Summary of the scientific contributions by the Nominee

Dr. Dutt has extensively contributed to our understanding of the pathobiology and genomics of several epithelial cancers. His work illustrates a unique blending of basic and translational cancer genomics research with detailed functional mechanistic insights. During his Ph.D. in Developmental Biology from the Univ of Zurich, Switzerland, Dr. Dutt presented the first evidence for differential activity of an EGF splice variant and its role in amplifying the inductive signal, mediated through a serine protease, ROM-1, during vulval development in *C elegans* (***PLoS Biol.* 2004**). In the United States, at the Broad Institute of MIT and Harvard, Dr. Dutt characterized novel oncogenic *FGFR2* mutations, leading to widespread therapeutic intervention in endometrial cancers (***PNAS* 2008, 2009, *Nature* 2009** and ***Nat Genet* 2009**).

Dr. Dutt's most significant contribution in cancer biology, as a PI from ACTREC, has been in understanding the complexity of cancers predominantly afflicting Indian patients. In lung cancer, his work elucidates the role of tyrosine kinases in the pathogenesis of disease, with considerable implications for therapeutics and diagnostics of the disease. He described the first comprehensive landscape of actionable mutations across ~450 lung adenocarcinoma patients. The functional work using elegant genetic, biochemical, and mouse-xenograft-based mechanistic characterization established novel *FGFR3* activating mutations in 5.5% of lung adenocarcinoma patients of Indian origin. Subsequently, he systematically described *FGFR1* as a therapeutic target by characterizing the genome of ~450 lung squamous subtypes. Dr. Dutt's work shows for the first time that treatment of lung squamous cancer cells harboring focally amplified *FGFR1* and lung adenocarcinoma cells harboring *FGFR3* mutations when treated with FGFR-specific shRNAs or with the FGFR small molecule inhibitor leads to cell growth inhibition. This work opens the possibility of subtype-specific lung cancer treatment by targeting FGFR family genes by adopting treatments approved for other cancers (***PLoS One 2011,* 2013; *Br. Journal Cancer 2016***; ***Annals of Oncology 2017, Oncotarget 2021***). These studies have been widely acknowledged globally, with over 700 citations in literature so far. More recently, Dr. Dutt developed a mouse system to model a phase III ADAURA clinical trial by injecting luciferase-tagged lung cancer cells through the mice tail vein that colonizes mice lungs within 24h (***Translational Oncology* 2021, 2022)**. The findings revealed that the desired effect could be achieved even by weekly dosing!! This is an important bench-to-bed contribution that is likely to reduce the cost of treatment by 1/7th from more than a lakh per month! This study has contributed to setting up a clinical trial, been set up, at the Tata Memorial Centre to lower the cost of the treatment.

In tongue cancer, Dr. Dutt addressed a critical issue of occult lymph nodal metastases. He presented the first landscape of genetic alterations among tongue cancer patients of Indian origin with evidence of a lack of HPV infection and the presence of a tobacco-associated signature. He established an essential and sufficient role of the miR-944/MMP10/AXL-axis in inducing the EMT phenotype using an elegant orthotopic in vivo tongue cancer mouse model. Dr. Dutt also identified a novel clinical and functional significance of NOTCH1 alterations-- essential for maintaining stem-like cells—to form a potential basis for therapeutic targeting in tongue cancer (***BMC Genomics* 2015**; ***Br. Journal Cancer 2016***; ***Oncotarget* 2016**). Further, Dr. Dutt identified MMP10 as a promising prognostic biomarker that could potentially aid in sparing a significant proportion of early-stage tongue cancer patients from mandatory elective neck dissection. A clinical trial at TMC is underway to validate the finding. More recently, Dr. Dutt described the first comprehensive landscape of infectious pathogens across breast, lung, gallbladder, cervical, colorectal, and oral cancer. His work establishes a significant prevalence of *Fusobacterium nucleatum* in tongue tumors that occurs mutually exclusive to Human papillomavirus. More recently, the study led by Dr. Dutt identified a novel fusion transcript, *UBE3C-LRP5*, in head and neck cancer, with potential clinical relevance. This fusion activates the Wnt/β-catenin pathway, driving cancer cell behaviors. The FDA-approved drug pyrvinium pamoate shows promise in inhibiting tumor growth linked to this fusion. This finding proposes a new therapeutic angle for head and neck cancer, warranting larger clinical trials. (***Neuro Oncology* 2024**; ***npj Precision Oncology* 2024**; ***Commun Biol* 2023**; ***Oral Oncology* 2017; *Briefings in Bioinformatics* 2021; *NAR Cancer*, 2022**).

