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for Diagnosis & Regeneration in Thoracic Diseases & Applied Immunology

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Inhibition of the prostaglandin-degrading enzyme 15-PGDH potentiates tissue regeneration

JournalClub 14.12.2015

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Facts

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- published on the 12th of June 2015

Background

- After **HSC (hematopoietic stem cells) transplantation**, individuals are at high risk of potentially lethal infections, while awaiting regneration of peripheral blood cells.

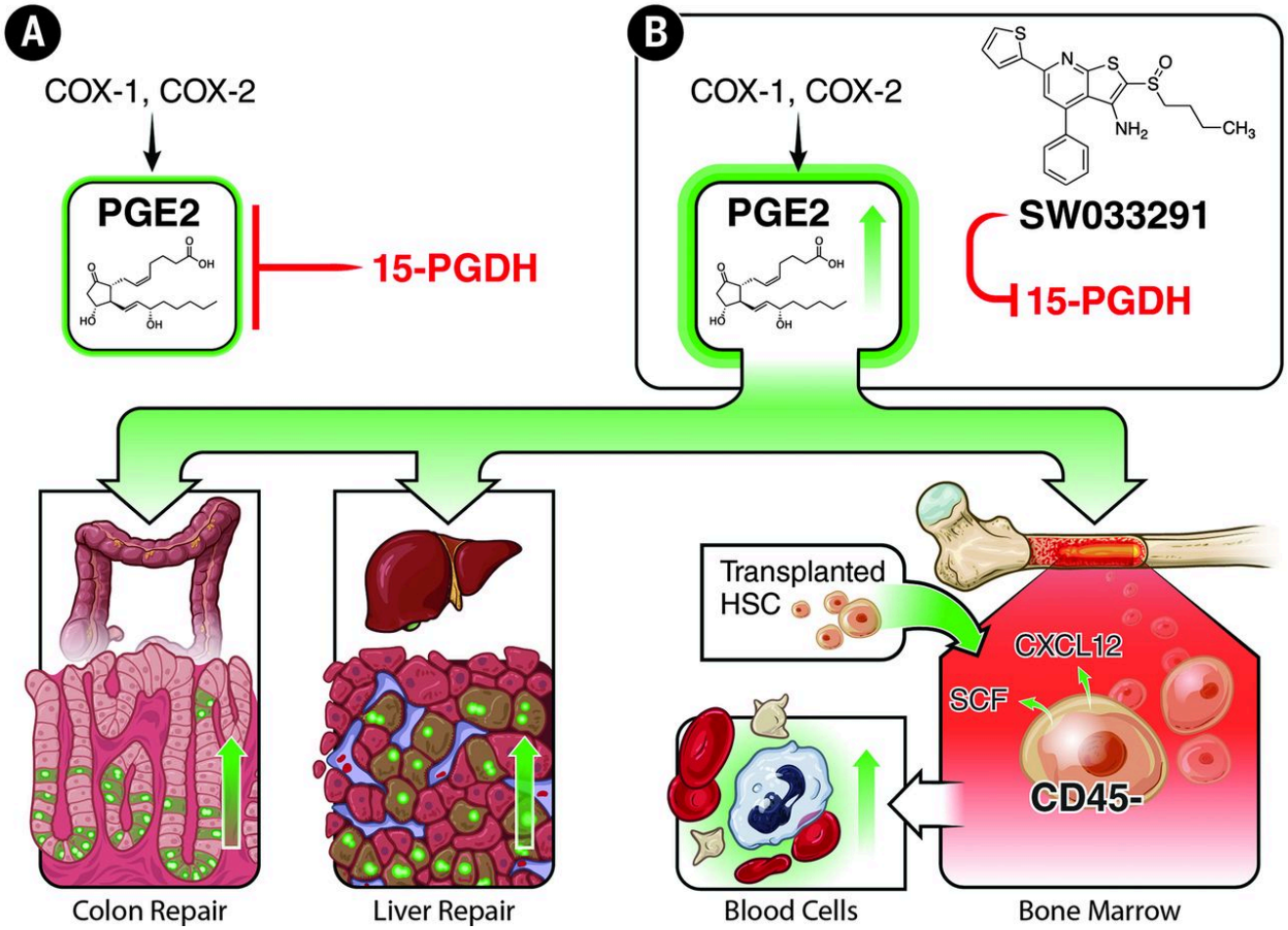
- **Ulcerative colitis** causes both gastrointestinal bleeding and diarrhea. Current treatments involve immune suppression, there are no therapies that potentiate healing and regeneration of damaged epithelium.

- Tissue regeneration is also required after **partial hepatic resection**, because the patient must regain adequate hepatic function**.**

Background

- Prostaglandin PGE2 is a candidate molecule for **potentiating regeneration** in multiple tissues.
- Hypothese: Alternative potential strategies for increasing PGE2-mediated tissue repair in vivo could be either to increase the synthesis of PGE2 or to inhibit the normally rapid in vivo **degradation of PGE2.**
- The enzym **15-PGDH** (15-hydroxyprostaglandin dehydrogenase**) is a negative regulator** of prostaglandin levels and activity.
- Explore: whether pharmacological **inhibition of 15-PGDH** can potentiate tissue repair in several mouse model of injury and disease.

Summary


A
COX-1, COX-2
PGE2
15-PGDH
B
COX-1, COX-2
PGE2
SW033291
15-PGDH
Transplanted HSC
CXCL12
SCF
CD45-
Colon Repair
Liver Repair
Blood Cells
Bone Marrow

Results

- Genetic deletion or pharmacologic **inhibition of 15-PGDH** increases tissue PGE2 levels
- 15-PGDH inhibition promotes **hematopoietic recovery** after bone marrow transplantation
- 15-PGDH inhibition protects mice from **colitis**
- 15-PGDH inhibition promotes **liver regeneration**

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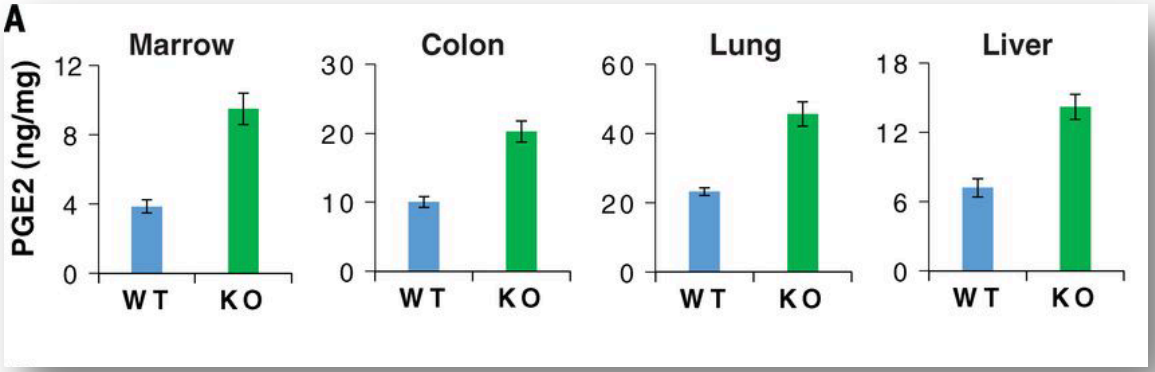
Biological effects of 15-PGDH inhibition in mice



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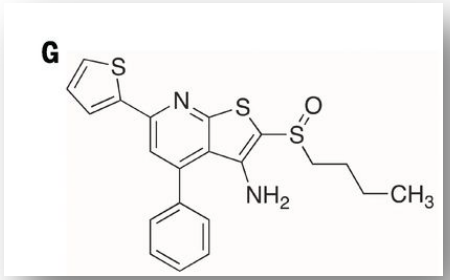
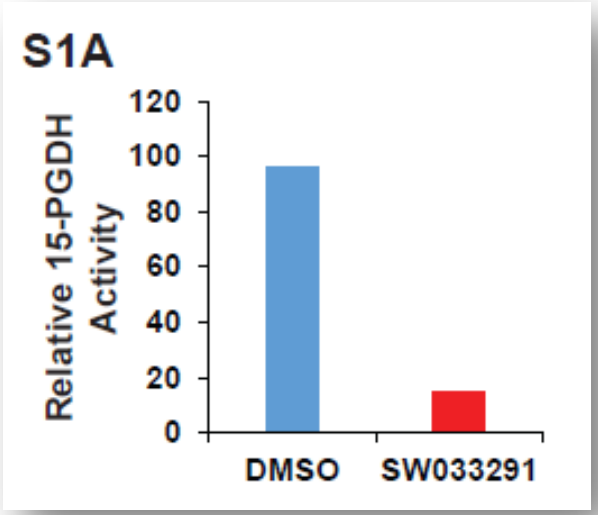
SW033291
The Inhibitor of 15-PGDH





