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The preclinical efficacy of a novel telomerase inhibitor, imetelstat, in AML: A randomized trial in patient-derived xenografts

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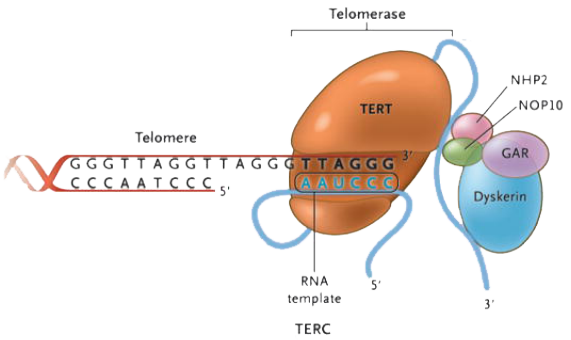
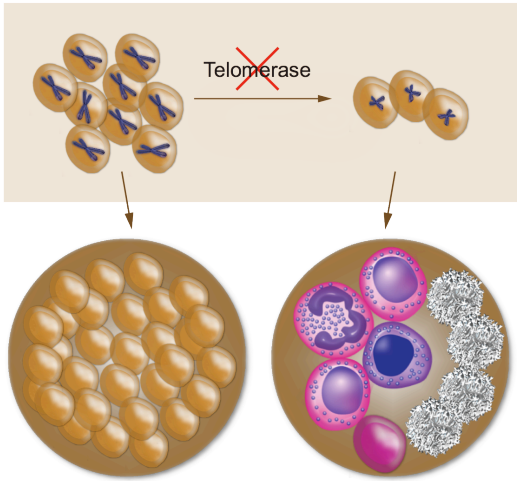
Headed by A/Professor Steven Lane

Telomerase is activated to maintain the long-term replicative potential in most cancers including AML



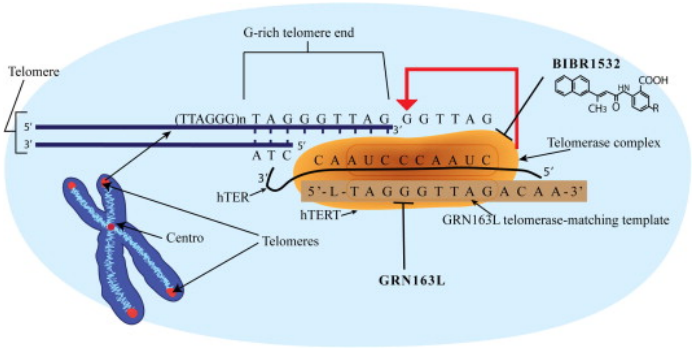
Calado and Young, N Engl J Med 2009



Bruedigam et al., Cell Stem Cell 2014-

- Telomerase is overexpressed in most AML
  Roth et al., Leukemia 2003
- AML oncogenes activate telomerase
  Gessner et al., Leukemia 2010
- LSC have shortened telomeres and increased telomerase activity
  Drummond et al., Leukemia 2005, Bernard et al., Leukemia 2009
- Genetic depletion of telomerase eradicates LSC upon enforced replication via cell cycle arrest and apoptosis
  Bruedigam et al., Cell Stem Cell 2014

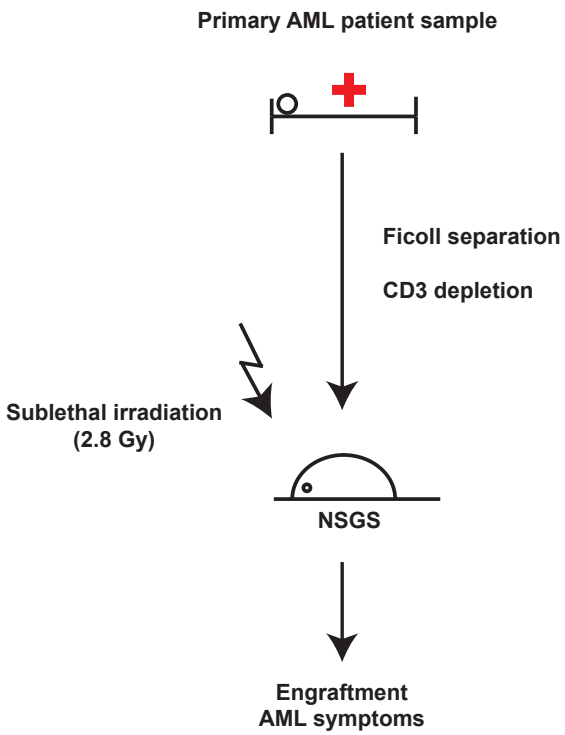
Imetelstat (JNJ-63935937) is a competitive inhibitor of telomerase activity

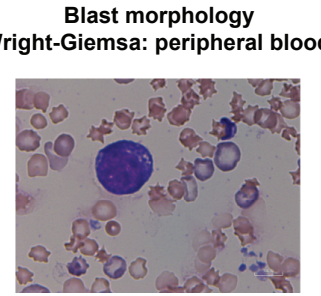


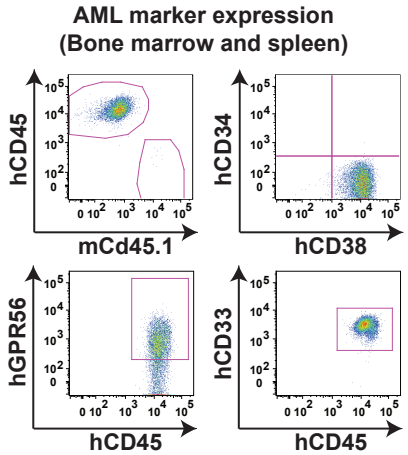
Ruden et al, Cancer Treatment Reviews 2013

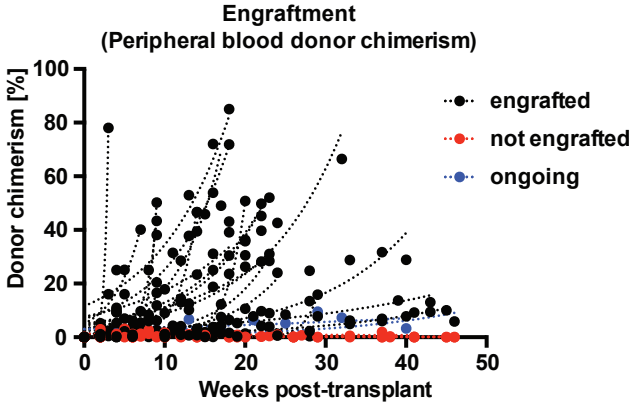
- Imetelstat is a covalently lipidated 13-mer oligonucleotide that binds the RNA template of telomerase
  Herbert et al., Oncogene 2005
- Imetelstat induced molecular and complete hematological responses in essential thrombocythemia (89%)
  Baerlocher et al., NEJM 2015
- Imetelstat showed efficacy in myelofibrosis (complete or partial remission in 21%)
  Tefferi et al., NEJM 2015
- Phase II / III trial to evaluate imetelstat in low or intermediate-1 risk myelodysplastic syndrome
  NCT02598661

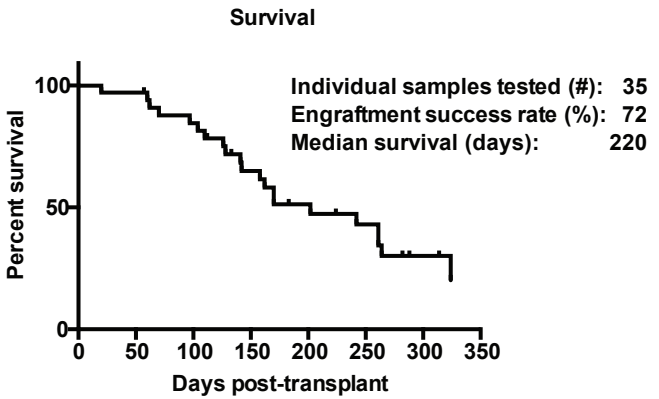
Generating an AML patient-derived xenograft inventory