In gallbladder cancer, Dr. Dutt described a carcinogenesis and dissemination model of how dysplasia as a premalignant lesion could develop into carcinoma *in situ* and invasive gallbladder adenocarcinoma, akin to the Vogelstein model for colorectal tumorigenesis (***Annals of Oncology* 2015**). These efforts identified a novel association of non-typhoidal *Salmonella* infection with gallbladder cancer as a potential inflammatory stimulus. Additionally, Dutt's work establishes that the presence of *KRAS* (G12V), but not *KRAS* (G13D) mutation, could predict response to anti-EGFR treatment in gallbladder cancer (***Infectious Agents and Cancer* 2015; *International Journal of Cancer* 2018***).

In breast cancer, to understand the molecular basis of how progesterone affects the outcome of PR-negative breast cancer cells, Dr. Dutt described an intricate convergence model indicating a

dual-phase regulation downstream to progesterone treatment to regulate the expression of a *Serum-and Glucocorticoid-regulated Kinase gene 1, SGK1*: predominantly driven as a direct transcriptional target, in PR-positive breast cancer cells; and, down-regulation of miR-29a and miR-101-1 targeting *SGK1* with relatively distinct effect in PR-negative breast cells in response to progesterone (***Breast Cancer Res* 2022**; ***Cancer Biol & Therapy* 2017*; Cellular Oncology* 2017*; J Biol Chem* 2018**).

सत्यमेव जयते

गिरीश साहनी
सचिव, भारत सरकार
वैज्ञानिक और औद्योगिक अनुसंधान विभाग, तथा
महानिदेशक
Girish Sahni
Secretary, Govt. of India
Department of Scientific & Industrial Research, and
Director General

वैज्ञानिक तथा औद्योगिक अनुसंधान परिषद्
अनुसंधान भवन, 2, रफी मार्ग, नई दिल्ली-110001
COUNCIL OF SCIENTIFIC & INDUSTRIAL RESEARCH
Anusandhan Bhawan, 2, Rafi Marg, New Delhi-110001

DG/HRD/SSB-17/Awardee(7)
26 September 2017

Dear Dr Dutt,

I am happy to inform that you have been selected for the award of "Shanti Swarup Bhatnagar (SSB) Prize" for the year 2017 in Medical Sciences.

Please accept my heartiest congratulations !

It is a rare distinction conferred upon scientists, who have demonstrated exceptional potential in Science and Technology. The award derives its value from its rich legacy of those who won this award before and added enormous value to Indian Science. I am certain that this recognition would encourage you and your group to scale new heights in the years to come. Now, the Nation will look upon you with higher expectation.

The SSB Prize comprising a citation, a plaque and a cash prize of Rs. 500000/- (Rupees five lakh only) would be presented to you at a formal function, generally presided over by the Prime Minister of India, who is the President, CSIR. In addition, CSIR will grant a special honorarium of Rs 15000/- p.m. with effect from 1st January 2017. I enclose a draft citation to be read at the Award Ceremony. Kindly verify the citation for factual accuracy. In case there is any inaccuracy in it, please intimate the same immediately.

On behalf of CSIR and on my own behalf, I extend to you very best wishes for a glorious future.

