Rational design of combination therapies and blockage of acquired targeted drug resistance

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Abstract:

Background: Recent successes of targeted drugs on end stage cancer patients highlight the value of mutation-based biomarkers for drug response. However, the impact of these drugs is often temporary and the patients progress to acquired resistance. A common mechanism of drug evasion involves feedback mechanisms that increase expression or phosphorylation-driven activation of an alternative oncogenic pathway. The objective of this work was to set up a streamlined methodology (kinome profiling, shRNA negative RNAi screens, evolution tracking etc.) for rational drug combination designs.

Material and methods: The research includes pre-clinical assessment of the novel drugs focused on cancer cases, refractory to biomarker predicted targeting and seeking combination therapies that would block the spontaneous drug evasion. We explored the efficacy of the combination approach on a panel of cancer patient derived xenografts in mice using tumor size or metabolic imaging as an end point. Each cancer case was subject to target somatic mutation screening, which resulted in a targeted drug recommendation and then mouse groups were treated either with sequencing-based therapy or with combination of these therapies with blockers of the suspected evasion mechanisms. As a blocker of the evasion mechanism and epithelial to mesenchymal transition, we characterized the utility of a novel molecule NT219 that leads to the destruction of IRS1/2 of the IGF1R pathway.

Results: Personalized treatments using targeted drugs for central oncogenic pathways, such as the EGFR inhibitor Erlotinib and the mTOR inhibitor Afinitor induced temporary regression of the patient-derived tumors followed by acquired resistance and tumor progression. Combined Therapy with the IRS1/2 Eliminator NT219 prevented acquired resistance to these drugs and some of the mice even achieved complete response with no detectable tumors long following end of treatment. Furthermore, combined treatment with NT219 re-sensitized tumors that have already acquired resistance to these drugs and led to regression of resistant tumors.

Conclusions: Elimination of IRS by NT219 as well as its potency in overcoming acquired drug resistance may open a new window of opportunity to a wide range of malignancies by blocking survival feedback mechanisms induced by these drugs.