



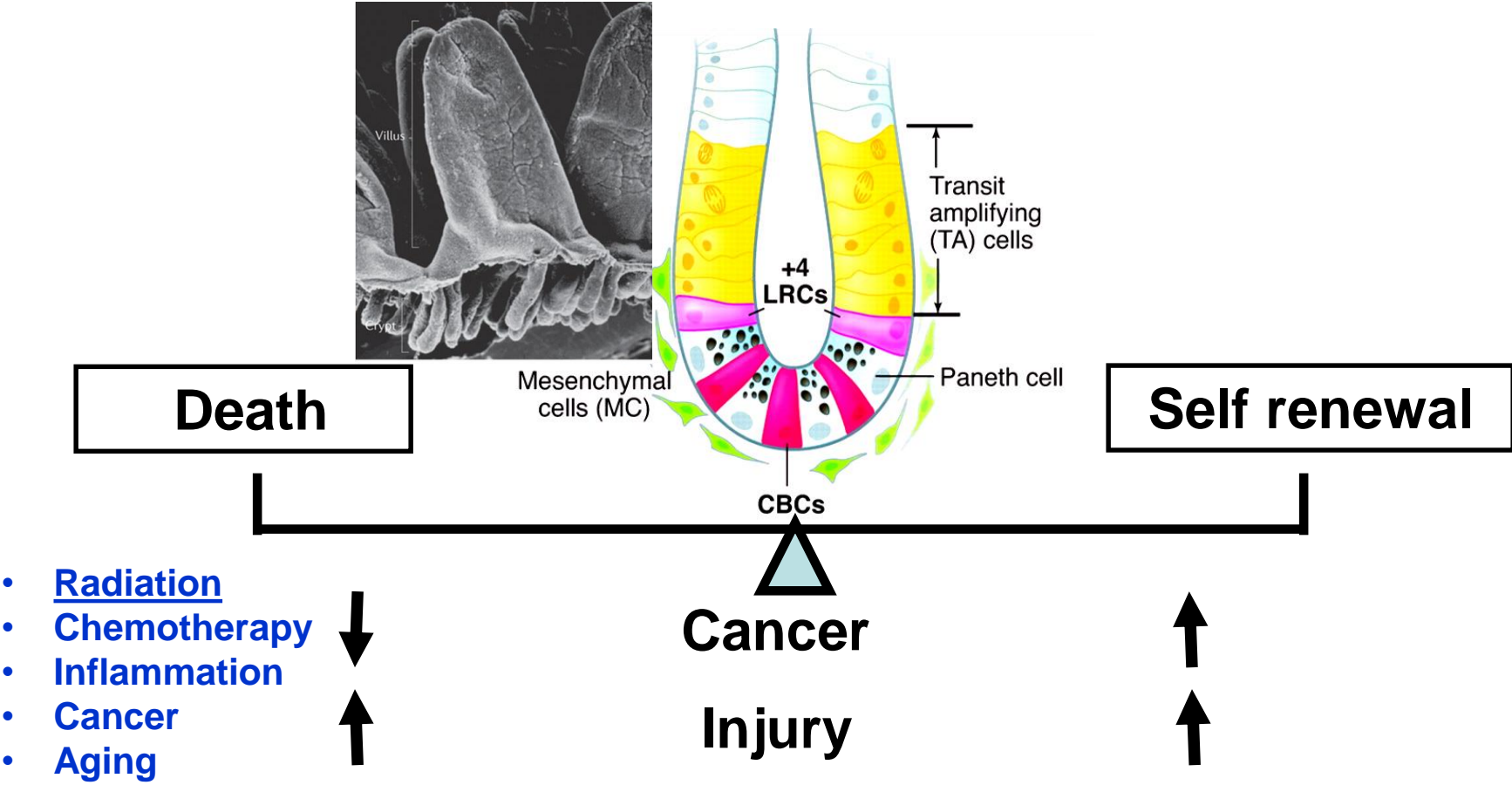
Intestinal stem cell protection by induced quiescence

**Jian Yu, Ph.D.
yuj2@upmc.edu**

**Professor of Pathology and Radiation Oncology
University of Pittsburgh School of Medicine
University of Pittsburgh Cancer Institute**

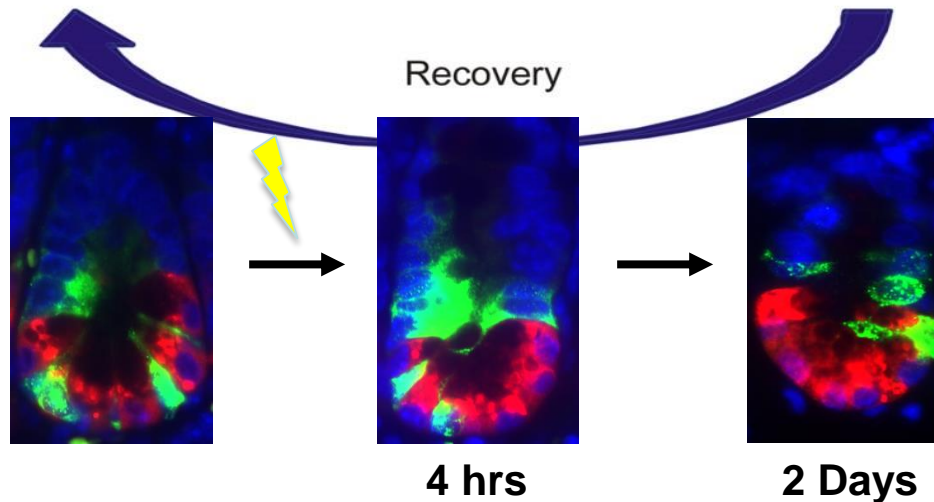
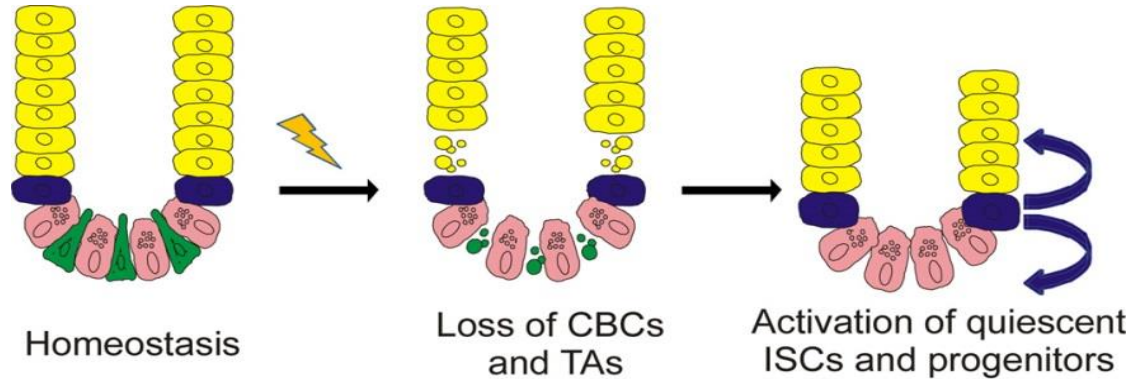
Nov 11 2016, GZ

