examining how these regulations are changed in cancer and inflammatory diseases. The overarching goal of her laboratory is to identify dysregulated pathways in macrophages and dendritic cells that can be harnessed to treat Cancer and Inflammatory diseases using both genetically engineered mouse models and human lesions to address these questions. To expand the understanding of immune cells contribution to human lesions, she founded in 2009, the human immune monitoring center at Mount Sinai to implement technology platforms to maximize information obtained from limited biological samples. In 2016, she has taken the leadership of the Precision Immunology Institute at the Icahn School of Medicine (PrIISM) to continue to lead initiatives to enhance human immunology science. PrIISM integrates immunological research programs with synergistic expertise in biology, medicine, technology, physics, mathematics and computational biology which come together to frame novel questions to understand the contribution of immune cells to disease initiation, progression and response to treatment, to implement cutting edge technologies and develop novel immunotherapy strategies for the treatment of human diseases. Dr. Merad has authored more than 180 primary papers and reviews in high profile journals. She receives generous funding from the National Institutes of Health (NIH) for her research on innate immunity and their contribution to human disease, and belongs to several NIH consortia. She is a member of the American Society of Clinical Investigation and the recipient of the William B. Coley Award for Distinguished Research in Basic and Tumor Immunology.

Poulikos Poulikakos received his Ph.D. in Biology in 2002 from the School of Biology, University of Athens, Greece and he subsequently pursued postdoctoral training on cancer biology and signaling, first in Dr. Joseph Testa’s laboratory, at the Fox Chase Cancer Center in Philadelphia, and subsequently in Dr. Neal Rosen’s laboratory, at Memorial Sloan Kettering Cancer Center (2006-2012) in New York. Since 2012 he is an Assistant Professor in the Department of Oncological Sciences and in the Department of Dermatology at the Icahn School of Medicine at Mount Sinai in New York. Dr Poulikakos’s research is focused on investigating mechanisms of growth factor signaling regulation and of tumor response to pharmacologic targeting of its components using small molecule inhibitors. During his postdoctoral training, he elucidated mechanisms of action of RAF inhibitors and identified mechanisms of clinical resistance to these drugs (Poulikakos, et al., Nature, 2010, 2011). As an Assistant Professor, Dr. Poulikakos research program builds logically on his previous work and is directed towards elucidating mechanisms of oncogenic signaling regulation to develop more effective pharmacologic therapeutic strategies in cancer (Karoulia et al., Cancer Cell, 2016; Karoulia et al., Nat Rev Cancer, 2017, Ahmed et al., Cell Reports, 2019). He has received a number of fellowships and awards, including the Sidney Kimmel Award for Cancer Research, The Society of Melanoma Research Young Investigator Award, as well as awards from the Melanoma Research Alliance, the Melanoma Research Foundation, The Dermatology Foundation and the Harry J. Lloyd Charitable Trust, among others.
MEET THE EXPERTS PRESENTER HIGHLIGHTS

Oussama Abla is a Lebanese native full Professor of Pediatrics at the University of Toronto and a pediatric oncologist at the Hospital for sick children in Toronto, Canada. His main clinical and research interests are focused on childhood Langerhans cell Histiocytosis (LCH), Rosai-Dorfman disease (RDD) and other rare histiocytic disorders, as well as childhood acute promyelocytic leukemia (APL) and rare lymphomas. He is the Principal Investigator of the Histiocyte Society- International Rare Histiocytic Disorders Registry (IRHDR) and Chair of the Rare Histiocytic Disorders Steering Committee since 2013. He has served on the Education Committee of the Histiocyte Society for two terms, and is currently a member of the Medical and Scientific Advisory Board of the Histiocyte Society Organization. Oussama has participated in the design of the Histiocyte Society LCH-IV International Trial of which is the Canadian national coordinator. In addition, he is one of the founding members of the North American Histiocytoses-NACHO network, and local Co-Investigator on many of the NACHO studies. He is the Co-Editor of the “Histiocytic Disorders” textbook, the “Acute Promyelocytic Leukemia: A Clinical Guide” textbook and the “Non-Hodgkin’s Lymphoma in Childhood and Adolescence” textbook. He is the Co-Founder and Co-Chair of the Asian and Middle Eastern (AME) Histiocytosis Network. Finally, Oussama has authored 105 research papers and book chapters which are mostly focused on histiocytic disorders, childhood leukemias & rare lymphomas.

Eli Diamond is a neuro-oncologist who specializes in the care of patients with brain tumors and the neurologic complications of cancer. He works together with neurosurgeons and radiation oncologists to provide the highest quality medical treatment and supportive care for patients with gliomas and glioblastomas, primary central nervous system lymphomas (brain and spinal cord), ependymomas, and other types of brain tumors. Together with his colleagues in the Memorial Sloan Kettering Counseling Center, he performs clinical research about quality of life, symptom management, and patient-physician communication for patients with brain tumors.

Kai Lehmberg completed his undergraduate medical training in Kiel, Essen (Germany), and London (UK). He is a paediatrician at the Department of Paediatric Haematology and Oncology and the Division of Paediatric Stem Cell Transplantation and Immunology at the University Medical Centre Hamburg Eppendorf (Germany). He has dedicated his scientific interest to clinical research in immune deficiencies and immune dysregulation with focus on haemophagocytic lymphohistiocytosis (HLH). His particular interest are stem cell transplantation for hereditary HLH and acquired forms of HLH with infectious, rheumatological, and malignant triggers. Dr. Lehmberg heads the German national reference center for HLH in Hamburg (genetics, clinical counselling, cytology) and co-ordinates the data management of the international HLH registry, run by the Histiocyte Society and the European Society for Immune Deficiencies. He managed the European CureHLH project and coordinated the treatment studies HLH-2004 and EURO-HIT-HLH studies in Germany. He chairs the HS study group on HLH subtypes.

Ken McClain has dedicated his clinical and research efforts on the histiocytic diseases for 40 years beginning with his oncology fellowship at the University of Minnesota. Since 1986 he has been at the Texas Children’s Cancer Center in Houston where he is a Professor of Pediatrics. In 2002 he organized a Histiocytosis Center and was joined by Dr. Carl Allen in 2006. Together they have developed a robust clinical program which has attracted many patients from around the world. Because of the large number of specimens collected from patients enrolled on research studies they have developed successful translational research studies with collaborators from several other institutions. LCH patients with neurologic dysfunction have been a special research interest leading to innovative therapies and new biologic understanding of this problem. Dr. McClain has cared for adult patients with histiocytic diseases for nearly 30 years. He is a past president of the Histiocyte Society and been a member of the education and scientific committees as well as worked with the Adult, HLH, LCH, and Rare Disease committees.

35 YEARS

2019 | MEMPHIS, TN USA

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Carl Allen is currently Co-Chair of the Lymphoma and Histiocytosis Programs at the Texas Children’s Cancer and Hematology Centers (TXCH), where he directs translational research efforts. His research focus is on understanding mechanisms of aberrant immune function in human disease, including histiocytic disorders, lymphoproliferative disorders and lymphomas. His team has a history of productive collaborations (Miriam Merad (Mount Sinai), Matthew Collin (Newcastle), Florent Ginhoux (Singapore) and Markus Manz (Zurich)) to use complementary experimental models and approaches to understand pathogenesis of Langerhans cell histiocytosis. Their work to date has contributed to re-defining the cell of origin as an immature myeloid precursor (Allen et al., JI 2010), determined that state of differentiation of cell of origin determines clinical manifestations of disease (Berres et al., JEM 2014), created the first mouse models of LCH (Berres et al., JEM 2014), and identified functionally active recurrent mutations in MAP2K1 and BRAF in LCH (Chakraborty et al., 2014; Chakraborty et al., 2016). Together with Carlos Rodriguez-Galindo, they were awarded a grant to establish the North American Consortium for Histiocytosis Research, now including more than 30 institutions, which has launched 2 clinical trials and a LCH correlative biology study.

Ed Behrens received his undergraduate training at The Johns Hopkins University where he majored in biology. He attended medical school at The University of Pennsylvania where he received the prestigious Howard Hughes Medical Institutes Medical Student Research Fellowship to train in the laboratory of Dr. Philip Cohen. After medical school, Ed completed a Pediatrics Residency and Pediatric Rheumatology Fellowship at The Children’s Hospital of Philadelphia. He performed two post-doctoral fellowships in the laboratories of Stefania Gallucci and Gary Koretzky, after which he joined the faculty of the Division of Rheumatology at CHOP as an Assistant Professor in 2009. Ed’s research interest is the pathogenesis and treatment of cytokine storm syndromes, including the hemophagocytic syndromes Hemophagocytic Lymphohistiocytosis (HLH) and Macrophage Activation Syndrome (MAS). These are uniquely pediatric immunologic conditions that result in severe systemic inflammation and death if unrecognized and untreated. Despite current therapies, mortality remains high for these conditions, hovering around 50% of patients. Ed has developed a novel murine model of MAS that has allowed the careful immunologic dissection of the mediators of disease. More recently, Ed has begun to work on novel mediators of HLH, and is developing a new immune modulating therapy to treat this disease. His work has been recognized with many awards from the American College of Rheumatology, the Histiocyte Society, and the Arthritis Foundation. He is the founding member of the International MAS Study Group and has given lectures internationally on MAS/HLH.

Zdenka Krenova is a current member of the Rare Histiocytic Disorders Steering Committee of the Histiocyte Society (HS). Dr Krenova is European coordinator for International Rare Histiocytic Disorders Registry (IRHDR). The rare histiocytic disorders (RHD), or non-Langerhans cell disorders, are a diverse group of disorders defined by the accumulation of histiocytes that do not meet the criteria for Langerhans cell histiocytosis (LCH) or hemophagocytic lymphohistiocytosis (HLH). They include: Juvenile xanthogranuloma family, Erdheim-Chester disease, Multifocal Reticulohistiocytosis, Rosai-Dorfman disease and the Malignant Histiocytoses. Dr. Krenova has a long time interest in rare histiocytoses and in her daily practice she takes care of children with both LCH and non-LCH diagnoses. Dr. Krenova is a pediatric oncologist whose research focuses on understanding the tumor microenvironment in lymphoma, LCH and non-LCH tumors of pediatric age. Dr. Krenova in her PhD work focuses on significance of an expression of Tregs, CD8+, and IDO, LAG3, PDL1/L2 on various cell types within the tumor microenvironment in tumors tissue, in regards to both prognostic markers and the efficacy of immune checkpoint inhibitor therapy in pediatrics. Problems of explaining what are the molecular mechanisms that explain the T cell- inflamed versus non inflamed tumor microenvironments, and possible conversion of immunotherapy non responsive/not inflamed tumors into responsive ones. Another study topic is analyzing mutational load, mutation accumulation and molecular signature in tumors of pediatric age, and encouraging so synergistic therapeutic combinations of immune checkpoints inhibitor, other immune modulators and molecularly targeted therapy. Research of the role of immune checkpoints in brain and possible role of immune modulating agents and immune checkpoint inhibitors for patients with LCH related neurodegeneration of brain.
**Ashish Kumar** received his medical degree from L.T.M. Medical College, Mumbai, India, his PhD in anatomy and cell biology from the University of Iowa, pediatric residency training at the Mayo Clinic and fellowship in pediatric hematology / oncology / BMT at the University of Minnesota. He is currently a professor of pediatrics at the University of Cincinnati College of Medicine in the Division of Bone Marrow Transplantation and Immune Deficiency at Cincinnati Children’s Hospital Medical center. Dr. Kumar’s laboratory research has focused on infant leukemia, and Langerhans Cell Histiocytosis. He is the director of the LCH center, and a key member of the HLH center at Cincinnati Children’s. He is also the director of pediatric hematology-oncology fellowship training program.

**Jennifer Picarsic** is a board certified Pediatric Pathologist and Associate Professor at Cincinnati Children’s Hospital Medical Center (CCHMC). Dr. Picarsic’s main academic interests are centered on the pathobiology of histiocytic neoplasms. Recent collaborative work with the histiocytic clinical research team at Memorial Sloan Kettering Cancer Center revealed molecular and histopathology correlations in pediatric solitary juvenile xanthogranuloma (JXG) family lesions. This work was awarded the 2018 Nesbit award in Clinical Science by the Histiocyte Society (HS) and has culminated in an upcoming *Nature Medicine* manuscript. Other recent work has identified the BRAF-V600E mutation in both aggressive pediatric CNS-JXG family neoplasms along within a novel mixed Rosai-Dorfman Disease/Langerhans cell histiocytosis. Dr. Picarsic is involved in a number of collaborative histiocytic research projects with other academic experts in the field, including using novel and innovative digital slide scanning technology for enhancement of diagnosis and education. Dr. Picarsic has authored numerous manuscripts, book chapters, and invited reviews on the topic while also serving as the North American pathology study reviewer for the International Rare Histiocytic Disease Registry, sponsored by the HS. Dr. Picarsic serves on both the Scientific Committee and Rare Histiocytic Disorders Committee for the Society.
MEETING AGENDA: SATURDAY • NOVEMBER 2, 2019

Attendance at the Steering Committee Meetings is limited to members of that Steering Committee. A detailed agenda will be provided by the Steering Committee Chairperson.

1000 – 1730  Executive Board Meeting* ........................................................................................................ Meeting Room 1
1300 – 1400  HS Board/ECD Global Alliance Joint Lunch .................................................................................. Meeting Room 3

Closed Meeting. Lunch will be provided in the Atrium for attendees of this luncheon.

1600 – 1630  Coffee Break ................................................................................................................................. Atrium
1730 – 1900  LCH Steering Committee Meeting* ............................................................................................... Meeting Room 2
1830 – 2000  Rare Histiocytic Disorders Steering Committee Meeting* .......................................................... Meeting Room 1

MEETING AGENDA: SUNDAY, NOVEMBER 3, 2019

Unless otherwise indicated, all sessions on this day are open.

0800 – 1700  Meeting Registration and Check-In .............................................................................................. Atrium
0830 – 0930  LCH-IV Study Management Group Session* .................................................................................. Closed Session

Session Moderator: Milen Minkov

0830 – 0930  Adult LCH Disease Discussion Session .......................................................................................... Meeting Room 3
0930 – 1000  Coffee Break .................................................................................................................................. Atrium
1000 – 1230  LCH Disease Discussion Session .................................................................................................. Lecture Hall
1230 – 1330  Lunch ............................................................................................................................................. Domino’s Event Center
1330 – 1500  Rare Histiocytic Disorders Discussion Session ................................................................................ Lecture Hall

Session Moderator: Oussama Abla

1330 – 1500  HLH Steering Committee Meeting* ............................................................................................... Meeting Room 2
1330 – 1500  HLH Education Session ................................................................................................................ Board Room

NEW PATHOPHYSIOLOGIC MODELS OF HLH: INFORMING THE NEXT GENERATION OF TARGETED THERAPIES

Ed Behrens
Children’s Hospital of Philadelphia, Philadelphia, PA USA

HLH 101 TO 2019
Ashish Kumar
Cincinnati Children’s Hospital Medical Center, Cincinnati, OH USA

1500 – 1530  Coffee Break ................................................................................................................................... Atrium
1530 – 1700  LCH Education Session ................................................................................................................ Board Room

Carl Allen
Texas Children’s Cancer and Hematology Center, Houston, TX USA

Patrick Campbell
St. Jude Children’s Research Hospital, Memphis, TN USA

* Indicates closed session
* Indicates that advance registration was required
### MEETING AGENDA: SUNDAY, NOVEMBER 3, 2019

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<td>1530–1800</td>
<td>HLH/MAS Discussion Session</td>
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<td>1700–1830</td>
<td>Rare Histiocytoses Education Session</td>
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<td>1830–2130</td>
<td>Welcome Reception</td>
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**CLINICAL ASPECTS OF THE “RARE” OR “NON-LCH” HISTIOCYTIC DISORDERS**
Zdenka Krenova
University Hospital, Faculty of Medicine MU Brno, ICRC, Brno, Czech Republic

**LATEST AND GREATEST: THE NEW SCIENTIFIC HORIZON FOR NON-LCH HISTIOCYTIC NEOPLASMS**
Jennifer Picarsic
Cincinnati Children’s Hospital Medical Center, Cincinnati, OH USA

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* Indicates closed session
* Indicates that advance registration was required
MEETING AGENDA: MONDAY, NOVEMBER 4, 2019

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<td>0800 – 0900</td>
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<td>0800 – 0900</td>
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<td>1330 – 1500</td>
<td>Scientific Session I: Oral Presentations</td>
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**NEW PARADIGMS IN LANGERHANS CELL HISTIOCYTOSIS**
Miriam Merad
Mount Sinai School of Medicine, New York, NY USA

**IL-18 AND MECHANISTICALLY (RE) CATEGORIZING HYPERINFLAMMATION**
Scott Canna
University of Pittsburgh Children’s Hospital, Pittsburgh, PA USA

**DIFFERENT FLAVORS OF THE INFLAMMASOMES PREDISPOSE TO IL-1 MEDIATED VS. IL-18 IMMUNOPATHOLOGY**
Raphaëla Goldbach-Mansky
National Institutes of Health, Bethesda, MD USA

**TARGETING THE INFLAMMASOME FOR THE TREATMENT OF INFLAMMATORY AND INFECTIOUS DISEASES**
Thirumala-Devi Kanneganti
St. Jude Children’s Research Hospital, Memphis, TN USA

**MONOMETHYL FUMARATE ACTS THROUGH HEME OXYGENASE 1 AS NOVEL THERAPY FOR MACROPHAGE ACTIVATION SYNDROME**
Edward Behrens, Niansheng Chu, Chhanda Biswas

**IFNg NEUTRALIZATION IN PATIENTS WITH NRLC4- AND CDC42-ASSOCIATED AUTOINFLAMMATORY DISEASES CHARACTERIZED BY RECURRENT AND SEVERE HLH**
Claudia Bracaglia, Antonella Insalaco, Giulia Marucci, Manuela Pardeo, Emanuela Sacco, Virginia Messia,
Giulio Principe, Ivan Caieilo, Sarka Fingerhutova, Pavla Dolezalova, Veronica Asnaghi, Maria Ballabio, Cristina de Min,
Fabrizio De Benedetti

**EMAPALUMAB (AN INTERFERON GAMMA (INFg)-BLOCKING MONOCLONAL ANTIBODY) IN PATIENTS WITH MACROPHAGE ACTIVATION SYNDROME (MAS) COMPLICATING SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS (SJIA)**
Fabrizio De Benedetti, Paul Brogan, Claudia Bracaglia, Manuela Pardeo, Giulia Marucci, Emanuela Sacco,
Despina Eleftheriou, Charalampa Papadopoulou, Alexei Grom, Pierre Quartier, Rayfel Schneider, Philippe Jacqmin,
Kathy De Graaf, Maria Ballabio, Cristina de Min

* Indicates closed session
* Indicates that advance registration was required
EFFECT OF DONOR-SOURCE AND CONDITIONING REGIMEN ON THE OUTCOME OF CHILDREN WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANTATION: A NATIONAL MULTICENTER
Yarden Greental Shinerman, Joanne Yacobovich, Amir A Kuperman, Jerry Stein, Ehud Even-Or, Irina Zaidman, Aharon Gefen, Neta Nevo, Amos Toren, Polina Stepensky, Bella Bielorai, Elad Jacoby

EXCESSIVE IL-10 COOPERATES WITH IL-18 TO DRIVE SEVERE HLH-LIKE DISEASE IN A TRANSGENIC MOUSE MODEL
Yuting Tang, Qian Xu, Erika Owsley, Rebecca Marsh, Gang Huang

PERFORIN-DEFICIENCY AND EXCESS INTERLEUKIN-18 INDEPENDENTLY PROMOTE MURINE VIRUS-INDUCED HYPERINFLAMMATION
Paul Tsoukas, Emily Rapp, Lauren Van Der Kraak, Vinh Dang, Corinne Schneider, and Scott Canna

1500 – 1530
Coffee Break

1530 – 1700
Scientific Session II: Presidential Symposium
Session Moderator: Milen Minkov

PRESENTATIONS NOMINATED FOR THE NESBIT PRIZE IN CLINICAL SCIENCE (see page 71 for more information)

POST-TRANSPLANT OUTCOMES OF CHILDREN WITH PRIMARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS GIVEN EMAPALUMAB TO CONTROL DISEASE
Michael B. Jordan, Franco Locatelli, Carl E. Allen, Simone Cesaro, Carmelo Rizzari, Anupama Rao, Barbara Degar, Timothy Garrington, Julian Sevilla, Maria Caterina Putti, Franca Fagioli, Martina Ahlmann, Jose-Luis Dapena, Michael Henry, Alexei A. Grom, Fabrizio De Benedetti, Maria Ballabio, Cristina de Min

THE TYPE OF ONCOGENIC BRAF MUTATION MATTERS: BRAF EXON 12 DELETIONS ARE ASSOCIATED WITH SUPERIOR EVENT-FREE SURVIVAL COMPARED TO BRAFV600E IN PEDIATRIC LCH
Paul Kemps, Timo Zondag, Jelske Borst, Eline Steenwijk, Rob Verdijk, Carel van Noesel, Arjen Cleven, Veronica Lang, Maarten Egeler, Nienke Solleveld-Westendorp, Ronald van Eijk, Tom van Wezel, Auke Beishuizen, Jan van Laar, Oussama Abia, Cor van den Bos, Astrid van Halteren

EARLY MORTALITY IN LANGERHANS CELL HISTIOCYTOSIS III (LCH-III) TRIAL SUGGESTS SOME PATIENTS REQUIRE MORE EFFECTIVE THERAPY EVEN BEFORE THE 1ST RESPONSE ASSESSMENT POINT AT 6 WEEKS
Stephan Ladisch, Johannes Visser, Ulrike Potschger, Elfriede Thiem, Milen Minkov, Maurizio Arico, Itziar Aslagnagara, Jorge Braier, Jean Donadieu, Nicole Grois, Helmut Gadner, Jan-Inge Henter, Gritta Janka-Schaub, Kenneth McClain, Sheila Weitzman, Kevin Windebank

PRESENTATIONS NOMINATED FOR THE NEZELOF PRIZE IN BASIC SCIENCE (see page 71 for more information)

NOVEL ALTERATIONS IN CSF1R, RET AND OTHER DIVERSE KINASES IN THE HISTIOCYTOSIS WITH BIOCHEMICAL AND STRUCTURAL INSIGHTS INTO THEIR MECHANISMS OF ACTIVATION
Benjamin Durham, Estibaliz Lopez-Rodrigo, Jennifer Picarsic, David Abramson, Veronica Rotemberg, Steven De Munck, Erwin Panneconque, Sydney Lu, Alessandro Pastore, Diana Mandelker, Ozge Birsoy, Gary Ulaner, Michael Walsh, Maniko Yabe, Kseniya Petrova-Drus, Maria Arcila, Marc Ladanyi, David Soilt, Michael Berger, David Hyman, Mario Lacouture, Michelle Ki, Ira Dunkel, Vicente Santa-Maria Lopez, Jaume Mora, Julien Haroche, Jean-Francois Emile, Olivier Decaux, Frederic Geissmann, Savvas Savvides, Alexander Drilon, Eli Diamond, Omar Abdel-Wahab

THE COMBINATION OF DEXAMETHASONE AND RUXOLITINIB SYNERGISTICALLY ATTENUATES DISEASE MANIFESTATIONS IN A PRECLINICAL MODEL OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS
Lauren Meyer, Katherine Verbist, Sabrin Albeituri, Rachel Bassett, Michelle Herriston, Kim Nichols

* Indicates closed session
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PLASMA PROTEIN AND CYTOTOXIC T-CELL GENE EXPRESSION PROFILES DISTINGUISH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS FROM OTHER HYPER-INFLAMMATORY DISEASES

1700 – 1900 Poster Presentation Session .......................................................................................................................... Meeting Room 5/Board Room

POSTERS NOMINATED FOR THE ROBERT J. ARCECI PRIZE FOR BEST POSTER (see page 72 for more information)

CLINICAL HLH POSTER NOMINEES

Poster Location #1
RISK FACTORS FOR MIXED CHIMERISM AFTER TREOSULFAN OR MELPHALAN BASED STEM CELL TRANSPLANTATION IN CHILDREN WITH PRIMARY HEMOPHAGOCYTIC HISTIOCYTOSIS
Kai Lehmberg, Katharina Wustrau, Gritta Janka, Stephan Ehl, Ingo Muller

Poster Location #2
THE FEASIBILITY OF NEWBORN MASS SCREENING FOR PRIMARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS USING DRIED BLOOD SPOT (DBS) PROTEOMICS
Hiroyumi Shibata, Takahiro Yasumi, Saeko Shimodera, Isa-Nishitani Masahiko, Kazushi Izawa, Hidenori Ohnishi, Daisuke Nakajima, Yusuke Kawashima, Ryuta Nishikomori, Osamu Ohara, and Junko Takita

CLINICAL LCH POSTER NOMINEES

Poster Location #3
PROGNOSTIC SIGNIFICANCE OF CELL-FREE BRAF-V600E QUANTITATIVE DETECTION AT DIAGNOSIS AND DURING CHEMOTHERAPY IN CHILDREN WITH LANGERHANS CELL HISTIOCYTOSIS
Lei Cui, Li Zhang, Hong-Hao Ma, Chan-Juan Wang, Dong Wang, Hong-Yun Lian, Wei-Jing Li, Qing Zhang, Na Li, Tian-You Wang, Zhi-Gang Li, and Rui Zhang

Poster Location #4
BRAFV600E-POSITIVE PRECURSORS AS MOLECULAR MARKERS OF BONE MARROW INVOLVEMENT IN PEDIATRIC LANGERHANS CELL HISTIOCYTOSIS
Ko Kudo, Rika Kanezaki, Masaru Imamura, Chihaya Imai, Masahiro Irie, Yoji Sasahara, Kumiko Ando, Harumi Kakuda, Takehiko Doi, Hiroshi Kagawuchi, Kazukuo Kudo, Hirokazu Kanegane, Tsutomu Toki, and Etsuro Ito

Poster Location #5
BRAFV600E MUTATED ALLELES PERSIST IN THE CIRCULATION OF NEWLY DIAGNOSED PEDIATRIC PATIENTS WITH MULTISYSTEM LANGERHANS CELL HISTIOCYTOSIS DESPITE 6 WEEKS OF TREATMENT WITH PREDNISOLONE AND VINBLASTINE
Paul Milne, Johannes Visser, Vasanta Nanduri, Matthew Collin

Poster Location #6
BRAFV600E ALLELE LOAD AS A BIOLOGICAL MARKER IN PATIENTS WITH LANGERHANS CELL HISTIOCYTOSIS ON VEMURAFENIB THERAPY
Daria Osipova, Dmitry Evseev, Elena Raykina, Zalina Abashidze, Irina Kalinina, Alexey Maschan, Michael Maschan

Poster Location #7
A PATIENT WITH LANGERHANS CELL SARCOMA ARISING FROM LANGERHANS CELL HISTIOCYTOSIS AND ACUTE LYMPHOBLASTIC LEUKEMIA
Yu Tian, Dong Wang, Rui Zhang, Tianyou Wang

CLINICAL RARE HISTIOCYTIC DISORDERS POSTER NOMINEES

Poster Location #8
GENOMIC CHARACTERIZATION OF A PEDIATRIC COHORT WITH NON-MALIGNANT LYMPHOPROLIFERATIVE DISORDERS
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Poster Location #9
LANGERHANS CELL SARCOMA AT THE MAYO CLINIC: CLINICAL FEATURES, MANAGEMENT, AND TREATMENT OUTCOMES
Susan Schram, Gaurav Goyal, Karen Rech, Jason Young, Ronald Go

POSTER PRESENTATIONS

BASIC HLH POSTER PRESENTATIONS

Poster Location #10
MUTATIONS AFFECTING TIM3 CHARACTERIZE SPTCL ASSOCIATED TO HLH
Fernando Sepulveda, Frederic Guerin, Sara Mouasni, Fatma Bagca, Alain Fische, David Michonneau, Benoicte Neven, Gael Menasche, Genevieve de Saint Basile

CLINICAL HLH POSTER PRESENTATIONS

Poster Location #11
ATYPICAL INTRACRANIAL LESIONS OF HLH IN A CHILD
Farranaz Alvarez Nunez, Shelley Crary, Kimo Stine

Poster Location #12
LONG TERM SURVIVAL AFTER EARLY ONSET LYSOSOMAL ACID LIPASE DEFICIENCY PRESENTING AS HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND BENEFIT OF ENZYMATIC REPLACEMENT TREATMENT WITH SEBELIPASE ALFA IN 2 PATIENTS

Poster Location #13
CLINICAL OUTCOMES OF ADULTS WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS TREATED WITH THE HLH-04 PROTOCOL: A RETROSPECTIVE ANALYSIS
Rachel Bubik, Dylan Barth, Robert Wolf, Jessica Muth, Kristin Mara, Ronald Go, Alexandra Wolanskyj-Spinner, Sameer Parikh

Poster Location #14
FLOW CYTOMETRIC PERFORIN AND CD107A SCREENING FOR THE DIAGNOSIS OF FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: REPORT FROM THE ITALIAN REGISTRY
Maria Luisa Coniglio, Martina Da Ros, Daniela Balasco, Virginia Brizzi, Fabiola Dell’Acqua, Carmela De Fusco, Alessandra Todesco, Fabio Timeus, Concetta Micalizzi, Claudio Favre, Elena Sieni, for the Italian Histiocytosis working group

Poster Location #15
HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: A MISSED DIAGNOSIS IN CHILDREN WITH NEUROLOGICAL MANIFESTATIONS
Yasmine El Chazli, Marwa Abd El-Maksoud, Asmaa Elsharkawy, Walaa Shoman, Nevine Mikhail, Ahmed El-beheiry

Poster Location #16
HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN EGYPTIAN CHILDREN: SINGLE CENTER EXPERIENCE
Yasmine El Chazli, Asmaa Elsharkawy, Marwa Abd El-Maksoud, Walaa Shoman, Nevine Mikhail

