Young Investigator Award Criteria

Young Investigator Award in Pediatric Hematology/Oncology

Presented by the American Society of Pediatric Hematology/Oncology

The ASPHO Young Investigator Award was established in 1989 to formally recognize excellence in research in pediatric hematology and oncology.

The qualifications for the award candidates are as follows:

- Must have **completed** a standard 3-year fellowship in pediatric hematology-oncology at the time of application
- Less than 4 years have elapsed since the completion of the standard 3-year pediatric hematology-oncology fellowship at the time of application
- The individual has conducted high-quality clinical or laboratory research on a project (described in the abstract) in which he or she participated actively in the design, conduct, and data analysis
- The candidate is committed to a career that includes clinical and/or laboratory investigation in pediatric hematology-oncology
- A member of ASPHO

To apply, please include the following:

- An abstract submitted with the young investigator designated as the **first** author
- The candidate's curriculum vitae
- A one-to-two page statement of career goals
- A supporting letter from the training program director or clinical or laboratory mentor attesting to the fact that the Young Investigator Award nominee has played a major role in the conduct of the research project, and confirming the candidate's promise as a young investigator in pediatric hematology-oncology

Winners are chosen by evaluation of abstracts submitted for presentation at the ASPHO Conference, together with review of each candidate's other research contributions and application materials. The award consists of $1,000 and a certificate.

Note:

- Abstract must be submitted by January 8, 2019 at 4 pm ET
- All award application materials must be received no later than January 8, 2019 at 4 pm ET.
- If successful, will present from the podium his or her paper at the 2019 ASPHO Conference in New Orleans, LA

To be considered for the award:

- Carefully review the criteria for the award to determine eligibility
- Complete the Appropriate Award Application Form
- Include all required supplemental materials to make your award application complete

Information about Awards:

- Only abstracts accepted for presentation will be considered for awards
- Each of these awards will be presented during the 2019 ASPHO Conference in New Orleans, LA

PERIPHERAL BLOOD MINIMAL RESIDUAL DISEASE IN CHILDHOOD B-PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA

Authors: Seham Gohar, Iman Sidhom, Nesreen Ali, Sonia Ahmed, Amr El Nashar, Magda Assem, Iman Attia, Dina Yassin, Sherine Salem, Sonya Soliman, Sarah Youssef, Khaled Shaaban

Background: Minimal residual disease (MRD) in childhood acute lymphoblastic leukemia (ALL) during the early stages of therapy may have significant impact on outcome.

Objective: To study the prognostic significance of MRD by flow-cytometry in peripheral blood (PB) after 1 week of multiagent induction treatment in childhood B-precursor ALL.

Design/Method: This study included 359 newly diagnosed pediatric B-precursor ALL patients treated at the Children's Cancer Hospital-Egypt. Patients were risk stratified and received risk directed therapy according to the total study XV protocol adopted from St. Jude Children Research Hospital.
PB-MRD was measured by flow-cytometry on day 8 in 128 patients and on day 12 in 231 patients as they received 4 days of prednisone pre-phase.

Results: The median follow-up of patients who are alive in complete remission was 54.8 months (range, 32 to 85).

The 5-year event free survival (EFS) and relapse free survival (RFS) of all patients with day 8 or day 12 PB-MRD <0.01% was 89.3±3% and 92.9±2.7% respectively (n=126); 83.1±3.8% and 87.3±3.5% for MRD 0.01-<0.1%, respectively (n=104); 70.4±4.2% and 78.7±4% for MRD ≥0.1%, respectively (n= 129). (p=0.001, and p=0.007, respectively).

For provisional low risk (LR) patients, the 5-year EFS and RFS was 92.7±3% and 94.5±2.8%; respectively for PB-MRD <0.01% (n=101), 83±4.3% and 87.5±3.9%; respectively for PB-MRD 0.01 -<0.1% (n=79), on the other hand it was 72.3±4.9% and 79.6±4.6%; respectively for PB-MRD ≥0.1% (n=91), (p=0.001 and p=0.007, respectively).

Provisional LR patients with ETV6-RUNX1 or hyperdiploid (DNA index ≥1.16) and PB-MRD <0.01% had 5-year EFS 96.4±2.6% (n=75) compared to 82.6±8.2% for other provisional LR with PB-MRD <0.01% but lacking favorable cytogenetic features (n=26) (p=0.021).

Conclusion: Early induction PB-MRD by flow-cytometry constitutes an early prognostic index for children with B-Precursor ALL and can help in identification of a subgroup of patients provisionally classified as low-risk ALL with either favorable DNA index or ETV6-RUNX1 having an excellent outcome that can be cured with limited therapy.

OUTCOME OF LIVER INVOLVEMENT IN PEDIATRIC LANGERHANS CELL HISTIOCYTOSIS

Authors: Seham Gohar, Mohamed Sedky, Nesreen Ali, Iman Zaky, Asmaa Salama, Hala Reda, Omayma Hassanain, Alaa EL Hadad

Background: Liver involvement in pediatric Langerhans' cell histiocytosis (LCH) usually presents as a part of a disseminated disease, its frequency is known to be high and is associated with adverse outcomes.

Objective: To assess the frequency and outcome of liver involvement in pediatric LCH.

Design/Method: A Retrospective study included 52 pediatric LCH patients with liver involvement. All patients treated at the Children's Cancer Hospital-Egypt during the 10 years period 2007 - 2017.
Patients from 2007 to 2011 were received therapy according to LCH-III protocol, while patients from 2012 to 2017 were treated according to LCH-IV protocol.
Liver involvement was determined by the following: unexplained liver enlargement more than 3 cm below the costal margin and/or dysfunction (Hypoalbuminemia, hyperbilirubinemia, hypoprothrombinemia and/or increased liver enzymes).

Results: Of 117 children with multisystem LCH, 52(44.4%) had liver involvement. The median follow-up of patients with liver involvement was 44 months (range, 2 to 131).

Of 52 studied patients, 30(57.6%) patients had hepatomegaly without disturbed liver function, 21(40.4%) patients had hepatomegaly with liver dysfunction, and one patient (2%) `had average-sized liver with disturbed function.

The 5-year overall survival (OS) and event free survival (EFS) of all patients with liver involvement was 65% and 38.5% respectively.
For patients with liver dysfunction (n=22), the 1-year OS and EFS was 63.3% and 35.8% respectively compared to 96.7% and 86.7% respectively for those with hepatomegaly (n=30). (P<.001, and P=.001 respectively).

At end of induction, disease progression was seen in 13/22 patients (59%) with liver dysfunction, of them 10/13 patients (77%) died, and in 4/30 patients (13%) with hepatomegaly, of them only one patient (25%) died.

Conclusion: Though Liver is considered as a high -risk organ in management of LCH , patients with disturbed liver functions tend to have a refractory disease and dismal outcome compared to those with hepatomegaly alone. Further studies are recommended to confirm this poor outcome and hence, this group of patients might benefit from upfront different therapeutic planning.

Recommendation Letter

I had the opportunity to work closely with Dr. Seham Gohar for 5 years during her work at the children's Cancer Hospital in Egypt. Seham is a dedicated hard work physician committed to her patients, and their wellbeing.

She is a very good Team player, with good relations with her superiors and her colleagues. She uses her initiative, to take on more than her share of tasks.

She always gives a chance for young generations to participate in active learning and patients rounds encouraging them to participate actively and discuss freely their opinion in an environment of free expression of ideas.

It was a great pleasure to work with her as any cooperation between us was always praised by higher management.

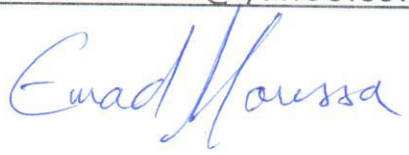
I highly recommend her to be nominated as an investigator in Pediatric Hematology /Oncology field.

Prof Dr. Emad A.H. Moussa

Consultant, Pediatric Hem/Onc.

The Children's Cancer Hospital EGYPT.

Mail: moussaemad1960@yahoo.co.uk

Signature: 

My name is Seham Hassan Gohar, I get my Master degree and M.D. in pediatric oncology .

I'm a consultant of pediatric oncology at Children Cancer Hospital – Egypt.

Since I join pediatric oncology department I decided to work hard, and take high care of those sick children who fight cancer.

I'm a member of acute lymphoblastic leukemia, and Langerhans Cell histiocytosis study teams in our hospital, within these study teams, we try to investigate our survival rate, and doing research aiming to improve our outcome

My goal is to continue research in pediatric oncology field for proper, updating management, and improve childhood cancer survival outcome comparable to the developed countries outcome.

Childhood without cancer is the goal of me and of my institution, this why medical research is encouraged in children cancer Hospital of Egypt.

CURRICULUM VITAE

PERSONAL DETAILS:

Name:	**Seham Mohamed Mahmoud Gohar** ***MB.BCh, MSc.***
Home Address:	8055, EL Ashgar St. Mokattam Cairo, Egypt.
Telephone:	**Mobile: (+) 201001776398**
E-mail:	Seham.m.gohar@57357.com

QUALIFICATIONS:

December 2002:	M.B., B.Ch. (Bachelor degree in Medicine and Surgery), Faculty of Medicine, Ain Shams University, Egypt. Signed up "Good"
May 2006:	Clinical Master Degree in Paediatrics, Faculty of Medicine, Ain Shams University, Egypt. Signed up "Good". Master Degree Thesis on Pediatric Hematology/Oncology & was titled "Clinico-epidemiological study and outcome of childhood primary brain tumors".
2015	M.D degree 1n Pediatric Hematology/Oncology, National Cancer Institute/ Cairo University, Egypt.

PUBLISHED WORK:

1- **Safinaz A. Elhabashy; E.M. Eid; A.M.Abd- Elmonem and Seham M Mahmoud. (2006):**

Demographic features and predictors of survival among children with brain tumors (Single Institution Experience). Egyptian journal of paediatrics; 23(4):537-550.

2- **Nesreen Ali, Seham Gohar, Iman Zaky, Ahmed El Ghoneimy , sarah Youssef, Gehad sameer, Dina Yassin, Sherine Salem, Hadeel Magdi, Iman Sidhom.(2018).**

Osteonecrosis in children with lymphoblastic leukemia: A report from children cancer hospital in Egypt. Pediatr Blood Cancer ;66(1):e27440.

3- **Dina ElHarouni, Dina Yassin, Nesreen Ali, Seham Gohar, Iman Zaky, Hassan Adwan and Iman Sidhom.(2018).** A Pharmacogenetic Study of VDR fok1 and TYMS Polymorphisms and Their Association With Glucocorticoid-Induced Osteonecrosis in Egyptian Children with Acute Lymphoblastic Leukemia. Front. doi: 10.3389/fonc.2018.00541.

CURRENT POSITION:

Pediatric Hematology/Oncology consultant- Children's Cancer Hospital of Egypt 57357.

A member of Acute lymphoblastic leukemia , and histiocytosis disorder study team- Children's Cancer Hospital of Egypt.

Employment History:

2007- 2012	Pediatric Hematology/Oncology Registrar- Children's Cancer Hospital Egypt 57357.
2012-2015	Pediatric Hematology/Oncology Assistant consultant - Children's Cancer Hospital of Egypt 57357.
2015 till now	Pediatric Hematology/Oncology consultant - Children's Cancer Hospital of Egypt 57357.

CONFERENCES AND MEETINGS ATTENDED:

Training course and workshop of pediatric solid tumors management (Ain Shams university-May2007).

Breaking New Frontiers in Pediatric Oncology(Children's Cancer Hospital Egypt -Scientific Conference – July 2009).

EASO (Euro- Arab School of Oncology) course on pediatric oncology (Children's Cancer Hospital Egypt -Scientific Conference –May 2013).

48th congress of the international society of pediatric oncology (SIOP), Dublin – Irland , October 19-22 ,2016.

EHA-SWG Scientific Meeting on New Molecular Insights and Innovative Management Approaches for Acute Lymphoblastic Leukemia, **Barcelona, Spain, April 12-14, 2018**

NELARABINE ABROGATES RELAPSE RATES IN CNS-3 T-ALL: A REPORT FROM CHILDREN'S ONCOLOGY GROUP AALL0434

Authors: Nathan Gossai, Stuart Winter, Meenakshi Devidas, Brent Wood, Patrick Zweidler-McKay, Karen Rabin, Mignon Loh, Elizabeth Raetz, Naomi Winick, Michael Burke, William Carroll, Natia Esiashvili, Nyla Heerema, Andrew Carroll, Stephen Hunger, Kimberly Dunsmore, David Teachey

Background: AALL0434 included a 2 x 2 pseudo-factorial randomization using an augmented BFM regimen. Patients were randomized to receive escalating dose Capizzi methotrexate plus pegaspargase (CMTX) or High Dose MTX (HDMTX) and intermediate (IR) and high-risk (HR) patients were randomized to receive or not receive six 5-day nelarabine (Nel) courses. IR/HR CNS1/CNS2 patients received 1200 cGy cranial radiation (CRT). CNS3 patients received 1800 cGy CRT, were non-randomly assigned to HDMTX arms and took part in the Nel randomization. Low-risk patients received no CRT and did not participate in the Nel randomization. We have reported that both CMTX and Nel improved event-free survival (EFS).

Objective: To assess outcomes of AALL0434 T-ALL patients based on CNS status at diagnosis.

Design/Method: A review of T-ALL patients enrolled on AALL0434 was performed. CNS status was assigned at diagnosis using microscopy and/or clinical features.

Results: From 2007-2014, 1550 T-ALL patients were enrolled and evaluable for analyses, including 1128 (72.8%) CNS1, 306 (19.7%) CNS2 and 116 (7.5%) CNS3. Five-year EFS rates for CNS1, 2, and 3 were 85.2%, 83.1%, and 71.4% respectively (p=0.0007) and overall survival (OS) rates were 90.4%, 89.2%, and 83.1% (p=0.0438). Five-year disease free survival (DFS) rates for Arm C (HDMTX without Nel) differed by CNS status: CNS1 87.2%, CNS2 80.0%, and CNS3 70.2% (p=0.0006), but 5-year DFS for Arm D (HDMTX+Nel) showed no statistically significant differences in outcome based on CNS status (p=0.35): CNS1 85.1%, CNS2 80.0%, and CNS3 93.1%. Nelarabine significantly improved DFS of CNS3 patients who received HDMTX (p=0.02): 93.1% with Nel (n=29) vs. 70.2% without (n=71). The 5-year cumulative incidence of isolated CNS relapse was significantly associated with CNS status: CNS1 1.0%, CNS2 4.2%, and CNS3 11.0%; p< 0.0001. However, there were no differences in 5-year DFS between CNS1 and CNS2 treated with CMTX (89.7% vs. 92.9%, p=0.17) or CMTX+Nel (91.8% vs. 89.9%; p=0.62).

