Imetelstat Inhibits Telomerase and Prevents Propagation of ADAR1-activated Myeloproliferative Neoplasm and Leukemia Stem Cells

Wenxue Ma[1], Larisa Balaian[1], Phoebe Mondala[1], Yudou He[1], Cayla Mason[1], Jessica Pham[1], Jeremy Lee[1], Raymond Diep[1], Sanja Coso[1], Kathleen Fisch[1], Adam Mark[1], Sheldon Morris[1], Qingfei Jiang[1], Thomas Whisenant[1], Aleksandra Rizo[2], Fei Huang[2], Mary Donohoe[1], Ludmil Alexandrov[1], and Catriona Jamieson[1*]

[1] Division of Regenerative Medicine, Department of Medicine, Moores Cancer Center, and Sanford Stem Cell Clinical Center, University of California San Diego, La Jolla, CA;
[2] Geron Corporation, Parsippany, NJ.

[*]Corresponding author:
Catriona Jamieson, MD PhD, Deputy Director, UC San Diego Moores Cancer Center and Director, Sanford Stem Cell Clinical Center, cjamieson@health.ucsd.edu

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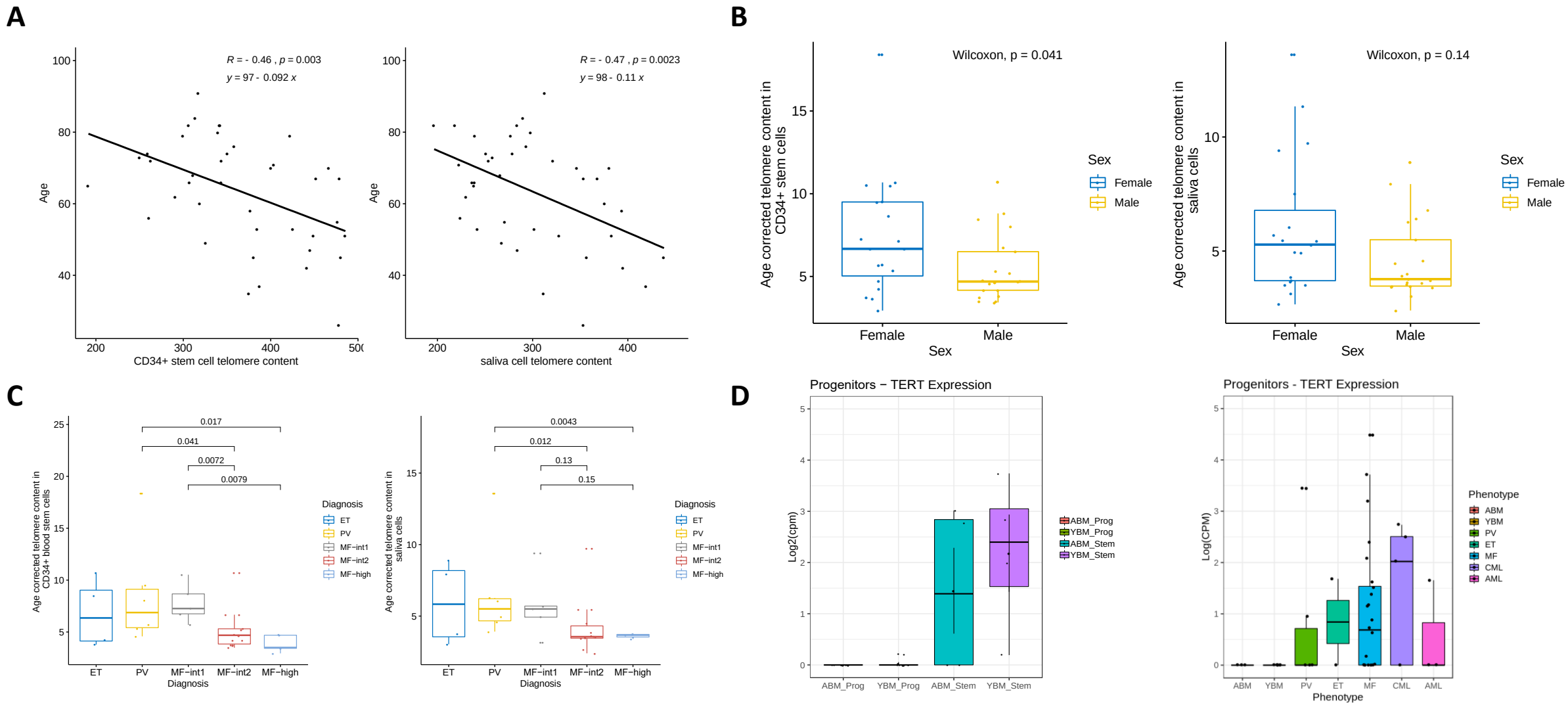
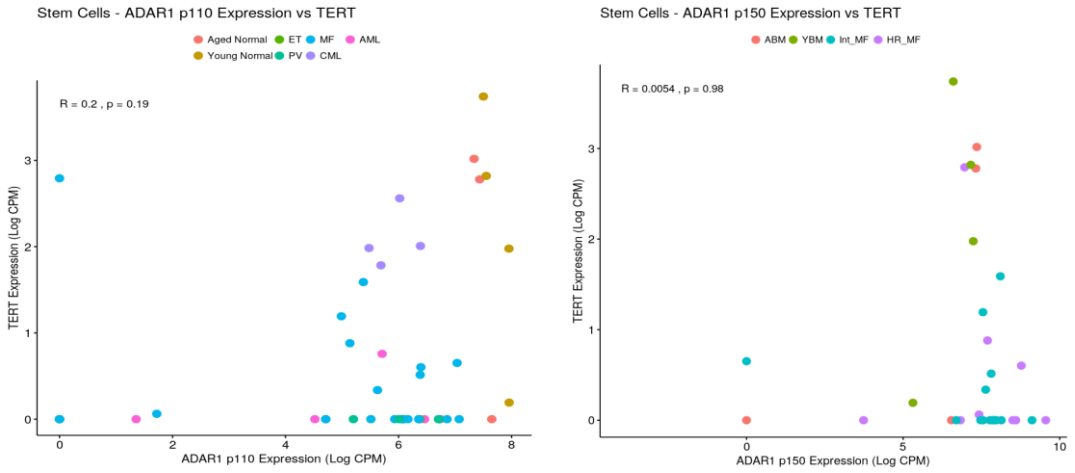
Fig. 1 Telomere Shortening Characterizes Pre-LSC and LSC