Poster Location #17
EFFECTIVENESS OF ETOPOSIDE THERAPY IN ADULT HLH - ANALYSIS FROM THE PALG HLH IN ADULTS DATABASE

WWW.HISTIOCYTESOCIETY.ORG 23
Poster Location #18
TWO NOVEL MUTATIONS IDENTIFIED IN A CHINESE CHILD WITH CHEDIAK-HIGASHI SYNDROME REPRESENTING WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS
Huirong Mai, Yunsheng Chen, Jian Guo, Bin Rao, Sixi Liu, Xinmin Fang, Changgang Li, Feiqiu Wen

Poster Location #19
RUXOLITINIB TREATMENT FOR STEROID-REFRACTORY ACUTE GVHD IN PATIENTS WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS UNDERGOING ALLO-HSCT
Guangqiang Meng, Jing-Shi Wang, Xin-Kai Wang, Yi-Ni Wang, Zhao Wang

Poster Location #20
HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: CLINICAL AND LABORATORY CHARACTERISTICS AND OUTCOMES OF PATIENTS IN A SINGLE INSTITUTION
Jessica Rodrigues, Monica dos Santos Cypriano

Poster Location #21
ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN TREATMENT OF LYMPHOMA ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS
Yue Song, Yue Song, Yini Wang, Jingshi Wang, Zhao Wang

Poster Location #22
DURABLE LONG-TERM SURVIVAL AND CHIMERISM AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION USING BUSULFAN AND FLUDARABINE BASED REDUCED INTENSITY CONDITIONING REGIMEN FOR PEDIATRIC PATIENTS WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS
Jong Jin Seo, Jin Kyung Suh, Sunhan Kang, So Yoon Min, Joo Hee Shin, Hyery Kim, Kyung-Nam Koh, Ho Joon Im

Poster Location #23
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Poster Location #24
THE RISK FACTORS IN THE EVALUATION OF PROGNOSIS IN ADULT PATIENTS WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS
Yini Wang, Tingting Cui, Yue Song, Zhili Jin, Na Wei, Jia Zhang, Jingshi Wang, Lin Wu

Poster Location #25
THE CLINICAL FEATURES AND OUTCOME OF FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS-2: AN EXPERIENCE FROM A SINGLE CENTER
TingTing Cui, Tingling Cui, Yini Wang, Jingshi Wang, Jia Zhang, Zhuo Gao, Zhao Wang

Poster Location #26
CLINICAL ANALYSIS OF HEPATITIS ASSOCIATED PLASTIC ANEMIA FIRST PRESENTING AS HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS
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Poster Location #27
CLINICAL ANALYSIS OF RUXOLITINIB IN THE TREATMENT OF RECURRENT AND REFRACTORY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN CHILDREN
Ang Wei, Hong-hao Ma, Li-ping Zhang, Ying Yang, Rui Zhang, Tian-you Wang

Poster Location #28
CLINICAL CHARACTERISTICS AND TREATMENT OF EPSTEIN-BARR VIRUS-ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN CHILDREN
Ang Wei, Ma Honghao, Wang Tianyou, Zhang Li, Lian Hongyun, Wang Dong, Zhao Yunze, Zhao Xiaoxi, Zhang Rui
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Poster Location #29
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Poster Location #30
OUTCOME OF CHILDREN WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH) TREATED AT KING HUSSEIN CANCER CENTER
Mayada Abu Shanap, Iyad Sultan, Rawad Rihani, Hasan Hashem, Eman Khattab, Fathi Azzuni Amal Abu Ghosh, Abdelghani Tbakhi, Fareed Barakat, Faris Madanat

Poster Location #31
CLINICAL ANALYSIS OF 8 CASES OF HEMOPHAGOCYTIC SYNDROME SECONDARY TO SUBCUTANEOUS PANNICULITIS-LIKE T-CELL LYMPHOMA
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Poster Location #32
HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR CENTRAL NERVOUS SYSTEM INVOLVEMENT WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN CHILDREN
Yuan Sun, Juan Xiao, Shifeng Fan, Xiaomei Liu, Zhouyang Liu, Fan Jiang, Chongfeng Gao, Shanshan Kang

Poster Location #33
THE GENETIC CHARACTERIZATION, CLINICAL EVALUATION OF PRIMARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND THE IMPORTANCE OF BILIRUBIN ABNORMALITY: A SINGLE CENTER EXPERIENCE
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Poster Location #34
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Qing Zhang, Lei Cui, Hong-Hao Ma, Dong Wang, Yun-Ze Zhao, Tian-You Wang, Zhi-Gang Li, Rui Zhang

Poster Location #35
CLINICAL FEATURES AND OUTCOMES OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AS AN ONSET OF AUTOINFLAMMATORY DISORDERS
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Poster Location #36
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Jin Zhili, Yini Wang, Na Wei, Zhao Wang

BASIC LCH POSTER PRESENTATIONS

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Thomas Burke, Brooks Scull, Harshal Abhyankar, Olive Eckstein, Alexei Grom, Kenneth McClain, Carl Allen

Poster Location #38
ISOLATED PULMONARY LANGERHANS CELL HISTIOCYTOSIS AND MULTIPLE SCLEROSIS. CASE REPORT
Candela Soledad, Guido Felizzi, Claudio Castaños, Laura Negrotto, Jorge Braier

Poster Location #39
PERSISTENT LYMPHOPENIA IN LCH PATIENTS LIKELY RELATED TO CONSTANTLY HIGH LEVELS OF IL-7 AND IL-21
Magdalini Lourda, Sofie Wideskold, Egle Kvedaraitė, Desiree Gavhed, Tatiana von Bahr Greenwood, Mattias Svensson, Selma Olsson-Akefeldt and Jan-Inge Henter

Poster Location #40
BRAF-V600E CAUSES INTRINSIC HYPER-RESPONSIVENESS OF DENDRITIC CELLS TO TLR4 STIMULI
Danielle Minichino, Edward Behrens
THE OPN LEVELS OF CEREBROSPINAL FLUID WERE SIGNIFICANTLY CORRELATED WITH PITUITARY INVOLVEMENT IN CHILDREN WITH LANGERHANS CELL HISTIOCYTOSIS
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CD207+/CD1A+ CIRCULATING CELLS SHOW HIGHER LEVELS OF TYRO3, MERTK, AND PROS1 IN PATIENTS WITH ACTIVE LANGERHANS CELL HISTIOCYTOSIS
Diego Rosso, Cinthia M. Olexen, Wanda Nowak, Andrea E. Errasti, Eugenio A. Carrera Silva

**CLINICAL LCH POSTER PRESENTATIONS**

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Ana Bom, Ana Paula Kuczynski, Paulo Taufi Maluf Filho, Maria Claudia Nogueira Zerbini, Marcia Olandoski

BONE LANGERHANS CELL HISTIOCYTOSIS TREATED WITH INDOMETHACIN: REVIEW OF CASES FROM A SINGLE INSTITUTION
Veronica Celis Passini, Veronica Celis, Jaume Mora, Vicente Santa-Maria, Maria Correia, Juan Muñoz

LANGERHANS CELL HISTIOCYTOSIS: A DISEASE MIMICKER IN PEDIATRICS
Irem Eldem, Chibuzo O’Suoji

CONGENITAL HIGH RISK LANGERHANS CELL HISTIOCYTOSIS. HIGHER RESPONSE WITH EMPIRICAL USE OF VEMURAGENIB. CASE REPORT
Guido Felizzia, Torre Lorena Soledad, Laura Galluzzo, Patricia Bellani, Jorge Braier, Jean Donadieu

TREATMENT OF RELAPSED AND REFRACTORY MULTIFOCAL BONE LANGERHANS CELL HISTIOCYTOSIS: A CASES SERIES
Yu Mei Liao

EFFECT ANALYSIS OF CLADRIBINE AND CYTARABINE COMBINATIONS IN TREATMENT OF REFRACTORY AND RELAPSED LANGERHANS CELL HISTIOCYTIC DISEASE IN CHILDREN
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SIMULTANEOUS OCCURRENCE OF MULTI-SYSTEM LANGERHANS CELL HISTIOCYTOSIS AND CUTANEOUS JUVENILE XANTHOGRANULOMA IN AN INFANT
Takanori Mizuno, Yoko Shioda, Kenichi Sakamoto, Ryota Shirai, Tomoo Osumi, Motohiro Kato, Daisuke Tomizawa, Kazue Yoshida, Osamu Miyazaki, Rie Irie, Takako Yoshioka, Kimikazu Matsumoto

A CASE OF A CHILD WITH NEURODEGENERATIVE DISEASE LANGERHANS CELL HISTIOCYTOSIS
Sonia Morales, Lilibeth Torno

OUTCOME OF PEDIATRIC PATIENTS DIAGNOSED WITH LANGERHANS CELL HISTIOCYTOSIS AT KING HUSSEIN CANCER CENTER
Mayada Abu Shanap, Iyad Sultan, Rawad Rihani, Hasan Hashem, Amal Abu Ghosh, Mohammad Sawahera, Bayan Alaraj, Fareed Barakat, Faris Madanat

ANALYSIS OF BONE LCH CASES TRIGGERED BY BRUISING; RESULT FROM JLSG-02 STUDY
Akira Morimoto, Yoko Shioda, Kenichi Sakamoto, Shinsaku Imashuku
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Poster Location #53
GENOMIC ANCESTRY AND LANGERHANS CELL HISTIOCYTOSIS CLINICAL CHARACTERISTICS
Erin Peckham-Gregory, Rikhia Chakraborty, Olive Eckstein, Harshal Abhyankar, Michael Scheurer, Kenneth McClain, Philip Lupo and Carl Allen

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Muhammad Rafie Raza, Sidra Maqsood, Nida Zia, Shamvil Ashraf

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Kenichi Sakamoto, Akira Morimoto, Yoko Shioda, Toshihiko Imamura, Shinshaku Imashuku, on behalf of the Japan LCH Study Group

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Francesca Stocchi, Michellina Santopietro, Francesca Romana Mauro, Giovanna Palumbo, Tiziana Di Pippo, Lorenzo Rizzo, Fiorina Giona

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Stefan Schlederer, Andrea Madunic, Elfriede Thiern, Gabriele Calaminus, Ina Haimann, Peter Kaatsch, Thomas Leimbecher, Ulrike Potschger, Milen Minkov

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<td>Meeting Registration and Check-In</td>
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<tr>
<td>0830 – 0915</td>
<td>Clinical Studies and Registries Update</td>
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<td>0915 – 1000</td>
<td>Jon Pritchard Lecture on the Nikolas Symposium</td>
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<td></td>
<td>Carl Allen</td>
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<td></td>
<td>Baylor College of Medicine, Texas Children's Cancer and Hematology Center, Houston, TX USA</td>
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<td>1000 – 1030</td>
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<td>Atrium</td>
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<td>1030 – 1230</td>
<td>Symposium: Exploring Mechanisms of LCH Pathogenesis Beyond BRAF</td>
<td>Auditorium</td>
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<td>HISTIOCYTOSIS: THE PRINCESS OF ALL POLYS</td>
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<td></td>
<td>Matthew Collin</td>
<td>University of Newcastle, Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle Upon Tyne, UK</td>
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<td>ROLES OF TISSUE ENVIRONMENT IN SHAPING MACROPHAGE IDENTITIES IN HEALTH AND DISEASE</td>
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<td>Christopher Glass</td>
<td>University of California San Diego, San Diego, CA USA</td>
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<td>NEXT GENERATION STRATEGIES TO TARGET ONCOGENIC RAS/ERK SIGNALING</td>
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<td></td>
<td>Poulikos Poulikakos</td>
<td>The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY USA</td>
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<tr>
<td>1230 – 1330</td>
<td>Lunch</td>
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<td>1230 – 1330</td>
<td>HLH Meet the Expert Lunch Session*</td>
<td>Meeting Room 2</td>
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<td>Lunch will be provided in the Atrium for HLH Meet the Expert attendees only. All other attendees should proceed to the Domino’s Event Center for lunch.</td>
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<td>Kai Lehmberg</td>
<td>University Medical Centre Hamburg Eppendorf, Hamburg, Germany</td>
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<tr>
<td>1230 – 1330</td>
<td>LCH Meet the Expert Lunch Session*</td>
<td>Meeting Room 5</td>
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<td>Lunch will be provided in the Atrium for LCH Meet the Expert attendees only. All other attendees should proceed to the Domino’s Event Center for lunch.</td>
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<td>Ken McClain</td>
<td>Texas Children’s Cancer Center, Houston, TX USA</td>
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<tr>
<td>1230 – 1330</td>
<td>Rare Histiocytoses Meet the Expert Lunch Session*</td>
<td>Meeting Room 3</td>
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<tr>
<td></td>
<td>Lunch will be provided in the Atrium for Rare Histiocytoses Meet the Expert attendees only. All other attendees should proceed to the Domino’s Event Center for lunch.</td>
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<td></td>
<td>Oussama Abla</td>
<td>The Hospital for Sick Children, Toronto, ON, Canada</td>
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<tr>
<td></td>
<td>Eli Diamond</td>
<td>Memorial Sloan Kettering Cancer Center, New York, NY USA</td>
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<tr>
<td>1230 – 1330</td>
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<td>Lecture Hall</td>
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<td></td>
<td>Lunch will be provided in the Atrium for AME-Histio Working Group attendees only. All other attendees should proceed to the Domino’s Event Center for lunch.</td>
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**MEETING AGENDA: TUESDAY, NOVEMBER 5, 2019**

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<td>Scientific Session III: Oral Presentations .......................................................................................... Auditorium</td>
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<tr>
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<td>Session Moderator: Itziar Astigarraga</td>
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<td></td>
<td>DIFFERENTIALLY EXPRESSED MICRORNAS IN PLASMA AND LESION OF LANGERHANS CELL HISTIOCYTOSIS PATIENTS: POTENTIAL CORRELATION TO MAPK ACTIVATION</td>
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<td>Harshal Abhyankar, Amel Sengal, Jessica Velazquez, Tiffany Chov, Howard Lin, Brooks Scull, Olive Eckstein, Tsz-Kwong Man, Kenneth L McClain, Carl E Allen, Rikhia Chakraborty</td>
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<td>DIFFERENTIAL REGULATION OF LANGERIN EXPRESSION BY MONOCYTES AND CD1C+ DENDRITIC CELL SUBSETS</td>
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<td>Paul Milne, Anastasia Resteu, Urszula Cytlak, Sarah Pagan, Tom Taghon, Venetia Bigley, Matthew Collin</td>
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<td>SUCCESSFUL SYSTEMATIC CENTRALISED TESTING FOR CIRCULATING MUTATED BRAFV600E IN UNITED KINGDOM LANGERHANS CELL HISTIOCYTOSIS PATIENTS TAKING PART IN INTERNATIONAL MULTICENTRE TREATMENT TRIAL</td>
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<td></td>
<td>Paul Milne, Johannes Visser, Vasanta Nanduri, Matthew Collin</td>
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<td>THE IMPACT OF GASTRO-INTESTINAL INVOLVEMENT AT DIAGNOSIS ON OVERALL SURVIVAL IN PATIENTS WITH LANGERHANS CELL HISTIOCYTOSIS (LCH) - A RETROSPECTIVE ANALYSIS OF DAL-HX, LCH-I, LCH-II, AND LCH-III</td>
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<td>Ulrike Potschger, Elfriede Thiem, Maurizio Arico, Itziar Astigarraga, Jorge Braier, Jean Donadieu, Nicole Grois, Helmut Gardner, Jan-Inge Henter, G. Janka-Schaub, Ken McClain, Sheila Weitzman, Kevin Windebank, Milen Minkov, Cor van den Bos, Oussama Abila</td>
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<td>CLINICAL CORRELATIONS OF PD-1 AND PD-L1 EXPRESSION IN PEDIATRIC LANGERHANS CELL HISTIOCYTOSIS (LCH)</td>
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<td>Sneha Tandon, Brooklyn Joyce, Cynthia Hawkins, Sheila Weitzman, Jim Whitlock, Bo Ngan, Oussama Abila</td>
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<tr>
<td>1500 – 1530</td>
<td>Presentation of Late Breaking Abstracts .................................................................................................. Auditorium</td>
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<td>Session Moderator: Patrick Campbell</td>
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<td>1530 – 1630</td>
<td>General Assembly Business Meeting* ......................................................................................................... Auditorium</td>
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<td>Presidential Transition Ceremony</td>
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<td>1630 – 1700</td>
<td>Executive Board Meeting* ................................................. Auditorium</td>
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<td>Education Committee Meeting* ................................................................................................................. Auditorium</td>
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<td>Scientific Committee Meeting* ................................................................................................................ Auditorium</td>
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<tr>
<td>1715 – 1900</td>
<td>Group Transportation to Histiocyte Society Annual Banquet ............................................................... Peabody Hotel Lobby</td>
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<td>Group will meet in hotel lobby for staggered bus transportation to the Annual Banquet</td>
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<tr>
<td>2000 – 2400</td>
<td>Histiocyte Society Annual Banquet, Closing Ceremonies &amp; Awards* .......................................................... Elvis’ Graceland Museum</td>
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<td>Awarding of Nesbit Prize for Excellence in Clinical Science</td>
<td>Elvis Presley Blvd</td>
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<td>Awarding of Nezelof Prize for Excellence in Basic Science</td>
<td>Mempos, TN 38116</td>
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<td>Awarding of Robert J. Arceci Prize for Best Poster</td>
<td>Phone: +1 901 332-3322</td>
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<td>Website: <a href="http://www.graceland.com">http://www.graceland.com</a></td>
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As part of the Annual Banquet, FREE tours of the Graceland Mansion will be available up to 1-hour prior to the start of the banquet. Attendees should meet in the lobby of The Peabody Hotel at the following times for bus transportation: 1715, 1745, 1815, 1900.

*Note: in order to participate in a tour of the Graceland Mansion, you MUST be on a bus no later than 1815pm. The final 1900pm bus will NOT be able to take the tour and will proceed straight to the museum for the banquet.

Buses will return to The Peabody on a looping schedule at 10pm, 11pm, and 12am.
POSTER LOCATION MAP: MEETING ROOM 5/BOARD ROOM

*Poster locations are approximate and subject to change upon arrival. Each poster will have a designated sign attached to the display board that will signify final location assignments.

IMPORTANT: Authors MUST use ONLY the mounting materials provided.

Posters MUST be REMOVED immediately following the poster session on Monday, November 4, 2019. Any remaining posters will be discarded.
With primary hemophagocytic lymphohistiocytosis (HLH),
THERE’S NO TIME TO WAIT

Sobi is a proud sponsor of the 2019 annual Histiocyte Society meeting. We are committed to raising awareness for Hemophagocytic lymphohistiocytosis (HLH), a rare and fatal disease. Without timely diagnosis and effective treatment, the median survival for patients with primary HLH is under 2 months.¹

Closely follow your patient’s responses to therapy, and for primary HLH patients with refractory, recurrent, or progressive disease or intolerance to conventional therapy consider Gamifant® (emapalumab-lzsg).¹³ Gamifant is the first and only FDA-approved treatment for primary HLH and is specifically designed to target and neutralize IFNγ, subduing the cytokine storm.²⁴

Learn more at Gamifant.com

Indication and Usage
Gamifant® (emapalumab-lzsg) is an interferon gamma (IFNγ)-blocking antibody indicated for the treatment of adult and pediatric (newborn and older) patients with primary hemophagocytic lymphohistiocytosis (HLH) with refractory, recurrent, or progressive disease or intolerance with conventional HLH therapy.

Important Safety Information
Before initiating Gamifant, patients should be evaluated for infection, including latent tuberculosis (TB). Prophylaxis for TB should be administered to patients who are at risk for TB or known to have a positive purified protein derivative (PPD) test result or positive IFNγ release assay.

Please see Important Safety Information and enclosed full Prescribing Information.
Important Safety Information

Before initiating Gamifant, patients should be evaluated for infection, including latent tuberculosis (TB). Prophylaxis for TB should be administered to patients who are at risk for TB or known to have a positive purified protein derivative (PPD) test result or positive IFNγ release assay.

During Gamifant treatment, patients should be monitored for TB, adenovirus, Epstein-Barr virus (EBV), and cytomegalovirus (CMV) every 2 weeks and as clinically indicated.

Patients should be administered prophylaxis for herpes zoster, *Pneumocystis jiroveci*, and fungal infections prior to Gamifant administration.

Do not administer live or live attenuated vaccines to patients receiving Gamifant and for at least 4 weeks after the last dose of Gamifant. The safety of immunization with live vaccines during or following Gamifant therapy has not been studied.

Infusion-Related Reactions

Infusion-related reactions, including drug eruption, pyrexia, rash, erythema, and hyperhidrosis, were reported with Gamifant treatment in 27% of patients. In one-third of these patients, the infusion-related reaction occurred during the first infusion.

Adverse Reactions

In the pivotal trial, the most commonly reported adverse reactions (≥10%) for Gamifant included infection (56%), hypertension (41%), infusion-related reactions (27%), pyrexia (24%), hypokalemia (15%), constipation (15%), rash (12%), abdominal pain (12%), CMV infection (12%), diarrhea (12%), lymphocytosis (12%), cough (12%), irritability (12%), tachycardia (12%), and tachypnea (12%). Additional selected adverse reactions (all grades) that were reported in less than 10% of patients treated with Gamifant included vomiting, acute kidney injury, asthenia, bradycardia, dyspnea, gastrointestinal hemorrhage, epistaxis, and peripheral edema.

Please see Important Safety Information and enclosed full Prescribing Information.

Hyperinflammation is a term meant to encompass Hemophagocytic Lymphohistiocytosis (HLH, familial, infection-, and malignancy-associated), Macrophage Activation Syndrome (MAS), cytokine release syndrome, hyperferritinemic sepsis/sepsis-MAS, and hemorrhagic fever syndromes. These syndromes are currently distinguished by their clinical context or environmental trigger, but such information is not usually available at disease onset and does not usually indicate a specific mechanism or treatment. For decades, studying the pathway linking cytotoxic impairment and FHL has illuminated one such mechanism, spurred several clinical trials, and established a standard of treatment. More recently, excessive production and signaling of the cytokine Interleukin (IL-18) has arisen as another likely mechanism driving hyperinflammation. This presentation will outline the rationale for use of IL-18 as a specific biomarker for susceptibility to MAS, the monogenic diseases in which excess IL-18 is likely a key driver of hyperinflammatory pathology, the relevant biology leading to pathogenic and bioactive IL-18, the mechanisms by which IL-18 may drive hyperinflammation, and the therapeutic implications of identifying elevated IL-18 in patients with suspected hyperinflammation.

Autoinflammatory diseases are immune-dysregulatory diseases that present with sterile systemic and disease-specific organ inflammation. Over the last decade, research in autoinflammation provided insights into innate immune mechanisms that amplify sterile innate immune dysregulation through inflammatory amplification loops that involve potent pro-inflammatory cytokines including: IL-1, Type-1 Interferons, the IL-17/IL-36 axis, ubiquitination of NFκB regulating proteins and the IL-18/Type-II interferon axis, and expand the therapeutic targets and treatment opportunities for patients with autoinflammatory diseases. The discovery of gain-of-function (GOF) mutations in the cytoplasmic inflammasome activating sensors, NLRP3 and NLRC4, as cause of the clinical spectrum of the cryopyrin-associated periodic fever syndromes (CAPS) and NLRC4-associated autoinflammatory disease respectively point to a difference in predominantly IL-1 vs. IL-18 mediated sterile inflammation and reveal different immune-dysregulatory pathways that lead to distinct and different phenotypes. The identification of novel monogenic and likely oligogenic diseases that present as “high IL-18 states” and are associated with an increased risk of developing macrophage activation syndrome (MAS) in the context of infections and other immunological stressors, start to reveal contributing factors and downstream pathways that mediate hyperferritinemic inflammation and imply a prominent role for Type-II IFN in the dysregulatory immune response, referred to as macrophage activation syndrome (MAS). The expanding spectrum of diseases and including Type-I interferonopathies that contribute to that phenotype point to the need to redesign screening methods that identify patients at predisposed to the development of MAS.

Inflammasomes are multimeric protein complexes that play a key role in innate immunity. They are formed in a cell to orchestrate host defense mechanisms in response to infectious pathogens and physiological aberration. Assembly of the inflammasome complex is initiated by nucleotide-binding domain and leucine-rich repeat receptors (NLRs) or absent in melanoma 2 (AIM2)-like receptors (ALRs). NLRs and ALRs mediate host recognition of pathogen-associated molecular patterns (PAMPs) released during bacterial, viral, fungal and protozoan infections or danger-associated molecular patterns (DAMPs) released during cellular damage. Activated NLRs and ALRs typically recruit a bipartite protein known as apoptosis-associated speck-like protein containing a caspase activation and recruitment domain (ASC) to engage caspase-1. NLR- and ALR-mediated caspase-1 activation drive pyroptosis, an inflammatory form of cell death, and release of the proinflammatory cytokines IL-1β and IL-18; these processes are largely beneficial to the host during an infection. However, dysregulated inflammasomes drive detrimental inflammation that contributes to autoinflammatory and metabolic diseases (such as CAPS, FMF etc.). Therefore, activation of inflammasomes and subsequently pyroptosis must be finely controlled. We investigated the mechanisms used by cells to maintain inflammasome quiescence while retaining the potential for rapid activation in response to various stressors. We have found that caspase-8 and FADD play critical roles in NLRP3 inflammasome activation and pyroptosis. Our studies revealed that ZBP1 is an influenza infection sensor and acts as a central regulator of influenza-induced programmed cell death and inflammation. We also showed that TAK1 is essential for controlling NLRP3 inflammasome quiescence and cellular
homeostasis and that IRF8 has a critical role in managing NLRC4 inflammasome activation. In addition, we elucidated a complex crosstalk between caspase-1 and caspase-8 in autoinflammatory diseases. We have also found an important crosstalk between cellular stress responses and inflammasome activation via the molecule DDX3X, a key stress granule component that also plays a role in the assembly of the NLRP3 inflammasome and acts as a live-or-die cell fate checkpoint in response to stress stimuli. Overall, these findings suggest an active role for innate immune receptor signaling molecules and their crosstalk with cell death-associated proteins in the assembly and activation of inflammasomes and innate immune responses. These findings pave the way to mechanistically target inflammasome-dependent diseases.
In 1981, a baby boy named Nikolas Kontoyannis was diagnosed with LCH and taken by his parents to the Dr John Pritchard, pediatric oncologist at Great Ormond Street Hospital in London. Grateful for Pritchard’s efforts and eager to advance understanding and treatment of LCH, Nikolas’s parents, Paul and Elizabeth sponsored a collaborative meeting of scientists and clinicians, many of whom would have had no prior exposure to the disease. The first meeting, organized in 1989 by Pritchard, became a series, The Nikolas Symposia, held annually, funded and inspired by the Kontoyannis family. The aim of the Symposia is the discovery of a rational cure for LCH by promoting collaboration among scientists and clinicians from the field of histiocytosis and other diverse disciplines. The enigmas of rare diseases have often provoked major conceptual advances in biology and medicine. Langerhans Cell Histiocytosis (LCH) is a conundrum, as the same somatic mutation in a myeloid progenitor cell results in a striking diversity of phenotypes ranging from subtle skin lesions to fatal disseminated disease, while also providing a rational therapeutic target in all of these settings. The coming of age of LCH is marked by development of molecular diagnosis and targeted therapy, however the disconnect between a patient’s genotype and their phenotype remains a profound puzzle. The long-standing mission of the Nikolas Symposium is to “search for a rationale cure” for children and adults with LCH. In alignment with that mission, 29th Nikolas Symposium organized discussion around the immune mechanisms that contribute to pathogenesis in LCH and potential immunotherapeutic strategies.

The discovery of somatic mutation in the MAP kinase pathway as the unifying molecular defect in Langerhans cell histiocytosis, resolved a decades-long debate over the fundamental nature of histiocytic disorders. Or did it? While the hematopoietic stem cell is involved in multi-system disease, how certain are we that distant lesions arise by hematogenous spread? Is it possible that multiple sites could be involved by a different mechanism? And even if we understand this, how does a solitary lesion evolve? What does ERK activation control in myeloid cells? Is a second inflammatory signal required to initiate a histiocytic lesion? Is histiocytosis a myeloproliferative neoplasm or something else? What determines the phenotype of lesional histiocytes? Are histiocytic disorders a unique category of disease or could other idiopathic conditions have a similar etiology? These questions remain largely unanswered but form a fundamental line of enquiry into human myeloid cell biology and a pursuit of immediate clinical relevance. In life-threatening LCH, restoration of the balance of ERK activation by MAP kinase inhibitors delivers one of the most impressive clinical responses in pediatric medicine. Yet converting this response to a stable treatment-free remission, is one of the most difficult challenges currently facing physicians. Langerhans cell histiocytosis (and related disorders) remains much courted, still mysterious and occasionally dangerous. Perhaps not an Imperial malady, but still a princess among polyps.

