



## **Prof. Dipendra K Mitra**

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### **VISION**

“The subject of Immunology has grown globally and in the country over the years. There are very few institutions in the country where Immunology is taught and these curriculum lack immune related applications targeted at patient care. AIIMS being most excellent tertiary patient care service with high patient load, suitable infrastructure cum expertise. Our department has been crucial in promoting clinical research in multiple areas of immunology. For the last more than four decades of existence, the department has been continuously providing patient care services including HLA typing and donor selection both for HSCT and organ transplantation, identification of donor specific antibodies by cross matches/PRA, diagnosis of HLA associated disease, Flowcytometry and other related clinical investigations. Several research activities were initiated and developed. These include role of HLA in disease susceptibility and progression, immunogenetics of autoimmune (RA, T1D, SLE, Celiac disease) and infectious diseases (Leprosy, Tuberculosis, Leishmaniasis, HIV/AIDS); Genomic diversity of HLA, HLA matching and transplant outcome, antibody basis of rejection, effector immune functions, immune

response genes, technology development etc., In the past 2 decades, the patient care services and research has expanded tremendously. The clinicians always being under extensive pressure of patient loads often demand more recent investigations like chimerism analysis for hematopoietic stem cell monitoring, donor specific antibody identification for renal transplantation, immunophenotyping for leukemia, diagnostics of primary immunodeficiency (PID) disorders (LAD1, LAD2, SCID, CVID, CGD etc., The department has already accomplished such additional investigations and perceives to further expand and utilize the expertise established for the benefit of clinical services on routine basis. Newer technologies now available in the department include Luminex based anti-donor antibody identification, Sequence based HLA typing and Flowcytometry based immunophenotyping. The department established an unrelated donor marrow donor registry (AIDMR) in 1994 for patients requiring stem cell transplantation but have no HLA matched family donor. We maintain the links with international donor pool as well. The department has been making extensive efforts in increasing donor recruitment drive using limited resources. Research areas of the department have been further expanded in the past few years. We have initiated studies on immunogenetics of HIV, role of non-classical HLA in organ and bone marrow transplantation and in TB, studies on the phenotypic and functional characterization of T cell subsets in shaping host immune response, pathways of immune suppression in diseases like TB, HIV, leprosy and visceral leishmaniasis. Our efforts are focused on improving patient services, on increasing capacity building as well as human resource development and we intend to continue with such objectives in future. The department intends to develop and boost national and international networking both in research and academia relating to molecular research in indigenous natural products such as plant derived medicinal ingredients as immunomodulator, potential immunotherapeutic agents. The department has been advised by the SFC sub-committee to initiate integrated MD+Ph.D and M.Sc+Ph.D curriculum in Medical and Experimental Immunology. In the long term the department intends to expand to a **Centre for Immunology and Molecular Medicine** ”

### **MILESTONES ACHIEVED**

The department continued its activities in teaching, research and hospital services related to a range of laboratory investigations for patients requiring organ and hematopoietic stem cell transplantation (HSCT) as well as those needing HLA test for disease diagnostic purposes. Several

sensitive assays such as the Luminex based HLA testing and antibody screening system have been well established and are in routine use. The solid phase assays provide crucial information on donor specific antibodies (DSA) and virtual cross match for patients referred to the Department from AIIMS and other centres in India. To that extent, the AIIMS laboratory continue to serve as the 'national referral centre' for HLA testing SPA based DSA determination and post transplant antibody monitoring. Further, a national level Quality Control and Quality Assurance (QC/QA) service is offered to nearly 15 centres engaged in HLA testing all over India. Services are also offered for the detection of non-HLA antibodies, particularly those directed to MHC class I related Antigen (MICA) system on case to case basis. Similarly SNP based genetic polymorphism analysis in cytokines and chemokine genes as well as Chimerism analysis for HSCT patients is offered on routine basis. The Department has been designated as 'Centre of Excellence in Molecular Medicine' by the Indian Council of Medical Research.

