In order of importance, list of ten best papers of the candidate, highlighting the important discoveries/contributions described in them briefly (not to exceed 3000 words)

1. A. Verma, A. Singh, M.P. Singh, M.A. Nengroo, K.K. Saini, S.R. Satrusal, M.A. Khan, P. Chaturvedi, A. Sinha, S. Meena, A.K. Singh, **D. Datta***, EZH2-H3K27me3 mediated KRT14 upregulation promotes TNBC peritoneal metastasis, ***Nat Commun***, 13 (2022) 7344. **(JIF:17.69) (*Corresponding author)**

   Significance: India is known to be the Triple-Negative Breast Cancer (TNBC) capital of the world for its high prevalence (18-31%) as compared to West (8-15%). Unlike other breast cancer subtypes in which three hormone receptors (ER, PR, HER2) are targeted, TNBC lacks these hormone receptors and considered the deadliest among all breast cancer subtypes as there is no targeted therapy for it. Our study reveals new therapeutic vulnerabilities of TNBC, in which we discover that functional hyper-activation of epigenetic modulator Enhancer of Zeste Homolog 2 (H3K27me3) alters TNBC metastatic landscape and fosters its peritoneal metastasis, particularly splenic. Instead of H3K27me3-mediated repression of gene expression; here, it promotes KRT14 transcription by attenuating binding of repressor SP1 to its promoter. Further, KRT14 loss significantly reduces TNBC migration, invasion, and peritoneal metastasis. Consistently, human TNBC metastasis displays positive correlation between H3K27me3 and KRT14 levels. EZH2 loss of function or H3K27me3 inhibition by FDA approved drug Tazemetostat reduces TNBC peritoneal metastasis. Altogether, we identify that the EZH2 inhibitor drug Tazemetostat (EPZ6438) can be a promising therapeutic option against the most aggressive TNBC subtype, where targeted therapy is still an enigma.

2. WO2022130411 - SMAC MIMETICS FOR TREATMENT OF CANCER, PROCESS FOR PREPARATION AND PHARMACEUTICAL COMPOSITION THEREOF (**Patent Link: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2022130411&_cid=P10-L50LD3-74541-1**)

   Principal Investigator: Dr. Dipak Datta

   Publication Number: WO/2022/130411, **Publication Date: 23.06.2022**, International Application No.PCT/IN2021/051182, International Filing Date:17.12.2021

   Name of Other Contributor: Haq W, Ali R, Singh A, Nengroo MA, Katekar R, Singh G, Vaishnav J, Afsar M, Singh M, Rath SK, Koley D, Mishra DP, Ramachandran R, Ampapathi RS, Gayen JR

   Highlights: The present invention relates to novel SMAC mimetic peptidomimetics useful for the treatment of proliferative diseases including cancer in mammals. The novel SMAC mimetics are prepared by incorporating (2S,5R)-5 -(5-methylfuran-2-yl) pyrrolidine-2-carboxylic acid, a novel unnatural amino acid that imparts exclusively trans amide bond geometry favorable for target protein binding.

   USP:

   a) Orally active, monovalent XIAP antagonist exhibits anti-tumor efficacy as a single agent
   b) nM level target binding with nM level in vitro efficacy against chemotherapy resistant cancer cells.
   c) Oral Bioavailability: 55% (mice), Rat (20%), Dog (50%)

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d) Better preclinical efficacy and bioavailability than existing Phase-II clinical trial comparator (Novartis LCL-161)
e) Detailed molecular mechanisms deciphered for its mode of action
f) Efficacy dose-2.5mg/kg in mice, NOAEL: 150mg/kg in 7-Day DRF in Rat
g) IND studies on-going

3. K.K. Saini, P. Chaturvedi, A. Sinha, M.P. Singh, M.A. Khan, A. Verma, M.A. Nengroo, S.R. Satrusal, S. Meena, A. Singh, S. Srivastava, J. Sarkar, **D. Datta***, Loss of PERK function promotes ferroptosis by downregulating SLC7A11 (System Xc^-) in colorectal cancer, ***Redox Biology,*** 65, (2023) 102833. **(JIF:11.4) (*Corresponding author)**

   Significance: Therapy resistance is a major cause for tumor relapse and recurrence in clinics. Tumor cells that are resistant to chemotherapeutic drugs called 'drug tolerant' or 'Persister' cells which have distinct vulnerability towards iron mediated cell death or ferroptosis, which is a genetically and biochemically distinct form of programmed cell death, is characterized by iron-dependent accumulation of lipid peroxides. Unfolded Protein Response (UPR) plays critical role for cancer cells to become drug tolerant. Tweaking the balance of UPR to make drug tolerant cells susceptible to Ferroptotic cell death could be an attractive therapeutic strategy. Here we pinpoint that selectively PERK arm of UPR protects cancer cells from ferroptotic cell death but not from classical apoptosis. Therefore, small molecule PERK inhibitor like HC-5404, currently in clinical trial, holds huge promise as novel therapeutics that can sensitize apoptosis resistant cancer cells towards Ferroptotic cell death.