Whole genome sequencing revealed significant telomere shortening in stem cells during myeloproliferative neoplasm (MPN) progression

Fig. 2 Pre-LSC and LSC Harbor Increased TERT and ADAR1 Expression

A



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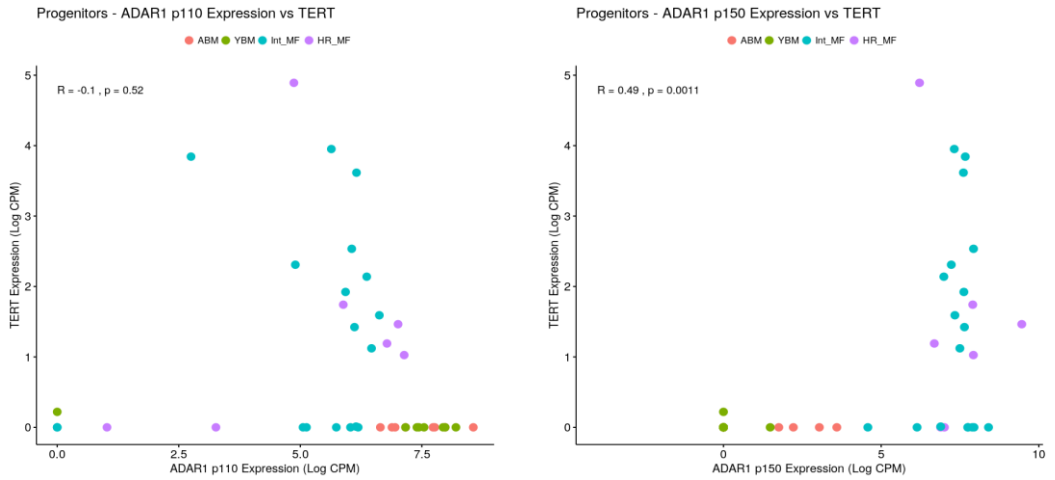