ISC injury underlies GI pathology



How fast: 3-5 days renewal cycle , 1% BW/Day

ISC injury and regeneration induced by radiation



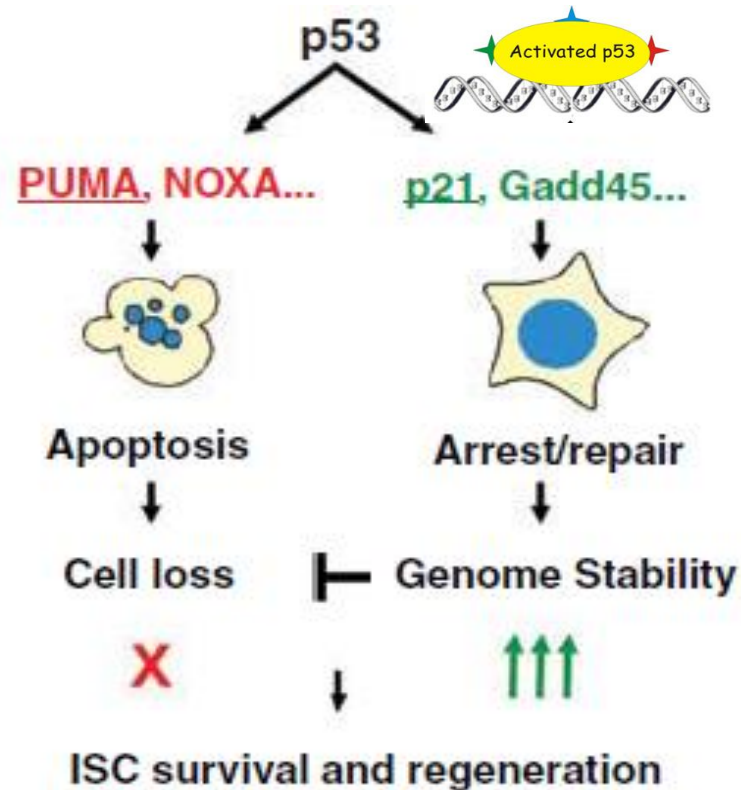
Yu Jian (2013)
Transl Cancer Res

2Qs in ISC longevity -Quantity and Quality

p53 and ISC DDR



IR, Chemo, Telomere loss...



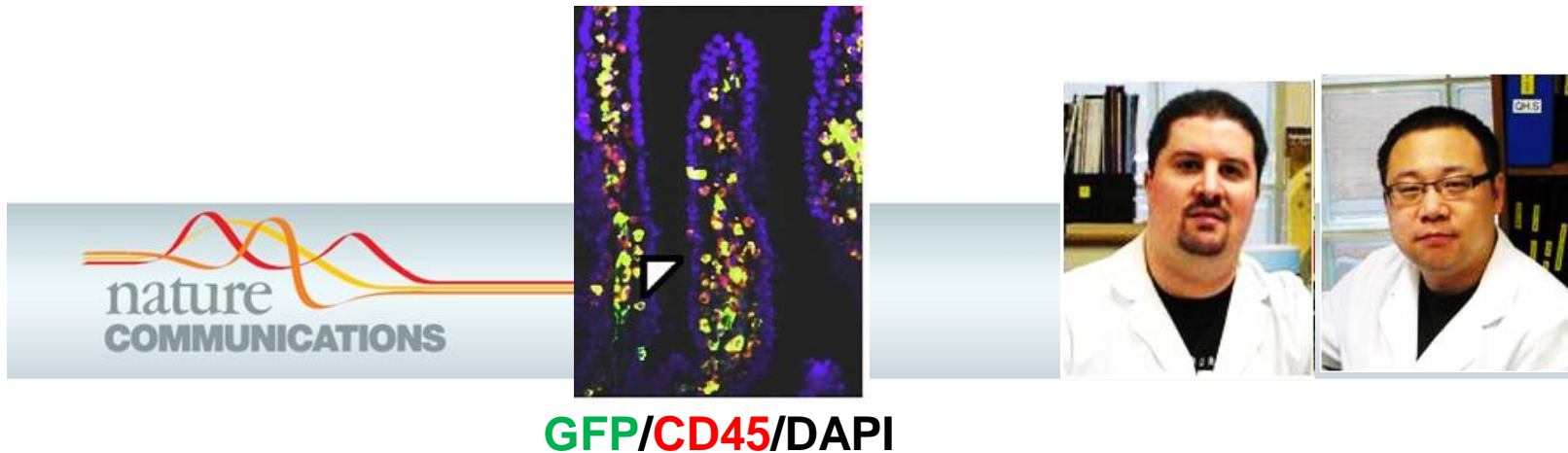
Qiu W *et al.*, *Cell Stem Cell* 2008, *Oncogene* 2011

Leibowitz B *et al.*, *Mol Can Res.*, 2011; *Nat. Comm.*, 2014

Wang X, *et al.*, *Sci Rep* 2015

Wang Y *et al.*, *Aging Cell* 2015

Epithelial damage underlies lethal GI syndrome



GFP/CD45/DAPI

ARTICLE

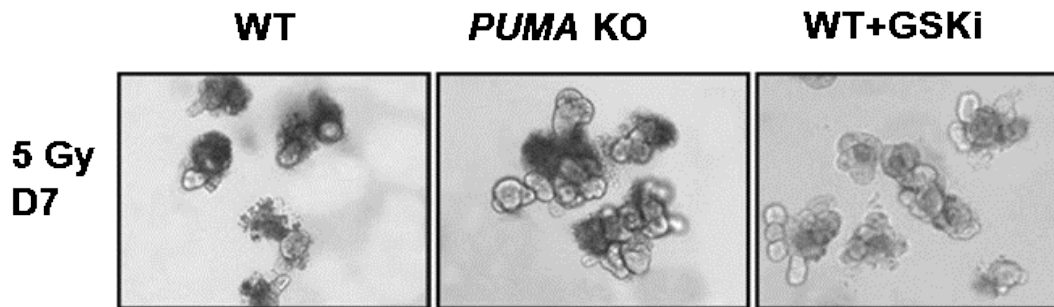
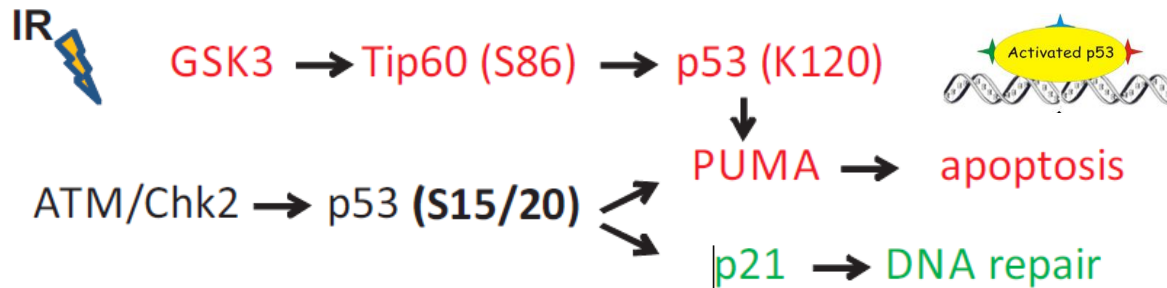
Received 1 Oct 2013 | Accepted 24 Feb 2014 | Published 18 Mar 2014

DOI: 10.1038/ncomms4494

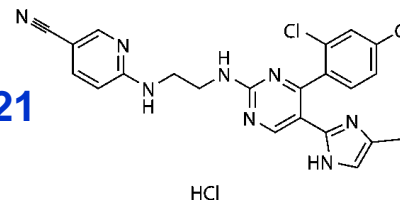
Ionizing irradiation induces acute haematopoietic syndrome and gastrointestinal syndrome independently in mice

Brian J. Leibowitz^{1,*}, Liang Wei^{1,*}, Lin Zhang², Xiaochun Ping³, Michael Epperly³, Joel Greenberger³, Tao Cheng^{3,4} & Jian Yu^{1,3}

PUMA mediates IR-induced ISC apoptosis *in vitro*



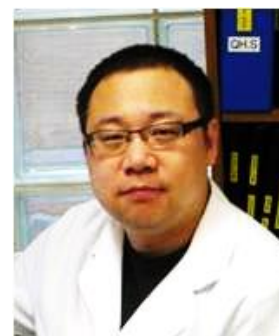
CHIR99021



Inhibition of CDK4/6 protects against radiation-induced intestinal injury in mice

