Meeting minutes: SCLC Consortium WebEx

November 1, 2018@ 1:30pm ET

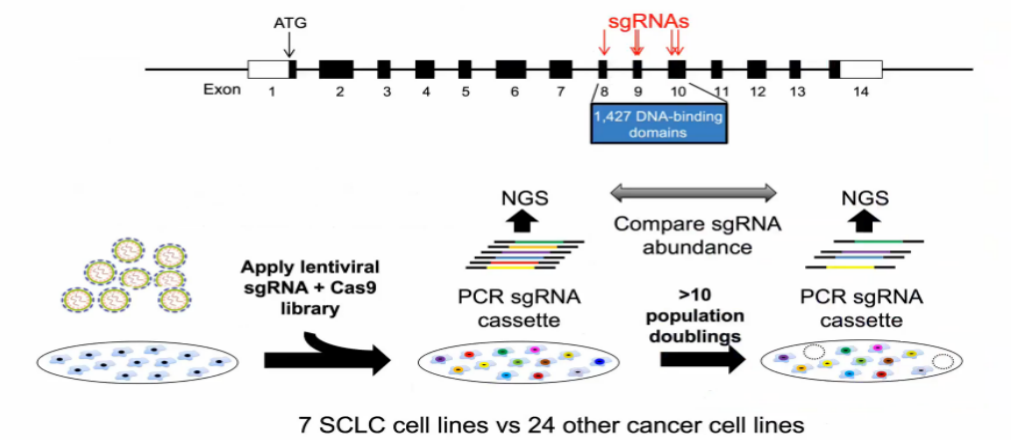
Announcements/Updates:

- NCI is putting a request out for community input on ideas of things that remain to be explored from basic through therapeutic areas for a funding opportunity

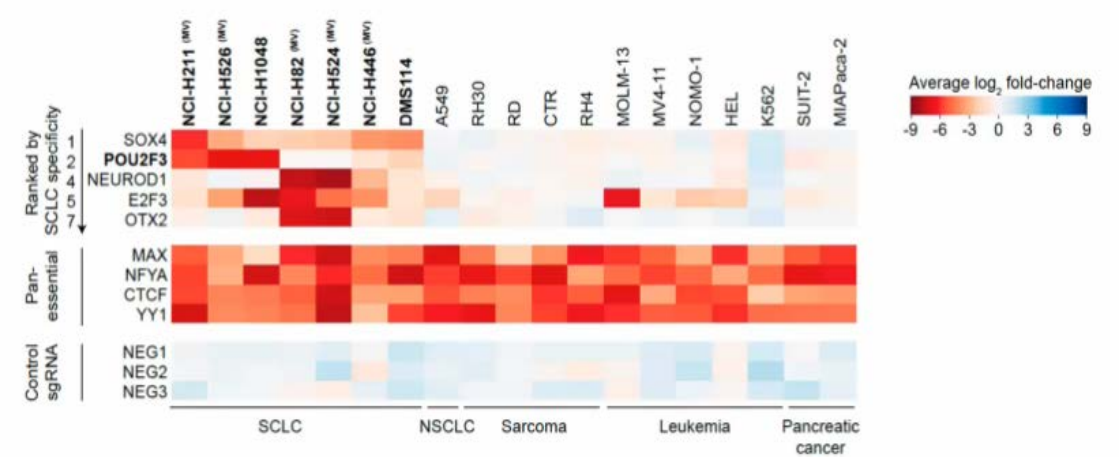
Title: A Tuft Cell Variant of Small Cell Lung Cancer

Dr. Chris Vakoc-Cold Spring Harbor Lab

- Using genetic screens to discover dependencies to epigenetic factors
- Cell lineage can be a source of inter-tumor heterogeneity
- Small cell lung cancer
  - The most aggressive form of lung cancer
  - No effective targeted therapies
  - Around 85% of SCLC tumors express neuroendocrine markers CHGA, ASCL1, INSM1
- However….
  - 15% of small cell lung cancers do not express neuroendocrine markers but have similar genetics and similar poor clinical outcomes as neuroendocrine-high tumors
  - What is the biological significance of the neuroendocrine-low variant of SCLC?
- A domain-focused CRISPR screen to identify essential transcription factors in SCLC cell lines



  - Made a library that knocks out every human transcription factor by targeting the exons that encode the DNA binding domains
- POU2F3 is a powerful dependency in a subset of SCLC cell lines



  - Every cell line addicted to POU2F3 expresses it at very high levels
  - No known role of POU2F3 in human cancer