Macrophages are myeloid-lineage cells that reside in nearly all tissues of the body and play key roles in innate and adaptive immune responses. Distinct populations of tissue macrophages also acquire context-specific functions that are important for normal tissue homeostasis and organ function. To address mechanisms specifying tissue-specific macrophage identities, we are investigating how the brain, liver and bone environments play instructive roles in establishing microglia, Kupffer cell and osteoclast phenotypes, respectively. We find that distinct combinations of signaling molecules in each respective tissue environment act to regulate the expression of transcription factors that function as ‘lineage-determining’ transcription factors for each type of resident macrophage. These factors work in a collaborative manner with general macrophage lineage determining factors to set up the cell-specific transcriptional regulatory landscapes of each cell type. Recent studies of osteoclasts have uncovered a novel pathway by which RANK signaling activates osteoclast lineage determining factors by a mechanism involving ERK1 and the histone methyltransferase SETD5. As the ERK1/SETD5 pathway is downstream of BRAF, we speculate that constitutive activation of this pathway due to mutations in BRAF associated with Langerhans cell histiocytosis may contribute to lytic bone lesions observed in this syndrome.
Pharmacologic targeting of oncogenic MAPK signaling using RAF and MEK inhibitors has shown clinical activity and has prolonged patient survival in many MAPK-driven cancers and disorders, including histiocytic neoplasms driven by mutually exclusive mutations of components of MAPK signaling. However the effectiveness of these drugs is often limited by toxicities (low therapeutic index) and by various mechanisms of adaptive and acquired resistance. A common mechanism of adaptive resistance is mediated by relief of negative feedback by inhibitor, and induction of Receptor Tyrosine Kinase (RTK) and RAS activation. RAS activation in turn promotes RAF dimerization, increased signaling flux and incomplete MAPK pathway inhibition by drug. Mechanistic insight on molecular determinants of cell response and adaptation to MAPK-directed therapeutics will be presented, indicating the need for next generation therapeutic strategies to overcome adaptive resistance, while retaining a high therapeutic index. Rationally-designed strategies using the recently developed SHP2 inhibitors in combination with MAPK signaling inhibitors, as well as combinations of state-selective RAF inhibitors with profound preclinical activity in various MAPK-driven tumor models, will be discussed. Further understanding of mechanisms of adaptive resistance and response to pharmacologic perturbations of oncogenic signaling will enable the rational design of more effective combinatorial strategies for the treatment of MAPK-driven cancers and neoplastic disorders.
MONOMETHYL FUMARATE ACTS THROUGH HEME OXYGENASE 1 AS NOVEL THERAPY FOR MACROPHAGE ACTIVATION SYNDROME

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PURPOSE: Macrophage activation syndrome (MAS) is marked by an increase in enzymes of iron metabolism including ferritin and heme-oxygenase 1 (HO-1). Since HO-1 is implicated in anti-inflammatory pathways, we reasoned that drugs that increase HO-1 activity may decrease disease activity in MAS. Dimethyl fumarate is an FDA approved drug for treatment of inflammation in multiple sclerosis; its active metabolite monomethyl fumarate (MmF) increases HO-1 activity. We tested whether MmF could ameliorate MAS in a murine model of the disease. METHODS: MAS was induced using the standardized TLR9-MAS protocol. MmF was injected i.p., 45 mg/kg twice daily, DMSO injections were used as control. Organ weights, serum cytokines, and complete blood counts were measured to assess disease activity. HO-1 floxed mice bred to LysM-Cre mice (HO-1ΔMac) were used to test the role of HO-1. HO-1 levels were examined by western blotting. Statistical testing was performed using Student's T-test or by 2-way ANOVA as appropriate. RESULTS: HO-1 is upregulated by TLR9 stimulation and is required for the majority of IL-10 induced by TLR9. Loss of HO-1 in the HO-1ΔMac mouse resulted in lower IL-10 in TLR9-MAS, but did not significantly affect any of disease parameters. Treatment with MmF increased HO-1 expression in splenic and peritoneal macrophages. Treatment with MmF during TLR9-MAS significantly improved anemia and splenomegaly, and increased serum IL-10 levels while decreasing INFγ and IL-12 levels. This improvement was only partially dependent on HO-1 in the monocyt/macrophage compartment as HO-1ΔMac mice were not as protected by MmF therapy as wild type mice. CONCLUSION: MmF was effective in reducing disease activity parameters of TLR9-MAS. MmF induced HO-1, which plays an important role in regulating MmF induced IL-10 and protection from TLR9-MAS. These results suggest that the parent compound, the FDA approved drug dimethyl fumarate, should be considered in future investigations of MAS therapy.

IFNg NEUTRALIZATION IN PATIENTS WITH NRLC4- AND CDC42-ASSOCIATED AUTOINFLAMMATORY DISEASES CHARACTERIZED BY RECURRENT AND SEVERE HLH

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PURPOSE: IFNg is considered a mediator of HLH. In autoinflammatory diseases, (AID) IL-18 is considered a predisposing factor, being a co-stimulus for IFNg. IL-18 transgenic or IL-18BP-deficient mice, triggered with TLR ligands, develop severe HLH: neutralization of IFNg leads to reversal of signs and symptoms, supporting the role of IFNg as one final downstream mediator.

METHODS: We report efficacy of emapalumab (anti-IFNg antibody) in patients with NRLC4- and CDC42-associated AID with high IL-18. RESULTS: NRLC4: pt1 (de novo pT337N) and pt2 (de novo pI343N) presented with neonatal onset of autoimmune inflammation and severe recurrent HLH. Pt1 had a HLH reactivation, sepsis triggered, at 4-months with multiple organ failure requiring ICU admission. Emapalumab, added to ongoing dexamethasone and cyclosporine-A, led to HLH resolution in 3 weeks. After 7 months of emapalumab, all therapies, including emapalumab, were discontinued, without HLH reactivation during a 4-year follow-up. In pt2, emapalumab was started during full-blown HLH, added to ongoing glucocorticoid and cyclosporine-A, with prompt resolution of HLH. During emapalumab two mild HLH episodes occurred, controlled with moderate intensification of glucocorticoids. CDC42: pt3 (de novo pR186C) presented with neonatal-onset of cytopenia, autoinflammation, rash, and recurrent HLH. Severe HLH flare, occurring while on anakinra and glucocorticoids, was successfully treated with the addition of emapalumab. She underwent successful HSCT. Markedly increased levels of IL-18 (>100,000 pg/ml) were observed in all patients with or without HLH at sampling. During HLH, increased production of IFNg was demonstrated by high levels of CXCL9 (3,310 to 380,074 pg/ml), which were strictly related to ferritin levels, by increased IFNg expression in NK cells and CD8T cells and by high levels of IFNg bound to circulating emapalumab. CONCLUSION: In monogenic AID associated with high IL-18 levels, emapalumab treatment was tolerated, no safety concern emerged and control of HLH flares was achieved.
EFFECT OF DONOR-SOURCE AND CONDITIONING REGIMEN ON THE OUTCOME OF CHILDREN WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANTATION: A NATIONAL MULTICENTER

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BACKGROUND: Hemophagocytic Lymphohistiocytosis (HLH) is an immune dysregulation disorder, caused by impaired lymphocyte cytotoxicity. Allogeneic hematopoietic stem-cell transplantation (HSCT) is currently the only curative option for familial or refractory HLH. Uncertainties exist regarding conditioning regimen and appropriateness of alternative donors. METHODS: We conducted a national, multi-center, retrospective study of children with HLH who underwent HSCT in 4 pediatric HSCT centers in Israel. Conditioning regimen was defined as myeloablative (MAC) or reduced intensity (RIC) according to EBMT/ESID guidelines. RESULTS: Between 2000 and 2018, 48 allogeneic HSCT procedures were performed in 47 children with HLH in Israel. Forty-three patients were diagnosed with familial HLH, and genetic diagnosis was confirmed in 33. All patients received anti-HLH therapy prior to HSCT. Donors were either HLA-matched (n=27), partially mismatched (n=7), haploidentical (n=9) or cord-blood (n=5). A MAC regimen was used in 27 procedures (44%), and RIC in 21 (56%). The median follow-up time was 4.2 years. Forty-five patients had primary engraftment, 2 had primary graft failure, 1 died prior to engraftment, and 2 developed secondary graft failure. Ten patients had mixed donor chimerism at day 30 (5-95%); two subsequently converted to complete donor chimerism and 5 achieved stable mixed chimerism by 1 year. The 5-year overall survival and event-free survival (EFS) were 84% and 83%, respectively. EFS trended lower for patients receiving RIC and following alternative-donor transplant (5-year EFS 69% vs 89% for both analyses, p=0.1), mostly due to increased transplant-related mortality. Of note, ex-vivo alpha-beta-TCR+T cell depletion haploidential HSCT resulted in 100% survival, with one of 5 patients requiring re-transplantation due to secondary rejection. CONCLUSION: Results of HSCT of HLH in Israel are comparable to other cohorts. Although better than previously reported, the use of alternative donors is still associated with inferior outcome, which may be improved using novel transplant techniques.

EXCESSIVE IL-10 COOPERATES WITH IL-18 TO DRIVE SEVERE HLH-LIKE DISEASE IN A TRANSGENIC MOUSE MODEL

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PURPOSE: Hemophagocytic lymphohistiocytosis (HLH) is a heterogenous disease with hyperinflammatory responses caused by overactivated macrophages and cytotoxic T cells. Significantly elevated serum IL-18 and IL-10 are hallmarks of secondary HLH patients. This study aims to understand the pathophysiological roles of these two cytokines in vivo in transgenic models. METHOD: We generated transgenic mouse models which overexpress murine IL-18 and IL-10 simultaneously (Mx1CreH1.1LSL-I18-2a/wt) or IL-18 alone (Mx1CreH1.1LSL-I18-2a/wt) driven by hematopoietic cell specific Mx1-Cre. The models were induced with Poly(I:C) in 8-week old mice to trigger excessive cytokine expression. Mice were analyzed five weeks after induction. Cre negative mice treated with the same doses of Poly(I:C) were used as controls. RESULTS: ELISA showed a 26-fold increase for IL-18 and an 85-fold increase for IL-10 in the serum of Mx1CreH1.1LSL-I18-2a/wt model mice compared to controls. These mice presented severe pancytopenia, anemia and splenomegaly. Disease progressed rapidly with a median survival of 58 days. We found a significant number of hemophagocytes in the bone marrow and spleens of these mice. Additionally, other HLH symptoms including hyperferritinemia, hypertriglyceridemia and low NK cell activity were also confirmed. Importantly, no signs of HLH symptoms were detected in the Mx1CreH1.1LSL-I18-2a/wt mice. These mice had a 10-fold increase in serum IL-18 but unaltered CBC and spleen size, suggesting a cooperative role for IL-18 and IL-10 in HLH development. Since inflammatory and caspases activation, which are physiologically inhibited by Xiap, are required for the clearance of pro-IL-18, we further bred Mx1CreH1.1LSL-I18-2a/wt mice with Xiap-/- mice to enhance the level of serum IL-18. Indeed, the Mx1CreH1.1LSL-I18-2a/wtXiap-/- mice, with 100-fold increases of both cytokines, presented more severe HLH including shorter survival (median 41 days) and higher frequency of hemophagocytes in tissues. CONCLUSION: IL-10 cooperates with IL-18 to drive HLH. These models will be useful for understanding HLH pathophysiology and developing novel therapies.

PERFORIN-DEFICIENCY AND EXCESS INTERLEUKIN-18 INDEPENDENTLY PROMOTE MURINE VIRUS-INDUCED HYPERINFLAMMATION

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PURPOSE: Hemophagocytic Lymphohistiocytosis (HLH) and Macrophage Activation Syndrome (MAS) are closely-related cytokine storm syndromes associated with underlying hematologic and rheumatic diseases, respectively. Mechanistically, cytotoxic impairment promotes the development of HLH and may contribute to MAS susceptibility in some patients. Interleukin (IL)-18 is increasingly appreciated as a specific biomarker of MAS susceptibility, and excess IL-18 promotes an innate immune MAS model. How IL-18 promotes MAS remains unknown. METHODS: To better understand IL-18 mediated susceptibility to cytokine storm, we infected Il18transgenic (Il18tg) mice with the canonical HLH trigger lymphocytic choriomeningitis virus (LCMV). We assessed for systemic inflammation, serum cytokines, antigen-specific responses, and viral clearance. RESULTS: Surprisingly, Il18tg mice developed immunopathology similar in character, and nearly as severe, as Prf1/-/- mice. Unlike Prf1/-/- mice, immunopathology in Il18tg mice was not associated with impaired viral clearance or prolonged antigen presentation, but depended on IL-18 sensing by T lymphocytes. The phenotype was largely rescued by either CD8 depletion or IFNβ blockade. Other models of excess IL-18 supported the necessity of chronic IL-18 overproduction for LCMV-induced immunopathology. Despite minimal inflammation in either Il18tg or Prf1/-/- mice in the absence of infection, mice harboring both susceptibility factors developed spontaneous and fatal MAS/HLH, associated with a massive expansion of activated CD8 T-cells. CONCLUSION: Excess IL-18 amplifies both innate and adaptive triggers to promote cytokine storm via a mechanism distinct from, and synergistic with, cytotoxic impairment.
PURPOSE: Primary hemophagocytic lymphohistiocytosis (pHLH) is characterized by hyper-inflammation and is driven by high production of interferon gamma (IFNγ). Hematopoietic stem cell transplantation (HSCT) is the only potentially curative option for pHLH and mortality remains high.

METHODS: In the pivotal trial (NCT01818492), overall response rate was 65% for patients who received emapalumab and proceeded to HSCT in the pivotal or extension therapy. In the pivotal trial (NCT02069899) were evaluated. METHODS: In the pivotal trial, patients were either treatment-naive (n=27). Emapalumab (1 mg/kg, every 3 days, with the potential to increase the dose to 10 mg/kg) was administered with dexamethasone (initially 10 mg/m2/day, then weaning) until the start of HSCT conditioning. Approximately one-half of patients received an almeztumab, fludarabine, and melphalan-based preparative regimen, with the remainder receiving busulfan/teosulfan-based regimens. Most patients received a bone marrow graft from a matched, unrelated donor. The data cut-off applied was July 20, 2017. RESULTS: Overall, 64.7% (22/34) of patients proceeded to HSCT. Median time to transplant was 100 days (95% CI: 73, 155 days). 86.4% (19/22) of HSCT recipients engrafted, and 90.9% (20/22) survived following HSCT. The 3 patients who failed to engraft received haploidentical transplants; 2 were rescued with a second allograft. Two patients died after HSCT due to septic shock or respiratory failure; 2 patients had HLH relapse after graft failure, and 7 patients developed graft-versus-host disease (GVHD). CONCLUSION: Patients who were treated with emapalumab and proceeded to HSCT experienced excellent post-HSCT overall survival, with a high rate of engraftment and an acceptable frequency of GVHD.

THE TYPE OF ONCOGENIC BRAF MUTATION MATTERS: BRAF EXON 12 DELETIONS ARE ASSOCIATED WITH SUPERIOR EVENT-FREE SURVIVAL COMPARED TO BRAFV600E IN PEDIATRIC LCH

PURPOSE: Langerhans Cell Histiocytosis (LCH) is characterized by constitutive activation of the MAPK signaling pathway. In approximately 50-60% of patients this is caused by the BRAFV600E mutation in exon 15 of the BRAF gene. We explored the incidence and clinical associations of alternative MAPK pathway mutations in a Dutch-Canadian LCH-patient cohort with long-term follow-up. METHODS: Formalin-fixed-paraffin-embedded tissue biopsies were analyzed for the presence of the BRAFV600E mutation by real-time and/or droplet digital PCR. BRAFV600E negative samples were subjected to Sanger sequencing (MAP2K1 exon 23; BRAF exon 12) and/or an AmpliSeq next-generation-sequencing panel containing primers to detect mutations in ARAF, BRAF, MAP3K1, KRAS, NRAS and many other cancer-associated genes. Clinical data were obtained using standardized case report forms. RESULTS: Alternative MAPK pathway mutations were detected in 64 BRAFV600E negative LCH-patients, including MAP2K1 mutations (n=38), BRAF exon 12 indels (n=13 deletions; n=2 insertions), BRAFV600E (n=4), KRAS mutations (n=2), NRAS amplifications (n=2), ARAF mutations (n=2) and a MAP3K1 mutation (n=1). Pediatric LCH-patients with a BRAF exon 12 deletion had superior 5-year event-free survival compared to BRAFV600E mutated patients (n=95, p=0.01), also after excluding MS-RO+ patients (0/13 BRAF exon 12 deletion positive patients vs. 10/85 BRAFV600E mutated patients; p=0.03). No significant difference in event-free survival was observed between BRAFV600E positive and MAP2K1 mutated (n=28) pediatric LCH-patients (p=0.48). Furthermore, in contrast to the two cases described by Herittier et al., the two pediatric patients with a BRAF exon 12 c.1511_1517+2dupTACCTGAGGT insertion did not have autoregressive bone LCH. Instead, both had multifocal bone disease, were treated with LCH IV stratum I chemotherapy, and required LCH IV stratum II chemotherapy due to disease reactivation. CONCLUSION: Our study identifies diverse alternative MAPK pathway mutations in BRAFV600E negative LCH-patients, and demonstrates that BRAF exon 12 deletions are associated with superior event-free survival compared to BRAFV600E in pediatric LCH.
SCIENTIFIC SESSION II - PRESIDENTIAL SYMPOSIUM

MONDAY, NOVEMBER 4, 2019 • 1530

AUDITORIUM

EARLY MORTALITY IN LANGERHANS CELL HISTIOCYTOSIS III (LCH-III) TRIAL SUGGESTS SOME PATIENTS REQUIRE MORE EFFECTIVE THERAPY EVEN BEFORE THE 1ST RESPONSE ASSESSMENT POINT AT 6 WEEKS

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PURPOSE: The timing and cause of death in patients who took part in the LCH-III trial were re-examined to inform future treatment strategies. METHODS: LCH-III was an international multicentre treatment trial for children with multisystem Langerhans cell histiocytosis (LCH). During the first 6 weeks all patients received weekly vinblastine + daily prednisolone and randomised to also receive 2-weekly methotrexate or not. The 1st response assessment was after 6 weeks. Data on the demographics, disease characteristics, treatment, timing and cause of death were obtained from the LCH-III database for all trial participants who died. RESULTS: 12 of the 43 patients who died, died during the first 6 weeks of therapy, representing 28% of deaths. A further 9 (21%) of the deaths occurred in week 7 - 13. The patients who died before the response assessment at 6 weeks, were all <2 years old, 7/12 were <1 year old and 3/12 <6 months old. All these patients had multisystem disease and 11/12 had risk organ involvement. The median duration of therapy at the time of death for this group was 18 days (range: 7-39; data unavailable for 1 patient). The recorded causes of death were: disease progression and infection (4), disease progression (3), infection (2), disease related respiratory failure (1), data unavailable (1). CONCLUSION: Response assessment at week 6 is too late to identify some patients who are in need of alternative, more effective therapy. The young age of these patients demands that alternative therapies be available in age appropriate formulations. Mitogen-activated protein kinase (MAPK) inhibitors are known to be effective in quickly controlling LCH symptoms in patients with refractory multisystem disease. In selected patients MAPK inhibitors may need to be introduced before the week 6 response assessment to avoid early mortality. Future trials should investigate the role of MAPK inhibitors in avoiding early mortality.

PRESENTATIONS NOMINATED FOR THE NEZELOF PRIZE IN BASIC SCIENCE

NOVEL ALTERATIONS IN CSF1R, RET, AND OTHER DIVERSE KINASES IN THE HISTIOCYTOSES WITH BIOCHEMICAL AND STRUCTURAL INSIGHTS INTO THEIR MECHANISMS OF ACTIVATION

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PURPOSE: We performed comprehensive genomic analyses of 270 patients with all subsets of histiocytoses, including monозygotic twins. In so doing, we uncovered and characterized a novel series of activating receptor tyrosine kinase (RTK) alterations in the histiocytoses, including recurrent, activating mutations in CSF1R, the RTK required for monocye/macrophage development, as well as the clinical importance of targeting rearrangements in RET and ALK. METHODS: We performed whole exome sequencing (WES) of skin lesions, blood, and fingernails from monozygotic twins with systemic juvenile xanthogranuloma (JXG). We then sequenced 100 ECD (37%), 92 LCH (34%), 55 JXG (21%), 17 Rosai-Dorfman Disease (RDD) (6%), and 6 histiocytic sarcoma (HS) (2%) lesions using WES and targeted DNA and RNA sequencing. We also performed biochemical and biophysical analyses to gain insights into the mechanisms of activation of selected, novel kinase alterations. RESULTS: We identified in-frame deletions in CSF1R546, K551del in the JXG lesions of both twins that were absent in their germline DNA. Interestingly, 11 patients had CSF1R mutations and are structurally categorized into those that might enhance the dimerization propensity of CSF1R, and those that might promote the receptor’s intrinsic kinase activity. Moreover, expression of CSF1R mutants from each of these two categories were identified to be biochemically activating. Additionally, CSF1R activating mutations were sensitive in vitro to CSF1R-specific inhibitors. Meanwhile, an ALK-rearranged ECD patient and RET-rearranged JXG patient required therapy with crizotinib and LOXO-292, respectively, that resulted in profound therapeutic improvement. CONCLUSION: The discovery of recurrent, activating mutations in RTKs highlight the potential for targeted inhibition of RTKs such as CSF1R, ALK, and RET in histiocytoses. In addition, the presence of CSF1R mutations in lesions from two monozygotic twins but absent from their blood or fingernails, suggest that histiocytoses may arise, in some cases, from a mutation in extra-embryonic macrophage progenitors.
THE COMBINATION OF DEXAMETHASONE AND RUXOLITINIB SYNERGISTICALLY ATTENUATES DISEASE MANIFESTATIONS IN A PRECLINICAL MODEL OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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PURPOSE: The goal of treatment for hemophagocytic lymphohistiocytosis (HLH) is suppression of excessive immune cell activation with lymphotoxic agents, including dexamethasone (DEX) and etoposide. Nevertheless, the mortality rate remains high, with five-year survival rates of only 50-60%. Recently, there has been interest in targeting hypercytokinemia, a hallmark of HLH, by inhibiting cytokine receptors or their signaling effectors, such as the Janus kinases (JAKs). The JAK1/2 inhibitor ruxolitinib (RUX) attenuates manifestations of HLH in murine models and demonstrates clinical efficacy in refractory HLH. Previously, we demonstrated that the JAK-dependent cytokine interferukin (IL)-7 confers DEX resistance in human T-cell leukemia in vitro, and that resistance is reversible with RUX. Similarly, we found that IL-2 confers DEX resistance in peripheral T-cells in vitro, which is also reversible with RUX. Here, we test the hypothesis that the combination of DEX and RUX might more potently attenuate inflammation in a preclinical model of HLH.

METHODS: Prf1-/- mice were infected with lymphocytic choriomeningitis virus to generate an in vivo model of HLH and were treated with DEX and/or RUX. Activated cytotoxic T-lymphocytes (CTLs) were employed to interrogate the mechanistic basis for functional interactions between DEX and RUX.

RESULTS: In vivo administration of DEX and RUX synergistically lessened signs of systemic inflammation, including splenomegaly, inflammatory cell number, and circulating levels of inflammatory cytokines. Ex vivo studies revealed that the JAK-dependent cytokines IL-2 and IL-12 conferred DEX resistance in CTLs through STAT5 activation and upregulation of anti-apoptotic proteins. Both in vivo and ex vivo, inhibition of cytokine receptor signaling restored the apoptotic potential of CTLs, as measured by BH3 profiling, thereby facilitating DEX-induced apoptosis. CONCLUSION: This study reveals a mechanism of cytokine-mediated DEX resistance in HLH and provides rationale for combining DEX and RUX as a means to augment DEX sensitivity and improve clinical outcomes for patients with HLH.

PLASMA PROTEIN AND CYTOTOXIC T-CELL GENE EXPRESSION PROFILES DISTINGUISH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS FROM OTHER HYPER-INFLAMMATORY DISEASES

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PURPOSE: Hemophagocytic Lymphohistiocytosis (HLH) is a life-threatening disorder that shares many overlapping clinical features with other hyper-inflammatory diseases including sepsis and systemic inflammatory response syndrome (SIRS). This study evaluates the plasma protein profiles of HLH, sepsis, and SIRS and the gene expression profiles of cytotoxic T-cells (CTLs) and monocyte/macrophages (Mono/Mac) in HLH compared to sepsis. METHODS: The Luminex platform measured 135 analytes in 41 patients with HLH to 47 patients with severe sepsis or SIRS in discovery and validation cohorts. Disease status comparisons and 3-Nearest Neighbors Prediction classifier were developed. CD3+8+ CTLs and CD3-66+ Mono/Mac were isolated from peripheral blood of 12 patients with HLH, 10 with severe sepsis, and 4 healthy controls. Gene expression data was analyzed using Gene Set Enrichment Analysis (GSEA). RESULTS: The number of significant analytes between groups included 54 - HLH vs controls, 15 - HLH vs sepsis/SIRS, 0 - primary vs secondary HLH, and only OPN - sepsis vs SIRS. A prediction classifier using ten analytes differentiate HLH from SIRS/sepsis with sensitivity 0.857 and specificity 0.833, and GSEA of HLH CD8+ T cells compared to SIRS/sepsis CD8+ T cells was enriched for an IFN-g signature. Elevated plasma CCL20 was associated with risk of death in the HLH cohort. CONCLUSION: This evaluation of plasma proteins demonstrated that HLH has a distinct inflammatory profile compared to severe sepsis and SIRS and IFN-3 response elements, CXCL9, CXCL10, and CXCL11, are all upregulated in HL.
PURPOSE: Reduced toxicity conditioning for hematopoietic stem cell transplantation (HSCT) of patients with hemophagocytic lymphohistiocytosis (HLH) results in favorable survival at the expense of relevant rates of mixed chimerism. Factors predisposing to mixed chimerism remain to be determined. METHODS: Patients with primary HLH transplanted 2009-2016 after treosulfan or melphalan based conditioning regimens were analyzed in a retrospective multicenter study for survival, engraftment, chimerism, and adverse events. Recipient chimerism was considered substantial if <25% donor chimerism occurred and/or if secondary cell therapy was administered (secondary HSCT, donor lymphocyte infusion, or stem cell boost). Donor type, graft source, type of alkylating agent, type of serotherapy, and remission status were analyzed as potential risk factors for the occurrence of substantial recipient chimerism in a multivariate logistic regression model (excluding haploidentical SCT). RESULTS: Five-year overall survival of 60 patients was 75% (median FU 2 years) and 95% of patients engrafted. Prevalence of any recipient chimerism was 50%. Substantial recipient chimerism was recorded in 32% of patients. Secondary post-SCT cell therapy was administered in 30% of patients (22% DLI, 7% SCT boost, and 20% 2nd SCT). A mismatched donor was the only significant risk factor for the occurrence of substantial recipient chimerism (p = 0.01, OR 5.8 CI95% 1.5-26.3). Adverse events included mild or moderate veno-occlusive disease without fatalities (10%), acute GvHD≥3° (15%), and limited chronic GvHD 3%. CONCLUSION: Substantial recipient chimerism in treosulfan or melphalan based conditioning in children and adolescents with familiar HLH is less frequent when a matched donor is used.

Poster Location #2

THE FEASIBILITY OF NEWBORN MASS SCREENING FOR PRIMARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS USING DRIED BLOOD SPOT (DBS) PROTEOMICS

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PURPOSE: Familial hemophagocytic lymphohistiocytosis (fHLH) is a fatal syndrome of immune dysregulation and hyper-inflammation. Despite advances in the treatment, overall survival of fHLH remains at about 60%. Recent report comparing the index fHLH cases with their affected siblings has shown that a preemptive hematopoietic cell transplantation before the onset of HLH symptom significantly improves the prognosis. However, fHLH diagnosis before the onset of hemophagocytosis remains almost impossible because hemophagocytosis itself is the only symptom for most patients. We previously reported that fHLH type 3 (fHLH3) can be screened by detecting intra-platelet munc13-4 protein expression, and that the pathogenicity of a reported UNC13D variant strongly correlates with the munc13-4 expression level. The purpose of this study is to examine the feasibility of newborn mass screening for IHLHs by quantifying the expression of their responsible proteins in Dried Blood Spot (DBS). METHODS: We first performed DBS proteome analysis to make a list of detectable proteins and then assessed if it is applicable to fHLH screening. RESULTS: We succeeded in semi-quantitative evaluation of more than 2,000 proteins from DBS. The list of detectable proteins included those associated with lysosome trafficking such as munc13-4, syntaxin11, munc18-2, and Rab27a. Furthermore, a parallel reaction monitoring (PRM) channel was established according to the identification information of munc13-4, which enable us to selectively detect the lack of munc13-4 peptide peaks from DBS of fHLH3 patients. CONCLUSION: A semi-quantitative analysis of munc13-4 protein from DBS was established, that could be used for newborn mass screening for fHLH3. The system can be applied for other types of HLH as well as congenital disorders caused by defective protein expression of their causative genes.