Liang Wei,¹ Brian J. Leibowitz,¹ Xinwei Wang,¹ Michael Epperly,² Joel Greenberger,² Lin Zhang,³ and Jian Yu^{1,2}

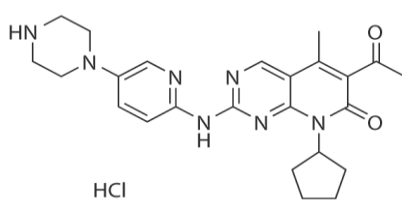
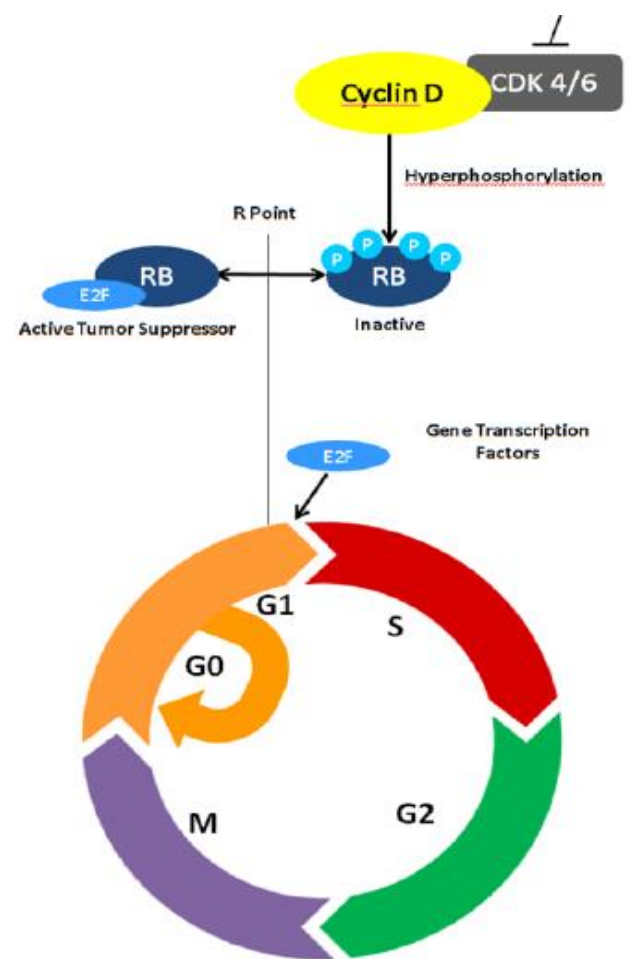
¹Department of Pathology, ²Department of Radiation Oncology, ³Department of Pharmacology and Chemical Biology, University of Pittsburgh School of Medicine, University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania, USA.



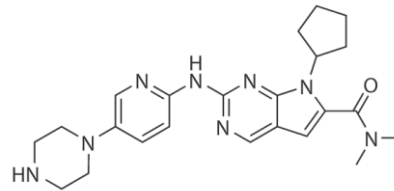
CDK4/6 inhibitors

- Palbociclib/PD0332991 is a FDA-approved oral, reversible and ATP competitive inhibitor of CDK4/6.
- Blocks Rb phosphorylation, E2F activation and the G1/S transition.

CDKi

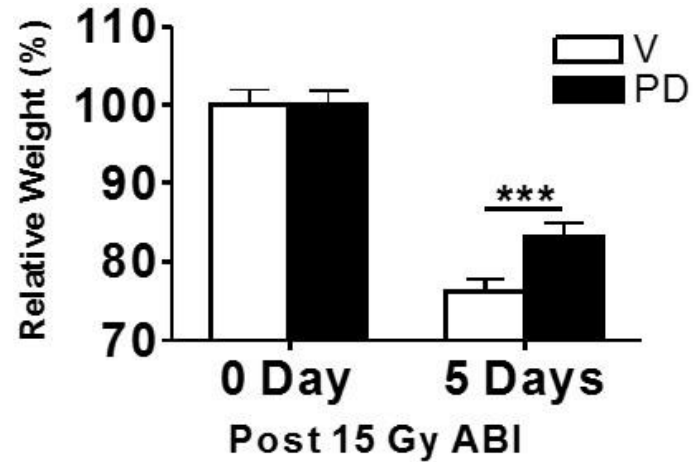
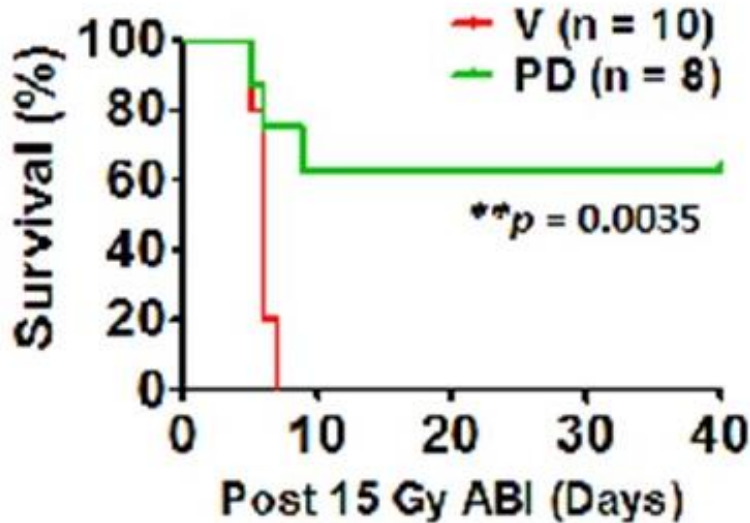
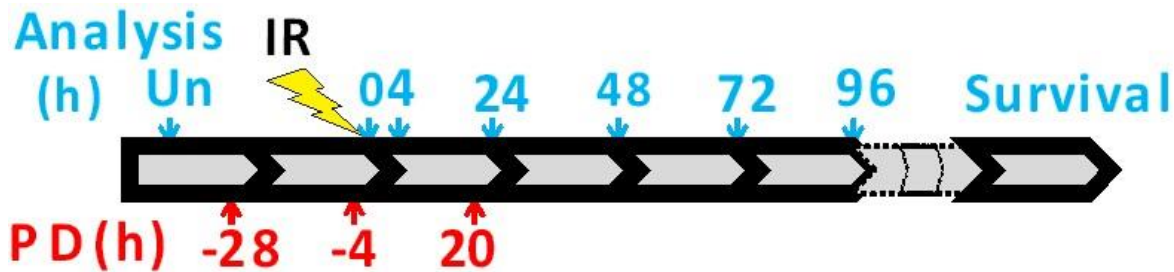