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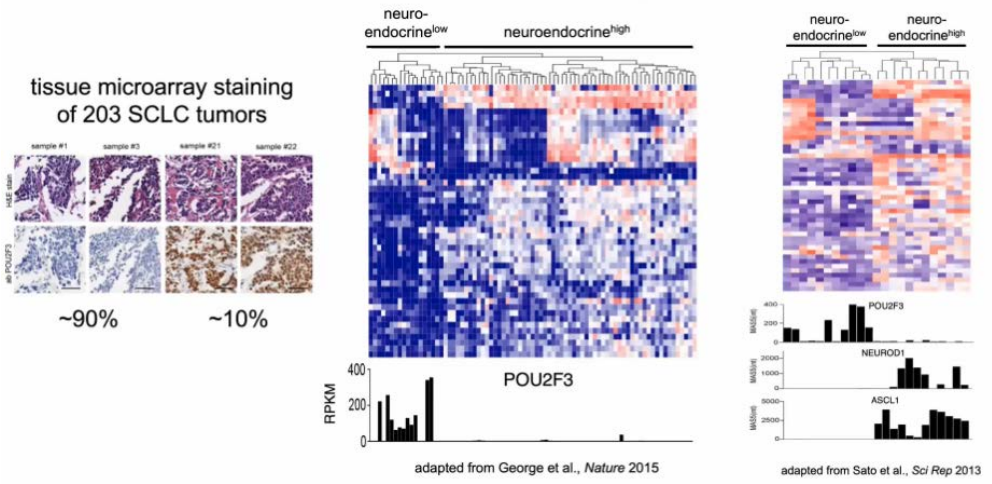
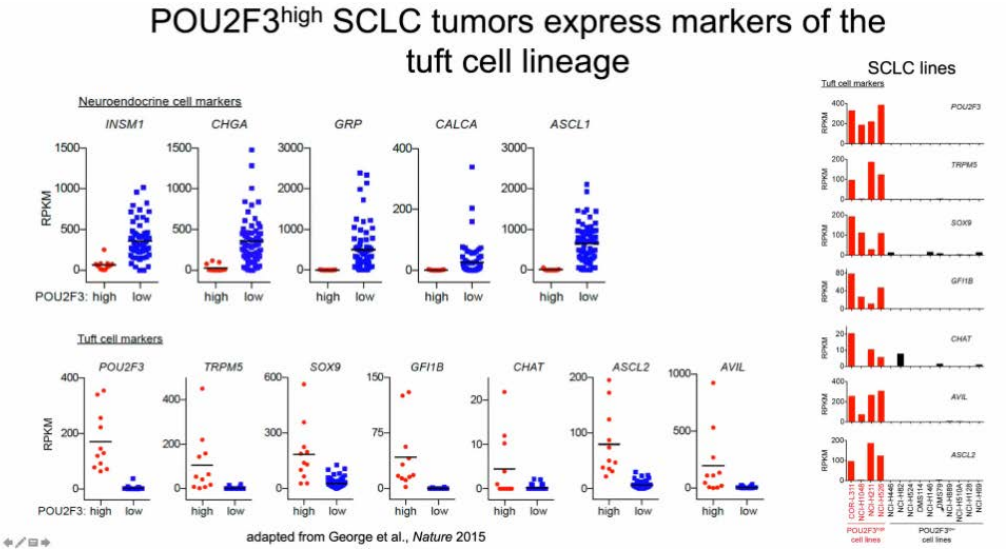
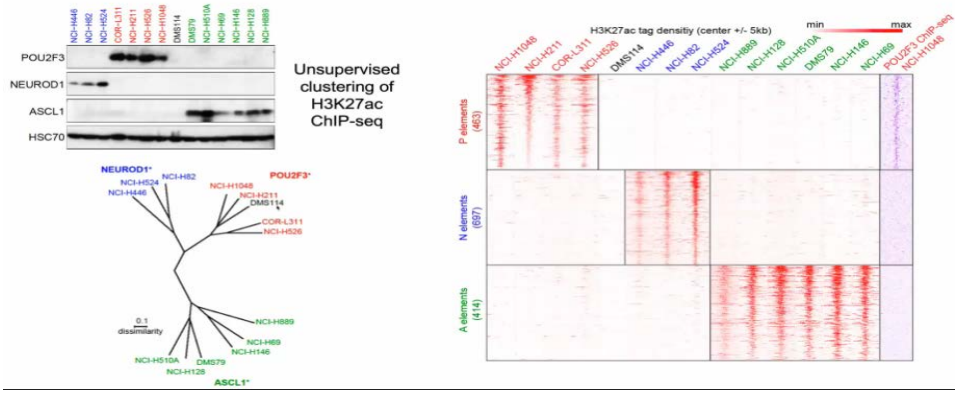
- POU2F3 is expressed in neuroendocrine ^{low} SCLC



- What is the cell lineage of POU2F3 + SCLC?
  - POU2F3 is a master regulator of the "tuft cell lineage" (aka solitary chemosensory cells, microvillous cells, brush cells)
  - Tuft lineage markers: POU2F3, TRPM5, SOX9, GRI1, CHAT, ASCL2, AVIL
  - Pou3f3$^{-/-}$ mice are viable, but lack tuft cells→defects in helminth immunity and in taste sensation