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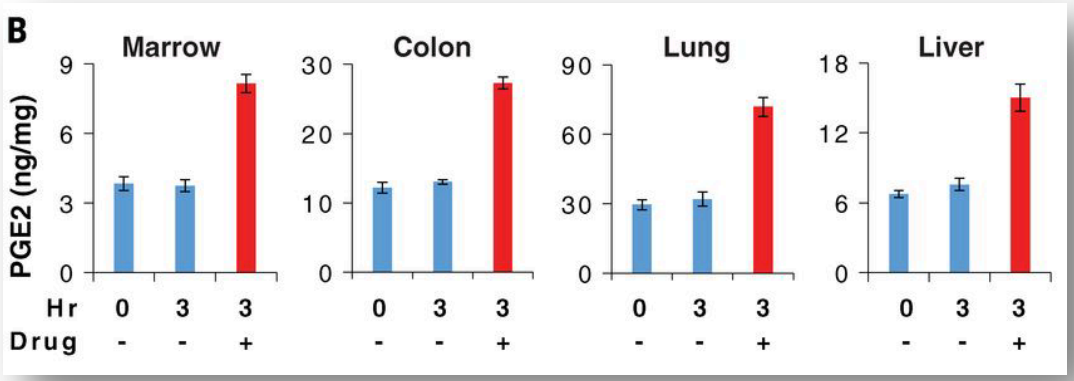
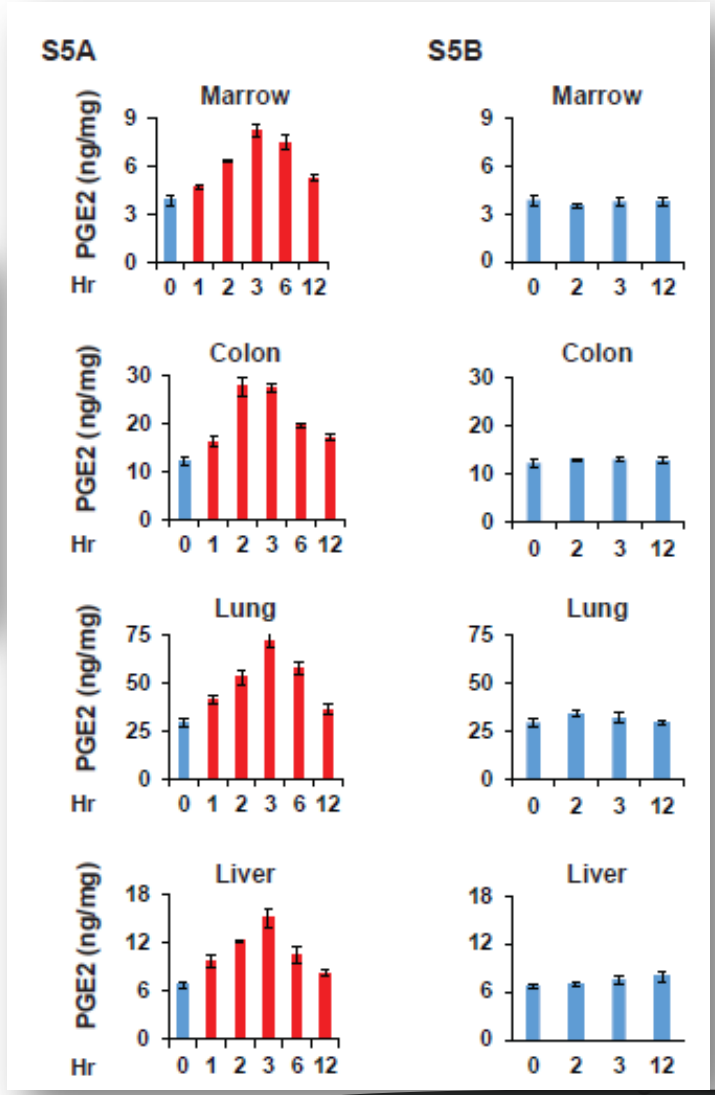
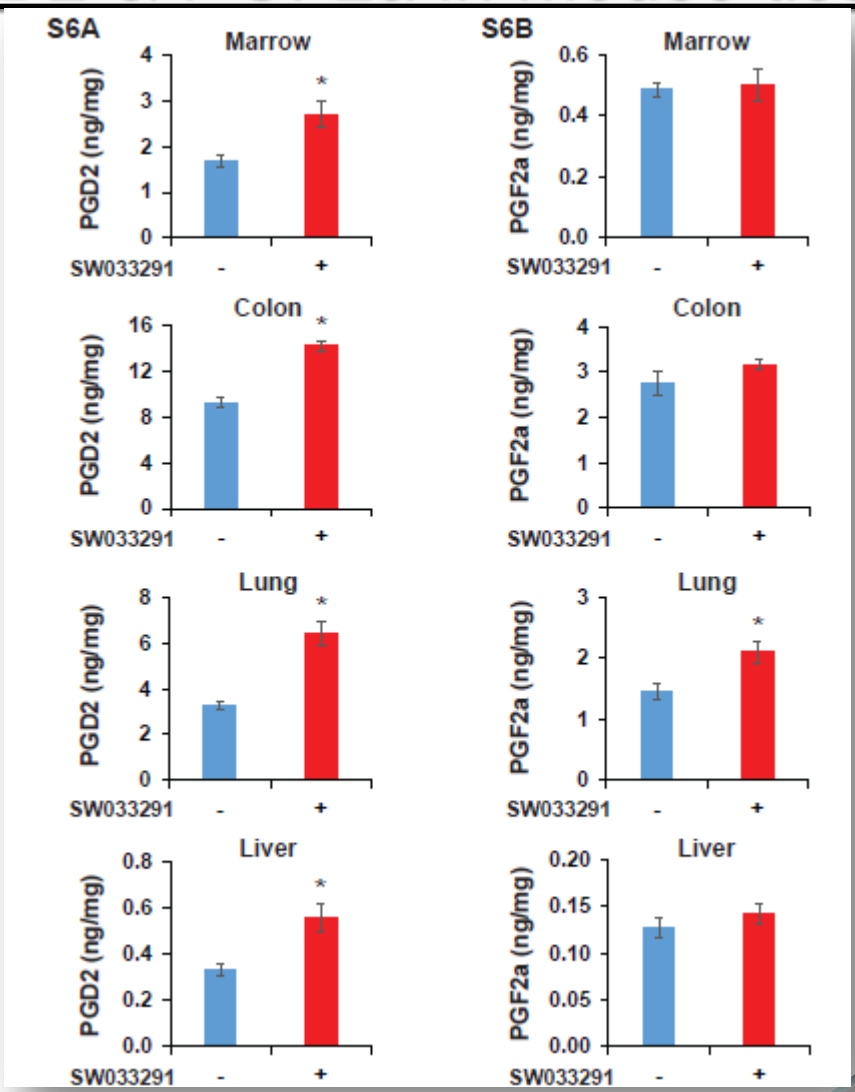
SW033291 induction of PGE2 in mouse tissues





SW033291 induction of PGD2 & PGF2a in mouse tissues



Results

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- 15-PGDH inhibition promotes **hematopoietic recovery** after bone marrow transplantation
- 15-PGDH inhibition protects mice from **colitis**
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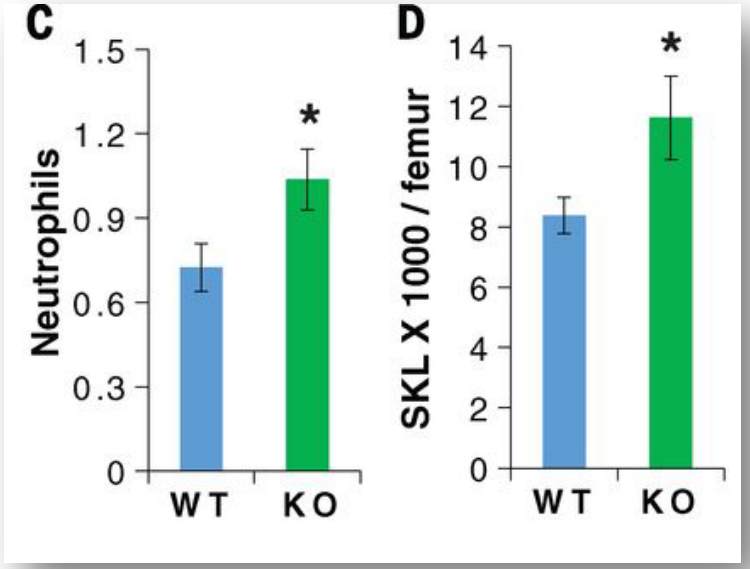
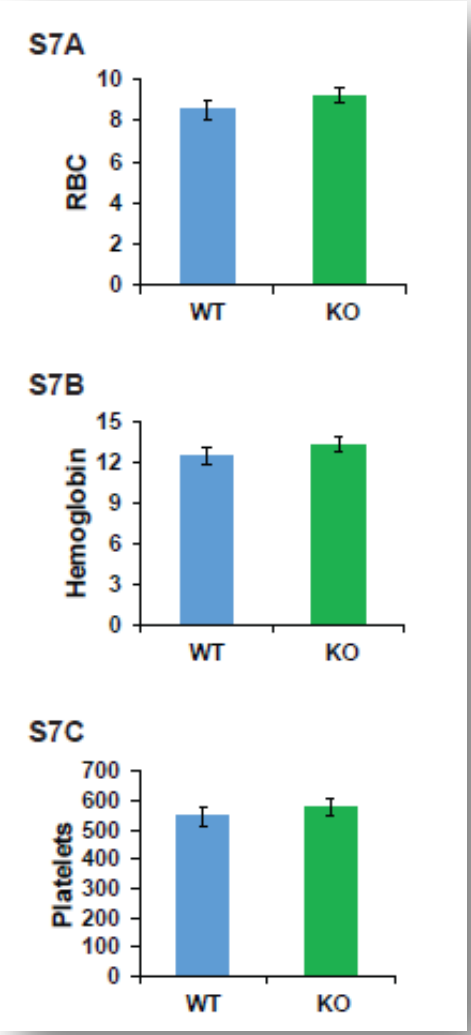
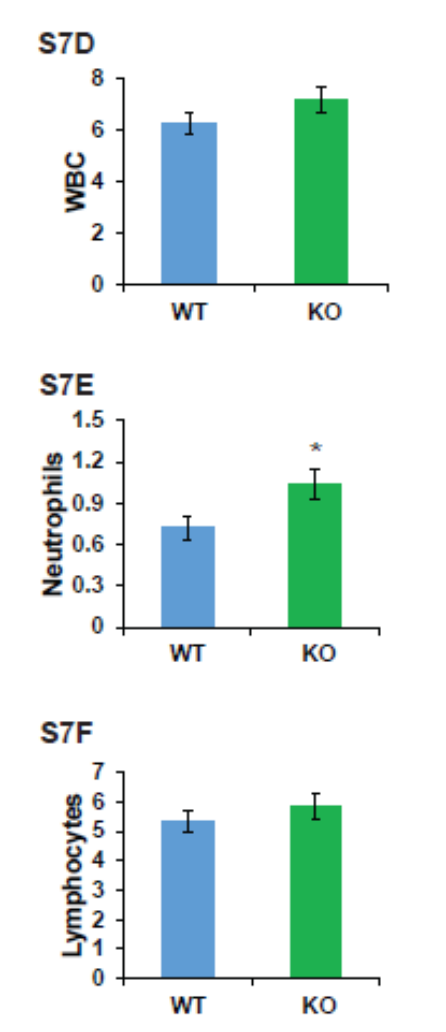
15-PGDH inhibition promotes hematopoetic recovery after bone marrow transplantation

Does 15-PGDH might regulate these responses?