Conclusion: CNS3 T-ALL patients treated on AALL0434 demonstrated increased risk of isolated CNS relapse and inferior EFS, despite receiving 1800 cGy CRT and additional CNS-directed chemotherapy. Strikingly, for CNS3 patients receiving HDMTX and CRT, the addition of Nel dramatically improved DFS and OS, producing outcomes similar to those for CNS1 and CNS2 patients. For AALL0434 patients receiving the superior CMTX arms, with or without Nel, outcome did not differ based on CNS1 vs. CNS2 status. Because most of these patients received 1200 cGy CRT, it is unclear if CNS1 vs. CNS2 status will impact outcome without CRT.

January 8, 2019

Young Investigator Committee
American Society of Pediatric Hematology/Oncology

Dear Colleague:

I am writing my strongest letter of support for Dr. Nathan Gossai, who is a new member of the Children's Oncology Group ALL committee, and presenting author for an abstract entitled, "Nelarabine abrogates relapse rates in CNS3 T-ALL: A report from Children's Oncology Group study AALL0434". In collaboration with Dr. Teachey, I have worked closely with Dr. Gossai in the preparation of this abstract, and can fully support his status as a promising Young Investigator.

Since joining Children's Minnesota in 2017, I have had the opportunity to work closely with Dr. Gossai in the clinical setting. Not yet three years from finishing his fellowship, Dr. Gossai has distinguished himself as a caring, astute and compassionate clinician. He has developed strong collaborations with his colleagues at the University of Minnesota, including the design and inception of a study to test the biological features of relapsing disease in the CNS compartment. As Director of the Leukemia and Lymphoma Team, Dr. Gossai has championed the importance of the multi-disciplinary Leukemia and Lymphoma Tumor Board, and has expressed a strong interest in leading clinical studies, both locally and nationally.

Dr. Teachey and I have encouraged Dr. Gossai to become involved in the COG ALL committee. During the 2018 Fall meeting, Dr. Gossai developed a project to investigate the impact of CNS2 and CNS3 disease on patient outcome. With support from the COG Data and Biostatistics Office, Dr. Gossai participated in teams-based discussions to analyze and present important data regarding the efficacy of nelarabine in preventing relapse in patients with CNS3 T-ALL disease. This paper will serve to continue the importance of the AALL0434 study's impact to change clinical practice, and Dr. Gossai is well-prepared to present and defend the clinical data related to his project.

During the course of my 30-year career, I have been the Director of an ACGME-accredited fellowship in Pediatric Hematology/Oncology, and the Vice Chair of Research for a department comprised largely of Young Investigators. In my capacity of Chief Research Officer at Children's Minnesota, I can attest that Dr. Gossai is exactly the type of Young Investigator we wish to support. His compassionate approach to clinical care and curiosity about the basic sciences will serve our profession magnificently in the years to come.

Sincerely yours,

Stuart S. Winter, MD
Chief Research Officer
Pediatric Blood and Cancer Program

2019 Young Investigator Award Statement of Career Goals

My career goals are best outlined in three areas, areas that overlap and inform one another to enliven my primary objective which is to provide optimal care for my patients at the bedside. Through my training and early career I have experienced many facets of our profession and have discerned the areas to best use my capacities. I have been fortunate to begin to focus my career on care for leukemia patients and I hope to continue to do so, with specific intention to improve care and outcomes for those with high-risk leukemias.

First, I have sought out and continue to seek out opportunities for collaborative translational research. At present, this entails working to establish cooperative IRB approved protocols with our local academic institution, the University of Minnesota, to ensure novel diagnostics and therapeutics will continue to be available to our patients.

Second, I have a great interest in taking part in ongoing leukemia clinical research studies. Throughout my training, and now into the early phases of my career, I have been fortunate in my proximity to and involvement in clinical research studies. This has taken the form of local protocol driven cohort studies, local retrospective reviews, small consortium studies (TACL) and involvement within Children's Oncology Group task forces. This multi-level approach to clinical research has been incredibly edifying as I set goals and objectives for ongoing research- knowing capacities and limitations at each level enables a greater efficiency and less duplicity.

Third, what I consider my most important goal, the goal that has always been my singular cause and that is informed by all my other work, is to optimize care for my patients. It is the bedside interactions with families and patients that initially sparked my interest in this field and that inspire me still. While there is inherent value in translational research for knowledge sake and benefit to clinical collaborative research for collective improvement to our craft, both to me are vehicles to improve my capacities for patients.

Each of these areas of interest and ongoing work have been supported and made possible by incredibly generous mentorship, and as such I also hold as a goal that with experience and wisdom gained with time that I too may provide mentorship and education to learners at all levels.

To put my goal succinctly, it is: to, through productive research and education, provide my patients academically informed and compassionately delivered care.

Curriculum Vitae

NATHAN GOSSAI

nathan.gossai@childrensmn.org
Office: 612-813-5940
Mobile: 612-310-0233

Education

CONCORDIA COLLEGE — Moorhead, MN
Bachelor of Arts in Biology and Classical Studies — May 2003

GEORGETOWN UNIVERSITY — Washington, D.C.
Master of Science in Physiology and Biophysics — August 2006

GEORGETOWN UNIVERSITY SCHOOL OF MEDICINE — Washington, D.C.
Doctor of Medicine — May 2010

Post-Graduate Training

UNIVERSITY OF MINNESOTA — Minneapolis, MN
Residency in Pediatrics — June 2013

UNIVERSITY OF MINNESOTA — Minneapolis, MN
Fellowship in Pediatric Hematology, Oncology and Blood and Marrow Transplantation — June 2016

Specialty Boards and Certification

Board Certification	Issue Date		Certificate#
Pediatrics	10.24.2013		106852

Certificates	Issue Date	Expiration
Neonatal Resuscitation	2010	2014
Ped. Advanced Life Support (PALS)	2010	2019

Licensure	Issue Date	Expiration	License #
Minnesota	7.13.2013	4.30.2019	56559
Wisconsin	10.16.2017	10.31.2019	68167-20
Drug Enforcement Agency (US DOJ)	3.6.2015	9.30.2020	

Faculty Appointments:

8/2016-Present, Staff Physician, Pediatric Hematology and Oncology, Children's Hospitals and Clinics of Minnesota, Minneapolis and St. Paul, Minnesota. 2525 Chicago Ave South Minneapolis, MN 55404

7/2016-Present, Adjunct Clinical Assistant Professor of Pediatrics, Department of Pediatrics, University of Minnesota, Minneapolis, Minnesota.

Hospital Staff Privileges:

8/2016-Present. Staff Physician, Children's Minnesota, Minneapolis and St. Paul, Minnesota.

Memberships in Professional Societies

- Fellow, American Academy of Pediatrics — 2010-Present
- Member of the Board of Directors — 2011-2013, 2014-2016
  - Minnesota Chapter of the American Academy of Pediatrics
- Member, Minnesota Medical Association — 2010-Present

- Member, Children's Oncology Group 2013-Present
- Member, American Society of Pediatric Hematology and Oncology 2013-Present
- Member, American Society for Blood and Marrow Transplantation 2013-2016
- Member, American Society of Hematology 2013-Present

Internal Leadership Positions:

- Director, Leukemia+Lymphoma Program, Children's Minnesota 2017-Present
- Member, Clinic Operations Leadership, Cancer and Blood Disorders, Children's Minnesota 2018-Present

Collaborative Research Protocol Leadership:

- Site Principal Investigator, Collection of cerebral spinal fluid for use in studying the role of the central nervous system niche in leukemia. Co-PI with Dr. Peter Gordon, University of Minnesota.
  Children's IRB # 1806-066 2018-Present
- Site Principal Investigator, Mechanisms of Inferior Outcomes in Acute Leukemia. Co-PI with Dr. Lucie Turcotte, University of Minnesota
  Children's IRB # 1811-131 2018-Present

NATIONAL ELECTED/APPOINTED LEADERSHIP AND COMMITTEE POSITIONS:

- 11/2016-Present Member/Principal Investigator, Treatment Advances in Childhood Leukemia & Lymphoma (TACL) Children's of Minnesota
- 11/2016-Present Site Principal Investigator, Matched Targeted Therapy (MTT) Recommendation for Patients with Recurrent, Refractory, or High Risk Leukemias. Children's Minnesota. Principal Investigator, Yana Pikman, MD Boston Children's Hospital.
- 11/2016-Present Children's Oncology Group (COG) T-ALL/TLLy Task Force: AALL1831, AALL1231 Successor Study. Novel Agents.
- 12/2016-Present Committee Member, TACL Study T2016-003 Decitabine/Vorinostat/FLAG in Children and Young Adults with Relapsed/Refractory AML.

Publications

Peer Reviewed Journal Publications

- Burke MJ, **Gossai N**, Wagner JE, Smith AR, Bachanova V, Cao Q, MacMillan ML, Stefanski HS, Weisdorf DJ, Verneris MR. Survival differences between adolescents/young adults and children with B precursor acute lymphoblastic leukemia after allogeneic hematopoietic cell transplant *Biol Blood Marrow Transplant* 2013 Jan, 19 (1) 138-142
- Burke MJ, **Gossai N**, Cao Q, MacMillan ML, Warlick E, Verneris MR. Similar Outcomes between Adolescent / Young Adults and Children with Acute Myeloid Leukemia Following Allogeneic Hematopoietic Cell Transplantation. *Bone Marrow Transplantation* 2014 (14) 174-178.
- **Gossai N**, Verneris MR, Karras NA, Gorman MF, Patel NJ, Burke MJ. A clofarabine-based bridging regimen in patients with relapsed acute lymphoblastic leukemia (ALL) and persistent minimal residual disease (MRD). B*one Marrow Transplantation* 2014 (49) 440-442.
- **Gossai N**, Hilgers MV, Polgreen LE, Greengard EG. Critical Hypercalcemia following Discontinuation of Denosumab Therapy for Metastatic Giant Cell Tumor of Bone. *Pediatric Blood and Cancer 2015; 62: 1078-1080*
- **Gossai N**, Biegel JA, Messiaen L, Berry SA, Moertel CL. Report of a Patient with a Constitutional Missense Mutation in *SMARCB1*, Coffin-Siris Phenotype and Schwannomatosis. *American Journal of Medical Genetics Part A*, 2015; 167(12):3186-91.
- **Gossai N**, Cafferty R, Weigel B. Chemotherapy Options for Poor Responders to Neoadjuvant Chemotherapy for Orbital Granulocytic Sarcoma. *Current Treatment Options in Oncology 2016* Jul; 17(7):38.
- **Gossai N**, Naumann J, Li N-S, Zamora E, Gordon DJ, Piccirilli JA, Gordon PM. Drug conjugated nanoparticles activated by cancer cell specific mRNA. *Oncotarget 2016*. 7 (25): 38243-38256
- **Gossai N**, Brown NM, Ameduri R, Zantek ND, St. Louis J, Steiner ME. Acquired von Willebrand Disease in

Children Supported with the Berlin Heart EXCOR Pediatric Ventricular Assist Device. *World Journal for Pediatric and Congenital Heart Surgery 2016*. 7(5): 614-618

- Li N-S, **Gossai N**, Naumann J, Gordon PM, Piccirilli J. Efficient Synthetic Approach to Linear Dasatinib-DNA Conjugates by Click Chemistry. *Bioconjugate Chemistry* 2016 27(10): 2575-2579
- Gaynes J, Jonart L, Zamora E, Naumann J, **Gossai N**, Gordon, PM. PBX1 up-regulation in leukemia cells in the central nervous system enhances leukemia chemo-resistance and self-renewal. *Haematologica.* 2017 102 (4): e136-e139
- **Gossai NP** and Gordon PM. The role of the central nervous system microenvironment in pediatric acute lymphoblastic leukemia. *Front. Pediatr 2017* **5**:90. doi: 10.3389/fped.2017.00090
- **Gossai N**, Boman L, Richards M, Gernbacher S, Perkins J, Bostrom B. Symptomatic Hyperammonemia with *Erwinia chrysanthemi* derived asparaginase in Pediatric Leukemia Patients. *J Pediatr Hematol Oncol.* 2018 May;40(4):312-315.

Abstracts

- **Gossai N**, Hennessy J, Moquist K, Nelson S. Successful use of Hydroxyurea in a very young child with Hemoglobin SD disease. *Journal of Sickle Cell Disease and Hemoglobinopathies* 2014 (1)
- **Gossai N**, Naumann J, Zamora E, Li N-S, Piccirilli J and Gordon PM. Drug-DNA Conjugated Gold Nanoparticles for the Treatment of Acute Myeloid Leukemia. *Blood.* Published Online 2015; 126 (23) 493.
- **Nathan Gossai,** Lara Boman, Michael Richards, Sara Gernbacher, Yoav Messinger, Joanna Perkins, Bruce Bostrom Symptomatic Hyperammonemia with Erwinia chrysanthemi in Pediatric Leukemia patients. *Pediatr Blood Cancer.* 2016; 63 (S1): S37
- Gaynes J , Jonart L, Naumann J, Zamora, E, **Gossai N**, Ebadi M, Gordon PM. Central Nervous System Microenvironment Influences the Leukemia Transcriptome and Enhances Leukemia Chemo-Resistance Published online *Blood* 2016 128:1515; Published online December 1, 2016.
- Bader P, Salzmann-Manrique E, Balduzzi A., Dalle J-H, Woolfrey AE, Bar M, Verneris MR, Borowitz MJ, Shah NN, **Gossai N**, Shaw PJ, Chen RA, Kreyenberg H, Yohe SL, Di Maio L, Eckert C, van der Velden VHJ, Lankester AC, Klingebiel T, Peters C, Grupp SA and Pulsipher MA. Monitoring of Minimal Residual Disease before and after Allogeneic Stem Cell Transplantation Childhood ALL - a Retrospective Assessment on Behalf of the PDWP of the EBMT, the COG, PBMTC, the I-BFM and the Westhafen-Intercontinental-Group *Blood* 2016 128:985; Published online December 1, 2016.
- Bader P, Salzmann-Manrique E, Balduzzi A., Dalle J-H, Woolfrey AE, Bar M, Verneris MR, Borowitz MJ, Shah NN, **Gossai N**, Shaw PJ, Chen RA, Kreyenberg H, Yohe SL, Di Maio L, Eckert C, van der Velden VHJ, Lankester AC, Klingebiel T, Peters C, Grupp SA and Pulsipher MA Monitoring of Minimal Residual Disease before and after Allogeneic Stem Cell Transplantation Childhood ALL – a Retrospective Assessment on Behalf of the PDWP of the EBMT, the COG, PBMTC, the I-BFM and the Westhafen-Intercontinental-Group. *Biol Blood Marrow Transplant* 23 (2017) S18–S391
- Pikman Y, Tasian SK, Place AE, Adhav AA, Conway AS, Stieglitz E, Sulis ML, Blonquist TM, Maloney KW, McNeer J, Pauly M, Shukla, N, Tyner J, Cole P, Burke MJ, **Gossai N**, Brown P, Gore L, Hunger SP, Cooper TM, Janeway KA, Silverman LB, Harris M, Loh ML, Stegmaier K. Matched Targeted Therapy for Pediatric Patients with Relapsed, Refractory or High-risk Leukemias: A Report from the LEAP Consortium, 2nd Pediatric Precision Oncology Conference. Scottsdale, AZ. March 4-7, 2018.
- Bruce Bostrom, Jack Knudson, **Nathan Gossai**, Joanna Perkins, Michael Richards, Julie Chu, Nancy McAllister, Susan Sencer, Yoav Messinger.Can Prophylactic Pamidrontrate Infusions Monthly Reduce the Incidence of Symptomatic Osteonecrosis in ALL Patients at High Risk? *Pediatr Blood Cancer* 2018; 65 (S1): s235-s236
- **Nathan Gossai**, Joanna Perkins, Michael K. Richards, Yoav Messinger and Bruce *Bostrom* BVGP: A Novel Protocol for Low Risk Hodgkin Lymphoma with Excellent Response, Minimal Acute Toxicity and Reduced Risk of Late Effects. *Pediatr Blood Cancer.* 2018; 65 (S1): s226-s227
- Yana Pikman, Sarah K. Tasian, Maria Luisa Sulis, Traci M. Blonquist, Kelly W. Maloney, Jennifer Lynn McNeer, Melinda Gordon Pauly, Neerav Narendra Shukla, Jeffrey Tyner, Peter D. Cole, Michael James Burke, **Nathan Gossai**, Patrick A. Brown, Lia Gore, Stephen Hunger, Todd Michael Cooper, Lewis B. Silverman, Marian H. Harris, Mignon L. Loh, Kimberly Stegmaier, Pediatric LEAP Consortium Matched targeted therapy

for pediatric patients with relapsed, refractory or high-risk leukemias: A report from the LEAP consortium. J Clin Oncol 36, 2018 (suppl; abstr 10518)

