【Grant-in-Aid for Scientific Research (S)】

Broad Section I

Title of Project： Development of novel therapeutic strategies for therapy-refractory leukemia

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Research Project Number: 20H05699 Researcher Number：00791972
Keyword：Acute myeloid leukemia, Acute lymphoblastic leukemia, CRISPR/Cas9 gene-editing tool

【Purpose and Background of the Research】

Adult acute leukemia is a devastating disease with a long-term survival rate of less than 40%. Why do some leukemias come back after chemo/radiotherapy? From genetic points of view, leukemia recurrence originates both at the cellular and organismal levels. At the cellular level, mutations in certain genes, such as *TP53* loss-of-function mutations, dictate poor response to chemotherapy. At the organismal level, intra- and inter-tumoral clonal heterogeneity in the genome, epigenome, transcriptome and/or proteome renders the eradication of leukemia cells by chemotherapy more challenging.

Recent progress in sequencing technologies helps unveiling a near complete picture of the leukemia genome. However, there are many unknowns as to 1) how mutated genes collaboratively function in leukemia development and progression; 2) how gene mutations affect sensitivity and resistance to drug treatment and 3) whether cancer cells with a specific mutation exhibit synthetic lethal relationships with a specific drug treatment.

Aims of this study are: to 1) identify drug targets for leukemias that exhibit poor prognosis, such as those harboring *TP53* mutations; 2) identify targets for novel combination chemotherapies and 3) to obtain the proof-of-concept evidence for developing drugs for molecules that we identify in aims 1) and 2).

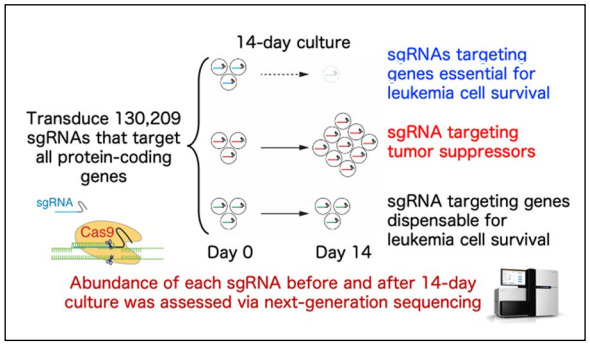

Figure 1. Genome-wide CRISPR/Cas9 screening

【Research Methods】

Genome-wide loss-of function screening using the CRISPR-Cas9 genome-editing technology is a powerful tool for functional genomics (Figure 1). However, identifying actionable targets has been challenging due, in part, to the complex genetic background of cell lines used for screening. To overcome this obstacle, we established mouse AML lines whose genetic backgrounds are well-defined (e.g. AML with *Trp53* mutations). We will perform genome-wide CRISPR/Cas9 screenings using these lines in the presence or absence of anti-AML drugs. We then elucidate molecular mechanisms behind the observed phenotypes using a series of molecular and genetic methods, including single-cell technologies, proteomics and PDX (patient-derived xenograft) models. Finally, we will determine whether the targets identified in aims 1/ 2 are amenable for drug development using the PROTAC (proteolysis targeting chimera) technology.

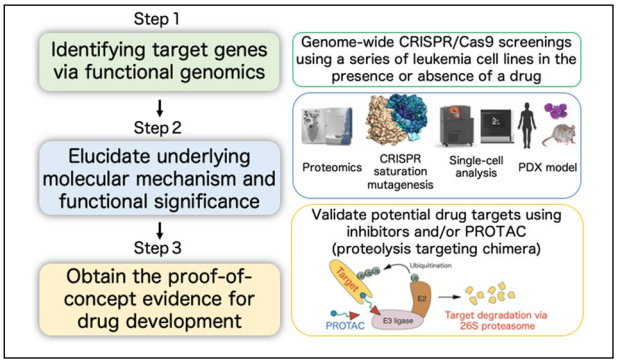

Figure 2. Overall design of the research project

【Expected Research Achievements and Scientific Significance】

We expect to elucidate molecular mechanisms underlying therapy-refractory leukemias and to identify new therapeutic targets to treat them. Our study is significant, because it may facilitate development of therapeutic strategies for therapy-refractory leukemias.

【Publications Relevant to the Project】

・ Masuda T et al. Transcription factors LRF and BCL11A independently repress expression of fetal hemoglobin. *Science*. 2016 Jan 15;351(6270):285-9.
・ Yamauchi T et al. Genome-wide CRISPR-Cas9 screen identifies leukemia-specific dependence on a pre-mRNA metabolic pathway regulated by DCPS enzyme. *Cancer Cell*. 2018 Mar 12;33(3):386-400.

【Term of Project】

FY2020-2024

【Budget Allocation】

151,300 Thousand Yen

【Homepage Address and Other Contact Information】

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