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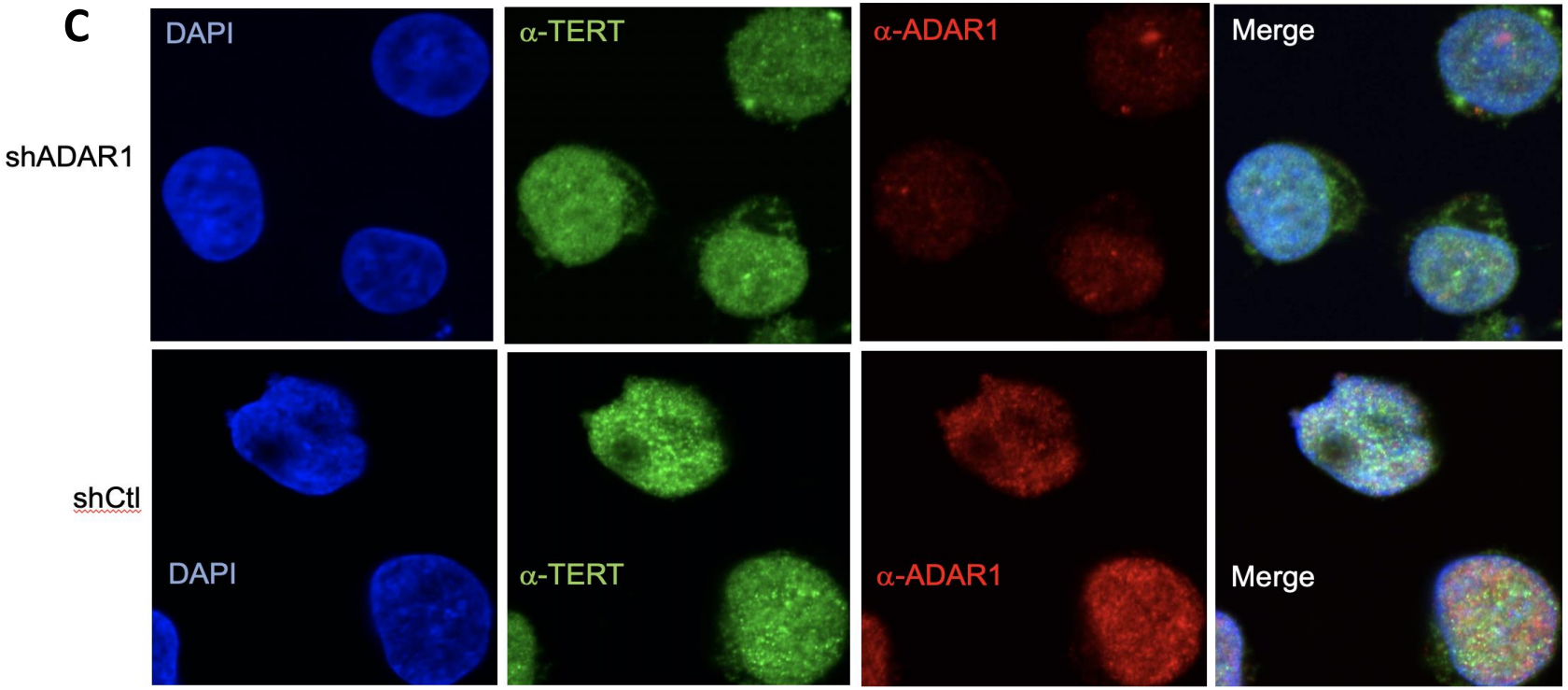
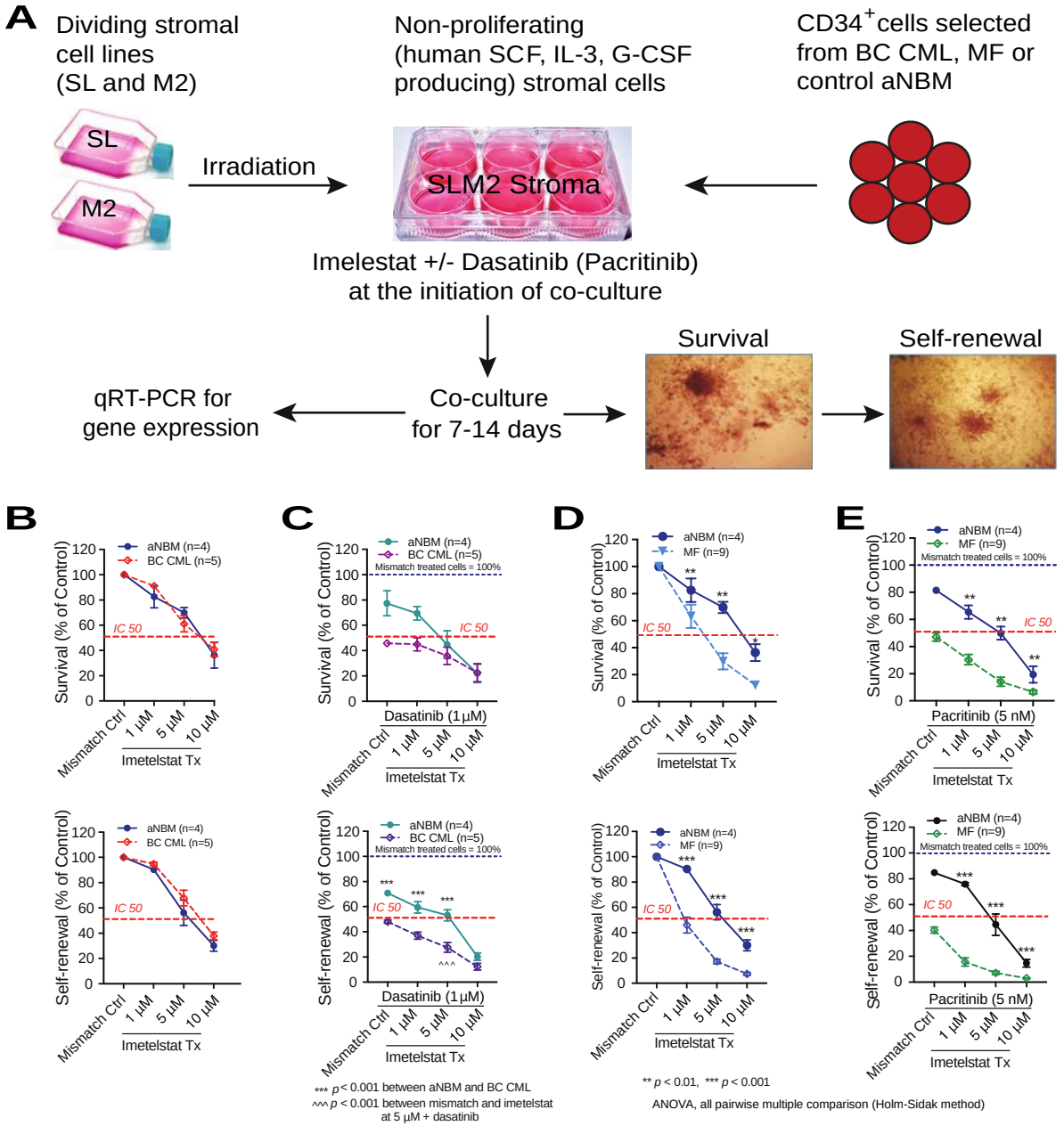