- Chromatin analysis of SCLC cell lines



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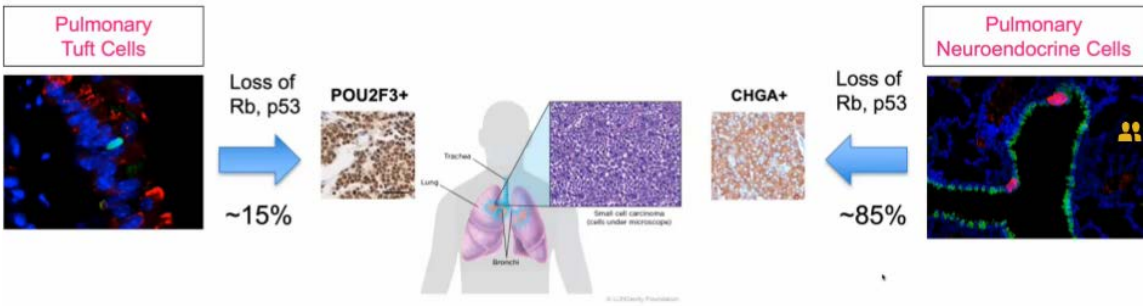
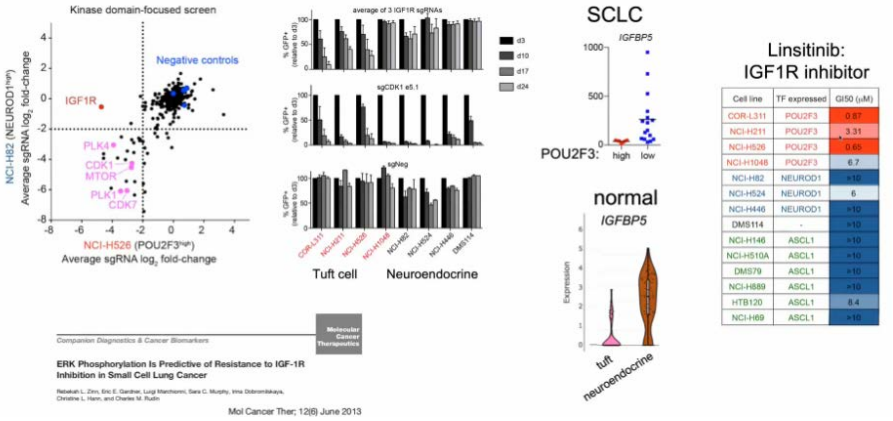
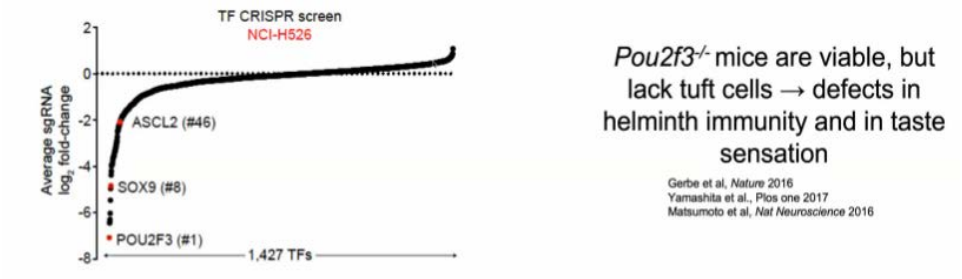
- Rare POU2F3-expressing cells exist in the mouse bronchial epithelium
    - POU2F3+ cells in the lung are bona fide tuft cells (brush cells) and regulate lung inflammation via IL-25
- Conclusion: Small cell lung cancers can be subclassified into neuroendocrine and tuft cell like lineages
    - Do these distinct tumor lineages reflect a difference of cell origin?
        - Rare pulmonary tuft cells can acquire somatic mutations in central air way locations that can give rise to SCLC that lack neuroendocrine fusions



    - In development: Pou2f3$^{knockin\text{-}CRE\text{-}ERT2}$;Rb2$^{flox/flox;}$Rb2$^{flox/flox;}$Trp53$^{flox/flox}$ tumor model
    - Unique epigenetic or signaling addictions?
    - Opportunity for personalized therapy?
    - IGF1R addiction Is linked to the tuft cell variant of SCLC



- Vakoc Lab Focus



Questions:

- These cells seem to be more permissive for infection with CRISPR. Is that why you focused on them?
    - The infection works fine in both cell line contexts. Mostly Slow growth rate of neuroendocrine human cell lines make them practical.

- Do POU2F3 positive cells grow as an adhesive monolayer or in suspension like the neuroendocrine cells?
    - Most grow as adhesive monolayers but there is some variability.
- POU2F3 antibody is disappearing from availability. Is there another marker that is tightly linked to POU2F3, like TRMP5?
    - In mouse, have tried TRMP5 but were unsuccessful. Have not tried any of the human agents yet.
- If you go back and look at tumors from publicly available data sets, small cell tumor sets are high in POU2F3 but do you know what they look like in terms of other genomic characteristics? For example, high tumor mutation burden or mutations that co-occur with them?
    - MIC expression tends to be higher in POU^{+} tumors compared to POU^{-} tumors
- Ever seen any resistant mutants to ASCL1 or NeuroD1?
    - Have not looked at resistance but we should start looking for it. This could be a dynamic trans-differentiation even occurring. Some evidence there is a common stem cell that gives rise to neuroendocrine and tuft cells.

Reminders:

- Next Call: December 6, 2018 from 1-2pm EST
- 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