LIST OF NOMINEES 10 MOST SIGNIFICANT RESEARCH PUBLICATIONS IN REFERRAL JOURNALS

Dr. Ashraf has conducted seminal work on thromboembolic diseases, as evidenced by his publications in high impact journals such as Blood, 2014; PNAS, 2017; EBiomedicine, 2017, Blood Advance, 2019, and Lancet 2022. The outcome of Dr Ashraf's research study elucidated the previously unknown cause of thrombus formation at high altitude. His publications **e**stablished that high-altitude induced thrombosis is centrally regulated by a complex network of coagulatory and inflammatory processes, critically linked through hypoxia inducible factors -1α (HIF-1α).This work has been *highlighted by Nature India,* doi:10.1038/nindia.2017.143*).* One of the studies published with editorial commentary has revealed the platelet specific novel biomarker for the detection of venous thrombogensis (formation of blood clots in legs, brain, lungs) at high altitude. The work also contributed exceptionally to proposing a novel biomarker 'Calpain' (Patent filed with IPO vide no. 733/DEL/2014) that will help in early diagnosis of thrombosis and provide timely treatment to Indian Army Jawans posted at extremely hostile terrain protecting our borders.

1. Nair V, Singh S, Ashraf MZ, Yanamandra U, Sharma V, Prabhakar A, Ahmad R, Chatterjee T, Behera V, Guleria V, Patrikar S, Gupta S, Vishnoi MG, Rigvardhan, Kalshetty K, Sharma P, Bajaj N, Thyelnai D. Khaling T, Wankhede TS, Bhattachar S, Datta R, Late Ganguli P. Epidemiology and pathophysiology of vascular thrombosis in acclimatized lowlanders at high altitude: A prospective longitudinal study.
   The Lancet Regional Health - Southeast Asia. 2022. https://doi.org/10.1016/j.lansea.2022.05.005
2. Gupta N, Sahu A, Prabhakar A, Chatterjee T, Tyagi T, Khan N, Nair V, Bajaj N, Sharma M, Ashraf MZ. Activation of NLRP3 inflammasome complex potentiates venous thrombosis in response to hypoxia.
   Proceedings of National Academy of Sciences USA 2017: 114(18):4763-4768. Impact Factor: 10 ; Citations: 141
3. Tarun Tyagi, Shadab Ahmad, Neha Gupta, Yasmin Ahmad, Shantanu Sengupta**, M. Zahid Ashra[f],**Altered expression of platelet proteins mediate hypoxia induced prothrombotic phenotype: Calpain playing a major role*?*
   Blood,20;123(8):1250-60. 2014. Impact Factor: 25.7, Citation: 117
4. Anita Sahu, Prabhash Kumar Jha, Prabhakar A, Chatterjee T, Tyagi T, Kumari B, Khan N, Nair V, **Ashraf MZ**, MicroRNA-145 impedes thrombus formation via targeting tissue factor in venous thrombosis
   EBioMedicine. 2017 Dec;26:175-186. Impact Factor: 11.2, Citations: 43
5. Aberrant promoter hypermethylation regulates thrombomodulin in high altitude induced deep vein thrombosis. Vijay A, Jha PK, Parveen S, Goel S, Prabhakar A, Sharma S, Kumar B, Chatterjee T, Bajaj N, Nair V, Sharma M,
   Ashraf MZ. Thromb Res. 2022 Jul;215:5-13. Impact Factor: 10.4

6. Jha PK, Vijay A, Prabhakar A, Chatterjee T, Nair V, Bajaj N, Kumar B, Sharma M, **Ashraf MZ.** Transcriptome Profiling Reveals the Endogenous Sponging Role of LINC00659 and UST-AS1 in High-Altitude Induced Thrombosis.
Thrombosis & Haemostasis. 2021 Nov;121(11):1497-1511. Impact Factor 6.8

7. Prabhakar A, Chatterjee T, Bajaj N, Tyagi T, Sahu A, Gupta N, Kumari B, Nair V, Kumar B, Ashraf MZ. Venous thrombosis at altitude presents with distinct biochemical profiles: a comparative study from the Himalayas to the plains.
Blood Advances. 2019 Nov 26;3(22):3713-3723. Impact Factor: 7.6, Citation: 14

8. Jha, P. K., A. Sahu, A. Prabhakar, T. Tyagi, T. Chatterjee, P. Arvind, J. Nair, Mohammad Zahid Ashraf. "Genome-Wide Expression Analysis Suggests Hypoxia-Triggered Hyper-Coagulation Leading to Venous Thrombosis at High Altitude."
Thrombosis & Haemostasis 2018;118, no. 7: 1279-95. **Impact Factor: 6.8** Citation: 26