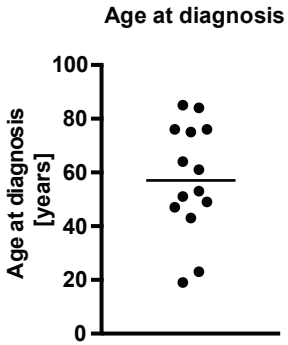


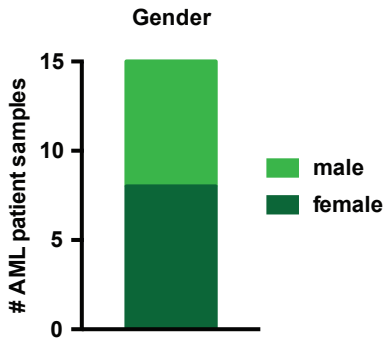


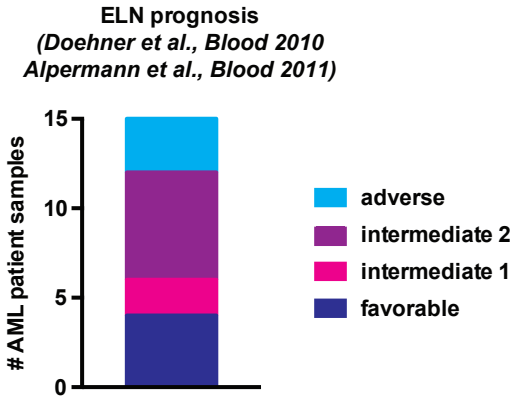


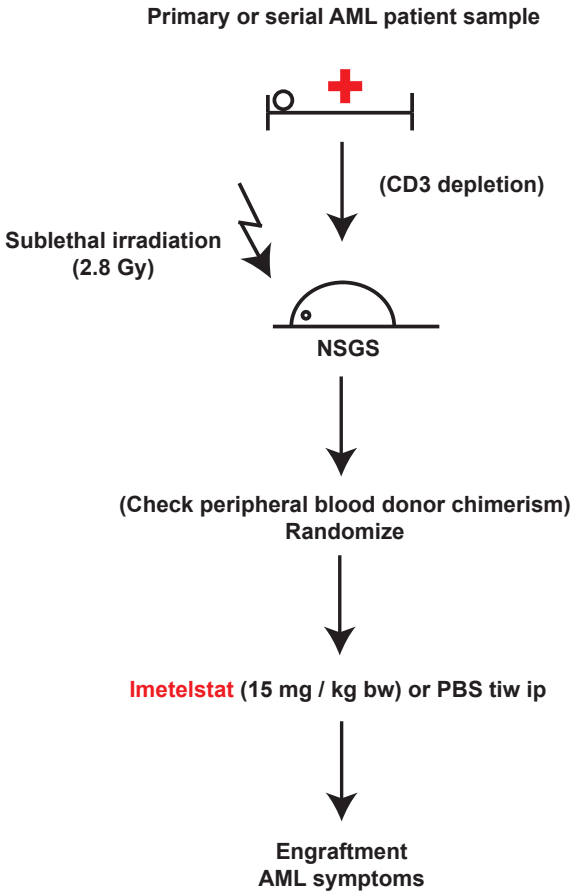


Preclinical testing of imetelstat in AML PDX

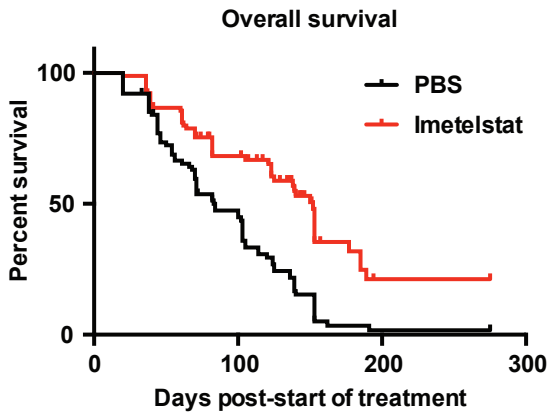








Imetelstat prolongs overall survival in AML PDX

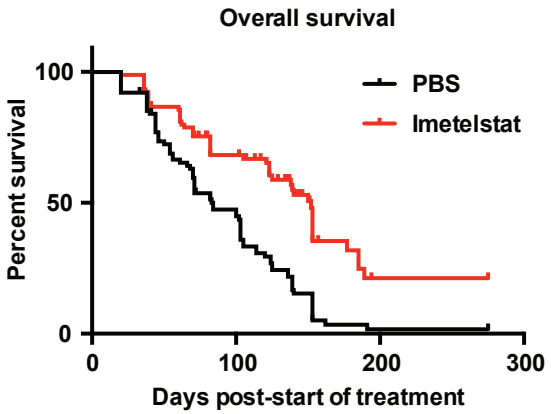


Median survival:

PBS: 83
Imetelstat: 153

$p < 0.0001$

Imetelstat suppresses AML expansion in 14 out of 15 PDX



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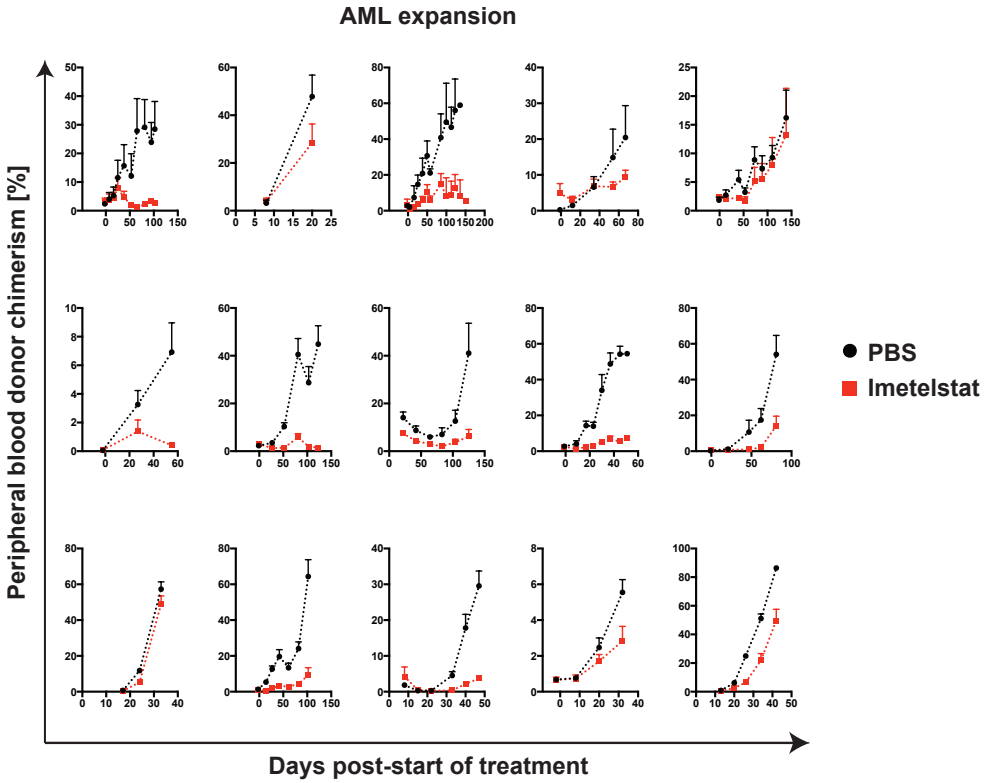
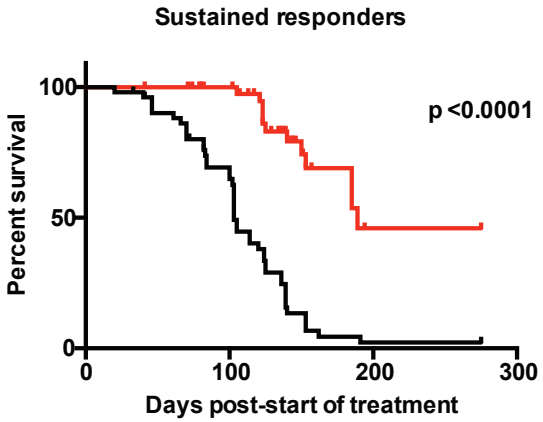
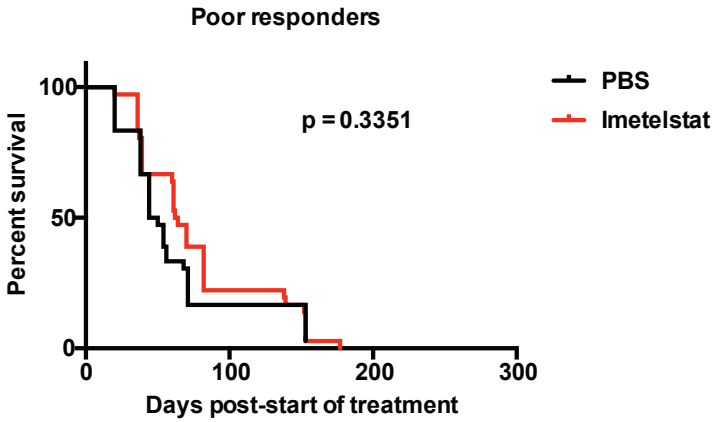
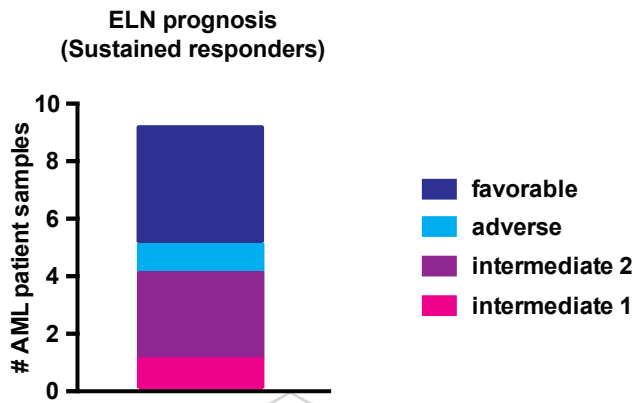
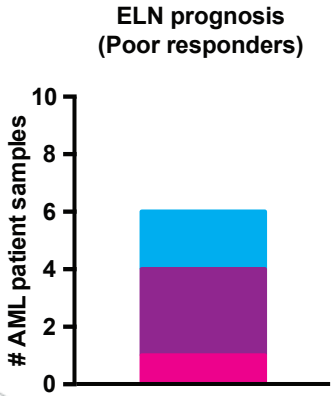


AML PDX can be separated into two groups with distinct response to imetelstat therapy

