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Our goal is to understand basic mechanisms of eukaryotic transcription control and clarify how these controls are subverted during oncogenesis. We hope to use this information to identify points of oncogenic susceptibility within the cell and thus identify potential targets for pharmacologic intervention. We employ biochemical, molecular, and cell biological approaches to study RNA polymerase II transcription regulation.

1. **Function and regulation of the human transcriptional Mediator**. As a dynamic multiprotein interface between gene-specific transcription factors and RNA polymerase II, Mediator fulfils and essential function as a sensor, integrator, and processor of regulatory signals that converge on the promoters of protein-coding genes. We are engaged in studies pertaining to the following issues with respect to Mediator: (1) the mechanism by which eukaryotic activators and repressors interface with Mediator to effect activation or repression of transcription; (2) the physical and functional interactions among individual Mediator subunits; (3) how developmental and oncogenic signaling pathways converge on hMediator and how these signals are, in turn, relayed to RNA polymerase II.

2. **BRCA1 and estrogen signaling in breast cancer**. Mutational inactivation of BRCA1 confers a cumulative lifetime risk of breast and ovarian cancers. However, the underlying basis for the tissue- and gender-specific tumor suppressor properties of BRCA1 remains poorly defined. Based on our prior discovery that BRCA1 suppresses the ligand-independent transcriptional activity of the estrogen receptor α (ERα), we hypothesize that BRCA1 represents a ligand-reversible barrier to transcriptional activation by unliganded promoter-bound ERα and, further, that mutational inactivation of BRCA1 promotes mammary epithelial cell proliferation through aberrant expression of estrogen-responsive genes. We study the following issues pertaining to the modulation of ER□ function by BRCA1: (1) the mechanism of BRCA1-mediated ligand-independent ER□ repression; (2) the regulation of BRCA1-mediated ERα repression by estrogen-dependent and -independent cell signals; (3) the biological role of BRCA1 in the cell growth control through modulation of ER□ activity.

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