9. Jha PK, Vijay A, Sahu A, **Ashraf MZ**. Comprehensive Gene expression meta-analysis and integrated bioinformatic approaches reveal shared signatures between thrombosis and myeloproliferative disorders.
Scientific Reports 2016 Nov 28;6:37099. doi: 10.1038/srep37099. Impact Factor: 4.3

10. Mishra A, Ashraf MZ. Using Artificial Intelligence to Manage Thrombosis Research, Diagnosis, and Clinical Management.
Semin Thromb Hemost. 2019 Sep 28. Impact Factor: 6.4 Citation: 14

HIGHLIGHTS OF RESEARCH CONTRIBUTIONS

Dr. Ashraf's research work on High altitude induced thromboembolism, especially in Indian sub-population address a huge lacuna in this field. Dr. Ashraf pioneered the establishment of a platform for altitude induced thrombotic studies in India. His study on the mechanisms by which thrombus formation is triggered under hypoxia is of immense fundamental importance in our understanding of thrombus formation on ascension to mountains, sports, pilgrimage, or other hypoxic environments. Owing to his work, we have now a clear view of about the cause of thrombus formation which remained hidden for the past several decades **(Blood, 2014; CATH, 2016; PNAS, 2017; EBiomedicine, 2017, The Lancet 2022)**. Work done by Dr. Ashraf is especially relevant in India, since the prevalence of thrombosis is comparable to western population is relatively higher in the Himalayan Mountain range and it is only Dr. Ashraf's lab where pre-clinical studies and testing is established in Indian Scenario. By virtue of his findings, the formation of blood clot can be prevented even at a very early stage.

Overall, his research has helped in improving the quality life of individuals (either defense personnel, paramilitary forces, native highland, and civil population) staying/posted at remote extreme altitude locations like Siachen Glacier, Indo-China Border etc. Nonetheless this will assist in better management and would reduce morbidity and mortality associated thrombotic event in

local population, visitors, tourist, and religious pilgrims. The outcome will benefit the Hotel & Tourism industry of hilly states like Jammu & Kashmir, Himachal, Uttarakhand, and the other Northeastern States where the incidence of this disease is higher than planes. His unequivocal contributions are enumerated as follows-

Contribution # 1: Epidemiology and pathophysiology of vascular thrombosis in acclimatized lowlanders at high altitude

Most recently Dr. Ashraf and his colleagues have determined the epidemiology, especially incidence, of thrombotic events in acclimatized healthy lowland soldiers, through the course of a two-year duty tenure at high altitude (HA)/extreme high altitude (EHA), along with the pathophysiological correlates at different time-points (**Lancet 2022**). This prospective observational study in healthy subjects presents the most robust estimate to date, of the incidence of thrombosis at high altitude and this is the only report to date that provides a comprehensive study of the chronic hypoxia-inflammation-endothelial/platelet activation-coagulation-fibrinolysis axis in cases of thrombosis and matched healthy comparison group at HA/EHA.

- *Nair V, Singh S, Ashraf MZ, Yanamandra U, Sharma V, Prabhakar A, Ahmad R, Chatterjee T, Behera V, Guleria V, Patrikar S, Gupta S, Vishnoi MG, Rigvardhan, Kalshetty K, Sharma P, Bajaj N, Thyelnai D. Khaling T, Wankhede TS, Bhattachar S, Datta R, Late Ganguli P. Epidemiology and pathophysiology of vascular thrombosis in acclimatized lowlanders at high altitude: A prospective longitudinal study.* ***The Lancet Regional Health - Southeast Asia. 2022.***

Contribution # 3: NLRP3 inflammasome responsible for thrombosis under hypoxia.

His studies on the mechanisms by which thrombus formation is triggered under hypoxia are of immense fundamental importance in our understanding of thrombus formation on ascension to mountains, air-travel or hypoxic environments. Owing to his work, we have now a clear view of about the cause of thrombus formation which remained hidden for the past several decades. His work has thrown light on the crosstalk between inflammation and coagulation and opened up a new aspect of inflammasomes, the early events even prior to inflammation. His work has given a new dimension for development of better thrombprophylactics. Dr. Ashraf's work has pioneered the view that thrombus formation in veins is triggered by activation of inflammatory response via NLRP3-caspase-1-IL-1β signaling regulated by the Hypoxia inducible factors-1α in response to hypoxia. The translational potential of pre-clinical observations was demonstrated in human patients of altitude induced venous thrombosis. The report presented by Dr. Ashraf suggests that the regulation of VTE by NLRP3-casapase inflammasomes has both basic and applied value since it helps us to understand the role of inflammasomes in disease as well as design of better intervention as thromboprophylactics.

