

Functional Profiling of Champions TumorGraft™ Models from Metastatic Melanoma Patients

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Introduction: Molecularly targeted agents, such as the BRAF inhibitor vemurafenib, may produce short-term responses in some patients; however, most patients are intrinsically resistant, or develop resistance through restructuring of signal transduction pathways. SnapPath™ is a live-cell-processing platform that utilizes ex vivo signal transduction modulation of live tumor samples to produce Functional Signaling Profiles (FSPs). Application of this technology to Champions TumorGraft models may provide novel insights to guide oncology drug development as these models preserve the biological properties of the original human tumor. **Methods:** Fresh melanoma tumor specimens were collected from patients and implanted into immunodeficient mice. Fine needle aspiration biopsies were performed on each melanoma TumorGraft model and processed on the SnapPath™ platform (BioMarker Strategies) to modulate tumor cell signal transduction networks through brief ex vivo exposure to the vemurafenib tool compound PLX-4720. Cell lysates were then analyzed using a multiplexed immunoassay to assess the inhibition of the downstream MAPK markers pMEK1 and pERK-1/2. FSPs were then created for each TumorGraft model based on baseline and modulated levels of each phosphoprotein. In parallel, the in vivo sensitivity to vemurafenib and *BRAF* mutation status was evaluated in each Champions TumorGraft model. FSPs were then compared with in vivo efficacy, gene expression and genotype data. **Results:** Functional profiling stratified the TumorGraft models into two distinct groups upon ex vivo exposure to a BRAF inhibitor: 1) MAPK markers suppressed and 2) MAPK markers not suppressed. As anticipated, TumorGraft models that showed resistance to ex vivo BRAF inhibition demonstrated vemurafenib resistance in vivo and were *BRAF* wild type. There were other models that displayed MAPK suppression with ex vivo BRAF inhibition and vemurafenib sensitivity in vivo or MAPK suppression with ex vivo BRAF inhibition but demonstrated vemurafenib resistance in vivo. One of these TumorGrafts contained a BRAF V600E mutation, suggesting the activation of an alternate pathway that conferred resistance. The other TumorGraft contained a novel BRAF insertion. The functional profiling suggests that this insertion may activate BRAF and is susceptible to vemurafenib inhibition, but the tumor may contain an alternate pathway that confers resistance. Analysis of gene expression data demonstrated hierarchical clustering of *BRAF* mutated TumorGraft models. **Conclusions:** These results demonstrate the capability of the SnapPath™ platform to generate FSPs from FNAs of Champions melanoma TumorGraft models. Overall, the combination of Champions TumorGraft models with functional profiling represents a powerful tool for pharmacodynamic assessment of targeted therapeutics in clinically relevant models and has the potential to guide oncology therapy.