List of 10 best papers highlighting the important contributions of the nominee
(*Corresponding Author)

1. Goel S, Bhatia V, Kundu S, Biswas T, Carskadon S, Gupta N, Asim M, Morrissey C, Palanisamy N, Ateeq B*. Transcriptional network involving ERG and AR orchestrates Distal-Less Homeobox-1 mediated prostate cancer progression. ***Nature Communications***. 2021 Sep 7;12(1):5325. Impact Factor: 14.919.
Discovery: We established the functional role of Distal-Less Homeobox-1 (DLX1) in tumorigenesis and metastases in prostate cancer. Our findings demonstrate that ablating DLX1 expression in prostate cancer cells led to reduced oncogenic properties and cancer stemness. Further, mice xenograft studies showed remarkable reduction in tumor growth and metastases in the mice implanted with DLX1 ablated cells compared to group implanted with DLX1-high cells. More so, in the bone metastases mice model, micro-computerized tomography (micro-CT) data indicates that the tibia of the mice implanted with DLX1 ablated prostate cancer cells showed less damage to the bone architecture. Moreover, we showed that ~60% of advanced-stage and metastatic patients display higher DLX1 levels. About ~96% of *TMPRSS2-ERG* fusion-positive and ~70% of androgen receptor (AR)-positive patients show elevated DLX1, associated with aggressive disease and poor survival. We also deciphered the mechanism involved in DLX1 upregulation in PCa, wherein ERG (produced as result of *TMPRSS2-ERG* gene fusion) and AR binds onto the regulatory regions of DLX1, and results in transcriptional activation of DLX1, leading to its higher levels in prostate cancer. Importantly, we have shown the effect of small molecule inhibitors against BET proteins in managing DLX1-mediated prostate cancer. We found that BET inhibitor either alone or in combination with anti-androgen drugs resulted in decreased expression of DLX1 and its downstream target genes. Likewise, in our preclinical mice model studies, we showed that administering either BET inhibitor alone or in combination with anti-androgen drugs result in about ~70% reduction in tumor burden accompanied with diminished metastases to distant organs. Conclusively, this study establishes DLX1 as a direct-target of ERG/AR with an oncogenic role and demonstrates the clinical significance of BETi and anti-androgens for DLX1-positive patients.
Contribution: As a sole corresponding author on this article, I conceptualized, designed and directed this study. I was also involved in executing some of the critical experiments, such as mouse xenograft experiments, bone metastases mice model, helped my students in acquisition and interpretation of the data.

2. Tiwari R†, Manzar N†, Bhatia V, Yadav A, Nengroo MA, Datta D, Carskadon S, Gupta N, Sigouros M, Khani F, Poutanen M, Zoubeidi A, Beltran H, Palanisamy N, **Ateeq B*.** Androgen deprivation upregulates SPINK1 expression and potentiates cellular plasticity in prostate cancer. ***Nature Communications.*** 2020 Jan 20;11(1):384. †Co-first authors. Impact Factor: 14.919.
Discovery: We discovered that SPINK1 is an androgen-repressed gene, and the use of androgen receptor (AR) antagonists relieves AR signaling mediated repression of SPINK1 resulting in its upregulation. We also demonstrated that REST, a co-factor of AR, along with AR gets recruited on the SPINK1 promoter in androgen-stimulated prostate cancer cells, confirming its role as an AR transcriptional co-repressor. Our data revealed that targeting the ubiquitin-dependent REST degradation using Casein Kinase 1 inhibitor results in reduced expression of SPINK1 and REST targets, subsequently leading to decrease in oncogenic properties. Collectively, our findings suggest that AR and REST modulate the expression of SPINK1, thus stabilizing REST levels may be an alternate therapeutic strategy for controlling SPINK1-mediated oncogenicity and progression to aggressive stage, known as neuroendocrine prostate cancer (NEPC). Notably, elevated levels of SPINK1 and NEPC markers are observed in the tumors of AR-antagonists treated mice, and in a subset of NEPC patients, warns against the detrimental effects AR antagonists as well as a plausible role of SPINK1 in treatment-related NEPC. Collectively, our findings provide an explanation for the paradoxical clinical-outcomes after androgen deprivation therapy, possibly due to SPINK1 upregulation, and offers strategy for adjuvant therapies.
Contribution: As a sole corresponding author on this article, I conceptualized, designed and directed this study. I was also involved in executing some of the critical experiments (creating stable cell lines, mouse

xenograft experiments and castration surgeries), and helped my students in acquisition and interpretation of the data.