- *Shankar Chanchal, Aastha Mishra, Manvendra Kumar Singh and Mohammad Zahid AshrafUnderstanding Inflammatory Responses in the Manifestation of Prothrombotic Phenotypes* ***Front. Cell Dev. Biol., 14 February 2020. [Impact Factor- 4.4]***

- *Mohammad S, Mishra A,* ***Ashraf MZ.*** *Emerging Role of Vitamin D and its Associated Molecules in Pathways Related to Pathogenesis of Thrombosis.* ***Biomolecules.*** *2019 Oct 24;9(11). pii: E649.* ***[IF-5]***
- *Gupta N, Sahu A, Prabhakar A, Chatterjee T, Tyagi T, Kumari B, Khan N, Nair V, Bajaj N, Sharma M, Ashraf MZ. Activation of NLRP3 inflammasome complex potentiates venous thrombosis in response to hypoxia.* ***Proceedings of National Academy of Sciences – USA 2017: 114(18):4763-4768. [Impact Factor- 10]***
- *Neha Gupta, Manish Sharma, Tathagata Chatterjee, Tarun Tyagi, Anita Sahu1, Amit Prabhakar, Mohammad Zahid Ashraf. Activation of NLRP3 Inflammasome Complex Regulates the Onset of Hypoxia I*nduced Thrombosis***, Arteriosclerosis, Thrombosis, and Vascular Biology*. 2015; 35, A605 [Impact Factor-6.6]**

Contribution # 4: Development of Artificial Intelligence based platform for managing thrombosis diagnosis, and clinical management.

Thrombosis requires a collective effort and data from numerous research studies to fully comprehend molecular mechanisms for prediction, prevention, treatment, and overall management of these conditions. To accomplish this arduous feat, a comprehensive approach is required that can compile thousands of available experimental data and transform these into more applicable and purposeful findings. Thus, large datasets could be utilized to generate models that could be predictive of how an individual would respond when subjected to any kind of additional risk factors or surgery, hospitalization, etc., or in the presence of some susceptible genetic variations. Artificial intelligence-based methods harness the capabilities of computer software to imitate human behaviors such as language translation, visual perception, and, most importantly, decision making. These emerging tools, if appropriately explored, might assist in processing of large data and tackle the complexities of identifying novel or interesting pathways that could otherwise be hidden due to their enormity. This narrative review attempts to compile the applications of various subfields of artificial intelligence and machine learning in the context of thrombosis research to date. It further reflects on the potential of artificial intelligence in transforming enormous research data into translational application in the form of predictive computational models.

- *Mishra A,* ***Ashraf MZ.*** *Using Artificial Intelligence to Manage Thrombosis Research, Diagnosis, and Clinical Management.* ***Semin ThrombHemost.*** *2019 Sep 28. doi: 10.1055/s-0039-1697949.*

Contribution # 5: Distinct biochemical patterns in Thrombotic cases from altitudes

A comprehensive comparative study led by Dr. Ashraf on range of parameters from hematology to coagulation, fibrinolysis, thrombophilia, lipid profile, stress and inflammatory responses, platelet hyperreactivity and endothelial cell activation on venous thrombotic patients from HA regions and sea level. His research presented distinct biochemical profiles in patients from HA with perturbation in platelet and endothelium hyper activation. The recommendation proposed by the team of Dr. Ashraf regarding distinct diagnostic and treatment modalities for patients from different altitudes will be immensely useful for operational requirements for Indian Armed Forces.

- *Prabhakar A, Chatterjee T, Bajaj N, Tyagi T, Sahu A, Gupta N, Kumari B, Nair V, Kumar B, Ashraf MZ. Venous thrombosis at altitude presents with distinct biochemical profiles: a comparative study from the Himalayas to the plains.* ***Blood Advances. 2019 Nov 26;3(22):3713-3723.***

Contribution # 6: Long noncoding RNAs (LncRNAs) landscape in High Altitude- Deep Vein Thrombosis.

