Ten representative publications of Prof. Ravishankar Ramachandran

(In his career spanning nearly 20 yrs as an independent investigator, there have been many important discoveries and it is difficult to rank them in order of importance as each of the discoveries have made significant impacts. The selected publications below represent different aspects of the work starting with the most recent ones)

Serial No.	Details of publication	Importance of the discovery/ contribution
1.	Phase III, Randomized, Double-Blind, Placebo Controlled Trial of Efficacy, Safety and Tolerability of Antiviral Drug Umifenovir vs Standard Care of Therapy in Non-Severe Covid-19 Patients **Ravishankar Ramachandran***, Bhosale, Vivek, Reddy, Himanshu, Atam, Virendra, Faridi, MMA, Fatima, Jalees, Shukla, Vaibhav, Singh, Vikram, Singh Negi, Mahendra Pal, Srivastava, Mukesh, Srivastava, Ajay Kumar and Tripathi, Chandra Bhushan, Ghosh, Nayan, Majumdar, Nilanjana, Tripathi, Raj Kamal, Rath, Srikanta Kumar, Mishra, Prabhat Ranjan, Sharma, Sharad and Kundu, Tapas K.*, (September 7, 2021). http://dx.doi.org/10.2139/ssrn.3919585 (*Preprint is available on the Lancet: Infectious Diseases preprint server*)	Prof. Ravishankar is leading a team, as the Nodal Scientist, for drug repurposing studies against COVID19. The drug Umifenovir (Arbidol) was identified and shortlisted based on the efficacy, toxicity, patent status and other favourable parameters. The interactions with SARS Cov-2 Spike (RBD) – Human Ace2 was evaluated *in vitro* using purified proteins, cell-culture inhibition experiments, other associated experiments and computational analysis. Since it is not available in India, the synthesis process was implemented and transferred to a company (M/s Medizest, Goa) for manufacture under GMP conditions. Careful analysis of the dosage needed for COVID19 patients was carried out based on the reported pharmacokinetics. DCGI permission was received and presently the Phase 3 clinical trials titled "*Phase 3, Randomized, Double-blind, Placebo control trial of Efficacy, Safety and Tolerability of Antiviral drug Umifenovir vs Standard care of therapy in non-severe COVID-19 patients*" involving 3 clinical trials centers has been completed. It was identified that Umifenovir meets the primary and secondary endpoint criteria and exhibits statistically significant efficacy for Mild-asymptomatic patients. It is efficacious, safe and well-tolerated

		at the tested dosage of 800mg BID, maximum 14 days. Commercialization and patent filing are in process at this important juncture of the pandemic.
2.	*M. tuberculosis* class II apurinic/apyrimidinic-endonuclease/3′-5′ exonuclease (XthA) engages with NAD^+ -dependent DNA ligase A (LigA) to counter futile cleavage and ligation cycles in Base Excision Repair. Taran Khanam, Mohammad Afsar, Ankita Shukla, Faiyaz Alam, Sanjay Kumar, Horam Soyar, Kunzes Dolma, Ashish, Mukesh Pasupuleti, Kishore Kumar Srivastava, Ravi Sankar Ampapathi & **Ravishankar Ramachandran*** *Nucleic Acids Research***. 48**, 4325-4343, 2020	We identified and characterized a fundamental and novel Base Excision Repair interaction that is necessary for effective and critical repair of damaged DNA. Disrupting this process can lead to new therapeutics for drug resistant bacteria/mycobacteria that have less toxic side-effects
3.	Leprosy drug Clofazimine activates peroxisome proliferator-activated receptor-γ and synergizes with imatinib to inhibit chronic myeloid leukemia cells. Harish Kumar, Sourav Chattopadhyay, Nabanita Das, Sonal Shree, Dinesh Patel, Jogeswar Mohapatra, Anagha Gurjar, Sapana Kushwaha, Abhishek Kumar Singh1, Shikha Dubey3, Kiran Lata3, Rajesh Kushwaha5, Riyazuddin Mohammed, Krishnarup Ghosh Dastidar4, Namrata Yadav4, Achchhe Lal Vishwakarma7, Jiaur Rahaman Gayen6,2, Sanghamitra Bandyopadhyay5, Abhijit Chatterjee4, Mukul Rameshchandra Jain4, Anil Kumar Tripathi8, Arun Kumar Trivedi, Naibedya Chattopadhyay, **Ravishankar Ramachandran**, Sabyasachi Sanyal *Haematologica* **105**, 971-986, 2020	Clofazimine, a drug used against Leprosy and drug-resistant TB, was identified to act synergistically with Imatinib to act against drug-resistant Chronic Myeloid Leukemia and the mechanism has been elucidated. This approach represents affordable treatment for patients. International patents have been granted and Phase II clinical trials are being proposed presently.