The research activities of the department span several key areas of translational value. These include i) Immunobiology of renal transplantation with specific focus on determining the clinical relevance of HLA and non-HLA specific antibodies, ii) Genetic architecture of autoimmune diseases with particular focus on type 1 diabetes and celiac disease and evaluation of HLA linked biomarkers, iii) Immunogenetic basis of susceptibility to HIV infections and disease progression to AIDS, iv) Immune predictors of early graft rejection, both in HSCT as well as organ transplantation. The focus here is to evaluate the relevance of MICA antibodies as well as soluble MICA levels as predictors of graft outcome, v) Immunological mechanisms underlying infectious diseases with particular focus on Leishmaniasis and tuberculosis, vi) Immunophenotyping of patients with various types of leukemia and evaluation of novel immunological tools, vii) Clinical significance of HLA-G molecule in hematopoietic stem cell transplantation, viii) HSCT monitoring and follow up using in-house STR kits for Chimerism analysis, ix) Expansion of the Asian Indian Donor Marrow Registry, x) Immunogenetic basis of nasopharyngeal carcinoma.

Professor Mitra and his group have published several original research papers in leading international journals. Currently 5 students are pursuing for Ph.D under his leadership. 4 of his students who have already been awarded Ph.D under him, occupy positions of eminence in India and abroad.

## **Areas of Interest:**

Understanding the role of various lymphocyte subsets, particularly at local pathological sites in disease pathogenesis.

Focussing on local immune response among patients with chronic intracellular infections (tuberculosis, leishmaniasis, leprosy, HIV-Tb), rheumatoid arthritis and transplant patients.

Offering diagnostic services for patients with Leukemia and Primary Immune Disorders.

Focussing on improving patient care services, on increasing capacity building as well as human resource development

Boosting national and international networking both in research and academia relating to molecular research in indigenous natural products such as plant derived medicinal ingredients as immunomodulators and potential immunotherapeutic agents.

Initiating integrated MD+Ph.D and M.Sc+Ph.D curriculum in Medical and Experimental Immunology.

Expanding the Department to a **Centre for Immunology and Molecular Medicine.**

## **Significant Events:**

Appointed as Head of the Department, Dept of TII, AIIMS in Dec, 2014.

## **Research**

### **A) Funded projects:**

#### **Projects-Completed:**

- (1) Role of FoxP3+ regulatory T cells in polarized immunity in leprosy patients. Funding agency: ICMR, duration 2010 -2013, Total Sanction: Rs. 75.20 Lacs (Project Investigator: Prof. D.K.Mitra)
- (2) CD 26 Mediated Chemokine Activation: Role in suppression of immunity among visceral Leishmaniasis patients. Funding agency: DBT, duration 2010 -2013, Total Sanction: Rs. 92.78 Lacs (Project Investigator: Prof. D.K.Mitra)
- (3) Impact of FoxP3+ Treg cells on the host immune response among HIV-TB co-infected patients: relevance in multidrug resistance tuberculosis (MDR-TB). Funding agency:

ICMR, duration 2011 -2013, Total Sanction: Rs. 49.40 Lacs (Project Investigator: Prof. D.K.Mitra)

**Projects-Ongoing:**

- (1) Representation, trafficking and functional interaction of effector and regulatory T cells: Impact on the local immune response in rheumatoid arthritis. Funding agency: DST, duration 2012 -2015, Total Sanction: Rs. 49.98 Lacs (Project Investigator: Prof. D.K.Mitra)
- (2) Impact of transcriptional gene silencing of HIV1C on ecto-enzymes and negative co-stimulatory molecules expressed by T cell subsets: relevance to chronic immune activation in HIV infection Funding agency: DBT, duration 2013-2016, Total Sanction: Rs. 75.24 Lacs (Project Investigator: Prof. D.K.Mitra)
- (3) Cytokine profile of poly functional T cells in Latent and Active Tuberculosis patients: Impact of regulatory T cells. Funding agency: ICMR, duration 2014 -2017, Total Sanction: Rs. 97.58 Lacs (Project Investigator: Prof. D.K.Mitra)