CLINICAL HLH POSTER NOMINEES

Poster Location #1

RISK FACTORS FOR MIXED CHIMERISM AFTER TREOSSULFAN OR MELPHALAN BASED STEM CELL TRANSPANTATION IN CHILDREN WITH PRIMARY HEMOPHAGOCYTIC HYSTEROCYTOSIS

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1.134

ROBERT J. ARCECI PRIZE FOR BEST POSTER

CLINICAL LCH POSTER NOMINEES

Poster Location #3

PROGNOSTIC SIGNIFICANCE OF CELL-FREE BRAF-V600E QUANTITATIVE DETECTION AT DIAGNOSIS AND DURING CHEMOTHERAPY IN CHILDREN WITH LANGERHANS CELL HISTIOCYTOSIS

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The aim of this study was to investigate the prognostic significance of cell-free (cf) BRAF-V600E detection during follow-up in a paediatric LCH cohort. Totally, 102 LCH patients with successfully determined BRAF status were included in this study to detect cfBRAF-V600E in plasma at diagnosis by a droplet-digital PCR assay. Among these patients, sequential samples during follow-up were obtained from BRAF-V600E-mutated LCH patients. cfBRAF-V600E at diagnosis was detected positive in 67.9% (55/81) of BRAF-V600E-mutated LCH patients. Positive cfBRAF-V600E at diagnosis was closely related to RO, skin, ear involvement and age of patients. The 6-week response rate was much lower in the children with positive cfBRAF-V600E than that in children with negative detection (34.6% vs 65.0%, P = 0.032). 2-year progression-free survival (PFS) was much lower in the cfBRAF-V600E positive group (34.7% ± 7.3% and 92.3% ± 5.2%, respectively; P < 0.001). Moreover, the prognostic impact of cfBRAF-V600E was most obvious in SS LCH patients. Multivariate analysis demonstrated that cfBRAF-V600E at diagnosis remained as an independent prognostic factor for PFS in childhood LCH (HR: 5.263, 95% CI: 1.134 - 24.425, P = 0.028). cfBRAF-V600E at week 6, week 12, week 52 of the first-line therapy or course 8 in the second-line therapy was also closely correlated to worse outcome of LCH patients, respectively. Dynamic monitoring cfBRAF-V600E during follow-up had instructional significance in the judgment of prognosis. These results indicated that quantitative cfBRAF-V600E analysis at diagnosis and during chemotherapy had significant impact on prognosis of children with LCH.
**Poster Location #4**

**BRAFV600E-POSITIVE PRECURSORS AS MOLECULAR MARKERS OF BONE MARROW INVOLVEMENT IN PEDIATRIC LANGERHANS CELL HISTIOCYTOSIS**

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**PURPOSE:** The BRAF mutation V600E, the most common somatic mutation in Langerhans cell histiocytosis (LCH), has been reported in approximately 50% of LCH patients and is associated with certain high-risk clinical features. Precursors harboring this mutation can differentiate into Langerhans cells resulting in infiltrates in multiple organs under inflammatory conditions. However, BRAF status in the bone marrow of pediatric LCH patients is unclear. The present study examined somatic mutations in paired tumor and bone marrow samples, using a highly sensitive assay involving next-generation targeted sequencing and droplet digital polymerase chain reaction (PCR) for pediatric LCH patients. **METHODS:** We retrospectively performed mutational analyses of 17 LCH cases using formalin-fixed paraffin-embedded LCH tumor specimens to provide templates for PCR-based targeted amplicon sequencing with customized primers to detect mutations in exons 12 and 15 in BRAF, and exons 2 and 3 in MAP2K1. Thereafter, we identified somatic mutations in the paired bone marrow samples via droplet digital allele-specific PCR, targeting BRAF V600E and BRAF exon 12 in-frame deletion 496-500 (Ex12 in-del). **RESULTS:** We detected BRAF V600E in 11 of 17 tumor samples (65%) and the BRAF Ex 12 in-del in 3 of 17 tumors (18%). We identified BRAF V600E in bone marrow samples in 10 of the 11 cases with the mutation in the tumor (90%). BRAF Ex 12 in-del was not detected in the bone marrow. Cases with detectable bone marrow involvement included eight patients with multi-system disease affecting multiple organs, one patient with multi-focal bone disease, and one patient with single system disease. Clinical phenotypes did not correlate with BRAF V600E upon detection in the bone marrow. **CONCLUSION:** Bone marrow involvement is frequently detectable at the molecular level in pediatric LCH with the BRAF V600E mutation. A prospective study is warranted to evaluate the clinical impact of this mutation.

**Poster Location #5**

**BRAFV600E MUTATED ALLELES PERSIST IN THE CIRCULATION OF NEWLY DIAGNOSED PAEDIATRIC PATIENTS WITH MULTISYSTEM LANGERHANS CELL HISTIOCYTOSIS DESPITE 6 WEEKS OF TREATMENT WITH PREDNISOLONE AND VINBLASTINE**

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**PURPOSE:** To use preliminary data from the United Kingdom Langerhans cell histiocytosis (LCH) biology study (running in parallel to LCH-IV study) to determine if the first 6 weeks of induction therapy (daily prednisolone and weekly vinblastine) clears BRAF V600E mutated alleles from the circulation. **METHODS:** Blood samples taken from newly diagnosed LCH patients enrolled on LCH-IV trial and the parallel biology study were analysed. Samples were taken before therapy started and then again 6 weeks later. Peripheral blood mononuclear cells (PBMCs) were isolated from whole blood using ficoll density gradient centrifugation. DNA was extracted from PBMCs and plasma using Qiagen DNA extraction kits. BRAFV600E is measured using a Taqman mutation detection assay. **RESULTS:** 17 patients with multi-system LCH were recruited and circulating BRAF V600E was detected in 12/17 cases. 4/12 of these patients had risk organ (liver / spleen / haemopoietic system) involvement. BRAF V600E mutated alleles remained detectable in all 12 cases at the 6 week disease reassessment. **CONCLUSION:** This pilot data shows that BRAF V600E mutated alleles are not cleared from the circulation of multisystem LCH patients during the first 6 weeks of therapy. Measurement of circulating BRAF V600E mutated alleles at additional time points during therapy and analysis of changes in the levels of circulating BRAF V600E mutated alleles, correlated with clinical outcomes, are required to further explore the possible prognostic value of this test.
A PATIENT WITH LANGERHANS CELL SARCOMA ARISING FROM LANGERHANS CELL HISTIOCYTOSIS AND ACUTE LYMPHOBLASTIC LEUKEMIA

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PURPOSE: Summarize and discuss the treatment of Langerhans cell sarcoma (LCS), arising from Langerhans cell histiocytosis (LCH) and Acute lymphoblastic leukemia (ALL), and pathogenesis of the clonal evolution. METHODS: Retrospectively summarize a case of LCS, arising from LCH and T-ALL in Beijing Children’s Hospital, and review the relevant literatures. RESULTS: A 15 years old female patient developed skin lesions during maintenance chemotherapy for T-ALL, which diagnosed 4 years ago. The biopsy from the skin lesions revealed LCH. She was stratified to multiple systemic involvement (skin, thyroid, thymus, lymph node) group. The patient was treated as LCH for 2 years, but the skin lesions and lymphadenopathy were refractory. Genomic analysis revealed mutations in KRAS, BRAF, FGFR4 genes, and amplification of Notch1. Positive mutation Exon2 c.G35A p.G12D of KRAS gene were discovered as the targeted drug-related gene. Therefore the patient took Trametinib with significant effect. Skin lesions and lymphadenopathy were relieved within a week. Three months later the patient developed new lymphadenopathy, which biopsy revealed LCS. PET/CT examination revealed high-metabolic in multiple lymph node, skin and subcutaneous tissue, hypothyroid, lung, liver, spleen and marrow, lesions progressed sharply and the patient expired 7 days after the diagnosis of LCS. LCH and LCS are clonal proliferations of Langerhans cells, which may occur concurrently or sequentially with T-ALL and other Lymphoid neoplasms. A few case reports in the literature describing LCS arising from LCH, or LCH arising from T-ALL, and few cases about LCS arising from LCH, T-ALL sequentially. It may relate to clonal evolution and transformation, rearrangement of IGH and TCRG gene, chemotherapy drugs, heredity, hematopoietic plasticity and other factors. CONCLUSION: A patient with LCH arising from T-ALL and transformed into LCS is extraordinarily rare, the mechanism remains unclear. Targeted agents are possible, but for the patient with multiple gene mutation and clonal evolution, hematopoietic stem cell transplantation may more efficacious.

CLINICAL RARE POSTER NOMINEES

Poster Location #8

GENOMIC CHARACTERIZATION OF A PEDIATRIC COHORT WITH NON-MALIGNANT LYPHOPROLIFERATIVE DISORDERS

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14 Center for Cell and Gene Therapy, Baylor College of Medicine, Houston, TX USA
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PURPOSE: Pediatric non-malignant lymphoproliferative disorders (LPDs) are a clinically and genetically heterogeneous group of disorders. Misdiagnosis or delayed diagnosis may contribute to substantial morbidity or mortality. Identification of the molecular causes and underlying disease mechanisms may facilitate timely interventions and potentially guide targeted or curative therapies. METHOD: Patients at Texas Children’s Hospital or collaborating referral centers who met criteria for non-malignant LPDs were offered participation in this study, approved by the Baylor College of Medicine Institutional Review Board. All subjects and/or family members provided written informed consent to have their clinical and genetic information published. Genetic testing was performed clinically or through research-based whole-exome sequencing (WES). RESULTS: 51 subjects (from 47 different families) with non-malignant LPDs were identified. Fifteen subjects (29%) met HLH-2004 diagnostic criteria for hemophagocytic lymphohistiocytosis. Twenty-one patients had EBV-associated lymphoproliferative disorders (EBV-LPD) and 6 of the 51 ultimately developed malignancy. Ten-year survival for the cohort was 72%. For patients with EBV-LPD, ten-year survival was 56%, and for patients meeting HLH criteria, it was 52%. Clinical genetic testing was performed for 29 patients, and research-based WES analysis was performed for 44 patients. Likely disease-causing genetic defects were identified in 62% of families. Of these pathogenic mutations, targeted therapies are available for treatment of at least 9 of the conditions (16 subjects 31% total; 48% of pathogenic mutations). Furthermore, successful outcomes have been reported after hematopoietic stem cell transplantation in 10 of the 20 recognized primary immunodeficiency diseases (18 subjects 35% total; 55% of pathogenic mutations). CONCLUSION: Pediatric non-malignant LPD represents a group of conditions with high risk of death. WES identified actionable mutations in the majority of LPD cases in this cohort. Early identification of these mutations can guide therapy by confirming diagnosis, revealing molecular targets and/or supporting definitive therapy with stem cell transplantation.
PURPOSE: Langerhans cell sarcoma (LCS) is a rare dendritic cell malignancy with poor prognosis. There are currently limited clinical and treatment data for LCS. In this study, we report our institutional experience of LCS. METHODS: We performed a retrospective review of all LCS cases seen at our institution between March 2002 and June 2019. Kaplan-Meier method was used to assess overall survival (OS). RESULTS: Our search included nine adult patients with LCS. The median age at diagnosis was 71 years (range 30-77). LCS involved a single organ system in 78% (n=7) and multiple systems in 22% (n=2) of cases. The lymph nodes (44%), skin (44%), and lungs (44%) were most commonly involved. Three patients underwent targeted next generation sequencing, one had a BRAF-V600E mutation, the second had SETD2, SMARCB1, NRAS, and TP53 mutations, and the third did not have targetable mutations. Two other patients had BRAF-V600E testing performed and were negative. Treatment and outcome data were available for six patients. Surgical resection and radiation therapy were used in two patients with localized LCS each that led to ongoing remission at 7 months and 3 years, respectively. Systemic treatments with cladribine + prednisone or trametinib failed to induce response in two patients, respectively. One patient had disease recurrence after surgical resection and adjuvant radiation, so underwent gemcitabine + cisplatin treatment, and was free of disease recurrence before being lost to follow up at 40 months. Another patient with multi-system disease died before initiating therapy. Median OS was 7 months (range 1-40). CONCLUSION: LCS demonstrates rarity as well as a poor prognosis. Surgical resection may be of benefit in localized cases. For multisystem disease, however, the prognosis remained poor despite systemic cytotoxic and targeted therapies. Further studies into the molecular basis of LCS pathogenesis are warranted to improve treatments and outcomes.
Sub-cutaneous panniculitis-like T-cell lymphomas (SPTCL), a non-Hodgkin lymphoma, can be associated with hemophagocytic lymphohistiocytosis (HLH), a life-threatening activation of the immune system. Recently we identified mutations in the coding gene of T-cell immunoglobulin mucin 3 (TIM-3), a critical immune checkpoint, as the underlying genetic cause of several cases of SPTCL associated to HLH (HLH/SPTCL). We identified two, loss-of-function, missense variants in highly conserved residues of TIM-3 expression. The lack of TIM-3 expression led to persistent immune activation, characterized by increased production of inflammatory cytokines by innate immune cells. Our findings highlight HLH/SPTCL as a new genetic entity where loss of the TIM-3 immune checkpoint is associated with T-cell infiltration of adipose tissue and inflammation. Current experiments aim to determine the pathophysiological bases of this severe condition.

Poster Location #11

ATYPICAL INTRACRANIAL LESIONS OF HLH IN A CHILD

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PURPOSE: To identify atypical intracranial presentations of Hemophagocytic Lymphohistiocytosis (HLH) in children. METHODS: Medical record review. RESULTS: A 2 year old female presented with seizures and septic shock. Her initial computed tomography (CT) scan was normal. Within 24 hours she was diagnosed with HLH based on fevers, splenomegaly and laboratory parameters: elevated ferritin, hypertriglyceridemia, low fibrinogen, pancytopenia. Hemophagocytosis was present in her bone marrow. Her cerebrospinal fluid had pleocytosis (24 white blood cells). She was found to have absent perinor expression in cytotoxic cells. Genetic testing confirmed heterozygosity for two different mutations in the PRF1 gene, and a heterozygous mutation in the RAB27A gene. On second week of chemotherapy per HLH2004 she turned comatose. Brain CT scan and magnetic resonance imaging showed large hemorrhagic mass-like lesions in bilateral frontal lobes extending to parietal cortex. She had persistent pleocytosis and developed further intracranial lesions despite administration of intrathecal chemotherapy. Neurologically was only able to maintain brainstem functions. Patient had multiple infectious complications including E. coli, Ehrlichia and Candida bacteremia, Candida pneumonia, angioinvasive fungal sinusitis, multiple fungi dermatitis (Candida, Aspergillus, Rhizopus, Coccidiobolus), and cytomegalovirus viremia and meningoencephalitis, that made her therapy difficult. She ultimately died but mother refused brain biopsy. CONCLUSION: HLH is a rare immune disease characterized by an abnormal and dysregulated inflammatory response. HLH triggers an exaggerated cytokine release that leads to tissue infiltration and destruction. The most common presenting symptoms include fever, hepatosplenomegaly, and cytopenia, but up to 63% of patients also have central nervous system (CNS) involvement. Establishing the diagnosis of CNS HLH in children is challenging and prognosis is poor. Numerous neuroradiological findings from individuals with HLH have been reported. Its appearance differs greatly between subjects, but overall mass-like lesions are rare. We present these imaging findings to further discuss distinct radiographic presentations of CNS HLH disease.

Poster Location #12

LONG TERM SURVIVAL AFTER EARLY ONSET LYSOSOMAL ACID LIPASE DEFICIENCY PRESENTING AS HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND BENEFIT OF ENZYMATIC REPLACEMENT TREATMENT WITH SEBELIPASE ALFA IN 2 PATIENTS

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PURPOSE: Lysosomal acid lipase deficiency (LAL-D) is a rare autosomal recessive lysosomal storage disease caused by mutations in the LIPA gene. Patients presenting in infancy have the most rapidly progressive disease, so called Wolman disease (WD), developing signs and symptoms in the first weeks of life and rarely surviving beyond 6 months of age without treatment. Few cases of LAL-D associated with Hemophagocytic Lymphohistiocytosis (HLH) have been reported. The purpose of the study is to present two cases of rapidly progressive LAL-D with some features overlapping with HLH. METHODS: Review of the initial clinical presentation of WD in 2 infants, and long term treatment response. RESULTS: Both patients, unrelated full term male newborns with normal birth weight and a history of consanguinity, started vomiting and presenting abdominal distension in the first days of life. They continued with vomiting, diarrhea, failure to thrive, malabsorption, and developed marked splenomegaly. Although the patients had no fever, some clinical and laboratory values were suggestive of HLH (splenomegaly, anemia, trombocytopenia, hypocalcemia and elevated triglycerides, ferritin and transaminases). Patient 1 underwent hematopoietic stem cell transplantation at 3 months of age, and started Enzymatic Replacement Therapy (ERT) with Sebelipase when it was available, at 7 years of age. Patient 2 initiated ERT at 2 months of age, with a rapid normalization of the laboratory parameters and megaliessies. The patients are now 12 and 2.5 years old and present normal neurocognitive and ponderal development. CONCLUSION: As LAL-D associated with Hemophagocytic Lymphohistiocytosis (HIST) disease.

Poster Location #10

MUTATIONS AFFECTING TIM-3 CHARACTERIZE SPTCL ASSOCIATED TO HLH

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Sub-cutaneous panniculitis-like T-cell lymphomas (SPTCL), a non-Hodgkin lymphoma, can be associated with hemophagocytic lymphohistiocytosis (HLH), a life-threatening activation of the immune system. Recently we identified mutations in the coding gene of T-cell immunoglobulin mucin 3 (TIM-3), a critical immune checkpoint, as the underlying genetic cause of several cases of SPTCL associated to HLH (HLH/SPTCL). We identified two, loss-of-function, missense variants in highly conserved residues of TIM-3 expression. The lack of TIM-3 expression led to persistent immune activation, characterized by increased production of inflammatory cytokines by innate immune cells. Our findings highlight HLH/SPTCL as a new genetic entity where loss of the TIM-3 immune checkpoint is associated with T-cell infiltration of adipose tissue and inflammation. Current experiments aim to determine the pathophysiological bases of this severe condition.

Poster Location #11

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Farranaz Alvarez Nunez, Shelley Crary, Kimo Stine

Department of Pediatrics, Hematology/Oncology Section, University of Arkansas for Medical Sciences, Little Rock, AR USA

PURPOSE: To identify atypical intracranial presentations of Hemophagocytic Lymphohistiocytosis (HLH) in children. METHODS: Medical record review. RESULTS: A 2 year old female presented with seizures and septic shock. Her initial computed tomography (CT) scan was normal. Within 24 hours she was diagnosed with HLH based on fevers, splenomegaly and laboratory parameters: elevated ferritin, hypertriglyceridemia, low fibrinogen, pancytopenia. Hemophagocytosis was present in her bone marrow. Her cerebrospinal fluid had pleocytosis (24 white blood cells). She was found to have absent perinor expression in cytotoxic cells. Genetic testing confirmed heterozygosity for two different mutations in the PRF1 gene, and a heterozygous mutation in the RAB27A gene. On second week of chemotherapy per HLH2004 she turned comatose. Brain CT scan and magnetic resonance imaging showed large hemorrhagic mass-like lesions in bilateral frontal lobes extending to parietal cortex. She had persistent pleocytosis and developed further intracranial lesions despite administration of intrathecal chemotherapy. Neurologically was only able to maintain brainstem functions. Patient had multiple infectious complications including E. coli, Ehrlichia and Candida bacteremia, Candida pneumonia, angioinvasive fungal sinusitis, multiple fungi dermatitis (Candida, Aspergillus, Rhizopus, Coccidiobolus), and cytomegalovirus viremia and meningoencephalitis, that made her therapy difficult. She ultimately died but mother refused brain biopsy. CONCLUSION: HLH is a rare immune disease characterized by an abnormal and dysregulated inflammatory response. HLH triggers an exaggerated cytokine release that leads to tissue infiltration and destruction. The most common presenting symptoms include fever, hepatosplenomegaly,
Poster Location #13

CLINICAL OUTCOMES OF ADULTS WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS TREATED WITH THE HLH-04 PROTOCOL: A RETROSPECTIVE ANALYSIS

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PURPOSE: Hemophagocytic lymphohistiocytosis (HLH) is a rare syndrome with high mortality rates. Although it mostly occurs in children, its recognition in adults is increasing. The treatment of choice in children, the HLH-04 protocol (consisting of etoposide, cyclosporine, and dexamethasone), has limited efficacy and outcomes data published in adults. We aimed to evaluate the complete response (CR), partial response (PR), and overall survival (OS) of adults receiving HLH-04 therapy. METHODS: We retrospectively analyzed adult patients receiving the HLH-04 protocol at Mayo Clinic from 1/1/2004 to 5/1/2018. CR was considered a normalization of all quantifiable markers of HLH. PR was considered ≥25% improvement in ≥2 laboratory markers. Descriptive statistics were used for response rates, Kaplan-Meier curves to estimate OS, and a univariate Cox analysis to assess the impact of various factors on survival. RESULTS: Thirty-one patients were included in the final analysis; their median age was 46 years, and 61% were male. The etiology of HLH was malignancy (n=9), autoimmune disorder (n=8), infection (n=8), and idiopathic (n=6). Eleven patients (35%) had no response, 6 (19%) had CR, and 14 (45%) had PR. Twenty died during follow-up (64.5%). The median OS of all patients was 3.2 months with a 1 year OS of 35%. Etoposide dose was adjusted in 23 (74.2%) patients and cyclosporine was omitted in 6 (19.4%) due to organ dysfunction. Univariate analysis showed longer survival for patients who received >5 etoposide doses (HR 0.22, p=0.003), and shorter survival for hemoglobin on admission <9 g/dL (HR 4.29, p=0.003), platelets <100 (HR 4.06, p=0.027), ANC<1000 (HR 5.24, p=0.001), total bilirubin >1.2 (HR 3.30, p =0.022), and infection-associated HLH (HR 4.24, p=0.04). CONCLUSIONS: The OS of adult HLH patients treated with the HLH-04 protocol remains dismal, especially for infection-associated HLH. The best treatment strategy for managing adult patients with HLH requires further investigation.

Poster Location #14

FLOW CYTOMETRIC PERFORIN AND CD107A SCREENING FOR THE DIAGNOSIS OF FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: REPORT FROM THE ITALIAN REGISTRY

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PURPOSE: To evaluate specificity, sensitivity and diagnostic accuracy of flow cytometric assays as a screening tool for diagnosis of familial hemophagocytic lymphohistiocytosis (FHL). METHODS: Intracytoplasmic expression of perforin and surface CD107a level on peripheral blood mononuclear cells (PBMCs) cytotoxic lymphocytes were detected by flow cytometry. Each test was performed simultaneously with a healthy control. RESULTS: Since 2012, functional test was performed in 503 patients referred to the Italian Registry for HLH. Median age 11.12 (range 0-81) years; 266 males, 237 females. A total of 354/378 and 323/381 patients analysed were evaluable for perforin and CD107a expression, respectively. Perforin expression was absent in 18 patients: 14 FHL2, 2 monoallelic, 2 wild type; partially reduced in 92: 5 FHL2, 32 monoallelic, 55 wild type and normal in 244: 1 FHL2 (A91V omozygous), 17 monoallelic, 56 wild type, 170 genetic analysis not performed. CD107a expression was absent in 28 patients: 10 FHL, 6 monoallelic, 12 wild type; partially reduced in 83: 4 FHL, 18 monoallelic, 61 wild type and normal in 212: 0 FHL, 14 monoallelic, 36 wild type, 162 genetic analysis not performed. Sensitivity and specificity versus genetic diagnosis were respectively 95% and 73% for the perforin assay; 100% and 69% for the degranulation test. CONCLUSION: These findings confirm high diagnostic accuracy of cytofumimetric tools for the functional screening of FHL in a large cohort of patients referred to the Italian Registry.
HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN EGYPTIAN CHILDREN: SINGLE CENTER EXPERIENCE

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PURPOSE: Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening condition, arising from a variety of underlying diseases. We aim to report our experience in HLH in an Egyptian university hospital. METHODS: Prospective observational study of HLH patients (according to the Histocyte Society HLH-2004 diagnostic criteria) at Alexandria University Children's Hospital from January 2016 to June 2019. RESULTS: Eighty-six patients were enrolled (41 males and 45 females). The median age at presentation was 11.7 months (range: 0 - 181 months). More than two thirds of patients had consanguineous parents, and one third of them had a history of an affected family member (HLH or death due to undiagnosed illness). The median time interval between the first HLH symptom and start of HLH-directed therapy was 36 days (range: 1 - 630 days). At diagnosis, 60 (69.7%) patients were deemed to have a genetic form of HLH (familial HLH, gray hair syndromes or other immunodeficiency syndromes). The remaining 26 patients were deemed to be secondary due to infections or rheumatological diseases. Genetic testing was done through international research cooperation. Several new mutations have been identified in the patients with genetic forms and 5 patients considered secondary at initial assessment proved to have an underlying genetic defect related to HLH, many others are still waiting for genetic confirmation. The mortality rate was 66.1%, most commonly due to uncontrolled disease activity. Six (6.9%) patients have undergone hematopoietic stem cell transplantation (HSCT), while 16 (18.6%) patients are maintained on chemotherapy (bridging to HSCT/no available donor). CONCLUSION: This is the first description of a large cohort of Egyptian HLH patients. The mortality rate was considerably high, hence the importance of early diagnosis and treatment. The distinction between primary and secondary forms of HLH was delayed due to lack of confirmatory genetic testing, highlighting the importance of collaborative studies.

EFFECTIVENESS OF ETOPOSIDE THERAPY IN ADULT HLH - ANALYSIS FROM THE PALG HLH IN ADULTS DATABASE

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PURPOSE: Hemophagocytic lymphohistiocytosis (HLH; hemophagocytic syndrome) is a hyperinflammation syndrome with high mortality. Etoposide is a cornerstone of the effective therapy, but in some adult patients with milder HLH, this syndrome may be controlled with other immunosuppressive agents (e.g. steroids). On the other hand in some severely ill patients etoposide is not used in fear of worsening their state. Also HLH trigger affects the choice of therapy. Highly elevated ferritin, although not pathognomonic, is the most characteristic feature of HLH. Aim of the study was assessment of etoposide therapy effectiveness in adult patients with HLH triggered by various factors. METHODS: Data of 100 adult (>18 years of age) patients with HLH from the HLH in Adults Database affiliated with PALG (Polish Adult Leukemia Group) were analyzed. Survival analysis was made by the log-rank and Cox regression tests. RESULTS: Median age of the analyzed group was 38 (18-82); 62% was male. 70 patients received at least one dose of etoposide. Its
use did not affect survival when analyzed in the whole group of patients. Also analyses of different triggering factors (alone or in combinations) did not show its advantage. Significant effect was shown in patients with the highest ferritin concentrations (>30,000 ng/ml): use of etoposide in this group provided longer survival (p=0.01 – log-rank) with a HR for death of 0.11 (95%CI: 0.03 - 0.46). CONCLUSION: Effectiveness of etoposide use is associated with HLH activity - in this study shown by ferritin concentration. Severity scoring system for HLH (based on more factors) could further optimize and standardize this approach.

Poster Location #18
TWO NOVEL MUTATIONS IDENTIFIED IN A CHINESE CHILD WITH CHEDIAK-HIGASHI SYNDROME REPRESENTING WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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PURPOSE: To investigate the diagnosis and treatment of chediak-higashi syndrome (CHS) in accelerated phrase. METHODS: The clinical data of a child with CHS were collected and analyzed, and the CHS pathogenic gene mutations were detected by target gene enrichment sequencing and Sanger validation. RESULTS: A Chinese boy aged 5 years who presented to us with fever for five days. The proband had pale skin, silvery hair and hepatosplenomegaly. His laboratory evaluation was remarkable for pancytopenia, high serum ferritin and hyperfibrinogenemia. Bone marrow aspirate revealed large inclusions in granulocytes and hemophagocytosis consistent with hemophagocytic lymphohistiocytosis (HLH). Two novel mutations were revealed by sequencing in the LYST gene of c.719C>T (p.R2387X) and c.4965delA (p.Q1655fs), which were not reported in the literature. Accelerated phrase of CHS was confirmed. He was treated by HLH 2004 protocol and got good control of HLH after 8 weeks’ treatment. We performed sibling HLA-matched hematopoietic stem cell transplantation (HSCT) in the remission of HLH. Bone marrow assessment post-HSCT revealed normal hematopoiesis. He had full donor chimerism with complete hematopoietic and immunological reconstitution at 37 months of follow-up. CONCLUSION: High-throughput sequencing is an effective way to detect genetic deficiency of HLH. HSCT might be an effective treatment for CHS in accelerated phrase. Awareness, early recognition and management of this condition may prevent the mortality associated with this case.

Poster Location #19
RUXOLITINIB TREATMENT FOR STEROID-REFRACTORY ACUTE GVHD IN PATIENTS WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSOS UNDERGOING ALLO-HSCT

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PURPOSE: Ruxolitinib is a promising option for treating steroid-refractory acute GVHD (SR-aGVHD) after allogeneic hematopoietic stem cell transplantation(allo-HSCT). We describe ruxolitinib treatment for SR-aGVHD in allo-HSCT patients with Hemophagocytic Lymphohistiocytosis(HLH) to evaluate its effectiveness. METHODS: We evaluated the outcomes of 12 patients who received ruxolitinib for SR-aGVHD, and 5 patients without ruxolitinib between January 2017 and March 2019. RESULTS: Of 12 patients received ruxolitinib, 7 patients achieved a CR, 3 had a PR, and 2 were TF. OS rate was 83.3%, and CR rate was 58.3%. aGVHD with skin involvement of 6 patients received CR. Of 5 patients without ruxolitinib, 1 patient achieved a CR, 2 had a PR, and 2 were TF. OS rate was 60.0%, and rate of CR was 20.0%. A high rate of OS and CR of ruxolitinib were observed in HSCT patients with HLH. However, there was no significant difference in the OS rate and CR rate between the two groups (P=0.538, P=0.294). The mean time of steroid application in the patients received ruxolitinib was 28.1 days, which was 59.6 days in the patients without ruxolitinib(P=0.003). Median survival after HSCT was 64.6 weeks versus 18.8 weeks (P=0.021). CONCLUSION: Ruxolitinib is an optimal choice to treat SR-aGVHD in patients with Epstein-Barr virus HLH (EBV-HLH).