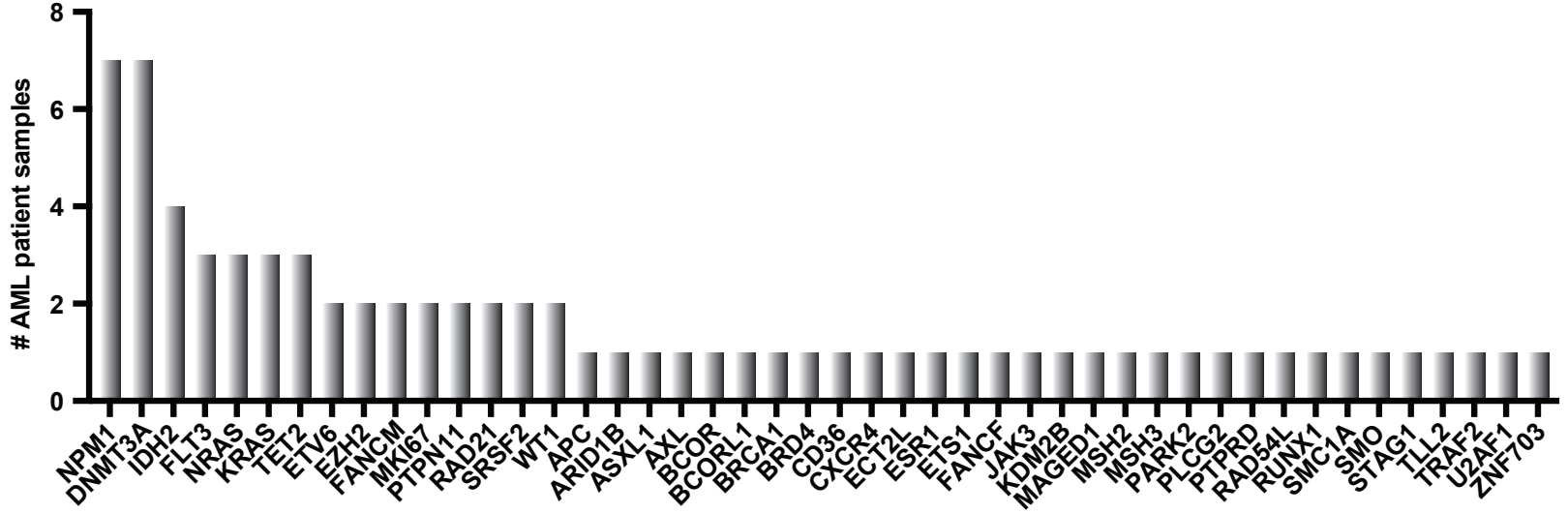






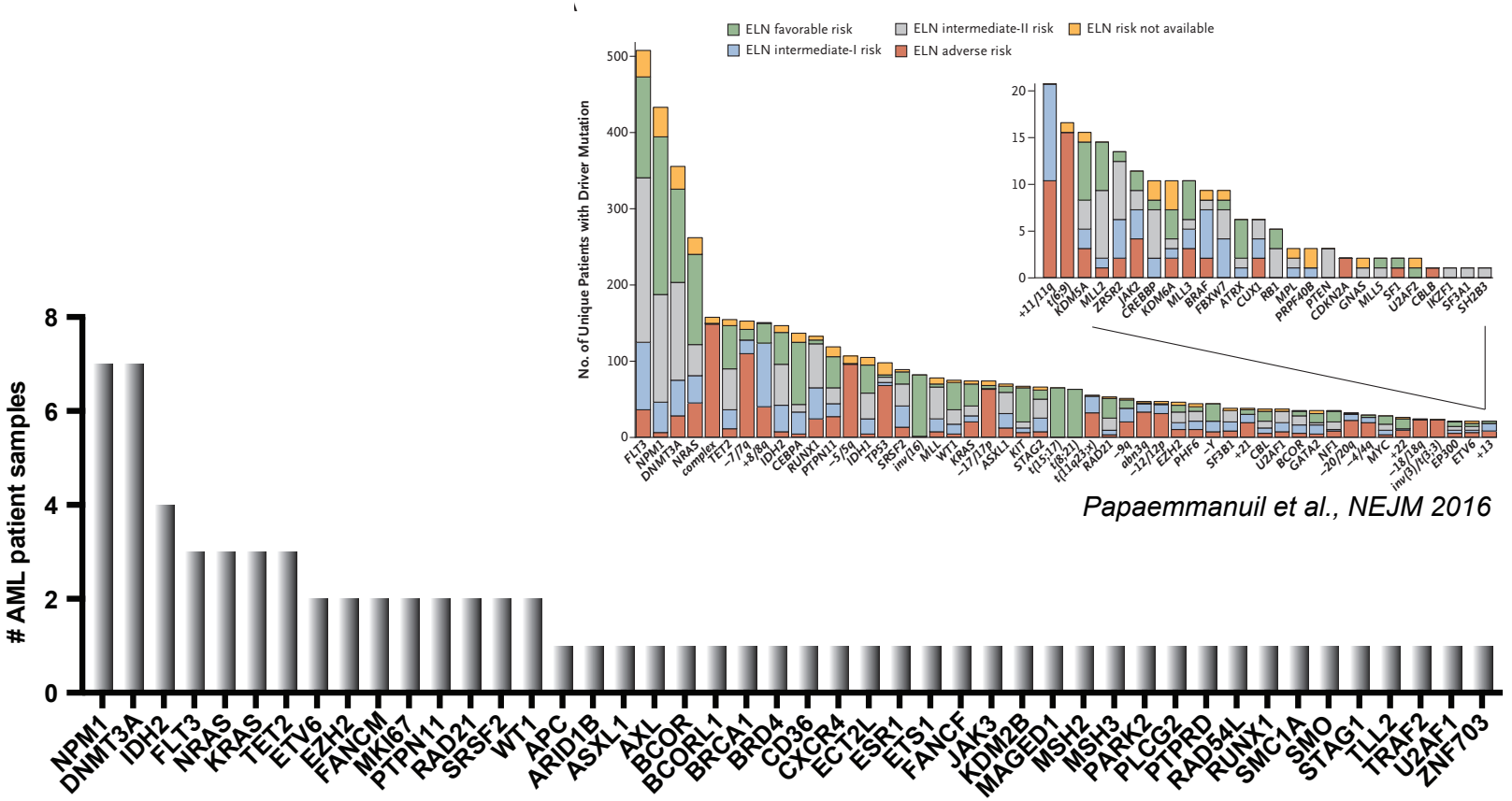


Next generation sequencing reveals baseline mutations in AML patient samples



HemePACT assay in collaboration with Stanley Chun-Wei Lee and Omar Abdel-Wahab, MSKCC

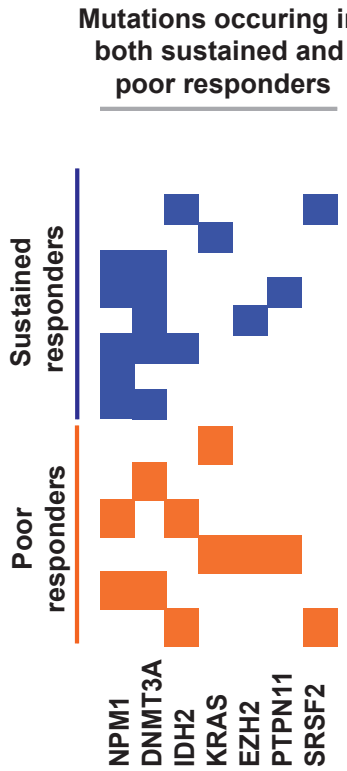
The identity and distribution of mutations in selected PDX reflects larger AML cohorts



Papaemmanuil et al., NEJM 2016

HemePACT assay in collaboration with Stanley Chun-Wei Lee and Omar Abdel-Wahab, MSKCC

Imetelstat response is correlated with a distinct mutational landscape



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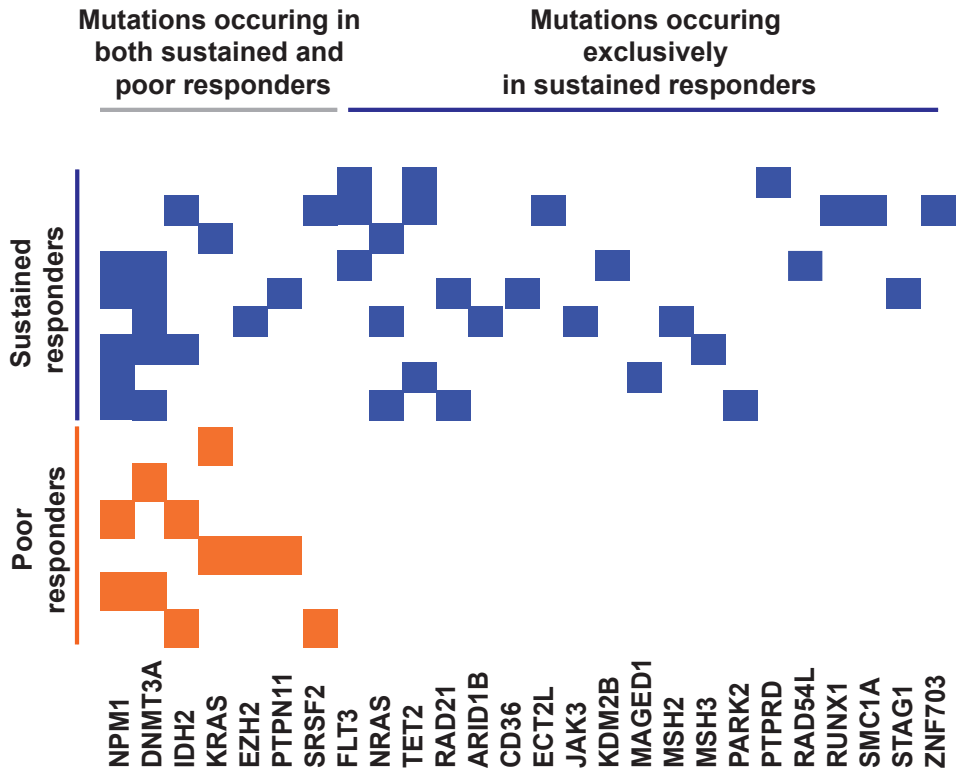