**(B) Collaborative Projects:**

1. Role of FoxP3+ regulatory T cells in polarized immunity in leprosy patients. Funding Agency - Indian Council of Medical Research (ICMR), Collaboration with Department of Dermatology & Venereal diseases, AIIMS & Central JALMA Institute for Leprosy & other Mycobacterial Diseases, Taj Ganj, Agra
2. CD26 mediated chemokine activation: role in suppression of immunity among visceral Leishmaniasis patients. Funding Agency - Department of Biotechnology, Government of India, collaboration with Balaji Utthan Sansthan Fraser Road, Patna-Bihar

3. Impact of FoxP3<sup>+</sup> Treg cells on the host immune response among HIV-TB co-infected patients: relevance in multidrug resistance tuberculosis (MDR-TB). Funding Agency - Indian Council of Medical Research (ICMR), collaboration with Dr. B C Roy Post-graduate Institute of Basic Medical Sciences (IPGME&R), 244B, AJC Bose Road, Kolkata
4. Impact of Regulatory T cells on host Immunity among older pulmonary tuberculosis patients. Funding Agency: Indian Council of Medical Research (ICMR), collaboration with Department of Medicine, AIIMS
5. Representation, trafficking and functional interaction of effector and regulatory T cells: Impact on the local immune response in rheumatoid arthritis. Funding Agency: Indian Council of Medical Research (ICMR), collaboration with Department of Medicine, AIIMS
6. Impact of transcriptional gene silencing of HIV1C on ecto-enzymes and negative co-stimulatory molecules expressed by T cell subsets: relevance to chronic immune activation in HIV infection Funding Agency: Department of Biotechnology, Government of India, collaboration with Department of Microbiology, Assam Medical College, Dibrugarh and Christian Institute of Health Sciences & Research, Dimapur
7. Cytokine profile of poly functional T cells in Latent and Active Tuberculosis patients: Impact of regulatory T cells. Funding Agency: Department of Biotechnology, Government of India, collaboration with Department of Microbiology, Assam Medical College, Dibrugarh

## **EDUCATION (Academic Activities)**

### ***Ph.D Students:***

#### ***(a) Awarded:***

- 1) **Amar Singh**, Ph.D Title: "Immunoregulatory Role of Co-stimulatory Molecules in Tuberculosis" (2012)

- 2) **Ankit Saxena**, PhD Title: “Studies on the role of Chemokines on T-cell mediated allo-reactivity in Renal Transplantation”(2012)
- 3) **Ambak K Rai**, Ph.D Title: “Studies on T-cell Mediated suppression of immunity in Visceral Leishmaniasis patients”(2010)
- 4) **Prabhat K**, Ph.D Title: “Immunology of Regulatory T-cell subsets in Human Tuberculosis”(2009)

***(b) Currently working :***

- i) Polarized Immunity in Human Leprosy: Role of effector and Regulatory T cell subsets in shaping host immune response (Student: **Soumi Sadhu**)
- ii) Study of T cell responses among older patients with TB (Student: **Manju Namdeo**)
- iii) Studies on Immunoregulatory mechanisms for host T cell response in human tuberculosis (Student: **Divya Kamboj**)
- iv) Studies of distinct T cell subsets in the pathogenesis of rheumatoid arthritis (Student: **Kaustav Chowdhury**)
- v) Phenotypic and functional characterization of various T cell subsets in Sarcoidosis (Student: **Rinkee Kumari**)

**Modules for laboratory training in Immunology and Immunogenetics:**

**Short term training:** During the year, 18 young scientists and clinicians from various universities and institutions in India received short term training for laboratory techniques in HLA testing, antibody determination, flow cytometry, Chimerism analysis and other immunological investigations.