Online Publications

- Shad A, **Gossai N** Late Effects of Childhood Cancer and Treatment*, eMedicine: Medscape http://emedicine.medscape.com/article/990815-overview* Published 9 December 2010, Republished 2 Jan 2015

Journal Reviews:

- Blood (1)

Presentations

- Lilly Call to Serve Vocational Research Scholarship Lecture *Faith and Healing: Medical Care for the Maasai of Northern Tanzania* Concordia College, Moorhead, Minnesota November 3, 2005
- Resident Oral Platform Presentation *Successful use of a clofarabine-based regimen in preparation for allogeneic hematopoietic cell transplantation in patients with relapsed acute lymphoblastic leukemia and persistent minimal residual disease* Pediatric Research, Education and Scholarship Symposium, University of Minnesota Department of Pediatrics, April 19, 2013
- Resident/Fellow Poster Presentation *Acquired von Willebrand Disease in Children Supported by the Berlin Heart EXCOR Pediatric Ventricular Assist Device* Pediatric Research, Education and Scholarship Symposium, University of Minnesota Department of Pediatrics, April 28, 2014
- Poster Presentation: *Successful use of Hydroxyurea in a very young child with Hemoglobin SD disease*. 8th Annual Sickle Cell Disease Research and Education Symposium and 37th Annual Sickle Cell Disease Scientific Meeting, Miami, Florida April 2014 (Presented by S. Nelson)
- Invited Presentation: *MIBG Therapy for Neuroblastoma* Association of Pediatric Hematology and Oncology Nurses, Annual Metro Conference, Minneapolis, Minnesota April 16, 2015
- Poster Presentation and Speedtalk *Bi-functional Drug-DNA Conjugated Gold Nanoparticles for the Treatment of Pediatric Acute Myeloid Leukemia*. Pediatric Research, Education and Scholarship Symposium, University of Minnesota Department of Pediatrics, April 17, 2015
- Poster Presentation: *Drug-DNA Conjugated Gold Nanoparticles for the treatment of Acute Myeloid Leukemia*. European School of Hematology Acute Myeloid Leukemia Molecular and Translational Conference, Budapest, Hungary September 10-12, 2015
- Invited Presentation: *Hyperammonemia from Erwinia asparaginase: An under recognized problem in leukemia patients.* Advancing Pediatric Cancer Care in Minnesota. Children's Hospitals and Clinics of Minnesota, Minneapolis October 23, 2015
- Poster Presentation: *Drug-DNA Conjugated Gold Nanoparticles for the treatment of Acute Myeloid Leukemia*. Advancing Pediatric Cancer Care in Minnesota. Children's Hospitals and Clinics of Minnesota, Minneapolis October 23, 2015
- Fellow Presentation: *Morbidity and Mortality* with Rachel Phelan, MD University of Minnesota Department of Pediatrics. Minneapolis January 21, 2016
- Poster Presentation: *Drug conjugated nanoparticles activated by cancer cell specific mRNA* Pediatric Research, Education and Scholarship Symposium, University of Minnesota Department of Pediatrics, April 15, 2016
- Poster Presentation: *Symptomatic hyperammonemia with Erwinia chrysanthemi derived asparaginase in pediatric leukemia patients* American Society of Pediatric Hematology and Oncology Annual Meeting. Minneapolis, MN May 12, 2016.
- Poster Presentation: *The Central Nervous System Microenvironment Influences the Leukemia Transcriptome and Enhances Leukemia Chemo-Resistance.* American Society of Hematology 58th Annual Meeting and Exposition, San Diego, CA December 3, 2016 (Presented by P. Gordon)
- Oral Presentation: *Monitoring of Minimal Residual Disease before and after Allogeneic Stem Cell Transplantation Childhood ALL – a Retrospective Assessment on Behalf of the PDWP of the EBMT, the COG, PBMTC, the I-BFM and the*

Westhafen-Intercontinental-Group. American Society of Hematology 58th Annual Meeting and Exposition, San Diego, CA December 5, 2016 (Presented by P. Bader)

- Oral Presentation: CIBMTR Best Abstract for Clinical Research Award *Monitoring of Minimal Residual Disease before and after Allogeneic Stem Cell Transplantation Childhood ALL – a Retrospective Assessment on Behalf of the PDWP of the EBMT, the COG, PBMTC, the I-BFM and the Westhafen-Intercontinental-Group.* BMT Tandem Meeting, Orlando, FL February 25, 2017 (Presented by P. Bader)
- Oral Presentation: Van Bekkum Award *Impact of MRD before and after Allogeneic Hematopoietic Cell Transplantation (HCT) of Childhood ALL by FC and RQ-PCR– a Retrospective Assessment on Behalf of the COG, PBMTC, the I-BFM, the PDWP of the EBMT, and the Westhafen-Intercontinental-Group.* 43rd Annual Meeting of the European Society for Blood and Marrow Transplantation (EBMT 2017), Marseille, France, March 26-29, 2017. (Presented by P. Bader)
- Poster Presentation: *Silent transient abnormal myelopoiesis as precursor to pediatric acute myeloid leukemia.* Pediatric Research, Education and Scholarship Symposium April 13, 2018 (Presented by S. Graf)
- Poster Presentation: *Can Prophylactic Pamidrontrate Infusions Monthly Reduce the Incidence of Symptomatic Osteonecrosis in ALL Patients at High Risk*? Bruce Bostrom, Jack Knudson, Nathan Gossai, Joanna Perkins, Michael Richards, Julie Chu, Nancy McAllister, Susan Sencer, Yoav Messinger. American Society of Pediatric Hematology and Oncology, National Conference. Pittsburgh, PA. May 3, 2018. (Presented by B. Bostrom)
- Poster Presentation: *BVGP: A Novel Protocol for Low Risk Hodgkin Lymphoma with Excellent Response, Minimal Acute Toxicity and Reduced Risk of Late Effects.* Nathan Gossai, Joanna Perkins, Michael K. Richards, Yoav Messinger and Bruce Bostrom. American Society of Pediatric Hematology and Oncology, National Conference. Pittsburgh, PA. May 4, 2018. (Presented by M. Richards)
- Poster Presentation: *Matched targeted therapy for pediatric patients with relapsed, refractory or high-risk leukemias: A report from the LEAP consortium* Yana Pikman, Sarah K. Tasian, Maria Luisa Sulis, Traci M. Blonquist, Kelly W. Maloney, Jennifer Lynn McNeer, Melinda Gordon Pauly, Neerav Narendra Shukla, Jeffrey Tyner, Peter D. Cole, Michael James Burke, Nathan Gossai, Patrick A. Brown, Lia Gore, Stephen Hunger, Todd Michael Cooper, Lewis B. Silverman, Marian H. Harris, Mignon L. Loh, Kimberly Stegmaier. American Society of Clinical Oncology, National Conference, Chicago, IL. June 2, 2018. (Presented by Y.Pikman)
- Invited Presentation: *CNS Consolidation in T-ALL Patients: Type, Timing and Implications for Future Directions.* Children's Oncology Group Fall Conference, Dallas, TX, October 3, 2018.
- Oral Presentation: *Matched targeted therapy for pediatric patients with relapsed, refractory or high-risk leukemias: A report from the LEAP consortium* Yana Pikman, MD, Sarah K. Tasian, MD, Maria Luisa Sulis, MD, Todd M Cooper, DO, Melinda Pauly, MD, Kelly W. Maloney, MD, Michael J. Burke, MD, Patrick Brown, MD, Nathan Gossai, MD, Peter Cole, MD, Jennifer McNeer, MD, MS, Neerav Shukla, MD, Beth Apsel Winger, MD, PhD, Asmani A Adhav, Traci M. Blonquist, MS, Amy Conway, Andrew E. Place, MD, PhD, Lia Gore, MD, Stephen P. Hunger, MD, Katherine Janeway, MD, MMSc, Lewis B. Silverman, MD, Jeffrey W. Tyner, PhD, Marian H. Harris, MD, PhD, Mignon L. Loh, MD and Kimberly Stegmaier, MD American Society of Hematology 60th Annual Meeting and Exposition, San Diego, CA December 1, 2018. (Presented by Y. Pikman)

Preceptorship

- Lauren Glennon, 4th yr med. stud., Midwestern College of Osteopathic Medicine, elective rotation, Oct. 2017
- Maddi Gemuenden, 4th yr student, Concordia College, Cooperative Education June 2017
- Kenzie Wild, 3rd yr student, Concordia College, Cooperative Education June 2017
- Mikaela Herberg, 4th yr student, Concordia College, Cooperative Education June 2018
- Annika Tureson, 4th yr student, Concordia College, Cooperative Education June 2018
- Joshua Schmidt, 3rd yr student, Concordia College, Cooperative Education June 2018

Bench Research Experience

- Gordon Laboratory: Masonic Cancer Center University of Minnesota. Principal Investigator: Peter M. Gordon M.D., PhD. Protocol: 1504-32560A *Testing of drug-conjugated gold nanoparticles for the therapy of leukemia using a mouse leukemia xenotransplantation model*
  Funding Sources: Leukemia and Lymphoma Society, Children's Cancer Research Fund

Gossai CV

Work Experience

CHILDREN'S HOSPITALS and CLINICS OF MINNESOTA — Minneapolis, MN
Health Unit Coordinator — June 2004-June 2005

- Collaborated directly with the dozens of physicians and hundreds of nurses facilitating open communication to ensure an environment that optimized patient care, serving as an intermediary between families and medical staff
- Directly observed scores of medical and surgical interventions, including all of the major neonatal cardiac operations, numerous otolaryngology procedures and care for children with cancer

CAMP METIGOSHE — Bottineau, ND
Camp Counselor and Primary Health Provider — Summers 2001, 2002, 2003

- Led diverse groups of campers through intentionally rustic camping, engendering camaraderie, teamwork and self-confidence in children aged 10-18 from North Dakota, Minnesota and Wisconsin, developmentally disabled children and adults aged 14-80 and children from the nearby Turtle Mountain Indian Reservation
- Cared for a staff of 50 and 1000+ campers throughout one summer, providing first aid and medications as prescribed by their physicians

Awards and Achievements

- Eagle Scout Award
  May 1999
- Lilly Call to Serve Vocational Research Scholarship Recipient
  February 2003
  - Concordia College, Moorhead, Minnesota
- Successful summit of Mount Kilimanjaro
  June 2002
- Finalist, *Cura Personalis* Award
  April 2008
  - Georgetown University School of Medicine, Washington DC.
- Resident Oral Platform Research Award
  April 2013
  - University of Minnesota, Dept. of Pediatrics
- Finalist, Mark Snelling Outstanding Fellow Teaching Award 2014, 2015, 2016
  - University of Minnesota, Department of Pediatrics
- Mark E. Nesbit Fellow International Travel Award
  June 2015
  - University of Minnesota, Divisions of Pediatric Hematology/Oncology and Pediatric Blood and Marrow Transplantation

International Public Health and Medical Experience

GEORGETOWN, GUYANA — March 2007

- Studied the application of Global AIDS Program/CDC funds for HIV/AIDS education in Guyana via Modeling and Reinforcement to Combat HIV/AIDS (MARCH) methodologies with Dereck Springer, MPH, MARCH Coordinator for Guyana
- Directly observed and collaborated with the Merundoi radio educational program

KITUMBEINE AND ARUSHA, TANZANIA — January-February 2004

- Worked as Clinical Care Volunteer in 14 rural dispensaries with Lutheran medical missionary Dr. Steven Friberg, providing triage services and wide breadth of clinical care from first-aid anti-septic care to a lion bite victim to critical care for a child with cerebral malaria

- Rounded daily with a med/peds resident and a pediatrician at Selian Lutheran Hospital experiencing the true essence of tropical medicine: patients with topical anthrax, tuberculosis, HIV, malaria, kwashiorkor among others

MBABANE, SWAZILAND February-March 2004

- Served as Public Health Volunteer with and for Ned Wallace M.D., M.P.H. addressing both the HIV and AIDS epidemics, by supporting the Luyengo Community Clinic in expansion of facilities and capabilities
- Advised the Anglican Diocese of Swaziland in formulating a long-term project proposal to mitigate the impact of AIDS at the community level
- Collaborated with existing Non-Governmental Organizations such as the World Health Organization, the National Emergency Response Committee for HIV and AIDS (NERCHA), UNICEF and UNAIDS to ascertain the most appropriate, plausible and beneficial plan of action for both the Clinic and Diocese

MECHANISMS OF RESISTANCE TO THE TYPE II JAK2 INHIBITOR CHZ868 IN B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

Authors: Loretta Li, Shannon Harkins, Kristen Stevenson, Sayalee Potdar, Praveen Anand, Olivia Plana, Catharine Leahy, Birgit Knoechel, David Weinstock

Background: Approximately 10-15% of pediatric B-cell acute lymphoblastic leukemias (B-ALLs) harbor CRLF2 gene rearrangements, which confer a poor prognosis. CRLF2-rearranged B-ALLs are addicted to signaling through Janus kinase 2 (JAK2). ATP-competitive (type I) JAK2 inhibitors like ruxolitinib have limited efficacy against these leukemias because other Janus kinases can trans-phosphorylate JAK2 and activate signaling. In contrast, type II inhibitors stabilize JAK2 in the inactive conformation. We previously showed that CHZ868, the first type II JAK2 inhibitor amenable to in vivo use, potently kills JAK2-dependent B-ALL cells, abrogates JAK2/STAT5 signaling, and prolongs overall survival in transgenic and xenograft models of JAK2-dependent B-ALL (1). However, all mice eventually progressed on therapy and succumbed to B-ALL.

