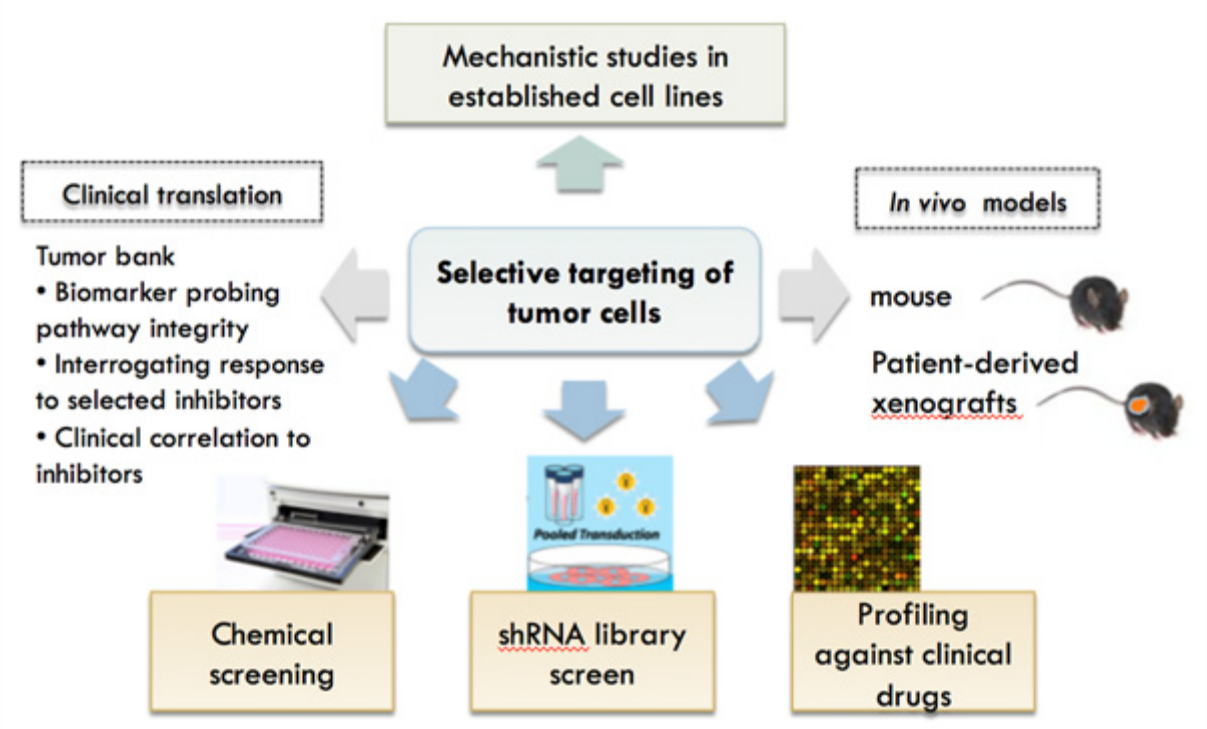
Research

TARGETING TUMOR VULNERABILITIES FOR PRECISION MEDICINE

My lab focuses on exploiting specific molecular defects in cancer cells for targeted therapy. We are interested in translating the concepts of synthetic lethality to effective cancer treatments. In a broader sense, synthetic lethality is used to describe functional interactions between two pathways/genes/mutations that synergistically reduce fitness and survival. This forms the basis for discovery screens that identified PARP1 inhibitors for use against BRCA-deficient tumors in cells, by exploiting the intrinsic vulnerability of BRCA-deficient tumors to specific alterations in DNA repair pathways.

We took the approach of using (1) “reverse” chemical biology approach to identify druggable pathways that renders selectivity cytotoxicity in tumor cells, and (2) inhibitors that selectively kills tumor cells by targeting these pathways and developing them as new modalities for cancer treatments. We validate the potential therapeutics in preclinical *in vitro* cytotoxic models and *in vivo* mouse xenografts with the ultimate aim for clinical translation. We collaborate closely with clinicians and scientists to integrate basic knowledge and translational research.



