| 1. Longitudinal Aging Study in India (LASI) Pilot study | |
|---|---|
| **Principal Investigator** | Dr. A.R. Risbud |
| **Co-Principal Investigator(s)** | Nil |
| **Other Investigator(s)** | Nil |
| **Category / Nature** | Basic Science |
| **Collaboration / Participating Centers** | Nil |
| **Funding Agency(ies) / Sponsors** | Harvard School of Public Health, Boston, United State |
| **Budget** | US $ 54798 |
| **Study Period** | 15/9/2011 to 31/8/2012 |
| **Objectives** | To perform bioassays of Dried blood spot (DBS) specimens that are being collected in the longitudinal Aging study in India (LASI) and to evaluate the quality of the assay data by comparing them to a matched set of venous samples and those done in other laboratories. |
| **Description** | The LASI study will collect dried blood sports from 3200 (1600x2) participants. Sample will be transported to NARI via Blue Dart, a certified blood courier. NARI will store the samples until testing begins. Based on the recommendation Indian helath and DBS experts, four key biomarkers were selected for analysis: C - reactive protein (CRP) hemoglobin (HB) Epstein Barr virus (EBV) and HbA1C. Each analysis will take the form of an enzyme- linked immunosorbent assay (ELISA) and requires a customized kit. All ELISAs will make use of NARI's automated plate washer and reader. |
| **Current Status** | All laboratory tests are completed, analysis is ongoing. Main study is expected to initiate in 2013 |
| **Publications** | Nil |
| **Presentations** | Nil |

| 2. Study on Global Health and Adult Health (SAGE) | |
|---|---|
| **Principal Investigator** | Dr. A.R. Risbud |
| **Co-Principal Investigator(s)** | Nil |
| **Other Investigator(s)** | Nil |
| **Category / Nature** | Basic Science |
| **Collaboration / Participating Centers** | Nil |
| **Funding Agency(ies) / Sponsors** | World Health Organization |
| **Budget** | US$ 188926 |
| **Study Period** | 23/5/2011 to 30/11/2011 |
| **Objectives** | To identify immunological responses and viral characteristics correlating with lower plasma viral load set point marker for disease progression in HIV infection. |
| **Description** | Coordinate the laboratory component of SAGE and running of assays on the DBS samples collected from SAGE respondents.<br><br>To obtain reliable valid and comparable data on levels of health on a range of key domains for older adult populations and To examine patterns and dynamics of age-related changes in health using a longitudinal design. |
| **Current Status** | Laboratory testing is ongoing |
| **Publications** | Nil |
| **Presentations** | Nil |

| 3. Immunological and virological characterization of early HIV infection | |
|---|---|
| **Principal Investigator** | Dr. Madhuri Thakar |
| **Co-Principal Investigator(s)** | Dr. A. R. Risbud, Dr. S. P. Tripathy, Dr. Manisha Ghate, Dr. Smita Kulkarni, Dr. R. S. Paranjape |
| **Other Investigator(s)** | Nil |
| **Category / Nature** | Research : HIV Biology |
| **Collaboration / Participating Centers** | NARI |
| **Funding Agency(ies) / Sponsors** | DBT & NARI Intramural |
| **Budget** | Rs. 94,83,737/- |
| **Study Period** | Continuous |
| **Objectives** | • To identify Innate and HIV-specific immune responses associated with low viral set point<br>• To characterize the viral factors associated with low viral set points<br>• To develop a repository of EBV transformed cell lines to study host genetic factors in future and to develop a repository of plasma and serum samples. |
| **Brief description (one paragraph)** | Early viral and immunological events in human immunodeficiency virus type 1 (HIV-1) infection may play a critical role in determining disease progression. Understanding the early dynamics of HIV infection prognostic of slow disease progression could prove to be important for vaccine design as substantial reduction in viremia may be a likely secondary end point in HIV vaccine efficacy trials. In a chronic infection like HIV, to understand the determinants of slow disease progression would require a longer follow up. The viral set point; the plasma viral load value between 6 to 12 months of infection would serve as a useful marker for disease progression. Hence we propose to use the viral set point as a surrogate marker for disease progression and identify immunological and virological factors related to low viral set point. The proposed study would generate information on immunological and virological determinants of slow disease progression in HIV-1 C infection. This exploratory study will provide basis for further in depth analysis of markers identified associated with disease progression. The |