Objective: To study mechanisms of acquired resistance to CHZ868.

Design/Method: Three CRLF2/Jak2 R683G-dependent murine B-ALL cell lines were cultured in escalating doses of drug to generate resistant lines that proliferate in 10 μM CHZ868. Whole exome sequencing (WES), RNA sequencing, and H3K27Ac chromatin immunoprecipitation sequencing (ChIP-seq) were performed on naïve and resistant cell line pairs.

Results: WES revealed JAK2 G993A as a new type II JAK2 inhibitor resistance mutation in 2 of 3 resistant cell lines. When recapitulated in Ba/F3 CRLF2 IL7R JAK2 R683G cells, this mutation confers >10-fold resistance to CHZ868. JAK2 G993A abrogates CHZ868 inhibition of pJAK2 and pSTAT5. This mutation does not confer cross-resistance to the type II JAK2 inhibitor BBT594 and is particularly interesting because G993 is the pre-DFG residue. Most kinases have an amino acid larger than glycine at this position. A 4-methyl group was strategically added to the benzimidazole ring of CHZ868 to increase steric hindrance with the binding pocket of other kinases and improve its selectivity compared to BBT594 (1). When JAK2 G993A is present, the bulkier alanine in the pre-DFG position likely inhibits CHZ868 binding, leading to the observed drug resistance. In the CHZ868-resistant cell line that does not harbor a JAK2 resistance mutation, we identified Ikzf1 alterations and through H3K27Ac ChIP-Seq found that Ets transcription factor binding sites within H3K27Ac peaks were differentially present between the naïve and the CHZ868-resistant cells ($p<10\text{-}80$). Pairing this with RNA-Seq data, we observed complete loss of Erg expression in the resistant cells. This finding was confirmed by qRT-PCR. Work is ongoing to better understand the interplay between ERG transcriptional control and JAK2 independence.

Conclusion: We have identified novel genetic and epigenetic mechanisms that confer resistance to CHZ868. Reference: 1. Wu et al., Cancer Cell, 2015.

DANA-FARBER CANCER INSTITUTE | BWH BRIGHAM AND WOMEN'S HOSPITAL
A Teaching Affiliate of Harvard Medical School

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Date: December 30, 2018
To: ASPHO Young Investigator Award Review Committee
Re: Mentor's letter for Loretta Li, M.D.

Dear Colleagues:

Loretta Li, M.D. has my strongest support in her application for the ASPHO Young Investigator Award. **She is a future leader in the field of pediatric leukemia research**. Loretta has conducted innovative research studying mechanisms of response and resistance to JAK2 kinase inhibition while developing new type II JAK2 inhibitors in collaboration with Nathanael Gray's lab. I will briefly summarize her qualifications and scientific progress and then update you on her career trajectory.

Loretta's education and training are outstanding. She graduated *cum laude* from Yale University and then completed her M.D. at Harvard Medical School. She was an intern and resident at Boston Children's Hospital before joining the Boston Children's Hospital / Dana-Farber Cancer Institute pediatric hematology/oncology fellowship in July of 2012. Her dedication to research extends back to high school, and she completed both summer research efforts and a Howard Hughes Medical Institute (HHMI) Research Training Fellowship for Medical Students. The latter was performed under the guidance of Kim Stegmaier and involved a gene expression signature-based approach to identify kinase inhibitors that promote AML differentiation.

Loretta entered my laboratory as a second-year Pediatric Oncology Fellow in the Fall of 2013. My lab has a long-standing interest in JAK2 signaling, first inspired by the identification of rearrangements in a subset of ALL that drive expression of the cytokine receptor CRLF2. These leukemias have a poor prognosis but could potentially be targeted with JAK2 inhibitors. We previously demonstrated that type I inhibitors (*i.e.* ATP-competitive) have very little activity in these leukemias (Weigert *et al*. J Exp Med 2012), which may result from *trans*-activation of JAK2 by other JAK family members in the presence of the inhibitors (Koppikar *et al*. Nature 2013). In collaboration with Novartis and Ross Levine, we tested the type II JAK2 inhibitor CHZ868 in cell lines and *in vivo* models.

Loretta joined this effort when we were first beginning the project and drove the pre-clinical studies. To summarize, type II inhibitors are 100-fold more potent in JAK2-dependent ALL cell lines than type I inhibitors. They have significant activity *in vivo* against either transgenic leukemias or primary human ALL xenografts, and they appear to synergize with dexamethasone. In contrast with type I inhibitors, they completely abrogate JAK2 activation both *in vitro* and *in vivo*. Loretta was a co-first author on the *Cancer Cell* paper describing these studies and was awarded a very prestigious Damon Runyon Physician-Scientist Training Award to support her ongoing research. She now leads all studies in the lab focused on JAK2 inhibition.

Loretta has been studying both inherent and acquired resistance to JAK2 inhibitors. Loretta established three JAK2-dependent murine B-ALL cell lines resistant to CHZ868; two of these harbored a novel JAK2 G993A resistance mutation. In the third CHZ868-resistant cell line that does

not harbor JAK2 G993A, Loretta found alterations of the Ikaros (IKZF1) transcription factor, which is commonly mutated in *CRLF2*-rearranged ALLs. In collaboration with Birgit Knoechel's lab, she performed H3K27Ac ChIP-Seq and identified a striking ($p < 10^{-80}$) enrichment of Ets-family transcription factor motifs depleted of H3K27ac in the CHZ868-resistant cell line. RNA-Seq identified complete loss of ERG expression, a factor known to drive a different subset of B-ALL. She is now exploring the link between the *Ikzf1* alterations, loss of *Erg* expression, and type II JAK2 inhibitor resistance.

To build on previous work from Ross Levine's lab, Loretta is applying an immunoprecipitation-mass spectrometry (IP-MS)-based approach to identify JAK2 binding partners capable of activating downstream signaling. Loretta has devoted significant time and effort to technical optimization of the IPs. She is collaborating with Dr. Guillaume Adelmant from the Blais Proteomics Center at DFCI to define JAK2 binding partners in the setting of both inherent and acquired resistance to the type I JAK2 inhibitor ruxolitinib.

Unfortunately, CHZ868 is not amenable to *in vivo* use in humans and Novartis has dropped its type II JAK2 program. Loretta's most translational progress has been in her efforts to identify new type II JAK2 inhibitors that can be brought to clinical trials. This is an idea that has been stewarded by Loretta and now involves a collaboration with Nathanael Gray, a world-class synthetic chemist. An initial screen of 5,000 potential type II kinase inhibitors from Nathanael's lab identified 11 "hits" with at least 5-fold greater activity in JAK2-dependent cells compared to ALK-dependent cells. Synthesis of analogs has yielded two novel series of compounds that we are moving forward. Loretta has validated the preclinical activity of novel compounds synthesized by the Gray lab. This work has resulted in three patent applications. In a very short time, Loretta has already advanced the leading analogs to *in vivo* pre-IND studies. This year, Loretta was selected as one of two recipients of the CureSearch Young Investigator in Pediatric Oncology Drug Development Award to continue this work. She participates and presents on a monthly conference call with leaders in the field of JAK2 biology, including Ross Levine, Steve Hubbard, Olli Silvennoinen, and Radek Skoda. My expectation is that we will commercialize the type II inhibitors within the next 2 months, which could ultimately lead to a new class of JAK inhibitors with far greater on-target activity than the available FDA-approved drugs. That's quite an accomplishment for Loretta and Nathanael's group.

In addition to her primary research projects, Loretta has coordinated efforts with Boston Children's Hospital to develop primary pediatric hematologic malignancy xenografts. I see this as both a contribution by Loretta and a major part of her training, as she is gaining invaluable skills in both the scientific and administrative aspects of leukemia xenografting and experimental therapeutics. My laboratory has led the DFCI effort to establish a repository of >300 leukemia, lymphoma and other xenografts in NSG mice. We have established >100 pediatric leukemia, lymphoma and solid tumor lines that propagate in animals and are available to the entire world (www.PRoXe.org) for studies of novel experimental therapeutics, genetic manipulations or other approaches. Loretta is co-author on a *Cancer Cell* manuscript describing our xenograft repository.

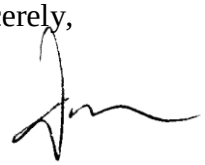
Loretta was appointed as an Instructor at Dana-Farber and Boston Children's Hospital in the summer of 2015. She is clearly headed for an independent, tenure track position leading her own lab. Loretta currently supervises a research technician who is 100% dedicated to her projects. She also serves as a resource to other investigators for xenograft selection and experimental design.

This year, Loretta participated in the European Hematology Association (EHA) / American Society of Hematology (ASH) Translational Research Training in Hematology (TRTH) program. Given her interest in translational research, and with my full support, she is currently enrolled in the Harvard Medical School Cancer Biology & Therapeutics: High Impact Cancer Research Program.

Over the coming year, she will put together a first-author manuscript focused on type II JAK2 inhibition. She will submit her NIH K08 application in February 2019 and apply for faculty positions in the Spring of 2019. At that point, she will be highly competitive for an Assistant Professor position, along with appropriate start-up funding and salary support.

To reiterate, Loretta Li, MD is the ideal candidate for the ASPHO Young Investigator Award. Please offer her every consideration possible and feel free to contact me with any questions.

Sincerely,



David Weinstock, MD

Career Goals **Loretta S. Li, M.D.**

I am a pediatric oncologist committed to establishing myself as a physician-scientist who advances the field through translational research. While encouraged by the multitude of clinical trials for patients with newly diagnosed or relapsed cancers, I have also faced the limitations of current medicine when caring for terminally ill patients. These humbling experiences have motivated me to go back to the lab where I am fueled by the potential benefits of translational research for patient care. My goal is to develop the skills necessary to become an independent investigator in the field of pediatric oncology at a leading academic research institution. I am interested in the development of more targeted therapies and the practice of personalized cancer medicine based on underlying genetic changes that drive a particular malignancy. In addition, I am committed to studying mechanisms of resistance to existing targeted therapies to guide combination strategies and the development of novel therapeutics. I aim to build a translational research program focused on experimental therapeutics and correlative biology studies for patients with leukemia and other hematologic malignancies. In the future, I would like to use my dual training in clinical medicine and laboratory research to more expeditiously bring promising novel therapies to clinical trials for patients.

I chose my post-doctoral research experience to help me achieve my career goals. In Dr. David Weinstock's laboratory at the Dana-Farber Cancer Institute, I have led an effort to evaluate the mechanisms of response and resistance to type II JAK2 inhibitors in B-cell acute lymphoblastic leukemia (B-ALL) and myeloproliferative neoplasms. Through this work, I have gained extensive experience in leukemia biology, mouse models of disease, and preclinical testing of novel targeted therapeutics. I am co-first author of a manuscript published in *Cancer Cell* describing the activity of CHZ868, the first type II JAK2 inhibitor amenable to *in vivo* use. We showed that CHZ868 is more potent than type I inhibitors like ruxolitinib against JAK2-dependent B-ALL cells, abrogates JAK2/STAT5 signaling, and improves overall survival in patient-derived xenograft (PDX) and transgenic models of *CRLF2*-rearranged B-ALL. We found that CHZ868 is synergistic with dexamethasone, suggesting a promising combination strategy for translation into clinical trials.

Neither CHZ868 alone nor in combination with dexamethasone was curative, however, and all the mice eventually succumbed to relapsed B-ALL. I am now studying mechanisms of inherent and acquired resistance to existing type I and type II JAK2 inhibitors to inform combination strategies that prevent or overcome this resistance and to guide the rational design of new type II JAK2 inhibitors. Our colleagues in Ross Levine's laboratory showed that persistent JAK2 signaling in ruxolitinib-resistant myeloid cells can occur because of *trans*-phosphorylation of JAK2 by other Janus kinase family members (*Nature* 2012). I am using multiple proteomic strategies to identify kinases that promote intrinsic and acquired resistance to ruxolitinib in our JAK2-dependent B-ALL and myeloid cells. As described in my submitted abstract, I have already identified both genetic and epigenetic mechanisms that confer *in vitro* resistance to type II inhibition. Future work will include studying mechanisms of *in vivo* resistance.

Unfortunately, CHZ868 cannot be tested in humans, and for strategic reasons, Novartis elected to no longer pursue its further development. To my knowledge, there are no pharmaceutical companies with active type II JAK2 inhibitor programs, so this represents an important niche to be filled by academic researchers. I am now collaborating with Dr. Nathanael Gray's medicinal chemistry lab to develop novel type II JAK2 inhibitors that will eventually be amenable to clinical testing. Through a screen of >5000 compounds collected and/or synthesized by the Gray lab, I identified 11 "hits" with at least 5-fold greater activity in JAK2-dependent cells compared to ALK-dependent cells. From these, I identified a lead compound with on-target biochemical and cellular activity against JAK2. Over the past year, I have been validating the preclinical activity of analogs generated by the Gray lab with optimized potency, selectivity, and pharmacokinetic properties. Three patent applications for novel type II JAK2 inhibitor scaffolds are pending, and I am now assessing the *in vivo* tolerability and efficacy of our top three compounds.

This work fills a niche currently left unserved by pharmaceutical companies, and I believe it will lay the foundation for first-in-human trials of type II JAK2 inhibitors. To gain additional experience in clinical trial design, I am enrolled in the Harvard Medical School Post-Graduate Certificate Program in Cancer Biology & Therapeutics: High-Impact Cancer Research. During this program, I will focus my efforts in the Therapeutic Development track, which will allow me to obtain additional training in target identification and pre-clinical drug discovery efforts that span the "valley of death" to clinical trials and eventual commercialization.

While in the Weinstock lab, I have also taken a leadership role in the development of pediatric acute leukemia xenografts. Together with the Hematologic Malignancy Program at Boston Children's Hospital / Dana-Farber Cancer Institute and the Weinstock lab, I coordinated efforts to xenograft samples from pediatric patients with untreated or relapsed leukemia and lymphoma. We have established >100 pediatric xenograft lines, and I am co-author of a *Cancer Cell* manuscript describing our Public Repository of Xenografts (PRoXe, www.proxe.org). In addition, I have served as a resource for investigators interested in using our xenografts for pre-clinical studies of experimental therapeutics or other assays. This has led to a co-author publication in the *British Journal of Haematology*.