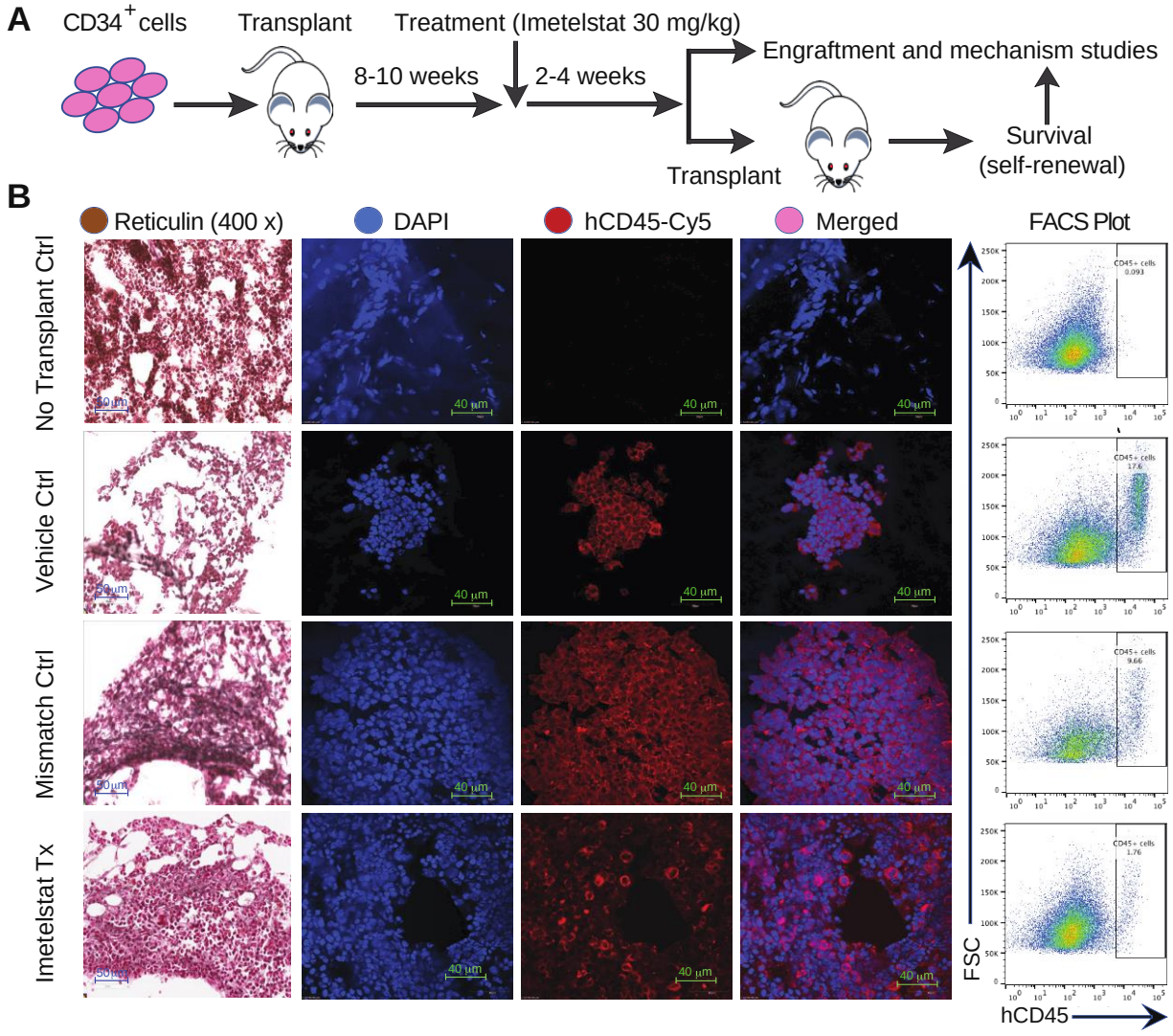
RNA-seq showed that ADAR1p150 increased in progenitors during MPN progression, which co-localized with TERT in TF1a leukemia cells, while lentiviral shRNA knockdown reduced ADAR1 and hTERT expression as shown by confocal fluorescence microscopy.

