I will discuss novel applications of the CRISPR/Cas9 for in vivo somatic editing. More specifically, I will present data showing that in vivo delivery of pairs of guide RNAs can be used to generate cancer-promoting chromosomal rearrangements, enabling us to rapidly generate more faithful mouse models of human cancers.

Lastly, I will discuss how we are applying this novel technology for functional genomic screens aimed at identifying cancer associated non-coding RNAs and DNA regulatory elements.

Intratumoral heterogeneity and EGFR-TKIs resistance

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Lung cancer is one of the malignant tumors with the highest degree of heterogeneity. Intratumoral heterogeneity includes histopathologic heterogeneity and genetic heterogeneity. Intratumoral heterogeneity, especially genetic heterogeneity, plays an important role in resistance to targeted therapy. Some previous studies have proved that Intratumoral heterogeneity is one of the mechanism of EGFR-TKIs resistance in lung cancer. The patients with NSCLC harboring T790M mutation before targeted therapy had a poor response to EGFR-TKIs. Besides, increasingly more lung cancers were identified to harbor EGFR mutations and ALK fusions concurrently with the development of gene detection technology. Current studies on the exploration of intratumoral heterogeneity did not go far enough. Firstly, not all T790M or C797S mutations which were identified in tumor cells after acquired resistance were present due to treatment selection. Secondly, the mechanism and treatment strategy for lung cancer with dual altered driver remain controversial. Finally, abundance of EGFR mutations caused by intratumoral heterogeneity may affect the response to EGFR-TKIs. Our team has done a lot of work on this aspect. Our study identified intratumoral heterogeneity in lung adenocarcinoma with dual oncogenic drivers. In addition, we found patients with low abundance of EGFR mutations had poor response to EGFR-TKIs. The ORR for patients with high abundance of EGFR mutations (HA-EGFR) was significantly higher compared with patients with low abundance of EGFR mutations (LA-EGFR) (72.9% vs. 11.7%, P<0.001). The median PFS in HA-EGFR group was also significantly longer than that in LA-EGFR group (19del subgroup: 15.0 vs 4.0 months, P<0.001; L858R subgroup: 12.0 vs 2.0, P<0.001). In conclusion, intratumoral heterogeneity may be an important reason for EGFR-TKIs resistance in lung cancer.