Poster Location #20
HEMOPHAGOCYTIC LIMPHOHISTIOCYTOSCS: CLINICAL AND LABORATORY CHARACTERISTICS AND OUTCOMES OF PATIENTS IN A SINGLE INSTITUTION

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INTRODUCTION: The hemophagocytic lymphohistiocitoscys (HLH), primary or secondary, comprises a systemic hyperactivation of macrophages that requires prompt recognition of symptoms and severity, early treatment and change of the patient’s prognosis. PURPOSE: To describe the clinical and laboratory characteristics, the therapeutic modality and the outcome of patients with HLH treated in a pediatric oncology hospital. METHOD: A retrospective, descriptive, quantitative study was carried out by searching the medical records of 13 patients diagnosed with HLH between January 2000 and December 2017 in a single institution. RESULTS: HLH mainly affected females (69%), with a mean age of 6.7 years (0.1 - 15 yr), 4 patients had primary/genetic HLH (PFR1 mutation, STXBP2 mutation, Chediak-Higashi and ataxia- telangiectasia syndrome), 4 had secondary disease (brain tumor, liver transplant, scarlet fever and leishmaniasis) and 5 patients were not tested for genetic mutations. Fever was the most frequent clinical sign and hyperferritinemia was the most prevalent laboratory abnormality at diagnosis. The protocols used were HLH - 94 in 2 patients (15.3%) and HLH - 04 in 10 patients (76.9%)/one patient did not follow protocols. The mean treatment time for all patients was 10.4 months; 3 (23.1%) patients underwent hematopoietic cell transplantation. The probability of resolution was 61.5%, of which 25% remained in remission until December 2017. The percentage of deaths was 46.1%. Overall survival for the whole group was 40.3% (95% CI: 16.4% - 69.3%). There was no statistically significant increase in the risk of death for patients with cytopenia, hypertriglyceridemia, hypofibrinogenemia central nervous system involvement, hemoglobin <9 ng / dl, neutrophils <1000 / ml and platelets <100000 / ml. Regarding the sequels presented, 2 patients evolved with epilepsy, 1 patient with Fanconi syndrome secondary to chemotherapy and 1 patient with systemic arterial hypertension. CONCLUSION: HLH has well-defined diagnostic criteria, but the clinical presentation is not always so.
**Poster Location #21**

**ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN TREATMENT OF LYMPHOMA ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS**

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PURPOSE: Hemophagocytic lymphohistiocytosis (HLH) is a rare and severe clinical syndrome characterized by a dysregulated hyperinflammatory immune response. Lymphoma associated HLH (LAHS) is one of the secondary HLH. It is generally considered to have the worst prognosis and allogeneic hematopoietic stem cell transplantation (allo-HSCT) is sometimes needed for long-survival time. Autologous HSCT plays an important role in treatment of lymphoma. Will auto-HSCT still be useful in LAHS? This study was aimed to analyze the effect of auto-HSCT in LAHS.

METHODS: A retrospective study of 138 patients with LAHS during February 2012 and December 2018 was conducted. Clinical features, type of lymphoma and treatment method were observed. Followed-up until June 1, 2019, survival statistics was analyzed.

RESULTS: Among these 138 patients, total of 22 patients went through HSCT (auto-HSCT for 8 and allo-HSCT for 14 cases). The total mortality rate is 60.8% (84/138). There is significant difference between patients who received HSCT and who did not (36.3% vs. 65.5%, P=0.010). For those 8 patients who received auto-HSCT, only 1 patient died of lymphoma relapse. The survival of auto-HSCT patients was significantly better than patients didn’t receive HSCT (P=0.004). Also, the survival between auto-HSCT patients (56.627[40.428, 72.825]) and allo-HSCT patients (44.087[23.189, 64.984]) showed no differences (P=0.093). CONCLUSION: Lymphoma associated HLH suffers a very poor prognosis, and HSCT is essential to improve the outcomes, especially for those who did not response well to traditional chemotherapy. As a form of HSCT, auto-HSCT can also significantly improve the prognosis of patients with LAHS, and may even achieve effects similar to allo-HSCT. Considering that auto-HSCT is safer, it may become a possible better choice in LAHS’s treatment.

**Poster Location #22**

**DURABLE LONG-TERM SURVIVAL AND CHIMERISM AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION USING BUSULFAN AND FLUDARABINE BASED REDUCED INTENSITY CONDITIONING REGIMEN FOR PEDIATRIC PATIENTS WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS**

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PURPOSE: Hematopoietic Stem Cell Transplantation (HSCT) is the only curative treatment for patients with familial, relapsing, or persistent hemophagocytic lymphohistiocytosis (HLH). Here, we present a single center experience of using busulfan (Bu) and fludarabine (Flu) based reduced intensity conditioning regimen (RIC) for treatment of HLH. METHODS: Medical records of pediatric patients with HLH, who received HSCT using Bu/Flu based RIC regimen from January 2008 to December 2017, were reviewed retrospectively. HSCT outcomes including engraftment, survival, and GVHD were analyzed. RESULTS: Nine patients were received HSCT using BuFlu based RIC regimen. Three patients received HSCT after diagnosis of familial HLH and the other 6 received after reactivation. All 3 patients with familial HLH had UNC113D mutations. Median 8.35x10^6/kg (range, 2.84-10.05x10^6) CD34 positive cells were infused. All patients achieved WBC and PLT engraftment at median 11 days (range, 10-21) and 19 days (range, 13-32) from HSCT with full donor chimerism which sustained until last visit. Cyclosporine and mycophenolate mofetil were applied as GVHD prophylaxis except one patient who received HSCT from syngeneic sibling. Three patients (33%) experienced acute graft-versus-host disease (GVHD) of grade 2 which was well controlled after conventional steroid treatment. Two patients (22%) underwent chronic GVHD, and one of them died. One patient (11%) had reactivation 4 months after HSCT from syngeneic sibling donor, and died. The 5-year overall survival was 78%. Two patients died; one died of disease and the other died of treatment related mortality (TRM). No TRM other than chronic GVHD was existed. CONCLUSION: Our experience suggests that Bu/Flu based RIC regimen can be effective option for pediatric patients with HLH who need HSCT showing durable chimerism and long-term survival with decreased toxicity.

**Poster Location #23**

**EBV RELATED LYMPHOPROLIFERATIVE DISEASE MISDIAGNOSED AS INFLAMMATORY BOWEL DISEASE**

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PURPOSE: Inflammatory bowel disease (IBD) and Epstein-Barr virus (EBV) related lymphoproliferative disease (LPD) have similar symptoms, signs and manifestations under gastroenteroscopy. EBV-DNA or EBER of intestinal mucosa are not routine detection, so it is easy to be misdiagnosed and delay treatment. METHODS: This study reported 6 patients of EBV-LPD or EBV associated hemophagocytic lymphohistiocytosis (EBV-HLH), all of which had been misdiagnosed as IBD. RESULTS: In this study, there were 6 patients, including 4 males and 2 females, with a median age of 33 years (range 25-53 years). The initial diagnosis of 6 patients was: 3 cases of ulcerative colitis; 2 cases of Behcet's disease; 1 case of Crohn's disease. All 6 patients had intermittent fever. Splenomegaly occurred in 2 patients, and the spleen size was normal in 4 patients. Three patients had intermittent abdominal pain and two patients had diarrhea. Two patients had rashes. Gastroenteroscopy shows multiple ulcers in the digestive tract. The median time interval between the diagnosis of IBD and the revised diagnosis of EBV-LPD was 48 months (range 6-96 months). All the 6 patients had positive EBER in intestinal pathology, 5 patients had positive EBV-DNA, and 1 patient had negative EBV-DNA. One of the 6 patients developed EBV-HLH. CONCLUSION: Patients with suspected IBD should be tested by EBER and EBV-DNA as early as possible to differential diagnosis EBV-LPD, because the treatment and prognosis of the two are completely different.
THE RISK FACTORS IN THE EVALUATION OF PROGNOSIS IN ADULT PATIENTS WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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PURPOSE: Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening disease with high heterogeneity in adults. To observe the risk factors influencing the prognosis of adult patients with HLH is helpful to establish a scoring system for prognostic of HLH. METHODS: We reviewed 228 cases of HLH which were diagnosed in 2017. All the patients were above 18 years old. Patients who received stem cell transplantation were excluded in this cohort. We collected 39 parameters which were obtained before treatment to analyze the relationship between clinical features and prognosis. RESULTS: Only 35% of the HLH patients who did not receive SCT survived. The underlying disease was the most important factor for prognosis. Patients with Epstein-Barr virus infection and lymphoma had more poor survival than others. The counts of leukocytes (P=0.003) and platelets (P=0.002) had significant differences between survival group and death group. Hyperbilirubinemia rather than elevated transaminases indicated worse of disease (P=0.004). Patients who had hypoproteinemia, especially hypoalbuminemia had poor prognosis (P<0.001). Patients with severe electrolyte disturbance or acidosis (P=0.002) prior to diagnosis were more difficult to treat. Refractory hyponatremia and hypocalcemia showed significant associations with mortality (P<0.001). High concentration of soluble CD 25 was associated with poor prognosis (P<0.001). High concentration of soluble CD 25 was associated with poor prognosis (P<0.001). Flips of CD107a expression was decreased more greatly in the patient with poor prognosis (P=0.012). The survival of patients who received initial etopside treatment within 4 weeks after diagnosis was significantly better than others without etopside (P<0.001). And the response to the induction therapy was closely associated with survival. Patients who achieved complete remission had more chance to live.

Conclusions: The above markers might play important roles in the risk stratification and prediction of HLH. It is necessary to establish a scoring system to validate its practical value.
PURPOSE: To investigate the efficacy and security of janus kinase inhibitor ruxolitinib in the treatment of recurrent and refractory hemophagocytic lymphohistiocytosis in children. METHODS: The clinical manifestations, laboratory examination and prognosis of 6 children with recurrent and refractory HLH in Beijing Children's Hospital, Capital Medical University, from October 2018 to March 2019 were analyzed retrospectively. RESULTS: In this group, 6 children were diagnosed with HLH, 4 with EBV-related HLH, 1 with unclear etiology and 1 with autoinflammatory disease related HLH. Before the addition of ruxolitinib, all patients received HLH-94 chemotherapy. After orally administered with ruxolitinib, all the patients' clinical performance was improved. Temperature was down to the normal and peripheral blood cells were elevated, within 48 hours. One case received clinical remission, while the other 5 cases didn't achieve partial remission. Doxorubicin, etoposide and prednisolone (DEP) were added for the five patients and pegaspargase was added for two patient at the same time. Two of the five patients received clinical remission, three were subsequently treated with hematopoietic stem cell transplantation, and all the six patients survived. CONCLUSION: For children with recurrent and refractory HLH, using ruxolitinib alone has poor therapeutic effect, and thus patients cannot achieve complete remission, which indicates the combination with other chemotherapy drugs. But ruxolitinib could keep the disease under control, buying time for further treatment and bone marrow transplantation.

PURPOSE: Unlike children, adult HLH patients are mostly secondary, early detection the cause may improve prognosis. Bone marrow (BM) flow cytometry has been widely used in patients with hematological diseases, but its value in adult HLH remains unclear. This study intends to analyze BM flow cytometry results and clinical data of adult HLH, and detect its value in etiology determination. METHODS: Retrospective analysis 78 adult HLH patients who had not been treated and had done BM examination at Beijing Friendship Hospital of Capital Medical University from June 2016 to May 2017. The clinical data and BM testing results were collected. RESULTS: Of 78 patients, 41 male and 37 female. Abnormal phenotypic cell populations were found in 24 patients, 5 cases of which were abnormal B cells (abnormal phenotype cells accounted for 1.02-23.01% of all lymphocytes), and 10 cases were abnormal NK cells (0.51-46.22%), 9 cases were abnormal T cells (0.29-39.46%). Among 5 patients with abnormal B cells, 2 diagnosed B-cell lymphoma by bone marrow pathology; 1 case unknown cause at initial, HLH recur 1 year later, lymph node biopsy confirmed DLBCL; 1 case diagnosed as DLBCL after spleen resection, 1 case still unclear. 10 patients with abnormal NK cells were all EBV-DNA positive, 1 was diagnosed as NK/T lymphoma, and 3 were diagnosed as EBV-LPD. Among 9 patients with abnormal T cells, 1 was primary HLH, 1 was pregnancy-related HLH, 2 unknown cause, 5 were EBV-HLH or EBV-LPD. CONCLUSION: Abnormal phenotype cell population is not rare in BM of adult HLH patients, especially EBV-HLH. When there is abnormal B cell in BM, it should be highly alert to B cell lymphoma. If abnormal T or NK cells are present, it is recommended to routinely detect EBV, but the diagnosis of lymphoma should be cautious, some may be reactive lymphocytosis.

PURPOSE: To investigate the clinical characteristics and treatment strategies of EBV-associated hemophagocytic lymphohistiocytosis (EBV-HLH) in children. METHODS: We retrospectively collected the clinical, laboratory data and treatment of EBV-HLH children admitted to the Hematological Tumor Center of Beijing Children's Hospital, Capital Medical University from September 2015 to December 2017. RESULTS: A total of 157 cases of EBV-HLH were admitted, accounting for 59.02% of 266 cases of HLH in the same period. 9 of them were finally diagnosed as primary HLH. Among 157 cases, 68 were males and 89 were females. The median age of onset was 42 months (3 months to 189 months). The clinical features of EBV-HLH are similar to those of other HLH. Compared with 9 cases of primary HLH, the absolute value of neutrophils, alanine aminotransferase and fibrinogen in EBV-HLH children with no genetic abnormalities were significantly different (P=0.027, 0.049, 0.033). The median follow-up time was 237 days (21-835 days). The overall survival rates of 1, 3, 6 and 12 months were 95.2%, 89.4%, 85.4% and 83.5% respectively. CONCLUSION: EBV-HLH is the most common type of HLH. It has various clinical manifestations, poor prognosis and high mortality. The clinical features and laboratory examinations are of little significance in distinguishing potential genetic abnormalities in EBV-HLH at diagnosis. Even if there is no hemophagoy phenomenon in bone marrow puncture, we should be highly alert to the possibility of HLH if there is persistent high fever, progressive reduction of blood cells with liver function damage. The reactivation of EBV infection is more likely to cause HLH, and the survival rate is lower than that of primary EBV infection. Early diagnosis, early treatment and active use of various means to control cytokine storm are of great benefit for better prognosis. Recurrent and refractory HLH should be treated with hematopoietic stem cell transplantation.
POSTER PRESENTATIONS - CLINICAL HLH

Poster Location #30

OUTCOME OF CHILDREN WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH) TREATED AT KING HUSSEIN CANCER CENTER

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PURPOSE: Hemophagocytic Lymphohistiocytosis (HLH) is a group of immune deficiency, characterized by severely dysregulated immune response. We aim to study the outcome of patients with HLH treated at a single center. METHOD: This is a retrospective analysis of children with HLH treated at our institution between 2003-2019. RESULTS: Study includes 30 patients with HLH, median age at diagnosis 14.4 months (range: 6-248), all patients presented with high-grade fever, other common clinical laboratory findings: Splenomegaly (97%), cytopenia (97%), hypofibrinogenemia (80%), hypertriglyceridemia (53%), hemophagocytosis (87%), serum ferritin >500 (90%). Secondary HLH was diagnosed in 9 patients due: Infections (3), rheumatological disorders (3), acute myeloid leukemia (1), langerhans cell histiocytosis (1), and metabolic disease (1). All patients received therapy targeted to triggering disease in addition to immunosuppression, 7 of 9 patients (88%) are alive at last follow up. Primary HLH was diagnosed in 21 patients: 3 patients had Chediak-Higashi, and 4 patients had Griscelli syndrome, 14 patients were presumed to have familial HLH due to family history, recurrence of disease over time, or diagnosis at young age, one of them diagnosis of familial HLH was confirmed by positive genetic testing of PRF1 mutation. All patients with primary HLH received induction therapy per HLH 2004/1994 protocol: 8 of 21 patients (38%) died of refractory disease, 13 of 21 patients (62%) achieved remission and underwent allogeneic hematopoietic stem cell transplantation (HCT). At median follow up of 91 months (range: 6-153), 5-year overall survival and 5-year event-free survival rates for 14 patients with HLH underwent HCT (n=13 primary, n=1 secondary) were 84%, 77% respectively. CONCLUSION: Primary HLH is fatal disease; making definitive diagnosis is essential as allogeneic (HCT) is the only curative treatment for primary HLH. Genetic study is helpful to guide definitive therapy, early referral to transplant and family counseling.

Poster Location #31

CLINICAL ANALYSIS OF 8 CASES OF HEMOPHAGOCYTIC SYNDROME SECONDARY TO SUBCUTANEOUS PANNICULITIS-LIKE T-CELL LYMPHOMA

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PURPOSE: To investigate the clinical characteristics and treatment of hemophagocytic syndrome secondary to subcutaneous panniculitis-like T-cell lymphoma. METHODS: Six patients with hemophagocytic syndrome secondary to subcutaneous panniculitis-like T-cell lymphoma were compared and their clinical manifestations, laboratory examinations, time spent in disease diagnosis, treatment options and prognosis were comprehensively analyzed. RESULTS: All 8 patients were diagnosed with hemophagocytic syndrome, including fever, splenomegaly, elevated ferritin, hemophagocytosis and abnormal liver function. It lasted 3 to 18 months from the diagnosis of hemophagocytic syndrome to the final diagnosis of lymphoma. Two patients gave up treatment and died. The rest received CHOP-based chemotherapy, one patient received sequential autologous hematopoietic stem cell transplantation, and three patients received allogeneic hematopoietic stem cell transplantation. Except one patient died of GVHD, the other patients were stable during the follow-up period. CONCLUSION: Hemophagocytic syndrome secondary to subcutaneous panniculitis-like T-cell lymphoma is rare in clinic. It is necessary to actively control the symptoms associated with hemophagocytic syndrome in order to make clear the diagnosis of the primary disease. The disease progresses rapidly in these patients. High-dose chemotherapy combined with autologous hematopoietic stem cell transplantation or allogeneic hematopoietic stem cell transplantation can be considered.

Poster Location #32

HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR CENTRAL NERVOUS SYSTEM INVOLVEMENT WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN CHILDREN

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BACKGROUND: Hemophagocytic lymphohistiocytosis with central nervous system involvement (CNS-HLH) occurs in severe HLH cases and develops progressively. The treatment regimen for CNS-HLH is challenging and important. PURPOSE: We summarized that 10 cases of CNS-HLH undergoing allogeneic hematopoietic stem cell transplantation (Allo-HSCT) in children. METHODS: 10 cases of CNS-HLH diagnosed by neurological symptoms, cerebrospinal fluid (CSF) evaluations and brain magnetic resonance imaging (MRI) findings from June 2016 to Dec 2018 in our center were analyzed. The median age of patients was 2.1 (1.0-7.8) years old. 6 patients were primary HLH, 2 patients were XLP and 2 patients were EBV-HLH. Chemotherapy before transplantation included HLH-1994 or 2004, E-CHOP, L-DEP etc. All cases received intrathecal injection including DLM and MTX. 7 patients were CR and 3 patients were PR before transplantation. We used the conditioning with etoposide, busulfan and fludarabine plus antithymocyte globulin (ATG) added cytosine arabinoside or not. 5 patients were with haploidentical donors, and 5 patients were with unrelated donors. RESULTS: All patients obtained hematopoietic reconstitution. A median follow-up of 28 (6-42) months showed that 6 patients are alive and well with negative clinical neurological examination. The incidence of acute GVHD was 20% and that of chronic GVHD was 43%. The incidence of Epstein-Barr virusemia was 10% and 60% in cytomegalovirus. The main causes of death were 2 cases of severe infection, 1 case of CNS-HLH relapse and 1 case of transplantation associated thrombotic microangiopathy. CONCLUSION: Under appropriate protocol, the good outcome could be acquired in CNS-HLH using allo-HSCT. For severe CNS-HLH in children, HSCT is inevitable and only one curative measure. Key Words: hemophagocytic lymphohistiocytosis; central nervous system involvement; Hematopoietic Stem Cell Transplantation.
THE GENETIC CHARACTERIZATION, CLINICAL EVALUATION OF PRIMARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND THE IMPORTANCE OF BILIRUBIN ABNORMALITY: A SINGLE CENTER EXPERIENCE

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PURPOSE: To clarify genetic and clinical characteristics of childhood primary hemophagocytic lymphohistiocytosis (pHLH) in China and analyze of prognostic factors. METHODS: A retrospective analysis was performed on 38 patients diagnosed with pHLH at Beijing Children's Hospital in China. RESULTS: Of these patients, 23 male and 14 female cases had a median age of 2.5 (0.1-13.7) years. All patients received the HLH-94/04 regimen, 26 patients (68.4%) had relieved (complete response: 52.6% and partial remission: 15.8%). At follow-up of 36 months, 30 patients were alive and 8 patients died. Median survival time was 23 months. Three-year probable overall survival (OS) was 74.7%. Genetic analysis showed that mutations in PRF1 (34.2%) and UNC13D (31.6%) were the most common mutations. Several genes (PRF1, UNC13D, STXBP2 and LYST) have been associated with the granule-mediated cytotoxicity. Remarkably, patients in cytotoxic pathway group (n=29) had higher sCD25 level than non-cytotoxic pathway group (n=9) (non-parametric test p=0.008). But the level of bilirubin and LDH in the non-cytotoxic pathway group were more elevated (p=0.012, 0.013). Three patients (10.3%) in cytotoxic pathway group had recurrence after complete response. Patients in non-cytotoxic pathway group had no recurrence. Furthermore, we also found the incidence of elevated bilirubin (≥30 umol/L) in short survival group (died within 3months) was significantly higher than that in long survival group (survived >3 months) (75.0% vs. 23.5%) (p=0.013). By Kaplan-Meier survival analysis 3-year OS of patients who had elevated bilirubin (>30 umol/L) was significantly lower than those patients without elevated bilirubin (44.6% vs. 82.6%) (p=0.026). Conclusions Our data indicated that PRF1 mutations were the most common mutations in Chinese children with pHLH. Patients in cytotoxic pathway group were prone to recurrence. Furthermore, patients with short survival had high incidence of bilirubin abnormalities. Bilirubin (>30 umol/L) was prognostic factor of the pHLH.

PROGNOSTIC SIGNIFICANCE OF PLASMA EBV DNA LOAD DURING TREATMENT IN CHILDREN WITH EPSTEIN-BARR VIRUS-ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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BACKGROUND: Reliable prognostic factors for patients with Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis (EBV-HLH) in children are not yet well established. Few studies have addressed the significance of plasma EBV DNA (P-EBV-DNA) level in EBV-HLH, especially during the treatment course. We conducted an analysis to identify the prognostic value of P-EBV-DNA during treatment. METHODS: We enrolled 66 Chinese pediatric patients with EBV-HLH in our center. We studied a series of P-EBV-DNA load during the clinical course and other parameters at diagnosis. Related data were retrospectively reviewed and analyzed. RESULTS: P-EBV-DNA at diagnosis could not be associated with a poor outcome. P-EBV-DNA load at the 2nd and 4th week after initiating treatment could be a good marker of disease in univariate analysis (P<0.001). In multivariate analysis, the prognostic value of P-EBV-DNA at 2nd week was lower compared to the 4th week, which was an independent prognostic factor (HR = 5.71; P = 0.036). Besides, central nervous system involvement (CNS, P=0.025) and severe neutropenia (ANC ≤0.5×109/L, P=0.041) at diagnosis are also associated with worse outcomes independently. CONCLUSIONS: Physicians must carefully monitor the changes of P-EBV-DNA level during the clinical course especially at the 4th week after treatment and administer an adaptive therapy promptly.
Deletion of TNFa in BRAFV600E-expressing mice made no detectable impact in organ mass (reflective of lesion burden) or formation of inflammatory lesions in spleen, liver and lungs, evaluated by PET-CT imaging and histopathology. CONCLUSION: Despite elevated TNFa expression in LCH, etanercept was not an effective therapy in a prospective phase II trial of patients with relapsed/refractory LCH. Plasma TNFa was significantly higher in LCH vs JIA patients, suggesting higher doses of TNFa inhibitors could be required for neutralization in LCH. However, genetic depletion of TNFa in a pre-clinical LCH mouse model suggests TNFa may be unlikely to play a driving role in LCH pathogenesis.

Poster Location #38
ISOLATED PULMONARY LANGERHANS CELL HISTIOCYTOSIS AND MULTIPLE SCLEROSIS. CASE REPORT
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Twenty-two-month-old girl that presented with tachypnea and dyspnea had a chest xray and a CT scan that showed multiple bilateral bullae and a pneumothorax. A pulmonary biopsy confirmed the diagnosis of Langerhans cell histiocytosis (LCH) without any other organ involvement. Initial therapy (Arm A of LCH II protocol of Histiocyte Society) was only complicated with multiple episodes of bilateral pneumothorax. She was treated per and had no evidence of active disease during and after continuation treatment. A CT scan done after completion of therapy showed no evidence of pulmonary involvement and patient achieved normal respiratory function tests. Twenty years later, she presented with painful ocular movements in both eyes and decreased visual acuity in the right eye. Dyschromatopsia was also observed with a right afferent pupillary defect. A brain MRI showed focal lesions in right capsule and medulla oblongata, in addition to punctate lesions at the posterior temporal subcortical level and left semi oval center. There was also a subtle signal alteration on the proximal intra-cranial part of the optic nerve that enhanced with contrast. IgG oligoclonal bands were positive in cerebral spinal fluid, but negative in serum. Anti-NMO and anti-MOG antibodies were negative in serum as well. Based on these findings, patient was diagnosed with multiple sclerosis (MS) on March 2018. She was treated with glatiramer acetate (GA) with stable clinical disease and no evidence of progressive disease on last MRI. In conclusion, isolated pulmonary LCH is extremely unusual in children and to our knowledge its association with MS has not been described in the literature. Given that both disorders may be related to immunological abnormalities, a challenge for the future will be to find links between them.
PERSISTENT LYMPHOPENIA IN LCH PATIENTS LIKELY RELATED TO CONSTANTLY HIGH LEVELS OF IL-7 AND IL-21

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PURPOSE: During a systemic inflammatory process, changes in blood cell counts and/or in cytokine concentrations may be observed. In the case of Langerhans cell histiocytosis (LCH), immune cells accumulate in one or more organs causing either mild or more severe disease followed by high cytokine production. The aim of our study was to evaluate systematically whether LCH patients had an altered blood cell phenotype and investigate any correlation with age at diagnosis, disease severity, treatment or cytokine levels. METHODS AND RESULTS: First, we reviewed the medical records of the LCH patients admitted to Astrid Lindgren Children’s Hospital over a 15-year period and found 8 times higher prevalence of lymphopenia in treatment-naive LCH patients at diagnosis (compared to healthy children), which was associated with earlier LCH onset. Notably, LCH patients had low lymphocyte counts even years after the end of therapy. Then, we counted the monocytes and the different lymphocyte subsets in additional LCH patients and pediatric controls. Our analyses revealed low counts of T cell subsets in LCH patients regardless of treatment or organ affected, while decreased counts for monocytes, B and NK cells were mainly observed in patients on treatment or with multi-system LCH. In addition, LCH patients had significantly higher levels of IL-7 and IL-21 than healthy controls or children with inflammatory bowel disease. CONCLUSION: The high prevalence of peripheral lymphopenia at LCH diagnosis, evident also in periods off treatment, indicates that lymphopenia is an important characteristic of LCH, associated with earlier disease onset and more severe disease course. We hypothesize that the high levels of IL-7 and IL-21 may contribute to the accumulation of lymphocytes in LCH lesions, thus resulting in impairment of resolution of LCH granulomas and low peripheral lymphocyte counts. Our findings indicate a likely important mechanism associated to LCH pathology.

BRAF-V600E CAUSES INTRINSIC HYPER-RESPONSIVENESS OF DENDRITIC CELLS TO TLR4 STIMULI

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PURPOSE: Despite advancements in understanding the molecular origins of Langerhans Cell Histiocytosis (LCH), the pathophysiology remains enigmatic. The conceptualization of LCH as neoplastic due to the prevalence of mutations in the Ras-ERK pathway has directed focus on dendritic cell (DC) intrinsic proliferation, survival, and accumulation, with consideration of inflammation as solely secondary to DC accumulation. However, DCs harbor a number of inflammatory receptors which utilize Erk as part of their signaling cascade including the Toll-like receptors (TLRs). We therefore hypothesized that LCH-DCs are intrinsically hyper-responsive to TLR stimuli. METHODS: We generated bone marrow derived DCs (BMDCs) by culture in GM-CSF for 7 days from wild type and CD11c-Cre:BRAF-V600E flox mice. Validation of acquisition of the BRAF-V600E allele was confirmed by allele specific qPCR and western blot for phospho-Erk. BMDCs were stimulated with LPS and cytokine levels were measured via ELISA and qPCR. Baseline and post-stimulated levels of TLR4 were measured by qPCR. Cell surface CD11c, MHC II, and CD80 were quantified by flow cytometric staining. RESULTS: BMDCs with the V600E allele secreted increased TNFa in response to LPS compared to wild type. Intriguingly, this is despite V600E BMDCs having significantly decreased TLR4 transcripts at baseline. Consistent with decreased TLR4, V600E BMDCs also had decreased TNFa transcripts after LPS stimulation compared to wild type. There was no difference in stimulated CD80, MHC II, or CD11c surface levels. CONCLUSION: The BRAF-V600E allele results in increased LPS-induced TNFa section from BMDCs suggesting a cell intrinsic effect of the LCH mutation in inflammation. Intriguingly, this is despite decreased TLR4 and TNFa mRNA levels, suggesting a dysregulation of cytokine secretion itself. Future work will be directed at understanding the relationship of this dysfunction to LCH inflammation in vivo.