With warm regards,

Yours sincerely,

Girish Sahni

[Girish Sahni]

Dr Amit Dutt
Advanced Centre for Treatment, Research and Education in Cancer
Tata Memorial Centre
Navi Mumbai 410 210

COUNCIL OF SCIENTIFIC & INDUSTRIAL RESEARCH, INDIA

SHANTI SWARUP BHATNAGAR PRIZE

FOR SCIENCE AND TECHNOLOGY

2017

CITATION

Dr Amit Dutt

The Shanti Swarup Bhatnagar Prize for the year 2017 in **Medical Sciences** has been awarded to **Dr Amit Dutt of Tata Memorial Centre, Mumbai**, for his outstanding contributions to cancer genetics especially related to the FGF Receptor family in lung cancer, including novel mutations in Indian patients. This has major implications for our understanding of the disease as well as translational possibilities.

डा. संजय मिश्रा
वरिष्ठ सलाहकार
Dr. SANJAY MISHRA
Senior Adviser

सत्यमेव जयते

स्वच्छ भारत
एक कदम स्वच्छता की ओर

भारत सरकार
विज्ञान और प्रौद्योगिकी मंत्रालय
बायोटेक्नोलॉजी विभाग
GOVERNMENT OF INDIA
MINISTRY OF SCIENCE & TECHNOLOGY
DEPARTMENT OF BIOTECHNOLOGY
Block-2, (7th Floor) CGO Complex
Lodhi Road, New Delhi-110003

D.O. No.: HRD-16012/6/2020-AFS-DBT **Dated: 29.03.2023**

Dear Dr. Dutt

I am pleased to inform you that you have been selected for the "**Tata Innovation Fellowship**" for the year 2022-23. This is a Prestigious Fellowship of Department of Biotechnology, Government of India in recognition of your outstanding research contributions. The fellowship is meant to honour and encourage scientists involved in translational research by innovative scientific knowledge and platform technologies. I extend my heartiest congratulations on being selected for this prestigious fellowship.

You may please send your acceptance to Dr. Suraksha S. Diwan, Scientist-'F', Program Officer, TATA Innovation Fellowship Program, Department of Biotechnology, Govt. of India at her email id ssdiwan.dbt@nic.in.

With best wishes,

Yours sincerely,

(Sanjay K. Mishra)

Dr. Amit Dutt
Principal Investigator,
ACTREC, Tata Memorial Centre,
Sector 22, Kharghar,
Navi Mumbai-410210.

Citation for Tata Innovation Fellowship Award 2023

14. Summary the most significant work of the applicant (not more than 100 words)

We described the first comprehensive landscape of actionable mutations across ~450 lung adenocarcinoma. Our work using elegant genetic, biochemical and mouse -xenograft based mechanistic characterization has led to discovering novel *FGFR3* activating mutations in lung adenocarcinoma patients of Indian origin. Subsequently, we systematically described *EGFR*, *PIK3CA* and *FGFR1* as a therapeutic target along with a global landscape of alterations across ~450 Indian lung squamous cancer. Our work shows that treatment of lung squamous cancer cells harboring focally amplified *FGFR1* and lung adenocarcinoma cells harboring *FGFR3* mutations when treated with FGFR-specific shRNAs or with the FGFR small molecule inhibitor leads to cell growth inhibition. This work opens the possibility of subtype-specific lung cancer treatment by targeting FGFR family genes. Additionally, we addressed a basic deficiency in the field by profiling *EGFR* and *KRAS* mutation frequency in 1000 odd samples derived from Indian lung cancer patients. His work revealed 23% *EGFR* and 19% *KRAS* mutation with 74% clinical response to EGFR tyrosine kinase inhibitors, which is markedly distinct from the previously known Caucasian (10-15%) and East-Asian populations (30-50%). Taken together, the work undertaken rationalizes targeted therapy among Indian lung cancer patients. These studies have been widely acknowledged globally, with over 700 citations in literature so far.