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Opinion Article

Phenotypic Drug Discovery in Acute Myeloid Leukemia

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DESCRIPTION

The discovery and development of effective drugs for cancer patients has shown limited clinical success as of Phase 1 trials. Due to the high failure rates of current drug development approaches, careful evaluation is required to better understand the factors that correlate or predict positive clinical outcomes. Here, we review approaches to preclinical drug development and perform a meta-analysis of 2918 clinical trials, including 466 unique drugs tested in Acute Myeloid Leukemia (AML) clinical trials. Our aim was to determine whether there are significant common preclinical characteristics that are ultimately associated with patient medication success or failure. We provide evidence-based recommendations for using phenotypic drug discovery over other drug discovery and development methods during preclinical development. Although our analysis was limited to AML, similar analyzes could benefit other tumor-specific drug discovery campaigns and inform basic discovery screens and platforms for other cancers. There is a possibility of improvement.

Developing new therapeutics from the lab bench to the patient bed is a major goal of drug discovery. Unfortunately, high turnover rates during clinical trials severely limit the number of drugs (called New Molecular Entities (NMEs)) that are approved by regulators and integrated into patient care. This limitation is most pronounced in oncology, where only 3.4% of clinically tested drugs are approved, while drug success rates for cardiovascular and metabolic diseases exceed 20%. To gain a more basic understanding of the factors contributing to this lack of success in oncology, we will assess the characteristics of successful oncology drugs to determine which factors in drug development predict better clinical outcomes. We focus on at least three different drug discovery platforms used to identify active ingredients. These include Targeted Drug Discovery (TDD), Phenotypic Drug Discovery (PDD), and Mechanism-Based Phenotypic Drug Discovery (MIPDD). Analyzes suggested that the use of different preclinical approaches correlated with the ultimate clinical outcome of the drug. However, these studies were limited to his 9-15 year drug development history prior to publication, and only approved NMEs were examined. Recognizing the value of these analyzes in understanding how outcomes in oncology drug development can be improved, we extend these paradigms to apply to both successful and successful drug studies, focused on Acute Myeloid Leukemia (AML). This focus allowed us to add depth to our analysis of a single cancer and to present a proof-of-principle of his AML that could be applied to other cancers.

AML is a malignant hematologic cancer defined by the accumulation of immature, non-functional myeloid progenitor cells in the bone marrow and peripheral blood. Disease initiation is associated with two classes of cell transformation. These events are thought to occur in hematopoietic stem cells and myeloid progenitors, which represent the top of the cellular hematopoietic hierarchy and are thought to give rise to transformed progenitor cells called Cancer Stem Cells (CSCs). There are thousands of known mutations and genetic aberrations in these two classes of transformation and patients with AML often acquire multiple aberrations, creating genetically distinct clonal subpopulations. These subpopulations continue to undergo genetic and epigenetic evolution that drives clonal diversification during disease progression. Through this evolutionary mechanism, CSCs contribute to the resurgence of drug resistance. This poses a major challenge to the current therapeutic landscape of AML and contributes to its poor survival rate of approximately 24%. The heterogeneity of the underlying disease biology also poses major challenges for drug discovery in AML, as it requires identification of effective drugs in multiple patient subtypes, a problem that does not occur in monogenic diseases. Although CSC was originally described in AML, additional studies on solid tumors such as breast, colon, and glioblastoma show his CSC-driven dynamics similar to those seen in AML disease. To date, AML remains the gold standard model for CSC dynamics, cancer biology, and drug resistance. This is important because many early findings in leukemia research show the potential for applying established concepts to other diseases.

In addition to heterobiology, AML has a long history of drug discovery, with the first drugs for AML approved in the mid-20th century and the latest in 2020. As a result, nearly 3000 clinical intervention studies have been conducted for drug development for AML. These trials are full of diversity and innovation, with

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both chemotherapeutic agents and targeted therapies spanning the list of approved NMEs and failed counterparts. An extensive timeline of approvals and failures covers the entire history of drug discovery, including his PDD peak from the 1960s to his 1970s and his TDD from the 1980s to the present. Taken together, these factors have selected AML as a model cancer to retrospectively review key features of early drug discovery and development success in oncology. PDD discovers compounds based on modulation of disease phenotypes and is not based on known or predetermined molecular targets. This biological mechanism-first and target-to-second approach enables the identification of new disease processes associated with cancer and avoids targeting with incomplete information or evidence of a cell-specific role. Common phenotypes evaluated in cancer drug discovery include cancer cell viability and growth arrest. These phenotypes were used in the discovery of cytarabine and daunorubicin, which have been standard chemotherapy drugs for treating AML for the past 50 years. Assays that detect compounds that modulate the phenotype of various diseases will enable the identification of a wider range of molecules. For example, because dysfunctional differentiation is a typical phenotype of AML, assays that measure the degree of differentiation are unique because they can be used to identify a broader spectrum of new chemical classes with potential clinical applications. This 'target-agnostic' approach is unique to PDD and has the advantage of capturing the polypharmacology of drugs.