4. M.A. Nengroo, S. Maheshwari, A. Singh, A. Verma, R.K. Arya, P. Chaturvedi, K.K. Saini, A.K. Singh, A. Sinha, S. Meena, A. Gupta, A. Mishra, J. Sarkar, **D. Datta***, CXCR4 intracellular protein promotes drug resistance and tumorigenic potential by inversely regulating the expression of Death Receptor 5, ***Cell Death Dis***, 12 (2021) 464. **(JIF:9.68) (*Corresponding author)**

   Significance: Drug resistance or inadequate chemotherapy response in patients is one of the pivotal reasons for cancer-associated mortality and morbidity. Therefore, there is a dire need to understand the molecular mechanisms lying behind cancer therapy resistance. Chemokine receptor CXCR4 overexpression in solid tumors has been strongly associated with therapy resistance, poor prognosis and adverse clinical outcome. However, blockade of CXCL12-CXCR4 signaling axis by inhibitors like Nox-A12, FDA approved CXCR4 inhibitor drug AMD3100 have shown limited clinical success in cancer treatment. Therefore, exclusive contribution of CXCR4-CXCL12 signaling in pro-tumorigenic function is questionable. In our pursuit to understand the impact of chemokine signaling in carcinogenesis, we reveal that instead of CXCR4-CXCL12 signaling, presence of CXCR4 intracellular protein augments therapy (paclitaxel) resistance and pro-tumorigenic functions. Irrespective of CXCR4 surface expression, by utilizing stable gain and loss of function approaches, we observe that intracellular CXCR4 protein selectively resists and sensitizes colon cancer cells against paclitaxel therapy in vitro and in vivo. Together, our data suggest that targeting CXCR4 intracellular protein may be critical to dampen the pro-tumorigenic functions of CXCR4. The whole concept has been summarised in one of our revew articles recently published in ***Biochim Biophys Acta Rev Cancer*** 1877 (2022) 188790. **(JIF:11.4)** (*M.A. Nengroo, M.A. Khan, A. Verma, **D. Datta***, Demystifying the CXCR4 conundrum in cancer biology: Beyond the surface signaling paradigm)*

5. S. Maheshwari, S.R. Avula, A. Singh, L.R. Singh, G.R. Palnati, R.K. Arya, S.H. Cheruvu, S. Shahi, T. Sharma, S. Meena, A.K. Singh, R. Kant, M. Riyazuddin, H.K. Bora, M.I. Siddiqi, J.R. Gayen, K.V. Sashidhara, **D. Datta***, Discovery of a Novel Small-Molecule Inhibitor that Targets PP2A-beta-Catenin Signaling and Restricts Tumor Growth and Metastasis, ***Mol Cancer Ther,*** 16 (2017) 1791-1805. **(JIF:6.0) (*Corresponding author)**

   Significance: Molecular hybridization of different pharmacophores to tackle both tumor growth and metastasis by a single molecular entity can be very effective and unique if the hybrid product shows drug-like properties. Here, we report synthesis and discovery of a novel small-molecule inhibitor (***Indian Patent Application Number 3716/DEL/2014***) of PP2A-β-catenin signaling that limits both in vivo tumor growth and metastasis. Our molecular hybridization approach resulted in cancer cell selectivity and improved drug-like properties of the molecule. Inhibiting PP2A and β-catenin interaction by selectively engaging PR55α-binding site, our most potent small-molecule inhibitor diminished the expression of active β-catenin and its target proteins c-Myc and Cyclin D1. Furthermore, it promotes robust E-cadherin upregulation on the cell surface and increases β-catenin-E-Cadherin association, which may prevent dissemination of metastatic cells. Altogether, we report synthesis and mechanistic insight of a novel drug-like molecule to differentially target β-catenin functionality via interacting with a particular subunit of PP2A.

