The emergence of technological innovations has created the opportunity to envision new approaches to discover therapeutics at scale. We combined advances in high-content microscopy with arrayed CRISPR genome editing technologies and machine learning (ML) to build a rigorously controlled dataset enabling exploration of biology and chemistry at scale. Phenotypes from millions of perturbations in multiple cell types were embedded in a unified representation space and leveraged to accelerate discovery and reverse translation, ultimately yielding novel biological insights, and optimizing the advancement of lead molecular series through structure-activity relationships (SAR). Here, we demonstrate the capability of our platform to discover potential cancer therapeutics with distinct mechanisms of action. First, we describe the identification of a novel compound series that potentiates the effects of immunotherapy in syngeneic mouse models, producing complete responses and immunological memory, while also limiting peripheral inflammation. Specific novel chemical entities (NCEs) caused robust CD45 cell influx to the tumor microenvironment and significantly depleted T and immunosuppressive macrophages, thereby enhancing anti-tumor immunity. Strikingly, the same NCEs suppressed peripheral inflammation while sustaining elevated levels of intra-tumoral proinflammatory cytokines. Second, we highlight a novel and differentiated strategy to potentiate PAPR inhibitor response in homologous repair deficient (HRD) - negative or HR proficient ovarian cancers. NCEs altered the expression of genes within the DNA damage repair (DDR) network and cell cycle checkpoints to synergize with PAPR inhibition in vivo and re-sensitized a PARP-resistant patient-derived xenograft (PDX) model. Collectively, we believe future efforts on this platform and integration of various technological-ology across biology, chemistry, automation, data science, and engineering will ultimately modernize drug discovery and radically improve patient lives.

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**References**