PD0332991

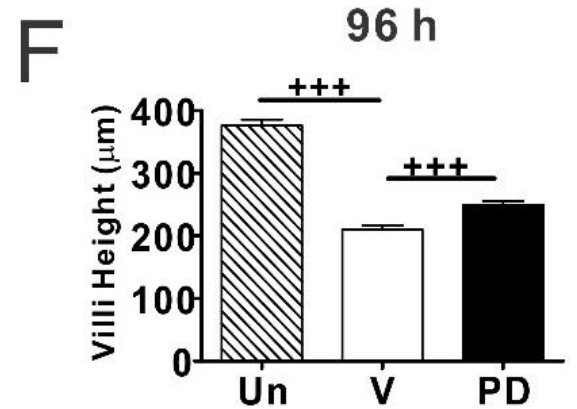
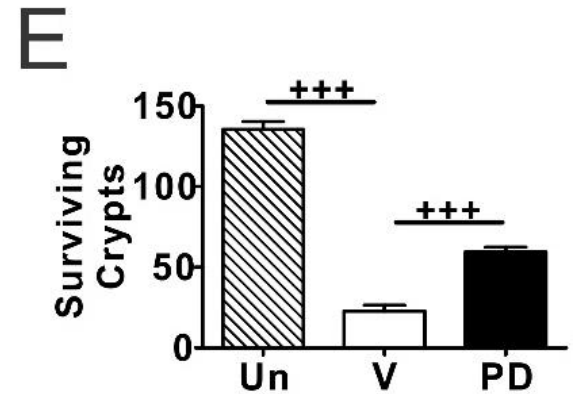
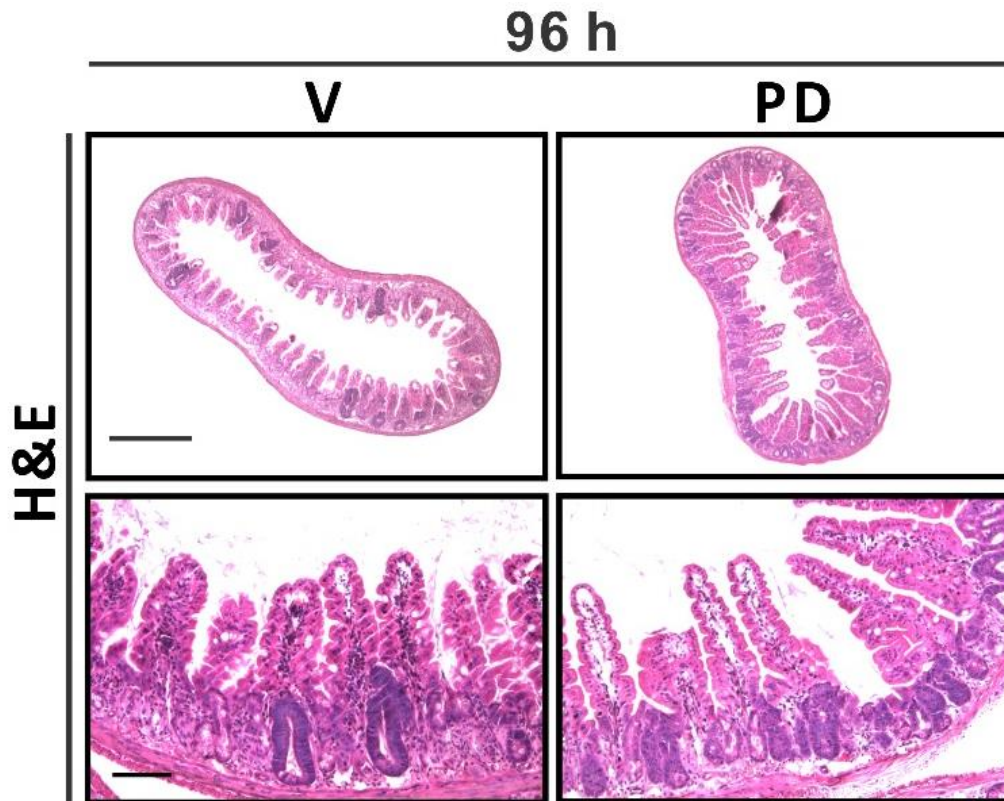


LEE011

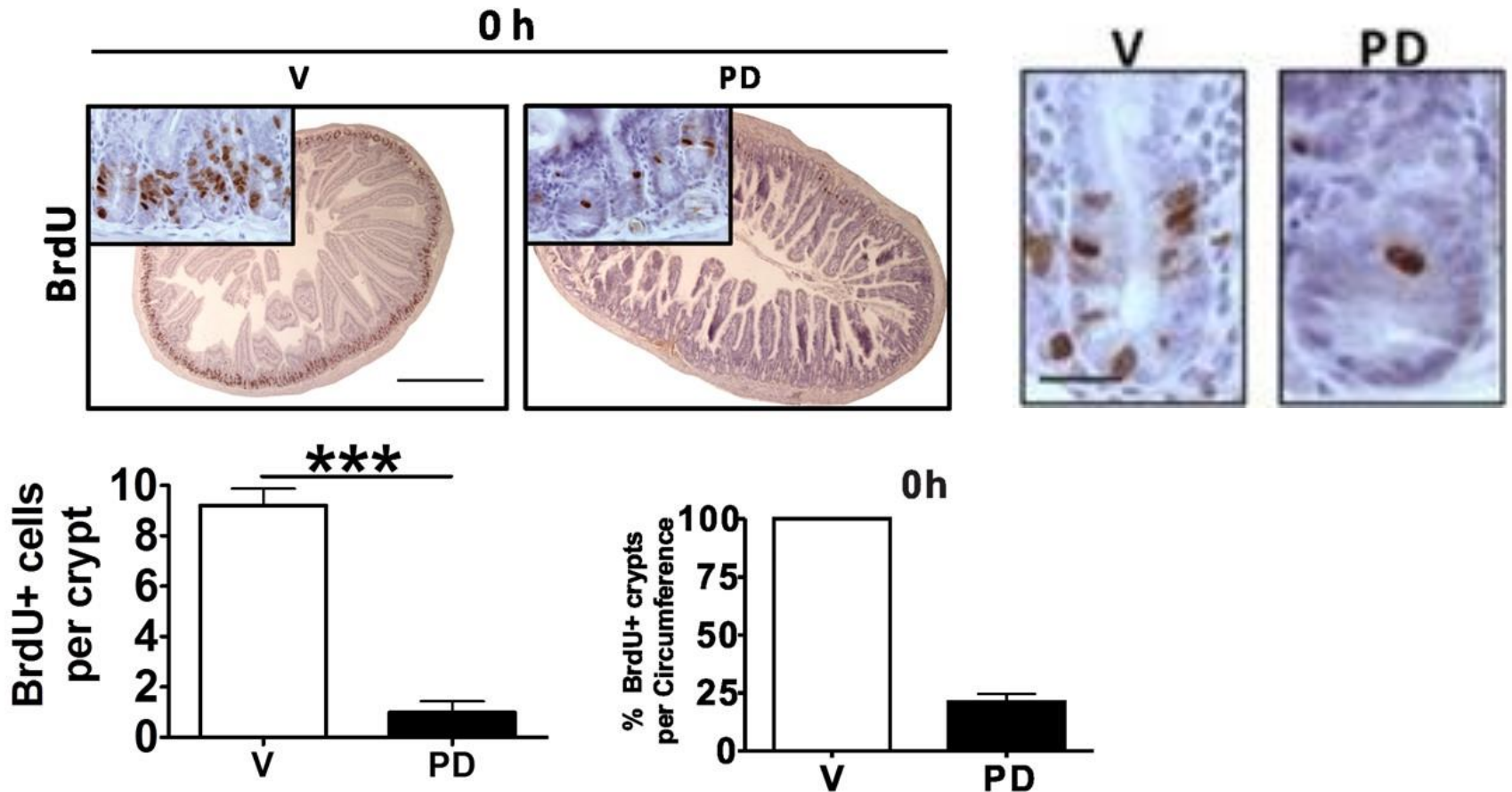
PD protects against IR-induced lethal GI injury



