CELL CYCLE-DEPENDENT EPIGENOMIC THERAPEUTICS IN PANCREATIC CANCER

Gwen Lomberk, PhD
Pancreatic cancer has the **lowest** relative survival rate of all major cancers.

(Source: American Cancer Society)

**Five-Year Survival Rate**

- **Nearly 100%**
- **90%**
- **16%**
- **6%**

(Source: American Cancer Society)
• In Wisconsin, the incidence of pancreatic cancer is 13.68 per 100,000 persons per year, which is significantly higher than the national average of 10.9 per 100,000 persons per year.

• In addition, Milwaukee County has one of the highest rates of pancreatic cancer mortality in the U.S., 15% higher than the national average.
EPIGENETICS IN CANCER

Lomberk Laboratory

Discovery of novel, druggable, epigenomic-based molecular mechanisms that operate during pancreatic carcinogenesis

Advance the field of experimental therapeutics by evaluating the effects of pharmacologically targeting these epigenomic pathways.
EPIGENETICS: DEFINITION AND HISTORY

C.H. Waddington coined the term epigenetics in 1942 to mean above or in addition to genetics to explain differentiation.
STRICT DEFINITION OF EPIGENETICS

The study of heritable changes in genome function that occur without alterations to the DNA sequence.
Particular states that define cell identity are attained by heritable instructions — the epigenetic marks that determine whether, when and how particular genetic information will be read.
Marks on the DNA and Surrounding Proteins (e.g.: Histones) Signal to Induce Transitions between Euchromatin (genes on) and Heterochromatin (genes off)

Physiological or Pathological Stimuli Chemically Modify (Mark) the Genome and the Epigenome. These Marks are Interpreted into Defined Patterns of Gene Expression that Give Rise to the Inheritable Phenotypes.
REGULATORS OF THE EPIGENETIC CODE: WRITERS, ERASERS AND READERS

Epigenetic Marks are deposited by writer enzymes to turn genes on/off
Epigenetic Marks are interpreted by reader proteins to turn genes on/off
Epigenetic Marks are removed by eraser enzymes to reverse previous codes

Modified histone residues serve as recognition marks that facilitate or prevent binding of proteins to TRANSLATE THE EPIGENETIC CODE
• Writer of the H3K9me2 mark

• Generally speaking, H3K9me2 is considered a repressive mark

• Several small molecule inhibitors have been developed against G9a
THE G9A “MARK” - H3K9ME2 IN HUMAN PDAC

• 53% (24/45) have high H3K9me2 levels
• H3K9me2-high vs H3K9me2-low tumors do not associate with a histological subtype
ONCOGENIC Kras INCREASES H3K9me2 LEVELS

Cre

KrasG12D/Creat

![Image of tissue samples and bar graph showing increased H3K9me2 levels in KrasG12D/Creat compared to Cre. The bar graph indicates a significant difference (**) between WT and KRAS groups.]
GENETIC INACTIVATION OF G9a IN THE KrasG12D MODEL OF PanIN FORMATION

Pdx1 or P48Cre/KrasG12D X G9a<sup>fl/fl</sup>

Pdx1 or P48Cre/KrasG12D/G9a<sup>fl/fl</sup>

8 weeks

-Histology
-Protein lysates
-RNA-seq

n=11-17; Scale bar=0.1mm; *p<0.05; **p<0.005
Advantages:

- Epigenomic events are reversible
- Increasing development of drugs targeting epigenetic regulators
- Several FDA approved

Remaining Challenges:

- Toxicity
- Limited knowledge to use these drugs effectively
- Are we taking advantage of what they can truly offer?

https://www.nature.com/articles/d42473-018-00054-8
Utility of Epigenomic Inhibitors within the Context of the Cell Cycle - Mechanistic Window of Opportunity?
Utility of Epigenomic Inhibitors within the Context of the Cell Cycle - Mechanistic Window of Opportunity?
AurkA and panH3K9 HMT inhibition induce mitotic aberrations which, when combined, cause significant mitotic catastrophe

Utility of Epigenomic Inhibitors within the Context of the Cell Cycle - Mechanistic Window of Opportunity?
ATR–CHK1 PATHWAY DURING DNA REPLICATION

https://www.nature.com/articles/ncb2897
DUAL TARGETING OF CHK1 AND G9a INHIBITS PDAC

2019 Scientific Retreat Together, Taking on Cancer’s Toughest Challenges
Combined prexasertib-BRD4770 treatment synergizes to trigger DNA replication arrest.
Combined CHK1 and G9a inhibition triggers DNA damage.

P-Ser139 H2A.X

% of cells

2019 Scientific Retreat Together, Taking on Cancer’s Toughest Challenges
Dual CHK1-G9a inhibition impedes replication forks.
Dual CHK1-G9a inhibition impedes replication forks.
Dual CHK1-G9a targeting triggers the RS response.
RS response occurs in combination-treated xenografts.

**P-H2A.X**

**P-RPA32**

**Ki-67**

**TUNEL**
SUMMARY

We have achieved a synergistic effect through the disruption of coordinated events at the replication fork, triggering replication stress and ultimately replication catastrophe from a deficiency in vital checkpoints.
CONCLUSION

Consideration for the utility of epigenomic inhibitors within the context of the cell cycle offers a mechanistic window of opportunity and a fine-tuned approach to use this class of inhibitors more effectively.
Together, Taking on Cancer’s Toughest Challenges

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If you want to go fast, go alone.

If you want to go far, go together.

– African Proverb

THANK YOU!