



Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Kosasih, HJ;Healey, G;Brennan, MS;Bjelosevic, S;Sadras, T;Jalud, FB;Ibnat, T;Ng, AP;Mayoh, C;Mao, J;Tax, G;Ludlow, LEA;Johnstone, RW;Herold, MJ;Khaw, SL;de Bock, CE;Ekert, PG

Title:

A novel MYB::PAIP1 oncogenic fusion in pediatric blastic plasmacytoid dendritic cell neoplasm (BPDCN) is dependent on BCL2 expression and is sensitive to venetoclax

Date:

2024-02-01

Citation:

Kosasih, H. J., Healey, G., Brennan, M. S., Bjelosevic, S., Sadras, T., Jalud, F. B., Ibnat, T., Ng, A. P., Mayoh, C., Mao, J., Tax, G., Ludlow, L. E. A., Johnstone, R. W., Herold, M. J., Khaw, S. L., de Bock, C. E. & Ekert, P. G. (2024). A novel MYB::PAIP1 oncogenic fusion in pediatric blastic plasmacytoid dendritic cell neoplasm (BPDCN) is dependent on BCL2 expression and is sensitive to venetoclax. *Hemasphere*, 8 (2), <https://doi.org/10.1002/hem3.1>.



Persistent Link:

<https://hdl.handle.net/11343/344472>

License:

CC BY

A novel MYB::PAIP1 oncogenic fusion in pediatric blastic plasmacytoid dendritic cell neoplasm (BPDCN) is dependent on BCL2 expression and is sensitive to venetoclax

Hansen J. Kosasih^{1,2}  | Gerry Healey^{3,4} | Margs S. Brennan^{3,5} |
 Stefan Bjelosevic^{6,7} | Teresa Sadras^{6,7} | Fatimah B. Jalud⁶ | Tasnia Ibat⁶ |
 Ashley P. Ng^{3,7,8} | Chelsea Mayoh² | Jie Mao² | Gabor Tax^{2,9} |
 Louise E. A. Ludlow^{1,10} | Ricky W. Johnstone^{6,7} | Marco J. Herold^{3,4,11,12} |
 Seong L. Khaw¹ | Charles E. de Bock^{2,13} | Paul G. Ekert^{2,6,7,9} 

Correspondence: Paul G. Ekert (pekert@ccia.org.au)

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare and aggressive hematological malignancy with a median survival of 14 months (with a survival window of 6–28 months) from diagnosis.¹ BPDCN is derived from the precursors of plasmacytoid dendritic cells² and is recognized as an independent entity of myeloid neoplasms in the 2016 updated World Health Organization classification.³ Although BPDCN predominantly affects adults with a median age in the 70s, cases involving younger adults and children have been reported. Unique clinical presentations of BPDCN include skin infiltration, and at the molecular level, BPDCN is characterized by an overexpression of CD123 (IL-3Ra).⁴ However, the pathogenesis of BPDCN remains incompletely understood. Here, we report a case of pediatric BPDCN with a novel MYB::PAIP1 rearrangement that is sufficient and necessary to drive leukemogenesis *in vivo* using a syngeneic murine transplant model.

The patient, a 10-year-old girl, presented with lethargy, generalized aches and a tender, violaceous skin lesion, and was found to have marked leukocytosis (white cell count $90 \times 10^9/L$) comprised mainly of circulating blasts. Bone marrow aspirate demonstrated a predominant population (85%) of small-to-medium-sized blasts without lineage-defining features. Lumbar puncture demonstrated no cerebrospinal fluid pleocytosis, and no blasts on cytopspin. The bone marrow blast

immunophenotype was CD45^{dim}, CD58+/CD56+/CD4+/CD123+. The karyotype was complex with loss of chr13, an unbalanced translocation between chr5q and chr6q, and derivative chr20 that matches previous aneuploidies (losses) of chromosomes 5, 6, and 13 reported in BPDCN.⁵ Microarray analysis showed deletion of chromosomes 6q23.3 (involving exons 9–16 of MYB), 7p12.2 (including IKZF1), and 9p21.3 (including CKDN2A/2B). Whilst BPDCN is classified as a myeloid neoplasm, there are features, such as IKZF1 and CDKN2A deletions, that are shared with lymphoid neoplasms.⁶ The patient was treated following the Interfant-06 protocol, selected based on inclusion on this protocol of myeloid-directed elements on a predominantly acute lymphoblastic leukemia (ALL)-based backbone, and previous reports of the superior efficacy of ALL-based compared to acute myeloid leukemia-based therapy in pediatric BPDCN.⁷ The patient had an excellent response to therapy and was in complete morphological remission at the end of induction therapy. She remained in remission and continued therapy following the same protocol until the end of the MARMA (methotrexate, ara-C, 6-mercaptopurine, PEG-asparaginase) block. Due to the lack of a validated assay for quantifying minimal residual disease and thus confirming the depth of response and high risk of relapse associated with this disease, the patient underwent matched sibling donor hematopoietic stem cell transplant

