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## Modeling Li-Fraumeni syndrome by induced pluripotent stem cells

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Li-Fraumeni syndrome (LFS) is a genetically inherited autosomal dominant cancer syndrome characterized by multiple tumors within an individual, early tumor onset and multiple affected family members. In contrast to other inherited cancer syndromes, which are predominantly characterized by site-specific cancers, LFS patients present with a variety of tumor types, including osteosarcoma, soft tissue sarcoma, breast cancer, brain tumors, leukemia, and adrenocortical carcinoma. Germline mutations in the p53 tumor suppressor gene are responsible for LFS. Mutations in p53 are found in 50-70% of human tumors. Although there has been extensive research on cancer cell lines and even mouse models of LFS to study the role of p53, these model systems do not fully recapitulate the range of human tumors or their properties. Here, we established human LFS disease model by using LFS patient induced pluripotent stem cells (iPSCs), to delineate the pathological mechanisms caused by mutant p53 in osteosarcoma. The osteoblasts, differentiated from LFS iPSC-derived mesenchymal stem cells (MSCs), recapitulate osteosarcoma features including defective osteoblastic differentiation and tumorigenic ability, suggesting that my established LFS disease model is a “disease in a dish” platform for elucidating p53 mutant-mediated disease pathogenesis. The gene expression patterns of LFS osteoblasts are similar to those of tumor samples obtained from osteosarcoma patients and these tumorigenic features strongly correlate with shorter tumor recurrence times and poorer patient survival rates. Our functional studies implicate the essential H19 gene in normal osteogenesis and inhibition of tumorigenesis. In order to decipher the underlying mechanisms by which H19 mediates osteogenesis and tumor suppression, we characterized and analyzed the human imprinted gene network (IGN) and revealed the unidentified role of p53 in regulating the IGN culminating in osteogenic differentiation defects and tumorigenesis. In summary, these findings imply the feasibility of studying inherited human cancer syndromes with iPSCs.

### Biography

Dung-Fang Lee is dedicated to understand cancer pathological mechanisms by using patient-specific iPSCs and/or engineered ESCs. He has established the first human Li-Fraumeni syndrome (LFS) disease model by using LFS patient-specific iPSCs to delineate the pathological mechanisms caused by mutant p53 in osteosarcoma and continues to apply TALENs and CRISPR/Cas9 genome editing tools to create variant p53 mutations in pluripotent stem cells (PSCs; e.g., iPSCs and ESCs) in order to explore the role of mutant p53 in osteosarcomagenesis. He also works on modeling other familial cancer syndromes with osteosarcoma predisposition by both iPSCs and PSCs. Currently, he applies whole genome sequencing, screening approaches and systems-level analyses to explore early genomic alterations and to understand dynamic alterations of the genomic landscape of LFS-associated osteosarcomas.

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