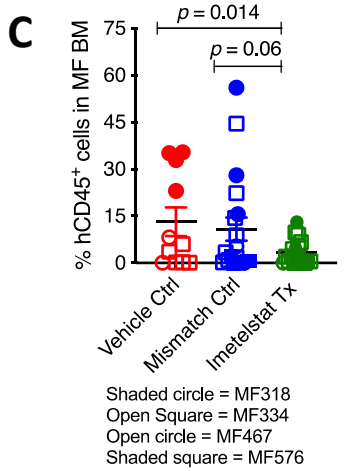
Fig. 3 Imetelstat Prevents Pre-LSC and LSC Maintenance In vitro

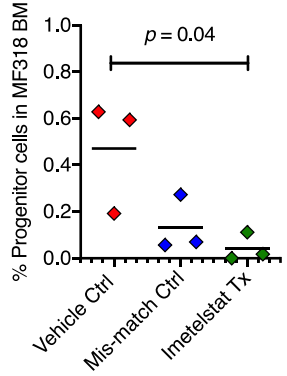


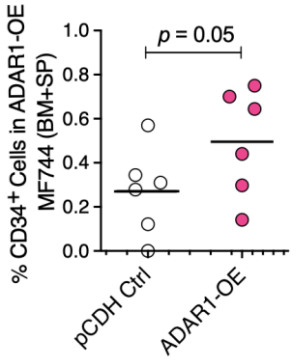
Imetelstat, a competitive inhibitor of telomerase enzymatic activity, selectively inhibited myelofibrosis (MF) stem cell survival and self-renewal in vitro, while combination of imetelstat with dasatinib was required to inhibit leukemia stem cell survival and self-renewal in blast crisis chronic myeloid leukemia (BC CML).

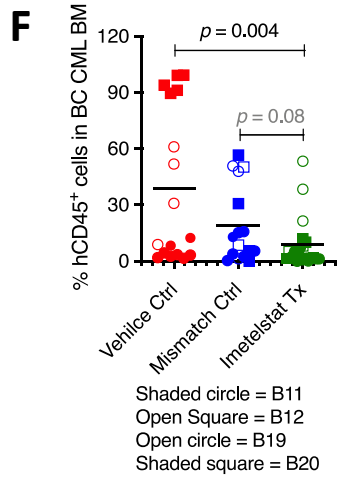
Fig. 4 Imetelstat Prevents Pre-LSC and LSC Maintenance In vivo

