Outline:

1. Prioritizing Key elements through mutation burden analysis
   1. Integrating covariate matrix
   2. Accurate gene mutation rate estimation
   3. Extended gene annotation by linking various non coding elements
   4. Improved burden analysis by synthesizing signals from both nc and coding elements from each gene
2. Prioritizing Key elements through gene expression analysis
   1. TF analysis
   2. RBP analysis
3. Prioritizing Key elements through network rewiring analysis
   1. Gene-gene mega network via proximal and distal regulatory elements
   2. Single node analysis
      1. Rank TFs according to rewiring measurements
      2. TFs Clustering according to rewiring status within K&G network
   3. Pairwise nodes analysis
      1. Disruption of co-associated TFs in tumor cells
      2. Change of co-association types (loregic)
   4. Topology analysis
      1. TF hierarchy changes in Tumor and normal cells
      2. TF motif gain and loss events in Tumor and normal
4. Prioritizing SNVs in Key elements discovered by 1-3
   1. Integrating element score and individual SNV score to have a finalized score
5. Experimental validation of key elements and SNV
   1. sh-RNAseq MCF-7
   2. Wild type and Mutant enhancers in MCF-7

Data Novelty:

1. Most comprehensive non-coding elements list that are linked to genes with high confidence in model tumor cell lines
   1. Experiments list includes:
      1. CHIP-seq (TF) -> TFBS
      2. CHIP-seq (Histone) + Enhancer-seq -> Enhancers
      3. Hi-C + CHIA-PET + CHIP-seq (Histone) -> Enhancer-gene linkage
      4. RAMPAGE -> accurate active promoter definitions
      5. iCLIP -> RNA-regulatory regions
2. Most comprehensive covariate list to better characterize the somatic mutational landscape
3. Most comprehensive list of CHIP-seq data for transcription factors activities in several cancer cells
4. Wild and mutation enhancer in luciferase assay for SNV effect analysis