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| | information would be useful in planning vaccine development strategies for primarily HIV-1 C affected population and in efficient patient management. |
| **Current status** | New enrolments and follow ups are going on. |
| **Publications** | • A single amino acid substitution in the C4 region in gp120 confers enhanced neutralization of HIV-1 by modulatingCD4binding sites and V3 loop.<br>Rajesh Ringe; Deepak Sharma; Susan Zolla-Pazner; Sanjay Phogat; Arun Risbud; Madhuri Thakar; Ramesh Paranjape; Jayanta Bhattacharya. Virology 418 (2011) 123–132.<br>• Irreversible Loss of pDCs by Apoptosis During Early HIV Infection May Be a Critical<br>Determinant of Immune Dysfunction.<br>Singh Meera, Thakar Madhuri, Ghate Manisha, and Paranjape Ramesh VIRAL IMMUNOLOGY Volume 23, Number 3, 2010<br>• InVitro Sensitization of T Cells with DC-Associated/Delivered HIVConstructs Can Induce a Polyfunctional CTLResponse, MemoryT-Cell Response, andVirus Suppression.<br>Swarali Kurle, Madhuri Thakar, Ashwini Shete, Ramesh Paranjape Viral Immunology 2012; 25 (1): 45-54 |
| **Presentations** | • Plasmacytoid Dendritic Cells (pDCs) Play Role in the Disease Progression among Persons Infected with HIV-1. Poster # MOPE0006 Meera Singh, Madhuri Thakar, Snehal Suregaonkar, Manisha Ghate, Ramesh Paranjape. XVII$^{th}$ International AIDS Conference, Mexico City, 3-8 August 2008.<br>• Genetic and Neutralization Properties of HIV-1 India Clade C Envelope in Recent Infection: Correlation with CCR5 usage and Clonal Divergence. Rajesh Ringe, Lavina Gharu, Anupindi Satyakumar, Sudhanshu Pandey, Madhuri Thakar and Jayanta Bhattacharya accepted for poster presentation at International AIDS Vaccine Conference, Cape Town, South Africa, October 2008 |

| **4. Diagnosis of active TB in HIV infected and uninfected young children in India.** | |
|---|---|
| **Principal Investigator** | Dr. R.S. Paranjape Director, NARI, Pune / Dr. Renu Bharadwaj, BJMC |
| **Co-Principal Investigator(s)** | Dr. Madhuri Thakar |
| **Other Investigator(s)** | Dr. Sanjay Jain, JHU, Baltimore, USA |
| **Category / Nature** | Basic Science |
| **Collaboration / Participating Centers** | BJMC,Pune |
| **Funding Agency(ies) / Sponsors** | NIH / ICMR |
| **Budget** | Rs. 70,00,000/- |
| **Study Period** | 3 Years |
| **Objectives** | Evaluating an enhanced ELISpot (measures IFN- γ release to several TB antigens in addition to ESAT-6/CFP-10), for the diagnosis of active TB in young children. |
| **Brief description (one paragraph)** | TB is the most common cause of morbidity/mortality in HIV infected individuals in India, which has among the world's highest burden of HIV and TB. However, Diagnosis of TB is particularly challenging in young children. Diagnosis test such as tuberculin skin test lack sufficient sensitivity has 30-40% sensitivity in young children and does not provide a diagnosis for weeks to months. IFN-γ release assay (IGRA) such as ELI Spot are newer diagnostic tests that measure T cells in response to *mycobacterium* TB specific antigens, and are more sensitive/specific then tuberculin test for the diagnosis of active TB in young children. We propose a collaborative Indo-US study that will evaluate this novel enhanced ELI Spot assay, for the diagnosis of active TB in young children in India. |
| **Current status** | • 261 blood samples were collected at BJMC and processed at NARI for Enhanced ELISpot. The Enhanced ELISpot assay carried on with various antigens. However, the results analysis of each assay will be carried out only after sample size of 400 is achieved.<br>• For children below 18 months HIV diagnosis is done by DBS DNA PCR as well as whole blood DNA PCR. About 25 DBS samples and 48 whole blood samples were received and processed for DNA PCR. |
| **Publications** | Nil |
| **Presentations** | Nil |

| **5. Development of Prospective Long Term Non - Progressor Cohort** | |
|---|---|
| **Principal Investigator** | Dr. R. S. Paranjape |
| **Co-Principal Investigator(s)** | Dr. M. R. Thakar |
| **Other Investigator(s)** | Nil |
| **Category / Nature** | Research - HIV Biology |
| **Collaboration / Participating Centers** | NARI |
| **Funding Agency(ies) / Sponsors** | Intramural |
| **Budget** | Rs. 10,00,000/- |
| **Study Period** | Continuous |
| **Objectives** | • To form a cohort of Long term non-progressors (LTNPs) patients and follow them up for studying Immunological and virological characteristics. |
| **Brief description (one paragraph)** | Long term non-progressors (LTNPs) is a population of HIV infected persons who have controlled their HIV infection successfully for long time. Ideally LTNPs have very low plasma virus load, stable CD4 counts and absence of opportunistic infections for a period of more than 12 years. It is intended to generate a cohort of such patients to investigate different host and viral factors associated with resistance to HIV disease progression. Project aiming for Studying Immunological and virological characteristics in such category patients. |
| **Current status** | New enrolments and follow ups are going on. |
| **Publications** | Nil |
| **Presentations** | Nil |

