Meeting minutes: SCLC Consortium WebEx
May 3rd @ 1:00pm ET

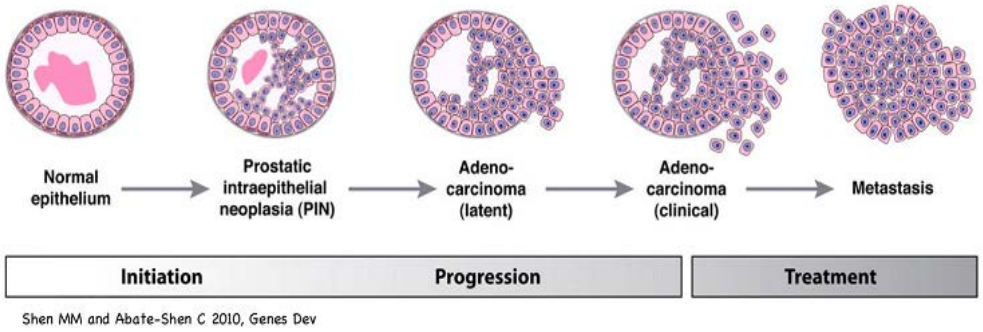
Announcements/Updates

- 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



Shen MM and Abate-Shen C 2010, Genes Dev

    - 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

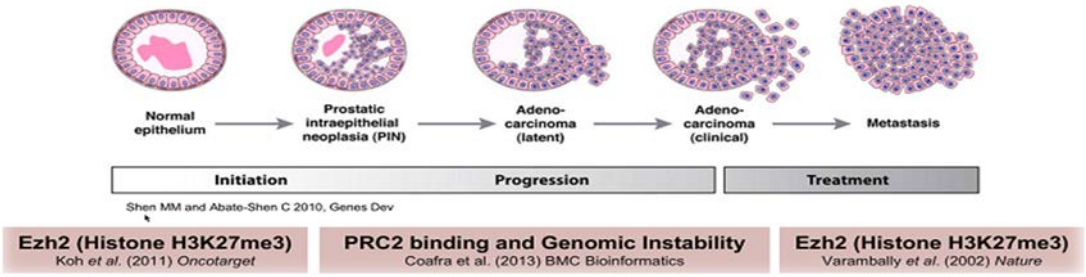
- 3 Basic Classifications

	Restored AR signalling	AR bypass signalling	Complete AR independence
Clinical relapse profile	• AR+ • Rising PSA	• AR+ • Rising PSA	• AR^{low} or AR− • Low PSA
Histological features	Adenocarcinoma	Adenocarcinoma	• SCC/NEPC • Novel subtypes?
Molecular features	• AR-activating mutations • AR active splice variants • Intratumoural DHT synthesis from adrenal precursors	GR upregulation	• *RB1* deletion • *TP53* deletion or mutation • *MYCN* gain • *AURKA* gain

Watson P, et al. (2011) *Nat Rev Cancer*
Ellis L, (2017) *Pharmacogenomics*
Davies AH, et al. (2018) *Nat Rev Urology*

- 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



1. Linage 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
    - Prostate cancer is a downstream transcriptional target of 2 biggest oncogenes
    - EZH2 is up-regulated along with catalytic activity
    - 50% of prostate cancers house tempers through ERG fusion through ERG DNA binding as the transcription factor
    - Altered AR cistrone due to chromatin remodeling considered a histone methyltransferase dependent mechanism because of catalytic activity
    - PTEN loss models with activated AKT1-resulted in phosphorylation of EZH2 at a p-ser21
- RB1 Regulates Cell Cycle and Pluripotency
    - RB2 is a molecular adaptor
    - Function is defined by gene and protein interactions
    - Interactions are regulated by post-translational modification
    - RB1 inactivation promotes reprogramming of differentiated cells to a pluripotent of cell cycle
    - RB1 act acts as global repressor of pluripotency networks
- Cancer Genetics and Epigenetics
    - 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
    - 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
    - P53 deletion did not separate tumors from DKO
- Inhibition of Ezh2 reverses therapy resistance and lineage plasticity

<u>Lab Work:</u>

1)
    a) How does Rb1 deletion influence chromatin remodeling?
    b) 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 base d on RB1 status-is positive protein expression enough?
    - From clincaltrials.gov
        - NCT02905318: mCRPC-CDK4/6 inhibitor (RB1 status required)
        - NCT02494921: mCRPC-CDK4/6 inhibitor (RB1 status NOT required)

- NCT02059213: mPC-CDK4/6 inhibitor (RB1 status required)

Moving Forward

- Better models and additional clinical studies needed (selection verse 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 verse 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