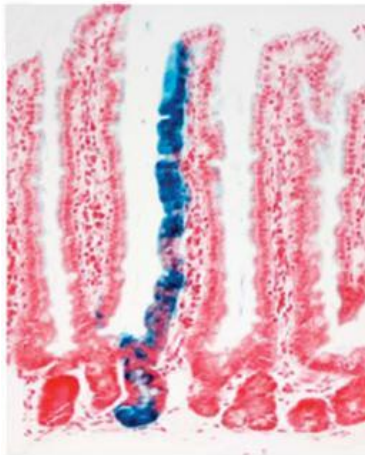
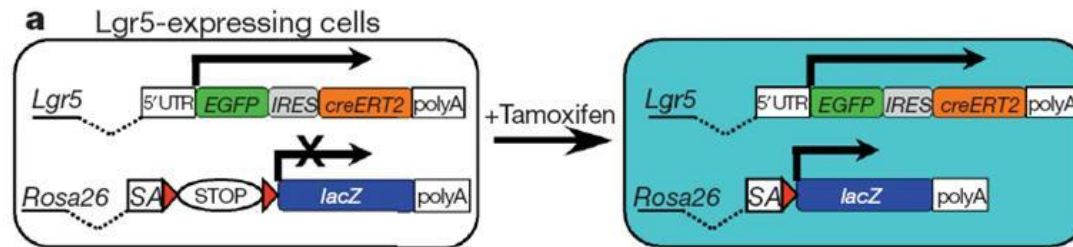
PD protects against IR-induced lethal GI damage



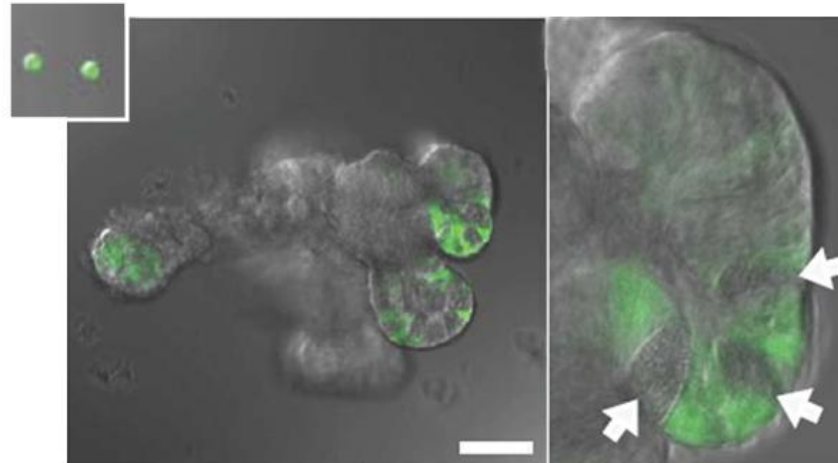
PD blocks the G1/S transition in intestinal epithelium



Lgr5 intestinal stem cells



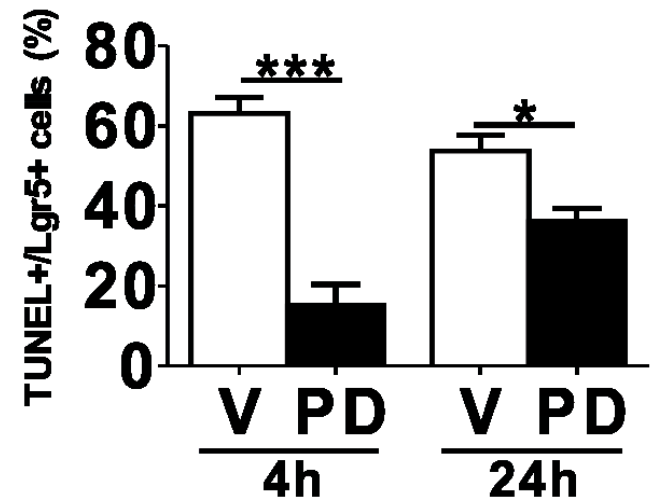
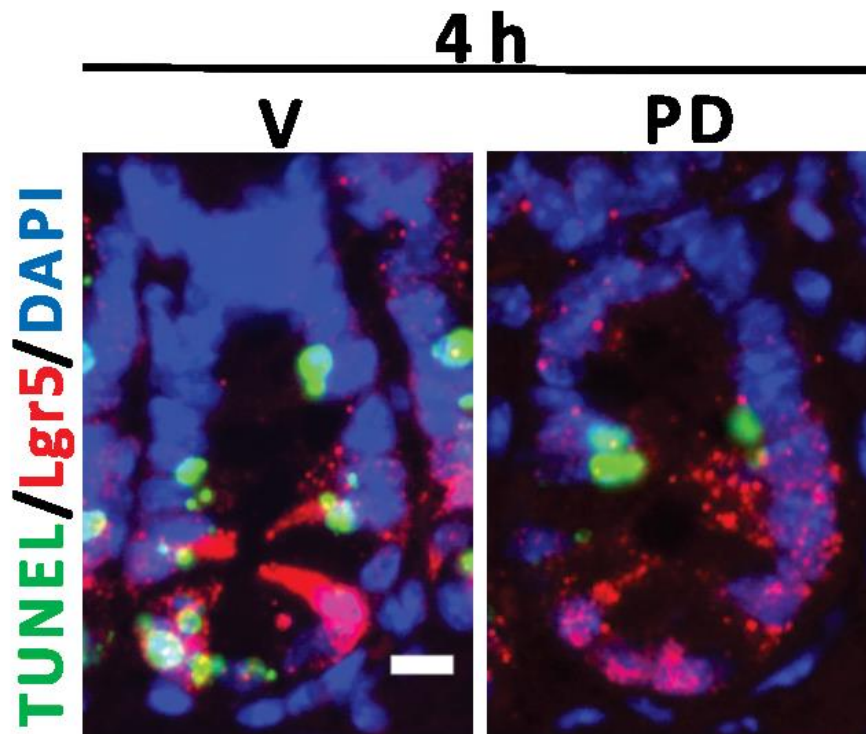
In Vivo



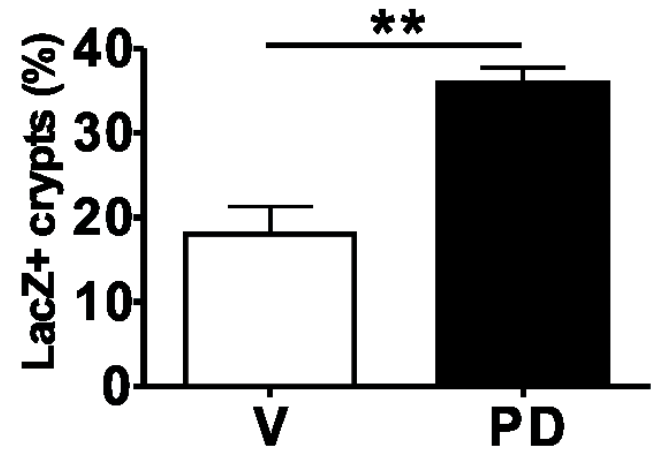
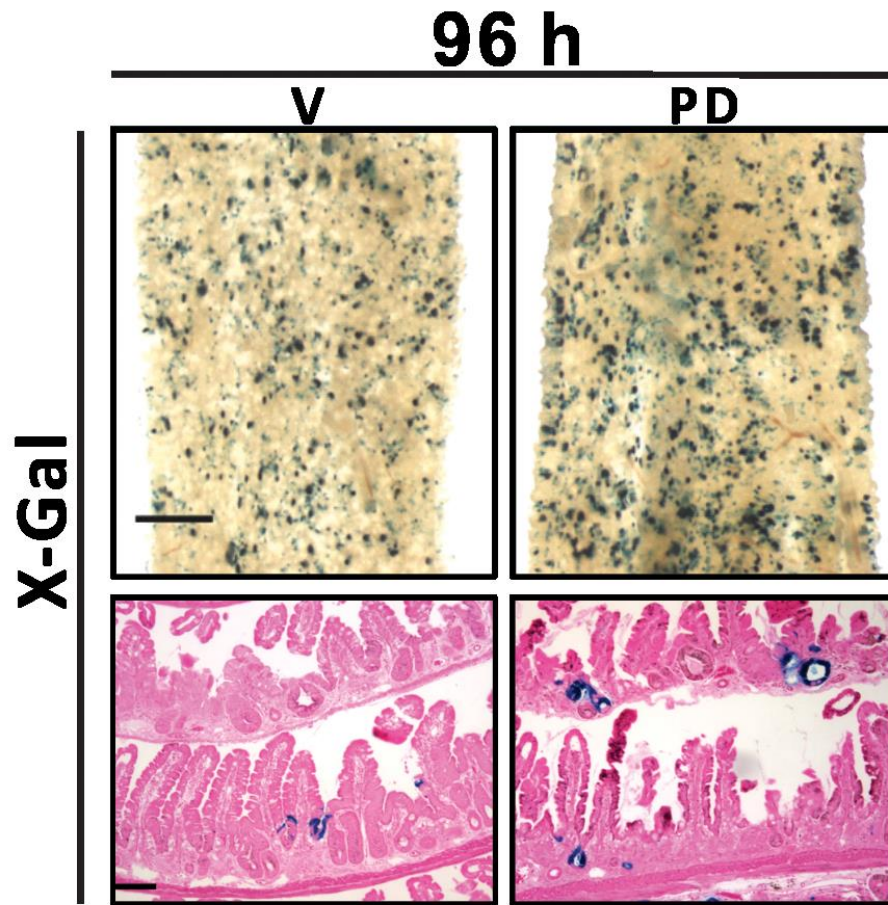
In Vitro

