

PI: Edward Hasty

Grant Number: R01ES022054

Grant Title: Study DNA repair in preventing MDS and AML after radiation and benzene exposure

Background/Context: P-benzoquinone (BQ) acts as a type 1 topoisomerase inhibitor. Crebbp+/- mice (gene-engineered for the transcriptional activator) develop Myelodysplastic syndrome (MDS), a group of disorders characterized by dysfunctional blood cells that can progress to acute myeloid leukemia (AML), over the first year of life. The data adds to the understanding of how DNA repair deficiency of this bone marrow disorder leads to AML.

NIEHS Note: This is an example of research conducted entirely within the fundamental questions category and bridges between nodes in this category.

Key Translational Milestones

- Confirmed that mouse models of MDS can be genetically engineered and faithfully recapitulate human disease
- Mouse embryonic stem cells mutated for Ercc1, Brca2 exon 27, Ku70 and Blm are hypersensitive to BQ.
- BQ causes chromosomal breaks and gross chromosomal rearrangements in control cells and defects in the DNA repair pathways (above) that elevate the number of breaks and rearrangements
- BQ induces DNA damage response consistent with defective replication fork progression. For example, BQ exposure induces 53BP1 and γ H2AX foci that do not merge. This is similar to camptothecin (type 1 topoisomerase inhibitor) and different than γ -radiation; both cause double strand breaks (DSBs), but only camptothecin causes DSB associated with replication forks
- BQ directly inhibits topo 1 at a low micromolar concentration.
- Crebbp-/- ES cells were very resistant to many genotoxic agents (>10 more cells were alive) including: etoposide, ICRF-193, γ -radiation, PBQ, aphidicolin, hydroxyurea, mitomycin C, MMS, ENU, streptonigrin, UV, DRB, 6-thioguanine, ABT888
- Mutation frequency is linked with γ -radiation spectrum
- Crebbp+/- hematopoietic populations have reduced non-homologous end-joining
- Crebbp+/- mice develop MDS over the period from 6 (asymptomatic) to 12 (symptomatic) months as the expression of most DNA repair genes decline. These include genes for homologous recombination and Fanconi anemia indicating a general decrease in DNA repair

Starting Point Description:

- Confirmed that mouse models of MDS can be genetically engineered and faithfully recapitulate human disease

Fundamental Science Interactions Ring:

Driver: Mechanistic Understanding

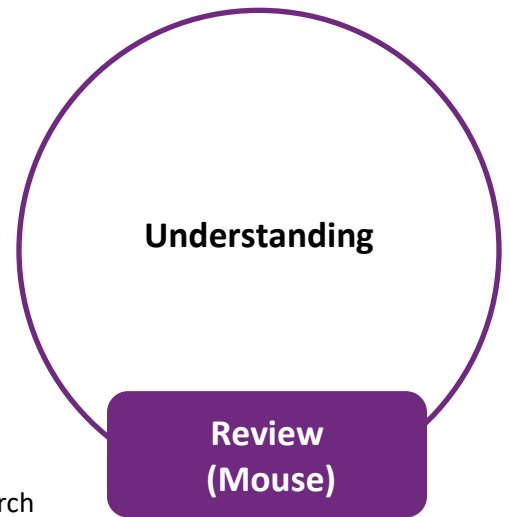
Experimental Setting: Review

Organism: Mouse

Timeframe: 2012-2014

Collaborators:

- Greehey Children's Cancer Research Institute, Department of Cellular and Structural Biology
- Department of Pathology, University of Texas Health Science Center at San Antonio
- The University of Queensland Diamantina Institute, Translational Research Institute
- Department of Medicine, Vanderbilt University Medical Center
- Greehey Children's Cancer Research Institute, Department of Cellular and Structural Biology, and Cancer Therapy and Research Center, University of Texas Health Science Center



Citation:

Zhou et al. 2015. Revisiting the case for genetically engineered mouse models in human myelodysplastic syndrome research. [Blood](#). 2015 Aug 27;126(9):1057-68. doi: 10.1182/blood-2015-01-624239.



Translational Narrative:

What led to the next step?

How did the idea evolve?

Who was involved?

What needed to happen (collaborations, tools, technologies, serendipity) to cross the translational bridge?