| **6. Identification of HIV modulated cell signalling pathways in context with persistence of HIV after activation** | |
|---|---|
| **Principal Investigator** | Dr. Ashwini Shete |
| **Co-Principal Investigator(s)** | Dr. Sampada Dhayarkar |
| **Other Investigator(s)** | Dr. Vijay Nema, Dr. Madhuri Thakar, Dr. R.R. Gangakhedkar |
| **Category / Nature** | HIV biology |
| **Collaboration / Participating Centers** | NARI, Pune |
| **Funding Agency(ies) / Sponsors** | DBT (RGYI) |
| **Budget** | Rs. 24,70,800/- |
| **Study Period** | 2 years |
| **Objectives** | • To determine mechanisms exploited by HIV interfering in elimination of HIV reservoir after activation with different strategies,<br>• To determine cell signalling pathways modulated by HIV after activation having role in the mechanisms interfering in HIV elimination.<br>• To establish an in vitro model of HIV latency to determine effect of activation on different mechanisms interfering in elimination of HIV |
| **Brief description (one paragraph)** | Activation of latent HIV infection has been attempted as one of the strategies for its elimination in presence of HAART. Activation of latently infected cells is expected to eliminate HIV reservoirs through CTL mediated killing, activation induced apoptosis and shortening half life by converting them into terminally differentiated effector cells. However, HIV can affect these mechanisms by modulating cell signalling pathways after activation, which can help in its persistence. The study is expected to have implications in devising strategies for HIV cure by identifying mechanisms used by HIV leading to its persistence in spite of activation. |
| **Current status** | Experiments for establishing in vitro model of HIV latency are underway. |
| **Publications** | Nil |
| **Presentations** | Nil |

| **7. Comparison of phenotypic and functional characteristics of M. tuberculosis specific T cells in active and latent tuberculosis** | |
|---|---|
| **Principal Investigator** | Dr. Ashwini Shete |
| **Co-Principal Investigator(s)** | Nil |
| **Other Investigator(s)** | Dr. Madhuri Thakar, Dr. R.R. Gangakhedkar, Dr. S.P Tripathy, Dr. Vishwanath Pujari, Dr. Dhamgaye |
| **Category / Nature** | TB biology |
| **Collaboration / Participating Centers** | NARI, BJMC |
| **Funding Agency(ies) / Sponsors** | Intramural |
| **Budget** | Rs. 5,00,000/- |
| **Study Period** | 2 years |
| **Objectives** | • To characterize phenotype of TB specific memory T cells in active and latent TB patients.<br>• To assess functionality of TB specific memory T cells in active and latent TB patients.<br>• To determine expression of homing and chemokine markers specific for lung as well as markers of exhaustion on TB specific memory cells in patients with active TB. |
| **Brief description (one paragraph)** | Transition from latent to active TB is likely to be dependent on loss of immune control and escalating mycobacterial load. This results in altered phenotype of cells of immune system. This study was designed for characterizing phenotype and functionality of TB specific memory T cells in patients with active and latent TB. Twenty participants from each of three groups viz. active pulmonary TB (ATB), healthy household contacts with latent TB infection (HTB) and community controls having latent TB infection (CCTB) are being enrolled in the study. Active pulmonary tuberculosis (ATB) is defined by smear and/or culture positivity for *M. tuberculosis* from one or more sputum specimens. Healthy household contacts (HTB) of sputum-positive TB patients with latent tuberculosis and community controls with latent tuberculosis without recent TB contact are identified based on TST reactivity of > 5mm (or positive interferon-γ Enzyme linked immunospot (ELISpot) response to ESAT-6 or CFP-10) and having a normal X-ray result, |

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| | no symptoms, and negative results in all sputum tests. |
| **Current status** | All 20 patients having active tuberculosis, 9 healthy controls and 4 contacts have been enrolled in the study till now. |
| **Publications** | Nil |
| **Presentations** | Nil |

| **8. Plasmacytoid dendritic cells in HIV-1 infection** | |
|---|---|
| **Principal Investigator** | Research Guide - Dr. R. S. Paranjape, Ph. D. Student - Mrs. Ashwini Dhamanage |
| **Co-Principal Investigator(s)** | Nil |
| **Other Investigator(s)** | Nil |
| **Category / Nature** | HIV Biology |
| **Collaboration / Participating Centers** | Nil |
| **Funding Agency(ies) / Sponsors** | Intramural and ICMR S.R.F. |
| **Budget** | Rs. 11,00,000/- |
| **Study Period** | 3 years |
| **Objectives** | To find out the reasons behind impairment of IFN-α production and loss of plasmacytoid dendritic cells in recent HIV-1 infection. |
| **Brief description (one paragraph)** | Plasmacytoid dendritic cells (pDCs) play a crucial role in innate immune response against viruses through secretion of plentiful amount of type I Interferons and various cytokines and chemokines which attract and activate other immune cells, establishing an effective immune response during primary infection. But it has been observed that in early stages of HIV-1 infection, pDCs are impaired in number and functionality from peripheral blood where functional impairment is mainly for secretion of type I interferons. Since the immune control of HIV multiplication in early HIV infection may influence the disease progression, understanding the mechanism of decline in numbers and functions of pDCs is necessary. For |