As I think about the next steps in my career, I would like to continue to devote 80% of my time to research, with a focus on leukemia biology. My clinical work will keep me updated about ongoing patient care needs and foster collaborations. I am now generating the preliminary data to apply for a NIH K08 award in February 2019. I expect to submit a first-author manuscript focused on JAK2 kinase inhibitor resistance and the development of novel type II JAK2 inhibitors over the next several months. Both the K08 and an additional first author manuscript will strengthen my competitiveness for a tenure-track Assistant Professor faculty position at a leading academic research institution.

Curriculum Vitae

Date Prepared: 11/10/18

Name: Loretta S. Li, M.D.

Office Address: Dana-Farber Cancer Institute
450 Brookline Ave, Dana 512
Boston, MA 02215

Home Address: 400 Brookline Ave, Apt 11G
Boston, MA 02215

Work Phone: 617-632-3446

Work Email: loretta_li@dfci.harvard.edu

Work FAX: 617-632-4410

Place of Birth: New York, NY

Education:

09/2000-05/2004	B.S. (*cum laude*)	Molecular, Cellular, and Developmental Biology	Yale University
09/2004-06/2009	MD	Medicine	Harvard Medical School

Postdoctoral Training:

07/2009-06/2010	Intern	Pediatrics	Boston Children's Hospital and Boston Medical Center
07/2010-06/2012	Resident	Pediatrics	Boston Children's Hospital and Boston Medical Center
07/2012-06/2015	Clinical Fellow	Pediatric Hematology / Oncology	Boston Children's Hospital and Dana-Farber Cancer Institute
10/2013-present	Research Fellow	Leukemia Biology, Laboratory of David Weinstock, M.D.	Dana-Farber Cancer Institute

Faculty Academic Appointments:

07/2015-present	Instructor	Pediatrics	Harvard Medical School

Appointments at Hospitals/Affiliated Institutions:

07/2009-06/2012	Teaching Fellow	Pediatrics	Boston University Medical School, Boston Medical Center

07/2009-06/2012	Clinical Fellow	Pediatrics	Harvard Medical School, Boston Children's Hospital
07/2012-06/2015	Clinical Fellow	Pediatrics, Division of Hematology / Oncology	Harvard Medical School, Boston Children's Hospital and Dana-Farber Cancer Institute
07/2015-present	Instructor / Attending Physician	Pediatrics, Division of Hematology / Oncology	Harvard Medical School, Boston Children's Hospital and Dana-Farber Cancer Institute

Committee Service:

National

2017	59th Annual Meeting of the American Society of Hematology (ASH) Abstract Review Committee, August 2017	American Society of Hematology, Abstract Reviewer for Category 618: Acute Lymphoblastic Leukemia: Biology, Cytogenetics, and Molecular Markers in Diagnosis and Prognosis

Professional Societies:

2003-	American Association for Cancer Research	Student Member (2003-2004), Associate Member (2005-2017), Active Member (2017-)
2012-	American Society of Pediatric Hematology/Oncology	Trainee Member (2012-2015), Member (2015-)
2012-	Children's Oncology Group	Fellow Member (2012-2015), Member (2016-)
2013-	American Society of Hematology	Associate Member (2013-2015), Member (2016-)
2014-2016	American Society of Clinical Oncology	Member

Editorial Activities:

Ad hoc Reviewer
Science Advances

Honors and Prizes:

2000	National Merit Scholarship Recipient	National Merit Scholarship Program
2000	Illinois State Scholar	Illinois State Scholars Program
2001, 2002	University of Chicago Howard Hughes Summer Undergraduate Research Fellow	University of Chicago
2002	Howard Hughes Summer Undergraduate Research Symposium Top 3 Presenter	University of Chicago
2003	Minisymposium Presentation at American Association for Cancer Research (AACR) Annual Meeting	American Association for Cancer Research (AACR)

2004	Poster Presentation and Travel Award Recipient at American Society of Hematology (ASH) Annual Meeting	American Society of Hematology (ASH)
2005	Alexandra J. Miliotis Fellowship in Pediatric Oncology	Alex's Team Foundation and Harvard Medical School
2006	Oral Presentation at Harvard Medical School's Soma Weiss Research Day	Harvard Medical School
2007	Howard Hughes Medical Institute (HHMI) Research Training Fellowship for Medical Students	Howard Hughes Medical Institute (HHMI)
2010	Fred Lovejoy House-staff Research and Education Fund Award Recipient	Boston Children's Hospital
2011	American Society of Hematology (ASH) Trainee Research Award	American Society of Hematology
2013	AACR Molecular Biology in Clinical Oncology Workshop Selected Participant	American Association for Cancer Research (AACR)
2014	Poster Presentation at AACR Special Conference on Hematologic Malignancies: Translating Discoveries to Novel Therapies	American Association for Cancer Research (AACR)
2014	Poster Presentation at American Society of Hematology Annual Meeting	American Society of Hematology
2015	"Speed Poster Talk" at FASEB Hematologic Malignancies Meeting	Federation of American Societies of Experimental Biology (FASEB)
2015	Young Investigator Award	Conquer Cancer Foundation of ASCO
2015	Physician-Scientist Training Award	Damon Runyon Cancer Research Foundation
2015, 2017	NIH Pediatric Loan Repayment Program Recipient	National Institutes of Health Division of Loan Repayment
2017	Moderator for American Society of Hematology (ASH) Annual Meeting Oral Abstract Session on Biology, Signaling Mechanisms, and Response in ALL	American Society of Hematology (ASH)
2018	Selected Participant for the Translational Research Training in Hematology (TRTH) Program	European Hematology Association (EHA) and American Society of Hematology (ASH)
2018	Young Investigator in Pediatric Oncology Drug Development	CureSearch for Children's Cancer

Report of Funded and Unfunded Projects

Funding Information:

Past

2013-2014 **Research Training in Pediatric Oncology**
NIH/NCI T32 CA136432 (PI: Stuart Orkin, M.D.)
Trainee
The major goal of this T32 program is to train physicians who will be the future academic leaders in basic and/or clinical pediatric oncology research. Performed research in the laboratory of David Weinstock, M.D. Evaluated the efficacy of type II JAK2 inhibitors in JAK2-dependent B-cell acute lymphoblastic leukemias (B-ALL) and studied mechanisms of resistance to these inhibitors.

2014-2015 **Training Program in Molecular Hematology**
NIH/NHLBI T32 HL116324 (Nancy Berliner, M.D.)
Trainee
This grant is focused on clinician scientists and aims to support a laboratory-based training program to nurture the next generation of hematologists focused on research in molecular hematology. Continuing to pursue post-doctoral research in the laboratory of David Weinstock, M.D. Studying the mechanisms of response and resistance to type II JAK2 inhibitors in JAK2-dependent B-ALL.

2015-2016 **Defining Mechanisms of Resistance to Type II JAK2 Inhibitors in B-cell Acute Lymphoblastic Leukemia**
Conquer Cancer Foundation of ASCO Young Investigator Award ($50,000)
PI
The major goal of this study is to determine what mechanisms mediate *in vitro* and *in vivo* resistance to JAK2 inhibitors in *CRLF2*-rearranged B-ALL.

2015-2016 **Identifying Mechanisms of Resistance to Type II JAK2 Inhibitors in B-ALL**
Rally Foundation/Bear Necessities Pediatric Cancer Foundation Research Grant ($50,000)
PI
The major goal of this study is to determine what mechanisms mediate *in vitro* and *in vivo* resistance to JAK2 inhibitors in CRLF2-rearranged B-ALL.

2015-2017 **Identifying Mechanisms of Resistance to JAK2 Inhibition in *CRLF2*-Rearranged B-ALL**
Pedals for Pediatrics Research Grant ($40,000)
PI
The major goals of this study are to identify which other kinases *trans*-phosphorylate JAK2 and promote resistance to a type I JAK2 inhibitor and to define mechanisms of *in vivo* resistance to a type II JAK2 inhibitor.

2016-2017 **Targeting JAK2 Addiction in B-cell Acute Lymphoblastic Leukemia**
Rally Foundation Research Grant ($50,000)
PI
The major goals of this study are to identify novel JAK2 inhibitors and assess their *in vivo* efficacy in patient-derived xenograft models of CRLF2/JAK2-dependent B-ALL.

2016-2017 **Development of Novel Type II JAK2 Inhibitors**
Team Path to the Cure Pilot Grant ($40,000)
PI
The major goals of this study are to validate the hits from a recent screen to identify novel type II JAK2 inhibitors and for medicinal chemistry development of analogs that will optimize potency, specificity, and physicochemical properties of these compounds.

Current

2015-2019 **Mechanisms of Disease and Resistance in CRLF2-Rearranged B-Cell Acute Lymphoblastic Leukemia**
Damon Runyon Physician Scientist Training Award ($460,000)
PI
The major goals of this study are to define mechanisms of resistance to JAK2 inhibitors and determine the role of gene deletions in P2RY8-CRLF2-rearranged B-ALL.

2018-2021 **JAK2 Inhibition and Degradation in B-Cell Acute Lymphoblastic Leukemia**
CureSearch Young Investigator Award in Pediatric Oncology Drug Development ($225,000)
PI
The major goals of this study are to identify and characterize novel type II JAK2 inhibitors and to validate the pre-clinical activity of JAK2 degraders in JAK2-dependent B-ALL.

Unfunded Current Projects

2014-present **Pediatric Hematologic Malignancy Xenograft Repository**
Liaison between clinical staff and Weinstock laboratory staff in an effort to xenograft samples from pediatric patients with a new or relapsed diagnosis of leukemia at Dana-Farber Cancer Institute / Boston Children's Hospital.

Report of Local Teaching and Training

Formal Teaching of Residents, Clinical Fellows and Research Fellows (post-docs):

2011-2012	Senior Rounds Pediatric senior residents and invited faculty	Boston Children's Hospital 10 hours of preparation and contact time.
2012-2013	Tumor Board Pediatric oncology fellows and faculty	Dana-Farber Cancer Institute 30 hours of preparation and contact time.
2013	Mini-Grand Rounds – Bone Marrow Transplant Case Presentation and Discussion	Boston Children's Hospital 5 hours of preparation and contact time.
2015-2016	Oncology Resident Teaching Pediatric junior residents	Boston Children's Hospital 2 hours of preparation and contact time.

Clinical Supervisory and Training Responsibilities:

2015-present	Attending supervision of residents, fellows, and nurse practitioners primarily on the inpatient Hematologic Malignancies Service at Boston Children's Hospital.	4 weeks/yr
2015-present	Attending supervision of fellows seeing oncology outpatients in the Jimmy Fund Clinic at Dana-Farber Cancer Institute.	2 half days/month (approximate)

Laboratory and Other Research Supervisory and Training Responsibilities:

2015-present	Supervision and training of a research technician in the Weinstock lab at Dana-Farber Cancer Institute.	40 hours/week
2017	Supervision and training of a summer undergraduate research student in the Weinstock lab at Dana-Farber Cancer Institute.	40 hours/week

Local Invited Presentations:

No presentations below were sponsored by outside entities

Those presentations below sponsored by outside entities are so noted and the sponsor(s) is (are) identified.

2015 JAK2 Inhibition in B-cell Acute Lymphoblastic Leukemia
Hematologic Neoplasia & Immunologic Therapies Seminar, Dana-Farber Cancer Institute

2015	JAK2 Inhibition in B-cell Acute Lymphoblastic Leukemia Sallan ALL Investigators' Meeting, Dana-Farber Cancer Institute

Report of Clinical Activities and Innovations

Current Licensure and Certification:

2012-present	Medical License, State of Massachusetts
2013-present	Board Certified in Pediatrics (American Board of Pediatrics)
2017-present	Board Certified in Pediatric Hematology / Oncology (American Board of Pediatrics)

Practice Activities:

2015-2016	Inpatient and outpatient pediatric hematology, oncology, and bone marrow transplant care.	Boston Children's Hospital and Dana-Farber Cancer Institute	4 weeks of inpatient attending time/yr. Twice monthly outpatient hematology and oncology clinics. Intermittent overnight hospitalist shifts on the bone marrow transplant service.
2016-present	Inpatient and outpatient pediatric oncology and bone marrow transplant care.	Boston Children's Hospital and Dana-Farber Cancer Institute	4 weeks of inpatient attending time/yr. Twice monthly oncology clinics. Intermittent overnight hospitalist shifts on the bone marrow transplant service.

Report of Education of Patients and Service to the Community

Activities

2012-present	The Hole in the Wall Gang Camp, Volunteer Physician Worked in the infirmary and attended to the medical needs of children with sickle cell disease, cancer, and other life threatening illnesses attending Camp for a week (June 2012, August 2013, August 2014, July 2015, July 2016, July 2017, June 2018).

Report of Scholarship

Peer-Reviewed Scholarship in print or other media:

Research Investigations

1. Echlin-Bell DR, Smith LL, **Li L**, Strissel PL, Strick R, Gupta V, Banerjee J, Larson R, Relling MV, Raimondi SC, Hayashi Y, Taki T, Zeleznik-Le N, Rowley JD. Polymorphisms in the *MLL* BCR. *Human Genet*. 2003; 113(1): 80-91.

2. Zhang Y, Zeleznik-Le N, Emmanuel N, Jayathilaka N, Chen J, Strissel P, Stick R, **Li L**, Neilly MB, Taki T, Hayashi Y, Kaneko Y, Schlegelberger B, Rowley JD. Characterization of genomic breakpoints in MLL and CBP in leukemia patients with t(11;16). *Genes Chromosomes Cancer*. 2004; 41(3): 257-265.

3. Hall MJ, **Li L**, Wiernik PH, Olopade OI. BRCA2 mutation and the risk of hematologic malignancy. *Leuk Lymphoma*. 2006; 47(4): 765-767.

4. Banerji V, Frumm SM, Ross KN, **Li LS**, Schinzel AC, Hahn CK, Kakoza RM, Chow KT, Ross L, Alexe G, Tolliday N, Inguilizian H, Glainsky I, Stone RM, DeAngelo DJ, Roti G, Aster JC, Hahn WC, Kung AL, Stegmaier K. The intersection of genetic and chemical genomic screens identifies GSK-3α as a target in human acute myeloid leukemia. *J Clin Invest*. 2012; 122(3): 935-947.