The Team led by Dr. Ashraf had done pioneering work in presenting the landscape of LncRNAs in disease progression of DVT at HA. The team developed a novel pipeline for analysis of RNA sequencing (RNA-Seq) data obtained from the peripheral blood, they identified widespread dysregulation of lncRNAs and protein-coding genes in HA-DVT patients when compared to the high-altitude controls. This pioneering study had successfully stratified HA-DVT patients from the high-altitude controls and sea level controls. Taken together, the comprehensive analysis identified lncRNA transcriptional signature display their functional prediction to be involved in pathways consistent with thrombotic pathophysiology. As a result, lncRNAs may serve as novel mechanistic insights and with further in-depth study it may be used as diagnostic and therapeutic targets for HA-DVT.

- *Prabhash K Jha,Aatira Vijay,Amit Prabhakar, Tathagat Chatterjee, Nitin Bajaj, Velu Nair, Bhuvnesh Kumar, Mohammad Z Ashraf, Manish Sharma. The Long Noncoding RNA Landscape of the High Altitude Induced Thromboembolic Disorder: Role of Endogenous miRNA Sponge* ***Circulation Research. 2019;125: A653 [Impact factor-15.2]***

- *Jha PK, Vijay A, Prabhakar A, Chatterjee T, Nair V, Bajaj N, Kumar B, Sharma M,* ***Ashraf MZ.*** *Transcriptome Profiling Reveals the Endogenous Sponging Role of LINC00659 and UST-AS1 in High-Altitude Induced Thrombosis.* ***Thrombosis & Haemostasis. 2021 Nov;121(11):1497-1511. [Impact Factor 5.3]***

Contribution # 7: Epigenetic regulation of gene expression at high altitude in VT.

Dr. Ashraf's team is leading a critical study on regulatory epigenetic mechanisms on thromboembolic disorders. DNA Methylation is considered as a dynamic epigenetic mechanism and alters according to lifestyle, exposure to air pollutants, environmental as well as psychological/stress related factors to which the cellular machinery works in coordination. The study led by Dr. Ashraf's team studied the effect of altitude exposure on subjects deployed to high altitude hypoxic environments leading to global methylation changes in the genome. The group conducted a meta-analysis of differential methylation in genome, where the results favored the exposed group and potentiates hypoxia as a predisposing factor for DNA methylation. Dr. Ashraf's team was able to provide a clear trend of increased ratio of methylation via candidate gene methylation profiling by bisulfite sequencing in Thrombomodulin gene-a natural anticoagulant, in VT patients when compared to healthy individuals. The contribution of hypoxia in small non-coding RNAs functioning via epigenetic alterations in venous thrombosis could lead to previously obscured dimension.

- *Aatira Vijay, Prabhash K Jha, Seema Parveen, Shailendra Goel, Amit Prabhakar, Bhuvnesh Kumar, Tathagat Chatterjee, Nitin Bajaj, Velu Nair, Manish Sharma, Mohammad Z Ashraf.Aberrant Promoter Hypermethylation Mediated Regulation of Thrombomodulin Gene in High Altitude Induced Deep Vein Thrombosis,* ***Circulation. 2019;140:A10076 [Impact Factor -23.6]***
- *Aatira Vijay, Prabhash Kumar Jha, Iti Garg, Manish Sharma,* ***Mohammad Zahid Ashraf*** *and Bhuvnesh Kumar. micro-RNAs dependent regulation of DNMT and HIF1a gene expression in thrombotic disorders.* ***Scientific Reports*** *2019;20;9(1):4815* ***[Impact Factor -4.3]***
- *Vijay A, Garg I,* ***Ashraf MZ.*** *Perspective: DNA Copy Number Variations in Cardiovascular Diseases.* ***Epigenet Insights.*** *2018 Dec 12; 11:2516865718818839*.

Contribution # 8: Screening of Herbal Compounds for their Anticoagulant Potential

Dr. Ashraf's lab has been in forefront of conducting *in silico* study on the herbal compound library to access their antithrombotic potential. The Factor Xa was chosen as the protein target for the study. The compounds belonging to different classes of plant secondary metabolites such as terpenes, flavonoids, polyphenols etc. were subjected to blind docking analysis. The various leads obtained from *in silico* analysis were subjected to wet lab assays. Interestingly, Pravastatin appeared to be a promising the first lead against high altitude thrombosis and validated in animal models. It was also tested for FXa assay and showed 50% inhibition at 10µm concentration. There was reduction in thrombus weight and size in the drug injected animals. This could result in a promising strategy towards drug repurposing. It will considerably reduce the resources needed for developing any new therapy and magnify the probability of Pravastatin entering into preclinical trial against VTE.