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| | this we are looking into signal transduction pathway of TLR-7 activation, mainly the effect of HIV on IRF-7 protein and PI3K/akt pathway. The impairment of this pathway by HIV-1 can lead to IFN-α impairment and/or apoptosis of pDCs. By in vitro studies on pDCs, we are trying to find reasons behind impairement of pDCs in recent HIV infection. |
| **Current status** | Standardization of assays |
| **Publications** | Nil |
| **Presentations** | Nil |

| **9. Role of binding antibodies in HIV-1 infection** | |
|---|---|
| **Principal Investigator** | Dr. Madhuri Thakar , Student- Sneha Talethi |
| **Co-Principal Investigator(s)** | Nil |
| **Other Investigator(s)** | Nil |
| **Category / Nature** | HIV Biology |
| **Collaboration / Participating Centers** | Nil |
| **Funding Agency(ies) / Sponsors** | Intramural / UGC-JRF |
| **Budget** | Rs. 10,00,000/- |
| **Study Period** | 3 years |
| **Objectives** | To estimate the non neutralizing activity of antibodies in sera of individuals from study group included & to correlate their presence with HIV disease progression. |
| **Brief description (one paragraph)** | Binding antibodies (esp.non neutralizing antibodies mediating ADCC/ADCVI) against HIV-1 appear in the circulation approximately 12 weeks after infection; along with the appearance of CTL's. The anti-HIV neutralizing antibodies are usually detected towards the end of the first year after infection. Recently published results of phase III trial RV144 and one study on breast milk ADCC antibodies carried out at Duke University have shown probability of protection against HIV due to these antibodies. Therefore renewed interests surround these antibodies against HIV as potential |

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| | therapeutic targets. The published data however shows conflicting results. Some studies have shown that non neutralizing mechanisms afford some protection from HIV-1 infection while some says it accelerates infection. Hence the role of ADCC /ADCVI mediating antibodies is not clearly known in HIV-1 disease progression. While this data is available on ADCC antibodies, the role of functional competence of effector cells of ADCC is not known. Therefore present study is planned to estimate and characterize the non-neutralizing mechanisms of anti-HIV antibodies in sera of patients with recent HIV infection and in patients with no/slow disease progression. The effector cells combining with these antibodies for proper functioning, such as natural killer (NK) cells, monocytes/macrophages and neutrophils will also be identified and their functional characteristics will be estimated. |
| **Current status** | Standardization of assays included in the study |
| **Publications** | Nil |
| **Presentations** | Nil |

| **10. The Role of Regulatory T cell in HIV-1 infection.** | |
|---|---|
| **Principal Investigator** | Guide - Dr. Madhuri Thakar, Student - Ms. Jyoti Patankar |
| **Co-Principal Investigator(s)** | Nil |
| **Other Investigator(s)** | Nil |
| **Category / Nature** | Basic Research |
| **Collaboration / Participating Centers** | Nil |
| **Funding Agency(ies) / Sponsors** | NARI |
| **Budget** | Rs. 20,00,000/- |
| **Study Period** | July 2011 to 2014 |
| **Objectives** | Treg suppress the activity of HIV specific-CD8 T cells via AHR pathway |
| **Brief description (one paragraph)** | HIV infection is associated with T cell abnormalities and altered effector function. The impact of regulatory T cells on HIV infection and disease progression may be highly significant. Expansion of Treg in HIV infection |

