

REPORT OF FELLOWSHIP

Dr Dharmagat Bhattarai	Award: Mid-term fellowship (Oct' 2021)
MBBS, MD, DM	Duration: 3 months
Country: Nepal	Period: May 2022- July 2022

ESID 2022 Mid-term Fellowship Award (Since May 2022 for period of 3 months)

Position: ESID Mid-Term International Fellowship at Children's Hospital of Philadelphia (*Affiliated with the Perelman School of Medicine of the University of Pennsylvania*, 3401, Civic Center Blvd, Philadelphia, PA-19104, USA

Department: Allergy & Immunology (Pediatrics)

Name of main contact/supervisor: Prof. Kathleen E. Sullivan (sullivank@chop.edu)

Postal address: Professor of Pediatrics, Chief of Allergy & Immunology, The Children's Hospital of Philadelphia, Sullivan's Lab, 3401, Civic Center Blvd, Philadelphia, PA-19104, USA

Summary of career aims: I am a young Immunologist from Nepal. To date, I am the only clinical immunologist in my country. Due to lack of awareness of inborn error of immunity (IEI) even among medical professionals, these children are either undiagnosed or misdiagnosed. My principal aim is to establish awareness, diagnosis, and treatment of all such patients in Nepal. In this mission, I have already established a centre to accomplish this mission.

Overall experience: I have come to the Children's Hospital of Philadelphia under the privilege of ESID-mid-term fellowship in May 1st, 2022 for 3 months period. My primary objective was to learn the advanced aspects of clinical and diagnostic immunology. Under supervision of luminary Professor K. Sullivan, I have been learning multiple aspects of clinical immunology including immunotherapy, advanced diagnostics, immunogenetics and bone marrow transplantation. It is fulfilling the lacunae of my immunological knowledge during my DM (PhD period). It has also boosted my experience on patient care and therapeutics.

Objectives:

1. To learn the advanced aspects of immunology, allergy science, immunogenetics and

cellular therapy.

2. To gather comprehensive knowledge of all phases of bone marrow transplantation

3. Research project: To study clinical, laboratory and molecular profile of patients with the chromosome 22q duplication syndrome.

Postings accomplished

1. May 2022

- Clinical immunology & allergy (inpatient and outpatient) (rotations in clinics, ward rounds, consultations, oral immunotherapy, and skin testing for allergies)
- DIRT (dysregulated immune response team) clinic
- Flow cytometry lab: Overview of staining and plot analysis
- Unit conferences, hospital grand rounds, presentations, symposium, and conferences

2. June 2022

- Bone marrow transplantation (inpatient sitting and ward rounds)
- PIICT Clinic (Every Tuesday)
- Flow analysis- combined panel analysis
- Conference of flow cytometry (web) and genetics symposium
- Unit conferences, hospital grand rounds, presentations

3. July 2022

- Bone marrow transplantation inpatients & DIRT clinic
- Immunology ward inpatients- rounds and consultations
- Research work completion
- Laboratory- Stem cell & gene therapy; Donor blood processing; cell depletion
 - HLA typing /mapping
 - Exome and genome sequencing overview, MLPA & immunogenetics
 - Immunofluorescence & ELISA
 - Serum allergy panel test

Objectives fulfilled:

1. I have learnt various common and rare clinical aspects of patients with inborn error of immunity and allergy (inpatient and outpatient). I have also learnt through various genetic tests, advanced flowcytometry, oral and parenteral immunotherapy, and dysregulated immune response team (DIRT) clinic

2: In bone marrow unit, I gained academic exposure and practical experience with selection, matching, enrolling, inpatient care, cell sorting, conditioning, graft-versus-host prophylaxis and treatment, other routine prophylaxis, management of complications, actual transplantation and follow up in Program for Integrated Immunodeficiency and Cellular Therapy (**PICT**) clinic.

3: Regarding research work on chr22q11.2 duplication syndrome, I have completed the study and write the manuscript. It's under process of critical revision for publications.

Conclusion of research done during fellowship

Though syndrome of deletion at chromosome 22q11.2 is well explored, the details of consequences of duplication at same site is not well understood yet. Moreover, there is no study on immunological studies in such patients. We had conducted observational study of record review of 216 patients of chromosome 22q11.2 duplications in single hospital cohort of CHOP with special focus of immunological profile on them. Though T cell populations were largely preserved, B cell subset and immunoglobulins levels were significantly reduced in a notable number of patients. Some of the patients with panhypogammaglobulinemia were on immunoglobulin therapy. This is novel study on this perspective. Findings are drafted and are on pipeline for publication.