5. Wu S-C[*], **Li LS**[*], Kopp N[*], Montero J, Chapuy B, Yoda A, Christie AL, Liu H, Christodoulou A, van Bodegom D, van der Zwet J, Layer JV, Tivey T, Lane AA, Ryan JA, Ng SY, DeAngelo DJ, Stone RM, Steensma D, Wadleigh M, Harris M, Mandon E, Ebel N, Andraos R, Romanet V, Dölemeyer A, Sterker D, Zender M, Rodig SJ, Murakami M, Hofmann F, Kuo F, Eck MJ, Silverman LB, Sallan SE, Letai A, Baffert F, Vangrevelinghe E, Radimerski T, Gaul C[*], Weinstock DM[*]. Activity of the type II JAK2 inhibitor CHZ868 in B-cell acute lymphoblastic leukemia. *Cancer Cell*. 2015; 28(1): 29-41. [*]equal contribution.

6. Townsend EC, Murakami MA, Christodoulou A, Christie AL, Koester J, DeSouza TA, Morgan EA, Kallgren SP, Liu H, Wu S-C, Plana O, Montero J, Stevenson KE, Andreeff M, Armand P, Ballen KK, Barzaghi-Rinaudo P, Cahill S, Clark RA, Cooke VG, Davids MS, DeAngelo DJ, Dorman DM, Eaton H, Ebert BL, Etchin J, Firestone B, Fisher DC, Freedman AS, Galinsky IA, Gao H, Garcia JS, Garnache-Ottou F, Graubert TA, Gutierrez A, Halilovic E, Harris MH, Herbert ZT, Horwitz SM, Inghirami G, Intlekofer AM, Ito M, Izraeli S, Jacobsen ED, Jacobson CA, Jeay S, Jeremias I, Kelliher MA, Koch R, Konopleva M, Kopp N, Kornblau SM, Kung AL, Kupper TS, LeBoeuf N, LaCasce AS, Lees E, **Li LS**, Look AT, Murakami M, Muschen M, Neuberg D, Ng SY, Odejide OO, Orkin SH, Paquette RR, Place AE, Roderick JE, Ryan JA, Sallan SE, Shoji B, Silverman LB, Soiffer RJ, Steensma DP, Stegmaier K, Stone RM, Tamburini J, Thorner AR, van Hummelen P, Wadleigh M, Wiesmann M, Weng AP, Wuerthner JU, Williams DA, Wollison BM, Lane AA, Letai A, Bertagnolli M, Ritz J, Brown M, Long H, Aster JC, Shipp M, Griffin JD, Weinstock DM. The Public Repository of Xenografts enables discovery and randomized phase II-like trials in mice. *Cancer Cell*. 2016; 29(4): 574-586.

7. Townsend EC, Murakami MA, Christodoulou A, Christie AL, Köster J, DeSouza TA, Morgan EA, Kallgren SP, Liu H, Wu SC, Plana O, Montero J, Stevenson KE, Rao P, Vadhi R, Andreeff M, Armand P, Ballen KK, Barzaghi-Rinaudo P, Cahill S, Clark RA, Cooke VG, Davids MS, DeAngelo DJ, Dorfman DM, Eaton H, Ebert BL, Etchin J, Firestone B, Fisher DC, Freedman AS, Galinsky IA, Gao H, Garcia JS, Garnache-Ottou F, Graubert TA, Gutierrez A, Halilovic E, Harris MH, Herbert ZT, Horwitz SM, Inghirami G, Intlekofer AM, Ito M, Izraeli S, Jacobsen ED, Jacobson CA, Jeay S, Jeremias I, Kelliher MA, Koch R, Konopleva M, Kopp N, Kornblau SM, Kung AL, Kupper TS, LeBoeuf NR, LaCasce AS, Lees E, **Li LS**, Look AT, Murakami M, Muschen M, Neuberg D, Ng SY, Odejide OO, Orkin SH, Paquette RR, Place AE, Roderick JE, Ryan JA, Sallan SE, Shoji B, Silverman LB, Soiffer RJ, Steensma DP, Stegmaier K, Stone RM, Tamburini J, Thorner AR, van Hummelen P, Wadleigh M, Wiesmann M, Weng AP, Wuerthner JU, Williams DA, Wollison BM, Lane AA, Letai A, Bertagnolli MM, Ritz J, Brown M, Long H, Aster JC, Shipp MA, Griffin JD, Weinstock DM. The Public Repository of Xenografts enables discovery and randomized phase II-like trials in mice. *Cancer Cell*. 2016; 30(1): 183.

8. Chiaretti S, Messina M, Piciocchi A, Fedullo AL, Di Giacomo F, Peragine N, Gianfelici V, Lauretti A, Bareja R, Martelli MP, Vignetti M, Apicella V, Vitale A, **Li LS**, Salek C, Elemento O, Inghirami G, Weinstock DM, Guarini A, Foa R. Rapid identification of BCR/ABL1-like acute lymphoblastic leukaemia

patients using a predictive statistical model based on quantitative real time-polymerase chain reaction: clinical, prognostic, and therapeutic implications. *Br J Haematol.* 2018; 181(5): 642-652.

DISCOVERING NONCODING GENETIC ELEMENTS THAT REGULATE GLOBIN SYNTHESIS

Authors: Akshay Sharma, Yu Yao, Jiyang Yu, Yongdong Wang, Shengdar Tsai, Kaitly Woodward, Mitchell Weiss

Background: Sickle cell disease (SCD) causes significant morbidity and mortality in millions of people worldwide. Elevated fetal hemoglobin (HbF) levels alleviate SCD pathology and clinical severity. The expression of HbF varies between individuals, primarily in accordance with genetic determinants. Human population studies have demonstrated that adult HbF levels are influenced by DNA sequence variations in noncoding regions that regulate the production of relevant transcription factors (TFs), such as BCL11A, MYB, and KLF1, and/or in their cognate DNA sequences in the extended β-globin locus. However, the known polymorphisms in these loci account for only approximately 50% of the variation in HbF expression. We hypothesized that the noncoding regions of these genes contain many currently unidentified cis-regulatory modules (CRMs) that regulate HbF expression.

Objective: To identify and validate novel CRMs in the topologically associating domains of TFs that regulate HbF expression.

Design/Method: Erythroid CRMs can be predicted with high accuracy by the presence of erythroid-specific DNase-hypersensitivity sites, the binding of erythroid TFs, and their physical interactions with target genes. We used these characteristics to predict 311 CRMs for BCL11A, MYB, KLF1, and the β-globin locus. Using a CRISPR/Cas9 genome-editing approach, we designed all possible single-guide RNAs (sgRNAs) within these regions and cloned them into a lentiviral vector library. Human umbilical cord blood–derived erythroid progenitor (HUDEP-2) cells co-expressing Cas9 protein were transduced with the lentiviral library at a low multiplicity of infection. Transduced HUDEP-2 cells were expanded, differentiated, and fractionated into HbF-high and HbF-low populations by fluorescence-activated cell sorting. Integrated sgRNAs were deep sequenced, and an enrichment score was calculated for each sgRNA by comparing the representation of the two cell populations.

Results: We have identified several candidate regulatory loci associated with HbF regulation, the most prominent one being the pseudogene HBBP1. HBBP1 is minimally transcribed but, nevertheless, has one of the most conserved nucleotide sequences in the region. Deleting this pseudogene increases fetal hemoglobin in HUDEP-2 cells, as well as in primary human CD34+ cell–derived erythroblasts.

Conclusion: These experiments suggest that the genomic repertoire of regulatory elements for any gene is much more diverse than previously imagined. We will not only define how these elements interact to “fine tune” the expression of several TFs and their effects on HbF expression but may also lead to novel targets for gene therapy of hemoglobinopathies. These studies will generate a high-throughput approach for identifying previously unknown genomic regulatory elements.

St. Jude Children's Research Hospital
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Finding cures. Saving children.

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Jan 07, 2019

Re: Akshay Sharma's application for the ASPHO Young Investigator Award

Dear Committee Members

It is a great pleasure for me to support Akshay Sharma's application for the ASPHO Young Investigator Award. I first met Akshay four years ago when he was a first-year clinical fellow in pediatric hematology/oncology and was searching for a research mentor. My colleagues at St. Jude recommended Akshay as an outstanding clinical trainee with strong motivation to pursue a career in academic medicine, focusing on nonmalignant hematology. We spent a week together on the hematology inpatient service at St. Jude, where he demonstrated outstanding clinical skills with an analytical problem-solving approach to patient problems and a strong interest in the mechanisms of disease. Although he had relatively little laboratory experience, I recruited Akshay into my laboratory because I was impressed with his clinical performance, enthusiasm, polite persistence, and genuine motivation to become accomplished in scientific research. After working with Akshay closely for the last three years, I recognize that he is exceptional and highly likely to succeed as a physician-scientist in academic hematology.

Akshay followed up on work by Liz Traxler, an MD/PhD student in my laboratory, who showed that CRISPR/Cas9-mediated disruption of a repressor element in the γ-globin gene promoter raises fetal hemoglobin to potentially therapeutic levels in $CD34^+$ cell–derived reticulocytes from patients with sickle cell disease (SCD). Dan Bauer at Harvard University showed that similar induction of fetal hemoglobin can be achieved by disrupting an erythroid enhancer in the *BCL11A* gene, which encodes a transcriptional repressor protein that facilitates the fetal-to-adult hemoglobin switch. Based on these findings, Akshay hypothesized that additional regulatory elements in the genome must also contribute to hemoglobin switching. Working with collaborators, including Ross Hardison at Penn State University and Ruopeng Feng, a postdoctoral fellow in my laboratory, Akshay used bioinformatic approaches to identify potential *cis*-regulatory modules in genes that regulate hemoglobin switching, including the extended β-globin locus, *KLF1*, *BCL11A*, and *MYB*. He designed a library of approximately 6000 guide RNAs (gRNAs) that tile across approximately 300 predicted DNA regulatory regions. He introduced this library, along with Cas9, into HUDEP-2 cells, a human erythroblast cell line that models hemoglobin switching, and identified gRNAs that stimulate fetal hemoglobin expression by disrupting specific regions of DNA.

An interesting result from this saturation mutagenesis screen was a pseudogene in the globin locus called *HBBP1*. This pseudogene does not produce a protein in humans and has a very low level of transcription in erythroid progenitors, yet it has one of the most conserved nucleotide sequences in the locus. Akshay was able to identify unique gRNAs with which to disrupt this locus and made clones of HUDEP-2 cells that had elevated fetal hemoglobin levels. Our colleagues Gerd Blobel and Peng Huang at the University of Pennsylvania identified differential chromatin interactions around this same

region in fetal vs adult erythroid cells and published their results, which were very similar to Akshay's findings, in *Genes and Development* a few months ago. Undiscouraged, Akshay was determined to improve his screening system for discovery of genetic regulatory elements. He had identified several shortcomings of the initial gRNA/Cas9-based approach and proposed that by expressing two gRNAs simultaneously in cells, he could produce tiled deletions that saturated large genomic regions. Akshay has been successful in turning around this very challenging project and has developed a novel, pragmatic, high-throughput screening method using paired gRNA-based tiled deletions. Akshay has demonstrated remarkable talent in the laboratory and is a pleasure to work with. His preliminary data identify a surprisingly high number of novel regulatory regions that control fetal hemoglobin expression, which is relevant to gene therapy for hemoglobinopathies and also has general implications for defining mechanisms of gene expression. Akshay is currently spearheading the clinical efforts at St. Jude to develop clinical trials of bone marrow transplant and gene therapy for patients with sickle cell disease and other hematological disorders.

The Division of Clinical Hematology within the Department of Hematology at St. Jude cares for approximately 900 patients with SCD. Our long-term goal is to cure this disorder through integrated basic, translational, and clinical research. Akshay's research and his career goal to become a physician-scientist focusing on bone marrow transplantation and gene therapy for nonmalignant pediatric blood disorders are highly consistent with the goals of my laboratory and the Department of Hematology at St. Jude.

There are two reasons why ASPHO should award the Young Investigator Award in Pediatric Hematology/Oncology to Akshay. First, the research is highly significant. He is using cutting-edge technologies to better understand human blood gene regulation in studies that are relevant to SCD, an underserved disorder that medical researchers are now in a position to cure. His preliminary data are potentially of high impact because they indicate that the network of *cis* elements regulating individual genes and the developmental process of hemoglobin switching are far more complex than previously imagined. However, the most important reason to is to support Akshay, an applicant with great potential who represents our future in academic nonmalignant hematology. Among the many biomedical research trainees with whom I have interacted over more than 20 years at Harvard and the University of Pennsylvania, Akshay is in the top 2% with respect to research creativity, motivation, and intellect. His research project and career aspirations are highly consistent with the mission of ASPHO, and I believe that he has the motivation and talent to become a successful physician-scientist. Fulfilling my long-term responsibility to Akshay will be enjoyable because he is talented, driven, and loves science. Akshay resembles my best trainees, who have taught me as much as I have taught them.

Please contact me if you have any questions or if there is anything else that I can do to support Akshay.

Sincerely,

Mitchell J. Weiss, MD, PhD

Career Development Statement

Career goals: My career goal is to become a clinician-scientist with expertise in the field of pediatric hematopoietic cell transplantation (HCT), and a focus on cellular and gene therapy for non-malignant hematological disorders, especially sickle cell disease (SCD). My clinical education and research training have provided me a strong foundation to advance my academic career. My laboratory research training under the supervision of Dr. Mitchell Weiss, has allowed us to better define the developmental γ-to-β-globin gene switch and has encouraged me to develop high throughput screening methods to agnostically identify novel genetic regulatory elements. I was among the 11 hematology-oncology fellows nationwide who were awarded grant funding (Research Training Award for Fellows) from the *American Society of Hematology* in 2017 for my laboratory research focusing on the use of CRISPR/Cas9 technology to identify novel genetic regulators of globin switching. More importantly, we have harnessed CRISPR/Cas9 genome editing technology to reverse the globin switch and de-repress fetal hemoglobin production as an approach to treat hemoglobinopathies. This is the basis of my clinical research proposed below.

Although my preclinical studies have generated important data, I have come to realize that my passion is in applying these findings through clinical research rather than continuing to focus my investigations on basic science as a laboratory scientist. As part of this transition, I have obtained a position in the Department of Bone Marrow Transplantation and Cellular Therapy (BMTCT) at St. Jude as clinician-scientist devoting at least 50% of my effort on clinical investigation. My long-term goal is to develop therapeutic trials and correlative studies for non-malignant hematological disorders, particularly sickle cell disease, that utilize hematopoietic cell transplantation, cellular and gene therapies.

1. Haploidentical HCT for SCD patients lacking a matched sibling donor

The only established cure for patients with SCD is allogeneic HCT using an HLA-matched sibling donor but less than 20% of the patients have such a donor available. Haploidentical HCT is a potential alternative for SCD patients but in its current form faces several obstacles such as GVHD, infertility and most importantly, a fixed risk of transplantation-related mortality. A reduced intensity conditioning (RIC) regimen that limits treatment related morbidity is currently being studied by Blood and Marrow Transplant Clinical Trials Network (BMT CTN) in a prospective, multicenter trial (BMT CTN 1507) using haploidentical donors for pediatric and young adult patients with SCD. I am the site principal investigator of this study at St. Jude. Building on this experience, as well as experience from participating in other collaborative consortia led clinical trials, I eventually plan on developing institutional transplant protocols for SCD to pilot novel conditioning regimens and transplant methods. I will then disseminate successful transplant regimens via clinical collaborations and by leading multi-center clinical trials.