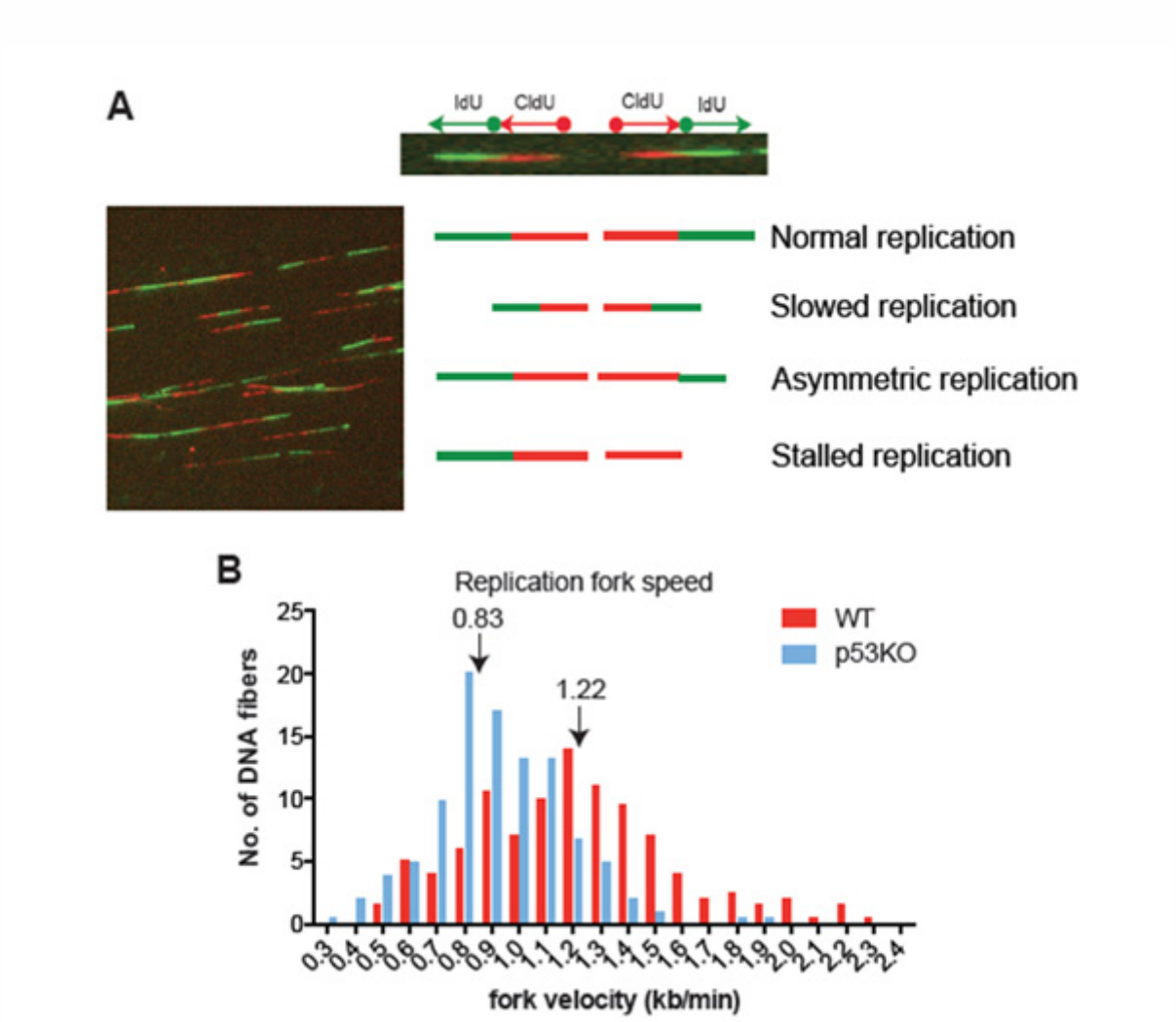
TARGETING DNA REPAIR AND GENOMIC INSTABILITY IN CANCER AND AGING

One of the underlying hallmarks of cancers is genomic instability. The accumulation of genetic mutations and DNA metabolic errors in cancer cells is often associated with a gain of oncogenic mutations or loss of tumor suppressor genes. Historically, DNA damage is a broad term used to describe the genetic instability observed in cancer cells. In the recent years, it is

becoming clear that not only can we identify specific DNA lesions and damage, but also proteins and pathways that directly prevent the occurrences and promote the repair of these DNA lesions. Therefore, by elucidating these molecular mechanisms in DNA damage response that are linked to either defects in tumor suppressors or oncogenes, it is possible to achieve precision targeting of cancer cells using specific inhibitors of DNA replication and repair.

We are exploring the molecular basis of how loss in certain tumor suppressor genes, such as p53 and BRCA1 and 2, promote genomic instability through noncanonical pathways affecting DNA replication. DNA replication stress appears to be unique to cancer cells. The net outcome of replication stress is the stalling and collapse of replication forks that can eventually lead to multiple inheritable errors in DNA replication, DNA recombination and crossovers, chromosomal missegregation, fueling tumorigenesis. We had demonstrated that loss in p53 tumor suppressor lead to defects in replication that surprisingly originates from transcription processes. We delineated the underlying mechanism and propose that conflicts between replication and transcription underlie the observed replication defects, and give rise to unresolved topological stress. As a proof-of-concept that it is possible to target replication stress, we demonstrated that inhibitors of topoisomerases which are needed to resolve the replication-associated topological problems in cells, led to selective toxicity in p53-mutated cells and mouse xenografts.

The importance of maintaining replication integrity is further illustrated in aging models. The accumulation of DNA damage, especially in stem cells, is largely related to the poor tissue regenerative capacity associated with aging. It is therefore not surprising that defects in multiple important genes involved in replication integrity such as ATR and p53 can promote aging. However, the molecular mechanisms linking genomic instability and aging are not exactly clear. We aim to study how replication errors and defects can lead to physiological aging and discover methods to limit replication stress and ameliorate the aging process.



A. DNA fiber labeling to probe the integrity of DNA replication. Red and green fibers represent IdU and CldU labeled DNA tracks. Schematic diagram show the different DNA replication parameters that can be quantified with this method. **B.** Replication rates are calculated based on fiber length and p53KO cells displayed an obvious shortening of DNA fiber track lengths compared to WT.