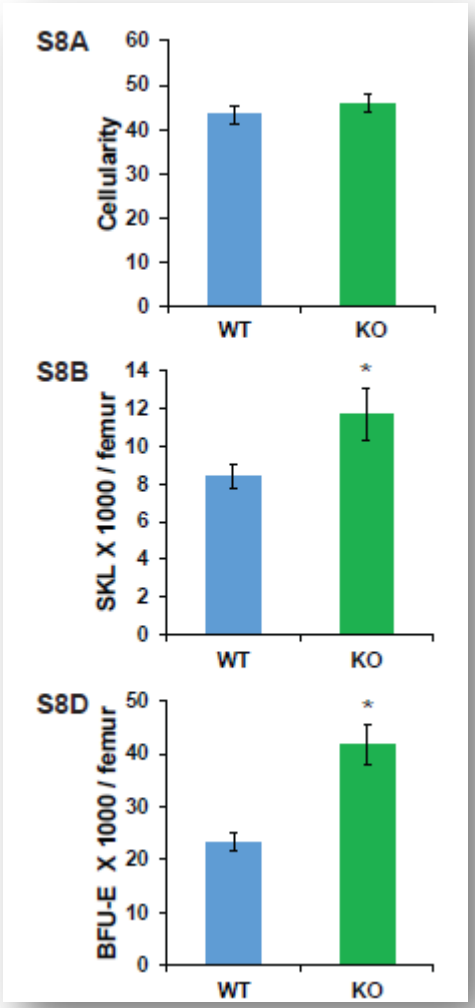


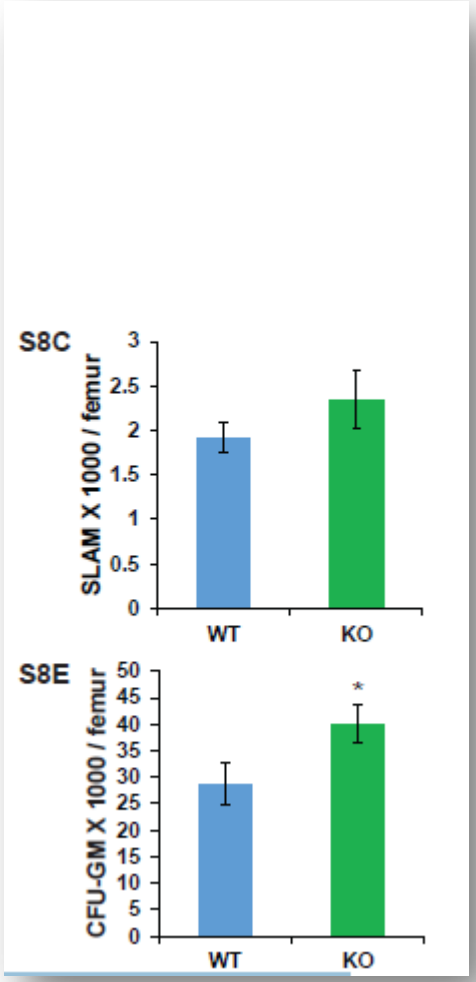
Comparison of peripheral blood counts from 15-PGDH WT and KO



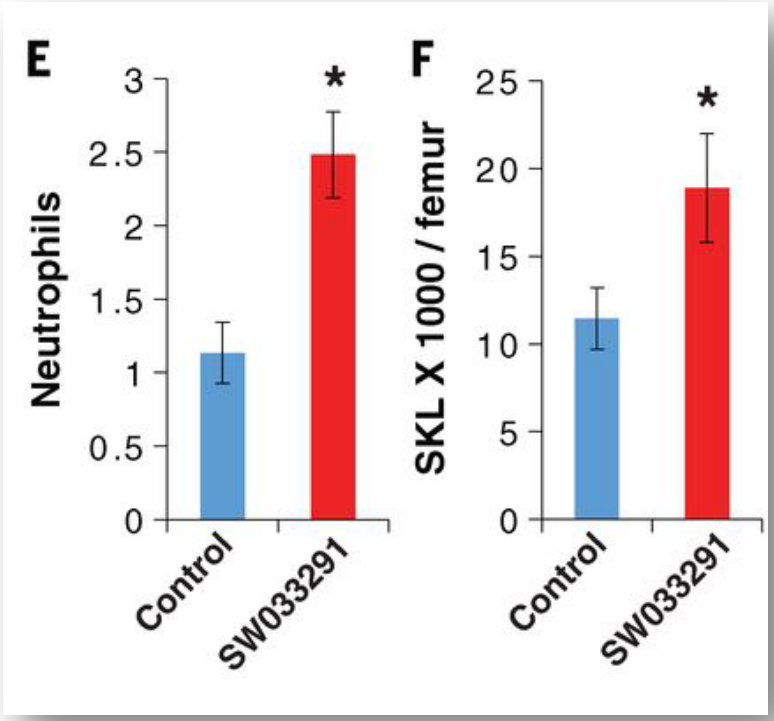


Comparison of bone marrow from 15-PGDH WT and KO

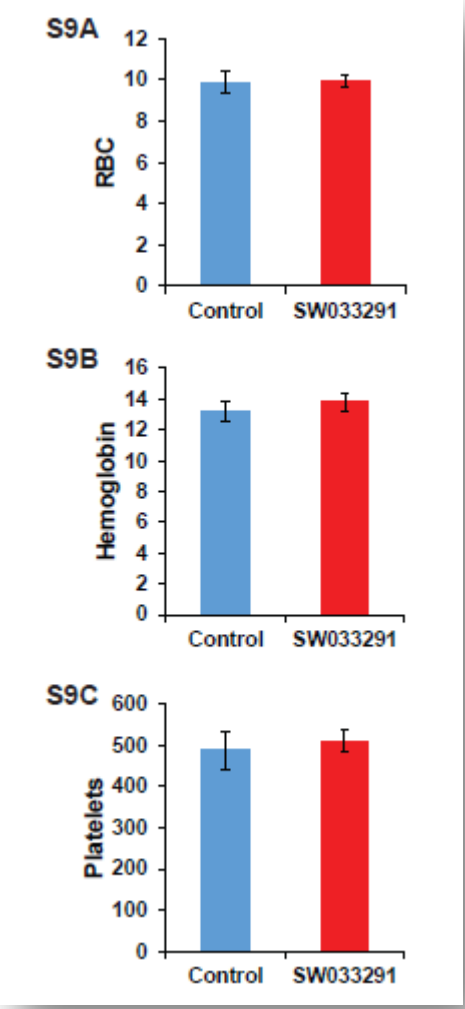


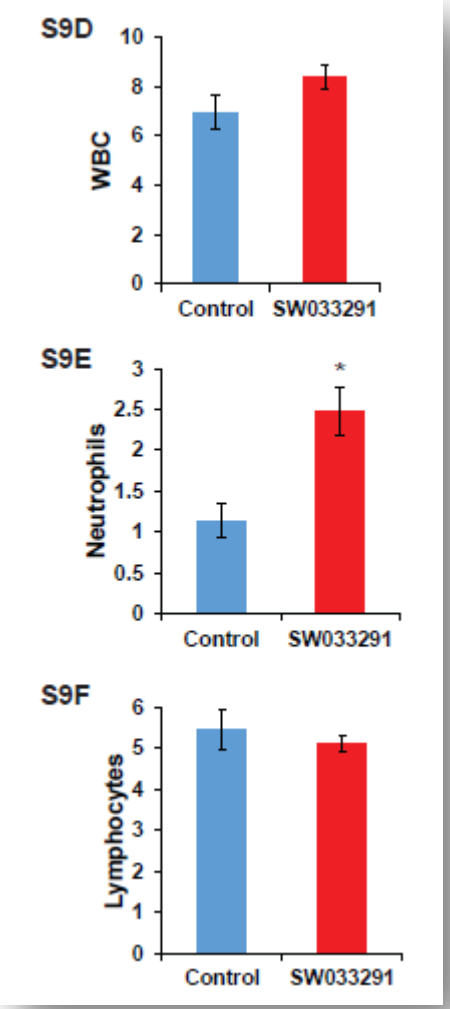


Does SW033291 might regulate these responses?