2. Gene therapy for SCD

While advances have been made in transplant immunology, the notion of correcting autologous stem cells remains the ultimate panacea for SCD. Dr. Mitchell Weiss' group has successfully developed a CRISPR/Cas9 based genome editing approach to effectively de-repress gamma globin and lead to production of high levels of fetal hemoglobin in the erythroid cells derived from the edited human CD34+ hematopoietic stem cells (HSCs). The preclinical experiments are being completed for an IND application to the FDA. This gene therapy product is expected to be available for clinical testing in another 1-2 years. With my laboratory experience, I will continue to help with the further development of this program as it matures towards human application and develop a phase I/II study to assess the safety and efficacy of ameliorating the symptoms of SCD following autologous transplant of HSCs edited using this approach.

Funding: My research will be supported through a variety of mechanisms. Institutional resources will support a portion of my time and can fully support the research if attempts to secure external funding are unsuccessful. Funding for the proposed gene therapy study will be provided through a recently awarded P01 grant entitled *Lentiviral Gene Therapy for Sickle Cell Disease and Immunodeficiency Disorders* and through institutional funds. Building upon my prior success with the ASH Research Training Award for Fellows, I will continue to seek charitable/foundation support for my proposed research. I will apply for a K23 to support my continued development as a clinical researcher and generate preliminary data from

pilot studies. This data will in turn support a subsequent application for R01 funding to expand this work to other groups as well as additional clinical trials.

Institutional environment: While my own background with gene editing and preclinical work on genetics of globin switching makes me uniquely qualified to lead these studies, my likelihood of success is furthered by the environment I will be working in. The Division of Clinical Hematology cares for about 900 pediatric patients with SCD, many of whom are at a high risk for developing severe debilitating sequelae of the disease and early mortality. These patients are extremely motivated to participate in research studies of curative approaches for SCD, including transplantation and gene therapy. In addition, the Department of BMTCT at St. Jude is one of the busiest pediatric transplant centers conducting about 100 pediatric transplants every year. Although the focus of BMTCT at St. Jude has been on haploidentical transplantation, our repertoire ranges from immunotherapy for refractory hematological neoplasms to gene therapy for primary immunodeficiencies. BMTCT is already conducting a gene therapy study of autologous HCT of lentivirus-modified CD34+ progenitor cells in infants with X-linked SCID and has recently opened its first cell therapy study with CAR-T cells. St. Jude has an ideal infrastructure to support my projects, which includes a vector core, a GMP facility that can prepare clinical grade lentiviral vectors and cell products, and a clinical research office. In addition, there is a strong biostatistics department to support clinical investigators in development of clinical trials and analysis of the results.

I will be mentored in the development of these gene therapy and HCT clinical trials by Dr. Mitchell Weiss, a global leader in red blood cell biology and genome editing, and Dr. Stephen Gottschalk, a distinguished clinician-scientist in the area of cancer immunotherapy. I have also worked successfully with other collaborators who will be helpful with planned correlative studies, including Dr. Shengdar Tsai, an expert on genome editing technology and off-target analysis, Dr. Marcin Wlodarski, a leader in bone marrow failure syndromes and Dr. Brandon Triplett, an expert on haploidentical transplantation. My prior successful collaborative research with all of them suggests a high likelihood of success in this new proposed work. In addition, Drs. Terrence Geiger, Ellis Neufeld (both at St. Jude) and Lakshmanan Krishnamurti (Emory University) who are all senior hematologists and established clinician-scientists will serve as my mentorship committee and I will meet with them regularly to discuss my progress and obtain career development advice. Combining my interest in non-malignant hematology, gene therapy and HCT with the institutional support from St. Jude provides me with a unique opportunity to advance clinical therapeutics, develop curative protocols, evaluate and recruit eligible patients for the transplant/gene therapy studies and lead the development of a cellular and gene therapy program for sickle cell disease.

Additional training: I will gain further clinical research skills through both institutional training and opportunities at national meetings. I will attend at least six Responsible Conduct of Research seminars yearly held at St. Jude, as well as didactic sessions at national meetings including ASPHO, ASH, Transplant and Cellular Therapy meetings, and the PBMTC. I am also applying for the ASH Clinical Research Training Institute and the ISCT-ASBMT Cell Therapy training Course. The formalized training at these courses would both accelerate my development as a researcher and indicate to others my knowledge and preparation for collaboration. I will also enroll in a MS course in clinical research and scientific investigation to further strengthen my clinical research skills and increase my repertoire to include biostatistics and clinical trial design.

AKSHAY SHARMA, MBBS

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Professional Appointments and Licensures

Current Position:	Instructor, Department of Bone Marrow Transplantation and Cellular Therapy, St. Jude Children's Research Hospital, Memphis, Tennessee.
Licensure/ Registration:	Tennessee Board of Medical Examiners, 57576 (2018-2020) Kentucky Board of Medical Licensure, 47961 (2015-2018) State Medical Board of Ohio, 57.023959 (2013-2015) Educational Commission for Foreign Medical Graduates (ECFMG), Certificate #07952609 (2011) Medical Council of India (2010)
Certifications:	American Board of Pediatrics 2015-2025 BLS and PALS Provider 2012-Present

Education and Postdoctoral Training

2015-2018	Clinical Fellowship, Pediatric Hematology and Oncology, Postdoctoral research in the laboratory of Mitchell J Weiss, MD, PhD St. Jude Children's Research Hospital, Memphis, Tennessee.
2012-2015	Residency, Department of Pediatrics, University of Kentucky College of Medicine, Lexington, Kentucky.
2011- 2012	Post-Doctoral Fellowship, Tumor Immunology and Transplantation Laboratory of Edmund K Waller, MD, PhD Emory University, Winship Cancer Institute, Atlanta, Georgia.
2004-2010	Bachelor of Medicine and Bachelor of Surgery (MBBS) Kasturba Medical College, Manipal University, Mangalore, India.

Academic Appointments

2010-2011	Junior Resident, Department of Pediatrics MM Institute of Medical Sciences and Research, MM University, Haryana, India

Honors and Awards

2018	First Prize, Annual Clinical Fellows Research Symposium, St. Jude Children's Research Hospital
2017	First Prize (Basic Science Category), Annual Clinical Fellows Research Symposium, St. Jude Children's Research Hospital
2017	ASBMT Annual Meeting Travel Grant

2016	Selected for AACR Molecular Biology in Clinical Oncology Workshop, Snowmass, CO
2015	Best Evidence Based Medicine Presentation, University of Kentucky Pediatrics Residency Program
2014	Outstanding Resident of the Year in Research, University of Kentucky Pediatrics Residency Program
2013	Outstanding Resident of the Year in Pediatric Hematology-Oncology, Pediatric Infectious Diseases and Pediatric Adolescent Medicine, University of Kentucky Pediatrics Residency Program
2013	Clinical House-Staff Teaching Award, University of Kentucky Healthcare
2013	Resident of the Month (May), University of Kentucky Healthcare
2010	Second Prize, South Asian Cochrane Network Essay Competition
2009	International Students' Congress of Medical Sciences (ISCOMS) Research Fellowship, University Medical Center Groningen, The Netherlands

Professional Affiliations

Professional Memberships:

2016-Present	American Society of Hematology
2015-Present	American Society for Blood and Marrow Transplantation
2012-Present	American Academy of Pediatrics
2011-Present	Indian Academy of Pediatrics

Leadership Positions:

2014-2015	President, Kentucky Medical Association - Resident and Fellows Section
2014-2015	Member, Kentucky Medical Association Board of Trustees
2014-2015	Member, Kentucky Medical Association - Commission on Young Physicians & Physicians in Training

Editorial Board Member:

2016-Present	The Journal of Health Design
2012-2014	BMJ Case Reports
2008-2011	Journal of Young Investigators

***Ad-hoc* Reviewer:**

Archives of Disease in Childhood (2016- Present), BMJ Case Reports (2010- Present), Australasian Medical Journal (2009-2010), Student BMJ (2008-2009)

Grant Support

2017	American Society of Hematology – Research Training Award for Fellows – To provide protected time for research during fellowship training.
2015	Children's Miracle Network Grant – To further develop, maintain and promote the automated text messaging-based immunization reminder system VaccineReminder.Org.
2014	American Academy of Pediatrics Community Access to Child Health

	(CATCH) Resident Grant – To develop an automated text message-based immunization reminder system.
2013	AAP & UN Foundation Shot@Life MiniGrant – To advocate for global vaccine access and availability.
2007	Indian Council of Medical Research, Short Term Studentship in Microbiology – To study the role of currency as fomites in the transmission of disease causing microorganisms.
2006	Indian Council of Medical Research, Short Term Studentship in Pharmacology – To identify the adverse effects caused by long-term use of non-steroidal anti-inflammatory drugs (NSAIDs).

Publications

Peer Reviewed Publications

1. Swimm A, Giver CR, DeFilipp Z, Rangaraju S, **Sharma A**, Ulezko Antonova A, Sonowal R, Capaldo C, Powell D, Qayed M, Kalman D, Waller EK. Indoles derived from intestinal microbiota act via type I interferon signaling to limit Graft-versus-Host-Disease. Blood. 2018 Dec 6;132(23):2506-2519. PubMed PMID: 30257880.
2. **Sharma A**, Kang G, Sunkara A, Inaba H, Jeha S, Cross SJ, Geiger T, Triplett B. Haploidentical donor transplantation using a novel clofarabine-containing conditioning regimen for very high-risk hematologic malignant neoplasms. Journal of Pediatric Hematology and Oncology. 2018 Nov;40(8):e479-e485. PubMed PMID: 29750747.
3. George AP, **Sharma A**, Day SB. Aeromedical transport of critically ill infants less than 3 months of age. Global Pediatric Health. 2017 Nov 14;4:2333794X17739743. doi: 10.1177/2333794X17739743. eCollection 2017. PubMed PMID: 29164175.
4. **Sharma A**, Geiger TL, Federico S, Kamens J, Giles F, Cunningham L. Hypocalcemic tetany after transfusion of a small amount of blood product. Journal of Pediatric Hematology and Oncology. 2017;39(8):629-632. PubMed PMID:28902075.
5. **Sharma A** Easow Mathew M, Sriganesh V, Reiss UM. Gene therapy for haemophilia (Revised). Cochrane Database of Systematic Reviews. 2016;12: CD010822. PubMed PMID: 27996087.
6. Jagannath VA, Fedorowicz Z, Al Hajeri A, **Sharma A**. Hematopoietic stem cell transplantation for people with ß-thalassaemia major (Revised). Cochrane Database of Systematic Reviews. 2016;11: CD008708. PubMed PMID: 27900772.
7. **Sharma A**, Hong-McAtee I. Case 2: Prolonged Hypoglycemia in an adolescent without diabetes. Pediatrics in Review. 2016;37(7):304-6. PubMed PMID: 27368362.
8. Easow Mathew M, **Sharma A**, Aravindakshan R. Splenectomy for people with thalassaemia major or intermedia. Cochrane Database of Systematic Reviews. 2016;6:CD010517. PubMed PMID: 27296775.
9. **Sharma A**, Maul E. Vasculitis causing complete occlusion of aorta. Journal of Pediatrics. 2015;167(1):206. PubMed ID: 25937429.
10. **Sharma A**, Behar M. Heterotopic ossification in fibrodysplasia ossificans progressiva. Journal of Pediatrics. 2015;166(1):204. PubMed ID: 25444017.
11. **Sharma A**, Myers K, Ye Z, D'Orazio J. Dyskeratosis congenita caused by a novel TERT point mutation in siblings with pancytopenia and exudative retinopathy. Pediatric Blood & Cancer. 2014;61(12):2302-4. PubMed ID: 25067791.
12. **Sharma A**, Easow Mathew M, Sriganesh V, Neely JA, Kalipatnapu S. Gene therapy for haemophilia. Cochrane Database of Systematic Reviews. 2014;11:CD010822. PubMed ID: 25394678.

13. Jagannath VA, Fedorowicz Z, Al Hajeri A, **Sharma A**. Hematopoietic stem cell transplantation for people with ß-thalassaemia major (Revised). Cochrane Database of Systematic Reviews. 2014;10:CD008708. PubMed ID: 25316103.
14. Lu Y, Giver CR, **Sharma A**, Li JM, Darlak KA, Owens LM, Roback JD, Galipeau J, Waller EK. IFN-γ and indoleamine 2,3-dioxygenase signaling between donor dendritic cells and T cells regulates graft versus host and graft versus leukemia activity. Blood. 2012;119(4):1075-85. PubMed ID: 22130799.
15. Malik B, Sharma PD, Bhardwaj AK, **Sharma A**. Sub-acute sclerosing pan encephalitis despite adequate vaccination. Australasian Medical Journal. 2012;5(7):359-61. PubMed ID: 22905063.
16. Jagannath VA, Fedorowicz Z, Al Hajeri A, Hu N, **Sharma A**. Hematopoietic stem cell transplantation for people with ß thalassaemia major. Cochrane Database of Systematic Reviews. 2011(10): CD008708. PubMed ID: 21975785.
17. Bhardwaj AK, Sharma PD, Mittal A, **Sharma A**. Bilateral cystic nephroma with pleuropulmonary blastoma. BMJ Case Reports. 2011 Aug 17;2011. pii: bcr0520114171. doi: 10.1136/bcr.05.2011.4171. PubMed ID: 22688934.
18. Bhardwaj AK, Sharma PD, **Sharma A**. Falciparum malaria masquerading as appendicitis. BMJ Case Reports. 2011 Mar 10;2011. pii: bcr0120113742. doi:10.1136/bcr.01.2011.3742. PubMed ID: 22701067.
19. Bhardwaj AK, Sharma PD, **Sharma A**. Neonatal varicella: A rare case report. Australasian Medical Journal. 2011;4(6):291-3. PubMed ID: 23386890.
20. **Sharma A**, Dhanashree B. Screening of currency in circulation for bacterial contamination. Current Science. 2011;100(6):822-5.
21. Rajeev A, **Sharma A**. Mortality and morbidity patterns among HIV patients with prognostic markers in a tertiary care hospital in Southern India. Australasian Medical Journal. 2011;4(5):273-6. PubMed ID: 23393520.
22. Mahboobi H, **Sharma A**, Khorgoei T, Jahanshahi K, Cottrell E. Evidence-based Medicine for Medical Students. Australasian Medical Journal. 2010;3(3):190-3.
23. Mahboobi H, Shahrzad M, Seddigh S, Hamedi Y, **Sharma A**, Khorgoei T, et al. Designing a research mentorship program (RMP) to enhance research productivity at Ebne- Sina psychiatric hospital. Australasian Medical Journal. 2010;3(2):180-2.
24. Oberoi DV, Kumar CJ, Baboo CA, Gawri A, Dargar P, Goraya H, **Sharma A**, et al. A tryst with the epidemiology of a re-emerging infection: clinical and socio-demographic profile of the Chikungunya epidemic of South India. Indian Journal of Public Health Research and Development. 2010;1(2):34-8.
25. **Sharma A**, D'Souza UJ. Extrasensory perception- A preliminary study. Borneo Journal of Medical Sciences. 2008;2(01):18-24.