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| | could hypothetically decrease the magnitude of T cell responses in viremic patients and make them more susceptible to other pathogens. There is a significant increase in the proportion of CD4CD25 Treg cells in HIV infection as compared to controls, and these cells are able to suppress both the proliferation and cytokine production of HIV-specific CD4 and CD8 cells, as well as the proliferation in response to polyclonal stimulation. Regulatory CD4CD25 T cells might be a key factor for the inefficiency of CD8 responses in viral persistence. The mechanisms of this suppression are not elucidated. Generation of CD8 T cell response following viral infection or vaccination is indispensable for infection control. In HIV infection the initial decrease in the viral load during primary HIV-1 infection (PHI) is temporally associated with the first emergence of virus-specific CD8 T cell responses. Several studies have provided strong evidence that HIV-1 specific CD8 T cell responses are cable of controlling viral replication. The Aryl Hydrocarbon Receptor (AHR) is a ligand-activated transcriptional regulator that binds dioxin and other exogenous contaminates and is responsible for their toxic effects, including immunosuppression. AHR present on the surface of immune cells also known to play a role in immune modulation. However AHR has been shown to interacts directly with viral proteins and also affects viral latency. While AHR clearly modulates host responses to viral infection, we still have much to understand about the complex interactions between immune cells, viruses and the host environment. We proposed that Treg mediated immunosuppression play an important role in CD8 T cell responses and this interaction might be working at least partly through the AHR on Treg cells. |
| **Current status** | Ongoing |
| **Publications** | Nil |
| **Presentations** | Nil |

| **11. Role of Natural killer T (NKT) cells in HIV-1 infection** | |
|---|---|
| **Principal Investigator** | Guide - Dr. Madhuri Thakar, Student - Dharmendra Pal Singh |
| **Co-Principal Investigator(s)** | Nil |
| **Other Investigator(s)** | Nil |
| **Category / Nature** | HIV Biology |
| **Collaboration / Participating Centers** | Nil |
| **Funding Agency(ies) / Sponsors** | Intramural funding, NARI |
| **Budget** | Rs. 10,00,000/- |
| **Study Period** | 3 Years |
| **Objectives** | To characterization (Phenotypic and functional) of NKT cells in HIV-1 infected patients with slow disease progression. |
| **Brief description (one paragraph)** | NKT cells are a unique small subpopulation of true T cells, with a T cell receptor (TCR) that play a major role in regulating immune response by bridging the innate and adaptive immune system NKT cells are rapid immune responders and mediate potent immunoregulatory and effector function. Several studies have shown rapid depletion of NKT cells in chronic HIV-1 infection. Some studies reported that impaired functions were not restored by ART and the NKT cell numbers did not recover in response to this treatment. However a few other studies reported recovery of NKT cells after varied period of ART. There are conflicting reports on whether initiation of HAART can prevent NKT cell depletion in HIV infection Hence a study is planned to characterize the NKT cells in HIV infected patients with slow disease progression, and Patients on ART, as well as uninfected controls. |
| **Current status** | • Standardization of protocol for NKT cells characterization for Frozen samples<br>• 15 Healthy controls have been characterized for quantification of NKT cells. |
| **Publications** | Nil |
| **Presentations** | Nil |

| 12. Gut Flora and HIV infection | |
|---|---|
| **Principal Investigator** | Dr. Vijay Nema |
| **Co-Principal Investigator(s)** | Nil |
| **Other Investigator(s)** | Nil |
| **Category / Nature** | Basic Sciences / Exploratory |
| **Collaboration / Participating Centers** | Dr. Yogesh Shouche, NCCS |
| **Funding Agency(ies) / Sponsors** | Intramural |
| **Budget** | Nil |
| **Study Period** | 2012 - 2014 |
| **Objectives** | To conduct a small scale study for understanding the effect of HIV infection on gut microbial community structure. |
| **Brief description: (one paragraph)** | A huge amount of data is emerging with the studies that have advanced the understanding of the microbiome and its effects on metabolism, obesity, and health. Also recent research has provided evidences describing interplay between gut microbiota and immune system. HIV infection is related with immune status and also HIV pathogen has reservoirs in gut. With these clues it was hypothesised that there would be a community change in gut microflora in HIV infection. Hence, screening samples from various stages of HIV infection and following the changes in gut microbial communities with the disease progression can provide some clues about the pattern of change in microbial communities and their role over host system. |
| **Current status** | Ongoing |
| **Publications** | **Nema V.** Rectification of artificial molecular recombination with the use of high fidelity enzyme in the amplification of 16S rDNA sequences from Stool sample. 2012. **All Res. J. Biol**., 2012, 3, 6-9.<br><br>**Nema V**, Nair R. Metagenomic analysis of diarrheal stool samples of HIV infected individual and HIV-uninfected individual using 16SrDNA sequencing. *In press of IJMM.* |
| **Presentations** | Nil |

