Announcements/Updates

- Getting exon sequencing on Small Cells in portal as IMPACT samples in the next few months
- If anyone has any new sets of models to add to portal, data gets richer with more samples
- New U54 grant from Vanderbilt in Small Cell Lung Cancer

Title: RB1 Loss Drives Prostate Cancer Lineage Plasticity and Therapeutic Resistance
Leigh Ellis Ph.D-Dana Farber Cancer Institute

- Prostate Cancer Initiation and Progression
  - Good News:
    - Highly curable if detected early-surgery/radiation
  - Bad News:
    - Approx 15% patients are diagnosed with mets at initial diagnosis
    - Approx 20-30% patients will metastasize post definitive treatment (surgery etc.)
    - Prostate cancer metastasis is not curable
    - Sustainable regression of disease is difficult

- Modeling Prostate Cancer Initiation and Progression

- Lab uses genetically modified mouse models
  1. Study disease initiation/progress
  2. Discover drivers of metastatic disease
  3. Discover drivers of therapeutic resistance
  4. Conduct informative pre-clinical trials

- Typical Responses to Antiandrogen Therapy
  - Prostate cancer is driven by androgen receptor reactivation
  - Charles Huggins discovered antiandrogen attacks on prostate was therapeutically beneficial which lead to surgical and estrogen chemical direction in the 1940’s
    - 20-30% of patients do become resistant
3 Basic Classifications

- Next generation ARPI’s increases patient population of AR indifferent tumors
  - Combined loss of tumor suppressor genes drives prostate cancer lineage plasticity
  - 2004 to now—clinical data and modeling data has come out that compliments each other
- Epigenetic (polycomb) re-wiring as a key molecular feature of neuroendocrine prostate cancer
  - 2 clinical papers in Vancouver compared adenocarcinoma and neuroendocrine cancer cohort that showed vast enrichment of polycomb EZH2 associated complex
  - Research at Cornell highlighted enrichment of EZH2, both expression and function
- EZH2 in Prostate Cancer Initiation and Progression

### Table

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References:
- Efthymiou S. (2017) Pharmacogenomics

### EZH2 Function and Role

1. **Lineage Plasticity**
2. **Immunity**

- **EZH2 Function and Role**
  - Polycomb Repressive Complex 2 (PRC2)
    - Cell Proliferation
    - Invasion
    - Mets
    - Tumor Formation
    - Cell Differentiation
    - Senescence
    - Lineage
    - Immune Regulation
• EZH2 in PCa Initiation and Progression
  o Prostate cancer is a downstream transcriptional target of 2 biggest oncogenes
  o EZH2 is up-regulated along with catalytic activity
  o 50% of prostate cancers house tempers through ERG fusion through ERG DNA binding as the transcription factor
  o Altered AR cistrome due to chromatin remodeling considered a histone methyltransferase dependent mechanism because of catalytic activity
  o PTEN loss models with activated AKT1-resulted in phosphorylation of EZH2 at a p-ser21
• RB1 Regulates Cell Cycle and Pluripotency
  o RB2 is a molecular adaptor
  o Function is defined by gene and protein interactions
  o Interactions are regulated by post-translational modification
  o RB1 inactivation promotes reprogramming of differentiated cells to a pluripotent cell cycle
  o RB1 acts as a global repressor of pluripotency networks
• Cancer Genetics and Epigenetics
  o How important is the rewiring of the epigenome?
• Loss of Rb1 induces metastatic progression in Pten deficient prostate cancer
• Loss of Rb1 induces lineage plasticity in Pten deficient prostate cancer
  o Used brainbow trans-genetic alleles in the mouse models to color the tumors by 4 different colors
• DKO murine PCa resembles human neuroendocrine prostate cancer
  o P53 deletion did not separate tumors from DKO
• Inhibition of Ezh2 reverses therapy resistance and lineage plasticity

Lab Work:
  1) How does Rb1 deletion influence chromatin remodeling?
     a) Gain deeper knowledge of Ezh2 dependence in chromatin remodeling downstream of Rb1 loss
  2) Validate Rb1 as a suppressor of PCa lineage plasticity
  3) Identifying synthetic lethal targets in prostate cancer with Rb1 loss-of-function
  4) Targeting RET Kinase in AVPC Patients
  5) Identifying novel master regulators of lineage plasticity in prostate cancer
• Testing MYBL2 as a driver of AVPC
• Tumor Evolution-Targeted Therapy Resistance Not just a Prostate Cancer Problem
• Treatment resistance after primary and secondary hormonal therapies involves re-activation of androgen receptor
• Clinical trial selection based on RB1 status—is positive protein expression enough?
  ▪ From clinicaltrials.gov
    • NCT02905318: mCRPC-CDK4/6 inhibitor (RB1 status required)
    • NCT02494921: mCRPC-CDK4/6 inhibitor (RB1 status NOT required)
Moving Forward

- Better models and additional clinical studies needed (selection versus adaptation)
  - Scenario 1: Pre-existing resistant clines exist in CRPC-Adeno. Elimination of drug sensitive clones paves way for expansion of drug resistant subpopulations
  - Scenario 2: Luminal prostate cancer cells adapt/de-differentiate/acquire characteristics that make them more "stem-like" and adopt NE features
- Understanding driving mechanisms of lineage plasticity-actionable targets
- Deeper understanding of RB1 deficiency (genetic versus epigenetic)
- Better identification of patients undergoing AVPC (CTCs, cfDNA, cfRNA)
- Using this information to better design clinical trials
- Measuring tumor heterogeneity (epigenetic plasticity)
  - John Dick stemness signature
    - NEPC score, AR score

Reminders:
- Next Call: 6/7/18-Vanderbilt Group