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Controlling Cell States in Neuroendocrine Cancer to Enhance Responses to Therapy

Heterogeneity and plasticity are defining hallmarks of human tumors that facilitate growth, metastasis, and therapeutic evasion. Resistance arises either through the selection of low-responsive cell states that outcompete sensitive populations or through the dynamic transition of sensitive cells into a non-responsive state, driving tumor recurrence. To overcome this problem, the Sage lab at Stanford has developed an approach to directly target cell-state dynamics by manipulating cells to stay in specific states or forcing cells to switch to states that are more amenable to therapy.

Plasticity and intratumoral heterogeneity drive rapid therapy resistance and disease progression in small cell lung cancer (SCLC). While SCLC is known to span a neuroendocrine (NE) to non-NE differentiation axis, the underlying transitional intermediates have remained poorly understood. Using single-cell multi-omics, the Sage lab uncovered distinct transcriptional SCLC cell states including a novel bipotent intermediate state with NE/nonNE differentiation potential. Furthermore, they developed a Boolean Bayes model for transcription factor networks (BoBa-T) to predict regulators of SCLC cell states, and revealed a list of transcription factors that could be targeted to force SCLC cells into a NE or low/nonNE state. This novel approach has the potential to advance therapeutic strategies for overcoming SCLC's plasticity and therapy resistance.

Stage of Development
Proof of concept

Applications

- Therapeutic approaches for neuroendocrine cancers
- Drug discovery and biomarker development

Advantages

- Identifies specific transcription factor targets enabling precision drug discovery development
- Overcomes treatment resistance by stabilizing cells in therapy responsive states

Publications

- Debadrita Bhattacharya, Sarah M. Groves, Cameron Walker, Gina N. Duorino, Marcus Hsieh, Yamina Chtourou, Griffin G. Hartmann, Wen-Hao Hsu, Candace Liu, Michael Angelo, Vito Quaranta, Julien Sage. Transcriptional networks underlying tumour plasticity in small-cell lung cancer. *bioRxiv* 2026.09.26.754526; doi: https://doi.org/10.64898/2026.09.26.754526

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