How did you know what to do next?

TRANSLATIONAL POINT 2

Translational Research Description:

- Mouse embryonic stem cells mutated for Ercc1, Brca2 exon 27, Ku70 and Blm are hypersensitive to BQ.

Science and Setting Translational Ring:

Driver: Understanding

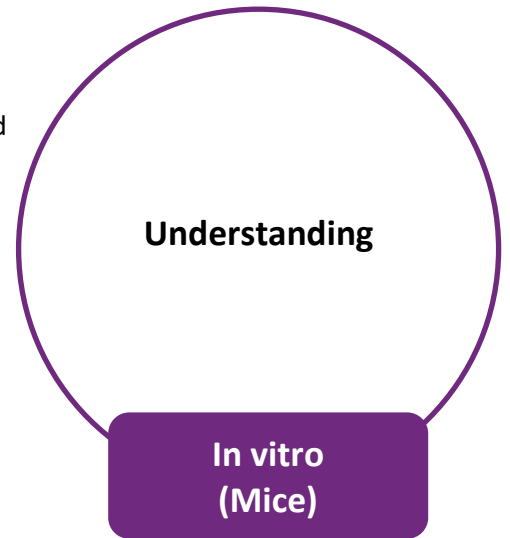
Experimental Setting: In vitro

Organism: Mice

Timeframe: 2012 - 2015

Collaborators:

- Department of Molecular Medicine and Institute of Biotechnology, University of Texas Health Science Center at San Antonio,
- Faculty of Health Sciences, University of Macau, Macau SAR China
- Department of Genetics, Cancer Genomics Netherlands,
- Department of Cellular and Structural Biology, University of Texas Health Science Center at San Antonio,
- The Cancer Therapy Research Center, University of Texas Health Science Center at San Antonio,
- The Barshop Center of Aging, University of Texas Health Science Center at San Antonio,
- Greehey Children's Cancer Research Center, University of Texas Health Science Center at San Antonio



Young Son et al. 2016. A mechanism for 1,4-Benzoquinone-induced genotoxicity. [Oncotarget](#). 2016 Jun 20. doi: 10.18632/oncotarget.



TRANSLATIONAL POINT 3

Translational Research Description:

- BQ causes chromosomal breaks and gross chromosomal rearrangements in control cells and defects in the DNA repair pathways that elevate the number of breaks and rearrangements

Science and Setting Translational Ring:

Driver: Understanding

Experimental Setting: In vitro

Organism: Mice

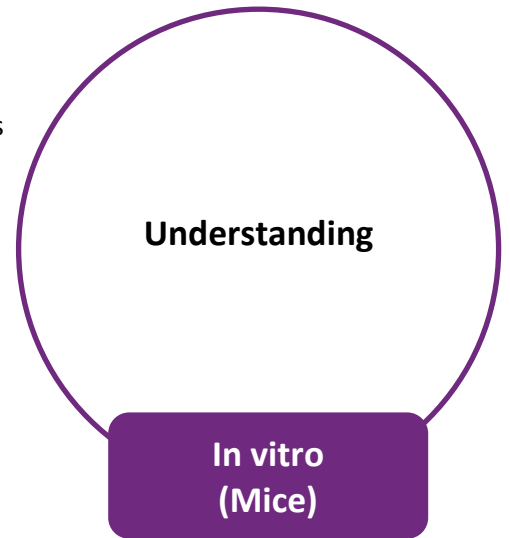
Timeframe: 2012 - 2015

Collaborators:

- Department of Molecular Medicine and Institute of Biotechnology, University of Texas Health Science Center at San Antonio,
- Faculty of Health Sciences, University of Macau, Macau SAR China
- Department of Genetics, Cancer Genomics Netherlands,
- Department of Cellular and Structural Biology, University of Texas Health Science Center at San Antonio,
- The Cancer Therapy Research Center, University of Texas Health Science Center at San Antonio,
- The Barshop Center of Aging, University of Texas Health Science Center at San Antonio,
- Greehey Children's Cancer Research Center, University of Texas Health Science Center at San Antonio

Citation:

Young Son et al. 2016. A mechanism for 1,4-Benzoquinone-induced genotoxicity. [Oncotarget](#). 2016 Jun 20. doi: 10.18632/oncotarget.