Barker N, et al. Nature 449, 1003-1008 (2007) Sato T, et al. Nature 459, 262-266 (2009)

PD protects Lgr5 stem cells



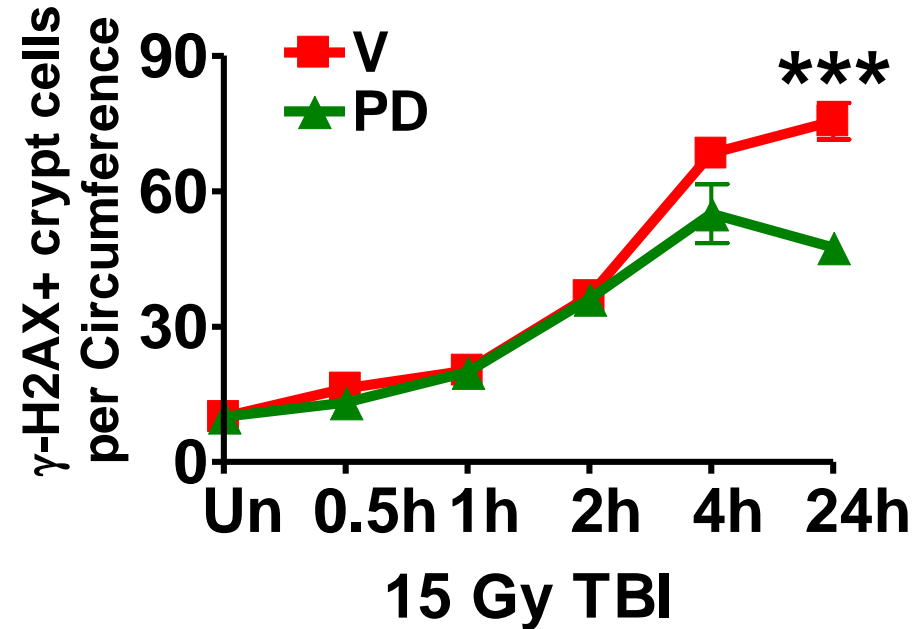
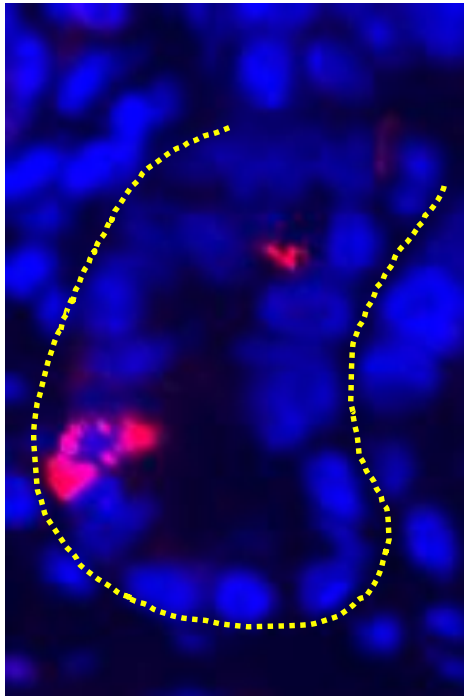
PD enhances Lgr5 cell regeneration