Presentations/ conferences/ symposium:

1. Clinical and molecular profile of Inborn errors of immunity in Nepal: An Everest ahead yet to be scaled
2. Inborn errors of Immunity: Spectrum from underdeveloped to developed country
3. Primary Immunodeficiency survey among laity and pediatrician of developed and developing country
4. Presentation at Immune dysregulation symposium
5. Flow-cytometry web-based symposium
6. Hereditary angioedema: An overview of clinical and therapeutic challenges
7. Research poster day and scientific symposium 2022, CHOP.
8. Genetics symposium
9. Many Immunology conferences (every Wednesday noon), Grand rounds (every Wednesday morning and Hospital grand round (every Friday).

Collaborative projects planned further

1. Study of ARPC1B deficiency with founder defects from Nepal: Case series comparison and comprehensive clinical review: ARPC1b study and review is planned and currently in internal revision phase.
2. Level of awareness, diagnostics, and therapeutics of inborn errors of immunity in resource limited countries: an observational study
3. Primary immunodeficiencies in Nepal: an Everest yet to be scaled

Recent work published (by fellow personally) during this period

1. Bhattarai D, Banday AZ, Nori H, Gupta A. Mycophenolate mofetil in the treatment of childhood systemic polyarteritis nodosa. *BMJ Case Rep.* 2022;15(2):e248477. doi:10.1136/bcr-2021-248477
2. Banday AZ, Kaur A, Akagi T, Bhattarai D, Muraoka M, Dev D, et al. A Novel CEBPE Variant Causes Severe Infections and Profound Neutropenia. *J Clin Immunol.* 2022 Jun 20. doi: 10.1007/s10875-022-01304-7. Epub ahead of print.
3. Patra PK, Banday AZ, Jindal AK, Bhattarai D, Patra N, Saikia UN, et al. DRESS syndrome due to first-line antitubercular therapy – A diagnostic imbroglio! *J Family Med Prim Care.* 2022 June. 11(6).p 3280-3286. doi: 10.4103/jfmprc.jfmprc_1031_21
4. Anjani G, Sudhakar M, Bhattarai D, Kumrah R, Vignesh P, Rawat A. Features of nephrotic syndrome in infants with severe combined immunodeficiency. *J Allergy Clin Immunol Pract.* 2022;10(1):356-357. doi:10.1016/j.jaip.2021.09.052

Prizes achieved during fellowship

1. Fellow certification on symposium ‘Immune Dysregulation: The Local Storm’ at Children’s Hospital of Philadelphia.
2. Nepal’s ministry of certification for achieving the prestigious ESID mid-term fellowship.
3. Felicitations from the Unit and global pediatric education team

Pipeline projects on publication process

1. Chromosome 22q11.2 duplication syndrome: Immunological, clinical and molecular profile in a single center cohort from North America
2. Association of Single Nucleotide Polymorphism rs113420705 of *CASP3* in children with Kawasaki disease from North India

3. Extensive Idiopathic Calcinosis in a child- a Diagnostic and Therapeutic Imbroglio

Concluding lines about fellowship

This fellowship has a great importance for young career immunologist like me. First, I would like to Thank ESID (especially Prof. Despina Moshous), CHOP and especially my mentor Professor Kathleen Sullivan. She not only taught me the details and advanced aspects of immunology, but also connected me to the relevant divisions to have the broader exposure to give me maximum exposure to immunogenetics, laboratory and cell therapy. She also gifted me a precious project of immunological studies in chromosome 22q11.2 duplication syndrome. With her constant support, I finished this study on time. Besides, I have experienced stem cell sorting and received exposure of advanced laboratory like multi-panel flow analysis, HLA typing and exome sequencing. In nutshell, I participated and acquired many aspects of advanced immunology during this stay. This mid-term fellowship has not only developed and augmented my clinical skills but also broadened my perspective and confidence. This is a milestone for my life. I would like to express my gratitude to ESID and Prof Kathleen.

Future plans:

There is gross lack of experts, lab facility and drugs required for the diagnosis and treatment of IEs. Back to my country, I will put my knowledge and experience gained here into practice. I have already started the immunology center in Nepal. With the exposure, knowledge and collaborations developed, I will be able to treat patients with inborn errors of immunity and immune-dysregulation better and will be heading to open a bone marrow transplantation center. I will continue and propagate research plans in collaboration. I will also start fellowships and exchange programs in India, United Kingdom and United States of America (USA). Meanwhile, I will expand diagnostics and therapeutics of IEs in Nepal through joint ventures and collaborations with different apex societies around the globe. I hope this will bring a meaningful change in immunological concerns in Nepal.

Dr Dharmagat Bhattarai

MBBS, MD, DM

Country: Nepal