Meeting minutes: SCLC Consortium WebEx

August 2, 2018 @ 1:00pm ET

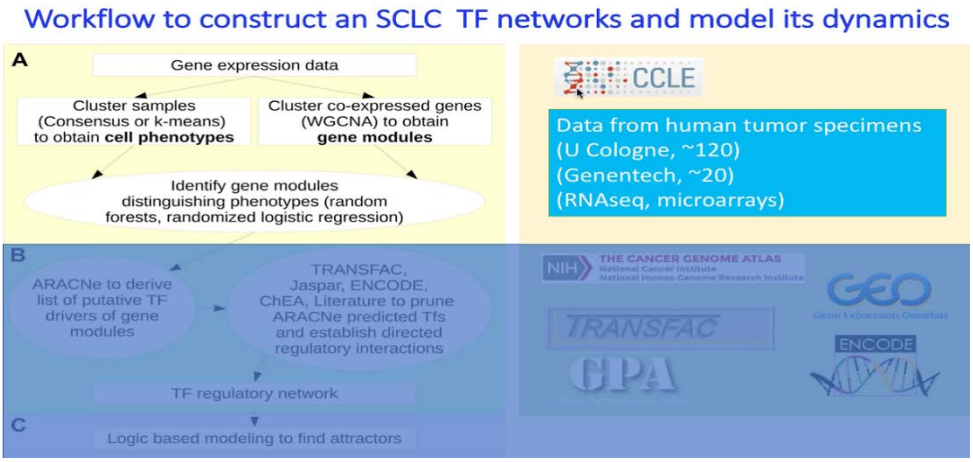
Announcements/Updates

- Annual Spring Meeting will be evening of April 3rd–April 5th 2019
  - Planning committee: Charles Rudin, JT Poirier, Trudy Oliver, Julie George and Taofeek Owonikoko
- NCI will be funding 3 new U01's on the therapy side and 3 new on the prevention side

Title: Center for Systems Biology of Small Cell Lung Cancer

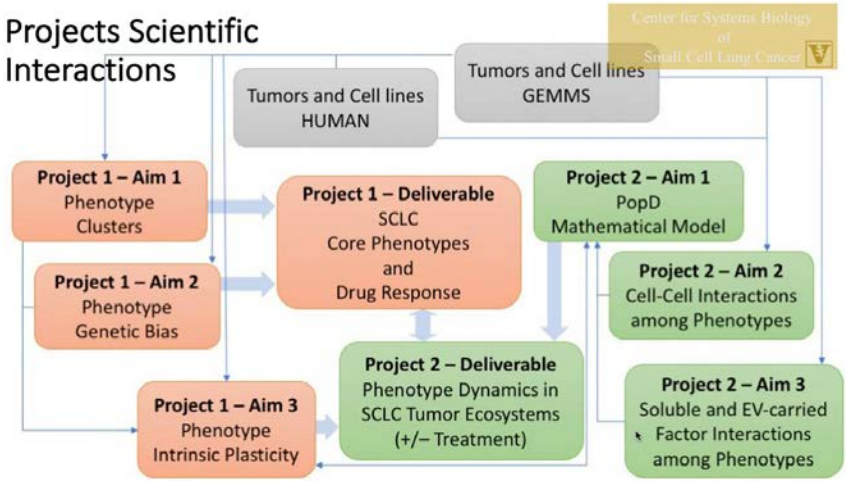
Dr. Vito Quaranta-Vanderbilt University Medical Center

- Conceptual background for Vanderbilt Cancer Systems Biology Group: "We believe that a systems level understanding of cancer heterogeneity and its interactions with the microenvironment, based on approaches that blend experimentation, computation and mathematical modeling, will lead to actionable findings including new treatment studies."
- Co-expression network analysis identifies Spleen Tyrosine Kinase (SYK) as a candidate oncogenic driver in a subset of SCLC
- Does SCLC phenotypic variants (subsets) result from equilibrium states (attractors) of a master gene regulatory Transcription Factor network?
  - Yes, a network of 33 TFs may control SCLC cell differentiation into phenotypic variants