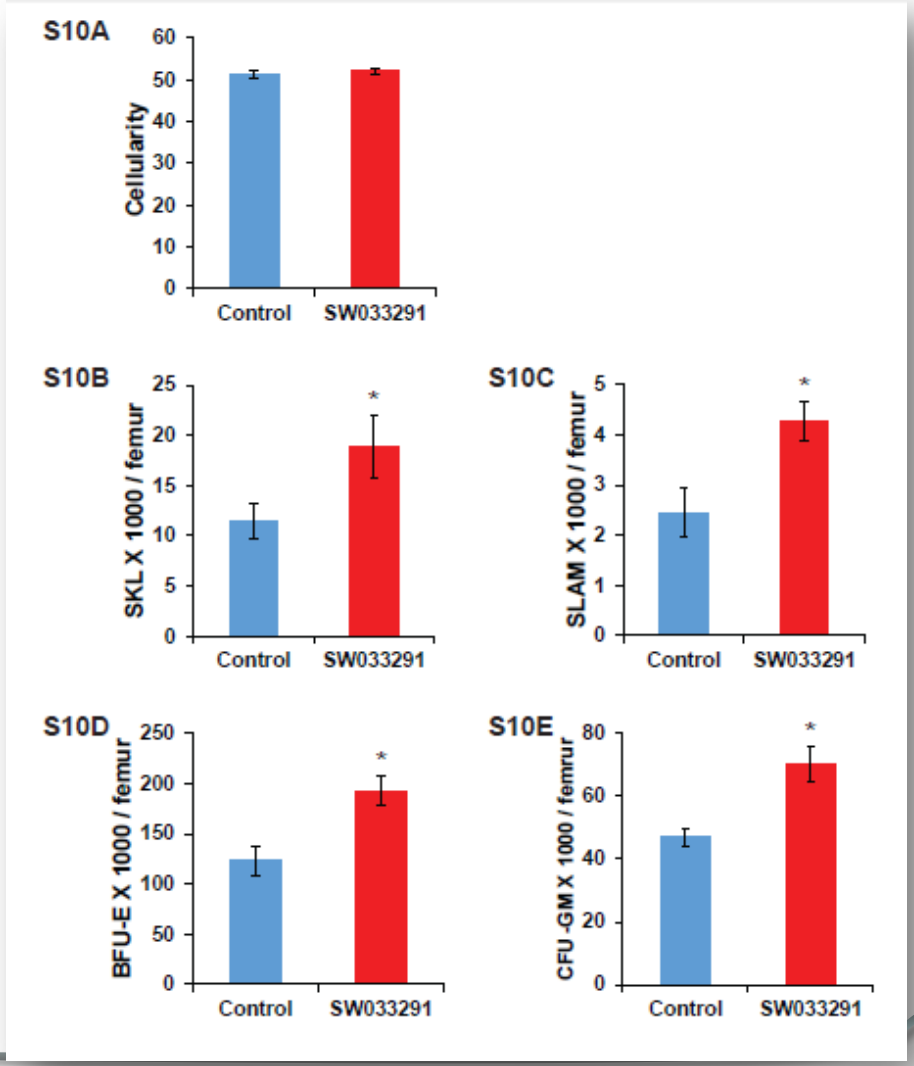


SW033291 effect on peripheral blood counts

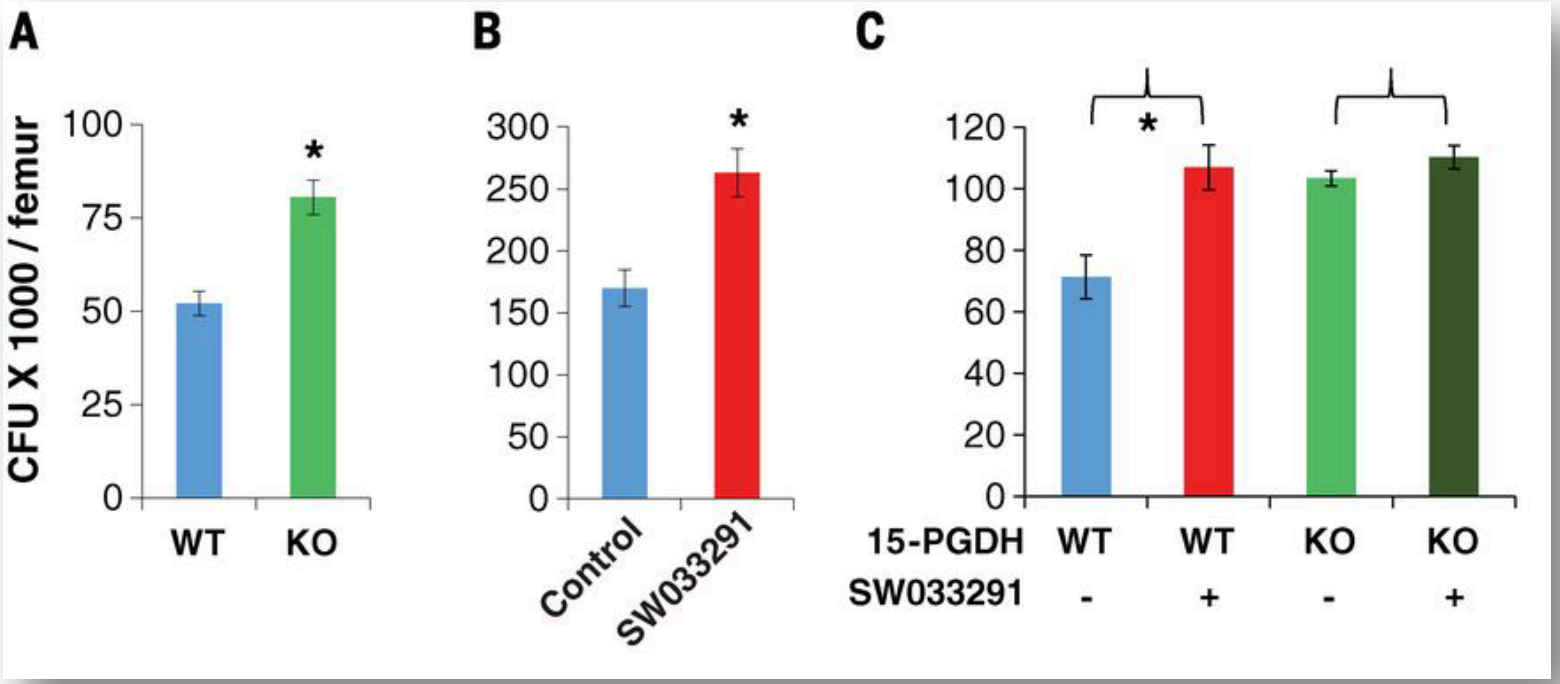




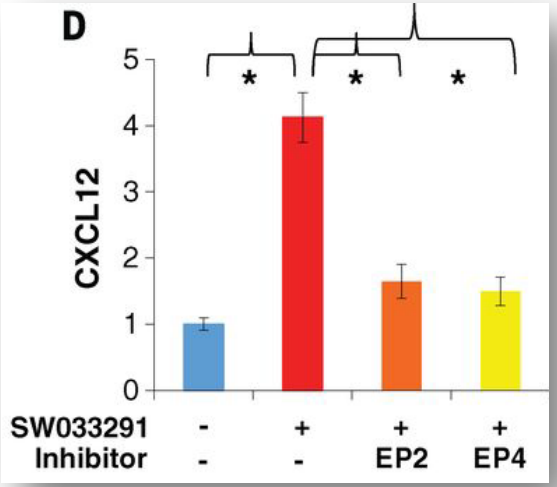
SW033291 effect on bone marrow

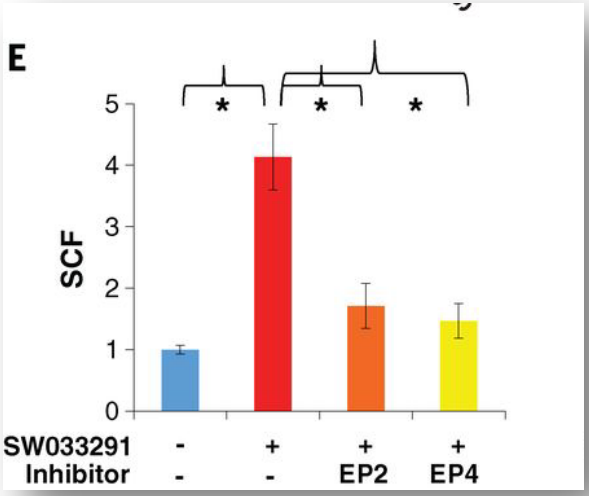


SW033291 directly targeting 15-PGDH

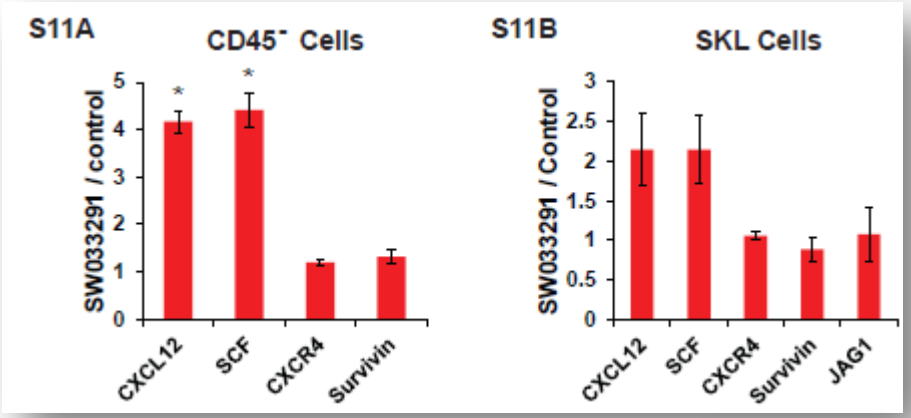


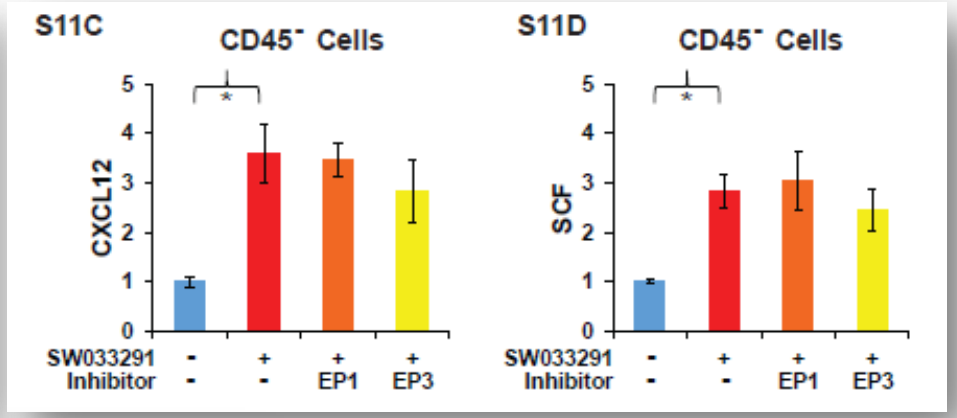
Effect of SW033291 on gene expression

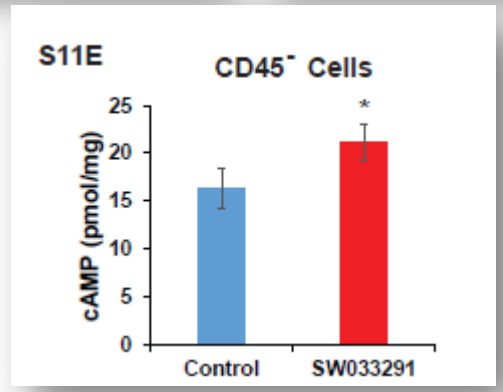




Effect of SW033291 on other gene expression







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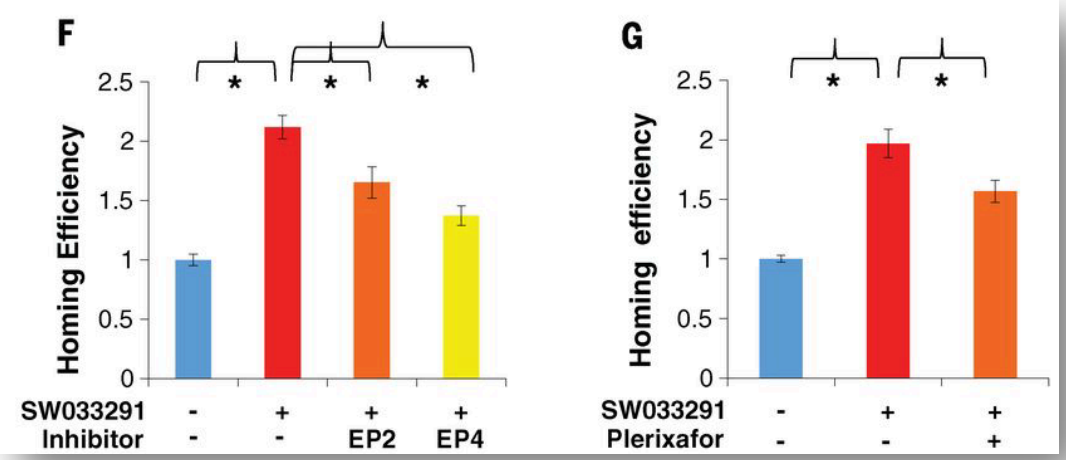
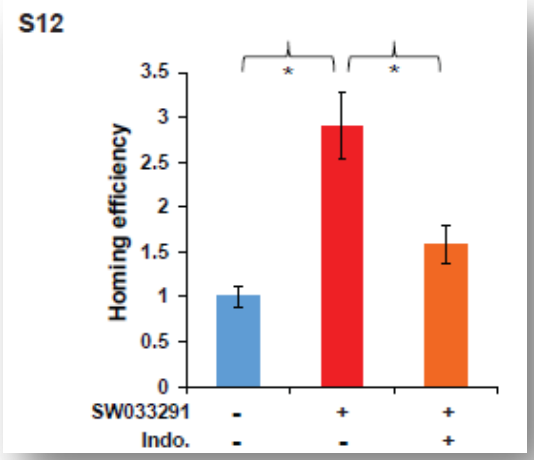
Homing efficiency after bone marrow transplant

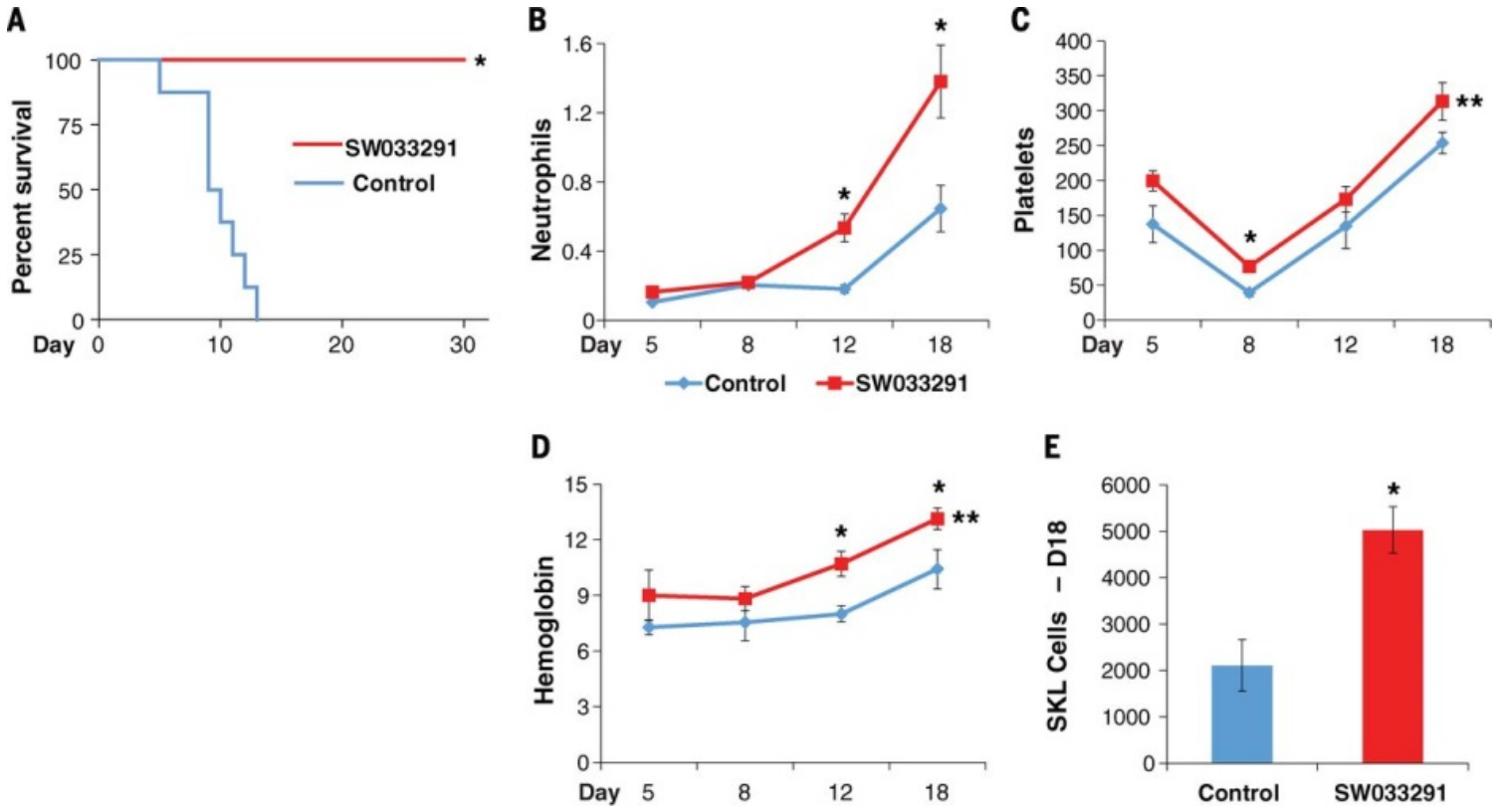




PATHWAY:

15-PGDH inhibition ->