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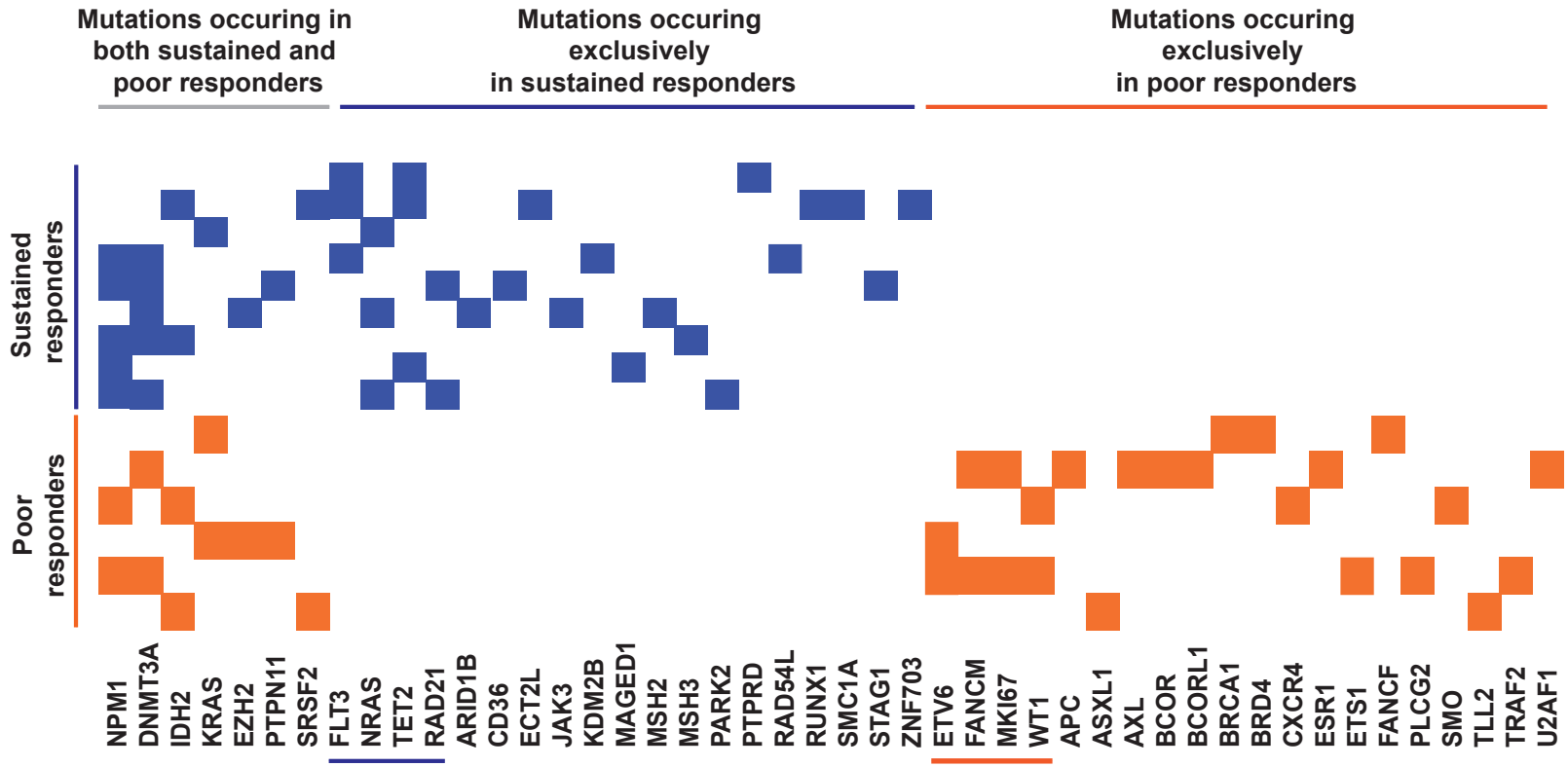
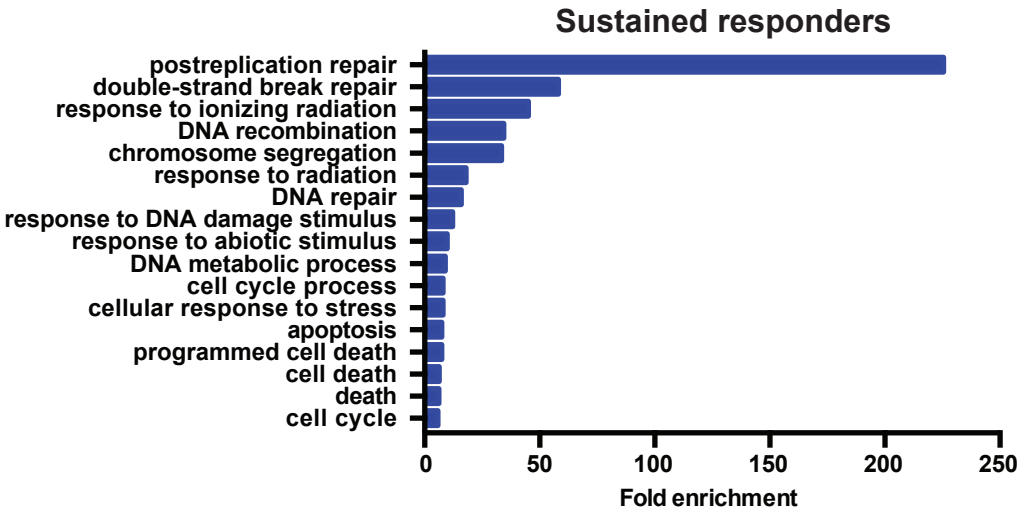
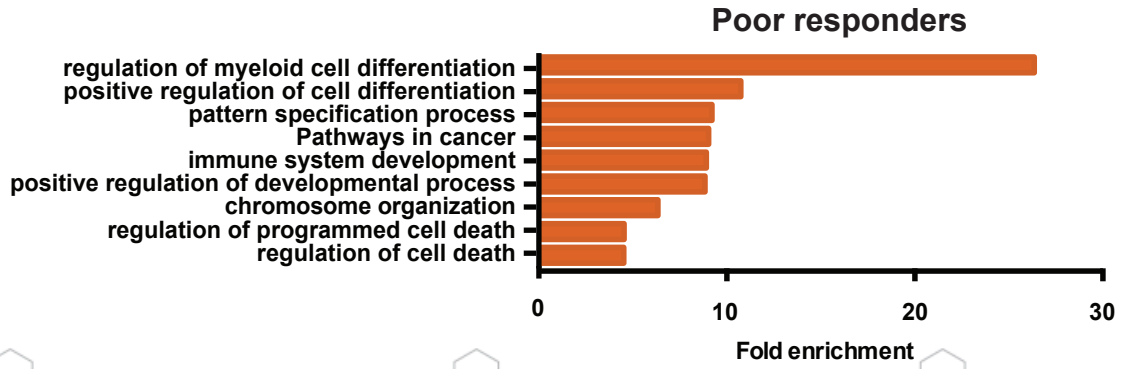


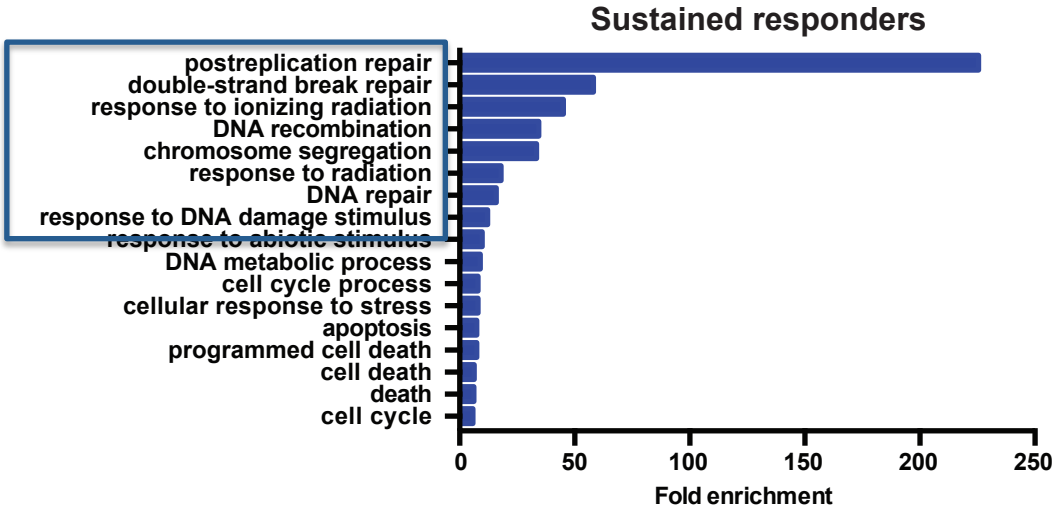
Gene ontology analysis of mutually exclusive mutations reveals distinct molecular pathways