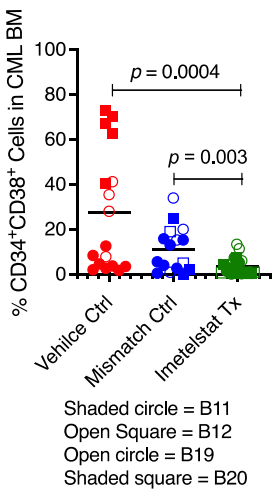


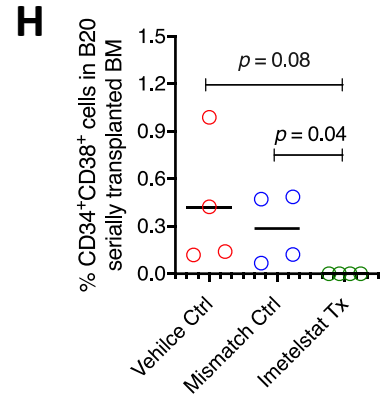


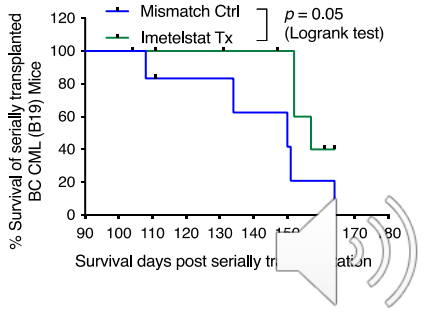






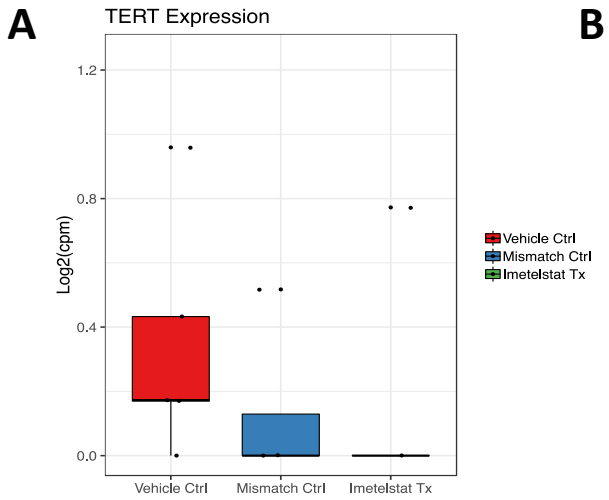


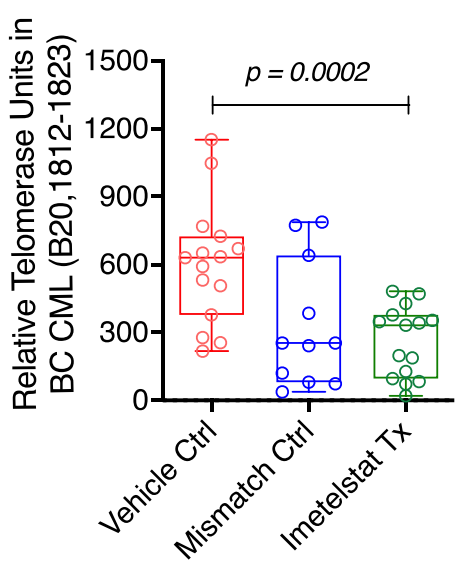


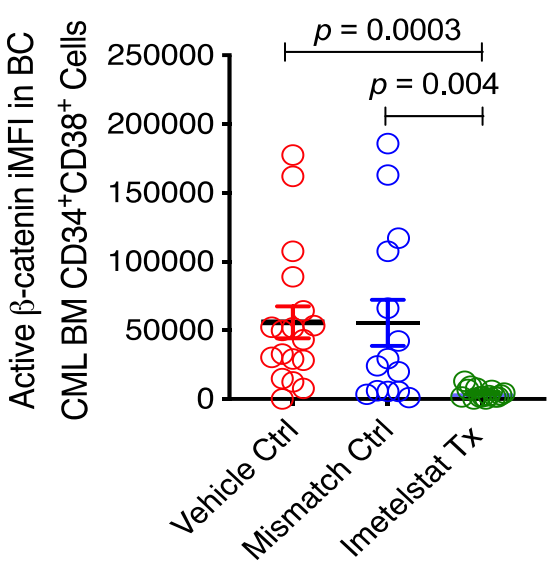


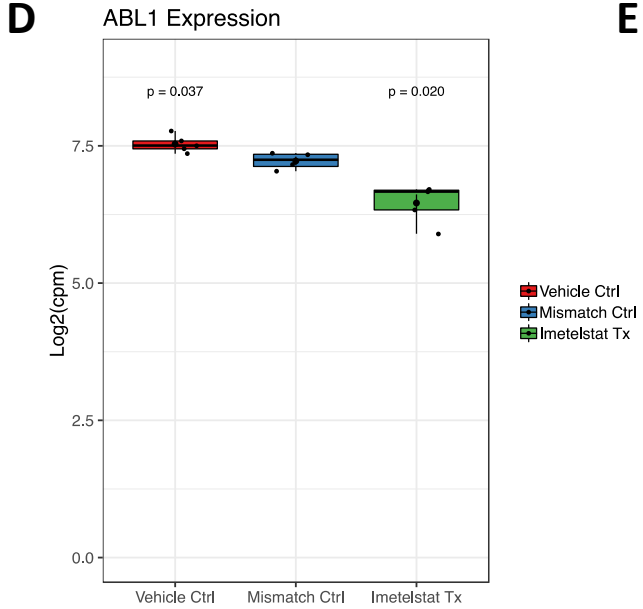
Imetelstat reduced MF progenitor engraftment in a humanized NSG-SGM3 mouse model and serial transplantation of human LSC engraftment in BC CML models.