6. A.K. Singh, S.S. Chauhan, S.K. Singh, V.V. Verma, A. Singh, R.K. Arya, S. Maheshwari, M.S. Akhtar, J. Sarkar, V.M. Rangnekar, P.M.S. Chauhan, **D. Datta***, Dual targeting of MDM2 with a novel small-molecule inhibitor overcomes TRAIL resistance in cancer, ***Carcinogenesis***, 37 (2016) 1027-1040. **(Editor's Choice Article) (JIF:5.1) (*Corresponding author)**

   Significance: MDM2 (Mouse double minute 2) protein functionally inactivates the tumor suppressor p53 in human cancer. Conventional MDM2 inhibitors provide limited clinical application as they interfere only with the MDM2-p53 interaction to release p53 from MDM2 sequestration but do not prevent activated p53 from transcriptionally inducing MDM2 expression. Here, we report a rationally synthesized a unique small-molecule inhibitor of MDM2 (CPI-7c), which not only inhibited MDM2-p53 interaction but also promoted MDM2 degradation. CPI-7c bound to both RING and N-terminal domains of MDM2 to promote its ubiquitin-mediated degradation and p53 stabilization. CPI-7c-induced p53 directly recruited to the promoters of DR4 and DR5 genes and enhanced their expression, resulting in sensitization of TNF-related apoptosis-inducing ligand (TRAIL)-resistant cancer cells toward TRAIL-induced apoptosis. Collectively, we identified CPI-7c as a novel small-molecule inhibitor of MDM2 with a unique two-prong mechanism of action that sensitized TRAIL-resistant cancer cells to apoptosis by modulating the MDM2-p53-DR4/DR5 pathway.

7. A.K. Singh, A. Verma, A. Singh, R.K. Arya, S. Maheshwari, P. Chaturvedi, M.A. Nengroo, K.K. Saini, A.L. Vishwakarma, K. Singh, J. Sarkar, **D. Datta***, Salinomycin inhibits epigenetic modulator EZH2 to enhance death receptors in colon cancer stem cells, ***Epigenetics***, 16 (2021) 144-161. **(JIF:4.8) (*Corresponding author)**

   Significance: Drug resistance is one of the trademark features of Cancer Stem Cells (CSCs). We and others have recently shown that paucity of functional death receptors (DR4/5) on the cell surface of tumour cells is one of the major reasons for drug resistance, but their involvement in the context of in CSCs is poorly understood. By harnessing CSC specific cytotoxic function of salinomycin, we discovered a critical role of epigenetic modulator EZH2 in regulating the expression of DRs in colon CSCs. Our unbiased proteome profiler array approach followed by ChIP

analysis of salinomycin treated cells indicated that the expression of DRs, especially DR4 is epigenetically repressed in colon CSCs. Concurrently, EZH2 knockdown demonstrated increased expression of DR4/DR5, significant reduction of CSC phenotypes such as spheroid formation in-vitro and tumorigenic potential in-vivo in colon cancer. TCGA data analysis of human colon cancer clinical samples shows strong inverse correlation between EZH2 and DR4. Taken together, this study provides an insight about epigenetic regulation of DR4 in colon CSCs and advocates that drug-resistant colon cancer can be therapeutically targeted by combining TRAIL and small molecule EZH2 inhibitors.

8. R. Tiwari, N. Manzar, V. Bhatia, A. Yadav, M.A. Nengroo, **D. Datta**, S. Carskadon, N. Gupta, M. Sigouros, F. Khani, M. Poutanen, A. Zoubeidi, H. Beltran, N. Palanisamy, B. Ateeq, Androgen deprivation upregulates SPINK1 expression and potentiates cellular plasticity in prostate cancer, ***Nat Commun***, 11 (2020) 384. **(JIF:17.69)**

   Significance: Emergence of an aggressive androgen receptor (AR)-independent neuroendocrine prostate cancer (NEPC) after androgen-deprivation therapy (ADT) is well-known. Nevertheless, the majority of advanced-stage prostate cancer patients, including those with SPINK1-positive subtype, are treated with AR-antagonists. Here, we show AR and its corepressor, REST, function as transcriptional-repressors of SPINK1, and AR-antagonists alleviate this repression leading to SPINK1 upregulation. Increased SOX2 expression during NE-transdifferentiation transactivates SPINK1, a critical-player for maintenance of NE-phenotype. SPINK1 elicits epithelial-mesenchymal-transition, stemness and cellular-plasticity. Conversely, pharmacological Casein Kinase-1 inhibition stabilizes REST, which in cooperation with AR causes SPINK1 transcriptional-repression and impedes SPINK1-mediated oncogenesis. Elevated levels of SPINK1 and NEPC markers are observed in the tumors of AR-antagonists treated mice, and in a subset of NEPC patients, implicating a plausible role of SPINK1 in treatment-related NEPC. Collectively, our findings provide an explanation for the paradoxical clinical-outcomes after ADT, possibly due to SPINK1 upregulation, and offers a strategy for adjuvant therapies.