THE OPN LEVELS OF CEREBROSPINAL FLUID WERE SIGNIFICANTLY CORRELATED WITH PITUITARY INVOLVEMENT IN CHILDREN WITH LANGERHANS CELL HISTIOCYTOSIS

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Langerhans cell histiocytosis (LCH) is caused by clonal proliferation of CD1a/CD207+ Langerhans cells and is known as a kind of blood tumor. At present, the diagnostic criteria for pituitary involvement of LCH are magnetic resonance imaging (MRI) result or diabetes insipidus (DI). However, some patients without symptoms of diabetes insipidus can’t be clearly diagnosed through MRI. Their MRI results were inconclusive, which usually requires a 3-month observation. Some of them developed DI during observation. High levels of osteopontin (OPN) existed in the cerebrospinal fluids (CSF) of LCH patients. In our study, we detected the OPN levels in CSFs of LCH children through Enzyme-Linked Immunosorbent Assay (ELISA). After retrospective analysis of OPN levels in CSFs of 50 children, we found that the OPN levels in CSF of LCH children with pituitary involvement were significantly higher than that of other groups. After Chi-square test and ROC curve analysis, we found that OPN levels were significantly correlated with pituitary involvement. The cut-off value was 106ng/ml. In the future, through the OPN levels in CSF of LCH patients, we can accurately judge the degree of pituitary gland involvement and implement accurate treatment plan. And then we can control the disease progression and reduce the incidence of diabetes insipidus. Establishment of OPN rapid hierarchical diagnosis technology will bring great benefits to the children with LCH and their families.
CD207+/CD1A+ CIRCULATING CELLS SHOW HIGHER LEVELS OF TYRO3, MERTK, AND PROS1 IN PATIENTS WITH ACTIVE LANGERHANS CELL HISTIOCYTOSIS

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TYRO3, AXL and MERTK (TAM) tyrosine kinase receptors and its agonist Protein S (PROS1) have been identified as negative regulators of the immune response, as well as non-classical proto-oncogenes aberrantly expressed in hematological and epithelial malignancies. Langerhans Cell Histiocytosis (LCH) is a disorder characterized by an abnormal accumulation of CD207+/CD1A+ myeloid cells in almost any tissue. The etiology of this disease is not completely understood and it is not clear if LCH results from malignant transformation, unbalanced immune response or both. Our aim was to determine the role of TAM axis in the pathogenesis of LCH in pediatric patients. Therefore, the expression of TAM receptors and PROS1 were measured in CD207+ and CD1A+ circulating cells gated in three myeloid fractions CD11bHighCD11cHigh, CD11bHighCD11cLow and CD11bLowCD11cLow from peripheral blood mononuclear cells of patients with active disease (AD), and compared with non-active disease (NAD) and adult controls by flow cytometry. All data is expressed as fold increase of mean fluorescence intensity referred to NAD and controls. We observed that CD207+ and CD1A+ cells showed higher expression levels of PROS1 and MERTK in the three myeloid populations of AD patients compared with NAD and adult controls. PROS1 was significantly higher in CD11bLowCD11cLow (~4.26-fold N=8); and MERTK in the three populations with an average of 4.8-fold (N=8). TYRO3 was significantly up-regulated in CD1A+ cells of the three fractions of AD donors with an average of 2.18-fold (N=8). Remarkable, we found that CD207+ or CD1A+ cells present in AD showed significantly higher levels of TYRO3, MERTK and PROS1 versus their own negative CD207/CD1A population. Our results indicate that higher levels of TYRO3, MERTK and PROS1 are associated with active LCH and the presence of CD207 and CD1A markers, suggesting that TAM axis could be involved in the expansion of precursor of pathological LC-like cells.

Poster Location #43
LANGERHANS CELL HISTIOCYTOSIS: EVALUATION OF 36 BRAZILIAN CHILDREN AT A SINGLE INSTITUTION

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PURPOSE: To determine the clinical characteristics and outcome of children with Langerhans cell histiocytosis (LCH) in a Brazilian pediatric hospital. METHODS: A retrospective analysis of 36 children was performed at Pequeno Principe, a pediatric hospital, in Curitiba-Parana, Brazil. According to clinical presentation and specific test results, two groups of patients were defined: group A, with single system disease (uni or multifocal) and group B, multisystem disease (with or without organ dysfunction). Patients were treated according to the initial presentation and to the LCH protocols. They were followed up at least for 9 years after diagnosis. RESULTS: Age at diagnosis ranged from 18 months to 11 years old in group A, and from 19 days to 3 years old in group B. Eighteen patients were male and eighteen were female. CD1a was positive in all patients analyzed. Sixteen children had single system disease: ten (62.5%), had unifocal and six (37.5%), had multifocal disease. Twenty patients had multisystem disease: five (25%), had no organ dysfunction and fifteen (75%), did have organ dysfunction. Only bones were affected in the single system group. The skull was the most affected bone, including in the multisystem group. Hepatomegaly, splenomegaly, enlarged lymph nodes and skin lesions were the most common presentation in multisystem form of the disease, and the organ dysfunction were related to poor prognosis. The overall survival rate for the whole group was 72.2% at 17 years. Nine (90%) of those patients who died belonged to group B (45% of 20 patients) and seven (77.8%) of these patients had organ dysfunction. Sequelae were detected in six patients: diabetes insipidus (3) and growth retardation (3), all of them had multiple skull lesions. CONCLUSION: The clinical characteristics of the children were related to the single and multisystem disease and organ dysfunction were related to poor prognosis.

Poster Location #44
BONE LANGERHANS CELL HISTIOCYTOSIS TREATED WITH INDOMETHACIN: REVIEW OF CASES FROM A SINGLE INSTITUTION

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PURPOSE: Langerhans cell histiocytosis (LCH) is a rare disease; bone is the most common single organ involved. Indomethacin (IM) is an inhibitor of cyclooxygenase 1 and 2 that participate in prostaglandin synthesis implicated in the pathogenesis of LCH.METHOD: A retrospective analysis of 18 LCH patients with single-system bone involvement which were treated with IM as the first or second line of treatment at San Juan de Du Hospital between 2010-2019.RESULT: 18 patients (14 male/4 female) received IM (2mg/kg/day). The median age was 8.3 years(2-16) with a median follow up of 3.8 years (0.5-9.6). The median duration of treatment was 16 months (6-24), and the median time free of reactivation was 13.5 months (9-18). 12 patients received IM as first therapy (9/12 had unifocal symptomatic bone involvement, and 3/12 had multifocal bone involvement). 6 patients received IM as salvage therapy after 1 or 2 lines of chemotherapy (4/6 had reactivations under chemotherapy, and 2/6 had active disease at the end of chemotherapy). All patients had nonactive disease (NAD) after eight weeks with IM and have complete bone regeneration with a median of 12 months (6-24). 2/18 presented reactivation, both with BRAFV600E mutation, one had NAD after reintroduction of IM and the second patient (femur bone involvement at diagnosis) presents reactivation in the bone marrow and central nervous system. 1/18 had a headache and mild intermittent palpebral edema, no other significant toxicities were evident. CONCLUSION: Although our findings are limited by small sample size, these data suggest that IM is effective, feasible and nontoxic at diagnosis or after reactivations. Indomethacin may be used as the first line of treatment for bone LCH(unifocal symptomatic/multifocal bone involvement).
LANGERHANS CELL HISTIOCYTOSIS: A DISEASE MIMICKER IN PEDIATRICS

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PURPOSE: To present four Langerhans Cell Histiocytosis (LCH) cases that initially mimicked other common pediatric problems. METHODS: Case series. RESULTS: The first case was a 6-month-old male presented with chronic eczematous rash over the scalp and trunk. He had been previously treated for scabies and atopic dermatitis. The skeletal survey showed a unifocal lucent lesion at right frontal lobe. The skin biopsy confirmed LCH and LCH-III protocol started due to multisystem involvement. The second case was a 4-year-old male presented with neck pain without any trauma. The imaging showed pathologic cervical spine 2 (C2) fracture with a lytic lesion. He had the surgery and pathology showed LCH of C2. The third case was an 11-month-old male with poor weight gain and developmental delay, presented with right pneumothorax. Thorax computed tomography (CT) was remarkable for innumerable cysts on both lungs. Skeletal survey showed multiple marked lytic lesions of skeleton and vertebral compression deformities. Bone biopsy confirmed LCH and he was started on protocol LCH III. Motor skills improved after chemotherapy, but he developed recurrent bilateral pneumothoraces requiring multiple chest tube placements and chemical pleurodesis. The last case was a 22-month-old male diagnosed with left adrenal gland neuroblastoma, who was successfully treated with surgery and chemotherapy. One year later, he presented with new onset left hip pain. Pelvic magnetic resonance imaging (MRI) showed a 4 cm erosive lesion with soft tissue involvement. Recurrent neuroblastoma was ruled out. Final diagnosis from left iliac lesion biopsy was LCH. CONCLUSION: LCH symptoms can mimic other childhood diseases such as as dermatitis, failure to thrive, fractures, joint pain and pneumothorax in our cases, which can be missed at routine pediatric setting. Having a high index of suspicion among pediatricians can lead to early recognition and help to improve outcomes especially in high risk patients.

LANGERHANS CELL HISTIOCYTOSIS: A CASES SERIES

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PURPOSE: To present the outcome of three patients with relapsed and refractory multifocal bone Langerhans cell histiocytosis (LCH) treated with various therapies. METHODS: The clinical data of three cases of multifocal bone LCH were retrospectively analyzed and the relevant literatures were reviewed. RESULTS: Case 1 presented LCH at 9 years with diabetes insipidus, Cushing syndrome, and skull lesions treated with radiotherapy only. At 11 years of age, she presented with skull relapse and treated with TPOG 2003 HR protocol due to progressive disease, and then switched to Ara-C based chemotherapy due to progressive disease. Hydroxyurea was then prescribed for 6 months. There is no evidence of active disease at 2 years follow up. Case 2 presented LCH at 9 years with diabetes insipidus, lung and skull lesions treated by TPOG 2003 HR protocol, At 11 years of age, she presented with skull relapse and treated with TPOG protocol, and then switched to HR protocol due to progressive disease, hydroxyurea was ever prescribed but progressive disease still noted, therefore, 2CDA was prescribed. This patient is currently under 2CDA treatment. CONCLUSION: In pediatric patients with LCH with relapsed and refractory MFB lesions, the optimal strategies that further improve the EFS and reduce sequelae are required.
EFFECT ANALYSIS OF CLADRIBINE AND CYTARABINE COMBINATIONS IN TREATMENT OF REFRACTORY AND RELAPSED LÄNGERHANS CELL Histiocytic Disease IN CHILDREN

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PURPOSE: To summarize the efficacy and toxicity of cladribine combined with cytarabine in the treatment of recurrent Langerhans cell histiocytosis in children. METHODS: We retrospectively analyzed the children with relapsed Langerhans cell histiocytosis disease treated with Ara-C+2-CD regimen in the Center for Hematological Tumors, Beijing Children's Hospital Affiliated to Capital Medical University from July 2014 to May 2017. RESULTS: 67 children was observed, among which 57 (85.07%) responded to treatment. There were 46 children with NAD (68.65%) and 11 children with AD-stable (16.42%). Only 1 case recurred during maintenance therapy and was effective in retreatment. After no improvement by Ara-C regimen, 6 children were treated with Ara-C+2-CD regimen, 5 with NAD and 1 with AD got improved. 5 cases of pulmonary involvement complicated with diabetes insipidus, among which 1 case of diabetes insipidus disappeared after treatment. The imaging morphology of pituitary was basically restored after reexamination of MRI. Other 4 cases of diabetes insipidus improved. All of them have begun maintenance therapy. Bone marrow depression and gastrointestinal reactions were found in all 67 children. And some of them had hepatobiliary system reactions, which could be tolerated. What's more, here was no chemotherapy-related death. CONCLUSION: With high efficiency, good tolerance and low recurrence rate, 2-CD can be used as a secondary treatment for refractory LCH. It has a certain effect on reversing pulmonary lesions of LCH. If the secondary treatment of Ara-C alone is ineffective, we can still consider the Ara-C+2-CD regimen. The long-term recurrence rate still needs further observation and follow-up.

A CASE OF A CHILD WITH NEURODEGENERATIVE DISEASE LANGERHANS CELL HISTIOCYTOSIS

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BACKGROUND: Langerhans cell histiocytosis (LCH) is a disorder characterized by clonal proliferation and accumulation of immature Langerhans cells (LC). Craniofacial lesions and diabetes insipidus predispose patients to neurodegenerative disease LCH (ND-LCH). The pathogenesis of ND-LCH may be due to chemokine/cytokine tissue damage or an autoimmune response to brain components. Recently, it was proposed that a hematopoietic clone causing the original LCH persists or re-emerges and serves as reservoir for future ND-LCH. CASE: We describe a case of a 5-year-old female with multisystem, non-risk organ involvement LCH who at the age of two presented with failure to thrive, an anterior mediastinal mass and abdominal pain at an outside hospital (OSH). She was diagnosed with LCH after endoscopic gastrointestinal (GI) biopsy that was positive for CD1a and langerin. She also had occipital calvarium lesion but without liver, spleen or bone marrow (BM) involvement. Subsequently, she responded to 12 cycles of prednisone and vinblastine. Due to disease recurrences cytarabine and later clofarabine were used. Patient had clinical and endoscopic resolution of disease after 6 clofarabine cycles. On presentation to our institution, patient had polyuria and polydipsia which prompted MRI imaging to assess pituitary function. Patient was otherwise asymptomatic, with normal laboratory values but with occasional abdominal pain. MRI imaging revealed a normal pituitary, however, suggestive of ND-LCH not previously seen on other imaging. Patient was neurologically intact and asymptomatic and thus a lumbar puncture to assess for biomarkers was not performed. Specimens collected from the OSH were sent for BRAF staining, which turned out to be positive. CONCLUSION: To our knowledge this is a first report of a pediatric patient with BRAF positive LCH in GIT, without BM involvement who was incidentally found to have brain MRI findings suggestive of ND-LCH.
OUTCOME OF PEDIATRIC PATIENTS DIAGNOSED WITH LANGERHANS CELL HISTIOCYTOSIS AT KING HUSSEIN CANCER CENTER

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PURPOSE: The clinical presentation, course and outcome of Langerhans cell histiocytosis (LCH) is variable, ranging from a single isolated, spontaneously reserving bony lesions to multisystemic disease with life-threatening organ dysfunction. Our aim is to study the outcome of children with LCH treated at a single center. METHODS: This is a retrospective analysis of children with LCH treated at our institution between Jan/1997-Oct/2017. Based on site and extent of disease at diagnosis, patients were either treated with chemotherapy per LCH III/IV, radiotherapy or local therapy (biopsy, curettage, and/or intralosional steroids). RESULTS: We studied 81 patients; the median age at diagnosis was 34 months (range, 0.2-176). Among these patients, 39 (44%) had single system (SS-LCH), 8 (9%) had multisystemic LCH with risk organ involvement (MS-RO+), and 14 (17%) had multisystemic LCH without risk organ involvement (MS-RO-). Bone was the most frequently affected organ (N=51, 84%) followed by skin (N=13, 21%), lymph node (N=11, 18%) and lung (N=4, 7%). Of the 51 patients with SS-bony disease, 44 (86%) had unifocal disease and 7 (14%) had multifocal disease. CNS-risk lesions were seen in 22 patients (27%) at diagnosis. Permanent consequences were observed in 7 patients: Diabetes insipidus occurred in 5 patients (8%), neurodegenerative CNS-LCH occurred in 2 patients (3%). At a median follow up of 23 months (range, 6-165), the 5-year overall survival (OS) rates in the SS, MS-RO-, and MS-RO+ groups were 94%, 92%, and 80% respectively (P=0.029), and the 5-year event free survival (EFS) rates were 55%, 52%, and 33% respectively (P=0.16). CONCLUSION: Poor overall survival in MS-RO+, reactivation and permanent consequences are main challenges in therapy of LCH. Upfront Intensification by Re-induction chemotheraphy and continuation therapy for 12-months both impact disease reactivation and survival. New targeted therapy added to standard therapy is needed.

ANALYSIS OF BONE LCH CASES TRIGGERED BY BRUISING; RESULT FROM JLSG-02 STUDY

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BACKGROUND: The development of bone lesions of Langerhans cell histiocytosis (LCH) may be triggered by bruising. METHODS: We identified 15 pediatric LCH patients who were enrolled to JLSG-02 study and had a bone lesion developing at the bruising site at diagnosis. A retrospective questionnaire survey was conducted to determine the clinical characteristics of such cases. RESULTS: Of these 15 cases, detailed information was available in 13 cases (8 male and 5 female). Analysis revealed that the mean age at bruising was 5.5 years (range: 0.8 - 11.7), and the median time from bruising to LCH diagnosis was 4.5 weeks (range: 1 - 10). The bruising sites were: 10 cases in the skull (5 in frontal bone, 3 in temporal bone and 2 in orbit), and one each in the humerus, lumbar spine and sciotic bone. At the time of injury, half of the cases developed a bump at the bruising site, which persisted more than 3 weeks in 3 cases. No patient had extradural hematoma. The incidence of bone LCH triggered by bruising was calculated as; 1/25 cases (4.0%) in single bone disease, 6/83 cases (7.2%) in multi-focal bone (MFB) disease, 6/75 cases (8.0%) in risk organ involvement (RO)-negative multi-system (MS) disease, and 0/78 (0.0%) in RO-positive MS disease. The treatment response was good in all cases and no patients died. Relapses were observed in 2 cases with MFB disease; one developed skin lesion and the other developed MFB lesions simultaneously at the healed bruising site and at another site. CONCLUSION: Bone LCH triggered by bruising occurs at relatively older age, with a male predominance, at various incidences depending on the LCH types, but with a good clinical course. The biological mechanism how LC cells are activated and resulted in LCH by physical damage remains to be determined.

GENOMIC ANCESTRY AND LANGERHANS CELL HISTIOCYTOSIS CLINICAL CHARACTERISTICS

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PURPOSE: Langerhans cell histiocytosis (LCH) is an inflammatory myeloid neoplasia characterized by lesions including pathogenic CD207+ dendritic cells among inflammatory infiltrate. LCH incidence varies across self-reported race/ethnicity however the influence of genomic ancestry, a far more precise measure, on LCH clinical characteristics is unknown. Therefore, we assessed whether the frequency of LCH clinical characteristics differs across genomic ancestral categories. METHODS: LCH cases (n=118) were recruited from Texas Children's Hospital. Genetic ancestry was determined in Structure2.3.4. using 179 ancestral informative markers and HapMap reference ancestral populations. European, African, and East Asian individuals were defined as having >90% European genetic ancestry, ≥70% African ancestry, and ≥70% East Asian ancestry, respectively. Hispanics were defined as individuals for whom the percentage of AmerIndian genetic ancestry was ≥10%. Data on risk organ involvement, degree of disease dissemination, number of disease sites, relapse, and BRAFV600E results were abstracted from medical records. The Fisher's exact test was used to assess distributional differences. RESULTS: The distribution of genomic ancestry among cases was: 61.9% European, 33.1% AmerIndian, 0.9% African, 0.9% Asian and 3.4% were of mixed genomic ancestry. The occurrence of a LCH relapse event was suggested to differ across genomic ancestral categories (P=0.07) and a difference in the distribution of risk organ involvement by genomic ancestry was marginally suggested (P=0.11), although these findings did not reach statistical significance. No strong differences in the distributions of disease dissemination (P=0.19), number of disease sites (P=0.83), or BRAFV600E mutation status (P=0.38) by genomic ancestral categories were identified. CONCLUSION: In this study, we identified a couple of clinical characteristics suggested to differ by genomic ancestry. Future studies will seek to gather genome-wide data on cases from collaborative sites and obtain comparable controls from each locale in order to further assess the impact of genomic ancestry on LCH susceptibility, clinical characteristics, and outcomes.
OUTCOME OF LANGERHANS CELL HISTIOCYTOSIS (LCH) - A SIXTEEN YEARS STUDY
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PURPOSE: Langerhans cell histiocytosis (LCH) is a rare disease, of unknown pathogenesis, characterized by intense and abnormal proliferation of bone marrow-derived histiocytes (Langerhans cells). It can present both local and systemic manifestations involving bone, skin, mucosal tissue and internal organs. There are several clinical trials were done, recently large clinical trials have shown that the response to initial treatment is a highly important prognostic factor in these patients. The study was conducted at Indus hospital on LCH patients in order to identify the characteristics, treatment response and survival of the patients. METHODS: This is a retrospective study and was conducted in the department of Pediatric Oncology, Indus Hospital Karachi. Data was collected from 2003 to 2018. Results: Out of 53 patients 47 were treated from which males were 25 (53%) and females were 22(47%). Other 6 patients were abandoned. Median age in months was 36 (5-192). Bone was the most common site of disease involvement (55% of cases). In Single System (SS) LCH patients, LCH II, LCH III, LCH IV and LCH-S 2005 protocol was given to 1(9%), 22(43%), 11(31%), 1(3%) and 1(3%) respectively. While in Multisystem (MS) LCH patients LCH III protocol were given to 5(42%), LCH IV to 5(42%) and LCH-S 2005 protocol were given to 2(16%). Reactivation of disease occurred in 12 patients. For reactivation TA III was given to 1 SS-LCH patient, TA IV Salvage was given to 1 SS-LCH and 2 MS-LCH patients and Modified Salvage was given to 6 SS-LCH and 2 MS-LCH patients. For this study the Overall survival (OS) was 80%, SS-LCH OS was 85% while MS-LCH OS was 66%. CONCLUSION: Most of the children received LCH III and LCH IV protocols. For reactivation modified Salvage protocol was very effective. In our study survival has improved considerably over time.

LONG-TERM EXPERIENCE IN A LARGE COHORT OF ADULTS WITH LANGERHANS CELL HISTIOCYTOSIS MANAGED AT A SINGLE INSTITUTION.
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PURPOSE: Our aim is to analyze clinical features and outcome of patients with Langerhans Cell Histiocytosis (LCH), treated at a single institution with different therapeutic approaches according to the disease classification. METHODS: One-hundred-forty-six adults (median age of 36 years; range: 19-71) with LCH were divided according to the GIMEMA LCH 2001 guidelines: unifocal single-system (SS), multifocal-SS, multisystem (MS) and pulmonary honey-combing (PHC) involvement. As first-line treatment, 91 patients were treated according to the GIMEMA LCH 2001 guidelines and 55 patients received various treatment. The response to first-line therapy was considered good (GR) or intermediate (IR) whether the lesions were reduced of ≥50%. RESULTS: The median follow-up is of 48 months (range 3 - 396). BRAFV600E mutation was detected in 16 of 41 tested patients (39%). The GR were significantly higher in the unifocal SS patients (82.9%), independently from involved sites and treatment, compared to 41.7%, 50.7% and 35.7% in those with multifocal-SS, MS and PHC LCH, respectively (p-value 0.003). No response or disease progression were recorded in 16.7%, 4.5% and 7.1% of unifocal-SS, MS and PHC, respectively. At 4 years of follow-up the progression-free survival is 83.7% and the overall survival (OS) is 84.2%, with the OS significantly affected by treatment response: 85.9% in the patients achieving a GR, while 90.6% and 56.3 for IR and non-responders, respectively (p value 0.001). The presence of BRAF mutation negatively but not significantly (p value 0.197) influenced the prognosis. CONCLUSION: Our experience suggests that the extension of disease affects the response to treatment, even though therapy choices for different groups weren’t uniform. Moreover, obtaining a response is crucial in terms of OS. Accordingly, we can suggest that specific risk-adapted therapies are needed in order of improving survival.

CNS-PERMANENT CONSEQUENCE IN PEDIATRIC LCH PATIENTS TREATED BY AN ARA-C CONTAINING REGIMEN: THE DATA FROM JLSG-96/02 STUDIES IN JAPAN
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PURPOSE: LCH causes various CNS-permanent consequences (PCs), such as endocrine deficiency (central diabetes insipidus; CDI), anterior pituitary hormone deficiency; APHD, neurodegenerative disease (ND), growth failure, hearing loss, etc. These PCs closely led to long-term impairments in quality of life (QOL), thus the prevention/management of CNS-PCs is critical in LCH treatment. We report here the long-term follow-up results on the incidence of PCs/ risk factors for developing PCs in Japan LCH Study Group (JLSG) cohort. METHODS: A total of 317 patients (111 with multifocal bone (MFB) and 196 with multisystem (MS) treated with JLSG-96/02 protocol from 1996 to 2009 have been followed up to 2019. Regimens of JLSG protocols contained cytarabine, vincristine and prednisolone. Statistical analysis was made by chi-square and Kaplan-Meier method with log-rank test. Cox proportion hazards regression was used for multivariate analysis. RESULTS: The median observation time of MFB and MS was 11.2(range 2.7 - 22.2) and 17.0(4.4 - 15.9), respectively. The incidence of all CNS-related PCs was 9.0% in MFB and 28.1% in MS patients. The 10-year cumulative incidence of CDI, clinical ND (cND), and APHD was 16.1, 4.1, and 7.0%, respectively. Most of patients with cND and/or APHD were accompanied with CDI. Further analysis revealed that the significant risk factors for CDI were disease type (MS), age, CNS risk lesion at LCH diagnosis, and relapse at CNS risk lesions, and the risk factor for cND and APHD development was prior CDI by multivariate analysis. CONCLUSION: The QOL in LCH patients mostly depends on if they develop CNS related PCs or not. Occurrence of CDI was associated with lesions at CNS risk sites at LCH diagnosis and relapse. Novel therapeutic approach is required to prevent CDI occurrence in such patients and reduce CNS related PCs.
LONG-TERM RISK OF RELAPSE IN PATIENTS WITH CHILDHOOD-ONSET LANGERHANS CELL HISTIOCYTOSIS: A REPORT OF TWO ADULT CASES WHO RELAPSED AT MORE THAN 15-YEAR INTERVALS.

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PURPOSE: Probability of relapse in children with Langerhans cell histiocytosis (LCH) is 30%-40%, and reactivation generally occurs within 2 years after remission. Relapse may occur several times during childhood and it is hard to tell when the disease is completely cured. We report here two adult cases with childhood-onset LCH who relapsed at intervals of more than 15 years. CASE 1: A 42-year-old man was diagnosed as multifocal bone LCH at 2 years of age. Central diabetes insipidus (CDI) occurred at the age of 3 years. Bone relapse and lymph node swelling occurred several times and were treated with PSL, VBL and MTX until the age of 18 years. After a remission period of 18 years, he developed osteolytic lesions at cranium, hip bone and spine between the age of 33 and 42 years. CASE 2: A 39-year-old woman was diagnosed as multisystem LCH in infancy without risk organ involvement. CDI occurred at 5 years of age. Refractory otitis media resulted in auditory disturbance, and she was treated by PSL, CFM, VP16 and MTX until teens. After a long remission interval, new cranial osteolytic bone lesion occurred at 26 and 30 years of age. In both cases, LCH lesions in the adulthood were restricted to bone. Recent brain MRI showed no signs of radiological CNS-neurodegenerative disease (ND) of cerebellum and basal ganglia. Both patients are working full time daily. DISCUSSION: Our experience on two adult relapsed patients with childhood-onset LCH suggests that LCH precursor cells may reside for more than 30 years during clinical remission. Despite the high potential risk of developing ND, no abnormal brain MRI findings have been identified to date. Further researches are required to clarify the mechanism of ND and the trigger of LCH recurrence after a long remission interval.

LÄNGERHANS CELL HISTIOCYTOSIS (LCH) BRAF V600E+ COMBINED WITH OTHER LYMPHOPROLIFERATIVE DISORDERS: AN INTRIGUING CASE

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PURPOSE: Gene expression profiling has revealed that the most likely origin of the LCH cell is a myeloid dendritic progenitor. We also know that the BRAF V600E mutation, present in 50% of cases of patients with Langerhans Cell Histiocytosis (LCH), is characteristic of malignancies. This is an intriguing case of a female patient with LCH who developed several lymphoproliferative disorders. METHODS: The diagnosis of LCH was made according to the HS criteria (CD1a+, S100+, CD207+). BRAF mutation analysis was performed in the histological sample at diagnosis. The mutational study of immunoglobulin heavy chains rearrangement is underway. We carefully collected and analyzed clinical data of the patient and we have followed her whole diagnostic-therapeutic course. RESULTS: Our patient with a previously diagnosis of low-risk chronic lymphocytic leukemia (CLL) at the age of 37 years, developed multisystem LCH at the age of 53 years with gastrointestinal, pulmonary, central nervous system involvement and diabetes insipidus. At the same time, a diagnosis of gastric MALT lymphoma was made. She received specific treatment for MALT lymphoma and, subsequently, Vinblastine+Prednisone and Cladribine for LCH. Three years later, she received a diagnosis of MGUS at the age of 56. CONCLUSION: The involvement of BRAF in LCH and in other neoplasms has already known, but its role on the development of concomitant neoplasms has not been demonstrated before. So far, only one case of mutated BRAF-V600E+ HCL and CLL has been reported. In this study, the role of BRAF mutation in the development of the second neoplasm (CLL) was excluded, while the same heavy chain immunoglobulins rearrangement was identified in both diseases. Investigations on the mutational state of heavy chain immunoglobulins rearrangement could identify a common origin in cases of coexistence of different neoplasms.
PRESENTATION OF INFANT WITH MULTISYSTEM LCH AND LUNG INVOLVEMENT RESULTING IN CHRONIC CYSTIC LUNG DISEASE

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PURPOSE: Describe a severe case of multisystem Langerhans cell histiocytosis (LCH) with pulmonary involvement in infant and subsequent clinical complications. METHODS: Review of patient medical records, imaging and pathology specimens and comprehensive literature review RESULTS: 4-month old infant presented with 3 weeks of fever, rash, vomiting, diarrhea and lymphadenopathy. Initial lab work significant for leukocytosis (56.6K/µL), thrombocytosis (866K/µL) thrombocytosis and elevated CRP (14.1 mg/dL). CXR obtained as part of fever workup showed diffuse bilateral patchy opacities prompting CT of chest which showed numerous pulmonary lesions including nodules with central cavitation and both thick and thin-walled cysts. At time of diagnosis, patient had no respiratory distress or supplemental oxygen requirement. CT scan of the liver showed numerous hypodense liver lesions. Broad workup done into etiology including unremarkable bronchoscopy, normal upper GI endoscopy, normal skin biopsy and lymph node biopsy that was consistent with diagnosis of LCH. BRAF VE1 immunohistochemistry stain on lymph node was negative. Subsequent skeletal survey and brain MRI were unremarkable. Patient was started on therapy per LCH-III with rapid resolution of fever, improved feeding tolerance downtrending of CRP and normalization of white blood cell count improved feeding tolerance. CT scans obtained at 6 weeks showed progression of lung disease to primarily thin-walled cystic lesions comprising significant portion of lung parenchyma and resolution of liver lesions. Over subsequent weeks, child began to develop more respiratory distress resulting in difficulty oral feeding and hypoxemia. Supportive care for cystic lung disease included oxygen supplementation, placement of gastrostomy tube for feedings, pavalizumab administration and vigilance for pneumothoraces.

CONCLUSION: Pulmonary manifestations of LCH occur in a minority of patients with multisystem LCH. However, it can be associated with significant morbidity both during initial presentation and after improvement of other symptoms of LCH due to lasting damage to lungs.