**Training to MD/DM students:** The Department continued to offer short term exposure in laboratory tools and technologies and their clinical significance to MD/MS students various departments of the institute. These include students from Pathology (8), Medical Oncology (2), Laboratory Medicine (7), and Hematology (3). Similarly, 4 doctors from the Department of Nephrology, Maulana Azad Medical College, Delhi undertook training and learnt techniques in

HLA testing and other immunological investigations. The Department continued to provide training to under graduate and post graduates students, both from within the institute and to those coming from other universities and research centres.

### **Visiting scientists:**

Dr.Samarjit Das, Ph.D, Assistant Professor, Department of Pathology, John Hopkins University, Baltimore, Maryland-21218, USA (30<sup>th</sup> May, 2014 and 10<sup>th</sup> Feb, 2015).

### **Publicatiions:**

Amar Singh, Aparajita Ballave Dey, Anant Mohan and **Dipendra K Mitra**. Programmed death-1 receptor suppresses g-IFN producing NKT cells in human tuberculosis. *Tuberculosis* 94 (2014) 197-206

Amar Singh, Anant Mohan, Aparajita Ballave Dey and **Dipendra K Mitra**. Inhibiting PD-1 pathway rescues M. tuberculosis specific IFN- $\gamma$  producing T cells from apoptosis among pulmonary tuberculosis patients. *Journal of Infectious Disease*. 2013;208:603–15 doi: 10.1093/infdis/jit206 (Impact Factor:6.410 )

Amar Singh, Aparajita Ballave Dey, Prabhat Kumar Sharma, Anant Mohan, and **Dipendra K Mitra**. Foxp3<sup>+</sup> regulatory T cells among tuberculosis patients: Impact on prognosis and restoration of antigen specific IFN-g producing T cells. *PLoS ONE* 2012;7(9):e44728. (Impact Factor: 4.41)

Amar Singh, Aparajita Ballave Dey, Anant Mohan and **Dipendra K Mitra**. Programmed death-1 receptor suppresses g-IFN producing NKT cells in human tuberculosis. *Tuberculosis* 94(2014) 197-206.

R. Ghosh, A. Sharma, **Dipendra K. Mitra**, S. K. Agarwal, A. K. Dinda, and Ankit Saxena. Study of CC chemokine receptor 5 in renal allograft rejection. *Indian J Nephrol*. 2013 May-Jun; 23(3): 196–200. doi: 10.4103/0971-4065.111848 (Impact Factor:0.867)



Saha PK, Sharma PK, Sharma SK, Singh A, **Mitra DK**. Recruitment of Th1 effector cells in human tuberculosis: hierarchy of chemokine receptor(s) and their ligands. *Cytokine*, 2013 Jul; 63(1):43-51. doi: 10.1016/j.cyto.2013.04.001. Epub 2013 May 1. (Impact factor 3.1).

Sinha M, Singh A, Shokeen A, Sharma P, Kaushik S, **Mitra DK**, Kaur P, Sharma S, Singh TP. Evidence of a novel allergenic protein narcisin in the bulbs of *Narcissus tazetta*. *Int J Biochem Mol Biol*. 2013 Jul 29; 4(2):95-101. Print 2013. PMID: 23936740 (Impact Factor: 1.318)

Sharma P, Yamini S, Dube D, Singh A, Mal G, Pandey N, Sinha M, Singh AK, Dey S, Kaur P, **Mitra DK**, Sharma S, Singh TP. Structural basis of the binding of fatty acids to peptidoglycan recognition protein, PGRP-S through second binding site. *Arch Biochem Biophys*. 2013 Jan 1;529(1):1-10. (Impact Factor: 2.935)

Ambak K. Rai, Chandreshwar P. Thakur and **Dipendra K. Mitra**,. Impaired Expression of CD26 Compromises T cell Recruitment in Human Visceral. *European Journal of Immunology*. 2012 42(10): 2782-91. (Impact Factor: 5.13)