increasing PGE2 levels in bone marrow ->
induces expression of CXCL12 and SCF ->
alter the bone marrow to better support homing in transplanted cells

SW033921 potentiates hematopoietic recovery after bone marrow transplantation



Survival Following Serial Rounds of Bone Marrow Transplantation

Founder Mouse Treatment	First Round Survival	Second Round Survival	Third Round Survival
Vehicle	5/5	5/5	4/5
SW033291	5/5	5/5	4/5

survival in each cohort is indicated as $\frac{\#\ of\ mice\ surviving\ at\ 8\ weeks\ post-transplant}{\#\ of\ mice\ bone\ marrow\ transplant\ recipient\ mice}$

Results

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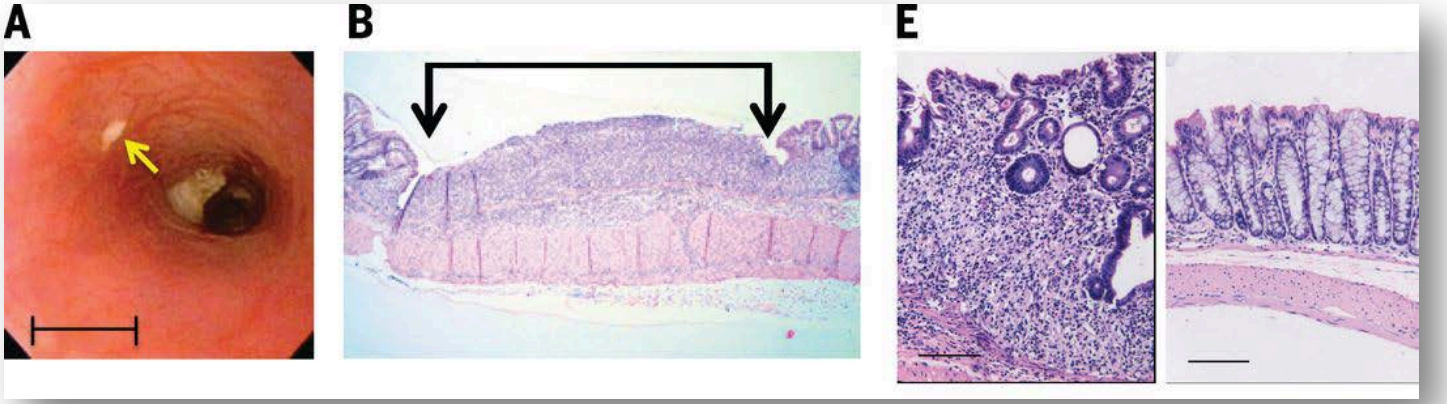
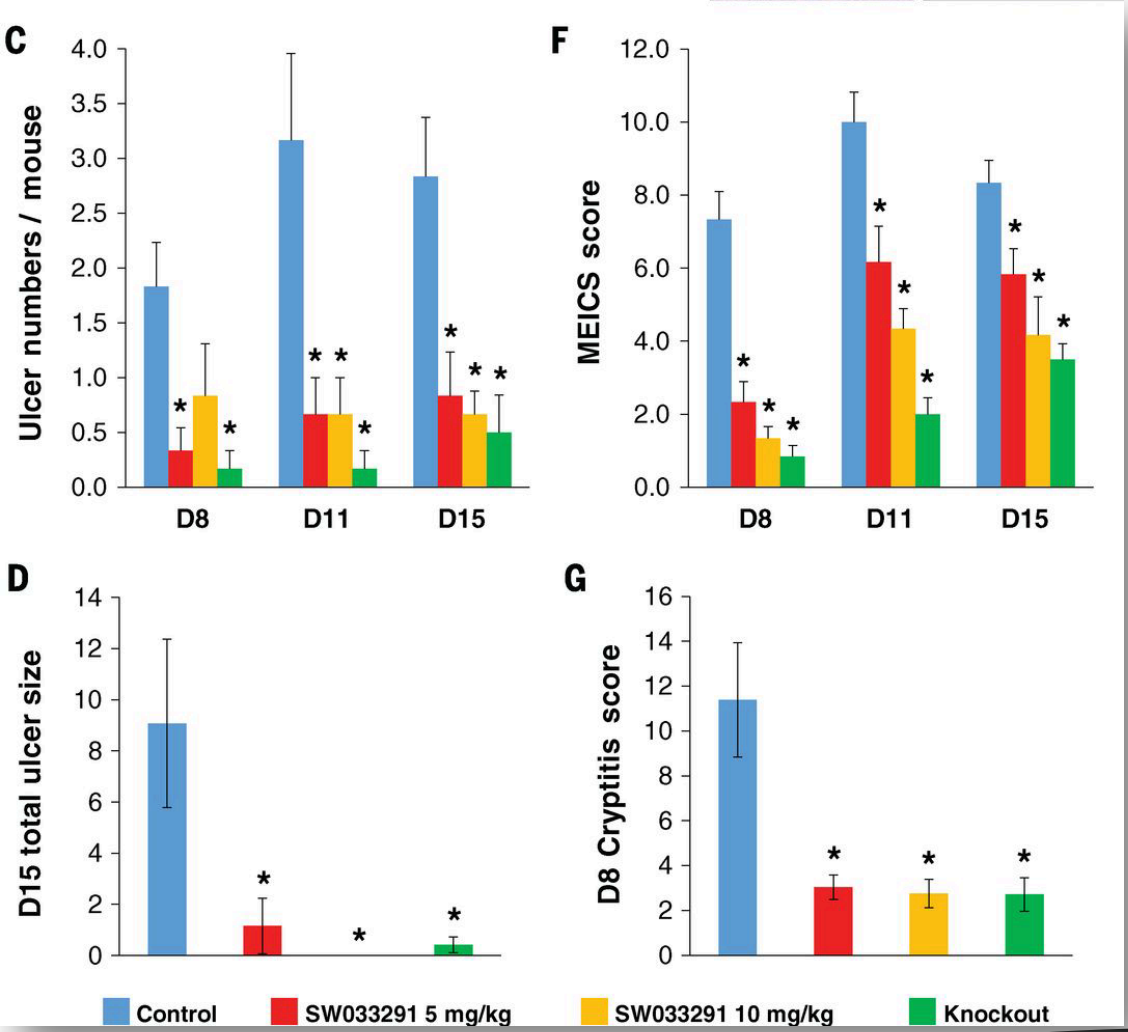
15-PGDH inhibition protects mice from colitis