REVEALING HOMOLOGOUS CLONALITY BY SYNCHRONOUS TRISOMY 8 IN LANGERHANS CELL HISTIOCYTOSIS AND ACUTE MYELOID LEUKEMIA

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PURPOSE: Langerhans cell histiocytosis (LCH) is a disorder in which excess immature Langerhans cells build up in the body. Increasing reports have revealed LCH may share a common origin with myeloid-derived malignancies. Here we report a case of a 45-year-old male, diagnosed as synchronous LCH and acute myeloid leukemia (AML). Relevant tests have been performed to investigate the clonal relationship between LCH and AML. METHODS: The diagnosis of LCH and AML were based on skin and bone marrow biopsy respectively in Beijing Friendship Hospital, Capital Medical University. No cytotoxic drugs were used before the two diseases were diagnosed. Immunophenotyping was run by immunochemistry or flow cytometry. Karyotype analysis was carried out with G-banding, and the findings were confirmed by fluorescence in situ hybridization (FISH). Mutational analysis of BRAF, KRAS and NRAS genes were performed by ARMS-PCR. Additional gene screening was detected by next-generation sequencing (NGS).

RESULTS: The case expressed CD1a, S-100, Langerin on the Langerhans cells and CD13, CD34, CD38, CD117, MPO on the leukemic blasts. No other intermingling markers was found on the LCH and AML except CD33 and CD68. Cytogenetic studies showed a karyotype with 47, XY, +8[10], and a confirmatory test revealed the existence of trisomy 8 in both skin and bone marrow lesions by FISH. Cell rate of trisomy 8 on skin, bone marrow and oral mucosa were 9%, 49% and 1%. Mutation analysis revealed BRAF_2173C>A (H725N), 2138C>A (S713Y) in exon 18 and KRAS_436G>A (A146T) in exon 4 in AML and LCH cells, but BRAF_1799T>A (V600E) in exon 15 only in LCH.

CONCLUSION: These findings suggest that cell origin of LCH is derived from myeloid precursors in this case, and BRAF mutation may play an important role in pathogenesis of LCH.
NEUROLOGIC INVOLVEMENT IN ERDHEIM-CHESTER DISEASE

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PURPOSE: To characterize the spectrum of neurologic involvement in Erdheim-Chester Disease (ECD), a treatable inflammatory neoplasm of histiocytes. METHODS: 62 patients with ECD were prospectively enrolled in a natural history study that facilitated collection of clinical, imaging, laboratory, neurophysiologic and pathologic data. RESULTS: 94% of the patients had objective neurologic findings, and 15% had neurologic symptoms as the initial feature of ECD. The most common findings were cognitive impairment, peripheral neuropathy, pyramidal tract signs, cranial neuropathies and cerebellar ataxia. Imaging revealed atrophy and demyelination along with focal lesions that were located throughout the nervous system, dura and extraaxial structures. The BRAF(V600E) variant correlated with cerebral atrophy. Brain pathology revealed lipid-laden, phagocytic macrophages (histiocytes) accompanied by demyelination and axonal degeneration. CONCLUSION: Neurologic manifestations of Erdheim-Chester Disease can cause significant morbidity and increased mortality. Its presentation overlaps with white matter inflammatory and infectious diseases or other neoplastic disorders. Neurologists play a critical role in the timely evaluation and treatment of these patients since early diagnosis and intervention can lead to better quality of life and improved outcomes.

IMMUNOGLOBULIN G4-RELATED DISEASE AS A MIMICKER OF HISTIOCYTIC DISORDERS IN ADULTS

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PURPOSE: To alert clinicians dealing with histiocytic disorders to Immunoglobulin G4-related disease (IgG4RD) as a differential diagnosis to histiocytic disorders. METHODS: case report and literature review. RESULTS: IgG4RD is a group of diseases that may affect various organs. Rarely, IgG4RD may present as a hyperinflammatory disorder with fever, organomegaly, lymphadenopathy, marked hyperferritinemia, and increased levels of soluble Interleukin-2 receptor and soluble CD163. Macrophage accumulation and histiocytes may be seen in bone marrow and lymph node biopsies in some cases of IgG4RD. Importantly, the characteristic “fibro-inflammatory” histopathologic features often seen in other tissues of patients with IgG4RD is rare in bone marrow or lymph nodes. Conversely, infiltration with IgG4 positive cells occur in the tissues of patients with eg. Rosai-Dorfman-Destombes disease without IgG4RD. Given its rarity, its organ-promiscuity, the heterogeneity in the presentation of IgG4RD, and the lack of characteristic findings in bone marrow and lymph nodes, recognition of the disease may be challenging to hematologists. The common presenting and discriminatory features of IgG4RD, IgG4RD-associated macrophage activation syndrome, hemophagocytic lymphohistiocytosis, and the histiocytic disorders in particular Erdheim-Chester Disease and Rosai-Dorfman-Destombes disease is presented. Multi-centric Castelman disease will be included in the comparison as it shares features with the inflammatory conditions. IgG4RD is often easily treatable with glucocorticoids. B-lymphocyte deletion with rituximab and disease modifying antirheumatic drugs are rescue treatments. CONCLUSION: IgG4RD is a group of diseases which attracts increasing focus. As there may be overlapping features with histiocytic disorders, physicians who are involved in the diagnostic workup and treatment of these diseases should be aware of the diagnosis. Given the importance of macrophages in the pathogenesis of some cases of IgG4RD - and recent promising results with janus kinase (JAK) inhibition in patients with macrophage-related disorders, it is possible that JAK-inhibition may prove of clinical benefit in patients with refractory IgG4RD.

EXTRACUTANEOUS/DISSEMINATED JUVENILE XANTHOGANULOMA (JXG) IN INFANCY. REPORT OF A CASE

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Extracutaneous/disseminated juvenile xanthogranuloma (JXG) may present as a challenging diagnosis. We present a two month-old-baby with two weeks of jaundice as the only clinical sign. An ultrasound and a CT scan were performed at the original hospital, and a dilated biliary tree and a tumor mass were found. The neoplasm was irregular, measured 29 x 28 x 28.5 cm and was located between liver hilum (compressing the extrahepatic biliary tree) and duodenum, and related to the left kidney. Serologic studies results showed:α fetoprotein: 7750ng/ml and β-HCG: 1mUI/ml. A biopsy was performed. The local pathologist reported a mesoblastic nephroma and a wide resection (including nephrectomy) was then achieved. We received both samples in consultation within a few days in between. There was an oval to spindle cell proliferation, with bland nuclei and few mitoses, and a very infiltrative pattern was obvious. Some pancreas parenchyma (acini and Langerhans/endocrine islands) was present in the first biopsy. In the second specimen the tumor was infiltrating the kidney, embracing it from the surrounding capsule and from the sinus. The cells showed some vacuolated cytoplasm and several multinucleated giant cells and of the Touton type were found. Extracutaneous/disseminated JXG may present as well as eosinophils. Immunostains were only positive for CD68. Ki67 showed a low index of proliferation. Extracutaneous/disseminated JXG was diagnosed. BRAF mutation was negative (RT-PCR). No bone lesions were found afterwards. Extracutaneous/disseminated JXG may present as a retroperitoneal tumor and small biopsies may not be diagnostic given the extreme rarity of the entity. Regarding the last Histiocytosis classification (2016) extracutaneous JXG shares the L group of diseases with LCH and ECD (with whom it shares very closely the histologic features). In this setting, an infant patient without bone affection, we preferred to name the disease as JXG.
Poster Location #65
IMPACT OF A MULTI-DISCIPLINARY TUMOR BOARD ON THE CARE OF PATIENTS WITH HISTIOCYTIC HISTIOCYTOSIS WORKING GROUP (HWG) EXPERIENCE

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PURPOSE: Histiocytic disorders present with diverse clinical manifestations and pose significant diagnostic and management challenges. Hence, a multidisciplinary approach may help improve patient outcomes. In this study, we report the Mayo Clinic HWG experience. METHODS: The Mayo Clinic HWG was established in June 2017. It consists of members from various subspecialties with expertise in management of histiocytosis: endocrinology, cardiology, dermatology, hematology, pathology, neurology, pulmonology, radiology, and rheumatology. HWG meets monthly to discuss cases in a multidisciplinary format, which includes a review of histopathologic and radiographic data along with input from all members. In this report, we reviewed the cases discussed at HWG over the first 2 years since its inception. June 2017 to June 2019. RESULTS: 37 cases with suspected histiocytic disorder were reviewed at the HWG tumor board during the study period. The initial diagnoses were: Erdheim-Chester disease (ECD, n=13); Langerhans cell histiocytosis (LCCH, n=13); Rosai-Dorfman disease (RDD, n=7); histiocytic sarcoma (n=1); Langerhans cell sarcoma (n=1); and IgG4-related disease (n=1). HWG tumor board discussion led to significant reformulation of plan in 15 (41%) patients. These changes were subdivided into three categories: change in diagnosis (n=6, 17%); change/formulation of treatment plan (n=7, 19%); and additional evaluation changes (n=2, 5%). Most notable diagnostic changes were seen among three patients who were initially consulted for ECD but later had diagnoses changed to IgG4-related disease, giant cell tumor of tendon sheath, and osteopoikilosis, respectively. Another patient who was on chemotherapy for a diagnosis of LCCH was presented at HWG which led to change in diagnosis to dermatopathic lymphadenopathy and chemotherapy was discontinued. CONCLUSION: Our report highlights the feasibility and benefits of a multidisciplinary tumor board for histiocytosis. The complexity of these cases along with the alteration in plan for 41% patients suggests that multidisciplinary evaluation is warranted for patients with histiocytic disorders.

Poster Location #66
BRAF V600E MUTATION CORRELATES WITH CARDIAC INVOLVEMENT ASSESSED BY HEART IMAGING IN A MONOCENTRIC SERIES OF 205 PATIENTS WITH ERDHEIM-CHESTER DISEASE

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PURPOSE: Erdheim-Chester disease (ECD), an inflammatory myeloid neoplasm, is an histiocytosis associated with multisystem infiltration. Cardiovascular involvement in ECD is under-diagnosed and associated with poor outcome. The targetable BRAFV600Emutation is present in up to 70% of all ECD. METHODS: Retrospective study of 205 patients (pts) with ECD who had cardiac imaging (195 MRI, 10 CT when MRI was contraindicated). We identified the types of lesions (infiltration, tumor, and effusion), localization (pericardial, myocardial, valvular) and consequences on cardiac function (coronary stenosis, atrial wall dyskinesia, diastolic and systolic functions). RESULTS: 141 (68.8%) pts were male. 30 (14.6%) had mixed histiocytosis (mainly ECD + langerhans cell histiocytosis). BRAF mutation (BRAF) was found in 112 (54.6%) cases, while 59 pts (28.8%) were Wild Type (WT) and 34 pts (7.5%) had unknown BRAF status. Among the 205 cardiac imaging, 101 (49.3%) were abnormal. Cardiac involvement was found in 93 pts (49%). Among these, 72 had an impairment of the right ventricular atrioventricular sulcus (74%), 65 of the right atrium (RA) enclosure (65%). Alteration of Tricuspid Annular Plane Systolic Excursion was found in 15% and correlated with the size of the tumor. Pericardial involvement (effusion, thickening or contrast enhancement) was found in 59 pts (29%). Among BRAF pts, 75 (67%) had a heart abnormality while 37 (33%) had normal imaging; Among WT pts 14 (23.7%) showed heart abnormality, whereas 45 (76.3%) had normal imaging (RR 2.8 (Cl: 1.8-4.5); p = 1.8*10^-7). A RA tumor was present in 51 (45.5%) BRAF pts but only 6 (12.7%) WT pts respectively (RR 6.5 (Cl: 2.0 -8.1); p = 7*10^-6). BRAF was also associated with aortic infiltration (RR 1.76 (Cl:1.2-2.5)) and pericardial involvement (RR 2.12 (Cl:1.1-3.9); p = 0.0017). CONCLUSION: Cardiac infiltration is frequent in ECD (49.3%), especially RA tumor. BRAF is associated with RA, aortic and pericardial involvements.
PURPOSE: Determine an effective therapy for Multicentric Reticulohistiocytosis. METHODS: Multicentric reticulohistiocytosis (MRH) is a rare non-Langerhans Cell Histiocytosis affecting skin and joints. Cutaneous lesions are red, brown or violaceous papules and nodules on the hands, fingers, face and trunk ranging in size from several millimeters to several centimeters often associated with pruritus. Clusters of periungual papules, referred to as 'coral beads' are considered pathognomonic of MRH. Arthritis associated with MRH frequently involves the distal and proximal interphalangeal joints and leads to destruction of the joints. Patients are frequently women in the first 4 decades of life who are afflicted by a variety of autoimmune diseases. We present the case of a 36 year old African-American woman who developed fatigue, decreased appetite, joint pain, Raynaud's phenomenon, alopecia, oral ulcers, sicca syndrome, 50 pound weight loss in one month, and progressive weakness. She was diagnosed with systemic lupus erythematosus and Sjogren's syndrome. Six months later, she developed nodular cutaneous lesions on her fingers, arms, and chest and back which were associated with intense pruritus. Biopsy of a nodule showed pathologic features consistent with MRH. RESULTS: In spite of combination treatment with methotrexate, etanercept, hydrochloroquine, prednisone, bisphosphonates and hydrazine, her MRH persisted and she was referred to our clinic at age 40 years. We initiated treatment with thalidomide 100 mg daily. After 3 months the nodules were decreasing in size and over the next 9 years the nodules on her fingers resolved and the papules under her eyes and on her chest were markedly improved. She remained on thalidomide for a total of 12.5 years before switching to lenalidomide because of persistent insomnia, her only toxicity. CONCLUSION: Thalidomide and lenalidomide are effective agents to treat MRH.

Poster Location #68
SUCCESSFUL TREATMENT OF MULTICENTRIC RETICULOHISTIOCYTOSIS WITH THALIDOMIDE AND LENALIDOMIDE
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PURPOSE: The North American Consortium for Histiocytosis (NACHO) was created in 2014 with the support of a St. Baldrick's Consortium Award, with the goal to enhance clinical and translational research for histiocytic disorders. Five years after its conception, NACHO is able to reflect on the growth and progress of the consortium alongside the landscape of histiocytic disorders, and has created new aims for a new period of scaling up: 1) Optimize, enhance and expand the NACHO network to advance clinical, translational and basic research in histiocytic disorders; 2) Develop and support clinical trials in areas of most significant unmet need including front-line and salvage therapies, and development of novel agents and personalized therapeutic strategies; and 3) Establish tissue resources to support basic and translational research to define mechanisms of pathogenesis and identify therapeutic opportunities. METHODS: NACHO has developed the infrastructure necessary to expand its reach and scope, and has incorporated new members to amplify its impact and facilitate access to better treatments to more patients. RESULTS: There are currently 51 member institutions in the NACHO Consortium. NACHO supports the implementation of LCH/I in North America, has a phase II study of clofarabine (LCH-CLO), a phase II study of cobimetinib (NACHO-COBI), a biology and registry study (NACHO-BIO), and developing a phase II of ruxolitinib for patients with HLH (NACHO-RUXO). NACHO has developed a strategy for finding continued funding for these clinical research initiatives and more clinical research concepts continue to be brought forth by NACHO members for future endeavors. CONCLUSIONS: NACHO has consolidated an infrastructure to support clinical and translational research in histiocytic disorders, and has expanded to incorporate more institutions, develop innovative treatments for these diseases, and impact patient outcomes globally.

Poster Location #69
NORTH AMERICAN CONSORTIUM FOR HISTIOCYTOSIS (NACHO)
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PURPOSE: Rosai-Dorfman Disease (RDD) is a rare non-Langerhans cell histiocytosis of unknown etiology which lacks clearly defined treatment options. We report our clinical experience and approach to diagnosis and treatment at our academic institution. METHODS: A case-series was established using chart review of three patients evaluated and followed in our Rheumatology clinic, with histopathologically-established RDD. RESULTS: We report three adult patients with evidence of extra-nodal disease although RDD typically presents as painless massive bilateral cervical lymphadenopathy in children with or without constitutional symptoms. Two of our cases presented with neurological symptoms and intracranial masses were identified by brain imaging. Our third case was heralded by a soft tissue breast mass, inflammatory arthritis with bone involvement and uveitis. In each case, dedicated nuclear medicine imaging was obtained. Both bone and PET scans were utilized to define extent of the disease. Ultimately tissue biopsies were obtained with several shared characteristics, first being gross "spindle-shape" or "storiform" appearance. Plasma cell populations were identified with s100-positive staining confirming histiocytes and allowing for recognition of the pathognomonic pattern of arrangement surrounding smaller cells, a process known as emperiploise. Our first case with localized intracranial mass improved after surgical resection. Second case with multisystem disease with uveitis, masses involving the breast and bone was treated with oral steroids initially, and later achieved remission with combination methotrexate and rituximab therapy. Similarly, our third patient with bone and intracranial mass (s/p resection) was started on methotrexate without development of breakthrough symptom and is awaiting debulking bone surgery. Despite widespread disease involvement, radiation was not required in any of our cases. CONCLUSION: Rheumatologists must be cognizant of RDD and the vast array of clinical manifestations which may create a diagnostic dilemma. Our cases help to outline the approach to diagnose this rare disease and formulate a management plan.
POSTER PRESENTATIONS - RARE HISTIOCYTOSES

Poster Location #71
HLH AND LCH DIAGNOSTIC OPPORTUNITIES: THE DISPARITIES IN THE AME-HISTIO NETWORK

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PURPOSE: The Asian Middle East (AME)-Histio Network's objective is to increase awareness about histiocytic disorders in the region and thereby improve access to diagnostic testing and proper treatment to all patients. To assess diagnostic opportunities, we distributed a survey to AME-Histio attendees requesting information on the various tests for hemophagocytic lymphohistiocytosis (HLH) and Langerhans cell histiocytosis (LCH).

METHODS: An email survey was distributed after the HS meeting in Singapore to all AME-Histio members and then personally redistributed at the Lisbon conference during the Network meeting. Members were asked to provide information regarding availability of the various tests for HLH and genetic tests for LCH samples.

RESULTS: Thirteen attendees representing 6 countries and 8 centers contributed information. In 3 centers in China and one in Japan complete HLH work-up and BRAF/non-BRAF mutations were available. The cost for HLH non-molecular testing (CD25, NK activity, CD107a, perforin flow cytometry, SAP/XIAP flow cytometry) was $800-900. Genetic testing cost $400-1200. The entire work-up was available at 1 center in Israel at the cost of $1700 for the diagnostic work-up, $400-3000 for molecular analysis (locally covered by insurance). In stark contrast, NO diagnostic work-up testing was locally available in Pakistan, in Lebanon only CD25 and BRAF mutations were performed and only CD25 and perforin by flow were easily available in Egypt.

CONCLUSIONS: There is great disparity in access to diagnostic testing for HLH and LCH within the AME-Histio Network. Outstandingly the three Middle Eastern/Eastern Asia countries, representing over 310 million people, had no opportunity to perform locally required tests to diagnose HLH and to genetically define LCH. Additionally, the Chinese represented only 2 cities that include <2% of the country's population. This study highlights an unmet need in the AME-Histio Network that requires networking and cooperation to create diagnostic opportunities for these underserved populations.

Poster Location #72
RARE HISTIOCYTOSSES – EXPERIENCES IN THE GERMAN REGISTRY AND CONSULTATION CASES

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BACKGROUND: Rare or Non-Langerhans cell histiocytoses (non-LCH) include many malignant and benign, localized or diffuse diseases. In pediatrics, the most frequent are Rosai-Dorfman disease (RDD) and (juvenile) xanthogranulomatosis (JXG), followed by Erdheim-Chester disease (ECD), and malignant histiocytoses. Frequently, the precise histological diagnosis is undefined. Recently, molecular genetic alterations, particularly in the ras-raf kinase pathway, were identified. METHODS: In 2012, the German registry and consultation study for non-LCH - part of the International Rare Histiocytic Disease Registry - was initiated. RESULTS: Fifty-nine patients were reported (26/29 female/male, 4 unknown; aged 0-4 years: 25; 5-9.9; 10-14.6; 15-19.8; 20-39.3; >39.7). Thirty-five patients are in observation (0-6 years), 6 patients died (aged: 1, 10, 42, 42, 51, 54 years); 18 lost to follow-up (lfu). Among 11 RDD patients (all survivors or lfu), 6 only had cervical lymphadenopathy (1 received steroids), 5 had extended disease (2 meningeal, 1 mediastinal/tracheal compression, 1 bone, 1 liver/lungs; 5 received steroids/polychemotherapy). Among 18 JXG patients (all survivors or lfu), 2 had localized, 4 generalized skin involvement, 2 bone, 3 CNS, 1 eye, 3 deep soft tissue, 2 skin/liver involvement, 2 mediastinal/tracheal compression. 5 patients received steroids/polychemotherapy. Two ECD patients were lfu. Three had histiocytic sarcoma (2 died despite polychemotherapy; one survived after polychemotherapy/BMT). One patient had Langerhans cell sarcoma (survivor after polychemotherapy). 1 had H syndrome. Non-LCH was undefined in 22 (4 deaths after different treatment attempts). One patient with ALK positive undefined non-LCH received Alectinib. Complete genetic workup was only performed in 9 patients; BRAF mutations were found in 3 patients (1 ECD, 1 XG, 1 undefined non-LCH); KRAS in 2 (1 RDD, 1 JXG); ALK in 2 (1 RDD, 1 undefined non-LCH). CONCLUSION: Rare histiocytoses represent a very heterogeneous disease spectrum. Appropriate consultation depends on international prospective data collection, which should be further propagated.
DIFFERENTIALLY EXPRESSED MICRONURNAS IN PLASMA AND LESION OF LANGERHANS CELL HISTIOCYTOSIS PATIENTS: POTENTIAL CORRELATION TO MAPK ACTIVATION

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LCH is an inflammatory myeloid neoplasia characterized by pathological CD207+ DCs with persistent mitogen-activated protein kinase (MAPK) pathway activation. In the past decade, non-coding RNAs - especially microRNAs (miRNAs) - have been identified as crucial regulators of various stages of tumorigenesis. miRNAs have been observed to regulate the ERK pathway at posttranscriptional level. Therefore, we investigated role of miRNAs in LCH disease pathogenesis. miRNA profiling was performed on plasma and lesion samples from LCH (n=10 and 8, respectively) and healthy controls (n=10 and 4, respectively) using NanoString platform. Principle component analysis (PCA) was performed to determine batch effects in plasma and lesion samples. Principal component analysis sequenced LCH samples from the control samples in each case. Out of the 139 and 38 differentially expressed miRNAs in plasma and lesion samples compared to respective controls, 22 were overlapping (12 up-regulated and 10 down-regulated in both lesion and plasma). The downregulated miRNAs significantly control selected pathways or target targets belonging to specific gene ontology (GO) categories. Target prediction of downregulated miRNAs using miRSystem showed that 81 of 272 genes involved in the KEGG MAPK signaling pathway are targets of the downregulated miRNAs, which might potentially contribute to MAPK pathway activation. EIF4G1 (encoding eukaryotic translation initiation factor 4G1) and MAZ1 (encoding MYC-associated zinc finger protein) were found to be common targets of three of the downregulated miRNAs, hsa-miR-33b-5p, hsa-miR-149-5p, and hsa-miR-4454. MAZ and MAPK pathway are known to mutually activate each other, resulting in activation of different pathways including matrix metalloproteinases (MMPs). Indeed, our previous gene expression analysis in LCH lesion CD207+ cells had shown upregulation of MMPs. Our results identify a unique microRNA expression profile characteristic of LCH which might be contributing to the MAPK pathway activation. The clinical and functional significance of differentially expressed miRNAs are currently being evaluated.

DIFFERENTIAL REGULATION OF LANGERIN EXPRESSION BY MONOCYTES AND CD1C+ DENDRITIC CELL SUBSETS

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PURPOSE: Following inflammation, resident Langerhans cells (LCs) emigrate and are replaced by waves of hematopoietic cells. Langerhans cell histiocytosis (LCH) cells are also potentially derived from related developmental pathways. We have previously shown that both monocytes and CD1c+ dendritic cells (DC) express langerin, under different conditions. Recently, CD1c+DC have been divided into two subsets with variable expression of DC and monocyte-related genes (DC2 and DC3, respectively).

METHODS: We examined the ability of flow-sorted CD14+Monocytes and CD1c+DCs to differentiate into LCs in response to GM-CSF+TGFb+Notch ligands. Input cells and langerin+ output were profiled by flow cytometry, electron microscopy, microarray and RNAseq to define different genetic expression and lineage-related features. Results: CD1c+DC were divided into BTLA+DC2 and BTLA-DC3. Upon exposure to GM-CSF+TGFb, the ability of CD1c+DC to express langerin, EpcAM and C-etherdin and to form Birbeck granules (BGs) segregated with expression of BTLA. CD14+Monocytes did not achieve high langerin expression under these conditions. Similar to monocytes, BTLA-DC3 did not express langerin with GM-CSF+TGFb. Exposure to notch ligands DLL1/4 increased langerin expression by monocytes and BTLA-DC3 to 60-70%. JAG1/2 did not cause appreciable langerin induction. Monocyte and DC3-derived LCs were indistinguishable by expression of EpcAM, C-etherdin and BG formation. Gene expression profiling showed expected upregulation of Langerin, CD1a, CD1c and EpcAM and loss of CD14 in both DC3 and monocyte-derived LCs. However, a strong lineage-specific signature remained in DC3-derived and monocyte-derived LCs defined by 275-419 differentially expressed genes. CONCLUSION: These results show that monocytes and BTLA+DC2 can both give rise to phenotypically close LCs while maintaining distinct gene expression programmes. Furthermore BTLA-DC3 behave like monocytes in relation to their requirements for in vitro LC formation. The data suggest that LC and LCH cells with distinct haematopoietic origins may be discernable by gene expression studies in vivo.

SUCCESSFUL SYSTEMATIC CENTRALISED TESTING FOR CIRCULATING MUTATED BRAFV600E IN UNITED KINGDOM LANGERHANS CELL HISTIOCYTOSIS PATIENTS TAKING PART IN INTERNATIONAL MULTICENTRE TREATMENT TRIAL

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PURPOSE: To enrol Langerhans Cell Histiocytosis IV (LCH-IV) trial patients in a parallel biology study to allow the systematic collection and analysis of tissue, blood and urine samples in a centralised laboratory. METHODS: LCH-IV trial participants are offered participation in the biology study and tissue, blood and urine samples in a centralised laboratory. METHODS: LCH-IV trial patients taking part in the biology study and consented. Blood and urine samples are collected at predetermined trial time points and sent by mail for next day delivery to a single laboratory. Peripheral blood mononuclear cells (PBMCs) are isolated from whole blood using ficoll density gradient centrifugation. DNA is extracted from PBMCs, plasma and urine using Qiagen DNA extraction kits. BRAFV600E is measured using a Taqman mutation detection assay. RESULTS: The parallel biology study is open in all 18 open LCH IV sites in the UK. 30/32(91%) Stratium [multisystem, isolated central nervous system(CNS) risk and multifocal bone], 1/1(100%) Stratium V[isolated tumorous and neurodegenerative CNS-LCH] and 5/25 (20%) Stratium V[observation of those not eligible for stratum I] patients were recruited. Blood samples at diagnosis were received and analysed in 35/36 (97%) of cases and compliance with follow up samples is >70%. Circulating mutated BRAFV600E was detected in 50% of cases. When paired testing was performed (15 cases), the median level of BRAF was 17 fold higher in plasma free DNA than in PBMC-derived DNA. Urine samples were only available in 50% of these cases. CONCLUSION: Systematic centralised testing for circulating mutated BRAFV600E from patients taking part in a multicentre treatment trial is feasible. The higher sensitivity of plasma cell-free DNA testing makes this the preferred screening test. Additional efforts are required to improve the recruitment of patients entering the observation arm of LCH-VI. Urine samples are less reliably submitted than blood samples but may provide an acceptable alternative to a blood sampling for patients entering the observation arm of LCH-VI.
THE IMPACT OF GASTRO-INTESTINAL INVOLVEMENT AT DIAGNOSIS ON OVERALL SURVIVAL IN PATIENTS WITH LANGERHANS CELL HISTIOCYTOSIS (LCH) - A RETROSPECTIVE ANALYSIS OF DAL-HX, LCH-I, LCH-II, AND LCH-III

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PURPOSE: LCH is a disease with wide range of clinical presentations and outcome. This retrospective analysis evaluates the impact of gastrointestinal involvement (GI-I) on overall survival. METHODS: As GI-I was restricted to patients with multi-system disease, the focus is on 1125 multi-system patients from DAL-HX (n=96), LCH-I (n=190), LCH-II (n=325) and LCH-III (n=514). RESULTS: The median follow-up was 5.2 years. 611 patients were males and 514 females. The median age at diagnosis was 1.5 years (0-18). At diagnosis, GI-I was present in 114 patients (10%), 64 of them were males and 50 females. The median age in this subgroup was 0.9 (0-14) years. GI-I was significantly more frequent in patients younger than 2 years at diagnosis: 90 of 702 patients (13%) below two years of age at diagnosis had GI-I versus 24 of 423 patients (6%) above two years of age (p<0.001). Furthermore, GI-I correlated with the involvement of risk organs (RO), i.e. liver, hematopoietic system and spleen. In patients without RO, GI-I was observed in 44 of 661 patients (6%) as compared to 70 of 464 patients (15%) with RO (p<0.001). Overall survival in patients without RO was excellent irrespective of GI-I: 5-year overall survival (OS) was 98% vs. 97% in patients with and without GI-I, respectively (p=0.789). In patients with RO, OS was 90% only and in this high-risk group, GI-I had a significant impact on survival: 5-year OS was 51% for 70 patients with GI-I as compared to 72% in 394 patients without GI-I (p<0.001). In a multivariable analysis (adjusted for participating country, study, RO, age, and lung involvement), GI-I was an independent prognostic factor with hazard ratios of 2.5 (95% CI: 1.6-3.7, p<0.001). CONCLUSION: In summary, additional risk-organ involvement, gastro-intestinal involvement was associated with poorer survival in MS-LCH.