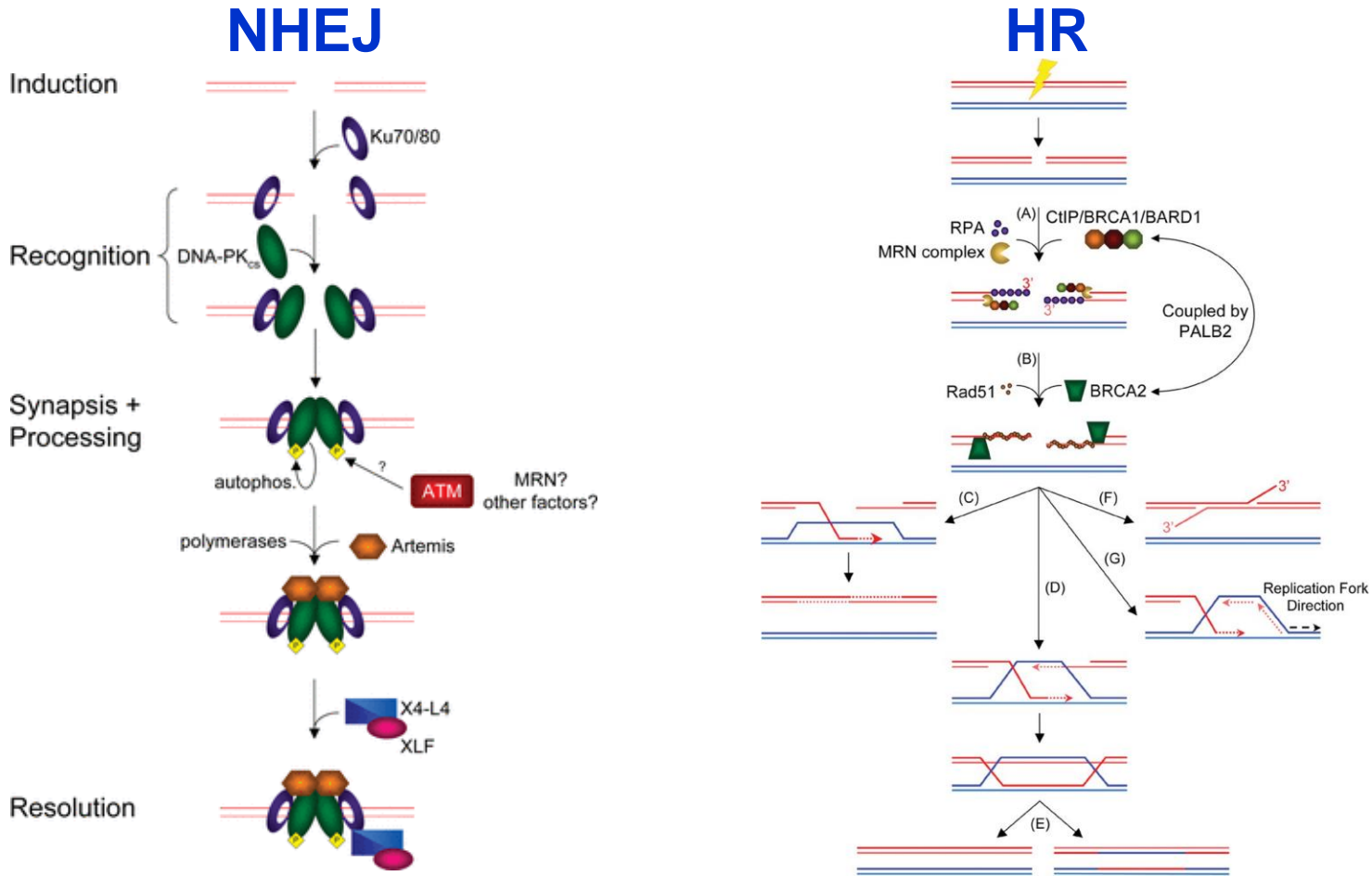
PD prevents DNA damage accumulation

V-4h

γ -H2AX/DAPI

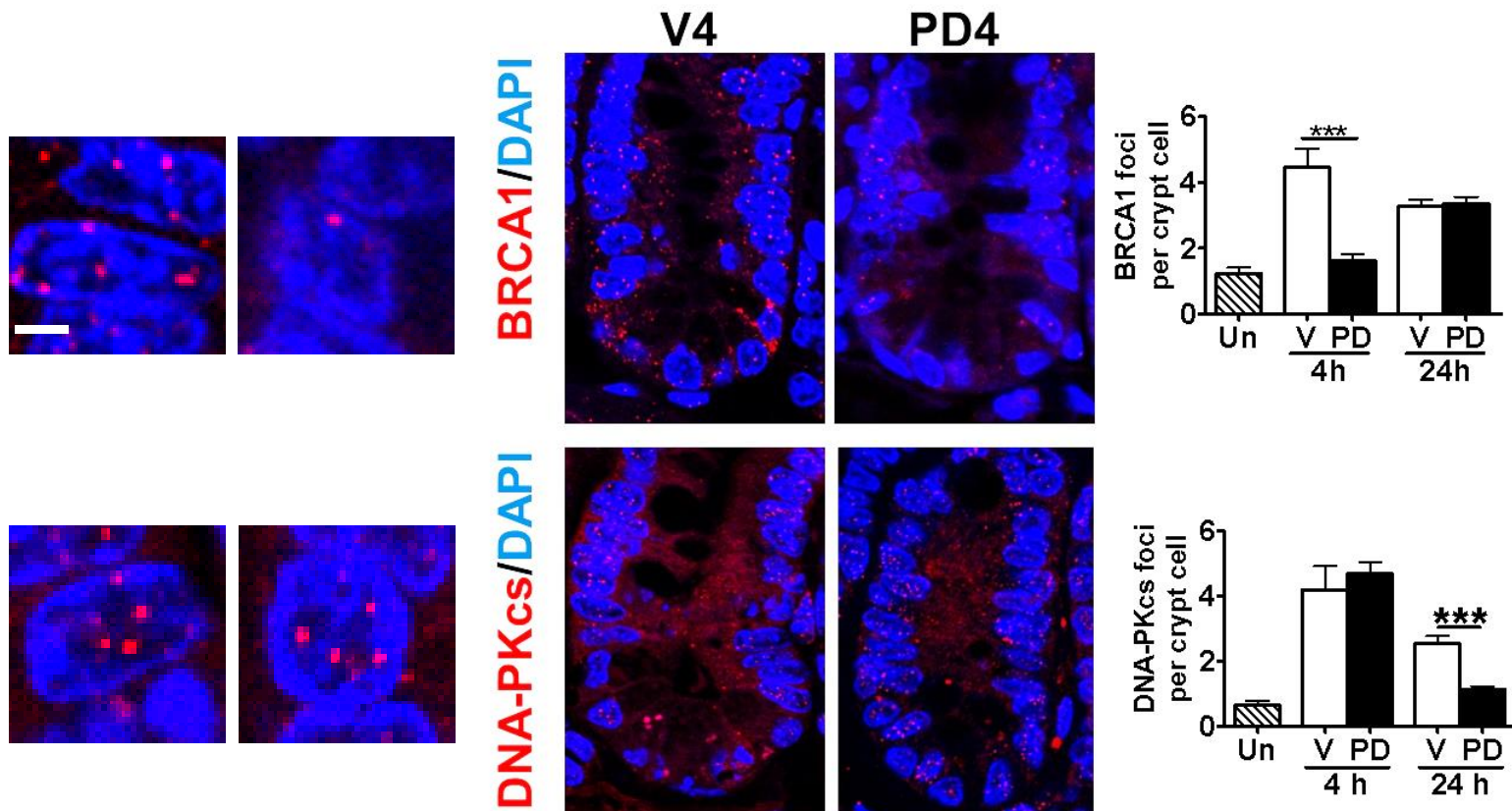


DNA double strand break repair



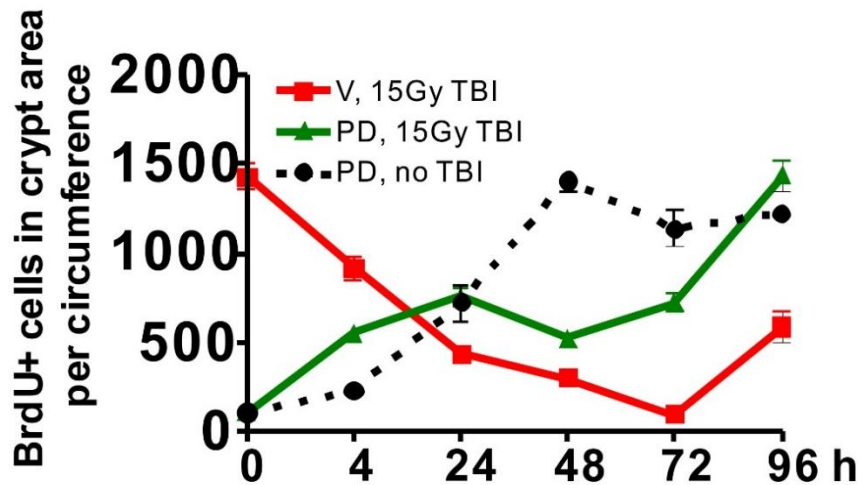
- Cell cycle & DNA sequence independent
- Adaptive Immunity VDJ

PD alters DNA repair pathway choice

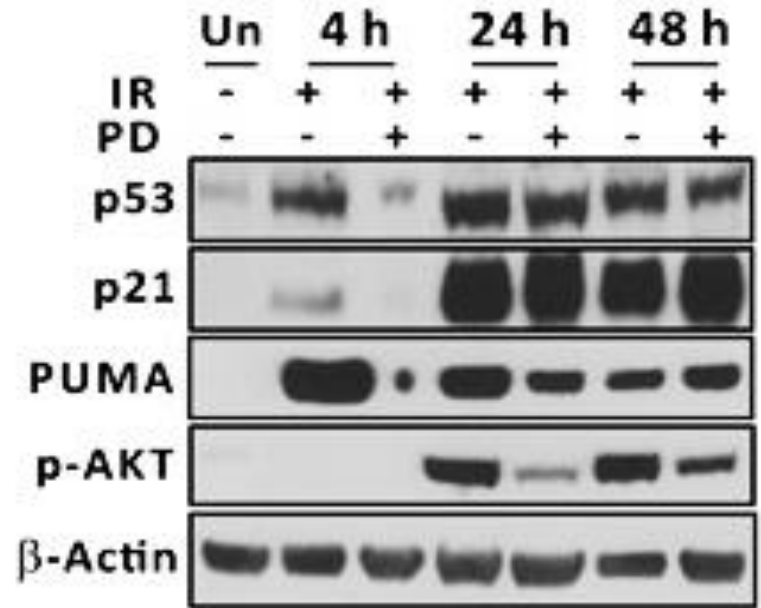


Not stem cell selective!