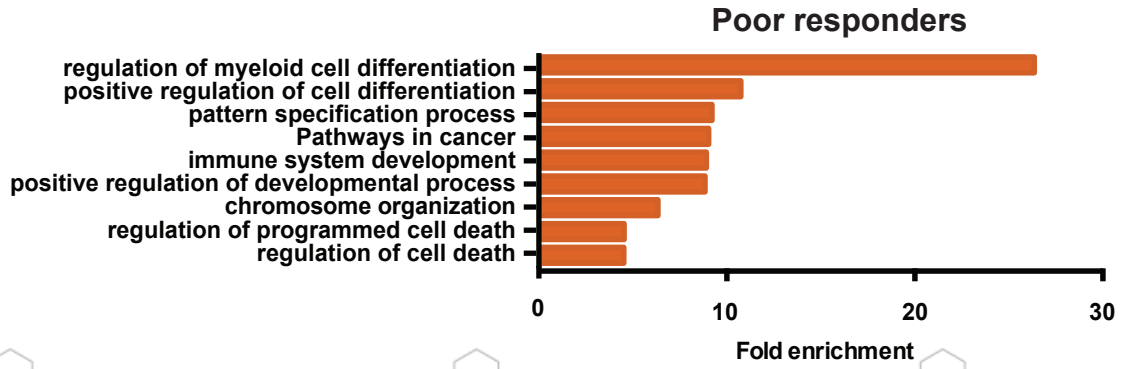




Gene ontology analysis of mutually exclusive mutations reveals distinct molecular pathways

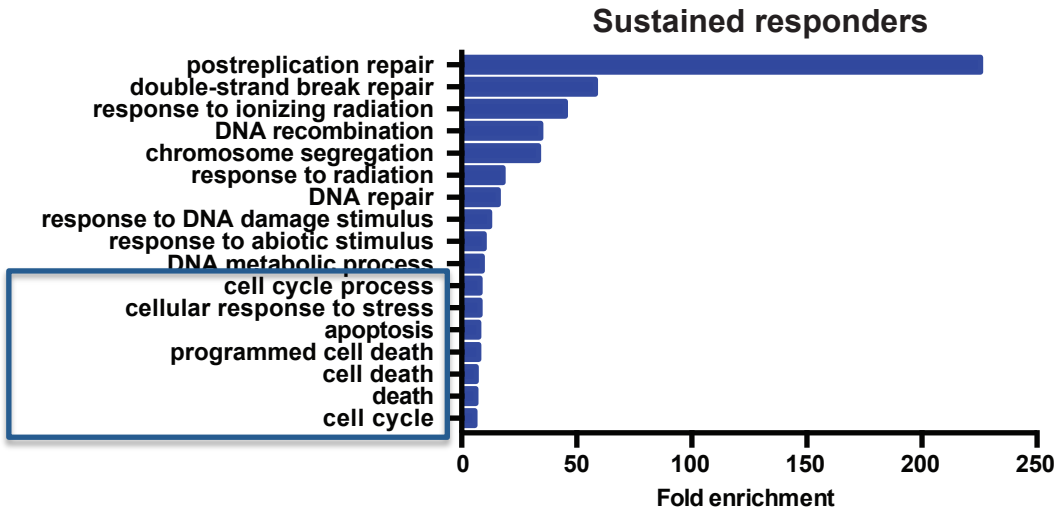
1. DNA repair

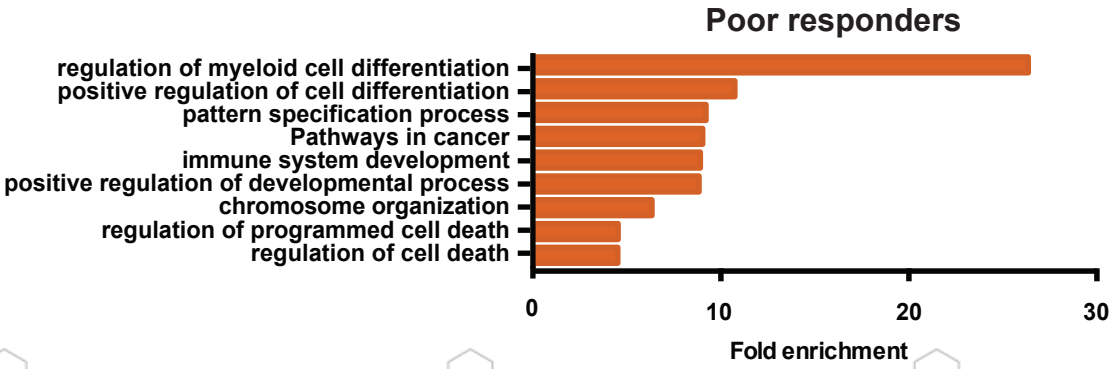




Gene ontology analysis of mutually exclusive mutations reveals distinct molecular pathways

1. DNA repair
2. Cell cycle





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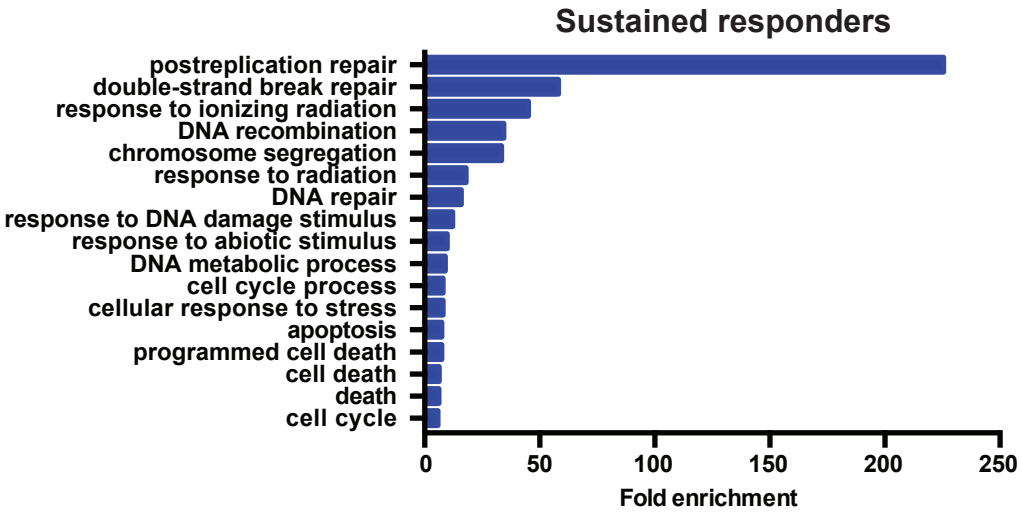
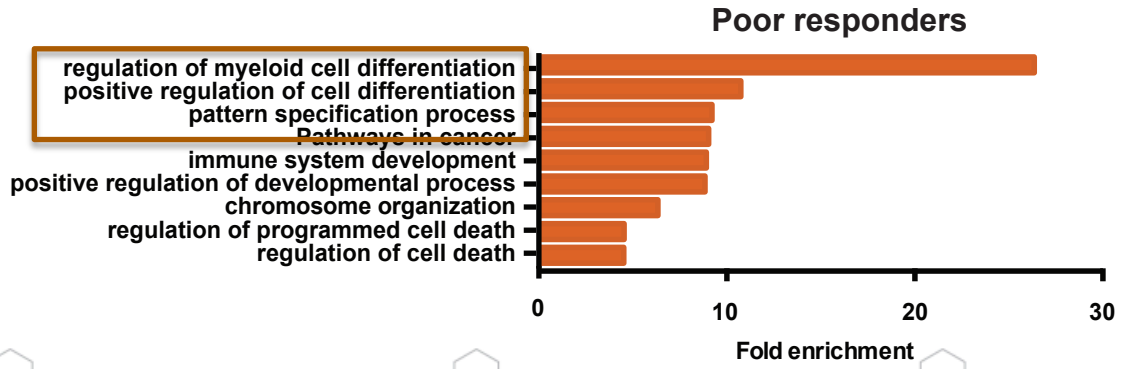