- *Ahmad I, Sharma S, Gupta N, Rashid Q, AbidM,* ***Ashraf MZ****, Jairajpuri MA. Antithrombotic potential of esculin 7, -O-pentasulfate (EPS) for its role in thrombus reduction using rat thrombosis model.* ***International Journal of Biology of Macromolecules****. 2018; 119:360-368. ISSN: 0141-8130*

Contribution # 9: Calpain as novel biomarker for HA-TED.

Dr. Ashraf's landmark discovery of Calpain as a key molecule for high altitude induced thrombosis is being seen a crucial lead for early diagnosis of this disease, a major concern for soldiers and other population staying at altitudes and thus, added a new paradigm by proposing a novel biomarker for thrombus formation. This finding has been published in a highly reputed medical weekly *Blood*, the official journal of American Society of Hematology with *editorial commentary***(Blood, 2014)**. While studying the variations in highly affected platelet proteins, the team of Dr. Ashraf found an increased activity of a key regulatory enzyme – Calpain. Interestingly, the investigations on the soldiers who developed thrombosis while serving at extreme altitude posts also revealed an increased activity of calpain indicating the relevance of the novel preclinical findings for clinical applications. Previously linked with neurological disorders and muscular

dystrophy, the molecule could become a crucial biomarker for an early prediction and diagnosis of high altitude induced thrombosis.

- *Tyagi T, Ahmad S, Gupta N, Sahu A, Ahmad Y, Nair V, Chatterjee T, Bajaj N, Sengupta S, Ganju L, Singh SB,* ***Ashraf MZ.*** *Altered expression of platelet proteins and calpain activity mediate hypoxia-induced prothrombotic phenotype.* ***Blood. 2014 Feb 20;123(8):1250-60. [Impact Factor 17.6]***
- *Tarun Tyagi, Amit Prabhakar, Shantanu Sengupta and* ***Mohammad Z Ashraf.****A Novel Role of Protein Disulfide Isomerase in Calpain Regulated Hypoxia Induced Prothrombotic Phenotype, 2014;* ***Blood****: 124 (21)* ***Blood. 2014 Feb 20;123(8):1250-60. [Impact Factor 17.6]***

Contribution # 10: MiRNA-145 as Antithrombotic Biomolecule.

While working on pathogenesis and pathophysiology of VTE, Dr. Ashraf and his team had comprehensively defined the role of miRNAs as antithrombotic biomolecule **(EBiomedicine,** in collaboration with **Cell Press** and **The Lancet, 2017)**. Dr. Ashraf had developed a miRNA-based therapy for inhibition of thrombosis using *in vivo* animal model system. His work demonstrated the delivery of miR-145 via *in vivo* miRNA mimic delivery which inhibited tissue factor expression, thereby attenuating thrombus formation in an animal model. These preclinical findings were further validated in human VTE patients that showed reduced level of miRNA-145 supporting the potential translational significance of miR-145 as therapeutic option for management of VTE. Dr. Ashraf proposed miRNAs-based therapy as one of the most promising new therapeutic paradigms in medicine that focuses on manipulating and inducing cellular re-equilibrium of deregulated miRNA expression profiles by the inhibition or overexpression of miRNA. MiRNA could be a promising strategy for venous thromboembolism which is prevalent at High altitude. It will assist in the better management and would reduce morbidity and mortality associated thrombotic events.

- *Anita Sahu, Prabhash Kumar Jha,Prabhakar A, Chatterjee T, Tyagi T, Kumari B, Khan N, Nair V,* ***Ashraf MZ****, MicroRNA-145 impedes thrombus formation via targeting tissue factor in venous thrombosis-* ***EBioMedicine****. 2017 Dec; 26:175-186.*

Contribution # 11: Identification of genes/pathways associated with VTpathophysiology.

Dr. Ashraf had provided the first report providing biological insights into the possible mechanism of HA induced DVT and explained that hypoxia at HA induce alterations in the expression of genes involved in hemostasis and blood coagulation pathway, which in turn causes platelet dysfunction and thereby lead to increased susceptibility to venous thrombosis. A cDNA microarray study led by Dr. Ashraf was performed to evaluate the gene expression profiles in DVT patients who developed the disease either at sea level (SL-DVT) or at high altitude (HA-DVT) locations. His study suggested that given the environmental condition the differential expression of hypoxia-responsive genes (AGN, EGR1, LMNA, MMP14, NF1, PDLIM1, PLOD1, SLCA4, SLC9A1, and TEK) in HA-DVT could be a determining factor to understand the pathophysiology of DVT at high altitude.