Non-Peer Reviewed Publications and Editorials

1. **Sharma A**, Johnson L, Brown A, Unguru Y, Lantos J. Ethics Rounds: An Extravagant Gift from a Grateful Patient. Pediatrics. 2018;141(6):e20172837.
2. **Sharma A**. Migration of medical graduates. National Medical Journal of India. 2012;25(6): 377-8. PubMed ID: 23998882.
3. **Sharma A**. Up in the Air. National Medical Journal of India. 2011;24(4): 231-2. PubMed ID: 22208145.
4. Sud V, Ejaz K, Fedorowicz Z, Mathew ME, **Sharma A**. Cochrane: spreading the message of research to students and juniors [Editorial]. Cochrane Database of Systematic Reviews. 2011(8): ED000026. PubMed ID: 21833984.
5. Jiwa M, Oberoi D, Cottrell E, **Sharma A**, Clark G, Hanson G. Writing for publication – raising standards at the AMJ. Australasian Medical Journal 2011;4(4):225-8. PubMed ID: 23393514.

6. **Sharma A**, Cottrell E. Migration and health. Australasian Medical Journal. 2010;3(1):3-8.

Book Chapters

1. D'Orazio J, **Sharma A**. Neutropenia and bone marrow failure. In: Zaoutis LB, Chiang VW, editors. Comprehensive Pediatric Hospital Medicine. Second ed. Philadelphia: McGrawHill 2017.
2. Zaidi AH, **Sharma A**. How to search in Search Engines? In: Kasi PM, editor. Research: What, Why and How?: A Treatise from Researchers to Researchers. Bloomington: AuthorHouse; 2009.

Presentations and Invited Talks

National/International

1. **Sharma A**, Kang G, Cunningham L, Madden R, Qudeimat A, Triplett BM. Allogeneic hematopoietic cell transplantation for acute megakaryoblastic leukemia: A single center experience. ASBMT-CIBMTR Tandem Meetings, Orlando, FL; Feb 2017. Abstract published in Biology of Blood and Marrow Transplantation. 2017;23(3):S299.
2. **Sharma A**, Northrip KD. Shot@Life: Engaging pediatric residents to advocate for vaccines in developing countries. Pediatric Academic Societies (Advocacy Training SIG), Vancouver, British Columbia, Canada; May 2014.
3. **Sharma A**, Duan M, Chowdhury R, Graiser M, Zhang H, Langston A, Lonial S, Flowers CR, Haight A, Waller EK. Bi-modal age distribution of patients with relapsed Hodgkin Lymphoma undergoing autologous stem cell transplantation correlates with markedly inferior survival among patients age 35 years and older. ASBMT-CIBMTR Tandem Meetings, San Diego, CA; Feb 2012. Abstract published in Biology of Blood and Marrow Transplantation. 2012;18(2):S296.
4. **Sharma A**, Rajeev A. Adrenal dysfunction in human immunodeficiency virus infected patients. International Students' Congress of Medical Sciences (ISCOMS) Groningen, The Netherlands; Jun 2009.
5. **Sharma A**. Stress related anxiety disorders in class XII science stream students. International Students' Congress of Medical Sciences (ISCOMS) Groningen, The Netherlands; Jun 2009.
6. **Sharma A**, Dhanashree B. Detection & typing of bacteria isolated from currency in circulation. First Asian and Second National Medical Students' Research Conference Pune, Maharashtra, India; 2008. Abstract published in Indian Journal of Medical Research. 2008;127(6):S698.
7. **Sharma A**, Rajeev A, Adhikari P, Ramapuram JT. Mortality and morbidity pattern among HIV patients with prognostic markers in a tertiary care hospital in Southern India. National Conference on Students' Medical Research. Thiruvananthapuram, Kerala, India; 2008.
8. **Sharma A**, Dhanashree B. Microbiological screening of currency in circulation. XXXI National Congress of Indian Association of Medical Microbiologists (IAMM) MICROCON Mangalore, Karnataka, India; 2007.

Regional

1. **Sharma A.** Sickle Cell Disease Cure: Transplantation. Sickle Cell Day, St. Jude Children's Research Hospital, Memphis, TN; June 2018.
2. **Sharma A.** Gene Therapy and Gene Editing. A New Era in Sickle Cell Disease Treatment: 2nd Biennial Pediatric-Adult Regional Sickle Cell Disease Conference. Memphis, TN; May 2018.

3. **Sharma A.** Curing Sickle Cell Disease. Grand rounds presentation, Kentucky Children's Hospital, Lexington, KY; May 2018.
4. **Sharma A**, George AP, Nataraj P, Wimberly KE, Kumar G, Northrip K. Automatic text message-based vaccination reminders to improve compliance. Southern Society for Pediatric Research (SSPR) Southern Regional Meetings, New Orleans, LA; Feb 2015. Abstract published in Journal of Investigative Medicine. 2015; 63(2):459.
5. **Sharma A**, Radulescu VC. Cutaneous lymphoma mimicking benign skin rash. Southern Society for Pediatric Research (SSPR) Southern Regional Meetings, New Orleans, LA; Feb 2015. Abstract published in Journal of Investigative Medicine. 2015; 63(2):329.
6. **Sharma A**. Global health vaccine jeopardy. Contemporary Pediatrics Conference, Lexington, Kentucky; May 2014.
7. **Sharma A**, Northrip KD. Rare Ovarian Tumor Masquerading as Hematometra. Southern Society for Pediatric Research (SSPR) Southern Regional Meetings, New Orleans, LA; Feb 2014. Abstract published in Journal of Investigative Medicine. 2014; 62(2):488.
8. **Sharma A**. Beginners guide to Evidence Based Medicine. 8th Winter Symposium, South Asian Cochrane Network & Centre, Vellore, Tamil Nadu, India; Jan 2010.

Institutional

1. **Sharma A**. Hematopoietic Cell Transplantation for Sickle Cell Disease: Progress and Challenges. LLH/BMTCT Conference, St Jude Children's Research Hospital, Memphis, TN; Aug 2018.
2. **Sharma A**, Yao Y, Yu J, Wang YD, Tsai S, Woodard K, Weiss MJ. Discovering Noncoding Genetic Elements Regulating Globin Synthesis. Annual Clinical Fellows Research Symposium, St Jude Children's Research Hospital, Memphis TN; April 2018.
3. **Sharma A**, Hatley M, Kesserwan C. Decoding DICER1. CTRST Conference, St Jude Children's Research Hospital, Memphis, TN; May 2017.
4. **Sharma A**, Yao Y, Yu J, Wang YD, Tsai S, Woodard K, Weiss MJ. Discovering Noncoding Genetic Elements Regulating Globin Synthesis. Annual Clinical Fellows Research Symposium, St Jude Children's Research Hospital, Memphis TN; April 2017.
5. **Sharma A**, Alford L, Woody K. When communication can prevent a medical error. Morbidity/Mortality Quality Improvement Conference, St Jude Children's Research Hospital, Memphis, TN; Jan 2017.
6. **Sharma A**, Weiss MJ, Byoung R. Curing Sickle Cell Disease. LLH/BMTCT Conference, St Jude Children's Research Hospital, Memphis, TN; Nov 2016.
7. **Sharma A**, Hankins J. When less is more: Restrictive transfusion practices. LLH/BMTCT Conference, St Jude Children's Research Hospital, Memphis, TN; Aug 2016.
8. **Sharma A.** Survivorship After Hematopoietic Stem Cell Transplantation. ACT clinic presentation, St Jude Children's Research Hospital, Memphis, TN; June 2016.
9. **Sharma A**, Maron G. CMV after HSCT: friend or foe? LLH/BMTCT Conference, St Jude Children's Research Hospital, Memphis, TN; May 2016.
10. Baker J, Baker B, Johnson L, **Sharma A**. In the eye of the beholder: CPR in an imminently dying child. Schwartz Center Rounds, St Jude Children's Research Hospital, Memphis, TN; May 2016.
11. **Sharma A,** Choi JK, Nichols K. Autoimmune Lymphoproliferative Syndrome (ALPS). LLH/BMTCT Conference, St Jude Children's Research Hospital, Memphis, TN; Apr 2016.

12. **Sharma A,** Seims A, Anghelescu D. Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in DSRCT: process, progress and problems? CTRST Conference, St Jude Children's Research Hospital, Memphis, TN; Mar 2016.
13. **Sharma A,** Nguyen R. Atypical hematologic manifestations in Neurofibromatosis type 1: Coincidence or pathophysiological link? LLH/BMTCT Conference, St Jude Children's Research Hospital, Memphis, TN; Jan 2016.
14. **Sharma A,** Janssen W, Triplett B. Graft manipulation strategies. LLH/BMTCT Conference, St Jude Children's Research Hospital, Memphis, TN; Nov 2015.
15. **Sharma A,** Sadighi Z, Sabin N. Altered mental status in a solid tumor patient. CTRST Conference, St Jude Children's Research Hospital, Memphis, TN; Oct 2015.
16. **Sharma A,** Flerlage T, Kundu M. Eosinophilia 101. LLH/BMTCT Conference, St Jude Children's Research Hospital, Memphis, TN; Oct 2015.
17. **Sharma A,** Bhattarai P. Acute ischemic stroke in pediatrics: current management principles and role of a hematologist. LLH/BMTCT Conference, St Jude Children's Research Hospital, Memphis, TN; Aug 2015.
18. **Sharma A.** Automatic text message-based vaccination reminders to improve compliance. Grand rounds presentation, Kentucky Children's Hospital, Lexington, KY; Apr 2015.
19. **Sharma A.** From the clinic to the Capitol: advocating for children. Grand rounds presentation, Kentucky Children's Hospital, Lexington, KY; Mar 2015.
20. **Sharma A**. Infant botulism. Resident morning report, Kentucky Children's Hospital, Lexington, KY; Dec 2014.
21. **Sharma A**. Evidence behind restrictive transfusion practices. Resident morning report EBM presentation, Kentucky Children's Hospital, Lexington, KY; Jul 2014.
22. **Sharma A**. Differential diagnosis of abdominal mass. Resident morning report, Kentucky Children's Hospital, Lexington, KY; Oct 2013.
23. **Sharma A**. Neonatal hyperbilirubinemia. Resident morning report, Kentucky Children's Hospital, Lexington, KY; Jul 2013.

Other Published Abstracts/Conference Proceedings

1. George AP, **Sharma A**, McCoy T, Marino S, Day SB. Aeromedical transport of pediatric patients less than three months of age. Pediatrics. 2016; 137(2) Supplement 3:620A.
2. George AP, **Sharma A**, Radulescu VC. Deep venous thrombosis and pulmonary embolism in a 15-year-old patient. Journal of Investigative Medicine. 2015; 63(2):393.
3. Waller EK, Giver CR, Rangaraju S, Swimm A, **Sharma A**, Qayed M, Defilipp Z, Kalman D. Administration of a tryptophan metabolite, Indole-3-Carboxaldehyde, reduces graft versus host disease morbidity and mortality and enhances gastrointestinal barrier function in a murine model of allogeneic bone marrow transplantation. Blood. 2014; 124(21):2420.
4. George A, **Sharma A**, Dang S. Bronze baby syndrome in a blue Fugate. Journal of Investigative Medicine. 2014; 62(2):492.
5. Oberoi D, Kumar J, Madhuripan N, **Sharma A**, Sathyanandan S, Mehta A, et al. Does absence of itch-response to mosquito bite enhance susceptibility to the Chikungunya virus infection? International Journal of Infectious Diseases. 2010;14(Supplement 2):15-16.

Advocacy, Teaching and Professional Service

COG Cellular Therapy Committee Task Force
Children's Oncology Group 2018
I am a member of the Children's Oncology Group (COG) Cellular Therapy Committee task force charged with determining whether COG should develop a transplant protocol to test the hypothesis that haploidentical transplant for acute leukemia will result in similar RFS as unrelated donor but significantly less chronic GVHD. Our goal is to determine the feasibility, potential obstacles and their solutions, trial design options, and endpoints of a clinical trial designed to answer the above question in the context of a cooperative group clinical trial.

NEJM Knowledge+ Pediatrics Board Review Author
I authored 2 questions in pediatric hematology oncology for a comprehensive lifelong learning product from the NEJM Group in 2018 (https://knowledgeplus.nejm.org).

AAP CATCH District Co-Facilitator
American Academy of Pediatrics, 2018-Present
The Community Access to Child Health (CATCH) Program is a national initiative of the American Academy of Pediatrics (AAP) that supports pediatricians to collaborate within their communities to advance the health of all children. I am the Tennessee AAP chapter CATCH co-facilitator. My role is to aid pediatricians within the state to develop and execute CATCH projects.

Resident Liaison
St. Jude Children's Research Hospital, Memphis, 2016-2018
I was the liaison for the pediatric residents from LeBonheur Children's Hospital rotating at St. Jude Children's Research Hospital during their clinical rotations. I conducted weekly didactic sessions for the residents and organized their pediatric hematology oncology teaching curriculum.

AdvoCats
Kentucky Children's Hospital, Lexington, 2012-2015
AdvoCats is a resident run child advocacy group concentrating on policy issues surrounding children. I was the Legislative Chair of the organization and was involved in designing the legislative and advocacy agenda for the residents. I also participated in our annual Children's Advocacy Day at the state capital in Frankfort, KY (2013 and 2015) and Washington, DC (2014) to discuss issues concerning children with the legislators.

Kentucky Children's Hospital Schwartz Center Rounds
Kentucky Children's Hospital, Lexington 2014-2015
I was a member of the planning committee for the Schwartz Center Rounds at the Kentucky Children's Hospital. Schwartz Center for Compassionate Healthcare is a non-profit organization, which promotes these meeting to nurture patient-caregiver relationships.

Helpline
Kasturba Medical College, Mangalore, 2005-2009
Helpline is a voluntary students' organization of the undergraduate students of Kasturba Medical College (KMC). It aims at providing aid to the poor patients of a number of government hospitals attached to the KMC by organizing monetary, drug and blood donations. I was a core committee member overseeing donations and managing financial responsibilities.