15-PGDH inhibition protects mice from colitis



DSS = dextran sodium sulfate

15-PGDH inhibition protects mice from colitis



MEICS Score = murine endoscopic index of colitis severity

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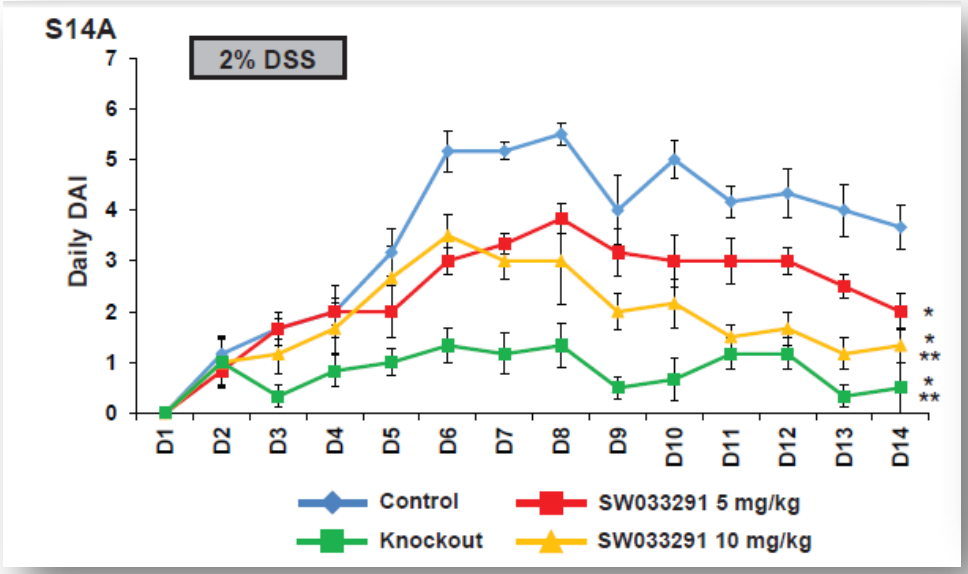
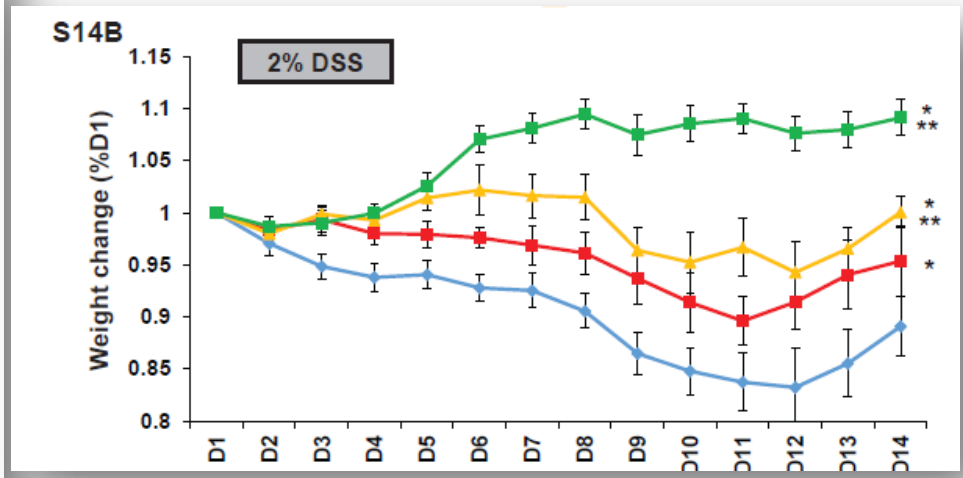
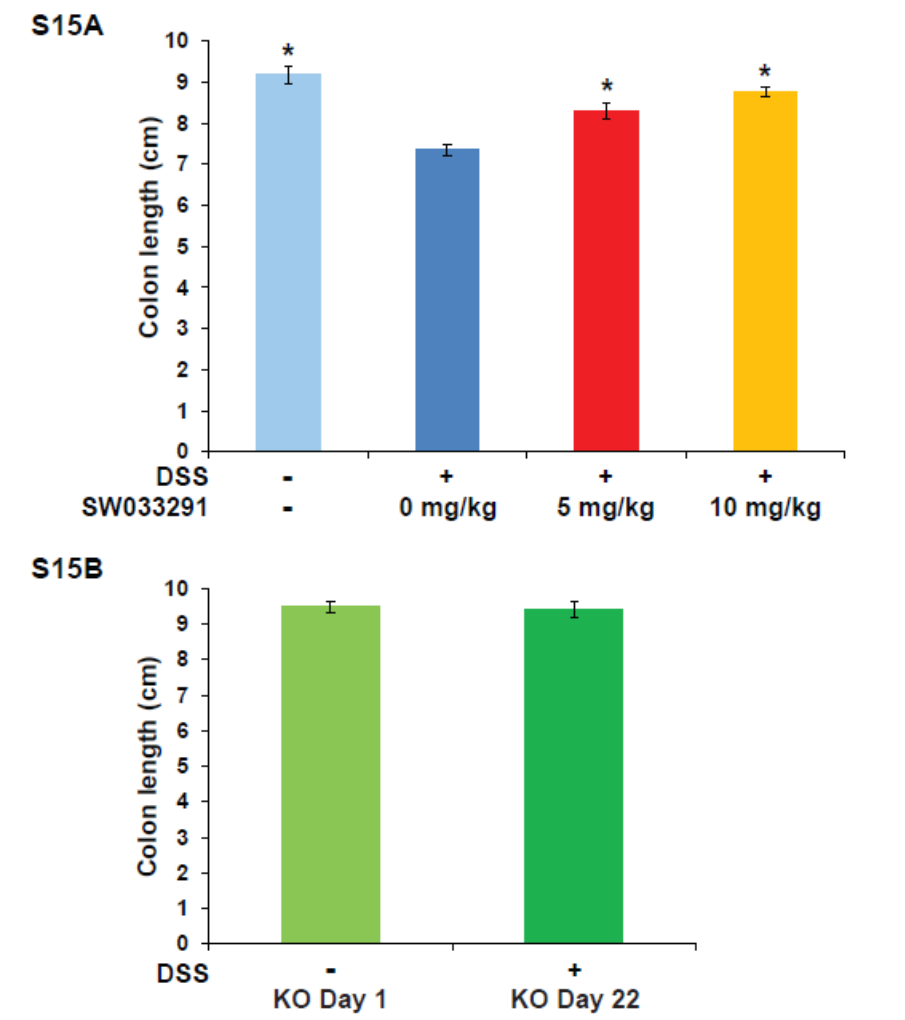
15-PGDH inhibition effects on DAI and weight





DAI= Desease activity index

15-PGDH inhibition effects on colon shortening



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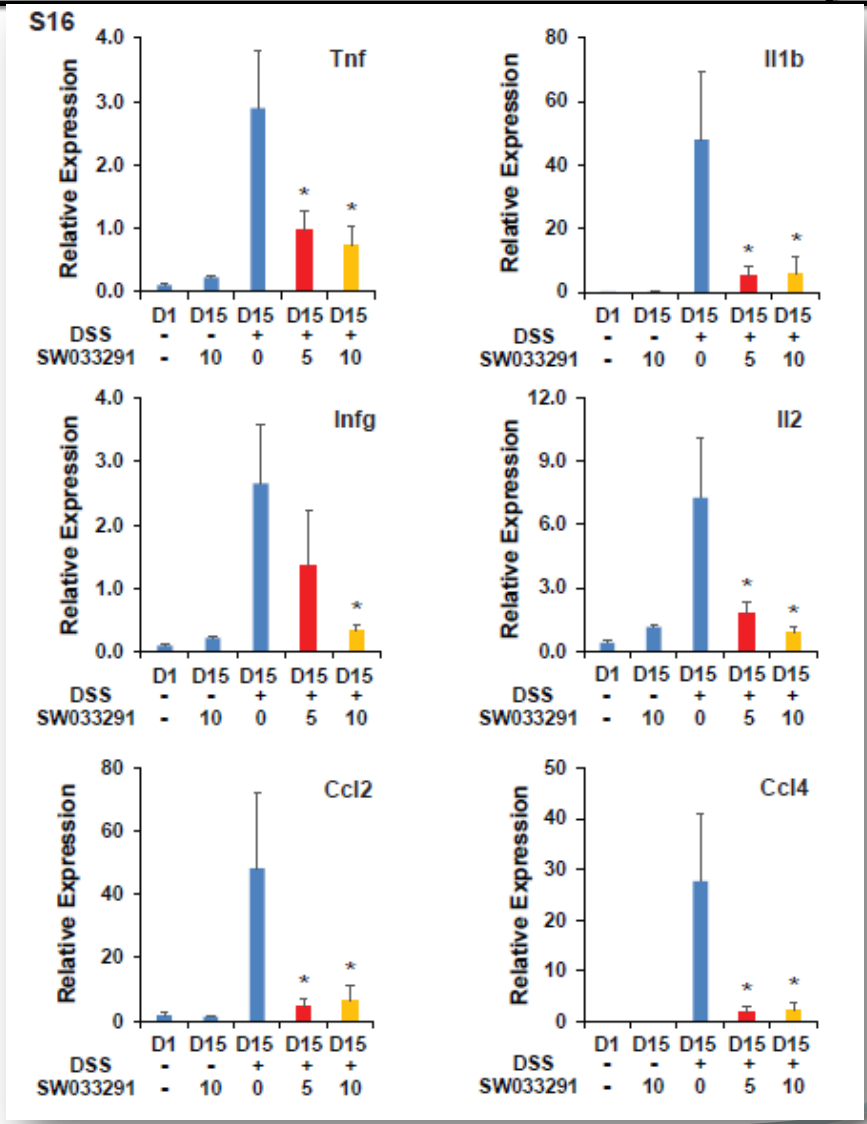
15-PGDH inhibition effects on colitis associated inflammatory cytokines



