Lung Cancer Promotion by Air Pollution

Biography

Professor Charles SWANTON completed his MBPhD training in 1999 at the Imperial Cancer Research Fund Laboratories and Cancer Research UK clinician scientist/medical oncology training in 2008. He is a senior Principal Investigator of the Cancer Evolution and Genome Instability Laboratory, and Deputy clinical director at the Francis Crick Institute and combines his research with clinical duties at University College London Hospitals (UCLH). As a thoracic oncologist, he focused on how tumours evolve over space and time. His research branched evolutionary histories of solid tumours, processes that drive cancer cell-to-cell variation in the form of new cancer mutations or chromosomal instabilities, and the impact of such cancer diversity on effective immune surveillance and clinical outcome. Charles is the chief investigator of TRACERx, a lung cancer evolutionary study and the national PEACE autopsy program, and about to start with TRACERx EVO.

Charles was made Fellow of the Royal College of Physicians in April 2011, appointed Fellow of the Academy of Medical Sciences in 2015, awarded the Royal Society Napier Professorship in Cancer in 2016, appointed Cancer Research UK's Chief Clinician in 2017, elected Fellow of the Royal Society in 2018, Fellow of the Academy of the American Association for Cancer Research in 2020, and appointed Deputy Clinical Director of the Francis Crick Institute in 2023. He is an editorial board member of Cell, Plos Medicine, Cancer Discovery and Annals of Oncology and an advisory board member for Nature Reviews Clinical Oncology and Cancer Cell. In 2016, he co-founded Achilles Therapeutics, a UCL/CRUK/Francis Crick Institute spin-out company, assessing the efficacy of T cells targeting clonal neoantigens.

Charles has been awarded several prizes including the Stand up to Cancer Translational Cancer Research Prize (2015), GlaxoSmithkline Biochemical Society Prize (2016), San Salvatore prize for Cancer Research (2017) and the Ellison-Cliffe Medal, Royal Society of Medicine (2017), recipient of the Gordon Hamilton Fairley Medal (2018), Massachusetts General Hospital, Jonathan Kraft Prize for Excellence in Cancer Research (May 2018), the ESMO Award for Translational Cancer Research (2019), Addario Lung Cancer Foundation Award and Lectureship, International Lung Cancer Congress (July 2020), the Weizmann Institute Sergio Lombroso Award in Cancer Research (2021), International Society of Liquid Biopsy (ISLB) Research Award (2021), the Memorial Sloan Kettering Paul Marks Prize for Cancer Research (2021), UCLH Celebrating Excellence Award for Contribution to World Class Research (2022), Inductee to OncLive's Giants of Cancer Care awards program (2023), SpringerNature CDD Award (2023) and the Jeantet-Collen Prize for Translational Medicine (2024).

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Abstract

A mechanistic basis for non-small cell lung cancer (NSCLC) initiation in never smokers, a disease with high frequency EGFR mutations (EGFRm), is unknown. Air pollution particulate matter (PM) is known to be associated with the risk of NSCLC, however a direct cause and mechanism remain elusive.

We analysed 463,679 individuals to address the associations of increasing 2.5um PM (PM2.5) concentrations with cancer risk. We performed ultra-deep profiling of 247 normal lung tissue samples, analysed normal lung tissue from humans and mice following exposures to PM, and investigated the consequences of PM in mouse lung cancer models.

Increasing PM2.5 levels are associated with increased risk of EGFRm NSCLC in England, S. Korea and Taiwan and with increased risk of mesothelioma, lung, in UK Biobank (HR>1.1 for each 1ug/m^3 PM2.5 increment). 18-53% of normal lung tissue samples harbour driver mutations in *EGFR* and *KRAS* in the absence of malignancy. PM promotes a macrophage response and a progenitor-like state in lung epithelium harbouring mutant EGFR. Consistent with PM promoting NSCLC in at-risk epithelium harbouring driver mutations, PM accelerates tumourigenesis in three EGFR or KRAS driven lung cancer models in a dose-dependent manner. Finally, we uncover an actionable inflammatory axis driven by IL1B in response to PM, in agreement with reductions in lung cancer incidence with anti-IL1B therapy.

These data reveal a mechanistic basis for PM driven lung cancer in the absence of classical carcinogen-driven mutagenesis, reminiscent of models of tumour initiation and promotion proposed 70 years ago, providing an urgent mandate to limit air pollution, revealing opportunities for molecular targeted cancer prevention.