



Presentation Abstract

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Presentation Title: Translational research platform (SnapPath™) for enabling drug development and personalized medicine in metastatic melanoma

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Abstract Body: **Introduction:** The approved BRAF inhibitor, vemurafenib, produces short-term responses in many metastatic melanoma patients; however, most patients develop resistance through reactivation of signal transduction pathways. More sophisticated tools for the analysis of signal transduction in preclinical models and clinical samples would vastly improve drug development and personalized cancer therapy. SnapPath™ is a live-cell-processing platform that utilizes ex vivo signal transduction modulation of tumor samples to produce Functional Signaling Profiles (FSPs), which can be used in drug development and clinical studies. **Methods:** Melanoma cell line xenografts (SK-Mel-28, SK-Mel-3, Colo829, MALME3M and A2058) were generated in athymic nude mice. Fine needle aspiration biopsies (FNA) were performed on each tumor type when tumor volumes reached 500mm³. One FNA sample consisted of 4 passes of a 23G, 1'' needle on a 10cc syringe. The live cell biopsies were processed on the SnapPath™ live-tumor-cell platform (BioMarker Strategies, LLC) to modulate tumor cell signal transduction networks through brief exposure to the BRAF inhibitor PLX-4720 (3uM) or IGF1 (100ng/ml). The resulting cell lysates were then analyzed using the Bio-Plex multiplexed immunoassay system for the following phosphoproteins: pIGF-1R, pMEK1, pErk-1/2, pAkt, pGSK3B, pp70S6 kinase and pStat3. Functional signaling profiles (FSP) were then created for each tumor based on baseline and modulated levels of each phosphoprotein. FSPs were then compared with known targeted drug sensitivity profiles. **Results:** Reproducible FSPs were obtained from FNA samples of each xenograft model. The FSPs obtained from FNA samples were similar to those derived from 2-dimensional in vitro cultures of the corresponding cell lines. Exposure of samples to the BRAF inhibitor PLX-4720 resulted in modulation of the MAPK pathway that corresponded to the anticipated activity of the drug. Responses of the xenograft samples to IGF1 growth factor stimulation differed between cell lines and may correlate with resistance mechanisms to BRAF inhibitors via PI3K, mTOR, or AKT, and may also correlate with responses to combination drug therapy. **Conclusions:** These results demonstrate the capability of the SnapPath™ platform to generate functional signaling profiles from fine needle aspiration biopsy samples of xenografted melanoma tumors. The derived FSPs correspond to anticipated drug effects on signal transduction and consequently represent a valuable tool for pharmacodynamic studies in preclinical xenograft and primary human tumorgraft models as well extension into the clinical setting. The elucidation of bypass pathways by SnapPath™ represents an important new tool for the analysis of resistance mechanisms in melanoma.

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