| **13. Molecular probing of the Mycobacterium tuberculosis isolates with respect to their resistance pattern and conservation pattern of new drug targets.** | |
|---|---|
| **Principal Investigator** | Dr. Vijay Nema |
| **Co-Principal Investigator(s)** | Dr. Arun R. Risbud, Dr. Shrikant P. Tripathy, Mr. Mycal Pereira |
| **Other Investigator(s)** | Nil |
| **Category / Nature** | Basic Sciences/ Exploratory |
| **Collaboration / Participating Centers** | Nil |
| **Funding Agency(ies) / Sponsors** | ICMR extramural grant under call for proposal |
| **Budget** | 40.7 Lakhs |
| **Study Period** | 2012 - 2014 |
| **Objectives** | • To explore if selected new drug target genes are broadly conserved in Mycobacterium tuberculosis isolates.<br>• To characterize Mycobacterium tuberculosis isolates for resistance using molecular tools and verifying its concurrence with phenotypic assays. |
| **Brief description: (one paragraph)** | Present drug targets in mycobacterium are becoming ineffectual because of the development of drug resistance. New and alternate drug targets are being explored for better treatment options. Proposed study plans to pick a few such targets for their genetic characterization. Genes being explored as unique targets for new drug discovery would be sequenced to understand if they are conserved or not. This area of exploration may contribute with handy information before we really introduce new molecules in existing drug regimen. |
| **Current status** | Ongoing |
| **Publications** | **Nema V.**, Pal S. K. Exploration of freely available web-interfaces for comparative homology modelling of microbial proteins. Bioinformation 9(15): 796-801 (2013) PMID: 24023424 |
| **Presentations** | Nil |

| **14. Genetic Variants of Matrix Metalloproteinase Enzyme in HIV- related Neurological disease** | |
|---|---|
| **Principal Investigator** | Dr. Hari Om Singh |
| **Co-investigators** | Dr. R.R. Gangakhedkar |
| **Other investigators (s)** | Nil |
| **Category/Nature** | Basic Science |
| **Collaboration/Participating centers** | Nil |
| **Funding Agency (ies)/Sponsors** | ICMR |
| **Budget** | 22.50 Lakh |
| **Study Period** | 2013 -2015 |
| **Objectives** | To study the frequency distribution of Matrix metalloproteinase Enzyme gene polymorphisms (*MMP-1, MMP-2 MMP-3 MMP-7, MMP-9*) in patients with HIV associated neurological disease (HAND).<br>To evaluate association of gene-gene (Haplotype) interactions (*MMPs)* in HIV associated neurological disease (HAND) (Gene-Gene interaction) |
| **Description** | **Background**<br>Matrix metalloproteinase enzymes are family of structurally similar enzyme which degrade the collagen, proteoglycon of extracellular matrix and play very important role in Neuro inflammatory diseases<br>**Aim**<br>Genetic susceptibility to HIV-related neurological disease (HAND) is influenced by polymorphism of Matrix metalloproteinase Enzyme gene. Therefore, aim of study to find out the polymorphism of MMPs gene associated with HAND<br>**Significance of Study**<br>HAND is now recognized as an important co-morbidity due to premature ageing associated with HIV, globally. *MMP* and *TIMP* deregulations may alter the inflammatory pathway leading to increased HAND associated pathological condition. For reasons not well known, the frequency of HAND is reported to lower and most often when it occurs it is in mild form among HIV infected individuals in India. It is possible that this may be due to differences in the polymorphisms. Hence understanding |

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| | polymorphisms amongst this family of enzyme genes will be important |
| **Current Status** | Recruitment of patients and genotyping of polymorphism of gene is going on |
| **Publications** | Nil |
| **Presentations** | Nil |

| **15. Genetic Susceptibility of APOBEC3G gene in HIV infected Patients** | |
|---|---|
| **Principal Investigator** | Dr. Hari Om Singh |
| **Co-investigators** | Dr. R.R. Gangakhedkar |
| **Other investigators (s)** | Nil |
| **Category/Nature** | Basic Science |
| **Collaboration/Participating centers** | Nil |
| **Funding Agency (ies)/Sponsors** | Submitted for funding to ICMR |
| **Budget** | 23.50 Lakh |
| **Study Period** | 2011 -2014 |
| **Objectives** | To study the frequency distribution of APOBEC3G gene polymorphisms (*APOBEC3G -90 C/G; -571 G/C; Intron 197193 T/C; Exon 40601 G/A; 5' UTR 199 G/A)* in HIV infected patients<br>To evaluate the association of gene polymorphisms of APOBEC3G (*APOBEC3G -90 C/G; -571 G/C; Intron 197193 T/C; Exon 40601 G/A; 5' UTR 199 G/A)* among individuals in different stages of HIV disease<br>To evaluate association of gene-gene (Haplotype) interactions (*APOBEC3G)* in HIV infected patients |
| **Description** | **Background**<br>APOBEC3G is host cellular protein. It play important role to resist the replication of HIV by creating G/A hypermutaion and rupturing of reading frame of viral gene. Thus play important role in innate antiviral immunity.<br>**Aim**<br>Genetic susceptibility to Infection and Progression of HIV Patients is influenced by polymorphism of APOBEC3G gene. Therefore, aim of study to find out the polymorphism of |