- *Jha PK, Sahu A, Prabhakar A, Tyagi T, Chatterjee T, Arvind P, Nair J, Gupta N, Kumari B, Nair V, Bajaj N, Shanker J, Sharma M, Kumar B,* ***Ashraf MZ*** *Genome-Wide Expression Analysis Suggests Hypoxia-Triggered Hyper-Coagulation Leading to Venous Thrombosis at High Altitude.* ***ThrombHaemost. 2018 Jul;118(7):1279-1295. doi: 10.1055/s-0038-1657770.***
- *Jha PK, Vijay A, Sahu A,* ***Ashraf MZ*** *Comprehensive Gene expression meta-analysis and integrated bioinformatic approaches reveal shared signatures between thrombosis and myeloproliferative disorders.* ***Sci Rep. 2016 Nov 28; 6:37099. doi: 10.1038/srep37099.***

Contribution # 11: Genetic polymorphisms associated with VT manifestations.

The study led by Dr. Ashraf revealed that single nucleotide polymorphisms that are associated with thrombotic episodes in western populations had distinct behavior in Indian population. His data suggested the limited role of established genetic variants in imparting susceptibility to VTE in Indian population and thus encourages the identification of novel genetic variants in Indians for the better understanding of the ethnicity-based differences in susceptibility of individuals. Additionally, study led by Dr. Ashraf demonstrated an association between elevated Plasma endothelin levels of VTE patients with the endothelin-1 polymorphism in Indian population. His research investigations suggested a significant role of endothelin-1 gene polymorphism in individual's susceptibility to the VTE and its clinical progression

- *Kumari B, Prabhakar A, Sahu A, Chatterjee T, Tyagi T, Gupta N, Nair V,* ***Ashraf MZ****. Endothelin-1 Gene Polymorphism and Its Level Predict the Risk of Venous Thromboembolism in Male Indian Population.* ***Clin Appl ThrombHemost.*** *2016 Aug*
- *Kumari B, Srivastava S, Chatterjee T, Vardhan R, Tyagi T, Gupta N, Sahu A, Chandra K,* ***Ashraf MZ****. Study of associated genetic variants in Indian subjects reveals the basis of ethnicity related differences in susceptibility to venous thromboembolism.* ***Thrombosis.****, 182762. Epub 2014 Sep 30. 2014*

OTHER CONTRIBUTIONS

Contribution # 1: Prediction of ischemic stroke in young Indians *(collaboration with Army Hospital Research & Referral, AIIMS, New Delhi)*

Protein S deficiency alone or protein S deficiency in combination with protein C deficiency as well as hyperhomocysteinemia are significantly associated with ischemic stroke in young Indians.

- *Prediction of ischemic stroke in young Indians: is thrombophilia profiling a way out?* ***Blood Coagul Fibrinolysis****.* **2013** *Jun;24(4):449-53.*

Contribution # 2: Association of gene polymorphisms with High Altitude Pulmonary Edema

(Collaboration with Molecular Biology Div. DIPAS & 153 General Hospital, Leh)

Variability in individual susceptibility to altitude sickness depending on genetic makeup. The renin-angiotensin-aldosterone system (RAAS) pathway plays a key role in regulation of vascular tone and circulatory homeostasis. Our study indicates the existence of ethnic variation between the high altitude native and the groups comprising lowlanders.

- *Association of polymorphisms in angiotensin and aldosterone synthase genes of the renin-angiotensin-aldosterone system with high-altitude pulmonary edema.J Renin Angiotensin Aldosterone Syst. 2012 Mar;13(1):155-60.*

Contribution # 3: High altitude induced systemic hypertension (*Multicentric clinical study involving Department of Physiology, Armed Forces Medical College, Pune; Command Hospital (Southern Command), Pune;Eastern Command Fort William, Kolkata; Army Hospital RR, Delhi and DIPAS, Delhi)*

The study suggests that previously normotensive lowlanders following acclimatisation and prolonged stay at moderately HA is a commonly encountered medical problem. HASH is associated with endothelial dysfunction in form of raised levels of sICAM-1 and VCAM-1.

