20th International p53 Workshop- Abstract Submission Template

Submission Deadline: January 31st 2026 (5pm EDT)
Notification of acceptance: By or before February 27, 2026

Title of study/project: Microenvironmental Control of mutp53-Driven Cell Competition

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Abstract:

Tumor development is driven by the accumulation of (epi)-genetic alterations that deregulate cell growth, together with the selection of cells capable of adapting to dynamic microenvironmental conditions such as hypoxia, nutrient fluctuations, and mechanical stress. Aging, the major risk factor for cancer, and its associated features including chronic inflammation and extracellular matrix (ECM) remodeling, generate permissive tissue environments that favor the expansion and evolution of preneoplastic clones harboring oncogenic mutations. Among these alterations, missense mutations in the tumor suppressor TP53 (mutp53) are highly prevalent.

Preneoplastic clones can colonize tissues through cell competition a process whereby "fitter" cells eliminate neighbouring less fit cells. However, the mechanisms governing cell competition remain poorly understood. Elucidating these mechanisms may uncover novel vulnerabilities in tumor initiation.

We previously demonstrated that microenvironmental cues, including mechanical signals, critically regulate stabilization/transcriptional activity of mutp53 (Ingallina et al., *Nat. Cell Biol.* 2018, Tombari et al *Nat. Commun.* 2023). Based on this, we hypothesized that microenvironmental cues promote mutp53 stabilization/function in preneoplastic cells, driving clonal expansion through cell competition. We generated ad hoc cellular models using CRISPR/Cas9 genome editing and ex vivo models derived from $p53^{WM}$ mice (Zhang et al., *Nat. Commun.* 2018), enabling the tracking of competing mutp53 and normal cells. We found that mutp53-expressing human breast epithelial cells acquire a competitive advantage over co-cultured normal cells in a context-dependent manner. Notably, increased ECM stiffness selectively enhanced the fitness of mutp53 cells. Transcriptomic profiling of competitive mutp53 cells identified a mutp53-dependent gene program associated with mechano-transduction and clonal dominance.

Conclusions:

We identified a mutp53-dependent gene program that promotes the expansion of preneoplastic cells at the expense of normal cells under conditions of increased ECM stiffness.

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