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DEPARTMENT OF SCIENCE & TECHNOLOGY

75 UNDER 50

SCIENTISTS SHAPING TODAY'S INDIA

PROF. AMIT DUTT

Revolutionizing Research

Prof. Amit Dutt's excitement about science was piqued in the elementary school when he dreamt of being a scientist. His father's deep scientific mindset profoundly impacted him and set him on the quest to understand cancer. However, Shilpee Raghav, his junior during post-graduation, worked as a catalyst for him to pursue understanding the complexity of the biological phenomenon that could lead to better cancer care.

The impact of Prof. Amit Dutt's work has been published in several reputed scientific journals with over 8,000 citations to his work. Prof. Dutt's current *h-index* is 29, and the *i10 index* is 44: an international metric that places him among the top tier scientists of his age across the globe.

Prof. Dutt holds a rare accomplishment in the field with a double PhD in biology. His first formal introduction to basic cancer research happened during his second PhD at the Department of Cancer Research, University Hospital, University of Zurich. His seminal work put forward the first evidence for a serine protease ROM-1 mediated amplification of an EGF oncogenic signal in *Caenorhabditis elegans*, a genetic model system. His work led to an understanding of mechanistic genetic pathways underlying the amplification of the inductive EGF signal. Prof. Dutt's work modified and extended the textbook view of vulval development in *C elegans*. In recognition of the high quality and novelty of his thesis, he was invited for a plenary talk to present his findings at the most formal annual *C elegans* meeting in Los Angeles, USA.

Prof. Dutt is the recipient of the prestigious international postdoctoral fellowship from the Swiss National Foundation (SNF), Switzerland. With SNF fellowship, Prof. Dutt joined the leading laboratory of Dr Matthew Meyerson in Cancer Genomics at the Broad Institute of Harvard and MIT/Dana Farber Cancer Institute, Harvard Medical School to pursue translational cancer research.

"In research the decision should be organic and driven more by passion to understand the mechanism for several enigmatic processes."

In the US, Prof. Dutt led a project to analyze the biology of tyrosine kinase genes in endometrial cancers. He discovered recurrent oncogenic mutations in the fibroblast growth factor receptor 2 gene, *FGFR2* in roughly 10 per cent of the cases – that remains to date as the most promising therapeutic target – in endometrial cancer. Prof. Dutt and his colleagues published the first integrated analysis of genome-wide expression and copy-number profiles in endometrial cancer. His work led to the identification of novel candidate mutation in the pleckstrin homology domain of all the members of AKT family. These studies are an important step towards a comprehensive analysis of the endometrial cancer genome and its relation to clinical presentation.

After relocating to India, Prof. Dutt's most significant contribution in Medical Sciences, as an independent scientist ACTREC-Tata Memorial Centre, has been to decipher the role of tyrosine kinases in the pathogenesis of lung cancer with implications in therapeutics and diagnostics of the disease. Prof. Dutt described the first comprehensive landscape of actionable mutations across ~450 lung adenocarcinoma. His 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, he systematically described *EGFR*, *PIK3CA*, *KRAS* and *FGFR1* as a therapeutic target along

Clockwise: Receiving the prestigious SSB Award in Medical Sciences from Prime Minsiter Narendra Modi, 2017

With his parents and siblings (1985). Amit is on the far right

Receiving the distinguished alumni award, Jamia Millia Islamia, 2017

With his wife Shilpee Dutt and children Shwetna Dutt and Audvik Dutt

With Nobel Laureate Prof. David Baltimore, Mathematician and Geneticist Prof. Eric Lander and Biologist Prof. Bob Weinberg

Delivering a talk at the Karolinska Institute, Stockholm

Inset: Delivering a talk at MD Anderson Center, Houston, US

AWARDS

- Distinguished Alumni Award, Jamia Millia Islamia (2017)
- Shanti Swarup Bhatnagar Prize (2017)
- Wellcome Trust/DBT India Alliance Intermediate Fellowship (2011)
- Ramalingaswami Fellowship Award (2010)
- Swiss National Science Foundation Postdoctoral Fellowship (2004)

PUBLICATION

- 'Up-regulation of the kinase gene *SGK1* by progesterone activates the AP-1-NDRG1 axis in breast cancer cells'. *J Biol Chem*. (2018).
- '*ERBB2* and *KRAS* alterations mediate response to EGFR inhibitors in early stage gallbladder cancer'. *Int J Cancer* (2018).
- 'Drug-sensitive *FGFR3* mutations in lung adenocarcinoma'. *Ann Oncol*. (2017).
- 'NGS-based approach to determine the presence of HPV and their sites of integration in human cancer genome'. *Br J Cancer* (2015).
- 'Drug-sensitive *FGFR2* mutations in endometrial carcinoma'. *PNAS* (2008).

with a global landscape of alterations across ~450 Indian lung squamous cancer. Prof. Dutt's 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. These works open the possibility of subtype-specific lung cancer treatment by targeting FGFR family genes.

Additionally, Prof. Dutt addressed a basic deficiency in the field by profiling *EGFR* and *KRAS* mutation frequency in 1000 odd samples derived from Indian lung cancer patients, along with his clinical colleague Dr Kumar Prabhash. 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%). The work undertaken rationalizes targeted therapy among Indian lung cancer patients and led to the adoption of a genetic diagnostic test to genotype *EGFR* mutations at affordable pricing, remarkably reducing its cost from ~$200 (as in 2010) to $12 per test, as offered at TMH on a routine basis. These studies have been widely acknowledged globally, with over 700 citations in literature so far.

Beyond lung cancer, Prof. Dutt has made several seminal contributions advancing our understanding across several other cancers among Indian patients. In brief, Prof. Dutt's works demonstrate *NOTCH1* as a therapeutic target and *MMP10* as a predictive marker for metastases in tongue cancer. He described the presence of *KRAS* mutations might preclude gallbladder cancer patients to respond to anti-EGFR treatment, similar to colorectal cancer. In breast cancer, Prof. Dutt described the role of kinases that underlie the clinical outcome of pre-operative progesterone intervention. In addition, Prof. Dutt developed "TMC-SNPdb" – the first open-source Indian SNP database, "HPVDetector" to detect HPV in cancer, and an automated computational pipeline IPD, to understand the pathogens associated with human cancer. Prof. Dutt also contributed to the COVID research by developing a one-step, one-tube real-time RT-PCR based assay that was transferred to industry, and a novel Raman spectroscopy-based framework to detect RNA viruses in saliva.

Overall, Prof. Dutt has made phenomenal contributions in a field undergoing a revolutionary transformation in technology and ideas: the interface between cancer genomics and cancer targeted therapy. •