- *Endothelial markers in high altitude induced systemic hypertension (HASH) at moderate high altitude.* **Med J Armed Forces India. 2017** *Oct;73(4):363-369.*
- *Hypertension at high altitude: the interplay between genetic and biochemical factors in the setting of oxidative stress.* Hypertens Res. 2016 *Apr;39(4):199-200. doi: 10.1038/hr.2015.140. Epub 2015 Dec 10.*

Contribution # 4: Natural Anticoagulant and their mode of action *(collaboration with Department of Biosciences, JMI, Delhi)*

The polyanionic nature and multispecificity of heparin pose several complications. Generally, the polysulfated compounds with antithrombotic potential are thought to have feasible synthetic procedures with much less bleeding, thus having favourable safety profiles. Our study presents trehalose octasulfate as a novel, effective, dual acting antithrombotic agent.

- *Polysulfated trehalose as a novel anticoagulant agent with dual mode of action.Biomed Res Int.* 2015*;2015:630482.*

Contributions as primary worker

Contribution # 1: Identification of a novel family of oxidized phospholipids that serve as ligands for the macrophage scavenger receptors CD36 and BI.

Dr. Ashraf haddescribed a novel family of oxidized choline glycerophospholipids($oxPC_{CD36}$) that are formed during the oxidation of LDL by multipledistinct pathways and are present *in vivo* in human and animalatherosclerotic lesions and also accumulate in hyperlipidemicplasma and in plasma of subjects with low HDL levels alongwith identification of a novel class ofoxidized phospholipids that serve as high affinity ligands for scavenger receptor BI as well. His work has been categorized one of the important advances in cardiovascular research and was published in a top scientific journal by the American Society for Biochemistry and Molecular Biology with international circulation **(Journal of Biological Chemistry, 2008)**. Since their publication and commercialization, these oxidized phospholipids have been utilized in a number of academic and clinical labs to speed up their discovery process for heart diseases treatment.

Contribution # 2: Inhibition of scavenger receptor-BI mediated selective uptake of cholesteryl esters by oxidized phospholipids.

Dr. Ashraf demonstrated that $oxPC_{CD36}$ bind specificallyto SR-BI and that binding of $oxPC_{CD36}$ prevents HDL associationbecause of the close proximity of the binding sites for thesetwo ligands on SR-BI. We then demonstrate that $oxPC_{CD36}$ is apotent inhibitor of SR-BI-mediated selective uptake of cholesterylesters in liver cells (hepatocytes). His results first time showed that under conditions of increased oxidativestress, accumulation of specific oxidized phospholipids maypromote atherosclerosis not only by inducing uptake of modifiedlipoproteins by macrophages via CD36, but can also interferewith reverse cholesterol transport by preventing SR-BI-mediatedselective cholesteryl ester uptake in hepatocytes. Dr. Ashraf comprehensively explained the fact that only oxidized phospholipids were able to inhibit reverse cholesterol transport which can be of great therapeutic importance. His approach represents a new direction in lipid research and our research identified a new mechanism by which specificoxidized phospholipids accumulated *in vivo* in oxidative stressmay inhibit reverse cholesterol transport and contribute tothe development of hypercholesterolemia and atherosclerosis. **(Journal of Biological Chemistry, 2008A)**.

Contribution # 3: Characterization of the binding site for specific oxidized phospholipids and oxidized low density lipoprotein of scavenger receptors.

The nominee had identified the structural basisfor the recognition of $oxPC_{CD36}$ by scavenger receptors - CD36 and SR-BI and demonstrated that positively charged amino acids representthe core of the binding site for $oxPC_{CD36}$ andthat the electrostatic interaction between evolutionary conserveddomains on scavenger receptors and oxidized phospholipid moieties is crucialin this binding. His research provided the molecular basis for the inhibition between the two ligands on cells and described a critical role of oxidized phospholipids in atherosclerоticlesion formation and a prothrombotic phenotype in the settingsof dyslipidemia **(Journal of Biological Chemistry, 2008 & 2010)**.

Contribution # 4: Oxidized high-density lipoprotein inhibits platelet activation and aggregation via scavenger receptor BI

Dr. Ashraf had great contributions in identification of OxHDL, but not native HDL, as a potent inhibitor of plateletactivation and aggregation induced by physiologic agonists. He explained that this antithrombotic effect was concentration and time dependentand positively correlated with the degree of lipoprotein oxidation. Dr. Ashraf's novel findings suggestthat contrary to the prothrombotic activity of oxidized low-densitylipoprotein (OxLDL), HDL upon oxidation acquires antithromboticactivity that depends on platelet SR-BI. This work was published in the prestigious journal ***Blood*** **with editorial.** In addition, OxHDL will find use in understanding the compensatory roles of bad cholesterol and good cholesterol in athero-thrombotic diseases, a fundamentally important scientific topic that requires much work to do. This beautiful concept will have tremendous impact on scientific community and drug discovery industries. (Blood, 2008;Int J Biochem Cell Biol. 2009;Biomol Concepts).

