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Patient derived xenograft models of melanoma as pre-clinical models for personalized medicine

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Abstract

The approval of three drugs targeting the MAPK pathway has led to new standard therapies for melanoma with BRAFV600E mutations. The excitement about these therapeutic successes is somewhat dampened by the relapse of most if not all treated patients due to the development of acquired (secondary) resistance. Currently, there is a lack of good translational models to study resistance pathways found in patients and test novel therapies capable of achieving durable responses in patients. We have developed a patient-derived xenograft (PDX) bank for assessing patients' responses to therapies. These PDX models are established by collecting and implanting fresh biopsy tissue or fine needle aspirate (FNA) samples in NSG mice. More than 120 samples have been established in a live tumor bank characterized for mutation status and linked to clinical data including patients relapsed on BRAF inhibitors. We were able to establish PDX models from either BRAFi or BRAF/MEKi combination therapy post-relapse biopsies (RPDX). To maintain drug pressure, animals were subsequently kept on diets mimicking clinical treatment regimens at approximately clinical plasma levels. Tumors grown under these conditions maintained protein levels of key pathways compared with untreated tumors. Histologic comparison of patients' tumors and RPDX showed tumor architecture and specific antigen expression to be in concordance. RPDX models are clinically relevant tools to understand the mechanisms of resistance in tumors from individual relapsed patients. We expect that 2nd line therapies to either of these treatment regimens will be (relatively) individualized based on patients' resistance mechanisms.

Biography

Clemens Krepler, M.D. is staff scientist in Meenhard Herlyn's lab at the Wistar Institute, Philadelphia, PA. As a dermatologist specializing in oncology, he is focusing on translational melanoma research and personalized medicine. He has extensive experience in all aspects of melanoma management from primary diagnosis to surgical, adjuvant, and systemic therapy. In his present role, Dr. Krepler is conducting preclinical research in targeted therapy of melanoma using advanced models such as 3D spheroid cultures and patient derived xenografts with an overarching goal of translating melanoma research into effective therapies for patients.