Sharma P, Yamini S, Dey S, **Mitra DK**, Kaur P, Sharma S, Singh TP. Structural studies on molecular interactions between camel peptidoglycan recognition protein, CPGRP-S, and peptidoglycan moieties N-acetylglucosamine and N-acetylmuramic acid. *J Biol Chem*. 2012 Jun 22;287(26):22153-64. doi: 10.1074/jbc.M111.321307. Epub 2012 May 9. (Impact factor 5.117)

Rao A, Gupta S, Dinda AK, Sharma A, Sharma VK, Kumar G, **Mitra DK**, Prashant CK, Singh G. Study of clinical, biochemical and immunological factors determining stability of disease in patients with generalized vitiligo undergoing melanocyte transplantation.. *Br J Dermatol*. 2012 Jun;166(6):1230-6. doi: 10.1111/j.1365-2133.2012.10886.x. (Impact factor 3.944)

Ambak K. Rai, Chandreshwar P. Thakur, Amar Singh, Tulika Seth, Sandeep K. Srivastava, Pushpendra Singh, **Dipendra K. Mitra**. Regulatory T cells Suppress T cell Activation at the

Pathologic Site of Human Visceral Leishmaniasis. PLoS ONE 2012; 7(2):e31551 (*Impact factor: 4.41*)

A. K. Rai, C. P. Thakur, T. Seth, **D K Mitra**. Enrichment of invariant natural killer T cells in the bone marrow of visceral leishmaniasis patients. *Parasite Immunol.* 2011 Dec; 33(12):688-91. (*Impact factor: 2.79*)

Pradeep Sharma, Divya Dube, Amar Singh, Biswajit Mishra, Nagendra Singh, Mau Sinha, Sharmistha Dey, Punit Kaur, **Dipendra K. Mitra**, Sujata Sharma and Tej P. Singh. Structural basis of recognition of pathogen-associated molecular patterns and inhibition of pro-inflammatory cytokines by camel peptidoglycan recognition protein. **JBC**, 2011 May 6:286(18):16208-16217. (*Impact factor: 4.8*)

Ambak K. Rai, Chandreshwar P. Thakur, T. Velpandian, Surendra K. Sharma, Balram Ghosh, **Dipendra K. Mitra**. High Concentration of Adenosine in Human Visceral Leishmaniasis: Despite Increased ADA and Decreased CD73. *Parasite Immunol.* 2011 Nov; 33(11):632-6. (*Impact factor: 2.795*)

A. K. Rai, C. P. Thakur, T. Seth, **D K Mitra**. Early activated Th-1 type and dominantly non-invariant natural killer T (CD3<sup>+</sup>CD161<sup>+</sup>V $\alpha$ 24<sup>-</sup>) cells in bone marrow among visceral leishmaniasis patients. *Int. J. Parasitology.* 2011 Aug 15;41(10):1069-77 (*Impact factor: 3.637*)

Saxena A, Rai A, Raina V, Seth T, **Mitra DK**. Expression of CD13/aminopeptidase N in precursor B-cell leukemia: role in growth regulation of B cells. *Cancer Immunol Immunother.* 2010 Jan; 59(1):125-35. (*Impact factor: 3.637*)

Sharma PK, Saha PK, Singh A, Sharma SK, Ghosh B, **Mitra DK**. FoxP3<sup>+</sup> regulatory T cells suppress effector T-cell function at pathologic site in miliary tuberculosis. *Am J Respir Crit Care Med.* 2009 Jun 1; 179(11):1061-70. (*Impact factor: 11.08*)

Sharma SK, Mohan A, Sharma A, **Mitra DK**. Miliary tuberculosis: new insights into an old disease. *Lancet Infect Dis*. 2005 Jul; 5(7):415-30. (*Impact factor: 19.966*)

**Mitra DK**, Sharma SK, Dinda AK, Bindra MS, Madan B, Ghosh B. Polarized helper T cells in tubercular pleural effusion: phenotypic identity and selective recruitment. *Eur J Immunol*. 2005 Aug; 35(8):2367-75. (*Impact factor: 5.635*)

