Abstract:
Cancer is driven by the accumulation of somatic genetic alterations that alter the activity of tumor suppressor and oncogenes. Therapeutics targeting a spectrum of oncogenes including BCR-ABL, BRAF, EGFR, cKIT, HER2, RET, ROS and ALK intervention have brought significant benefits to cancer patients harboring such alterations.

Advances in next-generation sequencing and projects including the Cancer Genome Anatomy project and the International Cancer Genome Consortium have given us a detailed descriptive cancer genome. This however, does not immediately lead to a detailed functional understanding of those genes whose protein products are necessary for the maintenance of cancer viability.

In order to more deeply understand the genes and pathways critical to the survival of cancer cells we have taken on the functional annotation of the Cancer Cell Line Encyclopedia (Nature 2012) through the use of deep pooled shRNA libraries. The resulting effort has led to the generation of drop-out shRNA data for 7,837 genes across 390 cancer cell lines (Cell 2017). The data from this effort are highly robust, identifying all known oncogenes mutated in the set of interrogated cell lines, along with multiple new cancer dependent features not previously described.

Most recently, this project led to the discovery of PRMT5 as a novel dependency in cancers harboring co-deletion of MTAP and CDKN2A (Science 2016), a finding that will be further described in the lecture.