TRANSLATIONAL POINT 4

Translational Research Description:

- BQ induces DNA damage response consistent with defective replication fork progression.

Science and Setting Translational Ring:

Driver: Understanding

Experimental Setting: In vitro

Organism: Mice

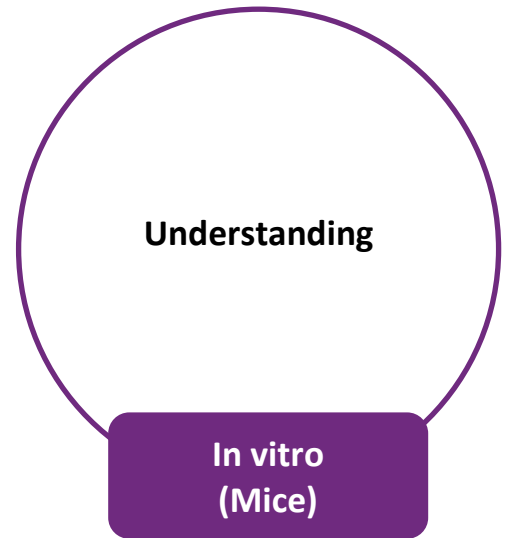
Timeframe: 2011 - 2014

Collaborators:

- Department of Molecular Medicine and Institute of Biotechnology, The Barshop Center of Aging, University of Texas Health Science Center, San Antonio
- Department of Genetics, Case Western Reserve University

Citation:

Kim et al. 2015. RECQL5 and BLM exhibit divergent functions in cells defective for the Fanconi anemia pathway. [Nucleic Acids Res.](#) 2015 Jan;43(2):893-903. doi: 10.1093/nar/gku1334.



TRANSLATIONAL POINT 5

Translational Research Description:

- BQ directly inhibits topo 1 at a low micromolar concentration

Science and Setting Translational Ring:

Driver: Understanding

Experimental Setting: In vitro

Organism: Mice

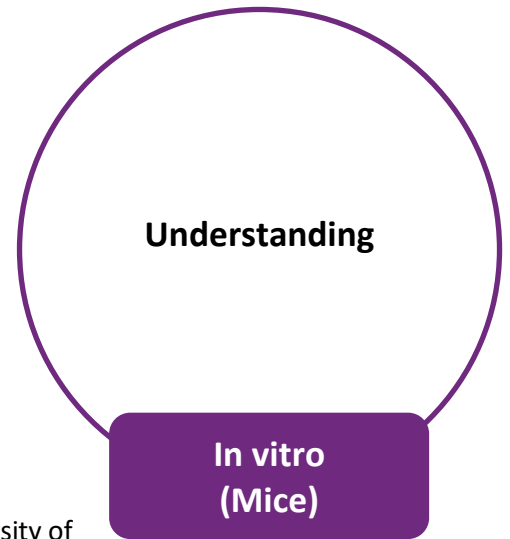
Timeframe: 2012 - 2015

Collaborators:

- Department of Molecular Medicine and Institute of Biotechnology, University of Texas Health Science Center at San Antonio,
- Faculty of Health Sciences, University of Macau, Macau SAR China
- Department of Genetics, Cancer Genomics Netherlands,
- Department of Cellular and Structural Biology, University of Texas Health Science Center at San Antonio,
- The Cancer Therapy Research Center, University of Texas Health Science Center at San Antonio,
- The Barshop Center of Aging, University of Texas Health Science Center at San Antonio,
- Greehey Children's Cancer Research Center, University of Texas Health Science Center at San Antonio

Citation:

Young Son et al. 2016. A mechanism for 1,4-Benzoquinone-induced genotoxicity. [Oncotarget](#). 2016 Jun 20. doi: 10.18632/oncotarget.



TRANSLATIONAL POINT 6

Translational Research Description:

- (C/ID) Crebbp^{-/-} ES cells were very resistant to many genotoxic agents

Science and Setting Translational Ring:

Driver: Understanding

Experimental Setting: In vitro

Organism: Mice

Timeframe: ?

