

REPORT

Report on participation of the ICMR International Fellow (ICMR-IF) in Training/Research abroad.

1. Name and designation of ICMR- IF : Ruchika Goel, Associate Professor
2. Address : Dept. of Clinical Immunology and Rheumatology, Christian Medical College, Vellore-632004
3. Frontline area of research in which training/research was carried out : Immunology- secondary immunodeficiency, microbiome studies and health informatics in vasculitis
4. Name & address of Professor and host institute : Prof. Lorraine Harper, Institute of Clinical Sciences, Queen Elizabeth Hospital, Birmingham
5. Duration of fellowship with exact date 2020 : 15th January 2020 to 15th August
6. Highlights of work conducted :
 - i) Technique/expertise acquired :

The objectives of this visit was to i) gain an experience in the conduct of translational research studies in systemic vasculitis and utilize the information generated to improve the long term survival of patients with systemic vasculitis, both in clinical practice and research studies, and ii) learn new data driven approaches to synthesize clinical and laboratory information in order to improve prognostication and management of patients with vasculitis.

During this fellowship, I have gained an understanding into the state of art investigations required for elucidating the cause of immunodeficiency and measures taken to reduce the impact of secondary immunodeficiency associated with the use of immunosuppression in patients with vasculitis. I have gained experience in the interpretation of flow cytometry panels designed for B cell and T cell immunophenotyping in order to classify immunodeficiency disorders. I had an exposure to standardizing and conducting functional antibody bead based Luminex assays for vaccine response studies in vasculitis. The effect of different rituximab regimens were analysed for their efficacy at maintaining disease remission and impact on infections rates. I have also gained a significant experience on classification, immunological and genetic work up and management of primary immunodeficiency disorders.

I gained an initial experience in the conduct of nasal microbiome studies in patients with ANCA associated vasculitis (AAV) which included handling and processing of samples for next

generation illumina sequencing for staphylococcus aureus. The laboratory studies on microbiome however were stalled due to closure of the university laboratories during corona virus related lockdown and is likely to resume only after September.

The lockdown period was utilised instead to learn data driven approaches as stated in second objective to understand outcomes of patients with AAV and Takayasu arteritis. IQVIA Medical Research Database is a UK electronic primary care records database that consists of anonymised medical records for over 15 million patients from 787 general practices. I have gained an extensive experience in the use of this database, including the analysis and integration of data and learnt clustering methodologies to sub-classify and predict prognosis of patients with ANCA associated vasculitis. I had been a part of case note review of deficiency of adenosine deaminase 2 associated polyarteritis, a novel primary immunodeficiency disorder predominantly presenting with young onset medium vessel vasculitis.

ii) Research results, including any papers, :
prepared/submitted for publication

A. Immunodeficiency (primary/secondary)

1. Study to compare efficacy and safety of reduced dose rituximab in maintenance of remission in AAV (submitted for publication) – The results of this study suggested reduced dose rituximab is equally efficacious in maintenance of remission in AAV and has a better safety profile in terms of secondary immunodeficiency.

2. Immunological predictors of poor response to antibiotic prophylaxis and Immunoglobulin requirement in patients with secondary immunodeficiency (being prepared) – The salient findings of this study was low plasmablasts at baseline to be associated with the need for IvIg replacement therapy in patients with autoimmune disorder. Absence of antibodies against pneumococcal serotype-5 after vaccination and pre-vaccination antibodies against Hemophilus influenza B tends to associate with IvIg therapy in future.

3. A study of immunological profile and prevalence of double negative T cells ($\alpha\beta$ CD4-CD8- T cells) in patients with common variable immunodeficiency (being analysed)

B. Data driven studies to classify and prognosticate patients with systemic vasculitis

4. Cardiovascular and renal morbidity in Takayasu arteritis: A population based retrospective study from the UK (sent for publication in Arthritis and Rheumatology (impact factor 9) and has received good comments from reviewers; the revisions have been submitted for consideration): The results of this study showed increased cardiovascular morbidity in patients with Takayasu arteritis.

5. Data driven classification of Granulomatous polyangitis (GPA) using novel cluster analysis method (being finalized to submit for publication). The results suggested 3 distinct clusters of GPA which were prognostically different.

iii) **Proposed utilization of the experience**

in India:

The research related to response to pneumococcal vaccination in vasculitis patients receiving immunosuppressive therapy was particularly interesting. I would like to use the expertise gained in standardizing assays for measuring vaccine response and T cell response to pneumococcal vaccination in patients with autoimmune disorders. There is still no data comparing immunodeficiency acquired as a result of non-biologic and biological DMARDS in Indian patients. Additionally, studies assessing immunological and clinical response to polysaccharide and conjugate vaccines against pneumococcal infection are lacking in Indian patients receiving B cell depletion therapy. Dr. Alex Richter, a member of faculty at the department of Clinical Immunology at University of Birmingham and Professor Lorraine Harper have very kindly agreed to guide the study which is planned to be submitted for funding once COVID-19 crisis is controlled. With the experience gained, we plan to start an immunodeficiency clinic in Christian Medical College, Vellore and establish the protocols to immune-phenotype and genotype patients with primary and secondary immunodeficiency. I would communicate to the ICMR as soon as this project is in its final form. A study on association of gut microbiome with infections in Indian patients with systemic lupus erythematosus is also being planned. As our department in CMC Vellore has a large cohort of patients with autoimmune diseases, we are exploring the use of clustering methods and the real world data to classify autoimmune diseases based on clinical phenotypic and genetic similarities. The banking of DNA is also underway. The knowledge gained here would be of immense help in planning the study.



Signature of ICMR-IF
(Ruchika Goel)

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