3. Singh A, Srivastava N, Yadav A, **Ateeq B*.** Targeting AGTR1/NF-κB /CXCR4 axis by miR-155 attenuates oncogenesis in Glioblastoma. ***Neoplasia.*** 2020 Sep 4;22(10):497-510. Impact Factor: 5.715
Discovery: We explored the underlying mechanism involved in upregulation of AGTR1 in GBM, and showed the role of miRNA-155 in the post-transcriptional regulation of AGTR1. Furthermore, stable miRNA-155 overexpressing GBM cells showed decrease in AGTR1-mediated cell proliferation, invasion, foci formation and anchorage-independent growth. Moreover, immunodeficient mice implanted with stable miRNA-155 overexpressing SNB19 cells show remarkable reduction (~95%) in tumor burden compared to control. We found that miR-155 attenuates NF-κB signaling downstream of AGTR1 leading to reduced CXCR4 and AGTR1 levels. Mechanistically, miR-155 mitigates AGTR1-mediated, angiogenesis, epithelial-to-mesenchymal transition, stemness, ERK/MAPK signaling and promotes apoptosis. Similar effects in cell-based assays were observed upon using pharmacological inhibitor of IκB Kinase (IKK) complex. We also showed that activation of AGTR1 via ATII stimulation in GBM cells activate NF-κB signaling leading to CXCR4 overexpression as well as AGTR1 upregulation, thereby forming a positive feedback regulatory loop. While ectopic expression of miR-155 in GBM cells attenuates AGTR1 downstream signaling thereby disrupting this regulatory loop. Alternatively, targeting NF-κB signaling by an IKK complex inhibitor, results in downregulation of AGTR1 and CXCR4 expression, leading to reduced AGTR1-mediated oncogenicity. Conclusively, this study reveals a novel regulatory mechanism involving miR-155, which targets AGTR1/NF-κB/CXCR4 axis and abrogates GBM progression.
Contribution: As a sole corresponding author on this article, I conceptualized, designed and directed this study. I was also involved in executing some of the critical experiments, and helped my students in acquisition and interpretation of the data.

4. Bhatia V, Yadav A, Tiwari R, Nigam S, Goel S, Carskadon S, Gupta N, Goel A, Palanisamy N, **Ateeq B*.** Epigenetic silencing of miRNA-338-5p and miRNA-421 drives SPINK1-positive prostate cancer. ***Clinical Cancer Research***. 2019 May 1;25(9):2755-2768. Impact Factor: 12.531.
Commentary on this article: *New Hope in Prostate Cancer Precision Medicine? miRNA Replacement and Epigenetics. Bjartell A.* ***Clinical Cancer Research. 2019*** *May 1;25(9):2679-2681.*
Discovery: We revealed a novel regulatory model involved in pathogenic overexpression of SPINK1 in multiple cancers including prostate, wherein miRNA-338-5p/miRNA-421, negative regulators of SPINK1, are epigenetically silenced by EZH2, a member of Polycomb Repressive Complex-2. We also showed that SPINK1-positive prostate cancer patients tend to have higher EZH2 expression, indicating its role in epigenetic silencing. From translational viewpoint, the finding has high clinical significance, since epigenetic drugs restore miRNA-338-5p/miRNA-421 expression, resulting reduced SPINK1 levels and its oncogenicity. This study laid solid foundation, and suggests alternative treatment avenues for SPINK1-positive malignancies, for instance, adjuvant therapy using inhibitors against DNA methyltransferases, Histone deacetylases, or EZH2, several of which are already in clinical trials.
A commentary on this article published in the same issue of Clinical Cancer Research by Dr. Anders Bjartell, a well-known Medical Oncologist and Urologist from Lund University, Sweden, accentuates the novelty and importance of this work, and warrants further exploration in clinical trials.
Contribution: As a sole corresponding author on this article, I conceptualized, designed and directed this study. I was also involved in executing some of the critical experiments (creating stable cell lines, immunofluorescence staining, mouse model), acquisition and interpretation of the data.

