Name of the Scholar: Manish Chandra Choudhary
Name of Supervisor: Dr. Syed Naqui Kazim
Centre: Centre for Interdisciplinary Research in Basic Sciences, Jamia Millia Islamia, New Delhi-110029
Name of Co-supervisor: Prof. Shiv Kumar Sarin
Professor and Head, Dept. of Hepatology
Institute of Liver and Biliary Sciences, New Delhi-110070
Title of the Thesis: Development of Molecular Markers for HCV-Mediated Progressive Liver Disease.

Research Findings:

- HCV genotype 3a contained 2 additional hypervariable regions in the E2 region, namely HVR496 and HVR576 with an additional putative glycosylation site.
- Phylogenetic analysis of full HCV genotype 3a from India revealed that Indian sequences cluster together and root out separately from other HCV genotype 3a sequences. Further, analysis revealed that the Indian HCV genotype 3a sequences are the ancestral sequences from which all other genotype 3a sequences have evolved and diversified over a period of time.
- HCV genotype 3a sequences from United Kingdom showed close similarity with Indian sequences. HCV genotype 3a sequences originated in Indian subcontinent and dispersed to United Kingdom and other parts of the world around World war II and during time of Indian independence.
- Further, HVR496 and HVR576 showed similar pattern of immunogenicity (predicted using *in-silico* approach) as compared to HVR1, hence, it is very likely that this region will also be immunogenic and potentially antigenic determinant region. We were able to efficiently clone and assemble full length HCV genotype 3a virus isolated from Indian patient. Infectious virus generation experimentation revealed that the replication was sub-optimal and need to be tried further with cell culture adaptive mutations specific to HCV genotype 3a.
- We identified a panel of differentially expressed autoantibodies in various stages of HCV infected liver disease patients. 4 of these autoantibodies namely, CTSB, TAGLN2, TNFSF15 and WISP1were validated on liver biopsy tissues from HCV fibrosis patients.
- WISP1, CTSB & TNFSF15 autoantibody expressions were positively correlated while TAGLN2 autoantibody expression was negatively associated with liver fibrosis stages.
- Using miRNA qpCR array, a panel of differentially expressed miRs in various stages of HCV infected liver disease patients were identified.
- miR-148b and miR-221 were expressed at higher levels, whereas miR-150, miR-342, let-7a-5p, let-7c and let-7f-5p expressed at lower levels in serum/plasma of patients with HCV infection as compared with healthy individuals, suggesting that these serum/plasma miRNAs may serve as potential biomarkers of HCV infection.
- Further, miR-148b and miR-221 expressions were positively correlated whereas miR-150, miR-342, let-7a-5p, let-7c and let-7f-5p expressions were negatively correlated with fibrosis stages in HCV genotype 3a infected patients.
- Bioinformatic analysis for let-7 miRs revealed its potential interaction with extracellular matrix receptor interaction with high confidence values, further confirming its role in liver fibrogenesis.

Conclusions:

- Large catalog of autoantibodies (WISP1, TNFSF15, CTSB, TAGLN2) and differentially expressed miRs (miR-148b, miR-221, miR-150, miR-342, let-7a, let-7c and let-7f) identified here should facilitate biomedical research into pathological conditions associated with HCV infection.
- Further, these molecules can be used as a possible target for therapeutic intervention together as a diagnostic tool in clinical practice.