¹Murdoch Children's Research Institute, Parkville, Victoria, Australia

²Children's Cancer Institute, Lowy Cancer Research Centre, UNSW Sydney, Kensington, New South Wales, Australia

³The Walter and Eliza Hall Institute of Medical Research, Parkville, Victoria, Australia

⁴Olivia Newton-John Cancer Research Institute, Heidelberg, Victoria, Australia

⁵Department of Medicine Huddinge, Centre for Haematology and Regenerative Medicine, Karolinska Institutet, Stockholm, Sweden

⁶Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

⁷The Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, Victoria, Australia

⁸Department of Biology, The University of Melbourne, Parkville, Victoria, Australia

⁹School of Clinical Medicine, UNSW Medicine & Health, UNSW Sydney, Sydney, New South Wales, Australia

¹⁰Department of Paediatrics, University of Melbourne, Parkville, Victoria, Australia

¹¹Department of Medical Biology, University of Melbourne, Parkville, Victoria, Australia

¹²School of Cancer Medicine, La Trobe University, Heidelberg, Victoria, Australia

¹³School of Women's and Children's Health, UNSW Sydney, Kensington, New South Wales, Australia

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2024 The Authors. *HemaSphere* published by John Wiley & Sons Ltd. on behalf of European Hematology Association.

(HSCT), with busulfan, fludarabine, and thiotepa conditioning. She had a relatively uncomplicated posttransplant course and remains in complete remission with good donor chimerism 4 years post-HSCT.

To further characterize this case at the molecular level, we performed RNA-sequencing (RNA-seq) on the diagnostic sample and used ALLSorts, a machine learning classifier of subtypes of B-cell ALL (B-ALL).⁸ This analysis revealed that this case of BPDCN was closely related to the BCL2/MYC subtype group, characterized by elevated BCL2 and MYC expression resulting from translocations linking the immunoglobulin locus with either BCL2 or MYC⁹ (Supporting Information S2: Figure 1A). This is consistent with reported upregulation of BCL2 and MYC expression in BPDCN.^{10,11} Using Arriba,¹² a fusion detection algorithm, a novel rearrangement between MYB (6q23.3) and PAIP1 (5p12) was identified (Figure 1A and Supporting Information S4: Table 1). This novel rearrangement was confirmed by reverse-transcriptase PCR across the breakpoint and Sanger sequencing (Figure 1A,B). The transcription factor MYB is essential for hematopoiesis and is a key regulator of MYC and BCL2.¹³ Different MYB rearrangements have previously been reported in 5/5 pediatric and 5/9 adult BPDCN cases.¹⁴ On the other hand, PAIP1 plays an important role in the regulation of protein translation by interacting with other co-activators to promote messenger RNA circularization that initiates the translation,¹⁵ and its upregulation was reported in several types of solid cancers.^{16,17} This novel rearrangement, between exon 8 of MYB and exon 3 of PAIP1, resulted in an in-frame MYB::PAIP1 fusion, consisting of the MYB DNA-binding domain, but lacking part of the MYB transcriptional activation domain and all of the negative regulatory domain, while also includes the MIF4G domain of PAIP1 and excludes some regions of PAIP1 that interact with translational initiation co-activators (Figure 1C).

