Meeting Summary

Workshop on Understanding Plasticity and its Role Across the Cancer Continuum

Dates: September 23-24, 2026

Sponsor: National Cancer Institute, Division of Cancer Biology

Background

Significant challenges remain in understanding and addressing tumor heterogeneity from cancer initiation through progression and treatment resistance. Cellular plasticity is central to this challenge, encompassing changes in cell identity, state, and behavior as early lesions form, tumors progress, and cancers respond to therapy. Its effects are context dependent and can be either protective or tumor-promoting. Although epigenetic, transcriptional, metabolic, and microenvironmental factors have been linked to cellular plasticity, the mechanisms governing key cell-state transitions remain incompletely understood. Key questions include what initiates these transitions, how cell identity is maintained or destabilized, and when transitions remain reversible. Further questions concern how specific cell populations and reciprocal tumor-microenvironment interactions shape protective or tumor-promoting outcomes, and how plasticity impacts genetic evolution.

The workshop aimed to define plasticity and understand its underlying mechanisms across cancer initiation, progression, metastasis, and treatment resistance. It also sought to identify shared biological mechanisms, methodological limitations, knowledge gaps, and opportunities to translate these insights into cancer prevention and treatment strategies.

Workshop Information

The workshop brought together investigators spanning developmental biology, tissue regeneration, cancer genetics, tumor progression and metastasis, therapy resistance, pathology, computational biology, and clinical oncology. Three scientific sessions and associated discussions addressed mechanisms, approaches for measuring plasticity, and possible therapeutic opportunities.

Major Topics of Discussion

1. Cellular Plasticity in Cancer Development and Initiation

Presentations described how developmental programs establish lineage boundaries and how injury can reopen normally restricted states. In the intestine, differentiated or lineage-committed cells can replenish stem-cell populations after injury, while tuft cells within pancreatic metaplastic lesions can restrain inflammation and neoplastic progression. Across prostate, lung, and colorectal models, lineage context, oncogenic signaling, and persistent regenerative programs influenced whether a state change remained adaptive or became

cancer permissive. Lung tumors displayed both discrete lineage switches and hybrid states with different drug sensitivities. Studies of pancreatic injury suggested that plasticity can also involve changes in nuclear organization and genome content, including polyploidy and transient aneuploidy, which may contribute to early neoplastic evolution.

Discussion focused on the conditions that distinguish protective repair from precancerous persistence, including cell of origin, mutation order, tissue context, inflammation, and failure to restore homeostasis.

2. Cellular Plasticity in Cancer Evolution and Progression

The second session considered initiation, progression, metastasis, and resistance as interconnected processes in which early cell states can shape later tumor behavior. Extracellular matrix mechanics altered epithelial-mesenchymal programs and invasive behavior. In small cell lung cancer, intermediate cells retained accessible regulatory regions associated with both neuroendocrine and non-neuroendocrine identities, suggesting the potential to adopt either identity. Metastatic colorectal cells accessed regenerative and oncofetal programs, while breast cancer cells dynamically acquired leader-cell and hybrid programs supporting invasion and dissemination. Melanoma lineage barcoding showed that treatment selected rare clones whose molecular states continued to evolve. Other findings highlighted how established cell identities are maintained through ongoing transcriptional and epigenetic activity. In pancreatic models, injury or loss of lineage-maintaining transcription factors could destabilize acinar identity, while oncogenic KRAS could stabilize otherwise reversible injury-associated programs. Intermediate states were not always viewed as temporary: some pancreatic cancer populations may represent relatively stable progenitor-like states capable of generating multiple identities, rather than transient states between classical and basal phenotypes.

Discussion addressed stress-response timing, intermediate-state stability, and how stromal and immune cells, cytokines, and tissue mechanics influence tumor-cell transitions.

3. Cellular Plasticity in Cancer Therapy Sensitivity and Resistance

Presentations described lineage change as a route to resistance in lung, prostate, gastrointestinal, and other cancers. Loss of lineage safeguards can permit lineage transformation, but developmental history and epigenetic state help determine which resistant identities become accessible. Studies identified high-plasticity or mixed-lineage populations that may precede neuroendocrine or other resistant states, while prostate cancer models suggested that some early transitions can be delayed or reversed by altering lineage signals. Work in cholangiocarcinoma and prostate cancer also showed that lineage identity can create distinct therapeutic dependencies. These findings highlighted opportunities to intervene before, during, or after a lineage transition.

Discussion focused on monitoring changes in tumor-cell identity, preventing or reversing transitions into resistant states, redirecting cells toward more treatable states, and targeting established resistant cells, with delayed resistance and longer responses as potential measures of benefit.

Summary

Together, the workshop presentations and discussions emphasized the need to follow cell-state changes over time and connect them to clonal history and microenvironmental context. Priorities included integrating lineage tracing with spatial and longitudinal profiling, and combining transcriptomic data with protein, metabolic, structural, and functional measurements. Participants also called for closer integration across developmental biology, tissue regeneration, cancer biology, computational approaches, and clinical oncology. Human tumor studies and experimental models were viewed as complementary approaches for defining mechanisms and identifying opportunities for intervention.