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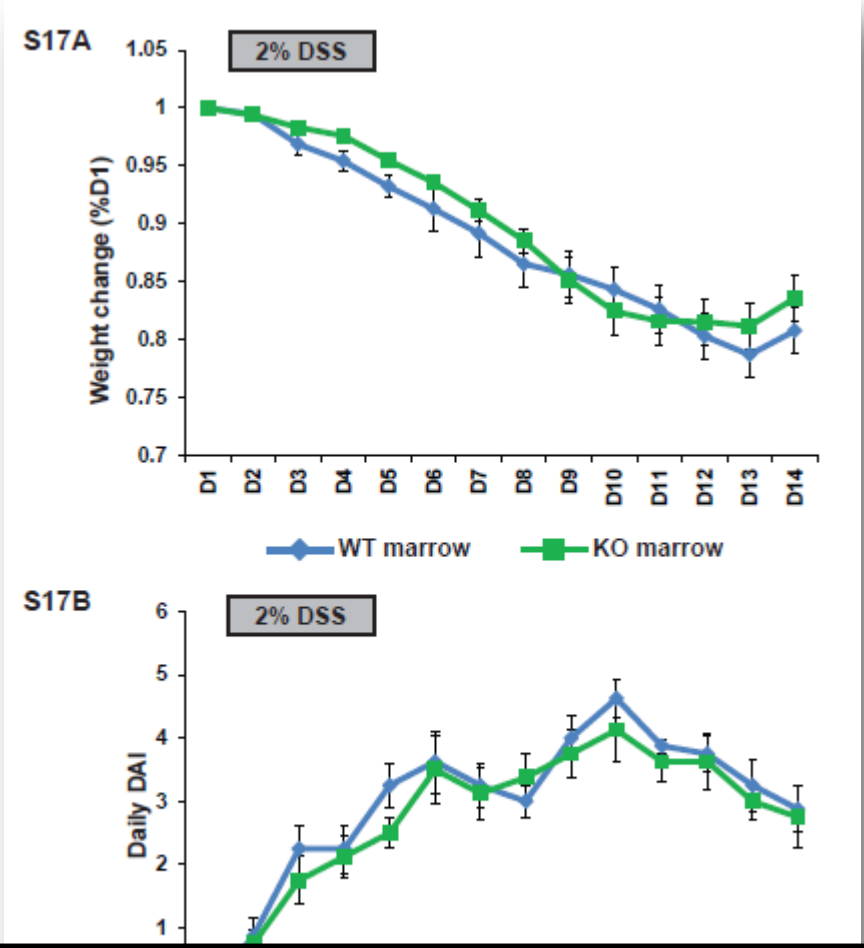
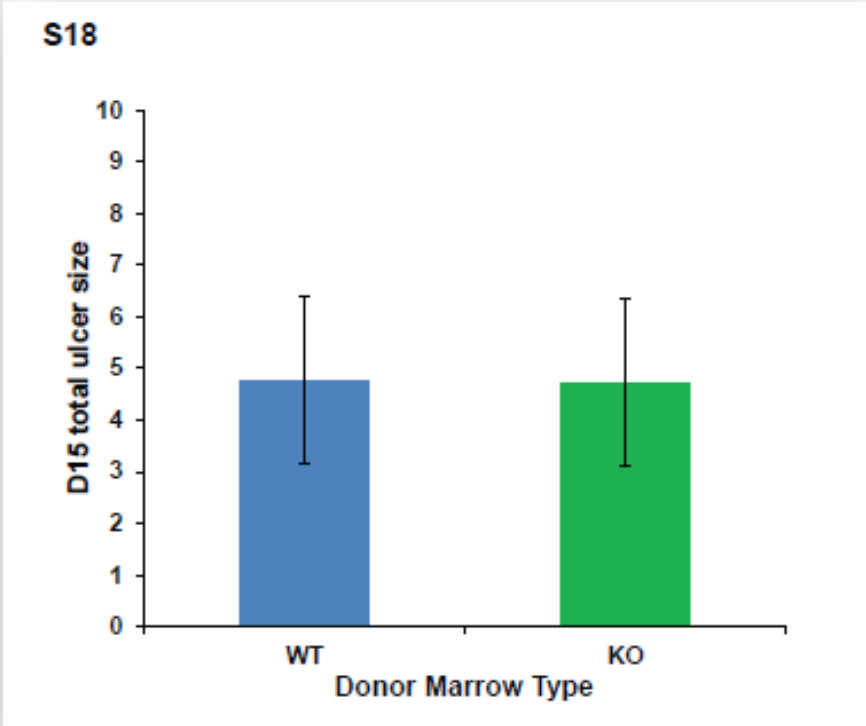
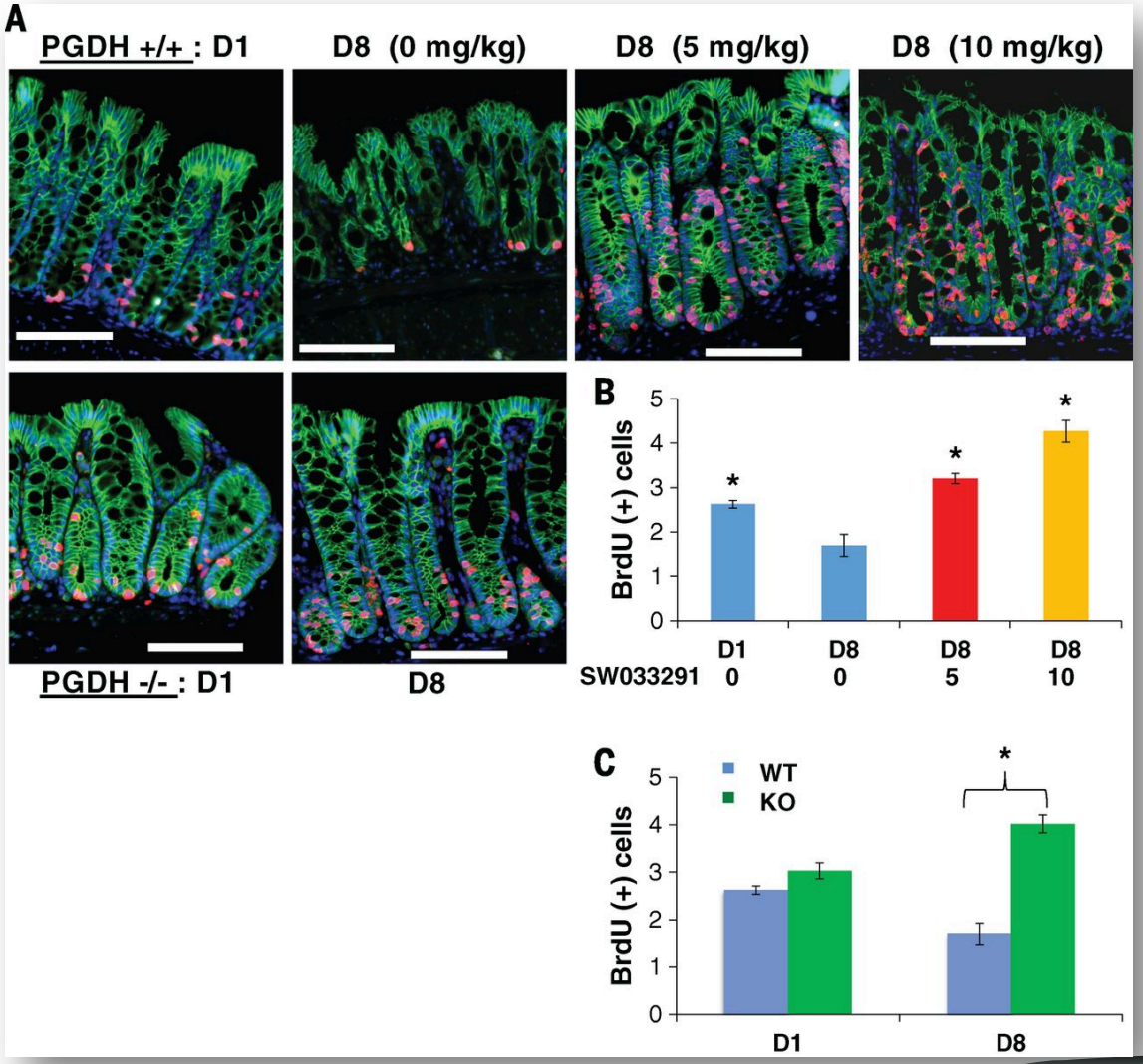
DSS effects in colon in chimeric mice





