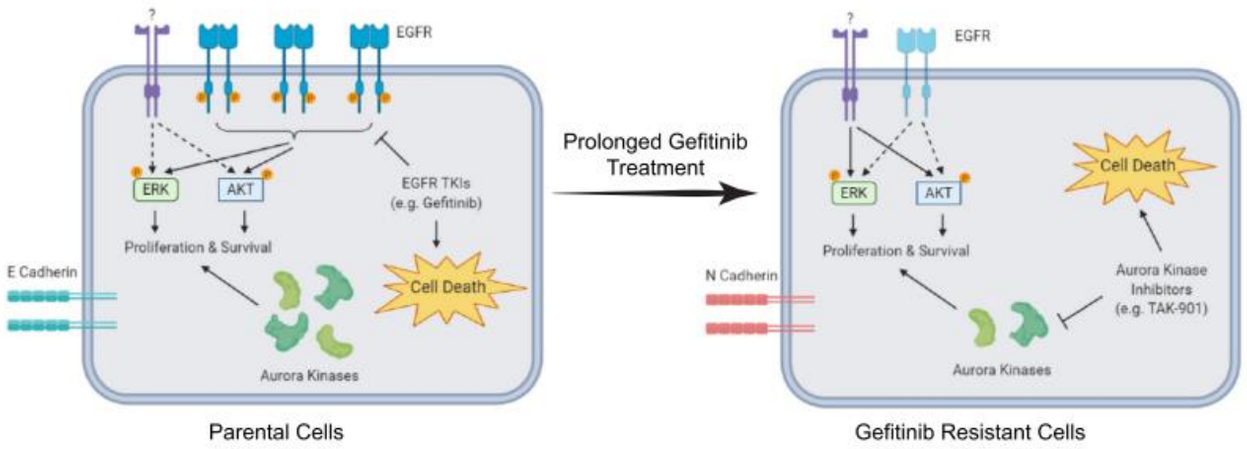
THERAPEUTIC VULNERABILITY OF DRUG-RESISTANT CANCER CELLS AGAINST AURORA KINASE INHIBITORS



Proposed model of gefitinib resistant in HNSCC cells with no EGFR T790M mutation. Artwork was generated using BioRender.

Overexpression of the epidermal growth factor receptor (EGFR) is commonly associated with a majority of head and neck squamous cell cancers (HNSCCs); yet drugs targeting EGFR function for the treatment of HNSCC have met with limited success in the clinic. This can be attributed to the rapid acquisition of drug-induced treatment resistance against EGFR-targeting tyrosine kinase inhibitor (TKI)-drugs, which results in early relapse or malignant progression of the primary cancer.

Previous studies in lung cancer have shown that the gain of drug resistance to TKIs can often be associated with acquired, activating mutations in EGFR. The aim of this study was to determine factors contributing to the lack of response to TKIs and identify alternative therapeutic susceptibilities in HNSCCs. We generated three HNSCC patient-derived tumour cell lines that were grown in culture dishes, and treated them with increasing dose of the TKI drug (Gefitinib) in order to isolate the Gefitinib-resistant cells that could survive high doses of the drug.

Surprisingly, genetic (mutational) analysis of the parental (Gefitinib-sensitive) versus the resistant cells failed to reveal any activating, resistance-associated mutations in EGFR. Instead, gene expression analysis revealed a marked change in the expression of genes associated with malignant progression of cancers. These data suggested that there are alternative strategies that cells might utilise to survive TKI treatment.

In depth analysis of the resistant cells revealed that they markedly reduced their rate of cell division and growth, which made them particularly sensitive to cell-cycle inhibitors. Indeed, high-throughput screening (HTS) of drug libraries on the resistant lines revealed that they gained therapeutic vulnerability against a class of cell-cycle inhibitors, namely Aurora kinase inhibitors (AKIs) and cyclin-dependent kinase (CDK) inhibitors.

Overall, our study demonstrated that in the absence of activating EGFR mutations, HNSCCs may gain resistance to TKIs through decreased cell proliferation, thereby making them exceptionally sensitive to cell-cycle inhibitors. Our results also demonstrated the potential clinical utility of AKIs and CDK-inhibitors to a selected pool of HNSCC patients who do not harbour activating EGFR mutations, but display resistance to EGFR-therapy, thus paving the way for genomics-guided precision medicine.

This work is the result of an exceptional and continued collaboration between the laboratories of Drs Ramanuj DasGupta and Gopal Iyer at the Genome Institute of Singapore, and the National Cancer Centre Singapore (NCCS), respectively. The study was published on *EBioMedicine* on 30 January 2021.