To investigate the oncogenic potential of this novel fusion, we cloned the fusion from cDNA derived from the tumor into a retroviral expression plasmid MSCV-IRES-GFP (MIG). The fusion was transduced into unsorted murine E14.5 fetal liver cells (FLCs) from humanized MCL1 (huMCL1) mice. The huMCL1 mouse strain (human MCL1 gene knocked -into the murine Mcl1 locus) is phenotypically indistinguishable from wild-type C57BL/6 (WT).¹⁸ The strain was previously established to allow more precise testing of efficacy and tolerability of MCL1 inhibitors because of their higher affinity (up to sixfold) for human MCL1 compared to the mouse protein.¹⁸ Transduced cells were transplanted into sublethally γ -irradiated syngeneic WT mice, while empty MIG vector-bearing transduced cells (empty vector [EV]) were separately transplanted as controls, as previously described.¹⁹ Mice transplanted with cells expressing the MYB::PAIP1 fusion succumbed to a hematological malignancy with a median survival of 108 days in two independent cohorts, while EV-transplanted mice did not develop the disease ($p < 0.0001$) (Figure 1D). MYB::PAIP1-transplanted mice had enlarged spleens infiltrated with blast cells compared to the control mice (median 1.84% of body weight vs. 0.20%, $p < 0.0001$) (Figure 1E and Supporting Information S2: Figure 1B). Fusion-bearing mice were anemic, and some had higher white blood count (WBC) compared to controls (median 16.57×10^9 vs. 10.07×10^9 cells/L, $p = 0.065$) (Supporting Information S2: Figure 1B). This observation was in accordance with the characteristics of BPDCN patients in whom anemia is often observed, while the WBCs are often within the normal range.²⁰ There was a marked infiltration of the bone marrow with a homogenous population of monocytic blast cells in the fusion-bearing mice (Figure 1E). Consistent with this observation, the MYB::PAIP1 fusion cells were exclusively GR1+CD11b- or GR1+CD11b+, and with relevance to BPDCN, also expressed higher levels of CD123 compared to the EV control cells (Figure 1F,G and Supporting Information S2: Figure 1C). To determine whether

expression of the truncated form of MYB in the absence of the 3' PAIP1 partner was sufficient to drive disease, an independent syngeneic mouse model experiment using FLCs from WT mice was undertaken comparing the leukemogenic potential of MYB portion present in the fusion (called MYB-trunc) with MYB::PAIP1. Only mice bearing the MYB::PAIP1 fusion, and not the MYB-trunc, succumbed to disease, with the MYB::PAIP1 disease also transplantable into secondary recipients resulting in reduced disease latency and demonstrating the presence of leukemic stem cells ($p = 0.0177$) (Supporting Information S3: Figure 1D). This finding indicates that PAIP1 portion is important to the function of this novel fusion. We speculate the MIF4G domain might recruit co-factors into a transcriptional complex that leads to deregulated gene expression.

We next assessed the transcriptomic profile of the MYB::PAIP1 cells and the EV cells harvested from the bone marrow (BM) of the huMCL1 cohorts. The cells were sorted for B220-/CD19- to compare a similar population of cells. Differential gene expression analyses revealed alterations in expression of genes (*Bcl2*, *Il3ra* that encodes for CD123, *Sox4*, *Igll1*, *Egfr*, *Irf4*, *Cxcr3*) that typically dysregulated in BPDCN (Figure 2A).²¹ Upregulation of *Myc* (Log FC 1.60, $p < 0.001$) and *Bcl2* (Log FC 1.73, $p < 0.001$) in the fusion-bearing cells were in concordance with the ALLSorts classification of the diagnostic patient sample (Figure 2A). Gene set enrichment analysis (GSEA) was enriched for MYB target genes, suggesting that MYB-dependent targets are critical to this model system (Figure 2B) and consistent with MYB-activating events seen in younger cases of BPDCN.¹⁴ GSEA also showed positive correlations with early to late progenitors of hematopoiesis, and negative correlation with mature hematopoietic cells in MYB::PAIP1 cells (Supporting Information S3: Figure 1E), implying the expression of this fusion blocked normal hematopoietic differentiation, in accordance with the observed morphology of the cells (Figure 1E). Importantly, the GSEA also showed positive correlations with MYC targets and E2F targets in the fusion-bearing cells, consistent with oncogene-associated signatures in BPDCN patients (Figure 2B and Supporting Information S3: Figure 1F).²¹

We then validated the upregulation of *Myc* and *Bcl2* at the protein level, with MYB::PAIP1 cells having higher expression of MYC and BCL2 compared to the EV-bearing cells. There was no significant difference in the expression of the other antiapoptotic proteins (BCL2L1, MCL1) (Figure 2C). On this basis, we hypothesized that the fusion-bearing cells would be uniquely sensitive to the BCL2 inhibitor venetoclax but not the MCL1 inhibitor S63845. The use of huMCL1 model allowed us to accurately assess the sensitivity of the cells to S63845, as we have previously shown.¹⁸ The MYB::PAIP1 fusion-bearing cells were more sensitive to venetoclax (half-maximal inhibitory concentration [IC₅₀] 1.032 nM) compared to S63845 (IC₅₀ 456.7 nM) (Figure 2D). The combination of S63845 and venetoclax was not synergistic in MYB::PAIP1 cells upon 24 h exposure, suggesting that these cells were acutely sensitive to BCL2 inhibition *in vivo* (Figure 2E and Supporting Information S3: Figure 1G). It is possible that the fusion-bearing cells could become sensitive to MCL1 or BCL2L1 inhibition after selection in venetoclax. Taken together, these data support the leukemogenic potential of the MYB::PAIP1 fusion through increased BCL2 expression that can be acutely exploited therapeutically via the BH3-mimetic venetoclax in this murine model system.

