Approaches Towards Verification and Validation of Model Systems

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Background: Improved model systems offer the promise of enhanced scientific insights and clinical advances for cancer patients. Limitations in preclinical models are a major weakness in cancer research and is directly associated with the low success rates for translating discoveries to clinical care. The use of patient derived xenografts (PDX) in basic science and individualized therapy is a rapidly evolving domain. PDX tumor models have demonstrated the ability to retain the genetic and epigenetic changes and recapitulate the inherent heterogeneity of the primary human tumor. Upon human tumor recapitulation in a mouse, how do we know if this model is good? To what extent does the mouse-derived tumor reflect the human tumor? To what degree is quantification possible? Regarding the evaluation of model systems, can bioinformatic approaches be developed in support of quantitative metrics to assist with the evaluation of model systems?

A clinical trial is underway at the University of Arkansas for Medical Sciences where patients with early stage non-small cell lung cancer have surgery for curative intent. Human tumors are grown in PDX models for individualizing therapy options upon recurrence. All tumors undergo extensive modalities of NGS (ie, DNA, RNA), therapeutic targets are assessed, and PDX models are tested.

Results: Multi-omic analyses will examine and contrast the human tumor along with the associated PDX recapitulation through one or more passages. Specifically, the analyses presented will show results pertaining to: i) copy number variation, ii) disease specific mutations via a high coverage panel, iii) expressed mutations, and iv) gene and isoform expression.

Conclusion: As model systems improve, so will the clinical outcomes for cancer patients. To improve model systems, robust bioinformatics approaches and toolkits are needed for initial model assessment as well as to aid in the complex analyses associated with drug-based individualized therapy programs.