Contribution # 5: Specific Oxidized Phospholipids Induce Foam Cell Formation via Inhibition of HDL Mediated Cholesterol Efflux

Dr. Ashraf had proposed a novel proatherogenic property of oxidized phospholipid particles, including their ability to induce cellular lipid accumulation by impairing cholesterol efflux with dysfunctional HDL and **demonstrated for the first time** the presence of single molecular species of oxidized phospholipids in HDL is sufficient to render HDL dysfunction even without modification of its proteins. He pioneered to demonstrate that oxidized phospholipid promote macrophage foam cell formation. Dr. Ashraf's study serves as a vital step to understand the molecular mechanism for novel proatherogenic activity of specific oxidized phospholipids through dysfunctional HDL that will certainly facilitate the drug discovery process for cardiovascular diseases**(Journal of Biological Chemistry, 2008 & 2010)**.

Contribution # 6: HOXA9 participates in the transcriptional activation of E-selectin in endothelial cells.

Dr. Ashraf had pioneered to evidence that in endothelial cells transcriptional activation of E-selectin byTissue Necrosis Factor-alpha mediated through the binding ofHOXA9 to a specific sequence. Dr. Ashraf, for the first time, revealed a pro-inflammatory role of HOXA9 in theinduction of an "activation gene" in EC and his work was published in reputed journal ***Molecular and Cellular Biology***. Nominee's findings are promising since all new drug candidates are structure related at the late stage of drug discovery and thus, this work will certainly stimulate many scientists working on cardiovascular gene regulation, drug discovery, and new molecular method development. (**Mol & Cell Biol, 2007)**.

Contribution # 7: Role of MAP Kinase Phosphatase-1 in Vascular Injury and Inflammation.

The remarkable work of the nominee demonstrating epidermal growth factor (EGF) and lysophophitidic acid (LPA) synergistically regulated MKP-1 gene induction in cultured endothelial cells got published in prestigious **American Heart Association,Journal-'Circulation Research'.** Dr. Ashraf is first to demonstrate that thrombin or LPA induction of MKP-1 is synergistically increased in presence of EGF in endothelial cells and to elucidate the signaling mechanism responsible the synergy expliciting the functional consequences of the activity with respect to endothelial cells migration and *in vitro* vasculogenesis (**Circ Res, 2010).**

Contribution # 8: The Role of Lysophospholipids in the Differentiation of Bone Marrow Derived Cells Towards Endothelial Progenitors

Dr. Ashraf had investigated the role of lysophospholipids (such as S1P and LPA) in EPC differentiation of non-adherent bone marrow cells (BMCs) and suggested that lipids provide a stimulus for these primitive hematopoietic stem cells to become more motile, leave the hematopoietic stem cell microenvironment and relocate to fresh sites vascular injury. Hence, factors such as S1P may provide a therapeutic benefit for cardiac complications by promoting BMC proliferation and differentiation to EPCs. The knowledge gained from Dr. Ashraf's study hasgreatly facilitated the design of new sphingolipid–related drugs that may provide new therapeutic strategies to intervene in cardiovascular disorders and other inflammatory diseases.

Contribution # 9: Antiatherosclerotic effects of dietary supplementations of garlic and turmeric and restoration of endothelial function.

The landmark outcomes from the doctoral work of the nominee on the atheroscleroprotective potential of diet supplementation of garlic and turmeric by measuring serum lipid profile, changes in cardiovascular parameters demonstrated that garlic and turmeric are potent vasorelaxants as well as reduce the atherogenic properties of cholesterol. Dr. Ashraf is one of the pioneer who has estabilished the mechanisms of action of the natural compounds and set standard methods for pharmacological evaluation of natural products.**(J Ethnopharmacol 2004; Life Sci 2007)**

Contribution # 10: Influence of influenza viral infection on airway smooth muscle activity.

Nominee's work on influence of influenza type A virus (H1N1) infection examined on ASM responsiveness to various bronchoactive agents gained international attention and was cited among one of most important findings on influenza virus by National Medical Council, UK. **(Indian J Exp Biol. 2001).**