There is currently no standardized therapy for pediatric BPDCN patients, with most patients receiving high-risk ALL treatment protocols. Tagraxofusp, a CD123-directed antibody conjugate, was recently approved for the treatment of BPDCN, but serious adverse events were common in adults and the clinical efficacy was

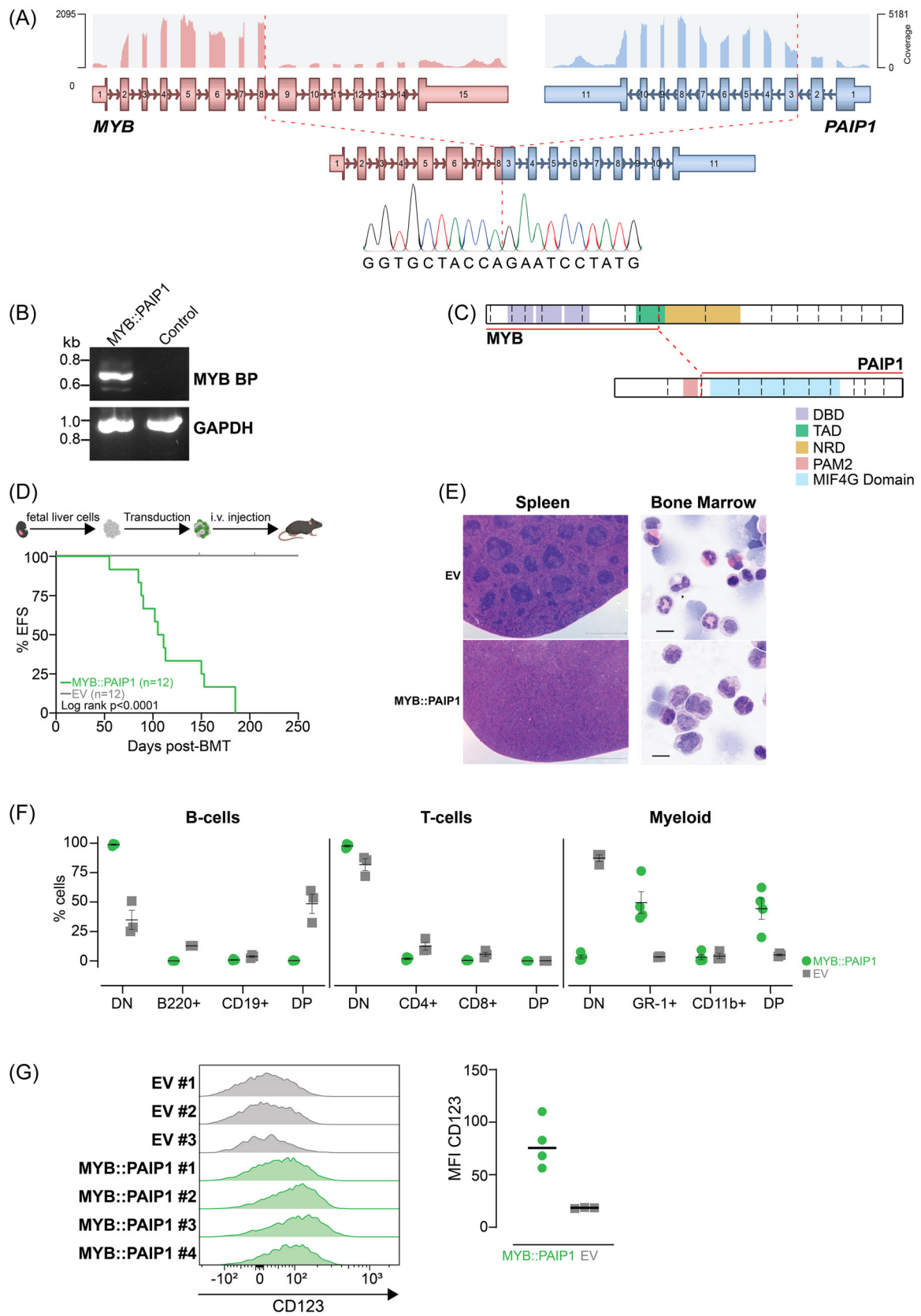


FIGURE 1 (See caption on next page).