5. Nunes JJ, Pandey SK, Yadav A, Goel S, **Ateeq B*.** Targeting NF-kappa B signaling by Artesunate restores sensitivity of castrate-resistant prostate cancer cells to anti-androgens. ***Neoplasia.*** vol 19 (4), p333-345, 2017 April. doi: 10.1016/j.neo.2017.02.002. Impact Factor: 5.715
Discovery: We re-purposed a WHO-approved malaria drug, Artesunate, and provided a compelling pre-clinical rationale that Artesunate could disrupt androgen receptor (AR)-antagonists (anti-androgen drugs) mediated resistance, frequently observed among castrate-resistant prostate cancer (CRPC) patients. We

have also shown that combinatorial treatment with Artesunate and anti-androgen drug (Bicalutamide) attenuates oncogenic properties of the castrate resistant prostate cancer cells by inhibiting NF-κB signaling and decreasing the expression of AR and its variants. Castrate-resistant tumor bearing mice, when administered with this drug combination showed remarkable regression in tumor burden and metastases.
To translate this finding into clinical use, we are collaborating with Dr. Kumar Prabhash and Dr. Sudeep Gupta, medical oncologists, at Tata Memorial Hospital Mumbai for conducting Artesunate clinical trial for the advanced stage castration-resistant PCa patients. If successful, this intervention will be highly beneficial for PCa patients who do not respond to anti-androgen therapies.
Contribution: As a sole corresponding author on this article, I conceptualized, designed and directed this study. I was also involved in executing mice xenograft experiment, acquisition and interpretation of the data.

6. **Ateeq B***, Kunju LP, Carskadon SL, Pandey SK, Singh G, Pradeep I, Tandon V, Singhai A, Goel A, Amit S, Agarwal A, Dinda AK, Seth A, Tsodikov A, Chinnaiyan AM, Palanisamy N. Molecular Profiling of ETS and Non-ETS Aberrations in Prostate Cancer Patients from Northern India. ***The Prostate.*** 2015 Jul 1;75(10):1051-62. Impact Factor: 4.104.
Discovery: This is first comprehensive molecular subtyping of prostate cancer patients from India based on the established genetic alterations, which set the stage for molecular diagnostics and precision medicine for Indian prostate cancer patients. In this report, we revealed that majority of PCa patients (~50%) from India harbor *TMPRSS2-ERG* gene fusion involving ETS transcription factor and androgen-regulated *TMPRSS2* promoter, while ~14% of the patients with advanced stage aggressive disease show many-fold higher levels of SPINK1. This work also highlighted the presence of actionable RAF kinase fusions in about ~6% of the patients, who could benefit by the FDA-approved RAF kinase inhibitors. Thus, ***this is the first study from India that laid the foundation of precision medicine for prostate cancer patients, and would impact clinical decision-making, diagnosis, and also aid in selection of therapeutic intervention.***
Contribution: As a sole corresponding author on this article, I conceptualized, designed and directed this study. I was also involved in execution of IHC and FISH experiments with co-author Dr. Palanisamy, and did acquisition and interpretation of the data.

7. Tiwari R, Pandey SK, Goel S, Bhatia V, Shukla S, Jing X, Dhanasekaran SM, **Ateeq B***. SPINK1 promotes colorectal cancer progression by downregulating Metallothioneins expression. ***Oncogenesis.*** 2015 Aug 10;4:e162. Impact Factor: 6.119.
Discovery: In this study we have unraveled the functional significance of SPINK1 in colorectal carcinoma, wherein ablating SPINK1 expression in CRC result in upregulation of various Metallothionein isoforms, known tumor suppressors, subsequently eliciting sensitivity towards chemotherapeutic drugs. These findings strengthen the rationale for combinatorial treatment approach by targeting SPINK1 for ~28% of SPINK1-positive colorectal carcinoma patients.
Contribution: As a lead and sole corresponding author on this article, I conceptualized, designed and directed this whole study. I was also involved in performing cell-based in-vitro assays and executing mice xenograft experiment, acquisition and interpretation of the data.

8. Singh A, Srivastava N, Amit S, Prasad S, Misra M, **Ateeq B***. Association of AGTR1 (A1166C) and ACE (I/D) polymorphisms with Breast Cancer risk in North Indian population. ***Translational Oncology.*** Vol 11(2), p233–242 April 2018. Impact Factor: 4.243.
Discovery: In this study we have shown that a single nucleotide polymorphism (SNP) A1166C located in 3′ untranslated region (UTR) of AGTR1 and an insertion/deletion (I/D) polymorphism present in intron 16 of ACE gene were associated with higher risk of breast cancer in women from the northern part of India. We show that women harboring DD genotype/D allele of ACE (I/D) and AC or CC genotype/C allele of AGTR1 (A1166C) polymorphism have a predisposition to develop more aggressive disease with advanced staging and larger tumor size, thus emphasizing the need for genetic screen for these polymorphisms among Indian women.

