Summary of the 30th Pezcoller Symposium: Overcoming the innate resistance of cancer to therapy.

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The 30th Pezcoller Symposium entitled " Overcoming the Innate Resistance of Cancer Therapy" was held in Trento in June 2018 and was opened with the Enrico Mihich lecture by Harold Varmus, 1986 Nobel Laureate.
summary of the meeting made

The outstanding meeting held in Trento on June 25-26th 2018 marked the 30th anniversary of the annual Pezcoller Symposium. The meeting was focused on the innate resistance of cancer cells to therapy and the strategies that can be employed to overcome such resistance. Models as well as human data were utilized to understand the mechanistic underpinnings of resistance. Different approaches were proposed including generation of tumor models derived from embryonal stem cells, establishment of patient-derived xenografts (PDX) or organoids (PDO). Of particular interest was the concept of "mouse clinics" devoted to the study of individual patient tumor avatars in which drug resistance can be tested in a personalized manner. A brief overview of the salient findings that were presented is outlined below.

The Dr. Harold Varmus gave the opening lecture and focused on lung cancer. The development of non-small cell lung cancer (NSCLC) models confirmed that the relatively common finding of mutual exclusivity of mutations in lung cancer and melanoma holds true in mouse models. In fact, genetically engineered lung cancer cells do not even tolerate simultaneous mutations of KRAS and EGFR, even though these occur in human cancer, albeit rarely. Similarly, melanoma cells cannot survive the concomitant mutation of NRAS and BRAF. Dr. Varmus showed that using human embryonal stem cells they were able to generate pulmonary neuroendocrine cells and to transform them into small cell lung cancer (SCLC) cells through the dual inhibition of the RB and NOTCH oncogenes.

Dr Anton Berns showed that induction of Nuclear Factor I B (NFIB) and knock-out of E-Cadherin (CDH1) confer chromosomal instability and invasive potential *in vitro*. Importantly, NFIB positive tumors appear to be more sensitive to cisplatin. Dr. Berns also showed that *in vivo* models of pleural mesothelioma have been established through the suppression of NF2 and BRCA Associated Protein 1 (BAP1). BAP1 causes an epigenetic switch mediated by EZH2 and therefore BAP1 deficient mesotheliomas are more sensitive to PARP and EZH2 inhibitors. In animal models of mesothelioma the morphological appearance of the tumor depends on the gene that is enforced, possibly allowing the pathologist to predict sensitive versus resistant tumors with traditional light microscopy approaches.

While tyrosine kinase inhibitors are effective in non-small-cell lung cancers (NSCLCs) with epidermal growth factor receptor (EGFR) mutations, relapse typically occurs within 1 year of continuous treatment, along with a histologic change from NSCLC to small-cell lung cancer (SCLC) in a subset of the resistant cancers. The molecular changes associated with this transformation remain undefined. Dr. Poirier analyzed tumor samples and cell lines derived from resistant EGFR mutant patients and showed