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| | APOBEC3G gene associated with Infection and Progression of HIV Patients.<br>**Novelty of Work**<br>*APOBEC3G* play important role in resistance of HIV infection. The molecular events associated with HIV infection and progression remains poorly understood. Investigating association between *APOBEC3G* gene polymorphism and HIV-infection & progression will provide genetic risk factor which either cause or likely to be responsible in pathogenesis of HIV-infected patients and may potentially provide genetic marker of vulnerability for incidence of HIV disease. |
| **Current Status** | Recruitment of patients and genotyping of polymorphism of gene is going on |
| **Publications** | Nil |
| **Presentations** | Nil |

| **16. Genetic susceptibility of Xenobiotic Drug metabolizing enzyme gene in ARV associated Hepatotoxicity** | |
|---|---|
| **Principal Investigator** | Dr. HariOm Singh |
| **Co-investigators** | Dr. R.R. Gangakhedkar |
| **Other investigators (s)** | Nil |
| **Category/Nature** | Basic Science |
| **Collaboration/Participating centers** | Nil |
| **Funding Agency (ies)/Sponsors** | NARI-ICMR intramural |
| **Budget** | 23.00 Lakh |
| **Study Period** | 2011 -2014 |
| **Objectives** | To examine the frequency distribution of Xenobiotic Drug Metabolizing Enzyme Genes (*GSTM1, GSTT1, GSTM3, GSTP1, & CYP1A1, CYP1A1 m1 & m2 & CYP2C9)* in HIV Infected patients with and without Hepatotoxicity to NNRTI-containing antiretroviral therapy. (Genotype-disease association)<br>To evaluate the association of Xenobiotic Drug Metabolizing Enzyme Genes among individuals in |

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| | different grades of Hepatotoxicity<br>To evaluate the association of gene-gene (XDME) interactions (Haplotype) in hepatotoxic patients |
| **Description** | **Background**<br>Xenobiotic Drug metabolizing enzyme genes are those enzymes which defense our body from environmental toxin & drug toxicity. It acts in two phases i.e. Phase I & Phase II. Phase I (CYP450**)** is multigene family of microsomal isozyme, play important role in metabolism of various drugs while as Phase II (GST & NAT) are a multifunctional enzymes, play a key role in cellular detoxification, protecting macromolecules from attack by reactive electrophiles<br>**Aim**<br>Genetic susceptibility to ARV associated Hepatotoxicity is influenced by polymorphism of Xenobiotic Drug metabolizing Enzymes genes. Therefore, aim of study to find out the polymorphism of Xenobiotic Drug metabolizing Enzymes gene associated with ARV associated Hepatotoxicity.<br>**Novelty of Work**<br>Finding of study may influence choice of antiretroviral regimens (NNRTI); which may be helpful in preventing chronic liver damage due to drug toxicity |
| **Current Status** | Recruitment of patients and genotyping of polymorphism of gene is going on. |
| **Publications** | Nil |
| **Presentations** | Nil |

| **17. Crosstalk between Notch-1 and EGFR during HIV-HPV co-infections** | |
|---|---|
| **Principal Investigator** | Dr Serena D'Souza, Scientist C |
| **Co-Principal Investigator(s)** | Dr.Arati Mane, Scientist D<br>Dr.Vandana Saxena, Scientist C<br>Dr.Sheela V.Godbole,Scientist E |
| **Other Investigator(s)** | NIL |
| **Category / Nature** | Basic Science-HIV Biology |
| **Collaboration / Participating Centers** | NIL |
| **Funding Agency(ies) / Sponsors** | ICMR |
| **Budget** | Rs 5 lakhs (ICMR Extramural Project : 5/2-3/LDCE/2014-ECD-II) |
| **Study Period** | August 2015 to July 2017 |
| **Objectives** | 1. TO identify role of Notch signaling pathways(s) during HIV-HPV co-infection<br>2. To determine the association between Notch and EGFR expression during HPV-induced tumor genesis in the presence of HIV infection |
| **Brief description (one paragraph)** | Viruses establish chronic infections in humans, where cancer development occurs by the accumulation of multiple co-operating events. They rely on their host's cellular proteins utilizing any achievable mechanism for their propagation. Viral oncoproteins usually reprogram me the host cells by hijacking and repurposing host regulatory components of the transcription network to promote cell survival and growth. Numerous viral on co proteins target the Notch Pathway to advance their own life-cycles emphasizing its significance in regulating cell growth and differentiation. The Notch pathway is an evolutionary conserved pathway fine-tuned to favor cell fate decisions from birth to death. Earlier studies have mentioned Notch- 1 being up regulated after retrovirs infection. Adenovirus, Human Papilloma Virus (HPV) and Simian Virus-40 are also known to interact with the Notch pathway. The Notch gene is abnormally activated in human malignancies .Aberrant Notch expression reported in a growing number of solid human tumors highlights the linkage between the activation of Notch pathway and tumor development. Recently it has been demonstrated that Notch contributes to the acquisition of the epithelial-mesenchymal transition phenotype critically associated with drug resistance. Increased expression of the Notch pathway components correlates with poor prognosis and shorter survival. Elevated levels of Notch-1 and its ligand (Jagged1) mRNA were correlated with poor prognosis in human breast cancer. Jagged-1 upregulated in human cervical tumors, is known to |