FIGURE 1 Novel MYB::PAIP1 fusion is sufficient and necessary to drive leukemia in vivo. (A) RNA-sequencing analysis identified a novel rearrangement between MYB (6q23.3) and PAIP1 (5p12), resulting in an in-frame MYB::PAIP1 fusion. Image shown was modified from Arriba. Sanger sequencing result of the breakpoint region was shown. (B) Reverse transcription-polymerase chain reaction of the patient with MYB::PAIP1 fusion and control patient sample. (C) Schematic illustrating the domains retained in the MYB and PAIP1 portions of the fusion. (D) Schematic showing the syngeneic mouse model used to determine the leukemogenic potential of MYB::PAIP1 fusion. Created with BioRender.com, and a Kaplan–Meier survival curve of mice receiving huMCL1 hematopoietic stem cells (HSCs) expressing the MYB::PAIP1 fusion ($n = 12$) or empty vector (EV) control ($n = 12$). There were two non-leukemic related deaths in the EV control as indicated by ticks. (E) Representative images of hematoxylin and eosin staining of spleens (left panel) and bone marrow (BM) cytopspins (right panel) from EV and MYB::PAIP1 mice. Scale bar of 200 μm on spleen histology and 10 μm on BM cytopspins were shown. (F) Immunophenotyping analysis of the MYB::PAIP1 (four independent mice) and the EV cells (three independent mice). Lines represent mean values (\pm SEM). (G) Flow cytometry analysis of cell surface CD123 expression in MYB::PAIP1 (four independent mice) and the EV splenocytes (three independent mice) gated on single cells, viability, and GFP+, and the associated median fluorescence intensity (MFI) plot of this staining. Median values of MFI were shown as lines. BMT, bone marrow transplant; DBD, DNA-binding domain; DN, double negatives; DP, double positives; EFS, event-free survival; HSC, hematopoietic stem cell; MIF4G, middle domain of eukaryotic initiation factor 4G; NRD, negative regulatory domain; PAM2, PABPC1-interacting motif-2; TAD, transcription activation domain.

disappointing.²² Our data suggest that in MYB-fusion-positive BPCDN cases, venetoclax may represent a possible targeted therapy since the fusion drives BCL2 expression, at least in our model. Indeed, the successful use of venetoclax has been reported in adult cases of BPCDN^{23,24} and is also being investigated in a current clinical

trial combining venetoclax with chemotherapy (HCVAD) and CD123-targeted therapy in adults.²⁵ One case report also mentioned the use of venetoclax combined with hyper-CVAD, in an 11-year-old boy who had relapsed BPCDN, where complete response was achieved.²⁶ Our study provides a strong molecular link and rationale for further