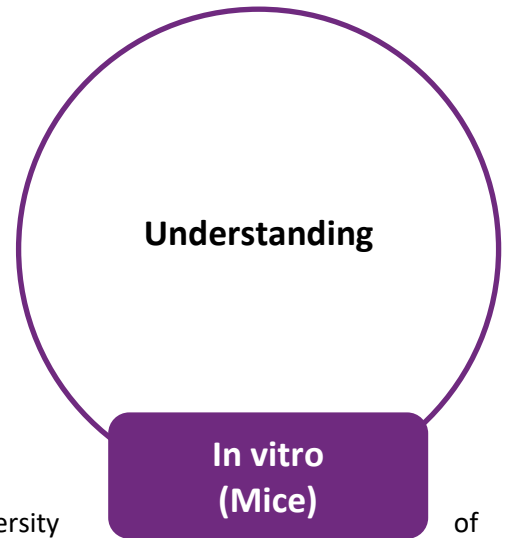
Collaborators:

- Department of Molecular Medicine and Institute of Biotechnology, University of Texas Health Science Center at San Antonio,
- Faculty of Health Sciences, University of Macau, Macau SAR China
- Department of Genetics, Cancer Genomics Netherlands,
- Department of Cellular and Structural Biology, University of Texas Health Science Center at San Antonio,
- The Cancer Therapy Research Center, University of Texas Health Science Center at San Antonio,
- The Barshop Center of Aging, University of Texas Health Science Center at San Antonio,
- Greehey Children's Cancer Research Center, University of Texas Health Science Center at San Antonio

Citation:

Young Son et al. 2016. A mechanism for 1,4-Benzoquinone-induced genotoxicity. [Oncotarget](#). 2016 Jun 20. doi: 10.18632/oncotarget.

Kim et al. 2015. Defining a genotoxic profile with mouse embryonic stem cells. [Exp Biol Med \(Maywood\)](#). 2013 Mar;238(3):285-93. doi: 10.1177/1535370213480700.



EMBARGOED: TRANSLATIONAL POINT 7

Translational Research Description:

- Soon to be published research on the mutation frequency and spectrum in hematopoietic population in Crebbp+/- mice as they age.

Science and Setting Translational Ring:

Driver: Understanding

Experimental Setting: Ex vivo

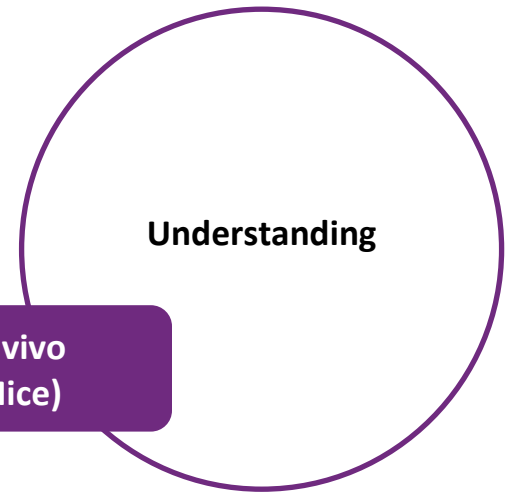
Organism: Mice

Timeframe: 2015-2016

Collaborators:

Source:

Grant Application.



EMBARGOED: TRANSLATIONAL POINT 8

Translational Research Description:

- Soon to be published research linking mutation frequency with γ -radiation spectrum

Science and Setting Translational Ring:

Driver: Understanding

Experimental Setting: In vivo

Organism: Mice

**In vivo
(Mice)**

Understanding

Timeframe: 2015-2016

Collaborators:

Source:

Grant Application.



EMBARGOED: TRANSLATIONAL POINT 9

Translational Research Description:

- Soon to be published research finding that Crebbp^{+/-} hematopoietic mice populations have reduced nonhomologous end-joining.
- Crebbp^{+/-} mice develop MDS as the expression of most DNA repair genes decline, including genes for homologous recombination and Fanconi anemia indicating a general decrease in DNA repair.

Science and Setting Translational Ring:

Driver: Understanding

Experimental Setting: Population

Organism: Mice

Timeframe: 2015-2016

Collaborators:

Source:

Grant Application.

Population
(Mice)

Understanding