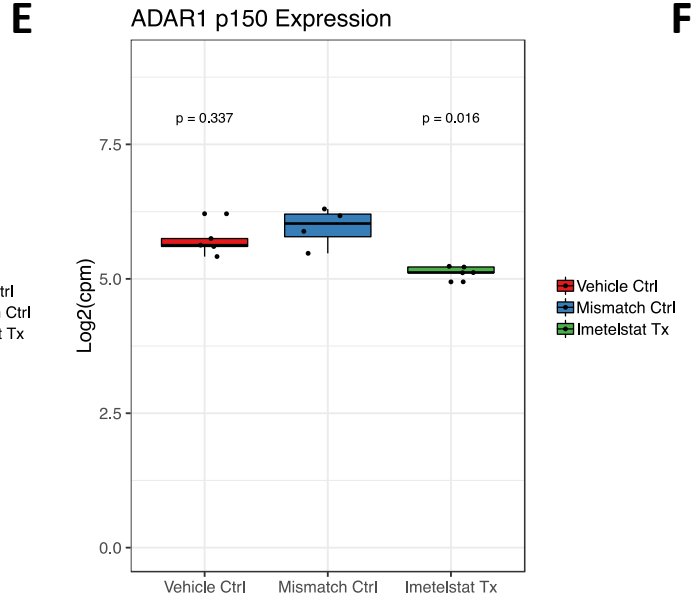
Fig. 5 Imetelstat Prevents ADAR1-mediated RNA Editing in LSC

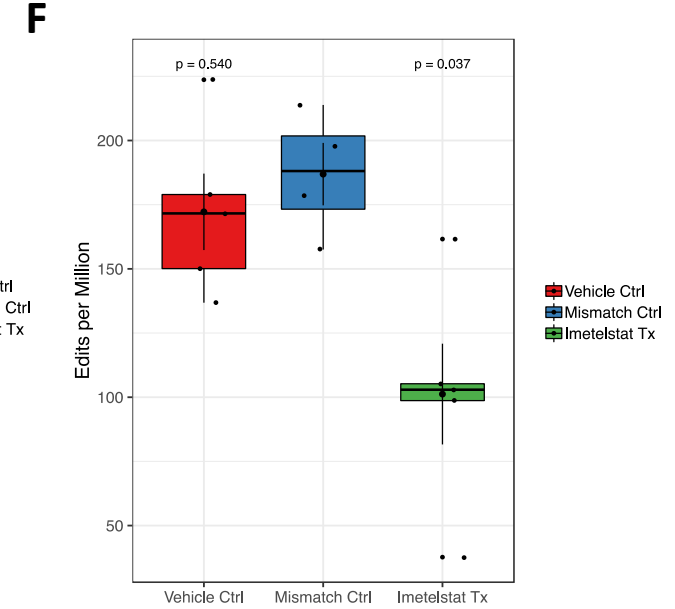












Human BC CML LSC eradication by imetelstat in mouse models was associated with decreased hTERT, telomerase activity, beta-catenin activity, ABL expression and ADAR1 activation

Conclusions

1. Whole genome sequencing revealed significant telomere shortening in stem cells during myeloproliferative neoplasm (MPN) progression.
2. Whole transcriptome sequencing (RNA-seq) revealed an increase in telomerase reverse transcriptase (hTERT)
3. RNA-seq showed that ADAR1p150 increased in progenitors during MPN progression, which co-localized with TERT in TF1a leukemia cells, while lentiviral shRNA knockdown reduced ADAR1 and hTERT expression as shown by confocal fluorescence microscopy.
4. Imetelstat, a competitive inhibitor of telomerase enzymatic activity, selectively inhibited myelofibrosis (MF) stem cell survival and self-renewal in vitro, while combination of imetelstat with dasatinib was required to inhibit leukemia stem cell survival and self-renewal in blast crisis chronic myeloid leukemia (BC CML)
5. Imetelstat also reduced MF progenitor engraftment in a humanized NSG-SGM mouse model and serial transplantation of human LSC engraftment in blast crisis BC CML models.
6. Human BC CML LSC eradication by imetelstat in mouse models was associated with decreased hTERT, telomerase activity, beta-catenin activity, ABL expression and ADAR1 activation
7. These data suggest that Imetelstat may prevent LSC-driven blast crisis transformation.

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