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| | sustain tumor progression by HPV-16 oncogenes. Dai et al (2009), who investigated the molecular mechanisms of Notch signaling, showed an increased expression of Epidermal Growth Factor Receptor (EGFR).Concomitantly, activation of EGFR tyrosine kinase signaling pathway culminates in processes crucial to cancer progression (17,18). Previous studies have indicated that Notch-1 protein over expresses ErbB2 a member of the EGFR family (19). ErbB2 has been also reported to co-operate with HPV viral oncoproteins E6 and E7 to induce neoplastic transformation in primary normal oral epithelial cells (20). E6 and E7 viral oncoproteins in high-risk HPV genotypes block pRb and p53 cellular proteins leading to unscheduled cell cycle activation, genomic instability and cancer progression |
| **Current status** | Ongoing |
| **Publications** | Nil |
| **Presentations** | Nil |

**Intra-mural project of Ph D Student:**

| **18. Genetic and neutralization properties of the envelope gene in HIV-1 and HIV-2 monotypic and dual infections.** | |
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| **Principal Investigator** | **Guide** - Dr. Smita Kulkarni, Scientist E, National AIDS Research Institute, Pune.. **Ph.D. Student:** Ms. Priyanka Shrikant Khopkar. |
| **Co-Principal Investigator(s)** | **Co-Guide:** Dr. Srikanth Tripathy, Scientist 'G' & Director, National JALMA Institute of Leprosy and Other Mycobacterial Infections, Agra.- |
| **Other Investigator(s)** | Nil |
| **Category / Nature** | HIV Biology |
| **Collaboration / Participating Centers** | Nil |
| **Funding Agency(ies) / Sponsors** | NARI Intramural |
| **Budget** | Rs. 15, 20,000/- |
| **Study Period** | Three Years (2012 to 2015) |
| **Objectives** | 1) Characterization of the *env* gene in HIV-1, HIV-2 monotypic and dual infections.<br>2) Assessing neutralization patterns in HIV-1, HIV-2 monotypic and dual infections. |
| **Brief description (one paragraph)** | HIV-2 reports a lower pathogenicity than HIV-1. HIV-2 sera depict a significant capacity to neutralize autologous and heterologous viruses, indicating rare viral escape to neutralization responses (nAb) in HIV-2 infection. It is known that the entry mediated via the HIV envelope glycoproteins is a key factor that impacts neutralization. Therefore, delinieating the characteristics of HIV-1/HIV-2 envelope gene in modulating the neutralization responses in HIV-1 and HIV-2 monotypic and dual infections may provide insights for designing anti-HIV therapeutic and vaccine modalities. |
| **Current status** | • Standardization of protocol for NKT cells characterization for Frozen samples<br>• 15 Healthy controls have been characterized for quantification of NKT cells. |
| **Publications** | Nil |
| **Presentations** | Nil |

| **19. Characterization of Tetherin/*BST-2* Gene in HIV Infected Long Term Non Progressors (LTNPs)** | |
|---|---|
| **Principal Investigator** | Dr. Dhanashree Jagtap |
| **Co-Investigator** | Dr. Madhuri Thakar |
| **Other Investigators** | Nil |
| **Category/Nature** | Research-HIV Biology |
| **Collaboration/Participating Centres** | NARI |
| **Funding Agency (ies)/Sponsors** | Intramural |
| **Budget** | Rs. 4, 00, 000/- |
| **Study Period** | 2 years |
| **Objectives:** | • To study the Tetherin/*BST-2* gene in HIV infected LTNPs versus Controls.<br>• To study the effect of Tetherin/*BST-2* gene variations in LTNPs if any, on Tetherin mRNA and protein expression levels. |
| **Description** | Tetherin/*BST-2* is a recently identified interferon induced host restriction factor which tethers newly formed HIV-1 virions to the surface of HIV infected cells, preventing HIV egress and further infection. LTNPs are rare individuals who are infected with HIV but control the infection without antiretroviral therapy. It is not known whether certain alterations in tetherin gene are associated with natural control of HIV-1 in LTNPs. Therefore, detection of unique molecular signatures in tetherin gene of LTNPs and investigating whether these contribute to altered tetherin mRNA or protein expression will lead to an understanding whether tetherin has any role in control of HIV infection by these individuals. |
| **Current Status** | The first objective is in progress. |
| **Publications** | Nil |
| **Presentations** | Nil |