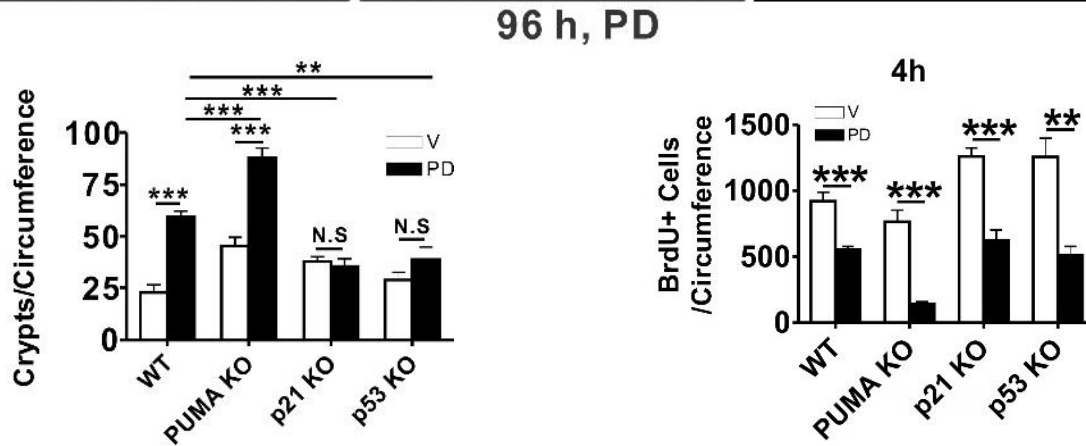
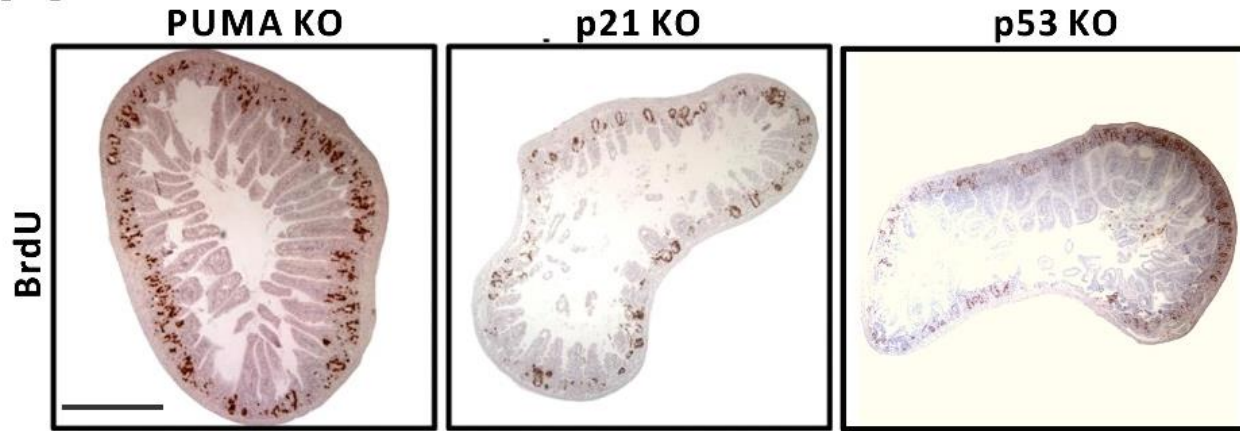
PD induces transient quiescence and p53 inactivation



↑ ↑ ↑ PD
 - 28/- 4 h +20 h



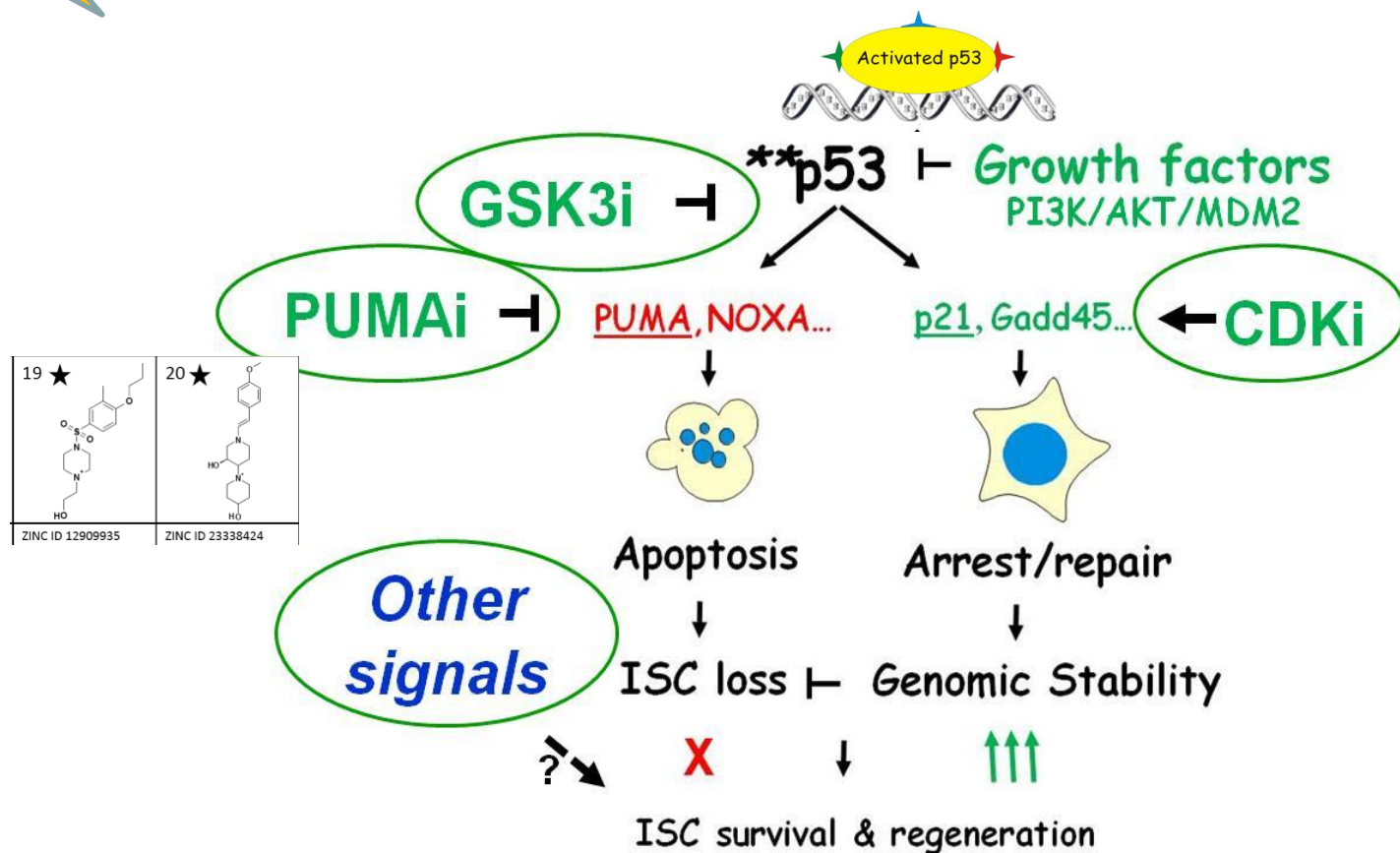
p53-dependent protection by PD is enhanced by *PUMA* KO



Sitting even tighter, and be bullet proof with p53!

Precision ISC protection

⚡ IR, Chemo, Telomere loss...





Acknowledgements

Current lab members

- Brian Leibowitz, Ph.D
- Liang Wei, Ph.D
- Hang Ruan, Ph.D
- Mei, Li, Ph.D
- Penny Peng
- Cheng Bi

Past members:

- Xinwei Wang, MD. Ph.D
- Wei Qiu, Ph.D
- Coleen Judge

Collaborators:

University of Pittsburgh

Lin Zhang, Ph.D

Joel S. Greenberger, MD

Tao Cheng, MD

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