ELSEVIER

Blood 142 (2023) 1583–1584

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

617.ACUTE MYELOID LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

Identification of Novel Transcripts and Potential Therapeutic Targets for Acute Leukemia

Fumiya Wada, MD[1,2], *Shoya Kato*[1], *Shruti Bhagat*[1], *Shigeki Hirabayashi, MD PhD*[3], *Raku Son*[4], *Akiko Oguchi*[4], *Kazuhiro Takeuchi*[1], *Sho Sekito*[1], *Tomoya Hirai*[4], *Zhiwei Zhang*[1,5], *Yoshihito Horisawa, MD*[2], *Makoto Iwasaki, MDPhD*[6], *June Takeda, MD*[2], *Junya Kanda*[7], *Takashi Sakamoto*[2], *Kotaro Shirakawa, MD PhD*[8], *Akifumi Takaori-Kondo, MDPhD*[7], *Yasuhiro Murakawa*[1,4,9]

[1] ASHBi Institute for the Advanced Study of Human Biology, Kyoto University, Kyoto, Japan
[2] Department of Hematology and Oncology, Graduate School of Medicine, Kyoto University, Kyoto, Japan
[3] Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan
[4] RIKEN-IFOM Joint Laboratory for Cancer Genomics, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan
[5] Department of Human Genetics, Faculty of Medicine and Health Science, McGill University, Montreal, Canada
[6] Department of Hematology and Oncology, Graduate School of Medicine, Kyoto University, Nara, Japan
[7] Department of Hematology and Oncology, Graduate School of Medicine, Kyoto University, Kyoto, Japan
[8] Department of Hematology and Oncology, Graduate School of Medicine, Kyoto University, Kyoto, Japan
[9] IFOM ETS - the AIRC Institute of Molecular Oncology, Milan, Italy

Acute leukemia is a heterogenous disease with many genomic scars. Recent advances in targeted therapy and immunotherapy have improved the prognosis of this disease. However, prognosis still remains poor, and the identification of novel leukemia-specific transcripts may provide new strategies for leukemia therapy. We developed a novel long-read transcriptome method for sequencing full-length RNAs by directly capturing the 5′-end cap structures and the 3′-end poly(A)-tails of individual RNA molecules. We applied this method to bone marrow samples with various acute leukemias, including acute myeloid leukemia, acute lymphoid leukemia, and other rare types of acute leukemia. We covered full-length poly(A)+ RNAs with an average length distribution of over 3,000 bp, a much longer size distribution than previously reported. This not only led to the discovery of a wide array of uncharacterized transcript isoforms of known genes, but also to the discovery of 1,903 novel genes that are not annotated in the current human gene database. We also found that more than 60% of these new human genes were single exon genes and that many of them emerged from primates. This implicates that these new genes may contribute to human-specific leukemia biology. In addition, among these new human genes, 485 genes were predicted to have the potential to encode putative proteins using a GeneMarkS-T program. A fraction of new genes identified in this study were highly leukemia specific as shown by bulk CAGE-seq analysis of over 100 blood tumor samples and by single-cell RNA sequencing analysis of more than 300,000 bone marrow cells from leukemia patients, highlighting their potential as useful biomarkers and novel therapeutic targets. In sum, we constructed a comprehensive atlas of full-length RNA molecules in acute leukemia and identified a large number of uncharacterized ones. Our study provides a versatile framework for exploring novel transcripts and future therapeutic strategies in human diseases.

Disclosures Kanda: *Janssen Pharmaceutical K.K.:* Honoraria; *CHUGAI PHARMACEUTICAL Co., Ltd.:* Honoraria; *Sanofi K.K.:* Honoraria; *Megakaryon Co:* Consultancy; *AbbVie Inc.:* Honoraria; *asclepia:* Honoraria; *MSD K.K.:* Honoraria; *NIPPON KAYAKU CO. LTD.:* Honoraria; *CSL Behring K.K.:* Honoraria; *Otsuka Pharmaceutical Co., Ltd.:* Honoraria; *Nippon Shinyaku Co., Ltd.:* Honoraria; *Amgen Pharma Inc.:* Honoraria; *Takeda Pharmaceutical Company Limited:* Honoraria; *ASAHI KASEI PHARMA CORPORATION:* Honoraria; *Novartis Pharma K.K.:* Honoraria; *Bristol-Myers Squibb Co:* Honoraria; *Wakunaga Pharmaceutical Co., Ltd.:* Honoraria; *Kyowa Kirin Co., Ltd.:* Honoraria; *Astellas Pharma Inc.:* Honoraria; *DAIICHI SANKYO Co., Ltd.:* Honoraria; *TERUMO CORPORATION:* Honoraria; *CHUGAIIGAKU CO., LTD.:* Honoraria; *Fujimoto Pharmaceutical Corporation.:* Honoraria; *Eisai:* Research Funding. **Takaori-Kondo:** *Kinshikourainin jin:* Other; *Ohara Pharmaceutical:* Other; *Eisai:* Other; *Chugai Pharmaceutical:* Other; *Kyowa Kirin:* Other: Subsidies ; *Takeda Pharmaceutical:* Other: Subsidies; *Pharma Essentia Japan:* Research Funding; *DKS Co. Ltd.:* Research Funding; *COGNANO:* Research Funding; *Ono Pharmaceutical:* Research Funding; *Megakaryon:* Honoraria; *Otsuka Pharmaceutical:* Honoraria, Other: Subsidies ; *Janssen Pharmaceutical K.K:* Honoraria; *Bristol*

Myers Squibb: Honoraria; *Nippon Shinyaku Co., Ltd.:* Honoraria, Other: Subsidies; *AbbVie:* Other; *Shionogi Pharma:* Other; *ASAHI KASEI PHARMA:* Other. **Murakawa:** *Revorf:* Current equity holder in publicly-traded company.

https://doi.org/10.1182/blood-2023-188008