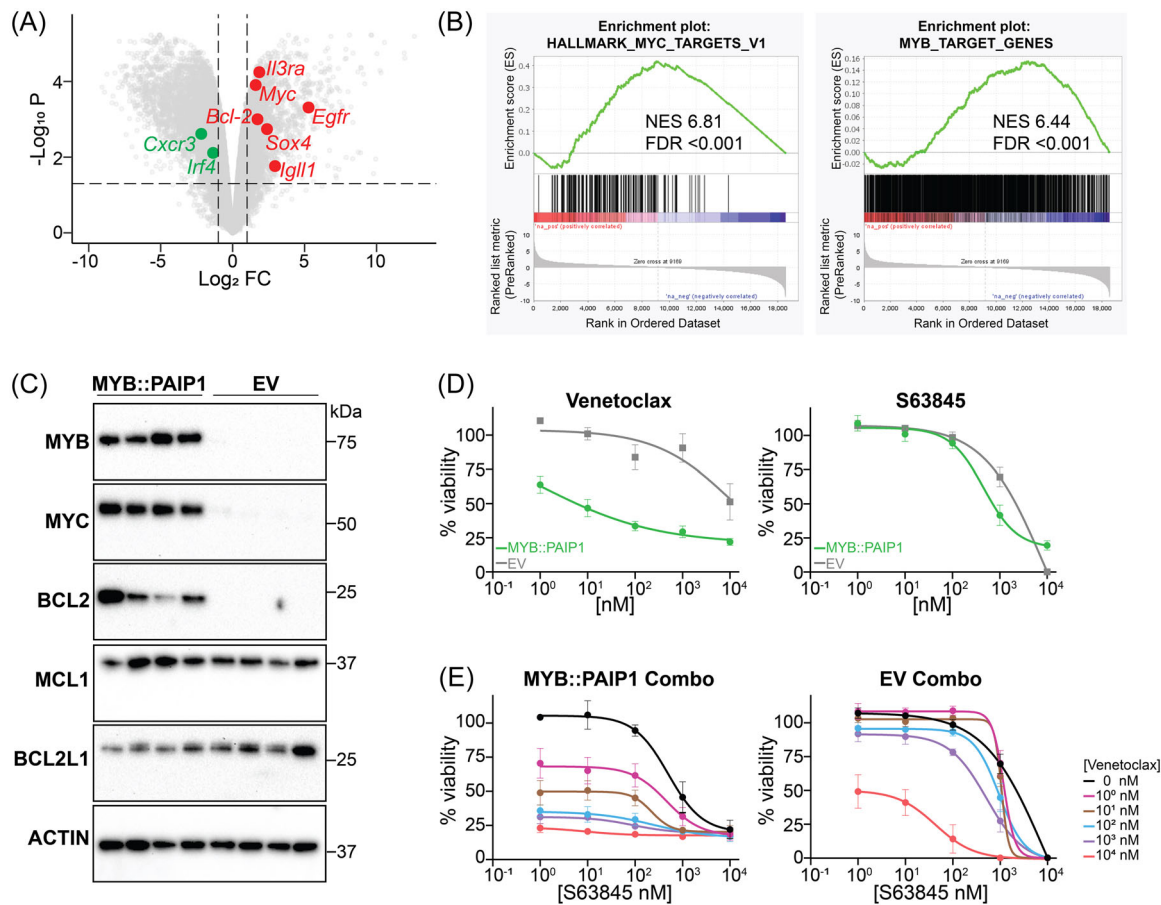


FIGURE 2 MYB::PAIP1 cells are dependent on BCL2 expression and are sensitive to venetoclax. (A) Volcano plot of differentially expressed genes between MYB::PAIP1 ($n = 3$) and empty vector (EV) control cells ($n = 3$). (B) Gene set enrichment analysis (GSEA) from the same RNA-sequencing experiment shows significant enrichment for hallmark MYC and MYB targets in MYB::PAIP1 cells. (C) Western blot analysis of MYB::PAIP1 and EV-bearing bone marrow cells for MYB, MYC, BCL2, MCL1, BCL2L1, and ACTIN loading control. (D) Dose response for MYB::PAIP1 cells treated with the BH3-mimetic venetoclax, and the MCL1 inhibitor S63845 after 24 h exposure. All treatments were done in technical duplicates, with three biological replicates. The cell viability data was normalized against the dimethyl sulfoxide-treated cells. Mean (\pm SEM) was shown. (E) Dose response for the combination of venetoclax and S63845 in MYB::PAIP1- and EV-bearing cells. Mean (\pm SEM) was shown. FDR, false discovery rate; NES, normalized enrichment score.

investigations of the clinical use of venetoclax in MYB-fusion-driven BPCDN that has the potential to improve the outcome of pediatric BPCDN patients.

ACKNOWLEDGMENTS

The authors thank the Children's Cancer Centre Tissue Bank of Murdoch Children's Research Institute for the patient samples, the Translational Genomics Unit of Victorian Clinical Genetics Services, the Murdoch Children's Research Institute flow cytometry and imaging service, the Peter Mac Animal Core, and Walter and Eliza Hall Institute bioservices facilities for technical assistance. Tumor samples and coded data were supplied by the Children's Cancer Centre Biobank at the Murdoch Children's Research Institute and The Royal Children's Hospital (<https://www.mcri.edu.au/research/projects/childrens-cancer-centre-biobank>). The establishment and running of the Children's Cancer Centre Biobank is made possible through generous support by Cancer In Kids @ RCH (<https://www.cika.org.au>), the Royal Children's Hospital Foundation, and the Murdoch Children's Research Institute. We acknowledge Dhanya Menon, Rejhan Idrizi, and the Centre for Advanced Histology & Microscopy at the Peter MacCallum Cancer Centre for their assistance with histology.

AUTHOR CONTRIBUTIONS

Hansen J. Kosasih and Paul G. Ekert conceived and designed the study. Hansen J. Kosasih performed all the experiments, analyzed the data, and wrote the manuscript. Gerry Healey, Margs S. Brennan, and Stefan Bjelosevic assisted in vivo experiments. Teresa Sadras, Fatimah B. Jalud, and Tasnia Ibnat performed the cytopins and imaged the tissue histologies. Ashley P. Ng imaged the cytopins and provided the assessments on the cell morphology. Jie Mao and Gabor Tax assisted in the analysis of the drug synergism experiment. Chelsea Mayoh and Jie Mao assisted in GSEA analysis. Ricky W. Johnstone and Marco J. Herold contributed to the conception and conduct of in vivo experiments. Louise E. A. Ludlow and Seong L. Khaw contributed to the identification of eligible samples and the collation and presentation of clinical data. Paul G. Ekert and Charles E. de Bock assisted in the analysis of experimental data and the writing of the manuscript. All authors contributed to the manuscript preparation.