**Mitra DK**, Singh HP, Singh M, Alwadi A, Kochupillai V, Raina V, Kumar L, Mehra NK. Reconstitution of naïve T cells and type 1 function after autologous peripheral stem cell transplantation: impact on the relapse of original cancer. *Transplantation*. 2002 Apr 27;73(8):1336-9. (*Impact factor: 3.498*)

De Rosa SC, **Mitra DK**, Watanabe N, Herzenberg LA, Herzenberg LA, Roederer M. Vdelta1 and Vdelta2 gammadelta T cells express distinct surface markers and might be developmentally distinct lineages. *J Leukoc Biol*. 2001 Oct;70(4):518-26. (*Impact factor: 4.60*)

Venuprasad K, Parab P, Prasad DV, Sharma S, Banerjee PR, Deshpande M, **Mitra DK**, Pal S, Bhadra R, Mitra D, Saha B. Immunobiology of CD28 expression on human neutrophils. I. CD28 regulates neutrophil migration by modulating CXCR-1 expression. *Eur J Immunol*. 2001 May;31(5):1536-43. (*Impact factor: 5.635*)

Roederer M, Raju PA, **Mitra DK**, Herzenberg LA, Herzenberg LA. HIV does not replicate in naive CD4 T cells stimulated with CD3/CD28. *J Clin Invest*. 1997 Apr 1; 99(7):1555-64. (*Impact factor: 15.387*)

**Mitra DK**, Mehra NK, Maiti TK, Banerjee A, Taneja V, Rajalingam R, Ahuja RK, Bhattacharya BC. CD4+ T-cell responses to recombinant hsp65 and hsp18 of *M. leprae* and their trypsin-digested fragments in leprosy: diversity in HLA-DR restriction. *Int J Lepr Other Mycobact Dis*. 1995 Dec; 63(4):518-28. (*Impact factor: 6.07*)

## **Patient care: (2013-'14)**

Facilities available in the Department: i) HLA matching, ii) Antibody determination, iii) Virtual cross match assays, iv) Flow Cytometry, v) Tissue Culture, vi) ELISA, vii) Chimerism assays, viii) Sequencing, ix) RT-PCR, x) SNP analysis

Free of cost service provided for Leukemia phenotyping and phenotyping for Primary Immunodeficiency diseases

## **TRANSPLANTATION(2013-'14)**

### **HLA matching**

	<b>Recipients</b>	<b>Donors</b>	<b>Total</b>
Renal Transplantation	309	252	561
<u>Hematopoietic Stem Cell Transplantation</u>			
Aplastic anemia	120	331	451
Acute Myeloid Leukemia	104	214	318
Acute Lymphocytic Leukemia	50	139	189
Chronic Myeloid Leukemia	7	14	21
Thalassemia	42	98	140
Others	47	110	157
<b>Total</b>	<b>370</b>	<b>986</b>	<b>1356</b>
<b>Cadaver Donor Organ Transplantation</b>			
Cadaver Donor	10	10	20

### **Cross Match test**

- Serology	515
- Flowcytometry	132

### **Panel reactive Antibody Screening**

Luminex PRA (screening)	183
Luminex PRA (class I and II)	225

## **DIAGNOSTICS**

Spondyloarthropathies – HLA-B27 screening	481
Other diseases (Behcets' Disease/Narcolepsy/Celiac Disease)	75

Chimerism testing	160
Leukocyte Adhesion deficiency/ Chronic Granulomatous disease	230
NK/Treg/T/B/Monocyte frequency	275
Unrelated Donor search for BMT	206

During the year, a total of 206 requests for search of unrelated HLA matched donors from the 'Asian Indian Donor Marrow Registry' for bone marrow transplantation (BMT) were received. These include 81 from USA, 49 from Europe, 54 from various Asian countries and 22 from India.