Contribution: As a lead and sole corresponding author on this article, I conceptualized, designed and directed this study. I was also involved in acquisition and interpretation of the data.

9. Brenner JC[#], **Ateeq B**[#], Li Y, Yocum AK, Cao Q, Asangani IA, Patel S, Wang X, Liang H, Yu J, Palanisamy N, Siddiqui J, Yan W, Cao X, Mehra R, Sabolch A, Basrur V, Lonigro RJ, Yang J, Tomlins SA, Maher CA, Elenitoba-Johnson KS, Hussain M, Navone NM, Pienta KJ, Varambally S, Feng FY, Chinnaiyan AM*. Rationale for Inhibition of Poly (ADP-Ribose) Polymerase in ETS Gene Fusion Positive Prostate Cancer. ***Cancer Cell.*** 2011 May 17; 19(5):664-78. (#**Equal contribution first author). Featured on Cover.** Impact Factor: 31.743.
Discovery: In this study, we discovered the underlying mechanisms by which *ETS* fusions mediate their oncogenic effects, wherein the fusion product of the predominant ETS gene fusion, *TMPRSS2-ERG*, interacts with the enzyme poly (ADP-ribose) polymerase 1 (PARP1) and the catalytic subunit of DNA protein kinase (DNA-PKcs) in a DNA-independent manner. *ETS* gene-mediated transcription and cell invasion require PARP1 and DNA-PKcs expression and its activity. Importantly, we show that pharmacological inhibition of PARP1 inhibits ETS-positive, but not ETS-negative, prostate cancer xenograft growth. Taken together, we propose that *TMPRSS2-ERG* fusion product induces DNA damage, which is potentiated by PARP1 inhibition in a manner similar to that of BRCA1/2 deficiency. Finally, our study motivates the assessment of *ETS* gene fusions as a potential biomarker of response in future clinical trials incorporating PARP inhibitors into the treatment of prostate cancer and other ETS fusion-positive malignancies.
Contribution: As a Co-First author on this study, I was involved in conceptualizing and designing the study with the co-first and corresponding authors. *In vitro* cell-based experiments and VCaP and patients derived xenografts mice experiments were conducted by me.

10. Palanisamy N[#], **Ateeq B**[#], Kalyana-Sundaram S[#], Pflueger D, Ramnarayanan K, Shankar S, Han B, Cao Q, Cao X, Suleman K, Kumar-Sinha C, Dhanasekaran SM, Chen YB, Esgueva R, Banerjee S, LaFargue CJ, Siddiqui J, Demichelis F, Moeller P, Bismar TA, Kuefer R, Fullen DR, Johnson TM, Greenson JK, Giordano TJ, Tan P, Tomlins SA, Varambally S, Rubin MA, Maher CA, Chinnaiyan AM*. Rearrangements of the RAF kinase pathway in prostate cancer, gastric cancer and melanoma. ***Nature Medicine.*** 2010 Jul; 16 (7):793-8. (#**Equal contribution first author**). [Faculty of 1000 Biology: Recommended]. Impact Factor: 49.248.
Discovery: In this study, we used paired-end transcriptome sequencing to discover *ETS* rearrangement–negative prostate cancers for targetable gene fusions, and identified the *SLC45A3-BRAF* and ESRP1-RAF1 gene fusions. We show that overexpressing *SLC45A3-BRAF* or *ESRP1-RAF1* in normal prostate cells induced a neoplastic phenotype, which exhibit sensitivity to the RAF and MAPK inhibitors. Also, screening a large cohort of prostate cancer patients, we found that, although rare, recurrent rearrangements in the RAF pathway tend to occur in advanced prostate cancers, gastric cancers and melanoma. Taken together, our findings emphasize the crucial role of RAF family gene rearrangements in cancer, and suggest that RAF and MEK inhibitors may be useful in a subset of gene fusion–harboring solid tumors. Screening for RAF kinase fusions may be useful in identifying people with cancer who may benefit from treatment with RAF kinase inhibitors.
Contribution: As a Co-first author on this study, I was involved in conceptualizing and designing the study with other co-first and corresponding authors. All gene fusion validation, *in vitro* cell-based experiments, exploration of biological mechanism and mice xenograft experiments were performed by me.