4.	Crystal Structure of Mycobacterium tuberculosis H37Rv AldR (rv2779c), a regulator of the ald gene: DNA-binding, and identification of small-molecule inhibitors Abhishek Dey, Sonal Shree, Sarvesh Kumar Pandey, Rama Pati Tripathi & **Ravishankar Ramachandran*** *J. Biol. Chem*. **291**, 11967-11980, 2016	First-in-class inhibitors for the regulator of the ald gene, that is suggested to be a top-3 target against TB-persistence, was identified using a combination of structural biology and rational inhibitor identification strategies in this work.
5.	The M. tuberculosis HAD phosphatase (Rv3042c) interacts with host proteins and is inhibited by Clofazimine Sonal Shree, Abhishek Kumar Singh, Richa Saxena, Harish Kumar, Aparna Agarwal,Vijay Kumar Sharma, Kanchan Srivastava, Kishore Kumar Srivastava, Sabyasachi Sanyal and **Ravishankar Ramachandran*** *Cell. Mol. Life Sci.* **73**, 3401-3417, 2016	We used a combination of phenotypic comparison, biophysics, and biochemistry techniques to identify that Mtb rv3042c is a drug target for Clofazimine, a drug being tested in MDR-TB clinical trials. An agreement with the 'Global TB Alliance' was signed to exploit this fundamental innovation and discovery further
6.	Mycobacterium tuberculosis class II apurinic/apyrimidinic-endonuclease/3'-5' exonuclease III exhibits DNA regulated modes of interaction with the sliding DNA β-clamp Taran Khanam, Niyati Rai & **Ravishankar Ramachandran*** *Mol. Microbiol*. **98**, 46-68, 2015	The work established for the first time a critical interaction in mycobacterial DNA Base excision repair involving the sliding DNA beta-clamp and an exonuclease that acts in the initial step of the pathway. The interaction mode was found to be substrate dependent and can be specifically disrupted using carefully designed inhibitors.
7.	Mechanistic insights from the crystal structures of a feast/famine regulatory protein from *Mycobacterium tuberculosis H37Rv* Tripti, S & **Ravishankar Ramachandran*** *Nucleic Acids Res.* **35***,* 7324-7335, 2007	This work helped establish feast/famine regulators functionally act through a molecular mechanism where the binding of an amino acid effector leads to quaternary structural changes or other subtle changes. They might have functions in packaging of genomic DNA and can form nucleosome like particles
8.	Ligand induced structural transitions, mutational analysis and 'open' quaternary structure of the *M. tuberculosis* Feast/famine regulatory protein (Rv3291c)	This work helped establish that the rarely observed 'open' quaternary structure is a functional necessity of feast/famine regulation and that quaternary structural changes in response to the binding of effectors,

	Tripti Shrivastava, Abhishek Dey & **Ravishankar Ramachandran*** *J. Mol. Biol.***392**, 1007-1019, 2009	are needed to bind to specific promoter binding regions. Firmly established that these proteins are novel anti-bacterial targets
9.	Mycobacterium tuberculosis NAD^+ -dependent DNA ligase is selectively inhibited by glycosylamines compared with human DNA ligase I. Srivastava SK, Dube D, Tewari N, Dwivedi, N, Tripathi RP & **Ravishankar Ramachandran*** *Nucleic Acids Res*. **33**, 7090-7101, 2005	DNA Ligase I and LigA are principal enzymes in humans and bacteria respectively. Due to the similarity of the co-factor binding sites, it is important to develop strategies that are able to distinguish between them for antibacterial therapeutic discovery and strategies. This work helped establish a platform for this and demonstrated that it is possible to distinguish between these enzymes using small-molecule inhibitors.
10.	Luthra A, Mahmood, A, Arora A & **Ravishankar Ramachandran*** Characterization of Rv3868: an essential hypothetical protein of the ESX-1 secretion system in *M. tuberculosis.* *J. Biol. Chem.*,**283**, 36532-36541, 2008	The ESX / Type-VII secretory systems in mycobacteria are critical for the export of essential virulence factors that interact with the host as part of the pathogenesis process. Hence targeting this process can abrogate mycobacterial infection. We characterized the EccA family of enzymes that form part of this pathway and showed how mechano-chemical changes that occur in the protein due to the AAA module in it can help transfer energy to partner proteins in the Esx pathway.
11.	Srivastava SK, Tripathi RP & **Ravishankar Ramachandran*** NAD^+ -dependent DNA ligase (rv3014c) from *M. tuberculosis*: Crystal structure of the adenylation domain and identification of novel inhibitors. *J. Biol. Chem.***280**, 30273-30281, 2005	The LigA enzymes are essential for bacteria and the first step to exploit them as drug targets is to structurally and functionally characterize them. The work reported the structural analysis of the adenylation domain of the enzyme and also identified and demonstrated that small molecule inhibitors that target the enzyme result in abolition of bacterial growth in a dose-dependent manner.
12.	**Ravishankar Ramachandran**, Hartmann, C., Song, H.K., Huber, R. & Bochtler, M. (2002) Functional	HslV-HslU are the prokaryotic homologs of the eukaryotic 20S proteasome. An important problem

	interactions of HslV (ClpQ) with the ATPase HslU (ClpY) *Proc. Natl. Acad. Sci. (USA)* 99, 7396-7401.	in literature was the orientation of the HslU partner vis-à-vis the HslV protein. Correct resolution of this is important to understand the molecular mechanism and functions of this molecular machine. The work used a combination of structure and biochemical analysis to identify the correct orientation and molecular mechanism of the HslUV molecular machine.