CONFLICT OF INTEREST STATEMENT

Paul G. Ekert and Seong L. Khaw are recipients of a share in milestone and royalty payments paid to the Walter and Eliza Hall Institute of Medical Research for the development of venetoclax.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the Supporting Information of this article. The breakpoint sequence and genomic locations of the novel MYB::PAIP1 fusion are provided in Supplementary Table 1 as part of the Arriba output. Detailed information can be obtained from the corresponding author upon reasonable request.

FUNDING

This work is supported by National Health and Medical Research Council Grants (1140626 to P. G. E.), and a SCOR Grant (7015-18 to P. G. E. and S. L. K.) from the Leukemia and Lymphoma Society. S. L. K. and H. J. K. were supported by the Children's Cancer Foundation and the Department of Health and Human Services through the Victorian Cancer Agency (Project 134). M. S. B. is supported by the Cancer Council Victoria Postdoctoral Fellowship and Swedish

Cancer Society (21 0355 PT). T. S. is supported by a Gilead Research Scholars Award and funding from the Kid's Cancer Project Mid-Career Fellowship. A. P. N. is supported by a grant-in-aid from Cancer Council Victoria, National Stem Cell Foundation of Australia Metcalf Prize for Stem Cell Research, Alessandra's Fight Against Leukaemia (GoFundMe), and a Leukaemia Foundation Breakthrough Fellowship. R. J. W. is supported by a project grant from Cancer Council Victoria, an investigator grant from the NHMRC, and a grant from the Kids' Cancer Project. We also acknowledge the support of Perpetual Trustees and the Samuel Nissen Foundation.

ORCID

Hansen J. Kosasih  <http://orcid.org/0000-0002-0428-6195>

Paul G. Ekert  <http://orcid.org/0000-0002-2976-8617>

SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

REFERENCES

1. Abdallah M, McCullough K, Ilyas R, et al. Abnormal karyotype is an independent predictor of inferior survival in blastic plasmacytoid dendritic cell neoplasm (BPDCN). *Blood Cancer J.* 2023;13(1):35. doi:10.1038/s41408-023-00812-y
2. Villani AC, Satija R, Reynolds G, et al. Single-cell RNA-seq reveals new types of human blood dendritic cells, monocytes, and progenitors. *Science.* 2017;356(6335):eaah4573. <https://pubmed.ncbi.nlm.nih.gov/28428369/>
3. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood.* 2016;127(20):2391-2405. doi:10.1182/blood-2016-03-643544
4. Pagano L, Valentini CG, Grammatico S, Pulsoni A. Blastic plasmacytoid dendritic cell neoplasm: diagnostic criteria and therapeutical approaches. *Br J Haematol.* 2016;174(2):188-202. doi:10.1111/bjh.14146
5. Leroux D. CD4(+), CD56(+) DC2 acute leukemia is characterized by recurrent clonal chromosomal changes affecting 6 major targets: a study of 21 cases by the Groupe Francais de Cytogenetique Hematologique. *Blood.* 2002;99(11):4154-4159. doi:10.1182/blood.v99.11.4154
6. Bastidas Torres AN, Cats D, Mei H, et al. Whole-genome analysis uncovers recurrent IKZF1 inactivation and aberrant cell adhesion in blastic plasmacytoid dendritic cell neoplasm. *Genes Chromosomes Cancer.* 2020;59(5):295-308. doi:10.1002/gcc.22831
7. Jegalian AG, Buxbaum NP, Facchetti F, et al. Blastic plasmacytoid dendritic cell neoplasm in children: diagnostic features and clinical implications. *Haematologica.* 2010;95(11):1873-1879. doi:10.3324/haematol.2010.026179
8. Schmidt B, Brown LM, Ryland GL, et al. ALLSorts: an RNA-Seq subtype classifier for B-cell acute lymphoblastic leukemia. *Blood Adv.* 2022;6(14):4093-4097. doi:10.1182/bloodadvances.2021005894
9. Gu Z, Churchman ML, Roberts KG, et al. PAX5-driven subtypes of B-progenitor acute lymphoblastic leukemia. *Nat Genet.* 2019;51(2):296-307. doi:10.1038/s41588-018-0315-5
10. Montero J, Stephansky J, Cai T, et al. Blastic plasmacytoid dendritic cell neoplasm is dependent on BCL2 and sensitive to venetoclax. *Cancer Discov.* 2017;7(2):156-164. doi:10.1158/2159-8290.CD-16-0999
11. Sapienza MR, Fuligni F, Agostinelli C, et al. Molecular profiling of blastic plasmacytoid dendritic cell neoplasm reveals a unique pattern and suggests selective sensitivity to NF- κ B pathway inhibition. *Leukemia.* 2014;28(8):1606-1616. doi:10.1038/leu.2014.64
12. Uhrig S, Ellermann J, Walther T, et al. Accurate and efficient detection of gene fusions from RNA sequencing data. *Genome Res.* 2021;31(3):448-460. doi:10.1101/gr.257246.119

