6.3 Molecular Pathology as part of the Translational Pipeline: Model Development, Drug Discovery, and Clinical Correlation.

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The treatment of rare molecular variant or treatment refractory cancers is challenging as well-funded and rigorous clinical trials generally do not focus on such cases. One example is melanoma. Despite the fact that $BRAF^{V600E}$ mutations are the most prominent activating mutations in melanoma, are recognized in several other cancers, and are increasingly targeted therapeutically, there is disagreement amongst medical oncologists as to how cases driven by mutations at the 601 locus should be approached. I will describe a translational study performed at the Ottawa Hospital and the Ottawa Hospital Research Institute that sought to better understand the treatment and clinical approach to patients with mutant $BRAF^{K601N}$ melanoma. The patient-derived model system was extensively characterized and utilized in the medium-throughput screening of an FDA-approved drug panel, which led to the elucidation of a possible unique role for MEK inhibition in such cases. This study also highlights the clinical utility of Cobimetinib monotherapy (MEK inhibition) in $BRAF^{K601N}$ melanoma. Lessons learned from this study highlight the importance of early molecular pathology testing for targetable cancers and introduce a possible approach of a personalized oncology platform for rare variant disease.

**Educational Objectives:**
By the end of the presentation, participants will be able:

1. Describe the targeted therapeutic approach to $BRAF^{V600E}$-activated melanoma and why this must be reconsidered for mutations at the 601 locus.
2. Understand the importance of accurate model systems and the role they can play in the development of novel therapeutic approaches to some cancers.

Describe the importance of early molecular pathology testing for treatment flow in the era of personalized oncology.