Evolutional Landscape of Ibrutinib Resistance

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Cancer progression, relapse and resistance are the result of an evolutionary optimization process. Vast intra-tumoral diversity provides the critical substrate for cancer to evolve and adapt to the selective pressures provided by effective therapy. Thus, understanding intra-tumoral diversity and evolutionary dynamics will be a critical step in the development of effective, curative therapies for cancer.

In order to study these questions, we characterized the intra-tumoral genetic heterogeneity of chronic lymphocytic leukemia (CLL) using massively parallel sequencing of large patient cohorts (Cell, 2013; Nature, 2015). These studies have shown that CLLs contain genetically distinct subpopulations that compete and mold the genetic makeup of the malignancy. Furthermore, we have demonstrated that this heterogeneity can help predict the future evolutionary trajectories of CLL, and that higher intra-tumoral heterogeneity in the pre-treatment sample predicts adverse outcome.

Ongoing efforts are dedicated to studying the quantitative evolutionary dynamics that enable the relapse clone to replace the pre-treatment clone. Using deep sequencing with high temporal resolution we determine the therapy specific clonal fitness with first line chemoimmunotherapy and targeted therapy (Nature Communications, 2016 & Nature Communications, 2017). These investigations offer a novel framework for the study of the evolutionary dynamics that underlie disease relapse, directly in patients.