9. M. Chakravarti, S. Dhar, S. Bera, A. Sinha, K. Roy, A. Sarkar, S. Dasgupta, A. Bhuniya, A. Saha, J. Das, S. Banerjee, M. Vernekar, C. Pal, N. Alam, **D. Datta**, R. Baral, A. Bose, Terminally exhausted CD8+ T cells resistant to PD-1 blockade promote generation and maintenance of aggressive cancer stem cells, ***Cancer Res***, 83 (2023). **(JIF:13.64)**

   Significance: Heterogeneity within the tumor-infiltrating lymphocytes (TIL) population limits immunotherapeutic efficacy against cancer. Between two subpopulations of exhausted CD8+ TILs (progenitor-exhausted; TPEX, terminally exhausted; TTEX), TTEX cells remain unresponsive to anti–programmed cell death protein 1(PD-1) therapy. Deciphering whether and how PD-1–resistant TTEX cells engage in tumor promotion could improve the response to immunotherapy. Here, we report that TTEX cells actively participate in tumor progression by modulating cancer stem cells (CSC). TTEX cells strongly correlated with elevated CSC frequency in poorly immune-infiltrated (CD8+ TIL low) advanced human breast and ovarian carcinomas. TTEX directly upregulated CSC frequency in vitro, which was not affected by anti–PD-1 treatment. The TTEX-influenced CSCs were highly clonogenic and exhibited a multidrug-resistant phenotype, overexpressing drug efflux pumps like ABCC1 and ABCB1. These CSCs were highly invasive, displaying increased invadopodia development and elevated cofilin, CXCR4, and matrix metalloproteinase 7 (MMP7) expression. The invasive properties along with epithelial–mesenchymal plasticity of TTEX-educated CSCs increased metastasis in vivo. TTEX increased cell surface

levels and activation of VEGFR2 in CSCs, and silencing or inhibition of VEGFR2 reversed the CSC-stimulatory effects of TTEX. LAMP3 and NRP1 on the surface of TTEX stimulated VEGFR2 in CSCs to promote aggressiveness. Cumulatively, these findings suggest that screening patients with carcinoma for both CD8+ TILs and TTEX frequency prior to anti–PD-1 therapy could improve patient outcomes. In addition, targeting the LAMP3/NRP1–VEGFR2 axis could be a therapeutic strategy in advanced patients with carcinoma with limited CD8+ T-cell infiltration and high TTEX frequency.

10. **D. Datta**, J.A. Flaxenburg, S. Laxmanan, C. Geehan, M. Grimm, A.M. Waaga-Gasser, D.M. Briscoe, S. Pal, Ras-induced modulation of CXCL10 and its receptor splice variant CXCR3-B in MDA-MB-435 and MCF-7 cells: relevance for the development of human breast cancer, ***Cancer Res***, 66 (2006) 9509-9518. **(JIF:13.64)**

    Significance: Interactions between chemokines and chemokine receptors have been proposed recently to be of importance in the development and progression of cancer. Human breast cancer cells express the chemokine CXCL10 (IP-10) and also its receptor CXCR3. In this study, we have investigated the role of Ras activation in the regulation of CXCL10 and its receptor splice variant CXCR3-B in two human breast cancer cell lines MDA-MB-435 and MCF-7. In cotransfection assays, using a full-length CXCL10 promoter-luciferase construct, we found that the activated form of Ras, Ha-Ras(12V), promoted CXCL10 transcriptional activation. Ras significantly increased CXCL10 mRNA and protein expression as observed by real-time PCR, fluorescence-activated cell sorting analysis, and ELISA. Selective inhibition of Ha-Ras by small interfering RNA (siRNA) decreased CXCL10 mRNA expression in a dose-dependent manner. Further, using effector domain mutants of Ras, we found that Ras-induced overexpression of CXCL10 is mediated primarily through the Raf and phosphatidylinositol 3-kinase signaling pathways. We also observed that the expression of the splice variant CXCR3-B, known to inhibit cell proliferation, was significantly down-regulated by Ras. Selective inhibition of CXCR3-B using siRNA resulted in an increase in CXCL10-mediated breast cancer cell proliferation through Gi proteins and likely involving CXCR3-A. Finally, we observed intense expression of CXCL10 and CXCR3 in association with human breast cancer in situ, indicating that these observations may be of pathophysiologic significance. Together, these results suggest that activation of Ras plays a critical role in modulating the expression of both CXCL10 and CXCR3-B, which may have important consequences in the development of breast tumors through cancer cell proliferation. Based on this concept, we published a review article in ***Cytokine Growth Factor Rev***, 24 (2013) 41-49. **(JIF:13.0, current citation 216)** A.K. Singh, R.K. Arya, A.K. Trivedi, S. Sanyal, R. Baral, O. Dormond, D.M. Briscoe, **D Datta***, Chemokine receptor trio: CXCR3, CXCR4 and CXCR7 crosstalk via CXCL11 and CXCL12.