Colitis protection is due to:
Inhibition of 15-PGDH IN COLONOCYTES

Effect of inhibiting15-PGDH on cell proliferation in colon



BrdU=
5-bromo-
2'-deoxyuridine

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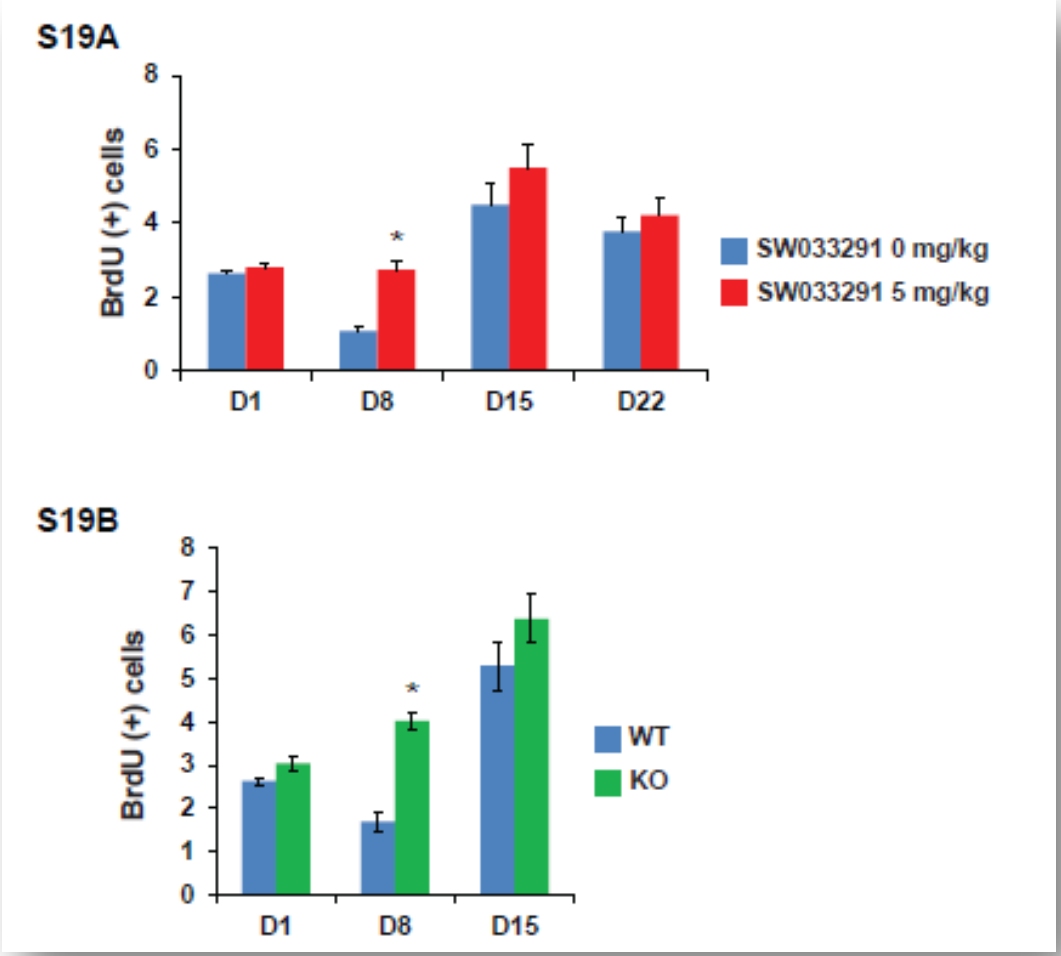
15-PGDH inhibition potentiates BrdU incorporation in colonic crypts



Protection of Colitis in mice:

Inhibition of 15-PGDH -> colonocyte proliferation in DSS-damaged mucosa

Results

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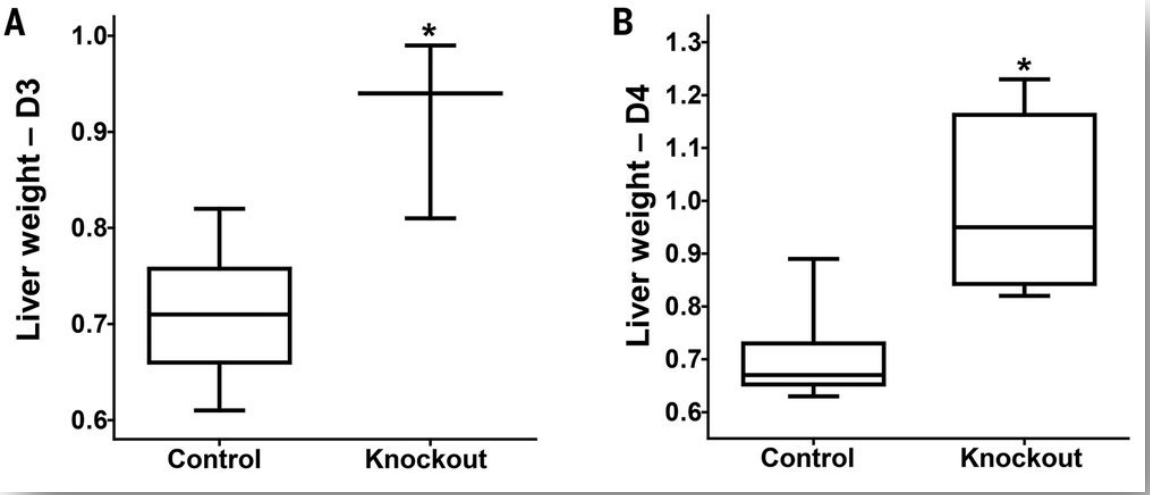
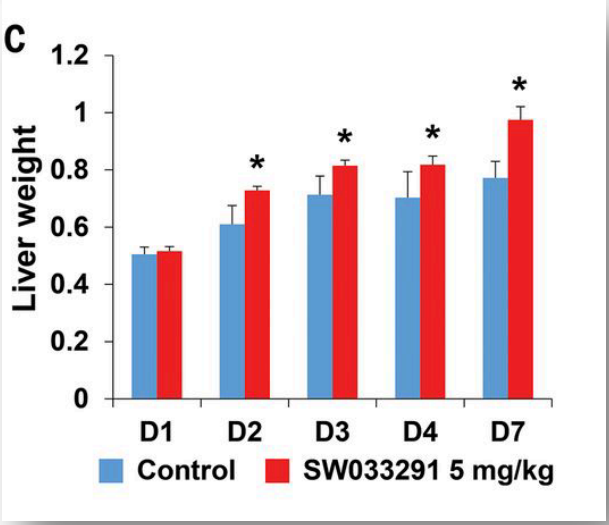
15-PGDH inhibition promotes liver regeneration

Effect of 15-PGDH inhibition on liver weight





D1-7: +0.27g

D1-7: +0.48g

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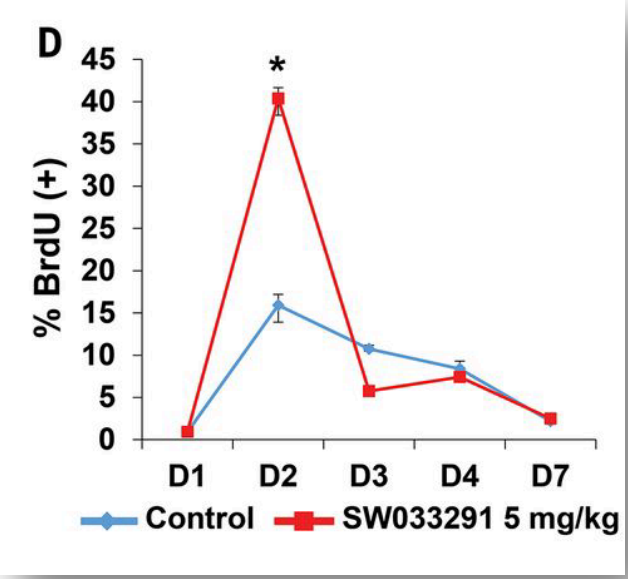
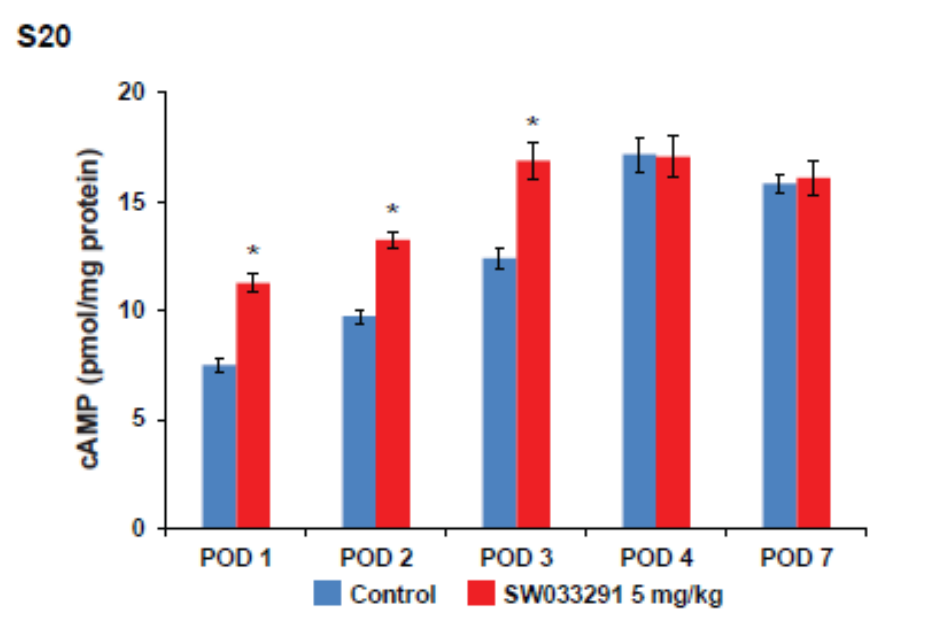
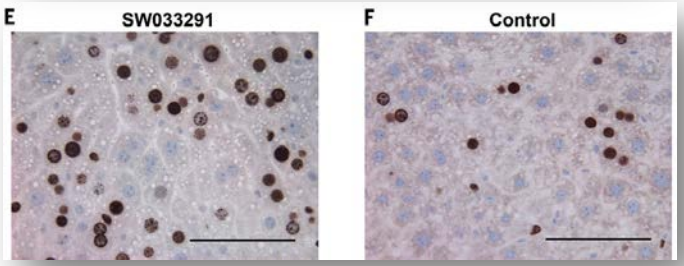
Effect of 15-PGDH inhibition on cell proliferation in the liver







Promoted liver regeneration due to:
15-PGDH-inhibitor increased proliferation in hepatocytes

Take home message