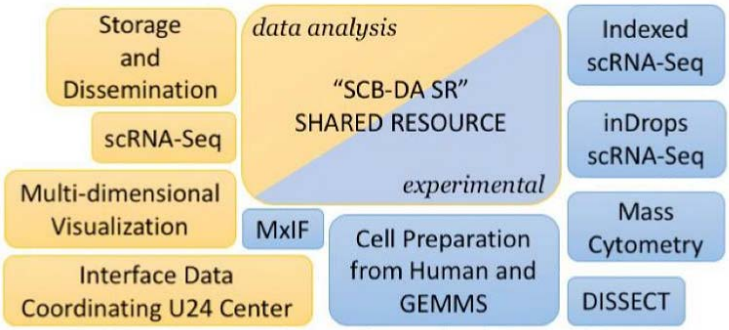
- Network of 33 TFs controls expression of SCLC co-expressed gene modules from a static SCLC TF network to dynamic simulations with:
  - Boolean Logic
  - Decision Trees
- Contrary to its homogeneous histopathology ("small blue round cells"), SCLC is phenotypically heterogeneous and SCLC variants are linked to aggressive disease in GEMMS
- Central Hypotheses for Center Grant: Heterogenous phenotypes and their interaction dynamics form a robust SCLC tumor ecosystem adaptable to perturbations and treatment
- Outreach Core
  - Aim 1: Disseminate Center expertise through educational hands-on workshops and online modular courses
  - Aim 2: Share experimental data, analysis tools, and models developed within the Center

- Project Scientific Interactions



- Project 1: Modeling the SCLC Phenotypic Space
    - Aim 1: Identify core of SCLC tumor phenotypes
        - Aim 1a: Characterize core phenotype clusters in human SCLC from transcriptomics data and functional ontologies
        - Aim 1b: Establish equivalency between human and mouse SCLC phenotypes using enrichment of gene modules and gene ontology methods
        - Aim 1c: Experimentally validates SCLC phenotypes at the single cell lever
    - Aim 2: Test the hypothesis that genomic alterations lead to bias in SCLC phenotype specification
        - Aim 2a: Map genomic alterations to SCLC phenotypes with Pathway Mutational Load (PML) analysis
        - Aim 2b: Experimentally test the role of key genomic alterations in driving SCLC subtype bias and treatment response
        - Aim 2c: Correlate SCLC genomic alterations with patient outcome and treatment response using longitudinal monitoring of cfDNA from SCLC patients
    - Aim 3: Modeling the SCLC Phenotypic Space
        - Aim 3a: Track phenotypic diversification in SCLC using DNA barcoding
        - Aim 3b: Quantify phenotypic plasticity in SCLC using information theoretic techniques
- Project 2: Phenotype interactions and dynamics in SCLC tumors
    - Aim 1: Build predictive models of SCLC cell phenotype
        - Aim 1a: Construction of a PopD model of SCLC phenotype interactions
        - Aim 1b: Stochastic simulations
        - Aim 1c: Ensemble-based parameter estimation and sensitivity analysis
    - Aim 2: Test the hypothesis that cell-cell interactions within SCLC tumors are critical for tumor growth and survival
        - Aim 2a: Functional interactions between SCLC phenotypes, focusing on TPCs
        - Aim 2b: Drivers controlling the phenotypes of SCLC subpopulations
        - Aim 2c: Singe-cell RNA-seq and flow cytometry for the unbiased identification of tumor cells and non-tumor cells in SCLC tumors
    - Aim 3: Identify secreted factors that control SCLC phenotype dynamics
        - Aim 3a: Characterize the secretome of TPC, Hes 1+, and CD44+ SCLC

        - Aim 3b: Determine the role of secreted factors in SCLC phenotype interactions and dynamics
        - Aim 3c: Test the role of specific secreted molecules in driving SCLC population dynamics
- The Single Cell Biology-Data Analysis Share Resource: a cutting edge, integrated one-stop shop for single-cell experiments and data analysis



Reminders:

- Next Call: September 6th
    - Dr. David MacPherson -Fred Hutchinson Cancer Research Center