13. Ramsay RG, Gonda TJ. MYB function in normal and cancer cells. *Nat Rev Cancer*. 2008;8(7):523-534. doi:10.1038/nrc2439
14. Suzuki K, Suzuki Y, Hama A, et al. Recurrent MYB rearrangement in blastic plasmacytoid dendritic cell neoplasm. *Leukemia*. 2017;31(7):1629-1633. doi:10.1038/leu.2017.101
15. Martineau Y, Derry MC, Wang X, et al. Poly(A)-binding protein-interacting protein 1 binds to eukaryotic translation initiation factor 3 to stimulate translation. *Mol Cell Biol*. 2008;28(21):6658-6667. doi:10.1128/MCB.00738-08
16. Piao J, Chen L, Jin T, Xu M, Quan C, Lin Z. Paip1 affects breast cancer cell growth and represents a novel prognostic biomarker. *Hum Pathol*. 2018;73:33-40. doi:10.1016/j.humpath.2017.10.037
17. Wang Y, Piao J, Wang Q, et al. Paip1 predicts poor prognosis and promotes tumor progression through AKT/GSK-3 β pathway in lung adenocarcinoma. *Hum Pathol*. 2019;86:233-242. doi:10.1016/j.humpath.2018.11.017
18. Brennan MS, Chang C, Tai L, et al. Humanized Mcl-1 mice enable accurate preclinical evaluation of MCL-1 inhibitors destined for clinical use. *Blood*. 2018;132(15):1573-1583. doi:10.1182/blood-2018-06-859405
19. Kosasih HJ, Davidson NM, Bjelosevic S, et al. MLL-TFE3: a novel and aggressive KMT2A fusion identified in infant leukemia. *Blood Adv*. 2020;4(19):4918-4923. doi:10.1182/bloodadvances.2020002708
20. Garnache-Ottou F, Vidal C, Biichlé S, et al. How should we diagnose and treat blastic plasmacytoid dendritic cell neoplasm patients? *Blood Adv*. 2019;3(24):4238-4251. doi:10.1182/bloodadvances.2019000647
21. Togami K, Chung SS, Madan V, et al. Sex-biased ZRSR2 mutations in myeloid malignancies impair plasmacytoid dendritic cell activation and apoptosis. *Cancer Discov*. 2022;12(2):522-541. doi:10.1158/2159-8290.CD-20-1513
22. Pemmaraju N, Lane AA, Sweet KL, et al. Tagraxofusp in blastic plasmacytoid dendritic-cell neoplasm. *N Engl J Med*. 2019;380(17):1628-1637. doi:10.1056/NEJMoa1815105
23. Agha ME, Monaghan SA, Swerdlow SH. Venetoclax in a patient with a blastic plasmacytoid dendritic-cell neoplasm. *N Engl J Med*. 2018;379(15):1479-1481. doi:10.1056/NEJMc1808354
24. Beziat G, Ysebaert L, Gaudin C, Steinmeyer Z, Balardy L. Venetoclax to treat relapsed blastic plasmacytoid dendritic cell neoplasm: a case-report and review of literature. *Leuk Res*. 2019;85:106199. doi:10.1016/j.leukres.2019.106199
25. Pemmaraju N, Wilson NR, Garcia-Manero G, et al. Characteristics and outcomes of patients with blastic plasmacytoid dendritic cell neoplasm treated with frontline HCVAD. *Blood Adv*. 2022;6(10):3027-3035. doi:10.1182/bloodadvances.2021006645
26. Ablal D, Abboud MR, Noun D, Tarek N, Pemmaraju N. Hyper-CVAD combined with venetoclax for relapsed pediatric blastic plasmacytoid dendritic cell neoplasm (BPDCN): a case report and literature review. *Leuk Res Rep*. 2022;17:100313. doi:10.1016/j.lrr.2022.100313