3. Development and differentiation



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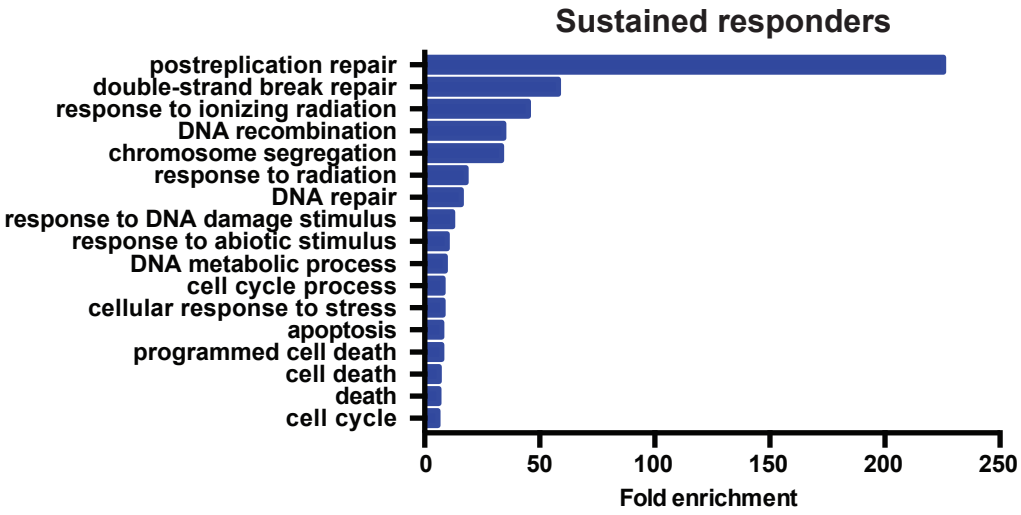
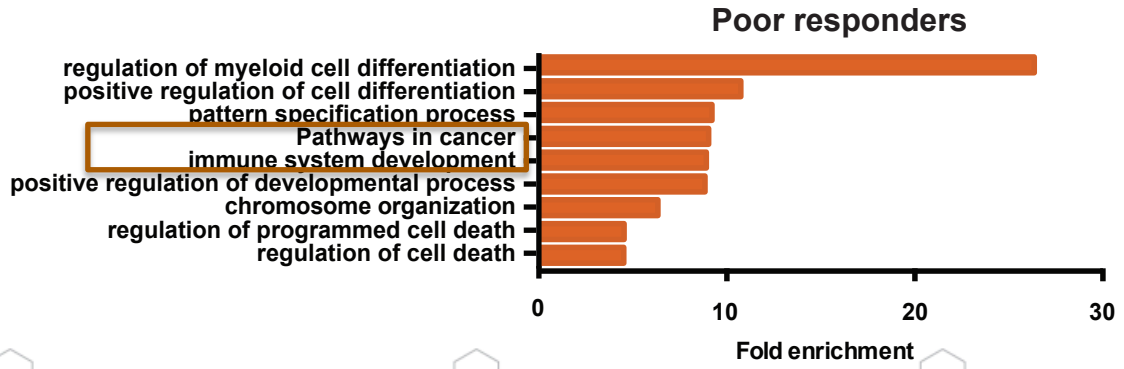
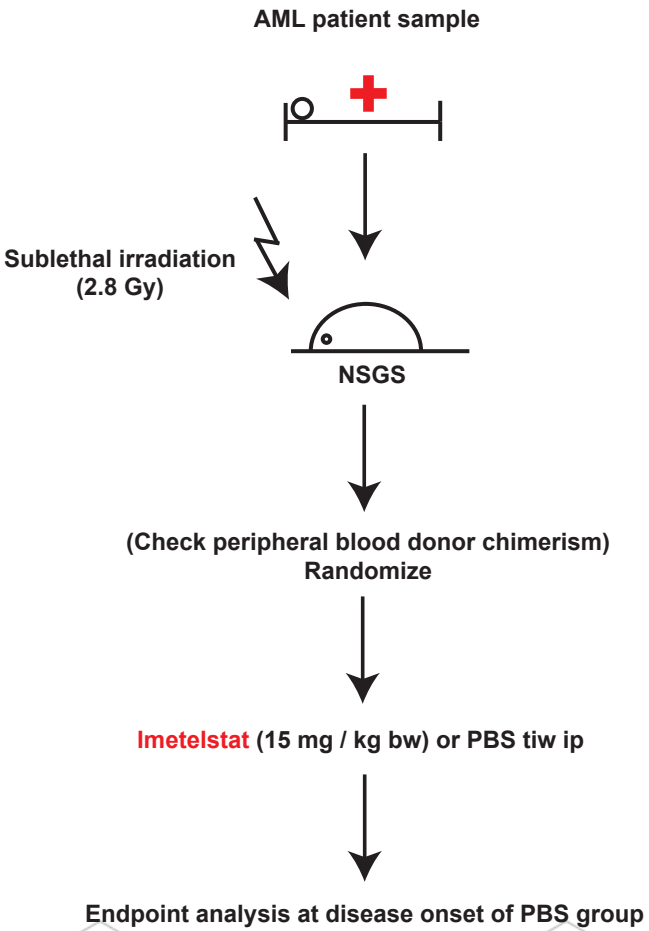
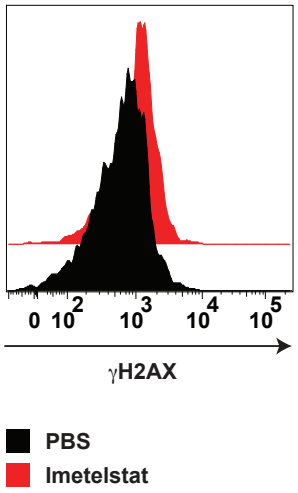


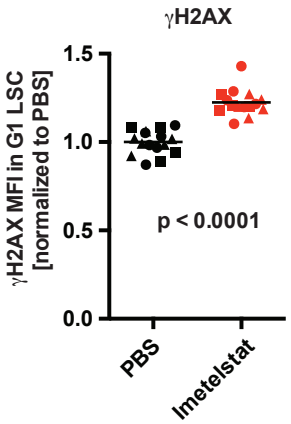
3. Development and differentiation
4. Pathways in cancer