CLINICAL CORRELATIONS OF PD-1 AND PD-L1 EXPRESSION IN PEDIATRIC LANGERHANS CELL HISTIOCYTOSIS (LCH)

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BACKGROUND: Programmed Cell Death-1 (PD-1) protein and its ligand PD-L1 are overexpressed in LCH, but their clinical significance is unknown. The availability of immune checkpoint inhibitors supports investigation into these proteins. We determined the expression of PD-1/PD-L1 in pediatric LCH, and their correlation with clinical features and BRAF-V600E status. METHODS: Single institution retrospective chart and pathology samples review. Samples were PD-L1+ if ≥2 intensity was observed in ≥5 % of LCH cells, while any PD-1+ lymphocytes was considered positive. BRAF-V600E protein was detected using immunohistochemistry. Event-free survival (EFS) was considered as absence of reactivations, death or late sequelae. RESULTS: 131 LCH samples were studied. Median age was 4 years (range, 1.6-8), M/F ratio was 1.5:1. Single-system LCH seen in 73%, multisystem 27%. Low-risk disease in 67% high-risk (RO+) in 13%. Six-week response evaluation showed slow early response (SER) in 34% (26%). Five-year EFS was 58%, OS 95% (median follow-up 5.3 years). Disease reactivation occurred in 28 (21.4%) at median 1.68 years; progressive disease occurred in 19. BRAF-V600E data (n=29) showed positive staining in 18 (62%). RO+ and SER were significantly higher in BRAF-V600E+ versus negative cases (44% vs. 6%, p=0.012) and (50% vs 9.1%, p=0.04) respectively, with reactivation in 9 (50%). Data on PD-1/PD-L1 expression (n=25) showed PD-1+ expression in 5 (20%), 2 were RO+, 1 had SER and significantly higher reactivation compared to negative cases (60% vs.25%, p=0.03). PD-L1 was positive in 16 (64%). 2 were RO+, 2 had SER and 5 (31%) reactivated. Late sequelae occurred in 8 (47%), 1 (20%) and 3 (19%) with BRAF-V600E+, PD-1+ and PD-L1+ respectively. CONCLUSIONS: PD-1+, PD-L1+ and BRAF-V600E+ immunophenotypes were associated with higher risk of reactivations and late sequelae. Immunostaining on 102 remaining samples is ongoing. Our results support investigation of immune checkpoint inhibitors in patients with refractory multisystem LCH.

SHORT-TERM EFFECTIVENESS AND SAFETY OF DABRAFENIB IN TREATMENT OF 18 CHINESE CHILDREN WITH BRAFV600E MUTATION-POSITIVE LANCERHANS CELL HISTIOCYTOSIS

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2 Laboratory of Hematologic Diseases, Beijing Pediatric Research Institute, Beijing Children’s Hospital, Capital Medical University, National Center for Children’s Health; Beijing Key Laboratory of Pediatric Hematology Oncology; Key Laboratory of Major Diseases in Children, Ministry of Education; National Key Discipline of Pediatrics, Ministry of Education, Beijing, China

PURPOSE: To investigate the short-term effectiveness and safety of dabrafenib in children with BRAFV600E mutation-positive Langerhans cell histiocytosis (LCH). METHODS: A retrospective analysis was performed on 18 children with BRAFV600E+ mutation-positive multisystem involved LCH (MS-LCH). The patients were treated with dabrafenib in our hospital from November 1, 2016 to November 30, 2018. RESULTS: The median age at onset of these patients was 1 year old (0.1-5.1 years old). The median age starting with dabrafenib was 2.3 years old (0.6-6.5 years old). The ratio of male to female was 13.5. The median follow-up time was 14 months (7-25 months). All the patients were treated with traditional chemotherapy for 0.5-17.8 months (the median duration of chemotherapy was 4.6 months) at the outset, then changed to targeted therapy due to poor control of the condition. The overall objective response rate (ORR) and the overall disease control rate (DCR) were 66.7% and 94.4%, respectively. There were 13 patients (72.2%) with risk organ (RO+) involvement, with overall ORR of 76.9% and DCR of 100%. All of the five patients associated with HLH got improvement. During the treatment, circulating cell-free BRAFV600E (cBRAFV600E) turned negative in 61.5% patients within the median time of 3.5 months. Grade 2 or 3 adverse effects occurred in 5 patients, while no grade 4 or above side effects occurred. CONCLUSION: The short-term efficacy of dabrafenib in BRAFV600E mutated LCH children is notable, especially for high risk patients with concomitant HLH. Dabrafenib can control the disease quickly and effectively. However, some patients with circulating cBRAFV600E positive persistently are prone to relapse. Monotherapy of dabrafenib has small adverse effects and high safety in the short term, but its long-term efficacy and safety still need further study.
The Histiocytes Society is offering an annual prize for the best clinical article at their Annual Meeting. It will be given in honor of Dr. Mark Nesbit, renowned pediatric oncologist, teacher, and supporter of the many families dealing with histiocytic disorders. The prize will be awarded to a physician or scientist who is carrying out clinical research to the therapy, biology or pathogenesis of one of the histiocytic disorders. The goal of the Award is to stimulate and promote the activities of clinical scientists from all around the world to study specific aspects of these puzzling diseases.

Dr. Mark Nesbit completed his medical training at George Washington Medical School in 1959. The remainder of his medical training was at the University of Minnesota where he specialized in pediatric hematology and oncology. In 1967 he joined the faculty at the University of Minnesota, achieving the rank of Professor of Pediatrics in 1973. Dr. Nesbit assumed the position of Director of the Division of Pediatric Hematology and Oncology at the University of Minnesota where he built one of the most productive and nationally recognized programs during his 14 year tenure. Professor Nesbit has been a leader in the development of clinical research for the treatment of leukemia and has a special interest in histiocytosis, bone tumors and the late complications of cancer survivors. In addition, Dr. Nesbit has helped countless young investigators with their careers in the field of pediatric hematology and oncology.

Of the contributions made by Professor Nesbit towards better understanding of the histiocytic disorders, we highlight the following three:

- Histiocytic disorders have been a continual interest from the onset of Professor Nesbit's career. His first publication was entitled: "Histiocytosis X".
- Dr. Nesbit played an important role in the organization of the Histiocyte Society. Besides his active input in the Epidemiology Study Group of the Histiocyte Society, he served on the Education Committee. His interest and initiative for increasing the activity and visibility of the Histiocyte Society has been an important part of the Society's evolution.
- Dr. Nesbit was a member and participant as a Board of Trustees member of the Histiocyte Society. His activities in the Association made him a national source of information on the diagnosis and treatment of histiocytosis. In 1990, Professor Nesbit received the Outstanding Investigator Award from the Histiocyte Association.

In conclusion, Dr. Nesbit has made substantial contributions to research in the field of histiocytosis. His dedication to the organization of interested investigators has resulted in a strong research agenda to better understand the etiology, diagnosis, treatment and long-term outcome of children with Langerhans cell histiocytosis. His compassion for patients and their families has always been evident, by his willingness to consult with both physicians and family members.

The Histiocytes Association and the Histiocyte Society thought it entirely compatible with the support and the work of Dr. Nesbit within the world of the histiocytes to offer this prize in his name. The candidates for the Nesbit Award need not be physicians, but the focus of the work should be on some aspect of the histiocytic disorders, be it in clinical medicine, allied pursuits such as nursing, psychology, social work, occupational therapy, etc.

Judgment will be based on a written abstract describing work done by the candidate him/herself. It is understood that the winning abstract may have co-authors, but that the first author must be the major contributor who is awarded the Nesbit Award. The Program Committee will provide time during the Annual Meeting for presentation of the winning paper. The decision by a special committee of the Histiocyte Society will be based on originality, completeness, scientific accuracy, and contribution to science. The prize will consist of $500 US and a certificate.

Dr. Christian Nezelof studied medicine in Paris, France during and after the Second World War. In 1948 he specialized in Pediatrics at the Hospital des Enfants Malades. In the early fifties, as a young pediatrician, he published the first clinical report on cystic fibrosis in France. In 1956 he worked in the Department of Pathology at the Sick Children Hospital in London under the direction of Professor Bodian, a famous British pathologist who first described cystic fibrosis in children. On returning to France he completed training in Pediatric Pathology. During the period of 1960-1968 Dr. Nezelof served as a full-time pathologist at Necker-Enfants Malades, where he became Chairman of the Department of Pathology in 1969. In parallel, from 1970, for 15 years he was Head of INSERM Research Unit and created the Groups of Pediatric Pathology located at the Necker-Enfants Malades Hospital.

The many contributions by Dr. Nezelof include:

- Dr. Nezelof contributed significantly to the development of Pediatric Pathology as a subspecialty by creating a network of various specialties and also trained many clinicians and foreign pathologists. He has served as a consultant for the world of histiocytosis, always giving a friendly and illuminating answer to anyone's questions.
- In 1960, Dr. Nezelof played a key role in describing a clinical condition of immunodeficiency in childhood, in which the existence of a "split" in the human lymphoid system toward T and B-cells was recognized. An immune-deficient child was described as afflicted by a thymic hypoplasia, but with normal level of immunoglobulins ("Lympho-cytopenie avec normogamma-globulinemie"). In the pediatric literature this condition became known as Nezelof's syndrome.
- In the field of histiocytosis, his seminal contribution was that Letterer-Siwe, Hand-Schuller-Christian and eosinophilic granuloma are linked to the same cell, having a common ultrastructural marker designated as the Langerhans body (Birbeck granule). In his paper "Histiocytose X: Histiogenetic arguments for Langerhans cell origin", he noted the dendritic lineage of this disease. Not long afterwards the term Langerhans cell histiocytosis was introduced.

Histiocytic disorders continue to be one of his major fields of interest. In 1982 Dr. Nezelof described the successful growth in nude mice of a tumor after injection of cells from the pleural effusion of a child with malignant histiocytosis. After this manuscript entitled: "Tumor cell line characterization of a malignant histiocytosis transplanted into nude mice" his team has described successful establishment in vitro of the Malignant Histiocytosis DEL cell line.

The Society thought it entirely consistent with Dr. Nezelof's great interest in new developments of basic pathophysiology, bridged with his key-role in supporting others that this prize be given in his honor. The awardee need not be a physician, but the focus of the work should be on some aspect of the pathophysiology of the histiocytic disorders.

Judgment will be based on a written abstract describing work done by the candidate him/herself. It is understood that the winning abstract may have co-authors, but that the first author must be the leader of the project and the one who is awarded the Nezelof Award. The Program Committee will provide time during the Annual Meeting for presentation of the winning paper. The decision by a special committee of the Histiocyte Society will be based on originality, completeness, scientific accuracy, and contribution to science. The prize will consist of $500 US and a certificate.
The Histiocyte Society is offering an annual prize for the best poster presented at the Annual Meeting. It will be given in honor of Dr. Robert J. Arceci, world-renowned pediatric oncologist, scientist and teacher with invaluable contributions to the field of histiocytoses.

Dr. Arceci completed his undergraduate studies at Trinity College, received his Ph.D. and M.D. from the University of Rochester, and then completed his Residency in Pediatrics and Fellowship in Pediatric Hematology/Oncology at Boston Children’s Hospital and Harvard Medical School. Following faculty appointments at Harvard Medical School, Dana-Farber Cancer Institute and Boston Children’s Hospital, he became Director of Pediatric Hematology/Oncology at Cincinnati Children’s Hospital Medical Center. In 2000, Dr. Arceci became Director and King Fahd Professor of Pediatric Oncology and Professor of Oncology and Pediatrics at the Johns Hopkins University School of Medicine where he worked until 2012.

In late 2012, Dr. Arceci joined Phoenix Children’s Hospital as Co-Director of the Ronald A. Matricaria Institute of Molecular Medicine and held the dual role of Division Chief for the Center for Cancer and Blood Disorders at Phoenix Children’s Hospital. He also served as a professor of Pediatrics at the University of Arizona College of Medicine-Phoenix, Department of Child Health.

Dr. Arceci was a member of numerous scientific and medical societies, advisory committees and review boards, and has been the recipient of several prestigious honors and awards. He has served on a variety of committees in the Pediatric Oncology Group, the Children’s Cancer Group and the Children’s Oncology Group, including Chairperson for the Myeloid Leukemia Committee and Vice-Chair of the Biology and Therapeutics Translational Committee. Dr. Arceci was Editor-in-Chief of Pediatric Blood and Cancer and previously served as Editor-in-Chief of the Journal of Pediatric Hematology/Oncology and Associate editor of the Journal of Pediatrics. In addition to these leadership roles, Dr. Arceci was an excellent clinician, known both nationally and internationally. He was considered one of the world’s experts on histiocytic disorders and pediatric acute myelocytic leukemia (AML).

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Dr. Arceci was an active member of the Histiocyte Society for many years and a beloved colleague, friend and mentor. In addition, he played an integral role as the Chairman of the Nikolas Symposium to promote translational research in Langerhans cell histiocytosis.

The prize will be awarded to (1) poster presenter whose poster demonstrates an exceptional level of science and relevance to the histiocytic disorders and is presented in a clear, original and organized manner.

The abstracts selected for poster presentations which receive one of the top ten scores will be recognized as finalists for consideration for this award. Final selection of the award winner will be made through a separate round of grading to occur during the Poster Presentation Session at the Annual Meeting. Only those poster presenters in attendance of this session will be considered eligible for the award.

It is understood that the winning poster may have co-authors, but that the first author must be the leader of the project and the one who is awarded the Robert J. Arceci Award for Best Poster. The decision by a special committee of the Histiocyte Society will be based on scientific content, originality, relevance and organization of presentation. The prize will consist of $250 US Dollars and a certificate. This award will be presented during the Closing Ceremonies of the Annual Meeting.
HISTIOCYTE SOCIETY GOVERNING BY-LAWS

The Society shall be governed and guided by the principles set forth in these By-Laws.

ARTICLE I
OFFICES, REGISTERED OFFICE, AND REGISTERED AGENT

Section 1. Offices. The principal office of Histioyte Society, Inc. (the "Corporation") shall be located within or without the State of New Jersey, at such place as the Board (as defined below), in its sole discretion, shall from time to time designate. The Corporation may also maintain additional offices at such other places as the Board may from time to time designate.

Section 2. Registered Office and Registered Agent. The Corporation shall have and continuously maintain a registered office and a registered agent in the State of New Jersey, as required by the New Jersey Nonprofit Corporation Act (the "Act"). The registered agent shall be either an individual resident of the State of New Jersey or a corporation authorized to transact business in the State of New Jersey, in accordance with the Act.

ARTICLE II
PURPOSES AND MISSION

Section 1. Purposes. The purposes for which the Corporation is formed are as set forth in the Corporation's Certificate of Incorporation (the "Certificate of Incorporation").

Section 2. Mission. The mission of the Corporation is to: (i) improve the state of knowledge of the histiocytic disorders and improve the welfare of patients with these disorders; (ii) promote, facilitate, and carry out research in histiocytic disorders; (iii) facilitate and provide a forum for health care professionals for effective communication concerning these aims; (iv) promote education and to educate physicians, scientists, and others in matters related to the histiocytic disorders; (v) advise lay organizations in educational and other matters concerning the histiocytic disorders; and (vi) collaborate with organizations that have common goals.

ARTICLE III
MEMBERSHIP

Section 1. Classes. The Corporation shall have three (3) classes of members: (i) ordinary members (the "Ordinary Members"); (ii) honored members (the "Honored Members"); and (iii) emeritus members (the "Emeritus Members").

A. Ordinary Members. Ordinary Members shall be health care professionals who are active in patient care, education or research in the histiocytic disorders. Ordinary Members pay dues, may participate in all activities of the Corporation, and hold office.

B. Honored Members. Honored Members are distinguished individuals, who, in the view of the Board, have made extraordinary contributions to the Corporation. Honored Members enjoy all the rights and privileges of Ordinary Members, but do not pay dues and may not hold office.

C. Emeritus Members. Emeritus Members are Ordinary Members who have retired from active involvement in the field. Emeritus Members enjoy all rights and privileges of Ordinary Members, but do not pay dues and may not hold office.

Section 2. Qualifications. The Board shall determine, in its sole discretion, the qualifications, dues, terms, and other conditions of each class of member.

Section 3. Voting Rights. All members shall have the right to vote on the following matters: (i) election of the Board and officers; (ii) election of members of the Education and Scientific Committees and other committees as deemed appropriate by the Board; (iii) approval of the annual budget proposed by the Board; (iv) approval of any amendments to these Amended and Restated Bylaws (these "Bylaws"); and (v) other issues as the Board may choose to bring before the members. Voting on all other matters is expressly reserved for the Board.

Section 4. Member Meetings. There shall be an annual meeting of the members upon such date, time, and place as the Board shall determine. Special meetings of the members may be called by the President or upon the request of a majority of the voting members.

Section 5. Notice. Members shall receive not less than thirty (30) nor more than sixty (60) calendar days prior written notice of all member meetings. Notice shall be given in the manner specified in Article VIII of these Bylaws. The purpose for which a special meeting is called shall be stated in the notice. Any member may waive notice of any meeting by a written (including electronic) statement, either before or after the meeting. Notwithstanding the foregoing, attendance and participation at a meeting without objection to notice shall constitute a waiver of notice.

Section 6. Quorum and Voting. Each voting member shall have one vote on each voting matter. A quorum shall consist of at least ten percent (10%) of the total voting members. A majority of the votes cast on each voting matter at which a quorum exists shall constitute a valid action of the members.

Section 7. Removal. Any member may be removed from membership by a majority vote of the Board only: (i) for cause, which is defined as failure to pay dues for three (3) consecutive years; or (ii) other causes as determined by the Board in its sole discretion. The Board shall be the sole judge of moral, ethical, and professional qualifications required for election to or termination of membership.

Section 8. Action by Written Consent. Except as otherwise expressly prohibited by the Act, applicable law, the Certificate of Incorporation or these Bylaws, any action required or permitted to be taken at a meeting of the members (other than the biennial election of Board members), may be taken without a meeting upon the written consent of members who would have been entitled to cast the minimum number of votes which would be necessary to authorize the action at a meeting at which all members entitled to vote thereon were present and voting; provided, that: (i) the Corporation provides to all other members advance notice of the proposed action; (ii) the proposed action is not consummated before the expiration of ten (10) days from the giving of the notice; (iii) the notice is given to all members entitled to vote thereon at least ten (10) days before the meeting; and (iv) the notice is given to the Corporation at least ten (10) days before the meeting.

ARTICLE IV
BOARD OF TRUSTEES

Section 1. Powers. There shall be a Board of Trustees of the Corporation (the "Board"), which shall supervise and control the business, property, and affairs of the Corporation, except as otherwise expressly provided by the Act, applicable law, the Certificate of Incorporation, or these Bylaws. All members of the Board shall serve without financial compensation.

Section 2. Number and Qualifications. The Board of the Corporation shall be composed of no less than five (5) and no more than nine (9) individuals. The number of Board members may be decreased (but in no event to fewer than three (3) members), however, no decrease shall have the effect of shortening the term of any incumbent member of the Board.

Section 3. Composition. The Board shall consist of those individuals then serving as the President, the President-Elect, the Past President, the Secretary, the Treasurer, and two Members-at-Large.

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ARTICLE V
OFFICERS

Section 1. Officers. The officers of the Corporation shall consist of: (i) president (the "President"); (ii) president-elect (the "President-Elect"), whenever this office is occupied in accordance with Section 1.B of this Article V below; (iii) immediate past-president (the "Past-President"), when this office is occupied in accordance with Section 1.C of this Article V below; (iv) secretary (the "Secretary"); (v) treasurer (the "Treasurer"); and (vi) two (2) members-at-large (each, a "Member-at-Large" and together, the "Members-at-Large"). The Corporation shall have such other assistant officers as the Board may deem necessary in its sole discretion, and such officers shall have such authority as prescribed by the Board. One person may hold more than one office.

A. President. The President shall give active direction and have control of the business and affairs of the Corporation for a 3-year term. The President may be elected for no more than two terms, provided, however, that such terms shall not be consecutive. The President may sign contracts and other instruments, which the Board has authorized to be executed, and shall perform all duties incident to the office of President, as may be prescribed by the Board.

B. President-Elect. The President-Elect is an officer of the Corporation and assumes the office of President two (2) years following such individual’s appointment as President-Elect. If for any reason, as determined by the Board, the President is unable to carry out the duties of such office, the President-Elect shall assume the office of President for the remainder of the President’s term. The President-Elect shall be elected by the voting members of the Corporation at the time of the annual meeting of the members that occurs one year following the annual meeting of the members that elected the President. For the avoidance of doubt, the President-Elect shall remain vacant during the term that the Past-President serves in office.

C. Past-President. After serving one full term as President, such individual becomes the Past-President and remains an officer of the Board for one year immediately thereafter.

D. Secretary. The Secretary shall keep or cause to be kept the minutes of all meetings of the Board and shall perform such other duties and possess such other powers as are incident to the office of Secretary or as shall be assigned to such individual by the President or the Board. The Secretary serves a two year term with two additional terms permitted by re-election.

E. Treasurer. The Treasurer shall, subject to oversight by the Board, maintain general supervision over the financial affairs of the Corporation and shall cause to be kept accurate books of account. The Treasurer shall oversee the disbursement of funds of the Corporation and shall from time to time, or upon request from the Board, account for all the transactions undertaken as Treasurer, and of the financial condition of the Corporation. The Treasurer serves a two year term with two additional terms permitted by re-election.

F. Members-at-Large. Each Member-at-Large shall assist the other Board members in the conduct of their duties as directed by the President or by consensus of the Board. Candidates for a Member-at-Large position shall be ordinary members who have not served on the Board for at least two years prior to assuming a term as a Member-at-Large. The Members-at-Large shall each serve a three year term with one additional term permitted by re-election.

Section 2. Election of Officers. The President-Elect, Secretary, Treasurer, and Members-at-Large shall be elected, as the case may be, by the voting members of the Corporation at an annual meeting of the members in
accordance with the applicable term structures set forth in Section 1 of this Article V.

Section 3. Term of Office. Each officer of the Corporation shall be installed at the annual meeting of members at which they are elected, and shall hold office for terms as set forth in Section 1 of this Article V, or until their respective successors shall have been duly elected and qualified, or their earlier removal, resignation or death.

Section 4. Resignation and Removal. Any officer may resign at any time by giving written notice to the President. Such resignation shall take effect at the time specified therein, or, if no time is specified, at the time of acceptance thereof as determined by the President. An officer may be removed with cause by vote of a two-thirds majority of the Board at a duly held meeting with a quorum present.

Section 5. Vacancies. Vacancies shall be filled by a majority vote of the Board.

ARTICLE VI
COMMITTEES

Standing Committees. Standing Committees include the: (i) nominating committee (the "Nominating Committee"); (ii) program committee (the "Program Committee"); (iii) scientific committee (the "Scientific Committee"); (iv) education committee (the "Education Committee"); and (v) disease steering committee (the "Disease Steering Committee"). The Board in its sole discretion may create other committees on an ad-hoc basis.

A. Nominating Committee. The Nominating Committee shall be composed of the President, President-Elect, Past-President, Secretary, and Treasurer, and shall be responsible for providing the Board with candidates for office, membership, and standing committees, as requested by the Board from time to time.

B. Program Committee. The Program Committee shall be composed of the President, Secretary, Chairperson of the Education Committee, Chairperson of the Scientific Committee, the Secretariat, and additional members chosen from among the members of the Corporation (as determined by the Board, in its sole discretion). The President shall act as Chairperson of the Program Committee. The Program Committee shall be responsible for planning, organizing, and executing the annual meeting of members and for presenting the program materials to the Board prior to Board approval. The Program Committee may, in its sole discretion, solicit assistance from others, who may or may not be members of the Corporation.

C. Scientific Committee. The Scientific Committee shall be composed of no less than five (5) and no more than nine (9) Ordinary Members. The Scientific Committee shall review proposals for research and related activities according to guidelines developed by the Board, make recommendations to the Board, and present the Board with annual reports and plans concerning the Corporation’s research activities. Members of the Scientific Committee will be elected by voting members of the Corporation at the time of the annual meeting. Members of the Scientific Committee will serve two (2) year terms and may serve up to six (6) consecutive years if re-elected. The Scientific Committee will select its own chairperson within ten (10) days of the close of the annual meeting.

D. Education Committee. The Education Committee shall be composed of no less than five (5) and no more than nine (9) Ordinary Members. The Education Committee will oversee the educational activities of the Corporation, and review and score the abstracts to be presented at the annual meeting of members. The Education Committee will also present the Board with annual reports and plans concerning the Corporation’s educational activities. Members of the Education Committee will be elected by voting members of the Corporation at the time of the annual meeting of the member.

Members will serve two (2) year terms and may serve up to six (6) consecutive years if re-elected. The Education Committee will select its own chairperson within ten (10) days of the close of the annual meeting.

E. Disease Steering Committees. The Disease Steering Committees shall oversee the scientific agenda for their respective diseases and will present the Board with annual reports and plans concerning the research and educational activities for those diseases. Members of the Disease Steering Committees will be appointed by the Board, per standard operating procedures as defined by the Board.

Committees and Task Forces. The Board may create and appoint members to such other committees and task forces, as it shall deem appropriate in its sole discretion. Such committees and task forces shall have the power and duties designated by the Board, and shall give advice and make recommendations to the Board.

Section 3. Vacancies. Temporary vacancies in the membership of committees may be filled by the Board until the time of an annual meeting and election as specified above.

Section 4. Rules. Each committee and task force may adopt rules for its meetings not inconsistent with the Act, applicable law, the Certificate of Incorporation, these Bylaws or any rules adopted by the Board.

ARTICLE VII
AGENTS

Section 1. Agents. The Board may appoint agents, such as a secretariat (the "Secretariat"), with such powers and to perform such acts and duties on behalf of the Corporation, as the Board may determine from time to time, in its sole discretion.

ARTICLE VIII
MISCELLANEOUS PROVISIONS

Section 1. Fiscal Year. The fiscal year of the Corporation shall be the calendar year.

Section 2. Notice Procedures. Whenever under the provisions of these Bylaws notice is required to be given to a Board member, officer, committee member or member, such notice shall be given in writing by first-class mail or overnight delivery service with postage prepaid to such individual at such individual’s address as it appears on the records of the Corporation. Such notice shall be deemed to have been given when deposited in the mail or the delivery service. Alternatively, notice may also be given by facsimile, electronic mail, or hand delivery, and will be deemed given when received.

ARTICLE IX
INDEMNIFICATION

Section 1. Indemnification Generally. Unless otherwise prohibited by the Act or applicable law, the Corporation may indemnify any current or former Board member or officer, and may by resolution of the Board indemnify any agent, against any and all expenses and liabilities incurred by such individual in connection with any claim, action, suit or proceeding to which such individual is made a party by reason of being a Board member, officer or agent. However, there shall be no indemnification in relation to matters as to which such individual shall be adjudged to be guilty of a criminal offense or liable to the Corporation for damages arising out of such individual’s own gross negligence in the performance of a duty to the Corporation. Amounts paid in indemnification of expenses and liabilities may include, but shall not be limited to, counsel fees and other fees, costs and disbursements, and judgments, fines, and penalties against, and amounts paid in settlement by, such Board member, officer or agent. The Corporation may advance
expenses or, where appropriate, may itself undertake the defense of any
officer or agent. However, such officer or agent shall repay such expenses if it
should be ultimately determined that such individual is not entitled to
indemnification under this Article IX.

Section 2. Insurance. The Board may also authorize the purchase of
insurance on behalf of any Board member, officer or other agent, against any
liability incurred by such individual which arises out of such individual’s status
as a Board member, officer or agent, whether or not the Corporation would
have the power to indemnify the person against that liability under the law.

ARTICLE X
DISTRIBUTION OF ASSETS UPON DISSOLUTION

Section 1. Distribution of Assets Upon Liquidation. In the event of the
liquidation or dissolution of the Corporation, after payment of all debts, all
remaining assets shall be distributed only as permitted by the Act, applicable
law, and the Certificate of Incorporation.

ARTICLE XI
AMENDMENTS TO BYLAWS

Section 1. Amendments to Bylaws. These Bylaws may be amended (or
new bylaws adopted) upon the affirmative vote of a majority of the voting
members; provided, that the proposed changes have been approved by the
Board, and circulated to the voting members not less than thirty (30) nor more
than sixty (60) calendar days prior to such vote to approve same.

HISTIOCYTE SOCIETY CONSTITUTION

Article I: Name
The name of the society shall be the “Histiocyte Society”. This is a non-profit organization duly registered in the United States of America.

Article II: Aims
1. To improve the state of knowledge of the histiocytic disorders and the welfare of patients with these disorders and their families.
2. To promote, facilitate and carry out research in histiocytic disorders.
3. To facilitate and provide a forum for health professionals for effective communication concerning these aims.
4. To promote education and to educate physicians, nurses, other health professionals, scientists, legislators, and other lay persons in matters related to the histiocytic disorders.
5. To advise lay organizations in educational and other matters concerning histiocytic disorders.
6. To collaborate with other organizations with common aims.

Article III: Amendments and Revisions
1. Changes may be made by an affirmative vote of two-thirds (2/3) of a quorum at a general meeting of the Society, provided proposed changes have been
submitted to and approved by the Board and circulated among the members at least one (1) month prior to the general meeting.
2. Proposed changes may originate with any ordinary member of the Society. They should be submitted to the Secretary at least two (2) months prior to the
general meeting.
3. Changes properly proposed to the Board will be presented at the next general meeting with the recommendation of the Board.

Article IV: Dissolution
1. Dissolution shall be proposed, processed, and voted on as for amendments and revisions, Article III.
2. In a case of dissolution of the Society, any funds remaining after payment of all outstanding debts will be donated to one or more organizations, with aims and
objectives consonant with those of the Society, to be selected by the Board.
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