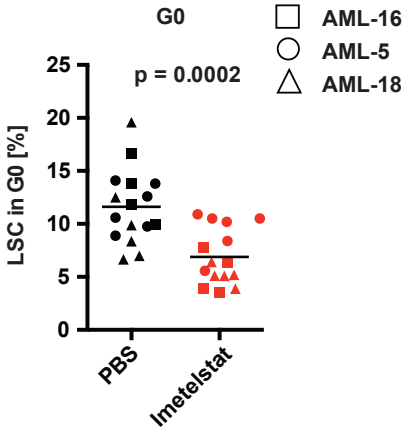


Imetelstat induces DNA damage and loss of quiescence in LSC *in vivo*

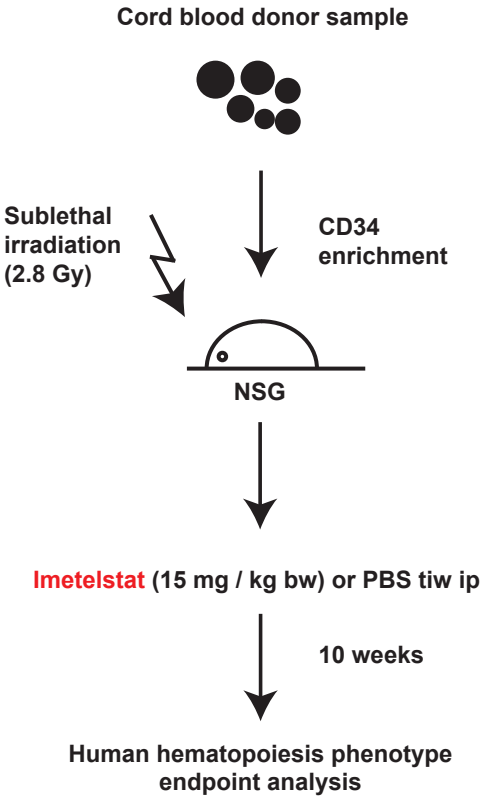




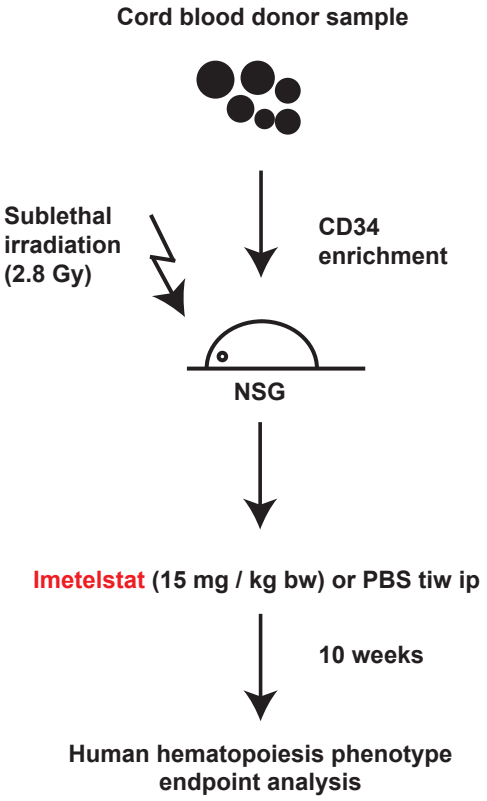


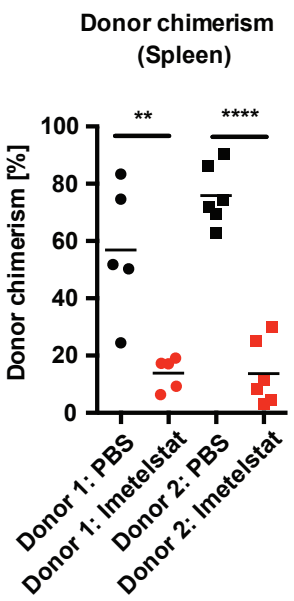


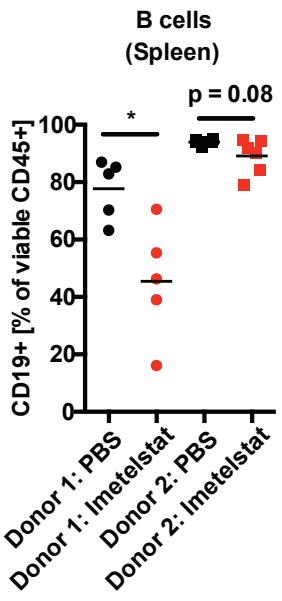
Modelling normal human hematopoiesis

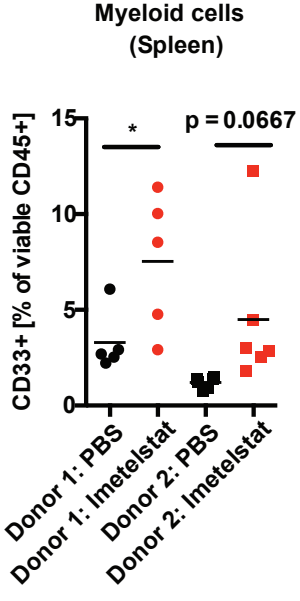


Imetelstat primarily depletes B lymphocytes

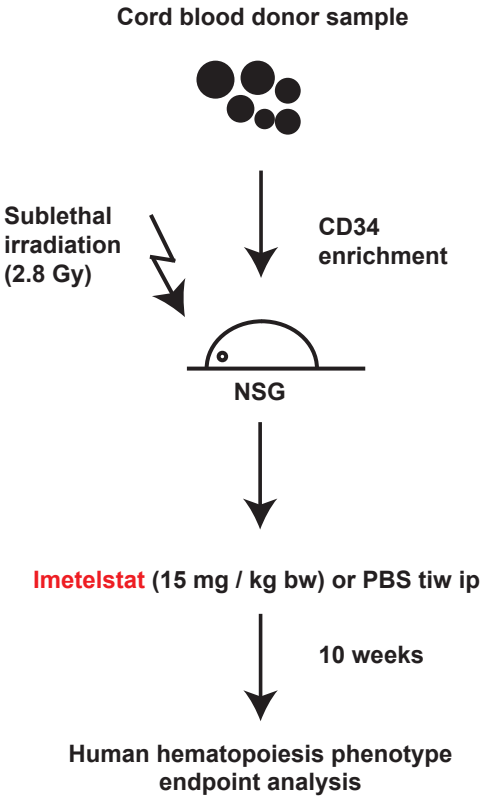


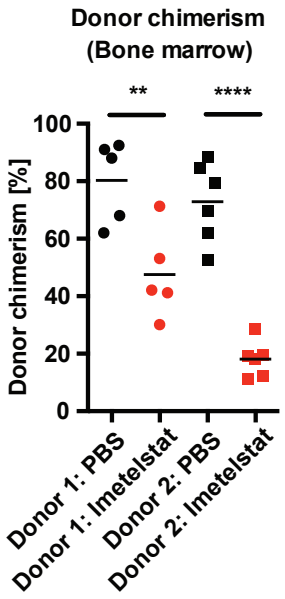


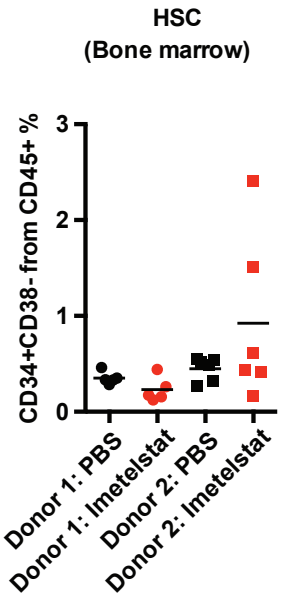


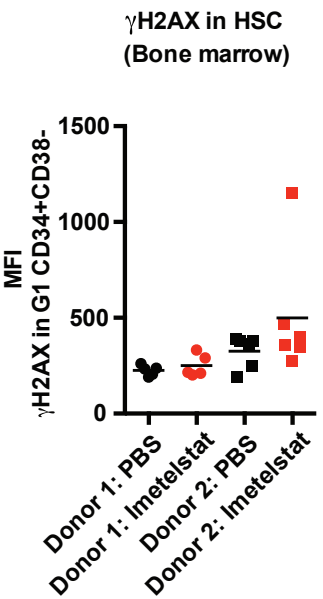


Human cord blood - derived stem cells are preserved during imetelstat treatment









Summary:
Preclinical efficacy of imetelstat in AML PDX

- Imetelstat is effective in a subgroup (60%) of AML patient samples
- Imetelstat prevents expansion and prolongs overall survival in AML PDX (PBS: 83 days; Imetelstat: 153 days post-start of treatment)
- Sustained responses to imetelstat are correlated with favorable cytogenetics, mutational profiles of DNA damage and activation of DNA damage response pathways
- This study has generated preclinical data to inform clinical trials and provide a precision approach to targeted therapies in patients with AML

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QIMR Berghofer Medical Research Institute

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- Rebecca Austin
- Emma Dishington
- Solene Guignes
- Jasmin Straube
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- Animal House: Sue, Jonathan, Dave
- Statistics: Leesa, Louise, Mandy, Peter

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